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Important Drug-Drug Interactions in HIV-Infected Persons on Antiretroviral Therapy: An Update on New Interactions Between HIV and Non-HIV Drugs

Alice Tseng · Michelle Foisy

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Abstract Advances in antiretroviral therapy have turned HIV into a chronic, manageable disease. Patients often require treatment for co-morbid conditions as well as HIV, and consequently, pharmacokinetic interactions between antiretrovirals (ARVs) and other drug classes are an increasing concern. Protease inhibitors and non-nucleoside reverse transcriptase inhibitors are involved in the CYP450 or other transporter systems, and may be associated with higher risk of clinically significant drug interactions. One reverse transcriptase inhibitor, abacavir, has demonstrated weak inhibition of CYP3A4, 2D6 and 2C9 in vitro, but is not associated with any clinically significant interactions involving the CYP450 system. The integrase inhibitor raltegravir is not involved in the CYP450 system, and may be a suitable option to use when trying to minimize interactions with other drug classes. This review summarizes recently published data on clinically significant drug interactions between ARVs and other drug classes including antineoplastics, immunosuppressant transplant drugs, directly acting antivirals for hepatitis C, antifungals, antimalarials, corticosteroids, psychotropics, hormonal contraceptives, anticoagulants, drugs for pulmonary hypertension, and herbal products. In situations of suspected or potential interactions, close monitoring is warranted, and dose adjustments or substitutions may be required.

Keywords Antiretrovirals · Drug interactions · Antineoplastics · Immunosuppressants · Boceprevir · Telaprevir · Voriconazole · Posaconazole · Anti-malarial agents · Corticosteroids · Quetiapine · Olanzapine · Oxycodone · Buprenorphine · Hormonal contraceptives · Anticoagulants · Bosentan · Sildenafil · Pulmonary arterial hypertension · *Echinacea purpurea*

A. Tseng (✉)
Toronto General Hospital,
585 University Avenue, 13N-1314,
Toronto, ON M5G 2N2, Canada
e-mail: alice.tseng@uhn.ca

M. Foisy
Northern Alberta HIV Program,
Faculty of Pharmacy and Pharmaceutical Sciences,
Edmonton Clinic Health Academy,
11405 - 87 Ave NW,
Edmonton, AB T6G 1C9, Canada
e-mail: mfoisy@pharmacy.ualberta.ca

Introduction

In the past decade, there have been numerous advances in HIV therapy, and the impact of combination antiretroviral therapy (cART) on reducing HIV-related morbidity and mortality is well-established. For adherent patients with undetectable viral loads, HIV has become a chronic manageable disease in an aging and genetically diverse population. Although the need for primary or secondary prophylaxis of opportunistic infections has declined due to potent cART, [1], many patients require treatment for other concomitant conditions such as cardiovascular disease, hyperlipidemia, hypertension, diabetes, gastrointestinal conditions, osteoporosis or renal disease which may be manifestations of long-term drug toxicity, increasing age, or the virus itself [2]. Furthermore, treatment may be required for other indications including hepatitis co-infection, psychiatric illness, substance use, oncology diagnoses, or solid-organ transplantation. Finally, patients may also be taking vitamins, food supplements, complementary/alternative medicine (CAM), or recreational agents on a regular or occasional basis. Therefore, there is a high potential for

drug interactions in this population, since protease inhibitors (PIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIs) are both substrates and inhibitors or inducers of CYP450 hepatic enzymes and drug transporters. Clinically significant drug interactions have been reported in 27%–40% of HIV patients on cART, with PI use, number of concomitant medications, current illicit drug use and hepatitis C co-infection identified as independent risk factors [3, 4]. The integrase inhibitor raltegravir is not involved in the CYP450 system, and may be a suitable option to use when trying to minimize interactions with other drug classes. In contrast, it should be noted that the investigational integrase inhibitor, elvitegravir, which is in late stage development, is a CYP3A4 substrate and requires boosting with an inhibitor to achieve therapeutic concentrations.

Negative consequences of drug interactions include viral breakthrough and development of resistance, sub-optimal disease/symptom management, or drug toxicity and possible non-adherence [4]. This review summarizes recently published data on clinically significant drug interactions between antiretrovirals (ARVs) and other drug classes including antineoplastic agents, immunosuppressant transplant drugs, directly acting antivirals for hepatitis C infection, oral antifungals, anti-malarial agents, corticosteroids, psychotropic drugs, hormonal contraceptives, anticoagulants, drugs for pulmonary hypertension, and herbal products.

Antineoplastic Agents

Avoiding and managing potential interactions between ARVs and antineoplastic agents is an increasingly important challenge. Patients who receive concomitant cancer chemotherapy and cART may achieve better response rates and higher rates of survival than patients who receive antineoplastic therapy alone, but may be at increased risk of pharmacokinetic or pharmacodynamic drug interactions. Such drug interactions may be associated with increased toxicity and/or decreased efficacy of treatment regimens for either disease state, possibly leading to clinically detrimental or devastating consequences. Readers are referred to comprehensive reviews on this topic [5•, 6]. Recent case reports and study findings highlight the nature and significance of interactions between antineoplastics and antiretroviral therapy. New data on vinblastine, docetaxel, paclitaxel, bexarotene, and CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) in the context of concomitant cART use will be reviewed.

In a retrospective review of 16 HIV-positive patients on cART (n=5 on boosted PI, 2 on unboosted PI, 8 on NNRTI, 1 on raltegravir) who received vinblastine (a CYP3A4 substrate)-based regimens for Hodgkin's lymphoma, PI use was independently associated with WHO grade III–IV neutropenia (OR 34.3, 95% CI 1.9–602.4; P=0.02) after controlling for CD4 counts less than 200 cells/mm3, zidovudine use and bone marrow involvement. An inverse correlation between ritonavir dose and mean nadir neutrophil count was found [7]. Another report noted the development of severe vinblastine-associated neurotoxicity in 3 patients during treatment with ABVD for Hodgkin's lymphoma while on concomitant lopinavir/ritonavir-based cART. Two cases were characterized by early-onset autonomic neuropathy with severe medical ileus requiring hospitalization, and the last patient developed late-onset but severe and painful peripheral neuropathy [8].

In a report of 3 HIV-positive patients on ritonavir-containing regimens (2 on atazanavir/ritonavir, 1 on lopinavir/ritonavir), administration of IV docetaxel resulted in severe hematological and cutaneous toxicity 3–7 days after the first infusion of docetaxel (70–100 mg/m^2), despite having normal baseline liver function and blood cell counts. Each patient recovered following the withdrawal of docetaxel. The mechanism was postulated to be CYP3A4 inhibition of docetaxel metabolism by ritonavir [9].

In 34 HIV-positive patients with advanced KS who received paclitaxel 100 mg/m^2, paclitaxel exposure was higher in patients taking PIs (primarily indinavir, nelfinavir, or a combination) compared to those who were not taking PIs. The increased exposure did not correlate with efficacy or toxicity. Of the 20 patients assessable for response, 6 (30%) had an objective response and median progression-free survival was 7.8 months (95% confidence interval, 5.6–21.0 months) [10]. These findings contrast to earlier reports of life-threatening paclitaxel toxicity in patients receiving concomitant indinavir/ritonavir or lopinavir/ritonavir [11]. The discrepancy in observations may be due to inclusion of ritonavir in the earlier cases, as ritonavir exhibits more potent CYP3A inhibiting effects as compared to indinavir or nelfinavir. In the study by Cianfrocca et al., while paclitaxel area under the curve (AUC) was significantly higher in the patients taking PIs compared to the patients not taking PIs, there was no difference in the duration spent at a paclitaxel concentration above 0.05 uM between the two groups, suggesting that unboosted PIs may have less pronounced and/or sustained effects on paclitaxel metabolism.

A negative, two-way interaction between bexarotene, a synthetic retinoid analogue and efavirenz, both substrates and inducers of CYP3A4, was illustrated in a recent case report. A 70-year old man, virologically suppressed for 12 years, experienced virological failure on efavirenz, 3TC and abacavir 2 months after starting bexarotene 300 mg daily for a neoplastic disorder. Coinciding with the viral breakthrough, subtherapeutic efavirenz concentrations were measured on two occasions (595 and 508 ng/mL compared to 1,478 ng/mL prior to the initiation of bexarotene); his efavirenz concentration returned to 1,354 ng/mL after his efavirenz dose was doubled. The patient's average bexarotene plasma concentrations were

approximately 50% lower compared to steady-state reference pharmacokinetic data, and only partial efficacy on his neoplastic lesions was observed [12]. The authors concluded that if concomitant therapy with efavirenz and bexarotene is required, therapeutic drug monitoring (TDM) of both drugs should be performed, with close monitoring for both antiviral and antineoplastic efficacy and response.

Because of the risk of potential negative interactions, clinicians may wish to consider using ARVs that do not impact the CYP450 system if possible. For instance, the successful use of a raltegravir-based regimen with concomitant chemotherapy has been reported. A 55 year old male with newly diagnosed advanced HIV and large B-cell lymphoma simultaneously began abacavir, lamivudine and raltegravir and CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) with intrathecal methotrexate. The patient achieved and maintained an undetectable viral load throughout 6 CHOP cycles. Two months after the patient completed chemotherapy, a positron emission tomography scan indicated no active lymphoma [13].

Transplant Drugs

The number of HIV-infected patients receiving solid-organ transplantation is increasing. One major challenge is the potential for significant interactions between immunosuppressive drugs and ritonavir-boosted PIs or NNRTIs. Cyclosporine, tacrolimus and sirolimus are CYP3A4 substrates and inhibitors of p-glycoprotein, while mycophenolic acid (MPA), the active metabolite of mycophenolate mofetil, is a substrate of glucuronyl transferase. Careful dose adjustments along with close monitoring of plasma immunosuppressant concentrations are often required with concomitant PI therapy. The use of raltegravir-based regimens may allow concomitant immunosuppressant treatment without dosing alterations. These points are illustrated in the literature described below.

A retrospective analysis of 5 HIV-positive patients receiving tacrolimus (4 for liver transplantation and 1 for Crohn's disease) with various cART regimens was conducted. Three liver transplant patients were on ritonavir-boosted PI therapy (1 on saquinavir 1,000 mg twice daily plus lopinavir 400/ritonavir 100 mg twice daily, 1 on fosamprenavir 700/100 mg twice daily, 1 on darunavir 600/ritonavir 100 mg twice daily), and received tacrolimus doses of 0.06, 0.03, and 0.08 mg daily, with median tacrolimus concentrations of 6.6, 3.0 and 7.9 ng/mL, respectively. Two other patients began raltegravir-based cART while on tacrolimus 1 or 2 mg twice daily; no tacrolimus dose adjustment was needed and tacrolimus plasma concentrations were not altered [14].

A case report describes a 53-year old HIV-positive, black male who received a renal transplant and was placed on mycophenolate mofetil and tacrolimus along with concomitant unboosted atazanavir, abacavir and lamivudine. The patient initially received tacrolimus 0.5 mg on day 2 post-transplant; however serum tacrolimus concentrations became subtherapeutic by 6 h. Therefore tacrolimus dosing was changed to 1 mg every 8 h, and subsequently to 1.5 mg every 12 h to maintain therapeutic concentrations and optimize patient convenience [15].

In a case series of 11 HIV-positive solid organ transplant (10 liver, 1 renal) patients who received raltegravir-based therapy (plus enfuvirtide, $n=2$) and tacrolimus (91%), the median CD4 increased to 380 cells/mm3 and VL remained suppressed to <50 copies/mL after a median follow-up of 57 weeks. No patients discontinued raltegravir, and no toxicity or interactions with tacrolimus were noted [16].

In a separate series, the pharmacokinetics of raltegravir 400 mg twice daily and mycophenolic acid were prospectively determined in 6 HIV-infected solid-organ transplant recipients. Raltegravir kinetics were not significantly different from historical controls, and MPA metabolism was not significantly altered by raltegravir [17].

Directly Acting Antivirals for Hepatitis C

HIV and hepatitis C (HCV) share common routes of transmission, and co-infection is common. Management of co-infected patients may involve multiple agents that have possible interactions and significant adverse effects related to each disease treatment. Two directly acting antivirals (DAAs), boceprevir and telaprevir, have recently been licensed in the United States for the treatment of genotype 1 chronic HCV, in combination with peg-interferon alfa and ribavirin. These NS3/4A PIs are substrates and inhibitors of CYP3A4 and p-glycoprotein; [18–20] thus, the possibility for interactions exists between these agents and ARVs including PIs, NNRTIs and maraviroc [21]. Initial in vitro and in vivo studies showed that the metabolism of telaprevir and boceprevir was substantially inhibited in the presence of low concentrations of ritonavir and a human pharmacokinetic model of telaprevir co-administered with low-dose ritonavir suggested that improved efficacy and/or dosing convenience may be feasible by pharmacokinetic enhancement with ritonavir [22]. The concept of using ritonavir as a boosting agent to improve pharmacokinetics, dosing frequency and convenience is already well established within HIV, most notably for PIs as well as emerging agents such as elvitegravir, an investigational integrase inhibitor. Applying this strategy to newly available DAAs is also very appealing, since both boceprevir and telaprevir need to be administered three times daily with food, totaling 6–12 pills per day. However, recent studies suggest that combining telaprevir or boceprevir with HIV PIs may be associated with complex and unexpected interactions.

Coadministration of boceprevir and efavirenz in healthy volunteers resulted in a 44% decrease in boceprevir trough concentrations and a 19% reduction in overall boceprevir exposures, while efavirenz AUC was increased 20%, compared to either drug administered alone [19]. As such, the product monograph recommends that this combination be avoided [23].

The potential impact of low-dose ritonavir on boceprevir kinetics was studied in 16 healthy subjects who received boceprevir 400 mg three times daily for 5 days, followed by randomization to either boceprevir 400 mg three times daily plus ritonavir 100 mg daily, or boceprevir 400 mg twice daily plus ritonavir 100 mg twice daily, each for 10 days. Coadministration of ritonavir 100 mg daily plus boceprevir three times daily resulted in a 19% decrease in boceprevir AUC and a 27% decrease in boceprevir Cmax, while the combination of ritonavir 100 mg twice daily plus boceprevir twice daily resulted in decreases in both boceprevir AUC and Cmax (18% and 34%, respectively) [19]. These results indicate that ritonavir has minimal effects on steady-state boceprevir exposure. While boceprevir undergoes oxidative metabolism via CYP3A4/5, metabolism through aldo-ketoreductases also plays an important role in drug disposition [18]. Thus, it is hypothesized that in the presence of ritonavir, metabolism primarily shifts to the aldo-ketoreductase pathway. While this characteristic may be advantageous for reducing the potential for significant interactions with agents affecting the CYP450 system, it appears that ritonavir-boosting to simplify boceprevir dosing is not feasible.

Three separate open-label, randomized, cross-over trials were conducted in HIV and HCV-negative volunteers to investigate pharmacokinetic interactions between telaprevir and ARVs [24]. In 2 studies, subjects received telaprevir 750 mg every 8 h for 10 days, followed by a washout and either atazanavir/ritonavir 300/100 mg once daily, darunavir/ritonavir 600/100 mg twice daily, fosamprenavir/ritonavir 700/100 mg twice daily, or lopinavir/ritonavir 400/100 mg twice daily (n=20 each) for 20 days with co-administration of telaprevir 750 mg every 8 h from day 11 onwards, or vice versa. All compounds were taken with food. Two-way interactions were observed between telaprevir and ritonavir-boosted PIs, with reductions in telaprevir exposures and variable effects on PI kinetics.

When telaprevir was coadministered with atazanavir/ritonavir, decreases in telaprevir AUC and Cmin (20% and 15%, respectively), were observed, while atazanavir AUC increased 17% and Cmin increased 85%. This combination is being evaluated in an ongoing study in HIV/HCV co-infected individuals [24]. More significant dual-negative drug interactions were noted between telaprevir and the remaining boosted PI combinations. With the coadministration of darunavir/ritonavir, telaprevir AUC decreased 35% and Cmin decreased 32%, while darunavir AUC decreased 40% and Cmin decreased 42%. When combined with fosamprenavir/ritonavir, telaprevir AUC and Cmin decreased by 32% and 30% respectively, and amprenavir AUC and Cmin were reduced by 47% and 56%, respectively. Finally, when telaprevir was coadministered with lopinavir/ritonavir, telaprevir AUC and Cmin were reduced by 54% and 52%, respectively, while lopinavir exposure was not significantly altered. The mechanism for these interactions has not yet been identified, but may include decreased bioavailability and/or effects on protein binding. Therefore, the manufacturer recommends that telaprevir should not be coadministered with ritonavir-boosted darunavir, fosamprenavir, or lopinavir [20].

In the final study in this series, 20 volunteers started telaprevir 750 mg every 8 h for 7 days followed by efavirenz and tenofovir at standard doses for 7 days after a washout. Subsequently, volunteers received either telaprevir 1,125 mg every 8 h plus efavirenz and tenofovir or telaprevir 1,500 mg every 12 h plus efavirenz and tenofovir for 7 days. Telaprevir was taken with food while efavirenz and tenofovir were taken on an empty stomach in the morning. With the combination of telaprevir 1,500 mg every 12 h plus efavirenz and tenofovir, telaprevir AUC and Cmin decreased by 20% and 48%, respectively, efavirenz AUC and Cmin decreased by 15% and 11%, respectively, and tenofovir AUC and Cmin increased by 10% and 6%, respectively. When telaprevir was dosed at 1,125 mg every 8 h with efavirenz and tenofovir, smaller reductions in telaprevir exposures were observed (AUC decreased 18% and Cmin decreased 25%). This higher dose of telaprevir may partly offset the interaction with efavirenz, and is being evaluated in an ongoing study in HIV/HCV co-infected individuals [24].

In a separate study, HIV-negative subjects received telaprevir 750 mg every 8 h alone, or 250 mg or 750 mg twice daily with ritonavir 100 mg twice daily. Doses were given with food for 14 days. Ritonavir did not exert a significant boosting effect on telaprevir exposures: when compared with telaprevir 750 mg every 8 h given alone (Group C), telaprevir pharmacokinetic parameters on Day 14 were 59%–75% lower when telaprevir 250 mg every 12 h was co-administered with ritonavir 100 mg every 12 h (Group A) and 15%–32% lower when telaprevir 750 mg every 12 h was co-administered with ritonavir 100 mg every 12 h (Group B). Of note, ritonavir exposures were higher when co-administered with telaprevir 750 mg every 12 h (Group B), compared with 250 every 12 h (Group A), suggesting that CYP3A inhibition by telaprevir was dose-dependent [25].

These studies illustrate the complexity of treating HIV and HCV co-infection. Further research is needed in this area in order to identify optimal combinations of agents in

patients with co-infection. A summary of potential and demonstrated pharmacokinetic interactions between ARVs and DAAs is included in Table 1.

Oral Antifungals

Two recent publications involving voriconazole and posaconazole interactions are noteworthy. For a more comprehensive summary on interactions between antifungals and ARVs, readers are referred to a recent review [26•].

Voriconazole is a substrate and inhibitor of CYP2C19, CYP3A4 and CYP2C9, and is subject to variable pharmacokinetics due to CYP2C19 genetic polymorphism [27, 28]. Thus, the interaction between voriconazole and ARVs, such as ritonavir and efavirenz, is complex and has been previously reviewed in detail [29]. A case report describing a three-way interaction between voriconazole, etravirine and darunavir/ritonavir further highlights the complexity of this interaction.

A 54 year old Caucasian male received darunavir 900/100 mg daily (a dose slightly higher than the currently

Table 1 Drug interactions between antiretrovirals and hepatitis C protease inhibitors

	Boceprevir (Victrelis®, BOC, SCH 503034) Merck	Telaprevir (Incivek®, TVR, VX-950) Vertex Pharmaceuticals
Adult dose	800 mg orally every 8 h with food (supplied as 200 mg capsules)	750 mg orally every 8 h with food (supplied as 375 mg tablets)
Kinetic characteristics	Boceprevir undergoes biotransformation by CYP3A4, CYP3A5 and aldoketoreductases [18]. Boceprevir appears to be a strong, reversible inhibitor of CYP3A4 and p-glycoprotein [19].	Substrate and inhibitor of CYP3A4 and p-glycoprotein [20].
Interactions:		
Atazanavir/ ritonavir		Telaprevir AUC ↓ 20% and Cmin ↓ 15%, while atazanavir AUC ↑ 17% and Cmin ↑ 85% with coadministration. Telaprevir 750 mg every 8 h with ATV/r is being evaluated in an ongoing study in HIV/HCV co-infected individuals [24].
Darunavir/ ritonavir		Coadministration of telaprevir and darunavir 600/100 mg twice daily led to telaprevir AUC ↓ 35% and Cmin ↓ 32%, while darunavir AUC ↓ 40% and Cmin ↓ 42% [24]. Darunavir/ritonavir and telaprevir should not be co-administered [20].
Efavirenz	Slight reduction in boceprevir $AUC_{(0–8h)}$ and C_{max} (19% and 8%, respectively), and a 44% decrease in boceprevir C_{min} when co-administered with efavirenz. Boceprevir slightly increased EFV $AUC_{(0–24h)}$ and C_{max} (20% and 11%, respectively) [19]. Avoid combination [23].	Telaprevir C_{min} ↓ 47% by efavirenz. A higher dose of telaprevir (1,125 mg every 8 h) could partly offset the interaction with EFV, and is being evaluated in an ongoing study in HIV/HCV co-infected individuals [24].
Fosamprenavir/ ritonavir		Telaprevir AUC ↓ 32% and Cmin ↓ 30%, while amprenavir AUC ↓ 47% and Cmin ↓ 56% [24]. Fosamprenavir/ritonavir and telaprevir should not be co-administered [20].
Lopinavir/ ritonavir		Telaprevir AUC ↓ 54% and Cmin ↓ 52%, while lopinavir AUC ↑ 6% and Cmin ↑ 14% [24]. Lopinavir/ritonavir and telaprevir should not be co-administered [20].
Ritonavir	In healthy subjects, ritonavir either 100 mg daily or twice daily had minimal effects on steady-state boceprevir exposure [19].	Ritonavir 100 mg twice daily did not exert a significant boosting effect on telaprevir exposures [25].
Tenofovir	In healthy subjects, there were no clinically relevant changes in boceprevir exposure when co-administered with tenofovir. Boceprevir also had no notable effect on tenofovir AUC or renal clearance, but increased tenofovir C_{max} by 32%. No boceprevir dosage adjustment is needed with co-administration tenofovir [19].	Tenofovir AUC_{24h} ↑ by 30% while telaprevir kinetics were not affected [95].

Key: *AUC* area under the concentration time curve, *Cmax* maximum serum concentration, *Cmin* minimum serum concentration

FDA- and Health-Canada approved dose of 800/100 mg once daily), etravirine 200 mg twice daily, tenofovir/emtricitabine 300 mg/200 mg daily and voriconazole 400 mg IV/PO twice daily for 6 weeks. Plasma trough concentrations (Cmin) were obtained after a total of 4 weeks of voriconazole therapy, and again 3 weeks after voriconazole discontinuation. Therapeutic voriconazole concentrations were achieved, while etravirine Cmin increased by 134%. Ritonavir Cmin was undetectable and darunavir Cmin was well below historical reference data. After voriconazole was discontinued, ritonavir Cmin increased to the same range as the historical control and darunavir Cmin increased by fourfold. The combination of etravirine/darunavir/ritonavir with voriconazole should be undertaken with caution and twice daily dosing of darunavir/ritonavir should be considered in this setting. Therapeutic drug monitoring should be utilized when available [30].

In contrast to voriconazole, posaconazole is substrate of P-glycoprotein and UGT1A4, and inhibits CYP3A4 and p-glycoprotein [26•]. Brüggemann et al., conducted a three period, cross-over, open-label multi-dose study where healthy volunteers received either posaconazole 400 mg twice daily, fosamprenavir 700/ritonavir 100 mg twice daily, or posaconazole plus fosamprenavir 700 mg twice daily for 10 days each separated by 17-day washout periods. When posaconazole and unboosted fosamprenavir were coadministered, a dual-negative interaction was observed with a 23% and 65% decrease in the AUC of posaconazole and amprenavir, respectively. While the mechanism of the interaction is unclear, the authors postulated that fosamprenavir-mediated induction of UGT1A4 and/or P-glycoprotein may have played a role. The combination of posaconazole and unboosted fosamprenavir should be avoided. Optimal dosing of posaconazole and boosted fosamprenavir has not yet been determined, and if concomitant therapy is required, boosted fosamprenavir is recommended and TDM should be performed for both fosamprenavir and posaconazole [31].

Antimalarials

A number of antimalarial drugs have the potential to interact with ARVs, particularly the PIs and NNRTIs. New updates on interactions with quinine, atovaquone/proguanil and doxycycline are reviewed. Quinine is mainly a CYP3A4 substrate, therefore with the exception of unboosted tipranavir, all PIs have the potential to increase quinine concentrations, while efavirenz, nevirapine and etravirine may decrease quinine concentrations. Soyinka et al., studied the impact of ritonavir 200 mg twice daily in 10 healthy volunteers who received a single dose of oral quinine 600 mg. Both the Cmax and AUC of quinine increased by about 2.8-fold and 3.4-fold respectively, and the quinine half-life$_2$ increased by 20% (from 11.15 to 13.37 h). The metabolism of quinine to its major active metabolite, 3-hydroxyquinine, was markedly inhibited by ritonavir. There was a 21% increase in the AUC of ritonavir, however this is not likely to be clinically significant. Although firm guidelines are not available on the correct dosing when quinine and ritonavir are coadministered, the authors concluded that a decreased dose of quinine is recommended in order to prevent cardiotoxicity and QTc prolongation [32]. It is likely that at least a 50% reduction in the quinine dose may be necessary with close cardiac monitoring if quinine therapy is required in patients on ritonavir-containing cART. Caution should also be exercised when coadministering quinine and CYP3A4 inducers such as NNRTIs, as there is a potential for reduced quinine concentrations and therapeutic failure [33]. If coadministration is necessary, it is recommended to monitor for reduced clinical effectiveness (response of parasitemia) and quinine levels if possible, and dose-adjust as necessary. Similar concerns exist with mefloquine, another CYP3A4 substrate. While mefloquine is no longer as commonly used due to CNS side effects, exposures have been shown to be significantly reduced by 68% in the presence of rifampin; [34] thus, mefloquine use should be avoided if co-administration of potent enzyme inducers, including NNRTIs, is necessary.

There is a growing body of evidence on interactions with atovaquone/proguanil (Malarone®) and cART, since atovaquone is mainly glucuronidated, while proguanil is partly metabolized by CYP2C19 [35]. A recent study administered a single dose of oral atovaquone/proguanil 250/100 mg to 76 participants who had been taking efavirenz 600 mg daily, atazanavir/ritonavir 300/100 mg daily, or lopinavir/ritonavir 400/100 mg twice daily or 800/200 mg once daily for at least 1 month. Compared to healthy volunteers, the AUC of both atovaquone and proguanil was decreased with all three cART regimens (46%–75% for atovaquone and about 40% for proguanil) [35]. The clinical relevance of these findings is unknown, since optimal plasma concentrations for malaria prophylaxis are not determined. Atovaquone/proguanil should be taken daily at the same time with a high-fat meal and strict adherence should be emphasized. Close monitoring for antimalarial treatment failure in individuals on these cART regimens is recommended. In addition, since the magnitude of the interaction was greatest in efavirenz and lopinavir/ritonavir-based regimens, a 50% increase in the dose of atovaquone/proguanil may be warranted.

The effect of doxycycline on antiretroviral drug concentrations was assessed for the first time in an open-label study of HIV-positive subjects on standard dose cART (n=1 atazanavir, n=14 atazanavir/ritonavir, n=23 lopinavir/

ritonavir, $n=17$ efavirenz, $n=10$ nevirapine) who started doxycycline for malaria prophylaxis. Antiretroviral troughs were measured after at least 15 days of doxycycline therapy. No statistically significant effect on PI or NNRTI concentrations was noted, and no patients were infected with malaria [36].

Corticosteroids

There have been numerous cases of steroid accumulation resulting in adrenal suppression and Cushing's syndrome reported with the combination of ritonavir and either inhaled or intranasally administered fluticasone propionate (a known CYP3A4 substrate) [37•, 38]. The combination is relatively contraindicated, unless the benefits outweigh the risks of therapy [39]. It is postulated that the interaction may be more pronounced with fluticasone than other inhaled steroids due to unique pharmacokinetic characteristics such as high lipophilicity, a large volume of distribution, a long half-life and an increase affinity for the corticosteroid receptor [37•]. However, recent cases of adrenal suppression with the coadministration of ritonavir and other steroids, including injectable triamcinolone, [40–43] inhaled or oral budesonide, [44–46] and corticosteroid topical eye drops and ointment [47] have been reported.

There have been 7 cases of Cushing's syndrome reported with the use of intra-articular triamcinolone injections in patients on ritonavir-boosted cART regimens (100–200 mg daily of ritonavir) [40–43]. In most cases cushingoid symptoms and profound adrenal suppression (i.e. low or undetectable morning cortisol and adrenocoticotropic hormone (ACTH)) presented about 2 weeks after a single injection of triamcinolone acetonide 40–80 mg. Three cases required supplemental oral hydrocortisone 10–30 mg daily for up to 8 months [40, 41]. Antiretroviral therapy was held or changed in two cases [42, 43]. Most cases resolved after several months; however there were two reports of avascular necrosis of the hip [40, 43] occurring at 2 and 11 months post-steroid exposure, respectively.

Five cases of budesonide-related adrenal suppression and Cushing's syndrome resulting from an interaction with ritonavir have been reported to date [44–46]. Kedem et al., described a case of a female adult who initially developed Cushing's syndrome 4 months after the coadministration of intermittent inhaled fluticasone/salmeterol 250/50 ug with tenofovir, emtricitabine and lopinavir/ritonavir 400/100 mg twice daily. Symptoms resolved 2 months after the fluticasone was discontinued. However, due to worsening asthma symptoms, inhaled budesonide/formeterol 160/4.5 ug twice daily was initiated. After 4 weeks, cushingoid symptoms reappeared. Despite an attempt to decrease the dose of ritonavir to 100 mg daily (when combined with fosamprenavir), the symptoms worsened. Cushingoid symptoms resolved a few weeks after budesonide was discontinued and replaced with oral montelukast [44]. Gray et al. report a case series of 3 pediatric patients ages 4–7 years old, who also developed Cushing's syndrome after the combined use of ritonavir and inhaled budesonide [45]. One patient failed to respond after a dosage reduction of budesonide from 1,200 ug daily to 200 ug daily and required budesonide discontinuation. Another patient had resolution 4 weeks after ritonavir was changed to efavirenz. The third patient failed to improve with a switch from inhaled fluticasone 50 ug daily to budesonide 100 ug twice daily. Six weeks after discontinuing budesonide, the morning cortisol and ACTH had improved. Finally, a 75 year-old male had symptoms compatible with Cushing's syndrome 12 days after starting the combination of oral budesonide 3 mg three times daily with an atazanavir/ritonavir-based cART regimen. Budesonide was discontinued after 3 weeks and 15 days later the edema had resolved and serum potassium and bicarbonate had improved [46].

A recent report documented the first case of Cushing's syndrome secondary to the co-administration of ritonavir with corticosteroid eye drops. A 51-year old HIV-positive woman on atazanavir/ritonavir and tenofovir/emtricitabine with suppressed viral load and CD4 count of 1,070 cells/mm3 presented with Cushingoid features, avascular necrosis of the hip, and adrenal axis suppression with low ACTH. She had been taking dexamethasone 0.1% eye drops six times daily, and betamethasone 0.1% eye ointment at night, in both eyes for over 8 months because of previous bilateral cytomegalovirus retinitis complicated by immune recovery uveitis with severe, chronic, cystoid macular edema. Atazanavir/ritonavir was replaced with efavirenz while continuing the steroid eye drops, and oral hydrocortisone 15 mg daily was added to avoid precipitating crisis due to adrenal insufficiency. Over the following year, the patient's weight declined, with marked improvement in her adrenal function [47].

These cases illustrate that extreme caution is warranted when inhaled, intra-articular or even topical steroids are coadministered with ritonavir-based cART. The use of inhaled fluticasone and ritonavir should be avoided if possible. Although budesonide is not contraindicated, based on these new case reports, caution is warranted. To our knowledge there have been no cases of interactions between ritonavir and inhaled beclomethasone, ciclesonide or mometasone; however vigilance is still required since all steroids are CYP3A4 substrates. Other non-steroidal options such as oral montelukast might be considered. If steroids are clearly indicated, ritonavir-based cART should be avoided if other cART options are feasible (e.g. NNRTIs, CCR5 antagonists and integrase inhibitors). When the combination of ritonavir and steroids are required, a thorough

baseline assessment is recommended and the lowest effective steroid dose should be used. Close monitoring for Cushing's syndrome is recommended as symptoms typically appear after several weeks and may take months to resolve once diagnosed. Patients who are taking ritonavir should be forewarned about the potential interaction with all corticosteroid products, including those administered topically, by inhalation, intraocularly or via intra-articular injection, as these medications are often prescribed by other clinicians who may be unaware of the potential dangers. In addition, consistent screening for the use of steroids at each clinic visit is warranted to prevent the interaction from occurring.

Psychotropics

Since quetiapine is mainly a CYP3A4 substrate it is anticipated that drug interactions would exist with the PIs. There is now growing evidence to support this prediction. A previous report described two patients with suspected interactions between quetiapine and atazanavir/ritonavir (rapid and severe weight gain and increased sedation and confusion) [48]. More recently, a report of a deep coma, sustained hypotension and a marked increase in quetiapine half-life from 22 to 62.4 h was reported after a patient voluntarily ingested quetiapine 8,000 mg while on atazanavir/ritonavir [49]. Geraci et al., reported a case of priapism starting 5–6 h after co-ingestion of perphenazine 8 mg daily (CYP2D6 substrate) and quetiapine 900 mg daily with lopinavir/ritonavir 400/100 mg twice daily, and lasting 42 h. Rapid elevations in the neuroleptic concentrations were postulated as the mechanism. The symptoms were managed with intracavernous ephedrine, irrigation and aspiration [50]. Although a formal pharmacokinetic trial is lacking, these cases illustrate that caution is warranted when quetiapine is coadministered with ritonavir-boosted regimens. A trial of lower quetiapine doses and cautious escalation may be warranted when given with ritonavir-based regimens.

A recent study looking at the interaction between olanzapine 15 mg and fosamprenavir/ritonavir 700/100 mg twice daily resulted in a similar AUC to olanzapine 10 mg given alone. Amprenavir pharmacokinetic parameters were similar to historical controls [51]. These findings are similar to previous data which showed a 53% decrease in the AUC of olanzapine when combined with high dose ritonavir (500 mg orally twice daily) [52]. Since olanzapine is a substrate of CYP1A2 and glucuronyl transferase it is likely that ritonavir coadministration resulted in induction of these enzymes and a subsequent decrease in olanzapine concentrations. The authors recommended that the dose of olanzapine should be increased by 50% when given with fosamprenavir/ritonavir [51].

Narcotics

While interactions between methadone and cART have been more widely studied, there is a relative lack of data with other narcotics. There have been recent reports on oxycodone and buprenorphine interactions with ARVs.

Oxycodone is mainly metabolized by CYP3A4/5 and several of the active metabolites via CYP2D6, [53] therefore it is subject to interactions with ART. Nieminen et al. conducted the first pharmacokinetic trial to look at the impact of ritonavir on oxycodone pharmacokinetics. Ritonavir 300 mg, lopinavir/ritonavir 400/100 mg or placebo all twice daily were given for 4 days, and single-dose oxycodone 10 mg orally on day 3. Both ritonavir and lopinavir/ritonavir significantly increased the oxycodone AUC by 3-fold and 2.6-fold, respectively and increased the self-reported drug effect of oxycodone. Therefore, an oxycodone dose reduction may be required during concomitant use of ritonavir-containing therapy to avoid opioid-related adverse effects. Careful titration of the oxycodone dose is warranted [53].

Buprenorphine is a semi-synthetic partial opioid agonist and is metabolized via CYP 3A4 and 2C8, while the active metabolite, norbuprenorphine, undergoes glucuronidation [54]. Since buprenorphine is an attractive alternative to methadone in the treatment of opioid dependent patients, a number of kinetic interaction studies have been conducted. The most recent ones include several nucleosides, nevirapine and ritonavir-boosted lopinavir and darunavir regimens [54–57]. Significant interactions were not observed with didanosine, lamivudine and tenofovir [54]. In 7 HIV-negative volunteers, there was a lack of a clinically significant interaction with nevirapine (9% reduction in AUC of buprenorphine and 14% reduction in AUC of norbuprenorphine), and standard doses of both agents are recommended [55]. Likewise, there was no significant interaction with the combination of lopinavir/ritonavir 800/100 mg daily and buprenorphine/naloxone, and standard doses of both agents can be used [56]. Finally, Sekar and colleagues studied 17 HIV-negative subjects on stable buprenorphine/naloxone. The addition of darunavir 600/100 mg twice daily for 7 days led to 71% increase in the Cmin and 46% increase in the AUC of norbuprenorphine, while kinetics of buprenorphine and naloxone were comparable to baseline. Although empiric dosage adjustments are not required, since the clinical significance of increased norbuphrenorphine exposure is unknown, close monitoring is still recommended with this combination [57].

Oral Contraceptives

There have been a number of interaction studies on hormonal contraceptives and cART recently published.

For a more comprehensive overview, readers are referred to a review by El-Ibiary and colleagues [58].

A previous study showed that unboosted atazanavir 400 mg daily led to an increase in ethinyl estradiol (EE) and norethindrome (NE) AUC by 48% and 110%, respectively [59]. Results from a more recent trial with atazanavir/ritonavir 300/100 mg PO daily and a combination product of EE 25 ug with norgestimate (NGM), resulted in a 19% decrease in the AUC of EE and an 85% increase in the AUC of the active NGM metabolite. It is likely that ritonavir-mediated induction of EE metabolism (via glucuronidation and CYP2C9) accounted for the discrepancy between the two studies. The authors concluded that contraceptive efficacy is not likely to be compromised when using formulations containing 30 ug or more of EE daily with ritonavir-boosted atazanavir, while the FDA recommends that oral contraceptive products contain at least 35 ug of EE daily in this setting [60, 61]. In contrast, EE doses should not exceed 30 ug daily when combined with unboosted atazanavir [61, 62].

Lopinavir/ritonavir has been shown to significantly reduce concentrations of EE and NE [63]. Transdermally delivered EE and norelgestromin (NGMN-an active metabolite of NGM) patch was recently studied in 8 HIV-positive females. A 45% decrease in the AUC of EE and an 83% increase in the AUC of NGMN were observed [64]. While the investigators concluded that overall efficacy of the patch was likely to be maintained due to higher NGMN concentrations, further efficacy studies are needed to confirm this. Similar to oral contraceptive formulations, the manufacturer recommends the use of additional or alternate methods of contraception [63].

There have been a few recent studies with efavirenz and contraceptives. Carten et al., found a 58% decrease in the AUC of levonorgestrel (LNG), when given as a 0.75 mg single dose for emergency contraception, after efavirenz 600 mg orally daily for 14 days [65]. These findings are consistent with another study showing an 83% decrease in the AUC of LNG [66]. Due to the potential failure of the progesterone component, dual methods of contraception, including a barrier device are recommended. Future studies with emergency contraception using double the dose of LNG (1.5 mg) are required. In addition, studies looking at the interaction between efavirenz and the third generation progesterone products (e.g. desogestrel or gestodene) are warranted. Another report noted that the contraceptive failures have occurred with implantable etonogestrel (Implanon®) in efavirenz-exposed patients and a barrier method is also recommended [67].

Previously nevirapine was shown to decrease the AUC of EE and NE by 29% and 18%, respectively [68]. Stuart and colleagues reported conflicting findings when they found the highest concentrations of both EE and norgestrel in patients taking nevirapine vs. those not taking cART. Ovulation was also suppressed in this Malawi-based group [69]. Due to the unexpected findings in this study, additional studies in other populations and settings are required. In the meantime, alternate methods of contraception such as barrier methods are recommended. In addition, one small study also supported the use of nevirapine and depo-medroxyprogestrone, with no pregnancies or ovulations found after 12 weeks of coadministration [70].

There was no clinically significant interaction found when raltegravir was given with a formulation of EE and NGM (Ortho Tri-Cyclen®), thus the combination can be coadministered at the usual doses [71]. Gilead Sciences' experimental quad ART tablet given once daily contains a new integrase inhibitor-elvitegravir, cobicistat, tenofovir and emtricitabine. This coformulation was studied with a combination of EE 25 ug and norgestimate (OrthoTri-Cyclen Lo®) in 12 healthy female subjects. There was a 25% decrease in the AUC of EE, and approximately a 2-fold increase in the AUC of the active NGMN metabolite. No changes in progesterone levels, and similar reductions in follicle-stimulating hormone (FSH) levels, were observed. A larger decrease in luteinizing hormone (LH) was observed in the quad group vs. the control group. These data suggest that FSH and LH secretion was still suppressed, despite lower EE concentrations. The authors recommend using formulations containing 30 ug or more of EE daily when given with the quad tablet [72].

Anticoagulants

Welzen et al., report a case describing the impact of various antiretroviral regimens on the International Normalized Ratio (INR) in a patient on acenocoumarol [73]. While on fixed-dose tenofovir/emtricitabine and an efavirenz-based regimen, the dose of acenocoumarol was increased from 4.2 mg/day to 6.7 mg/day to achieve a therapeutic INR (target 2.5–3.5). When switched to an atazanavir/ritonavir regimen, the dose of acenocoumarol was further increased to 8.3 mg/day, representing a doubling of the baseline dose. Following another antiretroviral change to raltegravir, the INR increased to 5.7 thus necessitating a decrease in the acenocoumarol dose to 6.4 mg/day. The active R-enantiomer of acecoumarol is mainly responsible for its pharmacological activity and is metabolized by CYP2C9, 1A2, 2C19 and 3A4 isoenzymes [74]. The authors postulated that both efavirenz and ritonavir served as inducers of acenocoumarol metabolism via CYP2C9 and CYP2C9/1A2 induction, respectively. There did not appear to be a significant interaction with raltegravir [73]. Since the metabolism of both acenocoumarol and warfarin is complex, caution is warranted when combined with ARVs

and readers are referred to more comprehensive reviews for further information [75, 76•].

Drugs for Pulmonary Hypertension

Pulmonary arterial hypertension (PAH) is a progressive, rare disease that results from chronic obstruction of small pulmonary arteries, leading to right ventricular failure, and eventually, death. PAH in the context of HIV is associated with a particularly poor prognosis, and prompt diagnosis and treatment is essential. PAH therapies include endothelin receptor antagonists, prostacyclin analogs, and phosphodiesterase type 5 inhibitors [77]. Prostacyclin analogs are not known substrates, inhibitors or inducers of the CYP450 system, and significant pharmacokinetic interactions with ARVs are not anticipated [78•]. A summary of known and potential interactions between PAH treatment and ARVs is included in Table 2.

Bosentan, a dual endothelin receptor antagonist (ERA) with affinity for both endothelin A and B (ETA and ETB) receptors, has demonstrated efficacy in HIV-associated PAH. Bosentan is a substrate of CYP2C9 and CYP3A4, and is an inducer of CYP2C9 and CYP3A4 [79, 80].

In a three-way, crossover study in twelve healthy males, participants received bosentan 125 mg twice daily and lopinavir/ritonavir 400/100 mg twice daily alone or in combination for 9.5 days. In the presence of bosentan, AUC values of lopinavir and ritonavir were reduced 14% and 17%, respectively, which was not considered to be clinically significant. In contrast, bosentan exposures were significantly increased. During the first 4 days of coadministration, bosentan concentrations increased up to 48-fold, and at steady-state, the geometric mean ratio (GMR) for AUC was 5.22 and for Cmax was 6.12. The increased exposure was associated with an increase in adverse events related to bosentan, primarily headache (all subjects) and vomiting (4 of 11 subjects). No subjects experienced an increase in liver enzymes [81]. Therefore, bosentan should only be initiated once boosted PIs have reached steady-state (i.e., at least 10 days of therapy) in order to avoid the peak inhibiting effect on bosentan metabolism. In patients on chronic PI therapy, bosentan may be started at a lower dose of 62.5 mg once daily or every other day. For patients on stable bosentan therapy who require initiation of a boosted PI regimen, bosentan should be discontinued for at least 36 h prior to starting the boosted PI, then reinstituted 10 days after PI initiation at 62.5 mg once daily or every other day [82•]. Response to bosentan therapy may be assessed by improvements in exercise tolerance, NYHA functional status severity and hemodynamic measures by right heart catheterization. Monitoring parameters for bosentan toxicity include headache, flushing, gastrointestinal effects, anemia, and signs and symptoms of liver injury (nausea, vomiting, fever, abdominal pain, elevated liver function tests, jaundice or fatigue), worsening congestive heart failure (weight gain, increased leg edema) and pulmonary edema (shortness of breath, painful or difficult breathing) [77].

While lopinavir and ritonavir concentrations were not significantly reduced by bosentan in the previous study, full enzyme induction by bosentan might not have been reached, and a further decrease in PI concentrations cannot be excluded [79]. Appropriate monitoring of antiretroviral efficacy and TDM is recommended, especially when using boosted PI regimens incorporating lower dosages of ritonavir (e.g., 100 mg daily). Bosentan is contraindicated with unboosted atazanavir, as plasma atazanavir concentrations may be decreased [62]. A previously published case report noted a possible interaction between bosentan and unboosted indinavir leading to a reduction in indinavir plasma concentrations [83].

The bosentan product monograph also states that coadministration with nevirapine is not recommended, due to the increased potential for nevirapine hepatotoxicity secondary to the impact bosentan has on the liver [79]. However, a recent report documented the successful, long-term coadministration of bosentan and nevirapine-based cART in a 51-year old HIV-positive woman with AIDS and HIV-associated PAH. At the time of PAH diagnosis, the patient had been on nevirapine, lamivudine and zidovudine for 3 years with good virological control (VL<50 copies/mL) and immune response (CD4 674 cells/mm3). The patient initially refused treatment for PAH, until 2 years later when her symptoms had markedly progressed. At that time, she was initiated on bosentan 62.5 mg twice daily, which was titrated to the standard dose of 125 mg twice daily thereafter. Over a 4-year follow-up period, the patient experienced significant clinical and hemodynamic improvement, and maintained complete viral suppression, therapeutic nevirapine trough concentrations, and excellent immunologic response [78•].

The phosphodiesterase type 5 (PDE5) inhibitors sildenafil and tadalafil are indicated for both treatment of erectile dysfunction and more recently PAH. These agents are substrates of CYP3A4 and are exquisitely sensitive to inhibition interactions. Sildenafil exposures are increased 2–11-fold in the presence of PIs [82•]. Significant increases in tadalafil concentrations have also been observed in conjunction with ritonavir and boosted tipranavir, and recurrent priapism secondary to an interaction between tadalafil and boosted fosamprenavir has been reported [84]. For the treatment of erectile dysfunction, significant dose reductions of PDE5 inhibitors are necessary (i.e., sildenafil 25 mg every 48 h, tadalafil 10 mg every 72 h) in the context of PI therapy. However, given the marked effect of

Table 2 Drug interactions between antiretrovirals and drugs used for the treatment of pulmonary arterial hypertension

	Protease inhibitors	Non-nucleoside reverse transcriptase inhibitors	Other antiretrovirals
Endothelin receptor antagonists			
Bosentan • substrate of CYP3A4, 2C9 • inducer of CYP2C9 and CYP3A4 [79, 80].	Significant ↑ bosentan concentrations with lopinavir/ritonavir (up to 48-fold ↑ during the first 4 days, with 5-fold ↑ AUC at steady state). Therefore, bosentan should only be initiated at a dose of 62.5 mg daily or every other day once boosted PIs have reached steady-state. For patients on stable bosentan therapy who require initiation of a boosted PI regimen, bosentan should be discontinued for at least 36 h prior to starting the boosted PI, then reinstituted 10 days after PI initiation at 62.5 mg once daily or every other day [82]. Bosentan is contraindicated with unboosted atazanavir, as plasma atazanavir concentrations may be decreased [62]. A case report noted a possible interaction between bosentan and unboosted indinavir leading to a reduction in indinavir plasma concentrations [83].	Long-term, safe co-administration of bosentan and nevirapine has been reported [78].	Potential for ↓ maraviroc concentrations. Avoid combination if possible.
Ambrisentan • substrate of UGT1A9S, 2B7S, and 1A3S, CYP3A4 and CYP2C19, OATP, and P-gp. • Does not inhibit or induce CYP450 or P-gp.	Potential for ↑ ambrisentan concentrations.	Monitor for potential ↓ ambrisentan concentrations.	
Sitaxsentan • substrate of CYP3A4/5 and 2C9 • inhibitor of CYP2C9, as well as 2C19, 3A4/5, and 2C8	Case report of an HIV-positive patient on tenofovir, 3TC and atazanavir with HIV-PAH who tolerated sitaxsentan 100 mg daily with clinical benefit [96].	Potential for ↑ NNRTI concentrations.	Potential for ↑ maraviroc concentrations.
Phosphodiesterase inhibitors			
Sildenafil • CYP3A4> >2C9 substrate; weak inhibitor of CYP1A2, 2C9, 2C19, 2D6, 2E1, 3A4—unlikely to cause significant interactions	Sildenafil exposures are ↑2–11-fold in the presence of PIs [82]. Sildenafil for treatment of PAH is contraindicated with all PIs.	In the presence of etravirine, sildenafil AUC ↓ 57%. Combination may be co-administered, adjust sildenafil dose according to response [85]. Similar interaction may be possible with other NNRTIs.	No pharmacokinetic interaction with maraviroc is expected, but both maraviroc and the PDE5 inhibitors have reported hypotension as adverse events; therefore, co-administer combination with caution.
Tadalafil • CYP3A4 substrate	Significant ↑in tadalafil concentrations with ritonavir and boosted tipranavir [97]. Recurrent priapism secondary to an interaction between tadalafil and boosted fosamprenavir reported [84]. For patients on stable PI treatment who require therapy for PAH, tadalafil may be initiated at a dose of 20 mg daily and ↑ to 40 mg daily based on tolerability. For patients already stabilized on tadalafil who require PI-based treatment, tadalafil should be discontinued at least 24 h prior to initiating the PI, and restarted 7 days after PI initiation at a dose of 20 mg once daily, ↑ to 40 mg once daily based on tolerability [82].	Potential for ↓ tadalafil concentrations. Dose adjustment may be necessary with coadministration.	No pharmacokinetic interaction with maraviroc is expected, but both maraviroc and the PDE5 inhibitors have reported hypotension as adverse events; therefore, co-administer combination with caution.

PIs on increasing sildenafil exposures, as well as the higher daily dose required for chronic treatment of PAH, sildenafil for treatment of PAH is contraindicated with all PIs [82•]. For patients on stable (i.e., greater than 7 days) PI treatment who require therapy for PAH, tadalafil may be initiated at a dose of 20 mg once daily and increased to the standard dose of 40 mg once daily based on tolerability. For patients already stabilized on tadalafil who require PI-based treatment, tadalafil should be discontinued at least 24 h prior to initiating the PI, and restarted 7 days after PI initiation at a dose of 20 mg once daily, increasing back to 40 mg once daily based on tolerability [82•].

Etravirine is a CYP3A4 inducer, and has been shown to reduce sildenafil exposures by 57% in healthy volunteers. This combination may be co-administered, with adjustment of sildenafil dose according to response such as exercise tolerance, NYHA functional status severity and hemodynamic measures [85]. The potential for similar interactions between etravirine and other PDE5 inhibitors exists, as they are also substrates of CYP3A4.

Herbals

The concomitant use of complementary and alternative medicine (CAM) with ARVs is a common reality, with up to 60% of HIV-infected individuals reporting the use of CAM in a recent survey [86]. Many concerns may be associated with broad and unreported use of CAM, including the risk of potential drug interactions or safety. Some products like *Hypericum perforatum* (St-John's Wort), *Echinacea purpurea*, garlic or ginkgo biloba have been shown to induce or inhibit important metabolic pathways like CYP450, UGT, and PGP which are involved in the metabolism of certain ARVs, [87•] and cases of antiretroviral toxicity [88] or viral failure and development of drug resistance secondary to CAM-antiretroviral interactions have been reported. St. John's Wort is contraindicated or not recommended for use with all protease inhibitors, NNRTIs and maraviroc due to the risk of significant reductions in ARV concentrations with loss of virologic response and possible development of resistance. Two recently published studies investigated the influence of *Echinacea purpurea*, an herbal product with purported immune stimulant properties commonly used for the prevention and treatment of upper respiratory tract infections or the common cold, on the pharmacokinetics of lopinavir/ritonavir and darunavir/ritonavir [89, 90].

In one study, healthy subjects received lopinavir/ritonavir 400/100 mg twice daily for 28 days and *Echinacea purpurea* 500 mg three times daily for 28 days with an overlap period of 14 days. Single oral doses of midazolam 8 mg and fexofenadine 120 mg were also administered before and after treatment with *Echinacea purpurea* in order to assess CYP3A and p-glycoprotein activity. Lopinavir and ritonavir pharmacokinetics were not significantly altered with in the presence of *Echinacea purpurea*, and vice versa. Fexofenadine pharmacokinetics were also not altered by *Echinacea purpurea*, but midazolam AUC decreased by 27% ($p=0.008$) with concomitant administration. The investigators concluded that *Echinacea purpurea* induced CYP3A activity but did not alter lopinavir concentrations, most likely due to the presence of the potent CYP3A inhibitor, ritonavir [89].

The second study was an open-label, fixed sequence study involving 15 HIV-infected patients on cART including darunavir 600/ritonavir 100 mg twice daily for at least 4 weeks. Participants were given *Echinacea purpurea* root extract capsules 500 mg every 6 h for 14 days. The GMR for darunavir administered in the presence of *Echinacea purpurea* relative to darunavir alone was 0.84 (90% CI, 0.63–1.12) for Cmin, 0.90 (90% CI, 0.74–1.10) for AUC, and 0.98 (90% CI, 0.82–1.16) for Cmax. Echinacea was well tolerated and all patients completed the study [90].

The results of these two studies suggest that while *Echinacea purpurea* exhibits CYP3A4 inducing activity, the impact on the pharmacokinetics of concomitantly administered boosted PIs is not likely to be clinically significant. Caution is warranted if using *Echinacea purpurea* chronically with other CYP3A substrates including unboosted PIs or maraviroc, and clinicians may wish to consider antiretroviral TDM.

Discussion

The advances in HIV therapy have turned HIV into a chronic, manageable disease in an aging population. Patients often require treatment for co-morbid conditions as well as HIV, and consequently, pharmacokinetic interactions between ARVs and other drug classes are an increasing concern. Pharmacokinetic drug interactions may result in subtherapeutic ARV concentrations which could lead to viral breakthrough and development of resistance or sub-optimal disease/symptom management, or supratherapeutic levels which may result in drug toxicity and possibly non-adherence and/or increased morbidity. The efficacy and toxicity of the interacting drug(s) may also be similarly affected.

Treatment regimens which include agents that are involved in the CYP450 or other transporter systems, notably PIs and NNRTIs, may be associated with higher risk of clinically significant drug interactions. The integrase inhibitor raltegravir is not a P450 substrate, inducer or inhibitor; thus it may be a suitable option to include in a regimen when trying to minimize drug interactions with other drug classes [13, 91].

Since interactions between ARVs and other drug classes have not been exhaustively elucidated, clinicians need to be aware of the pharmacological and pharmacokinetic characteristics of specific agents in order to identify and/or predict potential drug interactions. Using a systematic approach to identify, verify, assess and manage potential interactions is recommended in order to optimally manage a patient's drug therapy [92•].

Pertinent resources should be consulted to identify known interactions, while potential interactions may be predicted based upon the pharmacology and pharmacokinetics of the suspected medications. Obtaining further information from the literature on how an interaction was described (e.g., case report, in vitro study, retrospective observation or prospective, controlled pharmacokinetic study) can help to determine whether the data are applicable to a specific patient population. Consideration of additional factors such as time course, presence of clinical signs and symptoms, and other objective evidence such as drug concentrations can assist practitioners in developing monitoring plans and providing appropriate counselling to patients. For instance, enzyme inhibition interactions occur rapidly, once sufficient concentrations of the inhibiting agent are present. On the other hand, enzyme induction interactions do not usually become apparent for a week or more, since the enzyme inducer must first reach steady state, and new drug metabolizing enzymes need to be synthesized.

Management options may vary depending upon a number of factors, including the mechanism and clinical consequences of the interaction, availability of therapeutic alternatives, patient convenience, and cost. Strategies include adjusting the dose and/or dosing frequency of one or both interacting drugs, or replacing one agent with another drug with lower interaction potential. Often, close clinical, virological and TDM is warranted. For instance, if a patient is to initiate therapy with an agent that may potentially be increased by protease inhibitor therapy, the patient should be counselled to monitor for signs and symptoms of drug toxicity within the first few days of concomitant drug administration. Or if the index drug has a narrow therapeutic window, the clinician may wish to start with a reduced dose and titrate according to response. Conversely, if there is a risk for reduced exposures of either antiretroviral or co-administered therapy, patients should be monitored closely for therapeutic response, and TDM may be considered 2 weeks after initiation of the agent (s) with enzyme inducing potential.

Conclusions

Clinically significant drug interactions may occur between ARVs and other drug classes needed to treat co-morbid conditions in the HIV population. Thus, readers are encouraged to utilize resources including independently-ranked HIV interaction websites [93, 94•] for current information, and to consult with clinicians specialized in HIV pharmacology when making decisions regarding management.

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