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*EDITORIAL*

## **Leprosy and HIV, where are we at?**

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*Summary* The impact of leprosy and HIV co-infection is an evolving picture. Surprisingly the outcomes that were feared, of more lepromatous disease has not materialised. But with the roll-out of antiretroviral therapy, the emergence of leprosy as Immune Reconstitution Inflammatory Syndrome is re-focusing attention on the characteristics of this important co-infection.

### **Introduction**

Co-infection with HIV has a major effect on the natural history of many infectious diseases, particularly mycobacterial diseases such as tuberculosis. HIV infection causes loss of effective cell mediated immunity allowing opportunistic infections to occur. Early in the HIV epidemic it was predicted that HIV infection would worsen outcomes in leprosy patients with more patients developing lepromatous disease and patients having fewer immune mediated reactions. The limited published data 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.<sup>1</sup> In contrast, initiation of antiretroviral treatment (ART) has been reported to be associated with presentation of new leprosy lesions and worsening of existing leprosy lesions.<sup>2,3</sup> In this review we discuss the published data on HIV/leprosy co-infection highlighting new findings. The last major review on this co-infection was published before widespread roll-out of anti-retroviral therapy. The effects of ART need to be considered when reviewing any work on leprosy/HIV co-infection since ART profoundly alters the immune response. It is therefore very important that when studies are reported they should indicate whether patients are taking ART.

One new major observational study has been reported from Brazil.

Sarno and colleagues reported in 2008 on the largest HIV leprosy co-infection study to date. This retrospective longitudinal cohort study in Brazil, followed 59 co-infected patients and 967 leprosy only patients between 1996 and 2006. 37 (63%) of the HIV positive patients received HAART. This study will be referred to in several sections below.

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In 1993, Professor Lucas reviewed the potential interactions between leprosy and HIV in Leprosy Review.<sup>4</sup> With the HIV pandemic established, previously uncommon mycobacterial diseases, such as *Mycobacterium avium complex* and *Mycobacterium tuberculosis* were becoming more common. This led to concerns that patients with leprosy might also be affected by HIV, with increasing co-infection rate and severity of disease in co-infected patients. He posed a series of questions about potential interactions and we shall use a similar format here.

#### DOES HAVING HIV INCREASE THE RISK OF ACQUIRING M. LEPRAE INFECTION?

The few published small studies from the 1990's provide limited data on the course of leprosy in co-infected patients. HIV incidence was not increased amongst leprosy patients when compared with patients without leprosy.<sup>5,6</sup>

The HIV epidemic has also now become so generalised and has affected many countries where the two infections overlap including Brazil, Ethiopia and India without there being marked increases in patients with leprosy and HIV. We can therefore conclude that being HIV positive does not appear to increase the risk of developing leprosy.

#### DOES HAVING HIV ALTER THE CLINICAL FORM OF DISEASE?

It was predicted that HIV infection would cause patients to develop the lepromatous type of disease. However all types of leprosy have been reported in co-infected patients; with two East African studies from the early 1990's reporting an increase in multi-bacillary (MB) cases<sup>7,8</sup> in contrast a Brazilian study reported a predominance of pauci-bacillary (PB) cases.<sup>9</sup> Whilst these figures can only be interpreted in the context of data the pattern of leprosy types in the populations from which these patients were drawn these reports suggest that HIV infection has not increased the rate of lepromatous disease. The most contemporary data from the Sarno group suggest that now, in HIV co-infected patients, tuberculoid disease is the predominant form. In her cohort, 78% of co-infected patients had PB leprosy, compared to 50.6% in the HIV negative group. In comparison to the HIV negative group, the co-infected group showed a higher rate of borderline tuberculoid leprosy (66.7% vs. 32.7%); a lower mean BI at diagnosis and higher reaction rate at diagnosis. Most of the co-infected patients were diagnosed with HIV before the leprosy. A lower CD4 count at HIV diagnosis was associated with earlier manifestations of clinical leprosy. Of the 33 patients who had viral load measured, leprosy diagnosis occurred when they had a lower viral load and higher CD4 count.<sup>10</sup>

#### DOES HAVING HIV ALTER THE RESPONSE TO CHEMOTHERAPY?

It was feared that co-infected patients might have an impaired response to leprosy multi-drug therapy. Co-infected patients treated with standard length WHO-MDT regimens have responded adequately. However the Sarno study observed a 3.4% relapse rate in co-infected patients on ART compared to the 1.0% relapse rate in HIV negative patients.<sup>10</sup> This suggests that patients with co-infection should be monitored more closely for relapse after treatment. This should also be a marker that is closely monitored.

DOES HAVING HIV ALTER THE INCIDENCE OF REACTIONS AND NERVE DAMAGE?

It was predicted that since reactions and nerve damage are immune-mediated events the incidence of these in co-infected patients might be decreased.

A 1994 Ugandan study looking at 12 HIV seropositive and 40 seronegative MB patients, reported that MB leprosy patients with HIV had an increased risk of developing Type 1 Reactions.<sup>11</sup> However data from the large ALERT MDT Field Evaluation Study (AMFES) study in Ethiopia, suggested that HIV infection (n = 22) was not a risk factor for developing reversal reactions (both acute and chronic), although HIV patients did seem to be at higher risk of recurrent reversal reactions (RR 2.2, 95% CI 0.98–4.7).<sup>12</sup>

The most contemporary data comes from Sarno *et al.* where patients with HIV co-infection were more likely to be in reaction at diagnosis (31.5% vs. 18.8%). However, during the surveillance period the rates of reaction in the two groups were similar (59.3% vs. 53.1%).<sup>10</sup>

There is very little data on ENL in co-infected patients, The AMFES study reported a higher risk of ENL reactions (RR 5.2, 95% CI 1.7–15.9) but only 3 patients were affected.<sup>12</sup>

Thus a picture is emerging of patients being at higher risk of developing reactions, especially when they are on ART.

Patients with HIV are also at risk of developing peripheral nerve damage including generalised peripheral neuropathy and mono-neuritis multiplex through several mechanisms, namely, treatment with antiretrovirals and HIV infection *per se*. It was assumed that HIV co-infection would worsen nerve damage in leprosy patients. There were a few small studies in the 1990 which did not find increased nerve damage in co-infected patients.<sup>11,12</sup> A well designed prospective study of peripheral nerve function using sensitive tools to detect nerve damage in co-infected patients is needed to establish whether these patients do have increased rates of nerve damage both at diagnosis and at follow up (Table 1).

DOES HAVING HIV ALTER THE PATHOLOGY OF LEPROSY LESIONS?

It was predicted that co-infected patients would have more lepromatous type disease. Patients with tuberculoid leprosy have a good cell-mediated immune response to *M. leprae* resulting in a few skin lesions which histologically have well organised lymphocyte (CD68 + , CD3 + , CD8 + , CD4 + ) rich granulomas with predominantly CD4 T cells. In contrast, patients with lepromatous leprosy show poor or absent cell-mediated immunity towards

**Table 1.** Summary of impact of HIV-1 on leprosy: expected vs. actual

		Theory	In practice
Epidemiological Clinical	Incidence	Increase in leprosy	No change
	Lepromatous leprosy	Increase	No change
	Treatment response	Worsened	No change
	Type-1 reactional states	Fewer	Increased
	Neuritis	Worsened	?
Histopathological	Novel findings	Presentation as IRIS	
	Granuloma formation	Decreased	No change
	Bacterial Index	Increased	No change

*M. leprae*, resulting in uncontrolled growth of bacilli and disseminated skin lesions. Histological examination of biopsies from their lesions reveals that the granulomas are comprised of macrophages and a small numbers of CD8 T cells.<sup>9</sup> HIV affects cell-mediated immunity, and it was initially expected that, just as in *M. tuberculosis* infection, the decrease in CD4 cells would result in decreased capacity for mycobacterial containment and thus an increase in disseminated disease. But a Brazilian study by Sampaio and colleagues (1995) shows that HIV co-infected patients with borderline tuberculoid lesions CD4 counts, had lesions with well formed granuloma and normal CD4 cell numbers in their lesions even though they had low circulating CD4 counts. Co-infected patients with lepromatous leprosy lesions had loose infiltrates comprising of heavily parasitized macrophages and a small number of almost exclusively CD8 lymphocytes, which is similar to HIV negative patients.<sup>13</sup> Deps and Lucas (pers comm.) have also looked at a series of patients with co-infection and used a standardised methodology to assess the pathology of the skin lesions. Again all types of leprosy were seen and the lesions had histology that was typical for the leprosy type. There was some suggestion that the lesions from patients with active BT leprosy displayed compact granulomas, oedema and necrosis. This is compatible with up-regulation in BT leprosy. Thus evidence is accumulating for HIV/leprosy co-infection being associated with immune activation rather than immune paresis. It is surprising that *M. leprae* can attract CD4 + cells out of the circulation into leprosy skin lesions.

#### DOES HAVING LEPROSY WORSEN HIV INFECTION?

This is a difficult aspect to research since it is critically affected by the timing of HIV infection and the presence not just of leprosy but also other opportunistic infections. No clinical data has suggested that leprosy would worsen HIV infection. However Carvalho *et al.* (2008) looked at 28 Brazilian patients and found that the co-infected group (n = 7) had lower CD4:CD8 ratios, higher levels of CD8 + activation, increased V $\delta$ 1:V $\delta$ 2 T cell ratios and decreased percentages of plasmacytoid DCs as compared to HIV-1 mono-infected patients.<sup>14</sup> As these are all recognised features of progressive HIV disease, so leprosy co-infection may aggravate HIV pathogenesis and this is another area that deserves close monitoring.

The exact immune-pathological mechanism underlying the possible increase in 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, delayed clearance of *M. leprae* antigens due to the impaired phagocytic function of macrophages has also been implicated.

#### HOW DOES ART AFFECT LEPROSY/HIV CO-INFECTION?

Since the introduction of highly active antiretroviral therapy (HAART) in the management of HIV, especially in regions endemic for leprosy, leprosy is being increasingly 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 someone's immune response to a latent or sub-clinical process. The HAART regimes currently used increase production and redistribution of CD4 + cells' improved pathogen specific immunity, both to HIV and other pathogens. While improved immunity to HIV is the required effect from HAART, improved

immunity to other opportunistic pathogens or 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.<sup>15</sup> Risk factors for the development of IRIS include advanced HIV disease with a CD4 + T cell count under 50 cells/mm, unrecognised opportunistic infection or high microbial burden, and the number and presence of prior opportunistic infections. HAART triggers overt clinical manifestations of co-infection with tuberculosis (pneumonitis and lymphadenitis), MAC (lymphadenitis), cytomegalovirus (retinitis), herpes zoster, C and B hepatitis virus, leishmania and now leprosy.<sup>16</sup>

Since 2003, 23 reports of patients developing leprosy as IRIS have been published.<sup>2,3,13,14,17,18</sup> These were recently reviewed by Deps and Lockwood. The cases have been reported from areas where ART is more readily available so 70% were from S America (58% Brazil) and 20% from India. Borderline leprosy was the commonest form and T1R was always present. Ulceration, a highly unusual feature in leprosy lesions, was observed in 6 patients. It may be that the high proportion of borderline tuberculoid leprosy cases among the HIV-infected patients on HAART could shed light on the questions related to the kinetics of *M. leprae* infection and development of disease. Conversely, the high frequency of PB patients, low bacillary load and reactions among HIV-infected individuals, could be simply due to an earlier-than-usual detection of the disease in immune-reconstituted patients.

A case definition for leprosy-associated IRIS, has been proposed to facilitate correct identification of cases.<sup>19</sup> For patients to have leprosy associated IRIS they have to have the following features: (1) leprosy and/or leprosy reaction presenting within 6 months of starting HAART; (2) advanced HIV infection; (3) a low CD4 + count before starting 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 towards defining the causes and mechanisms of this phenomenon. Leprosy and HIV co-infection can present in various ways: a patient known to be HIV positive may develop signs of leprosy; a leprosy patient may be diagnosed as HIV positive and a patient may present with leprosy IRIS after starting HAART. Deps and Lockwood<sup>20</sup> have recently proposed such a subdivision attempting to separate unmasking episodes from those of overlap of immune restoration. Four types of presentation of IRIS were identified

1. Unmasking – when patients develop leprosy or T1R after starting HAART. These patients have not been diagnosed with leprosy. They are probably incubating leprosy and the disease is only manifest after the immune restoration occurs. This was seen in 58% of cases.
2. Overlap of immune restoration (paradoxical) – when leprosy has already been diagnosed before starting HAART. When MDT and HAART are started within 3 months, T1R occurs as a paradoxical reaction. This was seen in 10% of cases.
3. Undiagnosed leprosy or previously treated leprosy occurring at least 6 months before HAART. When HAART is introduced, T1R occurs. This was seen in 10% of cases.
4. Unmasking followed by overlap of immune restoration after HAART and MDT – When within 6 months after start HAART, leprosy has been diagnosed and MDT started. Later the patient develops T1R. This was seen in 21% of cases.

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. Whatever the underlying mechanisms, it is likely that leprosy-associated IRIS will be increasingly reported, especially as access to HAART becomes more widely available. There are also a number of case reports of patients being diagnosed with leprosy more than 6 months after the initiation of HAART. Although these patients can present with any kind of leprosy, including histoid leprosy,<sup>21</sup> the time lag of greater than 6 months since the initiation of HAART excludes the diagnosis of IRIS.

#### DOES BEING HIV POSITIVE AFFECT THE TREATMENT OF LEPROSY REACTION?

There is little good data on this. However leprosy patients, even if HIV positive, need immuno-suppression for treating 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. 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 for treating reactions to prevent nerve damage and disability.

### Conclusion

There are currently no good prospective clinical data on the clinical features of leprosy in HIV-infected patients, particularly the evolution of their skin lesions and progression of nerve damage, and response to MDT. There is a need for prospective multi-centre studies, including the African and Asian setting, with large numbers of patients and appropriate controls. The inclusion of HIV testing in sentinel studies of patients relapsing after multidrug therapy treatment would give some indication as to whether HIV infection is an important co-factor in relapse. Response to treatment for neuritis and reaction in co-infected patients needs to be studied carefully in prospective studies.

The influence of HIV infection on cell-mediated immune responses to *M. leprae* in the HIV-infected patient needs exploration, especially within the skin. The recognition of leprosy presenting as IRIS warrants immunological studies, using, for example, immunohistochemistry to delineate cellular phenotypes within the granuloma and mRNA and protein production to assess cytokine expression.

The impact of leprosy and HIV co-infection is an evolving picture and further research is needed to understand the mechanisms of disease and to develop better treatments.

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