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Clinically relevant drug-drug interactions between antiretrovirals and antifungals

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Abstract

Introduction—Complete delineation of the HIV-1 life cycle has resulted in the development of several antiretroviral drugs. Twenty-five therapeutic agents belonging to five different classes are currently available for the treatment of HIV-1 infections. Advent of triple combination antiretroviral therapy has significantly lowered the mortality rate in HIV patients. However, fungal infections still represent major opportunistic diseases in immunocompromised patients worldwide.

Areas covered—Antiretroviral drugs that target enzymes and/or proteins indispensable for viral replication are discussed in this article. Fungal infections, causative organisms, epidemiology and preferred treatment modalities are also outlined. Finally, observed/predicted drug-drug interactions between antiretrovirals and antifungals are summarized along with clinical recommendations.

Expert opinion—Concomitant use of amphotericin B and tenofovir must be closely monitored for renal functioning. Due to relatively weak interactive potential with the CYP450 system, fluconazole is the preferred antifungal drug. High itraconazole doses (> 200 mg/day) are not advised in patients receiving booster protease inhibitor (PI) regimen. Posaconazole is contraindicated in combination with either efavirenz or fosamprenavir. Moreover, voriconazole is contraindicated with high-dose ritonavir-boosted PI. Echino-candins may aid in overcoming the limitations of existing antifungal therapy. An increasing number of documented or predicted drug-drug interactions and therapeutic drug monitoring may aid in the management of HIV-associated opportunistic fungal infections.

Keywords

antiretrovirals; azole antifungals; clinical recommendations; human immunodeficiency virus infection; opportunistic infections; pharmacodynamic; pharmacokinetic; therapeutic drug monitoring

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Declaration of interest

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1. Introduction

Over the past decade, AIDS-related morbidity and mortality are significantly lower due to the advent of highly active antiretroviral therapy (HAART). Notable advances in the discovery of HIV biology have resulted in the discovery of several anti-HIV drugs. Currently, 25 antiretroviral agents belonging to five different classes have been approved by the US FDA for the treatment of HIV infections. The drug classes include entry and fusion inhibitors, nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), integrase strand transfer inhibitors (INSTIs) and protease inhibitors (PIs). These drugs target different enzymes and/or proteins that are indispensable for viral replication. The guidelines for the use of antiretroviral therapy (ART) in HIV-infected adults include a combination of two NRTIs and one drug from either class: NNRTI, INSTI or boosted PI. The drug combination is based on HIV viral load, patient's resistance testing, adverse effects, dosing frequency and pill burden, with an ultimate goal of achieving maximal viral suppression [1].

Despite the advances made in ART, opportunistic infections (OIs) resulting from immunosuppression still remains the principal cause of morbidity and mortality in HIV-infected individuals [2]. This is primarily due to three main reasons: i) 20% of HIV-infected persons are unaware of their infection; ii) infected individuals do not take ART due to social or economic factors; and iii) infected individuals who are prescribed ART show poor virological and immunological response due to unfavorable pharmacokinetics and other biological factors [3–5]. A bidirectional relation exists between HIV and OIs. HIV results in immunosuppression that permits the infection of several bacterial, fungal and viral pathogens. Further, these OIs can dramatically increase circulating viral load, accelerating HIV progression and transmission [6,7]. Among the OIs, fungal infections are frequently noticed in HIV-infected individuals. Although the incidence of opportunistic fungal infections has dramatically reduced in developed countries, they still represent a major problem in developing countries [8].

HIV patients are usually prescribed a number of medications, including antiretroviral drugs and antifungals. Drug--drug interactions (DDIs) are commonly observed in these patients, which often necessitate dosage adjustment to prevent potential adverse effects and treatment failure [9]. Based on the mechanism involved, the interactions can either be classified as pharmacodynamic or pharmacokinetic. Pharmacodynamic interactions lead to potentiating or antagonistic drug-response effects. Pharmacokinetic interactions involve the effect of one drug on the absorption, distribution, metabolism and excretion of another drug. Both interactions may result in unanticipated therapeutic outcomes. Hence, it is imperative that clinicians recognize these potential interactions between antiretroviral and antifungal drugs. This review highlights a general overview of antiretroviral and antifungal therapy, with a focus on known DDIs and recommendations for clinical management. Such information may aid in better clinical management of opportunistic fungal infections in HIV patients.

2. Antiretroviral therapy

2.1 HIV-1 life cycle

HIV-1 is a member of the *Lentivirus* genus of the *Retroviridae* family. The virus particle consists of two identical RNA copies of the genome. The HIV replication cycle can be divided into an early phase and a late phase. It can be summarized as the following steps: binding and entry, uncoating, reverse transcription, integration, viral protein synthesis, assembly and budding [10–12].

The attachment of virus particle to the host cells is considered as a first step in HIV infection. HIV-1 virus binds specifically to CD4 receptor and seven transmembrane coreceptor (CCR5 or CXCR4) expressing host cells. The process is initiated by binding of viral envelope gp120 spikes to CD4 receptor of host cell. This process triggers a change in gp120 configuration leading to coreceptor (CCR5 or CXCR4) engagement and fusion by viral gp41 protein. Following viral entry, the virus envelope dissociates and uncoating occurs. It facilitates the release of viral genetic material and other enzymes into host cells. The important early event in HIV life cycle is the reverse transcription of viral RNA to double-stranded DNA by virus-encoded reverse transcriptase enzyme. This pre-integration complex is then imported into the host nucleus via the interaction between cellular receptor and viral nuclear localization signal. The viral DNA complex integrates with the host cellular chromosomal DNA with the help of integrase enzyme. This stage is considered as the latent stage of HIV life cycle as the virus particles may remain inactive for several years.

Post integration, the virus enters a late phase of replication. The provirus utilizes various enzymes for transcription of DNA to multiple copies of full-length progeny viral RNA and mRNAs that are translated into various viral proteins. The longer HIV-1 polyproteins are cleaved by HIV protease into individual functional proteins and enzymes. Finally, various structural components are assembled together to produce a new mature HIV virion. These newly formed virions then bud off the host cell via the process of exocytosis and are able to infect other cells.

2.2 Current anti-HIV therapeutics

Comprehensive understanding about HIV-1 life cycle and the necessity to inhibit viral replication has resulted in the identification and development of several classes of anti-HIV-1 agents. Twenty-five therapeutic agents belonging to five different classes are currently available for the treatment of HIV-1 infections [13]. These classes include entry and fusion inhibitors, NRTIs, NNRTIs, INSTIs and PIs. List of drugs belonging to these different classes, their metabolic and transport characteristics and adverse effects have been summarized in Table 1.

2.2.1 Entry and fusion inhibitors—Enfuvirtide, a fusion inhibitor, blocks gp41-mediated viral and host cellular membrane fusion. Maraviroc, a CCR5 antagonist, inhibits the ability of viral gp120 to bind to the coreceptor. These molecules have a significant potential for treating HIV infections, particularly in patients resistant to other drugs. However, utilization of these drugs is limited due to the variability of viral envelope protein

and involvement of multiple coreceptors in viral entry [14]. The dose of enfuvirtide and maraviroc is 90 and 300 mg twice daily (b.i.d.), respectively. Plasma protein binding of enfuvirtide is reported to be 92%, whereas that of maraviroc is 76%.

2.2.2 Nucleoside/nucleotide reverse transcriptase inhibitors—NRTIs block HIV-1 reverse transcriptase, an enzyme that reverse transcribes viral RNA to cDNA. This class of drugs remains a cornerstone of ART combination therapy. Tenofovir disoproxil fumarate is the only nucleotide adenosine analog of this class, whereas others are nucleoside analogs. Among the nucleosides, abacavir is guanosine; didanosine is an adenosine; lamivudine and emtricitabine are cytidine; and zidovudine and stavudine are thymidine analogs. All NRTIs are inactive when administered and require intracellular phosphorylation to elicit antiretroviral activity. Nucleosides require three steps for phosphorylation as opposed to nucleotides, which require only two steps. The activation pathway is unique for different analogs. For instance, the phosphorylation of thymidine analogs is different from guanosine analogs. Following phosphorylation, a pool of dideoxynucleoside analog triphosphates are formed, which compete with intracellular deoxynucleotide triphosphates for binding to reverse transcriptase enzyme. During reverse transcription, phosphorylated NRTIs are incorporated into synthesized DNA, preventing further addition of nucleotides and terminating viral DNA replication [15,16].

Members of organic anion transporter (OAT) and organic cation transporter (OCT) families have been implicated in the uptake of few NRTIs [17]. With the exception of didanosine, all NRTIs can be administered without food restrictions. Didanosine is preferred to be administered in the fasted state. Most of the NRTIs exhibit a relatively high bioavailability. Emtricitabine and tenofovir have longer plasma half-lives, allowing less frequent dosing. Abacavir, lamivudine and zidovudine are 50, 36 and 34% protein-bound, respectively, whereas the other NRTIs are not highly bound to plasma proteins. Most importantly, NRTIs are neither substrates nor inhibitors of cytochrome P450 (CYP450) enzyme system, lowering the risk for potential DDIs [18,19].

2.2.3 Non-nucleoside reverse transcriptase inhibitors—NNRTIs also act by inhibiting reverse transcriptase enzyme. Unlike NRTIs, this class of drug molecules is active when administered and does not require intracellular phosphorylation. The compounds inhibit reverse transcription by binding to a hydrophobic pocket located in the p66 subunit at a distance of 10 Å from the catalytic site of viral enzyme. This binding induces a spatial conformational change and reduces polymerase activity. Studies using the crystal structures have demonstrated that the binding pocket is created only in the presence of an inhibitor. NNRTIs are non/uncompetitive inhibitors of only HIV-1 reverse transcriptase enzyme and have no activity against other retroviruses. Thus, the selectivity index for this class of drugs is very high [20,21].

NNRTIs are classified into first- and second-generation drugs. Nevirapine, delavirdine and efavirenz are first-generation inhibitors, whereas etravirine and rilpivirine belong to the second generation. First-generation molecules require only single point mutation, whereas second-generation drugs require more than one point mutation to elicit resistance. Although most NNRTIs are administered on a single daily regimen due to their longer half-lives,

delavirdine is indicated three times daily. All NNRTIs showed significant protein binding (~98%), except for nevirapine, which exhibited 62% binding. NNRTIs are predominantly metabolized by CYP450 enzyme system, including 3A4, 2D6, 2B6, 2C9 and 2C19 isoenzymes. Also they act as inhibitors or inducers of these enzymes, further complicating the potential for significant interactions with other drugs. NNRTIs are safe and well tolerated except for nevirapine, which causes severe hepatotoxicity [22,23].

2.2.4 Integrase strand transfer inhibitors—INSTIs prevent integration of proviral DNA into the host genome catalyzed by viral integrase enzyme. These drugs bind to a specific complex between viral DNA and integrase enzyme, causing displacement of reactive viral DNA and chelation of magnesium cofactors at the active catalytic site. INSTIs are active against multiple retroviruses, including HIV-1 and HIV-2. Raltegravir is the first-generation INSTI, whereas dolutegravir is the second-generation inhibitor used for treating raltegravir-resistant strains. Raltegravir is extremely potent, safe and very well tolerated. However, this drug exhibits inpatient and outpatient pharmacokinetic variability. Dolutegravir has low variability profile, extended half-life and more favorable resistance profile. Raltegravir is almost 83% protein-bound, whereas dolutegravir exhibits 98% protein binding [24–26]. Elvitegravir was approved by US FDA only in a fixed-dose combination tablet that includes cobicistat, tenofovir and emtricitabine. Since elvitegravir is metabolized primarily by CYP3A4, coadministration with a boosting agent (cobicistat) enhances systemic exposure of elvitegravir and facilitates once-daily dosing [27].

2.2.5 Protease inhibitors—PIs inhibit HIV protease, the enzyme responsible for processing viral gag and gag-pol polyprotein precursors into functional and structural proteins. Although, inhibition of protease does produce viral particles, they are immature and are noninfectious. Saquinavir, nelfinavir, ritonavir, indinavir and fosamprenavir are first-generation PIs and lopinavir, tipranavir, atazanavir and darunavir belong to the second generation. Tipranavir is the only non-peptidic inhibitor and the other PIs are competitive peptidomimetic inhibitors. All the PIs are administered orally and the oral bioavailability ranges from 4% for saquinavir to 70% for nelfinavir. These drugs exhibit extensive binding to plasma proteins (90 – 99%), predominantly to two proteins, albumin and α_1 -acid glycoprotein. Long-term side effects include visceral fat accumulation (lipodystrophy or fat redistribution syndrome) and metabolic disorders (insulin resistance, hyperlipidemia, hypertriglyceridemia) [28]. In order to enhance their pharmacokinetic profile, all PIs (except for nelfinavir) are boosted with low-dose ritonavir. Ritonavir, a potent inhibitor of CYP450 enzyme system (mainly CYP3A4) acts as a pharmacokinetic enhancer or boosting agent. This combination increases plasma concentration of coadministered drug, allowing simplified dosage regimen, reduced pill burden and improved patient compliance [29,30].

2.3 Highly active antiretroviral therapy

With the availability of drugs that act at different stages of viral replication, combination therapy incorporating various agents has evolved. A prototypical HAART combination includes two NRTIs as the backbone regimen plus one drug from NNRTI, INSTI or boosted PI (Table 2). These combination regimens have been very effective in suppressing viral replication and progression, by acting at different stages of HIV life cycle. Studies suggest

that HAART significantly improved patient's quality of life and survival rate and lowered viral loads. More importantly, combination regimen minimized development of resistance [31,32]. The goal of combination therapy is to achieve maximal and continuous suppression of HIV replication and improvement in patient's immunological function. Many trials have indicated that ART should be initiated at an early stage for better treatment of severe OIs [33–35].

3. Antifungal therapy

3.1 Opportunistic fungal infections

OIs still represent a major complication in HIV-infected individuals. Most of the life-threatening OIs occur when the CD4 count falls < 200 cells/mm³. The most common systemic fungal infections observed in AIDS patients include aspergillosis, coccidioidomycosis, cryptococcosis, esophageal and oropharyngeal candidiasis, histoplasmosis and penicilliosis [36]. Invasive aspergillosis is noticed in advanced stages of HIV infection. Predisposing risk factors for this fungal infection include neutropenia, lung diseases and corticosteroid therapy. The causative fungus, *Aspergillus fumigatus*, presents respiratory disorders such as necrotizing pneumonia and tracheobronchitis [37]. Coccidioidomycosis is caused by *Coccidioides immitis* and *C. posadasii*. This infection is endemic to southwestern USA and several central states. The incidence of coccidioidomycosis has significantly reduced since the advent of HAART. The common syndromes noticed with the infection include focal and diffuse pneumonia, cutaneous disease and meningitis [38]. Cryptococcal infection is a frequent life-threatening OI in both HIV-infected and uninfected patients. Although ART has significantly reduced incidence of cryptococcal meningitis in Western countries, this infection remains the leading cause of morbidity and mortality in HIV-infected patients in sub-Saharan Africa and southeast Asia [39]. The two main species responsible for the infection are *Cryptococcus neoformans* and *C. gattii*. The most common clinical indications include subacute meningitis or meningoencephalitis with malaise, headache, fever and visual disturbance and altered mental status. The infection is commonly disseminated to every organ system in the body [40].

Mucocutaneous candidiasis is the most commonly observed fungal infection in the global HIV setting. The causative organism for both esophageal and oropharyngeal candidiasis is *Candida albicans*. The occurrence of candidiasis is recognized as an indicator of immune suppression. The advent of HAART has caused a significant lowering in the prevalence of candidiasis. Esophageal candidiasis is characterized by retrosternal burning pain and odynophagia, whereas oropharyngeal candidiasis is characterized by painless, creamy white lesions on the buccal surface, palate, oropharyngeal mucosa or tongue [41]. The dimorphic fungus *Histoplasma capsulatum* is responsible for histoplasmosis. This infection is also endemic and limited to central and south USA. The common symptoms include fever, fatigue, weight loss and hepatosplenomegaly [42]. Penicilliosis, caused by the dimorphic fungus *Penicillium marneffei*, is endemic to southeast and eastern Asia. Such infection could be fatal if not treated appropriately. The symptoms include fever, anemia, weight loss and generalized skin papules [43]. The salient features (causative organism, epidemiology,

clinical manifestations and preferred treatment) of these infections have been summarized in Table 3. The preferred mainstay treatment for the fungal infections includes the administration of amphotericin B, azole antifungals and echinocandins.

3.2 Amphotericin B

Since its approval by the US FDA, amphotericin B is considered as the gold standard for invasive fungal infections. It has antifungal activity against a wide variety of yeasts and molds, including most *Candida*, *Aspergillus*, *Rhodotorula*, *Mucor* and *Rhizopus* species. The agent binds to ergosterol in the fungal cell membrane, increases permeability and cell death. Due to its high hydrophobicity and poor absorption through the gastrointestinal tract, it is administered intravenously. Amphotericin B is neither a substrate nor an inhibitor of the CYP450 enzyme system. It is associated with a high occurrence of nephrotoxicity and infusion-related reactions (fever, shaking chills, hypotension, anorexia, nausea, vomiting, headache, and tachypnea) [44]. Despite these side effects, the drug still remains the first line of treatment for severe and life-threatening systemic fungal infections. New amphotericin B formulations, such as liposomal AmB or lipid AmB complexes, minimize the toxic side effects associated with amphotericin B [45].

3.3 Azole antifungals

Azole antifungals have been indicated in the treatment of various topical and systemic fungal infections. These drugs inhibit lanosterol 14- α -demethylase enzyme. This CYP450 enzyme converts lanosterol to ergosterol, a vital component of fungal plasma membrane. Depletion of ergosterol and accumulation of toxic metabolites disrupt the structure and function of cell membrane, preventing the fungal cell growth and replication. Azole antifungal drugs differ in their potency and activity depending on their affinity for 14- α -demethylase enzyme. Azoles can be classified into two groups, namely, imidazoles (e.g., ketoconazole, miconazole and clotrimazole) and triazoles (e.g., fluconazole, itraconazole, posaconazole and voriconazole), based on their structural differences. Both imidazoles and triazoles have five-membered heterocyclic ring. Imidazoles have a two nitrogenazole ring, whereas triazoles have three nitrogenazole ring. Even though they share the same mechanism of action, imidazoles and triazoles differ in their spectrum of activity, pharmacokinetic profiles and toxicities. Triazoles are mainly indicated for the treatment of systemic infections since these compounds are less susceptible to metabolic degradation and exhibit favorable pharmacokinetic profiles than imidazoles. Due to the lack of enzyme specificity and adverse effects associated with systemic therapy, use of imidazoles has been restricted to the treatment of superficial fungal infections [46,47]. Many of the azoles can interact with CYP450 enzyme system, hence raising the possibility of DDIs [48]. The characteristics of few important azole antifungals have been described in the following sections.

3.3.1 Fluconazole—It is the first-generation triazole antifungal active against a majority of *Candida* species. Fluconazole is marginally lipophilic, highly water-soluble and weakly protein-bound. The compound does not undergo first-pass metabolism and has > 90% bioavailability. Absorption of fluconazole from the gastrointestinal tract is independent of the formulation, gastric acidity or concomitant food intake. This molecule displays low

nephrotoxicity (< 2%). Fluconazole is excreted unchanged by the kidneys, with a minor part (10%) being metabolized by CYP3A4. This agent is a potent inhibitor for CYP2C9 and moderate inhibitor for CYP3A4 enzymes system [49].

3.3.2 Itraconazole—Itraconazole is the first marketed orally bioavailable first-generation triazole which is active against both *Candida* and *Aspergillus* species. It is the most lipophilic and water-insoluble azole. The compound undergoes extensive hepatic metabolism and is excreted in an inactive form via liver and kidneys. The biotransformation pathways are complex and > 30 metabolites have been reported for itraconazole. This antifungal is highly efficacious because of its primary metabolite hydroxyitraconazole that can reach higher concentrations than the parent compound. The metabolite has considerable antifungal activity relative to parent drug. Itraconazole is a substrate and inhibitor of both P-glycoprotein (P-gp) and CYP3A4 [50].

3.3.3 Ketoconazole—Ketoconazole, an imidazole antifungal, is the first orally available azole antifungal for the treatment of topical and systemic fungal infections. It has been approved by the FDA for the treatment of mucocutaneous candidiasis, oral thrush, candiduria, coccidioidomycosis, histoplasmosis, chromomycosis and paracoccidioidomycosis. It is practically insoluble in water, rendering it unsuitable for intravenous formulation. Oral absorption of ketoconazole varies from 37 to 97% and it exhibits high plasma protein binding. Common side effects include nausea, vomiting and hepatotoxicity. Recently, this regimen is often substituted with more effective triazole drugs, fluconazole and itraconazole [51].

3.3.4 Posaconazole—Posaconazole is a potent second-generation triazole with broad spectrum activity against invasive fungal infections caused by *Candida*, *Aspergillus* and *Zygomycetes* species. It is more active than fluconazole and itraconazole and highly effective in the prophylaxis of fungal infections in immunocompromised patients with hematological complications. Posaconazole is structurally derived from itraconazole by replacement of chlorine with fluorine in the phenyl ring and hydroxylation of the triazolone side chain. Phase II biotransformation via glucuronidation is the primary metabolic pathway. Posaconazole has an oral bioavailability of 8 – 47% and must be administered with fatty food to achieve reasonable serum levels. Unlike itraconazole or ketoconazole, absorption of posaconazole is not significantly influenced by gastric pH. Posaconazole is highly plasma protein bound (> 95%). It is an inhibitor of P-gp and CYP3A4 enzyme. The common adverse effects include gastrointestinal disturbances, hypokalemia and hepatotoxicity [52].

3.3.5 Voriconazole—Voriconazole is a second-generation triazole effective against fluconazole-resistant species. It is available for both oral and intravenous administration. This drug is the first-line treatment for invasive aspergillosis. It is lipophilic and rapidly absorbed with high oral bioavailability. The compound is metabolized in the liver and exhibits nonlinear pharmacokinetics in adults. Voriconazole has a large volume of distribution (4 l/kg) and is ~ 60% plasma protein-bound. Voriconazole is prone to many interactions primarily due to its affinity for multiple CYP enzymes (highest for CYP2C19, followed by CYP2C9 and lower for CYP3A4) [53,54].

3.4 Echinocandins

Echinocandins represent the newest class in the antifungal armamentarium. They are semisynthetic lipopeptides that inhibit the synthesis of β -(1,3)-glucan, an essential fungal cell wall component, via noncompetitive inhibition of β -1,3-D-glucan synthase enzyme [55]. Echinocandins are widely used against most *Candida* and *Aspergillus* fungi in which β -(1,3)-glucan is a prominent cell wall component. As the target enzyme is absent in mammalian cell walls, this class of molecules are less toxic compared to other antifungals [56]. All echinocandin formulations are available for intravenous use since they have low oral bioavailability. These drugs have linear or moderately linear kinetics with a terminal half-life of 8 – 13 h facilitating once-a-day dosing. The molecules exhibit high protein binding (84 – 99.8%). Echinocandins are poor substrates, inhibitors or inducers of CYP450 system and do not interact with P-gp. Therefore, any serious DDIs are not anticipated when this class of molecules is coadministered with other drugs [57]. All three echinocandins (anidulafungin, caspofungin and micafungin) are generally well tolerated, although few hematological and gastrointestinal disturbances are observed [58].

3.4.1 Anidulafungin—Several clinical studies have indicated that anidulafungin is an effective antifungal agent used in the treatment of azole-refractory esophageal candidiasis, candidemia and invasive candidiasis. This molecule exhibits potent activity against fluconazole or amphotericin B-resistant *Aspergillus* and *Candida* species. Anidulafungin undergoes slow chemical degradation by nonspecific peptidases in the blood rather than being by metabolized in the liver [59]. Population pharmacokinetic analysis has suggested that the clearance of anidulafungin is not altered in presence of substrates, inhibitors or inducers of CYP450 system. Hence, interactions with other antiretro-virals are unlikely to occur and any dosage adjustment is not recommended [60].

3.4.2 Caspofungin—Caspofungin is active against most of *Candida* and *Aspergillus* species and does not possess activity against *Cryptococcus neoformans*. It is approved for the treatment of esophageal or oropharyngeal candidiasis and invasive aspergillosis. Caspofungin exhibits moderate nonlinear pharmacokinetics with a terminal half-life of 9 – 11 h and is extensively protein bound (~ 97%). The compound undergoes metabolism via nonenzymatic peptide hydrolysis and/or *N*-acetylation into inactive metabolites in the liver [61].

3.4.3 Micafungin—Micafungin (FK463), a water soluble antifungal agent, is active against *Candida* (*albicans* and non-*albicans*) and *Aspergillus* species but inactive against *Zygomycetes* and *Cryptococcus* species. This compound is more active than amphotericin B, caspofungin, fluconazole or itraconazole against most *Candida* species. Micafungin is characterized by linear pharmacokinetics and a mean terminal half-life of ~ 10 – 17 h. It is highly bound to plasma proteins (> 99%). This compound is metabolized in the liver by arylsulfatase and secondary metabolism by catechol-*O*-methyltransferase [62,63]. Table 4 summarizes the important antifungals, their metabolic and transport characteristics and adverse effects.

4. Drug-drug interactions

DDIs are often unavoidable in HIV-infected patients. Along with antiretroviral drug therapy, patients may receive other medications for supportive care, OIs and/or immunomodulation. These multidrug regimens can often alter the pharmacodynamics or pharmacokinetics of another drug, leading to clinically relevant DDIs [64]. Pharmacodynamic interactions result from combined treatment at the site of biological activity, leading to additive, synergistic or antagonistic pharmacological effects, without a net change in drug pharmacokinetic parameters. Additive effects arise when coadministration results in combined pharmacological activity, whereas a synergistic effect leads to an enhanced response greater than the additive effect. Antagonistic effects result in diminished pharmacological activity due to multidrug regimen. Pharmacokinetic drug interactions result from altered absorption, distribution and disposition. DDIs involving absorption or metabolism are most frequently encountered in HIV and OI patients [65,66].

Many membrane transporters, including P-gp, multidrug-resistant proteins, breast cancer-resistance protein (BCRP), OCTs, OATs and organic anion-transporting polypeptides are involved in the absorption and distribution of drug molecules [67]. Interactions involving metabolism can occur if a drug acts as a substrate, inhibitor or inducer of CYP450 enzyme system [68]. Plasma levels of drug molecules metabolized by CYP450 enzymes can be modulated by other inhibitors or inducers. Inhibition of CYP enzymes can either be competitive, noncompetitive or mechanism-based. In most cases, both substrate and inhibitor compete for the same catalytic site on the enzyme. Induction occurs when molecules bind to nuclear hormone receptors (pregnane X receptor and constitutive androstane receptor), activate transcriptional factors and increase translation of metabolic enzymes [69]. Also, a close overlap of tissue distribution and substrate specificity of metabolic enzymes and transporters further enhance the potential interactions of various drug combinations [70,71].

Given the above mechanistic basis, it is very important to assess the nature and magnitude of DDIs, since either type of interaction can result in altered safety and efficacy profile of a drug. A study/report of the potential anticipated interactions may facilitate any dosage adjustment, additional therapeutic monitoring and contraindication in multidrug therapy. The following subsections describe observed or predicted DDIs among different classes of antiretrovirals with important antifungals recommended in the treatment of major OIs. Although all the interactions have been summarized in Table 5, only few of them are described below.

4.1 Entry and fusion inhibitors

4.1.1 Enfuvirtide (T-20)—Majority of the drug interactions result due to changes in metabolic enzyme or transport characteristics. Enfuvirtide undergoes catabolic metabolism to its constituent amino acids. Due to further recycling of the amino acids, drug interactions appear unlikely. *In vitro* human microsomal studies have indicated that enfuvirtide is not an inhibitor of CYP450 enzymes. *In vivo* human metabolism studies have also revealed that enfuvirtide does not affect the metabolism of other coadministered drugs. Based on these

data, it is recommended that no dosage adjustments are required when enfuvirtide is coadministered with antifungal drugs [72–75].

4.1.2 Maraviroc—Human liver and recombinant microsomal studies revealed that CYP3A4 is the major metabolizing enzyme involved in *N*-dealkylation of maraviroc [76]. This drug does not inhibit any of the seven major CYP isoforms (1A2, 2B6, 2C9, 2C19, 2D6 and 3A4) at clinically relevant concentrations. Hence, it is unlikely to alter the plasma concentrations of other coadministered drugs. However, being a substrate of CYP3A4, maraviroc's metabolism can be modulated by CYP3A4 inhibitors. Open, randomized, placebo-controlled studies were conducted in healthy volunteers for pharmacokinetic assessments of maraviroc alone (100 mg b.i.d.) and in the presence of ketoconazole (400 mg/day). The pharmacokinetic parameters, that is, AUC_{τ} and $C_{\max}$ of maraviroc alone were reported to be $619 \pm 54 \text{ ng} \times \text{h/ml}$ and $155 \pm 74 \text{ ng/ml}$. AUC_{τ} and $C_{\max}$ were elevated by 5- and 3.4-fold, respectively in the presence of ketoconazole. This study recommended that the dose of maraviroc be reduced to almost 50% when coadministered with potent CYP3A4 inhibitors, including ketoconazole and itraconazole [77]. Fluconazole and voriconazole are moderate CYP3A4 inhibitors and the magnitude of their interaction with maraviroc is not reported. Although dosage adjustment is not recommended, maraviroc-related toxicity should be closely monitored [78].

Absorption of maraviroc is assessed *in vitro* using Caco-2 cell culture monolayers. Maraviroc exhibited poor apical to basolateral permeation, but higher transport from basolateral to apical direction. Transcellular efflux ratio was calculated to be > 10 . This ratio was significantly diminished in presence of P-gp inhibitors, suggesting the role of P-gp in transport of maraviroc. Further evidence is provided by assessing the pharmacokinetic parameters in wild-type and P-gp knockout mice (*mdr1a/mdr1b* knockout). Following oral administration, the knockout mice exhibited threefold higher AUC compared to control mice [79]. Although the data suggests involvement of P-gp in oral absorption of maraviroc, DDIs by this transport mechanism have not been conclusively established.

4.2 Nucleoside/nucleotide reverse transcriptase inhibitors

NRTIs are primarily eliminated by the kidneys. They are neither substrates of P-gp nor CYP3A4. Also, this class of antiretrovirals does not cause any inhibition or induction of the CYP450 system. Hence, any clinically relevant DDIs between NRTIs and antifungals may not occur. However, both tenofovir and amphotericin B can cause nephrotoxicity. Concomitant or sequential administration of these drugs must be closely monitored [80]. Similarly, combination therapy of zidovudine and amphotericin B may result in additive myelo-suppression (anemia, neutropenia). Close therapeutic monitoring of hematological function is recommended [81].

4.3 Non-nucleoside reverse transcriptase inhibitors

4.3.1 Delavirdine—Delavirdine is metabolized via CYP3A4 and inhibits 3A4, 2D6, 2C9 as well as 2C19. However, it does not induce any CYP450 enzymes. The pharmacokinetic parameters of delavirdine were assessed in the presence of potent CYP3A4 inhibitors, fluconazole and ketoconazole. No significant interactions have been observed between this

NNRTI and antifungals. However, the C_{min} of delavirdine was increased by 50% in presence of ketoconazole. Dosage adjustment of delavirdine in the presence of antifungals is not recommended [82].

4.3.2 Efavirenz—*In vitro* studies with human liver microsomes have suggested that efavirenz is primarily metabolized by CYP3A4 and CYP2B6 enzymes. Hence, plasma concentration can be altered by substrates, inhibitors or inducers of these enzymes. Also, studies have revealed that efavirenz can inhibit CYP2C9, 2C19 and 3A4. These CYP enzymes can alter plasma concentrations of the coadministered drug. Efavirenz can induce the CYP enzymes, 3A4 and 2B6, resulting in induction of its own metabolism. Likewise, this induction may alter the concentration of coadministered drugs that are metabolized by CYP3A4 and CYP2B6 [83].

When given simultaneously with fluconazole, the C_{max} of efavirenz remained unaltered with 16% rise in AUC. However, the pharmacokinetic parameters of fluconazole indicated no change compared to control. These interaction studies suggested that no dosage adjustment is required when efavirenz is given with fluconazole concomitantly. On coadministration with itraconazole, the plasma concentrations of efavirenz remained unaltered. Yet, AUC and C_{max} of itraconazole were diminished by 39 and 37%, respectively. Hence, alternative antifungal treatment should be considered in combination with efavirenz [84]. A similar trend was also observed in interaction studies of efavirenz with ketoconazole or posaconazole. AUC and C_{max} of efavirenz remained unaltered, whereas that of the antifungal agent reduced significantly. These studies clearly reinforce that coadministration should be avoided unless benefits outweigh the associated risks [85,86]. An open-label, multiple dose study was performed in healthy volunteers to study the interaction between efavirenz and voriconazole. Steady-state pharmacokinetic data revealed that AUC and C_{max} of efavirenz were elevated by 44 and 38% respectively, with a significant reduction in voriconazole AUC and C_{max} (77 and 61%). This interaction study demonstrates that dosage adjustment is necessary when efavirenz is indicated in combination with voriconazole. The dose of efavirenz should be reduced to 300 mg/day, whereas the dose of voriconazole is raised to 400 mg b.i.d. [87].

4.4 Integrase strand transfer inhibitors

4.4.1 Dolutegravir—Dolutegravir is primarily metabolized by UGT1A1 with minor contribution from CYP3A4 (10–15%). Since the azole antifungals are moderate to potent inhibitors of CYP3A4, coadministration of dolutegravir with these drugs may elevate dolutegravir plasma concentration. Dolutegravir is a potent inhibitor of OCT-2. Studies have demonstrated that dolutegravir does not inhibit or induce any CYP isoforms. According to this report, dolutegravir is not expected to affect the pharmacokinetics of azole antifungals [88].

4.4.2 Raltegravir—Raltegravir is eliminated via UGT1A1-mediated glucuronidation pathway. This antiretroviral is neither a substrate nor an inhibitor/inducer of CYP enzymes. Therefore, interactions of this INSTI with azole antifungals are unlikely to occur [89].

4.5 Protease inhibitors

4.5.1 Fosamprenavir—Fosamprenavir is a water-soluble phosphate prodrug of the PI amprenavir. Upon oral administration, fosamprenavir is rapidly hydrolyzed to the parent drug prior to reaching the systemic circulation. Amprenavir is metabolized in the liver by CYP3A4 enzyme. Hence coadministration of drugs that induce CYP3A4 may lower plasma concentration of amprenavir and *vice versa*. Studies also report that amprenavir induces CYP3A4. Also, this PI is a substrate and inducer for the efflux transporter, P-gp [90].

Fosamprenavir is not predicted to have any potential drug interactions with fluconazole. However, when administered simultaneously with itraconazole, the plasma concentrations of both amprenavir and itraconazole are expected to rise. Hence, any dose-related toxicity should be monitored. When fosamprenavir is boosted with ritonavir, the maximum dose of itraconazole should not exceed 200 mg/day [91]. An open-label pharmacokinetic interaction study was performed in 12 healthy volunteers to assess the interaction between amprenavir and ketoconazole. Simultaneous administration elevated AUC and C_{max} of amprenavir by 31 and 16%, respectively. Also, AUC and C_{max} of ketoconazole were elevated by 44 and 19%, respectively. This study demonstrated that simultaneous administration of amprenavir and ketoconazole results in higher concentrations of both drugs. Clinical observation is recommended for monitoring dose-related toxicities [92].

Pharmacokinetics of fosamprenavir in the presence of posaconazole was assessed in an open-label, randomized interaction study in 20 healthy subjects. When administered along with unboosted fosamprenavir, AUC and C_{max} of posaconazole were lowered by 23 and 21%. This report indicated that fosamprenavir and posaconazole should not be coadministered [93]. A combination of fosamprenavir and voriconazole may lead to elevated exposure of both the drugs via dual CYP3A4 inhibition. Therapeutic monitoring of both the drugs is required. Voriconazole is contraindicated in patients on fosamprenavir boosted with low-dose ritonavir. This interaction may occur due to CYP2C19/2C9 induction by ritonavir. As a result, voriconazole plasma concentration can be lower leading to loss of antifungal response [94].

4.5.2 Lopinavir/ritonavir—Lopinavir/ritonavir (LPV/r) is metabolized in the liver by CYP3A4. Therefore, drugs that induce CYP3A4 may lower plasma concentration of lopinavir. Similarly, drugs that inhibit CYP3A4 (e.g., azole antifungal) are expected to elevate lopinavir plasma concentrations. LPV/r can also inhibit CYP3A4, altering the plasma concentration of coadministered drugs. Clinically relevant drug interactions are not predicted to occur between LPV/r and fluconazole. Coadministration of LPV/r and itraconazole/ketoconazole are expected to increase plasma concentration of the antifungal drug. Hence, doses of itraconazole/ketoconazole > 200 mg/day are not recommended with LPV/r. No significant interactions have been reported with the antifungal drug posaconazole [95]. A randomized two-period study was performed in healthy male subjects to assess the steady-state pharmacokinetic and safety profile of ritonavir and voriconazole. Low-dose ritonavir (100 mg b.i.d.) lowered AUC and C_{max} of voriconazole by 39 and 24%, respectively. High-dose ritonavir (400 mg b.i.d.) significantly lowered AUC and C_{max} of voriconazole by 82 and 66%, respectively. These studies recommend that coadministration

of voriconazole with low-dose ritonavir should be prescribed with caution and high-dose ritonavir is contraindicated [96].

5. Conclusion

Introduction of HAART has not only suppressed the viral load in HIV-infected individuals but has also greatly improved their quality of life. However, opportunistic fungal infections still remain the primary cause of morbidity and mortality in these individuals. Multidrug oral regimens are often prone to clinically relevant interactions due to metabolism between CYP450 enzyme systems along with efflux by membrane transporters. It is very crucial that clinicians and healthcare providers be familiar with the possible interactions between various antiretrovirals and antifungals. The mechanistic basis for drug interactions facilitates various clinical management options, including dosage adjustment, contraindication for concomitant use or therapeutic drug monitoring (TDM). In the absence of specific interaction potential data, it is imperative that clinicians familiarize with the pharmacodynamic and pharmacokinetic characteristics of these drugs that assist them in predicting possible interactions and measures to mitigate the associated risks.

6. Expert opinion

The current antifungal arsenal in the treatment of OIs includes amphotericin B, azole antifungals and echinocandins. Amphotericin B is neither a substrate nor an inhibitor of the CYP450 enzymes system. Hence, pharmacokinetic interactions are not expected to occur between this antifungal and other antiretrovirals. However, amphotericin B causes significant nephrotoxicity. Therefore, concomitant use with other nephrotoxic drugs (such as tenofovir) must be closely monitored for renal function. Given its relatively weak interaction potential with CYP450 system, fluconazole is the preferred antifungal drug. It may increase the plasma concentrations of coadministered antiretrovirals moderately via CYP3A4 inhibition. Although dosage adjustments are not required; simultaneous administration of fluconazole and nevirapine must be monitored for nevirapine-associated toxicities. Also, high dose of fluconazole (> 200 mg/day) is not recommended along with tipranavir. Itraconazole is a highly effective therapeutic, since the primary metabolite has considerable antifungal activity compared to the parent drug. One important clinical recommendation is that high itraconazole doses (> 200 mg/day) are not advised in patients receiving boosted PI regimen.

Ketoconazole, the imidazole antifungal, has been mostly replaced by newer triazoles. Not many clinically relevant interactions have been reported with posaconazole, the second-generation triazole antifungal. Due to significant reduction in the plasma concentration of posaconazole, it is contraindicated in combination with efavirenz or fosamprenavir. The dose of voriconazole and efavirenz needs to be adjusted when prescribed simultaneously. The use of voriconazole must be avoided with a low-dose ritonavir-boosted PI, unless benefits outweigh the associated risks. Moreover, voriconazole is contraindicated with high-dose ritonavir-boosted PI. Echinocandins are less prone to DDIs since they are neither substrate of P-gp nor CYP450 enzymes. Therefore, these antifungals may substitute the current treatment options and aid in overcoming the limitations of existing antifungal

therapy. These increasing numbers of documented or predicted DDIs may be considered in clinical management of HIV and opportunistic fungal infections. Early diagnosis of fungal infections, standardized fungal susceptibility testing and adjunctive immune therapies may lead to effective management of invasive fungal infections in HIV patients.

Other area of management of DDIs includes TDM. TDM enables modification of dosing regimen in response to their plasma concentrations achieved. TDM can serve as a promising therapeutic modality for optimizing clinical efficacy of a medication, while lowering dose-dependent toxicities. However, significant barriers exist to widespread clinical application of TDM [97,98]. In the next few years, we may witness extensive research and well-designed trials to identify the role of TDM in management of ART. The ultimate goal is to follow a multidisciplinary approach to improve the quality of HIV-infected patients.

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Article highlights

- The guidelines for the use of antiretroviral therapy in HIV-infected adults include a combination of two nucleoside/nucleotide reverse transcriptase inhibitors and one drug from either of the classes: non-nucleoside reverse transcriptase inhibitor, integrase strand transfer inhibitor or boosted protease inhibitor (PI).
- The most common systemic fungal infections observed in HIV patients include aspergillosis, coccidioidomycosis, cryptococcosis, esophageal and oropharyngeal candidiasis, histoplasmosis and penicilliosis. The preferred treatment regimen for these infections includes the administration of amphotericin B or azole antifungals.
- Pharmacodynamic interactions may lead to additive, synergistic or antagonistic pharmacological effects, and pharmacokinetic drug interactions result from altered absorption, distribution or disposition characteristics.
- A study/report of the potential interactions can trigger a dosage adjustment, additional therapeutic monitoring and contraindication to concomitant use.
- Tenofovir and amphotericin B can cause nephrotoxicity. Concomitant or sequential administration of these drugs must be closely monitored for renal function.
- When efavirenz and voriconazole are administered concomitantly, efavirenz exposure is elevated, whereas that of voriconazole is diminished. Hence, the dose of efavirenz should be reduced to 300 mg/day and the dose of voriconazole should be raised to 400 mg b.i.d.
- Voriconazole is contraindicated in patients taking high-dose ritonavir-boosted PI. It may be due to the fact that ritonavir induces CYP2C19/2C9 and thereby lowers voriconazole plasma concentration leading to loss of antifungal activity.
- Therapeutic drug monitoring can serve as a useful tool for optimizing clinical efficacy of a medication, while lowering dose-dependent toxicities.

This box summarizes key points contained in the article.

Table 1

List of antiretrovirals approved by US FDA for the treatment of HIV infections.

Antirviral drug	Metabolic enzyme/transport characteristics			Adverse reactions
	Substrate	Inhibitor	Inducer	
Entry and fusion inhibitors				
Enfuvirtide (T-20)	×	×	×	Pneumonia, erythema, nodules, pruritus, ecchymosis, pancreatitis, anorexia and sinusitis
Maraviroc	CYP3A4, P-gp	×	×	Hepatotoxicity, cardiovascular events, severe skin and hypersensitivity reactions
Nucleoside/nucleotide reverse transcriptase inhibitors				
Abacavir	×	×	×	Hypersensitivity reactions, myocardial infarction, nausea, diarrhea, bronchitis, fat redistribution, lactic acidosis and hepatic steatosis
Didanosine	×	×	×	Blood, lymphatic, ophthalmic, exocrine gland, gastrointestinal, hepatobiliary, musculoskeletal and metabolic disorder
Emtricitabine	×	×	×	Immune reconstitution syndrome, gastrointestinal, respiratory, musculoskeletal and central nervous system disorder
Lamivudine	×	×	×	Headache, nausea, malaise, fatigue, nasal symptoms, diarrhea and cough
Stavudine	×	×	×	Headache, diarrhea, neuropathy, rash, nausea and vomiting
Tenofovir disoproxil fumarate	×	×	×	Hepatotoxicity, gastrointestinal disorders, headache, pain, depression and asthenia
Zidovudine	×	×	×	Malaise, headache, asthenia and gastrointestinal disorders
Non-nucleoside/nucleotide reverse transcriptase inhibitors				
Delavirdine	CYP3A4, CYP2D6	CYP3A4, CYP2C9, CYP2D6, CYP2C19	×	Skin rash, digestive, nervous,

Antirviral drug	Metabolic enzyme/transport characteristics			Adverse reactions
	Substrate	Inhibitor	Inducer	
				musculoskeletal and respiratory disorders
Efavirenz	CYP3A4, CYP2B6	CYP2C9, CYP2C19, CYP3A4	CYP3A4, CYP2B6	Rash, dizziness, nausea, headache, fatigue, insomnia and vomiting
Etravirine	CYP3A4, CYP2C9, CYP2C19	CYP2C9, CYP2C19, P-gp	CYP3A4	Skin and hypersensitivity reactions
Nevirapine	CYP3A4, CYP2B6	×	CYP3A4, CYP2B6	Hepatitis, hepatic failure, Stevens-Johnson syndrome, toxic epidermal necrolysis and hypersensitivity reactions
Rilpivirine	CYP3A4	×	×	Hepatic, depressive and gastrointestinal disorders
<i>Integrase strand transfer inhibitors</i>				
Dolutegravir	UGT1A1, CYP3A4, UGT1A3, UGT1A9, BCRP, P-gp	OCT2	×	Hypersensitivity reactions, nervous system and gastrointestinal disorders
Elvitegravir	CYP3A4, UGT1A1, UGT1A3	×	CYP2C9	Bronchitis, diarrhea, nausea, upper respiratory tract and urinary tract infections
Raltegravir	UGT1A1	×	×	Gastrointestinal and nervous disorders
<i>Protease inhibitors</i>				
Atazanavir	CYP3A4	CYP3A4, CYP2C8, UGT1A1	×	Nausea, jaundice/scleral icterus and rash
Darunavir	CYP3A4	×	×	Diarrhea, headache, abdominal pain and rash
Fosamprenavir	CYP3A4, P-gp	CYP3A4	CYP3A4, P-gp	Diarrhea, rash, nausea, vomiting, fatigue and headache
Indinavir	CYP3A4	CYP3A4, CYP2D6	×	Hyperbilirubinemia, pain, rash, nephrolithiasis/urolithiasis and gastrointestinal disorders
Lopinavir/ ritonavir	CYP3A4	CYP3A4	×	Diarrhea, gastrointestinal, eye, cardiac and hepatobiliary disorders
Nelfinavir	CYP3A4, CYP2C19	CYP3A4	×	Diarrhea, rash, nausea, pain, fever, gastrointestinal disorders and bleeding

Antirviral drug	Metabolic enzyme/transport characteristics			Adverse reactions
	Substrate	Inhibitor	Inducer	
Saquinavir	CYP3A4, P-gp	×	×	Nausea, vomiting, diarrhea, musculoskeletal, endocrine, skin, vascular, renal and respiratory disorders
Tipranavir	CYP3A4, P-gp	P-gp	P-gp	Diarrhea, nausea, pyrexia, vomiting, fatigue, headache, and abdominal pain

×: None reported; OCT2: Organic cation transporter 2; P-gp: P-glycoprotein

Table 2

Preferred and alternative regimens for ART [1].

ART regimen		Combination of antiretrovirals	
<i>NNRTI-based regimen</i>	<i>NNRTI</i>	<i>NRTI</i>	<i>NRTI</i>
Preferred	Efavirenz	Tenofovir	Emtricitabine
Alternative	Efavirenz	Abacavir	Lamivudine
	Rilpivirine	Tenofovir	Emtricitabine
	Rilpivirine	Abacavir	Lamivudine
<i>INSTI-based regimen</i>	<i>INSTI</i>	<i>NRTI</i>	<i>NRTI</i>
Preferred	Raltegravir	Tenofovir	Emtricitabine
Alternative	Elvitegravir/cobicistat	Tenofovir	Emtricitabine
	Raltegravir	Abacavir	Lamivudine
<i>PI-based regimen</i>	<i>PI/r (r: ritonavir boosted)</i>	<i>NRTI</i>	<i>NRTI</i>
Preferred	Atazanavir/r	Tenofovir	Emtricitabine
	Darunavir/r	Tenofovir	Emtricitabine
Alternative	Atazanavir/r	Abacavir	Lamivudine
	Darunavir/r	Abacavir	Lamivudine
	Fosamprenavir/r	Abacavir	Lamivudine
	Fosamprenavir/r	Tenofovir	Emtricitabine
	Lopinavir/r	Abacavir	Lamivudine
	Lopinavir/r	Tenofovir	Emtricitabine

ART: Antiretroviral therapy; INSTI: Integrase strand transfer inhibitors; NNRTI: Non-nucleoside reverse transcriptase inhibitor; NRTI: Nucleoside/ nucleotide reverse transcriptase inhibitor

Table 3

Summary of opportunistic fungal infections in HIV-infected individuals [2].

Opportunistic fungal infection	Causative organism	Epidemiology	Clinical manifestations	Preferred treatment
Aspergillosis	<i>Aspergillus fumigatus</i> <i>A. flavus</i> <i>A. niger</i> <i>A. terreus</i>	CD4 < 100 cells/mm ³	Necrotizing pneumonia, tracheobronchitis	Voriconazole
Coccidioidomycosis	<i>Coccidioides immitis</i> <i>C. posadasii</i>	CD4 < 250 cells/mm ³	Focal pneumonia, cutaneous disease, meningitis	Fluconazole
Cryptococcosis	<i>Cryptococcus neoformans</i> <i>C. gattii</i>	CD4 < 100 cells/mm ³	Subacute meningitis, meningoencephalitis	Amphotericin B, fluconazole
Esophageal candidiasis	<i>Candida albicans</i>	CD4 < 200 cells/mm ³	Retrosternal burning pain, odynophagia	Fluconazole, itraconazole
Histoplasmosis	<i>Histoplasma capsulatum</i>	CD4 < 150 cells/mm ³	Fever, fatigue, weight loss, hepatosplenomegaly, chest pain and dyspnea	Itraconazole
Penicilliosis	<i>Penicillium marneffei</i>	CD4 < 100 cells/mm ³	Fever, anemia, weight loss, generalized skin papules	Itraconazole
Oropharyngeal candidiasis	<i>C. albicans</i>	CD4 < 200 cells/mm ³	Lesions on buccal surface, palate, oropharyngeal mucosa, tongue surface	Fluconazole

Table 4

List of important antifungals for the treatment of opportunistic fungal infections

Antifungal drug	Metabolic enzyme/transport characteristics		Adverse reactions
	Substrate	Inhibitor	
Amphotericin B	×	×	Infusion-related reactions (fever, chills, back pain, hypotension), nephrotoxicity
<i>Azole antifungals</i>			
Fluconazole	CYP3A4(10%),	CYP2C9, CYP3A4, CYP2C19	Hepatotoxicity, rash, nausea, vomiting, diarrhea, abdominal discomfort, prolongation of the QT interval
Itraconazole	CYP3A4, P-gp	CYP3A4, P-gp	Hepatotoxicity, congestive heart failure, hypokalemia, rash, nausea, vomiting, diarrhea, abdominal pain
Ketoconazole	CYP3A4	CYP3A4, CYP2C9 CYP1A2, UGT, P-gp	Hepatotoxicity, nausea, vomiting, diarrhea, abdominal pain
Posaconazole	UGT1A4, P-gp	CYP3A4, P-gp	Hepatotoxicity, QTc prolongation, hypokalemia, rash, nausea, vomiting, diarrhea, abdominal pain
Voriconazole	CYP2C19 (major), CYP3A4, CYP2C9	CYP3A4, CYP2C9 CYP2C19	Hepatotoxicity, QTc prolongation, rash, visual disturbances (initial dosing), optic neuritis (> 28 days treatment)
<i>Echinocandins</i>			
Anidulafungin	×	×	Headache, histamine release, rash, liver toxicity
Caspofungin	×	×	Fever, headache, histamine release, rash, liver toxicity
Micafungin	×	×	Headache, histamine release, rash, liver toxicity

×: None reported; P-gp: P-glycoprotein

Table 5

Summary of observed/predicted drug-drug interactions between antiretrovirals and azole antifungals.

Anti retroviral	Antifungal	Interactions	Dosing recommendation/ clinical comments	Ref.
<i>Entry and fusion inhibitors</i>				
Enfuvirtide	Fluconazole	↔	↔	[72]
	Itraconazole	↔	↔	[72]
	Ketoconazole	↔	↔	[72]
	Posaconazole	↔	↔	[72]
	Voriconazole	↔	↔	[72]
Maraviroc	Fluconazole	Fluconazole may ↑ maraviroc concentration via CYP3A4 inhibition	Although dosage adjustment is not necessary maraviroc-related toxicity should be closely monitored	[78]
	Itraconazole	Itraconazole can ↑ maraviroc concentration via CYP3A4 inhibition	Maraviroc dose is recommended to be reduced to 150 mg b.i.d.	[77]
	Ketoconazole	Maraviroc AUC and C _{max} ↑ by 5- and 3.4-fold	Maraviroc dose is recommended to be reduced to 150 mg b.i.d.	[77]
	Posaconazole	Posaconazole may ↑ maraviroc concentration via CYP3A4 inhibition	lthough dosage adjustment is not necessary maraviroc-related toxicity should be closely monitored	[78]
	Voriconazole	Voriconazole may ↑ maraviroc concentration via CYP3A4 inhibition	Although dosage adjustment is not necessary maraviroc-related toxicity should be closely monitored	[78]
<i>Nucleoside/nucleotide reverse transcriptase inhibitors</i>				
	Fluconazole	↔	↔	[80,81,99–103]
	Itraconazole	↔	↔	
	Ketoconazole	↔	↔	
	Posaconazole	↔	↔	
	Voriconazole	↔	↔	
<i>Non-nucleoside reverse transcriptase inhibitors</i>				
Delavirdine	Fluconazole	↔	↔	[82]
	Itraconazole	↔	↔	[82]
	Ketoconazole	Delavirdine C _{min} ↑ by 50%	↔	[82]
	Posaconazole	↔	↔	[82]
	Voriconazole	↔	↔	[82]
Efavirenz	Fluconazole	Efavirenz AUC ↑ by 16%; no change in fluconazole AUC	Dosage adjustment is not necessary	[83]
	Itraconazole	No change in efavirenz AUC; itraconazole AUC and C _{max} ↓ by 39 and 37%	Coadministration should be avoided. If used concomitantly, therapeutic monitoring of itraconazole is needed	[84]
	Ketoconazole	No change in efavirenz AUC; ketoconazole AUC and C _{max} ↓ by 72 and 44%	Coadministration should be avoided	[86]
	Posaconazole	No change in efavirenz AUC; posaconazole AUC and C _{max} ↓ by 50 and 45%	Coadministration should be avoided unless benefits outweigh the risks. If used concomitantly therapeutic	[85]

Anti retroviral	Antifungal	Interactions	Dosing recommendation/ clinical comments	Ref.
			monitoring of posaconazole is needed	
	Voriconazole	Efavirenz AUC and C_{max} ↑ by 44 and 38%; voriconazole AUC and C_{max} ↓. by 77 and 61 %	Dosage adjustment is necessary. Reduce efavirenz dose to 300 mg/day and increase voriconazole dose to 400 mg b.i.d. Dosage adjustment is not	[87]
Etravirine	Fluconazole	Etravirine AUC ↑ by 86%; no		[104]
	Itraconazole	change in fluconazole AUC	necessary; use with caution	[104]
		Concomitant use may result in ↑ plasma concentration of etravirine and ↓. plasma concentration of itraconazole	Dose adjustments for itraconazole may be necessary; consider therapeutic monitoring	
	Ketoconazole	Concomitant use may result in ↑ plasma concentration of etravirine and ↓. plasma concentration of ketoconazole	Dose adjustments for ketoconazole may be necessary; consider therapeutic monitoring	[104]
	Posaconazole	Posaconazole may ↑ plasma concentration of etravirine	Dose adjustments for posaconazole may be necessary; consider therapeutic monitoring	[104]
	Voriconazole	Etravirine AUC ↑ by 36%; voriconazole AUC ↑ by 14%	Dosage adjustment is not necessary; use with caution	[104]
Nevirapine	Fluconazole	Nevirapine exposure ↑ by 100%; no change in fluconazole AUC	Use with caution. Increased risk of nevirapine-associated toxicities	[105]
	Itraconazole	No change in nevirapine AUC; itraconazole AUC and C_{max} ↓. by 61 and 38%	Consider itraconazole monitoring	[106]
	Ketoconazole	Nevirapine AUC ↑ by 15–20%; ketoconazole AUC and C_{max} ↓ by 72 and 44%	Avoid concomitant use; consider other antiretrovirals or antifungals	[105]
	Posaconazole	↔	↔	[105]
	Voriconazole	↔	↔	[105]
Rilpivirine	Fluconazole	Fluconazole may ↑ rilpivirine concentration via CYP3A4 inhibition	Dosage adjustment is not necessary; monitor for breakthrough fungal infections	[107]
	Itraconazole	Itraconazole may ↑ rilpivirine concentration via CYP3A4 inhibition	Dosage adjustment is not necessary; monitor for breakthrough fungal infections	[107]
	Ketoconazole	Rilpivirine AUC and C_{max} ↑ by 49 and 30%; ketoconazole AUC and C_{max} ↓. by 24 and 15%	Dosage adjustment is not necessary; monitor for breakthrough fungal infections	[107]
	Posaconazole	Posaconazole may ↑ rilpivirine concentration via CYP3A4 inhibition	Dosage adjustment is not necessary; monitor for breakthrough fungal infections	[107]
	Voriconazole	Voriconazole may ↑ rilpivirine concentration via CYP3A4 inhibition	Dosage adjustment is not necessary; monitor for breakthrough fungal infections	[107]
<i>Integrase strand transfer inhibitors</i>				
Dolutegravir	Fluconazole	↔	↔	[88]
	Itraconazole	↔	↔	[88]
	Ketoconazole	↔	↔	[88]
	Posaconazole	↔	↔	[88]
	Voriconazole	↔	↔	[88]

Anti retroviral	Antifungal	Interactions	Dosing recommendation/ clinical comments	Ref.
Elvitegravir/ cobicistat	Fluconazole	↔	↔	[108]
	Itraconazole	Concomitant use may result in ↑ itraconazole and/or elvitegravir and cobicistat concentrations	The maximum daily dose of itraconazole should not exceed 200 mg	[108]
	Ketoconazole	Concomitant use may result in ↑ ketoconazole and/or elvitegravir and cobicistat concentrations	The maximum daily dose of ketoconazole should not exceed 200 mg	[108]
	Posaconazole	↔	↔	[108]
	Voriconazole	Concomitant use may result in ↑ voriconazole and/or elvitegravir and cobicistat concentrations	An assessment of benefit:risk ratio is recommended to justify use of voriconazole with elvitegravir/cobicistat	[108]
Raltegravir	Fluconazole	↔	↔	[89]
	Itraconazole	↔	↔	[89]
	Ketoconazole	↔	↔	[89]
	Posaconazole	↔	↔	[89]
	Voriconazole	↔	↔	[89]
<i>Protease inhibitors (PIs)(/r represents ritonavir-boosted)</i>				
Atazanavir	Fluconazole	↔	↔	[109]
	Itraconazole	Concomitant use may result in negligible increase in atazanavir; ↑ concentration of itraconazole. Concomitant use of atazanavir/r may result in ↑ concentration of both PI and itraconazole	Dosage adjustment is not necessary; monitor for itraconazole-related toxicities	[109]
	Ketoconazole	Concomitant use may result in negligible increase in atazanavir; ↑ concentration of ketoconazole. Concomitant use of atazanavir/r may result in ↑ concentration of both PI and ketoconazole	Dosage adjustment is not necessary; monitor for ketoconazole-related toxicities	[109]
	Posaconazole	Concomitant use ↑ AUC of atazanavir by 268%. Concomitant use of atazanavir/r ↑ AUC of atazanavir by 146%	Dosage adjustment is not necessary; monitor for atazanavir-related toxicities	[85]
	Voriconazole	Concomitant use may affect atazanavir concentration. Concomitant use of atazanavir/r in patients with a functional CYP2C19 results in ↓ concentration of atazanavir and voriconazole; patients without a functional CYP2C19 results in ↓ concentration of atazanavir and ↑ voriconazole	Coadministration of atazanavir/r and voriconazole should be avoided unless benefits outweigh the risks. If used concomitantly, therapeutic monitoring is needed	[109]
Darunavir	Fluconazole	↔	↔	[110]
	Itraconazole	Concomitant use of darunavir/r and itraconazole may ↑ plasma concentration of darunavir and itraconazole	While administering with darunavir/r, the daily dose of itraconazole should not exceed 200 mg	[110]
	Ketoconazole	Concomitant use ↑ AUC and C _{max} of darunavir by 155 and 78%; no change in ketoconazole concentration. Concomitant use of darunavir/r ↑ AUC and C _{max} of darunavir by 42 and 21 %; ↑ AUC and C _{max} of ketoconazole by 212 and	While administering with darunavir/r, the daily dose of ketoconazole should not exceed 200 mg	[111]

Anti retroviral	Antifungal	Interactions	Dosing recommendation/ clinical comments	Ref.
		111 %		
	Posaconazole	↔	↔	[110]
	Voriconazole	Concomitant use of darunavir/r results in ↓. concentration of voriconazole	Coadministration of darunavir/r and voriconazole should be avoided unless benefits outweigh the risks	[94]
Fosamprenavir	Fluconazole	↔	↔	[91]
	Itraconazole	Concomitant use may result in ↑ concentration of amprenavir and itraconazole.	Dosage adjustment is not necessary; monitor for dose-related toxicities.	[91]
		Concomitant use of fosamprenavir/r may result in ↑ concentration of both PI and itraconazole	While administering with fosamprenavir/r, the daily dose of itraconazole should not exceed 200 mg	
	Ketoconazole	Concomitant use ↑ AUC and C _{max} of amprenavir by 31 and 16%; ↑ AUC and C _{max} of ketoconazole by 44 and 19%.	Dosage adjustment is not necessary; monitor for dose-related toxicities. While administering with fosamprenavir/r, the daily dose of ketoconazole should not exceed 200 mg	[92]
	Posaconazole	Concomitant use ↓. AUC and C _{max} of posaconazole by 23 and 21%	Do not coadminister	[93]
	Voriconazole	Concomitant use may ↑ fosamprenavir and voriconazole concentration via CYP3A4 inhibition Concomitant use of fosamprenavir/r results in ↓ concentration of voriconazole	Coadministration of fosamprenavir/r and voriconazole should be avoided unless benefits outweigh the risks	[94]
Indinavir	Fluconazole	↔	↔	[112]
	Itraconazole	Concomitant use may result in ↑ concentration of indinavir	Dosage adjustment is necessary. Reduce indinavir dose to 600 mg every 8 h	[112]
	Ketoconazole	Concomitant use may result in ↑ concentration of indinavir	Dosage adjustment is necessary. Reduce indinavir dose to 600 mg every 8 h	[112]
	Posaconazole Voriconazole	↔ Concomitant use of indinavir/r results in ↓. concentration of voriconazole	↔ Coadministration of indinavir/r and voriconazole should be avoided unless benefits outweigh the risks	[112] [94]
Lopinavir/r	Fluconazole	↔	↔	[95]
	Itraconazole	Concomitant use of lopinavir/r may result in ↑ concentration of itraconazole	While administering with lopinavir/r, the daily dose of itraconazole should not exceed 200 mg	[95]
	Ketoconazole	Concomitant use of lopinavir/r may result in ↑ concentration of ketoconazole	While administering with lopinavir/r, the daily dose of ketoconazole should not exceed 200 mg	[95]
	Posaconazole Voriconazole	↔ Concomitant use of lopinavir/r results in ↓. concentration of voriconazole	Coadministration of lopinavir/r and voriconazole should be avoided unless benefits outweigh the risks	[95] [94]
Nelfinavir	Fluconazole	Concomitant use may result in ↑ concentration of nelfinavir and fluconazole	Dosage adjustment is not necessary; monitor for dose-related toxicities	[113]

Anti retroviral	Antifungal	Interactions	Dosing recommendation/ clinical comments	Ref.
	Itraconazole	Concomitant use may result in ↑ concentration of nelfinavir and itraconazole	Dosage adjustment is not necessary; monitor for dose-related toxicities	[113]
	Ketoconazole Posaconazole	Concomitant use ↑ AUC and C _{max} of nelfinavir by 35 and 25%	Dosage adjustment is not necessary; monitor for dose-related toxicities	[113] [113]
	Voriconazole	Concomitant use may result in ↑ concentration of nelfinavir and posaconazole	Dosage adjustment is not necessary; monitor for dose-related toxicities	
	Voriconazole	Concomitant use of nelfinavir/r results in ↓. concentration of voriconazole	Coadministration of nelfinavir/r and voriconazole should be avoided unless benefits outweigh the risks	[94]
Saquinavir	Fluconazole	Concomitant use may result in ↑ concentration of saquinavir and fluconazole	Dosage adjustment is not necessary; monitor for dose-related toxicities	[114]
	Itraconazole	Concomitant use ↑ exposure of saquinavir and itraconazole	Dosage adjustment is not necessary; monitor for dose-related toxicities	[115,116]
	Ketoconazole	Concomitant use of saquinavir/r ↑ AUC and C _{max} of ketoconazole by 45 and 168%	While administering with saquinavir/r, the daily dose of ketoconazole should not exceed 200 mg	[117]
	Posaconazole	↔	↔	[114]
	Voriconazole	Concomitant use of saquinavir/r results in ↓. concentration of voriconazole	Coadministration of saquinavir/r and voriconazole should be avoided, unless benefits outweigh the risks	[94]
Tipranavir	Fluconazole	Concomitant use ↑ AUC and C _{max} of tipranavir by 56 and 46%; no change in fluconazole AUC	Dosage adjustment is not necessary; however doses > 200 mg/day are not recommended.	[118]
	Itraconazole	Possible ↑ itraconazole concentration	The daily dose of itraconazole should not exceed 200 mg	[119]
	Ketoconazole	Possible ↑ ketoconazole concentration	The daily dose of ketoconazole should not exceed 200 mg	[119]
	Posaconazole	↔	↔	[119]
	Voriconazole	Difficult to predict due to involvement of multiple CYP enzymes	Difficult to predict due to involvement of multiple CYP enzymes	[119]