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Successful administration of chemotherapy in HIV-infected patients: importance of cross-disciplinary collaboration

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Background

- Potent antiretroviral (ARV) therapy regimens (usually 2 nucleoside analogues plus a protease inhibitor, non-nucleoside inhibitor or integrase inhibitor) allow for durable suppression of HIV replication, resulting in significant increases in lifespan and reduction in AIDS-related illnesses.[1] In the aging HIV population, the prevalence of age-related comorbidities, including cancer,[2] is therefore now increasing.
- Many ARVs are substrates and potent inhibitors or inducers of the CYP450 and drug transporter systems,and can interact with multiple medications.[3]
- Interactions between ARVs and chemotherapy may lead to significant and possibly fatal chemotherapy toxicity and/or reduced ARV concentrations and HIV treatment failure.[4]
- An understanding of prior ARV treatment history, viral resistance profiles, and pharmacokinetic characteristics of ARVs and chemotherapy are critical to the construction of HIV regimens which may be safely coadministered with planned chemotherapy while ensuring continued HIV viral suppression.

Objectives

- Cases are used to describe therapeutic strategies which allowed co-administration of interacting chemotherapy with ARV regimens.
- In all cases, close collaboration between various disciplines (medicine, oncology, pharmacy, nursing) was required.

Case 1

- A 43 year old male was diagnosed with testicular cancer in 2008 and successfully treated with surgery and radiation. When he experienced a recurrence in 2013, he was also found to be HIV-positive (HIV RNA 5726 copies/mL, CD4 122 cells/mm3). His virus was sensitive to all ARV classes.
- **Planned Chemotherapy**: BEP (bleomycin, etoposide, cisplatin)
- **Potential interactions**:

Antineoplastic Agent	Antiretroviral	Potential Interaction
Etoposide (*CYP3A4 substrate*)	Protease Inhibitors (PIs)/cobicistat (3A4 inhibitors)	possible ↑ toxicity/↓ efficacy
Cisplatin	Tenofovir DF	possible ↑ nephrotoxicity

- **Management**: A protease-inhibitor sparing regimen of tenofovir, emtricitabine and raltegravir was selected to avoid CYP interactions with BEP. Increased monitoring for renal safety was conducted.
- **Outcome**: Successful completion of chemotherapy treatment. His HIV viral load has remained undetectable.

Case 2

- A 51 year old treatment-experienced HIV-positive male (HIV since 2002) on darunavir, ritonavir, etravirine, tenofovir, zidovudine and lamivudine was diagnosed with stage IVa Hodgkin's lymphoma in 2011 (HIV RNA <40 copies/mL, CD4 192 cells/mm3). He was resistant to nucleoside analogues, most PIs, and some nonnucleoside analogues.
- **Planned chemotherapy**: ABVD
- **Potential interactions**:

Antineoplastic Agent	Antiretroviral	Potential Interaction
Vinblastine (*CYP3A4 substrate*)	Darunavir/ritonavir (*3A4 inhibitors*)	↑ Vinblastine concentrations and toxicity
Doxorubicin, vinblastine, dacarbazine	Zidovudine/ lamuvidine	↑ Hematologic toxicity

- **Management**: Zidovudine and lamivudine were replaced with raltegravir, and darunavir/ritonavir was reduced to QD dosing. Vinblastine was omitted for cycles 7 & 8 due to peripheral neuropathy and filgrastim was added due to an episode of febrile neutropenia/pneumonia.
- **Outcome**: Eight 8 cycles of ABVD were completed by November 2011. The patient remains in remission five years post-treatment with an undetectable viral load and CD4 504 cells/mm3.

Case 3

- A 57 year old male treatment experienced HIV-positive male (HIV since 1984) was diagnosed with tonsillar cancer and lung metastases in late 2016. At the time of diagnosis his HIV had been suppressed since 2008 on a regimen of tenofovir, abacavir, darunavir/ritonavir, etravirine and maraviroc and his CD4 was 427 cells/mm3). He was highly resistant to all ARVs except for darunavir, etravirine, rilpivirine, maraviroc and integrase inhibitors.
- **Planned Chemotherapy**: radiation plus cisplatin and paclitaxel
- **Potential interactions**:

Antineoplastic Agent	Antiretroviral	Potential Interaction
Paclitaxel (*CYP3A4 substrate*)	Darunavir/ritonavir (*3A4 inhibitors*)	↑ paclitaxel concentrations and toxicity
Cisplatin	Tenofovir	possible ↑ nephrotoxicity

- **Management**: A novel protease-inhibitor sparing regimen of dolutegravir, rilpivirine and maraviroc was selected to avoid CYP interactions with paclitaxel, and tenofovir was discontinued to avoid additive nephrotoxicity with cisplatin.
- **Outcome**: The patient received one course or radiation therapy. He is tolerating his new ARV regimen and his HIV viral load remains suppressed. Systemic chemotherapy will soon be initiated.

Case 4

- A 57 year old treatment-experienced HIV-positive male (HIV since 1988) on darunavir, ritonavir, etravirine, tenofovir, emtricitabine and raltegravir (HIV RNA<40 copies/mL, CD4 >500) was diagnosed in 2015 with Gleason 4 + 5 prostate cancer with bone metastases and progressed despite bicalutamide and leuprolide. He was highly resistant to all ARVs except for darunavir, etravirine, rilpivirine, and integrase inhibitors.
- **Planned chemotherapy**: Enzalutamide, denosumab, leuprolide
- **Potential interactions**:

Antineoplastic Agent	Antiretrovirals	Potential Interaction
Denosumab, leuprolide *(no transporter/CYP effects known)*	None affected.	Significant interactions not anticipated.
Enzalutamide (*potent inducer of CYP3A4, 2C19, 2C9, UGT)*	Darunavir, ritonavir, etravirine, raltegravir *(3A4 or UGT substrates)*	↓↓ ARV concentrations & efficacy

- **Management**: Antiretroviral therapy was modified to a new combination with non-standard doses: darunavir 600 mg/ritonavir 200 mg BID (*double usual dose*), etravirine 200 mg BID, dolutegravir 50 mg BID (*double usual dose*) and tenofovir/emtricitabine daily.
- Therapeutic drug monitoring (TDM) was performed at baseline, weeks 2, 4, and 8 with monthly HIV viral load testing to ensure adequate ARV concentrations.
- **Outcome**: After 12 months, prostate-specific antigen (PSA) improved from 0.9 to 0.1 ug/L. ARV concentrations were 25-30% lower after enzalutamide initiation vs. baseline, but remained above minimum concentrations and HIV viral load remained undetectable.

Conclusions

- Modification of ARV and/or chemotherapy can allow successful treatment of oncology diagnoses in HIV-infected patients. Close monitoring is recommended, and additional interventions may be required.
- Cross-disciplinary collaboration (family medicine, infectious diseases, oncology, pharmacy, nursing) is critical in ensuring successful outcomes.

References

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Declaration of Interest

- SW has served on advisory boards and spoken at CME events by AbbVie, Bristol-Myers Squibb, Gilead, Merck and ViiV. SW also has career support from OHTN.
- AT has served on advisory boards and spoken at CME events by Gilead, Janssen and Merck.

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