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Management of Tuberculosis in HIV-Infected Patients

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Abstract

HIV-tuberculosis coinfection is currently one of the greatest health threats, affecting millions of people worldwide, with high morbidity and mortality. Treating both infections can be a challenge and requires some expertise due to multidirectional drug interactions, risk of overlapping side effects, high pill burden and risk of immune reconstitution inflammatory syndrome.
This article reviews the general management of tuberculosis/HIV coinfection, focusing on the optimal time to start antiretroviral therapy and which treatments can be safely used. The randomized clinical trials designed to answer the question of when to start antiretroviral therapy (SAPIT, CAMELIA, STRIDE and TIME), published in the last two years, are described and discussed in detail. Summarizing these trials' conclusions, antiretroviral therapy should be started within two weeks of starting tuberculosis treatment if the patient has less than 50 CD4/mm^3 and wait to the end of the induction phase (8-12 weeks after starting tuberculosis treatment) if higher CD4 cell counts exist. Treatment options for both tuberculosis and HIV, including the newer available drugs and those in clinical trials, are revised and recommendations for dose adjustments are made based on the latest available literature, with special attention to drug-drug interactions and the necessity of dose adjustments with some drug combinations. **(AIDS Rev. 2012;14:231-46)**
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Key words

Tuberculosis. HIV. Antiretroviral therapy. Drug-drug interaction. IRIS.

Introduction

Tuberculosis (TB) is one of the leading causes of morbidity and mortality worldwide in HIV-infected patients. The HIV/TB co-epidemics have been recognized by the World Health Organization (WHO) as one of the greatest health threats in the world and intensive interventions have been recommended for preventing, diagnosing, and treating TB in HIV-infected patients. As with other infections in HIV patients, such as viral hepatitis, both diseases act synergistically, making each other more aggressive. According to the WHO data, in 2010 there were 34 million people living with HIV. Also in 2010, there were 8.8 million incident cases of TB, most of them in Asia and Africa. Of them, 1.1 million were among HIV-infected patients and 350,000 patients with HIV died from TB. Twenty-four percent of all TB deaths were associated with HIV and 22% of HIV-related deaths were caused by TB[1]. It is estimated that the risk of developing TB is 20-30 times greater in HIV-infected patients compared to non-HIV patients. When available, antiretroviral therapy (ART) has greatly reduced morbidity and mortality in HIV/TB-coinfected patients[2]. The number of HIV patients with TB on ART has grown each year, reaching 200,000 in 2010[1]. However, even in patients receiving ART with controlled HIV-infection, the risk of developing TB is higher than in HIV-uninfected patients[3].

In the last two years, four randomized clinical trials designed to answer the question of when to start ART in HIV/TB-coinfected patients have been published. Regarding which drugs to use, the pipeline of new TB

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drugs is more robust than ever. However, until all these new drugs are available with enough data on efficacy, safety, and drug-drug interactions, we will have to optimize the use of the currently available drugs, ensuring efficacy and avoiding toxicity. Some of the treatment options with newer drugs may not be feasible in resource-limited settings where the major burden of the disease is found, but information regarding pharmacokinetic (PK) interactions between drugs, recommended dosages, or the optimum time to start ART will be useful in all kinds of settings. Thus, our aim is to review the general management of HIV/TB coinfection in adult patients, focusing in when to start ART and which combinations can be coadministered based on drug-drug interactions between ART and TB drugs.

When to start antiretroviral therapy?

It is clear that TB treatment has to be started as soon as TB is diagnosed, but there is controversy on when to start ART. Guidelines recommend starting ART in all HIV-infected patients with TB. The urgency of starting ART will strongly depend on the immunologic situation of the patient, and until now this decision has depended basically on the physician's criteria.

But there are several drawbacks for starting ART soon, apart from the drug-drug interactions that will be explained later in this manuscript. The first is the high pill burden that the HIV/TB combined treatment entails, especially during the TB induction phase, which can make adherence to both treatments difficult. We must bear in mind that many of these patients will just have been diagnosed with both diseases and will have to cope with the new diagnoses and both treatments at the same time.

Secondly, toxicity is higher with concurrent HIV and TB treatment compared to treatment of each infection separately. Sometimes it can be difficult to know if an adverse event is provoked by ART, TB treatment, or both. Some of the side effects can be indistinguishable between drugs (e.g. hepatotoxicity, rash, or gastrointestinal disturbances), in some cases they can be overlapping and/or additive, and sometimes other infections can be present (such as viral hepatitis), making it very difficult to know the causative agent of the side effect. The third factor is a paradoxical worsening or appearance of new TB symptoms after starting ART due to an improvement in host immunity, known as immune reconstitution inflammatory syndrome (IRIS). Risk of IRIS is higher in patients with rapid increase of CD4 cell counts and/or rapid decline in viral load, and can be severe and even life-threatening[4,5].

In order to answer the question of when is the best time to start ART in HIV/TB-coinfected patients, several randomized clinical trials have been performed in the last years. Before the results of these randomized studies were available, the only information we had was from observational retrospective studies, which suggested that simultaneous treatment of TB and HIV (simultaneous being not at the same time but starting ART within the first two months in two studies[6,7] and six months in another[8]) significantly reduced mortality in these patients, similar to what is seen with other opportunistic infections[9]. For this reason, the WHO guidelines recommend starting ART as soon as possible, within the first eight weeks of starting TB treatment, irrespective of CD4 cell counts. However, this recommendation of "as soon as possible" is quite vague and for this reason it is important to thoroughly analyze the latest available data from large randomized clinical trials, designed specifically to answer the question of when to start ART in HIV/TB-coinfected patients. The main studies are summarized in table 1.

SAPIT Study

SAPIT[10,11] (Starting Antiretroviral therapy at three Points In Tuberculosis) was an open-label, randomized controlled trial performed in South Africa. It included 642 HIV-infected treatment-naive patients with CD4 cell counts < 500 cell/mm^3 and smear-positive pulmonary TB. The primary outcome was all-cause mortality. The TB treatment consisted of a standard combination of isoniazid, rifampin, pyrazinamide, and ethambutol for two months (induction phase), plus streptomycin in TB treatment-experienced patients, followed by isoniazid and rifampin during the continuation phase. The ART consisted of didanosine, lamivudine, and efavirenz at standard doses. Patients were randomized to introduce ART at three different time points: (i) sequential therapy, at the end of TB treatment, (ii) early integrated therapy, within four weeks of starting TB therapy, and (iii) late integrated therapy, within four weeks of completion of the induction phase.

The sequential arm was prematurely discontinued by the data and safety monitoring board after a pre-planned interim analysis of sequential versus integrated (early and late) strategies, as the latter had a 56% decline in mortality (mortality rate of 12.1 vs. 5.4 per 100 person-years; HR: 0.44; 95% CI: 0.25-0.79; p = 0.003). Baseline CD4 cell counts independently predicted mortality in both groups, being significantly higher when CD4 counts were < 200 cells/mm^3. Virologic and TB outcomes were similar between arms. An increased

Table 1. Randomized studies on time of initiation of antiretroviral therapy in HIV/TB-coinfected subjects

Study	SAPIT[10,11]	CAMELIA[12]	ACTG 5221/STRIDE[13]	TIME[14]	TOROK, et al.[15]
Design and patients	RCT, open-label South Africa, 2005-2008 HIV ART naive, CD4 ≤ 500 Smear-positive TB Extrapulmonary TB 5.2% Median CD4: 150 cells/mm^3	RCT, open-label Cambodia, 2006-2009 HIV ART naive, CD4 ≤ 200 Smear-positive TB Pulmonary TB 84% Median CD4: 25 cells/mm^3	RCT, open-label 3 continents, 2006-2009 HIV ART naive, CD4 ≤ 250 TB confirmed (46%) or probable (53%) Median CD4: 77 cells/mm^3	RCT, open-label Thailand, 2009-2011 HIV ART naive CD4 ≤ 350 TB confirmed (65%) or probable (35%) Pulmonary TB: 47% Median CD4: 43 cells/mm^3	RCT, double-blind Vietnam, 2005-2007 HIV ART naive TB meningitis (definite, probable or possible) Median CD4: 41 cells/mm^3
Arms and treatments	– Sequential: after TB treatment (n = 213) – Early integrated: within 4 weeks TB treatment (n = 214) – Late integrated: within 8-12 weeks TB treatment (n = 215) ART: ddI+3TC+EFV	– Early ART: 2 weeks after starting TB treatment (n = 332) – Late ART: 8 weeks after starting TB treatment (n = 329) ART: d4T+3TC+EFV	– Early ART: within 2 weeks (n = 405) – Late ART: within 8-12 weeks (n = 401) ART: TDF+FTC+EFV	– 4-week arm of starting TB treatment (n = 79) – 12-week arm of starting TB treatment (n = 77) ART: TDF+FTC+EFV	– Immediate: within 1 week (n = 127) – Deferred: after 8 weeks (n = 126) ART: AZT+3TC+EFV
Primary end point and outcomes	All-cause mortality Sequential vs. integrated: 12.1 vs. 5.4 per 100 p-yr, (HR: 0.44; 95% CI: 0.25-0.79; p = 0.003). Higher if CD4 < 200 in both groups Early vs. late integrated: 6.9 vs. 7.8 per 100 p-yr, (IRR: 0.89; 95% CI: 0.44-1.79; p = 0.73). If CD4 < 50 cell/mm^3: 26.3 vs. 8.5 per 100 p-yr (IRR: 0.32; 95% CI: 0.07-1.13; p = 0.06) Similar virologic and TB outcomes.	Survival Mortality rate early vs. late: 8.3 vs. 13.87 per 100 p-yr. (Adjusted HR: 0.62; 95% CI: 0.44-0.86; p = 0.006) Similar virologic and TB outcomes.	Survival without new AIDS illness Early vs. late: 12.9 vs. 16.1% (Ratio 95% CI Δ: –1.8 to 8.1%; p = 0.45) If CD4 < 50 cell/mm^3: 15.5 vs. 26.6% (Ratio 95% CI Δ: 1.5-20.5; p = 0.02) No differences in virologic outcomes.	All-cause mortality (1 yr) 4-week vs. 12-week: 7.6 vs. 6.5% 8.8 vs. 7.3 per 100 p-yr. (RR: 0.85; 95% CI: 0.25-2.89; p > 0.99) If CD4 < 50 cell/mm^3: 8.7 vs. 13.1% 10.2 vs. 14.3 per 100 p-yr (RR: 1.59; 95% CI: 0.40-6.40; p = 0.73) Virologic or TB outcomes not reported.	Time to death (9 months) Immediate vs. deferred: 76 vs 70 patients (HR: 1.12; 95% CI: 0.81-1.55; p = 0 .50) Time to new AIDS or death: HR: 1.16; 95% CI: 0.87-1.55; p = 0.31
IRIS	Sequential vs. integrated: 3.8 vs. 12.4% (p < 0.001) No increased mortality or change of ART for this reason. Early vs. late integrated: 20 vs. 8.3% (p < 0.001), especially if CD4 < 50 (46.8 vs. 9.9 per 100 p-yr; p = 0.01)	Early vs. late: 3.76 vs. 1.53 per 100 p-yr (HR: 2.51; 95% CI: 1.78-3.59; p < 0.001) 6 deaths TB IRIS, all in early ART.	Early vs. late: 43 (11%) patients vs. 19 (5%) patients; p = 0.002 No deaths attributed to IRIS.	4-week vs. 12-week: 8.86 vs. 5.02 per 100 p-months; p = 0.069 One TB-IRIS death in the 4-week group.	No significant differences in CNS AE (including IRIS).

(continue)

Table 1. Randomized studies on time of initiation of antiretroviral therapy in HIV/TB-coinfected subjects *(continued)*

Study	SAPIT[10,11]	CAMELIA[12]	ACTG 5221/STRIDE[13]	TIME[14]	TOROK, et al.[15]
Adverse effects	Serious AE early vs. late: 42.8 vs 42.6 events per 100 p-yr (p = 0.98) More patients in early integrated had to switch ART because of AE (10 vs 1; p = 0.006).	Serious AE early vs. late: 2.93 vs 3.21 events per 100 p-month (p = 0.31)	Grade 3-4 AE early vs. late: 44 vs. 47% (p = NS)	Grade 3-4 AE 4-week vs. 12-week: 24 vs. 25% (p > 0.99)	Grade 3-4 AE immediate vs. deferred: 90 vs 89% (p = 0.84) Grade 4 immediate vs. deferred: 80 vs. 69% (p = 0.04)
Authors remarks	Initiation of ART during TB therapy improved survival. Early initiation of ART in patients with CD4 < 50 increased AIDS-free survival. Late integrated initiation of ART in patients with CD4 > 50 reduced the risk of IRIS and other ART-related AE without increasing the risk of AIDS or death.	Initiating ART 2 weeks after TB treatment start improved survival among patients with CD4 ≤ 200.	Overall, earlier ART did not reduce the rate of new AIDS-defining illness and death, as compared with later ART. In patients with CD4 < 50, earlier ART was associated with a lower rate of new AIDS-defining illnesses and death.	Immediate ART was not associated with survival advantages when compared to initiation of ART at 12 weeks.	Immediate ART did not improve outcome in patients with HIV-associated TB meningitis. Significantly more grade 4 AE in the immediate ART arm, supporting delayed initiation of ART in HIV-associated TB meningitis.

TB: tuberculosis; RCT: randomized clinical trial; ART: antiretroviral therapy; ddI: didanosine; AZT: zidovudine; d4T: stavudine; TDF: tenofovir disoproxil fumarate; 3TC: lamivudine; FTC: emtricitabine; EFV: efavirenz; p-yr: person-years; HR: hazard ratio; CI: confidence interval; IRR: incidence-rate ratio; RR: relative risk; AE: adverse event; IRIS: immune reconstitution inflammatory syndrome.

rate of IRIS was observed in the integrated arm (12.4 vs. 3.8% in the sequential arm; p < 0.001), but without increased mortality or change of treatment for this reason[10].

Recently, data comparing the early versus late integrated arms have been published[11]. The incidence rate of AIDS or death was 6.9 cases per 100 person-years in the early-integrated group versus 7.8 per 100 person-years in the late-integrated group (incidence rate ratio 0.89; 95% CI: 0.44-1.79; p = 0.73). Differences remained non-significant between groups after adjusting for baseline demographics, TB, or HIV characteristics. However, in the 72 patients with CD4 counts < 50 cells/mm^3, the AIDS or death incidence rates were higher in the late-integrated group, although this did not reach statistical significance: 26.3 (95% CI: 12.6-48.4) versus 8.5 (95% CI: 2.3-21.9) cases per 100 person-years (incidence rate ratio 0.32; 95% CI: 0.07-1.13; p = 0.06). The incidence of IRIS was significantly higher in the early-integrated compared to the late-integrated group (4.7 times higher in patients with CD4 counts < 50 cells/mm^3 and 2.2 times higher in patients with CD4 > 50 cells/mm^3). Also, more patients in the early-integrated group had to switch ART because of adverse events (10 vs. 1; p = 0.006). The TB or HIV outcomes did not differ significantly between groups, except for a higher increase in CD4 cell counts at 12 and 18 months in the early-integrated group, although these patients had been receiving ART for a longer period of time.

CAMELIA Study

CAMELIA[12] (CAMbodian Early versus Late Introduction of Antiretrovirals) was an open-label, multicentre, randomized controlled trial conducted in Cambodia. HIV-infected treatment-naive patients with CD4 cell counts ≤ 200 cells/mm^3 and smear-positive TB were included. The primary outcome was survival. The TB treatment consisted in isoniazid, rifampin, pyrazinamide, and ethambutol for two months followed by isoniazid and rifampin during four months. The 661 patients were randomized to introduce ART (stavudine, lamivudine and efavirenz) at two different time points, stratified by study site and baseline CD4 cell counts (≤ 50 or 51-200 cells/mm^3): an early arm, two weeks after starting TB therapy, and a late arm, eight weeks after starting TB treatment.

Of note, patients had at baseline a median CD4 cell count of 25 cells/mm^3. Significant differences were seen between arms, with a mortality rate of 8.28 per 100 person-years (95% CI: 6.42-10.69) in the early arm and 13.77 per 100 person-years (95% CI: 11.20-16.93) in the late arm, with an adjusted HR for death in the early versus late arm of 0.62 (95% CI: 0.44-0.86; p = 0.006).

Other factors also independently associated with increased risk of death were older age, lower body mass index, low Karnofsky score, or disseminated or drug-resistant TB, but not CD4 cell counts (although we must underscore that patients included in this study were deeply immunosuppressed, with 72% of patients having CD4 cell counts < 50 cells/mm^3). Virologic or TB outcomes were similar between arms. There was also an increased rate of IRIS in the early arm compared to the late arm (3.76 vs. 1.53 per 100 person-years; HR: 2.51; 95% CI: 1.78-3.59; p < 0.001), with six deaths directly related to TB IRIS, all in the early ART arm.

ACTG A5221 or STRIDE Study

The STRIDE Study[13] (STRategy study of Immediate versus DEferred initiation of ART for HIV-infected persons treated for TB) was an open-label, randomized controlled trial performed in patients from Africa (68%), Asia (7%), North America (5%), and South America (20%). HIV-infected treatment-naive patients with CD4 counts < 250 cells/mm^3 and confirmed or probable TB were included. Median baseline CD4 counts were 77 cells/mm^3 and 46% had confirmed TB. The primary combined outcome was the proportion of patients who survived without new AIDS-defining illnesses at 48 weeks. Finally, 806 patients were randomized to begin ART (tenofovir, emtricitabine, efavirenz) at two different time points: (i) early arm, two weeks after starting TB therapy, and (ii) late arm, 8-12 weeks after starting TB therapy.

There were no significant differences in the primary outcome between the early and late arms (12.9 vs. 16.1%; 95% CI Δ: −1.8-8.1%; p = 0.45). The rate of new AIDS/death was significantly lower in the early than in the late ART group in the pre-specified subgroup of 285 patients with < 50 cells/mm^3 (15.5 vs. 26.6%; 95% CI Δ: 1.5-20.5; p = 0.02). This difference was not observed in patients with CD4 counts > 50 cells/mm^3 (11.5 vs. 10.3%). In the whole study population, there were no differences between arms in virologic control of HIV after 48 weeks. There were significant differences (p = 0.002) regarding IRIS: 43 (11%) cases in the early arm (median 4.6 weeks after TB treatment start) versus 19 (5%) cases in the late arm (median 11.7 weeks after TB treatment start). There were no deaths attributed to IRIS.

TIME Study

TIME[14] was an open-label, randomized controlled trial performed in Thailand. A total of 156 HIV-naive patients with CD4 counts ≤ 350 cells/mm^3 (median 43 cells/mm^3) and confirmed or suspected TB (53% of disseminated or extrapulmonary TB) were included. Patients were randomized, without stratification, to receive ART (tenofovir, emtricitabine, efavirenz) at two time points after starting TB treatment (isoniazid, rifampin, pyrazinamide, and ethambutol): four and 12 weeks.

There were no significant differences in the primary outcome (one-year all-cause mortality): 7% (8.76 per 100 patient-years) in the four-week group versus 6% (7.25 per 100 patient-years) in the 12-week group (RR: 0.845; 95% CI: 0.247-2.893). No significant differences were found when patients were analyzed depending on baseline CD4 (< 100 or < 50 cells/mm^3). The TB-related IRIS was more frequent in the four-week group (8.86 vs. 5.02 per 100 person-months), but without significant differences (p = 0.069) and with only one death attributed to this cause in the four-week group.

Torok, et al. study

Recently, a double-blind, placebo-controlled, randomized clinical trial performed in Vietnam has been published, comparing immediate (at study entry) versus deferred (after eight weeks) ART in 253 HIV-infected patients with TB meningitis[15]. The primary outcome was death in the first nine months after randomization. No significant differences were seen between treatment arms in the primary outcome (76 deaths in the immediate vs. 70 deaths in the deferred arm; HR: 1.12; 95% CI: 0.81-1.55; p = 0.5) nor in HIV immunologic or virologic outcomes after 12 months. However, a significantly greater incidence of grade 3-4 side effects was seen in the immediate arm, although without a significant increase in neurological events (including IRIS).

In summary, the SAPIT trial showed that ART should not be deferred until finishing TB treatment and ART initiation will depend on CD4 cell count, starting in the first two weeks if < 50 cells/mm^3, as it decreases the risk of death, and waiting to finish the induction phase if higher CD4, as it decreases the risk of IRIS and of ART side effects without increasing the risk of AIDS or death. Similar conclusions can be drawn from the STRIDE trial. In the CAMELIA trial, there was higher mortality if ART was deferred to the end of the induction phase, but the great majority of patients in this trial had CD4 counts < 50 cells/mm^3, so the conclusions would be similar to the two prior studies in severely immunosuppressed patients. The TIME study showed no significant differences between early or late ART initiation,

even in patients with CD4 < 50 cells/mm^3, but this is a much smaller trial and the statistical potency was lower.

One of the main arguments against early ART is the risk of IRIS. In the prior studies, IRIS did not increase mortality or entail a treatment change, except for the six cases of TB/IRIS-related deaths in the early arm of the CAMELIA trial. In a recent review, a TB/IRIS mortality of 3.2% has been reported[16]. However, the potential risk of an IRIS reaction depends on the site in which it takes place. Thus, central nervous system (CNS) involvement can be more dangerous, as seen with *Cryptococcus neoformans*[17]. In the SAPIT and CAMELIA trials, most of the TB cases were pulmonary and this does not allow drawing conclusions about when to start ART when TB involves the CNS, but the Torok, et al. study pleads for deferring ART in TB meningitis. However, in this study only two time points were defined (immediate versus eight weeks after starting TB treatment) and we do not know if an intermediate option would be more appropriate in severely immunosuppressed patients.

In these studies[10-15], all patients had CD4 counts ≤ 500 cells/mm^3 and most of them had < 200 cells/mm^3. Thus, the results are only applicable to patients with these characteristics. It is not known when the optimal time to start ART is in the minority of patients with CD4 counts > 500 cells/mm^3 when TB is diagnosed, and whether waiting until TB treatment is finished could be an option in these patients.

Another completely different situation is when TB is diagnosed after ART has been started. This could be due to a new infection or to unmasking of a preexisting TB infection. In both cases ART should be continued, adjusting it according to drug-drug interactions.

What to start with?

The main problem when treating an HIV/TB-coinfected patient is the PK drug-drug interactions between the HIV and TB regimens, which can impact the therapeutic efficacy of both. Usually, the most relevant drug-drug interactions are those between rifamycins and ART.

Rifampin is one of the most potent inducers of different isoenzymes of the cytochrome P450 (CYP) enzymatic system, the main metabolizing pathway of ART in the liver. Rifampin also induces other enzymatic systems such as UDP-glucuronosyltransferase (UGT) and membrane transporters such as P-glycoprotein involved in ART metabolism. This can lead to subtherapeutic ART concentrations, with risk of virologic failure and selection of resistance mutations. Other rifamycins, such as rifabutin and rifapentine, have inducing effects, but not as strong as rifampin. Isoniazid, another first-line TB drug, has an inhibiting effect on the CYP system, but when given together with rifampin the inducing effect prevails[18] and interactions between isoniazid and ART are not usually clinically relevant, although no specific drug-drug interaction studies between isoniazid and ART in the absence of rifampin have been performed. Furthermore, some ART can also have inducing or inhibiting effects on TB drug metabolism, with risk of increased toxicity or of subtherapeutic concentrations with treatment failure and selection of resistance. Another important point is that ART and TB drugs may play an additive role in toxicity when given in combination, especially in the liver but also skin or gastrointestinal side effects. These multidirectional interactions and overlapping side effects make HIV/TB coinfection a complex scenario. In this setting, therapeutic drug monitoring can help in some instances, and it is one of the approved indications in many guidelines[19-22].

Tuberculosis treatment

The first decision that the physician must take is whether the patient is going to receive a TB treatment including rifamycins or not and if it does, which rifamycin.

The preferred treatment for drug-susceptible TB in HIV-infected patients is the same as in non-HIV patients, including rifampin. Rifampin has a proved efficacy and it can be given as fixed-dose combinations of TB drugs, favoring adherence[22]. However, rifampin reduces plasmatic drug concentrations of many of the ART, having to adjust the dose in some of them and in others coadministration is contraindicated (Table 2). Rifampin concentrations are not significantly modified by ART, and it can be given at standard doses adjusted by body weight. In HIV-infected patients it is advisable to give rifampin daily due to a higher risk of treatment failure and selection of resistance with intermittent TB therapy[22]. An alternative TB treatment without rifampin should be used only if it is not possible to build an adequate ART regimen with rifampin.

Rifabutin has some advantages and drawbacks compared to rifampin. The main advantage is that it is a weaker inducer of CYP than rifampin, and ART doses do not have to be adjusted. However, there is less experience with this drug (especially in HIV-infected patients), it is more expensive and difficult to find in resource limited settings. Moreover, it does not allow giving TB treatment in fixed-dose combinations, which can make adherence difficult. Also, rifabutin and its

Table 2. Drug-drug interactions between antiretroviral drugs and rifamycins and recommended dose adjustments

Antiretroviral	Rifampin	Rifabutin
NNRTI		
Efavirenz	EFV 600 mg qd Can increase EFV dose to 800 mg qd if body weight > 60 kg	Increase rifabutin dose to 450-600 mg daily
Nevirapine	NVP 200 mg bid Lead-in phase not necessary	No dose adjustment (300 mg daily)
Etravirine	No data, but coadministration not recommended	No dose adjustment in the absence of a PI/r. If PI/r present decrease rifabutin dose to 150 mg every other day
Rilpivirine	Do not co-administer	Do not co-administer
PI/r		
All PI/r (amprenavir, atazanavir, darunavir, indinavir, lopinavir, nelfinavir, saquinavir, tipranavir)	Do not co-administer	Decrease rifabutin dose to 150 mg every other day
Lopinavir/r	When no other options are available increased LPV/r doses (400/400 or 800/200 mg bid) can be used with concerns of higher toxicity	
Integrase inhibitor		
Raltegravir	Increase dose to 800 mg bid	No dose adjustment
Elvitegravir	Do not co-administer	Do not co-administer
Dolutegravir	Increase dose to 50 mg bid	No dose adjustment
CCR5 antagonist		
Maraviroc	MVC 600 mg bid Do not co-administer with rifampin plus EFV	No dose adjustment in the absence of a PI/r If PI/r present decrease rifabutin dose to 150 mg every other day
Enfuvirtide	No dose adjustment	No dose adjustment
NRTI	No dose adjustment	No dose adjustment

NNRTI: nonnucleoside reverse transcriptase inhibitor; PI/r: ritonavir-boosted protease inhibitor; NRTI: nucleoside/nucleotide reverse transcriptase inhibitor; EFV: efavirenz; NVP: nevirapine; LPV/r: ritonavir-boosted lopinavir; MVC: maraviroc; qd: once-daily; bid: twice-daily.

main metabolite 25-O-desacetylrifabutin are substrates of CYP3A, and its concentrations can vary significantly when given with CYP inhibitors/inducers such as some ART. For instance, when rifabutin is coadministered with ritonavir-boosted protease inhibitors (PI/r), a very important increase in rifabutin concentrations is seen and doses have to be adjusted to 150 mg every other day or three times a week (Table 2)[23]. When given with PI/r, rifabutin toxicity (uveitis, neutropenia) can increase and TB treatment can be jeopardized if the patient stops the PI/r without modifying the rifabutin dose (with risk of rifamycin resistance selection)[24,25]. Subtherapeutic concentrations have also been seen in patients receiving adjusted rifabutin doses with PI/r[24]. For this reason, there are currently ongoing studies to determine the optimum dose of rifabutin when coadministered with ART (French ANRS NCT00640887 and NCT00651066, ACTG5290). On the other hand, rifabutin concentrations decrease when administered with efavirenz (area under the concentration-time curve [AUC] by 38%, maximum concentration [C_{max}] by 32%, and minimum concentration [C_{min}] by 45%), and rifabutin doses should be increased to 450-600 mg daily[23]. When rifabutin is administered with nevirapine,

no dose adjustments are necessary (300 mg daily)[21]. These dose adjustments with PI/r and efavirenz make compliance more difficult. However, there is a recent meta-analysis reviewing the published evidence with rifabutin compared to rifampin, including a group of 585 HIV-infected patients (some of them treated with older non-boosted PI), in which no significant differences are seen in efficacy or toxicity between rifamycins[26].

Rifapentine is a very potent new rifamycin with a long half-life (five times that of rifampin), allowing twice-weekly administration in the induction phase and once a week during the continuation phase. It has shown its efficacy as a treatment for latent TB given together with isoniazid once a week for three months[27]. There are currently ongoing studies to find the best rifapentine dose for the treatment of active tuberculosis (TBTC29X trial, NCT00694629). However, there are concerns about the risk of rifamycin resistance selection in HIV-infected patients treated with intermittent rifapentine/isoniazid combinations during the continuation phase, and this option is not recommended[28]. There is scarce PK data analyzing drug-drug interactions between rifapentine and ART, although a strong inducing effect on CYP should be expected with rifapentine, similar to rifampin.

If rifamycins cannot be used due to interactions and/or toxicity, a regimen without these drugs can be built. The TB treatment not including rifamycins simplifies the selection of ART in an HIV/TB-coinfected patient, as no clinically significant interactions are present between other TB drugs and ART, although there is much less data with these combinations[29]. For instance, in other special populations with higher risk of TB in which drug-drug interactions can entail serious problems, such as solid organ transplantation receiving immunosuppressors, TB regimens not including rifamycins are frequently considered and alternative drugs such as fluoroquinolones (levofloxacin or moxifloxacin) are increasingly being used[30].

However, there are some drawbacks with these treatments. There is much less experience with regimens not containing rifamycins. Also, not using rifamycins significantly extends the duration of TB treatment, which is usually more expensive, with a higher pill count, and also with potentially serious long-term toxicity (risk of *Clostridium difficile* or tendon problems with fluoroquinolones, bone marrow toxicity with linezolid, central nervous system side effects with cycloserine, etc.).

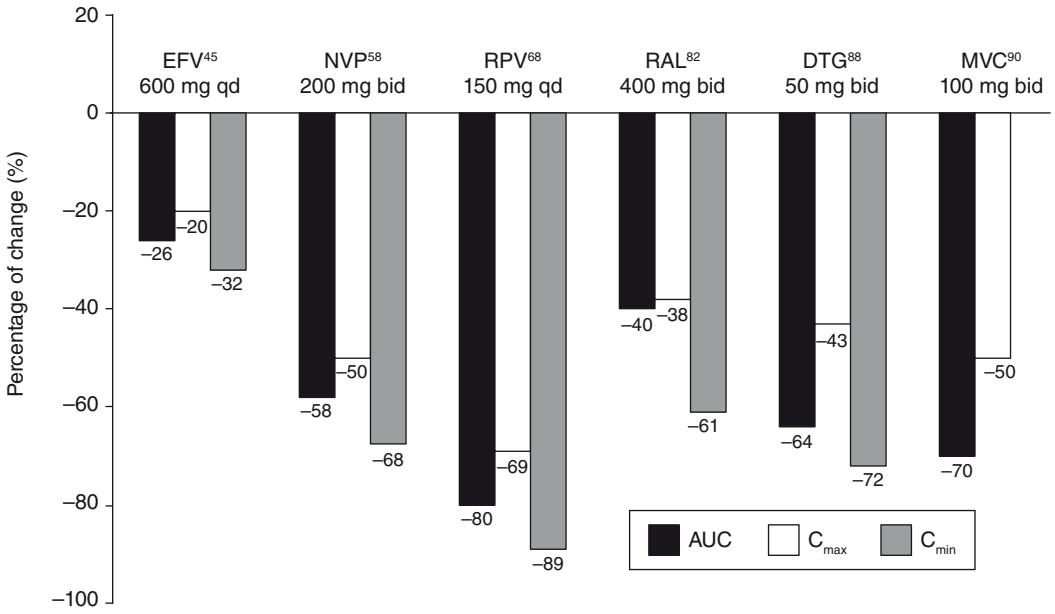
There are newer TB drugs that in the future might provide some advantages regarding HIV/TB-coinfected patients, being able to build potent TB treatments without rifamycins. These drugs are needed not only to avoid interactions with ART, but also to have shorter, simpler, more effective and better tolerated regimens[31]. Some of the new TB drugs or drug families in more advanced phases of development are:

- Bedaquiline (TMC-207): diarylquinoline with a very long terminal half-life (five months). It is a substrate of CYP3A, but it does not act as an inhibitor or inducer[32]. When given with rifampin, its concentrations are reduced by about 50%. Studies have been performed in healthy volunteers with single doses of bedaquiline and steady-state efavirenz[33], nevirapine[34] or lopinavir/r[35], without significant PK interactions, although it is possible that relevant interactions may be present at bedaquiline steady-state.
- Nitroimidazole: delamanid (OPC-67683) has no CYP metabolism and PA-824 has a small metabolism through CYP. Clinical trials are ongoing, but no significant interactions are expected with ART[36].
- SQ-109 is a [1,2]-ethylenediamine, similar to ethambutol but much more potent and with a longer half-life (40-50 hours). Metabolized through CYP (2D6, 2C19), there is a potential risk of PK interactions with ART, but studies have not yet been performed[37].
- Oxazolidinone: sutezolid (former PNU-100480) and AZD5847. Dose-finding studies are ongoing. Only 30% of their metabolism is through CYP[38].

Antiretroviral therapy

In HIV-infected naive patients without TB, the recommended ART regimen includes a combination of two nucleoside reverse transcriptase inhibitors (NRTI: tenofovir/emtricitabine or abacavir/lamivudine) plus a non-nucleoside reverse transcriptase inhibitor (NNRTI), a PI/r or an integrase inhibitor. In pretreated patients, three fully active antiretroviral drugs, based on resistance testing and history of tolerability and/or failure to prior drugs, are recommended[19,20].

Some important factors have to be taken into account when considering how to treat HIV infection in patients receiving TB therapy. As seen before, drug-drug interactions between HIV and TB regimens can be significant (Table 2). Also, the increased risk of adverse reactions and the risk for developing IRIS should be considered. However, the first thing that we have to consider when we analyze drug-drug interaction data or the safety and tolerability of some drug



AUC: area under the time-concentration curve; Cmax: maximum concentration; Cmin: minimum concentration; EFV: efavirenz; NVP: nevirapine; RPV: rilpivirine; RAL: raltegravir; DTG: dolutegravir; MVC: maraviroc; qd: once daily; bid: twice daily.

Figure 1. *Pharmacokinetic interactions between rifampicin and nonnucleoside reverse transcriptase inhibitors, integrase inhibitors or CCR5 antagonists. Changes are expressed as percentage of decrease in the antiretroviral drug concentration when given with rifampicin compared to the same dose without rifampicin.*

combinations is in what kind of patients the study has been conducted. We have seen in some studies that toxicity is higher in healthy volunteers compared to HIV-infected patients. One example is the hepatotoxicity of the rifampin-pyrazinamide combination to treat latent tuberculosis, much higher in healthy volunteers than in HIV patients[39,40]. Another example is the higher hepatotoxicity with the saquinavir/r-rifampin combination in healthy volunteers compared to HIV-infected patients[41-43]. Many hypotheses have arisen to explain this phenomenon. The most plausible is that there is a blunted inflammatory response in HIV patients due to the immunosuppression, which leads to less side effects. The order in which drugs are introduced may also be important: higher hepatotoxicity has been seen when rifampin was given first, maybe due to an increase in toxic PI intermediate metabolites due to a higher metabolism induced by rifampin[44]. Other factors are also important, such as age, race, weight, or concomitant hepatic disease (hepatitis B or C virus infection, toxics such as alcohol). Disease-related factors (both HIV and TB) could also alter the PK of ART and TB drugs. We have to look at these factors when analyzing the available data, as it might not be generalizable.

Nonnucleoside reverse transcriptase inhibitors

All available NNRTI are basically substrates and inducers of different CYP isoenzymes, P-gp and other metabolic pathways. Efavirenz and etravirine also inhibit some of them. The inducer effect of the NNRTI blunts the inducing effect of other drugs such as rifampin. For this reason, there are smaller decreases in NNRTI concentrations compared to other drugs such as PI when given with rifampin. Changes in NNRTI PK parameters when given with rifampin are described in figure 1.

Rifampicin produces a decrease in efavirenz plasmatic concentrations: AUC, C_{max} and C_{min} decrease 26, 20, and 32%, respectively[45]. High variability in efavirenz concentrations have been seen when administered with rifampin, but with good clinical outcomes[46,47]. Some studies have been performed in order to find if it is necessary to increase the efavirenz dose to 800 mg daily to overcome the rifampin-inducing effect[48-52].

Black patients frequently have higher efavirenz concentrations, but this is probably due to a higher incidence of a CYP2B6 516 G-T polymorphism, and the inducing effect of rifampin might be less relevant in them[53]. Probably for this reason, African patients have good outcomes with 600 mg and higher toxicity with 800 mg[51,54], whereas Asiatic patients have significant decreases in efavirenz concentrations when body weight increases[50]. Probably race is as important as body weight for predicting efavirenz concentrations. Guidelines give different recommendations regarding this issue. Thus, the British BHIVA guidelines recommend efavirenz 600 mg daily if body weight is < 60 kg and increasing the dose to 800 mg daily if the patient weighs more[21], the DHHS guidelines recommend efavirenz 600 mg daily and monitoring virologic response, giving the option to increase to 800 mg daily if the patient weighs more than 60 kg[19], while the WHO and GeSIDA Spanish guidelines recommend giving efavirenz 600 mg daily to all patients[20,22].

The inductor effect of rifampin on nevirapine is even higher than with efavirenz, with reductions on nevirapine plasma concentrations of 58% in AUC, 50% in C_{max}, and 68% in C_{min} when coadministered with rifampin[55-60]. Patients starting ART with nevirapine who are already receiving rifampin should start with full nevirapine dose, without the induction phase[22]. Some authors have tried to increase nevirapine doses to 300 mg twice daily, overcoming the rifampin-inducing effect[61-63]. However, in a randomized trial comparing standard (200 mg twice daily) versus 300 mg twice daily doses of nevirapine, the efficacy was similar with both doses, but the toxicity increased (25% of patients) with the higher dose[62].

There are observational cohort studies comparing efavirenz and nevirapine in HIV/TB-coinfected patients. One study showed equal efficacy[64] and another found a higher risk of virologic failure with nevirapine than with efavirenz[65]. There are two published randomized studies comparing efavirenz and nevirapine together with rifampin in HIV/TB-coinfected patients. In the first by Manosuthi, et al.[55], standard doses of efavirenz or nevirapine (randomized 1:1) were given with stavudine and lamivudine, together with standard TB treatment, to 142 Thai patients (with a mean weight of 53 kg). Although there were no significant differences in immunologic, virologic, or TB outcomes, the authors recommended using efavirenz rather than nevirapine because there were a higher proportion of patients with subtherapeutic concentrations in the nevirapine arm. In the second study, Swaminathan, et al.[56] randomized 116 patients in India to receive efavirenz or nevirapine, both once daily with didanosine and lamivudine, together with standard TB treatment. In the 24-week interim analysis, there were significantly higher rates of deaths, serious adverse events, and virologic failure with once-daily nevirapine, which led to halting the study at this point.

There are no clinical studies combining etravirine and rifampin, but interaction is expected due to metabolic pathways. Thus, at present coadministration is not recommended[66,67].

In a study in 16 healthy volunteers, rilpivirine was administered at doses of 150 mg daily (much higher than the licensed dose of 25 mg) together with 600 mg daily of rifampin. Significant decreases in rilpivirine C_{max} (69%), C_{min} (89%) and AUC (80%) were seen. Thus, the coadministration of rilpivirine with rifampin is contraindicated[68].

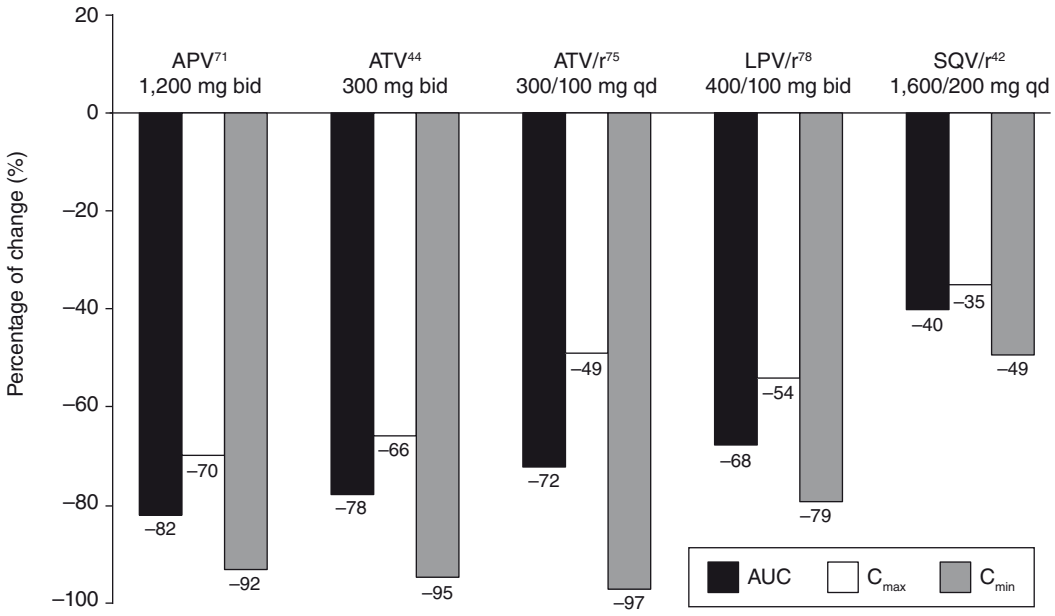
In all the published guidelines, the combination of efavirenz plus two NRTI (especially tenofovir/emtricitabine) is considered the first initial ART option in patients with rifampin-based TB therapy. Etravirine and rilpivirine are not recommended, and nevirapine is considered an alternative[20-22].

Protease inhibitors

Potent induction of the CYP system by rifampin significantly reduces plasmatic concentrations of all PI, which can lead to subtherapeutic levels and virologic failure. Changes in PI PK parameters when given with rifampin are described in figure 2. Several studies have been performed, increasing either the PI dose or the boosting ritonavir dose ("superboosting") in order to overcome the rifampin-inducing effect, with different results.

The PK drug-drug interaction data of rifampin and the old PI indinavir/r (at doses of 800/100 or 600/100 mg twice daily)[69], nelfinavir[70], and amprenavir (1200 mg twice daily)[71] contraindicate their coadministration.

In a study in 26 HIV/TB-coinfected patients, saquinavir/r 1600/200 once-daily (with didanosine and lamivudine) was administered together with standard TB treatment. Four patients had to stop treatment due to side effects and six had virologic failure (with C_{trough} < 0.1 in five patients). Saquinavir AUC, C_{max} and C_{min} decreased when coadministered with rifampin (40, 35, and 49%, respectively)[41,42]. There is a study in 30 HIV/TB-coinfected patients in which saquinavir/r was administered at doses of 400/400 mg twice daily with a rifampin-based treatment. All patients but one stopped the treatment due to toxicity, loss of follow-up, or



AUC: area under the time-concentration curve; C_{max}: maximum concentration; C_{min}: minimum concentration; APV: amprenavir; ATV: atazanavir; ATV/r: ritonavir-boosted atazanavir; LPV/r: ritonavir-boosted lopinavir; SQV/r: ritonavir-boosted saquinavir; bid: twice daily; qd: once daily.

Figure 2. *Pharmacokinetic interactions between protease inhibitors and rifampicin. Changes are expressed as percentage of decrease in the antiretroviral drug concentration when given with rifampin compared to the same dose without rifampicin.*

virologic failure[72]. Furthermore, a higher than expected rate of hepatotoxicity was seen in a study in healthy volunteers when rifampin and saquinavir/r were coadministered. The study was halted and a black box warning against this combination was inserted in the drug package information[43].

There was a significant decrease in atazanavir concentrations in three HIV-infected patients with TB treated with a rifampin-containing regimen and ART including atazanavir/r 300/100 mg once daily. In all three cases, atazanavir concentrations were below the minimum recommended trough plasma level for wild-type virus (150 ng/ml) more than 50% of the time[73]. There are three studies with increased atazanavir doses together with rifampin (atazanavir 300 or 400 mg twice daily in one, atazanavir/r 300/200 or 400/200 mg once daily in another, and atazanavir/r 300/100 mg twice daily in the third). Apart from the fact that increasing atazanavir doses did not overcome the rifampin-inducing effect, there was also higher toxicity in these patients[44,74,75].

Some studies have been performed co-administering rifampin and lopinavir/r. There are two studies in healthy volunteers with higher doses of lopinavir/r and rifampin. In the first, lopinavir/r 800/200 mg twice daily was compared to 400/400 mg twice daily and drug concentrations were within the therapeutic levels, but one-third of patients had to stop treatment due to hepatotoxicity[76]. In the other study, lopinavir/r 600/150 mg twice daily or 800/200 mg twice daily were coadministered together with rifampin, and 19 out of 22 patients had to stop treatment one week later due to hepatic or gastrointestinal toxicity and the study was prematurely halted[77]. High doses of lopinavir/r (600/150 mg twice daily and 800/200 mg twice daily) were also given to 21 HIV-infected patients without TB in order to study PK interactions and tolerability. Doubling the lopinavir/r dose overcame the rifampin-inducing effect, although 10 patients had some degree of hepatotoxicity[78]. These patients were already taking lopinavir/r as part of their HAART with undetectable viral load and this may have biased tolerability[79]. The same group also studied high lopinavir/r doses (11 with 800/200 mg twice daily and seven with 400/400 mg twice daily) in HIV-infected patients with TB. In this study, 77% of plasma samples were within adequate lopinavir concentrations and there were no grade 3-4 toxicities. Although seven

patients stopped treatment, only one was due to side effects with nausea attributed to ritonavir[80]. Another study retrospectively analyzed 32 HIV/TB-coinfected patients who had received lopinavir/r 400/400 mg twice daily in Vietnam. Eight patients presented hepatotoxicity, but only two patients had grade 3 and none had grade 4 toxicity. Eleven patients prematurely stopped the superboosted PI regimen: there were two patients with gastrointestinal adverse events, two deaths in patients with recurrent episodes of extrapulmonary TB, and seven losses to follow-up[81]. There are currently ongoing trials investigating different lopinavir/r doses given in combination with rifampin (NCT01138202, NCT00771498, ACTG 5290).

There are no studies to our knowledge with darunavir/r or tipranavir/r and rifampin in combination. Presumably, plasmatic concentrations will significantly decrease and the recommendations in guidelines are to not coadminister[21].

New boosters for ART are being developed, such as cobicistat (GS-9350). Studies of drug-drug interactions with these new boosters will be necessary to know their role in treating HIV/TB-coinfected patients.

Thus, the important drug-drug interactions between PI/r and rifampin contraindicate their coadministration. In the exceptional situation in which there are no therapeutic options against HIV without PI/r and for TB without rifampin, higher doses of the PI and/or ritonavir could be administered[79].

Integrase inhibitors

Integrase inhibitors are highly effective and well tolerated drugs, becoming an excellent alternative in the treatment of patients with HIV and TB. The only currently commercially available integrase inhibitor is raltegravir, but newer drugs of this family, such as elvitegravir (boosted with ritonavir or cobicistat) or dolutegravir, are in phase III studies and will be soon commercialized. Changes in integrase inhibitors PK parameters when given with rifampin are described in figure 1.

Raltegravir metabolism is mainly through glucuronidation (UGT1A1). Rifampin also induces, although to a lesser extent, this enzymatic system. In a study in healthy volunteers, raltegravir C_{max}, C_{min} and AUC decreased (38, 61, and 40%, respectively) when coadministered with 600 mg of rifampin. When the raltegravir dose was doubled (800 mg twice daily) this effect was partially overcome (C_{max} increased 62%, AUC increased 27%, but C_{min} still decreased 53% compared to raltegravir without rifampin)[82,83]. For this reason, the suggested raltegravir dose when coadministered with rifampin is 800 mg twice daily[84]. There is currently an ongoing phase II study (NCT00822315) comparing the efficacy and safety of raltegravir 400 or 800 mg twice daily, together with tenofovir and lamivudine, in naive HIV-infected patients receiving active TB treatment containing rifampin.

Recently, PK data combining raltegravir with rifapentine in healthy volunteers has been presented. A decrease in raltegravir C_{trough} was seen with daily rifapentine administration, while no significant interactions were seen with intermittent rifapentine administration. In that study, rifapentine showed less inductive effect on raltegravir metabolism than rifampin[85]. However, until more PK information is available for rifapentine, data should be extrapolated from rifampin interactions.

There is no published data on elvitegravir and rifampin coadministration. Elvitegravir has to be boosted with ritonavir or cobicistat as it is mainly metabolized through CYP, so interactions should be similar to those found with boosted PIs[86]. Thus, coadministration of elvitegravir and rifampicin is not recommended. Recently, a study in 12 healthy volunteers has been presented, combining cobicistat-boosted elvitegravir with rifabutin administered at doses of 150 mg every 48 hours. Rifabutin exposures were similar to those with 300 mg daily without cobicistat-boosted elvitegravir, while metabolite 25-O-desacetylrifabutin exposures were 4.8- to 6.3-fold higher. However, elvitegravir C_{trough} was lower with rifabutin and the authors concluded that coadministration is not recommended[87].

Dolutegravir is also metabolized primarily through UGT1A1 and much less through CYP3A4. A phase I study in healthy volunteers was recently presented, co-administering dolutegravir and rifampin. When dolutegravir doses were doubled (50 mg twice daily, the same dose as for integrase inhibitor-experienced patients) in the presence of rifampin, concentrations were similar to those obtained with dolutegravir 50 mg once daily alone, with good tolerability[88]. There is also a study combining dolutegravir (50 mg once daily) and rifabutin (300 mg once daily) in nine healthy volunteers. There were non-clinically significant changes in dolutegravir PK parameters (decreases in AUC and C_{trough} of 5 and 30% and increases in C_{max} of 15%)[89].

Viral entry inhibitors

CCR5 antagonists

Maraviroc is the only CCR5 antagonist available for the treatment of HIV infection. It is a substrate but not

an inhibitor or inducer of CYP3A4. Thus, it undergoes important PK interactions that force dose adjustments when given with inducers or inhibitors of this enzymatic system. There is only one published study with maraviroc and rifampin in combination in healthy subjects. Maraviroc was administered 100 mg twice daily (an unlicensed dose) together with rifampin 600 mg daily, and decreases of 70 and 50% in maraviroc AUC and C_{max} were seen (Fig. 1). These decreases were overcome when maraviroc dose was doubled to 200 mg twice daily (also an unlicensed dose)[90]. The manufacturer's recommendation is that the maraviroc dose should be increased to 600 mg twice daily when coadministered with rifampin[91]. However, there is scarce clinical experience with the maraviroc/rifampin combination and it should only be considered as an alternative. Also, the coadministration of rifampin and efavirenz (both with inducing effects) together with maraviroc has not been studied and it is not recommended[91].

No dose adjustment is required when maraviroc is given with rifabutin in the absence of a PI/r. If a PI/r is given, both maraviroc and rifabutin doses should be decreased (maraviroc 150 mg twice daily and rifabutin 150 mg every other day)[91].

Fusion inhibitors

Enfuvirtide is the only fusion inhibitor commercially available. It has to be administered subcutaneously twice daily and it has a high price and is not usually available in resource-limited countries. It is metabolized by proteolytic enzymes and does not undergo CYP metabolism. There are no known clinically significant interactions between enfuvirtide and other medications[92]. The drawbacks of this drug are evident and its use has declined significantly in the last years after the appearance of newer, more convenient ART.

However, given the lack of significant drug-drug interactions and the safety profile, enfuvirtide could become an option in selected cases, where other drugs could not be used due to resistance, intolerance or interactions.

Nucleoside/nucleotide analogue reverse transcriptase inhibitors

The CYP enzymatic system does not significantly intervene in the metabolism of NRTI, and no relevant interactions are seen between these drugs and TB drugs. In patients with TB, any NRTI can be used without dose adjustment.

Although NRTI-only regimens (with three or four NRTI) are accepted in the WHO guidelines as an alternative (after efavirenz- or nevirapine-based regimens with rifampin, and before PI/r with rifabutin or super-boosted PI with rifampin)[22], they have shown lower efficacy compared to treatments with two NRTI and efavirenz in HIV-infected patients without TB[93]. They can be an option in resource-limited settings in the absence of alternatives, as they do not have significant interactions (although there are no specific studies with 3-4 NRTI plus rifampin), but not if we have other treatment options.

Conclusions

HIV/TB-coinfection is one of the biggest health threats in the world. It is important to treat both diseases, starting with TB treatment and adding ART afterwards. The main problems in treating both diseases are drug-drug interactions, increased pill burden, overlapping toxicities, and the risk of developing IRIS.

The results of the retrospective studies and the more recently published randomized clinical trials clearly show that ART should not be delayed until finishing TB treatment. Also, it seems clear that in patients with CD4 < 50 cells/mm^3, HIV treatment should be started as soon as possible, not immediately but ideally within the first two weeks of TB therapy. More controversies can arise about when to start ART in patients with CD4 between 50 and 200 cells/mm^3, and risks and benefits should be balanced: improved immunity but increased risk of IRIS (which can be life-threatening, especially if CNS involvement), overlapping and often difficult to manage side effects and increased pill burden. Probably in these patients (as in those with more than 200 CD4/mm^3) ART should be deferred 8 weeks, after finishing the TB induction phase.

In ART-naive patients, standard rifampin-based TB treatment and efavirenz-based HIV regimen (with two NRTI, especially tenofovir/emtricitabine in fixed-dose combinations) should be the recommended option. Some patients cannot receive these drugs for different reasons: prior virologic failure and/or resistance mutations (especially in resource-limited settings, where administering single-dose nevirapine to pregnant women is frequent during delivery), risk of teratogenicity, or serious side effects (skin, liver, central nervous system) with efavirenz. In these patients, an ART regimen including three active ARV drugs that can be combined with the TB drugs should be designed. Some of the options could be: (i) raltegravir or, in the near future,

Table 3. Most common antiretroviral regimens used with rifamycins in patients with HIV infection and tuberculosis

TB treatment	HIV treatment
Rifampin-based	Efavirenz* + TDF/FTC (alternatively ABC/3TC)
	Raltegravir* + TDF/FTC (alternatively ABC/3TC)
	Nevirapine* + TDF/FTC (alternatively ABC/3TC)
Rifabutin-based*	PI/r (ATV, DRV or LPV) + TDF/FTC or ABC/3TC

TB: tuberculosis; TDF: tenofovir; FTC: emtricitabine; ABC: abacavir; 3TC: lamivudine; PI/r: ritonavir-boosted protease inhibitor; ATV: atazanavir; DRV: darunavir; LPV: lopinavir.
*For specific dose adjustments see table 2.

dolutegravir-based ART, with double doses of the integrase inhibitor and standard rifampin-based TB treatment, (ii) nevirapine-based ART and standard rifampin-based TB treatment, (iii) PI/r-based ART and rifabutin-based TB treatment, adjusting rifabutin dose, or (iv) TB therapy without rifamycins (i.e. with a quinolone), with multiple options regarding HIV treatment (Table 3). Exceptionally, other options such as maraviroc-based ART or NRTI-only ART could be used with caution.

Until new potent and well-tolerated drugs with lesser interactions are available, we will have to continue using the current ART, being aware of potential interactions and side effects.

Conflict of interest

All authors declare no conflicts of interest.

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