

Leprosy and HIV Coinfection: A Clinical, Pathological, Immunological, and Therapeutic Study of a Cohort from a Brazilian Referral Center for Infectious Diseases

Carolina Talhari,^{1,3} Marcelo Távora Mira,⁴ Cesare Massone,⁶ Andréa Braga,¹ Anette Chrusciak-Talhari,¹ Mônica Santos,^{1,3} Ana Tereza Orsi,¹ Christiane Matsuo,¹ Renata Rabelo,¹ Lisiane Nogueira,¹ Luiz Carlos de Lima Ferreira,² Rodrigo Ribeiro-Rodrigues,⁵ and Sinésio Talhari¹

Departments of ¹Dermatology and ²Pathology, Tropical Medicine Foundation of Amazonas, and ³State University of Amazonas, Manaus, ⁴Pontifical Catholic University of Parana, Curitiba, and ⁵Department of Pathology and Núcleo de Doenças Infecciosas, Vitória, Espírito Santo, Brazil; ⁶Department of Dermatology, Medical University of Graz, Graz, Austria

Background. Although awareness of the relevance of leprosy and human immunodeficiency virus (HIV) coinfection is increasing worldwide, several aspects of this co-occurrence are not fully understood.

Methods. We describe clinical, pathological, immunological, and therapeutic long-term follow-up of a cohort of 25 individuals with leprosy and HIV infection from Manaus, Amazonas.

Results. Careful description of our cohort indicates a higher prevalence of leprosy in an HIV-positive population than that in the general population. We also observed upgrading shifting of leprosy clinical forms after initiation of highly active antiretroviral therapy and multidrug therapy and an impact of HIV infection on leprosy granuloma formation, among other features.

Conclusion. Taken together, these new insights allow the proposition of a classification system that includes (1) leprosy and HIV true coinfection, (2) opportunistic leprosy disease, and (3) leprosy related to highly active antiretroviral therapy.

According to the World Health Organization, Brazil is one of the few countries where both leprosy and AIDS are endemic [1, 2]. In 2008, the prevalence of leprosy in Brazil was 2.21 cases per 10,000 individuals, with 45,847 registered patients [1, 3]. From 1980 through 2007, the country had registered 506,499 cases of human immunodeficiency virus (HIV) infection, with a detection rate of 17.8 cases per 100,000 individuals [2,

4]. Worldwide data indicate that, contrary to early expectations, no significant increase in leprosy and HIV infection co-occurrence has been reported [5]. Most of the larger studies on the subject were performed in the early to mid 1990s and examined the rate of HIV seropositivity among leprosy patients in India [6], Brazil [7, 8], and African countries [9–15]. In Brazil, studies suggest that in coinfecting patients, each disease progresses as a separate infection [16–20].

An interesting aspect of the pathogenesis of leprosy in patients with AIDS who have a low CD4⁺ T cell count is what has been called the granuloma paradox [5]: histopathological features of leprosy seem to be maintained in coinfecting patients [17–19, 21, 22], indicating an apparent preservation of the ability to form granulomas [18] that contrasts with what is observed in *Mycobacterium tuberculosis* and HIV coinfecting individuals. Our group previously observed that *Mycobacterium leprae*-infected and HIV-infected patients who manifest borderline lepromatous leprosy and AIDS might shift to borderline tuberculoid disease after implementation of highly active antiretroviral therapy

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Reprints or correspondence: Dr Carolina Talhari, Rua Pedro Texeira, 25, Manaus, Amazonas 69000-00, Brazil (carolinatalhari@gmail.com).

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(HAART) and leprosy multidrug therapy, which suggests that, in some patients, granuloma formation might be altered by a HAART-induced increase in the CD4⁺ T cell count [23, 24].

Another consequence of HAART-induced CD4⁺ T cell count improvement [25] is an apparent clinical deterioration that has been noted in a subgroup of patients, an immunopathological and inflammatory phenomenon known as immune reconstitution inflammatory syndrome (IRIS) [26]. Tuberculosis, *Mycobacterium avium* complex infection, cryptococcosis [27], cutaneous leishmaniasis [27, 28], and other infectious and noninfectious diseases have been associated with IRIS [27]. This syndrome was first associated with leprosy in 2003 [29]; since then, several cases have been reported [19, 23, 24, 30–37], usually developing within 6 months after initiating HAART [38]. However, there have been reports of periods longer than 10 months between initiation of HAART and onset of IRIS [23, 24, 36].

Although it has been argued that the association between *M. leprae* infection and HIV infection may have no impact on public health [5], the true magnitude of the problem remains to be elucidated. Also, despite advances in the study of this coinfection, several features deserve further investigation. This study describes a cohort of 25 HIV and *M. leprae* coinfecting patients, 6 of whom were partially described elsewhere in case reports [23, 24, 39]. By presenting the results of long-term, careful follow-up of these patients, some of them for up to 13 years, we expect to contribute to a better understanding of the clinical, histopathological, and immunological basis of leprosy and AIDS.

PATIENTS AND METHODS

Study population. The study population was composed of HIV and *M. leprae* coinfecting patients from Manaus, Ama-

Table 1. Clinical, Immunological, and Therapeutic Characteristics of 25 *Mycobacterium leprae* and Human Immunodeficiency Virus (HIV) Coinfecting Patients

Patient ID	Sex, age in years	Time to diagnosis, months ^a	Leprosy classification	Impaired tactile sensibility	CD4 cell count(s), cells/ μ L	Viral load, copies/ μ L	Leprosy treatment	HIV infection treatment
1	Male, 54	5; 13 ^b	BL-BT ^c	Yes	58; 153 ^d	... ^e	MB MDT	HAART
2	Male, 32	1; 10 ^b	BL-BT ^c	Yes	71; 257 ^d	160,000	MB MDT, steroid	HAART
3	Male, 33	6; 11 ^b	BL-BT ^c	Yes	... ^e ; 92 ^d	150,000	MB MDT, steroid	HAART
4	Male, 25	2; 4 ^b	BL-BT ^c	Yes	77; 158 ^d	100,000	MB MDT, steroid	HAART
5	Male, 48	2	BT	Yes	210	8614	PB MDT, steroid	HAART
6	Male, 44	3 weeks	BB	Yes	120	20,177	MB MDT, steroid	HAART
7	Male, 39	2	Neural	Yes	166	1724	Steroid	HAART
8	Male, 49	5	Neural with foot drop	No	320	7890	PB MDT	Untreated
9	Female, 30	3	BL	Yes	32	173,000	MB MDT, steroid	HAART
10	Male, 22	3	BL	No	6	183,000	MB MDT	Untreated
11	Female, 40	3 weeks	BT	Yes	... ^e	... ^e	PB MDT	NRTI
12	Male, 36	2	BT	Yes	349	17,645	PB MDT, steroid	HAART
13	Female, 48	4	BT	Yes	290	9500	PB MDT, steroid	HAART
14	Female, 30	1	BT	Yes	132	79,000	PB MDT	HAART
15	Male, 32	6	BT	Yes	20	26,000	PB MDT	Untreated
16	Female, 31	1 year	BT	Yes	457	34,851	PB MDT	HAART
17	Female, 30	4	BT	Yes	342	22,000	PB MDT	Untreated
18	Female, 20	3	BT	Yes	372	30,424	PB MDT	HAART
19	Female, 33	12	BT	Yes	223	5432	PB MDT	HAART
20	Male, 48	1	BT	Yes	39	17,530	PB MDT, steroid	HAART
21	Female, 31	4	BT	Yes	66	17,000	PB MDT	Untreated
22	Male, 57	2	TT	Yes	536	Undetected ^f	PB MDT, steroid	HAART
23	Male, 59	3	TT	Yes	175	15,723	PB MDT	HAART
24	Female, 21	1	I	No	278	20,624	PB MDT	Untreated
25	Male, 28	1	I	No	770	Undetected ^f	PB MDT	Untreated

NOTE. BB, borderline borderline; BL, borderline lepromatous; BT, borderline tuberculoid; HAART, highly active antiretroviral therapy; I, indeterminate; MB, multibacillary; MDT, multidrug therapy; NRTI, nucleoside reverse-transcriptase inhibitor; PB, paucibacillary; TT, tuberculoid.

^a Self-reported time interval from the appearance of the leprosy lesion to the date of diagnosis.

^b Time to appearance of BL lesions; time to appearance of BT lesions after initiating HAART.

^c These patients developed a shift from BL to BT.

^d CD4 cell count when borderline lepromatous leprosy was diagnosed; CD4 cell count when a new cutaneous biopsy was performed that displayed borderline tuberculoid leprosy.

^e Data not available.

^f Less than 500 copies of HIV per microliter (limit of detection).

zonas, Brazil. With the exception of 1 patient who received a diagnosis of leprosy elsewhere, all patients received diagnoses of and were monitored and treated for both HIV infection and leprosy at the Tropical Medicine Foundation of Amazonas (TMF-AM). From November 1996 through June 2009, all coinfecting patients who were referred to the TMF-AM were invited to participate and enrolled in the study. This group also included patients who tested positive for HIV type 1 who simultaneously or subsequently received a diagnosis of leprosy. Patients were followed up for a mean of 46.29 months (maximum duration of follow up, 158 months).

Patients who had a suspected coinfection underwent a detailed clinical and dermatological examination by dermatologists with expertise in leprosy and by specialists in infectious diseases. HIV infection and AIDS were defined according to the guidelines of the Brazilian Ministry of Health (AIDS was defined by a CD4⁺ T cell count of <200 cells/ μ L and/or clinical conditions that define the disease) [40]. Cases of leprosy were diagnosed according to clinical [41] and histopathological [42, 43] criteria and were clinically classified according to the spectral system of Ridley and Jopling [42, 43]. Peripheral nerve involvement was evaluated by means of nerve palpation during the physical examination. Thermal, pain, and tactile sensibility within the cutaneous lesions (sensory function) were tested using test tubes filled with cold or warm water, a pin prick, and the cotton wool touch test, respectively. Sensorial parameters were considered impaired when they were diminished or absent within the lesion. Muscular force was evaluated by means of the voluntary muscle test and graded from absent to

preserved [41, 44]. For treatment purposes, leprosy cases were classified as paucibacillary or multibacillary [41]. Indeterminate leprosy, tuberculoid leprosy, and borderline tuberculoid leprosy were included in the paucibacillary group, whereas cases of borderline leprosy, borderline lepromatous leprosy, or lepromatous leprosy were classified as multibacillary cases. Cases of neural leprosy were classified as paucibacillary or multibacillary on the basis of the result of anti-*M. leprae* phenolic glycolipid detection, as described elsewhere [45]. Patients with paucibacillary leprosy were treated for 6 months with rifampicin and dapsone, and patients with multibacillary leprosy were treated for 12–24 months with rifampicin, clofazimine, and dapsone [41]. Steroids (initial dosage, 1–2 mg per kilogram of body weight per day; the dose was slowly tapered according to clinical parameters) [41] were given to patients with a type 1 reaction and IRIS.

This study was approved by the local ethics review committee. Written informed consent was obtained from all participants prior to their enrollment.

Histopathological and immunostaining analysis. Skin biopsy specimens (4-mm punch) from 23 of the 25 HIV and *M. leprae* coinfecting patients who presented with cutaneous lesions were obtained after clinical diagnosis of leprosy and before the start of multidrug therapy. Biopsy specimens were fixed in 10% buffered formalin and subsequently embedded in paraffin. Sections were stained with hematoxylin, eosin and Wade staining for acid-fast bacilli. Histopathological classification was performed according to Ridley and Jopling [42, 43].

Detailed immunophenotypic analysis was performed on



Figure 1. Patient 10. *A*, Amyotrophy (*large arrows*) of the right foot dorsum and lipodystrophy (*small arrows*) of the left foot dorsum. *B* and *C*, Claw deformity of the right toes. *D*, Plantar perforating ulcer.

specimens from 17 patients, as described elsewhere [46]. In order to increase the sensitivity of CD4 characterization by immunostaining, the method was performed in 2 independent experiments with the use of monoclonal antibodies from 2 different suppliers (Novocastra and Dakopatts). CD8, phosphoglucomutase 1 (a macrophage CD68⁺ marker), and T cell intracellular antigen 1 (a marker of natural killer cells and natural killer–like cytotoxic T lymphocytes) were obtained from Dakopatts. Positive CD4 controls were run in parallel with each of the studied specimens.

RESULTS

Epidemiological, clinical, and immunological characteristics of *M. leprae* and HIV coinfecting patients. The mean age was 37.04 years (range, 20–59 years), and the male to female ratio was 1.5:1. Table 1 summarizes the characteristics of the studied population. Leprosy diagnosis was simultaneous with detection of HIV positivity for 3 (12%) patients and subsequent to detection of HIV positivity for the other 22 patients. At the time of the diagnosis of HIV and *M. leprae* coinfection, 21 (84%) individuals had AIDS. Paucibacillary leprosy was diagnosed in 18 (72%) patients and multibacillary leprosy in 2 (8%) patients, and borderline lepromatous leprosy was initially diagnosed in 4 (16%) patients, which shifted to borderline tuberculoid leprosy after the patients initiated HAART and multidrug therapy.

Of the patients with paucibacillary leprosy, 2 had clinical features of indeterminate leprosy, 2 had clinical features of tuberculoid leprosy, 12 had clinical features of borderline tuberculoid leprosy, and 2 (patients 7 and 8) had neural leprosy. Patient 7 had ulnar, posterior tibial, and external popliteal nerve enlargement, which appeared 8 months after initiation of HAART, and a history of being treated elsewhere for borderline leprosy 10 years before the diagnosis of AIDS. Patient 8 presented with foot drop and an electroneuromiograph suggestive of leprosy. Because the anti-*M. leprae* phenolic glycolipid test result was negative for both patients, they were classified as having paucibacillary leprosy. Another 2 individuals with paucibacillary leprosy deserve further consideration, given the unusual clinical aspects that were evident only upon long-term follow-up. Patient 12 had been treated for paucibacillary leprosy for 4 years before AIDS diagnosis. When referred to TMF-AM, the patient, who was already receiving HAART (CD4⁺ T cell count, 349 cells/ μ L), presented with an anesthetic area involving the external border and plantar region of the right foot; a new biopsy yielded a diagnosis of borderline tuberculoid leprosy, and the patient was again treated for paucibacillary disease. Ten years later, the patient returned presenting with apparent dorsal amyotrophy on both feet (Figure 1A); however, only the right foot showed impairment of muscular force, associated with claw deformity of the toes and a plantar perforating ulcer (Figures 1B–1D), which indicated in-

volvement of the right posterior tibial and external popliteal nerves. Patient 11 started multidrug therapy for borderline tuberculoid leprosy while receiving zidovudine monotherapy; 2 years after finishing leprosy treatment, the patient, who was already receiving HAART, presented with lipodystrophy of the dorsum and plantar regions of both feet, in a striking resemblance to patient 12 (Figures 2A and 2B); however, careful examination revealed preservation of muscular force on both feet.

Twenty-one patients (84%), regardless leprosy clinical manifestation, presented with cutaneous lesions with tactile sensibility impairment (eg, absent or decreased response to light touch with cotton wool) a mean of 17 weeks (range, 3 weeks to 12 months) after the appearance of the lesion. Interestingly, in 1 patient (patient 6), the tactile sensibility was restored within 3 months of initiating HAART, steroid therapy, and multidrug therapy (Figures 3A–3C).



Figure 2. Patient 11. A, Absence of pathological findings on the dorsum of both feet at the time of leprosy diagnosis and before initiating highly active antiretroviral therapy (HAART). B, Lipodystrophy of the dorsum of both feet 14 months after HAART initiation.

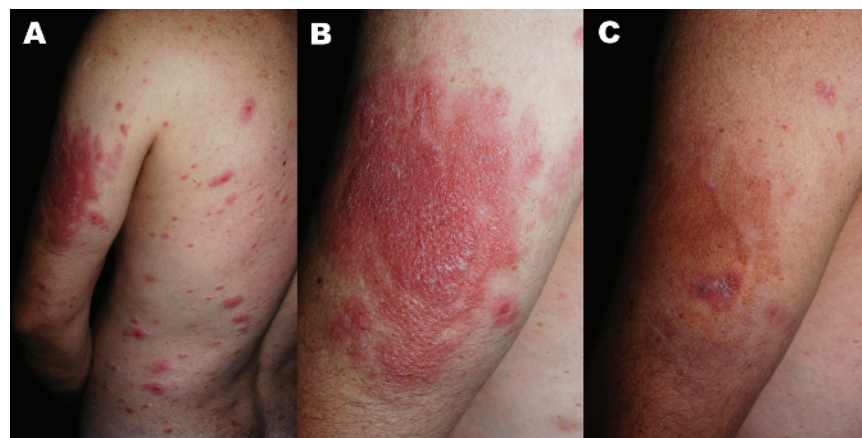


Figure 3. Patient 6. *A*, Infiltrated lesions on the trunk and upper left limb. *B*, Closer view of the same infiltrated lesion. *C*, Improvement of the lesion within 3 months of 60 mg of prednisone daily, multidrug therapy, and highly active antiretroviral therapy. This improvement was followed by recovery of tactile sensibility.

The great majority of patients presented with isolated and disseminated hypochromic patches, infiltrated plaques, papular lesions, and nodular lesions. Patients 3, 6, 18, and 20 (Figure 4A) had atypical, hiperkeratotic, eczematous lesions, as described elsewhere for patients 3 [23] and 18 [39]. Within 3 months of starting paucibacillary multidrug therapy and 40 mg daily of prednisone, in association with HAART, ulceration was seen in patient 20 at the same site of the eczematous lesions (Figure 4B). Moreover, 2 months after finishing paucibacillary multidrug therapy, the same patient presented with enlargement of a cutaneous nerve (Figure 4C).

Seven patients presented with leprosy as a primary manifestation of IRIS. Patient 5 presented with clinical and laboratory features of IRIS within 2 months after initiating HAART, patient 6 within 3 months, and patient 7 within 2 months. IRIS caused a shift from borderline lepromatous leprosy to borderline tuberculoid leprosy 13 months after patient 1 started HAART, 10 months after patient 2 started HAART, 4 months after patient 3 started HAART, and 11 months after patient 4 started HAART.

Two deaths were observed among the 25 patients: patient 10 died of neurocryptococcosis and sepsis, and patient 1 died of leukemia. Except for these 2, no patient was lost to follow-up until August 2009.

Histopathological and immunostaining analysis of leprosy skin lesions. Information about microanatomy, distinct cell phenotypes, presence of bacilli, and degree of nerve damage was obtained from the 23 patients who presented with cutaneous lesions. For patients 1, 2, 3, and 4, 2 skin biopsy specimens were collected that were representative of each borderline lepromatous and borderline tuberculoid disease episode that manifested during follow-up. The histopathological classification of the 27 skin biopsy specimens that were collected, as

shown in Table 2, were as follows: indeterminate (2 specimens), tuberculoid tuberculoid (2 specimens), borderline tuberculoid (16 specimens), borderline borderline (1 specimen), and borderline lepromatous (6 specimens); these histopathological classifications were in perfect correlation with the clinical classifications. Severe perineural and intraneural lymphohistiocytic infiltrates were observed in all of the patients who presented with impairment of tactile sensibility (Figure 5).

Immunostaining reactions revealed CD4⁺ T cells within epithelioid granulomas in 3 (16.66%) of 18 specimens (Table 2): 1 from an individual with borderline borderline disease and the other 2 from individuals with tuberculoid tuberculoid disease (Figure 6). Notably, CD4⁺ T cells were absent in all cases of borderline tuberculoid leprosy, in contrast with CD8, T cell intracellular antigen 1, and phosphoglucosylase 1, which were present in all specimens.

Therapeutic characteristics. Sixteen coinfecting patients were already receiving HAART when multidrug therapy was initiated, and 5 patients started both HAART and multidrug therapy regimens at the same time. Coinfecting patients were treated for HIV infection by the time of leprosy diagnosis with regimens containing 2 nucleoside reverse-transcriptase inhibitors in combination with a protease inhibitor (6 patients), a boosted protease inhibitor (7 patients), or a nonnucleoside reverse-transcriptase inhibitor (11 patients). With the exception of patients 1, 3, 11, who were treated with multidrug therapy for 15, 24, and 24 months, respectively, all patients were treated for leprosy according to the recommendations of the World Health Organization. No adverse effects due to this therapeutic combination were reported. As expected, all patients had significant increases in CD4⁺ T cell counts after initiating HAART.

Eleven patients concomitantly received oral steroids (1–2 mg of prednisone per kilogram of body weight per day) and/or

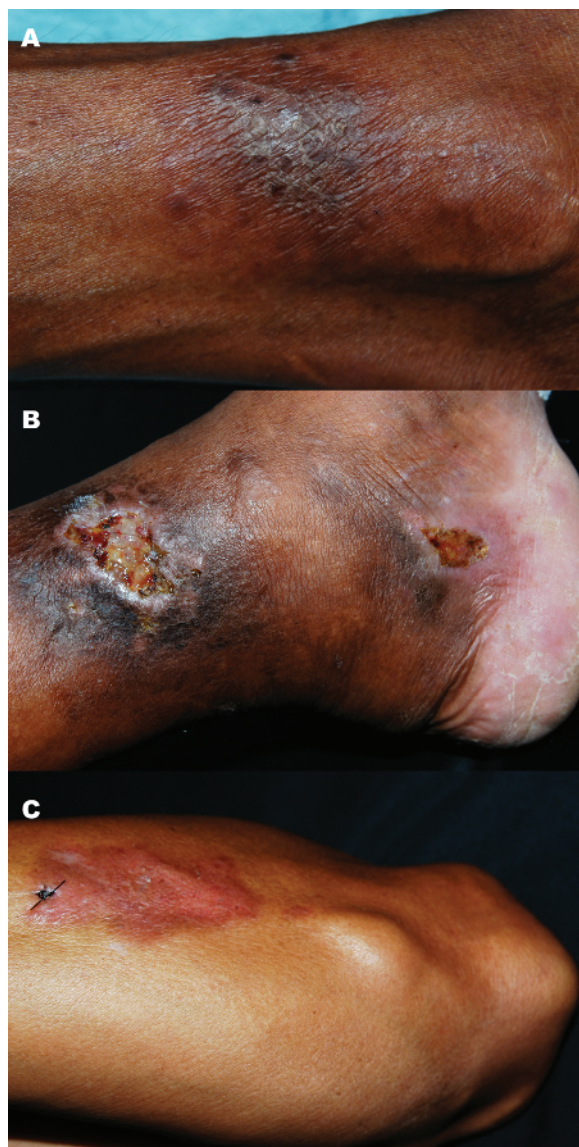


Figure 4. Patient 20. *A*, Atypical hyperkeratotic, eczematous lesion on the internal aspect of the left leg. *B*, Same site with ulceration within 3 months after the start of paucibacillary multidrug therapy and 40 mg daily of prednisone. *C*, Plaque lesion and severe enlargement of a cutaneous nerve at the external surface of left upper limb 2 months after finishing paucibacillary multidrug therapy.

intravenous steroids (patient 2 received 3 pulses of 1 g of methylprednisolone) [24], as detailed in Table 1. Because of the clinical severity of their disease, these patients were given steroid treatment for a mean of 14 months. With the exception of a case of staphylococcal sepsis that occurred in patient 2 after intravenous steroid treatment [24], no other adverse effects were noticed. Two patients developed scars due to the ulceration of the plaque lesions.

DISCUSSION

Here we present the results of a 13-year follow-up study of a well-characterized cohort of patients dually infected with HIV and *M. leprae* who showed several features of interest, including a higher leprosy prevalence among the HIV-positive individuals than in the general population, presentations that shifted from borderline lepromatous to borderline tuberculoid leprosy because of IRIS and/or upgrading type 1 reaction, and atypical cutaneous and neurological leprosy manifestations.

An important question that our study addressed was the true estimate of the prevalence of leprosy and HIV infection in populations exposed to both diseases. Our cohort was recruited in Manaus, a city where both leprosy and AIDS are endemic [1–4, 47]. Considering that the TMF-AM is a referral center for both diseases, we believe that 25 cases of *M. leprae* and HIV coinfection out of a total of 3290 HIV-positive individuals reported between 1996 and June 2009 [47] represent the closest estimate of the prevalence of this coinfection in a major Brazilian city. Because the prevalence of leprosy in the Amazonas State was 2.92 cases per 10,000 individuals in 2008 [3], our data clearly indicate a higher leprosy prevalence among HIV-positive individuals when compared with the general population.

Borderline tuberculoid leprosy was the most frequent clinical form of leprosy observed in the studied cohort (12 patients [45%]), which concurs with most post-HAART reports [18, 19, 29, 30, 32–35, 37, 48]. Six patients received a diagnosis of borderline lepromatous leprosy. One can speculate that this apparently low prevalence of multibacillary forms of leprosy is partially due to late AIDS diagnosis and treatment, leading to premature death. Concurring with this hypothesis is the case of patient 10, who had borderline lepromatous leprosy, presented with very advanced disease, and died of sepsis and neurocryptococcosis [39]. Interestingly, the initial diagnosis given to 4 (66.66%) of 6 patients with AIDS of borderline lepromatous leprosy shifted to borderline tuberculoid leprosy after the initiation of HAART and multidrug therapy—an event only noticed because (1) the leprosy diagnosis was made before or concomitant with HAART initiation and (2) careful, long-term clinical and histopathological follow-up was performed.

Once characterized, upgrading shifting of leprosy clinical form creates a number of interesting opportunities for discussion. First, it is possible that the high prevalence of borderline tuberculoid leprosy among HAART-treated and multidrug-treated individuals may also be a consequence of shifting from multibacillary disease. Second, whether IRIS or an upgrading type 1 reaction caused the shift is an interesting question. In our opinion, leprosy-associated IRIS corresponds to the classical upgrading type 1 reaction that is observed in immunocompetent patients. The precise cellular mechanism involved in IRIS and/or type 1 reaction remains to be investigated. Of

Table 2. Histopathological and Immunostaining Analysis Results for Skin Biopsy Specimens from 17 *Mycobacterium leprae* and Human Immunodeficiency Virus Coinfected Patients

Patient ID	Leprosy histopathological classification	CD4 ⁺ cells	CD8 ⁺ cells	PGM-1	TIA-1
1	BL	Negative	Positive	Positive	Positive
2	BL	Negative	Positive	Positive	Positive
2 ^a	BT	Negative	Positive	Positive	Positive
5	BT	Negative	Positive	Positive	Positive
6	BB	Negative	Positive	Positive	Positive
10	BL	Negative	Positive	Positive	Positive
14	BT	Negative	Positive	Positive	Positive
15	BT	Negative	Positive	Positive	Positive
16	BT	Negative	Positive	Positive	Positive
17	BT	Negative	Positive	Positive	Positive
18	BT	Negative	Positive	Positive	Positive
19	BT	Negative	Positive	Positive	Positive
20	BT	Negative	Positive	Positive	Positive
21	BT	Negative	Positive	Positive	Positive
22	TT	Positive	Positive	Positive	Positive
23	TT	Positive	Positive	Positive	Positive
24	I	Negative	Positive	Positive	Positive
25	I	Negative	Positive	Positive	Positive

NOTE. BB, borderline borderline; BL, borderline lepromatous; BT, borderline tuberculoid; I, indeterminate; PGM-1, phosphoglucomutase 1; TIA-1, T cell intracellular antigen 1; TT, tuberculoid.

^a An additional biopsy specimen was obtained from patient 2. The first biopsy was performed when the patient first received a diagnosis of leprosy (borderline lepromatous leprosy). The second biopsy was performed a few months later, when the patient presented different clinical aspects and a higher CD4 cell count. At that time, the patient received a diagnosis of borderline tuberculoid leprosy in association with immune reconstitution inflammatory syndrome.

note, 5 patients in our cohort developed IRIS within a period longer than 6 months of HAART initiation, as also observed elsewhere [36]. Although an early increase in both CD4⁺ T cells and memory CD4⁺ T lymphocytes can be noticed after 4 weeks of HAART, it has been shown to persist for 48 weeks [25]. Therefore, the timeline for IRIS occurrence might be longer than was previously proposed [38]. Third and critically important, histopathological follow-up of these 4 patients revealed the replacement, on initiation of HAART and multidrug therapy, of foamy histiocytes containing numerous acid-fast bacilli by granulomas consisting of lymphocytes and epithelioid cells with scanty or no acid-fast bacilli. These findings demonstrate a true impact of HIV infection, HAART, and multidrug therapy on leprosy granuloma formation, in contrast with the granuloma paradox that was proposed elsewhere [5, 18].

To further investigate the cellular nature of the granulomas in these coinfecting patients, immunostaining techniques were applied. The absence of CD4⁺ T cells was reported in all 10 (100%) granuloma specimens of the 10 examined borderline tuberculoid patients, in 2 independent experiments with different anti-CD4⁺ monoclonal antibodies. The role of CD4⁺ T

cells in granuloma formation in patients with borderline tuberculoid leprosy and HIV infection is somewhat controversial. Our findings diverge from those in a previous report showing high numbers of CD4⁺ T cells in biopsy specimens of 8 individuals with borderline tuberculoid leprosy and HIV infection [18], as well as from the findings in a report from our own group of CD4⁺ T cells in a biopsy specimen of patient 4 [24]. Unfortunately, this particular specimen could not be assessed for immunostaining and has not been included among the results of the 10 individuals with borderline tuberculoid leprosy described here. In contrast, our present data are in accordance with those from another Brazilian study that also failed to detect CD4⁺ T cells in 9 patients with borderline tuberculoid leprosy and HIV infection, using antibodies provided by 2 different suppliers, whereas CD3⁺ T cells, macrophages, and natural killer cells were observed within the granulomas [19]. These observations indicate that cell types other than CD4⁺ and CD8⁺ T lymphocytes may be playing a role in granuloma formation under the conditions observed for individuals with leprosy and HIV infection. Further studies aiming to investigate this possibility are currently ongoing.

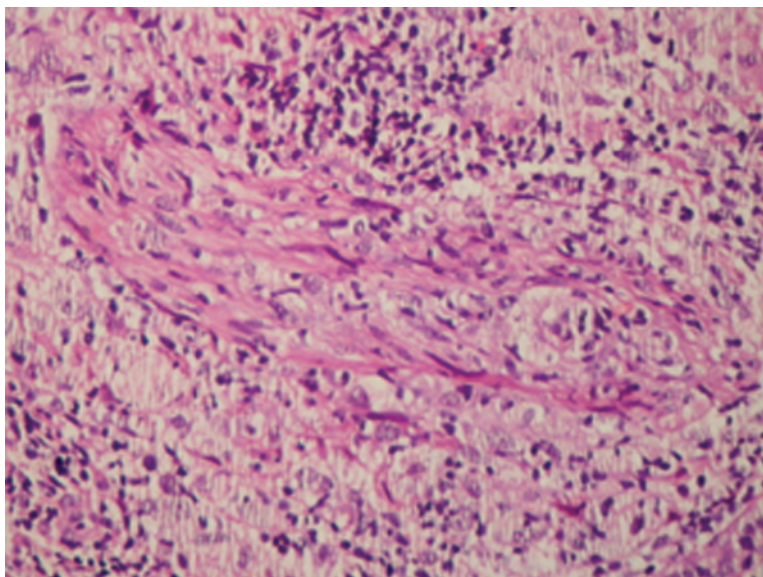


Figure 5. Light microscopic image showing a severe perineural and intraneural lymphohistiocytic infiltrate in a biopsy specimen from patient 6 (hematoxylin and eosin staining, original magnification $\times 400$).

The atypical cutaneous and neurological manifestations of leprosy in this particular context must not be overlooked. Four patients presented with chronic, hiperkeratotic, eczematous lesions, which indicates that although the majority of patients with leprosy and HIV infection maintain classic clinical features of leprosy [7, 16–19, 21, 22], diagnosing the disease may be challenging for a significant proportion of patients with AIDS. From the neurological perspective, peripheral nerve involvement in leprosy is well known; however, against a background

of HIV infection, it may be confounded with neuropathy associated with HIV [49] and/or with the effects of stavudine and other nucleoside-analogue reverse-transcriptase inhibitors [40]. If leprosy is considered to be the cause of nerve damage, then the challenge is to differentiate between relapse and silent neuropathy. In our cohort, patients 4, 7, and 12 exemplify this situation. Because patients 4, 7, and 12 were previously treated for leprosy, their cases may be diagnosed as relapse; however, silent neuropathy could be also considered for patient 7. Finally,

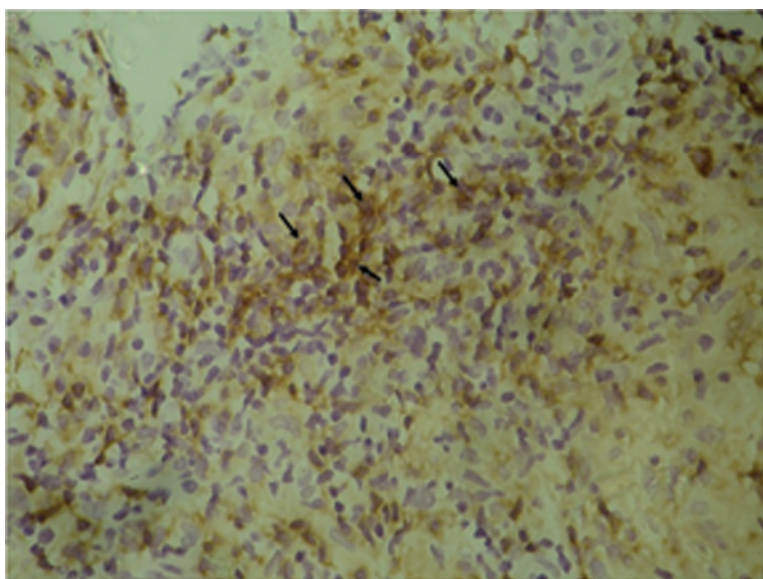


Figure 6. CD4⁺ T cells within an epithelioid granuloma in a biopsy specimen from patient 22 (hematoxylin and eosin staining, original magnification $\times 400$). Arrows indicate some of the positively stained cells.

in patient 12, amyotrophy, as observed on the right foot, should be differentiated from lipodystrophy induced by HAART [40], as seen in this patient's left foot and in both feet of patient 11. When differentiating such conditions, sensorial loss and muscular force impairment argue in favor of a diagnosis of leprosy.

Because most post-HAART, dually infected patients have cases of borderline tuberculoid leprosy and often present with a type 1 reaction [19, 29, 30, 32–35], an important question is whether it is safe to give HAART and steroids to an immunosuppressed patient presenting with AIDS, leprosy, and IRIS and/or a type 1 reaction. Steroid therapy was promptly introduced in all patients who had IRIS and/or a type 1 reaction reported in this study. Except for the staphylococcal sepsis presented by 1 patient [24], no other adverse effects were reported. Our data corroborate with those in other reports [19, 29, 31, 37, 48], showing that early steroid therapy may be used for patients with AIDS.

One last finding is noteworthy: 21 patients presented with early impairment of tactile sensibility, detected within a mean of 17 weeks from the initial appearance of the lesion. This clinical finding is known to occur several months or even years after the appearance of the lesion in immunocompetent hosts [50]. Notably, recovery of tactile sensibility was observed in patient 21 within 3 months of the start of multidrug therapy, steroid therapy, and HAART—again diverging from the current knowledge that, once it has developed, tactile sensibility impairment is irreversible [50]. Even though it is unknown whether HIV infection worsens nerve damage in leprosy, HIV is known to be neuropathic [49] and might act synergistically with *M. leprae* in dually infected individuals.

Detailed follow-up and description of our cohort led to the understanding that even though leprosy and HIV coinfection do not manifest homogeneously across affected populations, some features seem to be shared by certain subgroups. In this context, we propose a clinical classification of *M. leprae* and HIV coinfecting patients that includes the following: (1) a group of patients with *M. leprae* and HIV true coinfection, composed of HIV-positive individuals who do not fulfill AIDS criteria and therefore do not receive HAART, and so behave similarly to immunocompetent individuals (patients 8, 15, 17, 21, 24, and 25 in our cohort belong to this group); (2) a group of patients with opportunistic leprosy disease, composed of patients with AIDS who are not receiving HAART and usually present with multibacillary leprosy (in this group, leprosy manifests as an opportunistic mycobacteriosis, as expected in immunosuppressed individuals; patient 10 would fit these criteria); and (3) a group of patients with HAART-related leprosy, including patients with AIDS who present with all clinical forms of leprosy whether or not they are related to IRIS (this group would comprise patients 1–7, 9, 11–14, 16, 18–20, 22, and 23 in our

cohort). Importantly, groups 2 and 3 differ basically with respect to the initiation of HAART.

Leprosy is an ancient disease that, despite intense research efforts throughout the past centuries, is yet not fully understood. This already challenging clinical entity becomes even more complex against a background of HIV infection. Therefore, it is not surprising that leprosy and HIV coinfection manifest in different clinical presentations. Awareness of the complexity of this clinical scenario is mandatory to elucidate how *M. leprae* and HIV interact and ultimately gain a better understanding of the mechanisms of both diseases.

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