2014

HIV ONCOLOGY HANDBOOK

Antiretroviral Interactions with Chemotherapy Regimens

Alison Wong, B.pharm., M.Sc.
Chronic Viral Illness Service
McGill University Health Centre
Montreal, QC

Alice Tseng, Pharm.D., FCSHP, AAHIVP
Immunodeficiency Clinic
Toronto General Hospital
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Toronto General Hospital
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Contributors

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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.

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INTRODUCTION

Clinically significant interactions between chemotherapy regimens and antiretroviral therapy have been reported in the literature. In particular, the use of protease-inhibitor based antiretroviral treatment has been shown to increase the toxicity of several chemotherapy agents, primarily those which are known substrates of the cytochrome P450 system and/or p-glycoprotein. Similar concerns may also apply to antiretroviral regimens containing the pharmacokinetic enhancer, cobicistat as both protease-inhibitor based antiretroviral treatment and cobicistat are considered to be moderate-potent inhibitors of cytochrome P450 enzymes.

Conversely, most non-nucleoside reverse transcriptase inhibitors are moderate-potent inducers of cytochrome P450 enzymes, and could potentially reduce exposures of certain chemotherapy agents. However, clinical data on such combinations are much more limited.

Since standardized dosing algorithms do not exist for managing such interactions, increased monitoring for efficacy and toxicity is recommended when co-administering any chemotherapy regimen with antiretroviral therapy.

Purpose

This reference guide is intended to serve as a practical summary of available literature regarding interactions between antiretroviral agents and chemotherapy regimens and supportive therapy for lymphoma management. Due to the scarcity of available literature and the variability of the quality of evidence, clinical management should be assessed individually for each patient.

It is hoped that this information will increase the awareness of possible interactions between antiretrovirals and chemotherapy agents and promote communication between pharmacists and physicians of both specialized sectors. Interdisciplinary collaboration would allow clinicians to more effectively manage the interactions according to each situation, with the potential benefits of optimally treating both the oncology diagnoses and HIV infection while minimizing the risk of toxicity and adverse outcomes for the patient. Future studies are essential to further evaluate the impact of these interactions.

Data

An exhaustive review of currently published literature was conducted through Ovid Medline 1948 – November 2013 using MeSH terms for individual chemotherapy agents, keywords for chemotherapy regimens, and the following MeSH terms for HIV (HIV, Anti-HIV agents). Identification of pertinent references in the gray literature was done through the International AIDS Society USA abstract search engine. Quality of evidence was evaluated according to an adapted GRADE system.

Summary

Potential pharmacokinetic and pharmacodynamic interactions may occur between chemotherapy agents and antiretrovirals. Pharmacokinetic interactions may affect concentrations of one or both drugs, possibly leading to increased toxicity and/or decreased efficacy. Pharmacodynamic interactions may occur when agents with similar side effect profiles are co-administered, and may lead to increased toxicity. The following table summarizes the most commonly encountered types of interactions between antineoplastics and antiretrovirals. This table is not all-inclusive; readers are urged to consult the specific chemotherapy regimen summaries in this guide for more specific information.

	Antiretrovirals Involved (examples)	Chemotherapy Agents (examples)	Management
Pharmacokinetic Interactions			
Inhibition of CYP450 enzymes	Protease Inhibitors (including atazanavir, darunavir, lopinavir, ritonavir) cobicistat	CYP3A4 substrates: dexamethasone, etoposide, vincristine, vinblastine, others	Monitor for increased chemotherapy toxicity. Adjust dose or consider replacing antiretrovirals with alternate agents.*
Induction of CYP450 enzymes	Non-nucleoside reverse transcriptase inhibitors (including efavirenz, nevirapine, etravirine, rilpivirine)	As above.	Monitor for response to chemotherapy. Adjust dose or consider replacing antiretrovirals with alternate agents.*
Pharmacodynamic Interactions			
Bone marrow suppression	Zidovudine		
Peripheral neuropathy	Didanosine, stavudine	Vinca alkaloids	Potential for overlapping toxicity. Adjust dose or consider replacing antiretrovirals with alternate agents.*
Renal toxicity	Tenofovir	Cisplatin Cytarabine Methotrexate	Potential for overlapping toxicity. Adjust dose or consider replacing antiretrovirals with alternate agents.*
Increase in serum creatinine	Cobicistat, dolutegravir, rilpivirine	This effect does not target any specific chemotherapy agent. These agents however may cause an asymptomatic increase in secrum creatinine due to inhibition of tubular creatinine secretion.	Increase in serum creatinine appears within first few weeks of treatment and then remains stable; actual GFR is **not** affected. If further changes in serum creatinine are observed, consider other causes.

*modifications to antiretroviral treatment should be done in consultation with a physician and/or pharmacist experienced in HIV care.

Disclaimer: Considering the rapidly evolving literature in the HIV domain, clinicians are invited to consult the primary literature for the most accurate information.

PRINCIPLES OF HIV THERAPY

The intent of this section is to summarize the principles of HIV treatment in the context of treating a concomitant cancer diagnosis.

Summary

- All patients receiving chemotherapy should receive concomitant antiretroviral therapy (cART)
- cART consists of three or more active antiretroviral agents
- Individual agents should not be stopped
- Changes in antiretroviral therapy should be done in consultation with an HIV specialist, as knowledge of the patient's complete treatment history including resistance data is essential when devising alternate antiretroviral treatment options
- Primary prophylaxis of opportunistic infection may be required depending on the CD4 count

Should patients be on antiretroviral therapy?

Patients not previously on antiretroviral treatment

For patients not previously treated with antiretrovirals, two scenarios are possible. The patient could either be newly diagnosed with HIV at the time of diagnosis of the malignancy or the patient was previously known HIV but was not receiving antiretroviral treatment. In both situations, the patient should be started on antiretroviral treatment and should be maintained on antiretroviral therapy throughout chemotherapy. Concomitant administration of both antiretroviral therapy and chemotherapy has been shown to increase survival rates (1-5).

Patients previously on antiretroviral treatment

These patients should continue antiretroviral treatment during chemotherapy as interruption of treatment has been shown to increase mortality (6). In addition, HIV-HBV co-infected patients may be on antiretroviral therapy that treats both viruses. If HBV therapy is stopped, this could result in a hepatic flare possibly resulting in fulminant hepatitis (7). Antiretroviral therapy should not be changed without consulting the patient's HIV physician as full treatment history of the patient and resistance data of the virus must be taken into consideration to maintain an effective treatment.

Risk of interactions between antiretroviral therapy and chemotherapy

Antiretroviral agents have a high risk of interaction with numerous drugs due to their effect on the metabolism. Interactions between antiretroviral and chemotherapy agents are not well documented and no clear recommendations on the management of these interactions have been proposed. Nevertheless, interruption of therapy is **not** recommended as this has been associated with an increase in mortality (6).

Cessation of an individual antiretroviral thought to interact with the chemotherapy is **contra-indicated** as this will decrease the efficacy of the antiretroviral regimen and promote the development of resistance to the agents that will be continued.

However, in many instances, one or more components of a patient's antiretroviral regimen may be substituted in order to avoid risk of drug interaction or additive toxicity. For instance, certain nucleoside analogues are associated with side effects that may overlap with anticipated toxicities of chemotherapy, e.g:

- Zidovudine(Retrovir®, Combivir®, Trizivir®): risk of additive hematologic toxicity™(8)
- Stavudine (Zerit®): risk of additive peripheral neuropathy™(9)
- Didanosine (Videx EC®): risk of additive peripheral neuropathy (10)

It is important to contact the patient's HIV physician in order to discuss a change in therapy. It is important **not** to stop this agent alone or to empirically substitute this agent with another as a change in antiretroviral therapy should only be done with the patient's complete antiretroviral history and resistance data.

Principles of treatment

Standard HIV treatment generally consists of a combination of three or more active drugs, two nucleos(t)ide reverse transcriptase inhibitors (NRTIs) and a third agent from one of the other classes. However, some patients may present with atypical regimens. Please refer to the most current HIV treatment guidelines at: **http://www.aidsinfo.nih.gov/guidelines/html/1/adult-and-adolescent-arv-guidelines/0**

It is important to note that Norvir® (ritonavir) and Tybost® (cobicistat) are generally given to increase the plasma concentrations of other antiretroviral agents. Norvir® (ritonavir) and Tybost® (cobicistat) should therefore **not** be considered as an active drug.

Single Tablet Regimens	**Ingredients**	
Atripla®	Efavirenz, tenofovir, emtricitabine	
Complera®	Rilpivirine, tenofovir, emtricitabine	
Stribild®	Elvitegravir, cobicistat, tenofovir, emtricitabine	
N(t)RTI	**PI**	**NNRTI**
3TC ® (lamivudine)	Aptivus® (tipranavir)	Edurant® (rilpivirine)
Retrovir ® (zidovudine)	Crixivan® (indinavir)	Intelence® (etravirine)
Videx EC ® (didanosine)	Invirase® (saquinavir)	Sustiva® (efavirenz)
Viread ® (tenofovir)	Kaletra® (lopinavir/ritonavir)	Viramune® (nevirapine)
Ziagen® (abacavir)	Prezista® (darunavir)	
Zerit ® (stavudine)	Reyataz® (atazanavir)	**CCR5 antagonist**
Combinations	Telzir® (fosamprenavir)	Celsentri® (maraviroc)
Combivir® (zidovudine, lamivudine)	Viracept® (nelfinavir)	
Kivexa® (abacavir, lamivudine)	**Pharmacokinetic enhancers (booster)**	**Integrase inhibitors**
Trizivir® (abacavir,zidovudine, lamivudine)	Norvir® (ritonavir)*	Isentress® (raltegravir)
Truvada® (tenofovir, emtricitabine)	Tybost® (cobicistat)	Tivicay® (dolutegravir)
		Vitekta® (elvitegravir)

*Ritonavir belongs to the protease inhibitor class, but it is generally used at low doses to act as a pharmacokinetic enhancer, and is not considered an active antiretroviral drug.

N(t)RTI: nucleos(t)ide reverse transcriptase inhibitor; PI: protease inhibitor; NNRTI: non-nucleoside reverse transcriptase inhibitor; CCR5: C-C chemokine receptor 5

Risk of opportunistic infections

HIV-infected patients may have an increased risk of infection in comparison to the general population depending on their CD4 count. Thresholds for initiating primary prophylaxis of opportunistic infections are as follows (11):

CD4 count (cells/mm^3)	**Opportunistic infections**	**Primary prophylaxis**
≥ 200	None	None
101 – 200	*Pneumocystis jirovecii* pneumonia	TMP-SMX DS 1 tab Qday*
51 – 100	*Pneumocystis jirovecii* pneumonia *Toxoplasmosis gondii* encephalitis (if IgG +)	TMP-SMX DS 1 tab Qday
0 – 50	*Pneumocystis jirovecii* pneumonia *Toxoplasmosis gondii* encephalitis (if IgG +) *Mycobacterium avium* complex	TMP-SMX DS 1 tab Qday Azithromycin 1200 mg Qweek

* Note: alternative dosing regimens are possible

Comment on Rituximab

Rituximab, a monoclonal antibody directed against CD20, is often used for treatment of non-Hodgkin's lymphoma in immunocompetent patients. Though no pharmacokinetic interactions with antiretroviral agents are expected, its use in the HIV population is less well defined considering the potential increased risk of mortality due to infectious causes.

A recent pooled analysis of 1546 patients completed by Barta SK et al evaluated treatment factors affecting outcomes in HIV-associated non-Hodgkin's lymphoma. The authors showed that the use of rituximab in patients with CD4 counts ≥ 50 cells/μL increased the odds of complete response by 2.84 times ($p < 0.001$). This improvement was not observed in patients with a CD4 count < 50 cells/μL and may be due to an increased risk of infectious deaths due to use of rituximab. (12)

Of note, use of rituximab may be restricted in certain provinces in Canada. Verification of medication coverage by patient's insurance is essential prior to prescribing this agent.

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Available at: **http://aidsinfo.nih.gov/contentfiles/lvguidelines/adult_oi.pdf.**
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ANTIRETROVIRAL INTERACTIONS WITH CHEMOTHERAPY REGIMENS

Aggressive histology non-Hodgkin's lymphoma [NHL]:

Chemotherapy regimen: CHOP

Agents involved

• Doxorubicin	50 mg/m^2 IV	Day 1
• Vincristine	1.4 mg/m^2 IV	Day 1
• Cyclophosphamide	750 mg/m^2 IV in 250 mL of NS	Day 1
• Prednisone	100 mg po daily	Day 1– 5

Summary of possible interactions with antiretroviral agents

Antiretroviral agents to avoid

- Avoid zidovudine-containing regimens (Retrovir®, Combivir®, Trizivir®) as additive hematologic toxicity is possible (1-3). *(Quality of Evidence: very low)*
- Avoid stavudine (Zerit®), didanosine (Videx EC®) due to possible additive peripheral neuropathy (4, 5). *(Quality of Evidence: very low)*

If the patient is on one of the antiretroviral agents mentioned above, contact the HIV physician to request a change/substitution of antiretroviral agents.

Enzyme inhibition interactions[1]

- Possible increased vincristine toxicity (autonomic neurotoxicity) (6, 7) (*Quality of Evidence: moderate)*
- Possible increased cyclophosphamide toxicity due to decreased clearance (*Quality of Evidence: very low;* pharmacokinetic study of unknown clinical significance) (8)

Enzyme induction interactions[2]

(*Quality of Evidence: very low;* theoretical, unknown clinical significance)

- Possible decreased efficacy of doxorubicin and vincristine (9, 10)
- Possible decreased efficacy and increase in cyclophosphamide toxicity due to increased inactivation to toxic metabolites (9, 10)

Enzyme neutral agents[3]: unlikely to interact

(*Quality of Evidence: very low*; theoretical)

- According to the metabolic profile of the individual agents, pharmacokinetic interactions are unlikely to occur. Nonetheless, additive toxicity remains possible with certain agents depending on the safety profile.

Laboratory interactions

(*Quality of Evidence: high*; no clinical significance)

- Cobicistat (Stribild®, Tybost®), rilpivirine (Edurant®, Complera®) and dolutegravir (Tivicay®) containing regimens will increase serum creatinine by approximately 7-15 µmol/L during the first 4 weeks of treatment initiation due to inhibition of renal creatinine secretion. This does not reflect an actual decrease in renal function, and the effect is quickly reversible upon drug discontinuation.

Note: if interruption of any antiretroviral agent is considered necessary, contact the HIV physician to determine appropriate cessation of the antiretroviral therapy (certain antiretroviral regimens require sequential cessation of antiretroviral agents while others require immediate cessation of all antiretroviral agents at once). If treatment for hepatitis B (HBV) co-infection is required, consult the HIV physician, since some antiretroviral agents have activity against both HIV and HBV.

Literature

One study evaluated the clinical impact of co-administration of combination antiretroviral therapy (cART) with CHOP in the context of treatment for non-Hodgkin's lymphoma. They did not observe any difference in response rates, dose intensity or number of cycles of chemotherapy when CHOP was co-administered with 24 patients on a PI based cART (saquinavir, indinavir or ritonavir) in comparison to the 80 patients on CHOP alone. They did observe, however, an increased risk of grade 3 or 4 anemia and autonomic neurotoxicity. No difference was noted in regards to leucopenia, thrombocytopenia, mucositis or nausea. (6) It is important to note, however, that 58% of patients receiving cART had zidovudine in their regimen, likely explaining the increased risk of anemia.

Regarding the impact of CHOP on antiretroviral concentrations, one study also showed that the administration of CHOP and indinavir-based cART resulted in an **increase of indinavir AUC** in comparison to when indinavir was given without CHOP. No excess of toxicity was observed however (11). In contrast, another study showed a **lower indinavir AUC** when given with CHOP in comparison to a historical cohort. The decrease in HIV viral load and increase in CD4 count was considered to be similar to HIV patients without malignancies. (8)

Pharmacokinetic studies

Two studies evaluated the influence of cART on the pharmacokinetics of doxorubicin in the context of CHOP for the treatment of non-Hodgkin's lymphoma. One study in 19 patients reported **no significant difference in doxorubicin pharmacokinetic parameters** when patients used saquinavir, nelfinavir or indinavir in addition to two nucleoside reverse transcriptase inhibitors.(12) Another study in 29 patients showed **similar clearance rates of doxorubicin** when administered with an indinavir-based cART.(8) The same study evaluated the pharmacokinetics of cyclophosphamide. Co-administration with indinavir-based cART resulted in a **decrease of cyclophosphamide clearance** from 70 to 41-46 mL/min/m^2. This however, did not translate into excessive toxicity. (8)

No pharmacokinetic studies regarding interactions between antiretrovirals and vincristine, prednisone were identified.

Case reports

Administration with lopinavir/ritonavir

Two cases described **good tolerability** of dose-adjusted EPOCH (etoposide 200 mg/m^2, **vincristine** 1.6 mg/m^2, **cyclophosphamide** 748 mg/m^2, **doxorubicin** 40 mg/m^2 continuous infusion over 4 days, prednisone 60 mg/m^2 daily for 5 days) when administered with lopinavir/ritonavir for treatment of anaplastic large-cell lymphoma. Vincristine, cyclophosphamide and doxorubicin doses were similar to those used in CHOP. (13)

One case report described **increased vincristine toxicity** in the context of co-administration of CODOX-M (**vincristine** 4 mg IV, **doxorubicin** 40 mg/m^2 IV, **cyclophosphamide** 1600 mg/m^2 IV, cytarabine 140 mg IT, methotrexate 6720 mg/m^2 IV and methotrexate 15 mg IT per cycle) and lopinavir/ritonavir. The patient received one cycle of CODOX-M for treatment of Burkitt's lymphoma while on lopinavir/ritonavir based cART. On Day 12, the patient developed paralytic ileus which lasted for 10 days. Of note, vincristine dose administered was greater than that of CHOP. Two weeks after recovery, IVAC (ifosfamide 7.5 g/m^2; etoposide 300 mg/m^2; cytarabine 8 g/m^2) was administered with no complications. Two months after the first cycle, the patient was given CODOX-M; however, the vincristine component was changed to etoposide. This regimen, which included a similar dose of doxorubicin and a higher dose of cyclophosphamide compared to CHOP, was well tolerated. (7)

Administration with raltegravir

One case report described **good tolerability of CHOP** when administered with abacavir, lamivudine and raltegravir, a non-PI, non-NNRTI based antiretroviral regimen (14). Another case series of 7 patients also described good CHOP tolerability when administered with tenofovir, emtricitabine and raltegravir (15).

Metabolism of chemotherapy agents

Chemotherapy agent	Metabolism(9, 10)	Possible interaction(9, 10)	Clinical evidence
Doxorubicin	Aldoketoreductase and NADPH-dependent cytochrome reductase. Resulting aglycone derivatives (inactive metabolites) conjugated to a sulfate or glucuronide metabolite. Enzymes of cytochrome P450 involved in free radical generation in vitro; substrate of PgP which may influence intracellular concentrations; clinical significance unknown.	Enzyme inhibitors may decrease reduction to free radicals via inhibition of cytochrome P450 which may decrease both antineoplastic and cytotoxic properties; however, they may also increase intracellular accumulation of doxorubicin via inhibition of PgP, which may enhance cytotoxic effects and/or systemic toxicity. Enzyme inducers may do the opposite.	No change. Doxorubicin pharmacokinetics (context of CHOP) not affected by PI administration.(8, 12)
Vincristine	CYP 3A4	Possibility of increased levels leading to increased toxicity (peripheral and autonomic neuropathy, myelosuppression) with CYP 3A4 inhibitors. Possibility of decreased levels with 3A4 inducers.	Possible increased risk of autonomic neurotoxicity when administered with a PI based regimen. (6, 7) Good tolerability in 2 cases with lopinavir/ritonavir and DA-EPOCH for treatment of anaplastic large-cell lymphoma.(13)
Cyclophosphamide	Transformation to active metabolite: CYP2B6, 2C19 Transformation to inactive and possibly toxic metabolites: CYP 3A4	Ritonavir, nelfinavir, efavirenz and nevirapine may increase the amount of active metabolites formed by induction of CYP 2B6 leading to increased efficacy and toxicity of cyclophosphamide. Inhibition of 3A4 may increase drug availability for hydroxylation route thereby leading to increased efficacy and toxicity of cyclophosphamide. Induction of CYP 3A4 may increase neurotoxicity.	Decreased clearance of cyclophosphamide when administered with PIs. No excess toxicity observed.(8)
Prednisone	Converted to active metabolite prednisolone by non-CYP mediated route. Prednisone and prednisolone are also substrates of CYP 450 including CYP 3A4.	Possible increased toxicity with CYP 3A4 inhibitors. Possible decreased efficacy with CYP 3A4 inducers.	No evidence of increased toxicity found in the published literature.

Please consult http://hivclinic.ca/main/drugs_interact.html for more updated information.

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[1]Enzyme inhibitors include protease inhibitors (PIs): Crixivan® (indinavir), Invirase® (saquinavir), Kaletra® (lopinavir/ritonavir), Norvir®, Norvir sec® (ritonavir), Prezista® (darunavir), Reyataz® (atazanavir), Telzir® (fosamprenavir), Viracept® (nelfinavir); and the integrase inhibitor elvitegravir/cobicistat: available as a coformulated product with tenofovir/emtrictabine (Stribild®); pharmacokinetic enhancer cobicistat (Tybost®).

[2]Enzyme inducers include non-nucleside reverse transcriptase inhibitors (NNRTIs): Atripla® (efavirenz/tenofovir/emtricitabine), Complera® (rilpivirine/tenofovir/emtricitabine), Edurant® (rilpivirine), Intelence® (etravirine), Sustiva® (efavirenz), Viramune®, Viramune XR® (nevirapine) and the protease inhibitor Aptivus® (tipranavir)

[3] Enzyme neutral agents include nucleoside reverse transcriptase inhibitors (NRTIs) : 3TC® (lamivudine), Combivir® (lamivudine/zidovudine), Kivexa ® (abacavir/lamivudine), Retrovir® (zidovudine), Trizivir® (abacavir/zidovudine/lamivudine), Truvada® (tenofovir/emtricitabine), Videx EC® (didanosine), Zerit® (stavudine); integrase inhibitors Isentress® (raltegravir), Tivicay® (dolutegravir); entry inhibitors Fuzeon® (enfuvirtide), Celsentri® (maraviroc)

Chemotherapy regimen: CNS lymphoma High-dose methotrexate protocol

Agents involved

• Methotrexate	3500 mg/m^2 IV in 500 mL of D5W	Day 1
• Vincristine	1.4mg/m^2 IV in 50 mL of NS	Day 1 (odd cycles)
• Procarbazine	100 mg/m^2 po qhs	Day 1-7 (odd cycles)

Summary of possible interactions with antiretroviral agents

Antiretroviral agents to avoid

- Avoid zidovudine-containing regimens (Retrovir®, Combivir®, Trizivir®) as additive hematologic toxicity is possible (1-3). *(Quality of Evidence: very low)*
- Avoid stavudine (Zerit®), didanosine (Videx EC®) due to possible additive peripheral neuropathy (4, 5). *(Quality of Evidence: very low)*

If the patient is on one of the antiretroviral agents mentioned above, contact the HIV physician to request a change/substitution of antiretroviral agents.

Enzyme inhibition interactions[1]

- Possible increased vincristine toxicity (autonomic neurotoxicity) (6, 7) *(Quality of Evidence: moderate)*
- Possible increased procarbazine toxicity (8, 9) *(Quality of Evidence: very low;* theoretical, unknown clinical significance)

Enzyme induction interactions[2]

(Quality of Evidence: very low; theoretical, unknown clinical significance)

- Possible decreased efficacy of vincristine (8, 9)
- Possible increased toxicity of procarbazine (8, 9)

Enzyme neutral agents[3]: unlikely to interact

(*Quality of Evidence: very low*; theoretical)

- According to the metabolic profile of the individual agents, pharmacokinetic interactions are unlikely to occur. Nonetheless, additive toxicity remains possible with certain agents depending on the safety profile.

Particularities regarding nucleoside reverse transcriptase inhibitor backbone

(Quality of Evidence: very low; theoretical, unknown clinical significance)

- Potential additive renal toxicity with tenofovir (8, 9)

Laboratory interactions

(*Quality of Evidence: high*; no clinical significance)

- Cobicistat (Stribild®, Tybost®), rilpivirine (Edurant®, Complera®) and dolutegravir (Tivicay®) containing regimens will increase serum creatinine by approximately 7-15 μmol/L during the first 4 weeks of treatment initiation due to inhibition of renal creatinine secretion. This does not reflect an actual decrease in renal function, and the effect is quickly reversible upon drug discontinuation.

Note: if interruption of any antiretroviral agent is considered necessary, contact the HIV physician to determine appropriate cessation of the antiretroviral therapy (certain antiretroviral regimens require sequential cessation of antiretroviral agents while others require immediate cessation of all antiretroviral agents at once). If treatment for hepatitis B (HBV) co-infection is required, consult the HIV physician, since some antiretroviral agents have activity against both HIV and HBV.

Literature

No studies or case reports specifically regarding high-dose methotrexate protocol and antiretroviral agents were found. Data available from other regimens including similar antineoplastic agents are presented below.

CHOP

One study evaluated the clinical impact of co-administration of combination antiretroviral therapy (cART) with CHOP (cyclophosphamide, doxorubicin, **vincristine** 1.4 mg/m^2 [max 2 mg], prednisone) in the context of treatment for non-Hodgkin's lymphoma. In comparison to high-dose methotrexate protocol, the vincristine dose is the same; however it is given at each cycle unlike the current protocol. They did not observe any difference in response rates, dose intensity or number of cycles of chemotherapy when CHOP was co-administered in 24 patients with a PI based cART (saquinavir, indinavir or ritonavir) in comparison to 80 patients on CHOP alone. They did observe, however, an increased risk of grade 3 or 4 anemia and autonomic neurotoxicity. No difference was noted in regards to leucopenia, thrombocytopenia, mucositis or nausea. (6) It is important to note, however, that 58% of patients receiving cART had zidovudine in their regimen, likely explaining the increased risk of anemia.

CODOX-M

One case report described **increased vincristine toxicity** in the context of co-administration of CODOX-M (**vincristine** 4 mg IV, doxorubicin 40 mg/m^2 IV, cyclophosphamide 1600 mg/m^2 IV, cytarabine 140 mg IT, **methotrexate** 6720 mg/m^2 IV and methotrexate 15 mg IT per cycle) and lopinavir/ritonavir. The patient received one cycle of CODOX-M (**vincristine** 2 mg on D1 **and** D8) for treatment of Burkitt's lymphoma while on lopinavir/ritonavir based cART. Administered vincristine dose is largely superior to that given with high-dose methotrexate protocol. On Day 12, the patient developed paralytic ileus which lasted for 10 days. Two weeks after recovery, IVAC (ifosfamide 7.5 g/m^2; etoposide 300 mg/m^2; cytarabine 8 g/m^2) was administered with no complications. Two months after the first cycle, the patient was given CODOX-M; however, the vincristine component was changed to etoposide. This regimen, which included a higher IV methotrexate dose compared to the high dose methotrexate protocol, was well tolerated. (7)

DA-EPOCH

Two cases described **good tolerability** of dose-adjusted EPOCH (etoposide 200 mg/m^2, **vincristine** 1.6 mg/m^2, cyclophosphamide 748 mg/m^2, doxorubicin 40 mg/m^2 continuous infusion over 4 days, prednisone 60 mg/m^2 daily for 5 days) when administered with lopinavir/ritonavir for treatment of anaplastic large-cell lymphoma. Vincristine dose used is similar to that used in high-dose methotrexate protocol; however it was given at each cycle unlike the current protocol. (10)

Metabolism of chemotherapy agents

Chemotherapy agent	Metabolism (8, 9)	Possible interaction(8, 9)	Clinical evidence
Methotrexate	Almost all drug is excreted unchanged in urine.	Increased monitoring of renal function with concomitant tenofovir administration.	No methotrexate toxicity reported in one case where CODOX-M/IVAC was administered with lopinavir/ritonavir for treatment of Burkitt's lymphoma. (7)
Vincristine	CYP 3A4	Possibility of increased levels leading to increased toxicity (peripheral and autonomic neuropathy, myelosuppression) with CYP 3A4 inhibitors. Possibility of decreased levels with 3A4 inducers.	Possible increased risk of autonomic neurotoxicity when administered with a PI based regimen. (6, 7) Good tolerability in 2 cases with lopinavir/ritonavir and DA-EPOCH for treatment of anaplastic large-cell lymphoma.(10)
Procarbazine	Transformation to active metabolites: CYP2B6, 1A	Inhibition of CYP1A or 2B isoenzymes may result in decreased efficacy of procarbazine. Induction of CYP1A or 2B6 by nelfinavir, tipranavir, efavirenz, nevirapine and ritonavir may potentially ↑ activity and/or toxicity.	No studies or case reports found in the published literature.

Please consult http://hivclinic.ca/main/drugs_interact.html for more updated information.

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1. Retrovir. Product monograph. GlaxoSmithKline; 2009.
2. Combivir. Product Monograph. GlaxoSmithKline; 2007.
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10. Nagajothi N, Dham SK, Gelfand Y, Sanmugarajah J. Treatment of AIDS-associated anaplastic large-cell lymphoma with dose-adjusted EPOCH chemotherapy. J Natl Med Assoc. [Case Reports]. 2007 Jul;99(7):799-801.

[1]Enzyme inhibitors include protease inhibitors (PIs): Crixivan® (indinavir), Invirase® (saquinavir), Kaletra® (lopinavir/ritonavir), Norvir®, Norvir sec® (ritonavir), Prezista® (darunavir), Reyataz® (atazanavir), Telzir® (fosamprenavir), Viracept® (nelfinavir); and the integrase inhibitor elvitegravir/cobicistat: available as a coformulated product with tenofovir/emtrictabine (Stribild®); pharmacokinetic enhancer cobicistat (Tybost®).

[2]Enzyme inducers include non-nucleside reverse transcriptase inhibitors (NNRTIs): Atripla® (efavirenz/tenofovir/emtricitabine), Complera® (rilpivirine/tenofovir/emtricitabine), Edurant® (rilpivirine), Intelence® (etravirine), Sustiva® (efavirenz), Viramune®, Viramune XR® (nevirapine) and the protease inhibitor Aptivus® (tipranavir)

[3] Enzyme neutral agents include nucleoside reverse transcriptase inhibitors (NRTIs) : 3TC® (lamivudine), Combivir® (lamivudine/zidovudine), Kivexa ® (abacavir/lamivudine), Retrovir® (zidovudine), Trizivir® (abacavir/zidovudine/lamivudine), Truvada® (tenofovir/emtricitabine), Videx EC® (didanosine), Zerit® (stavudine); integrase inhibitors Isentress® (raltegravir), Tivicay® (dolutegravir); entry inhibitors Fuzeon® (enfuvirtide), Celsentri® (maraviroc)

Chemotherapy regimen: CODOX-M

Agents involved

• Vincristine	1.4 mg/m^2 IV	Day 1, 8
• Doxorubicin	50 mg/m^2 IV	Day 1
• Cyclophosphamide	800 mg/m^2 IV in 500 mL of NS	Day 1 – 2
• Cytarabine	50 mg IT	Days 1, 3
• Methotrexate	3000 mg/m^2 IV in 500 mL of D5W	Day 10
• Methotrexate	12 mg IT	Day 15

Summary of possible interactions with antiretroviral agents

Antiretroviral agents to avoid

- Avoid zidovudine-containing regimens (Retrovir®, Combivir®, Trizivir®) as additive hematologic toxicity is possible (1-3). (*Quality of Evidence: very low*)
- Avoid stavudine (Zerit®), didanosine (Videx EC®) due to possible additive peripheral neuropathy (4, 5). (*Quality of Evidence: very low*)

If the patient is on one of the antiretroviral agents mentioned above, contact the HIV physician to request a change/substitution of antiretroviral agents.

Enzyme inhibition interactions[1]

- Possible increased vincristine toxicity autonomic neurotoxicity) (6, 8) *(Quality of Evidence: moderate)*
- Possible increased cyclophosphamide toxicity due to decreased clearance (9) (*Quality of Evidence: very low;* pharmacokinetic study of unknown clinical significance)

Enzyme induction interactions[2]

(*Quality of Evidence: very low;* theoretical, unknown clinical significance)

- Possible decreased efficacy of doxorubicin and vincristine (10, 11)
- Possible decreased efficacy and increase in cyclophosphamide toxicity due to increased inactivation to toxic metabolites (10, 11)

Enzyme neutral agents[3]: unlikely to interact

(*Quality of Evidence: very low*; theoretical)

- According to the metabolic profile of the individual agents, pharmacokinetic interactions are unlikely to occur. Nonetheless, additive toxicity remains possible with certain agents depending on the safety profile.

Particularities regarding nucleoside reverse transcriptase inhibitor backbone

(*Quality of Evidence: very low;* theoretical, unknown clinical significance)

- Potential additive renal toxicity with tenofovir (10, 11)

Laboratory interactions

(*Quality of Evidence: high*; no clinical significance)

- Cobicistat (Stribild®, Tybost®), rilpivirine (Edurant®, Complera®) and dolutegravir (Tivicay®) containing regimens will increase serum creatinine by approximately 7-15 µmol/L during the first 4 weeks of treatment initiation due to inhibition of renal creatinine secretion. This does not reflect an actual decrease in renal function, and the effect is quickly reversible upon drug discontinuation.

Note: if interruption of any antiretroviral agent is considered necessary, contact the HIV physician to determine appropriate cessation of the antiretroviral therapy (certain antiretroviral regimens require sequential cessation of antiretroviral agents while others require immediate cessation of all antiretroviral agents at once). If treatment for hepatitis B (HBV) co-infection is required, consult the HIV physician, since some antiretroviral agents have activity against both HIV and HBV.

Literature

One retrospective study in 14 patients, 13 of whom received combination antiretroviral therapy (cART), showed adequate efficacy and tolerability of CODOX-M (vincristine 2.8 mg/m^2 IV, doxorubicin 50 mg/m^2 IV, cyclophosphamide 1600 mg/m^2 IV, cytarabine 140 mg IT, methotrexate 6720 mg/m^2 IV or 3000 mg/m^2 per cycle) and IVAC (ifosfamide 7.5 g/m^2; etoposide 300 mg/m^2; cytarabine 8 g/m^2) with or without rituximab 375 mg/m^2 for treatment of Burkitt's lymphoma. Indeed, the authors mention **no difference in toxicity according to the type of antiretroviral regimen** (protease inhibitor (PI) based vs non-PI based regimen) though no details were provided.(7)

One case report described **increased vincristine toxicity** in the context of co-administration of CODOX-M (vincristine 4 mg IV, doxorubicin 40 mg/m^2 IV, cyclophosphamide 1600 mg/m^2 IV, cytarabine 140 mg IT, methotrexate 6720 mg/m^2 IV and methotrexate 15 mg IT per cycle) and lopinavir/ritonavir. The patient received one cycle of CODOX-M for treatment of Burkitt's lymphoma while on lopinavir/ritonavir based cART. On Day 12, the patient developed paralytic ileus which lasted for 10 days. Two weeks after recovery, IVAC (ifosfamide 7.5 g/m^2; etoposide 300 mg/m^2; cytarabine 8 g/m^2) was administered with no complications. Two months after the first cycle, the patient was given CODOX-M; however, the vincristine component was changed to etoposide. This regimen was well tolerated.(8)

Data available from other regimens including the same antineoplastic agents are presented below.

CHOP

One study evaluated the clinical impact of co-administration of cART with CHOP (**cyclophosphamide** 750 mg/m^2, **doxorubicin** 50 mg/m^2, **vincristine** 1.4 mg/m^2 [max 2 mg], prednisone 100 mg/m^2) in the context of treatment for non-Hodgkin's lymphoma. In comparison to CODOX-M, cyclophosphamide and vincristine doses are far lower when used in CHOP whereas doxorubicin dose is similar. They did not observe any difference in response rates, dose intensity or number of cycles of chemotherapy when CHOP was co-administered in 24 patients with a PI based cART (saquinavir, indinavir or ritonavir) in comparison to 80 patients on CHOP alone. They did observe, however, an **increased risk of grade 3 or 4 anemia and autonomic neurotoxicity**. No difference was noted in regards to leucopenia, thrombocytopenia, mucositis or nausea. (6) It is important to note, however, that 58% of patients receiving cART had zidovudine in their regimen, likely explaining the increased risk of anemia.

CDE

Several studies regarding the concomitant use of CDE (**cyclophosphamide** 1 200 mg/m^2; **doxorubicin** 50 mg/m^2; etoposide 240 mg/m^2 continuous infusion over 4 days q4weeks) and antiretroviral therapy were available. Cyclophosphamide dose is lower in comparison to CODOX-M; however doxorobucin dose is identical. One study in 46 patients who received CDE for treatment of AIDS related lymphoma compared those who received a PI based cART to those who received a non-PI based cART. The groups showed similar overall response and survival rates; however, an **increased risk of severe infections (48% vs 25%; p<0.01) and neutropenia** (54% vs 38%; p =0.05) was observed in patients on a PI based cART compared to those on a non-PI based cART(11). Another study in 12 patients showed an **increased risk of severe mucositis** (67% vs 12%; p<0.01) when patients received a saquinavir-based cART in comparison to a historical cohort not on cART(13).

DA-EPOCH

Two cases described **good tolerability** of dose-adjusted EPOCH (etoposide 200 mg/m^2, **vincristine** 1.6 mg/m^2, **cyclophosphamide** 748 mg/m^2, **doxorubicin** 40 mg/m^2 continuous infusion over 4 days, prednisone 60 mg/m^2 daily for 5 days) when administered with lopinavir/ritonavir for treatment of anaplastic large-cell lymphoma. Compared to CODOX-M, doxorubicin dose is similar though the administered vincristine and cyclophosphamide doses per cycle are far lower. (14)

Pharmacokinetic studies

Two studies evaluated the influence of cART on the pharmacokinetics of doxorubicin 50 mg/m^2 in the context of CHOP for the treatment of non-Hodgkin's lymphoma. One study in 19 patients reported **no significant difference in doxorubicin pharmacokinetic parameters** when patients used saquinavir, nelfinavir or indinavir in addition to two nucleoside reverse transcriptase inhibitors (15). Another study in 29 patients showed similar clearance rates of doxorubicin when administered with an indinavir-based cART (9). The same study evaluated the pharmacokinetics of cyclophosphamide 750 mg/m^2 (lower dose than CODOX-M) in the context of CHOP showed a **decrease of cyclophosphamide clearance** from 70 mL/min/m^2 to 41-46 mL/min/m^2 when administered with an indinavir-based cART. This however, did not translate into excessive toxicity. (9) Considering the higher dose used in CODOX-M, closely monitor for increased cyclophosphamide toxicity.

Metabolism of chemotherapy agents

Chemotherapy agent	Metabolism(10, 11)	Possible interaction(10, 11)	Clinical evidence
Vincristine	CYP 3A4	Possibility of increased levels leading to increased toxicity (peripheral and autonomic neuropathy, myelosuppression) with CYP 3A4 inhibitors. Possibility of decreased levels with 3A4 inducers.	Possible increased risk of autonomic neurotoxicity when administered with a PI based regimen. (6, 8) Good tolerability in 2 cases with lopinavir/ritonavir and DA-EPOCH for treatment of anaplastic large-cell lymphoma.(14)
Doxorubicin	Aldoketoreductase and NADPH-dependent cytochrome reductase. Resulting aglycone derivatives (inactive metabolites) conjugated to a sulfate or glucuronide metabolite. Enzymes of cytochrome P450 involved in free radical generation in vitro; substrate of PgP which may influence intracellular concentrations; clinical significance unknown	Enzyme inhibitors may decrease reduction to free radicals via inhibition of cytochrome P450 which may decrease both antineoplastic and cytotoxic properties; however, they may also increase intracellular accumulation of doxorubicin via inhibition of PgP, which may enhance cytotoxic effects and/or systemic toxicity. Enzyme inducers may do the opposite.	No change. Doxorubicin pharmacokinetics (context of CHOP) not affected by PI administration.(9, 15)
Cyclophosphamide	Transformation to active metabolite: CYP2B6, 2C19 Transformation to inactive and possibly toxic metabolites: CYP 3A4	Ritonavir, nelfinavir, efavirenz and nevirapine may increase the amount of active metabolites formed by induction of CYP 2B6 leading to increased efficacy and toxicity of cyclophosphamide. Inhibition of 3A4 may increase drug availability for hydroxylation route thereby leading to increased efficacy and toxicity of cyclophosphamide. Induction of CYP 3A4 may increase neurotoxicity.	Decreased clearance of cyclophosphamide when administered with PIs. No excess toxicity observed.(9)
Cytarabine	Transformation to active metabolite by cytidine deaminase in the liver	Potential additive toxicity with other agents such as tenofovir (renal toxicity).	No cytarabine toxicity reported in one case where CODOX-M/IVAC was administered with lopinavir/ritonavir for treatment of Burkitt's lymphoma. (8)
Methotrexate	Almost all drug is excreted unchanged in urine.	Increased monitoring of renal function with concomitant tenofovir administration.	No methotrexate toxicity reported in one case where CODOX-M/IVAC was administered with lopinavir/ritonavir for treatment of Burkitt's lymphoma. (8)

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2. Combivir. Product Monograph. GlaxoSmithKline; 2007.
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5. Videx Ec. Product monograph. Bristol-Myers Squibb Canada; 2010.
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[1]Enzyme inhibitors include protease inhibitors (PIs): Crixivan® (indinavir), Invirase® (saquinavir), Kaletra® (lopinavir/ritonavir), Norvir®, Norvir sec® (ritonavir), Prezista® (darunavir), Reyataz® (atazanavir), Telzir® (fosamprenavir), Viracept® (nelfinavir); and the integrase inhibitor elvitegravir/cobicistat: available as a coformulated product with tenofovir/emtrictabine (Stribild®); pharmacokinetic enhancer cobicistat (Tybost®).

[2]Enzyme inducers include non-nucleside reverse transcriptase inhibitors (NNRTIs): Atripla® (efavirenz/tenofovir/emtricitabine), Complera® (rilpivirine/tenofovir/emtricitabine), Edurant® (rilpivirine), Intelence® (etravirine), Sustiva® (efavirenz), Viramune®, Viramune XR® (nevirapine) and the protease inhibitor Aptivus® (tipranavir)

[3] Enzyme neutral agents include nucleoside reverse transcriptase inhibitors (NRTIs) : 3TC® (lamivudine), Combivir® (lamivudine/zidovudine), Kivexa ® (abacavir/lamivudine), Retrovir® (zidovudine), Trizivir® (abacavir/zidovudine/lamivudine), Truvada® (tenofovir/emtricitabine), Videx EC® (didanosine), Zerit® (stavudine); integrase inhibitors Isentress® (raltegravir), Tivicay® (dolutegravir); entry inhibitors Fuzeon® (enfuvirtide), Celsentri® (maraviroc)

Chemotherapy regimen: CVP IV/CVP po

Agents involved

- CVP IV
  - Cyclophosphamide 650 mg/m^2 IV in 250 mL of NS Day 1
  - Vincristine 1.4 mg/m^2 IV in 50 mL of NS Day 1
  - Prednisone 100 mg po OD Days 1 – 5
- CVP po
  - Vincristine 1.4 mg/m^2 IV in 50 mL of NS Day 1
  - Cyclophosphamide 200 mg/m^2 po Day 1 – 5
  - Prednisone 100 mg po OD Days 1 – 5

Summary of possible interactions with antiretroviral agents

Antiretroviral agents to avoid

- Avoid zidovudine-containing regimens (Retrovir®, Combivir®, Trizivir®) as additive hematologic toxicity is possible (1-3). *(Quality of Evidence: very low)*
- Avoid stavudine (Zerit®), didanosine (Videx EC®) due to possible additive peripheral neuropathy (4, 5). *(Quality of Evidence: very low)*

If the patient is on one of the antiretroviral agents mentioned above, contact the HIV physician to request a change/substitution of antiretroviral agents.

Enzyme inhibition interactions[1]

- Possible increased vincristine toxicity (autonomic neurotoxicity) (6, 7) (*Quality of Evidence: moderate)*
- Possible increased cyclophosphamide toxicity due to decreased clearance (8) (*Quality of Evidence: very low;* pharmacokinetic study of unknown clinical significance)

Enzyme induction interactions[2]

(*Quality of Evidence: very low;* theoretical, unknown clinical significance)

- Possible decreased efficacy of vincristine (9, 10)
- Possible decreased efficacy and increase in cyclophosphamide toxicity due to increased inactivation to toxic metabolites (9, 10)

Enzyme neutral agents[3]: unlikely to interact

(*Quality of Evidence: very low*; theoretical)

- According to the metabolic profile of the individual agents, pharmacokinetic interactions are unlikely to occur. Nonetheless, additive toxicity remains possible with certain agents depending on the safety profile.

Laboratory interactions

(*Quality of Evidence: high*; no clinical significance)

- Cobicistat (Stribild®, Tybost®), rilpivirine (Edurant®, Complera®) and dolutegravir (Tivicay®) containing regimens will increase serum creatinine by approximately 7-15 μmol/L during the first 4 weeks of treatment initiation due to inhibition of renal creatinine secretion. This does not reflect an actual decrease in renal function, and the effect is quickly reversible upon drug discontinuation.

Note: if interruption of any antiretroviral agent is considered necessary, contact the HIV physician to determine appropriate cessation of the antiretroviral therapy (certain antiretroviral regimens require sequential cessation of antiretroviral agents while others require immediate cessation of all antiretroviral agents at once). If treatment for hepatitis B (HBV) co-infection is required, consult the HIV physician, since some antiretroviral agents have activity against both HIV and HBV.

Literature

No studies or case reports specifically regarding CVP and antiretroviral agents were found. Data available from other regimens including similar antineoplastic agents are presented below.

CHOP

One study evaluated the clinical impact of co-administration of combination antiretroviral therapy (cART) with CHOP (**cyclophosphamide** 750 mg/m^2, doxorubicin 50 mg/m^2, **vincristine** 1.4 mg/m^2 [max 2 mg], **prednisone** 100 mg/m^2) in the context of treatment for non-Hodgkin's lymphoma. In comparison to CVP, cyclophosphamide dose is slightly higher though the vincristine dose is the same. They did not observe any difference in response rates, dose intensity or number of cycles of chemotherapy when CHOP was co-administered in 24 patients with a PI based cART (saquinavir, indinavir or ritonavir) in comparison to 80 patients on CHOP alone. They did observe, however, an **increased risk of grade 3 or 4 anemia and autonomic neurotoxicity** when CHOP was co-administered in 24 patients with a PI based cART in comparison to 80 patients on CHOP alone. No difference was noted in regards to leucopenia, thrombocytopenia, mucositis or nausea. (6) It is important to note, however, that 58% of patients receiving cART had zidovudine in their regimen, likely explaining the increased risk of anemia.

Cyclophosphamide

One study in 29 patients evaluating the pharmacokinetics of cyclophosphamide 750 mg/m^2 (higher dose than CVP) in the context of CHOP showed a **decrease of cyclophosphamide clearance** from 70 to 41-46 mL/min/m^2 when administered with an indinavir-based cART. This however, did not translate into excessive toxicity. (8)

Vincristine

One case report described **increased vincristine toxicity** in the context of co-administration of CODOX-M (**vincristine** 4 mg IV, doxorubicin 40 mg/m^2 IV, **cyclophosphamide** 1600 mg/m^2 IV, cytarabine 140 mg IT, methotrexate 6720 mg/m^2 IV and methotrexate 15 mg IT per cycle) and lopinavir/ritonavir. The patient received one cycle of CODOX-M (vincristine 2 mg on D1 **and** D8) for treatment of Burkitt's lymphoma while on lopinavir/ritonavir based cART. Both vincristine and cyclophosphamide doses given was greater than that usually administered in the context of CVP. On Day 12, the patient developed paralytic ileus which lasted for 10 days. Two weeks after recovery, IVAC (ifosfamide 7.5 g/m^2; etoposide 300 mg/m^2; cytarabine 8 g/m^2) was administered with no complications. Two months after the first cycle, the patient was given CODOX-M; however, the vincristine component was changed to etoposide. This regimen was well tolerated.(7)

Two cases described **good tolerability** of dose-adjusted EPOCH (etoposide 200 mg/m^2, **vincristine** 1.6 mg/m^2, **cyclophosphamide** 748 mg/m^2, doxorubicin 40 mg/m^2 continuous infusion over 4 days, **prednisone** 60 mg/m^2 daily for 5 days) when administered with lopinavir/ritonavir for treatment of anaplastic large-cell lymphoma. Vincristine and cyclophosphamide doses were similar to those used in CVP. (11)

Metabolism of chemotherapy agents

Chemotherapy agent	Metabolism(9, 10)	Possible interaction(9, 10)	Clinical evidence
Cyclophosphamide	Transformation to active metabolite: CYP2B6, 2C19 Transformation to inactive and possibly toxic metabolites: CYP 3A4	Ritonavir, nelfinavir, efavirenz and nevirapine may increase the amount of active metabolites formed by induction of CYP 2B6 leading to increased efficacy and toxicity of cyclophosphamide. Inhibition of 3A4 may increase drug availability for hydroxylation route thereby leading to increased efficacy and toxicity of cyclophosphamide. Induction of CYP 3A4 may increase neurotoxicity.	Decreased clearance of cyclophosphamide when administered with PIs. No excess toxicity observed.(8)
Vincristine	CYP 3A4	Possibility of increased levels leading to increased toxicity (peripheral and autonomic neuropathy, myelosuppression) with CYP 3A4 inhibitors. Possibility of decreased levels with 3A4 inducers.	Possible increased risk of autonomic neurotoxicity when administered with a PI based regimen. (6, 7) Good tolerability in 2 cases with lopinavir/ritonavir and DA-EPOCH for treatment of anaplastic large-cell lymphoma.(11)
Prednisone	Converted to active metabolite prednisolone by non-CYP mediated route. Prednisone and prednisolone are also substrates of CYP 450 including CYP 3A4.	Possible increased toxicity with CYP 3A4 inhibitors. Possible decreased efficacy with CYP 3A4 inducers.	No evidence of increased toxicity found in the published literature.

Please consult http://hivclinic.ca/main/drugs_interact.html for more updated information.

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1. Retrovir. Product monograph. GlaxoSmithKline; 2009.
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[1]Enzyme inhibitors include protease inhibitors (PIs): Crixivan® (indinavir), Invirase® (saquinavir), Kaletra® (lopinavir/ritonavir), Norvir®, Norvir sec® (ritonavir), Prezista® (darunavir), Reyataz® (atazanavir), Telzir® (fosamprenavir), Viracept® (nelfinavir); and the integrase inhibitor elvitegravir/cobicistat: available as a coformulated product with tenofovir/emtrictabine (Stribild®); pharmacokinetic enhancer cobicistat (Tybost®).

[2]Enzyme inducers include non-nucleside reverse transcriptase inhibitors (NNRTIs): Atripla® (efavirenz/tenofovir/emtricitabine), Complera® (rilpivirine/tenofovir/emtricitabine), Edurant® (rilpivirine), Intelence® (etravirine), Sustiva® (efavirenz), Viramune®, Viramune XR® (nevirapine) and the protease inhibitor Aptivus® (tipranavir)

[3] Enzyme neutral agents include nucleoside reverse transcriptase inhibitors (NRTIs) : 3TC® (lamivudine), Combivir® (lamivudine/zidovudine), Kivexa ® (abacavir/lamivudine), Retrovir® (zidovudine), Trizivir® (abacavir/zidovudine/lamivudine), Truvada® (tenofovir/emtricitabine), Videx EC® (didanosine), Zerit® (stavudine); integrase inhibitors Isentress® (raltegravir), Tivicay® (dolutegravir); entry inhibitors Fuzeon® (enfuvirtide), Celsentri® (maraviroc)

Chemotherapy regimen: Dose adjusted EPOCH

Agents involved

• Etoposide	50 mg/m^2/d continuous IV infusion	D 1 – 4
• Doxorubicin	10 mg/m^2/d continuous IV infusion	D 1 – 4
• Vincristine	0.4 mg/m^2/d IV continuous IV infusion	D 1 – 4
• Cyclophosphamide	375 mg/m^2 IV (if CD4 > 100/µL) 187 mg/m^2 IV (if CD4 < 100/µL)	D 5
• Prednisone	60 mg/m^2 po OD	D 1 – 5

Summary of possible interactions with antiretroviral agents

Antiretroviral agents to avoid

- Avoid zidovudine-containing regimens (Retrovir®, Combivir®, Trizivir®) as additive hematologic toxicity is possible(1-3). *(Quality of Evidence: very low)*
- Avoid stavudine (Zerit®), didanosine (Videx EC®) due to possible additive peripheral neuropathy(4, 5). *(Quality of Evidence: very low)*

If the patient is on one of the antiretroviral agents mentioned above, contact the HIV physician to request a change/substitution of antiretroviral agents.

Enzyme inhibition interactions[1]

- Possible increased etoposide toxicity (infections, neutropenia, mucositis) (6, 7) (*Quality of Evidence: moderate)*
- Possible increased vincristine toxicity (autonomic neurotoxicity) (8, 9) (*Quality of Evidence: moderate)*
- Possible increased cyclophosphamide toxicity due to decreased clearance (*Quality of Evidence: very low;* pharmacokinetic study of unknown clinical significance) (10)

Enzyme induction interactions[2]

(*Quality of Evidence: very low;* theoretical, unknown clinical significance)

- Possible decreased efficacy of etoposide, doxorubicin and vincristine (11, 12)
- Possible decreased efficacy and increase in cyclophosphamide toxicity due to increased inactivation to toxic metabolites (11, 12)

Enzyme neutral agents[3]: unlikely to interact

(*Quality of Evidence: very low*; theoretical)

- According to the metabolic profile of the individual agents, pharmacokinetic interactions are unlikely to occur. Nonetheless, additive toxicity remains possible with certain agents depending on the safety profile.

Laboratory interactions

(*Quality of Evidence: high*; no clinical significance)

- Cobicistat (Stribild®, Tybost®), rilpivirine (Edurant®, Complera®) and dolutegravir (Tivicay®) containing regimens will increase serum creatinine by approximately 7-15 µmol/L during the first 4 weeks of treatment initiation due to inhibition of renal creatinine secretion. This does not reflect an actual decrease in renal function, and the effect is quickly reversible upon drug discontinuation.

Note: if interruption of any antiretroviral agent is considered necessary, contact the HIV physician to determine appropriate cessation of the antiretroviral therapy (certain antiretroviral regimens require sequential cessation of antiretroviral agents while others require immediate cessation of all antiretroviral agents at once). If treatment for hepatitis B (HBV) co-infection is required, consult the HIV physician, since some antiretroviral agents have activity against both HIV and HBV.

Literature

Two cases of good efficacy and tolerability of DA-EPOCH were described when co-administered with lopinavir/ritonavir, tenofovir and didanosine in the context of anaplastic large cell lymphoma. (13)
No studies specifically regarding DA-EPOCH and antiretroviral agents were found however. Data available from other regimens including similar antineoplastic agents are presented below.

CHOP

One study evaluated the clinical impact of co-administration of combination antiretroviral therapy (cART) with CHOP (**cyclophosphamide** 750 mg/m^2, **doxorubicin** 50 mg/m^2, **vincristine** 1.4 mg/m^2 [max 2 mg], **prednisone** 100 mg/m^2) in the context of treatment for non-Hodgkin's lymphoma. In comparison with DA-EPOCH, cyclophosphamide dose is higher although doxorubicin and vincristine doses are similar. They did not observe any difference in response rates, dose intensity or number of cycles of chemotherapy when CHOP was co-administered in 24 patients with a PI based cART (saquinavir, indinavir or ritonavir) in comparison to 80 patients on CHOP alone. They did observe, however, an **increased risk of grade 3 or 4 anemia and autonomic neurotoxicity**. No difference was noted in regards to leucopenia, thrombocytopenia, mucositis or nausea. (8) It is important to note, however, that 58% of patients receiving cART had zidovudine in their regimen, likely explaining the increased risk of anemia.

CDE

Several studies regarding the concomitant use of CDE (**cyclophosphamide** 1 200 mg/m^2; **doxorubicin** 50 mg/m^2; **etoposide** 240 mg/m^2 continuous infusion over 4 days q4weeks) and antiretroviral therapy were available. Cyclophosphamide dose is significantly higher in comparison to DA-EPOCH although doxorubicin and etoposide doses are similar. One study in 46 patients who received CDE for treatment of AIDS related lymphoma compared those who received a PI based cART (not further specified) to those who received a non-PI based cART. The groups showed similar overall response and survival rates; however, an **increased risk of severe infections** (48% vs 25%; $p<0.01$) and **neutropenia** (54% vs 38%; $p=0.05$) was observed in patients on a PI based cART compared to those on a non-PI based cART(6). Another study in 12 patients showed an **increased risk of severe mucositis** (67% vs 12%; $p<0.01$) when patients received a saquinavir-based cART in comparison to a historical cohort not on cART(7).

CODOX-M/IVAC

One case report described **increased vincristine toxicity** in the context of co-administration of CODOX-M (**vincristine** 4 mg IV, **doxorubicin** 40 mg/m^2 IV, **cyclophosphamide** 1600 mg/m^2 IV, cytarabine 140 mg IT, methotrexate 6720 mg/m^2 IV and methotrexate 15 mg IT per cycle) and lopinavir/ritonavir. The patient received one cycle of CODOX-M (**vincristine** 2 mg on D1 **and** D8) for treatment of Burkitt's lymphoma while on lopinavir/ritonavir based cART. Administered vincristine dose is largely superior to that given with DA-EPOCH. On Day 12, the patient developed paralytic ileus which lasted for 10 days. Two weeks after recovery, IVAC was administered with no complications. Two months after the first cycle, the patient was given CODOX-M; however, the vincristine component was changed to etoposide. This regimen, which included a similar doxorubicin dose but a lower cyclophosphamide dose compared to the DA-EPOCH protocol, was well tolerated. (6)

Pharmacokinetic studies

Two studies evaluated the influence of cART on the pharmacokinetics of doxorubicin at similar doses in the context of CHOP for the treatment of non-Hodgkin's lymphoma. One study in 19 patients reported **no significant difference in doxorubicin pharmacokinetic parameters** when patients used saquinavir, nelfinavir or indinavir in addition to two nucleoside reverse transcriptase inhibitors.(14) Another study in 29 patients showed **similar clearance rates of doxorubicin** when administered with an indinavir-based cART.(10) The same study evaluated the pharmacokinetics of cyclophosphamide at higher doses than DA-EPOCH. Co-administration with indinavir-based cART resulted in a **decrease of cyclophosphamide clearance** from 70 to 41-46 mL/min/m^2. This however, did not translate into excessive toxicity. (10)

No pharmacokinetic studies regarding interactions between antiretrovirals and etoposide, vincristine or prednisone were identified.

Metabolism of chemotherapy agents

Chemotherapy agent	Metabolism(11, 12)	Possible interaction(11, 12)	Clinical evidence
Etoposide	CYP 3A4 (main); CYP 2E1, 1A2 (minor)	Possibility of increased levels with 3A4 inhibitors which may increase the risk and severity of mucositis, myelosuppression and transaminitis. Possibility of decreased levels with 3A4 inducers.	Increased risk of etoposide toxicity shown in CDE regimen and PI-based regimen (infections, neutropenia, mucositis) (6, 7). Good tolerability in three cases with lopinavir/ritonavir and either DA-EPOCH or CODOX-M/IVAC for treatment of non-Hodgkin's lymphoma or Hodgkin's lymphoma, respectively.(9, 13)
Doxorubicin	Aldoketoreductase and NADPH-dependent cytochrome reductase. Resulting aglycone derivatives (inactive metabolites) conjugated to a sulfate or glucuronide metabolite. Enzymes of cytochrome P450 involved in free radical generation in vitro; substrate of PgP which may influence intracellular concentrations; clinical significance unknown.	Enzyme inhibitors may decrease reduction to free radicals via inhibition of cytochrome P450 which may decrease both antineoplastic and cytotoxic properties; however, they may also increase intracellular accumulation of doxorubicin via inhibition of PgP, which may enhance cytotoxic effects and/or systemic toxicity. Enzyme inducers may do the opposite.	No change. Doxorubicin pharmacokinetics (context of CHOP) not affected by PI administration.(10, 14)
Vincristine	CYP 3A4	Possibility of increased levels leading to increased toxicity (peripheral and autonomic neuropathy, myelosuppression) with CYP 3A4 inhibitors. Possibility of decreased levels with 3A4 inducers.	Possible increased risk of autonomic neurotoxicity when administered with a PI based regimen. (8, 9) Good tolerability in 2 cases with lopinavir/ritonavir and DA-EPOCH for treatment of anaplastic large-cell lymphoma. (13)
Cyclophospha-mide	Transformation to active metabolite: CYP2B6, 2C19 Transformation to inactive and possibly toxic metabolites: CYP 3A4	Ritonavir, nelfinavir, efavirenz and nevirapine may increase the amount of active metabolites formed by induction of CYP 2B6 leading to increased efficacy and toxicity of cyclophosphamide. Inhibition of 3A4 may increase drug availability for hydroxylation route thereby leading to increased efficacy and toxicity of cyclophosphamide. Induction of CYP 3A4 may increase neurotoxicity.	Decreased clearance of cyclophosphamide when administered with PIs. No excess toxicity observed.(10)
Prednisone	Converted to active metabolite prednisolone by non-CYP mediated route. Prednisone and prednisolone are also substrates of CYP 450 including CYP 3A4.	Possible increased toxicity with CYP 3A4 inhibitors. Possible decreased efficacy with CYP 3A4 inducers.	No evidence of increased toxicity found in the published literature.

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2. Combivir. Product Monograph. GlaxoSmithKline; 2007.
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12. Antoniou T, Tseng AL. Interactions between antiretrovirals and antineoplastic drug therapy. Clin Pharmacokinet. 2005;44(2):111-45.
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[1]Enzyme inhibitors include protease inhibitors (PIs): Crixivan® (indinavir), Invirase® (saquinavir), Kaletra® (lopinavir/ritonavir), Norvir®, Norvir sec® (ritonavir), Prezista® (darunavir), Reyataz® (atazanavir), Telzir® (fosamprenavir), Viracept® (nelfinavir); and the integrase inhibitor elvitegravir/cobicistat: available as a coformulated product with tenofovir/emtrictabine (Stribild®); pharmacokinetic enhancer cobicistat (Tybost®).

[2]Enzyme inducers include non-nucleside reverse transcriptase inhibitors (NNRTIs): Atripla® (efavirenz/tenofovir/emtricitabine), Complera® (rilpivirine/tenofovir/emtricitabine), Edurant® (rilpivirine), Intelence® (etravirine), Sustiva® (efavirenz), Viramune®, Viramune XR® (nevirapine) and the protease inhibitor Aptivus® (tipranavir)

[3] Enzyme neutral agents include nucleoside reverse transcriptase inhibitors (NRTIs) : 3TC® (lamivudine), Combivir® (lamivudine/zidovudine), Kivexa ® (abacavir/lamivudine), Retrovir® (zidovudine), Trizivir® (abacavir/zidovudine/lamivudine), Truvada® (tenofovir/emtricitabine), Videx EC® (didanosine), Zerit® (stavudine); integrase inhibitors Isentress® (raltegravir), dolutegravir (Tivicay®); entry inhibitors Fuzeon® (enfuvirtide), Celsentri® (maraviroc)

Chemotherapy regimen: Hyper CVAD

Agents involved

Cycle A

• Cyclophosphamide	300 mg/m^2 IV in 250 mL of NS	Days 1 – 3
• Dexamethasone	40 mg IV/po	Days 1 – 4; Days 11 – 14
• Methotrexate	12 mg IT	Day 2
• Doxorubicin	50 mg/m^2 IV	Day 4
• Vincristine	2 mg IV in 50 mL of NS	Day 4, 11
• Cytarabine	70 mg IT	Days 11

Cycle B

• Methotrexate	1000 mg/m^2 IV in 1250 mL of NS	Day 1
• Cytarabine	3 g/m^2 in 250 mL of NS q12h If > 60 years old: reduce to 1.5 g/m^2/dose	Days 2 – 3

Summary of possible interactions with antiretroviral agents

Antiretroviral agents to avoid

- Avoid zidovudine-containing regimens (Retrovir®, Combivir®, Trizivir®) as additive hematologic toxicity is possible(1-3). (*Quality of Evidence: very low*)
- Avoid stavudine (Zerit®), didanosine (Videx EC®) due to possible additive peripheral neuropathy (4, 5). (*Quality of Evidence: very low*)

If the patient is on one of the antiretroviral agents mentioned above, contact the HIV physician to request a change/substitution of antiretroviral agents.

Enzyme inhibition interactions[1]

- Possible increased vincristine toxicity (autonomic neurotoxicity) (6, 7) *(Quality of Evidence: moderate)*
- Possible increased cyclophosphamide toxicity due to decreased clearance (8) (*Quality of Evidence: very low;* pharmacokinetic study of unknown clinical significance)

Enzyme induction interactions[2]

(*Quality of Evidence: very low;* theoretical, unknown clinical significance)

- Possible decreased efficacy of doxorubicin and vincristine (9, 10)
- Possible decreased efficacy and increase in cyclophosphamide toxicity due to increased inactivation to toxic metabolites (9, 10)

Enzyme neutral agents[3]: unlikely to interact

(*Quality of Evidence: very low*; theoretical)

- According to the metabolic profile of the individual agents, pharmacokinetic interactions are unlikely to occur. Nonetheless, additive toxicity remains possible with certain agents depending on the safety profile.

Particularities regarding nucleoside reverse transcriptase inhibitor backbone

(*Quality of Evidence: very low;* theoretical, unknown clinical significance)

- Potential additive renal toxicity with tenofovir (9, 10)

Laboratory interactions

(*Quality of Evidence: high*; no clinical significance)

- Cobicistat (Stribild®, Tybost®), rilpivirine (Edurant®, Complera®) and dolutegravir (Tivicay®) containing regimens will increase serum creatinine by approximately 7-15 µmol/L during the first 4 weeks of treatment initiation due to inhibition of renal creatinine secretion. This does not reflect an actual decrease in renal function, and the effect is quickly reversible upon drug discontinuation.

Note: if interruption of any antiretroviral agent is considered necessary, contact the HIV physician to determine appropriate cessation of the antiretroviral therapy (certain antiretroviral regimens require sequential cessation of antiretroviral agents while others require immediate cessation of all antiretroviral agents at once). If treatment for hepatitis B (HBV) co-infection is required, consult the HIV physician, since some antiretroviral agents have activity against both HIV and HBV.

Literature

One study evaluated the use of hyper-CVAD for patients with HIV-associated Burkitt's leukemia/lymphoma. A total of 6/7 (86%) patients receiving a PI based cART achieved complete response and remained alive (median 29 month follow-up). HIV viral load remained undetectable for all adherent patients who received cART. For the 6 patients who did not receive cART during the entire chemotherapy treatment, 1 (17%) patient survived at 33 months follow-up with the use of cART (started after chemotherapy). The authors concluded that hyper-CVAD was highly effective within this context. Although no direct comparisons between patients receiving cART and those not receiving cART were made, they also stated that the use of cART with chemotherapy may be associated with a favorable outcome and that the administration of **cART was not associated with any identifiable increase in toxicity**. (11)

Data available from other regimens including similar antineoplastic agents are presented below.

CHOP

One study evaluated the clinical impact of co-administration of cART with CHOP (**cyclophosphamide** 750 mg/m^2, **doxorubicin** 50 mg/m^2, **vincristine** 1.4 mg/m^2 [max 2 mg], prednisone 100 mg/m^2) in the context of treatment for non-Hodgkin's lymphoma. In comparison to hyper CVAD, vincristine and cyclophosphamide doses per cycle are lower though doxorubicin dose is the same. They did not observe any difference in response rates, dose intensity or number of cycles of chemotherapy when CHOP was co-administered in 24 patients with a PI based cART (saquinavir, indinavir or ritonavir) in comparison to 80 patients on CHOP alone. They did observe, however, an **increased risk of grade 3 or 4 anemia and autonomic neurotoxicity** when CHOP was co-administered with a PI based cART in comparison to CHOP alone. No difference was noted in regards to leucopenia, thrombocytopenia, mucositis or nausea. (7) It is important to note, however, that 58% of patients receiving cART had zidovudine in their regimen, likely explaining the increased risk of anemia.

CDE

Several studies regarding the concomitant use of CDE (**cyclophosphamide** 1 200 mg/m^2; **doxorubicin** 50 mg/m^2; etoposide 240 mg/m^2 continuous infusion over 4 days q4weeks) and antiretroviral therapy were available. Cyclophosphamide dose is higher in comparison to hyper CVAD; however doxorubicin dose is the same. One study in 46 patients who received CDE for treatment of AIDS related lymphoma compared those who received a PI based cART to those who received a non-PI based cART. The groups showed similar overall response and survival rates; however, an **increased risk of severe infections (48% vs 25%; p<0.01) and neutropenia** (54% vs 38%; p =0.05) was observed in patients on a PI based cART compared to those on a non-PI based cART(12). Another study in 12 patients showed an **increased risk of severe mucositis** (67% vs 12%; p<0.01) when patients received a saquinavir-based cART in comparison to a historical cohort not on cART(13).

Pharmacokinetic studies

Two studies evaluated the influence of cART on the pharmacokinetics of doxorubicin 50 mg/m^2 in the context of CHOP for the treatment of non-Hodgkin's lymphoma. One study in 19 patients reported **no significant difference in doxorubicin pharmacokinetic parameters** when patients used saquinavir, nelfinavir or indinavir in addition to two nucleoside reverse transcriptase inhibitors (14). Another study in 29 patients showed similar clearance rates of doxorubicin when administered with an indinavir-based cART (8). The same study evaluated the pharmacokinetics of cyclophosphamide 750 mg/m^2 (lower dose than hyper CVAD) in the context of CHOP showed a **decrease of cyclophosphamide clearance** from 70 mL/min/m^2 to 41-46 mL/min/m^2 when administered with an indinavir-based cART. This however, did not translate into excessive toxicity. (8) Considering the higher dose used in hyper CVAD, closely monitor for increased cyclophosphamide toxicity.

Case report

One case report described **increased vincristine toxicity** in the context of co-administration of CODOX-M (**vincristine** 4 mg IV, **doxorubicin** 40 mg/m^2 IV, **cyclophosphamide** 1600 mg/m^2 IV, **cytarabine** 140 mg IT, **methotrexate** 6720 mg/m^2 IV and **methotrexate** 15 mg IT per cycle) and lopinavir/ritonavir. The patient received one cycle of CODOX-M (**vincristine** 2 mg on D1 **and** D8) for treatment of Burkitt's lymphoma while on lopinavir/ritonavir based cART. Administered vincristine dose is identical to that administered with hyper CVAD. On Day 12, the patient developed paralytic ileus which lasted for 10 days. Two weeks after recovery, IVAC (ifosfamide 7.5 g/m^2; etoposide 300 mg/m^2; **cytarabine** 8 g/m^2) was administered with no complications though cytarabine dose is lower than that used in cycle 2 of hyper CVAD. Two months after the first cycle, the patient was given CODOX-M; however, the vincristine component was changed to etoposide. This regimen was well tolerated and included similar doxorubicin dose and IT methotrexate dose; higher IV methotrexate, IV cyclophosphamide and IT cytarabine doses compared to hyper CVAD. (6)

Two cases described **good tolerability** of dose-adjusted EPOCH (etoposide 200 mg/m^2, **vincristine** 1.6 mg/m^2, **cyclophosphamide** 748 mg/m^2, **doxorubicin** 40 mg/m^2 continuous infusion over 4 days, prednisone 60 mg/m^2 daily for 5 days) when administered with lopinavir/ritonavir for treatment of anaplastic large-cell lymphoma. Compared to hyper-CVAD, doxorubicin and cyclophosphamide doses are similar though the administered vincristine dose per cycle is lower. (15)

Metabolism of chemotherapy agents

Chemotherapy agent	Metabolism(9, 10)	Possible interaction(9, 10)	Clinical evidence
Vincristine	CYP 3A4	Possibility of increased levels leading to increased toxicity (peripheral neuropathy, myelosuppression) with CYP 3A4 inhibitors. Possibility of decreased levels with 3A4 inducers.	Possible increased risk of autonomic neurotoxicity when administered with a PI based regimen. (6, 7) Good tolerability in 2 cases with lopinavir/ritonavir and DA-EPOCH for treatment of anaplastic large-cell lymphoma. (15)
Doxorubicin	Aldoketoreductase and NADPH-dependent cytochrome reductase. Resulting aglycone derivatives (inactive metabolites) conjugated to a sulfate or glucuronide metabolite. Enzymes of cytochrome P450 involved in free radical generation in vitro; substrate of PgP which may influence intracellular concentrations; clinical significance unknown.	Enzyme inhibitors may decrease reduction to free radicals via inhibition of cytochrome P450 which may decrease both antineoplastic and cytotoxic properties; however, they may also increase intracellular accumulation of doxorubicin via inhibition of PgP, which may enhance cytotoxic effects and/or systemic toxicity. Enzyme inducers may do the opposite.	No change. Doxorubicin pharmacokinetics (context of CHOP) not affected by PI administration.(8, 14)
Cyclophosphamide	Transformation to active metabolite: CYP2B6, 2C19 Transformation to inactive and possibly toxic metabolites: CYP 3A4	Ritonavir, nelfinavir, efavirenz and nevirapine may increase the amount of active metabolites formed by induction of CYP 2B6 leading to increased efficacy and toxicity of cyclophosphamide. Inhibition of 3A4 may increase drug availability for hydroxylation route thereby leading to increased efficacy and toxicity of cyclophosphamide. Induction of CYP 3A4 may increase neurotoxicity.	Decreased clearance of cyclophosphamide when administered with protease-inhibitors. No excess toxicity observed.(8)
Cytarabine	Transformation to active metabolite by cytidine deaminase in the liver	Potential additive toxicity with other agents such as tenofovir (renal toxicity).	No cytarabine toxicity reported in one case where CODOX-M/IVAC was administered with lopinavir/ritonavir for treatment of Burkitt's lymphoma (6)
Methotrexate	Almost all drug is excreted unchanged in urine.	Increased monitoring of renal function with concomitant tenofovir administration.	No methotrexate toxicity reported in one case where CODOX-M/IVAC was administered with lopinavir/ritonavir for treatment of Burkitt's lymphoma. (6)

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[1]Enzyme inhibitors include protease inhibitors (PIs): Crixivan® (indinavir), Invirase® (saquinavir), Kaletra® (lopinavir/ritonavir), Norvir®, Norvir sec® (ritonavir), Prezista® (darunavir), Reyataz® (atazanavir), Telzir® (fosamprenavir), Viracept® (nelfinavir); and the integrase inhibitor elvitegravir/cobicistat: available as a coformulated product with tenofovir/emtrictabine (Stribild®); pharmacokinetic enhancer cobicistat (Tybost®).

[2]Enzyme inducers include non-nucleside reverse transcriptase inhibitors (NNRTIs): Atripla® (efavirenz/tenofovir/emtricitabine), Complera® (rilpivirine/tenofovir/emtricitabine), Edurant® (rilpivirine), Intelence® (etravirine), Sustiva® (efavirenz), Viramune®, Viramune XR® (nevirapine) and the protease inhibitor Aptivus® (tipranavir)

[3] Enzyme neutral agents include nucleoside reverse transcriptase inhibitors (NRTIs) : 3TC® (lamivudine), Combivir® (lamivudine/zidovudine), Kivexa ® (abacavir/lamivudine), Retrovir® (zidovudine), Trizivir® (abacavir/zidovudine/lamivudine), Truvada® (tenofovir/emtricitabine), Videx EC® (didanosine), Zerit® (stavudine); integrase inhibitors Isentress® (raltegravir), dolutegravir (Tivicay®); entry inhibitors Fuzeon® (enfuvirtide), Celsentri® (maraviroc)

Chemotherapy regimen: IVAC

Agents involved

• Etoposide	60 mg/m^2 IV in 500 mL of NS	Days 1 – 5
• Ifosfamide/Mesna	1500/360 mg/m^2 in 500 mL of NS	Days 1 – 5
• Cytarabine	2000 mg/m^2 IV in 250 mL NS q12h	Days 1 – 2
• Methotrexate	12 mg/m^2 IT	Day 5

Summary of possible interactions with antiretroviral agents

Antiretroviral agents to avoid

- Avoid zidovudine-containing regimens (Retrovir®, Combivir®, Trizivir®) as additive hematologic toxicity is possible (1-3). *(Quality of Evidence: very low)*

If the patient is on zidovudine, contact the HIV physician to request a change/substitution of antiretroviral agents.

Enzyme inhibition interactions[1]

- Possible increased etoposide toxicity (infections, neutropenia, mucositis) (4, 5) (*Quality of Evidence: moderate)*
- Possible decreased efficacy of ifosfamide due to decreased activation (6, 7) (*Quality of Evidence: very low;* theoretical, unknown clinical significance)

Enzyme induction interactions[2]

(*Quality of Evidence: very low;* theoretical, unknown clinical significance)

- Possible decreased efficacy of etoposide (6, 7)
- Possible increased toxicity of ifosfamide due to increased activation (6, 7)

Enzyme neutral agents[3]: unlikely to interact

(*Quality of Evidence: very low*; theoretical)

- According to the metabolic profile of the individual agents, pharmacokinetic interactions are unlikely to occur. Nonetheless, additive toxicity remains possible with certain agents depending on the safety profile.

Particularities regarding nucleoside reverse transcriptase inhibitor backbone

(*Quality of Evidence: very low;* theoretical, unknown clinical significance)

- Potential additive renal toxicity with tenofovir (6, 7)

Laboratory interactions

(*Quality of Evidence: high*; no clinical significance)

- Cobicistat (Stribild®, Tybost®), rilpivirine (Edurant®, Complera®) and dolutegravir (Tivicay®) containing regimens will increase serum creatinine by approximately 7-15 μmol/L during the first 4 weeks of treatment initiation due to inhibition of renal creatinine secretion. This does not reflect an actual decrease in renal function, and the effect is quickly reversible upon drug discontinuation.

Note: if interruption of any antiretroviral agent is considered necessary, contact the HIV physician to determine appropriate cessation of the antiretroviral therapy (certain antiretroviral regimens require sequential cessation of antiretroviral agents while others require immediate cessation of all antiretroviral agents at once). If treatment for hepatitis B (HBV) co-infection is required, consult the HIV physician, since some antiretroviral agents have activity against both HIV and HBV.

Literature

One retrospective study in 14 patients, 13 of whom received combination antiretroviral therapy (cART), showed adequate efficacy and tolerability of CODOX-M (vincristine 2.8 mg/m^2 IV, doxorubicin 50 mg/m^2 IV, cyclophosphamide 1600 mg/m^2 IV, cytarabine 140 mg IT, methotrexate 6720 mg/m^2 IV or 3000 mg/m^2 per cycle) and IVAC (ifosfamide 7.5 g/m^2; etoposide 300 mg/m^2; cytarabine 8 g/m^2) with or without rituximab 375 mg/m^2 for treatment of Burkitt's lymphoma. Indeed, the authors mention **no difference in toxicity according to the type of antiretroviral regimen** (protease inhibitor (PI) based vs non-PI based regimen) though no details were provided.(8)

One case report described **good tolerability IVAC** after severe toxicity to CODOX-M. The patient received CODOX-M (vincristine 4 mg IV, doxorubicin 40 mg/m^2 IV, cyclophosphamide 1600 mg/m^2 IV, cytarabine 140 mg IT, methotrexate 6720 mg/m^2 IV and methotrexate 15 mg IT per cycle) for the treatment of Burkitt's lymphoma while on a lopinavir/ritonavir based cART. He developed paralytic ileus that lasted 10 days. Two weeks after his recovery, IVAC (ifosfamide 7.5 g/m^2; etoposide 300 mg/m^2; cytarabine 8 g/m^2) was administered and was well tolerated. Subsequent cycles of CODOX-M were administered with etoposide (dose not specified) replacing the vincristine component and was well tolerated.(9)

Data available from other regimens including similar antineoplastic agents are presented below.

CDE

Several studies regarding the concomitant use of CDE (cyclophosphamide 1 200 mg/m^2; doxorubicin 50 mg/m^2; **etoposide** 240 mg/m^2 continuous infusion over 4 days q4weeks) and antiretroviral therapy were available. Etoposide dose is lower in comparison to IVAC. One study in 46 patients who received CDE for treatment of AIDS related lymphoma compared those who received a PI based combination antiretroviral therapy (cART) to those who received a non-PI based cART. The groups showed similar overall response and survival rates; however, an **increased risk of severe infections** (48% vs 25%; $p<0.01$) and **neutropenia** (54% vs 38%; $p=0.05$) was observed in patients on a PI based cART compared to those on a non-PI based cART(4). Another study in 12 patients showed an **increased risk of severe mucositis** (67% vs 12%; $p<0.01$) when patients received a saquinavir-based cART in comparison to a historical cohort not on cART(5).

DA-EPOCH

Two cases described **good tolerability** of dose-adjusted EPOCH (**etoposide** 200 mg/m^2, vincristine 1.6 mg/m^2, cyclophosphamide 748 mg/m^2, doxorubicin 40 mg/m^2 continuous infusion over 4 days, prednisone 60 mg/m^2 daily for 5 days) when administered with lopinavir/ritonavir for treatment of anaplastic large-cell lymphoma. Etoposide dose was lower than that used in IVAC however. (10)

Metabolism of chemotherapy agents

Chemotherapy agent	Metabolism(6, 7)	Possible interaction(6, 7)	Clinical evidence
Etoposide	CYP 3A4 (main); CYP 2E1, 1A2 (minor)	Possibility of increased levels with 3A4 inhibitors which may increase the risk and severity of mucositis, myelosuppression and transaminitis. Possibility of decreased levels with 3A4 inducers.	Increased risk of etoposide toxicity shown in CDE regimen and PI-based regimen (infections, neutropenia, mucositis) (4, 5). Good tolerability in three cases with lopinavir/ritonavir and either DA-EPOCH or CODOX-M/IVAC for treatment of non-Hodgkin's lymphoma or Hodgkin's lymphoma, respectively. (9, 10)
Ifosfamide	CYP 3A4 to active metabolite, neurotoxic metabolite and detoxification. CYP 2B6 is involved in detoxicification.	Inhibition of CYP 3A4 may inhibit drug activation. Induction of CYP 3A4 may increase activation of ifosfamide but may also produce more potentially neurotoxic metabolites.	No ifosfamide toxicity reported in one case where CODOX-M/IVAC was administered with lopinavir/ritonavir for treatment of Burkitt's lymphoma. (9)
Mesna	Rapidly oxidized in plasma to dimesna and eliminated renally. No hepatic metabolism.(11)	Pharmacokinetic interactions unlikely.	No mesna toxicity reported in one case where CODOX-M/IVAC was administered with lopinavir/ritonavir for treatment of Burkitt's lymphoma. (9)
Cytarabine	Transformation to active metabolite by cytidine deaminase in the liver	Potential additive renal toxicity with other agents such as tenofovir.	No cytarabine toxicity reported in one case where CODOX-M/IVAC was administered with lopinavir/ritonavir for treatment of Burkitt's lymphoma.(9)
Methotrexate	Almost all drug is excreted unchanged in urine.	Increased monitoring of renal function with concomitant tenofovir administration.	No methotrexate toxicity reported in one case where CODOX-M/IVAC was administered with lopinavir/ritonavir for treatment of Burkitt's lymphoma. (9)

Please consult http://hivclinic.ca/main/drugs_interact.html for more updated information.

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[2]Enzyme inducers include non-nucleoside reverse transcriptase inhibitors (NNRTIs): Atripla® (efavirenz/tenofovir/emtricitabine), Complera® (rilpivirine/tenofovir/emtricitabine), Edurant® (rilpivirine), Intelence® (etravirine), Sustiva® (efavirenz), Viramune®, Viramune XR® (nevirapine) and the protease inhibitor Aptivus® (tipranavir)

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ANTIRETROVIRAL INTERACTIONS WITH CHEMOTHERAPY REGIMENS

Hodgkin's Lymphoma:

Chemotherapy regimen: ABVD

Agents involved

• Doxorubicin	25 mg/m^2 IV	Day 1, 15
• Vinblastine	6 mg/m^2 IV	Day 1, 15
• Bleomycin	10 U/m^2 IV in 100 mL of NS	Day 1, 15
• Dacarbazine	375 mg/m^2 IV in 500 mL of NS	Day 1, 15

Summary

Antiretroviral agents to avoid

Avoid zidovudine-containing regimens (Retrovir®, Combivir®, Trizivir®) as additive hematologic toxicity is possible [1-3]. *(Quality of Evidence: very low).*

If the patient is on one of the antiretroviral agents mentioned above, contact the HIV physician to request a change/substitution of antiretroviral agents.

Enzyme inhibition interactions[1]

- Possible increased vinblastine toxicity (*Quality of Evidence: moderate)*
  - Autonomic toxicity [5, 8, 9, 11]
  - Prolonged neutropenia [4, 8, 10, 11]

Enzyme induction interactions[2]

- Possible decreased efficacy of doxorubicin and vinblastine (*Quality of Evidence: very low;* theoretical, unknown clinical impact) [11, 12]

Enzyme neutral agents[3]: unlikely to interact

(*Quality of Evidence: very low*; theoretical)

- According to the metabolic profile of the individual agents, pharmacokinetic interactions are unlikely to occur. Nonetheless, additive toxicity remains possible with certain agents depending on the safety profile.

Laboratory interactions

(*Quality of Evidence: high*; no clinical significance)

- Cobicistat (Stribild®, Tybost®), rilpivirine (Edurant®, Complera®) and dolutegravir (Tivicay®) containing regimens will increase serum creatinine by approximately 7-15 µmol/L during the first 4 weeks of treatment initiation due to inhibition of renal creatinine secretion. This does not reflect an actual decrease in renal function and the effect is quickly reversible upon drug discontinuation.

Note: if interruption of any antiretroviral agent is considered necessary, contact the HIV physician to determine appropriate cessation of the antiretroviral therapy (certain antiretroviral regimens require sequential cessation of antiretroviral agents while others require immediate cessation of all antiretroviral agents at once). If treatment for hepatitis B (HBV) co-infection is required, consult the HIV physician, since some antiretroviral agents have activity against both HIV and HBV.

Literature

ABVD

A retrospective chart review of 16 HIV-infected patients with Hodgkin's lymphoma showed an **increased risk of grade III-IV neutropenia** (OR 34.3, 95% CI 1.9 – 602.4; p=0.02) when ABVD (n=13) or Stanford V (n=3) was administered with a PI-based combination antiretroviral therapy (cART) in comparison to a non PI-based cART. The authors also found an inverse correlation between ritonavir dose and mean nadir neutrophil count.[4]

Another retrospective chart review of 36 HIV-infected patients with Hodgkin's lymphoma evaluated the frequency and risk factors of ABVD (n = 29) or MOPP/ABV (n = 7) toxicity. Risk factors for **severe hematologic toxicity** were ritonavir (p=0.04) and lopinavir (p=0.02). Lopinavir use was also a risk factor for **increased grade 3 – 4 neurotoxicity** (p=0.05). [5]

Pharmacokinetic studies

Doxorubicin

Two studies evaluated the influence of cART on the **pharmacokinetics of doxorubicin** in the context of CHOP for the treatment of non-Hodgkin's lymphoma. One study reported **no significant difference** in doxorubicin pharmacokinetic parameters when patients used saquinavir, nelfinavir or indinavir in addition to two nucleoside reverse transcriptase inhibitors [6]. Another study showed **similar clearance rates** of doxorubicin when administered with an indinavir-based cART [7]. No pharmacokinetic studies regarding interactions between antiretrovirals and bleomycin, vinblastine, dacarbazine were identified.

Vinblastine

One study evaluated the pharmacokinetics of vinblastine in 3 different patients who received atazanavir/ritonavir (300/100 mg daily), darunavir/ritonavir (600/100 mg daily) and lopinavir/ritonavir (300/100 mg BID) in the context of ABVD for treatment of Hodgkin's lymphoma. **Vinblastine area under the curve (AUC) was increased** by 131% and 101% when given with atazanavir and darunavir 600/100 mg once daily, respectively. This increase appeared to be well tolerated as both patients only reported WHO grade 2 toxicity (not specified). In contrast, when vinblastine was administered with lopinavir, vinblastine AUC was 1.6 fold higher than that achieved with atazanavir or darunavir and **resulted in paralytic ileus and febrile neutropenia**. [8] The increased toxicity observed with lopinavir may be due to the higher dose of ritonavir used (100 mg BID).

Case reports (Table 1)

A total of 4 published case reports [9, 10] were found regarding **excessive toxicity** when ABVD was co-administered with a PI based cART for treatment of Hodgkin's disease. All patients were treated with lopinavir/ritonavir, tenofovir and emtricitabine or lamivudine. One patient also received enfuvirtide. The authors suggested that vinblastine toxicity was due to decreased metabolism secondary to inhibition by lopinavir/ritonavir. This hypothesis is supported by another case report of excessive vinblastine toxicity when administered concomitantly with a lopinavir/ritonavir based cART for multicentric Castleman's disease. [11]

Table 1. Case reports of ABVD co-administered with a lopinavir/ritonavir based cART for treatment of Hodgkin's disease

Author	Description	Intervention	Outcome	Comments
Cheung 2010[9] Patient 1	Abdominal distension, obstipation (D7 cycle 1a)	Ileocolic resection and end ileostomy	uCR (24 months) after 6 cycles of ABD	No mention of hematologic toxicity (primary prophylaxis with GCSF)
Cheung 2010[9] Patient 2	Neutropenia	8 one-week delays, numerous dose reductions (not specified)	Remission 15 months post-diagnosis, narcotic dependent for neuropathy	Primary prophylaxis with GCSF
	Peripheral neuropathy	Narcotic use required Vinblastine omitted from cycle 5A onwards		
Cheung 2010[9] Patient 3	Febrile neutropenia (8 days after cycle 1a)	Broad spectrum antibiotics, GCSF, IV fluids	No further neutropenic delays	GCSF not used for primary prophylaxis
	Distension of small and large bowel	NG and rectal tube placed; vinblastine omitted from further cycles	No further ileus/obstruction	
	Bleomycin induced pneumonitis (cycle 5a)	Bleomycin omitted from future cycles	Not specified.	
Makinson 2007 [10]	Febrile neutropenia	Interruption of LPV/r 48 hours before and after chemotherapy	CR Adequate control of HIV	Increase of GCSF dosage and decrease of vinblastine dosage were also attempted but had still resulted in prolonged neutropenia.
Kotb 2006 [11]	Severe constipation, persistent pancytopenia (leading to septic shock), peripheral neuropathy	cART stopped: vinblastine administered at increasing doses (up to 6 mg/m^2) and well tolerated	Not specified	One dose of vinblastine was initially administered without cART and was well tolerated. cART was then resumed and resulted in increased toxicity during two concomitant administrations of vinblastine and cART.

Abbreviations: ABD (doxorubicin, bleomycin, dacarbazine); CR (complete response); GCSF (granulocyte colony stimulating factor); LPV/r (lopinavir/ritonavir); NG (nasogastric); uCR (unconfirmed complete response)

Metabolism of chemotherapy agents

Chemotherapy agent	Metabolism [12, 13]	Possible interaction [12, 13]	Clinical evidence
Doxorubicin	Aldoketoreductase and NADPH-dependent cytochrome reductase. Resulting aglycone derivatives (inactive metabolites) conjugated to a sulfate or glucuronide metabolite. Enzymes of cytochrome P450 involved in free radical generation in vitro; substrate of PgP which may influence intracellular concentrations; clinical significance unknown.	Enzyme inhibitors may decrease reduction to free radicals via inhibition of cytochrome P450 which may decrease both antineoplastic and cytotoxic properties; however, they may also increase intracellular accumulation of doxorubicin via inhibition of PgP, which may enhance cytotoxic effects and/or systemic toxicity. Enzyme inducers may do the opposite.	No change. Doxorubicin pharmacokinetics (context of CHOP) not affected by PI administration.[6, 7]
Bleomycin	Hydrolysis by intracellular aminopeptidase. Evidence in rodents suggests possible inhibition of CYP450 system.	Possible increase of antiretroviral levels but potential for interactions appears low.	No studies or case reports found in the published literature.
Vinblastine	Metabolised by CYP 3A4. Vinblastine may also induce CYP3A4.	Possibility of increased levels (increased toxicity: autonomic, peripheral neuropathy, myelosuppression) with CYP 3A4 inhibitors. Possibility of decreased levels with 3A4 inducers.	Increased risk of grade III-IV neutropenia [4] and neurotoxicity [5] with PI-based cART. Increased vinblastine AUC when given with boosted PI possibly resulting in increased toxicity. [8] 5 case reports reporting increased toxicity (with lopinavir/ritonavir).[9-11]
Dacarbazine	CYP1A2 > 2E1 to reactive DNA methylating metabolites.	Risk of interaction unlikely.	No studies or case reports found in the published literature.

Please consult http://hivclinic.ca/main/drugs_interact.html for more updated information.

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[2]Enzyme inducers include non-nucleside reverse transcriptase inhibitors (NNRTIs): Atripla® (efavirenz/tenofovir/emtricitabine), Complera® (rilpivirine/tenofovir/emtricitabine), Edurant® (rilpivirine), Intelence® (etravirine), Sustiva® (efavirenz), Viramune®, Viramune XR® (nevirapine) and the protease inhibitor Aptivus® (tipranavir)

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Chemotherapy regimen: BEACOPP/escalated BEACOPP

Agents involved

- BEACOPP (escalated)

○ Doxorubicin	25 (35) mg/m^2 IV	Day 1
○ Etoposide	100 (200) mg/m^2 IV in 500 mL of NS	Day 1 – 3
○ Cyclophosphamide	650 (1200) mg/m^2 IV in 250 (500) mL of NS	Day 1
○ Procarbazine	100 mg/m^2 po qhs	Day 1 – 7
○ Prednisone	40 mg po OD	Day 1 – 14
○ Vincristine	1.4 mg/m^2 IV in 50 mL of NS	Day 8
○ Bleomycin	10 U/m^2 IV in 100 mL of NS	Day 8

Summary of possible interactions with antiretroviral agents

Antiretroviral agents to avoid

- Avoid zidovudine-containing regimens (Retrovir®, Combivir®, Trizivir®) as additive hematologic toxicity is possible (1-3). *(Quality of Evidence: very low)*
- Avoid stavudine (Zerit®), didanosine (Videx EC®) due to possible additive peripheral neuropathy (4, 5). *(Quality of Evidence: very low)*

If the patient is on one of the antiretroviral agents mentioned above, contact the HIV physician to request a change/substitution of antiretroviral agents.

Enzyme inhibition interactions[1]

- Possible increased vincristine toxicity (autonomic neurotoxicity) (8, 9) *(Quality of Evidence: moderate)*
- Possible increased etoposide toxicity (infections, neutropenia, mucositis) (6, 7) *(Quality of Evidence: moderate)*
- Possible increased cyclophosphamide toxicity due to decreased clearance (13) *(Quality of Evidence: very low;* pharmacokinetic study with unknown clinical significance)
- Possible increased procarbazine toxicity (*Quality of Evidence: very low;* theoretical, unknown clinical significance) (14, 15)

Enzyme induction interactions[2]

(*Quality of Evidence: very low;* theoretical, unknown clinical significance)

- Possible decreased efficacy of doxorubicin, etoposide, and vincristine (14, 15)
- Possible increase in cyclophosphamide and procarbazine toxicity (14, 15)

Enzyme neutral agents[3]: unlikely to interact

(*Quality of Evidence: very low*; theoretical)

- According to the metabolic profile of the individual agents, pharmacokinetic interactions are unlikely to occur. Nonetheless, additive toxicity remains possible with certain agents depending on the safety profile.

Laboratory interactions

(*Quality of Evidence: high*; no clinical significance)

- Cobicistat (Stribild®, Tybost®), rilpivirine (Edurant®, Complera®) and dolutegravir (Tivicay®) containing regimens will increase serum creatinine by approximately 7-15 µmol/L during the first 4 weeks of treatment initiation due to inhibition of renal creatinine secretion. This does not reflect an actual decrease in renal function, and the effect is quickly reversible upon drug discontinuation.

Note: if interruption of any antiretroviral agent is considered necessary, contact the HIV physician to determine appropriate cessation of the antiretroviral therapy (certain antiretroviral regimens require sequential cessation of antiretroviral agents while others require immediate cessation of all antiretroviral agents at once). If treatment for hepatitis B (HBV) co-infection is required, consult the HIV physician, since some antiretroviral agents have activity against both HIV and HBV.

Literature

No studies or case reports specifically regarding co-administration of BEACOPP and antiretroviral agents were found. Data available from other regimens including similar antineoplastic agents are presented below.

CDE

Several studies regarding the concomitant use of CDE (**cyclophosphamide** 1 200 mg/m^2; **doxorubicin** 50 mg/m^2; **etoposide** 240 mg/m^2 continuous infusion over 4 days q4weeks) and antiretroviral therapy were available. Cyclophosphamide and doxorobucin doses are higher in comparison to BEACOPP but the dose of etoposide is lower. One study in 46 patients who received CDE for treatment of AIDS related lymphoma compared those who received a PI based combination antiretroviral therapy (cART) to those who received a non-PI based cART. The groups showed similar overall response and survival rates; however, an **increased risk of severe infections** (48% vs 25%; p<0.01) and **neutropenia** (54% vs 38%; p =0.05) was observed in patients on a PI based cART compared to those on a non-PI based cART(6). Another study in 12 patients showed an **increased risk of severe mucositis** (67% vs 12%; p<0.01) when patients received a saquinavir-based cART in comparison to a historical cohort not on cART(7).

CHOP

One study evaluated the clinical impact of co-administration of cART with CHOP (**cyclophosphamide** 750 mg/m^2, **doxorubicin** 50 mg/m^2, **vincristine** 1.4 mg/m^2 (max 2 mg), **prednisone** 100 mg/m^2) in the context of treatment for non-Hodgkin's lymphoma. In comparison to BEACOPP, cyclophosphamide and doxorubicin doses are higher and the vincristine dose is identical. They did not observe any difference in response rates, dose intensity or number of cycles of chemotherapy when CHOP was co-administered in 24 patients with a PI based cART (saquinavir, indinavir or ritonavir) in comparison to 80 patients on CHOP alone. They did observe, however, an **increased risk of grade 3 or 4 anemia and autonomic neurotoxicity**. No difference was noted in regards to leucopenia, thrombocytopenia, mucositis or nausea. (8) It is important to note, however, that 58% of patients receiving cART had zidovudine in their regimen, likely explaining the increased risk of anemia.

CODOX-M/IVAC

One case report described **good tolerability of etoposide after severe vincristine toxicity**. The patient received CODOX-M (vincristine 2 mg on D1 and D8) for the treatment of Burkitt's lymphoma while on a lopinavir/ritonavir based cART. He developed paralytic ileus that lasted 10 days. The vincristine dose used per cycle was twice that used for BEACOPP or escalated BEACOPP. Two weeks after his recovery, IVAC (etoposide 300 mg/m^2 iv over 5 days) was administered and was well tolerated. Subsequent cycles of CODOX-M were administered with etoposide (dose not specified) replacing the vincristine component and was well tolerated.(9)

DA-EPOCH

Two cases described **good tolerability** of dose-adjusted EPOCH (**etoposide** 200 mg/m^2, **vincristine** 1.6 mg/m^2, **cyclophosphamide** 748 mg/m^2, **doxorubicin** 40 mg/m^2 continuous infusion over 4 days, **prednisone** 60 mg/m^2 daily for 5 days) when administered with lopinavir/ritonavir for treatment of anaplastic large-cell lymphoma. (10)

ABVD

A retrospective chart review of 32 HIV-infected patients with Hodgkin's lymphoma evaluated the frequency and risk factors of toxicity due to ABVD (**doxorubicin** 50 mg/m^2, vinblastine 12 mg/m^2, **bleomycin** 20 U/m^2, dacarbazine 740 mg/m^2 per cycle; n=13) or MOPP/ABV (mechlorethamine, vinblastine, procarbazine, prednisone/doxorubicin, bleomycin, vinblastine; n = 3) toxicity. The dose of bleomycin per cycle is twice that used in the BEACOPP regimen. A total of 20 patients were on a PI-based regimen. **No increased incidence of lung toxicity** was noted in comparison to a study in HIV-negative patients. (11)

Pharmacokinetic studies

Two studies evaluated the influence of cART on the pharmacokinetics of doxorubicin 50 mg/m^2 in the context of CHOP (for the treatment of non-Hodgkin's lymphoma). One study in 19 patients reported **no significant difference in doxorubicin pharmacokinetic parameters** when patients used saquinavir, nelfinavir or indinavir in addition to two nucleoside reverse transcriptase inhibitors (12). Another study in 29 patients showed **similar clearance rates of doxorubicin** when administered with an indinavir-based cART (13). The same study evaluated the pharmacokinetics of cyclophosphamide 750 mg/m^{2}at a higher dose than BEACOPP but lower dose than escalated BEACOPP. They showed a **decrease of cyclophosphamide clearance** from 70 to 41-46 mL/min/m^2 when administered with an indinavir-based cART. This however, did not translate into excessive toxicity. (13) Considering the higher dose used in escalated BEACOPP, closely monitor for increased cyclophosphamide toxicity.

No published literature was found regarding interactions between antiretroviral agents and procarbazine or prednisone.

Metabolism of chemotherapy agents

Chemotherapy agent	Metabolism(14,15)	Possible interaction(14, 15)	Clinical evidence
Doxorubicin	Aldoketoreductase and NADPH-dependent cytochrome reductase. Resulting aglycone derivatives (inactive metabolites) conjugated to a sulfate or glucuronide metabolite. Enzymes of cytochrome P450 involved in free radical generation in vitro; substrate of PgP which may influence intracellular concentrations; clinical significance unknown.	Enzyme inhibitors may decrease reduction to free radicals via inhibition of cytochrome P450 which may decrease both antineoplastic and cytotoxic properties; however, they may also increase intracellular accumulation of doxorubicin via inhibition of PgP, which may enhance cytotoxic effects and/or systemic toxicity. Enzyme inducers may do the opposite.	No change. Doxorubicin pharmacokinetics (context of CHOP) not affected by PI administration.(12, 13)
Etoposide	CYP 3A4 (main); CYP 2E1, 1A2 (minor)	Possibility of increased levels with 3A4 inhibitors which may increase the risk and severity of mucositis, myelosuppression and transaminitis. Possibility of decreased levels with 3A4 inducers.	Increased risk of etoposide toxicity shown in CDE regimen and PI-based regimen (infections, neutropenia, mucositis) (6, 7). Good tolerability in three cases with lopinavir/ritonavir and either DA-EPOCH or CODOX-M/IVAC for treatment of non-Hodgkin's lymphoma or Hodgkin's lymphoma, respectively. (9, 10)
Cyclophosphamide	Transformation to active metabolite: CYP2B6, 2C19 Transformation to inactive and possibly toxic metabolites: CYP 3A4	Ritonavir, nelfinavir, efavirenz and nevirapine may increase the amount of active metabolites formed by induction of CYP 2B6 leading to increased efficacy and toxicity of cyclophosphamide. Inhibition of 3A4 may increase drug availability for hydroxylation route thereby leading to increased efficacy and toxicity of cyclophosphamide. Induction of CYP 3A4 may increase neurotoxicity.	Decreased clearance of cyclophosphamide when administered with PIs. No excess toxicity observed.(13)
Procarbazine	Transformation to active metabolites: CYP2B, 1A	Inhibition of CYP1A or 2B isoenzymes may result in decreased efficacy of procarbazine. Induction of CYP1A or 2B6 by nelfinavir, tipranavir, efavirenz, nevirapine and ritonavir may potentially ↑ activity and/or toxicity.	No studies or case reports found in the published literature.
Prednisone	Converted to active metabolite prednisolone by non-CYP mediated route. Prednisone and prednisolone are also substrates of CYP 450 including CYP 3A4.	Possible increased toxicity with CYP 3A4 inhibitors. Possible decreased efficacy with CYP 3A4 inducers.	No evidence of increased toxicity was found in the published literature.
Vincristine	CYP 3A4	Possibility of increased levels leading to increased toxicity (peripheral and autonomic neuropathy, myelosuppression) with CYP 3A4 inhibitors. Possibility of decreased levels with 3A4 inducers.	Possible increased risk of autonomic neurotoxicity when administered with a PI based regimen. (8, 9) Good tolerability in 2 cases with lopinavir/ritonavir and DA-EPOCH for treatment of anaplastic large-cell lymphoma. (10)
Bleomycin	Hydrolysis by intracellular aminopeptidase. Evidence in rodents suggests possible inhibition of CYP450 system.	Possible increase of antiretroviral levels but potential for interactions appears low.	No studies or case reports found in the published literature.

Please consult http://hivclinic.ca/main/drugs_interact.html for more updated information.

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15. Antoniou T, Tseng AL. Interactions between antiretrovirals and antineoplastic drug therapy. Clin Pharmacokinet. 2005;44(2):111-45.

[1] Enzyme inhibitors include protease inhibitors (PIs): Crixivan® (indinavir), Invirase® (saquinavir), Kaletra® (lopinavir/ritonavir), Norvir®, Norvir sec® (ritonavir), Prezista® (darunavir), Reyataz® (atazanavir), Telzir® (fosamprenavir), Viracept® (nelfinavir); and the integrase inhibitor elvitegravir/cobicistat: available as a coformulated product with tenofovir/emtrictabine (Stribild®); pharmacokinetic enhancer cobicistat (Tybost®).

[2]Enzyme inducers include non-nucleside reverse transcriptase inhibitors (NNRTIs): Atripla® (efavirenz/tenofovir/emtricitabine), Complera® (rilpivirine/tenofovir/emtricitabine), Edurant® (rilpivirine), Intelence® (etravirine), Sustiva® (efavirenz), Viramune®, Viramune XR® (nevirapine) and the protease inhibitor Aptivus® (tipranavir)

[3] Enzyme neutral agents include nucleoside reverse transcriptase inhibitors (NRTIs) : 3TC® (lamivudine), Combivir® (lamivudine/zidovudine), Kivexa ® (abacavir/lamivudine), Retrovir® (zidovudine), Trizivir® (abacavir/zidovudine/lamivudine), Truvada® (tenofovir/emtricitabine), Videx EC® (didanosine), Zerit® (stavudine); integrase inhibitors Isentress® (raltegravir), Tivicay® (dolutegravir); entry inhibitors Fuzeon® (enfuvirtide), Celsentri® (maraviroc)

ANTIRETROVIRAL INTERACTIONS WITH CHEMOTHERAPY REGIMENS

Relapsed Hodgkin's or aggressive histology NHL (salvage chemotherapy regimens):

Chemotherapy regimen: DHAP

Agents involved

• Dexamethasone	40 mg IV/po in 50 mL of NS	Days 1 – 4
• Cisplatin	100 mg/m2 IV in 1000 mL of NS	Day 1
• Cytarabine	2 g/m2 IV in 250 mL of NS q12h	Day 2

Summary of possible interactions with antiretroviral agents

Antiretroviral agents to avoid

- Avoid zidovudine-containing regimens (Retrovir®, Combivir®, Trizivir®) as additive hematologic toxicity is possible (1-3). (Quality of Evidence: very low)

If the patient is on one of the antiretroviral agents mentioned above, contact the HIV physician to request a change/substitution of antiretroviral agents.

Enzyme inhibition interactions[1]

(Quality of Evidence: very low; theoretical, unknown clinical significance)

- Possible increased dexamethasone toxicity (4, 5)
- Possible decreased efficacy of PIs (4, 5)

Enzyme induction interactions[2]

(Quality of Evidence: very low; theoretical, unknown clinical significance)

- Possible decreased efficacy of dexamethasone (4, 5)
- Possible decreased efficacy of NNRTIs (4, 5)

Enzyme neutral agents[3]: unlikely to interact

(*Quality of Evidence: very low*; theoretical)

- According to the metabolic profile of the individual agents, pharmacokinetic interactions are unlikely to occur. Nonetheless, additive toxicity remains possible with certain agents depending on the safety profile.

Particularities regarding nucleoside reverse transcriptase inhibitor backbone

(Quality of Evidence: very low; theoretical, unknown clinical significance)

- Potential additive renal toxicity with tenofovir (4, 5)

Laboratory interactions

(*Quality of Evidence: high*; no clinical significance)

- Cobicistat (Stribild®, Tybost®), rilpivirine (Edurant®, Complera®) and dolutegravir (Tivicay®) containing regimens will increase serum creatinine by approximately 7-15 μmol/L during the first 4 weeks of treatment initiation due to inhibition of renal creatinine secretion. This does not reflect an actual decrease in renal function, and the effect is quickly reversible upon drug discontinuation.

Note: if interruption of any antiretroviral agent is considered necessary, contact the HIV physician to determine appropriate cessation of the antiretroviral therapy (certain antiretroviral regimens require sequential cessation of antiretroviral agents while others require immediate cessation of all antiretroviral agents at once). If treatment for hepatitis B (HBV) co-infection is required, consult the HIV physician, since some antiretroviral agents have activity against both HIV and HBV.

Literature

No studies or case reports specifically regarding DHAP and antiretroviral agents were found. Data available from other regimens including similar antineoplastic agents are presented below.

GDP

A retrospective single arm study evaluated the efficacy and safety of GDP (gemcitabine 2000 mg/m^2, **dexamethasone** 160 mg, **cisplatin** 75 mg/m^2 per cycle) for treatment of relapsed or refractory AIDS-related non-Hodgkin's lymphoma (NHL) when administered with efavirenz/lamivudine/zidovudine. The dose of dexamethasone is identical to that used in the DHAP regimen though the cisplatin dose is slightly lower. A total of 48 patients were included, of whom 21% had complete remission, 33% had partial remission; two-year overall survival was 71%. Regarding toxicity, 13% of patients required **dose reduction or elimination of zidovudine** in the HIV regimen due to leukopenia. Main grade 3/4 toxicities observed were anemia (8%), neutropenia (42%) and thrombocytopenia (58%). A total of 63% of patients had undetectable HIV viral load at the end of chemotherapy. The authors concluded that GDP was an effective salvage regimen with **tolerant toxicity** in patients with relapsed or refractory AIDS-NHL though further studies are warranted. (6)

Of note, low response to antiretroviral therapy is likely explained by previous exposure to efavirenz/lamivudine/zidovudine with a history of poor adherence in 71% of patients and dose reduction or elimination of zidovudine during chemotherapy in 13% of patients. This could contribute to development of HIV resistance and decreased efficacy of antiretroviral agents. Induction of efavirenz metabolism by dexamethasone may also have contributed to decreased antiretroviral efficacy.

Case reports

A case report showed severe hematological toxicity secondary to cisplatin and gemcitabine when administered with atazanavir, ritonavir, tenofovir, lamivudine for treatment of lung cancer. The patient received one cycle of **cisplatin** 80 mg/m^2 and gemcitabine 2000 mg/m^2 and had grade 3 appetite loss, grade 4 platelet toxicity and neutrophils/granulocytes. Of note, cisplatin dose is slightly lower to that used in the DHAP regimen. In the 3 subsequent cycles, cisplatin and gemcitabine doses were subsequently reduced to 60 and 1600 mg/m^2 respectively for 3 subsequent cycles, all of which were well tolerated. HIV viral load remained undetectable thorough out the course of chemotherapy. The patient had adequate response to therapy and was alive for 17 months at the time of publication. (7)

One case report described **good tolerability of IVAC** (ifosfamide 7.5 g/m^2, etoposide 300 mg/m^2 IV, **cytarabine** 8 g/m^2 IV per cycle) after severe vincristine toxicity during CODOX-M. The patient received CODOX-M for the treatment of Burkitt's lymphoma while on a lopinavir/ritonavir based combination antiretroviral therapy (cART). He developed paralytic ileus that lasted 10 days. Two weeks after his recovery, IVAC was administered and was well tolerated. Subsequent cycles of CODOX-M were administered with etoposide (dose not specified) replacing the vincristine component and was well tolerated. (8)

Metabolism of chemotherapy agents

Chemotherapy agent	Metabolism(4, 5)	Possible interaction (4, 5)	Clinical evidence
Dexamethasone	Substrate and inducer of CYP 3A4.	Increased risk of steroid related toxicity with CYP 3A4 inhibitors. Possible decreased efficacy with CYP 3A4 inducers. Dexamethasone may decrease levels of PIs and NNRTIs.	Possible decreased efficacy of efavirenz reported in a retrospective study. (6)
Cisplatin	Main route of elimination is renal.	Pharmacokinetic interactions unlikely. Cisplatin induced nephrotoxicity may necessitate dosage adjustments for certain antiretroviral agents. Potential additive renal toxicity with tenofovir.	Possible increased hematological toxicity of cisplatin in a case report with atazanavir/ritonavir for treatment of lung cancer. (7) No cisplatin toxicity or decreased efficacy reported in a retrospective study with efavirenz. (6)
Cytarabine	Transformation to active metabolite by cytidine deaminase in the liver.	Potential additive renal toxicity with other agents such as tenofovir.	No cytarabine toxicity reported in one case where CODOX-M/IVAC was administered with lopinavir/ritonavir for treatment of Burkitt's lymphoma. (8)

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2. Combivir. Product Monograph. GlaxoSmithKline; 2007[Accessed March, 2011].
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[1]Enzyme inhibitors include protease inhibitors (PIs): Crixivan® (indinavir), Invirase® (saquinavir), Kaletra® (lopinavir/ritonavir), Norvir®, Norvir sec® (ritonavir), Prezista® (darunavir), Reyataz® (atazanavir), Telzir® (fosamprenavir), Viracept® (nelfinavir); and the integrase inhibitor elvitegravir/cobicistat: available as a coformulated product with tenofovir/emtrictabine (Stribild®); pharmacokinetic enhancer cobicistat (Tybost®).

[2]Enzyme inducers include non-nucleside reverse transcriptase inhibitors (NNRTIs): Atripla® (efavirenz/tenofovir/emtricitabine), Complera® (rilpivirine/tenofovir/emtricitabine), Edurant® (rilpivirine), Intelence® (etravirine), Sustiva® (efavirenz), Viramune®, Viramune XR® (nevirapine) and the protease inhibitor Aptivus® (tipranavir)

[3] Enzyme neutral agents include nucleoside reverse transcriptase inhibitors (NRTIs) : 3TC® (lamivudine), Combivir® (lamivudine/zidovudine), Kivexa ® (abacavir/lamivudine), Retrovir® (zidovudine), Trizivir® (abacavir/zidovudine/lamivudine), Truvada® (tenofovir/emtricitabine), Videx EC® (didanosine), Zerit® (stavudine); integrase inhibitors Isentress® (raltegravir), Tivicay® (dolutegravir); entry inhibitors Fuzeon® (enfuvirtide), Celsentri® (maraviroc)

Chemotherapy regimen: ESHAP

Agents involved

• Methylprednisolone	500 mg IV in 100 mL of NS	Day 1
• Cisplatin	25 mg/m^2 IV in 500 mL of NS	Days 1 – 4
• Etoposide	40 mg/m^2 IV in 250 mL of NS	Days 1 – 4
• Cytarabine	2 g/m^2 IV in 250 mL NS	Day 5

Summary of possible interactions with antiretroviral agents

Antiretroviral agents to avoid

- Avoid zidovudine-containing regimens (Retrovir®, Combivir®, Trizivir®) as additive hematologic toxicity is possible (1-3). (Quality of Evidence: very low)

If the patient is on one of the antiretroviral agents mentioned above, contact the HIV physician to request a change/substitution of antiretroviral agents.

Enzyme inhibition interactions[1]

- Possible increased etoposide toxicity (infections, neutropenia, mucositis) (4, 5) (Quality of Evidence: moderate)
- Possible increased methylprednisolone toxicity (6, 7) (Quality of Evidence: very low; theoretical, unknown clinical significance)

Enzyme induction interactions[2]

(Quality of Evidence: very low; theoretical, unknown clinical significance)

- Possible decreased efficacy of etoposide and methylprednisolone (6, 7)

Particularities regarding nucleoside reverse transcriptase inhibitor backbone

(Quality of Evidence: very low; theoretical, unknown clinical significance)

- Potential additive renal toxicity with tenofovir (6, 7)

Enzyme neutral agents[3]: unlikely to interact

(*Quality of Evidence: very low*; theoretical)

- According to the metabolic profile of the individual agents, pharmacokinetic interactions are unlikely to occur. Nonetheless, additive toxicity remains possible with certain agents depending on the safety profile.

Laboratory interactions

(*Quality of Evidence: high*; no clinical significance)

- Cobicistat (Stribild®, Tybost®), rilpivirine (Edurant®, Complera®) and dolutegravir (Tivicay®) containing regimens will increase serum creatinine by approximately 7-15 μmol/L during the first 4 weeks of treatment initiation due to inhibition of renal creatinine secretion. This does not reflect an actual decrease in renal function, and the effect is quickly reversible upon drug discontinuation.

Note: if interruption of any antiretroviral agent is considered necessary, contact the HIV physician to determine appropriate cessation of the antiretroviral therapy (certain antiretroviral regimens require sequential cessation of antiretroviral agents while others require immediate cessation of all antiretroviral agents at once). If treatment for hepatitis B (HBV) co-infection is required, consult the HIV physician, since some antiretroviral agents have activity against both HIV and HBV.

Literature

No studies or case reports specifically regarding ESHAP and antiretroviral agents were found. Data available from other regimens including similar antineoplastic agents are presented below.

Cisplatin containing regimens

A retrospective single arm study evaluated the efficacy and safety of GDP (gemcitabine 2000 mg/m^2, dexamethasone 160 mg, **cisplatin** 75 mg/m^2 per cycle) for treatment of relapsed or refractory AIDS-related non-Hodgkin's lymphoma (NHL) when administered with efavirenz/lamivudine/zidovudine. The dose of cisplatin is slightly lower than that used in ESHAP. A total of 48 patients were included, of whom 21% had complete remission, 33% had partial remission; two-year overall survival was 71%. Regarding toxicity, 13% of patients required **dose reduction or elimination of zidovudine** in the HIV regimen due to leukopenia. Main grade 3/4 toxicities observed were anemia (8%), neutropenia (42%) and thrombocytopenia (58%). A total of 63% of patients had undetectable HIV viral load at the end of chemotherapy. The authors concluded that GDP was an effective salvage regimen with **tolerant toxicity** in patients with relapsed or refractory AIDS-NHL though further studies are warranted. (8)

Of note, low response to antiretroviral therapy is likely explained by previous exposure to efavirenz/lamivudine/zidovudine with a history of poor adherence in 71% of patients and dose reduction or elimination of zidovudine during chemotherapy in 13% of patients. This could contribute to development of HIV resistance and decreased efficacy of antiretroviral agents. Induction of efavirenz metabolism by dexamethasone may also have contributed to decreased antiretroviral efficacy.

A case report showed severe hematological toxicity secondary to cisplatin and gemcitabine when administered with atazanavir, ritonavir, tenofovir, lamivudine for treatment of lung cancer. The patient received one cycle of **cisplatin** 80 mg/m^2 and gemcitabine 2000 mg/m^2 and had grade 3 appetite loss, grade 4 platelet toxicity and neutrophils/granulocytes. Of note, cisplatin dose is slightly lower than that used in the ESHAP regimen. In the 3 subsequent cycles, cisplatin and gemcitabine doses were subsequently reduced to 60 and 1600 mg/m^2 respectively for 3 subsequent cycles, all of which were well tolerated. HIV viral load remained undetectable thorough out the course of chemotherapy. The patient had adequate response to therapy and was alive for 17 months at the time of publication. (9)

Etoposide, cytarabine containing regimen

One case report described **good tolerability of IVAC** (ifosfamide 7.5 g/m^2, **etoposide** 300 mg/m^2 IV, **cytarabine** 8 g/m^2 IV per cycle) after severe vincristine toxicity during CODOX-M. Both etoposide and cytarabine doses used were largely superior to those used in ESHAP. The patient received CODOX-M for the treatment of Burkitt's lymphoma while on a lopinavir/ritonavir based combination antiretroviral therapy (cART). He developed paralytic ileus that lasted 10 days. Two weeks after his recovery, IVAC was administered and was well tolerated. Subsequent cycles of CODOX-M were administered with etoposide (dose not specified) replacing the vincristine component and was well tolerated. (10)

Etoposide containing regimens

Several studies regarding the concomitant use of CDE (cyclophosphamide 1 200 mg/m^2; doxorubicin 50 mg/m^2; **etoposide** 240 mg/m^2 continuous infusion over 4 days q4weeks) and antiretroviral therapy were available. Etoposide dose is significantly higher in comparison to ESHAP. One study in 46 patients who received CDE for treatment of AIDS related lymphoma compared those who received a PI based combination antiretroviral therapy (cART) to those who received a non-PI based cART. The groups showed similar overall response and survival rates; however, an **increased risk of severe infections** (48% vs 25%; $p<0.01$) and **neutropenia** (54% vs 38%; $p=0.05$) was observed in patients on a PI based cART compared to those on a non-PI based cART(4). Another study in 12 patients showed an **increased risk of severe mucositis** (67% vs 12%; $p<0.01$) when patients received a saquinavir-based cART in comparison to a historical cohort not on cART(5).

Two cases described **good tolerability** of dose-adjusted EPOCH (**etoposide** 200 mg/m2, vincristine 1.6 mg/m2, cyclophosphamide 748 mg/m2, doxorubicin 40 mg/m^2 continuous infusion over 4 days, prednisone 60 mg/m2 daily for 5 days) when administered with lopinavir/ritonavir for treatment of anaplastic large-cell lymphoma. (11)

Metabolism of chemotherapy agents

Chemotherapy agent	Metabolism (6, 7)	Possible interaction (6, 7)	Clinical evidence
MP	CYP 3A4	Increased risk of steroid related toxicity with CYP 3A4 inhibitors. Possible decreased efficacy with CYP 3A4 inducers.	No studies or case reports found in the published literature.
Cisplatin	Main route of elimination is renal.	Pharmacokinetic interactions unlikely. Cisplatin induced nephrotoxicity may necessitate dosage adjustments for certain antiretroviral agents. Potential additive renal toxicity with tenofovir.	Possible increased hematological toxicity of cisplatin in a case report with atazanavir/ritonavir for treatment of lung cancer. (9) No cisplatin toxicity or decreased efficacy reported in a retrospective study with efavirenz. (8)
Etoposide	CYP 3A4 (main); CYP 2E1, 1A2 (minor)	Possibility of increased levels with 3A4 inhibitors which may increase the risk and severity of mucositis, myelosuppression and transaminitis. Possibility of decreased levels with 3A4 inducers.	Increased risk of etoposide toxicity shown in CDE regimen and PI-based regimen (infections, neutropenia, mucositis). (4, 5). Good tolerability in three cases with lopinavir/ritonavir and either DA-EPOCH or CODOX-M/IVAC for treatment of non-Hodgkin's lymphoma or Hodgkin's lymphoma, respectively. (10, 11)
Cytarabine	Transformation to active metabolite by cytidine deaminase in the liver	Potential additive renal toxicity with other agents such as tenofovir.	No cytarabine toxicity reported in one case where CODOX-M/IVAC was administered with lopinavir/ritonavir for treatment of Burkitt's lymphoma. (10)

MP: methylprednisolone

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[1]Enzyme inhibitors include protease inhibitors (PIs): Crixivan® (indinavir), Invirase® (saquinavir), Kaletra® (lopinavir/ritonavir), Norvir®, Norvir sec® (ritonavir), Prezista® (darunavir), Reyataz® (atazanavir), Telzir® (fosamprenavir), Viracept® (nelfinavir); and the integrase inhibitor elvitegravir/cobicistat: available as a coformulated product with tenofovir/emtrictabine (Stribild®); pharmacokinetic enhancer cobicistat (Tybost®).

[2]Enzyme inducers include non-nucleside reverse transcriptase inhibitors (NNRTIs): Atripla® (efavirenz/tenofovir/emtricitabine), Complera® (rilpivirine/tenofovir/emtricitabine), Edurant® (rilpivirine), Intelence® (etravirine), Sustiva® (efavirenz), Viramune®, Viramune XR® (nevirapine) and the protease inhibitor Aptivus® (tipranavir)

[3] Enzyme neutral agents include nucleoside reverse transcriptase inhibitors (NRTIs) : 3TC® (lamivudine), Combivir® (lamivudine/zidovudine), Kivexa ® (abacavir/lamivudine), Retrovir® (zidovudine), Trizivir® (abacavir/zidovudine/lamivudine), Truvada® (tenofovir/emtricitabine), Videx EC® (didanosine), Zerit® (stavudine); integrase inhibitors Isentress® (raltegravir), Tivicay® (dolutegravir); entry inhibitors Fuzeon® (enfuvirtide), Celsentri® (maraviroc)

Chemotherapy regimen: GDP

Agents involved

• Gemcitabine	1 g/m^2 IV in 250 mL of NS	Day 1
• Cisplatin	75 mg/m^2 IV in 500 mL of NS	Day 1
• Dexamethasone	20 mg po BID	Days 1 – 4

Summary of possible interactions with antiretroviral agents

Antiretroviral agents to avoid

- Avoid zidovudine-containing regimens (Retrovir®, Combivir®, Trizivir®) as additive hematologic toxicity is possible(1-3). (*Quality of Evidence: very low*)

If the patient is on one of the antiretroviral agents mentioned above, contact the HIV physician to request a change/substitution of antiretroviral agents.

Enzyme inhibition interactions[1]

(*Quality of Evidence: very low;* theoretical, unknown clinical significance)

- Possible increased dexamethasone toxicity (4, 5)
- Possible decreased efficacy of PIs (4, 5)

Enzyme induction interactions[2]

(*Quality of Evidence: very low*; theoretical, unknown clinical significance)

- Possible decreased efficacy of dexamethasone (4, 5)
- Possible decreased efficacy of NNRTIs (4, 5)

Enzyme neutral agents[3]: unlikely to interact

(*Quality of Evidence: very low*; theoretical)

- According to the metabolic profile of the individual agents, pharmacokinetic interactions are unlikely to occur. Nonetheless, additive toxicity remains possible with certain agents depending on the safety profile.

Particularities regarding nucleoside reverse transcriptase inhibitor backbone

(Quality of Evidence: very low; theoretical, unknown clinical significance)

- Potential additive renal toxicity with tenofovir (4, 5)

Laboratory interactions

(*Quality of Evidence: high*; no clinical significance)

- Cobicistat (Stribild®, Tybost®), rilpivirine (Edurant®, Complera®) and dolutegravir (Tivicay®) containing regimens will increase serum creatinine by approximately 7-15 μmol/L during the first 4 weeks of treatment initiation due to inhibition of renal creatinine secretion. This does not reflect an actual decrease in renal function, and the effect is quickly reversible upon drug discontinuation.

Note: if interruption of any antiretroviral agent is considered necessary, contact the HIV physician to determine appropriate cessation of the antiretroviral therapy (certain antiretroviral regimens require sequential cessation of antiretroviral agents while others require immediate cessation of all antiretroviral agents at once). If treatment for hepatitis B (HBV) co-infection is required, consult the HIV physician, since some antiretroviral agents have activity against both HIV and HBV.

Literature

A retrospective single arm study evaluated the efficacy and safety of GDP (gemcitabine 2000 mg/m^2, dexamethasone 160 mg, cisplatin 75 mg/m^2 per cycle) for treatment of relapsed or refractory AIDS-related non-Hodgkin's lymphoma (NHL) when administered with efavirenz/lamivudine/zidovudine. A total of 48 patients were included, of whom 21% had complete remission, 33% had partial remission; two-year overall survival was 71%. Regarding toxicity, 13% of patients required **dose reduction or elimination of zidovudine** in the HIV regimen due to leukopenia. Main grade 3/4 toxicities observed were anemia (8%), neutropenia (42%) and thrombocytopenia (58%). A total of 63% of patients had undetectable HIV viral load at the end of chemotherapy. The authors concluded that GDP was an effective salvage regimen with **tolerant toxicity** in patients with relapsed or refractory AIDS-NHL though further studies are warranted. (6)

Of note, low response to antiretroviral therapy is likely explained by previous exposure to efavirenz/lamivudine/zidovudine with a history of poor adherence in 71% of patients and dose reduction or elimination of zidovudine during chemotherapy in 13% of patients. This could contribute to development of HIV resistance and decreased efficacy of antiretroviral agents. Induction of efavirenz metabolism by dexamethasone may also have contributed to decreased antiretroviral efficacy.

A case report showed severe hematological toxicity secondary to cisplatin and gemcitabine when administered with atazanavir, ritonavir, tenofovir, lamivudine for treatment of lung cancer. The patient received one cycle of **cisplatin** 80 mg/m^2 and **gemcitabine** 2000 mg/m^2 and had grade 3 appetite loss, grade 4 platelet toxicity and neutrophils/granulocytes. Of note, cisplatin dose is similar to that used in the GDP regimen but the gemcitabine dose is largely superior. In the 3 subsequent cycles, cisplatin and gemcitabine doses were subsequently reduced to 60 and 1600 mg/m^2 respectively for 3 subsequent cycles, all of which were well tolerated. HIV viral load remained undetectable thorough out the course of chemotherapy. The patient had adequate response to therapy and was alive for 17 months at the time of publication. (7)

Metabolism of chemotherapy agents

Chemotherapy agent	Metabolism(4, 5)	Possible interaction(4, 5)	Clinical evidence
Gemcitabine	Intracellular activation of gemcitabine. Rapidly deaminated in the blood, liver, kidneys and other tissues. (8)	Pharmacokinetic interactions unlikely.	Possible increased hematological toxicity of gemcitabine in a case report with atazanavir/ritonavir for treatment of lung cancer. (7) No increased gemcitabine toxicity or decreased efficacy reported in a retrospective study with efavirenz. (6)
Cisplatin	Main route of elimination is renal.	Pharmacokinetic interactions unlikely. Cisplatin induced nephrotoxicity may necessitate dosage adjustments for certain antiretroviral agents. Potential additive renal toxicity with tenofovir.	Possible increased hematological toxicity of cisplatin in a case report with atazanavir/ritonavir for treatment of lung cancer. (7) No cisplatin toxicity or decreased efficacy reported in a retrospective study with efavirenz. (6)
Dexamethasone	Substrate and inducer of CYP 3A4.	Increased risk of steroid related toxicity with CYP 3A4 inhibitors. Possible decreased efficacy with CYP 3A4 inducers. Dexamethasone may decrease levels of PIs and NNRTIs.	Possible decreased efficacy of efavirenz reported in a retrospective study. (6)

Please consult http://hivclinic.ca/main/drugs_interact.html for more updated information.

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[2]Enzyme inducers include non-nucleside reverse transcriptase inhibitors (NNRTIs): Atripla® (efavirenz/tenofovir/emtricitabine), Complera® (rilpivirine/tenofovir/emtricitabine), Edurant® (rilpivirine), Intelence® (etravirine), Sustiva® (efavirenz), Viramune®, Viramune XR® (nevirapine) and the protease inhibitor Aptivus® (tipranavir)

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Chemotherapy regimen: ICE

Agents involved

• Etoposide	100 mg/m^2 IV in 500 mL of NS	Days 1 – 3
• Carboplatin	Target AUC of 5 in 100 mL of D5W	Day 2
• Ifosfamide/Mesna	5/5 g/m^2 in 1000 mL of NS	Day 2

Summary of possible interactions with antiretroviral agents

Antiretroviral agents to avoid

- Avoid zidovudine-containing regimens (Retrovir®, Combivir®, Trizivir®) as additive hematologic toxicity is possible(1-3). *(Quality of Evidence: very low)*

If the patient is on one of the antiretroviral agents mentioned above, contact the HIV physician to request a change/substitution of antiretroviral agents.

Enzyme inhibition interactions[1]

- Possible increased etoposide toxicity (infections, neutropenia, mucositis) (4, 5) (*Quality of Evidence: moderate)*
- Possible decreased efficacy of ifosfamide (6, 7) *(Quality of Evidence: very low;* theoretical, unknown clinical significance)
    - Contact the HIV physician to request a change/substitution to a non-PI, non-NNRTI based regimen

Enzyme induction interactions[2]

(Quality of Evidence: very low; theoretical, unknown clinical significance)

- Possible decreased efficacy of etoposide (6, 7)
- Possible increased toxicity of ifosfamide (6, 7)

Enzyme neutral agents[3]: unlikely to interact

(*Quality of Evidence: very low*; theoretical)

- According to the metabolic profile of the individual agents, pharmacokinetic interactions are unlikely to occur. Nonetheless, additive toxicity remains possible with certain agents depending on the safety profile.

Laboratory interactions

(*Quality of Evidence: high*; no clinical significance)

- Cobicistat (Stribild®, Tybost®), rilpivirine (Edurant®, Complera®) and dolutegravir (Tivicay®) containing regimens will increase serum creatinine by approximately 7-15 μmol/L during the first 4 weeks of treatment initiation due to inhibition of renal creatinine secretion. This does not reflect an actual decrease in renal function, and the effect is quickly reversible upon drug discontinuation.

Note: if interruption of any antiretroviral agent is considered necessary, contact the HIV physician to determine appropriate cessation of the antiretroviral therapy (certain antiretroviral regimens require sequential cessation of antiretroviral agents while others require immediate cessation of all antiretroviral agents at once). If treatment for hepatitis B (HBV) co-infection is required, consult the HIV physician, since some antiretroviral agents have activity against both HIV and HBV.

Literature

No studies or case reports specifically regarding ICE and antiretroviral agents were found. Data available from other regimens including similar antineoplastic agents are presented below.

CDE

Several studies regarding the concomitant use of CDE (cyclophosphamide 1 200 mg/m^2; doxorubicin 50 mg/m^2; **etoposide** 240 mg/m^2 continuous infusion over 4 days q4weeks) and antiretroviral therapy were available. Etoposide dose is slightly lower in comparison to ICE. One study in 46 patients who received CDE for treatment of AIDS related lymphoma compared those who received a PI based combination antiretroviral therapy (cART) to those who received a non-PI based cART. The groups showed similar overall response and survival rates; however, an **increased risk of severe infections** (48% vs 25%; p<0.01) and **neutropenia** (54% vs 38%; p =0.05) was observed in patients on a PI based cART compared to those on a non-PI based cART(4). Another study in 12 patients showed an **increased risk of severe mucositis** (67% vs 12%; p<0.01) when patients received a saquinavir-based cART in comparison to a historical cohort not on cART(5).

CODOX-M/IVAC

One case report described **good tolerability of etoposide and ifosfamide** after severe vincristine toxicity. The patient received CODOX-M for the treatment of Burkitt's lymphoma while on a lopinavir/ritonavir based cART. He developed paralytic ileus that lasted 10 days. Two weeks after his recovery, IVAC (ifosfamide 7.5 g/m^2, etoposide 300 mg/m^2 IV, cytarabine 8 g/m^2 IV per cycle) was administered and was well tolerated. The dose of ifosfamide used is higher than that used in ICE although the etoposide dose is the same. Subsequent cycles of CODOX-M were administered with etoposide (dose not specified) replacing the vincristine component and was well tolerated.(8)

DA-EPOCH

Two cases described **good tolerability** of dose-adjusted EPOCH (**etoposide** 200 mg/m^2, vincristine 1.6 mg/m^2, cyclophosphamide 748 mg/m^2, doxorubicin 40 mg/m^2 continuous infusion over 4 days, prednisone 60 mg/m^2 daily for 5 days) when administered with lopinavir/ritonavir for treatment of anaplastic large-cell lymphoma. (9)

Metabolism of chemotherapy agents

Chemotherapy agent	Metabolism (6, 7)	Possible interaction (6, 7)	Clinical evidence
Etoposide	CYP 3A4 (main); CYP 2E1, 1A2 (minor)	Possibility of increased levels with 3A4 inhibitors which may increase the risk and severity of mucositis, myelosuppression and transaminitis. Possibility of decreased levels with 3A4 inducers.	Increased risk of etoposide toxicity shown in CDE regimen and PI-based regimen (infections, neutropenia, mucositis) (4, 5). Good tolerability in three cases with lopinavir/ritonavir and either DA-EPOCH or CODOX-M/IVAC for treatment of non-Hodgkin's lymphoma or Hodgkin's lymphoma, respectively.(8, 9)
Carboplatin	Main route of elimination is renal.	Pharmacokinetic interactions unlikely.	No studies or case reports found in the published literature.
Ifosfamide	CYP 3A4 to active metabolite, neurotoxic metabolite and detoxification. CYP 2B6 is involved in detoxicification.	Inhibition of CYP 3A4 may inhibit drug activation. Induction of CYP 3A4 may increase activation of ifosfamide but may also produce more potentially neurotoxic metabolites.	No ifosfamide toxicity reported in one case where CODOX-M/IVAC was administered with lopinavir/ritonavir for treatment of Burkitt's lymphoma. (8)
Mesna	Rapidly oxidized in plasma to dimesna and eliminated renally. No hepatic metabolism. (10)	Pharmacokinetic interactions unlikely.	No mesna toxicity reported in one case where CODOX-M/IVAC was administered with lopinavir/ritonavir for treatment of Burkitt's lymphoma. (8)

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[2]Enzyme inducers include non-nucleside reverse transcriptase inhibitors (NNRTIs): Atripla® (efavirenz/tenofovir/emtricitabine), Complera® (rilpivirine/tenofovir/emtricitabine), Edurant® (rilpivirine), Intelence® (etravirine), Sustiva® (efavirenz), Viramune®, Viramune XR® (nevirapine) and the protease inhibitor Aptivus® (tipranavir)

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Chemotherapy regimen: Minibeam

Agents involved

• BCNU	60 mg/m^2 IV in 250 mL of D5W	Day 1
• Etoposide	75 mg/m^2 IV in 500 mL of NS	Days 1 – 4
• Cytarabine	100 mg/m^2 IV in 250 mL NS q12h	Days 1 – 4
• Melphalan	30 mg/m^2 IV	Day 5

Summary of possible interactions with antiretroviral agents

Antiretroviral agents to avoid

- Avoid zidovudine-containing regimens (Retrovir®, Combivir®, Trizivir®) as additive hematologic toxicity is possible (1-3). *(Quality of Evidence: very low)*

If the patient is on one of the antiretroviral agents mentioned above, contact the HIV physician to request a change/substitution of antiretroviral agents.

Enzyme inhibition interactions[1]

- Possible increased etoposide toxicity (infections, neutropenia, mucositis) (4, 5) (*Quality of Evidence: moderate)*

Enzyme induction interactions[2]

(*Quality of Evidence: very low;* theoretical, unknown clinical significance)

- Possible decreased efficacy of etoposide (6, 7)

Enzyme neutral agents[3]: unlikely to interact

(*Quality of Evidence: very low*; theoretical)

- According to the metabolic profile of the individual agents, pharmacokinetic interactions are unlikely to occur. Nonetheless, additive toxicity remains possible with certain agents depending on the safety profile.

Particularities regarding nucleoside reverse transcriptase inhibitor backbone

(*Quality of Evidence: very low;* theoretical, unknown clinical significance)

- Potential additive renal toxicity with tenofovir (6, 7)

Laboratory interactions

(*Quality of Evidence: high*; no clinical significance)

- Cobicistat (Stribild®, Tybost®), rilpivirine (Edurant®, Complera®) and dolutegravir (Tivicay®) containing regimens will increase serum creatinine by approximately 7-15 μmol/L during the first 4 weeks of treatment initiation due to inhibition of renal creatinine secretion. This does not reflect an actual decrease in renal function, and the effect is quickly reversible upon drug discontinuation.

Note: if interruption of any antiretroviral agent is considered necessary, contact the HIV physician to determine appropriate cessation of the antiretroviral therapy (certain antiretroviral regimens require sequential cessation of antiretroviral agents while others require immediate cessation of all antiretroviral agents at once). If treatment for hepatitis B (HBV) co-infection is required, consult the HIV physician, since some antiretroviral agents have activity against both HIV and HBV.

Literature

No studies or case reports specifically regarding MiniBeam and antiretroviral agents were found. Data available from other regimens including similar antineoplastic agents are presented below.

CDE

Several studies regarding the concomitant use of CDE (cyclophosphamide 1 200 mg/m^2; doxorubicin 50 mg/m^2; **etoposide** 240 mg/m^2 continuous infusion over 4 days q4weeks) and antiretroviral therapy were available. Etoposide dose is significantly lower in comparison to MiniBeam. One study in 46 patients who received CDE for treatment of AIDS related lymphoma compared those who received a PI based combination antiretroviral therapy (cART) to those who received a non-PI based cART. The groups showed similar overall response and survival rates; however, an **increased risk of severe infections** (48% vs 25%; p<0.01) and **neutropenia** (54% vs 38%; p =0.05) was observed in patients on a PI based cART compared to those on a non-PI based cART(4). Another study in 12 patients showed an **increased risk of severe mucositis** (67% vs 12%; p<0.01) when patients received a saquinavir-based cART in comparison to a historical cohort not on cART(5).

CODOX-M/IVAC

One case report described **good tolerability of etoposide and cytarabine** after severe vincristine toxicity. The patient received CODOX-M for the treatment of Burkitt's lymphoma while on a lopinavir/ritonavir based cART. He developed paralytic ileus that lasted 10 days. Two weeks after his recovery, IVAC (ifosfamide 7.5 g/m^2, **etoposide** 300 mg/m^2 IV, **cytarabine** 8 g/m^2 IV per cycle) was administered and was well tolerated. Comparatively to MiniBeam, etoposide dose is the same although cytarabine dose is significantly higher. Subsequent cycles of CODOX-M were administered with etoposide (dose not specified) replacing the vincristine component and was well tolerated. (8)

DA-EPOCH

Two cases described **good tolerability** of dose-adjusted EPOCH (**etoposide** 200 mg/m^2, vincristine 1.6 mg/m^2, cyclophosphamide 748 mg/m^2, doxorubicin 40 mg/m^2 continuous infusion over 4 days, prednisone 60 mg/m^2 daily for 5 days) when administered with lopinavir/ritonavir for treatment of anaplastic large-cell lymphoma. (9)

Metabolism of chemotherapy agents

Chemotherapy agent	Metabolism (6, 7)	Possible interaction (6, 7)	Clinical evidence
BCNU	Spontaneous degradation. (10)	Pharmacokinetic interactions unlikely.	No studies or case reports found in the published literature.
Etoposide	CYP 3A4 (main); CYP 2E1, 1A2 (minor)	Possibility of increased levels with 3A4 inhibitors which may increase the risk and severity of mucositis, myelosuppression and transaminitis. Possibility of decreased levels with 3A4 inducers.	Increased risk of etoposide toxicity shown in CDE regimen and PI-based regimen (infections, neutropenia, mucositis) (4, 5). Good tolerability in three cases with lopinavir/ritonavir and either DA-EPOCH or CODOX-M/IVAC for treatment of non-Hodgkin's lymphoma or Hodgkin's lymphoma, respectively. (8, 9)
Cytarabine	Transformation to active metabolite by cytidine deaminase in the liver	Potential additive renal toxicity with other agents such as tenofovir.	No cytarabine toxicity reported in one case where CODOX-M/IVAC was administered with lopinavir/ritonavir for treatment of Burkitt's lymphoma. (8)
Melphalan	Spontaneous chemical degradation in plasma to inactive metabolites.	Pharmacokinetic interactions unlikely.	No studies or case reports found in the published literature.

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[1]Enzyme inhibitors include protease inhibitors (PIs): Crixivan® (indinavir), Invirase® (saquinavir), Kaletra® (lopinavir/ritonavir), Norvir®, Norvir sec® (ritonavir), Prezista® (darunavir), Reyataz® (atazanavir), Telzir® (fosamprenavir), Viracept® (nelfinavir); and the integrase inhibitor elvitegravir/cobicistat: available as a coformulated product with tenofovir/emtrictabine (Stribild®); pharmacokinetic enhancer cobicistat (Tybost®).

[2]Enzyme inducers include non-nucleside reverse transcriptase inhibitors (NNRTIs): Atripla® (efavirenz/tenofovir/emtricitabine), Complera® (rilpivirine/tenofovir/emtricitabine), Edurant® (rilpivirine), Intelence® (etravirine), Sustiva® (efavirenz), Viramune®, Viramune XR® (nevirapine) and the protease inhibitor Aptivus® (tipranavir)

[3] Enzyme neutral agents include nucleoside reverse transcriptase inhibitors (NRTIs) : 3TC® (lamivudine), Combivir® (lamivudine/zidovudine), Kivexa ® (abacavir/lamivudine), Retrovir® (zidovudine), Trizivir® (abacavir/zidovudine/lamivudine), Truvada® (tenofovir/emtricitabine), Videx EC® (didanosine), Zerit® (stavudine); integrase inhibitors Isentress® (raltegravir), Tivicay® (dolutegravir); entry inhibitors Fuzeon® (enfuvirtide), Celsentri® (maraviroc)

ANTIRETROVIRAL INTERACTIONS WITH SUPPORTIVE THERAPY

Supportive therapy

Summary of interactions

Table 1. Summary of potential interactions between antiretroviral agents and supportive therapy

	Anti-emetics	Acid-suppressants	Steroids	Other
Interactions with enzyme inhibitors (protease inhibitors and elvitegravir/cobicistat)[1]	Aprepitant, alosetron, ondansetron, dimenhydrinate, diphenhydramine	Atazanavir with antacids, anti-H2 and/or proton pump inhibitors Elvitegravir with antacids	Dexamethasone, methylprednisolone, prednisone	Fluconazole
Interactions with enzyme inducers (NNRTIs)[2]	Aprepitant , dolasetron, granisetron, ondansetron	Rilpivirine with antacids, anti-H2, proton pump inhibitors	Dexamethasone, methylprednisolone, prednisone	Fluconazole
Interactions with enzyme neutral agents (integrase inhibitors, nucleoside reverse transcriptase inhibitors)[3]		Raltegravir or dolutegravir with antacids		Tenofovir and acyclovir Didanosine and allopurinol

[1]Enzyme inhibitors include protease inhibitors (PIs): Crixivan® (indinavir), Invirase® (saquinavir), Kaletra® (lopinavir/ritonavir), Norvir®, Norvir sec® (ritonavir), Prezista® (darunavir), Reyataz® (atazanavir), Telzir® (fosamprenavir), Viracept® (nelfinavir); and the integrase inhibitor elvitegravir/cobicistat: available as a coformulated product with tenofovir/emtrictabine (Stribild®); pharmacokinetic enhancer cobicistat (Tybost®).

[2]Enzyme inducers include non-nucleside reverse transcriptase inhibitors (NNRTIs): Atripla® (efavirenz/tenofovir/emtricitabine), Complera® (rilpivirine/tenofovir/emtricitabine), Edurant® (rilpivirine), Intelence® (etravirine), Sustiva® (efavirenz), Viramune®, Viramune XR® (nevirapine) and the protease inhibitor Aptivus® (tipranavir)

[3] Enzyme neutral agents include nucleoside reverse transcriptase inhibitors (NRTIs) : 3TC® (lamivudine), Combivir® (lamivudine/zidovudine), Kivexa ® (abacavir/lamivudine), Retrovir® (zidovudine), Trizivir® (abacavir/zidovudine/lamivudine), Truvada® (tenofovir/emtricitabine), Videx EC® (didanosine), Zerit® (stavudine); integrase inhibitors Isentress® (raltegravir), Tivicay® (dolutegravir); entry inhibitors Fuzeon® (enfuvirtide), Celsentri® (maraviroc)

Interactions with Anti-Emetics

Aprepitant (Emend®)

Aprepitant is metabolized primarily by CYP 3A4. In addition, it is also a moderate inhibitor and inducer of CYP 3A4 and a strong inducer of CYP 2C9.

With protease inhibitors and elvitegravir/cobicistat, an increase in aprepitant plasma concentrations may occur due to inhibition of CYP 3A4. With NNRTIs, a decrease in aprepitant plasma concentrations may occur secondary to CYP3A4 induction. Recommendations on dose adjustments are not available. Increased monitoring is recommended, with dose adjustments as necessary. (*Quality of Evidence: very low*; theoretical, unknown clinical significance)

Antiretroviral Class	Potential/Theoretical Interaction	Comment
Enzyme inhibitors (protease inhibitors, elvitegravir/cobicistat)	Potential ↑ aprepitant plasma concentrations via CYP3A4 inhibition	**No dosage adjustments have been recommended; however increased monitoring for aprepitant related adverse effects is warranted.** (*Quality of Evidence: very low*; theoretical, unknown clinical significance)
Enzyme inducers (NNRTIs)	Potential ↓ aprepitant plasma concentrations via CYP3A4 induction	**No dosage adjustments have been recommended; however a decrease in aprepitant efficacy may be observed and dose increase may be considered.** (*Quality of Evidence: very low*; theoretical, unknown clinical significance)
	Potential ↓ etravirine plasma concentrations via CYP2C9 induction	**No dosage adjustments have been recommended; monitor for antiviral efficacy or consider use of an alternate antiemetic.** (*Quality of Evidence: very low*; theoretical, unknown clinical significance)

Selective 5-HT$_3$ Receptor antagonists

According to the primary route of elimination/metabolism, less interaction with enzyme inhibitors is expected with dolasetron, granisetron and palonosetron compared to alosetron and ondansetron. **Suggest preferred use of dolasetron, granisetron and palonestron if possible with concomitant protease inhibitors and elvitegravir/cobicistat.** (*Quality of Evidence: very low*; theoretical, unknown clinical significance)

With enzyme inducers, ondansetron concentrations may be decreased due to CYP3A4 induction. Additive risk of QT prolongation with concomitant rilpivirine and dolastron, granisetron and ondansetron is also a potential concern. **Suggest preferred use of alosetron and palonosetron if possible with concomitant NNRTIs.** (*Quality of Evidence: very low*; theoretical, unknown clinical significance)

There are no anticipated interactions between anti-emetics and other classes of antiretrovirals.

	Primary route of elimination/metabolism	**Potential interaction with Protease Inhibitors and Elvitegravir/Cobicistat**	**Potential interaction with NNRTIs**
Alosetron (Lotronex®; available in US)	CYP1A2	Ritonavir containing regimens may decrease alosetron efficacy by induction of CYP1A2**. May consider use of an alternate agent in this class such as dolasetron, granisetron or palonestron.**	No major interactions expected.
Dolasetron (Anzemet®)	Carbonyl reductase	No major interactions expected	No pharmacokinetic interaction expected. However, an increased cumulative risk of QT prolongation is possible with rilpivirine. **Use of an alternate agent in this class such as alosetron (available in US) or palonestron is recommended.**
Granisetron (Kytril®)	N-demethylation, oxidation and conjugation	No major interactions expected	No pharmacokinetic interaction expected. However, an increased cumulative risk of QT prolongation is possible with rilpivirine. **Use of an alternate agent in this class such as alosetron (available in US) or palonestron is recommended.**
Ondansetron (Zofran®)	Hydroxylation; CYP3A4	Increased ondansetron plasma concentrations could be expected due to inhibition of CYP 3A4; increased risk of QT prolongation. **May consider use of an alternate agent in this class such as dolasetron, granisetron or palonestron.**	Decreased ondansetron plasma concentrations could occur due to induction of CYP 3A4; potential increased cumulative risk of QT prolongation is possible with rilpivirine. **Use of an alternate agent in this class such as alosetron (available in US) or palonestron is recommended.**
Palonosetron (Aloxi®)	40% urine excretion; 50% metabolised by various CYP enzymes	No major interactions expected.	No major interactions expected.

Dimenhydrinate/diphenhydramine

Both drugs are metabolized primarily by CYP 2D6. An increase in dimenhydrinate or diphenhydramine drug plasma concentrations could be expected due to inhibition of CYP 2D6 by ritonavir-boosted protease inhibitors or elvitegravir/cobicistat. **Consider starting dimenhydrinate/diphenhydramine at lower doses.** (*Quality of Evidence: very low*; theoretical, unknown clinical significance)

Interactions with other antiretroviral drug classes are not anticipated.

Antiretroviral Class	Potential/Theoretical Interaction	Comment
Enzyme inhibitors (protease inhibitors, elvitegravir/cobicistat)	Potential ↑ dimenhydrinate or diphenhydramine plasma concentrations via CYP2D6 inhibition	**No dosage adjustments have been recommended; however increased monitoring for related adverse effects is warranted.** (*Quality of Evidence: very low*; theoretical, unknown clinical significance)
Enzyme inducers (NNRTIs)	None anticipated.	None
Other antiretrovirals	None anticipated.	None

Steroids

Dexamethasone

Dexamethasone is a strong inducer of CYP3A4 and long-term use (> 2 weeks) may result in a decrease in concentrations of protease inhibitors, NNRTIs, elvitegravir/cobicistat, and maraviroc.
If prolonged use is necessary, use alternate steroid (eg., prednisone, methylprednisolone). (*Quality of Evidence: very low*; theoretical, unknown clinical significance)

Dexamethasone is also a CYP 3A4 substrate. There is an **increased risk of steroid related toxicity** when administered with CYP 3A4 inhibitors (eg., cobicistat or protease-inhibitor based regimens.) Conversely, there is a risk of decreased efficacy when coadministered with NNRTIs which are CYP3A4 inducers. (*Quality of Evidence: very low*; theoretical, unknown clinical significance)

Methylprednisolone

Methylprednisolone is a CYP 3A4 substrate. Co-administration of methylprednisolone and a protease inhibitor or cobicistat-based regimen may result in an increased risk of steroid related toxicity. Conversely, there is a risk of decreased efficacy when coadministered with NNRTIs which are CYP3A4 inducers. (Quality of Evidence: very low; theoretical, unknown clinical significance)

Prednisone

Prednisone is converted to the active metabolite prednisolone by a non-CYP mediated route. Prednisone and prednisolone are substrates of CYP 450 including CYP 3A4. Co-administration with a protease inhibitor or cobicistat-based antiretroviral regimen may result in an **increased risk of steroid related toxicity**. Conversely, there is a risk of decreased efficacy when coadministered with NNRTIs which are CYP3A4 inducers. (*Quality of Evidence: very low*; theoretical, unknown clinical significance)

Interactions Between Steroids and Antiretrovirals[1]

	Primary route of elimination/metabolism	**Potential interaction with Protease Inhibitors and Elvitegravir/Cobicistat**	**Potential interaction with NNRTIs**
Dexamethasone	3A4; also strong 3A4 inducer.	Potential ↑ dexamethasone plasma concentrations via CYP3A4 inhibition, and possible increased risk of steroid toxicity. Potential for ↓ antiretroviral concentrations. **If prolonged use is necessary, consider use of an alternate steroid (eg., prednisone, methylprednisolone) and monitor for steroid toxicity.**	Potential for ↓ steroid efficacy due to CYP3A4 induction. Monitor for steroid efficacy and adjust dose if necessary. Potential for ↓ antiretroviral concentrations. **If prolonged use is necessary, consider use of an alternate steroid (eg., prednisone, methylprednisolone) and monitor for steroid efficacy.**
Methylprednisolone	3A4	Potential ↑ methylprednisolone plasma concentrations via CYP3A4 inhibition, and possible increased risk of steroid toxicity.	Potential for ↓ steroid efficacy due to CYP3A4 induction. Monitor for steroid efficacy and adjust dose if necessary.
Prednisone	Converted to active metabolite prednisolone; both are 3A4 substrates	Potential ↑ prednisone/prednisolone plasma concentrations via CYP3A4 inhibition, and possible increased risk of steroid toxicity.	Potential for ↓ steroid efficacy due to CYP3A4 induction. Monitor for steroid efficacy and adjust dose if necessary.

Acid suppressants

Acid suppressing agents may interact with antiretrovirals through a variety of mechanisms, including:

- Change in gastric pH. Certain antiretrovirals require an acidic pH for optimal absorption. These interactions may sometimes be managed by spacing the antiretroviral(s) apart from the antacid or H2-blocker and/or adjusting the antiretroviral dose. Proton pump inhibitors may be contraindicated in some instances. (*Quality of Evidence: low-moderate*)
- Chelation. Antacids significantly reduce the oral bioavailability of integrase inhibitors due to the formation of nonabsorbable cation complexes. Integrase inhibitors should be administered apart from antacids to avoid this interaction. (*Quality of Evidence: moderate)*

Interactions between Acid-Reducing Agents and Antiretrovirals[1,4]

	Antacids	H2 Antagonists	Proton Pump Inhibitors
Integrase Inhibitors			
Dolutegravir	Separate by 2 hours before or 6 hours after medications containing polyvalent cations (e.g., Mg, Al, Fe, or Ca) including cation-containing antacids or laxatives, sucralfate, oral Fe or Ca supplements and buffered medications.	OK	OK
Elvitegravir	Separate by ≥2 hours from antacids containing Al, Mg, Ca.	OK	OK
Raltegravir	Separate by ≥2 hours from antacids.	OK	OK
NNRTIs			
Rilpivirine	Take antacid ≥2 hours before or ≥4 hours after rilpivirine.	Give rilpivirine ≥4 hours before or 12 hours after H2 antagonists.	**Contraindicated**
Protease Inhibitors			
Atazanavir	Take antacid 1 hour before or 2 hours after atazanavir.	Give atazanavir 300/100 mg QD with or 10 hours after H2 antagonists. Maximum famotidine 40 mg BID (treatment-naïve) or 20 mg BID (treatment-experienced). If also on tenofovir, ↑ to atazanavir 400/100 mg QD in experienced patients.	Not recommended. ↑ to atazanavir 400/100 mg with maximum 20 mg omeprazole or equivalent*.
Indinavir	Separate indinavir and antacid doses by 1 hour.	OK	Avoid combining unboosted indinavir with proton pump inhibitors. Boosted indinavir may be coadministered with proton pump inhibitors.

*lansoprazole 30 mg OD, pantoprazole 40 mg OD, rabeprazole 20 mg OD, esomeprazole 20 mg OD

Miscellaneous

Fluconazole

Nevirapine is a substrate and a potent inducer of CYP 3A4 and 2B6. Fluconazole is a substrate of CYP 3A4 and a weak inhibitor of CYP 3A4, 2C9 and 2C19. Co-administration of nevirapine and fluconazole (even at low doses) may result in an increase in nevirapine plasma concentrations leading to potential increased nevirapine toxicity. Fluconazole pharmacokinetics are not affected. **Avoid co-administration if possible. If co-administration is required, monitor for signs of increased nevirapine toxicity (hepatotoxicity).** (*Quality of Evidence: moderate*)

Possible interaction between fluconazole and **tipranavir**. Co-administration with fluconazole at doses greater than 200 mg once daily is not recommended as this may increase tipranavir plasma concentrations. (*Quality of Evidence: very low*; pharmacokinetic study, unknown clinical significance)

Acyclovir

Tenofovir: acyclovir may decrease the excretion of tenofovir. This may lead to possible increased tenofovir toxicity such as renal impairment. (*Quality of Evidence: very low*; theoretical, unknown clinical significance)

Allopurinol

Didanosine: co-administration with allopurinol is contra-indicated due to possible increased didanosine plasma concentration that may lead to increased didanosine toxicity. (*Quality of Evidence: very low*; pharmacokinetic study of unknown clinical significance)

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GLOSSARY

ABD	doxorubicin, bleomycin, dacarbazine
ABVD	doxorubicin, vinblastine, bleomycin, dacarbazine
Al	Aluminium
Anti-H2	H2 receptor antagonist
AUC	area under the curve
BCNU	carmustine
BEACOPP	doxorubicin, etoposide, cyclophosphamide, procarbazine, prednisone, vincristine, bleomycin
BID	twice a day
BL	Burkitt's lymphoma
Ca	calcium
cART	combination antiretroviral therapy
CCR	C-C chemokine receptor 5
CDE	cyclophosphamide, doxorubicin, etoposide
CHOP	cyclophosphamide, doxorubicin, vincristine, prednisone
CNS	central nervous system
CODOX-M	vincristine, doxorubicin, cyclophosphamide, cytarabine, methotrexate
CR	complete response
CVP	cyclophosphamide, vincristine, prednisone
CYP	hepatic cytochrome P450 isoenzyme
d	day
DA	dose-adjusted
DA-EPOCH	dose-adjusted etoposide, doxorubicin, vincristine, cyclophosphamide
D5W	5% dextrose in water
DHAP	dexamethasone, cisplatin, cytarabine
DLBCL	diffuse large B-cell lymphoma
EC	enteric coated
EPOCH	etoposide, vincristine, cyclophosphamide, doxorubicin, prednisone
ESHAP	methylprednisolone, cisplatin, etoposide, cytarabine
Fe	iron
g	gram
GCSF	granulocyte colony stimulating factor
GDP	gemcitabine, dexamethasone, cisplatin
hyper CVAD	cyclophosphamide, dexamethasone, methotrexate, doxorubicin, vincristine, cytarabine
ICE	etoposide, carboplatin, ifosfamide/mesna
IT	intrathecal
IV	intravenous
IVAC	ifosfamide, etoposide, cytarabine
LPV/r	lopinavir/ritonavir
m^2	square meter
mg	milligrams
Mg	magnesium
min	minute
minibeam	BCNU/carmustine, etoposide, cytarabine, melphalan
mL	millilitre
MOPP	mechlorethamine, vincristine, procarbazine, prednisone
MP	methylprednisolone
NADPH	nicotinamide adenine dinucleotide phosphate
NHL	non-Hodgkin's lymphoma
N(t)RTI	nucleos(t)ide reverse transcriptase inhibitor
NG	nasogastric
NNRTI	non-nucleoside reverse transcriptase inhibitor
NS	normal saline
OD	once daily
PgP	p-glycoprotein
PI	protease inhibitor
po	by mouth
q12h	every 12 hours
U	units
uCR	unconfirmed complete response
μmol	micromole
μL	microlitre

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