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Treatment Options for HIV-Associated Tuberculosis

Philip Chukwuka Onyebujoh[1], **Isabela Ribeiro**[1], and **Christopher Curtis Whalen**[2]

[1]United Nations Children's Fund/United Nations Development Programme/World Bank/World Health Organization Special Programme for Research and Training in Tropical Diseases (TDR), Geneva, Switzerland [2]Tuberculosis Research Unit, Department of Epidemiology and Biostatistics, Case Western Reserve University, Cleveland, Ohio

Abstract

The vicious interaction between the human immunodeficiency virus (HIV) infection and tuberculosis (TB) pandemics poses special challenges to national control programs and individual physicians. Although recommendations for the treatment of TB in HIV-infected patients do not significantly differ from those for HIV-uninfected patients, the appropriate management of HIV-associated TB is complicated by health system issues, diagnostic difficulties, adherence concerns, overlapping adverse-effect profiles and drug interactions, and the occurrence of paradoxical reactions after the initiation of effective antiretroviral therapy. In this article, recommended treatment strategies and novel approaches to the management of HIV-associated TB are reviewed, including adjuvant treatment and options for treatment simplification. A focused research agenda is proposed in the context of the limitations of the current knowledge framework.

As HIV-related immunosuppression increases, the clinical pattern of tuberculosis (TB) changes, with increasing numbers of smear-negative pulmonary TB and extrapulmonary TB cases [1]. TB is more likely to be disseminated and more difficult to diagnose as immunosuppression progresses. HIV-infected patients with TB also have increased morbidity due to other HIV-related diseases. The appropriate management of HIV-associated TB creates special challenges to diverse sectors within countries affected by the dual pandemic of HIV/AIDS and TB.

TREATMENT OF HIV-ASSOCIATED TB

Current recommended treatment of TB

With few exceptions, current recommendations for the treatment of HIV-associated TB are the same as those for the treatment of TB in HIV-uninfected adults [1]. The modern treatment strategy for TB is based on standardized short-course chemotherapy (SCC) regimens and proper case management to ensure completion of treatment and cure. Standardized treatment is a component of the TB control policy package, as set forth in the World Health Organization (WHO) expanded framework for effective TB control [2], and of the internationally recommended strategy for TB control known as "DOTS" (a term derived from "directly observed therapy, short-course" but no longer an acronym; it is used to describe a broader WHO public health strategy for TB control).

Reprints or correspondence: Dr. Philip Chukwuka Onyebujoh, United Nations Children's Fund/UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases, Centre Casai, Geneva, Switzerland (onyebujohp@who.int).

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The aim of TB treatment is to achieve cure, to prevent death and relapse, and to render patients noninfectious as rapidly as possible, as well as to prevent the emergence of drug resistance. Anti-TB agents are, therefore, selected (1) to kill the actively metabolizing bacilli in the cavities, (2) to destroy less actively replicating bacilli in the acidic and anoxic closed lesions, and (3) to kill near-dormant bacilli that might otherwise cause a relapse of the disease [3,4]. The most effective agents for the destruction of tubercle bacilli in the 3 categories described above are, respectively, isoniazid, pyrazinamide, and rifampin.

These 3 agents form the basis of modern regimens, which are divided into an initial 2-month intensive phase involving all 3 agents and, in most regimens, a fourth agent, which is usually ethambutol [4]. These agents destroy almost all bacilli in the 3 physiological categories during the initial intensive phase of treatment. This phase is followed by a continuation phase, usually a 4-month course of rifampin and isoniazid, to eliminate residual dormant bacilli and prevent the emergence of rifampin-resistant mutants.

The regimens recommended by the WHO [5] for 4 categories of patients are listed in table 1. In practice, the majority of patients are in category I. Six-month regimens with rifampin throughout are preferable.

Rifampin-based treatment regimens

There is now consensus that TB treatment regimens containing rifampin for the entire treatment period have better outcomes than do those including rifampin only for the initial 2 months. Studies performed in Africa and Singapore in the 1970s documented 2-year relapse rates of 0%–3% after receipt of 6 months of treatment with a regimen containing rifampin for the entire treatment period [6,7]. Other studies performed in Africa and in Madras, India, in 1972, 1974, and 1997 showed 2-year relapse rates of 7%–18% after receipt of 6 months of treatment with rifampin used only in the initial phase [8–10]. A large, multicenter study published by the International Union Against Tuberculosis and Lung Disease in 2004 [11] confirmed that a regimen including rifampin throughout was, for all outcomes, superior to regimens that included rifampin only in the intensive phase. This study demonstrated similar treatment response rates between HIV-infected and HIV-uninfected patients with TB receiving SCC. Another study, by Okwera et al. [12], further validates the superiority of rifampin over the ethambutol-containing regimens used throughout the course of SCC. A study in Malawi involving patients with sputum smear–negative pulmonary TB reported a higher case-fatality rate (CFR) among HIV-infected patients (59%) than among HIV-uninfected patients (26%). Furthermore, the CFR among sputum smear–positive patients who were HIV infected was 18%, whereas that among HIV-uninfected patients was 10%. Notably, among HIV-infected patients with TB, mortality was shown to be higher among patients receiving the regimen without rifampin [13].

The main remaining issues relate to the use of intermittent dosing of anti-TB medications and the length of treatment for HIV-associated TB. Existing guidelines regarding these issues have evolved from limited data and expert opinion.

With regard to intermittent dosing, the guidelines from the American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America contraindicate the use of isoniazid and rifapentine once weekly in the continuation phase in individuals with HIV/AIDS, because of a high rate of relapse and an increased rate of acquired resistance to rifamycins [14]. Among HIV-infected patients with advanced immunosuppression treated with twice-weekly rifampin- or rifabutin-based regimens, an increased rate of acquired rifampin resistance—often monodrug resistance—has also been noted [15,16]. Hence, current recommendations are to treat patients who have CD4 cell

counts <100 cells/mm^3 with daily or 3-times-weekly treatment for at least the first 2 months of intensive therapy.

Current recommendations for the duration of TB treatment among individuals with HIV/AIDS are for standard 6-month regimens and the extension of therapy to 9 months for patients with extrapulmonary disease or a delayed response [17]. A review of 6 studies of HIV-infected patients with TB and 3 studies of HIV-uninfected patients with TB with a similar duration of treatment with rifampin-containing regimens (6 months) showed cure rates of 59%–97% among HIV-infected patients, compared with 62%–88% among HIV-uninfected patients. In addition, successful treatment rates of 34%–100% were seen among HIV-infected patients with TB, compared with 91%–99% among HIV-uninfected patients, and relapse rates of 0%–10% were seen among HIV-infected patients, compared with 0%–3% among HIV-uninfected patients [18]. Furthermore, a recent randomized clinical trial compared 2 WHO-recommended 8-month regimens of ethambutol and isoniazid (2 months of daily treatment with ethambutol, isoniazid, rifampin, and pyrazinamide, followed by 6 months of treatment with isoniazid and ethambutol [2EHRZ/6HE] vs. 2 months of 3-times-weekly treatment with the same intensive-phase regimen, followed by 6 months of treatment with isoniazid and ethambutol [2{EHRZ}$_3$/6HE]) against a 6-month standard regimen in 1355 patients with newly diagnosed smear-positive pulmonary TB. At 2 months after treatment initiation, a significantly higher proportion of patients assigned to receive the daily intensive-phase regimen, compared with those assigned to receive the 3-times-weekly regimen, were culture negative (700 [85%] of 828 patients vs. 333 [77%] 433 patients; $P = .001$). At 12 months after the end of chemotherapy, both 8-month regimens were significantly inferior to the control 6-month standard regimen [11].

The role of rifabutin

Rifabutin—like rifampin—is a bactericidal antibiotic that inhibits DNA-dependent RNA polymerase activity in susceptible cells. It is well absorbed when taken orally and is distributed widely in body tissues and fluids, including the cerebrospinal fluid. It is metabolized in the liver and eliminated in bile and, to a much lesser extent, in urine, but dose adjustments are unnecessary with renal insufficiency [19]. Although rifabutin is structurally similar to rifampin, there are important pharmacokinetic differences between the 2 drugs. Rifabutin is more lipid soluble than is rifampin, which results in more-extensive tissue uptake, a larger volume of distribution, lower maximum plasma concentrations, lower trough concentrations, a longer terminal half-life, higher tissue-to-plasma drug concentration ratios, low protein binding, and minimal cytochrome P-450 3A induction [19–21]. In consequence of the latter, rifabutin can be used with certain protease inhibitors (PIs) or nonnucleoside reverse-transcriptase inhibitors (NNRTIs) (other than delavirdine) and has fewer problematic drug interactions than does rifampin. Adjustments in rifabutin dose or elements of the ART regimen might be necessary with certain combinations [22–24].

The available clinical data are encouraging. Rifabutin and rifampin have been shown to have similar time to smear conversion and relapse rates at 24 months from the initiation of treatment [25]. As with rifampin, lower plasma concentrations of rifabutin have been associated with acquired rifamycin resistance–associated failure or relapse in patients with TB and HIV infection treated with twice-weekly therapy [26]. The risk for acquired rifamycin resistance among HIV-infected persons with TB does not seem to depend on the rifamycin used but, rather, on the rifampin dosing schedule in the intensive phase of treatment [26,27].

One important hurdle for wider adoption of rifabutin in TB treatment has recently been removed. The initial patent for rifabutin was filed in June 1975. The drug came out of patent

in 2000 and 2001 in the United States and Europe, respectively [28], and can now be developed as a generic drug for use in resource-limited settings at lower costs.

At present, it remains to be determined whether rifabutin is a better option than rifampin for HIV-infected patients with TB who are at different stages of immunosuppression. It is unclear whether rifabutin use is associated with more-frequent immune reconstitution syndromes and what the impact and feasibility of treatment with rifabutin under programmatic conditions in resource-constrained settings would be.

CONCOMITANT TB/HIV INFECTION MANAGEMENT ISSUES

Managing HIV-infected patients with TB poses a challenge that extends beyond the boundaries of drug-based treatment, through health system considerations, including access to diagnoses and care facilities and the complexity of concurrent and timely use of both anti-TB and highly active antiretroviral therapy(HAART) medications under current routine program conditions in disease-endemic settings in resource-constrained countries. These issues are discussed elsewhere in this supplement [24,29].

When to initiate antiretroviral therapy (ART)

There is an array of recommendations on the timing of initiation of ART in patients with TB and HIV coinfection (summarized in table 2) [31–35]. In a consensus-building exercise, 2003 WHO guidelines for scaling up ART access in resource-limited settings recommended that, until more information is available, ART should be initiated in patients with TB if there is a very high risk of HIV disease progression and mortality [37]. This would occur mainly in patients with TB who have a CD4 cell count <200 cells/mm^3 and who fulfill criteria for WHO stage 4 HIV disease. Revisions of these guidelines to accommodate the experience gained in clinical use of ART were published at the end of 2003 (see table 3) [36], with further modifications considered. However, the absence of large, randomized, controlled clinical trials conducted in high-burden countries to define the patient population that would most benefit from HIV therapy limits the wider applicability of these recommendations and the degree of confidence with which they can be utilized by national programs in areas with high HIV prevalence.

Importantly, the current guidelines may represent “late initiation” of treatment. In sub-Saharan Africa, ~30% of HIV-infected patients with TB die within 12 months of initiating TB treatment [11], and up to 40% of these deaths occur during the first month of TB treatment. A review of 47 prospective studies of recurrence after cure of pulmonary TB to assess the influence of HIV/AIDS and rifampin treatment revealed that the recurrence rate among HIV-uninfected persons increased with decreasing duration of therapy [38]. In countries where HIV infection is endemic, TB recurrence may be reduced by administration of rifampin-based treatment for at least 6 months, in accordance with WHO recommendations [36]. On the basis of this information, early initiation of HAART among patients with TB receiving anti-TB drugs may reduce TB-associated mortality at the end of the 6 months of SCC, with accompanying reductions in relapse and reinfection.

A careful retrospective study [39] performed in the United Kingdom, evaluating the risks and benefits of administering HAART during the treatment of TB in 188 HIV-infected patients, recommended an early initiation of HAART in patients with advanced HIV disease (CD4 cell count, $<100 \times 10^6$ cells/ L). However, in clinically stable patients with CD4 cell counts $>100 \times 10^6$ cells/L, the initiation of HAART may be delayed until the continuation phase of TB treatment. Although the use of HAART led to significant reductions in viral load, AIDS-defining illness (3.5% vs. 24.5% of patients developing AIDS-defining illness; relative risk, 0.14), and mortality, coinfected patients commonly experienced adverse events

leading to interruptions in HAART and/or TB treatment. Adverse events occurred in 99 (54%) of 183 patients, one-third of whom changed or interrupted HAART and/or TB treatment [39].

In some cases, concomitant regimens of HAART and TB treatment may precipitate paradoxical reactions [40]. Therefore, some clinicians decide to withhold the use of HAART until the completion of the intensive phase of TB treatment [24].

Another retrospective cohort study was conducted in Thailand, involving ART-naive HIV-infected patients who presented with active TB and CD4 cell counts <200 cells/mm^3. All patients were naive to ART at the time of TB diagnosis and began receiving HAART during TB treatment [41]. Of the 29 patients studied (median CD4 cell count, 74 cells/mm^3 [range, 23–178 cells/mm^3]; median HIV RNA level, 229,000 copies/mL [range, 26,100–750,000 copies/mL]), 18 patients were cured, 8 completed treatment, 2 interrupted treatment, and 1 died of cytomegalovirus encephalitis. There was neither occurrence of new opportunistic infection nor relapse of TB in the 26 patients who completed 72 weeks of follow-up.

In a pilot study conducted in an urban TB clinic in South Africa, 20 HIV-infected patients with TB received once-daily HAART administered concomitantly with standard TB treatment. Seventeen patients completed combined standard TB and HIV therapy; 16 (80%) of the 20 enrolled patients, and 15 (88%) of 17 patients completing standard TB treatment achieved a viral load <50 copies/mL and a mean CD4 cell count increase of 148 cells/mm^3. TB was cured in 17 (85%) of 20 enrolled patients and in 17 (89%) of 19 of patients with drug-susceptible TB. Treatment was well tolerated, with minimal gastrointestinal, hepatic, cutaneous, or neurological toxicity [42].

In another study conducted in South Africa, it was shown that late initiation of ART (at a CD4 cell count of <200 cells/ mm^3 or during WHO stage 4 HIV disease) is associated with a high incidence of TB in ART programs. Although the reduction in TB incidence during ART is dependent on CD4 cell count, this study shows that, after 3 years of treatment, TB incidence among HIV-infected patients remains higher (5- to 10-fold) than that among HIV-uninfected individuals [43].

Dheda et al. [44], in a retrospective study conducted in the United Kingdom, reported that the use of HAART in coinfected patients results in a marked reduction in both mortality and the development of new AIDS-defining illnesses. In contrast, coinfected patients with a CD4 cell count <100 cells/mm^3 have a higher mortality rate or incidence of new AIDS-defining illnesses during the intensive phase of TB treatment.

In essence, the optimal timing of initiation of ART in patients with TB and HIV infection remains a controversial issue. Clinical trials are needed to clarify how the timing of ART affects the interplay of competing risks of HIV disease progression and drug toxicity profiles, adherence concerns, and immune re-constitution syndrome. Currently, there are no randomized, controlled clinical trials demonstrating TB treatment outcomes in HIV-infected patients with TB in countries where both diseases are endemic.

Selection of ART regimens

The discussion here will be limited to the WHO-recommended first-line ART regimens that can be concomitantly used with TB treatment (e.g., rifampin) throughout [45]. The current state of knowledge regarding the management of HIV-infected patients with TB focuses on the use of regimens (for the treatment of both diseases) that, to the best of our knowledge, are compatible in terms of their drug-drug interaction profiles. The WHO-recommended management of advanced HIV disease in patients who have severe TB is to initiate TB

treatment and, after 2 weeks, to initiate efavirenz-containing ART. The drawback to this approach is that the use of efavirenz is limited to male patients and to women who are not of childbearing potential or who are not pregnant. A further limitation is that, for patients for whom first-line treatment fails, the current TB chemotherapy regimen is incompatible with second-line ART regimens, which include PIs. There is an acute need to develop a TB treatment regimen that is compatible with the available second-line HAART regimen for wider populations than male patients [45]

Adherence issues

Adherence remains one of the key determinants of virological and CD4 cell count responses [46–49] and survival [50] among individuals living with HIV/AIDS. Studies have shown that missing as few as 2%–5% of scheduled doses leads to treatment failure in a high percentage of cases. As with HIV therapy, adherence to TB treatment is critical to treatment success [51,52]. Poor treatment compliance can promote the development of multidrug-resistant TB.

Despite recent improvements and simplification of combination ART and TB treatment regimens, adherence to any long-term therapy remains a challenge. Adherence to ART has been shown to decrease with increased complexity of the regimen and increased pill burden [53,54].

Although there are no published studies on the impact of TB treatment on the adherence to ART, pilot projects have been initiated to examine the impact of directly observed therapy (DOT) among HIV-infected individuals with and without TB [55]. In one study, the average HIV RNA level among patients receiving DOT was significantly lower than that among those not receiving DOT [56]. A small DOT program for HIV-infected individuals with a history of poor adherence revealed a significant reduction in plasma HIV RNA levels among those who remained in the program [57].

Studies of adherence among individuals living with HIV/ AIDS suggest the importance of the assessment and promotion of readiness to begin ART [58]. There is a well-recognized need to evaluate ways to broaden DOT to include more effective strategies for providing adherence support, including interventions to improve readiness to initiate treatment and assessment of psychological factors and social issues—for example, poverty, homelessness, and substance abuse—that are commonly present among patients with HIV-associated TB.

TREATMENT-SHORTENING STRATEGIES

Treatment-shortening approaches have the potential to decrease the incidence of adverse effects, improve patient compliance, and slow the spread of the disease and the development of multidrug-resistant strains of *Mycobacterium tuberculosis*. In recent years, a great deal of attention has been generated by the quinolone antibiotics, following the publication of clinical and preclinical studies confirming their potential for use in the treatment of TB.

Results of a successful treatment-shortening study conducted in India, in which ofloxacin was used in a 4-month regimen, were encouraging [59]. In this study, patients received a 3-month treatment regimen consisting of daily isoniazid, rifampin, pyrazinamide, and ofloxacin, followed by 1 or 2 months of twice-weekly isoniazid and rifampin, with cure rates of 92%– 98% and low relapse rates (2%–4%). The confidence limits for the relapse rates were, however, wide, and there was no 4-month control regimen of standard treatment without ofloxacin as a control. In experimental murine TB, moxifloxacin has shown sterilizing activity [60], whereas ofloxacin has not.

Gatifloxacin and moxifloxacin are particularly active, having MIC_{90} values of 0.031 mg/mL and 0.125 mg/mL, respectively, compared with 1 mg/mL for levofloxacin [61]. By use of a murine model that mimics treatment in humans, it was found that addition of moxifloxacin to the standard isoniazid, rifampin, and pyrazinamide regimen had only a modest effect on bactericidal activity and did not result in an improved rate of tissue sterilization. In a study by Burman et al. [62], it was also shown that the addition of moxifloxacin to isoniazid, rifampin, and pyrazinamide had no effect on the proportion of patients with negative sputum culture results at the end of 2 months of SCC. However, when moxifloxacin was substituted for isoniazid in the standard regimen, the time to sterilization was reduced by 2 months [63]. It is not clear whether this dramatic effect is due to synergy between moxifloxacin, rifampin, and pyrazinamide or relief from antagonism between isoniazid and rifampin.

Clinical studies are now ongoing to evaluate the efficacy and safety of new combinations, containing gatifloxacin and moxifloxacin. A phase 2 trial was recently concluded by the South African Medical Research Council in Durban, South Africa, in patients with TB and HIV coinfection [64]. The standard WHO-recommended treatment was compared with 2 other similar regimens that contained either ofloxacin or moxifloxacin. Treatment with either the gatifloxacin- or moxifloxacin-containing regimen was shown to be significantly more efficaceous than either the standard 6-month regimen (2 months of ethambutol, rifampin, isoniazid, and pyrazinamide, followed by 4 months of isoniazid and rifampin [2ERHZ/4HR]) or an ofloxacin-containing regimen (the same regimen, with ethambutol replaced by ofloxacin [2ORHZ/4HR]) after 2 months of treatment. Currently, a phase 3 clinical trial is ongoing to evaluate the efficacy and safety of gatifloxacin-containing TB treatment in a mixed population of HIV-infected and -uninfected patients with TB. Other novel anti-TB agents, such as nitromidazole (PA-824), quinolizines, and dihydroimadazo-oxazole, show potent in vitro activity against *M. tuberculosis* and show promise in shortening the length of therapy used in combination regimens [65].

ADJUNCTIVE THERAPY

Cotrimoxazole

In recent years, abundant data have accumulated on the benefits of adjunctive therapy with cotrimoxazole for patients with TB and HIV coinfection. In a placebo-controlled study performed in Côte d'Ivoire [66], 771 HIV-infected patients with TB were treated with daily cotrimoxazole, which resulted in a significant decrease in mortality and the number of hospital admissions. In a subsequent study performed in Malawi [67], among 717 patients with TB, the overall CFR fell from 37% to 29%—that is, for every 12.5 patients with TB treated, 1 death was averted. CFRs were unchanged over a period of 2 years among HIV-uninfected patients but fell among HIV-infected patients, from 43% to 24%. Improved survival became apparent after the first 2 months and was maintained beyond the end of treatment. In a large study in Uganda [68], an area with high rates of bacterial resistance to cotrimoxazole, the effect of such prophylaxis on morbidity, mortality, CD4 cell count, and viral load was evaluated among people with HIV infection. Cotrimoxazole prophylaxis was associated with a 46% reduction in mortality (hazard ratio, 0.54 [95% CI, 0.35–0.84]; $P = .006$) and the number of hospital admissions (hazard ratio, 0.69 [95% CI, 0.48–0.98]; $P = .04$). The annual rate of decline in CD4 cell count was lower during prophylaxis than before prophylaxis (77 vs. 203 cells/mm^3; $P < .0001$), and the annual rate of increase in viral load was lower (0.08 vs. 0.90 $\log_{10}$ copies/mL; $P = .01$). The effect on mortality was seen only among patients with CD4 cell counts <200 cells/mm^3 or with WHO stage 3 or 4 HIV disease, but the reductions in morbidity were seen among all HIV-infected patients. Additional studies corroborated these findings and the feasibility of implementing cotrimoxazole therapy within a TB control program [69,70].

Despite these findings, the routine application of cotrimoxazole in developing countries, particularly in sub-Saharan Africa, has been limited despite provisional recommendations from the WHO and the Joint United Nations Programme on HIV/AIDS. The interim policy on collaborative TB/HIV activities promotes cotrimoxazole use among individuals living with HIV/AIDS who have TB. A number of priority areas for research have been identified, which are discussed below [71].

Micronutrient Supplementation

Micronutrient supplements (vitamins, trace elements, and combinations of these) are simple, affordable public health interventions for which sound scientific evidence of effectiveness and safety are still lacking. A recent Cochrane meta-analysis demonstrated the current lack of conclusive evidence showing that micronutrient supplementation effectively reduces morbidity and mortality among HIV-infected adults [72]. The single exception is vitamin A supplementation in children, for which there is evidence of decreased mortality among HIV-infected children from a large placebo-controlled trial in Uganda [73]. The long-term clinical benefits, adverse effects, and optimal formulation of micronutrient supplements require further study.

Immunomodulation

Mounting evidence from clinical studies supports a concept of copathogenesis of TB and HIV infection, in which immune activation triggered by TB and mediated by cytokines stimulates viral replication and worsens HIV infection, especially when immune function is preserved [74]. Immunomodulators—including corticosteroids, therapeutic vaccines, and other drugs and biologics—have the potential to shorten TB treatment by modulating the host response and helping the immune system to eliminate persistent organisms. Immunotherapy is a novel approach to treatment shortening. Strategies studied to date in mouse models have been found to reduce the Th2 inhibitory effect on the protective Th1 response—either by inhibiting interleukin-4 production or by down-regulating the Th2 response. Studies in South Africa aimed at determining the effect of *Mycobacterium vaccae* immunotherapy showed no benefit when such therapy was added to standard TB chemotherapy [75].

In addition to treatment shortening, treatment outcomes might be improved by immunomodulation, using existing treatment protocols. The current understanding of severe TB is that the host inflammatory response induces pathology that contributes to mortality. The use of novel immunomodulators or adjunctive corticosteroids could down-regulate this response, with potentially superior treatment outcomes.

Tumor necrosis factor (TNF)–α antagonists and inhibitors—TNF, an important inflammatory mediator in TB, has been implicated in causing accelerated HIV disease progression in individuals with HIV-associated TB [76,77]. However, TNF blockade, particularly by monoclonal antibody, has been associated with the reactivation of latent *M. tuberculosis* infection by the impairment of mycobacterial immunity [78,79]. A number of different TNF-α antagonists and inhibitors, including pentoxyfilline, etanercept, and thalidomide, have been tested, with disappointing results. Minimal clinical benefits have been documented with these compounds, associated with clinically insignificant reductions in HIV RNA levels [80–82].

Corticosteroids—Corticosteroids, notably prednisolone, are also known to effectively suppress TNF-α. A 2003 systematic review of 11 clinical trials compared the outcomes of 1814 patients with moderate to severe active TB who used corticosteroids in conjunction with other therapy [83]. Although corticosteroids did not improve the rate of sputum

sterilization, they did provide broad and significant clinical benefits, such as earlier improvement in symptoms, increased weight gain, and more rapid resolution of lung infiltrates. Such benefits also were noted in patients with cavitary disease. Additional studies are clearly warranted to define the role of prednisolone in the adjuvant treatment of TB and HIV infection.

COLLABORATIVE ACTIVITIES BETWEEN TB AND HIV/AIDS CONTROL PROGRAMS

Because of the escalating burden of TB and HIV infection in affected populations, there is a need to establish collaborative activities between programs addressing the 2 diseases. The Stop TB Department and HIV/AIDS Department of the WHO identified an urgent need for joint strategic planning to facilitate the collaboration of TB and HIV/AIDS programs. A useful summary of the recommended collaborative activities is provided in the Appendix [71].

RESEARCH PRIORITIES

The Second Global Plan to Stop TB (2006–2015) has recently been published [84]. In this document, it is acknowledged that more than a decade of DOTS in countries with varied characteristics has offered 2 distinct lessons: (1) DOTS is central to TB control, but (2) the original 5 elements of DOTS are not enough to control TB globally, especially in settings of high HIV infection prevalence. The sixth element of the draft of the WHO-recommended Stop TB Strategy, which underpins the Global Plan, is to enable and promote research to improve program implementation and to develop new drugs, diagnostics, and vaccines.

In February 2005, an expert consultation meeting, convened by the Stop TB Department of the WHO, was held to define the TB/HIV research priorities in resource-limited settings [85]. The discussion of the recent Scientific Working Group on TB research convened by the Special Programme for Research and Training in Tropical Diseases, affirmed the WHO TB/HIV working group and expert consultation recommendations.

Among the specific issues related to the treatment of patients with TB and HIV coinfection that demand evaluation, we would like to highlight the following questions:

- Why does treatment fail despite good compliance to prescribed medications?
- How do we avoid poor treatment outcomes, especially in patients with TB and HIV coinfection?
- Why are HIV-infected patients with TB prone to the development of rifampin monoresistance?
- How do we effectively treat HIV-infected patients with TB to reduce mortality and relapse?
- Do concomitant and “early” ART and SCC improve survival and treatment outcomes among HIV-infected patients with TB?
- Does rifabutin offer a better option than rifampin for patients with HIV-associated TB?
- Is rifabutin use associated with more frequent immune reconstitution syndrome?
- What would be safe and effective second-line ART regimens for dually infected women?

- Can the use of moxifloxacin or gatifloxacin shorten TB treatment, especially among HIV-infected patients with TB?
- Can a moxifloxacin- or gatifloxacin-driven shortened TB treatment regimen be used concomitantly with ART among HIV-infected patients with TB?
- What is the role of cotrimoxazole in the context of ART?
- Are there clinical or nonlaboratory criteria to guide the decision to stop cotrimoxazole prophylaxis?
- What are the criteria for treatment with cotrimoxazole in patients with TB and HIV coinfection?
- What are the best delivery strategies to improve the uptake of cotrimoxazole prophylaxis?
- What is the role of TNF-α inhibitors/antagonists in the treatment of HIV-associated TB?
- What are the scenarios for the use of corticosteroids in the treatment of HIV-associated TB?
- What is the role of micronutrient supplementation in patients with TB and HIV coinfection who are at different levels of immunosuppression?

Planned and ongoing investigations to address some of the questions listed above are discussed in more detail in a separate article in this supplement [86]. Clinical trials will provide some answers to these questions. Mathematical modeling, operations research, and other implementation research approaches provide important ancillary information. The substantial morbidity and mortality among patients with TB and HIV coinfection necessitates a renewed focus on implementation research to identify practical diagnostic tools for coinfected patients, appropriate treatment strategies, and new models of collaboration and integration between TB and HIV programs and services.

THE WAY FORWARD

There is renewed hope for conducting effective and necessary research. This hope emanates from an unprecedented availability of funds and an improved recognition of the relevance of research in the control of infectious diseases, especially HIV-associated TB. The research community should, as of necessity, rise to the challenge and generate evidence for policy that will optimize clinical practice and improve treatment strategies quickly, to ensure that the fruits of research are applied within control settings as a complementary tool.

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APPENDIX

RECOMMENDED COLLABORATIVE TUBERCULOSIS (TB)/HIV ACTIVITIES

Establish the mechanisms for collaboration

1. Set up a coordinating body for TB/HIV activities effective at all levels
2. Conduct surveillance of HIV infection prevalence among patients with TB
3. Carry out joint TB/HIV planning
4. Conduct monitoring and evaluation

Decrease the burden of TB among people living with HIV/ AIDS

1. Establish intensified TB case finding
2. Introduce isoniazid preventive therapy
3. Ensure TB infection control in health care and congregate settings

Decrease the burden of HIV infection among patients with TB

1. Provide HIV testing and counseling
2. Introduce HIV infection prevention methods
3. Introduce cotrimoxazole preventive therapy
4. Ensure HIV/AIDS care and support
5. Introduce antiretroviral therapy (From [87].)

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Table 1

Short-course tuberculosis (TB) treatment regimens, according to patient category, as recommended by the World Health Organization (WHO).

TB diagnostic category	Condition	Treatment regimens[a]	
		Intensive phase	Continuation phase
I	New smear-positive pulmonary disease; new smear-negative pulmonary disease with extensive lung involvement; concomitant HIV disease or severe forms of extrapulmonary disease[b]	Preferred: 2HRZE;[c] optional: $2(HRZE)_3$ or 2HRZE[d]	Preferred: 4HR, $4(HR)_3$; optional: $4(HR)_3$ or 6HE[e]
II	Previously treated sputum smear–positive pulmonary TB: (1) relapse or (2) treatment after default	Preferred: 2HRZES/1HRZE;[f] optional: $2(HRZES)_3/1HRZE_3$	Preferred: 5HRE;[f] optional: $5(HRE)_3$
	Treatment failure of category I[g] in a setting with (1) adequate program performance or (2) representative data showing high rates of MDR-TB and/or capacity for DST of cases and availability of category IV regimens	Specially designed standardized or individualized regimens often needed	Specially designed standardized or individualized regimens often needed
	In setting where representative DRS data show low rates of MDR-TB or individualized DST shows drug-susceptible disease or in setting of (1) poor program performance and (2) absence of representative DRS data and insufficient resources to implement category IV treatment	Preferred: 2HRZES/1HRZE; optional: $2(HRZES)_3$, $1(HRZE)_3$	Preferred: 5HRE;[f] optional: $5(HRE)_3$
III	New smear-negative pulmonary TB (other than in category I), less-severe form of extrapulmonary TB	Preferred: 2HRZE;[h] optional: $2(HRZE)_3$ or 2HRZE	Preferred: 4HR, $4(HR)_3$; optional: $4(HR)_3$ or 6HE
IV	Chronic, still smear positive after supervised retreatment; proven or suspected MDR-TB cases[i]	Specially designed standardized or individual regimens	Specially designed standardized or individual regimens

NOTE. Adapted from the WHO [5]. DRS, drug resistance surveillance; DST, drug susceptibility testing; MDR-TB, multidrug-resistant TB.

[a] E, ethambutol; H, isoniazid; R, rifampin; S, streptomycin; Z, pyrazinamide. Nos. preceding regimens denote length of treatment (in months). Subscripts following regimens denote frequency of administration (days per week); when no subscripts are given, the regimen is daily. Direct observation of drug intake is always required during the initial phase of the treatment and is strongly recommended when R is used in the continuation phase and required when treatment is given intermittently. Fixed-dose combinations are highly recommended for use in both the intensive and the continuation phases of treatment.

[b] Severe forms of extrapulmonary TB are listed in [5].

[c] S may be used instead of E. In tuberculous meningitis, E should be replaced by S.

[d] Intermittent initial-phase therapy is not recommended when the continuation phase of H and E is used.

[e] This regimen may be considered in a situation in which the preferred regimen cannot be used as recommended. However, it is associated with a higher rate of treatment failure and relapse, compared with the 4HR continuation phase.

[f] Daily treatment is preferred. However, 3-times-weekly treatment in both phases is an acceptable option.

[g] Patients with treatment failure may be at increased risk for developing MDR-TB, particularly if R was used in the continuation phase. DST is recommended in these cases, if available. Patients with treatment failure with known or suspected MDR-TB must be treated with a category IV regimen.

[h] E in the initial phase may be omitted for patients with limited, noncavity, smear-negative TB who are known to be HIV negative, for patients with less severe forms of extrapulmonary TB, and for young children with primary TB.

[i] DST is recommended for patients who are contacts of patients with MDR-TB.

Table 2

Recommendations for when to initiate antiretroviral therapy for symptomatic HIV-infected patients.

Source of recommendation [reference]	Date of publication	CD4 cell count, cells/mm^3	Plasma HIV RNA level, copies/mL
International AIDS Society–USA Panel [30]	Jul 1998	Any	>5000–10,000
International AIDS Society–USA Panel [31]	Jan 2000	<500	>5000–30,000
Panel on Clinical Practices for Treatment of HIV [32]	Feb 2001	<350	>30,000
Panel on Clinical Practices for Treatment of HIV [33]	May 2002	<350	>55,000
International AIDS Society–USA Panel [34]	July 2002	>200	>50,000–100,000
Panel for Clinical Practices for Treatment of HIV [35]	Nov 2003	200–350	>55,000
WHO guidelines, 2003 revision [36]	Dec 2003	≤200	NA

NOTE. NA, not applicable; WHO, World Health Organization.

Table 3

Recommendations for individuals with tuberculosis (TB) disease and HIV coinfection.

CD4 cell count, cells/mm^3	Recommended regimen	Comments
<200	Start TB treatment; start ART as soon as TB treatment is tolerated (between 2 weeks and 2 months);[a] use EFV-containing regimens[b,c,d]	Recommend ART; EFV is contraindicated in pregnant women or women of childbearing potential without effective contraception
200–350	Start TB treatment; start one of the following regimens after the initiation phase (start earlier if patient is severely compromised): EFV-containing regimens[b] or NVP-containing regimens in case of a rifampin-free continuation-phase TB treatment regimen	Consider ART
>350	Start TB treatment	Defer ART[e]
Not available	Start TB treatment	Consider ART[a,f]

NOTE. Adapted from the World Health Organization [36]. ART, antiretroviral therapy; EFV, efavirenz, NVP, nevirapine.

[a] Timing of ART initiation should be based on clinical judgment in relation to other signs of immunodeficiency. For patients with extrapulmonary TB, ART should be started as soon as TB treatment is tolerated, irrespective of CD4 cell count.

[b] Alternatives to the EFV portion of the regimen include saquinavir (SQV)/ritonavir (RTV) (400/400 mg twice daily), SQV/low-dose ritonavir (SQV/r) (1600/200 mg daily in soft gel capsule), lopinavir/RTV (400/400 mg twice daily), and abacavir.

[c] NVP (200 mg daily for 2 weeks, followed by 200 mg twice daily) may be used in place of EFV in the absence of other options. NVP-containing regimens include stavudine (d4T)/lamivudine (3TC)/NVP or zidovudine (ZDV)/3TC/NVP.

[d] EFV-containing regimens include d4T/3TC/EFV and ZDV/3TC/EFV.

[e] Unless non–TB stage IV conditions are present; otherwise, initiate ART on completion of TB treatment.

[f] If no other signs of immunodeficiency are present and the patient is improving while receiving TB treatment, ART should be started on completion of TB treatment.