

Incidence of Tuberculosis during Highly Active Antiretroviral Therapy in High-Income and Low-Income Countries

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(See the article by The Antiretroviral Therapy Cohort Collaboration on pages 1772–82)

Highly active antiretroviral therapy (HAART) has revolutionized the care of HIV-infected individuals, causing major reductions in HIV-associated morbidity and mortality. Once blood CD4⁺ cell counts have reached stable levels of >200 cells/ μ L, the risk of developing opportunistic disease due to cytomegalovirus, *Pneumocystis jirovecii*, *Mycobacterium avium* complex (MAC), *Toxoplasma gondii*, and *Cryptococcus neoformans* is generally very low [1]. This reflects the fact that partial restoration of the immune system is sufficient to suppress these low-virulence pathogens. In contrast, however, it is emerging that patients receiving HAART retain a chronically heightened risk of disease due to other, more virulent pathogens, such as tuberculosis (TB) and invasive pneumococcal disease [2–4]. In the case of TB, it might be hypothesized that this observation might relate to the coexistence of other risk factors for TB or possibly to nosocomial TB exposure at HIV treatment facilities. However, a prin-

cipal underlying cause is undoubtedly the persistence of deficits in immune function during treatment [5]. Because the risk of TB is increased even among those with minor degrees of HIV-associated immunodeficiency, complete normalization of immune function during HAART would be required to reduce the risk of TB to background levels. Increasing evidence, however, shows that this goal is generally not attainable. Even among patients who have good responses to HAART, functional immunological deficits usually persist [5–7], including those specific to *Mycobacterium tuberculosis* [5, 8, 9].

Despite limitations in the extent to which TB-specific immunity may be restored [5], HAART nevertheless has a major impact on TB incidence in treated cohorts. Studies conducted in both countries with a high prevalence of TB and those with a low prevalence of TB have shown that HAART reduces the risk of TB by 70%–90% [3, 10–14]. The duration of follow-up in these studies was limited, however; therefore, these results may not reflect the full beneficial effects to be derived from HAART in the longer term.

The article by Girardi and colleagues [15] in this issue of *Clinical Infectious Diseases* reports the burden of TB during 3 years of HAART in cohorts in Europe and North America. In high-income countries in which TB prevalence is low, such a

study could only be achieved by collaborative analysis of data sets from multiple cohorts—a major strength of this article. A key finding was that HAART resulted in time-dependent reductions in TB incidence throughout follow-up. Although the greatest reduction was during the first year of treatment, the rate continued to decrease, with a ~5-fold reduction between the first and third years (figure 1). These changes are likely to reflect incremental gains in CD4⁺ cell count and function, which are greatest during the first 1–2 years of HAART, with only small additional increases occurring thereafter [16]. It remains an open question as to whether TB incidence rates may decrease further during long-term HAART and whether background rates are ultimately reached. In the study by Girardi and colleagues [15], the incidence at 3 years was still several-fold higher than the rates in the general population where these patients were treated. However, extrapolation of these data (figure 1) would suggest that any further decreases in TB incidence beyond 3 years are likely to be small. Moreover, it is actually impossible to define the background TB incidence rate for these cohorts, because the individuals included may differ from the general population in having other long-term risk factors for TB.

The TB incidence rate reported by Gir-

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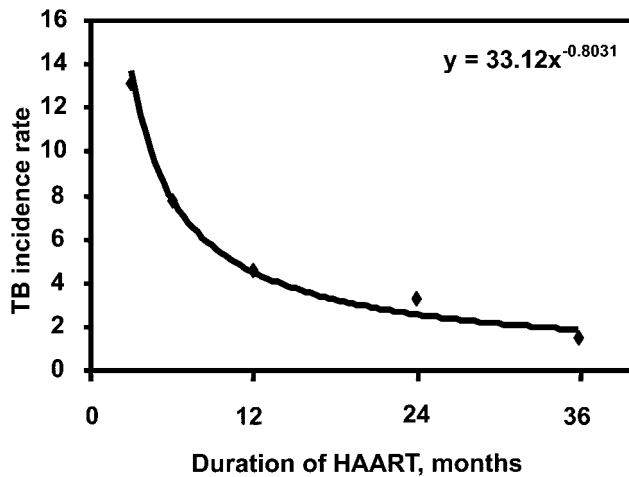


Figure 1. Changes in tuberculosis (TB) incidence during 3 years of HAART with regression curve fitted. TB incidence rate is expressed as number of cases per 1000 person-years of follow-up. Data are adapted from the study by the Antiretroviral Therapy Cohort Collaboration [15].

ardi and colleagues [15] was particularly high during the first 3 months of HAART. Several different reasons may underlie the presentation of cases during this interval: 1) many cases will have arisen at this time because of residual immunodeficiency, 2) intensive investigation of some patients with symptomatic disease during preparation for HAART may have yielded results that only became positive after HAART initiation, and 3) some cases of previously subclinical disease may have manifested as immune reconstitution disease [17], as has been reported by one of the centers collaborating in this study [18].

A substantial weakness of the study by Girardi and colleagues [15] was that patients with AIDS were excluded; such patients are the very individuals who have the greatest risk of TB [3]. Thus, the TB incidence rates reported in this study do not reflect the overall burden of HIV-associated TB in these cohorts. Moreover, because the extent of restoration of TB-specific immunity during HAART is limited, particularly among those with AIDS [5, 8], the long-term rates of TB among such patients are likely to be higher than those reported in this study.

Girardi and colleagues [15] identified risk factors for TB during HAART using multivariate analysis. The association of

TB risk with route of HIV acquisition is likely to be attributable to the association of this variable with country of origin or social factors, which are also risk factors for TB. Unfortunately, the ethnic origin of patients was not recorded. The strongest risk factor for AIDS-associated TB in London is African origin [19], and this increased risk is likely to persist during HAART. Confirmation of this might permit targeting of chemoprophylaxis to further reduce TB incidence among such high-risk groups.

Girardi and colleagues [15] also identified low baseline CD4⁺ cell count as an independent risk factor for the development of TB; in addition, risk of TB occurring after 6 months of HAART was associated, not only with baseline CD4⁺ cell count, but also with the CD4⁺ cell count at 6 months after initiation of HAART. With increasing duration of HAART, it might be hypothesized that the risk of TB would become more strongly associated with current CD4⁺ cell count and less strongly associated with baseline CD4⁺ cell count. Alternatively, because long-term failure of immune functional recovery is particularly associated with advanced pretreatment immunodeficiency [7, 8], it is possible that, among those with advanced disease, a low baseline CD4⁺ cell

count may actually predetermine a long-term increased risk of TB.

Access to HAART is now rapidly expanding in low-income countries where the prevalence of TB is high and TB is the predominant cause of HIV-associated morbidity and mortality [20]. In a cohort based in a hospital out patient service in Cape Town, South Africa, the TB incidence was 24 cases per 1000 person-years during a median of 16 months of follow-up [3]; after >3 years of follow-up, this rate was ~10 cases per 1000 person-years (unpublished data), which is ~7-fold higher than the rate found in the study by Girardi and colleagues [15]. The burden of TB during HAART is even greater within a local community-based antiretroviral program in Gugulethu (near Cape Town, South Africa), where the annual TB incidence in the general community exceeds 1000 cases per 100,000 population [21]. Among HIV-infected patients receiving HAART at that location, 10%–15% develop TB during the first year of HAART (unpublished data). This huge burden of disease has great implications in terms of morbidity, utilization of health resources, and difficulties associated with concurrent administration of both HAART and antituberculosis treatment. These difficulties relate to pill burden, patient adherence, pharmacokinetic interactions, and overlapping drug toxicities.

The implications go further. Because the TB incidence remains much higher among patients receiving HAART than among the general community, modelling analysis suggests that good, effective coverage with HAART may have relatively little impact on the overall burden of TB in communities in low-income countries over a 20-year time span [22]. The reason for this is that life expectancy is greatly extended during HAART, and therefore, although the risk of TB per unit time for individuals receiving HAART is greatly reduced, the lifetime risk of disease may not decrease [5, 22]. Background data for this modelling analysis, however, were derived from a cohort with a short duration of

follow-up, and longer term studies of the effect of HAART on incidence rates and risk factors for TB in low-income countries are needed.

A recently published study from Abidjan found that past history of TB was the sole risk factor for development of TB during HAART [23]. This article, however, has limitations related to the size of the study population, the number of TB cases, restricted cohort composition, and diagnostic criteria for TB, potentially confounding the findings [23, 24]. The study by Girardi and colleagues [15] excluded patients who received an AIDS diagnosis before initiation of HAART, thereby excluding those with a past history of TB and precluding examination of this variable as a risk factor. However, our findings in Cape Town, South Africa, agree with those of Girardi and colleagues [15]. We have found, in a prospective cohort study, that risk of TB was strongly associated with the pretreatment level of immunodeficiency, as reflected by the baseline CD4⁺ cell count and clinical stage of disease (as defined by the World Health Organization); past history of TB was not a risk factor [24]. Moreover, we also found that the immunological response to HAART was impaired among patients who developed TB, compared with those who remained free of TB (unpublished data), suggesting that poor treatment response was an important underlying mechanism. Again, this agrees with the findings of Girardi and colleagues [15].

Collectively, these data demonstrate that during the first 3 years of HAART, in both high- and low-income settings, risk of TB is associated with the baseline level of immunodeficiency. This has important implications for the antiretroviral treatment programs in low-income countries. The median blood CD4⁺ cell count among patients enrolling in our own community-based antiretroviral program in Cape Town is <100 cells/ μ L, as is typically the case among programs elsewhere in sub-Saharan Africa [25]. As a result of diminished capacity for immune recovery, ini-

tiation of HAART among patients with advanced disease may result in an expanding cohort of patients who remain vulnerable to TB. This may undermine the potential benefits of HAART in TB control, and barriers to earlier access to HAART in these settings need to be overcome.

In conclusion, despite major reductions in TB incidence among individuals receiving HAART, TB risk remains elevated among those receiving treatment in both high- and low-income countries. This ongoing burden of disease has major implications for antiretroviral programs in low-income countries and undermines the potential for HAART to contribute to TB control at the community level.

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