2013 Handbook of HIV Drug Therapy

VOLUME ONE

Treatment and Pharmacologic Information

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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**

TABLE OF CONTENTS FOR HIV DRUG THERAPY HANDBOOK 2013

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)
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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. HIV TREATMENT REGIMENS

REGIMEN	COST/ DAY ($)	LENGTH OF THERAPY	TOTAL COST ($)

A) MAINTENANCE THERAPY

Antiretrovirals

(to be used in combination; see guidelines in Federal register http://www.aidsinfo.nih.gov/guidelines/.) In general, a multi-class approach incorporating an NRTI backbone plus an option from any of the following three categories (NNRTI, PI or Integrase Inhibitor) is recommended:

	NRTI	NNRTI	PI	Integrase Inhibitor
Preferred	Tenofovir + emtricitabine (FTC)	Efavirenz	Atazanavir/ritonavir QD Darunavir/ritonavir QD	Raltegravir
Alternative	Abacavir or zidovudine + 3TC	Rilpivirine	Boosted: Fosamprenavir/r QD or BID Lopinavir/ritonavir QD or BID	Elvitegravir/ cobicistat
Acceptable	didanosine + 3TC	Nevirapine	Atazanavir QD Fosamprenavir BID Saquinavir/ritonavir BID	CCR5 Inhibitor: Maraviroc
Preferred for Pregnant Women: • Zidovudine/3TC + lopinavir/ritonavir BID				

**Please note that the individual agents classified as Recommended or Alternative may change as new data continue to emerge on long-term safety and toxicity. These classifications reflect current guidelines as of 2012. Clinicians are urged to regularly check the above resources for updates.

Single Tablet Regimen Products

a)	Atripla® (tenofovir 300 mg/emtricitabine 200 mg/ efavirenz 600 mg) 1 tablet daily	41.40		1242.00/mo
b)	Complera® (tenofovir 300 mg/emtricitabine 200 mg/ rilpivirine 25 mg) 1 tablet daily	43.66		1309.93/mo
c)	Stribild® (elvitegravir 150 mg/cobicistat 150 mg/ tenofovir 300 mg/emtricitabine 200 mg) 1 tablet daily	*79.17*	*Available in US*	*2375.00/mo (approximate wholesale acquisition cost, USD)*

Nucleoside Analogues (Combination products)

a)	Truvada® (tenofovir 300 mg/emtricitabine 200 mg) tablet : 1 tablet daily	26.63	according to factors including CD4, viral load, and clinical response	798.90/mo
b)	Kivexa® (abacavir 600 mg/lamivudine 300 mg) tablet: 1 tab QD	23.27		698.10/mo
c)	Combivir® (zidovudine 300 mg/lamivudine 150 mg) tablet: 1 tab BID	5.22-20.88		156.62-626.47/mo
d)	Trizivir® (abacavir 300 mg/lamivudine 150 mg/zidovudine 300 mg) tablet: 1 tab BID	35.35		1060.42/mo

Nucleoside Analogues (single agents):

a)	abacavir 300 mg po BID	13.74		412.16/mo

REGIMEN	COST/ DAY ($)	LENGTH OF THERAPY	TOTAL COST ($)
b) didanosine (ddI) EC (Videx EC):			
>60 kg: 400 mg once daily	11.54		346.36/mo
<60 kg: 250 mg once daily	7.20		216.04/mo
c) lamivudine (3TC) 150 mg po BID or 300 mg QD	7.25-9.67		217.61-290.15/mo
d) stavudine (d4T):			
>60 kg 40 mg po BID	8.93		268.03
<60 kg 30 mg po BID	-9.26		-277.83/mo
e) tenofovir 300 mg QD	17.83		534.9/mo
f) zidovudine (AZT): 200 mg po TID or 300 mg po BID	12.08		362.28/mo
Non-nucleoside Reverse Transcriptase Inhibitors (NNRTIs):			
a) efavirenz 600 mg daily	14.77		443.08/mo
b) rilpivirine 25 mg daily	13.80		413.91/mo
c) etravirine 200 mg po BID	21.80		654.00/mo
d) nevirapine 200 mg po BID or 400 mg QD NB: for first 14 days of therapy, start with 200 mg once daily	2.47		74.08/mo
e) delavirdine 400 mg po TID	8.61		258.41/mo
Protease Inhibitors (boosted):			
a) atazanavir 300mg/100 mg ritonavir QD	23.570		707.03/mo
b) darunavir 600 mg/100 mg BID or 800/100 mg QD	22.54 -32.91		676.41 -987.37/mo
c) fosamprenavir 700 mg/100 mg BID or 1400/200 mg QD	19.11		573.20/mo
d) indinavir 800/100 or 200 mg po BID	13.71 -16.64		411.22 -499.25/mo
e) lopinavir/ritonavir 400/100 mg po BID or 800/200 mg QD (for naive patients)	21.80		653.76/mo
f) saquinavir hard gel capsule (Invirase®) 1000 mg/ritonavir 100 mg BID	20.07		602.11/mo
g) tipranavir 500 mg/ritonavir 200 mg po BID	41.51		1245.25/mo
Protease Inhibitors (unboosted):			
a) atazanavir 400 mg QD	22.18		665.28/mo
b) fosamprenavir 1400 mg BID	32.35		970.36/mo
c) indinavir 800 mg po q8h	16.16		484.79/mo
d) nelfinavir 1250 mg BID	18.20		546.00/mo

REGIMEN	COST/ DAY ($)	LENGTH OF THERAPY	TOTAL COST ($)
Integrase Inhibitor:			
a) raltegravir 400 mg BID	27.00		810.00/mo
CCR5 antagonist:			
a) maraviroc 300 mg BID (150 or 600 mg BID if drug interactions)	35.64-71.28		1069.20-2138.40/mo
Fusion Inhibitor:			
a) enfuvirtide 90 mg SC BID	85.86		2575.80/mo

B) PROPHYLACTIC REGIMENS

Post-Exposure Prophylaxis (PEP):

NB: May depend upon source and type of exposure.
See *www.aidsinfo.nih.gov* for guidelines (last updated Sept 30, 2005). Note:

- **Avoid abacavir, didanosine/ stavudine combination, delavirdine, nevirapine in PEP cases**
- **Use of efavirenz should be avoided in women of child-bearing age and restricted to patients where protease inhibitor resistance is suspected from source case.**

a) Basic regimen (2 nucleosides):			
• Truvada® (tenofovir 300 mg/FTC 200 mg QD)	26.63	4 weeks	745.64
• Combivir® (AZT 300 mg/3TC 150 mg) 1 tablet BID	20.88		584.64
• Stavudine 40 mg BID + lamivudine 150 mg BID	19.54		547.12
b) Expanded regimen (2 NRTIs + 1 PI):			
• Truvada® (tenofovir 300 mg/FTC 200 mg) QD + lopinavir/ritonavir 400/100 mg BID	48.43	4 weeks	1356.04
• Truvada® (tenofovir 300 mg/FTC 200 mg) QD + darunavir 800 mg/ritonavir 100 mg QD	49.18		1377.04
• Truvada® (tenofovir 300 mg/FTC 200 mg) QD + atazanavir 300 mg/ritonavir 100 mg QD	50.20		1405.60
• Combivir® (AZT 300 mg/3TC 150 mg) 1 tablet BID + lopinavir/ritonavir 400/100 mg BID	42.68		1195.04
• Combivir® (AZT 300 mg/3TC 150 mg) 1 tablet BID + atazanavir 400 mg QD	43.06		1205.68
c) Other combinations of antiretrovirals may be used in special circumstances, including:			
• Truvada® (tenofovir 300 mg/FTC 200 mg) QD + raltegravir 400 mg BID	53.63		1501.64

REGIMEN	COST/ DAY ($)	LENGTH OF THERAPY	TOTAL COST ($)
Pre-Exposure Prophylaxis (PrEP): To reduce the risk of HIV infection in uninfected individuals who are at high risk of HIV infection and who may engage in sexual activity with HIV-infected partners. See http://aidsinfo.nih.gov for CDC statement (July 16, 2012).			
• Truvada® (tenofovir 300 mg/FTC 200 mg) QD	26.63		$798.90/mo

Vertical Transmission:

Consider combination antiretroviral regimens as appropriate to manage mother's HIV condition (refer to U.S. Public Health Service Task Force guidelines regarding use of antiretrovirals during pregnancy and reduction of perinatal transmission). In general, a multi-class approach incorporating the following components is recommended:

	NRTI	NNRTI	PI
Preferred	Zidovudine + lamivudine	Nevirapine*	Lopinavir/r
Alternative	Tenofovir + emtricitabine or lamivudine		Atazanavir/r Saquinavir/r
Special circumstances		Efavirenzϕ	Indinavir/r Nelfinavir
Insufficient Data		Etravirine Rilpivirine	Darunavir/r Fosamprenavir Tipranavir/r

NB- individual agents classified as Preferred or Alternative may change as new data continue to emerge on pharmacokinetics in pregnancy, safety and toxicity. These classifications reflect current guidelines as of September 14, 2011. Clinicians are urged to regularly check the above resources for updates.

*Avoid nevirapine if CD_4 count is > 250 cells/μL

** Potential for tenofovir to cause fetal bone and renal toxicity is limited- consider other options first.

ϕ Use efavirenz only after first trimester due to fetal neural tube defects- consider other options first.

AZT pre/postnatal regimen (ACTG076):			
i) at 14-34 wks gestation: AZT 500-600 mg po daily	12.08	until labour	362.28/mo
ii) during labour: AZT 2 mg/kg IV over 1 hr, then 1 mg/kg/h IV	16.17/ 200 mg	until delivery	n x 16.17
iii) neonate: 2 mg/kg q6h po syrup (beg. 8-12 hrs after birth)	46.00/ 240 mL	6 weeks	n x 46.00
Intrapartum/neonatal short course regimen (HIVNET 012): a) Nevirapine regimen: • *during labour:* 200 mg po at onset • *neonate*: 2 mg/kg within 72 hours of birth	1.23	Single dose each	2.47/24 hours
b) short course zidovudine regimen: • *during labour:* AZT 600 mg po at onset, then 300 mg q3h	6.03/300 mg dose	until delivery	~48.24/24 hrs
• *neonate*: 4 mg/kg BID po syrup	46.00/ 240 mL	7 days	n x 46.00

REGIMEN	COST/ DAY ($)	LENGTH OF THERAPY	TOTAL COST ($)
Other combinations of antiretrovirals may be used depending on individual circumstances.			
C) OPPORTUNISTIC INFECTIONS			
Bacillary angiomatosis:			
Treatment:			
a) erythromycin 500 mg po q6h	1.44	≥ 3 months; lifelong if relapse	43.20/mo
b) doxycycline 100 mg po BID	1.18		35.40/mo
c) clarithromycin 500 mg po BID	3.24		97.20/mo
d) azithromycin 600 mg po daily	6.00		180.00/mo
Candidiasis, oral/mucosal:			
1. Treatment/Suppression:			
a) clotrimazole 10 mg po troche po 5x/d	8.90	Initial episodes 7-14 day treatment (until symptoms resolve)	62.30-124.60
b) nystatin 5 mL (500 000 U) po S&S qid	1.00		7.00-14.00
c) fluconazole 100 mg po daily	3.24		22.68--45.36
d) itraconazole 200 mg po daily (suspension more effective than capsules)	15.60 (susp)		109.20-218.40
e) posaconazole solution 400 mg bid x 1, then 400 mg daily	94.00		658.00-1316.00
Candidiasis, esophageal:			
1. Treatment:	3.24	14-21 days	45.36
a) fluconazole 100-400 mg po daily	-12.96		-272.16
b) itraconazole 200 mg po daily (suspension preferred)	15.60 (susp)		218.40 -327.60
c) voriconazole 200 mg po BID	102.12		1429.68 -2144.52
d) posaconazole 400 mg po BID	188.00		2632.00 -3948.00
e) caspofungin 50 mg IV daily	222.00		3108.00 -4662.00
f) micafungin 150 mg IV daily	150.00		2100.00 -3150.00

REGIMEN	COST/ DAY ($)	LENGTH OF THERAPY	TOTAL COST ($)
g) amphotericin B deoxycholate 0.6 mg/kg/d IV	69.00 (50 mg vial)		
2. <u>Suppression:</u>			
a) fluconazole 100 mg po daily	3.24	Indefinite	97.20 /mo
b) itraconazole suspension 200 mg po daily	15.60 (susp)		468.00/mo
Cryptococcal Meningitis:			
1. <u>Treatment:</u>			
a) amphotericin B deoxycholate 0.7 mg/kg/d IV + flucytosine 25 mg/kg po q6h x 2/52 (or until clinically improved), then fluconazole 400 mg/d po x 8/52	69.00 163.94 12.96	10 weeks total	3986.92
b) amphotericin B lipid formulation 4-6 mg/kg/d IV+ flucytosine 25 mg/kg po q6h x 2/52, then fluconazole 400 mg/d po x 8/52	1526.56 163.94 12.96		24392.76
c) amphotericin B (deoxycholate or lipid formulation) + fluconazole 400 mg/d (PO or IV) x 2/52, then fluconazole 400 mg/d po x 8/52	69.00 12.96		1873.20
d) amphotericin B (deoxycholate or lipid formulation) x 2/52, then fluconazole 400 mg/d po x 8/52	69.00 12.96		1691.76
e) fluconazole 400-800 mg/d (PO or IV) plus flucytosine 25 mg/kg po q 6h x 4-6 weeks, then fluconazole 400 mg/d po x 8/52	12.96 -25.92 163.94 12.96		5678.96 -8699.88
2. <u>Suppression:</u>			
a) fluconazole 200 mg po daily	6.48	Continue until CD4 ≥200 cells/μL x ≥6 months + completed initial therapy + asymptomatic	194.40/mo
b) itraconazole 200 mg po daily	8.58 (cap)		257.40/mo

REGIMEN	COST/ DAY ($)	LENGTH OF THERAPY	TOTAL COST ($)
***Cryptosporidial Diarrhea*:**			
*** Effective ART (to ↑ CD4 > 100 cells/μL) is associated with resolution of cryptosporidiosis. Along with antiretroviral therapy, symptomatic treatment of diarrhea and rehydration/replacement of electrolyte loss is preferred therapy.**			
a) nitazoxanide 500 - 1000 mg po BID	49.90 -99.80		698.60-1397.20/mo
Cytomegalovirus Infection (CMV):			
1. Induction:			
a) ganciclovir ocular implant (replace every 6-8 months) plus valganciclovir 900 mg po BID	91.40 (oral valgancic lovir)	Treat until disease is stable	1279.60 -1919.40
b) valganciclovir 900 mg po BID	91.40	(14-21 days)	1279.60 -1919.40
c) ganciclovir 5 mg/kg IV BID	42.04 (500 mg vial)		
d) foscarnet 60 mg/kg IV TID or 90 mg/kg IV BID	406.56		5691.84 -8537.76
e) cidofovir 5 mg/kg IV once weekly + probenecid 2 g po pre dose, and 1 g po at 2 hours and 8 hours post dose (4 g total)	988.03 1.51		2968.62
2. Maintenance:			
a) valganciclovir 900 mg po daily	45.70	Continue until CD4 >100 cells/μL for ≥3-6 months + no evidence of active disease	1371.00/mo
b) ganciclovir 5 mg/kg IV daily 5-7 times weekly	42.04 (500 mg vial)		
c) foscarnet 120 mg/kg IV daily	264.26		7927.92/mo
d) cidofovir 5 mg/kg IV every 2 weeks + probenecid 2 g po pre dose, and 1 g po at 2 hours and 8 hours post dose (4 g total)	988.03 1.51		1979.08/mo
Herpes Simplex Infection:			
1. Orolabial Lesions and initial or recurrent genital lesions:			
a) valacyclovir 1 g po BID	6.10	Orolabial: 5-10 days	30.50 -85.40
b) famciclovir 500 mg po BID	3.38	Genital: 5-14 days	16.90 -47.32

REGIMEN	COST/ DAY ($)	LENGTH OF THERAPY	TOTAL COST ($)
c) acyclovir 400 mg po TID	3.81		19.05 -53.34
2. Severe mucocutaneous HSV infections: a) initial therapy acyclovir 5 mg/kg IV q 8 h (after lesions begin to regress, change to PO as above and continue until lesions completed healed)	11.16	until clinical response	55.80 -156.24
b) foscarnet 80-120 mg/kg/day IV in 2 -3 divided doses (acyclovir resistant)	180.20		901.00 -2522.80
3. HSV Encephalitis: a) acyclovir 10 mg/kg IV q8h	11.16	21 days	234.36
4. Suppression (patients with frequent or severe genital herpes): a) valacyclovir 500 mg po BID	2.56	indefinite	76.80/mo
b) famciclovir 500 mg po BID	3.38		101.40/mo
c) acyclovir 400 mg po BID	2.54		76.20/mo
Herpes Zoster Infection:			
a) valacyclovir 1 g po TID	9.15	7-10 days	64.05 -91.50
b) famciclovir 500 mg po TID	5.07		35.49 -50.70
c) acyclovir 800 mg po 5x daily	8.90		62.30 -89.00
Histoplasmosis:			
1. Treatment: a) liposomal amphotericin B 3 mg/kg/d IV x 2 weeks then itraconazole 200 mg po TID x 3/7 then 200 mg po BID	1090.40 17.16	Continue until: ≥ 1 year itraconazole therapy + negative blood cultures	15265.60 (lipo ampho), 514.80/mo (itra)
b) amphotericin B deoxycholate 0.7 mg/kg IV daily for 2 weeks then itraconazole 200 mg po TID x 3/7, then 200 mg po BID	69.00 17.16	+ CD4 count > 150 cells/μL for ≥ 6 months	966.00 (ampho), 514.80/mo (itra)

REGIMEN	COST/ DAY ($)	LENGTH OF THERAPY	TOTAL COST ($)
c) amphotericin B lipid complex 5 mg/kg IV daily for 2 weeks then itraconazole 200 mg po TID x 3/7, then 200 mg po BID	937.13 17.16	+ serum *Histoplasma* Ag < 2 units	13119.75 (ampho lipid), 514.80/mo (itra)
d) itraconazole 200 mg po TID x 3/7, then bid (less severe)	17.16 -25.74		514.80/mo
2. <u>Long term suppression (patients with severe disease or CNS infection and in patients who relapse):</u>			
a) itraconazole 200 mg po daily	8.58 (cap)	Indefinite	257.40/mo
***Microsporidiosis**:**			
*** Effective ART (↑ CD4 > 100 cells/μL) is associated with resolution of symptoms**			
a) albendazole 400 mg po BID	7.36	indefinite (continue until CD4 > 200 cells/μL x ≥6 months)	220.80/mo
b) fumagillin 20 mg po TID (for *Enterocytozoon bienuesi*)	N/A		N/A
Mycobacterium avium complex (MAC):			
1. <u>Treatment</u> (combination of the following, e.g., macrolide + ethambutol +/- rifabutin):			
a) clarithromycin 500 mg po BID	3.24	Treat until complete ≥ 12 months of therapy + CD4 > 100 cells/μL for ≥ 6 months + no symptoms	97.20/mo
b) azithromycin 500-600 mg po daily	3.78		113.40/mo
c) ethambutol 15 mg/kg/d	0.81		24.40/mo
d) rifabutin 300 mg po daily (adjust based on drug interactions)	8.38		251.40/mo
e) ciprofloxacin 500-750 mg po BID	2.10 -3.84		63.00 -115.20/mo
f) levofloxacin 500 mg po daily	2.11		63.30/mo
g) amikacin 10-15 mg/kg/d IV	55.00		1650.00/mo
h) moxifloxacin 400 mg po daily	5.94		178.20

REGIMEN	COST/ DAY ($)	LENGTH OF THERAPY	TOTAL COST ($)
2. <u>Prophylaxis (primary):</u>			
a) azithromycin 1200 mg po weekly	12.00/wk	Continue until CD4 > 100 cells/μL for ≥ 3 months in response to ART	48.00/mo
b) clarithromycin 500 mg po BID	3.24		97.20/mo
c) rifabutin 300 mg po daily (adjust based on drug interactions)	8.38		251.40/mo
d) azithromycin 600 mg po twice weekly	12.00/wk		48.00/mo
Pneumocystis jiroveci pneumonia (PCP):			
1. <u>Treatment:</u>			
a) TMP/SMX: 15 mg/kg/d (TMP) IV/po in 3-4 divided doses (usual oral dose TMP-SMX DS 2 tablets po TID)	0.72 tabs	21 days	15.12
b) trimethoprim 15 mg/kg/d po (3 div.doses) + dapsone 100 mg po daily	2.60 1.44		84.84
d) primaquine 15 mg po daily + clindamycin 300-450 mg po q6h OR 600 mg IV q8h	0.40 3.10-4.65 (po) 39.96 (IV)		73.50-106.05 (po); 847.56 (IV)
e) pentamidine 4 mg/kg/d IV	51.57		1082.97
f) atovaquone 750 mg po BID	27.54		504.00
If PaO2 < 70 mm Hg or A-a gradient > 35 mm Hg, add corticosteroids: prednisone 40 mg po BID x 5/7, then 40 mg po daily x 5/7, then 20 mg po daily x 11/7 (or x 5/7, then 10 mg po daily x 6/7)	0.052 -0.416		
2. **<u>Prophylaxis:</u>**		Continue until	
a) TMP/SMX i DS po 3-7x/wk, or i SS tablet daily	0.0482 -0.1221	CD4 > 200 cells/μL for	1.45 -3.66/mo
b) dapsone 100 mg po daily	1.44	≥ 3 months in response to ART	11.70/mo
c) aerosolized pentamidine 300 mg q month	51.57		51.57/mo
d) pentamidine IV 3-4 mg/kg/month	51.57		51.57/mo

REGIMEN	COST/ DAY ($)	LENGTH OF THERAPY	TOTAL COST ($)
e) dapsone 50 mg po daily + pyrimethamine 50 mg po weekly + leucovorin 25 mg po weekly	0.72 2.95/wk 27.20/wk		126.60/mo
f) dapsone 200 mg po weekly + pyrimethamine 75 mg po weekly + leucovorin 25 mg po weekly	2.88/wk 3.75/wk 27.20/wk		126.92/mo
g) atovaquone 1500 mg po daily	27.54		720.00/mo
Syphilis:			
1. <u>Early Disease (primary/secondary):</u>			
a) benzathine penicillin G 2.4 MU IM	84.00	1 dose	84.00
b) doxycycline 100 mg po BID	1.18	14 days	16.52
c) ceftriaxone 1 g IM or IV QD	23.80	8-10 days	190.40 -238.00
d) azithromycin 2 g po for 1 dose	15.12	1 dose	15.12
2. <u>Latent Disease (no CNS involvement)</u>			
a) benzathine penicillin G 2.4 MU IM/wk	84.00/wk	3 weeks	252.00
b) doxycycline 100 mg po BID	1.18	28 days	33.04
3. <u>Neurosyphilis:</u>			
a) Aq. penicillin G 3-4 MU IV q4h +/- benzathine penicillin G 2.4 MU IM weekly for 3 doses after completion of IV therapy	32.40- 43.20 84.00/wk	10-14 days	576.80 -856.80
b) procaine penicillin 2.4 MU IM/d, + probenecid 500 mg po QID +/- benzathine penicillin G 2.4 MU IM weekly for 3 doses after completion of above	N/a 0.75 84.00/wk	10-14 days	
c) ceftriaxone 2 g IM or IV/d	29.31	10-14 days	293.10 -410.34
Toxoplasma gondii infection:			
1. <u>Treatment:</u>			
a) pyrimethamine 200 mg x 1, then 50 mg (<60 kg body weight) or 75 mg (≥60 kg) po daily + sulfadiazine 1g (< 60 kg) or 1.5 g (≥60 kg) po q6h + folinic acid 25 mg po daily	4.14 27.84 27.20	6 weeks	2485.56

REGIMEN	COST/ DAY ($)	LENGTH OF THERAPY	TOTAL COST ($)
b) pyrimethamine 200 mg x 1, then 50 mg (<60 kg body weight) or 75 mg (≥60 kg) po daily + clindamycin 600 mg po/IV q6h + folinic acid 25 mg po daily	4.14 6.21 (po)-53.28 (iv) 27.20	6 weeks	1435.56 -3554.04
c) pyrimethamine 200 mg x 1, then 50 mg (<60 kg body weight) or 75 mg (≥60 kg) po daily + folinic acid 25 mg po daily + azithromycin 900-1200 mg po daily	4.14 27.20 12.00	6 weeks	1820.28
d) pyrimethamine 200 mg x 1, then 50 mg (<60 kg body weight) or 75 mg (≥60 kg) po daily + folinic acid 25 mg po daily + atovaquone 1500 mg po BID	4.14 27.20 55.08	6 weeks	3629.64
e) atovaquone 1500 mg po BID and sulfadiazine 1-1.5 g po q 6 h	55.08 27.84	6 weeks	3284.64
f) atovaquone 1500 mg po BID	55.08	6 weeks	2313.36
g) TMP-SMX (5 mg/kg TMP) IV/po BID	0.98	6 weeks	29.30
2. <u>Suppression:</u>			
a) pyrimethamine 25-50 mg po daily + sulfadiazine 2000-4000 mg po daily (in 2-4 divided doses) + folinic acid 10-25 mg po daily	1.38-2.76 9.28-18.56 12.40-27.20	Continue until CD4 >200 cells/μL for > 6 months + no signs and symptoms	691.80 -1455.60/mo
b) pyrimethamine 25-50 mg po daily + clindamycin 600 mg po q8h + folinic acid 10-25 mg po daily (should add additional agent to prevent PCP)	1.38-2.76 6.21 12.40-27.20		599.70 -1085.10/mo
c) atovaquone 750 mg po q6-12h +/- [(pyrimethamine 25 mg po daily + folinic acid 10 mg po daily) or sulfadiazine 2000-4000 mg po daily in 2-4 divided doses]	13.77-27.54 1.38 12.40 9.28-18.56		413.10-1383.00/mo
3. <u>Prophylaxis</u>			
a) TMP/SMX DS i daily	0.1221	Discontinue if CD4 > 200 cells/μL for > 3 months in response to ART	3.66/mo
b) TMP/SMX SS i daily	0.0482		1.45/mo

REGIMEN	COST/ DAY ($)	LENGTH OF THERAPY	TOTAL COST ($)
c) dapsone 50 mg daily	0.72		141.44/mo
+ pyrimethamine 50 mg/week	2.76/wk		
+ folinic acid 25 mg/week	27.20/wk		
d) atovaquone 1500 mg po daily	27.54		826.20/mo
e) atovaquone 1500 mg po daily	27.54		1239.60/mo
+ pyrimethamine 25 mg po daily	1.38		
+ folinic acid 10 mg po daily	12.40		

Tuberculosis:

NB: Please note that currently, the CDC recommends that persons with HIV-TB and CD4 cell counts <100/mm^3 should not be treated with intermittent (i.e., once- or twice-weekly) regimens. These patients should receive daily therapy during the intensive phase, and daily or three doses a week during the continuation phase. In this group of patients, CDC recommends directly observed therapy for both daily and three-doses-a-week regimens. (MMWR 2008;58(RR4).

Antituberculosis Drug Dosages (Adult)

Drug	Daily Dose (max)	Twice Weekly Dose** (max) **(not recommended if CD4<100)**	Three times/week Dose (max)
isoniazid	5 mg/kg (300 mg) po/im	15 mg/kg (900 mg) po/im	15 mg/kg (900 mg) po/im
ethambutol			
40-55 kg body weight	800 mg(14.5-20mg/kg)po	2000 mg (36.4-50 mg/kg)	1200 mg (21.8-30 mg/kg)
56-75 kg body weight	1200 mg (16-21mg/kg) po	2800 mg (37.3-50 mg/kg)	2000 mg (26.7-35.7 mg/kg)
> 75 kg body weight	1600 mg(17.8-21mg/kg) po	4000 mg (44.4-52.6 mg/ kg)	2400 mg (26.7-31.6 mg/kg)
pyrazinamide			
40-55 kg body weight	1000 mg(18.2-25mg/kg)po	2000 mg(36.4-50mg/kg)	1500 mg (27.3-37.5 mg/kg)
56-75 kg body weight	1500 mg(20-26.8mg/kg)po	3000 mg (40-53.6 mg/kg)	2500 mg (33.3-44.6 mg/kg)
> 75 kg body weight	2000 mg(22.2-26.3mg/kg) po	4000 mg (44.4-52.6 mg /kg)	3000 mg (33.3-44.6 mg/kg)
rifabutin plus :			
(w/o PIs or NNRTIs)	5 mg/kg (300 mg) po/iv	5 mg/kg (300 mg) po/iv	5 mg/kg (300 mg) po/iv
with PIs	150 mg po/iv	Not recommended	150 mg po/iv
with efavirenz	450-600 mg	450-600 mg	450-600 mg
rifampin (not recommended with PIs or maraviroc)	10 mg/kg (600 mg) po/iv	10 mg/kg (600 mg) po/iv	10 mg/kg (600 mg) po/iv
streptomycin	15 mg/kg (1 g) im/iv	25-30 mg/kg (1.5 g) im/iv	25-30 mg/kg (1.5 g) im/iv
pyridoxine	50 mg daily	100 mg	

1. Treatment (drug susceptible active TB): (*Caution: check for interactions with PIs/NNRTIs/maraviroc/raltegravir)

REGIMEN	COST/ DAY ($)	LENGTH OF THERAPY	TOTAL COST ($)
Initial phase: isoniazid + rifabutin or rifampin + pyrazinamide + ethambutol + pyridoxine		8 weeks	
Continuation phase: isoniazid + rifabutin or rifampin daily or 3x/w [or 2x/w (if CD4 > 100 cells/μL)] + pyridoxine		*Pulmonary TB* – 6 months (up to 9 months if cavitary lung lesions or culture + after 2 months of therapy) *Extra – pulmonary TB* 6-12 months (depends on site)	
2. Treatment for drug-resistant active TB: (*Caution: check for interactions with PIs/NNRTIs/maraviroc/raltegravir)			
Resistant to isoniazid : d/c isoniazid (and streptomycin, if used) rifabutin or rifampin + pyrazinamide + ethambutol		6 months	
rifabutin or rifampin + ethambutol (preferably with pyrazinamide for first 2 months)		12 months	
Resistant to rifamycins: isoniazid + pyrazinamide + ethambutol + pyridoxine + fluroquinolone followed by: isoniazid + ethambutol + fluroquinolone		8 weeks 10-16 months	
3. Prophylaxis:			
a) isoniazid 300 mg po daily + pyridoxine 50 mg po daily		9 months	
b) isoniazid 900 mg po 2x/wk + pyridoxine 50 mg po daily		9 months	
c) rifabutin (dose based on concomitant ART)		4 months	
d) rifampin 600 mg po daily		4 months	

REGIMEN	COST/ DAY ($)	LENGTH OF THERAPY	TOTAL COST ($)

D) CNS

HIV Associated Neurocognitive Disorders (HAND):

A penetration-effectiveness score of at least 2 is associated with lower CSF viral loads, however it is currently unclear if this corresponds with improved patient outcome.

	2010 CNS Penetration Effectiveness Score (Letendre et al. CROI 2010, #430)			
	4 (much above average)	3 (above average)	2 (average)	1 (below average)
NRTIs	Zidovudine	Abacavir Emtricitabine	Didanosine Lamivudine Stavudine	Tenofovir
NNRTIs	Nevirapine	Delavirdine Efavirenz	Etravirine	
PIs	Indinavir/r	Darunavir/r Fosamprenavir/r Indinavir Lopinavir/r	Atazanavir Atazanavir/r Fosamprenavir	Nelfinavir Ritonavir Saquinavir Saquinavir/r Tipranavir/r
CCR5 Inhibitor		maraviroc		
Fusion Inhibitor, Integrase Inhibitor		raltegravir		enfuvirtide

E) DERMATOLOGIC

Skin Rash:

a) diphenhydramine 25-50 mg po TID-QID	0.90-2.39	as required	26.91-71.76/mo
b) hydroxyzine 25 mg po TID-QID	0.42-0.57		12.825-17.10/mo
c) loratadine 10 mg po daily	0.52		15.51/mo
d) cetirizine 5-10 mg po daily	0.37-0.75		11.21-22.41/mo
e) fexofenadine 60 mg po BID	1.22		36.60/mo

F) ENDOCRINE/METABOLIC

Appetite/Weight gain:

a) megestrol acetate (Megace) 80 mg po TID (up to 800 mg/day)	6.05-20.15	as needed (to desired weight)	181.32-604.38/mo
b) nabilone (Cesamet) 1-2 mg po BID	13.34-26.68		400.22-800.45/mo
c) dronabinol (Marionol) 2.5-10 mg po BID	3.82-15.28		114.60-458.40/mo
d) nandrolone phenpropionate (Durabolin) 100 mg IM q2wks	92.75/dose		185.50mo

REGIMEN	COST/ DAY ($)	LENGTH OF THERAPY	TOTAL COST ($)
e) oxandrolone (Oxandrin) 5-10 mg po BID	33.04 -41.72		991.20 -1251.60/mo
f) recombinant human growth hormone 0.1 mg/kg/day SC (max. 6 mg daily)	342.82	12 weeks	28796.88
Hyperlipidemia:			
a) bezafibrate 400 mg daily	1.77	as needed to control hyperlipidemia	53.21/mo
b) fenofibrate micronized 200 mg daily	1.09		32.67/mo
c) gemfibrozil 600 mg BID	1.51		45.12/mo
d) niacin 1.5-6 g/day (BID – QID) (refractory cases only)	0.20-0.80		6.00 -24.00/mo
e) pravastatin 20-40 mg/ day	1.12-1.35		33.74 -40.62/mo
f) atorvastatin 10-20 mg/day	1.79 -2.24		53.67 -67.08/mo
g) fluvastatin 20-40 mg/day	0.91 -1.28		27.45 -38.54/mo
h) rosuvastatin 10-40 mg/day	1.46 -2.14		43.86 -64.18/mo
i) ezetimibe 10 mg/day	1.73		51.74/mo
j) salmon oil 1000 mg (180 EPA:120 DHA) 2 capsules TID with meals	0.62-1.19		~20-40/mo (price may vary depending on product used)
Osteoporosis:			
a) alendronate 10 mg daily (or 70 mg once weekly)	1.11	Indefinite	33.18/mo
b) etidronate 400 mg po daily x 14 days, then calcium 1000-1500 mg daily for 10 weeks		12 week cycle	19.99/12 week cycle
c) risedronate 5 mg/day (or 35 mg once weekly)	2.00	Indefinite	59.99/mo
d) vitamin D 400-800 IU daily			1.16-2.32/mo
e) calcium 1000-1500 mg/day			3.90-6.00/mo
Testosterone Deficiency:			
a) testosterone cypionate (Depo-Testosterone) 200-400 mg IM q3-4 weeks	5.68 -11.36/ dose		4.64-11.36/mo
b) testesterone enanthate (Delatestryl) 200-400 mg IM q4wks	5.25 -10.50/ dose	to therapeutic effect	5.25 -10.50/mo

REGIMEN	COST/ DAY ($)	LENGTH OF THERAPY	TOTAL COST ($)
c) transdermal testosterone patch (Androderm) 2.5 mg patch; 2 patches every 24 hours	3.87		116.00/mo
d) testosterone topical 1% gel (Androgel) apply 5-10 g qam (2.5 g and 5 g packets)	3.76-7.52		112.80 -225.60/mo

G) GASTROINTESTINAL

Diarrhea - Protease Inhibitor Associated:

a) oat bran 1500 mg BID		as required to suppress symptoms	
b) psyllium 1 tbsp or 2 bars daily	0.33		9.79/mo
c) calcium carbonate 500 mg po BID	0.13		3.90/mo
d) pancrelipase (Cotazym ECS 20) for protease-associated diarrhea 1 capsule TID-QID (with each meal or snack)	2.69 -3.59		80.78 -107.70/mo

Diarrhea - general:

a) loperamide 4 mg po x 1, then 2 mg post loose BM, max. 16 mg/day		as required to suppress symptoms	59.19/mo
b) diphenoxylate 5 mg po TID-QID (max 20 mg/d)	3.75		112.44/mo
c) codeine 15-60 mg po q4-6h	0.28 -1.00		8.27 -29.92/mo

Nausea (opioid-induced):

1. <u>Drugs that act on CTZ:</u>			
a) haloperidol 0.5-5 mg po daily	0.04 -0.15		1.16 -4.46/mo
b) prochlorperazine 5-10 mg po q4-6h	0.44 -0.81		13.30 -24.39/mo
c) chlorpromazine 10-25 mg po q4-6h	0.67 -1.01		20.10 -30.15/mo
2. <u>To control stomach motility:</u>			
a) metoclopramide 10 mg po TID-QID	0.18 -0.23		5.25 -7.00/mo
3. <u>To control vertigo:</u>			
a) dimenhydrinate 50-100 mg po q4-6h (max 300 mg)	0.38		11.24/mo
b) scopolamine transderm patches q3d	15.99/wk		63.96/mo
4. <u>For severe/intractable nausea:</u>			
a) dexamethasone 16-24 mg daily	6.76 -10.14		202.80 -304.20/mo

REGIMEN	COST/ DAY ($)	LENGTH OF THERAPY	TOTAL COST ($)
b) granisetron 1 mg po BID	38.70		1161.00/mo
c) dolasetron 50-200 mg po QD	15.35		460.51
	-61.40		-1842.02/mo
d) ondansetron 8 mg po q8h	34.55		1036.51/mo
H) PERIPHERAL NEUROPATHY			
a) amitriptyline 25-75 mg po qhs (target dose 100 mg daily)	0.10		2.99
	-0.37		-11.10/mo
b) nortriptyline 10 mg po qhs	0.13		3.76
(target dose 100mg daily)	-1.02	prn to control symptoms	-30.57/mo
c) desipramine 25 mg po qhs	0.26		7.63
(target dose 100 mg daily)	-0.82		-24.66/mo
d) lamotrigine 25 mg bid (max 300 mg/day)	0.42		12.60
	-2.51		-75.19/mo
e) carbamazepine 100-200 mg po TID/QID	0.23		6.93
	-0.76		-22.65/mo
f) phenytoin 200-400 mg daily	0.16		4.64
	-0.31		-9.28/mo
g) gabapentin 300-1200 mg po TID (max 3600 mg)	1.84		55.17
	-6.58		-197.24/mo

II. PHARMACOLOGIC PROPERTIES OF ANTIRETROVIRALS

Selected Properties of Maraviroc

Other names	UK-427,857, MVC, Celsentri®, Selzentry® (US)
Manufacturer	ViiV Healthcare ULC
Pharmacology/Mechanism of Action	Maraviroc is a selective, slowly reversible, small molecule antagonist of the interaction between human CCR5 and HIV-1 gp120. Blocking this interaction prevents CCR5-tropic HIV-1 entry into cells. CCR5 antagonists target a discrete step in the viral entry pathway. The mechanism of HIV entry into the host CD4 T cells involves a sequence of molecular interactions between the virion envelope glycoprotein (Env) and host cell surface receptors. Normally, the gp120 Env subunit binds to CD4, and subsequent binding of HIV to the host cell's coreceptors (CCR5 or CXCR4) causes a conformational change leading to membrane fusion into the host cell. Allosteric binding of a CCR5 antagonist results in a receptor conformation that the virus cannot bind to, thus interfering with the fusion process. NB: Use of maraviroc is not recommended in patients with dual/mixed or CXCR4-tropic HIV-1 as efficacy was not demonstrated in a phase 2 study of this patient group.
Activity	The mean EC_{50} value (50% effective concentration) for maraviroc against HIV-1 group M isolates (clades A to J) and group O isolates ranged from 0.1 to 1.25 nM (0.05 to 0.64 ng/mL) in cell culture. Mean potency against a range of CCR5-tropic clinical primary isolates: IC_{90} 2.03 nM (1.04 ng/mL). In 973 treatment-experienced HIV-1-infected subjects in studies A4001027 and A4001028, the C_{min}, baseline viral load, baseline CD4, cell count and overall sensitivity score (OSS) were found to be important predictors of virologic success (defined as viral load < 400 copies/mL at 24 weeks).
Resistance - genotypic	HIV-1 variants with reduced susceptibility to maraviroc have been selected in cell culture. The maraviroc-resistant viruses remained CCR5-tropic with no evidence of a change from a CCR5-tropic virus to a CXCR4-using virus. Amino acid residue substitutions or deletions in the V3-loop region of the HIV-1 envelope glycoprotein (gp160) were found to be associated with maraviroc resistance. The relevance of the specific gp120 mutations observed in maraviroc-resistant isolates selected in cell culture to clinical maraviroc resistance is not known.
Resistance - phenotypic	Maraviroc-resistant viruses are characterized phenotypically by concentration response curves that do not reach 100% inhibition in phenotypic drug assays, rather than increases in EC_{50} values.

<table>
<tr><td>Cross-Resistance</td><td>Maraviroc retains antiviral activity against HIV-1 clinical isolates resistant to NRTIs, NNRTIs, PIs and enfuvirtide in cell culture. Maraviroc-resistant viruses that emerged in cell culture remained susceptible to the fusion inhibitor enfuvirtide and the protease inhibitor saquinavir.</td></tr>
<tr><td>Oral Bioavailability</td><td>The absolute bioavailability of a 100 mg dose is 23% and is predicted to be 33% at 300 mg.</td></tr>
<tr><td>Effect of Food</td><td>Coadministration of a 300mg tablet with a high fat breakfast reduced maraviroc C_{max} and AUC by 33% in healthy volunteers.
Coadministration of a high fat meal with 100 mg and 600 mg maraviroc reduced bioavailability by 43% and 25%, respectively (Chan et al. 2007).

There were no food restrictions in the studies that demonstrated the efficacy and safety of maraviroc. Therefore, maraviroc can be taken with or without food at the recommended dose.</td></tr>
<tr><td>Protein Binding</td><td>Approximately 76% bound to human plasma proteins; maraviroc shows moderate affinity for albumin and alpha-1 acid glycoprotein.</td></tr>
<tr><td>Vd</td><td>194 L</td></tr>
<tr><td>Tmax</td><td>0.5-4 hours following single oral doses of 1-1200 mg administered to uninfected volunteers.</td></tr>
<tr><td>serum T ½</td><td>terminal half life at steady state is 14-18 hours</td></tr>
<tr><td>Drug Concentrations</td><td>The pharmacokinetics of oral maraviroc are not dose proportional over the dose range; estimated that doubling in dose will lead to 2.3-fold increase in mean AUC. In single-dose studies in humans, coefficients of variation of Cmax and AUC were generally between 20-40%.</td></tr>
<tr><td colspan="2">
<table>
<tr><th></th><th>Maraviroc dose</th><th>N</th><th>AUC_{12} (ng.h/mL)</th><th>C_{max} (ng/mL)</th><th>C_{min} (ng/mL)</th></tr>
<tr><td>Healthy volunteers (phase 1)</td><td>300 mg twice daily</td><td>64</td><td>2908</td><td>888</td><td>43.1</td></tr>
<tr><td>Asymptomatic HIV patients (phase 2a)</td><td>300 mg twice daily</td><td>8</td><td>2550</td><td>618</td><td>33.6</td></tr>
<tr><td>Treatment-experienced HIV patients (phase 3)*</td><td>300 mg twice daily</td><td>94</td><td>1513</td><td>266</td><td>37.2</td></tr>
<tr><td></td><td>150 mg twice daily (+ CYP3A inhibitor)</td><td>375</td><td>2463</td><td>332</td><td>101</td></tr>
</table>
* the estimated exposure is lower compared to other studies possibly due to food effect, compliance and concomitant medications.
</td></tr>
<tr><td></td><td>Gender does not affect maraviroc concentrations. In a population pharmacokinetic model, average maraviroc AUC was 26.5% higher in Asian versus non-Asian subjects, a difference that does not require a dosage adjustment (Chan et al. 2007).

In 11 asymptomatic treatment-experienced HIV-positive patients without clinical evidence of STDs who were taking maraviroc for at least 4 weeks, the median maraviroc seminal plasma concentration was 197 ng/mL (15.8–1650 ng/mL), with all samples exceeding the median serum-adjusted EC90 of 0.57 ng/mL by several-fold, and the median maraviroc seminal plasma:blood plasma ratio was 0.89 (0.06–31.4).[Tiraboschi et al. 2010b]</td></tr>
<tr><td>Minimum target trough concentrations (for wildtype virus)</td><td>Suggested target of Caverage ≥75 ng/mL based on exposure-response analysis from the MERIT study.</td></tr>
</table>

CSF (% of serum)	Preclinical data in the rat indicate CSF exposure with concentrations ~10% of free plasma concentrations. In seven HIV-positive, virally suppressed patients receiving maraviroc as part of therapy, maraviroc concentrations were measured in paired CSF and plasma samples. Samples were obtained at median 10.5 h after dosing. Maraviroc was detectable in all samples, with median plasma concentration of 94.9 ng/mL (range 21.4–478.0) and median CSF level of 3.63 ng/mL (range 1.83-12.2). All CSF samples exceeded the median EC90 of 0.57 ng/mL. The median CSF/plasma ratio was 0.03 (range 0.01–0.10), and correlated significantly to time after sampling. CSF maraviroc concentrations did not correlate with plasma concentrations, CSF albumin, the CSF/plasma albumin ratio, or the CSF white blood cells.[Yilmaz et al. 2009] In 12 HIV-positive, treatment-experienced patients receiving maraviroc for at least a month, median MVC concentrations in plasma were 124.75 (7.3–517) ng/mL. All CSF concentrations were within the EC90 range (0.06-10.70) with the exception of one patient who was receiving an incorrect MVC dose with concomitant nevirapine. The median MVC CSF: plasma ratio was 0.022 (0.004–0.17), and when the free MVC plasma concentration was used, 0.094 (2.58–27.44). CSF viral load was <40 copies/mL in all 9 patients with undetectable plasma viral load.[Tiraboschi et al. 2010a] In six HIV-infected patients with neurological symptoms receiving cART including maraviroc, week 4 median plasma Ctrough was 347 (12-2678) ng/mL; CSF maraviroc was detectable in 4 patients with a median Ctrough of 102 (35-173) ng/mL, which is above the protein-adjusted IC90 of 0.57 ng/mL. Plasma and CSF viral loads decreased significantly in all patients.[Melica et al. 2010] 2010 CNS Penetration Effectiveness (CPE) Score: 3 [Letendre S et al. 2010]
Metabolism	Metabolized by CYP3A4; P-glycoprotein substrate. Maraviroc does not inhibit activity of expressed enzymes (CYP1A2, CYP2C9, CYP2C19, or CYP3A4) in vitro up to 100uM. Weak inhibitor of CYP2D6 (IC_{50} 87uM). At supra-therapeutic concentrations, maraviroc is a weak inhibitor of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 and CYP3A4 in human liver microsomes (IC_{50} > 30uM). Maraviroc could inhibit P-glycoprotein in the gut and may thus affect bioavailability of certain drugs; however, systemic effects of P-glycoprotein are unlikely to be clinically significant.
Excretion	In the absence of metabolic inhibitors, renal clearance accounts for approximately 25% of total clearance of maraviroc.

<table>
<tr><td rowspan="3">Dosing – Adult</td><td>• When given with strong CYP3A inhibitors (with or without CYP3A inducers) including:
o PIs (except tipranavir/ritonavir)
o delavirdine
o ketoconazole, itraconazole, clarithromycin
o other strong CYP3A inhibitors (e.g., nefazodone, telithromycin)</td><td>150 mg BID</td></tr>
<tr><td>• With NRTIs, tipranavir/ritonavir, nevirapine, and other drugs that are not strong CYP3A inhibitors or CYP3A inducers</td><td>300 mg BID</td></tr>
<tr><td>• With CYP3A inducers (without a strong CYP3A inhibitor) including:
o efavirenz, etravirine
o rifampin
o carbamazepine, phenobarbital, phenytoin</td><td>600 mg BID</td></tr>
<tr><td>Dosing – Pediatric</td><td colspan="2">In an ongoing open-label, dose finding and safety/efficacy, multi-center study, treatment-experienced HIV-infected children received maraviroc 40-450 mg BID with optimized background therapy (OBT). Participants were dosed initially according to body surface area and OBT based on interactions with maraviroc (adult-recommended doses with/without CYP3A4 inhibitors/inducers). Dose adjustment and PK re-evaluation occurred if average maraviroc concentrations (C_{avg}) at Week 2 were < 100 ng/mL. Of the 22 subjects taking maraviroc with a PI, only one failed to meet the PK target with the initial dose due to poor compliance. Conversely, all five subjects not receiving a potent CYP3A4 inhibitor (two nevirapine-based regimens; two raltegravir-based regimens; one NRTI-regimen) required at least doubling of the initial maraviroc dose.[Vourvahis et al. 2011]</td></tr>
<tr><td>Special instructions for pediatric patients</td><td colspan="2">Data currently not available</td></tr>
<tr><td>Adjust in Liver Dysfunction</td><td colspan="2">The pharmacokinetics of single dose 300 mg maraviroc was studied in 3 groups of HIV-negative subjects: normal hepatic function, mild (Child-Pugh class A) and moderate (Child-Pugh class B) hepatic impairment. Mean maraviroc AUC was ↑ 32% and ↑ 45% in subjects with mild and moderate hepatic impairment compared to subjects with normal hepatic function. Mean apparent oral clearance of maraviroc decreased with increasing hepatic impairment. Maraviroc was well tolerated in all study participants. (Abel et al. 2007).

Caution advised in compromised hepatic function, including in patients with hepatitis B or C coinfection.

Maraviroc concentrations are higher when a dose of 150 mg is administered with a strong CYP3A inhibitor compared to following administration of 300 mg without a CYP3A inhibitor, so patients with moderate hepatic impairment who receive maraviroc 150 mg with a strong CYP3A inhibitor should be monitored closely for maraviroc associated adverse events.</td></tr>
</table>

	Maraviroc has not been studied in subjects with severe hepatic impairment.
Adjust in Renal Failure/Dialysis	In the absence of metabolic inhibitors, renal clearance accounts for approximately 25% of total clearance of maraviroc. However, in the presence of metabolic inhibitors, renal clearance may account for up to 70% of total clearance of maraviroc, hence renal impairment may result in increased maraviroc exposures in this case. Therefore, maraviroc should be used with caution in patients with renal impairment (CLcr < 80ml/min) who are also taking potent CYP3A4 inhibitors. Recommended doses of maraviroc for patients with impaired renal function (CrCl ≤ 80 mL/min) are based on the results of a pharmacokinetic study conducted in healthy subjects with various degrees of renal impairment. The pharmacokinetics of maraviroc in subjects with mild and moderate renal impairment was similar to that in subjects with normal renal function. A limited number of subjects with mild and moderate renal impairment in the Phase 3 clinical trials (n= 131 and n= 12, respectively) received the same dose of maraviroc as that administered to subjects with normal renal function. In these subjects there was no apparent difference in the adverse event profile for maraviroc compared to subjects with normal renal function. **Patients with severe renal impairment (CrCl<30 mL/min) or end-stage renal disease (ESRD) and:** a) **NOT receiving a concomitant potent CYP3A inhibitor or inducer.** If such patients experience any symptoms of postural hypotension while taking maraviroc 300 mg twice daily, the dose should be reduced to 150 mg twice daily. **b) Co-treated WITH potent CYP3A4 inhibitors or inducers.** No studies have been performed in subjects with severe renal impairment (CrCl<30 mL/min) or ESRD co-treated with potent CYP3A4 inhibitors or inducers. Hence, no dose of maraviroc can be recommended, and **maraviroc is contraindicated for these patients.** Canadian Product Monograph dosing guidelines (March 2010): Table 9 provides dose interval adjustment guidelines based on simulations of increasing renal impairment in patients being co-administered potent CYP3A4 inhibitors. The safety and efficacy of these dose interval adjustments have not been clinically evaluated. Therefore, clinical response to treatment and renal function should be closely monitored in these patients.

Table 9: Dose interval adjustments based on simulations of increasing renal impairment in patients being co-administered potent CYP3A4 inhibitors

Recommended CELSENTRI dose interval	Creatinine Clearance (CLcr) (ml/min)		
	50- 80 ml/min	30-50 ml/min	<30 ml/min
If co-administered without potent CYP3A4 inhibitors or coadministered with tipranivir/ritonavir	Every 12 hours	Every 12 hours	Every 12 hours
If co-administered with potent CYP3A4 inhibitors (e.g. PIs including lopinavir/ritonavir, darunavir/ritonavir, atazanavir/ritonavir (except tipranavir/ritonavir, saquinavir/ritonavir), ketoconazole, itraconazole, clarithromycin, telithromycin)	Every 24 hours	Every 24 hours	Every 24 hours
If co-administered with saquinavir/ritonavir	Every 24 hours	Every 48 hours	Every 72 hours

US Product Monograph dosing guidelines (May 2010):

Table 2 Recommended Dosing Regimens Based on Renal Function

Concomitant Medications*	SELZENTRY Dose Based on Renal Function				
	Normal	Mild	Moderate	Severe	End Stage Renal Disease (ESRD)
	CrCl >80 mL/min	CrCl >50 and ≤80 mL/min	CrCl ≥30 and ≤50 mL/min	CrCl <30 mL/min	On Regular Hemodialysis
Potent CYP3A inhibitors (with or without a CYP3A inducer)*	150 mg twice daily	150 mg twice daily	150 mg twice daily	NR	NR
Other concomitant medications*	300 mg twice daily	300 mg twice daily	300 mg twice daily	300 mg twice daily†	300 mg twice daily†
Potent CYP3A inducers (without a potent CYP3A inhibitor)*	600 mg twice daily	600 mg twice daily	600 mg twice daily	NR	NR

NR = not recommended
* See Table 1 for the list of concomitant medications.
† The SELZENTRY dose should be reduced to 150 mg twice daily if there are any symptoms of postural hypotension [see *Warnings and Precautions* (5.2)].

In subjects with ESRD, hemodialysis had minimal effect on maraviroc exposures. Therefore, maraviroc may be dosed without regard to dialysis.(Vourvahis et al. 2010)

Toxicity

The most common adverse reactions (>8% incidence) which occurred at a higher frequency compared to placebo are cough, pyrexia, upper respiratory tract infections, rash, musculoskeletal symptoms, abdominal pain, and dizziness.

Hepatotoxicity has been reported:
• May be preceded by evidence of a systemic allergic reaction (e.g., pruritic rash, eosinophilia or elevated IgE).
• Immediately evaluate patients with signs or symptoms of hepatitis or allergic reaction.
Discontinuation of maraviroc should be considered in any patient with signs or symptoms of hepatitis, or with increased liver transaminases combined with rash or other systemic symptoms.

Maraviroc antagonizes the CCR5 co-receptor located on some immune cells, and therefore could potentially increase the risk of developing infections. Patients should be monitored closely for evidence of infections while receiving maraviroc.

Use with caution in the following patient populations:
- patients with pre-existing liver dysfunction or who are co-infected with viral hepatitis B or C
- patients at increased risk for cardiovascular events
- patients with a history of postural hypotension or on concomitant medication known to lower blood pressure

Pregnancy & Lactation	Pregnancy category B. No apparent reproductive toxicity in rats at exposures significantly above maximal clinical dose. There are no adequate and well-controlled studies in pregnant women; therefore, safety for women of child-bearing age cannot be implied from available data. The pharmacokinetics of a single intrapartum dose of maraviroc was studied in pregnant rhesus macaques. Maraviroc was detected in the plasma of mothers up to 48 hours after dosing but only as long as 3.5 hours in the infants. The median fetal-maternal AUC-time curve ratio was 0.009 (range, 0.000 to 0.015). Maraviroc receptor occupancy data showed evidence of unprotected CCR5 receptors on $CD4^+$ cells in the mothers 24 to 48 hours after dosing. In summary, maraviroc was poorly transferred across the placenta and was quickly cleared from the infants' blood. The low concentrations of fetal maraviroc and short pharmacokinetic profile in infants suggest that a single maternal intrapartum dose of maraviroc would not be effective in reducing the risk of MTCT of HIV [Winters et al. 2010]. Studies in lactating rats indicate that maraviroc is extensively secreted into rat milk. It is not known whether maraviroc is secreted into human milk. **Because of the potential for both HIV transmission and serious adverse reactions in nursing infants, mothers should be instructed not to breast-feed if they are receiving maraviroc.**
Drug Interactions	Maraviroc is a substrate of CYP3A and Pgp and hence its pharmacokinetics are likely to be modulated by inhibitors and inducers of these enzymes/transporters. CYP 3A4/P-glycoprotein inhibitors (ketoconazole, saquinavir, lopinavir/ritonavir, atazanavir, ritonovir) cause significant increases in systemic exposure of maraviroc ranging from 2- to 5-fold mean increases in Cmax and 3- to 10-fold mean increases in AUC. CYP 3A4/P-gp inducers (efavirenz, rifampicin) resulted in significant reduction in maraviroc systemic exposure ranging from 56-70% mean reduction in Cmax and AUC. This effect was similar in the presence and absence of CYP 3A4 inhibitors (lopinavir/r, saquinavir/r). Cotrimoxazole resulted in a decreased renal clearance of maraviroc. Maraviroc does not induce CYP1A2 in vitro. In vitro results indicate that maraviroc could inhibit P-glycoprotein in the gut and may thus affect bioavailability of certain drugs. Maraviroc does not cause inhibition of CYP2D6 in vitro until concentrations > 100μM.
Baseline Assessment	Tropism testing, hepatic function (LFTs), blood pressure.
Routine Labs	LFTs

Dosage Forms	150 mg blue film-coated tablets, **DIN:** 02299844 300 mg blue film-coated tablets, **DIN:** 02299852
Storage	Store tablets at room temperature between 15-30°C.

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Selected Properties of Elvitegravir

Other names	GS-9137, JTK-303, EVG Combination formulation: • Stribild® (elvitegravir/cobicistat/emtricitabine/tenofovir)
Manufacturer	Gilead Sciences
Pharmacology/Mechanism of Action	Elvitegravir inhibits the strand transfer activity of HIV-1 integrase (integrase strand transfer inhibitor; INSTI), an HIV-1 encoded enzyme that is required for viral replication. Inhibition of integrase prevents the integration of HIV-1 DNA into host genomic DNA, blocking the formation of the HIV-1 provirus and propagation of the viral infection. Elvitegravir does not inhibit human topoisomerases I or II. Molecular weight: 447.9
Activity	Preclinical pharmacokinetic studies have demonstrated potent anti-HIV activity in vitro with a serum free IC_{50} of 0.2 nM and an EC_{90} in peripheral blood mononuclear cells of 12 nM. It has shown additive to synergistic activity with all other antiretrovirals. In vitro effects on HIV-1 clinical isolates: mean EC50 of 0.62 nM. Elvitegravir displays antiviral activity in cell culture against HIV-1 clades A, B, C, D, E, F, G, and O (EC50 values ranged from 0.1 to 1.3 nM) and activity against HIV-2 (EC50 value of 0.53 nM). Elvitegravir does not show inhibition of replication of HBV or HCV in cell culture.
Resistance - genotypic	HIV-1 isolates with reduced susceptibility to elvitegravir have been selected in cell culture. Reduced susceptibility to elvitegravir was associated with the primary integrase substitutions T66A/I, E92G/Q, S147G, and Q148R. Additional integrase substitutions observed in cell culture selection included D10E, S17N, H51Y, F121Y, S153F/Y, E157Q, D232N, R263K, and V281M.
Resistance - phenotypic	In treatment-naïve HIV-1 infected subjects: • Failure isolates expressing primary elvitegravir resistance-associated substitutions (N=11) had median decreases in susceptibility to elvitegravir of 44-fold (range: 6- to greater than 198-fold) and 33-fold (range: 4- to greater than 122-fold) compared to wild-type reference HIV-1 and to the respective baseline isolates, respectively. Most subjects (N=10) who developed integrase substitutions associated with elvitegravir resistance also developed the M184I/V RT substitutions, conferring reduced susceptibility to both elvitegravir and emtricitabine.
Cross-Resistance	In preclinical studies, this compound has been found to be fully active against nucleoside-, non-nucleoside- and PI-resistant isolates. Cross-resistance has been observed among INSTIs.

	Elvitegravir-resistant viruses showed varying degrees of cross-resistance in cell culture to raltegravir depending on the type and number of substitutions in HIV-1 integrase. Among the four primary elvitegravir resistance-associated substitutions detected in the STRIBILD-treatment virologic failure isolates, E92Q, Q148R, and N155H individually conferred reduced susceptibility both to elvitegravir (greater than 32-fold) and raltegravir (greater than 5-fold) when introduced into a wild-type virus by site-directed mutagenesis. The T66I substitution conferred greater than 14-fold reduced susceptibility to elvitegravir but less than 3-fold to raltegravir. Among the three primary raltegravir resistance-associated substitutions (Y143H/R, Q148H/K/R, and N155H), all but one (Y143H) conferred significant reductions in susceptibility to elvitegravir (greater than 5-fold).
Effect of Food	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 (~373 kcal, 20% fat) and by 87% and 56% with a high-fat meal (~800 kcal, 50% fat).[German et al. ICAAC 2009] Take fixed dose combination tablet with food.
Protein Binding	Approximately 98.8% protein bound. The mean blood-to-plasma ratio is 0.73.
Tmax	4 hours (when administered as Stribild®)
serum T ½	12.9 hours (when administered as Stribild®). After single dose administration of [14C] elvitegravir coadministered with 100 mg ritonavir, 94.8 % and 6.7 % of the administered dose was excreted in feces and urine, respectively.
Drug Concentrations	After single dose elvitegravir 50 mg/ritonavir 100 mg in 8 healthy male volunteers: elvitegravir Cmax 321 (30.2% CV) ng/mL, AUCinf 5430 ng.hr/mL (35.1% CV). Steady-state administration in healthy subjects: • EVG 150/rtv 100 mg QD: Ctrough 448 ng/mL • EVG 300/rtv 100 mg QD: Ctrough 502 ng/mL When administered as a fixed dose combination (elvitegravir 150 mg, emtricitabine 200 mg, tenofovir 300 mg, cobicistat 150 mg) in HIV-infected subjects, mean elvitegravir AUC 23.0 ± 7.5 ug.h/mL, Ctrough 0.45 ± 0.26 ug/mL, Cmax 1.7 ± 0.4 ug/mL. In a randomized study comparing the relative bioavailability and kinetics of elvitegravir 150/emtricitabine 200/tenofovir 300/cobicistat 150 mg fixed-dose tablet versus elvitegravir 150/ritonavir 100 mg plus tenofovir/emtricitabine in 42 healthy subjects, high EVG Ctrough and clinically equivalent tenofovir and FTC exposures were achieved with the fixed-dose tablet relative to ritonavir-boosted EVG.[German et al. JAIDS 2010] No clinically relevant pharmacokinetic differences have been observed between men and women for cobicistat-boosted

	elvitegravir, emtricitabine and tenofovir DF.
Minimum target trough concentrations (for wildtype virus)	Protein-adjusted, in vitro IC50: 7.17 ng/mL Protein-adjusted, in vitro IC95: 44.9 ng/mL Estimated IQ of elvitegravir 50/rtv 100 mg dose: 18.8 based on IC50.
Metabolism	The majority of elvitegravir metabolism is mediated by CYP3A enzymes. Elvitegravir also undergoes glucuronidation via UGT1A1/3 enzymes. Elvitegravir is a modest 2C9 inducer.
Excretion	95% dose excreted via feces
Dosing – Adult	Stribild®: 1 tablet daily with food. Elvitegravir: 85 mg daily if taken with concomitant atazanavir/ritonavir or lopinavir/ritonavir; 150 mg daily if taken with concomitant darunavir/ritonavir, fosamprenavir/ritonavir, or tipranavir/ritonavir
Dosing – Pediatric	The pharmacokinetics of elvitegravir or cobicistat in pediatric subjects (<18 years of age) have not been established.
Adjust in Liver Dysfunction	The pharmacokinetics of elvitegravir 150 mg/cobicistat 150 mg QD for 10 days were compared in HIV-negative subjects with normal and moderately impaired hepatic function (Child-Pugh Class B). Elvitegravir AUC, Cmax and Ctau were 35% ↑ , 41%% ↑ and 80% ↑ and cobicistat AUC, Cmax were unaffected and Ctau was 108% ↑, respectively, in subjects with hepatic impairment vs. normal hepatic function. These changes are not considered clinically relevant, and dose adjustment is not required in patients with mild to moderate hepatic impairment.[Ramanathan et al. 2012] No dose adjustment of Stribild® is required in patients with mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment. No pharmacokinetic or safety data are available regarding the use of Stribild® in patients with severe hepatic impairment (Child-Pugh Class C). Therefore, Stribild® is not recommended for use in patients with severe hepatic impairment.
Adjust in Renal Failure/Dialysis	Elvitegravir and cobicistat do not require dosage adjustment required for renal impairment. However, since Stribild® is a fixed-dose combination tablet which also contains tenofovir and emtricitabine, Stribild® should not be initiated in patients with estimated creatinine clearance <70 mL/min. Stribild® should be discontinued if estimated creatinine clearance declines below 50 mL/ min during treatment as dose interval adjustment required for emtricitabine and tenofovir disoproxil fumarate (tenofovir DF) cannot be achieved. The pharmacokinetics of elvitegravir 150 mg/cobicistat 150 mg QD for 7 days were compared in HIV-negative subjects with severe renal impairment (eGFR<30 mL/min) vs. those with normal renal function (eGFR ≥90 mL/min). Elvitegravir AUC, Cmax and Ctau were 25% ↓, 33% ↓ and 31% ↓ and cobicistat

	AUC, Cmax and Ctau were 25% ↑, 22% ↑ and 13% ↑, respectively, in subjects with renal impairment vs. normal renal function. Mean eGFR ↓ 11% in the renal impairment group and ↓ 9% in the normal renal function group at day 7 relative to day 1; mean eGFR returned to baseline by day 14; these decreases attributed to transient inhibition of proximal tubular secretion of creatinine by cobicistat.[German et al. 2012]
Toxicity	Most common adverse drug reactions (to Stribild®) are nausea and diarrhea (incidence greater than or equal to 10%, all grades). Effects reported with tenofovir or Stribild® include new onset or worsening renal impairment, and decreases in bone mineral density. Avoid administering Stribild® with concurrent or recent use of nephrotoxic drugs. NB: Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogs, including tenofovir disoproxil fumarate, a component of Stribild®.
Pregnancy & Lactation	Pregnancy category B. Elvitegravir is excreted in human breast milk.
Drug Interactions	Elvitegravir absorption is reduced 45% when administered simultaneously with antacids; separate dosing from antacids or vitamin or mineral supplements containing calcium, zinc or iron by at least 2 hours. Elvitegravir may be administered simultaneously with proton-pump inhibitors and H2-blockers. Stribild® can alter the concentration of drugs metabolized by CYP3A or CYP2D6. Drugs that induce CYP3A can alter the concentrations of one or more components of Stribild®. Elvitegravir (in Stribild®) should not be used in conjunction with protease inhibitors or non-nucleoside reverse transcriptase inhibitors due to potential drug-drug interactions including altered and/or suboptimal pharmacokinetics of cobicistat, elvitegravir, and/or the coadministered antiretroviral products. Stribild® should not be administered concurrently with products containing ritonavir or regimens containing ritonavir due to similar effects of cobicistat and ritonavir on CYP3A. Coadministration of Stribild® is contraindicated with drugs that are highly dependent on CYP3A for clearance and for which elevated plasma concentrations are associated with serious and/or life-threatening events. Elvitegravir (Stribild®) is also contraindicated with strong CYP3A inducers, which may lead to decreased exposure and possible loss of efficacy. See separate “Drug interactions with Integrase Inhibitors” table.

Baseline Assessment	Assess creatinine clearance (CLcr), urine glucose and urine protein before initiating treatment with Stribild®. Test for the presence of chronic hepatitis B virus (HBV) before initiating antiretroviral therapy. Severe acute exacerbations of hepatitis B have been reported in patients who are coinfected with HBV and HIV-1 and have discontinued emtricitabine or tenofovir DF, two of the components of Stribild®.
Routine Labs	Monitor CLcr, urine glucose, and urine protein in all patients. Monitor serum phosphorus in patients at risk for renal impairment. Cobicistat may cause modest increases in serum creatinine and modest declines in estimated creatinine clearance without affecting renal glomerular function. Patients who experience a confirmed increase in serum creatinine of greater than 0.4 mg per dL from baseline should be closely monitored for renal safety. Consider monitoring bone mineral density (BMD) in patients with a history of pathologic fracture or other risk factors of osteoporosis or bone loss.
Dosage Forms	Combination formulation: • Stribild®: elvitegravir 150 mg/cobicistat 150 mg/emtricitabine 200 mg/tenofovir disoproxil fumarate 300 mg • green, capsule-shaped, film-coated, debossed with "GSI" on one side and the number "1" surrounded by a square box (1) on the other side
Storage	Store at 25C (or between 15 and 30C) in original container.

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Selected Properties of Raltegravir

Other names	Isentress®, MK-0518
Manufacturer	Merck Canada Inc.
Pharmacology/Mechanism of Action	Raltegravir is a novel HIV-1 integrase strand transfer inhibitor. The bulk drug is a potassium salt of raltegravir with a molecular weight of 482.52. Raltegravir potently inhibits integrase catalyzed strand transfer, with an IC50 of 10 nM, close to the limit of the sensitivity of the assay. Inhibition of integrase prevents the covalent insertion, or integration, of unintegrated linear HIV-1 DNA into the host cell genome preventing the formation of the HIV-1 provirus. Raltegravir is selective for strand transfer, having much reduced activity on either assembly or 3' end processing when analyzed in staged enzymatic assays.
Activity	• HIV1: EC95: 31 ± 20 nM (in vitro) • HIV 1 - diverse, primary clinical isolates including isolates resistant to reverse transcriptase inhibitors & protease inhibitors: EC95: 6 to 50 nM (in vitro) • HIV 2: EC95 value = 6 nM (in vitro)
Resistance - genotypic	Resistance data are preliminary and limited. Raltegravir has a low genetic barrier (similar to the 1st generation NNRTI class). Resistance is associated with mutations at positions 148 (Q148H/K/R) or 155 (N155H) plus ≥ 1 additional substitution (i.e., L74M/R, E92Q, T97A, E138A/K, G140A/S, V151I, G163R, H183P,Y226D/F/H, S230R and D232N). Both of the integrase variants, Q148K and E138A/G140A/Q148K, engender a substantial loss of susceptibility to raltegravir. Another resistance pathway involves a mutation at position 143 (Y143C/H/R)
Cross-Resistance	There seems to be cross-resistance between raltegravir and elvitegravir. Viruses with integrase inhibitor resistance mutations remain fully sensitive to the effects of non-nucleoside reverse transcriptase inhibitors as well as nucleosides and protease inhibitors.
Oral Bioavailability	The absolute bioavailability of raltegravir has not been established. Based on a formulation comparison study in healthy adult volunteers, the chewable tablet has higher oral bioavailability than the film-coated tablet. The absorption of raltegravir, etravirine, emtricitabine, and tenofovir was not compromised when the drugs were crushed, dissolved in 60 mL warm water, and administered by gastrostomy tube to a 52 year old HIV-positive male with ulcerative esophagitis.[Sandkovsky et al. 2012]

Effect of Food	Film-coated tablets: A single dose pharmacokinetic study in healthy subjects (n = 20) showed that a high fat meal affected the rate but not the extent of absorption of raltegravir. Data from Phase II trials suggest that the effect of food on C12hr is not clinically important [Wenning et al. ICAAC 2007]. Raltegravir was administered without regard to food in Benchmrk-1 and Benchmrk-2 studies. In healthy volunteers who received raltegravir 400 mg BID for 10 days in conjunction with various meal types, a low-fat meal appeared to modestly decrease absorption with little effect on trough concentrations (C12h), a moderate-fat meal had little to no effect, and a high-fat meal appeared to modestly increase absorption, although none of these effects appear clinically meaningful.[Brainard et al. J Clin Pharmacol 2010]. Chewable tablets: Administration of chewable tablet with a high fat meal led to an average 6% decrease in AUC, 62% decrease in Cmax and 188% increase in C12hr compared to administration in the fasted state. Administration of the chewable tablet with a high fat meal does not affect raltegravir pharmacokinetics to a clinically meaningful degree and the chewable tablet can be administered without regard to food. **Raltegravir may be administered twice daily without regard to meals.**
Protein Binding	83% protein bound (over concentration range of 2 to 10 μM)
Tmax	Raltegravir is rapidly absorbed with median T_{max} 3 hours in the fasted state.
serum T ½	Concentrations declined in a biphasic manner with initial phase $t_{½}$ ~1 hr and terminal phase $t_{½}$ ~9 hours.
Drug Concentrations	Raltegravir displays dose proportional pharmacokinetics over the clinically relevant dose range (100 to 800 mg). Adults: In a single dose pharmacokinetic study in healthy subjects (n = 20), AUC $_{0-\infty}$ & Cmax of raltegravir were dose proportional for the dose range 100-1600 mg. Raltegravir C_{12h} increased proportionally from 100-800 mg, and slightly less than proportionally from 100-1600mg [Wenning et al. ICAAC 2007]. Considerable intersubject and intrasubject variability was observed in the kinetics. Subjects who received **400mg BID**: AUC 14.3 uM•hr, C12hr 142 nM. Gender, age, body mass index, race, and HIV status had no clinically meaningful effect on raltegravir pharmacokinetics. Similarly, in a study of 44 treatment-naïve African-American patients administered RAL 400 mg BID plus tenofovir/FTC, mean raltegravir AUC 5159 ng.hr/mL (CV 78%), Cmax 1315 ng/mL (CV 109%), C12h after 2nd dose was 166 ng/mL (CV 94%); these results were comparable to historical controls,

	suggesting no influence of race on raltegravir pharmacokinetics.[Wohl et al. 2010] The pharmacokinetics of single dose raltegravir was studied in subjects with generally **low UGT1A1 activity** (UGT1A1*28/*28 genotype) compared to subjects with normal activity (UGT1A1*1/*1 gentoype). Raltegravir AUC ↑ 41%, Cmax ↑ 40% and Cmin ↑ 91% in individuals with the UGT1A1*28/*28 genotype relative to the UGT1A1*1/*1 genotype. However, these differences are not considered to be clinically important, and the T_{max} and $t_{½}$ values were similar for both genotypes. No dose adjustment of raltegravir is required for individuals with the UGT1A1*28/*28 genotype.[Petry A et al. ICAAC 2008] HIV-infected patients given raltegravir by chewing showed higher drug absorption compared with patients given the drug by swallowing.[Gervasoni et al. IAC 2012] Simultaneous plasma and **cervicovaginal fluid (CVF)** samples were obtained in 7 HIV-negative women taking raltegravir for 7 days. Raltegravir was detectable in CVF 6 hours post-dose, Tmax 12h, CVF t½ 17 hours (vs. plasma t½ 7 hours), with CVF:plasma AUC ratio of 64% on day 1 and 93% on day 7. Raltegravir CVF concentrations were C12h 607 ng/mL, AUC 1677 ng.hr/mL.[Jones A et al. 10th IWCPHT 2009, #O_06]. In 6 HIV-positive women taking raltegravir 400 mg BID for at least 4 weeks, similar raltegravir CVF concentrations were observed.[Patterson et al. IAC 2010] Raltegravir concentrations and HIV-1 RNA levels were measured in simultaneous **semen** and plasma samples from 10 treatment-experienced patients on 24 weeks of raltegravir-based therapy. In all samples, semen RNA was <100 copies/mL and plasma RNA was <50 copies/mL. Median raltegravir concentration was 345 (83-707) ng/mL in semen and 206 (106-986) ng/mL in plasma, yielding a median semen:plasma ratio of 1.42 (0.52-6.66).[Barau et al. AAC 2010]. Plasma and **intracellular raltegravir** concentrations after single dose raltegravir 400 mg were measured for 48 hours in healthy subjects. Intracellular raltegravir concentrations were 24% of plasma concentrations, and intracellular:plasma ratios were stable without significant time-related trends suggesting no intracellular accumulation.[Wang et al. ICAAC 2010] Concentrations of raltegravir in gut-associated lymphoid tissue (GALT) were compared to blood plasma concentrations in healthy male volunteers who received raltegravir 400 mg BID for 7 days. After multiple doses, raltegravir AUCs in the terminal ileum, splenic flexure and rectal tissue were 84-fold, 679-fold and 239-fold higher than blood concentrations, respectively. The raltegravir accumulation ratio was 0.9 for terminal ileum, 8.4 for splenic flexure and 5.5 for rectal tissue. These data suggest

	that RAL may also have a role in PEP/PrEP and treatment of primary HIV infection.[Patterson et al. HIV PK 2012, #O_11] Pediatrics: Preliminary dose finding study suggest HIV infected adolescents (≥ 12 and < 19 yrs) receiving RAL 8mg/kg BID achieve systemic exposure similar to adults receiving 400mg BID. RAL well tolerated in this preliminary study.(Acosta et al. 2008)
Minimum target trough concentrations (for wildtype virus)	IC95 = 15 ng/mL In vitro simulations suggest that antiviral effect is consistent with AUC rather than trough [McSharry J et al. 10th IWCPHT 2009, #O_09]. Based on data from two healthy volunteer studies, C_{2h} or AUC_{0-3h} may be used to reliably predict AUC_{0-12h}, which may be a better PK parameter for raltegravir TDM.[Burger et al. 2010]
CSF (% of serum)	In 18 HIV-positive patients, raltegravir concentrations were measured in matched CSF and plasma samples. Raltegravir was present in all CSF specimens with a median concentration of 13.9 ng/mL (IQR 8.9, 24.6). The median CSF-to-plasma ratio was 7.3% (IQR 2.2%, 17%). CSF concentrations correlated with plasma concentrations (rho = 0.47, p = 0.03) but not with post-dose sampling time. Raltegravir concentrations in CSF exceeded the IC50 of wild-type HIV in all but 1 specimen by a median of 4.1-fold (IQR 2.6, 7.2).[Letendre S et al. ICAAC 2009] In 3 HIV-positive patients who started a raltegravir-based regimen and underwent lumbar punctures for clinical reasons, raltegravir CSF trough concentrations were above or very close to in-vitro 95% inhibitory concentration (IC95) (14.6 ng/ml).[Calcagno et al. 2010] In 27 HIV-positive patients on raltegravir who underwent lumbar punctures for clinical reasons, the median raltegravir CSF:plasma ratio was 0.25 (IQR 0.10-0.42). At the end of the dosing interval, patients on boosted PIs had higher CSF trough concentrations compared to those on other ARVs (difference not significant). Patients with altered BBB function had higher CSF:plasma ratios (0.57 vs. 0.18, p=0.01). In 4 patients on rifampin (3 on RAL 800 mg BID), CSF:plasma ratio was 0.31.[Calcagno et al. 2012] 2010 CNS Penetration Effectiveness (CPE) Score: 3 [Letendre S et al. 2010]
Metabolism	Raltegravir is not an inhibitor of cytochrome P450 enzymes, major UGTs, or P-glycoprotein and does not induce CYP3A. The major mechanism of clearance of raltegravir in humans is UGT1A1-mediated glucuronidation.
Excretion	Feces: 51% (only raltegravir was present, most of which is likely derived from hydrolysis of raltegravir-glucuronide secreted in bile). Urine: 32% (raltegravir + raltegravir glucuronide)

<table>
<tr><td>Dosing – Adult</td><td>400 mg BID with or without food.

Raltegravir film-coated tablets must be swallowed whole. Raltegravir chewable tablets may be chewed or swallowed whole.

Because the formulations are not bioequivalent, do not substitute chewable tablets for the 400 mg film-coated tablet.</td></tr>
<tr><td>Dosing – Pediatric</td><td>12 years of age and older:
• One 400 mg film-coated tablet orally, twice daily

6 to less than 12 years of age:
• If at least 25 kg in weight:
o One 400 mg film-coated tablet orally, twice daily OR
o Chewable tablets: weight based to maximum dose 300 mg, twice daily as specified in Table 1
• If <25 kg in weight:
o Chewable tablets: weight based to maximum dose 300 mg, twice daily as specified in Table 1

2 to less than 6 years of age, at least 10 kg in weight:
• Chewable tablets: weight based to maximum dose 300 mg, twice daily as specified in Table 1

Table 1. Dosing of raltegravir chewable tablets for pediatric patients 2 to <12 years of age:
<table><tr><th>Weight (kg)</th><th>Dose</th><th># of Chewable Tablets</th></tr><tr><td>10 to <14</td><td>75 mg BID</td><td>3 x 25 mg BID</td></tr><tr><td>14 to <20</td><td>100 mg BID</td><td>1 x 100 mg BID</td></tr><tr><td>20 to <28</td><td>150 mg BID</td><td>1.5* x 100 mg BID</td></tr><tr><td>28 to <40</td><td>200 mg BID</td><td>2 x 100 mg BID</td></tr><tr><td>At least 40</td><td>300 mg BID</td><td>3 x 100 mg BID</td></tr></table>* The weight-based dosing recommendation for the chewable tablet is based on approximately 6 mg/kg/dose twice daily.
The 100 mg chewable tablet can be divided into equal halves.

The safety and effectiveness of raltegravir in pediatric patients less than 2 years of age have not been established.</td></tr>
</table>

<table>
<tr><td></td><td>Summary of Raltegravir Dosing in Pediatrics (studies)

<table><tr><th>Age</th><th></th><th>RAL Dose</th><th>Ref</th></tr><tr><td>2-5 yo</td><td></td><td>6 mg/kg BID, max 300 mg BID (OCT)</td><td>Nachman et al. CROI 2011, #715</td></tr><tr><td>6-11 yo</td><td><25 kg</td><td>6 mg/kg BID, max 300 mg BID (OCT)</td><td>Nachman et al. CROI 2010, #161LB</td></tr><tr><td></td><td>≥25 kg</td><td>400 mg BID (AF)</td><td>Nachman et al. CROI 2010, #873</td></tr><tr><td>12-18</td><td></td><td>400 mg BID (AF)</td><td>ICAAC 2008; Wiznia et al. CROI 2009; Frenkel et al. ICAAC 2009.</td></tr></table>
OCT = oral chewable tablet; AF = adult formulation (400 mg tab)</td></tr>
<tr><td>Special instructions for pediatric patients</td><td>Raltegravir film-coated tablets must be swallowed whole. Raltegravir chewable tablets may be chewed or swallowed whole. The 100 mg chewable tablet can be divided into equal halves.

Because the formulations are not bioequivalent, do not substitute chewable tablets for the 400 mg film-coated tablet.

Raltegravir chewable tablets contain phenylalanine, a component of aspartame.
• each 25 mg chewable tablet contains approximately 0.05 mg phenylalanine.
• each 100 mg chewable tablet contains approximately 0.10 mg phenylalanine.
Phenylalanine can be harmful to patients with phenylketonuria.</td></tr>
<tr><td>Adjust in Liver Dysfunction</td><td>Moderate hepatic insufficiency (Child Pugh score 7 to 9) has no clinically meaningful effect on raltegravir pharmacokinetics (14% ↓ AUC, 37% ↓ Cmax and 26% ↑ C12 vs. healthy matched control subjects).(Iwamoto et al. 2009)

No dosage adjustment is necessary for patients with mild to moderate hepatic impairment.

The kinetics of raltegravir and darunavir were studied in five HIV-HCV co-infected patients with moderate to severe hepatic impairment (2 with chronic active hepatitis, 3 with cirrhosis). Plasma Ctrough samples were collected at days 14 and 30 after this new regimen was initiated; 24 matched HIV-1 patients with normal liver function treated with raltegravir and darunavir were used as a control group. Mean raltegravir Ctrough was 637 vs. 221 ng/mL in controls. Patients with cirrhosis had higher mean raltegravir Ctrough than patients with active non-cirrhotic hepatitis (665 vs. 581 ng/mL). No differences in viral/immunologic outcome or safety parameters were found between cirrhotic and non-cirrhotic patients. Use raltegravir with</td></tr>
</table>

	caution in patients with moderate to severe liver impairment because of the risk of additive toxicity.(Tommasi et al. 2010) The kinetics of multi-dose raltegravir 400 mg BID were studied in HIV/HCV coinfected patients with Child-Pugh grade C hepatic cirrhosis on stable cART (LPVr, FPVr or DRVr) with controlled viremia (<50 copies/ml) for at least 6 months. Compared to patients with no histologic liver damage, patients with advanced cirrhosis (Child-Pugh C) showed higher RAL exposure, with mean 72% ↑ AUC and 6.5-fold ↑ C12. No safety issues were identified and RAL was well tolerated by all patients.(Hernandez-Novoa et al. CROI 2012).
Adjust in Renal Failure/Dialysis	Severe renal insufficiency (Clcr<30 mL/min) has no clinically meaningful effect on pharmacokinetics of 400 mg raltegravir (15% ↓ AUC, 32% ↓ Cmax and 28% ↑ C12 vs. healthy matched control subjects). Raltegravir half-life (↑ t1/2α ~24%, ↑ t1/2β ~51%) was slightly prolonged in renal insufficiency, but these changes were not clinically important. No serious adverse events were observed.(Iwamoto et al. 2009) **No dosage adjustment is necessary in patients with renal insufficiency.** Antiretroviral pharmacokinetics were studied in a 49-year old HIV-positive man virologically suppressed on darunavir/ritonavir 600/100 mg twice daily, etravirine 200 mg twice daily and raltegravir 400 mg twice daily while undergoing hemodialysis three times weekly. The morning dose of the antiretrovirals was taken after completion of the 4-hour morning hemodialysis session. After dialysis, darunavir, etravirine, raltegravir and ritonavir concentrations were decreased by 57%, 29%, 82% and 60%, respectively compared to predialysis levels. A supplemental dose of 600 mg darunavir administered prior to the hemodialysis session was successful in restoring darunavir concentrations approximately equal to expected levels, while administration of a supplemental dose of raltegravir 400 mg was not, likely due to wide intra- and inter-patient variability. Dose supplementation of etravirine was not deemed necessary given the relatively low amount removed during hemodialysis. After 1 year of therapy, the patient maintained viral suppression.[Giguere et al. 2009] Pre- and post-dialysis raltegravir concentrations were measured in 2 ESRD HIV-infected patients. The hemodialysis extraction ratio and raltegravir hemodialysis clearance were 5.5% and 9.1 ml/min in patient 1, and 9.5% and 19.1 ml/min in patient 2. These results suggest **minimal raltegravir removal by hemodialysis** with no specific raltegravir dosage adjustments required.[Molto et al. 2010] An HIV-positive patient on continuous venovenous hemodiafiltration (CVVHDF) received raltegravir 400 mg BID, darunavir 600/100 mg BID, zidovudine 300 mg BID and 3TC 50 mg q24h in suspension via gastric port and simultaneous enteral feeding via the duodenal port of a double-lumen

	nasogastroduodenal tube. Pharmacokinetic sampling and analysis indicated that darunavir and raltegravir were removed by CVVHDF with approximately the same clearance as provided by a normally functioning kidney. Absorption of both drugs after suspension and application via the gastric port with continued administration of feed via the duodenal port of the double-lumen tube was good. As such, **dose adjustments are not required for patients receiving darunavir and/or raltegravir while undergoing CVVHDF** and that absorption of darunavir and raltegravir is not significantly affected by postpyloric enteral feeding.[Taegtmeyer et al. 2011]
Toxicity	Single dose PK study in healthy subjects (n = 20), single doses of raltegravir up to 1600 mg were generally well tolerated [Wenning et al. ICAAC 2007]. In the Benchmrk studies, the rate of side effects was similar for the raltegravir and placebo treatment groups. The most common ADRs (>10%) in these studies were: nausea, headache, diarrhea and pyrexia. CK elevations with myopathy and rhabdomyolysis have been reported. The relationship of Raltegravir to these events is not known. No lipid abnormalities have been reported so far with raltegravir. Severe, potentially life-threatening, and fatal skin reactions, including Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported. Hypersensitivity reactions have also been reported, characterized by rash, constitutional findings, and sometimes, organ dysfunction, including hepatic failure. Discontinue raltegravir and other suspect agents immediately if signs or symptoms of severe skin reactions or hypersensitivity reactions develop (including, but not limited to, severe rash or rash accompanied by fever, general malaise, fatigue, muscle or joint aches, blisters, oral lesions, conjunctivitis, facial edema, hepatitis, eosinophilia, angioedema). Clinical status including liver aminotransferases should be monitored and appropriate therapy initiated.
Overdose	• Doses as high as 1600-mg single dose and 800-mg twice-daily multiple doses were studied in healthy volunteers without evidence of toxicity. • Occasional doses of up to 1800 mg per day were taken in the P005/P018 & P019 studies without evidence of toxicity
Pregnancy & Lactation	*Pregnancy* • Third trimester and postpartum raltegravir pharmacokinetics were studied in 10 HIV-positive women receiving raltegravir 400 mg BID. Raltegravir kinetics showed extensive variability (consistent with observations in other populations), but exposure was not consistently altered during the 3rd trimester compared to post-partum and historical data. The cord blood:maternal plasma ration (n=6) was 0.98 (0.09-2.26).[Best et al. ICAAC 2010] Similar results were observed in 3rd trimester and post-partum concentrations in a cohort of 5 HIV-positive women on raltegravir 400 mg BID.[Colbers et al. 12th IWCPHT 2011]

	• Thus, raltegravir appears to readily cross the placenta and standard dosing may be used in pregnancy • High raltegravir concentrations were observed in 3 newborns whose mothers received raltegravir during pregnancy. Raltegravir concentrations in the neonates were disproportionately higher (209-3634 ng/mL at 5.5-13 hours post dose) compared to maternal raltegravir concentrations (22-493 ng/mL at 7-12 hours post dose), indicating effective placental transfer and possibly immature neonatal UGT1A1 mediated glucuronidation.[Rosenvinge M et al. 2010] • Placenta transfer of drug was demonstrated in both rats and rabbits. • Treatment related increases in the incidence of supernumerary ribs were seen in rats (exposures 3 fold the exposure at the recommended human dose) *Lactation* • It is not know if raltegravir is secreted in human milk. • Raltegravir is secreted in the milk of lactating rats. • It is recommended that HIV infected mothers not breast-feed their infants to avoid risking postnatal transmission of HIV
Drug Interactions	*See Drug interaction tables for more details* *Effect of Raltegravir on the Kinetics of Other Agents* • Does NOT inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, or CYP3A *in vitro* • Does NOT induce CYP3A4 *in vitro* *Effect of Other Agents on the Pharmacokinetics of Raltegravir* • Strong inducers of UGT1A1 (ex Rifampin) will reduce plasma concentrations of Raltegravir • Less strong inducers (e.g., efavirenz, nevirapine, rifabutin, St. John's wort) may be used without dose adjustment of Raltegravir. • Strong inhibitors or UGT1A1 (Ex ATV/r) will increase plasma concentrations of Raltegravir. In trials the combination of Raltegravir with ATV/r did not result in toxicity concerns. Therefore may use combination without dose adjustment.
Dosage Forms	400 mg tablets, DIN 02301881 Chewable tablets *(available in US):* ○ 100 mg, pale orange, oval-shaped, orange-banana flavoured ○ 25 mg, pale yellow, round, orange-banana flavoured
Storage	Store at room temperature (20-25°C); excursions permitted to 15-30°C.

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Selected Properties of Cobicistat

Other names	GS-9350 Combination formulation: • Stribild® (elvitegravir/cobicistat/emtricitabine/tenofovir)
Manufacturer	Gilead
Pharmacology/ Mechanism of Action	Potent, mechanism-based inhibitor of the P450 CYP3A family. Molecular weight 776.02.
Activity	Cobicistat has no detectable antiviral activity in cell culture against HIV-1, HBV, or HCV and does not antagonize the antiviral activity of elvitegravir, emtricitabine, or tenofovir.
Effect of Food	When administered as a fixed dose combination tablet (elvitegravir 150 mg, emtricitabine 200 mg, tenofovir 300 mg, cobicistat 150 mg) in healthy volunteers, cobicistat AUC_{inf} and C_{max} each ↑ 3% with a light meal, and ↓ 17% and 24% respectively with a high-fat meal. NB: 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.[German et al. 2010] Take fixed-dose combination tablet with food.
Protein Binding	97-98% Mean blood:plasma ratio is approximately 0.5.
Tmax	3 hours
serum T ½	3.5 hours (when administered as Stribild®)
Drug Concentrations	Following oral administration, systemic exposure is almost exclusively parent drug. When administered as a fixed dose combination (elvitegravir 150 mg, emtricitabine 200 mg, tenofovir 300 mg, cobicistat 150 mg) in HIV-infected subjects, mean cobicistat AUC 8.3 ± 3.8 ug.h/mL, Ctrough 0.05 ± 0.13 ug/mL, Cmax 1.1 ± 0.4 ug/mL. When administered as a single agent 150 mg tablet formulation, mean cobicistat AUC 11788.86 ng.h/mL, Ctau 58.29 ng/mL, Cmax 1557.73 ng/mL.
CSF (% of serum)	In rats, minimal transport of cobicistat across blood:brain and blood:testes barriers was observed.
Metabolism	Extensively metabolized via CYP3A4 and 2D6 (minor).
Excretion	Primarily eliminated in the feces (86%). Renal elimination is a minor pathway (<10% of a dose).
Dosing – Adult	Stribild®: 1 tablet daily with food.
Dosing – Pediatric	The pharmacokinetics of cobicistat in pediatric subjects (<18 years of age) have not been established.
Adjust in Liver Dysfunction	The pharmacokinetics of elvitegravir 150 mg/cobicistat 150 mg QD for 10 days were compared in HIV-negative subjects with normal and moderately impaired hepatic function (Child-Pugh Class B). Elvitegravir AUC, Cmax and Ctau were 35% ↑ , 41%% ↑ and 80% ↑ and cobicistat AUC, Cmax were unaffected and Ctau was 108% ↑, respectively, in subjects with hepatic impairment vs. normal

	hepatic function. These changes are not considered clinically relevant, and dose adjustment is not required in patients with mild to moderate hepatic impairment.[Ramanathan et al. 2012] No dose adjustment of Stribild® is required in patients with mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment. No pharmacokinetic or safety data are available regarding the use of Stribild® in patients with severe hepatic impairment (Child-Pugh Class C). Therefore, Stribild® is not recommended for use in patients with severe hepatic impairment.
Adjust in Renal Failure/Dialysis	Cobicistat does not require dosage adjustment required for renal impairment. However, since Stribild® is a fixed-dose combination tablet which also contains tenofovir and emtricitabine, Stribild® should not be initiated in patients with estimated creatinine clearance <70 mL/min. Stribild® should be discontinued if estimated creatinine clearance declines below 50 mL/ min during treatment as dose interval adjustment required for emtricitabine and tenofovir disoproxil fumarate (tenofovir DF) cannot be achieved. The pharmacokinetics of elvitegravir 150 mg/cobicistat 150 mg QD for 7 days were compared in HIV-negative subjects with severe renal impairment (eGFR<30 mL/min) vs. those with normal renal function (eGFR ≥90 mL/min). Elvitegravir AUC, Cmax and Ctau were 25% ↓, 33% ↓ and 31% ↓ and cobicistat AUC, Cmax and Ctau were 25% ↑, 22% ↑ and 13% ↑, respectively, in subjects with renal impairment vs. normal renal function. Mean eGFR ↓ 11% in the renal impairment group and ↓ 9% in the normal renal function group at day 7 relative to day 1; mean eGFR returned to baseline by day 14; these decreases attributed to transient inhibition of proximal tubular secretion of creatinine by cobicistat.[German et al. 2012] As cobicistat is highly bound to plasma proteins, it is unlikely that it will be significantly removed by hemodialysis or peritoneal dialysis.
Toxicity	Most common adverse drug reactions (to Stribild®) are nausea and diarrhea (incidence greater than or equal to 10%, all grades). Effects reported with tenofovir or Stribild® include new onset or worsening renal impairment, and decreases in bone mineral density. Avoid administering Stribild® with concurrent or recent use of nephrotoxic drugs. NB: Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogs, including tenofovir disoproxil fumarate, a component of Stribild®.
Pregnancy & Lactation	Pregnancy category B. Studies in rats have demonstrated that cobicistat is secreted in milk. It is not known whether cobicistat is excreted in human milk.

Drug Interactions	Cobicistat is an inhibitor of CYP3A and CYP2D6, as well as the transporters p-glycoprotein (P-gp), BCRP, OATP1B1 and OATP1B3. Thus, coadministration of Stribild® with drugs that are primarily metabolized by CYP3A or CYP2D6, or are substrates of P-gp, BCRP, OATP1B1 or OATP1B3 may result in increased plasma concentrations of such drugs. Cobicistat exerts no significant inhibition of 1A2, 2C9 or 2C19. Cobicistat 150 mg exhibits similar CYP3A4 inhibiting effect as ritonavir 100 mg. The inhibitory effects of cobicistat on CYP3A function will persist for approximately 7-10 days following discontinuation.
Baseline Assessment	Assess creatinine clearance (CLcr), urine glucose and urine protein before initiating treatment with Stribild®. Test for the presence of chronic hepatitis B virus (HBV) before initiating antiretroviral therapy. Severe acute exacerbations of hepatitis B have been reported in patients who are coinfected with HBV and HIV-1 and have discontinued emtricitabine or tenofovir DF, two of the components of Stribild®.
Routine Labs	Cobicistat inhibits tubular secretion of creatinine and causes modest increases in serum creatinine and modest declines in estimated creatinine clearance; in healthy volunteers, administration of cobicistat for 7 days was associated with a lower estimated GFR (onset in days, reversibility in days). Cobicistat had no effect on actual GFR [Cohen et al. 2010]. Patients who experience a confirmed increase in serum creatinine of greater than 0.4 mg per dL from baseline should be closely monitored for renal safety.
Dosage Forms	Stribild®: fixed dose combination of elvitegravir 150 mg, emtricitabine 200 mg, tenofovir 300 mg, cobicistat 150 mg green capsule-shaped, film-coated tablet.
Storage	Store at 25C (or between 15 and 30C) in original container.

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Selected Properties of Abacavir

Other names	Ziagen®, ABC, 1592U89 Combination formulations: • Trizivir®: zidovudine + lamivudine + abacavir • Kivexa®: abacavir + 3TC (Epzicom® in USA)
Manufacturer	ViiV Healthcare ULC
Pharmacology/Mechanism of Action	• Carbocyclic nucleoside analog. • Activated intracellularly to triphosphate derivative carbocyclic guanine analog which inhibits HIV reverse transcriptase. • In vitro studies have shown that abacavir exhibits marked synergy with AZT, amprenavir, nevirapine • Additive activity with ddI, ddC, 3TC
Activity	IC50 = 0.26 - 4.0 uM depending on cell type (MT-4 cells, PBMC's or macrophages) and HIV-1 source
Resistance - genotypic	Mutations in the reverse transcriptase gene associated with resistance to reverse transcriptase inhibitors (IAS-USA Fall 2005 Resistance Mutations): • K65R, L74V, Y115F, M184V* Requires multiple mutations in HIV-1 RT to confer modest (10 fold) reductions in abacavir susceptibility [3]. **M184 alone is not associated with reduced response to abacavir; when present with 2 or more TAMS, M184V contributes to reduced susceptibility to abacavir* • *Presence of TAMS confers cross-resistance: M41L, D67N, K70R, L210W, T215Y/F, K219Q/E* • *69 Insertion Complex is associated with resistance to all approved NRTIs when present with ≥1 TAM at codons 41, 210 or 215.* • *Q151M complex (with A62V, V75I, F77L, F116Y) is associated with resistance to all approved NRTIs except for tenofovir.*
Resistance - phenotypic	Phenotypic data on clinical virus isolates associated with various mutations using ViroLogic PhenoSense™ (http://hivdb.stanford.edu/): K65R: 2.6-fold ↑ (intermediate resistance) K65R + M184V: 10-fold ↑ (high resistance) L74V: 2.1-fold ↑ (low resistance) L74V + M184V: 5.7-fold ↑ (high resistance) Y115F + M184V: 9.8-fold ↑ (high resistance) M184V: 3.3-fold ↑ (intermediate resistance) M184V + TAMS: 5-9-fold ↑ (high resistance)

Cross-Resistance	• Minimal (1-4 fold ↑ IC_{50}) cross-resistance with other RTIs: • AZT resistant strain: 2-fold ↑ IC_{50} of abacavir • 3TC resistant strain: 2.2 fold ↑ IC_{50} of abacavir • ddI, ddC resistant strains (2-10 fold ↑ IC_{50}); 2.2 fold↑ IC_{50} of abacavir • many NNRTI resistant strains (>1000 fold ↑ IC_{50}); 1.3-fold↑ IC_{50} of abacavir
Oral Bioavailability	83% (adults)
Effect of Food	Food delays absorption and decreases abacavir Cmax but does not affect overall plasma concentrations (AUC). Therefore abacavir can be taken with or without food.
Protein Binding	50%
Tmax	1.5 hours (tablet), 1 hour (oral solution)
Serum T ½	1 - 1.3 hours
Intracellular T½	3.3 hours
Drug Concentrations	AUC and Cmax increase linearly with dose. At therapeutic dosages (300mg twice daily), the steady state Cmax of abacavir tablets is ~ 3 ug/mL, and the AUC over a dosing interval of 12 hours is approximately 6 ug.h/ml. The Cmax value for the oral solution is slightly higher than the tablet. There is no difference in AUC between tablets and solution. In pediatric patients, the pharmacokinetics of abacavir have been have been studied after either single or repeat dosing. Following multiple-dose administration of ZIAGEN 8 mg/kg twice daily, steady-state $AUC_{(0\text{-}12\ hr)}$ and Cmax were 9.8 ± 4.56 mcg•hr/mL and 3.71 ± 1.36 mcg/mL (mean ± SD), respectively.
CSF (% of serum)	18% (N=4). Mean CSF concentrations 0.5 uM (approx. twice IC_{50} of 0.26 uM). The distribution of abacavir into CSF was assessed by use of a population pharmacokinetics analysis. Plasma and CSF abacavir concentrations in 54 subjects were determined. The abacavir CSF/plasma ratio averaged 36% and increased throughout the dose interval.[Capparelli E et al. 2005] In 10 HIV-infected subjects on ABC/FPV regimens with matched CSF & plasma samples, ABC concentrations were similar in CSF & plasma, with a median CSF:IC50 ratio 0.98 (IQR 0.29-1.59). 50% of abacavir CSF concentrations were >IC50wt (458 ng/mL).[Letendre S et al. 2009] 2010 CNS Penetration Effectiveness (CPE) Score: 3 [Letendre S et al. 2010]
Metabolism	Alcohol dehydrogenase and glucoronidation pathways.
Excretion	3% excreted in urine over 24 hour period after single dose study

<table>
<tr><td>Dosing – Adult</td><td>Ziagen®: 300 mg po BID; 600 mg po once daily; take with or without food
Trizivir®: 1 tablet po BID (abacavir 300 mg + zidovudine 300 mg + 3TC 150mg BID)
Kivexa®: 1 tablet po daily (abacavir 600 mg + 3TC 300 mg QD)</td></tr>
<tr><td>Dosing – Pediatric</td><td>1-3 months: 8 mg/kg BID (investigational)
Pediatrics (three months to 12 years of age): 8 mg/kg BID (maximum 300 mg BID)

For pediatric patients weighing more than 14 kg and who can swallow tablets, the dosing regimen using the scored 300 mg tablet is as follows:
<table>
<tr><th rowspan="2">Weight (kg)</th><th colspan="2">Dosage Regimen Using Scored Tablet</th><th rowspan="2">Total Daily Dose</th></tr>
<tr><th>AM Dose</th><th>PM Dose</th></tr>
<tr><td>14 to 21</td><td>½ tablet (150 mg)</td><td>½ tablet (150 mg)</td><td>300 mg</td></tr>
<tr><td>>21 to <30</td><td>½ tablet (150 mg)</td><td>1 tablet (300 mg)</td><td>450 mg</td></tr>
<tr><td>≥ 30</td><td>1 tablet (300 mg)</td><td>1 tablet (300 mg)</td><td>600 mg</td></tr>
</table></td></tr>
<tr><td>Special instructions for pediatric patients</td><td>20mg/mL oral solution available
- watch for rash and other hypersensitivity symptoms
- company provides hypersensitivity warning card for patient</td></tr>
<tr><td>Adjust in Liver Dysfunction</td><td>In subjects with mild hepatic impairment and confirmed cirrhosis (Child-Pugh score 5-6), there was a mean 1.89-fold ↑ in abacavir AUC, and 1.58 fold ↑ in half-life.
The rates of formation & elimination of abacavir metabolites were ↓ , but overall AUCs were not affected.
In patients (n=9) with moderate cirrhosis (Child-Pugh score 5-6), abacavir AUC ↑ by 89%, t1/2 ↑ by 58% compared to healthy controls [Raffi et al. 2000] May consider using reduced abacavir dose (e.g., 150 mg BID) in patients with moderate hepatic impairment with cirrhosis, although the Ziagen® product monograph states that abacavir is contraindicated in patients with moderate or severe hepatic impairment.</td></tr>
<tr><td>Adjust in Renal Failure/ Dialysis
[a] CrCl (mL/min) for men:
(140 - age) (wt) x 60
(Scr) (50)

*CrCl (mL/min) for women:
as above multiplied by 0.85</td><td>Dosage adjustment is likely not necessary in renal dysfunction. Data from a single-dose pharmacokinetic study of abacavir ESRD patients (n=6) showed abacavir concentrations similar to those observed in normal renal function. The two major metabolites (5' - glucuronide and 5' -carboxylate metabolites) are likely to accumulate but are considered inactive.

No dosing modification of abacavir is recommended in patients with renal dysfunction. However, abacavir should be avoided in patients with end-stage renal disease.

Hemodialysis: abacavir may be administered without regard to dialysis schedule.</td></tr>
</table>

Toxicity	Nausea, vomiting, fever, diarrhea, anorexia, headache, asthenia, and rash*. Headache, nausea, persistent blood and protein in urine (2/15). *NB: 5% incidence **potentially fatal hypersensitivity**. Onset 3-42 days (median 9 days). Sx include nausea, vomiting, malaise, fatigue, diarrhea, abdominal pain, fever, dyspnea +/- morbiliform eruption (rash not always present). Physical findings include lymphadenopathy, ulceration of mucous membranes. Labs: elevated LFTs, CK, creatinine and lymphopenia. Symptoms worsen with each dose if drug is continued. Symptoms resolve 1-2 days after drug D/C; **do NOT rechallenge** (hypotension, hospitalizations,death reported). **Ziagen Support Line: 1-800-868-8898.** Lactic acidosis with severe hepatomegaly with steatosis reported (less likely than with ddI, d4T or ATZ).
Pregnancy & Lactation	There are no adequate and well-controlled studies of abacavir use in pregnant women. To monitor maternal-fetal outcomes of pregnant women exposed to abacavir, an Antiretroviral Pregnancy Registry has been established. Physicians are encouraged to register patients by calling GlaxoSmithKline's Drug Surveillance Department (1-800-387-7374). Abacavir and its metabolites are secreted into the milk of lactating rats. It is expected that these will also be secreted into human milk, although this has not been confirmed. There is no data available on the safety of Abacavir when administered to babies less than three months old.
Drug Interactions	In vitro evidence: alcohol dehydrogenase has a role in the metabolism of abacavir. Abacavir could compete for metabolism with alcohol resulting in increased concentrations of either agent; however, interaction study showed no clinically significant effects of combination. Drugs with high plasma protein binding could compete with abacavir for binding sites resulting in increased free concentrations of either drug in plasma. However, this effect would likely be transient as are most protein plasma binding interactions. See separate drug interaction chart.
Baseline Assessment	CBC/diff, electrolytes, anion gap, serum bicarbonate, LFTs

Routine Labs	CBC/diff, electrolytes, anion gap, serum bicarbonate, LFTs q3-6mos Measure serum lactate if low serum bicarbonate or high anion gap and Sx of lactic acidosis. Prodromal Sx include: nausea, anorexia, abdominal pain, vomiting, weight loss, fatigue. Rapidly progressive Sx: tachycardia, tachypnea, hyperventilation, dyspnea, muscular weakness, jaundice, mental status changes. May also progress to multi-organ failure (hepatic, pancreatitis, encephalopathy, respiratory) and death. **D/C drug**: hypersensitivity reaction, Sx of lactic acidosis, serum lactate > 5 mmol/L, LFTs >5xULN
Dosage Forms	300 mg coated tablets, DIN 02240357. 20 mg/mL oral solution (strawberry-banana flavour), 240 mL bottle, DIN 02240358. Oral solution contains sorbitol which may cause abdominal pain and diarrhea. Sorbitol is metabolised to fructose and is therefore unsuitable for patients who have hereditary fructose intolerance. **Trizivir®:** azidovudine 300 mg/lamivudine 150 mg/abacavir 300 mg tablet, DIN 02244757. **Kivexa®:** abacavir 600 mg/lamivudine 300 mg tablet, DIN 02269341.
Storage	Tablets and oral solution can be stored at room temperature.

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Selected Properties of Didanosine
****buffered tablets discontinued in Canada as of February 2006***

Other names	Videx®, Videx EC®, ddI
Manufacturer	BristolMyersSquibb
Pharmacology/Mechanism of Action	• adenine analogue, intracellular triphosphorylation to active form with preferential activity in resting cells • causes viral DNA chain termination via absence of 3'-hydroxyl group to inhibit HIV reverse transcription • competes with natural nucleoside substrate for binding to active site of reverse transcriptase
Activity	In vitro IC50 ranged from 2.5-10 µM (1 µM = 0.24 µg/mL) in lymphoblastic cell lines and 0.01-0.1 µM in monocyte/macrophage cell cultures.
Resistance - genotypic	Mutations in the reverse transcriptase gene associated with resistance to reverse transcriptase inhibitors (IAS-USA Fall 2005 Resistance Mutations): • K65R, L74V • *Presence of 3 of the following TAMS associated with resistance to didanosine: M41L, D67N, L210W, T215Y/F, K219Q/E (K70R and M184 not associated with decreased virologic response to didanosine)* • *69 Insertion Complex is associated with resistance to all approved NRTIs when present with ≥1 TAM at codons 41, 210 or 215.* • *Q151M complex (with A62V, V75I, F77L, F116Y) is associated with resistance to all approved NRTIs except for tenofovir.*
Resistance - phenotypic	Phenotypic data on clinical virus isolates associated with various mutations using ViroLogic PhenoSense™ (http://hivdb.stanford.edu/): K65R: 1.8-fold ↑ (intermediate resistance) L74V: 1.6-fold ↑ (intermediate resistance) L74V + M184V: 2.5-fold ↑ (intermediate resistance) M184V + TAMS: ↓ didanosine susceptibility
Cross-Resistance	Cross-resistance to other nucleoside analogues possible.
Oral Bioavailability	42%; susceptible to acid hydrolysis; food reduces absorption of buffered tablet by 50% • high gastric pH rapidly achieved after oral dosing with buffered ddI tablets, but duration of elevated gastric pH was approx. 25 minutes (14-60) Absorption of didanosine EC occurs mainly in the small intestine.
Effect of Food	Take on empty stomach. Buffered tablets require basic media for absorption (contains Al/Mg/Ca buffers).

	Delayed release capsules have ↓ Cmax 46% and ↓ AUC 19% when taken with food compared to the fasting state. VIDEX EC should be taken on an empty stomach. In a randomized, open-label label study of 28 days ddI monotherapy in HIV-infected, treatment-naïve subjects (n=21), mean ddI trough plasma levels at day 28 were 0.0234 mg/L for patients taking ddI on an empty stomach and 0.0227 mg/L for those taking it after a fat-rich breakfast, showing no statistically significant difference (P=0.96). There was no difference in the rate of decrease of HIV-1 RNA between the two groups (Hernandez-Novoa et al. 2008).
Protein Binding	<5%
Vd	1.08L/kg
Tmax	0.67 hours (buffered formulation), 2 hours (delayed release capsules)
Serum T ½	1.5h
Intracellular T½	8-24h
CSF (% of serum)	21% 2010 CNS Penetration Effectiveness (CPE) Score: 2 [Letendre S et al. 2010]
Metabolism	unclear % is liver or biliary; partly metabolized via hypoxanthine
Excretion	-30-50% renal excretion; likely active tubular secretion - renal clearance 400ml/min - clearance reduced 4-fold in uremia
Dosing – Adult	> 60kg: 200 mg po q 12h (buffered tabs) or 400 mg once daily (EC caps or buffered tabs) < 60kg: 125 mg po q 12h (buffered tabs) or 250 mg once daily (EC caps or buffered tabs) <u>Videx EC</u>: Take 1.5 hours before or 2 hours after food. <u>Videx Buffered Tablets</u>: Take 30 minutes before or 2 hours after food. For ddI tablets, adults and children should receive 2 tablets/dose to prevent gastric degradation. Tablets should be chewed, manually crushed, or placed in 30mL H2O and stirred until dispersion formed, and drank within 1hr. For further flavoring, the aqueous dispersion can be further diluted with 30mL of clear apple juice; stir and drink immediately. If a one-tablet dose is given, it should be placed in 15mL H20 rather than 30mL, and can be flavored with 15mL clear apple juice. Tablets can also be mixed with chocolate milk and taken within 30 min.
Dosing – Pediatric	**Neonate** (< 90 days) (PACTG 239): 50 mg/m^2/dose po bid

	Pediatric dose (tablets)[1] (>90 days): **120 mg/m^2/dose po q 12h** Range: 90-150 mg/m^2/dose po q 12h (Higher doses if risk of CNS disease, especially in young children with developmental delay.) **Pediatric dose for EC formulation**: The recommended total daily dose to be administered once daily to pediatric patients weighing at least 20 kg who can swallow capsules is based on body weight (kg), consistent with the recommended adult dosing guidelines: Recommended Dosage (Adult and Pediatric Patients) Body Weight — Dose 20 kg to less than 25 kg — 200 mg once daily 25 kg to less than 60 kg — 250 once daily At least 60 kg — 400 mg once daily
Special instructions for pediatric patients	**Note**: Children need minimum of 2 tablets or use oral solution. - chew tablets, crush or add 2 tablets to 30 mL cold water for 10 minutes, then stir, may then add 30 mL clear apple juice - do not give with other fruit juices or acidic drinks, feeds, or milk Children may take ddI with food (one published study) Pediatric powder for oral solution also available. Final admixture concentration 10mg/mL. Shake well. Keep refrigerated x 30 days. Consult product monograph for reconstitution directions. Not suitable for once daily dosing.
Adjust in Liver Dysfunction	Single 400 mg dose, non-randomized, open label study performed in Child Pugh Class B (n=8), Class C (n=4) and healthy matched controls (n=12). Exposure to ddI slightly ↑ in hepatically impaired pts: GMR Cmax: 1.13 (0.70-1.82), GMR AUC 1.19 (0.87 –1.61). CLT/F not dependent on Child Pugh Score. Slight elevation in ddI exposures not considered clinically relevant (Chien et al. 2008). No dose adjustment is needed, because a similar range and distribution of AUC and Cmax values was observed for subjects with hepatic impairment and matched controls.
Adjust in Renal Failure/ Dialysis [a] CrCl (mL/min) for men: (140 - age) (wt) x 60 (Scr) (50) *CrCl (mL/min) for women: as above multiplied by 0.85	Reduce dose in renal impairment based on CrCl[a]: Delayed release capsules (Videx EC): • 30-59mL/min: 200mg QD (125 mg QD if <60 kg) • 10-29 mL/min: 125mg QD (same dose if BW<60 kg) • <10 mL/min: 125 mg QD (avoid if BW<60 kg) Buffered tablets (Videx): • 30-59mL/min: 200mg QD (150 mg QD if <60 kg) • 10-29 mL/min: 150mg QD (100 mg QD if BW<60 kg) • <10 mL/min: 100 mg QD (75 mg QD if BW<60 kg) NB: - the MgOH and AlOH buffers may be an excessive load in renal failure (see Availability/Cost for quantities) - administer dose after hemodialysis; for CAPD dose as for CrCl <10mL/min

Toxicity	diarrhea (common), abdominal pain , nausea, vomiting peripheral neuropathy related to cumulative dose (12-34%) asymptomatic hypertriglyceridemia/hyperamylasemia (10%), pancreatitis (1-7%) (use with caution or avoid use in alcoholics, hx of pancreatitis; avoid with d4T, ddC, hydroxyurea, ribavirin) lactic acidosis and severe hepatomegaly with steatosis, including fatalities. rare: liver failure, non-chirrotic portal hypertension [Maida et al. 2006, Kovari et al. 2009, Vispo et al. 2010], anemia, thrombocytopenia, hyperuricemia, hyperglycemia, , retinal depigmentation in pediatrics
Pregnancy & Lactation	Pregnancy risk category B.~50% placental transfer. No reported teratogenic effects in animals. Use standard adult dose. Cases of fatal lactic acidosis have been reported in pregnancy women on ddI with d4T- avoid combination. Use ddI only as alternate agent.ddI is secreted into breast milk of lactating rats
Drug Interactions	**Potential for additive/synergistic toxicity when coadministered with neurotoxins or pancreatoxins.** In order to avoid absorption interactions, ddI tablets should be administered separately from **ketoconazole, itraconazole, indinavir, delavirdine, quinolones, tetracyclines, and ganciclovir**. See separate Drug Interaction chart.
Baseline Assessment	CBC/diff, electrolytes, anion gap, serum bicarbonate, amylase, triglycerides, LFTs, urate, neurological status
Routine Labs	CBC/diff, electrolytes, anion gap, serum bicarbonate, amylase/lipase, LFTs q3-6mos Measure serum lactate if low serum bicarbonate or high anion gap and Sx of lactic acidosis. Prodromal Sx include: nausea, anorexia, abdominal pain, vomiting, weight loss, fatigue. Rapidly progressive Sx: tachycardia, tachypnea, hyperventilation, dyspnea, muscular weakness, jaundice, mental status changes. May also progress to multi-organ failure (hepatic, pancreatitis, encephalopathy, respiratory) and death. **D/C drug**: Sx of lactic acidosis, serum lactate > 5 mmol/L, amylase >200 (asymptomatic), pancreatitis, LFTs >5xULN, ANC< 0.5, plt <25000, gout, painful neuropathy
Dosage Forms	**Enteric capsules (Videx EC)**: 125MG: DIN#02244596 200MG: DIN#02244597 250MG: DIN#02244598 400MG: DIN#02244599 **Pediatric Oral Powder for Solution**: 4g/240 mL bottle,

	DIN 01940635 (available via Special Access Program; call 514-333-2287) **Generic** delayed release capsule approved in the U.S. (200 mg, 250 mg, and 400 mg capsules, Barr Laboratories). *****buffered tablets discontinued in Canada as of February 2006*** **Tablets:** 25 & 50mg mint-flavored, 100 mg (DIN 01940546) & 150 mg (DIN 01940554) mandarin orange-flavored, chewable, dispersible 25 & 50mg tabs contain 25.3mEq Mg hydroxide and 15.7mEq Al hydroxide; 100 & 150mg tabs contain 8mEq Mg hydroxide
Storage	Store all dosage forms at room temperature. Reconstituted oral powder should be stored in refrigerator x 30 days.

References:

Bristol-Myers Squibb Canada. Videx EC® Product Monograph. Montreal, QC. May 12, 2010.

Chien C, Persson A, Sevinsky H, Dudley J, Lu M, Kaul S et al. Single-Dose pharmacokinetics of enteric-coated didanosine in subjects with hepatic impairment compared to healthy adult subjects [abstract P9]. 9th International Workshop on Clinical Pharmacology of HIV Therapy. New Orleans, USA, April 7-9, 2008.

Hernandez-Novoa et al. Effect of food on the antiviral activity of didanosine enteric-coated capsules: a pilot comparative study. HIV Med 2008;9:187-191.

Kovari H et al. Association of noncirrhotic portal hypertension in HIV-infected persons and antiretroviral therapy with didanosine: a nested case-control study. Clin Infect Dis 2009;49: 626-35.

Letendre S, Ellis RJ, Deutsch R, Clifford DB, Collier AC, Gelman GG, et al. Correlates of time-to-loss-of-viral-response in CSF and plasma in the CHARTER Cohort: CPE score predicts CSF suppression [abstract 430]. 17th Conference on Retroviruses and Opportunistic Infections, San Francisco, CA, February 16-19, 2010.

Maida I et al. Severe liver disease associated with prolonged exposure to antiretroviral drugs. J Acquir Immune Defic Syndr 2006;42:177-182.

Vispo E et al. Noncirrhotic portal hypertension in HIV-infected patients: unique clinical and pathological findings. AIDS, epub 17 March 2010.

Selected Properties of Emtricitabine

Other names	Emtriva®: FTC Combination formulations: **Truvada®:** emtricitabine/tenofovir **Atripla®:** efavirenz/emtricitabine/tenofovir **Complera®:** rilpivirine/emtricitabine/tenofovir **Stribild®:** elvitegravir/cobicistat/emtricitabine/tenofovir
Manufacturer	Gilead Sciences Canada, Inc.
Pharmacology/Mechanism of Action	• Cytosine analogue, intracellular triphosphorylation to active form with preferential activity in resting cell • Predominant mechanism of action is DNA chain termination via absence of 3'-hydroxyl group to inhibit HIV reverse transcription • Competes with natural nucleoside substrate for binding to active site of reverse transcriptase
Activity	IC_{50} = 0.0013 – 0.64 uM (in vitro) Active against HBV, but not adequately studied for this indication.
Resistance - genotypic	Mutations in the reverse transcriptase gene associated with resistance to reverse transcriptase inhibitors (IAS-USA Fall 2005 Resistance Mutations): • K65R, M184V/I • *Presence of TAMS confers cross-resistance: M41L, D67N, K70R, L210W, T215Y/F, K219Q/E* • *69 Insertion Complex is associated with resistance to all approved NRTIs when present with ≥1 TAM at codons 41, 210 or 215.* • *Q151M complex (with A62V, V75I, F77L, F116Y) is associated with resistance to all approved NRTIs except for tenofovir.*
Resistance - phenotypic	Phenotypic data on clinical virus isolates associated with various mutations using ViroLogic PhenoSense™ (http://hivdb.stanford.edu/): K65R: 9.7-fold ↑ (intermediate resistance) M184V: 200-fold ↑ (high resistance) K65R + M184V: 300-fold ↑ (high resistance)
Cross-Resistance	Emtricitabine-resistant isolates (M184V/I) were cross-resistant to lamivudine and zalcitabine but retained sensitivity to abacavir, didanosine, stavudine, tenofovir, zidovudine, and NNRTIs (delavirdine, efavirenz, and nevirapine).
Oral Bioavailability	93% The absorption of raltegravir, etravirine, emtricitabine, and tenofovir was not compromised when the drugs were crushed, dissolved in 60 mL warm water, and administered by gastrostomy tube to a 52 year old HIV-positive male with ulcerative esophagitis.[Sandkovsky et al. 2012]

Effect of Food	No effect on AUC; 29% decrease in Cmax with approximately 1000 kcal high-fat meal.
Protein Binding	< 4% plasma proteins
Tmax	1-2 hours
Serum T ½	10 hours
Intracellular T½	> 20 hours
Drug Concentrations	With steady-state dosing in adults, mean (± SD) plasma concentrations were: Cmax 1.8 ± 0.7 µg/mL AUC 10.0 ± 3.1 hr*µg/mL Ctrough 0.09 µg/mL The multiple dose pharmacokinetics of emtricitabine are dose proportional over a dose range of 25 to 200 mg. At peak plasma concentration, the mean plasma to blood drug concentration ratio was ~ 1.0 and the mean semen to plasma drug concentration ratio was ~ 4.0. In children receiving a daily dose of 6 mg/kg up to a maximum of 240 mg oral solution or a 200 mg capsule, emtricitabine exposure was similar to exposures achieved in adults receiving a once-daily dose of 200 mg. In neonates <3 months of age, a daily dose of 3 mg/kg produces plasma levels similar to those achieved in pediatric patients (3 months-17 years) receiving 6 mg/kg/day [Blum et al. 2006].
CSF (% of serum)	2010 CNS Penetration Effectiveness (CPE) Score: 3 [Letendre S et al. 2010]
Metabolism	Not a substrate of CYP450 enzymes.
Excretion	86% urine (13% as metabolites); 14% feces; undergoes glomerular filtration and active tubular secretion
Dosing – Adult	Emtriva® (emtricitabine 200 mg): one tablet with or without food. Truvada® (tenofovir 300 mg/emtricitabine 200 mg): one tablet once daily with or without food. Complera® (emtricitabine 200 mg/rilpivirine 25 mg/tenofovir 300 mg): one tablet daily with a meal.
Dosing – Pediatric	**Neonatal/Infant:** • **Oral Solution:** 3 mg/kg administered once daily orally. **Pediatric Patients (3 months through 17 years):** • **Oral Solution:** 6 mg/kg up to a maximum of 240 mg (24 mL) administered once daily orally. • **Capsules:** for children weighing more than 33 kg who can swallow an intact capsule, one 200 mg capsule administered once daily orally.
Adjust in Liver Dysfunction	No dosage adjustment is required.

<table>
<tr><td>Adjust in Renal Failure/ Dialysis
[a] CrCl (mL/min) for men:
(140 - age) (wt) x 60
(Scr) (50)

*CrCl (mL/min) for women:
as above multiplied by 0.85</td><td>In adult patients with creatinine clearance <50 mL/min or with end-stage renal disease (ESRD) requiring dialysis, Cmax and AUC of emtricitabine were increased. Reduce dose based on CrCl [a]:
<table><tr><th rowspan="2">Formulation</th><th colspan="4">Creatinine Clearance (mL/min)</th></tr><tr><th>≥50 mL/min</th><th>30–49 mL/min</th><th>15–29 mL/min</th><th><15 mL/min or on hemodialysis*</th></tr><tr><td>Capsule (200 mg)</td><td>200 mg every 24 hours</td><td>200 mg every 48 hours</td><td>200 mg every 72 hours</td><td>200 mg every 96 hours</td></tr><tr><td>Oral Solution (10 mg/mL)</td><td>240 mg every 24 hours (24 mL)</td><td>120 mg every 24 hours (12 mL)</td><td>80 mg every 24 hours (8 mL)</td><td>60 mg every 24 hours (6 mL)</td></tr></table>* Hemodialysis Patients: If dosing on day of dialysis, give dose after dialysis.
Hemodialysis: 200 mg q 96 h, post-dialysis; 30% removed in 3-hour hemodialysis session</td></tr>
<tr><td>Toxicity</td><td>Usually very well tolerated. Headache, diarrhea, nausea, rash, skin discoloration (pigmentation of palms/soles mainly in non-Caucasian).
Lactic acidosis, mitochondrial toxicity reported.
Severe acute exacerbations of HBV have been reported in patients who have discontinued emtricitabine. Monitor hepatic function closely for several months upon discontinuation.</td></tr>
<tr><td>Pregnancy & Lactation</td><td>Pregnancy risk category B. No studies in human pregnancy. Unknown if it is secreted into breast milk.</td></tr>
<tr><td>Drug Interactions</td><td>Potential for antagonism with 3TC or ddC, which are other cytidine analogues. Avoid coadministration.

See separate Drug Interaction chart.</td></tr>
<tr><td>Baseline Assessment</td><td>CBC/diff, electrolytes, anion gap, serum bicarbonate, LFTs</td></tr>
<tr><td>Routine Labs</td><td>CBC/diff, electrolytes, anion gap, serum bicarbonate, LFTs q3-6mos
Measure serum lactate if low serum bicarbonate or high anion gap and Sx of lactic acidosis. Prodromal Sx include: nausea, anorexia, abdominal pain, vomiting, weight loss, fatigue. Rapidly progressive Sx: tachycardia, tachypnea, hyperventilation, dyspnea, muscular weakness, jaundice, mental status changes. May also progress to multi-organ failure (hepatic, pancreatitis, encephalopathy, respiratory) and death.
D/C drug: Sx of lactic acidosis, serum lactate > 5 mmol/L, LFTs >5xULN</td></tr>
<tr><td>Dosage Forms</td><td>Emtriva®:
• 200 mg hard gelatin blue and white capsule, DIN 02272091
• 10 mg/mL oral solution (clear orange/dark orange), 170 mL bottle

Combination formulations:
• Truvada®: tenofovir 300 mg/emtricitabine 200 mg, DIN 02274906
• Atripla®: efavirenz 600 mg/emtricitabine 200 mg/tenofovir</td></tr>
</table>

	300 mg tablet, DIN 02300699 • Complera®: Emtricitabine 200 mg/rilpivirine 25 mg/tenofovir DF 300 mg tablet, DIN 02374129 • Stribild®: Elvitegravir 150 mg/cobicistat 150 mg/ emtricitabine 200 mg/ tenofovir DF 300 mg tablet
Storage	Store capsules at room temperature. Refrigerate oral solution at 2–8 °C (36–46 °F). Emtriva Oral Solution should be used within 3 months if stored by the patient at 25 °C (77 °F); excursions permitted to 15–30 °C (59–86 °F).

References:

Gilead Sciences Canada, Inc. Emtriva® Product monograph. Mississauga, Canada. March 13th, 2012.

Blum et al. Steady-state pharmacokinetic evaluation of emtricitabine in neonates exposed to HIV in utero [abstract 568]. Presented at the 13th Conference on Retroviruses and Opportunistic Infections, February 5-8, 2006, Denver, CO.

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Sandkovsky U, Swindells S, Moore R, Acosta EP, Fletcher CV. Acceptable plasma concentrations of raltegravir and etravirine when administered by gastrostomy tube in a patient with advanced multidrug-resistant human immunodeficiency virus infection. Pharmacotherapy 2012: 32(2):142–147.

Selected Properties of Lamivudine

Other names	3TC®, **3-thiacytidine; Epivir®**: 3TC (USA) Combination formulations: • **Combivir**®: 3TC + zidovudine • **Apo-Lamivudine-Zidovudine®**: 150/300 mg tablet • **Trizivir®:** zidovudine + 3TC + abacavir • **Kivexa®**: abacavir + 3TC (Epzicom® in the USA)
Manufacturer	ViiV Healthcare ULC
Pharmacology/Mechanism of Action	• Cytidine analogue, intracellular triphosphorylation to active form with preferential activity in resting cell • Predominant mechanism of action is DNA chain termination via absence of 3'-hydroxyl group to inhibit HIV reverse transcription • Competes with natural nucleoside substrate for binding to active site of reverse transcriptase
Activity	In vitro IC_{50} = 2 nM - 15 uM Active vs HBV
Resistance - genotypic	Mutations in the reverse transcriptase gene associated with resistance to reverse transcriptase inhibitors (IAS-USA Fall 2005 Resistance Mutations): • K65R, M184V/I • *Presence of TAMS confers cross-resistance: M41L, D67N, K70R, L210W, T215Y/F, K219Q/E* • *69 Insertion Complex is associated with resistance to all approved NRTIs when present with ≥1 TAM at codons 41, 210 or 215.* • *Q151M complex (with A62V, V75I, F77L, F116Y) is associated with resistance to all approved NRTIs except for tenofovir.*
Resistance - phenotypic	Phenotypic data on clinical virus isolates associated with various mutations using ViroLogic PhenoSense™ (http://hivdb.stanford.edu/): K65R: 9.7-fold ↑ (intermediate resistance) M184V: 200-fold ↑ (high resistance) K65R + M184V: 300-fold ↑ (high resistance)
Cross-Resistance	The clinical relevance of genotypic and phenotypic changes associated with lamivudine therapy has not been fully established. In some patients harbouring zidovudine-resistant virus, phenotypic sensitivity to zidovudine was restored after treatment with lamivudine.
Oral Bioavailability	86%; food (1,099 kcal; 75 grams fat, 34 grams protein, 72 grams carbohydrate) delays rate but not extent of absorption.
Effect of Food	Can take with or without food.
Protein Binding	<36%
Vd	1.3L/kg

Tmax	1-1.5h
Serum T ½	2-6h
Intracellular T½	10-15h
Drug Concentrations	After single 300 mg oral dose (adults): Cmax 2.6 ug/mL AUC 11 ug.hr/mL 300 mg QD vs. 150 mg BID dosing yields: similar plasma and intracellular AUCs, lower Ctrough in both plasma (53% ↓) and intracellular Pharmacokinetics in children (Burger et al. 2006): • Kinetic study in 40 children ages 1.7-18 years (median 7.3 yrs) taking 3TC 4 mg/kg BID revealed significantly ↑Cl/kg and Vd/kg in children 6 years and younger vs. those 7 years and up • Children under 7 years had 36% ↓ AUC and 40% ↓ Cmax of 3TC compared to older children; dosing on BSA may provide less variability in 3TC exposure
CSF (% of serum)	10% 2010 CNS Penetration Effectiveness (CPE) Score: 2 [Letendre S et al. 2010]
Metabolism	trans-sulfoxide is only known metabolite
Excretion	• 70% excreted unchanged; renal tubular secretion • renal clearance 280ml/min
Dosing – Adult	≥ 50 kg: 150 mg po bid or 300 mg po once daily <50kg: 2mg/kg po bid **Combination tablets** **Combivir®:** 300 mg zidovudine/150 mg lamivudine po BID **Trizivir®:** zidovudine 300 mg/lamivudine150 mg/abacavir 300 mg po BID Kivexa®: abacavir 600 mg/lamivudine 300 mg po QD
Dosing – Pediatric	**Neonate** (< 30 days): 2 mg/kg/dose po bid **Children (**3mo-12yrs): 4mg/kg po bid, max 150mg bid 10mg/mL oral solution available.
Special instructions for pediatric patients	If 3TC upsets the stomach, take with food. May cut tablet in half (not scored) or crush.
Adjust in Liver Dysfunction	No adjustment required.

Adjust in Renal Failure/ Dialysis [a] CrCl (mL/min) for men: (140 - age) (wt) x 60 (Scr) (50) *CrCl (mL/min) for women: as above multiplied by 0.85	- reduce dose based on CrCl[a]: >50ml/min: 300 mg QD or 150mg BID 30-49mL/min: 150mg QD 15-29mL/min: 150mg loading dose, then 100mg QD 5-14 mL/min: 150 mg loading dose, then 50 mg QD <5 mL/min: 50mg loading dose, then 25mg QD In one series of HIV-subjects with end-stage renal disease (n=9), 150 mg 3TC daily was well tolerated, despite AUCs elevated by 5-fold compared to subjects with normal renal function. Therefore, a dosage of 25 mg daily may be sufficient for this population. Administer lamivudine after completion of dialysis sessions.
Toxicity	Usually very well tolerated; headache, diarrhea, nausea, , nasal symptoms , fatigue dizziness, neutropenia , ↑ LFTs rare: rash, pancreatitis in pediatrics, ↑ amylase, sweating, taste disturbances, anemia, neuropathy; lactic acidosis, mitochondrial toxicity reported, however 3TC has a low potential for this vs. ddI, d4T, ddC, AZT. Severe acute exacerbations of HBV have been reported in patients who have discontinued lamivudine. Monitor hepatic function closely for several months upon discontinuation.
Pregnancy & Lactation	Pregnancy risk category C. ~100% placental transfer in humans. Use normal adult doses in pregnancy. Due to extensive experience and lack of evidence for teratogenicity, 3TC + AZT are recommended as the dual NRTI backbone of a regimen. Secreted in human breast milk at similar concentrations to those found in serum.
Drug Interactions	**trimethoprim** increases 3TC AUC 40% (adjust 3TC if renal dysfunction, monitor for 3TC toxicity) **3TC** and ddC compete for intracellular phosphorylation in vitro, both cytidine analogues, thus avoid combination. Similarly, avoid coadministration with emtricitabine. See separate Drug Interaction chart.
Baseline Assessment	CBC/diff, electrolytes, anion gap, serum bicarbonate, amylase, LFTs
Routine Labs	CBC/diff, electrolytes, anion gap, serum bicarbonate, amylase/lipase, LFTs q3-6mos Measure serum lactate if low serum bicarbonate or high anion gap and Sx of lactic acidosis. Prodromal Sx include: nausea, anorexia, abdominal pain, vomiting, weight loss, fatigue. Rapidly progressive Sx: tachycardia, tachypnea, hyperventilation, dyspnea, muscular weakness, jaundice, mental status changes. May also progress to multi-organ failure (hepatic, pancreatitis, encephalopathy, respiratory) and death. **D/C drug**: Sx of lactic acidosis, serum lactate > 5 mmol/L, amylase >200 (asymptomatic), pancreatitis, LFTs >5xULN, ANC< 0.5, painful neuropathy

Dosage Forms	**Tablet:** 3TC® 150mg (white, diamond-shaped); DIN 02192683 3TC® 300mg (gray-blue, diamond-shaped); DIN 02247825 Apo-Lamivudine® 150 mg tablet: 02369052 Apo-Lamivudine® 300 mg tablet: 02369060 **Oral Solution:** 10mg/mL (240mL); DIN 02192691; strawberry-banana flavor **Combination tablets:** **Combivir®:** 300 mg zidovudine/150 mg lamivudine; DIN 02239213 **Apo-Lamivudine-Zidovudine®**: 150/300 mg tablet, DIN 02375540 **Trizivir®:** zidovudine 300 mg/lamivudine150 mg/abacavir 300 mg tablet; DIN 02244757. **Kivexa®:** abacavir 600 mg + 3TC 300 mg tablet; DIN 02269341.
Storage	Store tabs and solution at room temperature.

References:

Burger D et al. Age-dependent pharmacokinetics of lamivudine in HIV-infected children [abstract 20]. Presented at the 7th International Workshop on Clinical Pharmacology of HIV Therapy, Lisbon, April 20-22nd, 2006.

ViiV Healthcare ULC. 3TC® Product monograph. Mississauga, Ont. August 10, 2010.

Izzedine H, Launay-Vacher V, Deray G. Dosage of lamivudine in a haemodialysis patient. Nephron. 2000 Dec;86(4):553.

Letendre S, Ellis RJ, Deutsch R, Clifford DB, Collier AC, Gelman GG, et al. Correlates of time-to-loss-of-viral-response in CSF and plasma in the CHARTER Cohort: CPE score predicts CSF suppression [abstract 430]. 17th Conference on Retroviruses and Opportunistic Infections, San Francisco, CA, February 16-19, 2010.

Selected Properties of Stavudine

Other names	d4T, Zerit®, Zerit XR® (in US only)
Manufacturer	Bristol-Myers Squibb Canada
Pharmacology/Mechanism of Action	• thymidine analogue, intracellular triphosphorylation to active form with preferential activity in active cell • competes with natural nucleoside substrate for binding to active site of reverse transcriptase • causes viral DNA chain termination via absence of 3'-hydroxyl group to inhibit HIV reverse transcription inhibits cellular DNA polymerase beta and gamma and reduces the synthesis of mitochondrial DNA
Activity	The concentration of drug necessary to inhibit HIV-1 replication by 50% (IC50) ranged from 0.009 to 4 μM against laboratory and clinical isolates of HIV-1.
Resistance - genotypic	Mutations in the reverse transcriptase gene associated with resistance to reverse transcriptase inhibitors (IAS-USA Fall 2005 Resistance Mutations): • M41L, *E44D*,* K65R, D67N, K70R, *V118I*,* L210W, T215Y/F, K219Q/E **increased level of resistance to stavudine & zidovudine in the setting of TAMS* • *Presence of TAMS confers cross-resistance: M41L, D67N, K70R, L210W, T215Y/F, K219Q/E* • *69 Insertion Complex is associated with resistance to all approved NRTIs when present with ≥1 TAM at codons 41, 210 or 215.* • *Q151M complex (with A62V, V75I, F77L, F116Y) is associated with resistance to all approved NRTIs except for tenofovir.*
Resistance - phenotypic	Phenotypic data on clinical virus isolates associated with various mutations using ViroLogic PhenoSense™ (http://hivdb.stanford.edu/): M41L/T215Y: 1.6-fold ↑ (intermediate resistance) M41L/210W/T215Y: 2.6-fold ↑ (intermediate resistance) D67N +K70R +K219Q: 1.5-fold ↑ (intermediate resistance) K70R: 1.1 fold ↑ (low resistance) M184V + TAMS: ↑ susceptibility to stavudine T215Y: 1.5 fold ↑ (intermediate resistance)
Cross-Resistance	Potential cross-resistance to ddI, ddC, (?AZT)
Oral Bioavailability	86.4 ± 18.2 (adults), 76.9 ± 31.7% (pediatrics)
Effect of Food	Can take with or without food. Food delays rate but not extent of absorption.
Protein Binding	negligible
Vd	46 ± 21 L
Tmax	0.5-0.7h

<table>
<tr><td>Serum T ½</td><td>1-2.5h</td></tr>
<tr><td>Intracellular T½</td><td>3.5h</td></tr>
<tr><td>Drug Concentrations</td><td>With 40 mg BID dosing (n=8 adults):
AUC 2568 ± 454 ng.h/mL
Cmax 536 ± 146 ng/mL
Cmin 8 ± 9 ng/mL</td></tr>
<tr><td>CSF (% of serum)</td><td>59 +/-35% (in pediatric patients)
2010 CNS Penetration Effectiveness (CPE) Score: 2
[Letendre S et al. 2010]</td></tr>
<tr><td>Metabolism</td><td>not metabolized</td></tr>
<tr><td>Excretion</td><td>Renal clearance is approximately 40% of total clearance. Renal clearance includes active tubular secretion as well as glomerular filtration; remaining 60% of drug eliminated by endogenous pathways.

Clearance decreases with renal impairment.</td></tr>
<tr><td>Dosing – Adult</td><td>Regular capsules:
≥60kg: 40mg po bid
<60kg: 30mg po bid

Zerit XR®:
≥60kg: 100 mg po once daily
<60kg: 75 mg po once daily</td></tr>
<tr><td>Dosing – Pediatric</td><td>Birth to 13 days old: 0.5 mg/kg/dose q12h
Pediatric (at least 14 days old): 1mg/kg/dose q12h (up to weight of 30 kg).
Pediatric patients weighing 30 kg or greater should receive the recommended adult dosage.</td></tr>
<tr><td>Special instructions for pediatric patients</td><td>If d4T upsets the stomach, take with food. May open capsule & give in small portion of food or 5-10 mL cool tap water.
1 mg/mL fruit-flavoured suspension available via SAP (613-941-2108). Shake well, refrigerate, 30 day expiry.</td></tr>
<tr><td>Adjust in Liver Dysfunction</td><td>No adjustment in hepatic impairment; single-dose stavudine kinetics not different in patients with cirrhosis (Child-Pugh classification B or C).</td></tr>
<tr><td>Adjust in Renal Failure/ Dialysis
[a] CrCl (mL/min) for men:
(140 - age) (wt) x 60
(Scr) (50)

*CrCl (mL/min) for women:
as above multiplied by 0.85</td><td>Stavudine terminal half life increases as creatinine clearance decreases. Reduce dose based on CrCl[a] and body weight (BW):

Regular capsules:
<table>
<tr><th rowspan="2">Creatinine Clearance (mL/min)</th><th colspan="2">Recommended ZERIT Dose by Patient Weight</th></tr>
<tr><th>≥ 60 kg</th><th>< 60 kg</th></tr>
<tr><td>> 50 *</td><td>40 mg every 12 hours*</td><td>30 mg every 12 hours *</td></tr>
<tr><td>26 - 50</td><td>20 mg every 12 hours</td><td>15 mg every 12 hours</td></tr>
<tr><td><25 †</td><td>20 mg every 24 hours</td><td>15 mg every 24 hours</td></tr>
</table>
* Normal dose, no adjustment necessary.</td></tr>
</table>

<table>
<tr><td></td><td>Extended release capsules (Zerit XR®):
<table>
<tr><th rowspan="2">Creatinine Clearance (mL/min)</th><th colspan="2">Recommended ZERIT XR Dose by Patient Weight</th></tr>
<tr><th>≥60 kg</th><th><60 kg</th></tr>
<tr><td>>50</td><td>100 mg once daily</td><td>75 mg once daily</td></tr>
<tr><td>26–50</td><td>50 mg once daily</td><td>37.5 mg once daily</td></tr>
<tr><td>10–25</td><td>50 mg every 48 hours</td><td>37.5 mg every 48 hours</td></tr>
<tr><td>Hemodialysis patients*</td><td>50 mg every 48 hours</td><td>37.5 mg every 48 hours</td></tr>
</table>
<u>Hemodialysis:</u>
The mean ± SD hemodialysis clearance value of stavudine was 120 ± 18 mL/min (n=12); the mean ± SD percentage of the stavudine dose recovered in the dialysate, was 31 ± 5%.

Regular capsules: Reduce stavudine dose to 20 mg every 24 hours (≥60 kg) or 15 mg every 24 hours (<60 kg), administered after the completion of hemodialysis and at the same time of day on non-dialysis days.
Extended-release capsules (Zerit XR®): 50 mg every 48 hours (≥60 kg) or 37.5 mg every 48 hours (<60 kg), administered after the completion of hemodialysis and at the same time of day on nondialysis days.
</td></tr>
<tr><td>Toxicity</td><td>

diarrhea, abdominal pain, nausea, vomiting, headache, rash, increased LFTs
peripheral neuropathy related to cumulative dose (52%)
hypertriglyceridemia (mainly, but may also increase LDL and total cholesterol)
pancreatitis when used with ddI (use with caution or avoid use in alcoholics, hx of pancreatitis; avoid with ddI, ddC, and other pancreatoxins)
Mitochondrial toxicity: lactic acidosis ± severe hepatomegaly with steatosis ± pancreatitis, including fatalities. May also have rapidly progressing ascending neuromuscular weakness that may mimic Guillain-Barré Syndrome; some patients develop ventilator-dependent respiratory failure. D/C all AVRs; partial or complete recovery may take months.
Lipoatrophy- peripheral fat loss (thinning face, arms, legs and buttocks)
</td></tr>
</table>

Pregnancy & Lactation	Pregnancy risk category C. ~76% placental transfer. No evidence of teratogenicity, Use standard adult dose. Cases of fatal lactic acidosis have been reported in pregnancy women on ddI with d4T- avoid combination. Use d4T only as alternate agent. Avoid use with zidovudine due to potential antagonism. - d4T is secreted into breast milk of lactating rats.
Drug Interactions	**Potential for additive/synergistic toxicity when coadministered with neurotoxins or pancreatoxins.** **AZT** intracellular phosphorylation inhibited in vitro by D4T (both thymidine analogues) thus avoid combination See separate Drug Interaction chart.
Baseline Assessment	CBC/diff, electrolytes, anion gap, serum bicarbonate, amylase, cholesterol profile, LFTs, neurological status
Routine Labs	CBC/diff, electrolytes, anion gap, serum bicarbonate, amylase/lipase, LFTs q3-6mos. Cholesterol profile at 3-6 months, then annually. Monitor for evidence of lipoatrophy. Measure serum lactate if low serum bicarbonate or high anion gap and Sx of lactic acidosis. Prodromal Sx include: nausea, anorexia, abdominal pain, vomiting, weight loss, fatigue. Rapidly progressive Sx: tachycardia, tachypnea, hyperventilation, dyspnea, muscular weakness, jaundice, mental status changes. May also progress to multi-organ failure (hepatic, pancreatitis, encephalopathy, respiratory) and death. **D/C drug**: Sx of lactic acidosis, serum lactate > 5 mmol/L, amylase >200 (asymptomatic), pancreatitis, LFTs >5xULN, ANC< 0.5, painful neuropathy
Dosage Forms	**Capsules:** 15 mg, DIN 02216086 20 mg, DIN 02216094 30 mg, DIN 02216108 40 mg (beige), DIN 02216116 **Zerit XR® sustained release capsules:** 37.5 mg, DIN 02247912 50 mg, DIN 02247913 75 mg, DIN 02247914 100 mg, DIN 02247915 **Oral solution**: 1 mg/mL fruit-flavoured solution (200 mL bottle); stable for 30 days in fridge. Shake well.
Storage	Refrigerate oral suspension; capsules stable at room temperature.

References:
Bristol-Myers Squibb Canada. Zerit® Product monograph. Montreal, QC. August 5th, 2010.

Letendre S, Ellis RJ, Deutsch R, Clifford DB, Collier AC, Gelman GG, et al. Correlates of time-to-loss-of-viral-response in CSF and plasma in the CHARTER Cohort: CPE score predicts CSF suppression [abstract 430]. 17th Conference on Retroviruses and Opportunistic Infections, San Francisco, CA, February 16-19, 2010.

Selected Properties of Zalcitabine

***product discontinued in Canada as of February 28, 2006**

Other names	Hivid®, dideoxycytidine, ddC 
Manufacturer	Hoffmann La-Roche
Pharmacology/Mechanism of Action	• cytidine analogue, intracellular triphosphorylation to active form with preferential activity in resting cell • causes viral DNA chain termination via absence of 3'-hydroxyl group to inhibit HIV reverse transcription • competes with natural nucleoside substrate for binding to active site of reverse transcriptase
Activity	In laboratory and clinical isolates, the IC50 and IC95 values were in the range of 30-500 nM and 100-1000 nM, respectively (1 nM=0.21 ng/mL).
Resistance - genotypic	Mutations in the reverse transcriptase gene associated with resistance to reverse transcriptase inhibitors (IAS-USA 2004 Resistance Mutations): K65R, T69D, L74V, M184V *Presence of NAMS confers cross-resistance:* *M41L, E44D, D67N, K70R, V118I, L210W, T215Y/F, K219Q/E*
Resistance - phenotypic	Phenotypic data on clinical virus isolates associated with various mutations using ViroLogic PhenoSense™ (http://hivdb.stanford.edu/): K65R: intermediate levels of resistance to zalcitabine L74V: 2- to 5-fold ↓ susceptibility to zalcitabine M184V + TAMS: ↓ susceptibility to zalcitabine
Cross-Resistance	Point mutations at positions 65, 74, 75, and 184 are associated with resistance to didanosine, 75 with resistance to stavudine, and L65A and M184V with resistance to lamivudine.
Oral Bioavailability	>80% (CV 30%).70-87%; food reduces peak concentration 39% and reduces bioavailability 14%
Effect of Food	Best on empty stomach, but can take with food.
Protein Binding	<4%
Vd	0.5L/kg
Tmax	0.8 hours
Serum T ½	0.3-1.2h
Intracellular T½	2.6-10h
Drug Concentrations	After 1.5 mg oral dose (fasting), Cmax 25.2 ng/mL, AUC 72 ng.h/mL.
CSF (% of serum)	9-37% following IV (average 15-20%) 2010 CNS Penetration Effectiveness (CPE) Score: 1 [Letendre S et al. 2010]
Metabolism	unclear
Excretion	-62-75% excreted unchanged - renal clearance 190ml/min

Dosing – Adult	0.75mg TID
Dosing – Pediatric	Neonatal/Infant: unknown Pediatric: 0.01 mg/kg/dose po q8h Pediatric syrup only available as clinical investigational drug.
Special instructions for pediatric patients	If ddC upsets the stomach, take with food
Adjust in Liver Dysfunction	-may exacerbate pre-existing liver dysfunction; monitor for toxicity - may consider using 0.75 mg q8h in moderate-severe hepatic dysfunction
Adjust in Renal Failure/ Dialysis [a] CrCl (mL/min) for men: (140 - age) (wt) x 60 (Scr) (50) *CrCl (mL/min) for women: as above multiplied by 0.85	In patients with impaired renal function (Clcf <55 mL/min), zalcitabine half-life prolonged up to 8.5 hours. - reduce dose in renal impairment based on CrCl[a]: 10-40mL/min - 0.75mg q12h <10mL/min - 0.75mg q24h Dialysis: -insufficient data to recommend dose adjustment during dialysis (dose as per Clcr<10 mL/min); administer zalcitabine after completion of dialysis sessions
Toxicity	peripheral neuropathy related to cumulative dose (17-35%), oral ulcers (13%), h/a (8%), myalgias (5%), anemia (5%), leukopenia (9%), thrombocytopenia (4%), ↑ AST >250 (5%), rash (8%); lactic acidosis, mitochondrial toxicity reported rare: dysphagia, abdominal pain, pancreatitis, hepatomegaly
Pregnancy & Lactation	Pregnancy risk category C. 30-50% placental transfer in monkeys. Shown to be teratogenic in mice at exposure levels 1365 and 2730X max human AUC; in rats was teratogenic at exposure level 2142X human AUC, but not at 485X human AUC. No human studies. Due to terotogenicty in animals and lack of data, ddC is **not recommended** in pregnancy. -unknown whether ddC excreted into breast milk
Drug Interactions	**Potential for additive/synergistic toxicity when coadministered with neurotoxins or pancreatoxins.** **3TC** and ddC compete for intracellular phosphorylation in vitro, both cytidine analogues, thus avoid combination. Potential for similar antagonistic interaction with emtricitabine; avoid coadministration. See separate Drug Interaction chart.
Baseline Assessment	CBC/diff, electrolytes, anion gap, serum bicarbonate, amylase, LFTs, neurological status

Routine Labs	CBC/diff, electrolytes, anion gap, serum bicarbonate, amylase/lipase, LFTs q3-6mos Measure serum lactate if low serum bicarbonate or high anion gap and Sx of lactic acidosis. Prodromal Sx include: nausea, anorexia, abdominal pain, vomiting, weight loss, fatigue. Rapidly progressive Sx: tachycardia, tachypnea, hyperventilation, dyspnea, muscular weakness, jaundice, mental status changes. May also progress to multi-organ failure (hepatic, pancreatitis, encephalopathy, respiratory) and death. **D/C drug**: Sx of lactic acidosis, serum lactate > 5 mmol/L, amylase >200 (asymptomatic), pancreatitis, LFTs >5xULN, ANC< 0.5, plt <25000, painful neuropathy, oral ulceration
Dosage Forms	**Tablets:** 0.75mg grey, film-coated tablet, DIN 01990896; 0.375 mg tablet not available in Canada **Pediatric Syrup:** 0.1mg/mL (30mL)- available only as a clinical investigational drug. ***product discontinued in Canada as of February 28, 2006*
Storage	Store tablets at room temperature. Store syrup at room temperature in original glass bottle.

References:

Hoffmann-La Roche Limited. Hivid Product monograph. Mississauga, Ont.: 2004.

Letendre S, Ellis RJ, Deutsch R, Clifford DB, Collier AC, Gelman GG, et al. Correlates of time-to-loss-of-viral-response in CSF and plasma in the CHARTER Cohort: CPE score predicts CSF suppression [abstract 430]. 17th Conference on Retroviruses and Opportunistic Infections, San Francisco, CA, February 16-19, 2010.

Selected Properties of Zidovudine

Other names	Retrovir®, AZT, ZDV Generic: Apo-Zidovudine (Apotex), Novo-AZT (Novopharm) Combination formulations: • **Combivir**®: lamivudine + zidovudine • **Generic**: Apo-Lamivudine-Zidovudine • **Trizivir®:** zidovudine + lamivudine + abacavir
Manufacturer	ViiV Healthcare ULC
Pharmacology/Mechanism of Action	• Thymidine analogue, intracellular triphosphorylation to active form with preferential activity in active cells • Causes viral DNA chain termination via absence of 3'-hydroxyl group (replaced by azido group) to inhibit HIV reverse transcription • Competes with natural nucleoside substrate for binding to active site of reverse transcriptase • Inhibits cellular DNA polymerase b and g to a minor extent
Activity	In vitro activity in laboratory and clinical isolates of HIV: IC50 and IC90 values of 0.003 to 0.013 and 0.03 to 0.13 mcg/mL, respectively (1 nM = 0.27 ng/mL). The IC50 and IC90 values of HIV isolates recovered from 18 untreated AIDS/ARC patients were in the range of 0.003 to 0.013 mcg/mL and 0.03 to 0.3 mcg/mL, respectively
Resistance - genotypic	Mutations in the reverse transcriptase gene associated with resistance to reverse transcriptase inhibitors (IAS-USA Fall 2005 Resistance Mutations): • M41L, *E44D**, D67N, K70R, *V118I**, L210W, T215Y/F, K219Q/E **increased level of resistance to stavudine & zidovudine in the setting of TAMS* • *Presence of TAMS confers cross-resistance: M41L, D67N, K70R, L210W, T215Y/F, K219Q/E* • *69 Insertion Complex is associated with resistance to all approved NRTIs when present with ≥1 TAM at codons 41, 210 or 215.* • *Q151M complex (with A62V, V75I, F77L, F116Y) is associated with resistance to all approved NRTIs except for tenofovir.*
Resistance - phenotypic	Phenotypic data on clinical virus isolates associated with various mutations using ViroLogic PhenoSense™ (http://hivdb.stanford.edu/): *M41L/T215Y: 19-fold ↑ (high resistance)* *M41L/210W/T215Y: 64-fold ↑ (high resistance)* *D67N +K70R +K219Q: 10-fold ↑ (high resistance)* *K70R: 4 fold ↑ (low resistance)* *M184V + TAMS: ↑ susceptibility to zidovudine* *T215Y: 10-fold ↑ (high resistance)*

Cross-Resistance	Potential for cross-resistance to other NRTIs depending upon what mutations develop.
Oral Bioavailability	65%; fatty meal delays rate (3x) and extent of absorption up to 50%
Effect of Food	Best on empty stomach. Can take with non-fatty meal to minimize nausea.
Protein Binding	<38 %
Vd	1.6+/- 0.6 L/kg
Tmax	0.5-1.5h (fasting)
Serum T ½	0.9-1.4h
Intracellular T½	3-4h
Drug Concentrations	AUC 1,400 +/- 200 ng.hr/mL
CSF (% of serum)	60% (4-262%) 2010 CNS Penetration Effectiveness (CPE) Score: 4 [Letendre S et al. 2010]
Metabolism	first pass effect; glucuronidation to GZDV (GAZT) and AMT
Excretion	• renal excretion of parent (14%) and glucuronide (75%) via tubular secretion • renal clearance is 0.34 L/hr/kg parent • clearance decreases to 18ml/min in uremia
Dosing – Adult	**po:** 600 mg/day in 2-3 divided doses **IV:** 1-2mg/kg IV over 1hr q4h (1mg/kg IV q4h = 100mg po q4h) **HIV dementia:** 500-1200mg/d po **ITP:** 500-900mg/d, dose-related response **Prevention of Vertical Transmission (based on** ACTG076 protocol)**:** • <u>During pregnancy:</u> 14-34 wks pregnancy, 100mg po 5x/day until start of labor (in clinical practice dose is 600 mg/day in 2-3 divided doses to increase compliance; in addition, at least 2 other antiretrovirals are prescribed). • <u>Intrapartum (maternal):</u> 2mg/kg (actual body weight) IV over 1h followed by infusion of 1mg/kg/hr until clamping of umbilical cord. • <u>Postpartum (newborn):</u> 2mg/kg po q6h beginning within 12h of birth, until 6 wks, or 1.5mg/kg IV over 30 min q6h **Post-Exposure Prophylaxis:** For high risk exposure, 300mg po bid + 3TC 150mg bid +/- protease inhibitor x 4wks (see guidelines) **Combination tablets** **Combivir®:** 300 mg zidovudine/150 mg lamivudine po BID **Trizivir®:** zidovudine 300 mg/lamivudine150 mg/abacavir 300 mg po BID

<table>
<tr><td>Dosing – Pediatric</td><td>
Pediatric (4 weeks to <18 years of age):

The recommended oral dosage in pediatric patients 4 weeks of age and older and weighing >4 kg is provided in Table 1. Zidovudine syrup should be used to provide accurate dosage when whole tablets or capsules are not appropriate.

Table 1: Recommended Pediatric Dosage of Retrovir
<table>
<tr><th rowspan="2">Body Weight (KG)</th><th rowspan="2">Total Daily Dose</th><th colspan="2">Dose Regimen and Dose</th></tr>
<tr><th>b.i.d.</th><th>t.i.d.</th></tr>
<tr><td>4 to <9</td><td>24 mg/kg/day</td><td>12 mg/kg</td><td>8 mg/kg</td></tr>
<tr><td>≥9 to <30</td><td>18 mg/kg/day</td><td>9 mg/kg</td><td>6 mg/kg</td></tr>
<tr><td>≥30</td><td>600 mg/day</td><td>300 mg</td><td>200 mg</td></tr>
</table>

Alternatively, zidovudine dosing can be based on body surface area (BSA) for each child. The recommended oral dose of zidovudine is 480 mg/m^2/day in divided doses (240 mg/m^2 twice daily or 160 mg/m^2 three times daily). In some cases the dose calculated by mg/kg will not be the same as that calculated by BSA.

IV: 120 mg/m^2/dose q6h or 20 mg/m^2/hour

Perinatal exposure/prevention: start dose within 8-12 hours after birth (if mother received full AZT regimen) OR start ≤6-12 hours after birth (if mother did not receive full AZT regimen) for 6 weeks as follows:

Neonate/Infant dose (Term to 6 weeks old) (ACTG 076):
Oral: 2 mg/kg/dose po q6h
IV: 1.5 mg/kg/dose IV q6h

Premature (< 35 weeks): 1.5 mg/kg/dose IV or 2 mg/kg/dose po q12h advancing to q 8 h intervals at 2 weeks of age if > 30 weeks gestation at birth, or at 4 weeks of age if < 30 weeks gestation at birth.
</td></tr>
<tr><td>Special instructions for pediatric patients</td><td>
- manufacturer recommends 30 minutes before meals or 1 hour after, but OK to take with food
- if ZDV upsets the stomach, take with food
- may open capsule & give in small portion of food or 5-10 mL cool tap water
- 10mg/mL syrup is also available
</td></tr>
<tr><td>Adjust in Liver Dysfunction</td><td>60-400% ↑ AUC observed in patients with moderate-severe liver disease compared to normal volunteers; reduction in daily dose may be necessary.</td></tr>
</table>

Adjust in Renal Failure/ Dialysis [a] CrCl (mL/min) for men: (140 - age) (wt) x 60 (Scr) (50) *CrCl (mL/min) for women: as above multiplied by 0.85	- may require dose reduction or increased dosing interval to 100-200mg q8-12h in renal dysfunction, but unclear -peritoneal or hemodialysis: 100mg q6-8h po, or 1mg/kg q6-8h IV Hemodialysis: minimal effect on AZT elimination, enhances GAZT elimination significantly. Administer dose after dialysis session to avoid potential clinically significant removal of metabolite.
Toxicity	Transient headache and insomnia, malaise (53%), nausea (50%), anorexia (20%), vomiting (17%), macrocytosis (90%) unresponsive to B12, anemia: Hgb <80 (1%) may be responsive to erythropoietin if low baseline endogenous erythropoetin; neutropenia: ANC< 0.5 (1.8%), myopathy (10%) related to cumulative dose and ↑ CK, myositis, nail pigmentation (40%). Rare: thrombocytopenia, hepatotoxicity, cardiomyopathy; Mitochodrial toxicity: lactic acidosis ± severe hepatomegaly with steatosis ± pancreatitis, including fatalities. Some patients develop ventilator-dependent respiratory failure. D/C all antiretrovirals; partial or complete recovery may take months.
Pregnancy & Lactation	Pregnancy risk category C. ~ 85% placental transfer. No evidence of human teratogenicity. No fetal malformations in animal studies, but embryotoxic to mouse embryo.Well-tolerated, short-term safety demonstrated for mother and infant. Use regular adult dosing during pregnancy. Preferred NRTI as part of HAART regimen in pregnancy. Avoid use if toxicity found or d4T is used. Unknown whether AZT excreted into human breast milk, however it is secreted into the milk of lactating mice; avoid breast-feeding to avoid postnatal HIV transmission Glaxo-Wellcome registry to follow prenatal exposure to antiretrovirals:1-800-387-7374
Drug Interactions	Potential for additive/synergistic toxicity when co-administered with: **bone marrow toxins:** Septra, ampho B, dapsone, flucytosine, pentamidine (CBC weekly, may hold AZT during acute PCP tx with Septra); - neutropenia with **ganciclovir** (hold AZT during induction, restart with caution); **sulfadiazine/ pyrimethamine** can ↑ anemia, ↓ AZT clearance, AZT may ↓ pyrimethamine effect vs toxo (may hold AZT during toxo tx, or switch antiviral) **D4T** inhibits AZT intracellular phosphorylation in vitro, both thymidine analogues thus avoid combination **Probenecid** ↑s AZT 80%, monitor closely or avoid combo See separate drug interaction chart.
Baseline Assessment	CBC/diff (incl MCV), CK, electrolytes, anion gap, serum bicarbonate, LFTs

Routine Labs	CBC/diff monthly, CK/LFTs, electrolytes, anion gap, serum bicarbonate q3-6mos Measure serum lactate if low serum bicarbonate or high anion gap and Sx of lactic acidosis. Prodromal Sx include: nausea, anorexia, abdominal pain, vomiting, weight loss, fatigue. Rapidly progressive Sx: tachycardia, tachypnea, hyperventilation, dyspnea, muscular weakness, jaundice, mental status changes. May also progress to multi-organ failure (hepatic, pancreatitis, encephalopathy, respiratory) and death. **D/C drug:** Sx of lactic acidosis, serum lactate > 5 mmol/L; sx of myopathy (4-8wk to resolve), Hgb <80 or persistent sx, ANC < 0.5, LFTs ↑ >4-5x ULN
Dosage Forms	**Retrovir®:** • **Capsule:** 100mg (white & blue); DIN 01902660 • **Syrup:** 50mg/5mL (240mL bottle), strawberry flavour; DIN 01902652 • **IV:** 200mg/20mL vial **Combination tablets** • **Combivir®:** 300 mg zidovudine/150 mg lamivudine tablet; DIN 02239213 • **Apo-Lamivudine-Zidovudine®**: 150/300 mg tablet, DIN 02375540 • **Trizivir®:** zidovudine 300 mg/lamivudine150 mg/abacavir 300 mg tablet; DIN 02244757. **Generic:** • Apo-Zidovudine® (Apotex) 100 mg capsule; DIN 01946323 • Novo-AZT® (Novopharm) 100 mg capsule; DIN 01953877
Storage	Store all dosage forms at room temperature.

References:

ViiV Healthcare ULC. Retrovir Product monograph. Montreal, QC, February 16th, 2010.

Letendre S, Ellis RJ, Deutsch R, Clifford DB, Collier AC, Gelman GG, et al. Correlates of time-to-loss-of-viral-response in CSF and plasma in the CHARTER Cohort: CPE score predicts CSF suppression [abstract 430]. 17th Conference on Retroviruses and Opportunistic Infections, San Francisco, CA, February 16-19, 2010.

Selected Properties of Tenofovir

Other names	**Viread®:** tenofovir disoproxil fumarate; TDF Combination formulations: **Truvada®:** emtricitabine/tenofovir **Atripla®:** efavirenz/emtricitabine/tenofovir **Complera®:** rilpivirine/emtricitabine/tenofovir **Stribild®:** elvitegravir/cobicistat/emtricitabine/tenofovir
Manufacturer	Gilead Sciences, Inc.
Pharmacology/Mechanism of Action	Nucleotide analogue. Tenofovir disoproxil fumarate is the water soluble diester prodrug of tenofovir. It requires diester hydrolysis for conversion to tenofovir. Subsequent phosphorylation by cellular enzymes forms tenofovir diphosphate (active form). The diphosphate form inhibits HIV reverse transcriptase via competition with the natural substrate deoxyadenosine 5'-triphosphate and once incorporated into DNA, by DNA chain termination.
Activity	IC_{50} = 0.04 – 8.5 uM (in vitro) Active vs HBV
Resistance - genotypic	Mutations in the reverse transcriptase gene associated with resistance to reverse transcriptase inhibitors (IAS-USA Fall 2005 Resistance Mutations): • K65R • *Presence of ≥3 TAMS inclusive of either M41L or L210W leads to reduced response: M41L, D67N, K70R, L210W, T215Y/F, K219Q/E* • *Slightly increased treatment responses observed if M184V present* • *69 Insertion Complex is associated with resistance to all approved NRTIs when present with ≥1 TAM at codons 41, 210 or 215.*
Resistance - phenotypic	Phenotypic data on clinical virus isolates associated with various mutations using ViroLogic PhenoSense™ (http://hivdb.stanford.edu/): K65R: 1.9-fold ↑ (intermediate resistance) M184V + TAMS: ↓ susceptibility to tenofovir 69 Insertion complex: 20-fold ↑ (high resistance)
Cross-Resistance	Pretreatment with didanosine, zalcitabine, or abacavir may select for K65R mutation.
Oral Bioavailability	25% (fasting); 39% (high-fat meal) The absorption of raltegravir, etravirine, emtricitabine, and tenofovir was not compromised when the drugs were crushed, dissolved in 60 mL warm water, and administered by gastrostomy tube to a 52 year old HIV-positive male with ulcerative esophagitis.[Sandkovsky et al. 2012]
Effect of Food	Increase absorption from 25% to 39%. Take with food if possible, however may also be taken on an empty stomach.

Protein Binding	0.7% (human plasma); 7.2% (serum proteins)
Vd	1.3 ± 0.6 L/kg
Tmax	1.0 ± 0.4 hours (food delays Tmax by 1 hour)
Serum T ½	17 hours
Intracellular T½	> 60 hours
Drug Concentrations	At 300 mg QD with food at steady state, Cmax 326 ± 119 ng/mL, AUC 3324 ± 1370 ng.h/mL In a single-dose bioequivalence study conducted under non-fasted conditions (dose administered with 4 oz. applesauce) in healthy adult volunteers, the mean C_{max} of tenofovir was 26% lower for the oral powder relative to the tablet formulation. Mean AUC of tenofovir was similar between the oral powder and tablet formulations. In HIV-infected adolescent patients (12 to <18 years old) taking tenofovir 300 mg QD, steady-state tenofovir PK were similar to exposures achieved in adults: mean (± SD) Cmax and AUCtau were 0.38 ± 0.13 mg/mL and 3.39 ± 1.22 mg·hr/mL, respectively. Tenofovir population pharmacokinetics were assessed in 47 HIV-infected patients 8 to 18 years of age participating in a multicentre protocol (IMPAACT). Apparent tenofovir plasma clearance was slightly higher in this population compared to adults (96.2 L/hr vs. 90.9 L/hr) and affected by creatinine clearance. Differences in rate of absorption were likely due to concomitant food intake. Age, sex, Tanner stage and concomitant medications did not affect tenofovir clearance or volume of distribution.[King J et al. 2010]. In a phase I trial, 36 pregnant women received a single dose of 900 mg tenofovir at the onset of labour or 4 hours prior to caesarean section, and their newborns received tenofovir 6 mg/kg for 3 doses (after birth, 72 hours and 120 hours). Median tenofovir cord blood concentration was 123 ng/mL, with a median cord blood:maternal plasma concentration ratio of 0.59.[Mirochnick et al. 2010] In a trial, of HIV-infected pregnant women and their infants, women received a single dose of either 600 mg TDF, 900 mg TDF, or 900 mg TDF-600 mg FTC at labor onset or prior to a cesarean section. Infants received no drug or a single dose of TDF at 4 mg/kg of body weight or of TDF at 4 mg/kg plus FTC at 3 mg/kg as soon as possible after birth. All regimens were safe and well tolerated. Maternal areas under the serum concentration-time curve (AUC) and concentrations at the end of sampling after 24 h (C_{24}) were similar between the two doses of TDF. The median ratio of the TFV concentration in cord blood to

<table>
<tr><td></td><td>that in the maternal plasma at delivery was 0.73 (range, 0.26 to 1.95). [Flynn PM et al. 2011]

In 22 HIV-infected pregnant women on tenofovir-containing cART, tenofovir exposures were ~25% lower in the 3rd trimester compared to post-partum; these results were independent of concomitant use of boosted PIs. The cord blood/maternal plasma ratio ranged from 0.66 to 1.10.[Colbers et al. 2012]</td></tr>
<tr><td>CSF (% of serum)</td><td>Not available.
2010 CNS Penetration Effectiveness (CPE) Score: 1
[Letendre S et al. 2010]</td></tr>
<tr><td>Metabolism</td><td>Not a substrate of CYP450 enzymes.</td></tr>
<tr><td>Excretion</td><td>32% ± 10% unchanged in the urine; undergoes glomerular filtration and active tubular secretion</td></tr>
<tr><td>Dosing – Adult</td><td>Viread® (tenofovir 300 mg): one tablet with or without food.
Truvada® (tenofovir 300 mg/emtricitabine 200 mg): one tablet once daily with or without food.
Complera® (emtricitabine 200 mg/rilpivirine 25 mg/tenofovir 300 mg): one tablet daily with a meal.

Viread® (tenofovir) oral powder formulation: For adults unable to swallow VIREAD tablets, the oral powder formulation (7.5 scoops once daily) may be used.

Recommended Dose in Adolescents (≥12 Years of Age and ≥35 kg/77 lb): 300 mg once daily taken orally, without regard to food.</td></tr>
<tr><td>Dosing – Pediatric</td><td>Tenofovir is indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection in adults and pediatric patients 2 years of age and older.

Recommended Dose (ages 2 to <18 years of age):
• 8 mg of tenofovir disoproxil fumarate/kg body weight (up to a maximum of 300 mg) once daily as oral powder or tablets.

<table>
<tr><th>Body Weight (kg)</th><th>Oral Powder QD (# scoops)</th><th>Tablets QD</th></tr>
<tr><td>10 to <12</td><td>2</td><td rowspan="3">Use tablets if child weighs ≥17 kg</td></tr>
<tr><td>12 to <14</td><td>2.5</td></tr>
<tr><td>14 to <17</td><td>3</td></tr>
<tr><td>17 to <19</td><td>3.5</td><td rowspan="2">17 to <22 kg:
150 mg</td></tr>
<tr><td>19 to <22</td><td>4</td></tr>
<tr><td>22 to <24</td><td>4.5</td><td rowspan="3">22 to <28 kg:
200 mg</td></tr>
<tr><td>24 to <27</td><td>5</td></tr>
<tr><td>27 to <29</td><td>5.5</td></tr>
</table>
</td></tr>
</table>

<table>
<tr><td></td><td>
<table>
<tr><td>29 to <32</td><td>6</td><td rowspan="3">28 to <35 kg:
250 mg</td></tr>
<tr><td>32 to <34</td><td>6.5</td></tr>
<tr><td>34 to <35</td><td>7</td></tr>
<tr><td>≥ 35</td><td>7.5</td><td>300 mg</td></tr>
</table>

Neonatal/Infant: unknown</td></tr>
<tr><td>Special instructions for pediatric patients</td><td>Tenofovir oral powder should be measured only with the supplied dosing scoop. One level scoop delivers 1 g of powder which contains 40 mg of tenofovir disoproxil fumarate. The oral powder should be mixed in a container with 2 to 4 ounces of soft food not requiring chewing (e.g., applesauce, baby food, yogurt). The entire mixture should be ingested immediately to avoid a bitter taste. Do not administer tenofovir oral powder in a liquid as the powder may float on top of the liquid even after stirring.

Tenofovir tablets may be split or chewed (bitter taste).
May dissolve tenofovir tablets in water, grape juice, or grapefruit juice. Once dissolved, take immediately.

Crushing Atripla® tablets: Bioequivalence of Atripla tablet and compounded oral liquid formulation in HIV-negative volunteers was not demonstrated. The 90% CI for FTC Cmax and AUC fell within the range of 0.8-1.25 thus, bioequivalence was met, but the 90% CI for efavirenz Cmax fell below the range of bioequivalence while efavirenz AUC∞ fell slightly above the range and tenofovir Cmax and AUC∞ fell above the range. Tenofovir Cmax and AUC∞ were approximately 40% and 20% higher, respectively with the liquid formulation. The clinical implications of these data are unknown.[Kiser et al. CROI 2010, #605].</td></tr>
<tr><td>Adjust in Liver Dysfunction</td><td>Tenofovir pharmacokinetics were similar in subjects with moderate or severe hepatic impairment relative to healthy controls and consistent with historical data in HIV+ patients [Kearney et al. 2004]. No dosage adjustment is required.</td></tr>
<tr><td>Adjust in Renal Failure/ Dialysis
[a] CrCl (mL/min) for men:
(140 - age) (wt) x 60
(Scr) (50)

*CrCl (mL/min) for women:
as above multiplied by 0.85</td><td>Reduce dose based on CrCl [a]:
≥ 50mL/min: 300 mg q 24 hours
30-49 mL/min: 300 mg q 48 hours
10-29 mL/min: 300 mg q72-96 hours

Tenofovir is efficiently removed by hemodialysis with an extraction coefficient of approximately 54%. End-stage renal disease or hemodialysis: 300 mg q 7 days, post-dialysis (assuming 3 x 4 hour sessions weekly); 10% removed in 4-hour hemodialysis session.

There are no data to recommend use of tenofovir tablets 150, 200 or 250 mg or tenofovir oral powder in patients with renal impairment.</td></tr>
<tr><td>Toxicity</td><td>Nausea, diarrhea, vomiting, flatulence, asthenia, headache

Lactic acidosis, mitochondrial toxicity is seen with the use of</td></tr>
</table>

	nucleoside analogs. Potential thought to be lower with tenofovir vs. ddI, d4T, ddC, AZT. Fatal lactic acidosis has been reported with tenofovir + didanosine. [Rivas P 2003, Murphy 2003, Guo Y 2004] **Pancreatitis** reported when used with full dose of didanosine. Dosage reduction of didanosine is recommended with combination (i.e. ddI EC 250 mg po once daily). Caution is still warranted even with dosage reduction. [Kirian, 2004] **Nephrotoxicity:** onset: weeks to months after therapy. Proximal tubulopathy leading to Fanconi syndrome (increased serum creatinine/blood urea, hypophosphoremia, hypouricemia, hypokalemia, non-anion gap metabolic acidosis, glucosuria, proteinuria, uricosuria, phosphaturia, and/or calcuria). [Gaspar G 2004, Rollot F 2003, Karras 2003] Nephrogenic diabetes insipidus, acute tubular necrosis, [Lee JC 2003] nephrolithiasis, hydronephrosis. [Cicconi P 2004] Use of didanosine and lopinaivr/ritonavir may further increase risk. **Bone toxicity:** osteomalacia and reduced bone density seen in animals at high doses. Decreases in bone mineral density, via increased bone turnover, have been observed in adolescents and adults. Assessment of bone mineral density (BMD) should be considered for adults and adolescents who have a history of pathologic bone fracture or other risk factors for osteoporosis or bone loss. Although the effect of supplementation with calcium and vitamin D was not studied, such supplementation may be beneficial for all patients. Severe acute exacerbations of **HBV** have been reported in patients who have discontinued tenofovir. Monitor hepatic function closely for several months upon discontinuation.
Pregnancy & Lactation	Pregnancy risk category B. Phase I study in late pregnancy in progress. Due to lack of data and concern about fetal bone effects, avoid use in pregnancy. Secreted into the breast milk of lactating rats.
Drug Interactions	Interactions observed with didanosine, atazanavir, lopinavir/r. Potential for interaction with other renally eliminated drugs. Should not be combined with certain antiretrovirals as first-line therapy in subjects with high viral load and low CD4 count. See separate Drug Interaction chart for more details.
Baseline Assessment	CBC/diff, electrolytes, serum creatinine, blood urea, anion gap, serum bicarbonate, LFTs, serum phosphate, uric acid, urinalysis
Routine Labs	CBC/diff, electrolytes, serum creatinine, blood urea, anion gap, serum bicarbonate, LFTs, serum phosphate, uric acid, urinalysis (glucosuria, proteinuria, uricosuria, phosphaturia, and/or calcuria) every 3 months. Consider monitoring bone mineral density (BMD) in patients with a history of pathologic fracture or other risk factors of

	osteoporosis or bone loss. Measure serum lactate if low serum bicarbonate or high anion gap and Sx of lactic acidosis. Prodromal Sx include: nausea, anorexia, abdominal pain, vomiting, weight loss, fatigue. Rapidly progressive Sx: tachycardia, tachypnea, hyperventilation, dyspnea, muscular weakness, jaundice, mental status changes. May also progress to multi-organ failure (hepatic, pancreatitis, encephalopathy, respiratory) and death. **D/C drug:** Sx of lactic acidosis, serum lactate > 5 mmol/L, amylase >200 (asymptomatic), pancreatitis, LFTs >5xULN, serum creatinine >175 mmol/L or grade 3 clinical or laboratory events (e.g., serum potassium < 2.5 mmol/L, serum phosphorus < 0.48 mmol/L)
Dosage Forms	Viread® (tenofovir) tablets: • 300 mg (light blue, almond-shaped); DIN 02247128 • 150 mg, 200 mg and 250 mg tablets *(available in U.S.)* Viread® (tenofovir) oral powder: *(available in U.S.)* • 40 mg per 1 gram of oral powder formulation **Combination formulations:** • Truvada®: tenofovir 300 mg/emtricitabine 200 mg, DIN 02274906 • Atripla®: efavirenz 600 mg/emtricitabine 200 mg/tenofovir 300 mg tablet, DIN 02300699 • Complera®: Emtricitabine 200 mg/rilpivirine 25 mg/tenofovir DF 300 mg tablet, DIN 02374129 • Stribild®: Elvitegravir 150 mg/cobicistat 150 mg/ emtricitabine 200 mg/ tenofovir DF 300 mg tablet
Storage	Store tablets at room temperature.

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Selected Properties of Delavirdine

Other names	Rescriptor®
Manufacturer	ViiV Healthcare ULC
Pharmacology/Mechanism of Action	Bisheteroarypiperazine (BHAP) compound. Non-competitive, selective binding to reverse transcriptase enzyme causing conformational change that inactivates the catalytic site, preventing proviral DNA synthesis in HIV-1. Does not require intracellular phosphorylation.
Activity	In clinical isolates: mean IC50: 0.038 uM (0.001-0.69) IC90: 0.05-0.1 uM
Resistance - genotypic	Mutations in the reverse transcriptase gene associated with resistance to reverse transcriptase inhibitors (IAS-USA Fall 2005 Resistance Mutations): **K103N***, ***V106M****, *Y181C*#, **Y188L***, P236L ***multi-NNRTI resistance** #*accumulation of ≥2 leads to multi-NNRTI resistance*
Resistance - phenotypic	Phenotypic data on clinical virus isolates associated with various mutations using ViroLogic PhenoSense™ (http://hivdb.stanford.edu/): K103N: 34-fold ↑ (high resistance) V106A: 5-fold ↑ (intermediate resistance) Y181C/I: 24-fold ↑ (high resistance) Y188L: 10-fold ↑ (low resistance) P236L (rare mutation): 53-fold ↑ (high resistance) K103N +Y181C: 250-fold ↑ (high resistance)
Cross-Resistance	Rapid emergence of HIV strains that are cross-resistant to NNRTIs observed in vitro. Mutations at positions 103 and 181 have been associated with resistance to other NNRTIs. Cross-resistance between delavirdine and protease inhibitors or nucleoside analogues unlikely because enzyme targets are different.
Oral Bioavailability	85% (increased by approx. 20% if administered as slurry)
Effect of Food	Minimal food effect. Can take with or without food.
Protein Binding	98% (albumin)
Tmax	1 hour
serum T ½	apparent plasma t1/2 increases with dose; mean t1/2 following 400 mg TID is 5.8 hours (range 2-11 hours)
Drug Concentrations	With 400 mg TID in HIV subjects (n=67): mean steady-state Cmax 35 ± 20 uM (range 2 to 100 uM), Cmin 15 ± 10 uM (range 0.1 to 45 uM), AUC 180 ± 100 uM.hr (range 5 to 515 uM • hr)

CSF (% of serum)	0.4% Steady-state delavirdine concentrations in saliva and semen were 6% and 2%, respectively, of corresponding plasma delavirdine concentrations. 2010 CNS Penetration Effectiveness (CPE) Score: 3 [Letendre S et al. 2010]
Metabolism	Metabolized via P450 3A4 oxidation, and 2D6 to a minor extent, followed by biliary excretion.
Excretion	44% of each dose excreted in feces. 5% renal excretion. Low renal clearance (<5mL/min).
Dosing – Adult	400mg TID 600 mg BID also being investigated. Can place 100 mg tablets (4 x 100 mg) in > 90 mL of water and wait for tablets to disintegrate, then stir to form suspension; this will increase the bioavailability 20%. The 200 mg tablets should be taken intact (USA only).
Dosing – Pediatric	Unknown
Special instructions for pediatric patients	Dissolve tablet in 30 mL water for a few minutes, stir and drink; rinse glass and drink again.
Adjust in Liver Dysfunction	Data not available. Use with caution in patients with impaired hepatic function.
Adjust in Renal Failure/Dialysis	Data not available, but no dosage adjustments likely required since delavirdine undergoes predominantly hepatic metabolism. Hemodialysis: administer after hemodialysis session, since hemodialysis removal of delavirdine has not been studied. CAPD: no dosage adjustment required.
Toxicity	**Rash:** mild rash +/- pruritus (35.4%), severe grade 3/4 rash (4.4%), SJS (0.1%). May be related to dose and blood levels. Can successfully continue drug in 85% if rash occurs, treat symptomatically with antihistamines, analgesics. **Discontinue** drug if severe rash or rash with constitutional symptoms (fever, blistering, oral lesions, conjunctivitis, swelling, muscle or joint aches, lymphadenopathy, increased LFTs or general malaise), and do not rechallenge. Rash typically occurs within first 4 wks of treatment. Avoid use of other NNRITs with history of severe rash to delavirdine. **Other, >5%:** nausea, vomiting, diarrhea, fatigue, headache, elevated LFTs.

Pregnancy & Lactation	Pregnancy category C drug. No adequate and well-controlled data in pregnant women. Excreted in the milk of lactating rats.
Drug Interactions	Delavirdine non-competetively inhibits P450 3A4. Also reduces CYP2C9 and CYP2C19 activity. See NNRTI interactions chart.
Baseline Assessment	CBC/diff, LFTs, examine skin for baseline.
Routine Labs	CBC/diff, LFTs q3-6mo. Assess for skin rash (most common in 1st 4 weeks of therapy). **D/C drug**: LFTs >5xULN, severe rash or rash with constitutional symptoms (see above under toxicity).
Dosage Forms	**100mg film-coated tablet** (DIN 02238348) 200 mg tablets available in the U.S.
Storage	Store at controlled room temperature 20° to 25°C (68° to 77°F).

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Selected Properties of Efavirenz

Other names	Sustiva® (North America), Stocrin® (Europe), DMP-266 Combination formulations: • Atripla®: efavirenz/emtricitabine/tenofovir
Manufacturer	Bristol-Myers Squibb Canada
Pharmacology/Mechanism of Action	Non-competitive, selective binding to reverse transcriptase enzyme causing conformational change that inactivates the catalytic site, preventing proviral DNA synthesis in HIV-1. Does not require intracellular phosphorylation.
Activity	$IC_{90\text{-}95}$: 1.7 - ≤25 nM (wild-type)
Resistance - genotypic	Mutations in the reverse transcriptase gene associated with resistance to reverse transcriptase inhibitors (IAS-USA Fall 2005 Resistance Mutations) *L100I*#, **K103N***, ***V106M****, V108I, *Y181C/I*#, **Y188L***, *G190S/A*#, P225H ***multi-NNRTI resistance** #*accumulation of ≥2 leads to multi-NNRTI resistance*
Resistance - phenotypic	Phenotypic data on clinical virus isolates associated with various mutations using ViroLogic PhenoSense™ (http://hivdb.stanford.edu/) K103N: 19-fold ↑ (high resistance) V106A: 1.9-fold ↑ (low resistance) Y188L: 130-fold ↑ (high resistance) G190A: 7-fold ↑ (intermediate resistance) G190S: 52-fold ↑ (high resistance) Multiple mutations confer high-level resistance (100-200 fold) to efavirenz: L100I + K103N: 274-fold ↑ (high resistance) G190A + K103N: 213-fold ↑ (high resistance) K103N + P225H: 100-fold ↑ (high resistance) K103N +Y188L: 270-fold ↑ (high resistance)
Cross-Resistance	K103N mutation confers high-level resistance to other NNRTIs. In vitro, efavirenz retains activity against variants containing V106A, Y181C, Y188C, G190A, and P236L mutations (all reported with other NNRTI therapies). Cross-resistance between efavirenz and protease inhibitors or nucleoside analogues unlikely because enzyme targets are different.
Effect of Food	Can take with or without food. High fat meal (670 kcal, 60% fat, 400 kcal fat) may ↑ EFV concentrations by 50%.
Protein Binding	99.75% (albumin)

Tmax	3 - 5 hours
serum T ½	40-55 hours after multiple doses
Drug Concentrations	Dose-related increases in Cmax and AUC seen for doses up to 1600 mg; may have diminished absorption at higher doses. In 35 patients receiving efavirenz 600 mg once daily, steady-state Cmax was 12.9 ± 3.7 µM (mean ± SD), steady state Cmin was 5.6 ± 3.2 µM, and AUC was 184 ± 73 µM•h.
Minimum target trough concentrations (for wildtype virus)	Cmin: >1000 ng/mL Cmax: <4000 ng/mL
CSF (% of serum)	In HIV-1 infected patients (n=9) who received efavirenz 200-600 mg once daily for at least one month, cerebrospinal fluid concentrations ranged from 0.26 to 1.19% (mean 0.69%) of the corresponding plasma concentration. This proportion is approximately 3-fold higher than the non-protein-bound (free) fraction of efavirenz in plasma. 2010 CNS Penetration Effectiveness (CPE) Score: 3 [Letendre S et al. 2010] Paired CSF and plasma samples were obtained from patients taking standard doses of efavirenz. Efavirenz concentrations were 0.5% of plasma concentrations. Efavirenz CSF concentrations:IC50wt (0.51 ng/mL) ratio was 26 (IQR 8-41). Two CSF concentrations (2.6%) were below the IC50.[Best B et al. CROI 2009]
Metabolism	Metabolism primarily via CYP 3A4, and 2B6; undergoes autoinduction (20-40%) during first two weeks of therapy; major metabolite (inactive): glucuronide conjugate
Excretion	14-34% (primarily hydroxylated metabolites) excreted in urine, 16-61% in feces.
Dosing – Adult	600 mg once daily preferably before bedtime. Can take with food, however high fat foods may increase the absorption by 50%, thus potentially increasing side effects. **NB: Efavirenz is contraindicated in pregnancy; women of childbearing potential should undergo pregnancy testing before initiation of efavirenz.**
Dosing – Pediatric	Neonatal/Infants: unknown. Pediatric (> 3 y.o.): All administered once daily. 10 to < 15 kg: 200 mg 15 to < 20 kg: 250 mg 20 to < 25 mg : 300 mg 25 to < 32.5 kg: 350 mg 32.5 to < 40 kg: 400 mg ≥ 40 kg: 600 mg. No data for dosing in children < 3 years old.

Special instructions for pediatric patients	Give at bedtime during first 2-4 weeks of therapy to decrease CNS effects Flavoured pediatric suspension available via expanded access (1-877-372-7097). Can open **capsules** and mix powder with apple sauce (but will result in hot "jalapeno" sensation). Try grape jelly to mask taste. For nasogastric administration, may open capsules and mix with either 5 mL MCT oil or 15 mL Ora-Sweet (grind powder first to enhance dissolution). Powder is insoluble in water; do NOT mix with polyethylene glycol (will ↓ bioavailability). **Efavirenz tablets** may be crushed (personal communication, Bristol Myers Squibb Medical Information, March 5, 2009). **Crushing Atripla® tablets:** Bioequivalence of Atripla tablet and compounded oral liquid formulation in HIV-negative volunteers was not demonstrated. The 90% CI for FTC Cmax and AUC fell within the range of 0.8-1.25 thus, bioequivalence was met, but the 90% CI for efavirenz Cmax fell below the range of bioequivalence while efavirenz AUC∞ fell slightly above the range and tenofovir Cmax and AUC∞ fell above the range. Tenofovir Cmax and AUC∞ were approximately 40% and 20% higher, respectively with the liquid formulation. The clinical implications of these data are unknown.[Kiser et al. CROI 2010, #605].
Adjust in Liver Dysfunction	Limited data available. In 10 volunteers with chronic liver disease, efavirenz Cmax was significantly lower compared to healthy volunteers (3.72 +/- 1.22 uM vs. 5.74 +/- 1.14 uM, respectively) while half-life was longer (152 +/- 41 h vs. 118 +/- 46 h, respectively). There were no significant differences in efavirenz AUC between the two groups (299 +/- 109 uM.h and 305 +/- 124 uM.h in the chronic liver disease and healthy volunteer subjects, respectively).(Fiske et al. CROI 99, #367). A case report documents elevated efavirenz and nelfinavir concentrations in 2 subjects with hepatic impairment, compared to controls (Maserati et al. 1999). Use with caution in patients with impaired hepatic function. Dosage adjustment may be required. In a case control study, HIV-positive subjects with hepatitis B or C coinfection and mild hepatic dysfunction (Child-Pugh score 5-6) did not experience significant differences in efavirenz levels over 2 years compared to a matched HIV-monoinfected control group.(Pereira et al. 2007)
Adjust in Renal Failure/Dialysis	No adjustment necessary in end-stage renal disease. Hemodialysis: Hemodialysis does not affect pharmacokinetics of efavirenz. In a prospective study of HIV-infected patients on hemodialysis taking efavirenz 600 mg QD (n=13), 24-hour PK was assessed. Mean Cmin, Cmax, and AUC of EFV was 1.81 mg/mL, 5.04 mg/mL and 71.5 mg h/mL, respectively for efavirenz. The AUC geometric mean ratio (90% CI) was 132% (89, 197). Efavirenz may be administered regardless of

	hemodialysis schedule because of its extensive hepatic metabolism.[Gupta et al. 2008] CAPD: impact of CAPD on efavirenz removal seems to be minimal. No dosage adjustment required.
Toxicity	**Rash** (26%): usually grade 1/2, can often treat through. Grade 3/4 rash (1%) . SJS (0.1%). Median time to onset 11 days, median duration 14 days. Mild rash treated symptomatically with antihistamines, analgesics/NSAIDs. **Discontinue** drug if severe rash or rash with constitutional symptoms (fever, blistering, oral lesions, conjunctivitis, swelling, muscle or joint aches, lymphadenopathy, increased LFTs or general malaise), and **do not rechallenge**. Avoid use of other NNRITs with history of severe rash to efavirenz. **CNS** (52%): dizziness, impaired concentration, somnolence, abnormal dreams, insomnia, confusion, agitation, depersonalization, amnesia, hallucinations, euphoria. Symptoms usually resolve within a few weeks without interrupting therapy, and may be minimized by bedtime dosing (2.6% discontinuation rate). Worsening of underlying mental illnesses and increased suicidal ideation has been observed. **Other:** teratogenic in monkeys, increased AST/ALT, false-positive cannabinoid test, nausea, vomiting, diarrhea, headache
Pregnancy & Lactation	**Pregnancy risk category D: <u>contra-indicated in pregnancy</u>.** Teratogenic effects (i.e. anencephaly, anophthalmia, cleft palate) seen in 3/20 (15%) of monkeys at efavirenz exposures similar to those seen in humans. There are 3 case reports of neural tube defects and 1 case of Dandy Walker Syndrome in humans with first trimester drug exposure. Use of efavirenz is contraindicated in the first trimester of pregnancy. Use after the 2nd trimester can be considered only if there are no other alternatives. Adequate contraception should be used post-partum and in all females of childbearing age. Women of childbearing potential should undergo pregnancy testing before initiation of efavirenz. Antiretroviral Pregnancy Registry to monitor fetal outcomes of pregnant women exposed to efavirenz: 1-800-258-4263. Studies in rats have shown that efavirenz is excreted in milk.
Drug Interactions	Efavirenz can either induce or inhibit CYP3A4. Also inhibits 2C9, 2C19. Efavirenz induces UGT1A1. See NNRTI interaction chart
Baseline Assessment	Psychiatric assessment (depression, sleep patterns, any CNS disturbances), pregnancy status and adequate contraception in females of childbearing age, CBC/diff, LFTs, examine skin for baseline.
Routine Labs	Psychiatric assessment ,CBC/diff, LFTs q3-6mo. Assess for skin rash and CNS effects every 1-2 weeks when starting therapy for

	the first 6 weeks. **D/C drug**: LFTs >5xULN, severe rash or rash with constitutional symptoms (see above under toxicity).
Dosage Forms	**Capsules:** • 600 mg (yellow), DIN 02246045 (30 tablets/bottle) • 200 mg (gold), DIN 02239888 (90 capsules/bottle) • 100 mg (white), DIN 02239887 (30 capsules/bottle) • 50 mg (gold and white), DIN 02239886 (30 capsules/bottle) **Pediatric Suspension** (strawberry-mint flavour) available via Expanded Access (1-877-372-7097). **Combination formulations:** • Atripla®: efavirenz 600 mg/emtricitabine 200 mg/tenofovir 300 mg tablet (DIN 02300699)
Storage	Efavirenz capsules and tablets should be stored at 25°C (77°F). Store suspension at room temperature.

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Selected Properties of Etravirine

Other names	Intelence, TMC-125
Manufacturer	Janssen Inc.
Pharmacology/Mechanism of Action	A di-aryl-pyrimidine (DAPY) derivative NNRTI. The inherent molecular flexibility of TMC125 relative to other NNRTIs permits the compound to retain its binding affinity to the reverse transcriptase in spite of the binding site changes induced by the presence of common NNRTI resistance mutations.
Activity	Shows high intrinsic activity against both wild-type HIV-1 and against HIV strains harboring resistance inducing mutations. TMC125 exhibits potent *in vitro* anti-HIV activity with an EC50 against wild-type HIV-1 of 1.4 nM, and little or no loss of activity (<5-fold reduction in susceptibility) against HIV-1 variants having key NNRTI resistance mutations. In extensive testing of more than 1,000 clinical HIV-1 isolates, all exhibiting resistance to at least one currently marketed NNRTI, the EC50 of TMC125 was below 100nM for 95% of the isolates. In addition, it appears that the development of resistance by the virus may be inhibited by TMC125's unique pharmacologic properties.
Resistance - genotypic	• Preliminary analyses of data from the DUET trials have identified 13 mutations associated with decreased virological responses to etravirine • Mutations: V90I, L100I, V106I, Y181C/I/V, A98G, K101E/P, V179D/F, G190A/S At least 3 of these mutations had to be present in combination before the response to etravirine was diminished to levels on par with that of placebo
Oral Bioavailability	Unknown The absorption of raltegravir, etravirine, emtricitabine, and tenofovir was not compromised when the drugs were crushed, dissolved in 60 mL warm water, and administered by gastrostomy tube to a 52 year old HIV-positive male with ulcerative esophagitis.[Sandkovsky et al. 2012]
Effect of Food	**Give with food. Type of meal not important.** • Fasted State: AUC ↓ 51% compared to a standard breakfast. • Light Breakfast (Croissant): AUC ↓ 20% compared to a standard breakfast. Not clinically relevant • Enhanced Fiber Breakfast: AUC ↓ 25% compared to a standard breakfast. Not clinically relevant • High Fat Breakfast (70g): AUC ↑ 9% compared to a standard breakfast. Not clinically relevant (Scholler-Gyure et al. 2008)

Protein Binding	>99.8%
Tmax	2.5 to 4 hours
serum T ½	41 +/- 20 hours
Drug Concentrations	Dose-proportional kinetics observed in healthy volunteer studies. The same daily dose of etravirine results in similar daily exposure whether given in a daily or BID regimen [Sholler-Gyure et al. 2007]. • **Etravirine 100mg BID with food** (n=23): Cmin 215 ± 86ng/ml; Cmax 471 ± 141 ng/ml, AUC12 3925 ± 1251 ng.h/ml • **Etravirine 200mg Daily with food** (n=24): Cmin 163 ± 76 ng/ml; Cmax 659 ± 177 ng/ml, AUC24 8054 ± 2748 ng.h/ml • **Etravirine 200mg BID with food** (n=39): Cmin 469 ± 149ng/ml; Cmax 959 ± 278 ng/ml, AUC12 8195 ± 2428 ng.h/ml • **Etravirine 400mg Daily with food** (n=37): Cmin 364 ± 133 ng/ml; Cmax 1393 ± 386 ng/ml, AUC24 17220 ± 5009 ng.h/ml Population PK data from Duet trials [Kakuda et al. 2008] • Mean AUC12H: 5506 ng.h/ml • Mean Cmax: 393ng/ml • Interpatient Variability: 60% • Intrapatient Variability: 40% • Similar ETR exposure for different races (Blacks, Caucasians, Asians) and between sexes (M/F) • Trend for higher ETR levels with increased age • Higher ETR levels with decreasing weight HBV/HCV coinfected patients had higher ETR exposures (see dosing in hepatic impairment). In healthy volunteers, etravirine 200-mg non-coated tablet displayed comparable single-dose pharmacokinetics to two 100-mg non-coated tablets.[Kakuda et al. 2011] In 12 HIV-infected women on etravirine for a median of 142 days in combination with a median of 3 other ARVs and undetectable VL in blood plasma (BP) and cervicovaginal fluid (CVF), etravirine demonstrated good penetration into the genital tract. CVF and BP etravirine concentrations were 857 ng/mL (385-1682) and 592 ng/mL (391-839), determined 13.25 (9.5-14) and 12.4(9-14) hours respectively after the last drug intake. CVF/BP ratio of etravirine concentrations was approximately 1.19 (0.4-4.80). The median etravirine CVF exposure was approximately 350 fold higher than the EC_{50} for wild type HIV-1 (0.3-2.3ng/ml), possibly contributing to virological control in the compartment.[Clavel et al. 2011]
CSF (% of serum)	2010 CNS Penetration Effectiveness (CPE) Score: 2 [Letendre S et al. 2010]

<table>
<tr><td>Metabolism</td><td>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.[Scholler-Gyure, 2008]</td></tr>
<tr><td>Dosing – Adult</td><td>200 mg po BID following a meal.

Patients who are unable to swallow etravirine tablets whole may disperse the tablets in a glass of water. Once dispersed, patients should stir the dispersion well and drink it immediately. The glass should be rinsed with water several times and each rinse completely swallowed to ensure the entire dose is consumed.

If one is switching to etravirine from efavirenz therapy, the switch may be made without adjustment to etravirine dosage.[Boffito M et al. 2009].</td></tr>
<tr><td>Dosing – Pediatric</td><td>Children 6 to less than 18 years old and weighing at least 16 kg:
<table><tr><th>Weight (kg)</th><th>Dose</th></tr><tr><td>16 to <20 kg</td><td>100 mg BID</td></tr><tr><td>20 to <25 kg</td><td>125 mg BID</td></tr><tr><td>25 to <30 kg</td><td>150 mg BID</td></tr><tr><td>≥30 kg</td><td>200 mg BID</td></tr></table>A population pharmacokinetic model indicates that etravirine 5.2mg/kg BID in children and adolescents (6-17 years) provides comparable exposure to adults receiving 200mg BID.[Kakuda et al. 2011].</td></tr>
<tr><td>Special instructions for pediatric patients</td><td>Patients should be instructed to swallow etravirine tablets whole with a liquid such as water. Patients who are unable to swallow the tablets whole may disperse the tablets in a glass of water. The patient should be instructed to do the following:

• place the tablet(s) in 5 ml (1 teaspoon) of water, or at least enough liquid to cover the medication,

• stir well until the water looks milky, if desired, add more water or alternatively orange juice or milk (patients should not place the tablets in orange juice or milk without first adding water). The use of grapefruit juice or warm (greater than 40°C) or carbonated beverages should be avoided.

• drink it immediately,

• rinse the glass several times with water, orange juice, or milk and completely swallow the rinse each time to make sure the patient takes the entire dose.</td></tr>
<tr><td>Adjust in Liver Dysfunction</td><td>The pharmacokinetics of etravirine 200mg BID were assessed in 16 HIV negative subjects with mild to moderate hepatic impairment, and compared to 16 healthy matched controls. No significant effect on etravirine kinetics was observed in patients with mild hepatic impairment (Child Pugh A). Patients with moderate hepatic impairment (Child Pugh B) had similar Cmin</td></tr>
</table>

	and AUC12h levels but significantly lower Cmax levels VS healthy controls (Day 1: 0.63; 95% CI 0.47-0.85. Day 8: 0.72; 95% CI 0.54-0.96). The authors suggest etravirine dose adjustment is not required in mild – moderate hepatic impairment [Sholler-Gyure et al. 2007]. In a case report where a woman with severe hepatic dysfunction (decompensated liver cirrhosis) received standard doses of tenofovir, etravirine and darunavir/ritonavir, etravirine levels were measured after 8 months of therapy (VL<50 copies/mL). The etravirine level was 3257 ng/mL (as compared to population PK Cmin from the DUET studies of approximately 300 ng/mL). Etravirine was discontinued, and levels measured 2 and 5 weeks later were 931 ng/mL and 100 ng/mL, respectively. An estimated half-life was calculated to be 237 hours. The patient did not experience any adverse event.[Aboud et al. 2009] HBV/HCV coinfection associated with 1.35 ↑ AUC12h (population PK data from Duet trials) [Kakuda et al. 2008].
Adjust in Renal Failure/Dialysis	Antiretroviral pharmacokinetics were studied in a 49-year old HIV-positive man virologically suppressed on darunavir/ritonavir 600/100 mg twice daily, etravirine 200 mg twice daily and raltegravir 400 mg twice daily while undergoing hemodialysis three times weekly. The morning dose of the antiretrovirals was taken after completion of the 4-hour morning hemodialysis session. After dialysis, darunavir, etravirine, raltegravir and ritonavir concentrations were decreased by 57%, 29%, 82% and 60%, respectively compared to predialysis levels. A supplemental dose of 600 mg darunavir administered prior to the hemodialysis session was successful in restoring darunavir concentrations approximately equal to expected levels, while administration of a supplemental dose of raltegravir 400 mg was not, likely due to wide intra- and inter-patient variability. Dose supplementation of etravirine was not deemed necessary given the relatively low amount removed during hemodialysis. After 1 year of therapy, the patient maintained viral suppression.[Giguere et al. 2009]
Toxicity	The most frequently reported adverse effects include rash and nausea. In general, in clinical trials, rash was mild to moderate, occurred primarily in the second week of therapy and was infrequent after Week 4. Rash generally resolved within 1-2 weeks on continued therapy. The incidence of rash was higher in women compared to men in etravirine arm. Patients with a history of NNRTI-related rash did not appear to be at increased risk for the development of etravirine-related rash compared to patients without a history of NNRTI-related rash. A total of 2% of HIV-1-infected subjects receiving etravirine discontinued from Phase 3 trials due to rash. Rash occurred most commonly during the first 6 weeks of therapy.

	Severe, potentially life-threatening, and fatal skin reactions have been reported. These include cases of Stevens-Johnson syndrome, toxic epidermal necrolysis and erythema multiforme. Hypersensitivity reactions have also been reported and were characterized by rash, constitutional findings, and sometimes organ dysfunction, including hepatic failure. In Phase 3 clinical trials, Grade 3 and 4 rashes were reported in 1.3% of subjects receiving etravirine compared to 0.2% of placebo subjects. Discontinue etravirine immediately if signs or symptoms of severe skin reactions or hypersensitivity reactions develop (including, but not limited to, severe rash or rash accompanied by fever, general malaise, fatigue, muscle or joint aches, blisters, oral lesions, conjunctivitis, facial edema, hepatitis, eosinophilia). Clinical status including liver transaminases should be monitored and appropriate therapy initiated. Delay in stopping etravirine treatment after the onset of severe rash may result in a life-threatening reaction.
Pregnancy & Lactation	*Pregnancy Category B*—Use during pregnancy only if the potential benefit justifies the potential risk. Antiviral Pregnancy Registry available. Register patients by calling 1-800-258-4263. Case series of etravirine use in 5 pregnant women; PK assessments in 3rd trimester showed etravirine concentrations comparable to those seen in non-pregnant adults. Therefore, no dosage adjustment required in pregnancy.[Izureita et al. 2009] Nursing Mothers: Mothers should not breastfeed due to the potential for HIV transmission.
Drug Interactions	Etravirine is metabolized by CYP3A4 & CYP2C. Etravirine induces CYP3A4 and inhibits CYP2C, 2C19 and p-glycoprotein. Effect of etravirine on the kinetics of other agents: • etravirine may ↓ plasma levels of drugs metabolized by CYP 3A4 • etravirine may ↑ plasma levels of drugs metabolized by CYP 2C, 2C19, and p-glycoprotein. Effect of other agents on the kinetics of etravirine: • Drugs that inhibit CYP 3A4 or CYP2C may ↑ etravirine plasma levels • Drugs that induce CYP 3A4 or CYP2C may ↓ etravirine plasma levels. Etravirine should not be co-administered with the following antiretrovirals: • Tipranavir/ritonavir, fosamprenavir/ritonavir, atazanavir/ritonavir • Protease inhibitors administered without ritonavir • NNRTIs Co-administration of etravirine with drugs that inhibit or induce

	CYP3A4, CYP2C9, and/or CYP2C19 may alter the therapeutic effect or adverse reaction profile of etravirine. Co-administration of etravirine with drugs that are substrates of CYP3A4, CYP2C9, CYP2C19 and/or p-glycoprotein may alter the therapeutic effect or adverse reaction profile of the co-administered drugs. Also refer to "Drug interactions with Non-Nucleoside Reverse Transcriptase Inhibitors" table.
Dosage Forms	100 mg oral tablets (F060 formulation), DIN 02306778. 200 mg oral tablets, DIN 02375931. 25 mg tablet for pediatric use (F066 formulation) – available in U.S.. Previous formulations: TF002 50 mg capsule (earliest clinical trials) TF035 200 mg tablet (phase IIb; dosed 800 mg BID)
Storage	Store at room temperature (15-30 C) in original bottle with dessicant. Tablets are hygroscopic and may soften or become harder to swallow if exposed to moisture (personal communications, Tibotec Canada Medical Information, July 2010).

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Selected Properties of Nevirapine

Other names	Viramune®, Auro-Nevirapine®
Manufacturer	Boehringer Ingelheim (Canada) Ltd., Aurobindo Pharma Limited
Pharmacology/Mechanism of Action	Dipyridodiazepinone derivative, considered a TIBO (tetrahydroimidazobenzodiazepinthione) -like compound, and structurally related to benzodiazepines. Non-competetive, selective binding to reverse transcriptase enzyme causing conformational change that inactivates the catalytic site, preventing proviral DNA synthesis in HIV-1. Does not require intracellular phosphorylation.
Activity	IC50: 10-100 nM against laboratory and clinical isolates of HIV-1
Resistance - genotypic	Mutations in the reverse transcriptase gene associated with resistance to reverse transcriptase inhibitors (IAS-USA Fall 2005 Resistance Mutations): *L100I*[#], **K103N***, ***V106A/M****[#], V108I, *Y181C/I*[#], **Y188C/L/H***, *G190A*[#] ***multi-NNRTI resistance** [#]*accumulation of ≥2 leads to multi-NNRTI resistance*
Resistance - phenotypic	Phenotypic data on clinical virus isolates associated with various mutations using ViroLogic PhenoSense™ (http://hivdb.stanford.edu/) WT IC50: 0.046-0.286 uM (Phenosense) K103N: 47-fold ↑ (high resistance) V106A: 64-fold ↑ (high resistance) Y181C/I: 85-fold ↑ (high resistance) Y188L: 450-fold ↑ (high resistance) Y188C/H: intermediate to high-level resistance G190A: 75-fold ↑ (high-level resistance) L100I + K103N: 78-fold ↑ (high resistance) K103N+Y181C: 400-fold ↑ (high resistance)
Cross-Resistance	Rapid emergence of HIV strains that are cross-resistant to NNRTIs observed in vitro. Cross-resistance between nevirapine and protease inhibitors or nucleoside analogues unlikely because enzyme targets are different.
Oral Bioavailability	>90%
Effect of Food	No effect of food. Can take with or without food.
Protein Binding	60%
Vd	nevirapine is highly lipophilic; Vd 1.21 +/- 0.09 L/kg (following IV dose). In one phase I study in healthy volunteers, the weight-adjusted apparent volume of distribution (Vdss/F) was higher in women vs. men (1.54 vs. 1.38 L/kg), but this was offset by a shorter terminal t1/2 in women, resulting in no overall difference in

	nevirapine clearance between genders.
Tmax	2 hours
serum T ½	25-30 hours
Drug Concentrations	Cmax (4 hours after single 200 mg dose): 2 ± 0.4 ug/mL (7.5 uM); At dose of 400 mg/day (n=242), Cmin at steady state: 4.5 ± 1.9 ug/mL (17 ± 7 uM). In 108 patients on a nevirapine-based regimen, median nevirapine Ctrough was 5624 ± 1812 vs. 4468 ± 1568 ng/mL in individuals with mutant allele (GT or TT, n=54) for CYP2B6 516 as compared to individuals with wild-type genotype (GG, n=54), p=0.001. The combined effect of additional SNPs ABCB1 3435C>T and 1236 C>T yielded a significant positive correlation with nevirapine Ctrough.(D'Avolio et al. 2010).
Minimum target trough concentrations (for wildtype virus)	3.4 mg/mL 4.30 mg/mL may be associated with lower probability of selection of nevirapine-associated primary resistance mutations in case of virologic failure.
CSF (% of serum)	45% (equal to unbound drug) 2010 CNS Penetration Effectiveness (CPE) Score: 4 [Letendre S et al. 2010]
Metabolism	>95% metabolism via P450 3A4 oxidation, and 2B6 to a minor extent, followed by biliary excretion.
Excretion	hydroxylated metabolites excreted in urine; <3% total dose excreted unchanged. Nevirapine is metabolized more quickly in pediatric patients vs. adults.
Dosing – Adult	200mg po once daily for 14 days (lead in), followed by 200 mg bid (immediate-release tablets) or 400 mg once daily (extended release tablet) Extended-release (400 mg XR) tablets must be swallowed whole; they must not be chewed, crushed or divided. **NB: avoid use in women with CD4 >250 (12-fold ↑ risk) and in men with CD4 >400 (3-fold ↑ risk) due to increased risk of symptomatic hepatotoxicity.** **If switching from efavirenz to nevirapine** (e.g., for CNS-related side effects), may use either standard nevirapine lead-in period or full BID dosing right away. In 39 patients on an efavirenz-based regimen with CNS toxicity, subjects were randomized to switch to nevirapine with either lead-in dosing or full dosing immediately. A higher percentage of patients in the full-dose arm achieved therapeutic nevirapine levels >3 ug/mL versus the lead-in dosing group (89 vs 44% at day 7, p=0.006, 82 vs 32% at day 14, p=0.003), but there was a trend to higher incidence of rash and hepatic toxicity in the full-dose arm. Rash

	was related to nevirapine plasma levels at day 7 (6.6 vs. 3.6 ug/mL in patients with or without rash, p=0.007). Of note, efavirenz plasma concentrations remained detectable after 14 days without differences in treatment arms.[Ribera et al. 2010]
Dosing – Pediatric	**Pediatric**[1]: 120 mg/m^2/dose po once daily for 14 days, then 120 mg/m^2/dose po bid range: 120-200 mg/m^2/dose bid if no rash or ADR **Neonate** (<3 months) (PACTG 365): 5 mg/kg/dose po once daily OR 120 mg/m^2/dose po once daily for 14 days, then 120 mg/m^2/dose po bid for 14 days, then 200 mg/m^2/dose po bid **Newborn prophylaxis**: mother 200 mg po x 1 at onset of labour; baby 2 mg/kg/dose po x 1 at 48-72 hours
Special instructions for pediatric patients	May crush immediate-release tablets, mix in water and give orally or by G-tube; liquid formulation available via SAP. Extended-release (400 mg XR) tablets must be swallowed whole; they must not be chewed, crushed or divided.
Adjust in Liver Dysfunction	Single-dose pharmacokinetics of nevirapine were assessed in 10 subjects with hepatic impairment, and compared to 8 subjects with normal hepatic function. Mild-moderate hepatic impairment (i.e., Child-Pugh score ≤7) had no significant effect on nevirapine kinetics. However, potential for nevirapine accumulation in subjects with severe hepatic dysfunction and/or moderate-severe ascites. In a cross-sectional study of nevirapine concentrations in HIV/HCV and HIV infected subjects, median NVP Cmin were similar between the 2 groups, but varied according to fibrosis stage. In co-infected subjects, those with cirrhosis (METAVIR fibrosis stage 4) had significantly higher NVP Cmin compared to the less fibrotic group.*[Dominguez et al. 2006]* In a prospective study, nevirapine Ctrough concentrations were significantly higher in HIV/HCV co-infected patients (n=9) compared to HIV monoinfected subjects (n=18): median Ctrough 5810 ng/mL vs 4826 ng/mL, respectively.*[Dragovic et al. 2007]* In a series of 51HIV-infected patients on chronic nevirapine treatment and who had various degrees of hepatic fibrosis including cirrhosis, trough plasma nevirapine concentrations were not significantly increased according to stage of fibrosis, and thus, no dose adjustment is warranted. [Cammett et al. 2009] Use nevirapine with caution in patients with impaired hepatic function. May consider empiric dosage reduction in significant hepatic dysfunction.
Adjust in Renal Failure/Dialysis	Single-dose kinetics of nevirapine were assessed in 23 subjects with mild (50 ≤Clcr<80 mL/min), moderate (30 ≤Clcr<50 mL/min) or severe (Clcr<30 mL/min) renal dysfunction or end stage renal

	disease (ESRD) requiring dialysis, as well as 8 subjects with normal renal function. Nevirapine pharmacokinetics were not changed in any category of renal impairment. Hemodialysis: In 3 HIV-positive subjects on hemodialysis taking nevirapine 200 mg BID, The geometric means of observed nevirapine Cmin were 4.77 and 4.01 mg/mL; and of systemic NVP clearance were 2.72 and 2.84 on nondialysis and dialysis days, respectively. Steady-state pharmacokinetics of NVP given 200 mg twice daily were similar to those in patients without renal failure, and only minimal differences in PK parameters between dialysis and nondialysis days were observed. No dose adjustment of nevirapine is required.[Cramer et al. JAIDS 2010] CAPD: no dosage adjustment required.
Toxicity	**Rash:** mild rash+/- pruritus (17%), severe grade3/4 rash (7%), SJS reported; fatality reported due to toxic epidermal necrolysis. Rash minimized by lead-in dosing of 200mg once daily x 14d. If rash occurs, escalation of dose to 200mg bid **should not occur** until rash resolution. Mild rash treated symptomatically with antihistamines, analgesics/NSAIDs. **Discontinue** drug if severe rash or rash with constitutional symptoms (fever, blistering, oral lesions, conjunctivitis, swelling, muscle or joint aches, lymphadenopathy, increased LFTs or general malaise), and **do not rechallenge**. Rash typically occurs within first 6 weeks of treatment. **Hepatic:** symptomatic events (4%); higher in women with CD_4 > 250 (11%) and men with CD_4 > 400 (6.3%). ~ 50% of cases accompanied by **skin rash** (± eosinophilia and systemic symptoms); may progress to fulminant hepatic failure with encephalopathy & fatal necrosis. Often presents with abrupt onset of flu-like symptoms (nausea, vomiting, fatigue, myalgias, abdominal pain, fever). May occur through 18 weeks. **Other, >5%:** fever, headache, somnolence, nausea, elevated GGT.
Pregnancy & Lactation	Nevirapine readily crosses the placenta and is found in breast milk. Nevirapine is pregnancy category C. Caution warranted (especially with CD_4 count > 250) since cases of severe and fatal hepatotoxicity often associated with rash have been reported in the first 6 weeks. Monitor closely for the first 18 weeks. Call 1-866-234-2345 to report ADRs. In a prospective pharmacokinetic study of Ugandan women receiving nevirapine-based therapy during pregnancy, intensive PK sampling was undertaken between weeks 20-24, 32-36 and six weeks post-partum. Nevirapine exposures were reduced approximately 20% during the 3rd trimester compared to post-partum. Adequate viral suppression was maintained in all patients.[Lamorde et al. 2010]
Drug Interactions	Nevirapine primarily induces enzymes of P450 3A. See NNRTI interaction chart.

Baseline Assessment	CBC/diff, LFTs, examine skin for baseline. Risk factors for hepatoxicity: higher CD4 count, female, pregnancy, elevated baseline ALT or AST, HBV or HCV co-infection, alcoholic liver, HIV (-) when used for PEP.
Routine Labs	Monitor LFTs (every 2 weeks x 1 month, then monthly x 3 months, then every 3 months). CBC/diff q3-6mo. Assess for skin rash (most common in 1st 6 weeks of therapy). **D/C drug**: LFTs >5xULN, hepatitis, severe rash or rash with constitutional symptoms (see above under toxicity).
Dosage Forms	**200mg (white) tablets** (DIN 02238748) 10mg/mL syrup; 240 mL bottle via SAP (ph: 613-941-2108) 400 mg extended release tablets (US) 200 mg tablets (generic): DIN 02318601
Storage	Store tablets and liquid at room temperature (15-30^{o}C).

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Selected Properties of Rilpivirine

Other names	Edurant®, TMC-278 Combination formulation: • Complera®: Emtricitabine/rilpivirine/tenofovir (marketed as Eviplera® in Europe)
Manufacturer	Janssen Inc.
Pharmacology/Mechanism of Action	A di-aryl-pyrimidine (DAPY) derivative NNRTI. The inherent molecular flexibility of rilpivirine relative to other NNRTIs permits the compound to retain its binding affinity to the reverse transcriptase in spite of the binding site changes induced by the presence of common NNRTI resistance mutations.
Activity	Shows high intrinsic activity against both wild-type HIV-1 and against HIV strains harboring resistance inducing mutations. Rilpivirine exhibits potent *in vitro* anti-HIV activity with an EC50 against wild-type HIV-1 of 0.5 nM, and little or no loss of activity (<5-fold reduction in susceptibility) against HIV-1 variants having key NNRTI resistance mutations. In extensive testing of more than 1500 clinical HIV-1 isolates, all exhibiting resistance to at least one currently marketed NNRTI, the EC50 of rilpivirine was below 100 nM for 95% of the isolates. In addition, the development of resistance was only seen *in vitro* when the rilpivirine concentration was very low (10 nM).
Resistance - genotypic	In mutation selection experiments using a concentration of 10 nM, virus breakthrough was observed on day 10; viruses selected contained up to eight mutations including L100I, V106I, Y181C and M230I, with a fold-change of 4.[De Bethune, 2005]
Resistance - phenotypic	In the pooled resistance analysis from the Phase 3 Studies C209 and C215 in treatment-naïve subjects, emerging NNRTI substitutions in the rilpivirine virologic failures included V90I, K101E/P/T, E138K/G, V179I/L, Y181I/C, V189I, H221Y, F227C/L and M230L, which were associated with a rilpivirine phenotypic fold change range of 2.6 - 621. The E138K substitution emerged most frequently on rilpivirine treatment commonly in combination with the M184I substitution.
Cross-Resistance	Cross-resistance has been observed among NNRTIs. The single NNRTI substitutions K101P, Y181I and Y181V conferred 52-fold, 15-fold and 12-fold decreased susceptibility to rilpivirine, respectively. The combination of E138K and M184I showed 6.7-fold reduced susceptibility to rilpivirine compared to 2.8-fold for E138K alone. The K103N substitution did not show reduced susceptibility to rilpivirine. Combinations of 2 or 3 NNRTI resistance-associated substitutions gave decreased susceptibility to rilpivirine (fold change range of 3.7 - 554) in 38% and 66% of mutants, respectively.

Oral Bioavailability	Absolute bioavailability is unknown.
Effect of Food	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.[Crauwels, 2008]
Protein Binding	99.7%
Tmax	4 hours
serum T ½	Terminal half-life of 50 hours
Drug Concentrations	In a single-dose study in healthy volunteers who received a fixed-dose tablet of emtricitabine 200 mg/rilpivirine 25 mg/tenofovir 300 mg versus the individual components, mean rilpivirine Cmax was 116 vs. 99.8 ng/mL and AUCinf was 3410 vs. 2900 ng.h/mL, respectively.[Mathias et al. 2010] Population pharmacokinetic estimates of rilpivirine 25 mg once daily in antiretroviral treatment-naïve HIV-1-infected subjects (pooled data from phase 3 trials to week 48): AUC 2204 ng.h/mL, Cmin 74 ng/mL Hepatitis B and/or C virus co-infection, gender, and race have no clinically relevant effect on the exposure to rilpivirine. Following a single 600 mg IM injection of long-acting rilpivirine in HIV-negative subjects, rilpivirine concentrations persisted in plasma for more than 84 days postdose. In females, rilpivirine cervicovaginal fluid and tissue concentrations approximated that in plasma. In males, rilpivirine concentrations in rectal tissue approximated that in plasma, while concentrations in rectal fluid were lower.[Else et al. HIVPK 2012, #O_12]
Metabolism	Metabolized primarily by CYP3A4, as well as CYP2C19, 1A2, 2C8/9/10 (minor).
Excretion	After single dose oral administration, 85% and 6.1% retrieved in feces and urine, respectively. In feces, unchanged rilpivirine accounted for on average 25% of the administered dose. Only trace amounts of unchanged rilpivirine (< 1% of dose) were detected in urine.
Dosing – Adult	Edurant® (rilpivirine 25 mg): 25 mg once daily with a meal in treatment-naïve adult patients.

	The following points should be considered when initiating therapy with rilpivirine: • More rilpivirine-treated subjects with HIV-1 RNA greater than 100,000 copies/mL at the start of therapy experienced virologic failure compared to subjects with HIV-1 RNA less than 100,000 copies/mL at the start of therapy • The observed virologic failure rate in rilpivirine treated subjects conferred a higher rate of overall treatment resistance and cross-resistance to the NNRTI class compared to efavirenz • More subjects treated with rilpivirine developed lamivudine/emtricitabine associated resistance compared to efavirenz Complera® (emtricitabine 200 mg/rilpivirine 25 mg/tenofovir 300 mg): one tablet daily with a meal.
Dosing – Pediatric	Safety and effectiveness in pediatric patients have not been established.
Adjust in Liver Dysfunction	In a study comparing 8 subjects with mild hepatic impairment (Child-Pugh score A) to 8 matched controls, and 8 subjects with moderate hepatic impairment (Child-Pugh score B) to 8 matched controls, the multiple dose exposure of rilpivirine was 47% higher in subjects with mild hepatic impairment and 5% higher in subjects with moderate hepatic impairment. No dose adjustment of rilpivirine is required in patients with mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment. Rilpivirine has not been studied in patients with severe hepatic impairment (Child-Pugh Class C).
Adjust in Renal Failure/Dialysis	Rilpivirine exposure is similar in HIV-1 infected subjects with mild renal impairment relative to HIV-1 infected subjects with normal renal function. No dose adjustment is required in patients with mild or moderate renal impairment. However, in patients with severe renal impairment or end-stage renal disease, rilpivirine should be used with caution and with increased monitoring for adverse effects, as rilpivirine concentrations may be increased due to alteration of drug absorption, distribution, and metabolism secondary to renal dysfunction. As rilpivirine is highly bound to plasma proteins, it is unlikely that it will be significantly removed by hemodialysis or peritoneal dialysis. Do not administer Complera® (emtricitabine/rilpivirine/tenofovir) in patients with creatinine clearance below 50 mL per minute.
Toxicity	Most common adverse drug reactions to rilpivirine (incidence greater than or equal to 2%, Grades 2-4) are depression, insomnia, headache and rash. In a prior thorough QT trial, rilpivirine 75mg qd and 300mg qd prolonged the QTc interval in a dose- and plasma-concentration-dependent manner. In a double-blind, placebo-controlled thorough QT trial in HIV-negative volunteers, no significant effect

	on QTcF interval was observed with rilpivirine 25mg daily or EFV 600mg daily. There was no effect of rilpivirine 25mg qd on heart rate or QTcB interval.[Vanveggel et al. EACS 2009] Rilpivirine should be used with caution when co-administered with a drug with a known risk of Torsade de Pointes. Severe depressive disorders (depressed mood, depression, dysphoria, major depression, mood altered, negative thoughts, suicide attempt, suicidal ideation) have been reported. Immediate medical evaluation is recommended for severe depressive disorders.
Pregnancy & Lactation	Pregnancy category B. Rilpivirine did not show teratogenic potential in rat and rabbit models at exposures 13- to 80-times higher than those seen in HIV-1-infected patients receiving rilpivirine 25mg daily at steady-state.[Desmidt et al. EACS 2009]. Use during pregnancy only if the potential benefit justifies the potential risk.
Drug Interactions	Metabolized primarily by CYP3A4, as well as CYP2C19, 1A2, 2C8/9/10 (minor). Moderate inducer of CYP2C19, slight inducer of CYP1A2, 2B6 and 3A4. No effect on CYP2E1 activity.[Van Heeswijk, 2007] Rilpivirine at a dose of 25 mg q.d. is not likely to have a clinically relevant effect on the exposure of medicinal products metabolised by CYP enzymes.[Crauwels, 2009] Rilpivirine is a weak substrate for the influx transporter OCT1 *in vitro*, but this is unlikely to have clinical significance. Rilpivirine is not a substrate for Pgp, OATP1A2, OATP1B1, OATP1B3, OAT1 or OAT3 *in vitro*. Rilpivirine inhibited both OCT1 and OATP1B1 *in vitro*, but inhibition was weak and unlikely to be relevant at RPV concentrations seen in patients.[Moss et al. CROI 2012] Rilpivirine plasma concentrations may be decreased if coadministered with CYP3A inducers or drugs that increase gastric pH, possibly resulting in loss of viral response and development of resistance. Rilpivirine is contraindicated with the following drugs: • Anticonvulsants (carbamazepine, oxcarbazepine, Phenobarbital, phenytoin) • Rifamycins (rifabutin, rifampin, rifapentine) • proton pump inhibitors (e.g., esomeprazole, lansoprazole, omeprazole, pantoprazole, rabeprazole) • systemic dexamethasone (more than a single dose) • St John's wort (*Hypericum perforatum*) Rilpivirine plasma concentrations may be increased if coadministered with CYP3A inhibitors. Caution should be given to prescribing with drugs that may reduce the exposure of rilpivirine.

Dosage Forms	Edurant®: 25 mg white, film-coated, round tablet, DIN 02370603. **Combination formulation:** • Complera®: Emtricitabine 200 mg/rilpivirine 25 mg/tenofovir DF 300 mg tablet, DIN 02374129.
Storage	Store tablets in the original bottle in order to protect from light. Store at 25°C (77°F), with excursions permitted to 15°-30°C (59°-86°F).

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Selected Properties of Atazanavir

Other names	BMS 232632, Reyataz®
Manufacturer	Bristol-Myers Squibb Canada
Pharmacology/Mechanism of Action	Atazanavir is an azapeptide HIV–1 protease inhibitor. The compound selectively inhibits the virus-specific processing of viral Gag and Gag-Pol polyproteins in HIV–1 infected cells, thus preventing formation of mature virions.
Activity	Atazanavir exhibits anti-HIV–1 activity with a mean 50% effective concentration (EC50) in the absence of human serum of 2-5 nM against a variety of laboratory and clinical HIV–1 isolates. Atazanavir has additive in vitro antiviral activity with the protease inhibitors (amprenavir, indinavir, lopinavir, nelfinavir, ritonavir, and saquinavir) and NRTIs (didanosine, lamivudine, stavudine, tenofovir, zalcitabine, and zidovudine) without enhanced cytotoxicity.
Resistance - genotypic	Mutations in the protease gene associated with resistance to protease inhibitors (IAS-USA Fall 2005 Resistance Mutations): Major: I50L, *I84V#,* N88S Minor: *L10I/F/V#, G16E#,* K20R/M/I, L24I, V32I, *L33I/F/V#*, M36I/L/V, *M46I/L#,* G48V, I54L/V/M/T, *D60E#*, I62V, A71V/I/T/L, G73C/S/T/A, V82A/T, *I85V#*, L90M, I93L **as major & minor mutations accumulate, susceptibility to PIs decreases* *#presence of 3 or more of these mutations predicts a reduced virologic response at 3 months, particularly when L90M is present*
Resistance - phenotypic	Phenotypic data on clinical virus isolates associated with various mutations using ViroLogic PhenoSense™ (http://hivdb.stanford.edu/): I50L: 6-fold ↑ (intermediate-to-high level resistance) I84V + L90M: 10-fold ↑ (high level resistance)
Cross-Resistance	Baseline phenotypic and genotypic analyses of clinical isolates from atazanavir clinical trials of protease inhibitor-experienced subjects indicate: • the I50L and I50V substitutions yield selective resistance to atazanavir and amprenavir, respectively, and do not appear to confer cross-resistance. • other atazanavir-resistant isolates are highly cross-resistant (51%-100%) to other protease inhibitors (amprenavir, indinavir, lopinavir, nelfinavir, ritonavir, and saquinavir). • a clear trend toward decreased atazanavir susceptibility as isolates exhibited resistance to multiple protease inhibitors.
Oral Bioavailability	Atazanavir solubility decreases as pH increases. Reduced plasma concentrations of atazanavir if antacids, buffered medications, H2-receptor antagonists, and proton-pump inhibitors are administrated with atazanavir. **Avoid**

<table>
<tr><td></td><td>concomitant use (kinetic study showed significantly reduced atazanavir exposure when coadministered with omeprazole; atazanavir absorption did not improve when given either boosted with ritonavir or with 8 oz cola).</td></tr>
<tr><td>Effect of Food</td><td>Administration of atazanavir and atazanavir/ritonavir with food enhances bioavailability (35-70% ↑ AUC) and reduces pharmacokinetic variability by 50%.(Giguere et al. 2010).</td></tr>
<tr><td>Protein Binding</td><td>86%, binds to both alpha-1-acid glycoprotein (AAG) and albumin to a similar extent (89% and 86%, respectively).</td></tr>
<tr><td>Tmax</td><td>2-2.5 hours</td></tr>
<tr><td>serum T ½</td><td>Approximately 7 hours</td></tr>
<tr><td>Drug Concentrations</td><td>Steady-state atazanavir concentrations in HIV-positive subjects after 400 mg QD administration with food:
Cmax 3152 ng/mL, Cmin 273 ng/mL, AUC 22262 ng.h/mL

Atazanavir plasma concentrations after 300/100 mg ritonavir QD: Cmax 5233 ng/mL, Cmin 862 ng/mL, AUC 53761 ng.h/mL

10 HIV positive patients on ATV 400mg daily switched to ATV 200mg BID, atazanavir kinetics assessed at baseline and after 10 days of BID regimen. Atazanavir 200mg BID led to higher plasma Ctrough, lower Cmax and similar AUC compared to standard ATV 400mg daily dose.(Bonora et al. 2008; Gonzalez de Requena, 2010.)
<table>
<tr><td>Mean plasma levels</td><td>ATV 400 mg daily (Baseline)</td><td>ATV 200 mg BID</td><td>Mean plasma GM ratios (ATV 200 BID:ATV 400 mg QD)</td></tr>
<tr><td>Ctrough</td><td>138 ng/ml</td><td>305 ng/mL</td><td>2.19</td></tr>
<tr><td>Cmax</td><td>2786 ng/ml</td><td>1314 ng/mL</td><td>0.48</td></tr>
<tr><td>AUC24h</td><td>20780 ng/ml.h</td><td>16904 ng/ml.h</td><td>0.8</td></tr>
<tr><td>Mean intracellular levels</td><td>ATV 400 mg daily (Baseline)</td><td>ATV 200 mg BID</td><td>Mean intracellular GM ratios (ATV 200 BID:ATV 400 mg QD)</td></tr>
<tr><td>Ctrough</td><td>465 ng/ml</td><td></td><td>2.93</td></tr>
<tr><td>Cmax</td><td>4058 ng/ml</td><td></td><td>1.27</td></tr>
<tr><td>AUC24h</td><td>35958 ng/ml.h</td><td></td><td>1.51</td></tr>
</table>
Increased bilirubin levels with BID regimen not clinically important. Atazanavir accumulates within the cell to a slightly greater extent versus plasma.

Open label, prospective, single center study to investigate kinetics of lower dose ATV/r. 22 Thai HIV infected adult patients suppressed on ATV/r 300mg/100mg daily were changed to 200mg/100mg daily (7 pts were also on TDF).</td></tr>
</table>

Median (+IQR)	ATV/r 300/100mg at baseline	ATV/r 200mg/100mg at day 14	p
AUC 0-12hr	65.4 mg/L.h	35.5 mg/L.h	<0.001
Cmax	6.1 mg/L	3.9 mg/L	<0.001
Cmin	1 mg/L	0.5 mg/L	<0.001

No patients had subtherapeutic levels (<0.15mg/L). (Gorowara M et al. 2008). Results of ATV/r 200/100mg daily in Thai subjects comparable to Caucasian population on standard dose (Burger et al AAC, 2006).

In 29 HIV-infected patients receiving atazanavir-based therapy (14 unboosted, 15 boosted), median intracellular atazanavir Ctrough concentrations were higher for boosted vs. unboosted atazanavir, and intracellular concentrations were higher than median plasma Ctrough:

	Unboosted ATV	Boosted ATV	p
Plasma Ctrough (ng/mL)	132 (111-184)	543 (393-1081)	
Intracellular Ctrough (ng/mL)	328 (168-440)	1032 (819-3091)	0.001
	P=0.001	P=0.005	

(Siccardi et al. 2010)

In 416 HIV-positive subjects on atazanavir-based regimens, routine atazanavir Ctrough was not significantly different between smokers (n=246) and non-/ex-smokers (n=170).[Guillemi et al. 2010]. In healthy subjects taking either atazanavir or atazanavir/ritonavir, moderate tobacco use (up to 10 cigarettes per day) was not associated with a significant difference in atazanavir pharmacokinetics.[Blonk et al. 2011]

In 18 HIV-infected women on ≥ 6 months of cART (tenofovir, emtricitabine, atazanavir, and ritonovir) with plasma viral loads < 50 copies/mL, blood and cervicovaginal samples were collected twice weekly for three weeks following menses. The ratio of cervicovaginal to plasma drug concentrations (geometric mean) was 11.6 for emtricitabine (CI 8.1-16.6), 3.18 for tenofovir (CI 1.94-5.21), 2.59 for atazanavir (CI 1.81-3.71), and 1.52 for ritonavir (CI 1.04-2.23). HIV-1 RNA was detected in 14 cervicovaginal samples (13.7%, CI 7.7%-24.1%) from 8 (44%) women; all virus-positive samples had virus loads < 500 copies/10 mL CVL.[Sheth et al. IAS 2011]

A case report of a 37 year old HIV/HCV coinfected male (60 kg) who **ingested 8700 mg atazanavir** without ritonavir; last ritonavir 100 mg dose was taken ~24 hours prior to overdose. Transient elevation in total bilirubin and Scr and asymptomatic increases in PR and QTc intervals were observed at 24-48

	hours post-overdose; values returned to baseline at one-month follow-up. Atazanavir plasma concentrations were 5400 ng/mL and 594 ng/mL at 22 and 62 hours post-overdose.[Toy et al. 2012]
Minimum target trough concentrations (for wildtype virus)	Median wild-type EC90 = 14 ng/mL Suggested minimum trough: 150 ng/mL.
CSF (% of serum)	In 4 HIV-positive subjects dosed with atazanavir 400 mg QD for 12 weeks, the cerebrospinal fluid/plasma ratio ranged between 0.0021 and 0.0226. In 26 participants receiving atazanavir 300/ritonavir 100 mg QD, ATV concentrations in the CSF were highly variable, and were 100-fold lower than plasma concentrations. 17 (65%) CSF samples were >11 ng/mL (ATV IC50 for WT) [Best et al. CROI 2006]. 2010 CNS Penetration Effectiveness (CPE) Score: 2 (boosted and unboosted atazanavir) [Letendre S et al. 2010]
Metabolism	Extensively metabolized by CYP3A4. Atazanavir inhibits CYP3A and UGT1A1 at clinically relevant concentrations. Atazanavir is a weak inhibitor of CYP2C8. Atazanavir does not inhibit CYP2C19 or CYP2E1 at clinically relevant concentrations.
Excretion	Approximately 7% excreted unchanged in the urine. 47 HIV-positive patients treated with ATV containing regimens were tested to determine if ABCB1 and CYP3A5 polymorphisms are associated with ATV concentrations and/or immunological responses. • ABCB1 haplotype (3435CT-2677GT) was significantly associated with faster ATV oral clearance than 3435CC-2677GG (mean 12.79 VS 7.3L/hr, p=0.018). Trend for ↑ clearance observed in C3435T and G2677T variant carriers • Mean CD4 counts were 375 for ABCB1 2677GG and 547 for 2677GT (p=0.036) • No relationships were identified with CYP 3A5 Authors state these pilot data provide rationale for the development of individualized ATV regimens [Ma et al. ICAAC 2007].
Dosing – Adult	Atazanavir 300 mg/ritonavir 100 mg once daily with food; for treatment-naïve individuals who cannot tolerate ritonavir, atazanavir 400 mg once daily with food may be used. If taken with efavirenz or tenofovir: atazanavir 300 mg /day + ritonavir 100 mg/day.
Dosing – Pediatric	Should not be administered to infants < 3 months due to risk of kernicterus (a type of brain damage caused by excessive levels of bilirubin). The recommended dosage of atazanavir for pediatric patients (6 to less than 18 years of age) is based on body weight and should not exceed the recommended adult dosage. Atazanavir

	capsules must be taken with food. Therapy-naïve patients: • 15 kg to less than 20 kg: atazanavir 8.5 mg/kg with ritonavir 4 mg/kg once daily with food. • at least 20 kg: atazanavir 7 mg/kg with ritonavir 4 mg/kg once daily with food not to exceed atazanavir 300 mg and ritonavir 100 mg Therapy-experienced patients: • atazanavir 7 mg/kg with ritonavir 4 mg/kg once daily with food not to exceed atazanavir 300 mg and ritonavir 100 mg
Special instructions for pediatric patients	Investigational oral powder used in trials. Powder may be mixed with small amount of water, applesauce, milk, or yogurt (consume within 3 hours of mixing). Do not mix with juices or foods with high pH. In an open label, multicentre study of atazanavir and atazanavir/ritonavir in children 91 days-21 years, the pharmacokinetics of atazanavir capsules and atazanavir orange-vanilla flavoured powder were studied. Day 7 atazanavir kinetics were compared in children of similar age receiving powder vs. capsules; the powder was found to be 40% less bioavailable at the same BSA-based dose. Therefore, suggest converting from powder to capsule by multiplying the powder dose by 0.6 and rounding up to the nearest 50 mg.[Kiser J et al. 2011] **Atazanavir capsules** may be opened and the contents mixed with applesauce for immediate ingestion with a light meal. In-house study showed that the bioavailability of the contents of two 200-mg atazanavir capsules mixed with applesauce was 91.7% relative to atazanavir capsules taken intact. In addition, administration of the contents of two 200-mg capsules was well tolerated (Bristol Myers Squibb, Personal Communication, October 22, 2008).
Adjust in Liver Dysfunction	In adults with moderate to severe hepatic impairment (Child-Pugh B and C), mean atazanavir AUC after a single 400 mg dose was 42% greater than in healthy volunteers, while the mean half-life was 12.1 hours compared to 6.4 hours. The following dosage adjustments are recommended: Child-Pugh Score 7-9: 300 mg QD Child-Pugh score >9: not recommended In a cohort of HIV/HCV coinfected patients on stable atazanavir 400 mg QD, median atazanavir Ctrough was 0.60 ug/mL vs. 0.24 ug/mL in HIV+/HCV- patients, p<0.001. Median atazanavir Ctrough with ATV 300/rtv 100 mg QD was not statistically different between the groups (0.70 vs. 0.73 ug/mL, respectively).[Regazzi et al. 2009]
Adjust in Renal Failure/Dialysis	In an open-label study in HIV-negative participants, steady-state kinetics of atazanavir 400 mg QD were compared between renally impaired (Clcr<30 mL/min) and non-renally impaired (Clcr>80 mL/min) subjects. Compared to controls, atazanavir

	AUC ↑ 19% and Cmin ↑ 96% in the renally impaired group. No dosage adjustment of atazanavir is necessary in renal impairment not managed with hemodialysis.[Agarwala et al. 2007] In subjects on hemodialysis, atazanavir exposures were ↓ 25-40% compared to non-renally impaired controls; atazanavir exposures were decreased independent of time of administration in relation to dialysis. Atazanavir dialysis clearance was low, with 2.1% of the administered dose eliminated over a 4 hour dialysis period. May wish to consider boosted atazanavir (300 mg/ritonavir 100 mg QD) in hemodialysis patients.[Agarwala et al. 2007]
Toxicity	Skin rash (21%), < 1% severe rash; asymptomatic indirect hyperbilirubinemia (30%), jaundice (10%), headache, fever, arthralgias, depression, insomnia, dizziness, nausea/vomiting/diarrhea, paresthesias, prolongation of PR interval of EKG. Protease class effects include: hyperlipidemia & hypertriglyceridemia (except atazanavir), hyperglycemia, fat maldistribution, weight gain, increase in LFTs, hepatitis, increased bleeding in hemophiliacs, osteonecrosis. Kidney Stones (uncommon) • American Reports: 30 cases ATV associated nephrolithiasis recorded between Dec 2002 to Jan 2007 in the US FDA Adverse Event Reporting System Database (Voluntary reporting) • French Case Series: 11/1134 patients developed ATV nephrolithiasis (Mar 2004 – Feb 2007). 4 pts had history of kidney stones before ATV exposure. Mean onset for ADR ~ 23 months. 1/6 patients that were kept on ATV developed recurrent kidney stones despite instructions to drink more fluids, including acidic beverages such as cola. • Reports suggest kidney stones composed of 60-100% ATV crystals • Exact mechanism for ADR is unknown. • 7% of the ATV dose is excreted unchanged in the urine. Like IDV, the solubility of ATV is increased in acid fluids Risk Factors: not drinking enough fluid, having urine that is not acidic, having a history of kidney stones. A case report of a 37 year old HIV/HCV coinfected male (60 kg) who ingested 8700 mg atazanavir without ritonavir; last ritonavir 100 mg dose was taken ~24 hours prior to overdose. Transient elevation in total bilirubin and Scr and asymptomatic increases in PR and QTc intervals were observed at 24-48 hours post-overdose; values returned to baseline at one-month follow-up. Atazanavir plasma concentrations were 5400 ng/mL and 594 ng/mL at 22 and 62 hours post-overdose.[Toy et al. 2012]
Pregnancy & Lactation	Pregnancy risk category B. No experience in human pregnancy. Theoretical risk with indirect hyperbilirubinemia which may be

	additive with neonatal elevations in bilirubin. Placental passage unknown, however it has been low with other PIs. Atazanavir exceeded the IC50wt in plasma, breast milk and vaginal secretions. Median percentage of plasma concentrations was 7.3% (day 5 breast milk), 7.9% (day 14 breast milk) and 4.8% (vaginal secretions).[Neely et al. 2009] In 6 HIV-infected pregnant women receiving atazanavir (all VL<40 copies/mL at delivery), mean atazanavir cord:mother blood concentration ratio was 0.18 (SD +/- 0.11); cord blood concentrations were below cut-off values in 2 (33.3%) of samples. Mean amniotic fluid:maternal plasma ratio for lopinavir was 0.25. Undetectable viral load was found in amniotic fluid and cord blood.[Ivanovic et al. 2010]. In a prospective study of atazanavir PK in pregnancy (with or without tenofovir), women received ATV 300/100 mg QD during the 2nd trimester, ATV 400/100 mg QD during the 3rd trimester, and 300/100 mg QD post-partum. Atazanavir exposures were low in the 2nd trimester but improved in the 3rd trimester with the dose increase. The median ATV cord blood concentration was 0.22 ug/mL and median cord blood:maternal plasma ratio was 0.18. ATV 400/100 mg QD provides adequate ATV exposure during the 3rd trimester and should be considered during the 2nd trimester as well.[Mirochnick et al. 2011]
Drug Interactions	Avoid concomitant administration with antacids, proton-pump inhibitors, or H2-blockers, as atazanavir absorption is significantly compromised. Atazanavir is an inhibitor of CYP3A and UGT1A1. Atazanavir is a weak inhibitor of CYP2C8. With boosted atazanavir, ritonavir appears to induce CYP2C8 and offset inhibition by ATV.(Sevinsky et al. 2008) See separate Drug Interaction Table for more information.
Baseline Assessment	Assess risk factors for diabetes, coronary artery disease (less with ATV), osteonecrosis (i.e. steroids, ETOH, diabetes, hyperlipidemia), and hepatic dysfunction (i.e. HBV/HCV, ETOH use). CBC/diff, LFTs, glucose, fasting cholesterol profile.
Routine Labs	CBC/diff, LFTs, glucose q 3 mos. Fasting lipids (8-12 hr level) q 3-6 months post-therapy, then annually. If TG > 2.3 mmol/L at baseline, repeat after 1-2 months.
Dosage Forms	*100 mg capsules (blue/white) available in U.S.* 150 mg capsules (blue/powder blue); DIN 02248610 200 mg capsules (blue/blue); DIN 02248611 300 mg capsules (blue/red); DIN 02294176
Storage	Store at room temperature.

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Selected Properties of Darunavir

Other names	Prezista®, TMC-114
Manufacturer	Janssen Inc.
Pharmacology/Mechanism of Action	Protease inhibitor with potent in vitro activity against both wild-type HIV-1 and a large panel of viruses resistant to currently licensed PIs. Is a sulfonamide; to date, no cross-sensitivity observed in subjects with sulfonamide allergy. Molecular weight: 547.656 (active moiety), 593.724 (TMC114-ethanolate)
Activity	In vitro EC_{50} 4.2 nM (2.5 ng/mL), EC_{90} 10 nM (5.5 ng/mL). Comparative EC50 values were found against WT-HIV1 and multi-PI-resistant primary isolates. The EC50 value of darunavir increases by a median factor of 5.4 in the presence of human serum. EC50WT is approximately 55 ng/mL.
Resistance - genotypic	Resistance data are preliminary and limited. Reductions in response are associated with increasing numbers of the following mutations: V11I, V32I, L33F, I47V, I50V, I54M/L, G73S, L76V, I84V, L89V. Some of these mutations appear to have a greater effect on susceptibility than others (e.g., I50V versus V11I).
Oral Bioavailability	Absolute oral bioavailability: 37% (alone) and 82% (after coadministration with ritonavir 100 mg BID) Oral suspension for pediatric use (100 mg/mL) is under development [Sekar et al. ICAAC 2009]. When coadministered with low-dose ritonavir, exposures comparable to that of darunavir tablets are noted.
Effect of Food	Bioavailability ↑ 30% 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. Oral suspension for pediatric use (100 mg/mL) is under development [Sekar et al. ICAAC 2009]. Bioavailability of the suspension is similar with or without food.
Protein Binding	95% (humans), primarily alpha-1-acid glycoprotein
Tmax	2.5-4 hours when given fed with ritonavir 100 mg BID
serum T ½	~ 15 hours when combined with ritonavir. 10.9-17.2 hours for various dosing regimens; ritonavir did not influence t1/2.
Drug Concentrations	400/100 mg BID with food for 7 days: • C12: 2038 +/- 607 ng/mL, AUC 33511 +/- 9540 ng.h/mL, Cmax 3913 +/- 873 ng/mL 800/100 mg BID with food for 7 days: • C12: 3239 +/- 2297 ng/mL, AUC 48243 +/- 22605 ng.h/mL,

	Cmax 5736 +/- 1879 ng/mL Darunavir 800mg/100mg daily X 7 days: conc remained above the protein-binding corrected in-vitro EC50 55ng/ml for ≥ 48 hours in healthy volunteers after last dose was administered (Boffito et al. 2008). Expanded Access Program Data (146 samples from 30 subjects): • Median DRV Ctrough: 3668 ng/ml • Interpatient CV: 30.7% (comparable previous data for other boosted PIs) • Intrapatient CV: 30.8% (lower than previous data for other boosted PIs) • Age, weight, BMI was not associated with DRV Ctrough HCV/HBV coinfection may potentially increase DRV/r conc (See dosing in hepatic dysfunction). Based on PK sampling data from the GRACE study, exposure to darunavir was not influenced by age, body weight, hepatitis B co-infection status, or use of etravirine or tenofovir. There were no clinically relevant differences in exposure to darunavir according to race or gender.(Kakuda et al. 2010) In healthy volunteers (n=23) who had previously participated in a pravastatin-darunavir/ritonavir interaction study, CYP3A5 and ABCB1 polymorphisms were not associated with variability in darunavir/ritonavir pharmacokinetics.(Torres et al. 2011) Darunavir concentrations were compared in 34 time-matched blood plasma and seminal plasma samples from 18 HIV-positive men. Good penetration of darunavir into the seminal fluid was observed, with concentrations approximately 10-20% of blood plasma levels. All seminal plasma darunavir were above the protein-corrected EC50 values for wild-type HIV-1 (55 ng/mL), and a third of all seminal plasma darunavir levels exceeded the protein-corrected EC50 required to inhibit protease inhibitor resistant HIV-1 (550 ng/mL).(Taylor et al. 2010) Intracellular darunavir concentrations are approximately 5-times higher than plasma concentrations, and are significantly correlated with plasma ritonavir exposures.(Dickinson et al. 2011) In a cross-sectional TDM database review of non-pregnant HIV-infected adults taking darunavir 800/100 mg QD, darunavir C24h obtained after morning dosing were significantly higher than those after evening dosing (1632 vs 1433 ng/mL, respectively, $p<0.0001$). The difference was more pronounced in women vs. men. Findings may represent Circadian variation in hepatic CYP3A4, intestinal P-gp and gastrointestinal mobility.[Ocadiz et al. 2012]

<table>
<tr><td></td><td>Bioequivalence demonstrated with 800 mg darunavir tablet to two 400 mg darunavir tablets, both given with ritonavir 100 mg.[Kakuda et al. 2012]</td></tr>
<tr><td>CSF (% of serum)</td><td>In 16 HIV-positive patients, darunavir concentrations were measured in matched CSF and plasma samples. Darunavir was present in all CSF with a median level of 56.9 ng/mL (IQR 39.6, 81.4). Median CSF-to-plasma ratio was 1.4% (IQR 0.9%, 1.8%) for total darunavir and 9.4% for unbound darunavir (IQR 6.8%, 14.2%) (z = 0.57, p > 0.10). Darunavir concentrations in CSF exceeded the IC50 of wild-type HIV in all specimens by a median of 20.7-fold (IQR 14.4, 29.6).[Letendre S et al. ICAAC 2009]

CSF darunavir and ritonavir concentrations were compared in HIV-infected patients receiving darunavir/ritonavir 800/100mg once daily vs 600/100mg twice daily. HIV-infected patients on once-daily darunavir/ritonavir had significantly lower CSF darunavir trough concentrations and CSF-to-plasma ratios than patients on darunavir/ritonavir twice-daily (10.7 versus 38.2ng/ml and 0.32 versus 0.90%; P<0.05). No significant effect of single-nucleotide polymorphisms in the genes encoding for blood–brain barrier transporters was noted apart from slightly higher CSF darunavir penetration in patients carrying OATP1A2 uncommon variants.[Calcagno et al. 2012]

2010 CNS Penetration Effectiveness (CPE) Score: 3 [Letendre S et al. 2010]</td></tr>
<tr><td>Metabolism</td><td>Substrate and inhibitor of CYP3A4.</td></tr>
<tr><td>Excretion</td><td>After single dose administration of darunavir 400/ritonavir 100 mg, 79.5% and 13.9% of the administered dose of ^{14}C-darunavir was recovered in the feces and urine, respectively.</td></tr>
<tr><td>Dosing – Adult</td><td>For treatment-experienced patients: 600/100 mg ritonavir po BID with food.

For treatment naïve patients: 800/100mg ritonavir po once daily with food.</td></tr>
<tr><td>Dosing – Pediatric</td><td>(age 6 to < 18 years):
Table 1: Recommended Dose for Pediatric Patients (6 to < 18 years of age) for Prezista Tablets with ritonavir
<table><tr><th colspan="2">Body Weight</th><th>Dose</th></tr><tr><th>(kg)</th><th>(lbs)</th><th></th></tr><tr><td>≥ 20 kg – < 30 kg</td><td>≥ 44 lbs – < 66 lbs</td><td>375 mg PREZISTA/50 mg ritonavir twice daily</td></tr><tr><td>≥ 30 kg – < 40 kg</td><td>≥ 66 lbs – < 88 lbs</td><td>450 mg PREZISTA/60 mg ritonavir twice daily</td></tr><tr><td>≥ 40 kg</td><td>≥ 88 lbs</td><td>600 mg PREZISTA/100 mg ritonavir twice daily</td></tr></table>The safety and efficacy of PREZISTA/rtv in pediatric patients</td></tr>
</table>

	3 to < 6 years of age have not been established. Darunavir should not be used in pediatric patients below 3 years of aged in view of the toxicity and mortality observed in juvenile rats observed up to post natal day 26.
Special instructions for pediatric patients	No pharmacokinetic data are available on chewing or crushing of PREZISTA film-coated tablets. However, since the tablets are not formulated as an extended release formulation, no potential problem is anticipated if the tablets are chewed or crushed for administration through a nasogastric (NG) tube. It is unlikely that chewing or crushing PREZISTA tablets would have a significant impact on pharmacokinetics (Data on File, Tibotec, November 2006). In two patients, one with dysphagia and Candida esophagitis and one with a stomach tube, who received darunavir tablets crushed and dissolved and administered with ritonavir oral solution, adequate plasma darunavir levels were achieved along with good virologic response.(Scholten et al. 2010)
Adjust in Liver Dysfunction	The pharmacokinetics and safety of darunavir 600 mg/ritonavir 100 mg BID for 7 days was assessed in HIV-negative volunteers with mild (Child-Pugh class A, n=8) and moderate (Child Pugh class B, n=8) hepatic impairment and compared with HIV-negative, healthy control volunteers (n=16). There were no differences in levels of either drug in subjects with mild hepatic impairment and controls (least square mean (LSM) ratios (90% confidence intervals) for DRV exposure (AUC_{12h}), maximum (C_{max}) and minimum (C_{min}) plasma concentrations were 0.94 (0.75–1.17), 0.88 (0.73–1.07) and 0.83 (0.63–1.10), respectively). In those with moderate hepatic impairment there was approximately 20% increase in AUC for DRV, and levels of RTV were increased approximately 50% compared to healthy controls but neither increase was considered clinically significant. In conclusion, no dose adjustments of DRV/r are needed in individuals with mild or moderate liver impairment.[1] In an open-label observational study of 11 HIV+ and 13 HIV/hepatitis B or C (Child Pugh score <6) receiving darunavir/ritonavir 600/100 mg BID, no significant association between extent of liver fibrosis and darunavir kinetics was observed. Median darunavir AUC12 was 41.7 mg.h/L in HIV+/HEP+ vs. 42.6 in HIV+ patients, p=0649. Median darunavir Ctrough was 2.7 mg/L and 2.0, respectively, p=0.776.[Molto et al. 2009]. The kinetics of raltegravir and darunavir were studied in five HIV-HCV co-infected patients with moderate to severe hepatic impairment (2 with chronic active hepatitis, 3 with cirrhosis).

	Plasma Ctrough samples were collected at days 14 and 30 after this new regimen was initiated; 24 matched HIV-1 patients with normal liver function treated with raltegravir and darunavir were used as a control group. Mean darunavir Ctrough was 8519 vs. 3236 ng/mL in controls. Mean darunavir Ctrough was consistently higher in cirrhotic vs. non-cirrhotic patients (9820 vs. 2016 ng/mL, respectively). No differences in viral/immunologic outcome or safety parameters were found between cirrhotic and non-cirrhotic patients. Use darunavir with caution in patients with moderate to severe liver impairment because of the risk of additive toxicity.(Tommasi et al. 2010) Kinetics of darunavir 800/100 mg QD and 600/100 mg BID in HIV-HCV coinfected patients with hepatic cirrhosis (74% Child-Pugh A, median MELD score 9), total serum unbound darunavir concentrations were similar to historical data in non-cirrhotic patients.[Curran et al. HIVPK 2012, #O_16]
Adjust in Renal Failure/Dialysis	Population pharmacokinetic analysis in HIV-infected subjects (n=20) with moderate renal impairment (Clcr 30-60 mL/min) showed that darunavir pharmacokinetics were not significantly affected. There are currently no pharmacokinetic data of darunavir in HIV-infected subjects with severe renal impairment or endstage renal disease; however a significant increase in darunavir would not be expected in such subjects, due to the limited renal clearance of darunavir. Antiretroviral pharmacokinetics were studied in a 49-year old HIV-positive man virologically suppressed on darunavir/ritonavir 600/100 mg twice daily, etravirine 200 mg twice daily and raltegravir 400 mg twice daily while undergoing hemodialysis three times weekly. The morning dose of the antiretrovirals was taken after completion of the 4-hour morning hemodialysis session. After dialysis, darunavir, etravirine, raltegravir and ritonavir concentrations were decreased by 57%, 29%, 82% and 60%, respectively compared to predialysis levels. A supplemental dose of 600 mg darunavir administered prior to the hemodialysis session was successful in restoring darunavir concentrations approximately equal to expected levels, while administration of a supplemental dose of raltegravir 400 mg was not, likely due to wide intra- and inter-patient variability. Dose supplementation of etravirine was not deemed necessary given the relatively low amount removed during hemodialysis. After 1 year of therapy, the patient maintained viral suppression.[Giguere et al. 2009] An HIV-positive patient on continuous venovenous hemodiafiltration (CVVHDF) received raltegravir 400 mg BID, darunavir 600/100 mg BID, zidovudine 300 mg BID and 3TC 50 mg q24h in suspension via gastric port and simultaneous enteral feeding via the duodenal port of a double-lumen nasogastroduodenal tube. Pharmacokinetic sampling and analysis indicated that darunavir and raltegravir were removed

	by CVVHDF with approximately the same clearance as provided by a normally functioning kidney. Absorption of both drugs after suspension and application via the gastric port with continued administration of feed via the duodenal port of the double-lumen tube was good. As such, **dose adjustments are not required for patients receiving darunavir and/or raltegravir while undergoing CVVHDF** and that absorption of darunavir and raltegravir is not significantly affected by postpyloric enteral feeding.[Taegtmeyer et al. 2011]
Toxicity	Darunavir contains a sulfonamide moiety. Use with caution in patients with a **known sulfonamide allergy**. The potential for cross-sensitivity between darunavir and the sulfonamide class is unknown. **Drug-induced hepatitis** (e.g., acute hepatitis, cytolytic hepatitis) has been reported with darunavir/rtv (0.5% in clinical development program, n=3063). Patients with preexisting liver dysfunction, including chronic active hepatitis B or C, have an increased risk for liver function abnormalities including severe hepatic adverse events. Postmarketing cases of liver injury, including some fatalities, have been reported. These have generally occurred in patients with advanced HIV1 disease taking multiple concomitant medications, having comorbidities including hepatitis B or C coinfection, and/or developing immune reconstitution syndrome. A causal relationship with darunavir/rtv therapy has not been established. If there is evidence of new or worsening liver dysfunction (including clinically significant elevation of liver enzymes and/or symptoms such as fatigue, anorexia, nausea, jaundice, dark urine, liver tenderness, hepatomegaly) in patients on darunavir/rtv, interruption or discontinuation of treatment must be considered."
Pregnancy & Lactation	Pregnancy category C. Use during pregnancy only if the potential benefit justifies the potential risk. In 2 HIV-infected pregnant women receiving darunavir/ritonavir (all VL<40 copies/mL at delivery), mean darunavir cord:mother blood concentration ratio was 0.11 (SD +/- 0.01); cord blood concentrations were below cut-off values in both samples. Mean amniotic fluid:maternal plasma ratio for darunavir was 0.16. Undetectable viral load was found in amniotic fluid and cord blood.[Ivanovic et al. 2010a]. In a treatment-naïve pregnant woman, darunavir 800/100 mg QD plus tenofovir/emtricitabine once daily was well-tolerated and resulted in undetectable viral load throughout the pregnancy. Darunavir concentrations were measured in pregnancy and post-partum. At week 21, darunavir Ctrough was 1877 ng/ml, and at week 37, darunavir Ctrough was 1407

	ng/mL. Calculated cord blood, amniotic and cervicovaginal fluid to mother plasma ratios were 0.11, 0.24 and 0.09, respectively.[Ivanovic et al. 2010b].
Drug Interactions	May be coadministered with omeprazole or ranitidine. Darunavir is an inhibitor of CYP3A4. Darunavir/r may induce CYP2C9, 2C19. Darunavir/r may possibly inhibit CYP2D6. See separate Drug Interaction Table.
Baseline Assessment	Appropriate laboratory testing of hepatic parameters should be conducted prior to initiating therapy with PREZISTA/rtv and patients should be monitored during treatment.
Routine Labs	Increased AST/ALT monitoring should be considered in patients with underlying chronic hepatitis, cirrhosis, or in patients who have pretreatment elevations of transaminases, especially during the first several months of PREZISTA/rtv treatment.
Dosage Forms	300 mg (orange) tablets, DIN 02284057 400 mg (light orange) tablets, DIN 02324057 600 mg (orange) tablets, DIN 02324024 75 mg (white) tablets, DIN 02338432 100 mg/mL oral suspension (available in U.S.)
Storage	Store tablets between 15-30C.

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Torres R, Anderson P, Kiser J, et al. No influence of CYP3A5 and ABCB1 polymorphisms on darunavir and ritonavir pharmacokinetics in HIV-negative Caucasian volunteers [abstract P_21]. 12th International Workshop on Clinical Pharmacology of HIV Therapy. New Orleans, USA, April 13-15, 2011.

Selected Properties of Fosamprenavir

Other names	Telzir®, Lexiva® (US), GW433-908
Manufacturer	ViiV Healthcare ULC
Pharmacology/Mechanism of Action	HIV aspartic protease is critical in the post-translational processing of the polyprotein products of gag and gag-pol genes into the functional core proteins and viral enzymes. Inhibition of viral protease prevents cleavage of the gag-pol polyprotein thus producing immature, non-infectious virions.
Activity	IC_{90}: 0.08 uM (in vitro) Highly specific for HIV-1 and HIV-2 *in vitro* – synergistic with ZDV, ABC, ddI, SQV; additive activity with IDV and RTV
Resistance - genotypic	Mutations in the protease gene associated with resistance to protease inhibitors (IAS-USA Fall 2005 Resistance Mutations): Major: I50V, I84V Minor: L10F/I/R/V, V32I, M46I/L, I47V, I54L/V/M, G73S, V82A/F/S/T, L90M **as major & minor mutations accumulate, susceptibility to PIs decreases*
Resistance - phenotypic	Phenotypic data on clinical virus isolates associated with various mutations using ViroLogic PhenoSense™ (http://hivdb.stanford.edu/): I50V: 8-fold ↑ (intermediate-to-high-level resistance) I84V: 3.9-fold ↑ (clinical resistance)
Cross-Resistance	*In vitro,* amprenavir-resistant isolates are highly susceptible to indinavir, saquinavir, and nelfinavir, but show reduced susceptibility to ritonavir. The principal protease mutation associated with cross-resistance to amprenavir following treatment failure with other protease inhibitors was I84V, particularly when mutations L10I/V/F were also present.
Oral Bioavailability	Fosamprenavir is a prodrug that is rapidly hydrolyzed to amprenavir via enzymes in the gut epithelium. The absolute bioavailability of amprenavir has not been determined in humans.
Effect of Food	**Tablets:** May be taken with or without food. A high fat meal (967 kcal, 67 grams fat, 33 grams protein, 58 grams carbohydrate) had no significant effect on standard amprenavir kinetic parameters. **Oral suspension: Take on an empty stomach.** Administration of the fosamprenavir calcium oral suspension formulation with a high fat meal reduced plasma amprenavir AUC by approximately 25% and Cmax by approximately 40% as compared to the fasted state. NB: U.S. product monograph states that adults should take the oral suspension without food; pediatric patients should take the suspension with food.
Protein Binding	~90% plasma protein bound (mainly AAG)

Vd	~430L in healthy adults or approximately 6 L/kg, with penetration freely into tissues beyond the systemic circulation (amprenavir). This value decreases approximately 40% when fosamprenavir is coadministered with ritonavir, most likely due to an increase in amprenavir bioavailability.
Tmax	1.5-4 hours (median 2.5 hours)
serum T ½	7.7 hours
Drug Concentrations	Median steady-state plasma amprenavir pharmacokinetic values: • 1400 mg BID dosing : Cmax 4.82 ug/mL, Cmin 0.35 ug/mL, AUC_{24} 33 ug.h/mL • 1400 mg QD/ritonavir 200 mg QD dosing: Cmax 7.24 ug/mL, Cmin 1.45 ug/mL, AUC_{24} 69.4 ug.h/mL • 700 mg BID/ritonavir 100 mg BID dosing: Cmax 6.08 ug/mL, Cmin 2.12 ug/mL, AUC_{24} 79.2 ug.h/mL In a retrospective analysis of 15 HIV/HCV coinfected patients without cirrhosis receiving fosamprenavir 1400 mg BID, mean amprenavir AUC12 was 35.3 mg.h/L, mean Ctrough 1.2 mg/L.[Barbarini G et al. 2009]
Minimum target trough concentrations (for wildtype virus)	0.4 mg/mL (unboosted amprenavir)
CSF (% of serum)	CSF/Plasma ratio: 0.45 – 1.30% (3 patients) (amprenavir) In 43 HIV-infected subjects on fosamprenavir regimens with matched CSF & plasma samples, amprenavir was present in all CSF samples, median 24 ng/mL. The median amprenavir CSF:plasma ratio was 0.013. CSF concentrations were not significantly different between those taking FPV/r vs. FPV (41 vs. 12 ng/mL, p=0.10). Amprenavir CSF concentrations >IC_{50}wt (5.6 ng/mL) in 42/43 samples by median 4.3 fold (IQR 2.9-7.8). Therefore, amprenavir is present in CSF at sufficiently high levels to inhibit wild-type HIV.[Letendre et al. 2009] 2010 CNS Penetration Effectiveness (CPE) Score: 3 (boosted fosamprenavir), 2 (unboosted fosamprenavir) [Letendre S et al. 2010]
Metabolism	Primarily metabolized by CYP3A4. Inhibitor of CYP3A4 (similar potency as indinavir and nelfinavir). Data also suggest that amprenavir induces CYP3A4. Amprenavir does not inhibit CYP2D6, CYP1A2, CYP2C9, CYP2C19, CYP2E1, or uridine glucuronosyltransferase (UDPGT).
Excretion	Primarily hepatic metabolized. Excretion via biliary route.
Dosing – Adult	PI-Naïve subjects: • **700 mg/100 mg ritonavir po BID** • **1400 mg/200 mg ritonavir po QD** • **1400 mg/100 mg ritonavir po QD (US monograph)** • **1400 mg BID (U.S. monograph only)** PI-Experienced subjects:

<table>
<tr><td></td><td>

- **700 mg/100 mg ritonavir po BID**

</td></tr>
<tr><td>Dosing – Pediatric</td><td>
Canadian monograph information:
Children (< 12 years of age) and Adolescents (12 to 18 years of age):
The safety and efficacy of TELZIR® in combination with ritonavir have not yet been established in these patient populations.

American monograph information:
Pediatric Patients (≥4 weeks to 18 years of age):
The dosage of Lexiva should be calculated based on body weight (kg) and not exceed the recommended adult dose.

Twice daily dosage regimens by weight with ritonavir are as follows:
• for protease inhibitor-naïve pediatric patients (≥4 weeks of age) and
• for protease inhibitor-experienced pediatric patients ≥6 months of age. (Lexiva plus ritonavir is not recommended for protease inhibitor experienced pediatric patients less than 6 month of age.)

<table>
<tr><th>Body weight</th><th>BID Dosing</th></tr>
<tr><td><11 kg:</td><td>Lexiva 45 mg/kg plus ritonavir 7 mg/kg</td></tr>
<tr><td>11 kg to <15 kg:</td><td>Lexiva 30 mg/kg plus ritonavir 3 mg/kg</td></tr>
<tr><td>15 kg to <20 kg:</td><td>Lexiva 23 mg/kg plus ritonavir 3 mg/kg</td></tr>
<tr><td>≥20 kg:</td><td>Lexiva 18 mg/kg plus ritonavir 3 mg/kg</td></tr>
</table>
</td></tr>
<tr><td>Special instructions for pediatric patients</td><td>
U.S. product monograph states that pediatric patients should take the suspension with food.

Fosamprenavir should only be administered to infants born at 38 weeks gestation or greater and who have attained a post-natal age of 28 days.

Alternatively, protease inhibitor naïve children 2 years of age and older can be administered Lexiva (without ritonavir) 30 mg/kg twice daily.

American monograph information:

For pediatric patients, pharmacokinetic and clinical data:

• do not support once-daily dosing of LEXIVA alone or in combination with ritonavir

• do not support administration of LEXIVA alone or in combination with ritonavir for protease inhibitor-experienced children younger than 6 months of age

• do not support twice-daily dosing of LEXIVA without ritonavir in pediatric patients younger than 2 years of age
</td></tr>
<tr><td>Adjust in Liver Dysfunction</td><td>The following dose reductions are recommended:
Mild Hepatic Impairment (Child-Pugh score ranging from 5 to 6):</td></tr>
</table>

	fosamprenavir should be used with caution at a reduced dosage of 700 mg twice daily without ritonavir (therapy-naive) or 700 mg twice daily plus ritonavir 100 mg once daily (therapy-naive or PI-experienced). Moderate Hepatic Impairment (Child-Pugh score ranging from 7 to 9): fosamprenavir should be used with caution at a reduced dosage of 700 mg twice daily (therapy-naive) without ritonavir, or 450 mg twice daily plus ritonavir 100 mg once daily (therapy-naive or PI-experienced). Severe Hepatic Impairment (Child-Pugh score ranging from 10 to 12): fosamprenavir should be used with caution at a reduced dosage of 350 mg twice daily without ritonavir (therapy-naive). The impact of mild, moderate and severe hepatic impairment on the pharmacokinetics of fosamprenavir/ritonavir in HIV-infected subjects was investigated. Subjects with normal hepatic function received fosamprenavir 700 mg/ritonavir 100 mg BID, while subjects with hepatic impairment received modified doses. In subjects with ***mild hepatic impairment***, fosamprenavir 700 mg BID plus ritonavir 100 mg QD resulted in 17% ↑ Cmax, 22% ↑ AUC, similar Ctau of amprenavir compared to subjects with normal hepatic function. In subjects with ***moderate hepatic impairment***, fosamprenavir 300 mg BID plus ritonavir 100 mg QD yielded 27% ↓ Cmax and AUC, 57% ↓ Ctau of amprenavir. In subjects with ***severe hepatic impairment***, fosamprenavir 300 mg BID plus ritonavir 100 mg QD yielded 19% ↓ Cmax, 23% ↓ AUC, 38% ↓ Ctau of amprenavir. No significant safety issues were identified, but plasma amprenavir and ritonavir concentrations were more variable in subjects with impaired hepatic function.[Pérez-Elías et al. 2009]
Adjust in Renal Failure/Dialysis	Dosage adjustment not required.
Toxicity	rash 19% (SJS < 1%), diarrhea, nausea, vomiting, headache, perioral tingling/numbness, hemolytic anemia (rare). **Other:** Protease class effects include: hyperlipidemia, hypertriglyceridemia, hyperglycemia, fat maldistribution, weight gain, increase in LFTs, hepatitis, increased bleeding in hemophiliacs, osteonecrosis. **Warning:** As amprenavir is a sulfonamide, there is potential for cross sensitivity in people with sulfonamide allergies.
Pregnancy & Lactation	Pregnancy risk category C. Not recommended due to lack of human data in pregnancy. In 2 HIV-infected pregnant women receiving fosamprenavir (all VL<40 copies/mL at delivery), mean fosamprenavir cord:mother blood concentration ratio was 0.21 (SD +/- 0.01); cord blood concentrations were below cut-off values in both samples. Undetectable viral load was found in amniotic fluid and cord blood.[Ivanovic et al. 2010].
Drug Interactions	Amprenavir is an inhibitor of CYP3A4. See separate Drug Interaction Table.
Baseline Assessment	Assess risk factors for diabetes, coronary artery disease, osteonecrosis (i.e. steroids, ETOH, diabetes, hyperlipidemia),

	and hepatic dysfunction (i.e. HBV/HCV, ETOH use). CBC/diff, LFTs, glucose, fasting cholesterol profile.
Routine Labs	CBC/diff, LFTs, glucose q 3 mos. Fasting lipids (8-12 hr level) q 3-6 months post-therapy, then annually. If TG > 2.3 mmol/L at baseline, repeat after 1-2 months.
Dosage Forms	700 mg pink film-coated tablets, DIN 02261545; 50 mg/mL grape bubblegum and peppermint flavoured oral suspension, 225 mL bottle, DIN 02261553.
Storage	Bottles of 60 tablets. Store at room temperature in tightly sealed container. Store oral suspension between 2-30^{o}C. Do not freeze. **Discard the suspension 28 days after first opening.**

References:

Barbarini G, Villani P, Cusato M, Sangiovanni L, Carbonara S, Ciraci E, et al. Free and total plasma concentrations of amprenavir in HIV-positive patients with hepatitis co-infection treated with unboosted fosamprenavir [abstract P_38]. 10th International Workshop on Clinical Pharmacology of HIV Therapy. Amsterdam, the Netherlands, April 15-17, 2009.

FDA approves administration of LEXIVA® with lower dose of "boosting" medication ritonavir [press release]. Research Triangle Park, NC: GlaxoSmithKline, Inc; October 12, 2007. (http://us.gsk.com/ControllerServlet?appId=4&pageId=402&newsid=1158)

Ivanovic J, Nicastri E, Viscione M, Bellagamba R, Signore F, Pisani G et al. Cord blood and amniotic fluid exposures of protease inhibitors and viral load quantification in HIV-infected pregnant women [abstract WEPE0100]. XVIII International AIDS Conference, Vienna, Austria, July 18-23rd, 2010.

Letendre S, Best B, Rossi S, Way L, Grant I, Ellis R, et al. Therapeutic amprenavir and abacavir concentrations in CSF from the same individuals [abstract P_18]. 10th International Workshop on Clinical Pharmacology of HIV Therapy. Amsterdam, the Netherlands, April 15-17, 2009.

Letendre S, Ellis RJ, Deutsch R, Clifford DB, Collier AC, Gelman GG, et al. Correlates of time-to-loss-of-viral-response in CSF and plasma in the CHARTER Cohort: CPE score predicts CSF suppression [abstract 430]. 17th Conference on Retroviruses and Opportunistic Infections, San Francisco, CA, February 16-19, 2010.

Mallolas J et al. Fosamprenavir/ritonavir dose adjustment for patients with mild and moderate hepatic impairment (APV10017) [abstract 1]. 8th International Workshop on Clinical Pharmacology of HIV Therapy. Budapest, Hungary, April 16-18, 2007.

Pérez-Elías M et al. Pharmacokinetics of fosamprenavir plus ritonavir in human immunodeficiency virus type 1-infected adult subjects with hepatic impairment. Antimicrob Agents Chemother 2009;53:5185-96.

ViiV Healthcare ULC. Telzir Product Monograph. Montreal, QC. January 24, 2011.

Selected Properties of Indinavir

Other names	Crixivan®
Manufacturer	Merck Canada Inc.
Pharmacology/Mechanism of Action	HIV aspartic protease is critical in the post-translational processing of the polyprotein products of gag and gag-pol genes into the functional core proteins and viral enzymes. Inhibition of viral protease prevents cleavage of the gag-pol polyprotein thus producing immature, non-infectious virions.
Activity	IC95 in test systems: 25-100 nM WT IC50: 0.0027-0.0171 uM (Phenosense)
Resistance - genotypic	Mutations in the protease gene associated with resistance to protease inhibitors (IAS-USA Fall 2005 Resistance Mutations): Major: M46I/L, V82A/F/T, I84V Minor: L10I/R/V, K20M/R, L24I, V32I, M36I, I54V, A71V/T, G73S/A, V77I, L90M **as major & minor mutations accumulate, susceptibility to PIs decreases*
Resistance - phenotypic	Phenotypic data on clinical virus isolates associated with various mutations using ViroLogic PhenoSense™ (http://hivdb.stanford.edu/): M46I: 7.8-fold ↑ (intermediate resistance) V82A/T/F/S with other mutations: 10- to 40-fold ↑ (high resistance) I84V with other mutations: 10- to 100-fold ↑ (high resistance)
Cross-Resistance	Varying degrees of cross-resistance have been observed between indinavir sulfate and other HIV-protease inhibitors.
Oral Bioavailability	F= 30% Best absorbed in acidic (normal) gastric pH.
Effect of Food	Food (784 kcal, 48.6 g fat, 31.3 g protein) ↓ AUC by 78%. Administration with lighter meals (e.g., dry toast with jelly, apple juice, and coffee with skim milk and sugar or a meal of corn flakes, skim milk and sugar) does not significantly affect indinavir AUC, Cmax Cmin.
Protein Binding	60%
Vd	Widely distributed in the body.
Tmax	0.8 hours
serum T ½	1.8 hours
Drug Concentrations	With 800 mg q8h dosing, steady-state indinavir plasma concentrations were: Cmin 251 ± 178 nM, Cmax 12,617 ± 4037 nM, and AUC 30,691 ± 11,407 nM•hour. In vivo intracellular accumulation: cell/plasma ratio 0.51-2.87 (indinavir alone), 4.87-7.45 when dosed with ritonavir. Drug concentrations in pregnancy: Dose of 800 mg TID yields suboptimal drug levels in pregnancy. In a kinetic study of 16 pregnant women, indinavir AUC was ↓ 74% compared to AUCs measured in post-partum women. Also,

	6/11 (55%) women in this kinetic study had undetectable indinavir Cmin at 8 hours post-dose. Therefore, indinavir use is NOT RECOMMENDED in HIV-infected pregnant women. In a Thai cohort of HIV-infected pregnant women receiving indinavir 400/ritonavir 100 mg BID, median indinavir AUC during the 2nd and 3rd trimesters were ~40% lower compared to post-partum, and ~30% of pregnant women failed to achieve an indinavir Ctrough >0.1 ug/mL. Use of a higher indinavir dose may be necessary to ensure adequate exposure throughout pregnancy.[Cressey et al. 2012]
Minimum target trough concentrations (for wildtype virus)	0.1 mg/mL
CSF (% of serum)	Some detected in animals. In series (n=25) of HIV-infected subjects taking combination therapy including indinavir, median CSF concentration was 210 nmol/L (>IC95 in vitro), suggesting that indinavir is present at therapeutic concentrations in CSF [Martin et al. 1999] 2010 CNS Penetration Effectiveness (CPE) Score: 4 (boosted indinavir), 3 (unboosted indinavir) [Letendre S et al. 2010]
Metabolism	Metabolized- 7 metabolites. CYP3A4 major enzyme involved in metabolism. Inhibits CYP3A4. May also be a weak inhibitor of CYP2D6.
Excretion	Primarily hepatically metabolized; 20% excreted unchanged in urine.
Dosing – Adult	**Unboosted dose:** 800mg po q8h Food ↓ AUC by 78%. Take on an **empty stomach** with plenty of **liquid** (1.5L/day)- water, coffee, tea, skim milk ok. -If nausea is a problem, take with a light meal low in protein and fat (ie. dry toast with jelly, corn flakes with skim milk and sugar). **Boosted dose:** 800 mg po BID + ritonavir 100-200 mg BID May take this combination with or without food, however food will help to minimize nausea. Fluid requirements of 1.5 L/day is still important.
Dosing – Pediatric	**Pediatric**[1]: 500 mg/m^2/dose po q8h (Range: 300-500 mg/m^2/dose po q8h) **Neonate**: Do not give to neonates due to risk of hyperbilirubinemia
Special instructions for pediatric patients	Can open capsule and mix with water (but very unpalatable, tastes bitter); drink lots of water. NB: 10 mg/mL indinavir syrup complex compounding formulation. Stable for 14 days in refrigerator, store in glass bottle. (Hugen et al. Am J Health Syst Pharm 2000; 57(14):1332-9).
Adjust in Liver Dysfunction	Subjects with mild/moderate hepatic insufficiency and clinical evidence of cirrhosis show 60% ↑ AUC compared to healthy controls, and ↑ t1/2 to 2.8 hours. Reduce indinavir to 600mg po q8h in mild-moderate hepatic failure due to cirrhosis.

Adjust in Renal Failure/Dialysis	Dosage adjustment not required. Use normal dosage in dialysis, irrespective of hemodialysis schedule.
Toxicity	**Renal:** dose-related nephrolithiasis- flank pain, hematuria, or kidney stones (4%)- **HYDRATION IMPORTANT**; can also see elevated creatinine, sterile pyuria, interstitial nephritis, hydronephrosis or renal atrophy **GI:** nausea, vomiting, diarrhea, abdominal pain, metallic taste **Hepatic:** indirect hyperbilirubinemia (unconjugated) (10-15%), ↑ LFTs, exacerbation of chronic liver disease **CNS:** headache, dizziness **Derm:** rash, dry skin, cracked lips, ingrown nails, alopecia **Other:** haemolytic anemia, thrombocytopenia Protease class effects include: hyperlipidemia, hypertriglyceridemia, hyperglycemia, fat malditribution, weight gain, increase in LFTs, hepatitis, increased bleeding in hemophiliacs, osteonecrosis.
Pregnancy & Lactation	Pregnancy risk category C. Minimal placental passage, however theorectical risk of exacerbation of hyperbilirunemia in the neonate. NB: Dose of 800 mg TID yields suboptimal drug levels; in a kinetic study in 16 pregnant women, indinavir AUC was ↓ 74% compared to AUCs measured in post-partum women. Also, 6/11 (55%) women in this kinetic study had undetectable indinavir Cmin at 8 hours post-dose. Therefore, indinavir use is NOT RECOMMENDED in HIV-infected pregnant women. Efficacy of ritonavir-boosted indinavir in this population is unknown. Consider use of other PIs in pregnancy (i.e. nelfinavir, saquinavir/ritonavir combination).
Drug Interactions	Indinavir is an inhibitor of CYP3A4. See Separate Drug Interaction Table.
Baseline Assessment	Assess risk factors for diabetes, coronary artery disease, osteonecrosis (i.e. steroids, ETOH, diabetes, hyperlipidemia), renal dysfunction, and hepatic dysfunction (i.e. HBV/HCV, ETOH use). CBC/diff, LFTs, Tbilirubin, glucose, fasting cholesterol profile, urinalysis.
Routine Labs	CBC/diff, LFTs, Tbilirubin, glucose, creatinine q 3 mos, urinalysis. Fasting lipids (8-12 hr level) q 3-6 months post-therapy, then annually. If TG > 2.3 mmol/L at baseline, repeat after 1-2 months.
Dosage Forms	200mg white capsule; DIN 02229161 400mg white capsule; DIN 02229196
Storage	Store at room temperature in tightly sealed container (with moisture sensitive- desiccant). Capsules likely stable for a few days with no desiccant.

References:

Cressey T, Best BM, Achalapong J, Stek A, Suriyachai P, Wang J, et al. Effect of pregnancy on pharmacokinetics of indinavir-boosted ritonavir [abstract P_37]. 13th International Workshop on Clinical Pharmacology of HIV Therapy, April 16-18th, 2012, Barcelona, Spain.

Ford J, Khoo SH, Back DJ. The intracellular pharmacology of antiretroviral protease inhibitors. JAC 2004 (advance on-line publication).

Letendre S, Ellis RJ, Deutsch R, Clifford DB, Collier AC, Gelman GG, et al. Correlates of time-to-loss-of-viral-response in CSF and plasma in the CHARTER Cohort: CPE score predicts CSF suppression [abstract 430]. 17th Conference on Retroviruses and Opportunistic Infections, San Francisco, CA, February 16-19, 2010.

Merck Canada Inc. Crixivan® Product Monograph. Kirkland QC. April 17th, 2012.

Martin C, Soennerborg A, Svensson JO, Stahle L. Indinavir-based treatment of HIV-1 infected patients: efficacy in the central nervous system. AIDS 1999;13:1227-32.

Selected Properties of Lopinavir/ritonavir

Other names	Kaletra®, ABT-378
Manufacturer	Abbott Laboratories, Ltd.
Pharmacology/Mechanism of Action	HIV aspartic protease is critical in the post-translational processing of the polyprotein products of gag and gag-pol genes into the functional core proteins and viral enzymes. Inhibition of viral protease prevents cleavage of the gag-pol polyprotein thus producing immature, non-infectious virions.
Activity	In vitro activity: in the presence of 50% human serum, mean EC50 of lopinavir against laboratory isolates ranged from 0.04-0.18 ug/mL.
Resistance - genotypic	Mutations in the protease gene associated with resistance to protease inhibitors (IAS-USA Fall 2005 Resistance Mutations): Major: V32I, I47V/A, V82A/F/T/S, Minor: L10F/I/R/V, K20M/R, L24I, L33F, M46I/L, I50V, F53L, I54V/L/A/M/T/S, L63P, A71V/T, G73S, I84V, L90M *Accumulation of ≥6 mutations is associated with reduced virologic response *There are emerging data that specific mutations, most notably I47A (and possibly I47V) and V32I are associated with high-level resistance.*
Resistance - phenotypic	Phenotypic data on clinical virus isolates associated with various mutations using ViroLogic PhenoSense™ (http://hivdb.stanford.edu/): 54V, 82A, 90M: 20-fold ↑ 46L, 54V, 82A, 90M: 33-fold ↑ 46I, 54V, 82A, 90M : 142-fold ↑ 46L, 48V, 54V, 82A, 90M: 55-fold ↑ 46I, 54V, 82T, 84V, 90M: 75-fold ↑ 46L, 48V, 54T, 82A : 75-fold ↑
Cross-Resistance	Varying degrees of cross-resistance with other PIs showed greater ↓ susceptibility to lopinavir
Oral Bioavailability	Not established in humans.
Effect of Food	Capsules/solution: Administration with a moderate fat meal (500-682 kcal, 23-25% calories from fat) increases lopinavir AUC 48%, Cmax 23%. Administration with a high fat meal (872 kcal, 56% calories from fat) increases lopinavir AUC 97%, Cmax 43%. Take capsules or oral solution with food. Tablets: Tablets may be taken with or without food. No clinically significant changes in C_{max} and AUC were observed following administration of Kaletra tablets under fed conditions compared to fasted conditions. Relative to fasting, administration of KALETRA tablets with a moderate fat meal (500 – 682 Kcal,

<table>
<tr><td></td><td>23 to 25% calories from fat) increased lopinavir AUC and C_{max} by 26.9% and 17.6%, respectively. Relative to fasting, administration of KALETRA tablets with a high fat meal (872 Kcal, 56% from fat) increased lopinavir AUC by 18.9%, but not C_{max}.</td></tr>
<tr><td>Protein Binding</td><td>98-99% (alpha-1-acid glycoprotein and albumin)</td></tr>
<tr><td>Tmax</td><td>4 hours</td></tr>
<tr><td>serum T ½</td><td>5-6 hours</td></tr>
<tr><td>Drug Concentrations</td><td>Ctrough 7.1 ± 2.9 ug/mL, Cmin 5.5 ± 2.7 ug/mL, AUC 92.6 ± 36.7 ug.h/mL
Body weight is a significant predictor of lopinavir kinetics (AUC, Cmax); subjects with lower body weight tend to have higher lopinavir Cmax and AUC [Bertz 2001]
In vivo intracellular accumulation: cell/plasma ratio 0.65-1.55 when dosed with ritonavir.

23 Thai HIV infected children (age 2-18 years) were randomized to standard dose of LPV (according to WHO dosing table) or low dose of LPV (70% of recommended dose); NRTI backbone was AZT + 3TC, kinetic study done at 4-6 weeks.
<table>
<tr><td></td><td>LPV/r standard dose
N = 11</td><td>LPV/r low dose
N =12</td></tr>
<tr><td>Median dose</td><td>288 mg/m2 BID</td><td>194 mg/m2 BID</td></tr>
<tr><td>Mean AUC 0-12hr</td><td>107.1 h.mg/L</td><td>84.6 h.mg/L</td></tr>
<tr><td>Mean Cmax</td><td>11.9 mg/L</td><td>9.8 mg/L</td></tr>
<tr><td>Mean Cmin</td><td>5.2 mg/L</td><td>3.8 mg/L</td></tr>
</table>
1 child in low dose group had subtherapeutic LPV/r concentration (< 1mg/L). There was no statistical difference in CD4 and VL between the groups (van Der Lugt et al. 2008).

Comparison of lopinavir and ritonavir tablet and soft gelatin capsule (SGC) pharmacokinetics in anti-retroviral naive HIV-1 infected subjects:
LPV 400mg/100mg BID: Tab formulation: LPV conc ↑ 14-25% VS SGC;
LPV/r 800mg/200mg OD: Tab formulation: LPV conc ↑19-38% VS SGC [Klein et al. 2008]</td></tr>
<tr><td>Minimum target trough concentrations (for wildtype virus)</td><td>4 mg/mL</td></tr>
<tr><td>CSF (% of serum)</td><td>10 HIV infected adults taking LPV/RTV 400/100mg BID for > 4 weeks. Subjects were given their morning dose with a standardized breakfast. 8 plasma samples were drawn over a</td></tr>
</table>

	12 hr period, 1 CSF sample was drawn • Median LPV Plasma kinetics: AUC: 71.3 h.ug/ml, Cmin 3.82ug/ml, Cmax 9.38 ug/ml, Conc at 9hrs: 5.42 ug/ml • Median CSF kinetics (IQR): Conc at 9hrs: 11.2 ng/ml (6.76-16.4), • **CSF: Plasma Ratio: 0.225% (0.194-0.324)** Authors state end of dosing interval LPV CSF concentrations were above the median IC_{50} for *wt*HIV-1 for this dosing regimen [Dicenzo et al. 2009]. 2010 CNS Penetration Effectiveness (CPE) Score: 3 [Letendre S et al. 2010]
Metabolism	CYP3A4 substrate; inhibits CYP3A4, 2D6 (to lesser extent). Induces glucuronyl transferases and possibly CYP1A2[3], CYP2C19 and 2C9.[4]
Excretion	After multiple dosing, <3% lopinavir excreted unchanged in urine
Dosing – Adult	• Lopinavir 400 mg/ritonavir 100 mg po BID (2 tablets BID) • Lopinavir 800 mg/ritonavir 200 mg once daily (4 tablets once daily) in patients with less than 3 mutations associated with lopinavir resistance. Once-daily dosing is NOT recommended in: o Patients with ≥3 of the following mutations: L10F/I/R/V, K20M/N/R, L24I, L33F, M36I, I47V, G48V, I54L/T/V, V82A/C/F/S/T, and I84V o Pediatric patients o Pregnant patient • • With efavirenz or nevirapine: o Treatment Naïve: LPV 400mg + RTV 100mg po BID (2 tablets BID) o Treatment Experienced: LPV 600mg + RTV 150mg po BID (3 tablets BID)
Dosing – Pediatric	Kaletra oral solution contains the excipients alcohol (42.4% v/v) and propylene glycol (15.3% w/v). KALETRA oral solution should not be administered to neonates before a postmenstrual age (first day of the mother's last menstrual period to birth plus the time elapsed after birth) of 42 weeks and a postnatal age of at least 14 days has been attained. Preterm neonates may be at increased risk of propylene glycol-associated adverse events due to diminished ability to metabolize propylene glycol, thereby leading to accumulation and potential adverse events. <u>Pediatrics (6 months to 18 years of age):</u> Dose based on weight or body surface area. Pediatric dosing guidelines for oral solution and tablets based on weight:

	<table><tr><th>Weight (kg)</th><th>Twice Daily Dose (mg/kg)*</th><th>Volume of Oral Solution Twice Daily (80 mg lopinavir/20 mg ritonavir per mL)†</th><th>Number of 100/25 mg Tablets Twice Daily‡</th></tr><tr><td>7 to < 15 kg</td><td>12 mg/kg</td><td></td><td rowspan="3">Tablets are not recommended. Use oral solution.</td></tr><tr><td>7 to 10 kg</td><td></td><td>1.25 mL</td></tr><tr><td>> 10 to < 15 kg</td><td></td><td>1.75 mL</td></tr><tr><td>15 to 40 kg</td><td>10 mg/kg</td><td></td><td></td></tr><tr><td>15 to 20 kg</td><td></td><td>2.25 mL</td><td>2</td></tr><tr><td>> 20 to 25 kg</td><td></td><td>2.75 mL</td><td>2</td></tr><tr><td>> 25 to 30 kg</td><td></td><td>3.50 mL</td><td>3</td></tr><tr><td>> 30 to 35 kg</td><td></td><td>4.00 mL</td><td>3</td></tr><tr><td>> 35 to 40 kg</td><td></td><td>4.75 mL</td><td>4 (or two 200/50 mg tablets)</td></tr><tr><td>> 40 kg</td><td colspan="3">See adult dosage recommendation</td></tr></table> * Dosing based on the lopinavir component of KALETRA® oral solution (80 mg/20 mg per mL). † KALETRA® oral solution should be taken with food. ‡ KALETRA® tablets may be taken with or without food. Refer to Kaletra product monograph for further details if dosing by body surface area or with concomitant NNRTIs, nelfinavir or amprenavir.
Special instructions for pediatric patients	Administer doses with a calibrated oral dosing syringe. Kaletra oral solution should not be used in preterm neonates in the immediate postnatal period because of possible toxicities. Kaletra oral solution contains the excipients alcohol (42.4% v/v) and propylene glycol (15.3% w/v). When administered concomitantly with propylene glycol, ethanol competitively inhibits the metabolism of propylene glycol, which may lead to elevated concentrations. Preterm neonates may be at increased risk of propylene glycol-associated adverse events due to diminished ability to metabolize propylene glycol, thereby leading to accumulation and potential adverse events. Postmarketing life-threatening cases of cardiac toxicity, lactic acidosis, acute renal failure, CNS depression and respiratory complications leading to death have been reported, predominantly in preterm neonates receiving Kaletra oral solution. Tablets should be swallowed whole and not chewed, broken, or crushed. Risk of tablets shattering if broken/crushed. Administration of crushed 200/50 mg lopinavir/ritonavir tablets to children significantly reduced lopinavir and ritonavir exposure with a decrease in AUC by 45% and 47%, respectively. Therefore, the use of crushed lopinavir/ritonavir tablets should be avoided, if possible.[Best et al. JAIDS 2011;58:385-91]
Adjust in Liver Dysfunction	No dosage recommendation available, use with caution in hepatic impairment. Steady-state 12-hour lopinavir/ritonavir pharmacokinetic profiles were assessed in 15 HIV-positive patients coinfected with HCV/HBV (Child-Pugh class A) taking 400/100 mg BID; data were compared to an HIV-positive cohort without hepatitis. Lopinavir pharmacokinetics were not altered in the presence of chronic HBV/HCV coinfection compared to the cohort without hepatitis.[von Hentig et al. 2010].

Adjust in Renal Failure/Dialysis	In a prospective study of HIV-infected patients on hemodialysis taking lopinavir/ritonavir capsules 400/100 mg BID (n=13), 12-hour PK was assessed. Mean Cmin, Cmax, and AUC were 2.76 mg/mL, 8.45 mg/mL and 69.6mg h/mL for lopinavir and 0.08mg/mL, 0.58mg/mL and 3.74mg h/mL for ritonavir. The AUC geometric mean ratios (90% CI) for LPV and RTV were 81% (67, 97), and 92% (76, 111), respectively. LPV Cmin was lower than expected in the hemodialysis group. No dosing adjustments are required in treatment-naïve patients. May wish to consider TDM in treatment-experienced patients. May administer drug regardless of hemodialysis schedule. [Gupta et al. 2008]
Toxicity	**GI**: abnormal stools, diarrhea, nausea, vomiting (higher incidence with QD dosing), abdominal pain, asthenia. **Other:** Protease class effects include: hyperlipidemia, hypertriglyceridemia, hyperglycemia, fat maldistribution, weight gain, increase in LFTs, hepatitis, increased bleeding in hemophiliacs, osteonecrosis.
Pregnancy & Lactation	Pregnancy risk category C. Limited experience in human pregnancy. When dosed at normal adult doses in pregnancy, lower than optimal drug concentrations may be seen. In a prospective, nonblinded, pharmacokinetic study in HIV-infected pregnant women, 33 subjects received 2 lopinavir tablets (400/100 mg) BID during the 2nd trimester, 3 tablets (600/150 mg) BID in the 3rd trimester, and 2 tablets (400/100 mg) BID post-delivery through 2 weeks postpartum. Median lopinavir AUC was 72, 96 and 133 ug.hr/mL and median lopinavir Cmin was 3.4, 4.9 and 6.9 ug/mL in the 2nd trimester, 3rd trimester and postpartum, respectively. Recommend using higher lopinavir dose in 2nd and 3rd trimesters of pregnancy to achieve exposures similar to those in non-pregnant subjects taking standard LPVr. May reduce to standard lopinavir dosing postpartum.[Best et al. 2010]. Secreted into breast milk of lactating rats. Call 1-800-258-4263 to register patients in Antiretroviral Pregnancy Registry. In 23 HIV-infected pregnant women receiving lopinavir/ritonavir (all VL<40 copies/mL at delivery), mean lopinavir cord blood concentration was 369.3 ng/mL (78.2% were below cut-off values). Mean amniotic fluid:maternal plasma ratio for lopinavir was 0.06. Undetectable viral load was found in amniotic fluid and cord blood.[Ivanovic et al. 2010].
Drug Interactions	Lopinavir is a substrate and weak inhibitor of CYP3A4. Potential for interactions with other enzyme inducers or inhibitors [see also Interactions with Ritonavir]. See separate Drug Interaction Table for more information.
Baseline Assessment	Assess risk factors for diabetes, coronary artery disease, osteonecrosis (i.e. steroids, ETOH, diabetes, hyperlipidemia),

	and hepatic dysfunction (i.e. HBV/HCV, ETOH use). CBC/diff, LFTs, glucose, fasting cholesterol profile.
Routine Labs	CBC/diff, LFTs, glucose q 3 mos. Fasting lipids (8-12 hr level) q 3-6 months post-therapy, then annually. If TG > 2.3 mmol/L at baseline, repeat after 1-2 months.
Dosage Forms	Oral solution: 80mg/20 mg per mL solution; DIN 02243644. NB: oral solution contains 42.4% alcohol (v/v) and 15.3% (w/v) propylene glycol. Combination yellow film-coated tablet (200 mg lopinavir/50 mg ritonavir), 120 tablets/bottle; DIN 02285533. 100/25 mg pale yellow film-coated tablet, 60 tablets/bottle, DIN 02312301. NB: soft-gel capsules were discontinued in July 2008. Combination orange coloured soft-gel capsule (133.3 mg lopinavir/33.3 mg ritonavir); DIN 02243643. Capsules contain lecithin and coconut oil. In Canada, lopinavir/ritonavir capsules are exposed to soy lecithin. As peanut and soy are from the same plant family, some patients allergic to peanuts may also be allergic to soy (consult an allergist prior to taking capsules). Propylene glycol content: capsules (64 mg), solution (153 mg/mL).
Storage	Solution: Stable in refrigerator until expiry date. Stable at room temperature (< 25°C) for 2 months. Store film-coated tablets at 20°- 25°C; excursions permitted to 15°-30°C. Exposure of tablets to high humidity outside the original container for longer than 2 weeks is not recommended.

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Selected Properties of Nelfinavir

<table>
<tr><td>Other names</td><td>Viracept®</td></tr>
<tr><td>Manufacturer</td><td>Pfizer Canada Inc.</td></tr>
<tr><td>Pharmacology/Mechanism of Action</td><td>HIV aspartic protease is critical in the post-translational processing of the polyprotein products of gag and gag-pol genes into the functional core proteins and viral enzymes. Inhibition of viral protease prevents cleavage of the gag-pol polyprotein thus producing immature, non-infectious virions.</td></tr>
<tr><td>Activity</td><td>The EC95 (95% effective concentration) of nelfinavir ranged from 7 to 196
NM in vitro.

WT IC50: 0.0015-0.0094 uM (Phenosense)
In vitro - synergistic activity with AZT, 3TC, ddC, additive with ddI, d4T</td></tr>
<tr><td>Resistance - genotypic</td><td>Mutations in the protease gene associated with resistance to protease inhibitors (IAS-USA Fall 2005 Resistance Mutations):
Major: D30N, L90M
Minor: L10F/I, M36I, M46I/L, A71V/T, V77I, V82A/F/T/S, I84V, N88D/S

*as major & minor mutations accumulate, susceptibility to PIs decreases</td></tr>
<tr><td>Resistance - phenotypic</td><td>Phenotypic data on clinical virus isolates associated with various mutations using ViroLogic PhenoSense™ (http://hivdb.stanford.edu/):
D30N: 14-fold ↑ (intermediate resistance)
D30N, N88D: 52-fold ↑ (high resistance)
84V, 90M: 18-fold ↑ (high resistance)</td></tr>
<tr><td>Cross-Resistance</td><td>Most patient-derived recombinant isolates with phenotypic and genotypic evidence of reduced susceptibility (>2.5-fold) to amprenavir, indinavir, lopinavir, and/or saquinavir demonstrated high-level cross-resistance to nelfinavir, in vitro. Mutations associated with resistance to other PIs (e.g. G48V, V82A/F/T, I84V, L90M) appeared to confer high-level cross-resistance to NFV.</td></tr>
<tr><td>Oral Bioavailability</td><td>F= good (20% monkeys, 52-80% rats)
NB: 625 mg tablet
Pfizer (Agouron) product: similar excipients, ↑ bioavailability, possibly ↑ diarrhea vs. 250 mg tablet
Roche product: different excipients, equivalent bioavailability, ↓ diarrhea vs. 250 mg tablet</td></tr>
<tr><td>Effect of Food</td><td>Food ↑ AUC by 2-3 times and decreases nelfinavir pharmacokinetic variability relative to the fasted state.
Changes in AUC, C_{max} and T_{max} for Nelfinavir in Fed State Relative to Fasted State Following 1250 mg VIRACEPT (5 x 250 mg tablets)
<table>
<tr><th>Number of Kcal</th><th>% Fat</th><th>Number of subjects</th><th>AUC fold increase</th><th>C_{max} fold increase</th><th>Increase in T_{max} (hr)</th></tr>
<tr><td>125</td><td>20</td><td>n=21</td><td>2.2</td><td>2.0</td><td>1.00</td></tr>
<tr><td>500</td><td>20</td><td>n=22</td><td>3.1</td><td>2.3</td><td>2.00</td></tr>
<tr><td>1000</td><td>50</td><td>n=23</td><td>5.2</td><td>3.3</td><td>2.00</td></tr>
</table></td></tr>
</table>

Protein Binding	>98% (98% AAG, 98% albumin)
Vd	2-7 L/kg
Tmax	2-4 hours (with food)
serum T ½	3.5-5 hours
Drug Concentrations	Steady-state plasma nelfinavir concentrations: 1250 mg BID (five 250 mg tablets): AUC24 52.8 ± 15.7 mg.h/L, Cmax 4.0 ± 0.8 mg/L, Ctrough morning 2.2 ± 1.3 mg/L, Ctrough evening 0.7 ± 0.4 mg/L 750 mg TID: AUC24 43.6 ± 17.8 mg.h/L, Cmax 3.0 ± 1.6 mg/L, Ctrough morning 1.4 ± 0.6 mg/L, Ctrough evening 1.0 ± 0.5 mg/L NB: Dosing with the 625 mg tablet yields 24% ↑ AUC, similar Cmax compared to the 250 mg tablets under fed conditions. In vivo intracellular accumulation: cell/plasma ratio 2.7-5.3 (nelfinavir alone), 2.3 (M8 metabolite)
Minimum target trough concentrations (for wildtype virus)	0.8 mg/mL
CSF (% of serum)	In the rat model, penetration noted; brain levels 40-fold higher than required for antiviral activity. 2010 CNS Penetration Effectiveness (CPE) Score: 1 [Letendre S et al. 2010]
Metabolism	Metabolized by CYP3A4 and CYP2C19. Inhibitor of CYP3A4. Induces CYP2B6, 2C8 and 2C9. The major oxidative metabolite (M8) has *in vitro* antiviral activity equal to the parent drug.
Excretion	-87% biliary/ fecal (78% as oxidative metabolites) -<2% renal
Dosing – Adult	**750 mg po TID or 1250 mg po BID.** Doses of 1500 mg BID are under study. **Take with a meal to increase absorption.**
Dosing – Pediatric	**Neonate** (<6 weeks) PACTG 353: [Bryson et al, 2002] *Protocol Dose*: 40 mg/kg/dose po bid (28% of infants were sub-therapeutic at this dose and higher doses of 50-55 mg/kg/dose po q12h under investigation). **Pediatric (2 to 13 years old)**: 50 mg/kg/dose po BID; range 45-55 mg/kg/dose po BID. Use multiples of 50 mg for powder or solubilized tablets. **Investigational (> 6 y.o.)**: 50-55 mg/kg/dose po bid
Special instructions for pediatric patients	**Tablets:** **-** both 250 mg and 625 mg tablets can be crushed and dispersed or added to food - Tablet dispersion: Use 250 mg tablet in 5 mL sterile water to yield a 50 mg/mL dispersion. Use syringe with 1 mL increments to measure. Round dose to nearest 50mg. - dispersed tabs can be added to milk or chocolate milk

	- crushed tabs can be added to pudding or other foods - due to bitter taste, avoid mixing with acidic food or juice (orange juice, apple juice, applesauce) - tablet or powder mixed with food or liquid is stable for 6 hours (refrigerated) **Powder:** - measure out powder & mix with water, milk, formula, pudding, ice cream, chocolate milk. Mix well as drug will settle. - powder has gritty & thick texture (G-tube blockage with powder or dissolved tablet) Do not reconstitute in original container–use special scoop.
Adjust in Liver Dysfunction	Nelfinavir pharmacokinetics were assessed in five HIV-positive patients with hepatitis C and liver disease.[Khaliq et al, 2000] Investigators found nelfinavir dosage adjustment to be useful in 2 patients with severe proven liver disease (i.e., AST, ALT 11-16 times upper limit of normal, ULN). Dosage reduction was not necessary in the remaining patients (AST <3-4 x ULN, ALT <4-12 x ULN). Manufacturer does not have specific dosage recommendations in hepatic impairment.
Adjust in Renal Failure/Dialysis	Dosage adjustment not required (<2% renal excretion). Dosage adjustments do not appear to be necessary in CAPD (Taylor et al. 2000).
Toxicity	**GI:** diarrhea (common), nausea, abdominal pain, flatulence **Hepatic:** ↑ LFTs , exacerbation of chronic liver disease **Derm:** rash **Other:** Protease class effects include: hyperlipidemia, hypertriglyceridemia, hyperglycemia, fat malditribution, weight gain, increase in LFTs, hepatitis, increased bleeding in hemophiliacs, osteonecrosis.
Pregnancy & Lactation	Pregnancy risk category B. Minimal placental passage. 1250 mg BID is recommended dose (750 mg TID may yield subtherapeutic concentrations). NB: Health Canada advises against using nelfinavir in pregnant women due to safety concerns regarding ethyl methanesulfonate during pregnancy (Health Canada Advisory, August 21, 2008. http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/_2008/2008_144-eng.php) Note that this is in contrast to the FDA, which removed its warning of process-related impurity with nelfinavir in May 2008, allowing nelfinavir to be prescribed as indicated to all patient populations (including children and pregnant women). http://aidsinfo.nih.gov/contentfiles/NFV_prescribing_info.pdf In 7 HIV-infected pregnant women receiving nelfinavir (all VL<40 copies/mL at delivery), mean nelfinavir cord:mother blood concentration ratio was 0.42 (SD +/- 0.27); cord blood concentrations were below cut-off values in 3 (42.8%) of samples. Undetectable viral load was found in amniotic fluid and cord blood.[Ivanovic et al. 2010].
Drug Interactions	Nelfinavir is an inhibitor of CYP3A4. See Separate Drug Interaction Table

Baseline Assessment	Assess risk factors for diabetes, coronary artery disease, osteonecrosis (i.e. steroids, ETOH, diabetes, hyperlipidemia), and hepatic dysfunction (i.e. HBV/HCV, ETOH use). CBC/diff, LFTs, glucose, fasting cholesterol profile, underlying diarrhea.
Routine Labs	CBC/diff, LFTs, glucose q 3 mos. Fasting lipids (8-12 hr level) q 3-6 months post-therapy, then annually. If TG > 2.3 mmol/L at baseline, repeat after 1-2 months. Assess for diarrhea, nausea.
Dosage Forms	**Tabs:** 250mg (light blue); DIN 02238617 625mg (white oval);DIN 02248761 **Powder:** 50mg/g (1g= level scoopful); DIN 02238618 *oral powder discontinued 2006
Storage	Store tablets at room temperature.

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Selected Properties of Ritonavir

Other names	Norvir®, ABT-538
Manufacturer	Abbott Laboratories, Ltd.
Pharmacology/Mechanism of Action	HIV aspartic protease is critical in the post-translational processing of the polyprotein products of gag and gag-pol genes into the functional core proteins and viral enzymes. Inhibition of viral protease prevents cleavage of the gag-pol polyprotein thus producing immature, non-infectious virions.
Activity	IC90: 0.11 uM (in vitro) WT IC50: 0.007-0.0436 uM (Phenosense)
Resistance - genotypic	Mutations in the protease gene associated with resistance to protease inhibitors (IAS-USA Fall 2005 Resistance Mutations): Major: V82A/F/T/S, I84V Minor: L10F/I/R/V, K20R/M, V32I, L33F, M36I, M46I/L, I50V, I54V/L, A71V/T, V77I, L90M **as major & minor mutations accumulate, susceptibility to PIs decreases*
Resistance - phenotypic	Phenotypic data on clinical virus isolates associated with various mutations using ViroLogic PhenoSense™ (http://hivdb.stanford.edu/): V82A/T/F/S : 1.3- to 4-fold ↑ 84V: 4.3-fold ↑ 84V, 90M: 17-fold ↑ 54V, 82A, 90M: 84-fold ↑ (high resistance) 54V, 82A: 22-fold ↑ 46I/V, 54V, 82A: 30- to 40-fold ↑ (high resistance)
Cross-Resistance	Cross- resistance with other PI's seen.
Oral Bioavailability	Absolute bioavailability not determined.
Effect of Food	Capsules: • food ↑ AUC by 13% Tablets (100 mg single dose): • with high fat meal (907 kcal; 52% fat, 15% protein, 33% carbohydrates), 23% ↓ in mean AUC, 23% ↓ in mean C_{max} relative to fasting conditions • with moderate fat meal, 21% ↓ mean AUC and 22% ↓ in mean C_{max} observed relative to fasting conditions. However, the type of meal administered did not change ritonavir tablet bioavailability when high fat was compared to moderate fat meals.
Protein Binding	98-99% (albumin and AAG)
Vd	0.41 ± 0.25 L/kg
Tmax	2 (fasting), 4 (with food)
serum T ½	3-5 hours

Drug Concentrations	Capsules (600 mg po q12h): • Cmax: 11.2 ± 3.6 ug/mL, Cmin 3.7 ±2.6 ug/mL In vivo intracellular accumulation: cell/plasma ratio 1.0 (range 0.6-2.28). Ritonavir tablets are not bioequivalent to ritonavir capsules. Under moderate fat conditions (857 kcal; 31% fat, 13% protein, 56% carbohydrates), when a single 100 mg ritonavir dose was administered as a tablet compared with a capsule, $AUC_{(0-\infty)}$ met equivalence criteria but mean C_{max} was ↑ by 26% (92.8% confidence intervals: ↑15 -↑39%). No information is available comparing tablets to capsules under fasting conditions.
Minimum target trough concentrations (for wildtype virus)	2.1 mg/mL
CSF (% of serum)	CSF concentrations usually < 0.05 mg/L (may have similar unbound drug concentrations as plasma) 2010 CNS Penetration Effectiveness (CPE) Score: 1 [Letendre S et al. 2010]
Metabolism	- metabolic auto-induction occurs in first 2 weeks- dose escalation necessary to avoid overdosing and minimize side-effects Ritonavir is metabolized to 5 major metabolites Ritonavir is the most potent inhibitor of the P450 enzyme system (CYP3A>2D6>2C9>2C19>2A6,2E1). Ritonavir also induces CYP1A2 and glucuronyl transferase activity. May also induce CYP2C9, 2C19. - isopropylthiazole oxidation metabolite(M-2) has activity similar to ritonavir, but conc. are low
Excretion	- 86% biliary/ fecal - 11% renal
Dosing – Adult	-**<u>High dose:</u>** 600 mg po q12h**; for better tolerability, start with 300 mg BID and increase dose at 2 to 3 day intervals by 100mg BID.** **<u>Low dose</u>** (for boosting other PIs): due to intolerance to RTV at high doses, ritonavir is mainly in lower doses as a metabolic booster of other PIs. The dosage varies depending on the respective drug used. See drug interaction tables for more detailed dosing. All formulations (including the tablet) must **be taken with meals**. To improve palatability, mix solution with Ensure or chocolate milk within 1 hour of dosing.
Dosing – Pediatric	<u>For children 1 month-2 years of age:</u> The recommended dosage of ritonavir in children > 1 month is 350 to 400 mg/m^2 twice daily by mouth and should not exceed 600 mg twice daily. Ritonavir should be started at 250 mg/m^2

	and increased at 2 to 3 day intervals by 50 mg/m^2 twice daily. If patients do not tolerate 400 mg/m^2 twice daily due to adverse events, the highest tolerated dose may be used for maintenance therapy in combination with other antiretroviral agents, however, alternative therapy should be considered. General Pediatric Dosing: 400 mg/m^2/dose po bid range: 350-400 mg/m^2/dose po bid **Initial**: start at 250 mg/m^2/dose & ↑ dose over 5 days: 250 mg/m^2/dose x **2/7** (or ↑ dose by 100 mg cap), then 300 mg/m^2/dose x **2/7**, then 350 mg/m^2/dose **1/7**, then 400 mg/m^2/dose po bid **Neonatal** (≤ 12 hrs postbirth) PACTG 354: *Protocol Dose*: 350 mg/m^2/dose po bid x 4 wks
Special instructions for pediatric patients	When possible, dose should be administered using a calibrated dosing syringe. **Liquid is unpalatable, bad aftertaste** 1) Dull taste buds: give **after** popsicle or frozen juice 2) Give with **fat**: ice cream, high fat yogurt, PC® Devon cream 3) **Coat** mouth: give after grape jelly, maple syrup or peanut butter on toast 4) **Mix** with: formula, milk, chocolate milk, ice cream, pudding, maple syrup, Tang®, Ensure® 5) Give **strong flavour** after dose: maple syrup, cheese, strong-flavoured chewing gum - flush g-tube with milk or enteral feed Avoid co-administration of amprenavir solution with ritonavir solution. A competitive metabolic interaction with propylene glycol contained in amprenavir (550 mg/ml) & ethanol in ritonavir (43% v/v ethanol) may occur. Both are substrates of alcohol dehydrogenase.
Adjust in Liver Dysfunction	No dosage recommendation available, use with caution in hepatic impairment.
Adjust in Renal Failure/Dialysis	Dosage adjustment not necessary. May administer drug regardless of hemodialysis schedule.
Toxicity	**Most of these toxicities are dose-related. When RTV is used in low doses, the toxicity is decreased.** **GI:** diarrhea, nausea, vomiting ,dyspepsia, abdominal discomfort, anorexia , taste disturbances , dehydration+ syncope/ hypotension/ renal insufficiency, pancreatitis **Hepatic:** ↑ transaminases >5x (2-15%), jaundice, (↑ risk in HBV/HCV), hepatotoxic fatalities reported Caution in liver failure, liver enzyme abnormalities, or hepatitis **CNS:** perioral & peripheral paresthesias asthenia, headache, fatigue, weakness, light-headedness, seizures **Derm:** Severe skin reactions such as Stevens-Johnson syndrome and toxic epidermal necroylsis have been reported. **Other:** Protease class effects include: hyperlipidemia,

	hypertriglyceridemia, hyperglycemia, fat maldistribution, weight gain, increase in LFTs, hepatitis, increased bleeding in hemophiliacs, osteonecrosis. Solution contains alcohol.
Pregnancy & Lactation	Pregnancy risk category B. Minimal placental transfer in humans. Low drug levels in pregnancy, therefore use only in low-doses to boost the concentration of other PIs (i.e. saquinavir, indinavir, lopinavir).
Drug Interactions	Ritonavir is the most potent inhibitor of the P450 enzyme system (CYP3A>2D6>2C9>2C19>2A6,2E1). Ritonavir also induces CYP1A2 and glucuronyl transferase activity. May also induce CYP2C9, 2C19. See Separate Drug Interaction Table The concomitant administration of ritonavir oral solution with disulfiram or other medicinal products that reduce alcohol metabolism (e.g. or preparations that contain alcohol is contraindicated. Do not coadminister with amprenavir oral solution.
Baseline Assessment	Assess risk factors for diabetes, coronary artery disease, osteonecrosis (i.e. steroids, ETOH, diabetes, hyperlipidemia), and hepatic dysfunction (i.e. HBV/HCV, ETOH use). CBC/diff, LFTs, glucose, fasting cholesterol profile.
Routine Labs	CBC/diff, LFTs, glucose q 3 mos. Fasting lipids (8-12 hr level) q 3-6 months post-therapy, then annually. If TG > 2.3 mmol/L at baseline, repeat after 1-2 months.
Dosage Forms	100mg (white) soft gel capsules; DIN 02241480 100 mg white, film-coated tablets; DIN 02357593, bottles of 30. Capsules contain lecithin and coconut oil. In Canada, ritonavir capsules are exposed to soy lecithin. As peanut and soy are from the same plant family, some patients allergic to peanuts may also be allergic to soy (consult an allergist prior to taking capsules). 80mg/ml oral solution (240ml bottles); DIN 02229145 Both capsules (12%v/v) and solution (43% v/v) contain ethanol.
Storage	Solution stable at room temperature and should be used by product expiration date. Capsules should be refrigerated until dispensed, then stable for 30 days at room temperature. – photosensitive. Tablets may be stored at room temperature; exposure to high humidity outside the original container for longer than 2 weeks is not recommended.

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Selected Properties of Saquinavir

Other names	Invirase®, Ro 31-8959 Fortovase® soft gel capsule – sale and distribution discontinued in 2006
Manufacturer	Hoffmann-La Roche
Pharmacology/Mechanism of Action	HIV aspartic protease is critical in the post-translational processing of the polyprotein products of gag and gag-pol genes into the functional core proteins and viral enzymes. Inhibition of viral protease prevents cleavage of the gag-pol polyprotein thus producing immature, non-infectious virions.
Activity	In vitro IC50 1-30 nM, IC90 5-80 nM; additive to synergistic effect with AZT, ddI, ddC, 3TC, d4T, nevirapine WT IC50: 0.001-0.0063 uM (Phenosense)
Resistance - genotypic	Mutations in the protease gene associated with resistance to protease inhibitors (IAS-USA Fall 2005 Resistance Mutations): Major: G48V, L90M Minor: L10I/R/V, I54V/L, A71V/T, G73S, V77I, V82A, I84V **as major & minor mutations accumulate, susceptibility to PIs decreases*
Resistance - phenotypic	Phenotypic data on clinical virus isolates associated with various mutations using ViroLogic PhenoSense™ (http://hivdb.stanford.edu/): 48V, 82A: 8.8-fold ↑ 48V, 90M: 19-fold ↑ 48V, 54V, 82A: 147-fold ↑ 48V, 54V, 82A, 90M: 322-fold ↑ 48V, 54V, 82A, 84V: 583-fold ↑
Cross-Resistance	Varying degrees of cross-resistance with other PI's
Oral Bioavailability	a) hard-gel capsule (Invirase): F= 4% with **food** - best with **fatty** foods -F=↓ 18x if taken when fasting -low F due to-limited absorption and extensive first-pass metabolism b) film-coated tablet (Invirase): Similar bioavailability was demonstrated when Invirase 500 mg film coated tablets (2 x 500 mg) and Invirase 200 mg capsule (5 x 200 mg) were administered with low dose ritonavir (100 mg) under fed conditions. c) soft-gel capsule (Fortovase): F= 12%
Effect of Food	Invirase® (hard-gel capsule): Heavy breakfast (48g protein, 60g carbohydrate, 57g fat; 1006 kcal): • AUC substantially ↑ (from 24 ng·h/mL to 161 ngAh/mL) • ↑ Tmax from 2.4 hours to 3.8 hours • ↑ Cmax from 3.0 ng/mL to 35.5 ng/mL. • The effect of food has been shown to be present for up to 2 hours after food intake. Invirase® (500 mg tablet):

	21 HIV patients on SQV/r 1000/100mg BID given within 15min of a meal underwent a kinetic study to compare the effect of a high fat meal (55g of fat/1291 kcal) VS a standard meal (15g of fat/651 kcal) on SQV plasma levels: • High Fat Meal: AUC 29,365ng.h/ml; Cmax: 4360ng/ml; Ctrough: 994ng/ml • Standard Meal: AUC 20,332ng.h/ml; Cmax: 3240ng/ml; Ctrough: 800ng/ml • SQV levels were mildly decreased with a standard meal VS high fat meal. All patients had Ctrough > cut off of 100ng/ml The authors conclude that SQV should be given with food, but the fat content of the meal is not critical [Boffito et al. ICAAC 2007]. Grapefruit juice: • AUC doubled when Invirase taken with double-strength grapefruit juice • AUC ↑ 30% when take with regular grapefruit juice
Protein Binding	>98%
Vd	- 700 L - considerable tissue binding
Tmax	2-4 hours
serum T ½	13.2 hours
Drug Concentrations	a) hard-gel capsules (Invirase) • 600 mg q8h: Cmax: 253 ng/mL; AUC 757.2 ng.h/mL • 1000 mg/100 mg ritonavir BID: Cmin 371 ng/mL, AUC 14607 ng.h/mL • 400 mg/400 mg ritonavir BID: Cmin 480 ng/mL, AUC 16000 ng.h/mL b) film-coated tablets (Invirase): • A gender difference was observed, with females showing higher saquinavir exposure than males (mean AUC increase of 56%, mean Cmax increase of 26%), in the relative bioavailability study comparing saquinavir 500 mg film coated tablets to the saquinavir 200 mg capsules in combination with ritonavir. There was no evidence that age and body weight explained the observed gender difference in concentrations. b) soft-gel capsules (Fortovase): • 1200 mg q8h: Cmin 216 ng/mL, AUC 21747 ng.h/mL • 1000 mg/100 mg ritonavir BID: Cmin 433 ng/mL, AUC 19085 ng.h/mL In vivo intracellular accumulation: cell/plasma ratio 4.94-9.45 (saquinavir alone), 2.74-4.01 when dosed with ritonavir.

Minimum target trough concentrations (for wildtype virus)	0.1 mg/mL
CSF (% of serum)	-negligible (n=2) 2010 CNS Penetration Effectiveness (CPE) Score: 1 [Letendre S et al. 2010]
Metabolism	Extensive first-pass metabolism; metabolized to inactive mono- and dihydroxylated metabolites by cytochrome P450 (90% by CYP3A4 isoenzyme). Saquinavir is also a substrate of p-glycoprotein (Pgp). Saquinavir is a weak inhibitor of CYP3A4.
Excretion	-nonrenal -88% biliary/fecal - <4% excreted in urine
Dosing – Adult	**Note: Fortovase® and Invirase® are not bioequivalent and cannot be used interchangeably.** **Boosted with ritonavir (recommended):** **Hard-gel capsules or tablets*:** SQV 1000 mg po BID + RTV 100 mg po BID SQV 400 mg po BID + RTV 400 mg po BID Take within 2 hours of a **meal or substantial snack, even when boosted with ritonavir** . Take ritonavir at the same time as saquinavir.
Dosing – Pediatric	**Neonatal/Infant:** unknown **Pediatric:** SQV-sgc 50 mg/kg/dose q 8h as a single PI therapy SQV-sgc 33 mg/kg/dose q 8h as usual therapy with nelfinavir
Special instructions for pediatric patients	• wear sunscreen (photosensitivity < 2% patients) • give within 2 hours of a full meal or large snack to increase absorption • give with grapefruit juice to increase absorption (if not on ritonavir) • unpalatable (very bitter) - **Invirase® HGC** contains powder in capsule that can be opened and sprinkled on food, water, simple syrup, baby formula or jelly jam, but has unpalatable taste. • In an open-label, randomized, 4 period study in adults, the bioavailability of 1000 mg opened saquinavir capsules suspended in simple syrup, baby formula and jelly jam (plus ritonavir 100 mg oral solution) was approximately 10%, 60% and 40% higher, respectively, than 1000 mg unopened saquinavir capsules plus ritonavir. In terms of palatability, saquinavir suspended in simple syrup or jelly jam ranked higher than saquinavir suspended in baby food.(McKay et al. 2007). - **Fortovase® SGC** contains liquid or gel in capsule - 6 x 200 mg Fortovase whole caps mixed with 50 mL of whole milk or Advera nutritional supplement took 5-15 minutes to dissolve when heated to 40, 60 or 80 degrees C. The mixture remained in solution for up to 1 hour at room temperature. If

	refrigerated for 24 hours, it turned into a gel, but reliquified after reheating to 30 degrees C. The drug was still stable at 24 hours. (data on file, Hoffmann-La Roche)
Adjust in Liver Dysfunction	No dosage recommendations available; use with caution in mild to moderate hepatic impairment. Contraindicated in severe hepatic impairment. The steady-state kinetics of saquinavir 1000/ritonavir 100 mg BID plus 2-3 NRTIs was investigated in treatment-experienced HIV patients with moderate hepatic impairment (n=7, all HCV coinfected, Child-Pugh grade B) and matched controls with normal liver function. In patients with hepatic impairment, saquinavir and ritonavir AUC was ↓ 35% and 25%, respectively versus controls. Dose adjustments are not required in patients with moderate liver disease.[Chang et al. 2010]
Adjust in Renal Failure/Dialysis	No dosage adjustment necessary. Administer regardless of dialysis schedule.
Toxicity	**GI:** diarrhea, abdominal pain, nausea **CNS:** headache, paresthesias Derm: photosensitivity reactions (use sunscreen) **HEPATIC:** mild ↑ LFTs **Other:** Protease class effects include: hyperlipidemia, hypertriglyceridemia, hyperglycemia, fat maldistribution, weight gain, increase in LFTs, hepatitis, increased bleeding in hemophiliacs, osteonecrosis. Potential risk of QT prolongation; avoid use in patients already taking medications known to cause QT interval prolongation such as Class IA (such as quinidine,) or Class III (such as amiodarone) antiarrhythmic drugs, or in patients with a history of QT interval prolongation [FDA advisory update, Feb 23, 2010].
Pregnancy & Lactation	Pregnancy risk category B. Inadequate drug levels when Fortovase® is used alone. Use Fortovase® (SQV-sgc) OR Invirase® (SQV-hgc) 1000 mg BID + ritonavir 100 mg BID. Considered a preferred PI combination in pregnancy. Saquinavir exposure is not reduced in 3rd trimester of pregnancy when administered as 1000 mg (2 x 500 mg tablets)/ritonavir 100 mg BID. No dose adjustment required (Van der Lugt et al. 2008)
Drug Interactions	Saquinavir is a substrate and weak inhibitor of CYP3A4; saquinavir is also a substrate of P-glycoprotein. Therefore, drugs that affect CYP3A4 and/or Pgp, may modify the pharmacokinetics of saquinavir. Similarly, saquinavir might also modify the pharmacokinetics of other drugs that are substrates for CYP3A4 or Pgp. See Separate Drug Interaction Table
Baseline Assessment	Assess risk factors for diabetes, coronary artery disease, osteonecrosis (i.e. steroids, ETOH, diabetes, hyperlipidemia),

	and hepatic dysfunction (i.e. HBV/HCV, ETOH use). CBC/diff, LFTs, glucose, fasting cholesterol profile.
Routine Labs	CBC/diff, LFTs, glucose q 3 mos. Fasting lipids (8-12 hr level) q 3-6 months post-therapy, then annually. If TG > 2.3 mmol/L at baseline, repeat after 1-2 months.
Dosage Forms	200mg (yellow & green) hard-gel capsule (Invirase®); DIN 02216965 500 mg (greyish-orange) film-coated tablets (Invirase®); DIN 02279320, bottles of 120. 200mg (beige) soft-gel capsule (Fortovase®); DIN 02239083 ** *discontinued in 2006*
Storage	Invirase®(hard-gel capsules and tablets): store at room temperature. Fortovase® (soft-gel caps): store in refrigerator until dispensed; once brought to room temperature, stable for 3 months. ** *discontinuation in 2006*

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Selected Properties of Tipranavir

Other names	Aptivus®, TPV, PNU-140690
Manufacturer	Boehringer Ingelheim (Canada) Ltd.
Pharmacology/Mechanism of Action	non-peptidic protease inhibitor
Molecular Weight	602.68
Activity	In vitro EC50 0.03-0.07 uM, EC90 0.07-0.18 uM. In vivo EC90 0.28-0.72 uM.
Resistance - genotypic	Mutations in the protease gene associated with resistance to protease inhibitors (IAS-USA Fall 2005 Resistance Mutations): Major: L33I/F, V82L/T, I84V Minor: L10V, I13V, K20M/R, E35G, M36I, K43T, M46L, I47V, I54A/M/V, Q58E, H69K, T74P, N83D, L90M **as major & minor mutations accumulate, susceptibility to PIs decreases*
Resistance - phenotypic	Phenotypic data on clinical virus isolates associated with various mutations using ViroLogic PhenoSense™ (http://hivdb.stanford.edu/): 32, 33, 45, 82, 84: 14-fold ↑ Approx. 3-fold ↑ IC90 after serial passage of virus in presence of tipranavir
Cross-Resistance	Only mild (6-fold ↑) in IC90 with ritonavir-resistance virus that is highly cross-resistant to indinavir, nelfinavir, and saquinavir.
Oral Bioavailability	
Effect of Food	Bioavailability of older formulation of tipranavir increased 2-fold with high-fat meal. Tipranavir capsules: When tipranavir 500 mg/ritonavir 200 mg BID was administered with food, tipranavir bioavailability was not altered compared to when TPV/r was administered in a fasting state.[La Porte, 2007] Tipranavir oral solution: When tipranavir 500 mg/ritonavir 200 mg BID as oral solution was administered with food, tipranavir Cmax ↑ 21% relative to fasting, with no change in AUC or Cmin.]La Porte, 2007] Tipranavir/ritonavir may be taken with or without food. May take with food to decrease potential for nausea and vomiting.
Protein Binding	>99.9%
Tmax	2.9-3 hours
serum T ½	5.5-6 hours
Drug Concentrations	Median steady-state tipranavir plasma concentrations with 500/200mg ritonavir BID: Ctrough 21.01-29.1 uM, Cmax 123.4

	uM, AUC 855.6 h.uM. Peak RNA reduction is correlated with Cmin. Significantly higher tipranavir Ctrough and lower inter-individual variability observed in women versus men [Solas et al. 2007].
Minimum target trough concentrations (for wildtype virus)	20 uM (preliminary target)
CSF (% of serum)	2010 CNS Penetration Effectiveness (CPE) Score: 1 [Letendre S et al. 2010]
Metabolism	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. When co-administered with ritonavir, net effect is CYP3A inhibition.
Excretion	4.4% dose excreted in urine.
Dosing – Adult	500 mg po BID + ritonavir 200 mg po BID with food
Dosing – Pediatric	For patients ages 2-18 years: 14 mg/kg with 6 mg/kg ritonavir (or 375 mg/m^2 co-administered with ritonavir 150 mg/m^2) BID (maximum tipranavir 500/ritonavir 200 mg BID). For children who develop intolerance or toxicity, dose reduction to tipranavir 12 mg/kg plus ritonavir 5 mg/kg (or tipranavir 290 mg/m^2 co-administered with 115 mg/m^2 ritonavir) BID may be considered, providing the virus is not resistant to multiple protease inhibitors.
Special instructions for pediatric patients	Patients taking tipranavir oral solution should be advised not to take supplemental vitamin E greater than a standard multivitamin, the oral solution contains 116 IU/mL of vitamin E which is higher than the Reference Daily Intake (adults 30 IU, pediatrics approximately 10 IU).
Adjust in Liver Dysfunction	No dosage recommendation; use with caution in patients with hepatic impairment; TPV/RTV is contraindicated in pts with moderate to severe (Child -Pugh Class B & C) hepatic insufficiency. Plasma tipranavir concentrations are increased in patients with significant liver fibrosis (Metavir score ≥ 2) [Morello et al. 2007].
Adjust in Renal Failure/Dialysis	Dosage adjustment not required since tipranavir is extensively metabolized.
Toxicity	**GI:** diarrhea, nausea, vomiting. Diarrhea occurs 4-5 days after starting; most cases improve over time. No trend of dose-dependence observed. **Rash:** Mild to moderate rashes including urticarial rash, maculopapular rash, and possible photosensitivity have been reported (8-14% in phase 2 and 3 trials). Female gender associated with increased frequency of skin rash. Additionally, in one drug interaction trial in healthy female volunteers given a single dose of ethinyl estradiol followed by tipranavir/ritonavir,

	33% of subjects developed a rash. Rash accompanied by joint pain or stiffness, throat tightness, or generalized pruritus (itching) has been reported in both men and women receiving tipranavir/ritonavir.
	Hepatotoxicity (Black Box warning): Tipranavir co-administered with low dose ritonavir has been associated with reports of clinical hepatitis and hepatic decompensation, including some fatalities. All patients should be followed closely with clinical and laboratory monitoring, especially those with chronic hepatitis B or C co-infection, as these patients have an increased risk of hepatotoxicity. Liver function tests should be performed at baseline and frequently through treatment. In addition, tipranavir is contraindicated in patients with moderate and severe (Child-Pugh Class B and C, respectively) hepatic insufficiency.
	Intracranial Hemorrhage (ICH) - Black Box Warning:
	• In clinical trials, TPV/r was associated with 14 ICH events including 8 fatalities, in 13 out of 6840 HIV-1 patients.
	• Many of these events occurred in patients who had other risk factors for ICH. These risk factors may have caused or contributed to ICH events
	  o Medical conditions: CNS lesions, head trauma, recent neurosurgery, coagulopathy, hypertension or alcohol abuse
	  o Concomitant medications: anticoagulants, antiplatelet agents
	• Median time to onset of an ICH event: 525 days after TPV/r initiation
	• In *in vitro* experiments, TPV was observed to inhibit human platelet aggregation at levels consistent with exposures observed in patients receiving TPV/r. In general no pattern of abnormal coagulation parameters has been observed in patients receiving TPV.
	• Therefore, routine measurement of coagulation parameters is not currently indicated in the management of patients on TPV.
	• TPV/r should be used with caution in patients who are at increased risk for ICH.
	• Aside – Risk Factors for ICH include: increased age, hypertension, high alcohol intake, smoking, CNS lesions, head trauma, recent neurosurgery, coagulopathy, male sex, non-white ethnicity, use of anticoagulants and/or antiplatelet agents.
	• It is important to note that an increased risk of ICH has previously been observed in patients with advanced HIV-1 disease / AIDS.
	Further investigations are ongoing to assess the role of TPV in ICH.
	
	Sulfa Allergy: Tipranavir should be used with caution in patients with a known sulfonamide allergy. Tipranavir contains a sulfonamide component. The potential for cross-sensitivity between drugs in the sulfonamide class and tipranavir is

	unknown. TPV/r did not prolong the QTc interval, exhibit QT prolongation or clinically important ECG effects with therapeutic dosing (TPV/r 500/200mg BID) or supra-therapeutic dosing (TPV/r 750/200mg BID) in 80 healthy subjects [Huettner et al. ICAAC 2007] Protease class effects include: hyperlipidemia, hypertriglyceridemia, hyperglycemia, fat maldistribution, weight gain, increase in LFTs, hepatitis, increased bleeding in hemophiliacs, osteonecrosis.
Pregnancy & Lactation	Pregnancy category C. No studies or experience in human pregnancy. Safety and pharmacokinetic in pregnancy data are insufficient to recommend use in pregnancy.
Drug Interactions	Tipranavir induces CYP3A, glucuronosyl transferase in vivo. Tipranavir is a slight inducer of CYP2C9, moderate inducer of CYP1A2, and potent inhibitor of CYP2D6.[Vourvahis, 2007] Tipranavir also induces p-glycoprotein activity. Tipranavir has been shown to significantly ↓ concentrations of several co-administered protease inhibitors. See separate Drug Interaction table for more information. Tipranavir capsules contain alcohol; use with caution with metronidazole (may produce disulfiram-like reaction).
Baseline Assessment	Assess risk factors for diabetes, coronary artery disease, osteonecrosis (i.e. steroids, ETOH, diabetes, hyperlipidemia), and hepatic dysfunction (i.e. HBV/HCV, ETOH use). CBC/diff, LFTs, glucose, fasting cholesterol profile.
Routine Labs	CBC/diff, LFTs, glucose q 3 mos. Fasting lipids (8-12 hr level) q 3-6 months post-therapy, then annually. If TG > 2.3 mmol/L at baseline, repeat after 1-2 months.
Dosage Forms	250 mg soft gel capsules, DIN 02273322; 100 mg/mL oral solution. Capsules contain alcohol.
Storage	Capsules stable under refrigeration for at least 18 months; when stored unopened at room temperature, capsules are stable for up to 90 days. When stored at room temperature and opened twice daily, capsules are stable for up to 60 days. Tightly cap bottles after each use. Tipranavir oral solution is stable for 12 months at room temperature. Do not refrigerate or freeze; tightly cap bottle after each use.

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Selected Properties of Enfuvirtide

Other names	Fuzeon®, T20
Manufacturer	Hoffmann- La Roche Limited
Pharmacology/Mechanism of Action	Enfuvirtide is an inhibitor of HIV-1 gp41 mediated fusion. Enfuvirtide binds to the first heptad-repeat (HR1) in the gp41 subunit of the viral envelope glycoprotein and prevents the conformational changes required for the fusion of viral and cellular membranes, and thus interferes with the entry of HIV-1 into cells.
Activity	The IC50 (50% inhibitory concentration) for enfuvirtide in laboratory and primary isolates representing HIV-1 clades A to G ranges from 4 to 280 nM (18 to 1260 ng/mL).
Resistance - genotypic	Mutations in the gp41 envelope gene associated with resistance (IAS-USA Fall 2005 Resistance Mutations): G36D/S, I37V, V38A/M/E, Q39R, Q40H, N42T, N43D
Resistance - phenotypic	In site-directed mutagenesis experiments, isolates with a single mutation display one- to 21-fold reductions in susceptibility, whereas isolates with two mutations display 15- to 500-fold reductions in susceptibility.
Cross-Resistance	No cross-resistance with other antiretroviral drug classes.
Oral Bioavailability	Not orally absorbed. SC: 84.3% compared to IV
Effect of Food	Not applicable
Protein Binding	92% bound to plasma proteins in HIV infected plasma over a concentration range of 2 to 10 μg/mL. It is bound predominantly to albumin and to a lower extent to alpha-1 acid glycoprotein.
Vd	5.5 ± 1.1 L
Tmax	Not available
serum T ½	3.8 hours
Drug Concentrations	Plasma Ctrough(ss): 2.6 to 3.4 μg/mL Single dose kinetics, mean (±SD): Cmax 4.59 ±1.5 μg/mL, AUC 55.8 ± 12.1 μg•h/mL
Minimum target trough concentrations (for wildtype virus)	The IC50 for baseline clinical isolates ranged from 0.089 to 107 nM (0.4 to 480 ng/mL) by the cMAGI assay (n=130).
CSF (% of serum)	N/a 2010 CNS Penetration Effectiveness (CPE) Score: 1 [Letendre S et al. 2010]
Metabolism	Catabolism to constituent amino acids.
Excretion	N/a
Dosing – Adult	90 mg (1 mL) subcutaneously (SC) BID. Inject into upper arm, anterior thigh or abdomen.
Dosing – Pediatric	Neonatal/Infant: not approved for < 6 years old. Pediatric (6-16 y.o.): 2mg/kg SC BID to a maximum of 90 mg (1 mL) BID. Inject into upper arm, anterior thigh or abdomen.

	Monitor weight closely and adjust dose accordingly.
Special instructions	Educate patients regarding sterile technique. It may take up to 45 minutes for the powder to solubilize. The reconstituted solution is stable for 24 hours in the fridge. It should be brought to room temperature prior to usage. Unused portions should be discarded. Ensure there are no bubbles or particulate matter prior to injection. Injection sites should be rotated. Avoid injecting into moles, scar tissue, bruises, the navel, sites with little SC fat, or sites of existing or previous reactions. Massage area after injection to reduce pain. Wear loose clothing around site of injection. A warm compress of analgesics may be required. Monitor carefully for local infection or cellulitis.
Adjust in Liver Dysfunction	No dosage recommendation available.
Adjust in Renal Failure/Dialysis	No dosage adjustment necessary in impaired renal function or hemodialysis.
Toxicity	Diarrhea, nausea, fatigue, eosinophilia Local injection site reactions (98%): pain, erythema, induration, cysts and nodules, pruritis, ecchymosis Increased rate of bacterial pneumonia (5.6% vs. 0.3% without enfuvirtide) Hypersensitiviy reaction (<1%): rash, fever, nausea & vomiting, chills, rigors, hypotension, and increased LFTs; may recur on re-challenge. D/C drug and seek immediate medical attention. Avoid re-challenge if possible. One report of successful desensitization protocol in a monitored ICU setting (Desimone et al. 2004). Immune-mediated reactions: primary immune complex reaction, respiratory distress, glomerulonephritis, Guillain-Barre syndrome have been reported.
Pregnancy & Lactation	Pregnancy risk category B. No human studies in pregnancy, therefore not recommended.
Drug Interactions	Unlikely to have significant drug interactions with concomitantly administered CYP450 substrates. No significant interactions identified with other antiretroviral agents.
Baseline Assessment	CBC/diff , LFTs, CK, electrolytes, glucose, fasting cholesterol profile.
Routine Labs	CBC/diff monthly, CK/LFTs, electrolytes, glucose q3 months.
Dosage Forms	Single-use vial: enfuvirtide 108 mg. Reconstitute with 1.1 mL of Sterile Water for infection. Final concentration 90 mg/mL. DIN 02247725 One-month convenience kit includes: 60 single use efuvirtide vials, 60 vials of diluent (sterile water for injection), 60 reconstitution syringes, 60 administration syringes (1 mL), and alcohol wipes.
Storage	Store powder for solution at room temperature. The reconstituted solution is stable for 24 hours in the fridge.

References:

Desimone JA, Ojha A, Pathak R, Cohn J. Successful desensitization to enfuvirtide after a hypersensitivity reaction in an HIV-1-infected man. Clin Infect Dis 2004;39(10):110-2.

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Mink M, Greenberg ML, Moshier S, Janumpalli S, Davison D, Jin L, Sista P, Melby T, Lambert D, Cammack N, Salgo M, Matthews TJ. Impact of HIV-1 gp41 amino acid substitutions (positions 36-45) on susceptibility to T-20 (enfuvirtide) in vitro: analysis of primary virus isolates recovered from patients during chronic enfuvirtide treatment and site-directed mutants in NL4-3. Antivir Ther. Vol. 7, 2002:S17.

Tebas P, Bellos N, Lucasti C, Richmond G, Godofsky E, Patel I et al. Enfuvirtide does not require dose-adjustment in patients with chronic kidney failure: results of a pharmacokinetic study of enfuvirtide in HIV-1-infected patients with impaired kidney function. JAIDS Journal of Acquired Immune Deficiency Syndromes. 47(3):342-345, March 1, 2008.

III. PHARMACOLOGIC PROPERTIES OF DIRECTLY ACTING ANTIVIRALS FOR HEPATITIS C

Selected Properties of Boceprevir

Other Names	Victrelis™ Combination formulation: Victrelis Triple™: boceprevir/ribavirin/peginterferon alfa-2b
Manufacturer	Merck Canada Inc.
Pharmacology/ Mechanism of action	Equal mixture of two diastereoisomers; the pharmacologically active SCH 534128 (S-isomer) and SCH 534129 (R-isomer). **Mechanism of Action:** Boceprevir is an inhibitor of the HCV NS3/4A protease. Boceprevir covalently, yet reversibly, binds to the NS3/4A protease active site serine (Ser139) through a (alpha)-ketoamide functional group to inhibit viral replication in HCV-infected host cells.
Activity	The IC50 and IC90 values for BOC were approximately 200 nM and 400 nM, respectively, in a 72-hour cell culture assay. Loss of replicon RNA appears to be first-order with respect to time of treatment. Treatment at IC90 for 72 hours resulted in a 1-log drop in replicon RNA. Prolonged exposure resulted in a 2-log decrease in RNA levels by Day 15. Boceprevir cell culture anti-HCV activity was approximately 2-fold lower for an HCV replicon derived from a single genotype 1a isolate, relative to the 1b isolate-derived replicon. Boceprevir had approximately 2-fold reduced activity against a genotype 2a isolate relative to genotype 1a and 1b replicon isolates. In a biochemical assay, boceprevir had approximately 3- and 2- fold reduced activity against NS3/4A proteases derived from single isolates representative of HCV genotypes 2 and 3a, respectively, relative to a genotype 1b-derived NS3/4A protease. The presence of 50 % human serum reduced the cell culture anti-HCV activity of BOC by approximately 3-fold. Evaluation of varying combinations of boceprevir and interferon alfa-2b that produced 90 % suppression of replicon RNA showed additivity of effect; no evidence of synergy or antagonism was detected.
Resistance – genotypic	The activity of boceprevir against the HCV NS3/4A protease or genotype 1b replicon was reduced (2-to 10- fold) by the following amino acid substitutions in the NS3/4A protease domain: V36A/I/M, Q41R, F43C/S, T54A/S, V55A/I, R155K/M/Q, V158I, V170A/T and M175L. A greater than 15-fold reduction in boceprevir anti-HCV activity was conferred by the substitutions: T54C, R155G/I/T and A156S/T/V. The fold decrease in boceprevir anti-HCV activity conferred by double resistance-associated substitutions was approximately equal to the product of that for the individual substitutions.
Resistance - phenotypic	In the pooled resistance analysis from the Phase 3 Studies SPRINT-2 and RESPOND-2, resistance associated polymorphisms were detected in viruses from 6.7 % of subjects at baseline; 5.4 % had

	genotype 1a virus and 1.3 % had genotype 1b viruses. Overall, the presence of baseline RAVs alone did not appear to have a notable association with treatment response in patients who received the combination of BOC with PegIFNα2b/RBV. Baseline resistance associated polymorphisms were detected in 7 % of subjects by a population based sequencing method. Overall, the presence of these polymorphisms alone did not impact SVR rates. However, among subjects with a relatively poor response to PegINFα2b/RBV during the 4-week lead-in period, the efficacy of boceprevir appeared to be reduced for those who had V36M, T54A, T54S, V55A or R155K at baseline. In a pooled analysis of patients who are previously untreated and patients who have failed previous therapy who received four weeks of PegIFNα2b/RBV followed by boceprevir 800 mg TID in combination with PegIFNα2b/RBV in two Phase 3 studies, post-baseline RAVs were detected in 53 % of non-SVR patients. Interferon responsiveness was associated with detection of fewer RAVs. The RAVs most frequently detected post-baseline (> 25 % of subjects) in non-SVR subjects were amino acid substitutions V36M (61%) and R155K (68 %) in subjects with genotype 1a viruses and T54A (42 %), T54S (37 %), A156S (26 %) and V170A (32 %) in subjects with genotype 1b viruses. One or more boceprevir-treatment-emergent substitutions remained detectable with a population-based sequencing assay in 25% of subjects after 2.5 years of follow-up. The most common NS3/4A substitutions detected after 2.5 years of follow-up were T54S and R155K. No data are available regarding the efficacy of boceprevir among subjects who were previously exposed to boceprevir, or who previously failed treatment with a boceprevir-containing regimen.
Cross-resistance	Many of the treatment-emergent NS3/4A amino acid substitutions detected in boceprevir-treated subjects who did not achieve SVR in the Phase 3 clinical trials have been demonstrated to reduce the anti-HCV activity of other HCV NS3/4A Protease Inhibitors (PIs) The impact of prior exposure to boceprevir or treatment failure on the efficacy of other HCV NS3/4A PIs has not been studied. The efficacy of boceprevir has not been established for patients with a history of exposure to other NS3/4A PIs. Cross-resistance is not expected between boceprevir and interferons, or boceprevir and ribavirin.
Oral Bioavailability	Unknown
Effect of Food	Boceprevir must be taken with food. Food enhanced the exposure of boceprevir by up to 60 % at the 800 mg TID dose when administered with a meal, relative to the fasting state. Bioavailability is similar regardless of meal type (e.g., high-fat vs. low-fat) or whether taken 5 minutes prior to eating, during a meal, or after a meal.
Protein Binding	75 %
Vd	717 L

Tmax	2 hours
Serum T ½	3 hours
Drug concentrations	In the plasma the diastereoisomer ratio is about 2:1 in favour of the active diastereoisomer, SCH 534128. The plasma concentrations of boceprevir described below consist of both diastereoisomers. In general, PK results were similar between healthy and HCV subjects. AUC, Cmax and Cmin increased in a less-than dose-proportional manner and individual exposures overlapped substantially at 800 mg and 1,200 mg, suggesting diminished absorption at higher doses. PPK individual prediction from sparse data in HCV patients (boceprevir 800 mg TID): Cmax: 1013 ng/mL Cmin: 213 ng/mL AUC: 4403 ng.hr/mL Population PK estimates HCV patients (boceprevir 800 mg TID): Cmax: 1084 ng/mL Cmin: 218 ng/mL AUC: 4642 ng.hr/mL Healthy subjects (non-compartmental analysis)(boceprevir 800 mg TID): Cmax: 1723 ng/mL Cmin: 88 ng/mL AUC: 5408 ng.hr/mL No gender, race or age-related PK differences have been observed.
CSF (% of serum)	Not studied
Metabolism	Boceprevir is metabolized primarily by aldo-ketoreductase (AKR). Boceprevir is partly metabolized by CYP3A4/5. *In vitro,* boceprevir has been shown to be also a substrate of p-glycoprotein.
Excretion	Boceprevir is eliminated primarly by the liver. Following a single 800 mg oral dose of 14C-boceprevir, 79 % and 9 % of the dose was excreted in feces and urine, respectively, with approximately 8 % and 3 % of the dosed eliminated as boceprevir in feces and urine.
Dosing – Adult	**Boceprevir should not be used as monotherapy but only in combination with PegIFNα/RBV.** **It is important that the dose of boceprevir (800 mg) be taken orally TID (every 7-9 hours)** with food (a meal or light snack). Response-Guided Therapy is recommended for most patients, but longer dosing is recommended in target groups (e.g. cirrhosis, prior null response). *Consult most up-to-date information for treatment duration and*

	strategies. **A) Patients without cirrhosis who are previously untreated or who are previous partial responders or relapsers to PegIFNα/RBV therapy:** 1) Initiate therapy with PegIFNα/RBV for 4 weeks (TWs 1-4). 2) Add boceprevir 800 mg (four 200 mg capsules) orally TID (every 7-9 hours) to PegIFNα/RBV regimen at TW 5. Treatment duration is based on whether patients are previously untreated or had previous treatment failures and their HCV-RNA levels at TW 8, TW 12 and TW 24 **B) Patients with prior null response** If considered for treatment, these subjects should receive 4 weeks of PegIFNα/RBV followed by 44 weeks of boceprevir 800mg (four 200 capsules) orally TID (every 7-9 hours) in combination with PegIFNα/RBV **C) Patients without cirrhosis who are previously untreated with a poor interferon response** (less than a 1.0-log10 decline in HCV-RNA at TW 4 with PegIFNα/RBV alone) 4 weeks PegIFNα/RBV followed by 44 weeks of boceprevir 800 mg (four 200 mg capsules) TID (every 7-9 hours) in combination with PegIFNα/RBV **D) Patients with compensated cirrhosis** 4 weeks PegIFNα/RBV followed by 44 weeks boceprevir 800 mg (four 200 capsules) orally TID (every 7-9 hours) in combination with PegIFNα/RBV.
Dosing - Pediatric	No data available
Special instructions for pediatric patients	No data available
Adjust in Liver Dysfunction	No clinically significant differences in PK parameters were found and no dosage adjustment is recommended in patients with mild, moderate or severe hepatic impairment. The PK of a single 400 mg dose of boceprevir under fasted conditions was studied in non HCV-infected males and females with mild (Child-Pugh score 5-6), moderate (Child-Pugh score 7-9), severe (Child-Pugh score 10-12) impairment and matched subjects with normal hepatic function. Mean CL/F values in subjects with moderate and severe hepatic impairment were decreased but remained in the range of healthy subjects. Fasted dosing, a less than therapeutic dose and non-final formulation, limits the generalizability of the conclusions. AUC (tf): Mild vs healthy: 107 % (90%CI: 75-152)

	Moderate vs healthy: 132 % (90%CI: 93-187) Severe vs healthy: 145 % (90%CI: 102-205) Cmax: Mild vs healthy: 115 % (90%CI: 71-188) Moderate vs healthy: 128 % (90%CI: 79-208) Severe vs healthy: 162 % (90%CI: 99-263) Estimates of steady-state maximum AUC and Cmax parameters of patients infected with HCV in the Phase 3 studies were 9,715 ng·h/mL and 2,377 ng/mL, respectively. PegIFNα2b/RBV is contraindicated in the hepatically impaired population. Thus, the use of boceprevir with PegIFNα2b/RBV is also contraindicated in this population.
Adjust in Renal Failure/Dialysis	No dosage adjustment is in patients with any degree of renal impairment. ESRD subjects and matched subjects with normal renal function were administered a single 800 mg dose of boceprevir/ ESRD subjects were dosed prior to dialysis (Day 1) and 4 hours prior to dialysis (Day 4). The difference in exposure compared with healthy subjects was not clinically relevant, and dialysis did not alter PK parameters
Toxicity	*Many of the side effects may be related to PegIFNα2b/RBV* Most common: Anemia (49% when used with PegIFNα2b/RBV) Fatigue, anemia, nausea, headache, and dysgeusia (> 35% when used with PegIFNα2b/RBV) Abdominal pain, constipation, diarrhea, dry mouth, vomiting, GERD Fever, chills, weight loss, decrease appetite, myalgia/arthralgia, dizziness Anxiety, depression, insomnia, irritability, mood alteration Cough, dyspnea Dry skin, pruritus, rash Neutropenia, Thrombocytopenia Blurred vision
Pregnancy & Lactation	Because boceprevir is used in combination with PegIFNα/RBV, it is therefore contraindicated in pregnant women and men whose female partners are pregnant. No studies in pregnant women are available. Pregnancy risk category B (all trimesters). No effects on fetal development have been observed in rats and rabbits with boceprevir exposures 11.8- and 2.0-fold higher, respectively, than those in humans at the recommended dose of 800 TID. Boceprevir has been shown in animals to distribute across the placenta to fetal blood and tissues.

	It is unknown whether boceprevir is excreted into human breast milk. Account the potential for adverse reactions from the drug in nursing infants vs the benefit of therapy for the mother. Available pharmacodynamic/toxicological data in animals have shown excretion of boceprevir and/or metabolites in milk. Consequently a risk to nursing newborns/infants cannot be excluded.
Drug interactions	**Effect of Other Drugs on boceprevir Pharmacokinetics** Boceprevir is partly metabolized by CYP3A4/5. Co-administration with drugs that induce or inhibit CYP3A4/5 could increase or decrease exposure to boceprevir. **Effects of boceprevir on Pharmacokinetics of Other Drugs** Boceprevir is a strong inhibitor of CYP3A4/5. Drugs metabolized primarily by CYP3A4/5 may have increased exposure, which could increase or prolong their therapeutic and adverse effects. *See separate drug interaction chart*. **Contraindicated Drugs**: alfuzosin, amiodarone, propafenone, quinidine, carbamazepine, phenobarbital, phenytoin, rifampin, dihydroergotamine, ergonovine, ergotamine, methylergonovine, cisapride, St. John's Wort, lovastatin, simvastatin, sildenafil or tadalafil when used for the treatment of pulmonary arterial hypertension, pimozide, drospirenone, astemizole, terfenadine, midazolam (orally administered), and triazolam (orally administered).
Baseline assessment	CBC (with WBC differential count) Pregnancy test in female patients and in female partners of male patients
Routine Labs	HCV-RNA levels should be monitored at Treatment Weeks (TWs) 8, 12, and 24, at the End of Treatment (EOT), during treatment follow-up, and for other time points as clinically indicated. In previously untreated subjects without cirrhosis, monitoring of HCV-RNA levels at TW 4 is recommended to determine interferon responsiveness. CBC (with WBC differential count) should be obtained at TWs 4, 8 and 12 and should be closely monitored at other time points as considered clinically appropriate. If serum hemoglobin is < 100 g/L, a decrease in dose or interruption of RBV may be warranted. Decreases in the neutrophil counts may require dose reduction or discontinuation of PegIFNα/RBV. Monthly pregnancy test in female patients and in female partners of male patients
Dosage Forms	Capsules (Hard-gelatin): 200 mg (yellowish-brown) DIN 02370816 Peelable aclar/PVC/aluminium blisters containing 12 capsules. 7 blisters per folding carton and 2 folding cartons per outer carton

	Combination formulations: Boceprevir 200 mg capsules plus Ribavirin 200 mg capsules plus peginterferon alfa-2b powder for solution in REDIPEN® single dose delivery system DIN: 02371448; 02371456; 02371464; 02371472 **Deliverable Dose 80 mcg/0.5 mL** A carton containing two boxes of 84 BOC capsules each for a total of 168 BOC capsules, two boxes of 28 RBV capsules each for a total of 56 RBV capsules, plus two PegIFNα2b REDIPEN® single dose delivery systems, 80 mcg/REDIPEN®, with two 30-gauge needles (0.3 x 8 mm), 4 alcohol swabs and two pen holders. **Deliverable Dose 100 mcg/0.5 mL** A carton containing two boxes of 84 BOC capsules each for a total of 168 BOC capsules, two boxes of 28 RBV capsules each for a total of 56 RBV capsules, plus two PegIFNα2b REDIPEN® single dose delivery systems, 100 mcg/REDIPEN®, with two 30-gauge needles (0.3 x 8 mm), 4 alcohol swabs and two pen holders. **Deliverable Dose 120 mcg/0.5 mL** A carton containing two boxes of 84 BOC capsules each for a total of 168 BOC capsules, two boxes of 35 RBV capsules each for a total of 70 RBV capsules, plus two PegIFNα2b REDIPEN® single dose delivery systems, 120 mcg/REDIPEN®, with two 30-gauge needles (0.3 x 8 mm), 4 alcohol swabs and two pen holders. **Deliverable Dose 150 mcg/0.5 mL** 1. A carton containing two boxes of 84 BOC capsules each for a total of 168 BOC capsules, two boxes of 42 RBV capsules each for a total of 84 RBV capsules, plus two PegIFNα2b REDIPEN® single dose delivery systems, 150 mcg/REDIPEN®, with two 30-gauge needles (0.3 x 8 mm), 4 alcohol swabs and two pen holders. 2. A carton containing two boxes of 84 BOC capsules each for a total of 168 BOC capsules, two boxes of 49 RBV capsules each for a total of 98 RBV capsules, plus two PegIFNα2b REDIPEN® single dose delivery systems, 150 mcg/REDIPEN®, with two 30-gauge needles (0.3 x 8 mm), 4 alcohol swabs and two pen holders.
Storage	Boceprevir capsules should be refrigerated at $2^{o}C$ – $8^{o}C$. Can also be stored at room temperature (15°C – 30°C) for up to 3 months. Store in the original container.

References

Victrelis™. Product Monograph. Merck Canada Inc, Kirkland, Quebec, Canada, June 13, 2012.

Selected Properties of Telaprevir

Other names	TVR, Incivek®
Manufacturer	Vertex Pharmaceuticals Incorporated
Pharmacology/ Mechanism of Action	Telaprevir is a direct-acting antiviral agent (DAA) against the hepatitis C virus. This agent is a specific inhibitor of the HCV NS3·4A protease which is essential for viral replication. The slow binding mechanism for the interaction of telaprevir with the HCVNS3•4A protease occurs in 2 steps, with formation of a weaker complex followed by rearrangement to the tightly bound form (covalent complex).
Activity	Telaprevir inhibits genotype 2 HCV NS3 serine protease with similar potency to genotype 1a or 1b HCV proteases while its activity against genotype 3 and 4 HCV proteases is reduced. The approved indication for telaprevir is for HCV genotype 1 infection only.
Resistance – genotypic	*In Vitro* Studies Variants V36A/M, T54A/S, R155K/T, and A156S conferred lower levels of in vitro resistance to telaprevir (3- to 25-fold increase in telaprevir IC50), and the A156V/T and V36M+R155K variants conferred higher levels of in vitro resistance to telaprevir (>25-fold increase in telaprevir IC50). All telaprevir-resistant variants studied remained fully sensitive to interferon-alfa and ribavirin. Clinical Virology Studies Predominant telaprevir-resistant variants at baseline (pre-treatment) were rare (V36M, T54A and R155K <1% and T54S 2.7%). Predominant baseline resistance to telaprevir did not preclude subjects from achieving an SVR with a telaprevir, peginterferon-alfa, and ribavirin regimen. Sequence analyses of HCV in subjects treated with telaprevir who had on-treatment virologic failure or relapse identified amino acid substitutions at 4 positions in the NS3-4A protease region, consistent with the mechanism of action for telaprevir (V36A/M, T54A/S, R155K/T, and A156S/T/V). On-treatment virologic failure during telaprevir treatment was predominantly associated with higher-level resistant variants, and relapse was predominantly associated with lower-level resistant variants or wild-type virus. Subjects with HCV genotype 1a predominately had V36M and R155K single and combination variants, while subjects with HCV genotype 1b predominately had V36A, T54A/S, and A156S/T/V variants. This difference is likely due to the higher genetic barrier for the V36M and R155K substitutions for genotype 1b than genotype 1a. Among subjects treated with telaprevir, on-treatment virologic failure was more frequent in subjects with genotype 1a than with genotype 1b and more frequent in prior null responders than in other populations (treatment naïve, prior relapsers, prior partial responders). Follow-up analyses of telaprevir-treated subjects who did not achieve an SVR show that the population of wild-type virus increased and the population of telaprevir-resistant variants became undetectable over time after the end of telaprevir treatment.
Cross-Resistance	There is some overlap between telaprevir and boceprevir primary resistance-associated variants:

<table>
<tr><td></td><td>
<table>
<tr><th>Telaprevir</th><th>Boceprevir</th></tr>
<tr><td>V36A/M</td><td>V36M</td></tr>
<tr><td>T54A/S</td><td>T54A</td></tr>
<tr><td>R155K/T</td><td>R155K</td></tr>
<tr><td>A156T/V</td><td>A156T</td></tr>
</table>
</td></tr>
<tr><td>Oral Bioavailability</td><td>Orally available, most likely absorbed in the small intestine, with no evidence for absorption in the colon.

Exposure to telaprevir is higher during co-administration of peginterferon alfa and ribavirin than after administration of telapreviralone.</td></tr>
<tr><td>Effect of Food</td><td>The systemic exposure (AUC) to telaprevir was decreased by about 73% when telaprevir was administered under fasting conditions compared to when telaprevir was administered following a standard fat meal (533 kcal, 21 g fat). The telaprevir exposure was decreased by about 39% with a low-fat meal (249 kcal, 3.6 g fat), while exposure was increased by about 20% with a high-fat meal (928 kcal, 56 g fat), compared to telaprevir administration with a standard fat meal. Therefore, telaprevir should always be taken with food (not low fat; ~ 20g fat content).</td></tr>
<tr><td>Protein Binding</td><td>Telaprevir is approximately 59% to 76% bound to human plasma proteins. Telaprevir binds primarily to alpha 1-acid glycoprotein and albumin and the binding is concentration dependent, decreasing with increasing concentrations of telaprevir.</td></tr>
<tr><td>Vd</td><td>Typical apparent volume of distribution is estimated to be 252 L with an inter-individual variability of 72%.</td></tr>
<tr><td>Tmax</td><td>In clinical studies in healthy subjects in which a single 750-mg dose of telaprevir was administered after a regular breakfast, the median time of maximum concentration (tmax) ranged from 4.0 to 5.0 hours.</td></tr>
<tr><td>Serum T ½</td><td>In clinical studies in healthy subjects in which a single 750-mg dose of telaprevir was administered after a regular breakfast, the mean half-life (t1/2) ranged from 4.0 to 4.7 hours. At steady state, the effective half-life is about 9 to 11 hours.</td></tr>
<tr><td>Drug Concentrations</td><td>Drug concentrations in adult health subjects and in subjects with chronic hepatitis C are displayed below:
<table>
<tr><th></th><th>Healthy Volunteers (n=39)</th><th>CHC treatment-naïve patients (n=641)</th><th>CHC treatment-experienced patients (n=191)</th></tr>
<tr><td>C_{max} (ng/mL)</td><td>3040 (662)</td><td>3260 (946)</td><td>3990 (1120)</td></tr>
<tr><td>C_{min} (ng/mL)</td><td>1960 (548)</td><td>2690 (827)</td><td>3340 (1170)</td></tr>
<tr><td>AUC_{8h} (ng*h/mL)</td><td>19,900 (4710)</td><td>24,400 (7180)</td><td>30,100 (8720)</td></tr>
</table>
</td></tr>
<tr><td>Minimum target trough concentrations (for wildtype virus)</td><td>In an HCV subtype 1b replicon assay, the telaprevir IC50 value against wild-type HCV was 0.354 µM, similar to a subtype 1a infectious virus assay IC50 of 0.28 µM.</td></tr>
<tr><td>Metabolism</td><td>Telaprevir is extensively metabolized in the liver, involving hydrolysis, oxidation, and reduction. CYP3A4 is the major CYP isoform responsible for telaprevir metabolism. However, non-CYP mediated metabolism likely plays a role after</td></tr>
</table>

<table>
<tr><td></td><td>multiple dosing of telaprevir.</td></tr>
<tr><td>Excretion</td><td>82% of dose recovered in feces
9% of dose recovered in expired air
1% of dose recovered in urine
(within 96 hours following administration of a single radiolabeled dose of telaprevir 750 mg)
Apparent total clearance (Cl/F) is estimated to be 32.4 L/h with an inter-individual variability of 27.2%.</td></tr>
<tr><td>Dosing – Adult</td><td>Telaprevir must not be administered as monotherapy and must only be prescribed with both peginterferon alfa and ribavirin

The recommended dose of telaprevir is 750 mg (two 375-mg tablets) taken orally 3 times a day (7-9 hours apart) with food (not low fat). The total daily dose is 6 tablets (2250 mg).

<u>If taken with efavirenz (not currently approved for use in HIV patients)</u>
1125 mg orally 3 times a day every 7-9 hours with food (not low fat)

<u>Treatment Duration</u>
The recommended duration of treatment with telaprevir is 12 weeks in combination with peginterferon alfa and ribavirin:

<table>
<tr><th colspan="4">Treatment-Naïve and Prior Relapse Patients</th></tr>
<tr><th>HCV-RNA</th><th>Triple Therapy (telaprevir, peginterferon alfa and ribavirin)</th><th>Dual Therapy (peginterferon alfa and ribavirin)</th><th>Total Treatment Duration</th></tr>
<tr><td>Undetectable at Weeks 4 and 12</td><td>First 12 weeks</td><td>Additional 12 weeks</td><td>24 weeks</td></tr>
<tr><td>Detectable (1000 IU/mL or less) at Weeks 4 and/or 12</td><td>First 12 weeks</td><td>Additional 36 weeks</td><td>48 weeks</td></tr>
<tr><th colspan="4">Prior Partial and Null Responder Patients</th></tr>
<tr><td></td><th>Triple Therapy (telaprevir, peginterferon alfa and ribavirin)</th><th>Dual Therapy (peginterferon alfa and ribavirin)</th><th>Total Treatment Duration</th></tr>
<tr><td>All Patients</td><td>First 12 weeks</td><td>Additional 36 weeks</td><td>48 weeks</td></tr>
</table>

<u>Treatment Failures</u>
Patients with inadequate viral response are unlikely to achieve SVR, and may develop treatment emergent resistance substitutions. Discontinuation of therapy is recommended in all patients with (1) HCV-RNA levels of greater than or equal to 1000 IU/mL at Treatment Week 4 or 12; or (2) confirmed detectable HCV-RNA levels at Treatment Week 24.
<table>
<tr><th>HCV-RNA</th><th>Action</th></tr>
<tr><td>Week 4 or Week 12: Greater than 1000 IU/mL</td><td>Discontinue telaprevir and peginterferon alfa and ribavirin</td></tr>
<tr><td>Week 24: Detectable</td><td>Discontinue peginterferon alfa and ribavirin</td></tr>
</table>
</td></tr>
</table>

	Missed Doses If a dose is missed within 4 hours of the scheduled time, it should be taken as soon as possible with food. If more than 4 hours has passed since the dose should have been taken, this dose should be skipped, and the usual dosing schedule resumed.
Dosing – Pediatric	The use of telaprevir in pediatric patients is not recommended. No clinical data are available regarding the use of telaprevir in children and adolescents younger than 18 years of age.
Adjust in Liver Dysfunction	Dose modification of telaprevir is not required when administered to subjects with mild hepatic impairment (Child-Pugh A, score 5- 6). Telaprevir is not recommended for use in patients with moderate or severe hepatic impairment (Child-Pugh B or C, score ≥ 7) or decompensated liver disease. • Steady-state exposure to telaprevir was reduced by 15% in HCV-negative subjects with mild hepatic impairment (Child-Pugh Class A) compared to healthy subjects. • Steady-state exposure to telaprevir was reduced by 46% in HCV-negative subjects with moderate hepatic impairment (Child-Pugh Class B) compared to healthy subjects. No pharmacokinetic or safety data are available regarding the use of telaprevir in HCV-infected patients with moderate or severe hepatic impairment (Child-Pugh B or C, score ≥ 7) or decompensated liver disease. • The pharmacokinetics of telaprevir In HCV-negative subjects with severe hepatic impairment (Child- Pugh Class C) were not studied. • The use of telaprevir in organ transplant patients is not recommended because the safety and efficacy of telaprevir in this patient population has not been established.
Adjust in Renal Failure/ Dialysis	No dose adjustment is necessary for telaprevir in HCV-infected patients with mild, moderate or severe renal impairment. • After administration of a single dose of 750 mg to HCV-negative subjects with severe renal impairment (CrCl < 30 mL/min), the mean telaprevir Cmax and AUC were increased by 10% and 21%, respectively, compared to healthy subjects. • The safety and efficacy of telaprevir combination therapy has not been established in HCV-infected subjects with a CrCl ≤ 50 mL/min • Telaprevir has not been studied in patients with end-stage renal disease (ESRD) or on hemodialysis • It is not known whether telaprevir is dialyzable by peritoneal or hemodialysis.
Toxicity	Common: The most frequent adverse effects when used in combination with peginterferon alfa and ribavirin include: >10-20%: fatigue, pruritus, nausea, headache, influenza-like illness, rash, anemia, insomnia, diarrhea, vomiting, pyrexia, hemorrhoids, and proctalgia Serious: The most frequent serious adverse events were anemia and rash • Rash: Serious skin reactions, including Drug Rash with Eosinophilia and Systemic Symptoms (DRESS) and Stevens-Johnson Syndrome (SJS), were reported in less than 1% of subjects who received telaprevir combination treatment compared to none who received peginterferon alfa and ribavirin alone. These serious skin reactions all required hospitalization and all patients recovered. The presenting signs of DRESS may include rash, fever, facial edema, and evidence of internal organ involvement (e.g., hepatitis, nephritis). Eosinophilia may or may not be present. The presenting signs of SJS may

	include fever, target lesions, and mucosal erosions or ulcerations (e.g., conjunctivae, lips). Telaprevir must not be restarted if discontinued due to rash (discontinuation of telaprevir combination treatment is not required for mild and moderate rash). • Anemia: In placebo-controlled Phase 2 and 3 clinical trials, the overall incidence and severity of anemia increased with telaprevir combination treatment compared to peginterferon alfa and ribavirin alone. Hemoglobin values of <100 g/L were observed in 33.7% of patients who received telaprevir combination treatment and in 13.6% of patients who received peginterferon alfa and ribavirin. Hemoglobin levels decrease sharply during the first 4 weeks of treatment, with lowest values reached at the end of telaprevir dosing. Hemoglobin values gradually improve after telaprevir dosing completion. Potential for QT Prolongation: A study conducted in healthy volunteers (n=41) showed a modest effect of telaprevir at a dose of 1875 mg q8h on the QTcF interval with a placebo-adjusted maximum mean increase of 8.0 msec (90% CI: 5.1-10.9). Exposure at this dose was comparable to the exposure in HCV-infected patients dosed at 750 mg telaprevir q8h plus peginterferon alfa and ribavirin. The potential clinical significance of these findings is uncertain. Use of telaprevir should be avoided in patients with congenital QT prolongation, or a family history of congenital QT prolongation or sudden death. Telaprevir should be used with caution in patients with a history of acquired QT prolongation; clinically relevant bradycardia (persistent heart rate <50 bpm); a history of arrhythmias (especially ventricular arrhythmias or atrial fibrillation); a history of heart failure with reduced left-ventricular ejection fraction; myocardial ischemia or infarction; cardiomyopathy; conduction system disease; or a requirement for drugs known to prolong the QT interval without CYP3A4 involvement by telaprevir (e.g., methadone).
Pregnancy & Lactation	U.S. FDA's Pregnancy Category: Category B (All Trimesters) Because telaprevir is to be taken in combination with peginterferon alfa and ribavirin, the warnings applicable to those drugs are also applicable to combination treatment. Refer also to the prescribing information for peginterferon alfa and ribavirin. Ribavirin may cause birth defects and/or death of the exposed fetus. Extreme care must be taken to avoid pregnancy in female patients and in female partners of male patients—both during treatment and for 6 months after the completion of all treatment. Telaprevir combination treatment should not be initiated unless a female patient has a negative pregnancy test immediately prior to initiation of treatment. Telaprevir treatment alone in mice and rats did not result in harm to the fetus. Telaprevir treatment alone had effects on fertility parameters in rats. These effects are likely associated with testicular toxicity in male rats but contributions of the female cannot be ruled out. It is not known whether telaprevir is excreted in human breast milk. When administered to lactating rats, levels of telaprevir were higher in milk compared to those observed in plasma. Because of the potential for adverse reactions in nursing infants, nursing must be discontinued prior to initiation of treatment.
Drug Interactions ***** See separate Drug Interaction Table.	Telaprevir is an inhibitor of CYP3A and P-glycoprotein (P-gp). Co-administration of telaprevir with drugs that are primarily metabolized by CYP3A and/or substrates for P-gp may result in increased plasma concentrations of such drugs, which could increase or prolong their therapeutic effect and adverse reactions Telaprevir is contraindicated when combined with drugs that are highly dependent on CYP3A for clearance and for which elevated plasma concentrations are associated with serious and/or life-threatening events (narrow therapeutic index).

	Telaprevir is also contraindicated when combined with drugs that strongly induce CYP3A and thus may lead to lower exposure and loss of efficacy of telaprevir: • Aldosterone antagonists (eplerenone) due to potential for hyperkalemia • Alpha 1-adrenoreceptor antagonists (alfuzosin) due to potential for hypotension or cardiac arrhythmia • Antiarrhythmics (quinidine, flecainide, propafenone, amiodarone) due to potential for serious and/or life-threatening reactions such as cardiac arrhythmias • Antimycobacterials (rifampin) because it reduces telaprevir plasma concentrations significantly • Ergot Derivatives (dihydroergotamine, ergonovine, ergotamine, methylergonovine) due to potential for acute ergot toxicity characterized by peripheral vasospasm or ischemia • St. John's Wort because it reduces telaprevir plasma concentrations • HMG-CoA Reductase Inhibitors (atorvastatin, lovastatin, simvastatin) due to potential for myopathy including rhabdomyolysis • Neuroleptics (pimozide) due to potential for serious and/or life-threatening adverse reactions such as cardiac arrhythmias secondary to increases in plasma concentrations of antiarrhythmics • PDE-5 Inhibitors due to potential for hypotension and/or cardiac arrhythmia (sildenafil: only when used for the treatment of pulmonary arterial hypertension) • Sedatives/Hypnotics (triazolam) due to potential for increased sedation or respiratory depression • Triptans (eletriptan) due to potential for coronary artery vasospasm, transient myocardial ischemia, myocardial infarction, ventricular tachycardia, and ventricular fibrillation. The potential for prolongation of the QT/QTc interval may be increased if telaprevir is administered in the presence of CYP3A4 inhibitors, such as ritonavir, ketoconazole, and erythromycin. Caution should be observed if these drugs are to be used concomitantly with telaprevir. Caution should also be observed when using telaprevir with drugs that can disrupt electrolyte levels. <u>Other significant DIs:</u> • Anticoagulants (warfarin) → concentrations of warfarin may be altered when coadministered with telaprevir. Monitor the INR • Immunosuppressants (cyclosporine, tacrolimus, sirolimus) because concentrations of immunosuppressants may be increased with telaprevir • Long Acting Beta-Adrenoceptor Agonists (salmeterol): Concentrations of salmeterol may be increased with telaprevir. Concurrent administration of salmeterol and telaprevir is not recommended. The combination may result in increased risk of cardiovascular adverse events associated with salmeterol, including QT prolongation, palpitations and sinus tachycardia. <u>Antiretroviral Interactions:</u> Telaprevir concentrations are reduced by ritonavir-boosted fosamprenavir, darunavir, lopinavir, and, to a lesser extent, atazanavir. Efavirenz also reduces blood concentrations of telaprevir, an effect that can, in part, be offset by using a higher telaprevir dose (1125 mg q8h). Telaprevir use significantly reduces concentrations of darunavir and fosamprenavir. • Avoid coadministration with DRV/r, FPV/r, LPV/r • ATV/r is considered compatible with telaprevir • EFV is considered compatible with telaprevir but with a dose increase of telaprevir (see dosing recommendations in section above) • TDF is considered compatible with telaprevir

	• RAL is considered compatible with telaprevir
Baseline Assessment	The following laboratory evaluations (complete blood count with white blood cell differential counts, electrolytes, serum creatinine, liver function tests, TSH, uric acid, serum cholesterol and LDL) must be conducted in all patients prior to initiating telaprevir combination treatment. These are recommended baseline values for initiation of telaprevir combination treatment: - Hemoglobin: ≥120 g/L (females); ≥130 g/L (males) - Platelet count ≥ 90,000/mm^3 - Absolute neutrophil counts ≥1500/mm^3 - Adequately controlled thyroid function (TSH) - Calculated creatinine clearance ≥50 mL/min - Potassium ≥3.5 mmol/L
Routine Labs	- Hemoglobin at least every 4 weeks - Chemistry (electrolytes, serum creatinine, uric acid, hepatic enzymes, bilirubin, TSH, serum cholesterol, and LDL) as frequently as the hematology evaluations or as clinically indicated - Hematology (incl. white cell differential count) at week 2, 4, 8, and 12 or as clinically appropriate thereafter
Dosage Forms	375 mg purple film-coated capsule-shaped tablets. Each tablet is debossed with the characters “V 375” on one side.
Storage	Store at 25ºC; excursions permitted to 15-30ºC.

References:

Asselah T, Marcellin P. New direct-acting antivirals’ combination for the treatment of chronic hepatitis C. Liver International 2011; 31 suppl 1: 68-77.

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Susser S, Welsch C, Wang Y, et al. Characterization of resistance to the protease inhibitor boceprevir in hepatitis C virus-infected patients. Hepatology 2009; 50(6):1709-18.

Thomas DL, Bartlett JG, Peters MG, et al. Provisional Guidance on the Use of Hepatitis C Virus Protease Inhibitors for Treatment of Hepatitis C in HIV-Infected Persons. CID 2011 (HIV/AIDS)

Vertex Pharmaceuticals Inc. INCIVEK Product Monograph. Laval, Qc. August 11, 2011.

IV. ADDITIONAL INFORMATION FOR PHARMACISTS AND PHYSICIANS

Information on Crushing Antiretrovirals

DRUG NAME	OTHER INFO
ABACAVIR 300mg tab	With or without food 20mg/ml suspension strawberry-banana liquid. Store at room temperature
DIDANOSINE 125,200,250, 400mg capsule 4g powder for oral suspension (10mg/ml)	Videx EC: 1.5 hr before or 2 hrs after food 4g powder for10mg/ml suspension – may be available through SAP (4g powder) Reconstitute powder with 200 ml sterile water, shake, then 200 ml antacid (Maalox Extra strength). Stable for 30 days in fridge.
EMTRICITABINE With Tenofovir	No food restrictions. Liquid available in U.S.
LAMIVUDINE 150, 300mg tab 10mg/ml soln	10mg/ml solution. Strawberry banana flavour. Stable room temperature. Solution contains 6% v/v alcohol and 3g sugar
STAVUDINE 15,20,30,40mg capsule 1mg/ml susp	Take with food if upset stomach. May open capsule & give in small portion of food or 5-10ml cool tap water. 1mg/ml suspension from SAP. Fruit-flavoured, stable 30 days in fridge.
TENOFOVIR 300mg tablet	Tablets may be split or chewed (bitter taste) May dissolve crushed tablet in 100 mL water, grape juice or grapefruit juice & take within 20 min. May split tab and insert in empty gelatin capsule to mask bitter taste.
ZIDOVUDINE 100mg capsule 10mg/ml soln	Solution strawberry flavoured. Stable at room temperature. May open capsules & give in small portion of food or 5-10ml cool tap water.
KIVEXA®	Abacavir 600mg & lamivudine 300mg daily Film coated immediate release tablet however no studies regarding stability of split or crushed tablets. (Email communication, GlaxoSmithKline, May 2008)
TRIZIVIR®	Abacavir 300mg, zidovudine 300mg & lamivudine 150mg BID Film coated immediate release tablet however no studies regarding stability of split or crushed tablets.
TRUVADA®	Emtricitabine 200mg & Tenofovir 300mg. No food restrictions. May split tablets. May crush and stir into water, grape juice or orange juice. The stability of the mixture is unknown. (Email communication, Gilead, July 2012)
COMBIVIR®	Zidovudine 300mg & lamivudine 150mg BID. Film coated immediate release tablet however no studies regarding stability of split or crushed tablets. (Email communication, GlaxoSmithKline, May 2008)
ATRIPLA®	Efavirenz 600mg, emtricitabine 200mg & tenofovir 300mg daily. Atripla FDC tablet crushed, dissolved in 5 mL of water and diluted to 20 mL with Ora-Sweet oral solution and used within 24 hours (JAIDS 2011; 56:e131-2) did not meet bioequivalence of Atripla whole tablet however clinical implications unknown. Efavirenz not soluble in water. (Email communication, Gilead, July 2012)

DRUG NAME	OTHER INFO
EFAVIRENZ 50,100,200mg capsule 600mg tablet	Not in pregnancy Can take with food but high fat foods may increase absorption by 50% thus increasing SE. 30mg/ml suspension available via Sustiva Oral liquid expanded access program at 1-877-372-7097 (Massachusetts). Strawberry-mint flavour. Store at room temperature in original container. Stable for 30 days after opening. Can open capsules and mix powder with apple sauce (will result in hot "jalapeno" sensation). Grape jelly may mask taste. For NG admin, open capsules, grind and mix with either 5ml MCT oil or 15ml Ora-Sweet. Do not mix with polyethylene glycol (will decrease bioavailability). Insoluble in water.
NEVIRAPINE 200mg tablet 400 mg XR 10mg/ml syrup	Avoid in women with CD4>250, men with CD4>400 due to hepatotoxicity. Liquid 10mg/ml available through SAP. Sweet-flavoured syrup, stable at room temperature. Can crush immediate release tablets (200 mg), mix in water and give orally or by G-tube. Extended release (XR) formulation must be swallowed whole.
ETRAVIRINE 100mg tablet 200 mg tablet	May disperse tablet in 100mL cold water by stirring tablet until homogenous, white, cloudy suspension obtained. Drink immediately. Rinse glass with water several times and swallow each rinse to ensure entire dose consumed. (Data on file, Janssen, July 2012)
RILPIVIRINE 25 mg tablet	Film coated tablet. No data available on stability of splitting or crushing rilpivirine tablets. Rilpivirine is insoluble in water over wide pH range. (Email communication, Janssen July 2012).
COMPLERA®	Tenofovir 300mg & Emtricitabine 200 mg & Rilpivirine 25 mg. Splitting or crushing Complera tablets into a liquid medium has not been studied and is not recommended. Rilpivirine hydrochloride is insoluble in water over a wide pH range. (Email communication, Gilead July 2012).

DRUG NAME	OTHER INFO
ATAZANAVIR 150,200, 300mg capsule	50g/1.5g dispersible oral powder, 180g bottle is investigational only. Powder may be mixed with small amount of water, applesauce, milk or yogurt (consume within 3 hours of mixing). Do not mix with juices or foods with high pH. Capsules may be opened and contents mixed with applesauce for immediate ingestion with a light meal. (Bristol Myers Squibb, Personal Communication, May 22, 2008).
DARUNAVIR 75 mg, 150 mg, 400mg, 600 mg tablet 100mg/mL oral susp (licensed in US)	No data available on chewing or crushing. No problems anticipated if film coated tablets chewed or crushed for administration through a nasogastric (NG) tube (Data on file, Janssen, July 2012)
FOSAMPRENAVIR 700mg tablet 50mg/mL susp	50mg/mL oral suspension; 0.6% propylene glycol Grape, bubblegum, peppermint flavour Take suspension on an empty stomach Store between 2-30℃. Shake well. Do not freeze. Discard suspension 28 days after opening. No data available regarding stability of crushed or dissolved tablet.
INDINAVIR 200, 400mg capsule	Unboosted: on empty stomach with plenty of water (>1.5l/day) Boosted with ritonavir: with or without food. Still need 1.5L/day of fluids Liquid being formulated. 10mg/ml indinavir syrup complex compounding formulation. Stable for 14 days in refrigerator, store in glass bottle. See Am J Health Syst Pharm 2000; 57(14):1332-9.
LOPINAVIR/ RITONAVIR 200/50mg tablet 100/25 mg tablet 80/20mg/ml liquid	? peanut allergy with pediatric preparation. 80mg LPV/20mg RTV per mL; 160ml bottle. Cotton-candy flavoured yellow-orange oral solution Stable at room temp for 42 days. 42.4% alcohol
NELFINAVIR 250, 625mg tablet	Take with meal to increase absorption. Powder 50mg/g oral powder (1g=1 level scoop) available through facilitated access. Can also dissolve tablets (250mg) in 5ml sterile water. Tablet or powder may be mixed with food or liquid up to 6 hours (refrigerated) before dose is taken.

RITONAVIR 100mg tablet 80mg/mL oral liquid	80mg/mL orange-coloured oral solution. Peppermint and caramel flavoured. Shake well before use. Store at room temperature in original container. Do not refrigerate. 43% v/v alcohol. Liquid is unpalatable, bad aftertaste. Tips: - Mix oral solution with milk/chocolate milk or pudding - Give after popsicle/frozen juice to dull taste buds - Give after grape jelly, maple syrup, or peanut butter which coats mouth -Give strong flavour after dose: syrup, cheese, chewing gum
SAQUINAVIR 200 mg capsule 500mg tablet	Hard gel caps may be opened and powder sprinkled on food, simple syrup or water (unpleasant taste). No liquid formulation due to unpalatability. Take within 2 hrs of a meal or substantial snack, even when boosted. Photosensitivity
TIPRANAVIR 250mg capsule	Soft gelatin capsules – cannot be split or crushed (Verbal communication, Boehringer Ingelheim, May 2008).

DRUG NAME	**OTHER INFO**
RALTEGRAVIR 400mg tablet	Crushing tablets not recommended. Granules (sub-units of the tablet) dissolve faster than intact tablets and may result in faster release of drug which could affect in-vivo performance. (Data on file, Merck Frosst, May 2008) Drug has a bitter taste which is masked by the film coating
MARAVIROC 150, 300mg tablet	Film coated immediate release tablet however no studies regarding stability of split or crushed tablets. (Verbal communication, Pfizer, May 2008).

Oral liquid information taken directly from chart on www.hivclinic.ca July 2012

Impact of Food/Meal on Antiretroviral Drug Absorption

Drug	Dose	Type of Meal	AUC	CV	Cmax	CV	Recommendation	Reference
PROTEASE INHIBITORS								
Atazanavir	400 mg	Light meal (357 kCal, 8.2 g fat, 10.6 g protein)	↑ 70%	~ ↓ 50%	↑ 57%	~ ↓ 50%	Administration of REYATAZ with food enhances bioavailability and reduces pharmacokinetic variability. REYATAZ capsules must be taken with food.	US Product Monograph, March 2007
	"	High fat meal (721 kcal, 37.3 g fat, 29.4 g protein)	↑ 35%	~ ↓ 50%	N/c	~ ↓ 50%		
	300/100 mg	High Fat (721 kCal, 37.3 g fat, 29.4 g protein)	↑ 35%	~ ↓ 50%	N/c	~ ↓ 50%		US Product Monograph, March 2007
	300/100 mg (15 day study in HIV-infected subjects)	Standardized meal (440 kCal, 10 g fat, 24 g protein) vs. fasting	↓41%		↓ 32%		ATV C24 ↓ 53% fasting vs. fed. RTV AUC ↓ 26%, Cmax ↑ 4%, C24 ↓ 53%. Take with food.	Giguere et al. 11th IWCPHT 2010, #30.
	300/100 mg	fasting	-	45%	-	49%	Atazanavir AUC with ritonavir is increased with a light meal, and C24 is ↑ with both a light or high fat meal, with lower variability under both fed conditions relative to fasting. Take with food.	Child et al. 8th IWCPHT 2007, #25.
	"	High fat (951 kcal, 52% fat)	No change	35%	↓ 11%	35%	Cmin ↑ 40% vs. fasting	
	"	Light meal (336 kcal, 14% fat)	↑ 33%	37%	↑ 40%	37%	Cmin ↑ 33% vs. fasting.	
Darunavir	600/100 mg BID	Exposure to darunavir unaffected by type of meal (standard, high-fat, nutritional protein rich drink, or croissant with coffee).	↑ 35%				Darunavir tablets, co-administered with ritonavir, should be taken with food, which could be a light snack.	Darunavir Clinical Overview, Tibotec, December 2005.
Fosamprenavir tablets	1400 mg	high-fat meal: 967kcal, 67g fat, 33g protein, 58g carbohydrate)	N/c		N/c		TELZIR™ tablets may be taken with or without food.	Canadian Product Monograph, December 2004.
Fosamprenavir calcium oral suspension		high fat meal	↓ 25%		↓ 40%		The TELZIR™ oral suspension should be taken without food and on an empty stomach at the same dose as the tablets.	Canadian Product Monograph, December 2004.
Lopinavir capsules	400/100 mg	Moderate fat meal (500-682 kcal, 23 to 25% calories from fat)	↑ 48%		↑ 23%		To enhance bioavailability and minimize pharmacokinetic variability KALETRA should be taken with food.	US Product Monograph, April 2005.

Drug	Dose	Type of Meal	AUC	CV	Cmax	CV	Recommendation	Reference
"	"	high fat meal (872 kcal, 56% from fat)	↑ 97%		↑ 43%			"
Lopinavir oral solution	400/100 mg	Moderate fat meal (500-682 kcal, 23 to 25% calories from fat)	↑ 80%		↑ 54%		To enhance bioavailability and minimize pharmacokinetic variability KALETRA oral solution should be taken with food.	"
"	"	high fat meal (872 kcal, 56% from fat)	↑ 130%		↑ 56%			"
Lopinavir tablets	400/100 mg	moderate fat meal (500 – 682 Kcal, 23 to 25% calories from fat)	↑ 26.9%	↓	↑ 17.6%	↓	Kaletra tablets may be taken with or without food.	US Product monograph, October 2005
"	"	high fat meal (872 Kcal, 56% from fat)	↑ 18.9%		N/c			"
Nelfinavir 250 mg tablets	1250 mg	125 Kcal, 20% calories from fat	2.2-fold ↑		2.0-fold ↑		VIRACEPT should be taken with a meal.	US Product Monograph, April 2004.
		500 Kcal, 20% calories from fat	3.1-fold ↑		2.3-fold ↑			"
		1000 Kcal, 50% calories from fat	5.2-fold ↑		3.3-fold ↑			"
"	"	Standard breakfast: 820 kcal (protein 110 kcal, fat 400 kcal, carbohydrates 310 kcal)	↑ 509%	15% ↓ (66.1 → 56.1%)	↑ 431%	44% ↓ (64.5 → 36.1%)	Decreased variability when administered with food.	Kaeser et al. Int J Clin Pharmacol Ther 2005;43:154-62.
Nelfinavir 625 mg tablets	1250 mg	Standard breakfast: 820 kcal (protein 110 kcal, fat 400 kcal, carbohydrates 310 kcal)	↑ 733%	20% ↓ (85.4 → 67.9%)	↑ 413%	38% ↓ (65.5 → 40.6%)	VIRACEPT should be taken with a meal. Decreased variability when administered with food.	"
Ritonavir 100 mg tablets	100 mg single dose	high fat meal (907 kcal; 52% fat, 15% protein, 33% carbohydrates) vs. fasting	23% ↓		23% ↓		The type of meal administered did not change ritonavir tablet bioavailability when high fat was compared to moderate fat meals. Take ritonavir tablets with meals.	US Product Monograph, February 2010.
		moderate fat meal vs fasting	21% ↓		22% ↓			
Saquinavir 200 mg hard gel capsules	600 mg	high-fat breakfast (48 g protein, 60 g carbohydrate, 57 g fat; 1006 kcal).	↑ 571%	N/c (35%)			The effect of food has been shown to persist for up to 2 hours. INVIRASE and ritonavir should be taken within 2 hours after a meal.	US Product Monograph December 2004
		Saquinavir 24-hour AUC and C_{max} (n=6) following the administration of a higher calorie						

Drug	Dose	Type of Meal	AUC	CV	Cmax	CV	Recommendation	Reference
		meal (943 kcal, 54 g fat) were on average 2 times higher than after a lower calorie, lower fat meal (355 kcal, 8 g fat).						
Saquinavir soft-gel capsules	1200 mg TID	Normal breakfast (600 kcal, 22 g or 33%, 16% protein, 51% carbohydrates)	1.25 mg/L*h		0.49 mg/L		Approximately 2-fold ↑ in saquinavir exposure with high-fat vs. normal meal.	Hugen et al. Pharmacy World Sci 2002;24:83-6.
		High fat breakfast (1040 kcal, 62 g or 54% fat, 15% protein, 31% carbohydrates)	3.8		0.88 mg/L		Saquinavir AUC ↑ 5-fold when taken with normal meal plus grapefruit juice compared to normal meal alone.	
		Normal breakfast + 250 mL single-strength grapefruit juice	5.2					
Saquinavir soft-gel capsules	1000/100 mg BID	Saquinavir exposure was similar when FORTOVASE plus ritonavir (1000-mg/100-mg bid) were administered following a high-fat (45 g fat) or moderate-fat (20 g fat) breakfast.						"
Saquinavir 500 mg tablets	1000/100 mg BID	Breakfast: 1091 kcal, 46 g fat; Dinner: 1080 kcal, 66 g fat	238% ↑		245% ↑		INVIRASE and ritonavir should be taken within 2 hours after a meal.	Boffito et al. 7th IWCPHT 2006, #66.
	"	Standard meal: 651 kcal, 15g fat versus High fat meal: 1291 kcal, 55g fat	31% ↓		26% ↓		Saquinavir levels were mildly decreased with a standard meal vs. a high fat meal. All patients had Ctrough > cut off of 100ng/ml. The authors conclude that SQV should be given with food, but the fat content of the meal is not critical.	Boffito et al. 47th ICAAC 2007, #A-1423.
Tipranavir	500/200 mg BID (old capsule formuation)	High-fat meal (868 kcal, 53% derived from fat, 31% derived from carbohydrates)	31% ↑		16% ↑		APTIVUS capsules co-administered with ritonavir should be taken with food.	US Product monograph, November 2005.
	500/200 mg BID capsules		No change		No change		Tipranavir/ritonavir may be taken with or without food.	La Porte et al. 8th IWCPHT 2007, #59.
	500/200 mg BID oral solution		23% ↑		14% ↑		Tipranavir/ritonavir may be taken with or without food.	La Porte et al. 8th IWCPHT 2007, #59.
OTHER ANTIRETROVIRALS								
Cobicistat	Administered as a	Light meal (373 kcal, 20% fat)	2% ↑		4% ↑		Take fixed-dose tablet with food.	German et al. ICAAC

Drug	Dose	Type of Meal	AUC	CV	Cmax	CV	Recommendation	Reference
	fixed dose combination tablet (elvitegravir, emtricitabine, tenofovir, cobicistat) in healthy volunteers	compared to fasted. High-fat meal (800 kcal, 50% fat) compared to fasted.	 17% ↓		 24% ↓			2009, #A1-1300.
Didanosine, enteric-coated (Videx EC®)	Open-label, single dose studies in healthy volunteers.	With a high-fat meal compared to fasted. With a light meal compared to fasted. Videx EC given 1.5 hours before a light meal. Videx EC given 2 hours after a light meal. Videx EC beadlets with yogurt or apple sauce compared to fasting. Administration of VIDEX EC capsules 1.5, 2 or 3 hours before a light meal resulted in equivalent C_{max} and AUC values compared to those obtained under fasting conditions.	19% ↓ 27% ↓ 24% ↓ 10% ↓ 20%↓ 18%↓		46% ↓ 22% ↓ 15% ↓ 15% ↓ 30% ↓ 24% ↓		VIDEX EC should be taken on an empty stomach, at least 1.5 hours before or 2 hours after a meal.	Damle B et al. J Clin Pharmacol 2002; 42:419-427.
	Randomized, open-label study of 28 days ddI monotherapy in HIV-infected, treatment-naïve subjects (n=21).	Didanosine-EC administered 1 hour before or 2 hours after breakfast, vs. administered with a fat-rich breakfast (350 kcal).					Mean ddI trough plasma levels at day 28 were 0.0234 mg/L for patients taking ddI on an empty stomach and 0.0227 mg/L for those taking it after a fat-rich breakfast, showing no statistically significant difference (P=0.96). There was no difference in the rate of decrease of HIV-1 RNA between the two groups.	Hernandez-Novoa et al. HIV Med 2008;9: 187-191.
Dolutegravir	50 mg single dose in healthy subjects	Fasted stated compared to: • low-fat (300 kcal, 7% fat) • moderate fat (600 kcal, 30% fat) • high fat (870 kcal, 53% fat)	 ↑ 33% ↑ 41% ↑ 66%		 ↑ 46% ↑ 52% ↑ 67%		Dolutegravir may be administered with or without food and without regard to fat content.	Song et al. 12th IWCPHT 2011, #P12.

Drug	Dose	Type of Meal	AUC	CV	Cmax	CV	Recommendation	Reference
		meal						
Etravirine	100 mg single dose tablet in healthy subjects	Fasted state compared to a standard breakfast (561 kCal, 15.3 g fat). Light Breakfast - croissant (345 kCal, 17.4 g fat) compared to a standard breakfast. Enhanced Fiber Breakfast (685 kCal, 3.1 g fat) compared to a standard breakfast. High Fat Breakfast (1160 kCal, 70.3 g fat) compared to a standard breakfast.	51% ↓ 20% ↓ 25% ↓ 9%↑		44% ↓ 3% ↓ 38% ↓ 5% ↓		Give with food. Type of meal not important.	Scholler-Gyure et al. Pharmacotherapy 2008;28(10):1215-22.
Elvitegravir	Administered as a fixed dose combination tablet (elvitegravir, emtricitabine, tenofovir, cobicistat) in healthy volunteers	Light meal (373 kcal, 20% fat) compared to fasted. High-fat meal (800 kcal, 50% fat) compared to fasted.	34% ↑ 87% ↑		22% ↑ 56% ↑		Take fixed-dose tablet with food.	German et al. ICAAC 2009, #A1-1300.
Nevirapine	200 mg single dose administered to 24 healthy subjects (12 male, 12 female)	High fat breakfast (857 kcal, 50 g fat, 53% of calories from fat) or antacid (Maalox® 30 mL) compared to fasting.	No change				Nevirapine may be administered with or without food or antacid.	Canadian Product Monograph, July 2009.
Raltegravir	400 mg single dose	standard moderate-fat meal (600 Kcal, 21 g fat) or in the fasted state	13%↑		5% ↑		Raltegravir C12 hr was 66% higher and Cmax was 5% higher following a moderate-fat meal compared to fasting and AUC was not affected in a clinically significant manner. Take raltegravir with or without food.	Canadian Product Monograph, September 2010.
	400 mg BID x 10/7 in healthy subjects	Fasting versus: • Low-fat meal: 2 slices bread,	↓ 46%		↓ 52%		Impact on C12 vs fasting: ↓ 14% (low fat), ↑ 66% (moderate fate), ↑ 313%	Brainard et al. J Clin Pharmacol

Drug	Dose	Type of Meal	AUC	CV	Cmax	CV	Recommendation	Reference
		2 packets jelly, 8 oz skim milk; ~300 kcal, 7% fat (2.5 g) • Moderate-fat meal: 4 slices bread, 2 slices American cheese, 2 slices low-fat ham, 8 oz skim milk; ~600 kcal, 31% fat (21 g) • High-fat meal: 2 eggs, 2 strips bacon, 4 oz hash browns, 2 slices bread, 2 teaspoons butter, 8 oz whole milk; ~825 kcal, 57% fat (52 g)	↑ 13% ↑ 111%		↑ 5% ↑ 96%		(high fat). In the current study, when raltegravir was given with food, considerable variability was seen, particularly with respect to C12h, which had coefficients of variation of 201%, 123%, and 221% for low-, moderate-, and high-fat meals, respectively, compared with only 47% for the fasted state. In summary, a low-fat meal appearing to modestly decrease absorption with little effect on trough concentrations (C12h), a moderate-fat meal having little to no effect, and a high-fat meal appearing to modestly increase absorption, although none of these effects appear clinically meaningful.	2011;51(3):422-7.
		Administration of the chewable tablet with a high fat meal vs fasting.	6% ↓		62% ↓		Impact on C12 vs fasting: 188% ↑ Administration of the chewable tablet with a high fat meal does not affect raltegravir pharmacokinetics to a clinically meaningful degree and the chewable tablet can be administered without regard to food.	US Product Monograph, December 2011.
Rilpivirine (TMC278)	75 mg tablet single dose in healthy subjects	• Fasting vs. standard breakfast (21 g fat, 533 kcal). • Protein rich nutritional drink (8 g fat, 300 kcal) vs standard breakfast • High Fat Breakfast (56 g fat, 928 kcal) compared to standard breakfast	43% ↓ 50% ↓ 8% ↓		46% ↓ 50% ↓ 8% ↓		Give rilpivirine with food (standard or high fat meal). Do not give rilpivirine on an empty stomach or with a protein rich nutritional drink.	Crauwels et al. 9th IWCPHT 2008, #P32.
HCV PROTEASE INHIBITORS								
Boceprevir	800 mg TID	• Administered with a meal vs.	↑ 60%				The bioavailability of boceprevir was	Victrelis Product

Drug	Dose	Type of Meal	AUC	CV	Cmax	CV	Recommendation	Reference
		fasting state • No difference between high-fat vs. low-fat					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. Boceprevir should be taken with a meal or light snack.	Monograph, Canada, July 2011.
Telaprevir	750 mg single dose in healthy volunteers	• Standard breakfast (533 kcal, 21 g fat) versus: • Fasting • Low-calorie/low-fat breakfast (249 kcal, 3.6g fat) • Low-calorie/high protein breakfast (260 kcal, 9g fat) • High-fat breakfast (928 kcal, 56g fat)	↓ 73% ↓ 39% ↓ 26% ↑ 20%		↓ 83% ↓ 38% ↓ 25% ↓ 1%		Take telaprevir with food or a snack that contains some fat (~20 g). The systemic exposure (AUC) to telaprevir was increased by 237% when telaprevir was administered with a standard fat meal (containing 533 kcal and 21 g fat) compared to when telaprevir was administered under fasting conditions. In addition, the type of meal significantly affects exposure to telaprevir. Relative to fasting, when telaprevir was administered with a low-fat meal (249 kcal, 3.6 g fat) and a high-fat meal (928 kcal, 56 g fat), the systemic exposure (AUC) to telaprevir was increased by approximately 117% and 330%, respectively. Doses of INCIVEK were administered within 30 minutes of completing a meal or snack containing approximately 20 grams of fat in the Phase 3 trials. Therefore, INCIVEK should always be taken with food (not low fat).	Van Heeswijk et al. 6th Int Workshop on Clin Pharmacol of Hepatitis Therapy 2011, #PK_19. Incivek Product Monograph, USA, May 2011.

HIV Medications at a Glance

	Generic Name	Trade Name	Strength	DIN	Usual Dosage
	Multi-Class Combination Products				
	Efavirenz/ emtricitabine/ tenofovir	Atripla	600/200/300 mg tablet	02300699	1 tablet daily
	Emtricitabine/ rilpivirine/ tenofovir	Complera	200/25/300 mg tablet	02374129	1 tablet daily
	elvitegravir/ cobicistat/ emtricitabine/ tenofovir	Stribild	150/150 mg/200/300 mg tablet	*available in U.S.*	1 tablet daily
	CCR5 Inhibitor				
	maraviroc	Celsentri *(US: Selzentry)*	150 mg and 300 mg tablets	02299844 (150 mg) 02299852 (300 mg)	150-600 mg BID
	Integrase Inhibitor				
	raltegravir	Isentress	400 mg tablets *100 mg, 25 mg chewable tablets*	02301881 *available in U.S.*	400 mg BID *75-300 mg BID based on weight (pediatric)*
	NRTIs (nucleoside reverse transcriptase inhibitors)				
	abacavir	Ziagen	300 mg tablet	02240357	300 mg BID or 600 mg QD
	AZT, zidovudine	Retrovir	100 mg capsule *300 mg tablet*	01902660 (100 mg) *available in U.S.*	300 mg BID, or 200 mg TID
		Apo-Zidovudine	100 mg capsule	01946323	
		Novo-AZT	100 mg capsule	01953877	
	3TC, lamivudine	3TC	150, 300 mg tablet	02192683 (150 mg) 02247825 (300 mg)	150 mg BID or 300 mg QD
		Apo-Lamivudine®	150, 300 mg tablet	02369052 (150 mg) 02369060 (300 mg)	
	ddI, didanosine	Videx	2g, 4 g bottles pediatric powder for oral solution	01940635 (4g)	400 mg daily, or 200 mg BID
	ddI, didanosine	Videx EC	125, 200, 250, 400 mg enteric coated capsules	02244596 (125 mg) 02244597 (200 mg) 02244598 (250 mg) 02244599 (400 mg)	400 mg daily
	d4T, stavudine	Zerit	15, 20, 30, 40 mg capsule	02216108 (30 mg); 02216116 (40 mg)	30-40 mg BID

	Generic Name	Trade Name	Strength	DIN	Usual Dosage
	FTC, Emtricitabine	Emtriva	200 mg capsule *10 mg/ml oral solution*	02272091; *available in U.S.*	200 mg once a day
	NRTIs: Combination Products				
	AZT/3TC	Combivir Apo-Lamivudine-Zidovudine	300 mg/150 mg tablet "	02239213 02375540	1 tablet BID
	AZT, 3TC, abacavir	Trizivir	300/150/300 mg tablet	02244757	1 tablet BID
	Abacavir, lamivudine	Kivexa *(US: Epzicom)*	600/300 mg tablet	02269341	1 tablet daily
	Tenofovir, emtricitabine	Truvada	300/200 mg tablet	02274906	1 tablet daily
	Nucleotide Reverse Transcriptase Inhibitors				
	tenofovir	Viread	300 mg tablet *150, 200, 250 mg tablets* *40 mg/1g oral powder*	02247128 *Available in U.S.*	300 mg once daily
	NNRTIs (Non-Nucleoside Reverse Transcriptase Inhibitors)				
	delavirdine	Rescriptor	100 mg tablet *(200 mg tablet in U.S.)*	02238348	400 mg TID
	efavirenz	Sustiva	200, 100, 50 mg capsule, 600 mg tablet	02239886 (50 mg), 02239887 (100 mg), 02239888 (200 mg), 02246045 (600 mg)	600 mg daily
	etravirine	Intelence	100, 200 mg tablets *(25 mg tablet in U.S.)*	02306778 (100 mg), 02375931 (200 mg)	200 mg BID
	nevirapine	Viramune Auro-Nevirapine	200 mg tablet 200 mg tablet (generic)	02238748 02318601	200 mg daily x 14 days, then 200 mg BID
	rilpivirine	Edurant	25 mg tablet	02370603	25 mg QD
	Protease Inhibitors				
	atazanavir	Reyataz	150, 200, 300 mg capsule	02248610 (150 mg); 02248611 (200 mg); 02294176 (300 mg)	400 mg QD, or 300 mg with 100 mg ritonavir QD
	darunavir	Prezista	75, 300, 400, 600 mg tablets *(100 mg/mL oral suspension in U.S.)*	02338432 (75 mg); 02284057 (300 mg); 02324016 (400 mg); 02324024 (600 mg)	600 mg plus 100 mg ritonavir BID or 800/100 mg QD for naive subjects
	fosamprenavir	Telzir *(US: Lexiva)*	700 mg tablet 50 mg/mL oral suspension	02261545 (700 mg), 02261553 (susp)	700 mg plus 100 mg ritonavir BID, or 1400 mg plus 100-200 mg ritonavir QD

	Generic Name	Trade Name	Strength	DIN	Usual Dosage
	indinavir	Crixivan	200, 400 mg capsules	02229161 (200 mg); 02229196 (400 mg)	800 mg q8h
 	lopinavir/ ritonavir	Kaletra	200/50 mg tablet 100/25 mg tablet 80mg/20 mg per mL solution	022285533 02312301 02243644	400/100 mg BID or 800/200 mg QD (naïve subjects)
	nelfinavir	Viracept	250 mg (blue), 625 mg tablet (white)	02238617 (250 mg); 02248761 (625 mg)	1250 mg BID or 750 mg TID
	ritonavir	Norvir	100 mg capsule 100 mg tablet 80 mg/mL solution	02229137 02357593 02229145	100-200 mg QD/BID as booster
	saquinavir	Invirase	200 mg hard gel capsule 500 mg film-coated tablet	02216965 02279320	1000 mg/100 mg rtv BID
	tipranavir	Aptivus	250 mg capsule	02273322	500 mg/200 mg ritonavir BID
	Fusion Inhibitor				
	enfuvirtide	Fuzeon	108 mg/vial (powder for injection)	02247725	90 mg SC BID

Discontinued HIV Medications

	Generic Name	Trade Name	Strength	DIN	Usual Dosage
	NRTIs (nucleoside reverse transcriptase inhibitors)				
	ddI, didanosine	Videx	25, 50, 100, 150 mg tablets	01940546 (100 mg) 01940554 (150 mg) D/C February 2006	400 mg daily, or 200 mg BID
	ddC, zalcitabine	Hivid	0.75 mg tablets	01990896 (0.75 mg) D/C February 28, 2006	0.75 mg TID
	Protease Inhibitors				
	amprenavir	Agenerase	50, 150 mg capsule	02243541 (50 mg), 02243542 (150 mg) D/C December 2006	1200 mg BID
	nelfinavir	Viracept	Oral powder 50mg/g (1g= level scoopful)	02238618 (D/C 2006)	
	saquinavir	Fortovase	200 mg soft gel capsule	02239083 (D/C 2006)	1200 mg TID or 1600 mg BID
	lopinavir/ ritonavir	Kaletra	133mg/33 mg capsule	02243643 (d/c July 11, 2008)	400/100 mg BID or 800/200 mg QD (naïve subjects)

Liquid Drug Formulations

Drug	Liquid available?	Formulation	Status	Cost	Comments
ANTIRETROVIRALS					
abacavir	yes	20 mg/mL oral solution; 240 mL bottle	facilitated access	$100.00/ bottle	Yellow, strawberry-banana flavoured liquid; store oral solution at room temperature. Tablet is film-coated, no data on whether can be crushed.
amprenavir	yes	15 mg/ml oral liquid; 240 mL bottle	section 8	$46.08/bottle	Yellow, grape/bubblegum flavoured liquid. Oral solution contains: vitamin E 46 IU/ml, propylene glycol 550 mg/ml, PEG400 170mg/ml, , saccharin Store at room temperature in original bottle. NB: due to high propylene glycol content, avoid in pregnancy, children <4 years, renal or hepatic dysfunction.
atazanavir	yes	50 mg/1.5 g dispersible oral powder, 180 g bottle	investigational only (PACTG 1020)	available in Europe	**Powder** may be mixed with small amount of water, applesauce, milk, or yogurt (consume within 3 hours of mixing). Do not mix with juices or foods with high pH. In an open label, multicentre study of atazanavir and atazanavir/ritonavir in children 91 days-21 years, the pharmacokinetics of atazanavir capsules and atazanavir orange-vanilla flavoured powder were studied. Day 7 atazanavir kinetics were compared in children of similar age receiving powder vs. capsules; the powder was found to be 40% less bioavailable at the same BSA-based dose. Therefore, suggest converting from powder to capsule by multiplying the powder dose by 0.6 and rounding up to the nearest 50 mg.[Kiser J et al. 2011] **Atazanavir capsules** may be opened and the contents mixed with applesauce for immediate ingestion with a light meal. In-house study showed that the bioavailability of the contents of two 200-mg atazanavir capsules mixed with applesauce was 91.7% relative to atazanavir capsules taken intact. In addition, administration of the contents of two 200-mg capsules was well tolerated (Bristol Myers Squibb, Personal Communication, October 22, 2008).

Drug	Liquid available?	Formulation	Status	Cost	Comments
AZT	yes	10 mg/mL oral syrup; 240 mL bottle	ODDMP	$43.39/bottle	Strawberry-flavoured; stable at room temperature. May open capsules & give in small portion of food or 5-10 mL cool tap water.
AZT/3TC (Combivir)	no	use AZT & 3TC liquid products	facilitated access		No data, but likely OK to crush tablets; crush immediately before ingestion. May have bitter taste.
AZT/3TC/ abacavir (Trizivir)	no	Use AZT, 3TC and abacavir liquid products	facilitated access		
darunavir	yes	100 mg/mL oral suspension	Licensed in U.S.		No pharmacokinetic data are available on chewing or crushing of PREZISTA film-coated tablets. However, since the tablets are not formulated as an extended release formulation, no potential problem is anticipated if the tablets are chewed or crushed for administration through a nasogastric (NG) tube. It is unlikely that chewing or crushing PREZISTA tablets would have a significant impact on pharmacokinetics (Data on File, Tibotec, November 2006). In two patients, one with dysphagia and Candida esophagitis and one with a stomach tube, who received darunavir tablets crushed and dissolved and administered with ritonavir oral solution, adequate plasma darunavir levels were achieved along with good virologic response.(Scholten et al. 2010)
d4T	yes	1 mg/mL oral suspension; 200 ml bottle	SAP	no charge	Fruit-flavoured; stable 30 days in fridge; can also open up capsules give in small portion of food or 5-10 mL cool tap water
ddC	no				Investigational oral solution is no longer available.

Drug	Liquid available?	Formulation	Status	Cost	Comments
ddI	yes	2 g and 4 g oral powder (pediatric solution); 10 mg/mL final concentration	SAP	$67.84/4 g bottle; $30/2 g bottle	Reconstitute oral powder with sterile water, then Mylanta TC suspension; stable for 30 days in fridge; available via SAP (call Maggie Jackson at 514-333-2287). (can also crush/dissolve buffered tablets in water, apple juice, or chocolate milk)
delavirdine	no				Can dissolve 100 mg tablets in water to make slurry (20% ↑ bioavailability). Disperse tablets in at least 90 mL of water, allow to stand for a few minutes, stir and consume.
efavirenz	yes	30 mg/mL; 180 mL bottle	pediatric suspension available via Sustiva Oral Liquid Expanded Access Program at 1-877-372-7097 (Massachusetts)		Strawberry-mint flavour. Store liquid at room temperature in original container; stable for 30 days after opening. Can open **capsules** and mix powder with apple sauce (but will result in hot "jalapeno" sensation); for nasogastric administration, may open capsules and mix with either 5 mL MCT oil or 15 mL Ora-Sweet (grind powder first to enhance dissolution). Powder is insoluble in water; do NOT mix with polyethylene glycol (will ↓ bioavailability).

Drug	Liquid available?	Formulation	Status	Cost	Comments
Efavirenz/ emtricitabine/ tenofovir (Atripla)	No	Atripla FDC tablet crushed, dissolved in 5 mL of water and diluted to 20 mL with Ora-Sweet oral vehicle. The solution was prepared within 24 hours of administration to ensure drug stability in solution.			Bioequivalence of Atripla tablet and compounded oral liquid formulation in HIV-negative volunteers was not demonstrated. The 90% CI for FTC Cmax and AUC fell within the range of 0.8-1.25 thus, bioequivalence was met, but the 90% CI for efavirenz Cmax fell below the range of bioequivalence while efavirenz AUC∞ fell slightly above the range and tenofovir Cmax and AUC∞ fell above the range. Tenofovir Cmax and AUC∞ were approximately 40% and 20% higher, respectively with the liquid formulation. The clinical implications of these data are unknown.[Kiser et al. JAIDS 2011;56(5):e131-2]. Splitting EFV/FTC/TDF tablets has not been studied and it is not recommended. There are no studies evaluating the pharmacokinetics of a split EFV/FTC/TDF tablet versus a whole tablet.
emtricitabine (FTC)	Yes (in US)		investigational only in Canada		200 mg capsules may be opened and mixed with water.

Drug	Liquid available?	Formulation	Status	Cost	Comments
etravirine	No				Patients who are unable to swallow etravirine tablets whole may disperse the tablets in a glass of water. A bioavailability study has shown that the PK of etravirine tablets when swallowed whole and when taken after dispersion in a glass of water are comparable. Stir the tablet in 100ml of cold water until a homogenous, white, cloudy, suspension is obtained. Once dispersed, patients should stir the dispersion well and drink it immediately. The glass should be rinsed with water several times and each rinse completely swallowed to ensure the entire dose is consumed. (Data on File, Tibotec) Do not chew the tablets (product monograph); no PK data available for crushing/chewing tablet. The absorption of raltegravir, etravirine, emtricitabine, and tenofovir was not compromised when the drugs were crushed, dissolved in 60 mL warm water, and administered by gastrostomy tube to a 52 year old HIV-positive male with ulcerative esophagitis.[Sandkovsky et al. 2012]
fosamprenavir	yes	50 mg/mL oral suspension, 225 mL bottle.	Section 8		Grape bubblegum and peppermint flavour. Suspension must be taken on an empty stomach. Store oral suspension between 2-30^{o}C. Do not freeze. Discard the suspension 28 days after first opening. No information on crushing or dissolution of 700 mg tablets.
indinavir	no		liquid being formulated		do NOT open capsules (bitter taste; stability?); NB: 10 mg/mL indinavir syrup complex compounding formulation . Stable for 14 days in refrigerator, store in glass bottle. (Hugen et al. Am J Health Syst Pharm 2000; 57(14):1332-9).

Drug	Liquid available?	Formulation	Status	Cost	Comments
Lamivudine (3TC)	yes	10 mg/mL oral solution; 240 mL bottle	facilitated access	$70.40/ bottle	Pale yellow, strawberry-banana flavoured solution; stable at room temperature. (Note:contains 6% v/v ETOH & 3g sugar) Can also crush tablets.
lopinavir/ ritonavir	yes	80 mg/20 mg per mL; 160 mL bottle	facilitated access	$316.27/ bottle	Cotton-candy flavoured yellow-orange oral solution; stable in refrigerator until expiry date; stable at room temperature for 42 days. Oral solution contains the excipients alcohol (42.4% v/v) and propylene glycol (15.3% w/v). Increased risk of toxicity in preterm infants. NB: tablets should be swallowed whole and not chewed, broken, or crushed. Risk of tablets shattering if broken/crushed. Administration of crushed 200/50 mg lopinavir/ritonavir tablets to children significantly reduced lopinavir and ritonavir exposure with a decrease in AUC by 45% and 47%, respectively. Therefore, the use of crushed lopinavir/ritonavir tablets should be avoided, if possible.[Best et al. JAIDS 2011;58:385-91]
maraviroc	no				No PK data available for crushing/chewing tablet. (Data on File, Pfizer) . While the company does not have any specific kinetic information, crushing or cutting the tablets is not expected to negatively affect bioavailability.
nelfinavir	yes	50 mg/g oral powder; 144 g bottle. (1g = 1 level scoop).	facilitated access	$52.42/ bottle	Can also dissolve tablets (i.e. 250 mg tablet in 5 mL sterile water to yield a 50 mg/mL liquid. Use syringe with 1 mL increments to measure. Round dose to nearest 50mg); tablet or powder may be mixed with food or liquid up to 6 hours (refrigerated) before dose is taken.
nevirapine	yes	10 mg/mL;240 mL bottle	SAP		Sweet-flavoured syrup; stable at room temperature. Can crush immediate-release (200 mg) tablets in water. NB: Extended-release (400 mg XR) tablets must be swallowed whole; they must not be chewed, crushed or divided.

Drug	Liquid available?	Formulation	Status	Cost	Comments
raltegravir	no				No PK data available for crushing/chewing tablet. Crushing tablets is not recommended; granules (sub-units of the tablet) dissolve faster than intact tablets and may result in faster release of drug which could affect in-vivo performance (Data on File, Merck Frosst, May 2008). Drug has bitter taste which is masked by the film coating. The absorption of raltegravir, etravirine, emtricitabine, and tenofovir was not compromised when the drugs were crushed, dissolved in 60 mL warm water, and administered by gastrostomy tube to a 52 year old HIV-positive male with ulcerative esophagitis.[Sandkovsky et al. 2012]
ritonavir	yes	80 mg/mL oral liquid; 240 mL bottle	facilitated access	$256.35/ bottle	Orange-coloured oral solution, peppermint & caramel-flavoured. 43% v/v alcohol. Shake well before each use. Stable at room temperature; do not refrigerate.
saquinavir	no		liquid not being formulated due to unpalatability		6 x 200 mg Fortavse whole caps mixed with 50 mL of whole milk or Advera nutritional supplement took 5-15 minutes to dissolve when heated to 40, 60 or 80 degrees C. The mixture remained in solution for up to 1 hour at room temperature. If refrigerated for 24 hours, it turned into a gel, but reliquified after reheating to 30 degrees C. The drug was still stable at 24 hours. (data on file, Hoffmann-LaRoche)
tenofovir	yes		40 mg per 1 gram of oral powder formulation (available in US)		Crushed tablet dissolves in 100 mL water in 20 minutes; grape juice may also be used. NB: crushed tablets have very disagreeable taste. May also try splitting tablets and inserting into empty gelatin capsules to mask taste.

Drug	Liquid available?	Formulation	Status	Cost	Comments
Tenofovir/ emtricitabine (Truvada®)	Yes (individual components)				May split tablets. May crush and stir into water, grapefruit juice or orange juice. The stability of the mixture is unknown. (Email communication, Gilead, May 2008). The absorption of raltegravir, etravirine, emtricitabine, and tenofovir was not compromised when the drugs were crushed, dissolved in 60 mL warm water, and administered by gastrostomy tube to a 52 year old HIV-positive male with ulcerative esophagitis.[Sandkovsky et al. 2012]
tipranavir	no		investigational only in Canada		250 mg capsule. No information on opening or dissolution.
OTHER MEDICATIONS:					
acyclovir	yes	200 mg/5 mL;125 mL bottle	Facilitated access	$30,72/ bottle	Banana-flavoured suspension; store between 15-25C.
azithromycin	yes	pediatric oral powder/suspension 100 mg/5 mL (300 mg bottle) OR 200 mg/5 mL (600 & 900 mg bottles)	limited use	$23.77/ 600mg bottle	Cherry-flavoured suspension. Dispose unused suspension after 10 days; may also open capsules and mix with water (ingest immediately on empty stomach, follow with full glass of water)
clarithromycin	yes	125 mg/5 mL & 250 mg/5mL; 55, 105 and 150 mL bottles			Fruit-flavoured suspension. Shake well before use. Store reconstituted liquid at room temperature.
Fenofibrate (Lipidil Supra, Lipidil EZ)	no				Tablets are not enteric-coated or sustained-release. Therefore while the company does not have any specific kinetic information, crushing or cutting the tablets is not expected to negatively affect bioavailability.
hydroxyurea	no				Can open up capsules and mix with water; take immediately. Some inert material (used as a vehicle in capsule) may not dissolve, and may float on top. Do not allow powder to come in contact with skin and mucous membranes. Avoid inhalation of powder when opening capsules.

Drug	Liquid available?	Formulation	Status	Cost	Comments
rifabutin	no				Can open capsules (experience in pediatrics: OK to mix with applesauce, syrup, cherry syrup); drug not soluble in water
TMP/SMX	yes	pediatric suspension 40 mg/200 mg per 5 mL (= ½ SS tablet); 400 & 800 mL bottles	formulary	$0.20/10 mL (=1 SS tablet)	Cherry-flavoured. Store at Room temperature (Septra brand)

Key: ODDMP: Ontario Drug Distribution/Monitoring Program, SAP= Special Access Program, Health Protection Branch, Ottawa (ph: 613-941-2108; fax: 613-941-3194; http://www.hc-sc.gc.ca/hpfb-dgpsa/tpd-dpt/sap_requestform_e.html)

Nucleoside Reverse Transcriptase Inhibitors (NRTIs)	
Abacavir (ZIAGEN®, ABC)	
Dose	Neonatal/Infant: • Not approved for infants < 3 months. Pediatric (3 months to 16 years): • 8 mg/kg/dose po BID • Maximum: 300 mg po BID • If clinically stable with undetectable viral load and stable CD4 cell count, may consider once daily ABC as 16 mg/kg/dose to maximum of 600 mg po once daily. Adolescent(≥16 years)/Adult: • 300 mg po BID or 600 mg once daily
How Supplied/ Storage	• 20 mg/mL banana-strawberry liquid (240 mL bottle). Store at room temperature. • 300 mg tablet • Scored 300mg tablet for pediatric use (> 14 kg) (available in US only) • Combination tablet: – TRIZIVIR® = 300 mg zidovudine; 150 mg lamivudine; 300 mg abacavir – KIVEXA® = 600 mg abacavir; 300 mg lamivudine
Food Restrictions	May take with or without food.
Comments	• Test patients for HLA-B*5701 allele before starting therapy to predict risk of hypersensitivity. If positive for HLA-B*5701, do not use abacavir. • Watch for hypersensitivity reaction (~ 5% incidence; usually within first 6 weeks): fever, rash, fatigue, n/v, diarrhea, abdominal pain and respiratory symptoms. • **Do NOT rechallenge if suspect hypersensitivity.** • KIVEXA®: Film coated immediate release tablet however no studies regarding stability of split or crushed tablets. (Email communication, GlaxoSmithKline, May 2008) • TRIZIVIR®: Film coated immediate release tablet however no studies regarding stability of split or crushed tablets.
Didanosine (VIDEX®, VIDEX EC®, ddI)	
Dose	Neonatal/Infant (2 weeks to less than 3 months): • 50 mg/m^2/dose po BID recommended by ARV Guidelines[1] • manufacturer recommends 100 mg/m^2/dose po BID Infant dose (*>3 mos to 8 mos):* • 100 mg/m^2/dose po BID *Pediatric dose of oral solution (>8 months):* • 120 mg/m^2/dose po BID (range 90 – 150 mg/m^2/dose po BID, maximum 200 mg BID)

Nucleoside Reverse Transcriptase Inhibitors (NRTIs)	
	Pediatric dose of Videx EC or generic capsules for ages 6 years to 18 years and body weight ≥ 20 kg: 20 to < 25 kg: 200 mg po once daily 25 to < 60 kg: 250 mg po once daily ≥60 kg: 400 mg po once daily • Treatment naïve (3-21 years): 240 mg/m^2/dose po once daily (oral solution or capsules) to a maximum of 400 mg once daily has been used with effective viral suppression. Adult/Adolescent : – < 60 kg: 250 mg once daily – ≥60 kg: 400 mg once daily
How Supplied/ Storage	• 4 g pediatric powder for oral solution (final concentration of 10 mg/mL). Refrigerate for up to 30 days (shake well before using). **Available through Special Access Program**[2]. • VIDEX EC delayed release capsules: 125 mg, 200mg, 250 mg and 400 mg
Food Restrictions	• Take on an empty stomach. Do not give with fruit juices or acidic drinks, feeds or milk. To improve adherence some practitioners administer ddI without regard to timing of food.
Comments	• 4 g: Add 200 mL purified water to powder, shake, and then add 200 mL antacid (suitable antacid: MAALOX Extra Strength). • ddI oral solution contains antacids which may interfere with absorption of some medications if given at the same time. • Combination of d4T and ddI is not recommended (unless benefits outweigh the risks) due to overlapping toxicities. • Until further information is available, combination of ddI and tenofovir should be avoided wherever possible due to high failure rates (in combination with NNRTIs) and decline in absolute CD4 cells.
Lamivudine (3TC®)	
Dose	Neonatal/Infant (age < 4 weeks): • 2 mg/kg/dose po BID Pediatric (age ≥ 4 weeks): • 4 mg/kg/dose po BID; maximum 150 mg po BID Adult/Adolescent (age ≥ 16 years): • ≥ 50 kg: 150 mg po BID or 300 mg po once daily • <50 kg: 4 mg/kg/dose po BID (maximum 150 mg po BID)
How Supplied/ Storage	• 10 mg/mL strawberry-banana oral liquid (240 mL bottle). Store at room temperature. • 150 mg and 300 mg tablets • Combination tablets: – COMBIVIR® = 300 mg zidovudine;150 mg lamivudine – TRIZIVIR® = 300 mg zidovudine; 150 mg lamivudine; 300 mg abacavir – KIVEXA® = 600 mg abacavir, 300 mg lamivudine

Nucleoside Reverse Transcriptase Inhibitors (NRTIs)	
Food Restrictions	Take with or without food.
Comments	May cut lamivudine tablet in half (not scored) or crush.

Stavudine (ZERIT®, d4T)	
Dose	Neonatal/Infant (birth up to 13 days) : • 0.5 mg/kg/dose po q12h Pediatric (14 days up to a weight of 30 kg): • 1 mg/kg/dose po q12h Adult/Adolescent (body weight ≥30 kg) • 30 to < 60 kg: 30 mg po BID • ≥60 kg: 40 mg po BID
How Supplied/ Storage	• 1 mg/mL fruit flavored suspension (200 mL bottle). **Available through Special Access program**[2]. Stable for 30 days in fridge. Shake well. • 15, 20, 30, 40 mg capsules
Food Restrictions	Take with or without food.
Comments	• May open capsule and give in small portion of food or 5-10 mL cool tap water. • Should not be administered with zidovudine due to poor antiretroviral effect. • Combination of d4T and ddI is not recommended (unless benefits outweigh the risks) due to overlapping toxicities.
Tenofovir (VIREAD®, TDF)	
Dose	Neonatal/Infant: • Not approved for use. Pediatric (2 years to <18years): • Not approved for use in children less than 2 years. • Recommended oral dose is 8 mg/kg (up to a maximum dose of 300 mg) once daily as powder or tablets (see Viread product monograph, US) Adolescent (weight ≥35 kg)/Adult: • 300 mg once daily • Oral powder (7.5 scoops) may be used if can't swallow tab (available in US only) –
How Supplied/ Storage	• 150 mg, 200 mg , 250 mg, 300 mg tablet (only 300 mg available in Canada as of July 2012) • Oral powder (40mg per 1g of powder) (US only as of July 2012)

	• Combination tablets: – TRUVADA® = 300 mg tenofovir; 200 mg emtricitabine – ATRIPLA® = 300 mg tenofovir; 200 mg emtricitabine; 600 mg efavirenz – COMPLERA® = 300 mg tenofovir; 200 mg emtricitabine; 25 mg rilpivirine
Food Restrictions	Take with or without food.
Comments	• Tenofovir: Crushed tabs dissolve in 100mL of water, grape juice, or grapefruit juice within 20 minutes. Consume immediately. Unpalatable bitter taste. May split tab and insert in empty gelatin capsule to mask bitter taste. • Decreases in BMD have been reported in both adult and pediatric studies. • Oral powder should be mixed in a container with 2 to 4 ounces of soft food not requiring chewing (e.g., applesauce, baby food, yogurt). Entire mixture should be ingested immediately to avoid a bitter taste. Do not administer in a liquid as the powder may float on top even after stirring. • Tenofovir may decrease atazanavir (ATV) plasma concentrations. In adults, a boosting dose of 100 mg ritonavir is recommended (ATV 300 mg/RTV 100 mg) if coadministered with tenofovir. • TRUVADA®: May split tablets. May crush and stir into water, grape juice or orange juice. The stability of the mixture is unknown. (Email communication, Gilead, July 2012) • ATRIPLA®: Atripla FDC tablet crushed, dissolved in 5 mL of water and diluted to 20 mL with Ora-Sweet oral solution and used within 24 hours (JAIDS 2011; 56:e131-2) did not meet bioequivalence of Atripla whole tablet however clinical implications unknown. Efavirenz not soluble in water. (Email communication, Gilead, July 2012).
Zidovudine (RETROVIR®, AZT, ZDV)	
Dose	Dose for infant < 35 weeks gestation for prevention of transmission or treatment: • For prevention of transmission, start ZDV immediately (no longer than 6-12 hours after birth) and administer for 6 weeks. • *Less than 30 weeks gestation*: – PO: 2 mg/kg/dose po q12h for 4 weeks, then q8h for last 2 weeks – IV: 1.5 mg/kg/dose IV q12h for 4 weeks, then q8h for last 2 weeks • *30 – 34 weeks gestation:* – PO: 2 mg/kg/dose po q12h for 2 weeks, then q8h for last 4 weeks – IV: 1.5 mg/kg/dose q12h for 2 weeks, then q8h for last 4 weeks *I*nfant ≥ 35 weeks gestation for prevention of transmission or treatment (up to 6 weeks of age)*:* – PO: 4 mg/kg/dose po q12h – IV: 1.5 mg/kg/dose IV q6h Pediatric dose (6 weeks to < 18 years): • PO: 180 - 240 mg/m^2/dose po q12h or 160 mg/m^2/dose po q8h (range 90-180) or: • MG/KG DOSING: – 4 kg to < 9kg: 12 mg/kg BID – 9 kg to < 30 kg: 9 mg/kg BID

	– ≥ 30kg: 300 mg BID <u>Adult/Adolescent (18 years or older):</u> • 300 mg BID
How Supplied/ Storage	• 10 mg/mL strawberry syrup (240 mL bottle). Store at room temperature. • 100 mg capsules • 200 mg/20 mL vial (intravenous) • <u>Combination tablets:</u> – COMBIVIR® = 300 mg zidovudine;150 mg lamivudine – TRIZIVIR® = 300 mg zidovudine; 150 mg lamivudine; 300 mg abacavir
Food Restrictions	Take with or without food.
Comments	• If zidovudine upsets stomach, take with food. • Should not be administered with d4T due to poor antiretroviral effect. • May open capsule and give in small portion of food or 5 – 10 mL cool tap water. • COMBIVIR®: Film coated immediate release tablet; however no studies regarding stability of split or crushed tablets. (Email communication, GlaxoSmithKline, May 2008) • TRIZIVIR®: Film coated immediate release tablet; however no studies regarding stability of split or crushed tablets.

Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)	
Efavirenz (SUSTIVA®, EFV)	
Dose	Neonatal/Infant: • Not approved for use. Pediatric (< 3 years): • no data are available on the appropriate EFV dose for children < 3 years Pediatric (more than 3 years and ≥ 10 kg): • Give once daily (PO) • 10 to < 15 kg: 200 mg • 15 to <20 kg: 250 mg • 20 to < 25 kg: 300 mg • 25 to < 32.5 kg: 350 mg • 32.5 to <40 kg: 400 mg • ≥ 40 kg: 600 mg • Pediatric patients with virologic rebound or lack of response may require higher doses (367 mg/m2/dose to maximum of 600 mg po once daily) Adult/Adolescent (weight ≥40 kg): • 600 mg po once daily
How Supplied/ Storage	• Pediatric suspension 30 mg/mL (180 mL bottle) strawberry mint. Available through expanded access program[3] (1-877-372-7097). • 50, 200 mg capsules • 600 mg tablet • Combination tablet: – ATRIPLA® = 300 mg tenofovir; 200 mg emtricitabine; 600 mg efavirenz
Food Restrictions	May take with or without food but do not take with high fat meal (significantly increases AUC and side effects).
Comments	• Bedtime dosing recommended first 2-4 weeks to decrease CNS side effects. • Capsules may be opened and added to liquids or foods but peppery taste. Grape jelly may mask taste. • Efavirenz: For NG administration, may open capsules and mix with 15 mL Ora-Sweet (grind powder to enhance dissolution). Powder insoluble in water. Do not mix with polyethylene glycol - will decrease bioavailability. Insoluble in water. • EFV should be used with caution in adolescent women of childbearing potential because of the risk of teratogenicity. • Mixed inducer/inhibitor of CYP450 3A4. **CHECK FOR DRUG INTERACTIONS.** • ATRIPLA®: Atripla FDC tablet crushed, dissolved in 5 mL of water and diluted to 20 mL with Ora-Sweet oral solution and used within 24 hours (JAIDS 2011; 56:e131-2) did not meet bioequivalence of Atripla whole tablet however clinical implications unknown. Efavirenz not soluble in water. (Email communication, Gilead, July 2012)

Etravirine (Intelence® ETR)	
Dose	Neonate/ Infant • Not approved for use. Pediatric (6 to <18 years of age): ≥16 kg to < 20 kg: 100 mg bid ≥ 20 kg to < 25 kg: 125 mg bid ≥ 25 kg to < 30 kg: 150 mg bid ≥ 30 kg: 200 mg bid Adult (antiretroviral experienced): • 200 mg po BID
How Supplied/ Storage	• 25 mg tablets (US only as of July 2012) • 100 mg tablets • 200 mg tablets • Tablets sensitive to moisture. Store in original container with dessicant at room temperature.
Food Restrictions	• Take with food.
Comments	• Inducer of CYP3A4; Inhibitor of CYP2C9/2C19. **CHECK FOR DRUG INTERACTIONS.** • May disperse tablets in a small amount of water, stir, and consume immediately. Rinse glass with water several times and swallow rinses to ensure entire dose consumed.
Nevirapine (VIRAMUNE®, NVP)	
Dose	Newborn perinatal prophylaxis (see Perinatal guidelines for more information on use of NVP for prophylaxis of mother to child transmission of HIV): 3 doses in first week of life (1st dose within 48 hours of birth; 2nd dose 48 hours after 1st dose; 3rd dose 96 hours after 2nd dose): • Birth weight < 1.5 kg: 2 **mg/kg per dose** PO **(note: dose per kg for this weight)** • Birth weight 1.5-2 kg: 8 mg **per dose** PO • Birth weight > 2 kg: 12 mg **per dose** PO Pediatric: *≥ 15 days to < 8 years:* • 200 mg/m^2/dose po once daily x 14 days, then 200 mg/m^2/dose po BID (if no rash or ADRs; maximum 200 mg per dose) *≥8 years of age:* • 120-150mg/m^2/dose po once daily X 14 days, then 120-150mg/m^2/dose po BID (if no rash or ADRs; maximum 200 mg per dose) Adult/Adolescent: • 200 mg po BID (Note: Initiate dose at 200 mg once daily x 14 days then increase dose to 200 mg po BID) • 400 mg extended release once daily (Note: initiate therapy with 200 mg immediate release tablet once daily for the first 14 days than increase to 400 mg once daily if no rash; extended release not approved for use in children)

How Supplied/ Storage	• 10 mg/mL sweet flavored syrup (240 mL bottle). **Available through Special Access program**[2]. Store at room temperature. • 200 mg tablet • 400 mg extended release tablet
Food Restrictions	May take with or without food.
Comments	• Do not increase dose if rash occurs within 1st 14 days. • May crush immediate release tablets, mix in water and give orally or by G-tube. • Induces CYP450 3A4 – may need to increase dose of other drugs metabolized by P450 enzymes in the liver. **CHECK FOR DRUG INTERACTIONS.** • If nevirapine dosing is interrupted for > 7 days, should be restarted with once daily dosing for 14 days followed by dose escalation. • When switching from efavirenz to nevirapine, the 14-day escalation of nevirapine is not required. Full doses of nevirapine can be used as of the first day.
Rilpivirine (EDURANT®, RPV)	
Dose	<u>Neonate/infant dose:</u> • RPV is not approved for use in neonates/infants. <u>Pediatric:</u> • RPV is not approved for use in children <u>Adult (antiretroviral-naïve patients only):</u> • 25 mg once daily
How Supplied/ Storage	• 25 mg tablet • COMPLERA® = 300 mg tenofovir; 200 mg emtricitabine; 25 mg rilpivirine
Food Restrictions	Must take with food (at least 400 kcal recommended).
Comments	• RPV is metabolized by CYP4503A4. CHECK FOR DRUG INTERACTIONS. • Use RPV with caution in patients with baseline VL > 100 000 copies/mL.

Protease Inhibitors (PIs)	
Atazanavir (Reyataz®, ATV)	
Dose	Neonate/infant: • Not approved for use. • Should not be administered to neonates due to risk associated with hyperbilirubinemia. Pediatric (≥6 to <18 years): – 15 to < 25 kg: ATV150 mg/RTV 80 mg po once daily (treatment naïve only) – 25 to < 32 kg: ATV 200 mg/RTV 100 mg po once daily – 32 to < 39 kg: ATV 250 mg/RTV 100 mg po once daily – ≥ 39 kg: ATV 300 mg/RTV 100mg po once daily Adult/Adolescent (≥18 years): • *Antiretroviral naïve:* ATV 300 mg + RTV 100 mg po once daily or ATV 400 mg po once daily (If unboosted ATV is used in adolescents, higher doses than those used in adults may be required to achieve target drug levels). • *Antiretroviral experienced*: 300 mg ATV/100 mg RTV both po once daily • *Atazanavir in combination with efavirenz:* 400 mg ATV/100 mg RTV both po once daily (*naïve only*) • *Atazanavir in combination with tenofovir:* 300 mg ATV/100 mg RTV both po once daily •
How Supplied/ Storage	• 150, 200, and 300 mg capsules • 50 mg/1.5 g dispersable oral powder (180 g/bottle) – investigational use only in Europe
Food Restrictions	Take with food.
Comments	• Antacids and buffered medications (including ddI buffered tablets) decrease ATV concentrations if taken at the same time – space by 1 – 2 hours. • H_2 receptor antagonists and proton pump inhibitors decrease ATV levels. Check drug interaction resource for recommendations on dosing ATV when coadministered with H2 receptor antagonists. . • Coadministration of atazanavir and proton pump inhibitors is **NOT** recommended. • Protease inhibitors are extensively metabolized by as well as inhibit CYP450 3A4. **CHECK FOR DRUG INTERACTIONS.**
Darunavir (TMC 114, Prezista®, DRV)	
Dose	Neonate/ Infant: • Not approved for use. Pediatric (< 3 years): • DRV should not be used in pediatric patients < 3 years. Pediatric (3 years to < 18 years) • See product monograph for dosing recommendations for oral solution for pediatric patients weighing 10 kg to < 15 kg.

Protease Inhibitors (PIs)	
	• ≥ 15 kg-< 30 kg: 375 mg DRV/50 mg RTV po BID • ≥ 30 kg-< 40 kg: 450 mg DRV/60 mg RTV po BID • ≥ 40kg: 600 mg DRV/100 mg RTV po BID • *Do not use once daily dosing in children < 12 years or in any patient < 18 years who is treatment experienced. Once daily dosing (DRV 800 mg + RTV 100 mg) may be used in treatment naïve pediatric patients 12-18 years of age and body weight > 40 kg. Adult/Adolescent (≥18 years): • 600 mg darunavir/100 mg ritonavir po BID (treatment experienced with at least one DRV mutation) • 800 mg darunavir/100mg ritonavir po daily (ARV-naïve or experienced with no darunavir specific mutations)
How Supplied/ Storage	• 75 mg, 150 mg, 400 mg, 600 mg tablets (only 400 mg and 600 mg tablets available in Canada as of July 2012) • 100mg/mL Oral suspension (US only as of July 2012)
Food Restrictions	Take with food.
Comments	• Darunavir specific mutations: V11I, V32I, L33F, I47V, I50V, I54L, I54M, T74P, L76V, I84V and L89V • Darunavir contains a sulfonamide moiety. The potential cross-sensitivity with other sulfa drugs is unknown – caution in patients with sulfonamide allergy. • Protease inhibitors are extensively metabolized by as well as inhibit CYP450 3A4. **CHECK FOR DRUG INTERACTIONS.** • No data available on chewing or crushing. No problems anticipated if tablets chewed or crushed for administration through a nasogastric (NG) tube (Data on file, Tibotec, May 2008)
Fosamprenavir (TELZIR®, f-APV	
Dose	Neonate: • Not approved for use. Pediatric (4 weeks -18 years): • *Oral suspension (antiretroviral naïve >4 weeks or ARV experienced >6 months)* – <11 kg: f-APV 45 mg/kg plus ritonavir 7 mg/kg both BID 11 kg to <15 kg: f-APV 30 mg/kg plus ritonavir 3 mg/kg both BID – 15 kg to <20 kg: f-APV 23 mg/kg plus ritonavir 3 mg/kg both BID – ≥20 kg f-APV 18 mg/kg plus ritonavir 3 mg/kg both BID OR in protease inhibitor naïve >2 years: 30mg/kg f-APV BID Adult/Adolescent (>18 years): • *Antiretroviral naïve:* – 1400 mg po BID (no ritonavir) – 1400 mg f-APV /100-200 mg RTV, both po once daily – 700 mg f-APV /100 mg RTV, both po BID • *Protease-inhibitor experienced*: 700 mg f-APV/100 mg RTV, both po BID

Protease Inhibitors (PIs)	
How Supplied/ Storage	• 700 mg tablet (prodrug, equivalent to 600 mg amprenavir) • 50 mg/mL oral suspension (225 mL bottle) [calcium prodrug, equivalent to 43 mg/mL amprenavir]. Contains 0.6% propylene glycol. Store suspension between 2-30℃. Discard 2 8 days after opening. Shake well.
Food Restrictions	• F-APV tablets without RTV may be taken with or without food. F-APV with RTV should be taken with food. • Oral suspension should be taken on an empty stomach (1 hr before or 2 hours after food) in adults. Oral suspension should be given with food in pediatric patients.
Comments	• Fosamprenavir calcium tablets and suspension are equivalent on a mg per mg basis. • APV is a sulfonamide. In pivotal studies there was no evidence of increased rash in patients with a history of sulfonamide allergy. Caution in patients with sulfonamide allergy. • The suspension contains propyl and methyl hydroxybenzoate which may cause allergic reactions (delayed in some cases). • Protease inhibitors are extensively metabolized by as well as inhibit CYP450 3A4. **CHECK FOR DRUG INTERACTIONS.** • No data available regarding stability of crushed or dissolved tablet.
Lopinavir/ Ritonavir (KALETRA®, LPV/RTV)	
Dose	Neonate (age < 14 days):: No data on appropriate dose or safety of LPV/r in this age group. Do not administer to neonates before a postmenstrual age of 42 weeks and a post-natal age of at least 14 days Infant dose (age 14 days – 6 months): *Without NVP or EFV*: • 16 mg/kg LPV BID or 300 mg LPV/m^2/dose po BID • LPV/r is not recommended in combination with nevirapine, efavirenz, fosamprenavir, or nelfinavir in patients <6 months of age. • Once daily dosing is not recommended Pediatrics/Adolescent (>6 months – 18 years): • *Without NVP or EFV:* – <15 kg: 12 mg/kg LPV po BID (approx. 230 mg/m^2 LPV/dose) – ≥ 15 to 40 kg: 10 mg/kg LPV po BID (approx. 230 mg/m^2 LPV/dose) – ≥ 40 kg: 400 mg LPV/100 mg RTV po BID • *With NVP or EFV:* • <15 kg: 13 mg/kg LPV po BID (approx. 300 mg/m^2 LPV/dose) • ≥15 to45 kg: 11 mg/kg LPV po BID • ≥45 kg: 600 mg LPV/150 mg RTV po BID tablets or 533 mg bid LPV solution • Once daily dosing is not recommended.

Protease Inhibitors (PIs)	
	Adult (> 18 years): • *Without NVP or EFV:* – 400 mg LPV /100 mg RTV po BID (2 tablets po BID) or – 800 mg LPV/200 mg RTV po once daily (4 tablets po daily) for patients with < 3 LPV-associated mutations • *With NVP or EFV:* – 500 mg LPV/125 mg RTV po BID – LPV/r once daily is not recommended with NVP or EFV
How Supplied/ Storage	• Cotton candy flavored oral solution: 80 mg LPV/20 mg RTV per mL (160 mL bottle). Contains alcohol 42.4% v/v and propylene glycol 153 mg/mL. Solution should be refrigerated until dispensed and then stored up to 42 days at room temperature. • 100 mg lopinavir/25 mg ritonavir **pediatric** tablet; 200 mg lopinavir/50 mg ritonavir **adult** tablet. Tablets should be stored at room temperature. Tablets must be swallowed whole; they cannot be broken, chewed, or crushed.
Food Restrictions	• Solution: Take with food to enhance absorption. • Tablets: Take with or without food.
Comments	• Liquid formulation contains alcohol therefore avoid co-medication with metronidazole. • Protease inhibitors are extensively metabolized by as well as inhibit CYP450 3A4. **CHECK FOR DRUG INTERACTIONS.**
Nelfinavir (Viracept®, NFV)	
Dose	Neonatal/Infant (less than 6 weeks) • Not approved for use in children < 2 years. • *NICHD/HPTN 040/PACTG 1043:* – More than 3 kg: 200 mg po BID – 2-3 kg: 150 mg po BID – 1.5-2 kg: 100 mg po BID – Less than 1.5 kg: not studied (Alberta Health Services perinatal protocol recommends 50 mg/kg/dose PO q 12 h in infants with birth weight < 1.5 kg) Pediatric (2 – 13 years): • 50 mg/kg/dose po BID (range 45 – 55 mg/kg/dose) Adult/Adolescent: • 1250 mg po BID
How Supplied/ Storage	250 mg and 625 mg tablets
Food Restrictions	Give with food or shortly after food for optimal absorption.
Comments	• **Tabs:** Dissolve a 250 mg tablet in 5 ml of sterile water (50 mg/ml). Measure out dose with a syringe that has 1 ml

Protease Inhibitors (PIs)	
	increments. Round dose of tablets to closest 50 mg. Do not mix with formula. • For older children, tablets readily dissolve in water and produce dispersion that can be mixed with milk/chocolate milk. Tablets can be crushed and given with pudding. Tablet may be mixed with food or liquid up to 6 hours (refrigerated) before dose is taken. • Do not mix with acidic food/juice (orange or apple juice) due to bitter taste. • Protease inhibitors are extensively metabolized by as well as inhibit CYP450 3A4. **CHECK FOR DRUG INTERACTIONS.**
Ritonavir (NORVIR®, RTV)	
Dose	• Ritonavir is now used solely as a pharmacokinetic enhancer of other protease inhibitors. For dosing, see specific protease inhibitors.
How Supplied/ Storage	• 80 mg/mL peppermint/caramel liquid (240 mL bottle). Recommended to be stored at room temperature and to use by product expiration date (limited shelf-life). (43% v/v ethanol) • 100 mg tablet. Store at room temperature. • 100 mg soft elastic capsule. Refrigerate until dispensed then stable at room temperature x 30 days. (12% v/v ethanol)
Food Restrictions	Take with food.
Comments	• Liquid is unpalatable, bad aftertaste. Tips: – Mix oral solution with milk/chocolate milk, or pudding. – Give after popsicle/frozen juice to dull taste buds. – Give after grape jelly, maple syrup, or peanut butter which coats mouth. – Give strong flavor after dose: syrup, cheese, chewing gum • During encapsulation process, exposure to soya protein lecithin and fractionated coconut oil occurs. As peanut and soy are from the same plant family, some patients allergic to peanuts may also be allergic to soy. Consult an allergist prior to taking capsules. • Liquid formulation contains alcohol therefore avoid co-medication with metronidazole. • Protease inhibitors are extensively metabolized by as well as inhibit CYP450 3A4. **CHECK FOR DRUG INTERACTIONS.**

Protease Inhibitors (PIs)	
Tipranavir (APTIVUS®, TPV)	
Dose	Neonate/Infant: • Not approved. Pediatric (2-18 years): • 14 mg/kg TPV + 6 mg/kg RTV po BID (375 mg/m^2 TPV + 150 mg/m^2 RTV both BID) (max. 500 mg TPV + 200 mg RTV BID) Adult/Adolescent: • 500 mg TPV +200 mg RTV po BID •
How Supplied/ Storage	• 250 mg capsule • Refrigerate the capsules until dispensed then stable at room temperature x 60 days • 100 mg/mL oral solution available in the **US only**. Note: solution contains 116 IU/mL vitamin E. • Store oral solution at room temperature (25°C). Use solution within 60 days of opening the bottle.
Food Restrictions	Take with food.
Comments	• Indicated for adults who are highly treatment experienced or have resistance to multiple PIs. • TPV is a sulfonamide. The potential cross-sensitivity with other sulfonamide drugs is unknown – caution in patients with sulfonamide allergy. • Protease inhibitors are extensively metabolized by as well as inhibit CYP450 3A4. **CHECK FOR DRUG INTERACTIONS.** • Cannot be split or crushed (Verbal communication, Boehringer Ingelheim, May 2008).

Entry and Fusion Inhibitors	
Enfuvirtide (Fuzeon®, T-20)	
Dose	Neonate/ Infant/ Pediatrics (less than 6 years): • Not approved for use in children less than 6 years. Pediatric/Adolescent (6-16 years): • For children 6 years or more: 2 mg/kg/dose twice daily, maximum dose 90 mg (1 mL) twice daily injected subcutaneously into upper arm, anterior thigh, or abdomen. Adult/Adolescent (more than 16 years): • 90 mg (1 mL) twice daily injected subcutaneously into the upper arm, anterior thigh, or abdomen.
How Supplied/ Storage	• Injection: lyophilized powder for injection 108 mg of enfuvirtide, when reconstituted with 1.1 mL sterile water to deliver 90 mg/mL. • Convenience kit: 60 single use vials of enfuvirtide (90 mg strength), 60 vials of sterile water for injection, 60 reconstitution syringes (3 mL), 60 administration syringes (1 mL), alcohol wipes • Reconstituted vial should be allowed to stand until the powder goes completely into solution (may take up to 45 min). Do not shake. • Once reconstituted, enfuvirtide should be injected immediately or stored in the fridge in the original vial until use. Must be used within 24 hrs after reconstitution
Comments	Injection sites should be rotated. Enfuvirtide should not be injected into moles, scar tissue, bruises, or the navel.
Maraviroc (Celsentri®, MVC)	
Dose	Pediatric/ Adolescent (< 16 years): • Not approved for use in children less than 16 years. Adult/Adolescent (≥16 years): • With CYP inhibitor (i.e. protease inhibitors (except TPV), delavirdine, ketoconazole, itraconazole, clarithromycin): 150 mg MCV po BID • Not CYP inducer/inhibitor (i.e. TPV, NVP, T-20, NRTIs): 300 mg MVC po BID • With CYP inducer (i.e. EFV, ETR, rifampin, carbamazepine, phenobarbital, phenytoin) and not taking potent CYP3A inhibitor: 600 mg MVC po BID
How Supplied/ Storage	150 mg and 300 mg film-coated tablets. Store between 15-30℃ in a USP tight container.
Food Restrictions	Take with or without food.
Comments	• CYP450 3A and PGP substrate. **CHECK FOR DRUG INTERACTIONS.** • Must have HIV tropism checked to exclude CXCR4/mixed tropic strain. • Film coated immediate release tablet however no studies regarding stability of split or crushed tablets. (Verbal communication, Pfizer, May 2008).

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Pediatric/Neonatal Doses of Antiretroviral Drugs

Integrase Inhibitors	
Raltegravir (Isentress®, RAL)	
Dose	Pediatric/Adolescent: Children aged 2 years to less than 12 years of age and at least 10 kg: • Dosing for chewable tablets based on approximately 6 mg/kg/dose po BID - 10 to less than 14 kg: 75 mg twice daily 3 x 25 mg twice daily - 14 to less than 20 kg: 100 mg twice daily 1 x 100 mg twice daily - 20 to less than 28 kg: 150 mg twice daily 1.5 x 100 mg twice daily (divide 100 mg tablet into equal halves) - 28 to less than 40 kg: 200 mg twice daily 2 x 100 mg twice daily - at least 40 kg: 300 mg twice daily 3 x 100 mg twice daily Adult/Pediatrics (≥12 years): • 400 mg RAL film-coated tablet po BID
How Supplied/ Storage	400 mg film-coated tablet. Store at room temperature (15-30℃). 25mg, 100 mg scored chewable tablet (not available yet it in Canada)_
Food Restrictions	Take with or without food
Comments	• Clearance through UGT1A1. **CHECK FOR DRUG INTERACTIONS.** • Crushing film coated tablets not recommended. Granules (sub-units of the tablet) dissolve faster than intact tablets and may result in faster release of drug which could affect in-vivo performance. (Data on file, Merck Frosst, May 2008) • Drug has a bitter taste which is masked by the film coating. • Chewable tablet may be chewed or swallowed whole. • Chewable and film-coated tablets are NOT interchangeable

Footnotes

1. Panel on Antiretroviral Therapy and Medical Management of HIV-Infected Children. Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection. August 11, 2011. Available at http://www.aidsinfo.nih.gov/contentfiles/lvguidelines/pediatricguidelines.pdf .
2. Contact one of the outpatient pharmacies (UAH or RAH) to initiate the ordering process. For nevirapine, didanosine and stavudine liquids, additional paperwork is required in addition to the special access request forms which are available on the Health Canada website (http://www.hc-sc.gc.ca/dhp-mps/acces/drugs-drogues/sapf1_pasf1-eng.php). Special Access Program ph: 613-941-2108.
3. To obtain the Sustiva liquid, call 1-877-372-7097. The Pediatric Research Nurses should be consulted first since appropriate physician/institution documentation must be in place prior to use of the liquid formulation.
4. AJHP 2000;57:1332-9.

References:

• Panel on Antiretroviral Therapy and Medical Management of HIV-Infected Children. Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection. August 11, 2011; pp 1-268. Available at http://aidsinfo.nih.gov/ContentFiles/PediatricGuidelines.pdf. Accessed (30 December 2011)

- Panel on Treatment of HIV-Infected Pregnant Women and Prevention of Perinatal Transmission. Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States. September 14, 2011; pp 1-207. Available at http://aidsinfo.nih.gov/ContentFiles/PerinatalGL.pdf. Accessed (30 December 2011) [pages 138 - 140]
- Tseng A, Foisy M. Handbook of HIV Drug Therapy, 2010.
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- Etravirine (Intelence®) USA Product Monograph © 2012

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V. REIMBURSEMENT INFORMATION

Summary of Requirements to Qualify For Prescription Reimbursement In Ontario

	Special Conditions	Paperwork
1. Ontario Drug Benefit (via standard criteria/Trillium program):		
a) ODB Formulary	None	None
b) Limited Use	Indication must match one(s) listed in ODB formulary	Include LU code on prescription.
c) Facilitated Access	MD must be registered with Ministry of Health	CPSO # on prescription
d) Exceptional Access Program (EAP)	Must demonstrate need for treatment with specific agent (e.g., indicate diagnosis, previous/concurrent therapies, etc.). Must meet criteria as defined by EAP program.	EAP application form submitted to ministry.
2. Other:		
a) Antiretrovirals	Patient needs valid Ontario Health Card #. Specific criteria (e.g., CD_4 count, concomitant antiretroviral therapy) may exist for certain agents. Pick up medication at designated hospital-affiliated pharmacies.	Register with Ontario Drug Distribution/Monitoring Program (ODDMP).
b) Anti-TB drugs	1st line agents via Ont. Department of Health. Pick up 2nd line medications at designated pharmacies.	Write "for resistant TB requiring second line drugs" on standard prescription.

PRESCRIPTION REIMBURSEMENT PLANS IN ONTARIO

In Ontario, coverage for drugs commonly prescribed in HIV/AIDS may often be obtained via various routes. Please note that eligibility criteria may vary depending upon the individual patient, the program, and the prescribed drug.

Ontario Drug Benefit Program (ODB): Ontario residents with a current and active drug card may have non-investigational medications covered via one of the following categories:

a) ODB Formulary: Agents listed in the ODB formulary may be prescribed by any physician, without specifying the indication.

b) Facilitated Access: ODB patients may receive these agents free of charge as long as the prescribing physician is registered with the Ministry of Health as a participating physician for ODB/AIDS treatment drugs. The physician's CPSO registration number should be included on each prescription for purposes of verification. In some cases, a Limited Use form should also be completed if the product is normally reimbursed via this mechanism. For further information, call the Drug Programs Branch at: **(416) 327-8109**.

c) Limited Use (LU): For each LU prescription, the physician must include the appropriate LU or RFU (reason for use) code as "LU 123" or "RFU 123". A regular prescription form may be used. The LU prescription form will be valid for one year from the initial date it was completed and signed by the prescriber. In some cases, LU drugs used for chronic conditions will be granted indefinite authorization periods.

d) Exceptional Access Program: Application for coverage of drugs not falling into any of the previous categories is done through the Exceptional Access Program (EAP). To apply through EAP, the patient's physician must submit a request documenting complete and relevant medical information to the ministry, providing the clinical rationale for requesting the unlisted drug and reasons why covered benefits are not suitable. All requests are reviewed according to the guidelines and criteria established by the CED and include a thorough assessment of the patient's specific case and clinical circumstances, as provided by the physician, as well as the scientific evidence available. The reimbursement criteria must always be met - even in cases where EAP drug coverage is required to provide continued treatment that was previously supplied through a clinical trial, or paid for by other means (such as a third party payor).

Selected drug-specific criteria used in the consideration of EAP requests are posted on the ministry website at:
http://www.health.gov.on.ca/english/providers/program/drugs/eap_criteria.html

A standard form is also available on the ministry website:
http://www.forms.ssb.gov.on.ca/mbs/ssb/forms/ssbforms.nsf/FormDetail?OpenForm&ACT=RDR&TAB=PROFILE&SRCH=&ENV=WWE&TIT=eap&NO=014-4406-87

In addition, for a limited group of drugs, requests may be submitted through the Telephone Request Service for faster approval.
http://www.health.gov.on.ca/english/providers/program/drugs/eap_trs.html

Submissions should be submitted by mail or fax to:

Exceptional Access Program
3rd Floor, 5700 Yonge St.
North York, ON M2M 4K5
Phone : 416-327-8109 or 1-866-811-9893
Fax : 416-327-7526 or 1-866-811-9908

Trillium Drug Program: Ontario residents who do not meet criteria for ODB may be eligible to receive drug reimbursement via the Trillium Drug Program, after paying a certain amount of their family income for prescription medications. This program pays for the same drugs and products that are covered under the ODB program. Similar procedures apply for reimbursement of limited use, facilitated access, or Exceptional Access Program drugs. To obtain application kits or for further information, call **1-800-575-5386**. More details are available at:
http://health.gov.on.ca/en/public/programs/drugs/programs/odb/opdp_trillium.aspx

Ontario Drug Distribution/Monitoring Program (ODDMP): Patients living in Ontario who are registered with the ODDMP are eligible to receive certain medications (e.g., aerosolized pentamidine) free of charge, regardless of ODB status. Prescriptions for these agents may be filled at designated pharmacies. For further information, call **(416) 480-4451**.

M. tuberculosis Treatment: Antimycobacterials (i.e., isoniazid, rifampin, ethambutol, pyrazinamide, pyridoxine) are provided free of charge for patients with M. tuberculosis infection, but not for infection with M. avium complex (MAC). These drugs are prescribed directly through the Ontario Department of Health Communicable Disease Control Notification Unit (CDCNU) at **(416) 392-7411**. Second-line agents for treatment of drug-resistant M. tuberculosis will be paid for by the City of Toronto, Public Health Department, provided the precription includes the indication (e.g., "for resistant TB requiring second line drugs) and is filled at a designated hospital out-patient pharmacy.

Special Access Program (SAP; formerly Emergency Drug Release Program, EDRP): This program allows prescribers to obtain medications that are currently not licensed in Canada for patients with serious or life-threatening conditions when conventional therapies have failed, are not appropriate, unavailable, or offer limited options. The Therapeutics Products Programme must be contacted at **(613) 941-2108 (08:30-16:30 hours EST), (613) 941-3194 (fax), or e-mail: SAPdrugs@hg-sc.gc.ca**. Requests are made on a per patient basis, and in some cases, the drug manufacturer should also be contacted. These drugs are often (but not always) provided free of charge (depending upon the particular product and company), and a dispensing fee may be charged.
For additional information:
http://www.hc-sc.gc.ca/dhp-mps/acces/drugs-drogues/sapfs_pasfd_2002-eng.php

Compassionate-Release: Manufacturers may occasionally provide agents (either investigational or licensed) free of charge on a compassionate basis, for patients who cannot otherwise afford the medication. Further information may be obtained by contacting the manufacturer directly.

Reimbursement Status of HIV Medications in Ontario

	Ont. Drug Distr. Monitoring Program	Ontario Drug Benefit/Trillium: *Formulary*	*Facilitated Access (F/A)*	*Limited Use*	*Exceptional Access Program*	Other
Antiretrovirals	AZT 100 mg capsules		NRTIs (single): • Abacavir, 3TC, d4T, ddI EC, tenofovir NRTIs (combination): • AZT/3TC (Combivir®), AZT, 3TC, abacavir (Trizivir®), abacavir/3TC (Kivexa®), tenofovir/FTC (Truvada®), emtricitabine/ tenofovir/ efavirenz (Atripla®) NNRTIs: • delavirdine, efavirenz, etravirine, nevirapine, rilpivirine PIs: • Darunavir, fosamprenavir, indinavir, lopinavir/ritonavir, nelfinavir, ritonavir, saquinavir Integrase Inhibitors: • raltegravir		PIs: • tipranavir (Aptivus®) Entry inhibitors: • enfuvirtide, maraviroc	Didanosine pediatric powder (SAP), d4T oral liquid (SAP)

	Ontario Drug Benefit/Trillium:				Other
	Formulary	***Facilitated Access (F/A)***	***Limited Use***	***Exceptional Access Program***	
Antivirals		Acyclovir, Ganciclovir IV	Acyclovir 800 mg tablets, famciclovir 500 mg tablets, ganciclovir IV, valacyclovir, valganciclovir	entecavir	Foscarnet, Cidofovir (SAP)
Antifungals	Clotrimazole vag tabs, Nystatin, Ketoconazole, IV Ampho B	Fluconazole, Itraconazole capsules and solution	Fluconazole, voriconazole	Liposomal amphotericin (Ambisome)	Ampho B lozenges, Ampho B oral solution, Clotrimazole troches, Flucytosine (SAP)
Hepatitis C directly acting antivirals				boceprevir	
PCP/Toxo Agents	TMP/SMX, TMP, Clindamycin, Folinic Acid	Atovaquone liquid, Pyrimethamine		Dapsone, Pentamidine, Primaquine	Sulfadiazine, Trimetrexate (SAP)
Mycobacterials	Isoniazid, Rifampin, Pyrazinamide, Ethambutol, B_6, Clarithromycin tabs and liquid, Azithromycin 250 mg tabs or liquid	Azithromycin 600 mg tablets	Rifabutin, Ciprofloxacin	Amikacin, gentamycin	Clofazimine, streptomycin (SAP); INH, RIF, ETM, PZA, B_6 (CDCNU); 2nd line TB drugs (Toronto Public Health)
Misc.	Megace, nabilone, most NSAIDs, codeine, morphine, hydromorphone, oxycodone + AAS or acetaminophen	Doxycycline, paramomycin, nutritional products, pneumococcal vaccine, potassium supplements	Fentanyl patch, gabapentin, ondansetron, pancreatic enzyme (Cotazyme ECS 20), interferon α-2a, interferon α-2b, diphenoxylate / atropine, loperamide, dronabinol, oxycodone, testosterone patch (Androderm), testosterone gel (Androgel)	Ketorolac, G-CSF (Neupogen), octreotide, somatropin (Serostim), imiquimod (Aldara)	Albendazole, aldesleukin, GM-CSF, Thalidomide (SAP); oxandrolone (SAP - but need to pay in advance: call (613) 957-1063); Altiretinoin (Panretin®) - SAP

Obtaining Antiretrovirals in Ontario

Drug	Status	Patient Criteria	MD Criteria	Paperwork/Pharmacy	Cost/Month
Fixed Dose Combination products:					
Emtricitabine 200 mg/ tenofovir 300 mg/ efavirenz 600 mg tablets (Atripla®)	ODB Facilitated Access	• ODB/Trillium plan	MD on ODB Facilitated Access List	• Physician's CPSO number on prescription.	$1242.00
Emtricitabine 200 mg/ tenofovir 300 mg/ rilpivirine 25 mg tablets (Complera®)	ODB Exceptional Access Program	• ODB/Trillium plan		• Individual Clinical Review (ICR) application made to Director of Drug Programs Branch, fax (416) 327-7526	
Nucleoside Reverse Transcriptase Inhibitors (combination products):					
Emtricitabine 200 mg/ tenofovir 300 mg tablets (Truvada®)	ODB Facilitated Access	• ODB/Trillium plan	MD on ODB Facilitated Access List	• Physician's CPSO number on prescription.	$798.90
abacavir 600 mg/ 3TC 300 mg tablets (Kivexa®)	ODB Facilitated Access	• ODB/Trillium plan	MD on ODB Facilitated Access List	• Physician's CPSO number on prescription.	$698.10
AZT 300 mg/3TC 150 mg tablets (Combivir®, generic)	ODB Facilitated Access	• ODB/Trillium plan	MD on ODB Facilitated Access List	• Physician's CPSO number on prescription.	$156.62-626.47
AZT 300 mg/ 3TC 150 mg/abacavir 300 mg tablets (Trizivir®)	ODB Facilitated Access	• ODB/Trillium plan	MD on ODB Facilitated Access List	• Physician's CPSO number on prescription.	$1060.42
Nucleoside Reverse Transcriptase Inhibitors (single source products):					

Drug	Status	Patient Criteria	MD Criteria	Paperwork/Pharmacy	Cost/Month
abacavir (Ziagen®)	ODB Facilitated Access	• ODB/Trillium plan	MD on ODB Facilitated Access List	• Physician's CPSO number on prescription.	$412.16
AZT, zidovudine 100 mg capsules (Retrovir®)	Ont. Drug Distribution/ Monitoring Program	• Ontario Health Card • CD_4<500		• Antiretroviral Registration Form to Ont. Drug Distribution/Monitoring Program • follow-up info q3months • Pick up Rx at designated hospital pharmacy	$362.28
ddI pediatric oral solution (Videx®)	Ont. Drug Distribution/ Monitoring Program, ODB Exceptional Access Program	• Ontario Health Card • CD_4<200		• Antiretroviral Registration Form to Ont. Drug Distribution/Monitoring Program; follow-up info q3months • Pick up Rx at designated hospital pharmacy • Individual Clinical Review (ICR) application (incl. cost of Maalox & extemporaneous compounding) made to Director of Drug Programs Branch, fax (416) 327-7526	ddI + cost of Maalox + $11.99 disp. Fee
ddI enteric coated tablets	ODB Facilitated Access	• ODB/Trillium plan	MD on ODB Facilitated Access List	• Physician's CPSO number on prescription.	$346.36
Lamivudine (3TC®, generic)	ODB Facilitated Access	• ODB/Trillium plan	MD on ODB Facilitated Access List	• Physician's CPSO number on prescription.	$217.61-290.15
d4T, stavudine (Zerit®)	ODB Facilitated Access	• ODB/Trillium plan	MD on ODB Facilitated Access List	• Physician's CPSO number on prescription.	$296.18
tenofovir (Viread®)	ODB Facilitated Access	• ODB/Trillium plan	MD on ODB Facilitated Access List	• Physician's CPSO number on prescription.	$534.90
Integrase Inhibitor:					
raltegravir (Isentress®)	ODB Facilitated Access	• ODB/Trillium plan	MD on ODB Facilitated Access List	• Physician's CPSO number on prescription.	$810.00
Non-Nucleoside Reverse Transcriptase Inhibitors:					
Delavirdine (Rescriptor®)	ODB Facilitated Access	• ODB/Trillium plan	MD on ODB Facilitated Access List	• Physician's CPSO number on prescription.	$258.41

Drug	Status	Patient Criteria	MD Criteria	Paperwork/Pharmacy	Cost/Month
efavirenz (Sustiva®)	ODB Facilitated Access	• ODB/Trillium plan	MD on ODB Facilitated Access List	• Physician's CPSO number on prescription.	$443.08
etravirine (Intelence®)	ODB Facilitated Access	• ODB/Trillium plan	MD on ODB Facilitated Access List	• Physician's CPSO number on prescription.	$654.00
nevirapine (Viramune®, generic)	ODB Facilitated Access	• ODB/Trillium plan	MD on ODB Facilitated Access List	• Physician's CPSO number on prescription.	$74.08-296.30
rilpivirine (Edurant®)	ODB Facilitated Access	• ODB/Trillium plan	MD on ODB Facilitated Access List	• Physician's CPSO number on prescription.	$413.91
Protease Inhibitors:					
atazanavir (Reyataz®)	ODB Facilitated Access	• ODB/Trillium plan	MD on ODB Facilitated Access List	• Physician's CPSO number on prescription.	$665.33 (unboosted); $707.03 (boosted)
darunavir (Prezista®)	ODB Facilitated Access	• ODB/Trillium plan	MD on ODB Facilitated Access List	• Physician's CPSO number on prescription.	$676.41 (QD dosing); $987.37 (BID dosing)
fosamprenavir (Telzir®)	ODB Facilitated Access	• ODB/Trillium plan	MD on ODB Facilitated Access List	• Physician's CPSO number on prescription.	$970.36 (unboosted); $573.20 (boosted)
indinavir (Crixivan®)	ODB Facilitated Access	• ODB/Trillium plan	MD on ODB Facilitated Access List	• Physician's CPSO number on prescription.	$411.22-499.25 (boosted)
lopinavir/ ritonavir (Kaletra®)	ODB Facilitated Access	• ODB/Trillium plan	MD on ODB Facilitated Access List	• Physician's CPSO number on prescription.	$653.76
nelfinavir (Viracept®)	ODB Facilitated Access	• ODB/Trillium plan	MD on ODB Facilitated Access List	• Physician's CPSO number on prescription.	$546.00
ritonavir tablets (Norvir®)	ODB Facilitated Access	• ODB/Trillium plan	MD on ODB Facilitated Access List	• Physician's CPSO number on prescription.	$44.01 (100 mg QD); $88.02 (100 mg BID)

Drug	Status	Patient Criteria	MD Criteria	Paperwork/Pharmacy	Cost/Month
ritonavir liquid (Norvir®)	ODB Facilitated Access	• ODB/Trillium plan	MD on ODB Facilitated Access List	• Physician's CPSO number on prescription.	$44.01 (100 mg QD); $88.02 (100 mg BID)
Saquinavir 500 mg tablet (Invirase®)	ODB Facilitated Access	• ODB/Trillium plan	MD on ODB Facilitated Access List	• Physician's CPSO number on prescription.	$602.11 (boosted)
Tipranavir (Aptivus®)	ODB Exceptional Access Program	• ODB/Trillium plan		• Individual Clinical Review (ICR) application made to Director of Drug Programs Branch, fax (416) 327-7526	$1245.25 (boosted)
Fusion Inhibitors					
Enfuvirtide (Fuzeon®)	ODB Exceptional Access Program	• ODB/Trillium plan • ≥6 months therapy with each ARV class and documented resistance mutations to ≥2 drugs in each class • virologic failure (RNA>50 copies/mL after 6 months and <1 log drop after 12 weeks on most recent regimen) • use in combination with ≥1 other sensitive ARV		• Individual Clinical Review (ICR) application made to Director of Drug Programs Branch, fax (416) 327-7526	$2575.80
CCR5 Inhibitor:					
maraviroc (Celsentri®)	ODB Exceptional Access Program	• ODB/Trillium plan		• Individual Clinical Review (ICR) application made to Director of Drug Programs Branch, fax (416) 327-7526	$1069.20

Access and Coverage of Antiretroviral Drugs Across Canada

Drug	Dose	Form	Provinces/Territory												
			Alberta	British Columbia	Manitoba	New Brunswick	Newfoundland & Labrador	Northwest Territories	Nova Scotia	Nunavut	Ontario	Prince Edward Island	Quebec	Saskatchewan	Yukon
Triple Combination tablets															
efavirenz/emtricitabine/tenofovir (Atripla)	600mg/ 200mg/ 300mg	tab	●	●	EDS	●	SA	●	●	●	●	●	●	EDS	EDS
rilpivirine/emtricitabine/tenofovir (Complera)	25mg/ 200mg/ 300mg	tab		ETO			SA	●	●	●			●	EDS	
Nucleoside/tide Reverse Transcriptase Inhibitors															
abacavir	300mg	tab	●	●	●	●	●	●	●	●	●	●	●	EDS	●
abacavir liquid	20mg/mL	sol	●	●	●	●	●	●	●	●	●		●	EDS	●
abacavir/lamivudine (Kivexa)	600mg/ 300mg	tab	●	●	●	●	●	●	●	●	●	●	●	EDS	●
abacavir/lamivudine/zidovudine (Trizivir)	300mg/ 150mg/ 300mg	tab	●	●	●	●	●	●	●	●	●	●	●	EDS	●
emtricitabine/tenofovir (Truvada)	200mg/ 300mg	tab	●	●	EDS	●	SA	LUB	●	LUB	●	●	●	EDS	EDS
didanosine EC	125mg	Cap	●	●	●	●	NFDR	●	●	●	●	●	●	EDS	●
didanosine EC	200mg	cap	●	●	●	●	●	●	●	●	●	●	●	EDS	●
didanosine EC	250mg	cap	●	●	●	●	●	●	●	●	●	●	●	EDS	●
didanosine EC	400mg	cap	●	●	●	●	●	●	●	●	●	●	●	EDS	●
Didanosine powder for oral suspension	4g	Pwd	SAP	SAP	SAP	SAP	SAP	SAP	SAP	SAP	SAP	SAP	SAP	SAP	SAP
lamivudine (generic: Apo-)	150mg	tab									●				
lamivudine (generic: Apo-)	300mg	tab									●				
lamivudine (3TC)	150mg	tab	●	●	●	●	●	●	●	●		●	●	EDS	●
lamivudine (3TC)	300mg	tab	●	●	●	●	●	●	●	●		●	●	EDS	●
lamivudine liquid	10mg/ml	sol	●	●	●	●	●	●	●	●	●		●	EDS	●
lamivudine/zidovudine (generic: Apo)	150mg/ 300mg	tab				SA					●	●			
lamivudine/zidovudine (Combivir)	150mg/ 300mg	Tab	●	●	●	SA	●	●	●	●		●	●	EDS	●
stavudine	15mg	Cap	●	●	●	●	●	●	●	●	●	●	●	EDS	●
stavudine	20mg	Cap	●	●	●	●	●	●	●	●	●	●	●	EDS	●
stavudine	30mg	Cap	●	●	●	●	●	●	●	●	●	●	●	EDS	●
stavudine	40mg	cap	●	●	●	●	●	●	●	●	●	●	●	EDS	●
stavudine liquid	1mg/mL	Sol	SAP	SAP	SAP	SAP	SAP	SAP	SAP	SAP	SAP	SAP	SAP	SAP	SAP
tenofovir	300mg	tab	●	●	EDS	SA	SA	LUB	●	LUB	●	●	●	EDS	EDS
zidovudine (generic: Apo-, Novo-)	100mg	cap	●		●	●	●	●	●	●		●	●	EDS	●
zidovudine (Retrovir)	100mg	cap	●	●	●	●	NFDR	●	●	●	ODDMP	●	●	EDS	●
zidovudine liquid	10mg/mL	syr	●	●	●	●	●	●	●	●	ODDMP		●	EDS	●
Non-Nucleoside Reverse Transcriptase Inhibitors															
delavirdine	100mg	tab	●	●	●	SA	●		●		●		●	EDS	●
efavirenz	50mg	Cap	●	●	●	●	●	●	●	●	●	●	●	EDS	●
efavirenz	200mg	cap	●	●	●	●	●	●	●	●	●	●	●	EDS	●

Drug	Dose	Form	Provinces/Territory												
			Alberta	British Columbia	Manitoba	New Brunswick	Newfoundland & Labrador	Northwest Territories	Nova Scotia	Nunavut	Ontario	Prince Edward Island	Quebec	Saskatchewan	Yukon
efavirenz	600mg	tab	●	●	●	●	●	●	●	●	●	●	●	EDS	●
efavirenz liquid	30mg/mL	sol	SAP	SAP	SAP	SAP	SAP	SAP	SAP	SAP	SAP	SAP	SAP	SAP	SAP
etravirine	100mg	tab	●	ETO	EDS	SA	●	LUB	●	LUB	●	●	MDE	EDS	
etravirine	200mg	tab	●	ETO			●		●		●		MDE	EDS	
nevirapine (generic: Auro- or Teva-)	200mg	tab	●		●	●	●	●	●	●	●		●	EDS	●
nevirapine (Viramune)	200mg	tab	●	●	●	●		●	●	●		●	●**	EDS	●
nevirapine XR	400mg	tab		●		SA			●		●		PDE		
nevirapine liquid	50mg/mL	susp	SAP	SAP	SAP	SAP	SAP	SAP	SAP	SAP	SAP	SAP	SAP	SAP	SAP
rilpivirine	25mg	tab		ETO			SA	●	●	●	●		●	EDS	
Protease Inhibitors															
atazanavir	150mg	cap	●	●	●	●	●	●	●	●	●	●	●	EDS	●
atazanavir	200mg	cap	●	●	●	●	●	●	●	●	●	●	●	EDS	●
atazanavir	300mg	cap	●	●	●	●	●	●	●	●		●	●	EDS	●
darunavir	75mg	tab	●	ETO	●	SA	SA	●	●	●	●		●	EDS	
darunavir	150mg	tab		ETO			NFDR		●				PDE		
darunavir	400mg	tab	●	ETO	●	SA	SA	●	●	●	●	SA	●	EDS	
darunavir	600mg	tab	●	ETO	●	SA	SA	●	●	●	●	SA	MDE	EDS	
fosamprenavir	700mg	tab	●	●	●	●	●	●	●	●	●	●	●	EDS	
fosamprenavir liquid	50mg/mL	susp	●	●	EDS	●	NFDR	●	●	●	●		●	EDS	
indinavir	200mg	cap	●	●	●	●	●	●	●	●	●	●	●	EDS	●
indinavir	400mg	cap	●	●	●	●	●	●	●	●	●	●	●	EDS	●
lopinavir/ritonavir	100mg/ 25mg	tab	●	●	●	●	NFDR	●	●	●	●		●	EDS	
lopinavir/ritonavir	200mg/ 50mg	tab	●	●	●	●	●	●	●	●	●	●	●	EDS	●
lopinavir/ritonavir liquid	80mg/ 20mg/mL	sol	●	●	●	●	●	●	●	●	●		●	EDS	
nelfinavir	250mg	tab	●	●	●	●	●	●	●	●	●	●	●	EDS	●
nelfinavir	625mg	tab	●	●	●	●	●	●	●	●	●	●	●	EDS	
Nelfinavir powder for oral solution	50mg/g	pwd	●		●	SA	●	●	●	●	●		PDE		●
ritonavir	100mg	cap	●	●	●	SA	●	●	●	●	●	●	●	EDS	●
ritonavir	100mg	tab	●	●	●	SA	●	●	●	●	●	●	●	EDS	●
ritonavir liquid	80mg/mL	sol	●	●	●	SA	●	●	●	●	●		●	EDS	●
saquinavir	200mg	cap	●	●	●	●	●	●	●	●	●	●	●	EDS	●
saquinavir	500mg	tab	●	●	●	●	●	●	●	●	●	●	●	EDS	
tipranavir	250mg	cap	●	ETO	EDS	SA	SA	LUB	●	LUB	EAP		MDE	EDS	
Integrase inhibitors															
raltegravir	400mg	tab	●	ETO	EDS	SA	●*	LUB	●	LUB	●	●	●	EDS	EDS
CCR5 antagonists															
maraviroc	150mg	tab	●	ETO	EDS	SA	SA	LUB	●	LUB	EAP	●	MDE	EDS	
maraviroc	300mg	tab	●	ETO	EDS	SA	SA	LUB	●	LUB	EAP	●	MDE	EDS	
Fusion inhibitors															
enfuvirtide	108mg/vial	inj	●	ETO	EDS	SA	NFDR		●		EAP	SA	MDE	EDS	

Legend

●	Open access coverage for those enrolled in the provincial/territorial drug program
●*	Open access for treatment-experienced only; need authorization for coverage for a naïve patient
●**	Covered if specified on the prescription "do not substitute"
EAP	Exceptional Access Program (of the Ontario Drug Program); written requests are sent for approval to ensure reimbursement criteria are met
EDS	Exception Drug Status In Manitoba, requests for approval can be requested by phone, fax, or mail except enfuvirtide, fosamprenavir liquid, and tipranavir which require a written request to be submitted to the Manitoba Drug Standards and Therapeutics Committee In Saskatchewan, requests for all ARVs can be submitted by phone, fax, or mail by a prescribing physician or pharmacist (except designated ID physicians who have pre-approval status and automatic coverage provided) In the Yukon, a written application must be submitted for a drug that has exception drug status. To provide coverage while the application is being reviewed, a pharmacist may obtain a 30d approval by telephone.
ETO	Extended Therapy Only; certain restriction apply, contact St. Paul's ambulatory pharmacy for further information
LUB	Limited Use Benefit (of the NIHB program); prior approval is required to ensure criteria are met for coverage
MDE	Médicament d'exception form required; need to meet criteria for coverage (If does not meet criteria, a "patient d'exception" request can be made)
ODDMP	Ontario Drug Distribution and Monitoring Program; patient is enrolled in the program and drug is provided free of charge
PDE	Patient d'exception; request for special consideration of coverage including those who do not meet the médicament d'exception criteria (request may be refused)
SAP	Specialized Access Program; letter of request must be sent to Health Canada (http://www.hc-sc.gc.ca/dhp-mps/acces/drugs-drogues/index-eng.php) to obtain access to drug not marketed in Canada
SA	Special Authorization required
NFDR	Non-funded Drug Request; letter can be written to the Medical Director of the program for special consideration

The federal, provincial, and territorial governments of Canada are responsible for the administration of their own publicly-funded out-patient prescription drug benefit program. Each offers varying levels of coverage, with different eligibility criteria, enrolment processes, deductibles and/or co-pays. Each province/territory recognizes the high costs of antiretroviral therapy and has an associated program to provide various levels of insurance for patients with HIV; however, each province/territory makes decisions on how the antiretroviral is listed on their formulary (eg. open access, pre-defined criteria). Many programs will follow recommendations made by The Common Drug Review at the Canadian Agency for Drugs and Technologies in Health. Their review and recommendation can be found at http://www.cadth.ca/en/products/cdr

Canadian residents moving from one province/territory to another whose health coverage is not covered by a federal program continue to be covered by their "home" province/territory for a maximum period of 3 months. Upon moving, an individual should be advised to immediately apply for health coverage in the new province/territory and start the process of obtaining drug coverage if an application is required. After maximum waiting period of 3 months, the new province/territory assumes the health coverage and it is hoped the drug coverage will also have been approved in this time-period. **Patients should be advised to obtain a 3 month supply of their medications from their "home" province/territory to bridge this gap and minimize the risk of an interruption to their therapy.**

The federal programs are portable across the country. The various federal programs (http://www.hc-sc.gc.ca/hcs-sss/pharma/acces/fedprog-eng.php) provide drug coverage to various groups such as First Nations and Inuit, members of the military and RCMP, and refugee claimants. Such programs include:

Non-Insured Health Benefits (NIHB) Program
The NIHB program provides coverage for drugs listed on the "Drug Benefit List" (http://www.hc-sc.gc.ca/fniah-spnia/nihb-ssna/provide-fournir/pharma-prod/med-list/index-eng.php) for eligible First Nations people and Inuit. A summary of the antiretrovirals covered by the NIHB program can be found under the Northwest Territories or Nunavut heading as both territories use this formulary.

Interim Federal Health (IFH) program
The IFH program provides limited temporary health insurance to protected persons, including resettled refugees, and refugee claimants in Canada through three basic types of coverage (http://www.cic.gc.ca/english/refugees/outside/arriving-healthcare.asp). Most antiretrovirals are covered but require pre-authorization (https://provider.medavie.bluecross.ca/welcome). Some provinces or territories may pick up coverage of a drug the IFHP does not.

Canadian Forces Health Services (CFHS)
The CFHS is the designated health care provider for Canada's military personnel. There is no formulary list of all drugs covered; however, most medications are covered and can be filled at the pharmacy on base without any costs. If filled at an outside pharmacy that is not registered with the CFHS, the patient pays upfront and is then reimbursed the cost.

Veterans Affairs Canada (VAC)
The VAC provides both disability pensions and health treatment benefits (through VACs 14 Programs of Choice) for both the Royal Canadian Mounted Police members and Canadian Veterans. The VAC will consider coverage of medications only after the provincial/territorial program is accessed first.

Province	Process to get ARV coverage	Restrictions on prescriber	Restrictions on pharmacy dispensing ARVs
Alberta	All eligible residents of Alberta must register with the Alberta Health Care Insurance Plan (AHCIP) ARVs are 100% covered by the Specialized High Cost program of the AHCIP (see chart for exceptions) http://www.health.alberta.ca/health-care-insurance-plan.html	**Northern Alberta** -Infectious disease MD with HIV specialty practice -HIV pharmacists with prescribing authorization -HIV nurse practitioner **Southern Alberta** -MDs and pharmacists practicing at the Southern Alberta Clinic (SAC) -MDs in hospital may prescribe in consultation with the specialists at SAC	**Northern Alberta** -Rexall outpatient pharmacies at the University of Alberta and Royal Alexandra hospitals **Southern Alberta** -SAC has a dispensing pharmacy on-site -medications are shipped across the province as needed
British Columbia	A BC resident with active BC Personal Health Number or Interim Federal Health coverage and documented HIV infection are eligible for enrolment in the BC Centre for Excellence (BC-CfE) HIV Drug Treatment Program ARVs are 100% covered by provincial program (see chart for exceptions) If covered by the Non-Insured Health Benefits (NIHB) for First Nations and Inuit, client can "opt-out" of provincial plan (nb. Most will use the provincial program and not NIHB) If private insurance covers an ARV not covered by province, patient can be part of both programs and can fill drug at outside pharmacy. Otherwise, most private insurance will not pick up the costs of any ARV that can be filled by the province. http://www.cfenet.ubc.ca/healthcare-providers	No restriction on prescriber but prescriptions require pre-authorization through the BC-CfE Drug Treatment program	**Coquitlam** Product Distribution Centre (nb. Incarcerated in a provincial facility) **Kelowna** Lakeside Medicine Centre **Nanaimo** Nanaimo Regional General Hospital pharmacy **Vancouver** St. Paul's Hospital – ambulatory pharmacy BC Children/Womens Hospital – ambulatory pharmacy Downtown Community Health Clinic pharmacy **Victoria** Royal Jubilee Hospital Any community pharmacy for those using NIHB coverage
Manitoba	Manitoba residents without 100% private insurance (or other provincial or federal coverage) who have Manitoba Health coverage can obtain provincial coverage of ARVs by enrolling into the Pharmacare program, a family plan that includes dependents for children <18 years of age. A one page application needs to be submitted. There is an annual deductible based on the adjusted family income and is calculated as a percentage of the total family income. Once paid, the government pays 100% of the cost of the meds for the remainder of the Pharmacare year (April 1 – March 31). Application can be made to divide annual deductible into monthly installments. For individuals that have partial private insurance, the provincial plan is used first, then the insurance coverage is applied to the deductible. For Manitoba residents who are on social assistance/family services, meds that are listed on the provincial formulary are paid for 100% by the government, with no co-pay.	No restrictions on prescriber	Any pharmacy can dispense ARVs

Province	Process to get ARV coverage	Restrictions on prescriber	Restrictions on pharmacy dispensing ARVs
	http://www.gov.mb.ca/health/pharmacare/index.html		
New Brunswick	Residents of New Brunswick with New Brunswick Medicare with HIV AND have no private coverage, are eligible to be registered to the "Prescription Drug Program – HIV/AIDS" (Plan U) by their physician. Patients are required to pay 20% of the costs for each prescription up to a maximum of $20 (maximum co-pay of $500 per family unit in one fiscal year) If patients have a health card for prescription drugs through the department of social services, the co-pay is $4 per prescription for adults and $2 for children (maximum co-pay of $250 per family unit in one fiscal year) If the patient has only partial private insurance (eg. 80%), they are not eligible for Plan U and the remaining co-payments are not assisted by the province http://www.gnb.ca/0212/NBPDPFormulary-e.asp	The prescriber must be an infectious disease specialist or medical microbiologist.	All provincially covered ARVs must be filled at: Meditrust Pharmacy Services Saint John, NB 506-674-4444
Newfoundland & Labrador	There are 4 plans under the Newfoundland and Labrador Prescription Drug Program (NLPDP) that a patient may qualify for to cover ARVs: - Foundation Plan – for clients who qualify for income support benefits; 100% coverage - Access Plan – for clients with low family incomes; co-pay based on income and drug costs, and is a percentage of prescription costs. - Assurance Plan – for clients with very high costs; co-pay based on income and drug costs, and is a percentage of prescription costs. - 65Plus Plan – covers medications costs only; clients must pay the associated professional fees Those with private insurance with a high associated co-pay, can apply for an NLPDP card but insurance must be used first. The provincial plan is always the payer of last resort. http://www.health.gov.nl.ca/health/prescription/covered.html	No restriction on prescriber	Any pharmacy can dispense ARVs (Currently the NLPDP needs to be informed to allow a community pharmacy to electronically bill the program)
Northwest Territories	All permanent residents of the Northwest Territories are eligible to register for the "Northwest Territories health care plan" and obtain coverage of their ARVs through an application to the Extended Health Benefits for Specific Disease Conditions. The prescription drug benefits are administered through Alberta Blue Cross on behalf of the government of the Northwest Territories and provides up to 100% coverage for drugs listed on the drug benefit list (the Non-Insured Health Benefits formulary). Any drug not covered by the NIHB formulary can be requested through an "Exception Drug Request form" that is sent to Alberta Blue Cross. The Extended Health Benefits program is the payment agency of last resort. Private insurance must be accessed first. Those registered as First Nations or recognized Inuit can access their ARVs through the Non-Insured Health Benefits Program. http://www.hc-sc.gc.ca/fniah-spnia/nihb-ssna/provide-fournir/pharma-prod/med-list/index-eng.php	No restrictions on prescriber	Any pharmacy can dispense
Nova Scotia	A Nova Scotia resident with a Nova Scotia Health Card (MSI) qualifies for ARV coverage All marketed ARVs are 100% covered by provincial program	MD and pharmacist in HIV clinic only	**For clients with private insurance:** Any pharmacy can order and dispense ARVs **For clients without private insurance**

Province	Process to get ARV coverage	Restrictions on prescriber	Restrictions on pharmacy dispensing ARVs
	If client has private insurance but significant co-pay, eg. 20%, the fee can be charged back to the provincial AIDS program. http://www.gov.ns.ca/health/Pharmacare/formulary.asp		ARVs are dispensed by designated hospital pharmacy eg. VG Pharmacy in Halifax (refills can be mailed to client)
Nunavut	A permanent resident of Nunavut or a person holding an employment or student visa valid for one year or more is eligible and covered under the Nunavut Health Care plan. Extended Health Benefit program offers coverage for those with a chronic disease and covers the full cost of ARVs listed in the NIHB formulary Non Insured Health Benefits (NIHB) is available to eligible Land Claim Beneficiaries and covers the full cost of ARVs listed in the NIHB formulary http://www.hc-sc.gc.ca/fniah-spnia/nihb-ssna/provide-fournir/pharma-prod/med-list/index-eng.php Claims must be made through the third party insurance program before making a claim through any government insurance program.	Any physician may prescribe	Any pharmacy can dispense
Ontario	A resident of Ontario without private insurance is eligible for the Ontario Drug Benefit program and depending on income, would qualify for - **Trillium Drug Program** -family drug program with a yearly deductible (~4% of household income), then $2 per prescription -can be used to help with remainder of cost not covered by private insurance - Social Assistance - **Ontario Works (OW) program** – $2 for every prescription - **Ontario Disability Support program (ODSP**) – $2 co-pay for every prescription - **Assistance for Children With Severe Disabilities** (ACSD) - this is in-addition to the Trillium, OW or ODSP program the child may be enrolled in - based on parents' income, children can receive up to $440/month for prescription drugs - child must be under 18 years of age - application forms available through Regional Offices of the Ministry of Children and Youth Services Children eligibility: -all dependents independent of age are covered as long as they live with the parent/parents, do not pay rent, and are financially dependent on the parent(s) -university students who are financially dependent on their parents remain as dependents even though they may reside away at school -the previous year's income taxes for both parent and dependent (child) are the basis for financial evaluation A person enrolled in the Home Care system would also receive drug coverage through the Ontario Drug Benefit program All above programs require application, not automatic with Ontario health card. Seniors (65+) are automatically enrolled into the Ontario Drug Benefit program - high-income senior - $100 deductible, the $6.11 co-pay per prescription - low-income senior – no deductible, $2 co-pay per prescription Patients with partial private insurance (eg. 80%) can apply to the Trillium Drug Program to help with costs but insurance must be used first. The Trillium deductible must be met before 100% coverage is provided. However, the client usually must pay the costs up-front and submit the receipts for reimbursement.	Prescriber must be on the Facilitated Access to HIV/AIDs drugs access list	Any pharmacy can dispense ARVs obtained through the Ontario Drug Distribution and Monitoring program (eg. AZT) must be obtained from designated hospital pharmacy (416-480-6146)

Province	Process to get ARV coverage	Restrictions on prescriber	Restrictions on pharmacy dispensing ARVs
	http://www.health.gov.on.ca/english/providers/program/drugs/odbf_eformulary.html		
Prince Edward Island (PEI)	To obtain coverage of antiretrovirals in PEI, the physician must submit a request for the patient to be registered in the "AIDS/HIV Program" of PEI Medicare. Antiretrovirals are 100% covered by the program (see chart for exceptions) http://healthpei.ca/formulary	No restrictions on prescriber	All provincially covered ARVs must be filled at: (patient pays for delivery of meds) The Provincial Pharmacy 16 Fitzroy Street Charlottetown, PEI 902-368-4947
Quebec	In Quebec, everyone must be covered by prescription drug insurance. If a patient does not have private insurance, application can be made to the public plan, Régie de l'assurance maladie du Québec (RAMQ) by phone or internet. There is no costs for the following populations : - holders of a claim slip (eg. patient receiving welfare) - persons age 65 or older receiving 94-100% of guaranteed income (eg. those living almost entirely off their pension) - children under age 18 (covered by parents' coverage eg. private or RAMQ) - adults 18-25, full time students, without a spouse, and living with their parents For everyone else in the public plan, a yearly premium is paid based on income Certain patients with partial private insurance (eg. 80%) can also enroll in the RAMQ to help with costs. http://www.ramq.gouv.qc.ca/en/publications/citizens/legal-publications/Pages/list-medications.aspx	No restrictions on prescriber	Any pharmacy can dispense
Saskatchewan	There are two systems to obtain ARV coverage in Saskatchewan: 1. **The Saskatchewan Drug Plan** Various programs are available to those with Saskatchewan health care that require registration with different co-pay. Programs are not automatic with Saskatchewan health card (except children's plan) a. **Special Support** -co-pay is a calculated percentage based on the family's annual adjusted income. Lower co-pays are possible if the total drug costs exceed 3.4% of the adjusted family income. The lowest possible co-pay is 1% of total drug cost b. **Children & Senior's Plan** (children ≤14yrs or seniors ≥65yrs) -$20 for each prescription (can apply for Special Support and pay the lower of the two programs) c. **Supplementary Health (Social Assistance)** -$2 co-pay for each prescription or no charge depending on level of coverage 2. **Non-Insured Health Benefits Plan (NIHB)** For patients who are treaty or status; no co-pays. (see Northwest Territory column for ARVs covered by NIHB; however, in Saskatchewan, Truvada is available as an open benefit, not requiring prior approval unless supply requested exceeds $1000. Additionally, in Saskatchewan, lifetime approvals are granted for limited use benefit antiretrovirals vs. approval to a specific pharmacy for duration of the prescription For those with partial private insurance, the third party insurance program will be billed after the provincial program.	Prescriber must be an ID specialist, has had a discussion with a specialist, or has pre-approval status. Designated physician can have pre-approval status and do not need to call for ARV coverage approval	Any pharmacy can order and dispense ARVs

Province	Process to get ARV coverage	Restrictions on prescriber	Restrictions on pharmacy dispensing ARVs
	All ARVs listed in the chart are covered by the Saskatchewan Drug Plan but require Exceptional Drug Status (EDS) approval where certain criteria must be met. The criteria for most ARVs are "if used for the treatment of HIV under the guidance of an ID specialist". http://formulary.drugplan.health.gov.sk.ca/		
Yukon	There are 4 drug programs that a patient living in the Yukon may qualify for to cover ARVs: 1. **Chronic Disease Program** - physician must apply for benefits on behalf of patient; annual deductible of $250 (max $500/family) which can be reduced or waived based on income and family size 2. **Pharmacare Program** - persons at least 65 years of age and spouse aged 60 years or older; automatic enrolment with no deductible **3. Children Drug and Optical Program (CDOP)** - for children under 19 years of age; automatic enrolment with no deductible 4. **Non-Insured Health Benefits program** - for registered First Nations and recognized Inuit; see Northwest Territory column for ARVs covered by NIHB Those who have prescription drug costs covered by private insurance must use that plan first Many ARVs are considered case-by-case as the jurisdiction is too small to review every drug for formulary and decisions are often made after a request for a specific drug for a patient is made. Recommendations from The Common Drug Review (http://www.cadth.ca/en/products/cdr) are often followed. http://www.hss.gov.yk.ca/pdf/yukon_drug_programs_formulary.pdf	Based on recommendation by ID specialist	Any pharmacy can dispense ARVs

VI. MANUFACTURER CONTACT INFORMATION

Manufacturer Contact Information

Drug	Trade Name	Manufacturer	Phone Number (medical info)	Internet
abacavir	Ziagen	ViiV Healthcare ULC	1-877-393-8448	www.viivhealthcare.com
abacavir/ lamivudine	Kivexa	ViiV Healthcare ULC	1-877-393-8448	www.viivhealthcare.com
abacavir/ lamivudine/ zidovudine	Trizivir	ViiV Healthcare ULC	1-877-393-8448	www.viivhealthcare.com
acyclovir	Zovirax	ViiV Healthcare ULC	1-877-393-8448	www.viivhealthcare.com
amphotericin B injection, lozenges, oral suspension	Fungizone	Bristol-Myers Squibb	1-866-463-6267	www.bmscanada.ca
atazanavir	Reyataz	Bristol-Myers Squibb	1-866-463-6267	www.bmscanada.ca
atovaquone	Mepron	ViiV Healthcare ULC	1-877-393-8448	www.viivhealthcare.com
azithromycin	Zithromax	Pfizer	1-800-463-6001	www.pfizer.ca
cidofovir	Vistide	Gilead Sciences	1-866-207-4267	www.gilead.ca
ciprofloxacin	Cipro	Bayer Inc.	1-800-265-7382	www.bayer.ca
clarithromycin	Biaxin	Abbott Laboratories	1-800-699-9948	www.abbott.ca
dapsone	Dapsone	Jacobus Pharmaceutical Co.	416-438-6727	
darunavir	Prezista	Janssen Inc.	1-800-567-3331	www.janssen.ca www.janssenmedicalinformation.ca
ddI (didanosine)	Videx EC	Bristol-Myers Squibb	1-866-463-6267	www.bmscanada.ca
delavirdine	Rescriptor	ViiV Healthcare ULC	1-877-393-8448	www.viivhealthcare.com
efavirenz	Sustiva	Bristol-Myers Squibb	1-866-463-6267	www.bmscanada.ca
efavirenz/ emtricitabine/ tenofovir	Atripla	Bristol-Myers Squibb & Gilead Sciences	1-866-463-6267 1-866-207-4267	www.bmscanada.ca www.gilead.ca
emtricitabine	Emtriva	Gilead Sciences	1-866-207-4267	www.gilead.ca
emtricitabine/ tenofovir	Truvada	Gilead Sciences	1-866-207-4267	www.gilead.ca
elvitegravir/ cobicistat/ emtricitabine/ tenofovir	Stribild	Gilead Sciences	1-866-207-4267	www.gilead.ca www.stribild.com
enfuvirtide	Fuzeon	Hoffmann-LaRoche	1-888-762-4388	www.rochecanada.com www.fuzeon.com
etravirine	Intelence	Janssen Inc.	1-800-567-3331	www.janssen.ca www.janssenmedicalinformation.ca

Drug	Trade Name	Manufacturer	Phone Number (medical info)	Internet
ethambutol	Etibi	Valeant Canada Ltd.	1-800-361-1448	www.valeant.com
fluconazole	Diflucan	Pfizer	1-800-463-6001	www.pfizer.ca
fosamprenavir	Telzir	ViiV Healthcare ULC	1-877-393-8448	www.viivhealthcare.com
ganciclovir	Cytovene	Hoffmann-LaRoche	1-888-762-4388	www.rochecanada.com
indinavir	Crixivan	Merck Canada	1-800-567-2594	www.merck.com
isoniazid	Isotamine	Valeant Canada Ltd.	1-800-361-1448	www.valeant.com
itraconazole	Sporanox	Janssen Inc.	1-800-567-3331	www.janssen.ca www.janssenmedicalinformation.ca
ketoconazole	Nizoral	Janssen Inc.	1-800-567-3331	www.janssen.ca www.janssenmedicalinformation.ca
lamivudine	3TC	ViiV Healthcare ULC	1-877-393-8448	www.viivhealthcare.com
lamivudine/ zidovudine	Combivir	ViiV Healthcare ULC	1-877-393-8448	www.viivhealthcare.com
lopinavir/ritonavir	Kaletra	Abbott Laboratories	1-800-699-9948	www.abbott.ca
maraviroc	Celsentri	ViiV Healthcare ULC	1-877-393-8448	www.viivhealthcare.com
megestrol acetate	Megace	Bristol-Myers Squibb	1-866-463-6267	www.bmscanada.ca
nelfinavir	Viracept	Pfizer	1-800-463-6001	www.pfizer.ca
nevirapine	Viramune	Boehringer Ingelheim	1-800-263-5103 ext 84633	www.boehringer-ingelheim.ca
pentamidine	pentamidine	Hospira Healthcare Corp	1-514-905-2600	
posaconazole	Posanol	Merck Canada	1-800-567-2594	www.merck.com
pyrimethamine	Daraprim	GlaxoSmithKline	1-800-387-7374	www.gsk.ca
raltegravir	Isentress	Merck Canada	1-800-567-2594	www.merck.com www.isentress.com
rifabutin	Mycobutin	Pfizer	1-800-463-6001	www.pfizer.ca
rifampin	Rifadin	Sanofi-Aventis Canada Inc.	1-800-265-7927	www.sanofi.ca
ritonavir	Norvir	Abbott Laboratories	1-800-699-9948	www.abbott.ca
saquinavir	Invirase	Hoffmann-LaRoche	1-888-762-4388	www.rochecanada.com
stavudine	Zerit	Bristol-Myers Squibb	1-866-463-6267	www.bmscanada.ca
tenofovir	Viread	Gilead Sciences	1-866-207-4267	www.gilead.ca
tipranavir	Aptivus	Boehringer Ingelheim	1-800-263-5103 ext 84633	www.boehringer-ingelheim.ca
valacyclovir	Valtrex	Glaxo-Smith Kline	1-800-387-7374	www.gsk.ca
valganciclovir	Valcyte	Hoffmann-LaRoche	1-888-762-4388	www.rochecanada.com

Drug	Trade Name	Manufacturer	Phone Number (medical info)	Internet
zidovudine	Retrovir	ViiV Healthcare ULC	1-877-393-8448	www.viivhealthcare.com

VII. GLOSSARY

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
ddI	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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