The Case for Integrating Tuberculosis and HIV Treatment Services in South Africa

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Integration of human immunodeficiency virus (HIV) and tuberculosis (TB) services is critical to effectively addressing both epidemics in South Africa. Examples of the specific need to integrate TB and HIV services are presented from a community in Cape Town, South Africa, with high burdens of HIV infection and TB and from an antiretroviral therapy (ART) program in a peri-urban township. TB and HIV service integration is needed in 3 specific scenarios presented in this article: for the public health control of TB, in the use of a TB diagnosis as an impetus for entry into an ART program, and to manage incident TB in patients in an ART program.

Annual tuberculosis (TB) notification rates have increased 2- to 3-fold in many sub-Saharan African countries since 1990 [1]. The failure of the present strategy for control of Mycobacterium tuberculosis infection is primarily related to the HIV epidemic in the region. The rapid escalation of rates of TB disease is undermining progress toward achieving the Millennium Development Goals for TB Control in Africa, and the World Health Organization (WHO) has declared TB to be a regional emergency [2]. The impact of HIV infection is particularly accentuated in populations with high preexisting TB case rates [3], and the need to ensure effective collaboration between HIV and TB services has been highlighted [4].

In this article, examples are presented of the specific need to integrate HIV and TB services in both a Cape Town, South Africa, community with high burdens of HIV infection and TB and an antiretroviral therapy (ART) program in a peri-urban township. TB and HIV service integration is needed in 3 specific scenarios presented in this article: for the public health control of TB, in the use of a TB diagnosis as an impetus for entry into an ART program, and to manage incident TB in patients in an ART program.

PUBLIC HEALTH CONTROL OF TB

We enumerated the population of a well-demarcated township with high burdens of both TB and HIV infection, by means of successive household censuses [5]. In 2005, the total population of this community was 13,711 individuals; 10,407 of these individuals were adults, and the prevalence of HIV infection among these adults was 23%. The number of TB notifications has increased markedly over the past 10 years, as the prevalence of HIV infection among these adults was 23%. The number of TB notifications has increased markedly over the past 10 years, as the prevalence of HIV infection among these adults was 23%. The number of TB notifications has increased markedly over the past 10 years, as the prevalence of HIV infection among these adults was 23%. The number of TB notifications has increased markedly over the past 10 years, as the prevalence of HIV infection among these adults was 23%.
Despite stabilization of the HIV infection prevalence, TB notifications have continued to increase, reaching ~2000 cases/100,000 population in 2005–2006. The greatest TB burden now occurs among individuals 20–45 years of age. However, the greatest proportional increase in the number of TB cases has occurred among adolescents 10–19 years of age, a group that was unaffected by TB 10 years ago [5]. TB notification data also underestimate the true community burden of TB that may be demonstrated by active case finding. A population-based survey of HIV infection and TB was performed in 2005 by use of laboratory analyses of induced sputum samples together with anonymous, linked HIV testing [6]. The prevalence of smear-positive pulmonary TB, as determined by direct testing of smear samples, was 519 and 4441 cases/100,000 population, and the calculated proportion of reported cases divided by the total number of cases of smear-positive disease was 67% and 36%, for HIV-negative and HIV-positive individuals, respectively [6]. The TB control program based on passive case finding can thus be shown to be performing very differently for HIV-positive and HIV-negative individuals in the same community. The present TB control program performs inadequately for HIV-positive individuals, resulting in significantly more untreated person-years spent within the community for HIV-positive individuals with either smear-positive or smear-negative TB, as determined by direct testing of smear samples.

In Gugulethu township, the W-Beijing strain, which has been associated with multidrug resistance [7, 8], was present in 54% of HIV-infected individuals with TB, compared with 21% of HIV-uninfected individuals with TB [9]. In this community, population TB control may require age-specific interventions, with particular targeting of adolescents and young adults. If undiagnosed HIV infection/TB is fueling this rapidly growing epidemic, a strategy of increased screening for TB at the time of diagnosis of HIV infection, during voluntary counseling and testing, may be needed.

**BURDEN OF TB AT ENTRY INTO AN ART PROGRAM**

The Gugulethu ART program, which was initiated as a community pilot project in 2002 [10], has now screened >2500 patients for initiation of ART. The majority (67%) of individuals accessing ART either had a recent history of receiving treatment for TB or presented with prevalent TB. A total of 15% of patients were receiving TB medication at the time of referral, and an additional 10% of patients received a new diagnosis of TB during the ART screening process [11]. The risk factors for prevalent TB include a prior AIDS or WHO stage 3 diagnosis and a CD4 cell count of <100 cells/mm^3 [11]. A history of receiving previous treatment for TB is associated with a markedly reduced risk of prevalent TB. Patients with TB treated >3 years previously had a protection rate of 50%, and those with TB treated 2 years previously had a protection rate of 80%, compared with the rate noted for untreated individuals [11]. At present, a recent TB diagnosis provides a major point of entry into ART programs in South Africa. Both the TB control and ART programs deal with very large burdens of disease, and integration of services could overburden existing, stressed TB clinics. Management of TB within ART programs is a constraint to the rapid rollout of ART in South Africa. Wider availability of CD4 cell count determination may allow earlier initiation of ART before the onset of TB, resulting in a decreased burden of very sick patients with a high mortality rate in both the TB control and ART programs.

**MANAGEMENT OF INCIDENT TB DURING ART**

ART has been shown to reduce the TB incidence in a South African cohort by ~90% [12]. Absolute decreases in the TB incidence, however, will depend on the background TB notification rates of the populations in which individuals are resident. In Gugulethu, a poor peri-urban township with a population of 600,000, TB notification rates are in excess of 1000 cases/100,000 population. Patients receiving ART experience a reduction in TB incidence from 13.4 cases in the first year of therapy (95% confidence interval [CI], 10.4–16.9 cases) to 4.5 cases (95% CI, 1.59–5.55 cases) after 3 years [11]. The TB incidence after receipt of ART for 3 years, however, remains 4.5-fold higher than the TB notification rate noted for the general population and is ~8-fold higher than the TB notification rate noted for the non–HIV-infected population. Therefore, ART, as it is presently used, may not result in significantly improved population TB control [13]. ART may even have a negative impact on TB control as the number of individuals susceptible to TB within the population continues to increase.

In the Gugulethu program, delays in initiating ART result from both the time delays necessary for establishing a TB diagnosis for suspected infected individuals and the program delays in initiating ART. The delay in initiating ART is associated with a very high mortality rate, which approaches 50% at 90 days after diagnosis. In contrast, individuals with a recent diagnosis of TB who are commencing ART have a low mortality rate but are at increased risk for immune restoration disease (IRD). Initiation of ART within 1 month of diagnosis of TB results in IRD in ~90% of patients with advanced immune suppression (CD4 cell count, <100 cells/mm^3) [14]. IRD was not associated with a high mortality rate, but the consequent morbidity further constrains the ART program.

A 6-month course of TB medication did not appear to have a significant negative impact on the long-term success of ART among patients receiving a standard efavirenz-based regimen. Both the CD4 cell count recovery and the proportion of patients achieving viral suppression who survived to 48 weeks after having TB diagnosed were similar to the data for patients who...
did not have TB diagnosed [11]. HIV loads were suppressed to <400 copies/mL in 94% of patients at 16 and 48 weeks after diagnosis, regardless of whether the patients received concurrent treatment containing rifampin for TB. The fact that virological responses were not undermined by early initiation of ART during anti-TB treatment supports policies favoring early initiation of ART [15].

Although the rate of new incident cases of TB markedly decreases soon after commencement of ART, the absolute incidence remains high, requiring active screening for TB to be continued. Initiation of ART in individuals with profound immune suppression early after a diagnosis of TB is necessary to reduce mortality but results in very high rates of IRD. There is an urgent need for development of management algorithms for IRD in South African ART programs.

**CONCLUSIONS**

The existing DOTS (directly observed treatment, short course) TB control strategy, which is based on passive case finding, appears to perform less efficiently for HIV-positive individuals than for HIV-negative individuals. The role of ART in TB control is complex, and, at present, ART is initiated when CD4 cell counts are low, when the majority of individuals accessing ART in South Africa have already developed TB disease. Earlier initiation of ART, when individuals have higher CD4 cell counts, will add to the caseload of ART programs, but there will be a resultant decrease in the TB caseload. Although integration of existing TB and HIV infection treatment services may streamline health systems, reduce referral delays, and improve individual case management, the integration of these services alone is unlikely to be sufficient to control TB at a population level. Program changes emphasizing earlier identification of HIV-infected individuals, before they develop the symptoms associated with advanced immune suppression, will be required, along with subsequent access to monitoring of HIV progression together with ongoing active TB case finding.

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**References**