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Drug Interactions and Antiretroviral Drug Monitoring

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Abstract

Due to the improved longevity afforded by combination antiretroviral therapy (cART), HIV-infected individuals are developing several non-AIDS related comorbid conditions. Consequently, medical management of the HIV-infected population is increasingly complex, with a growing list of potential drug-drug interactions (DDIs). This article reviews some of the most relevant and emerging potential interactions between antiretroviral medications and other agents. The most common DDIs are those involving protease inhibitors or non-nucleoside reverse transcriptase inhibitors which alter the cytochrome P450 enzyme system and/or drug transporters such as p-glycoprotein. Of note are the new agents for the treatment of chronic hepatitis C virus infection. These new classes of drugs and others drugs which are increasingly used in this patient population represent a significant challenge with regard to achieving the goals of effective HIV suppression and minimization of drug-related toxicities. Awareness of DDIs and a multidisciplinary approach are imperative in reaching these goals.

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Compliance with Ethics Guidelines

Conflict of Interest

Matthew Foy, C. John Sperati, Gregory M. Lucas, and Michelle M. Estrella declare that they have no conflict of interest

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

Keywords

drug-drug interactions; HIV; antiretroviral; hepatitis C virus; therapeutic drug monitoring

INTRODUCTION

Since 1987, the armamentarium of antiretroviral drugs has expanded dramatically. The notable effectiveness of combination antiretroviral therapy (cART) has led to significantly improved survival of HIV-infected individuals, with more than half of HIV-infected persons in the U.S. estimated to be 50 years or older by 2015.^{1,2} With the aging of this population, growing burden of traditional chronic co-morbid conditions such as diabetes and hypertension, and emerging treatment options for hepatitis C virus (HCV) infection,³ HIV-infected individuals face a significant risk for drug-related adverse events.

Among approximately 1500 participants in the Swiss Cohort, 68% were receiving other types of medications in addition to cART.⁴ The most common type of medication co-administered with antiretroviral medications was cardiovascular (56%). This was followed by medications for the central nervous system (CNS, 31%) such as antidepressants and antipsychotics. In this study, 40% of participants had at least one potential drug-drug interaction. These drug-drug interactions (DDIs) could lead to serious, lethal supratherapeutic drug toxicities or, conversely, decreased efficacy of co-administered medications.

Drug-drug interactions between antiretroviral and other medications can occur through several mechanisms. Most well-recognized are those drugs metabolized through the cytochrome P450 (CYP450) enzymes. Among antiretroviral drug classes, protease inhibitors (PIs) are known to inhibit CYP3A4;⁵ therefore, concurrent administration of drugs metabolized through the CYP450 system can lead to supratherapeutic levels of these drugs. In contrast, non-nucleoside reverse transcriptase inhibitors (NNRTIs) generally induce CYP450 enzymes which can lead to subtherapeutic levels of co-administered drugs that are metabolized via these enzymes. Of emerging importance in DDIs are drug-uptake and efflux transporters which play a critical role in determining drug absorption, cellular entry, and elimination.⁶ Similar to the CYP450 enzymes, these transporters may be inhibited or induced by certain antiretrovirals and other drugs.⁷ Additional pathways which could lead to drug-drug interactions with antiretrovirals include alterations of pH-dependent drug absorption and glucuronidation.^{8,9}

In this review, we describe select DDIs in the context of HIV-infection treatment and management of accompanying conditions, with emphasis on new findings in the medical literature. We also present general approaches on the clinical monitoring for minimizing the risks and adverse consequences resulting from DDIs with antiretroviral medications.

DRUG INTERACTIONS AMONG ANTIRETROVIRAL MEDICATIONS

The major drug interactions among antiretroviral medications were previously reviewed in detail by Jiménez-Nácher and colleagues and updated regularly by the Department of

Human Health and Services (<http://aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf>).^{10,11} With the exception of approved paired nucleoside reverse transcriptase inhibitors (NRTIs) and ritonavir (RTV)-boosting of other PIs, co-administration of antiretroviral medications from the same class is generally avoided. In addition, concurrent use of PIs and NNRTIs are generally avoided due to potentially sub-therapeutic PI plasma concentrations.

More recently, studies have implicated interactions between tenofovir disoproxil fumarate (TDF) and ritonavir. This is of clinical importance as TDF is a component of several first line cART regimens against HIV¹¹ and is often co-administered with RTV-boosted PIs.¹² Pharmacokinetic studies demonstrated that RTV use, including its use as a PI-booster, increases the area under the curve (AUC) of tenofovir by 30–50%.^{13–15} The mechanism by which RTV affects circulating tenofovir concentrations remains unclear. Earlier studies suggested RTV-related effects on the human organic anion transporters 1 and 3 (hOAT 1 and hOAT3) and/ or multidrug resistance proteins 2 and 4 (MRP2/4) lead to elevated tenofovir plasma concentrations;¹⁶ however, a subsequent study demonstrated that RTV concentrations achieved with the dosage used for PI-boosting does not substantially alter hOAT3 transport.¹⁷ Instead, RTV may impair p-glycoprotein-mediated efflux of TDF, increase p-glycoprotein expression and decrease intestinal TDF hydrolysis, thereby increasing TDF absorption through the gastrointestinal tract.¹⁸ Whether the interaction between RTV and TDF augments tenofovir-related nephrotoxicity remains unknown. In an open label 48-week trial in which participants were randomized to either TDF/nevirapine (NVP) or TDF/ritonavir-boosted atazanavir, (ATV/r), participants randomized to the latter group had a greater decline in estimated glomerular filtration rate (eGFR) compared to those in the TDF/NVP arm (–7 vs. 3 ml/min/1.73 m²).¹⁹ These observations were corroborated by a recent analysis of the Optimal Combination Therapy After Nevirapine Exposure (OCTANE) trial which examined 741 HIV-infected women treated with TDF/emtricitabine (FTC) in combination with either RTV-boosted lopinavir (LPV/r) or NVP and showed a 3.2-fold greater odds of renal adverse events in those who received LPV/r.²⁰ In this study with careful kidney function monitoring, the overall rate of adverse renal events was 3.2% over a median follow-up of 2.3 years; however, tenofovir-related proximal tubule injury was not assessed.

DRUG-DRUG INTERACTIONS WITH NEW DRUGS FOR TREATMENT OF HCV INFECTION

HCV infection occurs in a significant proportion of HIV-infected individuals, with up to 70% prevalence among injection drug users and a rising prevalence among men who have sex with men (MSM).^{21,22} Early cART initiation is associated with slower HCV-related liver disease progression^{23,24}, and new direct-acting antiviral (DAA) and host-targeted agents against HCV provide the promise of cure in a large proportion of HCV-infected individuals. However, these new HCV treatment options present DDI challenges which are detailed in Table 1.

Currently, there are four DAAs which have been FDA-approved for the treatment of HCV infection: 1) first-generation NS3/4A protease inhibitors [telaprevir, boceprevir, and

simeprevir] for the treatment of genotype 1 HCV infection; and 2) nucleotide analogue [sofosbuvir] for the treatment of genotypes 1, 2, 3 or 4 HCV infection.²⁵ Telaprevir and boceprevir inhibit the CYP3A system, while simeprevir is a weak inhibitor of CYP1A2 and intestinal CYP3A4. In addition, telaprevir and simeprevir are both inhibitors and substrates of p-glycoprotein. Simeprevir also inhibits OATP1B1/3 transporters.

Co-administration of drugs which are metabolized via CYP3A could alter levels of these NS3/4A PIs. In particular, concomitant use of PIs with telaprevir or boceprevir leads to bidirectional DDIs.^{26–28} Among 39 healthy participants, boceprevir AUCs decreased by 32% and 45% when given concurrently with the RTV-boosted PIs darunavir (DRV/r) and LPV/r, respectively.²⁷ In this study, the plasma levels of DRV, LPV, and RTV were also reduced significantly. Similar findings occurred when telaprevir or boceprevir were given concurrently with RTV-boosted fosamprenavir (FPV/r).²⁸ A recent study suggests that RTV may play a major role in these observed DDIs. Among 14 HIV/HCV co-infected individuals receiving ATV/r and telaprevir, RTV discontinuation increased telaprevir AUC (19%), C_{max} (12%), and C_{min} (18%) and surprisingly increased ATV AUC (39%), C_{max} (19%), and C_{min} (48%) with a notably shorter terminal half-life of 10.4 hours (versus 22.6 hours with RTV).²⁹ Because these first generation DAAs have low resistance barriers, such DDIs can lead to insufficient drug levels and promote drug-resistant HCV strains. In contrast, simeprevir co-administration with RTV-boosted PIs may increase simeprevir plasma concentrations. Among 25 adults, concurrent RTV-boosted PI use with simeprevir resulted in a 2.5-fold increase in AUC and a 1.7-fold increase in the C_{max} of simeprevir.³⁰ Consequently, co-administration of the first generation DAAs with anti-HIV PIs with the exception of ATV/r should be avoided.

Similarly, concurrent use of these DAAs with NNRTIs leads to significant DDIs. For example, co-administration of boceprevir and rilpivirine (RPV), also a CYP3A substrate, is associated with a 39% and 15% increase in RPV AUC and C_{max} , respectively.³¹ In addition, NVP which induces CYP3A4 could lower telaprevir or boceprevir exposures.^{28,31} Reduced etravirine (ETR) exposure has also been demonstrated with boceprevir-ETR co-administration, although dose adjustments are deemed unnecessary.³¹ Efavirenz (EFV) has also been shown to significantly lower simeprevir levels. In 23 healthy adults, concurrent EFV with simeprevir reduced simeprevir AUC and C_{max} by 71% and 51%, respectively.³⁰ While dose adjustments are not recommended for the NNRTIs, vigilance for DDI-related adverse effects is recommended.

Additional drugs which may interact with these DAAs are maraviroc (MVC), TDF, elvitegravir (EVG), and cobicistat (COBI). As MVC is a CYP3A substrate, co-administration with telaprevir or boceprevir could result in increased MVC exposure; therefore, MVC is contraindicated with these drugs. Concurrent exposure to telaprevir and TDF increases tenofovir C_{max} (30%), AUC (30%) and C_{min} (40%); in turn, telaprevir concentrations are variably decreased (18–20%).²⁸ As EVG is also metabolized by CYP3A4, its co-administration with boceprevir could lead to higher EVG concentrations. Concomitant use telaprevir or boceprevir with the pharmacokinetic booster, COBI, which inhibits CYP3A and P-glycoprotein could lead to variable concentrations of these drug.²⁸

Therefore, concomitant use of the combination drug COBI/EVG/FTC/TDF with these first-generation DAAs is not recommended.¹¹

Sofosbuvir is metabolized in the liver where it is activated into GS-461203.³² While sofosbuvir is a p-glycoprotein and breast cancer resistance protein (BCRP) substrate, its active metabolite is not. Co-administration of drugs that inhibit p-glycoprotein such as RTV may lead to increased sofosbuvir, but not GS-461203 levels. This was demonstrated in 18 individuals who received concurrent DRV/r and sofosbuvir; they had increased sofosbuvir levels, but GS-461203 levels were unchanged. Similar findings were observed when EFV, FTC or RPV were co-administered with sofosbuvir. While raltegravir (RAL) similarly had minimal effect on sofosbuvir and GS-331007 levels, RAL AUC and C_{max} decreased by 27% and 43%, respectively with concomitant sofosbuvir. Consequently, these drug combinations are not recommended.³² Several other DAAs are being evaluated, including daclatasvir and asunaprevir which are likely to have notable DDIs with antiretrovirals as well.³³

DRUG-DRUG INTERACTIONS FOR THE TREATMENT OF CHRONIC CO-MORBID CONDITIONS

Antihypertensive Drugs

The prevalence of hypertension among different HIV-infected cohorts has varied widely from 5.9% to as high as 36.5%.^{34–37} Among the antihypertensive agents, calcium channel blockers (CCB) appear to have the greatest potential to interact with antiretroviral medications.³⁸ The dihydropyridine CCBs, verapamil and diltiazem, inhibit CYP3A4.³⁹ Therefore these medications interact with antiretrovirals that also utilize CYP3A4, including the NNRTI CYP3A4 inducers (e.g. NVP and EFV), or drugs that inhibit this enzyme (e.g. PIs and COBI) (Table 1).

Other antihypertensive agents can also interact with antiretroviral medications. Several of the β -blockers, including propranolol, carvedilol, metoprolol, pindolol, and timolol are metabolized by CYP2D6.⁴⁰ These drugs may interact with CYP2D6 inhibitors, such as EFV or RTV, and clinical monitoring is advised.³⁸ In general, ACE inhibitors and angiotensin II receptor blockers (ARBs) have few interactions with antiretrovirals, with the notable exception of losartan. Losartan is bioactivated by CYP2C9 and further metabolized by CYP3A4, making it susceptible to interactions with inhibitors of CYP2C9, such as EFV or EVG, and of CYP3A4, such as PIs.³⁸

Antiplatelet and Anticoagulation Drugs

Of the antiretroviral agents, PIs and NNRTIs are the most likely to interact with warfarin.⁴¹ Existing as equal part enantiomers, S-warfarin is metabolized primarily through hepatic CYP2C9, whereas R-warfarin is metabolized through CYP3A4, CYP1A2, and CYP2C19.⁴¹ *In vitro* analysis of NNRTIs has demonstrated CYP2C9 inhibition with EFV, ETR, and delavirdine (DLV), and CYP2C9 induction with NVP. Liedtke and Rathburn identified clinical cases of excess anticoagulation using warfarin with EFV and the PI, saquinavir (SQV), and subtherapeutic INR levels with NVP as well as LPV, RTV, and nelfinavir (NFV).⁴¹

Clinical studies of warfarin-antiretroviral interactions, however, have yielded mixed results. Consistent with the above findings, a retrospective analysis of 73 HIV-infected patients on maintenance warfarin therapy noted that patients on EFV required lower dose of warfarin compared those on PI-based regimens to maintain therapeutic levels.⁴² In this analysis, the mean warfarin dose was 46 mg/week for patients on EFV compared to 68 mg/week for patients on LRPV/r ($p = 0.01$) and 71 mg/week for patients on ATV/r ($p = 0.007$). In contrast, the warfarin maintenance dose was higher for 7 patients on EFV compared to age-, sex-, and race-matched controls (mean difference of 3.7 mg, $p < 0.01$); this may be due to EFV-mediated CYP3A4 induction rather than CYP2C9 inhibition. Given the variable effects of NNRTIs and PIs on warfarin metabolism, close monitoring of INR levels in HIV-infected patients on warfarin therapy and cART is essential, especially during drug initiation, dosage changes or changes in antiretroviral class.

Among newer cardiovascular medications are novel oral anticoagulants (NOACs) and antiplatelet agents, such as clopidogrel, prasugrel, or ticagrelor. There is a paucity of published data on the interactions between ARVs and these newer agents. The NOACs, rivaroxaban and apixaban, are metabolized by CYP3A4 and are therefore more likely to interact with PIs, NNRTIs and COBI.⁴³ In a pharmacokinetic study of 12 healthy volunteers, the mean AUC and C_{max} of rivaroxaban increased by 153% and 55%, respectively, when co-administered with RTV.⁴⁴ Since dabigatran is cleared renally, it is less likely to interact with antiretrovirals; however, its prodrug which is a p-glycoprotein substrate, may interact with RTV.⁴³

Clopidogrel requires activation through CYP2C19, and to a lesser extent, CYP2C9,⁴⁵ it but has limited interaction with CYP3A4. Therefore, it is less likely to interact with PIs. Since EFV and ETR inhibit CYP2C19 and CYP2C9, they may decrease the effectiveness of clopidogrel when given concurrently. Among 10 healthy volunteers receiving concurrent prasugrel and RTV, RTV decreased both the C_{max} and AUC of the active form of prasugrel by 45% and 38%, respectively. This is due to decreased prasugrel activation through RTV inhibition of CYP3A4.⁴⁶ Cobicistat may have a similar effect on prasugrel.⁴³ Ticagrelor does not require activation, but is metabolized by and inhibits CYP3A4,⁴⁷ thereby increasing the risk of excess anticoagulation if used in conjunction with other CYP3A4 inhibitors.⁴³

HMG-CoA Reductase Inhibitors (Statins)

Dyslipidemia occurs commonly among HIV-infected patients due to HIV-related effects and antiretroviral medications,⁴⁸ and it contributes to the increased cardiovascular risk among HIV-infected persons.⁴⁹ Of the statins, simvastatin, lovastatin, and atorvastatin are most extensively metabolized by CYP3A4 and therefore, are most likely to interact with PIs especially RTV-boosted PI-based regimens (Table 1).⁴⁹ Because of increased risk of myopathy and rhabdomyolysis, the use of simvastatin or lovastatin in combination PIs is contraindicated, and atorvastatin requires lower doses.⁵⁰

In contrast, pravastatin and rosuvastatin are excreted renally via hOAT3 in proximal tubular cells.⁴⁹ Serum concentrations of pravastatin are reduced by NFV and SQV and may be modestly increased by DRV and LPV.⁴⁹ However, a more recent analysis failed to

demonstrate a significant pravastatin-DRV interaction.⁵¹ Interactions between rosuvastatin and PIs has been reviewed extensively by Chauvin *et al.*⁴⁹ The most substantial interactions occur with increased AUCs of ATV (213%) and LPV (108%). In addition, co-administration rosuvastatin with DRV/r in 12 healthy adult results in a 2.4-fold increase in the C_{max} and a 1.5-fold increase in the AUC of rosuvastatin, without any significant change in the steady-state pharmacokinetics of DRV or RTV.⁵² Although multiple studies have demonstrated altered pharmacokinetics with concomitant rosuvastatin and PI use, one clinical trial showed the combination to be well-tolerated and to lead to better reductions in LDL and triglyceride levels when compared to pravastatin. In this multi-center, open label trial, HIV-infected patients on cART that included a RTV-boosted PI were randomized to receive either pravastatin or rosuvastatin and were followed with serial measurements of serum lipid levels on days 15 and 45, as well as PI trough concentrations on day 15.⁵³ The patients were on a variety of RTV-boosted PIs, with a majority in both arms (~79–83%) taking LPV, FPV, or ATV. At the end of the study, patients in the rosuvastatin arm had a 37% reduction in their LDL-c levels compared with a 19% reduction in the pravastatin group ($p < 0.001$). Triglyceride levels decreased by 19% in the rosuvastatin group compared to 7% in those taking pravastatin ($p < 0.035$). Both rosuvastatin and pravastatin trough levels were within expected ranges, and no adverse effects were observed. Despite these findings, caution is advised with the use of rosuvastatin in combination with PIs, with a recommended starting dose of 5 mg and a maximum dose of 10 mg.⁴⁹

In addition to RTV-boosted PI therapy, interest in the interaction between COBI, and statins has emerged. In a recent analysis of 10 healthy subjects co-administered COBI/EVG with rosuvastatin, there was an increase in the rosuvastatin C_{max} of 89%, but only a 38% increase in the AUC, with no changes in the T_{max} or the $T_{1/2}$ of the drug.⁵⁴ There were no differences in the pharmacokinetics of COBI or EVG when administered with rosuvastatin.⁵⁴ Based on the findings of this study, the authors recommended that rosuvastatin could be co-administered with COBI/EVG.

The newer statin, pitavastatin, is taken up by hepatic OAT1B1 and excreted largely unchanged.⁵⁵ Among 23 healthy subjects, the combination of pitavastatin and twice daily LPV/r did not demonstrate significant differences in serum concentrations of all three drugs when given concurrently versus individually.⁵⁶ Recently the INTREPID study (NCT01301066) was conducted to assess the effects of pitavastatin versus pravastatin in lowering cholesterol in HIV-infected adults receiving cART.⁵⁷ In this multicenter, 12-week, randomized, trial followed by a 40-week safety extension study, patients were randomized to receive either pitavastatin or pravastatin. Participants randomized to pitavastatin had greater reductions of LDL-c levels and had similar adverse event rates compared to those randomized to pravastatin (9.8% difference, $p < 0.01$).

Transplant Medications

With improved survival, HIV-infected persons are developing end-stage liver and kidney diseases leading to an increasing need for solid-organ transplantation. Several multicenter studies have demonstrated the safety of liver and kidney disease transplantation among highly selected HIV-infected patients;^{58–60} however, a huge challenge in managing HIV-

infected transplant recipients is the potential for several interactions between certain antiretroviral and immunosuppressive medications (Table 1).

Most transplant centers rely on a combination of a calcineurin inhibitor (CNI [either cyclosporine or tacrolimus]), prednisone, and mycophenolate mofetil (MMF); less commonly, the mTOR inhibitor, sirolimus, is substituted for the CNIs. The CNIs and sirolimus are metabolized by hepatic CYP3A4 but are also substrates for intestinal CYP3A4 and p-glycoprotein;⁶¹ consequently, co-administration of RTV and other PIs results in significant increases in plasma CNI concentrations.⁶² This was demonstrated in a study of 18 HIV-infected individuals who underwent either kidney or liver transplantation. Participants who received PIs developed a 3-fold increase in cyclosporine AUC when cyclosporine was given concurrently.⁶³ Frassetto and colleagues reported on HIV-infected patients who underwent liver (n=13), kidney (n=20), or combined liver-kidney (n=2) transplantation and had pharmacokinetic studies performed 2–4 weeks and 12 weeks post-transplant and after a modification in immunosuppressive or cART regimens.⁶⁴ Transplant recipients who were on any PI needed a 4- to 5-fold lower cyclosporine dose and a 1.5 fold increase in dosing interval compared to recipients receiving NNRTIs; decreases in dosing and frequency associated with concurrent PI and cyclosporine use were more pronounced in those with RTV-boosted PIs. Co-administration of PIs with tacrolimus led to an 80% decrease in tacrolimus dosing and a 7-fold lengthening of the dosing interval.

Fewer studies have focused on the interactions between NNRTIs and immunosuppressive drugs. Based on the study by Frassetto and colleagues, NVP-cyclosporine co-administration resulted in similar cyclosporine troughs.⁶⁴ In contrast, concurrent EFV-cyclosporine use led to a 45% increased dose requirement for cyclosporine. No reports on the remaining NNRTIs and their interactions with CNIs were identified. Similarly, very little has been reported on DDIs between sirolimus and antiretroviral medications. In the study by Frassetto, sirolimus concentrations were significantly increased and dosing intervals were prolonged among patients who received concurrent PIs; however, no patient received sirolimus in combination with NNRTIs.⁶⁴ When co-administered with NFV in one patient, the 24-hour plasma sirolimus trough level increased by 5-fold and the half-life prolonged by 60%.⁶⁵

Mycophenolate mofetil is a prodrug for mycophenolic acid which, in turn, is metabolized via glucuronidation.⁶⁶ As it is not eliminated by the CYP3A system, drug interactions with PIs or NNRTIs are not anticipated; however, some NRTIs which are also metabolized via glucuronidation may have higher clearance. Contrary to this, there were no differences in the pharmacokinetics among those receiving abacavir or indinavir with versus without MMF after 8 weeks of steady regimens in a study of 19 HIV-infected persons receiving these antiretrovirals as part of cART.⁶⁷ *In vitro* studies have shown that mycophenolic acid may augment antiviral effects of NRTIs through depletion of intracellular deoxyguanosine triphosphate.⁶⁸ When MMF was administered to five patients receiving abacavir, didanosine or TDF, 4 of 5 had a more than 0.5 log₁₀ copies/mL decrease in HIV-1 RNA; however, half lost this decline after 8 weeks.⁶⁹ While no studies specifically evaluated interactions between antiretrovirals and the alternative formulation, mycophenolate sodium, it is expected to have similar drug interactions as MMF.⁷⁰

The integrase inhibitor, RAL, in combination with two NRTIs is a preferred regimen that is an alternative to cART regimens which contain PIs or NNRTIs. Unlike PIs or NNRTIs, RAL is not metabolized by the CYP450 system, rather it is metabolized primarily by the UGT1A1 UDP-glucuronosyltransferase.⁷¹ In a study of 8 liver and 5 kidney transplant recipients who switched from a PI-based cART regimen to one comprised of RAL and two NRTIs, 6 switched to the RAL regimen immediately post-transplant;⁷² target CNI levels were achieved quickly and safely using standard doses. Conversely, the 7 recipients who changed to the RAL regimen at a later time point post-transplant (median 21 months) experienced a significant decline in CNI plasma concentrations and required a 5- to 15-fold up-titration of their CNI doses. Based on the various observed interactions between immunosuppressive and antiretroviral drugs, HIV-infected patients who undergo organ transplantation require careful monitoring for drug toxicity/ efficacy perioperatively and during longitudinal follow-up.

Gastric Acid-Reducing Medications

A large proportion of HIV-infected patients suffer from gastroesophageal reflux or peptic ulcer disease and are often treated with antacids, histamine 2-receptor blockers (H₂R-blockers) and/or proton-pump inhibitors (PPIs), some of which are available over-the-counter. These drugs may influence antiretroviral drug absorption through the gastrointestinal tract by altering gastric acidity or interfering with antiretroviral metabolism or mechanism of action. Ramanathan and colleagues recently characterized the pharmacokinetic changes associated with concurrent use of EVG and acid-reducing medications as EVG binds the integrase enzyme that chelates divalent cations.⁷³ The combination of EVG/r with a divalent-rich antacid decreased EVG AUC by 55%; however, this reduction was mitigated by avoiding EVG administration within 2 hours of antacid intake. Similar drug interactions between antacids and the integrase inhibitors, RAL and dolutegravir, and the PI TPV, have been reported.^{11,74,75}

Ramanathan and colleagues also evaluated antiretroviral drug interactions with H₂R-blockers.⁷⁶ Famotidine co-administered with COBI-boosted EVG, did not influence either EVG or COBI pharmacokinetics, suggesting that reductions in EVG with antacids was likely due to antiretroviral chelation of the cations rather than changes in gastric acidity.⁷⁶ The interaction between ATV, which relies on a low gastric pH for absorption, and famotidine was described among 40 HIV-infected adults receiving ATV/r with or without TDF.⁷⁷ Famotidine co-administration at 40 mg twice daily led to a 23–24% and 20–25% decline in ATV AUC and C_{min}, respectively; this effect on ATV was diminished when famotidine was given at 20 mg twice daily. Similar DDIs have been described between FPV and ranitidine in which FPV AUC declined by 30% and C_{max} by 51%.⁷⁸

All PPIs are metabolized by CYP2C19 and CYP3A4 with the exception of rabeprazole which undergoes sulfoxide reduction. As a result, concurrent use of PIs and PPIs alter antiretroviral concentrations. In an extensive review by McCabe and colleagues, significant reductions in ATV's AUC ranging from 76% to 94% have been reported with co-administration with lansoprazole or omeprazole.⁷⁸ Similar effects have been reported with omeprazole co-administration with NFV or RPV. Conversely, concurrent use of SQV with

omeprazole leads to increased SQV exposure (82% increase in AUC). Concomitant use of FPV with esomeprazole or omeprazole does not modify FPV pharmacokinetics. EVG is also metabolized by CYP3A4 and undergoes glucuronidation by UGT1A1/3.⁷⁹ When COBI-boosted EVG was concurrently used with omeprazole, neither EVG or COBI pharmacokinetics were changed.⁷⁶ In contrast, RAL AUCs were 3- to 4-fold higher when co-administered with omeprazole in 14 healthy subjects.⁸⁰ This increased RAL exposure was attributed to increased drug absorption with higher gastric pH and/or omeprazole inhibition of p-glycoprotein.

MANAGEMENT OF DRUG-DRUG INTERACTIONS

Because of the large number of antiretroviral drugs that depend on the CYP450 system and/or various transporters and the need to treat a growing number of co-morbid conditions, polypharmacy and DDIs are of great concern among HIV-infected patients, especially among the elderly. Appropriate management of HIV-infected patients requires awareness of DDIs as well as vigilance for drug-related adverse effects and drug efficacy. This approach involves collaboration and effective communication among patients and their clinicians, infectious disease specialists, and pharmacists. While generalizations with regard to the potential for drug interactions can be made for certain drug classes such as PIs and NNRTIs, the same cannot be applied in others. The metabolism of drugs within a given class (e.g. statins and PPIs) varies significantly due to differences on the degree to which they are metabolized by and inhibit/ induce specific enzymes. Inter-individual variability in enzyme activity due to genetic polymorphism also impacts drug interactions. Therefore, the specific drugs being co-administered must be considered in determining drug interactions.

An important aspect in the management of potential drug interactions in HIV-infected patients includes the impact on drug efficacy and toxicity when adding new medications to an existing regimen or withdrawing drugs which interact with the remaining drugs in the regimen.⁸¹ When adding a new drug, one should evaluate its potential interaction with the patient's current list of medications, including those which are over-the-counter. If a potential drug-drug interaction is identified and the potential benefits of adding the new medication outweighs the risks, an alternative agent with less potential for drug interaction should be considered. In addition, empiric dose modification should be considered upon withdrawal of a drug with a known interaction which could affect therapeutic levels of the remaining drugs (e.g. RTV discontinuation for boosted PIs). Krakower and colleagues reviewed several online resources to facilitate the recognition of DDIs.⁸² One notable online resource is the Guidelines for the Use of Antiretroviral Agents in HIV-Infected Adults and Adolescents provided by the U.S. Department of Health and Human Services. This free online resource is updated regularly by a panel of experts.¹¹

Therapeutic drug monitoring has been proposed as an approach to ensure effective viral suppression while minimizing risk for drug toxicity and enhancing treatment adherence. However, randomized clinical trials and cohort studies have demonstrated conflicting results as to the benefit of this approach.⁸³ These findings may result from significant intra-individual variability in drug plasma levels perhaps due to DDIs, food-drug interactions, assay variability, and inaccurate patient recall of last dose.⁸⁴ With these caveats aside,

therapeutic drug monitoring may have a role in patients who are at significant risk DDIs (e.g. co-administration with PI or NNRTI) or have failed to attain virologic suppression, or in whom prediction of systemic drug exposure is less reliable (pediatric patients).^{83,85}

CONCLUSIONS

Interactions among antiretroviral medications and other drugs used for the treatment of chronic co-morbid conditions in HIV-infected patients occur frequently. These interactions have important implications for maintenance of therapeutic drug levels, avoidance of inducing HIV and HCV drug resistance, and minimization of drug-related adverse effects. Several websites geared for clinicians caring for HIV-infected patients exist which provide up-to-date information on potential drug interactions and guidance on managing patients at risk. To achieve the goal of effective viral suppression while minimizing drug toxicity, a multidisciplinary approach is ideal.

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Table 1

Drug-Drug Interactions between Antiretroviral Drugs and Common Drugs

CO-ADMINISTERED DRUG	ANTIRETROVIRAL DRUG	EFFECT	RECOMMENDED ACTION
ANTI-HCV DRUGS			
NS3/4A protease inhibitors (e.g. telaprevir, boceprevir, and simprevir)	DRV/r	↓ telaprevir/boceprevir ↑ simeprevir ↓ anti-HIV PI	Co-administration with anti-HIV PIs should be avoided except ATV/r
	LPV/r		
	FPV/r		
	RPV	↓ telaprevir, boceprevir ↑ RPV	Avoid concurrent use
	EFV	↓ simeprevir	Avoid concurrent use
	NVP	↓ telaprevir/boceprevir ↑ NVP	Avoid concurrent use
	ETR	↓ telaprevir/boceprevir ↓ ETR	↑ telaprevir dose; no dose adjustment of boceprevir indicated
	MVC	↑ MVC	Avoid concurrent use
	TDF	↓ telaprevir ↑ TDF	Clinical monitoring for TDF toxicity
	EVG/COBI/TDF/FTC	No data	Avoid concurrent use
Nucleotide analogue (sofosbuvir)	RAL	↓ RAL	Avoid concurrent use
ANTIHYPERTENSIVE DRUGS			
Dihydropyridine CCBs (e.g. verapamil, diltiazem)	All PIs	↑ CCB	↓ CCB dose and titrate slowly
	NNRTIs	↓ CCB	Adjust CCB dose as needed to therapeutic level
	EVG/COBI/TDF/FTC	↑ CCB	Clinical monitoring advised
β-blockers (e.g. metoprolol, timolol)	RTV	↑ CCB	Clinical monitoring advised
	EFV	↓ CCB	Adjust CCB dose as needed to therapeutic level
	EVG/COBI/TDF/FTC	↑ β-blockers	Clinical monitoring advised
Losartan	PIs	↓ losartan	Adjust losartan dose as needed to therapeutic level
	EFV		
	EVG/COBI/TDF/FTC		
ANTIPLATELET/ANTICOAGULANT DRUGS			
Warfarin	All PIs	Variable effects on warfarin	Monitor INR and adjust warfarin dose when initiating/ discontinuing PI or NNRTI
	EFV, ETR, DLV	Variable effects on warfarin	
	EVG/COBI/TDF/FTC	Potential ↓ warfarin	Monitor INR and adjust warfarin dose when initiating/ discontinuing EVG/ COBI/TDF/FTC
Novel oral anticoagulants (e.g. rivaroxaban, apixaban, dabigatran)	All PIs	↑ rivaroxaban/apixaban	Avoid concurrent use; consider dabigatran if needed
Antiplatelet agents (e.g. clopidogrel, prasugrel, ticagrelor)	RTV	↓ active prasugrel ↑ ticagrelor	Avoid concurrent use with prasugrel or ticagrelor

CO-ADMINISTERED DRUG	ANTIRETROVIRAL DRUG	EFFECT	RECOMMENDED ACTION
	EFV or ETR	↓ active clopidogrel/ prasugrel/ ticagrelor	Concurrent clopidogrel with EFV or ETR not recommended
	NVP	↓ active prasugrel/ticagrelor	
	COBI	↓ active prasugrel ↑ ticagrelor	Avoid concurrent use with prasugrel or ticagrelor
HMG CoA-REDUCTASE INHIBITORS (STATINS)			
Atorvastatin	All PIs	↑ atorvastatin	Avoid concurrent use of TPV/r. For other PIs use lowest dose needed and day
	EFV, ETR	↓ atorvastatin	Adjust atorvastatin dose for therapeutic level
	EVG/COBI/TDF/FTC	↓	Use lowest dose of atorvastatin needed
Lovastatin	All PIs	↑↑ lovastatin	Avoid concurrent use
	ETR	↓ lovastatin	Adjust lovastatin dose for therapeutic level. Avoid concurrent use if ETR used in conjunction with RTV-boosted PI
	EVG/COBI/TDF/FTC	↑↑ lovastatin	Avoid concurrent use
Pitavastatin	ATV	↑ pitavastatin	No dose adjustment indicated
	LPV/r	↓ pitavastatin	
Pravastatin	DRV/r	↑ pravastatin	Use lowest dose of pravastatin when combined with DRV/r. No dose adjustment indicated with LPV/r or SQV/r
	LPV/r	↑ pravastatin	
	SQV/r	↓ pravastatin	
	EFV	↓ pravastatin	Adjust pravastatin dose for therapeutic level
Rosuvastatin	ATV/r, LPV/r, DRV/r, TPV/r	↑ rosuvastatin	Use lowest dose of rosuvastatin needed. Do not exceed 10 mg per day when given with either ATV/r or LPV/r
	EVG/COBI/TDF/FTC	↑ rosuvastatin	Use lowest dose of rosuvastatin needed
Simvastatin	All PIs	↑↑ simvastatin	Avoid concurrent use
	NVP, ETR	↓ simvastatin dose	Adjust simvastatin dose for therapeutic level. Avoid concurrent use if NVP or ETR used in conjunction with RTV- boosted PI
	EVG/COBI/TDF/FTC	↑↑ simvastatin	Avoid concurrent use
TRANSPLANT MEDICATIONS			
Calcineurin inhibitors (e.g. cyclosporine, tacrolimus)	All PIs	↑↑ cyclosporine/tacrolimus	Start at lower doses and monitor CNI trough levels; potentially less DDI risk with RAL-based cART
	EFV, NFV	↑ cyclosporine/tacrolimus	
Sirolimus	All PIs	↑↑ sirolimus	
GASTRIC ACID-REDUCING MEDICATIONS			
Antacids	ATV, ATV/r, FPV, TPV/r	↓ level of PI	Administer PI 2h before/2h after antacid

CO-ADMINISTERED DRUG	ANTIRETROVIRAL DRUG	EFFECT	RECOMMENDED ACTION
	RPV	↓ RPV	Administer RPV 4h before/ 1h after antacid
	EVG/r, EVG/COBI/TDF/FTC	↓ EVG	Administer EVG 2h before/ after antacid
H₂ Receptor-Blocker	ATV, ATV/r	↓ ATV	Administer ATV 2h before H ₂ R-blocker; do not exceed famotidine 20 mg twice daily or dose equivalent
	FPV	↓ FPV	Administer FPV 2h before H ₂ R-blocker; consider RTV- boosting
	RPV	↓ RPV	Administer RPV 4 h before/12h after H ₂ R- blocker
Proton Pump Inhibitors (PPIs)	ATV, ATV/r	↓ ATV	Avoid concomitant PPIs with unboosted ATV. Administer PPI 12h before ATV/r. Do not exceed PPI dose equivalent of omeprazole 20 mg daily
	DRV/r, TPV/r	↓ omeprazole	May require higher omeprazole dose
	NFV	↓ NFV	Avoid concomitant use
	SQV	↑ SQV	Monitor for SQV toxicity
	RPV	↓	Avoid concomitant use
	RAL	↑RAL	No dose adjustment indicated

Abbreviations: Protease Inhibitors (PIs): ATV, atazanavir; DRV, darunavir; FPV, fosamprenavir; NFV, nelfinavir; RTV, ritonavir; SQV, saquinavir; TPV, tipranavir Non-nucleoside Reverse Transcriptase Inhibitors (NNRTIs): DLV, dlatravir; EFV, efavirenz; ETR, etravirine; NVP, nevirapine; RVP, rilpivirine; Other antiretrovirals: MVC, maraviroc; EVG, elvitegravir; COBI, cobicistat; TDF, tenofovir; FTC, emtricitabine; RAL, raltegravir