

## Chemotherapy regimen: CODOX-M

### Agents involved

• Vincristine	1.4 mg/m <sup>2</sup> IV	Day 1, 8
• Doxorubicin	50 mg/m <sup>2</sup> IV	Day 1
• Cyclophosphamide	800 mg/m <sup>2</sup> IV in 500 mL of NS	Day 1 – 2
• Cytarabine	50 mg IT	Days 1, 3
• Methotrexate	3000 mg/m <sup>2</sup> 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<sup>1</sup>

- 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<sup>2</sup>

(*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<sup>3</sup>: 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.

# Antiretroviral-Chemotherapy Interactions: CODOX-M regimen

## 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<sup>2</sup> IV, doxorubicin 50 mg/m<sup>2</sup> IV, cyclophosphamide 1600 mg/m<sup>2</sup> IV, cytarabine 140 mg IT, methotrexate 6720 mg/m<sup>2</sup> IV or 3000 mg/m<sup>2</sup> per cycle) and IVAC (ifosfamide 7.5 g/m<sup>2</sup>; etoposide 300 mg/m<sup>2</sup>; cytarabine 8 g/m<sup>2</sup>) with or without rituximab 375 mg/m<sup>2</sup> 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<sup>2</sup> IV, cyclophosphamide 1600 mg/m<sup>2</sup> IV, cytarabine 140 mg IT, methotrexate 6720 mg/m<sup>2</sup> 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<sup>2</sup>; etoposide 300 mg/m<sup>2</sup>; cytarabine 8 g/m<sup>2</sup>) 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<sup>2</sup>, **doxorubicin** 50 mg/m<sup>2</sup>, **vincristine** 1.4 mg/m<sup>2</sup> [max 2 mg], prednisone 100 mg/m<sup>2</sup>) 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<sup>2</sup>; **doxorubicin** 50 mg/m<sup>2</sup>; etoposide 240 mg/m<sup>2</sup> continuous infusion over 4 days q4weeks) and antiretroviral therapy were available. Cyclophosphamide dose is lower in comparison to CODOX-M; however doxorubicin 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<sup>2</sup>, **vincristine** 1.6 mg/m<sup>2</sup>, **cyclophosphamide** 748 mg/m<sup>2</sup>, **doxorubicin** 40 mg/m<sup>2</sup> continuous infusion over 4 days, prednisone 60 mg/m<sup>2</sup> 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<sup>2</sup> 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<sup>2</sup> (lower dose than CODOX-M) in the context of CHOP showed a **decrease of cyclophosphamide clearance** from 70 mL/min/m<sup>2</sup> to 41-46 mL/min/m<sup>2</sup> 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.

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### Metabolism of chemotherapy agents

Chemotherapy agent	Metabolism(10, 11)	Possible interaction(10, 11)	Clinical evidence
<b>Vincristine</b>	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)
<b>Doxorubicin</b>	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)
<b>Cyclophosphamide</b>	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)
<b>Cytarabine</b>	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)
<b>Methotrexate</b>	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)

## Antiretroviral-Chemotherapy Interactions: CODOX-M regimen

Please consult [http://hivclinic.ca/main/drugs\\_interact.html](http://hivclinic.ca/main/drugs_interact.html) for more updated information

## 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. 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.
7. Rodrigo JA, Hicks LK, Cheung MC et al. HIV-associated Burkitt lymphoma: good efficacy and tolerance of intensive chemotherapy including CODOX-M/IVAC with or without rituximab in the HAART era. *Adv in Hematol* 2012.
8. 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.
9. 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.
10. 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.
11. Antoniou T, Tseng AL. Interactions between antiretrovirals and antineoplastic drug therapy. *Clin Pharmacokinet*. 2005;44(2):111-45.
12. 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.
13. Sparano JA, Wiernik PH, Hu X, Sarta C, Henry DH, Ratach 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.
14. 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.
15. 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.

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<sup>1</sup>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/emtricitabine (Stribild®); pharmacokinetic enhancer cobicistat (Tybost®).

<sup>2</sup>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)

<sup>3</sup> 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)