Chemotherapy regimen: IVAC

Agents involved

• Etoposide	60 mg/m^2 IV in 500 mL of NS	Days 1 – 5
• Ifosfamide/Mesna	1500/360 mg/m^2 in 500 mL of NS	Days 1 – 5
• Cytarabine	2000 mg/m^2 IV in 250 mL NS q12h	Days 1 – 2
• Methotrexate	12 mg/m^2 IT	Day 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)*

If the patient is on zidovudine, contact the HIV physician to request a change/substitution of antiretroviral agents.

Enzyme inhibition interactions[1]

- Possible increased etoposide toxicity (infections, neutropenia, mucositis) (4, 5) (*Quality of Evidence: moderate)*
- Possible decreased efficacy of ifosfamide due to decreased activation (6, 7) (*Quality of Evidence: very low;* theoretical, unknown clinical significance)

Enzyme induction interactions[2]

(*Quality of Evidence: very low;* theoretical, unknown clinical significance)

- Possible decreased efficacy of etoposide (6, 7)
- Possible increased toxicity of ifosfamide due to increased activation (6, 7)

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.

Particularities regarding nucleoside reverse transcriptase inhibitor backbone

(*Quality of Evidence: very low;* theoretical, unknown clinical significance)

- Potential additive renal toxicity with tenofovir (6, 7)

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.

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^2 IV, doxorubicin 50 mg/m^2 IV, cyclophosphamide 1600 mg/m^2 IV, cytarabine 140 mg IT, methotrexate 6720 mg/m^2 IV or 3000 mg/m^2 per cycle) and IVAC (ifosfamide 7.5 g/m^2; etoposide 300 mg/m^2; cytarabine 8 g/m^2) with or without rituximab 375 mg/m^2 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.(8)

One case report described **good tolerability IVAC** after severe toxicity to CODOX-M. The patient received 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) for the treatment of Burkitt's lymphoma while on a lopinavir/ritonavir based cART. He developed paralytic ileus that lasted 10 days. Two weeks after his recovery, IVAC (ifosfamide 7.5 g/m^2; etoposide 300 mg/m^2; cytarabine 8 g/m^2) 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)

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/m^2; doxorubicin 50 mg/m^2; **etoposide** 240 mg/m^2 continuous infusion over 4 days q4weeks) and antiretroviral therapy were available. Etoposide dose is lower in comparison to IVAC. 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(4). 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(5).

DA-EPOCH

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. Etoposide dose was lower than that used in IVAC however. (10)

Metabolism of chemotherapy agents

Chemotherapy agent	Metabolism(6, 7)	Possible interaction(6, 7)	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) (4, 5). 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)
Ifosfamide	CYP 3A4 to active metabolite, neurotoxic metabolite and detoxification. CYP 2B6 is involved in detoxicification.	Inhibition of CYP 3A4 may inhibit drug activation. Induction of CYP 3A4 may increase activation of ifosfamide but may also produce more potentially neurotoxic metabolites.	No ifosfamide toxicity reported in one case where CODOX-M/IVAC was administered with lopinavir/ritonavir for treatment of Burkitt's lymphoma. (9)
Mesna	Rapidly oxidized in plasma to dimesna and eliminated renally. No hepatic metabolism.(11)	Pharmacokinetic interactions unlikely.	No mesna toxicity reported in one case where CODOX-M/IVAC was administered with lopinavir/ritonavir for treatment of Burkitt's lymphoma. (9)
Cytarabine	Transformation to active metabolite by cytidine deaminase in the liver	Potential additive renal toxicity with other agents such as tenofovir.	No cytarabine toxicity reported in one case where CODOX-M/IVAC was administered with lopinavir/ritonavir for treatment of Burkitt's lymphoma.(9)
Methotrexate	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. (9)

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-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)