Emerging antiretroviral drug interactions

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With HIV-infected patients living longer and recommendations to initiate antiretrovirals (ARVs) being made earlier, the likelihood for potential drug–drug interactions between ARVs and concurrent medications used to manage co-morbid conditions will increase. In order to maximize the clinical benefit and minimize potential toxicity of ARVs and co-administered medications, it is important for clinicians to recognize significant drug–drug interactions. This article highlights clinically significant drug–drug interactions with antituberculosis agents, antimalarials, anticoagulants, chemotherapeutic agents and pulmonary antihypertensive agents when they are co-administered with newer ARVs (e.g. darunavir, raltegravir, maraviroc and etravirine).

Keywords: antituberculosis, anticoagulants, pulmonary hypertension, chemotherapy, HIV

Introduction

Management of antiretroviral (ARV) drug–drug interactions remains a critical component of HIV care. The US Department of Health and Human Services (DHHS) guidelines now recommend treating HIV-infected patients with CD4 counts less than 500 cells/mm³ and to consider treatment in patients with CD4 counts greater than 500 cells/mm³. This decision was driven by findings from large observational cohort studies showing mortality benefit when treatment is started before CD4 counts drop below 350 cells/mm³. With more patients starting ARVs earlier, the likelihood for potential drug–drug interactions between ARVs and concurrent medications used to manage co-morbid conditions will increase. In order to maximize the clinical benefit and minimize potential toxicity of ARVs and co-administered medications, it is important for clinicians to recognize significant drug–drug interactions. Here we highlight clinically significant drug–drug interaction involving newer ARVs (e.g. darunavir, raltegravir, maraviroc and etravirine) and several classes of drugs now commonly combined with ARVs.

Drug interactions with drugs used to treat tuberculosis and malaria

Tuberculosis remains one of the most common co-morbid conditions affecting HIV-infected patients, especially in sub-Saharan Africa. A randomized study comparing early highly active ARV therapy (HAART) initiation (within 2 months of tuberculosis therapy) versus deferred treatment (starting HAART after completion of antituberculosis agents) found a 55% reduction in mortality in patients treated with HAART within 2 months of starting tuberculosis therapy. Although there is clinical benefit in starting HAART concurrently with tuberculosis therapy, the cytochrome P450 induction properties of rifamycins, especially rifampicin, may lead to significant decreases in concentrations of HIV protease inhibitors (PIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIs).

Rifampicin decreases PI concentrations by as much as 80%, and therefore co-administration is contraindicated. Attempts to overcome rifampicin induction by doubling the dose of some PIs such as lopinavir/ritonavir resulted in significant gastrointestinal intolerance and hepatotoxicity. With lopinavir/ritonavir co-administration, dose-adjusted rifabutin (150 mg once every other day) has been recommended; however, this approach may lead to sub-therapeutic rifabutin concentrations in some patients. Although serum concentrations of dose-adjusted rifabutin when co-administered with darunavir/ritonavir appear adequate, monitoring of rifabutin concentrations should be considered in patients with a high body mass index (BMI) and in patients with advanced tuberculosis to prevent rifamycin resistance. Rifampicin decreases the maraviroc area under the concentration–time curve (AUC) by 78%; although the maraviroc dose could be increased to 600 mg twice daily to overcome this interaction, there are no clinical data, and this combination should be avoided if possible. Rifabutin, a less potent CYP3A4 inducer, is likely to cause only modest decreases in maraviroc concentrations.

Rifampicin induction of glucuronidation results in raltegravir AUC and trough decreases of 40% and 61%, respectively. Doubling the dose of raltegravir increases the AUC, but trough concentrations are still decreased. Since there is no clinical correlation between raltegravir trough concentrations and virological outcome, the clinical significance of this interaction is not known. More clinical data are needed before raltegravir can be recommended with rifampicin. Rifabutin does not significantly interact with raltegravir and is preferred over rifampicin in HIV tuberculosis co-infected patients.
Malaria and HIV co-infections are prevalent in many resource-limited countries. Since many antimalarial drugs are metabolized by cytochrome P450 isoenzymes, there are potential drug–drug interactions with PIs and NNRTIs. Clinical data with ARVs and antimalarial drugs are limited to several small pharmacokinetic studies. Mefloquine, lumefantrine and artemisinin derivatives are CYP3A4 substrates, therefore serum concentrations are expected to increase with darunavir/ritonavir and decrease with etravirine co-administration. However, co-administration of mefloquine with ritonavir did not significantly affect mefloquine serum concentrations.8 This finding suggests the important role of other mefloquine metabolic pathways in vivo and/or ritonavir mixed CYP3A4 inhibitory and induction properties. On the other hand, the lumefantrine AUC was increased by 193% with lopinavir/ritonavir co-administration.8 Although there were concerns for QTc prolongation with high lumefantrine concentrations, the risk is low in patients without underlying cardiovascular risk factors.9 Significant drug–drug interactions between antimalarial drugs and maraviroc or raltegravir are unlikely due to the lack of significant inhibition or induction of drug metabolizing enzymes or drug transport proteins. Additional pharmacokinetic and clinical data are needed to guide dosing recommendations when antimalarial drugs are co-administered with ARVs.

Interactions with anticoagulants

An older HIV-infected population and more patients with thrombotic events means a greater need for anticoagulation. Warfarin exists in a racemic mixture of two isomers that differ in potency and route of metabolism. S-warfarin is 2 to 5 times more potent than R-warfarin. Although the more potent S-isomer is a CYP2C9 substrate, the R-isomer is metabolized via CYP1A2 and CYP3A4.10,11 Although the majority of significant warfarin drug interactions have been attributed to inhibition or induction of CYP2C9, affecting CYP1A2 and CYP3A4 can also lead to significant changes in warfarin concentrations. Several case reports of significant drug–drug interactions between PIs, NNRTIs and warfarin have been described. Increased warfarin requirements have been reported with nevirapine and lopinavir/ritonavir co-administration.12 Since ritonavir is a mixed CYP3A4 inhibitor and inducer and a mild CYP2C9 inhibitor, single-dose co-administration may result in supra-therapeutic international normalized ratio (INR). However, at steady state, sub-therapeutic warfarin concentrations as a result of CYP3A4 enzyme induction may occur.13–15 It is important to note that these reports used higher than currently recommended doses of ritonavir. Darunavir/ritonavir (600/100 mg twice daily) also decreases the mean S-warfarin AUC by 29%.16 Although both efavirenz and etravirine inhibit CYP2C9 and 2C19 in vitro, at steady state efavirenz mainly induces CYP2C9 and CYP2C19 substrates (e.g. voriconazole) in humans.17 This may lead to an increase in warfarin requirements. On the other hand, etravirine is a mild inhibitor of CYP2C9 in vivo.18 Although S-warfarin concentrations are not significantly increased with etravirine co-administration, the ratio of S-warfarin parent drug to 7-OH-S-warfarin metabolites increased by 82%.18 The clinical significance of this interaction remains to be determined.

Significant interactions with warfarin are unlikely to occur with raltegravir and maraviroc since they do not affect CYP2C9, 1A2 or 3A4. Due to the mixed cytochrome P450 enzyme induction and inhibition properties of PIs and NNRTIs, predictions of warfarin requirements are difficult. Close INR monitoring should be performed when initiating warfarin in patients on PI- and NNRTI-based regimens and when a PI or NNRTI are discontinued in patients on a stable warfarin dose.

Omeprazole, a CYP2C19 inhibitor, decreases the antiplatelet activity of clopidogrel by inhibiting the biotransformation of the clopidogrel prodrug into its active metabolite.19 In patients who have been hospitalized for acute coronary syndrome, this interaction is associated with a 27% increased risk of death or rehospitalization.20 By analogy, inhibition of CYP2C19 by etravirine may also inhibit clopidogrel antiplatelet activity. Until more data become available, the co-administration of CYP2C19 inhibitors (e.g. etravirine and azoles) and clopidogrel is not recommended.21

Interactions with chemotherapeutic agents

With effective HAART, the incidence of non-Hodgkin’s lymphoma (NHL) and Kaposi’s sarcoma has significantly declined; however, AIDS patients remain at increased risk for other cancers, including Hodgkin’s lymphoma.22 Before the availability of HAART, response to chemotherapy and prognosis of NHL were poor. A retrospective study comparing survival rates between patients diagnosed with NHL pre-HAART (1988–1996) and post-HAART (after 1996) found a 47% improvement in lymphoma-free survival in patients treated with chemotherapy plus HAART.23 Similarly, a multi-cohort European study identified 1176 patients with NHL and found a 1 year survival rate of 66% for systemic NHL in the HAART era.24 For Hodgkin’s lymphoma, the combination of chemotheraphy plus HAART produced a significantly better 2 year overall survival compared with patients not receiving HAART (74% versus 30%, P < 0.001).25

Since many chemotherapeutic agents are CYP3A4 substrates, there is a potential for drug–drug interactions with HIV PIs and NNRTIs. One retrospective study found a higher incidence of anaemia, leucopenia and peripheral neuropathy in patients treated with cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP) plus PI-based HAART.26 An observational study evaluated 65 patients with intermediate- to high-grade HIV-associated NHL treated with full-dose CHOP or modified CHOP (half-dose cyclophosphamide and doxorubicin, combined with full-dose vincristine and prednisone); although cyclophosphamide clearance was decreased by 50%, no significant difference in toxicity between the two regimens was observed. However, complete response was 30% versus 48% in the modified CHOP and full-dose CHOP, respectively.27 The German AIDS-related Lymphoma Study Group investigated PI-based HAART administered concomitantly with CHOP in 72 patients who were stratified into standard- and high-risk groups. The high-risk group was defined as having two or three of the following criteria: CD4 <50 cells/mm³, WHO performance status ≥3 and/or previous AIDS-defining opportunistic infections. Complete remission was achieved in 79% of patients in the standard-risk group and 29% of patients in the high-risk group. It is encouraging to
see that the standard-risk patients median survival rates were comparable to those achieved in non-HIV-infected patients with lymphoma.28

Atazanavir and indinavir are also potent inhibitors of glucuronidation as well as CYP3A4 metabolism. This may result in significant elevation of irinotecan concentrations and increase the risk of severe neutropenia. Conversely, CYP3A4 enzyme inducers such as NNRTIs (e.g. efavirenz, nevirapine and etravirine) can potentially decrease concentrations of chemotherapeutic agents that are 3A4 substrates (e.g. doxorubicin, cyclophosphamide and vincristine) and potentially decrease chemotherapy efficacy. A list of potential drug–drug interactions between ARVs and chemotherapy is provided in Table 1.

Clinicians are frequently faced with a clinical dilemma of switching to an alternative HAART regimen or stopping HAART during chemotherapy cycles. Based on improved survival rates associated with continuing HAART in combination with chemotherapy, stopping HAART is generally not recommended. Since raltegravir and maraviroc are not inhibitors or inducers of cytochrome P450, they are unlikely to interact with chemotherapeutic agents. If the ARV regimen contains zidovudine, prevention of additive bone marrow suppression by switching to an alternative nucleoside reverse transcriptase inhibitor (NRTI) is recommended. Guidelines on empirical dose adjustment of chemotherapy when co-administered with interacting ARVs need to be developed. Close monitoring for potential reduced chemotherapy efficacy or increased toxicity when NNRTIs (e.g. efavirenz, nevirapine and etravirine) and PIs (e.g. darunavir, atazanavir, lopinavir and ritonavir) are co-administered is critical.

### Table 1. Potential drug–drug interactions with chemotherapeutic agents

<table>
<thead>
<tr>
<th>Chemotherapy</th>
<th>Route of metabolism</th>
<th>Management recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alkylating agents (e.g. cyclophosphamide)</td>
<td>CYP2B6, CYP2C9, CYP2C19 and CYP3A4/5</td>
<td>♤ cyclophosphamide AUC by 50%; ♤ myelosuppression, nausea/vomiting, arrhythmia and haemorrhagic cystitis; co-administer with close monitoring</td>
</tr>
<tr>
<td>Anthracyclines (e.g. doxorubicin)</td>
<td>CYP3A4, CYP2D6</td>
<td>♤ myelosuppression; no significant change in doxorubicin AUC with PI co-administration; co-administer with close monitoring</td>
</tr>
<tr>
<td>Vinca alkaloids (e.g. vincristine)</td>
<td>CYP3A4</td>
<td>♤ vincristine concentration and ♤ autonomic/peripheral neuropathy and myelosuppression; co-administer with close monitoring</td>
</tr>
<tr>
<td>Glucocorticoids (e.g. prednisone and dexamethasone)</td>
<td>CYP3A4</td>
<td>♤ prednisone and dexamethasone serum concentrations; dexamethasone may also decrease PI and NNRTI concentrations; glucocorticoid dose may need to be decreased</td>
</tr>
<tr>
<td>Podophyllotoxins (e.g. etoposide and teniposide)</td>
<td>CYP3A4, CYP2E1 and CYP1A2</td>
<td>♤ etoposide concentration and ♤ mucositis, myelosuppression and transaminitis; co-administer with close monitoring</td>
</tr>
<tr>
<td>Camptothecins (e.g. irinotecan)</td>
<td>CYP3A4 and UGT1A1</td>
<td>♤ myelosuppression; contraindicated with atazanavir (and potentially indinavir); use with caution with other PIs</td>
</tr>
<tr>
<td>Taxanes (paclitaxel and docetaxel)</td>
<td>CYP2C8 and CYP3A4</td>
<td>♤ taxane concentration and ♤ myelosuppression and peripheral neuropathy; case reports of severe toxicity with lopinavir/ritonavir co-administration; clinical trial supports low-dose paclitaxel with PI co-administration;35 co-administer with close monitoring</td>
</tr>
<tr>
<td>Antimetabolites (e.g. methotrexate, floxuridine, capecitabine and cytarabine), cisplatin, mitomycin and rituximab</td>
<td>independent of CYP3A4 oxidation</td>
<td>Drug–drug interactions with PIs and NNRTIs unlikely; use standard doses</td>
</tr>
</tbody>
</table>

### Interactions with agents for pulmonary hypertension

Pulmonary hypertension may be associated with HIV infection. In a case series, 8.1% of patients presenting with cardiopulmonary complaints were diagnosed with primary pulmonary hypertension.29 In a retrospective analysis, treated patients with both HIV and pulmonary hypertension had favourable survival rates, with an overall survival of 88% at 1 year and 72% at 3 years.30 Drug interactions with agents used to treat pulmonary hypertension are possible (Table 2).

The co-administration of bosentan (a CYP3A4 substrate) and lopinavir/ritonavir resulted in a 48-fold increase in bosentan serum concentrations on day 4, but a 5-fold increase at steady state on day 10. Therefore co-administration is only recommended when lopinavir/ritonavir has reached steady state. In patients who have been treated with lopinavir/ritonavir for more than 10 days, low-dose bosentan (62.5 mg once daily or every other day) can be co-administered. In patients on bosentan who need to be started on lopinavir/ritonavir, discontinuation of bosentan for at least 36 h prior to initiating lopinavir/ritonavir, then reinstituting low-dose bosentan after lopinavir/ritonavir has reached steady state (10 days) is recommended.1 Although there are no data with other PIs, a similar dosing approach should be considered, with close monitoring. In order to prevent rebound pulmonary hypertension, an alternative agent should be given during the transition period. With the proper dose adjustment, bosentan co-administration with HAART resulted in symptomatic improvements (e.g. better 6 min walk distance), decreased pulmonary vascular resistance and favourable overall survival.31
Ambrisentan, an alternative endothelin-1 receptor antagonist, is metabolized by CYP3A, CYP2C19 and glucuronosyltransferases. There is a 35% increase in ambrisentan AUC with co-administration of ketoconazole, a moderate inhibitor of CYP3A4. Since there is only a modest increase in ambrisentan concentrations when co-administered with CYP3A4 inhibitors, co-administration with PI-based HAART can be considered with close monitoring in patients unable to tolerate bosentan.

PIs increase sildenafil serum concentrations by up to 11-fold. Although low-dose sildenafil (25 mg every 48 h) can be co-administered with PI for the treatment of erectile dysfunction, high-dose sildenafil is not recommended. With PI co-administration due to an increased risk of severe hypotension. For the treatment of pulmonary hypertension in patients on PI s, clinicians can consider reducing the dose of sildenafil to 10 mg/day with slow titration. In severe pulmonary hypertension, epoprostenol should be considered. Epoprostenol is hydrolysed non-enzymatically in plasma to 6-keto-prostaglandin F-1 alpha, with low potential for drug–drug interactions. The standard epoprostenol dose can be given with PIs and NNRTIs.

Conclusions

The management of HIV infection continues to evolve and drug–drug interactions are becoming increasingly complex. Although drug interaction databases (e.g., www.hopkins-hivguide.org and www.clinicalcareoptions) are available to assist clinicians with the management of these interactions, clinicians should also recognize drugs with the highest potential for interactions. Close monitoring is critical when potent CYP3A4 inducers (e.g., rifampicin and most NNRTIs) or potent inhibitors (e.g., PIs and azole antifungals) are added or removed from a medical regimen. As HIV-infected patients grow older, drug interactions arising from the management of other health problems will be more common in the future.

Transparency declarations

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References


Table 2. Drug–drug interactions with agents for pulmonary hypertension

<table>
<thead>
<tr>
<th>Agents for pulmonary hypertension</th>
<th>Route of metabolism</th>
<th>Management recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bosentan</td>
<td>CYP3A4 and CYP2C9</td>
<td>significant increase in bosentan concentrations with LPV/r co-administration; co-administer bosentan at a reduced dose (62.5 mg once daily or every other day) only when LPV/r has reached steady state; LPV pharmacokinetics not significantly affected; use standard LPV/r dose</td>
</tr>
<tr>
<td>Ambrisentan</td>
<td>CYP3A, CYP2C19 and glucuronosyltransferases</td>
<td>ambrisentan concentrations may be increased; with PI co-administration, initiate low-dose ambrisentan and titrate slowly</td>
</tr>
<tr>
<td>Sildenafil</td>
<td>CYP3A4</td>
<td>sildenafil AUC increased 11-fold with ritonavir-boosted PI; high-dose sildenafil is not recommended with PIs; with PI co-administration, consider sildenafil 10 mg/day with slow titration</td>
</tr>
<tr>
<td>Epoprostenol</td>
<td>non-enzymatic hydrolysis</td>
<td>drug–drug interactions unlikely with PIs and NNRTIs; use standard doses</td>
</tr>
</tbody>
</table>

LPV/r, lopinavir/ritonavir.
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