Optimal Treatment of Codisease Due to HIV and Tuberculosis

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Tuberculosis remains the most common cause of death from human immunodeficiency virus (HIV) infection in most areas of the developing world, and a broad array of approaches are being studied and implemented to reduce mortality from HIV-associated tuberculosis [1]. Prevention is, of course, paramount, and measures that are of proven or potential benefit include intensified case finding, infection control measures, isoniazid preventive therapy (IPT), initiation of antiretroviral therapy (ART), and immunization with new tuberculosis vaccines, an approach we might call "the 5 i's" of prevention [2, 3]. Early diagnosis is also critical, and has been aided by the recognition of subclinical tuberculosis during HIV infection, the increasing recognition of smear-negative and even culture-negative disease, and the introduction of more rapid and sensitive diagnostic tests [4, 5].

Since current diagnostic tests do not detect all cases of HIV-associated tuberculosis, another emerging concept is the broader use of empiric treatment for active tuberculosis in high-risk subgroups of patients with HIV infection, especially those hospitalized with advanced AIDS [6–8]. Once active tuberculosis is suspected or confirmed, aggressive clinical management is critical to reduce the known enhanced mortality risk of HIV and tuberculosis codisease (often and inappropriately considered "coinfection," a term that should be reserved for latent tuberculosis infection in the setting of HIV).

Optimal treatment of HIV-associated tuberculosis requires treatment with 2 multidrug regimens: typically 6 months of a 4-drug, then 2-drug, regimen to treat tuberculosis, and a lifelong 3-drug ART regimen to reverse the functional immunosuppression that resulted in the development of active tuberculosis and to halt the further acceleration of HIV disease induced by active tuberculosis. Until recently, expert opinion had favored initial treatment for tuberculosis with subsequent initiation of ART 2–6 months later to avoid drug interactions, combined side effects, and the potential for increasing the rate of immune reconstitution inflammatory syndrome (IRIS).

Three randomized, controlled trials have now demonstrated the safety and superiority of initiating ART as soon as 2 weeks after the initiation of treatment for active tuberculosis, rather than at intervals >2–6 months later. In the 642-subject SAPiT (Starting Antiretroviral Therapy at Three Points in Tuberculosis Therapy) study from South Africa, an ART regimen of didanosine, lamivudine, and efavirenz was started early in 2 integrated therapy groups (<4 weeks or 8–12 weeks after initiation of tuberculosis treatment) and delayed until 6 months (after completion of tuberculosis treatment) in the comparison group. Mortality was reduced by 56%, from 12.1/100 person-years to 5.4/100 person-years, in the integrated therapy group (P = .003) [9]. Subsequent analysis of data showed that the rate of the composite endpoint of AIDS/death did not differ between the 2 integrated therapy groups, but was lower in the CD4 <50 cells/µL subgroup with treatment at <4 weeks versus 8–12 weeks (P = .06). The rate of IRIS in the CD4 <50 cells/µL group was 47% with treatment at <4 weeks, compared with 10% with treatment at 8–12 weeks [10].

In the CAMELIA (Cambodian Early Versus Late Introduction of Antiretrovirals) study from Cambodia, 661 HIV-infected subjects with newly diagnosed tuberculosis were randomized to an ART regimen of stavudine, lamivudine, and efavirenz, starting either 2 weeks or 8 weeks after initiation of treatment for tuberculosis. There was a statistically significant 34% reduction in the mortality rate in the 2-week versus the 8-week group, from 13.8/100 person-years to 8.3/100 person-years; rates of IRIS were 3 times higher in the 2-week group [11].

The STRIDE ACTG 5221 trial enrolled codisease patients with CD4 <250 cells/µL, and randomized patients to an immediate (<2 weeks) or early (8–12 weeks) 3-drug ART regimen. The composite
The primary endpoint was a composite of CD4 <250 cells/µL, an AIDS-defining condition, or death, and was reached by 16% of subjects with early ART compared with 23% with delayed ART by study completion (P = .17). Although ART was only administered for 6 months in the early treatment group, the favorable trend in the composite endpoint was supported by a statistically significant difference in event-free survival at 12 months, and a predictable loss of this effect at 24 months. Tuberculosis treatment outcomes did not differ. Grade 3 or 4 serious adverse events, most importantly leukopenia, were more common in the delayed therapy group. Although rates of IRIS would have been expected to be low in this cohort with high baseline CD4 counts, it was surprising that no cases were detected.

The study from Uganda provides reassurance that early initiation of ART is safe and advisable in patients with CD4 counts >350 cells/µL, and may be associated with a reduced risk of adverse events. It is reasonable to assume that with the current standard of care, lifelong continuation of a currently recommended ART regimen after a diagnosis of active tuberculosis will result in more substantial clinical benefit.

What questions remain unanswered by the studies reviewed here? The most important relates to a shortcoming of many studies on the treatment of tuberculosis: the frequent limitation of cases to patients with a positive sputum smear, a subset that may represent only 30%–40% of all cases of HIV-associated pulmonary tuberculosis [13]. Newer diagnostic tests should increase the proportion of patients for whom same-day confirmation of diagnosis will be possible. But it will be important to know if study results in patients with multibacillary disease detectable by smear or molecular methods will be applicable to patients with paucibacillary smear-negative disease detected only by culture. The South African, Cambodian, and Ugandan studies were conducted almost exclusively on patients with smear-positive disease.

There is also a substantial subset of HIV-infected patients with smear- and culture-negative pulmonary disease who meet a rigorous clinical and radiologic case definition of tuberculosis, including response to specific tuberculosis therapy after absence of response to treatment for community-acquired pneumonia [3]. Is this an even more paucibacillary form of disease analogous to tuberculoid leprosy and associated with a more robust mycobacterial immune response? Might ART be associated with higher rates of IRIS in this subgroup?

Another challenging and urgent issue relates to hospitalized patients with advanced AIDS, CD4 <75 cells/µL, and extrapulmonary disseminated tuberculosis. These patients with fever and wasting are often misdiagnosed pre-mortem and have a high short-term mortality rate because sputum and x-ray studies may be negative and blood cultures, if available, may not turn positive for Mycobacterium tuberculosis until after death [8]. Early ART is likely to be critically important in these patients.

Nutritional supplementation during treatment for HIV-associated tuberculosis also deserves further study and current consideration in clinical treatment. Many HIV-infected patients with active tuberculosis are malnourished. Low body mass index (BMI), especially at values <17–18.5, has been shown to be a risk factor for mortality from HIV-associated tuberculosis and for overall HIV-associated mortality [11, 16–18]. These observations have led to studies of adjunctive protein calorie supplementation during tuberculosis treatment. Limited trials performed to date have shown modest though promising benefit [19–21]. A randomized, controlled study of protein calorie supplementation for HIV-infected women with tuberculosis will be started by the DarDar Consortium later this year in Tanzania. Until further data are available it seems prudent to provide nutritional counseling to all patients with HIV-associated tuberculosis and to consider nutritional supplementation for those with low BMIs. For severely malnourished patients, nutritional supplementation should be initiated gradually and progressively over 1–2 weeks to prevent the potentially severe metabolic consequences of the refeeding syndrome (electrolyte shifts, arrhythmias, organ failure) [22].
It is now clear that HIV-infected patients in all CD4 cell count ranges who are started on treatment for smear-positive tuberculosis will benefit from initiation of ART within 8 weeks (early). Patients with CD4 counts <50 cells/μL should be started on ART within 2 weeks (immediate). Immediate ART should also be considered for other subgroups judged by the clinician to be at increased risk of short-term mortality (eg, low BMI, poor Karnofsky score, disseminated tuberculosis). Since benefits are likely to be the same in smear-negative patients, clinicians should not wait for culture results to start ART in patients started on empiric treatment for tuberculosis. Recent data support delayed initiation of ART in patients with tuberculosis meningitis [23]. Careful follow-up for management of IRIS is indicated in all cotreated patients.

Improving treatment outcomes for HIV-associated tuberculosis should not distract us from wider development and application of measures proven to prevent HIV-associated tuberculosis: IPT and ART at the currently recommended CD4 threshold of <350 cells/μL and immunization with an inactivated whole-cell mycobacterial vaccine [2, 3]. Full application of these strategies would have prevented many of the cases of HIV-associated tuberculosis reported in the treatment trials reviewed here.

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**References**