The treatment of tuberculosis in HIV-infected persons

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AIDS 1999, **13**:435–445

Keywords: HIV, AIDS, tuberculosis, treatment, antiviral therapy, drug interactions

Introduction

Tuberculosis (TB) is one of the most important infections affecting HIV-positive patients in the world. Rates of HIV-related TB have risen in countries in Europe, United States and South America [1,2], and the rates have increased so rapidly in India and the rest of Asia that they may equal those in sub-Saharan Africa by the year 2000 [1,3,4]. One in 11 cases of TB are attributed to HIV globally and will rise to one in seven by the year 2000 [5]. As therapy for HIV disease becomes more available, physicians need to know how to treat these two diseases effectively while minimizing the risk of drug interactions and maintaining the shortest possible duration of treatment for TB. Problems arise both when patients are contemplating starting antiretroviral therapy and when they are already on such therapy and TB is diagnosed. Some guidelines regarding the treatment of TB and HIV already exist [6] and usually require modification to either TB therapy or antiviral drugs. These interactions are problematic because rifampicin-based regimens are the gold standard for short-course TB therapy and should be used wherever possible. Major drug–drug interactions can occur especially between the rifamycins and protease inhibitors and non-nucleoside reverse transcriptase inhibitors (NNRTI). Unfortunately, there are little or no data on what are the optimal regimens when TB and HIV are being treated concomitantly, but priority should be given to treating and notifying TB [7].

This review will examine the evidence from clinical trials for the efficacy of rifamycin-based (rifampicin, rifabutin and rifapentine) short-course regimens for TB when rifamycin is used for the whole treatment period or only in the intensive phase. It will examine the drug–drug interactions between anti-TB and antiretroviral drugs and discuss possible TB regimens that might be used in HIV-positive patients on or starting antiretroviral therapy, and suggests best practice treatment strategies.

TB chemotherapy

Each of the main anti-TB drugs varies in its capacity to kill bacteria, prevent the emergence of drug resistance, and sterilize lesions. Isoniazid is the most potent bactericidal drug and kills more than 90% of bacilli within 7 days by acting on metabolically active bacilli. It is also quite effective at preventing the emergence of drug resistance. Rifampicin is also a good bactericidal drug, with a potent sterilizing effect, and the ability to prevent the emergence of drug resistance. In addition to acting on rapidly dividing bacilli, it kills so-called 'persisters', which remain inactive for long periods but have intermittent periods of metabolism, with only short drug exposure. This is crucial to its sterilizing ability, and also confirms experimental studies of TB of both early bactericidal activity [8,9] and sterilizing activity [10–12]. Pyrazinamide, although bactericidal, is mainly used for its sterilizing effect. It is particularly effective at killing intracellular bacilli sequestered inside macrophages in an acid environment [12]. Ethambutol and streptomycin are less potent drugs, ethambutol probably only being bactericidal at high concentrations. They are less effective at preventing emergence of resistance to rifampicin and isoniazid. A fourth drug (such as ethambutol or streptomycin) can play a role in

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Date of receipt: 6 August 1998; revised: 12 October 1998; accepted: 5 November 1998.

patients with an increased risk of drug resistance, such as in HIV-positive individuals, and must be included in the initial phase of treatment of such patients [7,13–15].

There is a close correlation between the power of a regimen to convert a sputum smear and culture-positive case to sputum culture-negative at 2 months and its overall sterilizing efficacy (i.e., the higher the culture-negative rate at 2 months, the higher the cure rate, or conversely, the lower the relapse rate after 6 months of total treatment). Six-month short-course chemotherapy is now the gold standard against which regimens have to be compared, and has the key elements of pyrazinamide for 2 months in the initial phase, and rifampicin in both the initial and continuation phases, whether the dosing schedule is daily throughout, daily for the initial phase and intermittently in the continuation phase, or intermittently throughout.

Rifampicin

Initial and continuation phases

Table 1 shows some of the data on the efficacy of 6-month regimens of rifampicin. These data are for fully sensitive organisms. Any reduction below the 6-month total treatment gives an unacceptably high relapse rate [16,17]. The relapse rate is also significantly higher for isoniazid or streptomycin and isoniazid-resistant organisms [18].

Initial phase only

Table 2 shows data on studies where rifampicin was omitted from the continuation phase mainly on grounds of cost. Six-month regimens had inadequate sterilization and higher relapse rates even for sensitive organisms. To obtain the results quoted, some also required the first 2 months of the rifampicin-containing initial phase to be given in hospital. Some of these regimens would not be appropriate for HIV-positive individuals because they contain thiacetazone, but have been shown to be effective in International Union Against Tuberculosis and Lung Disease-assisted programme conditions [19]. There is however the problem of greatly increased toxicity to thiacetazone in HIV-positive patients in Africa [13], where such regimens have been used with great success. To overcome this, ethambutol may have to be substituted for thiacetazone [19]. When rifampicin is not used in the continuation phase there is also a significantly increased failure rate if the organism is found to have initial isoniazid resistance [18].

Rifabutin instead of rifampicin in standard regimens

Rifabutin, a different rifamycin from rifampicin, has been used for TB therapy. Experimental work suggests that rifabutin has a lower early bactericidal activity, by a factor of 2.73 compared with rifampicin [8]. The limited data for the use of rifabutin in controlled trials for treatment of TB are shown in Table 3. A further uncontrolled study of 50 HIV-positive cases in Uganda also showed similar efficacy [20]. Although superficially rifabutin seems to perform as well as rifampicin, not all patients in the trials have reached 24 months of evaluation after cessation of treatment, and there has been no information on how such regimens perform in the

Table 1. Six-month short-course regimens.

Country [reference]	Regimen*	No. patients	Bacteriological relapse (%)
Daily throughout			
Singapore [16,42]	2 SHRZ/4 HRZ	78	1
	2 SHRZ/4 HR	80	2
United Kingdom [43]	2 SHRZ/4 HR	125	1
	2 EHRZ/4 HR	132	2
Hong Kong [44–46]	2 EHRZ/4 EHRZ	163	1
US Trial 21 [47]	2 HRZ/4 HR	273	4
Daily initial phase and intermittent continuation phase			
Singapore [48,49]	2 SHRZ/4 HR (3)	97	1
	1 SHRZ/5 HR (3)	94	1
	2 HRZ/4 HR (3)	109	1
Poland [50]	2 HRZ/4 HR (2)	116	4
	2 SHRZ/4 HR (2)	56	2
Intermittent throughout			
Hong Kong [44–46]	6 SHRZE (3)	152	1
	6 SHRZ (3)	151	1
	6 HRZE (3)	160	2
Hong Kong [51]	2 SHRZ (3)/2 SHR (3)/2 HR (3)	149	3
	4 SHRZ (3)/2 HR (3)	133	6
	4 SHRZ (3)/2 HRZ (3)	142	1
	2 HRZ (3)/4 HRZ (3)	135	4
United States [52]	0.5 SHRZ/1.5 SHRZ (2)/4 HR (2)	125	2

*The number in front of the letters represents the duration of treatment in months, and the number in parentheses after the letters represents the number of doses per week. S, Streptomycin; H, isoniazid; R, rifampicin; Z, pyrazinamide; E, ethambutol.

Table 2. Rifampicin in initial phase only.

Location [reference]	Regimen*	No. patients	Bacteriological relapse (%)
East Africa [53]	2 SHRZ/4TH	179	7
East Africa [54]	2 SHRZ/4TH	75	13
	2 SHR/4TH	82	18
	2 SHRZ/6TH	81	0
	2 SHR/6TH	77	6
	1 SHRZ/5TH	79	18
	1 SHRZ/7TH	58	7
	1 SHRZ/5 SHZ (2)	75	9
	1 SHRZ/7 SHZ (2)	88	2
India [55,56]	2 SHRZ (3)/4 SH (2)	89	8
	2 SHRZ (2)/4 SH (2)	95	13
	2 SHRZ/3 SHZ (2)	129	7
	2 SHRZ/5 SHZ (2)	132	4
Hong Kong [57,58]	2 SHRZ/4 SHZ (2)	87	7
	2 SHRZ/6 SHZ (2)	87	3
	2 SHRE/4 SHE (2)	84	23
	2 SHRE/6 SHE (2)	84	10
	4 SHRZ (3)/2 SHZ (2)	71	6
	4 SHRZ (3)/4 SHZ (2)	83	1

*The number in front of the letters represents the duration of treatment in months, and the number in parentheses after the letters represents the number of doses per week. S, Streptomycin; H, isoniazid; R, rifampicin; Z, pyrazinamide; E, ethambutol; T, thiacetazone.

presence of initial isoniazid resistance, having only been tested on fully susceptible organisms [21,22].

Rifapentine instead of rifampicin in standard regimens

Rifapentine has recently been approved as part of combination treatment of pulmonary TB [23] when given weekly with isoniazid in the continuation phase (after 2 months of four-drug treatment with isoniazid, rifampicin, streptomycin and pyrazinamide). The potential advantages over rifampicin were its use once weekly in the continuation phase, and a better adverse events profile. The disadvantage was the higher bacteriological relapse rate (Table 3).

Table 3. Rifabutin/rifapentine for treatment of pulmonary tuberculosis.

Country [reference]	Regimen*	No. patients	Bacteriological relapse (%)
South Africa [21]	2 RHZE/4 RHE (2)	106	3.8
	2 RbHZE/4 RbHE (2)†	98	5.1
Argentina/ Thailand/ Brazil [22]	2 HRZE/4 HR		
	2 RbHZE/4 RbH†	171	1.2
	2 RbHZE/4 RbH‡	174	1.2
Hong Kong [23]	2 HSRZ (3) + 4 HR (3)	190	3.2
	4 HRp (1)	199	7.5
	4 HRp (1)§	203	9.4

*The number in front of the letters represents the duration of treatment in months, and the number in parentheses after the letters represents the number of doses per week. †Rifabutin dosage 300 mg daily. ‡Rifabutin dosage 150 mg daily. §Every second or third dose omitted. S, Streptomycin; H, isoniazid; R, rifampicin; Z, pyrazinamide; E, ethambutol; Rb, rifabutin; Rp, rifapentine.

Regimens containing neither rifampicin nor isoniazid

Such regimens should really only be used for treating multidrug-resistant (MDR)-TB. Because by definition there is resistance to both rifampicin and isoniazid, both the main bactericidal drug (isoniazid) and the main sterilizing drug (rifampicin) have been lost, such regimens have to include multiple drugs, often second-line agents. Additional drug resistance often accompanies those of rifampicin and isoniazid. The treatment of such cases is prolonged, expensive, and success rates of only just over 55% have been reported [24]. Improved outcome has been reported in both HIV-negative and HIV-positive patients with MDR-TB when appropriate therapy was started promptly and maintained [25–27]. Although there have been no controlled studies of treatment for MDR-TB, several principles of treatment can be derived [28–30]. First, a single drug should never be added to a failing regimen, because to do so is likely to promote further drug resistance. Second, a drug regimen should include four and preferably five drugs to which the patient's organism has been shown to be susceptible on *in vitro* testing, and ideally which have not been used on the patient before, and should also include an injectable medication. Finally, the therapy of all patients with MDR-TB, both as an inpatient and as an outpatient, should be directly observed. To ensure that these criteria are met, it is best that only physicians with substantial experience of drug-resistant TB manage cases of suspected or proven MDR-TB.

The role of rifabutin in the management of MDR-TB is controversial. First, there is the major problem that only one-third of rifampicin-resistant organisms retain susceptibility to rifabutin because of cross-resistance [31,32]. One open study showed a bacteriological response in up to 60% at dosages of 450–600 mg daily, but this may have been to other concurrent agents, particularly fluoroquinolones [33]. In a controlled study [34], rifabutin at 450–600 mg once daily was no better than including rifampicin, and no significant difference in outcome was noted.

Length of treatment

There is debate on how long patients with HIV disease with TB should be treated, and guidelines therefore vary. The British Thoracic Society recommend standard short-course TB treatment regimens [7], but one study [35] supported a 12-month total treatment period, which appears to be the basis of some recommendations. The apparently better results with 12-month regimens may be because, in the short term (e.g., at 18 months), reinfection is less likely in patients treated for 12 versus 6 months. If physicians wish to treat for prolonged periods, then the continuation phases should be extended accordingly for all the short-course regimens.

Highly active antiretroviral therapy

Several clinical endpoint studies have shown the benefit of highly active antiretroviral therapy (HAART) on morbidity and mortality from HIV disease [36–38]. Most HAART will result in HIV viral loads below the limit of detectability and substantial rises in CD4 cell count; these surrogate marker responses will, in most patients, translate into clinical benefit with decreased morbidity and mortality. Because TB can occur at any stage of immune suppression, patients may already be on antiviral therapy when TB treatment is started. Others may request or be advised to start concomitant anti-HIV therapy on the basis of the risk of developing further opportunistic infections or overall poor prognosis, and many guidelines indicate when antiviral therapy should be started [39,40]. According to the latest guidelines [41], potential choices of HAART regimens might be a protease inhibitor and two nucleoside reverse transcriptase inhibitors (NRTI), an NNRTI and two NRTI, or two protease inhibitors with or without NRTI. In clinical practice, many other HIV regimens are used, such as protease inhibitors and NNRTI, or triple NRTI. In the short-term, triple NRTI regimens using abacavir have also been shown to have marked effects on surrogate markers. It should be noted that for HIV-infected patients with TB, the viral load and CD4 cell count may be adversely affected by the TB itself and may not be an accurate guide to the patients' viral setpoint or usual CD4 cell count [41].

Adverse reactions to medication

Anti-TB therapy

Adverse reactions to many drugs used for prophylaxis and treatment of opportunistic infections occur with increased frequency amongst HIV-infected patients [59,60]. Many of the reports documenting adverse reactions to anti-TB therapy in patients coinfected with HIV predate the introduction and widespread use of HAART.

High rates of adverse reactions requiring changes in therapy due to anti-TB therapy have been reported. Several studies have compared both HIV-infected and HIV-uninfected patients with TB. These have shown higher rates of adverse reactions in HIV-infected patients. In a study by Chaisson *et al*. [61], rates of adverse reactions were 26% in HIV-infected patients and 3% in uninfected patients. In a study by Soriano *et al*. [62], rates of adverse reaction to anti-TB therapy were 39% in HIV-infected patients and 22% in those uninfected by HIV. In a study by Small *et al*. [63], 18% of patients with TB coinfected with HIV experienced adverse reactions to therapy; however, only 3.7% of those with TB who were not coinfected with HIV experienced adverse events. In all these studies the majority of adverse reactions occurred within the first 2 months of starting therapy, and rifampicin was frequently implicated, accounting for almost two-thirds of adverse events in the study from Small *et al*. [63]. Thiacetazone, previously widely used in cash-poor environments, has a significant adverse reaction profile [64].

In the general population, hepatotoxicity due to isoniazid increases with age: ≤ 0.3% in those under 35 years versus ≤ 2.3% in those older than 50 years. It is also more likely in those with heavy alcohol intake and hepatitis C infection [65] and those who are receiving co-therapy with rifampicin. Fast acetylators have an increased likelihood of toxic reactions resulting from the formation of acetylhydrazine, which is subsequently metabolized by cytochrome P450 into reactive metabolites. Slow acetylators may be at even greater risk of hepatotoxicity, which occurs through a separate pathway of metabolism that results in the formation of hydrazine, which may itself be toxic [66].

Options in a patient who experiences an adverse reaction to anti-TB therapy are to continue the therapy with close clinical and laboratory monitoring, to stop therapy if the reaction is severe and to consider restarting once the reaction has settled, or to desensitize the patient.

Desensitization

In patients intolerant of anti-TB therapy, desensitization may be attempted. This technique is widely performed for HIV-infected patients who are intolerant of trimethoprim–sulphmethoxazole [67]. There are reports of successful desensitization to rifampicin, ethambutol and isoniazid in HIV-uninfected persons [68,69].

Malabsorption

Malabsorption of antimycobacterial drugs, including rifampicin, ethambutol, pyrazinamide, isoniazid, ethionamide and cycloserine, has been reported in persons with AIDS and *Mycobacterium tuberculosis* and disseminated *Mycobacterium avium* complex [70–72]. This has been ascribed to HIV-associated enteropathy resulting in subtherapeutic serum drug levels and associated treatment failure. In this setting the development of drug-resistant TB has been reported [71]. The possibility of malabsorption should be considered in HIV-infected persons, with or without chronic diarrhoea or other clinical signs of malabsorption, who fail to respond to therapy despite good compliance or directly observed therapy. Here, measurement of serum concentrations of antimycobacterial agents is indicated [70].

Drug interactions

Drugs other than antiretrovirals

Many of the drugs used to treat *M. tuberculosis* have overlapping toxicities or share routes of metabolism and elimination with other drugs taken by persons with HIV infection. These interactions have been reviewed in detail elsewhere [60,73].

Absorption of rifampicin is reduced by up to 36% by coadministration of antacids, including aluminium hydroxide, magnesium trisilicate and sodium hydroxide, all of which produce an increase of gastric pH. In addition, aluminium may form chelates, which are less soluble and less well absorbed, and magnesium trisilicate may adsorb rifampicin, thus reducing absorption. Rifamycins [rifampicin (rifampin), rifabutin and rifapentine] are metabolized by hepatic microsomal cytochrome P450 and induce their own metabolism. Induction of liver enzymes results in accelerated metabolism of other drugs sharing this route of metabolism. The effects of enzyme induction may be seen within a few days starting a rifamycin, but maximum induction takes more than 7 days to occur.

Clinically important drug interactions occur between rifamycins and several agents (Table 4); for each drug the effect of the rifamycin is to reduce its area under the curve (AUC) by increasing its metabolism. Care should be taken if any of these agents are used in combination with a rifamycin, and the possibility of subtherapeutic effect should be considered. Consideration should also be given to monitoring drug levels in persons failing to respond/deteriorating on therapy if they are also receiving a rifamycin as cotherapy.

Rifampicin interacts with azoles. Rifampicin reduces the AUC of ketoconazole by more than 80% and the AUC of fluconazole by about 23%. In turn, ketoconazole lowers the serum concentration of rifampicin, the mechanism of this interaction is by ketoconazole causing reduced absorption of rifampicin [74]. Fluconazole, and potentially the other azoles, may cause elevations of serum rifabutin levels [75].

If rifampicin is given to an individual taking dapsone for prophylaxis of *Pneumocystis carinii* pneumonia there is a 7–10-fold reduction in dapsone levels rendering this latter drug ineffective [76]. The AUC of clarithromycin is reduced by approximately 90% if rifampicin is coadministered (and is reduced by approximately 50% if rifabutin is given). In addition, because clarithromycin itself inhibits cytochrome P450, it may bring about increases in serum concentration and the AUC of rifabutin by up to 77% [77]. Rifampicin reduces the AUC of metronidazole by 33% and its clearance by 44% [78]. Rifampicin also reduces the steady-state concentration of atovaquone by 50% [79]. Some patients, so-called poor metabolizers, have marked reductions of serum doxycycline levels when this drug is coadministered with rifampicin. The mechanism of this interaction is not established but it is thought to be a direct effect of rifampicin inducing the metabolism of doxycycline [80]. Cidofovir is usually taken with probenicid and may bring about increases in serum rifabutin levels by reducing renal clearance of rifabutin; foscarnet may do the same. The significance of these interactions is uncertain.

Table 4. Clinically significant interactions between rifamycins and other therapies taken by HIV-infected persons resulting in reduced plasma concentrations/area under the curve.

Atovaquone	Ketoconazole
Chlorpropamide	Methadone*
Clarithromycin	Metronidazole
Corticosteroids	Phenytoin
Dapsone	Terbinafine
Doxycycline	Tolbutamide
Fluconazole	Warfarin
Itraconazole	

*Also other opiates.

Isoniazid, by inhibiting cytochrome P450, may produce significant increases in the AUC of phenytoin, carbamazepine and warfarin. Isoniazid induces the metabolism of ketoconazole [73] and reduces its plasma level; isoniazid may also have a similar effect on itraconazole levels. Ethambutol is both filtered and actively excreted by the kidney; absorption from the stomach is reduced by coadministration with aluminium-containing compounds. If given together, these drugs should be separated by 2 h. Care should be taken if other potentially nephrotoxic drugs are administered with ethambutol, such as amphotericin B, foscarnet, cidofovir with probenicid, or intravenous pentamidine. There is a clinically important interaction between pyrazinamide and probenicid [81]. Pyrazinamide prolongs the half-life of probenicid by inhibiting its metabolism; in turn, probenicid reduces the renal excretion of pyrazinamide. Care should be taken if pyrazinamide is coadministered with probenicid/procaine penicillin, because increased toxicity may be encountered from the penicillin.

Antiretroviral therapy

The study of drug interactions between TB drugs and antiretrovirals is a constantly changing field of knowledge. As new antiretroviral agents are developed and undergo clinical evaluation in trials and finally enter clinical practice, so new adverse reactions have been noted and new drug interactions have been described. In contrast to descriptions of interactions between antimycobacterial agents and other drugs that are well-characterized in steady-state experimental or clinical conditions, many reports of antiretroviral–anti-TB drug–drug interactions are single-dose evaluations or are descriptions based on 'class effect' predictions. In this context, clinically significant drug interactions occur as a result of both induction and inhibition of metabolic pathways [82].

As discussed above, the rifamycins (rifampicin, rifabutin and rifapentine) are all metabolized by hepatic cytochrome P450 isoenzyme 3A4 (CYP3A4). *In vitro* studies using primary human hepatocytes show that rifampicin is a slightly more potent inducer of CYP3A4 than rifapentine, and both have a significantly higher induction potential than rifabutin [83]. *In vivo*, rifabutin

has less enzyme-inducing effect than rifampicin [84]. Interactions that reduce the AUC or shorten the half-life of drugs used as HAART may be clinically important in the development of viral resistance.

Rifamycins and NRTI's

The interactions between the rifamycins and antiretroviral therapy are shown in Table 5. Rifampicin reduces the AUC and increases the clearance of zidovudine via the mechanism of rifampicin induced, increased glucuranation of zidovudine [85]. This is not clinically significant and dose alteration is not required. In contrast, rifabutin does not appear to affect the clearance of zidovudine.

In didanosine, the presence of the buffer (calcium carbonate and magnesium hydroxide) in the chewable/dispersible tablets, or the unbuffered powder, which is reconstituted with water and antacid, raises gastric pH in order to improve didanosine absorption. By doing this, the solubility and thus absorption of rifampicin is reduced. To reduce the effect of the interaction between didanosine and rifampicin, these two drugs should be administered at least 2 h apart [86].

Rifamycins and protease inhibitors

Protease inhibitors are both substrates and inhibitors of cytochrome P450 isoenzyme CYP3A4.

Saquinavir is a weak inhibitor of CYP3A4 and thus has the potential to increase plasma concentrations of drugs sharing this route of metabolism [82]. Coadministration of rifampicin or rifabutin results in subtherapeutic levels of saquinavir hard gel formulation. Rifampicin reduces plasma saquinavir levels by approximately 80% and rifabutin reduces plasma saquinavir levels by approximately 40%. There are currently no data on the interaction between rifamycins and saquinavir soft gel and their concomitant use cannot be recommended at present.

Table 5. Interactions between rifampicin, rifabutin and antiretroviral therapy.

Antiretrovirals	Rifampicin	Rifabutin
Nucleoside analogue RTI		
Zidovudine	↓	NS
Didanosine	⇓	NS
Zalcitabine	NA	NA
Stavudine	NA	NA
Lamivudine	NA	NA
Abacavir	NA	NA
Protease inhibitors		
Saquinavir (hard gel)	↓	↓
Indinavir	↓	↓⇑
Ritonavir	↓⇑	⇑
Nelfinavir	↓	↓⇑
Amprenavir	↓	⇑
Non-nucleoside RTI		
Nevirapine	↓	(NA)
Delavirdine	↓	↓⇑
Efavirenz	↓	⇓

The absence of interaction data does not mean that a drug–drug interaction does not occur. RTI, Reverse transcriptase inhibitors; ⇑, increase in area under the curve (AUC) of rifamycin; ↓, reduction in AUC of antiretroviral; ⇓, reduction in AUC of rifamycin; NA, no data available (probably no significant interaction); (NA), no data available (probable interaction on basis of 'class effect' but may not be clinically significant); NS, no significant interaction.

Indinavir has a similar drug interaction profile to saquinavir but is a more potent enzyme inhibitor. The result is that indinavir increases plasma concentration of drugs metabolized by CYP3A4 to a greater extent than saquinavir and also plasma levels of indinavir are reduced to a lesser extent by enzyme inducers such as rifamycins when compared with their effect on saquinavir. If rifabutin is given with indinavir, there are reductions in plasma indinavir levels of approximately 33%, and in addition, indinavir increases the plasma levels of rifabutin [87]. In clinical practice, if these two drugs are coadministered, increased doses of indinavir are prescribed (i.e., 1.0–1.2 g three times daily and 150 mg once daily rather than 300 mg once daily of rifabutin is used) [82]. Rifampicin is not used with indinavir because of its greater potential for enzyme induction and thus increased metabolism of indinavir, producing markedly subtherapeutic indinavir levels.

Ritonavir has a greater effect on inhibition of CYP3A4 and also inhibits isoenzymes CYP2D6 and CYP2C9, thus increasing the potential for drug interactions [82]. A combination of ritonavir is currently contraindicated with rifamycins because of the significant increases in AUC of rifabutin caused by inhibition of its metabolism by ritonavir [88]. Such increases in AUC of rifabutin are associated with a marked increase in adverse reactions, including arthralgia, uveitis and leukopenia. The combination of ritonavir and rifampicin is contraindicated because this would result in marked increases in plasma rifampicin levels and marked reductions in ritonavir levels. In theory, ritonavir could be used in combination with alternate-day half-dose rifabutin (i.e., 150 mg). However, until more data are available, this combination cannot be recommended for clinical use.

Rifampicin causes a decrease in nelfinavir levels of 82% and these drugs should not be used together. Rifabutin decreases nelfinavir levels by 32%. In turn, nelfinavir increases rifabutin by 200%. If coadministered, the dose of nelfinavir should be increased to 1 g three times daily and the dose of rifabutin halved to 150 mg.

Amprenavir (141W94), like other protease inhibitors, is both a substrate and inhibitor of CYP3A4. It is currently recommended that the dose of rifabutin is reduced if it is coadministered with amprenavir. In multiple-dose studies in healthy volunteers, coadministration of amprenavir resulted in increases in rifabutin levels of between threefold and sixfold. In contrast, rifabutin produced reductions in AUC of amprenavir

of approximately 15%. When amprenavir was coadministered with rifampicin, the AUC of amprenavir was reduced by 81%; therefore, these drugs should not be used together [89,90].

If rifampicin is to be started in a patient already taking protease inhibitors, consideration should be given to a washout period. Either 2 or 3 days washout is allowed after stopping the protease inhibitor, or alternatively, if the rifampicin is needed urgently (e.g., in a sick patient), the protease inhibitor is discontinued and rifampicin is begun, initially at half dose, increasing to full dose after 1 week. In contrast, if HAART, including a protease inhibitor, is to be commenced in a patient who is already taking rifampicin and the rifampicin is going to be changed to rifabutin, a 3-week interval should be allowed for reduction of the enzyme-inducing activity of rifampicin prior to commencing HAART.

Rifamycins and NNRTI's

NNRTI are also metabolized by cytochrome P450 isoenzyme CYP2B6 and to a lesser extent by CYP3A4 [82].

Nevirapine clearance is significantly increased by rifampicin, resulting in a 58% decrease in minimum concentration of nevirapine. There is no change seen in steady state rifampicin AUC and the maximum concentration. It might be possible to overcome this by increasing the dose of nevirapine by 50% to 300 mg twice daily [91]. There are no safety data available for nevirapine at this dose. There are also no data for rifabutin/nevirapine interactions, but this interaction may not have significant effects in clinical practice.

Delavirdine trough levels are markedly reduced by rifabutin and rifampicin, both of which induce metabolism of delavirdine. With rifabutin there is a fivefold increase and with rifampicin a 27-fold increase in delavirdine clearance. In addition, the AUC of rifabutin is increased by 100% if it is coadministered with delavirdine. Thus, the probability of rifabutin-induced adverse reactions is increased [92,93]. Interestingly, in another study in which delavirdine was coadministered with rifabutin, dose increases of delavirdine to greater than 600 mg three times daily were required to produce similar effects to the conventional dose of 400 mg three times daily given to persons who were not taking rifabutin [94].

Twelve healthy volunteers receiving efavirenz in steady-state conditions were coadministered 600 mg rifampicin for 7 days. (It is important to note that the maximum enzyme-inducing ability of rifampicin may take longer than 7 days.) At this time, there was a mean decrease in maximum concentration of 20% and a 26% decrease in the AUC of efavirenz in 10 subjects; rifampicin metabolism was not affected [95]. An increase in efavirenz dosage was suggested when coadministered with rifampicin, but there are no safety data on this dosage adjustment. The provisional data on rifabutin 300 mg/efavirenz 600 mg interaction showed no significant effect of rifabutin on efavirenz pharmacokinetics but a decrease in rifabutin AUC by about 30%. The rifabutin dose may need to be increased by 50% if the drugs are to be used together with no change in efavirenz dosage [96].

Other interactions

NRTI

The NRTI didanosine, zalcitabine and stavudine may all produce peripheral neuropathy and thus there is potential for additive toxicity if isoniazid is coadministered. The mechanisms by which drug-induced toxicity occurs are different, but in clinical practice it may be difficult to ascertain which drug is responsible for peripheral neuropathy. Pyridoxine should routinely be given to patients receiving isoniazid [7]. Absorption of isoniazid is reduced by zalcitabine, and zalcitabine also increases the rate of clearance of isoniazid [86].

There is a theoretical interaction between abacavir and isoniazid. Both drugs may be metabolized by cytosolic enzymes. Isoniazid may act both as a substrate for alcohol dehydrogenase and induce uridine diphosphate glucorosyl transferase (UDPGT). Abacavir is metabolized by both ADH and UDPGT. An increase in plasma concentration of isoniazid and a decrease in abacavir concentration may occur if they are coadministered. However, because abacavir can be glucoronidated, this interaction is probably of little significance. Coadministration of protease inhibitors with isoniazid may result in greater potential for isoniazid-induced side-effects as a result of inhibition of isoniazid metabolism by the protease inhibitors.

Treating TB and HIV together

In patients with HIV infection who have TB, there is no doubt that the priority is to treat TB, especially in smear-positive cases where there is an important public health element involved. However, patients with TB can have antiretroviral therapy concomitant with their anti-TB therapy, but this needs to be managed very carefully. The role of drug levels of both antiviral and anti-TB drugs in patient management needs to be defined.

Patients should be managed and notified by physicians with experience in TB and who should work closely with colleagues who have the experience in using antiretroviral therapy. The best practice and most rapidly curative treatment for TB is short-course chemotherapy with rifampicin throughout. This also has the potential of reversing the deleterious effects of TB on HIV suggested by *in vitro* and *in vivo* studies [97]. Short-course therapy also has much the best quality and quantity of evidence to make it the gold standard.

Recommendations for treatment regimens of TB from best to worst would be as follows:

(1) standard short-course therapy with rifampicin throughout (Table 1) for 6 months;

(2) standard 2-month initial phase (rifampin, isoniazid, pyrazinamide, ethambutol); substitute rifabutin in continuation phase for 4 months;

(3) use rifabutin instead of rifampicin throughout (Table 3) for 6 months;

(4) standard 2-month initial phase and use non-rifamycin continuation phase for 6 months (Table 2); total length of regimen 8 months;

(5) non-rifamycin regimen used, but for 18 months.

(6) The centers for Disease Control and Prevention have suggested that for HIV-infected patients receiving protease inhibitors treatment for 9 months with streptomycin, isoniazid and pyrazinamide be considered as an alternative to regimens using rifamycins [98].

Because there have been few data collected regarding drug–drug interactions, we have divided suggestions for antiretroviral therapy concomitant with TB regimens into four possible levels of evidence. First is 'best practice', based on available data. Second is 'alternative to best practice', again based on available data. Third is 'theoretically possible', extrapolated from knowledge of class effects. The fourth level includes 'possible therapies with little data and cannot be recommended'. All of these recommendations and suggestions are unaffected by the use of twice or three times weekly regimens for TB.

Table 6. Tuberculosis treatment regimens and antiviral regimens.

TB regimen	Rifamycin used	Time (months)	Antiviral regimen
1	Rifampicin	1–6†	None Triple NRTI
2	Rifampicin	1–2	None Triple NRTI
	Rifabutin	3–6	Nelfinavir, indinavir, amprenavir efavirenz or Nevirapine*
3	Rifabutin	1–6	Nelfinavir, indinavir, amprenavir efavirenz or Nevirapine*
4	Rifampicin	1–2	None Triple NRTI
	None	3–8†	Any PI (e.g., saquinavir, ritonavir) Any NNRTI
5	None	1–18	Any PI Any NNRTI

*Theoretical based on class effect. †Some clinicians prefer to treat for longer periods. NRTI, Nucleoside reverse transcriptase inhibitor; PI, Protease inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor.

A patient who is HIV-positive who is on no antiretroviral therapy

If the risk of progression of the HIV disease is not thought to be significant within the next 6 months, then the patient should be given a rifampicin-based regimen throughout (regimen 1). If antiretrovirals are required after this there should be a proper washout period of 3 weeks after finishing anti-TB therapy.

If the patient is thought to require antiretroviral therapy for HIV disease because the risk of progression within the next 6–12 months is unacceptable, TB regimen (regimen 1) could be given with a triple NRTI combination with a change of antiviral therapy if needed after 6 months. Alternatively, a rifabutin-based regimen (regimen 3) for TB could be given and the patient could then be prescribed an indinavir, nelfinavir or amprenavir antiretroviral regimen with two NRTI. Finally, a NNRTI plus two NRTI could in theory be given if rifabutin was used throughout (TB regimen 3). The antiretroviral regimen could be changed after the TB treatment was completed.

A decision might be made that the risk of progression of HIV disease was intermediate, no antiretrovirals given until after 2 months and then started after 2 months, ensuring that the proper washout period was observed (TB regimen 2). Alternatively, a non-rifampicin-containing regimen could be given for 6 months after this initial 2 months (regimen 4). Finally, if it was decided to give antiretroviral therapy that interacted with rifampicin and rifabutin, then a non-rifampicin regimen would have to be used throughout, extending the period of treatment to about 18 months (regimen 5). However, this cannot be recommended.

Patients already on protease inhibitors who develop TB

The patient could stop the antiretroviral therapy for 6 months and a rifampicin-based regimen given (TB regimen 1) or the antiretroviral therapy could be stopped for 2 months and the rifampicin-based regimen given for the intensive phase, but the continuation phase could be one in which rifabutin or a non-rifampicin-based regimen could be given and protease inhibitor reintroduced (TB regimen 2 or 4). Much consideration would have to go into this sort of decision especially around the severity of the TB, viral load, set point, CD4 cell count and the monitoring of these surrogate markers [99]. If the patient is on indinavir, nelfinavir or amprenavir, they could be treated with a rifabutin-based regimen (TB regimen 3). A patient on saquinavir or ritonavir should swap protease inhibitors

to one of the above. Alternatively, patients on a protease inhibitor regimen could be changed to a triple NRTI regimen and given TB regimen 1 or 2. In theory they could be given a NNRTI-based regimen and rifabutin given as the basis of the anti-TB therapy. If they continued on saquinavir or ritonavir, then TB regimen 5 would have to be given.

Patients already on NNRTI

The antiviral drugs might be stopped or swapped to triple NRTI for 6 months and TB regimen 1 given. They could be stopped for the first 2 months and regimen 4 given. If rifabutin were used (regimen 3), delavirdine would have to be stopped and changed to efavirenz or amprenavir, nelfinavir or indinavir. If the patient was on nevirapine then this might also be changed but in theory could be continued.

Double protease inhibitor or protease inhibitor–NRTI combinations

These regimens have been increasingly used for so-called 'salvage'. Eighteen months non-rifamycin-based therapy would have to be given if the patient was on a double protease inhibitor combination of ritonavir–saquinavir or ritonavir–indinavir or nelfinavir–saquinavir and wanted to stay on that therapy (regimen 5). This cannot be recommended as good practice and alternatives (if any remain for individual patients) should be considered. All of these regimens, plus those such as efavirenz–indinavir and indinavir–nelfinavir, require drug–drug interaction studies to be performed before specific TB recommendations can be made.

Other compounds

There are no data for interactions with adefovir or hydroxyurea. These compounds would probably be little affected or unaffected by rifampicin.

Conclusions

The treatment of TB and HIV together is problematic and requires expert knowledge of anti-TB and antiretroviral therapy. Drug–drug interactions are complex and much more research is required to understand them. Antiviral therapy can be given to patients with TB, but the priority is to treat TB effectively. This requires more than prescribing the appropriate drug regimen, and issues around compliance and directly observed therapy, for example, are beyond the scope of this article, but may well apply to the use of both TB and antiviral therapy drugs. The role of drug level monitoring of anti-TB and protease inhibitors–NNRTI should be defined, because this may be a useful tool in the management of these patients. Because antiretrovirals are being used more and more, especially in developing countries, it is important that a treatment policy is developed that is based on evidence rather than theory or opinion.

Acknowledgements

The authors thank R. Heylen, specialist HIV/AIDS pharmacist at University College London, for helpful comments on the manuscript, and to C. Talbot for her perseverance in typing the manuscript.

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