Novel Developments in the Epidemic of Human Immunodeficiency Virus and Tuberculosis Coinfection

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Tuberculosis (TB) disease remains one of the highest causes of mortality in HIV-infected individuals, and HIV–TB coinfection continues to grow at alarming rates, especially in sub-Saharan Africa. Surprisingly, a number of important areas regarding coinfection remain unclear. For example, increased risk of TB disease begins early in the course of HIV infection; however, the mechanism by which HIV increases this risk is not well understood. In addition, there is lack of consensus on the optimal way to diagnose latent TB infection and to manage active disease in those who are HIV infected. Furthermore, effective point-of-care testing for TB disease remains elusive. This review discusses key areas in the epidemiology, pathogenesis, diagnosis, and management of active and latent TB in those infected with HIV, focusing attention on issues related to high- and low-burden areas. Particular emphasis is placed on controversial areas where there are gaps in knowledge and on future directions of study.

Keywords: tuberculosis; HIV; diagnosis; management; epidemiology

Concurrent infection with HIV and *Mycobacterium tuberculosis* (MTb) remains a serious and evolving global health crisis. There are 34 million persons infected with HIV worldwide and 15 million are also infected with MTb (1). Tuberculosis disease (TB) is a leading cause of death among HIV-infected persons, and diagnosis of TB remains challenging in HIV-infected persons because of limited resources and atypical presentations. Alarmingly, early reports suggested mortality approached 100% in HIV-infected persons infected with multidrug-resistant (MDR) or extensively drug-resistant (XDR) MTb (2, 3), although more recent reports suggest mortality may not be as high (4). Despite the enormity of the crisis, there remains limited understanding of the underlying mechanisms driving high susceptibility to TB in HIV-infected patients and incomplete and sometimes conflicting clinical data to direct diagnosis and management in coinfected patients.

This review focuses on adult HIV–TB coinfection and emphasizes the current unique and expansive challenges facing this highly vulnerable and expanding population. Particular emphasis is placed on identifying select gaps in knowledge in the understanding of HIV–TB coinfection in the areas of global epidemiological trends, cellular responses, latent infection, diagnosis, and management.

EPIDEMIOLOGY OF HIV–TB COINFECTION

Although the global incidence of TB has stabilized since 2004, data from the World Health Organization (WHO, Geneva, Switzerland) indicate that the percentage of HIV-associated TB is significantly greater than previously estimated, with disease burden in Africa responsible for most of this increase (1). In 2008, there were 9.4 million new cases of TB and 1.78 million deaths from TB worldwide; of these, 1.4 million cases (15%) occurred in HIV-infected individuals, resulting in 0.5 million deaths (28% of total deaths from TB) (5). This estimate, double the 2006 estimate of HIV-associated TB (0.7 million), is the result of increased reporting of HIV prevalence in TB cases, suggesting significant deficiencies in surveillance that may result in further increases in the future, particularly with newer active case-finding approaches (6). The relative risk of developing TB in HIV-positive individuals, compared with HIV-negative individuals, is 21 in high HIV prevalence countries and 37 in low HIV prevalence countries (1). Geographically, sub-Saharan Africa continues to shoulder the vast majority of disease burden. In 2008, 78% of HIV-associated TB cases occurred in Africa, with the highest incidence in South Africa, and 13% of cases occurred in the Southeast Asia region (mainly India) (5).

Despite the global rise in TB incidence in the 1990s attributable to the HIV epidemic and the rapid progression to active TB disease in patients with HIV (7), the overall prevalence of TB has been declining since 1990 (1). This paradox may be explained, in part, by the relatively shorter duration of disease in HIV-infected individuals seen in some communities, with increased mortality (8). Because prevalence is the greatest factor in disease transmission rates, HIV may not be a significant factor contributing to the increase in global transmission rates. However, individual cohort studies have shown HIV-driven increases in TB transmission in some communities (9). Another important factor affecting the impact of HIV on TB disease transmission is the relative infectiousness of coinfected patients. HIV-infected patients have a lower rate of sputum smear positivity, which is the strongest predictor of infectivity (10). However, several reports of nosocomial outbreaks of TB have been reported among HIV-infected individuals (11). Studies of this topic are conflicting; a meta-analysis from 2001 concluded that HIV has no impact on the infectiousness of TB, both in the nosocomial and community settings (11). A study of guinea pigs exposed to air from a TB ward showed that patients coinfected

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with HIV and TB demonstrated marked variability in infectiousness, and 90% of transmission in this case resulted from a few suboptimally treated patients with MDR TB (12).

Because HIV is associated with both malabsorption of TB drugs (3) and higher rates of TB treatment failure (3), HIV may be a risk factor for TB drug resistance. Although institutional outbreaks of drug-resistant TB have affected primarily HIV-infected patients, including the first report of XDR TB in South Africa (2), whether HIV is an independent risk factor for drug-resistant TB in the community remains unclear. This may be due primarily to the lack of available drug susceptibility testing in most of the world (13). The limited available data, summarized in a meta-analysis review (14), thus far have shown that HIV is a risk factor for primary (transmitted), but not acquired, drug-resistant TB. However, small studies on this topic in various settings have suggested that HIV is a risk for rifampin resistance (15, 16). The most recent analysis from the Global Project on Anti-tuberculosis Drug Resistance reported drug resistance stratified by HIV status from only 7 of 83 countries. Of these, five countries (Cuba, Honduras, Russia [17], Spain, Uruguay) showed no association between MDR TB and HIV. However, two countries—Latvia and Ukraine—reported a significant association, with odds ratios of 2.1 and 1.5, respectively (17). Significantly, the area of greatest burden, Africa, did not report resistance according to HIV status, thus leaving the association between HIV and MDR TB unclear.

Although the risk of TB disease increases as $CD4^+$ T-cell counts decline (18), TB still occurs at a higher rate in HIV-infected persons with preserved $CD4^+$ T-cell counts. A longitudinal study of South African gold miners who received regular HIV and TB testing showed that within 1 year of HIV seroconversion and in the absence of highly active antiretroviral therapy (HAART) or TB preventive therapy, the incidence of TB doubled compared with HIV-negative peers (19). Although limited in generalizability given the unique susceptibility of this population to inhalational disease, this study nonetheless may provide some important insights into the effects of HIV on TB incidence and transmission in a high-prevalence community. Restricted fragment length polymorphism analysis suggests that the early cases of active TB are due to reactivation and the later cases to primary infection (19). Extension of the study to 11 years of follow-up revealed a persistent, linear increase in TB risk over time and, importantly, that onward transmission, measured by the doubling of TB incidence in HIV-negative workers, contributes to this risk (9) (*see* Figure 1A).

HAART reduces the incidence of TB in HIV-infected individuals by up to 90% (20–22) in studies with follow-up averaging 5 years. Despite this efficacy, there seems to remain a persistently elevated risk of TB above population baseline levels (23) (*see* Figure 1B). This risk is greatest in those who have the lowest $CD4^+$ T-cell counts at HAART initiation (21, 24). Furthermore, several studies have noted an unchanged or temporary increase in TB incidence in the first 3 months after HAART initiation (24, 25), possibly due to increased case detection and the impact of immune reconstitution. Finally, because HAART increases the life expectancy of HIV-infected persons without eliminating the increased risk of TB, limited data suggest that it is unclear whether HAART alone will significantly decrease the overall community burden of TB, particularly without simultaneous active case finding and widespread institution of isoniazid preventative therapy (IPT) for latent tuberculosis infection (LTBI) (26, 27).

PATHOGENESIS OF HIV–TB COINFECTION

Although the biological synergy between HIV and MTb is well described, a number of aspects concerning the pathogenesis of HIV–TB coinfection are not well understood. It is clear that TB infection greatly impacts the course of HIV disease in several ways. TB disease is associated with a 10-fold increase in serum viral load for a given $CD4^+$ T-cell count (28), and HIV mRNA levels are highest in lung areas with active TB infection (29). MTb infection directly increases viral production in both lymphocytes (30) and alveolar macrophages (31). Severe pulmonary TB infection is also associated with a fall in the $CD4^+$ T-cell count (32). Consequently, TB infection in HIV-infected persons is associated with an almost twofold increase in the risk of death at 1 year (33), with a threefold increase in death for subjects with a $CD4^+$ T-cell count greater than 200 cells/μl (33). Why TB in particular increases the risk of death in early HIV infection, more so than bacterial pneumonias that also occur early in the course of HIV infection and have similar effects on viral replication, is incompletely understood.

It is also well known that the risk of TB is greatly increased in HIV-infected persons, and some of the underlying mechanisms are being elucidated. Effective immunity to TB involves coordination of responses between the innate and adaptive immune systems, both of which are altered by HIV (34). The strongest risk factor for developing TB disease in HIV lies in helper T-cell type 1 (Th1) adaptive immunity, specifically the progressive decline in $CD4^+$ T-cell count associated with advanced HIV (26). In patients with prior TB exposure as assessed by a positive PPD response, the incidence of TB is 2.6%/year for those with a $CD4^+$ T-cell count greater than 350/μl, 6.5%/year for those with a $CD4^+$ T-cell count from 200 to 350/μl, and 13.3%/year for those with a $CD4^+$ T-cell count less than 200/μl (35). With decline of the $CD4^+$ T-cell count, there is also a higher risk of anergy to skin test reactions, suggesting dysfunction of delayed-type hypersensitivity dependent on Th1-type immunity (36). There is also *in vitro* evidence for qualitative dysfunction of $CD4^+$ T cells in HIV. Compared with TB-infected patients without HIV infection, peripheral blood mononuclear cells from patients coinfected with HIV and TB have decreased proliferative T-cell responses and reduced IFN-γ production to MTb *in vitro*, whereas antiinflammatory IL-10 production is preserved (37).

However, the observation that TB incidence increases shortly after HIV seroconversion, and before reduction in peripheral blood $CD4^+$ T-cell counts (19), suggests that HIV confers additional mechanisms of susceptibility to TB infection. Investigations into the progression of primary HIV infection to AIDS suggest that primary HIV infection is associated with a precipitous decrease in mucosal $CD4^+$ memory T cells (38), which may set the stage for chronic immune activation and $CD4^+$ T-cell depletion through mucosal translocation of bacteria through the gut (39). Thus, mucosal $CD4^+$ memory T-cell depletion may provide a potential mechanism to account for disrupted T-cell function in early HIV infection, although whether similar events occur in the lung mucosa has not yet been established (40). Indeed, primary HIV infection is associated with decreased PPD-specific IFN-secreting T cells (41, 42) and ESAT (early secreted antigenic target)-6–specific T cells (42) in the blood, suggesting that early depletion of memory T cells may affect specific immunity to TB. Lung lavage enzyme-linked immunospot (ELISPOT) studies also suggest decreased bacillus Calmette-Guérin (BCG)– or PPD-specific pulmonary $CD4^+$ T cells in asymptomatic HIV-infected persons compared with HIV-negative persons (43). HIV–TB coinfection may also be associated with increased serum levels of IL-4, an anti-Th1 type cytokine that hinders immune response to MTb (44). Interestingly, alveolar lavage cells from coinfected individuals may have intact ability to secrete IFN-γ in response to MTb antigens *in vitro* (45), although this may not translate to equivalent cell function and cell numbers *in vivo*.

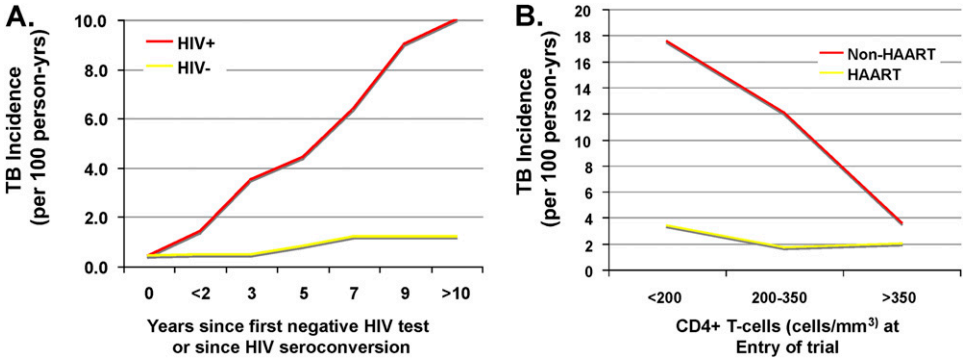

Figure 1. Increased incidence of tuberculosis (TB) early in HIV and incomplete protection from TB after HAART. (*A*) Incidence of TB in South African gold miners who are HIV negative or who have seroconverted to HIV-infected as a function of years since negative HIV test or date of seroconversion. Data show early doubling in incidence of TB among HIV seroconverters after first year and continued rise thereafter. Adapted from Reference 9. (*B*) Incidence of TB among South African cohorts divided who are HIV-infected and taking or not taking highly active antiretroviral therapy (HAART) therapy, as a function of initial $CD4^+$ T-cell count at commencement of study. Data show that although HAART significantly reduced TB incidence especially among those with low $CD4^+$ T-cells counts, protection is incomplete, and among those with relatively high $CD4^+$ T-cell count, protection is minimal during study period (approximate follow-up, 16 mo). Adapted from Reference 20.

Independent of $CD4^+$ T-cell count, HIV also affects the function of innate immune cells, especially alveolar macrophages (AMs), which serve as the main reservoir for MTb infection (46, 47). MTb has evolved to persist within macrophages in part through prevention of MTb phagosomal fusion with lysosomes, thus preventing intracellular killing of MTb (48, 49). AMs can combat intracellular parasitization by releasing immune-activating cytokines or chemokines, and by programmed cell death or apoptosis (50, 51). Apoptosis benefits the host by promoting intracellular killing of MTb (50, 51) and improving antigen presentation by additional phagocytes to activate adaptive immunity (52, 53) (*see* Figure 2). Whereas asymptomatic HIV infection does not affect the intracellular growth of MTb (43, 54), AMs from asymptomatic HIV-infected subjects have increased phagocytosis of MTb (54, 55), decreased release of specific cytokines and chemokines (56), and similarly impaired MTb phagosomal maturation (49) compared with AMs from healthy subjects. AMs from HIV-infected subjects also have decreased apoptosis in response to MTb (55) (*see* Figure 2); the mechanism may involve increased lung levels of IL-10 in HIV, which up-regulates BCL-3 (B-cell lymphoma 3–encoded protein), an apoptosis inhibitor (57). HIV infection of macrophages also inhibits autophagy (58), another cellular process that may be critical for macrophage intracellular killing of MTb (59).

As stated previously, HAART reduces the risk of TB in HIV (20–22), but not to the level of non–HIV-infected subjects (23). *In vitro* studies have found qualitative impairment in the T-cell response to PPD in patients receiving HAART therapy (undetectable viral load with $CD4^+$ T-cell count > 300 cells/μl), with decreased percentages of PPD-specific IFN-γ–producing T cells when compared with HIV-negative patients (41). This provides further evidence that immune recovery with HAART is incomplete.

LATENT TB INFECTION IN HIV

In patients with HIV and latent TB infection (LTBI), the rate of progression to active tuberculosis disease is 5–8%/year, compared with a 10% lifetime risk in the general population (7). Among risk factors for progression, HIV (relative risk [RR], 9.9) ranks the highest compared with old healed tuberculosis (RR, 5.2), chronic renal failure (RR, 2.4), or infliximab therapy (RR, 2.0) (60). HIV is also associated with higher rates of extrapulmonary and disseminated TB disease. For these reasons, LTBI testing and treatment in HIV-infected patients is a priority, and this is apparent in the available treatment guidelines from low-burden countries, as reflected by Centers for Disease Control and Prevention (CDC, Atlanta, GA) recommendations (61), and in high-burden countries, as reflected by WHO recommendations in the "Three I's" strategy (62). The "Three I's" of Isoniazid Preventive Treatment, Intensified case finding for active TB, and TB Infection control are key public strategies focused on decreasing the impact of TB on people living with HIV (62).

The diagnosis of LTBI requires a positive tuberculin skin test (TST) or IFN-γ release assay (IGRA), or a compelling history of likely infection such as recent close contact (61). In HIV-infected individuals, a positive TST is defined as an induration of at least 5 mm in response to intradermal placement of PPD. IGRAs are more recently developed assays that detect *in vitro* IFN-γ release by peripheral blood monocytes in response to MTb-specific peptides (61). However, controversy exists as to the equivalence of a positive IGRA and TST. Given the T-cell defects of HIV-infected patients, both of these tests underperform in this setting, and render false negative results, but this should not preclude routine screening (61, 63). In addition, retesting after reconstitution of the immune system in patients receiving HAART has merit as LTBI test performance improves as $CD4^+$ T-cell counts recover to greater than 200 cells/mm^3 (61).

IGRAs, the QuantiFERON-TB Gold In-Tube (QFT; Cellestis Limited, Carnegie, Victoria, Australia) and T-SPOT.TB (Oxford Immunotec Ltd, Abingdon, UK) tests, are commercially available worldwide. Compared with TST, IGRAs offer the advantage of a lower false positive rate due to BCG vaccination, better standardization of testing, and lack of need for a repeat visit (63). However, sensitivity may be similar to TST (64). Studies generally suffer from the lack of a "gold standard" in the diagnosis of LTBI, and therefore data are extrapolated from results in patients with active TB. In this regard, the T-SPOT.TB, an ELISPOT assay, may have improved sensitivity compared with the QFT (64), and in one small series from Zambia, T-SPOT.TB had 90% sensitivity in HIV-infected patients with active TB (65). Of major concern, however, is that there are few longitudinal studies of patients with positive IGRA assays, and therefore, it is unclear how these sensitivities predict the risk of developing TB disease with LTBI. One study from Austria found QFT to have a 90.9% rate of predicting active TB disease in HIV-infected subjects. However, this study was limited by its low-prevalence setting, as active TB disease occurred in only 3 of 37 QFT-positive subjects (a rate of 8.1%) (66). A comparison of the tests for LTBI is presented in Table 1.

There are few studies that specifically compare the accuracy of TST and IGRA for screening for LTBI in HIV-infected populations. These studies show a number of discordant results,

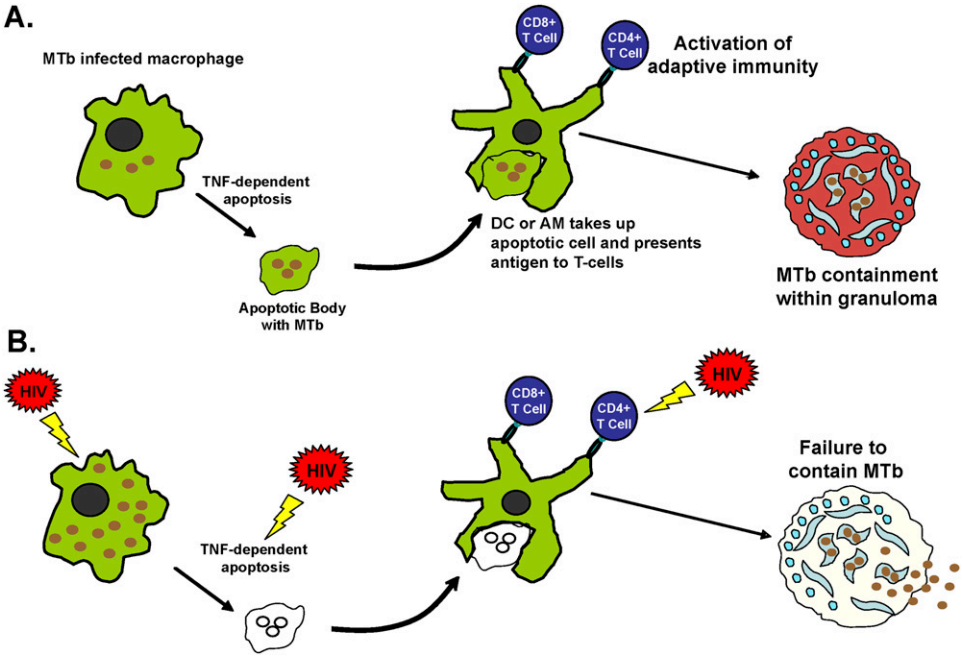

Figure 2. Immunity against *Mycobacterium tuberculosis* (MTb) and the effects of HIV. (*A*) Alveolar macrophages (AMs) are the first cells to encounter and engulf MTb bacteria when they are inhaled deeply into the lungs. MTb bacteria have evolved to escape intracellular killing by AMs by arresting phagosomal maturation and possibly escaping the phagosome to allow for persistence and growth within AMs. The defense mechanisms against this include chemokines/cytokine secretion which activate antimycobacterial defenses and adaptive immunity (56, 142, 143), autophagy (59), and apoptosis (51) among others. (*B*) HIV is known to affect a number of these steps, including increased phagocytosis of MTb to allow access to intracellular environment (54, 55), decreased AM apoptosis (55) in response to MTb, decreased autophagy (58), and decreased chemokine/cytokine production (56). HIV also affects function and numbers of $CD4^+$ T cells, leading to increased bacillary loads, inadequate granuloma formation, and dissemination (144). DC = dendritic cell; TNF = tumor necrosis factor.

where one test is positive and the other negative (65, 67, 68). TST-positive/IGRA-negative results may be explained, in part, by BCG vaccination although the rate of false negatives is unclear. It is similarly unclear whether TST-negative/IGRA-positive tests are true positives due to better IGRA sensitivity or false positives. For example, one study in a low TB prevalence country (the United States), performed by Luetkemeyer and colleagues, found that the QFT and TST were concordant in only 28% of patients with a positive result of either test (67). In addition, 16% of subjects from this study with a $CD4^+$ T-cell count less than 100 cells/mm^3 had an indeterminant QFT result (defined as a lack of interferon response to the assay's positive control, making the test uninterpretable).

A study in a high TB prevalence area (South Africa), performed by Rangaka and colleagues, found that the IGRA tests had a higher rate of positivity in HIV-infected persons compared with TST (69), and that the T-SPOT.TB had a significantly higher positivity rate than QFT or TST among subjects with $CD4^+$ T-cell counts less than 250 cells/mm^3. Also observed was a poor correlation between the IGRA and the TST in HIV-uninfected persons (69). Similar results were obtained by Dheda and colleagues (70) and Hoffman and colleagues (71) in low TB prevalence areas in HIV-infected subjects. These data suggest that the T-SPOT.TB ELISPOT may have the highest sensitivity for LTBI in HIV-infected subjects and therefore may be the best option for screening in this population. However, more studies with longitudinal follow-up are needed to determine how predictive T-SPOT.TB ELISPOT testing is for the development of active TB. In addition, expense, need for trained operators and specific laboratory equipment, may limit its utility in resource-poor settings. Because of incomplete and sometimes conflicting data on the IGRAs, national guidelines differ on their use. Some recommend using either TST or IGRA (61), whereas others suggest use of the IGRA as an adjunct to TST (72–74).

Before initiating treatment of LTBI, it is important to first rule out active TB disease, which can be difficult in HIV-infected

TABLE 1. COMPARISON OF TESTS FOR LATENT TUBERCULOSIS INFECTION

	TST	QFT	T-SPOT.TB
Relative sensitivity (drops with decreasing $CD4^+$ T-cell count)	++	++*	+++*
Specificity	+ (for BCG vaccinated); +++ (for non-BCG)	+++	+++
Benefit of treating positives by IPT	Yes†	Unclear†	Unclear†
Reproducibility	+	+++	+++
Costs	+	+++	+++
Laboratory infrastructure required	No	Yes	Yes
Need for repeat visit	Yes	No	No
Trained personnel required	+	++	+++

Definition of abbreviations: IGRA = IFN-γ release assay; IPT = isoniazid preventive therapy; LTBI = latent tuberculosis infection; QFT = QuantiFERON-TB Gold In-Tube test; TST = tuberculin skin test.

Adapted from Reference 61.

+, indicates a comparison with other tests in Table 1.

* Data are based on studies of persons with active TB disease, which may or may not correlate with persons having LTBI. Data are suggestive that QFT has a sensitivity similar to TST, while T-SPOT.TB may have increased sensitivity compared to TST, and the sensitivity of all three tests decreases with decreasing $CD4_+$ T-cell count. However, prospective studies are needed in subjects with HIV to confirm that these findings can be applied to evaluating risk and initiating IPT.

† There are no prospective trials of IGRAs evaluating the benefit of IPT.

patients because of atypical presentations (61). A large study of HIV-infected subjects in Southeast Asia suggests that a screening strategy focusing on three questions (cough for any duration, fever, and night sweats lasting 3 wk or more) is adequate. Absence of these symptoms accurately rules out TB in the vast majority of patients (75) and this may in turn allow for safe initiation of IPT. Similar results were obtained in a study from South Africa emphasizing that absence of cough alone is inadequate for ruling out TB in HIV (76). The current recommendations for LTBI treatment in HIV-infected patients are isoniazid prophylaxis therapy (IPT) for 9 months; 6 months has reduced efficacy (61). Several groups have shown that treatment of LTBI in HIV-infected patients is both safe and effective in preventing tuberculosis reactivation in both low TB prevalence areas (77) and high TB prevalence areas (78), without evidence of increased drug resistance (79–81). However, in a study by Grant and colleagues, overall TB incidence in the population remained high despite prophylactic therapy (79). Data also suggest that primary prophylaxis of LTBI coupled with secondary prophylaxis of previously infected individuals may provide an additional benefit in high-prevalence areas (82, 83). However, few high-prevalence countries follow these practices because of concerns regarding drug toxicity and resistance, nonadherence, poor coordination of HIV and TB programs, and reinfection issues (84). Optimal management of LTBI likely involves concurrent initiation of HAART and IPT (83). Studies suggest that concurrent HAART with IPT carries no increase in drug toxicity (85). Therefore, HIV antiretroviral therapy clinics may represent an ideal setting to provide IPT (83). However, there are clear concerns in having patients potentially coinfected with HIV and TB in the same area as other HIV-infected individuals.

ACTIVE TB DISEASE DIAGNOSIS IN HIV

The diagnostic imperative for HIV-infected patients regarding active tuberculosis remains early and accurate detection of TB and drug-resistant TB. This task demands sensitive, specific, and relatively rapid testing algorithms and tools, and is made more challenging by the altered clinicopathological presentation of HIV-associated TB (76, 86, 87).

In the presence of HIV coinfection, the clinical presentation of active TB is increasingly modified as the $CD4^+$ T-cell count declines (88). Clinicians evaluating patients with HIV should recognize the importance of testing for active TB in patients presenting with nonspecific symptoms. An especially challenging aspect of this is in recognizing atypical presentations in patients with undiagnosed HIV presenting with TB as their first opportunistic infection. Not only are HIV-associated TB symptoms more diverse than in non-HIV TB, but the differential diagnosis of conventional cough, fever, and malaise is much more extensive in the presence of HIV coinfection (89). For this reason, if an HIV-infected patient suspected of having TB is not shown to have active TB disease, that patient should not necessarily proceed straight to IPT, but rather remain under evaluation until the cause of their symptoms is revealed (which could still include active TB) or the symptoms resolve. Conventional radiological hallmarks of pulmonary TB such as cavitation and apical localization are also less common (88). Sputum production is often attenuated, which compromises collection of adequate diagnostic specimens, and culture-positive pulmonary TB is more frequently smear negative (88, 90, 91). For example, 69% of HIV-infected persons diagnosed with active TB were smear negative in one study (92). HIV-infected patients also more commonly contract extrapulmonary TB (EPTB) (50 vs. 15%), which evades or delays diagnosis, and are more likely to have disseminated disease (10 vs. 1%) (93).

Although smear microscopy is less frequently positive in patients infected with HIV and TB, advances in fluorescence microscopy (94–97) and optimization of smear preparation (98–101), coupled with important steps toward so-called front-loaded microscopy, in which two samples are taken on the same day (102), ensure that smear microscopy remains the mainstay of diagnosis of TB globally. However, new diagnostic tools for the detection of TB and drug-resistant TB have been developed on the basis of both phenotypic and genotypic methods. Liquid culture, which is more sensitive and rapid than TB culture on solid media (making it particularly useful in HIV coinfection) (103–105), has been endorsed by the WHO (62) and there are both commercial and noncommercial methods available. Culture requires a greater incubation time compared with that for non–HIV-infected patients, consistent with lower bacillary load of sputum (106). The study from Southeast Asia suggests that in HIV-infected subjects with a positive screen for TB (presence of cough, fever, or night sweats), TB could be reliably ruled out only with a negative sputum culture, although TB was relatively uncommon in patients with two negative smears, negative chest radiograph, and a $CD4^+$ T-cell count equal to or exceeding 350 cells/mm^3 (75). Molecular (polymerase chain reaction [PCR]– or gene probe–based) tests generally perform less well on lower bacillary load smear-negative samples (107), suggesting lower sensitivity with HIV. However, one study showed high sensitivity for detecting TB in smear-positive sputum from HIV-infected subjects, using the AMPLICOR PCR (Roche Diagnostic Systems, Branchburg, NJ) (99.7%), and no significant difference in sensitivity compared with smear-negative culture-positive specimens from HIV-negative subjects (89 vs. 95%) (108). Urine detection of the MTb cell wall component lipoarabinomannan may improve detection in smear-negative HIV-infected patients with advanced immunosuppression in a high-prevalence setting (109, 110). Serological tests currently have no proven role in the diagnosis of active TB with or without HIV (111) and IFN-γ release assays (IGRAs) do not help to distinguish latent from active TB (63).

Large studies comparing diagnostic approaches to HIV-associated EPTB are limited. Because most of this burden falls on resource-limited settings, there are significant obstacles in the diagnosis of EPTB. These include limited imaging capacity, limited ability to obtain adequate tissue specimens (which could potentially require laparoscopic peritoneal biopsy, computed tomography–guided biopsy, or mediastinoscopy), and limited availability of DNA amplification technology.

Although it is controversial whether HIV per se is associated with drug resistance, the potential for rapid progression of untreated or inadequately treated HIV-associated TB is clear, and thus there is a need for rapid detection and treatment of drug-resistant TB in HIV-infected patients (33). Drug resistance can be identified phenotypically by culture-based methods or (for some agents) genotypically by molecular methods to determine the presence or absence of resistance-conferring gene mutations. The performance of drug susceptibility–testing methods in patients infected with HIV and TB does not differ significantly from that for non-HIV populations, although methods such as the microscopic observation drug susceptibility (MODS) assay demonstrated to be effective when performed directly on smear-negative, culture-positive sputum samples do confer a time advantage (*see* Figure 3) (112). The MODS assay may also be effective as part of a screening strategy to rule out active MTb disease before initiating IPT (113) and has been recommended by the WHO for interim use until capacity for genotypic or automated liquid culture susceptibility testing is available (114, 115). Molecular methods, such as line probe assays (116), can offer rapid detection of isoniazid and rifampicin resistance from

smear-positive sputum samples and culture isolates, and are now recommended by the WHO (117). Amplification of DNA from paraffin-embedded biopsy samples can also identify MTb and drug-resistant EPTB if cultures are not helpful (118).

Inexpensive and easily administered point-of-care tests remain a desirable goal but are not currently available. All existing diagnostic tests and strategies require infrastructure (with varying safety, maintenance, and cost implications) and personnel (who need to be trained and retained) and a strong quality assurance system. These remain huge challenges common to all diagnostic test implementation programs even before consideration of unit costs for tests, and whom to target for testing. However, developments using gene amplification technology (Xpert MTB/RIF; Cepheid, Sunnyvale, CA) that can detect MTb and rifampin resistance simultaneously from sputum samples in a rapid assay (90 min), with minimal training required, with high sensitivity in smear-negative samples (70% when using one Xpert cartridge), and with minimal requirement for biosafety facilities represent a significant advance, although expense may still be too great for resource-poor settings (119).

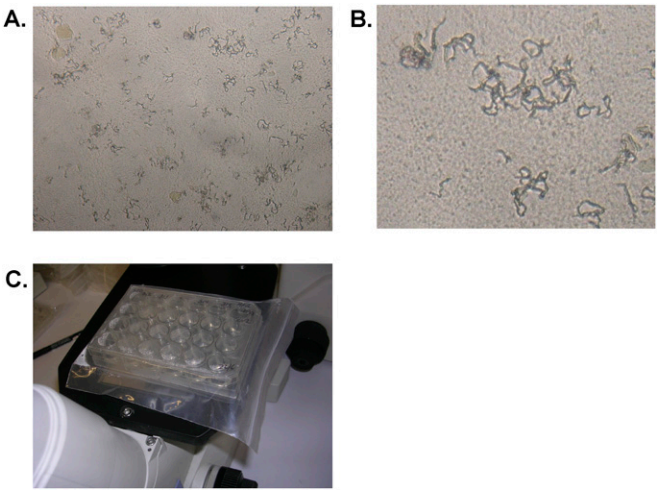

Figure 3. The microscopic-observation drug susceptibility (MODS) assay. (*A*) Typical cording formation characterized by *M. tuberculosis* growth in liquid medium visualized by an inverted light microscope at an original magnification of ×400. (*B*) Magnification of typical cords of MTb. (*C*) Picture of MODS culture plate. Cultures are prepared in a 24-well tissue culture plate in six columns of four wells each. Each column of four wells is used for a single sample–two wells are drug free and one each contains rifampicin and isoniazid. Six columns allow for five samples per plate and one negative control column. Plates are permanently sealed inside Ziploc bags after inoculation to avoid cross-contamination and for safety and are examined within bags daily for 15 days and then on alternate days until Day 21. Nontuberculous mycobacteria do not form cords, except for *M. chelonae,* which can be identified by rapid growth.

MANAGEMENT OF HIV–TB COINFECTION

The standard treatment of drug-susceptible active TB in HIV-infected patients does not differ significantly from the standard regimen for HIV-uninfected patients. It consists of an initial phase of four drugs (isoniazid, rifampin, ethambutol, and pyrazinamide) for 2 months, followed by a continuation phase of isoniazid and rifampin for 4 to 6 months (120). However, there are several considerations in administering this regimen to HIV-infected persons. Several aspects of this topic have been reviewed in detail elsewhere (120, 121). In resource-poor settings, because of cost constraints, rifampin is sometimes omitted in the continuation phase. However, there is clear evidence that continuation phase non–rifampin-based regimens are associated with higher relapse rates (122–124).

The optimal duration of anti-TB treatment in patients coinfected with HIV and TB is controversial. There is some evidence to suggest that longer treatment regimens reduce relapse rates (125, 126) but not survival (127, 128) and a meta-analysis suggests no statistically significant benefit beyond 6 months of therapy (123). However, more studies are required to resolve this controversy, particularly because the influence of early HAART on treatment duration is not well understood. Because of the concerns of added complexity in treating HIV-infected patients differently from non–HIV-infected patients, WHO and CDC guidelines recommend at least 6 months of standard daily short-course therapy and suggest that therapy should be similar regardless of HIV infection status (61, 129). Longer courses may be used in those with extensive disease, sputum positivity at 2 months with confirmed drug-sensitive TB, and in high-burden settings in retreatment cases as part of an 8-month regimen with a 5-month continuation phase. It should also be noted that adverse events in response to antituberculous drugs are more common in HIV-coinfected patients compared with uninfected persons and in those HIV-infected persons with lower $CD4^+$ T-cell counts (130), which may contribute to high rates of nonadherence in high-prevalence settings (131).

There is some controversy as to the timing of HAART and TB therapy in coinfected patients. The three main concerns for concurrent HAART and anti-TB treatment include overlapping toxicities, drug interactions, and immune reconstitution inflammatory syndrome (IRIS). The main overlapping toxicities are skin reactions, hepatitis, peripheral neuropathy, and gastrointestinal side effects. An important strategy for managing toxicities includes initiating anti-TB treatment shortly before initiating HAART, thus ensuring tolerability. The interactions between HAART and anti-TB treatment are complex and reviewed in detail elsewhere (132). Drug interactions arise from rifampin and, to a lesser extent, rifabutin-associated induction of several enzyme systems including the P450 cytochrome system (132) (*see* Table 2). This results in a variable reduction of protease inhibitor (PI), nonnucleoside reverse transcription inhibitor (NNRTI), integrase inhibitor, and fusion inhibitor levels, but not levels of nucleoside reverse transcriptase inhibitors (NRTIs). Hence the WHO recommends that the first-line regimen should be two NRTIs plus one NNRTI (typically efavirenz). Furthermore, when a PI is required and rifabutin is not available (often due to cost in high-prevalence settings), ritonavir-boosted lopinavir or saquinavir is recommended in conjunction with rifampicin-based anti-TB treatment. This regimen should be closely monitored for treatment failure (129). Significantly, work by the Clinton Foundation has lowered the price of rifabutin, which may make this drug more accessible in resource-limited settings (133).

Paradoxical IRIS occurs when clinical deterioration, not due to other opportunistic infection, drug resistance, or relapse, occurs in individuals who commence HAART while already undergoing antituberculous therapy (134, 135). By contrast, unmasking IRIS occurs when paucisymptomatic individuals who commence HAART develop clinical features of active TB, although it may be impossible to determine whether the event is due to recent infection or subclinical disease merely unmasked by immune reconstitution. In either case, and by definition, it is imperative to exclude nonadherence, drug-resistant TB, and other opportunistic infections (134–136). The median duration from treatment initiation to the development of paradoxical IRIS is about 4 to 6 weeks. It is associated with a short interval between TB treatment initiation and

TABLE 2. SUMMARY OF INTERACTIONS BETWEEN RIFAMYCINS AND ANTIRETROVIRALS

	Rifampin	Rifabutin
Cytochrome P450 interaction	+++	+
Interactions with PIs	++++, recommended for use only with a regimen that includes two PIs	++, PIs boost Rif levels requiring reduction of dose
Interactions with NNRTIs	+, slightly decreases levels of efavirenz, but is favored regimen	++, decreased levels of Rif with efavirenz requiring increased Rif dose. Should not be used with delaviridine
Interactions with CCR-5 receptor antagonists	+	+
Interactions with integrase inhibitors	+	+
Cost and availability	++	++++, expensive and less available in resource-poor settings
Efficacy	++++	++++

Definition of abbreviations: NNRTIs = nonnucleoside reverse transcription inhibitors; PIs = protease inhibitors; Rif = Rifabutin.

HAART, low $CD4^+$ T-cell counts, rapid reduction in viral load, and disseminated TB and may be life-threatening (134). Most cases, however, can be managed symptomatically (antipyretics and antiinflammatory agents), although in a minority of cases, aspiration of sterile abscesses, discontinuation of HAART, or initiation of corticosteroids may be required. A randomized controlled trial by Meintjes and colleagues suggested that corticosteroids reduce the need for hospitalization and procedures, and resulted in symptom improvement in patients with IRIS (137).

Given these considerations, the psychological burden of dealing with two diseases, and the high associated pill burden, initiation of HAART has been delayed in some patients coinfected with TB and HIV, particularly those with higher $CD4^+$ T-cell counts. However, in high-burden countries, mortality is high in coinfected individuals immediately after TB diagnosis, suggesting specific HIV therapy may be of further benefit (138). Hence, the WHO recommends that HAART be commenced as soon as possible after initiation of TB treatment (and within the first 8 wk) in all HIV-infected individuals with active TB, regardless of $CD4^+$ T-cell count (139). These guidelines are based, in part, on a randomized controlled trial of HIV-infected individuals with $CD4^+$ T-cell counts not exceeding 500 cells/ml, which showed a mortality benefit of integrated HAART and TB therapy (average HAART commenced about 70 d after anti-TB therapy) compared with sequential therapy (HAART commenced after TB therapy was completed) in patients both below and above the cutoff of 200 cells/μl (140). Although not published, preliminary results of the CAMELIA (Cambodian Early versus Late Introduction of Antiretroviral Drugs) trial (available at www.nih.gov/news/health/jul2010/niaid-22.htm) showed a 33% reduction in mortality in coinfected subjects with a $CD4^+$ T-cell count less than 200 cells/mm^3 begun on HAART 2 weeks after anti-TB therapy compared with 8 weeks after anti-TB therapy. This study and additional prospective studies, such as the A5221, of the Adult AIDS Clinical Trials Group of the Division of AIDS (141), may further refine these guidelines, and further study is needed to determine whether they are applicable to high- and low-resource settings. Last, data are required to guide the initiation of HAART in patients who have MDR and XDR TB, although preliminary data indicate that HAART is relatively well tolerated with second-line anti-TB drugs (4).

CONCLUSION

Increasing rates of HIV–MTb coinfection worldwide pose not only an enormous threat to the HIV-infected population, but may also pose a threat to the non–HIV-infected population especially in resource-limited settings. Despite the magnitude of the problem, our understanding of the underlying causes of coinfection and our ability to combat it remain limited. This review highlights a number of areas where further study may greatly improve efforts to prevent and treat coinfection. In particular, several key areas such as impact of HAART on TB risk, diagnosis and treatment of LTBI in resource-poor settings, and rapid point-of-care diagnosis for active TB disease with susceptibility testing, optimal timing of treatment of coinfection, and management of IRIS are areas of critical need and the subjects of ongoing research. Significant progress has been made, but much remains to be done. Given the enormity of the problem, it is possible that targeted study and implementation of simple interventions have the potential to provide tremendous benefit in the care of these patients, especially in resource-poor settings.

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