Tuberculosis (TB) and HIV infection are the 2 leading causes of infectious diseases–related mortality worldwide. An estimated one-third of the world’s population (~2 billion people) are currently infected with Mycobacterium tuberculosis. In addition, 8 million new cases of active TB are estimated to occur worldwide annually, with more cases seen currently than at any time in history [1, 2]. The collision of TB and HIV infection has resulted in an estimated 12–14 million people coinfected with both HIV and M. tuberculosis, the majority of whom live in sub-Saharan Africa [3]. In some countries in this region, the percentage of patients with active TB who are coinfected with HIV exceeds 70% [2].

Despite appropriate management of drug-susceptible TB and the initiation of antiretroviral therapy, patients with HIV and TB coinfeciton in resource-limited settings have increased mortality rates, a consequence of both advanced TB and HIV-related complications. This high early mortality is associated with low CD4 cell counts at the start of therapy and is most dramatic during the first 3 months after initiation of HAART. Mortality rates remain stable thereafter, at rates similar to those seen in resource-rich countries [4, 5]. This observation, among others, has led to advocacy for the integration of health care services for TB and HIV infection and the early initiation of HAART for coinfected patients [6, 7]. However, the treatment of HIV infection in the context of active TB treatment may be complicated by drug interactions, additive toxicities of antiretroviral and antituberculosis medications [8], difficulty in adherence to multiple medications, and immune reconstitution inflammatory syndrome (IRIS) [9–13]. The concern about the occurrence and dangers of TB IRIS has likely been most responsible for delaying the initiation of HAART for patients with coinfection who are receiving antituberculosis therapy.

The current mechanism underlying TB IRIS in coinfected patients is believed to be related to HAART-induced suppression of viral replication and immune recovery, with resultant restoration of TB-specific immune responses. These, in turn, may generate necrotizing and granulomatous inflammation. Although largely beneficial in most patients, an overly exuberant host response in some patients may lead to TB IRIS in 1 of 2 forms: a “paradoxical” transient clinical deterioration after clinical improvement or the uncovering of active disease in patients with unrecognized “occult” TB. Predictors of TB IRIS include low CD4 cell count, early initiation of HAART, and extrapulmonary TB disease, which is likely to be a measure of advanced HIV disease. Both forms of TB IRIS are associated with new onset of constitutional signs and symptoms and most commonly involve the lungs, but also frequently involve the lymph nodes, skin, CNS, and gastrointestinal tract. The clinical presentations vary widely with regard to the manifestations and severity. Although TB IRIS can be clinically challenging and can cause substantial morbidity, it is infrequently fatal [12, 13]. There is no gold standard or single diagnostic test that can confirm the diagnosis. As a consequence, TB IRIS can be underdiagnosed or misdiagnosed, resulting, in part, in a widely differing incidence in different studies (range, 5%–40%). In addition, in some patients, clinicians may have difficulty distinguishing TB IRIS from other HIV-related opportunistic diseases or drug-resistant TB, resulting in important and potentially deleterious consequences for patients. Management of TB IRIS has not been well studied, but an-
ecdotal evidence indicates that it usually responds to nonsteroidal anti-inflammatory agents in milder cases and glucocorticoids in more-severe cases. To improve the diagnosis and management of IRIS, investigators and clinicians have struggled to create a clinical case definition of sufficient sensitivity and specificity to be widely and reliably applicable [9, 12–14]. Most recently, an international working group has proposed and published a consensus definition for use in resource-limited settings [15].

In this issue, Meintjes et al. [16] have identified and described the largest reported prospectively evaluated cohort of patients with suspected IRIS. One hundred South African cases thought to be TB IRIS were referred to the authors from local primary care physicians. The recently published consensus case definition [15], which specifies the exclusion of patients with diagnosed drug-resistant TB (mainly to rifampin), was used to define TB IRIS. The patients who were referred and evaluated in the study had advanced HIV disease (median baseline CD4 cell count, 50 cells/µL) and initiated antituberculosis therapy in accordance with South African Guidelines. Symptoms of TB IRIS began a median of 14 days (interquartile range, 26–94 days) after initiation of HAART. Consistent with guidelines and the usual program practice in South Africa, a substantial proportion of the patients in the study did not have initial or subsequent microbiologic confirmation of their TB diagnosis, nor did they have drug susceptibility testing performed.

Of the initial 100 patients with suspected TB, after re-evaluation, 7 had alternative opportunistic diseases and 4 had rifampin-resistant TB; these patients were excluded, which resulted in 89 patients fulfilling the TB IRIS case definition. However, 9 of these patients subsequently received a diagnosis of rifampin-resistant TB and, in accordance with the existing case definition, were secondarily excluded. Of note, however, the 13 patients with rifampin-resistant TB had typical TB IRIS signs and symptoms; they experienced initial improvement while receiving TB treatment and subsequent deterioration. The authors were unable to clinically distinguish TB IRIS among those with and without drug-resistant TB. The results confirm that a clinical assessment of TB IRIS should include evaluation for other opportunistic diseases and testing for TB drug resistance. But the authors further argue, based on the results of this case series, that TB IRIS and drug resistance should no longer be considered to be mutually exclusive diagnoses. Those providing treatment for patients with drug-resistant TB and HIV coinfection may readily support this view, because TB IRIS certainly occurs in this population and may be more severe in these patients than in patients with drug-susceptible TB as a result of the slower clearing of organisms by second-line TB drug treatment or partial clearing by remaining active drug in the initial first-line regimen.

The analysis by Meintjes et al. [16] of drug-resistant TB and TB IRIS is welcome and timely. The global presence of multidrug-resistant and extensively drug-resistant TB has reached epidemic proportions in South Africa and, quite possibly, in other sub-Saharan countries [17–21]. In areas where drug-resistant TB has been studied in South Africa, the HIV coinfection rate is extremely high, and increasing numbers of patients with diagnosed and unrecognized drug-resistant TB are and will be receiving antiretroviral therapy. These patients are at risk for TB IRIS and/or may present with signs and symptoms that mimic TB IRIS but that are a consequence of incomplete clinical response to standard TB therapy. A frustrating paradox is that TB drug resistance testing is most limited in settings where TB IRIS is most likely to occur. At the present time, the vast majority of patients with suspected TB in sub-Saharan Africa do not have microbiologic culture confirmation or drug susceptibility testing available because of limited laboratory infrastructure. In the study by Meintjes et al. [16], the authors were fortunate to employ a rapid test to identify rifampin resistance (FASTplaque assay), thus enabling the recognition of multidrug-resistant TB (but not extensively drug-resistant TB, because second-line agents are not included in this test). The validation of such rapid diagnostic technologies is currently underway, and the wide availability of these tests is desperately needed to rationalize the treatment of patients with TB with and without HIV coinfection and with and without TB IRIS.

The results of the study by Meintjes et al. [16] indicate that the available case definition for TB IRIS, under usual program conditions in sub-Saharan Africa, is useful but remains insufficiently sensitive and specific, and further refinement and testing is necessary. This is particularly so in the setting of high prevalence of drug-resistant TB. Should one conclude that the inability to fully confirm the diagnosis of TB IRIS and its consequences and the limited availability of laboratory infrastructure are sufficient reasons to delay initiation of HAART for patients with TB and HIV coinfection? The occurrence of TB IRIS, although challenging, infrequently causes death, and the attendant diagnostic uncertainties must be placed in the context of the high early mortality among patients with both diseases and the possibility that early initiation of HAART, even with the possibility of TB IRIS, might be life saving. This might be even more likely for drug-resistant TB, which is associated with an extremely high mortality rate among HIV-coinfected patients [19]. Several randomized trials have been designed and are in progress to address the issue of timing of initiation of HAART for drug-susceptible TB and HIV coinfection; thus, answers may be forthcoming. Although, as with the initiation of therapy for HIV infection in general, the “golden moment” of initiation of HAART during the course of therapy for TB remains to be determined, the preliminary results from the Starting Antiretroviral Therapy in Three Points in Tuberculosis Therapy (SAPIT)
References and HIV coinfection will be lowered. initiation of HAART for patients with TB is one of the strongest barriers to the early of corticosteroid treatment for TB IRIS, they show significant benefit from the use well-characterized TB IRIS cohort. The be an additional useful product of this controlled trial of corticosteroid treatment of TB IRIS, and better defining the benefit and risk of corticosteroid treatment may be an additional useful product of this well-characterized TB IRIS cohort. The trial results are anxiously awaited and, if they show significant benefit from the use of corticosteroid treatment for TB IRIS, one of the strongest barriers to the early initiation of HAART for patients with TB and HIV coinfection will be lowered.

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References