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.

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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]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)