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Clinical Outcomes among HIV-Tuberculosis Coinfected Patients Developing Immune Reconstitution Inflammatory Syndrome after HAART Initiation in South India

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Abstract
Introduction: We determine the frequency and immunological outcome of developing immune reconstitution inflammatory syndrome (IRIS) among HIV-tuberculosis (TB) coinfected Indians receiving highly active antiretroviral therapy (HAART).

Methods: Patients coinfected with TB and HIV who initiated HAART were classified based on treatment outcomes (IRIS and non-IRIS) utilizing an observational HIV/AIDS cohort. Results: A total of 1731 HIV-TB coinfected patients initiated HAART, and 95 of these patients (5.5%) developed TB-IRIS, with an incidence rate of 0.26 per 100 person-years. Patients who developed IRIS had significantly higher CD4 counts than non-IRIS patients at the time of initiating HAART, as well as after 6 months, 18 months, and 24 months following HAART initiation (P < .05). Conclusions: TB-HIV coinfected patients who developed IRIS following HAART initiation had equivalent clinical outcomes compared with their TB-HIV coinfected counterparts who did not develop IRIS, suggesting minimal long-term risks associated with IRIS.

Keywords
IRIS, tuberculosis, HIV/AIDS, India, HAART

Introduction
In resource-limited settings, HIV-infected patients often present to care with advanced immunodeficiency, including opportunistic infections such as tuberculosis (TB). Despite the immune restorative effects of highly active antiretroviral therapy (HAART) and its ability to reduce HIV-associated morbidity and mortality, some patients experience a temporary exacerbation of symptoms, signs, and manifestations of TB.¹ This clinical phenomenon of an exuberant immune response that generally develops within 2 to 3 months of initiating ART has been called immune reconstitution inflammatory syndrome (IRIS).²

In light of the high burden of TB in resource-limited settings coupled with an increasing number of HIV-infected patients gaining access to ART, a significant proportion of TB occurring soon after initiating therapy could be complicated by IRIS. To date the clinical and epidemiological information about the IRIS of TB among patients coinfected with TB and HIV remains limited with small samples and widely varying estimates with limited long-term outcome data.²³ An earlier study at our center documented 11 cases of IRIS of TB.⁴ The current study was undertaken to determine the frequency and clinical response of developing IRIS among HIV-TB coinfected South Indian patients receiving HAART.

Methods
Setting
Since 1996, YRG Center for AIDS Research and Education (YRG CARE), VHS Chennai, has provided a continuum of care for over 10 000 HIV-infected individuals. All patients were treated according to the World Health Organization (WHO)
tuberculosis or positive sputum or aspirate tests for acid-fast bacilli, radiological features suggestive of TB, or clinical and radiological improvement in response to antituberculosis treatment. Immune reconstitution inflammatory syndrome was defined based on the clinical criteria suggested by French et al. A minimum of 9 months had elapsed between patients who experienced multiple TB diagnoses.

### Statistical Analysis

Descriptive statistics were calculated with mean and standard deviation for variables that were normally distributed; and the median and interquartile range (IQR) were calculated for variables influenced by extreme values. To compare proportions, chi-square ($\chi^2$) statistics were used, and the Mann-Whitney $U$ test was used to compare median durations. Statistical analyses were performed with SPSS software (version 13.0; SPSS, Chicago, Illinois). A $P$ value less than .05 was considered statistically significant.

### Results

Between February 1996 and March 2008, 1731 HIV-TB co-infected patients initiated generic HAART. Among this HIV-TB co-infected population, 95 patients (5.5%) developed IRIS. The incidence rate of TB-IRIS was 0.26 per 100 person-years. Most patients (88.4%) were men and had been infected with HIV via heterosexual transmission (>95%); the median age was 34 years (see Table 1). Over half of the patients (56.8%) had developed extrapulmonary TB and 43.1% had developed pulmonary TB. The median time from TB diagnosis to initiation of HAART was 17 days (IQR: 3-65.5 days). The median time to developing IRIS after initiating HAART was 86 days (IQR: 38-218 days). A fifth of patients (20%) developed IRIS within 30 days of initiating HAART, and an additional quarter of patients (25.3%) developed IRIS between 30 and 60 days of initiating HAART. At the time of developing IRIS, the median CD4 count was 290 cells/mm$^3$ (IQR: 128-326). No patients died and none had to stop HAART after developing IRIS.

When patients who developed TB-IRIS were compared with patients who only developed TB (the non-IRIS group) during the 24 months of patient follow-up, it was found that the median CD4 counts varied at different levels between the 2 groups. Overall, both groups regardless of IRIS demonstrated robust increases in CD4 counts over time. At the time of initiating HAART, patients who developed IRIS had a significantly higher CD4 count compared with non-IRIS patients (88 cells/mm$^3$ vs 70 cells/mm$^3$; $P = .023$). Patients who developed IRIS had a higher CD4 count than non-IRIS patients after 6 months (315 cells/mm$^3$ vs 291 cells/mm$^3$; $P = .032$), after 18 months (421 cells/mm$^3$ vs 367 cells/mm$^3$; $P = .047$), and after 24 months of initiating HAART (411 cells/mm$^3$ vs 349 cells/mm$^3$; $P = .042$). Among patients who developed IRIS, 6 patients (6.3%) were diagnosed with TB a second time. The median time from the first TB diagnosis was 1281 days (IQR: 526-1652 days), and the median time since IRIS was 769 days (IQR: 281-1592 days). Among non-IRIS patients, 46 (2.8%)...
patients were diagnosed with TB a second time, and the median time from the first TB diagnosis was 750 days (IQR: 524-1268, days).

**Discussion**

The development of IRIS is an important concern for patients concurrently receiving treatment for both TB and HIV. In the current study, the frequency of TB-IRIS among this TB-HIV coinfected patient population after initiating ART was 5.8%, which was relatively low compared to some other recent studies (ranging 30%-45%). Patients who developed IRIS had good clinical outcomes over time assessed by CD4 count, which was at times even better than their non-IRIS comparison cohort. The findings of the present study are similar to other reports which documented that TB-IRIS generally develops within the first 90 days of initiating HAART, which suggests the need for close clinical monitoring of patients soon after initiating HAART. Unlike earlier studies that had identified extrapulmonary TB as a major risk factor for later development of TB-IRIS, in the current study extrapulmonary TB was not associated with the later development of TB-IRIS. This may be related to the finding in the current study that patients who developed IRIS had higher CD4 counts than their non-IRIS TB-HIV coinfected counterparts, prior to initiating HAART.

It has been suggested that delaying HAART in patients coinfected with TB and HIV could dually decrease potential side effects and the incidence of IRIS; however, this strategy is unlikely to be feasible in resource-limited settings, such as the current study, where many patients are initiating HAART at advanced immunodeficiency. Studies have consistently demonstrated that low baseline CD4 counts are a risk factor for later development of IRIS. Patients diagnosed with IRIS have been shown to initiate HAART in closer proximity to the diagnosis of their opportunistic infection compared to patients who did not develop IRIS. However, the current study did not document this temporal difference in HAART initiation and diagnosis of opportunistic infection between patients who developed IRIS and non-IRIS patients. The spectrum of IRIS documented at our clinic has primarily been due to TB rather than other infection processes, which could be attributed to the relatively lower CD4 counts that cytomegalovirus and progressive multifocal leukoencephalopathy IRIS present as compared with TB-IRIS, as well as the high prevalence of TB in this patient population. Further proactive efforts must be taken to initiate patients on ART at higher CD4 counts before the development of opportunistic infections and the increased risk of developing IRIS.

The finding that patients who experienced IRIS had higher CD4 counts after 6, 18, and 24 months of initiating HAART demonstrates that patients with TB-IRIS can have good long-term immunological outcomes. Similar to an earlier report from our center, all TB-IRIS patients are currently clinically stable with no further AEs, which suggests the minimal long-term risks associated with IRIS. Despite growing evidence of the clinical features of IRIS and predictive models to assist in its diagnosis, there is a need for greater identification of factors associated with the development and outcome of IRIS that can assist in more precise preventive and therapeutic strategies, including the use of corticosteroids.

Close clinical monitoring is warranted in the first few months after initiating HAART, especially in resource-limited settings where TB is rampant. Further studies are needed to determine the appropriate time of initiating ART and the management of IRIS in this patient population. Immune reconstitution inflammatory syndrome is a syndrome that develops when a patient has an exuberant immune response to the effects of ART. In resource-limited settings with a high burden of TB and an increasing availability of HAART,
clinicians should include IRIS in their differential diagnosis of patients who present with an inflammatory process soon after initiating therapy.

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Declaration of Conflicting Interests
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