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Editorial

HUMAN IMMUNODEFICIENCY VIRUS AND LEPROSY

From the earliest reports of what has since become the pandemic of human immunodeficiency virus (HIV) infection, a close association between HIV infection and a previously uncommon mycobacterial disease—that due to infection with *Mycobacterium avium* complex (MAC)—was evident.[1] Then and since, clinically significant disease due to MAC is restricted to HIV-positive people in industrialized countries. Later it was realized that *M. tuberculosis* is associated with HIV infection to the extent that, in sub-Saharan Africa, tuberculosis is clinically the most important opportunistic disease in HIV-positive people.[2] A significant proportion of the population there is latently infected with *M. tuberculosis*, and it is thought that HIV infection, by its progressive destruction of cell-mediated immunity, permits the reactivation of tuberculous lesions.

What about *M. leprae* and HIV? In Africa, which today has the greatest number of HIV-infected people of all the continents, leprosy is still relatively common. Further, India has the greatest number of known cases of leprosy in the world, and appears to be on the rising curve of an HIV epidemic potentially as significant as that in Africa.[3] So, an interaction between the two infections could be important. In fact, despite expectations,[4–7] little interaction has been observed.

The potential interactions and complications are many. HIV infection could:

1 increase the probability of infection with *M. leprae*;
2 increase the probability of clinical leprosy developing in a dually infected person;
3 alter the clinical pattern of leprosy;
4 alter the response to antileprosy chemotherapy.

Similarly, prior infection with *M. leprae*—latent or as clinical leprosy—might:

5 increase the probability of acquiring HIV infection;
6 alter the temporal cadence of HIV infection and progression to AIDS;
7 alter the clinical patterns of HIV-associated opportunistic diseases.

There are other potential interactions:

8 leprosy might confound HIV serology;
9 HIV-associated neuropathy might be confused with or exacerbate leprosy neuritis;
10 neuropathy due to antiretroviral chemotherapy might be confused with leprosy;
11 nonleprosy mycobacterioses in HIV-positive people might be confused diagnostically with leprosy;

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12 national policies on BCG vaccination might be amended because of endemic HIV infection;
13 slit-skin smear taking could spread HIV infection;
14 leprosy workers may become increasingly involved with the problems of HIV counselling.

The first 11 propositions listed above will be briefly discussed here; the last 3 have been considered elsewhere.[8–10]

The studies presented to date on propositions 1–7 are either case reports[11–16] or cross-sectional surveys, usually of leprosy patients,[4,17–26] and rarely of patients with AIDS.[27] A few contain longitudinal data on clinical development[11,14,15,26] and some describe the histopathology of the leprosy lesions.[11–15,21,25]

Propositions 1 and 5: *M. leprae* and HIV are reciprocally promoting

That HIV and *M. leprae* infections each might reciprocally increase the probability of later infection with the other is, on theoretical grounds, unlikely. For example, unlike many sexually transmitted diseases, leprosy seldom causes genital ulcer and is rarely, if ever, transmitted by sexual contact. Meticulously selected control groups would be needed to pursue these propositions, and not least, a sensitive and specific test for preclinical infection with *M. leprae* would be required, which currently does not exist. If a cross-sectional study of patients with leprosy shows a higher HIV-seroprevalence than among comparable nonleprosy patients, it could indicate that leprosy promotes the acquisition of HIV infection. It could also, and more probably, indicate that HIV infection predisposes to development of clinical leprosy.

Propositions 2, 3 and 4: Clinical, therapeutic and epidemiological associations between leprosy and HIV

Early studies of leprosy patients in Africa found prevalences of HIV-positivity ranging from 0%[17] to 30%[18], the latter higher than in controls. More recent studies, involving more than 100 people per group, have not found significant differences in HIV prevalence between leprosy patients and control nonleprosy subjects.[22–25] The reason for these discrepancies is not faulty HIV serology (see below) but the selection of cases and appropriate controls. Leprosy patients examined in hospital are often self-reporting and unrepresentative of patients diagnosed in the field (the majority of leprosy cases). They usually have more severe leprosy disease, and may have other nonleprosy ailments that are associated with HIV infection. Further, immigrant leprosy patients may have higher HIV prevalences than resident patients. These and other confounding factors in such epidemiological studies are discussed in a recent study from Malawi.[25]

One early expectation was that HIV infection would, through immunosuppression, increase the ratio of multibacillary to paucibacillary cases of leprosy. The relevant studies—all from Africa where paucibacillary leprosy is more frequent than multibacillary—all found no such change associated with HIV.[20,22,24–26]

Related to this is the expectation that bacillary relapse might be frequent in HIV-

positive, treated leprosy patients. The published case reports detailing response to therapy all indicate resolution of skin lesions at the normal rate.[11,13–16] Relapse has been noted once, in a lepromatous patient with a CD4+ T-lymphocyte count of 121/mm^3, but the only documentation is 'a bacterial index of 1+ on the scale of Ridley'.[12] Concerning leprosy reactions in HIV-positive patients, an abstract from Haiti described HIV-positive treated tuberculoid leprosy patients who developed 'new skin lesions and lepromin anergy' on treatment, at a greater frequency than HIV-negative patients.[20,27] Whether the 'new skin lesions' were delayed hypersensitivity reactions or bacterial relapses is unclear. A possible reversal reaction was reported in an HIV-positive patient treated for 'pure cutaneous leprosy' who 5 years later developed mononeuritis multiplex with tuberculoid skin histology; there were no acid-fast bacilli and the lepromin test was positive.[12] No case of erythema nodosum leprosum (ENL) in an HIV-positive patient has been reported.

A potentially important clinical difference is described from Zambia. Out of 82 new leprosy cases seen in a hospital (8 HIV-positive), 'active neuritis' was equally frequent at presentation in HIV-positive and -negative groups (50%). On standard management, with steroids, the HIV-positive group had less good recovery of nerve function. However, the numbers were small, and the selection of controls was erratic.[26]

One case report details the histopathology and immunocytochemical studies of a leprosy skin lesion in an HIV-positive patient.[14] The histology was multibacillary BL leprosy, about half the lesional T-cells were CD4+ (despite a depressed blood CD4+ T-lymphocyte count of 300/mm^3), and there was no local interferon-gamma production as judged by absence of HLA-DR staining of the epidermis above the lesion. Unfortunately, this and the other single case reports do not really provide much illumination since it is not evident how representative they are of local case material. Conversely, case reports that show strikingly unusual features of leprosy in an HIV-positive patient might indicate a route for further research. These are still awaited.

Concerning lepromin tests, most of the large surveys have not included them in evaluation. Whilst the study from Haiti found that the HIV-positive tuberculoid leprosy patients who developed new lesions on chemotherapy became lepromin negative,[20] other reports note 4 co-infected patients with positive lepromin tests, 1 of whom had a CD4+ T-lymphocyte count of only 12/mm^3.[12,13,16]

Most of the studies on HIV and leprosy concern HIV-1 infection. HIV-2 infection is mainly restricted to West Africa, and also causes AIDS.[28] Determined rates of HIV-2 infection in patients with leprosy were described in 2 studies. In Mali, HIV-2 and dual HIV-$\frac{1}{2}$ infection occurred at the same prevalence in leprosy patients (both paucibacillary and multibacillary) as in nonleprosy controls.[24] Similarly, although the figures are not given, HIV-2 was found at expected prevalences in leprosy patients in Senegal and the Côte d'Ivoire.[28]

Finally, a survey of hospitalized patients with AIDS in Burundi found 4 patients with leprosy (all female, representing 6% of those studied); no further data are provided.[27]

Propositions 6 and 7: leprosy may influence the course of HIV disease

Several authors have suggested that *M. leprae* infection may accelerate the course of HIV infection.[20,22,29] The argument is that many mycobacterial infections induce cell secretion of tumour necrosis factor (TNF-α). Whilst TNF-α is important in granuloma formation,

it promotes production of HIV in monocytes and lymphocytes, hence increasing the cytopathic effects of HIV, reducing CD4+ T-lymphocyte levels and causing a more rapid progression to AIDS.[30] Case reports quote a range of blood CD4+ T-lymphocyte counts at presentation with leprosy in HIV-positive patients: 12, 121, 300, and 350 per mm^3.[12–15] A few studies indicate deaths—from AIDS-defining conditions such as tuberculosis or HIV encephalopathy—following diagnosis and treatment of leprosy.[11,14,26] Generally there is little published information on HIV-related sequelae in *M. leprae*/HIV co-infected people. None of this confirms or refutes the propositions. In order to do this the following studies would be needed:

natural history studies of leprosy patients with and without HIV infection;
2 analyses of cytokine expression and HIV replication (ideally) or surrogate markers of HIV expression (such as β_2-microglobulin) in leprosy patients and controls; [30]
3 proper evaluation of mortality with determination of the causes of death. This may require autopsy and is not easy—for example whilst the fact of increased mortality in tuberculosis patients with HIV-infection compared with HIV-negatives is well known, the actual causes of death are still unclear.[31,32]

Proposition 8: leprosy and HIV serology

Some early studies reported false-positive HIV serology in leprosy patients[24]. Four percent of sera from Indonesian patients with leprosy were HIV-positive on screening tests including ELISA, although Western blots were negative;[33] 5% of leprosy patients in Zaire also gave false-positive ELISAs.[17] This suggested that antibody cross-reactions could reduce the specificity of HIV serology in leprosy patients (particularly lepromatous) in tropical countries. This was the case with the first generation HIV ELISAs used in Africa, being affected by malaria antibodies.[34] Potentially confusing bands on Western blots in patients with tuberculosis and leprosy have also been reported.[35] However, a larger study in Malawi examining several HIV-serotesting strategies found no excess of problematic sera from leprosy compared with nonleprosy patients. Moreover, most of the problems in the leprosy group were in tuberculoid rather than lepromatous patients, the former having low leprosy specific antibody titres.[36] With the recent HIV tests, false-positive serology due potentially to leprosy is effectively eliminated.

Propositions 9 and 10: neuropathy, HIV and leprosy

HIV itself is a cause of several peripheral neuropathy syndromes including distal symmetrical neuropathy, mononeuritis multiplex, and autonomic neuropathy.[37,38] No reports of such neuropathies clinically mimicking leprosy have yet appeared. Histologically these neuropathies may show perivascular intra-neural inflammation, sometimes necrotizing vasculitis,[39] but not granulomatous inflammation (nor, of course, acid-fast bacilli). By in-situ hybridization, HIV can be demonstrated in inflammatory cells in the endoneurium and epineurium.[39]

It has been suggested that HIV and *M. leprae* may enhance each other so causing a more fulminant neuritis than is seen in HIV-negative leprosy patients.[26,40] The limited

histopathological studies on leprosy neuritis in Malawian patients have not shown any difference between HIV-positives and negatives.[21] The Malawi survey, moreover, found that all the incident leprosy patients who had disability (indicating severe neuritis) were HIV-negative.[25] Again, this emphasizes the importance of studying large numbers of patients with appropriate controls. Although theoretically possible, such an intraneural interaction awaits further support.

Antiretroviral chemotherapy with the dideoxynucleoside analogues ddI and ddC has been associated with a reversible distal sensory neuropathy.[38] This is unlikely to be a clinical problem in poor, leprosy-endemic countries given the high costs of these drugs.

Proposition 11: non-leprosy lesions resembling leprosy

The non-specific rashes that, in Africa, are commonly associated with HIV-infection[21,41] are unlikely to be clinically confused with leprosy. A potential histological confusion is of multibacillary mycobacterial histiocytosis in immunosuppressed patients (due usually to a MAC infection), resembling lepromatous leprosy and even a histoid.[42,43] One case report documents a retroperitoneal lymph node in an HIV-positive patient containing *M. scrofulaceum* and showing histology similar to lepromatous leprosy lymphadenitis.[44]

Summary and conclusions

In summary, clinical leprosy does not appear to be more frequent in HIV-positive than in HIV-negative people in areas where both infections are endemic. There is no evidence that the paucibacillary to multibacillary distribution of patients is altered by HIV infection. There are reports that neuritis is more severe in co-infected people, and that reversal reactions (or, at least, new lesions) may be more frequent after therapy; but these reports are either poorly documented or poorly controlled.

In several ways, this lack of expected leprosy is similar to the patterns of other low-virulent infections in HIV-positive patients in the tropics, such as MAC infection, *Pneumocystis carinii* and cytomegalovirus infection.[45] Despite the presence of the agents in the environment and/or in the human host, they are infrequently encountered clinicopathologically.[46,47] This is in marked contrast to their importance in industrialized countries. One explanation, as yet unproven, is that HIV-positive patients in the tropics do not live long enough in states of severe immunosuppression to develop these infections. Perhaps the same applies to *M. leprae* infection, whose incubation period can be measured in decades and whose clinical course may evolve over years, in contrast to the common reactivation of latent, virulent *M. tuberculosis* infection with its high morbidity.

There may also be an analogy between leprosy and infection with *Plasmodium falciparum*, *Strongyloides stercoralis* and *Entamoeba histolytica*: these infections are controlled (or at least influenced) by cell-mediated immunity and, theoretically, should be more frequent in HIV-positive people than HIV-negatives. In fact they are not, and leprosy may be regarded as another 'missing infection in AIDS'.[48] As noted previously, 'the immunology of leprosy is once again not as we thought it would be'.[8]

The cynic might conclude that further investigation of associations between leprosy and HIV infection are a waste of time and money, given the epidemic status of HIV

infection and AIDS and the comparative unimportance, demographically, of leprosy. In the future, national leprosy control programmes may well have some of their previous government funding diverted to AIDS control programmes. A lack of interest would be short-sighted. With greater case numbers, and especially if survival with HIV infection lengthens, there may be some perceptible changes in the local clinical cadences of leprosy associated with HIV. More representative studies of CD4+ T-lymphocyte counts in HIV-positive and HIV-negative leprosy patients, with follow-up evaluations during treatment, should be done. These should also be correlated with lepromin test results. Coupled with laboratory studies of the cellular interactions between HIV and *M. leprae*—using immunocytochemical techniques on lesions and (*pace* tuberculosis) studies of HIV expression and cytokines—such research will provide valuable information on this still-mysterious host–parasite relationship called leprosy.

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