Managing Drug Interactions in the Treatment of
HIV-Related Tuberculosis

CDC

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Introduction

Worldwide, tuberculosis is the most common serious opportunistic infection among people with HIV infection. The World Health Organization estimates that of the 8.7 million individuals who developed incident tuberculosis in 2011, 1.1 million, or 13%, were co-infected with HIV.[2] Further, of those who suffer tuberculosis-related mortality, 31% are HIV-infected. Despite the complexities of simultaneously treating two infections requiring multidrug therapy, antiretroviral therapy is life-saving among patients with tuberculosis and advanced HIV disease.[4-7]

Timing of initiation of antiretrovirals among patients with HIV requiring tuberculosis treatment.

There is now clear evidence that providing antiretroviral therapy to HIV-infected adults during tuberculosis treatment, rather than waiting until completion of tuberculosis therapy, reduces mortality, particularly among those with advanced HIV disease. In one randomized controlled clinical trial among HIV-infected adults in South Africa, initiating antiretroviral therapy during tuberculosis therapy rather than waiting until tuberculosis treatment was completed reduced the hazard of all-cause mortality by 56% and was beneficial regardless of CD4 count.[3] Subsequent clinical trials evaluating the optimal timing of initiation of antiretroviral therapy during tuberculosis treatment were conducted.[4-7] Results from these trials, all of which were conducted in high prevalence/low resource settings, indicated that earlier initiation of ART significantly reduced mortality in persons with (non-meningitis) HIV-TB and CD4 cell count below 50/mm³. Based on the results of these trials, the Department of Health and Human Services and Infectious Diseases Society of America now recommend that antiretroviral treatment be started two weeks after initiation of tuberculosis treatment for most patients with CD4 counts less than 50 cells/mm³.[8]

Challenges of co-treatment of HIV and tuberculosis.

Concurrent treatment of tuberculosis and HIV is complicated by
- the adherence challenges of polypharmacy,
- overlapping side effect profiles of antituberculosis and antiretroviral drugs,
- immune reconstitution inflammatory syndrome, and
- drug-drug interactions.[9]

The focus of this document is the drug-drug interaction between rifamycin antibiotics (rifampin, rifabutin, and rifapentine) and four classes of antiretroviral drugs: protease inhibitors, non-nucleoside reverse-transcriptase inhibitors (NNRTI), CCR5-receptor antagonists, and integrase inhibitors.[10, 11] Only two of the currently available antiretroviral drug classes, the nucleoside/nucleotide analogues (NRTI) [with the exception of zidovudine [12, 13]] and the entry inhibitor enfuvirtide (given parenterally)[14] are free of clinically-significant interactions with the rifamycins. Although serum concentrations of the NRTI zidovudine are diminished by co-administration of rifamycins, no dose adjustment is recommended as the relationship between zidovudine plasma concentrations and efficacy is unclear.

Objectives of these guidelines.

The purpose of these guidelines is to provide the clinician with updated recommendations for managing the drug-drug interactions that occur when using antiretroviral therapy during tuberculosis treatment. (Table 1) Changes from previous versions of these guidelines include:

- a summary of data from clinical trials regarding timing of initiation of antiretroviral therapy among patients with tuberculosis;

- drug interaction data for new antiretroviral drugs; and

- changes in dosing guidelines

  » for rifabutin when co-administered with protease inhibitors,

  » for nevirapine when co-administered with rifampin, and

  » for raltegravir when co-administered with rifampin.

- more detailed recommendations regarding co-treatment of tuberculosis and HIV among children and pregnant women

We include pharmacokinetic data as well as data about immunologic response and virologic suppression (where available) for antiretroviral drugs that are licensed and available for use in the United States when administered in combination with antituberculosis drugs.

Methodology for Preparation of these Guidelines

These guidelines were developed by the HIV-TB Drug Interaction Guideline Development Group (hereafter, Guideline Development Group). The Guideline Development Group consisted of experts in tuberculosis and HIV treatment and pharmacokinetics from CDC and other institutions (see listing of the Guideline Development Group at the end of this document on page 15). Members of the Guideline Development Group were selected by the chair and co-chairs. They sought to include as members some persons who had participated in preparation and review of the prior version of these guidelines. Particular effort was made to include staff from the U.S. National Institutes of Health (NIH), in order to coordinate these recommendations with those of the Federally-approved HIV/AIDS medical practice guidelines available online at http://www.aidsinfo.nih.gov/. No members of the Guideline Development Group were deemed to have substantial competing interests related to the recommendations in these guidelines. Guideline Development Group member competing interests are listed on page 16.

A literature search was conducted to extract articles that met the following inclusion criteria: clinical studies involving healthy volunteers or patients with HIV or HIV/TB co-infection with relevant PK, safety, or HIV (viral load suppression, change in CD4 count) endpoints. Our search strategy was as follows: (1) between March 2011 and May 2012 we searched in Pubmed and Embase for English and French articles published from 1990 to 2012. We used as MeSH terms "tuberculosis," "HIV," and the names of the drugs being evaluated. (2) After articles were extracted and selected, we hand-searched references at the end of included

articles, and we searched trials listed at www.clinicaltrials.gov. (3) We reviewed abstracts from meetings (International AIDS Conference; International AIDS Society conference; Conference on Retroviruses and Opportunistic Infections; World Lung Health Conference; Workshop on Clinical Pharmacology of TB Drugs) at which data from HIV and/or TB clinical trials are commonly presented; these were included if they met the inclusion criteria cited above; most of these abstract reports had not yet completed the process of peer review and publication . (4) We reviewed package inserts for included drugs specifically looking for drug interaction data. Articles and abstracts were screened and selected using the inclusion criteria. One hundred seventeen articles and abstract met the inclusion criteria and were included in the body of evidence. These are included in the list of referenced articles and abstracts at the end of this document. The body of evidence was not graded for quality.

The chair of the Guideline Development Group reviewed the previous version of these guidelines (at http://www.cdc.gov/tb/publications/guidelines/TB_HIV_Drugs/default.htm), and then reviewed the references accumulated through the search strategy and inclusion criteria described above. The chair then drafted an updated revision of the guideline, which was reviewed and discussed with the two Guideline Development Group co-chairs. Agreed revisions were made, and the revised document was then submitted to the rest of the members of the Guidelines Development Group Each member of the Guideline Development Group reviewed the revised guideline draft and provided written comments and suggested revisions. Final recommendations were developed by the Guideline Development Group; the strength of each recommendation was not graded. In one instance where the Guideline Development Group's view conflicted with that of the product manufacturer, the chair and co-chairs of the Guideline Development Group held two teleconferences with representatives of the manufacturer, staff of NIH, and staff of the U.S. Food & Drug Administration (FDA), to share and discuss unpublished data underlying the different views [see Rifampin and Efavirenz, below].

Following this discussion, and with the concurrence of NIH and FDA members, the Guideline Development Group chose to include the following clarification, which is quoted directly from the introduction to the U.S. adult AIDS treatment guidelines, where it was intended to address similar issues: "... the science [underlying this guideline] evolves rapidly, [and] the availability of new agents and new clinical data may change therapeutic options and preferences. *Information included in these guidelines may not be consistent with approved labeling for the particular products or indications in question, and the terms "safe" and "effective" may not be synonymous with the Food and Drug Administration (FDA)-defined legal standards for product approval.* The guidelines are updated [periodically].... However, the guidelines cannot always keep pace with the rapid evolution of new data in this field, and they cannot provide guidance for all patients. Clinicians should exercise clinical judgment in management decisions tailored to unique patient circumstances."[1]

Recommendations

The Role of Rifamycins in Tuberculosis Treatment

Rifamycins are an essential part of successful tuberculosis treatment.

Rifamycins play a key role in the success of tuberculosis treatment. Therefore, despite the complexity of drug interactions between rifamycins and antiretrovirals, treatment of HIV-related tuberculosis requires their co-administration. This should not be avoided by using tuberculosis treatment regimens that do not include a rifamycin or by withholding antiretroviral therapy until completion of anti-tuberculosis therapy. 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.[15, 16] Although efforts are underway to identify new sterilizing drugs that can prevent relapse as effectively as rifampin, there are currently no good substitutes for rifamycins. 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 (Tables 1a and 1b).

Frequency of rifamycin dosing

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-, twice-, or thrice-weekly, especially during the intensive phase (first 2 months) of therapy, when bacillary load is still quite high. [17-19] *Tuberculosis drugs, especially rifamycins, should be administered 5 to 7 days per week for at least the first 2 months of treatment to patients with advanced HIV disease.*[19a]

Predicting drug interactions involving rifamycins

Rifamycins are notorious for causing drug interactions because they induce (or upregulate) multiple drug metabolizing enzymes and drug transporters. Rifampin, for example, is a potent inducer of cytochrome P450 enzyme 3A, the enzyme subfamily responsible for metabolizing a large proportion of drugs currently on the market, as well as other cytochrome P450 enzymes. The rifamycins vary in their potential to induce cytochrome P450 enzymes, with rifampin and rifapentine being much more potent inducers than rifabutin. Rifampin also induces Phase II metabolizing enzymes, which are responsible for biotransformations such as glucuronidation and sulfation, as well as the efflux pump p-glycoprotein and other drug transporters.

Induction of these enzymes can lead to reduced plasma concentrations of co-administered drugs that are substrates of these enzymes. For example, since most of the protease inhibitor and NNRTI classes of antiretrovirals as well as the CCR5 antagonist maraviroc are metabolized by CYP3A4, induction of CYP3A4 by rifampin can lead to reduced serum concentrations of these antiretroviral drugs with the attendant risks of HIV treatment failure and emergence of antiretroviral drug resistance. Similarly, rifampin upregulates the synthesis of UDP-glucuronosyltransferase 1A1, which is the enzyme that metabolizes integrase inhibitors, including raltegravir.[20] Knowledge of the metabolic pathway(s) of a drug can help the clinician predict the likelihood of a drug interaction with co-administered rifamycins. The magnitude and the clinical relevance of the interaction, however, usually must be determined experimentally in clinical studies.

Managing Drug Interactions with Antiretrovirals and RIFAMPIN

Rifampin and NNRTIs

In areas with high rates of both tuberculosis and HIV, initial antiretroviral drug regimens usually include efavirenz or nevirapine in combination with NRTIs (often in fixed-dose combinations). Thus, drug-drug interactions involving rifampin and the NNRTIs are of high importance in these settings. Furthermore, efavirenz-based therapy is a preferred option for initial antiretroviral therapy in developed countries because of its potency, availability in a once-daily co-formulation with tenofovir and emtricitabine, and durability of efficacy in randomized clinical trials.[1]

Rifampin and efavirenz

Initial studies evaluating the effects of rifampin on efavirenz pharmacokinetics demonstrated a modest decrease in efavirenz concentrations,[21-23] but subsequent prospective studies have failed to show statistically significant reductions in concentrations of efavirenz during rifampin therapy.[24] (Table 2) Further, there is significant inter-patient variability in the effect that rifampin has on efavirenz concentrations. In patients with certain genetic polymorphisms that result in slow metabolism of efavirenz (e.g., *CYP 2B6* 516 G>T), high concentrations of efavirenz are common, even among patients also taking rifampin.[25-27]

When given at the standard dose of 600 mg daily, the trough concentration of efavirenz (which is the best predictor of its virological activity) remains well above the concentration necessary to suppress HIV *in vitro* among the vast majority of patients on concomitant rifampin.[28, 29] More importantly, multiple cohort studies and a randomized controlled trial have shown that the standard adult efavirenz dose (600 mg daily) together with 2 NRTIs is well-tolerated and highly efficacious in achieving complete viral suppression among adults on concomitant rifampin-based tuberculosis treatment.[30, 31] Furthermore, in certain populations, a higher dose of efavirenz (800 mg daily) has been associated with high serum concentrations and neurotoxicity.[32] There is limited evidence that sub-therapeutic efavirenz concentrations may be more likely among patients who weigh more than 60 kilograms and who are taking standard-dose efavirenz together with rifampin;[33, 34] however, findings of sub-therapeutic concentrations in such persons have not been consistent.[25, 30] Recently, the FDA approved a revised label for Sustiva® (efavirenz). The revision recommends that, if efavirenz is co-administered with rifampin, then the dose of efavirenz should be increased to 800 mg in patients who weigh over 50 kg. This recommendation is based on pharmacokinetic modeling using data from several trials. No prospective trial has shown a reduction in anti-viral treatment failure with this strategy, or an increase in failure without it, Moreover, few published studies have evaluated this increased efavirenz dose or compared the 600 mg and 800 mg dose among patients who weigh over 50 kg.[21, 35]

Therefore, because of its potency, simplicity, and proven clinical efficacy, use of efavirenz 600mg with 2 NRTIs, along with rifampin-based tuberculosis treatment is the preferred strategy for co-treatment of HIV and tuberculosis (Table 1a). Some clinicians may increase the dose of efavirenz to 800mg in persons weighing >50kg. We consider that data are insufficient to support a definitive statement in this regard.

What if efavirenz cannot be used?

Alternatives to efavirenz-based antiretroviral treatment are needed for some patients with HIV-related tuberculosis who are taking rifampin. Efavirenz is often avoided during the first trimester of pregnancy, some patients are intolerant of efavirenz, and some are infected with NNRTI-resistant strains of HIV. Additionally, efavirenz cannot be used in HIV-infected children under the age of 3 years because appropriate dosing has not been determined for that age group (see section: Children). Alternatives discussed below include other NNRTIs, protease inhibitors, triple and quadruple NRTI regimens, integrase inhibitors, and CCR5 antagonists.

Rifampin and nevirapine

Nevirapine is typically given to adults at a dose of 200 mg once a day for the first two weeks of treatment (initiation) followed by 200 mg twice daily or 400 mg once daily (extended release formulation) (maintenance therapy). This dosing strategy (of initiation followed by maintenance therapy) is used for two reasons: (1) nevirapine induces its own metabolism, and, in most cases, its concentrations decline with continued dosing; and (2) high initial nevirapine concentrations have been associated with toxicities, such as skin rash. In the U.S., initiation of nevirapine-based antiretroviral treatment is not recommended for adult or adolescent patients with higher CD4 cell counts (> 400 cells/mm^3 for men, > 250 cells/mm^3 for women) because of increased risk of severe hypersensitivity reactions, including hepatotoxicity.[1] The World Health Organization, though, recommends nevirapine as an option for women with CD4 cell counts up to 350 cells/mm^3.[36] Taking nevirapine-based antiretroviral therapy together with tuberculosis treatment is complicated both by pharmacokinetic interactions related to rifampin and by overlapping toxicities of nevirapine and the first-line antituberculosis drugs, notably skin rash and hepatotoxicity.

Several studies have found that rifampin reduces serum concentrations of nevirapine by 20-55%.[37-40] (Table 1). Decreases in serum concentrations caused by rifampin raise concerns about the efficacy of nevirapine-based antiretroviral therapy during rifampin-based tuberculosis treatment. Fortunately, results from recent prospective studies provide information for dosing strategies that may be helpful in this situation. One study conducted in South Africa found that patients who initiated nevirapine-based antiretroviral therapy during tuberculosis treatment (200 mg once daily for two weeks, then 200 twice daily) had a nearly two-fold higher risk of having a detectable HIV viral load after six months compared to those taking nevirapine who did not have tuberculosis.[30] Those patients who were already on nevirapine at maintenance doses (200 mg twice daily) when they started tuberculosis treatment did not have a higher risk of HIV virologic failure. This suggests that if nevirapine is initiated when the patient has already been receiving rifampin-containing tuberculosis treatment, the lead-in period puts patients at risk of virologic failure because of suboptimal nevirapine concentrations during the first two weeks of therapy. A pharmacokinetic study in Uganda confirmed that concentrations of nevirapine were often subtherapeutic when patients were receiving either 200 mg once daily or 200 mg twice daily, together with rifampin-based tuberculosis treatment.[41] Among Thai patients with advanced HIV, virologic and immunologic responses to nevirapine-based antiretroviral therapy when given at a dose of 200 mg twice daily were similar for those receiving rifampin-containing tuberculosis treatment and those who were not.[42] However, in a head-to-head comparison of antiretroviral therapy containing nevirapine 200 twice daily versus efavirenz 600 mg once daily, 65% of patients taking nevirapine and 70% of patients taking efavirenz had HIV viral loads less than 50 copies/mL after 48 weeks of treatment, and rates of hepatotoxicity were similar in the two groups.[43] Similarly, among patients in India randomized to receive either nevirapine (200 mg once daily for 14 days followed by 200 mg twice-daily) or efavirenz 600 mg daily together with rifampin-containing tuberculosis treatment, those receiving nevirapine were more likely to suffer virologic failure, severe toxicity, or death, and the trial was stopped early.[44] Together, these data demonstrate that *efavirenz is more effective and less toxic than nevirapine for HIV-TB patients receiving antiretroviral therapy and rifampin-containing tuberculosis treatment.* However,

giving nevirapine twice daily with rifampin (with no once-daily lead-in phase) may be an alternative when efavirenz cannot be used. Increasing the maintenance dose to 300 mg twice daily may cause higher rates of hepatotoxicity.[45] Drug interaction studies with rifampin and the new 400 mg once-daily extended release formulation of nevirapine have not been performed, so this combination cannot be recommended.

In light of these recent findings, for patients already receiving rifampin-containing tuberculosis therapy, *we recommend that if nevirapine must be used,[1] it should be initiated without the once-daily lead-in dosing. That is, ART should be initiated with twice-daily nevirapine dosing (adult dose, 200 mg twice daily) and twice-daily dosing should continue throughout co-treatment. Close monitoring of adherence and plasma HIV RNA is warranted. Therapeutic drug monitoring, if available, should be considered.*

Rifampin and other NNRTIs

Rilpivirine, a second-generation NNRTI, was approved by the United States Food and Drug Administration in May of 2011 and is available as a fixed-dose combination with tenofovir and emtricitabine. *Rifampin reduces rilpivirine AUC by 80% and trough concentrations by 89%, so the two drugs should not be co-administered.*[46] Rifampin is also predicted to substantially reduce the concentration of etravirine, another second-generation NNRTI, though this interaction has never been tested.[47]

Rifampin and protease inhibitors

Protease inhibitor-based antiretroviral regimens remain an important option for the treatment of HIV infection. Unfortunately, when co-administered with rifampin, concentrations of many standard-dose protease inhibitors are severely diminished (>90%) compromising HIV treatment efficacy.[48-52] The Guideline Development Group did not find studies evaluating drug interaction involving rifampin and darunavir. Several pharmacokinetic studies have been conducted to evaluate either higher doses of the protease inhibitor or higher doses of the pharmacologic boosting agent, ritonavir, or both.[49, 51, 53, 54] Two strategies for dosing boosted protease inhibitors together with rifampin have been evaluated: super-boosting (giving standard-dose protease inhibitor plus a higher-than-usual dose of ritonavir) versus double dosing (doubling the dose of both the protease inhibitor and ritonavir). While these strategies may result in adequate protease inhibitor concentrations,[51, 55] several studies involving healthy volunteers have reported unacceptable rates of hepatotoxicity. [51, 56-58]

 It is unclear if HIV-infected patients with tuberculosis will have the same high rates of hepatotoxicity as healthy HIV-uninfected volunteers when treated with super-boosted protease inhibitors (standard-dose protease inhibitors given together with high doses of ritonavir) or double-dose protease inhibitor/ritonavir combinations. Clinical experience with these strategies has recently been growing as clinicians and treatment programs try to find ways to treat patients who have NNRTI-resistant HIV and require tuberculosis treatment.[59] In a small study in South Africa among adults with HIV (but not tuberculosis) who were already taking standard-dose lopinavir/ritonavir 400mg/100mg twice-daily with suppressed viral loads, rifampin 600 mg daily was started, and lopinavir/ritonavir dosing was gradually increased over two weeks to a maximum dose of 800mg/200mg twice-daily (double dose).[55] Therapeutic lopinavir concentrations were achieved, and the regimen was relatively well-tolerated, though two of twenty-one patients had grade 3 or 4 hepatotoxicity. These initial positive clinical and experimental experiences with double-dose lopinavir/ritonavir suggest that these regimens may be tolerable and effective among at least some patients with HIV-related tuberculosis, but prospective data to guide patient and dose selection are still limited. *Higher-dose lopinavir/ritonavir should only be used with close clinical and laboratory monitoring for possible hepatotoxicity in cases where there is a pressing need to start antiretroviral therapy and no other antiretroviral drug options are available.*

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1   Due to intolerance of or resistance to efavirenz, pregnancy, or young age (see above)

Rifampin and triple or quadruple nucleos(t)ide regimens

Regimens composed entirely of NRTIs are less effective than combinations of two classes of antiretroviral drugs (e.g., NNRTI + NRTI).[60-63] For example, virologic suppression achieved with zidovudine and lamivudine combined with efavirenz is superior to that observed with zidovudine, lamivudine, and abacavir, regardless of pre-treatment viral load.[60] Similarly, among adults receiving zidovudine and lamivudine plus either abacavir or nevirapine, the nevirapine-based regimen results in better immunologic and virologic responses than the triple-NRTI regimen, particularly among those with baseline HIV viral levels > 100,000 copies/mL.[61, 62] A regimen of zidovudine, lamivudine, and the nucleotide agent, tenofovir, has been reported to be effective among some patients on rifampin-based tuberculosis treatment.[63] However, this regimen has not been compared to standard initial antiretroviral therapy (e.g., efavirenz + 2 NRTIs) among patients taking rifampin. Finally, a quadruple drug regimen of zidovudine, lamivudine, abacavir, and tenofovir was reported to be as active as an efavirenz-based regimen in initial small trials,[64, 65] but a subsequent larger study suggested that a quadruple nucleos(t)ide regimen of tenofovir, emtricitabine, zidovudine, and abacavir was less active than tenofovir-emtricitabine plus either efavirenz or ritonavir-boosted atazanavir.[66] *While these regimens of nucleosides and nucleotides alone cannot be recommended as preferred therapy among patients receiving rifampin because they have not been rigorously evaluated, the lack of predicted clinically-significant interactions between these agents and rifampin make them an acceptable alternative during tuberculosis therapy for patients with lower plasma HIV RNA levels (<100,000 copies/mL) who are unable to take NNRTIs.*[64, 67] However, among patients who have HIV that is known to be resistant to NNRTIs or who have failed a first-line regimen (but for whom resistance testing is not available), this strategy may be inadvisable because these patients are at high risk of having HIV with NRTI resistance mutations.

Rifampin with integrase inhibitors:

Raltegravir, the first-in-class integrase inhibitor, is increasingly being used in both treatment-naïve and treatment-experienced adults with HIV. In pharmacokinetic studies among HIV-uninfected healthy volunteers, rifampin decreased the trough concentrations of raltegravir 400 mg twice daily by ~ 60%.[68] Doubling the dose of raltegravir to 800 mg twice daily improved overall raltegravir exposures, but trough concentrations were still reduced by 53% when compared to raltegravir 400 mg twice daily without rifampin.[68] However, in dose-ranging studies among patients with HIV infection, the antiviral activity of raltegravir 200 mg twice daily was very similar to the activity of the licensed 400 mg twice-daily dose, suggesting that the drug can still be effective even at reduced concentrations.[69] However, in a recent trial of once-daily dosing (800 mg) versus twice-daily dosing (400 mg) among treatment-naïve adults with HIV, low raltegravir trough concentrations in the daily dosing arm (but not the twice-daily arm) were associated with virologic failure.[70] Thus, given the reductions in trough concentrations when raltegravir is given with rifampin, *it is recommended to double the dose of raltegravir to 800 mg twice daily in adults taking rifampin for tuberculosis.* Though there have not yet been published prospective studies evaluating this regimen, raltegravir 800 mg twice-daily given with rifampin has been shown to be effective in some clinical reports.[71, 72] Raltegravir doses of 800 mg twice-daily and 400 mg twice daily have been tested in a clinical trial among patients with HIV receiving rifampin-containing TB treatment.[73] Pending the availability of full trial results, *this combination (of raltegravir 800mg twice daily and rifampin-containing TB therapy) should be used with caution, particularly among patients with high HIV viral loads who are just beginning antiretroviral therapy.* There is little clinical experience with use of concomitant raltegravir and rifampin, and safety and tolerability have yet to be explored in larger trials. While awaiting efficacy data from the study evaluating double-dose raltegravir among patients with HIV and TB taking rifampin, clinicians may prefer to use rifabutin (where rifabutin is available). Elvitegravir co-formulated with cobicistat, tenofovir, and emtricitabine (Stribild™, or the "Quad" pill) was recently approved by the Food & Drug Administration. Stribild should not be given together with rifampin, as rifampin is expected to reduce concentrations of both elvitegravir and cobicistat.

Rifampin and CCR5-receptor antagonists:

Rifampin has substantial interactions with the CCR5-receptor antagonist, maraviroc. An increased dose of maraviroc has been recommended to allow concomitant use of rifampin and maraviroc,[36] but there is no reported clinical experience with this combination. Additional clinical studies will be needed to further evaluate whether or not these new agents can be used among patients receiving rifampin-containing tuberculosis treatment.

Managing Drug Interactions with Antiretrovirals and RIFABUTIN

Until recently, rifampin was the only rifamycin available in many settings. Rifabutin, though, is now off-patent and available in many countries; access to this drug is rapidly expanding.[74] Rifabutin taken at a dose of 300 mg once-daily might be as effective for tuberculosis treatment as rifampin.[75-79] Compared to rifampin, though, rifabutin has significantly less effect on drugs metabolized by cytochrome p450 3a enzymes;[80] this may reduce the magnitude of drug-drug interactions (Table 3). However, several issues have negatively influenced its clinical utility. First, cost and/or access have historically precluded its use in most countries with high rates of HIV-related tuberculosis;[74] this situation is now changing. Second, drugs that induce or inhibit CYP3A metabolizing enzymes can influence rifabutin concentrations leading to the need for rifabutin dose adjustment, which adds to the complexity of co-treatment. Finally, if a patient whose rifabutin dose was decreased to avoid drug interactions related to co-treatment with antiretroviral therapy subsequently stops taking the interacting antiretroviral drug (e.g., ritonavir), the resulting rifabutin concentrations can become sub-therapeutic, putting the patient at risk of tuberculosis treatment failure or emergence of rifamycin resistance.

Rifabutin and protease inhibitors

Rifabutin has little, if any, effect on the serum concentrations of ritonavir-boosted protease-inhibitors. However, rifabutin concentrations are increased when rifabutin is taken together with protease inhibitors. To mitigate the risk for rifabutin-related toxicity (such as uveitis or neutropenia), the previous edition of this guideline recommended giving rifabutin at a dose of 150 mg thrice-weekly to adults taking boosted protease inhibitors. While cohort studies have yielded favorable virological and immunological outcomes of protease-inhibitor-based antiretroviral therapy in the setting of rifabutin-based tuberculosis treatment [17, 81] clinical evaluation of the anti-tuberculosis efficacy of that combination remains limited. Some studies suggest that rifabutin concentrations among patients are too low with rifabutin 150 mg given thrice-weekly.[82, 83]

In a trial among adults co-infected with HIV and tuberculosis taking ritonavir-boosted lopinavir, a dose of rifabutin 150 mg once daily was relatively well-tolerated and was more likely to achieve target rifabutin concentrations than thrice-weekly dosing of 150 mg.[84] *Given the risk of acquired rifamycin resistance with low rifabutin concentrations,[85] we recommend rifabutin at a dose of 150 mg daily when given with a boosted protease inhibitor in adults.* [82, 84, 86] However, clinicians should recognize that there are limited safety data with this dose and combination, and it is unclear whether or not the increase in concentrations of rifabutin and its metabolite resulting from this dose will lead to higher risk of uveitis, neutropenia, or hepatotoxicity. *Patients taking this combination should be monitored for rifabutin-related toxicities.* [87] [88]

In addition, therapeutic drug monitoring, if available, is one method for verifying that the desired rifabutin concentrations have been achieved. Since rifabutin 150 mg once daily would be sub-therapeutic if the patient stopped taking the protease inhibitor, 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 a once-daily protease-inhibitor at the same time as the directly observed dose of tuberculosis treatment.

Rifabutin and other antiretrovirals

Because efavirenz reduces the concentration of co-administered rifabutin, rifampin is the rifamycin of choice for patients taking efavirenz-based antiretroviral therapy. In a study that evaluated rifabutin concentrations among patients receiving rifabutin twice-weekly, increasing the rifabutin from 300 mg to 600 mg in patients taking efavirenz-based antiretroviral therapy resulted in concentrations that were similar to those achieved among patients taking rifabutin 300 mg without efavirenz.[89] However, other rifabutin dosing frequencies, such as thrice-weekly or daily, have not been evaluated.

Given that nevirapine concentrations may be diminished among patients taking rifampin-containing tuberculosis treatment, *rifabutin may be an option for patients taking nevirapine-based antiretroviral treatment*. In a pharmacokinetic study among patients receiving nevirapine at standard doses and rifabutin at 300 mg daily, neither drug significantly impacted the concentrations of the other.[90] Therefore, dose adjustment is unlikely to be necessary, although clinical evaluations of the safety and efficacy of this combination in larger numbers of patients are needed.

Trough concentrations of etravirine are reduced by 35% by rifabutin, and etravirine reduces rifabutin concentrations by 17%. These changes are unlikely to be clinically significant, so no dose adjustment is recommended.[47] There is, however, limited clinical experience with this combination. Although overall raltegravir concentrations are not significantly affected by rifabutin, trough raltegravir concentrations are diminished modestly (by about 20%) when the two drugs are co-administered.[91] *Until additional data become available, we recommend using standard-dose raltegravir (400 mg twice daily) with rifabutin.* Trough concentrations of elvitegravir are reduced by 67% when cobicistat-boosted elvitegravir is given together with rifabutin, so co-dosing of these drugs is not recommended.[92]

Treatment of Latent TB Infection with Rifampin or Rifapentine

Treatment of latent TB infection (LTBI) is increasingly advocated in persons with HIV co-infection. Recommended options include daily self-administered isoniazid 300 mg for 9 months (9H) or daily self-administered rifampin 600 mg for 4 months (4R).[93] *Isoniazid is the clear preference for treating LTBI in a patient on drugs that have unfavorable interactions with rifamycins.* No adjustment of ART dosing is required with the 9H regimen. Use of 4R would require the same dose adjustments as noted above for rifampin-based therapy of active TB disease. There are no published data on the use of rifabutin for LTBI. The Guideline Development Group suggests that rifabutin should be used for LTBI only if there is a compelling need for short-course treatment of LTBI, and/or if neither 9H nor 4R can be used. Recently a new regimen of 12 once-weekly doses of isoniazid 900 mg plus rifapentine 900 mg administered as directly observed therapy (DOT) has been recommended for use in persons who are HIV-uninfected or in persons with HIV who are otherwise healthy and not receiving ART.[94] There are no data yet regarding the magnitude of induction of metabolizing enzymes that would be expected with once-weekly rifapentine at the recommended dose for LTBI; a manufacturer-sponsored study evaluating the effects of both once-weekly and daily rifapentine on efavirenz is underway.

Treating Pregnant Women with Tuberculosis and HIV Co-infection

Limitations in antiretroviral agents that can be used during pregnancy

A number of issues complicate the treatment of the HIV-infected pregnant woman on antiretrovirals who has active tuberculosis. Most importantly, the choice of antiretroviral drugs among pregnant women is limited. Efavirenz is not generally recommended during the first trimester of pregnancy because of concerns

about potential teratogenicity, although recent data do not suggest an elevation in this risk.[95-97] Furthermore, pregnant women have an increased risk of severe toxicity from didanosine and stavudine and, therefore, this dual NRTI combination is not recommended.[98] Women with CD4 cell counts > 250 cells/mm^3 at the time that antiretroviral therapy is initiated have an increased risk of nevirapine-related hepatotoxicity. Consequently, initiation of NVP among women with CD4 cell counts > 250 cells/mm^3 is not recommended in the United States, while World Health Organization guidelines allow for its use in women with CD4 counts up to 350 cells/mm^3.[1,36, 99]

Because of concerns about potential fetal bone effects based on non-human primate data, tenofovir is considered an alternative rather than a preferred antiretroviral drug during pregnancy (unless chronic hepatitis B virus infection is also present).[100] The pharmacokinetics and safety of etravirine and maraviroc among pregnant women have yet to be established. In a small study of HIV-infected pregnant women, raltegravir appeared to be safe, and drug concentrations during the third trimester among trial participants were similar to their postpartum concentrations.[101]

The Department of Health and Human Services Panel on Treatment of HIV-Infected Pregnant Women and Prevention of Perinatal Transmission provides detailed recommendations regarding use of antiretroviral drugs in HIV-infected pregnant women (available at http://AIDSInfo.nih.gov).[100] Antiretroviral drugs that are preferred in pregnancy include zidovudine, lamivudine, nevirapine, and ritonavir-boosted lopinavir. Alternative NRTIs include abacavir, didanosine, emtricitabine, stavudine, and tenofovir; alternative protease inhibitors include ritonavir-boosted atazanavir or saquinavir. Use of efavirenz after the first trimester can be considered in special circumstances, such as if an HIV-infected pregnant woman requires tuberculosis therapy with rifampin and nevirapine is not tolerated. If efavirenz is continued postpartum, adequate contraception must be assured.

The effect of pregnancy on the pharmacokinetics of antiretroviral drugs

Pregnancy alters the pharmacokinetics of a number of drugs, including antiretrovirals.[102] For nevirapine, the data are mixed, with some studies showing decreased concentrations in pregnant women and others showing similar pharmacokinetics in pregnant and nonpregnant women.[103-106]

Small sample sizes and highly variable intra-patient plasma concentrations complicate interpretation of these comparative pharmacokinetic studies.[107] Pharmacokinetic and efficacy data for efavirenz in pregnancy are limited, but a study of 25 women receiving efavirenz during the third trimester and postpartum found standard dosing to be adequate.[108] The concentrations of ritonavir-boosted lopinavir are decreased during the latter stages of pregnancy, and some recommend increasing the dose to 600 mg lopinavir/150 mg ritonavir twice daily during the third trimester of pregnancy, while others think standard-dose lopinavir/ritonavir with appropriate monitoring is sufficient.[109-113] Once-daily lopinavir-ritonavir is not recommended in pregnancy because there are no data to address adequacy of drug levels.

Treatment of HIV-related tuberculosis among pregnant women

There are no published data on the combined effects of pregnancy and rifampin on antiretroviral drug concentrations and HIV treatment efficacy. With limited 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. There is clearly an urgent need for research in this arena.

For women with a CD4 count less than 250 cells/mm^3 receiving rifampin-based tuberculosis treatment, nevirapine-based HIV treatment could be used, but the optimal dose is not known.[114] Pregnant women

already receiving nevirapine-based regimens can continue nevirapine regardless of CD4+ cell count, as toxicity appears limited to those first initiating nevirapine-based therapy. Efavirenz-based therapy may be an option after the first trimester of pregnancy. The quadruple nucleoside/nucleotide regimen (zidovudine, lamivudine, abacavir, and tenofovir) is an alternative, especially for women with high CD4+ lymphocyte counts who are receiving antiretroviral drugs for prevention of perinatal transmission rather than for maternal health indications, though additional experience during pregnancy is needed. Rifabutin is classified as pregnancy class B by the United States Food and Drug Administration,[115] and lopinavir/ritonavir with rifabutin is also a reasonable option. Pregnant women receiving both antiretroviral and anti-tuberculosis drugs should have HIV RNA levels monitored more frequently, and if virologic response is less than expected, therapeutic drug monitoring or a change in regimen should be considered.

Treating Children with HIV-associated Tuberculosis

Special challenges related to treating children with HIV and tuberculosis

HIV-infected children in high-burden countries have very high rates of tuberculosis, often with severe, life-threatening manifestations (e.g., extensive pulmonary disease, 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 HIV. In addition to the complexities raised by the drug interactions discussed above, treatment of pediatric HIV-related tuberculosis has additional challenges. There are limited data on the absorption, metabolism, and elimination of anti-tuberculosis drugs in children, particularly in very young children (< 2 years of age). The World Health Organization has recently compiled pharmacokinetic and efficacy data for children and updated their treatment guidelines for pediatric tuberculosis.[116] The new guidelines suggest that higher doses of first-line tuberculosis drugs, including most notably isoniazid and rifampin, be used. Pediatric formulation and dosing guidelines for rifabutin are not available for children.

Some antiretroviral drugs are not available in liquid formulations (though increasingly, chewable and dissolvable tablets are becoming available for pediatric use), and there are limited pharmacokinetic data for many antiretroviral drugs among young children. NNRTI-based therapy is not recommended as preferred therapy for perinatally-infected infants under age 1 year, whether or not they were exposed to single-dose nevirapine as part of maternal-child HIV transmission prophylaxis, because of higher failure rates compared to those initiating ritonavir-boosted lopinavir-based therapy.[117-120] This inability to use NNRTI-based antiretroviral therapy limits options for antiretroviral therapy among children less than 1 year of age receiving rifampin-based tuberculosis treatment.(Tables 1b and 2b) More specifically, limited pharmacokinetic data in children younger than age 3 or who weigh less than 13 kg have shown that it is difficult to achieve target efavirenz trough concentrations in this age group, even with very high (>30 mg/kg) doses of an investigational liquid formulation. Thus, efavirenz is not recommended for use in children younger than age 3 years at this time.

Rifampin and protease inhibitors for children with HIV and tuberculosis

There are emerging pharmacokinetic data and clinical experiences with protease-inhibitor-based antiretroviral therapy among children with HIV-related tuberculosis. Ritonavir alone should not be used as the protease inhibitor component of antiretroviral therapy in children receiving tuberculosis therapy. [121] Ritonavir-boosted lopinavir, though, may be a reasonable option. Optimal dosing for ritonavir-boosted lopinavir in children with HIV-related tuberculosis is being explored. In one study, children treated with super-boosted lopinavir (ritonavir in addition to doses of co-formulated lopinavir/ritonavir to achieve mg to mg parity of ritonavir and lopinavir) while on rifampin-based tuberculosis treatment achieved serum concentrations of lopinavir

comparable to those of children treated with standard dose lopinavir/ritonavir in the absence of rifampin.[122] In a separate study of 15 South African children, while oral clearance was higher among children on tuberculosis treatment receiving super-boosted lopinavir than among children receiving standard pediatric ritonavir-boosted lopinavir doses who were not taking tuberculosis treatment, trough concentrations were therapeutic in all children. [123] Retrospective studies suggest that virologic response among children receiving super-boosted lopinavir and rifampin appears to be similar to that of children receiving standard-dose lopinavir/ritonavir without tuberculosis treatment. However, response to double-dose lopinavir plus rifampin appears to be inferior.[124] [125] *The preferred antiretroviral regimen among children on rifampin-based tuberculosis treatment is super-boosted lopinavir plus appropriate NRTI drugs.* Additional prospective studies are needed to evaluate whether or not the higher doses of rifampin now recommended for children will affect the activity of super-boosted lopinavir. Additional research will also be needed to determine whether or not double-dose lopinavir/ritonavir will be as efficacious among children receiving rifampin-containing tuberculosis treatment as super-boosted lopinavir.

Rifampin and NNRTIs for children with HIV and tuberculosis

Efavirenz and rifampin for children

In a small pharmacokinetic study conducted among South African children with a median age of 6 years, efavirenz concentrations were commonly subtherapeutic with standard weight-based dosing of efavirenz, whether or not they were taking rifampin.[126] However, among children age >3 years participating in a retrospective cohort study in South Africa, those receiving efavirenz-based antiretroviral therapy had high rates of viral suppression whether or not they were taking concomitant rifampin-containing tuberculosis therapy.[125]

Although more data are needed, use of standard dose efavirenz-based antiretroviral therapy may be considered in children over age 3 years receiving concurrent rifampin-containing tuberculosis therapy when the recommended antiretroviral regimen with super-boosted lopinavir-ritonavir is not tolerated or contraindicated.[127] Careful virologic monitoring to ensure that viral suppression is achieved is recommended. Therapeutic drug monitoring to evaluate efavirenz levels may be considered, if available. Additional studies are required to determine the appropriate dose of efavirenz in infants and young children. Furthermore, studies on efavirenz pharmacokinetics in older children receiving the higher dose of rifampin recommended by the World Health Organization are needed.

Nevirapine and rifampin for children

Data on the influence of concomitant rifampin on nevirapine levels in HIV-infected children are very limited. Substantial reductions in nevirapine concentrations were observed in a pharmacokinetic study in 21 Zambian HIV-infected children with tuberculosis treated with nevirapine, stavudine, and lamivudine antiretroviral therapy and receiving concurrent rifampin-based tuberculosis treatment.[128] No studies were found of increased nevirapine dosing in children receiving rifampin-containing tuberculosis therapy. Therefore, *there are insufficient data to recommend use of nevirapine-based antiretroviral therapy in children receiving rifampin*.

Rifampin and triple nucleos(t)ide regimens for children with HIV and tuberculosis

The triple nucleoside regimen of zidovudine, lamivudine, and abacavir has been suggested for young children who are taking rifampin-based tuberculosis treatment.[129] However, there is limited published clinical experience with this regimen among young children with HIV, with or without concomitant tuberculosis. Furthermore, young children often have very high HIV RNA levels, raising the concern for increased risk of treatment failure with triple NRTI regimens. *Until additional studies become available, and given the limited number of treatment options available for young children with HIV and tuberculosis, the triple-nucleoside regimen is recommended as an alternative for children <3 years receiving rifampin-based tuberculosis treatment*.

Co-treatment of Multidrug-resistant Tuberculosis and HIV

Multidrug resistant tuberculosis (tuberculosis resistant to rifampin and isoniazid) is a growing public health threat and may be particularly lethal among patients infected with HIV.[2] Although knowledge of the metabolic pathways of some second-line drugs (e.g. ethionamide, cycloserine, para-amino salicylate) is incomplete because many of these drugs were developed and licensed decades ago, it is believed (based on knowledge of chemical structure, metabolic pathways, and/or metabolism of related agents) that most of these drugs do not have significant drug-drug interactions with antiretrovirals. The second-line aminoglycoside antituberculosis drugs (capreomycin, kanamycin, and amikacin) are primarily renally excreted as unchanged compounds and are unlikely to have metabolic drug interactions with antiretrovirals. Fluoroquinolones (like ofloxacin, moxifloxacin, or levofloxacin) are also unlikely to have significant drug interactions with antiretrovirals. Since patients with multidrug-resistant tuberculosis do not receive rifampin, the risk of clinically-significant drug interactions is markedly reduced. However, overlapping toxicities such as nephrotoxicity, QT prolongation on the electrocardiogram, psychiatric side effects, and gastrointestinal intolerance may limit options for co-treatment of HIV and multidrug-resistant tuberculosis.

Limitations of these Guidelines

The limitations of the information available for writing these guidelines should be noted. First, drug-drug interaction studies are often done among healthy HIV-uninfected volunteers. Such studies reliably predict the nature of a drug-drug interaction (e.g., that rifampin decreases the serum concentrations of efavirenz). In cases of extreme interactions, such as that between rifampin and unboosted protease-inhibitors, data from healthy volunteers can be definitive. However, healthy volunteer studies seldom provide the needed data regarding tolerability, dosing, and pharmacokinetic variability to determine the optimal management of an interaction in patients with HIV-related tuberculosis receiving multidrug therapy. In this update of the guidelines we emphasize studies performed among patients with HIV-related tuberculosis, particularly those that evaluate HIV treatment outcomes (like virologic suppression or immunologic response to antiretrovirals) or tuberculosis treatment outcomes (such as treatment failure with emergence of resistance, or relapse after antituberculosis treatment). Second, rates of drug metabolism often differ markedly between individuals; 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 genetically different populations. Third, we included in the body of evidence 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, while pharmacokinetic and efficacy data in pregnant women and children receiving tuberculosis drugs and antiretrovirals are limited, we highlighted key recent findings that shed light on management options in these populations. Our recommendations for these key special populations are based primarily on expert opinion.

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Competing Interests

Members of the writing group were asked if they served as employees, if they served on a paid advisory board, if they owned stock, if they received grants, or if they received speaker fees from companies whose products were reviewed. The following competing interests were reported:

NAME	Employee	Paid advisory board	Own stock	Received grant(s)	Speaker fees
Benator	N	N	N	N	N
Benson	N	N	N	N	N
Burger	N	Y	N	Y	N
Burman	N	Y (DSMB)	N	N	N
Cotton	N	N	N	Y (2)	Y (in 2010)
Dooley	N	N	N	Y	N
Kaplan	N	N	N	N	N
Maartens	N	N	N	N	N
McIlleron	N	N	N	N	N
Miro	N	Y	N	Y	Y
Mofenson	N	N	N	N	N
Pau	N	N	N	N	N
Peloquin	N	N	N	Y (Indirect)	N
Pham	N	Y	N	N	N
Siberry	N	N	N	N	N
Sterling	N	N	N	Y (thru Univ.)	N
Struble	N	N	N	N	N
Tuset	N	N	N	Y	Y
Watts	N	N	N	N	N
Weidle	N	N	N	N	N
Weiner	N	N	N	Y	N

N=No competing interest

Y=Yes, possible competing interest as noted

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

Combined regimen for treatment of HIV and tuberculosis	PK effect of the rifamycin on ART	Tolerability / toxicity	Antiviral activity when used with rifamycin	Recommendation (comments)
Efavirenz-based antiretroviral therapy (ART)* with rifampin-containing tuberculosis treatment	Well-characterized, modest decrease in concentrations in some patients	Low rates of discontinuation	Excellent	Preferred (efavirenz should not be used during the first trimester of pregnancy)
PI-based ART* with rifabutin-containing tuberculosis 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[†] (caution to ensure patients who discontinue PIs do not continue to receive reduced rifabutin dose)
Nevirapine-based ART with rifampin-containing tuberculosis treatment	Moderate decrease in concentrations	Concern about hepatotoxicity when used with isoniazid, rifampin and pyrazinamide	Suboptimal when nevirapine is initiated using once-daily dosing; largely favorable when nevirapine is given twice-daily throughout co-treatment	Alternative for patients who cannot take efavirenz, though efavirenz is preferred (nevirapine should not be initiated among women with CD4>250 or men with CD4>400 cells/μL). Viral load monitoring is recommended.
Raltegravir-based ART* with rifampin-containing tuberculosis treatment	Significant decrease in concentrations with standard dosing	Limited experience	Limited published clinical experience	Alternative at higher doses for patients who cannot take efavirenz and who have baseline viral load <100,000 copies/mL
Zidovudine / lamivudine / abacavir / tenofovir with rifampin-containing tuberculosis treatment	50% decrease in zidovudine, possible effect on abacavir not evaluated	Anemia	No published clinical experience, but this combination is less effective than efavirenz- or atazanavir-based regimens in persons not taking rifampin	Alternative for patients who cannot take efavirenz or NVP and if rifabutin not available
Zidovudine / lamivudine / tenofovir with rifampin-containing tuberculosis 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 abacavir and if rifabutin not available
Zidovudine / lamivudine / abacavir with rifampin-containing tuberculosis treatment	50% decrease in zidovudine, possible effect on abacavir not evaluated	Anemia	Early favorable experience, but this combination is less effective than efavirenz- or nevirapine-based regimens in persons not taking rifampin	Alternative for patients who cannot take efavirenz and tenofovir and if rifabutin not available
Super-boosted[‡] lopinavir-based ART or double-dose lopinavir/ ritonavir based ART with rifampin-containing tuberculosis treatment	Modest decrease in concentrations	Hepatitis	Early favorable experience of super-boosting among young children and double-dose among adults already on antiretroviral drugs at the time of rifampin initiation	Alternative if rifabutin not available; double dose an option among adults already taking lopinavir-based ART and virologically suppressed at the time of tuberculosis treatment initiation; super boosting has not been adequately tested in adults but may be effective

* with 2 nucleoside analogues

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

‡ Super-boosting of lopinavir is achieved by giving lopinavir 400 mg together with 400 mg ritonavir twice daily. Double-dose lopinavir/ritonavir is lopinavir 800 mg plus ritonavir 200 mg twice daily.

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

Combined regimen for treatment of HIV and tuberculosis	PK effect of the rifamycin	Tolerability / toxicity	Antiviral activity when used with rifampin	Recommendation (comments)
Super-boosted lopinavir-ritonavir‡ based ART with rifampin-containing tuberculosis treatment	Modest effect	Hepatitis	Early favorable experience of super-boosting among young children	Double dose lopinavir-ritonavir is not recommended
Efavirenz-based ART with rifampin-containing tuberculosis treatment	Well-characterized, modest effect	Low rates of discontinuation	Limited study; careful virologic monitoring recommmended	Alternative for children >3 years (and >10 kg) for whom super-boosted lopinavir/ritonavir is not tolerated or is contraindicated.
Zidovudine / lamivudine / abacavir with rifampin-containing tuberculosis treatment	50% decrease in zidovudine, possible effect on abacavir not evaluated	Anemia	Early favorable experience, but this combination is less effective than efavirenz- or nevirapine-based regimens in adults not taking rifampin	Alternative for children <3 years or for patients for whom super- boosted lopinavir/ritonavir is not tolerated or is contraindicated

‡ Super-boosting of lopinavir in children is achieved by giving standard-dose lopinavir/ritonavir plus additional ritonavir to achieve mg for mg parity of ritonavir and lopinavir.

Table 2a. Recommendations for coadministering antiretroviral drugs with rifampin in adults – 2013

Non-nucleoside reverse transcriptase inhibitors

	Recommended change in dose of antiretroviral drug	Recommended change in dose of rifampin	Comments
Efavirenz	None; some clinicians may increase the dose to 800mg in persons weighing >50kg.	No change (600 mg/day)	Effect on efavirenz AUC is highly variable. Efavirenz should not be used during the 1st trimester of pregnancy.
Nevirapine	Initiate at a dose of 200 mg twice daily rather than 200 mg once daily (use the same maintenance dose of 200 mg twice daily)	No change (600 mg/day)	Efavirenz is preferred, but if nevirapine must be used, lead-in dosing at 200 mg once-daily should be avoided, as this may increase risk of virologic failure. Because of this risk, monitoring of adherence and viral load is recommended. If available, consider therapeutic drug monitoring.
Rilpivirine	Rifampin and rilpivirine should not be used together		Rilpivirine AUC ↓ by 80%, Cmin decreased 89%
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
Atazanavir	Rifampin and atazanavir should not be used together		Atazanavir AUC ↓ by >95%. Increasing the dose to 300 mg twice daily or 400 mg twice daily still resulted in subtherapeutic atazanavir concentrations.

Ritonavir-boosted protease inhibitors

	Recommended change in dose of antiretroviral drug	Recommended change in dose of rifampin	Comments
Lopinavir / ritonavir (Kaletra™)	Lopinavir 800 mg plus ritonavir 200 mg twice daily (double dose)	No change (600 mg/day)	Use with caution; this combination resulted in hepatotoxicity in all adult healthy volunteers in an initial study. It was better-tolerated among adult patients already taking lopinavir/ritonavir based ART with increase to 600 mg/150 mg after one week, then 800 mg/200 mg one week later.
"Super-boosted" lopinavir / ritonavir (Kaletra™)	Lopinavir 400 mg plus ritonavir 400 mg twice daily (super boosting)	No change (600 mg/day)	Use with caution; this combination resulted in hepatotoxicity among adult healthy volunteers. It has not been adequately tested in patients with HIV.
Atazanavir / ritonavir	Rifampin and atazanavir/ritonavir should not be used together.		Atazanavir trough concentration ↓ by > 90%. Doubling the dose to 300/100 twice daily resulted in hepatotoxicity in healthy volunteers.
Darunavir / ritonavir	Rifampin and darunavir/ritonavir should not be used together		No drug interaction studies of darunavir and rifampin have been conducted.
Fosamprenavir / ritonavir	Rifampin and fosamprenavir/ritonavir should not be used together		Fosamprenavir Cmax decreased by 70%, AUC decreased 82%, trough decreased 92%
Saquinavir / ritonavir	Rifampin and saquinavir/ritonavir should not be used together.		The combination of saquinavir (1000 mg twice-daily), ritonavir (100 mg twice-daily), and rifampin caused unacceptable rates of hepatotoxicity among healthy volunteers. In tuberculosis patients, 400/400 twice daily caused similar rates of hepatotoxicity.

Table 2a. (cont.) Recommendations for coadministering antiretroviral drugs with rifampin in adults – 2013

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)	The reductions in maraviroc concentrations related to rifampin co-administration may be overcome by increasing the dose, though the 600 mg twice-daily dose has not been formally tested. Use with caution, as there is 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	Increase dose to 800 mg twice daily	No change (600 mg/day)	Raltegravir trough concentrations reduced by 53% even with increased dose to 800 mg twice daily despite reasonable overall exposures. The clinical significance of this is unknown. Use this dose with caution and employ viral load monitoring, if available.
Elvitegravir co-formulated with cobicistat, tenofovir, and emtricitabine (Stribild™)	Stribild and rifampin should not be used together		Marked decrease in elvitegravir and cobicistat concentrations predicted based on metabolic pathways of these drugs

Table 2b. Recommendations for coadministering antiretroviral drugs with rifampin in children – 2013

Antiretroviral drug regimen choices*	Recommended change in dose of antiretroviral drug	Recommended change in dose of rifampin	Comments
"Super-boosted" lopinavir / ritonavir + 2 NRTIs	Pediatric weight-adjusted dosing for lopinavir/ ritonavir* (Kaletra™) PLUS added ritonavir to reach mg to mg parity of lopinavir and ritonavir doses	No change	Preferred.
Zidovudine/lamivudine/ abacavir	None (standard pediatric weight-adjusted dosing*)	No change	Alternative for children <3 years
Efavirenz + 2 NRTIs	None (standard pediatric weight-adjusted dosing*)	No change	Efavirenz AUC ↓ by 20-30% on average, though effect is highly variable. Alternative for children age >3 years. Careful monitoring of virologic response; therapeutic drug monitoring of efavirenz levels if available

* For pediatric dosing see: Panel on Antiretroviral Therapy and Medical Management of HIV-Infected Children. Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection. August 11, 2011; pp 1-268. Available at http://aidsinfo.nih.gov/ContentFiles/PediatricGuidelines.pdf.

Table 3. Recommendations for coadministering antiretrovirals with rifabutin in adults* – 2013

Non-nucleoside reverse-transcriptase inhibitors

	Antiretroviral dose change	Rifabutin dose change	Comments
Efavirenz	No change	↑ to 600 mg (daily or thrice-weekly)	If efavirenz is used, the rifamycin of choice is rifampin. Efavirenz reduces rifabutin concentrations, so if rifabutin is to be used, increasing rifabutin dose to 600 mg may compensate for the inducing effect of efavirenz. Employ caution as this strategy has not been tested among patients taking rifabutin daily or thrice-weekly. Efavirenz should not be used during the 1st trimester of pregnancy.
Nevirapine	No change	No change (300 mg daily)	Rifabutin and nevirapine AUC not significantly changed.
Rilpivirine	Rifabutin and rilpivirine should not be used together		Rilpivirine AUC ↓ by 46%; and Cmin ↓ by 49%.
Etravirine	No change	No change (300 mg daily)	No clinical experience; etravirine Cmin ↓ by 35% and rifabutin AUC reduced 17%; these changes are unlikely to be clinically relevant, so no dose adjustment is necessary. Since ritonavir-boosted darunavir and saquinavir also diminish etravirine concentrations, the combination of these boosted PIs, etravirine, and rifabutin is not recommended.

Single protease inhibitors

	Antiretroviral dose change	Rifabutin dose change	Comments
Atazanavir	No change	↓ to 150 mg once daily	No published clinical experience.

Dual protease inhibitor combinations

	Antiretroviral dose change	Rifabutin dose change	Comments
Lopinavir / itonavir (Kaletra™)	No change	↓ to 150 mg once daily	In patients with HIV taking lopinavir/ritonavir, 150 mg once daily of rifabutin produces favorable rifabutin pharmacokinetics. Clinical safety data are limited. Monitor closely for potential rifabutin toxicity – uveitis, hepatotoxicity, and neutropenia.
Fosamprenavir/ritonavir	No change	↓ to 150 mg once daily	In healthy volunteers, a dose of 150 mg every other day of rifabutin given together with standard dose boosted fosamprenavir resulted in an increase in amprenavir AUC and Cmax by 35% and no change in Cmin. Limited clinical data among patients with HIV. Monitor closely for uveitis, hepatotoxicity, and neutropenia.
Ritonavir (any dose) with saquinavir, indinavir, amprenavir, fos-amprenavir, atazanavir, tipranavir or darunavir	No change	↓ to 150 mg once daily	Rifabutin AUC ↑ and 25-O-des-acetyl rifabutin AUC ↑, by varying degrees. Monitor closely for uveitis, hepatotoxicity, and neutropenia.

Table 3. (cont.) Recommendations for coadministering antiretrovirals with rifabutin in adults* – 2013

CCR-5 receptor antagonists

Maraviroc	No change	No clinical experience; a significant interaction is unlikely, but this has not yet been studied

Integrase inhibitors

Raltegravir	No change	When given with standard-dose rifabutin (300 mg daily), raltegravir AUC increased 19%, $C_{\tau min}$ decreased 20%, and C_{max} increased 39%. These changes are unlikely to be clinically-significant.
Elvitegravir co-formulated with cobicistat, tenofovir, and emtricitabine (Stribild™)	Stribild™ and rifabutin should not be used together	When given with rifabutin 150 mg thrice-weekly, elvitegravir Cmin reduced 64%, cobicistat Cmin reduced 71%, and 25-O-desacetylrifabutin AUC increased 6-fold.

*Pediatric formulation and pharmacokinetic data are not available in children.