HIV-*M. Leprae* Interaction: Can HAART Modify the Course of Leprosy?

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SYNOPSIS

It has been speculated that, as seen in tuberculosis, human immunodeficiency virus (HIV) and *Mycobacterium leprae* (*M. leprae*) co-infection may exacerbate the pathogenesis of leprosy lesions and/or lead to increased susceptibility to leprosy. However, to date, HIV infection has not appeared to increase susceptibility to leprosy. In contrast, initiation of antiretroviral treatment (ART) has been reported to be associated with anecdotal activation of *M. leprae* infection and exacerbation of existing leprosy lesions.

To determine whether ART is associated with worsening of the manifestations of leprosy, a cohort of leprosy patients recruited between 1996 and 2006 at the Oswaldo Cruz Foundation (FIOCRUZ) Leprosy Outpatient Clinic in Rio de Janeiro, Brazil, was studied longitudinally. ART treatment of HIV/leprosy co-infection was associated with the tuberculoid type, paucibacillary disease, and lower bacillary loads. CD4 lymphocyte counts were higher among HIV/leprosy patients at the time of leprosy diagnosis, while viral loads were lower compared with the time of HIV diagnosis. The conclusion was that ART and immune reconstitution were critical factors driving the development and/or clinical appearance of leprosy lesions.

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Leprosy is a contagious infectious disease of chronic duration caused by *Mycobacterium leprae* (*M. leprae*). If left untreated, it may lead to serious physical disabilities. The disease is found worldwide, especially in countries situated in tropical and subtropical regions.[1] With the success of multidrug therapy (MDT) in treating the infection, the focus of health-care workers has shifted to leprosy reactions. Reactional episodes are immune-inflammatory processes seen in paucibacillary (PB) as well as in multibacillary (MB) patients. The frequency of reaction has been reported to range from 2.6% to 20.0% of PB patients[2] and from 15% to 60% of MB cases.[3,4] Reactions in leprosy are more frequently observed during MDT, but may also occur before, during, or after leprosy treatment.[2,4] It is broadly accepted that reaction is the result of shifts in the patients' level of inflammation and/or cell-mediated immunity which, in turn, leads to accelerated nerve damage and more severe skin lesions.[5]

Human immunodeficiency virus (HIV)/acquired immunodeficiency syndrome (AIDS) is a viral disease that represents one of the greatest health problems due to its pandemic nature and high morbidity and mortality rates. In the absence of treatment, HIV infection usually leads to premature death. The World Health Organization (WHO) estimates that in 2006 there were on average 39.5 million (range = 34.1 to 47.1 million) people living with HIV around the globe.[6] On the other hand, the global registered prevalence of leprosy at the beginning of 2006 stood at 219,826 cases, whereas the number of new cases detected during 2005 was 296,499.[7] Many countries have reported that the two diseases often overlap. This observation has focused attention on the possibility that co-infection with HIV and *M. leprae* may exacerbate the pathogenesis of leprosy lesions and/or lead to increased susceptibility to leprosy as is seen with tuberculosis (TB).[8] However, to date, HIV infection has not been reported to increase susceptibility to leprosy or to have a significant effect on the pathogenesis of the neural or skin lesions.[9] In contrast, initiation of antiretroviral treatment (ART) has been reported to be associated with activation of subclinical *M. leprae* infection and exacerbation of existing leprosy lesions.[10,11]

In Brazil, 47,612 new leprosy cases were diagnosed in 2006, a detection rate of 2.35/10,000 inhabitants, 2,449 of whom were in the state of Rio de Janeiro.[12] On the other hand, the estimated HIV prevalence rate in Brazilian adults (aged 15 to 49 years) was 0.5% (range = 0.3–1.6) in 2005. For the same year, the national AIDS rate was 18.0 per 100,000 inhabitants, while in Rio de Janeiro it was 33.2.[13] In the present study, interaction between the two overlapping epidemics was examined in 1,026 patients treated at the Leprosy Outpatient Clinic at the Oswaldo Cruz Foundation (FIOCRUZ) to determine whether ART is associated with increased susceptibility or worsening of the manifestations of leprosy.

SUBJECTS AND METHODS

The Leprosy Outpatient Clinic at FIOCRUZ has been a reference center for HIV and *M. leprae* co-infected patients since 1989. However, the present study only included the patients evaluated since the introduction of highly active ART (HAART) for HIV treatment. Data on all leprosy patients aged 15 years or older, diagnosed between the years of 1996 and 2006 at the clinic, were analyzed. Out of a total of 1,026 patients, 59 (5.8%) were HIV-positive (HIV+). Although 67 patients were confirmed to be HIV-negative (HIV−), all of the other patients were also considered negative even if they had not been tested for HIV, due to the remote possibility of their being HIV+ (probability of 0.015).

The retrospective longitudinal cohort selected for this study was composed of all known HIV co-infected leprosy patients diagnosed with leprosy between 1996 and 2006. Pertinent data on these patients were collected from patient charts at both the Leprosy Outpatient Clinic and the Evandro Chagas Clinical Research Institute (IPEC)—the FIOCRUZ HIV reference center. At IPEC, patients are routinely treated for AIDS and receive specific treatment for opportunistic infections. Patients with TB take monthly rifampicin in addition to their anti-TB treatment, as the latter has no effect on leprosy disease. The HIV+ patients were followed for an average of 33 months (up to a maximum of 117 months). Four of the 59 HIV+ patients were excluded from the follow-up analysis, as they either abandoned leprosy treatment or died before the end of MDT.

All patients followed a routine dermatological and neurological evaluation. Leprosy was diagnosed and classified according to Ridley-Jopling criteria,[14] including pure neural (PN) and indeterminate (I) leprosy. PN was clinically diagnosed and confirmed by histopathology and/or polymerase chain reaction (PCR) for *M. leprae* DNA or presence of anti-PGL-I antibodies as stipulated by Jardim et al.[15] The patients were divided up for treatment according to the WHO operational classification into PB if their bacilloscopic index (BI) of six sites was negative, or MB if their BI was positive.[16] The variables under consideration at diagnosis were gender, age, clinical form of the disease, WHO operational classification, BI, and duration of time from HIV diagnosis and from initiation of ART to time of leprosy diagnosis.

Diagnosis of HIV infection followed the Brazilian Ministry of Health regulations,[17] which include the performance of two tests—the immune-enzymatic method (ELISA) plus immune-fluorescence, or Western Blot. The CD4 cell count and viral loads were determined near to the HIV diagnosis and at leprosy diagnosis (defined as the first time the patient visited a health center with signs of leprosy). HAART was started when the CD4 cell count was ≤200 cells/mm^3 or if an opportunistic infection was diagnosed. Patients who were nonadherent to HAART were considered as not treated. The study was approved by the ethics committee of the Oswaldo Cruz Foundation and IPEC.

Statistical analysis was performed using SPSS 11.0.[18] Possible associations among variables were tested by way of the two sample independent *t*-tests or the Mann-Whitney test (continuous variables) and by the Chi-square test or Fisher's exact test (categorical variables). Dependent variables were evaluated by the Wilcoxon signed ranks test. Uni- and multivariate survival analysis was performed using Cox regression. A *p*-value of ≤0.05 was considered statistically significant.

Table 1. Diagnosis of leprosy and HIV co-infection between 1996 and 2006 at the Leprosy Outpatient Clinic, FIOCRUZ, Rio de Janeiro, Brazil

Year MDT	*HIV−* N *(percent)*	*HIV+* N *(percent)*	*Total* N
1996	82 (95)	4 (5)	86
1997	70 (96)	3 (4)	73
1998	102 (97)	3 (3)	105
1999	137 (97)	4 (3)	141
2000	125 (94)	8 (6)	133
2001	85 (91)	8 (9)	93
2002	79 (94)	5 (6)	84
2003	83 (98)	2 (2)	85
2004	64 (90)	7 (10)	71
2005	79 (93)	7 (7)	86
2006	68 (89)	8 (11)	76
Total	967 (94)	59 (6)	1,026

HIV = human immunodeficiency virus
HIV+ = HIV positive
HIV− = HIV negative
FIOCRUZ = Oswaldo Cruz Foundation
MDT = multidrug therapy

RESULTS

An increasing prevalence of HIV/AIDS among leprosy patients has been observed over the last decade in the Leprosy Outpatient Clinic (Table 1). The baseline characteristics of the study population are shown in Table 2. Both the HIV+ (n=59) and HIV− (n=967) leprosy patients were similar in age and gender. However, a clear difference between the two groups was noted in the distribution of the clinical forms of leprosy and the BIs. A higher percentage (78.0%) of HIV co-infected leprosy patients was PB (χ^2=15.17, p<0.0001) compared with the more equal distribution of the PB (50.6%) vs. the MB (49.4%) forms among HIV− patients (Table 2).

Patients were then compared in terms of the clinical classification demonstrating that, although the borderline tuberculoid (BT) form predominated in both groups, it comprised a significantly higher proportion of co-infected patients (66.7%) than of HIV− patients (32.7%). Among all MB patients, the mean BI was significantly lower (Mann-Whitney U=1,424.50, p=0.003) in the HIV+ group as compared with leprosy patients alone (Table 2). In response to MDT, the BI reduction was significantly more pronounced in HIV+ than in HIV− patients. For example, BIs at the end of MDT were higher in the HIV− patient group (data not shown) (Wilcoxon signed rank test Z=−11.653, p<0.0001). Thus, co-infected leprosy patients tended to have the tuberculoid type of disease and lower bacillary loads as compared with HIV− leprosy patients.

Although both groups of patients had a similar proportion of reactions during the surveillance period (512 [53.1%] non-HIV patients and 35 [59.3%] co-infected patients), co-infected patients had significantly more reaction recorded at the time of diagnosis compared with HIV− patients (χ^2=5.224, p=0.032).

With respect to HIV+ patients, 46/59 (78.0%) were initially diagnosed with HIV prior to leprosy diagnosis. Five of these patients were first diagnosed with leprosy and only later were diagnosed with HIV infection. Eight patients had a simultaneous diagnosis, as the time interval between diagnoses of the two infections was ≤3 months. The median time from HIV diagnosis to leprosy diagnosis was 10.6 months (range = −12.2 to 165.8 months). Two leprosy patients presented typical leprosy lesions after MDT and were considered to be undergoing leprosy relapse. One of these patients relapsed as BT, 15 years after the end of MDT and 30 months after the HIV diagnosis, maintaining the same clinical form of the first diagnosis. The other patient, who was already co-infected upon the first leprosy diagnosis, was retreated as MB 12 months after ending treatment for PB disease due to the appearance of new leprosy lesions and presence of a positive BI.

A total of 37 out of the 59 co-infected patients (63%) were treated with HAART. Other ART schemes, mainly zidovudine alone, were adopted for 13 patients, and nine patients did not receive any ART. The majority of patients (39/47, or 83%) started ART prior to leprosy diagnosis, and the median duration of ART up

Table 2. Characteristics of the two leprosy patient groups (HIV+ and HIV−) at the beginning of MDT. NB[a]

	HIV status	*HIV+ (n=54)*	*HIV− (n=967)*	P-*value*
Age in years (mean ± SD)		39.8 ± 11.45	41 ± 16.10	0.441
Gender *N* (percent)	Male Female	31 (57.40) 23 (42.60)	570 (58.90) 397 (41.10)	0.465
Clinical form *N* (percent)	PB MB	42 (77.80) 12 (22.20)	489 (50.60) 478 (49.40)	<0.0001[b]
Immunohistologic form *N* (percent)	PN I TT BT BB BL LL	1 (1.90) 5 (9.30) 0 (0) 36 (66.70) 7 (13.00) 4 (7.40) 1 (1.90)	109 (11.30) 62 (6.40) 5 (0.50) 316 (32.70) 123 (12.70) 146 (15.10) 205 (21.20)	
Disability grade *N* (percent)	0 1 2 N/A	36 (66.70) 12 (22.20) 5 (9.30) 1 (1.90)	602 (62.30) 177 (18.30) 174 (18.00) 14 (1.40)	0.244
BI of MB patients Median (minimum–maximum)		0.54 (0.16–4.16)	3.00 (0.16–5.50)	0.003[b]
Leprosy reactions *N* (percent)		17 (31.50)	182 (18.80)	0.032[b]

[a]Five patients were excluded because they were diagnosed with leprosy before HIV.

[b]Statistically significant

HIV = human immunodeficiency virus

HIV+ = HIV positive

HIV− = HIV negative

MDT = multidrug therapy

NB = *nota bene* (Latin for "note well")

SD = standard deviation

PB = paucibacillary

MB = multibacillary

N/A = not available

PN = pure neural

I = indeterminate

TT = tuberculoid

BT = borderline tuberculoid

BB = borderline borderline

BL = borderline lepromatous

LL = lepromatous

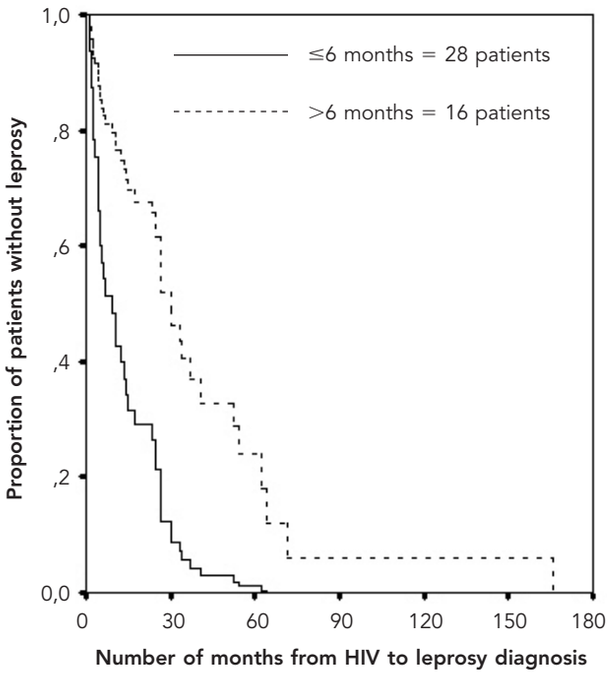
BI = bacilloscopic index

to leprosy diagnosis was five months (range = −10 to 156 months).

After excluding the five patients initially diagnosed with leprosy, multivariate analysis showed an association between the initiation of ART and leprosy diagnosis. In those patients who initiated ART soon after HIV diagnosis (≤6 months), the length of time covered up to leprosy diagnosis was significantly shorter (p=0.001) (Figure). Thus, initiation of ART, usually related to reduced CD4 cell counts, was associated with leprosy diagnosis. In other words, patients with lower CD4 lymphocyte counts at the time of HIV diagnosis took significantly less time to develop leprosy than patients with higher CD4 lymphocyte counts (Mantel-Cox p=0.0355).

Among the subjects for whom viral load data were

Figure. Proportion of patients without leprosy since HIV diagnosis according to period of months in ART[a]



[a]Nine patients did not receive ART and one patient had no information regarding initiation date of ART. The five patients who were diagnosed with leprosy prior to HIV diagnosis were not included in this analysis.

HIV = human immunodeficiency virus

ART = antiretroviral therapy

available (33/54), 33% had undetectable viral loads (<80 copies/µl) upon leprosy diagnosis. Viral loads at this time were significantly lower than at HIV diagnosis (Wilcoxon signed ranks test $Z=-3.258$, $p=0.001$). When T lymphocyte counts and viral load were compared at the time of HIV vs. leprosy diagnoses (Table 3), CD4 lymphocyte counts but not CD8 lymphocyte counts were significantly higher in patients at the time of diagnosis of leprosy (Wilcoxon signed ranks test $Z=-2.744$, $p=0.006$). Thus, leprosy diagnosis was associated with improved immune status (increased CD4 T-cell count) and reduced viral loads.

DISCUSSION

Although an increase in lepromatous leprosy was predicted at the start of the HIV/AIDS pandemic, the present study shows that HIV infection is preferentially associated with the emergence of previously undiagnosed BT/PB leprosy. Among HIV-infected individuals, diagnosis of leprosy was associated with improved immune status, as manifested by higher CD4+ lymphocyte counts and lower viral loads. Thus, the appearance of the clinical signs of *M. leprae* infection in HIV-infected individuals is, in fact, not a manifestation of immune suppression but rather of immune reconstitution, which is probably due to initiation of ART. The increase in CD4+ lymphocyte counts after initiation of HAART may lead to recovery of the innate immune function mediated by natural killer cells and macrophages, in addition to the enhancement of *M. leprae*-specific T-cell-mediated immune responses.[19] This observation provides support for previous reports suggesting that *M. leprae* may be one of the organisms associated with the immune reconstitution syndrome.[10,11,20]

The high percentage of HIV co-infected leprosy

Table 3. Immunological and viral load characteristics of 54 HIV-*M. leprae* co-infected patients

	At HIV diagnosis					*At leprosy diagnosis*					
	N[a]	*Mean*	*Median*	*Minimum*	*Maximum*	N[a]	*Mean*	*Median*	*Minimum*	*Maximum*	P-*value*
CD4 (cells/ml)	31	205	149	7	711	44	330	307	24	883	0.006
CD8 (cells/ml)	16	842	778	73	2,699	31	974	779	379	3,564	0.241
Viral load ($x10^3$ copies/µl)	23	543.640	41.000	<0.080[b]	5,700.000	35	37.390	1.022	<0.080[b]	400.000	0.001

[a]Number of patients with available data

[b]Undetectable

HIV = human immunodeficiency virus

M. leprae = *Mycobacterium leprae*

patients observed in our cohort (5.8%) does not represent a true prevalence within the Brazilian population as a whole. As our Leprosy Outpatient Clinic is a reference center, the sample of patients seen is biased toward those with a more severe or complicated disease. A previous study performed in Rio de Janeiro reported a seroprevalence of 0.3% of HIV in 1,016 leprosy patients tested between the years 1990 and 1992.[21] Considering this data, in addition to the fact that 67 patients were confirmed negative, it is valid to assume that most, if not all, of the leprosy patients not tested for HIV were negative. Gender distribution in the co-infected patient group studied also differed from the currently described distribution among Brazilian HIV patients, where males are more frequently affected than females.[22] However, we observed that the gender distribution was similar to that found in patients with leprosy alone, suggesting that these co-infected patients are a distinct epidemiologic group within the overall HIV-infected population.

Several studies have reported no significant difference between the ratios of lepromatous and tuberculoid leprosy in HIV co-infected individuals.[23–25] In contrast, in the present cohort, most of the co-infected individuals were PB. This difference may be explained by the introduction of HAART in this cohort. In previously published studies, the evaluations were done in the pre-HAART era.[26–28] Therefore, it may be that the high percentage of BT leprosy among the HIV-infected patients on HAART could shed light on some of the questions related to the kinetics of *M. leprae* infection and development of disease.

The BT form of disease is expected to manifest two to five years after infection, at which time specific cell-mediated immunity is strong enough to provoke tissue damage as well as kill or at least control mycobacterial growth. On the other hand, MB forms appear in patients after longer periods of incubation (five to 10 years), during which a large number of bacilli have accumulated in the tissue due to progressive reduction of CMI. Although HIV+ patients are typically more aware of their health condition and would easily detect small PB lesions, the high frequency of PB patients and reactions among HIV-infected individuals, and the low bacillary load among the co-infected MB patients, strongly suggests an earlier-than-usual detection of the disease in immune-reconstituted patients. In addition, leprosy relapse observed in the co-infected patients was high (3.4%) as compared with leprosy relapse in HIV− patients, in whom an approximate rate of 1.0% is observed (calculation based on the National Health Services data), suggesting that immune reconstitution may also influence this occurrence.

It is well known that HAART dramatically decreases the rate of AIDS-related opportunistic infections[29] in association with increasing the amount of CD4+ lymphocyte-mediated pathogen-specific immunity.[22,30] Some authors have argued that *M. leprae* could be an opportunistic pathogen in HIV-infected individuals.[31] Conversely, others have suggested that the incidence of overt clinical leprosy may be lower among profoundly immunosuppressed HIV-infected individuals.[10] In addition, clinical leprosy in HIV co-infected patients frequently occurs simultaneously with reversal reaction (RR) in both PB and MB patients.[32] Preliminary observations suggest that co-infected HIV/leprosy patients on HAART have a higher risk of developing RR than non-co-infected leprosy patients.[10] Preservation of T-cell-mediated responses to *M. leprae* at the tuberculoid end of the spectrum in HIV-infected patients has been reported.[9,33] Taken together, these observations suggest that the HIV-*M. leprae* interaction is substantially different from the HIV-*M. tuberculosis* interaction. In the latter, the interaction between the two pathogens is a manifestation of HIV-induced immune suppression and reduced CD4+ lymphocyte counts.[8] Understanding why *M. leprae* differs from *M. tuberculosis* in its interaction with HIV in co-infected patients should help explain the pathogenesis of opportunistic infections and the nature of the immune compromise seen in AIDS patients.

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