Recurrent Tuberculosis: Relapse, Reinfection, and HIV

Richard E. Chaisson[1] and Gavin J. Churchyard[2]

[1]Center for Tuberculosis Research, Johns Hopkins University School of Medicine, Baltimore, Maryland; [2]Aurum Institute for Health Research, Johannesburg, South Africa

(See the article by Narayanan et al, on pages 691–703, and the article by Glynn et al, on pages 704–711.)

The catastrophic collision of tuberculosis and human immunodeficiency virus (HIV) has yielded an extraordinary burden of suffering and death at both the individual and population levels. The convergence of these twin epidemics resulted in 1.8 million deaths due to tuberculosis disease in 2007, 24% of which were among people with HIV infection, whereas among the 2 million deaths of people with AIDS, 22% were caused by tuberculosis infection [1]. Tuberculosis is thus the leading cause of death in people with HIV/AIDS, and HIV infection contributes to a substantial proportion of tuberculosis deaths. Interventions to control tuberculosis and HIV therefore need to take into account the unique and deadly synergy between these 2 infections.

There are many challenges that clinicians and public health programs must confront when trying to manage and prevent HIV-related tuberculosis, including prompt diagnosis, effective treatment, and successful prevention strategies. One problem that receives little attention is recurrence of tuberculosis following completion of treatment. Historically, patients properly treated with a 4-drug regimen have a very high treatment success rate and very low (2%–3%) incidence of recurrence. In HIV-infected patients, the risk of recurrent disease is higher, and previous work has demonstrated that this can be due to treatment failure, emergence of drug resistance during therapy, or reinfection with a new strain of *Mycobacterium tuberculosis* [2–4]. Recurrence of tuberculosis after treatment among both HIV-infected and HIV-uninfected individuals is not a trivial problem. On a patient level, recurrent tuberculosis requires another round of treatment with a regimen that, in many parts of the world, is more toxic, takes longer to complete, and may, ironically, amplify drug resistance. On a public health level, recurrent tuberculosis may account for 10%–30% of all cases within some weaker tuberculosis control programs, particularly those that do not use at least 6 months of rifampin treatment [5], and contributes to ongoing transmission of infection to contacts of cases in the home, community, and health facilities, largely from HIV-uninfected patients [6].

In this issue of the *Journal* are 2 articles that examine the epidemiological profile of recurrent tuberculosis in populations with a high prevalence of HIV infection. Narayanan et al [7] from India report on 2 cohorts of patients with tuberculosis who were followed up for recurrence and then underwent DNA typing of initial and recurrence *M. tuberculosis* isolates to distinguish exogenous reinfection from relapse. Among HIV-infected patients whose initial episode of tuberculosis was deemed cured, 14% experienced a recurrence of tuberculosis, of which just over half of infecting strains typed. Among these, 22 (88%) of 25 cases were due to reinfection with a different strain of *M. tuberculosis.* In a sample of HIV-uninfected patients with recurrent tuberculosis (rates of recurrence are not reported for these patients), only 9% of second episodes were due to reinfection, with the remainder being relapses of the initial infection. One possible explanation for the difference in levels of relapse among HIV-uninfected patients is that many were treated with nonstandard, abbreviated regimens that included ofloxacin in a clinical trial that failed to include an appropriate control regimen; these relapses may simply have been the result of inadequate therapy. Importantly, one-fourth of HIV-related recurrences were with multidrug-resistant strains of *M. tuberculosis*, with a smaller number of resistant recurrences found among HIV-uninfected patients.

Although rates of recurrent tuberculosis cannot be compared by HIV status in this report, it is clear that recurrent disease is more common than would be expected among HIV-infected patients with tuber-

Received 5 November 2009; accepted 5 November 2009; electronically published 1 February 2010.

Potential conflicts of interest: none reported.

Financial support: none reported.

Reprints or correspondence: Dr Richard E. Chaisson, Johns Hopkins Center for TB Research, 1550 Orleans St, 1M.08, Baltimore, MD 21231 (rchaiss@jhmi.edu).

The Journal of Infectious Diseases 2010;201:653–655

0022-1899/2010/20105-0004$15.00
DOI: 10.1086/650531

culosis in this Indian setting, and that almost all recurrences are due to exogenous reinfection. Narayanan et al [7] used rigorous typing methods, with 3 independent techniques, and took great care to exclude the possibility of laboratory contamination. Although the study breaks no new ground with respect to the existence of exogenous *M. tuberculosis* reinfection causing disease [4], particularly in HIV-infected patients, it is nonetheless noteworthy for documenting the potential frequency of this phenomenon in developing countries, where recurrences are generally attributed to treatment failure due to either noncompliance or drug resistance. In this study, all of the multidrug-resistant recurrences among HIV-infected patients were reinfections, whereas both multidrug-resistant cases among HIV-uninfected patients were due to acquired or amplified resistance during treatment. These data confirm what has been inferred from outbreaks of multidrug and extensively drug-resistant tuberculosis among people with HIV infection in other settings: that much drug-resistant tuberculosis in HIV-infected patients is transmitted from others, rather than acquired by ineffective or insufficient therapy [8].

A second article in this issue of the *Journal*, by Glynn et al [9], reports on rates of recurrent tuberculosis in mine workers in South Africa. These authors followed 2 cohorts of tuberculosis patients—one with HIV infection and one without, whose illness was initially diagnosed and who underwent HIV testing in the 1990s—and determined the rates of recurrent disease that occurred at least 2 years following cure of the initial episode. The authors assumed that these late recurrences were due to reinfection rather than relapse, on the basis of previous observations, supported by the data from Narayanan et al [7], that almost all relapses occur in the first 2 years following treatment. Glynn et al [9] found recurrence rates of 24.4 cases per 100 person-years at risk for initially HIV-infected miners following their index episode and 4.7 cases per 100 person-years at risk among those who were HIV-negative at the index episode. Strikingly, rates of recurrent tuberculosis were dramatically higher than incident tuberculosis rates among both HIV-infected and HIV-uninfected miners. These results are consistent with those from a study of another high tuberculosis transmission setting where reinfection rates following treatment exceeded rates of incident disease [10].

The work of Glynn et al [9] requires more assumptions about the source of recurrence and has less direct evidence than the study by Narayanan et al [7]. No DNA typing was performed to confirm that recurrences were actually reinfections and not relapses; repeat HIV testing was not performed among the initially HIV-seronegative men, despite known high rates of HIV acquisition during the time of the study; and considerable attrition from the cohorts over time occurred, which could affect incidence estimates. Despite these limitations, the study demonstrates convincingly that recurrent tuberculosis is exceedingly common among miners in South Africa and is seen in both HIV-infected and HIV-uninfected men. Work by the same group and others [11, 12] previously documented high rates of reinfection in this setting, so it is quite credible that a large proportion of these recurrent cases were, indeed, new infections.

What can be done to reduce the frequency of recurrent tuberculosis, whether due to relapse or reinfection, in patients with and without HIV infection? In fact, quite a lot can be done, and the evidence base for a number of interventions is robust. First, ensuring completion of appropriate therapy for all patients with tuberculosis is extremely important. Although rates of treatment completion worldwide are now close to 85% for patients cared for in directly observed treatment short-course programs, the real completion rate when all patients are accounted for is substantially lower, particularly in Africa [1]. Failure to complete tuberculosis treatment is associated with very high rates of recurrent disease, especially in HIV-infected patients [13, 14]. In addition, although 5.5% of all new tuberculosis cases worldwide have multidrug or extensively drug-resistant disease, only a tiny fraction of these are actually detected and receive appropriate treatment [1]. Improving case detection, easier access to care, improving cure rates with community-based interventions, developing new effective shorter regimens [15], and conducting baseline drug susceptibility testing will all reduce relapses and the evolution of drug resistance. Earlier detection of multidrug-resistant tuberculosis, through use of rapid rifampin resistance assays such as line probe assays, and earlier effective treatment should also reduce recurrence due to reinfection with multidrug-resistant tuberculosis in HIV-infected patients [16].

Because reinfection is common in HIV-infected patients in high burden settings, secondary preventive therapy with isoniazid is another strategy for reducing recurrences. One small controlled trial and one observational study have documented the effectiveness of secondary isoniazid for reducing recurrences in patients with HIV-related tuberculosis [17, 18]. In a nonendemic setting, the risk of recurrence among HIV-infected persons was reduced with longer duration of tuberculosis treatment [19].

Low CD4 cell counts are a major predictor of recurrent tuberculosis due to both relapse and reinfection in HIV-infected patients, and treatment with antiretroviral therapy decreases the likelihood of recurrence by at least 50% [12, 13]. Widespread use of antiretroviral therapy for all HIV-infected patients with tuberculosis is now supported by evidence from a clinical trial and from observational studies [20, 21]. Scaling up antiretrovirals for patients with tuberculosis will also reduce recurrent disease, as suggested by a study in Rio de Janeiro, Brazil [13].

A critically needed intervention to reduce reinfection tuberculosis is the implementation of infection control measures in clinical and community settings. Because patients with tuberculosis and with

HIV infection congregate in the same clinic waiting rooms, offices, laboratories, and hospital wards in much of the world, ongoing transmission is a significant cause of new disease, especially drug-resistant disease, as Narayanan et al [7] demonstrate. HIV and antiretroviral clinics in resource-poor settings have unwittingly become cauldrons of tuberculosis transmission, seriously undermining the impact of HIV therapies. The first step in reducing institutional and community transmission of *M. tuberculosis* infection is the detection of prevalent, undiagnosed cases and the initiation of appropriate therapy. Administrative measures to separate infectious patients from others, engineering and air flow management ranging from opening windows and doors to more sophisticated air handling techniques, and the use of personal protective equipment in more exposure-intense situations are all approaches that need to be ramped up worldwide, given the clear evidence of nosocomial transmission of tuberculosis infection among those with HIV infection [22].

Finally, what about vaccination as a strategy for preventing recurrent tuberculosis infections? Both Narayanan et al [7] and Glynn et al [9] suggest that development of a therapeutic vaccine or immunotherapy as an adjunct treatment for tuberculosis might help reduce relapse and reinfection episodes in those with exquisite susceptibility to the disease. Although this is an attractive concept in theory, the feasibility of this approach is currently quite limited. What is eminently sensible, however, is a primary vaccine for tuberculosis that prevents the development of disease in the first place. The current tuberculosis vaccine, BCG, appears to protect infants from severe forms of disease but does not prevent pulmonary tuberculosis in adults. We know from previous experience that a preventive vaccine can work, but in the case of BCG the protective effects of the vaccine most likely have become attenuated because of continuing evolution during laboratory passage [23]. Thus, prospects for new pre- and post-exposure preventive vaccines are bright [24]. The potential for an effective primary vaccine to control initial and thus recurrent tuberculosis, especially among HIV-infected persons, is enormous. After all, the best way to ensure that patients avoid a second episode of tuberculosis is to make certain that the first episode never occurs.

References

1. World Health Organization. WHO Report **2009**. Global tuberculosis control: epidemiology, strategy, financing. http://www.who.int/tb/publications/global_report/2009/pdf/full_report.pdf. Published 24 March 2009. Accessed 23 January 2010.
2. Sterling TR, Alwood K, Gachuhi R, et al. Relapse rates after short-course (6-month) treatment of tuberculosis in HIV-infected and uninfected persons. AIDS **1999**; 13:1899–1904.
3. Vernon A, Burman W, Benator D, Khan A, Bozeman L, for the Tuberculosis Trials Consortium. Acquired rifamycin monoresistance in patients with HIV-related tuberculosis treated with once-weekly rifapentine and isoniazid. Lancet **1999**; 353:1843–1847.
4. Small PM, Shafer RW, Hopewell PC, et al. Exogenous reinfection with multidrug-resistant *Mycobacterium tuberculosis* in patients with advanced HIV infection. N Engl J Med **1993**; 328:1137–1144.
5. Korenromp EL, Scano F, Williams BG, Dye C, Nunn P. Effects of human immunodeficiency virus infection on recurrence of tuberculosis after rifampin-based treatment: an analytical review. Clin Infect Dis **2003**; 37:101–112.
6. Corbett EL, Bandason T, Cheung YB, et al. Prevalent infectious tuberculosis in Harare, Zimbabwe: burden, risk factors and implications for control. Int J Tuberc Lung Dis **2009**; 13:1231–1237.
7. Narayanan S, Swaminathan S, Supply P, et al. Impact of HIV infection on the recurrence of tuberculosis in South India. J Infect Dis **2010**; 201:691–703 (in this issue).
8. Gandhi NR, Moll A, Sturm AW, et al. Extensively drug-resistant tuberculosis as a cause of death in patients co-infected with tuberculosis and HIV in a rural area of South Africa. Lancet **2006**; 368:1575–1580.
9. Glynn JR, Murray J, Bester A, Nelson G, Shearer S, Sonnenberg P. High rates of recurrence in HIV-infected and HIV-uninfected patients with tuberculosis. J Infect Dis **2010**; 201: 704–711 (in this issue).
10. Verver S, Warren RM, Beyers N, et al. Rate of reinfection tuberculosis after successful treatment is higher than rate of new tuberculosis. Am J Respir Crit Care Med **2005**; 171: 1430–1435.
11. Sonnenberg P, Murray J, Glynn JR, Shearer S, Kambashi B, Godfrey-Faussett P. HIV-1 and recurrence, relapse, and reinfection of tuberculosis after cure: a cohort study in South African mineworkers. Lancet **2001**; 358: 1687–1693.
12. Charalambous S, Grant AD, Moloi V, et al. Contribution of reinfection to recurrent tuberculosis in South African gold miners. Int J Tuberc Lung Dis **2008**; 12:942–948.
13. Golub JE, Durovni B, King BS, et al. Recurrent tuberculosis in HIV-infected patients in Rio de Janeiro, Brazil. AIDS **2008**; 22:2527–2533.
14. Korenromp EL, Scano F, Williams BG, Dye C, Nunn P. Effects of human immunodeficiency virus infection on recurrence of tuberculosis after rifampin-based treatment: an analytical review. Clin Infect Dis **2003**; 37:101–112.
15. Rosenthal IM, Zhang M, Williams KN, et al. Daily dosing of rifapentine cures tuberculosis in three months or less in the murine model. PLoS Med **2007**; 4(12):e344.
16. Barnard M, Albert H, Coetzee G, O'Brien R, Bosman ME. Rapid molecular screening for multidrug-resistant tuberculosis in a high-volume public health laboratory in South Africa. Am J Respir Crit Care Med **2008**; 177: 787–792.
17. Fitzgerald DW, Desvarieux M, Severe P, Joseph P, Johnson WD Jr, Pape JW. Effect of post-treatment isoniazid on prevention of recurrent tuberculosis in HIV-1-infected individuals: a randomised trial. Lancet **2000**; 356(9240): 1470–1474.
18. Churchyard GJ, Fielding K, Charalambous S, et al. Efficacy of secondary isoniazid preventive therapy among HIV-infected Southern Africans: time to change policy? AIDS **2003**; 17:2063–2070.
19. Nahid P, Gonzalez LC, Rudoy I, et al. Treatment outcomes of patients with HIV and tuberculosis. Am J Respir Crit Care Med **2007**; 175:1199–1206.
20. Abdool Karim SS, Naidoo K, Grobler A, et al. Effect of initiating antiretroviral therapy during tuberculosis treatment in HIV-infected individuals: results of a randomized controlled trial in TB-HIV co-infected patients in South Africa (SAPiT Study). N Engl J Med **2010**, in press.
21. Velasco M, Castilla V, Sanz J, et al. Effect of simultaneous use of highly active antiretroviral therapy on survival of HIV patients with tuberculosis. J Acquir Immune Defic Syndr **2009**; 50(2):148–152.
22. World Health Organization. WHO Policy on TB infection control in health-care facilities, congregate settings and households. Geneva, World Health Organization, **2009**.
23. Mostowy S, Tsolaki AG, Small PM, Behr MA. The in vitro evolution of BCG vaccines. Vaccine **2003**; 21:4270–4274.
24. Barker LF, Brennan MJ, Rosenstein PK, Sadoff JC. Tuberculosis vaccine research: the impact of immunology. Curr Opin Immunol **2009**; 21(3):331–338.