

## Chemotherapy regimen: DHAP

### Agents involved

- Dexamethasone 40 mg IV/po in 50 mL of NS Days 1 – 4
- Cisplatin 100 mg/m<sup>2</sup> IV in 1000 mL of NS Day 1
- Cytarabine 2 g/m<sup>2</sup> IV in 250 mL of NS q12h Day 2

### 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 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>

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

- Possible increased dexamethasone toxicity (4, 5)
- Possible decreased efficacy of PIs (4, 5)

#### Enzyme induction interactions<sup>2</sup>

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

- Possible decreased efficacy of dexamethasone (4, 5)
- Possible decreased efficacy of NNRTIs (4, 5)

#### 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 (4, 5)

#### 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: DHAP Regimen

### Literature

No studies or case reports specifically regarding DHAP and antiretroviral agents were found. Data available from other regimens including similar antineoplastic agents are presented below.

### GDP

A retrospective single arm study evaluated the efficacy and safety of GDP (gemcitabine 2000 mg/m<sup>2</sup>, **dexamethasone** 160 mg, **cisplatin** 75 mg/m<sup>2</sup> per cycle) for treatment of relapsed or refractory AIDS-related non-Hodgkin's lymphoma (NHL) when administered with efavirenz/lamivudine/zidovudine. The dose of dexamethasone is identical to that used in the DHAP regimen though the cisplatin dose is slightly lower. A total of 48 patients were included, of whom 21% had complete remission, 33% had partial remission; two-year overall survival was 71%. Regarding toxicity, 13% of patients required **dose reduction or elimination of zidovudine** in the HIV regimen due to leukopenia. Main grade 3/4 toxicities observed were anemia (8%), neutropenia (42%) and thrombocytopenia (58%). A total of 63% of patients had undetectable HIV viral load at the end of chemotherapy. The authors concluded that GDP was an effective salvage regimen with **tolerant toxicity** in patients with relapsed or refractory AIDS-NHL though further studies are warranted. (6)

Of note, low response to antiretroviral therapy is likely explained by previous exposure to efavirenz/lamivudine/zidovudine with a history of poor adherence in 71% of patients and dose reduction or elimination of zidovudine during chemotherapy in 13% of patients. This could contribute to development of HIV resistance and decreased efficacy of antiretroviral agents. Induction of efavirenz metabolism by dexamethasone may also have contributed to decreased antiretroviral efficacy.

### Case reports

A case report showed severe hematological toxicity secondary to cisplatin and gemcitabine when administered with atazanavir, ritonavir, tenofovir, lamivudine for treatment of lung cancer. The patient received one cycle of **cisplatin** 80 mg/m<sup>2</sup> and gemcitabine 2000 mg/m<sup>2</sup> and had grade 3 appetite loss, grade 4 platelet toxicity and neutrophils/granulocytes. Of note, cisplatin dose is slightly lower to that used in the DHAP regimen. In the 3 subsequent cycles, cisplatin and gemcitabine doses were subsequently reduced to 60 and 1600 mg/m<sup>2</sup> respectively for 3 subsequent cycles, all of which were well tolerated. HIV viral load remained undetectable thorough out the course of chemotherapy. The patient had adequate response to therapy and was alive for 17 months at the time of publication. (7)

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

## Metabolism of chemotherapy agents

Chemotherapy agent	Metabolism(4, 5)	Possible interaction (4, 5)	Clinical evidence
<b>Dexamethasone</b>	Substrate and inducer of CYP 3A4.	Increased risk of steroid related toxicity with CYP 3A4 inhibitors. Possible decreased efficacy with CYP 3A4 inducers.  Dexamethasone may decrease levels of PIs and NNRTIs.	Possible decreased efficacy of efavirenz reported in a retrospective study. (6)
<b>Cisplatin</b>	Main route of elimination is renal.	Pharmacokinetic interactions unlikely.  Cisplatin induced nephrotoxicity may necessitate dosage adjustments for certain antiretroviral agents. Potential additive renal toxicity with tenofovir.	Possible increased hematological toxicity of cisplatin in a case report with atazanavir/ritonavir for treatment of lung cancer. (7) No cisplatin toxicity or decreased efficacy reported in a retrospective study with efavirenz. (6)
<b>Cytarabine</b>	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. (8)

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

# Antiretroviral-Chemotherapy Interactions: DHAP Regimen

## References

1. Retrovir. Product monograph. GlaxoSmithKline; 2009[Accessed March, 2011].
2. Combivir. Product Monograph. GlaxoSmithKline; 2007[Accessed March, 2011].
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6. Zhong DT, Shi CM, Chen Q, et al. Study on effectiveness of gemcitabine, dexamethasone, and cisplatin (GDP) for relapsed or refractory AIDS-related non-Hodgkin's lymphoma. Ann Hematol 2012;91:1757-63.
7. Okuma Y, Hosomi Y, Takagi Y et al. Long-term survival following metachronous intratumoral hemorrhage in an HIV-infected patient with lung cancer. Int J Clin Oncol 2010;15:515-8.
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.

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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)