

## CORRESPONDENCE



## Timing of Antiretroviral Therapy for HIV-1–Associated Tuberculosis

**TO THE EDITOR:** Three randomized trials reported by Blanc et al.,<sup>1</sup> Havlir et al.,<sup>2</sup> and Abdool Karim et al.<sup>3</sup> (Oct. 20 issue) consolidate the evidence base underpinning recommendations on when to start antiretroviral therapy (ART) in patients with human immunodeficiency virus (HIV)–associated tuberculosis. However, more than 80% of the global burden of this disease is in sub-Saharan Africa, where the health care infrastructure is weak and a lack of integration of the health care pathway represents a major hurdle to timely initiation of ART.<sup>4</sup> Patients typically attend completely separate HIV and tuberculosis clinics in different localities. In a township in South Africa, we found that delays in starting ART were almost three times as high in patients who were referred between nonintegrated tuberculosis services and ART clinics as in those with tuberculosis that was diagnosed in the ART clinic.<sup>5</sup> Thus, among patients with CD4 counts of less than 50 cells per cubic millimeter who were

referred to tuberculosis clinics, only 11% started ART within 4 weeks after receiving a diagnosis of tuberculosis. This is a prime example of how a lack of integration of tuberculosis and ART services compromises patient care. Progress toward integration is slow and must be accelerated. The time between tuberculosis diagnosis and initiation of ART might be a useful indicator of successful integration.

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1. Blanc FX, Sok T, Laureillard D, et al. Earlier versus later start of antiretroviral therapy in HIV-infected adults with tuberculosis. *N Engl J Med* 2011;365:1471-81.
2. Havlir DV, Kendall MA, Ive P, et al. Timing of antiretroviral therapy for HIV-1 infection and tuberculosis. *N Engl J Med* 2011;365:1482-91.
3. Abdool Karim SS, Naidoo K, Grobler A, et al. Integration of antiretroviral therapy with tuberculosis treatment. *N Engl J Med* 2011;365:1492-501.
4. Lawn SD, Campbell L, Kaplan R, et al. Time to initiation of antiretroviral therapy among patients with HIV-associated tuberculosis in Cape Town, South Africa. *J Acquir Immune Defic Syndr* 2011;57:136-40.
5. Lawn SD, Campbell L, Kaplan R, Little F, Morrow C, Wood R. Delays in starting antiretroviral therapy in patients with HIV-associated tuberculosis accessing non-integrated clinical services in a South African township. *BMC Infect Dis* 2011;11:258.

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**TO THE EDITOR:** Török and Farrar<sup>1</sup> summarize the findings of three controlled trials of when to start ART in HIV-associated tuberculosis and raise a number of practical issues to consider outside of the research setting. A practical point not considered is the setting of ART initiation. Loss to follow-up is typically the largest contrib-

utor to attrition from HIV care,<sup>2</sup> and initiating ART in patients in the hospital is associated with a doubling of the risk of loss to follow-up as compared with initiating ART in patients who are not in the hospital.<sup>3</sup>

Inpatient ART initiation will be necessary in severely immunocompromised patients or those with long hospital stays, in which case adequate linkage to community programs must be ensured. Studies show that ART can safely be delayed in less severely immunocompromised patients with the possible advantages of reduced risks of immune reconstitution inflammatory syndrome (IRIS) and adverse events leading to switches in antiretroviral drugs.

Outpatient ART initiation should be the preferred option whenever possible. Adequate linkage to outpatient care allowing prompt ART initiation in the community will also be important in securing the success of this approach.

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

1. Török ME, Farrar JJ. When to start antiretroviral therapy in HIV-associated tuberculosis. *N Engl J Med* 2011;365:1538-40.
2. Fox MP, Rosen S. Patient retention in antiretroviral therapy programs up to three years on treatment in sub-Saharan Africa, 2007-2009: systematic review. *Trop Med Int Health* 2010;15: Suppl:1-15.
3. Boyles TH, Wilkinson LS, Leisegang R, Maartens G. Factors influencing retention in care after starting antiretroviral therapy in a rural South African programme. *PLoS One* 2011;6(5):e19201.

**DR. BLANC AND COAUTHORS REPLY:** Lawn and Wood point out that a major hurdle to rapidly initiating ART in patients with HIV-associated tuberculosis is the separation between tuberculosis and HIV services that is typical of most resource-limited settings. We cannot agree more. On the basis of the results of the Cambodian Early versus Late Introduction of Antiretrovirals trial (CAMELIA; ClinicalTrials.gov number, NCT00226434) and two other recent studies, which show that early initiation of ART in very immunosuppressed patients with tuberculosis decreases mortality, it is no longer acceptable to allow patients to wait for treatment while being referred from tuberculosis services to HIV services or vice versa. In these patients, tuberculosis treatment and ART should be initiated at the same place to save time and to ultimately save

lives. Therefore, to reduce the interval between the start of treatment for each of the two infections, we urge early initiation of ART in tuberculosis services and an expedited process for patients to receive tuberculosis treatment in HIV services. We anticipate that this strategy, which was successfully accomplished in Cambodia during the CAMELIA trial, will have a considerable impact on the mortality associated with tuberculosis and HIV coinfection.

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**DR. HAVLIR AND COAUTHORS REPLY:** Delivering antiretroviral therapy as early as 2 weeks after a tuberculosis diagnosis will require major adaptations in health delivery for patients with HIV and tuberculosis. As reported by Lawn and Wood, inadequate integration of HIV and tuberculosis services leads to delays in antiretroviral initiation and excess mortality.<sup>1</sup> Several models to deliver integrated care are emerging and include “partial integration,” in which tuberculosis clinics manage antiretroviral therapy during tuberculosis treatment and “co-location” of HIV and tuberculosis clinics. With any model, streamlined HIV counseling, provider education including management of the IRIS, and rigorous infection-control policies to reduce transmission of tuberculosis are essential components.<sup>2</sup> Integration of some HIV and tuberculosis activities such as HIV testing among tuberculosis patients has increased over the past few years.<sup>3</sup> New data from our study and others call for acceleration of the integration of HIV and tuberculosis services and early delivery of HIV antiretroviral therapy to reduce mortality and AIDS among HIV-infected patients who acquire tuberculosis.

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1. Lawn SD, Campbell L, Kaplan R, et al. Time to initiation of antiretroviral therapy among patients with HIV-associated tuberculosis in Cape Town, South Africa. *J Acquir Immune Defic Syndr* 2011;57:136-40.
2. Howard AA, El-Sadr WM. Integration of tuberculosis and HIV services in sub-Saharan Africa: lessons learned. *Clin Infect Dis* 2010;50:Suppl:S238-S244.
3. Uyei J, Coetzee D, Macinko J, Guttmacher S. Integrated delivery of HIV and tuberculosis services in sub-Saharan Africa: a systematic review. *Lancet Infect Dis* 2011;11:855-67.

**THE EDITORIALISTS REPLY:** The health care setting in which ART is initiated is one of the factors associated with successful care of patients with HIV-associated tuberculosis. However, such decisions need to take into account the patient, his or her community, the clinical facilities available, and the extent to which tuberculosis and HIV care is integrated. The recent studies suggest that early ART initiation is beneficial in patients with opportunistic infections and advanced immunosuppression, with the exception of those with central nervous system infections. In patients with severe or life-threatening HIV-related illnesses, initiation of ART in the inpatient setting is clearly prudent. For patients who are not hospitalized, outpatient initiation of ART

is preferable. Even in the outpatient setting, however, delays in the initiation of ART<sup>1</sup> and loss to follow-up<sup>2,3</sup> are common. Loss to follow-up may result from poor coordination of HIV and tuberculosis services, rather than simply being a consequence of where the ART was initiated. The key to improving outcomes for patients with HIV-associated tuberculosis is coordinated and integrated HIV and tuberculosis services.<sup>4</sup> How that is achieved requires a locally relevant, flexible, and pragmatic approach.

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1. Lawn SD, Campbell L, Kaplan R, Little F, Morrow C, Wood R. Delays in starting antiretroviral therapy in patients with HIV-associated tuberculosis accessing non-integrated clinical services in a South African township. *BMC Infect Dis* 2011;11:258.
2. Fox MP, Rosen S. Patient retention in antiretroviral therapy programs up to three years on treatment in sub-Saharan Africa, 2007-2009: systematic review. *Trop Med Int Health* 2010;15:Suppl:1-15.
3. Bassett IV, Chetty S, Wang B, et al. Loss to follow-up and mortality among HIV-infected people co-infected with TB at ART initiation in Durban, South Africa. *J Acquir Immune Defic Syndr* 2012;59:25-30.
4. Lawn SD, Harries AD, Wood R. Strategies to reduce early morbidity and mortality in adults receiving antiretroviral therapy in resource-limited settings. *Curr Opin HIV AIDS* 2010;5:18-26.

## Glucocorticoids plus N-Acetylcysteine in Alcoholic Hepatitis

**TO THE EDITOR:** The study by Nguyen-Khac et al. (Nov. 10 issue)<sup>1</sup> sidesteps old contentious issues regarding the use of glucocorticoid therapy in alcoholic hepatitis. Among the 8 references cited in support of glucocorticoid treatment, 2 in fact concluded that the therapy was of no benefit.<sup>2,3</sup> In addition, 8 of 13 clinical trials published since 1971 showed that glucocorticoid therapy had no benefit as compared with placebo, although 5 of these did suggest an association with decreased short-term mortality.

The rationale for treating alcoholic hepatitis with antiinflammatory agents is soft. It is illogical to inhibit cytokines instead of targeting the putative pathogens that induce them. Exposing immunocompromised patients with severe alcoholic hepatitis to high-dose steroids exacerbates

their already increased risk of infection, and the benefits are far from proven. In a multicenter trial of prednisolone and infliximab in the treatment of severe alcoholic hepatitis, increased mortality in the infliximab group caused premature termination of the study.<sup>4</sup>

In the study by Nguyen-Khac et al., N-acetylcysteine was associated with fewer infectious complications, but the primary outcome was not improved. The idea of adding one unproven treatment to another has little merit.

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