

Chemotherapy regimen: BEACOPP/escalated BEACOPP

Agents involved

- BEACOPP (escalated)
 - Doxorubicin 25 (35) mg/m² IV Day 1
 - Etoposide 100 (200) mg/m² IV in 500 mL of NS Day 1 – 3
 - Cyclophosphamide 650 (1200) mg/m² IV in 250 (500) mL of NS Day 1
 - Procarbazine 100 mg/m² po qhs Day 1 – 7
 - Prednisone 40 mg po OD Day 1 – 14
 - Vincristine 1.4 mg/m² IV in 50 mL of NS Day 8
 - Bleomycin 10 U/m² 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 interactions¹

- 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 interactions²

(*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 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.

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Antiretroviral-Chemotherapy Interactions: BEACOPP Regimen

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/m²; **doxorubicin** 50 mg/m²; **etoposide** 240 mg/m² continuous infusion over 4 days q4weeks) and antiretroviral therapy were available. Cyclophosphamide and doxorubicin 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/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 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/m² 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/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. (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/m², vinblastine 12 mg/m², **bleomycin** 20 U/m², dacarbazine 740 mg/m² 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/m² 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/m² 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/m² 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.

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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.

Antiretroviral-Chemotherapy Interactions: BEACOPP Regimen

References

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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/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)