

Chemotherapy regimen: CHOP

Agents involved

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|--------------------|--|----------|
| • 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 interactions¹

- 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 interactions²

(*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 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: CHOP Regimen

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/m². 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/m², **vincristine** 1.6 mg/m², **cyclophosphamide** 748 mg/m², **doxorubicin** 40 mg/m² 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. 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/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 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/m²; etoposide 300 mg/m²; cytarabine 8 g/m²) 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).

Antiretroviral-Chemotherapy Interactions: CHOP Regimen

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.

Antiretroviral-Chemotherapy Interactions: CHOP Regimen

References

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14. Fulco PP, Hynicka L, Rackley D. Raltegravir-based HAART regimen in a patient with large B-cell lymphoma. *Ann Pharmacother*. Feb;44(2):377-82.
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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), Tivicay® (dolutegravir); entry inhibitors Fuzeon® (enfuvirtide), Celsentri® (maraviroc)