

TUBERCULOSIS COMMENTARY

Issues in the Treatment of Active Tuberculosis in Human Immunodeficiency Virus–Infected Patients

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It is estimated that there are 14–15 million persons infected with HIV globally, and that nearly 6 million of these persons are also infected with *Mycobacterium tuberculosis*. The majority of persons co-infected with HIV and *M. tuberculosis* reside in poor countries, with most cases occurring in sub-Saharan Africa and South and Southeast Asia [1, 2].

In the developed world, the epidemic of co-infection with HIV and *M. tuberculosis* is of a lesser magnitude, but still significant. It has been estimated that 8% of the >750,000 HIV-infected persons in North America are also infected with *M. tuberculosis* [1, 2]. In the United States (and elsewhere), the incidence of HIV infection in patients with active tuberculosis is difficult to determine with accuracy because of incomplete HIV testing and reporting in persons with tuberculosis. However, recent data reported to the Centers for Disease Control and Prevention (CDC) indicate that in certain areas of the country, HIV co-infection is extremely common among young patients (ages 25–44 years) with active tuberculosis (table 1).

Although the focus of this article is the impact of HIV on the treatment and outcome of patients with tuberculosis, it is worth noting that tuberculosis seems to affect the natural history of AIDS in co-infected patients in a negative way, probably through direct stimulation of viral replication. Accelerated replication of HIV occurs both locally in the lung and systemically, as viral load studies have demonstrated. This increase in viral replication can be stimulated directly by *M. tuberculosis* and/or its cellular components [3–5].

The mortality rate for HIV-infected patients with tuberculosis is higher than that for HIV-infected patients without tuberculosis, even when matched for CD4⁺ cell count. This effect is dramatically accelerated in patients with multidrug-resistant tuberculosis (MDR-TB) [6–8]. The results of these studies imply strongly that effective treatment of tuberculosis will have

a beneficial effect on patients with AIDS, over and above cure of their mycobacterial infections.

Treatment of Tuberculosis in HIV-Infected Patients**Efficacy of Chemotherapy**

Early bacterial response and sputum clearance in AIDS patients with tuberculosis appear to be similar to those seen in non-HIV-infected patients [9]. However, questions remain regarding the relapse rate for AIDS patients treated for tuberculosis, and the optimal duration of therapy. Current American Thoracic Society guidelines allow 6 months of therapy in drug-susceptible disease but suggest treating for 6 months after culture conversion if the response to therapy has not been prompt [10]. Several studies have been published that address this issue.

Perriens et al. [11] reported that relapse rates among patients co-infected with HIV and tuberculosis in Zaire who were receiving 2 months of therapy with isoniazid, rifampin, pyrazinamide, and ethambutol followed by 4 months of therapy with isoniazid and rifampin, or 2 months of therapy with isoniazid, rifampin, pyrazinamide, and ethambutol followed by 10 months of therapy with isoniazid and rifampin, were 9% and 1.9%, respectively, compared with 5.3% in the HIV-negative control group treated for 6 months. Nearly all relapses were caused by isolates that were susceptible to all first-line agents, although restriction fragment length polymorphism (RFLP), or DNA fingerprinting, analysis to exclude reinfection was not performed as a part of this study. In addition, in the continuation phase of treatment, only half of the doses were observed. Furthermore, in the study by Perriens et al., there appeared to be less follow-up after completion of therapy in the 12-month group; therefore, the reported relapse rate of 1.9% might be somewhat of an underestimate of the true relapse rate at 24 months. Kassim et al. [12] reported that cure rates for using a standard 6-month short-course regimen in Côte d'Ivoire were ~87% for both HIV-infected and non-HIV-infected patients. Relapse rates at 18 months ranged from 3% to 7%, although relapses were not confirmed by culture in this study. Rather, relapses were defined as either a recurrence of smear-positive disease or clinical diagnosis of extrapulmonary tuberculosis following apparent cure. Chaisson et al. [13] reported no statis-

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Table 1. Prevalence of HIV infection among persons with tuberculosis, age 25–44 years, 1996.

Region	Percentage of HIV-infected persons with tuberculosis
District of Columbia	51.2
Florida	55.9
Louisiana	25.6
Maryland	29
Mississippi	16.7
Nevada	18.2
New York City	56.8
North Carolina	21.2
Tennessee	29.8
Utah	41.2

Data are from [50].

tically significant difference in relapse rates for HIV-infected compared with non-HIV-infected patients with tuberculosis who were treated with a standard 6-month regimen by directly observed therapy (DOT) in Haiti. It is notable that the mean CD4⁺ cell counts were somewhat higher in the study by Chaisson et al. than in the study of Perriens et al. Most recently, El-Sadr and colleagues [14] reported statistically identical (and low) relapse rates in HIV-positive patients randomized to a nearly fully intermittent, 6-month or 9-month regimen for the treatment of drug-susceptible tuberculosis.

The importance of ensuring adherence to therapy in patients with HIV infection and tuberculosis cannot be overstated. Compliance with self-administered therapy for tuberculosis is often extremely poor [15]. The impact of this poor adherence has dangerous consequences, both for individual patients and for the public health in general. Untreated or poorly treated tuberculosis is likely to result in increased morbidity and mortality, not only from mycobacterial disease but also from accelerated progression of AIDS, and disease can spread rapidly through vulnerable, immunocompromised populations when a source case remains infectious for a prolonged period. Outbreaks of multidrug-resistant tuberculosis associated with high mortality rates among patients with AIDS are testimony to this [8]. Fortunately, widespread implementation of programs of DOT has addressed these problems directly. Treatment completion rates in DOT programs routinely exceed 90%, and use of DOT in communities where tuberculosis is common leads to a decrease in the incidence of MDR-TB [16–18]. In addition, it is possible that once-daily antiretroviral therapy may be developed in the near future; therefore, combined DOT for tuberculosis and HIV infection may be feasible. DOT programs routinely provide incentives or enablers to increase adherence, although the effects of differing types and levels of incentives are not well characterized [19].

Risk Factors for Poor Survival

Several studies have indicated that there are several predictors of poor survival in HIV-infected patients with tubercu-

losis [7, 20, 21]. These predictors include low CD4⁺ cell counts, no DOT, the presence of MDR-TB, and a history of intravenous drug use. In addition, extrapulmonary tuberculosis has been associated with poor survival, perhaps because of delays in diagnosis.

Impact of Therapy with Protease Inhibitors on Tuberculosis Treatment in AIDS Patients

Highly active antiretroviral therapy (HAART), employing both the protease inhibitor (PI) class of drugs and the nonnucleoside reverse transcriptase inhibitors (NNRTIs), has come into wide use among HIV-infected individuals. Because of the risk of substantial drug interactions between the PI class of antiretrovirals and the rifamycins (in general, serum protease inhibitor levels are lowered substantially and rifamycin levels increase to 2–3 times the usual serum concentrations), significant concerns have been raised concerning the optimal therapy for both tuberculosis and HIV infection in HIV-infected patients who may be receiving or who would like to receive HAART. Several strategies are possible in this circumstance. The first is to simply abandon the use of rifamycins in HIV-infected patients with tuberculosis who are also receiving HAART. Treatment of tuberculosis in such instances would then proceed as if the patient had rifampin-monoresistant tuberculosis (see section on drug-resistant tuberculosis). Alternatively, since the extent and magnitude of the interaction between protease inhibitors and rifamycins seem least when either indinavir or nelfinavir is used in combination with rifabutin, one might substitute rifabutin (in a dosage as low as 150 mg/d) for rifampin and treat in an otherwise usual fashion. There is good support for the efficacy of rifabutin as an antituberculosis agent [22–25], although the drug has not been used extensively in patients concurrently receiving protease inhibitors (or the NNRTI delavirdine). Finally, one might choose to delay or interrupt HAART in patients with AIDS who develop tuberculosis so that the mycobacterial disease can be treated completely and effectively with a proven regimen. It is not likely that this strategy would be attractive in view of the obvious and substantial potential benefits of HAART to patients. Most current recommendations suggest that HAART be provided to all symptomatic HIV-infected patients, and AIDS patients with tuberculosis certainly fall into this category [26, 27].

Rifabutin Therapy for Tuberculosis in HIV-Infected and Non-HIV-Infected Patients

There is substantial evidence to indicate that rifabutin should be a clinically useful rifamycin in the treatment of patients with active tuberculosis [22–25]. The potential utility of rifabutin is supported by both laboratory and clinical studies. MICs for rifabutin are somewhat lower than those for rifampin, although early bactericidal activity appears slightly less.

Reports of three controlled trials of rifabutin in the treatment of tuberculosis have been published [23–25]. In a study of 520 randomized HIV-infected patients, Gonzalez-Montaner et al. [23] found equivalent culture conversion and treatment success rates for patients receiving rifabutin at a dosage of 150 mg/d or 300 mg/d as compared with those receiving standard rifampin-containing regimens. McGregor [24] found equal culture conversion and 24-month relapse rates in 225 non-HIV-infected patients randomized to either 2 months of therapy with isoniazid, rifabutin, pyrazinamide, and 3 months of ethambutol followed by 4 months of therapy with isoniazid and rifabutin and 3 months of therapy with ethambutol or 2 months of therapy with isoniazid, rifampin, pyrazinamide, and ethambutol followed by 4 months of therapy with isoniazid, rifampin, and ethambutol, where the daily dose of rifabutin was 300 mg. In a preliminary study of patients with AIDS, Schwander [25] studied 49 HIV-infected patients with tuberculosis who were randomized to either 2 months of therapy with isoniazid, rifabutin, pyrazinamide, and ethambutol followed by 4 months of therapy with isoniazid and rifabutin or 2 months of therapy with isoniazid, rifampin, pyrazinamide, and ethambutol followed by 4 months of therapy with isoniazid and rifampin. It is of interest that culture conversion at 2 months was 81% in the rifabutin group and 48% in the rifampin group. In all of these studies, treatment-limiting side effects of rifabutin were uncommon, particularly at a dosage of 150 mg/d.

Rifampin-Free and Rifampin-Minimal Regimens for Tuberculosis

Several trials have been reported, mostly conducted by the British Medical Research Council in the pre-AIDS era in Hong Kong or Africa, which provide some information about rifampin-free or rifampin-minimal regimens for treatment of tuberculosis (table 2). A small number of reports about the use of similar regimens in patients with AIDS have recently been published (table 3); most of these show very poor results with unacceptably high relapse rates in HIV-infected persons.

Of all the rifampin-free regimens that have been studied, the most potentially useful seems to be a program of isoniazid, pyrazinamide, and streptomycin given for 9 months on a daily, twice-weekly, or thrice-weekly schedule; this regimen achieves rapid sputum conversion and a relapse rate of 5% to 6%. This regimen has not been studied in HIV-infected patients [29].

Treatment of Drug-Resistant Tuberculosis in AIDS Patients

The most common pattern of drug resistance is that of resistance to isoniazid alone. For this type of resistance, however, a good outcome can be expected almost uniformly. Treatment for isoniazid-resistant tuberculosis in HIV-negative persons consists of rifampin, pyrazinamide, and ethambutol given for

6 months. This regimen should be effective in patients with HIV infection, although some physicians may prefer to extend treatment to 9 months for patients with risk factors suggestive of a poor outcome. The rifampin/pyrazinamide/ethambutol regimen has not been demonstrated to be effective when given on a fully intermittent basis, so at present daily administration seems most prudent. Some physicians choose to include isoniazid in the regimen for isoniazid-resistant tuberculosis if the MIC for isoniazid is $>0.1 \mu\text{g/mL}$ but $<1.0 \mu\text{g/mL}$. This strategy is based on the high achievable serum concentrations routinely seen with isoniazid administration, and also on the fact that at least one of the studies supporting rifampin, pyrazinamide, and ethambutol therapy for isoniazid-resistant tuberculosis did in fact retain isoniazid in the regimen [36]. However, there is no evidence to support including isoniazid in a regimen if the MIC for that drug is $>1.0 \mu\text{g/mL}$.

Rifampin is the most active of the first-line antituberculosis agents, and it is the cornerstone of all short-course chemotherapy regimens. Fortunately, rifampin-monoresistant tuberculosis is an uncommon clinical entity, although, when it does occur, it is usually in the setting of HIV infection [37, 38]. The reason for this is unclear, although it is possible that concurrent azole administration leads to selective reduction of serum concentrations of some antituberculosis drugs so patients may receive relatively unopposed rifampin for considerable periods. The treatment of rifampin-resistant tuberculosis is based on the same principles as the treatment of patients who are intolerant of the drug or unable to take it because of concurrent use of protease inhibitors. The shortest course of rifampin-free therapy for tuberculosis is obtained with a regimen of streptomycin, pyrazinamide, and isoniazid given on a daily or intermittent schedule for 9 months [28, 39]. There is no published experience with this regimen in AIDS patients, and it is unclear whether this regimen needs to be extended (to 12 months perhaps) in such cases. Alternatively, if injectable agents are to be avoided, a regimen based on isoniazid and ethambutol for 18 months (with perhaps the addition of a quinolone, although there are no data supporting increased effectiveness of the regimen with this class of drugs) has been shown to be effective therapy for tuberculosis in non-HIV-infected patients [40–42].

Several studies have demonstrated markedly decreased survival among AIDS patients with MDR-TB as compared with HIV-infected patients with drug-susceptible disease or non-HIV-infected patients with MDR-TB [7, 43]. However, it has been shown that survival can be improved by the rapid institution of the best available regimens within a few weeks of diagnosis of tuberculosis. There are no specific guidelines validated in clinical trials for the treatment of drug-resistant tuberculosis in patients with AIDS. In the absence of such guidelines, most clinicians follow guidelines for the treatment of drug-resistant tuberculosis in immunocompetent patients, although the duration of treatment is often longer in AIDS patients [44].

Table 2. Trials of rifampin-free or rifampin-minimal regimens for the treatment of tuberculosis in non-AIDS patients.

Reference	Location	Therapy regimen	Percentage of patients with relapse	DOT
[28]	Hong Kong	Stm + INH + PZA q.d./6 mo	18	Yes
		Stm + INH + PZA t.i.d./6 mo	24	Yes
		Stm + INH b.i.d./6 mo	21	Yes
		Stm + INH + PZA q.d./9 mo	5	Yes
		Stm + INH + PZA t.i.d./9 mo	6	Yes
		Stm + INH + PZA b.i.d./9 mo	6	Yes
[29]	Algeria	INH + Rif + PZA + Eth q.d./2 mo, then INH + Rif q.d./4 mo	3	No
		Stm + INH + Eth q.d./1 mo, then INH + Eth q.d./11 mo	17	No
[30]	East Africa	Stm + INH + Rif q.d./6 mo	2	Yes
		Stm + INH + PZA q.d./6 mo	11	Yes
		Stm + INH + T q.d./6 mo	22	Yes
		Stm + INH q.d./6 mo	29	Yes
		Stm + T + INH q.d./2 mo, then T + INH q.d./16 mo	4	No
[31]	East Africa	Stm + INH + Rif + PZA q.d./2 mo, then T + INH q.d./4 mo	13	Yes
		Stm + INH + Rif + PZA q.d./1 mo, then T + INH q.d./5 mo	8	Yes
		Stm + INH + Rif + PZA q.d./1 mo, then Stm + INH + PZA b.i.d./5 mo	9	Yes
		Stm + INH + Rif q.d./2 mo, then T + INH q.d./4 mo	18	Yes
		Stm + INH + Rif + PZA q.d./2 mo, then T + INH q.d./6 mo	0	6 mo only
		Stm + INH + Rif + PZA q.d./1 mo, then T + INH q.d./7 mo	7	6 mo only
		Stm + INH + Rif + PZA q.d./1 mo, then Stm + INH + PZA b.i.d./7 mo	2	6 mo only
		Stm + INH + Rif q.d./2 mo, then T + INH q.d./6 mo	6	6 mo only
[32]	India	Stm + INH + Rif + PZA q.d./2 mo, then INH + Rif q.d./4 mo	5.9	?
		Stm + INH + PZA + Cpx q.d./2 mo, then INH + Cpx q.d./4 mo	16.6?	

NOTE. Cpx = ciprofloxacin; DOT = directly observed therapy; Eth = ethambutol; INH = isoniazid; PZA = pyrazinamide; Rib = rifabutin; Rif = rifampin; Stm = streptomycin; T = thioacetazone.

New Agents of Potential Utility in the Treatment of HIV-Associated Tuberculosis

Antibiotics

The quinolones are widely used in the treatment of MDR-TB, in both HIV-infected and non-HIV-infected patients, although few studies provide solid data regarding the true efficacy of these agents and their place in the treatment of tuberculosis (either drug-susceptible or resistant). A small study by Mohanty and Dhamgaye [32] of HIV-negative patients in which ciprofloxacin was substituted for rifampin was associated with a high relapse rate. Kennedy et al. [45] compared 6 months of isoniazid, rifampin, pyrazinamide, and ethambutol with 4 months of isoniazid, rifampin, and ciprofloxacin, followed by 2 months of isoniazid and rifampin in HIV-infected

and non-HIV-infected patients and found slower culture conversion and higher relapse rates in the ciprofloxacin-containing regimen. These results were more pronounced in the HIV-infected patients. More recently, El-Sadr and colleagues [14] found no benefit to adding levofloxacin to a standard regimen in the treatment of drug-susceptible tuberculosis in HIV-infected patients. Although in vitro studies suggest that newer quinolones such as ofloxacin, levofloxacin, and sparfloxacin have greater antituberculous activity than ciprofloxacin, there are no clinical data that support the substitution of a quinolone for a rifamycin as a first-line agent in the treatment of tuberculosis.

Immunomodulating Agents

INF- γ is capable of activating macrophages in a variety of ways and has been shown to produce clinical improvement

Table 3. Trials of non-rifampin-free or rifampin-minimal regimens in the treatment of tuberculosis in HIV-infected patients.

Reference	Location	Therapy regimen	Percentage of patients with relapse/HIV status
[33]	Zaire	Stm + T + INH q.d./2 mo, then T + INH q.d./10 mo	18/HIV+ 6/HIV-
[34]	Zambia	Stm + T + INH q.d./2 mo, then T + INH q.d./10 mo	19/HIV+
		Stm + T + INH + Rif + PZA q.d./2 mo, then T + INH q.d./6 mo	31/HIV+
[35]	Kenya	Stm + T + INH q.d./2 mo, then T + INH q.d./10 mo	18.3/HIV+ 1/HIV-
[35]	Kenya	Stm + INH + Rif + PZA q.d./2 mo, then T + INH q.d./6 mo	11/HIV+ 0/HIV-

NOTE. None of the patients underwent directly observed therapy. INH = isoniazid; PZA = pyrazinamide; Rif = rifampin; Stm = streptomycin; T = thioacetazone.

when administered systemically to non-AIDS patients with disseminated *Mycobacterium avium* complex (MAC) infections [46]. Recently, Condos et al. [47] reported on the administration of IFN- γ via aerosol to five patients with refractory MDR-TB; one patient was HIV positive [47]. The drug was well tolerated and was associated with weight gain, radiographic improvement, and improvements in sputum smear status in all patients.

Thalidomide is an inhibitor of TNF- α production and has recently been given to a group of HIV-infected and non-HIV-infected patients with tuberculosis [48]. Levels of IFN- γ increased after treatment, stimulated TNF production decreased, serum TNF levels fell, and weight gain was enhanced during thalidomide treatment.

In addition, pentoxifylline is an inhibitor of TNF synthesis, and also blocks the effect of this cytokine on target cells. In a randomized trial in 107 HIV-infected patients with tuberculosis in Uganda, there were trends toward decreased TNF levels and improved performance status, although there was no improvement in body mass, CD4⁺ cell count, or overall survival [49]. Immunomodulating therapies may be useful adjuncts in the treatment of HIV-associated tuberculosis, but only in the earliest stages of clinical evaluation.

Summary

Most HIV-infected patients with tuberculosis can be treated satisfactorily with standard regimens with expectations of good results. Treatment of tuberculosis in these patients has been complicated by the introduction of HAART, which relies on drugs that interfere with the most potent class of antituberculous medications. Rifampin-free regimens or regimens that employ rifabutin may be acceptable strategies for patients who are receiving protease inhibitors, although these regimens have not been rigorously evaluated in patients with AIDS. At present, there is good reason to believe that a 6-month course of

a rifabutin-containing regimen or a 9–12-month course of a regimen of streptomycin, isoniazid, and pyrazinamide should be adequate therapy for most patients with drug-susceptible disease. As the treatment of HIV infection with antiretroviral agents evolves, the treatment of tuberculosis in patients with AIDS is likely to evolve as well. This will require careful coordination of antituberculosis and antiretroviral therapies.

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