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The challenge of the HIV-associated tuberculosis epidemic in sub-Saharan Africa: will antiretroviral therapy help?

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HIV-associated tuberculosis – a huge challenge

The Millennium Development Goals targets for global tuberculosis (TB) control are to halt and start to reverse the rising incidence of TB and to halve the 1990 TB prevalence and death rates by 2015. Although progress is being made, one of the major obstacles to meeting these targets is the HIV-associated epidemic. Of the estimated 9.3 million new TB cases that occurred worldwide in 2007, 1.37 million (14.8%) were associated with HIV (1).

Sub-Saharan Africa has borne the burden of this co-epidemic. Over the past 20 years, HIV has fuelled TB notification rates, which have increased 3- to 5-fold in many African countries. By 2007, the continent accounted for 79% of the global burden of HIV-associated TB (1). Worst affected are those countries in the east and south of the continent where HIV prevalence rates are highest. In South Africa and Swaziland, approximately 1% of the population develops TB annually. Notification rates in some poor communities in South Africa have even increased to over 2% per year – rates that are almost unprecedented in the era of short-course multi-drug chemotherapy (2, 3). South Africa alone accounts for a staggering one in four of the world's cases of HIV-associated TB (1).

Approximately 0.5 million HIV-associated TB deaths occurred in 2007 worldwide, representing an estimated 23% of the global AIDS-related mortality (1). Sub-Saharan Africa again accounted for many of these deaths. In the World Health Organization (WHO) African region in 2007, the estimated mortality rate attributable to HIV-associated TB was between 20- and 60-fold higher than rates in the other five world regions. South Africa alone accounted for approaching 100,000 HIV-associated TB deaths in 2007 (1).

Why have traditional TB control strategies failed?

The WHO DOTS strategy (Directly Observed Treatment Short course) has been the foundational TB control strategy globally. Between 1995 and 2008, 36 million people were treated worldwide and up to 8 million deaths were averted. However, DOTS has failed to control the African HIV-associated TB epidemic, even in countries considered to have 'model' programmes such as Tanzania and Malawi.

Why has DOTS failed to control this epidemic? This is not simply due to poor programme implementation in some regions, but relates to the fundamental epidemiological interaction between TB and HIV. The DOTS strategy aims to diagnose and effectively treat infectious pulmonary TB cases and thereby reduce onward transmission and avert secondary cases. DOTS, however, does not prevent reactivation of latent TB infection (LTBI). When the HIV epidemic arrived, existing rates of LTBI were extremely high in many communities, with over two-thirds of adults in poor South African communities for example, being infected. In those with HIV co-infection, subsequent risk of developing TB through reactivation of LTBI is extremely high, with overall rates reaching as high as 20-30% per year in those with the most advanced immunodeficiency.

Another key issue is that DOTS does not reduce the very high susceptibility of HIV-infected individuals to develop rapidly progressive disease following exposure (exogenous infection). Thus, although DOTS reduces transmission risk in the community, this may be out-weighed many-fold by the greatly increased risk of rapidly progressive disease in HIV-infected people who are nevertheless exposed. Major increases in incidence rates of TB may further contribute to transmission, although this is off-set to some extent by the fact that HIV-associated TB cases are generally less infectious than disease in HIV-uninfected people.

In addition, DOTS is insufficient as an intervention to adequately reduce mortality risk in those with HIV-associated TB since many of the deaths are caused by other HIV-associated pathologies such as bacterial sepsis, other infections and neoplasia. Moreover, DOTS programmes have traditionally focussed on diagnosing and treating patients with sputum smear-positive TB whereas HIV-infected patients with advanced immunodeficiency and high mortality risk tend to have sputum smear-negative disease.

DOTS programmes have been severely strained and demoralised by the escalating caseload and poor outcomes and this has further exacerbated the challenge. It is clear that DOTS alone cannot control this epidemic (4) and that multiple synergistic interventions are needed.

Other interventions?

Additional interventions to improve TB control include the use of active TB case finding to shorten the period of infectiousness prior to TB diagnosis, thereby reducing TB transmission. Use of TB preventive therapy (isoniazid monotherapy) is associated with substantial reductions in risk of HIV-associated TB in those with latent infection. Co-trimoxazole prophylaxis in patients being treated for HIV-associated TB reduces risk of acute sepsis and other infections and halves the mortality risk.

However, neither DOTS nor any of these additional interventions address the fundamental issue – that of immunodeficiency. High incidence rates of HIV-associated TB and associated high mortality risk are driven by immunodeficiency as reflected by the blood CD4 cell count. Without addressing this, approaches to TB control are flawed. Antiretroviral therapy (ART) must clearly be central to both treatment and prevention strategies.

Impact of antiretroviral therapy

ART reduces the risk of TB by approximately two-thirds in patients treated in both high-income and resource-limited settings (5, 6). Reductions in TB incidence are time-dependent, with most benefit occurring during the first 2-3 years of treatment. The risk reduction is directly related to increases in blood CD4 cell counts and to restoration of TB-specific immune responses (5, 7). As CD4 counts increase from <100 cells/uL to >500 cells/uL, the risk of TB decreases approximately 10-fold (8).

The TB preventive effects of ART are observed across a wide spectrum of baseline CD4 cell counts, including those with the very lowest counts (5). Benefits are also observed regardless of tuberculin skin test responses, in other words, it works equally well in those with and without evidence of LTBI. ART also reduces TB risk in those with a history of previous TB, with an approximate halving of TB recurrence rates. Thus, ART is potentially a potent preventive tool for addressing the HIV-associated TB epidemic.

In addition, ART transforms the prognosis of patients with HIV-associated TB, reducing mortality risk by 64-95% (5). It is therefore absolutely essential that all patients with TB are HIV-tested so that those who test positive may receive the benefits of ART and co-trimoxazole preventive therapy. However, although rates of HIV testing in TB patients in Africa are improving, the proportion was still only 37% in 2007 (9). The change within the 2010 South African national ART guidelines to extend eligibility to all TB patients with CD4 counts <350 cells/uL (10) is an important development that will help to reduce mortality risk among such patients.

Why is the TB preventive effect of ART likely to be limited?

The TB risk reduction observed in individuals receiving ART is very substantial and yet the likely long-term impact of ART on TB rates at a population level is likely to be somewhat limited as currently implemented. Multiple factors underlie this:

1) Coverage with ART reaches only a limited proportion of the HIV-infected population who need it. Achieving high coverage is likely to be resource-intensive and challenging.

2) A substantial proportion of HIV-infected patients enter the health care system with HIV-associated TB as their first presenting problem. For these, patients, it is already too late to prevent this TB episode.

3) Patients entering ART programmes typically have low CD4 cell counts. Many have active TB diagnosed when screened on entry to the ART programme or remain at high TB risk during ART until substantial CD4 cell count recovery has occurred (9, 11).

4) During long-term ART, TB incidence rates remain several-fold higher than rates among HIV-uninfected people living in the same community (8, 9) and this risk is likely to be sustained throughout their life-span. Their life-span is, in turn, greatly increased by ART and so cumulative risk of TB over time will remain high.

5) TB risk may remain high in some patients due to poor immunological response to ART, poor treatment adherence, ART failure, nosocomial TB transmission (resulting from treatment in hospital) or being lost to follow-up.

As a result of the above factors, the cumulative lifetime risk of TB in patients enrolling in ART programmes may therefore remain extremely high. How can ART be better used to reduce this overall risk?

Optimum use of ART

The potential preventive impact of ART on the HIV-associated TB epidemic is likely to be far greater than will actually be observed in practice with current standards of implementation. The impact could be improved by the following measures:

1) Rates of HIV testing must be greatly increased, such that HIV is diagnosed before patients develop HIV-associated TB and before their CD4 cell counts fall to very low levels.

2) The earlier ART is started the greater the potential to prevent TB cases (11). Empiric observations and modelling suggest the greatest impact would be derived from annual HIV testing and initiation of ART as soon as HIV diagnosis is established (‘test and treat’ strategy) (8, 13). However, the current South African national ART guidelines for patients without TB and who are not pregnant is to start ART when the CD4 cell count is <200 cells/uL and this strategy will inevitably miss much of the potential for TB prevention (10).

3) Adjunctive strategies are needed to be used in tandem with ART, including TB preventive therapy using isoniazid before and / or during ART as these interventions have additive effects (6). Rigorous

infection control in ART clinics is also needed to reduce nosocomial TB transmission.
4) High rates of effective ART coverage are needed by providing widespread ART access and effectively retaining patients on long-term treatment.

ART not a magic bullet

Through restoration of immune function, ART revolutionises the prognosis of patients with HIV-associated TB and has a major TB preventive effect for HIV-infected patients without TB. However, ART is not a magic bullet for reducing HIV-associated TB rates at population level but it should rather be seen as a foundational element within a series of overlapping interventions that include DOTS, isoniazid preventive therapy, intensified case finding and infection control (the latter three interventions are collectively termed the WHO three I's strategy). The higher the rates of HIV testing in communities and the earlier ART is started, the greater the likely benefit. These interventions must be implemented vigorously and, in the short term, national ART guidelines should be brought in line with current WHO recommendations that recommend that all patients with CD4 cell counts <350 cells/uL should receive ART. In addition, longer-term studies are needed to evaluate the feasibility and impact of the more radical approach - the 'test and treat' strategy - for both HIV prevention and for TB control.

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