

# Immunosuppression and Leprosy

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## Introduction

This chapter discusses the presentation and management of leprosy in an immunosuppressed host. An immunocompromised host is a patient who does not have the ability to respond normally to an infection due to an impaired or weakened immune system. Immunodeficiency may be inherited (e.g., hypogammaglobulinemia) or acquired as a result of certain conditions such as HIV/AIDS, some cancers, malnutrition, diabetes, splenectomy, and trauma. Many drugs will also cause immunosuppression: chemotherapy, corticosteroids, and immunosuppressants used in organ transplants or autoimmune diseases.

A leprosy reaction is an immunological response to the *M. leprae* antigen and is treated with immunosuppressant drugs, which may in turn put the patient at risk of complications (see Chapter 2.2). Opportunistic infections are also an important risk to an immunocompromised patient (see Chapter 2.4).

## Leprosy and HIV

Co-infection with HIV has a major effect on the natural history of many infectious diseases, particularly mycobacterial diseases. Many countries endemic for leprosy also have a high prevalence of HIV, increasing the possibility of an HIV-leprosy co-infection. Early in the HIV epidemic, it was predicted that an HIV infection would worsen leprosy outcomes, with more patients developing lepromatous disease, an impaired response to multi-drug therapy (MDT), and fewer reactions. However, studies on the epidemiological and clinical aspects of leprosy suggest that the course of

leprosy in co-infected patients has not been greatly altered by HIV infection (1). In contrast, the initiation of antiretroviral treatment (ART) for HIV has been reported to be associated with the activation of a subclinical *M. leprae* infection and the exacerbation of existing leprosy lesions (2, 3).

The few studies published on the course of leprosy in co-infected patients provide limited data. HIV incidence was not found to be increased among leprosy patients in comparison to non-leprosy patients (4, 5). All types of leprosy can occur in co-infected patients, with two East African studies reporting an increase in multibacillary (MB) cases (6, 7) and four Brazilian studies reporting a predominance of paucibacillary (PB) cases (8, 9, 10, 11). Co-infected patients treated with standard length WHO MDT have responded adequately, although there might be a possibility of an increased relapse rate (12).

A Ugandan study demonstrated an increased risk of developing Type 1 reactions (T1R; see Chapter 2.2) in MB leprosy patients with HIV (13). Similarly, an Ethiopian study showed increased recurrence rates of T1R (14). The largest cohort study in Brazil followed 40 co-infected patients, concluding that reactions in general, although similar in severity grading, were less common in this group but lasted for a shorter length of time and recurred less frequently compared to reactions in leprosy patients without HIV (11). Case reports of *erythema nodosum leprosum* (ENL, Type 2 reactions; see Chapter 2.2) in co-infected patients have also been published.

Patients with HIV are also at risk of developing peripheral nerve damage, including generalized peripheral neuropathy and mono-neuritis multiplex, through several mechanisms, namely, treatment with ART and HIV infection per se. Analogous to tuberculosis in HIV co-infected individuals, it was assumed that an HIV co-infection would worsen nerve damage in leprosy patients. However, there are a few early studies reporting no increase in nerve damage in co-infected patients (13, 14, 15).

**TABLE 1 Summary of impact of HIV-1 on leprosy: Expected vs. actual findings**

	<b>Impact on</b>	<b>Theory</b>	<b>In practice (References)</b>
<b>Epidemiological</b>	Incidence	Increase in leprosy	No change (1)
<b>Clinical</b>	Lepromatous leprosy	Increase	No change (6–11)
	Treatment response	Worsened	No change (12)
	Type-1 reactional states	Worsened	Less severe (11)
	Neuritis	Worsened	No change (13–15)
	Novel findings	Presentation as IRIS	(2, 3)
<b>Histopathological</b>	Granuloma formation	Decreased	Possibly increased (8–10)
	Multibacillary	Increased	No change (8–10)

## IMMUNOLOGY OF HIV AND LEPROSY CO-INFECTION

Patients with tuberculoid leprosy (TT) have a good cell-mediated immune (CMI) response (see Chapter 6.2) to *M. leprae*, resulting in a few skin lesions which histologically have well-organized lymphocyte (CD68+, CD3+, CD8+, CD4+)-rich granulomas (see Chapter 2.4) with predominantly CD4 T-cells. In contrast, patients with lepromatous leprosy (LL) have a strong humoral response but poor or absent cell-mediated immunity, resulting in the uncontrolled growth of bacilli and disseminated skin lesions (see Chapter 6.2). A histological examination of biopsies from the lesions reveals that the granulomas are comprised of macrophages and a small numbers of CD8 T-cells (9).

HIV affects cell-mediated immunity. It was initially expected that, just as in an *M. tuberculosis* infection, the decrease in CD4 cells would result in a decreased capacity for mycobacterial containment and thus an increase in disseminated disease. But studies have shown that HIV co-infected patients with a low CD4 count had borderline tuberculoid (BT) lesions with well-formed granuloma and normal numbers of CD4 cells (16). In contrast, co-infected patients with LL lesions had loose inflammatory infiltrates comprised of macrophages and a small number of almost exclusively CD8 lymphocytes (17, 18). Carvalho et al. found that a co-infected group exhibits lower CD4:CD8 ratios, higher levels of CD8+ activation, increased V $\delta$ 1:V $\delta$ 2 T cell ratios (see Chapter 6.2), and decreased percentages of plasmacytoid dendritic cells as compared to HIV-1 mono-infected patients (18). The exact immunopathological mechanism underlying the possible increase in the frequency of leprosy reactions is not clear. Dysregulation of the immune system and the heightened state of immune activation in HIV infection may be responsible. In addition, a delayed clearance of the *M. leprae* antigen due to an impaired phagocytic function of macrophages has also been implicated.

## EFFECT OF ANTIRETROVIRAL THERAPY ON HIV AND LEPROSY CO-INFECTION

So far, an HIV infection has not been reported to increase a patient's susceptibility to leprosy or to have a significant effect on the pathogenesis of neural or skin lesions. This lack of interaction between leprosy and HIV, especially in comparison to tuberculosis, has been puzzling.

A Brazilian study following 25 co-infected patients reported on the outcomes of 16 patients already receiving highly active antiretroviral therapy (HAART) when MDT was initiated and 5 patients who started both HAART and MDT at the same time. (The remaining 4 patients were not started on HAART.) No adverse effects due to the therapeutic combination were reported (10). But since the introduction of HAART in the management of HIV, especially in regions endemic for leprosy, leprosy is increasingly being reported as part of the Immune Reconstitution Inflammatory Syndrome (IRIS).

IRIS is a paradoxical deterioration in clinical status after starting HAART, a deterioration that is attributable to the recovery or reactivation of an individual's immune response to a latent or sub-clinical process. The HAART regimes currently in use increase the production and redistribution of CD4+ cells with improved pathogen-specific immunity, both to HIV and other pathogens. While improved immunity to HIV is the required effect from HAART, increased immune responses to other opportunistic pathogens or the development of autoimmunity can result in IRIS. The prevalence of IRIS in cohort studies of HIV-positive patients ranges from 3% to more than 50%, varying greatly with the AIDS-defining illness affecting the patient at the start of HAART therapy (19). The risk factors for the development of IRIS include advanced HIV disease with a CD4+ T-cell count under 50 cells/mm, an unrecognized opportunistic infection or high microbial burden, and the presence of numerous prior opportunistic infections. In addition to leprosy, HAART triggers overt clinical manifestations of co-infection with tuberculosis, cytomegalovirus, herpes zoster, and hepatitis viruses C and B.

Since 2003, numerous reports of patients from all over the world developing leprosy as IRIS have been published. Most of these patients had borderline types of leprosy, and IRIS presented as a T1R. Ulceration, an unusual skin manifestation in leprosy lesions, was observed in a few patients. It may be that the high proportion of BT leprosy cases among HIV-infected patients on HAART could shed light on questions related to the kinetics of the *M. leprae* infection and the development of the disease. BT leprosy manifests two to five years after infection, at which time specific cell-mediated immunity is strong enough to cause tissue damage as well as kill, or at least control, mycobacterial growth. On the other hand, lepromatous (BL and LL ) forms appear in patients after longer periods of incubation (five to ten years), during which a large number of bacilli have accumulated in the tissue due to the progressive reduction of a CMI response. Although HIV patients are typically more aware of their health status and would easily detect small lesions, the high number of PB patients and a high frequency of reactions among HIV-infected individuals, and the low bacillary load among co-infected MB patients, strongly suggest an earlier-than-usual detection of the disease in immune-reconstituted patients.

To facilitate the recognition and classification of leprosy-associated IRIS, the following case definition has been suggested (20):

1. leprosy and/or leprosy reaction presenting within six months of starting HAART;
2. an advanced HIV infection;
3. low CD4+ count (<200cells/mm<sup>3</sup>) before initiating HAART;
4. CD4+ count increasing after HAART has been started.

Subdividing leprosy-associated IRIS into groups according to data on timing and clinical presentation may help define the causes and mechanisms of this phenomenon. Deps and Lockwood (21) proposed such a subdivision, attempting to separate unmasking episodes from those of overlapping immune restoration.

There are several possible mechanisms for the pathogenesis of leprosy IRIS. Leprosy has a long incubation period and HAART may provide the immunological trigger of normal disease. Another explanation is that leprosy-associated IRIS is similar to a T1R. An alternative hypothesis would have to assume that immunosuppression occurring secondary to the HIV infection itself causes leprosy reactions. Whatever the underlying mechanisms, it is likely that leprosy-associated IRIS will be increasingly reported, especially as HAART becomes more widely available. There are also a number of case reports of patients being diagnosed with leprosy more than six months after the initiation of HAART. Although these patients can present with any kind of leprosy, including histoid leprosy (22) (see Chapter 2.4), the time lag of greater than six months since the initiation of HAART excludes the diagnosis of IRIS.

## MANAGEMENT OF REACTION IN LEPROSY–HIV CO-INFECTED PATIENTS

Leprosy patients, even if HIV positive, may need immunosuppression for the treatment of leprosy reactions and neuritis. There is substantial evidence that leprosy reactions are an important part of the clinical disease picture seen in HIV-leprosy co-infection. Two Brazilian cohort studies following a total of 51 co-infected patients with reactions reported no adverse effects from treating the patients with steroids and found that the response to treatment with the usual dosages and course of prednisolone was good (10, 11). Patients being treated with steroids need careful monitoring to ensure that other opportunistic infections such as tuberculosis and strongyloidiasis are detected early and treated. The balance of benefit is the treatment of reactions to prevent nerve damage and disability.

## CONCLUSION

From the available data we can conclude that the treatment of leprosy patients with a concurrent HIV infection does not differ from that of a seronegative leprosy patient. Standard WHO-MDT can be safely administered in conjunction with HAART. The treatment of reactions can be managed with corticosteroids as appropriate.

There are currently no good prospective clinical data on the role played by HIV in leprosy relapse. The inclusion of HIV testing in sentinel studies of patients relapsing after MDT would give some indication as to whether HIV infection is an important cofactor in relapse.

The influence of the infection on CMI responses to *M leprae* in an HIV-infected patient needs exploration, especially within the skin. The recognition of leprosy presenting as IRIS warrants immunological studies. These studies can use immunohistochemistry and other techniques to delineate cellular phenotypes within the granuloma, and mRNA and protein production to assess cytokine expression. A recent study concluded that, despite the tendency of co-infected patients to have higher levels of autoantibodies, no correlation was observed between clinical signs and

levels of autoantibodies (23). Our understanding of leprosy and HIV co-infection is evolving with ongoing discoveries, and further research is needed.

## Leprosy Management in Other Immunocompromised Patients – Special Cases

Leprosy in patients with iatrogenic immunosuppression for the management of malignant tumors is rarely reported, particularly in contrast with the increasing number of reports of leprosy in transplant patients and in patients in rheumatology clinics.

The occurrence of leprosy in heart transplant, allogenic hematopoietic stem cell transplant patients, and liver and kidney transplant recipients has been reported (24, 25). No guidelines are available for managing leprosy in immunocompromised individuals at present. Nevertheless, reports indicate a similar response in these patients to standard MDT without need of modification. In solid organ transplant recipients, anti-leprosy therapy also requires particular attention to potential drug interactions (e.g., rifampin-induced lowering of cyclosporine blood levels) that may end in graft rejection. Leprosy reactions respond well to an increase in prednisolone doses (25).

Of note is the need to maintain a high level of suspicion for leprosy in rheumatology clinics in leprosy endemic areas or in patients originating from these areas. Leprosy-related arthritis is often misdiagnosed as rheumatoid arthritis, systemic lupus erythematosus, or spondyloarthropathy (26, 27). Cases of leprosy have been reported among rheumatology patients being treated with anti-TNF  $\alpha$  agents such as infliximab and adalimumab, resulting in the onset or worsening of leprosy reactions when these medications are stopped (28, 29). The exact mechanism by which TNF $\alpha$  blockers cause the reactivation of latent granulomatous infections such as leprosy is not well known. However, it has been speculated that the disorganization of the granuloma could be directly related to TNF and to the imbalance between the production and release of IFN $\gamma$  and IFN $\alpha$ . Alternately, granuloma disorganization could also be related to the complex interaction among circulating lymphocytes and epithelioid cells and local macrophages (innate immunity [see chapter 6.1] and acquired immunity [see Chapter 6.2]) (29). Evaluating patients for any risk of leprosy prior to commencing treatment with anti-TNF  $\alpha$  agents is important so that signs are recognized early and leprosy treatment initiated. For those patients who have received MDT, case reports are being published on the effectiveness of anti-TNF  $\alpha$  agents in the management of leprosy reactions, both T1R (30) and ENL (31, 32, 33).

As leprosy reactions are treated with immunosuppression, it is of the utmost importance to keep a close eye on patients for any opportunistic infections (see Chapter 3.4) that may compromise

them as well as worsen the severity of the reactions. In clinical practice co-infections such as tuberculosis, helminthiasis, including strongyloidiasis, and severe soft tissue and bone infections are commonly observed. These conditions need prompt treatment.

## Summary

The treatment of leprosy in immunocompromised patients does not differ from the usual treatment of leprosy patients. The management of leprosy reactions in immunocompromised patients, whether because of an HIV co-infection, organ transplant, or another immune modulatory disease or treatment, includes additional prednisolone to control reaction and nerve damage. Opportunistic infections are an important risk to the immunocompromised patient and require active screening.

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