



## ISSUES IN MEDICINE

## Tuberculosis control in South Africa – will HAART help?

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The countries of southern Africa are currently at the epicentre of the HIV pandemic, and as a consequence of this annual tuberculosis (TB) notification rates in these countries have increased 2- to 5-fold since 1990.<sup>1</sup> An estimated 2.4 million new TB cases and 540 000 TB-related deaths occur in sub-Saharan Africa annually and this regional epidemic is fuelling a global increase in TB incidence of 1% per annum.<sup>1,2</sup> In response to this HIV-associated TB epidemic the World Health Organization (WHO) Committee for Africa declared an African regional emergency mandating 'urgent and extraordinary actions'.<sup>3</sup>

In South Africa some communities have among the highest TB incidence rates in the world, with annual TB notification rates in some townships in the Western Cape exceeding 1 000/100 000 in 2003.<sup>4</sup> We have more recently described a community with TB notification rates approaching 1 500/100 000 and rates of over 2 500/100 000 among those aged 30 - 49 years.<sup>5</sup> The majority of this disease burden is HIV-associated, and even in townships where HIV prevalence rates are now stabilising, the sobering reality is that TB incidence rates are likely to continue to rise in these communities for a further number of years.<sup>2,5</sup> This lag between the epidemics is because as the HIV epidemic in a community matures, the proportion of individuals with advanced immunodeficiency continues to increase after HIV prevalence has plateaued. Thus, although TB incidence has reached unprecedented levels in many communities heavily affected by HIV, further increases may occur for some years to come in the absence of further effective interventions.

Although the WHO TB control strategy based on DOTS (directly observed treatment, short course) is central to TB control efforts globally, it has failed to contain the African TB

epidemic. It is now clear that although the DOTS strategy is necessary, it is insufficient. Additional measures are needed in countries with high HIV prevalence. The WHO has therefore formulated a strategic framework aimed at functional integration of control programmes for TB and HIV/AIDS.<sup>6</sup> It is hoped that a combination of multiple interventions may provide a more concerted approach to these epidemics.

Highly active antiretroviral treatment (HAART) potentially has a significant role to play within that strategic framework. Since HAART is associated with huge reductions in HIV-associated morbidity and mortality,<sup>7,8</sup> one might anticipate that, as access to HAART is scaled up in resource-limited settings, this might have a beneficial impact on TB control. In support of this supposition, numbers of cohort studies from both high-income and resource-limited settings have demonstrated that HAART reduces TB incidence by 70 - 90% during short-term follow-up.<sup>9</sup> In a study in Cape Town this benefit was observed among patients with a broad range of baseline blood CD4 cell counts and WHO clinical stages of disease.<sup>10</sup> Paradoxically, however, mathematical modelling calculations suggest that widespread use of HAART may have very limited impact on TB burden.<sup>11</sup> Here we explore the reasons why.

The proven efficacy of HAART in reducing short-term risk of TB in a treatment cohort does not necessarily reflect the likely long-term impact of HAART as a TB control intervention at the community level. Four additional factors are also of great importance.

### Long-term risk of incident TB during HAART

Antiretroviral treatment (ART) is extremely effective in reducing the risk of end stage opportunistic infections such as cryptococcal meningitis and pneumocystis pneumonia by increasing CD4 cell counts above a safe threshold level. In contrast, the risk of TB is increased even among patients with high CD4 cell counts and so a safe CD4 cell count threshold for minimising risk of TB does not exist. Moreover, although HAART substantially restores functional TB-specific immune responses, this is almost certainly incomplete in the long term.<sup>9</sup> This is likely to explain why TB incidence rates in the Cape Town AIDS cohort have remained elevated at 1 000/100 000/year after 5 years of HAART.<sup>12</sup> Furthermore, in a community-based treatment cohort in Gugulethu, we estimate that the TB incidence of individuals receiving HAART for 3 years

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remains more than 5-fold greater than the rate among non-HIV-infected individuals living in the same community (S Lawn – unpublished data, 2006). Thus, although HAART is associated with a very substantial reduction in risk of TB, the effect is nevertheless suboptimal.

## Effective ART coverage

The effective coverage of HAART (reflecting both access and adherence to treatment) achieved in a community is obviously another important factor affecting the impact of HAART on TB control. Although high levels of adherence have been demonstrated to be achievable in South African communities,<sup>13</sup> national HAART coverage was estimated at just 10 - 14% in June 2005.<sup>14</sup> Therefore, at present the low levels of coverage are unlikely to have much impact on TB rates at the national level.

## How early HAART is initiated

In high TB prevalence settings, the timing of HAART initiation may have a major impact on an individual's lifetime risk of TB. If HAART is initiated late in the course of the disease, a significant proportion of HIV-infected individuals will have had TB before initiating HAART. For example, in a community-based ART service in Gugulethu, patients have a median baseline CD4 cell count of < 100 cells/ $\mu$ l;<sup>15</sup> 51% of them have had TB before programme entry, most of which was HIV-associated (S Lawn – unpublished data, 2006). HAART would have to be commenced earlier in the course of disease to have a more significant impact on TB burden in these individuals.

In South Africa utilisation of the WHO 2002 recommendations<sup>16</sup> in the national antiretroviral treatment guidelines<sup>17</sup> restricts treatment in the public sector to those with an AIDS diagnosis or a CD4 cell count < 200 cells/ $\mu$ l. In contrast, many other countries in sub-Saharan Africa are using the revised 2003 guidelines,<sup>18</sup> which recommend earlier initiation of therapy. One of the consequences of South African policy may be to limit the potential impact of ART on TB-related morbidity and mortality as is suggested by previous mathematical modelling calculations.<sup>11</sup>

## Increased life expectancy

A further critical variable in determining the impact of HAART on TB control is the extent to which this treatment prolongs life. We have shown that HAART in Cape Town leads to a dramatic decrease in HIV-associated mortality.<sup>14</sup> If patients do not die then they of course remain at risk of developing TB and adding to the community burden of disease. Therefore, if HAART were to reduce the annual risk of TB 10-fold, for example, and yet prolong life expectancy 10-fold, then there would be no net reduction in the individual's lifetime risk of TB during HAART. If risk of TB were reduced 10-fold and life

expectancy increased 15-fold, however, then lifetime risk of TB could paradoxically increase.

In conclusion, HIV is driving the current TB epidemic in South Africa and rates of HIV-associated TB may continue to increase even in communities where HIV prevalence has stabilised. HAART roll-out is unlikely to have a substantial beneficial impact on this TB epidemic in the foreseeable future because: (i) although TB risk reduction is substantial during HAART it is incomplete; (ii) patients typically initiate HAART with advanced immunodeficiency and this is associated with high risk of TB both before and during early HAART; (iii) community coverage with HAART is currently low; and (iv) life expectancy is increased by HAART, greatly extending the period during which patients may develop TB. Sentinel communities with good disease surveillance are needed to better understand the dynamics of the TB epidemic during HAART roll-out. Meanwhile, increased resources are needed to strengthen the South African HIV prevention and TB control programmes. Additional TB control strategies such as active TB case finding and use of isoniazid prophylaxis need to be evaluated and where appropriate implemented urgently.

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