

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 interactions¹

- 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 interactions²

(*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 agents³: 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.

Antiretroviral-Chemotherapy Interactions: DA-EPOCH regimen

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/m², **doxorubicin** 50 mg/m², **vincristine** 1.4 mg/m² [max 2 mg], **prednisone** 100 mg/m²) 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/m²; **doxorubicin** 50 mg/m²; **etoposide** 240 mg/m² 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/m² IV, **cyclophosphamide** 1600 mg/m² IV, cytarabine 140 mg IT, methotrexate 6720 mg/m² 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/m². This however, did not translate into excessive toxicity. (10)

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

Antiretroviral-Chemotherapy Interactions: DA-EPOCH regimen

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)
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.(10)
Prednisone	Converted to active metabolite prednisolone by non-CYP mediated route. Prednisone and prednisolone	Possible increased toxicity with CYP 3A4 inhibitors. Possible decreased efficacy with CYP 3A4 inducers.	No evidence of increased toxicity found in the published literature.

Antiretroviral-Chemotherapy Interactions: DA-EPOCH regimen

	are also substrates of CYP 450 including CYP 3A4.		
--	---	--	--

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

Antiretroviral-Chemotherapy Interactions: DA-EPOCH regimen

References

1. Retrovir. Product monograph. GlaxoSmithKline; 2009.
2. Combivir. Product Monograph. GlaxoSmithKline; 2007.
3. Trizivir. Product Monograph. GlaxoSmithKline; 2008.
4. Zerit. Product monograph. Bristol-Myers Squibb Canada; 2010.
5. Videx Ec. Product monograph. Bristol-Myers Squibb Canada; 2010.
6. Bower M, McCall-Peat N, Ryan N, Davies L, Young AM, Gupta S, et al. Protease inhibitors potentiate chemotherapy-induced neutropenia. *Blood*. 2004 Nov 1;104(9):2943-6.
7. Sparano JA, Wiernik PH, Hu X, Sarta C, Henry DH, Ratech H. Saquinavir enhances the mucosal toxicity of infusional cyclophosphamide, doxorubicin, and etoposide in patients with HIV-associated non-Hodgkin's lymphoma. *Med Oncol*. 1998 Apr;15(1):50-7.
8. Vaccher E, Spina M, di Gennaro G, Talamini R, Nasti G, Schioppa O, et al. Concomitant cyclophosphamide, doxorubicin, vincristine, and prednisone chemotherapy plus highly active antiretroviral therapy in patients with human immunodeficiency virus-related, non-Hodgkin lymphoma. *Cancer*. 2001 Jan 1;91(1):155-63.
9. Leveque D, Santucci R, Pavillet J, Herbrecht R, Bergerat JP. Paralytic ileus possibly associated with interaction between ritonavir/lopinavir and vincristine. *Pharm World Sci*. 2009 Dec;31(6):619-21.
10. Ratner L, Lee J, Tang S, Redden D, Hamzeh F, Herndier B, et al. Chemotherapy for human immunodeficiency virus-associated non-Hodgkin's lymphoma in combination with highly active antiretroviral therapy. *J Clin Oncol*. 2001 Apr 15;19(8):2171-8.
11. Antoniou T, Tseng A. Potential interactions between antineoplastics and antiretrovirals. In: Tseng A, Foisy M, editors. *Handbook of HIV drug therapy*. 2010 ed. Toronto 2010. p. 373-92.
12. Antoniou T, Tseng AL. Interactions between antiretrovirals and antineoplastic drug therapy. *Clin Pharmacokinet*. 2005;44(2):111-45.
13. 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.
14. Toffoli G, Corona G, Cattarossi G, Boiocchi M, Di Gennaro G, Tirelli U, et al. Effect of highly active antiretroviral therapy (HAART) on pharmacokinetics and pharmacodynamics of doxorubicin in patients with HIV-associated non-Hodgkin's lymphoma. *Ann Oncol*. 2004 Dec;15(12):1805-9.

¹Enzyme 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/emtricitabine (Stribild®); pharmacokinetic enhancer cobicistat (Tybost®).

²Enzyme 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)

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)