

Rapid Increase in Tuberculosis Incidence Soon after Infection with HIV—A New Twist in the Twin Epidemics

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(See the article by Sonnenberg et al., on pages 150–8.)

Over the course of the AIDS pandemic, we have learned a considerable amount about the intersection of HIV infection and tuberculosis (TB). TB is a leading cause of death among people living with HIV; worldwide, 14 million people are coinfecting with *Mycobacterium tuberculosis* and HIV [1]. HIV infection increases the risk of reactivating latent *M. tuberculosis* infection, placing HIV-positive persons at increased risk for developing TB [2]. HIV infection also increases the risk of rapid TB progression after primary *M. tuberculosis* acquisition or reinfection [3]. TB may accelerate the progression of HIV disease via immune activation and is associated with a higher mortality rate and shorter survival in HIV-positive persons [4]. The risk of TB increases as CD4 cell counts decrease; similarly, the highest mortality rates associated with TB occur in persons with the lowest CD4 cell counts [5].

It has been assumed that, very early during the natural history of HIV disease—before a significant decrease in CD4 cell count occurs—the risk of TB is rela-

tively low. Hence, it is both surprising and fascinating that, in this issue of *The Journal of Infectious Diseases*, Sonnenberg et al. report evidence to the contrary. In a large cohort of gold miners in South Africa, the authors found that the risk of TB doubled within the first year of infection with HIV. Not unexpectedly, this risk further increased in subsequent years.

Previous studies have suggested the possibility that TB incidence may increase soon after infection with HIV, but these studies have lacked the power to quantify a statistically significant risk. There were several features of the cohort analyzed by Sonnenberg et al. that enabled them to evaluate the temporal risk pattern of TB after HIV seroconversion: the incidence of TB in the cohort was very high, and the cohort had a high rate of HIV seroconversion. Sonnenberg et al. were able to examine outcomes among 23,874 miners, including 2737 miners with documented HIV seroconversion. TB diagnostic capacity permitted the definitive diagnosis of TB, and the cohort had consistent access to reliable health care.

In the study, miners who were tested for HIV at sexually transmitted disease (STD) clinics, during hospitalization, or as part of seroprevalence surveys during the designated study period were eligible for enrollment. Miners were followed until they developed pulmonary TB, died, or

left the mines. HIV-negative miners were also censored from analysis at 1 year after the last negative HIV test. TB was detected during routine annual screenings or patient-initiated visits to the hospital or an STD clinic. Throughout the study period, repeat HIV tests were performed primarily during patient-initiated visits to the hospital or STD (or other) clinics, as well as during seroprevalence surveys.

The careful and complex analytic design of Sonnenberg et al.'s study was necessitated by the open nature of the cohort and a desire to minimize the inclusion of incident TB among miners with unclear or unknown HIV status. The highly variable frequency and location of HIV tests raises the question of whether the risks of TB were different, for example, between miners who were tested for HIV only once during a seroprevalence survey and miners who were tested multiple times at patient-initiated visits to an STD clinic. Sonnenberg et al. dealt with this potential bias in sensitivity analyses by excluding HIV tests performed at medical or TB wards, and the authors report a similar increased incidence of TB within the first year of HIV seroconversion.

When the methods of TB diagnosis in miners are considered, which included evaluation after patient-initiated presentation to the hospital or medical clinics and routine annual screenings, the issue

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of ascertainment bias arises. Sonnenberg et al. correctly state that physicians at the gold mines are likely to have a high level of suspicion of TB regardless of a miner's HIV status, because of the incidence and prevalence of TB at the mines. Nevertheless, HIV-positive miners may present to medical facilities more frequently because of the development of HIV-related clinical symptoms of illness, thus potentially biasing toward greater evaluation for, and detection of, TB among HIV-positive miners. Another challenge that arises is the differing rates of attrition between HIV-positive and -negative miners in the analysis. For HIV-negative miners with only 1 HIV test, the period of follow-up included in the analysis would be only 1 year, whereas, for HIV-positive miners, the follow-up period included in the analysis would likely be, on average, longer. A shorter duration of follow-up for HIV-negative miners may translate into a decreased chance of detecting the development of TB, potentially decreasing the estimated incidence of TB in this population. However, a median of 1.1 years of follow-up for HIV-positive and -negative miners provides sufficient data to reveal the most fascinating finding of Sonnenberg et al.'s study: the doubling of the incidence of TB within the first year of HIV seroconversion.

Why is the risk of developing TB increased early during the course of HIV infection? The profound immune dysregulation that occurs soon after infection with HIV may play a role. Immediately after acute HIV infection, a person undergoes a period of generalized immunosuppression that is marked by diminished responsiveness to previously exposed antigens [6, 7]. This T cell dysfunction, which is not clearly correlated with CD4 cell counts and may last for months [7], may be one mechanism that would allow early progression to TB after infection with HIV. The temporal course of the loss of response to *M. tuberculosis* antigens beginning at the time of acute HIV in-

fection bears further investigation, for it may shed additional light on this issue.

Another possible explanation for Sonnenberg et al.'s finding of an increased risk of TB early during the course of HIV infection is that the miners who developed TB during the first year of infection with HIV represent a subset of rapid progressors. In early studies of AIDS, only 2%–3% of patients progressed to a clinical diagnosis of AIDS within 2–3 years of HIV seroconversion [8]. However, coinfection with >1 strain of HIV has been increasingly reported in African cohorts [9, 10], and the rates of rapid HIV disease progression may be much higher in these dually infected persons. In a recent study of 34 HIV-positive patients with known seroconversion dates and disease-outcome data, 5 were found to be dually infected (i.e., they either were coinfecting with 2 viral variants at the time of seroconversion or were superinfected with a second viral variant at a later date); in all 5 of these patients, the time to a CD4 cell count of <200 cells/ μ L was <3.1 years, which is much shorter than the typical time of 8–10 years [9]. In Sonnenberg et al.'s study, of the 138 miners in the incident-HIV-infection group (i.e., those who seroconverted during the study period) who developed TB during the study period, 30 developed the disease during the first year of HIV infection. It is possible that some of these miners were infected with >1 strain of HIV, resulting in a more rapid decrease in CD4 cell count, which led to reactivation of latent *M. tuberculosis* infection.

It is interesting to contemplate whether the increased risk of TB early during the course of HIV infection is due to reactivation or to a newly acquired *M. tuberculosis* infection. To shed light on this question, Sonnenberg et al. performed molecular fingerprinting on available isolates. Among HIV seroconverters, the authors found that unique TB isolates were present in 57% (8/14) of miners who developed TB within 2 years of HIV seroconversion, compared with 20% (3/15)

who developed TB later. Patients with unique isolates are more likely to have developed TB via reactivation, whereas patients with isolates that are shared among a cohort are thought to have been recently infected. Both reactivation and newly acquired *M. tuberculosis* infection are plausible in the context of the acute immunosuppression that is associated with primary HIV infection and with rapidly progressive HIV disease and decrease in CD4 cell count. The numbers in Sonnenberg et al.'s study are too small to draw a definitive conclusion with regard to the type of TB that predominated after HIV seroconversion. It is possible that the risks of both new *M. tuberculosis* infection and reactivation disease increased.

The increased risk of TB early during the course of HIV infection has several important implications for predicting the impact of HIV on the global TB epidemic. Although it is difficult to generalize the magnitude of the increase in incidence found in this highly specialized population of gold miners and apply it to the rest of the developing world, it is likely that some significant increase in incidence does occur during the first year after HIV seroconversion. Although current models that estimate the global burden of TB acknowledge the strong association between TB incidence and adult HIV prevalence [11, 12], they do not account for the increased risk of TB early during the course of HIV infection. Reframing these models in the context of these new data is likely to affect the calculated burden of TB—and not just for HIV-positive persons, but for the general community as well [13].

The increased risk of TB early during the course of HIV infection also has important implications for the prevention of TB in HIV-positive persons. Potential methods include the use of antiretroviral drugs and chemoprophylaxis for latent TB infection. Data from South Africa suggest that the use of highly active antiretroviral therapy is effective in reducing the incidence of HIV-associated TB in persons with CD4 cell counts <350

cells/ μ L [14]. If persons who develop TB early during the course of HIV infection represent rapid progressors with low CD4 cell counts, then determination of CD4 cell counts may be all that is necessary to identify the subset of persons who are at highest risk.

Alternatively, if most persons who develop TB early during the course of HIV infection have high CD4 cell counts and no indications for antiretroviral therapy, then the treatment of latent *M. tuberculosis* infection may be the most feasible way to reduce the risk of TB. Data from Uganda suggest that treatment of latent *M. tuberculosis* infection can provide protection against TB in HIV-positive persons; the duration of protection was lengthened to 3 years by use of treatment regimens that combined isoniazid with rifampicin [15]. However, defining and implementing optimal preventive therapy for TB in Africa is a challenging endeavor. The optimal duration of treatment and the optimal regimens are unknown and are currently under investigation. Preventive therapy programs also require the exclusion of active TB, which may be difficult in resource-constrained settings.

Perhaps the most immediate and universal implication of these important data from Sonnenberg et al.'s study is the need to expand reliable and affordable HIV testing services in areas where TB is endemic. The accurate identification of undiagnosed HIV infection is the necessary first step in the implementation of prevention measures that aim to curtail the spread of *M. tuberculosis* and HIV coinfection. The timely and reliable evaluation of TB

in HIV-positive persons is another key component that needs to be further strengthened to curb the epidemic. The ProTEST initiative that has been established in 3 sub-Saharan African countries by the World Health Organization aims to develop a more coherent response to TB in settings where HIV prevalence is high by combining improved access to high-quality HIV counseling and rapid testing services with intensified screening for TB [16]. Preliminary reports from these sites indicate that such collaborative efforts between HIV/AIDS and TB control programs are feasible and effective [16]. Improvement of the links between the HIV and TB clinical and public-health services will be critical to effectively handling the challenges of this coepidemic.

References

1. The Stop TB Partnership. TB/HIV: facts at a glance. Available at: <http://www.stoptb.org/events/internationalaidsconference/xv/assets/InfoPack/IGB.pdf>. Accessed 14 September 2004.
2. Bucher HC, Griffith LE, Guyatt GH, et al. Isoniazid prophylaxis for tuberculosis in HIV infection: a meta-analysis of randomized controlled trials. *AIDS* **1999**; *13*:501–7.
3. Daley CL, Small PM, Schecter GF, et al. An outbreak of tuberculosis with accelerated progression among persons infected with the human immunodeficiency virus. An analysis using restriction-fragment-length polymorphisms. *N Engl J Med* **1992**; *326*:231–5.
4. Whalen CC, Nsubuga P, Okwera A, et al. Impact of pulmonary tuberculosis on survival of HIV-infected adults: a prospective epidemiologic study in Uganda. *AIDS* **2000**; *14*:1219–28.
5. Shafer RW, Bloch AB, Larkin C, et al. Predictors of survival in HIV-infected tuberculosis patients. *AIDS* **1996**; *10*:269–72.
6. Malhotra U, Berrey MM, Huang Y, et al. Effect of combination antiretroviral therapy on T-cell immunity in acute human immunodeficiency virus type 1 infection. *J Infect Dis* **2000**; *181*:121–31.
7. Musey LK, Krieger JN, Hughes JP, Schacker TW, Corey L, McElrath MJ. Early and persistent human immunodeficiency virus type 1 (HIV-1)-specific T helper dysfunction in blood and lymph nodes following acute HIV-1 infection. *J Infect Dis* **1999**; *180*:278–84.
8. Phair J, Jacobson L, Detels R, et al. Acquired immune deficiency syndrome occurring within 5 years of infection with human immunodeficiency virus type-1: the Multicenter AIDS Cohort Study. *J Acquir Immune Defic Syndr* **1992**; *5*:490–6.
9. Gottlieb GS, Nickle DC, Jensen MA, et al. Dual HIV-1 infection associated with rapid disease progression. *Lancet* **2004**; *363*:619–22.
10. Grobler J, Gray CM, Rademeyer C, et al. Incidence of HIV-1 dual infection and its association with increased viral load set point in a cohort of HIV-1 subtype C-infected female sex workers. *J Infect Dis* **2004**; *190*:1355–9.
11. Dye C, Garnett GP, Sleeman K, Williams BG. Prospects for worldwide tuberculosis control under the WHO DOTS strategy: directly observed short-course therapy. *Lancet* **1998**; *352*:1886–91.
12. Williams BG, Dye C. Antiretroviral drugs for tuberculosis control in the era of HIV/AIDS. *Science* **2003**; *301*:1535–7.
13. Sonnenberg P, Glynn JR, Fielding K, Murray J, Godfrey-Faussett P, Shearer S. HIV and pulmonary tuberculosis: the impact goes beyond those infected with HIV. *AIDS* **2004**; *18*:657–62.
14. Badri M, Wilson D, Wood R. Effect of highly active antiretroviral therapy on incidence of tuberculosis in South Africa: a cohort study. *Lancet* **2002**; *359*:2059–64.
15. Johnson JL, Okwera A, Hom DL, et al. Duration of efficacy of treatment of latent tuberculosis infection in HIV-infected adults. *AIDS* **2001**; *15*:2137–47.
16. World Health Organization (WHO). Report of a “lessons learnt” workshop on the six ProTEST pilot projects in Malawi, South Africa, and Zambia [WHO/HTM/TB/2004.336]. Geneva: WHO, **2004**.