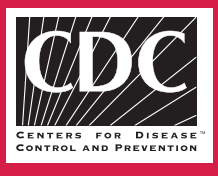
Managing Drug Interactions in the Treatment of HIV-Related Tuberculosis



Department of Health and Human Services
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Managing Drug Interactions in the Treatment of HIV-Related Tuberculosis

Centers for Disease Control and Prevention
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Table of Contents

Introduction

Worldwide, tuberculosis is the most common opportunistic infection among people with HIV infection. In addition to its frequency, tuberculosis is also associated with substantial morbidity and mortality. Despite the complexities of treating two infections requiring multidrug therapy at the same time, antiretroviral therapy can be life-saving among patients with tuberculosis and advanced HIV disease. Observational studies in a variety of settings have shown that use of antiretroviral therapy during tuberculosis treatment results in marked decreases in the risk of death or other opportunistic infections among persons with tuberculosis and advanced HIV disease [1, 2].

Concomitant use of treatment for tuberculosis and antiretroviral therapy is complicated by the adherence challenge of polypharmacy, overlapping side effect profiles of antituberculosis drugs and antiretroviral drugs, immune reconstitution inflammatory syndrome, and drug-drug interactions [3]. The key interactions, and the focus of this document, are those between the rifamycin antibiotics and four classes of antiretroviral drugs: protease inhibitors, non-nucleoside reverse-transcriptase inhibitors [NNRTI], CCR5-receptor antagonists, and integrase inhibitors [3]. Only two of the currently available antiretroviral drug classes, the nucleoside analogues (other than zidovudine [4]) and enfuvirtide (a parenteral entry inhibitor) do not have significant interactions with the rifamycins.

The purpose of this summary is to provide the clinician with updated recommendations for managing the drug-drug interactions that occur when using antiretroviral therapy during tuberculosis treatment. Changes from previous versions of these guidelines include: an effort to obtain and summarize the clinical experience of using specific antiretroviral regimens during tuberculosis treatment (not just pharmacokinetic data), a table summarizing the clinical experience with key antiretroviral regimens and providing recommended regimens (Table 1), and sections on treatment for special populations (young children, pregnant women, patients with drug-resistant tuberculosis). We include drug-drug interaction data for antiretroviral drugs that have been approved or are currently available through expanded access programs in the United States; these recommendations will be updated as additional antiretroviral drugs progress become available.

The Role of Rifamycins in Tuberculosis Treatment

Despite the complexity of these drug interactions, the key role of the rifamycins in the success of tuberculosis treatment mandates that the drug-drug interactions between the rifamycins and antiretroviral drugs be managed, not avoided by using tuberculosis treatment regimens that do not include a rifamycin or by withholding antiretroviral therapy until completion of anti-tuberculosis therapy among patients with advanced immunodeficiency. In randomized trials, regimens without rifampin or in which rifampin was only used for the first two months of therapy resulted in higher rates of tuberculosis treatment failure and relapse [5, 6]. The sub-optimal performance of the regimen of two months of rifampin (with isoniazid, pyrazinamide, and ethambutol) followed by 6 months of isoniazid + ethambutol was particularly notable among participants with HIV co-infection [5]. Therefore, patients with HIV-related tuberculosis should be treated with a regimen including a rifamycin for the full course of tuberculosis treatment, unless the isolate is resistant to the rifamycins or the patient has a severe side effect that is clearly due to the rifamycins.

Furthermore, patients with advanced HIV disease (CD4 cell count < 100 cells/mm^3) have an increased risk of acquired rifamycin resistance if treated with a rifamycin-containing regimen administered once or twice-weekly [1, 7]. The rifamycin-based regimen should be administered daily (5-7 days per week) for at least the first 2 months of treatment among patients with advanced HIV disease [8, 9].

Predicting Drug Interactions Involving Rifamycins

Knowledge of the mechanisms of drug interactions can help predict the likelihood of an interaction, if that specific combination of drugs has not been formally evaluated. The rifamycin class upregulate (induce) the synthesis of several classes of drug transporting and drug metabolizing enzymes. With increased synthesis, there is increased total activity of the enzyme (or enzyme system), thereby decreasing the serum half-life and serum concentrations of drugs that are metabolized by that system. The most common locus of rifamycin interactions is the cytochrome P450 enzyme system, particularly the CYP3A4 and CYP2C8/9 isozymes. To a lesser extent, rifampin induces the activity of the CYP2C19 and CYPD6 isozymes. The rifamycins vary in their potential as CYP450 inducers, with rifampin being most potent, rifapentine intermediate, and rifabutin being much less active. Rifampin also upregulates the synthesis of cytosolic drug-metabolizing enzymes, including glucuronosyl transferase, an enzyme involved in the metabolism of zidovudine [10] and raltegravir.

Rifampin and Antiretroviral Therapy

The most important drug-drug interactions in the treatment of HIV-related tuberculosis are those between rifampin and the NNRTIs, efavirenz and nevirapine. Rifampin is the only rifamycin available in most of the world, and initial antiretroviral regimens in areas with high rates of tuberculosis consist of efavirenz or nevirapine (in combination with nucleoside analogues). Furthermore, because of its potency and durability in randomized clinical trials, efavirenz-based therapy is a preferred option for initial antiretroviral therapy in developed countries.

Rifampin and Efavirenz

Rifampin causes a measurable, though modest, decrease in efavirenz concentrations [11, 12] (Table 2). Increasing the dose of efavirenz from 600 mg daily to 800 mg daily compensates for the effect of rifampin [11, 12], but it does not appear that this dose increase is necessary to achieve excellent virological outcomes of therapy [12]. Trough concentrations of efavirenz, the best predictor of its virological activity, remain well above the concentration necessary to suppress HIV in vitro among patients on concomitant rifampin [13].
A testament to the potency of efavirenz against HIV is that the standard dose of efavirenz results in very high rates of complete viral suppression despite 10-fold interpatient differences in trough concentrations. Therefore, it is unlikely that the 20% decrease in serum concentrations resulting from rifampin will have a clinically-significant effect on antiretroviral activity. In several cohort studies, antiretroviral therapy of standard-dose efavirenz + 2 nucleosides was well-tolerated and highly efficacious in achieving complete viral suppression among patients receiving concomitant rifampin-based tuberculosis treatment [14, 15]. Furthermore, there was no apparent benefit from a higher dose of efavirenz (800 mg daily) in one randomized trial [12], and a small observational study documented high serum concentrations and neurotoxicity among 7 of 9 patients receiving the 800 mg dose with rifampin [16]. Therefore, this combination – efavirenz-based antiretroviral therapy and rifampin-based tuberculosis treatment, at their standard doses – is the preferred treatment for HIV-related tuberculosis (Table 1). Some experts recommend the 800 mg dose of efavirenz for patients weighing > 60 kg.

Alternatives to Efavirenz-Based Antiretroviral Therapy

Alternatives to efavirenz-based antiretroviral therapy are needed for patients with HIV-related tuberculosis: efavirenz cannot be used during pregnancy (at least during the first trimester), some patients are intolerant to efavirenz, and some are infected with NNRTI-resistant strains of HIV.

Rifampin and Nevirapine

Rifampin decreases serum concentrations of nevirapine by 20-55% [17, 18] (Table 1). The common toxicities of nevirapine – skin rash and hepatitis – overlap common toxicities of some first-line antituberculosis drugs. Furthermore, nevirapine-based regimens are not recommended for patients with higher CD4 cell counts (> 350 cells/mm^3 for men, > 250 cells/mm^3 for women) because of increased risk of severe hypersensitivity reactions. Therefore, there are concerns about the efficacy and safety of using nevirapine-based antiretroviral therapy during rifampin-based tuberculosis treatment. At present, there have been no studies comparing efavirenz vs. nevirapine-based antiretroviral therapy among patients being treated for tuberculosis. Trough serum concentrations of nevirapine among patients on concomitant rifampin often exceed the concentration necessary to suppress HIV in vitro [17, 19]. Several cohort studies have shown high rates of viral suppression among patients receiving nevirapine-based antiretroviral therapy [17, 20]. The risk of hepatitis among such patients was also comparable to patients receiving first-line tuberculosis treatment without antiretroviral therapy [20]. Despite the interaction with rifampin, nevirapine-based antiretroviral therapy appears to be reasonably effective and well-tolerated among patients being treated for tuberculosis.

These studies are neither adequately powered nor reported in sufficient detail to fully answer the concerns about the efficacy and safety of nevirapine-based antiretroviral therapy during tuberculosis treatment. However, the collected experience is sufficient to make nevirapine an alternative for patients unable to take efavirenz and who do not have access to rifabutin. Some investigators have suggested using an increased dose of nevirapine among patients on rifampin [18]. However, a recent randomized trial comparing standard dose nevirapine (200 mg twice-daily) to a higher dose (300 mg twice daily) among patients on rifampin demonstrated an increased risk of nevirapine hypersensitivity among patients randomized to the higher dose of nevirapine [21]. Therefore, the standard dose of nevirapine should be used among patients on rifampin (200 mg daily for 2 weeks, followed by 200 mg twice-daily).

Other Antiretroviral Regimens for use with Rifampin

For patients who are infected with NNRTI-resistant HIV, neither efavirenz nor nevirapine will be effective. Unfortunately, there is little clinical experience with alternatives to NNRTI-based therapy among patients being treated with rifampin. Standard doses of protease inhibitors cannot be given with rifampin (Table 1); the > 90% decreases in trough concentrations of the protease inhibitors would surely make them ineffective [22-24]. Most protease inhibitors are given with low-dose ritonavir (100-200 mg per dose of the other protease inhibitor). However, low-dose ritonavir does not overcome the effects of rifampin; serum concentrations of indinavir, lopinavir, and atazanavir were decreased by > 90% when given with the standard ritonavir boosting dose (100 mg) in the presence of rifampin [23-25], and a once-daily regimen of ritonavir-boosted saquinavir (saquinavir 1600 mg + ritonavir 200 mg) resulted in inadequate concentrations of saquinavir [26, 27]. Therefore, standard protease inhibitor regimens, whether boosted or not, cannot be given with rifampin.

The dramatic effects of rifampin on serum concentrations of other protease-inhibitors can be overcome with high-doses of ritonavir (400 mg twice-daily, "super-boosted protease inhibitors") or by doubling the dose of the co-formulated form of lopinavir/ritonavir [23]. However, high rates of hepatoxicity occurred among healthy volunteers treated with rifampin and ritonavir-boosted saquinavir (saquinavir 1000 mg + ritonavir 100 mg twice-daily [28]) and those treated with rifampin and lopinavir/ritonavir (either as lopinavir 400 mg + 400 mg ritonavir twice-daily or as lopinavir 800 mg + ritonavir 200 mg twice-daily) [23, 29].

Whether patients with HIV-related tuberculosis will have the same high rates of hepatotoxicity when treated with super-boosted protease inhibitors or double-dose lopinavir/ritonavir has not been adequately studied. Among patients receiving rifampin-based tuberculosis treatment, the combination of ritonavir-boosted saquinavir (400 mg of each, twice daily) was not well-tolerated [30]. The initial positive experience with super-

boosted lopinavir among young children (see below) suggests that these regimens may be tolerable and effective among at least some patients with HIV-related tuberculosis. However, these regimens should only be used with close clinical and laboratory monitoring for possible hepatoxicity, when there is a pressing need to start antiretroviral therapy.

Regimens composed entirely of nucleoside analogues are less active than combinations of two classes of antiretroviral drugs (e.g., NNRTI + nucleosides) [31]. A regimen of zidovudine, lamivudine, and the nucleotide agent, tenofovir, has been reported to be active among patients on rifampin-based tuberculosis treatment [32]. However, this regimen has not been compared to standard initial antiretroviral therapy (e.g., efavirenz + 2 nucleosides). Finally, a quadruple regimen of zidovudine, lamivudine, abacavir, and tenofovir has been reported to be as active as an efavirenz-based regimen in an initial small trial [33]. While these regimens of nucleosides and nucleotides cannot be recommended as preferred therapy among patients receiving rifampin, their lack of predicted clinically-significant interactions with rifampin make them an acceptable alternative, for patients unable to take NNRTIs or those with NNRTI-resistant HIV [32, 34].

Rifampin has substantial interactions with the recently-approved CCR5-receptor antagonist, maraviroc [35]. An increased dose of maraviroc has been recommended to allow concomitant use of rifampin and maraviroc, but there is no reported clinical experience with this combination. Rifampin decreases the trough concentrations of raltegravir, the recently-approved integrase inhibitor, by ~ 60% [36]. Because the antiviral activity of raltegravir 200 mg twice daily was very similar to the activity of the licensed dose (400 mg twice-daily), the current recommendation is to use the standard dose of raltegravir in a patient receiving concomitant rifampin. However, this combination should be used with caution – there is very little clinical experience with using concomitant raltegravir and rifampin. Finally, rifampin is predicted to substantially decrease the concentrations of etravirine (a second-generation NNRTI [37] currently available through an expanded access program). Additional drug-interaction studies will be needed to further evaluate whether these new agents can be used among patients receiving rifampin-based tuberculosis treatment.

Rifabutin and Antiretroviral Drugs

Rifabutin is as effective for tuberculosis treatment as rifampin [38, 39], but has much less effect on drugs metabolized through the CYP3A system [40] (Table 3). However, rifabutin is either not available or is very expensive in countries with high rates of HIV-related tuberculosis. Furthermore, some antiretroviral drugs have a substantial effect on rifabutin concentrations, necessitating somewhat complex dosing guidelines for rifabutin in the setting of antiretroviral therapy (see Table 3). In addition to their complexity, there is another potential problem of using rifabutin for tuberculosis treatment. If a patient whose rifabutin dose was decreased in response to antiretroviral therapy then stops taking the interacting drug (e.g., ritonavir), the resulting rifabutin concentrations are likely to be sub-therapeutic. These factors, in addition to the limited availability of the drug, limit the use of rifabutin in the treatment of HIV-related tuberculosis.

Rifabutin and Protease Inhibitors

Rifabutin has little, if any effect on the serum concentrations of protease-inhibitors (other than unboosted saquinavir) [22]. Cohort studies have shown favorable virological and immunological outcomes of protease-inhibitor-based antiretroviral therapy in the setting of rifabutin-based tuberculosis treatment [1, 41]. Though no comparative studies have been done, the combination of rifabutin (if available) with protease-inhibitor based antiretroviral therapy is the preferred form of therapy for patients unable to take NNRTI-based antiretroviral therapy (Table 1). As above, there are concerns about the safety of super-boosted protease-inhibitors and the efficacy of nucleoside-only regimens in the setting of rifampin-based tuberculosis treatment.
The protease-inhibitors, particularly if pharmacologically boosted with ritonavir, markedly increase serum concentrations and toxicity of rifabutin [42]. Therefore, the dose of rifabutin should be decreased when used with protease-inhibitors (Table 3). As above, the decreased dose of rifabutin would be sub-therapeutic if

the patient stopped taking the protease-inhibitor without adjusting the rifabutin dose. Therefore, adherence to the protease-inhibitor should be assessed with each dose of directly observed tuberculosis treatment; one convenient way to do so is to give a supervised dose of protease-inhibitor at the same time as the directly observed dose of tuberculosis treatment.

Special Populations

Pregnant women

A number of issues complicate the treatment of the HIV-infected woman who is pregnant and has active tuberculosis. Efavirenz is contraindicated during at least the first 1-2 trimesters. Furthermore, pregnant women have an increased risk of severe toxicity from didanosine and stavudine [43], and women with CD4 cell counts > 250 cells/mm^3 have an increased risk of nevirapine-related hepatitis [44]. Therefore, the choice of antiretroviral agents is limited among pregnant women.

Pregnancy alters the distribution and metabolism of a number of drugs, including antiretroviral drugs [45] (there is very little information on whether the metabolism of anti-tuberculosis drugs is altered during pregnancy). Notably, the serum concentrations of protease-inhibitors are decreased during the latter stages of pregnancy [46, 47]. There are no published data on drug-drug interactions between anti-tuberculosis and antiretroviral drugs among pregnant women. However, it is likely that the effects of rifampin on protease inhibitors are exacerbated during pregnancy.

In the absence of pharmacokinetic data and published clinical experience it is difficult to formulate guidelines for the management of drug-drug interactions during the treatment of HIV-related tuberculosis among pregnant women. Nevirapine-based therapy could be used among women on rifampin-based tuberculosis treatment, with the caveat that there be a good monitoring system for symptoms and laboratory tests for hepatotoxicity. Efavirenz-based therapy may be an option during the later stages of pregnancy. The quadruple nucleoside/nucleotide regimen (zidovudine, lamivudine, abacavir, and tenofovir) is an alternative, though additional experience is required, particularly during pregnancy. Finally, despite their sub-optimal activity, triple nucleoside or nucleoside/nucleotide regimens are an alternative during pregnancy. Where rifabutin is available, the preferred option is protease-inhibitor-based antiretroviral therapy.

Children

HIV-infected children in high-burden countries have very high rates of tuberculosis, often with severe, life-threatening manifestations (e.g., disseminated disease, meningitis). Such children may also have advanced and rapidly-progressive HIV disease, so there are pressing reasons to assure potent treatment for both tuberculosis and AIDS. In addition to the complexities raised by the drug interactions discussed above, children with HIV-related tuberculosis raise other challenges. There are very limited data on the absorption, metabolism, and elimination of anti-tuberculosis drugs among children, particularly among very young children (< 2 years of age).

Some antiretroviral agents are not yet available in suspension formulations, and there are limited pharmacokinetic data for all antiretroviral drugs among young children. The use of single-dose nevirapine selects for NNRTI-resistant strains among those infants who are infected despite perinatal prophylaxis, and such children have inferior outcomes if subsequently treated with nevirapine-based combination antiretroviral therapy [48]. Therefore, there is understandable reluctance to use NNRTI-based therapy among perinatally-infected infants who were exposed to single-dose nevirapine. As above, the inability to use NNRTI-based antiretroviral therapy limits options for antiretroviral therapy among children receiving rifampin-based tuberculosis treatment.

There are emerging, though unpublished, pharmacokinetic data and clinical experience with using protease-inhibitor-based antiretroviral therapy among young children (< 5 years of age) with HIV-related tuberculosis. Children treated with super-boosted lopinavir (ritonavir in addition to doses of co-formulated lopinavir/ritonavir) while on rifampin-based tuberculosis treatment had serum concentrations of lopinavir comparable to those of children treated with standard dose lopinavir/ritonavir in the absence of rifampin [49]. Furthermore, a cohort study found similar virological and immunological outcomes of antiretroviral therapy among children treated with super-boosted lopinavir and rifampin-based tuberculosis treatment compared with children treated with standard dose lopinavir/ritonavir [50]. Therefore, super-boosted lopinavir plus appropriate nucleoside agents is the preferred antiretroviral regimen among children on rifampin-based tuberculosis treatment.

The triple nucleoside regimen of zidovudine, lamivudine, and abacavir has been suggested for young children who are taking rifampin-based tuberculosis treatment [51]. However, there is limited published clinical experience with this regimen among young children, with or without concomitant tuberculosis. Furthermore, young children often have very high HIV RNA levels, suggesting the need for highly-potent antiretroviral regimens. While awaiting additional studies, the triple-nucleoside regimen is an alternative for young children receiving rifampin-based tuberculosis treatment.

In an initial pharmacokinetic study, efavirenz concentrations were not significantly different among children on rifampin, compared to children without tuberculosis [49]. However, efavirenz concentrations were sub-optimal in both groups, raising concerns about the adequacy of current efavirenz dosing recommendations among children [52]. However, efavirenz-based antiretroviral therapy is highly-active among older children [53, 54], and can be used with rifampin-based tuberculosis treatment.

Patients with Multidrug-Resistant Tuberculosis

Outbreaks of multidrug-resistant tuberculosis among HIV-infected patients have been documented since the 1980s. Recently, an outbreak of highly-lethal multidrug-resistant tuberculosis was discovered in South Africa, primarily involving HIV-infected patients [55]. Prompt initiation of antiretroviral therapy may be one way to decrease the alarmingly high death rate among HIV-infected patients with multidrug-resistant tuberculosis.

Most of the drugs used to treat multidrug-resistant tuberculosis (the "second-line drugs": fluoroquinolone antibiotics, ethionamide, cycloserine, kanamycin, amikacin, capreomycin, para-amino salicylate) were developed and approved nearly 40 years ago, prior to the development of modern laboratory techniques to determine pathways of drug metabolism. Furthermore, there are no published studies of possible drug-drug interactions between second-line antituberculosis drugs and antiretroviral drugs. Based on the existing, albeit incomplete, knowledge of the metabolism of the second-line drugs, only ethionamide has a significant possibility of an interaction with antiretroviral drugs [22] (ethionamide is thought to be metabolized by the CYP450 system, though it is not known which of the CYP isozymes are responsible). Whether doses of ethionamide and/or certain antiretroviral drugs should be modified during the co-treatment of multidrug-resistant tuberculosis and HIV disease is completely unknown.

Limitations of these Guidelines

The limitations of the information available for writing these guidelines should be appreciated. First, drug-drug interaction studies are often done among healthy volunteers. While such studies reliably predict the nature of a drug-drug interaction (e.g., that rifampin decreases the serum concentrations of efavirenz), they seldom provide the optimal management of that interaction among patients with HIV-related tuberculosis (in cases of extreme interactions, such as that between rifampin and unboosted protease-inhibitors, the data from healthy volunteers can be definitive). In this update of the guidelines we emphasize studies done

among patients with HIV-related tuberculosis, particularly those that evaluate treatment outcomes of the two diseases. However, such studies often had small sample sizes, limiting the generalizability of their findings. Second, rates of drug metabolism often differ markedly between individuals, and part of that variance may be due to genetic polymorphisms in drug-metabolizing enzymes. Therefore, drug interactions and their relevance may not be the same in different populations. Third, in the attempt to provide the most up-to-date information we include studies that have been presented at international conferences, but that have not yet completed the peer review process and been published. Fourth, it is very difficult to predict the outcome of complex drug interactions, such as those that might occur when three drugs with CYP3A activity are used together (e.g., rifabutin, atazanavir and efavirenz). Therapeutic drug monitoring, if available, may be helpful in such situations. Finally, in the Special Populations section, we highlighted the lack of pharmacokinetic data on two key populations of patients with HIV-related tuberculosis – pregnant women and children. We provide recommendations for these key populations, but these are based primarily on expert opinion because of the lack of pharmacokinetic data.

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Table 1. Recommendations for regimens for the concomitant treatment of tuberculosis and HIV infection

Combined regimen for treatment of HIV and tuberculosis	PK effect of the rifamycin	Tolerability / toxicity	Antiviral activity when used with rifampin	Recommendation (comments)
Efavirenz-based ART * with rifampin-based TB treatment	Well-characterized, modest effect	Low rates of discontinuation	Excellent	Preferred (efavirenz should not be used during the first trimester of pregnancy)
PI-based ART * with rifabutin-based TB treatment	Little effect of rifabutin on PI concentrations, but marked increases in rifabutin concentrations	Low rates of discontinuation (if rifabutin is appropriately dose-reduced)	Favorable, though published clinical experience is not extensive	Preferred for patients unable to take efavirenz †
Nevirapine-based ART with rifampin-based TB treatment	Moderate effect	Concern about hepatotoxicity when used with isoniazid, rifampin and pyrazinamide	Favorable	Alternative for patients who cannot take efavirenz and if rifabutin not available
Zidovudine / lamivudine / abacavir / tenofovir with rifampin-based TB treatment[10]	50% decrease in zidovudine, possible effect on abacavir not evaluated	Anemia	No published clinical experience	Alternative for patients who cannot take efavirenz and if rifabutin not available
Zidovudine / lamivudine / tenofovir with rifampin-based TB treatment	50% decrease in zidovudine, no other effects predicted	Anemia	Favorable, but not evaluated in a randomized trial	Alternative for patients who cannot take efavirenz and if rifabutin not available
Zidovudine / lamivudine / abacavir with rifampin-based TB treatment	50% decrease in zidovudine, possible effect on abacavir not evaluated	Anemia	Early favorable experience, but this combination is less effective than efavirenz-based regimens in persons not taking rifampin	Alternative for patients who cannot take efavirenz and if rifabutin not available
Super-boosted lopinavir-based ART with rifampin-based TB treatment	Little effect	Hepatitis among healthy adults, but favorable experience, among young children (< 3 years)	Good, among young children (< 3 years)	Alternative if rifabutin not available; preferred for young children when rifabutin not available

ART: antiretroviral therapy

** with 2 nucleoside analogues*

† includes patients with NNRTI-resistant HIV, those unable to tolerate efavirenz, women during the first 1-2 trimesters of pregnancy

Table 2. Recommendations for coadministering antiretroviral drugs with RIFAMPIN – 2007

Non-nucleoside reverse transcriptase inhibitors			
	Recommended change in dose of antiretroviral drug	**Recommended change in dose of rifampin**	**Comments**
Efavirenz	None (some experts recommend 800 mg for patients > 60 kg)	No change (600 mg/day)	Efavirenz AUC ↓ by 22%; no change in rifampin concentration. Efavrirenz should not be used during the 1st trimester of pregnancy.
Nevirapine	No change	No change (600 mg/day)	Nevirapine AUC ↓ 37-58% and Cmin ↓ 68% with 200 mg 2x/day dose.
Delavirdine	Rifampin and delavirdine should not be used together		Delavirdine AUC ↓ by 95%
Etravirine	Etravirine and rifampin should not be used together		Marked decrease in etravirine predicted, based on data on the interaction with rifabutin
Single protease inhibitors			
	Recommended change in dose of antiretroviral drug	**Recommended change in dose of rifampin**	**Comments**
Ritonavir	No change	No change (600 mg/day)	Use with caution. Ritonavir AUC↓ by 35%; no change in rifampin concentration. Monitor for antiretroviral activity of ritonavir.
fos-Amprenavir	Rifampin and fos-amprenavir should not be used together		
Atazanavir	Rifampin and atazanavir should not be used together		Atazanavir AUC ↓ by >95%
Indinavir	Rifampin and indinavir should not be used together		Indinavir AUC ↓ by 89%.
Nelfinavir	Rifampin and nelfinavir should not be used together		Nelfinavir AUC ↓ 82%
Saquinavir	Rifampin and saquinavir should not be used together		Saquinavir AUC ↓ by 84%

Table 2. (cont.) Recommendations for coadministering antiretroviral drugs with RIFAMPIN – 2007

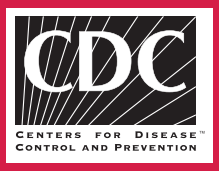
Dual protease-inhibitor combinations			
	Recommended change in dose of antiretroviral drug	**Recommended change in dose of rifampin**	**Comments**
Saquinavir/ritonavir	Saquinavir 400 mg + ritonavir 400 mg twice-daily	No change (600 mg/day)	Use with caution; the combination of saquinavir (1000 mg twice-daily), ritonavir (100 mg twice-daily), and rifampin caused unacceptable rates of hepatitis among healthy volunteers
Lopinavir/ritonavir (Kaletra™)	Increase the dose of lopinavir / ritonavir (Kaletra ™) – 4 tablets (200 mg of lopinavir with 50 mg of ritonavir) twice-daily	No change (600 mg/day)	Use with caution; this combination resulted in hepatitis in all adult healthy volunteers in an initial study.
"Super-boosted" lopinavir /ritonavir (Kaletra™)	Lopinavir / ritonavir (Kaletra ™) – 2 tablets (200 mg of lopinavir with 50 mg of ritonavir) + 300 mg of ritonavir twice-daily	No change (600 mg/day)	Use with caution; this combination resulted in hepatitis among adult healthy volunteers. However, there are favorable pharmacokinetic and clinical data among young children
CCR-5 receptor antagonists			
	Recommended change in dose of antiretroviral drug	**Recommended change in dose of rifampin**	**Comments**
Maraviroc	Increase maraviroc to 600 mg twice-daily	No change (600 mg/day)	Maraviroc Cmin ↓ by 78%. No reported clinical experience with increased dose of maraviroc with rifampin
Integrase inhibitors			
	Recommended change in dose of antiretroviral drug	**Recommended change in dose of rifampin**	**Comments**
Raltegravir	No change	No change (600 mg/day)	No clinical experience; raltegravir concentrations ↓ by 40-61%

Table 3. Recommendations for coadministering antiretroviral drugs with RIFABUTIN – 2007

Non-nucleoside reverse-transcriptase inhibitors			
	Antiretroviral dose change	**Rifabutin dose change**	**Comments**
Efavirenz	No change	↑ to 450-600 mg (daily or intermittent)	Rifabutin AUC ↓ by 38%. Effect of efavirenz + protease inhibitor(s) on rifabutin concentration has not been studied. Efavrirenz should not be used during the 1st trimester of pregnancy.
Nevirapine	No change	No change (300 mg daily or thrice-weekly)	Rifabutin and nevirapine AUC not significantly changed.
Delavirdine	Rifabutin and delavirdine should not be used together		Delavirdine AUC ↓ by 80%; rifabutin AUC↑ by 100%.
Etravirine	No change	No change (300 mg daily or thrice-weekly)	No clinical experience; etravirine Cmin ↓ by 45%, but this was not thought to warrant a change in dose
Single protease inhibitors			
	Antiretroviral dose change	**Rifabutin dose change**	**Comments**
fos-Amprenavir	No change	↓to 150 mg/day or 300 mg 3x/week	No published clinical experience
Atazanavir	No change	↓to 150 mg every other day or 3x/week	No published clinical experience. Rifabutin AUC ↑ by 250%
Indinavir	1000 mg every 8 hours	↓ to 150 mg/day or 300 mg 3x/week	Rifabutin AUC ↑ by 170%; indinavir concentrations ↓ by 34%
Nelfinavir	No change	↓ to 150 mg/day or 300 mg 3x/week	Rifabutin AUC ↑ by 207%; insignificant change in nelfinavir concentration

Table 3.(cont.) Recommendations for coadministering antiretroviral drugs with RIFABUTIN – 2007

	Antiretroviral dose change	Rifabutin dose change	Comments
Dual protease inhibitor combinations			
Lopinavir/ritonavir (Kaletra ™)	No change	↓ to 150 mg every other day or 3x/week	Rifabutin AUC ↑ by 303%; 25-O-des-acetyl rifabutin AUC ↑ by 47.5 fold.
Ritonavir (any dose) with saquinavir, indinavir, amprenavir, fos-amprenavir, atazanavir, tipranavir or darunavir	No change	↓ to 150 mg every other day or 3x/week	Rifabutin AUC ↑ and 25-O-des-acetyl rifabutin AUC ↑, by varying degrees.
CCR-5 receptor antagonists			
Maraviroc	No change	No change	No clinical experience; a significant interaction is unlikely, but this has not yet been studied
Integrase inhibitors			
Raltegravir	No change	No change	No clinical experience; a significant interaction is unlikely, but this has not yet been studied



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