2013 Handbook of HIV Drug Therapy

VOLUME TWO

Drug Interactions

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HIV MEDICATIONS AT A GLANCE

Single Tablet Regimens	Nucleos(t)ide Reverse Transcriptase Inhibitors			Non-Nucleoside Reverse Transcriptase Inhibitors		Protease Inhibitors			Integrase Inhibitor
Atripla (efavirenz 600 mg, tenofovir 300 mg, emtricitabine 200 mg)	**Truvada** (tenofovir 300 mg, emtricitabine 200 mg)	**3TC** (lamivudine 150 mg, 300 mg)	**Retrovir** (zidovudine 100 mg)	**Edurant** (rilpivirine 25 mg)	**Sustiva** (efavirenz 200 mg, 600 mg)	**Aptivus** (tipranavir 250 mg)	**Prezista** (darunavir 400 mg, 600 mg)	**Norvir** (ritonavir 100 mg)	**Isentress** (raltegravir 400 mg)
Complera (rilpivirine 25 mg, emtricitabine 200 mg, tenofovir 300 mg)	**Kivexa** (abacavir 600 mg, lamiduvine 300 mg)	**Viread** (tenofovir 300 mg)	**Videx EC** (didanosine 400 mg)	**Intelence** (etravirine 200 mg)	**Viramune** (nevirapine 200 mg) **Viramune XR** (nevirapine 400 mg)	**Crixivan** (indinavir 400 mg)	**Reyataz** (atazanavir 150 mg, 200 mg, 300 mg)		
Stribild (Elvitegravir 150 mg, cobicistat 150 mg, tenofovir 300 mg, emtricitabine 200 mg)	**Combivir** (lamivudine 150 mg, zidovudine 300 mg)	**Ziagen** (abacavir 300 mg)	**Zerit** (stavudine 30 mg, 40 mg)	**Rescriptor** (delavirdine 100 mg)		**Invirase** (saquinavir 500 mg)	**Telzir** (fosamprenavir 700 mg)	**Fusion Inhibitor**	**CCR5 Inhibitor**
	Trizivir (abacavir 300 mg, lamivudine 150 mg, zidovudine 300 mg)					**Kaletra** (lopinavir 100 mg, ritonavir 25 mg,) (lopinavir 200 mg, ritonavir 50 mg)	**Viracept** (nelfinavir 625 mg)	**Fuzeon** (enfuvirtide 108 mg/vial))	**Celsentri** (maraviroc 150 mg, 300 mg))

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Additional information and updates may be found at: **www.hivclinic.ca**

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ACKNOWLEDGEMENTS

Contributors

We would like to gratefully acknowledge the contributions of the following co-authors:

- **Dr. Christine Hughes, Pharm.D.**, Faculty of Pharmacy & Pharmaceutical Sciences, University of Alberta, Edmonton (Opportunistic Infections and Symptom Management Guidelines and drug costs, Pediatric/Neonatal Doses of Antiretrovirals, Crushing Antiretrovirals chart, antimalarial, azole antifungal, and oral contraceptive interaction tables)
- **Dr. Tony Antoniou, Pharm.D.**, St. Michael's Hospital, Toronto (methadone, chemotherapy agents, and recreational drug interaction tables)
- **Cara Hills-Nieminen, B.Sc.(Phm).**, Ambulatory Pharmacy, St. Paul's Hospital, Vancouver (Antihypertensive and oral contraceptive interaction tables, Pediatric/Neonatal Doses of Antiretrovirals, Crushing Antiretrovirals chart)
- **Dr. Tamar Koleba, Pharm.D., Erin Yakiwchuk, BSP**, and **Dr. Stan Houston, MD**, Northern Alberta HIV Program, Alberta Health Services, Edmonton (antimalarial drug interaction table)
- **Dr. Trish Marr, Pharm.D.**, Family Medicine Program, Toronto Western Hospital (antiretroviral pharmacologic properties charts and lipid-lowering interaction tables)
- **Bill Cornish, RPh, BScPhm, ACPR**, Drug Information, Sunnybrook Health Sciences Centre (antihyperglycemics comparison chart & interaction table)
- **Dr. Deborah Yoong, Pharm.D.**, St. Michael's Hospital, Toronto (antiretroviral coverage in Canada)
- **Dr. Natalie Dayneka, Pharm.D.**, Children's Hospital of Eastern Ontario, Ottawa (pediatric dosing sections in the pharmacological properties tables)
- **Aneeta Lal, B.Sc.Phm.,** Clinic Pharmacy, Toronto General Hospital (drug cost data)
- **Alison Wong, M.Sc.Phm.**, McGill University Health Centre, Montreal (chemotherapy interaction table)
- **Dominic Martel, M.Sc.Phm.**, Montreal (boceprevir chart)
- **Marie-Hélène Irvine, Pharm.D.**, Toronto (telaprevir chart)
- **Chelsey Cabaj**, Alberta Health Services, Edmonton (smoking cessation table)
- **Mielen Mistry**, Pharmacy student, University Health Network, Toronto, ON (smoking cessation table)
- **Adriana Chubaty BscPharm**, Pharmacy resident, Northern Alberta HIV Program, Alberta Health Services, Edmonton (Crushing Antiretrovirals chart, adapted from original by **Gloria Tsang**, Oak Tree Clinic, Vancouver, BC)

We would also like to acknowledge the efforts of **Dr. David Fletcher** in his tremendous contributions and support in the creation and development of the initial versions of this book.

In addition, the following people contributed to past versions of this booklet:

- Nelson DaSilva, B.Sc.Phm., Michelle Diment, Pharm.D., Ian Hawes, Pharm.D., Dominic Khoo, B.Sc.Phm., Christine Malmberg, Pharm.D., Morenike Olaosebikan, B.Sc.Phm., Manish Patel, Pharm.D., Mary Nguyen, Pharm .D., Jessy Samuel, B.Sc.Phm.

This work would not have been possible without their assistance.

Sponsorship

The 1992 and 1994 editions of the Handbook were produced in-house through Toronto General Hospital. The 1996, 1997, 1998, 1999, 2002, and 2005 editions were produced through unrestricted educational grants from GlaxoSmithKline. The 2009 edition was jointly supported through unrestricted educational grants from GlaxoSmithKline and Abbott Canada. The print production of the 2013 edition is supported through unrestricted educational grants from Bristol-Myers Squibb, ViiV Canada, Abbott, Gilead, Merck Frosst Canada, and Janssen.

Staffing

The 1992, 1994, 1996 and 1997 editions of the Handbook provided information on commonly used treatment regimens in HIV and associated costs, and were co-authored by Alice Tseng, Pharm.D., and David Fletcher, M.D. In 1998, the Handbook was expanded to include selected drug properties and drug interactions of available antiretrovirals, and Michelle Foisy, Pharm.D. joined as a co-author. Since then, the content of the Handbook has significantly expanded, with the primary focus on pharmacology-related antiretroviral information.

Distribution

The 2013 Handbook on HIV Therapy is available in print and e-book versions. The information in this book is also available at: **www.hivclinic.ca**, and is updated on a regular basis.

Disclaimer

The information in this Handbook is intended for use by and with experienced physicians and pharmacists. The information is not intended to replace sound professional judgment in individual situations, and should be used in conjunction with other reliable sources of information. Due to the rapidly changing nature of information about HIV treatment and therapies, users are advised to recheck the information contained herein with the original source before applying it to patient care. Decisions about particular medical treatments should always be made in consultation with a qualified medical practitioner knowledgeable about HIV-related illness and the treatments in question.

Neither Toronto General Hospital, the Northern Alberta Program, nor the authors and contributors are responsible for deletions or inaccuracies in information or for claims of injury resulting from any such deletions or inaccuracies. Mention of specific drugs, drug doses or drug combinations within this book does not constitute endorsement by the authors, Toronto General Hospital, or the Northern Alberta Program.

INTRODUCTION

Since its original conception in 1992, this booklet has undergone many updates and transformations. This 2013 version includes updated sections on antiretroviral pharmacologic and pharmacokinetic properties and additional and expanded drug interaction tables. As principles of HIV therapy evolve, and as new agents continue to emerge, antiretroviral combination regimens become increasingly complex. Now, more than ever, factors such as efficacy, toxicity, drug interactions, medication adherence, and cost need to be carefully considered when designing a particular treatment regimen for an individual patient. A new section on pharmacology of directly acting antivirals (DAAs) for hepatitis C infection has also been added.

Costs of various treatment protocols are listed in Canadian dollars. Please note that the prices are approximate, and are based on 2012 data from sources including the Ontario Drug Benefit Formulary, the Alberta Drug Benefit List, average wholesale prices (for non-formulary drugs, 3%-6% savings may be applied to direct orders where applicable), and the Johns Hopkins HIV Guide **(http://www.hopkins-hivguide.org)**. Also, please note that total costs of each regimen do NOT include a dispensing fee. Where drug dosage is on a mg/kg basis, doses have been calculated for an average body weight of 70 kg.

Please note that the treatment protocols described are merely recommendations summarized from currently available practice guidelines. Since the standards of care in HIV are continually changing, and new therapeutic options are constantly emerging, it is the responsibility of each practitioner to stay abreast of new developments. These protocols are not meant to be absolute nor universal, and should always be utilized in conjunction with the informed clinical judgement of the practitioner.

Information in the **pharmacologic and drug interactions** sections are based on currently available data, including product monographs, published references, conference abstracts and posted guidelines (as noted in the Reference section). However, given the rapid pace of developments in this therapeutic area, it is acknowledged that these tables are not all-inclusive. Not all possible drug combinations have been studied for potential interaction, and new drug combinations are continually being developed. Therefore, please use caution whenever adding or modifying therapy, and consult a health care professional when possible. Readers may also refer to the clinic website: **www.hivclinic.ca**, for additional information and regular updates.

I. ANTIRETROVIRAL DRUG INTERACTION TABLES

Antiretroviral Interactions

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Drug Interactions with CCR5 Antagonists

	Maraviroc, MVC, Celsentri® (Pfizer)	**Aplaviroc (GSK) (***no longer in clinical studies)**	**Vicriviroc (Merck) (***no longer in clinical studies)**
Doses under study	150-600 mg BID, depending on concomitant medications	400-600 mg BID	5-15 mg QD, 10-50 mg BID
Metabolism	3A4, Pgp	3A4, 2C19 (minor), weak 3A inhibitor [1] Substrate of P-glycoprotein.	CYP3A4
Food Effect	↓ 33% AUC with high fat meal	↑ 47-63% AUC[2]	↓ rate of absorption and ↓ Cmax 58%, AUC not significantly affected by high-fat meal. Administer with or without food.[3]
Interactions with Antiretrovirals:			
atazanavir	When maraviroc 300 mg BID was given with atazanavir 400 mg QD, maraviroc AUC ↑ 3.6-fold, Cmax ↑ 2.1-fold, Cmin ↑ 4.2-fold. Reduction of maraviroc dose by 50% in the presence of protease inhibitors/potent CYP3A4 inhibitors is recommended.[4]		
Atazanavir/ritonavir	When maraviroc 300 mg BID was given with atazanavir 300/ritonavir 100 mg QD, maraviroc AUC ↑ 4.9-fold, Cmax ↑ 2.7-fold, Cmin ↑6.7-fold. Reduction of maraviroc dose by 50% in the presence of protease inhibitors/potent CYP3A4 inhibitors is recommended.[4] In 15 HIV-positive patients who received maraviroc 150 mg plus atazanavir 300/100 mg daily as part of a PK substudy of a randomized 48 week trial comparing MVC/ATVr vs ATVr + TDF/FTC, adequate maraviroc exposures were achieved at week 2: AUC 4330 ng.h/mL, Cavg 180 ng/mL, Cmax 650 ng/mL, Cmin 37 ng/mL. All subjects achieved the targeted Cavg >75 ng/mL for near maximal virologic efficacy based upon	Combination of aplaviroc 400 mg BID or 800 mg QD plus atazanavir 300 mg/ritonavir 100 mg QD in healthy volunteers resulted in significant increases in aplaviroc exposures (7-13 fold ↑ AUC, 2-5 fold ↑ C_T,) with a greater effect when aplaviroc was dosed QD. Atazanavir kinetics were not significantly changed in the presence of aplaviroc.[8]	The combination of vicriviroc 15 mg/ritonavir 100 mg QD plus atazanavir 300 mg QD in healthy volunteers did not lead to significant changes in vicriviroc plasma levels, compared to vicriviroc 15 mg QD /ritonavir 100 mg BID alone. Vicriviroc may be added to a ritonavir-boosted PI regimen without dosage adjustment.[9]

	Maraviroc, MVC, Celsentri® (Pfizer)	Aplaviroc (GSK) (***no longer in clinical studies)	Vicriviroc (Merck) (***no longer in clinical studies)
	exposure-response analysis from the MERIT study.[5] Week 24 interim analysis results of the randomized trial showed similar outcomes in both arms.[6] Modeling of maraviroc kinetics showed that **maraviroc 150 mg QD plus ATV 300/100 mg QD** in HIV-positive subjects yielded lower Cmax and Cavg but higher Cmin and effective constant concentrations compared to maraviroc 300 mg BID alone in healthy volunteers.[7]		
AZT/3TC	In healthy volunteers, Combivir 1 tab BID + maraviroc 300 mg BID/placebo for 7 days showed no clinically relevant effect on the kinetics of AZT/3TC.[10]		In healthy volunteers, Combivir 1 tab BID + vicriviroc 50 mg BID for 7 days showed no clinically relevant effect on the kinetics of AZT/3TC or of vicriviroc.[11]
Darunavir/ritonavir	In healthy subjects, **maraviroc 150 mg BID plus darunavir 600/ritonavir 100 mg BID** resulted in 2.3-fold ↑ Cmax, 4-fold ↑ AUC of maraviroc vs. maraviroc administered alone. Reduce maraviroc dose to 150 mg BID when coadministering with darunavir/ ritonavir.[12] In a retrospective review, peak and trough levels were compared in HIV-positive patients taking either maraviroc 300 mg BID plus tenofovir/FTC, **maraviroc 300 mg QD plus darunavir 800/100 mg QD** or **maraviroc 150 mg QD plus darunavir 800/100 mg QD**. Maraviroc concentrations were comparable between the groups and all Ctrough >25 ng/mL. Cpeak did not exceed 1000 ng/mL and no		Open label, multidose study in healthy adult subjects (n=12) to investigate the PK effects of vicriviroc 30mg daily + RTV 100mg BID +/- DRV 600mg BID. Addition of darunavir led to 7%↓ AUC, 17% ↓ Cmax, 3% ↑ Cmin of vicriviroc. Darunavir did not alter VCV levels to clinically important extent. No dose adjustment required.[14]

	Maraviroc, MVC, Celsentri® (Pfizer)	Aplaviroc (GSK) (***no longer in clinical studies)	Vicriviroc (Merck) (***no longer in clinical studies)
	cases of postural hypotension were noted. In the BID group, median Cpeak was 384 and Ctrough was 48 ng/mL, in the MVC 300 mg QD group, median Cpeak was 773 and Ctrough was 70 ng/mL, and in the MVC 150 mg QD group, median Ctrough was 50 ng/mL. All darunavir concentrations were therapeutic.[13] See additional entry for **darunavir/ritonavir + etravirine plus maraviroc.**		
Efavirenz	When maraviroc 100 mg BID was given with efavirenz 600 mg QD, maraviroc AUC ↓ 50%, Cmax ↓ 60%. Doubling maraviroc dose to 200 mg BID corrected maraviroc exposures. **When administering maraviroc with EFV (in the absence of PIs), doubling maraviroc dose is recommended**.[4] An in vitro-in vivo extrapolation model was developed to describe the kinetics of maraviroc in HIV-infected patients switching from efavirenz-containing therapy. The model predicted that MVC exposures similar to those with MVC 300 mg BID alone could be achieved via two scenarios following a switch from EFV: • MVC 600 mg BID x 1 week followed by standard 300 mg BID dosing • MVC 450 mg BID x 2 weeks followed by standard BID dosing[15]	In healthy adults, coadministration of aplaviroc 600 mg BID and efavirenz 600 mg QD for 10 days led to 57% ↓ AUC and 61% ↓ C_T of aplaviroc. Efavirenz exposures were not significantly different compared to historical controls.[16] Co-administration with a boosted PI regimen (e.g., FPV/rtv 700/100 mg BID) may be effective in counter-acting the inductive effects of EFV.[17]	In healthy adults, coadministration of efavirenz 600 mg QD and vicriviroc 10 mg QD for 14 days resulted in 81% ↓ AUC, 67% ↓ Cmax of vicriviroc vs. vicriviroc alone. When vicriviroc was given with **efavirenz plus ritonavir 100 mg QD**, vicriviroc AUC ↑ 384%, Cmax ↑ 196% vs. vicriviroc alone.[18]
Elvitegravir/ ritonavir	In a randomized, healthy subject study (n=28), volunteers received EVG/r 150/100mg QD for 10 days followed by EVG 150/100mg		

	Maraviroc, MVC, Celsentri® (Pfizer)	Aplaviroc (GSK) (***no longer in clinical studies)	Vicriviroc (Merck) (***no longer in clinical studies)
	QD plus maraviroc 150mg BID for 10 days or vice versa. No clinically relevant changes in EVG/rtv kinetics were observed with the combination, while maraviroc exposures were ↑ in the presence of EVG/rtv (maraviroc AUC ↑ 2.15 fold, Cmax ↑ 2.86 fold). Therefore, **reduce maraviroc dose to 150mg BID when used with EVG/r** (same as dose recommendation for MVC + other CYP 3A4 inhibitors).[19]		
Etravirine *See additional entry for **darunavir/ritonavir + etravirine plus maraviroc.**	Total maraviroc concentrations over a 12-hour period are reduced by 53% (AUC_{12}) and peak levels of maraviroc (C_{max}) by 60% in the presence of etravirine. Therefore, if a patient isn't also taking a potent CYP3A4 inhibitor such as RTV-boosted protease inhibitor, **maraviroc dose should be increased to 600mg twice daily**. No dose adjustment of etravirine is required. In 64 HIV-positive patients taking maraviroc 300 or 600 mg BID plus etravirine 200 mg BID without PIs, 67% Ctrough were <75 ng/mL (75% with maraviroc 300 mg BID and 63% with maraviroc 600 mg BID). Mean maraviroc Ctrough was 53 and 60 ng/mL in the 300 and 600 mg BID groups, respectively. Etravirine Ctrough was 723 ng/mL, approximately 180-fold higher than the protein-adjusted EC50 for wild type virus[20] In a cohort of patients receiving maraviroc and raltegravir with or without etravirine, significantly lower		

	Maraviroc, MVC, Celsentri® (Pfizer)	Aplaviroc (GSK) (***no longer in clinical studies)	Vicriviroc (Merck) (***no longer in clinical studies)
	maraviroc Ctrough were observed when combined with etravirine vs. without etravirine (57 vs 173.5 ng/mL respectively, p=0.01). Patients treated with maraviroc had significantly greater CD4 increases versus those not on maraviroc.[21]		
Fosamprenavir	In healthy volunteers, combination of maraviroc 300 mg BID plus fosamprenavir 1400 mg BID led to reduced concentrations of both drugs:[22] • MVC AUC ↓13%, Cmax ↓ 11%, Cmin ↓28% • APV AUC ↓ 44%, Cmax ↓ 51%, Cmin ↓ 1% Data suggest that standard dose maraviroc may be used with fosamprenavir.		
Fosamprenavir/ ritonavir	In healthy volunteers, combination of maraviroc 300 mg BID plus fosamprenavir 1400/ritonavir 100 mg QD led to reduced concentrations of both drugs:[22] • MVC AUC ↓2%, Cmax ↓ 7%, Cmin ↓23% • APV AUC ↓ 21%, Cmax ↓ 32%, Cmin ↓ 36% In same study, combination of maraviroc 300 mg BID plus fosamprenavir 700/ritonavir 100 mg BID led to: • MVC AUC ↓66%, Cmax ↓ 70%, Cmin ↓54% • APV AUC ↓ 26%, Cmax ↓ 31%, Cmin ↓ 24% Need for MVC dose ↑ with FPV/r BID is unknown.[22] In an open-label, fixed sequence study in healthy volunteers, cohort 1 received **maraviroc 300 mg BID** alone, **fosamprenavir 700/100 mg BID** alone, then the combination. With coadministration, maraviroc AUC ↑ 2.49 fold, Cmax ↑		The combination of vicriviroc 15 mg QD plus fosamprenavir 700 mg/ritonavir 100 mg BID in healthy volunteers did not lead to significant changes in vicriviroc plasma levels, compared to vicriviroc 15 mg QD/ritonavir 100 mg BID alone. Vicriviroc may be added to a ritonavir-boosted PI regimen without dosage adjustment.[9]

	Maraviroc, MVC, Celsentri® (Pfizer)	Aplaviroc (GSK) (***no longer in clinical studies)	Vicriviroc (Merck) (***no longer in clinical studies)
	52% and Ctau ↑ 4.74-fold, while amprenavir AUC ↓ 35%, Cmax ↓ 34% and Ctau ↓ 36%. In cohort 2, volunteers received **maraviroc 300 mg QD** alone, **fosamprenavir 1400/100 mg QD** alone, then the combination. With coadministration, maraviroc AUC ↑ 2.26 fold, Cmax ↑ 45% and Ctau ↑ 1.8-fold, while amprenavir AUC ↓ 30%, Cmax ↓ 29% and Ctau ↓ 15%. The combination was well tolerated. Further investigation of maraviroc 300 mg QD with fosamprenavir 1400/100 mg QD is suggested.[23]		
Indinavir/ritonavir			The combination of vicriviroc 15 mg QD plus indinavir 800 mg/ritonavir 100 mg BID in healthy volunteers did not lead to significant changes in vicriviroc plasma levels, compared to vicriviroc 15 mg QD/ritonavir 100 mg BID alone. Vicriviroc may be added to a ritonavir-boosted PI regimen without dosage adjustment.[9]
Lamivudine	Maraviroc had no effect on the pharmacokinetics of lamivudine.[24]		
Lopinavir/ritonavir	When maraviroc 100 mg BID was given with lopinavir/ritonavir 400/100 mg BID, maraviroc AUC ↑ 3.8-fold, Cmax ↑ 1.8-fold, Cmin ↑ 9.2-fold. Reduction of maraviroc dose to 50 mg BID resulted in maraviroc AUC ↑ 1.6-fold. **Maraviroc 50% dose reduction in the presence of protease**		Vicriviroc exposure ↑ similarly by ritonavir or lopinavir/ritonavir: In healthy subjects, vicriviroc 10 mg QD was given alone or with ritonavir 100 mg QD or lopinavir/ritonavir 400 mg QD for 14 days. In the presence of ritonavir, vicriviroc

	Maraviroc, MVC, Celsentri® (Pfizer)	Aplaviroc (GSK) (***no longer in clinical studies)	Vicriviroc (Merck) (***no longer in clinical studies)
	inhibitors/potent CYP3A4 inhibitors is recommended.[4] When maraviroc was given as 150 mg QD with lopinavir/ritonavir 400/100 mg BID in HIV-infected subjects (n=10), median (IQR) maraviroc concentrations were as follows: AUC_{24h} 4694 (3923-5516) hr*ng/ml, C_{avg} 179 (159 -221) ng/ml, C_{max} 601 (491-689) ng/ml, C_{min} 59 (39-64) ng/ml. All 10 subjects achieved the targeted C_{avg} (> 75 ng/ml).[25]		AUC ↑ 5.4-fold and Cmax ↑ 2.5-fold, while in the presence of lopinavir/rtv, vicriviroc AUC ↑ 4.2-fold and Cmax ↑ 2.3-fold. Both combinations were well tolerated.[26]
nelfinavir			The combination of vicriviroc 15 mg QD /ritonavir 100 mg BID plus nelfinavir 1250 mg BID in healthy volunteers did not lead to significant changes in vicriviroc plasma levels, compared to vicriviroc 15 mg QD /ritonavir 100 mg BID alone. Vicriviroc may be added to a ritonavir-boosted PI regimen without dosage adjustment.[9]
Nevirapine	In a cohort of HIV+ subjects (n=8) stabilized on nevirapine, 3TC and tenofovir, kinetics of single dose maraviroc 300 mg were unchanged vs. control data in HIV+ subjects receiving maraviroc alone for 10 days.[27]		
Raltegravir	In an open-label, fixed sequence study, healthy subjects (n=18) received raltegravir 400 mg BID for 3 days, then maraviroc 300 mg BID for 6 days, then both drugs together for 3 days. Plasma drug concentrations were measured on the last day of each phase. When maraviroc and raltegravir		

	Maraviroc, MVC, Celsentri® (Pfizer)	Aplaviroc (GSK) (***no longer in clinical studies)	Vicriviroc (Merck) (***no longer in clinical studies)
	were co-administered, mean maraviroc AUC ↓ 14% and Cmax ↓ 20% and mean raltegravir AUC ↓ 37% and Cmax ↓ 33% respective relative to each drug administered alone. The mechanism may be via decreased absorption or increase in first-pass metabolism. The authors considered these changes not to be clinically significant, and dose adjustments are not suggested. Monitoring for safety and efficacy is recommended with this combination.[28]		
Ritonavir	When maraviroc 100 mg BID was given with ritonavir 100 mg BID, maraviroc AUC ↑ 2.6-fold, Cmax ↑ 1.3-fold. Reduction of maraviroc dose to 50 mg BID gave similar exposures as maraviroc 100 mg BID alone. Maraviroc 50% dose reduction in the presence of protease inhibitors/potent CYP3A4 inhibitors is recommended.[4]		In healthy volunteers, ritonavir 100 mg QD or 100-400 mg BID plus vicriviroc 10 mg BID significantly ↑ SCH AUC 500% (469-585%) and Cmax 350% (301-395%), regardless of ritonavir dose.[29]
saquinavir	When maraviroc 100 mg BID was given with saquinavir-sgc 1200 mg TID, maraviroc AUC ↑ 4.3-fold, Cmax ↑ 3.3-fold. Reduction of maraviroc dose by 50% in the presence of protease inhibitors/potent CYP3A4 inhibitors is recommended.[4]		
Saquinavir/ritonavir	When maraviroc 100 mg BID was given with saquinavir-sgc/ritonavir 1000/100 mg BID, maraviroc AUC ↑ 9.8-fold, Cmax ↑ 4.8-fold. Reduction of maraviroc dose to 25 mg BID resulted in maraviroc AUC ↑ 1.4-fold. Maraviroc 50% dose reduction in the presence of protease inhibitors/potent		The combination of vicriviroc 15 mg QD plus saquinavir-sgc 1000 mg/ritonavir 100 mg BID in healthy volunteers did not lead to significant changes in vicriviroc plasma levels, compared to vicriviroc 15 mg QD/ritonavir 100 mg

	Maraviroc, MVC, Celsentri® (Pfizer)	Aplaviroc (GSK) (***no longer in clinical studies)	Vicriviroc (Merck) (***no longer in clinical studies)
	CYP3A4 inhibitors is recommended.[24]		BID alone. Vicriviroc may be added to a ritonavir-boosted PI regimen without dosage adjustment.[9]
tenofovir	Maraviroc 300 mg BID did not affect kinetics of tenofovir 300 mg QD.[4]	Healthy volunteer, randomized study of tenofovir 300 mg daily and aplaviroc 600 mg BID showed no significant effect of tenofovir on aplaviroc AUC or Cmax, and a moderate increase in C_T of 80%. Tenofovir pharmacokinetics were not changed in the presence of aplaviroc.[30]	In healthy volunteers, tenofovir 300 mg QD plus vicriviroc 10 mg BID for 7 days showed no clinically relevant effect on the kinetics of either drug. Tenofovir was given with the morning vicriviroc dose with food.[31]
Tipranavir/ ritonavir	Combination of maraviroc 150 mg BID plus tipranavir 500/200 mg BID in healthy subjects did not lead to any significant changes in maraviroc exposures.[32] Regular dosing of maraviroc (i.e., 300 mg BID) may be used with tipranavir/ritonavir.		Vicriviroc 15 mg QD was administered with ritonavir 200 mg BID or with tipranavir 500 mg/ ritonavir 200 mg BID in healthy subjects. When compared to VCV values with RTV alone, the addition of tipranavir did not significantly alter VCV exposure. Vicriviroc dose adjustment is not required when co-administering with tipranavir/ ritonavir.[33]
Zidovudine	Maraviroc had no effect on the pharmacokinetics of zidovudine.[24]		
Multi-ARV drug interactions:			
Darunavir/ritonavir + etravirine	Co-administration of **etravirine/darunavir/ritonavir** with maraviroc increased the exposure of maraviroc by 210% (AUC_{12}) and peak levels (C_{max}) by 77% compared to maraviroc alone. Thus, if maraviroc is being dosed alongside etravirine and darunavir together, a		

	Maraviroc, MVC, Celsentri® (Pfizer)	Aplaviroc (GSK) (***no longer in clinical studies)	Vicriviroc (Merck) (***no longer in clinical studies)
	maraviroc dose reduction to 150mg twice daily is necessary. No dose adjustment of ETV is necessary.[34]		
Efavirenz plus fosamprenavir/ ritonavir		Co-administration of aplaviroc 400 mg BID, fosamprenavir 700 mg/ritonavir 100 mg BID and efavirenz 600 mg QD led to a 2.6-fold ↑ AUC and 2.5-fold ↑ Ctau of aplaviroc compared to aplaviroc alone.[17] Therefore, co-administration with a boosted PI regimen appears to be effective in counter-acting the inductive effects of EFV.	
Efavirenz plus lopinavir/ritonavir	When maraviroc 300 mg BID was given with lopinavir/ritonavir 400/100 mg BID plus efavirenz 600 mg QD, maraviroc AUC ↑ 2.5-fold, Cmax ↑ 1.3-fold, Cmin ↑ 6.3-fold vs. maraviroc alone.[24] Maraviroc 150 mg BID dose recommended.[24]		
Efavirenz plus saquinavir/ritonavir	When maraviroc 100 mg BID was given with saquinavir-sgc/ritonavir 1000/100 mg BID plus efavirenz 600 mg QD, maraviroc AUC ↑ 5-fold, Cmax ↑ 2.3-fold, Cmin ↑ 8.4-fold vs. maraviroc alone.[24] Maraviroc 150 mg BID dose recommended.[24]		
Interactions with other medications:			
Carbamazepine			In healthy volunteers who received carbamazepine plus vicriviroc 30 mg with or without ritonavir, carbamazepine did not

	Maraviroc, MVC, Celsentri® (Pfizer)	Aplaviroc (GSK) (***no longer in clinical studies)	Vicriviroc (Merck) (***no longer in clinical studies)
			alter VCV exposure when dosed with 100 mg BID RTV. If CBZ is coadministered with VCV in a RTV-boosted PI-containing regimen, no VCV dose adjustment is required, but the RTV dose should be increased, to 100 mg BID or 200 mg QD.[35]
Digoxin	In healthy subjects who received maraviroc 300 mg BID for 6 days, the pharmacokinetics of single dose digoxin 0.25 mg were not altered in the presence of maraviroc compared to digoxin administered alone. This suggests that maraviroc is not a P-gp inhibitor and that dose adjustments are not required.[36]		
Hmg Co-A Reductase Inhibitors (statins)	CCR5 receptors, are located on cholesterol-rich 'lipid rafts' within cell membranes. Statins may reduce lipid raft numbers, potentially altering CCR5 availability and efficacy. A post-hoc analysis of the MOTIVATE studies assessed viral load and CD4 counts in 84 patients (of 840 total number of subjects) on statins (i.e., on statins at baseline and throughout study or at least 300 days). There was no difference in mean VL reduction, % achieving <50 copies/mL and CD4 increases at 48 weeks between study subjects on vs. not on statins.[37]		
Ketoconazole	When given with ketoconazole 400 mg QD, maraviroc AUC ↑ 5-fold, Cmax ↑ 3.4-fold. Reduction of maraviroc dose by 50% in the presence of protease inhibitors/potent CYP3A4 inhibitors is recommended.[4]		In healthy volunteers who received ketoconazole plus vicriviroc 30 mg with or without ritonavir, exposure of VCV was substantially increased (503% based on AUC) when administered

	Maraviroc, MVC, Celsentri® (Pfizer)	Aplaviroc (GSK) (***no longer in clinical studies)	Vicriviroc (Merck) (***no longer in clinical studies)
			concomitantly just with keto, while keto only modestly increased VCV concentrations (136% based on AUC) in the presence of RTV, compared to VCV alone.[35]
Midazolam	Maraviroc 300 mg BID had no effect on single-dose exposure of midazolam 7.5 mg.[4]		In healthy volunteers who received midazolam plus vicriviroc 30 mg with or without ritonavir, midazolam exposure was not affected by VCV administered alone, but was markedly increased when VCV was administered with RTV, a potent CYP3A4 inhibitor. [35]
Oral contraceptives	Maraviroc 100 mg BID had no effect on exposure of ethinylestradiol 30ug/levonorgestrel 150ug QD.[4]		
Phosphodiesterase-5 Inhibitors	No pharmacokinetic interaction is expected, as maraviroc does not inhibit CYP3A4. However, the PDE-5 inhibitors can decrease blood pressure and maraviroc doses >600 mg can increase the risk of postural hypotension. Maraviroc 300 mg BID should be administered with caution.[38] In 18 healthy subjects who received maraviroc 300 mg BID for 3 days plus single-dose vardenafil 20 mg, no clinically significant additive declines in systolic or diastolic blood pressures (both standing and supine) were noted.[39]		
Rifabutin			In healthy volunteers who received rifabutin plus vicriviroc 30 mg with or without ritonavir, rifabutin did

	Maraviroc, MVC, Celsentri® (Pfizer)	Aplaviroc (GSK) (***no longer in clinical studies)	Vicriviroc (Merck) (***no longer in clinical studies)
			not alter VCV exposure when dosed with 200 mg QD RTV. If rifabutin is coadministered with VCV in a RTV-boosted PI-containing regimen, no VCV dose adjustment is required, but the RTV dose should be increased, to 100 mg BID or 200 mg QD.[35]
Rifampin	When maraviroc 100 mg BID was given with rifampin 600 mg QD, maraviroc AUC and Cmax ↓ 70%, Cmin ↓ 78%. Doubling maraviroc dose to 200 mg BID corrected maraviroc exposures.[4] When administering maraviroc with rifampin, doubling maraviroc dose (to 600 mg BID) is recommended.		In healthy volunteers who received rifampin plus vicriviroc 30 mg with or without ritonavir, rifampin markedly decreased VCV exposure when dosed with 100 mg BID RTV; the relative oral bioavailability of VCV + RTV with rifampin compared to VCV + RTV alone was 11.6% based on AUC. Coadministration of rifampin with VCV is not recommended.[35]
Rifapentine	Reduction in maraviroc exposure anticipated with coadministration. **Avoid combination.**[40]		
Trimethoprim	Maraviroc 300 mg BID did not affect kinetics of trimethoprim 960 mg BID.[4]		

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Drug Interactions with Integrase Inhibitors

	Dolutegravir (S/GSK 1349572)	**Elvitegravir (GS-9137), Stribild®**	**Raltegravir (MK-0518), Isentress®**
Usual/Studied Dose(s)	50 mg QD (integrase-naïve), 50 mg BID being studied for integrase-experienced patients	150 mg QD (boosted with cobicistat 150 mg)	400 mg po BID
Kinetic Characteristics	Dolutegravir is a substrate of UGT1A1 (primary pathway) and CYP3A4 (10-15%). It is not a CYP inducer in vitro and at clinically relevant concentrations does not inhibit CYP, UGT or major transporters except for OCT2.[1]	Elvitegravir is metabolized via a combination of oxidative (CYP3A) and glucoronidation pathways. It is a modest inducer of CYP2C9 and may decrease the plasma concentrations of CYP2C9 substrates.	Raltegravir is primarily metabolized by glucuronidation (UGT1A1) and has no inhibitory or inductive potential in vitro.[2]
Food	Dolutegravir absorption is modestly increased with food according to fat content. Dolutegravir AUC ↑ 33%, 41% and 66% when administered with low-fat (300 kcal, 7% fat), moderate fat (600 kcal, 30% fat) and high fat food (870 kcal, 53% fat), respectively. Dolutegravir may be administered with or without food and without regard to fat content.[3]	When administered as a fixed dose combination tablet with emtricitabine, tenofovir and cobicistat in healthy volunteers, elvitegravir AUC_{inf} and C_{max} ↑ by 34% and 22%, respectively, with a light meal and by 87% and 56% with a high-fat meal.[4] Take with food.	Moderate and high-fat meals had no clinically meaningful effect on the PK parameters.
1) ANTIRETROVIRALS			
Atazanavir	In a randomized, open-label, two-period, crossover study, healthy adult subjects received dolutegravir 30 mg QD for 5 days, followed by the addition of either atazanavir 300/100 mg QD or atazanavir 400 mg QD for 14 days. Coadministration with ATV/RTV resulted in ↑ AUC 62%, ↑ Cmax 34% and ↑ Ctrough 121% of dolutegravir. Coadministration with atazanavir 400 mg QD resulted in ↑ AUC 91%, ↑ Cmax 50% and ↑ Ctrough 90% of dolutegravir. The combinations were well tolerated. No dose adjustment is necessary when dolutegravir is coadministered	<u>Using ritonavir as a booster</u>: Randomized, crossover, multiple dose study in healthy subjects (n=14) to investigate whether atazanavir could effectively boost EVG levels • EVG 300 mg/ATV 400 mg daily vs. EVG 300 mg/ ritonavir 100 mg daily: ↑ Cmax: 8%, ↑AUC: 7%, ↓ Cmin 10.1% • ATV and RTV showed similar inhibition of CYP 3A activity using midazolam probe • ATV + EVG vs. historical controls: ↓ ATV AUC 30%, ↓ ATV Cmin: 46%, potential of EVG to induce ATV metabolism? This requires further study. Atazanavir 400mg daily has potential to boost EVG levels	In two healthy volunteer studies, raltegravir kinetics were measured in the presence of steady-state boosted or unboosted atazanavir. In the presence of chronic **atazanavir 400 mg QD**, single dose **raltegravir 100 mg** resulted in raltegravir AUC ↑ 72%, Cmax ↑ 53%, C12 ↑ 95% compared to raltegravir alone. In an open-label, random order, crossover study, healthy volunteers received either RAL 400 mg BID or **RAL 400/ATV 400 mg QD** each for 7 days. In the presence of ATV, RAL Cmax ↑ 37% (p=0.4), Cmin ↓ 68% (P<0.001), AUC unchanged, and formation of RAL-

	Dolutegravir (S/GSK 1349572)	Elvitegravir (GS-9137), Stribild®	Raltegravir (MK-0518), Isentress®
	with boosted or unboosted atazanavir.[5]	when RTV sparing regimen desired.[6] <u>Using cobicistat as a booster</u>: A fixed sequence, crossover study in healthy subjects compared **EVG 85/co 150 mg plus ATV 300 mg QD** to either EVG 150/co 150 mg QD or ATV 300/ritonavir 100 mg QD: • ***EVG 85/co 150/ATV 300 mg QD vs. EVG 150/co 150 mg QD:*** 17% ↑ AUC, 16% ↓ Cmax, 83% ↑ Ctau of EVG • ***EVG 85/co 150/ATV 300 mg QD vs. ATV 300/ritonavir 100 mg QD:*** 10% ↓ AUC, 24% ↓ Cmax, 19% ↓ Ctau of atazanavir; changes not considered clinically relevant All ATV, EVG, cobicistat PK were comparable with reference/historical data.[7]	glucuronide was significantly decreased. RAL pk showed high interindividual variability and significant intra-individual diurnal variation.[8] In an open-label, fixed sequence study, HIV-infected subjects received ATV 400 mg QD for 2 weeks, followed by **ATV 400/RAL 800 mg QD** for 10 days. Concomitant tenofovir, proton-pump inhibitors and other interacting drugs were not allowed. Compared to historical data of RAL 400 mg single dose, RAL Cmax ↑ 2.81-fold, AUC ↑ 18%, Ctrough ↓ 85%. 4/15 subjects had RAL Ctrough <33 nM. Atazanavir concentrations were not reported.[9] In an open-label, sequential, two-period study, 17 HIV-infected, virally suppressed subjects with no history of virologic failure received **ATV 600 mg daily** plus **RAL 400 mg BID** for 2 weeks then **800 mg daily plus ATV 600 mg QD** for 4 weeks, concomitantly with 3TC or FTC. The AUC over 24 hours of QD RAL was not significantly different from that of BID RAL, while the Cmax was 33% higher and Cmin was 81% lower with QD vs. BID RAL. Atazanavir kinetics were similar with both RAL dosing regimens. All patients maintained an undetectable viral load and the regimens were well tolerated.[10] Six HIV-infected patients on **ATV 300/100 mg QD** were intensified **with RAL 400 mg QD** for 10 days. RAL exposure was adequate in

	Dolutegravir (S/GSK 1349572)	Elvitegravir (GS-9137), Stribild®	Raltegravir (MK-0518), Isentress®
			most patients with only 1 Ctrough <15 ng/mL (IC95). Atazanavir concentrations were similar to historical controls and all Ctrough>150 ng/mL.[11] In 21 HIV-infected treatment-experienced subjects who switched to **ATV 200/RAL 400 mg BID** due to resistance or toxicity issues, mean ATV AUC was 6257 ng/mL.hr, Ctrough was 227 ng/mL (122-332), with 24% having ATV Ctrough <150 ng/mL. Mean RAL AUC was 9085 ng/mL.h and Ctrough 132 ng/mL. 62% subjects had VL<50 at study entry, all reached undetectable after 2 weeks.[12] In healthy subjects, coadministration of **atazanavir 300 mg BID and raltegravir 400 mg BID** resulted in 11% ↓ Cmax, 17% ↓ AUC and 29% ↓ Cmin of atazanavir compared to atazanavir 300 mg BID alone; mean ATV Cmin was 817 ng/mL. Raltegravir AUC ↑ 54%, Cmax ↑ 39% and Cmin ↑48% when given with atazanavir. Mean QRS and PR interval increases were observed with atazanavir alone, and remained when raltegravir was coadministered; the clinical relevance of these changes is unclear.[13] In 22 HIV-positive subjects who switched to **atazanavir 300 mg BID plus raltegravir 400 mg BID**, steady-state pharmacokinetics were assessed. Geometric mean atazanavir AUC, Cmax and C12h were 14454 ng.h/mL, 2275 ng/mL and 419 ng/mL,

	Dolutegravir (S/GSK 1349572)	Elvitegravir (GS-9137), Stribild®	Raltegravir (MK-0518), Isentress®
			respectively. Raltegravir geometric mean AUC, Cmax and C12 were 7112 ng.h/mL, 1680 ng/mL and 62 ng/mL, respectively. Three subjects (14%) had atazanavir Ctrough <100 ng/mL. At the time of switch, 79% of patients had VL<50 copies/mL; by 24 weeks, all subjects had undetectable viral loads.[14]
Atazanavir/ ritonavir	In a randomized, open-label, two-period, crossover study, healthy adult subjects received dolutegravir 30 mg QD for 5 days, followed by the addition of either atazanavir 300/100 mg QD or atazanavir 400 mg QD for 14 days. Coadministration with ATV/RTV resulted in ↑ AUC 62%, ↑ Cmax 34% and ↑ Ctrough 121% of dolutegravir. Coadministration with atazanavir 400 mg QD resulted in ↑ AUC 91%, ↑ Cmax 50% and ↑ Ctrough 90% of dolutegravir. The combinations were well tolerated. No dose adjustment is necessary when dolutegravir is coadministered with boosted or unboosted atazanavir.[5]	Two kinetic studies with ATV/r + EVG were completed in healthy subjects: • **Study 1:** EVG 200/100mg daily + ATV/r 300/100mg daily. Combination led to ↑ EVG exposures compared to EVG 200/100mg daily alone. Proposed mechanism: inhibition of UGT1A1/3 metabolism by ATV/r. Combination also led to modestly ↓ ATV exposures compared to ATV/r 300/100mg daily alone. • **Study 2:** EVG 85/100 mg daily + ATV/r 300/100mg daily. Combination led to equivalent EVG exposures compared to the usual EVG 150mg daily dose. ATV exposure unchanged with EVG 85mg daily compared to ATV/r 300/100mg alone. Authors state an 85mg dose of EVG should be used when given with ATV/r.[15]	In a healthy volunteer study, raltegravir 400 mg BID plus **atazanavir 300/ritonavir 100 mg QD** for 10 days resulted in modest increases in raltegravir plasma levels (AUC ↑ 41%, Cmax ↑ 24%, C12 ↑ 77%) compared to raltegravir alone.[16] These interactions are not considered clinically meaningful. Based on these data, UGT1A1 inhibitors such as atazanavir and tenofovir may be coadministered with raltegravir without adjustment in the dose of raltegravir.[2]
Darunavir/ ritonavir	In an open-label, multiple dose, 2-period, 2-sequence crossover study, healthy subjects received dolutegravir 30 mg QD for 5 days followed by randomization to lopinavir/ritonavir 400/100 mg BID or darunavir/ritonavir 600/100 mg BID plus dolutegravir 30 mg QD for 14 days. Steady-state	In a crossover study, healthy volunteers were randomized to receive either elvitegravir 125 mg/ritonavir 100 mg QD, darunavir 600 mg/ritonavir 100 mg BID, or **elvitegravir 125 mg QD plus darunavir 600 mg/ritonavir 100 mg BID**, each for 14 days. Treatment was well tolerated, and there were no clinically-	In an open-label, sequential 2-period study, 18 healthy subjects received raltegravir 400 mg BID for 4 days followed by **raltegravir 400 mg BID plus darunavir 600/ritonavir 100 mg BID** for 12 days. Eight subjects developed rash (7 mild-moderate, 1 serious) between days 8-12 of period 2, and

	Dolutegravir (S/GSK 1349572)	Elvitegravir (GS-9137), Stribild®	Raltegravir (MK-0518), Isentress®
	dolutegravir kinetics were not altered in the presence of lopinavir/ritonavir. In the presence of darunavir/ritonavir, dolutegravir AUC ↓ 22%, Cmax ↓ 11% and Ctrough ↓ 38%; these changes were considered not clinically significant. No dosage adjustment for dolutegravir is required when used with lopinavir/ritonavir or darunavir/ritonavir.[17]	relevant effects on PK parameters for either drug suggesting that this combination can be co-administered without dose adjustment.[18]	only six subjects completed the study. Based on limited data, raltegravir exposure appeared to be slightly decreased in the presence of darunavir/ritonavir (raltegravir AUC ↓ 29%, Cmax ↓ 33%, Cmin ↑ 38%), while darunavir parameters were similar to historical controls.[19] In 29 HIV-positive subjects receiving regimens including **raltegravir, raltegravir/darunavir 600 mg/ritonavir 100 mg BID,** or **raltegravir/darunavir/ritonavir/ etravirine BID**, no differences in raltegravir Ctrough were noted between the groups.[20] 14 HIV-positive patients on stable cART with VL<50 copies/mL participated in a 3 period, phase I pk study of TDF/FTC plus **DRVr 800/100 mg QD** (period 1), TDF/FTC/DRVr plus **RAL 400 mg BID** (period 2), and DRVr/RAL (period 3). Intensive PK were performed at steady-state in each period. No statistically significant differences in PK parameters were observed between period 2 versus 1. In period 3, darunavir Ctrough ↓ 36% and $t_{1/2}$ ↓ 31% compared to period 1, while DRV AUC, Cmax and RTV pk were not significantly changed. No difference in RAL pk was observed between periods 2 & 3. Four subjects had DRV Ctrough < 550 ng/mL (IC50 for PI-resistant virus) in period 3 only, all levels were >55 ng/mL.[21] In 15 HIV-positive subjects receiving **DRV 800/100 mg**

	Dolutegravir (S/GSK 1349572)	Elvitegravir (GS-9137), Stribild®	Raltegravir (MK-0518), Isentress®
			QD plus RAL 400 mg BID, favourable pharmacokinetics of both drugs were observed and all patients had VL<37 copies/mL at week 24.[22] In 24 HIV-positive subjects, no evidence of a pharmacokinetic interaction was found between **DRVr 800/100 mg QD plus RAL 400 mg BID or 800 mg QD**.[23] In 55 HIV-positive patients receiving darunavir-containing regimens with either NRTI or raltegravir, 117 darunavir Ctrough samples were measured. The mean (± sd) darunavir concentration was higher in the NRTI group as compared to the raltegravir group (4.20 ± 2.35 vs. 2.63 ± 1.84 mg/L, p=0.018). However, the proportion of subjects with VL<50 copies/mL was higher in the raltegravir vs. NRTI arm (76.5% vs. 44%, respectively, p=0.041). In a multivariate linear regression model, raltegravir was independently related to lower darunavir levels. The mechanism for this unexpected interaction is unclear, but does not appear to be virologically significant.[24]
Efavirenz	In an open-label, single sequence crossover study, healthy volunteers received dolutegravir 50 mg once daily for 5 days followed by dolutegravir 50 mg and efavirenz 600 mg QD for 14 days. In the presence of efavirenz, dolutegravir AUC ↓ 57%, Cmax ↓ 39% and Ctrough ↓ 75%, likely via enzyme induction of UGT1A1 and CYP3A4. Dolutegravir concentrations remained 4-5 fold higher than the protein-	Three-period study in healthy subjects of EVG/COBI/ FTC/TDF (Quad) for 1 week followed by washout, efavirenz/FTC/TDF (Atripla®) for 2 weeks, then Quad for 5 weeks. Following the switch from Atripla® to the Quad, elvitegravir exposures were lower: • Day 35: AUC ↓ 37%, Cmax ↓ 19%, Ctau ↓ 67% • Day 42: AUC ↓ 29%, Cmax ↓ 11%, Ctau ↓ 54% Cobicistat Ctau was ↓ 35% at	In a placebo-controlled, 2 period study in 12 subjects who received 400 mg raltegravir alone or in combination with 600 mg EFV for 14 days, raltegravir kinetic parameters were modestly reduced in the presence of EFV: $C_{12\ hr}$ GMR [90% CI] = 0.79 [0.49, 1.28], $AUC_{0-\infty}$ = 0.64 [0.52, 0.80] and C_{max} = 0.64 [0.41, 0.98]. There were no substantial differences in T_{max} or $t_{½}$. This interaction is likely

	Dolutegravir (S/GSK 1349572)	Elvitegravir (GS-9137), Stribild®	Raltegravir (MK-0518), Isentress®
	adjusted IC90 for WT virus. No dose adjustment required for coadministration in integrase-naïve patients. [25]	day 14 post-switch. AUC of EVG glucuronidated metabolite were ↑ 46% and ↑ 32% on days 35 and 42, respectively. Mean EVG Ctrough was ~3-fold and ~5-fold > than protein-adjusted IC95 of 45 ng/mL on days 35 and 42, respectively, and 7-8 fold ↑ at 5 weeks post switch.[26]	not clinically meaningful.[27] Based on these data, efavirenz may be coadministered with raltegravir without dose adjustment.[2]
Etravirine	In an open-label, two-period, crossover study, healthy adult subjects received dolutegravir 50 mg QD for 5 days, then added etravirine 200 mg BID with food for 14 days. In the presence of etravirine, dolutegravir AUC ↓ 70%, Cmax ↓ 52% and Ctrough ↓ 88%. In a second randomized, open-label crossover study, healthy subjects began with dolutegravir 50 mg QD for 5 days, then added etravirine 200 mg BID plus either lopinavir/ritonavir 400/100 mg BID or darunavir 600/100 mg BID for 14 days. Dolutegravir kinetics were not significantly altered when given with etravirine plus lopinavir/ritonavir. When coadministered with etravirine plus darunavir/ritonavir, dolutegravir AUC ↓ 25%, Cmax ↓ 12% and Ctrough ↓ 37%. These changes were considered not clinically significant. Dolutegravir may be coadministered with etravirine without a dosage adjustment if lopinavir/ritonavir or darunavir/ritonavir is concurrently administered.[28]	In healthy subjects, no clinically relevant PK changes were observed for elvitegravir/ritonavir 150/100mg daily and etravirine 200mg BID compared to either drug administered alone. These 2 antiretrovirals can be used together without dose adjustment.[29]	In healthy subjects, raltegravir 400 mg BID and etravirine 200 mg BID for 4 days resulted in modest decreases in raltegravir concentrations (AUC ↓ 10%, 11% ↓ Cmax, 34% ↓ C12h) compared to raltegravir alone, while etravirine levels were not altered. These changes are not considered to be clinically meaningful; etravirine may be coadministered with raltegravir without dose adjustment.[30] In 29 HIV-positive subjects receiving regimens including raltegravir, raltegravir/darunavir 600 mg/ritonavir 100 mg BID, or raltegravir/darunavir/ritonavir/ etravirine BID, no differences in raltegravir Ctrough were noted between the groups.[20] A pharmacokinetic substudy was conducted in 10 HIV-positive subjects participating in the ANRS TRIO study. Patients received raltegravir 400 mg BID and darunavir 600/100 mg BID on day 1, and etravirine 200 mg BID was added on day 7. PK parameters were measured on days 6 and 28. Raltegravir and darunavir PK (Cmax, Cmin and AUC) were not significantly different in the

	Dolutegravir (S/GSK 1349572)	Elvitegravir (GS-9137), Stribild®	Raltegravir (MK-0518), Isentress®
			presence of etravirine.[31]
Fosamprenavir/ ritonavir	Healthy volunteers received dolutegravir 50 mg daily for 5 days followed by the addition of fosamprenavir/r 700/100 mg BID for 10 days. In the presence of fosamprenavir/r, dolutegravir AUC ↓ 35%, Cmax ↓ 24% and Cт ↓ 49%, while amprenavir pharmacokinetics were similar to historical values. Despite the reductions, dolutegravir concentrations remained well above the protein-adjusted IC90 for wild-type HIV, and no dose adjustment is needed when dolutegravir is co-administered with fosamprenavir/r in integrase inhibitor-naïve subjects.[32]	Healthy volunteers were randomized to receive either elvitegravir 125 mg/ritonavir 100 mg QD followed by elvitegravir 125 mg QD plus fosamprenavir 700 mg/ritonavir 100 mg BID, or fosamprenavir 700 mg/ritonavir 100 mg BID followed by elvitegravir 125 mg QD plus fosamprenavir 700 mg/ritonavir 100 mg BID, each for 14 days. Treatment was well tolerated, and there were no clinically relevant effects on PK parameters for either drug suggesting that this combination can be co-administered without dose adjustment.[33]	In an open-label, 3-period study, subjects received raltegravir 400mg BID for 7days, then were randomized to 14 days of either fosamprenavir 1400mg BID, FPV/r 700mg/100mg BID, or FPV/r 1400mg/100mg QD alone or with RAL; subjects continued their randomized dose of FPV for 14 more days, adding or removing RAL based on receipt in Period 2. With fosamprenavir, raltegravir PK decreased, especially at higher RTV doses, but RAL GM C_{min} were 3-9.4-fold >RAL IC_{95} for WT HIV (14.6ng/mL). With RAL, amprenavir PK decreased modestly; APV GM C_{min} for FPV/r 700/100 BID and FPV/r 1400/100 QD were 2.1-7.8-fold >APV EC_{90} documented for PI-naïve HIV+ pts (228ng/mL). The clinical implications of these results have yet to be determined.[34]
Lersivirine (UK-453,061, a next-generation NNRTI)			Healthy volunteers were randomized to receive lersivirine 1000 mg QD, raltegravir 400 mg BID or the combination, each for 10 days. Lersivirine exposures were not affected by raltegravir (AUC ↓ 2%, Cmax ↑ 5%), while raltegravir AUC ↓ 15%, Cmax ↓ 28% and Cmin ↑ 25% in the presence of lersivirine. A clinically relevant interaction is unlikely.[35]
Lopinavir/ ritonavir	In an open-label, multiple dose, 2-period, 2-sequence crossover study, healthy subjects received dolutegravir 30 mg QD for 5 days followed by randomization to lopinavir/ritonavir 400/100 mg BID or darunavir/ritonavir 600/100 mg BID plus	Healthy volunteers (n=27) were randomized to receive either elvitegravir (EVG)/ritonavir 125/100mg daily for 2 weeks, then EVG/r 125/100 mg daily plus LPV/r 400/100mg BID for 2 weeks (group 1) or LPV/r 400/100mg BID for 2 weeks, then EVG/r	Open label, 3 period, sequential, crossover, multiple dose study in healthy subjects (n=12) to investigate kinetics of RAL 400 mg BID +/- LPV/r 400 mg/100mg BID. LPV/r had no effect on RAL AUC (RAL alone vs. combo: 5.3mg/L.h VS 5.4 mg/L.h) or

	Dolutegravir (S/GSK 1349572)	Elvitegravir (GS-9137), Stribild®	Raltegravir (MK-0518), Isentress®
	dolutegravir 30 mg QD for 14 days. Steady-state dolutegravir kinetics were not altered in the presence of lopinavir/ritonavir. In the presence of darunavir/ritonavir, dolutegravir AUC ↓ 22%, Cmax ↓ 11% and Ctrough ↓ 38%; these changes were considered not clinically significant. No dosage adjustment for dolutegravir is required when used with lopinavir/ritonavir or darunavir/ritonavir.[17]	125/100 mg daily plus LPV/r 400/100mg BID for 2 weeks (group 2). EVG exposures were significantly increased in the presence of LPV/r: 75% ↑ $AUC_{tau,}$ 52% ↑ Cmax, 1382% ↑ Ctau, possibly via inhibition of UGT1A1/3 metabolism. LPV and RTV exposures were unchanged. Based on simulations, the authors recommend the dose of EVG be ↓ to 85mg daily when used with LPV/r.[36]	Cmax (RAL alone vs combo: 1698ng/ml VS 1687 ng/ml). Concomitant use of LPV/r led to ↓ RAL C12h 30% (49.4ng/ml VS 34.4ng/ml). Raltegravir Cmin stayed above IC95 (15ng/ml). Dose adjustment not recommended.[37]
Maraviroc		In a randomized, healthy subject study (n=28), volunteers received EVG/r 150/100mg QD for 10 days followed by EVG 150/100mg QD plus maraviroc 150mg BID for 10 days or vice versa. No clinically relevant changes in EVG/rtv kinetics were observed with the combination, while maraviroc exposures were ↑ in the presence of EVG/r (maraviroc AUC ↑ 2.15 fold, Cmax ↑ 2.86 fold). Therefore, **reduce maraviroc dose to 150mg BID when used with EVG/r** (same as dose recommendation for MVC + other CYP 3A4 inhibitors).[38]	In an open-label, fixed sequence study, healthy subjects (n=18) received raltegravir 400 mg BID for 3 days, then maraviroc 300 mg BID for 6 days, then both drugs together for 3 days. Plasma drug concentrations were measured on the last day of each phase. When maraviroc and raltegravir were co-administered, mean maraviroc AUC ↓ 14% and Cmax ↓ 20% and mean raltegravir AUC ↓ 37% and Cmax ↓ 33% respective relative to each drug administered alone. The mechanism may be via decreased absorption or increase in first-pass metabolism. The authors considered these changes not to be clinically significant, and dose adjustments are not suggested. Monitoring for safety and efficacy is recommended with this combination.[39]
Nevirapine			Drugs may be coadministered. No Raltegravir dose modification is required.[2]

	Dolutegravir (S/GSK 1349572)	Elvitegravir (GS-9137), Stribild®	Raltegravir (MK-0518), Isentress®
Nucleoside reverse transcriptase inhibitors		In healthy subjects, elvitegravir 200 mg/ritonavir 100 mg QD did not have significant effects on the kinetics of single doses of abacavir or stavudine, or multiple dose zidovudine. Didanosine AUC ↓ 14%, Cmin ↓ 25% in the presence of elvitegravir/ritonavir. Elvitegravir exposure was not significantly affected by coadministration of the NRTIs. Elvitegravir may be coadministered with abacavir, didanosine, stavudine and zidovudine without dose adjustment.[40]	
Rilpivirine			In healthy volunteers, coadministration of rilpivirine 25 mg QD and raltegravir 400 mg BID for 11 days did not significantly alter the pharmacokinetics of either drug compared to each drug administered alone. The combination may be administered without dose adjustment.[41]
Ritonavir		In healthy volunteers, ritonavir doses of 50, 100, and 200 mg plus elvitegravir 125 mg led to 41%, 54% and 56% ↓, respectively in apparent oral clearance of elvitegravir relative to 20 mg ritonavir. A ritonavir dose approaching 100 mg provided maximal inhibition of CYP activity. These data support a once-daily ritonavir dose of 100 mg when combined with elvitegravir.[42]	In a placebo-controlled, 2 period study in 12 subjects, the combination of 400 mg raltegravir and 100 mg RTV BID did not affect raltegravir parameters compared to raltegravir 400 mg administered alone.[27] The effect of ritonavir 100 mg BID on the kinetics of single-dose raltegravir 400 mg was studied in 12 healthy volunteers. Coadministration resulted in 22% ↑ AUC, 20% ↓ Cmax and 3.57-fold ↑ C12 of raltegravir.[43]
Tenofovir	No clinically relevant drug interaction observed when healthy subjects received dolutegravir 50 mg QD and tenofovir 300 mg QD for 5 days compared to either drug	No clinically relevant drug interaction observed when healthy subjects (n=24) received GS-9137 50 mg/rtv 100 mg QD with or without emtricitabine 200 mg/tenofovir	In an open-label, 3-period study in 10 healthy subjects, combination of 400 mg raltegravir BID and 300 mg QD of tenofovir for 4 days led to modest increases in

	Dolutegravir (S/GSK 1349572)	Elvitegravir (GS-9137), Stribild®	Raltegravir (MK-0518), Isentress®
	administered alone. Dolutegravir and tenofovir can be coadministered without dose adjustment.[44]	300 mg QD.[45] Combination may be coadministered without dosage adjustment.	raltegravir AUC (49%) and Cmax (64%) while Cmin was unchanged; tenofovir AUC ↓ 10% and Cmin ↓ 13%.[46] Dose adjustment likely not necessary.
Tipranavir	In an open-label, single sequence crossover study, healthy volunteers received dolutegravir 50 mg once daily for 5 days, then tipranavir/ritonavir 500/200 mg BID for 7 days, followed by dolutegravir 50 mg QD and tipranavir/ritonavir 500/200 mg BID for 5 days. In the presence of tipranavir/ritonavir, dolutegravir AUC ↓ 59%, Cmax ↓ 46% and Ctrough ↓ 76%, likely via enzyme induction of UGT1A1 and CYP3A4. Four of 18 subjects discontinued the study due to increases in ALT during the TPV/r dosing alone. Dolutegravir concentrations remained 4-5 fold higher than the protein-adjusted IC90 for WT virus. No dose adjustment required for coadministration in integrase-naïve patients. [25]	In a crossover study, healthy volunteers were randomized to receive either elvitegravir 200 mg/ritonavir 100 mg QD, tipranavir 500 mg/ritonavir 200 mg BID, or elvitegravir 200 mg QD plus tipranavir 500 mg/ritonavir 200 mg BID, each for 14 days. Treatment was well tolerated, and there were no clinically relevant effects on PK parameters for either drug suggesting that this combination can be co-administered without dose adjustment.[18]	In an open-label, 3 period study in 15 healthy subjects, addition of 400 mg raltegravir BID to steady-state TPV 500/rtv 200 mg BID for 4 days led to a 55% ↓ in raltegravir Cmin, while AUC ↓ 24% and Cmax ↓ 18%. The combination was generally well tolerated.[47] Although this result is borderline for clinical significance for C12 hr, there are considerable safety and efficacy data available for the concomitant use of tipranavir and raltegravir from the Phase III studies, which support the efficacy of this combination. There was no clinically meaningful difference in the efficacy profile of raltegravir with or without coadministration of tipranavir. Based on these data, tipranavir may be coadministered with raltegravir without dose adjustment. In an open-label study of 7 treatment-experienced patients initiating salvage therapy, optimized background therapy (OBT) and raltegravir 400 mg BID were initiated, with tipranavir 500/ritonavir 200 mg BID added on 4 days later; intensive 12-hour PK was performed at days 4 and 19. In the presence of steady-state tipranavir/ritonavir, raltegravir AUC ↓ 28%, Cmax ↑ 5% and C12 ↑ 7% compared to raltegravir without TPV/r. At week 24,

	Dolutegravir (S/GSK 1349572)	Elvitegravir (GS-9137), Stribild®	Raltegravir (MK-0518), Isentress®
			viral load was <50 in all patients (n=6) who completed the study; 1 patient discontinued at week 3 due to GI intolerance. Two subjects developed grade 3 transaminase elevations which resolved (1 spontaneously, one upon dose reduction to tipranavir 500/100 mg BID).[48]
2) OTHER AGENTS			
Acid-reducing agents	Healthy volunteers received four single-dose treatments: dolutegravir (DTG) 50 mg alone, DTG 50 mg with a **multivitamin** (One a Day Maximum), DTG 50 mg with a liquid **antacid** (Maalox Advanced Maximum Strength), and DTG 50 mg 2 hours before an antacid. Dolutegravir AUC was ↓ by 33% when coadministered with a multivitamin. Dolutegravir AUC was ↓ 74% with simultaneous antacid administration, and ↓ 26% with staggered antacid administration.[49] In an open-label study, healthy subjects received a single fasted dose of dolutegravir 50 mg, followed by **omeprazole 40 mg** once daily fasted for 5 days and a second single fasted dose of dolutegravir 50mg administered 2 hours following omeprazole on day 5. The combination was well tolerated. Omeprazole co-administration had no significant effect on dolutegravir exposure. Increased gastric pH by omeprazole had no effect on dolutegravir absorption; therefore, dolutegravir may be co-administered with PPIs or	In a study of healthy volunteers, subjects received elvitegravir 50 mg/ritonavir 100 mg alone or with **antacid** (administered simultaneously or 2-4 before) or omeprazole 40 mg (given simultaneously). Simultaneous administration with antacid led to 45% ↓ AUC, 47% ↓ Cmax and 41% ↓ Cmin of elvitegravir. Separating antacid administration by 2 hours decreased elvitegravir exposure by 10-20%, while separating antacid administration by 4 hours did not affect elvitegravir exposure. Simultaneous administration of **omeprazole** did not affect elvitegravir exposure, while omeprazole concentrations were consistent with historical controls.[50] **Elvitegravir/ritonavir should be separated by at least 2 (preferably 4) hours from antacids or vitamin or mineral supplements containing calcium, zinc or iron.[50]** In healthy subjects, the effects of omeprazole 20 mg QD or famotidine 40 mg QD were studied on the kinetics of elvitegravir/cobicistat. The	In a prospective crossover study, healthy volunteers received single-dose raltegravir 400 mg with and without an **antacid** (Maalox Plus® Extra Strength). In the presence of an antacid, raltegravir AUC0-12 was unchanged, but Tmax occurred sooner and C12 was reduced by 65% (p<0.0001)' and 75% of subjects had C12<15 ng/mL (RAL IC95). The clinical relevance of this interaction is unclear. Further studies are needed to determine if this interaction remains after multiple dosing to steady state, and if it is mitigated by temporal separation.[52] In healthy subjects who received **omeprazole 20 mg daily** for 4 days followed by a single dose of raltegravir 400 mg two hours after omeprazole on day 5, raltegravir AUC ↑ 3-fold, Cmax ↑ 4-fold and Cmin ↑ 46% in the presence of omeprazole. Raltegravir T_{max} and $t_{½}$ were not significantly affected. The mechanism is likely a consequence of increased bioavailability as raltegravir solubility is higher at higher gastric pH levels.[53]

	Dolutegravir (S/GSK 1349572)	Elvitegravir (GS-9137), Stribild®	Raltegravir (MK-0518), Isentress®
	H2-antagonists without dose adjustment.[49] **Dolutegravir can be taken with proton pump inhibitors, H2-antagonists and multivitamins without dose adjustment but should be administered 2 hours before or 6 hours after antacids.**	exposures of EVG/cobi were not significantly altered when omeprazole was administered 2 hours before or 12 hours apart, or when famotidine was administered simultaneously or 12 hours apart.[51] **Elvitegravir/ritonavir and elvitegravir/cobicistat may be given with proton pump inhibitors and H2-blockers without dosage adjustment.**	HIV-positive subjects stable on raltegravir 400 mg BID received single dose **famotidine 20 mg or omeprazole 20 mg once daily** for 5 days (each given 2 hours prior to raltegravir). Coadministration of famotidine resulted in 45% ↑ AUC, 60% ↑ Cmax and 6% ↑ Ctrough of raltegravir. In the presence of omeprazole, raltegravir AUC, Cmax and Ctrough were increased by 39%, 51% and 24%, respectively. These increases are not likely clinically significant, and raltegravir may be coadministered with famotidine or omeprazole without dose adjustment.[54]
Buprenorphine/ naloxone		potential ↑ buprenorphine concentrations	In 12 HIV-negative subjects stabilized on at least 3 weeks of buprenorphine/naloxone therapy, administration of **raltegravir 400 mg BID** did not significantly affect AUC and Cmax of buprenorphine and norbuprenorphine compared to baseline values, while Tmax of both buprenorphine and norbuprenorphine increased significantly. Naloxone AUC and Cmax concentrations were also unchanged in the presence of steady-state raltegravir, and objective opioid withdrawal was not observed. The AUC0-24h and Cmin of RAL did not significantly differ from historical controls (5553 vs. 4428 hr*ng/mL) and (1070 vs. 1266 ng/mL). As such, buprenorphine/naloxone and raltegravir can be safely co-administered without dosage modification.[55]
Colchicine		Potential ↑ colchicine concentrations. Do not coadminister in patients with	

	Dolutegravir (S/GSK 1349572)	Elvitegravir (GS-9137), Stribild®	Raltegravir (MK-0518), Isentress®
		renal or hepatic impairment. Refer to monograph for specific dosing recommendations.[56]	
Digoxin		Administration of digoxin 0.5 mg single dose with cobicistat 150 mg once daily resulted in 41% ↑ Cmax and 8% ↑ AUC of digoxin. Use combination with caution, monitor digoxin drug concentrations.[56]	No interaction anticipated.
Glucocorticoids		**Systemic dexamethasone** may ↓ elvitegravir and cobicistat concentrations.[56] Avoid coadministration if possible. Potential for ↑ fluticasone concentrations; consider alternative corticosteroid[56] such as beclomethasone.	Drugs may be coadministered. No Raltegravir dose modification is required.[2]
HmgCoA reductase inhibitors (statins): atorvastatin lovastatin pravastatin rosuvastatin simvastatin		<u>Using cobicistat as a booster</u>: Fixed sequence, crossover study in healthy subjects of EVG 150/co 150 mg daily alone or with single dose **rosuvastatin 10 mg**. With coadministration: • Kinetics of EVG were unaffected • 89% ↑ Cmax, 38% ↑ AUC of rosuvastatin Dose adjustment likely not necessary.[7] Potential for ↑ **atorvastatin** concentrations; initiate with lowest starting dose of atorvastatin and titrate to response.[56] **Stribild® is contraindicated with lovastatin and simvastatin.[56]**	In healthy adults who received **pravastatin 40 mg QD** plus raltegravir 400 mg BID for 4 days, pravastatin exposures were not significantly affected in the presence of raltegravir. Raltegravir AUC ↑ 13%, Cmax ↑ 31% and C12 ↓ 41% when coadministered with pravastatin; however, since raltegravir efficacy is better correlated with AUC, this interaction is not likely to be clinically significant, and no dose adjustments are required.[57]
Ketoconazole		In a healthy volunteer study, subjects received elvitegravir 150/ritonavir 100 mg daily alone and then with ketoconazole 200 mg BID, each for 10 days, followed by 4 more days of ketoconazole 200 mg BID alone. In the	The effect of ketoconazole 200 mg BID on the kinetics of single-dose raltegravir 400 mg was studied in 12 healthy volunteers. Coadministration resulted in 94% ↑ AUC, 75% ↑ Cmax and 3.35-fold ↑ C12 of raltegravir.[43]

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		presence of ketoconazole, modest increases in elvitegravir exposures were observed: 17% ↑ Cmax, 48% ↑ AUC, 67% ↑Cmin. A maximum ketoconazole dose of 200 mg once daily is recommended when coadministering with boosted elvitegravir.[58]	
Lamotrigine			In healthy subjects, raltegravir 400 mg BID for five days did not affect the pharmacokinetics of single dose lamotrigine 100 mg. The mean ratio of the AUC of lamotrigine-2N-glucuronide to lamotrigine was similar when lamotrigine was taken alone (0.35) or when taken with raltegravir (0.36). Raltegravir does not influence the glucuronidation of lamotrigine.[59]
Methadone	No effect in vivo on pharmacokinetics of methadone.[1]	Combination not studied; potential for ↑ methadone concentrations. Monitor for effect and adjust methadone dose as needed.	No dose adjustment is required for methadone when co-administered with raltegravir.[60]
Midazolam	No effect in vivo on pharmacokinetics of midazolam.[1]	**Oral midazolam is contraindicated.** Parenteral midazolam: potential for ↑ midazolam concentrations. Coadministration should be done in a setting that ensures close clinical monitoring and appropriate medical management in case of respiratory depression and/or prolonged sedation. Dosage reduction for midazolam should be considered, especially if more than a single dose of midazolam is administered.[56]	In healthy volunteers, coadministration of raltegravir 400 mg BID with single dose midazolam 2 mg did not affect midazolam kinetics, confirming the lack of CYP3A4 inhibition/inducing activity of raltegravir.
Oral contraceptives		In healthy female subjects on OrthTri-Cyclen Lo® (norgestimate-NGM/ethinyl estradiol-EE 25 ug) for at least 2 months, the fixed dose	Coadministration of Ortho Tri-Cyclen™ (or generic equivalent) plus raltegravir 400 mg BID in healthy female subjects for 21 days did not

	Dolutegravir (S/GSK 1349572)	Elvitegravir (GS-9137), Stribild®	Raltegravir (MK-0518), Isentress®
		tablet of elvitegravir/cobicistat/ FTC/tenofovir was co-administered daily on days 12-21 of the second cycle. When coadministered with Stribild®, there was a 25% ↓ EE AUC and a 2-fold ↑ AUC and Cmax of NGM-active metabolite relative to NGM/EE administered alone. Elvitegravir and cobicistat concentrations were similar to historical controls. Compared to baseline, there was no change in progesterone levels, a similar ↓ in FSH and a larger ↓ in LH during treatment with the Quad + NGM/EE vs. NGM/EE alone. The investigators recommend that an oral contraceptive containing at least 30 ug of EE be used when taking Stribild®.[61] Consider risks and benefits of coadministering nergestimate/ ethinyl estradiol. Consider alternative (non-hormonal) methods of contraception.[56]	substantially alter plasma exposure levels of either ethinyl estradiol or norelgestromin. It is unlikely for an alteration in the efficacy of Ortho Tri-Cycle™ for contraception to occur upon coadministration with raltegravir.[62]
Phosphodiester-ase 5 (PDE5) inhibitors Sildenafil Tadalafil Vardenafil		For treatment of pulmonary arterial hypertension:[56] • sildenafil: contraindicated • tadalafil: if already on Stribild®, start tadalafil 20 mg daily, ↑ to 40 mg daily based on tolerability. If on tadalafil and starting Stribild®, stop tadalafil at least 24 hours prior; after at least 1 week, resume tadalafil at 20 mg daily, ↑ to 40 mg daily based on tolerability. For erectile dysfunction:[56] • sildenafil: 25 mg every 48 hours • vardenafil: 2.5 mg every 72 hours • tadalafil: 10 mg every 72 hours	No interaction anticipated.

	Dolutegravir (S/GSK 1349572)	Elvitegravir (GS-9137), Stribild®	Raltegravir (MK-0518), Isentress®
Phenobarbital		Potential for significant ↓ in elvitegravir and cobicistat concentrations. Consider alternate anticonvulsants.[56]	The impact on UGT1A1 is unknown. Use with caution.[2]
Phenytoin		Potential for significant ↓ in elvitegravir and cobicistat concentrations. Consider alternate anticonvulsants.[56]	The impact on UGT1A1 is unknown. Use with caution.[2]
Pioglitazone			Drugs may be coadministered. No Raltegravir dose modification is required.[2]
Ribavirin			In a retrospective analysis of 12 HIV/HCV co-infected subjects on RAL 400 mg BID prior to initiating ribavirin/pegylated interferon therapy, median RAL Ctrough was 0.071 mg/L at baseline and 0.051 mg/L when coadministered with ribavirin/peg IFN (p=0.98). Viral load remained undetectable and early HCV virologic response occurred in 8 patients. The combination was well tolerated, and no patient experienced major hepatic toxicity.[63] In 14 healthy subjects who received raltegravir 400 mg BID for 5 days plus single dose ribavirin 800 mg, raltegravir pharmacokinetics were not significantly affected by ribavirin. Ribavirin Cmax ↓ 21% and Tmax ↑ 39%, while Cmin and AUC were unchanged in the presence of raltegravir. This is unlikely to be of clinical significance or have an impact on the antiviral effects of ribavirin in HIV-1 and HCV co-infected subjects.[64]
Rifabutin	In healthy volunteers, coadministration of dolutegravir 50 mg QD alone or with rifabutin 300 mg QD for 14 days resulted in 5% ↓ AUC, 15% ↑ Cmax and 30%	<u>Using ritonavir as a booster:</u> Randomized, sequential, crossover study in HIV negative healthy volunteers: • Treatment A: EVG/r 300mg/100mg daily	In healthy adults who received raltegravir 400 mg BID with or without rifabutin 300 mg daily, coadministration of rifabutin resulted in 20% ↓ Cmin, 19% ↑ AUC and 39% ↑ Cmax of

	Dolutegravir (S/GSK 1349572)	Elvitegravir (GS-9137), Stribild®	Raltegravir (MK-0518), Isentress®
	↓ Ctau of dolutegravir. This change is unlikely to be clinically significant effect in integrase-naïve patients.[65]	(n=19) • Treatment B: EVG/r 300mg/100mg +/- rifabutin 150mg every other day (n=19) • Treatment C: Rifabutin 300mg daily (n=18) EVG/r + RFB (150mg every other day): equivalent EVG AUC and RFB AUC relative to EVG/r or RFB (300mg daily) PK alone. Total antimycobacterial AUC ↑ 50% during coadministration. This is consistent with data from drug interaction studies with other RTV boosted agents.[66] **Decrease rifabutin to 150mg every other day or 150mg three times weekly when administered with EVG/r.** <u>Using cobicistat as a booster</u>: Fixed sequence, crossover study in healthy subjects of EVG 150/co 150 mg daily alone, then with **rifabutin 150 mg q2d**, followed by rifabutin 300 mg QD after a 10-day washout. With coadministration of EVG 150/co150 mg and rifabutin 150 mg q2d: • 67% ↓ Ctrough of EVG • Rifabutin exposures comparable to rifabutin 300 mg QD alone • 4.8-6.3-fold ↑ exposures of 25-desacetyl-RFB, resulting in 21% higher total antimycobacterial activity. **Coadministration of EVG/co with rifabutin is not recommended**.[7, 56]	raltegravir; these changes are not considered to be clinically significant, and rifabutin may be coadministered with raltegravir without dose adjustment.[2, 67]
Rifampin	In open-label, three-period, fixed-sequence, single center pharmacokinetic (PK) drug interaction study, healthy volunteers received dolutegravir 50 mg once daily for 7 days (period 1), then	**Combination is contraindicated.**[56]	In healthy subjects, single dose raltegravir 400 mg in the presence of rifampin 600 mg daily led to 61% ↓ Ctrough, 40% ↓ AUC and 38% ↓ Cmax of raltegravir. When raltegravir 800 mg BID was

	Dolutegravir (S/GSK 1349572)	Elvitegravir (GS-9137), Stribild®	Raltegravir (MK-0518), Isentress®
	DTG 50 mg twice daily for 7 days (period 2), then DTG 50 mg twice daily together with rifampin 600 mg once daily (period 3) for 14 days. Dolutegravir 50 mg BID plus rifampin achieved mean AUC 33% ↑ and Ctau 22% ↑ versus DTG 50 mg daily alone. There were no discontinuations for adverse events (AEs) and no Grade 3 or higher AEs.[68]		coadministered with rifampin 600 mg daily for 14 days, raltegravir C12 was ↓ 53%, AUC ↑ 27% and Cmax ↑ 62% in the presence of rifampin.[69] **Product monograph recommends increasing raltegravir dose to 800 mg twice daily during coadministration with rifampin.**[2] The effect of rifampin 600 mg QD on the kinetics of single-dose raltegravir 400 mg was studied in 12 healthy volunteers. Coadministration resulted in 55% ↓ C12, 40% ↓ AUC and 25% ↓ Cmax of raltegravir.[43] Administration of raltegravir 800 mg BID in two HIV-positive subjects receiving rifampin 600 mg QD for treatment of active tuberculosis resulted in raltegravir kinetic parameters comparable to historical data in HIV-positive subjects taking raltegravir 400 mg BID without rifampin. In the two cases, raltegravir was well tolerated.[70]
Rifapentine		Potential for significant ↓ elvitegravir and cobicistat concentrations. Coadministration is not recommended.[56]	In a 3-period study in healthy volunteers, raltegravir 400 mg BID was administered alone or with rifapentine 900 mg taken once weekly or 600 mg daily (5 of 7 days/week). Once-weekly rifapentine co-administration resulted in a 73% ↑ AUC, 89% ↑ Cmax and 44% ↓ Cmin of raltegravir. Daily rifapentine coadministration did not change mean AUC or Cmax of raltegravir, but the C_{min} ↓ 43%. Inter-patient variability was high. Rifapentine demonstrated less inductive effect on RAL concentrations

	Dolutegravir (S/GSK 1349572)	Elvitegravir (GS-9137), Stribild®	Raltegravir (MK-0518), Isentress®
			than reported for rifampin.[71]
Sirolimus			Raltegravir may avoid interactions with certain immunosuppressives as it is primarily metabolized via glucuronidation and not by CYP3A4. Case report of the successful use of raltegravir/3TC/abacavir and sirolimus in a 49 year old HIV/HCV+ patient who underwent liver transplantation. The patient was switched to this regimen after a series of medication modifications. Patient had developed renal insufficiency with hyperpotasemia and metabolic acidosis due to increased tacrolimus levels (> 25 ng/ml) related to atazanavir use.[72]
St Johns Wort		**Combination is contraindicated.[56]**	Drugs may be coadministered. No Raltegravir dose modification is required.[2]
Telaprevir			In an open-label cross-over study in 20 HIV/HCV-negative healthy volunteers, co-administration of raltegravir 400 mg BID and telaprevir 750 mg q8h for 6 days with food did not affect telaprevir pharmacokinetics, while raltegravir exposures were increased (Cmin ↑ 78%, Cmax ↑ 26% and AUC ↑ 31%) possibly due to inhibition of intestinal P-gp by telaprevir. Exposure to raltegravir-glucuronide was similarly increased. This effect was not considered to be clinically relevant.[73]
Warfarin		Potential for warfarin concentrations to be affected. Monitor INR and adjust warfarin dose accordingly.[56]	No interaction anticipated.

Please note: This chart summarizes some of the major drug interactions identified to date, based on current available data; other drug interactions may exist. Please use caution whenever adding/modifying therapy. The information in this table is intended for use by experienced physicians and pharmacists. It is not intended to replace sound professional judgment in individual situations, and should be used in conjunction with other reliable sources of information. Due to the rapidly changing nature of information about HIV treatment and therapies, users are advised to recheck the information contained herein with the original source before applying it to patient care.

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Drug Interactions with Non-Nucleoside Reverse Transcriptase Inhibitors

	Delavirdine (Rescriptor®)	Efavirenz (Sustiva®)	Etravirine (Intelence®)	Nevirapine (Viramune®)	Rilpivirine (Edurant®)
Usual Dose	400 mg po TID; 600 mg BID under study	600 mg po daily at bedtime.	200 mg BID following a meal	200 mg po BID (lead-in dosing of 200 mg daily for first 14 days)	25 mg QD following a meal
Kinetic Characteristics	pH-dependent oral absorption; highly protein bound; metabolized via CYP3A4; also inhibits 3A4, as well as 2C9, 2C19.[1]	In vitro is a potent inducer and inhibitor of CYP3A4. Efavirenz induces 2B6[2] and UGT1A1.[3] Also inhibits CYP2C9, 2C19. Substrates of CYP3A4 should be monitored carefully for effect and toxicity when used in combination with efavirenz.[3]	Etravirine is a substrate of CYP3A4, CYP2C9, and CYP2C19. Etravirine is a weak inducer of CYP3A4, weak inhibitor of CYP2C9 and a moderate inhibitor of CYP2C19. Etravirine also inhibits p-glycoprotein. Etravirine has no clinically relevant effect on CYP1A2 or CYP2D6.[4, 5]	Substrate and potent inducer of CYP3A4 and 2B6 enzymes.[2]	Metabolized primarily by CYP3A4, as well as CYP2C19, 1A2, 2C8/9/10 (minor). Moderate inducer of CYP2C19, slight inducer of CYP1A2, 2B6 and 3A4. A clinically relevant effect on CYP enzyme activity is considered unlikely with 25 mg dose.[6, 7] No effect on CYP2E1 activity.[8]
Food	May take with or without a meal (based on steady state studies).[1]	May be administered with or without food.[3]	The effect of different types of food on the bioavailability of single dose etravirine 100 mg was examined in 24 healthy volunteers. **Fasted State:** etravirine AUC ↓ 51% compared to a standard breakfast. **Light Breakfast** (Croissant): AUC ↓ 20% compared to a standard breakfast. **Enhanced Fiber Breakfast:** AUC ↓ 25% compared to a standard breakfast. **High Fat Breakfast (70g):** AUC ↑ 9% compared to a standard breakfast. Recommendations: Give etravirine following a meal; the type of meal is not important.[9]	May be administered with or without food or antacids.[2]	The effect of different types of food on the bioavailability of single dose rilpivirine 75 mg tablet was examined in 20 healthy subjects. **Fasting conditions:** rilpivirine Cmax ↓ 46%, AUC ↓ 43% compared to standard breakfast (21 g fat, 533 kcal). **Protein rich nutritional drink (8 g fat, 300 kcal):** similar exposures to fasting conditions (Cmax & AUC ↓ 50% compared to standard breakfast). **High Fat Breakfast (56 g fat, 928 kcal):** rilpivirine Cmax ↓ 8%, AUC ↓ 8% compared to standard breakfast. **Recommendations**: Give rilpivirine with food (standard or high fat meal). Do not give rilpivirine on an empty stomach or with a protein rich nutritional drink.[10]

	Delavirdine (Rescriptor®)	Efavirenz (Sustiva®)	Etravirine (Intelence®)	Nevirapine (Viramune®)	Rilpivirine (Edurant®)
Cranberry juice		Prospective, observational, cross-sectional study in HIV-positive patients (n=120) on ARVs for at least 12 weeks, and reporting current cranberry juice intake (median 237 mL once-twice daily for median 4.5 years) or no cranberry juice intake. No significant difference in efavirenz levels in patients on efavirenz +/- cranberry juice. EFV Cmin: EFV alone group: 2099 ng/ml, n=3; EFV + Cranberry juice group: 3948ng/ml, n=3[11]			
INTERACTIONS WITH ANTIRETROVIRALS:					
Amprenavir (see separate entry for Fosamprenavir)	Amprenavir 1200 mg +/- delavirdine 600 mg BID (healthy volunteer study) significantly increased amprenavir concentrations (4-fold ↑ AUC, 6-fold ↑ Cmin, 1.3 fold ↑ Cmax); no change in delavirdine concentrations.[1] In a separate healthy volunteer multi-dose study, administration of APV 600 mg BID +/- DLV 600 mg BID resulted in ↑ APV Cmin 133% & AUC 117%; however, median DLV Cmin ↓ 88%. Suggest avoiding this dosage combination until further data available.[12]	**APV 1200 mg BID + EFV 600** mg: 36% ↓ AUC, 39% ↓ Cmax, 43% ↓ Cmin APV; 15% ↑ EFV AUC[13]. Avoid negative interaction by adding either: • 200/500 mg RTV BID, or • 1250 mg nelfinavir BID to APV 1200 mg BID plus EFV 600 mg qhs.[14] Other dosage combinations that yielded stable APV conc.: • **APV 600 mg/ rtv 200 mg BID** + EFV[15] • **APV 1200 mg/ rtv 300 mg QD** plus EFV[16] • APV/EFV + **NFV 1250 mg BID**[17] • APV/EFV **+ IDV 1200 mg BID**[17] • APV/EFV + **RTV**		With **APV 600/RTV 100 mg BID/NVP 400 mg QD**, APV Cmin and Cmax ↓ 80%, AUC ↓ 77%. APV plasma levels stable with **APV 450/RTV 200 mg BID plus NVP 400 mg daily.**[18] Therefore, recommend APV 450/RTV 200 mg BID with NNRTIs.	

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		100 mg BID[17]			
Atazanavir (ATV) Take with a light meal for improved absorption.		Study in healthy subjects of **ATV 400 QD** +/- efavirenz 600 mg QD with a light meal (n=27): ATV Cmax ↓ 59% and AUC ↓74% with concomitant EFV; EFV kinetics not significantly altered.[19] In a healthy volunteer study, coadministration of **atazanavir 300/ritonavir 100 mg QD** plus efavirenz x 2 weeks resulted in 39% ↑ atazanavir AUC vs. atazanavir 400 mg QD alone, while ATV 600 mg QD plus efavirenz resulted in 21% ↓ ATV AUC vs. ATV 400 mg QD alone.[20] In healthy subjects, **ATV 400/ ritonavir 100 mg QD** plus EFV results in ATV AUC and Cmax comparable to ATV/r 300/100 alone, but ATV Cmin ↓ 42%. **ATV Cmin may not be optimal for treatment experienced patients.** RTV Cmax ↓ 15%, AUC ↓ 31%, Cmin ↓ 60% with combination, which may have contributed to lower ATV exposures.[21]	In healthy subjects (n=14), **ATV 400 mg QD** administered with etravirine 800 mg BID (old formulation) for 7 days resulted in 47% ↑ Cmax , 50% ↑ AUC and 58% ↑ Cmin of TMC125, while atazanavir AUC ↓ 17% and Cmin ↓ 47%.[22] Combination of unboosted atazanavir and etravirine is not recommended.[4] In healthy subjects, **ATV 300/rtv 100 mg QD** plus TMC125 800 mg BID (old formulation) led to 100% ↑ AUC and 26% ↑ Cmin of etravirine, while atazanavir AUC ↓ 14% and Cmin ↓ 38%.[22] HIV-infected subjects on stable ATV 300/100 mg QD regimens (not including tenofovir) were randomized to receive either ATV 300/100 mg QD or 400/100 mg QD with etravirine 200 mg BID. In the presence of etravirine, ATV 300/100 mg dosing led to 4% ↓ AUC and 18% ↓ Cmin of atazanavir, and 1.24-fold ↑ etravirine AUC*. In ATV 400/100 mg group, there was no change in AUC and 9% ↓ Cmin of atazanavir while etravirine AUC* was ↓ 16% with coadministration.	In an open-label cohort study of HIV+ subjects stable on 2-3 NRTIs and either NVP 200 mg BID or ATV 300/rtv 100 mg QD, the NVP group received NVP plus ATV 300/100 mg QD for 10 days, then NVP plus ATV 400/100 mg QD for 10 days. Compared to the group that continued ATV 300/100 mg QD alone (mean ATV Cmin 533 ng/mL): • **NVP plus ATV/r 300/100mg** daily led to ↓ Cmax 38%, ↓ AUC 42%, ↓ Cmin 72% of ATV (mean Cmin 150 ng/mL). • **NVP plus ATV/r 400/100mg** daily led to 19% ↓ AUC and 59% ↓ Cmin of ATV (mean Cmin 216 ng/mL). These ATV values were higher than historical ATV 400 mg QD alone. RTV AUC ↓ 40% in presence of NVP, which may have contributed to ↓ ATV levels, while ATV/r increased NVP AUC by 25%.[24] Open label, multiple dose study in HIV infected patients (n=11) to study the kinetics of **ATV/r 300mg/100mg** +/- NVP 200mg BID.	Potential for ↑ concentrations of rilpivirine. Rilpivirine is not expected to affect the plasma concentrations of co-administered PIs.[7]

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			These changes were smaller than interaction observed previously in healthy volunteers.[23] *NB: etravirine concentrations were compared to historical data from the DUET studies where etravirine was administered with darunavir/r BID. Coadministration is contraindicated in the US & Canadian Monographs,[4] but the European SPC says they can be coadministered without dose adjustment.	Combination led to: • ↓ ATV levels: ↓ Ctrough 41% (631 vs 316ng/ml); ATV Ctrough remained higher than historical controls taking ATV 400mg daily • ↑ NVP Ctrough12 (GMR 1.46) compared to historical controls not taking ATV/r. Monitoring ATV Cmin is recommended, and a dose increase in ATV may be necessary.[25]	
Darunavir		Multidose study of efavirenz 600 mg QD plus **darunavir (oral solution) 300 mg/ritonavir 100 mg BID** led to 31% ↓ Cmin and 13% ↓ AUC of darunavir, while EFV exposure ↑ 20%. Combination may be used without dose adjustments.[26] In a single sequence, 3-period PK study in healthy volunteers who received **DRV 900/r100 mg QD** x 10d, DRV/r + EFV 600 mg QD x 14d, then EFV x 14 d): • 57% ↓ Cmin, 14% ↓ AUC of darunavir • Mean 1138 vs. 2127 ng/mL, p=0.0003; all Cmin>55 ng/mL • No difference in EFV PK Clinical significance in HIV-positive patients not yet determined, combination may	Pharmacokinetic interaction study of **etravirine 200 mg BID added to darunavir 600/100 mg BID** in HIV-infected subjects (n=10) led to ~30% ↓ AUC of etravirine compared to historical controls, not considered clinically significant. Kinetics of darunavir were unchanged.[28] Similar interaction observed in healthy subjects.[29] A pharmacokinetic substudy was conducted in 10 HIV-positive subjects participating in the **ANRS TRIO** study. Patients received raltegravir 400 mg BID and darunavir 600/100 mg BID on day 1, and etravirine 200 mg BID was added on day 7. PK parameters were measured on days	In an open-label, randomized, crossover study, 19 HIV-positive subjects received nevirapine 200 mg BID plus NRTIs with or without darunavir (either 300/100 mg BID DRV oral solution or 400/100 mg BID DRV tablet) in two 14-day sessions. In the presence of DRV/r, NVP AUC ↑ 27%, while DRV and RTV exposures were similar to historical data.[32] In a population cohort analysis of 51 HIV-infected patients taking nevirapine (n=42 with other NRTIs, n=9 on concomitant darunavir/ritonavir), nevirapine Ctrough were 45% higher in the group taking darunavir/ritonavir vs. those on NRTIs only (p<0.05).[33] **No dose adjustment** is	In a randomized, crossover study in healthy volunteers, subjects received either rilpivirine 150mg daily for 22 days, or darunavir 800/100mg QD for 11 days followed by DRV 800/100mg QD plus rilpivirine 150mg QD from days 12-22. Co-administration of DRV/r increased exposures of rilpivirine: AUC24h ↑ 2.3 fold; Cmax ↑ 1.79 fold, Cmin ↑ 2.78 fold, likely a result of CYP3A4 inhibition. No clinically relevant changes in DRV exposure were observed in the presence of rilpivirine.[35] No dose adjustment is required with coadministration.[7]

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		provide sufficient efficacy in naïve-patients with no pre-existing mutations.[27]	6 and 28. Raltegravir and darunavir PK (Cmax, Cmin and AUC) were not significantly different in the presence of etravirine.[30] In a phase II single arm study, ARV-naïve HIV-infected subjects received **etravirine 400 mg QD, darunavir 800/100 mg QD**, or the combination (plus tenofovir/FTC) each for 14 days. There was no change in ETV pk in the presence of DRV/r. Mean ETV Cmin was >50x higher than protein-adjusted EC50 for WT virus, with and without DRV/r. DRV pk was slightly higher and RTV was slightly lower vs. historical controls (ARTEMIS week 4 pk substudy).[31] Combination may be coadministered without dose adjustment.[4]	currently recommended, but literature indicates that changes in plasma NVP levels can lead to significant toxicity concerns, including hepatotoxicity. Monitor closely for dose-related nevirapine toxicity.[34]	
Darunavir/rtv + maraviroc			Co-administration of **etravirine/darunavir/ritonavir** with maraviroc increased the exposure of maraviroc by 210% (AUC_{12}) and peak levels (C_{max}) by 77% compared to maraviroc alone. Thus, if maraviroc is being dosed alongside etravirine and darunavir together, a maraviroc dose reduction to 150mg twice daily is necessary. No dose adjustment of		

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			ETV is necessary.		
Didanosine	37% ↓ DLV Cmax, 22% ↓ ddI concentration; thus, administer 1 hour before ddI if possible.[6]	No effect on EFV concentrations when administered with 30 mL Mylanta DS (AlOH, MgOH, simethicone);[7] therefore, ddI buffer should not affect EFV concentrations.	In a crossover study of healthy volunteers, no clinically relevant interaction was observed between etravirine 800 mg BID with food and ddI-EC 400 mg QD (given 2 hours before etravirine on an empty stomach). No dosage adjustments required for combination.[36]	May be administered together.[2]	No dose adjustment is required. However, didanosine should be administered on an empty stomach at least 2 hours before or 4 hours after rilpivirine, which should be administered after a meal.[7]
Dolutegravir (DTG; S/GSK1349572 , integrase inhibitor)		In an open-label, single sequence crossover study, healthy volunteers received dolutegravir 50 mg once daily for 5 days followed by DTG 50 mg and efavirenz 600 mg QD for 14 days. In the presence of efavirenz, DTG AUC ↓ 57%, Cmax ↓ 39% and Ctrough ↓ 75%, likely via enzyme induction of UGT1A1 and CYP3A4. Dolutegravir concentrations remained 4-5 fold higher than the protein-adjusted IC90 for WT virus. No dose adjustment required for coadministration in integrase-naïve patients. [37]	In an open-label, two-period, crossover study, healthy adult subjects received dolutegravir 50 mg QD for 5 days, then added etravirine 200 mg BID with food for 14 days. In the presence of etravirine, dolutegravir AUC ↓ 70%, Cmax ↓ 52% and Ctrough ↓ 88%. In a second randomized, open-label crossover study, healthy subjects began with dolutegravir 50 mg QD for 5 days, then added etravirine 200 mg BID plus either lopinavir/ritonavir 400/100 mg BID or darunavir 600/100 mg BID for 14 days. Dolutegravir kinetics were not significantly altered when given with etravirine plus lopinavir/ritonavir. When coadministered with etravirine plus darunavir/ritonavir, dolutegravir AUC ↓ 25%, Cmax ↓ 12% and Ctrough ↓ 37%. These changes were considered		In an open-label, two-cohort, single sequence crossover study, healthy subjects, received either DTG 50mg daily for 5days or S/GSK1265744 30mg daily for 12 days (Period 1), rilpivirine 25 mg daily for 11-12 days (Period 2) and rilpivirine 25 mg daily plus DTG 50 mg daily or S/GSK1265744 30 mg daily for 12 days (Period 3); all doses were administered following a moderate fat meal. The combinations of RPV + DTG and RPV + S/GSK1265744 were well-tolerated and no significant changes in the PK parameters of any drug were observed.[39]

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			not clinically significant. Dolutegravir may be coadministered with etravirine without a dosage adjustment if lopinavir/ritonavir or darunavir/ritonavir is concurrently administered.[38]		
Efavirenz			Steady-state efavirenz 600 mg QD plus single-dose etravirine 900 mg resulted in 41% ↓ AUC and 18% ↓ Cmax of etravirine.[40] Etravirine and other NNRTIs should not be co-administered.[4] In a healthy volunteer study, etravirine was administered 400 mg QD or 200 mg BID for 14 days at baseline and then again after 14 days of efavirenz treatment to assess for any continued effects of efavirenz enzyme induction on etravirine metabolism. Steady-state ETV parameters were significantly reduced after EFV intake in both QD and BID dosing arms: ETV AUC ↓ 28-29%, Cmax ↓ 21-22%, Ctrough ↓ 33-37%. These changes are likely not clinically significant as all subjects had ETV levels well above 4 ng/mL (protein binding-adjusted EC50) and ETV concentrations are comparable to those observed in clinical trials where ETV was co-	Combination of nevirapine 400 mg daily plus efavirenz 600 mg daily in HIV-infected individuals resulted in reduced efavirenz concentrations (22% ↓ AUC, 36% ↓ Cmin); nevirapine levels were not changed. Thus, may need to administer higher doses of efavirenz (e.g., 800 mg daily) in conjunction with nevirapine.[42]	In HIV infected patients on steady state efavirenz, administration of a single dose of rilpivirine 75 mg resulted in 70% ↓ AUC and 30% ↓ Cmax of rilpivirine compared to rilpivirine alone (historical controls). Do not coadminister rilpivirine and efavirenz.[7] In healthy volunteers, subjects received rilpivirine 25 mg QD for 14 days (period A) followed by a 14-21 day washout, then efavirenz 600 mg QD for 14 days (period B), followed immediately by rilpivirine 25 mg QD for 28 days (period C). At days 1, 14 and 21 of period C, rilpvirine AUC and Cmax were lower than in period A: day 1 - AUC ↓ 46%, Cmax ↓ 36%, day 14 – AUC ↓ 18%. Cmax ↓ 19%, Cmin ↓ 28%, day 21 - AUC ↓ 16%. Cmax ↓ 13%, Cmin ↓ 28%. By day 28 of period C, rilpivirine AUC and Cmin were similar to period A, while Cmin ↓ 25%. Plasma EFV was undetectable by 7 days after period

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			administered with darunavir/ritonavir. Therefore, authors suggest that switching from EFV to ETV QD or BID may be done without dose adjustment.[41]		B.[43]
Elvitegravir		Three-period study in healthy subjects of EVG/COBI/ FTC/TDF (Quad) for 1 week followed by washout, efavirenz/FTC/TDF (Atripla®) for 2 weeks, then Quad for 5 weeks. Following the switch from Atripla® to the Quad, elvitegravir exposures were lower: • Day 35: AUC ↓ 37%, Cmax ↓ 19%, Ctau ↓ 67% • Day 42: AUC ↓ 29%, Cmax ↓ 11%, Ctau ↓ 54% Cobicistat Ctau was ↓ 35% at day 14 post-switch. AUC of EVG glucuronidated metabolite were ↑ 46% and ↑ 32% on days 35 and 42, respectively. Mean EVG Ctrough was ~3-fold and ~5-fold > than protein-adjusted IC95 of 45 ng/mL on days 35 and 42, respectively, and 7-8 fold ↑ at 5 weeks post switch.[44]		In healthy subjects, no clinically relevant PK changes were observed for elvitegravir/ritonavir 150/100mg daily and etravirine 200mg BID compared to either drug administered alone. These 2 antiretrovirals can be used together without dose adjustment.[45]	
Enfuvirtide			Use of enfuvirtide had no effect on etravirine AUC12h from population PK data from substudy in Duet trials.[46]		
Etravirine	Potential for increased etravirine concentrations. Combining two NNRTIs has not been shown to be	Steady-state efavirenz 600 mg QD plus single-dose etravirine 900 mg resulted in 41% ↓ AUC and 18% ↓		Steady-state nevirapine 200 mg BID plus single-dose etravirine 900 mg resulted in 55% ↓ AUC and 36% ↓	Rilpivirine should not be co-administered with other NNRTIs.[7]

	Delavirdine (Rescriptor®)	Efavirenz (Sustiva®)	Etravirine (Intelence®)	Nevirapine (Viramune®)	Rilpivirine (Edurant®)
	beneficial. Etravirine should not be coadministered with other NNRTIs.[4]	Cmax of etravirine.[40] Etravirine should not be coadministered with other NNRTIs.[4] In a healthy volunteer study, etravirine was administered 400 mg QD or 200 mg BID for 14 days at baseline and then again after 14 days of efavirenz treatment to assess for any continued effects of efavirenz enzyme induction on etravirine metabolism. Steady-state ETV parameters were significantly reduced after EFV intake in both QD and BID dosing arms: ETV AUC ↓ 28-29%, Cmax ↓ 21-22%, Ctrough ↓ 33-37%. These changes are likely not clinically significant as all subjects had ETV levels well above 4 ng/mL (protein binding-adjusted EC50) and ETV concentrations are comparable to those observed in clinical trials where ETV was co-administered with darunavir/ritonavir. Therefore, authors suggest that switching from EFV to ETV QD or BID may be done without dose adjustment.[41]		Cmax of etravirine.[40] Etravirine should not be coadministered with other NNRTIs.[4]	
Fosamprenavir		In healthy volunteer study, **FPV 700/rtv 100 mg BID plus EFV** did not change APV levels vs. FPV/rtv alone. However, with **FPV 1395/rtv 200 mg QD**, addition of EFV	In an open-label interaction trial of HIV-infected subjects on stable FPV 700/rtv 100 mg BID, addition of etravirine 800 mg BID for 14 days (phase II	In HIV+ subjects, **FPV 1400 mg BID + NVP** 200 mg BID for 14 days led to 33% ↓ AUC, 39% ↓ Cmin of APV, and 29% ↑ AUC and 34% ↑ Cmin of NVP.[49]	Potential for ↑ concentrations of rilpivirine. Rilpivirine is not expected to affect the plasma concentrations of co-administered PIs.[7]

	Delavirdine (Rescriptor®)	Efavirenz (Sustiva®)	Etravirine (Intelence®)	Nevirapine (Viramune®)	Rilpivirine (Edurant®)
		led to 13% ↓ AUC, 36% ↓ Cmin of APV. Negative interaction corrected when rtv dose ↑ to 300 mg QD.[47] **Therefore, when coadministering FPV/r and EFV: no change in FPV dose if BID regimen used; if QD, use FPV 1400 mg/rtv 300 mg QD.**	formulation) led to 69% ↑ AUC, 62% ↑ Cmax and 77% ↑ Cmin of amprenavir compared to FPV/rtv alone. Etravirine parameters were similar to historical controls.[48] Etravirine should not be co-administered with fosamprenavir/ritonavir.[4]	When **FPV 700/rtv 100 mg BID** administered with NVP for 14 days, APV AUC ↓ 11%, Cmin ↓19%, NVP AUC ↑14%, Cmin ↑ 21% vs. controls.[49] Recommend **FPV 700/rtv 100 mg BID with NVP 200 mg BID.**	
Indinavir	IDV 600 mg q8h + DLV: ↑ IDV AUC, Cmin vs. IDV 800 mg q8h alone.[50, 51] Thus, ↓ IDV to 600 mg q8h with delavirdine. Healthy volunteer study of IDV/DLV BID regimens: a) 800/600 mg BID: similar AUC, Cmax, but Cmin IDV ↓ 35-40% (vs. IDV 800 mg q8h) b) 1200/600 mg BID: similar Cmin, ↑ AUC (50-70%), ↑ Cmax (20-50%) Thus, 1200/600 mg BID may be preferable (NB: risk nephrolithiasis?); may take +/- food.[52]	**IDV alone:** 30-35% ↓ indinavir levels; no change in efavirenz levels. Increase IDV dosage to 1000 mg q8h.[53] **<u>Indinavir/rtv BID</u>** When efavirenz was added to IDV 800 mg/RTV 100 mg BID regimen, IDV exposure was significantly reduced (19% ↓ AUC, 48% ↓ Cmin). May wish to consider ↑ to indinavir 800 mg/ritonavir 200 mg BID.[54] **<u>indinavir/rtv QD:</u>** When efavirenz was added to IDV/RTV once daily regimens (800/100, 800/200, 1200/100), significant ↓ in IDV <u>and</u> RTV concentrations (esp. C24) were observed. Avoid using EFV with once daily IDV/RTV regimens.[55]	Steady-state study of etravirine 1600 mg BID plus indinavir 800 mg TID (n=10) resulted in 51% ↑ AUC and Cmax of etravirine, likely due to CYP3A inhibition; indinavir AUC ↓ 46%, Cmax ↓28%.[40] Etravirine should not be co-administered with PIs without low-dose ritonavir.[4]	28% ↓ IDV AUC, <10%↓ NVP AUC (non-significant). Suggest ↑ IDV dose to 1000 mg q8h when using with NVP 200 mg BID.[56] Preliminary data suggest that dosing nevirapine 400 mg once daily may have a more pronounced effect on decreasing indinavir concentrations compared to nevirapine dosed 200 mg twice daily (median 31% decrease). These findings require further substantiation; may consider monitoring indinavir levels/response if switching nevirapine dosage regimen.[57]	Potential for ↑ concentrations of rilpivirine. Rilpivirine is not expected to affect the plasma concentrations of co-administered PIs.[7]
Lopinavir/ ritonavir	In a healthy volunteer study (n=26), DLV 600 mg BID plus lopinavir 400/100 mg BID resulted in higher lopinavir levels (Cmin ↑ 53%, AUC ↑ 24%, Cmax 13%); however, DLV exposure was	**<u>With LPV/r capsules:</u>** • EFV 600 mg + LPV/r 400/100 mg BID resulted in 25% ↓ AUC and 44% ↓ Cmin of lopinavir. Using lopinavir	In healthy volunteers, coadministration of etravirine 200 mg BID and lopinavir/ritonavir tablets 400/100 mg BID for 8 days resulted in 45% ↓ Cmin, 30% ↓ Cmax and 35% ↓ AUC of	**<u>With LPV/r capsules:</u>** • Nevirapine ↓ lopinavir AUC and Cmin. Using lopinavir 533 mg/ritonavir 133 mg BID plus nevirapine will result in	In healthy volunteers, rilpivirine 150 mg QD plus LPV/r 400/100 mg BID soft gel capsules resulted in 52% ↑ AUC, 29% ↑ Cmax, 74% ↑ Cmin of rilpivirine; LPV kinetics not

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	↓25-30%. Further studies are ongoing to establish optimal doses of both agents.[58]	533 mg/ritonavir 133 mg BID plus EFV resulted in similar lopinavir concentrations to those achieved in the absence of EFV.[59] **With LPV/r tablets:** • Can use 400/100 mg BID with EFV in ARV-naïve subjects • ↑ to 600/150 mg (3 tablets) BID in treatment-experienced subjects; this significantly ↑ LPV concentrations ~35% and RTV concentrations ~56-92% versus LPV/r tablets 400/100 mg BID without EFV[60] • in 19 healthy volunteers, **LPV/r 500/125 mg BID** plus EFV 600 mg led to similar LPV levels as seen with LPV/r 400/100 mg BID alone (6% ↑ AUC, 10% ↓ Cmin)[61] • QD lopinavir/rtv in the presence of NNRTIs may not provide adequate lopinavir Ctrough[62]	ETV, and 20% ↓ Cmin, 11% ↓ Cmax and 13% ↓ AUC of LPV compared to each drug administered alone.[63] Because the ↓ in mean ETV exposures in the presence of LPVr is similar to the ↓ observed in the presence of darunavir/ ritonavir, ETV and LPVr may be co-administered without dose adjustment.[4] Etravirine 800 mg BID did not affect kinetics of **LPV 400/RTV 100/SQV 800-1000 mg BID** in 15 HIV-infected male subjects.[64]	similar lopinavir concentrations to those achieved in the absence of nevirapine.[65] **With LPV/r tablets:** • Can use 400/100 mg BID with NVP in ARV-naïve subjects • ↑ to 600/150 mg (3 tablets) BID when co-administering in treatment-experienced subjects	affected.[66] No dose adjustment is required with coadministration.[7]
Maraviroc		When maraviroc 100 mg BID was given with efavirenz 600 mg QD, maraviroc AUC ↓ 50%, Cmax ↓ 60%. Doubling maraviroc dose to 200 mg BID	Total maraviroc concentrations over a 12-hour period are reduced by 53% (AUC_{12}) and peak levels of maraviroc (C_{max}) by 60% in the presence of	In a cohort of HIV+ subjects (n=8) stabilized on nevirapine, 3TC and tenofovir, kinetics of single dose maraviroc 300 mg were	

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		corrected maraviroc exposures. When administering maraviroc with EFV (in the absence of PIs), doubling maraviroc dose is recommended.[67] An in vitro-in vivo extrapolation model was developed to describe the kinetics of maraviroc in HIV-infected patients switching from efavirenz-containing therapy. The model predicted that MVC exposures similar to those with MVC 300 mg BID alone could be achieved via two scenarios following a switch from EFV: • MVC 600 mg BID x 1 week followed by standard 300 mg BID dosing • MVC 450 mg BID x 2 weeks followed by standard BID dosing[68]	etravirine. Therefore, if a patient isn't also taking a potent CYP3A4 inhibitor such as RTV-boosted protease inhibitor, **maraviroc dose should be increased to 600mg twice daily**. No dose adjustment of etravirine is required. In 64 HIV-positive patients taking maraviroc 300 or 600 mg BID plus etravirine 200 mg BID without PIs, 67% Ctrough were <75 ng/mL (75% with maraviroc 300 mg BID and 63% with maraviroc 600 mg BID). Mean maraviroc Ctrough was 53 and 60 ng/mL in the 300 and 600 mg BID groups, respectively. Etravirine Ctrough was 723 ng/mL, approximately 180-fold higher than the protein-adjusted EC50 for wild type virus[69] In a cohort of patients receiving maraviroc and raltegravir with or without etravirine, significantly lower maraviroc Ctrough were observed when combined with etravirine vs. without etravirine (57 vs 173.5 ng/mL respectively, p=0.01). Patients treated with maraviroc had significantly greater CD4 increases versus those not on maraviroc.[70]	unchanged vs. control data in HIV+ subjects receiving maraviroc alone for 10 days.[71]	

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			See additional entry for **darunavir/ritonavir + etravirine plus maraviroc.**		
Nelfinavir	Interaction data in HIV subjects taking DLV 600 mg TID + standard NFV: approx. 2-fold ↑ NFV AUC, and DLV Cmin similar to that with DLV 400 mg TID alone. [72] Recommendations on dosage adjustments not available. Use together with caution and monitor for drug toxicities, incl. Neutropenia. Regimens currently being studied: NFV 750 mg TID + DLV 600 mg TID, and NFV 1250 mg BID + DLV 600 mg BID.	Healthy volunteer study: efavirenz 600 mg + nelfinavir 750 mg q8h x 7 days: 20% ↑ NFV levels, 37% ↓ M8 levels; no change in efavirenz levels.[73] However, subsequent kinetic study in HIV+ subjects of efavirenz 600 mg qhs and nelfinavir 1250 mg BID showed ↓ 65% nelfinavir Cmin (p=0.04), ↓ 38% AUC and ↓ 21% Cmax at 32 weeks.[74] Therefore, monitor for antiretroviral efficacy when using this combination. Nelfinavir dosage adjustment may be necessary, consider therapeutic drug monitoring where available.	Potential for increased nelfinavir concentrations. Etravirine should not be co-administered with PIs without low-dose ritonavir.[4]	No statistically significant changes in NFV levels after the addition of NVP (AUC +8%, Cmax +14%, and Cmin +2%). Compared to historical controls, NVP levels appear to be unchanged.[75] Similar results were demonstrated in a separate study, and NFV Cmin remained above minimum effective concentration during nevirapine coadministration.[76] Thus, dosage adjustments not required.	Potential for ↑ concentrations of rilpivirine. Rilpivirine is not expected to affect the plasma concentrations of co-administered PIs.[7]
Nevirapine		Combination of nevirapine 400 mg daily plus efavirenz 600 mg daily in HIV-infected individuals resulted in reduced efavirenz concentrations (22% ↓ AUC, 36% ↓ Cmin); nevirapine levels were not changed. Thus, may need to administer higher doses of efavirenz (e.g., 800 mg daily) in conjunction with nevirapine.[42]	Steady-state nevirapine 200 mg BID plus single-dose etravirine 900 mg resulted in 55% ↓ AUC and 36% ↓ Cmax of etravirine.[40] Etravirine should not be coadministered with other NNRTIs.[4]		In HIV infected patients on steady state nevirapine, administration of a single dose of rilpivirine 50 mg did not significantly alter rilpivirine exposures compared to rilpivirine alone (historical controls). Rilpivirine should not be co-administered with other NNRTIs.[7]
Raltegravir		In a placebo-controlled, 2 period study in 12 subjects who received 400 mg MK-0518 alone	In healthy subjects, raltegravir 400 mg BID and etravirine 200 mg BID for 4 days resulted in	Drugs may be coadministered. No Raltegravir dose modification is required.[80]	In healthy volunteers, coadministration of rilpivirine 25 mg QD and raltegravir 400

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		or with 600 mg EFV for 14 days, MK-0518 kinetic parameters were modestly reduced in the presence of EFV: $C_{12\ hr}$ GMR [90% CI] = 0.79 [0.49, 1.28], $AUC_{0-\infty}$ = 0.64 [0.52, 0.80] and C_{max} = 0.64 [0.41, 0.98]. There were no substantial differences in T_{max} or $t_{½}$. This interaction is likely not clinically meaningful.[77]	modest decreases in raltegravir concentrations (AUC ↓ 10%, 11% ↓ Cmax, 34% ↓ C12h) compared to raltegravir alone, while etravirine levels were not altered. These changes are not considered to be clinically meaningful; etravirine may be coadministered with raltegravir without dose adjustment.[78] In 29 HIV-positive subjects receiving regimens including raltegravir, raltegravir/darunavir 600 mg/ritonavir 100 mg BID, or raltegravir/darunavir /ritonavir/ etravirine BID, no differences in raltegravir Ctrough were noted between the groups.[79]		mg BID for 11 days did not significantly alter the pharmacokinetics of either drug compared to each drug administered alone. The combination may be administered without dose adjustment.[81]
Rilpivirine	Rilpivirine should not be co-administered with other NNRTIs.[7]	In HIV infected patients on steady state efavirenz, administration of a single dose of rilpivirine 75 mg resulted in 70% ↓ AUC and 30% ↓ Cmax of rilpivirine compared to rilpivirine alone (historical controls). Rilpivirine should not be co-administered with other NNRTIs.[7] In healthy volunteers, subjects received rilpivirine 25 mg QD for 14 days (period A) followed by a 14-21 day washout, then efavirenz 600 mg QD for 14 days (period B), followed immediately by rilpivirine 25 mg QD	Rilpivirine should not be co-administered with other NNRTIs.[7]	In HIV infected patients on steady state nevirapine, administration of a single dose of rilpivirine 50 mg did not significantly alter rilpivirine exposures compared to rilpivirine alone (historical controls). Rilpivirine should not be co-administered with other NNRTIs.[7]	

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		for 28 days (period C). At days 1, 14 and 21 of period C, rilpvirine AUC and Cmax were lower than in period A: day 1 - AUC ↓ 46%, Cmax ↓ 36%, day 14 – AUC ↓ 18%. Cmax ↓ 19%, Cmin ↓ 28%, day 21 - AUC ↓ 16%. Cmax ↓ 13%, Cmin ↓ 28%. By day 28 of period C, rilpivirine AUC and Cmin were similar to period A, while Cmin ↓ 25%. Plasma EFV was undetectable by 7 days after period B.[43]			
Ritonavir	70% ↑ RTV concentrations; kinetics of delavirdine and its metabolite unchanged with concomitant administration of full dose therapy.[82, 83] Similar effect (80% ↑ ritonavir AUC) seen in healthy volunteers given delavirdine 600 mg BID plus ritonavir 100 mg BID. No effect on delavirdine kinetic parameters[84]	Healthy volunteer study of EFV 600 mg/day + RTV 500 mg BID: 21% ↑ EFV AUC, 17% ↑ RTV AUC. Combination associated with higher frequency of adverse effects (e.g., dizziness, nausea, paresthesia) and ↑ LFTs. Recommended to monitor LFTs when using combination; if RTV intolerance occurs, may consider RTV dosage reduction.[85]	Single dose etravirine 400 mg plus steady-state ritonavir 600 mg BID (n=11) resulted in 46% ↓ AUC and 32% ↓ Cmax of etravirine, likely due to induction of glucuronidation.[40] Ritonavir concentrations not measured. Etravirine should not be co-administered with ritonavir 600 mg BID.[4] In healthy volunteers, there was no evidence of a pharmacokinetic interaction between **single-dose etravirine 200 mg and single-dose ritonavir 100 mg** administered either simultaneously after breakfast, or when ritonavir was given 4 hours before or after etravirine. Simultaneous administration of ritonavir 400 mg plus etravirine 200	11% ↓ RTV AUC, no effect on NVP levels. Interaction considered clinically insignificant; no dosage adjustment suggested.[87] Preliminary data suggest that dosing nevirapine 400 mg once daily may have a more pronounced effect on decreasing indinavir concentrations compared to nevirapine dosed 200 mg twice daily (median 31% decrease). These findings require further substantiation; may consider monitoring indinavir levels/response if switching nevirapine dosage regimen.[57]	

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			mg also had no effect on etravirine exposure relative to ritonavir 100 mg.[86]		
Saquinavir	Delavirdine 400 mg TID + saquinavir-hgc 600 mg TID in healthy volunteers: 5-fold ↑ SQV AUC, Cmin, Cmax; monitor LFTs during initial weeks of combination therapy. Dosage adjustments not necessary.[88] In a randomized study in HIV-subjects (n=10), these regimens were compared: • SQV-sgc 1200 mg TID • SQV-sgc 1400 mg + delavirdine 600 mg BID • SQV-sgc 1000 mg + delavirdine 400 mg TID When combined with DLV, SQV exposure was ↑ vs. SQV alone; SQV Cmin was higher in the TID vs. BID arm, both were greater than Cmin SQV alone.[89]	Multiple dose healthy volunteer study of efavirenz 600 mg/day + SQV-sgc 1200 mg q8h: 12% ↓ efavirenz AUC (not clin. significant), and 62% ↓ SQV AUC. [90] Can avoid this negative interaction by adding ritonavir to combination at the following doses: • saquinavir-sgc 400 mgBID • ritonavir 400 mg BID • efavirenz 600 mg qhs[91]	Etravirine AUC ↓ 33% when co-administered with **Saquinavir 1000 /ritonavir 100 mg BID**. No dose adjustments required.[4] Etravirine 900 mg BID at steady state plus **single-dose saquinavir 1200 mg** (n=12) resulted in 52% ↓ AUC and 46% ↓ Cmax of saquinavir, likely due to CYP3A induction.[40] Etravirine concentrations not measured. Etravirine should not be administered with unboosted PIs. [4] Etravirine 800 mg BID did not affect kinetics of **LPV 400/RTV 100/SQV 800-1000 mg BID** in 15 HIV-infected male subjects.[64]	27% ↓ SQV AUC; clinical significance unknown.[92]	Potential for ↑ concentrations of rilpivirine. Rilpivirine is not expected to affect the plasma concentrations of co-administered PIs.[7]
Tenofovir		In healthy volunteers, tenofovir 300 mg daily plus efavirenz 600 mg daily did not result in significant changes to the kinetics of either drug. Efavirenz and tenofovir may be coadministered without dosage adjustment.[93]	Coadministration of tenofovir 300 mg QD plus etravirine 200 mg BID in healthy volunteers led to 19% ↓ Cmax and AUC and 18% ↓ Cmin of etravirine, while tenofovir Cmax and AUC ↑ 15%. Combination may be coadministered without dosage adjustment.[94] Tenofovir was associated with 26% ↓ etravirine AUC12h from population PK data from substudy in	Trough nevirapine levels (23-25 hours post-dose) were obtained in subjects taking NVP 400 mg QD with or without concomitant tenfovir. The mean NVP concentration was 3420 (range 3170-3670) ng/mL in those taking NVP and tenofovir (n=171) and 3260 (range 2980-3540) ng/mL in those taking NVP without tenofovir (n=87).[95] No dosage adjustments necessary.	In healthy volunteers, coadministration of rilpivirine 150 mg QD and tenofovir 300 mg QD for 8 days resulted in 24% ↑ AUC, 21% ↑ Cmax and 24% ↑ Cmin of tenofovir, while kinetics of rilpivirine were not affected.[96] No dosage adjustments necessary.

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			DUET trials.[46]		
Tipranavir		Healthy volunteer open-label, randomized, parallel group study (n=68) of either **TPV/r 500 mg/100 mg or TPV/r 750 mg/200 mg** plus EFV 600 mg daily. PK sampling done after single dose and at steady state. At steady state, ↑ in TPV AUC, Cmax and C12h observed with EFV.[97] In a separate healthy subject study (n=16), **EFV 600 mg QD plus** TPV/r 500/200mg BID **for 14 days did not result in clinically important changes on the steady state PK of TPV or RTV, and EFV AUC levels were comparable to historical controls.[98]** May consider using TPV/RTV plus EFV without further dosage adjustment.	In healthy volunteers, tipranavir 500 mg/rtv 200 mg BID plus TMC125 800 mg BID (old formulation) led to 71% ↓ Cmax, 76% ↓ AUC and 82% ↓ Cmin of TMC125, while TPV AUC ↑ 18%. Do not co-administer tipranavir/ritonavir and etravirine.[4]	Healthy volunteer study of 1250 mg TPV BID plus 200 mg BID NVP +/- 200 mg RTV BID:[99] • no sig. impact on TPV levels • NVP AUC ↓37% by TPV (stat. sig),; levels improved with addition of RTV • RTV clearance was sig. ↑ in presence of TPV and NVP, but still higher than historical controls May consider using TPV/RTV plus NVP without further dosage adjustment.	Potential for ↑ or ↓ concentrations of rilpivirine. Rilpivirine is not expected to affect the plasma concentrations of co-administered PIs.[7]
Zidovudine *(GT 60-75% > CYP3A, minor)*	No kinetic interaction noted. May prevent emergence of AZT resistance.[100]	No interaction noted with combination.[101]		No interaction noted.[102]	
INTERACTIONS WITH OTHER AGENTS:					
Acetaminophen					In HIV negative subjects, coadministration of rilpivirine 150 mg QD for 11 days and single dose acetaminophen 500 mg did not significantly affect acetaminophen exposure. No dose modification of rilpivirine is needed.[8]

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Antacids (see separate entries for H2-blockers and proton-pump inhibitors)	50% ↓ DLV AUC; administer DLV 1 hour before antacids.	No effect on EFV concentrations when administered with 30 mL Mylanta DS (AlOH, MgOH, simethicone).[101]		Absorption of NVP not affected by antacids.[102]	Use combination with caution. Antacids should be administered at least 2 hours before or at least 4 hours after rilpivirine.[7]
Antihistamines, non-sedating (i.e., astemizole, terfenadine) *(CYP3A4)*	Potential cardiotoxicity; combination contraindicated.[100]	Possible ↑ antihistamine AUC and cardiotoxicity. **Avoid combination.**[101]			Avoid combination.
Atovaquone/ progruanil (Malarone®) Atovaquone: GT Proguanil: CYP2C19 to active metabolite, cycloguanil, 40-60% Clr		In 20 HIV-positive patients on EFV, single dose atovaquone 250/ proguanil 100 mg resulted in atovaquone AUC ↓ 75% and proguanil AUC ↓ 69% (only in those who had no CYP2C19*2 or -*3 alleles) compared to healthy volunteers.[103]			
Benzodiazepine • alprazolam, midazolam, triazolam, zolpidem (CYP3A4) • diazepam (2C19>3A4)	Potential for ↑ sedation. Avoid combination if possible or adjust BZ dose.[100]	Risk of prolonged sedation. **Avoid combination**, or use agents which are glucuronidated (e.g., lorazepam, oxazepam, temazepam).[101]			
Cisapride *(CYP3A4)*	Potential cardiotoxicity; combination contraindicated.[100]	Possible ↑ cisapride AUC and cardiotoxicity. **Avoid combination.**[101]			
Clarithromycin *(parent: CYP3A4; inhibits CYP3A4, 1A2?) (CLA-14 OH: renal, CYP3A4)*	Clarithromycin AUC doubled.[100] Inhibition of CLA-OH metabolite (i.e., ↓ Gram-neg. activity, such as H. flu) observed (data on file, Pharmacia & Upjohn). Adjust clarithromycin dose in renal impairment.[100]	39% ↓ clarithromycin AUC, 34% ↑ CLA-OH AUC; clinical significance unknown. 11% ↑ efavirenz AUC observed, not clinically important. However, ↑ incidence of rash observed; may wish to consider alternatives to clarithromycin. No significant interaction with azithromycin.[104]	In healthy subjects, clarithromycin 500 mg BID plus etravirine 200 mg BID led to 46% ↑ Cmax, 42% ↑ AUC and 46% ↑ Cmin of etravirine, with a corresponding 39% ↓ clarithromycin AUC and 21% ↑ in CLA-OH AUC. For treatment of MAC infection, may wish to consider using azithromycin instead, since CLA-OH metabolite is 4-7 times less active than parent against MAC.[4]	Interaction study of NVP 200 mg BID + clarithromycin 500 mg BID: significant reduction in CLA concentrations: 29.5% ↓AUC, 20.8% ↓ Cmax, 46% ↓ Cmin; also 27% ↑ AUC of CLA-OH metabolite. Since ↑ metabolite ≅ same magnitude as ↓ in parent drug, dosage adjustment of CLA likely not necessary with NVP.[105]	Coadministration of macrolides including clarithromycin, erythromycin and troleandomycin with rilpivirine should be done with caution, as rilpivirine concentrations may be increased. Azithromycin does not inhibit CYP3A4 and is the preferred macrolide option.[7]

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			No dose adjustment for clarithromycin or etravirine needed in patients with normal renal function; consider clarithromycin dose adjustment for patients with impaired renal function.		
Clopidogrel *(metabolized to its active metabolite, in part by CYP2C19)*			Avoid concomitant use of drugs that inhibit CYP2C19, including etravirine, as coadministration may result in ↓ concentrations of the active metabolite of clopidogrel and a reduction in platelet inhibition.[4, 106]		
Digoxin			Open label randomized crossover trial in male volunteers (n=16) to evaluate effect of ETR 200mg BID on single dose digoxin 0.5mg. Co-administration led to 19% ↑ Cmax, 18% ↑ AUC of digoxin, no change in urinary excretion. ETR mean Cmax and AUC12 comparable to historical controls. Authors recommend to monitor digoxin levels.[107] Manufacturer recommends that for patients initiating etravirine and digoxin therapy, the lowest dose of digoxin should be initially prescribed. For patients on a stable digoxin regimen who are initiating etravirine, no dose adjustment of either ETV or digoxin is required. Serum digoxin		

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			concentrations should be monitored.[4]		
Diltiazem		In a pharmacokinetic study of healthy subjects, efavirenz 600 mg plus diltiazem 240 mg for 14 days led to a significant decrease in AUC of diltiazem and its two major metabolites (69% ↓ and 36-74% ↓, respectively), while efavirenz AUC ↑ 11% (not clinically relevant). If co-administration is required, adjustments in diltiazem dose may be required based on response.[108]			
Ergot alkaloids *(CYP3A>others)*	Use DLV with caution in combination with ergot derviatives; potential for ↑ drug concentrations and toxicity.[100]	Use combination with caution and monitor for potential toxicity.	Avoid combination until data available.		
Fluconazole *(~80% Clrenal, 11% metabolized via CYP3A4; inhibits 3A4 (weak), 2C9, 2C19)*	No interaction noted.[100]	No interaction noted with combination.[109]	In healthy volunteers, coadministration of etravirine 200 mg BID plus fluconazole 200 mg daily for 9 days resulted in 109% ↑ Cmin, 75% ↑ Cmax and 86% ↑ AUC of etravirine, while fluconazole parameters were unchanged compared to either drug administered alone. The combination was well tolerated.[110]	In a study of 24 HIV+ subjects, combination of nevirapine 200 mg BID and fluconazole 200 mg daily resulted in ~100% ↑ AUC of nevirapine compared with historical data; 25% of subjects also developed elevated liver transaminases >5 times upper limit of normal. Nevirapine did not affect the pharmacokinetics of fluconazole.[111] In a retrospective study of 122 HIV-infected patients receiving nevirapine, those also taking fluconazole 200 or 400 mg daily (n=41) had NVP Cmin 76% higher compared to	Potential for increased concentrations of rilpivirine and decreased azole concentrations with concomitant administration. No rilpivirine dose adjustment is required. Monitor for breakthrough fungal infections.[7]

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				those not taking fluconazole. One patient on fluconazole developed clinical hepatitis.[112] **Use combination with caution.**	
Ginko biloba	Potential for ↓ delavirdine concentrations due to CYP3A induction by ginko biloba.[113] Case report of viral breakthrough and resistance to efavirenz after introduction of ginko biloba.[114] **Avoid concomitant use.**	Case report of HIV-positive male on efavirenz/tenofovir/ emtricitabine who developed viral breakthrough and resistance with K103N and M184V mutations after two years of therapy with excellent adherence and viral suppression. Efavirenz concentrations were 1.48 mg/L while the patient was suppressed, and 0.48 mg/L after viral breakthrough. The only change in the patient's routine was the addition of ginko biloba, a known CYP3A inducer.[114] **Avoid concomitant use.**	Potential for ↓ etravirine concentrations due to CYP3A induction by ginko biloba.[113] Case report of viral breakthrough and resistance to efavirenz after introduction of ginko biloba.[114] **Avoid concomitant use.**	Potential for ↓ nevirapine concentrations due to CYP3A induction by ginko biloba.[113] Case report of viral breakthrough and resistance to efavirenz after introduction of ginko biloba.[114] **Avoid concomitant use.**	Potential for ↓ rilpivirine concentrations due to CYP3A induction by ginko biloba.[113] Case report of viral breakthrough and resistance to efavirenz after introduction of ginko biloba.[114] **Avoid concomitant use.**
H2-antagonists (including cimetidine, famotidine, nizatidine, ranitidine, etc.)	Take H2-blocker at night if possible and ingest DLV with acidic beverage.[100] Similar measures may need to be followed with concomitant proton-pump inhibitor therapy.[115]	No effect on EFV concentrations when administered with 40 mg famotidine.[101]	In healthy subjects, single-dose etravirine 100 mg was administered in the presence of steady-state ranitidine 150 mg BID; etravirine AUC and Cmax were 86% and 94% compared to etravirine alone. Etravirine may be coadministered with H2-antagonists without dose adjustments.[116]	Steady-state NVP trough concentrations ↑ 21% with concurrent cimetidine; clinical significance unknown.[102]	In healthy subjects, single dose rilpivirine 150 mg was administered alone, two hours after, four hours before, or twelve hours after famotidine 40 mg. When rilpivirine was administered 2 hours after famotidine, rilpivirine Cmax and AUC were reduced by 85% and 76%, respectively. Rilpivirine concentrations were not affected when rilpivirine was administered either 4 hours before or 12 hours after famotidine; famotidine

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					pharmacokinetics were unchanged by rilpivirine. Therefore, rilpivirine should be separated at least 4 hours before or 12 hours following famotidine.[117]
Hmg-CoA Reductase inhbitors • atorvastatin *(CYP3A)* • fluvastatin *(2C9>>3A)* • pravastatin *(40-50% Clr, > 3A4)* • simvastatin *(CYP3A)*	Potential for ↑ concentrations of atorvastatin and simvastatin, possibly fluvastatin due to enzyme inhibition by delavirdine. Consider using pravastatin if treatment with an Hmg-CoA reductase inhibitor is desired, or use a fibric acid derivative for hypertriglyceridemia.	Potential for ↓ concentrations of Hmg-CoA reductase inhibitor, due to enzyme induction by efavirenz. In a prospective kinetic study, efavirenz 600 mg/day significantly ↓ **simvastatin** AUC by 58% (active metabolite AUC ↓ 60%) and **atorvastatin** AUC ↓ 43% (active metabolite AUC ↓ 48%); EFV concentrations not affected. Patients on combination should be closely monitored for anti-lipid activity; statin dose may need to be titrated.[118]	In healthy volunteers, atorvastatin 40 mg QD plus etravirine 800 mg BID (old formulation) led to 37% ↓ AUC of atorvastatin and 27% ↑ AUC atorvastatin active metabolite. Etravirine exposures were not affected. Combination may be coadministered.	Potential for ↓ concentrations of Hmg-CoA reductase inhibitor, due to enzyme induction by nevirapine.	In healthy volunteers, atorvastatin 40 mg QD plus rilpivirine 150 mg QD did not lead to significant alterations in plasma exposures of either rilpivirine or atorvastatin. A modest increase in exposure to atorvastatin hydroxylated metabolites (via mild induction of CYP3A activity by rilpivirine) resulted in an increase in the total lipid-lowering activity of atorvastatin during rilpivirine coadministration; this was considered clinically relevant. Combination may be coadministered without dose adjustment.[119]
Itraconazole		In a pharmacokinetic study of healthy subjects, efavirenz 600 mg plus itraconazole 200 mg BID for 14 days led to a 39% ↓ AUC of itraconazole and 37% ↓ AUC of its hydroxyl-metabolite; EFV exposures were not affected. There are no data using higher doses of itraconazole; therefore, no dose recommendation can be made. Use of alternate treatment may be necessary for optimal antifungal	Itraconazole is a potent inhibitor as well as substrate of CYP3A4. Concomitant systemic use of itraconazole and etravirine may ↑ plasma concentrations of etravirine. Simultaneously, plasma concentrations of itraconazole may be decreased by etravirine. Dose adjustments for itraconazole may be necessary depending on other co-administered drugs.[4, 122]	In a healthy volunteer, cross-over study of itraconazole 200 mg QD, nevirapine 200 mg QD or the combination (each for 7 days), itraconazole Cmax ↓ 38% and AUC ↓ 61% in the presence of nevirapine. NVP parameters were not changed.[123] **Avoid combination if possible.** If coadministered, monitor itraconazole concentration and	Potential for increased concentrations of rilpivirine and decreased azole concentrations with concomitant administration. No rilpivirine dose adjustment is required. Monitor for breakthrough fungal infections.[7, 122]

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		therapy.[108] Case report of HIV-positive male with disseminated histoplasmosis who had undetectable itraconazole concentrations and persistently elevated urinary *Histoplasma* antigen levels while on efavirenz and itraconazole 200 mg BID. Therapeutic itraconazole levels and a decrease in urinary Histoplasma antigen levels were observed after efavirenz was replaced with atazanavir/ritonavir.[120] In a retrospective cohort analysis, itraconazole levels were assessed in 10 HIV-positive patients with disseminated histoplasmosis; 4 patients were on PI therapy, 4 on NNRTIs, and 2 on both PIs and NNRTI therapy. All NNRTI patients had undetectable itraconazole concentrations, vs.1/4 PI patients. Two patients who switched from NNRTI to PI therapy subsequently had therapeutic itraconazole levels.[121] **Avoid this combination if possible.** If coadministered, closely monitor itraconazole concentration and adjust dose accordingly.[122] Use of alternate antifungal treatment		adjust dose accordingly.[122]	

	Delavirdine (Rescriptor®)	Efavirenz (Sustiva®)	Etravirine (Intelence®)	Nevirapine (Viramune®)	Rilpivirine (Edurant®)
		may be necessary or replacement of efavirenz with a non-inducing class of antiretrovirals such as protease inhibitors, integrase or CCR5 inhibitors if possible.			
Ketoconazole *(CYP3A4; inhibits 3A, 2C9)*	No delavirdine dosage adjustment recommended with inhibitors of CYP3A4 or CYP2D6.[100]	In a pharmacokinetic study of 12 HIV-infected patients, the kinetics of single-dose ketoconazole 400 mg was measured alone and after 14 days of efavirenz/3TC/d4T. In the presence of steady-state efavirenz, ketoconazole Cmax ↓ 44% and AUC ↓ 72%.[124]	Ketoconazole is a potent inhibitor as well as substrate of CYP3A4. Concomitant systemic use of ketoconazole and etravirine may ↑ plasma concentrations of etravirine. Simultaneously, plasma concentrations of ketoconazole may be decreased by etravirine. Dose adjustments for ketoconazole may be necessary depending on other co-administered drugs.[4]	Ketoconazole levels sig. reduced (63% ↓ AUC, 40% ↓ Cmax,) 15-20% ↑ NVP concentrations. Consider alternative antifungal.[125]	In healthy subjects, steady-state coadministration of rilpivirine 150 mg QD plus ketoconazole 400 mg QD, rilpivirine AUC ↑ 49%, Cmax ↑ 30% and Cmin ↑ 76%, while ketoconazole AUC ↓ 24%, Cmax ↓ 15% and Cmin ↓ 66% compared to each agent alone.[126] No rilpivirine dose adjustment is required. Monitor for breakthrough fungal infections.[7]
Methadone *(CYP3A4>>GT; weak inhibitor of CYP2D6)*	In study of HIV-negative volunteers on stable methadone (n=16) and 15 controls, addition of delavirdine 600 mg BID for 5 days did not alter the kinetics of delavirdine or its metabolite. Effects of delavirdine on methadone not studied.[127]	Significant decreases in methadone concentrations may occur, with risk of withdrawal occurring within 4-10 days after starting efavirenz.[128, 129] Monitor for withdrawal with concomitant therapy; methadone dosage ↑ may be necessary.	In 16 subjects stabilized on methadone maintenance therapy, addition of TMC125 100 mg BID for 14 days led to 11% ↓ Cmax, AUC and Cmin of S-Methadone and 6% ↑ AUC of R-methadone. Combination may be coadministered.[4]	Significant decreases in methadone concentrations may occur, with risk of withdrawal occurring within 4-10 days after starting nevirapine.[130 129] Monitor for withdrawal with concomitant therapy; methadone dosage ↑ may be necessary.	In the presence of rilpivirine, active R-isomer exposures decreased (mean Cmin ↓ 22%, Cmax ↓ 14%, AUC ↓ 16%); exposures of inactive S-methadone also decreased to a similar extent. The AUC ratio for S-/R-methadone did not change. No methadone withdrawal symptoms were observed. No dose adjustment of methadone is recommended. Patients should be monitored for symptoms of clinical withdrawal in case methadone dosage needs to be adjusted.[7]
Mycophenolate mofetil (MMF)				In a small case series (n=6) of HIV+	

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				subjects receiving ddI, 3TC, abacavir, indinavir 800/ ritonavir 100 mg BID and nevirapine 200 mg BID, NVP clearance ↑ 27% in the presence of chronic MMF administration. Clinical significance unclear.[123]	
Oral Contraceptives *(GT, sulphatase (primary)> CYP3A (~30%); inhibits 1A2, 3A)* *See separate entry for depo-medroxy-progesterone acetate (Depo-Provera®) below *Please also see separate chart on "Interactions between antiretrovirals and hormonal contraceptives".*	A clinically significant interaction is unlikely, since delavirdine does not have any effect on oral contraceptive metabolism (conjugation).	No pharmacokinetic interaction observed in healthy volunteer PK study.[131] In a separate healthy volunteer study of women taking Ortho Cyclen® alone or with EFV 600 mg daily for 14 days, ethinyl estadiol Cmax and AUC were unchanged in the presence of EFV. However, concentrations of norelgestromin and levonorgestrel (active metabolites of norelgestromin) were significantly reduced (64% and 83% ↓ AUC, respectively). Therefore, alternate methods of contraception are recommended.[132] In 21 HIV-negative women, the effect of EFV 600 mg QD for 14 days on the kinetics of **single dose levonorgestrel 0.75 mg** (dose for emergency contraception) was studied. In the presence of EFV, levonorgestrel AUC ↓ 56%, and Cmax and Cmin were also significantly reduced. While the minimum effective concentration of	In a study of 30 HIV negative volunteers, ↑ 22% AUC24H ethinyl estradiol when given with etravirine BID X 15 days. No loss in contraceptive efficacy of OC is expected when etravirine is coadministered.[134]	20% ↓ AUC of ethinyl estradiol and norethindrone when coadministered with nevirapine.[135] **Use alternate methods of contraception.** The steady-state kinetics of a combined OC (norgestrel 300 mg and ethinyl estradiol 30 ug) once daily were studied in 3 groups of women: HIV-positive on nevirapine plus 3TC/d4T (group 1), HIV-positive not on antiretrovirals (group 2), and HIV-negative (group 3). Median levonorgestrel AUC and Cmin and ethinyl estradiol AUC were highest in group 1, and women in group 1 demonstrated ovulation suppression.[136]	When rilpivirine 25 mg daily was coadministered with norethindrone 1 mg/ethinylestradiol 0.035 mg in 18 HIV-negative women, no statistically significant changes in norethindrone PK and ethinylestradiol AUC and Cmin were observed. Ethinylestradiol Cmax ↑ 17% in the presence of rilpivirine, but this is not expected to be clinically significant. **Rilpivirine 25 mg daily can be co-administered with norethindrone/ ethinylestradiol-based contraceptives without dose modifications.**[137]

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		levonorgestrel is unknown, higher doses may be needed to prevent pregnancy in women taking EFV. Alternate methods of contraception, including barrier methods, are recommended.[133]			
Depo-medroxy-progesterone acetate, DMPA (Depo-Provera®) *Please also see separate chart on "Interactions between antiretrovirals and hormonal contraceptives".*		In a prospective, open-label study of 15 HIV-infected women on stable EFV therapy, EFV AUC was not significantly altered in the presence of DMPA. Efficacy of DMPA did not appear to be altered, with no evidence of ovulation occurring based on progesterone levels through week 12.[138] In an open-label, nonrandomized, clinical trial, 30 HIV-infected women (15 on AZT, 3TC and EFV, 15 not on ARVs) received a single injection of DMPA 150 mg IM. AUC, Cmin, t1/2 of DMPA were similar between the 2 groups, suggesting that EFV-based therapy is not likely to interfere with the contraceptive effectiveness of DMPA.[139]		In a prospective, open-label study of 14 HIV-infected women on stable NVP therapy, NVP AUC was higher in the presence of DMPA, although this increase was not felt to be clinically relevant. Efficacy of DMPA did not appear to be altered, with no evidence of ovulation occurring based on progesterone levels through week 12.[138]	
Posaconazole *(UGT1A4; inhibits CYP3A4)* *Please also see separate chart on "Interactions between antiretrovirals*		In healthy subjects randomized to receive EFV 400 mg QD alone or with posaconazole 400 mg BID for 10 days, posaconazole Cmax ↓ 45% and AUC ↓ 50% in the presence of	Possible ↑ etravirine concentrations due to CYP3A4 inhibition by posaconazole. No anticipated effect on posaconazole concentrations.[4]	Potential for ↓ posaconazole levels; avoid co-administration until further data are available.	Potential for increased concentrations of rilpivirine and decreased azole concentrations with concomitant administration. No rilpivirine dose adjustment is

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and oral azole antifungal agents".		efavirenz. **Avoid co-administration unless benefit to patient outweighs the risk.**[140]			required. Monitor for breakthrough fungal infections.[7]
Proton-pump inhibitors (PPIs), including esomeprazole, lansoprazole, omeprazole, pantoprazole, rabeprazole, etc.	Take H2-blocker at night if possible and ingest DLV with acidic beverage.[100]Similar measures may need to be followed with concomitant proton-pump inhibitor therapy.[115]		In healthy subjects, single-dose etravirine 100 mg was administered in the presence of steady-state omeprazole 40 mg QD; etravirine AUC and Cmax were 141% and 117% compared to etravirine alone. Etravirine may be coadministered with proton-pump inhibitors without dose adjustments.[116]		In healthy subjects, coadministration of omeprazole 20 mg QD and rilpivirine 150 mg QD led to 40% ↓ in Cmax and AUC and 37% ↓ Cmin of rilpivirine, while omeprazole AUC ↓ 14%. **Therefore, rilpivirine should not be coadministered with proton pump inhibitors**.[7]
Rifabutin *(CYP3A > deacetylase; moderate inducer of CYP3A)*	50-60% ↓ delavirdine concentrations[141] (not adequately compensated with 600 mg TID dose); also >200% ↑ RFB AUC.[142] Therefore, avoid concomitant use.	Rifabutin AUC ↓ 38%. Case report of treatment failure with combination; rifabutin levels remained below target despite ↑ rifabutin dose to 1350 mg daily.[143] Increase rifabutin to 450-600 mg/day or 600 mg three times per week with concomitant efavirenz.[144-146]	In healthy subjects, rifabutin 300 mg QD plus etravirine 800 mg BID (old formulation) led to 37% ↓ Cmax and AUC and 35% ↓ Cmin of etravirine, while rifabutin AUC ↓ 17% and Cmin ↓ 24%. If etravirine is NOT co-administered with a boosted PI, then rifabutin 300 mg QD is recommended. If etravirine is co-administered with darunavir/ritonavir or saquinavir/ritonavir, then rifabutin should not be co-administered due to the potential for significant reductions in etravirine exposure.[4]	16% ↓ nevirapine concentrations, no significant changes in rifabutin concentrations. Combination may be safely co-administered without dosage adjustment.[147] May give rifabutin 300 mg daily or 3 times per week.[146]	In healthy subjects, coadministration of rilpivirine 150 mg QD and rifabutin 300 mg QD for 11 days resulted in 46% ↓ AUC, 35% ↓ Cmax and 49% ↓ Cmin of rilpivirine compared to rilpivirine dosed alone. Exposures of rifabutin and its active metabolite were not significantly changed in the presence of rilpivirine. Avoid concomitant use since rilpivirine efficacy may be compromised.[148]
Rifampin *(Deacetylase> hydrolysis, GT?, CYP?; potent inducer of CYP3A and GT)*	Virtually undetectable DLV concentrations; **combination contraindicated.**[149]	26% ↓ AUC, 20% ↓ Cmax of efavirenz; clinical significance unknown.[150] Two retrospective analyses of TDM databases indicated	Avoid combination as significant decreases in etravirine exposure may occur.[4]	No change in RIF AUC or Cmax; 58% ↓ NVP average levels, 68% ↓ Cmin. Authors suggest ↑ NVP dose by 50% (i.e., to 300 mg BID) with concomitant	In healthy subjects, coadministration of rilpivirine 150 mg QD and rifampin 600 mg QD resulted in 80% ↓ AUC, 69% ↓ Cmax and 89% ↓ Cmin of rilpivirine

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		no difference in EFV levels when given at either 600 or 800 mg daily with rifampin.[151, 152] A randomized trial in Thai subjects (median weight 50 kg) receiving EFV 600 or 800 mg plus RIF, median plasma EFV levels were 3.02 mg/L (range 0.07-12.21) in the 600 mg group and 3.39 mg/L (range 1.03-21.31) in the 800 mg group (P = 0.632). Plasma EFV levels were < 1 mg/l in 3/38 (7.9%) patients in the 600 mg group and in none of the 800 mg group (P = 0.274). ~40 and 45% of patients had EFV levels > 4 mg/L, respectively.[153] Similar virologic & immunologic outcomes were noted at 48 weeks.[154] NB: these results may not be applicable to other populations with higher body weight. HIV/TB coinfected patients from Cote d'Ivoire receiving RIF were randomized to receive EFV 600 or 800 mg QD (n=65 per group). Plasma EFV levels were higher at months 3 and 6 in the 800 mg group (>4 mg/mL) compared to the 600 mg group (~2 mg/mL), with a higher incidence of adverse events (17% vs. 7%, respectively). At 24 weeks, 59% in the 800 mg group had VL<300 copies/mL		RIF therapy.[157] **However, caution re: ↑ risk hepatotoxicity.** In a separate study of 10 subjects with HIV/TB coinfection, NVP exposure was reduced in the presence of rifampin (31% ↓ AUC, 36% ↓ Cmax, 21% ↓ Cmin); however, NVP Cmin remained above IC50 wild type.[158] **Avoid combination if possible.[122]** In a case series (n=32) of HIV-infected patients with TB, coadministration of rifampin 600 mg/d and nevirapine 400 mg/d for a median of 9 months resulted in 100% clinical and microbiological cure of TB; mean NVP Cmin was 4.5 +/- 1.9 ug/mL.[159] In a prospective study in 140 treatment-naïve HIV-positive Thai subjects (70 with active TB and on rifampin 450-600 mg/day), **those taking rifampin + NVP had significantly ↓** (17.7% lower, p=0.048) **median NVP plasma levels** vs. those taking NVP without RIF. However, in this cohort, there was no different in viral or immunologic response at 24 weeks between the two treatment arms.[160]	compared to rilpivirine dosed alone. Exposures of rifabutin and its active metabolite were not significantly changed in the presence of rilpivirine. Avoid concomitant use since rilpivirine efficacy may be compromised.[164]

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		vs. 70% in the 600 mg group, p=0.38.[155] Individuals from the CIPRA-South Africa cohort taking EFV-based therapy with concomitant TB received either 600 or 800 mg EFV during TB treatment with RIF; after TB therapy, all individuals took 600 mg EFV. EFV levels were measured after 4 weeks of concomitant EFV and RIF therapy, and ≥4 weeks after completion of TB therapy. EFV concentrations in the 800 mg group were higher with RIF than without (2.9 vs. 2.1 mg/L, respectively, p=0.0003). In the 600 mg EFV group, there was no significant difference in EFV concentrations with RIF or without (2.4 vs. 2.2 mg/L, respectively. There was no increase in EFV-linked adverse effects in either group. The proportion of virologically suppressed individuals at 48 weeks was similar in both groups. Dose escalation of EFV 600 mg to 800 mg is not required during concomitant TB therapy in South Africa.[156] **The efavirenz product monograph recommends increasing EFV dose to 800 mg**		In a prospective randomised open-label trial comparing NVP 400mg (without lead-in dosing) vs. EFV 600mg -based ART initiated 4 weeks after starting TB therapy with rifampin, NVP pk was measured in 20 patients during RIF co-administration and 4 weeks after completion of RIF therapy. NVP Ctrough at 2 weeks was 5.83 mg/L (target >3 mg/L), and 89.5% patients achieved VL<400 at week 12. **Upon completion of RIF therapy, NVP Cmin ↑ 14% and AUC ↑ 20%.**[161] In a prospective evalution of 20 HIV-patients on stable nevirapine who started rifampin-based TB treatment, **nevirapine AUC ↓ 22%** by day 14. Six patients had subtherapeutic levels at day 14, with the reduction beginning as early as day 3.[162] In an open-label, multi-centre study, HIV+ patients with TB were given a standard short course 4-drug anti-TB regimen for 2 months and then randomized to receive once daily efavirenz (600 mg) or once daily nevirapine (400 mg with lead-in dosing) plus ddI/3TC with continued isoniazid/ rifampin for an	

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		daily with rifampin in patients weighing >50 kg. However, current guidelines suggest that standard EFV dose may be used with close monitoring of EFV drug levels and virologic response.[122]		additional 4 months. At 24 weeks, 50/59 patients in the efavirenz group and 37/57 patients in the nevirapine group had virological suppression (p=0.024). There were no deaths, 1 SAE, and 5 treatment failures in the EFV arm, compared with 5 deaths, 2 SAEs, and 10 treatment failures in the NVP arm. The authors concluded that the **NVP-based regimen was inferior and was associated with more frequent virologic failure and death** compared to the efavirenz arm, presumably due to the magnitude of the induction effect of rifampicin on nevirapine.[163]	
Rifapentine	Significant reduction in NNRTI concentrations expected with coadministration. **Avoid combination**.[122]				
Sildenafil/ Viagra® *(CYP3A4>>2C9 ; weak inhibitor of CYP1A2, 2C9, 2C19, 2D6, 2E1, 3A4 - unlikely to cause significant interactions)*	Elevated concentrations of sildenafil expected with combination. Do not exceed sildenafil dose of 25 mg every 48 hours.[100]	No information on combination. Since efavirenz may act as either an inducer or inhibitor of CYP3A4, consider starting with an initial sildenafil dose of 25 mg q24-48 hours and titrating up based on patient response and tolerability.[165]	In healthy volunteers, single-dose sildenafil 50 mg in the presence of steady-state etravirine led to 57% ↓ in exposures of sildenafil and its active metabolite. Combination may be co-administered, adjust sildenafil dose according to response.[166]	No information on combination. Expected that 3A4 inducers will ↓ sildenafil levels. Titrate sildenafil dose based on patient response and tolerability.	In healthy volunteers taking rilpivirine 75 mg once daily for 12 days, the kinetics of single dose sildenafil 50 mg were similar as compared to sildenafil alone. In the presence of steady-state rilpivirine, sildenafil AUC ↓ 3% and Cmax ↓ 7% and N-desmethyl sildenafil AUC ↓ 8% and Cmax ↓ 10%. Rilpivirine exposures were not affected by sildenafil. Combination may be coadministered without dose modifications.[167]
Sulfamethoxazo	No interaction			May be ↑ risk rash	

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le (SMX) *(primarily N-acetylase> GT > CYP2C9 (minor)*	noted.[100]			with combination.[102]	
Trimethoprim *(10-20% metabolized, via CYP?)*	No interaction noted.[100]				
Voriconazole *(CYP2C19, 2C9, 3A; inhibits CYP3A4, 2C9, 2C19)*	Although not studied *in* vivo, *in vitro* studies show that the metabolism of voriconazole may be inhibited by delavirdine. Voriconazole may also inhibit the metabolism of an NNRTI. Use combination with caution and monitor closely for toxicity. (Vfend prescribing info).	**Standard voriconazole dose contraindicated** with efavirenz because of 77% ↓ voriconazole AUC and 44% ↑ in efavirenz concentrations. (Vfend prescribing info). If Sustiva is coadministered with voriconazole, the voriconazole maintenance dose should be increased to 400 mg every 12 hours and the efavirenz dose should be decreased to 300 mg once daily using the capsule formulation. Case report of HIV positive subject with cirrhosis on stable EFV regimen (600mg/day) who required addition of IV voriconazole at 3 times normal dose to amphotericin/ flucytosine for disseminated cryptococcosis. Patient experienced remission of cryptococcal symptoms, viral load < 50 copies/ml. After 35 days, patient was switched to maintenance voriconazole 300mg po BID + EFV 600mg daily. TDM was performed q3weeks. EFV was ↓ to 400 mg/day	In healthy volunteers, coadministration of etravirine 200 mg BID plus voriconazole 200 mg BID for 9 days resulted in 52% ↑ Cmin, 26% ↑ Cmax and 36% ↑ AUC of etravirine, and 23% ↑ Cmin and 14% ↑ AUC of voriconazole (although no ↑ was observed in carriers of CYP2C19*2 allele) compared to either drug administered alone. The combination was well tolerated.[110] Dose adjustments are not required. Monitor closely for toxicity.	Although not studied, the metabolism of voriconazole may be induced by nevirapine. Voriconazole may also inhibit the metabolism of an NNRTI. Use combination with caution and monitor closely for efficacy and toxicity. (Vfend prescribing info).	Potential for increased concentrations of rilpivirine and decreased azole concentrations with concomitant administration. No rilpivirine dose adjustment is required. Monitor for breakthrough fungal infections.[7]

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		and then to 300 mg/day. Voriconazole was ↓ to 200 mg BID when EFV was ↓ to 300 mg/day. Authors comment that EFV 300mg daily + voriconazole maintenance dose which is 2X that recommended for cirrhotic patients (Child Pugh A) appeared effective and safe during long term follow up.[168]			
Warfarin, Acenocoumarol /nicoumalone *(racemic mixture; R: CYP1A2, 3A, 2C19; S: 2C9 primarily)* *NB:* The S-enantiomer of warfarin exhibits 2 to 5 times more anticoagulant activity than the R-enantiomer in humans, but generally has a more rapid clearance. The R(+) and S(−) enantiomers of acenocoumarol have comparable anticoagulant effects, but the S-enantiomer has a very short half-life; thus only the R-enantiomer provides a pharmacologic effect in vivo.	May potentially inhibit anticoagulant metabolism; monitor for ↑ INR and adjust anticoagulant dose accordingly when starting and discontinuing therapy.	May potentially induce or inhibit anticoagulant metabolism. One patient required a 4-fold reduction in warfarin dose while on concomitant efavirenz and warfarin,[169] while another patient required a 50% increase in acenocoumarol dosage after initiating efavirenz therapy.[170] Monitor for changes in INR and adjust anticoagulant dose accordingly when starting and discontinuing therapy.	Anticoagulant concentrations may be increased when co-administered with etravirine. The international normalized ratio (INR) should be monitored when an anticoagulant is combined with etravirine.[4]	May potentially induce anticoagulant metabolism; case reports where warfarin dosage had to be doubled or exceeded maximum recommended daily dose to maintain therapeutic INR.[171] Monitor for ↓ INR and adjust anticoagulant dose accordingly when starting and discontinuing therapy.	May potentially induce anticoagulant metabolism. Monitor for ↓ INR and adjust anticoagulant dose accordingly when starting and discontinuing therapy.
Enzyme Inducers (e.g., phenytoin, phenobarbital,	Significant ↓ delavirdine concentrations. Concomitant use of	Possible ↓ efavirenz concentrations. Dosage adjustments may be	Possible ↓ etravirine concentrations. Avoid combination.	Potential for ↓ NVP concentrations with concomitant use of agents which	Avoid concomitant administration with potent CYP3A4 inducers, as

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carbamazepine, oxcarbazepine)	DLV and CYP3A inducers not recommended.[100]	required.	[4]	induce CYP3A4.	rilpivirine concentrations may be reduced.
Enzyme Inhibitors (e.g., fluconazole, macrolides, nefazodone)	No delavirdine dosage adjustment recommended with inhibitors of CYP3A4 or CYP2D6.[100]			Potential for ↑ NVP concentrations.	Coadministration of CYP3A4 inhibitors with rilpivirine should be done with caution, as rilpivirine concentrations may be increased. Alternative agents without CYP3A4 inhibitory effects should be used whenever possible. If there is no alternative, additional safety monitoring is strongly recommended, including ECGs at baseline and 3-7 days following initiation of the enzyme inhibitor.
Other classes: analgesics, antiarrhythmics, antidepressants, calcium channel blockers, neuroleptics, psychotropics.	Use delavirdine with caution in combination with calcium channel blockers, ergot derivatives (potential for ↑ drug conc. and toxicity).[100]	Efavirenz should not be administered concurrently with astemizole, bepridil, cisapride, midazolam, pimozide, triazolam, or ergot derivatives because competition for CYP3A4 by efavirenz could result in inhibition of metabolism of these drugs and create the potential for serious and/or life-threatening adverse events (eg, cardiac arrhythmias, prolonged sedation, or respiratory depression).	Concentrations of antiarrhythmics may be decreased in presence of etravirine. Coadminister with caution and measure drug concentrations if possible.[4]	Potential for ↓ in concentrations of agents which are substrates of CYP3A4.	

Please note: This chart summarizes some of the major drug interactions identified to date, based on current available data; other drug interactions may exist. Please use caution whenever adding/modifying therapy. The information in this table is intended for use by experienced physicians and pharmacists. It is not intended to replace sound professional judgment in individual situations, and should be used in conjunction with other reliable sources of information. Due to the rapidly changing nature of information about HIV treatment and therapies, users are advised to recheck the information contained herein with the original source before applying it to patient care.

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DRUG INTERACTIONS WITH PROTEASE INHIBITORS
(NB: for additional interaction data involving amprenavir, indinavir, nelfinavir and unboosted saquinavir-soft gel capsules (Fortovase), please refer to the chart "Drug Interactions with Secondary Protease Inhibitors")

	Atazanavir (Reyataz®)	Darunavir (Prezista®)	Fosamprenavir (Telzir®)	Lopinavir/ ritonavir (Kaletra®)	Ritonavir (Norvir®)	Saquinavir (Invirase®)	Tipranavir (Aptivus®)
I) DOSING INFORMATION:							
Usual Dose	400 mg po QD or 300 mg/100 mg ritonavir QD	600 mg/100 mg ritonavir BID	PI-naïve subjects: • 1400 mg BID (US monograph only) • 1400 mg/ritonavir 100 mg QD PI-experienced: • **700 mg/100 mg ritonavir BID**	400 mg/100 mg po BID	Boosting doses: 100-200 mg QD-BID Single agent (rarely used): 600 mg po BID (titrate dose when initiating therapy; e.g., 300 mg po BID x 3/7, 400 mg po BID x 4/7, 500 mg po BID x 5/7, then full dose)	1000 mg/100 mg ritonavir BID	500 mg/200 mg ritonavir BID
Kinetic Characteristics	Primarily metabolized by CYP3A4; also inhibits CYP3A and UGT1A1.[1] Atazanavir alone does not induce glucuronidation, while atazanavir/ ritonavir does induce glucuronidation.[2]	Primarily metabolized by CYP3A4. Inhibits CYP3A4.[3]	Primarily metabolized by CYP3A4. Inhibitor of CYP3A4 (similar potency as indinavir and nelfinavir)[4]; also induces CYP3A4[5].	Lopinavir is primarily metabolized by CYP3A4. Kaletra inhibits CYP3A4, 2D6 (to lesser extent). Induces glucuronyl transferases and possibly CYP1A2, CYP2C19 and 2C9.[6]	Potent inhibitor of CYP enzymes in following order: 3A>2D6>2C9, 2C19>>2A6, 2E1. Induces glucuronyl transferases, CYP1A2, CYP2B6, CYP2C9 and CYP2C19.[6-8] Formulations contain alcohol.	Primarily metabolized by CYP3A4 and P-gp. Weak inhibitor of CYP3A4 and P-gp.[8, 9]	Substrate of CYP3A4 and P-gp. Inducer of CYP3A4, P-gp, glucuronyl transferase, slight inducer of CYP2C9, moderate inducer of CYP1A2, and potent inhibitor of CYP2D6.[10] When co-administered with ritonavir, net effect is CYP3A inhibition.[11] Capsules contain alcohol; avoid use of disulfiram and metronidazole.
Food (NB: **garlic**: see entries for Saquinavir and Ritonavir)	Take with a light meal for improved absorption (AUC ↑ 35% with a high fat meal, and ↑ 70% when given with a low fat meal, vs. taking on a fasted state).[12] In HIV-infected patients taking atazanavir 300/100 mg QD, atazanavir AUC ↓ 41%, Cmax ↓ 32% and Ctrough ↓	Bioavailability ↑ 42% when taken in fed conditions with ritonavir versus fasting conditions. Type of meal (standard breakfast, high-fat breakfast, nutritional protein drink, croissant + coffee) had very little impact on exposure.	Amprenavir: May be taken with or without food. Avoid taking with high-fat meal.[14] Administer amprenavir liquid solution at least 1 hour apart from other medications that contain sorbitol. Fosamprenavir: May be taken with or without food; high fat meal does not affect absorption.[15]	Take capsules with food (regular or high-fat meal ↑ AUC 12%, ↑ Cmin 44%, ↓ variability in drug concentrations).[16] Kaletra tablets may be taken with or without food.	Take with food. (15% ↑ AUC with food). OK with Advera, Ensure, & chocolate milk. In a kinetic study of healthy volunteers, 4 days of **garlic** administration did not significantly affect the kinetics of single-dose ritonavir. Impact of chronic co-administration of both agents remains	Take within 2 hours of meal (almost 7-fold ↑ AUC with food).	Take with food. When given as a single dose (without ritonavir) with a high-fat meal, tipranavir absorption ↑ 32%. Tipranavir capsules: When tipranavir 500 mg/ritonavir 200 mg BID was administered with food, tipranavir bioavailability was not altered compared to when

	Atazanavir (Reyataz®)	Darunavir (Prezista®)	Fosamprenavir (Telzir®)	Lopinavir/ ritonavir (Kaletra®)	Ritonavir (Norvir®)	Saquinavir (Invirase®)	Tipranavir (Aptivus®)
	53% when administered fasting versus with food.[13]				unclear.[17]		TPV/r was administered in a fasting state.[18]
Cranberry Juice	Prospective, observational, cross-sectional study in HIV-positive patients (n=120) on ARVs for at least 12 weeks, and reporting current cranberry juice intake (median 237 mL once-twice daily for median 4.5 years) or no cranberry juice intake. No significant difference in ATV levels in patients on atazanavir 300/ritonavir 100 mg QD +/- cranberry juice. ATV Cmin: ATV alone group: 183 ng/ml, n=6; ATV + Cranberry juice group: 197ng/ml, n=7[19]		Prospective, observational, cross-sectional study in HIV-positive patients (n=120) on ARVs for at least 12 weeks, and reporting current cranberry juice intake (median 237 mL once-twice daily for median 4.5 years) or no cranberry juice intake. No significant difference in amprenavir levels in patients on fosamprenavir 700/ritonavir 100 mg BID +/- cranberry juice. APV Cmin: fosamprenavir alone group: 2132 ng/ml, n=4; FPV + Cranberry juice group: 1292ng/ml, n=2[19]	Prospective, observational, cross-sectional study in HIV-positive patients (n=120) on ARVs for at least 12 weeks, and reporting current cranberry juice intake (median 237 mL once-twice daily for median 4.5 years) or no cranberry juice intake. No significant difference in LPV levels in patients on lopinavir 400/ritonavir 100 mg BID +/- cranberry juice. LPV Cmin: LPV alone group: 4482 ng/ml, n=29; LPV + Cranberry juice group: 4175ng/ml, n=13[19]			
Grapefruit juice *NB: in vitro data suggest **pomegranate juice** may also have CYP3A inhibiting activity similar to grapefruit juice, although no kinetic studies in humans.[20]	Not studied.		No significant changes in amprenavir concentrations when administered with 200 mL grapefruit juice.[21]	Not studied.	Not studied.	40-100% ↑ saquinavir AUC. Take 150 mL juice with each dose.[22]	
II) ANTI-	**RETROVIRAL**	**INTERACTIONS**					
Atazanavir (ATV)		In healthy volunteers, ATV 300 mg QD plus darunavir/rtv	Combination of ATV with amprenavir in HIV-infected peripheral blood	In TDM case series, **ATV 300/ LPV 800/rtv 200 mg QD** yielded ATV Ctrough	Additive-synergistic antiviral activity in vitro.[24] In healthy volunteer	Additive-synergistic antiviral activity in vitro.[24]	Healthy volunteer study of steady-state atazanavir 300/100 mg, tipranavir

	Atazanavir (Reyataz®)	Darunavir (Prezista®)	Fosamprenavir (Telzir®)	Lopinavir/ ritonavir (Kaletra®)	Ritonavir (Norvir®)	Saquinavir (Invirase®)	Tipranavir (Aptivus®)
		400/100 mg BID led to 50% ↑ Cmin, 11% ↓ Cmax and no change in AUC of ATV compared to ATV 300/rtv 100 mg alone. Ritonavir exposure ↑ 51-59% when ATV added to darunavir/rtv. There were similar rates of hyperbilirubinemia and elevated lipase levels when subjects were given ATV/r alone and in combination with DRV/r.[23] ATV 300mg daily may be given with DRV/r BID without dose adjustment.	mononuclear cells yielded additive to moderately synergistic antiviral effects.[24] In healthy subjects, **ATV 300 mg QD plus FPV 700/100 mg BID** showed no significant change in amprenavir concentrations and ATV Ctrough, and 24% ↓ Cmax and 22% ↓ AUC of ATV.[25] In a healthy volunteer study, **ATV 400/FPV 1400 mg QD** for 14 days yielded APV Cmin comparable to FPV 1400 mg BID, while ATV AUC ↓ 33%, C_{24} ↓ 57% vs. ATV 400 mg QD alone.[26] In a case series of treatment-experienced patients, 14 subjects received **ATV 150 or 200/FPV 700/rtv 100 mg BID** (9 were on concomitant tenofovir/FTC); three patients received **ATV 400/FPV 700 mg BID**. All regimens produced ATV and APV C_{trough} well above the minimum acceptable concentrations. Mean ATV Ctrough was 0.96-1.66 ug/mL in ATV	levels approx. 5-fold higher (mean 736 ng/mL) vs. ATV 400 mg QD (mean 122 ng/mL).[28] In a 2-phase kinetic study in HIV-infected men, this dosing combination yielded steady-state ATV Cmin of 541 ± 245 ng/mL and LPV Cmin 1424 ± 1423 ng/mL.[29] A small study in HIV-infected subjects on either stable **ATV 300/100 mg QD or LPV 400/100 mg BID** showed no changes in ATV concentrations and slight decreases in LPV exposure (16% ↓ AUC, 35% ↓ Cmin) when drugs were coadministered.[30] In HIV-negative subjects, **ATV 300 mg QD plus LPV/r 400/100 mg BID** led to 45% ↑ ATV Cmin (no change in AUC or Cmax) compared to ATV 300 mg/rtv 100 mg QD; LPV levels were not significantly different from historical controls.[31] A similar study in HIV-positive subjects yielded ATV AUC 38% ↓ similar Cmin vs. 300/100 mg (historical controls);	study, addition of **ritonavir 100-200 mg to ATV 200 or 400 mg daily** resulted in significantly ↑ ATV exposure.[34] Separate steady-state study in healthy volunteers (n=30) of **ATV 300/ritonavir 100 mg QD** with a light meal resulted in 1.86-fold ↑ Cmax and 3.38-fold ↑ AUC of ATV; ritonavir kinetics not affected.[35] Current dosage recommendation: atazanavir 300 mg/ ritonavir 100 mg QD with food. In a cross-over, single-blind, two period study, healthy volunteers received **ATV 300 mg with either RTV 100 mg or 50 mg** for 10 days, 15 days apart. Ritonavir Cmax and AUC were lower with the 50 mg dose vs. 100 mg dose and all/most RTV Ctrough were below the level of detection. No differences in ATV exposures were noted between the 50 vs 100 mg RTV dose treatments and all ATV Ctrough were >0.15 mg/L (0.59 vs. 0.79 mg/L,	In 21 HIV+ subjects, **ATV 400 mg/SQV-hgc 1200 mg QD** led to higher proportion of patients with ATV Ctrough< IC90 vs. ATV 400 mg alone; SQV Ctrough <MEC in most patients. Additional dosage adjustment and/or RTV boosting may be required to optimize drug levels.[37] When ATV 300 mg added to **SQV 1600/r 100 mg QD** in 20 HIV+ subjects, SQV AUC ↑ 60%, Cmax ↑ 42%, Ctrough ↑ 112% (p <0.05) after 30 days. ATV levels were similar to those seen with ATV/r; total and indirect bilirubin ↑ by 5 times after 10 days of ATV therapy.[38] In TDM case series, **ATV 300/ SQV2000/rtv 100-200 mg QD** yielded ATV Ctrough levels approx. 6-fold higher (mean 749 and 899 ng/mL, respectively) vs. ATV 400 mg QD (mean 122 ng/mL).[28] In a healthy volunteer study, **ATV 200/SQV 1500 mg BID** led to ATV Cmin comparable to ATV 400 mg QD, while SQV Cmin	500/100 mg BID, or tipranavir 500/100 mg BID + atazanavir 300 mg QD showed 68% ↓ AUC, 81% ↓ Cmin of ATV, and 20% ↑ AUC, 75% ↑ Cmin of TPV when drugs were coadministered.[40] Combination not recommended.

	Atazanavir (Reyataz®)	Darunavir (Prezista®)	Fosamprenavir (Telzir®)	Lopinavir/ ritonavir (Kaletra®)	Ritonavir (Norvir®)	Saquinavir (Invirase®)	Tipranavir (Aptivus®)
			150/FPV 700/rtv 100 mg BID, 0.77-2.4 ug/mL in ATV 200/FPV 700/rtv 100 mg BID and 0.53-1.38 ug/mL in ATV 400/FPV 700 mg BID arms. Mean APV Ctrough was 1.19-2.71 ug/mL in ATV 150/FPV 700/rtv 100 mg BID, 1.23-2.71 ug/mL in ATV 200/FPV 700/rtv 100 mg BID and 0.81-2.43 ug/mL in ATV 400/FPV 700 mg BID arms.[27]	LPV concentrations were not affected by ATV.[32] In a separate kinetic study in HIV-positive subjects, this combination resulted in significantly ↑ LPV levels compared to historical controls, while ATV levels were similar to historical controls taking ATV 300/rtv 100 mg QD. Combination was well tolerated.[33] In a 2-phase kinetic study in HIV-infected men, **LPV/r 400/100mg BID and ATV 150mg BID** yielded mean LPV Cmin of 4644 ± 1965μg/L and AUC 87016 ± 27172μg/L.h, and ATV Cmin 1196 ± 433μg/L and AUC 21493 ± 6424μg/L.h.[29]	respectively, p=0.132). The 50 mg ritonavir dose was associated with a lower impact on serum lipids.[36]	was 0.129 ug/mL (75% were > 0.1 ug/mL).[39]	
Brecanavir (BCV)	In healthy adults, brecanavir 300 mg/rtv 100 mg BID plus atazanavir 300 mg QD led to 44% ↑ Cmin, 38% ↑ AUC and 48% ↑ Cmax of BCV, and 111%↑ Cmin, 44% ↑ AUC, 21% ↑ Cmax of ATV (compared to ATV 300/rtv 100 mg QD alone). Higher incidences of grade 4 bilirubin ↑ and premature study d/c with combination.			In healthy adults, brecanavir 300 mg BID plus lopinavir 400/100 mg BID led to 16% ↓ Cmin and AUC of BCV vs. BCV 300/rtv 100 mg BID alone; lopinavir exposures were not affected. Combination was well-tolerated, may be co-administered without dosage reduction.[41]			In healthy adults, a study of brecanavir 600 mg BID plus tipranavir 500/rtv 200 mg BID was stopped prior to collection of steady-state data due to asymptomatic LFT ↑ (all grades 1-2 except one subject with grade 3-4). All LFTs returned to baseline following study discontinuation. Do not co-administer this combination.[41]

	Atazanavir (Reyataz®)	Darunavir (Prezista®)	Fosamprenavir (Telzir®)	Lopinavir/ ritonavir (Kaletra®)	Ritonavir (Norvir®)	Saquinavir (Invirase®)	Tipranavir (Aptivus®)
	Reduction in ATV dose may be considered (dose recommendation not available).[41]						
Capravirine				Capravirine 700 mg BID plus lopinavir/r resulted in 79% ↓ CPV clearance, and 63% ↑ LPV clearance; recommend ↑ LPV/r to 533/133 mg BID when dosing with CPV 700 mg BID.[42]		Addition of SQV 1000 mg BID to dual PI regimen of CPV 400 mg BID plus LPV/r 400/100 mg BID or CPV 700 mg BID plus LPV/r 533/133 mg BID did not affect PK of either SQV or LPV. No further dosage adjustment needed.[43]	
Cobicistat (GS-9350, a CYP3A4 inhibitor lacking anti-HIV activity)	In healthy subjects, co-administration of either ritonavir 100 mg or cobicistat 150 mg plus atazanavir led to equivalent atazanavir exposures.[44]	In healthy subjects, co-administration of either **cobicistat 150 mg or ritonavir 100 mg plus darunavir 800 mg QD** for 10 days resulted in equivalent darunavir Cmax and AUC.[45] In healthy subjects, the kinetics of two fixed-dose tablets of **darunavir 800 mg/ cobicistat 150 mg** were compared to darunavir 800/ritonavir 100 mg QD given as single agents. Comparable bioavailability was demonstrated for darunavir Cmax and AUC, while Cmin was 26-31% ↓ with darunavir/cobicistat vs. darunavir/ritonavir. This difference was not felt to be clinically relevant.[46]					In a fixed-sequence crossover study, healthy volunteers received **tipranavir 500 mg BID** boosted **with** either **cobicistat 150 mg BID** or ritonavir 200 mg BID. In the presence of tipranavir, cobicistat AUC ↓ 90% vs. cobicistat 150 mg BID and tipranavir AUC ↓ 54%, Cmax ↓ 38%, Ctrough ↓ 86%.[47]

	Atazanavir (Reyataz®)	Darunavir (Prezista®)	Fosamprenavir (Telzir®)	Lopinavir/ ritonavir (Kaletra®)	Ritonavir (Norvir®)	Saquinavir (Invirase®)	Tipranavir (Aptivus®)
		In a fixed-sequence crossover study, healthy volunteers received **darunavir 600 mg BID boosted with either cobicistat 150 mg BID or ritonavir 100 mg BID**. When darunavir was boosted with cobicistat, darunavir exposures were bioequivalent to darunavir/ritonavir, while cobicistat AUC was 47% ↓ vs. cobicistat 150 mg BID alone. Coadministration of elvitegravir 150 QD or etravirine 200 mg BID did not affect darunavir concentrations, while EVG and ETV exposures were comparable to historical data.[47]					
Darunavir (TMC114, *substrate of CYP3A4)*	In healthy volunteers, ATV 300 mg QD plus darunavir/rtv 400/100 mg BID led to 50% ↑ Cmin, 11% ↓ Cmax and no change in AUC of ATV compared to ATV 300/rtv 100 mg alone. Ritonavir exposure ↑ 51-59% when ATV added to darunavir/rtv. There were similar rates of hyperbilirubinemia and elevated lipase levels when subjects were given ATV/r alone and in			Combination of **lopinavir/ritonavir 400/100 mg BID plus darunavir 300 mg BID** (as oral solution) led to a 53% ↓ darunavir relative bioavailability and 19% ↓ in lopinavir exposure. Addition of extra ritonavir 100 mg BID did not impact reduction of darunavir exposure, while LPV bioavailability ↑ 37%. In a pk study of HIV-	Kinetics of single-dose darunavir 800 mg increased in presence of ritonavir 600 mg BID; Cmax ↑ 2-fold, AUC ↑ 9-fold, C12 ↑ 30-fold.	Darunavir 400 mg BID plus saquinavir 1000/ritonavir 100 mg BID led to significant ↓ in darunavir exposure. darunavir Cmin ↓ 42%, Cmax ↓ 17%, AUC ↓26% with combination, while no significant changes in SQV kinetics were observed. Therefore, not recommended to combine SQV and darunavir /ritonavir.[50]	

	Atazanavir (Reyataz®)	Darunavir (Prezista®)	Fosamprenavir (Telzir®)	Lopinavir/ ritonavir (Kaletra®)	Ritonavir (Norvir®)	Saquinavir (Invirase®)	Tipranavir (Aptivus®)
	combination with DRV/r.[23, 48] ATV 300mg daily may be given with DRV/r BID without dose adjustment.			infected subjects, **darunavir 1200/rtv 100 mg BID plus LPV 400/100 mg BID** led to 9% ↑ AUC, 23% ↑ Cmin of LPV, but 38% ↓ AUC, 21% ↓ Cmax and 51% ↓ Cmin of darunavir. In the same study, **darunavir 1200 mg BID + LPV 533/rtv 133 mg BID** led to 9% ↑ LPV AUC but 41% ↓ darunavir AUC.[49] **Therefore, this combination is not recommended.**			
Delavirdine	Potential for increased atazanavir concentrations. Appropriate doses have not yet been established.		Amprenavir 1200 mg +/- delavirdine 600 mg BID (healthy volunteer study) significantly increased amprenavir concentrations (4-fold ↑ AUC, 6-fold ↑ Cmin, 1.3 fold ↑ Cmax); no change in delavirdine concentrations.[51] In a separate healthy volunteer multi-dose study, administration of APV 600 mg BID +/- DLV 600 mg BID resulted in ↑ APV Cmin 133% & AUC 117%; however, median DLV Cmin ↓ 88%. Suggest avoiding this dosage combination until further data	In a healthy volunteer study (n=26), DLV 600 mg BID plus lopinavir 400/100 mg BID resulted in higher lopinavir levels (Cmin ↑ 53%, AUC ↑ 24%, Cmax 13%); however, DLV exposure was ↓25-30%. Further studies are ongoing to establish optimal doses of both agents.[53]	70% ↑ RTV concentrations; kinetics of delavirdine and its metabolite unchanged with concomitant administration of full dose therapy.[54, 55] Similar effect (80% ↑ ritonavir AUC) seen in healthy volunteers given delavirdine 600 mg BID plus ritonavir 100 mg BID. No effect on delavirdine kinetic parameters[56]	Delavirdine 400 mg TID + saquinavir-hgc 600 mg TID in healthy volunteers: 5-fold ↑ SQV AUC, Cmin, Cmax; monitor LFTs during initial weeks of combination therapy. Dosage adjustments not necessary.[57]	

	Atazanavir (Reyataz®)	Darunavir (Prezista®)	Fosamprenavir (Telzir®)	Lopinavir/ ritonavir (Kaletra®)	Ritonavir (Norvir®)	Saquinavir (Invirase®)	Tipranavir (Aptivus®)
			available.[52]				
Didanosine	Simultaneous administration of atazanavir, ***didanosine tablets*** and stavudine resulted in 89% ↓ Cmax and 87% ↓ AUC of atazanavir; kinetics of didanosine and stavudine were not affected. When atazanavir was administered 1 hour apart from didanosine, atazanavir concentrations were not affected. Recommend giving ddI-tablets 30 minutes before or 2 hours after atazanavir (which is taken with food).[12] ***ddI-EC*** should be given 1.5 hours before or 2 hours after atazanavir (which is taken with food).	In healthy volunteers, didanosine 400 mg QD on an empty stomach and darunavir 600 mg/ritonavir 100 mg BID with food (2 hours after ddI intake) did not significantly affect plasma levels of either drug. No dosage adjustment is required.[58]	No significant changes in amprenavir AUC or Cmin observed when administered: • concurrently with ddI-EC (in fasting state) • concurrently with ddI tablets (in fasting state) • 1 hour prior to ddI tablets (fasting) compared to amprenavir alone in the fasting state. Authors suggest amprenavir may be dosed concurrently with both ddI tablets and enteric-coated capsules in the fasting state.[59]	Dosage adjustment not required. However, since didanosine needs to be administered on an empty stomach, it should be given 1 hour before or 2 hours after lopinavir/r (given with food).	13% ↓ ddI AUC. Clinical significance unknown.[60]	Dosage adjustment not required. However, since didanosine needs to be administered on an empty stomach, it should be given 1 hour before or 2 hours after saquinavir (given with a full meal).	Healthy volunteer, randomized, parallel group study (n=23) of either **TPV/r 500 mg/100 mg or TPV/r 750 mg/200 mg** plus **ddI EC** 400 mg daily. At steady state, 32% ↑ Cmax and 34%↓ C12h of TPV, although overall TPV AUC unchanged; no change in ddI PK observed.[61] **Suggest giving ddI EC 2 hours apart from TPV/r.**
Dolutegravir (DTG; S/GSK1349572, integrase inhibitor)	In a randomized, open-label, two-period, crossover study, healthy adult subjects received dolutegravir 30 mg QD for 5 days, followed by the addition of either atazanavir 300/100 mg QD or atazanavir 400 mg QD for 14 days. Coadministration with ATV/RTV resulted in ↑ AUC 62%, ↑ Cmax 34%	In an open-label, multiple dose, 2-period, 2-sequence crossover study, healthy subjects received dolutegravir 30 mg QD for 5 days followed by randomization to lopinavir/ritonavir 400/100 mg BID or darunavir/ritonavir 600/100 mg BID plus dolutegravir 30 mg QD for 14 days. In the presence of darunavir/ritonavir, dolutegravir AUC ↓	Healthy volunteers received dolutegravir 50 mg daily for 5 days followed by the addition of fosamprenavir/r 700/100 mg BID for 10 days. In the presence of fosamprenavir/r, dolutegravir AUC ↓ 35%, Cmax ↓ 24% and C_T ↓ 49%, while amprenavir pharmacokinetics were similar to historical values. Despite the	In an open-label, multiple dose, 2-period, 2-sequence crossover study, healthy subjects received dolutegravir 30 mg QD for 5 days followed by randomization to lopinavir/ritonavir 400/100 mg BID or darunavir/ritonavir 600/100 mg BID plus dolutegravir 30 mg QD for 14 days. Steady-state dolutegravir kinetics were not altered in			In an open-label, single sequence crossover study, healthy volunteers received dolutegravir 50 mg once daily for 5 days, then tipranavir/ritonavir 500/200 mg BID for 7 days, followed by dolutegravir 50 mg QD and tipranavir/ritonavir 500/200 mg BID for 5 days. In the presence of tipranavir/ritonavir, dolutegravir AUC ↓

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	and ↑ Ctrough 121% of dolutegravir. Coadministration with atazanavir 400 mg QD resulted in ↑ AUC 91%, ↑ Cmax 50% and ↑ Ctrough 90% of dolutegravir. The combinations were well tolerated. No dose adjustment is necessary when dolutegravir is coadministered with boosted or unboosted atazanavir.[62]	22%, Cmax ↓ 11% and Ctrough ↓ 38%; these changes were considered not clinically significant. No dosage adjustment for dolutegravir is required when used with darunavir/ritonavir.[63]	reductions, dolutegravir concentrations remained well above the protein-adjusted IC90 for wild-type HIV, and no dose adjustment is needed when dolutegravir is co-administered with fosamprenavir/r in integrase inhibitor-naïve subjects.[64]	the presence of lopinavir/ritonavir. No dosage adjustment for dolutegravir is required when used with lopinavir/ritonavir.[63]			59%, Cmax ↓ 46% and Ctrough ↓ 76%, likely via enzyme induction of UGT1A1 and CYP3A4. Four of 18 subjects discontinued the study due to increases in ALT during the TPV/r dosing alone. Dolutegravir concentrations remained 4-5 fold higher than the protein-adjusted IC90 for WT virus. No dose adjustment required for coadministration in integrase-naïve patients.[65]
Efavirenz	Study in healthy subjects of **ATV 400 QD** +/- efavirenz 600 mg QD with a light meal (n=27): ATV Cmax ↓ 59% and AUC ↓74% with concomitant EFV; EFV kinetics not significantly altered.[66] In a healthy volunteer study, coadministration of **atazanavir 300/ritonavir 100 mg QD** plus efavirenz x 2 weeks resulted in 39% ↑ atazanavir AUC vs. atazanavir 400 mg QD alone, while ATV 600 mg QD plus efavirenz resulted in 21% ↓ ATV AUC vs. ATV 400 mg QD	Multidose study of efavirenz 600 mg QD plus **darunavir (oral solution) 300 mg/ritonavir 100 mg BID** led to 31% ↓ Cmin and 13% ↓ AUC of darunavir, while EFV exposure ↑ 20%. Combination may be used without dose adjustments.[69] In a single sequence, 3-period PK study in healthy volunteers who received **DRV 900/r100 mg QD** x 10d, DRV/r + EFV 600 mg QD x 14d, then EFV x 14 d): • 57% ↓ Cmin, 14% ↓ AUC of darunavir • Mean 1138 vs. 2127 ng/mL,	In healthy volunteer study, **FPV 700/rtv 100 mg BID plus EFV** did not change APV levels vs. FPV/rtv alone. However, with **FPV 1395/rtv 200 mg QD**, addition of EFV led to 13% ↓ AUC, 36% ↓ Cmin of APV. Negative interaction corrected when rtv dose ↑ to 300 mg QD.[71] **Therefore, when coadministeringFPV/r and EFV: no change in FPV dose if BID regimen used; if QD, use FPV 1400 mg/rtv 300 mg QD.**	**<u>LPV/r capsules:</u>** Efavirenz 600 mg daily + lopinavir 400 mg/ritonavir 100 mg BID resulted in 25% ↓ AUC and 44% ↓ Cmin of lopinavir. Using lopinavir 533 mg/ritonavir 133 mg BID plus EFV resulted in similar lopinavir concentrations to those achieved in the absence of EFV.[72] **<u>LPV/r tablets:</u>** • Can use 400/100 mg BID with EFV in ARV-naïve subjects • ↑ to 600/150 mg (3 tablets) BID when co-administering in treatment-experienced	Healthy volunteer study of EFV 600 mg/day + RTV 500 mg BID: 21% ↑ EFV AUC, 17% ↑ RTV AUC. Based on these data, may use RTV 500 mg BID with EFV 600 mg daily; if RTV intolerance occurs, may consider RTV dosage reduction.[76]	Multiple dose healthy volunteer study of efavirenz 600 mg/day + SQV-sgc 1200 mg q8h: 12% ↓ efavirenz AUC (not clinically significant), and 62% ↓ SQV AUC.[77] Can avoid this negative interaction by adding ritonavir to combination at the following doses: • saquinavir-sgc 400 mg BID • ritonavir 400 mg BID • efavirenz 600 mg qhs[78]	Healthy volunteer open-label, randomized, parallel group study (n=68) of either **TPV/r 500 mg/100 mg or TPV/r 750 mg/200 mg** plus EFV 600 mg daily. PK sampling done after single dose and at steady state. At steady state, ↑ in TPV AUC, Cmax and C12h observed with EFV.[61] In a separate healthy subject study (n=16), EFV 600 mg QD plus **TPV/r 500/200mg BID** for 14 days did not result in clinically important changes on the steady state PK of TPV or RTV, and EFV AUC levels

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	alone.[67] In healthy subjects, **ATV 400/ ritonavir 100 mg QD** plus EFV results in ATV AUC and Cmax comparable to ATV/r 300/100 alone, but ATV Cmin ↓ 42%. **ATV Cmin may not be optimal for treatment experienced patients.** RTV Cmax ↓ 15%, AUC ↓ 31%, Cmin ↓ 60% with combination, which may have contributed to lower ATV exposures.[68]	p=0.0003; all Cmin>55 ng/mL • No difference in EFV PK Clinical significance in HIV-positive patients not yet determined, combination may provide sufficient efficacy in naïve-patients with no pre-existing mutations.[70]		subjects; this significantly ↑ lopinavir plasma concentrations ~35% and ritonavir concentrations ~56-92% compared to KALETRA tablets 400/100 mg twice-daily without efavirenz[73] • in 19 healthy volunteers, **LPV/r 500/125 mg BID** plus EFV 600 mg led to similar LPV levels as seen with LPV/r 400/100 mg BID alone (6% ↑ AUC, 10% ↓ Cmin)[74] • QD lopinavir/rtv in the presence of NNRTIs may not provide adequate lopinavir Ctrough[75]			were comparable to historical controls.[79] May consider using TPV/RTV plus EFV without further dosage adjustment.
Elvitegravir (GS-9137, integrase inhibitor)	Randomized, crossover, multiple dose study in healthy subjects (n=14) assessed EVG/ATV 300mg/400mg daily vs. EVG/r 300mg/100g daily: ATV and RTV showed similar inhibition of CYP 3A activity using midazolam probe. ATV + EVG vs historical controls: ↓ ATV AUC 30%, ↓ ATV Cmin: 46% - ? potential of EVG to induce ATV	In a crossover study, healthy volunteers were randomized to receive either elvitegravir 125 mg/ritonavir 100 mg QD, darunavir 600 mg/ritonavir 100 mg BID, or elvitegravir 125 mg QD plus darunavir 600 mg/ritonavir 100 mg BID, each for 14 days. Treatment was well tolerated, and there were no clinically-relevant effects on PK parameters for either drug suggesting that this combination can	Healthy volunteers were randomized to receive either elvitegravir 125 mg/ritonavir 100 mg QD followed by elvitegravir 125 mg QD plus fosamprenavir 700 mg/ritonavir 100 mg BID, or fosamprenavir 700 mg/ritonavir 100 mg BID followed by elvitegravir 125 mg QD plus fosamprenavir 700 mg/ritonavir 100 mg BID, each for 14 days. Treatment was well tolerated, and	Healthy volunteers (n=27) were randomized to receive either elvitegravir (EVG)/ritonavir 125/100mg QD for 2 weeks, then EVG/r 125/100 mg QD plus LPV/r 400/100mg BID for 2 weeks (group 1) or LPV/r 400/100mg BID for 2 weeks, then EVG/r 125/100 QD plus LPV/r 400/100mg BID for 2 weeks (group 2). EVG exposures were significantly increased in the	In healthy volunteers, ritonavir doses of 50, 100, and 200 mg plus elvitegravir 125 mg led to 41%, 54% and 56% ↓, respectively in apparent oral clearance of elvitegravir relative to 20 mg ritonavir. A ritonavir dose approaching 100 mg provided maximal inhibition of CYP activity. These data support a once-daily ritonavir dose of 100 mg when combined with elvitegravir.[85]		In a crossover study, healthy volunteers were randomized to receive either elvitegravir 200 mg/ritonavir 100 mg QD, tipranavir 500 mg/ritonavir 200 mg BID, or elvitegravir 200 mg QD plus tipranavir 500 mg/ritonavir 200 mg BID, each for 14 days. Treatment was well tolerated, and there were no clinically relevant effects on PK parameters for either drug suggesting that this combination can

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	metabolism. This requires further study. ATV 400mg daily has potential to boost EVG levels when RTV sparing regimen desired.[80] Two kinetic studies in healthy subjects: • **EVG 200/100mg QD** plus **ATV/r 300/100mg QD** led to ↑ EVG exposures vs. EVG 200/100mg QD alone, likely via inhibition of UGT1A1/3 metabolism by ATV/r. ATV exposure was modestly ↓ vs. ATV/r 300/100mg daily alone. • **EVG 85/100 mg daily + ATV/r 300/100mg QD** led to equivalent EVG exposures compared to the usual EVG 150mg daily dose; ATV exposure unchanged compared to ATV/r 300/100mg alone. Authors state an 85mg dose of EVG should be used when given with ATV/r.[81]	be co-administered without dose adjustment.[82]	there were no clinically relevant effects on PK parameters for either drug suggesting that this combination can be co-administered without dose adjustment.[83]	presence of LPV/r: 75% ↑ $AUC_{tau,}$ 52% ↑ Cmax, 1382% ↑ Ctau, possibly via inhibition of UGT1A1/3 metabolism. LPV and RTV exposures were unchanged. Based on simulations, the authors recommend the dose of EVG be ↓ to 85mg daily when used with LPV/r.[84]			be co-administered without dose adjustment.[82]
Enfuvirtide	No clinically significant interaction expected.	Analysis of PK data of 292 subjects in the POWER 3 trial showed no interaction between enfuvirtide and darunavir.[86]	No clinically significant interaction expected.	No clinically significant interaction expected. In the RESIST-1 and-2 studies, median lopinavir Cmin was 19%	No clinically relevant interaction noted with co-administration of enfuvirtide 90 mg SC BID and ritonavir 200 mg BID for 4 days in 12 HIV-	No clinically relevant interaction noted with co-administration of enfuvirtide 90 mg SC BID and saquinavir 1000 mg/ ritonavir 100 mg BID	In a series of 39 subjects taking TPV/r with or without concomitant enfuvirtide, serial TPV Ctroughs were obtained (average 3.4/pt). In subjects

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		In 11 patients receiving darunavir 600/100 mg BID plus enfuvirtide, darunavir concentrations were measured before and 24 weeks after enfuvirtide was replaced by raltegravir. Following the switch to raltegravir, darunavir Cmin ↓ 33%, Cmax ↓ 32% and AUC ↓ 37%; no significant changes in ritonavir kinetics were noted. Mechanism and clinical significance of this interaction are not clear.[87]		higher in the LPV/r plus enfuvirtide arm (n=60) compared to the LPV/r without enfuvirtide arm (n=240): i.e., 5.12 ug/mL vs. 3.84 ug/mL, respectively. Despite this, ALT elevation rates and investigator-reported rates of clinical hepatic events were lower in the comparator PI/r plus enfuvirtide arm compared to the comparator PI/r without enfuvirtide.[88]	infected subjects.[89]	for 4 days in 12 HIV-infected subjects.[89] In the RESIST-1 and-2 studies, median saquinavir Cmin was 39% higher in the SQV/r plus enfuvirtide arm (n=27) compared to the SQV/r without enfuvirtide arm (n=110): i.e., 0.49 ug/mL vs. 0.38 ug/mL, respectively. Despite this, ALT elevation rates and investigator-reported rates of clinical hepatic events were lower in the comparator PI/r plus enfuvirtide arm compared to the comparator PI/r without enfuvirtide.[88]	receiving both TPV/r and ENF, TPV Ctrough ↑ 53% and RTV Ctrough ↑ 55% compared to those on TPV/r without ENF. In 3 cases, the addition or removal of ENF led to changes in TPV levels that reflected this trend. Mechanism and clinical significance unclear.[90] Similarly, in 7 patients receiving tipranavir/ritonavir plus enfuvirtide, tipranavir concentrations were measured before and 24 weeks after enfuvirtide was replaced by raltegravir. Following the switch to raltegravir, tipranavir Cmin ↓ 31%, Cmax ↓ 57% and AUC ↓ 43%; no significant changes in ritonavir kinetics were noted. Mechanism and clinical significance of this interaction are not clear.[87] A separate kinetic study conducted in 12 HIV-positive patients (8 with and 4 without ENF) did not show a significant difference in TPV levels between the 2 groups.[91]

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							In the RESIST-1 and-2 studies, median tipranavir Cmin was 31% higher in the TPV/r plus enfuvirtide arm (n=154) compared to the TPV/r without enfuvirtide arm (n=507): i.e., 41.34 umol/L vs. 27.53 umol/L, respectively. Despite this, rates of grade 3-4 transaminase elevations were significantly lower in the TPV/r plus enfuvirtide arm compared to the TPV/r without enfuvirtide ($p<0.05$).[88]
Etravirine, TMC125, *(diaminopyrimi-dine NNRTI; inducer of CYP3A)*	In healthy subjects (n=14), **ATV 400 mg QD** administered with etravirine 800 mg BID (old formulation) for 7 days resulted in 47% ↑ Cmax , 50% ↑ AUC and 58% ↑ Cmin of TMC125, while atazanavir AUC ↓ 17% and Cmin ↓ 47%.[92] Combination of unboosted atazanavir and etravirine is not recommended.[93] In healthy subjects, **ATV 300/rtv 100 mg QD** plus TMC125 800 mg BID (old formulation) led to 100% ↑ AUC and	Pharmacokinetic interaction study of etravirine 200 mg BID added to **darunavir 600/100 mg BID** in HIV-infected subjects (n=10) led to ~30% ↓ AUC of etravirine compared to historical controls, not considered clinically significant. Kinetics of darunavir were unchanged.[95] Similar interaction observed in healthy subjects.[96] A pharmacokinetic substudy was conducted in 10 HIV-positive subjects participating in the ANRS TRIO study.	In an open-label interaction trial of HIV-infected subjects on stable FPV 700/rtv 100 mg BID, addition of etravirine 800 mg BID for 14 days (phase II formulation) led to 69% ↑ AUC, 62% ↑ Cmax and 77% ↑ Cmin of amprenavir compared to FPV/rtv alone. Etravirine parameters were similar to historical controls.[99] Etravirine should not be co-administered with fosamprenavir/ ritonavir.[93]	In healthy volunteers, coadministration of etravirine 200 mg BID and lopinavir/ritonavir tablets 400/100 mg BID for 8 days resulted in 45% ↓ Cmin, 30% ↓ Cmax and 35% ↓ AUC of ETV, and 20% ↓ Cmin, 11% ↓ Cmax and 13% ↓ AUC of LPV compared to each drug administered alone.[100] Because the ↓ in mean ETV exposures in the presence of LPVr is similar to the ↓ observed in the presence of	Single dose etravirine 400 mg plus steady-state ritonavir 600 mg BID (n=11) resulted in 46% ↓ AUC and 32% ↓ Cmax of etravirine, likely due to induction of glucuronidation.[102] Ritonavir concentrations not measured. Etravirine should not be co-administered with ritonavir 600 mg BID.[93] In healthy volunteers, there was no evidence of a pharmacokinetic interaction between **single-dose etravirine 200 mg**	Etravirine AUC ↓ 33% when co-administered with **saquinavir 1000/ritonavir 100 mg BID**. No dose adjustments required.[93] Etravirine 900 mg BID at steady state plus **single-dose saquinavir 1200 mg** (n=12) resulted in 52% ↓ AUC and 46% ↓ Cmax of saquinavir, likely due to CYP3A induction.[102] Etravirine concentrations not measured. Etravirine should not be administered with unboosted PIs. [93]	In randomized, cross-over study in healthy subjects, etravirine 800 mg BID plus TPV 500/rtv 200 mg BID led to significant reductions in etravirine concentrations (71% ↓ Cmax, 76% ↓ AUC, 82% ↓ Cmin), while TPV exposure was slightly increased (18% ↑ AUC, 14% ↑ Cmax, 24% ↑ Cmin).[104] Do not co-administer tipranavir/ritonavir and etravirine. [93]

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	26% ↑ Cmin of etravirine, while atazanavir AUC ↓ 14% and Cmin ↓ 38%.[92] HIV-infected subjects on stable ATV 300/100 mg QD regimens (not including tenofovir) were randomized to receive either **ATV 300/100 mg QD or 400/100 mg QD with etravirine 200 mg BID**. In the presence of etravirine, ATV 300/100 mg dosing led to 4% ↓ AUC and 18% ↓ Cmin of atazanavir, and 1.24-fold ↑ etravirine AUC. In ATV 400/100 mg group, there was no change in AUC and 9% ↓ Cmin of atazanavir while etravirine AUC was ↓ 16% with coadministration. These changes were smaller than interaction observed previously in healthy volunteers.[94] *NB: etravirine concentrations were compared to historical data from the DUET studies where etravirine was administered with darunavir/r BID. Coadministration is contraindicated in the US & Canadian	Patients received raltegravir 400 mg BID and **darunavir 600/100 mg BID** on day 1, and etravirine 200 mg BID was added on day 7. PK parameters were measured on days 6 and 28. Raltegravir and darunavir PK (Cmax, Cmin and AUC) were not significantly different in the presence of etravirine.[97] In a phase II single arm study, ARV-naïve HIV-infected subjects received **etravirine 400 mg QD, darunavir 800/100 mg QD**, or the combination (plus tenofovir/FTC) each for 14 days. There was no change in ETV pk in the presence of DRV/r. Mean ETV Cmin was >50x higher than protein-adjusted EC50 for WT virus, with and without DRV/r. DRV pk was slightly higher and RTV was slightly lower vs. historical controls (ARTEMIS week 4 pk substudy).[98] Combination may be coadministered without dose adjustment.[93]		darunavir/ ritonavir, ETV and LPVr may be co-administered without dose adjustment.[93] Etravirine 800 mg BID did not affect kinetics of **LPV 400/RTV 100/SQV 800-1000 mg BID** in 15 HIV-infected male subjects.[101]	**and single-dose ritonavir 100 mg** administered either simultaneously after breakfast, or when ritonavir was given 4 hours before or after etravirine. Simultaneous administration of ritonavir 400 mg plus etravirine 200 mg also had no effect on etravirine exposure relative to ritonavir 100 mg.[103]	Etravirine 800 mg BID did not affect kinetics of **LPV 400/RTV 100/SQV 800-1000 mg BID** in 15 HIV-infected male subjects.[101]	

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	Monographs,[93] but the European SPC says they can be coadministered without dose adjustment.						
Fosamprenavir (FPV)	Combination of ATV with amprenavir in HIV-infected peripheral blood mononuclear cells yielded additive to moderately synergistic antiviral effects.[24] In healthy subjects, **ATV 300 mg QD plus FPV 700/100 mg BID** showed no significant change in amprenavir concentrations and ATV Ctrough, and 24% ↓ Cmax and 22% ↓ AUC of ATV.[25] In a healthy volunteer study, ATV 400/FPV 1400 mg QD for 14 days yielded APV Cmin comparable to FPV 1400 mg BID, while ATV AUC ↓ 33%, C_{24} ↓ 57% vs. ATV 400 mg QD alone.[26] In a case series of treatment-experienced patients, 14 subjects received **ATV 150 or 200/FPV 700/rtv 100 mg BID** (9 were on concomitant tenofovir/FTC); three patients received			**<u>LPV/r capsules:</u>** • In a healthy volunteer multi-dose study, **LPV/r + APV 750 mg BID** gave similar APV AUC, and 4.6-fold ↑ Cmin vs. APV 1200 mg BID alone. However, LPV and RTV conc. were ↓ in presence of APV (LPV AUC ↓ 38%, Cmin ↓57%).[105] • Similar findings observed in cohort of HIV+ subjects with both APV and FPV formulations.[106 107] **Optimal doses for co-administration not yet defined. Separating LPV and FPV doses by 4 or 12 hours did not improve APV conc.[108] Suggest TDM when using this combination.**[109] In an open-label study of HIV-positive subjects stabilized on either **APV 750 mg BID + LPV/r 533/133 mg BID** or **FPV 1400 mg BID +**	In healthy volunteers, **FPV 1400mg/rtv 100 mg BID** led to 54% ↑ AUC, 26% ↑ Cmin of APV vs. FPV 700/rtv 100 mg BID regimen. **FPV 1400 mg/rtv 200 mg BID** led to 26% ↑ AUC, 32% ↑ Cmin of APV but ↑ incidence of ALT, AST elevations, and therefore is not recommended.[111] In a healthy volunteer pharmacokinetic study, **FPV 1400/rtv 100 mg QD** led to 10% ↓AUC, 38% ↓ Cmin of APV vs. FPV 1400/rtv 200 mg QD, although Cmin remained 5.9-fold higher than IC50 WT.[112] In both a retrospective cohort (n=51) of patients taking FPV 1400 mg/ritonavir 100-200 mg QD,[113] and in a prospective, open-label study of 12 HIV-infected subjects stabilized on FPV 1400 mg/rtv 200 mg QD then switched to FPV	In a group of 18 HIV+ subjects, **SQV-hgc 1000/FPV 700 mg BID plus either RTV 100-200 mg BID** resulted in: - non-sig. ↓ in SQV AUC_{0-12}, C_{trough} and C_{max} (14%, 24%, 9% respectively) with RTV 100 mg BID - non-sig. ↑ in SQV AUC_{0-12}, C_{trough} and C_{max} (12%, 3%, 20% respectively) with RTV 200 mg BID FPV levels not affected by SQV co-administration.[116] May wish to consider TDM if using RTV 100 mg BID dose with this combination.	Pharmacokinetic analysis in treatment-experienced subjects taking TPV 500 mg/APV 600 mg/rtv 200 mg BID showed 45% ↓ AUC, 40% ↓ Cmax, 56% ↓ Cmin of APV compared to APV 600/rtv 200 mg BID alone.[117] In a series of HIV-positive patients receiving TPV 500/FPV 1400/rtv200 mg BID, therapeutic LPV levels (>1.25 ug/mL) were observed in 67% of subjects.[118] Use combination with caution, and consider therapeutic drug monitoring if available.

	Atazanavir (Reyataz®)	Darunavir (Prezista®)	Fosamprenavir (Telzir®)	Lopinavir/ ritonavir (Kaletra®)	Ritonavir (Norvir®)	Saquinavir (Invirase®)	Tipranavir (Aptivus®)
	ATV 400/FPV 700 mg BID. All regimens produced ATV and APV C_{trough} well above the minimum acceptable concentrations. Mean ATV Ctrough was 0.96-1.66 ug/mL in ATV 150/FPV 700/rtv 100 mg BID, 0.77-2.4 ug/mL in ATV 200/FPV 700/rtv 100 mg BID and 0.53-1.38 ug/mL in ATV 400/FPV 700 mg BID arms. Mean APV Ctrough was 1.19-2.71 ug/mL in ATV 150/FPV 700/rtv 100 mg BID, 1.23-2.71 ug/mL in ATV 200/FPV 700/rtv 100 mg BID and 0.81-2.43 ug/mL in ATV 400/FPV 700 mg BID arms.[27]			**LPV/r 533/133 mg BID**, switching from APV to FPV resulted in steady-state ↑ APV C_{max} 75%, C_{min} ↑58% and AUC_{tau} ↑ 76%. No change in tolerability was observed.[110] **<u>LPV/r tablets:</u>** • Can use 400/100 mg BID with FPV in ARV-naïve subjects • May ↑ to 600/150 mg (3 tablets) BID when co-administering in treatment-experienced subjects	1400 mg/rtv 100 mg QD for 4 weeks,[114] median amprenavir exposures were not statistically different between the 100 mg and 200 mg ritonavir doses. Ritonavir ↑ plasma APV to similar extent with either APV or FPV. Therefore, FPV may replace APV, and metablic APV interactions are applicable to FPV.[115]		
Indinavir	Combination ATV with indinavir in HIV-infected peripheral blood mononuclear cells yielded additive to moderately synergistic antiviral effects.[24] However, **combination not recommended** due to the risk for additive hyperbilirubinemia.[1]		Single dose study: 31%↑ Cmax and 18% ↑ AUC of amprenavir, 35% ↓ AUC and 23% ↓ Cmax of indinavir. Multiple-dose study: 33% ↑ APV AUC, 38% ↓ IDV AUC, 27% ↓ Cmin. No dosage adjustments recommended for either drug.[119] In HIV-infected subjects receiving indinavir 800/ritonavir 100 mg BID, addition of fosamprenavir 700 mg BID for 5 days	**Indinavir 800 mg BID + LPV/r:** In HIV+ subjects (n=5), steady-state PK of combination yielded IDV PK similar to IDV 800/r 100 mg BID; median LPV PK slightly ↓ than expected.[121] **Indinavir 600 mg BID + LPV/r:** <u>Healthy volunteer study</u>: similar IDV AUC, ↓ Cmax, 3.5-fold ↑ Cmin vs. IDV 800 mg q8h alone; LPV kinetics not affected.[122, 123] <u>HIV+ subjects</u>: In an open-label PK study (n=11), both IDV &	***IDV/RTV 400/400 mg BID*** in healthy volunteers yielded indinavir AUC similar to those achieved with IDV 800 mg po q8h alone.[127] Also improved IDV PK profile: 62% ↓ Cmax, 3-fold ↑ Cmin, less impact of food on IDV absorption when given with RTV vs. alone,[128] ↓ nephrolithiasis in one case series.[129] ***IDV 800/RTV 100-200 mg BID*** also results in ↑ IDV trough levels compared to those	Hgc: 5- to 8-fold ↑ SQV AUC;[140] in vitro study suggests synergy at low doses and antagonism at high doses.[141] Sgc: 620% ↑ SQV AUC (1200 mg SQV single dose + IDV 800 mg q8h x 2 days); no apparent clinically relevant changes to IDV.[142]	Potential for decreased indinavir concentrations secondary to enzyme induction by tipranavir. Optimal dosages for co-administration have not yet been established.

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			resulted in 20% ↓ Cmax, 30% ↓ AUC and 20% ↓ C12 of indinavir, but these differences were not statistically significant. Median amprenavir levels (AUC 46.5 hr*mg/L, C12 2852 ng/mL) were comparable to historical controls. This dosage combination appears to be pharmacokinetically compatible.[120]	LPV PK parameters ↓ up to 64% vs. values seen with coadministration in healthy subjects.[124] **Indinavir 400 mg BID + LPV/r:** In a case series of HIV+ men taking lopinavir/r, addition of indinavir 400 mg BID did not significantly alter median lopinavir kinetics; indinavir Cmin were above target in 5/8 subjects.[125] A separate study showed no significant changes in LPV or IDV Cmin with combination.[126]	with IDV 800 mg q8h alone;[130, 131] however, ↑ IDV peak levels[132], possible ↑ risk nephrolithiasis[133] or other adverse events.[134] IDV 600/RTV 200 mg BID may provide increased IDV Cmin without significantly increasing IDV Cmax.[135] ***IDV 400/RTV100 mg BID*** (open study, n=17): ↑ Cmin (~0.5 ug/mL), ↓ Cmax vs. IDV 800mg q8h.[136] Preliminary data on ***once daily dosing*** (1200/100-200 mg IDV/RTV) regimens show ↑ Cmax, and Cmin = those with 800 mg q8h.[137, 138] 1200/200mg QD regimen well-tolerated in naïve-subjects (n=40) up to 24 weeks; 1200/400 QD also under study.[139]		
Lersivirine (UK-453,061, a next-generation NNRTI. Primarily metabolized via UGT2B7, weak inducer of CYP3A).	In healthy subjects receiving either **atazanavir 400 mg QD or atazanavir 300/100 mg QD** plus lersivirine 500 mg BID or placebo for 12 days, atazanavir concentrations were not significantly affected by lersivirine. With unboosted atazanavir, AUC ↓ 2%, Cmax ↑ 3%, Cmin ↓ 18%, while	In healthy subjects receiving lersivirine 1000 mg QD with or without darunavir 600 mg/ritonavir 100 mg BID for 10 days, lersivirine AUC ↓ 22% and Cmax ↓ 17% in the presence of darunavir/rtv. A dose increase of lersivirine may be required if co-administering with darunavir/ ritonavir.[144]					

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	with boosted atazanavir, AUC ↓ 0.6%, Cmax ↑ 2%, Cmin ↓ 7% in the presence of lersivirine.[143]						
Lopinavir/ ritonavir (capsules)	In TDM case series, **ATV 300/ LPV 800/rtv 200 mg QD** yielded ATV Ctrough levels approx. 5-fold higher (mean 736 ng/mL) vs. ATV 400 mg QD (mean 122 ng/mL).[28] In a 2-phase kinetic study in HIV-infected men, this dosing combination yielded steady-state ATV Cmin of 541 ± 245 ng/mL and LPV Cmin 1424 ± 1423 ng/mL.[29] A small study in HIV-infected subjects on either stable **ATV 300/100 mg QD or LPV 400/100 mg BID** showed no changes in ATV concentrations and slight decreases in LPV exposure (16% ↓ AUC, 35% ↓ Cmin) when drugs were coadministered.[30] In HIV-negative subjects, **ATV 300 mg QD plus LPV/r 400/100 mg BID** led to 45% ↑ ATV Cmin (no change in AUC or Cmax) compared to ATV 300 mg/rtv	Combination of **lopinavir/ritonavir 400/100 mg BID plus darunavir 300 mg BID** (as oral solution) led to a 53% ↓ darunavir relative bioavailability and 19% ↓ in lopinavir exposure. Addition of extra ritonavir 100 mg BID did not impact reduction of darunavir exposure, while LPV bioavailability ↑ 37%. In a pk study of HIV-infected subjects, **darunavir 1200/rtv 100 mg BID plus LPV 400/100 mg BID** led to 9% ↑ AUC, 23% ↑ Cmin of LPV, but 38% ↓ AUC, 21% ↓ Cmax and 51% ↓ Cmin of darunavir. In the same study, **darunavir 1200 mg BID + LPV 533/rtv 133 mg BID** led to 9% ↑ LPV AUC but 41% ↓ darunavir AUC.[49] **Therefore, this combination is not recommended.**	In a healthy volunteer multi-dose study, **LPV/r + APV 750 mg BID** gave similar APV AUC, and 4.6-fold ↑ Cmin vs. APV 1200 mg BID alone. However, LPV and RTV conc. were ↓ in presence of APV (LPV AUC ↓ 38%, Cmin ↓57%).[105] Similar findings observed in cohort of HIV+ subjects with both APV and FPV formulations.[106 107] **Optimal doses for co-administration not yet defined. Separating LPV and FPV doses by 4 or 12 hours did not improve APV conc.[108] Suggest TDM when using this combination.**[109] In an open-label study of HIV-positive subjects stabilized on either **APV 750 mg BID + LPV/r 533/133 mg BID** or **FPV 1400 mg BID + LPV/r 533/133 mg BID**, switching from APV to FPV resulted in steady-state ↑		In HIV+ subjects dosed for 24 weeks, lopinavir/ritonavir at 400/100 mg BID provides mean lopinavir exposures at least 30-fold above the protein binding-adjusted IC50 for wild-type virus.[145] In a retrospective cohort of subjects (n=12) taking ritonavir 100 mg BID with various protease inhibitors, ritonavir Cmin was approx. 3-fold lower when combined with lopinavir vs. saquinavir or indinavr.[146] Clinical relevance of these data is unclear, since ritonavir is only used for kinetic-enhancing purposes, and lopinavir levels remained therapeutic. No additional dosage adjustments recommended at this time. Pilot study in ARV-experienced subjects (n=33) of higher dose LPV: - LPV/r 667/167 mg (i.e., five 133/33 mg LPV/r caps)	**Saquinavir-hgc 600-800 mg BID + lopinavir/r:** In 12 HIV-positive, ARV-naive subjects, both SQV doses resulted in SQV PK parameters similar to historical data of SQV 1000/rtv 100 mg BID; LPV PK also not affected.[148]	Pharmacokinetic analysis in treatment-experienced subjects taking TPV 500 mg/LPV 400 mg/rtv 100 mg BID showed 49% ↓ AUC, 43% ↓ Cmax, 55% ↓ Cmin of LPV compared to LPV/r 400/100 mg BID alone. Clinical significance not established, no current dosage recommendations available.[117] In an open-label pilot study of 12 HIV-infected subjects on stable LPV/r, two dosing regimens were studied: a) TPV 500/LPV 400/rtv 300 mg BID b) TPV 500/LPV 533/rtv 233 mg BID LPV Ctrough were generally higher compared to LPV/r alone (7.05 ug/mL group A, 5.2 ug/mL group B vs. ~4 ug/mL), but greater interpatient variability was also observed.[149] In a series of HIV-positive patients

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	100 mg QD; LPV levels were not significantly different from historical controls.[31] A similar study in HIV-positive subjects yielded ATV AUC 38% ↓ similar Cmin vs. 300/100 mg (historical controls); LPV concentrations were not affected by ATV.[32] In a separate kinetic study in HIV-positive subjects, this combination resulted in significantly ↑ LPV levels compared to historical controls, while ATV levels were similar to historical controls taking ATV 300/rtv 100 mg QD. Combination was well tolerated.[33] In a 2-phase kinetic study in HIV-infected men, **LPV/r 400/100mg BID and ATV 150mg BID** yielded mean LPV Cmin of 4644 ± 1965μg/L and AUC 87016 ± 27172μg/L.h, and ATV Cmin 1196 ± 433μg/L and AUC 21493 ± 6424μg/L.h.[29]		APV C_{max} 75%, C_{min} ↑58% and AUC_{tau} ↑ 76%. No change in tolerability was observed.[110]		BID, OR - 400/300 mg (i.e., three 133/33 mg LPV/r caps and two 100 mg ritonavir) BID: LPV C_{trough} values were similar for both regimens, 60 to 70% higher compared with LPV/r 400/100 mg twice weekly.[147]		receiving TPV 500/LPV 533/rtv233 mg BID, therapeutic LPV levels (>3 ug/mL) were observed in 74% of subjects.[118] Use combination with caution, and consider therapeutic drug monitoring.
Lopinavir/ritonavir (tablets)			**<u>LPV/r tablets:</u>** • Can use 400/100 mg BID with FPV in ARV-naïve subjects May ↑ to 600/150 mg (3 tablets) BID				

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			when co-administering in treatment-experienced subjects				
Maraviroc	When maraviroc 300 mg BID was given with **atazanavir 400 mg QD,** maraviroc AUC ↑ 3.6-fold, Cmax ↑ 2.1-fold.[150] When maraviroc 300 mg BID was given with **atazanavir 300/ritonavir 100 mg QD**, maraviroc AUC ↑ 4.9-fold, Cmax ↑ 2.7-fold. Reduction of maraviroc dose by 50% in the presence of protease inhibitors/potent CYP3A4 inhibitors is recommended.[150] In 15 HIV-positive patients who received **maraviroc 150 mg plus atazanavir 300/100 mg daily** as part of a PK substudy of a randomized 48 week trial comparing MVC/ATVr vs ATVr + TDF/FTC, adequate maraviroc exposures were achieved at week 2: AUC 4330 ng.h/mL, Cavg 180 ng/mL, Cmax 650 ng/mL, Cmin 37 ng/mL. All subjects achieved the targeted Cavg >75 ng/mL for near maximal virologic	In healthy subjects, **maraviroc 150 mg BID plus darunavir 600/ritonavir 100 mg BID** resulted in 2.3-fold ↑ Cmax, 4-fold ↑ AUC of maraviroc vs. maraviroc administered alone. Reduce maraviroc dose to 150 mg BID when coadministering with darunavir/ ritonavir.[154] In a retrospective review, peak and trough levels were compared in HIV-positive patients taking either **maraviroc 300 mg BID** plus tenofovir/FTC, **maraviroc 300 mg QD plus darunavir 800/100 mg QD** or **maraviroc 150 mg QD plus darunavir 800/100 mg QD**. Maraviroc concentrations were comparable between the groups and all Ctrough >25 ng/mL. Cpeak did not exceed 1000 ng/mL and no cases of postural hypotension were noted. All darunavir concentrations were therapeutic.[155]	In healthy volunteers, combination of maraviroc 300 mg BID plus **fosamprenavir 1400 mg BID** led to reduced concentrations of both drugs:[157] • MVC AUC ↓13%, Cmax ↓ 11%, Cmin ↓28% • APV AUC ↓ 44%, Cmax ↓ 51%, Cmin ↓ 1% In same study, maraviroc plus **fosamprenavir 1400/ritonavir 100 mg QD** led to:[157] • MVC AUC ↓2%, Cmax ↓ 7%, Cmin ↓23% • APV AUC ↓ 21%, Cmax ↓ 32%, Cmin ↓ 36% while maraviroc plus **fosamprenavir 700/ritonavir 100 mg BID** led to:[157] • MVC AUC ↓66%, Cmax ↓ 70%, Cmin ↓54% • APV AUC ↓ 26%, Cmax ↓ 31%, Cmin ↓ 24% These data suggest that standard dose maraviroc may be used with fosamprenavir. In an open-label,	When maraviroc 100 mg BID was given with lopinavir/ritonavir 400/100 mg BID, maraviroc AUC ↑ 3.8-fold, Cmax ↑ 1.8-fold. Reduction of maraviroc dose to 50 mg BID resulted in maraviroc AUC ↑ 1.6-fold. Maraviroc 50% dose reduction in the presence of protease inhibitors/potent CYP3A4 inhibitors is recommended.[150] When maraviroc was given as 150 mg QD with lopinavir/ritonavir 400/100 mg BID in HIV-infected subjects (n=10), median (IQR) maraviroc concentrations were as follows: AUC_{24h} 4694 (3923-5516) hr*ng/ml, C_{avg} 179 (159 -221) ng/ml, C_{max} 601 (491-689) ng/ml, C_{min} 59 (39-64) ng/ml. All 10 subjects achieved the targeted C_{avg} (> 75 ng/ml).[159]	When maraviroc 100 mg BID was given with ritonavir 100 mg BID, maraviroc AUC ↑ 2.6-fold, Cmax ↑ 1.3-fold. Reduction of maraviroc dose to 50 mg BID gave similar exposures as maraviroc 100 mg BID alone. Maraviroc 50% dose reduction in the presence of protease inhibitors/potent CYP3A4 inhibitors is recommended.[150]	When maraviroc 100 mg BID was given with **saquinavir-sgc/ritonavir 1000/100 mg BID**, maraviroc AUC ↑ 8.3-fold, Cmax ↑ 4.2-fold. Reduction of maraviroc dose to 25 mg BID resulted in maraviroc AUC ↑ 1.4-fold. Maraviroc 50% dose reduction in the presence of protease inhibitors/potent CYP3A4 inhibitors is recommended.[150]	Combination of maraviroc 150 mg BID plus tipranavir 500/200 mg BID in healthy subjects did not lead to any significant changes in maraviroc exposure.[160] Regular dosing of maraviroc (i.e., 300 mg BID) may be used with tipranavir/ritonavir.

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	efficacy based upon exposure-response analysis from the MERIT study.[151] Week 24 interim analysis results of the randomized trial showed similar outcomes in both arms.[152] Modeling of maraviroc kinetics showed that **maraviroc 150 mg QD plus ATV 300/100 mg QD** in HIV-positive subjects yielded lower Cmax and Cavg but higher Cmin and effective constant concentrations compared to maraviroc 300 mg BID alone in healthy volunteers.[153]	Co-administration of **etravirine/darunavir/ritonavir with maraviroc** increased the exposure of maraviroc by 210% (AUC_{12}) and peak levels (C_{max}) by 77% compared to maraviroc alone. Thus, if maraviroc is being dosed alongside etravirine and darunavir together, a maraviroc dose reduction to 150mg twice daily is necessary. No dose adjustment of ETV is required.[156]	fixed sequence study in healthy volunteers, cohort 1 received **maraviroc 300 mg BID** alone, **fosamprenavir 700/100 mg BID** alone, then the combination. With coadministration, maraviroc AUC ↑ 2.49 fold, Cmax ↑ 52% and Ctau ↑ 4.74-fold, while amprenavir AUC ↓ 35%, Cmax ↓ 34% and Ctau ↓ 36%. In cohort 2, volunteers received **maraviroc 300 mg QD** alone, **fosamprenavir 1400/100 mg QD** alone, then the combination. With coadministration, maraviroc AUC ↑ 2.26 fold, Cmax ↑ 45% and Ctau ↑ 1.8-fold, while amprenavir AUC ↓ 30%, Cmax ↓ 29% and Ctau ↓ 15%. The combination was well tolerated. Further investigation of maraviroc 300 mg QD with fosamprenavir 1400/100 mg QD is suggested.[158]				
Nelfinavir			Amprenavir 800 mg q8h + nelfinavir 750 mg po q8h: 2.89-fold ↑ Cmin of APV (but no overall change in AUC) , 15%↑ NFV AUC. No dosage adjustment required	**LPV/r capsules:** • Multi-dose study in healthy volunteers of LPV/r 400/100 mg BID and NFV 1000 mg BID resulted in NFV concentrations	162% ↑ NFV AUC, 9% ↑ RTV AUC. [162] ***RTV 400 mg BID plus NFV 500-750 mg BID***: NFV AUC similar to that seen with NFV 750 mg TID alone;	SQV levels ↑, no significant changes in NFV concentrations with combination of SQV-hgc plus NFV. [166-168] Final 48-week analysis showed durable viral	Potential for decreased nelfinavir concentrations secondary to enzyme induction by tipranavir. Optimal dosages for co-administration have not yet been

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			for either drug.[119]	similar to those with NFV 1250 mg BID alone; LPV levels significantly ↓ in the presence of nelfinavir (LPV Cmax ↓ 21%, AUC ↓ 27%, Cmin ↓ 33%).[161] • LPV dosage may need to be adjusted if coadministered with nelfinavir. **LPV/r tablets:** • Can use 400/100 mg BID with NFV in ARV-naïve subjects • May ↑ to 600/150 mg (3 tablets) BID when co-administering in treatment-experienced subjects	M8 [ ] higher with NFV 750 BID regimen. Higher RTV AUC, Cmin values when combined with NFV 500 mg vs. 750 mg BID. Overall, PK benefits similar with 2 regimens.[163] ***RTV 100-200 mg BID added to NFV 1250 mg BID*** resulted in 30%↑ NFV AUC; steady-state a.m. predose NFV concentrations ↑ 45-90%.[164] In healthy volunteers, nelfinavir 2000 mg/ritonavir 200 mg once daily provided ↑ AUC, Cmax and comparable Cmin compared to nelfinavir 1250 mg BID.[165]	suppression with either SQV-hgc 600/NFV 750 mg TID or 1 g SQV/1250 mg NFV BID.[169]	established.
Nevirapine	In an open-label cohort study of HIV+ subjects stable on 2-3 NRTIs and either NVP 200 mg BID or ATV 300/rtv 100 mg QD, the NVP group received NVP plus ATV 300/100 mg QD for 10 days, then NVP plus ATV 400/100 mg QD for 10 days. Compared to the group that continued ATV 300/100 mg QD alone: • **NVP plus ATV/r 300/100mg** daily led to ↓ Cmax	In an open-label, randomized, crossover study, 19 HIV-positive subjects received nevirapine 200 mg BID plus NRTIs with or without darunavir (either 300/100 mg BID DRV oral solution or 400/100 mg BID DRV tablet) in two 14-day sessions. In the presence of DRV/r, NVP AUC ↑ 27%, while DRV and RTV exposures were similar to historical	In HIV+ subjects, **FPV 1400 mg BID + NVP** 200 mg BID for 14 days led to 33% ↓ AUC, 39% ↓ Cmin of APV, and 29% ↑ AUC and 34% ↑ Cmin of NVP.[174] When **FPV 700/rtv 100 mg BID** administered with NVP for 14 days, APV AUC ↓ 11%, Cmin ↓19%, NVP AUC ↑14%, Cmin ↑ 21% vs. controls.[174] Recommend **FPV 700/rtv 100 mg BID with NVP 200 mg**	**LPV/r capsules:** • Nevirapine ↓ lopinavir AUC and Cmin. Using lopinavir 533 mg/ritonavir 133 mg BID plus nevirapine will result in similar lopinavir concentrations to those achieved in the absence of nevirapine.[175] **LPV/r tablets:** • Can use 400/100 mg BID with NVP in ARV-naïve subjects	11% ↓ RTV AUC, no effect on NVP levels. Interaction considered clinically insignificant; no dosage adjustment suggested.[176] Preliminary data suggest that dosing nevirapine 400 mg once daily may have a more pronounced effect on decreasing ritonavir concentrations compared to nevirapine dosed 200 mg twice daily (median 31%	27%↓ SQV AUC; clinical significance unknown.[178] Preliminary data suggest that dosing nevirapine 400 mg once daily may have a more pronounced effect on decreasing saquinavir concentrations compared to nevirapine dosed 200 mg twice daily (median 31% decrease). These findings require further substantiation; may	Healthy volunteer study of 1250 mg TPV BID plus 200 mg BID NVP +/- 200 mg RTV BID:[179] • no sig. impact on TPV levels • NVP AUC ↓37% by TPV (stat. sig),; levels improved with addition of RTV • RTV clearance sig. ↑ in presence of TPV and NVP, but still higher than historical

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	38%, ↓ AUC 42%, ↓ Cmin 72% of ATV • **NVP plus ATV/r 400/100mg** daily led to 19% ↓ AUC and 59% ↓ Cmin of ATV. These ATV values were higher than historical ATV 400 mg QD alone. RTV AUC ↓ 40% in presence of NVP, which may have contributed to ↓ ATV levels, while ATV/r increased NVP AUC by 25%.[170] Open label, multiple dose study in HIV infected patients (n=11) to study the kinetics of **ATV/r 300mg/100mg** +/- NVP 200mg BID. Combination led to ↓ ATV levels: ↓ Ctrough 41% (631 vs 316ng/ml); ATV Ctrough remained higher than historical controls taking ATV 400mg daily; ↑ NVP Ctrough12 (GMR 1.46) compared to historical controls not taking ATV/r. Monitoring ATV Cmin is recommended, and a dose increase in ATV may be necessary.[171]	data.[172] In a population cohort analysis of 51 HIV-infected patients taking nevirapine (n=42 with other NRTIs, n=9 on concomitant darunavir/ritonavir), nevirapine Ctrough were 45% higher in the group taking darunavir/ritonavir vs. those on NRTIs only (p<0.05).[173] **No dose adjustment** is currently recommended, but literature indicates that changes in plasma NVP levels can lead to significant toxicity concerns, including hepatotoxicity. Monitor closely for dose-related nevirapine toxicity.[3]	**BID.**	• ↑ to 600/150 mg (3 tablets) BID when co-administering in treatment-experienced subjects	decrease). These findings require further substantiation; may consider monitoring ritonavir levels/response if switching nevirapine dosage regimen.[177]	consider monitoring saquinavir levels/response if switching nevirapine dosage regimen.[177]	controls May consider using TPV/RTV plus NVP without further dosage adjustment.
Raltegravir, MK-0518 (integrase inhibitor)	In two healthy volunteer studies, raltegravir kinetics	In an open-label, sequential 2-period study, 18 healthy	In an open-label, 3-period study, subjects received	Open label, 3 period, sequential, crossover, multiple	In a placebo-controlled, 2 period study in 12 subjects,		In an open-label, 3 period study in 15 healthy subjects,

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	were measured in the presence of steady-state boosted or unboosted atazanavir. In the presence of chronic **atazanavir 400 mg QD**, single dose **raltegravir 100 mg** resulted in raltegravir AUC ↑ 72%, Cmax ↑ 53%, C12 ↑ 95% compared to raltegravir alone. In an open-label, random order, crossover study, healthy volunteers received either RAL 400 mg BID or **RAL 400/ATV 400 mg QD** each for 7 days. In the presence of ATV, RAL Cmax ↑ 37% (p=0.4), Cmin ↓ 68% (P<0.001), AUC unchanged, and formation of RAL-glucuronide was significantly decreased. RAL pk showed high interindividual variability and significant intra-individual diurnal variation.[180] In an open-label, fixed sequence study, HIV-infected subjects received ATV 400 mg QD for 2 weeks, followed by **ATV 400/RAL 800 mg QD** for 10 days. Concomitant tenofovir, proton-	subjects received raltegravir 400 mg BID for 4 days followed by raltegravir 400 mg BID plus darunavir 600/ritonavir 100 mg BID for 12 days. Eight subjects developed rash (7 mild-moderate, 1 serious) between days 8-12 of period 2, and only six subjects completed the study. Based on limited data, raltegravir exposure appeared to be slightly decreased in the presence of darunavir/ritonavir (raltegravir AUC ↓ 29%, Cmax ↓ 33%, Cmin ↑ 38%), while darunavir parameters were similar to historical controls.[187] In 29 HIV-positive subjects receiving regimens including raltegravir, raltegravir/darunavir 600 mg/ritonavir 100 mg BID, or raltegravir/darunavir/ ritonavir/ etravirine BID, no differences in raltegravir Ctrough were noted between the groups.[188] 14 HIV-positive patients on stable cART with VL<50 copies/mL participated in a 3	raltegravir 400mg BID for 7days, then were randomized to 14 days of either fosamprenavir 1400mg BID, FPV/r 700mg/100mg BID, or FPV/r 1400mg/100mg QD alone or with RAL; subjects continued their randomized dose of FPV for 14 more days, adding or removing RAL based on receipt in Period 2. With fosamprenavir, raltegravir PK decreased, especially at higher RTV doses, but RAL GM C_{min} were 3-9.4-fold >RAL IC_{95} for WT HIV (14.6ng/mL). With RAL, amprenavir PK decreased modestly; APV GM C_{min} for FPV/r 700/100 BID and FPV/r 1400/100 QD were 2.1-7.8-fold >APV EC_{90} documented for PI-naïve HIV+ pts (228ng/mL). The clinical implications of these results have yet to be determined.[193]	dose study in healthy subjects (n=12) to investigate kinetics of RAL 400 mg BID +/- LPV/r 400 mg/100mg BID. LPV/r had no effect on RAL AUC (RAL alone VS combo: 5.3mg/L.h VS 5.4 mg/L.h) or Cmax (RAL alone vs combo: 1698ng/ml VS 1687 ng/ml). Concomitant use of LPV/r led to ↓ RAL C12h 30% (49.4ng/ml VS 34.4ng/ml). Raltegravir Cmin stayed above IC95 (15ng/ml). Dose adjustment not recommended.[194]	the combination of 400 mg raltegravir and 100 mg RTV BID did not affect raltegravir parameters compared to raltegravir 400 mg administered alone.[195]		addition of 400 mg raltegravir BID to steady-state TPV 500/rtv 200 mg BID for 4 days led to a 55% ↓ in raltegravir Cmin, while AUC ↓ 24% and Cmax ↓ 18%. The combination was generally well tolerated.[196] Although this result is borderline for clinical significance for C12 hr, there are considerable safety and efficacy data available for the concomitant use of tipranavir and raltegravir from the Phase III studies, which support the efficacy of this combination. There was no clinically meaningful difference in the efficacy profile of raltegravir with or without coadministration of tipranavir. Based on these data, tipranavir may be coadministered with raltegravir without dose adjustment. In an open-label study of 7 treatment-experienced patients initiating salvage therapy, optimized background therapy (OBT) and raltegravir 400 mg BID were initiated, with tipranavir

	Atazanavir (Reyataz®)	Darunavir (Prezista®)	Fosamprenavir (Telzir®)	Lopinavir/ ritonavir (Kaletra®)	Ritonavir (Norvir®)	Saquinavir (Invirase®)	Tipranavir (Aptivus®)
	pump inhibitors and other interacting drugs were not allowed. Compared to historical data of RAL 400 mg single dose, RAL Cmax ↑ 2.81-fold, AUC ↑ 18%, Ctrough ↓ 85%. 4/15 subjects had RAL Ctrough <33 nM. Atazanavir concentrations were not reported.[181] In an open-label, sequential, two-period study, 17 HIV-infected, virally suppressed subjects with no history of virologic failure received **ATV 600 mg daily** plus **RAL 400 mg BID** for 2 weeks then **800 mg daily plus ATV 600 mg QD** for 4 weeks, concomitantly with 3TC or FTC. The AUC over 24 hours of QD RAL was not significantly different from that of BID RAL, while the Cmax was 33% higher and Cmin was 81% lower with QD vs. BID RAL. Atazanavir kinetics were similar with both RAL dosing regimens. All patients maintained an undetectable viral load and the regimens were well tolerated.[182] Six HIV-infected	period, phase I pk study of TDF/FTC plus DRVr 800/100 mg QD (period 1), TDF/FTC/DRVr plus RAL 400 mg BID (period 2), and DRVr/RAL (period 3). Intensive PK were performed at steady-state in each period. No statistically significant differences in PK parameters were observed between period 2 versus 1. In period 3, darunavir Ctrough ↓ 36% and $t_{1/2}$ ↓ 31% compared to period 1, while DRV AUC, Cmax and RTV pk were not significantly changed. No difference in RAL pk was observed between periods 2 & 3. Four subjects had DRV Ctrough < 550 ng/mL (IC50 for PI-resistant virus) in period 3 only, all levels were >55 ng/mL.[189] In 15 HIV-positive subjects receiving **DRV 800/100 mg QD plus RAL 400 mg BID**, favourable pharmacokinetics of both drugs were observed and all patients had VL<37 copies/mL at week 24.[190] In 24 HIV-positive					500/ritonavir 200 mg BID added on 4 days later; intensive 12-hour PK was performed at days 4 and 19. In the presence of steady-state tipranavir/ritonavir, raltegravir AUC ↓ 28%, Cmax ↑ 5% and C12 ↑ 7% compared to raltegravir without TPV/r. At week 24, viral load was <50 in all patients (n=6) who completed the study; 1 patient discontinued at week 3 due to GI intolerance. Two subjects developed grade 3 transaminase elevations which resolved (1 spontaneously, one upon dose reduction to tipranavir 500/100 mg BID).[197]

	Atazanavir (Reyataz®)	Darunavir (Prezista®)	Fosamprenavir (Telzir®)	Lopinavir/ ritonavir (Kaletra®)	Ritonavir (Norvir®)	Saquinavir (Invirase®)	Tipranavir (Aptivus®)
	patients on **ATV 300/100 mg QD** were intensified **with RAL 400 mg QD** for 10 days. RAL exposure was adequate in most patients with only 1 Ctrough <15 ng/mL (IC95). Atazanavir concentrations were similar to historical controls and all Ctrough>150 ng/mL.[183] In 21 HIV-infected treatment-experienced subjects who switched to **ATV 200/RAL 400 mg BID** due to resistance or toxicity issues, mean ATV AUC was 6257 ng/mL.hr, Ctrough was 227 ng/mL (122-332), with 24% having ATV Ctrough <150 ng/mL. Mean RAL AUC was 9085 ng/mL.h and Ctrough 132 ng/mL. 62% subjects had VL<50 at study entry, all reached undetectable after 2 weeks.[184] In healthy subjects, coadministration of **atazanavir 300 mg BID and raltegravir 400 mg BID** resulted in 11% ↓ Cmax, 17% ↓ AUC and 29% ↓ Cmin of atazanavir compared to	subjects, no evidence of a pharmacokinetic interaction was found between **DRVr 800/100 mg QD plus RAL 400 mg BID or 800 mg QD**.[191] In 55 HIV-positive patients receiving darunavir-containing regimens with either NRTI or raltegravir, 117 darunavir Ctrough samples were measured. The mean (± sd) darunavir concentration was higher in the NRTI group as compared to the raltegravir group (4.20 ± 2.35 vs. 2.63 ± 1.84 mg/L, p=0.018). However, the proportion of subjects with VL<50 copies/mL was higher in the raltegravir vs. NRTI arm (76.5% vs. 44%, respectively, p=0.041). In a multivariate linear regression model, raltegravir was independently related to lower darunavir levels. The mechanism for this unexpected interaction is unclear, but does not appear to be virologically significant.[192]					

	Atazanavir (Reyataz®)	Darunavir (Prezista®)	Fosamprenavir (Telzir®)	Lopinavir/ ritonavir (Kaletra®)	Ritonavir (Norvir®)	Saquinavir (Invirase®)	Tipranavir (Aptivus®)
	atazanavir 300 mg BID alone; mean ATV Cmin was 817 ng/mL. Raltegravir AUC ↑ 54%, Cmax ↑ 39% and Cmin ↑48% when given with atazanavir. Mean QRS and PR interval increases were observed with atazanavir alone, and remained when raltegravir was coadministered; the clinical relevance of these changes is unclear.[185] In 22 HIV-positive subjects who switched to **atazanavir 300 mg BID plus raltegravir 400 mg BID**, steady-state pharmacokinetics were assessed. Geometric mean atazanavir AUC, Cmax and C12h were 14454 ng.h/mL, 2275 ng/mL and 419 ng/mL, respectively. Raltegravir geometric mean AUC, Cmax and C12 were 7112 ng.h/mL, 1680 ng/mL and 62 ng/mL, respectively. Three subjects (14%) had atazanavir Ctrough <100 ng/mL. At the time of switch, 79% of patients had VL<50 copies/mL; by 24 weeks, all subjects had						

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	undetectable viral loads.[186]						
Rilpivirine	Potential for ↑ concentrations of rilpivirine. Rilpivirine is not expected to affect the plasma concentrations of co-administered PIs.[198]	In a randomized, crossover study in healthy volunteers, subjects received either rilpivirine 150mg daily for 22 days, or darunavir 800/100mg QD for 11 days followed by DRV 800/100mg QD plus rilpivirine 150mg QD from days 12-22. Co-administration of DRV/r increased exposures of rilpivirine: AUC24h ↑ 2.3 fold; Cmax ↑ 1.79 fold, Cmin ↑ 2.78 fold, likely a result of CYP3A4 inhibition. No clinically relevant changes in DRV exposure were observed in the presence of rilpivirine.[199] No dose adjustment is required with coadministration.[198]	Potential for ↑ concentrations of rilpivirine. Rilpivirine is not expected to affect the plasma concentrations of co-administered PIs.[198]	In healthy volunteers, rilpivirine 150 mg QD plus LPV/r 400/100 mg BID resulted in 52% ↑ AUC, 29% ↑ Cmax, 74% ↑ Cmin of rilpivirine; LPV kinetics not affected.[200] No dose adjustment is required with coadministration.[198]		Potential for ↑ concentrations of rilpivirine. Rilpivirine is not expected to affect the plasma concentrations of co-administered PIs.[198]	Potential for ↑ or ↓ concentrations of rilpivirine. Rilpivirine is not expected to affect the plasma concentrations of co-administered PIs.[198]
Ritonavir	Additive-synergistic antiviral activity in vitro.[24] In healthy volunteer study, addition of **ritonavir 100-200 mg to ATV 200 or 400 mg** daily resulted in significantly ↑ ATV exposure.[34] Separate steady-state study in healthy volunteers (n=30) of **ATV**		In healthy volunteers, **FPV 1400mg/rtv 100 mg BID** led to 54% ↑ AUC, 26% ↑ Cmin of APV vs. FPV 700/rtv 100 mg BID regimen. **FPV 1400 mg/rtv 200 mg BID** led to 26% ↑ AUC, 32% ↑ Cmin of APV but ↑ incidence of ALT, AST elevations, and therefore is not recommended.[111]	In HIV+ subjects dosed for 24 weeks, lopinavir/ritonavir at 400/100 mg BID provides mean lopinavir exposures at least 30-fold above the protein binding-adjusted IC50 for wild-type virus.[145] In a retrospective cohort of subjects (n=12) taking ritonavir 100 mg BID	*Results from a cross-study analysis of ritonavir plus various protease inhibitors suggest that for a given PI dose, increasing the ritonavir dose will increase PI Cmin, while the PI Cmax remains relatively unchanged.[201] In other words, for dual protease inhibitor	***400 mg SQV/400 mg RTV BID:*** • 1587% ↑ SQV AUC[142, 202, 203], well tolerated.[204] ***1600 mg SQV-sgc/RTV 100 mg QD:*** • Preliminary data in healthy volunteers: 300-800% ↑ SQV AUC, Cmin > than with SQV-sgc 1200 mg TID.[205]	Open-label, dose-ranging study in healthy subjects of TPV 250, 500, 750, 1000, or 1250 mg BID + 100/200 mg RTV BID: TPV Cmax, AUC ↑ at least 4-fold and TPV Cmin ↑ at least 20-fold when combined with RTV. More consistent inhibition of CYP3A4 activity with RTV 200 mg vs. 100 mg dose.[209]

	Atazanavir (Reyataz®)	Darunavir (Prezista®)	Fosamprenavir (Telzir®)	Lopinavir/ ritonavir (Kaletra®)	Ritonavir (Norvir®)	Saquinavir (Invirase®)	Tipranavir (Aptivus®)
	300/ritonavir 100 mg QD with a light meal resulted in 1.86-fold ↑ Cmax and 3.38-fold ↑ AUC of ATV; ritonavir kinetics not affected.[35] Current dosage recommendation: atazanavir 300 mg/ ritonavir 100 mg QD with food. In a cross-over, single-blind, two period study, healthy volunteers received **ATV 300 mg with either RTV 100 mg or 50 mg** for 10 days, 15 days apart. Ritonavir Cmax and AUC were lower with the 50 mg dose vs. 100 mg dose and all/most RTV Ctrough were below the level of detection. No differences in ATV exposures were noted between the 50 vs 100 mg RTV dose treatments and all ATV Ctrough were >0.15 mg/L (0.59 vs. 0.79 mg/L, respectively, p=0.132). The 50 mg ritonavir dose was associated with a lower impact on serum lipids.[36]		In a healthy volunteer pharmacokinetic study, **FPV 1400/rtv 100 mg QD** led to 10% ↓AUC, 38% ↓ Cmin of APV vs. FPV 1400/rtv 200 mg QD, although Cmin remained 5.9-fold higher than IC50 WT.[112] In both a retrospective cohort (n=51) of patients taking FPV 1400 mg/ritonavir 100-200 mg QD,[113] and in a prospective, open-label study of 12 HIV-infected subjects stabilized on FPV 1400 mg/rtv 200 mg QD then switched to FPV 1400 mg/rtv 100 mg QD for 4 weeks,[114] median amprenavir exposures were not statistically different between the 100 mg and 200 mg ritonavir doses. Ritonavir ↑ plasma APV to similar extent with either APV or FPV. Therefore, FPV may replace APV, and metablic APV interactions are applicable to FPV.[115]	with various protease inhibitors, ritonavir Cmin was approx. 3-fold lower when combined with lopinavir vs. saquinavir or indinavr. [146] Clinical relevance of these data is unclear, since ritonavir is only used for kinetic-enhancing purposes, and lopinavir levels remained therapeutic. No additional dosage adjustments recommended at this time. Pilot study in ARV-experienced subjects (n=33) of higher dose LPV: - **LPV/r 667/167 mg** (i.e., five 133/33 mg LPV/r caps) **BID**, OR - **400/300 mg** (i.e., three 133/33 mg LPV/r caps and two 100 mg ritonavir) **BID**: LPV C_{trough} values were similar for both regimens, 60 to 70% higher compared with LPV/r 400/100 mg twice weekly.[147]	combinations involving ritonavir: • to increase PI Cmin, one should increase the ritonavir dose • to increase PI Cmax, AUC, one should increase the PI dose	• Kinetic substudy in 13 HIV+ subjects stabilized on combination showed equivalent SQV kinetic parameters (GMR of hgc/sgc for AUC 1.40, Cmax 1.23, and Cmin 1.46) when SQV-sgc replaced by SQV-hgc[206] • Intracellular t1/2 of SQV & RTV longer than plasma (median 4.5 & 5.9 hrs, p=0.034, and 4.1 & 6.2 hrs, p=0.033, respectively)[207] ***1000 mg SQV/100 mg RTV BID*:** • SQV-hgc/r gave significantly ↑ SQV levels vs. SQV-sgc/r (Cmin: 217 vs 153 ng/mL, p=0.0147, AUC 15798 ng.h/mL vs. 11655 ng.h/mL, p=0.0043); also significantly less GI side effects with SQV-hgc/r vs. SQV-sgc/r, possibly due to capmul content of SQV-sgc.[208]	
Saquinavir	Additive-synergistic antiviral activity in vitro.[24] In 21 HIV+ subjects,	Darunavir 400 mg BID plus saquinavir 1000/ritonavir 100 mg BID led to significant ↓ in	In a group of 18 HIV+ subjects, **SQV-hgc 1000/FPV 700 mg BID plus either RTV 100-200 mg**	**Saquinavir-hgc 600-800 mg BID + lopinavir/r:** In 12 HIV-positive, ARV-naive subjects,	***400 mg SQV/400 mg RTV BID:*** • 1587% ↑ SQV AUC[142, 202, 203], well tolerated.[204]		Pharmacokinetic analysis in treatment-experienced subjects taking TPV

	Atazanavir (Reyataz®)	Darunavir (Prezista®)	Fosamprenavir (Telzir®)	Lopinavir/ ritonavir (Kaletra®)	Ritonavir (Norvir®)	Saquinavir (Invirase®)	Tipranavir (Aptivus®)
	ATV 400 mg/SQV-hgc 1200 mg QD led to higher proportion of patients with ATV Ctrough< IC90 vs. ATV 400 mg alone; SQV Ctrough <MEC in most patients. Additional dosage adjustment and/or RTV boosting may be required to optimize drug levels.[37] When ATV 300 mg added to **SQV 1600/r 100 mg QD** in 20 HIV+ subjects, SQV AUC ↑ 60%, Cmax ↑ 42%, Ctrough ↑ 112% (p <0.05) after 30 days. ATV levels were similar to those seen with ATV/r; total and indirect bilirubin ↑ by 5 times after 10 days of ATV therapy.[38] In TDM case series, **ATV 300/ SQV2000/rtv 100-200 mg QD** yielded ATV Ctrough levels approx. 6-fold higher (mean 749 and 899 ng/mL, respectively) vs. ATV 400 mg QD (mean 122 ng/mL).[28] In a healthy volunteer study, ATV 200/SQV 1500 mg BID led to ATV Cmin comparable to ATV 400 mg QD, while SQV Cmin was 0.129 ug/mL (75%	darunavir exposure. darunavir Cmin ↓ 42%, Cmax ↓ 17%, AUC ↓26% with combination, while no significant changes in SQV kinetics were observed. Therefore, not recommended to combine SQV and darunavir /ritonavir.[50]	**BID** resulted in: - non-sig. ↓ in SQV AUC_{0-12}, C_{trough} and C_{max} (14%, 24%, 9% respectively) with RTV 100 mg BID - non-sig. ↑ in SQV AUC_{0-12}, C_{trough} and C_{max} (12%, 3%, 20% respectively) with RTV 200 mg BID FPV levels not affected by SQV co-administration.[116] May wish to consider TDM if using RTV 100 mg BID dose with this combination.	both SQV doses resulted in SQV PK parameters similar to historical data of SQV 1000/rtv 100 mg BID; LPV PK also not affected.[148] **Saquinavir-sgc 1000 mg BID + lopinavir/r:** In a cohort of ARV-experienced subjects (n=27), combination gave therapeutic SQV levels (median trough 1.25 ug/mL); lopinavir levels were not affected.[210]	***1600 mg SQV-sgc/RTV 100 mg QD:*** • Preliminary data in healthy volunteers: 300-800% ↑ SQV AUC, Cmin > than with SQV-sgc 1200 mg TID.[205] • Kinetic substudy in 13 HIV+ subjects stabilized on combination showed equivalent SQV kinetic parameters (GMR of hgc/sgc for AUC 1.40, Cmax 1.23, and Cmin 1.46) when SQV-sgc replaced by SQV-hgc[206] • Intracellular t1/2 of SQV & RTV longer than plasma (median 4.5 & 5.9 hrs, p=0.034, and 4.1 & 6.2 hrs, p=0.033, respectively)[207] ***1000 mg SQV/100 mg RTV BID*:** • SQV-hgc/r gave significantly ↑ SQV levels vs. SQV-sgc/r (Cmin: 217 vs 153 ng/mL, p=0.0147, AUC 15798 ng.h/mL vs. 11655 ng.h/mL, p=0.0043); also significantly less GI side effects with SQV-hgc/r vs. SQV-sgc/r, possibly due to capmul content of		500 mg/SQV 1000 mg/rtv 200 mg BID showed 70% ↓ AUC, 66% ↓ Cmax, 81% ↓ Cmin of SQV compared to boosted SQV alone. Clinical significance not established, no current dosage recommendations available. Use combination with caution.[117]

	Atazanavir (Reyataz®)	Darunavir (Prezista®)	Fosamprenavir (Telzir®)	Lopinavir/ ritonavir (Kaletra®)	Ritonavir (Norvir®)	Saquinavir (Invirase®)	Tipranavir (Aptivus®)
	were > 0.1 ug/mL).[39]				SQV-sgc.[208]		
Tenofovir	Combination of atazanavir and tenofovir (at standard doses) resulted in 25% ↓ AUC and 40% ↓ Cmin of atazanavir, while tenofovir AUC was ↑ by 24%.[211] With **atazanavir 300 mg/ ritonavir 100 mg QD** plus tenofovir**,** ATV AUC ↓ 11%, Cmin ↓ 20% while tenofovir AUC ↑ 37% and Cmin ↑ 29%. [212]		In healthy volunteers, tenofovir 300 mg daily plus **fosamprenavir 1400/ritonavir 100-200 mg QD** for 14 days showed no change in amprenavir AUC and a non-significant ↑ in Cmin. A non-significant ↑ in ritonavir AUC and Cmax were observed in the FPV 1400/rtv 200 mg arm in the presence of tenofovir.[213] Similarly, in an open-label study of 15 treatment-naïve subjects, **FPV 1400/rtv 200**/tenofovir 300/emtricitabine 200 mg QD for 48 weeks yielded antiretroviral concentrations similar to historical controls.[114] In a cohort of 21 HIV-infected subjects taking **fosamprenavir 700/ritonavir 100 mg BID** plus tenofovir and an NRTI, steady-state Cmin concentrations of amprenavir, ritonavir and tenofovir were within the therapeutic range and comparable to historical controls.[214]	*Impact on tenofovir:* In healthy volunteers, tenofovir 300 mg daily plus lopinavir 400/ritonavir 100 mg BID resulted in slight ↑ AUC, Cmax of tenofovir; lopinavir AUC and Cmax were ↓ 15%, but Cmin unchanged and lopinavir IQ-wild type >90. These changes not likely clinically significant.[216] In a crossover study in healthy volunteers, TDF plus LPV/r with food led to ↑ 32% tenofovir AUC, while LPV and RTV kinetics were not affected. Clinical significance unclear.[217] In tenofovir compassionate access study, (median duration of 63 weeks), 94% of patients received TDF + LPV/r (n = 274/291), with no significant nephrotoxicity observed.[217] *Impact on lopinavir/ritonavir concentrations:* In patients taking LPV/r and TDF (n=14), mean lopinavir Ctrough was 5.6 ug/mL vs. 7 ug/mL in patients taking LPV/r plus other NRTIs	Retrospective data from a series of HIV subjects showed no effect of tenofovir on lopinavir and ritonavir Cmin at steady-state.[220] Ritonavir and tenofovir may be coadministered without dosage adjustment.	In cohort (n=14) of patients on **saquinavir-hgc 1600 mg/ ritonavir 100 mg QD**, no significant difference in saquinavir Cmin when NRTI backbone switched from ddI/d4T to tenofovir/3TC.[221] Separate study of **saquinavir-hgc 1000 mg/ritonavir 100 mg BID** and tenofovir (n=18 HIV+ adults) showed no change in tenofovir PK parameters with coadministration.[222] Similar effect observed in healthy volunteer study.[223]	Healthy volunteer, randomized, parallel group study (n=49) of either **TPV/r 500 mg/100 mg or TPV/r 750 mg/200 mg** plus tenofovir 300 mg daily. At steady state, a dose-dependent ↓ in TDF Cmax of 23%–38% was shown, and 17% and 11% ↓ in TPV at the 500/100 and 750/200 doses, respectively.[61] May consider using TPV/r plus tenofovir without further dosage adjustment.

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			In a healthy volunteer study, subjects received tenofovir 300 mg QD for 7 days (period 1), and then were randomized to receive fosamprenavir 1400 mg BID or fosamprenavir 700/rtv 100 mg BID alone and with tenofovir or vice versa (periods 2 & 3). Tenofovir Cmin, Cmax and AUC ↓ 12%, 25% and 15% with fosamprenavir and ↓ 9%, 18% and 7% with boosted fosamprenavir, respectively. In the presence of tenofovir, amprenavir Cmin, Cmax and AUC ↑ 31%, 3% and 7% (unboosted) and ↑ 31%, 4% and 16% (boosted). These changes are not likely clinically significant.[215]	(n=15).[218] In a kinetic interaction study in experienced patients (n=18), lopinavir Cmin ↓ by 34% (mean 4.61 vs. 3.06 ug/mL, p=0.04), while ritonavir Cmin ↓ by 44% (mean of 0.63 vs. 0.35 ug/mL, p=0.014) in the presence of tenofovir.[219] Recommendations on dosage adjustment not established. Monitor for tenofovir toxicity and possibly lopinavir efficacy, particularly in treatment-experienced patients. Consider TDM (if available) with possible dosage increase of lopinavir if suboptimal lopinavir concentrations and/or inadequate viral response.[219]			
Tipranavir *(inducer of CYP3A4, P-gp and glucuronyl transferase)*	Healthy volunteer study of steady-state atazanavir 300/100 mg, tipranavir 500/100 mg BID, or tipranavir 500/100 mg BID + atazanavir 300 mg QD showed 68% ↓ AUC, 81% ↓ Cmin of ATV, and 20% ↑ AUC, 75% ↑ Cmin of TPV when drugs were coadministered. [40]		Pharmacokinetic analysis in treatment-experienced subjects taking TPV 500 mg/APV 600 mg/rtv 200 mg BID showed 45% ↓ AUC, 40% ↓ Cmax, 56% ↓ Cmin of APV compared to APV 600/rtv 200 mg BID alone.[117] In a series of HIV-	Pharmacokinetic analysis in treatment-experienced subjects taking TPV 500 mg/LPV 400 mg/rtv 100 mg BID showed 49% ↓ AUC, 43% ↓ Cmax, 55% ↓ Cmin of LPV compared to LPV/r 400/100 mg BID alone. Clinical significance not established, no	Open-label, dose-ranging study in healthy subjects of TPV 250, 500, 750, 1000, or 1250 mg BID + 100/200 mg RTV BID: TPV Cmax, AUC ↑ at least 4-fold and TPV Cmin ↑ at least 20-fold when combined with RTV. More consistent inhibition of CYP3A4 activity with RTV 200 mg	Pharmacokinetic analysis in treatment-experienced subjects taking TPV 500 mg/SQV 1000 mg/rtv 200 mg BID showed 70% ↓ AUC, 66% ↓ Cmax, 81% ↓ Cmin of SQV compared to boosted SQV alone. Clinical significance not established, no current dosage	

	Atazanavir (Reyataz®)	Darunavir (Prezista®)	Fosamprenavir (Telzir®)	Lopinavir/ ritonavir (Kaletra®)	Ritonavir (Norvir®)	Saquinavir (Invirase®)	Tipranavir (Aptivus®)
	Combination not recommended.		positive patients receiving TPV 500/FPV 1400/rtv200 mg BID, therapeutic LPV levels (>1.25 ug/mL) were observed in 67% of subjects.[118] Use combination with caution, and consider therapeutic drug monitoring if available.	current dosage recommendations available.[117] In an open-label pilot study of 12 HIV-infected subjects on stable LPV/r, two dosing regimens were studied: c) TPV 500/LPV 400/rtv 300 mg BID d) TPV 500/LPV 533/rtv 233 mg BID LPV Ctrough were generally higher compared to LPV/r alone (7.05 ug/mL group A, 5.2 ug/mL group B vs. ~4 ug/mL), but greater interpatient variability was also observed.[149] In a series of HIV-positive patients receiving TPV 500/LPV 533/rtv233 mg BID, therapeutic LPV levels (>3 ug/mL) were observed in 74% of subjects.[118] Use combination with caution, and consider therapeutic drug monitoring.	vs. 100 mg dose.[209]	recommendations available. Use combination with caution.[117]	
Vicriviroc (VVC)	The combination of vicriviroc 15 mg/ritonavir 100 mg QD plus atazanavir 300 mg QD in healthy volunteers did not lead to significant changes in vicriviroc plasma	Open label, multidose study in healthy adult subjects (n=12) to investigate the PK effects of vicriviroc 30mg daily + RTV 100mg BID +/- DRV 600mg BID.	The combination of vicriviroc 15 mg QD plus fosamprenavir 700 mg/ritonavir 100 mg BID in healthy volunteers did not lead to significant changes in vicriviroc plasma levels,	Vicriviroc exposure ↑ similarly by ritonavir or lopinavir/ritonavir: In healthy subjects, vicriviroc 10 mg QD was given alone or with ritonavir 100 mg	Vicriviroc exposure ↑ similarly by ritonavir or lopinavir/ritonavir: In healthy subjects, vicriviroc 10 mg QD was given alone or with ritonavir 100 mg	The combination of vicriviroc 15 mg QD plus saquinavir-sgc 1000 mg/ritonavir 100 mg BID in healthy volunteers did not lead to significant changes in vicriviroc plasma	

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	levels, compared to vicriviroc 15 mg QD /ritonavir 100 mg BID alone. Vicriviroc may be added to a ritonavir-boosted PI regimen without dosage adjustment.[224]	Addition of darunavir led to 7%↓ AUC, 17% ↓ Cmax, 3% ↑ Cmin of vicriviroc. Darunavir did not alter VCV levels to clinically important extent. No dose adjustment required.[225]	compared to vicriviroc 15 mg QD/ritonavir 100 mg BID alone. Vicriviroc may be added to a ritonavir-boosted PI regimen without dosage adjustment.[224]	QD or lopinavir/ritonavir 400 mg QD for 14 days. In the presence of ritonavir, vicriviroc AUC ↑ 5.4-fold and Cmax ↑ 2.5-fold, while in the presence of lopinavir/rtv, vicriviroc AUC ↑ 4.2-fold and Cmax ↑ 2.3-fold. Both combinations were well tolerated.[226]	QD or lopinavir/ritonavir 400 mg QD for 14 days. In the presence of ritonavir, vicriviroc AUC ↑ 5.4-fold and Cmax ↑ 2.5-fold, while in the presence of lopinavir/rtv, vicriviroc AUC ↑ 4.2-fold and Cmax ↑ 2.3-fold. Both combinations were well tolerated.[226]	levels, compared to vicriviroc 15 mg QD/ritonavir 100 mg BID alone. Vicriviroc may be added to a ritonavir-boosted PI regimen without dosage adjustment.[224]	
Zidovudine *(GT 60-75% > CYP3A, minor)*	In healthy volunteers (n=20), atazanavir 400 mg daily plus Combivr BID at steady-state did not result in any significant changes to PK parameters of any drug.[227] Atazanavir may be coadministered with zidovudine and lamivudine without dosage adjustment.		Amprenavir may inhibit ZDV glucuronidation to a small degree; no dosage adjustment necessary.[228]	Potential for ↓ zidovudine concentrations due to induction of glucuronyl transferases; clinical significance unknown, no dosage adjustments recommended.[175]	25% ↓ zidovudine AUC. May need to ↑ zidovudine dose.[7]	No interaction.	Healthy volunteer, randomized, parallel group study (n=60) of either **TPV/r 500 mg/100 mg or TPV/r 750 mg/200 mg** plus AZT 300 mg BID. At steady state, TPV/r caused a 56%–61% ↓ in ZDV Cmax and a 33%–43% ↓ in AUC. ZDV did not affect the PK of TPV/r.[61] May consider using TPV/r plus AZT at usual doses.
III)	**INTERACTIONS**	**WITH OTHER**	**MEDICATIONS**				
Albendazole					In healthy volunteers, single dose albendazole 400 mg was given alone or after 1 day or 8 days ritonavir 200 mg BID. Albendazole kinetics were unchanged by short-term ritonavir dosing, but AUC ↓ 27% and Cmax ↓ 26% in the presence		

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					of chronic ritonavir administration.[229]		
Antacids (NB: see separate entries for H2-blockers and Proton-pump inhibitors)	Atazanavir solubility decreases with increasing gastric pH. Administer atazanavir 2 hours before or 1 hour after antacids.[1]		In a single-dose healthy volunteer study, co-administration of 30 mL Maalox TC with 1400 mg fosamprenavir led to 18% ↓ in APV AUC_{last}, 35% ↓ C_{max}, and 14% ↑ C_{12}. **FPV may be coadministered with antacids without concern and without separation in dosing.**[230]	In a prospective observation of treatment-naïve subjects receiving LPV/r BID or QD, no significant differences in LPV levels were noted in the presence of either antacids, H2 blockers, or proton pump inhibitors.[231]	Effect of antacid coadministration on ritonavir absorption not studied.		In healthy volunteers, coadministration of single-dose Maalox on tipranavir 500 mg/ritonavir 200 mg BID resulted in 25-29% ↓ in tipranavir AUC, Cmax and C12 (p<0.01). May consider separating tipranavir/rtv and antacid doses by at least 1 hour.[232]
Antihistamines, non-sedating (i.e., astemizole, terfenadine) *(CYP3A4)*	Possible ↑ antihistamine AUC and cardiotoxicity. **Avoid combination.**		Possible ↑ antihistamine AUC and cardiotoxicity. **Avoid combination.**[4]	Possible ↑ antihistamine AUC and cardiotoxicity. **Avoid combination.**[175]	Possible ↑ antihistamine AUC and cardiotoxicity. **Avoid combination**.[7]	368% ↑ terfenadine AUC; **avoid combination**. [142] Potential for similar interaction with astemizole.	
Atovaquone/ progruanil (Malarone®) Atovaquone: GT Proguanil: CYP2C19 to active metabolite, cycloguanil, 40-60% Clr	In 19 HIV-positive patients on atazanavir/rtv, single dose atovaquone 250/ proguanil 100 mg resulted in atovaquone AUC ↓ 46% and proguanil AUC ↓ 70% (only in those who had no CYP2C19*2 or -*3 alleles) compared to healthy volunteers.[233]			In 19 HIV-positive patients on LPV/r, single dose atovaquone 250/ proguanil 100 mg resulted in atovaquone AUC ↓ 74% and proguanil AUC ↓ 68% (only in those who had no CYP2C19*2 or -*3 alleles) compared to healthy volunteers.[233]			
Benzodiazepines • alprazolam, midazolam, triazolam, zolpidem (CYP3A4) • diazepam (2C19>3A4)	Risk of prolonged sedation. **Avoid combination**, or use agents which are glucuronidated (e.g., lorazepam, oxazepam, temazepam).		Risk of prolonged sedation. **Avoid combination**, or use agents which are glucuronidated (e.g., lorazepam, oxazepam, temazepam).[4]	Risk of prolonged sedation. Midazolam, triazolam are contraindicated with lopinavir/ ritonavir.[175]	Risk of prolonged sedation. **Avoid combination**, or use agents which are glucuronidated (e.g., lorazepam, temazepam).[7] Recent single-dose	Possible risk of prolonged sedation. Use with caution.[9]	

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					PK study suggests that alprazolam may also be safe to use with ritonavir.		
Cisapride *(CYP3A4)*	Possible ↑ cisapride AUC and cardiotoxicity. **Avoid combination.**		Possible ↑ cisapride AUC and cardiotoxicity. **Avoid combination.**[4]	Possible ↑ cisapride AUC and cardiotoxicity. **Avoid combination.**[175]	Possible ↑ cisapride AUC and cardiotoxicity. **Avoid combination**.[7]	Possible ↑ cisapride AUC and cardiotoxicity. **Avoid combination**.[9]	
Calcium channel blockers, e.g. • amlodipine, diltiazem, felodipine, nifedipine, nimodipine, verapamil (CYP3A substrates)	Potential for ↑ calcium channel blocker concentrations with concomitant protease inhibitor therapy. In healthy subjects on indinavir 800/ritonavir 100 mg BID, steady-state amlodipine AUC ↑ 90% and diltiazem AUC ↑ 27% (NB: 2/13 subjects (15%) had >4-fold ↑ diltiazem AUC).[234] If coadministration is necessary, initiate calcium blocker therapy at low doses, with careful titration to response and side effects.	Potential for ↑ calcium channel blocker concentrations with concomitant protease inhibitor therapy. In healthy subjects on indinavir 800/ritonavir 100 mg BID, steady-state amlodipine AUC ↑ 90% and diltiazem AUC ↑ 27% (NB: 2/13 subjects (15%) had >4-fold ↑ diltiazem AUC).[234] If coadministration is necessary, initiate calcium blocker therapy at low doses, with careful titration to response and side effects.	Potential for ↑ calcium channel blocker concentrations with concomitant protease inhibitor therapy. In healthy subjects on indinavir 800/ritonavir 100 mg BID, steady-state amlodipine AUC ↑ 90% and diltiazem AUC ↑ 27% (NB: 2/13 subjects (15%) had >4-fold ↑ diltiazem AUC).[234] If coadministration is necessary, initiate calcium blocker therapy at low doses, with careful titration to response and side effects.	Potential for ↑ calcium channel blocker concentrations with concomitant protease inhibitor therapy. In healthy subjects on indinavir 800/ritonavir 100 mg BID, steady-state amlodipine AUC ↑ 90% and diltiazem AUC ↑ 27% (NB: 2/13 subjects (15%) had >4-fold ↑ diltiazem AUC).[234] Extreme bradycardia with complete AV block and hypotension occurred in a patient on stable therapy including lacidipine, ramipril, levothyroxine, rosuvastatin, metoprolol and ASA; symptoms developed 48 hours after starting tenofovir, emtricitabine, and lopinavir/ritonavir for post-exposure prophylaxis. An interaction between lopinavir/ritonavir and metoprolol and lacidipine was hypothesized to be	Potential for ↑ calcium channel blocker concentrations with concomitant protease inhibitor therapy. In healthy subjects on indinavir 800/ritonavir 100 mg BID, steady-state amlodipine AUC ↑ 90% and diltiazem AUC ↑ 27% (NB: 2/13 subjects (15%) had >4-fold ↑ diltiazem AUC).[234] If coadministration is necessary, initiate calcium blocker therapy at low doses, with careful titration to response and side effects.	Potential for ↑ calcium channel blocker concentrations with concomitant protease inhibitor therapy. In healthy subjects on indinavir 800/ritonavir 100 mg BID, steady-state amlodipine AUC ↑ 90% and diltiazem AUC ↑ 27% (NB: 2/13 subjects (15%) had >4-fold ↑ diltiazem AUC).[234] If coadministration is necessary, initiate calcium blocker therapy at low doses, with careful titration to response and side effects.	Potential for ↑ calcium channel blocker concentrations with concomitant protease inhibitor therapy. In healthy subjects on indinavir 800/ritonavir 100 mg BID, steady-state amlodipine AUC ↑ 90% and diltiazem AUC ↑ 27% (NB: 2/13 subjects (15%) had >4-fold ↑ diltiazem AUC).[234] If coadministration is necessary, initiate calcium blocker therapy at low doses, with careful titration to response and side effects.

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				the cause of this adverse event.[235] If coadministration is necessary, initiate calcium blocker therapy at low doses, with careful titration to response and side effects.			
Clarithromycin *(parent: CYP3A4; inhibits CYP3A4, 1A2?)* *(CLA-14 OH: renal, CYP3A4)*	In healthy subjects, clarithromycin 500 mg BID plus atazanavir 400 mg QD resulted in 28% ↑ ATV AUC, and 50%↑ Cmax, 94% ↑ AUC clarithromycin and 70% ↓ CLA-14 OH metabolite.[236] Recommend 50% dosage reduction of clarithromycin since QTC prolongations have been reported with elevated clarithromycin levels. Consider alternate agent for infections other than M. avium complex since clarithromycin metabolite levels reduced.[1]	Combination of darunavir 400/100 mg BID and clarithromycin 500 mg BID led to a 57% ↑ in clarithromycin exposure, while darunavir exposure was not affected. For patients with renal impairment, clarithromycin dosage should be adjusted as follows: • Clcr 30-60 mL/min: 50%↓ clarithromycin dose • Clcr <30 mL/min: 75%↓ clarithromycin dose	Multi-dose trial in healthy volunteers, using 1200 mg APV BID + 500 mg CLA BID: 18% ↑ APV AUC, 10% ↓ CLA Cmax, 35% ↓ AUC of CLA-14 OH metabolite. No dosage adjustment necessary for either drug.[237]	Potential for ↑ clarithromycin exposure. Reduce clarithromycin dosage if renal failure:[175] • ↓ dose 50% if Clcr 30-60 mL/min • ↓ dose 75% if Clcr <30 mL/min	77% ↑ AUC of clarithromycin. Reduce dose only if renal failure. Inhibition of CLA-OH metabolite (i.e., ↓ Gram-neg. activity, such as H. influenzae).[238]	177% ↑ SQV-sgc AUC; 45% ↑ clarithromycin AUC.[142]	In healthy volunteers, coadministration of tipranavir 500/rtv 200 mg BID plus clarithromycin 500 mg BID led to 68% ↑ clarithromycin Cminss and almost full inhibition of CLA-14OH metabolite, while steady-state TPV AUC ↑ 59%, Cmax ↑ 43%, and Cmin ↑ 112%. **No dosage adjustment needed for clarithromycin in subjects with normal renal function.**[239] However, inhibition of CLA-OH metabolite will ↓ Gram-neg. activity, such as H. influenzae. In patients with Clcr 30-60 mL/min, ↓ clarithromycin dose 50%; if Clcr<30 mL/min, ↓ clarithromycin dose 75%.
Colchicine *(biliary, renal excretion; p-glycoprotein substrate)*	Potential for significant ↑ colchicine AUC due to P-gp inhibition and ↓ biliary	Potential for significant ↑ colchicine AUC due to P-gp inhibition and ↓ biliary	Potential for significant ↑ colchicine AUC due to P-gp inhibition and ↓ biliary	Potential for significant ↑ colchicine AUC due to P-gp inhibition and ↓ biliary	In the presence of ritonavir 100 mg BID, colchicine AUC ↑ 296%, Cmax ↑ 184%.	Potential for significant ↑ colchicine AUC due to P-gp inhibition and ↓ biliary	Potential for significant ↑ colchicine AUC due to P-gp inhibition and ↓ biliary

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	excretion. For treatment of gout flares: use colchicine 0.6 mg x 1 dose, followed by 0.3 mg 1 hour later. Do not repeat dose for at least 3 days. For prophylaxis of gout flares: use colchicine 0.3 mg once daily or every other day. For treatment of familial Mediterranean fever: Do not exceed colchicine 0.6 mg once daily or 0.3 mg BID.[240] Monitor for colchicine toxicity.	excretion. For treatment of gout flares: use colchicine 0.6 mg x 1 dose, followed by 0.3 mg 1 hour later. Do not repeat dose for at least 3 days. For prophylaxis of gout flares: use colchicine 0.3 mg once daily or every other day. For treatment of familial Mediterranean fever: Do not exceed colchicine 0.6 mg once daily or 0.3 mg BID.[240] Monitor for colchicine toxicity.	excretion. **For fosamprenavir/ ritonavir:** For treatment of gout flares: use colchicine 0.6 mg x 1 dose, followed by 0.3 mg 1 hour later. Do not repeat dose for at least 3 days. For prophylaxis of gout flares: use colchicine 0.3 mg once daily or every other day. For treatment of familial Mediterranean fever: Do not exceed colchicine 0.6 mg once daily or 0.3 mg BID.[240] **For unboosted fosamprenavir:** For treatment of gout flares: use 1.2 mg x 1 dose and no repeat dose for at least 3 days. For prophylaxis of gout flares: use colchicine 0.3 mg BID or 0.6 mg once daily or 0.3 mg once daily. For treatment of familial Mediterranean fever: Do not exceed 1.2 mg once daily or 0.6 mg BID.[240] Monitor for colchicine toxicity.	excretion. For treatment of gout flares: use colchicine 0.6 mg x 1 dose, followed by 0.3 mg 1 hour later. Do not repeat dose for at least 3 days. For prophylaxis of gout flares: use colchicine 0.3 mg once daily or every other day. For treatment of familial Mediterranean fever: Do not exceed colchicine 0.6 mg once daily or 0.3 mg BID.[240] Monitor for colchicine toxicity.	For treatment of gout flares: use colchicine 0.6 mg x 1 dose, followed by 0.3 mg 1 hour later. Do not repeat dose for at least 3 days. For prophylaxis of gout flares: use colchicine 0.3 mg once daily or every other day. For treatment of familial Mediterranean fever: Do not exceed colchicine 0.6 mg once daily or 0.3 mg BID.[240] Monitor for colchicine toxicity.	excretion. For treatment of gout flares: use colchicine 0.6 mg x 1 dose, followed by 0.3 mg 1 hour later. Do not repeat dose for at least 3 days. For prophylaxis of gout flares: use colchicine 0.3 mg once daily or every other day. For treatment of familial Mediterranean fever: Do not exceed colchicine 0.6 mg once daily or 0.3 mg BID.[240] Monitor for colchicine toxicity.	excretion. For treatment of gout flares: use colchicine 0.6 mg x 1 dose, followed by 0.3 mg 1 hour later. Do not repeat dose for at least 3 days. For prophylaxis of gout flares: use colchicine 0.3 mg once daily or every other day. For treatment of familial Mediterranean fever: Do not exceed colchicine 0.6 mg once daily or 0.3 mg BID.[240] Monitor for colchicine toxicity.
Corticosteroids (oral/inhaled, injectable or	One case report of Cushing's syndrome and adrenal	In an open-label, prospective, randomized study,	**Avoid coadministration of fluticasone** and	A drug interaction study in healthy subjects has shown	In healthy subjects, ritonavir 100 mg BID plus **fluticasone**	**Avoid coadministration of fluticasone** and	**Avoid coadministration of fluticasone** and

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topical) e.g., betamethasone, budesonide, dexamethasone, fluticasone, prednisone, triamcinolone *Note: see also Salmeterol*	suppression in a patient on atazanavir/ritonavir and **dexamethasone 0.1% eye drops six times daily, and betamethasone 0.1% eye ointment** at night, in both eyes for over 8 months. ATVr was replaced with efavirenz while continuing the steroid eye drops, and oral hydrocortisone 15 mg daily was added to avoid precipitating crisis due to adrenal insufficiency. Over the following year, the patient's weight declined, with marked improvement in her adrenal function.[241] **Avoid coadministration of fluticasone** and boosted protease inhibitors. Inhaled beclomethasone or ciclesonide, or intranasal beclomethasone or triamcinolone may be safer alternatives, but caution is still warranted. Use lowest possible corticosteroid dose and monitor closely for systemic corticosteroid side effects.[242]	healthy volunteers received **inhaled beclomethasone** 160 mcg twice a day alone, or with either ritonavir 100 mg BID or darunavir 600/ ritonavir 100 mg BID, each for 14 days. The AUC of 17-BMP (the active metabolite of beclomethasone) was not significantly increased by DRVr, whereas in the presence of ritonavir 100 mg BID, the AUC of 17-BMP ↑ 2-fold, which is considered clinically inconsequential.[243] In the above study, ACTH stimulation tests were conducted on days 1, 14, 28, and 42. Combined use of BDP and RTV or DRV/r for 28 days did not cause significant adrenal suppression.[244] **Avoid coadministration of fluticasone** and boosted protease inhibitors. Inhaled beclomethasone or ciclesonide, or intranasal beclomethasone or triamcinolone may be safer alternatives, but caution is still warranted. Use	boosted protease inhibitors. Inhaled beclomethasone or ciclesonide, or intranasal beclomethasone or triamcinolone may be safer alternatives, but caution is still warranted. Use lowest possible corticosteroid dose and monitor closely for systemic corticosteroid side effects.[242]	that ritonavir significantly ↑ plasma **fluticasone propionate** exposures, resulting in significantly ↓ serum cortisol concentrations. Similar effects may be expected with the combination of lopinavir/rtv and fluticasone. Therefore, **coadministration of fluticasone and lopinavir/rtv is not recommended** unless the potential benefit to the patient outweighs the risk of systemic corticosteroid side effects.[7] Four cases of **budesonide**-related adrenal suppression and Cushing's syndrome secondary to an interaction with lopinavir/ritonavir (n=1) or ritonavir (n=3 pediatric patients) have been reported.[245, 246] Seven cases of Cushing's syndrome have been reported with the use of **intra-articular triamcinolone injections** in patients on ritonavir-boosted regimens (100-200 mg daily of ritonavir).[247-250] In most cases, cushingoid	**propionate aqueous nasal spray** for 7 days led to 350-fold ↑ AUC and 25-fold ↑ Cmax of fluticasone, resulting in an 86% ↓ in plasma cortisol AUC.[7] Several reports of Cushing's syndrome with combination of inhaled **fluticasone** and ritonavir. Therefore, **combination is not recommended**. Of note, use of **Advair® (fluticasone/salmeterol)** should be avoided with ritonavir, due to the additional interaction risk between ritonavir and salmeterol.[7] Symbicort® (budesonide/formoterol) Turbuhaler may be a suitable alternative to Advair®.[242] In healthy volunteers, **prednisone** 20 mg in the presence of ritonavir 200 mg BID led to 28-37% ↑ prednisolone AUC.[251] Five cases of **budesonide**-related adrenal suppression and Cushing's syndrome secondary to an interaction with	boosted protease inhibitors. Inhaled beclomethasone or ciclesonide, or intranasal beclomethasone or triamcinolone may be safer alternatives, but caution is still warranted. Use lowest possible corticosteroid dose and monitor closely for systemic corticosteroid side effects.[242]	boosted protease inhibitors. Inhaled beclomethasone or ciclesonide, or intranasal beclomethasone or triamcinolone may be safer alternatives, but caution is still warranted. Use lowest possible corticosteroid dose and monitor closely for systemic corticosteroid side effects.[242]

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		lowest possible corticosteroid dose and monitor closely for systemic corticosteroid side effects.[242]		symptoms and profound adrenal suppression appeared about 2 weeks after a single injection of triamcinolone acetonide 40-80 mg. Three cases required supplemental hydrocortisone 10-30 mg po daily for up to 8 months.[247, 248] Most cases resolved after several months, however there were two reports of avascular necrosis of the hip[247, 250] at 2 and 11 months post-steroid exposure, respectively. Inhaled beclomethasone or ciclesonide, or intranasal beclomethasone or triamcinolone may be safer alternatives, but caution is still warranted. Use lowest possible corticosteroid dose and monitor closely for systemic corticosteroid side effects.[242]	lopinavir/ritonavir (n=1), ritonavir (n=3 pediatric patients) or atazanavir/ritonavir (n=1) have been reported.[245, 246, 252] Seven cases of Cushing's syndrome have been reported with the use of **intra-articular triamcinolone injections** in patients on ritonavir-boosted regimens (100-200 mg daily of ritonavir).[247-250] In most cases, cushingoid symptoms and profound adrenal suppression appeared about 2 weeks after a single injection of triamcinolone acetonide 40-80 mg. Three cases required supplemental hydrocortisone 10-30 mg po daily for up to 8 months.[247, 248] Most cases resolved after several months, however there were two reports of avascular necrosis of the hip[247, 250] at 2 and 11 months post-steroid exposure, respectively. One case report of Cushing's syndrome and adrenal suppression in a patient on		

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					atazanavir/ritonavir and **dexamethasone 0.1% eye drops six times daily, and betamethasone 0.1% eye ointment** at night, in both eyes for over 8 months. ATVr was replaced with efavirenz while continuing the steroid eye drops, and oral hydrocortisone 15 mg daily was added to avoid precipitating crisis due to adrenal insufficiency. Over the following year, the patient's weight declined, with marked improvement in her adrenal function.[241] Inhaled beclomethasone or ciclesonide, or intranasal beclomethasone or triamcinolone may be safer alternatives, but caution is still warranted. Use lowest possible corticosteroid dose and monitor closely for systemic corticosteroid side effects.[242]		
Digoxin *(p-glycoprotein substrate, 57-80% Clr)*	Potential for ↑ digoxin concentrations via PI-mediated inhibition of renal p-glycoprotein. Use combination with caution. Monitor digoxin levels and	An interaction trial with darunavir 600/ritonavir 100 mg BID plus single dose digoxin 0.4 mg showed 77% ↑ AUC digoxin. Recommend using lowest dose of	Potential for ↑ digoxin concentrations via PI-mediated inhibition of renal p-glycoprotein. Use combination with caution. Monitor digoxin levels and	Potential for ↑ digoxin concentrations via PI-mediated inhibition of renal p-glycoprotein. Use combination with caution. Monitor digoxin levels and	In healthy volunteers, ritonavir 300 mg BID plus digoxin 0.5 mg ↑ digoxin AUC by 86%, likely via inhibition of renal p-gp.[253] Case report of woman	Potential for ↑ digoxin concentrations via PI-mediated inhibition of renal p-glycoprotein. Use combination with caution. Monitor digoxin levels and	Potential for ↑ digoxin concentrations via PI-mediated inhibition of renal p-glycoprotein. Use combination with caution. Monitor digoxin levels and

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	response, and adjust dose if necessary.	digoxin, monitor digoxin levels and titrate dose to clinical effect.[3]	response, and adjust dose if necessary.	response, and adjust dose if necessary.	maintained on indinavir, 3TC, d4T and digoxin 0.25 mg/d who experienced acute digoxin toxicity 3 days after ritonavir 200 mg BID added to regimen. Symptoms resolved after ritonavir discontinued, and patient resumed original HAART without incident.[254]	response, and adjust dose if necessary.	response, and adjust dose if necessary.
Ergot alkaloids *(CYP3A>others)*	**Coadministration is contraindicated.**[1]	**Coadministration is contraindicated.**[3]	**Concurrent administration is contraindicated.**[4]	Postmarketing reports of acute ergot toxicity with ritonavir. **Ergot derivatives are contraindicated with Kaletra.**[175]	Postmarketing reports of acute ergot toxicity with combination.[255-257] **Combination contraindicated.**[7]	**Coadministration is contraindicated.**[9]	**Coadministration is contraindicated.**[11]
Fluconazole *(~80% Clrenal, 11% metabolized via CYP3A4; inhibits 3A4 (weak), 2C9, 2C19)*	In healthy subjects, coadministration of atazanavir 300/rtv 100 mg QD plus fluconazole 200 mg QD for 10 days did not result in changes to pharmacokinetic parameters of either ATV, rtv or fluconazole. Combination may be given without dosage adjustment.[258]			Clinically significant interaction not expected.[175]	12% ↑ RTV AUC. Clinical significance unclear.[7]		In healthy volunteers, coadministration of TPV 500/rtv 200 mg BID with fluconazole 100 mg QD resulted in 56%↑ AUC, 46% ↑ Cmax, 104% ↑ C12 of TPV; fluconazole PK parameters not significantly changed.[239] Fluconazole doses >200 mg/day are not recommended.
Ginko biloba *(CYP3A inducer)*	Potential for ↓ atazanavir concentrations due to CYP3A induction by ginko biloba.[259] Case report of viral breakthrough and resistance to efavirenz after introduction of ginko biloba.[260] **Avoid**	Plasma exposure of boosted protease inhibitors unlikely to be affected by ginko biloba;[259] however, concentrations of unboosted PIs may be decreased.	Potential for ↓ amprenavir concentrations due to CYP3A induction by ginko biloba.[259] Case report of viral breakthrough and resistance to efavirenz after introduction of ginko biloba.[260] **Avoid**	In healthy subjects, chronic administration of ginko biloba 120 mg BID reduced midazolam AUC by 33% (presumably via CYP3A induction), while steady-state LPV/r exposure was not	Plasma exposure of boosted protease inhibitors unlikely to be affected by ginko biloba;[259] however, concentrations of unboosted PIs may be decreased.	Plasma exposure of boosted protease inhibitors unlikely to be affected by ginko biloba;[259] however, concentrations of unboosted PIs may be decreased.	Plasma exposure of boosted protease inhibitors unlikely to be affected by ginko biloba;[259] however, concentrations of unboosted PIs may be decreased.

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	concomitant use with unboosted atazanavir.		**concomitant use with unboosted fosamprenavir.**	affected.[259]			
H2 blockers (including cimetidine, famotidine, nizatidine, ranitidine, etc.)	In healthy volunteers, **40 mg famotidine BID plus atazanavir 400 mg QD** led to 47%↓ Cmax, 41% ↓ AUC and 42% ↓ Cmin of atazanavir; coadministration of cola did not mitigate this effect.[261] In a 2-cohort, 3-period, multi-dose sequential interaction study, HIV-infected subjects received **atazanavir 300/ ritonavir 100 mg QD ± tenofovir** with **famotidine 20 mg or 40 mg BID**. When FAM 20 mg BID was administered simultaneously with ATV/r, ATV AUC ↓ 13% while Cmin was unchanged. When FAM 20 mg BID was temporally separated from ATV/r plus tenofovir, ATV AUC ↓ 21% and Cmin ↓ 19%. With FAM 40 mg BID, ATV AUC and Cmin ↓ 20-23% in those not on tenofovir and 23-25% in those on tenfovir.[262] In an open-label, 3 period, multi-dose	No significant change in darunavir kinetic parameters when coadministered with ranitidine 150 mg BID.[264] Combination may be coadministered.	In a single-dose healthy volunteer study, co-administration of ranitidine 300 mg with 1400 mg fosamprenavir led to 30% ↓ in APV AUC_{last} and 51% ↓ C_{max}, C12 unchanged. **Use caution when FPV is coadministered with H2-blockers**.[230]	Lopinavir capsules: In a prospective observation of treatment-naïve subjects receiving LPV/r BID or QD, no significant differences in LPV levels were noted in the presence of either antacids, H2 blockers, or proton pump inhibitors.[231] Lopinavir tablets: In a randomized, healthy volunteer study, subjects received LPV/r BID or QD at standard doses plus ranitidine 150 mg 1 hour before breakfast. LPV exposure was not affected by the presence of ranitidine.[265]		Healthy volunteer study of SQV-sgc 1200 mg TID vs. SQV 1200 mg BID plus cimetidine 400 mg BID: SQV AUC ↑ 120%, Cmax ↑ 179%, Cmin stable in presence of cimetidine.[266]	

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	sequential cross-over study in 24 HIV-infected subjects on stable ATV 300/100 mg, tenofovir 300 mg + ≥1 NRTI, subjects increased to **ATV 400/100 mg QD (+ TDF**/NRTIs) and took **famotidine 20 mg BID** for 7 days, then **famotidine 40 mg BID** for 7 days, both simultaneously with ATV in the morning after a meal. Famotidine 40 mg BID with ATV 400/100 mg QD resulted in similar ATV exposures compared to ATV 300/100 mg without famotidine (ATV Cmax ↓ 5%, AUC ↓ 2%, Ctrough ↑ 1%). Famotidine 20 mg BID with ATV 400/100 mg QD resulted in 18% ↑ AUC & Cmax, 24% ↑ Ctrough of ATV relative to ATV 300/100 mg QD without famotidine.[263] Management options: • Give **ATV 300/100 rtv QD with famotidine simultaneously or 10 hours after H2RA.** Maximum 40 mg BID (treatment-naïve) or 20 mg BID (treatment-						

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	experienced) of famotidine. • If also on tenofovir, increase to ATV 400/100 mg QD in experienced patients.						
Hmg-CoA Reductase inhibitors • atorvastatin *(CYP3A)* • fluvastatin *(2C9>>3A)* • lovastatin *(CYP3A)* • pitavastatin *(UGT1A3,UGT 2B7>> CYP2C9, 2C8)* • pravastatin *(40-50% Clr, > 3A4)* • rosuvastatin *(10% via 2C9, 2C19)* • simvastatin *(CYP3A)*	Potential for ↑ concentrations of statins due to enzyme inhibition by atazanavir. **Pitavastatin** may be used without dose limitations with boosted and unboosted atazanavir.[267] **Limit rosuvastatin dose to 10 mg once daily** with boosted or unboosted atazanavir.[267] **Lovastatin and simvastatin** are contraindicated with all HIV protease inhibitors.[267]	Combination of **atorvastatin** 10 mg daily plus darunavir 300/ritonavir 100 mg BID led to 15% ↓ atorvastatin AUC vs. atorvastatin 40 mg QD alone. **Do not exceed 20 mg atorvastatin daily**.[267] **Pravastatin** and **pitavastatin** may be used without dose limitations.[267] **Lovastatin and simvastatin** are contraindicated with all HIV protease inhibitors.[267]	In healthy volunteers, FPV 1400 mg BID or FPV 700 mg/ ritonavir 100 mg BID plus **atorvastatin 10 mg** led to significant ↑ in atorvastatin Cmax (404% and 284%, respectively) and AUC (230% and 253%, respectively); APV levels were not affected.[268] **Do not exceed 20 mg atorvastatin daily** with either boosted or unboosted fosamprenavir.[267] **Lovastatin and simvastatin** are contraindicated with all HIV protease inhibitors.[267]	**Atorvastatin**: potential for ↑ atorvastatin concentrations. Use combination with caution, use lowest atorvastatin dose necessary.[267] In an open-label, 3-phase pharmacokinetic study in healthy volunteers, the combination of **rosuvastatin** 20 mg/day plus LPV/r 400/100 mg BID for 7 days led to a 2.1-fold ↑ AUC and 4.7-fold ↑ Cmax of rosuvastatin, compared to rosuvastatin alone ($p<0.0001$). LPV levels were not changed in the presence of rosuvastatin.[269] **Limit rosuvastatin dose to 10 mg once daily** with lopinavir/ritonavir.[267] **Pravastatin** and **pitavastatin** may be used without dose limitations.[267] **Lovastatin and simvastatin** are contraindicated with	Pharmacokinetic study in HIV-negative subjects taking saquinavir 400 mg/ritonavir 400 mg BID plus 40 mg of **atorvastatin, pravastatin, or simvastatin** revealed the following effects: • 35% ↓ AUC pravastatin • 31.6 fold ↑ AUC simvastatin • 4.5-fold ↑ AUC atorvastatin[270] **Lovastatin and simvastatin** are contraindicated with all HIV protease inhibitors.[267]	Pharmacokinetic study in HIV-negative subjects taking saquinavir 400 mg/ritonavir 400 mg BID plus 40 mg of atorvastatin, pravastatin, or simvastatin revealed the following effects: • 35% ↓ AUC pravastatin • 31.6 fold ↑ AUC simvastatin • 4.5-fold ↑ AUC atorvastatin[270] **Pravastatin** may be administered without dosage adjustment. **Do not exceed 20 mg atorvastatin daily.** **Lovastatin and simvastatin** are contraindicated with all HIV protease inhibitors.[267]	Potential for ↓ /↑ concentrations of **lovastatin, and simvastatin**, possibly **fluvastatin** due to enzyme induction by tipranavir or enzyme inhibition by ritonavir. In healthy volunteers, coadministration of **atorvastatin 10 mg** with tipranavir 500 mg/ritonavir 200 mg BID resulted in 9-fold ↑ in atorvastatin AUC compared to atorvastatin alone.[232] **Avoid using atorvastatin and tipranavir**.[267] In 16 healthy volunteers, **tipranavir 500/ritonavir 200 mg BID** plus single dose rosuvastatin 10 mg led to 37% ↑ AUC and 123% ↑ Cmax of rosuvastatin; TPV and RTV levels were not changed in the presence of rosuvastatin. Use lowest dose of rosuvastatin (5 mg/day) and titrate

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				all HIV protease inhibitors.[267]			slowly to treatment response.[271] **Lovastatin and simvastatin** are contraindicated with all HIV protease inhibitors.[267]
Itraconazole *(CYP3A4; inhibits 3A, 2C9)*	Potential for increased itraconazole and/or atazanavir concentrations. Clinical significance unclear, monitor for dose-related toxicities.	Coadministration of darunavir 400/100 mg BID and ketoconazole 200 mg BID led to 212% ↑ ketoconazole exposure and 42% ↑ darunavir exposure.[272] Do not exceed 200 mg ketoconazole or itraconazole per day while on darunavir.	Potential for increased itraconazole and/or amprenavir concentrations. Clinical significance unclear, monitor for dose-related toxicities.	In a case report of an HIV-positive patient on itraconazole 200 mg QD and lopinavir/r, itraconazole levels were significantly ↑ (similar to itraconazole 400 mg QD alone) and hydroxy-itraconazole levels were significantly ↓. Lopinavir/r levels not affected.[273] Similarly, in another case report of an HIV-positive patient with disseminated histoplasmosis infection, lopinavir concentrations remained stable after initiation of itraconazole 200 mg daily, and therapeutic antifungal levels (itraconazole + hydroxy-itraconazole) were achieved along with clinical response.[274] Itraconazole doses >200 mg/day not recommended.[175]	In a case report, itraconazole blood levels in a patient taking ritonavir and saquinavir showed more than five-fold ↑ increase half-life, and therapeutic levels of itraconazole were still detectable even 27 days after discontinuation of the drug.[275] Use combination with caution.	5-fold increase in saquinavir exposure when hard-gel capsules coadministered with itraconazole 200 mg;[276] In a prospective randomized study in 17 HIV-infected subjects, saquinavir-sgc 800 or 1200 mg BID plus itraconazole 100 mg daily resulted in SQV concentrations equivalent to SQV-sgc 1400 mg BID alone.[277]	No data, use with caution. Do not exceed itraconazole 200 mg daily.
Ketoconazole *(CYP3A4; inhibits 3A, 2C9)*	In a healthy volunteer study, coadministration of 400 mg atazanavir	Coadministration **of darunavir 400 mg BID and ketoconazole 200**	32% ↑ amprenavir AUC, 44% ↑ ketoconazole AUC. Clinical significance	Single 200 mg ketoconazole dose had no significant effect on lopinavir/r	Coadministration of ketoconazole 200 mg daily ritonavir 500 mg BID (n=12)	**Saquinavir 1200 mg TID** plus ketoconazole 400 mg QD: 1.5-fold ↑	No data, use with caution. Do not exceed ketoconazole 200

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	plus 200 mg ketoconazole daily did not result in significant changes in atazanavir concentrations. Combination may be administered without dosage adjustment.[278]	**mg BID** in healthy volunteers (n=6) led to 155% ↑ AUC, 179% ↑ Cmin of darunavir, and no significant change in ketoconazole levels. Coadministration **of darunavir 400/100 mg BID and ketoconazole 200 mg BID** in healthy volunteers (n=17) led to 212% ↑ ketoconazole exposure and 42% ↑ darunavir exposure. Do not exceed 200 mg ketoconazole per day while on darunavir/ritonavir.[272]	unclear.[279]	concentrations.[175] Lopinavir/r AUC increased 3-fold. Ketoconazole doses >200 mg/day not recommended. Monitor for dose-related toxicities.	resulted in an 18% ↑ ritonavir AUC, and 3.4 fold ↑ ketoconazole AUC and 55% ↑ Cmax. Manufacturer suggests using no more than 200 mg daily ketoconazole with concomitant ritonavir.[7]	saquinavir AUC. Dosage adjustment not necessary.[9] Multiple dose study of **SQV/r 1000/100mg BID** and ketoconazole 200mg daily in healthy subjects resulted in: • Ketoconazole ↑ AUC 168%, ↑ Cmax 45%. • No substantial change in saquinavir and ritonavir exposures [280] In 25 patients stable on SQV/r 2000/100 mg QD, switching to SQV 2000 mg plus ketoconazole 400 mg QD for 2 weeks led to 80% lower SQV exposures. Mean SQV AUC and Cmin were 57.93 mg/h/L and 0.35 mg/L when boosted with ritonavir, versus 12 mg/h/L and 0.03 mg/L, respectively when boosted with ketoconazole. Boosting of saquinavir by ketoconazole is not recommended.[281]	mg daily.
Levothyroxine *(GT)*	Ritonavir induces glucuronyl transferase, and may potentially ↑ clearance of levothyroxine. Close monitoring of thyroid hormone indices is recommended when levothyroxine is co-	Ritonavir induces glucuronyl transferase, and may potentially ↑ clearance of levothyroxine. Close monitoring of thyroid hormone indices is recommended when levothyroxine is co-	Ritonavir induces glucuronyl transferase, and may potentially ↑ clearance of levothyroxine. Close monitoring of thyroid hormone indices is recommended when levothyroxine is co-	Case report of 58-year old woman on stable Combivir/Kaletra therapy with persistent hypothyroidism following thyroidectomy despite daily	Case report of a 29-year old male stabilized on levothyroxine 125 ug/day for an auto-immune thyroiditis induced by interferon therapy. One month starting ritonavir 600	Ritonavir induces glucuronyl transferase, and may potentially ↑ clearance of levothyroxine. Close monitoring of thyroid hormone indices is recommended when levothyroxine is co-	Ritonavir induces glucuronyl transferase, and may potentially ↑ clearance of levothyroxine. Close monitoring of thyroid hormone indices is recommended when levothyroxine is co-

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	administered with ritonavir-boosted protease inhibitor regimens. Adjustment of levothyroxine dosage may be necessary.	administered with ritonavir-boosted protease inhibitor regimens. Adjustment of levothyroxine dosage may be necessary.	administered with ritonavir-boosted protease inhibitor regimens. Adjustment of levothyroxine dosage may be necessary.	levothyroxine up to 225 ug/day and introduction of liothyronine. TSH and T4 parameters normalized when HAART was withdrawn, but hypothyroidism recurred 1 month after lopinavir therapy was reinitatiated. Replacing lopinavir/ritonavir with nelfinavir did not improve TSH and T4. Normalization of thyroid tests only occurred when patient was switched to a triple nucleoside regimen. Mechanism of interaction postulated to be ritonavir-mediated induction of glucuronyl transferases.[282]	mg BID, his TSH serum level increased to 18 mIU/l and the patient became lethargic. Doubling his levothyroxine dose to 0.25 mg daily reduced his TSH to 7.35 mIU/l. After ritonavir was discontinued, the patient was able to return to his original dose of levothyroxine. Subsequent administration of indinavir 800 mg q8h did not affect the patient's thyroid indices, and no further levothyroxine dosage alterations were required.[283]	administered with ritonavir-boosted protease inhibitor regimens. Adjustment of levothyroxine dosage may be necessary.	administered with ritonavir-boosted protease inhibitor regimens. Adjustment of levothyroxine dosage may be necessary.
Mebendazole					In healthy volunteers, single dose mebendazole 1000 mg was given alone or after 1 or 8 days ritonavir 200 mg BID. Mebendazole kinetics were unchanged by short-term ritonavir dosing, but AUC ↓ 43% and Cmax ↓ 41% in the presence of chronic ritonavir administration.[229]		
Mefloquine *(CYP3A?, GT)*					In a healthy volunteer study, ritonavir had no		

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					effect on mefloquine kinetics; ritonavir AUC ↓ 35%, Cmax ↓ 38%, Cmin ↓ 54% in presence of mefloquine.[284]		
Methadone *(CYP3A4, 2C19, 2B6>>GT; weak inhibitor of CYP2D6)* **See also "Antiretroviral-Methadone Interaction Chart" for additional information*	Prospective, open-label study of atazanavir 400 mg QD for 14 days in 16 HIV-negative subjects on chronic methadone. In the presence of atazanavir, no significant changes were observed in the pharmacokinetic parameters of the active (R)-isomer of methadone; exposure to the inactive (S)-isomer was modestly reduced but changes were not deemed significant. No clinical symptoms of opiate withdrawal were observed. Kinetic parameters of atazanavir were comparable to previously reported data.[285] Atazanavir and methadone may be co-adnimistered without dosage adjustment.	Monitor for methadone withdrawal when initiating darunavir/ritonavir in subjects stabilized on methadone, as reductions in methadone exposures have been noted with ritonavir administration.[286, 287, 288] Adjustment of methadone dosage may be necessary. Formal drug-drug interaction study underway.	In HIV-negative subjects (n=16) maintained on methadone for at least 30 days, addition of amprenavir 1200 mg BID for 10 days resulted in delayed APV absorption, 13% ↓ AUC of active methadone enantiomer. No clinical evidence of methadone withdrawal was observed. Compared to a non-matched historical control group, 30%, 27%, and 25% ↓ in AUC, Cmax, and Cmin of amprenavir was observed. May wish to consider alternative antiretroviral therapy, as amprenavir may be less effective and methadone dosage may need to be increased when these drugs are coadministered.[4, 289]	Approximately 55%↓ methadone concentrations.[175] Monitor for symptoms of methadone withdrawal; adjustment of methadone dosage may be necessary.	In vitro study showed 2-fold ↑ methadone conc., but healthy volunteer study showed 36% ↓ methadone AUC, no change in $t_{1/2}$ when given with ritonavir.[286] Similar observations in HIV-infected subjects.[287, 288] Monitor for methadone withdrawal when initiating ritonavir in subjects stabilized on methadone.	Likelihood of interaction low, since saquinavir is a weak CYP3A4 inhibitor.	Pharmacokinetic study in 15 adult healthy volunteers on steady-state tipranavir 500/ritonavir 100 mg BID plus single-dose methadone 5 mg resulted in 53% ↓ methadone levels; large ↓ in both R- and S-enantiomers. Dosage of methadone may need to be increased when co-administered with tipranavir and 200 mg of ritonavir.[290]
Minocycline	Twelve adult HIV-infected subjects on stable ATV/r 300/100 mg QD received minocycline 100 mg BID for 14 days, and then minocycline plus valproid acid 250 mg						

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	BID for 14 days. Atazanavir AUC ↓ 33%, Cmin ↓ 50% and Cmax ↓ 25% in the presence of minocycline; the addition of valproic acid did not mediate this effect. Ritonavir concentrations were not significantly altered by concomitant minocycline with or without valproic acid, suggesting that decreased absorption may be the most likely reason for ↓ atazanavir concentrations. Clinical significance is unclear and it is not known whether minocycline affects concentrations of other protease inhibitors.[291]						
Oral Contraceptives *(GT, sulphatase (primary)> CYP3A (~30%); inhibits 1A2, 3A)*	Twenty-two healthy women stabilized on an OC regimen (ethinyl estradiol/ norethindrone) received **atazanavir 400 mg/d** for 2 weeks. Vs. OC alone, ethinyl estradiol AUC ↑48% and norethindrone AUC ↑110% in presence of ATV.[67] Use lowest effect dose of each contraceptive component and monitor for side effects (incl. ↓ HDL and ↑ insulin	Eighteen healthy women stabilized on an OC regimen (ethinyl estradiol/ norethindrone) received darunavir 600/rtv 100 mg BID for 2 weeks. Ethinyl estradiol AUC ↓44% and Cmin ↓ 62%, and norethindrone AUC ↓14% and Cmin ↓30% in presence of darunavir/rtv. Alternative or additional contraceptive measures should to be used when	Ethinyl estradiol 0.035 mg/ norethindrone 1 mg daily for one cycle plus amprenavir 1200 mg BID resulted in a 22% ↓ AUC and 20% ↓ Cmin of amprenavir; Cmin of oral contraceptives ↑ 32-45%, no significant change in AUC. Furthermore, co-administration of fosamprenavir/ ritonavir and Brevinor resulted in clinically significant hepatic	42% ↓ ethinyl estradiol AUC, 17% ↓ norethindrone AUC; use additional/alternate methods of contraception.[175] The pharmacokinetic interaction between lopinavir/ritonavir and **transdermally delivered ethinyl estradiol (EE) and norelgestromin (NGMN)** was investigated in 8 HIV-positive women on stable LPV/r and compared to a	40% ↓ ethinyl estradiol AUC. Use alternate methods of contraception.[295]	In a pharmacokinetic study in healthy women, oral contraceptives did not affect the kinetics of single 600 mg saquinavir-hgc.[296]	50% ↓ ethinyl estradiol AUC and Cmax. Use alternate methods of contraception Women using estrogen may have an increased risk of non-serious rash. Women using estrogens for hormone replacement therapy should be monitored clinically for signs of estrogen deficiency.

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	resistance, esp. in diabetic women).[1] Healthy women stabilized on Ortho Tricyclen (ethinyl estradiol 35 ug plus norgestimate/NGM 0.18/0.215/ 0.25) received Ortho Tricylen LO (EE 25 ug + NGM 0.18/ 0.215/0.25) plus **ATV/r 300/100mg QD** for 14 days. In the presence of ATV/r, EE AUC ↓ 20%, while 17-deacetyl NGM AUC ↑ 85%. Thus, an oral contraceptive with 35ug EE plus ATV/r is expected to produce EE exposures similar to EE 25ug alone.[292]	estrogen-based contraceptives are co-administered with darunavir/rtv.[293]	transaminase elevations in some healthy subjects.[4] Therefore, oral contraceptives should not be taken with fosamprenavir. Use alternate non-hormonal methods of contraception.[4]	control group of 24 women not on HAART. Also, EE AUC after a single dose of a combination oral contraceptive pill including EE and norethindrone was measured before patch placement and was compared with patch EE AUC in both groups. Patch EE median AUC was 45% ↓ and pill EE AUC was 55% ↓ in women on LPVr vs. controls (p=0.064 and p=0.003, respectively). Patch NGMN AUC was 83% ↑ in LPVr group vs. controls (p=0.036). The investigators concluded that although the kinetics of EE and NGMN were significantly altered in the presence of LPVr, the contraceptive efficacy of the patch was likely to be maintained.[294]			
Phosphodiester-ase Type 5 (PDE5) Inhibitors • sildenafil (Viagra®, Revatio®); *(CYP3A4>>2C 9 substrate; weak inhibitor of CYP1A2, 2C9, 2C19, 2D6, 2E1, 3A4*	**For treatment of erectile dysfunction:**						
	Potential for increased **sildenafil** concentrations. Use with caution at a dose of 25 mg every 48 hours, and monitor for adverse effects. **Tadalafil:**[297] • on demand dosing while on	Administration of single-dose **sildenafil 25 mg** mg in the presence of darunavir 400/ritonavir 100 mg BID yielded sildenafil concentrations similar to 100 mg sildenafil alone. The pharmacokinetics of darunavir were not	No information on combination. Consider starting with an initial sildenafil dose of 25 mg q24-48 hours and titrating up based on patient response and tolerability.[300] Case report of a 36-	Potential for increased sildenafil concentrations. Case report of a 44yr old HIV+ male patient on LPV/r 666/166mg/day and indinavir 1200mg/day who started **sildenafil** 25 mg q8h for treatment of pulmonary arterial	Coadministration of ritonavir (500 mg bid at steady state) with sildenafil (100 mg single dose) resulted in a 300% (4-fold) increase in sildenafil Cmax and a 1,000% (11-fold) increase in sildenafil plasma AUC. At 24 hours the plasma levels of	Coadministration of Fortovase at steady state (1200 mg tid) with sildenafil (100 mg single dose) resulted in a 140% increase in **sildenafil** Cmax and a 210% increase in sildenafil AUC; sildenafil had no effect on saquinavir	In healthy subjects, **tadalafil 10 mg** was administered after single dose tipranavir 500/ritonavir 200 mg and steady-state TPV/rtv BID. After the first dose of TPV/rtv, tadalafil AUC ↑ 133%, Cmax ↓ 22% and Cmin ↑

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- unlikely to cause significant interactions) • tadalafil (Cialis®, Adcirca®); *CYP3A4 substrate* • vardenafil (Levitra®); substrate of *CYP3A4>3A5, 2C*	PIs or other CYP3A4 inhibitors: 10-20 mg q48h, max 3 times per week • daily dosing: 5 mg/day (no dose adjustment needed if on PIs) **Vardenafil is contraindicated** with ritonavir.[298]	significantly affected by sildenafil. Use no more than 25 mg **sildenafil** in a 48-hour period in the presence of darunavir/ ritonavir.[299] **Tadalafil:**[297] • on demand dosing while on PIs or other CYP3A4 inhibitors: 10-20 mg q48h, max 3 times per week • daily dosing: 5 mg/day (no dose adjustment needed if on PIs) **Vardenafil is contraindicated** with ritonavir.[298]	year old man on fosamprenavir 700/100 mg BID who experienced recurrent priapism after taking **tadalafil** 10 mg for recreational purposes.[301] **Tadalafil:**[297] • on demand dosing while on PIs or other CYP3A4 inhibitors: 10-20 mg q48h, max 3 times per week • daily dosing: 5 mg/day (no dose adjustment needed if on PIs) **Vardenafil is contraindicated** with ritonavir.[298] **Vardenafil is contraindicated** with ritonavir.[298]	hypertension; sildenafil AUC and t/12 of were approximately doubled vs. healthy controls. Authors postulated that effect of RTV on CYP3A activity may be different after single dose vs. chronic therapy. Coexistence of immediate competitive and irreversible mechanism-based inhibition of CYP3A with delayed PXR induction (receptor plays a central role in regulating hepatic and intestinal CYP3A4 and also MDR1 transcription) may explain the different effects of RTV (and possibly PIs) on PK of sildenafil. Authors recommend combined monitoring of the sildenafil plasma concentration, pulmonary function, and physical performance.[302] Use with caution at a dose of 25 mg every 48 hours, and monitor for adverse effects.[175] **Tadalafil:**[297] • on demand dosing while on PIs or other CYP3A4	sildenafil were still ~200 ng/mL, compared to approximately 5 ng/mL when sildenafil was dosed alone. Sildenafil had no effect on ritonavir pharmacokinetics. **Avoid combination if possible**. If coadministration is absolutely necessary, do not take more than 25 mg of sildenafil within a 48-hour period.[303] **Tadalafil:**[297] • AUC of tadalafil ↑ 124% with ritonavir 200 mg BID. • on demand dosing while on PIs or other CYP3A4 inhibitors: 10-20 mg q48h, max 3 times per week • daily dosing: 5 mg/day (no dose adjustment needed if on PIs) 49-fold ↑vardenafil AUC in presence of ritonavir 600 mg BID; **vardenafil is contraindicated with ritonavir**.[298]	pharmacokinetics. Consider a 25mg q24-48 hours starting dose of Viagra when administered to patients also taking Fortovase.[303] **Tadalafil:**[297] • on demand dosing while on PIs or other CYP3A4 inhibitors: 10-20 mg q48h, max 3 times per week • daily dosing: 5 mg/day (no dose adjustment needed if on PIs) **Vardenafil is contraindicated** with ritonavir.[298]	44% relative to tadalafil 10 mg alone. At TPV/rtv steady state, tadalafil AUC and Cmin were unaltered and Cmax ↓ 30% relative to tadalafil alone. Administer tadalafil at lowest possible dose if using within first days of TPV/rtv therapy; if TPV/rtv steady state has been achieved (i.e., after 7-10 days), no dose adjustment of tadalafil is required.[304] Combination not studied. Use with caution. Start with **sildenafil** dose of 25 mg q48 hours. **Tadalafil:**[297] • on demand dosing while on PIs or other CYP3A4 inhibitors: 10-20 mg q48h, max 3 times per week • daily dosing: 5 mg/day (no dose adjustment needed if on PIs) **Vardenafil is contraindicated** with ritonavir.[298]

	Atazanavir (Reyataz®)	Darunavir (Prezista®)	Fosamprenavir (Telzir®)	Lopinavir/ ritonavir (Kaletra®)	Ritonavir (Norvir®)	Saquinavir (Invirase®)	Tipranavir (Aptivus®)
				inhibitors: 10-20 mg q48h, max 3 times per week • daily dosing: 5 mg/day (no dose adjustment needed if on PIs) **Vardenafil is contraindicated** with ritonavir.[298]			
	For treatment of pulmonary arterial hypertension (PAH): • **Sildenafil use for PAH is contraindicated with all PIs.**[240] • Tadalafil: o For patients on stable (i.e,. greater than 7 days) PI treatment who require therapy for PAH: tadalafil may be initiated at a dose of 20 mg once daily and increased to 40 mg once daily based on tolerability. o For patients already stabilized on tadalafil who require PI-based treatment: tadalafil should be discontinued at least 24 hours prior to initiating the PI, and restarted 7 days after PI initiation at a dose of 20 mg once daily, increasing to 40 mg once daily based on tolerability.[240]						
Posaconazole *(UGT1A4; inhibits CYP3A4)*	In healthy subjects randomized to receive **ATV 300 mg QD or ATV 300/r 100 mg QD** alone or with posaconazole 400 mg BID each for 7 days: ATV AUC ↑ 3.7-fold and Cmax ↑ 2.6-fold with ATV and posaconazole co-administration ATV AUC ↑ 2.5-fold and Cmax ↑ 1.5-fold with ATV/r and posaconazole co-administration Posaconazole concentrations were not affected by the presence of ATV or ATV/r. Frequent monitoring for PI dose-related toxicity is recommended when posaconazole is coadministered with boosted or unboosted ATV.[305]	Potential for ↑ concentrations of protease inhibitor. Monitor for PI dose-related toxicity when agents are co-administered.	In a 3 period, cross-over, open-label multi-dose study, healthy volunteers received either posaconazole 400 mg BID, fosamprenavir 700/ritonavir 100 mg BID, or posaconazole plus fosamprenavir 700 mg BID for 10 days separated by 17 day washout periods. When posaconazole and fosamprenavir were coadministered, posaconazole AUC ↓ 23% and Cmax ↓ 21% vs. posaconazole alone, and amprenavir AUC ↓ 65% and Cmax ↓ 36% compared to fosamprenavir-ritonavir. Avoid posaconazole and	Potential for ↑ concentrations of protease inhibitor. Monitor for PI dose-related toxicity when agents are co-administered.	In HIV infected patients on stable doses of AZT, 3TC and ritonavir 600 mg BID or indinavir 800 mg every 8 h, Cmax and AUC of these antiretrovirals was not affected by posaconazole 200 mg daily for 10 days. Posaconazole exposures were unchanged in the presence of ritonavir 600 mg BID. No dosage adjustments required.(Posanol® prescribing information, Schering-Plough, 2008). 80% ↑ AUC RTV with RTV 100mg daily x 14 days and posaconazole 400mg twice daily x 7 days.[307] When RTV is used	Potential for ↑ concentrations of protease inhibitor. Monitor for PI dose-related toxicity when agents are co-administered.	Potential for ↑ concentrations of protease inhibitor. Monitor for PI dose-related toxicity when agents are co-administered.

	Atazanavir (Reyataz®)	Darunavir (Prezista®)	Fosamprenavir (Telzir®)	Lopinavir/ ritonavir (Kaletra®)	Ritonavir (Norvir®)	Saquinavir (Invirase®)	Tipranavir (Aptivus®)
			unboosted fosamprenavir; optimal dosing of posaconazole and boosted fosamprenavir has not yet been determined. If concomitant therapy is required, use boosted fosamprenavir and consider TDM of both fosamprenavir and posaconazole.[306]		in lower boosting doses of 100mg twice daily, empiric dosage adjustments are likely not required. However if used in larger doses, ↓ RTV dose may be warranted. Monitor for RTV-related toxicity. In cases of suspected toxicity, TDM may be useful to dose-adjust.		
Prasugrel *(converted to active metabolite via 3A4, 2B6>2C9, 2C19)*	Ketoconazole 400 mg daily did not affect prasugrel-mediated inhibition of platelet aggregation or the active metabolite's AUC and T_{max}, but decreased the C_{max} by 34 to 46%. Therefore, CYP3A inhibitors are not anticipated to have a significant effect on the pharmacokinetics of the active metabolite.[308]				In vitro, ritonavir inhibited dose-dependent inhibition of prasugrel metabolism via inhibition of CYP3A4 and 2B6.[309] Clinical significance unclear, as ritonavir may induce 2B6 in vivo.	Ketoconazole 400 mg daily did not affect prasugrel-mediated inhibition of platelet aggregation or the active metabolite's AUC and T_{max}, but decreased the C_{max} by 34 to 46%. Therefore, CYP3A inhibitors are not anticipated to have a significant effect on the pharmacokinetics of the active metabolite.[308]	
Proton-pump inhibitors (PPIs), including esomeprazole, lansoprazole, omeprazole, pantoprazole, rabeprazole, etc.	Pharmacokinetic studies: When **omeprazole 40 mg** was given 2 hours before **ATV 400 mg QD**, ATV AUC, Cmax and Cmin ↓ by >93% vs. ATV 400 mg alone.[310] In a randomized, open-label, multi-dose study, administration of **omeprazole 40 mg** QD 2 hours before **atazanavir 300/rtv 100 mg QD** led to 76% ↓ AUC and 78% ↓ Cmin of ATV. This interaction was not overcome with either ↑ ATV to 400 mg/rtv 100 mg QD or co-	No significant change in darunavir kinetic parameters when coadministered with **omeprazole 20 mg QD**.[264] Combination may be coadministered. Open label randomized crossover study in 12 healthy volunteers of darunavir 600 mg/ritonavir 100mg BID plus single dose **omeprazole 40 mg** led to ↓ omeprazole to 5-OH-omeprazole AUC ratio by 31% suggesting induction of CYP2C19 enzyme	In a randomized, open-label, multi-dose study in healthy subjects, coadministration of **esomeprazole 20 mg QD** with either FPV 1400 mg BID or FPV 700/rtv 100 mg BID for 14 days did not affect steady-state amprenavir kinetics. Esomeprazole AUC ↑ 55% when coadministered with FPV, but did not change when given with FPV/r.[320] FPV and FPV/r may be coadministered with PPIs. Prospective, open-	Lopinavir capsules: In a prospective observation of treatment-naïve subjects receiving LPV/r BID or QD, no significant differences in LPV levels were noted in the presence of either antacids, H2 blockers, or proton pump inhibitors.[231] In a separate healthy volunteer study, LPV/r increased CYP2C19 activity and ↑ omeprazole metabolism. Higher doses of omeprazole may be needed.[321]		In healthy subjects taking SQV tablets 1 g/100 mg rtv BID with or without **omeprazole 40 mg**, saquinavir exposure was significantly increased (Cmin ↑ 2-fold, Cmax ↑ 75%, AUC ↑ 82%) in the presence of omeprazole. No short-term saquinavir toxicity was observed. Mechanism of interaction unknown.[323] In HIV-positive subjects on SQV 1 g/rtv 100 mg BID, addition of **omeprazole 40 mg**	In an open-label study of healthy subjects, the effect of **omeprazole 40 mg** QD for 5 days on single-dose tipranavir 500/ ritonavir 200 mg was studied. No significant effect of omeprazole on tipranavir pharmacokinetics was observed.[18]

	Atazanavir (Reyataz®)	Darunavir (Prezista®)	Fosamprenavir (Telzir®)	Lopinavir/ ritonavir (Kaletra®)	Ritonavir (Norvir®)	Saquinavir (Invirase®)	Tipranavir (Aptivus®)
	administering with 8 oz cola[311]. In a healthy volunteer study, administration of **atazanavir 400 mg QD plus lansoprazole 60 mg QD** led to a 94% ↓ in ATV AUC.[312] In healthy volunteers**, 20 mg omeprazole qpm** plus **atazanavir 300/rtv 100 mg qam** resulted in: • 27% ↓ ATV AUC and Cmin with steady-state omeprazole • no change in ATV after single-dose omeprazole[313, 314] In a separate healthy volunteer study, **ATV 400/rtv 100 mg QD** plus **omeprazole 20 mg QD** either 1 hour before or 12 hours apart led to ~30% ↓ ATV exposures, relative to ATV 300/rtv 100 mg QD alone.[315] Case reports/series: Case series of 14 treatment-experienced subjects on atazanavir +/- rtv and gastric modifying agents; virologic suppression maintained or achieved in 12/14	activity. May be attributed to coadministration of RTV.[319]	label, crossover study with healthy volunteers to assess the kinetics of **FPV/r 1400mg/200mg once daily** (morning) alone and in combination with **omeprazole 20mg daily** (evening): when coadministered with omeprazole (multidose phase): APV AUC24h ↓ 4%, APV Cmin ↓ 2%. This effect is not clinically important. As well, single dose omeprazole did NOT significantly affect APV trough concentrations. FPV and PPIs may be safely coadministered.[314]	Lopinavir tablets: In a randomized, healthy volunteer study, subjects received LPV/r BID or QD at standard doses plus **omeprazole 40 mg** 1 hour before breakfast. LPV exposure was not affected by the presence of omeprazole.[265] Similarly in HIV-infected subjects stabilized on LPV/r BID, the addition of **omeprazole 40 mg QD** for 7 days did not significantly alter lopinavir or ritonavir concentrations.[322]		**QD** led to 54% ↑ AUC, 73% ↑ Cmin and 55% ↑ Cmax of SQV when administered simultaneously, and 67% ↑ AUC, 97% ↑ Cmin and 65% ↑ Cmax of SQV when administered 2 hours apart. No short-term SQV toxicities were noted.[324]	

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	subjects.[316] Separate case report of therapeutic ATV levels and viral suppression in treatment-experienced subject on lansoprazole 30 mg BID and ATV/r.[317] In a prospective, open-label study of HIV-infected subjects on ATV 300/rtv 100 mg QD, ATV Cmin were not significantly different in those taking ATV/r alone (n=107) or with a PPI (n=17) (median 500 and 551 ng/mL, respectively). ATV Cmin in both groups were lower than historical controls in healthy subjects, possibly due to reduced gastric acid secretion in HIV.[318] **Until additional data available, avoid administering with omeprazole or other PPIs. If co-administration is necessary, boosted ATV may be preferable, along with TDM (if available).**						
Rifabutin *(CYP3A > deacetylase; moderate inducer of CYP3A)*	**ATV 400 mg + rifabutin 150 mg QD** in healthy subjects did not result in any significant changes	Reports of lymphopenia and influenza-like illness in subjects participating in a study of darunavir	In healthy volunteers, fosamprenavir 700 mg/ritonavir 100 mg BID plus rifabutin 150 mg Q2D for 14	303% ↑ rifabutin AUC and 47.5-fold ↑+ metabolite AUC; **rifabutin 150 mg daily** had no significant effect on	400% ↑ rifabutin AUC, risk of toxicity.[7] Recommend reducing rifabutin dose to 150 mg 2-3	40% ↓ saquinavir AUC. **Avoid combination** if using saquinavir as sole protease inhibitor.[336]	In healthy volunteers, administration of single dose rifabutin 150 mg to steady-state tipranavir

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	in ATV kinetics (vs. ATV 400 mg alone); 2.5-fold ↑ rifabutin & metabolite exposure vs. standard 300 mg dose. Reduce rifabutin dosage by at least 75% (i.e., max. 150 mg q2d or 3 times/week); monitor for adverse events and further decrease rifabutin dose if necessary.[325] In healthy subjects, **ATV 300/rtv 100 mg plus rifabutin 150 mg twice weekly** resulted in rifabutin Cmax ↑ 149%, Cavg ↑ 48% and Cmin ↑ 40% and 25-*O*-desacetylrifabutin Cmax ↑ 7.8-fold, Cavg ↑ 10.9-fold and Cmin ↑ 11.5-fold. Total activity was estimated to have ↑ 119% and be similar to that of rifabutin 300 mg QD. 13/18 subjects in the combination arm discontinued due to mild-moderate neutropenia or pyrexia, versus 1/15 subjects (for cough) on rifabutin 150 mg QD alone. Monitoring for neutropenia is recommended with this combination.[326] Case report of 3 HIV patients with low CD4 (<50 cells/mm^3) and prior episodes	400/100 mg BID plus rifabutin 150 mg QD; limited PK (n=1) suggest ↑ exposure to rifabutin and metabolite. Healthy volunteers who received darunavir 600/rtv 100 mg BID plus **rifabutin 150 mg q2d** had 881% ↑ AUC of 25-*O*-desacetylrifabutin, 57% ↑ darunavir AUC and 66% ↑ ritonavir AUC compared to levels observed with standard doses of each drug alone. Half the ubjects discontinued the study prematurely due to safety reasons, primarily headache, diarrhea, back pain, dizziness and vomiting. Therefore, increased monitoring for rifabutin-related adverse events is warranted in patients receiving the combination with darunavir/r.[328] Case report of 3 HIV patients with low CD4 (<50 cells/mm^3) and prior episodes of drug-sensitive TB who relapsed with rifamycin-resistant *M. tuberculosis* infection despite receiving fully supervised directly	days yielded similar RFB exposures compared to rifabutin 300 mg QD alone. **RFB 150mg Q2D is recommended when co-administered with FPV/RTV 700mg/100mg BID.**[329] Case report of 3 HIV patients with low CD4 (<50 cells/mm^3) and prior episodes of drug-sensitive TB who relapsed with rifamycin-resistant *M. tuberculosis* infection despite receiving fully supervised directly observed therapy including rifabutin 150 mg q2d or 3x/week, plus either atazanavir/rtv or lopinavir/rtv-based HAART.[327] **When co-administering with boosted protease inhibitors, rifabutin 150 mg once daily or 300 mg three times a week is recommended, along with close monitoring for antimycobacterial activity and therapeutic drug monitoring if available.**[240]	lopinavir/r concentrations.[175] Reduce rifabutin dosage by at least 75% (i.e., max. 150 mg q2d or 3 times/week);[330] monitor for adverse events and further decrease rifabutin dose if necessary. In healthy subjects, **LPV 400/rtv 100 mg BID mg plus rifabutin 150 mg 3 times weekly** resulted 3-fold ↑ in sum exposures of rifabutin and 25-*O*-desacetylrifabutin compared to rifabutin 150 mg QD alone. 13/14 subjects in the combination arm experienced at least 1 ADR including fever, rash, neutropenia or lymphopenia. Future studies of this combination in healthy subjects is not recommended.[331] Kinetics of rifabutin and 25-*O*-desacetylrifabutin were measured in 10 HIV-patients with active TB **with RFB dosed 300 mg 3x/week, RFB 150 mg 3x/week plus LPVr 400/100 mg BID, and RFB 300 mg 3x/week plus LPVr** if RFB plasma	times per week.[334] For combination ritonavir 400 mg BID + saquinavir 400 mg BID, may be possible to administer RFB 150 mg q3days.[335] Case report of 3 HIV patients with low CD4 (<50 cells/mm^3) and prior episodes of drug-sensitive TB who relapsed with rifamycin-resistant *M. tuberculosis* infection despite receiving fully supervised directly observed therapy including rifabutin 150 mg q2d or 3x/week, plus either atazanavir/rtv or lopinavir/rtv-based HAART.[327] **When co-administering with boosted protease inhibitors, rifabutin 150 mg once daily or 300 mg three times a week is recommended, along with close monitoring for antimycobacterial activity and therapeutic drug monitoring if available.**[240]	For combination **ritonavir 400 mg BID + saquinavir 400 mg BID,** may be possible to administer RFB 150 mg q3days.[335] Case report of 3 HIV patients with low CD4 (<50 cells/mm^3) and prior episodes of drug-sensitive TB who relapsed with rifamycin-resistant *M. tuberculosis* infection despite receiving fully supervised directly observed therapy including rifabutin 150 mg q2d or 3x/week, plus either atazanavir/rtv or lopinavir/rtv-based HAART.[327] In healthy volunteers, coadministration of rifabutin 150 mg q3d plus **SQV 1000/rtv 100 mg BID** showed no significant impact on protease inhibitor levels. In contrast, AUC of RFB + active metabolite ↑ 134% and 60% when **RFB was dosed 150 mg every 3 or 4 days**, respectively with SQV/rtv BID compared to RFB 150 mg daily alone. Monitor for neutropenia and elevated LFTs while on combination.[337]	500/rtv 200 mg BID led to significant ↑ in exposure to rifabutin and its metabolite. Single-dose rifabutin did not affect the kinetics of tipranavir/rtv. Recommend rifabutin 150 mg 3 times/week with this combination.[239] Case report of 3 HIV patients with low CD4 (<50 cells/mm^3) and prior episodes of drug-sensitive TB who relapsed with rifamycin-resistant *M. tuberculosis* infection despite receiving fully supervised directly observed therapy including rifabutin 150 mg q2d or 3x/week, plus either atazanavir/rtv or lopinavir/rtv-based HAART.[327] **When co-administering with boosted protease inhibitors, rifabutin 150 mg once daily or 300 mg three times a week is recommended, along with close monitoring for antimycobacterial activity and therapeutic drug monitoring if available.**[240]

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	of drug-sensitive TB who relapsed with rifamycin-resistant *M. tuberculosis* infection despite receiving fully supervised directly observed therapy including rifabutin 150 mg q2d or 3x/week, plus either atazanavir/rtv or lopinavir/rtv-based HAART.[327] **When co-administering with boosted protease inhibitors, rifabutin 150 mg once daily or 300 mg three times a week is recommended, along with close monitoring for antimycobacterial activity and therapeutic drug monitoring if available.[240]**	observed therapy including rifabutin 150 mg q2d or 3x/week, plus either atazanavir/rtv or lopinavir/rtv-based HAART.[327] **When co-administering with boosted protease inhibitors, rifabutin 150 mg once daily or 300 mg three times a week is recommended, along with close monitoring for antimycobacterial activity and therapeutic drug monitoring if available.[240]**		concentrations were below target. Rifabutin at 300 mg without LPVr yielded low *C*max in 5/10 patients. After LPVr was added and RFB was reduced to 150 mg, 9/10 had low *C*max values. Eight patients had RFB dose ↑ to 300 mg with LPVr. Most RFB *C*max values were below the tuberculosis MIC and most AUC values were lower than those associated with treatment failure or relapse and with acquired rifamycin resistance. One of the 10 patients experienced relapse with acquired rifamycin resistance. 8/18 LPV Cmin measurements were also lower than target of 4 mg/L.[332] Case report of 3 HIV patients with low CD4 (<50 cells/mm^3) and prior episodes of drug-sensitive TB who relapsed with rifamycin-resistant *M. tuberculosis* infection despite receiving fully supervised directly observed therapy including **rifabutin 150 mg q2d or 3x/week,** plus either atazanavir/rtv or lopinavir/rtv-based		**When co-administering with boosted protease inhibitors, rifabutin 150 mg once daily or 300 mg three times a week is recommended, along with close monitoring for antimycobacterial activity and therapeutic drug monitoring if available.[240]**	

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				HAART.[327] In 16 TB/HIV co-infected patients, the kinetics of rifabutin were measured alone (300 mg QD) and in conjunction with LPVr 400/100 mg BID either as RFB 150 mg daily or 3 times weekly. Median rifabutin AUC and Cmax were 3026 ng/mL.h and 297 ng/mL (RFB alone), 2307 and 168 (150 mg 3x/wk with LPVr) and 5010 and 311 (150 mg QD with LPVr). **Rifabutin 150 mg daily** combined with LPV/r produces C_{max} concentrations within the recommended target range of 300 to 900 ng/mL.[333] **When co-administering with boosted protease inhibitors, rifabutin 150 mg once daily or 300 mg three times a week is recommended, along with close monitoring for antimycobacterial activity and therapeutic drug monitoring if available.**[240]			
Rifampin *(Deacetylase> hydrolysis, GT?, CYP?; potent inducer of CYP3A*	In an open-label, randomized study of healthy subjects, coadministration of rifampin 600 mg QD		81% ↓ AUC and 91% ↓ Cmin of amprenavir. **Avoid combination**.[341]	75% ↓ LPV AUC. **Avoid combination**.[175] In a healthy	35% ↓ ritonavir AUC. May need to ↑ ritonavir dose.[7] NB: In HIV-negative	80% ↓ saquinavir AUC. **Avoid combination**.[9] Addition of ritonavir	Combination not studied. Coadministration not recommended.

	Atazanavir (Reyataz®)	Darunavir (Prezista®)	Fosamprenavir (Telzir®)	Lopinavir/ ritonavir (Kaletra®)	Ritonavir (Norvir®)	Saquinavir (Invirase®)	Tipranavir (Aptivus®)
and GT)	plus **atatazanavir/r at 300/100 or 300/200 mg QD** led to significant ↓ in ATV AUC (57 and 31%, respectively) and Cmin (93 and 80%, respectively) vs. ATV 400 mg QD alone. **ATV/r 400/200 mg** plus rifampin led to comparable ATV AUC but 60% ↓ Cmin vs. ATV alone.[338] In a separate study in HIV-infected individuals receiving active TB therapy (n=3), ATV Cmin was undetectable and AUC was significantly reduced in the presence of rifampin.[339] In healthy subjects, steady-state atazanavir C12 was 811 ng/mL with ATV 300 mg BID alone, 44 ng/mL with **ATV 300 mg BID plus rifampin 600 mg QD**, and 113 ng/mL with **ATV 400 mg BID plus rifampin 600 mg QD**.[340] **Avoid concurrent rifampin administration until further study.**			volunteer study, subjects received LPV/r 400/100 mg BID (days 1-15), plus RIF 600 mg/d (days 11-24), and then were randomized to receive either LPV/rtv 800/200 or 400/400 mg BID (days 16-24) with RIF: • no change in rifampin Cmax vs. historical data • 56% ↓ lopinavir Cmin with 800/200 mg BID dose, vs. 400/100 mg BID dose • overall, no statistically sig. change in LPV Cmin with 400/400 mg BID dose, although ↓ seen in some subjects[342] In a healthy volunteer study of RIF 600 mg plus **LPV 600/rtv 150 mg BID or LPV 800/200 mg BID**, an **unexpected high incidence of nausea and vomiting** (10/11 subjects) and **elevated AST/ALT levels** (11/11 subjects) was observed after LPV/rtv was added to RIF therapy; the study was prematurely discontinued.[343]	subjects taking rifampin >2 weeks, administration of indinavir 800/ritonavir 100 mg resulted in 81% ↓ indinavir AUC and 89% ↓ ritonavir AUC compared to controls, while rifampin AUC was ↑ 25%. **Avoid concurrent rifampin administration until further study**.[345]	(e.g., **saquinavir/ritonavir 400/400 mg BID, or 1000/100 mg BID**) may provide therapeutic concentrations in presence of rifampin.[346, 347] However, in a Phase I, randomized, open-label, multi-dose study in healthy volunteers, 11/28 (39.3%) of subjects who received **rifampin 600 mg QD plus SQV 1000/rtv 100 mg BID** developed **significant hepatocellular toxicity**, including transaminase elevations of up to > 20X upper limit of normal values. LFTs returned to normal upon drug discontinuation. Therefore, **rifampin should not be given to patients receiving boosted saquinavir therapy** (Dear Healthcare Provider Letter, Roche Laboratories, USA, February 2005).	

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				In a cohort of HIV-infected patients suppressed on a lopinavir/ritonavir 400/100 mg BID regimen, rifampin 600 mg daily was initiated and LPVr dose was sequentially increased to 600/150 mg BID and then 800/200 mg BID at weekly intervals. Lopinavir exposures achieved with 800/200 mg BID in the presence of rifampin were similar to baseline values prior to starting rifampin. Two patients developed grade 3-4 ALT elevations. **Doubling the dose of LPVr overcomes the induction effect of rifampin.**[344]			
Rifapentine	**Reducted exposures of protease inhibitors expected with combination. Do not coadminister rifapentine and PIs.**[240]						
Salmeterol/ Serevent®, Advair® (with fluticasone) *(CYP3A4)* *See also entry for Corticosteroids, Oral/inhaled.*	**Potential for ↑ salmeterol exposure with CYP3A inhibitors.** Coadministration of ketoconazole, a strong CYP3A4 inhibitor, at a dose of 400 mg/day with salmeterol at a dose of 50 mcg twice daily for 7 days led to a significant 16-fold ↑ in salmeterol AUC and a significant 1.4-fold ↑ in salmeterol Cmax versus salmeterol plus placebo. The mean QTc was not significantly affected by coadministration of ketoconazole and salmeterol; however, concomitant use was associated with a higher rate of increases in QTc duration compared with salmeterol and placebo. Although not studied with ritonavir, also a strong CYP3A4 inhibitor, the risk of cardiovascular adverse events may be increased**. The concomitant use of ritonavir and salmeterol is contraindicated.**[7]. If concurrent use is required, consider monitoring the patient for increased salmeterol plasma levels and cardiovascular adverse events including QT prolongation, palpitations and sinus tachycardia. Other beta-agonists such as salbutamol, formoterol, fenoterol, terbutaline may be safter options. Of note, use of Advair® (fluticasone/salmeterol) should be avoided with ritonavir, due to the additional interaction risk between ritonavir and fluticasone.[7] Symbicort® (budesonide/formoterol) Turbuhaler may be a suitable alternative to Advair®.[242]						
Sulfamethoxazole (SMX) *(primarily N-acetylase> GT > CYP2C9 (minor)*				Clinically significant interaction not expected.[175]	20% ↓ SMX AUC. May need to ↑ SMX dose.[7]		
Theophylline *(CYP1A2 (>70%) >2E1>3A4*					43% ↓ theophylline AUC. May need to ↑ theophylline dose.[7]		

	Atazanavir (Reyataz®)	Darunavir (Prezista®)	Fosamprenavir (Telzir®)	Lopinavir/ ritonavir (Kaletra®)	Ritonavir (Norvir®)	Saquinavir (Invirase®)	Tipranavir (Aptivus®)
(minor)							
Trimethoprim *(10-20% metabolized, via CYP?)*				Clinically significant interaction not expected.[175]	20% ↑ TMP AUC. Clinical significance unknown.[7]		
Voriconazole *(CYP2C19, 2C9, 3A; inhibits CYP3A4, 2C9, 2C19)*	Case report of positive immunologic and virologic response in a patient with multidrug-resistant HIV on **atazanavir 300 mg QD,** raltegravir 400 mg BID and tenofovir/emtricitabine concurrently with **voriconazole 200 mg twice daily**.[348] An open-label nonrandomized study assessed the impact of atazanavir/ritonavir 300/100-mg QD on the kinetics of voriconazole in CYP2C19 extensive metabolizers (EMs) and poor metabolizers (PMs). Among EMs, coadministration resulted in 33% ↓ AUC and ↓ 39% Cmin of voriconazole, and 12% ↓ AUC and 20% ↓ Cmin of atazanavir. Among PMs, coadministration resulted in ↑ voriconazole Cmax, AUC and Cmin by 4.4-, 5.6-, and 7.7-fold, while atazanavir AUC ↓	Combination has not been studied. Administration of voriconazole with ritonavir 100 mg BID led to 39% ↓ AUC of voriconazole. Case report of a patient on **darunavir 900/100 mg QD, etravirine 200 mg BID, 2 NRTIs and voriconazole 400 mg BID** for 6 weeks. Drug levels were obtained during voriconazole co-administration and 3 weeks after voriconazole discontinuation. Therapeutic voriconazole levels were achieved, while etravirine Ctrough ↑ 134%, ritonavir Ctrough was undetectable and darunavir Ctrough was well below historical reference data. After voriconazole was discontinued, ritonavir Ctrough increased to the same range as the historical control and darunavir Ctrough increased by four-fold. The combination of etravirine/darunavir/ritonavir with	A dual inhibition interaction is possible via CYP 3A4 inhibition by unboosted PI and voriconazole. CYP2C19 poor metabolizers may be at increased risk of higher voriconazole concentrations due to preferential CYP3A4 inhibition. Potential for ↑ concentrations of unboosted PIs and voriconazole. Monitor for both PI and voriconazole toxicity. Consider TDM of both drugs.	With RTV 100 mg twice daily: 39% ↓ voriconazole AUC; 14% ↓ RTV AUC[351, 352] Use of low boosting doses of RTV (i.e. 100mg twice daily) combined with any of the other PIs should be **avoided** unless the benefits outweigh the risks of antifungal failure.[175, 353] Consider voriconazole TDM or use other antifungals that do not interact significantly with RTV.	Coadministration of voriconazole 200 mg BID with **ritonavir 400 mg Q12h is contraindicated** because of 82% ↓ AUC, ↓ Cmax 66% of voriconazole healthy subjects after 9 days of coadministration; ritonavir concentrations were unaffected.[351] **Ritonavir 100 mg BID** plus voriconazole 200 mg BID led to significant decrease Voriconazole levels: 39% ↓ $AUC_{0\text{-}12Hr}$, 24% ↓ Cmax of voriconazole, and slight reduction in ritonavir levels (14% ↓ $AUC_{0\text{-}12Hr}$, 24% ↓ Cmax). Try to avoid low dose RTV and voriconazole combination.[351] In a study in healthy individuals stratified by CYP2C19 genotype, a 42% ↓ in voriconazole clearance was observed in all phenotypes after coadministration of **ritonavir 300 mg BID** plus single-dose voriconazole.[354]		No data, but potential for bi-directional inhibition between voriconazole and PIs exists. RTV 400 mg BID ↓ voriconazole AUC by 82%. Effect of low dose RTV (100-400 mg/day) has not been studied. Some suggest not to co-administer until data become available.

	Atazanavir (Reyataz®)	Darunavir (Prezista®)	Fosamprenavir (Telzir®)	Lopinavir/ ritonavir (Kaletra®)	Ritonavir (Norvir®)	Saquinavir (Invirase®)	Tipranavir (Aptivus®)
	20%, Cmax ↓ 19% and Cmin ↓ 31%. Ritonavir AUC and Cmax did not change substantially with voriconazole codosing in either study group.[349] **Avoid combination** unless the benefits outweigh the risks of antifungal failure.	voriconazole should be undertaken with caution and BID dosing of darunavir/ritonavir should be considered in this setting. Therapeutic drug monitoring should be utilized when available.[350] Avoid co-administration with darunavir/ ritonavir unless potential benefits outweigh possible risks.			Therefore, combination should be avoided; risk of short-term voriconazole toxicity particularly in CYP2C19 poor metabolizers, and potential long-term loss of voriconazole efficacy.		
Warfarin, Acenocoumarol/ nicoumalone *(racemic mixture; R: CYP1A2, 3A, 2C19; S: 2C9 primarily)* *NB:* The S-enantiomer of warfarin exhibits 2 to 5 times more anticoagulant activity than the R-enantiomer in humans, but generally has a more rapid clearance. The R(+) and S(–) enantiomers of acenocoumarol have comparable anticoagulant effects, but the S-enantiomer has a very short half-life; thus only the R-enantiomer provides a	May potentially inhibit anticoagulant metabolism; monitor for ↑ INR and adjust anticoagulant dose accordingly when starting and discontinuing therapy.[1] Case report of a patient who required doubling of acenocoumarol dose to maintain therapeutic INR while on atazanavir 300/100 mg daily. When atazanavir/ritonavir was replaced with raltegravir, the acenocoumarol dose was reduced and therapeutic INR was maintained.[355]	May induce anticoagulant metabolism. Monitor for ↓ INR and adjust anticoagulant dose accordingly when starting and discontinuing therapy.[3] Open label randomized crossover study in 12 healthy volunteers of darunavir 600 mg/ritonavir 100mg BID plus single dose **warfarin 10 mg** led to ↓ S-Warfarin AUC 21% suggesting induction of CYP2C9 enzyme activity. May be attributed to co administration of RTV.[319]	May potentially inhibit anticoagulant metabolism; monitor for ↑ INR and adjust anticoagulant dose accordingly when starting and discontinuing therapy.	Three case reports where INR declined significantly and warfarin dosage was increased 40-140% in order to achieve therapeutic INR following initiation of lopinavir/ritonavir therapy.[356-358] Monitor for changes in INR and adjust anticoagulant dose accordingly when starting and discontinuing therapy.	May induce anticoagulant metabolism. Case reports where warfarin dosage was almost doubled to maintain INR with ritonavir[359, 360] and a 3-fold increase in acenocoumarol dose was noted.[361] However, another case report documented the opposite effect (increased INR requiring vitamin K and decrease in warfarin dose).[362] Monitor for changes in INR and adjust anticoagulant dose accordingly when starting and discontinuing therapy.	May inhibit anticoagulant metabolism; case report of hypo-prothrombinemia which required 20% ↓ warfarin dose with concomitant saquinavir.[363] Monitor for ↑ INR and adjust anticoagulant dose accordingly when starting and discontinuing therapy.	May induce anticoagulant metabolism. Monitor for ↓ INR and adjust anticoagulant dose accordingly when starting and discontinuing therapy. Use combination with caution as tipranavir has been associated with increased risk of intracranial hemorrhage.[11]

	Atazanavir (Reyataz®)	Darunavir (Prezista®)	Fosamprenavir (Telzir®)	Lopinavir/ ritonavir (Kaletra®)	Ritonavir (Norvir®)	Saquinavir (Invirase®)	Tipranavir (Aptivus®)
pharmacologic effect in vivo.							

Please note: This chart summarizes some of the major drug interactions identified to date, based on current available data; other drug interactions may exist. Please use caution whenever adding/modifying therapy. The information in this table is intended for use by experienced physicians and pharmacists. It is not intended to replace sound professional judgment in individual situations, and should be used in conjunction with other reliable sources of information. Due to the rapidly changing nature of information about HIV treatment and therapies, users are advised to recheck the information contained herein with the original source before applying it to patient care.

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Drug Interactions with Secondary Protease Inhibitors

	Amprenavir (Agenerase®)	Indinavir (Crixivan®)	Nelfinavir (Viracept®)	Saquinavir hgc-(Invirase®) sgc-(Fortovase®)
I) DOSING	**INFORMATION**			
Usual Dose	Amprenavir: 1200 mg po BID *NB: Amprenavir is 14% less bioavailable from liquid vs. capsules; therefore not interchangeable on a mg-per-mg basis.*	800 mg po q8h	Adults: 750 mg po TID or 1250 mg po BID Children (2-13 years old): 20-30 mg/kg/dose TID	hgc: 600 mg po q8h sgc: 1200 mg TID or 1600 mg BID
Kinetic Characteristics	Primarily metabolized by CYP3A4. Inhibitor of CYP3A4 (similar potency as indinavir and nelfinavir)[1]; also induces CYP3A4[2].	Primarily metabolized by CYP3A4. Inhibitor of CYP3A4; may also be weak inhibitor of CYP2D6.[3, 4] Requires acidic pH for optimal absorption.	Metabolized by CYP3A4 and CYP2C19. Inhibitor of CYP3A4.[5, 6] Induces CYP2B6, 2C8 and 2C9.[7]	Primarily metabolized by CYP3A4. Weak inhibitor of CYP3A4.[3]
Food (NB: **garlic**: see entries for Saquinavir and Ritonavir)	May be taken with or without food. Avoid taking with high-fat meal.[1] Administer amprenavir liquid solution at least 1 hour apart from other medications that contain sorbitol.	Take on empty stomach or with light meal. (77% ↓ AUC with full meal)[8]	Take with meal or light snack (2-5 fold ↑ in Cmax, AUC). Highest nelfinavir levels observed with greater food intake, i.e., 500-1000 kCal and 20-50% fat.[9]	Take within 2 hours of meal (almost 7-fold ↑ AUC with food). In a kinetic study of healthy volunteers, chronic **garlic** administration plus saquinavir-sgc 1200 mg TID led to a 51% ↓ saquinavir AUC. Use caution when combining garlic supplements with saquinavir used as a sole protease inhibitor.[10]
Grapefruit juice	No significant changes in amprenavir concentrations when administered with 200 mL grapefruit juice.[11]	No change in indinavir concentrations when administered with 6 oz. Double-strength grapefruit juice.[12]	Not studied.	40-100% ↑ saquinavir AUC. Take 150 mL juice with each dose.[13]
Vitamins	**Vitamin E:** Each amprenavir capsule contains 109 IU **vitamin E** ∴ avoid additional vit. E supplements.	**Vitamin C:** In a study of healthy volunteers, Vit C 1 g daily resulted in a significant ↓ in IDV C_{max} (-20%, p = 0.04) and steady-state AUC_{8hr} (-14%, p <0.05); IDV C_{min} was 32% lower with Vit C (265 vs. 181 ng/mL, p = 0.09). Clinical significance unclear, use combination with caution.[14]		
II) ANTI-	**RETROVIRAL**	**INTERACTIONS**		
Amprenavir (APV), fos-amprenavir (FPV)		Single dose study: 31%↑ Cmax and 18% ↑ AUC of amprenavir, 35% ↓ AUC and 23% ↓ Cmax of indinavir. Multiple-dose study: 33% ↑ APV AUC, 38% ↓ IDV AUC, 27% ↓ Cmin. No dosage adjustments recommended for either drug.[15]	Amprenavir 800 mg q8h + nelfinavir 750 mg po q8h: 2.89-fold ↑ Cmin of APV (but no overall change in AUC) , 15%↑ NFV AUC. No dosage adjustment required for either drug.[15]	*Amprenavir:* In a randomized, prospective study of 11 HIV+ subjects, SQV AUC ↓ 81% and C_{12} ↓ 61% when given in a regimen of SQV 1000/rtv 100/APV 600 mg BID vs. SQV 1000/rtv 100 mg BID in the absence of APV. APV exposure was not affected. When doses

	Amprenavir (Agenerase®)	Indinavir (Crixivan®)	Nelfinavir (Viracept®)	Saquinavir hgc-(Invirase®) sgc-(Fortovase®)
				were adjusted to **SQV 1400/rtv 200/APV 600 mg BID**, SQV exposure returned to baseline.[16] May wish to consider TDM if using RTV 100 mg BID dose with this combination.
Atazanavir (ATV)	Combination of ATV with amprenavir in HIV-infected peripheral blood mononuclear cells yielded additive to moderately synergistic antiviral effects.[17] In a series of expanded access subjects (n=30), combination of ATV 400 mg QD, APV 1200 mg/d, and tenofovir 300 mg/d led to lower ATV Ctrough (0.073 ug/mL) vs. either ATV/APV or ATV alone (0.11 and 0.251 ug/mL, respectively).[18]	Combination ATV with indinavir in HIV-infected peripheral blood mononuclear cells yielded additive to moderately synergistic antiviral effects.[17] However, **combination not recommended** due to the risk for additive hyperbilirubinemia.[19]	Combination of ATV with nelfinavir in HIV-infected peripheral blood mononuclear cells yielded additive to moderately synergistic antiviral effects.[17]	Additive-synergistic antiviral activity in vitro.[17] In healthy volunteers, ATV 400 mg QD plus **saquinavir-sgc 800, 1200, or 1600 mg QD** resulted in 5.4- to 7.1-fold ↑ AUC and 6.6- to 17.6-fold ↑ Cmin of saquinavir; ATV kinetics not affected.[20]
Capravirine			Healthy volunteer, multi-dose study of CPV 1400 mg BID + nelfinavir 1250 mg BID with food: ↑ CPV Cmax 84%, AUC ↑ 138%, Cmin ↑ 263%, NFV kinetics unchanged.[21]	Addition of SQV 1000 mg BID to dual PI regimen of CPV 400 mg BID plus LPV/r 400/100 mg BID or CPV 700 mg BID plus LPV/r 533/133 mg BID did not affect PK of either SQV or LPV. No further dosage adjustment needed.[22]
Darunavir, TMC114 *(substrate of CYP3A4)*				Saquinavir-sgc: Single dose SQV-sgc 1200 mg plus 1200 mg TMC-114 BID led to 5-fold ↑ SQV AUC and Cmax and 1.4-fold ↑ TMC AUC.
Delavirdine	Amprenavir 1200 mg +/- delavirdine 600 mg BID (healthy volunteer study) significantly increased amprenavir concentrations (4-fold ↑ AUC, 6-fold ↑ Cmin, 1.3 fold ↑ Cmax); no change in delavirdine concentrations.[23] In a separate healthy volunteer multi-dose study, administration of APV 600 mg BID +/- DLV 600 mg BID resulted in ↑ APV Cmin 133% & AUC 117%; however, median DLV Cmin ↓ 88%. Suggest avoiding this dosage	IDV 600 mg q8h + DLV: ↑ IDV AUC, Cmin vs. IDV 800 mg q8h alone.[25, 26] Thus, ↓ IDV to 600 mg q8h with delavirdine. Healthy volunteer study of IDV/DLV BID regimens: a) 800/600 mg BID: similar AUC, Cmax, but Cmin IDV ↓ 35-40% (vs. IDV 800 mg q8h) b) 1200/600 mg BID: similar Cmin, ↑ AUC (50-70%), ↑ Cmax (20-50%) Thus, 1200/600 mg BID may be preferable (NB: risk nephrolithiasis?); may take +/- food.[27]	Interaction data in HIV subjects taking DLV 600 mg TID + standard NFV: approx. 2-fold ↑ NFV AUC, and DLV Cmin similar to that with DLV 400 mg TID alone. [28] Recommendations on dosage adjustments not available. Use together with caution and monitor for drug toxicities, incl. Neutropenia. Regimens currently being studied: NFV 750 mg TID + DLV 600 mg TID, and NFV 1250 mg BID + DLV 600mg BID.	Delavirdine 400 mg TID + saquinavir-hgc 600 mg TID in healthy volunteers: 5-fold ↑ SQV AUC, Cmin, Cmax; monitor LFTs during initial weeks of combination therapy. Dosage adjustments not necessary.[29] In a randomized study in HIV-subjects (n=10), these regimens were compared: • SQV-sgc 1200 mg TID • SQV-sgc 1400 mg + delavirdine 600 mg BID • SQV-sgc 1000 mg + delavirdine 400 mg TID When combined with DLV,

	Amprenavir (Agenerase®)	Indinavir (Crixivan®)	Nelfinavir (Viracept®)	Saquinavir hgc-(Invirase®) sgc-(Fortovase®)
	combination until further data available.[24]			SQV exposure was ↑ vs. SQV alone; SQV Cmin was higher in the TID vs. BID arm, both were greater than Cmin SQV alone.[30]
Didanosine	No significant changes in amprenavir AUC or Cmin observed when administered: • concurrently with ddI-EC (in fasting state) • concurrently with ddI tablets (in fasting state) • 1 hour prior to ddI tablets (fasting) compared to amprenavir alone in the fasting state. Authors suggest amprenavir may be dosed concurrently with both ddI tablets and enteric-coated capsules in the fasting state.[31]	Indinavir requires acidic pH for best absorption. Separate doses by 1 hour.[4, 32] No difference in pharmacokinetics of indinavir observed when coadministered with 400 mg enteric-coated didanosine in healthy volunteers.[33]	Dosage adjustment not required. However, since didanosine needs to be administered on an empty stomach, it should be given 1 hour before or 2 hours after nelfinavir (given with food/snack).	Dosage adjustment not required. However, since didanosine needs to be administered on an empty stomach, it should be given 1 hour before or 2 hours after saquinavir (given with a full meal).
Efavirenz	**APV 1200 mg BID + EFV 600** mg: 36% ↓ AUC, 39% ↓ Cmax, 43% ↓ Cmin APV; 15% ↑ EFV AUC[34]. Avoid negative interaction by adding either: • 200/500 mg RTV BID, or • 1250 mg nelfinavir BID to APV 1200 mg BID plus EFV 600 mg qhs.[35] Other dosage combinations that yielded stable APV conc.: • **APV 600 mg/ rtv 200 mg BID** + EFV[36] • **APV 1200 mg/ rtv 300 mg QD** plus EFV[37] • APV/EFV + **NFV 1250 mg BID**[38] • APV/EFV **+ IDV 1200 mg BID**[38] • APV/EFV + **RTV 100 mg BID**[38]	**IDV alone:** 30-35% ↓ indinavir levels; no change in efavirenz levels. Increase IDV dosage to 1000 mg q8h.[39] **Indinavir/rtv BID** When efavirenz was added to IDV 800 mg/RTV 100 mg BID regimen, IDV exposure was significantly reduced (19% ↓ AUC, 48% ↓ Cmin). May wish to consider ↑ to indinavir 800 mg/ritonavir 200 mg BID.[40] **indinavir/rtv QD:** When efavirenz was added to IDV/RTV once daily regimens (800/100, 800/200, 1200/100), significant ↓ in IDV and RTV concentrations (esp. C24) were observed. Avoid using EFV with once daily IDV/RTV regimens.[41]	Healthy volunteer study: efavirenz 600 mg + nelfinavir 750 mg q8h x 7 days: 20% ↑ NFV levels, 37% ↓ M8 levels; no change in efavirenz levels.[42] However, subsequent kinetic study in HIV+ subjects of efavirenz 600 mg qhs and nelfinavir 1250 mg BID showed ↓ 65% nelfinavir Cmin (p=0.04), ↓ 38% AUC and ↓ 21% Cmax at 32 weeks.[43] Therefore, monitor for antiretroviral efficacy when using this combination. Nelfinavir dosage adjustment may be necessary, consider therapeutic drug monitoring where available.	Multiple dose healthy volunteer study of efavirenz 600 mg/day + SQV-sgc 1200 mg q8h: 12% ↓ efavirenz AUC (not clinically significant), and 62% ↓ SQV AUC.[44] Can avoid this negative interaction by adding ritonavir to combination at the following doses: • saquinavir-sgc 400 mg BID • ritonavir 400 mg BID • efavirenz 600 mg qhs[45]
Enfuvirtide	No clinically significant interaction expected.	No clinically significant interaction expected.	No clinically significant interaction expected.	No clinically relevant interaction noted with co-administration of enfuvirtide 90 mg SC BID and saquinavir 1000 mg/ ritonavir 100 mg BID for 4 days in 12 HIV-infected subjects.[46]
Etravirine, TMC125, *(diaminopyrimidine NNRTI; inducer of*	Potential for decreased amprenavir concentrations secondary to enzyme induction by etravirine. Optimal dosages for co-	Steady-state study of etravirine 1600 mg BID plus indinavir 800 mg TID (n=10) resulted in 51% ↑ AUC and Cmax of	Potential for decreased nelfinavir concentrations secondary to enzyme induction by etravirine.	Etravirine 900 mg BID at steady state plus single-dose saquinavir 1200 mg (n=12) resulted in 52% ↓ AUC and 46% ↓ Cmax of

	Amprenavir (Agenerase®)	Indinavir (Crixivan®)	Nelfinavir (Viracept®)	Saquinavir hgc-(Invirase®) sgc-(Fortovase®)
CYP3A)	administration have not yet been established.	etravirine, likely due to CYP3A inhibition; indinavir AUC ↓ 46%, Cmax ↓28%.[47] Guidelines for dosage adjustment not available; avoid combination if possible, until further information available.	Etravirine should not be co-administered with PIs without low-dose ritonavir.[48]	saquinavir, likely due to CYP3A induction.[47] Etravirine concentrations not measured. Guidelines for dosage adjustment not available; avoid combination if possible, until further information available. Etravirine 800 mg BID did not affect pharmacokinetics of **LPV 400/RTV 100/SQV 800-1000 mg BID** in 15 HIV-infected male subjects.[49]
Indinavir	Single dose study: 31%↑ Cmax and 18% ↑ AUC of amprenavir, 35% ↓ AUC and 23% ↓ Cmax of indinavir. Multiple-dose study: 33% ↑ APV AUC, 38% ↓ IDV AUC, 27% ↓ Cmin. No dosage adjustments recommended for either drug.[15]		In a single dose study, 83% ↑ NFV AUC, 51% ↑ IDV AUC observed.[50] In multi-dose trial of HIV-infected subjects (n=20), IDV 1200 mg and NFV 1250 mg BID provided IDV kinetics similar to IDV 800 mg q8h alone; indinavir had no effect on nelfinavir kinetics, and NFV Cmin was similar to values seen with 750 mg TID.[51]	Hgc: 5- to 8-fold ↑ SQV AUC;[52] in vitro study suggests synergy at low doses and antagonism at high doses.[53] Sgc: 620% ↑ SQV AUC (1200 mg SQV single dose + IDV 800 mg q8h x 2 days); no apparent clinically relevant changes to IDV.[54]
Lopinavir/ ritonavir	**<u>LPV/r capsules:</u>** • In a healthy volunteer multi-dose study, **LPV/r + APV 750 mg BID** gave similar APV AUC, and 4.6-fold ↑ Cmin vs. APV 1200 mg BID alone. However, LPV and RTV conc. were ↓ in presence of APV (LPV AUC ↓ 38%, Cmin ↓57%).[55] • Similar findings observed in cohort of HIV+ subjects with both APV and FPV formulations.[56 57] • In a prospective cohort (n=27) of experienced patients, combination of **LPV/r 400/100 mg BID and APV 600 mg BID** led to a 54% ↓ APV exposure vs. APV/r 600/100mg BID. Addition of additional RTV 100 mg BID to combination did not improve APV levels.[58] • In cohort of experienced HIV-subjects (n=46),	**Indinavir 800 mg BID + LPV/r:** In HIV+ subjects (n=5), steady-state PK of combination yielded IDV PK similar to IDV 800/r 100 mg BID; median LPV PK slightly ↓ than expected.[61] **Indinavir 600 mg BID + LPV/r:** <u>Healthy volunteer study</u>: similar IDV AUC, ↓ Cmax, 3.5-fold ↑ Cmin vs. IDV 800 mg q8h alone; LPV kinetics not affected.[62, 63] <u>HIV+ subjects</u>: In an open-label PK study (n=11), both IDV & LPV PK parameters ↓ up to 64% vs. values seen with coadministration in healthy subjects.[64] **Indinavir 400 mg BID + LPV/r:** In a case series of HIV+ men taking lopinavir/r, addition of indinavir 400 mg BID did not significantly alter median lopinavir kinetics; indinavir Cmin were above target in 5/8 subjects.[65] A separate	**<u>LPV/r capsules:</u>** Multi-dose study in healthy volunteers of LPV/r 400/100 mg BID and NFV 1000 mg BID resulted in NFV concentrations similar to those with NFV 1250 mg BID alone; LPV levels significantly ↓ in the presence of nelfinavir (LPV Cmax ↓ 21%, AUC ↓ 27%, Cmin ↓ 33%).[67] LPV dosage may need to be adjusted if coadministered with nelfinavir. **<u>LPV/r tablets:</u>** • Can use 400/100 mg BID with NFV in ARV-naïve subjects May ↑ to 600/150 mg (3 tablets) BID when co-administering in treatment-experienced subjects	**Saquinavir-sgc 800-1200 mg BID + lopinavir/r:** Healthy volunteer study showed 6.3-fold ↑ AUC, 9.6-fold ↑ Cmax, 16.7-fold ↑ Cmin compared to saquinavir 1200 mg TID alone. Similar SQV concentrations were observed with 1200 mg BID plus lopinavir/r. Single and steady-state saquinavir-sgc 800 mg BID had no effect on lopinavir/r kinetics.[62, 63] **Saquinavir-sgc 1000 mg BID + lopinavir/r:** In a cohort of ARV-experienced subjects (n=27), combination gave therapeutic SQV levels (median trough 1.25 ug/mL); lopinavir levels were not affected.[68]

	Amprenavir (Agenerase®)	Indinavir (Crixivan®)	Nelfinavir (Viracept®)	Saquinavir hgc-(Invirase®) sgc-(Fortovase®)
	APV 600-750 mg + LPV/r 400/100 mg BID retrospectively compared to APV 600-750 mg/RTV 100 mg BID: • with APV 600 mg dose, APV Cmin ↓ 51% with LPV/r vs. RTV alone (p=0.004) • with APV 750 mg, Cmin ↓ 33 % with LPV/r vs. RTV alone (not statistically sig.) • median LPV Cmin not affected by APV dose • Clinical significance unclear, since 85% of APV/LPV/r subjects had APV Cmin ≤3-fold Cmin with APV 1200 mg BID alone. In a prospective cohort of 12 HIV+, treatment-exp. subjects starting LPV/r plus APV 600 mg BID, 50% req. LPV/r dose ↑ to **533/133 mg or 666/166 mg BID** to achieve target LPV Cmin.[59] **Optimal doses for co-administration not yet defined.** **Suggest TDM when using this combination.**[60]	study showed no significant changes in LPV or IDV Cmin with combination.[66]		
Maraviroc				When maraviroc 100 mg BID was given with **saquinavir-sgc 1200 mg TID**, maraviroc AUC ↑ 4.3-fold, Cmax ↑ 3.3-fold.[69] When maraviroc 100 mg BID was given with **saquinavir-sgc/ritonavir 1000/100 mg BID**, maraviroc AUC ↑ 8.3-fold, Cmax ↑ 4.2-fold. Reduction of maraviroc dose to 25 mg BID resulted in maraviroc AUC ↑ 1.4-fold. Maraviroc 50% dose reduction in the presence of protease inhibitors/potent CYP3A4 inhibitors is recommended.[69]
Nelfinavir	Amprenavir 800 mg q8h +	In a single dose study,		At steady-state, 169% ↑

	Amprenavir (Agenerase®)	Indinavir (Crixivan®)	Nelfinavir (Viracept®)	Saquinavir hgc-(Invirase®) sgc-(Fortovase®)
	nelfinavir 750 mg po q8h: 2.89-fold ↑ Cmin of APV (but no overall change in AUC) , 15%↑ NFV AUC. No dosage adjustment required for either drug.[15]	83% ↑ NFV AUC, 51% ↑ IDV AUC observed.[50] In multi-dose trial of HIV-infected subjects (n=20), IDV 1200 mg and NFV 1250 mg BID provided IDV kinetics similar to IDV 800 mg q8h alone; indinavir had no effect on nelfinavir kinetics, and NFV Cmin was similar to values seen with 750 mg TID.[51]		SQV-soft gel capsules AUC, no significant changes in NFV concentrations[44]; may use lower dose of SQV-SGC (i.e., 800 mg vs. 1200 mg TID + NFV 750 mg TID, or SQV-sgc 1200 mg BID + NFV 1250 mg BID).[54, 70, 71]
Nevirapine	With **APV 600/RTV 100 mg BID/NVP 400 mg QD**, APV Cmin and Cmax ↓ 80%, AUC ↓ 77%. APV plasma levels stable with **APV 450/RTV 200 mg BID plus NVP 400 mg daily.**[72] Therefore, recommend APV 450/RTV 200 mg BID with NNRTIs.	28% ↓ IDV AUC, <10%↓ NVP AUC (non-significant). Suggest ↑ IDV dose to 1000 mg q8h when using with NVP 200 mg BID.[73] Preliminary data suggest that dosing nevirapine 400 mg once daily may have a more pronounced effect on decreasing indinavir concentrations compared to nevirapine dosed 200 mg twice daily (median 31% decrease). These findings require further substantiation; may consider monitoring indinavir levels/response if switching nevirapine dosage regimen.[74]	No statistically significant changes in NFV levels after the addition of NVP (AUC +8%, Cmax +14%, and Cmin +2%). Compared to historical controls, NVP levels appear to be unchanged.[75] Similar results were demonstrated in a separate study, and NFV Cmin remained above minimum effective concentration during nevirapine coadministration.[76] Thus, dosage adjustments not required.	27%↓ SQV AUC; clinical significance unknown.[77] Preliminary data suggest that dosing nevirapine 400 mg once daily may have a more pronounced effect on decreasing saquinavir concentrations compared to nevirapine dosed 200 mg twice daily (median 31% decrease). These findings require further substantiation; may consider monitoring saquinavir levels/response if switching nevirapine dosage regimen.[74]
Rilpivirine	Potential for ↑ concentrations of rilpivirine. Rilpivirine is not expected to affect the plasma concentrations of co-administered PIs.[78]	Potential for ↑ concentrations of rilpivirine. Rilpivirine is not expected to affect the plasma concentrations of co-administered PIs.[78]	Potential for ↑ concentrations of rilpivirine. Rilpivirine is not expected to affect the plasma concentrations of co-administered PIs.[78]	Potential for ↑ concentrations of rilpivirine. Rilpivirine is not expected to affect the plasma concentrations of co-administered PIs.[78]
Ritonavir	Amprenavir AUC, C_{min} and C_{max} were ↑ by 131%, 484% and 33%, respectively, when ritonavir 200mg BID was given with amprenavir 1200mg BID.[79] Amprenavir AUC, Cmin significantly ↑, ↓ Cmax when combined with ritonavir in the following dosages:[80-82] • 450/300 mg BID • 600/100 mg BID • 1200/200 mg once daily. Preliminary clinical data (12 weeks) promising for 600/100 mg BID and 1200/200 mg QD.[83] Ritonavir ↑ plasma APV to similar extent with either APV or FPV. Therefore,	***IDV/RTV 400/400 mg BID*** in healthy volunteers yielded indinavir AUC similar to those achieved with IDV 800 mg po q8h alone. [85] Also improved IDV PK profile: 62% ↓ Cmax, 3-fold ↑ Cmin, less impact of food on IDV absorption when given with RTV vs. alone,[86] ↓ nephrolithiasis in one case series.[87] ***IDV 800/RTV 100-200 mg BID*** also results in ↑ IDV trough levels compared to those with IDV 800 mg q8h alone;[88, 89] however, ↑ IDV peak levels[90], possible ↑ risk nephrolithiasis[91] or other adverse events.[92] IDV 600/RTV 200 mg BID	162% ↑ NFV AUC, 9% ↑ RTV AUC. [98] ***RTV 400 mg BID plus NFV 500-750 mg BID***: NFV AUC similar to that seen with NFV 750 mg TID alone; M8 levels higher with NFV 750 BID regimen. Higher RTV AUC, Cmin values when combined with NFV 500 mg vs. 750 mg BID. Overall, PK benefits similar with 2 regimens.[99] ***RTV 100-200 mg BID added to NFV 1250 mg BID*** resulted in 30%↑ NFV AUC; steady-state a.m. predose NFV concentrations ↑ 45-	***400 mg SQV-sgc /400 mg RTV BID:*** • 121% ↑ SQV AUC[102] ***800 mg SQV-sgc/200-400 mg RTV BID:*** • 1589-2158% ↑ SQV AUC[44] ***1600 mg SQV-sgc/RTV 100 mg QD:*** • Preliminary data in healthy volunteers: 300-800% ↑ SQV AUC, Cmin > than with SQV-sgc 1200 mg TID.[103] • Kinetic substudy in 13 HIV+ subjects stabilized on combination showed equivalent SQV kinetic parameters (GMR of hgc/sgc for AUC 1.40, Cmax 1.23, and Cmin

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	FPV may replace APV, and metablic APV interactions are applicable to FPV.[84]	may provide increased IDV Cmin without significantly increasing IDV Cmax.[93] ***IDV 400/RTV100 mg BID*** (open study, n=17): ↑ Cmin (~0.5 ug/mL), ↓ Cmax vs. IDV 800mg q8h.[94] Preliminary data on ***once daily dosing*** (1200/100-200 mg IDV/RTV) regimens show ↑ Cmax, and Cmin = those with 800 mg q8h.[95, 96] 1200/200mg QD regimen well-tolerated in naïve-subjects (n=40) up to 24 weeks; 1200/400 QD also under study.[97]	90%.[100] In healthy volunteers, nelfinavir 2000 mg/ritonavir 200 mg once daily provided ↑ AUC, Cmax and comparable Cmin compared to nelfinavir 1250 mg BID.[101]	1.46) when SQV-sgc replaced by SQV-hgc[104] • Intracellular t1/2 of SQV & RTV longer than plasma (median 4.5 & 5.9 hrs, p=0.034, and 4.1 & 6.2 hrs, p=0.033, respectively)[105] ***1000 mg SQV/100 mg RTV BID***: • Compared SQV-sgc vs. SQV-hgc plus RTV in healthy subjects • SQV-hgc/r gave significantly higher SQV levels vs. SQV-sgc/r (Cmin: 217 vs 153 ng/mL, p=0.0147, AUC 15798 ng.h/mL vs. 11655 ng.h/mL, p=0.0043); also significantly less GI side effects with SQV-hgc/r vs. SQV-sgc/r, possibly due to capmul content of SQV-sgc.[106]
Saquinavir	In a randomized, prospective study of 11 HIV+ subjects, SQV AUC ↓ 81% and C_{12} ↓ 61% when given in a regimen of SQV 1000/rtv 100/APV 600 mg BID vs. SQV 1000/rtv 100 mg BID in the absence of APV. APV exposure was not affected. When doses were adjusted to **SQV 1400/rtv 200/APV 600 mg BID**, SQV exposure returned to baseline.[16]	Hgc: 5- to 8-fold ↑ SQV AUC;[52] in vitro study suggests synergy at low doses and antagonism at high doses.[53] Sgc: 620% ↑ SQV AUC; no apparent clinically relevant changes to IDV.[54]	SQV levels ↑, no significant changes in NFV concentrations with combination of SQV-hgc plus NFV. [107-109] Final 48-week analysis showed durable viral suppression with either SQV-hgc 600/NFV 750 mg TID or 1 g SQV/1250 mg NFV BID.[110]	
Tenofovir	In healthy volunteers, tenofovir 300 mg daily plus fosamprenavir 1400/ritonavir 100-200 mg QD for 14 days showed no change in amprenavir AUC and a non-significant ↑ in Cmin. A non-significant ↑ in ritonavir AUC and Cmax were observed in the FPV 1400/rtv 200 mg arm in the presence of tenofovir.[111] In a cohort of 21 HIV-infected subjects taking fosamprenavir 700/ritonavir 100 mg BID plus tenofovir and an NRTI, steady-state Cmin concentrations of amprenavir, ritonavir and tenofovir were within the	In healthy volunteers, tenofovir 300 mg daily plus indinavir 800 mg q8h resulted in slightly delayed Tmax and ↓ Cmax of indinavir, but overall AUC was unchanged; tenofovir Cmax was slightly ↑ but AUC unchanged. These changes not likely to be clinically significant; indinavir and tenofovir may be coadministered without dosage adjustment.[113]	In 18 patients stabilized on nelfinavir 1250 mg BID, addition of tenofovir 300 mg QD for 7 days did not affect the AUC of nelfinavir. Combination may be coadministered without dosage adjustment.[114]	In cohort (n=14) of patients on **saquinavir-hgc 1600 mg/ ritonavir 100 mg QD**, no significant difference in saquinavir Cmin when NRTI backbone switched from ddI/d4T to tenofovir/3TC.[115] Separate study of **saquinavir-hgc 1000 mg/ritonavir 100 mg BID** and tenofovir (n=18 HIV+ adults) showed no change in tenofovir PK parameters with coadministration.[116] Similar effect observed in healthy volunteer study.[117]

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	therapeutic range and comparable to historical controls.[112]			
Tipranavir *(inducer of CYP3A4 and glucuronyl transferase)*	Pharmacokinetic analysis in treatment-experienced subjects taking TPV 500 mg/APV 600 mg/rtv 200 mg BID showed 45% ↓ AUC, 40% ↓ Cmax, 56% ↓ Cmin of APV compared to APV 600/rtv 200 mg BID alone. Clinical significance not established, no current dosage recommendations available. Use combination with caution.[118]	Potential for decreased indinavir concentrations secondary to enzyme induction by tipranavir. Optimal dosages for co-administration have not yet been established.	Potential for decreased nelfinavir concentrations secondary to enzyme induction by tipranavir. Optimal dosages for co-administration have not yet been established.	Pharmacokinetic analysis in treatment-experienced subjects taking TPV 500 mg/SQV 1000 mg/rtv 200 mg BID showed 70% ↓ AUC, 66% ↓ Cmax, 81% ↓ Cmin of SQV compared to boosted SQV alone. Clinical significance not established, no current dosage recommendations available. Use combination with caution.[118]
Vicroviroc			The combination of vicriviroc 15 mg QD /ritonavir 100 mg BID plus nelfinavir 1250 mg BID in healthy volunteers did not lead to significant changes in vicriviroc plasma levels, compared to vicriviroc 15 mg QD /ritonavir 100 mg BID alone. Vicriviroc may be added to a ritonavir-boosted PI regimen without dosage adjustment.[119]	
Zidovudine *(GT 60-75% > CYP3A, minor)*	Amprenavir may inhibit ZDV glucuronidation to a small degree; no dosage adjustment necessary.[120]	Slight ↑ in AUCs of both drugs. No dosage modification necessary.[4]	Nelfinavir dosage adjustment not required with zidovudine, lamivudine, or stavudine.[6]	No interaction.
III)	**INTERACTIONS WITH OTHER**	**MEDICATIONS:**		
Antacids (NB: see separate entries for H2-blockers and Proton-pump inhibitors)	Separate doses by at least an hour to avoid potential interference with absorption.[79]	Indinavir requires acidic pH for best absorption. Separate indinavir and antacid doses by 1 hour.[4]		
Antihistamines, non-sedating (i.e., astemizole, terfenadine) *(CYP3A4)*	Possible ↑ antihistamine AUC and cardiotoxicity. **Avoid combination.**[79]	Possible ↑ antihistamine AUC and cardiotoxicity. **Avoid combination**.[4]	↑ terfenadine AUC; **avoid combination**.[50] Potential for similar interaction with astemizole.	368% ↑ terfenadine AUC; **avoid combination**. [54] Potential for similar interaction with astemizole.
Benzodiazepine • alprazolam, midazolam, triazolam, zolpidem (CYP3A4) • diazepam (2C19>3A4)	Risk of prolonged sedation. **Avoid combination**, or use agents which are glucuronidated (e.g., lorazepam, oxazepam, temazepam).[79]	Risk of prolonged sedation. Use with caution.[4]	Risk of prolonged sedation. **Avoid combination**, or use agents which are glucuronidated (e.g., lorazepam, oxazepam, temazepam).[6]	Possible risk of prolonged sedation. Use with caution.[121]
Calcium channel blockers, e.g. • amlodipine, bepredil, diltiazem,	Potential for ↑ calcium channel blocker concentrations with concomitant protease inhibitor therapy. If coadministration is	Healthy subjects on steady-state indinavir 800/ritonavir 100 mg BID received either either diltiazem 120 mg daily or amlodipine 5 mg daily for 7	Potential for ↑ calcium channel blocker concentrations with concomitant protease inhibitor therapy. If coadministration is	Potential for ↑ calcium channel blocker concentrations with concomitant protease inhibitor therapy. If coadministration is

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felodipine, nicardipine, nimodipine, verapamil (CYP3A substrates)	necessary, initiate calcium blocker therapy at low doses, with careful titration to response and side effects	days. In the presence of indinavir/ritonavir, amlodipine AUC ↑ 90% and diltiazem AUC ↑ 27%. 2/13 subjects (15%) had >4-fold ↑ diltiazem AUC. Desacetyldiltiazem AUC ↑ by 102% and desmethyldiltiazem AUC ↓ by 27%. Steady-state AUCs of indinavir and ritonavir were not affected by either amlodipine or diltiazem. If coadministration is necessary, initiate calcium blocker therapy at low doses, with careful titration to response and side effects.[122]	necessary, initiate calcium blocker therapy at low doses, with careful titration to response and side effects	necessary, initiate calcium blocker therapy at low doses, with careful titration to response and side effects
Caspofungin			Open-label study in 9 healthy male subjects, who received a 14 day course of caspofungin 50 mg intravenously along with nelfinavir 1250 mg twice daily. Steady-state caspofungin levels were unaltered in the presence of nelfinavir. No dosage adjustments necessary.[123]	
Cisapride *(CYP3A4)*	Possible ↑ cisapride AUC and cardiotoxicity. **Avoid combination.**[79]	Possible ↑ cisapride AUC and cardiotoxicity. **Avoid combination**.[4]	Possible ↑ cisapride AUC and cardiotoxicity. **Avoid combination**.[6]	Possible ↑ cisapride AUC and cardiotoxicity. **Avoid combination**.[121]
Clarithromycin *(parent: CYP3A4; inhibits CYP3A4, 1A2?) (CLA-14 OH: renal, CYP3A4)*	Multi-dose trial in healthy volunteers, using 1200 mg APV BID + 500 mg CLA BID: 18% ↑ APV AUC, 10% ↓ CLA Cmax, 35% ↓ AUC of CLA-14 OH metabolite. No dosage adjustment necessary for either drug.[124]	29% ↑ indinavir AUC, 53% ↑ clarithromycin AUC. No dose modification necessary.[4]	Nelfinavir may be administered with macrolides (including azithromycin, clarithromycin, erythromycin) without dosage adjustment.[5] In healthy volunteers, coadminstration of NFV 750mg TID plus 1200 mg azithromycin resulted in 28% ↓ NFV and 23% ↓ M8 AUC (not clin. significant), and >100% ↑ azithromycin AUC.[125]	177% ↑ SQV-sgc AUC; 45% ↑ clarithromycin AUC.[54]
Colchicine *(biliary, renal excretion; p-glycoprotein substrate)*	Potential for significant ↑ colchicine AUC due to P-gp inhibition and ↓ biliary excretion. **For fosamprenavir/ ritonavir:** For treatment of gout flares: use colchicine 0.6 mg x 1 dose, followed by 0.3 mg 1 hour later. Do not repeat	Potential for significant ↑ colchicine AUC due to P-gp inhibition and ↓ biliary excretion. For treatment of gout flares: use colchicine 0.6 mg x 1 dose, followed by 0.3 mg 1 hour later. Do not repeat dose for at least 3 days. For prophylaxis of gout	Potential for significant ↑ colchicine AUC due to P-gp inhibition and ↓ biliary excretion. For treatment of gout flares: use colchicine 0.6 mg x 1 dose, followed by 0.3 mg 1 hour later. Do not repeat dose for at least 3 days. For prophylaxis of gout	Potential for significant ↑ colchicine AUC due to P-gp inhibition and ↓ biliary excretion. For treatment of gout flares: use colchicine 0.6 mg x 1 dose, followed by 0.3 mg 1 hour later. Do not repeat dose for at least 3 days. For prophylaxis of gout

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	dose for at least 3 days. For prophylaxis of gout flares: use colchicine 0.3 mg once daily or every other day. For treatment of familial Mediterranean fever: Do not exceed colchicine 0.6 mg once daily or 0.3 mg BID.[126] **For unboosted fosamprenavir:** For treatment of gout flares: use 1.2 mg x 1 dose and no repeat dose for at least 3 days. For prophylaxis of gout flares: use colchicine 0.3 mg BID or 0.6 mg once daily or 0.3 mg once daily. For treatment of familial Mediterranean fever: Do not exceed 1.2 mg once daily or 0.6 mg BID.[126] Monitor for colchicine toxicity.	flares: use colchicine 0.3 mg once daily or every other day. For treatment of familial Mediterranean fever: Do not exceed colchicine 0.6 mg once daily or 0.3 mg BID.[126] Monitor for colchicine toxicity.	flares: use colchicine 0.3 mg once daily or every other day. For treatment of familial Mediterranean fever: Do not exceed colchicine 0.6 mg once daily or 0.3 mg BID.[126] Monitor for colchicine toxicity.	flares: use colchicine 0.3 mg once daily or every other day. For treatment of familial Mediterranean fever: Do not exceed colchicine 0.6 mg once daily or 0.3 mg BID.[126] Monitor for colchicine toxicity.
Digoxin *(p-glycoprotein substrate, 57-80% Clr)*	Potential for ↑ digoxin concentrations via PI-mediated inhibition of renal p-glycoprotein. Use combination with caution. Monitor digoxin levels and response, and adjust dose if necessary.	Case report of woman maintained on indinavir, 3TC, d4T and digoxin 0.25 mg/d who experienced acute digoxin toxicity 3 days after ritonavir 200 mg BID added to regimen. Symptoms resolved after ritonavir discontinued, and patient resumed original HAART without incident.[127]	Potential for ↑ digoxin concentrations via PI-mediated inhibition of renal p-glycoprotein. Use combination with caution. Monitor digoxin levels and response, and adjust dose if necessary.	Potential for ↑ digoxin concentrations via PI-mediated inhibition of renal p-glycoprotein. Use combination with caution. Monitor digoxin levels and response, and adjust dose if necessary.
Ergot alkaloids *(CYP3A>others)*	Concurrent administration is contraindicated.[79]			
Fluconazole *(~80% Clrenal, 11% metabolized via CYP3A4; inhibits 3A4 (weak), 2C9, 2C19)*		No clinically significant effect on indinavir AUC. OK to use combination.[4]	Nelfinavir may be administered with azoles (including fluconazole, itraconazole, and ketoconazole) without dosage adjustment.[128]	
H2 blockers (including cimetidine, famotidine, nizatidine, ranitidine, etc.)		Coadministration of cimetidine (600 mg twice daily for 6 days) and indinavir (400 mg single dose) to 12 subjects led to a 7% ↑ in Cmax, 2% ↓ AUC, and 18% ↓ Cmin of IDV.[4] Combination may be coadministered.		Healthy volunteer study of SQV-sgc 1200 mg TID vs. SQV 1200 mg BID plus cimetidine 400 mg BID: SQV AUC ↑ 120%, Cmax ↑ 179%, Cmin stable in presence of cimetidine.[129]
Ginko biloba	Potential for ↓ amprenavir	Potential for ↓ indinavir	Potential for ↓ nelfinavir	Potential for ↓ saquinavir

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(CYP3A inducer)	concentrations due to CYP3A induction by ginko biloba.[130] Case report of viral breakthrough and resistance to efavirenz after introduction of ginko biloba.[131] **Avoid concomitant use with unboosted amprenavir.**	concentrations due to CYP3A induction by ginko biloba.[130] Case report of viral breakthrough and resistance to efavirenz after introduction of ginko biloba.[131] **Avoid concomitant use.**	concentrations due to CYP3A induction by ginko biloba.[130] Case report of viral breakthrough and resistance to efavirenz after introduction of ginko biloba.[131] **Avoid concomitant use.**	concentrations due to CYP3A induction by ginko biloba.[130] Case report of viral breakthrough and resistance to efavirenz after introduction of ginko biloba.[131] **Avoid concomitant use with unboosted saquinavir.**
Hmg-CoA Reductase inhibitors • atorvastatin *(CYP3A)* • fluvastatin *(2C9>>3A)* • lovastatin *(CYP3A)* • pitavastatin *(UGT1A3,UGT2B7>> CYP2C9, 2C8)* • pravastatin *(40-50% Clr, > 3A4)* • rosuvastatin *(10% via 2C9, 2C19)* • simvastatin *(CYP3A)*	Potential for ↑ concentrations of statins due to enzyme inhibition by amprenavir. Use combination with caution, use lowest atorvastatin or rosuvastatin dose necessary, or use a fibric acid derivative for hypertriglyceridemia. **Lovastatin and simvastatin** are contraindicated with all HIV protease inhibitors.[132]	Potential for ↑ concentrations of statins due to enzyme inhibition by by indinavir. Use combination with caution, use lowest atorvastatin or rosuvastatin dose necessary, or use a fibric acid derivative for hypertriglyceridemia. **Lovastatin and simvastatin** are contraindicated with all HIV protease inhibitors.[132]	Pharmacokinetic study in HIV-negative subjects taking nelfinavir 1250 mg BID plus either 10 mg **atorvastatin** or 20 mg **simvastatin** resulted in[133]: • 506% ↑ AUC simvastatin • 74% ↑ AUC atorvastatin Do not exceed **40 mg atorvastatin** daily with nelfinavir. **Lovastatin and simvastatin** are contraindicated with all HIV protease inhibitors.[132]	Pharmacokinetic study in HIV-negative subjects taking saquinavir 400 mg/ritonavir 400 mg BID plus 40 mg of atorvastatin, pravastatin, or simvastatin revealed the following effects: • 35% ↓ AUC pravastatin • 31.6 fold ↑ AUC simvastatin • 4.5-fold ↑ AUC atorvastatin[134] **Pravastatin** may be administered without dosage adjustment. **Do not exceed 20 mg atorvastatin daily.** **Lovastatin and simvastatin** are contraindicated with all HIV protease inhibitors.[132]
Itraconazole *(CYP3A4; inhibits 3A, 2C9)*	Potential for increased itraconazole and/or amprenavir concentrations. Clinical significance unclear, monitor for dose-related toxicities.	In a multiple-dose study, administration of itraconazole 200 mg BID with indinavir 600 mg every 8 hours resulted indinavir AUC similar to what would be expected from indinavir 800 mg every eight hours alone.[4] Consider reducing indinavir dose to 600 mg q8h.	Potential for increased itraconazole and/or nelfinavir concentrations. Clinical significance unclear, monitor for dose-related toxicities.	In a prospective randomized study in 17 HIV-infected subjects, saquinavir-sgc 800 or 1200 mg BID plus itraconazole 100 mg daily resulted in SQV concentrations equivalent to SQV-sgc 1400 mg BID alone.[135]
Ketoconazole *(CYP3A4; inhibits 3A, 2C9)*	32% ↑ amprenavir AUC, 44% ↑ ketoconazole AUC. Clinical significance unclear.[136]	Single-dose study of indinavir 400 mg and ketoconazole 400 mg: 68% ↑ indinavir AUC. Reduce indinavir dose to 600 mg q8h.[4]	35% ↑ NFV AUC. No dosage adjustment required.[50]	1.5-fold ↑ saquinavir AUC. Dosage adjustment not necessary.[121]
Levothyroxine *(GT)*		Case report of a 36 year old woman receiving chronic levothyroxine 0.75 mg/day, who developed a pharmacological hyperthyroidism within 1 month after starting an indinavir-containing regimen. Her symptoms resolved and thyroid	Nelfinavir induces glucuronyl transferase, and may potentially ↑ clearance of levothyroxine. See case report described under "Lopinavir-ritonavir and levothyroxine".	

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		hormone parameters returned to baseline after her levothyroxine dose was reduced to 0.12 mg/day. The authors hypothesized that indinavir may have inhibited glucuronidation of levothyroxine.[137]		
Mefloquine *(CYP3A?, GT)*		Case report of patient on indinavir 800 mg q8h and mefloquine 250 mg/week for 16 weeks: therapeutic levels of both drugs observed; no side effects reported.[138]	Case report of patient on nelfinavir 1250 mg BID and mefloquine 250 mg/week for 6 weeks: therapeutic levels of both drugs observed; no side effects reported.[138]	
Methadone *(CYP3A4>>GT; weak inhibitor of CYP2D6)*	In HIV-negative subjects (n=16) maintained on methadone for at least 30 days, addition of amprenavir 1200 mg BID for 10 days resulted in delayed APV absorption, 13% ↓ AUC of active methadone enantiomer. No clinical evidence of methadone withdrawal was observed. Compared to a non-matched historical control group, 30%, 27%, and 25% ↓ in AUC, Cmax, and Cmin of amprenavir was observed. May wish to consider alternative antiretroviral therapy, as amprenavir may be less effective and methadone dosage may need to be increased when these drugs are coadministered.[79, 139]	In vitro study: 30% ↑ methadone concentrations. However, no significant changes in concentrations of either drug were observed with coadministration in blinded, randomized, crossover study in 12 HIV-negative methadone maintenance subjects,[140] as well as a case series (n=6) of HIV-positive subjects.[141]	29-50% ↓ methadone concentrations when nelfinavir given to patients on stable methadone dosages.[141, 142] Monitor for symptoms of methadone withdrawal; adjustment of methadone dosage may be necessary. In an open study of healthy volunteers (n=16) stable on methadone 40-120 mg/day, coadministration of NFV 1250 mg BID for 5 days resulted in ↑ NFV parent and ↓ M8 exposure vs. controls.[143] Clinical significance unclear.	Likelihood of interaction low, since saquinavir is a weak CYP3A4 inhibitor.
Milk thistle		Interaction study in healthy volunteers (n=10) who took milk thistle 175 mg (= silymarin 153 mg) TID for 3 weeks, and indinavir 800 mg q8h at baseline, end of week 3, and after an 11-day washout period. After 3 weeks of milk thistle, indinavir AUC ↓ by 9% and Ctrough ↓ 25%. Authors concluded that these changes were not significant, and that these two products may be coadministered.[144]		
Mycophenolate mofetil (MMF) *(active metabolite,*		In a small case series (n=6) of HIV+ subjects receiving ddI, 3TC, abacavir, indinavir 800/		

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mycophenolic acid: GT)		ritonavir 100 mg BID and nevirapine 200 mg BID, there was no significant change in indinavir concentrations in the presence of chronic MMF administration.[145]		
Oral Contraceptives *(GT, sulphatase (primary)> CYP3A (~30%); inhibits 1A2, 3A)*	Ethinyl estradiol 0.035 mg/ norethindrone 1 mg daily for one cycle plus amprenavir 1200 mg BID resulted in a 22% ↓ AUC and 20% ↓ Cmin of amprenavir; Cmin of oral contraceptives ↑ 32-45%, no significant change in AUC. Oral contraceptives should not be taken with amprenavir. Use alternate non-hormonal methods of contraception.[79]	Slight ↑ in oral contraceptive AUC. No dose modification necessary.[4]	47% ↓ ethinyl estradiol AUC; use alternate methods of contraception.[50] **Depo-medroxy-progesterone acetate, DMPA (Depo-Provera®):** In a prospective, open-label study of 20 HIV-infected women on stable NFV therapy, NFV AUC was not significantly altered in the presence of DMPA. Efficacy of DMPA did not appear to be altered, with no evidence of ovulation occurring based on progesterone levels through week 12.[146]	In a pharmacokinetic study in healthy women, oral contraceptives did not affect the kinetics of single 600 mg saquinavir-hgc.[147]
Phosphodiester-ase Type 5 (PDE5) Inhibitors • sildenafil (Viagra®, Revatio®); *(CYP3A4>>2 C9 substrate; weak inhibitor of CYP1A2, 2C9, 2C19, 2D6, 2E1, 3A4 - unlikely to cause significant interactions)* • tadalafil (Cialis®, Adcirca®); *CYP3A4 substrate* • vardenafil (Levitra®); substrate of *CYP3A4>3A5 , 2C*	Potential for increased **sildenafil** concentrations. Use with caution at a dose of 25 mg every 48 hours, and monitor for adverse effects. Case report of a 36-year old man on fosamprenavir 700/100 mg BID who experienced recurrent priapism after taking **tadalafil** 10 mg for recreational purposes.[148] **Tadalafil:**[149] • on demand dosing while on PIs or other CYP3A4 inhibitors: 10-20 mg q48h, max 3 times per week • daily dosing: 5 mg/day (no dose adjustment needed if on PIs) **Vardenafil is contraindicated** with ritonavir.[150]	Potential for increased **sildenafil** concentrations. Use with caution at a dose of 25 mg every 48 hours, and monitor for adverse effects. **Tadalafil:**[149] • on demand dosing while on PIs or other CYP3A4 inhibitors: 10-20 mg q48h, max 3 times per week • daily dosing: 5 mg/day (no dose adjustment needed if on PIs) **Vardenafil is contraindicated** with indinavir and ritonavir.[150]	Potential for increased **sildenafil** concentrations. Use with caution at a dose of 25 mg every 48 hours, and monitor for adverse effects. **Tadalafil:**[149] • on demand dosing while on PIs or other CYP3A4 inhibitors: 10-20 mg q48h, max 3 times per week • daily dosing: 5 mg/day (no dose adjustment needed if on PIs) **Vardenafil is contraindicated** with ritonavir.[150]	Potential for increased **sildenafil** concentrations. Use with caution at a dose of 25 mg every 48 hours, and monitor for adverse effects. **Tadalafil:**[149] • on demand dosing while on PIs or other CYP3A4 inhibitors: 10-20 mg q48h, max 3 times per week • daily dosing: 5 mg/day (no dose adjustment needed if on PIs) **Vardenafil is contraindicated** with ritonavir.[150]
Posaconazole *(UGT1A4, Pgp substrate, inhibits*	Possible ↑ PI concentrations due to CYP3A4 inhibition by posaconazole. Monitor for	Possible ↑ PI concentrations due to CYP3A4 inhibition by posaconazole. Monitor for	Possible ↑ PI concentrations due to CYP3A4 inhibition by posaconazole. Monitor for	Possible ↑ PI concentrations due to CYP3A4 inhibition by posaconazole. Monitor for

	Amprenavir (Agenerase®)	Indinavir (Crixivan®)	Nelfinavir (Viracept®)	Saquinavir hgc-(Invirase®) sgc-(Fortovase®)
CYP3A4, possibly Pgp)	PI toxicity.	PI toxicity.	PI toxicity.	PI toxicity.
Proton-pump inhibitors (PPIs), including esomeprazole, lansoprazole, omeprazole, pantoprazole, rabeprazole, etc.		Coadministration of single-dose **omeprazole 40 mg** and IDV 800 mg in healthy subjects (n=14) led to 47% ↓ AUC and 55% ↓ Cmin of IDV. This effect was reversed when ritonavir 200 mg was coadministered. Avoid combining unboosted IDV with omeprazole and other PPIs.[151].	In an open-label, healthy volunteer study, coadministration of nelfinavir 1250 mg BID plus **omeprazole 40 mg QD** for 4 days resulted in significant reductions in NFV (↓ 36% AUC, 37% ↓ Cmax, 39% ↓ Cmin) and M8 (↓ 92% AUC, 89% ↓ Cmax, 75% ↓ Cmin). Co-administration of omeprazole and nelfinavir is not recommended.[152]	In healthy subjects taking SQV tablets 1 g/100 mg rtv BID with or without **omeprazole 40 mg**, saquinavir exposure was significantly increased (Cmin ↑ 2-fold, Cmax ↑ 75%, AUC ↑ 82%) in the presence of omeprazole. No short-term saquinavir toxicity was observed. Mechanism of interaction unknown.[153]
Ravuconazole *(may act as CYP3A4 inhibitor after single dose, and as CYP3A/2B inducer with chronic dosing)*			32% ↑ NFV AUC (day 2) and 16% ↓ NFV AUC (day 29) after ravuconazole 400 mg daily and nelfinavir 750 mg given as two single doses in healthy male subjects. Standard doses of both drugs may be given.[154]	
Rifabutin *(CYP3A > deacetylase; moderate inducer of CYP3A)*	14% ↓ amprenavir, 3-6 fold ↑ rifabutin Cmin. Decrease dose of rifabutin to 150 mg daily or 300 mg 3 times weekly to avoid toxicity.[155, 156] Case report of 3 HIV patients with low CD4 (<50 cells/mm^3) and prior episodes of drug-sensitive TB who relapsed with rifamycin-resistant *M. tuberculosis* infection despite receiving fully supervised directly observed therapy including rifabutin 150 mg q2d or 3x/week, plus either atazanavir/rtv or lopinavir/rtv-based HAART. **Higher doses of rifabutin and a ritonavir-boosted HIV protease inhibitor as treatment for tuberculosis should be studied further.[157]**	Interaction study of half-dose RFB + indinavir: 155% ↑ rifabutin AUC, 33% ↓ indinavir AUC. **Thus, ↑ indinavir to 1000 mg q8h and ↓ rifabutin to 150 mg daily or 300 mg three times weekly**.[4, 158, 156] This dosing regimen results in ↑ AUC of RFB and its metabolite by 60% and 125% vs. RFB 300 mg alone.[159] Case report of 3 HIV patients with low CD4 (<50 cells/mm^3) and prior episodes of drug-sensitive TB who relapsed with rifamycin-resistant *M. tuberculosis* infection despite receiving fully supervised directly observed therapy including rifabutin 150 mg q2d or 3x/week, plus either atazanavir/rtv or lopinavir/rtv-based HAART. **Higher doses of rifabutin and a ritonavir-boosted HIV protease inhibitor as treatment for tuberculosis should be studied further.[157]**	32% ↓ NFV AUC, 3-fold ↑ RFB AUC. Reduce rifabutin dose to 150 mg/day or 300 mg three times per week.[50] Increase nelfinavir to 1000 mg q8h.[156] May have more consistent NFV concentrations with 1250 mg BID plus 150 mg RFB daily (or 300 mg 3 times weekly).[158, 160]	40% ↓ saquinavir AUC. **Avoid combination** if using saquinavir as sole protease inhibitor.[161] For combination ritonavir 400 mg BID + saquinavir 400 mg BID, may be possible to administer RFB 150 mg q3days.[162] Case report of 3 HIV patients with low CD4 (<50 cells/mm^3) and prior episodes of drug-sensitive TB who relapsed with rifamycin-resistant *M. tuberculosis* infection despite receiving fully supervised directly observed therapy including rifabutin 150 mg q2d or 3x/week, plus either atazanavir/rtv or lopinavir/rtv-based HAART. **Higher doses of rifabutin and a ritonavir-boosted HIV protease inhibitor as treatment for tuberculosis should be studied further.[157]**
Rifampin *(Deacetylase>*	81% ↓ AUC and 91% ↓ Cmin of amprenavir. **Avoid**	Indinavir AUC ↓ 89% after 1 week rifampin 600	82% ↓ NFV AUC. **Avoid combination.**[50]	80% ↓ saquinavir AUC. **Avoid combination**.[121]

	Amprenavir (Agenerase®)	Indinavir (Crixivan®)	Nelfinavir (Viracept®)	Saquinavir hgc-(Invirase®) sgc-(Fortovase®)
hydrolysis, GT?, CYP?; potent inducer of CYP3A and GT)	**combination**.[155]	mg/day administration. **Avoid combination**.[4] NB: In HIV-negative subjects taking rifampin >2 weeks, administration of ***indinavir 800/ritonavir 100 mg*** resulted in 81% ↓ indinavir AUC and 89% ↓ ritonavir AUC compared to controls, while rifampin AUC was ↑ 25%.[163] Similarly, in 6 HIV-infected individuals on stable ***indinavir 800/ritonavir 100 mg BID***, 4 days of rifampin 300 mg/day resulted in 87%↓ indinavir Cmin.[164] Eighteen Thai HIV+ patients receiving rifampin for active TB were given **indinavir 600/100 mg BID** plus 2 NRTIs; IDV pk was measured at 2 weeks, and Ctrough at 4, 8 and 12 weeks, as well as at least 4 weeks after RIF discontinuation (whereby IDV ↓ to standard Thai dose of 400/100 mg BID). Mean IDV Ctrough was significantly reduced in the presence of RIF (0.03 vs. 0.68 mg/L, p=0.004).[165] **Avoid concurrent rifampin administration.**	NB: In a 7-month old infant with HIV/TB co-infection, addition of ritonavir improved nelfinavir kinetic parameters in the presence of rifampin therapy.[166] However, optimal dosages have not yet been determined.	Addition of ritonavir (e.g., **saquinavir/ritonavir 400/400 mg BID, or 1000/100 mg BID**) may provide therapeutic concentrations in presence of rifampin.[167, 168] However, in a Phase I, randomized, open-label, multi-dose study in healthy volunteers, 11/28 (39.3%) of subjects who received **rifampin 600 mg QD plus SQV 1000/rtv 100 mg BID** developed **significant hepatocellular toxicity**, including transaminase elevations of up to > 20X upper limit of normal values. LFTs returned to normal upon drug discontinuation. Therefore, **rifampin should not be given to patients receiving boosted saquinavir therapy** (Dear Healthcare Provider Letter, Roche Laboratories, USA, February 2005).
Sildenafil/ Viagra®, Tadalafil/Cialis®, vardenafil/Levitra® *(CYP3A4>>2C9 ; weak inhibitor of CYP1A2, 2C9, 2C19, 2D6, 2E1, 3A4 - unlikely to cause significant interactions)*	No information on combination. Consider starting with an initial sildenafil dose of 25 mg q24-48 hours and titrating up based on patient response and tolerability.[169] Use **tadalafil** with caution at reduced doses of 10 mg every 72 hours with increased monitoring for adverse events. Use **vardenafil** with caution at reduced doses of no more than 2.5 mg every 24 hours with increased monitoring	Coadministration of indinavir 800 mg q8h at steady state with sildenafil 25 mg in HIV-infected subjects resulted in 4.4 fold ↑ sildenafil concentrations; sildenafil had no significant effects on indinavir pharmacokinetics.[170] Pharmacologic effects of sildenafil persisted up to 72 hours post-ingestion in some subjects. Thus, a starting dose of 12.5 mg sildenafil may be considered in order to minimize dose-related toxicity. Use **tadalafil** with caution at reduced doses of 10 mg	Nelfinavir concentrations not significantly changed in presence of sildenafil (n=5); sildenafil levels not measured.[171] Potential for increased sildenafil concentrations. Consider starting with an initial sildenafil dose of 25 mg q24-48 hours and titrating up based on patient response and tolerability.[169] Use **tadalafil** with caution at reduced doses of 10 mg every 72 hours with increased monitoring for adverse events.	Coadministration of Fortovase at steady state (1200 mg tid) with sildenafil (100 mg single dose) resulted in a 140% increase in sildenafil Cmax and a 210% increase in sildenafil AUC; sildenafil had no effect on saquinavir pharmacokinetics. Consider a 25mg q24-48 hours starting dose of Viagra when administered to patients also taking Fortovase.[172] Use **tadalafil** with caution at reduced doses of 10 mg every 72 hours with increased monitoring for adverse

	Amprenavir (Agenerase®)	Indinavir (Crixivan®)	Nelfinavir (Viracept®)	Saquinavir hgc-(Invirase®) sgc-(Fortovase®)
	for adverse events.[19]	every 72 hours with increased monitoring for adverse events. 16-fold ↑ **vardenafil** AUC, 30% ↓ indinavir AUC with combination; use vardenafil 2.5 mg every 24 hours.[19]		events. Use **vardenafil** with caution at reduced doses of no more than 2.5 mg every 72 hours with increased monitoring for adverse events.[19]
Sulfamethoxazole (SMX) *(primarily N-acetylase> GT > CYP2C9 (minor)*		No interaction.[4]		
Trimethoprim *(10-20% metabolized, via CYP?)*		19% ↑ trimethoprim AUC. No dose modification necessary.[4]		
Voriconazole *(CYP2C19, 2C9, 3A; inhibits CYP3A, 2C9, 2C19)*	Potential for ↑ concentrations of unboosted PIs and voriconazole. Monitor for both PI and voriconazole toxicity. Consider TDM of both drugs.	In healthy volunteers, coadministration of voriconazole 200 mg BID and indinavir 800 mg q8h for 7 days did not affect the pharmacokinetics of either drug.[173]	Potential for ↑ concentrations of unboosted PIs and voriconazole. Monitor for both PI and voriconazole toxicity. Consider TDM of both drugs.	Potential for ↑ concentrations of unboosted PIs and voriconazole. Monitor for both PI and voriconazole toxicity. Consider TDM of both drugs.
Warfarin *(racemic mixture; R: CYP1A2, 3A, 2C19; S: 2C9 primarily)*	May potentially inhibit warfarin metabolism; monitor for ↑ INR and adjust warfarin dose accordingly when starting and discontinuing therapy.	May potentially inhibit warfarin metabolism; however, paradoxical effect observed in 1 case report, where warfarin dosage needed to be increased to maintain INR with indinavir.[174] Monitor for changes in INR and adjust warfarin dose accordingly when starting and discontinuing therapy.	May potentially inhibit or induce warfarin metabolism; one case report where warfarin dosage was tripled to maintain INR with nelfinavir.[175] Monitor for changes in INR and adjust warfarin dose accordingly when starting and discontinuing therapy.	May inhibit warfarin metabolism; case report of hypo-prothrombinemia which required 20% ↓ warfarin dose with concomitant saquinavir.[176] Monitor for ↑ INR and adjust warfarin dose accordingly when starting and discontinuing therapy.

Please note: This chart summarizes some of the major drug interactions identified to date, based on current available data; other drug interactions may exist. Please use caution whenever adding/modifying therapy. The information in this table is intended for use by experienced physicians and pharmacists. It is not intended to replace sound professional judgment in individual situations, and should be used in conjunction with other reliable sources of information. Due to the rapidly changing nature of information about HIV treatment and therapies, users are advised to recheck the information contained herein with the original source before applying it to patient care.

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Drug Interactions with Nucleoside Reverse Transcriptase Inhibitors

	Abacavir (ABC) Ziagen®[1]	Zidovudine (AZT) Retrovir® [2]	Lamivudine (3TC) 3TC®[3]	Didanosine (ddI) Videx®, Videx EC®[4]	Zalcitabine (ddC) Hivid®[5]	Stavudine (d4T) Zerit®[6]
Usual Dose	300 mg po BID	200 mg po q8h (TID), or 300 mg po BID	150 mg po BID or 300 mg once daily	*Buffered tablets (ddI-BT):* >60 kg = 200 mg po q12h or 400mg QD; <60 kg = 125 mg po BID or 250mg QD *Enteric capsule (ddI-EC):* > 60kg =400mg q24h; <60kg = 250mg q24h	0.75 mg po TID	>60 kg: 20-40 mg po BID <60 kg: 15-30 mg po BID
Kinetic Characteristics	18% CSF penetration; hepatic metabolism via alcohol dehydrogenase and glucuronidation pathways.	15-135% (average 60%) CSF penetration; first pass metabolism, hepatic glucuronidation; 14% (parent) and 75% (metabolite) renal elimination.	10% CSF penetration; 70% renal elimination.	Requires basic media for absorption (tablet contains Mg/ Ca buffers); 21% CSF penetration; partially metabolized via hypoxanthine; 30-50% renal elimination.	15-20% CSF penetration; 62-75% renal elimination.	16-72% (average 30%) CSF penetration; not metabolized; 34-43% renal elimination.
Food	Can take with or without food.[7]	Best on an empty stomach. Can take with a non-fatty meal to minimize nausea. Fatty foods result in a 57% ↓ in AZT concentrations.[8]	Can take with or without food. Diabetics should be warned that the solution contains 20g/100ml of sucrose. Solution is now alcohol-free.	*Buffered tablets (ddI-BT):* ddI AUC ↓ 47% with food; take on empty stomach (30min before or 2 hours after meals). *Enteric capsule (ddI-EC):*	Best on an empty stomach, but can take with or without food.	Can take with or without food.

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				Reductions in ddI Cmax and AUC [9]): • High fat meal (↓ 46%, 19%) • Light meal (↓ 22%, 27%) • 1.5 hours before a light meal (15%, 24%) • 2 hours after a light meal (15%, 10%) • with yogurt: (30%, 20%) • with applesauce: (24%, 18%) **Administer 1.5 hours before or 2 hours after food.**		
Acyclovir		Case report of profound lethargy.[10] No drug interaction seen in larger study.[11]				
Alcohol	No disulfiram reaction noted, no change in EtOH PK, 41% ↑ ABC AUC (not clinically significant).[12]					

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Allopurinol			`	122% ↑ ddI AUC, 116% ↑ Cmax in healthy subjects. Clinical significance unclear[13] Allopurionol 300mg/day + ddI buffered tabs 200mg/day resulted in similar ddI AUC as ddI 200mg BID.[14] **Combination is contraindicated** based on the ↑ potential for ddI-associated toxicity due to increase in didanosine levels.[4]		
Amprenavir (APV)	29% ↑ APV AUC. No change in ABC concentrations.[15] Synergistic activity in vitro.[16]	31% ↑ AZT AUC. 13% ↑ APV AUC No dosage adjustment is required.[17]	No significant interaction.[17]	No significant changes in amprenavir AUC or Cmin observed when administered: concurrently with ddI-EC (in fasting state) concurrently with ddI tablets (in fasting state) 1 hour prior to		

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				ddI tablets (fasting) compared to amprenavir alone in the fasting state. Authors suggest amprenavir may be dosed concurrently with both ddI tablets and enteric-coated capsules in the fasting state.[18]		
Antacids				May ↑ ddI levels. Additive antacid side-effects (i.e. diarrhea).[4]	25% ↓ ddC levels. Space out by 2 hours.[5]	
Antineoplastics, flucytosine, trimetrexate		Increased hematotoxicity. No significant kinetic interaction with antineoplastics.[19]		Additive neuropathy with vinca alkaloids.	Additive neuropathy with vinca alkaloids.	Additive neuropathy with vinca alkaloids.
Atazanavir		In healthy volunteers (n=20), atazanavir 400 mg daily plus Combivir BID at steady-state did not result in any significant changes to PK parameters of any drug.[20] Atazanavir may be	In healthy volunteers (n=20), atazanavir 400 mg daily plus Combivir BID at steady-state did not result in any significant changes to PK parameters of any drug.[20] Atazanavir may be	Simultaneous administration of atazanavir, ***didanosine tablets*** and stavudine resulted in 89% ↓ Cmax and 87% ↓ AUC of atazanavir; kinetics of didanosine and		Simultaneous administration of atazanavir, didanosine tablets and **stavudine** resulted in 89% ↓ Cmax and 87% ↓ AUC of atazanavir (likely due to buffer in ddI tablets); kinetics of

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		coadministered with zidovudine and lamivudine without dosage adjustment.	coadministered with zidovudine and lamivudine without dosage adjustment.	stavudine were not affected. When atazanavir was administered 1 hour apart from didanosine, atazanavir concentrations were not affected. Recommend taking ddI-tablets 30 minutes before or 2 hours after atazanavir (which is taken with food).[21] ***ddI-EC*** should be given 1.5 hours before or 2 hours after atazanavir (which is taken with food).		didanosine and stavudine were not affected.[21] No dosage adjustment required for simultaneous administration of d4T and atazanavir.
Atovaquone		35% ↑ AZT AUC. No dosage adjustment recommended. Monitor for AZT toxicity.[22]				
Azithromycin		10% ↑ in AZT AUC. No dosage adjustment recommended.[23]				
Cimetidine		Inhibition of AZT clearance,		May ↑ ddI levels. Monitor for ddI	36% ↑ ddC AUC. Give ddC 2 hours	

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		however dosage adjustment not warranted.[24]		toxicity.	before cimetidine, or use sucralfate instead.[5]	
Clarithromycin		10-25% ↓ AZT AUC. Consider spacing out administration by 2 hours. Monitor for AZT efficacy.[25]				
Dapsone		↑ hematotoxicity; dapsone induced methemoglobinemia in mouse model.[26]		Early reports of dapsone failure,[27], however no kinetic interaction.[28] Spacing of doses is not required. Additive neuropathy.	20% ↓ dapsone clearance.[29] Additive neuropathy.	Additive neuropathy.
Darunavir	No drug interaction expected, based on different elimination pathways (i.e., renal excretion) of NRTIs.[30]	No drug interaction expected, based on different elimination pathways (i.e., renal excretion) of NRTIs.[30]	No drug interaction expected, based on different elimination pathways (i.e., renal excretion) of NRTIs.[30]	In healthy volunteers, didanosine 400 mg QD on an empty stomach and darunavir 600 mg/ritonavir 100 mg BID with food (2 hours after ddI intake) did not significantly affect plasma levels of either drug. No dosage adjustment is required.[31]	No drug interaction expected, based on different elimination pathways (i.e., renal excretion) of NRTIs.[30]	No drug interaction expected, based on different elimination pathways (i.e., renal excretion) of NRTIs.[30]
Delavirdine		No kinetic		37% ↓ DLV AUC		

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(DLV)		interaction.[32] Additive-synergistic effect in vitro with combination.[32]		and 22% ↓ ddI AUC. Give DLV 1 hour before ddI if possible.[32, 33]		
Didanosine (ddI)		19% ↓ ddI AUC; 35% ↑ AZT AUC. No dosage adjustments required. [34] Another study showed no interaction.[35]			Additive toxicities. **Avoid combination**.[5, 36]	No kinetic interaction.[37] Additive neuropathy.
Efavirenz	No significant interaction.[38]	No significant interaction.[39]	No significant interaction. [39]	EFV does not interact with antacids, therefore ddI buffer should not interfere with EFV absorption.[39]		
Elvitegravir (GS-9137)	In healthy subjects, elvitegravir 200 mg/ritonavir 100 mg QD did not have significant effects on the kinetics of single dose abacavir, and vice versa. No dose adjustments of elvitegravir are required.[40]	In healthy subjects, elvitegravir 200 mg/ritonavir 100 mg QD did not have significant effects on the kinetics of multi-dose zidovudine, and vice versa. No dose adjustments of elvitegravir are required.[40]		In healthy subjects, elvitegravir 200 mg/ritonavir 100 mg QD plus single dose didanosine resulted in 14% ↓ AUC and 25% ↓ Cmin of didanosine, while elvitegravir exposure was not significantly altered. No dose adjustments of		In healthy subjects, elvitegravir 200 mg/ritonavir 100 mg QD did not have significant effects on the kinetics of single dose stavudine and vice versa. No dose adjustments of elvitegravir are required.[40]

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				elvitegravir are required.[40]		
Emtricitabine (FTC)		Prospective, single-dose kinetic study in healthy volunteers of 200 mg FTC plus 300 mg zidovudine resulted in 26% ↑ AUC and 66% ↑ Cmax of zidovudine. FTC kinetics were unchanged. Clinical significance unknown, but dosage adjustments may not be needed.[41]				Prospective, single-dose kinetic study in healthy volunteers of 200 mg FTC plus 40 mg stavudine resulted in no change in kinetics of either drug. Dosage adjustments not required.[41]
Fexofenadine				May ↓ fexofenadine absorption. Give fexofenadine 2 hours before or after ddI.[42]		
Foscarnet		Increased risk of anemia.[43]				
Fluconazole		74% ↑ AZT AUC. Monitor for AZT toxicity.[44]		No kinetic interaction with either ddI-BT or ddI-EC.[45, 46]		No kinetic interaction.[47]

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Ganciclovir (GCV) *see also Valganciclovir		Additive hematotoxicity which can be serious. Best to avoid combination, or use lower doses of AZT during GCV induction therapy.[48] PO GCV: 19.5% ↑ AZT AUC; no change in GCV AUC.[49]		PO GCV: >100% ↑ ddI AUC and 23% ↓ ganciclovir AUC (*if ddI given 2 hours before GCV*) & no effect on GCV AUC (*ddI given at same time as GCV*). Consider administration of PO GCV at the same time as ddI.[49, 50] IV GCV: >70% ↑ ddI AUC.[51] For both IV and PO GCV, monitor for ddI toxicity (pancreatitis, neuropathy).[4] Mechanism possibly related to phosphorylated GCV metabolite inhibition of purine nucleoside phosphorylase enzyme (PNP), which is responsible for ddI breakdown.[52]		
GS9137 (integrase		No clinically relevant drug	No clinically relevant drug			

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inhibitor)		interaction observed when healthy subjects (n=24) received GS-9137 200 mg/rtv 100 mg QD with or without zidovudine 300 mg BID.[53]	interaction observed when healthy subjects (n=24) received GS-9137 50 mg/rtv 100 mg QD with or without **emtricitabine 200 mg/tenofovir 300 mg QD**.[54] As such, no significant interaction is expected between lamivudine and GS-9137/ritonavir.			
Indinavir (IDV)	No significant interaction.[38]	13% ↑ IDV AUC; 17% ↑ AZT AUC. No dosage adjustment is required.[55]		84% ↓ IDV AUC. Administer indinavir ≥ 1 hour prior to ddI-BT.[56, 57] Enteric coated formulation of didanosine (ddI-EC) may be coadministered with indinavir.[9]		25% ↑ d4T AUC. Monitor for d4T toxicity.[55] Prospective study in healthy volunteers of d4T 40 mg single plus indinavir 800mg resulted in no significant changes in d4T AUC or Cmax. When d4T was coadministered with indinavir 800 mg/ritonavir 200 mg, d4T Cmax

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						was unchanged, while d4T AUC ↑ 24%; this was not felt to be clinically significant, and no dosage adjustments are recommended.[58]
Itraconazole		No significant interaction.[59]		Undetectable itraconazole levels (capsules only). Give itraconazole 2 hours before or after ddI-BT.[60] No change in itraconazole concentration when co-administered with ddI-EC.[46]		
Ketoconazole				May reduce ketoconazole levels. Give ketoconazole 2 hours before or after ddI.[57] Enteric coated formulation of didanosine (ddI-EC) may be coadministered with ketoconazole.[9]		
Lamivudine	15% ↓ 3TC AUC.	No significant			Antagonism.	

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(3TC)	No change in ABC levels.[61]	kinetic interaction.[3] Case reports of profound anemia with combination.[62, 63] 3TC may resensitize AZT to HIV.[64]			**Avoid combination.**[65]	No kinetic interaction.[6]
Lopinavir/ ritonavir						
Maraviroc		Maraviroc had no effect on the pharmacokinetics of zidovudine.[66]	Maraviroc had no effect on the pharmacokinetics of lamivudine.[66]			
Methadone (oral) Other opioid dependence therapies LAAM (l-alpha-acetylmethadol), buprenorphine, naltrexone	↓ ABC Cmax, ↑ Tmax, likely not clinically significant; minor ↑ methadone clearance with ABC.[67]	41% ↑ AZT levels. Monitor for AZT toxicity.[68] No significant interaction seen with LAAM (l-alpha-acetylmethadol), buprenorphine, naltrexone.[69]		41% ↓ ddI AUC. Significance of interaction unknown.[70] Analysis of methadone's effect on ddI exposure showed that ddI Cmax and AUC ↓ less than 20% with the enteric coated capsules, while ddI Cmax ↓ 40% and AUC ↓ 30% when given as buffered tablets. Since formulation characteristics for the pediatric		27% ↓ d4T AUC. Significance of interaction unknown, but may require higher doses of d4T.[70]

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				powder and the buffered tablet are similar, **do not coadminister methadone with ddI pediatric powder** due to significant ↓ in ddI concentrations. If coadministration of methadone and didanosine is necessary, use ddI EC formulation and monitor for HIV clinical response.[4]		
Mycophenolate mofetil (MMF) *(active metabolite, mycophenolic acid: GT)*			In a small case series (n=6) of HIV+ subjects receiving ddI, 3TC, abacavir, indinavir 800/ ritonavir 100 mg BID and nevirapine 200 mg BID, there was no significant change in intracellular abacavir TP concentrations in the presence of chronic MMF administration.[71]	MMF absorption may be decreased in the presence of antacids containing magnesium and aluminum. Administer MMF at least 1 hour prior or 2 hours after ddI buffered tablets.		
Nelfinavir		35% ↓ AZT AUC. Monitor for AZT	10%↑ 3TC AUC.[72]	No interaction, however NFV		No significant

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		efficacy.[72]		should be given with food, and ddI on an empty stomach.[72]		interaction.[72]
Nevirapine (NVP)		32% ↓ AZT AUC. Monitor for AZT efficacy. [73]	No significant interaction.[74]	No significant interaction.[75, 76]	No significant interaction.[75, 76]	
NSAIDS (i.e. naproxen, indomethacin)		Neither indomethacin nor naproxen significantly affect AZT levels.[77, 78]				
Pentamidine		Increased hematotoxicity.	Additive pancreatoxicity.	Additive pancreatoxicity. Due to prolonged half-life of pentamidine, do not restart didanosine until one week after pentamidine therapy is concluded.[79] Monitor amylase, lipase monthly. **Avoid combination if possible**	Additive pancreatoxicity. Due to prolonged half-life of pentamidine, do not restart zalcitabine until one week after pentamidine therapy is concluded.[79] Monitor amylase, lipase monthly. **Avoid combination if possible**	Additive pancreatoxicity. Due to prolonged half-life of pentamidine, do not restart stavudine until one week after pentamidine therapy is concluded.[79] Monitor amylase, lipase monthly. **Avoid combination if possible**
Phenytoin		30% ↓ AZT clearance. Monitor for AZT toxicity.[2]				
Probenecid		80% ↑ AZT AUC. Consider reducing			50% ↑ ddC AUC. Monitor for ddC	

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		AZT dosage. Monitor for AZT toxicity, rash, and flu-like symptoms.[80]			toxicity. May require ddC dose reduction.[5]	
Pyrazinamide (PZA)		Potential ↓ PZA AUC and efficacy. Clinical significance unknown.[81]				
Quinolones (ciprofloxacin, gatifloxacin, levofloxacin, moxifloxacin)				98% ↓ ciprofloxacin AUC. Give ciprofloxacin 2 hours before or 6 hours after ddI.[82, 83] Enteric coated formulation of didanosine (ddI-EC) may be co-administered with ciprofloxacin.[9]		
Ribavirin	Ribavirin is a guanosine analogue. Theoretically, ribavirin and abacavir may compete for intracellular phosphorylation, possibly reducing anti-HCV activity of ribavirin.	In vitro, ribavirin may antagonize AZT via competition for phosphorylation.[92] In vivo, a case series failed to show increased viral loads with patients on HAART, suggesting that AZT may be used	In a prospective kinetic study, ribavirin 800 mg/daily did not affect the intracellular phosphorylation or plasma kinetics of ZDV, 3TC, or d4T in HCV/HIV-co-infected patients when assessed after 8-12 weeks	*In vitro,* ribavirin ↑ levels of active ddI metabolite, dideoxyadenosine 5'-triphosphate (ddATP). Potential for ↑ mitochondrial toxicity (i.e. pancreatitis, hyperlactatemia, fatal lactic acidosis,		In vivo, a case series failed to demonstrate increased viral loads with patients on HAART, suggesting that d4T may be used with ribavirin.[93] In a prospective kinetic study, ribavirin 800 mg/daily did not

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	Some controversy exists whether concomitant abacavir therapy may be associated with a reduced response to pegylated interferon and ribavirin,[84-86] but a recent in vitro study showed that the anti-HCV activity of ribavirin was not modified by abacavir[87]. In a pharmacokinetic substudy in patients from the ANRS CO-13 HEPAVIH cohort, ribavirin Cmin was similar in abacavir users and non-users, and there was no evidence that abacavir use affected HCV treatment outcomes including rapid (RVR), early	with ribavirin.[93] In a prospective kinetic study, ribavirin 800 mg/daily did not affect the intracellular phosphorylation or plasma kinetics of ZDV, 3TC, or d4T in HCV/HIV-co-infected patients when assessed after 8-12 weeks of co-administration.[94] **However, potential for ↑ mitochondrial toxicity (e.g., lactic acidosis) & hematotoxicity.** In a cohort of 50 HIV/HCV subjects on HAART who started pegylated interferon and weight-adjusted ribavirin, 8/20 (40%) on concomitant AZT developed grade 1 or higher anemia, versus 4/30	of co-administration.[94]	peripheral neuropathy).[97-100 101] Given availability of other NRTIs and the concern for potential didanosine-induced hepatotoxicity in patients with underlying liver disease (those receiving ribavirin as part of Hepatitis C treatment), the **coadministration of ribavirin and didanosine is now contraindicated**.[4]		affect the intracellular phosphorylation or plasma kinetics of ZDV, 3TC, or d4T in HCV/HIV-co-infected patients when assessed after 8-12 weeks of co-administration.[94] **Avoid combination if possible. Potential for ↑ mitochondrial toxicity (i.e. pancreatitis, lactic acidosis).[97-99]**

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	(EVR) and sustained (SVR) virological response.[88] Achieving adequate ribavirin trough levels via weight-based dosing should overcome any potential negligible effect of abacavir,[89, 90] and there is insufficient evidence to recommend avoiding this combination.[91]	(13.3%) of those not on AZT, p=0.04.[95] **Therefore, avoid combination whenever possible;[96] otherwise, close monitoring for toxicity is recommended.**				
Rifabutin		32% ↓ AZT AUC. May require higher AZT doses. [102]		Kinetic study showed no significant interaction.[103] However, case report of undetectable rifabutin levels when co-administered with once daily ddI-BT, due to ↑amount of buffer. Separate once daily ddI-BT from rifabutin by at least 2 hrs to avoid		No significant interaction.[47]

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				interaction.[104]		
Rifampin		48% ↓ AZT AUC. and 89% ↑ AZT clearance. May require higher AZT doses.[2, 105, 106]	Population pharmacokinetics of 3TC in 16 HIV-positive subjects were similar before and during rifampin-based therapy for tuberculosis. Interaction unlikely to be of clinical significance.[107]			
Rilpivirine				No dose adjustment is required. However, didanosine should be administered on an empty stomach at least 2 hours before or 4 hours after rilpivirine, which should be administered after a meal.[108]		
Ritonavir		25% ↓ AZT AUC. Dosage adjustment not recommended.[109, 110]		13% ↑ ddI AUC. Space out by 2.5 hours due to potential formulation incompatibilities.[57, 109, 111]		Prospective study in healthy volunteers of d4T 40 mg single dose plus indinavir 800 mg/ritonavir 200 mg resulted in unchanged d4T

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						Cmax, while d4T AUC ↑ 24%; this was not felt to be clinically significant, and no dosage adjustments are recommended.[58]
Saquinavir		No significant interaction.[112]			No significant interaction.[112]	
Stavudine (d4T)		Antagonism. **Avoid combination.**[6, 113]	No significant interaction.[6]	No kinetic interaction.[37] Additive neuropathy.	Additive neuropathy.	
Tenofovir	See separate table for tenofovir drug interactions.					
Tetracycline				May ↓ tetracycline levels. Give tetracycline 2 hours before or after ddI.[57]		
Tipranavir	Abacavir ↓ 35-44%. Appropriate doses for the combination of ABC and TPV/r have not been established.	The addition of **tipranavir 900, 1200 or 1500 mg TID** to stable AZT 300 mg BID (n=16) resulted in 46% ↓ AZT AUC (p<0.01); investigators concluded this was not clinically significant.[114]	The addition of **tipranavir 900, 1200 or 1500 mg TID** to a stable regimen of 3TC 150 mg BID (n=30) resulted in 27% ↓ 3TC AUC (p<0.01); investigators concluded that this was not clinically	The addition of **tipranavir 900, 1200 or 1500 mg TID** to a stable regimen of **ddI tablets** 200 mg BID (n=4) resulted in 46% ↓ ddI AUC (p=0.22). Investigators concluded that this difference was not		The addition of **tipranavir 900, 1200 or 1500 mg TID** to a stable regimen of d4T 40 mg BID (n=15) resulted in 15% ↓ d4T AUC (p<0.02). Investigators concluded that this difference was not clinically

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		Healthy volunteer, randomized, parallel group study (n=60) of either **TPV/r 500 mg/100 mg or TPV/r 750 mg/200 mg** plus AZT 300 mg BID. At steady state, TPV/r caused a 56%–61% ↓ in ZDV Cmax and a 33%–43% ↓ in AUC. ZDV did not affect the PK of TPV/r.[115] Appropriate doses for the combination of ZDV and TPV/r have not been established.	significant.[114]	clinically significant.[114] Healthy volunteer, randomized, parallel group study (n=23) of either **TPV/r 500 mg/100 mg or TPV/r 750 mg/200 mg** plus **ddI EC** 400 mg daily. At steady state, 32% ↑ Cmax and 34%↓ C12h of TPV, although overall TPV AUC unchanged; no change in ddI PK observed. [115] **Suggest giving ddI EC 2 hours apart from TPV/r.**		significant.[114]
Trimethoprim-Sulfamethoxazole		23% ↑ in AZT AUC due to TMP component. May be more pronounced in hepatic failure. Monitor for AZT toxicity.[116]	43% ↑ 3TC AUC. No dosage adjustment required. Monitor for 3TC side-effects (i.e. GI, headache, fatigue, myalgias, ↓ ANC).[117]			

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Valganciclovir				Case report of acute pancreatitis with combination. Given significant interaction with ddI and ganciclovir, caution is warranted with this combination.[118]		
Valproic acid		80% ↑ AZT AUC.[119] Use together with caution, and monitor for AZT toxicity; severe anemia has been reported with combination secondary to increased levels of AZT.[120]				
Zalcitabine (ddC)		No significant interaction.[5]	Antagonism. **Avoid combination.**[65]	Additive toxicities. **Avoid combination**[5, 36]		Additive neuropathy.
Zidovudine (AZT)	24% ↑ AZT AUC. No change in ABC levels.[61]		No significant kinetic interaction.[3] Case reports of profound anemia with combination.[62, 63] 3TC may resensitize AZT to HIV.[64]	19% ↑ ddI AUC; 35% ↓ AZT AUC. No dosage adjustments required. [34]	No significant interaction.[5]	Antagonism. **Avoid combination.**[6, 113]

Please note: This chart summarizes some of the major drug interactions identified to date, based on current available data; other drug interactions may exist. Please use caution whenever adding/modifying therapy. The information in this table is intended for use by experienced physicians and pharmacists. It is not intended to replace sound professional judgment in individual situations, and should be used in conjunction with other reliable sources of information. Due to the rapidly changing nature of information about HIV treatment and therapies, users are advised to recheck the information contained herein with the original source before applying it to patient care.

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Pharmacokinetic and Pharmacodynamic Drug Interactions with Tenofovir (Viread®)

	Interaction	Dosing Recommendation
Usual Dose	300 mg once daily with food.	
Kinetic Characteristics	Following oral administration, tenofovir is hydrolyzed in the systemic circulation into active parent nucleotide which is almost exclusively renally cleared by a combination of glomerular filtration and active tubular transport.	
Food	Take with food.	
A) PHARMACOKINETIC INTERACTIONS: *a.* ***NUCLEOSIDE ANALOGUES***		
Abacavir	In a pharmacokinetic study of 8 HIV+ individuals, single dose abacavir was administered alone and with tenofovir. The pharmacokinetics of both drugs were unchanged during coadministration compared to historical controls.[1] In a separate prospective study of 15 patients on stable tenofovir/abacavir/3rd NRTI, intracellular concentrations of tenofovir DP were not significantly altered in either the presence or absence of abacavir and vice versa. Therefore, an intracellular drug interaction between tenofovir and abacavir does not appear to exist.[2] In contrast, a non-additive antiviral effect was observed when abacavir and tenofovir were administered for 7 days alone or in combination in 21 HIV-infected, treatment naïve subjects in a randomized trial. In study participants, the viral decay during ABC and TDF dual-therapy was similar to that during ABC therapy alone. This negative pharmacodynamic interaction was not explained by changes in CBV-TP or TFV-DP concentrations. Rather, modest increases in endogenous dATP pools were associated with reduced antiviral potency of TDF during co-administration with ABC.[3]	No dosage adjustment required. Suboptimal virologic response of QD tenofovir, abacavir and lamivudine may be due to a negative pharmacodynamic effect. **see also section (B) for information on pharmacodynamic interactions.*
Didanosine (ddI)	TDF kinetics are unchanged, however ddI kinetics are significantly altered depending on the ddI formulation used. ***ddI-tablets (BT):*** Tenofovir 300 mg daily plus ddI 400 mg 1 hour before in healthy volunteers: 40% ↑ AUC and 28% ↑ Cmax of ddI.[4] ***ddI-EC:*** **400 mg + TDF:** • staggered dosing (ddI-EC given fasting, 2 hours before TDF): 48% ↑ Cmax & AUC of ddI-EC • coadministered with light meal: 64%↑ Cmax, 60% ↑AUC ddI-EC[5] **ddI-EC 250 mg + TDF:** • staggered dosing (ddI-EC given fasting, 2 hours before TDF), or simultaneous dosing with/ without a light meal: ddI AUC equivalent to that of 400 mg ddI alone[6] Mechanism possibly related to phosphorylated tenofovir	**Use 250 mg ddI-EC when coadministering with tenofovir 300 mg with food.** **Monitor for ddI-related toxicities.** Discontinue ddI if signs/symptoms of pancreatitis, symptomatic hyperlactatemia, or lactic acidosis develop. **see also section (B) for information on pharmacodynamic*

	Interaction	Dosing Recommendation
	metabolite inhibition of purine nucleoside phosphorylase enzyme (PNP), which is responsible for ddI breakdown.[7] A significant intracellular interaction between ddI and tenofovir has not been observed.[8, 9]	*interactions with ddI.*
NB: The European Medicines Agency (EMEA) issued a statement on March 3, 2005, alerting health care providers to safety and efficacy concerns regarding tenofovir and ddI coadministration. In its statement, the EMEA noted that using ddI and tenofovir together was not recommended in any combination of anti-HIV agents, particularly in PHAs with high viral loads (100,000 copies or greater) or low CD4+ cell counts (less than 200 cells). The EMEA noted that rare, occasionally fatal, cases of pancreatitis and lactic acidosis have been observed when the drugs have been used together and advised that if using ddI and tenofovir together was "strictly necessary", subjects should be closely monitored for ddI-related side effects as well as regimen efficacy. *[EMEA. Efficacy and safety concerns regarding the co-administration of tenofovir disoproxil fumarate (TDF, Viread) and didanosine (ddI, Videx). Public Statement 3 March, 2005. http://www.emea.eu.int/pdfs/human/press/pus/6233105en.pdf]*		
Emtricitabine (FTC)	In healthy volunteers, coadministration of tenofovir 300 mg QD and FTC 200 mg QD for 7 days did not affect steady-state concentrations of either drug.[10]	Combination may be coadministered without dosage adjustment.
Lamivudine (3TC)	In healthy volunteers, tenofovir 300 mg daily plus 3TC 150 mg BID resulted in slightly delayed Tmax and ↓ Cmax of 3TC, but overall 3TC AUC was unchanged; tenofovir kinetics were not altered.[11] In HIV-infected subjects, no interaction was observed between tenofovir and lamivudine at the plasma and intracellular levels.[12]	Combination may be coadministered without dosage adjustment.
Stavudine (d4T)	Kinetic study in 18 healthy volunteers of tenofovir +/- d4T XR 100 mg showed no differences in kinetics of either drug when coadministered.[13]	Combination may be coadministered without dosage adjustment.
b. NON-NUCLEOSIDE ANALOGUES		
Efavirenz	In healthy volunteers, coadministration of tenofovir 300 mg and efavirenz 600 mg did not affect steady-state concentrations of either drug.[11]	Combination may be coadministered without dosage adjustment.
Etravirine	Coadministration of tenofovir 300 mg QD plus etravirine 200 mg BID in healthy volunteers led to 19% ↓ Cmax and AUC and 18% ↓ Cmin of etravirine, while tenofovir Cmax and AUC ↑ 15%. Combination may be coadministered without dosage adjustment.[14] Tenofovir was associated with 26% ↓ etravirine AUC12h from population PK data from substudy in DUET trials.[15]	Combination may be coadministered without dosage adjustment.
Nevirapine	Trough nevirapine levels (23-25 hours post-dose) were obtained in subjects taking NVP 400 mg QD with or without concomitant tenfovir. The mean NVP concentration was 3420 (range 3170-3670) ng/mL in those taking NVP and tenofovir (n=171) and 3260 (range 2980-3540) ng/mL in those taking NVP without tenofovir (n=87).[16]	Combination may be coadministered without dosage adjustment.
Rilpivirine	In healthy volunteers, coadministration of rilpivirine 150 mg QD and tenofovir 300 mg QD for 8 days resulted in 24% ↑	No dosage adjustments of either

	Interaction	Dosing Recommendation
	AUC, 21% ↑ Cmax and 24% ↑ Cmin of tenofovir, while kinetics of rilpivirine were not affected.[17]	drug recommended.
c. PROTEASE INHIBITORS		
Atazanavir	Combination of atazanavir and tenofovir (at standard doses) resulted in 25% ↓ AUC and 40% ↓ Cmin of atazanavir, while tenofovir AUC was ↑ by 24%; avoid concomitant use.[18] In a separate randomized multi-dose interaction study in healthy volunteers, 2 dosing strategies involving unboosted ATV and tenofovir were studied:[19] a) ATV 400 mg QD am plus tenofovir 300 mg QD pm: • ↓ Cmax 10%, ↓ AUC 17%, ↓ Cmin 28% of ATV • ↑ Cmax 43%, ↑ AUC 37%, ↑ Cmin 38% of TDF b) ATV 600 mg plus tenofovir 300 mg both Qam: • ↑ Cmax 27%, ↑ AUC 36%, ↑ Cmin 41% of ATV • ↑ Cmax 41%, ↑ AUC 59%, ↑ Cmin 74% of TDF	Use **atazanavir 300 mg/ ritonavir 100 mg QD plus tenofovir** (results in higher Cmin of atazanavir vs. atazanavir 400 mg alone).
Atazanavir/ ritonavir	In a pharmacokinetic substudy (n=10) of HIV+ subjects participating in the Puzzle2-ANRS 107 study, the pharmacokinetics of atazanavir 300/ritonavir 100 mg QD were assessed before and after the addition of tenofovir and other optimized NRTIs. After the addition of tenofovir, atazanavir AUC ↓ 25% (p=0.05) and Cmin ↓ 23% (p=n.s.); tenofovir exposure was not assessed.[20] In an open-label study of healthy volunteers, temporal separation of tenofovir and atazanavir 300/ritonavir 100 mg 11% ↓ AUC, 20% ↓ Cmin of atazanavir, and 37% ↑ AUC and 29% ↑ Cmin of tenofovir. Simultaneous administration of tenofovir and atazanavir 400/100 mg led to 38% ↑ AUC and 33% ↑ Cmin of atazanavir compared to 300/100 mg alone, but tenofovir AUC ↑ 55% and Cmin ↑ 70%; thus, this dosage combination is not recommended.[21]	Clinical significance unclear. Dosing tenofovir separately from atazanavir/rtv does not offer any clinical advantages over simultaneous administration. Monitor for atazanavir efficacy and tenfovir toxicity.
Brecanavir (GW640385)/ ritonavir	In a randomized, open-label crossover study in healthy volunteers, the combination of brecanavir 300 mg/ritonavir 100 mg BID plus tenofovir 300 mg daily resulted in increased tenofovir exposure (24% ↑ Cmax, 32% ↑ AUC) and modest increases in brecanavir exposure (14% ↑ AUC, 17% ↑ Cmax, 20% ↑ Cmin).[22]	Combination may be coadministered without dosage adjustment. Monitor for potential tenofovir toxicity.
Darunavir (TMC114)/ ritonavir	Multidose study of tenofovir 300 mg QD plus darunavir (oral solution) 300 mg/ritonavir 100 mg BID led to 22% ↑ tenofovir exposure (statistically significant), while darunavir kinetics were not significantly affected.	Combination may be used without dose adjustments.
Fosamprenavir/ ritonavir	In healthy volunteers, tenofovir 300 mg daily plus fosamprenavir 1400/ritonavir 100 mg QD or fosamprenavir 1400/ritonavir 200 mg QD for 14 days showed no change in amprenavir AUC and a non-significant increase in Cmin. A non-significant increase in ritonavir AUC and Cmax were	Combination may be coadministered without dosage adjustment.

	Interaction	Dosing Recommendation
	observed in the FPV 1400/rtv 200 mg arm in the presence of tenofovir.[23] Similarly, in an open-label study of 15 treatment-naïve subjects, FPV 1400/rtv 200/tenofovir 300/emtricitabine 200 mg QD for 48 weeks yielded antiretroviral concentrations similar to historical controls.[24] In a cohort of 21 HIV-infected subjects taking fosamprenavir 700/ritonavir 100 mg BID plus tenofovir and an NRTI, steady-state Cmin concentrations of amprenavir, ritonavir and tenofovir were within the therapeutic range and comparable to historical controls.[25] In a healthy volunteer study, subjects received tenofovir 300 mg QD for 7 days (period 1), and then were randomized to receive fosamprenavir 1400 mg BID or fosamprenavir 700/rtv 100 mg BID alone and with tenofovir or vice versa (periods 2 & 3). Tenofovir Cmin, Cmax and AUC ↓ 12%, 25% and 15% with fosamprenavir and ↓ 9%, 18% and 7% with boosted fosamprenavir, respectively. In the presence of tenofovir, amprenavir Cmin, Cmax and AUC ↑ 31%, 3% and 7% (unboosted) and ↑ 31%, 4% and 16% (boosted). These changes are not likely clinically significant.[26]	
Indinavir (IDV)	In healthy volunteers, tenofovir 300 mg daily plus indinavir 800 mg q8h resulted in slightly delayed Tmax and ↓ Cmax of indinavir, but overall AUC was unchanged; tenofovir Cmax was slightly ↑ but AUC unchanged. These changes not likely to be clinically significant.[11]	Combination may be coadministered without dosage adjustment.
Lopinavir/ ritonavir	*Impact on tenofovir:* • In healthy volunteers, tenofovir 300 mg daily plus lopinavir 400/ritonavir 100 mg BID resulted in slight ↑ AUC, Cmax of tenofovir; lopinavir AUC and Cmax were ↓ 15%, but Cmin unchanged and lopinavir IQ-wild type >90. These changes not likely clinically significant.[11] • In a crossover study in healthy volunteers, TDF plus LPV/r with food led to ↑ 32% tenofovir AUC, while LPV and RTV kinetics were not affected. Clinical significance unclear.[27] • In tenofovir compassionate access study, (median duration of 63 weeks), 94% of patients received TDF + LPV/r (n = 274/291), with no significant nephrotoxicity observed.[28] • In a small cross-sectional study of HIV-positive subjects on tenofovir with lopinavir/ritonavir or nevirapine, tenofovir Cmax ↑ 39% and AUC ↑ 72% in the presence of lopinavir/ritonavir versus nevirapine. Intracellular tenofovir-diphosphate AUC was also ↑ 35% in the	Recommendations on dosage adjustment not established. **Monitor for tenofovir toxicity and possibly lopinavir efficacy**, particularly in treatment-experienced patients. Consider TDM (if available) with possible dosage increase of lopinavir if suboptimal lopinavir concentrations and/or inadequate viral response.[31]

	Interaction	Dosing Recommendation
	presence of lopinavir/ritonavir compared to nevirapine.[12] *Impact on lopinavir/ritonavir concentrations:* • Retrospective data from a series of HIV subjects (n=10) showed no effect of tenofovir on lopinavir and ritonavir Cmin at steady-state.[29] • In patients taking LPV/r and TDF (n=14), mean lopinavir Ctrough was 5.6 ug/mL vs. 7 ug/mL in patients taking LPV/r plus other NRTIs (n=15).[30] • In a pharmacokinetic interaction study in experienced patients (n=18), lopinavir Cmin ↓ by 34% (mean 4.61 vs. 3.06 ug/mL, p=0.04), while ritonavir Cmin ↓ by 44% (mean of 0.63 vs. 0.35 ug/mL, p=0.014) in the presence of tenofovir.[31]	
Nelfinavir	In 18 patients stabilized on nelfinavir 1250 mg BID, addition of tenofovir 300 mg QD for 7 days did not affect the AUC of nelfinavir.[32] A separate pharmacokinetic study in 29 healthy volunteers showed no significant changes in the kinetics of nelfinavir/M8 or tenofovir when coadministered at usual doses.[33]	Combination may be coadministered without dosage adjustment.
Ritonavir	An in vitro study using renal epithelial cell lines overexpressing MRP2 showed that tenofovir alone was not nephrotoxic, even at high doses. However, when tenofovir was combined with MRP2 inhibitors such as LPV, RTV, cyclosporine or MK571, TDF efflux was reduced and intracellular TDF concentrations increased, with cellular toxicity observed at high concentrations.[34] In a retrospective database analysis, tenofovir subjects receiving ritonavir-boosted regimens appeared to be predisposed to developing renal insufficiency.[35]	Recommendations on dosage adjustment not established. **Monitor for tenofovir toxicity.**
Saquinavir	In cohort (n=14) of patients on **saquinavir-hgc 1600 mg/ ritonavir 100 mg QD**, no significant difference in saquinavir Cmin when NRTI backbone switched from ddI/d4T to tenofovir/3TC.[36] Separate study of **saquinavir-hgc 1000 mg/ritonavir 100 mg BID** and tenofovir (n=18 HIV+ adults) showed no change in tenofovir PK parameters with coadministration.[37] Similar effect observed in healthy volunteer study.[38]	Combination may be coadministered without dosage adjustment.
Tipranavir	Healthy volunteer, randomized, parallel group study (n=49) of either TPV/r 500 mg/100 mg or TPV/r 750 mg/200 mg plus tenofovir 300 mg daily. At steady state, a dose-dependent ↓ in TDF Cmax of 23%–38% was shown, and 17% and 11% ↓ in TPV at the 500/100 and 750/200 doses, respectively.[39]	May consider using TPV/r plus tenofovir without further dosage adjustment.
d. CCR5 ANTAGONISTS		
Aplaviroc	Healthy volunteer, randomized study of tenofovir 300 mg daily and aplaviroc 600 mg BID showed no significant effect of tenofovir on aplaviroc AUC or Cmax, and a moderate	Combination may be coadministered without dosage adjustment.

	Interaction	Dosing Recommendation
	increase in C_T of 80%. Tenofovir pharmacokinetics were not changed in the presence of aplaviroc.[40]	
Maraviroc	Healthy volunteer, randomized, placebo-controlled crossover trial in 11 healthy subjects of maraviroc 300 mg BID + tenofovir 300 mg QD/placebo for 7 days showed no significant changes in maraviroc AUC and Cmax in the presence of tenofovir.[41]	Combination may be coadministered without dosage adjustment.
Vicriviroc	Healthy volunteer, randomized study of vicriviroc 10 mg BID +/- tenofovir 300 mg QD for 7 days showed no significant changes in vicriviroc Cmax, AUC, clearance or terminal t1/2 in the presence of tenofovir.[42]	Combination may be coadministered without dosage adjustment.
e. INTEGRASE INHIBITORS		
Dolutegravir (S/GSK1349572)	No clinically relevant drug interaction observed when healthy subjects received dolutegravir 50 mg QD and tenofovir 300 mg QD for 5 days compared to either drug administered alone. Dolutegravir and tenofovir can be coadministered without dose adjustment.[43]	Combination may be coadministered without dosage adjustment.
Elvitegravir (GS-9137)	No clinically relevant drug interaction observed when healthy subjects (n=24) received GS-9137 50 mg/rtv 100 mg QD with or without emtricitabine 200 mg/tenofovir 300 mg QD.[44]	Combination may be coadministered without dosage adjustment.
Raltegravir	In an open-label, 3-period study in 10 healthy subjects, combination of 400 mg MK-0518 BID and 300 mg QD of tenofovir for 4 days led to modest increases in MK-0518 AUC (49%) and Cmax (64%) while Cmin was unchanged; tenofovir AUC ↓ 10% and Cmin ↓ 13%.[45]	Dose adjustment likely not necessary.
f. OTHER MEDICATIONS		
Adefovir	The single dose kinetics of adefovir were studied alone and in the presence of multi-dose tenofovir in 22 subjects. The pharmacokinetic parameters of both adefovir and tenofovir (including renal clearance) were unchanged when both drugs were given together.[46]	Dose adjustment not necessary.
Boceprevir	In healthy subjects, there were no clinically relevant changes in boceprevir exposure when co-administered with tenofovir. Boceprevir also had no notable effect on tenofovir AUC or renal clearance, but increased tenofovir C_{max} by 32%.[47]	Combination may be coadministered without dosage adjustment.
Buprenorphine	In 27 opioid-dependent, buprenorphine/naloxone-maintained, HIV-negative volunteers, no significant changes in buprenorphine pharmacokinetics were observed following ddI, 3TC and tenofovir administration, and buprenorphine had no statistically significant effect on NRTI concentrations.[48]	Dose adjustment not necessary.
Methadone (oral)	Methadone pharmacokinetics and dynamics not affected by tenofovir. Combination appears safe.[49]	Dose adjustment likely not necessary.
Oral Contraceptives	In an open-label, 29 day study in healthy volunteers, coadministration of tenofovir 300 mg and oral contraceptives did not affect steady-state concentrations of tenofovir or	Combination may be coadministered without dosage adjustment.

	Interaction	Dosing Recommendation
	either the estrogenic or progestational components of oral contraceptives.[50]	
Ribavirin	Kinetic study in 22 healthy subjects of single 600 mg dose ribavirin and multi-dose tenofovir showed no significant changes in ribavirin PK.[51]	Dose adjustment likely not necessary.
Rifampin	Steady-state interaction study in healthy subjects of tenofovir and rifampin 600 mg daily did not show clinically significant changes in PK of either drug.[52]	Combination may be coadministered without dosage adjustment.
Telaprevir	In a randomized, open-label study, healthy volunteers received tenofovir 300 mg daily, telaprevir 750 mg q8h, or both drugs, each for 7 days. In the presence of telaprevir, tenofovir AUC_{24h} was increased by 30% while telaprevir kinetics were not affected.[53] In an open-label study, 20 HIV/HCV-negative volunteers started telaprevir 750 mg every 8 hours for 7 days followed by EFV/tenofovir disoproxil fumarate (TDF) 600/300 mg once daily for 7 days after a washout. Subsequently, volunteers received telaprevir 1125 mg every 8 hours and EFV/TDF 600/300 mg once daily for 7 days or telaprevir 1500 mg every 12 hours and EFV/TDF 600/300 mg once daily for 7 days in a randomized order without a washout. Telaprevir was taken with food and EFV/TDF was taken on an empty stomach in the morning. With TVR 1125 mg q8h plus efavirenz/TDF/FTC, telaprevir AUC ↓ 18%, Cmin ↓ 25%, EFV AUC ↓ 18%, Cmin ↓ 10%, and tenofovir AUC ↑ 10% and Cmin ↑ 17%. With TVR 1500 mg q8h plus EFV/TDF/FTC, telaprevir AUC ↓ 20%, Cmin ↓ 48%, EFV AUC ↓ 15%, Cmin ↓ 11%, and tenofovir AUC ↑ 10% and Cmin ↑ 6%.[54]	Combination may be coadministered without dosage adjustment.
B) PHARMACODYNAMIC INTERACTIONS: ***a. ANTIRETROVIRAL COMBINATIONS TO AVOID BECAUSE OF DECREASED VIRAL EFFICACY*** ***1) Initiation Studies in Naïve Subjects***		
Tenofovir, lamivudine, didanosine	In a small pilot study (n=22) of treatment-naïve subjects started on didanosine + tenofovir + lamivudine, a high rate (91%) of virologic failure (defined as <2 log reduction of HIV-RNA by week 12) was seen observed.[55]	**3-NRTI regimen of TDF/3TC/ddI should not be used in any patient.[55]**
Tenofovir, lamivudine, abacavir	In an interim analysis of treatment naïve patients randomized to receive abacavir/lamivudine plus tenofovir or efavirenz (n=194 with 8 week data), those randomized to abacavir/tenofovir/lamivudine had a significantly higher rate of early virologic non-response (defined as <2 log drop in viral load by week 8 or 1 log rebound from nadir) compared to patients treated with efavirenz/abacavir/lamivudine (49% vs. 5%, p<0.001).[56]	**3-NRTI regimen of TDF/3TC/ abacavir should not be used in any patient.[56]**
Tenofovir, didanosine, efavirenz	A randomized, open-label study of ddI/efavirenz plus tenofovir (n=41) or lamivudine (N=36) in 77 naïve patients was terminated prematurely, following an unplanned interim	**Until further information are available, avoid**

	Interaction	Dosing Recommendation
	analysis. At week 4 (ITT), the tenofovir and lamivudine groups had similar viral loads, but by week 12, the tenofovir group had a significantly higher VL compared to the 3TC group (2.28 log copies/mL vs. 1.83, p=0.013), and there were 5 failures with emergent RT mutations in the TDF arm vs. 0 in the 3TC arm, p<0.05. All failures had VL>100,000 and CD4<200, with >99% adherence, and 3 subjects showed low efavirenz levels.[57] An open-label, randomized pilot study comparing tenofovir/ddI-EC 250 mg/efavirenz +/- lopinavir/ritonavir in naïve subjects was terminated prematurely, following an unplanned interim analysis. At 3 months follow-up in 29 patients, 7/15 (46.7%) of the 3-ARV arm developed early virologic failure by ITT (5 had virologic failure defined as drop of <2 log at month 3 or rebound >1 log from nadir, 1 lost, 1 switch), compared to 2/14 in the LPV/r arm (1 lost, 1 switch), P=0.109. In the 3-ARV arm, all 6 subjects who experienced virologic failure had baseline VL>100,000 and CD4<200. The following resistance mutations were detected at failure: G190S/E +/- K103N (n=5), K103N/L100I/V108I (n=1), L74V/I (n=4) and K65R (n=2).[58] In a prospective, single-arm study of tenofovir, ddI-EC 250 mg and efavirenz in naïve-subjects, an unplanned interim analysis of 35 subjects who reached week 12 showed a 28% (n=11) virological failure rate (ITT). Of these, 8 subjects failed to achieve VL<400 by week 12, and 3 rebounded to VL>400 between weeks 12 and 24. Six of 11 patients with virologic failure had initial viral load > 100,000 copies/mL and CD4+ count < 200 cells/mm^3.[59] A prospective, randomized pilot in naïve subjects compared AZT/3TC/lopinavir-ritonavir (n=8), tenofovir/3TC/efavirenz (n=10) and tenofovir/ddI/efavirenz (n=10). By week 28, 87.5% of the AZT/3TC arm vs. 100% of TDF/3TC arm vs. 60% of the TDF/ddI arm reached undetectable RNA. The HIV-RNA slope was significantly slower in the TDF/ddI arm vs. TDF/3TC arm at days 1, 3, 7, 14 and 28, p<0.0001. Efavirenz AUC values were lower in the TDF/ddI arm compared to the TDF/3TC arm, especially in subjects with early virologic failure.[60]	**tenofovir/ddI/ efavirenz regimen in patients with VL>100,000 and CD4<200.**
Tenofovir, didanosine EC, efavirenz or nevirapine	In a retrospective database analysis of 5000 naïve subjects initiated on HAART between October 2002-March 2004, 14 patients received tenofovir, ddI EC and either efavirenz (n=10) or nevirapine (n=4) once daily. After 12 weeks of treatment, 5/14 (36%) of these patients experienced suboptimal virologic responses (viral load drop <2 log), and 2 additional patients who responded at week 12 experienced virologic rebound (>200 copies/mL on 2 separate occasions) by week 24. Overall, the 7/14 (50%) patients with viral failure (2/4 on NVP, 5/10 on EFV), had a median baseline VL of 5.8	**Until further information are available, use caution when coadministering tenofovir/ddI EC and efavirenz or nevirapine in treatment-naïve patients with high**

	Interaction	Dosing Recommendation
	(4.7-6) and CD4 126 (24-281). Resistance mutations at failure: K65R and L74V (n=4), one or more of L100I, K103N/R/T, Y181C, G190E/Q/S (n=7).[61]	**baseline viral loads.**
Tenofovir, 3TC and nevirapine	In a prospective, randomized, open-label clinical trial of tenofovir, 3TC and nevirapine QD vs. AZT/3TC and nevirapine BID in 71 antiretroviral naïve subjects, 9/36 (25%) virologic failures (<2 log drop or rebound >1 log after initial decline) were noted in the QD, 8 of which occurred by week 12, as compared to 1/35 virologic failure (3%) after week 12 in the BID arm. Those with virologic failure had significantly lower baseline CD4 cell counts (110 vs. 223 cells/mm^3) and higher baseline viral loads (262,747 vs. 51,189 copies/mL) than those with virologic success (p=.004 and .002, respectively); nevirapine trough concentrations were not correlated with risk of failure. A high incidence of NNRTI resistance mutations were seen among the virologic failures (K65R mutation in 6/9, Y181C/A in 7/9, two or more mutations in 5/9). The reasons for the failures are unclear.[62] Similar results were observed in an open-label trial of 23 antiretroviral naïve subjects prescribed the same QD regimen. In this group, only 10/23 (43%) achieved viral success (VL<75 copies/mL) at 24 weeks ITT; among patients who failed, 7 had virologic failure (6 within the first 8 weeks of treatment), 3 developed rash and 3 were lost to followup. Genotypic analysis of the 7 virologic failures showed Y181C mutation in 5/7 patients, M184V in 3/7 patients, and K65R in 1/7 patients. All 7 virologic failures reported 100% adherence rates.[63]	**Until further information are available, may wish to avoid using the combination of tenofovir, 3TC and nevirapine in treatment-naïve patients, particularly those with high baseline viral loads and low CD4 counts.**
	2) Switch Studies in Suppressed Subjects	
Tenofovir plus 2 NRTIs	In a review, 55 patients previously suppressed on a stable regimen (VL<50 for 24 months) were switched to tenofovir plus 2 NRTIs, primarily for toxicity or intolerance (74%); 65.5% had previously broken through on a 3TC-containing regimen or had received suboptimal NRTI therapy. After 24 weeks, only 17 (31%) remained suppressed; 26 (47%) had VL>50 copies/mL, 10 (18%) stopped due to toxicity, and 2 (4%) were lost to follow-up. When compared with other regimens, a regimen that included ddI had a significantly poorer virological success rate (1/21 (5%) vs. 16/34 (47.1%), p=0.001), whereas those that included AZT did relatively better (3/4 (75%) remained suppressed versus 14/51 (27%), p=0.083). In multivariate analysis, use of ddI + tenofovir was significantly associated with a higher probability of failure (OR=17.7, p=0.007). Genotype testing on 8 subjects at failure revealed K65R (n=4) plus either M184V or TAM.[64]	**Simplification strategy to a tenofovir-2 NRTI regimen (particularly those containing ddI) should used with caution, especially in those with previous RT mutations.**
Abacavir, 3TC, tenofovir	In a retrospective database review, 8 subjects previously suppressed on a stable regimen (VL<50 for median 14.2 months) were switched to abacavir-3TC-tenofovir for simplification or toxicity reasons. Five of 8 subjects had viral rebound after a median 130 days (54-160). Four of the 5	**Simplification strategy to abacavir-3TC-tenofovir should used with caution, especially in those**

	Interaction	Dosing Recommendation
	subjects had either K65R, M184V/I or both at failure.[65]	**with previous RT mutations.**
b. *INCREASED TOXICITY*		
Didanosine	Paradoxical ↓ in CD4 counts in patients virally suppressed on combination.[66, 67] Using 250 mg ddI with TDF may lead to partial improvement in CD4 counts.[68]	**Reduce didanosine dose to 250 mg QD when administering with tenofovir. Monitor response, including CD4 counts, particularly after 6 months of therapy.**
	Case reports of pancreatitis[69, 70], fatal lactic acidosis[71, 72], and/or renal failure[73] reported with combination of didanosine and tenofovir.	**Monitor for toxicity.**

NB: The European Medicines Agency (EMEA) issued a statement on March 3, 2005, alerting health care providers to safety and efficacy concerns regarding tenofovir and ddI coadministration. In its statement, the EMEA noted that using ddI and tenofovir together was not recommended in any combination of anti-HIV agents, particularly in PHAs with high viral loads (100,000 copies or greater) or low CD4+ cell counts (less than 200 cells). The EMEA noted that rare, occasionally fatal, cases of pancreatitis and lactic acidosis have been observed when the drugs have been used together and advised that if using ddI and tenofovir together was "strictly necessary", subjects should be closely monitored for ddI-related side effects as well as regimen efficacy.
[EMEA. Efficacy and safety concerns regarding the co-administration of tenofovir disoproxil fumarate (TDF, Viread) and didanosine (ddI, Videx). Public Statement 3 March, 2005. http://www.emea.eu.int/pdfs/human/press/pus/6233105en.pdf]

Please note: This chart summarizes some of the major drug interactions identified to date, based on current available data; other drug interactions may exist. Please use caution whenever adding/modifying therapy. The information in this table is intended for use by experienced physicians and pharmacists. It is not intended to replace sound professional judgment in individual situations, and should be used in conjunction with other reliable sources of information. Due to the rapidly changing nature of information about HIV treatment and therapies, users are advised to recheck the information contained herein with the original source before applying it to patient care.

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II. INTERACTIONS WITH OTHER DRUG CLASSES

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Suggestions for Management of Anticonvulsant-Antiretroviral Interactions In HIV

Avoid: **carbamazepine, phenytoin, phenobarbital, primidone, felbamate, oxcarbazepine when possible**

- **All are enzyme inducers and can decrease protease inhibitor, NNRTI and elvitegravir/cobicistat levels, which may impact viral efficacy. If these anticonvulsants are required, consult interaction table for suggested dosage adjustments or alternatives.**
- In the U.S. Military HIV Natural History Study, virologic response was assessed in 19 patients taking enzyme-inducing (EI) antiepileptics (AEDs) (n=12 phenytoin, n=6 carbamazepine, n=1 phenobarbital) versus 85 patients taking non-enzyme inducing antiepileptics (n=88 gabapentin, n=2 pregabalin, n=1 levetiracetam) while on cART concomitantly for at least 28 consecutive days. Virologic failure was defined as having 2 consecutive viral loads ≥400 copies/mL after 6 months of cART or having all VLs in the first 6 months of cART ≥400 c/mL. Patients on EI-antiepileptics had significantly greater virologic failure (10/16, 63%) compared to other AED patients (20/75, 27%) for the first cART/AED period (OR 4.6 [1.5-14.3];P<0.01). Average VL was also greater during cART in the EI-AED group (3.3 log +/-1.3) than the other AED group (2.4 log +/-1.2; P<0.01). A multivariate model adjusting for both year starting and VL at cART showed similar results (OR 4.7 [0.9-23.6]; P=0.06). Analysis of multiple overlap periods yielded consistent and significant results with higher rates of VF in the EI-AED group (OR 4.2 [1.5-11.4]; P<0.01). Therefore, concurrent use of enzyme-inducing anti-epileptics and cART should be avoided whenever possible.[Okulicz et al. 2011]

1) Depending on seizure type, ***consider using other 2nd-line anticonvulsants*** to minimize interactions with protease inhibitors, NNRTIs and elvitegravir/cobicistat.

Best choices:
- Gabapentin
- Lamotrigine- a significant decrease in lamotrigine concentrations may be seen when used with ritonavir-based regimens
- Levetiracetam
- Vigabatrin
- Pregabalin

Caution Warranted:
- Valproic acid- monitor viral load closely; avoid combination with zidovudine due to cases of severe anemia
- Zonisamide- potential for increased zonisamide concentrations; a decreased dose may be required
- Topiramate- small potential for increased topiramate concentrations; topiramate is a mild CYP3A4 inducer (may impact PI, NNRTI and elvitegravir/cobicistat concentrations)
- Tiagabine- potential for increased tiagabine concentrations; a decreased dose may be required
- Anticonvulsants and protease inhibitors and/or tenofovir- potential for additive bone toxicity (osteonecrosis, osteopenia)

2) ***Change antiviral or drug dose if possible***:
- If possible, consider using a raltegravir-based regimen.

- Use ritonavir boosted protease inhibitor regimens (minimum ritonavir) 200mg/day to overcome induction. This is still a preliminary recommendation, since data are limited with this approach. Therapeutic drug monitoring of antiretrovirals is recommended if available.
- Empirically increase Kaletra (lopinavir/ritonavir) dose to 3 tablets BID (i.e. 600/150 mg BID) when combined with enzyme inducing

anticonvulsants. This is still a preliminary recommendation, since data are limited with this approach. Therapeutic drug monitoring of both the antiretrovirals and anticonvulsants is recommended if available (see table for details).

- Preliminary evidence suggest that darunavir/ritonavir (DRV/RTV) combined with carbamazepine may be a viable option. Although it is unlikely the dose of DRV/RTV requires adjustments, a 25-50% decrease in carbamazepine dose may be required. Therapeutic drug monitoring of both the antiretrovirals and carbamazepine is recommended if available (see table for details).

Appendix I: Antiepileptic Drugs of Choice in the General Population

Seizure Type	First-line Therapy	Second-line Therapy
a) Generalized		
Tonic-Clonic	VPA, CBZ, PHT	CLB, FBM, ?GBP, LTG, ?LEV, OXC, PB, PRM, ?TGB, TPM, ?VGB, ZNS
Absence	VPA, ESM	AZM, CLB, ?FBM, LTG, ?LEV, ?TPM, ZNS
Myoclonic	VPA	AZM, CLB, CZP, ?FBM, ?LTG, ?LEV, ?TPM, ZNS
Atonic	VPA	CLB, FBM, LTG, TGM
b) Partial		
Simple or complex ± secondary generalization	CBZ, PHT	CLB, FBM, GBP, LTG, LEV, OXC, PB, PGB, PRM, TGB, TPM, VGB, VPA, ZNS
Benign rolandic epilepsy	CBZ	CLB, GBP, PHT
Juvenile myoclonic epilepsy	VPA	CLB, LTG, TPM, CBZ, PHT (for gen. T-C seizures)
Lennox-Gastaut	VPA	CLB, CZP, FBM, LTG, TPM, VGB
West Syndrome (infantile spasms)	VGB superior toACTH	CLB, CZP, LTG, steroids, VPA
c) Women		
Idiopathic generalized epilepsy	VPA	
Idiopathic generalized epilepsy (pregnancy)	LTG	

ACTH= adrenocorticotropic hormone; AZM= acetazolamide; CBZ= carbamazepine; CLB= clobazam; CZP= clonazepam; ESM= ethosuximide; FBM= felbamate; GBP= gabapentin; LTG= lamotrigine; LEV= levetiracetam; OXC= oxcarbazepine; PB= phenobarbital; PGB= pregabalin; PHT= pheytoin; PRM= primidone; TGB= tiagabine; TPM= topiramate; VGB= vigabatrin; VPA= valproic acid; ZNS= zonisamide. ? = unclear

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Actual and Predicted Pharmacokinetic Interactions Between Anticonvulsants and Antiretrovirals

NB: please see "SUGGESTIONS FOR MANAGEMENT OF ANTICONVULSANT-ANTIRETROVIRAL INTERACTIONS IN HIV" for further discussion on anticonvulsants of choice in HIV

	Anticonvulsant Route of Metabolism[1-5]	**Protease Inhibitors** atazanavir (Reyataz®)[6] darunavir (Prezista®)[7] fosamprenavir (Telzir®)[8] indinavir (Crixivan®)[9] lopinavir/ritonavir (Kaletra®)[10] nelfinavir (Viracept®)[11] ritonavir (Norvir®)[12] saquinavir (Invirase®)[13] tipranavir (Aptivus®)[14]	**NNRTIs** efavirenz (Sustiva®)[15] etravirine (Intelence®)[16] nevirapine (Viramune®)[17] rilpivirine (Edurant®)[18]	**Integrase Inhibitors** elvitegravir/cobicistat (Stribild®, single-tablet regimen with tenofovir/emtricitabine)[19] raltegravir (Isentress®)[20] **CCR5 Inhibitor** maraviroc (Celsentri®)[21]
Hepatic Substrate		Mainly CYP3A4	Efavirenz, nevirapine: CYP3A4, 2B6 (minor) Etravirine: CYP3A4, CYP2C9, and CYP2C19. Rilpivirine: CYP3A4 (major), as well as CYP2C19, 1A2, 2C8/9/10 (minor).	Elvitegravir is metabolized via CYP3A and UGT1A1/3. Raltegravir is primarily metabolized by glucuronidation (UGT1A1). Maraviroc is a substrate of CYP3A4 and p-glycoprotein.[21]
Hepatic Inducer		Nelfinavir: UGT, 2C9/19 Ritonavir: UGT, CYP1A2, CYP2C9/19, 2B6 Tipranavir: mixed induction/inhibition effects; often acts as inducer of CYP3A4 and UGT, even when boosted with ritonavir	Efavirenz: 3A4 (potent), 2B6[22] and UGT1A1[23] Etravirine[16]: 3A4 (weak) Nevirapine[17]: 3A4, 2B6 (potent) Rilpivirine: 2C19 (moderate), CYP1A2, 2B6 and 3A4 (weak).[24] A clinically relevant effect on CYP enzyme activity is considered unlikely with the 25 mg dose.[18]	Elvitegravir: CYP2C9 (modest) Raltegravir has no inhibitory or inductive potential in vitro.[25]
Hepatic Inhibitor		Mainly CYP3A4 (darunavir,	Efavirenz inhibits 2C9, 2C19 (?	Cobicistat: CYP3A, CYP2D6;

	Anticonvulsant Route of Metabolism[1-5]	**Protease Inhibitors** atazanavir (Reyataz®)[6] darunavir (Prezista®)[7] fosamprenavir (Telzir®)[8] indinavir (Crixivan®)[9] lopinavir/ritonavir (Kaletra®)[10] nelfinavir (Viracept®)[11] ritonavir (Norvir®)[12] saquinavir (Invirase®)[13] tipranavir (Aptivus®)[14]	**NNRTIs** efavirenz (Sustiva®)[15] etravirine (Intelence®)[16] nevirapine (Viramune®)[17] rilpivirine (Edurant®)[18]	**Integrase Inhibitors** elvitegravir/cobicistat (Stribild®, single-tablet regimen with tenofovir/emtricitabine)[19] raltegravir (Isentress®)[20] **CCR5 Inhibitor** maraviroc (Celsentri®)[21]
		indinavir, nelfinavir, amprenavir >> saquinavir) Ritonavir: CYP3A4 (potent)> >2D6 >2C9 >2C19 >2A6 >1A2>2E1 At low boosting doses, ritonavir has a negligible effect in CYP2D6 inhibition.[26] Ritonavir inhibits CYP2B6 in vitro,[27] but induces 2B6 in vivo.[28] Nelfinavir inhibits 2B6 in vitro.	Clinical significance). Etravirine[16]: CYP2C9 (weak), CYP2C19 (moderate), p-glycoprotein (weak)	also p-glycoprotein (P-gp), BCRP, OATP1B1 and OATP1B3.[19] Raltegravir has no inhibitory or inductive potential in vitro.[25] Maraviroc is unlikely to inhibit the metabolism of co-administered drugs that aremetabolized by cytochrome P450 enzymes because it does not inhibit the seven major CYP450 isoenzymes (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 and CYP3A4) at clinically relevant concentrations *In Vitro.* Maraviroc could inhibit P-glycoprotein in the gut and may thus affect bioavailability of certain drugs; systemic effects of P-glycoprotein inhibition are unlikely to be of relevance.[21]
Carbamazepine (CBZ) Tegretol®	Parent: CYP3A>> 2C8, 1A2 Induces CYP3A, 2C9,	likely ↑ CBZ levels, and ↓ protease inhibitor levels and loss of efficacy; **avoid combination as antiretroviral therapy may**	likely ↓ CBZ levels and ↓ NNRTI levels and loss of efficacy; dosing adjustments not yet studied for all drugs; in	Potential for significant ↓ in **elvitegravir and cobicistat** concentrations. Consider alternate anticonvulsants.[19]

	Anticonvulsant Route of Metabolism[1-5]	Protease Inhibitors atazanavir (Reyataz®)[6] darunavir (Prezista®)[7] fosamprenavir (Telzir®)[8] indinavir (Crixivan®)[9] lopinavir/ritonavir (Kaletra®)[10] nelfinavir (Viracept®)[11] ritonavir (Norvir®)[12] saquinavir (Invirase®)[13] tipranavir (Aptivus®)[14]	NNRTIs efavirenz (Sustiva®)[15] etravirine (Intelence®)[16] nevirapine (Viramune®)[17] rilpivirine (Edurant®)[18]	Integrase Inhibitors elvitegravir/cobicistat (Stribild®, single-tablet regimen with tenofovir/emtricitabine)[19] raltegravir (Isentress®)[20] CCR5 Inhibitor maraviroc (Celsentri®)[21]
	2C19, UGT and possibly 1A2 Active metabolite: epoxide hydrolase (CBZ-10,11- epoxide)	**be significantly compromised due to enzyme induction, and carbamazepine toxicity may occur**. In a 20 y.o. patient, addition of **ritonavir (200 mg dose)** to CBZ and **zonisamide** resulted in 70-87% ↑ serum CBZ levels and toxicity (vomiting, vertigo). Zonisamide concentrations were unchanged. Ritonavir levels were not measured. Doses of anticonvulsants were reduced by 1/3.[29] Several other case reports have reported acute CBZ toxicity (ataxia, vertigo, disorientation, diplopia, drowsiness) within 2-4 days of adding RTV.[30-33] In an open-label, 2 phase, crossover interaction study in healthy volunteers, steady-state coadministration of **darunavir 600/100 mg BID** plus CBZ 200 mg BID resulted in 14% ↓ Cmin, 1.2% ↑ AUC of darunavir, 54% ↑ Cmin, 45% ↑ AUC of CBZ and	general, **avoid combination as antiretroviral therapy will be significantly compromised due to enzyme induction**. Negative dual interaction with **efavirenz** observed in a pharmacokinetic study in healthy subjects (n=36). Co-administration of EFV 600 mg QD with CBZ 400 mg QD at steady-state. • EFV:↓ AUC 36%, Cmax 21%, Cmin 47% • CBZ: ↓ AUC 27%, Cmax 20%, Cmin 35%. The kinetics of the active CBZE metabolite were unchanged. Upward dosage titration of both efavirenz and CBZ is likely required. Therapeutic drug monitoring would be useful. If possible, use alternate anticonvulsant such as vigabatrin or gabapentin .[39] In a phase 1, two-period, 9	**Raltegravir**: The impact on UGT1A1 is unknown. Use with caution.[20] Increase **maraviroc** dose to 600 mg BID if using concomitant potent CYP3A4 inducer.[21]

	Anticonvulsant Route of Metabolism[1-5]	Protease Inhibitors atazanavir (Reyataz®)[6] darunavir (Prezista®)[7] fosamprenavir (Telzir®)[8] indinavir (Crixivan®)[9] lopinavir/ritonavir (Kaletra®)[10] nelfinavir (Viracept®)[11] ritonavir (Norvir®)[12] saquinavir (Invirase®)[13] tipranavir (Aptivus®)[14]	NNRTIs efavirenz (Sustiva®)[15] etravirine (Intelence®)[16] nevirapine (Viramune®)[17] rilpivirine (Edurant®)[18]	Integrase Inhibitors elvitegravir/cobicistat (Stribild®, single-tablet regimen with tenofovir/emtricitabine)[19] raltegravir (Isentress®)[20] CCR5 Inhibitor maraviroc (Celsentri®)[21]
		52% ↓ Cmin, 54% ↓ AUC of CBZ-epoxide compared to either drug administered alone. Suggest monitoring for CBZ efficacy and possibly ↓ CBZ dose by 25-50% if necessary. Dosage adjustment for darunavir/ritonavir likely not required.[34] A 39 y.o. African male experienced CBZ central nervous system toxicity one week after starting on **lopinavir/ritonavir 600/150 mg BID** with CBZ 400 mg BID. The dose of CBZ was decreased by 25%, while the lopinavir/ritonavir dose (50% increase) was maintained to compensate for the inductive interaction.[35] A 50-year-old HIV-positive male developed excessive drowsiness secondary to carbamazepine when a regimen containing **lopinavir/ritonavir** was introduced, and his CBZ serum concentration ↑ 46%. When lopinavir/ritonavir was replaced	group study, a single dose of carbamazepine 400 mg given with **single dose nevirapine 200 mg** in healthy non-pregnant women significant ↓ nevirapine $t_{1/2}$ by 18.8 hours and ↓ time to undetectable NVP levels by 4 days compared to single-dose NVP administered alone (median t1/2 with single-dose NVP alone was 53.9 hours, time to undetectable NVP was 15.5 days).[40] In a 1:1 randomized study, HIV-infected ARV-naïve pregnant women were given single-dose **nevirapine** 200 mg vs.single dose nevirapine 200 mg + CBZ 400mg at delivery in an attempt to increase nevirapine clearance and decrease resistance. One week post-dose, the nevirapine concentrations were 36% lower in the CBZ group with a trend toward fewer resistance mutations at 6 weeks (21% vs.	

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		by **nelfinavir,** serum CBZ concentrations ↑ 53% within 3 days, and the patient again developed excessive drowsiness and became unsteady on his feet. In both instances, ↓ CBZ dosage by 33% resulted in resolution of symptoms.[36] Report of antiretroviral failure with concomitant CBZ-**indinavir** therapy. ↓ IDV concentrations to 4-25% of mean population values.[37] **Tipranavir/ritonavir:** CBZ 200mg BID with tipranavir resulted in a 23% ↑ in CBZ and CBZ-10, 11-epoxide Cmin and a 61% ↓ in tipranavir Cmin (compared to historical controls). This may compromise tipranavir efficacy. Higher doses of CBZ may lead to even larger decreases in tipranavir concentrations.[38] The combination should likely be avoided.	11%).[41] **Rilpivirine:** CBZ is contraindicated due to potential for decreased rilpivirine AUC and virologic failure/resistance.[18] **Etravirine:** Avoid use with CBZ due to potential for decreased etravirine AUC and virologic failure/resistance.[16]	

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Clobazam Frisium®	Parent: CYP3A4, 2C19 Inhibits CYP2C9/19 Metabolite (active): N-desmethyl (norclobazam).[42]	Inhibitors of CYP450 may ↑ clobazam concentrations; monitor for toxicity and reduce dose if necessary	potential for ↓ clobazam concentrations; monitor for efficacy and increase dose if necessary **Etravirine** induces CYP3A4 and induces 2C9/2C19. One case report of increased clobazam concentrations and onset of neurotoxic symptoms after etravirine was added to an HIV patient's regimen. Drug concentrations returned to baseline and symptoms resolved after clobazam dose was reduced by 50%.[43]	**Elvitegravir/cobicistat:** potential for ↑ clobazam concentrations; monitor for toxicity and reduce dose if necessary.
Clonazepam Rivotril®	CYP3A4	potential for ↑ clonazepam concentrations	possible ↓ clonazepam concentrations and withdrawal	**Elvitegravir/cobicistat:** potential for ↑ clonazepam concentrations.[19]
Ethosuximide Zarontin®	CYP3A4 (40%)>others	potential for ↑ ethosuximide concentrations; monitor for toxicity and reduce dose if necessary	potential for ↓ ethosuximide concentrations; monitor for efficacy and increase dose if necessary	**Elvitegravir/cobicistat:** potential for ↑ ethosuximide concentrations.[19]
Felbamate Felbatol®	CYP3A4 Inhibits CYP2C19 Induces CYP3A4	likely ↑ felbamate levels, and ↓ protease levels and loss of efficacy; dosing adjustments not yet studied. **Avoid combination as**	likely ↓ felbamate levels and ↓ NNRTI levels and loss of efficacy; dosing adjustments not yet studied; **avoid combination as antiretroviral**	**Elvitegravir/cobicistat:** potential for ↑ felbamate and/or ↓ elvitegravir/cobicistat concentrations; **avoid combination if possible**.

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		antiretroviral therapy will be significantly compromised due to enzyme induction.	**therapy will be significantly compromised due to enzyme induction**.	Potential for ↓ **maraviroc** concentrations. Avoid combination if possible.
Gabapentin Neurontin®	excreted unchanged in urine	no interaction anticipated	no interaction anticipated	no interaction anticipated
Lamotrigine Lamictal®	Parent: mainly UGT Induces UGT (mild)	potential for ↓ lamotrigine concentrations due to GT induction by nelfinavir; monitor for efficacy and increase dose if necessary In a pharmacokinetic study in healthy subjects, lamotrigine Cmin ↓ 56% when administered with **lopinavir/ritonavir** for 10 days, lopinavir concentrations unaffected. Doubling the lamotrigine dose to 200 mg BID appeared to overcome this interaction.[44] Monitor for lamotrigine efficacy and ↑ dose if necessary when coadministering with ritonavir-containing regimens. In a pharmacokinetic study in healthy volunteers of single dose lamotrigine 10 mg in the presence of steady state	Potential for ↓ lamotrigine concentrations due to GT induction by **tipranavir**; monitor for efficacy and increase dose if necessary. In healthy subjects**, raltegravir 400 mg BID** did not affect the pharmacokinetics of single-dose lamotrigine 100 mg compared to lamotrigine administered alone, and raltegravir exposures in the presence of lamotrigine were comparable to historical controls.[46]	In healthy subjects, **raltegravir 400 mg BID** for five days did not affect the pharmacokinetics of single dose lamotrigine 100 mg. The mean ratio of the AUC of lamotrigine-2N-glucuronide to lamotrigine was similar when lamotrigine was taken alone (0.35) or when taken with raltegravir (0.36). Raltegravir does not influence the glucuronidation of lamotrigine.[46]

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		atazanavir 400 mg QD or atazanavir 300/ritonavir 100 mg QD, lamotrigine concentrations were unaffected with unboosted atazanavir, while 32% ↓ lamotrigine AUC was observed with ATV/r. Atazanavir and ritonavir concentrations were comparable to historical controls in the presence of lamotrigine.[45]		
Levetiracetam Keppra®	24% enzymatic hydrolysis (not CYP450) 66% renal unchanged	no interaction anticipated In a 22 y.o. female with advanced HIV, low albumin and a **lopinavir/ritonavir**-based regimen, **phenytoin** 300 mg daily yielded toxic concentrations when corrected for the low albumin and increased seizure frequency. To simplify therapy, phenytoin was changed to **levetiracetam** and the patient stabilized. Virologic data was not presented.[47]	no interaction anticipated	no interaction anticipated
Oxcarbazepine Trileptal®	Parent: Reduction via cystolic enzymes Metabolite (active): 10-mono-hydroxy which is metabolized via UGT.	Potential for ↓ protease inhibitor concentrations. **Avoid combination as antiretroviral therapy will be significantly compromised due**	Potential ↓ NNRTI concentrations and efficacy. **Avoid combination as antiretroviral therapy will be significantly compromised**	Potential for significant ↓ in **elvitegravir and cobicistat** concentrations. Consider alternate anticonvulsants.[19]

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	Inhibits CYPC19 Induces CYP3A4 (mild), UGT	**to enzyme induction**.	**due to enzyme induction**. Case report of a patient receiving an **efavirenz**-based regimen who experienced treatment failure shortly after initiating oxcarbazepine. The patient had WT virus at baseline, but showed M184V, K103N and 225H mutations at viral rebound. The patient's efavirenz levels were measured before, during, and after concomitant oxcarbazepine use, and were not changed in the presence of oxcarbazepine. At all time points, his EFV exposure was approximately in the 25th percentile, failure likely due to nonadherence.[48] **Rilpivirine:** oxcarbazepine is contraindicated due to potential for decreased rilpivirine AUC and virologic failure/resistance.[18]	**Raltegravir**: The impact on UGT1A1 is unknown. Use with caution.[20] Potential for ↓ **maraviroc** concentrations. Avoid combination if possible.
Phenobarbital (PHB)	Parent: CYP450 oxidative hydroxylation	Potential for ↓ protease inhibitor concentrations	Potential for ↓ NNRTI concentrations.	Potential for significant ↓ in **elvitegravir and cobicistat**

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	via 2C9/19 Inducer (potent): CYP3A4, 1A2, 2C9/19, UGT	**Avoid combination as anticonvulsant and/or antiretroviral therapy may be significantly compromised due to enzyme induction.** Case report of patient started on **ritonavir** 300mg BID, **saquinavir** 400mg BID, **nevirapine** 200mg/day while on PHB 250mg/day, CBZ 400mg TID and phenytoin 500mg/day. After 2 days, CBZ toxicity was noted (99.4% ↑ CBZ concentrations); 32.7% ↓ phenytoin levels; no change in PHB levels. Ritonavir levels were not measured.[31] Case report of a 49 yr old white HIV+ male on stable phenobarbital therapy (100mg daily; level 16ug/ml) for seizure prevention who seized 4 weeks after starting a new salvage ARV regimen: ABC, ddI, **tipranavir/ritonavir** (TPV/r) (500/200 mg BID), T20. Phenobarbital level was found to	**Nevirapine:** After PHB 200 mg single dose, there was no significant change in the mean half-life of nevirapine.[50] **Rilpivirine:** PHB is contraindicated due to potential for decreased rilpivirine AUC and virologic failure/resistance.[18] **Etravirine:** Avoid use with PHB due to potential for decreased etravirine AUC and virologic failure/resistance.[16]	concentrations. Consider alternate anticonvulsants.[19] **Raltegravir**: The impact on UGT1A1 is unknown. Use with caution.[20] Increase **maraviroc** dose to 600 mg BID if using concomitant potent CYP3A4 inducer.[21]

	Anticonvulsant Route of Metabolism[1-5]	**Protease Inhibitors** atazanavir (Reyataz®)[6] darunavir (Prezista®)[7] fosamprenavir (Telzir®)[8] indinavir (Crixivan®)[9] lopinavir/ritonavir (Kaletra®)[10] nelfinavir (Viracept®)[11] ritonavir (Norvir®)[12] saquinavir (Invirase®)[13] tipranavir (Aptivus®)[14]	**NNRTIs** efavirenz (Sustiva®)[15] etravirine (Intelence®)[16] nevirapine (Viramune®)[17] rilpivirine (Edurant®)[18]	**Integrase Inhibitors** elvitegravir/cobicistat (Stribild®, single-tablet regimen with tenofovir/emtricitabine)[19] raltegravir (Isentress®)[20] **CCR5 Inhibitor** maraviroc (Celsentri®)[21]
		be reduced by ~ 50% in presence of TPV/r (level: 8.1ug/ml). Phenobarbital was ↑ 150 mg daily with subsequent plasma level increasing to 17ug/ml (similar to previous value). Trough TPV concentration was 34,837 ng/mL on Phenobarbital. This was similar to a population mean value 30,760 ng/mL. Authors suggest, net effect of coadministration of TPV/r was probably induction of CYP2C9 and/or CYP2C19 leading to clinically significant decrease of phenobarbital plasma exposure. Combination of TPV/r + Phenobarbital warrants careful monitoring.[49]		
Phenytoin Dilantin®	Parent: CYP2C9 (70%)>2C19 (minor); Inducer (potent): CYP3A4, 2C9/19, UGT	Potential for ↓ protease inhibitor concentrations and/or ↑ phenytoin concentrations; **avoid combination as antiretroviral therapy will be significantly compromised due to enzyme induction**. Healthy volunteer kinetic study	Potential for ↓ NNRTI concentrations. **Avoid combination as antiretroviral therapy will be significantly compromised due to enzyme induction.** Case report of suboptimal **efavirenz** levels in a subject	Potential for significant ↓ in **elvitegravir and cobicistat** concentrations. Consider alternate anticonvulsants.[19] **Raltegravir**: The impact on UGT1A1 is unknown. Use with caution.[20]

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		(n=24) of **lopinavir/ritonavir** 400/100 mg BID and phenytoin 300 mg daily resulted in negative 2-way interaction: lopinavir AUC ↓ 33%, Cmin ↓ 46%, ritonavir AUC ↓ 28%, Cmin ↓ 47%, and phenytoin AUC ↓ 31% and Cmin ↓ 34%. Dosage adjustments of one or both drugs likely necessary.[51] Authors suggested a dosage increase in lopinavir/r may be necessary (i.e. 533/133 mg BID of Kaletra capsules). Since the capsules are no longer available, the dosage of Kaletra tablets that may be required is 600/150 mg BID. Therapeutic drug monitoring is recommended for both lopinavir/ritonavir and phenytoin. Two cases describe the safe and effective use of **lopinavir/ritonavir** with phenytoin. In both cases a 50% increase in the dose of lopinavir/ritonavir (600/150 mg BID) was empirically used to compensate for the potential	receiving concomitant phenytoin 300 mg BID; when phenytoin was replaced by levetiracetam, therapeutic efavirenz levels were achieved. Elevated phenytoin levels were also noted after initiation of efavirenz.[54] Case report of a 35 yr old newly diagnosed HIV+ male who experienced undetectable efavirenz levels while taking efavirenz 800mg/day and phenytoin (Dose Range 400 – 800mg/day) for partial tonic seizures. Dramatic decrease in efavirenz levels when used with phenytoin. **Avoid combination**.[55] In a phase 1, two-period, 9 group study, a single dose of phenytoin 184 mg for 3 or 7 days given with single dose **nevirapine (NVP)** 200 mg in healthy non-pregnant women significant ↓ NVP $t_{1/2}$ by 16.9-	Increase **maraviroc** dose to 600 mg BID if using concomitant potent CYP3A4 inducer.[21]

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		interaction. The dose of phenytoin required a 12 to 20% increase from baseline. Another case reported a low darunavir Cmin when **darunavir/ritonavir** 900/100 mg daily was given with phenytoin 450 mg daily. The darunavir Cmin was therapeutic when the dose was changed to 600/100 mg BID. The dose of phenytoin remained stable. In all cases, the patients remained virologically suppressed.[35] In a 22 y.o. female with advanced HIV, low albumin and a **lopinavir/ritonavir**-based regimen, **phenytoin** 300 mg daily yielded toxic concentrations when corrected for the low albumin and increased seizure frequency. To simplify therapy, phenytoin was changed to **levetiracetam** and the patient stabilized. Virologic data was not presented.[47] Caution with other ritonavir-boosted protease inhibitor	19 hours and ↓ time to undetectable NVP levels by 7-8.5 days compared to single-dose NVP administered alone (median t1/2 with single-dose NVP alone was 53.9 hours, time to undetectable NVP was 15.5 days).[40] **Rilpivirine:** Phenytoin is contraindicated due to potential for decreased rilpivirine AUC and virologic failure/resistance[18]. **Etravirine:** Avoid use with phenytoin due to potential for decreased etravirine AUC and virologic failure/resistance.[16]	

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		regimens. **Nelfinavir:** One healthy volunteer study of nelfinavir 1250 mg BID + phenytoin 300 mg daily x 14/7 showed ~30% reduction in phenytoin AUC; 20-34% decrease in M8 exposure. The nelfinavir Ctrough was within an acceptable range.[52] Also a case report of a patient stable on phenytoin and phenobarbital for 17 years. One month after **nelfinavir** was started, phenytoin levels ↓ by 58%. Phenobarbital and nelfinavir levels were stable. The patient experienced seizures after 3 months on the combination. [53]		
Pregabalin Lyrica®	excreted unchanged in urine[56] not metabolized; no impact on hepatic enzymes	no interaction anticipated	no interaction anticipated	No interaction anticipated
Primidone Mysoline®	metabolized to phenobarbital	Potential for ↓ protease inhibitor concentrations and/or ↑ phenobarbital concentrations. **Avoid combination as**	Potential for ↓ NNRTI concentrations; **avoid combination as antiretroviral therapy will be significantly**	Potential for significant ↓ in **elvitegravir and cobicistat** concentrations. Consider

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		antiretroviral therapy will be significantly compromised due to enzyme induction. Case report of patient started in 3TC, ddI, ritonavir 600mg BID, and saquinavir 400mg BID while stable on phenytoin 450mg/day and CBZ 600mg/day. After 2 months ongoing CBZ toxicity was seen (177% ↑ CBZ levels) . Phenytoin levels were unchanged. The CBZ was replaced with primidone 500mg/day and the patient did well in follow-up with undetectable VL. RTV levels were not measured.[33] Until further data are available, **avoid combination as antiretroviral therapy may be significantly compromised due to enzyme induction**	**compromised due to enzyme induction**	alternate anticonvulsants. **Raltegravir**: The impact on UGT1A1 is unknown. Use with caution.[20] Potential for ↓ **maraviroc** concentrations. Avoid combination if possible.
Tiagabine Gabitril® USA	CYP3A4 > UGT	potential for ↑ tiagabine concentrations	potential for ↓ tiagabine concentrations	Potential for ↑ tiagabine concentrations with **elvitegravir/cobicistat**. No interaction anticipated with **raltegravir or maraviroc**.

	Anticonvulsant Route of Metabolism[1-5]	**Protease Inhibitors** atazanavir (Reyataz®)[6] darunavir (Prezista®)[7] fosamprenavir (Telzir®)[8] indinavir (Crixivan®)[9] lopinavir/ritonavir (Kaletra®)[10] nelfinavir (Viracept®)[11] ritonavir (Norvir®)[12] saquinavir (Invirase®)[13] tipranavir (Aptivus®)[14]	**NNRTIs** efavirenz (Sustiva®)[15] etravirine (Intelence®)[16] nevirapine (Viramune®)[17] rilpivirine (Edurant®)[18]	**Integrase Inhibitors** elvitegravir/cobicistat (Stribild®, single-tablet regimen with tenofovir/emtricitabine)[19] raltegravir (Isentress®)[20] **CCR5 Inhibitor** maraviroc (Celsentri®)[21]
Topiramate Topamax®	CYP 450 enzymes (minor) 55-97% excreted unchanged in urine Induces 3A4 (mild) Inhibits 2C19	no major interaction anticipated; potential for small ↑ topiramate concentrations	no major interaction anticipated; potential for small ↓ topiramate concentrations	**Elvitegravir/cobicistat**: potential for small ↑ topiramate concentrations and/or ↓ in elvitegravir/cobicistat concentrations. Potential for ↓ **maraviroc** concentrations (clinical significance unknown). Avoid combination if possible.
Valproic Acid Epival®, Depakene®	Parent: UGT (50%), mitochondrial β-oxidation (40%), minor CYP-dependent oxidation pathway (<10%) Inhibits: UGT, CYP2C9/19 NB: Cautious use with **zidovudine**- severe anemia has been reported secondary to increased levels of AZT (proposed mechanism is valproic acid inhibition of AZT glucuronidation).[57,]	Unlikely; possible ↓ valproate concentrations & loss of valproate efficacy with nelfinavir (induces glucuronidation). Valproic acid may increase HIV viral replication *in vitro*, however it does not significantly affect antiretroviral drug concentrations.[59-61] Clinical significance is unknown, however one case series reported no impact on viral load in patients on HAART.[62] These findings are also confirmed by a larger study assessing the cumulative impact of anticonvulsant therapy on HIV	In one study in HIV-positive subjects on stable **efavirenz** therapy, administration of valproic acid 250 mg BID for 7 days did not affect efavirenz exposure.[65] Case report demonstrating a 50% ↓ in valproate levels when co-administered with an efavirenz-based regimen. A valproate dosage increase from 1.5 g/day to 4 g/day was required to achieve therapeutic concentrations (doubling the dose). Efavirenz-mediated UGT induction is a proposed mechanism, though not	**Raltegravir** is not expected to alter the metabolism of drugs that are metabolized by UGT1A4, such as valproic acid.[69]

	Anticonvulsant Route of Metabolism[1-5]	**Protease Inhibitors** atazanavir (Reyataz®)[6] darunavir (Prezista®)[7] fosamprenavir (Telzir®)[8] indinavir (Crixivan®)[9] lopinavir/ritonavir (Kaletra®)[10] nelfinavir (Viracept®)[11] ritonavir (Norvir®)[12] saquinavir (Invirase®)[13] tipranavir (Aptivus®)[14]	**NNRTIs** efavirenz (Sustiva®)[15] etravirine (Intelence®)[16] nevirapine (Viramune®)[17] rilpivirine (Edurant®)[18]	**Integrase Inhibitors** elvitegravir/cobicistat (Stribild®, single-tablet regimen with tenofovir/emtricitabine)[19] raltegravir (Isentress®)[20] **CCR5 Inhibitor** maraviroc (Celsentri®)[21]
	58	proliferation.[63] Caution with combination is still warranted. In 12 HIV-infected patients on stable **atazanavir 300/ritonavir 100 mg QD**, atazanavir exposures were significantly reduced in the presence of valproic acid 250 mg BID and minocycline 100 mg BID for 2 weeks (ATV AUC ↓ 33%, Cmin ↓ 50%, Cmax ↓ 25% vs. ATV/rtv alone).[64] When combined with valproate, **lopinavir** concentrations tended to be higher (geometric mean ratio of the AUC with and without valproate was 1.38). Valproate trough not significantly changed.[65] One case report of reduced valproic acid concentrations (48% ↓) 21 days after **lopinavir/ritonavir** initiated; VA dosage was doubled and levels re-stabilized. Mechanism postulated to be induction of	confirmed.[67] Valproic acid may increase HIV viral replication *in vitro*, however it does not significantly affect antiretroviral drug concentrations.[59-61] Clinical significance is unknown, however one case series and a small prospective study using NNRTIs[68] reported no impact on viral load in patients on HAART.[62] These findings are also confirmed by a larger study assessing the cumulative impact of anticonvulsant therapy on HIV proliferation.[63] Caution with combination is still warranted.	

	Anticonvulsant Route of Metabolism[1-5]	Protease Inhibitors atazanavir (Reyataz®)[6] darunavir (Prezista®)[7] fosamprenavir (Telzir®)[8] indinavir (Crixivan®)[9] lopinavir/ritonavir (Kaletra®)[10] nelfinavir (Viracept®)[11] ritonavir (Norvir®)[12] saquinavir (Invirase®)[13] tipranavir (Aptivus®)[14]	NNRTIs efavirenz (Sustiva®)[15] etravirine (Intelence®)[16] nevirapine (Viramune®)[17] rilpivirine (Edurant®)[18]	Integrase Inhibitors elvitegravir/cobicistat (Stribild®, single-tablet regimen with tenofovir/emtricitabine)[19] raltegravir (Isentress®)[20] CCR5 Inhibitor maraviroc (Celsentri®)[21]
		glucuronidation by ritonavir.[66] **Tipranavir/ritonavir:** ↓ valproic acid levels predicted; may require increased dose of valproic acid.[38]		
Vigabatrine Sabril®	excreted unchanged in urine	no interaction anticipated	no interaction anticipated	no interaction anticipated
Zonisamide Zonegran® USA	Parent: CYP3A4, UGT Inhibits CYP2A6, 2C9/19,	potential for ↑ zonisamide concentrations, caution is warranted. In a 20 y.o. patient, addition of **ritonavir** (200 mg dose) to CBZ and zonisamide resulted in 70-87% ↑ serum CBZ levels and toxicity (vomiting, vertigo). Zonisamide concentrations were unchanged. Ritonavir levels were not measured. Doses of both anticonvulsants were reduced by 1/3.[29] Since potential for ↑ zonisamide concentrations exist, caution is warranted.	potential for ↓ zonisamide concentrations	**Elvitegravir/cobicistat:** potential for ↑ zonisamide concentrations, caution is warranted. No interaction anticipated with raltegravir or maraviroc.

CYP= Hepatic Cytochrome P450 isoenzyme; AD= Alcohol dehydrogenase; TCA= tricyclic antidepressant; MAOI= monoamine oxidase inhibitor; SSRI= selective serotonin reuptake inhibitor; Substrate= route of hepatic elimination of that specific drug (specified by a specific cytochrome P450 isoenzyme); inducer= leads to more rapid clearance of substrates of a specific hepatic isoenzyme (lowers serum concentrations of the respective drug and may lead to decreased efficacy); inhibitor = leads to decreased clearance of substrates of a specific hepatic isoenzyme (increases serum concentrations of a respective drug and may lead to toxicity); UGT= Uridine diphosphate glucuronyltransferase

Please note: This chart summarizes some of the major drug interactions identified to date, based on current available data; other drug interactions may exist. Please use caution whenever adding/modifying therapy. The information in this table is intended for use by experienced physicians and pharmacists. It is not intended to replace sound professional judgment in individual situations, and should be used in conjunction with other reliable sources of information. Due to the rapidly changing nature of information about HIV treatment and therapies, users are advised to recheck the information contained herein with the original source before applying it to patient care.

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Antihyperglycemic Agents Comparison Chart

Parameter	Metformin	Sulfonylureas	Meglitinides	Glitazones (TZD's)
Mechanism of Action	↓ Hepatic glucose output ↑ Peripheral glucose uptake by enhancing insulin action	↑ insulin secretion (both basal & prandial)	↑ insulin secretion (primarily prandial)	↑ Peripheral glucose uptake by enhancing insulin action ↓ Hepatic glucose output
Efficacy (A1c Reduction)	1 – 1.5 %	1 – 1.5 %	Repaglinide 1 – 1.5 % Nateglinide 0.6 – 1 %	1 – 1.5 %
Hypoglycemia Risk	0	Glyburide ++++ Glimepiride +++ Gliclazide ++	+	0
Weight Change	↓	↑	↑	↑↑
Suitability for use in heart failure	OK in stable heart failure; Monitor renal function; consider stopping metformin if significant reduction in GFR (see above)	OK	OK	Avoid in all stages of heart failure; CDA guidelines state may be used in mild, stable CHF if patient is closely monitored by a specialist
Metabolism & Excretion	• Negligible metabolism • Excreted 100% as unchanged drug by glomerular filtration plus active tubular secretion	Sulfonylureas are extensively metabolized primarily via CYP2C9. Excreted primarily as inactive or weakly active metabolites. • Gliclazide: metabolized to inactive compounds • Glimepiride: metabolized to inactive compounds • Glyburide: metabolized in part to weakly active metabolites that may accumulate in renal impairment	Repaglinide: • Extensively metabolized to inactive compounds primarily via CYP2C8 & to lesser extent via 3A4 • Excreted as inactive metabolites primarily in the bile; very little excreted as unchanged in urine Nateglinide: • Extensively metabolized to inactive compounds primarily via CYP 2C9 (70%) & to lesser extent via 3A4 • Excreted primarily as metabolites; only 15% as unchanged drug in urine	Pioglitazone: • Extensively metabolized to inactive compounds primarily via CYP2C8 & to a lesser extent 3A4; (H) • Excreted as inactive metabolites primarily via fecal route Rosiglitazone: • Extensively metabolized to weakly active compounds primarily via CYP2C8 with minor pathway 2C9 • Excreted as metabolites in urine
Suitability for use in renal insufficiency	Caution if GFR 30-60 mL/min; Avoid if GFR < 30	Gliclazide & Glimepiride OK Glyburide – caution if GFR < 30	OK	OK

Parameter	Metformin	Sulfonylureas	Meglitinides	Glitazones (TZD's)
Pharmacokinetic Drug Interactions Notes: (1) None of the antihyperglycemic agents is an important cause of drug interactions (no strong inhibitors or inducers). (2) Most of the pharmacokinetic data presented here describing alterations in the disposition of antihyperglycemic agents caused by inhibition or induction of metabolizing enzymes are of unknown clinical significance. Indeed, many are likely of no clinical significance based on the small magnitude of the effect. Exceptions include those for which it is recommended to "avoid" the combination and those for which an alteration in dosage of antihyperglycemic agent is recommended.	Cimetidine ↑ metformin AUC 50% (competitive inhibition of active renal tubular secretion)	**Sulfonylureas:** **↑ AUC due to CYP2C9 inhibitor:** • Clarithromycin ↑ glyburide 35% • Fluconazole ↑ glimepiride 138% • Co-trimoxazole (TMP/SMX) ↓ clearance of tolbutamide 25% and ↑ half-life 30% **↓ AUC due to CYP2C9 inducer:** • Rifampin ↓ gliclazide 70% • Rifampin ↓ glimepiride 34% • Rifampin ↓ glyburide 39%	**Repaglinide** **↑ AUC due to CYP inhibitor:** • Clarithromycin 40% (3A4) • Cyclosporine 144% (3A4) • Gemfibrozil 712% (2C8 and OATP1B1); **avoid** combined use with repaglinide • Itraconazole 41% (3A4 and OATP1B1) • Itraconazole + gemfibrozil 1839% (20-fold increase) (2C8 & 3A4); **avoid** combined use of both drugs with repaglinide • Ketoconazole 15% (3A4) • Telithromycin 77% (3A4) • Trimethoprim 61% (2C8) **↓ AUC due to CYP inducer:** • Rifampin 32-85% (3A4) **Nateglinide** **↑ AUC due to CYP inhibitor:** • Fluconazole 48% (2C9) • Gemfibrozil + itraconazole 47% (2C8 & 3A4) **↓ AUC due to CYP inducer:** • Rifampin 24% (2C9 & 3A4)	**Pioglitazone** **↑ AUC due to CYP2C8 inhibitor:** • Gemfibrozil 230%; consider limiting dose of pioglitazone to 15 mg daily • Trimethoprim 42% **↓ AUC due to CYP2C8 inducer:** • Rifampin 54% **Rosiglitazone** **↑ AUC due to CYP inhibitor:** • Fluvoxamine 21% (2C8) • Gemfibrozil 130% (2C8); consider limiting dose of rosiglitazone to 4 mg daily • Ketoconazole 47% (3A4) • Trimethoprim 35% (2C8) **↓ AUC due to CYP inducer:** • Rifampin 60% (2C8; also 2C9)
Products & Dosage Forms	• Metformin (Glucophage & generics) 500, 850 mg • Glumetza extended release (ER) 500, 1000 mg Combination products: • Avandamet – see Glitazones • Janumet – see DPP-4 Inhibitors	• Gliclazide (Diamicron & generics) 80 mg modified release (MR) 30 mg • Glimepiride (Amaryl & generics) 1 mg, 2 mg, 4 mg • Glyburide (Diabeta & generics) 2.5, 5 mg	• Repaglinide (Gluconorm & generics) 0.5 mg, 1 mg, 2 mg • Nateglinide (Starlix) 60, 120, 180 mg	• Pioglitazone (Actos & generics) 15, 30, 45 mg • Rosiglitazone (Avandia) 2, 4, 8 mg • Avandamet = Rosiglitazone + Metformin 1/500 mg, 2/500 mg, 4/500 mg, 2/1000 mg, 4/1000 mg

Parameter	Metformin	Sulfonylureas	Meglitinides	Glitazones (TZD's)
Dosage	***To improve GI tolerability, start with a low dose and increase slowly every 3-5 days*** • Metformin is taken 2-3 times per day with or after meals; Start with 500 once or twice daily; increase by 500 mg/day as tolerated; max 2.5 g /day • Glumetza is taken once daily with evening meal; start with 1 g and increase by 500 mg at weekly intervals; max 2 g/day	***Most of the benefit of a sulfonylurea is achieved in most patients at half the max daily dose listed below*** • Gliclazide is taken twice daily before breakfast & supper; start with 80 mg BID; max 160 mg BID • Glimepiride is taken once daily before breakfast; start with 1 mg daily; increase every 1-2 weeks; max 8 mg daily • Glyburide is taken once daily or twice daily if the dose/day exceeds 10 mg; start with 2.5 to 5 mg daily; increase every 1-2 weeks; max 20 mg/day	***Meglitinides are to be taken within 30 min prior to a meal and only if patient will be eating.*** ***If a meal is delayed or will not be eaten, the dose should usually be delayed or omitted.*** • Repaglinide: start with 0.5 to 1 mg TID; max 12 mg/day • Nateglinide: start with 120 mg TID; max 540 mg/day	***Before increasing dose, allow 8-12 weeks to assess full benefit*** • Pioglitazone is taken once daily without regard to mealtimes; start with 15 or 30 mg daily; max 45 mg/day • Rosiglitazone is taken once daily without regard to mealtimes; start with 4 mg daily; max 8 mg/day
Cost per month for most common dose < $15 $ $16-35 $$ $36-70 $$$ $71-100 $$$$ > $100 $$$$$	Metformin $ Glumetza $$$	Gliclazide $ Gliclazide MR $ Glimepiride $$ Glyburide $	Repaglinide $$ Nateglinide $$$	Pioglitazone $$$ Rosiglitazone $$$$ Avandamet $$$$ to $$$$$
Coverage by public drug plan (ODB)	Metformin YES Glumetza NO	Gliclazide YES Glyburide YES Glimepiride NO	NO	NO
Advantages	• Efficacy (major A1c reduction) • More durable glycemic control than sulfonylurea • No hypoglycemia • No weight gain; possible modest weight loss • Possible CV benefit • Best oral agent for use with insulin (less weight gain; lower insulin dose) • Low cost generics • ODB coverage	• Efficacy (major A1c reduction) • Well tolerated • OK in renal insufficiency (caution: glyburide) • Once-daily dosing possible • Low cost generics • ODB coverage for some (glyburide & gliclazide)	• Efficacy: A1c reduction with Repaglinide is similar to sulfonylureas (but less with Nateglinide) • Less hypoglycemia than sulfonylureas (especially in patients who may miss meals) • Well tolerated • OK in renal insufficiency	• Efficacy (major A1C reduction) • More durable glycemic control than sulfonylurea • No hypoglycemia • OK in renal insufficiency • Well tolerated • Once-daily dosing

Parameter	Metformin	Sulfonylureas	Meglitinides	Glitazones (TZD's)
Disadvantages or Factors Limiting Use	• Dose-related GI intolerance initially (5-20%) • Malabsorption of vitamin B12 may result in anemia • Many precautions or contraindications (risk factors for lactic acidosis) - Renal impairment - Hepatic disease - Alcoholism - Severe heart failure - Severe respiratory disease	• Hypoglycemia • Risk ranking highest to lowest: glyburide > glimepiride > gliclazide • Weight gain • Efficacy declines over time more than metformin or glitazones	• Compliance may be a challenge (TID ac dosing) • Nateglinide A1C ↓ modest • Higher cost than sulfonylureas • No ODB coverage	• Slow onset of maximal glucose-lowering effect (8-12 wks) • Many precautions or contraindications: - Fluid retention, edema - Risk of new or worsened heart failure is double that of other agents - Contraindicated in any stage of heart failure - Weight gain can be significant - Fracture risk is doubled - Rosiglitazone may increase risk of myocardial infarction by 30-40% - Pioglitazone doubles risk of bladder cancer • Moderately expensive • No ODB coverage
Place in Therapy	• Drug of choice for all patients as monotherapy or combination therapy, especially insulin-requiring patients	• Second line therapy, for addition to metformin or for initial use when metformin is not an option	• Useful in patients who require an insulin secretagogue but who are at risk of sulfonylurea-induced hypoglycemia (especially that which may be due to an irregular meal schedule)	• Glitazones are less commonly used now (DPP-4 inhibitors have become preferred third-line agents, particularly since coverage by public drug plan [ODB] was introduced) • Pioglitazone is the preferred agent in class • Rosiglitazone is rarely used, and only if all other therapies are deemed to be unsuitable

Parameter	DPP-4 Inhibitors	GLP-1 Agonists	Insulin	Acarbose
Mechanism of Action	Enhance incretin activity ↑ Insulin secretion (primarily prandial) ↓ Glucagon secretion These actions occur only when blood glucose levels are elevated; they do not cause hypoglycaemia or impair ability to recover from hypoglycemia	Enhance incretin activity ↑ Insulin secretion (primarily prandial) ↓ Glucagon secretion These actions occur only when blood glucose levels are elevated; they do not cause hypoglycaemia or impair ability to recover from hypoglycemia	Corrects insulin deficiency ↑ Peripheral glucose uptake ↓ Hepatic glucose output	Alpha-glucosidase inhibitor Slows digestion of carbohydrate, thereby slowing postprandial glucose absorption
Efficacy (A1C Reduction)	0.5 - 1%	Exenatide 0.5 – 1.0% Liraglutide 0.8 – 1.5%	Variable (1.5 – 3.5 %)	0.5 – 1%
Hypoglycemia	0	0	+++++	0
Weight Change	0	↓↓ (dose-related)	↑↑↑ (dose-related)	0
Suitability in heart failure	OK	OK	OK (Caution: ↑ risk of HF if used in combination with a glitazone)	OK

Parameter	DPP-4 Inhibitors	GLP-1 Agonists	Insulin	Acarbose
Metabolism & Excretion	**Linagliptin:** • Minimal metabolism • Excreted primarily as unchanged drug (85%) via fecal route **Saxagliptin:** • Extensively metabolized via CYP3A4/5 (1 active metabolite) • Excreted primarily as inactive metabolites; 24% as unchanged drug; 26% as active metabolite **Sitagliptin:** • Minor metabolism via CYP3A4 & 2C8 to inactive compounds • Excreted primarily as unchanged drug in urine (80%) **Alopgliptin:** • Minimal metabolism • Excreted primarily as unchanged drug in urine (95%) **Vildagliptin:** • Extensively metabolized (55%) to inactive compounds via non-CYP hydrolysis • Excreted primarily as inactive metabolites (21-33% as unchanged drug)	**Exenatide:** • Minimal metabolism • Excreted renally unchanged **Liraglutide:** • Extensively metabolized to inactive compounds by endogenous endopeptidases • Excreted as inactive metabolites	Exogenous insulin is cleared primarily by the kidneys	Acarbose is metabolized to inactive compounds in GI tract and < 2% reaches systemic circulation
Suitability for use in renal insufficiency (Health Canada approvals)	• Linagliptin not renally excreted; but still “not recommended” if GFR < 30 (based on a lack of experience in these patients) • Saxagliptin approved at 2.5 mg daily for GFR 10-50 mL/min • Sitagtliptin ““not recommended” if GFR < 50 (based on a lack of experience in these patients) • Janumet: see metformin	• Exenatide contraindicated if GFR < 30; caution if GFR 30-50 • Liraglutide “not recommended” if GFR < 50 (based on a lack of experience in these patients)	OK	OK

Parameter	DPP-4 Inhibitors	GLP-1 Agonists	Insulin	Acarbose
Pharmacokinetic Drug Interactions Note: most of the pharmacokinetic data presented here describing alterations in the disposition of antihyperglycemic agents caused by inhibition or induction of metabolizing enzymes are of unknown clinical significance. Indeed, many are likely of no clinical significance based on the small magnitude of the effect. Exceptions include those for which it is recommended to "avoid" the combination and those for which an alteration in dosage of antihyperglycemic agent is recommended.	**Saxagliptin** ↑ **AUC due to CYP3A4 inhibitor:** • Diltiazem 109% • Ketoconazole 145%; consider reducing dose of saxagliptin by 50% (to 2.5 mg daily) ↓ **AUC due to CYP3A4 inducer:** • Rifampin 76% **Linagliptin** No significant metabolic drug interactions **Sitagliptin** No significant metabolic interactions **Alogliptin** No metabolic drug interactions **Vildagliptin** No metabolic drug interactions	No known pharmacokinetic drug interactions	No known pharmacokinetic drug interactions	Digestive enzyme products containing amylase may reduce the effect of acarbose; avoid concomitant administration (H)
Products & Dosage Forms	• Linagliptin (Trajenta) 5 mg • Saxagliptin (Onglyza) 2.5, 5 mg • Sitagliptin (Januvia) 100 mg • Janumet (sitagliptin 50 mg + metformin 500, 850, or 1000 mg)	• Exenatide (Byetta) 1.2 mL or 2.4 mL prefilled disposable pens • Liraglutide (Victoza) 18 mg per 3 mL prefilled disposable pen	• Rapid-acting analogues (aspart, glulisine, lispro) • Short-acting insulin ("regular insulin") • Intermediate-acting insulin (NPH insulin) • Long-acting analogues (detemir, glargine)	Acarbose (Glucobay) 50, 100 mg

Parameter	DPP-4 Inhibitors	GLP-1 Agonists	Insulin	Acarbose
Dosage	***DPP-4 inhibitors are taken once daily without regard to mealtimes*** • Linagliptin 5 mg once daily • Saxagliptin 5 mg once daily or 2.5 mg once daily if GFR 10-15 mL/min • Sitagliptin 100 mg once daily • Janumet (sitagliptin + metformin) is taken BID with or after meals	***GLP-1 agonists must be injected subcutaneously.*** • Exenatide is injected twice daily 0-60 min before breakfast & supper. Start with 5 mcg SC BID for first month; if tolerated, may increase to 10 mg SC BID • Liraglutide is injected once daily without regard to mealtimes. Start with 0.6 mg SC once daily for at least first week; if tolerated, increase to 1.2 mg SC once daily; max 1.8 mg/day	Variable	• Acarbose must be taken with the first bite of a meal (if taken after meal, efficacy is significantly reduced). If no meal is to be eaten, dose should be omitted. • To improve GI tolerability, start with a low dose and increase slowly every 3-5 days • Start with 25 mg 1-2 times/day; increase dose by 25-50 mg/day if tolerated every 3-5 days; usual max 150 mg/day (higher doses are poorly tolerated)
Cost per month for most common dose < $15 $ $16-30 $$ $31-70 $$$ $71-100 $$$$ > $100 $$$$$	$$$$	$$$$$	**Varies by product & dosage** Initial basal insulin regimen: • NPH daily at bedtime (50 units) $$$ • Detemir or Glargine once daily (50 units) $$$$	$$
Coverage by oublic drug plan (ODB)	Linagliptin NO Saxagliptin YES Sitagliptin YES Janumet YES	NO	YES	YES
Advantages	• No hypoglycemia • No weight gain (neutral effect) • Well tolerated • Fewer safety concerns than with the glitazones • Once daily dosing “anytime” and no dosage titration required • ODB coverage (most products)	• Efficacy: A1c reduction with Liraglutide may be similar to metformin, sulfonylureas, glitazones (greater than DPP-4 inhibitors and exenatide) • No hypoglycemia • Dose-related weight loss	• Greatest potential A1c reduction • Uniquely effective when oral agents prove inadequate • Consistently effective (lower failure rate) • Prompt improvement in blood glucose • Well tolerated • Cost of therapy can be reasonable (if regimen is simple and/or human insulin is used) • ODB coverage	• No hypoglycemia • Weight neutral • No systemic toxicity (negligible absorption) • OK in renal insufficiency

Parameter	DPP-4 Inhibitors	GLP-1 Agonists	Insulin	Acarbose
Disadvantages or Factors Limiting Use	• A1C ↓ somewhat less than metformin, sulfonylureas, and glitazones • Long-term efficacy and safety unknown • Pancreatitis: avoid use of DPP-4 inhibitors in patients with risk factors: very high triglycerides; alcoholism; history of pancreatitis • Expensive	• Long-term efficacy unknown • Long-term safety unknown (thyroid cancer?) • Pancreatitis: avoid use of GLP-1 agonists in patients with risk factors: very high triglycerides; alcoholism; history of pancreatitis • Renal insufficiency: exenatide is contraindicated if GFR < 30; caution for both agents if GFR < 50 • Must be injected (not attractive to patients with aversion to needle) • Major dose-related GI intolerance (30-50%) primarily during initial month • Most expensive drug class • No ODB coverage	• Hypoglycemia • Weight gain (dose-related) • Self-monitoring of blood glucose is a requirement • Dosage adjustments are usually required • Vision and dexterity problems may limit use • Low acceptance among many patients and perhaps also health care providers • Can be expensive (intensive regimens using analogues)	• A1C ↓ modest • Major dose-related GI intolerance (10-35%), particularly initially, requiring slow upward dosage titration • Compliance may be a challenge (must be taken with first bite of meals)
Place in Therapy	• Third-line agents for addition in patients not controlled on metformin + a secretagogue • Alternative to basal insulin when hypoglycemia and/or weight gain are concerns or patient refuses insulin injections	• Role not yet well established • May be considered for patients in whom weight loss is a primary goal and avoidance of hypoglycaemia is important	Type 2 diabetes: • Usually added when patients fail to achieve target A1c despite use of 2-3 agents • Also used temporarily in patients with severe metabolic stress (trauma, surgery, infection, MI)	• Limited role as an alternative when other agents are deemed unsuitable • Most useful when A1c is near target, and/or main problem is postprandial hyperglycemia

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Actual and Predicted Pharmacokinetic Interactions Between Antihyperglycemic Agents and Antiretrovirals

Antiretroviral Pharmacokinetic Characteristics (summary):

	Protease Inhibitors (PIs) atazanavir (Reyataz®)[1], darunavir (Prezista®)[2], fosamprenavir (Telzir®)[3], indinavir (Crixivan®)[4], lopinavir/ritonavir (Kaletra®)[5], nelfinavir (Viracept®)[6], ritonavir (Norvir®)[7], saquinavir (Invirase®)[8], tipranavir (Aptivus®)[9]	**Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)** efavirenz (Sustiva®)[10], etravirine (Intelence®)[11], nevirapine (Viramune®)[12], rilpivirine (Edurant®)[13]	**Integrase Inhibitors** elvitegravir/cobicistat (Stribild®, single-tablet regimen with tenofovir/emtricitabine)[14], raltegravir (Isentress®)[15]
Metabolism	Mainly CYP3A4	Efavirenz, nevirapine: CYP3A4, 2B6 (minor) Etravirine: CYP3A4, CYP2C9, and CYP2C19. Rilpivirine: CYP3A4 (major), as well as CYP2C19, 1A2, 2C8/9/10 (minor).	Elvitegravir: CYP3A, UGT1A1/3 Cobicistat: CYP3A, 2D6 (minor) Raltegravir: UGT1A1
Hepatic Inhibitor	Mainly CYP3A4 (darunavir, indinavir, nelfinavir, amprenavir >> saquinavir) Ritonavir: CYP3A4 (potent)> >2D6 >2C9 >2C19 >2A6 >1A2>2E1 At low boosting doses, ritonavir has a negligible effect in CYP2D6 inhibition.[5] Ritonavir inhibits CYP2B6 in vitro,[16] but induces 2B6 in vivo.[17] Nelfinavir: 2B6 in vitro.	Efavirenz: 2C9, 2C19[10] (? Clinical significance). Etravirine[11]: CYP2C9 (weak), CYP2C19 (moderate), p-glycoprotein (weak) Delavirdine (Rescriptor®)[18]; 3A4 (potent)	Cobicistat: CYP3A, CYP2D6; also p-glycoprotein (P-gp), BCRP, OATP1B1 and OATP1B3. Raltegravir has no inhibitory or inductive potential in vitro.[15]
Hepatic Inducer	Nelfinavir: UGT, 2C9/19 Ritonavir: UGT, CYP1A2, CYP2C9/19, 2B6 Tipranavir: mixed induction/inhibition effects; often acts as inducer of CYP3A4 (potent) and UGT, even when boosted with ritonavir[9]	Efavirenz: 3A4 (potent), 2B6[19] and UGT1A1[20] Etravirine[11]: 3A4 (weak) Nevirapine[12]: 3A4, 2B6 (potent) Rilpivirine: 2C19 (moderate), CYP1A2, 2B6 and 3A4 (weak).[21] A clinically relevant effect on CYP enzyme activity is considered unlikely with the 25 mg dose.[13]	Elvitegravir: CYP2C9 (modest) Raltegravir has no inhibitory or inductive potential in vitro.[15]

Drug	Initial (Max) Dose	Kinetics[22-29]	Protease Inhibitors (PIs)	Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)	Elvitegravir/ cobicistat
SULFONYLUREAS					
Gliclazide (Diamicron®)	BID before breakfast & supper; start with 80 mg BID; max 160 mg BID. Gliclazide MR Once daily before breakfast; start with 30 mg *Most of the benefit of a sulfonylurea is achieved in most patients at half the max daily dose.*	Metabolized via 2C9 to inactive compounds.	Nelfinavir and ritonavir may ↓ sulfonylurea concentrations via 2C9 induction. Use with caution. Adjust sulfonylurea dose as needed. NB: rifampin ↓ gliclazide AUC 70%	Etravirine, efavirenz may ↑ sulfonylurea concentrations via 2C9 inhibition. Use with caution. Adjust sulfonylurea dose as needed.	Elvitegravir may ↓ sulfonylurea concentrations via 2C9 induction. Use with caution. Adjust sulfonylurea dose as needed.
Glimepiride (Amaryl®)	Once daily before breakfast; start with 1 mg daily; increase every 1-2 weeks; max 8 mg daily. *Most of the benefit of a sulfonylurea is achieved in most patients at half the max daily dose.*	Metabolized via 2C9, 2C19 to inactive compounds.	Nelfinavir and ritonavir may ↓ sulfonylurea concentrations. Use with caution. Adjust sulfonylurea dose as needed. NB: rifampin ↓ glimepiride AUC 34%	Etravirine, efavirenz may ↑ sulfonylurea concentrations via 2C9 inhibition. Use with caution. Adjust sulfonylurea dose as needed. NB: fluconazole ↑ glimepiride AUC 138%	Elvitegravir may ↓ sulfonylurea concentrations via 2C9 induction. Use with caution. Adjust sulfonylurea dose as needed.
Glyburide (Diabeta®)	Once daily or twice daily if the dose/day exceeds 10 mg; start with 2.5 to 5 mg daily; increase every 1-2 weeks; max 20 mg/day. *Most of the benefit of a sulfonylurea is achieved in most patients at half*	Metabolized via 2C9 in part to weakly active metabolites that may accumulate in renal impairment.	Nelfinavir and ritonavir may ↓ sulfonylurea concentrations. Use with caution. Adjust sulfonylurea dose as needed. NB: rifampin ↓ glyburide AUC 39%	Etravirine, efavirenz may ↑ sulfonylurea concentrations via 2C9 inhibition. Use with caution. Adjust sulfonylurea dose as needed.	Elvitegravir may ↓ sulfonylurea concentrations via 2C9 induction. Use with caution. Adjust sulfonylurea dose as needed.

Drug	Initial (Max) Dose	Kinetics[22-29]	Protease Inhibitors (PIs)	Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)	Elvitegravir/ cobicistat
	the max daily dose.				
BIGUANIDES					
Metformin (Glucophage®, Glumetza® extended release) Also combination products: • Avandamet® (rosiglitazone/ metformin) • Janumet® (sitagliptin/ metformin)	*To improve GI tolerability, start with a low dose and increase slowly every 3-5 days.* Metformin is taken 2-3 times per day with or after meals. Start with 500 mg once or twice daily; increase by 500 mg/day as tolerated; max 2.5 g /day. Glumetza is taken once daily with evening meal; start with 1 g and increase by 500 mg at weekly intervals; max 2 g/day.	No liver metabolism. Excreted 100% as unchanged drug by glomerular filtration plus active tubular secretion.	Pharmacokinetic interaction not expected. In patients at risk of/already experiencing mitochondrial toxicity (esp. secondary to prolonged NRTI use), use with caution due to risk of hyperlactatemia or lactic acidosis.	Pharmacokinetic interaction not expected. In patients at risk of/already experiencing mitochondrial toxicity (esp. secondary to prolonged NRTI use), use with caution due to risk of hyperlactatemia or lactic acidosis.	In patients at risk of/already experiencing mitochondrial toxicity (esp. secondary to prolonged NRTI use), use with caution due to risk of hyperlactatemia or lactic acidosis.
MEGLITINIDES					
Repaglinide (GlucoNorm®)	Start with 0.5 to 1 mg TID; max 12 mg/day *Take within 30 min prior to a meal and only if patient will be eating. If a meal is delayed or will not be eaten, the dose should usually be delayed or omitted.*	Extensively metabolized to inactive compounds primarily via CYP2C8 & to lesser extent via 3A4. Also handled by OATP1B1. Excreted as inactive metabolites primarily in the bile; very little excreted as unchanged in urine.	Potential ↑ repaglinide. Monitor and adjust repaglinide dose as needed. **NB: ↑ repaglinide AUC with other inhibitors:** • 144% ↑ with cyclosporine (3A4) •	Potential ↓ repaglinide. Monitor and adjust repaglinide dose as needed.	Potential ↑ repaglinide concentrations via 3A4 inhibition. Monitor and adjust repaglinide dose as needed. **NB: ↑ repaglinide AUC with other inhibitors:** • 40% ↑ with

Drug	Initial (Max) Dose	Kinetics[22-29]	Protease Inhibitors (PIs)	Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)	Elvitegravir/ cobicistat
					itraconazole (3A4 & OATP1B1) • 712% ↑ with gemfibrozil (2C8 & OATP1B1); avoid coadministration
Nateglinide (Starlix®)	Start with 120 mg TID; max 540 mg/day *Take within 30 min prior to a meal and only if patient will be eating. If a meal is delayed or will not be eaten, the dose should usually be delayed or omitted.*	Extensively metabolized to inactive compounds primarily via CYP 2C9 (70%) & to lesser extent via 3A4. Excreted primarily as metabolites; only 15% as unchanged drug in urine	Potential ↓/↑ nateglinide concentrations via 2C9 induction or 3A4 inhibition. Monitor and adjust nateglinide dose as needed.	Potential ↓/↑ nateglinide concentrations via 2C9 inhibition or 3A4 induction. Monitor and adjust nateglinide dose as needed.	Potential ↓/↑ nateglinide concentrations via 2C9 induction or 3A4 inhibition. Monitor and adjust nateglinide dose as needed.
THIAZOLIDINEDIONES (TZDs)					
Pioglitazone (Actos®)	Once daily without regard to mealtimes; start with 15 or 30 mg daily; max 45 mg/day. *Before increasing dose, allow 8-12 weeks to assess full benefit.*	Extensive liver metabolism: 2C8, 3A4 >> 1A1. Excreted as inactive metabolites primarily via fecal route.	Potential ↑ pioglitazone. Monitor and adjust pioglitazone dose as needed. **NB: ↑ pioglitazone AUC with other inhibitors:** • 130% ↑ with gemfibrozil (2C8)	Potential ↓ pioglitazone. Monitor and adjust pioglitazone dose as needed. NB: 54% ↓ with rifampin.	Potential ↑ pioglitazone via 3A4 inhibition. Monitor and adjust pioglitazone dose as needed.
Rosiglitazone (Avandia®)	Once daily without regard to mealtimes; start with 4 mg daily; max 8 mg/day. *Before increasing dose,*	Extensive liver metabolism primarily to inactive compounds by 2C8, also 2C9 (minor). Excreted as inactive metabolites in urine.	An open label single sequence crossover study in healthy subjects (n=14) to evaluated the effect of **ATV 400mg** daily	Potential ↓ rosiglitazone. Monitor and adjust rosiglitazone dose as needed.	Potential ↓ rosiglitazone concentrations via 2C9 induction. Monitor and adjust rosiglitazone dose

Drug	Initial (Max) Dose	Kinetics[22-29]	Protease Inhibitors (PIs)	Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)	Elvitegravir/ cobicistat
	allow 8-12 weeks to assess full benefit.		and **ATV/r 300mg/100mg** daily on the kinetics of rosiglitazone 4mg daily (CYP 2C8 probe). Atazanavir ↑ rosiglitazone AUC 35%; atazanavir/r ↓ rosiglitazone AUC 17%. ATV is a weak inhibitor of CYP2C8, while ATV/r appears to induce CYP2C8 and offset inhibition by ATV.[30] Monitor for ↑/↓ effect with PIs and adjust rosiglitazone dose as needed.	NB: 60% ↓ with rifampin. An open-label prospective trial in outpatients with HIV receiving backbone ARV therapy consisting of 2-3 NRTIs. In 4 patients taking nevirapine, rosiglitazone ↓ Cmax 44% and there was a trend to ↓ AUC 41% (not signif).[31]	as needed.
DPP-4 INHIBITORS[28]					
Alogliptin (n/a in Canada or US)		Not metabolized. Excreted primarily as unchanged drug in urine (95%).	Pharmacokinetic interaction not expected.	Pharmacokinetic interaction not expected.	Pharmacokinetic interaction not expected.
Linagliptin (Trajenta®)	5 mg once daily without regard to mealtimes.	CYP3A4, Pgp substrate and weak inhibitor.[32] Primarily eliminated unchanged as parent compound (> 80%) via fecal route. Only 17% is metabolized to inactive compound.	In combination with ritonavir 200 mg BID, linagliptin Cmax and AUC ↑ to approximately 3-fold and 2-fold, respectively.[32] This increase may not be clinically significant, since linagliptin is	Potential ↓ linagliptin.	Potential ↑ linagliptin but may not be clinically significant, since linagliptin is primarily excreted unchanged, and has a large safety window.

Drug	Initial (Max) Dose	Kinetics[22-29]	Protease Inhibitors (PIs)	Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)	Elvitegravir/ cobicistat
			primarily excreted unchanged, and has a large safety window.[32]		
Saxagliptin (Onglyza®)	5 mg once daily without regard to mealtimes; 2.5 mg once daily if GFR 10-50 mL/min.	Extensively metabolized via CYP3A4/5 (1 active metabolite). Excreted primarily as inactive metabolites; 24% as unchanged drug; 26% as active metabolite.	Potential ↑ saxagliptin; clinical significance unknown since DPP-4 inhibitors have a large safety window. NB: 145% ↑ AUC with ketoconazole	Potential ↓ saxagliptin. . NB: 76% ↓ AUC with rifampin	Potential ↑ saxagliptin; clinical significance unknown since DPP-4 inhibitors have a large safety window.
Sitagliptin (Januvia®)	100 mg once daily without regard to mealtimes. Janumet (sitagliptin + metformin) is taken BID with or after meals.	Pgp substrate, minor metabolism via CYP3A4 & 2C8 to inactive compounds. Excreted primarily as unchanged drug in urine (80%).	Potential ↑ sitagliptin, but may not be clinically significant, since sitagliptin is primarily excreted unchanged and has a large safety window.	Potential ↓ sitagliptin.	Potential ↑ sitagliptin, but may not be clinically significant, since sitagliptin is primarily excreted unchanged and has a large safety window.
Vildagliptin (Galvux®) (n/a in Canada or US)		Extensively metabolized (55%) to inactive compounds via non-CYP hydrolysis. Excreted primarily as inactive metabolites (21-33% as unchanged drug).	Pharmacokinetic interaction not expected.	Pharmacokinetic interaction not expected.	Pharmacokinetic interaction not expected.
α GLUCOSIDASE INHIBITORS					
Acarbose (Prandase®, Glucobay®)	Must be taken with first bite of a meal (if taken after meal, efficacy is significantly reduced). If no meal is to be eaten,	Acarbose is metabolized to inactive compounds in GI tract and < 2% reaches systemic circulation.	Pharmacokinetic interaction not expected.	Pharmacokinetic interaction not expected.	Pharmacokinetic interaction not expected.

Drug	Initial (Max) Dose	Kinetics[22-29]	Protease Inhibitors (PIs)	Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)	Elvitegravir/ cobicistat
	dose should be omitted. To improve GI tolerability, start with a low dose and increase slowly every 3-5 days. Start with 25 mg 1-2 times/day; increase dose by 25-50 mg/day if tolerated every 3-5 days; usual max 150 mg/day (higher doses are poorly tolerated)				
Miglitol (n/a in Canada)		Minimal absorption.	Pharmacokinetic interaction not expected.	Pharmacokinetic interaction not expected.	Pharmacokinetic interaction not expected.
Voglibose (n/a in Canada)		Minimal absorption.	Pharmacokinetic interaction not expected.	Pharmacokinetic interaction not expected.	Pharmacokinetic interaction not expected.
HUMAN GLUCAGON-LIKE PEPTIDE (GLP-1 AGONISTS)					
Exenatide (Byetta®)	Exenatide is injected twice daily 0-60 min before breakfast & supper. Start with 5 mcg SC BID for first month; if tolerated, may increase to 10 mg SC BID.	Minimal metabolism. Excreted renally unchanged.	Pharmacokinetic interaction not expected.	Pharmacokinetic interaction not expected.	Pharmacokinetic interaction not expected.
Liraglutide (Victoza®)	Liraglutide is injected once daily without regard to mealtimes. Start with 0.6 mg SC once daily for at least first week; if tolerated, increase to 1.2 mg SC once daily; max 1.8	Not metabolized via P450. Extensively metabolized to inactive compounds by endogenous endopeptidases. Excreted as inactive metabolites.	Pharmacokinetic interaction not expected. Liraglutide can cause PR prolongation; caution if	Pharmacokinetic interaction not expected. Liraglutide can cause PR prolongation; caution if coadministering	Pharmacokinetic interaction not expected.

Drug	Initial (Max) Dose	Kinetics[22-29]	Protease Inhibitors (PIs)	Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)	Elvitegravir/ cobicistat
	mg/day.		coadministering with other drugs that can also cause PR prolongation, including PIs and rilpivirine.	with other drugs that can also cause PR prolongation, including PIs and rilpivirine.	

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Actual and Predicted Pharmacokinetic Interactions Between Antihypertensives and Antiretrovirals

Antiretroviral Pharmacokinetic Characteristics (summary):

	Protease Inhibitors (PIs) atazanavir (Reyataz®)[1], darunavir (Prezista®)[2], fosamprenavir (Telzir®)[3], indinavir (Crixivan®)[4], lopinavir/ritonavir (Kaletra®)[5], nelfinavir (Viracept®)[6], ritonavir (Norvir®)[7], saquinavir (Invirase®)[8], tipranavir (Aptivus®)[9]	**Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)** efavirenz (Sustiva®)[10], etravirine (Intelence®)[11], nevirapine (Viramune®)[12], rilpivirine (Edurant®)[13]	**Integrase Inhibitors** elvitegravir/cobicistat (Stribild®, single-tablet regimen with tenofovir/emtricitabine)[14], raltegravir (Isentress®)[15]
Metabolism	Mainly CYP3A4	Efavirenz, nevirapine: CYP3A4, 2B6 (minor) Etravirine: CYP3A4, CYP2C9, and CYP2C19. Rilpivirine: CYP3A4 (major), as well as CYP2C19, 1A2, 2C8/9/10 (minor).	Elvitegravir: CYP3A, UGT1A1/3 Cobicistat: CYP3A, 2D6 (minor) Raltegravir: UGT1A1
Hepatic Inhibitor	Mainly CYP3A4 (darunavir, indinavir, nelfinavir, amprenavir >> saquinavir) Ritonavir: CYP3A4 (potent)> >2D6 >2C9 >2C19 >2A6 >1A2>2E1 At low boosting doses, ritonavir has a negligible effect in CYP2D6 inhibition.[5] Ritonavir inhibits CYP2B6 in vitro,[16] but induces 2B6 in vivo.[17] Nelfinavir: 2B6 in vitro.	Efavirenz: 2C9, 2C19[10] (? Clinical significance). Etravirine[11]: CYP2C9 (weak), CYP2C19 (moderate), p-glycoprotein (weak) Delavirdine (Rescriptor®)[18]; 3A4 (potent)	Cobicistat: CYP3A, CYP2D6; also p-glycoprotein (P-gp), BCRP, OATP1B1 and OATP1B3. Raltegravir has no inhibitory or inductive potential in vitro.[15]
Hepatic Inducer	Nelfinavir: UGT, 2C9/19 Ritonavir: UGT, CYP1A2, CYP2C9/19, 2B6 Tipranavir: mixed induction/inhibition effects; often acts as inducer of CYP3A4 (potent) and UGT, even when boosted with ritonavir[9]	Efavirenz: 3A4 (potent), 2B6[19] and UGT1A1[20] Etravirine[11]: 3A4 (weak) Nevirapine[12]: 3A4, 2B6 (potent) Rilpivirine: 2C19 (moderate), CYP1A2, 2B6 and 3A4 (weak).[21] A clinically relevant effect on CYP enzyme activity is considered unlikely with the 25 mg dose.[13]	Elvitegravir: CYP2C9 (modest) Raltegravir has no inhibitory or inductive potential in vitro.[15]

Drug	Usual Dose (essential hypertension)	Metabolism[22]	Protease Inhibitors (PIs)	Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)	**Integrase Inhibitor** (**i.e.,elvitegravir/cobicistat**; generally no predicted interactions with raltegravir based on pharmacokinetic properties)
ANGIOTENSIN-CONVERTING ENZYME (ACE) INHIBITORS					
Benazepril (Lotensin®) Captopril (Capoten®) Cilazapril (Inhibace®) Enalapril (Vasotec®) Fosinopril (Monopril®) Lisinopril (Prinvil®, Zestril®) Perindopril (Coversyl®) Quinapril (Accupril®) Ramipril (Altace®) Trandolapril (Mavik®, Tarka®)		Other than captopril and lisinopril, ACE inhibitors are prodrug esters that must be converted in the liver and/or GI tract to active metabolites. Elimination of unchanged drug or metabolites may be renal or fecal.	no predicted effect	no predicted effect	no predicted effect
ANGIOTENSIN II RECEPTOR BLOCKERS (ARBs)					
Candesartan (Atacand®)	8-32 mg once daily	2C9 (minor), biliary excretion	Possible ↓ ARB (nelfinavir, ritonavir), may not be clinically significant.	Possible ↑ ARB (efavirenz, etravirine), may not be clinically significant.	Possible ↓ ARV, may not be clinically significant.
Eprosartan (Teveten®)	600 mg once daily (max 800 mg once daily or 400 mg BID)	Biliary excretion	no predicted effect	no predicted effect	no predicted effect
Irbesartan (Avapro®)	150 mg once daily (max 300 mg)	2C9, biliary excretion	Possible ↓ ARB (nelfinavir, ritonavir), may not be clinically significant.	Possible ↑ ARB (efavirenz, etravirine), may not be clinically significant.	Possible ↓ ARV, may not be clinically significant.
Losartan	50-100 mg once	2C9>>3A4 to	Possible ↓ in active metabolite	Possible ↑ in active metabolite	Net effect difficult to predict.

Drug	Usual Dose (essential hypertension)	Metabolism[22]	Protease Inhibitors (PIs)	Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)	Integrase Inhibitor (i.e.,elvitegravir/cobicistat; generally no predicted interactions with raltegravir based on pharmacokinetic properties)
(Cozaar®)	daily	active metabolite, E-3174	formation and ↓ efficacy	formation and ↑ effect	
Olmesartan (Olmetec®)	20-40 mg once daily	Biliary excretion	no predicted effect	no predicted effect	no predicted effect
Telmisartan (Micardis®)	80 mg once daily (40 mg in hepatic impairment)	Biliary excretion	no predicted effect	no predicted effect	no predicted effect
Valsartan (Diovan®)	Starting dose 80 mg, max 320 mg once daily	Biliary excretion	no predicted effect	no predicted effect	no predicted effect
BETA-BLOCKERS					
Acebutolol (Monitan®)	100 mg BID (max 400 mg BID)	2D6	Possible ↑ beta-blocker with ritonavir	no predicted effect	Possible ↑ beta-blocker; monitor for effect and decrease beta-blocker dose if necessary.[14]
Atenolol (Tenormin®, Tenoretic® - atenolol-chlorthalidone)	50 mg once daily (max 100 mg)	Renal	no predicted effect **Atazanavir** 400 mg daily plus atenolol 50 mg daily for 5 days did not cause a substantial increase in the PR interval. Also, minimal changes in atenolol (34% ↑ C_{max}, 25% ↑ AUC, 2% ↑ C_{min}) and atazanavir levels (7% ↓ AUC and 26% ↓ C_{min}). No dose adjustment needed.[1] **Lopinavir/ritonavir** and drugs that prolong the PR have not	no predicted effect	no predicted effect

Drug	Usual Dose (essential hypertension)	Metabolism[22]	Protease Inhibitors (PIs)	Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)	Integrase Inhibitor (i.e.,elvitegravir/cobicistat; generally no predicted interactions with raltegravir based on pharmacokinetic properties)
			been studied. Caution is warranted as there are post-marketing reports of second and third degree heart block in patients receiving drugs that prolong PR interval (such as beta-blockers).[23] Cardiac events, have been reported with patients on **ritonavir** and beta blockers.[7] PR prolongation may occur and caution is warranted.		
Carvedilol (Coreg®)	6.25 mg BID (max 25 mg BID)	2D6, 2C9>1A2, 2E1, 3A4	Possible ↑ beta-blocker **Lopinavir/ritonavir** and drugs that prolong the PR have not been studied. Caution is warranted as there are post-marketing reports of second and third degree heart block in patients receiving drugs that prolong PR interval (such as beta-blockers).[23] Cardiac events, have been reported with patients on **ritonavir** and beta blockers.[7] PR prolongation may occur and caution is warranted.	Possible ↓ beta-blocker	Possible ↑/↓ beta-blocker; monitor for effect and adjust beta-blocker dose if necessary.[14]
Labetalol (Trandate®)	Starting dose 100 mg BID after food, range 200-400 mg BID (max 600 mg BID)	2D6	Possible ↑ beta-blocker with ritonavir. Cardiac events, have been reported with patients on **ritonavir** and beta blockers.[7] PR prolongation may occur	no predicted effect	Possible ↑ beta-blocker; monitor for effect and decrease beta-blocker dose if necessary.[14]

Drug	Usual Dose (essential hypertension)	Metabolism[22]	Protease Inhibitors (PIs)	Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)	Integrase Inhibitor (i.e.,elvitegravir/cobicistat; generally no predicted interactions with raltegravir based on pharmacokinetic properties)
			and caution is warranted. **Lopinavir/ritonavir** and drugs that prolong the PR have not been studied. Caution is warranted as there are post-marketing reports of second and third degree heart block in patients receiving drugs that prolong PR interval (such as beta-blockers).[23]		
Metoprolol (Betaloc®, Lopresor®)	50-100 mg BID (max 200 mg BID)	2D6	Possible ↑ beta-blocker with ritonavir. Cardiac events, have been reported with patients on **ritonavir** and beta blockers.[7] PR prolongation may occur and caution is warranted. Extreme bradycardia (20-25 bpm) with complete AV block and severe hypotension (BP 50/20 mmHg) occurred in a patient on stable therapy including lacidipine and metoprolol; symptoms developed 48 hours after starting tenofovir, emtricitabine, and **lopinavir/ritonavir** for post-exposure prophylaxis. An interaction between lopinavir/ritonavir and metoprolol and lacidipine was hypothesized to be the cause	no predicted effect	Possible ↑ beta-blocker; monitor for effect and decrease beta-blocker dose if necessary.[14]

Drug	Usual Dose (essential hypertension)	Metabolism[22]	Protease Inhibitors (PIs)	Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)	**Integrase Inhibitor** (**i.e.,elvitegravir/cobicistat**; generally no predicted interactions with raltegravir based on pharmacokinetic properties)
			of this adverse event.[24]		
Nadolol (Corgard®)	Starting dose 40-80 mg once daily, usual dose 320 mg daily (max 640 mg per day)	Renal	no predicted effect **Lopinavir/ritonavir** and drugs that prolong the PR have not been studied. Caution is warranted as there are post-marketing reports of second and third degree heart block in patients receiving drugs that prolong PR interval (such as beta-blockers).[23] Cardiac events, have been reported with patients on **ritonavir** and beta blockers.[7] PR prolongation may occur and caution is warranted.	no predicted effect	no predicted effect
Pindolol (Visken®)	Starting dose 5 mg BID with meals, usual dose 15-45 mg daily	2D6	Possible ↑ beta-blocker with ritonavir. Cardiac events, have been reported with patients on **ritonavir** and beta blockers.[7] PR prolongation may occur and caution is warranted. **Lopinavir/ritonavir** and drugs that prolong the PR have not been studied. Caution is warranted as there are post-marketing reports of second and third degree heart block in patients receiving drugs that prolong PR interval (such as	no predicted effect	Possible ↑ beta-blocker; monitor for effect and decrease beta-blocker dose if necessary.[14]

Drug	Usual Dose (essential hypertension)	Metabolism[22]	Protease Inhibitors (PIs)	Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)	**Integrase Inhibitor** (**i.e.,elvitegravir/cobicistat**; generally no predicted interactions with raltegravir based on pharmacokinetic properties)
			beta-blockers).[23]		
Propranolol (Inderal LA®)	Starting dose 80 mg once daily, usual dose 160-320 mg once daily	2D6, 3A4, 2C19	Possible ↑ beta-blocker. **Lopinavir/ritonavir** and drugs that prolong the PR have not been studied. Caution is warranted as there are post-marketing reports of second and third degree heart block in patients receiving drugs that prolong PR interval (such as beta-blockers).[23] Cardiac events, have been reported with patients on **ritonavir** and beta blockers.[7] PR prolongation may occur and caution is warranted.	Possible ↓ beta-blocker	Possible ↑ beta-blocker; monitor for effect and decrease beta-blocker dose if necessary.[14]
CALCIUM CHANNEL BLOCKERS (CCB)					
Amlodipine (Norvasc®)	5 mg once daily (max 10 mg)	CYP3A	In healthy subjects on **indinavir 800/ritonavir 100 mg BID**, steady-state amlodipine AUC ↑ 90%.[25] If coadministration is necessary, initiate calcium blocker therapy at low doses, with careful titration to response and side effects. PR prolongation may occur with the combination of CCBs and **ritonavir-based regimens**; caution is warranted as there are post-	Possible ↓ CCB concentrations; titrate to response with careful monitoring	Possible ↑ CCB; monitor for effect and decrease CCB dose if necessary.[14]

Drug	Usual Dose (essential hypertension)	Metabolism[22]	Protease Inhibitors (PIs)	Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)	**Integrase Inhibitor** (**i.e.,elvitegravir/cobicistat**; generally no predicted interactions with raltegravir based on pharmacokinetic properties)
			marketing reports of second and third degree heart block in patients receiving drugs that prolong PR interval such as CCBs.[7]		
Diltiazem (Cardizem CD®, Tiazac®)	180-240 mg once daily (max 360 mg)	CYP3A, plasma and tissue esterases, sulfation and glucuridonation. Active metabolite 25 to 50% as potent as diltiazem. 2 to 4% unchanged in the urine[26]	In healthy subjects on **indinavir 800/ritonavir 100 mg BID**, steady-state diltiazem AUC ↑ 27% (NB: 2/13 subjects (15%) had >4-fold ↑ diltiazem AUC).[25] If coadministration is necessary, initiate calcium blocker therapy at low doses, with careful titration to response and side effects. **Atazanavir 400 mg daily** with diltiazem 180 mg daily increased diltiazem plasma concentrations, C_{min}, and AUC by approx. 2-fold (n=28). There was also an additive PR effect. There was no significant change in the pharmacokinetics of atazanavir (n=30). A dose reduction of diltiazem by 50% should be considered. Coadministration of atazanavir/ritonavir with diltiazem has not been studied, however similar recommendations would	Possible ↓ CCB concentrations; titrate to response with careful monitoring. Coadministration of **efavirenz** (600 mg for 14 days) resulted in ↓ 60% C_{max}, ↓ 69% AUC and ↓ 63% C_{min} of diltiazem. Higher doses of diltiazem may be required. No dose adjustment of efavirenz is necessary.[28] Potential drug interaction between **nevirapine** and diltiazem, which may cause decreased diltiazem plasma concentrations.[29] Higher doses of diltiazem may be required.	Possible ↑ CCB; monitor for effect and decrease CCB dose if necessary.[14]

Drug	Usual Dose (essential hypertension)	Metabolism[22]	Protease Inhibitors (PIs)	Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)	Integrase Inhibitor (i.e.,elvitegravir/cobicistat; generally no predicted interactions with raltegravir based on pharmacokinetic properties)
			apply.[1] Coadministration with **tipranavir/ritonavir** has not been studied; the net effect on dilitiazem is difficult to predict given the conflicting effect of tipranavir and ritonavir on substrates of both CYP3A and P-gp. Caution is warranted.[27] PR prolongation may occur with the combination of CCBs and **ritonavir-based regimens**; caution is warranted as there are post-marketing reports of second and third degree heart block in patients receiving drugs that prolong PR interval such as CCBs.[7]		
Felodipine (Plendil®, Renedil®)	5 mg once daily (range 2.5-10 mg daily)	CYP3A	↑ CCB concentrations; initiate therapy at low doses, with careful titration to response and side effects. Case report of patient on stable fixed dose combination of felodipine 5 mg and metoprolol 50 mg daily who was started on **nelfinavir** 2000 mg daily, with zidovudine and lamivudine for post-exposure prophylaxis (PEP). After 3 days, the patient experienced	Possible ↓ CCB concentrations; titrate to response with careful monitoring	Possible ↑ CCB; monitor for effect and decrease CCB dose if necessary.[14]

Drug	Usual Dose (essential hypertension)	Metabolism[22]	Protease Inhibitors (PIs)	Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)	Integrase Inhibitor (i.e.,elvitegravir/cobicistat; generally no predicted interactions with raltegravir based on pharmacokinetic properties)
			edema, dizziness, fatigue and orthostatic hypotension. The authors concluded that the patient developed side effects due to an increase in felodipine concentrations mediated due to nelfinavir-mediated CYP3A4 inhibition.[30] PR prolongation may occur with the combination of CCBs and **ritonavir-based regimens**; caution is warranted as there are post-marketing reports of second and third degree heart block in patients receiving drugs that prolong PR interval such as CCBs.[7]		
Ladicipine (not currently available in Canada)	2 mg once daily (max 6 mg)	CYP3A4, possible P-gp	↑ CCB concentrations; initiate therapy at low doses, with careful titration to response and side effects. Extreme bradycardia (20-25 bpm) with complete AV block and severe hypotension (BP 50/20 mmHg) occurred in a patient on stable therapy including lacidipine and metoprolol; symptoms developed 48 hours after starting tenofovir, emtricitabine, and **lopinavir/ritonavir** for post-	Possible ↓ CCB concentrations; titrate to response with careful monitoring	Possible ↑ CCB; monitor for effect and decrease CCB dose if necessary.[14]

Drug	Usual Dose (essential hypertension)	Metabolism[22]	Protease Inhibitors (PIs)	Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)	**Integrase Inhibitor** (**i.e.,elvitegravir/cobicistat**; generally no predicted interactions with raltegravir based on pharmacokinetic properties)
			exposure prophylaxis. An interaction between lopinavir/ritonavir and metoprolol and lacidipine was hypothesized to be the cause of this adverse event.[24] PR prolongation may occur with the combination of CCBs and **ritonavir-based regimens**; caution is warranted as there are post-marketing reports of second and third degree heart block in patients receiving drugs that prolong PR interval such as CCBs.[7]		
Nifedipine (Adalat XL®)	20-30 mg once daily (max 90 mg)	CYP3A (major), 1A2, 2A6	↑ CCB concentrations; initiate therapy at low doses, with careful titration to response and side effects. A severe interaction resulting in acute renal insufficiency, hypotension and edema was noted when a regimen containing **lopinavir/ritonavir** was started in a patient receiving nifedipine 30 mg twice a day; the symptoms resolved upon discontinuation of the HAART regimen, and re-emerged after lopinavir/ritonavir was re-introduced.[31]	Possible ↓ CCB concentrations; titrate to response with careful monitoring	Possible ↑ CCB; monitor for effect and decrease CCB dose if necessary.[14]

Drug	Usual Dose (essential hypertension)	Metabolism[22]	Protease Inhibitors (PIs)	Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)	Integrase Inhibitor (i.e.,elvitegravir/cobicistat; generally no predicted interactions with raltegravir based on pharmacokinetic properties)
			A 51-year-old man with HIV infection who was receiving extended-release nifedipine (60 mg/day) developed symptomatic orthostasis and heart block after starting antiretroviral therapy that included **nelfinavir** 1250 mg twice daily. Medication was changed, however, the patient developed orthostatic symptoms after restarting nelfinavir. Subsequent administration of antiretroviral therapy containing indinavir/ritonavir with extended-release nifedipine resulted in recurrence of his orthostatic symptoms.[32] PR prolongation may occur with the combination of CCBs and **ritonavir-based regimens**; caution is warranted as there are post-marketing reports of second and third degree heart block in patients receiving drugs that prolong PR interval such as CCBs.[7]		
Verapamil (Isoptin SR®, Lovera-HS®)	180-240 mg once daily (max 480 mg)	CYP3A (major), 1A2, 2C9, 2C19. Active metabolite norverapamil has	↑ CCB concentrations; initiate therapy at low doses, with careful titration to response and side effects.	Possible ↓ CCB concentrations; titrate to response with careful monitoring	Possible ↑ CCB; monitor for effect and decrease CCB dose if necessary.[14]

Drug	Usual Dose (essential hypertension)	Metabolism[22]	Protease Inhibitors (PIs)	Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)	**Integrase Inhibitor** (**i.e.,elvitegravir/cobicistat**; generally no predicted interactions with raltegravir based on pharmacokinetic properties)
		20% activity of verapamil.	PR prolongation may occur with the combination of CCBs and **ritonavir-based regimens**; caution is warranted as there are post-marketing reports of second and third degree heart block in patients receiving drugs that prolong PR interval such as CCBs.[7]		
DIURETICS					
Chlorthalidone (Hygroton®; Tenoretic® - atenolol-chlorthalidone)	12.5-50 mg once daily	Negligible hepatic metabolism 30-65% renal excretion as unchanged drug[33]	no predicted effect	no predicted effect	no predicted effect
Furosemide (Lasix®)	20-40 mg BID	Renal (90%); hepatic metabolism mainly glucuronidation. Proportion of hepatic clearance increases substantially (4x) in severe renal failure.[34]	no predicted effect	no predicted effect	no predicted effect
Hydrochloro-thiazide	12.5-50 mg once daily	Renal	no predicted effect	no predicted effect	no predicted effect

Drug	Usual Dose (essential hypertension)	Metabolism[22]	Protease Inhibitors (PIs)	Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)	**Integrase Inhibitor** (**i.e.,elvitegravir/cobicistat**; generally no predicted interactions with raltegravir based on pharmacokinetic properties)
Indapamide (Lozide®)	1.25 mg once daily in the morning (max 2.5 mg once daily)	2C9, 2D6, 3A4	Possible ↑ indapamide	Possible ↓ indapamide	Possible ↑/↓ indapamide concentrations; monitor for effect and adjust indapamide dose if necessary.
Metolazone (Zaroxolyn®)	2.5-5 mg once daily (max 10 mg)	Renal	no predicted effect	no predicted effect	no predicted effect
Spironolactone (Aldactone®)	50-100 mg daily (max 200 mg daily)	Renal	no predicted effect	no predicted effect	no predicted effect

Please note: This chart summarizes some of the major drug interactions identified to date, based on current available data; other drug interactions may exist. Please use caution whenever adding/modifying therapy. The information in this table is intended for use by experienced physicians and pharmacists. It is not intended to replace sound professional judgment in individual situations, and should be used in conjunction with other reliable sources of information. Due to the rapidly changing nature of information about HIV treatment and therapies, users are advised to recheck the information contained herein with the original source before applying it to patient care.

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Interactions between Antimalarial Agents and Antiretrovirals

Note: *The intention of this chart is to summarize the literature on drug interactions between antimalarial and antiretroviral agents. Suggestions on the management of these interactions are provided when possible. However, clinical judgment in the context of the patient is advised.*
Delavirdine drug interactions are not included in this table

Overview of Antimalarial Agents

Generic Name	Trade Name(s)	Pharmacologic Class
Amodiaquine	Camoquin, Flavoquine	Quinine Derivative
Artemether		Artemisinins
Artemether/ Lumefantrine	Coartem/Riamet	Combination Antimalarials
Artemisinin		Artemisinins
Artesunate	Arzuna	Artemisinins
Atovaquone/ Proguanil	Malarone	Combination Antimalarials
Chloroquine	Aralen	Quinine Derivative
Clindamycin	Dalacin C	Antibiotics
Dapsone/ Pyrimethamine	Maloprim or Deltaprim	Combination Antimalarials
Dihydroartemisinin		Artemisinins
Doxycycline	Vibramycin	Antibiotics
Halofantrine	Halofan	Halofantrine
Mefloquine	Lariam	Quinine Derivative
Primaquine	Primaquine	8-Aminoquinolines
Pyrimethamine/ Sulfadoxine	Fansidar	Combination Antimalarials
Quinidine	Qualaquin, Quindex, others	Quinine Derivative
Quinine	Pro-Quinine, Quinine-Odan, Teva-Quinine	Quinine Derivative
Tetracycline	Achromycin	Antibiotics
Trimethoprim/ Sulfamethoxazole	Co-trimoxazole, Septra, Septrin	Combination Antimalarials

Antimalarial Agent (Brand)	Pharmacokinetic Characteristics	Relevant HIV Drug Interactions *Suggested Management
Quinine Derivatives		
Amodiaquine (Camoquin, Flavoquine)	Metabolism: via CYP 2C8 to N-desethylamodiaquine (DEAQ), with amodiaquine being up to threefold more potent than DEAQ[1] However, as metabolism to DEAQ occurs rapidly, it is considered the major active component.	NRTI · **Zidovudine**: overlapping adverse effect profile (agranulocytosis, pancytopenia, hepatitis).[2] In one study of amodiaquine + artesunate for treatment of malaria in HIV-infected children, risk of neutropenia was significantly higher in those on ART (75 vs. 26%, p=0.001).[3] 11/12 had AZT in their regimen. All HIV+ children were also on cotrimoxazole prophylaxis. *Monitor CBC + ALT if coadministering. NNRTI · **Efavirenz**: Inhibits CYP 2C8 in vitro and therefore may ↑ amodiaquine levels.[4] This should not affect therapeutic efficacy as both amodiaquine and its metabolite DEAQ are active antimalarials, but it may have implications for toxicity. In a case report 114% and 302% ↑ AUC of amodiaquine when administered with EFV and artesunate in two HIV patients.[5] Both patients developed asymptomatic but significant elevations in hepatic transaminases 5-6 weeks following treatment and the study was terminated (ALT peaks 206, 868 U/L, AST 78, 559 U/L). *Study authors suggest liver function monitoring may be appropriate in individuals requiring amodiaquine/artesunate therapy for malaria in the setting of chronic EFV therapy. • **Nevirapine**: In an open-label, parallel group study, the kinetics of amodiaquine-artesunate (AQ-AS) 600/200 mg QD for 3 days were compared in HIV-positive subjects on stable nevirapine-based therapy vs. ART-naïve controls. No significant differences in AQ or DEAQ kinetics were noted between the groups.[6] PIs · **SQV, LPV, TPV,[4] high-dose RTV**[7] were potent CYP 2C8 inhibitors in vitro at clinically relevant concentrations which may increase the risk of amodiaquine adverse effects if coadministered.

Chloroquine (Aralen)	Metabolism: 50% excreted renally unchanged; CYP 3A4 and 2D6 metabolize to active metabolites mono- and bis-desethyl chloroquine.[8] Enzyme Inhibition: some CYP 2D6; however, effect less pronounced in vivo[9]	PIs · **Saquinavir**: one in vitro study suggested antagonistic HIV effects between chloroquine and SQV,[10] however, another found a synergistic anti-HIV effect between the two drugs.[11] Clinically significant effects unlikely.[12] · **Ritonavir**: potential for increase in chloroquine levels due to inhibition of CYP 3A4 and 2D6. This interaction has not been studied.[11] Integrase inhibitor • **Elvitegravir/cobicistat**: potential for increase in chloroquine levels due to inhibition of CYP 3A4 and 2D6. This interaction has not been studied. Other · **Co-trimoxazole**: potential increased risk of cardiotoxicity (QT-interval prolongation) when used concurrently.[13,14] Theoretical interaction, unlikely to be clinically significant.
Mefloquine (Lariam)	Metabolism: via CYP 3A4 to inactive carboxy metabolite[8,12]	***Avoid use in treatment in pregnancy[15] and in prophylaxis in 1st trimester of pregnancy** (↑ risk of spontaneous abortion[16]) unless perceived benefits outweigh the risks. If a woman who is receiving mefloquine prophylaxis becomes pregnant, this is not an indication for termination of pregnancy. Drug of choice in 2nd and 3rd trimester in chloroquine-resistant areas for chemoprophylaxis in pregnant women travelers.[17,18] NNRTIs Potential for ↓ mefloquine levels due to CYP 3A induction PIs · **Ritonavir**: 31% ↓ in AUC and 43% ↓ in Cmin of ritonavir after multiple concurrent dosing; mefloquine pharmacokinetics unchanged[19]. *Likely safe to co-administer without dose adjustments.[11] · **Nelfinavir and indinavir**: Report of two patients on stable HAART regimens, one on nelfinavir 1250mg bid and one on indinavir 800mg tid, both taking mefloquine 250mg weekly for at least 16 weeks for malaria prophylaxis.[20] Levels of the PIs and mefloquine were therapeutic and no side effects were reported. · **Tipranavir (unboosted)**: Potential for ↓ mefloquine levels due to CYP3A induction Integrase inhibitor • **Elvitegravir/cobicistat**: potential for increase in mefloquine levels due to inhibition of CYP 3A4. This interaction has not been studied. Other · **Rifampin**: 68% ↓ AUC and 19% ↓ Cmax of mefloquine likely due to induction of CYP 3A4 by rifampin and therefore increased risk of protozoal resistance and treatment failure.[21] *Study authors recommend avoiding simultaneous use of rifampin and mefloquine.

Quinine	Metabolism: via CYP 3A4 (minor contribution from 2C19) to active metabolite 3-hydroxyquinine (toxic); also 20% excreted renally unchanged[8]	NNRTIs · **Efavirenz and etravirine** may ↓ quinine exposure to subtherapeutic range due to induction of CYP 3A4.[11,22] *Monitor for reduced clinical effectiveness (response of parasitemia) and quinine levels if possible; dose-adjust as necessary. · **Nevirapine:** A single 600mg dose of quinine was administered to 14 patients on and off steady-state nevirapine 200mg bid.[23] Compared to quinine alone, quinine + nevirapine resulted in ~AUC ↓33%, Cmax ↓36%, $t_{1/2}$ ↓25% and oral clearance ↑33% of quinine. Cmax and AUC of the metabolite 3-hydroxyquinine and ratio AUC metabolite:quinine also increased significantly in the presence of nevirapine. Authors suggest an ↑ in quinine dose may be required when given with nevirapine. *Monitor for reduced clinical effectiveness (response of parasitemia) and quinine levels if possible; dose-adjust as necessary. Case report of an HIV-positive patient on abacavir, lamivudine and nevirapine who developed Plasmodium falciparum malaria and failed to respond to therapy with quinine, amoxicillin/clavulanic acid and clarithromycin. A negative interaction between nevirapine and quinine was suspected, and the patient was switched to atovoquone/ proguanil(Malarone®) with improvement and subsequent discharge after 48 hours.[24] PIs · **All protease inhibitors**: potential for ↑ quinine levels through inhibition of CYP 3A4-mediated quinine metabolism. *Caution warranted; monitor closely for adverse effects, including cardiac monitoring or ECG monitoring of QT interval with IV quinine.[12,25] Consider therapeutic drug monitoring of quinine if possible with maintenance dose-adjustment as necessary. · **Lopinavir/ritonavir:** In healthy volunteers, steady-state lopinavir/ritonavir significantly decreased the exposure of quinine and its major active metabolite, 3-hydroxyquinine, in both total and free (unbound) forms. A decline in quinine exposure may compromise clinical efficacy.[26] · **Ritonavir:** Ten healthy volunteers on steady-state ritonavir 200mg bid received a single dose of quinine 600 mg.[27] Both the AUC and Cmax of quinine increased about 4-fold in the presence of ritonavir, and quinine $t_{1/2}$ increased from 11.15 to 13.37 hrs. The metabolism of quinine to its major metabolite, 3-hydroxyquinine, was markedly inhibited by ritonavir. Ritonavir pharmacokinetics were not affected.

		Quinine dose adjustment necessary when administered with ritonavir. · **Tipranavir** (unboosted) may ↓ quinine exposure to subtherapeutic range due to induction of CYP 3A4. Monitor for reduced clinical effectiveness (response of parasitemia) and quinine levels if possible; dose-adjust as necessary. Integrase inhibitor • **Elvitegravir/cobicistat**: potential for increase in quinine levels due to inhibition of CYP 3A4. This interaction has not been studied. Other · **Rifampin**: ↓ quinine levels due to increased clearance from rifampin-mediated induction of CYP 3A4. ***Avoid combination if possible** due to significantly higher malaria treatment failure rates when used in combination (5-fold increase in likelihood of malaria recrudescence compared to quinine alone).[28] Quinine dose should probably be increased in patients already receiving rifampin for treatment of TB.[23]
Quinidine (Qualaquin, Quindex, others)	Metabolism: via CYP 3A4 Enzyme Inhibition: Potent inhibitor of CYP 2D6[8]	NNRTIs · **Nevirapine, efavirenz, etravirine**: potential for ↓ quinidine concentration and therapeutic failure. *Caution warranted; therapeutic drug monitoring recommended if available.[11,21] PIs · **All protease inhibitors**: ↑ quinidine exposure due to inhibition of CYP 3A4 increases the likelihood of cardiotoxic adverse effects from quinidine. ***Combination not recommended**. If necessary to use concurrently, monitor closely for adverse effects, including cardiac monitoring, consider therapeutic drug monitoring of quinidine with dose-adjustment as necessary. → **Contraindicated by manufacturer**: in combination with **NFV, RTV, SQV, tipranavir/RTV**[29,30,31,32] → Combination cautioned by manufacturer: ATV, darunavir, IDV, LPV/RTV[33,34,35,36] · **Tipranavir** alone (unboosted) may ↓ quinidine exposure to subtherapeutic range due to induction of CYP 3A4. Monitor for reduced clinical effectiveness (response of parasitemia) and quinine levels if possible; dose-adjust as necessary. Integrase inhibitor • **Elvitegravir/cobicistat**: potential for increase in quinidine levels due to inhibition of CYP 3A4. This interaction has not been

		studied. Other · **Rifampin**: ↓ quinidine plasma levels and effectiveness via induction of CYP 3A4[37,38]. *Consider quinidine dose increase if using concurrently – monitor quinidine plasma levels if possible.[12]
Artemisinins		
Artemisinin	Metabolism: primarily via CYP 2B6, with CYP 3A4 likely playing a role in patients with decreased CYP 2B6 activity, to inactive metabolites[8,39] Enzyme Induction: may induce CYP 2C19[8]	***Not recommended for 1st trimester of pregnancy** but should not be withheld if lifesaving for the mother; may used in later pregnancy when other treatments are considered unsuitable.[40] Some reports of potential embryotoxicity and morphological abnormalities in animal studies,[41] however, in almost 1000 documented cases of exposures during pregnancy, no adverse pregnancy effects on the mother or fetus have been reported.[42] NNRTIs: potential ↓ in artemisinin levels due to CYP 2B6 induction PIs: potential ↓ in artemisinin levels due to induction of CYP 2B6 by **ritonavir;** In vitro study suggesting potential antagonism of artemisinin endoperoxide activity vs. *P. falciparum* when combined with PIs (studied PIs included RTV, SQV, IDV). Clinical significance is unknown, however caution is warranted with artemisinin monotherapy and PIs.[43] · **Ritonavir:** Thirty-four healthy subjects were randomized to receive pyronaridine/artesunate (PA) alone for 3 days or with steady-state ritonavir 100 mg BID. In the presence of ritonavir, artesunate AUC ↑ 27% and DHA AUC ↓ 38%, while pyronaridine pharmacokinetics were not affected. Ritonavir exposure was increased 3.2-fold in the presence of PA.[44] Integrase inhibitor • **Elvitegravir/cobicistat**: potential for increase in artemisinin levels due to inhibition of CYP 3A4. This interaction has not been studied.
Dihydroartemisinin	Metabolism: unclear, likely metabolized in the liver by glucuronidation and eliminated via biliary and renal excretion[8]	***Pregnancy** see artemisinin entry **Nelfinavir, ritonavir, tipranavir:** Caution may be warranted when using with dihydroartemisinin as these PIs may induce glucuronyltransferase activity.
Artemether	Metabolism: via CYP 3A4/5 to active metabolite dihydroartemisinin (more potent antimalarial than parent compound)[11] Enzyme Induction: CYP 3A4 and CYP	***Pregnancy** see artemisinin entry All PIs (**see artemether/lumefantrine and artemisinin entries**) · potential ↓ in artemether's conversion to active metabolite via CYP 3A4 inhibition. *Likely not clinically significant, as parent also active, but data lacking.[11]

	2C19[11] Enzyme Inhibition: potential CYP 1A2 inhibition[45]	NNRTIs (**see artemether/lumefantrine entry**) · potential ↓[11] or ↑ in artemether's conversion to active metabolite via CYP 3A4 inhibition or induction (clinically, induction generally predominates). *Likely not clinically significant, but data lacking.[11] Integrase inhibitor • **Elvitegravir/cobicistat**: potential for increase in artemether levels due to inhibition of CYP 3A4, and possible ↓ elvitegravir and cobicistat concentrations. This interaction has not been studied; avoid combination if possible.
Artesunate (Arzuna)	Metabolism: rapidly metabolized to dihydroartemisinin (active form) in vivo, then glucuronidated.[8]	***Pregnancy** see artemisinin entry
8-Aminoquinolines		
Primaquine	Metabolism: via CYP 1A2, 2D6, 3A4[46], to inactive carboxyprimaquine. Non-CYP-mediated oxidative processes may also play an important role in metabolism.[8]	***Avoid in pregnancy due to ↑ risk of hemolysis and methemoglobinemia in the fetus; use chloroquine prophylaxis for the duration of the pregnancy, then use primaquine after delivery**.[16] NRTIs · **Zidovudine**: both drugs may cause hematotoxicity[12,47] therefore, the potential exists for additive hematotoxicity when used in combination. *Screening for glucose-6- phosphate-dehydrogenase deficiency prior to use should eliminate the risk of serious hematological toxicity from primaquine. NNRTIs/PIs As multiple metabolic pathways are involved in primaquine metabolism, drug interactions are difficult to predict. No published reports of interactions with NNRTIs/PIs. Integrase inhibitor • **Elvitegravir/cobicistat**: potential for increase in primaquine levels due to inhibition of CYP 3A4 and 2D6. This interaction has not been studied.

Halofantrine		
Halofantrine (Halofan)	Metabolism: via CYP 3A4 to active metabolite N-desbutylhalofantrin (parent compound has a narrow therapeutic window and is cardiotoxic)[8]	Contraindicated in pregnancy[48] Food - Ingestion with food, especially when high in fat, markedly increases serum levels NNRTIs · **Efavirenz, etravirine, nevirapine:** halofantrine has a narrow therapeutic index and potential inhibition[11] or induction of CYP 3A4 by NNRTIs may ↑ toxicity or ↓efficacy of halofantrine. Clinically, induction of CYP 3A4 generally prevails with NNRTIs. Avoid combination if possible, use with caution if necessary. PIs · **All (APV, ATZ, Darunavir, IDV, LPV, NFV, RTV, SQV, Tipranavir/RTV)**: ↑ halofantrine plasma levels ↑ risk of halofantrine-induced cardiotoxicity due to inhibition of CYP 3A4 by PIs.[11] **Avoid combination.** Integrase inhibitor • **Elvitegravir/cobicistat**: potential for increase in halofantrine levels due to inhibition of CYP 3A4. This interaction has not been studied.
Antibiotics		
Clindamycin (Dalacin C)	Metabolism: via CYP 3A4[49]	None known Integrase inhibitor • **Elvitegravir/cobicistat**: potential for increase in clindamycin levels due to inhibition of CYP 3A4. This interaction has not been studied.

Doxycycline (Vibramycin)	Metabolism: Not fully elucidated. May be metabolized in the liver, excreted unchanged in urine and bile or partially deactivated in the intestine by chelate formation[12,50]	**Contraindicated in pregnancy** NNRTIs, PIs: • The effect of doxycycline on antiretroviral drug levels was assessed in an open-label study of HIV-positive subjects on standard dose cART (n=1 ATV, n=14 ATV/r, n=23 LPV/r, n=17 EFV, n=10 NVP) who started doxycycline for malaria prophylaxis. ARV Ctrough were measured after at least 15 days of doxycycline therapy. No statistically significant effect on PI or NNRTI concentrations was noted, and no patient was infected with malaria.[51] Other · **Rifampin**: 130% ↑in doxycycline clearance when used in combination with rifampin and significantly lower doxycycline AUC have been reported; possibly due to induction of CYP enzymes involved in doxycycline metabolism.[52] *Avoid combination for malaria prophylaxis if possible. Monitor closely for therapeutic efficacy of doxycycline if using in combination.
Tetracycline (Achromycin)	Metabolism: none; excreted unchanged in urine and bile[12]	**Contraindicated in pregnancy** No known drug interactions with antiretrovirals
Combination Antimalarials		
Artemether/ Lumefantrine (Coartem/Riamet)	Metabolism: Artemether and lumefantrine are both metabolized by CYP 3A4[11] Enzyme Induction: Artemether induces CYP 3A4 and 2C19[11] Enzyme Inhibition: Lumefantrine inhibits CYP 2D6[11] – unclear clinical significance[8]	**Artemether: also see section on "Artemisinins"** **Lumefantrine:** Cardiotoxicity: No clinical adverse event attributable to QTc prolongation (e.g. syncope, sudden death) or dose related changes in ECG have been reported[53,54,55,56,57,58,59] Lumefantrine has the theoretical potential to cause QTc prolongation due to its chemical similarity to halofantrine,[11] although both Canadian[16] and WHO[60] guidelines for the treatment of malaria explicitly state that lumefantrine does not cause cardiotoxicity. The WHO guidelines go on to state that lumefantrine appears to be remarkably well tolerated and that there is no evidence that drug interactions lead to any clinically harmful effects. NNRTIs • **Nevirapine**: HIV-positive adults received 6-dose artemether/lumefantrine 80/480 mg before and at steady-state nevirapine. Coadministration resulted in significant reductions in artemether (61% ↓ Cmax, 72% ↓ AUC), dihydroartemisinin (45% ↓ Cmax, 37% ↓ AUC) and NVP (42% ↓ Cmax, 46% ↓ AUC) exposures, which is likely to increase risk of treatment failure.

		Alternative anti-malarials should be considered for HIV/malaria co-infected patients receiving nevirapine.[61] • In HIV-positive subjects on nevirapine-based treatment (n=18) or who were antiretroviral-naïve (n=18) received 6 doses of artemether-lumefantrine (80 mg/480 mg). Day 7 lumefantrine concentrations were significantly higher (86%) while median artemether and dihydroartemisinin AUC were significantly lower in the nevirapine vs. naïve subjects.[62] · **Efavirenz:** HIV-positive adults received 6-dose artemether/lumefantrine 80/480 mg before and at steady-state efavirenz. Coadministration resulted in significant reductions in artemether (59% ↓ Cmax, 79% ↓ AUC), dihydroartemisinin (78% ↓ Cmax, 75% ↓ AUC), and lumefantrine (28% ↓ Cmax, 56% ↓ AUC) exposures, which is likely to increase risk of treatment failure. Efavirenz concentrations were not altered by artemether-lumefantrine. Alternative anti-malarials should be considered for HIV/malaria co-infected patients receiving efavirenz.[63] · **Etravirine:** in healthy volunteers, coadministration of etravirine 200 mg BID plus artemether 80/lumefantrine 480 mg resulted in 38% ↓ AUC artemether, 15% ↓ AUC dihydroartemisinin and 13% ↓ AUC of lumefantrine; etravirine pharmacokinetics were not affected. Coadministration of etravirine with artemether/lumefantrine may lower antimalarial activity of artemether; use combination with caution.[64] <u>PIs</u> · **All (APV, ATZ, Darunavir, IDV, LPV, NFV, RTV, SQV, Tipranavir/RTV)**: ↑ lumefantrine plasma levels ↑ risk of toxicity due to inhibition of CYP 3A4 by PIs. Concurrent use is **contraindicated by manufacturer**[47] but others suggest may use with caution,[11] or that the drug interaction may not be clinically significant[52,53] · **Lopinavir/ritonavir:** Co-administration of artemether/lumefantrine (AL) with steady-state LPV/RTV 400/100mg bid ↑ lumefantrine AUC 193% but treatment was well-tolerated in 10 subjects studied.[65] Lumefantrine levels were within the normal range of concentrations found in patients not on PIs (historical controls). Authors suggest no dosage adjustments required and that ↑ lumefantrine levels may be beneficial as lumefantrine exposure has been correlated with treatment response. In another study, 10 healthy volunteers received a standard,

		three-day course of AL with and without concomitant steady-state lopinavir/ritonavir 400/100mg bid.[66] In the presence of LPV/RTV, lumefantrine AUC ↑ 2-3 fold, there was a trend toward artemether Cmax and AUC ↓, and dihydroartemisinin (DHA, active artemether metabolite) Cmax and AUC decreased. DHA:artemether AUC ratios and LPV/RTV pharmacokinetics were not affected. Authors suggest that AL and LPV/RTV may be safely coadministered in patients with malaria and HIV, as lumefantrine AUC is a key parameter with respect to malarial cure and due to the excellent safety profile of AL. In an open-label, parallel study, HIV-positive patients who were ART-naïve or on stable LPVr received standard AL 80mg/480mg dosing for 3 days. Lumefantrine AUC was 9.3-fold higher in the LPVr arm vs. the non-ART arm, but an increase in adverse effects was not observed. Artemether and dihydroartemisinin concentrations were also significantly increased by LPVr, but to a lesser extent.[Kredo et al. CROI 2012, #613] The kinetics of single-dose artemether/lumefantrine were investigated in HIV-infected subjects either on stable lopinavir/ritonavir-based therapy or who were treatment-naïve. In the presence of lopinavir/ritonavir, artemether Cmax ↓ 50%, AUC ↓ 43%, lumefantrine Cmax ↑ 280%, AUC ↑ 486%, and dihydroartemisinin kinetics were not significantly altered.[67] · **Darunavir/ritonavir**: in healthy volunteers, coadministration of darunavir 600/ritonavir 100 mg BID plus artemether 80/lumefantrine 480 mg resulted in 16% ↓ AUC artemether, 18% ↓ AUC dihydroartemisinin and 2.75-fold ↑ AUC of lumefantrine; darunavir and ritonavir pharmacokinetics were not affected. Darunavir/ritonavir and artemether/lumefantrine may be coadministered without dose adjustment; avoid use with other drugs that may cause QTc prolongation.[Kakuda et al. HIVPK 2012, #O_05] <u>Integrase inhibitor</u> · **Elvitegravir/cobicistat**: potential for ↑in artemether and lumafantrine levels due to inhibition of CYP 3A4, and possible ↓ elvitegravir and cobicistat concentrations. This interaction has not

		been studied; avoid combination if possible.
Atovaquone/ Proguanil (Malarone)	Metabolism: *Atovaquone* is 94% eliminated unchanged in the feces; *proguanil* is 40-60% excreted unchanged by the kidneys, with the remainder metabolized by CYP 2C19 and CYP 3A4 to its more active metabolite, cycloguanil.[8]	NRTIs · **Zidovudine:** 33% ↑ in AUC of AZT (given as 200mg q8h) with atovaquone (given as 750mg bid).[68] *Likely not clinically significant for most patients, either for prophylaxis or treatment of malaria . Dosage modifications not recommended but may be considered in patients with evidence of bone marrow toxicity.[11,12] NNRTIs · **Efavirenz:** A recent study administered a single dose of Malarone™ to HIV+ individuals who had been taking EFV for at least one month.[69] AUC ↓~70% for atovaquone and 50% for proguanil compared with healthy volunteers. Decreases in atovaquone exposure have been associated with malaria treatment failure.[70] *Clinical significance unknown – study authors suggest taking Malarone™ with a high-fat meal and that dosage increase may be required for prophylaxis.[58] Dosage increases may also be warranted for treatment in this setting. Another kinetic study in 15 healthy subjects found a 115% ↑ AUC of proguanil, and a 68% ↓ in the ratio of the active cycloguanil metabolite/parent drug. Cycloguanil Cmin was > MIC of most malaria strains, therefore a dosage adjustment was not empirically recommended.[71] Until further information on interaction is available,[72] suggest avoiding co-administration if other options available. • **Etravirine:** Case report of a 32 year-old Caucasian female on maraviroc, raltegravir, etravirine and unboosted saquinavir who started atovaquone/proguanil prophylaxis; antiretroviral drug concentrations were measured at baseline and 20 days after initiation of atovaquone/proguanil. In the presence of atovaquone/ proguanil, a marked increase in etravirine and saquinavir concentrations (+55% and +274%, respectively) was observed. A slight decrease in raltegravir and maraviroc AUC0-12h (-23% and -9%, respectively), was also noted, but these changes were not considered clinically significant. No notable side effects were reported by the patient.[73] PIs · **Indinavir**: 23% ↓ in trough levels of unboosted IDV when combined with atovaquone.[74] Another study found 5% ↓ in IDV AUC and 13%↑ in atovaquone AUC with co- administration.[75] *Combination may be given together without dose adjustment.[11] • **Saquinavir:** Case report of a 32 year-old Caucasian female on

		maraviroc, raltegravir, etravirine and unboosted saquinavir who started atovaquone/proguanil prophylaxis; antiretroviral drug concentrations were measured at baseline and 20 days after initiation of atovaquone/proguanil. In the presence of atovaquone/ proguanil, a marked increase in etravirine and saquinavir concentrations (+55% and +274%, respectively) was observed. A slight decrease in raltegravir and maraviroc AUC0-12h (-23% and -9%, respectively), was also noted, but these changes were not considered clinically significant. No notable side effects were reported by the patient.[76] · **Lopinavir/ritonavir or ritonavir-containing regimens**: may ↓ atovaquone plasma concentrations (likely due to enhanced glucuronyl transferase activity with RTV).[27,33,77] A recent study administered a single dose of Malarone™ to HIV+ individuals who had been taking LPV/RTV and ATV/RTV for at least one month.[58] In patients taking LPV/RTV, AUC ↓~70% for atovaquone and 50% for proguanil compared with healthy volunteers. In patients taking ATV/RTV, AUC ↓ 40-50% for atovaquone and 50% for proguanil. Decreases in atovaquone exposure have been associated with malaria treatment failure.[78] *Clinical significance unknown – study authors suggest taking Malarone™ with a high-fat meal and that Malarone™ dosage increase may be required for prophylaxis in patients taking LPV/RTV.[58] Dosage increases may also be required for treatment in this setting. Until further information on interaction is available,[60] suggest avoiding co-administration if other options available. <u>Integrase inhibitor</u> • **Elvitegravir/cobicistat**: potential for increase in proguanil levels due to inhibition of CYP 3A4. This interaction has not been studied. <u>Other</u> · **Rifabutin**: A 34% ↓ in atovaquone AUC and a 19% ↓ in rifabutin AUC were observed when these drugs were used in combination.[61] ***Combination not recommended.**[12] · **Rifampin**: A 50% ↓ in atovaquone levels has been observed when used in combination with rifampin[61] ***Combination not recommended.**[12] · **Tetracycline**: A 40% ↓ in atovaquone plasma concentration has been observed when used with tetracycline.[61] Mechanism of interaction unknown. ***Combination not recommended** due to

		risk of therapeutic failure.
Pyrimethamine/ Sulfadoxine (Fansidar)	Metabolism: *Sulfadoxine* is metabolized in the liver via conjugation, acetylation and glucuronidation.[12] *Pyrimethamine* is hepatically metabolized.[8]	NRTIs · **Zidovudine**: risk of additive hematotoxicity when used in combination. * Monitor CBC and co-administer cautiously in patients already anemic.[23] NNRTIs · **Nevirapine:** risk of severe adverse hepatic/cutaneous reactions with both medications. While the severe cutaneous reactions seen with Fansider™ in malaria prophylaxis have only rarely been observed with intermittent preventive treatment (IPT),[79] HIV infected individuals may be at greater risk of adverse reactions.[43] *Recommend staggering the introduction of Fansidar™ and nevirapine by minimum 4 weeks if possible to reduce potential for diagnostic confusion should adverse events occur .[23] Nevirapine when given as a single dose in perinatal prophylaxis has not been associated with severe adverse effects in the mother.[23] PIs · **Ritonavir**: one author suggests caution with coadministration,[11] however, based on metabolism of drugs[8.12] and lack of clinical evidence for interaction,[80] combination is likely safe to use. Other · **Co-trimoxazole**: ↑ risk of severe adverse skin (approximately 100-fold compared to HIV negative individuals)[81], hematologic and hepatic interactions[23] when used in combination. ***Avoid coadministration.** Suggest initiating co-trimoxazole at least 4 weeks after last sulfadoxine/pyrimethamine dose.[23] WHO suggests that pregnant women on cotrimoxazole prophylaxis should not receive intermittent preventive treatment (IPT) with Fansidar™ and that malarial illness in HIV-infected pregnant women who receive cotrimoxazole prophylaxis should be managed with antimalarial medicines that do not contain sulfonamides or sulfones.[2] Potential for *P. falciparum* cross-resistance between trimethoprim/sulfamethoxazole and sulfadoxine/pyrimethamine [82,83]

Dapsone/ Pyrimethamine (Maloprim or Deltaprim)	Metabolism: *Dapsone* >50% metabolized by N-acetyl-transferase to the active metabolite monoacetyl-dapsone, with the remainder metabolized via CYP 3A4-mediated hydroxylation.[8]	NRTIs · **Zidovudine**: potential for additive hematological adverse effects when used in combination.[11,84] *Combination not recommended. Monitor CBC if combination therapy necessary. Screening for glucose-6- phosphate-dehydrogenase deficiency prior to use may decrease risk of some hematological toxicity. · **Stavudine**: potential for increased risk of peripheral neuropathy due to overlapping toxicity profiles.[85] *Avoid combination if other options available. PIs · **All protease inhibitors:** potential ↑ dapsone plasma levels and risk of toxicity due to inhibition of CYP 3A4.[27,86] As metabolism of dapsone is primarily via N-acetylation, clinically significant interactions are unlikely but cannot be excluded.[11,12] * Monitor for adverse effects, especially hematological, if combination therapy necessary. · **Tipranavir** (unboosted): potential for ↓ dapsone exposure via CYP3A induction Integrase inhibitor • **Elvitegravir/cobicistat**: potential for ↑ dapsone levels due to inhibition of CYP 3A4. This interaction has not been studied. Other · **Rifabutin**: potential ↓ dapsone effectiveness due to induction of dapsone metabolism. Manufacturer suggests dapsone dosage increases may be necessary.[87] However, given that Maloprim™ and Deltaprim™ are fixed-dose combination products with a low dose of dapsone given once weekly, use in combination with rifabutin for malaria prophylaxis should likely be avoided. · **Rifampin**: 7-10-fold ↓ dapsone levels have been observed when used in combination with rifampin.[88] Dapsone dose adjustment is not required in the context of leprosy treatment.[12] However, dapsone doses for malaria prophylaxis are much lower and rifampin doses much higher for the treatment of TB than used in leprosy treatment *Avoid combination. · **Co-trimoxazole**: potential for additive hematological adverse effects, including megaloblastic anemia[89] when used with dapsone and/or pyrimethamine.[11,74,90] *Combination not recommended. Monitor CBC closely if using in combination.[12]
Trimethoprim/ Sulfamethoxazole	Metabolism: *Trimethoprim* 60% excreted unchanged by the kidney, and	NRTIs · **Lamivudine (3TC):** combination may ↓ lamivudine clearance.[91]

(Co-trimoxazole, Septra, Septrin)	the rest is metabolized in the liver.[8] *Sulfamethoxazole* is metabolized in the liver by acetylation and glucuronidation.[8] Enzyme Inhibition: both trimethoprim and sulfamethoxazole may have inhibitory effects on CYP 2C9.[8]	*Not clinically significant.[92] · **Zidovudine:** potential for additive hematological toxicity when used in combination.[2] *Combination used commonly in clinical practice. Monitor CBC when using combination. NNRTIs · **Nevirapine**: potential for severe skin reactions if initiated concurrently; space initiation of TMP-SMX/NVP by 2-4 weeks if possible.[23] Other · **Rifabutin**: Induction of sulfamethoxazole metabolism by rifabutin ↑ exposure to the sulfamethoxazole toxic metabolite, sulfamethoxazole hydroxylamine (↑AUC 50%).[93] *Monitor for adverse dermatologic, hematologic, and hepatic effects when using in combination. · **Sulfadoxine/Pyrimethamine:** ↑ risk of severe adverse skin (approximately 100-fold compared to HIV negative individuals)[67], hematologic and hepatic interactions[23] when used in combination. ***Avoid coadministration as compounds have very similar activity and toxicity profiles.** Suggest initiating co-trimoxazole at least 4 weeks after last sulfadoxine/pyrimethamine dose.[23] WHO suggests that pregnant women on cotrimoxazole prophylaxis should not receive intermittent preventive treatment (IPT) with Fansidar™ and that malarial illness in HIV-infected pregnant women who receive cotrimoxazole prophylaxis should be managed with antimalarial medicines that do not contain sulfonamides or sulfones.[2] Potential for *P. falciparum* cross-resistance between trimethoprim/sulfamethoxazole and sulfadoxine/pyrimethamine.[68,69]

Abbreviations: **APV** amprenavir; **ATV** atazanavir; **AUC** area under the plasma concentration versus time curve; **AZT** zidovudine; **CBC** complete blood count; **Cmin** minimum plasma concentration; **CYP** cytochrome P450; **EFV** efavirenz; **IDV** indinavir; **LPV** lopinavir; **NNRTI** non-nucleoside reverse transcriptase inhibitor; **NRTI** nucleoside reverse transcriptase inhibitor; **NFV** nelfinavir; **NVP** nevirapine; **PI** protease inhibitor; **PJP** pneumocystis jirovecii pneumonia; **PK** pharmacokinetic; **RTV** ritonavir; **SQV** saquinavir

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Potential Interactions Between Antineoplastics and Antiretrovirals

Drug	Class	Metabolism	Actual/Theoretical Interaction	Comments
Altretamine[1]	Alkylating Agents	Hepatic microsomal oxidation to active and cytotoxic derivatives. Exact isoenzyme unknown.	Potential for ↓ efficacy with P-450 inhibitors.	May need to hold antiretroviral regimens with 3A4 inhibiting drugs, or change to agents that do not inhibit 3A4 when concurrent therapy with altretamine needed.
Anastrozole[2, 3] (Arimidex®)	Endocrine Therapies	Metabolized by N-dealkylation, hydroxylation and glucuronidation. Metabolites inactive. Exact isoenzymes unknown (3A4 possible).	Induction of glucuronidation may ↓ levels of drug and subsequently affect efficacy. CYP450 inhibitors may ↑ levels of anastrozole; inducers may do opposite.	Monitor for ↓ efficacy with ritonavir or nelfinavir (↑ glucuronidation) and nevirapine or efavirenz (induce 3A4) Possible ↑ risk and severity of side effects with PIs, delavirdine, or elvitegravir/cobicistat (e.g. hot flushes, peripheral edema, constitutional symptoms etc.).
Bexarotene[4]	Synthetic retinoid analog	Metabolized by CYP3A4 to oxidative metabolites, which are active (degree of activity unknown). Oxidative metabolites may be glucuronidated. Auto-induction occurs with chronic administration, particularly with doses >300 mg/m2/day.	Inhibition or induction of CYP3A4 may affect levels of bexarotene and subsequently affect efficacy or toxicity. Induction of glucuronidation may promote clearance of active metabolites and possibly impact efficacy. Bexarotene may induce metabolism of CYP3A4 substrates, including PIs and NNRTIs. Virological failure was reported in a 70-year old man on **efavirenz**, 3TC and abacavir (VL<50 for 12 years) 2 months after starting bexarotene 300 mg QD for a neoplastic disorder. Efavirenz plasma concentration was 595 ng/mL compared to 1478 ng/mL prior to initiation of bexarotene. Bexarotene concentrations were approximately 50% lower vs. steady-state reference pharmacokinetic data.[5]	Potential for ↓ bexarotene concentrations with NNRTIs, and ↑ concentrations with PIs and elvitegravir/cobicistat; bexarotene may ↓ concentrations of NNRTIs, PIs, and elvitegravir/cobicistat. Consider TDM of bexarotene and antiretrovirals if available, and monitor closely for efficacy/response. May wish to consider using ARV agents that do not impact CYP450 system if possible.

Drug	Class	Metabolism	Actual/Theoretical Interaction	Comments
Bleomycin[6, 7] (Blenoxane®)	Antitumour antibiotics	Hydrolysis by intracellular aminopeptidase. Evidence in rodents suggests possible inhibition of CYP450 system.	Possible ↑ ARV levels, but potential for interactions appears low.	Monitor for PI, NNRTI and elvitegravir/cobicistat-related side effects.
Bortezomib[8-10] (Velcade®)	Proteosome inhibitor	Metabolized primarily by CYP3A4, 2C19, 1A2, and 2D6 and 2C9 to a minor extent. In vitro, bortezomib is a weak inhibitor of CYP1A2, 2C9, 2D6, 3A4; it may inhibit 2C19 at clinically relevant dosages.	Potential for ↑ or ↓ bortezomib concentrations with potent CYP inhibitors or inducers of CYP3A4 and 2C19. Coadministration of ketoconazole led to 35% ↑ in bortezomib concentrations, while concomitant omeprazole did not affect bortezomib pharmacokinetics.	Use with caution with concurrent CYP inhibitors or inducers of CYP3A4 and 2C19. Efavirenz and etravirine inhibit 2C19 and induce CYP3A4. Clinical significane unknown; monitor for bortezomib efficacy & toxicity. Rilpivirine induces CYP2C19; monitor for efficacy.
Busulfan[11-15] (Myleran®, Busulfex®)	Alkylating Agents	Glutathione-S-transferase (isoform GSTA-1-1). Animal data does not support role for CYP450 system.	Little potential for interaction with ARVs; however, itraconazole ↓ busulfan clearance by average of 20% in one study. Therefore, monitor closely when used concomitantly with HAART.	Concurrent use of 3A4 inhibitors may ↑ risk and severity of myelosuppression.
Capecitabine[16] (Xeloda®)	Antimetabolite	Prodrug of 5-fluorouracil. Inhibits CYP2C9.	Potential for ↑ concentrations of CYP2C9 substrates; significant interactions have been noted with warfarin and phenytoin.[16, 17] Caution with concomitant etravirine, which is partially metabolized by CYP2C9. Case series of 4 HIV/HCV-coinfected subjects with advanced hepatocarcinoma on HAART (agents not specified) who received oxaliplatin and capecitabine with no apparent interaction or increased toxicity.[18]	
Chlorambucil[19, 20] (Leukeran®)	Alkylating Agents	CYP450 enzymes not involved in metabolism in one animal study.	Potential for pharmacokinetic interactions with ARVs appears minimal, but very little known about chlorambucil metabolism in humans.	In absence of data, consider possibility for ↑ risk and severity of myelosuppression with CYP450 inhibitors.
Cisplatin and	Alkylating	Main route of elimination is	Potential for pharmacokinetic	Monitor serum creatinine and

Drug	Class	Metabolism	Actual/Theoretical Interaction	Comments
Carboplatin[21-23] (Platinol-AQ®) (Paraplatin®)	Agents	renal.	interactions with ARVs appears minimal. However, cisplatin induced nephrotoxicity may necessitate dosage adjustment for certain ARVs. Potential additive renal toxicity with tenofovir.	creatinine clearance; adjust antiretroviral doses accordingly as needed.
Cyclophosphamide[24-27] (Procytox®, Cytoxan®)	Alkylating Agents	CYP2B6 > 2C19 to active metabolite. 3A4 to inactive and possibly toxic metabolites.	Induction of 2B6 may ↑ amount of active metabolite formed. Inhibition of 2B6 may prevent activation of the drug. Induction of 3A4 may ↑ neurotoxicity, whereas inhibition of 3A4 may make more drug available for 4-hydroxylation route (i.e. possibly ↑ efficacy/toxicity). Inhibition of 2C19 may impact activation of the drug, although this may be compensated for by increased shunting through 2B6 pathway. Case report of a 55 year old male with newly diagnosed advanced HIV and large B-cell lymphoma who simultaneously began **abacavir, lamivudine and raltegravir** and CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) with intrathecal methotrexate. The patient achieved and maintained an undetectable viral load throughout 6 CHOP cycles. Two months after the patient completed chemotherapy, a positron emission tomography scan indicated no active lymphoma.[28]	CYP2B6 inducers (e.g., ritonavir, nelfinavir, efavirenz, nevirapine) and CYP3A4 inhibitors (e.g., PIs, elvitegravir/cobicistat) may ↑ efficacy and toxicity of cyclophosphamide (i.e. myelosuppression, nausea and vomiting). Efavirenz and etravirine inhibit 2C19; co-administration may impact activation of cyclophosphamide, although this may be compensated for by increased shunting via 2B6 pathway. Clinical significance unknown; monitor for efficacy. Rilpivirine induces CYP2C19; monitor for toxicity.
Cytarabine (ara-C) (Cytosar®)	Anti-metabolite	Metabolized in liver by cytidine deaminase	Potential additive toxicity with other agents.	Main toxicities of cytarabine include dose-limiting myelosuppression, nausea, vomiting, urinary retention, renal failure (rare). Caution with AZT;

Drug	Class	Metabolism	Actual/Theoretical Interaction	Comments
				tenofovir (??) – renal toxicity
Dacarbazine[29] (DTIC®)	Alkylating Agents	CYP1A2 > 2E1 to reactive DNA methylating metabolites.	Inhibition of CYP1A2 and 2E1 may decrease concentrations of pharmacologically active metabolite.	Use of concurrent ritonavir at therapeutic doses may ↑ formation of active metabolites. May ↑ efficacy and risk of nausea, vomiting and myelosuppression.
Dactinomycin[30] (Cosmegen®)	Antitumour antibiotics	Minimally metabolized. Unclear which enzyme system involved.	Unlikely to result in significant cytochrome-mediated interactions, given low extent of metabolism (1-4%).	No detrimental pharmacokinetic interactions anticipated with combined HAART.
Dasatinib[31, 32] (Sprycel®)	Tyrosine kinase inhibitor	Extensively metabolized by CYP3A4 to an active metabolite with activity comparable to parent compound. Other enzymes involved in metabolism include UGT and flavin-containing monooxygenase (FMO3). Dasatinib also acts as a CYP3A4 inhibitor.	Possibility of ↑ levels of dasatinib and ↑ toxicity when concomitant 3A4 inhibitors are administered. A decrease in the dosage or an adjustment of the dosing interval of dasatinib may be necessary for patients requiring co-administration with strong CYP3A inhibitors such as ritonavir.[33] In a study of 18 patients with solid tumors, dasatinib 20 mg daily coadministered with ketoconazole 200 mg BID led to four- and five-fold increase of dasatinib Cmax and AUC, respectively. Conversely, possibility of ↓ levels and risk of therapeutic failure with 3A4 inducers. In a healthy subject study, administration of single dose dasatinib in the presence of chronic rifampin 600 mg daily, mean Cmax and AUC of dasatinib were ↓ by 81% and 82%, respectively.	Co-administration of dasatinib and potent CYP3A4 inhibitors including PIs and elvitegravir/cobicistat is not recommended; use of an alternate antiretroviral with minimal CYP3A4 inhibition is preferred. If this is not possible, a reduction in dasatinib dose to 20 or 40 mg daily and close monitoring for dasatinib toxicity is recommended. Concomitant use of potent CYP3A4 inducers including NNRTIs with dasatinib is not recommended. In patients in whom rifampicin or other CYP3A4 inducers are indicated, alternative agents with less enzyme induction potential should be used.

Drug	Class	Metabolism	Actual/Theoretical Interaction	Comments
			Also potential for ↑ concentrations of concomitant PIs, NNRTIs, or elvitegravir/cobicistat. In healthy subjects, coadministration of single dose dasatinib 100 mg and simvastatin resulted in 37% ↑ Cmax and 20% ↑ AUC of simvastatin.	
Daunorubicin[34-36] (Cerubidine®)	Antitumour antibiotics	Generally similar to doxorubicin.	Likely similar to doxorubicin.	Likely similar to doxorubicin.
Daunorubicin, liposomal[37-41]	Antitumour antibiotics	Appears similar in pattern to free doxorubicin, but smaller ratio of daunorubicinol:daunorubicin with liposomal preparation.	Likely similar to doxorubicin.	Likely similar to doxorubicin.
Dexamethasone[42-50]	Steroids	CYP3A4 Dexamethasone is a 3A4 inducer.	↑ risk of steroid related toxicity with 3A4 inhibitors. Possible ↓ efficacy with 3A4 inducers. Dexamethasone may ↓ levels of NNRTIs, PIs and elvitegravir/cobicistat.	Possible ↑ levels and pharmacodynamic effects of steroids when used concurrently with PIs, elvitegravir/cobicistat and delavirdine. Opposite effect likely with NNRTIs. Consider use of non-3A4 inducing steroid, antiretroviral therapeutic drug monitoring, or modifying to a non-CYP based cART regimen (e.g., raltegravir).
Docetaxel[51-53] (Taxotere®)	Taxanes	CYP3A4	Possibility of ↑ levels of taxane when concomitant 3A4 inhibitor administered. Conversely, possibility of ↓ levels with 3A4 inducers. Effect may be more pronounced with docetaxel, since 3A4 is main enzyme involved in metabolism. Case report of a 40 year-old HIV+ male on **LPV/r, TDF, 3TC** who experienced febrile neutropenia (NE 450 cells/µl) with high CRP (196mg/L) levels 8 days after starting	↑ taxane levels may ↑ risk and severity of myelosuppression, constitutional symptoms and peripheral neuropathy.

Drug	Class	Metabolism	Actual/Theoretical Interaction	Comments
			docetaxel (25 mg/m^2) for treatment of KS. Microbiological tests were negative and the neutropenia resolved in the following week. Authors hypothesize that RTV inhibited CYP3A4, leading to increased docetaxel levels, and thus may have caused this febrile neutropenia.[54] In a small group of patients with solid tumours who received **oral docetaxel 100 mg with ritonavir 100 mg** given simultaneously or 1 hour beforehand, the apparent oral bioavailability of docetaxel was 131% and 161%, respectively, compared to IV administration. These findings suggest that ritonavir has a marked inhibitory effect on gut wall and/or hepatic metabolism. The oral combination of docetaxel and ritonavir was well tolerated.[55] In 3 HIV-positive patients on ritonavir-containing regimens (2 on **ATV/r**, 1 on **LPV/r**), administration of **IV docetaxel** resulted in severe hematological and cutaneous toxicity 3-7 days after the first infusion of docetaxel (70-100 mg/m^2), despite having normal baseline liver function and blood cell counts. Each patient recovered following the withdrawal of docetaxel. The mechanism is postulated to be CYP3A4 inhibition of docetaxel metabolism by ritonavir.[56]	

Drug	Class	Metabolism	Actual/Theoretical Interaction	Comments
Doxorubicin[57-62]	Antitumour antibiotics	Several routes: aldoketoreductase and NADPH-dependent cytochrome reductase. Resulting aglycone derivatives conjugated to a sulfate or glucuronide metabolite. Enzymes of cytochrome P450 involved in free radical generation in vitro; clinical significance unknown.	Potential for interactions unknown, given uncertainty about role of cytochrome P450 in free radical generation. A pharmacokinetic analysis was conducted in 19 HIV-positive patients with non-Hodgkin's lymphoma treated with CHOP (cyclophosphamide, vincristine, doxorubicin and prednisone) with and without concurrent **PI-based HAART**. Doxorubicin pharmacokinetics were not affected by concomitant PI administration, and PI exposures were not altered by doxorubicin.[63] Case report of a 55 year old male with newly diagnosed advanced HIV and large B-cell lymphoma who simultaneously began **abacavir, lamivudine and raltegravir** and CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) with intrathecal methotrexate. The patient achieved and maintained an undetectable viral load throughout 6 CHOP cycles. Two months after the patient completed chemotherapy, a positron emission tomography scan indicated no active lymphoma.[28]	Enzyme inhibitors may ↓ reduction to free radical, which may decrease both antineoplastic and cytotoxic properties. Enzyme inducers may do the opposite.
Doxorubicin, liposomal[64, 65]	Antitumour antibiotics	Appears similar in pattern to free doxorubicin, but less doxorubicinol detected in plasma.	Similar to doxorubicin.	Similar to doxorubicin.

Drug	Class	Metabolism	Actual/Theoretical Interaction	Comments
Droloxifene[66-68]	Endocrine Therapies	Glucuronidation (main) to inactive metabolites.	Induction of glucuronidation may ↓ levels of drug and subsequently affect efficacy.	Nelfinavir and ritonavir may ↓ efficacy through induction of glucuronidation.
Epirubicin[69-73] (Pharmorubicin®)	Antitumour antibiotics	Similar to doxorubicin, except both parent drug and epirubicinol metabolite undergo glucuronidation to inactive metabolites. Glucuronides constitute main metabolites.	Potential for increased conversion to inactive glucuronide derivatives with inducers of glucuronidation.	Ritonavir and nelfinavir may ↓ efficacy of epirubicin by increasing glucuronidation.
Erlotinib[74]	Epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor	Primarily metabolized by CYP3A4. Metabolized to a lesser extent by CYP1A2 and 1A1.	Potential for ↑ levels with **3A4 inhibitors**; coadministration of erlotinib and ketoconazole 200 mg BID for 5 days led to 86% ↑ AUC and 69% ↑ Cmax of erlotinib. When erlotinib was coadministered with ciprofloxacin (an inhibitor of CYP3A4 and 1A2), erlotinib AUC ↑ 39% and Cmax ↑ 17%. Potential for ↓ levels and efficacy with 3A4 inducers. Co-administration with chronic rifampicin resulted in 69% ↓ AUC of erlotinib. In a separate study, subjects pre-treated with rifampin experienced 57.5% ↓ AUC of erlotinib after single dose administration; however, systemic exposure to the active metabolites OSI-413 and OSI-420 was largely unaffected by rifampicin treatment. As a result, the active metabolites consist of 18% of the total erlotinib exposure following the concomitant administration compared to only 5% when erlotinib was given alone. Case report of an HIV-infected	Caution with concomitant administration of CYP3A4 or 1A2 inhibitors such as PIs and elvitegravir/cobicistat. Erlotinib dose should be reduced if toxicity is observed. Potential for reduced efficacy with CYP3A4 inducers such as NNRTIs. Alternative treatments lacking potent CYP3A4 inducing activity should be considered when possible. If this is not possible, the erlotinib dose may be increased from 150 mg up to 450 mg per day.[76]

Drug	Class	Metabolism	Actual/Theoretical Interaction	Comments
			woman with bronchioloalveolar carcinoma on cART (individual agents not specified) who responded to erlotinib therapy.[75]	
Estramustine[77] (EMCYT®)	Alkylating agent	Dephosphorylated during absorption, then undergoes extensive first-pass metabolism to its active components, estromustine, estramustine, estrone and estradiol.	Potential for cytochrome-mediated interactions with ARVs appears minimal.	Unlikely to result in detrimental pharmacokinetic interactions with cART.
Etoposide[78-81] (Vepesid®)	Epipodophyllotoxins	CYP3A4 (main); CYP2E1, 1A2 (minor)	Possibility of ↑ levels with 3A4 inhibitors, and ↓ levels with 3A4 inducers.	↑ etoposide levels may ↑ risk and severity of mucositis, myelosuppression and transaminitis. ↑ teniposide levels may ↑ risk and severity of myelosuppression.
Exemestane[3] (Aromasin®)	Endocrine Therapies	Metabolized by CYP3A4 and aldoketoreductases.	Potential for ↑ levels with 3A4 inhibitors; possible ↓ levels and efficacy with 3A4 inducers.	Nevirapine and efavirenz may ↓ efficacy of drug; avoid combination if possible. ↑ levels with PIs and delavirdine may ↑ risk and severity of adverse effects (e.g. musculoskeletal pain, constitutional symptoms, peripheral edema, hot flashes etc.)
Fludarabine (Fludara®)	Antimetabolite	Rapidly converted into active metabolite (2-FLAA) after administration. ~40% renally excreted.	Potential for cytochrome-mediated interactions with ARVs appears minimal.	Unlikely to result in detrimental pharmacokinetic interactions with combined HAART.
5-Fluorouracil[82]	Antimetabolite	Converted to 5-6-dihydrofluorouracil by the enzyme dihydropyrimidine dehydrogenase (DPD). 7-20% renally excreted. Strong inhibitor of CYP2C9.[83]	Significant interactions have been noted between capecitabine (5-FU prodrug) and warfarin and phenytoin, likely via CYP2C9 inhibition.[16, 17, 84] A similar interaction may occur with 5-FU.[83, 85] Potential for ↑ exposures of	

Drug	Class	Metabolism	Actual/Theoretical Interaction	Comments
			etravirine via 2C9 inhibition. Clinical significance unknown, close monitoring and/or TDM may be considered. Case series of 21 HIV-positive subjects on **cART** (7 NRTI only, 6 on PI, 6 on NNRTI and 2 on PI/NNRTI containing regimens) with anal carcinoma who received radiotherapy plus mitomycin C and 5-fluourouracil without need for dose reductions. The complete response rate was 81%, and 62% remained free of any tumor relapse during additional follow-up (median, 53 months), and there was no increased risk of HIV progression.[86] Case series of 5 HIV-positive patients on **cART (4 PI, 1 NRTI)** with advanced colorectal cancer who were treated with oxaliplatin, leucovorin and fluourouracil (FOLFOX-4 regimen) without apparent increase in antineoplastic-associated toxicity.[87] Treatment compliance, toxicity and clinical outcomes of chemoradiotherapy (fluorouracil, mitomycin radiation) for anal carcinoma were retrospectively compared in 45 HIV-negative vs. 25 HIV-positive patients on cART between 1997 and 2008. CRT was completed in all patients. Chemotherapy was reduced in 28% and 9% and radiation was interrupted	

Drug	Class	Metabolism	Actual/Theoretical Interaction	Comments
			in 8% and 11% of HIV-positive and HIV-negative patients, respectively. Rates of grade 3-4 toxicity were similar, and long-term local control and survival were not significantly different between the groups.[88]	
Formestane[89]	Endocrine Therapies	Two pathways: reductive metabolism by hepatic hydroxysteroid dehydrogenase and glucuronidation.	Induction of glucuronidation may ↓ levels of drug and subsequently affect efficacy.	Nelfinavir and ritonavir may ↓ efficacy through induction of glucuronidation.
Gefitinib[90] (Iressa®)	Epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor	Primarily metabolized by CYP3A4. Major metabolite O-desmethyl gefitinib is produced via CYP2D6	Potential for ↑ levels with 3A4 inhibitors; in healthy volunteers, coadministration of gefitinib and itraconazole led to 80% ↑ AUC of gefitinib. Potential for ↓ levels and efficacy with 3A4 inducers. In healthy volunteers, co-administration with rifampicin resulted in 83% ↓ AUC of gefitinib.	Caution with concomitant administration of CYP3A4 or 2D6 inhibitors such as PIs or elvitegravir/cobicistat, as adverse effects of gefitinib are related to dose and exposure. Potential for reduced efficacy with CYP3A4 inducers such as NNRTIs.
Gemcitabine (Gemzar®)	antimetabolite	extensively metabolized to 2',2'-difluorodeoxyuridine (dFdU) after continuous oral dosing. The main metabolite dFdU has a long terminal half-life after oral administration. After 1 week, 92-98% dose is recovered in the urine.	Potential for cytochrome-mediated interactions with ARVs appears minimal.	Unlikely to result in detrimental pharmacokinetic interactions with cART.
Idarubicin[69, 91, 92] (Idamycin PFS®)	Antitumour antibiotics	Converted mainly to idarubicinol by aldoketoreductase (as active as parent drug). Less superoxide generation in vitro relative to daunorubicin and doxorubicin.	Potential for cytochrome-mediated interactions with ARVs appears minimal.	Unlikely to result in detrimental pharmacokinetic interactions with cART.

Drug	Class	Metabolism	Actual/Theoretical Interaction	Comments
Ifosfamide[93, 94] (Ifex®)	Alkylating Agents	CYP3A4 to active metabolite. 3A4 and 2B6 involved in detoxification. 3A4 metabolism of (S)-ifosfamide may generate neurotoxic metabolite.	Induction of 3A4 may ↑ activation of the drug, but may also produce more potentially neurotoxic metabolite. Inhibition of 3A4 is not recommended, since it would theoretically inhibit drug activation.	May need to hold antiretrovirals or change to regimen without potential for 3A4 inhibition if concomitant therapy with ifosfamide needed. Induction of 3A4 may ↑ efficacy and toxicity of ifosfamide (i.e. myelosuppression, arrhythmia, hemorrhagic cystitis).
Imatinib[95] (Gleevec®)	Tyrosine kinase inhibitor	Extensively metabolized by CYP3A4; other P450 enzymes play minor role. An N-demethylated piperazine derivative is the main circulating metabolite, which has in vitro activity similar to the parent compound. In vitro, imatinib was metabolized to the active metabolite CGP74588 by CYP3A4 and CYP3A5 and, to a lesser extent, by CYP2D6. Imatinib significantly inhibits CYP3A4 activity in vitro.	Caution is recommended when administering imatinib with CYP3A4 inhibitors; potential for ↑ plasma levels of imatinib. Imatinib may also theoretically ↑ levels of PIs, NNRTIs, and elvitegravir/cobicistat. 11 cancer patients receiving imatinib for at least 2 months were administered **ritonavir 600 mg daily** for 3 days. Imatinib AUC was unchanged from days 1 to 4, and ritonavir day 4 AUC and Cmax were comparable to historical data. In vitro, ritonavir (1 micromol/L) completely inhibited CYP3A4-mediated metabolism of imatinib to CGP74588 but inhibited metabolism in microsomes by only 50%. At steady state, it appears that imatinib is insensitive to potent CYP3A4 inhibition and relies on alternate elimination pathways. However, these findings may not be representative of chronic co-administration of both drugs[96].	Monitor patients for signs of imatinib dose-related adverse events (fluid retention/weight gain, nausea and vomiting, neutropenia).
Irinotecan[97] (Camptosar®)	Camptothecins	hCE2 to SN-38 metabolite (active); CYP3A4 and glucuronidation to inactive metabolites.	Inhibition of 3A4 may ↑ formation of SN-38. Induction of 3A4 or glucuronidation may ↑ conversion of SN-38 to inactive metabolites.	Inhibition of 3A4 may ↑ risk and severity of myelosuppression. Induction of 3A4 or glucuronidation may ↓ efficacy of

Drug	Class	Metabolism	Actual/Theoretical Interaction	Comments
			The effect of **lopinavir/ritonavir** on the pharmacokinetics of irinotecan (CPT11) was investigated in 7 patients with Kaposi's sarcoma. Coadministration of LPV/RTV resulted in 47% ↓ clearance of CPT11 (P=0.0008), and was associated with an 81% ↓ in AUC (P=0.02) of the oxidized inactive metabolite APC (7-ethyl-10-[4-N- (5-aminopentanoic-acid)-1-piperidino]-carbonyloxycamptothecin). LPV/RTV also inhibited the formation of SN38 glucuronide (SN38G), with a 36% ↓ in the SN38G/SN38 AUCs ratio (P=0.002) consistent with UGT1A1 inhibition by LPV/RTV. This dual effect resulted in increased availability of CPT11 for SN38 conversion and reduced inactivation on SN38, leading to a 204% increase (P=0.0001) in SN38 AUC in the presence of LPV/RTV. One patient had to stop irenotecan therapy despite 50% dose ↓ due to persistent grade 2 neutropenia. The clinical significance of this interaction requires further investigation.[98] Potential for ↑ irenotecan-related toxicities with atazanavir, which also inhibits UGT1A1.	drug.

Drug	Class	Metabolism	Actual/Theoretical Interaction	Comments
Lapatinib[99] (Tykerb®)	Dual tyrosine kinase inhibitor	Extensively metabolized by CYP3A4. Lapatinib inhibits CYP3A4 and 2C8. Lapatinib is also a substrate for P-gp and BCRP, and inhibits P-gp, BCRP and OATP1A1 in vitro.	Potential for ↑ lapatinib concentrations with CYP3A4 inhibitors including PIs and elvitegravir/cobicistat. In healthy subjects, coadministration of ketoconazole 200 mg BID for 7 days plus lapatinib resulted in 3.6-fold ↑ lapatinib AUC. Potential for ↓ lapatinib concentrations with CYP3A4 inducers including NNRTIs. In healthy subjects, administration of lapatinib in the presence of chronic carbamazepine resulted in 72% ↓ lapatinib AUC. Potential for lapatinib to ↑ levels of PIs, NNRTIs, and elvitegravir/cobicistat.	Avoid concomitant use of strong CYP3A4 inhibitors or inducers if possible, or consider dose adjustment of lapatinib. With strong CYP3A4 inhibitors, dose reduction from 1250 mg to 500 mg daily is anticipated to provide lapatinib AUC in the target range. If the strong CYP3A4 inhibitor is discontinued, a one week washout period is recommended before the lapatinib dose is readjusted upwards. Coadministration with moderate CYP3A4 inhibitors should be done with caution, and patients should be carefully monitored for adverse reactions. If patients require therapy with a strong CYP3A4 inducer, the lapatinib dose may be titrated gradually from 1250 mg up to 4500 mg daily based on tolerability. If the strong inducer is discontinued, lapatinib dose should be reduced over approximately 2 weeks to the indicated dose.
Lenalidomide[100] (Revlimid®)	Immunomodulatory agent	In vitro lenalidomide is not a substrate, inhibitor or inducer of cytochrome P450 enzymes.	Cytochrome-mediated interactions are unlikely.	No detrimental pharmacokinetic interactions anticipated with combined HAART.
Letrozole[3, 101] (Femara®)	Endocrine Therapies	Metabolized to carbinol metabolite (inactive) by CYP2A6 and 3A4. Inhibits CYP2A6 and 2C19.	Potential for ↑ levels with 3A4 inhibitors; possible ↓ levels and efficacy with 3A4 inducers.	Similar interaction potential as with exemestane.

Drug	Class	Metabolism	Actual/Theoretical Interaction	Comments
Lomustine[102, 103] (Ceenu®)	Alkylating Agents	Extensive first pass metabolism to metabolites with ↑ activity and ↓ toxicity relative to parent. Exact isoenzymes involved unknown.	Potential for interaction with CYP450 inhibitors (i.e. ↑ availability of parent drug, therefore ↓ efficacy and ↑ toxicity).	May need to hold antiretrovirals or consider use of non-CYP inhibiting regimen during concomitant lomustine therapy.
Mechlorethamine[104] (Mustargen®)	Alkylating Agents	Rapid chemical transformation.	Cytochrome-mediated interactions are unlikely.	No detrimental pharmacokinetic interactions anticipated with cART.
Melphalan[105] (Alkeran®)	Alkylating Agents	Spontaneous chemical degradation in plasma to inactive metabolites.	Cytochrome-mediated interactions are unlikely.	No detrimental pharmacokinetic interactions anticipated with cART.
Mercaptopurine[106] (Purinethol®)	Antimetabolite	Converted into active thioguanine nucleotides by the enzyme xanthine oxidase. Also undergoes methylation by enzyme thiopurine methyltransferase to form S-methylated nucleotides, which are also cytotoxic.	Cytochrome-mediated interactions are unlikely.	No detrimental pharmacokinetic interactions anticipated with cART.
Methylprednisolone[42-50]	Steroids	CYP3A4	↑ risk of steroid related toxicity with 3A4 inhibitors. Possible ↓ efficacy with 3A4 inducers.	Possible ↑ levels and pharmacodynamic effects of steroids when used concurrently with PIs, elvitegravir/cobicistat and delavirdine. Opposite effect likely with NNRTIs. May need to consider use of non-3A4 inducing steroid, antiretroviral therapeutic drug monitoring, modifying to a non-CYP cART regimen.
Methotrexate (Metoject®)	Antimetabolite	Metabolized in the liver; almost all drug is excreted unchanged in urine.	Avoid concomitant therapy with cotrimoxazole, pyrimethamine, NSAIDS (with high-dose methotrexate) due to increased risk of methotrexate toxicity. Increased monitoring of renal function with concomitant tenofovir may be warranted.	Methotrexate toxicity includes leukopenia, thrombocytopenia, anemia, nephrotoxicity, mucosal ulcerations.

Drug	Class	Metabolism	Actual/Theoretical Interaction	Comments
Mitomycin[59, 107-110]	Antitumour antibiotics	Exact pathway unclear. CYP450 may be involved in reductive bioactivation, but multiple other enzymes also participate in this process.	Potential for interactions with ARVs unclear. Since multiple pathways for bioactivation, modulation of CYP450 may not be significant. Case series of 21 HIV-positive subjects on **HAART** (7 NRTI only, 6 on PI, 6 on NNRTI and 2 on PI/NNRTI containing regimens) with anal carcinoma who received radiotherapy plus mitomycin C and 5-fluourouracil without need for dose reductions. The complete response rate was 81%, and 62% remained free of any tumor relapse during additional follow-up (median, 53 months), and there was no increased risk of HIV progression.[86] Treatment compliance, toxicity and clinical outcomes of chemoradiotherapy (fluorouracil, mitomycin radiation) for anal carcinoma were retrospectively compared in 45 HIV-negative vs. 25 HIV-positive patients on HAART between 1997 and 2008. CRT was completed in all patients. Chemotherapy was reduced in 28% and 9% and radiation was interrupted in 8% and 11% of HIV-positive and HIV-negative patients, respectively. Rates of grade 3-4 toxicity were similar, and long-term local control and survival were not significantly different between the groups.[88]	Further study needed.
Mitoxantrone[111-115]	Antitumour antibiotics	Metabolized to inactive carboxylic acid derivatives (exact pathway unclear). In	Potential for interactions unknown. In vitro inhibition of CYP450 ameliorates mitoxantrone	Possible ↓ efficacy and toxicity with inhibitors of CYP450. Further study needed.

Drug	Class	Metabolism	Actual/Theoretical Interaction	Comments
		vitro evidence that CYP450 involved in oxidation to reactive intermediate.	cytotoxicity; impact on antiproliferative effect unknown.	
Nilotinib[116] (Tasigna®)	Protein tyrosine kinase inhibitor	Primarily metabolized by CYP3A4; also a substrate for P-gp. Nilotinib is a competitive inhibitor of CYP3A4, CYP2C8, CYP2C9, and CYP2D6 *in vitro.* It also inhibits P-gp at an intracellular level.	Possibility of ↑ levels of nilotinib and ↑ toxicity with CYP3A4 inhibitors, including PIs and elvitegravir/cobicistat. A decrease in the dosage or an adjustment of the dosing interval of nilotinib may be necessary for patients requiring co-administration with strong CYP3A inhibitors such as ritonavir[33] or cobicistat. In healthy volunteers, the bioavailability of nilotinib was increased 3-fold when coadministered with ketoconazole. Potential for ↓ nilotinib concentrations with CYP3A4 inducers including NNRTIs. An 80% ↓ nilotinib concentrations was observed in the presence of chronic rifampin.[76] Potential for ↑ concentrations of PIs, NNRTIs, and elvitegravir/cobicistat.	The administration of nilotinib with strong CYP3A4 inhibitors should be avoided. If this is not possible, it is recommended to interrupt nilotinib therapy, otherwise close monitoring for QT interval prolongation is indicated. Based on pharmacokinetic data, nilotinib dose may be reduced from 400 mg twice daily to once daily in the presence of strong CYP3A4 inhibitors.[76] In patients for whom CYP3A4 inducers are indicated, alternative agents with less enzyme induction potential should be considered. May also wish to consider antiretroviral TDM.
Oxaliplatin[117] (Eloxatin®)	Alkylating Agent	Undergoes extensive nonenzymatic biotransformation. There is no evidence of cytochrome P450-mediated metabolism in vitro.	Potential for interactions with ARVs appears minimal. Case series of 5 HIV-positive patients on **HAART (4 PI, 1 NRTI)** with advanced colorectal cancer who were treated with oxaliplatin, leucovorin and fluourouracil (FOLFOX-4 regimen) without apparent increase in antineoplastic-associated toxicity.[87]	No detrimental interactions anticipated with cART.

Drug	Class	Metabolism	Actual/Theoretical Interaction	Comments
			Case series of 4 HIV/HCV-coinfected subjects with advanced hepatocarcinoma on **cART** (agents not specified) who received oxaliplatin and capecitabine with no apparent interaction or increased toxicity.[18]	
Paclitaxel[118-121] (Taxol®)	Taxanes	CYP2C8 > CYP3A4	Case reports of ↑ paclitaxel levels and toxicity when concomitant 3A4 inhibitors were administered. Conversely, possibility of ↓ levels with 3A4 inducers. Effect may be more pronounced with docetaxel, since 3A4 is main enzyme involved in metabolism. Life-threatening paclitaxel toxicity was observed in two HIV-positive patients treated with paclitaxel 100 mg/m2 IV for refractory KS. The first patient was on didanosine, delavirdine and **lopinavir/ritonavir**. Two days after receiving paclitaxel, he developed myalgias and arthralgias, and by day 8 he was acutely ill, neutropenic and died of sepsis. The second patient was on **indinavir 800/ritonavir 200 mg BID** and developed febrile neutropenia on day 7 after starting paclitaxel. A second course of paclitaxel resulted in profound cytopenia and total body alopecia. Subsequently, his paclitaxel dose was reduced to 60 mg/m2 and was tolerated for 6 cycles.[122] In 34 HIV-positive patients with KS	↑ taxane levels may ↑ risk and severity of myelosuppression, liver function test elevations, constitutional symptoms and peripheral neuropathy.

Drug	Class	Metabolism	Actual/Theoretical Interaction	Comments
			who received paclitaxel 100 mg/m^2, paclitaxel exposure was higher in patients taking protease inhibitors (either **indinavir, nelfinavir, or both**) compared to those who not taking protease inhibitors. The increased exposure did not correlate with efficacy or toxicity. Of the 20 patients assessable for response, 6 (30%) had an objective response and median progression-free survival was 7.8 months (95% confidence interval, 5.6, 21.0 months).[123] In a study evaluating the efficacy of paclitaxel 100mg/m^2 q2weeks for treatment of AIDS-related KS (n=107), 44% received **indinavir, saquinavir, ritonavir or nelfinavir** and no increase in adverse effects was noted in comparison to those not on PIs.[124] In a case report of an HIV-positive patient with Kaposi's sarcoma who received paclitaxel 100 mg/m2 with concomitant **nevirapine**-based therapy, nevirapine concentrations were not altered in the presence of paclitaxel, and paclitaxel concentrations were comparable to historical controls.[125]	
Prednisone[126-129]	Steroids	Converted to active metabolite prednisolone by 11β-hydroxy-dehydrogenase (non-CYP mediated). Prednisone and prednisolone also substrates of cytochrome	↑ risk of steroid related toxicity with 3A4 inhibitors (possible lower propensity for adverse interaction relative to dexamethasone or methylprednisolone). Possible ↓ efficacy with 3A4 inducers.	Monitor for ↑ pharmacodynamic effects with PIs, elvitegravir/cobicistat and delavirdine. Monitor for loss of efficacy with nevirapine and efavirenz.

Drug	Class	Metabolism	Actual/Theoretical Interaction	Comments
		P450 system; 3A4 likely involved, but other isoenzymes also probable.	Case report of a 55 year old male with newly diagnosed advanced HIV and large B-cell lymphoma who simultaneously began **abacavir, lamivudine and raltegravir** and CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) with intrathecal methotrexate. The patient achieved and maintained an undetectable viral load throughout 6 CHOP cycles. Two months after the patient completed chemotherapy, a positron emission tomography scan indicated no active lymphoma.[28]	
Procarbazine[130, 131]	Alkylating Agent	CYP2B > 1A to active metabolites.	Inhibition of CYP1A or 2B isoenzymes may ↓ efficacy of drug. Induction of CYP1A or 2B may potentially ↑ activity and/or toxicity.	Potential for ↑ efficacy/toxicity of drug with CYP2B6 or 1A inducers (e.g., ritonavir, nelfinavir, efavirenz, nevirapine, tipranavir).
Sorafenib[132] (Nexavar®)	Multikinase inhibitor	Metabolized by CYP3A4 and glucuronidated by UGT1A9. Sorafenib inhibits UGT1A1 and UGT1A9. Sorafenib also inhibts CYP2B6 and 2C8 in vitro. Sorafenib does not inhibit or induce CYP3A4, 2D6, or 2C19.	Coadministration of sorafenib and ketoconazole once daily for 7 days in healthy male volunteers did not alter the mean AUC of 50 mg single dose sorafenib, likely due to sorafenib metabolism via alternate pathways including UGT1A9.[132] Therefore, interactions between sorafenib and CYP3A4 inhibitors thought to be unlikely. Case report of an HIV/HCV coinfected male with advanced hepatocellular carcinoma who received sorafenib 400 mg BID concomitantly with antiretroviral therapy (tenofovir, emtricitabine and **atazanavir)**; after 3 months, a partial response was noted and sorafenib	Caution is recommended when administering sorafenib together with compounds that are metabolized/eliminated predominantly by the UGT1A1 and UGT1A9 pathways (eg, irinotecan). Raltegravir clearance is mediated by UGT1A1, and hence concentrations may potentially by ↑ by sorafenib. However, the clinical significance of this is unclear, as raltegravir is generally well tolerated and toxicity does not appear to be dose-related.

Drug	Class	Metabolism	Actual/Theoretical Interaction	Comments
			was continued; at the same time, atazanavir was replaced with **darunavir/ritonavir BID** due to incomplete viral suppression. After 23 months of therapy, he had durable stable disease, with a concomitant suppressed viral load. The simultaneous administration of these therapies was well tolerated. No grade 3 or 4 toxicities were observed.[133] Potential for ↓ levels and efficacy with 3A4 inducers including NNRTIs. Co-administration with chronic rifampicin resulted in 24% ↓ combined AUC of sorafenib plus its primary active metabolite; clinical significance is unknown.	
Sunitinib[134] (Sutent®)	Multitargeted tyrosine kinase inhibitor	Metabolized primarily by CYP3A4 to active metabolite SU012662 which is also metabolized by CYP3A4. Sunitinib does not inhibit or induce CYP3A4 or other CYP isozymes in vitro.	Potential for ↑ concentrations with CYP3A4 inhibitors. In healthy volunteers, coadministration of single dose sunitinib and ketoconazole led to 49% ↑ Cmax and 51% ↑ AUC of sunitinib plus its active metabolite. Potential for ↓ concentrations with CYP3A4 inducers. In healthy volunteers, coadministration of single dose sunitinib and rifampin led to 23% ↓ Cmax and 46% ↓ AUC of combined sunitinib plus its active metabolite.	Avoid concomitant administration of CYP3A4 inhibitors such as PIs and elvitegravir/cobicistat, or inducers such as NNRTIs if possible. Sunitinib dose may be reduced in 12.5 mg/day increments down to 25 mg/day in patients receiving CYP3A4 inhibitors, and may be increased in 12.5 mg/day increments up to 50 mg mg/day in patients receiving CYP3A4 inducers. Clinical response and tolerability should be monitored carefully.
Streptozocin[135, 136] (Zanosar®)	Alkylating Agents	Spontaneous degradation to active methylcarbonium ion. Other metabolites present,	Potential for interactions with antiretrovirals is unknown.	In absence of data, monitor for changes in serum creatinine, urea and proteinuria, since major

Drug	Class	Metabolism	Actual/Theoretical Interaction	Comments
		although route of metabolism unclear.		dose limiting side effect is nephrotoxicity.
Tamoxifen[137-151] (Tamofen®)	Endocrine Therapies	Multiple isoenzymes involved: 3A4>1A2 to N-desmethyltamoxifen (main route) 2D6, 2C9/19, 3A4 and 2B6 to trans-4-hydroxytamoxifen (minor route) 3A4 may also be involved in generation of toxic α-OH metabolites and DNA adducts. May induce 3A4.	CYP3A4 induction may ↓ levels of parent and metabolite. Inhibition of 3A4 may ↑ efficacy (↑ substrate available for conversion to active metabolites by other isoforms) and ↑ risk of tamoxifen side effects. Induction of 3A4 by tamoxifen may ↓ NNRTI, PI or elvitegravir/cobicistat levels. Pharmacokinetic interaction with CYP2D6 inhibitors, showing a reduction in plasma level of an active tamoxifen citrate metabolite, 4-hydroxy-N-desmethyltamoxifen (endoxifen), has been reported in the literature.	May need to consider using non-CYP3A4 dependent regimen in patients receiving concurrent tamoxifen, due to potential for ↓ PI, NNRTI or elvitegravir/cobicistat levels. Inhibition of 3A4 may ↑ risk and severity of tamoxifen related side effects (e.g. hot flushes, nausea and vomiting). Avoid concomitant use of CYP2D6 inhibitors (risk of ↓ concentrations of active metabolite).
Temozolomide[152] (Temodal®)	Alkylating agent	Undergoes non-enzymatic hydrolysis to MTIC, followed by renal excretion. Cytochrome P450-mediated metabolism does not contribute significantly to the plasma clearance of temozolomide.	Potential for pharmacokinetic interactions with ARVs appears minimal. In a small case series, continuous low-dose temozolomide treatment was well tolerated in two HIV-positive patients on cART (agents not specified) with glioblastoma multiforme.[153]	No detrimental pharmacokinetic interactions anticipated with cART. Monitor for additive lymphopenia with zidovudine.
Temsirolimus[154] (Torisel®)	mTOR inhibitor	CYP3A4 to five metabolites, including active metabolite sirolimus. Temsirolimus inhibits CYP3A4 and 2D6 in vitro. It is also a substrate and potential inhibitor of P-glycoprotein.	Potential for ↑ temsirolimus concentrations with CYP3A4 inhibitors including PIs and elvitegravir/cobicistat. In healthy subjects, coadministration of temsirolimus and ketoconazole 400 mg did not significantly affect temsirolimus pharmacokinetics, but sirolimus AUC ↑ 3.1-fold, and	Concomitant use of strong CYP3A4 inhibitors or inducers should be avoided. In patients who are on CYP3A4 inhibitors, temsirolimus dose reduction to 12.5 mg per week may be considered, although this is not supported by clinical data.[76] In patients on a CYP3A4

Drug	Class	Metabolism	Actual/Theoretical Interaction	Comments
			AUCsum ↑ 2.3-fold compared to temsirolimus alone. A 51% ↑ in sirolimus half-life and 69% ↓ in clearance were also observed.[155] Potential for ↓ temsirolimus concentrations with CYP3A4 inducers, including NNRTIs. When co-administered with rifampin 600 mg, temsirolimus pharmacokinetics were not significantly affected, but sirolimus Cmax ↓ 65% and AUC ↓ 56%, while AUCsum ↓ 41% compared to temsirolimus alone.[156] In healthy subjects, co-administration of single dose administration of desipramine (a CYP2D6 substrate) 50 mg and 25 mg IV temsirolumus did not alter exposure of desipramine and the combination was well tolerated.[157]	inducer, temsirolimus dose increase to 50 mg per week may be considered, based on pharmacokinetic modeling.[76] Caution should be taken when temsirolimus is co-administered with agents that are metabolized by CYP2D6.
Teniposide[78-81] (Vumon®)	Epipodophyllo-toxins	CYP3A4 (main); CYP2E1, 1A2 (minor)	Possibility of ↑ levels with 3A4 inhibitors, and ↓ levels with 3A4 inducers.	↑ etoposide levels may ↑ risk and severity of mucositis, myelosuppression and transaminitis. ↑ teniposide levels may ↑ risk and severity of myelosuppression.
Thalidomide[158] (Thalomid®, Celgene®)	Immunomodula ting agent	Undergoes non-enzymatic hydrolysis in plasma.	Cytochrome-mediated interactions are unlikely.	Use with caution with agents that may cause peripheral neuropathy, including didanosine and stavudine.
Thioguanine[159] (Lanvis®)	Antimetabolite	Undergoes methylation to 2-amino-6-methyl-thiopurine and deamination to 2-hydroxyl-6-mercaptopurine.	Cytochrome-mediated interactions are unlikely.	No detrimental pharmacokinetic interactions anticipated with cART.
Thiotepa[160-163]	Alkylating Agents	CYP3A4 > 2B6 to active metabolite (TEPA).	Induction of 3A4 may ↑ TEPA production, whereas inhibition may ↓	May need to modify cART to agents that do not inhibit 3A4

Drug	Class	Metabolism	Actual/Theoretical Interaction	Comments
			formation of pharmacologically active metabolite.	when concurrent therapy with thiotepa needed.
Topotecan[164-166] (Hycamtin®)	Camptothecins	Non-enzymatic hydrolysis to inactive species (main). CYP450 system (minor; isoenzyme unknown), glucuronidation (minor).	CYP450 induction may ↑ conversion to active metabolite; may ↓ drug efficacy if ↓ in lactone exposure > metabolite production. Inhibition of CYP450 may not be clinically relevant, since minor route of metabolism.	Induction of CYP450 and/or glucuronidation may ↓ efficacy of topotecan.
Toremifene[167]	Endocrine Therapies	CYP3A4 to active metabolites.	Induction of CYP3A4 may ↓ levels of both parent and active metabolite (N-demethyltoremifene). Inhibition of 3A4 may ↑ levels of parent drug and/or compromise efficacy.	Nevirapine and efavirenz may compromise toremifene efficacy by ↓ levels of drug. Inhibition of 3A4 may ↑ risk and severity of side effects.
Vincristine (Oncovin®), vinblastine (Velbe®) and vinorelbine[168-173] (Navelbine®)	Vinca Alkaloids	CYP3A4 Vinblastine may induce CYP3A4.[174]	Possibility of ↑ levels with 3A4 inhibitors, and ↓ levels with 3A4 inducers. Case report of a potentially life-threatening interaction between vinblastine and antiretroviral therapy in an HIV-postive patient receiving abacavir, lamivudine, zidovudine, nevirapine and **lopinavir/ritonavir** along with vinblastine for multicentric Castleman's disease. The first course of vinblastine was well tolerated at the usual dose of 6 mg/m2, in the absence of cART. cART was subsequently resumed for two following courses of vinblastine therapy, resulting in unexpected severe digestive and haematological toxicities, and moderate renal failure. cART was discontinued and vinblastine was again tolerated without toxicity. When cART was reinitiated, a decreased vinblastine	↑ vinca levels may ↑ risk and severity of autonomic and peripheral neuropathy, and myelosuppression.

Drug	Class	Metabolism	Actual/Theoretical Interaction	Comments
			dose of 2 mg/m2 was well tolerated.[175] Case report of an HIV-infected patient on abacavir, 3TC and **lopinavir/ritonavir** who was diagnosed with Burkitt lymphoma and received cyclophosphamide, doxorubicin, methotrexate and vincristine. At day 12 the patient developed paralytic ileus lasting 10 days. For the subsequent cycle of chemotherapy, vincristine was replaced with etoposide and was well tolerated. The authors speculated that an interaction between lopinavir/ritonavir and vincristine was responsible for the adverse event.[176] In a retrospective comparison of HIV-positive patients treated with cyclophosphamide, doxorubicin, vincristine and prednisolone (CHOP) for non-Hodgkin lymphoma with and without concurrent **PI-based cART**, the patients on cART had a significantly higher incidence of autonomic neuropathy (17% vs 0%, respectively, p = 0.002). This was presumed to be due to the interaction between vincristine and PIs. Severe anemia and CSF use was higher in the cART group (58% were on zidovudine/lamivudine), other toxicity was similar in the two groups. Compared to the non-cART group, the cART group had a significantly lower incidence of opportunistic infections (18% vs. 52%, p = 0.05)	

Drug	Class	Metabolism	Actual/Theoretical Interaction	Comments
			and mortality (38% vs. 85%, p = 0.001).[177] In a retrospective review of 16 HIV-positive patients on cART (n=5 on boosted PI, 2 on unboosted PI, 8 on NNRTI, 1 on raltegravir) who received vinblastine-based regimens for Hodgkin's lymphoma, PI use was independently associated with WHO grade III–IV neutropenia (OR 34.3, 95%CI 1.9–602.4; P=0.02). An inverse correlation between ritonavir dose and mean nadir neutrophil count was found.[178] Report of 3 patients who experienced severe vinblastine-associated neurotoxicity during treatment with ABVD for Hodgkin's lymphoma while on lopinavir/ritonavir-based cART. Two cases were characterized by early-onset autonomic neuropathy with severe medical ileus requiring hospitalization, and the last patient developed late-onset but severe and painful peripheral neuropathy.[179] Case report of a 55 year old male with newly diagnosed advanced HIV and large B-cell lymphoma who simultaneously began **abacavir, lamivudine and raltegravir** and CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) with intrathecal methotrexate. The patient achieved and maintained an undetectable viral load throughout 6 CHOP cycles. Two months after the	

Drug	Class	Metabolism	Actual/Theoretical Interaction	Comments
			patient completed chemotherapy, a positron emission tomography scan indicated no active lymphoma.[28]	
Vorinostat[180] (Zolinza®)	Histone deacetylase inhibitor	Major pathways of metabolism include glucuronidation and hydrolysis followed by β-oxidation; neglible involvement of CYP enzymes.	Cytochrome-mediated interactions are unlikely.	No detrimental pharmacokinetic interactions anticipated with cART.

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Interactions Between Azole Antifungals and Antiretrovirals

	Fluconazole	Itraconazole	Ketoconazole	Posaconazole	Ravuconazole	Voriconazole
Kinetic Characteristics	Substrate of CYP3A4 (11%)[1], p-glycoprotein[2]. Inhibits CYP3A4, 2C9[3], 2C19[3], UGT[4, 5]	Substrate of CYP3A4[6], p-glycoprotein[2]. Inhibits CYP3A4[6], p-glycoprotein[2].	Substrate of CYP3A4. Inhibits CYP3A4 (potent), 2C9, 1A2, p-glycoprotein[7], UGT.[4, 5]	Substrate of p-glycoprotein, UGT1A4. Inhibits CYP3A4, p-glycoprotein.	Inhibits CYP3A4. Induces CYP3A, 2B (preliminary data in animal studies).	Substrate of CYP2C19 (major), CYP3A4, CYP2C9. Inhibits CYP3A4[8], 2C9, 2C19.
CCR5 Inhibitor						
Maraviroc (metabolized by CYP3A4 and p-glycoprotein.[9])	Potential for fluconazole to ↑ maraviroc concentrations via CYP3A4 inhibition. Administration of the standard maraviroc dose (300 mg BID) should be done with caution.[9]	Potential for itraconazole to ↑ maraviroc concentrations via CYP3A4 inhibition. Reduction of maraviroc dose by 50% in the presence of protease inhibitors/potent CYP3A4 inhibitors is recommended.[9]	When given with ketoconazole 400 mg QD, maraviroc AUC ↑ 5-fold, Cmax ↑ 3.4-fold.[10] Reduction of maraviroc dose by 50% in the presence of protease inhibitors/potent CYP3A4 inhibitors is recommended.[9]	Potential for posaconazole to ↑ maraviroc concentrations via CYP3A4 inhibition. Reduction of maraviroc dose by 50% in the presence of protease inhibitors/potent CYP3A4 inhibitors is recommended.[9]		Potential for ↑ maraviroc concentrations due to CYP3A4 inhibition by voriconazole. Since voriconazole is considered a moderate CYP3A4 inhibitor, the magnitude of the interaction is likely less than with more potent inhibitors. Monitor closely for maraviroc-related toxicity if maraviroc 300mg twice daily dose is used.[9] It is unclear whether a dosage ↓of maraviroc to 150 mg twice daily is recommended as it is with other more potent CYP3A4 inhibitors (i.e. ketonazole, itraconazole, clarithromycin).[9]
Integrase Inhibitor						
Elvitegravir (metabolized by CYP3A4, UGT1A1/3, moderate 2C9 inducer) Boosted by cobicistat (3A4,	Potential for ↑ fluconazole and/or elvitegravir and cobicistat concentrations.	Potential for ↑ itraconazole and/or elvitegravir and cobicistat concentrations. Do not exceed maximum daily dose of itraconazole 200 mg[11]	In a healthy volunteer study, subjects received elvitegravir 150/ritonavir 100 mg daily alone and then with ketoconazole 200 mg BID, each for 10 days, followed by 4	Potential for ↑ posaconazole and/or elvitegravir and cobicistat concentrations.	Potential for ↑ ravuconazole and/or ↑/↓ elvitegravir and cobicistat concentrations.	Potential for ↑ voriconazole and/or elvitegravir and cobicistat concentrations.[11]

	Fluconazole	Itraconazole	Ketoconazole	Posaconazole	Ravuconazole	Voriconazole
2D6 substrate, inhibitor of 3A4, 2D6, P-glycoprotein)			more days of ketoconazole 200 mg BID alone. In the presence of ketoconazole, modest increases in elvitegravir exposures were observed: 17% ↑ Cmax, 48% ↑ AUC, 67% ↑Cmin. A maximum ketoconazole dose of 200 mg once daily is recommended when coadministering with boosted elvitegravir.[12]			
Raltegravir (metabolized by UGT1A1 and has no inhibitory or inductive potential in vitro.[13])	Interactions are unlikely based on raltegravir metabolism. Use standard doses of both drugs.	Interactions are unlikely based on raltegravir metabolism. Use standard doses of both drugs.	Interactions are unlikely based on raltegravir metabolism. Use standard doses of both drugs.	Interactions are unlikely based on raltegravir metabolism. Use standard doses of both drugs.	Interactions are unlikely based on raltegravir metabolism. Use standard doses of both drugs.	Interactions are unlikely based on raltegravir metabolism. Use standard doses of both drugs.
NNRTIs						
Delavirdine (metabolized via CYP3A4; also inhibits 3A4, as well as 2C9, 2C19.[14])	A dual inhibition interaction is possible via CYP 3A4 inhibition by delavirdine and fluconazole. No interaction noted.[15] Use standard doses of both drugs.	A dual inhibition interaction is possible via CYP 3A4 inhibition by delavirdine and itraconazole. Monitor for both delavirdine and itraconazole toxicity (i.e. hepatotoxicity).	A dual inhibition interaction is possible via CYP 3A4 inhibition by delavirdine and ketoconazole. No delavirdine dosage adjustment recommended with inhibitors of CYP3A4 or CYP2D6.[15] Monitor for both delavirdine and ketoconazole toxicity (i.e. hepatotoxicity).	Possible ↑ delavirdine concentrations due to CYP3A4 inhibition by posaconazole. Monitor for delavirdine toxicity.		
Efavirenz (In vitro is a potent inducer and inhibitor of CYP3A4. Induces 2B6.[16] Also inhibits CYP2C9, 2C19.[3])	Potential for dual induction/inhibition interaction due to efavirenz-mediated CYP3A4 induction and fluconazole-related CYP3A4 inhibition. No	In a pharmacokinetic study of healthy subjects, efavirenz 600 mg plus itraconazole 200 mg BID for 14 days led to a 39% ↓ AUC of itraconazole and 37%	In a pharmacokinetic study of 12 HIV-infected patients, the kinetics of single-dose ketoconazole 400 mg was measured alone and after 14 days of efavirenz/3TC/d4T. In	Posaconazole AUC ↓ 50% by efavirenz,[23, 24] likely via efavirenz-mediated induction of posaconazole glucuronidation. **Avoid combination**		Dual induction/inhibition interaction likely due to efavirenz-mediated CYP3A4, 2C9, 2C19 induction of voriconazole and voriconazole-related

	Fluconazole	Itraconazole	Ketoconazole	Posaconazole	Ravuconazole	Voriconazole
	interaction noted with combination.[17] Use standard doses of both drugs.	↓ AUC of its hydroxyl-metabolite; EFV exposures were not affected.[18] Case report of HIV-positive male with disseminated histoplasmosis with undetectable itraconazole concentrations and persistently elevated urinary *Histoplasma* antigen levels while on efavirenz and itraconazole 200 mg BID. Therapeutic itraconazole levels and a decrease in urinary Histoplasma antigen levels were observed after efavirenz was replaced with atazanavir/ritonavir.[19] In a retrospective cohort analysis, itraconazole levels were assessed in 10 HIV-positive patients with disseminated histoplasmosis; 4 patients were on PI therapy, 4 on NNRTIs, and 2 on both PIs and NNRTI therapy. All NNRTI patients had undetectable itraconazole concentrations, vs.1/4 PI patients. Two patients who switched from NNRTI to PI	the presence of steady-state efavirenz, ketoconazole Cmax ↓ 44% and AUC ↓ 72%.[22] Avoid concomitant use; consider alternate antiretroviral or antifungal therapy.	unless the benefits clearly outweigh the risks of antifungal failure. Consider posaconazole TDM to dose-adjust.[21]		CYP3A4 inhibition of efavirenz metabolism. 80% ↓ voriconazole AUC; 43% ↑ efavirenz AUC when given as **voriconazole 400 mg every 12 hours (day 1), then 200 mg every 12 hours and efavirenz 400 mg daily** x 9 days.[25] 55% ↓ voriconazole AUC; 1% ↑ efavirenz AUC when given as voriconazole 300 mg every 12 hours and efavirenz 300 mg daily.[26] 7% ↓ voriconazole AUC; 17% ↑ efavirenz AUC when given as **voriconazole 400 mg every 12 hours and efavirenz 300 mg daily**. These values are similar to monotherapy with either agent alone. [26] Case report in 40 year-old male with mild HCV-related cirrhosis and cryptococcal meningitis requiring a dosage adjustment of oral voriconazole titrated to **200 mg twice daily and efavirenz 300mg once daily** to yield therapeutic concentrations of both drugs and positive

	Fluconazole	Itraconazole	Ketoconazole	Posaconazole	Ravuconazole	Voriconazole
		therapy subsequently had therapeutic itraconazole levels.[20] No data using higher doses of itraconazole. **Avoid this combination if possible.** If coadministered, closely monitor itraconazole concentration and adjust dose accordingly.[21] Use of alternate antifungal treatment may be necessary or replacement of efavirenz with a non-inducing class of antiretrovirals such as protease inhibitors, integrase or CCR5 inhibitors if possible.				clinical outcomes.[27] **Contraindicated** at standard doses.[17] Recommended dosage adjustment: ↑ voriconazole maintenance dose to 400 mg twice daily (from 200mg twice daily) ↓ efavirenz dose to 300mg once daily (from 600mg once daily). Use the capsule formulation to obtain this dose since efavirenz 600mg tablets should not be broken.[17] Short-term co-administration (i.e. a few days) may not require empiric dosage adjustments. When either agent is discontinued, dosage readjustments are required.
Etravirine (substrate of CYP3A4, CYP2C9, and CYP2C19. Weak inducer of CYP3A4, weak inhibitor of CYP2C9 and a moderate inhibitor of CYP2C19. Also inhibits p-glycoprotein. No clinically relevant effect on CYP1A2 or CYP2D6.[28, 29])	In healthy volunteers, coadministration of etravirine 200 mg BID plus fluconazole 200 mg daily for 9 days resulted in 109% ↑ Cmin, 75% ↑ Cmax and 86% ↑ AUC of etravirine, while fluconazole parameters were unchanged compared to either drug administered alone. The combination was well tolerated.[30] Use	Possible ↑ etravirine concentrations and/or ↓ concentrations of itraconazole. Dose adjustments for itraconazole may be necessary.[21, 28] Consider TDM of both drugs if possible.	Possible ↑ etravirine plasma concentrations and/or ↓ plasma concentrations of ketoconazole.[28] Dose adjustments for ketoconazole may be necessary. Monitor for ketoconazole efficacy.	Possible ↑ etravirine concentrations due to CYP3A4 inhibition by posaconazole.[28] No anticipated effect on posaconazole concentrations. Monitor for etravirine-related toxicity.		In healthy volunteers, coadministration of etravirine 200 mg BID plus voriconazole 200 mg BID for 9 days resulted in 52% ↑ Cmin, 26% ↑ Cmax and 36% ↑ AUC of etravirine, and 23% ↑ Cmin and 14% ↑ AUC of voriconazole (although no ↑ was observed in carriers of CYP2C19*2 allele) compared to either drug administered

	Fluconazole	Itraconazole	Ketoconazole	Posaconazole	Ravuconazole	Voriconazole
	standard doses of both drugs. Monitor for side effects of etravirine.					alone. The combination was well tolerated.[30] Dose adjustments are not required. Monitor closely for toxicity. *****see also entry for darunavir/ritonavir plus etravirine plus voriconazole***
Nevirapine (substrate and potent inducer of CYP3A4 and 2B6 enzymes.[2])	In a study of 24 HIV+ subjects, combination of nevirapine 200 mg BID and fluconazole 200 mg daily resulted in ~100% ↑ AUC of nevirapine compared with historical data; 25% of subjects also developed elevated liver transaminases >5 times upper limit of normal. Nevirapine did not affect the pharmacokinetics of fluconazole.[31] In a retrospective study of 122 HIV-infected patients receiving nevirapine, those also taking fluconazole 200 or 400 mg daily (n=41) had NVP Cmin 76% higher compared to those not taking fluconazole. One patient on fluconazole developed clinical hepatitis.[32] In a prospective placebo-controlled trial, low-dose fluconazole (200mg 3x/weekly) resulted in a 29% ↑ AUC of nevirapine.	In a healthy volunteer, cross-over study of itraconazole 200 mg QD, nevirapine 200 mg QD or the combination (each for 7 days), itraconazole Cmax ↓ 38% and AUC ↓ 61% in the presence of nevirapine. Nevirapine parameters were not changed.[34] **Avoid combination if possible.** If coadministered, monitor itraconazole concentration and adjust dose accordingly.[21]	Ketoconazole levels sig. reduced (63% ↓ AUC, 40% ↓ Cmax,) 15-20% ↑ NVP concentrations.[35] Avoid concomitant use; consider alternate antiretroviral or antifungal therapy.	Possible ↑ nevirapine concentrations due to CYP3A4 inhibition by posaconazole. No anticipated effect on posaconazole concentrations. Monitor for nevirapine-related toxicity.		Potential ↓ voriconazole AUC and ↑ nevirapine AUC. Avoid combination if possible. If using the combination, consider TDM of both agents to dose-adjust. Monitor for nevirapine toxicity and voriconazole efficacy.

	Fluconazole	Itraconazole	Ketoconazole	Posaconazole	Ravuconazole	Voriconazole
	There was no additional risk of hepatotoxicity with the combination.[33] Use combination with caution. Monitor closely for nevirapine associated adverse effects including hepatotoxicity.					
Rilpivirine (metabolized primarily by CYP3A4, as well as CYP2C19, 1A2, 2C8/9/10 (minor). Moderate inducer of CYP2C19, slight inducer of CYP1A2, 2B6 and 3A4. A clinically relevant effect on CY3A activity is considered unlikely with phase III dose.[36] No effect on CYP2E1 activity.[37])	Fluconazole is the preferred azole option for patients taking rilpivirine. Potential for increased concentrations of rilpivirine and decreased azole concentrations with concomitant administration. No rilpivirine dose adjustment is required. Monitor for breakthrough fungal infections.[38].	Potential for increased concentrations of rilpivirine and decreased azole concentrations with concomitant administration. No rilpivirine dose adjustment is required. Monitor for breakthrough fungal infections.[21, 38]	In healthy subjects, steady-state coadministration of rilpivirine 150 mg QD plus ketoconazole 400 mg QD, rilpivirine AUC ↑ 49%, Cmax ↑ 30% and Cmin ↑ 76%, while ketoconazole AUC ↓ 24%, Cmax ↓ 15% and Cmin ↓ 66% compared to each agent alone.[39] No rilpivirine dose adjustment is required. Monitor for breakthrough fungal infections.[38]	Potential for increased concentrations of rilpivirine and decreased azole concentrations with concomitant administration. No rilpivirine dose adjustment is required. Monitor for breakthrough fungal infections.[38]		Potential for increased concentrations of rilpivirine and decreased azole concentrations with concomitant administration. No rilpivirine dose adjustment is required. Monitor for breakthrough fungal infections.[38]
PIs						
Atazanavir (Primarily metabolized by CYP3A4; also inhibits CYP3A and UGT1A1.[40] Atazanavir alone does not induce glucuronidation, while atazanavir/ ritonavir does induce glucuronidation.[41])	In healthy subjects, coadministration of atazanavir 300/rtv 100 mg QD plus fluconazole 200 mg QD for 10 days did not result in changes to pharmacokinetic parameters of either ATV, rtv or fluconazole.[42] Use standard doses of both drugs.	Potential for ↑ concentrations of PIs and/or itraconazole via CYP 3A4 inhibition by both agents. Clinical significance unclear, monitor for dose-related toxicities.	In a healthy volunteer study, coadministration of 400 mg atazanavir plus 200 mg ketoconazole daily did not result in significant changes in atazanavir concentrations.[43] Dosage adjustment not necessary with unboosted atazanavir.	Atazanavir: 268% ↑ AUC atazanavir when given as 300 mg daily x 14 days with posaconazole 400 mg twice daily x 7 days Atazanavir/RTV: 146% ↑ AUC atazanavir when given as 300 mg/100 mg daily x 14 days with posaconazole 400 mg twice daily x 7 days.[23, 24]		Paradoxical interaction displaying short-term inhibition followed by induction at steady-state. • Short-term: ↑ voriconazole concentrations initially due to RTV-related CYP3A4 inhibition, particularly in CYP2C19 poor

	Fluconazole	Itraconazole	Ketoconazole	Posaconazole	Ravuconazole	Voriconazole
				Empiric dosage adjustments are not recommended. Monitor for atazanavir-related toxicity. In cases of suspected toxicity, TDM may be useful to dose-adjust.		metabolizers. • Steady-state: ↓ voriconazole concentrations due to CYP2C19/2C9 induction. With RTV 100 mg twice daily: 39% ↓ voriconazole AUC; 14% ↓ RTV AUC[44, 45] Use of low boosting doses of RTV (i.e. 100mg twice daily) combined with any of the other PIs should be **avoided** unless the benefits outweigh the risks of antifungal failure.[40, 45] Case report of positive immunologic and virologic response in a patient with multidrug-resistant HIV on **atazanavir 300 mg QD,** raltegravir 400 mg BID and tenofovir/emtricitabine concurrently with **voriconazole 200 mg twice daily**.[46] An open-label nonrandomized study assessed the impact of atazanavir/ritonavir 300/100-mg QD on the kinetics of voriconazole in CYP2C19 extensive

	Fluconazole	Itraconazole	Ketoconazole	Posaconazole	Ravuconazole	Voriconazole
						metabolizers (EMs) and poor metabolizers (PMs). Among EMs, coadministration resulted in 33% ↓ AUC and ↓ 39% Cmin of voriconazole, and 12% ↓ AUC and 20% ↓ Cmin of atazanavir. Among PMs, coadministration resulted in ↑ voriconazole Cmax, AUC and Cmin by 4.4-, 5.6-, and 7.7-fold, while atazanavir AUC ↓ 20%, Cmax ↓ 19% and Cmin ↓ 31%. Ritonavir AUC and Cmax did not change substantially with voriconazole codosing in either study group.[47] **Avoid combination** unless the benefits outweigh the risks of antifungal failure.
Darunavir (Primarily metabolized by CYP3A4. Inhibits CYP3A4.[48])	Potential for ↑ concentrations of PIs and/or fluconazole via CYP 3A4 inhibition by both agents. Monitor for both PI and fluconazole toxicity (i.e. hepatotoxicity).	Coadministration of darunavir 400/100 mg BID and ketoconazole 200 mg BID led to 212% ↑ ketoconazole exposure and 42% ↑ darunavir exposure.[49] A similar interaction may be possible with itraconazole. Do not exceed 200 mg itraconazole per day while on darunavir/ritonavir.	Coadministration of darunavir 400 mg BID and ketoconazole 200 mg BID in healthy volunteers (n=6) led to 155% ↑ AUC, 179% ↑ Cmin of darunavir, and no significant change in ketoconazole levels. Coadministration of darunavir 400/100 mg BID and ketoconazole 200 mg BID in healthy	Possible ↑ PI concentrations due to CYP3A4 inhibition by posaconazole. Monitor for PI-related toxicity.		Paradoxical interaction displaying short-term inhibition followed by induction at steady-state. • Short-term: ↑ voriconazole concentrations initially due to RTV-related CYP3A4 inhibition, particularly in CYP2C19 poor metabolizers. • Steady-state: ↓

	Fluconazole	Itraconazole	Ketoconazole	Posaconazole	Ravuconazole	Voriconazole
			volunteers (n=17) led to 212% ↑ ketoconazole exposure and 42% ↑ darunavir exposure.[49] Do not exceed 200 mg ketoconazole per day while on darunavir/ritonavir.			voriconazole concentrations due to CYP2C19/2C9 induction. With RTV 100 mg twice daily: 39% ↓ voriconazole AUC; 14% ↓ RTV AUC[44, 45] Use of low boosting doses of RTV (i.e. 100mg twice daily) combined with any of the other PIs should be **avoided** unless the benefits outweigh the risks of antifungal failure.[45, 48] Consider voriconazole TDM or use other antifungals that do not interact significantly with RTV.
Darunavir/r plus etravirine						Case report of a patient on darunavir 900/100 mg QD, etravirine 200 mg BID, 2 NRTIs and voriconazole 400 mg BID for 6 weeks. Drug levels were obtained during voriconazole co-administration and 3 weeks after voriconazole discontinuation. Therapeutic voriconazole levels were achieved, while etravirine Ctrough ↑ 134%, ritonavir Ctrough was undetectable and

	Fluconazole	Itraconazole	Ketoconazole	Posaconazole	Ravuconazole	Voriconazole
						darunavir Ctrough was well below historical reference data. After voriconazole was discontinued, ritonavir Ctrough increased to the same range as the historical control and darunavir Ctrough increased by four-fold. The combination of etravirine/darunavir/ritonavir with voriconazole should be undertaken with caution and BID dosing of darunavir/ritonavir should be considered in this setting. Therapeutic drug monitoring should be utilized when available.[50]
Fosamprenavir (Primarily metabolized by CYP3A4. Inhibitor of CYP3A4 (similar potency as indinavir and nelfinavir)[51]; also induces CYP3A4[52].)	Potential for ↑ concentrations of PIs and/or fluconazole via CYP 3A4 inhibition by both agents. Monitor for both PI and fluconazole toxicity (i.e. hepatotoxicity).	Potential for ↑ concentrations of PIs and/or itraconazole via CYP 3A4 inhibition by both agents. Clinical significance unclear, monitor for dose-related toxicities.	32% ↑ amprenavir AUC, 44% ↑ ketoconazole AUC.[53] Clinical significance unclear. Monitor for ketoconazole-related toxicities (e.g., hepatotoxicity).	In a 3 period, cross-over, open-label multi-dose study, healthy volunteers received either posaconazole 400 mg BID, fosamprenavir 700/ritonavir 100 mg BID, or posaconazole plus fosamprenavir 700 mg BID for 10 days separated by 17 day washout periods. When posaconazole and fosamprenavir were coadministered, posaconazole AUC ↓ 23% and Cmax ↓ 21% vs. posaconazole alone, and amprenavir AUC		A dual inhibition interaction is possible via CYP 3A4 inhibition by unboosted PI and voriconazole. CYP2C19 poor metabolizers may be at increased risk of higher voriconazole concentrations due to preferential CYP3A4 inhibition. Potential for ↑ concentrations of unboosted PIs and voriconazole. Monitor for both PI and voriconazole toxicity. Consider TDM of both drugs.

	Fluconazole	Itraconazole	Ketoconazole	Posaconazole	Ravuconazole	Voriconazole
				↓ 65% and Cmax ↓ 36% compared to fosamprenavir-ritonavir. Avoid posaconazole and unboosted fosamprenavir; optimal dosing of posaconazole and boosted fosamprenavir has not yet been determined. If concomitant therapy is required, use boosted fosamprenavir and consider TDM of both fosamprenavir and posaconazole.[54]		
Indinavir (Primarily metabolized by CYP3A4. Inhibitor of CYP3A4; may also be weak inhibitor of CYP2D6.[55, 56])	No clinically significant effect on indinavir AUC.[56] Use standard doses of both drugs.	In a multiple-dose study, administration of itraconazole 200 mg BID with indinavir 600 mg every 8 hours resulted indinavir AUC similar to what would be expected from indinavir 800 mg every eight hours alone.[56] Consider reducing unboosted indinavir dose to 600 mg q8h.	Single-dose study of indinavir 400 mg and ketoconazole 400 mg: 68% ↑ indinavir AUC.[56] If using unboosted indinavir, reduce indinavir dose to 600 mg q8h.	Possible ↑ PI concentrations due to CYP3A4 inhibition by posaconazole. Monitor for PI-related toxicity.		No significant interaction with indinavir.[57] Effects with RTV-boosting unknown. Unboosted indinavir can be co-administered with voriconazole at the usual doses. Caution if using ritonavir-boosted PIs since voriconazole concentrations may ↓ (see ritonavir recommendations).
Lopinavir/ritonavir (Primarily metabolized by CYP3A4. Kaletra inhibits CYP3A4, 2D6 (to lesser extent). Induces glucuronyl transferases and possibly CYP1A2,	Clinically significant interaction not expected.[59] Use standard doses of both drugs.	In a case report of an HIV-positive patient on itraconazole 200 mg QD and lopinavir/r, itraconazole levels were significantly ↑ (similar to itraconazole 400 mg QD alone) and hydroxy-itraconazole	Single 200 mg ketoconazole dose had no significant effect on lopinavir/r concentrations.[59] Lopinavir/r AUC increased 3-fold. Ketoconazole doses >200 mg/day not recommended. Monitor for dose-	Possible ↑ PI concentrations due to CYP3A4 inhibition by posaconazole. Monitor for PI-related toxicity.		Paradoxical interaction displaying short-term inhibition followed by induction at steady-state. • Short-term: ↑ voriconazole concentrations initially due to RTV-related CYP3A4

	Fluconazole	Itraconazole	Ketoconazole	Posaconazole	Ravuconazole	Voriconazole
CYP2C19 and 2C9.[58])		levels were significantly ↓. Lopinavir/r levels not affected.[60] Similarly, in another case report of an HIV-positive patient with disseminated histoplasmosis infection, lopinavir concentrations remained stable after initiation of itraconazole 200 mg daily, and therapeutic antifungal levels (itraconazole + hydroxy-itraconazole) were achieved along with clinical response.[61] Itraconazole doses >200 mg/day not recommended.[59]	related toxicities.			inhibition, particularly in CYP2C19 poor metabolizers. • Steady-state: ↓ voriconazole concentrations due to CYP2C19/2C9 induction. With RTV 100 mg twice daily: 39% ↓ voriconazole AUC; 14% ↓ RTV AUC[44, 45] Use of low boosting doses of RTV (i.e. 100mg twice daily) combined with any of the other PIs should be **avoided** unless the benefits outweigh the risks of antifungal failure.[45, 59] Consider voriconazole TDM or use other antifungals that do not interact significantly with RTV.
Nelfinavir (Metabolized by CYP3A4 and CYP2C19. Inhibitor of CYP3A4.[62, 63] Induces CYP2B6, 2C8 and 2C9.[64])	Potential for ↑ concentrations of PIs and/or fluconazole via CYP 3A4 inhibition by both agents. Nelfinavir may be administered with azoles including fluconazole, itraconazole and ketoconazole without dosage adjustment.[65]	Potential for ↑ concentrations of PIs and/or itraconazole via CYP 3A4 inhibition by both agents. Clinical significance unclear, monitor for dose-related toxicities.	35% ↑ NFV AUC.[66] Use standard doses of both drugs.	Possible ↑ PI concentrations due to CYP3A4 inhibition by posaconazole. Monitor for PI-related toxicity.	Ravuconazole may exhibit CYP 3A4 inhibitory effects on nelfinavir after a single dose and induction effects of CYP3A and 2B after multiple dosing. 32% ↑ AUC nelfinavir (day 2) and 16% ↓AUC nelfinavir (day 29) after ravuconazole 400 mg daily and nelfinavir 750 mg given as two single doses.[67] Use standard	A dual inhibition interaction is possible via CYP 3A4 inhibition by unboosted PI and voriconazole. CYP2C19 poor metabolizers may be at increased risk of higher voriconazole concentrations due to preferential CYP3A4 inhibition. Potential for ↑ concentrations of unboosted PIs and voriconazole. Monitor for both PI and

	Fluconazole	Itraconazole	Ketoconazole	Posaconazole	Ravuconazole	Voriconazole
					doses of both drugs.	voriconazole toxicity. Consider TDM of both drugs.
Ritonavir (Potent inhibitor of CYP enzymes in following order: 3A>2D6>2C9, 2C19>>2A6, 2E1. Induces glucuronyl transferases, CYP1A2, CYP2B6, CYP2C9 and CYP2C19.[5-7])	12% ↑ RTV AUC. Clinical significance unclear.[68] Use standard doses of both drugs.	In a case report, itraconazole blood levels in a patient taking ritonavir and saquinavir showed more than five-fold ↑ increase half-life, and therapeutic levels of itraconazole were still detectable even 27 days after discontinuation of the drug.[69] Use combination with caution and monitor for itraconazole-related toxicities (e.g., hepatotoxicity).	Coadministration of ketoconazole 200 mg daily ritonavir 500 mg BID (n=12) resulted in an 18% ↑ ritonavir AUC, and 3.4 fold ↑ ketoconazole AUC and 55% ↑ Cmax.[68] Ketoconazole doses >200 mg/day not recommended. Monitor for dose-related toxicities.	80% ↑ AUC RTV with RTV 100mg daily x 14 days and posaconazole 400mg twice daily x 7 days.[24] RTV 600mg twice daily had no significant effect on posaconazole concentrations.[70] When ritonavir is used in lower boosting doses of 100mg twice daily, empiric dosage adjustments are likely not required. However if used in larger doses, a ↓ in ritonavir dose may be warranted. Monitor for ritonavir-related toxicity. In cases of suspected toxicity, TDM may be useful to dose-adjust.		Paradoxical interaction displaying short-term inhibition followed by induction at steady-state. • Short-term: ↑ voriconazole concentrations initially due to RTV-related CYP3A4 inhibition, particularly in CYP2C19 poor metabolizers. • Steady-state: ↓ voriconazole concentrations due to CYP2C19/2C9 induction. RTV 100 mg twice daily: 39% ↓ voriconazole AUC; 14% ↓ RTV AUC[44, 45] RTV 300 mg twice daily: 4.5- fold ↑ voriconazole AUC; 43% ↓ voriconazole clearance. More pronounced effect in CYP2C19 poor metabolizers 9- fold ↑ voriconazole AUC; 86% ↓ voriconazole clearance.[71] RTV 400 mg twice daily: 82% ↓ voriconazole AUC[44] Use of high-dose ritonavir (i.e. 400-

	Fluconazole	Itraconazole	Ketoconazole	Posaconazole	Ravuconazole	Voriconazole
						600mg twice daily) with voriconazole is **contraindicated** due to significant reduction in voriconazole plasma concentrations.[45, 68] Use of low boosting doses of RTV (i.e. 100mg twice daily) combined with any of the other PIs should be **avoided** unless the benefits outweigh the risks of antifungal failure.[40, 45, 48, 59] Consider voriconazole TDM or use other antifungals that do not interact significantly with RTV.
Saquinavir (Primarily metabolized by CYP3A4 and P-gp. Weak inhibitor of CYP3A4 and P-gp.[55, 72])	Potential for ↑ concentrations of PIs and/or fluconazole via CYP 3A4 inhibition by both agents. Monitor for both PI and fluconazole toxicity (i.e. hepatotoxicity).	5-fold increase in saquinavir exposure when hard-gel capsules were coadministered with itraconazole 200 mg.[73] In a prospective randomized study in 17 HIV-infected subjects, saquinavir-sgc 800 or 1200 mg BID plus itraconazole 100 mg daily resulted in SQV concentrations equivalent to SQV-sgc 1400 mg BID alone.[74] Clinical significance unclear. Consider TDM of saquinavir.	Saquinavir 1200 mg TID plus ketoconazole 400 mg QD: 1.5-fold ↑ saquinavir AUC. Dosage adjustment not necessary.[72] Multiple dose study of SQV/r 1000/100mg BID and ketoconazole 200mg daily in healthy subjects resulted in ketoconazole ↑ AUC 168%, ↑ Cmax 45%. No substantial change in saquinavir and ritonavir exposures [75] Dosage adjustment not necessary with unboosted saquinavir. If using boosted	Possible ↑ PI concentrations due to CYP3A4 inhibition by posaconazole. Monitor for PI-related toxicity.		

	Fluconazole	Itraconazole	Ketoconazole	Posaconazole	Ravuconazole	Voriconazole
			saquinavir, ketoconazole doses > 200 mg/day not recommended.			
Tipranavir (Substrate of CYP3A4 and P-gp. Inducer of CYP3A4, P-gp, glucuronyl transferase, slight inducer of CYP2C9, moderate inducer of CYP1A2, and potent inhibitor of CYP2D6.[76] When co-administered with ritonavir, net effect is CYP3A inhibition.[77])	In healthy volunteers, coadministration of TPV 500/rtv 200 mg BID with fluconazole 100 mg QD resulted in 56%↑ AUC, 46% ↑ Cmax, 104% ↑ C12 of TPV; fluconazole PK parameters not significantly changed.[78] Fluconazole doses >200 mg/day are not recommended.[77]	Potential for ↑ concentrations of tipranavir and/or itraconazole via CYP 3A4 inhibition by both agents. Use combination with caution and monitor for dose-related toxicities (e.g., hepatotoxicity). Do not exceed itraconazole 200 mg daily.	Potential for increased ketoconazole and/or tipranavir concentrations. Use combination with caution and monitor for dose-related toxicities (e.g., hepatotoxicity). Do not exceed ketoconazole 200 mg daily.	Possible ↑ PI concentrations due to CYP3A4 inhibition by posaconazole. Monitor for PI-related toxicity.		Net effect difficult to predict given multiple CYP isoenzymes involved.[77] Potential ↑ or ↓ of one or both agents. Caution or avoid combination until further data are available.

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Drug Interactions with Hepatitis C Protease Inhibitors

	Boceprevir (Victrelis®, BOC, SCH 503034) Merck	**Telaprevir (Incivek®, TVR, VX-950) Vertex Pharmaceuticals**
Adult Dose	800 mg po q8h with food (supplied as 200 mg capsules)	750 mg po q8h with food (supplied as 375 mg tablets)
Impact of Food	Boceprevir AUC ↑ 60% when administered with a meal vs on an empty stomach. The bioavailability of boceprevir was similar regardless of meal type (e.g., high-fat vs. low-fat) or whether taken 5 minutes prior to eating, during a meal, or immediately following completion of the meal. Therefore, boceprevir may be taken without regard to either meal type or timing.[1]	Compared to a regular breakfast, telaprevir AUC ↓ by 73%, 39% and 26% after administration under fasting conditions, low-calorie/low fat breakfast, and low-calorie/high protein breakfast, respectively. Telaprevir AUC ↑ 20% with a high-fat breakfast. Telaprevir should be taken with food or a snack that contains at least 20 g fat.[2]
Kinetic Characteristics	Boceprevir undergoes biotransformation by CYP3A4, CYP3A5 and aldoketoreductases.[3] Boceprevir appears to be a strong, reversible inhibitor of CYP3A4 and p-glycoprotein.[4] In a healthy volunteer study, boceprevir does not appear to exert significant P-gp inhibition at clinically relevant concentrations.[5]	Substrate and strong inhibitor of CYP3A4 and p-glycoprotein.[6]
Effect of hepatic impairment		HCV-negative volunteers with no, mild or moderate hepatic impairment received telaprevir 750 mg as a single dose, then 750 mg q8h for 5 days. All subjects with hepatic impairment were cirrhotics. Mild hepatic impairment did not have a clinically significant effect on telaprevir AUC and Cmax, while moderate hepatic impairment resulted in 49% ↓ Cmax and 46% ↓ AUC of telaprevir compared to controls. A positive correlation between albumin levels and telaprevir exposure was observed.[7]
Other	In a population pharmacokinetic analysis, no significant covariate effects on boceprevir pharmacokinetic parameters were identified for age, body weight, BMI, Black race, Asian race, renal function and hepatic function. A modest effect of gender (23% ↑ AUC and 22% ↑ Cmax in females) and HCV status (15-20% ↓ Cmax) was observed, but not anticipated to be clinically meaningful.[8]	
1) ANTIRETROVIRALS		
Atazanavir/ ritonavir	In healthy volunteers, coadministration of boceprevir and atazanavir/ritonavir resulted in 49% ↓ Ctrough, 35% ↓ AUC and 25% ↓ Cmax of atazanavir and ↓ 34% ritonavir AUC; boceprevir exposures were not altered.[9]	In an open-label, randomized, cross-over study, 20 HIV/HCV-negative volunteers received 2 treatments: telaprevir 750 mg every 8 hours for 10 days followed by a washout and ATV/r 300/100 mg once daily for 20 days with co-administration of

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	Coadministration of boceprevir and ritonavir-boosted protease inhibitors is not recommended.[10] The European Medicine Agency stated that coadministration of boceprevir with ritonavir-boosted atazanavir may be considered on a case-by-case basis if deemed necessary in patients with suppressed HIV viral loads and with an HIV strain without any suspected resistance to the HIV regimen. Increased clinical and laboratory monitoring is warranted in such cases.[11]	telaprevir 750 mg every 8 hours from day 11 onwards, or *vice versa*. All compounds were taken with food. With coadministration, telaprevir AUC ↓ 20% and Cmin ↓ 15%, while atazanavir AUC ↑ 17% and Cmin ↑ 85%.[12] In HIV/HCV co-infected subjects participating in a phase 2 randomized study of telaprevir vs. placebo plus pegylated-interferon plus ribavirin, the kinetics of telaprevir were compared in patients on stable ATV/r therapy to patients not receiving concomitant antiretroviral therapy. In patients receiving concomitant ATV/r, telaprevir Cavg was 9% ↑ compared to patients not receiving concomitant antiretroviral therapy. Median atazanavir concentrations were 16% higher during telaprevir treatment vs. before HCV treatment. Dose adjustment is not required when atazanavir/ritonavir is administered with telaprevir.[13]
Darunavir/ ritonavir	In healthy volunteers, coadministration of boceprevir and darunavir/ritonavir resulted in 59% ↓ Ctrough, 44% ↓ AUC and ↓ 36% Cmax of darunavir and 27% ↓ ritonavir AUC, while boceprevir exposure was ↓ by 32%.[9] Coadministration of boceprevir and ritonavir-boosted protease inhibitors is not recommended.[10]	In an open-label, randomized, cross-over study, 20 HIV/HCV-negative volunteers received 2 treatments: telaprevir 750 mg every 8 hours for 10 days, followed by a washout and DRV/r 600/100 mg twice daily for 20 days with co-administration of telaprevir 750 mg every 8 hours from day 11 onwards, or *vice versa*. All compounds were taken with food. With coadministration, telaprevir AUC ↓ 35% and Cmin ↓ 32%, while darunavir AUC ↓ 40% and Cmin ↓ 42%.[12] Darunavir/ritonavir and telaprevir should not be co-administered.[6]
Efavirenz	In healthy subjects, there was a slight reduction in BOC $AUC_{(0-8h)}$ and C_{max} (19% and 8%, respectively), and a 44% decrease in BOC C_{min} when co-administered with efavirenz. BOC slightly increased EFV $AUC_{(0-24h)}$ and C_{max} (20% and 11%, respectively).[4] **Avoid combination**.[1]	In healthy volunteers, multiple-dose administration of efavirenz 600 mg daily and telaprevir 750 mg q8h resulted in 9% ↓ Cmax, 47% ↓ Cmin and 26% ↓ AUC of telaprevir.[14] In an open-label study, 20 HIV/HCV-negative volunteers started telaprevir 750 mg every 8 hours for 7 days followed by EFV/tenofovir disoproxil fumarate (TDF) 600/300 mg once daily for 7 days after a washout. Subsequently, volunteers received telaprevir 1125 mg every 8 hours and EFV/TDF 600/300 mg once daily for 7 days

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		or telaprevir 1500 mg every 12 hours and EFV/TDF 600/300 mg once daily for 7 days in a randomized order without a washout. Telaprevir was taken with food and EFV/TDF was taken on an empty stomach in the morning. With TVR 1125 mg q8h plus efavirenz/TDF, telaprevir AUC ↓ 18%, Cmin ↓ 25%, EFV AUC ↓ 18%, Cmin ↓ 10%, and tenofovir AUC ↑ 10% and Cmin ↑ 17%. With TVR 1500 mg q12h plus EFV/TDF, telaprevir AUC ↓ 20%, Cmin ↓ 48%, EFV AUC ↓ 15%, Cmin ↓ 11%, and tenofovir AUC ↑ 10% and Cmin ↑ 6%.[12] In HIV/HCV co-infected subjects participating in a phase 2 randomized study of telaprevir vs. placebo plus pegylated-interferon plus ribavirin, the kinetics of telaprevir 1125 mg q8h were compared in patients on stable efavirenz therapy to patients on telaprevir 750 mg q8h not receiving concomitant antiretroviral therapy. In patients receiving efavirenz, telaprevir Cavg was 4% ↓ compared to patients not receiving concomitant antiretroviral therapy. Median efavirenz concentrations were 6% lower during telaprevir treatment vs. before HCV treatment. A higher dose of telaprevir (1125 mg every 8 hours) given with efavirenz provides similar telaprevir exposures as seen in the absence of efavirenz.[13]
Elvitegravir/ cobicistat	Potential for concentrations of DAA and/or elvitegravir/cobicistat to be affected; avoid coadministration until more data are available.	Potential for concentrations of DAA and/or elvitegravir/cobicistat to be affected; avoid coadministration until more data are available.
Etravirine	In healthy volunteers, coadministration of boceprevir 800 mg q8h with etravirine 200 mg BID for 11-14 days resulted in ↓ 23% AUC, ↓ 24% Cmax and ↓29% Cmin of etravirine and ↑10% AUC and Cmax and ↓ 12% Cmin of boceprevir compared to either drug administered alone. Impact on boceprevir concentrations not considered clinically relevant; impact on etravirine concentrations could be clinically significant.[15]	In healthy volunteers, coadministration of telaprevir 750 mg TID with etravirine 200 mg BID for 11 days resulted in ↓ 6% AUC, ↓ 7% Cmax and ↓3% Cmin of etravirine and ↓ 16% AUC, ↓ 10% Cmax and ↓ 25% Cmin of telaprevir compared to either drug administered alone. These changes are not considered clinically relevant, combination may be given without dose adjustment.[16]
Fosamprenavir/ ritonavir		In an open-label, randomized, cross-over study, 20 HIV/HCV-negative volunteers received 2 treatments: telaprevir 750 mg every 8 hours for 10 days, followed by a washout and fosamprenavir/r 700/100 mg

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		twice daily for 20 days with co-administration of telaprevir 750 mg every 8 hours from day 11 onwards, or *vice versa*. All compounds were taken with food. With coadministration, telaprevir AUC ↓ 32% and Cmin ↓ 30%, while amprenavir AUC ↓ 47% and Cmin ↓ 56%.[12] Fosamprenavir/ritonavir and telaprevir should not be co-administered.[6]
Lopinavir/ritonavir	In healthy volunteers, coadministration of boceprevir and lopinavir/ritonavir resulted in 43% ↓ Ctrough, 34% ↓ AUC and ↓ 30% Cmax of lopinavir and 22% ↓ ritonavir AUC, while boceprevir exposure was ↓ by 45%.[9] Coadministration of boceprevir and ritonavir-boosted protease inhibitors is not recommended.[10]	In an open-label, randomized, cross-over study, 20 HIV/HCV-negative volunteers received 2 treatments: telaprevir 750 mg every 8 hours for 10 days, followed by a washout and lopinavir/r 400/100 mg twice daily for 20 days with co-administration of telaprevir 750 mg every 8 hours from day 11 onwards, or *vice versa*. All compounds were taken with food. With coadministration, telaprevir AUC ↓ 54% and Cmin ↓ 52%, while lopinavir AUC ↑ 6% and Cmin ↑ 14%.[12] Lopinavir/ritonavir and telaprevir should not be co-administered.[6]
Raltegravir	In an open-label, randomized, cross-over study, 24 healthy volunteers, received boceprevir 800 mg TID for 10 days plus single dose raltegravir 400 mg on day 10 followed by a wash-out period and single-dose raltegravir 400 mg on day 38, or the same medications in reverse order. Raltegravir exposures were not altered in the presence of boceprevir. The combination may be used without dosage adjustment.[17]	In an open-label cross-over study in 20 HIV/HCV-negative healthy volunteers, co-administration of raltegravir 400 mg BID and telaprevir 750 mg q8h for 6 days with food did not affect telaprevir pharmacokinetics, while raltegravir exposures were increased (Cmin ↑ 78%, Cmax ↑ 26% and AUC ↑ 31%) possibly due to inhibition of intestinal P-gp by telaprevir. Exposure to raltegravir-glucuronide was similarly increased. This effect was not considered to be clinically relevant.[18] No dose adjustment is needed for telaprevir when given with raltegravir.
Rilpivirine		In healthy volunteers, coadministration of telaprevir 750 mg TID with rilpivirine 25 mg daily for 11 days resulted in ↑ 78% AUC, ↑ 49% Cmax and ↑ 93% Cmin of rilpivirine and ↓ 8% AUC, ↓ 5% Cmax and ↓ 13% Cmin of telaprevir compared to either drug administered alone. These changes are not considered clinically relevant, combination may be given without dose adjustment.[16] May wish to avoid using combination in patients at increased risk for Torsade de Pointes, or who are on other drugs that may ↑ rilpivirine levels or that are known to cause

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		QTc prolongation.
Ritonavir	In human liver microsomes, the metabolism of telaprevir and boceprevir was substantially inhibited in the presence of low concentrations of ritonavir. With co-dosing of ritonavir in rats, the plasma exposure of both HCV agents was increased by more than 15-fold, and plasma concentrations 8 hours after dosing were increased by > 50-fold.[19] In healthy subjects, ritonavir had minimal effects on steady-state BOC exposure. RTV 100 mg daily plus BOC three times daily resulted in BOC AUC ↓ 19% and Cmax ↓ 27%, while ritonavir 100mg BID plus BOC twice daily resulted in decreased BOC AUC_t by 18% and Cmax ↓ 34%.[4]	In human liver microsomes, the metabolism of telaprevir and boceprevir was substantially inhibited in the presence of low concentrations of ritonavir. With co-dosing of ritonavir in rats, the plasma exposure of both HCV agents was increased by more than 15-fold, and plasma concentrations 8 hours after dosing were increased by > 50-fold. A human pharmacokinetic model of telaprevir co-administered with low-dose ritonavir suggested that improved efficacy and/or dosing convenience may be feasible by pharmacokinetic enhancement with ritonavir.[19] HIV-negative subjects received telaprevir 750 mg q8h alone, or 250 mg or 750 mg BID with ritonavir 100 mg BID. Doses were given with food for 14 days. Ritonavir did not exert a significant boosting effect on telaprevir exposures: when compared with TVR 750 mg q8h given alone (Group C), TVR PK parameters on Day 14 were 59% to 75% lower when TVR 250 mg q12h was co-administered with RTV 100 mg q12h (Group A) and 15% to 32% lower when TVR 750 mg q12h was co-administered with RTV 100 mg q12h (Group B). Of note, RTV exposures were higher when co-administered with TVR 750 mg q12h (Group B), compared with 250 q12h (Group A), suggesting that CYP3A inhibition by TVR was dose-dependent.[20]
Tenofovir	In healthy subjects, there were no clinically relevant changes in BOC exposure when co-administered with tenofovir. BOC also had no notable effect on tenofovir AUC or renal clearance, but increased tenofovir C_{max} by 32%. No BOC dosage adjustment is needed with co-administration tenofovir.[4]	In a randomized, open-label study, healthy volunteers received tenofovir 300 mg daily, telaprevir 750 mg q8h, or both drugs, each for 7 days. In the presence of telaprevir, tenofovir AUC_{24h} was increased by 30% while telaprevir kinetics were not affected.[21] In an open-label study, 20 HIV/HCV-negative volunteers started telaprevir 750 mg every 8 hours for 7 days followed by EFV/tenofovir disoproxil fumarate (TDF) 600/300 mg once daily for 7 days after a washout. Subsequently, volunteers received telaprevir 1125 mg every 8 hours and EFV/TDF 600/300 mg once daily for 7 days or telaprevir 1500 mg every 12 hours and EFV/TDF 600/300 mg once daily for 7 days in a randomized order without a washout. Telaprevir was taken with food and

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		EFV/TDF was taken on an empty stomach in the morning. With TVR 1125 mg q8h plus efavirenz/TDF/FTC, telaprevir AUC ↓ 18%, Cmin ↓ 25%, EFV AUC ↓ 18%, Cmin ↓ 10%, and tenofovir AUC ↑ 10% and Cmin ↑ 17%. With TVR 1500 mg q8h plus EFV/TDF/FTC, telaprevir AUC ↓ 20%, Cmin ↓ 48%, EFV AUC ↓ 15%, Cmin ↓ 11%, and tenofovir AUC ↑ 10% and Cmin ↑ 6%.[12]
2) OTHER MEDICATIONS		
Alprazolam	No interaction studies have been done with intravenous benzodiazepines. Close clinical monitoring for respiratory depression and/or prolonged sedation should be exercised during co-administration of boceprevir with **intravenous benzodiazepines (alprazolam, midazolam, triazolam).** Dose adjustment of the benzodiazepine should be considered.[1]	In healthy subjects who received a single dose of alprazolam 0.5 mg alone and in combination with multiple doses of telaprevir 750 mg po q8h, alprazolam AUC ↑ 35% and the mean t1/2 increased from 13.4 hours to 18.7 hours in the presence of telaprevir.[22]
Amlodipine	Combination not studied. Potential for ↑ amlodipine concentrations in the presence of boceprevir. Use combination with caution and monitor for dose-related amlodipine toxicity.	In healthy subjects, the kinetics of single dose amlodipine 5 mg/atorvastatin 20 mg (coformulated) were assessed alone and with steady-state telaprevir 750 mg q8h. In the presence of telaprevir, amlodipine Cmax ↑ 27% and AUC ↑ 179%. Monitor for dose-related amlodipine toxicity when coadministering with telaprevir.[23]
Buprenorphine	In HCV-negative volunteers on stable, maintenance doses (8/2 mg to 24/6 mg QD) of buprenorphine/naloxone, coadministration of boceprevir 800 mg q8h for 6 days did not have a clinically significant impact on the pharmacokinetics of buprenorphine (AUC ↑ 20%, Cmax ↑ 18%) or naloxone (AUC ↑ 30%, Cmax ↑ 9%). Boceprevir exposures in the presence of buprenorphine/naloxone were similar to historical controls. Dose adjustment is likely not necessary when boceprevir is co-administered with buprenorphine/naloxone.[24]	In HCV-negative volunteers on stable, maintenance doses of buprenorphine/naloxone, coadministration of telaprevir 750 mg q8h for 7 days did not have a clinically significant impact on the pharmacokinetics or pharmacodynamic effects of buprenorphine. Telaprevir exposure was consistent with historical control when co-administered with buprenorphine/naloxone. Dose adjustment is not necessary when telaprevir is co-administered with buprenorphine/naloxone.[25]
Clarithromycin	In healthy subjects, clarithromycin had minimal effects on steady-state BOC exposure. Clarithromycin (in the presence of diflunisal) increased BOC AUC by 21% and Cmax by 36%.[4]	
Corticosteroids (oral/inhaled, injectable or topical)	<u>Inhaled/nasal fluticasone and budesonide</u>: Potential for ↑ corticosteroid concentrations resulting in significantly reduced serum cortisol concentrations. Avoid co-	<u>Inhaled/nasal fluticasone and budesonide</u>: Potential for ↑ corticosteroid concentrations resulting in significantly reduced serum cortisol concentrations. Co-administration of

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e.g., betamethasone, budesonide, dexamethasone, fluticasone, prednisone, triamcinolone	administration if possible, particularly for extended durations.[1] Inhaled beclomethasone or ciclesonide, or intranasal beclomethasone or triamcinolone may be safer alternatives, but caution is still warranted. Use lowest possible corticosteroid dose and monitor closely for systemic corticosteroid side effects.[26] Systemic dexamethasone: Potential for ↓ boceprevir concentrations via CYP3A4 induction by dexamethasone. Avoid combination if possible, use with caution if necessary.[1]	fluticasone or budesonide and telaprevir is not recommended unless the potential benefit to the patient outweighs the risk of systemic corticosteroid side effects.[6] Inhaled beclomethasone or ciclesonide, or intranasal beclomethasone or triamcinolone may be safer alternatives, but caution is still warranted. Use lowest possible corticosteroid dose and monitor closely for systemic corticosteroid side effects.[26] Systemic dexamethasone: Potential for ↓ telaprevir concentrations via CYP3A4 induction by dexamethasone. Use combination with caution or consider altenate agents.[6]
Cyclosporine	In healthy volunteers, the kinetics of single-dose cyclosporine 100 mg was assessed alone and in the presence of single dose BOC 800 mg and steady-state BOC 800 mg TID. In the presence of BOC, cyclosporine AUC ↑ 2.7-fold and Cmax ↑ 2-fold; BOC pharmacokinetics were not affected by cyclosporine. Co-administration of cyclosporine with boceprevir may require dose adjustment of CsA and close monitoring of cyclosporine blood levels as well as frequent assessments of renal function and CsA-related side effects.[27]	In healthy subjects, the pharmacokinetics of single dose cyclosporine was assessed alone at 100 mg and in the presence of steady-state telaprevir 750 mg q8h at a dose of 10 mg on day 1 and day 8. When coadministered with telaprevir, cyclosporine exposure ↑ 4.6-fold and the elimination t1/2 increased from 12 to 42 hours; the effect of first dose of telaprevir on cyclosporine kinetics was similar to the effect of steady-state telaprevir. Telaprevir kinetics were similar to historical data, suggesting no major effect of cyclosporine on telaprevir.[28] In a case series, patients with recurrent HCV post-liver transplant with null response (<2 log ↓) to pegylated-interferon/ribavirin (PR) for ≥12 weeks received a 4 week lead-in with PEG-IFN α2b with ribavirin 600-1000 mg/d followed by addition of telaprevir 750 mg q8h. Patients on tacrolimus were converted to cyclosporine prior to starting telaprevir. On the first day of telaprevir therapy, the cyclosporine dose was decreased from an average of 200 mg to 25 mg per day, with a target CsA trough of 100 ng/mL. To date, 4 subjects have completed 12 weeks of telaprevir therapy. The average CsA dose at week 16 was 68 mg. All patients required ↓ in ribavirin dose; no episodes of renal toxicity secondary to ↑ CsA levels or rejection following the end of telaprevir therapy were observed.[29]
Digoxin	In an open-label, randomized crossover study, healthy volunteers received single	In an open-label study, healthy subjects received single doses of IV midazolam 0.5

	Boceprevir (Victrelis®, BOC, SCH 503034) Merck	Telaprevir (Incivek®, TVR, VX-950) Vertex Pharmaceuticals
	dose digoxin 0.25 mg alone or in combination with multiple-dose boceprevir 800 mg TID. In the presence of boceprevir, digoxin AUC was ↑ 19% and Cmax ↑ 18%, while terminal t½ was unchanged. These results suggest that dosage adjustment of digoxin is not necessary with concomitant boceprevir therapy, and that boceprevir does not appear to exert significant P-gp inhibition at clinically relevant concentrations.[5] Patients receiving treatment with both boceprevir and digoxin should be monitored appropriately.[1]	mg, and oral midazolam 2 mg with oral digoxin 0.5 mg administered sequentially alone and in combination with multiple-dose telaprevir 750 mg q8h. In the presence of telaprevir, digoxin Cmax ↑ 50% and AUC ↑ 85%, while renal clearance was not changed.[30] Initiate digoxin at the lowest dose, and monitor serum digoxin concentrations to titrate to desired clinical effect.[6]
Escitalopram	In healthy volunteers, the kinetics of single dose escitalopram 10 mg were not altered to a clinically significant manner in the presence of multiple dose boceprevir 800 mg TID. The pharmacokinetics of boceprevir were similar with and without coadministration of escitalopram. No dosage adjustment is expected to be required with coadministration of this combination.[31]	In healthy volunteers, coadministration of escitalopram 10 mg daily with telaprevir 750 mg q8h for 7 days resulted in 35% ↓ escitalopram AUC, while telaprevir exposures were not affected. May need to titrate escitalopram dose according to clinical response.[32]
HmgCoA reductase inhibitors (statins): atorvastatin lovastatin pravastatin rosuvastatin simvastatin	In healthy volunteers, the kinetics of single dose **atorvastatin 40 mg** in the presence of steady-state BOC 800 mg TID were significantly increased (atorvastatin AUC ↑ 130% and Cmax ↑ 170%) compared to administration alone. BOC kinetics were not significantly affected by atorvastatin coadministration. A lower maintenance dose of atorvastatin may be warranted with concomitant BOC therapy; additional clinical monitoring for symptoms of statin toxicity is recommended if atorvastatin doses of greater than 40 mg daily are used.[33] In healthy volunteers, the kinetics of single dose **pravastatin 40 mg** in the presence of steady-state BOC 800 mg TID were increased (pravastatin AUC ↑ 60% and Cmax ↑ 50%) compared to administration alone. BOC kinetics were not significantly affected by pravastatin coadministration. This slight increase may reflect potential inhibition of OATP by BOC, since pravastatin is not metabolized to a significant extent by CYP450 and is a substrate of OATP1B1 and OATP2B1, but	In healthy subjects, the kinetics of single dose amlodipine 5 mg/atorvastatin 20 mg (coformulated) were assessed alone and with steady-state telaprevir 750 mg q8h. In the presence of telaprevir, atorvastatin Cmax ↑ 10.6-fold and AUC ↑ 7.88-fold.[23] **Atorvastatin, lovastatin and simvastatin are contraindicated with telaprevir**.[34]

	Boceprevir (Victrelis®, BOC, SCH 503034) Merck	Telaprevir (Incivek®, TVR, VX-950) Vertex Pharmaceuticals
	not of P-gp. It is anticipated that pravastatin treatment can be initiated at the recommended dose when co-administered with BOC, with close clinical monitoring.[33] **Lovastatin and simvastatin are contraindicated with boceprevir**.[34]	
Ketoconazole	In healthy subjects, ketoconazole (KCZ) increased BOC AUC ↑131%, Cmax ↑ 41%.[4] When coadministration is required, doses of ketoconazole and itraconazole should not exceed 200 mg/day.[1]	In healthy subjects, the effect of single dose ketoconazole 400 mg on the kinetics of single dose (750 mg) or multiple dose (750 mg q8h) telaprevir was studied. When single doses of both drugs were coadministered, telaprevir Cmax ↑ 24% and AUC ↑ 62%. However, after multiple doses of telaprevir, there was no discernible effect of ketoconazole on telaprevir exposure. High (>200 mg per day) doses of ketoconazole or itraconazole are not recommended with telaprevir.[14]
Methadone	In HCV-negative volunteers on stable, maintenance doses (20-150 mg QD) of methadone, boceprevir 800 mg q8h was coadministered for 6 days. In the presence of boceprevir, exposures of R-methadone were decreased (AUC ↓ 16%, Cmax ↓ 10%) and S-methadone were decreased (AUC ↓ 22%, Cmax ↓ 17%). These changes did not result in clinically significant effects including withdrawal. Boceprevir exposures in the presence of methadone were similar to historical controls. Dose adjustment is likely not necessary when boceprevir is co-administered with methadone.[24] Clinical monitoring is recommended, with dose adjustments of methadone if necessary during concomitant treatment with boceprevir.[1]	In HCV-negative volunteers on stable methadone maintenance therapy (median methadone dose 85 mg, range 40-120 mg/day), telaprevir 750 mg q8h was co-administered for 7 days. In the presence of telaprevir, R-methadone Cmin ↓ 31%, Cmax ↓ 21% and AUC ↓ 21%. The AUC ratio of S-/R-methadone was comparable before and during coadministration of telaprevir. The median unbound fraction of R-methadone ↑ from 7.92% to 9.98% during coadministration with telaprevir, but the median unbound Cmin of R-methadone was similar before and during telaprevir coadministration. A priori methadone dose adjustments are not required when initiating telaprevir, but close monitoring is recommended, with dose adjustments if necessary.[35]
Midazolam	In healthy subjects, coadministration of oral midazolam plus steady-state BOC resulted in increased MDZ exposure: 177% ↑ C_{max} and 430% ↑ $AUC_{0\text{-}24\ h}$.[4] **Boceprevir is contraindicated with oral midazolam**.[1] No interaction studies have been done with intravenous benzodiazepines. Close clinical monitoring for respiratory depression and/or prolonged sedation should be exercised during co-administration of	In an open-label study, healthy subjects received single doses of IV midazolam 0.5 mg, and oral midazolam 2 mg with oral digoxin 0.5 mg administered sequentially alone and in combination with multiple-dose telaprevir 750 mg q8h. In the presence of telaprevir, midazolam IV AUC ↑ 3.4 fold, and midazolam oral Cmax ↑ 2.86-fold and AUC ↑ 8.96-fold. In the presence of telaprevir, digoxin Cmax ↑ 50% and AUC ↑ 85%, while renal clearance was not changed.[30] **Telaprevir is contraindicated with oral**

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	boceprevir with **intravenous benzodiazepines (alprazolam, midazolam, triazolam).** Dose adjustment of the benzodiazepine should be considered.[1]	**midazolam.**[6] Co-administration of telaprevir and **parenteral midazolam** should be done in a setting which ensures clinical monitoring and appropriate medical management in case of respiratory depression and/or prolonged sedation.[6]
NSAIDS	In healthy subjects, co-administration of diflunisal or ibuprofen (aldo ketoreductase inhibitors) had little effect on the steady-state exposure to BOC.[4]	
Oral contraceptives	In healthy subjects, there were no clinically relevant changes in BOC exposure when co-administered with drospirenone (DRSP)/ethinyl estradiol (EE). BOC increased DRSP $AUC_{(0-24h)}$ and C_{max} (99% and 57%, respectively); and decreased EE AUC (24%) with no effect on EE $C_{max.}$.[4] Alternative methods of non-hormonal contraception are recommended. Co-administration of BOC with drospirenone (Yaz®, Yasmin®, Angeliq®) is contraindicated.[1]	In healthy women receiving Modicon (0.5 mg norethindrone (NE) and 0.035 mg ethinyl estradiol (EE) for at least 3 months, the effect of steady-state telaprevir 750 mg q8h on the steady-state pharmacokinetics of EE and NE was assessed. In the presence of telaprevir, EE Cmax ↓ 26%, Cmin ↓ 37% and AUC ↓ 28%. NE and telaprevir exposures were not significantly affected. LH and FSH concentrations at day 7 also ↑, corresponding with the ↓ EE concentrations. **Alternative methods of contraception should be used when estrogen-based contraceptives are coadministered with telaprevir**.[36]
Pegylated interferon alfa-2b	In healthy subjects, there were no clinically relevant changes in either BOC or PEG2b exposure when co-administered with pegylated interferon alfa-2b. No BOC dosage adjustment is needed with co-administration.[4]	
Phosphodiester-ase Type 5 (PDE5) Inhibitors • **sildenafil** (Viagra®, Revatio®); *(CYP3A4>>2C9 substrate; weak inhibitor of CYP1A2, 2C9, 2C19, 2D6, 2E1, 3A4 - unlikely to cause significant interactions)* • **tadalafil** (Cialis®, Adcirca®); *CYP3A4*	↑ in PDE-5 inhibitor concentrations are expected, and may result in an increase in adverse effects, including hypotension, syncope, visual disturbances, and priapism. **<u>For treatment of pulmonary arterial hypertension (PAH):</u>**[1] • **Sildenafil or tadalafil use for PAH is contraindicated with boceprevir.** **<u>For treatment of erectile dysfunction:</u>** Use with caution and increased monitoring for PDE-5 inhibitor-associated toxicities. Do not exceed the following doses:[1] • sildenafil: 25 mg every 48 hours • tadalafil: 10 mg every 72 hours • vardenafil: 2.5 mg every 24 hours (NB:	↑ in PDE-5 inhibitor concentrations are expected, and may result in an increase in adverse effects. **<u>For treatment of pulmonary arterial hypertension (PAH):</u>**[6] • **Sildenafil use for PAH is (contraindicated with telaprevir.** • Co-administration of tadalafil and telaprevir for PAH treatment is not recommended. **<u>For treatment of erectile dysfunction:</u>** Use with caution and increased monitoring for PDE-5 inhibitor-associated toxicities. Do not exceed the following doses:[6]

	Boceprevir (Victrelis®, BOC, SCH 503034) Merck	Telaprevir (Incivek®, TVR, VX-950) Vertex Pharmaceuticals
substrate • **vardenafil** (Levitra®); substrate of *CYP3A4>3A5, 2C*	this dose not approved in Canada; therefore, combination is not recommended)	• sildenafil: 25 mg every 48 hours • tadalafil: 10 mg every 72 hours • vardenafil: **contraindicated**
Rifampin	Coadministration is contraindicated, as boceprevir concentrations may be significantly reduced, possibly leading to decreased virologic response.[1]	In healthy subjects, coadministration of rifampin 600 mg daily at steady-state and single dose telaprevir 750 mg led to 86% ↓ Cmax and 92% ↓ AUC of telaprevir. Coadministration of rifampin and telaprevir is contraindicated.[14]
Tacrolimus	In healthy volunteers, the kinetics of single-dose tacrolimus 0.5 mg was assessed alone and in the presence of single dose BOC 800 mg and steady-state BOC 800 mg TID. In the presence of BOC, tacrolimus AUC ↑ 17-fold and Cmax ↑ 9.9-fold; BOC pharmacokinetics were not affected by tacrolimus. Coadministration of BOC and tacrolimus would likely require significant dose reduction of tacrolimus and/or prolongation of the dosing interval, with close monitoring of tacrolimus concentrations and frequent assessments of renal function and tacrolimus-related side effects.[27]	In healthy subjects, the pharmacokinetics of single dose tacrolimus was assessed alone (2 mg) and at a dose of 0.5 mg in the presence of steady-state telaprevir 750 mg q8h. When coadministered with telaprevir, tacrolimus exposure ↑ 70-fold and the elimination t1/2 increased from 40.7 to 196 hours; telaprevir kinetics were similar to historical data, suggesting no major effect of tacrolimus on telaprevir.[28] In a case series, HCV-1a infected, post-liver transplant patients received pegylated interferon 2a/b, ribavirin, and telaprevir. All subjects were on stable tacrolimus dosing prior to starting antiviral therapy. Tacrolimus doses were pre-emptively reduced to 50% of pre-treatment doses and given once weekly. Trough TAC levels were checked q2d for the first 2 weeks, then weekly until telaprevir therapy was complete. Baseline TAC dosing was resumed after 5 days of stopping telaprevir. No episodes of acute rejection or TAC toxicity were noted; 4 patients had early rapid virologic response, 2 patients had complete early virologic response, 1 patient was a non-responder. The main adverse effect was anemia (n=6 required transfusions); dehydration, renal insufficiency and infections also reported.[37]
Warfarin	Combination has not been studied. Potential for altered warfarin concentrations in the presence of boceprevir. Monitor INR when coadministering warfarin and boceprevir.[1]	In vitro, the effect of 14C-telaprevir at various concentrations on the protein-binding of 3H-warfarin was evaluated in human plasma. Protein-binding of 14C-telaprevir in human plasma was 59.1-75.6% over the concentration range of 0.1 to 20 uM. The free fraction of 14C-telaprevir ↑ ~30% in the presence of warfarin at low 14C-telaprevir concentrations, but this was not observed at high 14C-telaprevir doses.

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		Protein binding of 3H-warfarin in human plasma was 98% and was unchanged by the presence of telaprevir over the concentration range of 0.1 to 20 uM. At low 14C-telaprevir concentrations, warfarin and other ligands with high affinity binding to albumin or alpha1-acid glycoprotein may displace 14C-telaprevir from protein binding sites and ↑ the free fraction of telaprevir.[38] Monitor INR when coadministering warfarin and telaprevir.[6]
Zolpidem		In healthy subjects who received a single dose of zolpidem 5 mg alone and in combination with a single 750 mg telaprevir dose and multiple telaprevir doses of 750 mg po q8h, zolpidem exposures were unchanged after single dose telaprevir, while zolpidem Cmax ↓ 42% and AUC ↓ 47% after steady-state dosing of telaprevir. The mean t1/2 of zolpidem decreased from 4.32 hours to 3.37 hours following multiple doses of telaprevir.[22]

Please note: This chart summarizes some of the major drug interactions identified to date, based on current available data; other drug interactions may exist. Please use caution whenever adding/modifying therapy. The information in this table is intended for use by experienced physicians and pharmacists. It is not intended to replace sound professional judgment in individual situations, and should be used in conjunction with other reliable sources of information. Due to the rapidly changing nature of information about HIV treatment and therapies, users are advised to recheck the information contained herein with the original source before applying it to patient care.

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Antiretroviral Treatment Options for Patients on Boceprevir or Telaprevir

	Boceprevir (Victrelis®) 800 mg q8h with food	**Telaprevir (Incivek®)** 750 mg po q8h with food
PIs	Not recommended with ATVr, DRVr, LPVr[1, 2]	Avoid DRVr, FPVr, LPVr[3, 4]
	Possible ATVr?[5]	ATVr OK[3]
NNRTIs	Avoid Efavirenz[6, 7]	Dose ↑ to 1125 mg q8h with Efavirenz[3, 8]
	Etravirine (?)[9]	Etravirine OK[10]
	No data	Rilpivirine OK*[10]
InSTIs	Raltegravir OK[11, 12]	
	Elvitegravir/cobicistat: no data but potential for interaction based on pharmacokinetic properties.[13] Avoid combination until further data available.	
Maraviroc	No data *potential ↓/↑ MVC; potential benefit on fibrosis?*	
NRTIs	Tenofovir OK[6, 14]	
	Avoid AZT (anemia)	

*caution in patients on other drugs which may ↑ rilpivirine concentrations, prolong QTc, or who are at risk for Torsade de Pointes

Key: = avoid combination = caution/dose adjustment = combination OK

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Lipid-Lowering Agents

Drug	Dose	Metabolism	Efficacy	Onset	Interactions	Side Effects	Cost
FIBRIC ACID DERIVATIVES							
bezafibrate Bezalip® (Roche)	400 mg SR once daily or 200 mg tid with meals	Clrenal (50% unchanged, 20% glucuronides) - hydroxylation and glucuronidation	↓ 20% total cholesterol, ↓ (50%) TG, ↓ 20% LDL, variable ↑ 20% HDL	Decrease in TG within 1-2 months, increase HDL in 3-6 months	Decrease dose in renal failure; ritonavir & nelfinavir may ↑ clearance via GT induction	GI disturbances, rash, headache, insomnia, myositis, elevated CPK	usual: $1.60/day (ODB) $1.60/400 mg $0.6183/200 mg
clofibrate Atromid-S® (Ayerst)	1 g bid with food	Esterase to CPIB (active form), then GT	↓ 20% total cholesterol, ↓ 45% TG, ↓ variable LDL, variable ↑ HDL	Effect within 2-5 days, max response in 21 days	Caution with ritonavir; ritonavir & nelfinavir may ↑ clearance via GT induction	GI disturbances, potential carcinogenicity, rash, headache, myositis, elevated CPK	not covered by ODB
fenofibrate Lipidil®, Lipidil Micro® (Fournier)	200 mg daily with food (max. 300 mg/day)	Prodrug, - hydrolyzed to fenofibric acid and GT; Clrenal	↓ 30% total cholesterol, ↓↓ 50%TG, ↓ 20% LDL, ↑ 15% HDL	Effect within 6-8 weeks	Decrease dose in renal failure; ritonavir & nelfinavir may ↑ clearance via GT induction	GI disturbances, rash, headache, myositis, elevated CPK	usual: $1.21/day (ODB) $0.4325/100 mg $1.21/200 mg
gemfibrozil Lopid® (Parke Davis)	600 mg BID (max. 1200 mg/day)	30-50% GT, CYP (?)	↓ 10% total cholesterol, ↓ 45% TG, ↓ variable LDL, ↑ 15% HDL	Max. response in 4weeks	Ritonavir & nelfinavir may ↑ clearance via GT induction. In a healthy volunteer study, subjects received single dose gemfibrozil 600 mg before and after 14 days of **LPV 400/rtv 100 mg BID**. In the presence of steady-state LPVr, gemfibrozil AUC was ↓ 41%.[1]	GI distress and rash	usual: $1.19/day (ODB) $0.2964/300 mg
HMG-COA-REDUCTASE INHIBITORS							
atorvastatin Lipitor® (Parke Davis)	10 mg qhs, max. 80 mg/day;	CYP3A4	↓ 28-40% total cholesterol, ↓ 13-32% TG,	Effect within 2 weeks, maximum	Pharmacokinetic studies in HIV-negative subjects: a) **saquinavir** 400	Abdominal cramps, nausea, myalgia, thrombocytopenia,	usual: $2.00/day (ODB)

Drug	Dose	Metabolism	Efficacy	Onset	Interactions	Side Effects	Cost
	make dose changes q4 weeks		↓ 38-51% LDL, ↑ 5-6% HDL	response at 2-4 weeks	mg/ritonavir 400 mg BID plus 40 mg atorvastatin resulted in a 4.5-fold ↑ AUC atorvastatin.[2] Do not exceed 20 mg atorvastatin daily with saquinavir.[3] b) **nelfinavir** 1250 mg BID plus 10 mg atorvastatin resulted in 74% ↑ AUC atorvastatin.[4] Do not exceed 40 mg atorvastatin daily with nelfinavir.[3] c) **lopinavir** 400 mg/ritonavir 100 mg BID plus 20 mg atorvastatin resulted in 5.9-fold ↑ AUC.[2, 5] Use lowest atorvastatin dose necessary.[3] d) **fosamprenavir** 1400 mg BID or fosamprenavir 700 mg/ritonavir 100 mg BID plus atorvastatin 10 mg resulted in significant ↑ in atorvastatin Cmax (404% and 284%, respectively) and AUC (230% and 253%, respectively); APV levels were not affected.[6] Do not exceed 20 mg atorvastatin daily with boosted or	↑CPK, ↑LFTs	$1.60/10 mg $2.00/20 mg $2.15/40 mg

Drug	Dose	Metabolism	Efficacy	Onset	Interactions	Side Effects	Cost
					unboosted fosamprenavir.[3] e) **tipranavir** 500 mg/ ritonavir 200 mg BID led to 9-fold ↑ atorvastatin AUC.[7] Avoid atorvastatin use with tipranavir.[3] f) Combination of atorvastatin 10 mg daily plus **darunavir 300/ritonavir** 100 mg BID led to 15% ↓ atorvastatin AUC vs. atorvastatin 40 mg QD alone. Do not exceed 20 mg atorvastatin daily with darunavir.[3] With **efavirenz** 600 mg/d and atorvastatin 10 mg/d: - significant ↓ **atorvastatin** AUC by 43% (total active atorvastatin exposure ↓ 34%); EFV concentrations not affected. Patients on combination should be closely monitored for anti-lipid activity; statin dose may need to be titrated.[8] In healthy volunteers, atorvastatin 40 mg QD plus **etravirine** 800 mg BID (old formulation) led to 37% ↓ AUC of		

Drug	Dose	Metabolism	Efficacy	Onset	Interactions	Side Effects	Cost
					atorvastatin and 27% ↑ AUC atorvastatin active metabolite. Etravirine exposures were not affected. Combination may be coadminstered.[9] In healthy volunteers, atorvastatin 40 mg QD plus **rilpivirine 150 mg QD** did not lead to significant alterations in plasma exposures of either rilpivirine or atorvastatin. A modest increase in exposure to atorvastatin hydroxylated metabolites (via mild induction of CYP3A activity by rilpivirine) resulted in an increase in the total lipid-lowering activity of atorvastatin during rilpivirine coadministration; this was considered clinically relevant. Combination may be coadministered without dose adjustment.[10] Potential for ↑ atorvastatin concentrations with **elvitegravir/cobicistat**; initiate with lowest starting dose of atorvastatin and titrate to response.[11]		
fluvastatin	20 mg qhs	extensive 1st-pass;	↓ 13-23% total	maximum	May be less likely to	Same as above	(ODB)

Drug	Dose	Metabolism	Efficacy	Onset	Interactions	Side Effects	Cost
Lescol® (Novartis)	(max. 40 mg qhs or 20 mg BID)	CYP2C9 >>3A4 (minor) ; weak inhibitor of 2C9	cholesterol, ↓ 5-15% TG, ↓ 17-34% LDL, ↑ 1-7% HDL	response within 4 weeks	interact with PIs; caution with ritonavir (induces 2C9 but inhibits 3A). Potential for ↓/↑ concentrations with **elvitegravir/cobicistat.**	- dyspepsia and lupus-like syndrome	$0.75/20 mg $1.05/40 mg
lovastatin Mevacor® (Merck)	10-20 mg cc (max. 40 mg BID or 80 mg cc)	hydrolysis to active form, CYP3A4, also 2D6, 2C9	↓ 21-36% total cholesterol, ↓ 12-13% TG, ↓ 29-48% LDL, ↑ 7-8% HDL	Effect within 3 days, maximum response at 4-6 weeks	Elevated liver function tests, myalgias reported with concomitant use of lovastatin and PI therapy.[12] **Lovastatin** is contraindicated with all HIV protease inhibitors and elvitegravir/cobicistat.[3, 11]	Same as atorvastatin -lupus-like syndrome and ↑LFTS 3x normal	(ODB) $1.2985/20 mg $2.3951/40 mg
Pitavastatin (Livalo® - not available in Canada)		Primarily via UGT1A3 and UGT2B7. Minimal CYP450 metabolism (mostly CYP2C9, 2C8).			In healthy volunteers, administration of pitavastatin 4 mg daily in the presence of steady-state **lopinavir/ritonavir 400/100 mg BID** did not result in clinically significant changes in pharmacokinetic exposures of either drug.[13] In healthy volunteers, coadministration of pitavastatin 4 mg and **darunavir 800/100 mg** QD resulted in 26% ↓ AUC of pitavastatin, and no significant changes in darunavir exposures compared to either drug administered alone.[14] **Pitavastatin** may be		

Drug	Dose	Metabolism	Efficacy	Onset	Interactions	Side Effects	Cost
					used without dose limitations with boosted or unboosted atazanavir, darunavir/ritonavir and lopinavir/ritonavir.[3]		
pravastatin Pravachol® (Squibb)	10-20 mg qhs (max. 40 mg qhs)	40-54% Clrenal; >50% metab. by CYP3A(?)	↓ 13-24% total cholesterol, ↓ 10-15% TG, ↓ 19-34% LDL, ↑ 3-10% HDL	Effect within 3 days, maximum response at 4-6 weeks	Pharmacokinetic studies in HIV-negative subjects: a) **saquinavir 400 mg/ritonavir 400 mg BID** plus 40 mg pravastatin resulted in a 35% ↓ AUC of pravastatin.[2] b) **lopinavir 400 mg/ ritonavir 100 mg BID** + pravastatin 20 mg: 30% ↑ pravastatin AUC[5] c) **darunavir 600 mg/ rtv 100 mg BID** plus single-dose pravastatin 40 mg led to 81% ↑ pravastatin AUC.[15] d) **Nelfinavir 1250 mg BID** + pravastatin 40 mg QD: 46.5% ↓ pravastatin AUC.[16] Addition of pravastatin 40 mg daily to either **indinavir, saquinavir, or ritonavir**-containing regimens (n=15) did not result in any significant changes to PI concentrations.[17] **Pravastatin** may be used without dose limitations with	Same as atorvastatin	(ODB) $1.0593/10 mg $1.2495/20 mg $1.505/40 mg

Drug	Dose	Metabolism	Efficacy	Onset	Interactions	Side Effects	Cost
					darunavir/ritonavir and lopinavir/ritonavir.[3] With **efavirenz** 600 mg/d and pravastatin 40 mg/d, **pravastatin** AUC ↓ 40%; EFV concentrations not affected. Patients on combination should be closely monitored for anti-lipid activity; statin dose may need to be titrated.[8] In healthy adults who received pravastatin 40 mg QD plus **raltegravir** 400 mg BID for 4 days, pravastatin exposures were not significantly affected in the presence of raltegravir. Raltegravir AUC ↑ 13%, Cmax ↑ 31% and C12 ↓ 41% when coadministered with pravastatin; however, since raltegravir efficacy is better correlated with AUC, this interaction is not likely to be clinically significant, and no dose adjustments are required.[18] Potential for ↓/↑ concentrations with **elvitegravir/cobicistat.**		
rosuvastatin Crestor® (Astra	5-20 mg once daily (max. 40 mg daily).	Minimal (10%) hepatic metabolism,	28-30%↓ total cholesterol, ↓ 40-58%↓ LDL,	Within 2 weeks, maximal	Prospective study with 6 healthy adult volunteers of **ATV/r 300mg/100mg**	Headache, asthenia, upper respiratory infections,	(ODB) $1.36/10 mg $1.70/20 mg

Drug	Dose	Metabolism	Efficacy	Onset	Interactions	Side Effects	Cost
Zeneca)	May be given with/ without food at any time of day.	mostly through CYP2C9, 2C19. Mostly excreted in bile.	12-15% ↓ TG, 7-12% ↑ HDL	response at 6-12 weeks.	**daily** for 7 days and rosuvastatin 10mg single dose led to 213% ↑ rosuvastatin AUC, 600% ↑ Cmax vs. rosuvastatin alone. Rosuvastatin-lactone AUC ↑ 61%, no change in N-desmethyl rosuvastatin levels.[19] **Limit rosuvastatin dose to 10 mg once daily** with boosted or unboosted atazanavir.[3] In healthy volunteers who received rosuvastatin 10 mg daily alone or with **darunavir 600/100 mg BID** for 7 days, mean rosuvastatin AUC ↑ 48% and Cmax ↑ 144% in the presence of darunavir/ritonavir. Darunavir kinetics were not significantly affected by rosuvastatin. Lipid-lowering effects of rosuvastatin were not significantly altered in the presence of darunavir/ritonavir.[20] In a prospective study of healthy volunteers, **FPV/r 700mg/100mg BID** for 7 days did not affect the AUC or Cmax of rosuvastatin 10mg (single dose) or N-desmethyl Rosuvastatin	gastrointestinal symptoms, and myalgia have been reported; myopathy has occurred rarely	$1.99/40 mg

Drug	Dose	Metabolism	Efficacy	Onset	Interactions	Side Effects	Cost
					levels (metabolite). FPV/r ↑ rosuvastatin-lactone AUC (metabolite) by 76%. Based on PK data, no dose adjustments required when combination is used.[19] In a prospective cohort of HIV-positive subjects (n=14) on **lopinavir/r** regimens, LPV Cmin were not changed during 12 weeks of rosuvastatin therapy;[21] however, rosuvastatin concentrations were 1.5-2-fold higher compared to historical data.[22] In an open-label, 3-phase pharmacokinetic study in healthy volunteers, the combination of **rosuvastatin 20 mg/day plus LPV/r 400/100 mg BID** for 7 days led to a 2.1-fold ↑ AUC and 4.7-fold ↑ Cmax of rosuvastatin, compared to rosuvastatin alone ($p<0.0001$). LPV levels were not changed in the presence of rosuvastatin.[23] Case report of rhabdomyolysis in a patient on lopinavir/ritonavir after switching from		

Drug	Dose	Metabolism	Efficacy	Onset	Interactions	Side Effects	Cost
					pravastatin to rosuvastatin.[24] **Limit rosuvastatin dose to 10 mg once daily** with lopinavir/ritonavir.[3] In 16 healthy volunteers, **tipranavir 500/ritonavir 200 mg BID** plus single dose rosuvastatin 10 mg led to 37% ↑ AUC and 123% ↑ Cmax of rosuvastatin; TPV and RTV levels were not changed in the presence of rosuvastatin. Use lowest dose of rosuvastatin (5 mg/day) and titrate slowly to treatment response.[7] Randomized, crossover study in healthy subjects of **elvitegravir 150mg/ cobicistat 150 mg daily** alone or with rosuvastatin 10 mg. Elvitegravir kinetics were unaffected with coadministration, while rosuvastatin Cmax ↑ 89%, AUC ↑ 38%. Dose adjustment likely not necessary.[25]		
simvastatin Zocor® (Merck Frosst)	5-10 mg before supper or hs (max. 20 mg BID or 40 mg before	hydrolysis to active form, CYP3A; also CYP2D6, 2C9	↓ 21-30% total cholesterol, ↓ 12-15% TG, ↓ 28-39% LDL, ↑ 7-10% HDL	Effect within 3 days, maximum response at 4-6 weeks	Pharmacokinetic studies in HIV-negative subjects: a) saquinavir 400 mg/ritonavir 400 mg BID plus 40 mg simvastatin resulted	Same as atorvastatin - lupus-like syndrome and thrombocytopenic purpura	(ODB) $0.90/5 mg $1.78/10 mg $2.20/20 mg $2.20/40 mg $2.20/80 mg

Drug	Dose	Metabolism	Efficacy	Onset	Interactions	Side Effects	Cost
	supper or hs)				in a 31.6 fold ↑ AUC simvastatin.[2] b) nelfinavir 1250 mg BID plus 20 mg simvastatin resulted in 506% ↑ AUC simvastatin [4] **Simvastatin** is contraindicated with all HIV protease inhibitors and elvitegravir/cobicistat.[3, 11] With **efavirenz** 600 mg/d and simvastatin 40 mg/d: - significant ↓ **simvastatin** AUC by 58% (active HMG-CoA reductase inhibitory activity ↓ 60%); EFV concentrations not affected. Patients on combination should be closely monitored for anti-lipid activity; statin dose may need to be titrated.[8]		
CHOLESTEROL ABSORPTION INHIBITORS							
Ezetimibe (Ezetrol®)	10 mg once daily +/- food	Glucuronidated in gut wall to active metabolite	Monotherapy: 18%↓ LDL, 5% ↓ TG, 4%↑ HDL; Combined with atorvastatin: 54.5%↓ LDL, 33%↓ TG, 7%↑ HDL (all	Onset within 1 week, peak ↓ LDL within 2-4 weeks	**Fibrates:** ezetimibe concentrations ↑ 1.7-fold with gemfibrozil, ↑ 1.5-fold with fenofibrate; fibrates ↑ cholesterol excretion into bile, leading to ↑ risk cholelithiasis. Avoid co-administration, may	GI: dyspepsia, diarrhea	(ODB): $1.58/10 mg

Drug	Dose	Metabolism	Efficacy	Onset	Interactions	Side Effects	Cost
			parameters sig. > vs. atorvastatin alone)		need to ↑ ezetimibe dose. **Cyclosporine**: 12-fold ↑ ezetimibe levels reported in renal transplant patient, mechanism unknown. Co-administer with caution. **Lopinavir/rtv:** Ezetimibe 10 mg QD for 12-18 weeks did not affect steady-state kinetics of lopinavir/ritonavir in HIV-infected subjects.[26, 27] **Raltegravir:** Steady-state kinetics of raltegravir 400 mg BID were not affected by ezetimibe 10 mg QD for 10 days in healthy subjects.[28]		
BILE ACID SEQUESTRANTS							
cholestyr-amine Questran® (Bristol)	4 g 30-60 min before 1-2 main meals (max. 8g before 2-3 meals)	not metabolized	↓ (15-30%) LDL; may ↑ (15-25%) TG (via compensatory ↑ hepatic synthesis of VLDL?)	Effect within 24-48 hrs and cont'd up to 12 months	May ↓ absorption of other drugs (e.g., thiazides, propranolol, thyroxine, warfarin, cardiac glycosides, fat-soluble vitamins); take other drugs 1 hr before or 2-4 hrs after bile acid resin	GI: dyspepsia, N/V, abdominal discomfort, bloating, constipation; no systemic s/e	(ODB) $19.92/42 doses $0.6407/ pouch
colestipol HCl Colestid® (Pharmacia & Upjohn)	5 g 30-60 min before 1-2 main meals (max. 10 g before 2-3 meals)	not metabolized	↓ LDL; may ↑ TG (via compensatory ↑ hepatic synthesis of VLDL?)	Effect within 24-48 hrs, maximum response at 1 month	as above	GI: dyspepsia, N/V, abdominal discomfort, bloating, constipation; no systemic side effects	(ODB) $0.8183/5g $0.8183/7.5 g $46.00/60 doses

Drug	Dose	Metabolism	Efficacy	Onset	Interactions	Side Effects	Cost
OTHER							
niacin/ nicotinic acid/vitamin B3	250-500 mg BID after meals (max. 1-2 g BID-TID pc); use immediate-release form to ↓ risk liver toxicity	Metabolized to active metabolite niacinamide	↓ (20-35%) LDL, ↓(20-40%) TG,↑ (10-20%) HDL, ↓ lipoprotein a	Effect within 3-5 weeks	Increased effect of insulin and oral hypoglycemics -increased myopathy when administered with statins or fibric acid derivatives. Potential for overlapping toxicities with PIs, especially ritonavir.	flushing, pruritus, N/GI discomfort, gastritis, blurred vision; alters serum glucose, uric acid levels; Long term: hyperuricemia, hepatotoxicity, PUD; rhabdomyolysis (in combination with HMG-CoA reductase inhibitors)	$0.0295/100 mg

Please note: This chart summarizes some of the major drug interactions identified to date, based on current available data; other drug interactions may exist. Please use caution whenever adding/modifying therapy. The information in this table is intended for use by experienced physicians and pharmacists. It is not intended to replace sound professional judgment in individual situations, and should be used in conjunction with other reliable sources of information. Due to the rapidly changing nature of information about HIV treatment and therapies, users are advised to recheck the information contained herein with the original source before applying it to patient care.

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Antiretroviral-Methadone Interactions

Antiretroviral	Study Type	Patient(s)	Nature of interaction	Recommendation
Integrase Inhibitors				
Elvitegravir/ cobicistat[1]	Pharmacokinetic study	11 subjects on stable methadone (80-120 mg/day) who received elvitegravir 150 mg/cobicistat 150 mg daily for 10 days.	The kinetics of R-methadone were unaffected in the presence of elvitegravir/ cobicistat (AUC ↑ 7%, Cmin ↑ 10%); elvitegravir and cobicistat exposures were similar to historical controls.	No dose adjustments are needed.
Raltegravir[2]	Pharmacokinetic (randomized, placebo-controlled, 2-period crossover study)	Twelve HIV negative male and female patients on methadone maintenance therapy who received either 400-mg raltegravir or matching placebo every 12 hours from days 1 through 10 for each treatment period with a washout of 7 days between periods.	The geometric mean ratio (GMR) (90% CI) for (methadone + raltegravir/ methadone) was 1.00 (0.93, 1.09) for $AUC_{0\text{-}24hr}$ and 1.00 (0.94, 1.07) for C_{max}. There were no serious clinical or laboratory adverse experiences.	No dose adjustment is required for methadone when co-administered with raltegravir.[3]
NNRTIs				
Delavirdine[4]	Pharmacokinetic	16 HIV negative volunteers maintained on methadone and 15 controls, each treated with delavirdine 600 mg bid for 5 days.	Methadone did not alter pharmacokinetics of delavirdine or N-delavirdine. Effect of delavirdine on methadone not studied.	Since delavirdine an inhibitor of 3A4, monitor for symptoms of opiate toxicity (e.g. miosis, drowsiness, ↓ rate and depth of respiration, N/V, constipation, bradycardia, hypotension) until further data available.
Efavirenz[5]	Pharmacokinetic	11 patients on stable methadone maintenance,	EFV ↓ methadone Cmax (p=0.007) and ↓ methadone AUC by mean of 60%. 9/11	Monitor for symptoms of opiate withdrawal (e.g.

Antiretroviral	Study Type	Patient(s)	Nature of interaction	Recommendation
		due to begin antiretroviral therapy with two reverse transcriptase inhibitors and efavirenz	patients complained of symptoms of methadone withdrawal from day 8-10 onwards of starting efavirenz, and received ↑ in methadone dose in increments of 10 mg until symptoms resolved (mean ↑ in methadone dose required: 22%)	lacrimation, rhinorrhea, diaphoresis, restlessness, insomnia, dilated pupils, piloerection) and adjust methadone dose if necessary.[6]
Efavirenz[7]	Case report	1 patient on methadone 100 mg a day for over one year; switched from nelfinavir/lamivudine/stavudine to an efavirenz containing regimen.	Four weeks after the introduction of efavirenz, patient reported tiredness, headache, cold sweats and shivering. Concentrations of (R)-methadone (active enantiomer of methadone) before and after the introduction of efavirenz were 168 and 90 ng/ml, respectively. Dose of methodone ↑ to 180 mg/day before symptoms disappeared.	
Efavirenz[8]	Case report	3 HIV infected IV drug users on methadone treatment.	Opiate withdrawal symptoms emerged 4 to 7 days following the introduction of efavirenz. Methadone levels were obtained in one patient and were 65% lower with efavirenz than at baseline. Patients required a 66-133% ↑ in methadone dose to compensate.	
Nevirapine, then Efavirenz[9]	Case report	Patient stabilized on methadone 40 mg daily. Antiretroviral therapy changed from zidovudine/lamivudine to d4T/ddI/nevirapine, and later d4T/ddI/efavirenz.	2 days following change, patient experienced symptoms compatible with opiate withdrawal (i.e. cramps, tremor, rhinorrhea etc). Symptoms stopped with the discontinuation of nevirapine, and recurred with nevirapine rechallenge. Symptoms recurred again following change to efavirenz, in spite of dose ↑ to 80 mg/day. Methadone levels stable despite dose increase.	
Etravirine[10]	Open-label interaction trial	16 male volunteers on stable methadone	No clinically relevant effect of combination; methadone dose adjustment not required	Methadone dosage adjustment likely not

Antiretroviral	Study Type	Patient(s)	Nature of interaction	Recommendation
		maintenance therapy received etravirine 100 mg BID for 14 days.	and no withdrawal symptoms were observed.	necessary when coadministered with etravirine.
Lersivirine[11]	Open-label, single-sequence study	13 HIV-negative volunteers on stable methadone maintenance therapy (50-150 mg QD) for ≥3 months received lersivirine 1000 mg daily plus their same methadone dose to steady-state (Days 2-11).	No clinically relevant change in R/S-methadone exposure resulted from co-administration. Opioid withdrawal symptoms were not observed when lersivirine was co-administered with methadone.	No methadone dose adjustment is required when lersivirine is administered.
Nevirapine[12]	Case report	1 patient on methadone 80 mg/day for 3 years; switched from ddI/d4T/SQV-hgc/NFV after 1 month (because of ddI intolerance) to d4T/NFV/SQV-sgc/nevirapine.	One week following the change to a nevirapine containing regimen, the patient experience symptoms of methadone withdrawal (total body pain, nausea, vomiting, insomnia, sweats, sense of impending doom). Over the course of 4 weeks, the dose ↑ to 130 mg/day and her symptoms resolved.	Monitor for symptoms of opiate withdrawal (see under “Efavirenz”) and adjust methadone dose if necessary.
Nevirapine[13]	Retrospective chart review.	7 patients on chronic methadone maintenance following initiation of treatment with nevirapine containing regimens.	Methadone withdrawal precipitated in all patients within 4-8 days of initiating treatment with nevirapine. Methadone levels were determined for 3 patients, and were subtherapeutic in each case. Dose ↑ necessary, and 4 patients chose to discontinue therapy.	

Antiretroviral	Study Type	Patient(s)	Nature of interaction	Recommendation
Nevirapine[14]	Case series	5 patients on methadone maintenance program starting nevirapine based HAART.	4 of the 5 patients exhibited symptoms consistent with opiate withdrawal 6-15 days after beginning nevirapine therapy. Two patients discontinued therapy; two patients remained on therapy but required ↑ in methadone dose of 33% and 100%.	
Nevirapine[15]	Prospective study	45 intravenous drug users, stabilized on methadone and treated with nevirapine, didanosine and lamivudine, all once a day.	30% of the 45 patients required ↑ in their methadone dose due to withdrawal symptoms.	
Nevirapine[16]	Pharmacokinetic study	8 patients on stable daily methadone, beginning treatment with nevirapine based HAART.	Nevirapine ↓ methadone AUC by a mean of 50%. 6 of the 8 patients reported symptoms of methadone withdrawal from days 8-10 onwards of starting nevirapine, and received an ↑ in methadone dose in increments of 10 mg (mean ↑ in methadone dose required: 16%).	
Nevirapine[17]	Pharmacokinetic study	24 patients on stable methadone, beginning treatment with nevirapine based HAART. 12-hour PK measurements done at baseline and after 28 days.	Nevirapine ↓ methadone AUC by mean of 40%; mean methadone dose ↑ by 24% (range 0-80%) during study.	
Rilpivirine[18]	Pharmacokinetic study	13 HIV-negative volunteers on stable methadone received rilpivirine 25 mg daily for 11 days.	In the presence of rilpivirine, active R-isomer exposures decreased (mean Cmin ↓ 22%, Cmax ↓ 14%, AUC ↓ 16%); exposures of inactive S-methadone also decreased to a similar extent. The AUC ratio for S-/R-methadone did not change. No methadone withdrawal symptoms were observed.	No a-priori adjustment of methadone dosage is recommended. Patients should be monitored for symptoms of clinical withdrawal in case methadone dosage needs to be adjusted.[19]
Protease Inhibitors				

Antiretroviral	Study Type	Patient(s)	Nature of interaction	Recommendation
Amprenavir[20]	Pharmacokinetic study	Methadone blood concentrations were measured in five patients receiving methadone maintenance therapy before and after introduction of abacavir plus amprenavir for 14 days.	Methadone concentrations ↓ by 35% (range 28-87%, p = 0.043). Two patients reported on several occasions nausea in the morning before the intake of the daily methadone dose, which is suggestive of a withdrawal reaction.	
Amprenavir[21, 22]	Pharmacokinetic study	16 opiate dependent, HIV-patients on at least 30 days stable methadone treatment; methadone levels reassessed after 10 days of amprenavir 1200 mg bid.	Prospective, open-label study in HIV-negative subjects (n=19) maintained on methadone for at least 30 days, addition of amprenavir 1200 mg BID for 10 days resulted in delayed APV absorption, 13% ↓ AUC, 21% ↓ Cmin of active methadone enantiomer. The inactive S-enantiomer AUC and Cmin were decreased by 40% and 52%, respectively. No clinical evidence of methadone withdrawal was observed, and no methadone dosage was adjusted in any patient. Compared to a non-matched historical control group, a 30%, 27%, and 25% ↓ in AUC, Cmax, and Cmin of amprenavir was observed. Clinical significance unclear.	Methadone dosage adjustment likely not necessary when coadministered with amprenavir. Monitor for amprenavir efficacy.
Atazanavir[23]	Pharmacokinetic study	16 HIV-negative subjects on chronic methadone received concomitant atazanavir 400 mg daily for 14 days.	Prospective, open-label study; in the presence of atazanavir, no significant changes were observed in the pharmacokinetic parameters of the active (R)-isomer of methadone; exposure to the inactive (S)-isomer was modestly reduced but changes were not deemed significant. No clinical symptoms of opiate withdrawal were observed. Pharmacokinetic parameters of atazanavir were comparable	Atazanavir and methadone may be co-adnimistered without dosage adjustment.

Antiretroviral	Study Type	Patient(s)	Nature of interaction	Recommendation
			to previously reported data.	
Darunavir/ ritonavir[24]	Pharmacokinetic study	16 HIV-negative subjects on stable methadone (range 55-200 mg/day, mean dose 86 mg, median dose 75 mg) received **darunavir 600/100 mg BID** for 7 days	Prospective, open-label study; in the presence of darunavir/ritonavir, mean *R*-METH Cmin, Cmax, and AUC24h were decreased by 15%, 24%, and 16%, respectively, while mean *S*-METH Cmin, Cmax, and AUC24h values were decreased by 40%, 44%, and 36%, respectively. Coadministration of DRV/r with METH results in a greater decrease in *S*-isomer exposure than *R*-isomer exposure.	Methadone dose adjustment is not likely to be required during DRV/r coadministration because the *R*-isomer is the biologically active enantiomer; however, monitoring for withdrawal symptoms during initial combination treatment should still be considered.
Fosamprenavi r/ritonavir[25]	Pharmacokinetic	19 methadone-maintained, healthy subjects received fosamprenavir 700 mg/ ritonavir 100 mg BID for 14 days.	AUC and Cmax of active (R-) methadone ↓ 18% and 21%, respectively, while AUC and Cmax of inactive (S-) methadone ↓ 42% and 43%, respectively. Pharmacokinetics of amprenavir were similar to historical controls. No subject experienced symptoms of opiate withdrawal and methadone dosage adjustment was not required during the study.	Methadone dosage adjustment likely not necessary when coadministered with fosamprenavir/ritonavir.
Indinavir[26]	Pharmacokinetic	12 HIV + patients on methadone 20 – 60 mg per day; indinavir 800 mg po q8h added.	No significant effect of indinavir on methadone AUC when compared to historical controls. No significant effect of methadone on indinavir AUC, but ↑ indinavir Cmin 50-100% and ↓ indinavir Cmax 16-36%, all vs. historical controls.	Combination appears safe.
Indinavir, Nelfinavir, Ritonavir, Saquinavir[27]	Case series	Methadone levels measured prior to and at least one week following addition of a PI to stable dual RTI therapy in ten patients on methadone	Methadone concentrations unchanged in six patients switched to indinavir and one patient switched to saquinavir; methadone steady state concentrations ↓ 40-50% in one patient switched to ritonavir and two patients switched to nelfinavir.	Monitor for symptoms of opiate withdrawal (see under “Efavirenz”) with neflvinavir and ritonavir; adjust methadone dose if necessary.

Antiretroviral	Study Type	Patient(s)	Nature of interaction	Recommendation
		maintenance program.		
Lopinavir/ ritonavir (Kaletra)[28]	Pharmacokinetic	Eleven healthy volunteers received a single 5 mg dose of methadone. Methadone levels measured prior to and following ten days of lopinavir/ritonavir (400mg/100mg twice a day).	Lopinavir/ritonavir ↓ methadone AUC and Cmax 47%.	Observed decreases in methadone levels not always associated with opioid withdrawal symptoms; possible that lopinavir/ritonavir may produce stereoselective induction of methadone metabolism that would differentially decrease concentrations of the inactive S-isomer more than the active R-isomer. Likely no need for routine methadone dose adjustment when initiating lopinavir/ritonavir; however, as a precaution it is still recommended to monitor for opioid withdrawal (see under "Efavirenz") when initiating therapy.
Lopinavir/ ritonavir vs. ritonavir[29]	Pharmacokinetic	In two parallel, PK studies, healthy subjects on stable methadone received 7 days of either lopinavir/ritonavir 400/100 mg BID or ritonavir 100 mg BID.	Methadone AUC ↓ 26%, Cmax and Cmin ↓ 28% in presence of lopinavir/r, and was associated with a significant ↑ in number of opiate withdrawal symptoms. In contrast, methadone PK were not affected by ritonavir alone.	
Lopinavir/ ritonavir[30]	Pharmacokinetic study	Eight HIV-infected patients on methadone maintenance (median dose, 80 mg; range, 40–100 mg) initiated lopinavir/ritonavir plus 2 NRTIs.	A 36% ↓ in methadone AUC0–24h occurred after 14 days of lopinavir/ritonavir. However, none of the patients experienced opioid withdrawal symptoms or needed supplemental methadone added to their maintenance dose.	
Lopinavir/ ritonavir[31]	Observational study	Twenty HIV-positive subjects maintained on methadone for >1 month initiated lopinavir/rtv HAART regimens. Changes in methadone dose and opioid withdrawal symptoms were assessed daily for 28 days. Median (range) methadone dose at study entry was 95 (40–	None of the 18 evaluable patients experienced symptoms of opioid withdrawal and no patients requested a change in methadone dosing during the evaluation period.	

Antiretroviral	Study Type	Patient(s)	Nature of interaction	Recommendation
		130) mg/d. Two subjects did not complete the observational period.		
Nelfinavir[32]	Prospective pharmacokinetic study.	14 patients stabilized on a fixed methadone dose for at least 1 month before nelfinavir 1250 mg po bid for 8 days was added	Levels of (+)-methadone and (-)-methadone ↓ by 47% and 39%, respectively. No patient exhibited withdrawal symptoms, and no dosage adjustments were necessary.	Observed decreases in methadone levels not always associated with opioid withdrawal symptoms. Monitor for symptoms of opiate withdrawal (see under "Efavirenz") and adjust methadone dose if necessary.
Nelfinavir[33]	Retrospective case series	75 patients on stable methadone dose started on nelfinavir.	2 of 75 patients needed slight ↑ in methadone dose (10 mg/day). Otherwise, no impact of nelfinavir on methadone.	
Nelfinavir[34]	Case report	Patient on stable methadone dose of 100 mg daily, indinavir and ddC; d4T and nelfinavir added to regimen.	Within 6 weeks of medication change, patient began to complain of opiate withdrawal symptoms, which ↑ in severity over 3 months. Methadone dose ↑ at 1-2 week intervals, and subtherapeutic methadone levels documented until dose of 285 mg/d attained.	
Nelfinavir[35]	Pharmacokinetic	16 non-HIV infected volunteers on stable methadone dose for 4 weeks and 13 controls; received NFV 1250 mg po bid for 5 days.	Nonsignificant ↑ in median NFV 12 hour trough with methadone. 12 hour AUC of M8 53% lower vs. control.	
Nelfinavir[36]	Multi-site, retrospective	32 patients on stable methadone dose, receiving NFV based HAART; 84% of patients co-infected with hepatitis C.	17% of patients required methadone dose adjustments (mean 26 mg); otherwise, well tolerated combination.	
Ritonavir/ Saquinavir[37]	Case report	1 patient on methadone 90 mg/day for 2 years. Antiretrovirals changed from indinavir, lamivudine,	One week following initiation of ritonavir containing regimen, patient was admitted to hospital with shakiness, diaphoresis, blurred vision, anxiety and hypotension.	Potential for ↓ methadone with higher doses of ritonavir. Monitor for symptoms of opiate

Antiretroviral	Study Type	Patient(s)	Nature of interaction	Recommendation
		and zidovudine to ritonavir 400 mg/saquinavir 400 mg BID and stavudine because of virologic progression.	Methadone plasma level on admission was 210 ng/ml (within therapeutic range, however no levels prior to initiation of ritonavir). Methadone dose was gradually ↑ to 130 mg/day.	withdrawal (see under "Efavirenz") and adjust methadone dose if necessary.
Ritonavir/ Saquinavir[38]	Pharmacokinetic	12 HIV negative volunteers on stable methadone dose evaluated before and after 14 days of once daily saquinavir/ritonavir 1600mg/100mg.	Clinically insignificant change in unbound methadone levels. 83% of subjects had Cmin of saquinavir > EC_{50}.	Methadone dosage adjustment may not be necessary when using doses of ritonavir.
Ritonavir/ Saquinavir[39]	Pharmacokinetic	12 HIV negative volunteers on stable methadone maintenance therapy (60-120 mg daily); evaluated effect of saquinavir/ritonavir 1000/100 mg BID for 14 days on the pharmacokinetics of methadone	A 19% ↓ AUC of R-methadone was observed in the presence of saquinavir/ritonavir, with no significant plasma protein-binding displacement of methadone. No clinically significant adverse effects were observed. There appears to be no need for methadone dose adjustment when methadone (60-120 mg qd) and SQV/RTV (1000/100 mg bid) are coadministered.	
Ritonavir/ Saquinavir[40]	24 hour pharmacokinetic study before and after 15 days of antiretroviral therapy to examine effect of ritonavir/saquinavir on methadone kinetics.	12 patients receiving stable methadone dose for at least 2 weeks.	↓ S-methadone AUC 40%, and ↓ R-methadone AUC 32%. However, when change in methadone AUC expressed in terms of unbound methadone, change in AUC was no longer significant; no evidence of opiate withdrawal.	
Ritonavir/ Saquinavir[41]	Retrospective	18 HIV + patients beginning once daily therapy with ritonavir 100 mg and saquinavir – soft gel capsule 1600 mg and 5 HIV + patients beginning once	No patient required methadone dose adjustment.	

Antiretroviral	Study Type	Patient(s)	Nature of interaction	Recommendation
		daily therapy with ritonavir 200 mg and indinavir 1200 mg. All patients on methadone, 19 patients co-infected with hepatitis C.		
Tipranavir[42]	Pharmacokinetic study	15 adult healthy volunteers on steady-state tipranavir 500/ritonavir 100 mg BID plus single-dose methadone 5 mg	53% ↓ methadone levels; large ↓ in both R- and S-enantiomers.	Dosage of methadone may need to be increased when co-administered with tipranavir and 200 mg of ritonavir.
Reverse Transcriptase Inhibitors				
Abacavir[43]	Pharmacokinetic study.	19 patients titrated to constant methadone dose (≥ 40 mg/day) over 14 days. Days 15-28, received concomitant methadone and abacavir.	Slight ↑ in clearance of methadone by abacavir; no statistically significant change in Cmax, half-life or renal clearance of methadone. Methadone causes slight delay in rate but not extent of abacavir absorption.	Combination appears safe.
Didanosine buffered tablets (ddI), stavudine (d4T)[44]	Pharmacokinetic study	17 patients on methadone maintenance and 10 control patients. Two pharmacokinetic studies were completed for each study subject and control (one each for ddI and d4T).	d4T AUC ↓ 23% ddI tablets AUC ↓ 57% Effect primarily related to reduced bioavailability.	Greater reduction in ddI exposures when given as buffered tablet vs. EC capsule with methadone. If coadministration of methadone and didanosine is necessary, use ddI EC formulation and monitor for HIV clinical response.[45] Since formulation characteristics for the pediatric powder and the buffered tablet are similar, **do not**

Antiretroviral	Study Type	Patient(s)	Nature of interaction	Recommendation
				coadminister methadone with ddI pediatric powder due to significant ↓ in ddI concentrations.
Didanosine enteric-coated (EC) capsule[46]	Pharmacokinetic	HIV-negative patients (n = 17) on stable methadone dose; randomized to EC or tablet formulation, and crossed-over to alternative regimen after PK monitoring over 24 hours; comparisons made to historical data in non-methadone patients.	ddI buffered tablet: trend to decreased ddI AUC in presence of methadone. EC formulation provided ddI plasma AUC levels comparable to historical controls in non-methadone patients.	If coadministration of methadone and didanosine is necessary, use ddI EC formulation and monitor for HIV clinical response.[45]
Tenofovir[47]	Pharmacokinetic study	13 HIV-negative subjects on stable methadone received 14 days of tenofovir 300 mg daily; kinetics of methadone and its R- and S-isomers done at baseline and on day 14. Short Opiate Withdrawal Scale (SOWS) questionnaire and pupillary diameter measurements also done at baseline and on day 14.	No change in kinetics of total methadone, R- and S-isomers when coadministered with tenofovir versus alone. No clinical or laboratory signs of opiate-related toxicity or withdrawal (including changes in SOWS scores or pupillary diameters) were noted.	Methadone pharmacokinetics and dynamics not affected by tenofovir. Combination appears safe.
Zidovudine[48]	Pharmacokinetic study	14 HIV positive patients on methadone maintenance for at least 6 months and five control patients. Patients were receiving zidovudine 200 mg po	Zidovudine AUC ↑ 43% vs. control. No effect on methadone maintenance.	Monitor for zidovudine related toxicities, such as nausea, vomiting, and bone marrow suppression. Other opioid

Antiretroviral	Study Type	Patient(s)	Nature of interaction	Recommendation
		every 4 hours.		pharmacotherapies such as l-a-acetylmethadol LAAM, buprenorphine, or naltrexone not found to significantly affect zidovudine pharmacokinetics.[49]
Zidovudine[50]	Phamacokinetic within subject study.	8 patients started on acute methadone therapy as inpatients. Both oral and intravenous zidovudine pharmacokinetics determined before starting methadone, following acute methadone treatment and following two months of daily methadone.	Zidovudine AUC ↑ 41% during acute methadone treatment, and 29% during chronic treatment.	

Key: AUC = area under the concentration-time curve, bid = twice daily, Cmax = maximum plasma concentration, ddC = zalcitabine, ddI = didanosine, d4T = stavudine, EFV = efavirenz, HAART = highly active antiretroviral therapy, PI = protease inhibitor, NFV = nelfinavir, RTI = reverse transcriptase inhibitor, SQV-hgc = hard gel saquinavir

Please note: This chart summarizes some of the major drug interactions identified to date, based on current available data; other drug interactions may exist. Please use caution whenever adding/modifying therapy. The information in this table is intended for use by experienced physicians and pharmacists. It is not intended to replace sound professional judgment in individual situations, and should be used in conjunction with other reliable sources of information. Due to the rapidly changing nature of information about HIV treatment and therapies, users are advised to recheck the information contained herein with the original source before applying it to patient care.

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Interactions Between Opioids and Antiretrovirals

Antiretroviral Pharmacokinetic Characteristics (summary):

	Protease Inhibitors (PIs) atazanavir (Reyataz®)[1], darunavir (Prezista®)[2], fosamprenavir (Telzir®)[3], indinavir (Crixivan®)[4], lopinavir/ritonavir (Kaletra®)[5], nelfinavir (Viracept®)[6], ritonavir (Norvir®)[7], saquinavir (Invirase®)[8], tipranavir (Aptivus®)[9]	**Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)** efavirenz (Sustiva®)[10], etravirine (Intelence®)[11], nevirapine (Viramune®)[12], rilpivirine (Edurant®)[13]	**Integrase Inhibitors** elvitegravir/cobicistat (Stribild®, single-tablet regimen with tenofovir/emtricitabine)[14], raltegravir (Isentress®)[15]
Metabolism	Mainly CYP3A4	Efavirenz, nevirapine: CYP3A4, 2B6 (minor) Etravirine: CYP3A4, CYP2C9, and CYP2C19. Rilpivirine: CYP3A4 (major), as well as CYP2C19, 1A2, 2C8/9/10 (minor).	Elvitegravir: CYP3A, UGT1A1/3 Cobicistat: CYP3A, 2D6 (minor) Raltegravir: UGT1A1
Hepatic Inhibitor	Mainly CYP3A4 (darunavir, indinavir, nelfinavir, amprenavir >> saquinavir) Ritonavir: CYP3A4 (potent)> >2D6 >2C9 >2C19 >2A6 >1A2>2E1 At low boosting doses, ritonavir has a negligible effect in CYP2D6 inhibition.[5] Ritonavir inhibits CYP2B6 in vitro,[16] but induces 2B6 in vivo.[17] Nelfinavir: 2B6 in vitro.	Efavirenz: 2C9, 2C19[10] (? Clinical significance). Etravirine[11]: CYP2C9 (weak), CYP2C19 (moderate), p-glycoprotein (weak) Delavirdine (Rescriptor®)[18]; 3A4 (potent)	Cobicistat: CYP3A, CYP2D6; also p-glycoprotein (P-gp), BCRP, OATP1B1 and OATP1B3. Raltegravir has no inhibitory or inductive potential in vitro.[15]
Hepatic Inducer	Nelfinavir: UGT, 2C9/19 Ritonavir: UGT, CYP1A2, CYP2C9/19, 2B6 Tipranavir: mixed induction/inhibition effects; often acts as inducer of CYP3A4 (potent) and UGT, even when boosted with ritonavir[9]	Efavirenz: 3A4 (potent), 2B6[19] and UGT1A1[20] Etravirine[11]: 3A4 (weak) Nevirapine[12]: 3A4, 2B6 (potent) Rilpivirine: 2C19 (moderate), CYP1A2, 2B6 and 3A4 (weak).[21] A clinically relevant effect on CYP enzyme activity is considered unlikely with the 25 mg dose.[13]	Elvitegravir: CYP2C9 (modest) Raltegravir has no inhibitory or inductive potential in vitro.[15]

	Narcotic Route of Metabolism[22] [23, 24]	Protease Inhibitors atazanavir (Reyataz®)[1], darunavir (Prezista®)[2], fosamprenavir (Telzir®)[3], indinavir (Crixivan®)[4], lopinavir/ritonavir (Kaletra®)[25], nelfinavir (Viracept®)[6], ritonavir (Norvir®)[7], saquinavir (Invirase®)[8], tipranavir (Aptivus®)[9]	NNRTIs efavirenz (Sustiva®)[10], etravirine (Intelence®)[11], nevirapine (Viramune®)[12], rilpivirine (Edurant®)[13]	Integrase Inhibitor (**i.e. elvitegravir/cobicistat**; generally no predicted interactions with raltegravir based on pharmacokinetic properties)
Alfentanil **Alfenta®**	Parent: CYP3A	potential ↑ alfentanil concentration	potential ↓ alfentanil concentration	potential ↑ alfentanil concentration
Buprenorphine ***Partial agonist*** **BuTrans®** (Transdermal Patch) **Suboxone®** (buprenorphine/ naloxone)	Parent: CYP3A4, 2C8 Metabolite (active): norbuprenorphine inhibits CYP3A4, 2D6 (this inhibition is not likely to lead to clinically significant interactions);[26] buprenorphine and norbuprenorphine undergo glucuronidation.[27]	potential ↑ buprenorphine concentration. Case report of 3 subjects on **atazanavir 300/ritonavir 100 mg** who experienced symptoms of opiate excess when initiated on buprenorphine 8-14 mg/day. In all cases, symptoms improved with reduction of buprenorphine to 8 mg daily or every other day. Potential mechanism may be due to CYP3A4 inhibition by atazanavir or ritonavir, or inhibition of glucuronidation by atazanavir. Until further data are available, initiate buprenorphine at reduced doses and titrate slowly.[28] A prospective, open-label, multiple dose study assessed the kinetics of buprenorphine (BUP) + **ATV 400 mg or ATV/r 300mg/100mg daily** in opioid dependent buprenorphine/naloxone maintained HIV negative volunteers. In order to determine the effect of BUP on the kinetics of ATV +/- RTV, subjects were compared with non-opioid dependent healthy controls (n=10 per group). Results: • BUP treatment did not significantly alter ATV or RTV concentrations	potential ↓ buprenorphine concentration In 7 HIV-negative volunteers, there was a lack of a clinically significant interaction with **nevirapine** (9% ↓ AUC of buprenorphine and 14% ↓ AUC of norbuprenorphine) **.** Standard doses of both agents are recommended.[35] In a study of HIV-negative opioid-dependent patients receiving chronic buprenorphine/naloxone, the addition of **efavirenz** 600 mg per day for 15 days resulted in a 50% ↓ in the AUC of buprenorphine and 71% ↓ AUC of norbuprenorphine.[36] Despite these significant decreases in the presence of efavirenz, no participants showed evidence of opiate withdrawal symptoms. Efavirenz kinetics were not affected by buprenorphine. In a study of HIV-negative opioid-dependent patients receiving chronic buprenorphine/naloxone, the	potential ↑ buprenorphine concentration.

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		(~31% ↓ in AUC and ~33% ↓ in Cmin of ATV when BUP was given concomitantly). • The coadministration of ATV +/- RTV with BUP for 5 days significantly ↑ BUP and BUP metabolite levels. ○ ATV + BUP: BUP AUC ↑ 1.9 fold; BUP Cmax ↑ 1.6 fold; BUP Cmin ↑ 2 fold ○ ATV/r + BUP: BUP AUC ↑ 1.7 fold; BUP Cmax ↑ 1.37 fold; BUP Cmin ↑ 1.7 fold 3 participants reported increased sedation with the combination. It is unclear why this occurred. Concentrations of BUP/metabolites were not higher in these 3 subjects compared to the other 7 subjects who did not develop sedation. The authors caution that buprenorphine dose reduction may be required when given with ATV +/-RTV.[29] A prospective cohort study did not observe hepatic pharmacodynamic interactions (i.e. significant elevations in liver transaminases) in patients on buprenorphine/naloxone with **atazanavir ± ritonavir**.[30] In 17 HIV-negative subjects on stable buprenorphine/naloxone, the addition of **darunavir 600/100 mg BID** for 7 days led to 71% ↑ Cmin, 36% ↑ Cmax	addition of **tipranavir 500/ritonavir 200 mg BID** for 7 days resulted in ~80% ↓ AUC, Cmax and C24h of norbuprenorphine (the major metabolite of buprenorphine) and 44% ↓ AUC and 36% ↓ Cmax of naloxone. There was no clinical evidence of opioid withdrawal and no need to modify buprenorphine dose. In the presence of buprenorphine/naloxone, tipranavir AUC ↓ 19% and Cmin ↑ 3%, and ritonavir AUC ↓ 36% compared to historical controls.[37] No modification of buprenorphine/naloxone is required when co-administered with tipranavir/r, but tipranavir may be less effective due to decreased tipranavir plasma concentrations; coadminister combination with caution.[37] **Etravirine:** Interaction study recently completed and results are pending.[38] In a study of HIV-negative opioid-dependent patients receiving chronic buprenorphine/naloxone, the	

	Narcotic Route of Metabolism[22] 23, 24	Protease Inhibitors atazanavir (Reyataz®)[1], darunavir (Prezista®)[2], fosamprenavir (Telzir®)[3], indinavir (Crixivan®)[4], lopinavir/ritonavir (Kaletra®)[25], nelfinavir (Viracept®)[6], ritonavir (Norvir®)[7], saquinavir (Invirase®)[8], tipranavir (Aptivus®)[9]	NNRTIs efavirenz (Sustiva®)[10], etravirine (Intelence®)[11], nevirapine (Viramune®)[12], rilpivirine (Edurant®)[13]	Integrase Inhibitor (**i.e. elvitegravir/cobicistat**; generally no predicted interactions with raltegravir based on pharmacokinetic properties)
		and 46% ↑ AUC of norbuprenorphine, while kinetics of buprenorphine and naloxone were comparable to baseline. Clinical significance of ↑ norbuphrenorphine exposure is unknown, close monitoring is recommended with this combination.[31] In 21 opioid-dependent, buprenorphine-naloxone-maintained, HIV-negative volunteers, the impact of **darunavir/ritonavir 800/100 mg QD** (n=11) or **fosamprenavir/ ritonavir 1400/200 mg QD** (n=10) for 15 days on the kinetics of buprenorphine and its metabolites were assessed. In the presence of PI therapy, there were no changes in buprenorphine or PI plasma levels and no significant changes in medication adverse effects or opioid withdrawal. Increased concentrations of the inactive metabolite buprenorphine-3-glucuronide suggested that darunavir-ritonavir and fosamprenavir-ritonavir induced glucuronidation. Dose adjustments are not likely to be necessary.[32] In a study of 10 HIV-negative opioid-dependent patients receiving chronic buprenorphine/naloxone, the addition of **lopinavir/ritonavir 400/100 mg BID** for 7 days did not affect buprenorphine or norbuprenorphine AUC	addition of **delavirdine** 600 mg BID for 7 days resulted in 325% ↑ AUC of buprenorphine but a 61% ↓ AUC of norbuprenorphine, with an overall net effect of 87% ↑ exposure to buprenorphine plus norbuprenorphine.[36] A significant increase in the reporting of drowsiness was observed. Delavirdine kinetics were not affected by buprenorphine. Other: In 12 HIV-negative subjects stabilized on at least 3 weeks of buprenorphine/naloxone therapy, administration of **raltegravir 400 mg BID** did not significantly affect AUC and Cmax of buprenorphine and norbuprenorphine compared to baseline values, while Tmax of both buprenorphine and norbuprenorphine increased significantly. Naloxone AUC and Cmax concentrations were also unchanged in the presence of steady-state raltegravir, and objective opioid withdrawal was not observed. The AUC0-24h and Cmin of RAL did not significantly differ from historical controls (5553 vs. 4428	

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		(norbuprenorphine Cmax ↓). No participants showed evidence of opiate withdrawal symptoms or toxicity. Lopinavir/ritonavir AUC ↑ 15% in the presence of buprenorphine, not likely clinically significant.[33] In the same study, the addition of **ritonavir** 100 mg BID for 7 days resulted in 57% ↑ in buprenorphine AUC and ↑ norbuprenorphine AUC. No participants showed evidence of opiate withdrawal symptoms or toxicity. Ritonavir AUC was not affected by buprenorphine.[33] In 12 HIV-negative subjects on stable buprenorphine/naloxone therapy, administration of **lopinavir/r 800/100 mg QD** for 10 days did not have any significant impact on naloxone AUC or Cmax, buprenorphine AUC or Cmax, and AUC of norbuprenorphine. Cmax of norbuprenorphine was significantly reduced in the presence of LPVr (3.11 vs 5.29 ng/mL, $p<0.05$) but objective opioid withdrawal was not observed. Lopinavir Cmax and AUC were not significantly different compared to historical controls. Therefore, this combination may be coadministered without dose adjustment.[34] In a study of 10 HIV-negative opioid-dependent patients receiving chronic	hr*ng/mL) and (1070 vs. 1266 ng/mL). As such, buprenorphine/naloxone and raltegravir can be safely co-administered without dosage modification.[39] In 27 opioid-dependent, buprenorphine/naloxone-maintained, HIV-negative volunteers, no significant changes in buprenorphine pharmacokinetics were observed following **ddI, 3TC and tenofovir** administration, and buprenorphine had no statistically significant effect on NRTI concentrations.[40]	

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		buprenorphine/naloxone, the addition of **nelfinavir** 1250 mg BID for 5 days did not affect buprenorphine or norbuprenorphine AUC (Cmax ↓ norbuprenorphine). No participants showed evidence of opiate withdrawal symptoms Nelfinavir AUC was not affected by buprenorphine.[33]		
Butorphanol Apo®-Butorphanol *Agonist/ Antagonist*	Parent: Extensive liver metabolism via oxidation and conjugation to inactive metabolites	unknown	unknown	unknown
Codeine	Parent: UGT (to codeine-6-glucuronide); >CYP2D6 (to morphine-active) >CYP3A (to norcodeine-active) Rapid metabolizers of codeine via 2D6 may lead to high levels of morphine and toxicity.	Unlikely with unboosted PIs. Net effect unknown with ritonavir, as ritonavir may induce UGT and inhibit CYP3A.	Unlikely	Net effect unknown. Inhibition of 2D6 and 3A4 may ↓ formation of active metabolite.
Diphenoxylate Lomotil®	Parent: ester hydrolysis Metabolite (active): difenoxine (UGT)	No anticipated effect with unboosted atazanavir or fosamprenavir. Nelfinavir or ritonavir-boosted PIs may ↓ metabolite concentration via UGT induction.	no anticipated effect	no anticipated effect
Fentanyl Duragesic®	Parent: CYP3A	potential ↑ narcotic concentration 174% ↑ fentanyl AUC with **ritonavir 900 mg/day**. Monitor for respiratory and CNS depression.[41] Concentrations of fentanyl are	potential ↓ narcotic concentration	potential ↑ narcotic concentration

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		expected to increase with **ritonavir** coadministration. Careful monitoring of therapeutic and adverse effects (including respiratory depression) is recommended when **ritonavir** is co-administered with fentanyl, including extended release, transdermal or transmucosal preparations.[7]		
Heroin	**Heroin** (diacetylmorphine) undergoes deacetylation to 6-monoacetylase morphine and morphine. Morphine undergoes glucuronidation(UGT) to morphine-6-glucuronide. Parent: Deacetylase Metabolite: UGT (6-monoacetylase morphine) Morphine and morphine-6-glucuronide are also P-glycoprotein substrates.	No anticipated effect with unboosted atazanavir or fosamprenavir. **Nelfinavir or ritonavir**: may facilitate the conversion of morphine to the active metabolite morphine-6-glucuronide via induction of UGT; clinical significance is unknown.[42] **Ritonavir** is a potent inhibitor of P-glycoprotein, therefore it may potentiate the effects of opiates in the CNS.[42]	No anticipated effect.	Potential ↑ opiate.
Hydrocodone Hycodan®	Parent: CYP2D6, 3A Metabolite (active): hydromorphone via 2D6 Poor metabolizers of 2D6 will not produce hydromorphone and	potential ↑ hydrocodone concentration Ritonavir may ↓ metabolite concentration (hydromorphone), clinical significance unclear.	potential ↓ hydrocodone concentration	potential ↑ hydrocodone concentration Cobicistat may ↓ metabolite concentration (hydromorphone), clinical significance unclear.

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	derive little/no analgesic benefit			
Hydromorphone Dilaudid® Jurnista®	Parent: UGT> ketoreductase	No anticipated effect with unboosted atazanavir or fosamprenavir. **Nelfinavir and ritonavir** may ↓ hydromorphone concentration via UGT induction.	no anticipated effect	no anticipated effect
Levomethadyl (LAAM; levo-alpha-acetyl methadol) Orlaam® USA **Note: product D/C due to severe cardiac events (April 2004)**	Parent: CYP3A4 Metabolites: norLAAM, dinorLAAM[43]	potential ↑ narcotic concentration Single dose study of ketoconazole and LAAM resulted in 5.29-fold ↑ LAAM AUC, 2.25-fold ↑ norLAAM AUC, and 1.21-fold ↑ dinorLAAM AUC. Could result in serious cardiac effects. **AVOID with CYP3A4 inhibitors**.[44] **Nelfinavir**: ↓ LAAM & dinorLAAM concentrations; ↑ norLAAM concentrations. No change in nelfinavir concentrations.[45] Interaction not clinically significant.	potential ↓ narcotic concentration	potential ↑ narcotic concentration
Loperamide Imodium®	Parent: CYP 2C8, 3A4, UGT, Pgp	In healthy subjects, loperamide 16 mg plus **ritonavir 200 mg BID** for 5.5 days led to ↑ AUC of both loperamide and its metabolite by 121% and 44%, respectively. However, the respiratory response to loperamide in combination with RTV was not different from that to loperamide alone, and there was no evidence that loperamide had opioid effects in the central nervous system.[46] In healthy subjects, loperamide 16mg and **saquinavir 600mg** resulted in a	no anticipated effect	potential ↑ narcotic concentration

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		46.3% ↓ saquinavir Cmax and 53.7 ↓ in saquinavir AUC and 40% ↑ in loperamide AUC. The decrease in saquinavir AUC may be due to decreased absorption mediated by the effect of loperamide on the GI tract. Avoid use for a prolonged period of time.[47] In healthy subjects, loperamide 16 mg plus **tipranavir** 750 mg BID for 5.5 days or **tipranavir 750 mg/ritonavir 200 mg BID** for 10.5 days led to ↓ loperamide AUC by 51% and 63%, respectively, and ↓ AUC of its metabolite by 72% and 77% compared to loperamide administered alone. The respiratory response to loperamide in combination with TPV and/or RTV was not different from that to loperamide alone, and there was no evidence that loperamide had opioid effects in the central nervous system. Loperamide can be safely coadministered with tipranavir/ritonavir.[46]		
Meperidine Demerol®	Parent: CYP2B6>>3A4>2C19 Metabolite: normeperidine[48]	potential ↑ meperidine concentration with unboosted PIs. With ritonavir-boosted PIs, may see ↓ meperidine concentration due to enzyme induction. **Meperidine is no longer contraindicated** in Norvir® product	potential ↓ narcotic concentration.	potential ↑ narcotic concentration

	Narcotic Route of Metabolism[22] [23, 24]	Protease Inhibitors atazanavir (Reyataz®)[1], darunavir (Prezista®)[2], fosamprenavir (Telzir®)[3], indinavir (Crixivan®)[4], lopinavir/ritonavir (Kaletra®)[25], nelfinavir (Viracept®)[6], ritonavir (Norvir®)[7], saquinavir (Invirase®)[8], tipranavir (Aptivus®)[9]	NNRTIs efavirenz (Sustiva®)[10], etravirine (Intelence®)[11], nevirapine (Viramune®)[12], rilpivirine (Edurant®)[13]	Integrase Inhibitor (**i.e. elvitegravir/cobicistat**; generally no predicted interactions with raltegravir based on pharmacokinetic properties)
		monograph. Single dose study with meperidine 50mg and **ritonavir 500mg BID** x 10 days showed a 67% ↓ meperidine AUC, and 47% ↑ normeperidine AUC.[49] **Therapy can likely be cautiously initiated for short periods; however, potential for diminished analgesia and normeperidine toxicity (i.e. seizures) with prolonged or high-dose therapy, particularly in renal dysfunction. Therefore, close monitoring is still suggested. Long-term co-administration is not recommended.** **Tipranavir/rtv:** ↓ meperidine and ↑ normeperidine.[9]		
Methadone	Parent: CYP3A, 2B6 (*S* isomer), 2C19 (*R** isomer), 2D6 Inhibits: CYP2D6 (weak) * The *R* isomer is active	**(refer to separate chart on Methadone-Antiretroviral Drug Interactions)**		
Morphine	Parent: UGT Metabolite (active): morphine-6-glucuronide (renal)	No anticipated effect with unboosted atazanavir and fosamprenavir. **Nelfinavir and ritonavir** may ↓ morphine concentration and ↑ active metabolite concentration.	no anticipated effect	no anticipated effect
Nalbuphine Nubain® ***Agonist/ antagonist***	Parent: liver metabolism to inactive metabolites	unknown	unknown	unknown

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Naloxone ***Opioid antagonist*** **Suboxone®** (buprenorphine/ naloxone) **Targin®** (naloxone/ oxycodone)	Parent: UGT	No anticipated effect with unboosted atazanavir and fosamprenavir. **Nelfinavir and ritonavir** may ↓ naloxone concentration. **Also see entries under "Buprenorphine" for interaction data with buprenorphine/naloxone**.	no anticipated effect	no anticipated effect
Naltrexone ***Opioid antagonist*** **ReVia®**	Parent: Not via CYP450; metabolized via dihydrodiol dehydrogenase Metabolite (active): 6-B-naltrexol	unlikely An HIV cohort study naltrexone was only rarely associated with hepatotoxicity (i.e. significant elevations in liver transaminases). The majority of patients were also hepatitis C co-infected, had an alcohol dependency and were on antiretroviral therapy (including PIs and NNRTIs).[50]	unlikely An HIV cohort study naltrexone was only rarely associated with hepatotoxicity (i.e. significant elevations in liver transaminases). The majority of patients were also hepatitis C co-infected, had an alcohol dependency and were on antiretroviral therapy (including PIs and NNRTIs).[50]	unlikely
Oxycodone **OxyContin®** **OxyNEO®** **Supeudol®** **Endocet®** **Percocet®** (acetaminophen/ oxycodone) **Targin®**	Parent: CYP2D6, 3A4 Metabolites (active): oxymorphone via 2D6; noroxycodone via 3A4. Poor 2D6 metabolizers will not get analgesic effect.	potential ↑ oxycodone concentration In a randomized study of healthy volunteers, **ritonavir 300 mg, lopinavir/ritonavir 400/100 mg** or placebo **BID** was given for 4 days, with 10 mg oxycodone administered orally on day 3. Ritonavir and lopinavir/ritonavir increased oxycodone AUC 3.0-fold (range 1.9- to 4.3-fold; P <0.001) and 2.6-fold (range	potential ↓ oxycodone concentration	potential ↑ oxycodone concentration

	Narcotic Route of Metabolism[22 23, 24]	**Protease Inhibitors** atazanavir (Reyataz®)[1], darunavir (Prezista®)[2], fosamprenavir (Telzir®)[3], indinavir (Crixivan®)[4], lopinavir/ritonavir (Kaletra®)[25], nelfinavir (Viracept®)[6], ritonavir (Norvir®)[7], saquinavir (Invirase®)[8], tipranavir (Aptivus®)[9]	**NNRTIs** efavirenz (Sustiva®)[10], etravirine (Intelence®)[11], nevirapine (Viramune®)[12], rilpivirine (Edurant®)[13]	**Integrase Inhibitor** (**i.e. elvitegravir/cobicistat**; generally no predicted interactions with raltegravir based on pharmacokinetic properties)
(naloxone/ oxycodone)		1.9- to 3.3-fold; P <0.001), respectively. Both ritonavir (P <0.001) and lopinavir/ritonavir (P <0.05) increased the self-reported drug effect of oxycodone. Therefore, oxycodone dose reduction may be needed during concomitant use of ritonavir-containing therapy to avoid opioid-related adverse effects.[51]		
Pentazocine ***Agonist/ antagonist*** **Talwin®**	Parent: extensive liver metabolism with inactive glucuronide metabolite	unknown	unknown	unknown
Propoxyphene Darvon-N® ***(discontinued in 2010 due to risk of QT prolongation)***	Parent: extensive liver metabolism Metabolite (active): norpropoxyphene	unknown	unknown	unknown
Tramadol **Ralivia®, Tridural®, Ultram®, Zytram XL® Tramacet®** (acetaminophen/ tramadol)	Parent: CYP 3A4, 2B6, CYP2D6 Metabolite (active): O-desmethyl tramadol via 2D6[52] Inhibition of 2D6 may lead to ↓ therapeutic response	potential ↑ tramadol concentration	potential ↓ tramadol concentration	potential ↑ tramadol concentration

Key: CYP= Hepatic Cytochrome P450 isoenzyme; AD= Alcohol dehydrogenase; AUC= area under the concentration-time curve. Substrate= route of hepatic elimination of that specific drug (specified by a specific cytochrome P450 isoenzyme); inducer= leads to more rapid clearance of substrates of a specific hepatic isoenzyme (lowers levels of the respective drug and may lead to decreased efficacy); inhibitor= leads to decreased clearance of substrates of a specific hepatic isoenzyme (increases levels of a respective drug and may lead to toxicity). UGT= Uridine diphosphate glucuronyltransferase

Please note: This chart summarizes some of the major drug interactions identified to date, based on current available data; other drug interactions may exist. Please use caution whenever adding/modifying therapy. The information in this table is intended for use by experienced physicians and pharmacists. It is not intended to replace sound professional judgment in individual situations, and should be used in conjunction with other reliable sources of information. Due to the rapidly changing nature of information about HIV treatment and therapies, users are advised to recheck the information contained herein with the original source before applying it to patient care.

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Interactions between Antiretrovirals (ARVs) and Hormonal Contraceptives

This document consists of the following sections:

1. Combined Oral Contraceptives (COC)
2. Transdermal Contraceptives (e.g., Evra®)
3. Implantable Contraceptive (e.g., Implanon®)
4. Depo-medroxyprogesterone (DMPA, Depo-Provera®)
5. Levonorgestrel-releasing Intrauterine System (LNG-IUS) (e.g., Mirena®, Nova-T®)
6. Canadian Contraceptives Overview

1. ARV and Combined Oral Contraceptive (COC) Drug Interactions

Drug	ARV Kinetic Characteristics	Interaction	Suggestion
Nucleotide Reverse Transcriptase Inhibitor			
Tenofovir (Viread®)	Minimal systemic metabolism. Not substrate of CYP 450 enzymes. Renal elimination.	No effect on norgestimate (NGM)-ethinyl estradiol (EE) levels after taking tenofovir 300mg daily for 7 days.[1]	**No specific action required.**
Protease Inhibitors			
Atazanavir (Reyataz®)	Metabolism: CYP3A4 substrate Enzyme Inhibition: Inhibits CYP3A4	↑ 48% AUC of EE and ↑ 110% AUC of norethindrone (NE) after taking atazanavir 400mg daily for 2 weeks.[2] ↓ 19% AUC, ↓ 16% C_{max} of EE; ↑ 85% AUC, ↑ 68% C_{max} of NGM with atazanavir 300mg/ritonavir 100mg for 14 days. Authors concluded that 35 µg EE + ATV/RTV is expected to produce EE exposures similar to EE 25 µg without ATV/RTV.[3]	Atazanavir/Ritonavir: Use OC with **minimum 30 µg ethinyl estradiol** (manufacturer recommendation). Atazanavir: Use OC with **no more than 30 µg ethinyl estradiol** (manufacturer recommendation). Monitor for side effects of increased progesterone levels (including acne,and ↓ HDL and ↑ insulin resistance esp. in diabetic women). Use of other hormonal products (i.e. patch/ring/injectable) not recommended.[4]
Darunavir (Prezista®)	Metabolism: CYP3A4 substrate Enzyme Inhibition: Inhibits CYP3A4	↓ 44% AUC, ↓ 62% C_{min} of EE and ↓ 14% AUC, ↓ 30% C_{min} of NE after taking darunavir/ ritonavir 600/100mg bid for 2 weeks.[5]	**Use alternate/additional methods of contraception** (latex condom) secondary to loss of OC efficacy.
Fos/amprenavir (Telzir®)	Metabolism: CYP3A4 substrate	Amprenavir studies: ↓ 22% AUC, ↓ 20% C_{min} of amprenavir; ↑ 32% C_{min}	**Use alternate/ additional non-hormonal methods of contraception** (latex

Abbreviations: COC=combined oral contraceptive, EE= ethinyl estradiol, LNG= levonorgestrel, NE= norethindrone, NGM= norgestimate, NGMN= norelgestromin

Drug	ARV Kinetic Characteristics	Interaction	Suggestion
	Enzyme Induction: Induces CYP3A4 Enzyme Inhibition: Inhibits CYP3A4	of EE; ↑ 45% C_{min}, ↑ 18% AUC of NE with oral contraceptives containing EE 0.035 mg/NE 1mg.[6] May lead to loss of virologic response and possible resistance to amprenavir. Fosamprenavir studies: No change pk of amprenavir; ↓ 28% C_{max}, ↓ 37% AUC of EE; ↓ 38% C_{max}, ↓ 34% AUC, ↓ 26% C_{min} norethisterone after fosamprenavir 700 mg/ritonavir 100mg bid for 21 days.[6] Significant hepatic enzyme elevations and increased ritonavir levels also seen when boosted fosamprenavir used with COC.[6]	condom).
Indinavir (Crixivan®)	Metabolism: CYP3A4 substrate Enzyme Inhibition: Inhibits CYP3A4	↑ 24% AUC of EE; ↑ 26% AUC of NE.[7]	**No specific action required.**
Lopinavir (Kaletra®)	Metabolism: CYP3A4 substrate Enzyme Induction: Induces GT and possibly CYP1A2, 2C19, 2C Enzyme Inhibition: Inhibits CYP3A4>2D6	↓ 42% AUC, ↓ 41% C_{max}, ↓ 58% C_{min} of EE and ↓ 17% AUC, ↓ 16% $C_{max,}$ ↓ 32% C_{min} of NE.[8]	**Use alternate/ additional methods of contraception** (latex condom) secondary to loss of OC efficacy. **Use Progestin based contraceptives (Depo-Provera®)**. However, delavirdine, lopinavir/ritonavir, nelfinavir, and ritonavir might ↑ concentration of progestin-based contraceptives (metabolized by CYP 3A4). Monitor for the development of adverse effects with Depo-Provera®.[9]
Nelfinavir (Viracept®)	Metabolism: CYP3A4>2C19 Enzyme Induction: Induces CYP2B6, 2C8 and 2C9	↓ 47% AUC, ↓ 28% C_{max} of EE; ↓ 18% AUC of NE after nelfinavir 750mg q8h for 7 days. C_{max} NE unchanged.[10]	**See Lopinavir** **See DMPA chart**

Drug	ARV Kinetic Characteristics	Interaction	Suggestion
	Enzyme Inhibition: Inhibits CYP3A4		
Ritonavir (Norvir®)	Metabolism: CYP3A4>2D6 Enzyme Induction: Induces glucuronyl transferases (GT), CYP1A2, 2B6, 2C9, 2C19 Enzyme Inhibition: CYP3A>2D6>2C9, 2C19>>2A6, 2E1	↓ 40% AUC, ↓ 32% C_{max} of EE after ritonavir 500mg q12h for 16 days.[11]	**See Lopinavir**
Saquinavir (Invirase®)	Metabolism: CYP3A4 substrate Enzyme Inhibition: Weak inhibitor of CYP3A4	Single dose saquinavir levels were not affected by combined low-dose OC (0.03 mg EE, 0.075 mg gestodene).[12]	Due to use of saquinavir in combination with ritonavir, use **alternate/ additional methods of contraception** (latex condom).
Tipranavir (Aptivus®)	Metabolism: CYP3A4, p-glycoprotein (Pgp) substrate Enzyme Induction: Induces CYP3A4, GT, Pgp>CYP 1A2>2C9 Enzyme Inhibition: Inhibits CYP2D6 Note: When given with ritonavir, net effect is CYP3A inhibition.	↓ 50% AUC and C_{max} of single dose EE; no change in NE after tipranavir 500mg/ritonavir 100mg twice daily.[13]	Use **alternate/ additional methods of contraception** (latex condom) secondary to loss of OC efficacy.[13]
CCR5 Antagonist			
Maraviroc (Celsentri®)	Metabolism: CYP3A4, Pgp substrate	No change in C_{max} or AUC of oral contraceptives (30mcg EE/150 mcg levonorgestrel (LNG)) with low dose maraviroc (100mg twice daily).[14]	**No specific action required**. **More research needed** with full dose maraviroc (300mg twice daily).
Integrase Inhibitor			

Drug	ARV Kinetic Characteristics	Interaction	Suggestion
Raltegravir (Isentress®)	Metabolism: UGT1A1-mediated glucuronidation	↓ 12% AUC of EE; ↑ 14% AUC of norelgestromin (NGMN).[15] ↓ 2% AUC, ↑ 6% Cmax of EE; ↑14% AUC, ↑ 29% C_{max} of NGMN when taken with raltegravir 400mg twice daily for 21 days.[16]	**No specific action required**.
Elvitegravir (GS-9137) Quad tablet (elvitegravir/cobicistat/ emtricitabine/tenofovir)	Metabolism: combination of oxidative (CYP3A) and glucoronidation pathways Enzyme Induction: moderate inducer of CYP3A	↓ 25% AUC of EE; ↑ 2-fold AUC/C_{max} of NGM-active metabolite with stable OrthoTri-Cyclen Lo (EE 25 μg/NGM 180/215/250 μg)and Quad tablet daily for 14 days. No change progesterone level, similar ↓ FSH, larger ↓ LH during co-administration with Quad versus EE/NGM alone.[17]	**Authors recommend using oral contraceptive with minimum of 30 μg EE.**
Non-nucleoside Reverse Transcriptase Inhibitors			
Delavirdine (Rescriptor®)	Metabolism: CYP3A4>>2D6 substrate Enzyme Inhibition: Inhibits CYP3A4, 2C9,2C19	Concentrations of ethinyl estradiol may increase. However, the clinical significance is unknown.[18]	**No specific action required.**
Efavirenz (Sustiva®)	Metabolism: CYP3A4, 2B6 substrate Enzyme Induction: Induces CYP3A4 Enzyme Inhibition: Inhibits CYP3A4, 2C9, 2C19	↑ 37% AUC of EE 50 μg after 10 days of efavirenz (EFV) 400mg.[19] However, EFV found to interfere with the estradiol ELISA assay. This may artificially elevate estradiol levels if ELISA assay used.[20] No change EE level (LC-MS/MS assay); ↓ 64% AUC of NGM and ↓ 83% AUC of LNG (active metabolite of NGM) after EFV 600mg for 14	**Potential for failure of progesterone component.** May need to increase progesterone dose when used for daily or emergency contraception (i.e. use third generation progesterone such as desogestrel or gestodene which have higher affinity for progesterone receptor). **Alternative methods of contraception (latex condom) recommended.**

Abbreviations: COC=combined oral contraceptive, EE= ethinyl estradiol, LNG= levonorgestrel, NE= norethindrone, NGM= norgestimate, NGMN= norelgestromin

Drug	ARV Kinetic Characteristics	Interaction	Suggestion
		days.[21] ↓ 56% AUC of LNG (0.75 mg single dose for emergency contraception) after EFV 600mg for 14 days.[22]	
Etravirine (Intelence®)	Metabolism: CYP 3A4, 2C9, 2C19 substrate Enzyme Induction: Induces CYP3A4 Enzyme Inhibition: Inhibits CYP2C9, 2C19, mildly inhibits Pgp	↑ 22% AUC of EE; no change in AUC of NE after 15 days of ETV 200mg twice daily.[23]	**No specific action required.**
Nevirapine (Viramune®)	Metabolism: CYP3A4>>2B6 substrate Enzyme Induction: Induces CYP3A4, 2B6	↓ 20 % AUC of EE; ↓ 19% AUC, ↓ 16% C_{max} of NE.[24] ↓ 29% AUC EE; ↓ 18% AUC of NE.[25] Steady-state kinetics of COC (EE 30 μg and norgestrel 300 μg for at least 6 weeks) were studied in 3 groups of women: Group 1: HIV-positive on nevirapine (plus 3TC/d4T) for 90 days minimum Group 2: HIV-positive not on ARVs Group 3: HIV-negative Group 1: Highest AUC of EE; Highest AUC, C_{min} of LNG; ovulation suppressed. Conflicting evidence from previous studies, further study needed.[26]	**Use alternate/ additional methods of contraception** (latex condom) secondary to loss of OC efficacy. **Use Progestin based contraceptives (Depo-Provera®)**. **See DMPA chart.**

Drug	ARV Kinetic Characteristics	Interaction	Suggestion
Rilpivirine	Metabolism: CYP3A4> CYP2C19, 1A2, 2C8/9/10 (minor). Enzyme Induction: CYP2C19,> CYP1A2, 2B6, 3A4. (unlikely clinically relevant)	↑ 17% C_{max} of EE; pK of NE unaffected after 15 days of rilpivirine 25mg daily.[27]	**No specific action required.**

COC metabolism:
Ethinyl Estradiol:GT, sulphatase, substrate CYP3A4 > 2C9; Inhibits CYP1A2, 3A
Progestins: if contain ethinyl group-may inhibit CYP enzymes

2. ARV-Transdermal Contraceptive Drug Interactions

Name	Ingredients
Evra®	Ethinyl estradiol 35 µg/norelgestromin 200 µg once a week for 3 weeks out of 4

Drug	ARV Kinetic Characteristics	Interaction	Suggestion
Protease Inhibitors			
Lopinavir (Kaletra®)	Metabolism: CYP3A4 substrate Enzyme Induction: Induces GT and possibly CYP1A2, 2C19, 2C Enzyme Inhibition: Inhibits CYP3A4>2D6	**Transdermally** delivered EE and NGMN was studied in 8 HIV positive women on stable Kaletra® (LPV/r) compared to 24 women not on ARVs. Also, EE AUC after a single dose of a COC pill (EE/NE) was measured before patch placement and was compared with patch EE AUC in both groups. ↓ 45% AUC EE patch; ↓ 55% AUC EE pill in women on LPVr vs. controls (p=0.064 and p=0.003, respectively). ↑ 83% AUC NGMN in LPVr group vs. controls (p=0.036).[28]	The investigators concluded that although the kinetics of EE and NGMN were significantly altered in the presence of LPV/r, the contraceptive efficacy of the patch was likely to be maintained due to the increased NGMN levels. **The manufacturer recommends alternative/additional contraception with the contraceptive patch.**[8]

3. ARV-Implantable Contraceptive Drug Interactions

Name	Ingredients
Implanon®	Etonogestrel 68 μg ***not available in Canada**

Drug	ARV Kinetic Characteristics	Interaction	Suggestion
Non-nucleoside Reverse Transcriptase Inhibitors			
Efavirenz (Sustiva®)	Metabolism: CYP3A4, 2B6 substrate Enzyme Induction: Induces CYP3A4 Enzyme Inhibition: Inhibits CYP3A4, 2C9, 2C19	Etonogestrel exposure may be decreased (although not studied) due to postmarketing reports of contraceptive failure with etonogestrel in efavirenz-exposed patients.[29-33]	**Use alternate/ additional methods of contraception** (latex condom) secondary to loss of OC efficacy.

4. ARV-Depo-medroxyprogesterone (DMPA) Drug Interactions

Name	Ingredients
Depo-Provera®	depo-medroxyprogesterone 150 μg IM every 3 months

Drug	ARV Kinetic Characteristics	Interaction	Suggestion
Protease Inhibitors			
Nelfinavir (Viracept®)	Metabolism: CYP3A4>2C19,2D6 substrate Enzyme Inhibition: Inhibits CYP3A4	In 21 HIV patients, no change in AUC of nelfinavir 4 weeks after DMPA administered. After 12 weeks, no pregnancies, no women appeared to ovulate based on progesterone levels.[33] No affect on CD4 or HIV RNA levels.[34]	DMPA appears effective and safe in patients on nelfinavir.[31]
Atazanavir (Reyataz®)	Metabolism: CYP3A4 substrate Enzyme Inhibition: Inhibits CYP3A4	Not studied.	Manufacturer does not recommend use of injectable contraceptives.[4]
Non-nucleoside Reverse Transcriptase Inhibitors			

Drug	ARV Kinetic Characteristics	Interaction	Suggestion
Efavirenz (Sustiva®)	Metabolism: CYP3A4, 2B6 substrate Enzyme Induction: Induces CYP3A4 Enzyme Inhibition: Inhibits CYP3A4, 2C9, 2C19	In 17 HIV patients, no change in AUC of efavirenz 4 weeks after DMPA administered. After 12 weeks, no pregnancies, no women appeared to ovulate based on progesterone levels.[33] No affect on CD4 or HIV RNA levels.[34] In 30 HIV+ women, pK of DMPA similar with women on ARVs (EFV/AZT/3TC) versus no ARVs.[35]	DMPA appears effective and safe in patients on efavirenz.[31]
Nevirapine (Viramune®)	Metabolism: CYP3A4>>2B6 substrate Enzyme Induction: Induces CYP3A4, 2B6	In 16 HIV patients, small increase in nevirapine AUC 4 weeks after DMPA administered. After 12 weeks, no pregnancies, no women appeared to ovulate based on progesterone levels. [33] No affect on CD4 or HIV RNA levels.[34]	DMPA appears effective and safe in patients on nevirapine. Increased nevirapine levels do not appear to be clinically significant.[31]

DMPA metabolism: CYP3A4 substrate

5. ARV-Levonorgestrel-releasing Intrauterine System (LNG-IUS) Drug Interactions

Name	Ingredients
Mirena®	Intrauterine system /levonorgestrel 52 mg
Nova-T®	Intrauterine copper

Drug	Interaction	Suggestion
HAART (Nine different combinations of reverse transcriptase inhibitors and protease inhibitors)	In a study of 12 HIV + women, 83% on HAART, LNG levels slightly decreased over the 12 month study period. Estradiol levels remained in the follicular-phase range (>70 pmol/l). No pregnancies were reported. No affect on CD4 or HIV RNA levels.[36]	**More research on interactions with specific antiretrovirals needed. Currently use of LNG-IUS and copper IUD recommended by CDC.[37]**

Canadian Contraceptives Overview

Oral Contraceptives

Low Dose EE	Ingredients
Alesse® Aviane®	Ethinyl estradiol 20 µg/levonorgestrel 100 µg
Linessa®	Ethinyl estradiol 25 µg/desogestrel 100/125/150 µg
Minestrin®	Ethinyl estradiol 20 µg/norethindrone acetate 1mg
Tri-Cyclen Lo®	Ethinyl estradiol 25 µg/ norgestimate 180/215/250 µg
Yaz®	Ethinyl estradiol 20 µg/ drospirenone 3 mg
High Dose EE	**Ingredients**
Cyclen®	Ethinyl estradiol 35 µg/norgestimate 250 µg
Ovral®	Ethinyl estradiol 50 µg/norgestrel 250 µg
Tri-Cyclen®	Ethinyl estradiol 35 µg/norgestimate 180/215/250 µg
Brevicon 0.5/35® Ortho 0.5/35®	Ethinyl estradiol 35 µg/norethindrone 0.5mg
Brevicon 1/35® Ortho 1/35®	Ethinyl estradiol 35 µg/norethindrone 1mg
Synphasic ®	Ethinyl estradiol 35 µg/norethindrone 0.5/1/0.5mg
Ortho 7/7/7®	Ethinyl estradiol 35 µg/norethindrone 05/0.75/1 mg

Third Generation Progesterones

Name	Ingredients
Apri®	Ethinyl Estradiol 30 µg/ desogestrel 150 µg
Linessa®	Ethinyl estradiol 25 µg/ desogestrel 100/125/150 µg
Marvelon®	Ethinyl Estradiol 30 µg/ desogestrel 150 µg
Ortho-Cept®	Ethinyl Estradiol 30 µg/ desogestrel 150 µg

Transdermal Contraceptives

Name	Ingredients
Evra®	Ethinyl estradiol 35 µg/norelgestromin 200 µg once a week for 3 weeks out of 4

Implatable Contraceptives-not available in Canada

Name	Ingredients
Implanon®	Etonogestrel 68 µg

Injectable Contraceptives

Name	Ingredients
Depo-Provera®	depo-medroxyprogesterone 150 µg IM every 3 months

Intrauterine Contraceptives

Name	Ingredients
Mirena®	Intrauterine system /levonorgestrel 52 mg
Nova-T®	Intrauterine copper

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Predicted Interactions Between Psychotropics and Antiretrovirals

Antiretroviral Pharmacokinetic Characteristics (summary):

	Protease Inhibitors (PIs) atazanavir (Reyataz®)[1], darunavir (Prezista®)[2], fosamprenavir (Telzir®)[3], indinavir (Crixivan®)[4], lopinavir/ritonavir (Kaletra®)[5], nelfinavir (Viracept®)[6], ritonavir (Norvir®)[7], saquinavir (Invirase®)[8], tipranavir (Aptivus®)[9]	**Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)** efavirenz (Sustiva®)[10], etravirine (Intelence®)[11], nevirapine (Viramune®)[12], rilpivirine (Edurant®)[13]	**Integrase Inhibitors** elvitegravir/cobicistat (Stribild®, single-tablet regimen with tenofovir/emtricitabine)[14], raltegravir (Isentress®)[15]
Metabolism	Mainly CYP3A4	Efavirenz, nevirapine: CYP3A4, 2B6 (minor) Etravirine: CYP3A4, CYP2C9, and CYP2C19. Rilpivirine: CYP3A4 (major), as well as CYP2C19, 1A2, 2C8/9/10 (minor).	Elvitegravir: CYP3A, UGT1A1/3 Cobicistat: CYP3A, 2D6 (minor) Raltegravir: UGT1A1
Hepatic Inhibitor	Mainly CYP3A4 (darunavir, indinavir, nelfinavir, amprenavir >> saquinavir) Ritonavir: CYP3A4 (potent)> >2D6 >2C9 >2C19 >2A6 >1A2>2E1 At low boosting doses, ritonavir has a negligible effect in CYP2D6 inhibition.[5] Ritonavir inhibits CYP2B6 in vitro,[16] but induces 2B6 in vivo.[17] Nelfinavir: 2B6 in vitro.	Efavirenz: 2C9, 2C19[10] (? Clinical significance). Etravirine[11]: CYP2C9 (weak), CYP2C19 (moderate), p-glycoprotein (weak) Delavirdine (Rescriptor®)[18]; 3A4 (potent)	Cobicistat: CYP3A, CYP2D6; also p-glycoprotein (P-gp), BCRP, OATP1B1 and OATP1B3. Raltegravir has no inhibitory or inductive potential in vitro.[15]
Hepatic Inducer	Nelfinavir: UGT, 2C9/19 Ritonavir: UGT, CYP1A2, CYP2C9/19, 2B6 Tipranavir: mixed induction/inhibition effects; often acts as inducer of CYP3A4 (potent) and UGT, even when boosted with ritonavir[9]	Efavirenz: 3A4 (potent), 2B6[19] and UGT1A1[20] Etravirine[11]: 3A4 (weak) Nevirapine[12]: 3A4, 2B6 (potent) Rilpivirine: 2C19 (moderate), CYP1A2, 2B6 and 3A4 (weak).[21] A clinically relevant effect on CYP enzyme activity is considered unlikely with the 25 mg dose.[13]	Elvitegravir: CYP2C9 (modest) Raltegravir has no inhibitory or inductive potential in vitro.[15]

	Psychotropic Route of Metabolism[22-26]	Protease Inhibitors atazanavir (Reyataz®)[1], darunavir (Prezista®)[2], fosamprenavir (Telzir®)[3], indinavir (Crixivan®)[4], lopinavir/ritonavir (Kaletra®)[27], nelfinavir (Viracept®)[6], ritonavir (Norvir®)[7], saquinavir (Invirase®)[8], tipranavir (Aptivus®)[9]	NNRTIs efavirenz (Sustiva®)[10], etravirine (Intelence®)[11], nevirapine (Viramune®)[12], rilpivirine (Edurant®)[13]	Integrase Inhibitor elvitegravir/cobicistat (Stribild®, single-tablet regimen with tenofovir/emtricitabine)[14], raltegravir (Isentress®)[15]
Antidepressants - Tricyclic (TCA's), selective serotonin reuptake inhibitors (SSRIs), monoamine oxidase inhibitors (MAOIs), and others				
Amitriptyline Elavil®	Parent: CYP2D6, 2C19, 3A> GT Metabolite: CYP2D6 (nortriptyline)	Possible ↑ TCA concentrations	Possible ↓ TCA concentrations **Etravirine:** Possible ↑ or ↓ amitriptyline concentrations.[28]	Potential for ↑ TCA concentrations with **elvitegravir/cobicistat.** Monitor for response and adjust antidepressant dose accordingly.[14]
Bupropion Wellbutrin® Zyban®	Parent: CYP2B6 Metabolite (active): hydroxybupropion Inhibitor: CYP2D6 (parent and active metabolite)[29]	In vitro data suggest a strong potential for **nelfinavir** and **ritonavir** to inhibit bupropion metabolism. **Indinavir, saquinavir** and **amprenavir** were only weakly inhibitory of bupropion; hence no or only minor increase in bupropion concentrations anticipated.[16] However, in vivo data suggest induction. In an open-label, 3-phase pharmacokinetic study in healthy volunteers, exposure of bupropion and its active metabolite were both significantly reduced (AUC ↓ 57% and 50%, respectively) in the presence of steady state **lopinavir/ritonavir**. No significant changes in lopinavir kinetics were observed. Mechanism is postulated to be induction of CYP2B6 and UDP-	In vitro data suggest a strong potential for ***efavirenz*** to inhibit bupropion metabolism.[16] However, in 13 healthy volunteers, co administration of **efavirenz 600 mg QD** and single dose bupropion 150 mg showed 55% ↓ AUC and 34% ↓ Cmax of bupropion and ↓ t1/2 of hydroxybupropion (active metabolite).[19] Monitor for therapeutic response when using combination. One case series (n=11) where HIV-infected subjects received bupropion 150-300 mg daily for a median of 8 months in conjunction with either **nelfinavir, efavirenz, or ritonavir 100 mg BID** reported no episodes of seizures.[32] ***Delavirdine*** and ***nevirapine*** were	Potential for ↑ bupropion concentrations with **elvitegravir/cobicistat.** Monitor for response and adjust antidepressant dose accordingly.[14]

	Psychotropic Route of Metabolism[22-26]	Protease Inhibitors atazanavir (Reyataz®)[1], darunavir (Prezista®)[2], fosamprenavir (Telzir®)[3], indinavir (Crixivan®)[4], lopinavir/ritonavir (Kaletra®)[27], nelfinavir (Viracept®)[6], ritonavir (Norvir®)[7], saquinavir (Invirase®)[8], tipranavir (Aptivus®)[9]	NNRTIs efavirenz (Sustiva®)[10], etravirine (Intelence®)[11], nevirapine (Viramune®)[12], rilpivirine (Edurant®)[13]	Integrase Inhibitor elvitegravir/cobicistat (Stribild®, single-tablet regimen with tenofovir/emtricitabine)[14], raltegravir (Isentress®)[15]
		glucuronyltransferase.[30] In a pharmacokinetic study in healthy volunteers the effect of steady-state **ritonavir** at given at a high dose (600 mg BID) and low dose (100 mg BID) on single-dose **bupropion** 150 mg was studied. Bupropion AUC was decreased by 62% and 21% in each group, respectively, which demonstrates a dose-related interaction. An increase in the dose of bupropion may be required when given with ritonavir, however the authors recommend not to exceed the maximum daily bupropion dose.[31] One case series (n=11) where HIV-infected subjects received bupropion 150-300 mg daily for a median of 8 months in conjunction with either **nelfinavir, efavirenz, or ritonavir 100 mg BID** reported no episodes of seizures.[32]	only weakly inhibitory of bupropion; hence no or only minor increase in bupropion concentrations anticipated.[16] Coadministration of **tipranavir 500/ritonavir 200 mg BID** plus bupropion 150 mg BID in healthy volunteers resulted in 49% ↓ AUC, 60% ↓ Ctrough and 44% ↓ Cmax of bupropion, as well as approximately 25% ↓ in exposure of the active metabolite hydroxybupropion. Increased ALT was observed in 6/16 subjects after 1 week of tipranavir/ritonavir, but returned to baseline by the end of the study in 5/6 subjects.[33]	
Citalopram Celexa®	Parent: CYP2C19, 3A4>>2D6. Inhibitor (weak): CYP 2D6, 2C19; negligible	Possible ↑ SSRI concentrations. Use with ritonavir-boosted PIs with caution (may wish to start with ½ dose antidepressant).	Possible ↓ SSRI concentrations **Etravirine:** Possible ↑ or ↓ citalopram concentrations.[28]	Potential for ↑ SSRI concentrations with **elvitegravir/cobicistat.** Monitor for response and

	Psychotropic Route of Metabolism[22-26]	Protease Inhibitors atazanavir (Reyataz®)[1], darunavir (Prezista®)[2], fosamprenavir (Telzir®)[3], indinavir (Crixivan®)[4], lopinavir/ritonavir (Kaletra®)[27], nelfinavir (Viracept®)[6], ritonavir (Norvir®)[7], saquinavir (Invirase®)[8], tipranavir (Aptivus®)[9]	NNRTIs efavirenz (Sustiva®)[10], etravirine (Intelence®)[11], nevirapine (Viramune®)[12], rilpivirine (Edurant®)[13]	Integrase Inhibitor elvitegravir/cobicistat (Stribild®, single-tablet regimen with tenofovir/emtricitabine)[14], raltegravir (Isentress®)[15]
	effect on CYP 3A4, 1A2[34]			adjust antidepressant dose accordingly.[14]
Escitalopram Lexapro® Cipralex® (S-enantiomer of citalopram)	Parent: CYP2C19, 3A4 >> 2D6 Inhibitor (weak or negligible): CYP2D6, 1A2, 2C9, 2C19, 2E1, 3A4[35]	Possible ↑ SSRI concentrations. 18 healthy subjects received escitalopram 20mg and **ritonavir** 600 mg single dose. No significant interaction found.[36]	Possible ↓ SSRI concentrations **Etravirine:** Possible ↑ or ↓ escitalopram concentrations.[28]	Potential for ↑ SSRI concentrations with **elvitegravir/cobicistat.** Monitor for response and adjust antidepressant dose accordingly.[14]
Clomipramine Anafranil®	Parent: CYP2D6, 1A2, 2C19, 3A Metabolite: CYP2D6 (desmethyl)	Possible ↑ TCA concentrations	Possible ↓ TCA concentrations **Etravirine:** Possible ↑ or ↓ clomipramine concentrations.[28]	Potential for ↑ TCA concentrations with **elvitegravir/cobicistat.** Monitor for response and adjust antidepressant dose accordingly.[14]
Desipramine Pertofrane®	Parent: CYP2D6>>UGT	No anticipated effect with unboosted PIs. **Ritonavir** (high dose): 145% ↑ desipramine AUC; consider desipramine dose reduction by 50%.[37] Lower boosting doses of ritonavir unlikely to have same degree of interaction as per lopinavir/r data. **Lopinavir/ritonavir**: no significant effect on desipramine pharmacokinetics.[38]	No anticipated effect	Desipramine 50 mg single dose administered with **elvitegravir/cobicistat:** 24% ↑ Cmax and 65% ↑ AUC of desipramine. Monitor for response and adjust antidepressant dose accordingly.[14]
Desvenlafaxine Pristiq®	UGT>>3A4 (Major active metabolite of venlafaxine)	Desvenlafaxine concentrations were ↑ 43% by ketoconazole 200 mg BID; use of potent	Possible ↓ desvenlafaxine.	Potential for ↑ desvenlafaxine concentrations with

	Psychotropic Route of Metabolism[22-26]	Protease Inhibitors atazanavir (Reyataz®)[1], darunavir (Prezista®)[2], fosamprenavir (Telzir®)[3], indinavir (Crixivan®)[4], lopinavir/ritonavir (Kaletra®)[27], nelfinavir (Viracept®)[6], ritonavir (Norvir®)[7], saquinavir (Invirase®)[8], tipranavir (Aptivus®)[9]	NNRTIs efavirenz (Sustiva®)[10], etravirine (Intelence®)[11], nevirapine (Viramune®)[12], rilpivirine (Edurant®)[13]	Integrase Inhibitor elvitegravir/cobicistat (Stribild®, single-tablet regimen with tenofovir/emtricitabine)[14], raltegravir (Isentress®)[15]
	Inhibits 2D6 at high doses; does not have a clinically relevant effect on CYP2D6 metabolism at 100 mg daily. In vitro, no inhibiting/inducing effects on 3A4, no inhibiting effects on P-gp. However, in a clinical study, the AUC of single dose midazolam (a CYP3A4 substrate) was ↓ 31% in the presence of desvenlafaxine 400 mg daily. Therefore, possibility that desvenlafaxine may act as an inducer in vivo.	CYP3A4 inhibitors may result in ↑ concentrations of desvenlafaxine. Potential for desvenlafaxine to ↓ concentrations of CYP3A4 substrates. Clinical significance with HIV protease inhibitors unclear. Monitor for HIV efficacy, consider TDM.		**elvitegravir/cobicistat.** Monitor for response and adjust antidepressant dose accordingly.[14]
Doxepin Sinequan®	Parent: hepatic metabolism (? CYPs) Metabolite (active): desmethyldoxepin	Unknown; possible ↑ doxepin concentrations	Unknown; possible ↓ doxepin concentrations	Unknown; possible ↑ doxepin concentrations with **elvitegravir/cobicistat.**
Duloxetine (Cymbalta®)	Parent:CYP1A2, 2D6; inactive metabolites Inhibitor (moderate): CYP2D6	Unboosted PIs unlikely to have a major interaction. Potential for ritonavir-boosted PIs to ↑ or ↓ duloxetine concentrations. Monitor for efficacy/toxicity.	Unlikely to have a major interaction. **Rilpivirine** is a slight inducer of CYP1A2; potential for ↓ duloxetine concentrations.	Potential for ↑ duloxetine concentrations with **elvitegravir/cobicistat.** Monitor for response and adjust antidepressant dose accordingly.[14]

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		At low boosting doses, **ritonavir** does not inhibit CYP2D6 at clinically relevant concentrations, but has a more potent inhibitory effect at higher therapeutic doses.[7, 27] It may also induce CYP1A2. **Tipranavir/r** inhibits CYP2D6 and induces CYP1A2, therefore an interaction is difficult to predict.[9]		
Fluoxetine Prozac®	Parent: CYP2D6 Inhibits: CYP2D6 (potent) Metabolite (active): norfluoxetine	No anticipated effect of unboosted PIs on fluoxetine. Potential for ↑ SSRI concentrations with higher doses of **ritonavir**, but unlikely with lower boosting doses of ritonavir. Kinetic study showing 19% ↑ **ritonavir** AUC.[39, 40] Post-marketing reports of cardiac and neurologic events with combination.[7] Serotonin syndrome reported in a case series of patients when **ritonavir** based HAART (100-600mg BID) was added to fluoxetine. Symptoms included mental changes (confusion, mania, agitation, paranoia,	No anticipated effect on fluoxetine or NNRTIs. In a retrospective review, the pharmacokinetics of **efavirenz** did not appear to be significantly affected by concomitant use of selective serotonin reuptake inhibitors.[42] In one cohort study, fluoxetine did not significantly impact **nevirapine** clearance. However, the dose-normalized concentrations of fluoxetine and the active metabolite, norfluoxetine, were decreased by 65% and 35%, respectively. Monitor closely for the clinical response to fluoxetine; possible	Potential for ↑ SSRI concentrations with **elvitegravir/cobicistat.** Monitor for response and adjust antidepressant dose accordingly.[14]

	Psychotropic Route of Metabolism[22-26]	Protease Inhibitors atazanavir (Reyataz®)[1], darunavir (Prezista®)[2], fosamprenavir (Telzir®)[3], indinavir (Crixivan®)[4], lopinavir/ritonavir (Kaletra®)[27], nelfinavir (Viracept®)[6], ritonavir (Norvir®)[7], saquinavir (Invirase®)[8], tipranavir (Aptivus®)[9]	NNRTIs efavirenz (Sustiva®)[10], etravirine (Intelence®)[11], nevirapine (Viramune®)[12], rilpivirine (Edurant®)[13]	Integrase Inhibitor elvitegravir/cobicistat (Stribild®, single-tablet regimen with tenofovir/emtricitabine)[14], raltegravir (Isentress®)[15]
		anxiety), myoclonus, fever, diarrhea, nausea, vomiting, and diaphoresis. Most symptoms resolved by discontinuation of RTV or fluoxetine, or by lowering dosages of fluoxetine by 50% and RTV to 100mg BID (if used to boost other protease inhibitors).[41]	dose increases may be required.[43] **Delavirdine:** 50% ↑ delavirdine trough concentrations with combination. Cautious use of combination is warranted.[18]	
Fluvoxamine Luvox®	Parent:CYP2D6> 1A2 Inhibits: 1A2 (potent), 3A4, 2C (moderate), 2D6 (weak)	No major anticipated effect with unboosted PIs. Potential for ↑ SSRI concentrations with higher doses of ritonavir, but unlikely with lower boosting doses of ritonavir. Potential for fluvoxamine to modestly ↑ PI concentrations. Clinical significance unknown, monitor for toxicity.	Potential for fluvoxamine to modestly ↑ NNRTI concentrations. Clinical significance unknown, monitor for toxicity. In one cohort study, fluovoxamine inhibited the clearance of **nevirapine** by 33.7% in a dose-dependent manner; the dose-normalized concentration of fluvoxamine was not significantly altered. Close monitoring for nevirapine toxicity is warranted, particularly when high doses of fluvoxamine are used.[43] **Etravirine:** Possible ↑ etravirine concentrations.[28]	Potential for ↑ SSRI concentrations with **elvitegravir/cobicistat.** Monitor for response and adjust antidepressant dose accordingly.[14]
Imipramine Tofranil®	Parent: CYP2D6, 1A2, 2C19, 3A > UGT Metabolite (active): CYP2D6 (desipramine)	Possible ↑ TCA concentrations	Possible ↓ TCA concentrations **Etravirine:** Possible ↑ or ↓	Potential for ↑ TCA concentrations with **elvitegravir/cobicistat.** Monitor for response and

	Psychotropic Route of Metabolism[22-26]	Protease Inhibitors atazanavir (Reyataz®)[1], darunavir (Prezista®)[2], fosamprenavir (Telzir®)[3], indinavir (Crixivan®)[4], lopinavir/ritonavir (Kaletra®)[27], nelfinavir (Viracept®)[6], ritonavir (Norvir®)[7], saquinavir (Invirase®)[8], tipranavir (Aptivus®)[9]	NNRTIs efavirenz (Sustiva®)[10], etravirine (Intelence®)[11], nevirapine (Viramune®)[12], rilpivirine (Edurant®)[13]	Integrase Inhibitor elvitegravir/cobicistat (Stribild®, single-tablet regimen with tenofovir/emtricitabine)[14], raltegravir (Isentress®)[15]
			imipramine concentrations.[28]	adjust antidepressant dose accordingly.[14]
Maprotiline Ludiomil®	Parent:CYP2D6 Metabolite: UGT (hydroxyl)	Interaction unlikely with unboosted PIs. Potential ↑ maprotiline concentrations with higher doses of ritonavir, but unlikely with lower boosting doses of ritonavir.	Interaction unlikely	Potential for ↑ maprotiline concentrations with **elvitegravir/cobicistat.** Monitor for response and adjust antidepressant dose accordingly.[14]
Milnacipran Ixel®	UGT. Not a substrate of P450 system	Interaction unlikely with unboosted atazanavir or fosamprenavir. Potential ↓ milnacipran concentrations via UGT induction by ritonavir or nelfinavir.	Potential ↓ milnacipran concentrations	Interaction unlikely.
Mirtazapine Remeron®	CYP2D6, 1A2, 3A4 Is not an enzyme inhibitor or inducer[44]	Possible ↑ mirtazapine concentrations with unboosted PIs. Possible ↑↑ mirtazapine levels with ritonavir-boosted PIs due to inhibition of 3A4 and possibly 2D6. Monitor for acute somnolence if ritonavir is added. Consider mirtazapine dosage decrease if combination is used.	Possible ↓ mirtazapine concentrations. **Etravirine:** Possible ↓ mirtazapine concentrations.[28]	Potential for ↑ mirtazapine concentrations with **elvitegravir/cobicistat.** Monitor for response and adjust antidepressant dose accordingly.[14]
Moclobemide Manerix®	Parent: CYP2C19>2D6 Inhibits: CYP2C19>2D6	No anticipated effect with unboosted PIs. Possible ↑ or ↓ moclobemide	Efavirenz and etravine are weak-moderate inhibitors of CYP2C19, and thus may possibly ↑ moclobemide concentrations.	Potential for ↑ moclobemide concentrations with **elvitegravir/cobicistat.** Monitor for response and

	Psychotropic Route of Metabolism[22-26]	Protease Inhibitors atazanavir (Reyataz®)[1], darunavir (Prezista®)[2], fosamprenavir (Telzir®)[3], indinavir (Crixivan®)[4], lopinavir/ritonavir (Kaletra®)[27], nelfinavir (Viracept®)[6], ritonavir (Norvir®)[7], saquinavir (Invirase®)[8], tipranavir (Aptivus®)[9]	NNRTIs efavirenz (Sustiva®)[10], etravirine (Intelence®)[11], nevirapine (Viramune®)[12], rilpivirine (Edurant®)[13]	Integrase Inhibitor elvitegravir/cobicistat (Stribild®, single-tablet regimen with tenofovir/emtricitabine)[14], raltegravir (Isentress®)[15]
		concentrations with ritonavir-boosted PIs.	Rilpivirine is a moderate inducer of CYP2C19, and may possibly ↓ moclobemide concentrations. Monitor for efficacy & toxicity.	adjust antidepressant dose accordingly.[14]
Nefazodone Serzone® *(*drug discontinued in Canada in 2003)*	Parent:CYP3A Inhibits: CYP3A (potent) Metabolite: CYP2D6 (hydroxy-nefazodone)	Unboosted PIs may ↑ nefazodone concentrations; potential ↑ ↑ nefazodone concentrations with ritonavir-boosted PIs. Potential for nefazodone to ↑ PI concentrations and toxicity.	Likely ↓ nefazodone concentrations. Potential for nefazodone to ↑ NNRTI concentrations and toxicity **Etravirine:** Possible ↓ nefazodone concentrations and ↑ etravirine concentrations. [28] Potential for ↑ **rilpivirine** concentrations; AVOID co-administration.	Potential for ↑ nefazodone concentrations with **elvitegravir/cobicistat.** Monitor for response and adjust antidepressant dose accordingly.[14]
Nortriptyline Norventyl®	Parent: CYP2D6 Metabolite (active): 10-hydroxynortriptyline	No anticipated effect with unboosted PIs. Potential ↑ TCA concentrations with higher doses of ritonavir, but unlikely with lower boosting doses of ritonavir.	No anticipated effect	Potential for ↑ TCA concentrations with **elvitegravir/cobicistat.** Monitor for response and adjust antidepressant dose accordingly.[14]
Paroxetine Paxil®	Parent:CYP2D6 Inhibits: CYP2D6 (potent)	Based on paroxetine metabolism potential for ↑ paroxetine concentrations exists with higher doses of ritonavir, but unlikely with lower boosting doses of ritonavir. However, interaction is complex and difficult to predict. For example, in the cases of	No anticipated effect; In a retrospective review, the pharmacokinetics of **efavirenz** did not appear to be significantly affected by concomitant use of selective serotonin reuptake inhibitors.[42]	Potential for ↑ SSRI concentrations with **elvitegravir/cobicistat.** Monitor for response and adjust antidepressant dose accordingly.[14]

	Psychotropic Route of Metabolism[22-26]	Protease Inhibitors atazanavir (Reyataz®)[1], darunavir (Prezista®)[2], fosamprenavir (Telzir®)[3], indinavir (Crixivan®)[4], lopinavir/ritonavir (Kaletra®)[27], nelfinavir (Viracept®)[6], ritonavir (Norvir®)[7], saquinavir (Invirase®)[8], tipranavir (Aptivus®)[9]	NNRTIs efavirenz (Sustiva®)[10], etravirine (Intelence®)[11], nevirapine (Viramune®)[12], rilpivirine (Edurant®)[13]	Integrase Inhibitor elvitegravir/cobicistat (Stribild®, single-tablet regimen with tenofovir/emtricitabine)[14], raltegravir (Isentress®)[15]
		fosamprenavir/r and darunavir/r the AUC of paroxetine was decreased by 58% and 39%, respectively (see below).[45, 46] In healthy volunteers, paroxetine 20 mg QD plus **fosamprenavir/r** 700/100 mg BID for 10 days resulted in ↓ 58% paroxetine AUC, while amprenavir kinetics were similar to historical controls. Mechanism unknown; monitor for efficacy and ↑ paroxetine dose if required.[46] Co administration of **darunavir/r** 400/100 mg BID and paroxetine 20 mg QD led to 39% ↓ paroxetine exposure; darunavir levels were not affected. Monitor for antidepressant efficacy and ↑ paroxetine dose if required.[45]	In healthy volunteers, paroxetine 20 mg QD plus **etravirine** (TMC125) 800 mg BID (old formulation) did not result in significant changes in exposures of either drug. No dosage adjustment is required.[11]	
Phenelzine Nardil®	Acetylation inhibits: CYP (weak)	Unlikely	Unlikely	Unlikely
Reboxetine Edronax®	3A4 substrate	Potential for ↑ reboxetine concentrations	Potential for ↓ reboxetine concentrations	Potential for ↑ reboxetine concentrations with **elvitegravir/cobicistat.** Monitor for response and adjust antidepressant dose accordingly.[14]
Selegiline (transdermal patch)	2B6, 1A2 substrate	Unlikely interaction with unboosted PIs.	Potential for ↓ selegiline concentrations	

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EMSAM®		Potential for ↓ selegiline concentrations with ritonavir-boosted PIs.		
Sertraline Zoloft®	Parent:CYP2B6 > 2C9/19, 3A4, 2D6, UGT1A1(possible)[47] Inhibits: CYP2D6 (moderate)	Potential ↑ or ↓ sertraline concentrations due to complex metabolism of sertraline. Co-administration of **darunavir/r** 400/100 mg BID and sertraline 50 mg QD led to 49% ↓ sertraline exposure; darunavir levels were not affected. Monitor for antidepressant efficacy and ↑ sertraline dose if required.[45]	Potential for ↓ sertraline concentrations due to enzyme induction. Sertraline AUC↓ by 39%, **efavirenz** kinetics not affected.[10, 42] **Etravirine:** Possible ↑ or ↓ sertraline concentrations.[28]	Potential for ↑ SSRI concentrations with **elvitegravir/cobicistat.** Monitor for response and adjust antidepressant dose accordingly.[14]
St. John's Wort (hypericum perforatum)	Induces CYP3A4 and P-gp	Significantly reduces **indinavir** exposure (57% ↓ AUC, 81% ↓ Cmin)[48]; similar interaction may be likely with other substrates of CYP3A4. **Avoid concomitant use of PIs and NNRTIs with St. John's wort.** **Maraviroc: Avoid concomitant use with St. John's wort.[49]**	St. John's Wort reduces **nevirapine** concentrations 35%.[50] **Avoid concomitant use of PIs and NNRTIs with St. John's wort.**	**Coadministration with elvitegravir/cobicistat is contraindicated.[14]**
Tranylcypromine Parnate®	hepatic metabolism	Possible ↑ MAOI concentrations	Possible ↓ MAOI concentrations	Possible ↑ MAOI concentrations with **elvitegravir/cobicistat.**
Trazodone Desyrel®	Parent:CYP2D6> CYP3A	Possible ↑ trazodone concentrations	Possible ↓ trazodone concentrations	Potential for ↑ trazodone concentrations with

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	Metabolite: CYP2D6 (m-CPP)	**Indinavir:** strong inhibitor of trazodone *in vitro*. Monitor for trazodone toxicity (i.e. nausea, hypotension, syncope, somnolence, anticholinergic side-effects). **Saquinavir and nelfinavir:** weak inhibitors *in vitro*; interaction is unlikely.[51] **Ritonavir:** potent inhibitor of trazodone *in vitro*.[51] 10 healthy subjects received trazodone 50 mg with RTV 4 x 200mg doses: significant increase in trazodone concentrations (52% ↓ CL, 122% ↑ T 1/2, 34% ↑ Cmax).[7] Sedation, fatigue, impaired performance, nausea, dizziness, hypotension, syncope reported.[52] **When combined with ritonavir-based regimens, use with caution and consider a lower dose of trazodone.**[7]		**elvitegravir/cobicistat.** Monitor for response and adjust antidepressant dose accordingly.[14]
Trimipramine Surmontil®	Parent: CYP2D6 Metabolite (active): Desmethytrimipramine	No anticipated effect with unboosted PIs. Potential ↑ TCA concentrations with higher doses of ritonavir, but unlikely with lower boosting doses of ritonavir.	No anticipated effect	Potential for ↑ TCA concentrations with **elvitegravir/cobicistat.** Monitor for response and adjust antidepressant dose accordingly.[14]

	Psychotropic Route of Metabolism[22-26]	Protease Inhibitors atazanavir (Reyataz®)[1], darunavir (Prezista®)[2], fosamprenavir (Telzir®)[3], indinavir (Crixivan®)[4], lopinavir/ritonavir (Kaletra®)[27], nelfinavir (Viracept®)[6], ritonavir (Norvir®)[7], saquinavir (Invirase®)[8], tipranavir (Aptivus®)[9]	NNRTIs efavirenz (Sustiva®)[10], etravirine (Intelence®)[11], nevirapine (Viramune®)[12], rilpivirine (Edurant®)[13]	Integrase Inhibitor elvitegravir/cobicistat (Stribild®, single-tablet regimen with tenofovir/emtricitabine)[14], raltegravir (Isentress®)[15]
Venlafaxine Effexor®	Parent: CYP2D6 > CYP3A4 (minor) Inhibits: CYP2D6 (weak) Metabolite (active): UGT (O-desmethylvenlafaxine, ODV)[53]	Possible ↑ venlafaxine concentrations with unboosted PIs; however interaction study with **indinavir** showed ↓ in indinavir concentrations (28% ↓ AUC, 36% ↓ Cmax); no change in venlafaxine concentrations.[54] CYP2D6 inhibitors may ↓ the metabolism of venlafaxine to ODV, resulting in ↑ plasma concentrations of venlafaxine and ↓ concentrations of ODV. However, as venlafaxine and ODV are both pharmacologically active, the product monograph states that no dosage adjustment is required when venlafaxine is coadministered with a CYP2D6 inhibitor.[53]	Possible ↓ venlafaxine concentrations **Etravirine:** Possible ↓ venlafaxine concentrations. [28]	Potential for ↑ venlafaxine concentrations with **elvitegravir/cobicistat.** Monitor for response and adjust antidepressant dose accordingly.[14]
Neuroleptics				
Amisulpride Solian® Special Access in Canada	Parent: 50 % renal; no clinically relevant metabolism[25]	Unlikely	Unlikely	Unlikely
Aripiprazole Abilify®	Parent: CYP 3A4, 2D6[25] Metabolite (active): dehydro-aripiprazole	Possible ↑ aripiprazole concentrations. A 43 y.o. male was on **aripiprazole** 50 mg daily and **duloxetine** 60 mg daily	Possible ↓ aripiprazole concentrations	Potential for ↑ aripiprazole concentrations with **elvitegravir/cobicistat.** A decrease in neuroleptic dose may be required.[14]

	Psychotropic Route of Metabolism[22-26]	Protease Inhibitors atazanavir (Reyataz®)[1], darunavir (Prezista®)[2], fosamprenavir (Telzir®)[3], indinavir (Crixivan®)[4], lopinavir/ritonavir (Kaletra®)[27], nelfinavir (Viracept®)[6], ritonavir (Norvir®)[7], saquinavir (Invirase®)[8], tipranavir (Aptivus®)[9]	NNRTIs efavirenz (Sustiva®)[10], etravirine (Intelence®)[11], nevirapine (Viramune®)[12], rilpivirine (Edurant®)[13]	Integrase Inhibitor elvitegravir/cobicistat (Stribild®, single-tablet regimen with tenofovir/emtricitabine)[14], raltegravir (Isentress®)[15]
		(CYP2D6 inhibitor) for depression/anxiety in addition to a **darunavir/ritonavir** 800/100 mg daily based regimen (CYP3A4 inhibitor). The patient developed CNS symptoms (confusion, loss of coordination) and was later hospitalized with fever, cough headache, neck stiffness, back pain, and blurred vision. All investigations were negative except for lymphadenopathy. A random aripiprazole serum concentration was elevated at 1100 ng/mL (therapeutic is 100-200 ng/mL) 49 days after hospital discharge and apipiprazole was discontinued. [55] Caution is warranted when PIs and aripiprazole are coadmininstered and lower aripiprazole doses may be required.		
Asenapine Saphris®	Substrate of UGT1A4, CYP1A2>> CYP3A4, CYP2D6. Weak inhibitor of CYP2D6. Asenapine does not cause induction of CYP1A2 or CYP3A4.	Possible ↓ asenapine concentrations with boosted PIs or nelfinavir.	Possible ↓ asenapine concentrations	Possible ↑ asenapine concentrations with **elvitegravir/cobicistat.** A decrease in neuroleptic dose may be required.[14]
Chlorpromazine Largactil®	Parent:CYP2D6, CYP1A2?, GT	Unlikely interaction with unboosted PIs.	Unlikely	Potential for ↑ neuroleptic concentrations with

	Psychotropic Route of Metabolism[22-26]	Protease Inhibitors atazanavir (Reyataz®)[1], darunavir (Prezista®)[2], fosamprenavir (Telzir®)[3], indinavir (Crixivan®)[4], lopinavir/ritonavir (Kaletra®)[27], nelfinavir (Viracept®)[6], ritonavir (Norvir®)[7], saquinavir (Invirase®)[8], tipranavir (Aptivus®)[9]	NNRTIs efavirenz (Sustiva®)[10], etravirine (Intelence®)[11], nevirapine (Viramune®)[12], rilpivirine (Edurant®)[13]	Integrase Inhibitor elvitegravir/cobicistat (Stribild®, single-tablet regimen with tenofovir/emtricitabine)[14], raltegravir (Isentress®)[15]
	Metabolite: GT (7-OH-CPZ)	Potential ↑ chlorpromazine concentrations with higher doses of ritonavir, but unlikely with lower boosting doses of ritonavir.		**elvitegravir/cobicistat.** A decrease in neuroleptic dose may be required.[14]
Clozapine Clozaril®	Parent: CYP1A2> 2C19, 3A4, 2D6[25] Metabolite (active): norclozapine	Possible ↑ clozapine concentrations with unboosted PIs. Potential for ↓ or ↑ clozapine concentrations due to ritonavir-mediated CYP1A2 induction and/or CYP3A4 inhibition. Interaction difficult to predict. **Combination no longer contraindicated in product monograph.**[7]	Possible ↓ clozapine concentrations	Potential for ↑ neuroleptic concentrations with **elvitegravir/cobicistat.** A decrease in neuroleptic dose may be required.[14]
Flupenthixol Fluanxol®	Parent: Extensive hepatic metabolism (not well defined)	Possible ↑ flupenthixol concentrations	Possible ↓ flupenthixol concentrations	Potential for ↑ neuroleptic concentrations with **elvitegravir/cobicistat.** A decrease in neuroleptic dose may be required.[14]
Fluphenazine Modecate®	Parent: Extensive hepatic metabolism	Possible ↑ fluphenazine concentrations	Possible ↓ fluphenazine concentrations	Potential for ↑ neuroleptic concentrations with **elvitegravir/cobicistat.** A decrease in neuroleptic dose may be required.[14]
Haloperidol Haldol®	Parent: CYP2D6>3A4	Possible ↑ haloperidol concentrations	Possible ↓ haloperidol concentrations	Potential for ↑ neuroleptic concentrations with **elvitegravir/cobicistat.** A decrease in neuroleptic dose

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				may be required.[14]
Loxapine Loxapac®	Parent: Extensive hepatic metabolism	Possible ↑ loxapine concentrations	Possible ↓ loxapine concentrations	Potential for ↑ neuroleptic concentrations with **elvitegravir/cobicistat.** A decrease in neuroleptic dose may be required.[14]
Methotrimeprazine (levomepromazine) Nozinan®	Parent: Extensive hepatic metabolism Inhibits CYP2D6	Possible ↑ methotrimeprazine concentrations	Possible ↓ methotrimeprazine concentrations	Potential for ↑ neuroleptic concentrations with **elvitegravir/cobicistat.** A decrease in neuroleptic dose may be required.[14]
Olanzapine Zyprexa®	Parent: CYP1A2 >> 2D6; UGT1A4[25] Inhibits: CYP1A2, 2D6, 3A4 (weak)	No anticipated effect with most unboosted PIs; **nelfinavir and ritonavir** may ↓ olanzapine concentrations by inducing glucuronidation. Healthy volunteer study of olanzapine 10 mg +/- **ritonavir 500 mg BID** resulted in 53%↓ AUC of olanzapine. Higher olanzapine dosages may be necessary to maintain therapeutic effect.[56] In a healthy volunteer study, subjects received single dose olanzapine 10 mg alone or olanzapine 15 mg with steady-state **fosamprenavir 700/100 mg BID**. Olanzapine 15 mg in	No anticipated effect. Potential for olazapine to cause minor ↑ NNRTI concentrations and toxicity.	Potential for ↑ neuroleptic concentrations with **elvitegravir/cobicistat.** A decrease in neuroleptic dose may be required.[14]

	Psychotropic Route of Metabolism[22-26]	Protease Inhibitors atazanavir (Reyataz®)[1], darunavir (Prezista®)[2], fosamprenavir (Telzir®)[3], indinavir (Crixivan®)[4], lopinavir/ritonavir (Kaletra®)[27], nelfinavir (Viracept®)[6], ritonavir (Norvir®)[7], saquinavir (Invirase®)[8], tipranavir (Aptivus®)[9]	NNRTIs efavirenz (Sustiva®)[10], etravirine (Intelence®)[11], nevirapine (Viramune®)[12], rilpivirine (Edurant®)[13]	Integrase Inhibitor elvitegravir/cobicistat (Stribild®, single-tablet regimen with tenofovir/emtricitabine)[14], raltegravir (Isentress®)[15]
		the presence of fosamprenavir/ritonavir resulted in similar AUC and 32% ↑ Cmax as that observed with olanzapine 10 mg alone. Amprenavir pharmacokinetic parameters were similar to historical controls. Increase olanzapine dose by 50% when combining with boosted fosamprenavir.[57] Potential for olanzapine to ↑ protease concentrations and toxicity (likely not clinically significant).		
Paliperidone Invega®, Invega Sustenna®	Parent: potential for some (minimal?) involvement in P450 metabolism; substrate of CYP3A4, P-gp >> 2D6. Not expected to cause clinically significant interactions with P450 substrates. Paliperidone is the major active metabolite of risperidone.	Possible ↑ paliperidone concentrations. No clinically significant effect noted when paliperidone was coadministered with paroxetine, a potent 2D6 inhibitor.	Possible ↓ paliperidone concentrations. Monitor for efficacy. Co-administration of paliperidone with carbamazepine 200 mg BID (a 3A4 & P-gp inducer) caused a 37% ↓ in AUC of paliperidone.	Potential for ↑ neuroleptic concentrations with **elvitegravir/cobicistat.** A decrease in neuroleptic dose may be required.[14]
Perphenazine Trilafon®	Parent: CYP2D6 Inhibits: CYP2D6	Interaction unlikely with unboosted PIs. Potential ↑ perphenazine concentrations with higher doses	Unlikely	Potential for ↑ neuroleptic concentrations with **elvitegravir/cobicistat.** A decrease in neuroleptic dose may be required.[14]

	Psychotropic Route of Metabolism[22-26]	**Protease Inhibitors** atazanavir (Reyataz®)[1], darunavir (Prezista®)[2], fosamprenavir (Telzir®)[3], indinavir (Crixivan®)[4], lopinavir/ritonavir (Kaletra®)[27], nelfinavir (Viracept®)[6], ritonavir (Norvir®)[7], saquinavir (Invirase®)[8], tipranavir (Aptivus®)[9]	**NNRTIs** efavirenz (Sustiva®)[10], etravirine (Intelence®)[11], nevirapine (Viramune®)[12], rilpivirine (Edurant®)[13]	**Integrase Inhibitor** elvitegravir/cobicistat (Stribild®, single-tablet regimen with tenofovir/emtricitabine)[14], raltegravir (Isentress®)[15]
		of ritonavir, but unlikely with lower boosting doses of ritonavir. See "quetiapine" for case report of priapism associated with perphenazine and quetiapine with concomitant lopinavir/ritonavir.[58]		
Pimozide Orap®	Parent: CYP3A	Unboosted PIs may ↑ pimozide concentrations; **avoid** if possible. **Contraindicated with ritonavir;** potential ↑↑ pimozide concentrations.[7]	Likely ↓ pimozide concentrations	**Coadministration with Stribild® is contraindicated** due to potential for serious and/or life-threatening events such as cardiac arrhythmias.[14]
Pipotiazine Piportil L4	Parent: Extensive hepatic metabolism	Possible ↑ pipotiazine concentrations	Possible ↓ pipotiazine concentrations	Potential for ↑ neuroleptic concentrations with **elvitegravir/cobicistat.** A decrease in neuroleptic dose may be required.[14]
Quetiapine Seroquel®	Route of Metabolism: CYP3A4 >> 1A2 [59] Is not an enzyme inhibitor or inducer	Possible ↑↑ quetiapine concentrations. Report of two patients who experienced serious quetiapine adverse effects secondary to possible/probable interactions with **atazanavir/ritonavir**. One patient developed rapid and severe weight gain when quetiapine was added to his stable ARV regimen, while another patient stabilized on quetiapine developed increased	Possible ↓ quetiapine concentrations.	Potential for ↑ neuroleptic concentrations with **elvitegravir/cobicistat.** A decrease in neuroleptic dose may be required.[14]

	Psychotropic Route of Metabolism[22-26]	Protease Inhibitors atazanavir (Reyataz®)[1], darunavir (Prezista®)[2], fosamprenavir (Telzir®)[3], indinavir (Crixivan®)[4], lopinavir/ritonavir (Kaletra®)[27], nelfinavir (Viracept®)[6], ritonavir (Norvir®)[7], saquinavir (Invirase®)[8], tipranavir (Aptivus®)[9]	NNRTIs efavirenz (Sustiva®)[10], etravirine (Intelence®)[11], nevirapine (Viramune®)[12], rilpivirine (Edurant®)[13]	Integrase Inhibitor elvitegravir/cobicistat (Stribild®, single-tablet regimen with tenofovir/emtricitabine)[14], raltegravir (Isentress®)[15]
		sedation and mental confusion shortly after initiating atazanavir/ritonavir. In both cases, symptoms resolved after discontinuation of quetiapine.[60] Another report of a deep coma, sustained hypotension, and ↑ t1/2 of quetiapine (62.4h) after an overdose of quetiapine 8000mg in a patient on **atazanavir/ritonavir**.[61] Case report of priapism lasting 42 hours with an onset of 5-6 hours after co-ingestion of perphenazine and quetiapine with **lopinavir/ritonavir**. Rapid elevations in the neuroleptic concentrations were postulated as the mechanism. The symptoms were managed with intracavernous ephedrine, irrigation and aspiration.[58]		
Risperidone Risperdal®	Parent: CYP2D6, 3A4[25] Active metabolite: 9-OH risperidone (paliperidone) (renal)	Potential ↑ risperidone concentrations with ritonavir-boosted PIs. One case of extrapyramidal symptoms (dysphagia, dysphonia, difficulty breathing, and worsening tremors) with risperidone 2mg/day + **indinavir/ritonavir** (IDV/RTV)	Unlikely	Potential for ↑ neuroleptic concentrations with **elvitegravir/cobicistat.** A decrease in neuroleptic dose may be required.[14]

	Psychotropic Route of Metabolism[22-26]	Protease Inhibitors atazanavir (Reyataz®)[1], darunavir (Prezista®)[2], fosamprenavir (Telzir®)[3], indinavir (Crixivan®)[4], lopinavir/ritonavir (Kaletra®)[27], nelfinavir (Viracept®)[6], ritonavir (Norvir®)[7], saquinavir (Invirase®)[8], tipranavir (Aptivus®)[9]	NNRTIs efavirenz (Sustiva®)[10], etravirine (Intelence®)[11], nevirapine (Viramune®)[12], rilpivirine (Edurant®)[13]	Integrase Inhibitor elvitegravir/cobicistat (Stribild®, single-tablet regimen with tenofovir/emtricitabine)[14], raltegravir (Isentress®)[15]
		800mg/200mg BID.[62] One case of neuroleptic malignant syndrome with risperidone 1.5mg/day + IDV 800mg/RTV 400mg daily.[63] Reversible coma reported with risperidone 3mg BID + IDV 400mg/RTV 200mg BID.[64]		
Thioridazine Mellaril®	Parent: CYP2D6 Inhibits: CYP2D6 Metabolite (active): (mesoridazine, sulforidazine)	Interaction unlikely with unboosted PIs. Potential ↑ thioridazine concentrations with higher doses of ritonavir, but unlikely with lower boosting doses of ritonavir.	Unlikely	Potential for ↑ neuroleptic concentrations with **elvitegravir/cobicistat.** A decrease in neuroleptic dose may be required.[14]
Ziprasidone Geodon®, Zeldox®	Parent: CYP3A4 Is not an enzyme inhibitor or inducer[65]	Potential ↑ ziprasidone concentrations	Potential ↓ ziprasidone concentrations	Potential for ↑ neuroleptic concentrations with **elvitegravir/cobicistat.** A decrease in neuroleptic dose may be required.[14]
Zuclopenthixol Clopixol®	Parent: Extensive hepatic metabolism	Potential ↑ zuclopenthixol concentrations	Potential ↓ zuclopenthixol concentrations	Potential for ↑ neuroleptic concentrations with **elvitegravir/cobicistat.** A decrease in neuroleptic dose may be required.[14]

Other				
	Psychotropic Route of Metabolism[22-26]	**Protease Inhibitors** atazanavir (Reyataz®)[1], darunavir (Prezista®)[2], fosamprenavir (Telzir®)[3], indinavir (Crixivan®)[4], lopinavir/ritonavir (Kaletra®)[27], nelfinavir (Viracept®)[6], ritonavir (Norvir®)[7], saquinavir (Invirase®)[8], tipranavir (Aptivus®)[9]	**NNRTIs** efavirenz (Sustiva®)[10], etravirine (Intelence®)[11], nevirapine (Viramune®)[12], rilpivirine (Edurant®)[13]	**Integrase Inhibitor** elvitegravir/cobicistat (Stribild®, single-tablet regimen with tenofovir/emtricitabine)[14], raltegravir (Isentress®)[15]
Buspirone Buspar®	Parent: CYP3A4 Metabolite (active): 1-pyrimidinyl piperazine Buspirone has immunomodulating properties. A significant ↑ in CD4/CD8 ratio, and a ↓ in CD8+ T-cell counts was observed in HIV patients who were not on antiretrovirals.[66]	possible ↑ buspirone concentrations Case report of patient with Parkinson-like symptoms (ataxia, shuffling gait, cogwheel rigidity, resting tremor, and sad affect) 6 weeks after **indinavir/ritonavir** (400mg/400mg BID) were added to buspirone 40mg am/30mg pm.[67]	possible ↓ buspirone concentrations and withdrawal	Potential for ↑ buspirone concentrations with **elvitegravir/cobicistat.** A decrease in buspirone dose may be required.[14]
Dextroamphetamine Dexedrine®	Parent: hepatic metabolism (deamination and hydroxylation)	Possible ↑ dextroamphetamine concentrations	Possible ↓ dextroamphetamine concentrations	Possible ↑ dextroamphenatime concentrations with **elvitegravir/cobicistat.**
Lithium Carbolith®	None (renal)	None	None	None
l-Tryptophan Tryptan®	Parent: metabolized via tryptophan hydroxylase Metabolite: nicotinic acid > serotonin	Unlikely	Unlikely	Unlikely
Methylphenidate Ritalin® Concerta®	Parent: hepatic and tissue nonmicrosomal hydrolytic esterases Inhibits: not well described- ?CYP3A, ?2D6, Metabolite: renal (ritalinic acid- inactive)	Possible ↑ methylphenidate concentrations	Possible ↓ methylphenidate concentrations	Possible ↑ methylphenidate concentrations with **elvitegravir/cobicistat.**
Modafinil Alertec®	Parent: CYP3A Inhibits 2C19, 2C9; may	Possible ↑ modafinil concentrations, potential ↓	Possible ↓ modafinil concentrations, potential ↓ NNRTI	Potential for ↑ modafinil concentrations and/or ↓

	Psychotropic Route of Metabolism[22-26]	Protease Inhibitors atazanavir (Reyataz®)[1], darunavir (Prezista®)[2], fosamprenavir (Telzir®)[3], indinavir (Crixivan®)[4], lopinavir/ritonavir (Kaletra®)[27], nelfinavir (Viracept®)[6], ritonavir (Norvir®)[7], saquinavir (Invirase®)[8], tipranavir (Aptivus®)[9]	NNRTIs efavirenz (Sustiva®)[10], etravirine (Intelence®)[11], nevirapine (Viramune®)[12], rilpivirine (Edurant®)[13]	Integrase Inhibitor elvitegravir/cobicistat (Stribild®, single-tablet regimen with tenofovir/emtricitabine)[14], raltegravir (Isentress®)[15]
	induce 3A4, 1A2, 2B6	protease inhibitor concentrations; if possible, avoid use with CYP3A4 substrates until further data available. Antiretroviral therapeutic drug monitoring may be useful.	concentrations and efficacy. If possible, avoid use with CYP3A4 substrates until further data available. Antiretroviral therapeutic drug monitoring may be useful.	**elvitegravir/cobicistat** concentrations. Avoid combination if possible.

Key: CYP= Hepatic Cytochrome P450 isoenzyme; AD= Alcohol dehydrogenase; TCA= tricyclic antidepressant; MAOI= monoamine oxidase inhibitor; SSRI= selective serotonin reuptake inhibitor Substrate= route of hepatic elimination of that specific drug (specified by a specific cytochrome P450 isoenzyme); inducer = leads to more rapid clearance of substrates of a specific hepatic isoenzyme (lowers serum concentrations of the respective drug and may lead to decreased efficacy); inhibitor= leads to decreased clearance of substrates of a specific hepatic isoenzyme (increases serum concentrations of a respective drug and may lead to toxicity). Pgp= P-glycoprotein; UGT= Uridine diphosphate glucuronyltransferase.

Please note: This chart summarizes some of the major drug interactions identified to date, based on current available data; other drug interactions may exist. Please use caution whenever adding/modifying therapy. The information in this table is intended for use by experienced physicians and pharmacists. It is not intended to replace sound professional judgment in individual situations, and should be used in conjunction with other reliable sources of information. Due to the rapidly changing nature of information about HIV treatment and therapies, users are advised to recheck the information contained herein with the original source before applying it to patient care.

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Interactions between Antiretrovirals and Drugs for Treatment of Pulmonary Arterial Hypertension

	Protease Inhibitors	Non-Nucleoside Reverse Transcriptase Inhibitors	Other Antiretrovirals
Prostaglandin (prostacyclin) analogs			
Epoprostenol (IV) • *Undergoes rapid hydrolyzation* Treprostinil (IV or SC infusion) • *substantially metabolized by the liver, but precise enzymes unknown* • *does not inhibit CYP-1A2, 2C9, 2C19, 2D6, 2E1, or 3A* Iloprost (inhalation) • *CYP enzymes play minor role in biotransformation; iloprost does not inhibit CYP450 system (in vitro)*	Significant pharmacokinetic interactions with antiretroviral agents are not anticipated.		
Endothelin receptor antagonists			
Ambrisentan (Volibris®) • *substrate of UGT1A9S, 2B7S, and 1A3S, CYP3A4 and CYP2C19, OATP, and P-gp.* • *does not inhibit UGT1A1, UGT1A6, UGT1A9, UGT2B7 or CYP450 enzymes 1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1 and 3A4. Additional in vitro studies showed that ambrisentan does not inhibit P-gp, NTCP, OATP or BSEP. Furthermore, ambrisentan does not induce MRP2, P-gp or BSEP.*	Potential for ↑ ambrisentan concentrations with concomitant CYP3A4 inhibitors.	Monitor for potential ↓ ambrisentan concentrations. No clinically relevant effect on ambrisentan exposure by day 8, following administration of multiple doses of rifampin. No dose adjustment of ambrisentan is needed with concomitant rifampin therapy.	Potential for ↑ ambrisentan concentrations with elvitegravir/cobicistat.
Bosentan (Tracleer®)	In a healthy volunteer	A recent report	Potential for ↑ bosentan

	Protease Inhibitors	Non-Nucleoside Reverse Transcriptase Inhibitors	Other Antiretrovirals
• *substrate of CYP2C9 and CYP3A* • *inducer of CYP2C9 and CYP3A4.*[1, 2]	study involving coadministration of bosentan 125 mg BID and **lopinavir/ritonavir 400/100 mg BID**, bosentan concentrations increased up to 48-fold during the first 4 days, and at steady-state, the GMR for AUC was 5.22 and for Cmax was 6.12. Therefore, bosentan should only be initiated once boosted PIs have reached steady-state (i.e., at least 10 days therapy). In such patients, bosentan may be started at a dose of 62.5 mg once daily or every other day. For patients on stable bosentan therapy who require initiation of a boosted PI regimen, bosentan should be discontinued for at least 36 hours prior to starting the boosted PI, then reinstituted 10 days after PI initiation at 62.5 mg once daily or every other day.[3] Do not give bosentan with **unboosted atazanavir**, as plasma atazanavir concentrations may be decreased.[4] A case report noted a possible interaction between bosentan and unboosted **indinavir** leading to a reduction in indinavir plasma concentrations.[5]	documented the successful, long-term coadministration of bosentan and **nevirapine**-based cART in a 51-year old HIV-positive woman with AIDS and HIV-associated PAH. Over a four-year follow-up period, the patient experienced significant clinical and hemodynamic improvement on bosentan 125 mg BID, and maintained complete viral suppression, therapeutic nevirapine trough concentrations, and excellent immunologic response.[6]	concentrations with elvitegravir/cobicistat. In patients on Stribild® for at least 10 days, start bosentan at 62.5 mg once daily or q2days based on individual tolerability. If initiating Stribild® in patients already on bosentan, discontinue bosentan at least 36 hours prior, and resume at 62.5 mg once daily or q2days at least 10 days following Stribild® initiation.[7] Potential for ↓ maraviroc concentrations. Avoid combination if possible.
Sitaxsentan (Thelin®; discontinued in 2010) • *substrate of*	Case report of an HIV-positive patient on tenofovir, 3TC and	Potential for ↑ etravirine concentrations. Possible ↑ other NNRTI	Potential for ↑/↓ sitaxsentan and ↑ elvitegravir and cobicistat

	Protease Inhibitors	Non-Nucleoside Reverse Transcriptase Inhibitors	Other Antiretrovirals
CYP3A4/5 and 2C9 • *inhibitor of CYP2C9, as well as 2C19, 3A4/5, and 2C8*	**atazanavir** with HIV-PAH who was initially well-controlled on bosentan 125 mg BID, but who required discontinuation of bosentan after 18 months due to persistent nasal/sinus congestion. Bosentan was replaced with sitaxsentan 100 mg daily, with rapid resolution of nasal congestion and continued clinical benefit.[8]	concentrations.	concentrations. Potential for ↑ maraviroc concentrations.
Phosphodiesterase inhibitors			
Sildenafil (Revatio®) • *CYP3A4>>2C9 substrate; weak inhibitor of CYP1A2, 2C9, 2C19, 2D6, 2E1, 3A4 - unlikely to cause significant interactions*	Sildenafil exposures are ↑2-11-fold in the presence of PIs.[3] Sildenafil for treatment of PAH is **contraindicated** with all PIs.	In the presence of etravirine, sildenafil AUC ↓ 57%. Combination may be co-administered, adjust sildenafil dose according to response.[9] In healthy volunteers taking rilpivirine 75 mg once daily for 12 days, the kinetics of single dose sildenafil 50 mg were similar as compared to sildenafil alone, and rilpivirine exposures were not affected by sildenafil. The combination may be coadministered without dose modifications.[10] Potential for ↓ sildenafil concentrations with other NNRTIs.	No pharmacokinetic with maraviroc is expected, but both Maraviroc and the PDE5 inhibitors have reported hypotension adverse; therefore, co-administer combination with caution. Sildenafil for treatment of PAH is contraindicated with elvitegravir/cobicistat.[7]
Tadalafil (Adcirca®) • *CYP3A4 substrate*	Significant ↑in tadalafil concentrations with ritonavir and boosted tipranavir.[11] Recurrent priapism secondary to an interaction between tadalafil and boosted	Potential for ↓ tadalafil concentrations. Dose adjustment may be necessary with coadministration.	No pharmacokinetic with maraviroc is expected, but both maraviroc and the PDE5 inhibitors have reported hypotension adverse; therefore, co-administer combination

	Protease Inhibitors	Non-Nucleoside Reverse Transcriptase Inhibitors	Other Antiretrovirals
	fosamprenavir has been reported.[12] For patients on stable (i.e,. greater than 7 days) PI treatment who require therapy for PAH: tadalafil may be initiated at a dose of 20 mg once daily and increased to 40 mg once daily based on tolerability. For patients already stabilized on tadalafil who require PI-based treatment: tadalafil should be discontinued at least 24 hours prior to initiating the PI, and restarted 7 days after PI initiation at a dose of 20 mg once daily, increasing to 40 mg once daily based on tolerability.[3]		with caution. Potential for ↑ tadalafil concentrations with elvitegravir/cobicistat. If already on Stribild®, start tadalafil 20 mg daily, ↑ to 40 mg daily based on tolerability. If on tadalafil and starting Stribild®, stop tadalafil at least 24 hours prior; after at least 1 week, resume tadalafil at 20 mg daily, ↑ to 40 mg daily based on tolerability.[7]

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Postulated and Actual Interactions Between Recreational Drugs and Antiretrovirals

Drug	Metabolism	Actual/Potential Interaction	Potential Significance	Recommendation
Alcohol	Principally metabolized by alcohol dehydrogenase and aldehyde dehydrogenase. Acute ingestion may lead to enzyme inhibition. Chronic alcohol use may induce activity of CYP2E1 and 3A.	Due to the induction of CYP 3A, it is possible that chronic alcohol use may induce the metabolism of drugs which are substrates of the 3A system (i.e. protease inhibitors, NNRTIs, elvitegravir/cobicistat).	Induction of the metabolism of ARVs may result in subtherapeutic levels of these agents, predisposing to resistance and decreasing efficacy.	The possible deleterious effects of alcohol on PIs, NNRTIs or elvitegravir/cobicistat would be expected only with chronic use. Such effects need to be confirmed by appropriately conducted pharmacokinetic studies before dosage adjustments can be recommended.
		Theoretical possibility of an interaction between ***abacavir*** and ethanol, since both are metabolized by alcohol dehydrogenase.	In a cross-over study of HIV-infected subjects, no change in ethanol parameters or disulfiram reaction was noted with concomitant administration of 600 mg abacavir and 0.7 g/kg ethanol, while 41% ↑ abacavir AUC was observed[1]	Interaction not likely to be clinically significant.
Amphetamines	CYP 2D6[2-4]	Possible ↑ levels with ritonavir and cobicistat.	Hypertension, hyperthermia, seizures, arrhythmias, tachycardia, tachypnea.	Avoid combination with ritonavir or cobicistat if possible; alternatively, start with ¼ - ½ of initial amount of amphetamine used.
Cocaine	3 pathways: • serum and hepatic cholinesterases to 1ecgonine methyl ester (32-49%)	A potential interaction could exist between cocaine and inhibitors of CYP 3A3/4. (incl. protease inhibitors, elvitegravir/cobicistat, delavirdine, macrolides, azoles), by increasing levels of	Clinical significance unclear, since other metabolic pathways involved in cocaine metabolism; risk may be higher if patient is cholinesterase deficient.	Monitor for signs and symptoms of cocaine toxicity, such as: • CNS: tremor, muscle twitches, or seizures, severe agitation, anxiety, paranoid ideation • cardiovascular: increased

Drug	Metabolism	Actual/Potential Interaction	Potential Significance	Recommendation
	• spontaneous hydrolysis and hepatic carboxyesterase to benzoylecgonine (35-45%) • CYP 3A4 to norcocaine (< 10%) Cocaine may also induce CYP 2B1 with chronic use, while acute use may inhibit CYP 1A2, 2A4/5 and 2CX.	parent compound. CYP3A inducers (e.g., rifamycins, nevirapine, efavirenz) may lead to increasing amounts of the norcocaine metabolite being produced.	Increased levels of norcocaine may predispose patients to increased cocaine toxicity; patients who are cholinesterase deficient may be at risk of life threatening cocaine toxicity, as a greater proportion of cocaine will be available for metabolism by the CYP 3A4 pathway. In animal models, high levels of norcocaine have led to hepatotoxicity (the significance of this finding in humans is unclear).	blood pressure, headache, pallor, rapid weak pulse, increase in body temperature • GI: nausea, vomiting • respiratory: rapid, irregular, shallow respiration
Codeine	3 pathways:[5] • Glucuronidation to codeine-6-glucuronide (~ 70%) • N-demethyla-tion to nor-codeine (3A4) (< 10%) • O-demethyl-ation to morphine (2D6) (10-15%)[6-11]	↓ morphine levels: 2D6 inhibition (inhibit O-demethylation) 3A4/glucuronide induction (less substrate available for 2D6) ↑ morphine levels: 3A4 inhibition (shunting of substrate to 2D6 pathway)	Opiate withdrawal, loss of analgesia Opiate toxicity	Monitor for signs/symptoms of opiate withdrawal (see under "Meperidine"). Reassess level of analgesia. Monitor for signs/symptoms of opiate toxicity (e.g. miosis, drowsiness, ↓ rate and depth of respiration, N/V, constipation, hypotension, bradycardia).
Gamma hydroxy-butyrate (GHB)	Expired breath as CO_2 First pass metabolism[12-14]	Possible ↑ levels/prolonged effect with antiretrovirals, especially ritonavir or cobicistat.	1 case GHB toxicity with ritonavir/saquinavir.[15] Myoclonic or seizure activity, bradycardia, respiratory depression, loss of consciousness.	Use cautiously with inhibitors of the cytochrome P-450 system (i.e. PIs, elvitegravir/cobicistat, and delavirdine). Ensure patient aware of signs/symptoms of GHB toxicity.
Heroin	Rapidly metabolized to 6-	As heroin is rapidly converted to morphine,	Possible opiate withdrawal, loss of analgesia, although	Monitor for signs/symptoms of opiate withdrawal (e.g.

Drug	Metabolism	Actual/Potential Interaction	Potential Significance	Recommendation
	monoacetyl-morphine & morphine by plasma and liver esterases, respectively. Blood levels of heroin and 6-monoacetyl-morphine attain maximal levels within minutes and are cleared rapidly, while morphine levels rise and decrease more slowly.	potential interactions of concern would be similar to those noted with morphine: ***Nelfinavir*** and ***ritonavir*** may ↑ glucuronidation: accelerate morphine metabolism, ↓ levels of morphine, ↑ levels of pharmacologically active M6G.	may be attenuated by ↑ formation of M6G.	lacrimation, rhinorrhea, diaphoresis, restlessness, insomnia, dilated pupils, piloerection).
Ketamine	CYP 2B6 (main) 3A, 2C9 (both to lesser extent)[16-19]	Possible ↑ levels with antiretrovirals, especially with ritonavir and cobicistat-boosted agents.	Respiratory depression, loss of consciousness, hallucinations.	Use cautiously with inhibitors of the cytochrome P-450 system, especially ritonavir and cobicistat-boosted ARVs. Ensure patient aware of signs/symptoms of ketamine toxicity.
Lysergic acid diethylmide (LSD)	Unknown[20, 21]	Possible ↑ LSD concentrations.	Hallucinations, agitation, psychosis, “flashbacks”	Use cautiously with inhibitors of the cytochrome P-450 system (i.e. PIs, elvitegravir/cobicistat, and delavirdine). Ensure patient aware of signs/symptoms of LSD toxicity.
Meperidine	2 pathways: Hydrolysis to meperidinic acid by liver carboxylesterases and demethylation by cytochrome P-450 system to normerperidine	AUC of meperidine ↓ 67% and AUC of normeperidine ↑ 47% in open label study of eight volunteers receiving treatment with 50 mg meperidine prior to and following 10 days of treatment with ritonavir.[24]	Possible opiate withdrawal, loss of analgesia. Possible ↑ risk of seizures with normeperidine accumulation.	Monitor for signs/symptoms of opiate withdrawal (e.g. lacrimation, rhinorrhea, diaphoresis, restlessness, insomnia, dilated pupils, piloerection). Reassess level of analgesia. Avoid combination of ritonavir and meperidine in patients with

Drug	Metabolism	Actual/Potential Interaction	Potential Significance	Recommendation
	(exact isoenzyme unknown)[22, 23]			renal failure and patients who use meperidine regularly for analgesia or recreationally due to risk of neurotoxicity.
Methylenedioxy - methamphetamine (MDMA), "Ecstasy"	CYP 2D6 (main)[25-27], 1A2, 2B6, 3A4 (to lesser extent)[27]	Possible ↑ levels with PIs and elvitegravir/cobicistat.	1 death reported (see text)[28] Monitor for dose-related toxicities, including hyponatremia, hyperthermia, arrhythmias, tremor, hyperreflexia, sweating, seizures, tachycardia, rhabdomyolysis.	Avoid combining with ritonavir or cobicistat if possible. Alternatively, advise patient to use ~ ¼ - ½ of usual amount used, and watch for signs of MDMA toxicity. Other precautions include staying well hydrated at party, avoiding alcohol and taking breaks from dancing.
Morphine	Glucuronidated to morphine-6-glucuronide (M6G) and morphine-3-glucuronide (M3G)[29-31]	***Nelfinavir*** and ***ritonavir*** may ↑ glucuronidation: accelerate morphine metabolism, ↓ levels of morphine, ↑ levels of pharmacologically active M6G.	Possible opiate withdrawal, loss of analgesia, although may be attenuated by ↑ formation of M6G.	Monitor for signs/symptoms of opiate withdrawal (e.g. lacrimation, rhinorrhea, diaphoresis, restlessness, insomnia, dilated pupils, piloerection). Reassess level of analgesia.
Oxycodone	3 pathways: CYP2D6 to oxymorphone CYP3A4 to noroxycodone ketoreductase[32]	<u>↓ levels oxymorphone</u> Inhibition of 2D6 3A4 induction (less substrate for 2D6 pathway) <u>↑ oxymorphone levels</u> 3A4 inhibition (shunting to 2D6 pathway)	Possible opiate withdrawal and loss of analgesia, although ↓ oxymorphone levels does not appear to alter pharmacodynamics of oxycodone. Possible opiate toxicity.	Monitor for signs/symptoms of opiate withdrawal (see under "Meperidine"). Reassess level of analgesia. Monitor for signs/symptoms of opiate toxicity (see under "Codeine").
Phencyclidine (PCP)	CYP 3A[33], CYP2C11[34], inhibits CYP2B1[35]	Possible ↑ levels with antiretrovirals	Seizures, hypertension, rhabdomyolysis, hyperthermia	Use cautiously with inhibitors of the cytochrome P-450 system (i.e. PIs, elvitegravir/cobicistat, and delavirdine). Ensure patient aware of signs/symptoms of PCP toxicity.
Tetrahydro-cannabinol	Hydroxylated to several active	<u>↑ THC concentrations</u>: Drugs which inhibit CYP3A or	Dose-related effects of THC (e.g. hallucinations,	Considering the widespread use of THC derivatives for

Drug	Metabolism	Actual/Potential Interaction	Potential Significance	Recommendation
(THC; active moiety of marijuana, hashish and hash oil) [34-36]	metabolites. CYP3A3/4, 2C9 and 2C6 likely involved in metabolism. Levels of active metabolites vary with the route of administration. In general, oral administration produces more active metabolite than either IV or inhaled routes, probably due to a significant first pass effect.	2C9 (e.g., protease inhibitors or cobicistat) ↓ THC concentrations: Drugs which induce CYP3A (e.g., efavirenz, nevirapine) Indinavir, nelfinavir: • Patients on stable indinavir or nelfinavir therapy were randomized to receive either 4% THC cigarettes, THC 2.5 mg capsules or placebo TID • Nelfinavir and indinavir levels were obtained at baseline and on day 14. • Smoked THC ↓ nelfinavir AUC by 17%, and ↓ indinavir Cmax 21% (both statistically sig.). Oral THC did not produce significant changes in indinavir or nelfinavir kinetics.[36]	delusions, paranoid thinking, altered time sense, anxiety, panic, depersonalization, loss of insight, orthostatic hypotension, ↑ heart rate). Potential for ↓ duration of THC effect. The long-term clinical consequence of these changes is unknown, but with increasing use of boosted protease inhibitor regimens, such changes are unlikely to significantly impact antiviral efficacy.	appetite stimulation and control of nausea and vomiting, and the lack of reports documenting deleterious effects secondary to the combination of THC and protease inhibitors, a clinically significant drug interaction may not exist when THC is used in moderate amounts. Patients who use THC and are beginning antiretrovirals should be warned about a possible accentuating of the effects of THC, and that they may need to use less THC for the same effect following treatment initiation. If using non-boosted protease inhibitor regimen, may consider therapeutic drug monitoring.
		Atazanavir: In a series of 67 HIV-positive subjects with or without substance-related disorders who were taking **atazanavir**, significant ↓ ATV Ctrough among tobacco and marijuana users were noted, with 36%	The cause of this association remains to be determined.	

Drug	Metabolism	Actual/Potential Interaction	Potential Significance	Recommendation
		tobacco and 50% marijuana users having an ATV Ctrough below the therapeutic range as compared to non-users ($p<0.05$).[37]		

Key: AUC = area under the concentration-time curve, Cmax = maximum plasma concentration, CYP = cytochrome P450, HAART = highly active antiretroviral therapy, IV = intravenous, PIs = protease inhibitors, sgc = soft gel capsule

Please note: This chart summarizes some of the major drug interactions identified to date, based on current available data; other drug interactions may exist. Please use caution whenever adding/modifying therapy. The information in this table is intended for use by experienced physicians and pharmacists. It is not intended to replace sound professional judgment in individual situations, and should be used in conjunction with other reliable sources of information. Due to the rapidly changing nature of information about HIV treatment and therapies, users are advised to recheck the information contained herein with the original source before applying it to patient care.

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Interactions Between Sedatives/Hypnotics/Anxiolytics and Antiretrovirals

Antiretroviral Pharmacokinetic Characteristics (summary):

	Protease Inhibitors (PIs) atazanavir (Reyataz®)[1], darunavir (Prezista®)[2], fosamprenavir (Telzir®)[3], indinavir (Crixivan®)[4], lopinavir/ritonavir (Kaletra®)[5], nelfinavir (Viracept®)[6], ritonavir (Norvir®)[7], saquinavir (Invirase®)[8], tipranavir (Aptivus®)[9]	**Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)** efavirenz (Sustiva®)[10], etravirine (Intelence®)[11], nevirapine (Viramune®)[12], rilpivirine (Edurant®)[13]	**Integrase Inhibitors** elvitegravir/cobicistat (Stribild®, single-tablet regimen with tenofovir/emtricitabine)[14], raltegravir (Isentress®)[15]
Metabolism	Mainly CYP3A4	Efavirenz, nevirapine: CYP3A4, 2B6 (minor) Etravirine: CYP3A4, CYP2C9, and CYP2C19. Rilpivirine: CYP3A4 (major), as well as CYP2C19, 1A2, 2C8/9/10 (minor).	Elvitegravir: CYP3A, UGT1A1/3 Cobicistat: CYP3A, 2D6 (minor) Raltegravir: UGT1A1
Hepatic Inhibitor	Mainly CYP3A4 (darunavir, indinavir, nelfinavir, amprenavir >> saquinavir) Ritonavir: CYP3A4 (potent)> >2D6 >2C9 >2C19 >2A6 >1A2>2E1 At low boosting doses, ritonavir has a negligible effect in CYP2D6 inhibition.[5] Ritonavir inhibits CYP2B6 in vitro,[16] but induces 2B6 in vivo.[17] Nelfinavir: 2B6 in vitro.	Efavirenz: 2C9, 2C19[10] (? Clinical significance). Etravirine[11]: CYP2C9 (weak), CYP2C19 (moderate), p-glycoprotein (weak) Delavirdine (Rescriptor®)[18]; 3A4 (potent)	Cobicistat: CYP3A, CYP2D6; also p-glycoprotein (P-gp), BCRP, OATP1B1 and OATP1B3. Raltegravir has no inhibitory or inductive potential in vitro.[15]
Hepatic Inducer	Nelfinavir: UGT, 2C9/19 Ritonavir: UGT, CYP1A2, CYP2C9/19, 2B6 Tipranavir: mixed induction/inhibition effects; often acts as inducer of CYP3A4 (potent) and UGT, even when boosted with ritonavir[9]	Efavirenz: 3A4 (potent), 2B6[19] and UGT1A1[20] Etravirine[11]: 3A4 (weak) Nevirapine[12]: 3A4, 2B6 (potent) Rilpivirine: 2C19 (moderate), CYP1A2, 2B6 and 3A4 (weak).[21] A clinically relevant effect on CYP enzyme activity is considered unlikely with the 25 mg dose.[13]	Elvitegravir: CYP2C9 (modest) Raltegravir has no inhibitory or inductive potential in vitro.[15]

	Sedative Route of Metabolism[22, 23]	Protease Inhibitors atazanavir (Reyataz®)[1], darunavir (Prezista®)[2], fosamprenavir (Telzir®)[3], indinavir (Crixivan®)[4], lopinavir/ritonavir (Kaletra®)[24], nelfinavir (Viracept®)[6], ritonavir (Norvir®)[7], saquinavir (Invirase®)[8], tipranavir (Aptivus®)[9]	NNRTIs efavirenz (Sustiva®)[10], etravirine (Intelence®)[11], nevirapine (Viramune®)[12], rilpivirine (Edurant®)[13]	Integrase Inhibitor elvitegravir/cobicistat (Stribild®, single-tablet regimen with tenofovir/emtricitabine)[14], raltegravir (Isentress®)[15]
Alprazolam (APZ) Xanax®	Parent: CYP3A Metabolite: UGT (4 &alpha hydroxy)	Possible ↑ alprazolam concentrations. **Alprazolam is no longer contraindicated** in the Norvir® product monograph.[7] Short-term study of 1mg alprazolam with 4 doses of **ritonavir 200 mg** resulted in 148% ↑ alprazoma AUC and ↑ t ½ from 13 to 30 hours.[25] Steady-state study of 1 mg alprazolam with 12 days of ritonavir resulted in a 12% ↓ alprazolam AUC.[26] This likely reflects early inhibitory and chronic induction effects of ritonavir. **Based on this, therapy can likely be initiated using very low alprazolam doses, and monitoring for tolerability and efficacy. After 2-3 weeks, alprazolam dosage may need to be increased.**	possible ↓ alprazolam concentrations and withdrawal	**Elvitegravir/cobicistat:** possible ↑ alprazolam concentrations. Monitor and reduce benzodiazepine dose if necessary.[14]
Bromazepam Lectopam®	Parent: Hydroxylation	Possible ↑ bromazepam concentrations	possible ↓ bromazepam concentrations and withdrawal	**Elvitegravir/cobicistat:** possible ↑ bromazepam concentrations. Monitor and reduce benzodiazepine dose if necessary.[14]
Buspirone Buspar®	Parent: CYP3A4 Buspirone has immunomodulating properties. A significant ↑ in CD4/CD8 ratio, and a ↓ in CD8+ T-cell counts was observed in HIV patients who were not on antiretrovirals.[27]	possible ↑ buspirone concentrations Case report of patient with Parkinson-like symptoms (ataxia, shuffling gait, cogwheel rigidity, resting tremor, and sad affect) 6 weeks after **ritonavir/indinavir (400mg/400mg BID)** were added to buspirone 40mg am/30mg pm.[28]	possible ↓ buspirone concentrations and withdrawal	**Elvitegravir/cobicistat:** possible ↑ buspirone concentrations. Monitor and reduce benzodiazepine dose if necessary.[14]
Chloral hydrate	Parent: AD	no predicted effect	no predicted effect	No predicted effect

	Sedative Route of Metabolism[22, 23]	Protease Inhibitors atazanavir (Reyataz®)[1], darunavir (Prezista®)[2], fosamprenavir (Telzir®)[3], indinavir (Crixivan®)[4], lopinavir/ritonavir (Kaletra®)[24], nelfinavir (Viracept®)[6], ritonavir (Norvir®)[7], saquinavir (Invirase®)[8], tipranavir (Aptivus®)[9]	NNRTIs efavirenz (Sustiva®)[10], etravirine (Intelence®)[11], nevirapine (Viramune®)[12], rilpivirine (Edurant®)[13]	Integrase Inhibitor elvitegravir/cobicistat (Stribild®, single-tablet regimen with tenofovir/emtricitabine)[14]; raltegravir (Isentress®)[15]
(Novo, PMS)	Metabolite: UGT (trichloroethanol)			
Clonazepam Rivotril®	Parent: CYP3A4	possible ↑ clonazepam concentrations	possible ↓ clonazepam concentrations and withdrawal	**Elvitegravir/cobicistat:** potential for ↑ clonazepam concentrations.[14]
Clorazepate Tranxene®	Parent: Acid hydrolysis Metabolites (active): nordiazepam, 2C19-desmethyldiazepam	possible ↑ metabolite concentrations **Clorazepate is no longer contraindicated** in the Norvir® product monograph;[7]; use with caution.	possible ↓ metabolite concentrations and withdrawal	Possible ↑ metabolite concentrations with **elvitegravir/cobicstat.**
Diazepam Valium®	Parent: CYP2C19>3A Metabolites (active): nordiazepam, N-desmethyldiazepam, temazepam	possible ↑ diazepam and nordiazepam concentrations **Diazepam is no longer contraindicated** in the Norvir® product monograph;[7]; use with caution.	possible ↓ diazepam and nordiazepam concentrations and withdrawal	**Elvitegravir/cobicistat:** possible ↑ diazepam concentrations. Monitor and reduce benzodiazepine dose if necessary.[14]
Estazolam Prosom®	Parent: CYP3A4[29]	possible ↑ estazolam concentrations	possible ↓ estazolam concentrations and withdrawal	**Elvitegravir/cobicistat:** possible ↑ estazolam concentrations. Monitor and reduce benzodiazepine dose if necessary.[14]
Eszopiclone Lunesta®	Parent: CYP3A4, 2E1[30]	possible ↑ eszopiclone concentrations	possible ↓ eszopiclone concentrations and withdrawal	**Elvitegravir/cobicistat:** possible ↑ eszopiclone concentrations. Monitor and reduce benzodiazepine dose if necessary.[14]
Flurazepam Dalmane®	Parent: liver Metabolites (active): desalkyl, hydroxyethyl	possible ↑ flurazepam concentrations **Flurazepam is no longer contraindicated** in the Norvir® product monograph;[7]; use with caution.	possible ↓ flurazepam concentrations and withdrawal	**Elvitegravir/cobicistat:** possible ↑ flurazepam concentrations. Monitor and reduce benzodiazepine dose if necessary.[14]
Lorazepam Ativan®	Parent: UGT	**Nelfinavir, ritonavir and tipranavir** may ↓ lorazepam concentrations via	**Tipranavir** may ↓ lorazepam concentrations (via UGT	No predicted effect.

	Sedative Route of Metabolism[22, 23]	Protease Inhibitors atazanavir (Reyataz®)[1], darunavir (Prezista®)[2], fosamprenavir (Telzir®)[3], indinavir (Crixivan®)[4], lopinavir/ritonavir (Kaletra®)[24], nelfinavir (Viracept®)[6], ritonavir (Norvir®)[7], saquinavir (Invirase®)[8], tipranavir (Aptivus®)[9]	NNRTIs efavirenz (Sustiva®)[10], etravirine (Intelence®)[11], nevirapine (Viramune®)[12], rilpivirine (Edurant®)[13]	Integrase Inhibitor elvitegravir/cobicistat (Stribild®, single-tablet regimen with tenofovir/emtricitabine)[14], raltegravir (Isentress®)[15]
		UGT induction.	induction); no predicted effect with the NNRTIs.	
Midazolam (MDZ) Versed®	Parent: CYP3A Metabolite: UGT (hydroxy)	**Contraindicated** in product monographs. Possible ↑↑ midazolam concentrations. **Saquinavir:** case report of prolonged sedation requiring flumazenil with combination. [31] Kinetic study showing 5-fold ↑ PO MDZ AUC and 2.4-fold ↑ IV MDZ AUC.[32] In a retrospective cohort study, 51 patients were exposed to midazolam and **PIs** while undergoing bronchoscopy. The relative risk of severe prolonged sedation was 6.21 (9.80% in PI exposed vs. 1.58% in PI non-exposed). The length of hospitalization was 3 days longer in the PI exposed group. Coadministration of these agents should be avoided and alternate sedatives used for procedures. If the combination is used, intensive monitoring is required.[33]	possible ↓ midazolam concentrations and efficacy	**Oral midazolam is contraindicated with elvitegravir/cobicistat.**[14] Parenteral midazolam: potential for ↑ midazolam concentrations with **elvitegravir/cobicistat**. Coadministration should be done in a setting that ensures close clinical monitoring and appropriate medical management in case of respiratory depression and/or prolonged sedation. Dosage reduction for midazolam should be considered, especially if more than a single dose of midazolam is administered.[14]
Nitrazepam Mogadon®	Parent: nitro-reduction, acetylation	possible ↑ nitrazepam concentrations	possible ↓ nitrazepam concentrations and withdrawal	Possible ↑ nitrazepam concentrations with **elvitegravir/cobicstat.**
Oxazepam Serax®	Parent: UGT	**Nelfinavir, ritonavir and tipranavir** may ↓ oxazepam concentrations via UGT induction.	**Tipranavir** may ↓ oxazepam concentrations (via UGT induction); no predicted effect with the NNRTIs.	No predicted effect.
Propofol Diprivan®	Parent: CYP2B6 >UGT	Possible ↓ propofol concentrations with ritonavir-boosted regimens.	Possible ↓ propofol concentrations with efavirenz or nevirapine-based regimens.	
Ramelteon	Parent: CYP1A2 >2C,	Possible ↓ ramelteon concentrations	no major predicted effect	Possible ↑ ramelteon

	Sedative Route of Metabolism[22, 23]	Protease Inhibitors atazanavir (Reyataz®)[1], darunavir (Prezista®)[2], fosamprenavir (Telzir®)[3], indinavir (Crixivan®)[4], lopinavir/ritonavir (Kaletra®)[24], nelfinavir (Viracept®)[6], ritonavir (Norvir®)[7], saquinavir (Invirase®)[8], tipranavir (Aptivus®)[9]	NNRTIs efavirenz (Sustiva®)[10], etravirine (Intelence®)[11], nevirapine (Viramune®)[12], rilpivirine (Edurant®)[13]	Integrase Inhibitor elvitegravir/cobicistat (Stribild®, single-tablet regimen with tenofovir/emtricitabine)[14], raltegravir (Isentress®)[15]
Rozerem®	3A4[34]	with ritonavir-boosted regimens via 1A2, 2C9 induction; clinical significance unknown since ritonavir is also a potent CYP3A4 inhibitor. Use with caution and monitor for efficacy/ toxicity.		concentrations with **elvitegravir/cobicstat.** Use with caution and monitor for efficacy/toxicity.
Temazepam Restoril®	Parent: UGT>>CYP (2B6, 2C, 3A) [35]	**Nelfinavir, ritonavir and tipranavir** may ↓ temazepam concentrations via UGT induction.	no predicted effect	No predicted effect.
Triazolam (TZL) Halcion®	Parent: CYP3A Metabolite: GT (4 & alpha hydroxy)	**Contraindicated** in product monographs; possible ↑ triazolam concentrations. *In vitro* study showed ritonavir is a strong inhibitor of triazolam.[36] Short-term study of 0.125mg triazolam with 4 doses of ritonavir 200 mg resulted in ↑ triazolam half-life from 3.7 to 50 hours.[37, 38] This likely reflects early inhibitory effects of ritonavir, but does not account for chronic induction.	possible ↓ triazolam concentrations and withdrawal	**Triazolam is contraindicated with elvitegravir/cobicistat.**[14]
Valerian Root	May inhibit CYP3A4.[39, 40]	A significant interaction is unlikely.	A significant interaction is unlikely. Potential for additive CNS toxicity when starting EFV.	A significant interaction is unlikely.
Zaleplon Starnoc®	Aldehyde oxidase > CYP3A4[41]	Possible ↑ zaleplon concentrations.	Possible ↓ zaleplon concentrations.	Possible ↑ zaleplon concentrations with **elvitegravir/cobicstat.** Use with caution and monitor for efficacy/toxicity.
Zolpidem Ambien®	Parent: CYP3A (61%) >> 2C9 (22%), 1A2 (14%) >> 2D6, 2C19 (<3%)	possible ↑ in zolpidem concentrations **No longer contraindicated** in Norvir® product monograph.[7] *In vitro* study showed RTV is a less potent inhibitor of zolpidem than triazolam. In addition, short-term study of zolpidem 5.0 mg with 4 doses of RTV 200mg resulted in	Possible decrease in zolpidem concentrations and withdrawal	**Elvitegravir/cobicistat:** possible ↑ zolpidem concentrations. Monitor and reduce zolpidem dose if necessary.[14]

	Sedative Route of Metabolism[22, 23]	Protease Inhibitors atazanavir (Reyataz®)[1], darunavir (Prezista®)[2], fosamprenavir (Telzir®)[3], indinavir (Crixivan®)[4], lopinavir/ritonavir (Kaletra®)[24], nelfinavir (Viracept®)[6], ritonavir (Norvir®)[7], saquinavir (Invirase®)[8], tipranavir (Aptivus®)[9]	NNRTIs efavirenz (Sustiva®)[10], etravirine (Intelence®)[11], nevirapine (Viramune®)[12], rilpivirine (Edurant®)[13]	Integrase Inhibitor elvitegravir/cobicistat (Stribild®, single-tablet regimen with tenofovir/emtricitabine)[14], raltegravir (Isentress®)[15]
		an insignificant increase in t ½ from 2 to 2.4 hours. There were no clinical sequelae seen.[38] A 50% zolpidem dosage reduction may be warranted when used with potent enzyme inhibitors.[35]		
Zopiclone Imovane®	Parent: CYP3A4> 2C8, 2C9[35]	possible ↑ zopiclone concentrations. A 50% zopiclone dosage reduction may be warranted when used with potent enzyme inhibitors.[35]	possible ↓ zopiclone concentrations and withdrawal	**Elvitegravir/cobicistat:** possible ↑ zopiclone concentrations. Monitor and reduce zopiclone dose if necessary.[14]

Key: CYP= Hepatic Cytochrome P450 isoenzyme; AD= Alcohol dehydrogenase; substrate= route of hepatic elimination of that specific drug (specified by a specific cytochrome P450 isoenzyme); inducer= leads to more rapid clearance of substrates of a specific hepatic isoenzyme (lowers levels of the respective drug and may lead to decreased efficacy); inhibitor= leads to decreased clearance of substrates of a specific hepatic isoenzyme (increases levels of a respective drug and may lead to toxicity). UGT= Uridine diphosphate glucuronyltransferase

Please note: This chart summarizes some of the major drug interactions identified to date, based on current available data; other drug interactions may exist. Please use caution whenever adding/modifying therapy. The information in this table is intended for use by experienced physicians and pharmacists. It is not intended to replace sound professional judgment in individual situations, and should be used in conjunction with other reliable sources of information. Due to the rapidly changing nature of information about HIV treatment and therapies, users are advised to recheck the information contained herein with the original source before applying it to patient care.

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Comparison of Medications used for Smoking Cessation

Medication	Contraindications	Adverse Effects**	Dosage	Onset/Duration	Interactions
Nicotine Replacement Therapy (NRT)					
Nicotine Patch (NicoDerm®, Habitrol®, other pharmacy store brands) 7 mg, 14 mg, 21 mg per 24 hours Average $3-$4/day *No prescription required*	***All NRT Products:*** - Avoid during immediate post-myocardial infarction period, angina (severe or worsening), life-threatening arrhythmias - Uncontrolled hypertension - Recent stroke - Severe kidney/ liver disease - Pregnancy & lactation - Allergy to nicotine - Non-smokers *Nicotine can cause tachycardia and worsen underlying cardiac conditions. It may cause delayed healing of peptic ulcer disease and worsen vasospastic diseases.* ***Patch Only (in addition to above)*** - Adhesive allergy - Use during MRI – thermal burns reported due to aluminum lining. ***Gum Only (in addition to above)*** - TMJ (temporomandibular joint disorder) - Caution with dentures ***Lozenge Only (in addition to above)*** - Caution with dentures ***Nasal Spray Only (in addition to above)*** -Chronic nasal disorders (i.e. allergies, rhinitis, polyps, sinusitis)	***All NRT Products:*** - Headache - Insomnia - Dyspepsia, nausea ***Patch Only (in addition to above)*** - Skin irritation or sensitivity, pruritis - Vivid dreams (only wear patch during the day with occurrence) ***Gum Only (in addition to above)*** - Mouth or throat soreness - Jaw muscle ache - Hiccups - Taste perversion - Flatulence ***Inhaler Only (in addition to above)*** - Cough - Mouth or throat soreness - Hiccups - Rhinitis ***Lozenges Only (in addition to above)*** - Mouth or throat soreness - Hiccups ***Oral Spray Only*** - Tingling lips (avoid spraying on lips) - Hiccups ***Intranasal Spray Only*** (usually diminished after 1 week) - Transient burning and stinging of nasal mucosa - Throat irritation - Flushing - Cough - Sneezing	*****Patients are to stop smoking while using ***** ***Heavy smokers > 20/day:*** *One strategy:* 21 mg/day x 6 wk, 14 mg/day x 2 wk, 7 mg/day x 2 wk. ***Light smokers, heart disease or < 45 kg:*** *One strategy:* 14 mg/day x 6 wk, 7 mg/day x 2 – 4 wk *Titration schedule should be personalized.* *Rotate patch site daily to avoid skin irritation* *Wear patch for 16-24 hours* *Never cut patch*	Onset of action (Tmax): - Patch: 6-8 hours (slow) - Gum/ Lozenge/Inhaler: 20-60 min (intermediate) - Oral spray: 1 min (fast) - Intranasal spray: 5-20 min (fast) Duration of therapy: Up to 12 weeks or longer if needed. Do not use for > 6 months without consulting physician. Typically, gradual withdrawal with personalized titration schedule and duration is recommended.	Smokers: Nicotine itself does not impact hepatic enzymes and is not subject to cytochrome P-450 interactions. Tobacco smoke however produces polycyclic aromatic hydrocarbons (PAHs) which are potent inducers of CYP1A1, 1A2, and possibly 2E1. Smokers may require increased doses of substrate drugs. In contrast, when smoking is discontinued, the substrate drug may require a dosage decrease over a period of several days. Some authors have suggested a 10% daily-dose reduction over 4 days for substrates that have a narrow therapeutic range. (14,15) CYP1A1, 1A2 substrates: Theophylline Caffeine Clozapine Olanzepine Fluvoxamine Tacrine TCAs (partial substrate) Nicotine: Nicotine is metabolized via CYP2A6, but is not an inducer or inhibitor of CYP450 isoenzymes. (16) There are no anticipated kinetic interactions. Monitor for treatment emergent hypertension when NRT is combined with bupropion.
Nicotine Gum (Nicorette®, other pharmacy store brands) 2 mg, 4 mg Average $2-$8/day (6-25 pieces) *No prescription required*			Bite gum once or twice, then "park it" between cheek and gum. Wait and repeat, (one piece will last for approx 30 minutes). Chew slowly. ***Use 2 mg:*** *< 25 cigarettes/day or smokes after first 30 minutes of waking.* ***Use 4 mg:*** *> 25 cigarettes/day or smokes within 30 minutes of waking.* 10 – 12 pieces/day chewed every 1 – 2 hour for first month. Maximum dose: 20 pieces /day *Titration schedule should be personalized.* *Avoid acidic beverages (i.e. coffee, colas and citrus juices – prevent absorption)*		
Nicotine Lozenge (Nicorette® 2 mg, 4 mg; Thrive® 1 mg, 2 mg) Average $4-$10/day (6-15 lozenges) *No prescription required*			Nicorette: ***Use 2mg:*** *smokes after first 30 minutes of waking.* ***Use 4mg:*** *smokes within 30 minutes of waking.* Slowly dissolve 1 lozenge in mouth, moving side to side over 20-30 minutes. Typically use 1 lozenge every 1-2 hours for 6 weeks, then every 2-4 hours for 3 weeks, then every 4-8 hours for 3 weeks. Maximum dose 15 lozenges/dayx2mg lozenges. Do not chew or swallow whole. *Titration schedule should be personalized.* *Avoid eating or drinking 15 minutes before or while using the lozenge.* Thrive Lozenge: **1 mg** for less than a pack per day (max 25/day) **2mg** for more than a pack per day (max 15/day)		
Nicotine Inhaler (Nicorette® Inhaler)			Usual dose: 6 – 12 cartridges/day by frequent continuous puffing over 5--20 minutes. Inhale as		

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Medication	Contraindications	Adverse Effects**	Dosage	Onset/Duration	Interactions
4 mg per cartridge Average $6-$12/day (6-12 cartridges) *No prescription required*		- Rhinorrhea - Lacrimation	puffs through the tapered end of mouthpiece as required to control cravings. Maximum: 12 cartridges/day *Titration schedule should be personalized.* *Recommended use only at room temperature*		
Nicotine Oral Spray (Nicorette QuickMist®) 1 mg nicotine per spray (150 doses per device) ~$48.00/device *No prescription required*			1- 2 sprays into the mouth when patient would normally smoke a cigarette or have cravings to smoke. Use one spray first and if cravings do not disappear within a few minutes use the second spray. If 2 sprays are required, future doses may be delivered as 2 consecutive sprays. For most smokers this means about 1 or 2 sprays every 30 minutes to 1 hour. The maximum dose is 2 sprays at a time, 4 sprays per hour and 64 sprays per day.		
Nicotine Nasal Spray (Nicotrol NS®) 0.5 mg nicotine per spray (10 mg/mL, 10mL bottle) Available in USA- Pfizer			1-2 doses intranasally (2-4 sprays)/ hour; maximum 5 doses (10 sprays) per hour and 40 doses (80 sprays) per day. Use a minimum of 8 doses/day for efficacy. 0.5 mg nicotine per spray 1.0 mg nicotine per dose (2 sprays, one spray per nostril)		
Other Drugs					
Bupropion SR (Zyban®) 150 mg tabs Average of $2-$3/day *Prescription required*	*Not recommended for those at high risk of seizures or those who have a seizure disorder.* - Current seizure disorder - Brain tumor, brain surgery, closed head injury - Eating disorders (inc. seizures with anorexia/bulimia) - Abrupt alcohol, benzodiazepine or other sedative withdrawal - MAO Inhibitors within 14 days - Thioridazine - Caution in stroke patients (particularly if recent stroke and prone to seizures).	- Agitation type events with self-harm. - Anorexia, nausea - Xerostomia - Tremor - Tachycardia - Dizziness - Headache - Insomnia - Agitation, Anxiety - Hallucinations - Seizures (at higher than recommended doses) - Hypotension	150 mg once daily x 3 days, then 150 mg twice daily (minimum 8 hr dosing interval; take the 2nd dose by early evening to minimize insomnia) Initiate while still smoking Quit smoking after 7 – 14 days of therapy Max total daily dose: 300 mg Max single dose: 150 mg *Do not chew, divide or crush tablets*	7 – 12 weeks, or longer if necessary *Discontinue current treatment course if patient not abstinent by 7th wk of therapy.* Maintenance (prevention of relapse) 300 mg/day for up to 1 year on individual basis	***Contraindicated with MAO inhibitors and thioridazine. Caution with levodopa and amantadine (increased CNS side-effects).*** (12) **CYP2B6 substrate (metabolized to active hydroxybupropion); CYP2D6 inhibitor.** (12) -Caution with drugs that lower seizure threshold (i.e. antipsychotics, antidepressants, theophylline, systemic steroids, etc.) (12) - CYP2B6 inhibitors or inducers may increase or decrease bupropion concentrations, respectively. - Potent inducers of various CYPs may also decrease bupropion concentrations (i.e. rifampin, carbamazepine, phenytoin, phenobarbital), **Antiretrovirals (AVRs):**

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Medication	Contraindications	Adverse Effects**	Dosage	Onset/Duration	Interactions
					-Ritonavir- boosted ARVs: *in vitro* data suggest an increase in bupropion concentrations. (17) However, *in vivo* up to57% decrease AUC bupropion is seen, depending on dose and duration of ritonavir therapy. *May require an increase in bupropion dosage*.(18-20) -Nelfinavir & Efavirenz: *in vitro* data suggest an increase in bupropion concentrations due to CYP2B6 inhibition. (17) One case series reported no increased episodes of seizures with either nelfinavir, ritonavir or efavirenz. (21) One study with efavirenz showed a 55% decrease AUC of buproprion. (22) *May require an increase in bupropion dosage when combined with efavirenz.* Bupropion may **increase the levels of CYP2D6 substrates**. Caution is warranted ;a decreased dosage of the substrate drug may be required (i.e. antidepressants, antipsychotics, beta-blockers, type 1C antiarrhythmics). (12)
Bupropion SR & Nicotine Transdermal System (Patch) Combination Average $5-$7/day (patch and bupropion) *See Individual Agents*	Caution in patients with hypertension *See Individual Agents*	*See Individual Agents*	Initiate while still smoking: Buproprion 150 mg daily X 3 days, then 2 times daily (minimum 8 hr dosing interval; take the 2nd dose by early evening to minimize insomnia). Add nicotine patch to buproprion after 1 week of stop smoking. 21 mg/d x 7 wk, 14 mg/d x 1 wk then 7 mg/d x 1 wk. Taper patch during week 8 and 9.	10 – 12 weeks, or longer if necessary	*See Individual Agents* Monitor for treatment emergent hypertension when NRT is combined with bupropion.
Varenicline (Champix®) 0.5 mg, 1 mg tabs Average $4-$4.50/day *Prescription required*	- Pregnancy and lactation - Use cautiously in those with schizophrenia, bipolar disorder or another major depressive disorder. - Use cautiously in those with kidney disease. Dosage adjustment required if the creatinine clearance is < 30 mL/minute. *Not studied in the following*	- Nausea - Constipation, flatulence - Xerostomia - Insomnia - Abnormal dreams (vivid) - Headache - Agitation, depression, suicidal thoughts , changes in behavior, worsening of pre-existing psychiatric disorders in patients with or without psychiatric	Varenicline 0.5 mg once daily for 3 days, then 0.5 mg twice daily for 4 days, then 1 mg twice daily (interval of at least 6 hours between doses). Take with food and water to minimize nausea. Initiate while still smoking. Quit smoking after 7-14 days of therapy.	12 weeks or longer if necessary	Not hepatically metabolized. Mainly excreted unchanged in the urine. No known clinically significant interactions. (13) Nicotine transdermal & varenicline may result in increased side-effects (i.e. nausea, headache, dizziness, and fatigue) In patients with severe renal

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Medication	Contraindications	Adverse Effects**	Dosage	Onset/Duration	Interactions
	populations; safety and efficacy data is lacking and caution is warranted (psychiatric disorders, pediatrics, epilepsy, gastro-intestinal disease such as irritable bowel syndrome, heart disease, COPD, chemotherapy, uncontrolled hypertension, controlled diabetes).	disorders (Black Box Warning)			impairment, the concomitant use of cimetidine and varenicline, as well as other inhibitors of hOCT2, such as trimethoprim, ranitidine or levofloxacin should be avoided. Alcohol intake may increase risk of psychiatric side effects.

ARVs= antiretrovirals; AUC= area under the concentration-time curve; CNS= central nervous system; COPD= chronic obstructive pulmonary disease; hOCT2= human organic cation transporter; MAO= monoamine oxidase; NRT= Nicotine Replacement Therapy; TCAs= tricyclic antidepressants; Tmax= time to peak concentration

** Note: Smoking cessation and resulting nicotine withdrawal may mimic certain adverse effects of smoking cessation medications. Symptoms of **nicotine withdrawal** may include: cravings, depression, insomnia, irritability, anxiety, nervousness, drowsiness, increased appetite & weight gain. **Nicotine toxicity** is characterized by: nausea, salivation, abdominal pain, vomiting, diarrhea, diaphoresis, flushing, dizziness, confusion, palpitations, etc.

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Antiretroviral Interactions With Transplant Medications

	Cyclosporine (Neoral®)	Tacrolimus (Prograf®, Advagraf®) and Sirolimus (Rapamune®)	Mycophenolate Mofetil (CellCept®)
Pharmacokinetic characteristics	>90% metabolized (substrate and inhibitor of CYP3A4; also inhibits P-glycoprotein[1])	>90% metabolized (substrate of CYP3A4) substrate and inhibitor of P-glycoprotein	MPA, the active metabolite is a substrate of glucuronyl transferase
Integrase Inhibitors			
Elvitegravir Metabolized by 3A4, UGT1A1/3; moderate 2C9 inducer. Boosted with cobicistat, an inhibitor of 3A4, 2D6 and p-glycoprotein	Potential for ↑ immunosuppressant concentrations. Therapeutic monitoring of immunosuppressant is recommended.[2]	Potential for ↑ immunosuppressant concentrations. Therapeutic monitoring of immunosuppressant is recommended.[2]	Potential for ↑ immunosuppressant concentrations. Therapeutic monitoring of immunosuppressant is recommended.[2]
Raltegravir Metabolized by UGT1A1.	Case report of an HIV-positive liver transplant recipient who received cyclosporine and raltegravir post-transplant. Cyclosporine concentrations were measured regularly and remained therapeutic. Pre- and post dose raltegravir levels were measured at weeks 4 and 8, and were comparable with published data. The authors concluded that raltegravir and cyclosporin may be coadministered without dose adjustment.[3] In 13 HIV-infected transplant patients (n=8 liver, n=5 kidney) who received raltegravir + 2 NRTIs, median raltegravir Ctrough was 507 ng/mL (range 176-890) and target Ctrough of tacrolimus or cyclosporine were achieved with standard doses. After a median follow-up of 9 months (range: 6-14), all patients were alive with	Raltegravir may avoid interactions with certain immunosuppressives as it is primarily metabolized via glucuronidation and not by CYP3A4. Case report of the successful use of raltegravir/3TC/abacavir and sirolimus in a 49 year old HIV/HCV+ patient who underwent liver transplantation. The patient was switched to this regimen after a series of medication modifications. Pt had developed renal insufficiency with hyperpotasemia and metabolic acidosis due to increased tacrolimus levels (> 25 ng/ml) related to atazanavir use.[5] In 13 HIV-infected transplant patients (n=8 liver, n=5 kidney) who received raltegravir + 2 NRTIs, median raltegravir Ctrough was 507 ng/mL (range 176-890) and target Ctrough of tacrolimus or	The pharmacokinetics of raltegravir 400 mg BID and mycophenolic acid were prospectively determined in 6 HIV-infected solid-organ transplant recipients. Raltegravir kinetics were not significantly different from historical controls, and MPA metabolism was not significantly altered by raltegravir.[8]

	Cyclosporine (Neoral®)	Tacrolimus (Prograf®, Advagraf®) and Sirolimus (Rapamune®)	Mycophenolate Mofetil (CellCept®)
	satisfactory graft function.[4]	cyclosporine were achieved with standard doses. After a median follow-up of 9 months (range: 6-14), all patients were alive with satisfactory graft function.[4] In a case series of 11 HIV-positive solid organ transplant (10 liver, 1 renal) patients who received raltegravir/2 NRTI therapy (plus enfuvirtide, n=2) and tacrolimus (91%), median CD4 increased to 380 cells/mm3 and VL remained <50 copies/mL after a median follow-up of 57 weeks. No patients discontinued raltegravir, and no toxicity or interactions with tacrolimus were noted.[6] Two HIV-positive patients began raltegravir-based cART while on tacrolimus 1 or 2 mg twice daily (1 for liver transplantation and 1 for Crohn's disease); no tacrolimus dose adjustment was needed and tacrolimus blood levels were not altered.[7]	
Protease inhibitors			
Amprenavir/ fosamprenavir Primarily metabolized by CYP3A4. Inhibitor of CYP3A4 (similar potency as indinavir and nelfinavir)[9]; also induces CYP3A4[10].	May ↑/↓ CsA concentrations via CYP3A4 inhibition or induction	May ↑/↓ tacrolimus concentrations via CYP3A4 inhibition or induction. In a case series of HIV-positive patients undergoing liver transplantation, tacrolimus levels were markedly ↑ in the	

	Cyclosporine (Neoral®)	Tacrolimus (Prograf®, Advagraf®) and Sirolimus (Rapamune®)	Mycophenolate Mofetil (CellCept®)
		presence of PI-based HAART regimens (LPV/r, APV, and NFV).[11] In a separate report, a 61-year old patient on fosamprenavir/ritonavir was started on 0.5 mg QD tacrolimus post-renal transplant; target tacrolimus concentrations were reached within 2 days and tacrolimus was discontinued due to high (37 ng/mL) levels. Target levels were subsequently achieved with tacrolimus 0.5 mg every 4 days.[12] In four HIV-infected liver transplant patients who switched from nelfinavir to fosamprenavir, mean tacrolimus Ctrough ↓ significantly from 6.9 to 3.2 ng/mL before vs. after the switch. Tacrolimus dose increase was needed, from an average of 0.29 mg/day to 0.48 mg/day (p=0.046) to attain the desired target of 8.7 +/- 2.3 ng/mL. These findings suggest that fosamprenavir may be less potent than nelfinavir in inhibiting tacrolimus clearance.[13] A retrospective analysis of HIV-positive patients receiving tacrolimus with various cART regimens was conducted. Three liver transplant patients were on ritonavir-boosted PI therapy (1	

	Cyclosporine (Neoral®)	Tacrolimus (Prograf®, Advagraf®) and Sirolimus (Rapamune®)	Mycophenolate Mofetil (CellCept®)
		on saquinavir 1000 mg BID plus lopinavir 400/ritonavir 100 mg BID, 1 on **fosamprenavir 700/100 mg BID**, 1 on darunavir 600/ritonavir 100 mg BID), and received tacrolimus doses of 0.06, 0.03, and 0.08 mg daily, with median tacrolimus levels of 6.6, 3.0 and 7.9 ng/mL, respectively. Two other patients began raltegravir-based cART while on tacrolimus 1 or 2 mg twice daily; no tacrolimus dose adjustment was needed and tacrolimus blood levels were not altered.[7] Monitor tacrolimus levels.	
Atazanavir Primarily metabolized by CYP3A4; also inhibits CYP3A.	May ↑ CsA concentrations via CYP3A4 inhibition	May ↑ tacrolimus concentrations via CYP3A4 inhibition. A case report describes a 53-year old HIV-positive, African-American man who received a renal transplant and was placed on mycophenolate mofetil and tacrolimus along with concomitant **unboosted atazanavir**, abacavir and lamivudine. The patient initially received tacrolimus 0.5 mg on day 2 post-transplant, but serum tacrolimus levels became subtherapeutic by 6 hours, so tacrolimus dosing was changed to 1 mg every 8 hours, and	

	Cyclosporine (Neoral®)	Tacrolimus (Prograf®, Advagraf®) and Sirolimus (Rapamune®)	Mycophenolate Mofetil (CellCept®)
		subsequently to 1.5 mg every 12 hours to maintain therapeutic levels and optimize patient convenience.[14] Monitor tacrolimus levels, renal & hepatic function and serum electrolytes.	
Darunavir Primarily metabolized by CYP3A4; also inhibits CYP3A.	May ↑ CsA concentrations via CYP3A4 inhibition.	May ↑ tacrolimus concentrations via CYP3A4 and/or P-gp inhibition. Case report of a patient with HIV-associated focal segmental glomerulosclerosis who underwent a kidney cadaveric transplantation and was started on a regimen including darunavir/ritonavir. This resulted in a marked increased in tacrolimus trough levels to 106.7 ng/ml (target range 6-7 ng/ml). A decrease in tacrolimus dosage to a single dose of 0.5 mg/week (3.5% of the usual dose) enabled maintenance of stable tacrolimus trough levels.[15] A retrospective analysis of HIV-positive patients receiving tacrolimus with various cART regimens was conducted. Three liver transplant patients were on ritonavir-boosted PI therapy (1 on saquinavir 1000 mg BID plus lopinavir 400/ritonavir 100 mg BID, 1 on fosamprenavir 700/100 mg BID, 1 on **darunavir 600/ritonavir**	

	Cyclosporine (Neoral®)	Tacrolimus (Prograf®, Advagraf®) and Sirolimus (Rapamune®)	Mycophenolate Mofetil (CellCept®)
		100 mg BID), and received tacrolimus doses of 0.06, 0.03, and 0.08 mg daily, with median tacrolimus levels of 6.6, 3.0 and 7.9 ng/mL, respectively. Two other patients began raltegravir-based cART while on tacrolimus 1 or 2 mg twice daily; no tacrolimus dose adjustment was needed and tacrolimus blood levels were not altered.[7]	
Indinavir Primarily metabolized by CYP3A4; also an inhibitor of CYP3A4.[16]	May ↑ CsA concentrations via CYP3A4 inhibition. In liver transplant patient (n=1), prolonged $t_{1/2}$ of CsA observed with concomitant IDV/r regimen; daily doses of CsA ↓ 5-20% to maintain serum CsA trough levels.[17]	May ↑ tacrolimus concentrations via CYP3A4 inhibition. In a case series of HIV-positive patients undergoing liver transplantation, tacrolimus levels were markedly ↑ in the presence of PI-based HAART regimens (LPV/r, APV, and NFV)[11] and IDV, NFV[18] Monitor tacrolimus levels.	In a small case series (n=6) of HIV+ subjects receiving ddI, 3TC, abacavir, indinavir 800/ ritonavir 100 mg BID and nevirapine 200 mg BID, there was no significant change in indinavir concentrations in the presence of chronic MMF administration.[19]
Lopinavir/ritonavir Lopinavir is primarily metabolized by CYP3A4. Kaletra inhibits CYP3A4, 2D6 (to lesser extent). At clinically relevant concentrations, Kaletra does not inhibit CYP2C9, 2C19, 2E1, 2B6 or 1A2. Induces glucuronyl transferases and possibly CYP1A2[20], CYP2C19 and 2C9.[21]	In liver transplant patients (n=2), prolonged $t_{1/2}$ of CsA observed with concomitant LPV/r; daily doses of CsA ↓ 5-20% to maintain serum CsA trough levels.[17]	May ↑ tacrolimus concentrations via CYP3A4 inhibition. In a case series of HIV-positive patients undergoing liver transplantation, tacrolimus levels were markedly ↑ in the presence of PI-based HAART regimens (LPV/r, APV, and NFV).[11] When a **LPV/r** based regimen was added to tacrolimus regimen (range 1-6mg BID; target steady state conc:	- may ↓ MMF via GT induction

	Cyclosporine (Neoral®)	Tacrolimus (Prograf®, Advagraf®) and Sirolimus (Rapamune®)	Mycophenolate Mofetil (CellCept®)
		5-10ng/ml) in 7 HCV-HIV coinfected liver transplant patients, the tacrolimus dose was reduced by 99% (to 0.5 - 1.5mg every 7- 25 days) to maintain target tacrolimus concentrations. Concentrations of LPV were within the ranges published for patients with normal liver function tests.[22] Similarly, a 41-year old patient on lopinavir/ritonavir was started on 1 mg QD tacrolimus post-renal transplant; target tacrolimus concentrations were reached within 12 hours and the patient was maintained on a dose of 0.5 mg tacrolimus every 8 days.[23] A retrospective analysis of HIV-positive patients receiving tacrolimus with various cART regimens was conducted. Three liver transplant patients were on ritonavir-boosted PI therapy (1 on **saquinavir 1000 mg BID plus lopinavir 400/ritonavir 100 mg BID**, 1 on fosamprenavir 700/100 mg BID, 1 on darunavir 600/ritonavir 100 mg BID), and received tacrolimus doses of 0.06, 0.03, and 0.08 mg daily, with median tacrolimus levels of 6.6, 3.0 and 7.9 ng/mL, respectively. Two other patients	

	Cyclosporine (Neoral®)	Tacrolimus (Prograf®, Advagraf®) and Sirolimus (Rapamune®)	Mycophenolate Mofetil (CellCept®)
		began raltegravir-based cART while on tacrolimus 1 or 2 mg twice daily; no tacrolimus dose adjustment was needed and tacrolimus blood levels were not altered.[7] Monitor tacrolimus levels.	
Nelfinavir Primarily metabolized by CYP3A4; minor pathways include CYP2C19, CYP2D6, others. Inhibitor of CYP3A4.[24]	May ↑ CsA concentrations via CYP3A4 inhibition	Case reports of patients undergoing liver transplantation who received nelfinavir; in each instance, tacrolimus concentration rose to toxic levels, and patient developed severe, prolonged tacrolimus toxicity.[25] Significant ↓ in nelfinavir dosages (up to >95% ↓) were required.[25, 26] In a case series of HIV-positive patients undergoing liver transplantation, tacrolimus levels were markedly ↑ in the presence of PI-based HAART regimens (LPV/r, APV, and NFV)[11] and IDV, NFV.[18] In a separate case series, 2 HIV-infected liver transplant recipients on NFV + 2 NRTIs experienced ↑ tacrolimus half-life; therapeutic tacrolimus levels were maintained with a 75-93% decrease in the daily dose of tacrolimus. Low NFV concentrations were seen in 1 patient (details not provided).[22] Monitor tacrolimus levels.	- may decrease MMF via GT induction

	Cyclosporine (Neoral®)	Tacrolimus (Prograf®, Advagraf®) and Sirolimus (Rapamune®)	Mycophenolate Mofetil (CellCept®)
Ritonavir Potent inhibitor of CYP enzymes in following order: 3A>2D6>2C9>2C19>> 2A6>2E1. Induces glucuronyl transferases and CYP1A2. [16] May also induce CYP2C9, 2C19.	Low dose ritonavir (as booster) shown to ↑ $t_{1/2}$ of CsA in liver-transplant patients (n=3); daily doses of CsA ↓ 5-20% to maintain serum CsA trough levels.[17]	Case report of HCV/HIV patient who underwent liver transplantation; patient received saquinavir, ritonavir, and nelfinavir at various times with tacrolimus. In each instance, tacrolimus concentration rose to toxic levels, and patient developed severe, prolonged tacrolimus toxicity.[26] Monitor tacrolimus concentrations and adjust dosage accordingly.	- may decrease MMF via GT induction
Saquinavir Primarily metabolized by CYP3A4. Weak inhibitor of CYP3A4.[16]	Case report of an HIV-positive renal transplant patient whose cyclosporine levels tripled 3 days after initiation of SQV; postulated mechanism was competition for CYP3A metabolism and P-glycoprotein drug transport by SQV.[27]	Case report of HCV/HIV patient who underwent liver transplantation; patient received saquinavir, ritonavir, and nelfinavir at various times with tacrolimus. In each instance, tacrolimus concentration rose to toxic levels, and patient developed severe, prolonged tacrolimus toxicity.[26] A retrospective analysis of HIV-positive patients receiving tacrolimus with various cART regimens was conducted. Three liver transplant patients were on ritonavir-boosted PI therapy (1 on **saquinavir 1000 mg BID plus lopinavir 400/ritonavir 100 mg BID**, 1 on fosamprenavir 700/100 mg BID, 1 on darunavir 600/ritonavir 100 mg BID), and received tacrolimus doses of 0.06, 0.03, and 0.08 mg daily, with median tacrolimus levels of 6.6, 3.0 and 7.9	

	Cyclosporine (Neoral®)	Tacrolimus (Prograf®, Advagraf®) and Sirolimus (Rapamune®)	Mycophenolate Mofetil (CellCept®)
		ng/mL, respectively. Two other patients began raltegravir-based cART while on tacrolimus 1 or 2 mg twice daily; no tacrolimus dose adjustment was needed and tacrolimus blood levels were not altered.[7] Monitor tacrolimus concentrations and adjust dosage accordingly.	
NNRTIs			
Efavirenz induces CYP3A4 and inhibits 2C9, 2C19, and 3A4 isoezymes[3]	In a renal transplant patient on stable CsA who initiated an efavirenz-containing regimen, CsA concentrations ↓ 54% after 5 days and declined by a total of 75% after 1 month.[28]	In a case series of HIV-positive patients undergoing liver transplantation, tacrolimus levels were markedly ↓ in the presence of EFV-based HAART regimens.[11] When an **EFV** based regimen was added to tacrolimus in 4 HCV-HIV coinfected liver transplant patients, very little change in tacrolimus dosing was required.[22] Concentrations of EFV were within the ranges published for patients with normal liver function tests. Monitor tacrolimus concentrations and adjust dosage accordingly.	
Nevirapine Potent inducer of CYP3A4 and 2B6 enzymes.[2]	May ↓ CsA concentrations via CYP3A induction	May ↓ tacrolimus concentrations via CYP3A induction. In a case series of HIV-positive patients undergoing liver transplantation, no changes in tacrolimus levels were observed in patients on nevirapine,	In a small case series (n=6) of HIV+ subjects receiving ddI, 3TC, abacavir, indinavir 800/ ritonavir 100 mg BID and nevirapine 200 mg BID, NVP clearance ↑ 27% in the presence of chronic MMF administration. Clinical

	Cyclosporine (Neoral®)	Tacrolimus (Prograf®, Advagraf®) and Sirolimus (Rapamune®)	Mycophenolate Mofetil (CellCept®)
		Trizivir,or tenofovir.[11]	significance unclear.[19]
NRTIs			
Tenofovir		In a case series of HIV-positive patients undergoing liver transplantation, no changes in tacrolimus levels were observed in patients on nevirapine, Trizivir,or tenofovir.[11] When **TDF/3TC/ddI** were added to tacrolimus in 1 HCV-HIV coinfected liver transplant patient, very little change in tacrolimus dosing was required.[22]	
Zidovudine		In a case series of HIV-positive patients undergoing liver transplantation, no changes in tacrolimus levels were observed in patients on nevirapine, Trizivir,or tenofovir.[11]	Zidovudine - both are substrates of glucuronyl transferase; competitive inhibition may result in ↑AZT or MPA

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III. GLOSSARY

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aa	apply as directed
ABC	abacavir
AD	Alcohol dehydrogenase
ALT	alkaline phosphatase
ANC	absolute neutrophil count
APV	amprenavir
ATV	atazanavir
AUC	area under the curve
BID	twice a day
BM	bowel movement
BOC	Boceprevir
BW	body weight
CAPD	continuous ambulatory peritoneal dialysis
CBC/diff	complete blood count/differential
CK	creatine kinase
Cmax	maximum (peak) concentration
Cmin	minimum (trough) concentration
CNS	central nervous system
Css	concentration at steady-state
CTZ	chemoreceptor-trigger zone
CYP	Hepatic Cytochrome P450 isoenzyme
D/C	discontinue
Derm	dermatologic
d4T	Stavudine
ddl	Didanosine
DLV	Delavirdine
DRV	Darunavir
EFV	Efavirenz
ENF	enfuvirtide
ESRD	end stage renal disease
ETV	etravirine
F/A	Facilitated Access (via ODB)
FPV	Fosamprenavir
GGT	gamma glutamyl transferase
GT	Glucuronyl transferase
gtts	drops
HGC	hard gel capsule
Hgb	hemoglobin
hs	at bedtime
i DS	one double strength tablet
i SS	one single strength tablet
IDV	Indinavir
IM	intramuscular
IV	intravenous
LFTs	liver function tests
LPV/r	lopinavir/ritonavir
MD	medical doctor
mcg	micrograms

MCV	mean corpuscular volume
mg	milligrams
MU	million units
MVC	maraviroc
NAM	nucleoside analogue-associated mutation
NFV	Nelfinavir
NVP	Nevirapine
PBMC	peripheral blood mononuclear cells
PI	protease inhibitor
pk	pharmacokinetics
plts	platelets
po	by mouth
pr	per rectum
prn	as required
pts	patients
q6h	every 6 hours
q8h	every 8 hours
QID	four times daily
RAL	Raltegravir
RPV	Rilpivirine
RTV	Ritonavir
Rx	prescription
S&S	swish and swallow
SC	subcutaneous
SJS	Stevens-Johnson Syndrome
SGC	soft gel capsule
SMX	Sulfamethoxazole
SQV	Saquinavir
ss	steady-state
Sx	symptoms
TAMs	thymidine analogue-associated mutations
TID	three times daily
TMP	Trimethoprim
TPV	Tipranavir
TVR	Telaprevir
ULN	upper limit of normal
USD	US dollars
Vd	volume of distribution
wks	weeks
[ ]	concentration

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