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COMMENTARY

Leprosy and HIV Infection (Rarely the Twain Shall Meet?)

In this issue of the JOURNAL, Hussein and colleagues report data from a long term seroprevalence study to evaluate the association of HIV infection and leprosy among patients seen at their clinic in Agra, India ([8]). In the period from 1989 to 1993, 5 of 4025 leprosy patients (0.12%) were HIV positive, whereas in the period from 1999 to 2004, 5 of 2125 (0.38%) were HIV positive. This increase is not significant despite the apparent major increase in HIV infections among subjects screened at the same clinic. In 2004, among 387 persons who were "voluntarily" screened at their request, the HIV prevalence was 40.3%, and it was 43.4% among 106 persons referred for screening ([8]). From this it appears that the prevalence of HIV infection has not increased in patients with leprosy despite evidence of a substantial HIV epidemic among the population served by the clinic.

So why hasn't the HIV prevalence increased in a comparable fashion among leprosy patients? Are they resistant or immune to HIV infection? In the past few years some individuals have been identified who are immune to HIV infection despite repeated exposure to the virus. One such group are persons who are homozygous for a 32 base pair deletion in the CCR5 gene that renders them completely resistant to infection with HIV-1 viruses that require attachment to the CCR5 co-receptor to enter the target CD4+ lymphocyte and replicate ([3, 11]). Individuals who are heterozygous for the CCR5 deletion are partially resistant to HIV-1 infection and progress more slowly after infection ([14]). Also persons with genetic mutations in the CCR2 and SDF-1 genes progress more slowly after acquiring an HIV-1 infection ([16]). These critically important discoveries have had major ramifications in our understanding of the biology of HIV-1 infections in humans.

Another group of individuals who are partially resistant to HIV-1 infection are those who are heterozygous for HLA alleles ([9]). Also, subjects who are heterozygous for HLA-B or DR alleles when compared to their HIV-1 positive sex partner appear to be less readily infected than persons who are homozygous with their partner for these genetic loci. However, this resistance to transmission is only relative, not absolute like homozygozity for the 32 base pair deletion in the CCR5 receptor ([3, 6]).

In addition, some patients appear to acquire relative resistance to HIV infection or progression of HIV. Persons who are co-infected with GB virus C, a retrovirus that also infects macrophages and lymphocytes, appear to have slower progression of HIV, and lower HIV viral loads during their GB virus viremia, which is often chronic ([7, 19, 20]). Whether or not they are resistant to HIV-1 transmission, as well, has not been determined. Other infections, which have been reported to slow or delay the progression of HIV, and decrease the HIV-1 viral load in infected individuals, include scrub typhus (*O. tsutsugamushi*), Dengue, and measles ([13, 17, 15]). The proposed mechanism for the negative interaction between these infections and HIV-1 also involve the CCR5 co-receptor, which is also the receptor for the Beta chemokines, MIP-1 alpha, MIP-1 beta, SDF-1 and RANTES. These chemokines regulate the immune response and attach to receptors on CD4+ lymphocytes blocking the ability of HIV-1 to attach to and enter CD4+ lymphocytes to produce more viral copies.

Could *M. leprae* infection also interfere with HIV-1 attachment and entry into CD4+ lymphocytes by attaching to the chemokine receptor? This seems very doubtful for a number of reasons. Whereas untreated patients with polar or borderline lepromatous

leprosy may have high levels of bacteremia, mid-borderline or tuberculoid patients do not. Chemokines are often increased as an acute phase reaction to a systemic infection. But this is probably not characteristic of leprosy patients. However, I am not aware that a systematic study of chemokine levels in untreated leprosy patients has been done. If not, it might provide some useful information.

It seems much more likely that the low rates of HIV-1 co-infection in leprosy patients living in HIV-endemic areas in Africa and Asia, which have been reported in several studies ([1, 4, 10, 12, 15]), can be best explained on the basis of the epidemiology of the two infections. Clearly, tuberculosis and *Mycobacterium avium* complex infections have increased dramatically in areas having major AIDS epidemics. Indeed, both of these mycobacterial infections can be classified as "AIDS-related opportunistic infections." In fact, worldwide the major cause of death among AIDS patients is tuberculosis, so it is the most important opportunistic infection in AIDS patients globally.

Why is leprosy so different? Despite the pandemic of AIDS with over 40 million people infected and living with HIV/AIDS and over 30 million deaths, the virus is quite difficult to transmit. It requires sexual contact or parenteral exposure through injection drug use or a transfusion, or perinatal transmission from an infected mother to her infant. Even sexual transmission through unprotected sex is quite inefficient, varying from a transmission rate of 2 to 3/1,000 episodes of unprotected sexual intercourse in the absence of an active STD to as high as 5 to 6/100 such exposures when one or both partners have an active STD. Injection drug use may be somewhat more effective in transmitting HIV-1 but the prevalence rates are seldom above 25% to 50% among daily injectors in a city with an active AIDS epidemic.

Although many seroprevalence studies of HIV-1 infection have been reported among leprosy patients in several African countries experiencing major HIV/AIDS epidemics ([1, 4, 10, 12, 15]), these studies have not been accompanied by behavioral data, so that one cannot gauge whether the patient population studied was actually exposed to a source of HIV-1 infection or how frequently exposure had occurred. Since HIV-1 is not casually transmitted, the HIV-1 prevalence in the area where the leprosy patients are being treated is somewhat irrelevant. It would be important for a leprosy researcher working in an AIDS endemic area to screen the sex partners of the leprosy patients for HIV to determine whether the leprosy patients have actually been exposed or how many have been exposed. As far as I am aware, such data have not been reported.

Why then is there such a major difference between the TB/HIV co-infection rate and the leprosy/HIV co-infection rate in AIDS epidemic areas. Clearly the data suggest that a much higher proportion of the population has a latent tuberculosis infection than has a latent or incubating an infection with *M. leprae*. Tuberculin skin test surveys suggest that 30% of the world's population, or about 1 billion persons, have a latent tuberculosis infection. When a major HIV epidemic infects a population, the rates of TB reactivation increase dramatically as cellular immunity is abrogated by the HIV-1 infection. In addition, an HIV-1 infected person who acquires a new *M. tuberculosis* infection has a 30 to 40% chance of developing clinical tuberculosis within a year or two of infection with *M. tuberculosis*, compared to a 5% chance of active tuberculosis in an HIV-1 uninfected person.

It seems very likely that latent *M. leprae* infections are not too common, even in endemic countries. Many such latent *M. leprae* infections may have been suppressed, or perhaps cured, with exposure to antibiotics like Rifampin, a Macrolide antibiotic or to BCG. So when a person develops an HIV-1 infection in these countries, leprosy does not follow. These ideas are only speculation. It is not possible to reliably measure latent *M. leprae* as effectively as latent TB can be diagnosed using the tuberculin test. Some investigators have tested for phenolic glycolipid-1 in sera from HIV-1 infected persons and controls to estimate the prevalence of *M. leprae* infection ([5]). One intriguing study from Cuba found that 14.9% of 437 HIV infected patients compared to 1.3% of blood donors had antibodies to PGL-1 ([5]). However, this test may not be completely specific in HIV-1 infected persons. The specificity could be studied by testing sera from HIV positive population in which leprosy is rare or absent. Furthermore, a positive PGL-1

antibody test may not indicate an active *M. leprae* infection compared to a previous infection that has been cured. Clearly, newer methods are needed to detect latent *M. leprae* infections. Such data together with careful epidemiological studies of the rates of exposure to HIV-1 among leprosy patients might clarify why leprosy seems not to be an AIDS-related opportunistic infection or whether leprosy patients are relatively resistant to HIV-1 infection.

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