SUPPLEMENT ARTICLE

Integration of Tuberculosis and HIV Services in Sub-Saharan Africa: Lessons Learned

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Promoting linkages between tuberculosis (TB) and human immunodeficiency virus (HIV) treatment and prevention programs in resource-constrained environments where both diseases are prevalent is essential to improve the diagnosis, treatment, and outcomes for patients affected by both diseases. In this article, we share insights based on our experiences supporting integrated TB and HIV service delivery programs, including intensified TB case finding, isoniazid preventive therapy, infection control, and initiation of antiretroviral therapy. Our experience indicates that successful integration of TB and HIV services in resource-constrained environments is feasible, although programmatic, infrastructural, and staffing challenges remain. Successful implementation of TB and HIV collaborative activities requires consideration of the realities that exist on the ground and the importance of tailoring interventions in a manner that enables their seamless introduction into existing programs that are often overwhelmed with large numbers of patients and a paucity of human and other resources.

An estimated 33 million persons were infected with human immunodeficiency virus (HIV) in 2007, of whom 22 million were in sub-Saharan Africa [1]. Among ~9.27 million incident cases of tuberculosis (TB) in 2007, 2.88 million were in Africa, where 38% of persons with TB were coinfected with HIV [2]. The combined impact of the HIV and TB epidemics has challenged the weak health care systems in resource-limited countries. Traditionally, national AIDS- and TB-control programs have functioned separately and are mirrored by distinct service delivery structures with little coordination of HIV and TB services for individual patients. To improve the diagnosis, treatment, and outcomes for patients with both diseases, the World Health Organization (WHO) developed a framework of strategic collaborative activities to be performed as part of the health sector response to control HIV infection–related TB [3]. These activities include measures to decrease the burden of TB among persons with HIV infection or AIDS and to decrease the burden of HIV infection among persons with TB [4]. Proposed activities to decrease the impact of TB among persons with HIV infection or AIDS include the "3 I's": intensified TB case finding, isoniazid preventive therapy (IPT), and TB infection control [5]. To ensure that persons with TB who have HIV coinfection achieve the best possible outcomes, proposed activities include introducing HIV counseling and testing, trimethoprim-sulfamethoxazole preventive therapy, and antiretroviral therapy (ART).

Scale-up of HIV programs through national efforts and funding support from the US President's Emergency Plan for AIDS Relief; the Global Fund for AIDS, TB and Malaria; and other donors in countries severely affected by HIV infection and TB has offered the opportunity to implement the aforementioned activities. On the basis of our experience in supporting programs that provide integrated TB and HIV services in sub-Saharan Africa, we offer insights that may inform efforts to implement components of this framework. Successful implementation of the framework requires consideration of the realities that exist on the ground and the importance of tailoring interventions in a manner that enables their seamless introduction into exist-

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INTENSIFIED TB CASE FINDING

Early identification of individuals suspected of having TB, followed by a timely diagnostic examination and prompt initiation of treatment, can improve patient outcomes and reduce transmission in communities and health care settings [6, 7]. TB screening is also essential in evaluating persons with HIV infection or AIDS for IPT eligibility, by ensuring exclusion of TB disease to avoid the risk of isoniazid monotherapy [8].

Intensified TB case finding in resource-limited settings has largely relied on use of screening tools for symptoms related to TB. Although there is no consensus on what items to include in a screening questionnaire, studies suggest that a combination of symptoms has better sensitivity and negative predictive value than any single symptom [9]. Some studies have shown that the diagnostic accuracy of a screening algorithm is improved with addition of a chest radiograph [10]; however, in many settings, this test is not routinely available.

To achieve TB case finding through standardized screening in the context of high-volume clinics providing HIV care, we developed a simple 5-item questionnaire that can be rapidly administered by diverse cadres of health care workers (Figure 1). Modified from a TB screening questionnaire developed for use for patients with advanced HIV disease [11], this questionnaire was designed for ease of use and to favor sensitivity over specificity. If patients answer affirmatively to any question, they are considered to be "TB suspects" and are recommended for diagnostic testing (eg, sputum smear for acid fast bacilli, chest radiograph, and sputum culture), in accordance with national guidelines. Initially piloted in Rwanda [12], the TB screening questionnaire is now used to screen persons with HIV infection or AIDS for TB at >450 HIV care and treatment sites supported by our programs in 9 sub-Saharan African countries.

Our experience indicates that integration of this symptom questionnaire into routine HIV care in low-resource settings is feasible and results in a substantial number of persons with HIV infection or AIDS receiving a diagnosis of and receiving treatment for TB. During the first quarter of 2009, 8 country programs reported data on TB screening of persons with HIV infection or AIDS who were newly enrolled in HIV care at 360 sites. Overall, 64% (interquartile range, 60%–100%) of the 32,731 newly enrolled persons with HIV infection or AIDS were screened using the questionnaire. A mean of 22% (interquartile range, 5%–29%) of these patients screened positive, of whom a mean of 12% received a diagnosis of TB and initiated treatment. With continued use of the questionnaire at a particular site, screening coverage improved over time and was accompanied by an increase in TB case detection. In an analysis of quarterly aggregate data from 58 long-standing HIV care and treatment sites from 6 sub-Saharan African countries, our data indicate that the proportion of persons with HIV infection or AIDS who were screened for TB at enrollment in care increased from 44% to 76% over an 18-month period and was accompanied by an increase in the proportion of newly enrolled patients initiating TB treatment (from 4% to 6%; $P = .016$ for both) [13].

Persons with HIV infection or AIDS remain at risk of TB throughout the course of their HIV disease, including after ART initiation [14, 15]. Thus, screening for TB should be done repeatedly during follow-up care. Performance of TB screening at every clinical encounter can be challenging in resource-constrained environments, particularly at sites that serve large numbers of persons with HIV infection or AIDS and where continuity care is a new paradigm. We found that providers are more apt to use the screening questionnaire consistently

	YES	NO
1. Has the individual had a cough for >2 weeks?	[]	[]
2. Has the individual had fevers for >2 weeks?	[]	[]
3. Has the individual had an observed weight loss >3 kg in last 4 weeks?	[]	[]
4. Has the individual had night sweats for >2 weeks?	[]	[]
5. Has the patient been in close contact with someone with TB in the past year? (optional)	[]	[]
6. If done, does the patient have a Tuberculin Skin Test (TST) induration of >5 mm? (optional)	[]	[]

If 'YES' to Question 1, patient is a pulmonary TB suspect, regardless of answers to other questions, begin evaluation for TB.

If 'NO' to Question 1 but 'YES' to any other question, patient is a TB suspect. Begin evaluation for TB.

If 'NO' to all questions, patient is not a TB suspect. Repeat TB screening in 3-6 months time.

Figure 1. Tuberculosis (TB) screening questionnaire (modified from [11]).

and to record responses in a standardized fashion when it is incorporated into the HIV clinical record. At 9 HIV care and treatment sites in Nelson Mandela Bay District, Eastern Cape, South Africa, the proportion of newly enrolled persons with HIV infection or AIDS who were screened for TB increased from 73% in the first half of 2007 to 95% in the latter half of 2008, after introduction of a clinical record that incorporated the screening questionnaire [16]. This led to TB diagnosis and treatment in a substantial number of persons with HIV infection or AIDS: 24% of those with a positive screen result and 6% of those without a TB diagnosis at enrollment.

Although the aforementioned screening tool appears to have aided HIV programs in identifying patients with TB and enrolling them in TB treatment, its operating characteristics have not been rigorously assessed. Other tools that have been described in the literature have not been used on a wide scale in the context of HIV program scale-up [10, 17]. An important question that remains unanswered is the optimal frequency of TB screening in persons with HIV infection or AIDS.

IPT

The efficacy of IPT in the prevention of a first episode of TB among persons with HIV infection or AIDS has been well demonstrated. A meta-analysis found that provision of IPT to persons with HIV infection or AIDS in the absence of ART reduced TB incidence by 33% overall and by 64% among individuals with positive tuberculin skin test results, compared with placebo [18]. Observational studies suggest that IPT reduces the risks of TB and death during early ART [19] and that IPT and ART in combination result in a greater reduction in TB risk than does either treatment alone [20]. Despite this evidence, implementation of IPT in HIV care and treatment programs in resource-constrained environments has been limited. One reason for poor uptake includes concerns about emergence of isoniazid resistance because of difficulty excluding TB before starting IPT, despite findings from a systematic review suggesting that the effect of IPT on isoniazid resistance is likely to be small [21]. Other concerns raised include the limited durability of isoniazid's protective benefit and the need to provide adherence support to achieve high rates of adherence and treatment completion [22].

Before the scale-up of ART in resource-limited countries, pilot projects, including the Botswana IPT Program and the WHO ProTEST initiative, demonstrated that IPT implementation in the context of a TB and HIV collaborative framework was feasible [23, 24]. However in the ProTEST project, which involved provision of IPT after HIV counseling and testing, uptake of and adherence to IPT were low, with the proportion of patients completing 6 months of IPT varying from 24% to 59% at the 6 pilot sites [24]. Factors that enhanced adherence included attending clinic support groups, empathic and nondiscriminatory clinic services, and support from family members and the community. However, other data from South Africa indicated that IPT uptake at a workplace HIV prevention and care program for miners was high, with 82% of eligible persons with HIV infection or AIDS initiating IPT, although monitoring adherence to treatment was difficult [25]. Factors identified as contributing to the program's acceptability included use of lay counselors, attention to confidentiality, and efforts to minimize stigma.

We found that IPT implementation at HIV care and treatment settings is facilitated by linking it to routine TB case finding activities. In Ethiopia, >3347 persons with HIV infection or AIDS initiated IPT at HIV care and treatment facilities that we support in the first quarter of 2009. To achieve this, the aforementioned TB screening questionnaire was combined with an IPT checklist, so that clinicians could assess patients with a negative screen result for IPT eligibility. In a report from Namibia, IPT implementation was accelerated by use of adherence counselors to identify candidates for IPT [26]. After training and distribution of a checklist to the counselors, the proportion of eligible patients receiving IPT increased from 2% to 42% over a 1-year period.

Several measures can be taken to support adherence to IPT among persons with HIV infection or AIDS. Data from Mozambique indicate that intensive counseling before IPT initiation and adherence promotion by all health care workers involved in the patient's care during follow-up were essential to ensuring treatment completion [27]. Identification and tracking of patients receiving IPT were enhanced by recording IPT use on the patient HIV card and medical record, in addition to the IPT register. Coordination of IPT follow-up visits with HIV-related visits to the health care facility, including ART pharmacy pick-up, were also instrumental in reducing the number of missed visits and delays in IPT pick-up. In a report from an HIV care program in Kenya, high IPT completion rates were attributed to a strong outreach and social support program, which included home visits for patients who missed clinic visits to bring them back into care [28].

These programmatic experiences demonstrate that implementation of IPT for persons with HIV infection or AIDS in resource-constrained environments is feasible. Nevertheless, additional research is required to determine factors associated with uptake and adherence to IPT in these settings and to evaluate the safety and effectiveness of IPT, particularly with concurrent ART use. It is hoped that the evidence of feasibility will facilitate scale-up of IPT in settings with a high prevalence of HIV infection and TB.

INFECTION CONTROL IN HEALTH CARE SETTINGS

Persons with infectious TB may be found in any service area, including voluntary counseling and testing sites, HIV clinics, maternal and child health clinics, general outpatient departments, and inpatient wards. Delays in TB diagnosis and treatment initiation, especially under conditions of crowding and poor ventilation, facilitate nosocomial transmission of TB among patients and health care workers [7]. Persons with HIV infection or AIDS are particularly vulnerable, because they are at higher risk of developing TB after infection [29]. Recently reported outbreaks of multidrug-resistant (MDR) and extremely drug-resistant (XDR) TB have heightened awareness of the need to reduce exposure to TB in health care settings [30]. As HIV programs in resource-constrained environments provide more TB services, the need to implement infection-control measures to protect both staff members and patients who access these services becomes increasingly important [31].

The WHO and Centers for Disease Control and Prevention recommend a number of infection control measures to reduce the risk of TB transmission in HIV care and treatment settings in resource-constrained environments [31]. Administrative control measures include promptly identifying persons with TB symptoms, separating infectious patients, controlling spread through cough etiquette and respiratory hygiene, and minimizing time spent in health care facilities for persons suspected to have TB and persons who have received a diagnosis of TB. Environmental control measures include the use of ventilation and ultraviolet germicidal irradiation. Personal protective measures include use of particulate respirators during high-risk aerosol-generating procedures and when providing care to patients with MDR- or XDR-TB. In general, administrative control measures have the greatest impact on preventing TB transmission in health care settings and should be prioritized [32]. Until recently, implementation of infection-control measures in health care settings in resource-constrained environments has been largely neglected [33]. Challenges to implementing these measures include limited TB diagnostic methods, crowded and older facilities, and restricted budgets for technological interventions.

An innovative and feasible approach to the implementation of infection control in resource-constrained settings is the motivation of health care workers to protect themselves through attention to activities that promote rapid identification of individuals with TB and prompt initiation of TB treatment [34]. At HIV care and treatment sites in Eastern Cape, South Africa, that we support, all staff cadres receive comprehensive training on infection control, and a multidisciplinary infection control committee is established to draft facility-specific policies. A triage form is used by lay workers to screen persons with HIV infection or AIDS for cough at arrival to the health care facility. This form prompts triage staff to direct patients who report this symptom to a separate well-ventilated waiting area, instruct them on cough hygiene, provide them with a tissue, and place them at the front of the queue for evaluation by a health care provider [34]. Sputum specimens from persons suspected of having TB are obtained promptly in an outdoor courtyard, with a staff member observing from the window for proper technique. These simple practices have had a measurable effect on the time that persons suspected of having TB spend at the health care facility. For example, at Chatty Primary Healthcare Clinic, the mean time to consultation is 15 min for persons suspected of having TB, compared with 146 min for persons not suspected of having TB, and mean total time at the facility is 44 min and 180 min, respectively. A key element to the success of this program is the commitment to TB infection control embodied by the facility manager, who in turn, motivates staff members to adhere to these work practices.

After a nosocomial outbreak of MDR- and XDR-TB at Church of Scotland Hospital in Tugela Ferry, South Africa [30, 35], a multifaceted infection-control program was instituted to reduce the risk of TB transmission. A dedicated infection control officer was appointed, and cough officers were placed in all ambulatory care areas to screen patients entering the facility. Efforts were made to reduce inpatient admissions and length of stay. Extractor fans were installed and an open-window policy was instituted. An N95 respirator use policy was developed, and staff education and fit testing were conducted. Regular screening of staff members for TB was instituted, and voluntary counseling and testing was promoted. If a staff member reports being HIV infected, he or she is provided with access to ART and is discreetly moved to a lower-risk area of the facility. Since instituting this infection control program, a substantial decrease in the point prevalence of culture-positive TB in the inpatient TB ward has been observed (from 88% on a single day in 2005 to 26% in 2008) [36].

INITIATING ART

In African countries with the highest prevalence of HIV infection, >75% of TB cases are associated with HIV infection [37]. TB case-fatality rates are 16%–35% among persons with HIV infection or AIDS in the absence of ART and 4%–9% among HIV-uninfected persons [38]. HIV testing and counseling for patients with TB offers an entry point for care and treatment of HIV infection and AIDS. Evidence from clinical trials has shown that trimethoprim-sulfamethoxazole preventive therapy reduces mortality among persons with HIV infection or AIDS and TB [39, 40]. Recent data from the Starting Antiretroviral Therapy at Three Points in Tuberculosis (SAPIT) trial demonstrated that initiating ART during TB treatment greatly im-

proves survival for persons with HIV infection or AIDS who have $CD4^+$ T cell counts <500 cells/mm^3, compared with starting ART after TB treatment is completed [41]. However, treatment of patients with TB and HIV coinfection requires expertise and experience. Providers must be knowledgeable of drug-drug interactions and overlapping toxicities between anti-TB drugs and antiretroviral drugs, to choose compatible regimens and to appropriately manage adverse events [42]. They must also be adept at recognizing and managing immune reconstitution inflammatory syndrome, which occurs with increased frequency among persons with HIV infection or AIDS and TB [43]. In addition, enhanced adherence support for patients with TB and HIV coinfection is needed to assist them through the arduous process of completing TB treatment.

In many settings, patients with TB who receive a diagnosis of HIV infection obtain their anti-TB treatment in TB clinics, with referral to HIV care after completion. This approach leads to unnecessary delays between TB diagnosis and ART initiation, resulting in high mortality rates. Provision of care in 2 distinct settings by HIV and TB providers may lead to prescription of incompatible regimens, mismanagement of adverse events, or inadequate adherence support.

In Rwanda, an innovative approach was developed whereby persons with HIV infection or AIDS and TB receive comprehensive HIV and AIDS services and TB care at the TB clinic for the duration of their TB treatment, with transfer to an HIV program after completion of the TB treatment [44]. Provider-initiated counseling and testing is provided to all patients with TB who have an unknown HIV status at the TB clinic. $CD4^+$ T cell count testing is performed for all patients found to be HIV infected, and trimethoprim-sulfamethoxazole preventive therapy and ART are dispensed to eligible patients. From the first quarter of 2004 through last quarter of 2007, the proportion of patients with TB who underwent HIV testing in Rwanda increased from 45% to 91%. In 2007, 69% of HIV-infected patients with TB received trimethoprim-sulfamethoxazole preventive therapy, and 39% received ART. This care model not only ensured timely initiation of ART for patients with TB and HIV coinfection but also has the added benefit of preventing TB transmission in HIV care settings, by limiting contact of patients with TB with large numbers of persons with HIV infection or AIDS early during TB treatment, when they are most infectious.

NUTRITION INTERVENTION SERVICES

Nutrition intervention services, including nutrition assessment, education, and counseling; prescription of targeted nutrition supplements; and food support, are important components of comprehensive care for persons with HIV infection and TB, particularly in areas where malnutrition and food insecurity are common. Persons with HIV infection or AIDS are at risk of nutritional deficiency at all stages of HIV disease [45], and malnutrition is a strong predictor of early mortality after the initiation of ART [46, 47]. TB is also associated with malnutrition [48], particularly among persons with HIV infection or AIDS [49, 50], and nutritional status is an important determinant of early death during TB treatment [51].

Nutrition intervention services have been integrated with HIV and TB care and treatment programs using varied approaches. In the Academic Model Providing Access to Healthcare (AMPATH) program in western Kenya, nutritionists complete a food security assessment for all persons with HIV infection or AIDS at enrollment in HIV care, and 6 monthly "food prescriptions" are written for families who are unlikely to meet minimal daily nutritional requirements [52]. In this innovative program, the demand for food is met through a combination of food production, donations, and an effective food distribution infrastructure. In a pilot food supplementation program in Zambia, household food security assessments were performed by community health care workers as part of a home-based adherence support program, and food-insecure patients received monthly rations provided by the World Food Programme [53]. Data from this program demonstrated that patients receiving rations were more likely to be adherent to ART than were food-insecure persons enrolled in clinics not yet receiving food aid. An integral part of the community-based MDR-TB treatment program in Lesotho is provision of a monthly food package to all patients receiving treatment, the majority of whom are also infected with HIV [54].

These programmatic experiences demonstrate that integration of nutrition intervention services with other TB and HIV services is feasible. However, additional research is needed to determine the most effective ways to incorporate nutrition interventions in programs serving persons with HIV infection and TB and to evaluate the clinical outcomes associated with provision of these services. The evidence of feasibility will hopefully facilitate donor funding for scale-up of nutrition support services as part of comprehensive TB and HIV care and treatment programs in resource-poor settings.

CONCLUSION

As recently as 2003, 50,000 persons with HIV infection or AIDS were receiving ART in sub-Saharan Africa [55]. By 2008, >3 million adults in low- and middle-income countries had received ART, resulting in the first decrease in the number of annual AIDS-related deaths since HIV was first recognized [56]. However, without a collaborative response to the HIV and TB coinfection epidemic, the survival gains made through expanded access to ART may be compromised. In addition, to improve outcomes in patients with TB and HIV coinfection, laboratory infrastructure must be strengthened and health care worker capacity must be improved. There are a myriad of ways

in which HIV programs can contribute to optimal care of persons with HIV infection or AIDS and TB and to TB control in general. Attention to the realities that HIV programs face and capitalizing on the resources available through the latter programs can result in a win-win situation.

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