Epidemiology of Tuberculosis and HIV

Recent Advances in Understanding and Responses

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Although tuberculosis (TB) continues to cause enormous suffering and overwhelm health care systems in areas with high HIV prevalence, there have been a number of recent significant advances in knowledge regarding the epidemiology, management, and control of HIV-related TB. TB remains the most common serious opportunistic infection in people with HIV infection and the leading cause of death. However, there is some reason for optimism. First, two trials addressing when to start antiretroviral therapy (ART) in HIV-infected adults with newly diagnosed TB have shown that earlier initiation of ART reduces mortality significantly. Second, there is trial evidence of efficacy in giving long-term isoniazid preventive treatment (IPT) to HIV-infected adults in high HIV–prevalence settings where TB reinfection is frequent (much like cotrimoxazole). Third, the search for an inexpensive, rapid, sensitive, and specific TB diagnostic that is able to replace smear and delayed mycobacterial culture has yielded promising results. Responding to massive TB epidemics in high HIV–prevalence settings, the World Health Organization has supplemented its directly observed treatment short-course strategy with one called the 3I's to actively screen and diagnose TB cases (intensified case finding), prevent new cases of TB with IPT, and prevent transmission of TB in congregate settings such as hospitals and clinics (infection control). Combating TB in high HIV–prevalence settings requires rapid and massive implementation of the 3I's with initiation of antiretrovirals and more effective efforts to prevent new HIV infections.

Keywords: preventive treatment; antiretroviral therapy; Xpert MTB Rif; intensified case finding

Tuberculosis (TB) is inseparably linked to the HIV epidemic; this relationship is especially stark in resource-limited settings. In sub-Saharan Africa, TB is the most common serious opportunistic infection and is the leading cause of death in HIV-infected adults before and while receiving highly active antiretroviral therapy (ART) (1–3). Furthermore, an increasing proportion of TB among persons living with HIV is multidrug resistant (MDR) or extensively drug resistant (XDR), complicating management. Moreover, the transmission of TB in HIV clinics and other health settings is a risk to patients and health care workers. In recent years, a number of important advances have been made in elucidating the epidemiology of HIV-related TB and in methods to diagnose, treat, and prevent TB and to reduce mortality in TB/HIV coinfected patients. This review highlights these findings with special reference to Southern Africa, where the TB/HIV coinfection epidemic is particularly severe.

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EPIDEMIOLOGY

HIV is the most potent risk factor for TB. HIV-infection increases the risk of TB 20-fold compared with HIV-seronegative individuals in high HIV–prevalence countries (4), and TB in HIV-infected individuals has resulted in escalating public health emergencies in high HIV–prevalence settings. In the five southern African countries of Zimbabwe, South Africa, Lesotho, Swaziland, and Botswana, annual TB incidence and resultant caseloads have increased enormously over the past 20 years, shifting TB from a relatively stable public health problem to a crisis (Figure 1). For example, in South Africa and Swaziland, population-wide TB notifications increased from 300/1,000 and 200/100,000 in 1990 to 970/100,000 and 1,257/100,000 in 2009, respectively (5). As a comparison, in the United States and in the United Kingdom, rates of TB in 2009 were 4/100,000 and 12/100,000, respectively.

TB-related mortality is poorly documented in routine reporting but has increased. In South Africa, where one quarter of all global HIV/TB coinfections occurred in 2007 (6), TB is the leading cause of death recorded on death certificates (7). In hospitalized patients for whom mycobacterial cultures are included in an infectious disease workup, *Mycobacterium tuberculosis* is the leading cause of bloodstream infection in sub-Saharan Africa (8).

Epidemiologically, TB in high-burden countries parallels the HIV epidemic, with young women and men bearing the brunt. Several sociodemographic and clinical factors, including smoking, have been linked to TB (Table 1). Recent work in the Soweto Lung Cohort in South Africa, funded by the National Heart, Lung and Blood Institute's Pulmonary HIV Cohort Studies program, confirms that two risk factors for TB, previously identified in predominantly HIV-seronegative populations, are implicated HIV-infected individuals: (*1*) HIV-infected adults with normal or low baseline BMI had higher annual incidences of TB compared with overweight and obese subjects (9), and (*2*) smoking appears to confer a risk for TB disease in HIV-infected individuals (10).

Like all opportunistic illnesses in HIV-infected individuals, TB risk increases at lower CD4 counts (11, 12), but in miners, an increased risk of TB was demonstrated within the first year of HIV seroconversion, when CD4 counts are likely still normal (13) and, unlike other opportunistic infections, TB occurs at all CD4 counts (14). In addition to HIV, crowded conditions and silicosis—both hazards of mining—increase TB risk (15). In gold mines in South Africa, the overall incidence of TB is extremely high at approximately 4,000/100,000 per year, and the rate in HIV-seronegative miners is approximately 1,000/100,000 (16, 17). Moreover, the prevalence of latent TB in miners has been reported to be between 66 and 89% (18). Miners returning to their communities continue to experience high rates of TB (19–21) and transmit TB to their families; having a mine worker in a household increased the risk for tuberculin skin test (TST) positivity in children under 5 years almost 3-fold in Botswana (22). Clearly, mining is an important contributor to the propagation of the TB epidemic in Southern Africa (23).

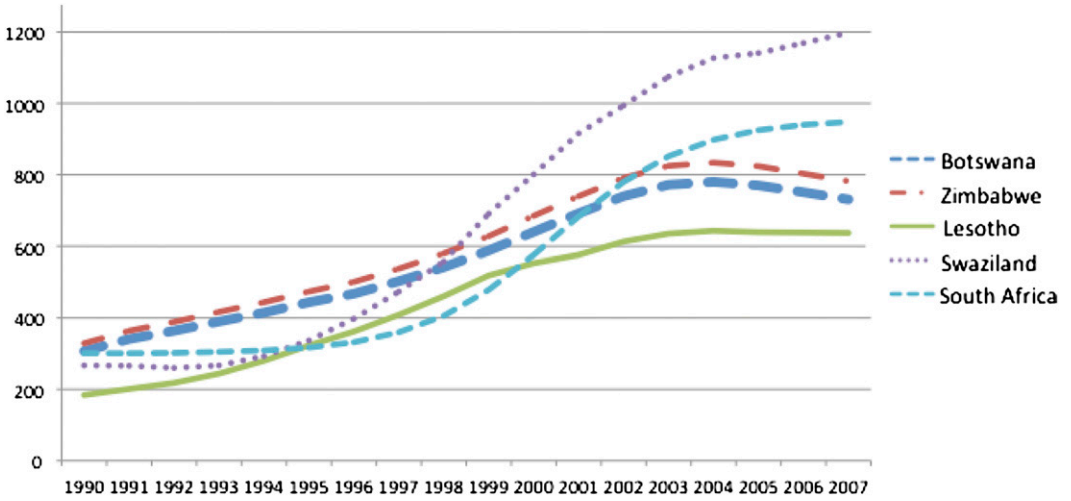

Figure 1. Estimated incidence of all forms of tuberculosis in five selected Southern African Countries (6).

The majority of individuals with TB in Southern Africa (60–80%) are HIV coinfected, creating a large pool of potentially infectious patients. A variety of studies have confirmed TB transmission by coinfected individuals (24–26). However, given the large population of people with HIV and TB, it is unclear whether ongoing transmission of TB is more likely attributed to HIV-infected patients with TB or their seronegative counterparts. A measure of TB transmission is the duration of active TB disease before diagnosis, estimated by dividing point prevalence by simultaneously measured incidence in the same community. Duration of active TB disease in HIV-infected adults is markedly shorter compared with HIV-seronegative adults (9 vs. 60 wk in gold miners [27] and 18 vs. 83 wk in workers in Harare, respectively [28]). Preliminary data from South Africa appear to confirm this: A study of household TB contacts in South Africa found high rates of confirmed and probable TB in contacts who were predominantly HIV seronegative, whereas almost 80% of index cases were HIV infected (29), suggesting that HIV-infected adults who progress to active TB rapidly are an indicator of recent close contact with a TB transmitter who is most likely HIV seronegative.

Further complicating our understanding of the epidemiology of TB transmission in Southern Africa are the high rates of TB infection observed before adulthood. A recent TST survey from Cape Town indicates that over 80% of the population has evidence of latent TB infection by the age of 35, with maximal increase in rates of TB infections occurring in children aged 5 to 13 years (30). This suggests perhaps that preventive measures to combat TB acquisition should be targeted at young children and that preventive treatment for latent TB infection could be given to high school pupils. Active TB in children is similarly problematic; TB incidence estimates from Cape Town in HIV-infected infants ($\leqslant$ 12 mo) in 2004 to 2006 were 1,596/100,000 in HIV-infected infants, 24-fold that in HIV-negative infants (31).

The clinical presentation of TB in HIV-infected individuals varies by CD4 count. Among those with higher CD4 counts, the presentation and progression of TB is similar to the non–HIV-infected population, with subacute symptoms of cough, fevers, night sweats, and weight loss, and, usually, apical infiltrates or cavities on chest radiography. The disease presentation and rate of progression is markedly different among individuals with advanced HIV and CD4 counts of less than 250 cells/mm^3. Among persons with lower CD4 counts, invasive extrapulmonary disease is more common, and symptoms may be subacute or acute with rapid progression and death. Autopsies of patients who died of AIDS-related TB report disseminated TB with multiple organ involvement (32–34).

PREVENTION

Preventing new HIV infections and improving the immune status of those infected with HIV would have the greatest impact on reducing incident TB in high HIV–prevalence settings. While waiting for reductions in population HIV prevalence, several approaches to reduce TB burden in HIV-infected persons have been adopted and sanctioned by the World Health Organization (WHO): isoniazid preventive therapy (IPT), infection control, and intensified case finding, dubbed "The 3I's" (35).

Since the initial development of isoniazid as treatment for TB in the early 1950s, isoniazid has been investigated as a preventive treatment against latent TB, with consistent reports of efficacy from villages, hospital wards, and individuals involved in these trials (36). More recently, the efficacy of 6 months of daily monotherapy with isonaizid for HIV-infected patients who do not have active TB has been demonstrated in more than a dozen randomized clinical trials performed before combination ART became widely available. Combined, the studies in HIV-infected adults with latent TB infection showed a 64% reduction in new cases of TB compared with placebo and a 32% reduction overall, including TST-negative and untested patients (37).

Although the efficacy of preventive treatment was detectable 19 years after receipt of IPT (38) in the pre-HIV era, this is not the case in HIV-infected individuals. Two studies with longer follow-up in the pre-ART era show that TB rates return to those of the placebo arm 2 years after the initiation of IPT (39, 40). Although active TB is prevented, the first IPT trial in HIV-

TABLE 1. FACTORS ASSOCIATED WITH TUBERCULOSIS IN HIV-INFECTED INDIVIDUALS

Characteristics Associated with Increased Risk of Tuberculosis	Characteristics Associated with Decreased Risk of Tuberculosis
Sociodemographic factors	Clinical factors
Residence in high prevalence area	High body mass index
Work or residence in institutions with high prevalence	Higher CD4 cell count
Recent exposure to infectious case	Low or undetectable viral load
Tobacco smoking*	Treatment factors
Clinical factors	Isoniazid or other preventive therapy
Lower body mass index	Antiretroviral therapy
Latent tuberculosis infection	
Silicosis	
Lower CD4 cell count	
High HIV viral load	

* Putative risk extrapolated from HIV-seronegative populations.

infected adults was the only one to show a reduction in mortality (41).

To address the limited durability of 6 months of IPT, three randomized trials of long-term isoniazid (3 yr or more) have had preliminary data reported. Two were undertaken in Southern Africa (Botswana and South Africa) and one in India. The Botswana trial included TST-positive and TST-negative individuals and reported a 56% reduction in TB incidence in HIV-infected adults randomized to receive long-term preventive treatment, but protection was limited to TST-positive participants (42). In the South African trial, which recruited TST-positive participants (≥5 mm diameter), there was no significant benefit of long-term IPT in the intent-to-treat analysis, including all person time (43). However, an as-treated analysis compared incident TB or death while actively taking long-term IPT with all follow-up time in the IPT for 6-month arm and reported a 58% reduction in incident TB or death while taking long-term IPT compared with that in the INH for the 6-month IPT arm. The trial from India, on the other hand, showed no benefit in the use of long-term IPT compared with a 6-month regimen of isoniazid with ethambutol (44). The latter finding may be due to the far lower risk of reinfection likely to be found in India where annual TB incidence is substantially less than in Southern Africa. Despite multiple trials and observational studies supporting the use of IPT and the WHO endorsement of using IPT among persons living with HIV, only 0.1% of eligible HIV-infected adults receive IPT (6).

Infection control has an important role in preventing TB acquisition by persons living with HIV, especially in congregate settings like clinics or hospital waiting rooms where the risk of infection may be extremely high. The importance of adequate infection control was recently highlighted by the outbreak of extensively drug-resistant (XDR) TB in Tugela Ferry, South Africa, where almost half of the patients with XDR were thought to have acquired it in the hospital (45). In addition, data from the same province showed that health workers had 5.5 and 6.7 times the risk of hospitalization for MDR and XDR, respectively, than the people for whom they work (46). Implementing infection control measures (47) is difficult while people at high risk for the acquisition of TB wait and are treated in poorly ventilated settings and mingle with patients with pulmonary TB.

The potential of intensified case finding for prevention of TB has been best illustrated in a community-based study from Zimbabwe. In that study, two community-based TB screening methods were compared. A mobile van approach was better than door-to-door case finding, but overall they caused a 40% reduction in the prevalence of smear-positive TB (48).

Among persons living with HIV, numerous cohort studies have shown that antiretroviral therapy (ART) reduces TB risk in adults (49), with maximal effectiveness shown after 4 to 5 years on ART (50, 51). Similar reductions in TB incidence after ART initiation are reported in HIV-infected children (52, 53). Moreover, TB surveillance data from Cape Town suggest that widespread access to ART reduces population prevalence of TB in HIV-infected individuals (54). Observational evidence suggests compelling evidence for IPT and ART sequentially or simultaneously. In two cohort studies, Brazilian and South African HIV-infected adults who received ART or 6 months of IPT alone had a reduced risk of TB of 40 to 60% compared with patients receiving neither treatment, whereas treatment with IPT then ART or both IPT with ART reduced TB rates by 80 to 90% (55–57). A nonrandomized study suggested that IPT also reduced mortality when started shortly after ART initiation (58). There are currently at least two randomized trials testing IPT initiated with or soon after ART to validate these observational reports. Intensified case finding for TB in patients about to initiate ART using sputum smear and culture seems to reduce incident TB in the first months after ART initiation (59), suggesting that a proportion of the TB occurring in the first months of ART is subclinical at baseline. For patients who develop TB soon after ART initiation, treatment with prednisone for 1 month has been shown to reduce hospitalization and improve symptoms in patients with TB immune reconstitution inflammatory syndrome (60).

TB MORTALITY AND ITS PREVENTION

In a variety of hospital settings, the case fatality rate in predominantly HIV-infected patients hospitalized with TB in Southern Africa is approximately 25%; the majority of deaths occur in the days or weeks after admission (61–63). Although most deaths are attributed to overwhelming TB, severe bacterial infections—particularly nontyphi salmonella—may contribute in many (32). In recent post mortem mycobacterial culture data from South Africa, where a representative sample of all nontraumatic and nonobstetric adult deaths in a hospital were sampled, virtually all 236 cadavers were HIV-infected, half had culture evidence of TB but only half of these had been diagnosed with TB before death, and 17% had multi–drug-resistant strains (64). Similarly, a post mortem study assessing causes of death histologically and with mycobaterial and bacterial cultures showed that TB contributed to death in 17 of 25 adults receiving ART at the time of death (65). Extremely drug-resistant TB carries a very poor prognosis, particularly in HIV-infected adults, 51% of whom were reported to have died within 30 days of its diagnosis (66), and in those who survived long enough to initiate XDR treatment, 55% died while receiving treatment (67).

Cotrimoxazole added to standard TB treatment has proven efficacy in reducing mortality in coinfected patients (68, 69) and in reducing mortality in patients receiving ART (70). Until recently, there was uncertainty about the timing of ART initiation in HIV-infected patients started on TB treatment, particularly because TB treatment with cotrimoxazole and ART includes nine different therapeutic agents. Two landmark trials have shown that early ART after TB diagnosis reduces the high mortality among TB/HIV coinfected patients. The initial analysis of the Starting Antiretroviral Therapy at Three points in TB randomized trial from Durban, South Africa showed 56% reduction in mortality in HIV-infected patients with TB whose CD4 count was less than 5000 cells/l who received early ART (71). The trial randomized adults with TB into three groups according to when ART was started in relation to TB treatment initiation: at TB treatment start, completion of the initial intensive phase of TB treatment, or after completion of TB treatment. Comparisons between the two early ART initiation arms have yet to be published. Preliminary data from the Cambodian Early versus Late Introduction of Antiretroviral Drugs (CAMELIA) study showed that in the group of TB/HIV coinfected patients with CD4 less than 2000 cells/l, initiation of ART 2 weeks after starting TB treatment in adults with confirmed TB had a one third reduction in mortality; 59 of 332 patients who started ART within 2 weeks of TB treatment died, whereas 90 of 329 who delayed ART initiation until 8 weeks after starting TB treatment died (72). The mortality impact was seen 1 year after enrollment, suggesting that the long-term benefit of ART was the key to survival rather than a shorter-term benefit from surviving TB. Further support for the long-term effect of ART is a randomized trial from Uganda of early versus delayed ART in patients whose CD4 count was above 350. In that study, ART with TB treatment was not shown to improve responses to TB treatment compared with

those who did not receive ART (73). The high initial mortality driven by TB after starting ART raises the issue of whether empiric TB treatment should be started in all, or possibly a subset, of patients initiating ART with low CD4 counts while awaiting laboratory results.

DIAGNOSIS OF TB

In HIV-infected adults, sensitivity and specificity of sputum smear to detect acid fast bacilli, the mainstay of diagnosis in developing settings, is reduced because of the lower mycobacterial burden in sputum (74, 75). This problem is compounded by subclinical (or asymptomatic) active TB in HIV-infected adults (28, 76–78), suggesting that TB screening algorithms must have a low threshold for identifying a TB suspect requiring further investigation. An intensified case finding study from three Southeast Asian countries assessing symptoms that predicted TB in HIV-infected outpatients not on ART showed that, rather than using cough lasting for weeks to identify patients with suspected TB, a combination of symptoms over the past 4 weeks accurately divided participants into patients with suspected TB and those not requiring further investigation. The symptoms reported as being highly sensitive and specific in ruling out TB were any duration of cough and fever with night sweats for longer than 3 weeks (79). Investigation of TB in HIV-infected individuals should include sputum smear, mycobacterial culture, and a possibly chest radiograph as part of the process, although these are not available in many high HIV–prevalence settings.

A massive breakthrough in TB diagnostics was made recently. The Xpert MTB/RIF, based on the GeneXpert rapid PCR diagnostic platform, is a robust TB diagnostic with very high sensitivity and specificity in smear-positive and, importantly for HIV-infected adults, smear-negative adults (80). Developed in conjunction with the Foundation for Innovative New Diagnostics, the product provides a result in 1.75 hours, which includes the presence of genotypic rifampin resistance, with a sensitivity and specificity of 97.6% and 98.1%, respectively. Moreover, it does not require sophisticated specimen preparation. Pilot sites in a variety of settings and applications are planned or underway, but use in resource-limited settings may be limited by cost and availability of uninterrupted electrical supply.

Another potential rapid diagnostic test is the urinary TB antigen lipoarabinomannan, which holds some promise in the diagnosis of TB in HIV-infected patients with low CD4 counts (81, 82). This technology could be particularly useful if incorporated into a point-of-care urine dipstick because urine samples avoid the use of sharps and the creation of infectious aerosols.

Although similar breakthroughs in the treatment of drug-sensitive TB have yet to be made, the TB drug pipeline has never been larger (83, 84), and a recent report of the efficacy of TMC207, a dairylquinalone in the treatment of MDR TB, is welcomed. The cornerstone of effective TB treatment remains an uninterrupted supply of fixed-dose combination tablets combined with excellent individual adherence. A safe and effective TB therapy that could shorten the current 6-month regimen is unfortunately still a distant goal.

CONCLUSION

Despite important advances in the understanding of HIV-associated TB, its rapid diagnosis, and modalities to prevent and reduce its mortality, the rates of TB and the attendant mortality in high HIV–prevalence settings are far too high. Our challenge is the rapid, efficient, and broad implementation of research advances in low-resource settings.

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