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JAMA. 2008;300(4):423-430 (doi:10.1001/jama.300.4.423)

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Opportunities and Challenges for HIV Care in Overlapping HIV and TB Epidemics

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OF ALL THE COMPLICATIONS associated with human immunodeficiency virus (HIV) disease, tuberculosis (TB) represents the greatest challenge. Tuberculosis results in enormous suffering and stigma, is a threat throughout the course of HIV disease, and is a leading cause of death.^{1,2} Tuberculosis is one of the few transmissible agents in the health care setting that poses a risk not only to patients seeking care but to the health care workforce in resource-limited settings, which is already short staffed.³⁻⁵

There are now an estimated 10 000 health facilities providing antiretroviral therapy (ART), including 4200 in Africa.⁶ As HIV care expands further, there is both an opportunity and necessity for incorporation of TB control activities into these programs. Tuberculosis programs simply do not have the capacity to provide ongoing TB screening, prevention, and treatment for millions of individuals receiving HIV care. We review key interactions between HIV and TB for HIV care programs, a framework for HIV programs to incorporate TB activities, and global progress in implementation.

See also Patient Page.

Tuberculosis (TB) and the emerging multidrug-resistant TB epidemic represent major challenges to human immunodeficiency virus (HIV) care and treatment programs in resource-limited settings. Tuberculosis is a major cause of mortality among patients with HIV and poses a risk throughout the course of HIV disease, even after successful initiation of antiretroviral therapy (ART). Progress in the implementation of activities directed at reducing TB burden in the HIV population lags far behind global targets. HIV programs designed for longitudinal care are ideally suited to implement TB control measures and have no option but to address TB vigorously to save patient lives, to safeguard the massive investment in HIV treatment, and to curb the global TB burden. We propose a framework of strategic actions for HIV care programs to optimally integrate TB into their services. The core activities of this framework include intensified TB case finding, treatment of TB, isoniazid preventive treatment, infection control, administration of ART, TB recording and reporting, and joint efforts of HIV and TB programs at the national and local levels.

JAMA. 2008;300(4):423-430

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HIV and TB Interactions

Risk of TB Among Individuals With HIV Living in TB Endemic Areas in the ART Era. Tuberculosis is an opportunistic infection with an increasing risk throughout the course of HIV disease, including after ART initiation (FIGURE).⁷⁻¹³ This increased risk is detectable as early as HIV seroconversion.⁷ In a prospective cohort of 23 874 South African miners, TB incidence doubled the first year after HIV seroconversion.⁷ Tuberculosis risk further increases as CD4 cell levels decrease. For example, in Cape Town, South Africa, the incidence of TB was 17.5 cases per 100 person-years, 12.0 cases per 100 person-years, and 3.6 cases per 100 person-years for individuals with CD4 cell counts of less than

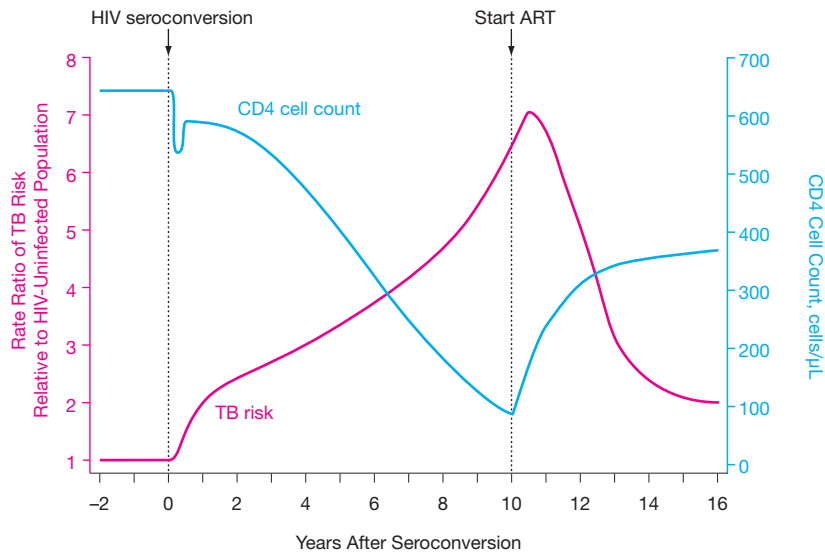
200 cells/ μ L, 200 to 350 cells/ μ L, and more than 350 cells/ μ L, respectively.⁸

ART significantly reduces the risk of TB. Tuberculosis case rates decreased shortly after the first introduction of ART.¹⁴⁻¹⁶ Reductions in TB rates in highly TB endemic settings associated with ART have been dramatic (TABLE 1).^{8-11,17-21} In Cape Town, South Africa, ART use was associated with an 81% risk reduction for TB.⁸ Several studies^{8-10,17,19} reported a paradoxical increase in TB diagnosis within the first

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Figure. Schematic of Risk of TB and Change in CD4 Cell Count From Onset of HIV Seroconversion



TB indicates tuberculosis; ART, antiretroviral therapy; HIV, human immunodeficiency virus. Schematic of risk of TB and CD4 cell count decline from onset of HIV seroconversion until 6 years after ART initiation for an individual living in a TB endemic area. This hypothetical individual presents to HIV care and starts ART when the CD4 cell count is 100 cells/ μ L. Fold change risk of TB is relative to HIV-uninfected population. Schema is based on data from published cohort studies.⁷⁻¹³

year of ART, mostly due to a combination of undiagnosed cases of TB, activation of latent TB infection, and new TB infections.²²

Rates of TB remain substantial and above the background rates in HIV-uninfected populations despite ART use.^{10,20} An incomplete immune restoration of TB-specific immune responses to ART may explain this observation.²³⁻²⁵ The extent to which ART protective effects for TB are sustained among individuals living in TB endemic areas is unknown. Waning ART adherence rates and treatment interruptions have the potential to reverse the protective effects of ART.²⁶ Although treatment interruptions of ART are not recommended, breaks in ART supply will unfortunately continue to occur in resource-constrained settings placing patients at increased risk for TB. Tuberculosis risk in patients receiving ART with suboptimal immunological responses or virologic rebound also remains to be determined.

Isoniazid preventive therapy (IPT) also reduces risk of TB among patients with HIV. Studies demonstrate an approximately 60% reduction in TB, with lower rates among individuals with a negative purified protein derivative (tuberculin) skin test.^{27,28} Protection can be detected from 18 months to 4 years.^{29,30} The inability of IPT strategies to provide durable protection against TB may be due to repeated infections of TB that occur in persons with HIV, particularly among patients with severe immunosuppression living in TB-endemic regions. IPT added to the preventive benefit of ART in 1 retrospective study in Brazil,⁹ although these data require confirmation in prospective studies. The role of isoniazid after TB treatment in the ART era remains an important and unanswered question.^{31,32}

Emerging Epidemic of Multidrug-Resistant and Extensively Drug-Resistant TB. One of the utmost threats at the intersection of HIV and TB is extensively drug-resistant TB. Extensively drug-resistant TB is defined as TB

with resistance to at least isoniazid and rifampin (multidrug resistant) plus resistance to any fluoroquinolone, and to a second-line injectable drug.³³ The study of multidrug-resistant and extensively drug-resistant TB from Tugela Ferry, South Africa,³ came as no surprise to those investigators working with HIV and TB. Weakened TB control programs, absent infection control, delayed access to diagnostic testing for TB isolates in the setting of large numbers of individuals with severe immune suppression and HIV has led to a recapitulation of epidemics of multidrug-resistant TB observed in the United States in the 1980s.^{34,35} Although the extent of this epidemic in Africa is unknown, multidrug-resistant and extensively drug-resistant TB has recently been reported in Botswana and Namibia; it is also occurring at alarming rates among persons with HIV in Eastern Europe.³⁶

The high mortality rates of multidrug-resistant and extensively drug-resistant TB have the potential to undermine progress in the rollout of ART, particularly in sub-Saharan Africa. In a study of multidrug-resistant TB cases among individuals with HIV occurring before the Tugela Ferry outbreak, mortality ranged between 72% and 98%.³⁷ In Tugela Ferry, 52 of 53 patients died, with a median survival time from collection of sputum to death of 16 days.³ Molecular fingerprinting studies confirmed multidrug-resistant and extensively drug-resistant TB was being transmitted in both the community and health care facilities. In addition, some of the cases acquired in the hospital were individuals already under treatment with a drug-sensitive TB strain who were then reinfected with a drug-resistant strain.³⁸ This epidemic highlights the importance of rapid diagnostic tests to screen for multidrug-resistant and extensively drug-resistant TB and the need for far more effective infection control measures.

Diagnosis and Treatment of TB in the HIV Population. Tuberculosis diagnosis remains extremely challenging in the HIV-infected population.

Autopsy studies conducted in Africa confirm that unsuspected TB is often present among patients dying with AIDS.³⁹⁻⁴² Smear-negative pulmonary TB is common in the HIV population, disseminated disease is often smear-negative with nonspecific symptoms, and extrapulmonary disease is frequent. Pulmonary TB clinical presentation becomes increasingly atypical in the setting of severe immune suppression.^{43,44} With the exception of smear-positive pulmonary TB, a diagnosis of TB may be thus often dependent on clinical judgment alone. In addition, there is a subpopulation of individuals with HIV with culture-positive pulmonary TB who are completely asymptomatic.^{45,46}

Patients with HIV have acceptable cure rates with a standard TB treatment course that includes a rifampicin-containing continuation phase.⁴⁷ High

mortality rates observed in patients with HIV and TB are more likely attributed to missed or delayed diagnosis of TB and long delays in ART initiation.⁴⁸ Despite inherent challenges in treating TB in patients who require ART, it is extremely encouraging that TB does not jeopardize virologic responses to ART.^{10,49}

Patient management is complicated by drug interactions between ART and rifampin. Rifampin reduces efavirenz, nevirapine, and protease inhibitor levels via induction of hepatic enzymes.⁵⁰⁻⁵² In first-line ART, efavirenz is recommended because reduction in levels are less than those with nevirapine. When both are contraindicated, such as in women of child-bearing potential with high CD4 cell counts, certain triple nucleoside regimens are an alternative.⁵³ Patients with TB requiring rifampin and protease inhibitors must use either ritonavir-boosted,

saquinavir-boosted, or lopinavir-boosted protease inhibitor regimens. Higher than standard ritonavir doses are needed, and hepatotoxicity may be limiting.⁵⁴ Wider availability and access to rifabutin, a less potent inducer of protease inhibitor metabolism than rifampin, may improve this situation.^{50,55} Optimal timing of ART initiation for patients with TB is currently unknown. Pending results of ongoing clinical trials, the World Health Organization (WHO) has issued interim guidelines balancing risks of untreated HIV disease against those of simultaneous treatment of both diseases.^{54,56}

Exaggerated inflammatory responses (paradoxical reactions) in persons with TB are more common in patients with HIV who initiate ART compared with patients uninfected with HIV.^{57,58} Fortunately, these events are

Table 1. Tuberculosis Incidence Rates Among HIV-Infected Cohorts With and Without Antiretroviral Therapy in Resource-Limited Settings

Source	Setting	No. of Patients in the Cohort	TB Incidence Rates per 100 Person-Years		Comment
			With Antiretroviral Therapy	Without Antiretroviral Therapy	
Seyler et al, ¹⁷ 2005	Abidjan, Côte d'Ivoire	129	4.8	NA	TB incidence 11.3 per 100 person-years with prior TB; 3.0 per 100 person-years with no prior TB
Badri et al, ⁹ 2002	Cape Town, South Africa	1034	2.4	9.7	Adjusted relative risk, 0.19; 95% CI, 0.09-0.38 for antiretroviral therapy vs no antiretroviral therapy
Brinkhof et al, ¹⁸ 2007	Africa Latin America Asia	4540	10.7 (1-3 mo) 7.5 (4-6 mo) 5.2 (7-12 mo)	NA	
Lawn et al, ¹¹ 2005	Cape Town, South Africa	346	3.35 (year 1) 1.56 (year 2) 1.36 (year 3) 0.90 (year 4) 1.01 (year 5)	NA	
Bonnet et al, ¹⁹ 2006	Cambodia Kenya Malawi Cameroon	3151	4.8-17.6 (pulmonary TB) 0-12.7 (extrapulmonary TB)	NA	
Golub et al, ⁹ 2007	Rio de Janeiro, Brazil	11 026	1.90	4.01	Rates with isoniazid preventive therapy plus antiretroviral therapy, 0.80 per 100 person-years
Moore et al, ²⁰ 2007	Tororo, Uganda	1044	3.9	NA	
Lawn et al, ¹⁰ 2006	Gugulethu Community Healthcenter, South Africa	1002	23.0 (1-3 mo) 10.7 (3-6 mo) 7.0 (6-12 mo) 3.7 (12-24 mo) 7.4 (>2 y)	NA	67% of patients with previous or prevalent TB at start of antiretroviral therapy
Walters et al, ²¹ 2008	Cape Town, South Africa	290	6.4	53.3	Pediatric cohort study

Abbreviations: CI, confidence interval; HIV, human immunodeficiency virus; NA, not available; TB, tuberculosis.

Table 2. HIV Programmatic Activities for Prevention and Treatment of TB in HIV Care and Treatment Programs

Activity	Purpose	Frequency/Indication
Intensified case finding	Early identification and treatment of TB; rapid identification of multidrug-resistant and extensively drug-resistant TB	Entry to HIV care; routine clinic visits; household contacts of TB cases
Treatment of TB cases	Successfully treat TB, deliver antiretroviral therapy and TB compatible regimens as indicated, provide cotrimoxazole and manage immune reconstitution events	For each TB episode
Isoniazid preventive treatment	Prevent TB	Isoniazid preventive therapy for every patient after excluding active TB
Antiretroviral therapy	Prevent TB	According to national guidelines
Infection control	Reduce TB transmission	Continuous
TB reporting	Contribute to national and global TB monitoring efforts	Report isoniazid preventive therapy, TB cases, and drug resistance to TB control programs on annual basis
Joint HIV/TB planning	Coordinate HIV/TB action at all levels	HIV/TB coordinating body with at least bi-annual meetings

Abbreviations: HIV, human immunodeficiency virus; TB, tuberculosis.

rarely fatal, ART can be continued, and prednisone can be used to control excessive inflammatory responses. However, excluding other causes for clinical worsening is time-consuming and difficult for clinicians, particularly when diagnostic capabilities are limited. In a recent study from South Africa,⁵⁹ some cases classified as having immune reconstitution events among patients with TB receiving TB treatment and ART were actually due to a second infection with drug-resistant TB.

Thus, persons with HIV are at risk for TB from onset of HIV disease, diagnosis is limited by inadequate TB diagnostics and atypical presentations of TB, and management is complicated by drug interactions. Tuberculosis risk can be reduced through IPT and ART. However, even with these interventions, and even among persons successfully treated for an episode of TB, individuals with HIV living in TB endemic areas remain at increased risk for TB, including repeated TB episodes.^{60,61} Ongoing TB transmission and repeated infections are driving the TB epidemic, and the risk for

TB among patients with HIV may be further amplified in resource-constrained settings where health care facilities are often cramped, with little ventilation, and patients with infectious TB are numerous. Multidrug-resistant and extensively drug-resistant TB represent immediate threats for both the HIV and TB communities.

Strategic Approaches to Reduce TB Burden for HIV Care and Treatment Programs

Finding and treating TB cases, administering ART and IPT, and infection control are critical activities to incorporate into HIV care programs, the first chronic care models to emerge in many developing countries (TABLE 2). Because patients with HIV are at risk for TB throughout life, activities should be ongoing in pediatric and adult ART clinics, pre-ART clinics (keeping relatively healthy patients engaged in care), and maternal health programs.

TB Intensified Case Finding. Finding and treating TB promptly is the most effective TB control measure. Intensi-

fied case finding includes both active identification of TB among patients with HIV in care and screening their household members for active TB. Simple questionnaires and diagnostic algorithms to identify patients with TB should be administered on clinic entry and at routine examinations; the role of a screening chest radiograph in asymptomatic patients is not clear.⁶²⁻⁶⁹ Facilities for expectorated or induced sputum collection need to be safe, convenient, and set up so as not to expose patients with HIV to infectious TB cases. Fluorescence rather than conventional microscopy should be used to increase yield of TB identification.⁷⁰ HIV programs should establish transport operations to access laboratories using the most rapid TB culture and drug susceptibility methods. New molecular TB diagnostic and drug resistance tools appear promising, and cost savings may emerge from expanded molecular diagnostic capabilities in HIV laboratories.⁷¹

Extending active TB case finding to household members identifies undiagnosed HIV and TB. These efforts can also be extended to identify those individuals in need of IPT.⁷² In 64% of 596 culture-proven pediatric TB cases in Cape Town, South Africa, there were missed opportunities for IPT before TB diagnosis.⁷³ Whether intensified case finding at the household level should be under HIV programs or TB control or a combination of the 2 is not clear. What is clear is that this activity is feasible and that even in a severely resource-constrained setting, such as Malawi, the yield was high.⁷⁴ Operational research is ongoing to determine whether household contact investigation is most efficiently implemented primarily at the home or the clinic. Transportation, convenience, and stigma all contribute to this equation. At present, identifying patients with TB through some form of contact tracing is the minimum that programs should pursue—with appropriate safeguards to prevent TB transmission.

Treating Individuals With Active TB. Patients with HIV and active TB

may be most often treated in TB clinics with subsequent referral to HIV care. This model has evolved because TB can be the presenting HIV condition, TB clinics have the capacity and experience to diagnose and treat TB according to national guidelines, and there are 10- to 50-fold more clinics providing TB care vs those providing HIV treatment in high HIV burden countries. The downside of this arrangement is that prolonged delays between TB diagnosis and ART initiation may result in extraordinarily high rates of mortality in severely immune-compromised patients.^{48,75} Reductions of such delays require either TB staff to initiate ART, collocation of a government TB clinic and HIV clinic to facilitate cross-referral and convenience for the patient, or decentralization of ART clinics with capacity to treat TB.⁷⁶

We propose expansion of a care model whereby TB is treated by HIV programs. HIV care staff are trained to diagnose and treat a wide array of infections associated with HIV disease. Tuberculosis should be no exception.⁷⁵ This arrangement requires that HIV programs link to TB clinics to facilitate early referral of patients. HIV caregivers must be familiar with TB drug dosing, toxicities, and drug interactions, and evaluation and management of paradoxical reactions.

Empirical treatment for smear-negative TB in patients who are seriously ill should be prescribed according to recently revised guidelines.^{77,78} Administration of cotrimoxazole, an intervention demonstrating survival benefits among patients with TB, should be prescribed according to current guidelines.⁷⁹⁻⁸² HIV clinic management must ensure access to an uninterrupted supply of TB medications. Delivery of TB therapy should occur through adaptation of adherence activities already in place for ART or through partnering with government TB facilities implementing the Stop TB Strategy.⁸³

HIV programs are actively engaged in developing tracking mechanisms for patients who fail to appear for clinic. As HIV programs address and imple-

ment TB treatment, they will need to either develop the capacity or collaborate with TB programs to ensure that patients complete TB treatment and report the outcome of each treated patient to national TB programs. In areas with multidrug-resistant or extensively drug-resistant TB, HIV care programs will need to work with public health authorities and community activist groups to advocate for access to TB drug susceptibility testing and second-line TB agents and to establish safe and effective venues for treatment.⁸⁴

Isoniazid Preventive Therapy. HIV programs may need to work with country policymakers to permit IPT administration, which in some countries is either against national policy or impossible because of the stringent requirements for the exclusion of TB before IPT initiation. Research into improved IPT regimens and diagnostic screening algorithms is ongoing and should not be used as an excuse to delay IPT scale-up. Tuberculosis screening is the starting point for IPT. Based on the best available data and the epidemiology of the region, HIV programs need to systematically and routinely screen individuals and classify each one as having either no evidence of active TB, active TB, or as being indeterminate for TB. Patients in the first group should receive IPT and patients in the second group should receive TB treatment. The third group of patients merit further observation or diagnostic studies until active TB can be ruled out with an acceptable level of confidence. Delivery of IPT and ensuring adherence should be incorporated into ongoing program education, supporting and monitoring patients in adherence to cotrimoxazole and ART.

Antiretroviral Therapy. ART is one of the most powerful weapons against TB. HIV treatment programs have overcome substantial barriers to provide ART to millions of individuals, although there remain huge unmet needs. From the perspective of TB prevention, the earlier that ART is initiated, the less the risk for TB. Where multidrug-resistant TB strains are circulat-

ing, those individuals with compromised immune systems starting ART gain the added theoretical benefit of a reduced risk for acquiring multidrug-resistant TB. One of the most impressive success stories of the preventive effect of ART on TB is the Brazil experience. Tuberculosis rates among persons with HIV were reduced by 81% after ART introduction.⁸⁵

There is no controversy surrounding the implementation of ART according to current WHO guidelines as a measure among other measures to reduce TB. Concerns that ART will unleash a sizable epidemic of TB are exaggerated, although it is theoretically possible that as more individuals live longer with HIV, and even with a reduced risk of TB, that TB burden could increase. Should ART be initiated earlier than current guidelines recommend for solely the purpose of reducing TB? In a model addressing this approach, high ART coverage and high rates of adherence were required before a preventive benefit of ART was observed.⁸⁶ However, assumptions in this model need to be updated with new data, and ongoing research studies will address this strategy in a randomized trial.

TB Infection Control. Many of the activities discussed above such as intensified case finding and IPT reduce TB transmission and thus are important components of TB infection control. One of the most challenging areas in TB infection control is the implementation of measures in both outpatient and inpatient health care facilities that will reduce the risk of TB transmission and protect health care workers. HIV care programs can no longer afford to take a passive approach to this situation for the sake of both their patients and their staff. As HIV programs provide more TB care and treatment, clinics must take measures to prevent HIV clinics from becoming a nidus for TB transmission.

Tuberculosis infection control guidelines exist but are rarely implemented.⁸⁷ Although infection control was in the spotlight with extensively

drug-resistant TB, transmission of drug-sensitive TB in care facilities occurs at a much greater magnitude. Effective respiratory infection control measures should be introduced in HIV care services. Patients with suspected TB should be separated from other patients until TB is excluded.⁸⁸⁻⁹² Respirators such as N-95 masks should be provided to health care workers likely to be exposed to infectious patients with TB. Infection control approaches that include patient separation and masks can engender additional stigma for an already highly stigmatized population.

Thus, HIV programs will need to harness community support and use education as a tool to assist in implementing measures designed to protect staff and patients. These include advocacy and communication to ensure the community is aware of the risks posed by TB and the way it is transmitted, together with the hygienic measures that should be taken by patients with cough (handkerchief, cloth, or surgical mask to absorb respiratory secretions and reduce aerosolization). Ensuring maximal natural ventilation in HIV clinics is also important, does not generate stigma, and should be a priority. Simple measures such as opening windows and doors maximize natural ventilation so that the risk of airborne contagion is much lower and is particularly suited to tropical climates. In a recent study,⁹³ a combination of approaches including ventilation, drug resistance testing, and isolation facilities would avert 48% of extensively drug-resistant TB cases. Every facility should have an infection control plan with an individual responsible for enforcing it.

TB Recording and Reporting. Diagnosing and reporting TB is another crucial activity for HIV services. National TB control programs are responsible within countries to collect TB data within their country and to report these data to the WHO. For these agencies to effectively track the TB epidemic, it is essential that HIV care programs adhere to TB reporting requirements. Standardized recording and reporting formats in accordance with national TB

and AIDS control guidelines should be used.

Joint HIV/TB Planning. The successful implementation of TB interventions in HIV services requires effective communication, coordination, and collaboration with TB control programs. Medium-term and long-term plans that are jointly prepared with TB control programs are crucial during the initiation and scaling-up phases. Some countries have demonstrated that effective HIV/TB coordinating bodies, which are functional at all levels, were instrumental in facilitating collaboration and coordination between the HIV and TB stakeholders.⁹⁴ The joint plan should define the roles and responsibilities of each stakeholder for implementation and identify the best ways to maximize existing opportunities, including resource mobilization. Necessary planning elements include staff recruitment and training, financial resources, and ensuring a sustainable and effective commodity and supplies mechanism. The expansion of laboratory facilities and implementation of infection control require a joint and unified effort of the HIV and TB programs. The power of community advocacy in achieving these goals should not be underestimated.⁸⁴

Progress in Implementation of Key HIV and TB Activities

The only current global monitoring system to assess progress of HIV/TB activities relies on information provided by countries to the WHO. This system is currently under revision to improve and harmonize reporting of HIV/TB activities to the WHO and other primary funding agencies, such as President's Emergency Plan for AIDS Relief (PEPFAR).⁹⁵ Despite limitations of the current monitoring systems, there is evidence of some progress in HIV and TB activities. The number of countries reporting a mechanism to coordinate HIV and TB increased from 11 in 2002 to 102 in 2006.⁹⁶ During this time, countries with routine HIV testing for patients with TB increased from 9 to 128. By the end of 2006, data from 202

countries showed 12% of all notified patients with TB were tested for HIV—22% of patients with TB in Africa.⁹⁶ Of those patients with TB and known HIV, 78% were administered cotrimoxazole and 41% started ART. Some select countries such as Rwanda, Brazil, Thailand, and South Africa have made admirable progress in the scale-up of testing of known patients with TB for HIV and starting these patients on ART.⁹⁶ Nigeria reported that 86 897 patients in HIV care were screened for TB in 2007.⁹⁷ India has spearheaded cross-referral programs between HIV and TB clinics leading to increased TB detection in the HIV population.⁹⁸

Even with these advances, progress in implementation of all HIV/TB activities is lagging far behind global targets. Tuberculosis screening and IPT among persons with HIV remain abysmally low in the reported global data with 314 394 individuals, and 27 000 individuals having received these services, respectively, in 2006.⁹⁶ ART was provided to only a small fraction of patients with TB. Infection control programs are just being started and global targets are under development.

Conclusions

HIV care programs must take a bold approach to TB prevention, diagnosis, and treatment to successfully address the catastrophic and intersecting epidemics of HIV and TB. HIV programs need to take advantage of new earmarked funds for HIV/TB activities from agencies such as PEPFAR and the Global Fund to Fight HIV, TB, and Malaria. They must push for access for rapid TB diagnostic tests, conduct operational research, and launch educational efforts in partnership with the community to reduce TB transmission. Shortages in the health care workforce and laboratory capabilities clearly represent the greatest obstacles. However, the possibility for progress has never been greater with the global commitment to health care infrastructure strengthening geared toward consolidating the momentum through disease-specific efforts such as those involving HIV and TB.

Author Contributions: Dr Havlir had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Havlir, Getahun, Sanne, Nunn.

Acquisition of data: Getahun, Nunn.

Drafting of the manuscript: Havlir.

Critical revision of the manuscript for important intellectual content: Havlir, Getahun, Sanne, Nunn.

Administrative, technical, or material support: Getahun, Sanne, Nunn.

Study supervision: Havlir.

Financial Disclosures: None reported.

Funding/Support: This work was supported by grant A151982 from the National Institute of Allergy and Infectious Diseases.

Role of the Sponsor: The National Institute of Allergy and Infectious Diseases had no role in the preparation, review, or approval of the manuscript.

Disclaimer: Drs Getahun and Nunn are staff members of the World Health Organization. They alone are responsible for the views expressed in this article and do not necessarily represent the decisions or policies of the World Health Organization.

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