HIV Infection–Associated Tuberculosis: The Epidemiology and the Response

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Of the 33.2 million persons infected with human immunodeficiency virus (HIV), one-third are estimated to also be infected with *Mycobacterium tuberculosis*. In 2008, there were an estimated 1.4 million new cases of tuberculosis (TB) among persons with HIV infection, and TB accounted for 26% of AIDS-related deaths. The relative risk of TB among HIV-infected persons, compared with that among HIV-uninfected persons, ranges from 20- and 37-fold, depending on the state of the HIV epidemic. In 2008, 1.4 million patients with TB were tested globally for HIV, and 81 countries tested more than half of their patients with TB for HIV. Only 4% of all persons infected with HIV were screened for TB in the same year. Decentralization of HIV treatment services and strengthening of its integration with TB services are essential. Use of the highly decentralized TB services as an entry point to rapidly expand access to antiretroviral therapy and methods for prevention of HIV infection must be pursued aggressively.

The intricate linkage of tuberculosis (TB) and human immunodeficiency virus (HIV) infection for nearly the past 3 decades poses a major threat to the international community's effort to achieve the health-related United Nations Millennium Development Goals for TB and HIV infection [1] and other global commitments, such as universal access to comprehensive services for HIV infection prevention, treatment, and care [2] and the Stop TB Partnership's targets [3]. Despite the alarming increase in the number of TB cases in countries with a high prevalence of HIV infection during the early period of the epidemic, sometimes despite the implementation of good-quality directly observed therapy short-course (DOTS) programs, coordinated responses addressing both TB and HIV infection were slow and minimal. In 1989, the first international meeting organized by the World Health Organization (WHO) to discuss the dual epidemic of TB and HIV infection concluded that the priority of the countries with poor TB-control programs, which at the time included most countries with an increasing HIV burden, should be to improve the treatment and cure of patients through the DOTS strategy [4].

After a decade of almost no action, the WHO started pilot projects in 1997 in 3 sub-Saharan African countries (Malawi, Zambia, and South Africa) to promote voluntary HIV testing as an entry point for access to TB screening and preventive therapy for persons infected with HIV [5]. These so-called ProTEST (promotion of voluntary testing) projects aimed to develop a district-based strategy for a joint TB and HIV program response. Evaluation of these projects demonstrated that HIV/AIDS- and TB-control program can work together effectively, from subdistrict to national level, and the results convinced policy makers and program managers that these collaborative activities were both necessary and feasible [5]. In response to demand from countries, the Global TB/HIV Working Group was established in 2001 under the auspices of the Stop TB Partnership, with the Secretariat based in the WHO [6]. The Working Group has been instrumental in advising the WHO to develop policy and program guidance on the basis of the best available evidence [7–11].

The development of the WHO Policy on Collaborative TB/HIV Activities identified the key interventions

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to decrease the burden of TB and HIV infection and AIDS in populations affected by both diseases, through effective collaboration between the 2 disease-control programs [9]. Countries have found that the policy is particularly useful in guiding their response to the problem. This article reviews the current epidemiology of HIV infection–associated TB and the global progress in the implementation of these interventions.

EPIDEMIOLOGY OF GLOBAL TB, HIV INFECTION, AND HIV INFECTION–ASSOCIATED TB

Epidemiology of TB. Globally, TB remains among the leading causes of death from an infectious agent. In 2008, the estimated global TB incidence rate was 139 cases per 100,000 population, which equates to 9.4 million (range, 8.9–9.9 million) incident TB cases. This represents an 11% increase in TB incidence rate and a 40% increase in the number of TB cases, compared with estimates from 1990 [12]. This global increase in rates was attributable to increases in the sub-Saharan African and European regions and was mainly driven by the HIV epidemic. Particularly in sub-Saharan Africa, mirroring the HIV epidemic, TB incidence and TB-associated death rates have doubled, and the number of TB cases and TB-related deaths has tripled in comparison with estimated figures from 1990 [12]. Globally, incidence rates have been decreasing slowly (by <1% annually) since 2004 [12], although the number of TB cases is still increasing as a result of increases in the population. More than half (55%) of the estimated number of TB cases in 2008 were in Asia, followed by Africa (30%), with the other 15% divided among the remaining regions. In 2008, a total of 5.7 million incident TB cases were notified by national TB-control programs globally; 22% of patients with TB were tested for HIV infection [12].

Epidemiology of HIV infection. By the end of 2008, an estimated 33.2 million persons were infected with HIV, of whom 2.1 million were children. Similarly, an estimated 2.7 million persons were newly infected with HIV in 2007, and 2.1 million died of AIDS. Approximately two-thirds of all persons infected with HIV live in sub-Saharan Africa [13]. The majority of HIV-infected persons do not know their HIV status, and there are no comparable global data to exactly quantify the proportion of the population that knows their HIV status. However, there has recently been substantial expansion of HIV testing services in many countries. Comparable data provided to the WHO from 17 countries showed that the number of HIV testing facilities increased by 2.5 fold between 2006 and 2007 [2]. Although variable with a wide range, several studies showed that only 1 of 5 persons knows his or her HIV status in many settings with a high prevalence of HIV infection [2, 14].

Globally, an estimated 80% of all HIV infections are sexually transmitted, and 10% of all new infections are in injection drug users [2]. By the end of 2008, >4 million persons were receiving antiretroviral therapy (ART), which was 1 million more than in 2007 [15]. The world had met the "3-by-5" target of providing ART to 3 million persons in low- and middle-income countries by 2005, but did so in 2007, 2 years after the target year. This is in contrast to the prediction of many persons that the target was unachievable when the initiative was launched in 2003 [2].

Epidemiology of HIV infection–related TB. Globally, ~30% of HIV-infected persons are estimated to have concomitant (usually latent) infection with *M. tuberculosis;* this percentage varies from 14% in Europe to 46% in Southeast Asia [16]. The HIV epidemic increased the number of TB cases in countries with a high prevalence of HIV infection starting in the late 1980s, with a 3-fold increase in the number of TB case notifications over the decade, particularly in sub-Saharan Africa [17]. These increases mirrored the increase in the prevalence of HIV infection but with a 4–7-year delay [18, 19].

In 2008, nearly 1 of 3 TB-related deaths (29%) worldwide was considered to be related to HIV infection, and TB contributed to 26% of the estimated deaths due to HIV infection [20]. There were an estimated 1.4 million new cases of TB in HIV-infected persons and 520,000 deaths, which was double the previous estimates. This was not a true increase, but rather, the expansion of HIV testing and the availability of reliable and representative data on prevalence of HIV infection among patients with TB necessitated revision of the estimates. According to the revisions, the number of HIV-infected patients with TB peaked in 2004, with 1.39 million cases and 550,000 deaths [20]. Countries in sub-Saharan Africa accounted for ~80% of the estimated global burden of HIV infection–associated TB in 2007, followed by countries in Southeast Asia (10%). South Africa alone accounts for nearly one-third of the global burden.

Similarly, the expansion of HIV testing for patients with TB on a larger scale and the availability of more-representative data showed that the relative risk of TB among HIV-infected persons, compared with HIV-uninfected persons (ie, incidence rate ratio), was higher than previously estimated [16, 21]. The incidence rate ratio was estimated to be 20.6 (95% confidence interval [CI], 15.4–27.5) in 2007 in countries with a generalized HIV epidemic, 26.7 (95% CI, 20.4–34.9) in countries with concentrated epidemics, and 36.7 (95% CI, 11.6–116) in countries with low prevalence of HIV infection (Table 1) [20].

Epidemiology of multidrug-resistant (MDR) TB and extensively drug-resistant TB among HIV-infected persons. The global epidemiology of drug-resistant TB in HIV-infected persons is not known because of lack of information. The Global Project of Anti-Tuberculosis Drug Resistance, which has

Table 1. HIV Epidemic State and Estimated Relative Risk of Developing Tuberculosis (TB) in HIV-Infected Persons in Comparison with HIV-Uninfected Persons (Incidence Rate Ratio)

	Incidence rate ratio	
HIV epidemic situation	Revised (95% confidence interval)	Previous (range)
Generalized: prevalence of HIV infection consistently >1% among pregnant women	20.6 (15.4–27.5)	30 (21–39)
Concentrated: prevalence of HIV infection consistently >5% in at least in 1 defined subpopulation and <1% among pregnant women in urban areas	26.7 (20.4–34.9)	6 (3.5–8.0)
Low-level: prevalence of HIV infection has not consistently exceeded 5% in any defined subpopulation	36.7 (11.6–116)	6 (3.5–8.0)

been gathering data since 1994, included data on the interaction between HIV infection and drug-resistant TB only in its most recent report; this report includes data from 7 settings, none of which have a high prevalence of HIV infection. There was no association between HIV infection and MDR-TB in 5 of these countries, whereas a significant association was observed between MDR-TB and HIV infection in 2 settings in Latvia (odds ratio, 2.1; 95% CI, 1.4–3.0) and Ukraine (odds ratio, 1.5; 95% CI, 1.1–2.0) [22]. Both of these studies were population based and of significant size, examining all patients in Latvia and a large Ukrainian oblast (Donetsk) during a full calendar year. Several other studies reported no association between MDR-TB and HIV infection in countries in sub-Saharan Africa [23–26], Southeast Asia [27, 28], and elsewhere [29, 30]. Similarly, a systematic review including 32 studies from 17 countries could not demonstrate an overall association between MDR-TB and HIV infection [31]. However, these studies included small numbers of MDR-TB cases, many were conducted before the exacerbation of the HIV and TB coepidemics, and there was lack of adjustment for potential confounders of individual studies [29–31].

On the other hand, published literature over the past 2 decades showed that institutional outbreaks of drug-resistant TB primarily affect HIV-infected persons and are associated with a significantly higher mortality rate and short survival period [32, 33]. The outbreaks were largely linked to poor infection-control practices and occurred before the availability of ART [32]. However, concomitant ART did not improve survival or survival time among cases in the Tugela Ferry outbreak in South Africa [33]. Although acquired rifampicin resistance has been established in HIV-infected persons [34–36], drug-resistant TB in HIV-infected persons is often a result of exogenous transmission [31–33]. A statistically significant association between HIV status and the direct transmission of an MDR strain of *M. tuberculosis* was observed (prevalence ratio, 2.72; 95% CI, 2.03–3.66) in a systematic review [31]. Few data are available on MDR-TB and extensively drug-resistant TB in HIV-infected children.

DIAGNOSIS OF TB IN PERSONS INFECTED WITH HIV

Diagnosis of active TB disease in HIV-infected persons is difficult, because patients with HIV-associated TB have fewer bacilli in their sputum [37] than do HIV-uninfected patients with pulmonary TB. In addition, it has been observed that presence of a cough for >3 weeks is not sensitive enough on its own as a symptom of TB in HIV-infected persons [38].

Because diagnosis in most regions depends on microscopic examination of Ziehl-Neelsen–stained sputum smears, which has low sensitivity among HIV-infected persons, most HIV-infected persons are not tested with the standard diagnostic methodology. The specific impact of methods that optimize the use of smear microscopy, such as sputum processing (liquefaction or concentration through sedimentation), and the use of fluorescence microscopy is not well understood for HIV-infected persons. Mycobacterial culture is the gold standard for TB diagnosis and is now routinely recommended to assist the diagnosis of TB in HIV-infected persons [39], although it is frustratingly slow. HIV infection compromises the validity and effectiveness of chest radiography in the diagnosis of pulmonary TB in HIV-infected persons, and the findings could be normal for up to 14% of HIV-infected persons who have culture-confirmed pulmonary TB [40]. However, chest radiography remains an important adjunct in the diagnosis of TB, and its use must be expanded, including the use of advanced and innovative technology, such as digital imaging [41].

POLICY AND PROGRAM RESPONSE

Provider-initiated HIV testing is recommended for all patients with TB and patients presenting with symptoms and signs of TB as standard of care [42]. By the end of 2008, nearly 1.4 million patients with TB were tested for HIV across 143 coun-

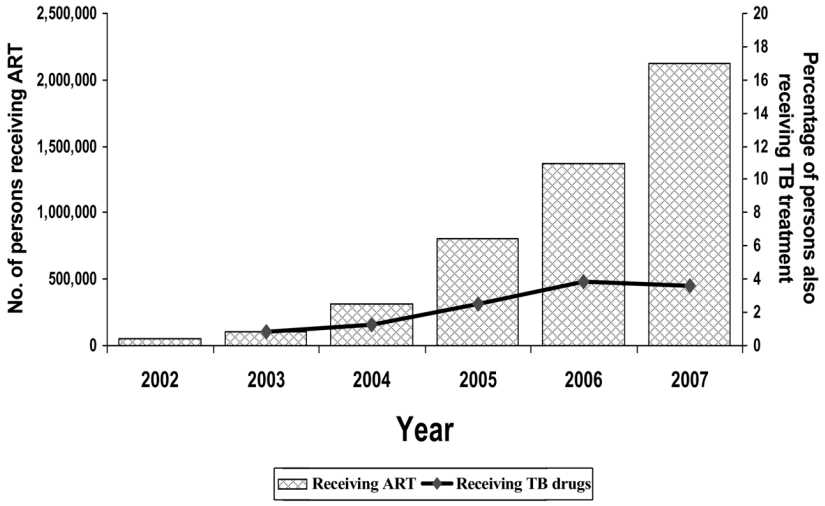

Figure 1. Number of HIV-infected persons receiving antiretroviral treatment (ART) and percentage of persons receiving concomitant tuberculosis (TB) treatment in Africa, 2002–2007.

tries in the world, which was a 64-fold increase over 6 years since 2002 [20]. Figure 1 shows 22% of all notified patients with TB in 2008. The rapid expansion of HIV testing for patients with TB is particularly encouraging in Africa. In 2004, only 4% of notified patients with TB in the region were tested for HIV, but in 2008, that number increased to 45%, with 11 countries testing >75% of all patients with TB who received a new diagnosis of HIV infection [20]. Globally, 50 countries tested at least 75% of their patients with TB for HIV by the end of 2008. Similarly, 200,000 HIV-infected patients with TB received trimethoprim-sulfamethoxazole treatment to prevent opportunistic infections and 100,000 received ART in 2008. One-third of the HIV-infected patients who received a diagnosis of TB initiated ART, representing only 7% of the estimated incident cases of HIV infection–related TB [20] and 2.5% of all those who received ART in 2008 [2]. Outcome data from 55 countries show that HIV-infected patients with TB are 4 times more likely to die during TB treatment than are HIV-uninfected patients with TB [20].

The overall implementation of collaborative TB/HIV activities that are recommended to reduce the burden of TB among HIV-infected persons—namely, intensified TB case finding, isoniazid preventive therapy, and infection control for TB (which are branded as the 3 I's for HIV infection and TB)—has been slow. However, the number of HIV-infected persons screened for TB increased from 600,000 to 1.4 million from 2007 to 2008 [12]; this was a 14-fold increase from the number of HIV-infected persons screened for TB in 2005. Similarly, in 2007, only 29,000 HIV-infected persons were offered isoniazid preventive therapy [20]; this number increased to 50,000 in 2008 [12]. The number of countries implementing and reporting these 2 important activities has increased from 4 each in 2002 to 82 for intensified case finding and 42 for isoniazid preventive therapy in 2008 [20].

TB infection control is a complex intervention with implications that go beyond health care settings to community, family, and individual levels. In the Global WHO TB/HIV Monitoring System, there were no indicators to monitor the global progress of implementation of TB infection-control interventions, with the exception of assessment of the policy and program environment. However, the inclusion of new indicators of TB infection control as an integral part of the monitoring and evaluation of collaborative TB/HIV activities at the country level will significantly improve the assessment of progress. The newly introduced indicators are the proportion of health care facilities providing services for HIV-infected persons that have infection-control practices that include TB control and the proportion of health care workers employed in facilities providing care for HIV-infected persons who developed TB during the reporting period [43].

HIV INFECTION–RELATED TB IN SPECIAL POPULATIONS

Women infected with HIV. By the end of 2007, relatively more women had TB detected than men in countries with a prevalence of HIV infection of >1%. This finding is in contrast to the preponderance of adult men with TB being detected globally, compared with adult women. The mean male-to-female ratio of notified smear-positive cases in 2007 was 1:1.3 in Africa overall and >1:2.0 in 8 countries [20]. Studies from South Africa reported that HIV-infected pregnant women had active TB at ~10 times the rate among HIV-uninfected women [44], and TB accounted for ~15% of maternal mortality in teaching

hospitals [45]. Similarly, in Zambia, the number of TB-associated deaths during pregnancy has increased, and the majority of the increase was associated with the HIV epidemic [46]. Therefore, TB screening, diagnosis, and prevention should be integral parts of maternal health services in settings with a high prevalence of HIV infection.

Issues need to be considered when addressing HIV infection–related TB in women, particularly women of reproductive age. Efavirenz-containing regimens are not recommended during the first trimester of pregnancy or for women with childbearing potential, unless effective contraception is ensured. A change from an efavirenz-containing regimen to a nevirapine-containing regimen can be considered after TB treatment is completed [47]. Moreover, the management of MDR-TB during pregnancy involves multiple difficulties [48].

Drug users infected with HIV. An estimated 20% of the 15 million injection drug users worldwide have HIV infection [49] and account for 10% of the global HIV burden [2]. Injection drug use has driven the HIV epidemic in many settings, and harm-reduction methods can decrease the impact of HIV infection. In the absence of HIV infection, rates of TB disease are 6–10-times higher among injection drug users than among the general population [50]. This further compounds the impact of HIV infection–related TB in drug users who are either HIV infected or vulnerable to HIV infection. Access to effective interventions for HIV-infected patients with TB who are also drug users is worsened by poor treatment access, low rates of TB treatment completion, and exposure to prison settings [51]. Early introduction of harm-reduction measures in Australia and New Zealand led to a rate of HIV infection of 1.5% among drug users, and in eastern Europe, South Asia, and Latin America, rates are upward of 40% [49]. The WHO, in collaboration with the United Nations Joint Programme on HIV/AIDS and United Nations Office on Drug and Crime, developed guidelines to address HIV infection–related TB in drug users. The guidelines defined ways for coordinated delivery of collaborative TB/HIV activities, with ample consideration of the specific needs of drug users through collaborative planning among HIV and TB services, specialist drug services, and the criminal justice system [52]. The implementation of these guidelines in countries with drug use problems is essential and critical to the health of drug users and also contributes toward universal access of TB and HIV services for HIV-infected persons.

HIV-infected persons living in congregate settings. HIV-infected persons in congregate settings, such as prisons and centers for refugees or internally displaced persons, have a higher risk and incidence of TB, HIV infection, and drug use in many countries [53–55]. There is often increased transmission of HIV and TB, including MDR-TB, in prisons [51, 54, 56]. The crowded living conditions in most congregate settings facilitate the transmission of TB. In addition, poor nutritional status and other coexistent illnesses in many prisoners and refugees weaken their immune systems and make them more vulnerable to developing active TB. Refugees, internally displaced persons, and prisoners have a right to a standard of health care equivalent to that for persons living outside these settings. Collaborative TB/HIV services should thus be provided to these segments of the society, with close collaboration and consultation between national TB- and HIV-control programs and other stakeholders dealing with these special groups, such as the prison health care service. Local ownership has to be promoted, and the local political, social, and cultural context needs to be taken into account when designing such programs, with particular emphasis on control of TB transmission and promotion of prevention of HIV infection.

CONCLUSIONS

The dual HIV and TB epidemic poses one of the greatest challenges for public health and the clinical treatment of HIV-infected persons. The massive investments and the gains obtained to expand HIV treatment in resource-constrained settings should be safeguarded through bold action, mainly by stakeholders in HIV services [57], who will need to be very vigilant as the global economic crisis threatens these gains. Earlier identification of persons with signs and symptoms of TB and provision of TB prevention and treatment in a safe environment with no risk of TB transmission are crucially needed.

Nationwide scale-up of collaborative TB/HIV activities should be accelerated in all countries with an HIV burden. Data obtained from 8 countries that contributed nearly one-fifth of the global burden of HIV infection–associated TB in 2007 showed that, on average, there are up to 5 decentralized TB treatment facilities per every ART facility [20]. This excellent opportunity of using TB services as an entry point to rapidly expand access to ART and methods for prevention of HIV infection has to be pursued aggressively. This entails delegating clinical core functions of the management of ART from highly specialized to less specialized health care workers [58, 59], decentralizing care, and adapting national AIDS and TB policies accordingly. Providing HIV testing not only to patients with TB but also to persons who present with signs and symptoms of TB should be part of standard quality care, regardless of the HIV epidemic situation in a country.

The lack of rapid and accurate TB diagnostic tools and the lack of a standardized symptom- and sign-based screening strategy has posed a challenge to accelerating implementation of intensified TB case finding and the provision of isoniazid preventive therapy for HIV-infected persons in resource-limited settings. Available information, experience, and data have to be used to develop a simple and standardized TB screening strategy for use in settings with a high prevalence of HIV infection,

while accelerating the research and development for transformational TB diagnostic tools. In addition, the expanded use of all available TB diagnostic methods needs to be supported. Promoting research interest and investment to yield a rapid, simple, and transformational tool that can accurately diagnose TB and effective drugs that can shorten the treatment duration of TB, whether it is drug susceptible or resistant, will ultimately be essential for the eradication of one of the major global plagues.

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