

Timing of Antiretroviral Drugs during Tuberculosis Therapy

TO THE EDITOR: In the Starting Antiretroviral Therapy at Three Points in Tuberculosis (SAPIT) study (Feb. 25 issue),¹ the sequential-therapy group included patients with CD4+ counts of <200 cells per cubic millimeter. In this group, patients started antiretroviral therapy up to 4 weeks after completing tuberculosis treatment, delaying antiretroviral therapy up to 9 months by design (the regimen for retreatment for tuberculosis is 8 months). The mean delay to the initiation of antiretroviral therapy in this group was 260±71 days.

We question whether equipoise existed to justify randomly assigning patients with CD4+ counts of <200 cells per cubic millimeter to receive antiretroviral therapy only after such long delays. Observational data show high rates of death among such patients who are not treated with antiretroviral therapy.^{2,3} Early antiretroviral therapy increases the incidence of the paradoxical immune reconstitution inflammatory syndrome, but this is associated with a low risk of death.⁴ Virologic outcomes of efavirenz regimens are not compromised by concomitant tuberculosis treatment.⁵

The South African National Department of Health guidelines at the time of the study recommended initiating antiretroviral therapy in patients with CD4+ counts of <200 cells per cubic millimeter after they have completed 2 months of tuberculosis treatment. The SAPIT study did not offer the standard of care to patients in the sequential-therapy group, resulting in advanced immunosuppression that remained untreated for up to 9 months and higher mortality.

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No potential conflict of interest relevant to this letter was reported.

1. Abdool Karim SS, Naidoo K, Grobler A, et al. Timing of initiation of antiretroviral drugs during tuberculosis therapy. *N Engl J Med* 2010;362:697-706.
2. Connolly C, Davies GR, Wilkinson D. Impact of the human immunodeficiency virus epidemic on mortality among adults with tuberculosis in rural South Africa, 1991-1995. *Int J Tuberc Lung Dis* 1998;2:919-25.
3. van den Broek J, Mfinanga S, Moshiro C, O'Brien R, Mugomra A, Lefi M. Impact of human immunodeficiency virus infection on the outcome of treatment and survival of tuberculosis pa-

tients in Mwanza, Tanzania. *Int J Tuberc Lung Dis* 1998;2:547-52.

4. Lawn SD, Bekker LG, Miller RF. Immune reconstitution disease associated with mycobacterial infections in HIV-infected individuals receiving antiretrovirals. *Lancet Infect Dis* 2005;5:361-73.

5. Friedland G, Khoo S, Jack C, Laloo U. Administration of efavirenz (600 mg/day) with rifampicin results in highly variable levels but excellent clinical outcomes in patients treated for tuberculosis and HIV. *J Antimicrob Chemother* 2006;58:1299-302.

TO THE EDITOR: Abdool Karim et al. do not discuss some points regarding the immune reconstitution inflammatory syndrome that warrant consideration, since this syndrome is one of the major concerns regarding early initiation of antiretroviral drugs during tuberculosis therapy. The syndrome can be quite dramatic in some patients, especially in those with extrapulmonary tuberculosis.¹ However, the presence of extrapulmonary tuberculosis is anecdotal in the present study (approximately 5% of patients). The role of early initiation of antiretroviral therapy in patients with extrapulmonary tuberculosis needs further study to have enough tools to make recommendations.

Furthermore, we have some concerns about the extrapolation of these results to areas outside Africa. The immune reconstitution inflammatory syndrome is related to the elevation of proinflammatory cytokines, and this elevation is closely related to genetic, nutritional,² and environmental factors, specifically sunlight exposure.³ All these factors are particular to Africa and different from other areas.⁴

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1. Dooley DP, Carpenter JL, Rademacher S. Adjunctive corticosteroid therapy for tuberculosis: a critical reappraisal of the literature. *Clin Infect Dis* 1997;25:872-87.
2. Katona P, Katona-Apte J. The interaction between nutrition and infection. *Clin Infect Dis* 2008;46:1582-8.
3. Wilkinson RJ, Llewelyn M, Toossi Z, et al. Influence of vitamin D deficiency and vitamin D receptor polymorphisms on

susceptibility to tuberculosis amongst Gujarati Asians in west London: a case-control study. *Lancet* 2000;355:618-21.

4. Velez DR, Wejse C, Stryjewski ME, et al. Variants in toll-like receptors 2 and 9 influence susceptibility to pulmonary tuberculosis in Caucasians, African-Americans, and West Africans. *Hum Genet* 2010;127:65-73.

TO THE EDITOR: The study by Abdool Karim et al. is commendable for its clinical relevance. The authors report that the outcomes were similar in patients who received new treatment for the first episode of tuberculosis and patients who received repeated therapy for tuberculosis. However, information regarding the frequency of drug-resistant tuberculosis and its influence on the outcome in the two study groups is missing. This could be an important confounding factor in a setting such as South Africa, where alarmingly high rates of multidrug resistance (MDR), including extensively drug-resistant tuberculosis, have been reported in patients with human immunodeficiency virus (HIV) infection.¹⁻³ Despite the fact that patients were randomly assigned to the study treatments, it is imperative to know that drug resistance was not differentially distributed between the study groups. This information is crucial to the interpretation of the findings of the present study.

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1. Pepper DJ, Rebe K, Morroni C, Wilkinson RJ, Meintjes G. Clinical deterioration during antitubercular treatment at a district hospital in South Africa: the importance of drug resistance and AIDS defining illnesses. *PLoS One* 2009;4(2):e4520.
2. Hassim S, Shaw PA, Sangweni P, et al. Detection of a substantial rate of multidrug-resistant tuberculosis in an HIV-infected population in South Africa by active monitoring of sputum samples. *Clin Infect Dis* 2010;50:1053-9.
3. Cowley D, Govender D, February B, et al. Recent and rapid emergence of W-Beijing strains of *Mycobacterium tuberculosis* in Cape Town, South Africa. *Clin Infect Dis* 2008;47:1252-9.

THE AUTHORS REPLY: Wilson and Meintjes question the equipoise in the SAPIT trial, asserting that available treatment guidelines were definitive. We disagree. In fact, the 2003 World Health Organization (WHO) guidelines, which were the basis of the 2004 South African guidelines, categorically state that recommendations on the initiation of antiretroviral therapy in tuberculosis are “provisional” and “pending ongoing studies,”

since the “optimal time to initiate [antiretroviral agents] in patients with [tuberculosis] is not known.”¹ Such tentative guidance can hardly be considered a definitive standard or a proven intervention. Further, a 2005 WHO consultation² concluded that the “optimal time for initiating antiretroviral therapy” in coinfecting patients is “the major research priority.” Thus, there was no conclusive evidence to define optimal HIV-tuberculosis therapy, and equipoise was never compromised. Nonetheless, to ensure patient safety and clinician primacy in decision making, the SAPIT protocol states: “In the event that a patient shows signs of clinical or lab parameter deterioration, the clinician will be at liberty to initiate antiretroviral therapy based on their judgement of the best interests of the patients”; 7% of the patients received antiretroviral therapy on this basis.

Concerns about drug interactions, tolerability, and the potentially life-threatening immune reconstitution inflammatory syndrome are key reasons why the initiation of antiretroviral therapy is often postponed in patients with tuberculosis. Although individual studies on the immune reconstitution inflammatory syndrome differ widely, a review³ showed that 29 to 36% of patients with tuberculosis in whom antiretroviral therapy was initiated had the syndrome, and a meta-analysis⁴ showed a 3.2% rate of death associated with it. These findings contrast with the assertion by Wilson and Meintjes that deaths from this syndrome are infrequent. Similarly, uncertainty regarding the rifampin-efavirenz drug interaction remains. Contrary to the view of Wilson and Meintjes, the Food and Drug Administration recently concluded that “the available data are insufficient to support definitive dosing recommendations for coadministration of efavirenz and rifampin.”⁵

We appreciate that the timing of initiation of antiretroviral therapy in patients with tuberculosis is controversial. By rigorously evaluating the risks and benefits associated with integrated versus sequential treatment, SAPIT provided the evidence needed to craft authoritative guidelines that policymakers and clinicians can use with confidence. SAPIT provided the evidence cited in the 2009 WHO guidelines on cotreatment. In South Africa, SAPIT spurred the new policy on cotreatment of HIV infection and tuberculosis.

We agree with Garcia-Vidal et al. and Kadhiraivan that data are needed to establish optimal

treatment in patients with HIV infection and extrapulmonary or MDR tuberculosis. We have no reason to suspect that MDR tuberculosis was unequally distributed in SAPIT study groups, since patients were randomly assigned to treatment and patients with previous tuberculosis at high risk for resistance were evenly distributed among the study groups.

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Since publication of their article, the authors report no further potential conflict of interest.

1. Scaling up antiretroviral therapy in resource-limited settings: treatment guidelines for a public health approach. Geneva: World Health Organization, 2003. (Accessed May 18, 2010, at <http://whqlibdoc.who.int/publications/2004/9241591552.pdf>.)
2. TB/HIV research priorities in resource-limited settings: Report of an expert consultation. Geneva: World Health Organization, 2005. (Accessed May 18, 2010, at http://whqlibdoc.who.int/hq/2005/WHO_HTM_TB_2005.355.pdf.)
3. Lawn SD, Bekker LG, Miller RF. Immune reconstitution disease associated with mycobacterial infections in HIV-infected individuals receiving antiretrovirals. *Lancet Infect Dis* 2005;5:361-73.
4. Müller M, Wandel S, Colebunders R, Attia S, Furrer H, Egger M. Immune reconstitution inflammatory syndrome in patients starting antiretroviral therapy for HIV infection: a systematic review and meta-analysis. *Lancet Infect Dis* 2010;10:251-61.
5. DiGiacinto JL, Chan-Tack KM, Robertson SM, Reynolds KS, Struble KA. Are literature references sufficient for dose recommendations? An FDA case study of efavirenz and rifampin. *J Clin Pharmacol* 2008;48:518-23.

Tuberculosis Screening and Diagnosis in People with HIV

TO THE EDITOR: Cain et al. (Feb. 25 issue)¹ conclude that screening for tuberculosis in people with human immunodeficiency virus (HIV) infection should include questions about a combination of symptoms rather than just chronic cough. They suggest that the recently published World Health Organization (WHO) approach² for the diagnosis of tuberculosis among people with HIV has a sensitivity of less than 33%. However, they restrict the WHO approach to the diagnosis of pulmonary tuberculosis and do not consider extrapulmonary tuberculosis. For extrapulmonary tuberculosis, the WHO recommends taking into account other characteristics, such as weight loss, fever, and night sweats. We agree, however, that the use of the three screening criteria (cough of any duration, fever of any duration, and night sweats lasting 3 or more weeks in the preceding 4 weeks) proposed by Cain et al. simplifies the screening and diagnosis of pulmonary and extrapulmonary tuberculosis and will facilitate the implementation of screening and diagnosis at the country level.

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1. Cain KP, McCarthy KD, Heilig CM, et al. An algorithm for tuberculosis screening and diagnosis in people with HIV. *N Engl J Med* 2010;362:707-16.
2. Improving the diagnosis and treatment of smear-negative pulmonary and extrapulmonary tuberculosis among adults and adolescents: recommendations for HIV-prevalent and resource-constrained settings. Geneva: World Health Organization, 2007.

THE AUTHORS REPLY: Koole and colleagues note that our analysis of the WHO approach to tuberculosis screening in people with HIV did not address extrapulmonary tuberculosis. The WHO has guidelines for the diagnosis of extrapulmonary tuberculosis but no explicit guidelines regarding screening.¹ The guidelines include several symptoms that might prompt a clinician to consider extrapulmonary tuberculosis, but there is no explicit recommendation to screen for them in all patients or to trigger a diagnostic evaluation for tuberculosis when one of them is present. Chronic cough is the only symptom explicitly noted for routine tuberculosis screening.¹

We reported on symptom screening when patients with all types of tuberculosis were included. We analyzed the data again after excluding the 25 patients who had only extrapulmonary tuberculosis. The sensitivity of cough lasting 2 to 3 weeks