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Alwyn Rapose
University of Massachusetts Medical School

Et al.

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Tuberculosis, human immunodeficiency virus, and the immune reconstitution inflammatory syndrome

A Rapose and S Karande[1]

Department of Clinical Medicine, Division of Infectious Diseases, University of Massachusetts Medical School and Reliant Medical Group, Worcester, Massachusetts, USA
[1]Department of Pediatrics, Seth G. S. Medical College and K. E. M. Hospital, Mumbai, Maharashtra, India
Address for correspondence: Dr. Rapose A, E-mail: alwyn.rapose@reliantmedicalgroup.org

Tuberculosis (TB) continues to remain a major health problem in India in spite of achieving nationwide coverage with directly observed therapy since 2006. The estimated incidence of 2.2 million TB cases and a prevalence of 2.5 million in the year 2015 make India the country with the highest burden of TB in the world.[1] In addition, it is estimated that a substantial part of the healthy population (up to 40%) has latent (inactive) TB.

India had estimated 2.1 million people living with the human immunodeficiency virus (HIV) in the year 2015.[2] HIV infection left untreated is associated with a profound immunosuppression secondary to direct invasion and destruction of CD4 cells by the virus.[3,4] With the introduction of antiretroviral therapy (ART) targeting HIV infection, individuals with HIV infection are now living longer and healthier lives. While ART is destroying the HIV, the infected individuals' immune system recovers to a state of near normal,[5] thus protecting that individual from previously described HIV-associated opportunistic infections and opportunistic malignancies.[6] The National AIDS Control Program has initiated free ART since 2004 which has contributed to a decline in new cases as well as deaths related to HIV. As of January 2017, there are 10.5 lakh Indians living with HIV who are on ART.[7]

HIV and TB coinfection creates a perfect storm in terms of poor outcomes secondary to the multiple challenges in the management of these two infections.[8,9,10] In an HIV patient, TB often presents atypically both clinically as well as radiologically, resulting in delayed diagnosis and hence delayed initiation of therapy.[8] In addition, with the multiple medications used to treat HIV (3 or more agents) and TB (4 or more agents), there is a need for dose modification on account of drug-drug interactions. For example, ritonavir which is used in ART is a cytochrome p450 enzyme inhibitor while rifampicin which is used in the treatment of TB is an inducer of the cytochrome p450 enzyme. The high pill burden involved in treating HIV and TB coinfection (7 or more agents) is also associated with reduced compliance resulting in the development of drug-resistant TB as well as the possibility of drug-resistant HIV.[9,11]

In patients with HIV and TB coinfection, anti-TB medications are initiated first. ART is then recommended within the next 2–8 weeks.[12,13,14] Unfortunately, in some individuals, initiation of ART is associated with clinical deterioration. This is in the form of either worsening of a previously diagnosed TB infection

or clinical manifestation of a concomitant undiagnosed TB infection. The term "immune reconstitution inflammatory syndrome (IRIS)" is used to describe this apparent clinical worsening when an HIV-infected patient is initiated on ART. Although Shelburne *et al*.,[15] were the first to coin this term in 2002, the phenomenon of clinical deterioration following the initiation of ART had been previously reported by others like French *et al*.,[16,17] and Fox *et al*.[18] in the 1990s who described this as "immune restoration disease," proposing that the phenomenon was actually an indication of an improvement in host immunity rather than a true deterioration.

This phenomenon of apparent worsening manifestations has been described with a wide variety of infectious agents including Mycobacteria (*Mycobacterium tuberculosis*, *Mycobacterium avium*, and *Mycobacterium leprae*),[15,19,20,21,22] *Pneumocystis*, *Cryptococcus*, *Candida*, parasites, and viruses[15,18,23,24] and noninfectious conditions such as malignancies.[15,24]

There are currently no official data on the incidence of TB-IRIS in India. The reported incidence of around 7.5% by Kumarasamy *et al*.[25] and Karmakar *et al*.[26] may be an underestimation because it is quite possible that many patients suffering from HIV and TB coinfection and receiving free treatment may be developing TB-IRIS which may be going undetected or misdiagnosed. On the other hand, the high incidence (nearly 30%) noted by Kumar *et al*.[27] in their cohort of patients initiating ART may be biased by the fact that the study was conducted in TB clinics, and the criteria used for predicting IRIS were only 22% specific, indicating a high likelihood of overdiagnosis of IRIS.

Patients with TB-IRIS can present with symptoms that can be divided into two broad categories:

1. Previously diagnosed TB could appear to be getting worse when the patient is started on ART. For example, an HIV patient diagnosed with pulmonary TB and improving on anti-TB medications can develop worsening respiratory symptoms and appearance of new pulmonary lesions on radiologic imaging when he or she is initiated on ART.[22,28] In some cases, there could be new manifestations of TB at sites distant from the underlying pulmonary disease, for example, new lesions in the brain, eye, heart, or lymph nodes[29,30,31,32]
2. There could be new clinical symptoms of a previously undiagnosed TB that manifest after initiation of ART.[8,28] In these cases, when the HIV-positive individual is initiated on ART, a few weeks later the patient develops new clinical manifestations leading to diagnosis of the apparently new TB infection.

In either of the above two categories, the clinical manifestations can be highly variable. In some patients, the manifestations may be mild with low-grade fever, arthralgia, or lymphadenopathy, while in other patients, TB-IRIS is associated with severe clinical deterioration in the form of neurologic (meningitis or tuberculoma), pulmonary (pleural effusions and empyema), gastrointestinal (obstruction or perforation), or organ (liver or kidney) failure. Increased mortality is seen in patients who develop severe IRIS after initiation of ART.[12,31]

Researchers have tried to identify subsets of HIV- and TB-coinfected patients who are at increased risk of developing IRIS. Some of these risk factors include very low initial CD4 count, with a rapid rise in CD4 count after initiation of ART,[23,29,33] deregulation of T-cell responses,[20,34,35] and altered ratios of various cytokines.[22,36,37] These studies may be tantalizing to research scientists. Unfortunately, there are very few – if any – easily available laboratory tests to diagnose or predict IRIS in any given individual. Hence, the diagnosis of TB-IRIS is mainly clinical. Laboratory studies that support the diagnosis include evidence of a rapid rise in CD4 count and associated fall in viral load.[23,26,29,33]

Management of TB-IRIS is challenging. There is ongoing research into the best approach. One group of researchers is studying the role of prednisone as a preventive agent in patients with HIV and TB

coinfection initiating ART – the PredART trial.[38] Results of the study are awaited. Another research group has evaluated whether there was any benefit of HIV chemokine receptor-5 antagonist – maraviroc – as part of initial ART. Unfortunately, it did not reveal any meaningful protection against IRIS.[39] An older study proposing the beneficial effect of interleukin-2 and granulocyte-macrophage colony-stimulating factor immunotherapy also did not prove to be of clinical benefit.[40]

In most clinical situations, when a patient who is initiated on a new medication develops an unexpected reaction, the most recently introduced medication is implicated as the cause of that reaction, and the reflex action is to discontinue that medication. However, when evaluating a patient with HIV and TB coinfection who develops IRIS after ART is initiated, it is very important to understand that the apparent clinical deterioration is in fact due to an immunologic improvement as seen by improved CD4 count compared to baseline.[6,15,33]

The first step in the management of suspected TB-IRIS is to review all the medications (ART and anti-TB medications) in detail, evaluating for potential side effects and drug-drug interactions.[8] Once adverse effect of the medications is ruled out, it is very important that ART and anti-TB medications be continued.[8,9,12,32] Patients with TB-IRIS who present with mild reactions can be treated with nonsteroidal anti-inflammatory medications (ibuprofen, naproxen, and piroxicam).[8,32] In contrast, TB-IRIS manifesting with severe reactions such as complicated pulmonary, cardiac, or neurologic symptoms are treated with systemic corticosteroids[8,33,41] with the caveat that corticosteroids themselves carry a risk of worsening infection and increased mortality in HIV patients.[42]

With the high prevalence of both TB and HIV in India, physicians need to be acutely aware of the possibility of IRIS in a patient with HIV and TB coinfection who develops an apparent deterioration after the initiation of ART. With improving access to ART, treating physicians should be alert to the manifestations of IRIS and take prompt and sound clinical measures to ensure that IRIS is diagnosed early and treatment measures are initiated appropriately. When the diagnosis of TB-IRIS is made, it is very important that ART not be interrupted because it remains the backbone of therapy to improve survival of HIV-infected individuals.

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