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Addressing Antiretroviral Therapy-Associated Drug-Drug Interactions in Patients Requiring Treatment for Opportunistic Infections in Low-Income and Resource-Limited Settings

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Abstract

An increasing number of human immunodeficiency virus (HIV)-infected patients are achieving virologic suppression on antiretroviral therapy (ART) limiting the use of primary and secondary antimicrobial prophylaxis. However, in low-income and resource-limited settings, half of those infected with HIV are unaware of their diagnosis, and fewer than 50% of patients on ART achieve virologic suppression. Management of comorbidities and opportunistic infections among patients on ART may lead to inevitable drug-drug interactions (DDIs) and even toxicities. Elderly patients, individuals with multiple comorbidities, those receiving complex ART, and patients living in low-income settings experience higher rates of DDIs. Management of these cytochrome P450-mediated, nonmediated, and drug transport system DDIs is critical in HIV-infected patients, particularly those in resource-limited settings with few options for ART. This article critically analyzes and provides recommendations to manage significant DDIs and drug toxicities in HIV-infected patients receiving ART.

Keywords

antiretroviral therapy, drug-drug interactions, opportunistic infections, HIV, AIDS

Burden of Human Immunodeficiency Virus Worldwide

Approximately 37 million people worldwide are living with human immunodeficiency virus (HIV), of which almost half remain undiagnosed.[1] According to the World Health Organization (WHO)/UNAIDS, close to 95% of HIV infections are in individuals living in developing countries, and two thirds of them live in sub-Saharan Africa. In this context the designation of a developing country is important to conceptualize: it refers to countries with a less-developed industrial base and a low human development index compared to other countries. Similarly, the World Bank divides countries or economies into 4 income groups: low, lower-middle, upper-middle, and high. Low-income economies are defined by a gross national income per capita of less than $1025 in 2015. A complementary categorization of nations based on financial resources defines low-resource settings as those state nations where there are insufficient financial resources to cover healthcare costs on an individual or societal basis, leading to poor access to medications and other medical interventions. Based on any of the above categorizations, the greatest burden of disease caused by HIV infection continues to occur among people living in low-income and resource-limited settings. In many of these settings acquired immune deficiency syndrome (AIDS)-related morbidity and mortality due to opportunistic infections (OIs) remain unacceptably high. Although the introduction of antiretroviral therapy (ART) and antimicrobial prophylaxis has significantly decreased the incidence of OIs, they continue to cause significant morbidity and mortality both among infected persons not on ART and among those who are unable to achieve virologic suppression.[1,2]

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Achieving virologic suppression is the ultimate goal of ART that provides important individual benefits but also provides a population-based benefit by decreasing further HIV transmission. Yet, among all patients infected with HIV, only 30% in the United States achieve virologic suppression, compared to 32% in sub-Saharan Africa, 52% in France, and 68% in Switzerland.[3] Furthermore, worldwide only 41% of those affected with HIV/AIDS are receiving ART, with an average CD4 less than 350 cells/mm^3 at initiation of therapy,[4,5] despite clear guidance from the WHO recommending that ART be initiated in everyone living with HIV at any CD4 cell count.[6] In low-income and resource-limited settings many patients do not receive ART until their CD4 cell count has decreased to less than 200 cells/mm^3.[7] Overall, AIDS-related mortality has shifted to include non-HIV-related infections in those maintaining virologic suppression with ART.[8] In contrast, mortality in resource-limited settings remains high and is commonly linked to OIs, particularly tuberculosis and cryptococcal meningitis.[7]

Given the increasing deployment of ART to low-income and resource-limited settings coupled with existing limitations in terms of clinical and pharmacologic monitoring of patients in many of these settings, it is crucial to reduce any potential pharmacologic drug toxicities. The potential for drug-drug interactions (DDIs) is increasing as a result of medical management of acute and chronic comorbid disease states coupled with early ART initiation and a longer life expectancy.[9,10] High rates of DDIs have been reported in a variety of patient populations.[11,12] Although newer antiretroviral agents tend to be less problematic with respect to adverse effects and DDIs, options for ART in low-income and resource-limited settings are often limited due to cost or infrastructural constraints, which results in inevitable DDIs and toxicities. Continued use of older, less optimal ART, typically reserved as second- or third-line throughout much of the world, represents a major obstacle in achieving virologic suppression due to lower genetic barriers and worse tolerability and patient satisfaction. Unfortunately, for these reasons, many patients progress, developing AIDS with concomitant occurrence of OIs that require management with antimicrobial agents, which continue to be identified as common causes of DDIs. Pharmacokinetic (PK) DDI studies focusing on clinical outcomes are scarce owing to the inconsistencies between theoretical and clinical practice.[13] Therefore, the purpose of this review article is to critically and systematically summarize clinically significant DDIs and drug toxicities in patients receiving ART in low-income or resource-limited settings. This is an important intervention given the fact that HIV-infected individuals in these settings often require antimicrobial drugs for the prevention or treatment of OIs or drug treatment of other comorbidities, or there may be insufficient resources for ART modification.

Methods

A systematic electronic literature search of the PubMed, MEDLINE, and Google Scholar databases was performed to identify articles related to ART and relevant DDIs. The following search terms were used either independently or in combination for all databases: antiretroviral agents, nucleoside reverse transcriptase inhibitors, nucleotide reverse transcriptase inhibitors, nonnucleoside reverse transcriptase inhibitors, HIV protease inhibitors, integrase strand transfer inhibitors, CCR5 receptor antagonist, specific antiretroviral drug names, drug interactions, PK, *Pneumocystis jirovecii* pneumonia (PCP), *Toxoplasma gondii*, *Mycobacterium tuberculosis* (TB), *Mycobacterium avium* complex (MAC), and *Cryptococcus neoformans*. English language trials published from 1995 to March 2017 were considered. Articles were screened by title and abstract for inclusion, and references within articles of interest were searched for any additional manuscripts.

Discussion

Mechanisms for Drug-Drug Interactions

Clinically significant DDIs occur frequently in HIV-infected patients treated with ART, with an increased incidence among the elderly, those with multiple comorbid conditions, those receiving complex regimens, and those living in low-income or resource-limited settings.[11,12,14] The majority of DDIs are the result of ART metabolism via the cytochrome P450 (CYP) system, particularly CYP3A, CYP2D6, CYP2C9/19, and CYP2B6, but may also be mediated through drug transporters such as organic anion transporting polypeptide or elimination mechanisms including p-glycoprotein (PGP).[15,16]

Metabolic Pathways for Antiretroviral Therapy. Nucleos(t)ide reverse transcriptase inhibitors, the backbone of ART, typically do not undergo CYP metabolism, making them less prone to DDIs[17,18] (Table 1[18–37]). Alternatively, nonnucleoside reverse transcriptase inhibitors undergo extensive hepatic metabolism. Nevirapine has the largest list of involved CYP isozymes, whereas rilpivirine has the fewest. Although efavirenz is widely believed to induce CYP3A4 via activation of human nuclear pregnane X receptor, recent data suggest that the parent molecule is actually a CYP3A activator.[24,26] CYP3A activation, preferentially through the human constitutive

Table 1. Metabolic Pathways of Antiretroviral Drugs

Antiretroviral Drug	Substrate	Inhibits	Induces
Nucleos(t)ide reverse transcriptase inhibitors			
Abacavir[17–19]	UGT1A1	...	...
Emtricitabine[17–19]	...	...	...
Lamivudine[17–19]	...	...	...
Tenofovir alafenamide[19,20]	PGP OATP	...	...
Tenofovir disoproxil fumarate[17–19]	PGP OATP	...	...
Zidovudine[21–23]	Glucuronidation	...	...
Nonnucleoside reverse transcriptase inhibitors			
Efavirenz[18,19,24–26]	CYP3A CYP2B6 CYP2A6	CYP2C9 CYP2C19	CYP3A activator CYP3A4 CYP2B6
Etravirine[18,19,27]	CYP3A CYP2B6 CYP2D6	CYP2C9 CYP2C19	CYP3A4
Nevirapine[18,19,28]	CYP3A CYP2B6 CYP2D6	CYP1A2	CYP3A4 CYP2B6
Rilpivirine[18,19,29]	CYP3A4	...	...
Protease inhibitors			
Atazanavir[19,30,31]	CYP3A PGP	CYP3A CYP2C8 UGT1A1 OATP	...
Darunavir[19,30,32]	CYP3A PGP	CYP3A OATP	CYP2C9
Fosamprenavir[19,30]	CYP3A PGP	CYP3A	CYP3A4
Lopinavir[19,30,33]	CYP3A PGP	CYP3A OATP	...
Saquinavir[19,30,34]	CYP3A PGP	CYP3A OATP	...
Ritonavir[19,30]	CYP3A PGP	CYP3A CYP2D6 OATP	CYP3A4 CYP1A2 CYP2C8 CYP2C9 CYP2C19 UGT1A1
Tipranavir[19,30,35]	CYP3A PGP	CYP2D6	CYP3A4 CYP1A2 CYP2C19
Integrase strand transfer inhibitors			
Raltegravir[19,39]	UGT1A1 UGT1A3 UGT1A9 CYP3A	...	...
Elvitegravir[19,36]	CYP3A UGT1A1 UGT1A3	...	CYP2C9
Dolutegravir[19,36]	UGT1A1 UGT1A3 UGT1A9 CYP3A PGP BCRP	...	...
Entry and fusion inhibitors			
Maraviroc[19,37]	CYP3A PGP	...	...
Enfuvirtide[19]	...	...	...
Pharmacokinetic enhancers			
Cobicistat[19]	CYP3A	CYP3A CYP2D6	...

BCRP indicates breast cancer resistance protein; CYP, cytochrome P; OATP, organic anion transporting polypeptide; PGP, p-glycoprotein; UGT, uridine diphosphate glucuronosyltransferase.

androstane receptor, occurs almost immediately, whereas induction is a slower process requiring gene transcription to produce an increased concentration of the enzyme. Protease inhibitors are extensively metabolized via CYP3A and are both substrates and inhibitors of PGP.[17,18,30] The integrase strand transfer inhibitors have exclusive PK properties, many involving metabolism by uridine diphosphate (UDP)-glucuronosyltransferase (UGT).[36] Maraviroc, a CCR5 receptor antagonist, is primarily metabolized by CYP3A and is a substrate of PGP.[37]

The Effects of Inflammation and Infection on Drug Metabolism and Transport. Inflammation and infectious diseases may downregulate CYP enzymes, leading to 20% to 70% decreased metabolism of CYP substrates or diminished activity of compounds requiring bioactivation.[38,39] The effects of inflammatory cytokines, including interleukin-6, interleukin-1β, tumor necrosis factor-α, and interferons α and γ have been identified as mechanisms of CYP regulation during inflammatory processes.[40] Additionally, decreased capacity of drug transporter proteins, such as breast cancer resistance protein and PGP, has been reported.

HIV, a disease characterized by inflammation and immune activation, may affect the metabolism, distribution, and elimination of drugs, including ART.[38,39] Increased concentrations of soluble CD14 (sCD14) and sCD163, biomarkers of monocyte activation leading to inflammatory cytokine release, have been observed in HIV-infected patients with ongoing viral replication.[41–43] Concern exists that

untreated HIV may downregulate drug transporters, drug-metabolizing enzymes, and clinically significant DDIs secondary to ongoing inflammation. Higher concentrations of inflammatory markers are directly associated with higher viral loads, lower CD4 counts, older age, ethnicities excluding African, diabetes mellitus, cardiovascular disease, renal disease, coinfection with hepatitis, higher body weight, and smoking.[44]

Some evidence suggests that patients treated with ART continue to have 40% to 60% higher concentrations of interleukin-6 compared to seronegative individuals,[45] and other studies have shown reductions in inflammatory cytokines following ART initiation.[46] These contradictory findings may be related to the effects of different ART regimens on inflammation. Decreases in inflammatory biomarkers were observed following switches from ritonavir-boosted protease inhibitor-, nonnucleoside reverse transcriptase inhibitor-, or fusion inhibitor- to raltegravir-based regimens.[47–50] Similarly, a recent randomized trial revealed significantly greater decreases in biomarkers of monocyte activation and systemic inflammation with coformulated elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate compared with efavirenz/emtricitabine/tenofovir disoproxil fumarate.[51]

Normalization of drug transporter and DME function is expected to occur with decreasing inflammation and immune activation following ART initiation and reductions in viral replication. The potential for significant DDIs may increase as CYP enzymes and drug transporter proteins return to normal levels. As a result, negative consequences may occur including viral breakthrough, resistance, suboptimal disease state management, or drug toxicity.

Opportunistic Infections

Pneumocystis jirovecii Pneumonia

Pneumocystis jirovecii, formerly *Pneumocystis carinii*, is responsible for causing PCP in HIV-infected individuals, particularly those who are not linked to care, noncompliant, or unaware of their HIV infection.[52–55] Trimethoprim/sulfamethoxazole (TMP/SMX) remains the drug of choice.[56] For patients unable to tolerate TMP/SMX, alternatives include dapsone and TMP, primaquine and clindamycin, atovaquone, or intravenous pentamidine. ART should be initiated within 2 weeks following PCP diagnosis, as data suggest decreased rates of AIDS progression and mortality.

TMP and SMX undergo hepatic metabolism to form multiple metabolites.[57] SMX is partially acetylated and glucuronide-conjugated via CYP2C9. Clinically significant CYP-mediated DDI with TMP/SMX and concomitant ART are nonexistent. TMP may decrease the renal elimination of emtricitabine, lamivudine, and zidovudine due to inhibition renal drug transporters, organic cation transporter 2, and multidrug and toxin extrusion proteins MATE1 and MATE2-K.[58] Dose modification for emtricitabine, lamivudine, or zidovudine is not warranted.[21,58,59]

Dapsone, a major substrate of CYP3A and minor substrate of CYP2C19, CYP2C8, CYP2C9, and CYP2E1,[60] is contraindicated with saquinavir/ritonavir due to the potential for QT prolongation and development of life-threatening arrhythmias[34] (Table 2[15,22,23,25,27,28,31–37,56,60–67–97]). Primaquine undergoes CYP2D6- and CYP3A-mediated metabolism while inhibiting and inducing CYP1A2.[69] Concomitant administration with ART has not been well studied but does not require dose adjustments. Caution is advised with ART that may prolong the QT interval. Coadministration of CYP3A inhibitors or CYP3A4 inducers, such as protease inhibitors or etravirine, respectively, may alter serum concentrations of clindamycin but does not necessitate dose adjustments.[96] Atovaquone is eliminated almost exclusively via feces with no significant hepatic metabolism.[61] Lower atovaquone areas under the concentration-time curve (AUCs) were observed when it was administered with lopinavir/ritonavir, atazanavir/ritonavir, and efavirenz, by 70%, 50%, and 75%, respectively, as a result of glucuronidation.[62] Standard doses of atovaquone should be administered with high-fat meals to increase bioavailability and avoid subtherapeutic concentrations. Intravenous pentamidine is metabolized by CYP2C19, CYP2D6, and CYP1A1 and weakly inhibits CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4.[68] Pentamidine may prolong the QT interval and should be used cautiously in patients treated with ART that may cause additive effects.

TMP/SMX should be preferentially used for the treatment of mild-to-moderate and moderate-to-severe PCP due to minimal DDIs with ART.

Toxoplasmic Encephalitis

The incidence of encephalitis caused by *Toxoplasma gondii* is reflective of seropositivity, ranging from 11% in the United States to >80% in European, Latin American, and African countries.[81] It most commonly occurs in patients with CD4 counts <100 cells/mm^3 not receiving prophylaxis.[97,98] Preferred therapy includes a combination of pyrimethamine and sulfadiazine.[56] Clindamycin may be substituted for patients unable to tolerate sulfadiazine, and TMP/SMX monotherapy may be used if pyrimethamine is not readily available.[56,97–101] ART should be started within 2 to 3 weeks of toxoplasmic encephalitis diagnosis.

Table 2. Dosing Recommendations for Managing Common Antiretroviral Therapy-Associated Drug Interactions

Drug	Standard Dosing	Dosing Modifications/Comments
Atovaquone[56,61,62]	750 mg twice daily, oral	• No dosing modifications required • Administer with high-fat meals
Dapsone[34,60]	100 mg daily, oral	• No dosing modifications required • Caution with drugs that prolong QT interval
Clarithromycin[25,27,28,31–37,56,63,64]	500 mg twice daily, oral	• Avoid with all nonnucleoside reverse transcriptase inhibitors • No dosing modifications required with protease inhibitors in absence of renal dysfunction, except atazanavir (decrease clarithromycin by 50%) • No dosing modifications required with integrase strand transfer inhibitors in absence of renal dysfunction • Decrease maraviroc to 150 mg twice daily in absence of renal dysfunction
Fluconazole[22,23,25,27,56,65–67]	100-800 mg daily, intravenous or oral	• No dosing modifications required with nucleos(t)ide reverse transcriptase inhibitors • No dosing modifications required with nucleoside reverse transcriptase inhibitors, but avoid with nevirapine • No dosing modifications required with protease inhibitors, except tipranavir/ritonavir (limit fluconazole to 200mg/day) • No dosing modifications required with integrase strand transfer inhibitors
Isoniazid[15,56]	300 mg daily, oral	• No dosing modifications required • Supplement with pyridoxine for isoniazid-associated peripheral neuropathy • Caution with drugs that cause peripheral neuropathy
Pentamidine (intravenous)[56,68]	4 mg/kg, intravenous	• No dosing modifications required • Caution with drugs that prolong QT interval
Primaquine[56,69]	30 mg (base) daily, oral	• No dosing modifications required • Caution with drugs that prolong QT interval
Pyrimethamine[56,70,71]	≤ 60 kg: 50 mg daily, oral > 60 kg: 75 mg daily, oral	• No dosing modifications required • Supplement with leucovorin to prevent myelosuppression
Rifabutin[56,72–81]	5 mg/kg daily, oral (maximum dose 300 mg/d)	• Decrease rifabutin to 150 mg once daily with all protease inhibitors, except atazanavir/ritonavir (150 mg 3 times per week) • Increase efavirenz to 450 mg once daily • Avoid with rilpivirine due to increased risk of QT prolongation • No dosing modifications required with nevirapine or etravirine • No dosing modifications required with raltegravir or dolutegravir • Avoid with elvitegravir-containing regimens • No dosing modifications required with maraviroc
Rifampin[56,82–97]	10 mg/kg daily, oral (maximum dose 600 mg/d)	• Avoid with all protease inhibitors • Avoid starting nevirapine in ART-naive patients, can continue if ART-experienced on nevirapine-containing regimen • Efavirenz 600 mg once daily unless >60 kg, increase to 800 mg once daily • Avoid with rilpivirine • Avoid with etravirine • Increase raltegravir to 800 mg twice daily • Avoid with elvitegravir-containing regimens • Increase dolutegravir to 50 mg twice daily • Increase maraviroc to 600 mg twice daily

ART indicates antiretroviral therapy.

Pyrimethamine is metabolized via hepatic enzymes with a half-life of 96 hours and inhibits CYP2C8, CYP2C9, and CYP2D6.[70] Supplementation with leucovorin, folinic acid, is recommended because pyrimethamine may cause folic acid deficiency resulting in bone marrow suppression.[77] Although ART dose adjustments are not required, concomitant administration of zidovudine may increase the risk of myelosuppression, necessitating more frequent hematologic monitoring if unavoidable.

Sulfadiazine is a major substrate and inhibitor of CYP2C9.[102] Administration with ritonavir-boosted protease inhibitors or elvitegravir may decrease sulfadiazine concentrations via CYP2C9 induction.[103] Increasing sulfadiazine doses to overcome induction is not recommended because clinical outcomes are unchanged.[104] More frequent monitoring of renal function is warranted for earlier identification of renal dysfunction or acute renal failure secondary to crystalluria or urolithiasis associated with higher concentrations of sulfadiazine hydroxylamine metabolite.

Due to limited data evaluating concomitant use of protease inhibitor- or integrase strand transfer inhibitor-based ART with pyrimethamine and sulfadiazine, patients should be monitored frequently for clinical improvement and laboratory abnormalities.

Mycobacterium tuberculosis

Reactivation of TB may occur after HIV infection at any CD4 cell count[105] and is associated with an estimated risk of 3% to 16% annually.[106] Worldwide, an estimated 1.1 million individuals with HIV were diagnosed with TB in 2013,[107] with 80% occurring in Africa.[80] Despite clinical and survival benefit with concomitant treatment of HIV and TB, only one third of coinfected patients are started on ART due to concerns with adherence, DDIs, adverse events, toxicities, and immune reconstitution inflammatory syndrome.[56,108,109]

Treatment for latent TB includes isoniazid and pyridoxine for 9 months.[56] Isoniazid undergoes acetylation via N-acetyl transferase 2 to inactive compounds.[110,111] Didanosine and stavudine should be avoided in patients receiving isoniazid due to increased risk of peripheral neuropathy.[56]

Initially, a 4-drug induction regimen consisting of a rifamycin, isoniazid, pyrazinamide, and ethambutol should be administered in HIV-infected patients undergoing treatment for TB, followed by a combination rifamycin and isoniazid.[56] If rifampin resistance is suspected, the initial regimen should be modified to include at least a fluoroquinolone, levofloxacin or moxifloxacin, an aminoglycoside, amikacin or kanamycin, or capreomycin based on susceptibility testing. Initiation of TB therapy in patients treated with ART should be done with caution due to the risk of DDI, particularly with rifamycins.[82]

The rifamycins, including rifampin, rifapentine, and rifabutin, are moderate to potent CYP inducers.[82] Rifampin is a potent inducer of CYP3A4 and CYP2C metabolism as well as an inducer of PGP, leading to increased drug efflux. Coadministration may decrease serum concentrations of protease inhibitors by up to 95%,[83] which cannot be overcome by boosting with ritonavir.[84] Doubling the dose of ritonavir-boosted protease inhibitors, including atazanavir[83] and lopinavir,[85] in patients receiving rifampin led to gastrointestinal intolerance, hepatoxicity, and premature drug discontinuation[84,86] and therefore should be avoided.

Compared to protease inhibitors, the extent of rifampin-induced metabolism of nonnucleoside reverse transcriptase inhibitors is far less.[82] Nevirapine is metabolized by CYP3A, CYP2B6, and CYP2D6. When administered with rifampin, nevirapine concentrations are decreased by up to 55%.[15,87] In addition, increased rates of hypersensitivity reactions were observed following increased doses of nevirapine[88] and should not be started in ART-naive patients. Interestingly, nevirapine-containing regimens can be continued in those contracting TB while on nevirapine-based ART as the addition of anti-TB therapy did not increase the risk of virologic failure.[89] Conflicting data exist surrounding optimal efavirenz dosing in combination with rifampin, although this may be attributed to varying pharmacogenetic characteristics between ethnicities and races.[90,91] While efavirenz AUC and minimum concentrations (C_{min}) are decreased, standard efavirenz doses of 600 mg per day are recommended in most patients treated with rifampin.[56] Efavirenz doses should be increased to 800 mg per day in patients weighing more than 60 kg. Rilpivirine and etravirine are metabolized via similar metabolic pathways and should be avoided in combination with rifampin based on data revealing decreased rilpivirine AUCs by up to 80%.

Trough concentrations of raltegravir may be decreased by approximately 60% with concomitant rifampin-based anti-TB therapy.[92] Increasing raltegravir to 800 mg twice daily may provide adequate drug exposure, but low trough concentrations persist. Although not directly correlated with virologic outcomes,[93] raltegravir trough concentrations were observed to be above the minimum effective concentration 1 and 2, as previously identified.[94,95] If coadministration is unavoidable, doubling the dose of raltegravir with daily or 3 times per week rifampin is recommended to ensure viral suppression.[96] Significantly decreased serum concentrations of elvitegravir, most commonly administered as elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate

or elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide, are expected with concomitant rifampin due to CYP3A4 induction and should be avoided.[56] Limited data suggest that dolutegravir 50 mg twice daily provides comparable concentrations to that of once daily dolutegravir 50 mg, with and without rifampin, respectively.[81] However, this dosing scheme should not be used in patients with baseline integrase strand transfer inhibitor resistance.

Because maraviroc is a CYP3A and PGP substrate, concurrent use with rifampin led to a decrease in maraviroc concentration and AUC.[97] Doubling the dose of maraviroc in combination with rifampin yields similar concentrations and AUC to those observed without rifampin. Maraviroc 600 mg twice daily should be used when it is concomitantly administered with rifampin.

Historically, rifabutin has been unavailable in resource-limited settings due to limited access and cost until recently.[112] Compared to rifampin, rifabutin is a weak CYP3A4 inducer but is also a CYP3A substrate.[72] DDIs are much more manageable, but rifabutin concentrations may be affected by concomitant CYP3A inhibitors or CYP3A4 inducers. Clinically, it is as efficacious as rifampin-based TB therapy.[56]

Rifabutin does not significantly affect serum concentrations or therapeutic efficacy of protease inhibitors, contrary to rifampin.[72] Instead, protease inhibitors significantly increase rifabutin concentrations, although decreasing rifabutin doses may lead to subtherapeutic concentrations and promote acquired rifamycin resistance.[56] Administration of rifabutin 150 mg once daily in HIV-infected patients receiving lopinavir/ritonavir-containing ART achieved therapeutic concentrations more often than those receiving rifabutin 150 mg 3 times per week, and it was well tolerated.[73] Alternatively, higher rates of neutropenia were observed in HIV-negative patients receiving atazanavir/ritonavir with rifabutin 150 mg once daily compared to twice weekly.[74] Simulation data revealed that 3 times per week dosing achieved comparable concentrations to standard rifabutin dosing. Based on these data, rifabutin 150 mg daily should be administered with all protease inhibitor-based ART except for atazanavir/ritonavir, when it should be administered as 150 mg 3 times per week.[75]

Combinations of standard doses of nevirapine and rifabutin 300mg once daily had no impact on PK data, therefore negating the requirement for dose adjustments.[76] Although rifabutin did not alter efavirenz concentrations, efavirenz decreased rifabutin mean concentration and AUC by 29% and 37%, respectively.[77] Increasing the dose of rifabutin to 450 mg once daily provides therapeutic concentrations sufficient to overcome efavirenz based induction.[75] The AUC of rilpivirine was reduced by 46% with concurrent rifabutin.[56] This combination should be avoided due to the increased risk of QT prolongation associated with increasing rilpivirine doses.[75] No clinically significant DDIs exist between rifabutin and etravirine; therefore, standard dosing is recommended.[75,78]

Limited data are available detailing the effect of rifabutin on serum concentrations of integrase strand transfer inhibitors. Despite raltegravir being an UGT1A1 substrate, rifabutin does not significantly alter its PK or serum concentrations, allowing for standard dosing of each drug.[75,79] Rifabutin significantly decreased elvitegravir/cobicistat concentrations by 67%, and concomitant administration should be avoided.[75,80] Similarly to raltegravir, dolutegravir concentrations with or without concurrent rifabutin are comparable and do not require dose adjustment.[81]

Although maraviroc is a CYP3A substrate, standard doses of 300 mg twice daily are recommended with concomitant rifabutin 300 mg once daily.[75]

Fluoroquinolones used for multidrug-resistant TB, including levofloxacin or moxifloxacin, should be used with caution in patients receiving ART known to prolong the QT interval. Although this was thought to be a class effect, recent data suggest that the risk of QT interval prolongation is severalfold higher with moxifloxacin than with levofloxacin.[113] If coadministration is unavoidable, the QT interval should be monitored. Aminoglycosides and capreomycin are predominately excreted via renal mechanisms and may cause nephrotoxicity.[114] Concomitant administration with ART that is renally eliminated or potentially nephrotoxic should be used with caution.

Based on the data presented above, rifampin should be avoided in the treatment of TB in patients on ART, and rifabutin substituted if available, with appropriate dose adjustments for concomitant therapy. No significant DDIs are expected with use of isoniazid, pyrazinamide, or ethambutol in combination with ART, and standard dosing should be administered.[15]

Mycobacterium avium Complex

Disseminated MAC affects up to 40% of HIV-infected patients with CD4 cell counts <50 cells/mm^3, with an incidence of 2.5 cases per 1000 person-years.[115] Combination therapy with a macrolide antibiotic, ethambutol, and rifabutin decreases the risk of drug resistance and is associated with improved survival.[116–119] Although clarithromycin is preferred due to extensive research and more rapid sterilization of blood, it is commonly replaced with azithromycin to avoid DDIs and adverse events. Initiation of ART should occur after 2 weeks of treatment for MAC in ART-naive patients to limit DDIs and adverse events and decrease the possibility of immune reconstitution inflammatory syndrome.[56]

Clarithromycin is a major substrate and strong inhibitor of CYP3A as well as a weak inhibitor of CYP1A2 and PGP.[120] It is metabolized to an active metabolite, 14-hydroxyclarithromycin, which has reduced activity against MAC. Both the parent drug and metabolite are renally eliminated. Although clarithromycin does not significantly affect the metabolism or concentration of nevirapine, nevirapine induced the metabolism of clarithromycin, decreasing the maximum concentration (C_{max}), AUC, and C_{min} by 20%, 29%, and 46%, respectively.[28] Additionally, the AUC of 14-hydroxyclarithromycin is increased by 27%, and therefore, coadministration should be avoided. Similarly, concomitant administration with efavirenz should be avoided due to decreased clarithromycin C_{max} by 26% and AUC by 39%, while the AUC of 14-hydroxyclarithromycin is decreased by 34%.[25] A bidirectional interaction exists with etravirine and clarithromycin.[27] Etravirine C_{max}, AUC, and C_{min} are increased by 46%, 42%, and 46%, respectively, whereas coadministration resulted in a 34% reduction in clarithromycin C_{max}, a 37% reduction in AUC, and a 53% reduction in C_{min}. C_{max}, and AUC of 14-hydroxyclarithromycin are increased by 33% and 21%, respectively. No dose adjustments have been established or recommended when clarithromycin is used concomitantly with nonnucleoside reverse transcriptase inhibitors; therefore azithromycin is preferred.[56]

All protease inhibitors are expected to interact with clarithromycin. The effect on ritonavir 200 mg every 8 hours by clarithromycin 500 mg once day was minimal, with increased C_{max} of 15% and AUC of 13%.[63] Alternatively, ritonavir increased the C_{max} of clarithromycin by 31% with an even greater increase in AUC and C_{min} of 77% and 182%, respectively. Ritonavir limited the formation of the 14-hydroxyclarithromycin metabolite to undetectable concentrations in most subjects. Similar effects are expected with ritonavir-boosted protease inhibitors due to CYP3A inhibition.[32–36,56,64] No dose adjustment of protease inhibitors, except atazanavir, or clarithromycin is required in patients with normal renal function, whereas clarithromycin should be decreased by 50% in patients with a creatinine clearance (CrCl) between 30 and 60 mL/min and by 75% in those with CrCl <30 mL/min due to impaired renal elimination of the parent drug and active metabolite.[31] Clarithromycin should be reduced by 50% when administered with atazanavir without concomitant ritonavir to avoid the potentially increased risk of QT prolongation.

Although no clinical trials have been performed to evaluate the interaction of integrase strand transfer inhibitors with clarithromycin, concentrations of elvitegravir, cobicistat, and clarithromycin may be increased.[56] Standard clarithromycin doses should be used in patients with CrCl >60 mL/min, but the dose of clarithromycin should be decreased by 50% in those with CrCl 50 to 60 mL/min as a result of decreased renal clearance of the parent drug and active metabolite.

Due to the potential for increased maraviroc concentrations, the dose should be decreased to 150 mg twice daily in all patients with CrCl ≥30 mL/min receiving concomitant clarithromycin.[37,56] Concurrent use is contraindicated with CrCl <30 mL/min.

The addition of rifabutin to the macrolide-ethambutol combination should be considered in patients not being treated with ART or those with CD4 cell counts <50 cells/mm^3.[56] Unfortunately, significant bidirectional CYP-mediated DDIs are associated with the concurrent use of clarithromycin and rifabutin. Clarithromycin inhibits the metabolism of rifabutin via CYP3A4, leading to increased concentrations of the 25-O-desacetyl-rifabutin metabolite.[121] The result of this interaction may lead to rifabutin toxicity manifesting as uveitis, leukopenia, or thrombocytopenia.[122–127] Concomitant rifabutin decreased clarithromycin AUC by 44% while it increased the AUC of 14-hydroxyclarithromycin by up to 57%.[121,126] The significant increase in 14-hydroxyclarithromycin is likely the result of CYP3A4 induction by rifabutin, decreasing the overall efficacy against MAC. Coadministration should be avoided.

Azithromycin is a minor CYP3A substrate and does not induce or inhibit hepatic CYP enzymes.[120] Replacement of clarithromycin with azithromycin at standard doses is recommended in all patients, including those with renal dysfunction, receiving protease inhibitor-, nonnucleoside reverse transcriptase inhibitor-, integrase strand transfer inhibitor-, or fusion inhibitor–based ART.

In an effort to avoid the increased risk of potential DDIs and adverse events with concomitant ART, azithromycin should be substituted for clarithromycin for the treatment of MAC. If available, rifabutin should be added with appropriate dose adjustments in patients receiving ART with CD4 cell count <50 cells/mm^3.

Cryptococcus neoformans Meningoencephalitis

Dissemination of inhaled *Cryptococcus neoformans* spores may lead to subacute meningitis or meningoencephalitis, particularly in individuals with CD4 cell counts <100 cells/mm^3.[128] Annually, however, approximately 1 million individuals are diagnosed with *C neoformans* meningitis, with an estimated mortality rate of 630,000 persons per year. Antifungal treatment is divided into 3 distinct phases: induction with amphotericin B formulations and flucytosine, followed by consolidation and maintenance with long-term fluconazole.[56] Conflicting data exist regarding the most

appropriate time to initiate ART in patients with cryptococcal meningitis, but ideally it should be deferred for at least 5 weeks or up to 10 weeks in patients with increased intracranial pressure or decreased white blood cell count from CSF to decrease the risk of immune reconstitution inflammatory syndrome and overall mortality.[56,129–131]

DDIs are not expected with amphotericin B formulations due to its lack of CYP-mediated metabolism.[65] Use of amphotericin B is not without risks, however.[132] Overlapping toxicities with ART include nephrotoxicity and electrolyte abnormalities with tenofovir disoproxil fumarate and anemia with zidovudine. Flucytosine does not undergo hepatic metabolism and is primarily renally eliminated.[133] Concomitant use with amphotericin B may decrease renal function, leading to supratherapeutic concentrations of flucytosine resulting in myelosuppression. Coadministration with zidovudine should be avoided. Nausea, vomiting, and anorexia are frequently associated with flucytosine, which may influence compliance and absorption of ART.

Fluconazole does not undergo hepatic metabolism.[134] It is a modest inhibitor of CYP3A, CYP2C9, CYP2C19, and UDP-UGTs as well as a weak inhibitor of CYP1A2. DDIs with most nucleos(t)ide reverse transcriptase inhibitors are not expected. An increase in zidovudine AUC has been observed with concomitant fluconazole.[22,23] Dose adjustments are not required for nucleos(t)ide reverse transcriptase inhibitors or fluconazole, but patients should be monitored for zidovudine-related toxicities if this drug is coadministered with fluconazole.

Increased concentrations of protease inhibitors are expected with concurrent administration of fluconazole as a result of CYP3A inhibition, although that effect is clinically insignificant.[65] Dose adjustments for protease inhibitors or fluconazole are not required.[56,65] The only exception is to limit fluconazole doses to 200 mg once daily in combination with tipranavir/ritonavir.

Fluconazole may increase concentrations of nonnucleoside reverse transcriptase inhibitors via CYP3A inhibition. Nevirapine concentrations are significantly increased up to 100% by fluconazole without evidence of hepatotoxicity.[66] Coadministration with efavirenz led to an unchanged efavirenz C_{max} but a 16% increase in AUC with no change in fluconazole AUC.[25] Similarly, the AUC and C_{min} of etravirine were increased by 86% and 109%, respectively, with fluconazole.[27] Fluconazole may increase serum concentrations of rilpivirine via CYP3A inhibition.[25] Due to negligible effects on fluconazole concentrations, no dose adjustments are required for patients receiving fluconazole with efavirenz, etravirine, or rilpivirine. Fluconazole should be avoided in patients receiving nevirapine-based ART if possible due to increased rates of nevirapine-associated adverse events and hepatotoxicity.[66]

DDIs with fluconazole and integrase strand transfer inhibitors, including elvitegravir/cobicistat combinations, are unlikely due to minimal CYP-mediated elimination.[36] Standard dosing should be administered. Fluconazole is a moderate CYP3A inhibitor but does not alter maraviroc PK enough to require dose adjustments.[67]

Induction therapy with amphotericin B and flucytosine is not expected to result in clinically significant DDIs in patients already receiving ART at the time of diagnosis of *C neoformans* meningoencephalitis. Increased monitoring of electrolytes and cell counts should be performed to avoid the electrolyte abnormalities and myelosuppressive effects of amphotericin and flucytosine. Due to long-term use of fluconazole, protease inhibitor- or integrase strand transfer inhibitor–based regimens should be preferentially used to avoid DDIs. Emphasis should also be placed on delaying initiation of ART for at least 5 weeks or up to 10 weeks to minimize the risk of immune reconstitution inflammatory syndrome and mortality.

Conclusion

Worldwide, an increasing number of individuals with known HIV infection are being successfully started and maintained on ART and are achieving virologic suppression. However, overall rates remain low. Although reductions in the use of primary and secondary antimicrobial prophylaxis against OIs have occurred, the risk of clinically significant DDIs persists. Unfortunately, in many settings but particularly in low-income or resource-limited settings, a large population of individuals remains unaware of their HIV-serostatus; and less than 50% of patients on ART achieve virologic suppression in most countries. Inevitably, many patients continue to be identified with advanced HIV-infection resulting in the persistent occurrence of OIs. Antimicrobial management of OIs often results in clinically significant DDIs with potential life-threatening consequences with minimal guidance available. Concomitantly many patients receiving ART may have other comorbidities or may develop them while receiving ART. Due to limited clinical outcomes data, monitoring and management of potential DDIs must be done with caution. Similar to high-income settings, addressing potential DDIs in resource-limited settings requires focusing on high-risk populations including: elderly patients, individuals with multiple comorbidities, and those receiving complex ART that often includes antiretroviral drugs associated with increased toxicity profiles. Clinicians must be aware of CYP-

mediated, nonmediated, and drug transport system DDIs. Although challenging and potentially complex, management of these potentially unavoidable DDIs is critical in an ever changing HIV-infected patient population.

Conflicts of Interest

All authors declare no conflicts of interest.

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