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## LEPROSY REACTION AND IMMUNE RECONSTITUTION SYNDROME IN AIDS

### ABSTRACT

The authors report seven cases of borderline leprosy in AIDS patients whose presentation form was of a type I reaction diagnosed soon HAART introduction, which led to the discussion of the immunological aspects involved in the reaction to leprosy and the immune reconstitution syndrome. The patients were in frank AIDS-induced immune deterioration, which was the reason they met the criteria to initiate HAART treatment. It is likely that due to this fact, the amount of CD4 cells increased at the same time that a reduction of the viral load occurred, allowing the installation of a basically Th1 immunological profile. Therefore, the leprosy infection, which was dormant and unable to express itself was exteriorized in the form of a reverse reaction.

### INTRODUCTION:

Few cases of *Mycobacterium leprae* infection in association with HIV infection have been reported after the advent of the AIDS epidemic, although HIV was commonly diagnosed in areas of high leprosy endemicity<sup>1,2,3</sup>. One of the plausible hypothesis for this rare association in the pre-HAART era is that AIDS-related deaths occurred before the long incubation period led to the appearance of clinical signs and symptoms of *M. leprae*<sup>4,5</sup>. Leprosy is an endemic disease in Brazil, where 38410 new cases were diagnosed in 2005, eventhough free access to treatment is provided by the government<sup>6</sup>. In Brazil the AIDS epidemic assumed enormous proportions and great

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impact on public health. Since 1996 HIV-1 infected subjects in Brazil receive all available antiretroviral drugs, for free, in public health clinics<sup>7</sup>. In 2008, there were 506499 AIDS patients reported in Brazil, and around 94% are receiving free antiretrovirals<sup>8</sup>. Consequently, HIV- infected subjects are presenting longer survival periods, allowing a long-term follow-up<sup>7</sup>. In contrast to what would be expected, the number of HIV and leprosy co-infections does not seem to be increasing, and most cases are not multibacillary.

With the introduction of HAART, clinical improvement, and increase in the CD4 lymphocytes and a HIV viral suppression is observed. Paradoxically, some patients, in the context of this immunological restoration, present the so-called immune reconstitution syndrome, which is characterized by episodes of worsening of cutaneous infections such as herpes zoster (HZV), herpes simplex (HSV), *molluscum contagiosum* (MC), mycobacterial infections and papiloma virus infections (HPV), eosinophylic folliculitis (EF) and leprosy<sup>8,9,10,11, 15, 16</sup>.

The interaction between this two major public

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health issues: leprosy and AIDS is discussed in editorials of important medical publications<sup>8</sup>. We present seven cases of borderline leprosy (four of borderline borderline leprosy (BB) and three of tuberculoid borderline (BT)) in HIV-infected subjects, occurring soon after HAART introduction. Subjects presented with a leprosy type I reaction, which led to the discussion of the immunological aspects involved in the reaction to leprosy and in the immune reconstitution syndrome.

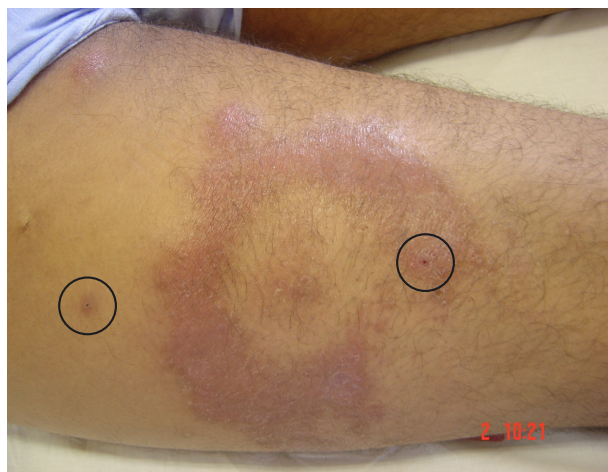
## CASE REPORTS

**Patient 1** – A 31 years old man, mulatto, born and resident in Rio de Janeiro, HIV infected subject who started HAART (Efavirenz, zidovudine and lamivudina) and PCP prophylaxis with sulfamethoxazole and trimethoprim about three months before the current picture. His CD4 count was 40 cells / mm<sup>3</sup> and the viral load (VL) 81,000 copies/ml when he started HAART. Approximately two months later, red maculae appeared, associated with burning and itching, on the trunk. Initially, the use of sulfamethoxazole and trimethoprim was interrupted, and later, ARV; however worsening of the condition continued and he was referred to a dermatologist. The dermatological examination revealed erythematous-infiltrated plaques on the trunk and lower limbs and an erythematous-infiltrated lesion poorly delimited, on the upper right limb. He presented a swollen right ulnar nerve, painful at touch (fig. 1). With the diagnostic impression of MHBB and type I reaction, skin biopsy and bacilloscopy were accomplished. The latter was positive with presence of globia. The histopathological examination confirmed the clinical impression. Administration of prednisone at 1mg/kg/day, was initiated associated to polychemotherapy for multibacillary leprosy (WHO-MDT). The dermatological lesions, as well as the associated symptoms, presented progressive regression.



**Figure 1** Patient 1: Erythematous-infiltrated plaque poorly delimited, on the upper right limb.

**Patient 2** - A 33 years old man, mulatto, military policeman born and resident in Rio de Janeiro, HIV infected. He started ARV treatment (Efavirenz, zidovudine and lamivudine) when his CD4 count was 47 cells / mm<sup>3</sup> and the VL 87,000 copies/ml. Approximately one month after, he presented erythematous-edematous plaques and nodules located in the thighs, legs, trunk, and left scapular area that became painful and warm. On the posterior side of the left thigh, a large erythematous-edematous plaque with a clear center and erythematous-infiltrated satellite lesions were noticed. A few isolated small necrotic crusts were seen inside those lesions. All lesions showed alterations of sensitivity to heat and pain (Fig. 2). After two months, CD4 count was 643 cells / mm<sup>3</sup>. With the diagnostic hypothesis of BB and type I reaction, skin biopsies were done, confirming the clinical impression. Treatment with WHO-MDT associated to prednisone at 1 mg/kg/day was initiated with favorable evolution.



**Figure 2** Patient 2: On the posterior side of the left thigh, a large erythematous-edematous plaque with a clear center and erythematous-infiltrated satellite lesions were noticed. Small necrotic crusts were seen sparsely.

**Patient 3** - A 30 years old white woman, student, born and resident in Rio de Janeiro, with HIV infection diagnosed during pregnancy, (she was approximately in the 30<sup>th</sup> week of pregnancy), was referred to the infectious diseases outpatient clinic. She began HAART, with efavirenz, lamivudine and nevirapine, and approximately two weeks later, presented a cutaneous eruption in her arms and legs, reason for a referral to the dermatology clinic for evaluation of the possibility of a drug eruption. At the dermatological examination, she presented infiltrated erythematous-violet plaques of approximately four centimeters in diameter, on the right upper limb, and a bigger plaque (approximately 10 cm) with superficial desquamation and necrotic crusts (Fig. 3), besides presence of satellite lesions, in her thigh and right buttock. All of the lesions presented impairment of the thermal sensitiv-

ity. She also presented a swollen right fibular nerve. Her viral load was undetectable. Skin biopsy confirmed the clinical impression of BT leprosy and type 1 reaction. One week after, the patient entered labor and was submitted to a Cesarean section. One month after childbirth, she began WHO-MTD, with good response and regression of the lesion, in spite of her precarious adhesion to the treatment. The therapeutics with corticosteroid was not done, because the lesion was already in regression. The CD4 count on that occasion was 475 cells /mm<sup>3</sup>. HAART had been discontinued by the patient.



**Figure 3** Patient 3: Infiltrated erythematous-violet plaque of approximately four centimeters in diameter, on the right upper limb, superficial desquamation and necrotic crusts.

*Patient 4* - A 33 years old man, mulatto, administrative officer, born and resident in Rio de Janeiro, had HIV infection diagnosed since 1997, and was under medical accompaniment. In May / 2004, he went to a dermatological consultation complaining of lack of sensibility in a certain area of the chest. Though not having any dermatological lesion, he was submitted to a skin biopsy. The histological examination suggested indetermined leprosy. He returned only four months later, informing that he had been hospitalized for tuberculous meningitis, when he started HAART. After 3 months of having started the ARV therapy, he noted erythematous lesions on his body. At the dermatological examination, he presented infiltrated erythematous plaques of approximately ten centimeters in diameter, in the trunk, with foveolar aspect and similar smaller lesions on the right arm (Fig. 4), thighs and buttocks. All the lesions presented impairment of the thermal sensitivity. A new skin biopsy was obtained, and confirmed the clinical impression of BT. WHO-MDT was started.



**Figure 4** Patient 4: Infiltrated erythematous plaques with foveolar aspect, in the trunk.

*Patient 5* - A 50 years old white man, born and resident in Rio de Janeiro, HIV infected presented with asymptomatic eritemato-violaceous maculas and papules, localized on his lower limbs, associated with a mild eritematous lesion on his right elbow, approximately two months after HAART introduction, associated with PCP profilaxis with dapsona. He was submitted to cutaneous biopsy with the clinical impression of drug reaction. A week after, he returned presenting new lesions scattered in his trunk and arms, worsened of the established ones, with intense necrosis and ulceration (Fig. 5). Besides, he showed edema of the lower right limb, and palpable peripheral nerves. Eventhough, he had no fever, neither systemic symptoms. Dermatological examination revealed thermal and tactil impairment. Since the introduction of HAART, he had improved his CD4 count from 19 to 288 cells / mm<sup>3</sup>. With these new clinical features, we changed our clinical impression to MHBT and type I reaction, associated with immune reconstitution syndrome. The bacilloscopy accomplished was negative, and histopathological examination confirmed this clinical hypothesis. He was given prednisone at 1mg/kg/day, associated to polychemotherapy for multibacillary leprosy (WHO-MDT). The dermatological lesions, as well as the associated symptoms, presented progressive regression.



**Figure 5** Patient 5: Irregular ulcerated lesions, with focal necrotic crusts and edema, in the lower right limb.

*Patient 6* - A thirty two years old AIDS patient went to dermatologist presenting thousands of plane warts lesions, some of them showing Koebner phenomenon, disseminates on the neck, trunk and limbs. He had began HAART (Biovir, Kaletra) shortly before, and was also under PCP profilaxis with sulxadiazina, pirimetamina and folinic acid. After a few mouths, he presented fever, erythematopapulous lesions disseminated on the trunk and limbs, resembling multiforme erythema. He also had infiltrated auricular lobes, enlarged ulnar nerves and swollen wrists and hands (Fig. 6). These lesions were painful. The bacilascopy was positive (2+) and a cutaneous biopsy was done, confirmig the clinical hypoathesis of leprosy. WHO- MDT, prednisone and thalidomida were started with progressive involution of the lesions. HAART and PCP profilaxis were carried on.



**Figure 6** Swollen fingers, wrists and hands; plane warts are also seen.

*Patient 7*- A 52 years old, female AIDS patient, under irregular anti-retroviral therapy. She noticed erythema-

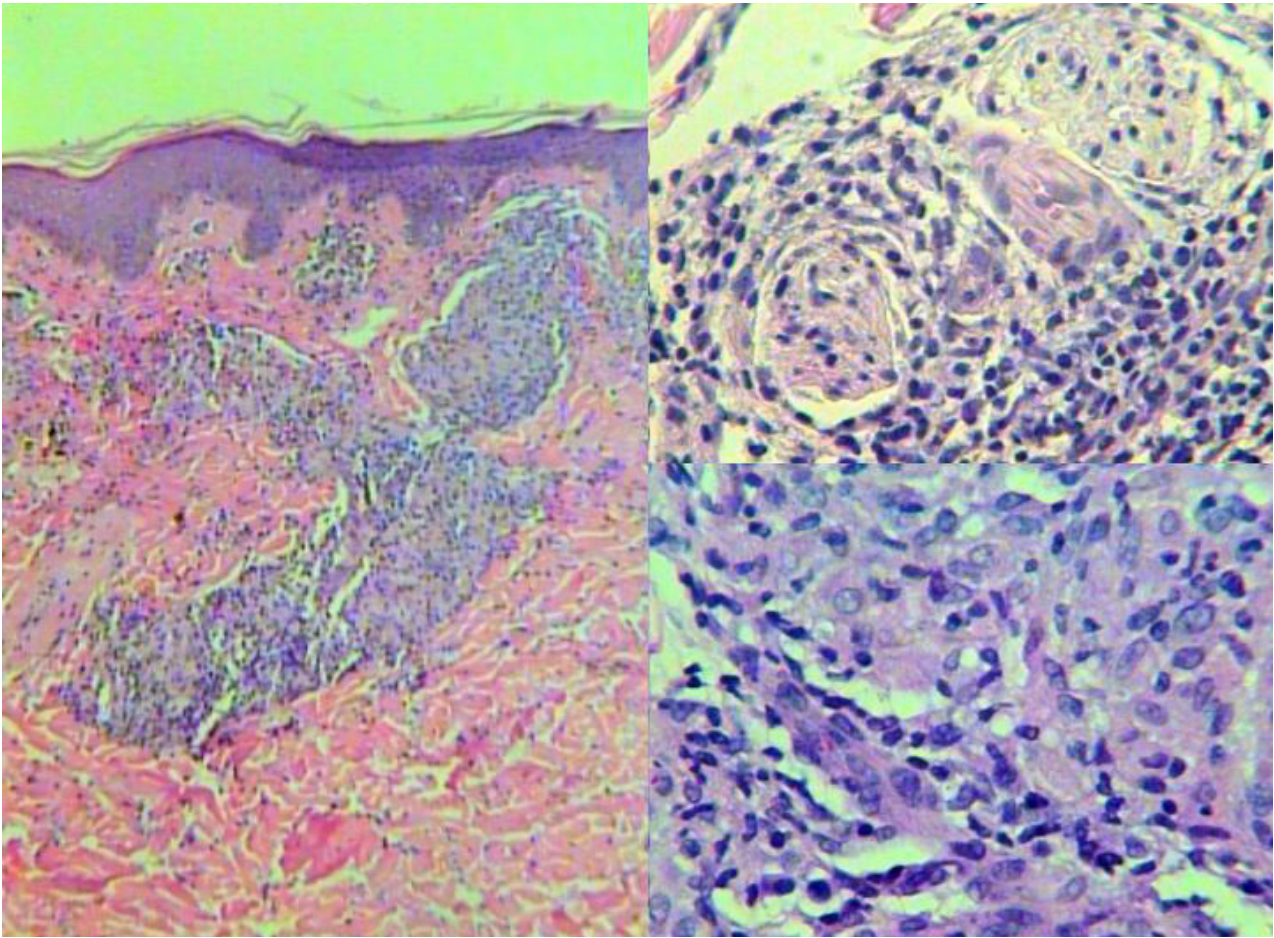
tous lesions on her legs around six months before it began to drain a purulent exudate and presented fever. On dermatological examination, could be observed erythematous violaceous irregular plaques with marked limits, on her legs. These lesions were infiltrated, anesthetic and some of them showed necrosis and ulcerated areas (Fig. 7). A skin biopsy was performed and confirmed the clinical impression of borderline leprosy. She started WHO-MDT and HAART (D4T, 3TC, Ritonavir e Indinavir). The ulcers healed and the lesions became hyperchromic macules. Her viral load lower than 400 copies and CD4 was 461 cells / mm<sup>3</sup> when leprosy was diagnosed, while it was indetectable and 813 cells / mm<sup>3</sup> respectively after the leprosy treatment.



**Figure 7** Erythematous irregular plaques with marked limits with ulcerated areas, on the lower limbs.

### HISTOLOPATHOLOGICAL FINDINGS

The histopathological examination of all the seven cases were similar revealing epithelioid granulomas, lymphoid cells and vacuolized macrophages, throughout the entire dermis, preferably around the neurovascular plexus and adnexial structures, extending also to the hypodermis. In the papillary dermis, areas with edema were observed, and the superficial vascular plexus showed tumefaction of endothelial cells and narrowed lumina, with presence of neutrophiles in the vascular wall. There were discreet focuses of spillover of red cells and a small degree of nuclear fragmentation (Fig. 8). Special staining (Wade method) revealed BAAR in focal distribution with granular morphology in cases 1 and 6.



**Figure 8** Epitelioid granulomas, lymphoid cells and vacuolized macrophages, preferably around the neurovascular plexus and adnexial structures. In the papillary dermis, and the superficial vascular plexus showed tumefaction of endothelial cells and narrowed lumina, with presence of neutrophils in the vascular wall. (HE, x40; x100; x400)

## DISCUSSION AND COMMENTS

The human immunodeficiency virus (HIV) infects, although not exclusively, the helper T lymphocytes (CD4), leading to their destruction. Therefore, as the HIV disease develops, a progressive decrease in the absolute and relative counting of the CD4 cells occurs. When this count is around 200 cells / mm<sup>3</sup> the chance for opportunistic infections is very strong, signaling for need to introduce ARV therapy<sup>8</sup>. In the initial phases of the HIV infection, the patient immune response is mainly of the Th-1 cell type, mediated by interleukin-1 (IL)-2, IL-12 and alpha interferon (INF $\alpha$ ). As the infection progresses, the viral load (VL) increases and CD4 cell count decreases, the patient begins to have a response of the preferably humoral type Th-2, mediated by IL -4, IL-5 and IL-10<sup>8,12</sup>.

With the advent of HAART and its free and universal availability, through the DST/AIDS Program of the Brazilian Ministry of Health, a great impact in the natural

history of AIDS occurred. The patients started not only to present interruption in their progressive immunological deterioration, but also a real reconstruction of their immunological status, with progressive increase of the CD4 cells and decrease of VL, that in several patients remained undetectable during long periods. Such fact resulted in a marked decrease of the opportunist infection episodes - the cause of great morbidity among HIV infected patients and consequently, longer survival and decrease of the mortality rate<sup>7</sup>.

Dermatological alterations occur in the definition of AIDS in almost 68% of the cases<sup>13</sup>. In the patients follow-up emergence of dermatoses are observed. They can then be considered as indicators of immunological stabilization or therapeutic effectiveness, often signaling for a need of a reassessment of ARV therapy. Through cutaneous manifestation, the dermatologist can speculate regarding the patient immunological status, forecasting and helping to implement important therapeutic measures, such as a change of the ARV and the introduction of specific prophylaxes.

It was believed that the frequency of the dermatoses, as well as their clinical profile, would diminish with the adoption of HAART. However, extensive and aggressive pictures of HZV, HSV, HPV, MC, EF and leprosy<sup>8,9,10,11, 15, 16</sup> have been reported, in otherwise healthy patients, during

the improvement phases of their immunological status, the so called "Immunological Reconstitution Syndrome"<sup>7</sup>. These patients would possibly be latent carriers of such etiological agents. When their Th-1 response pattern is rebuilt, they would express the dermatosis in a clinically exuberant way, similar to the reaction of an upgrading of leprosy<sup>8</sup>. In spite of denoting a trend for improvement, the consequences of the immunological restructuring in the skin should be quickly recognized and medicated to avoid future sequels. These sequels can be both aesthetic and functional. The reactive neuritis from leprosy can lead to disability, pain, functional impotence, blindness and sterility, increasing the stigma for these patients.

Leprosy is a chronic, infective contagious illness, caused by the obligatory intracellular parasite *Micobacterium leprae*. Its clinical spectrum is ample and is related to the immune response of the host, specific and genetically defined. While the polar forms (tuberculoid and lepromatous) are immune-defined, the intermediate (borderline) are unstable and subject to modifications both for improvement (approaching immunologically the tuberculoid pole), and for worsening (when approaching the lepromatous pole). These episodes of modification of the immunological profile are called leprosy reactions and are clinically represented by acute outbreaks of the illness. These reactions are classified as type I, that represent improvement reactions inside the spectrum (up-grading) and type II, when they denote immunological worsening (down-grading). The type I reaction is also called reverse reaction, a term that refers to the immunological improvement that occurs in the borderline spectrum, and could be associated with conversion of the Mitsuda reaction and with destruction of BAAR.

The clinical observations suggest that the reactions to leprosy are induced by several factors that interfere with the balance resulting from the interaction of the inherent factors to the host and those inherent to the bacilli. Thus, concurrent infections, the therapeutic effect of the specific medication and the persistence of circulating antigens (bacillary remains or persistent bacilli) are capable to trigger reaction pictures. Thus the reactions can occur as a form of presentation of leprosy, during its treatment or even after suspension of the medication (WHO-MDT)<sup>13, 14, 15</sup>.

Deeps and Lockwood, in a recent paper reported that

since 2003, 19 cases of leprosy reactions were published as IRIS all over the world<sup>7</sup>. We report a series of 7 patients, the largest series to our knowledge.

This seven patients presented were in immunological deterioration induced by AIDS (table 1), before the leprosy diagnosis, meeting the criteria to begin HAART. Due to this, probably, the amount of CD4 cells increased at the same time that a decrease of the viral load occurred, allowing the installation of an immunological profile, basically Th1. In this way, the leprosy infection, that was latent, was exteriorized for the first time, already in a context of reactive improvement.

Skin smears were positive in 3 of our cases, without any correlation with the clinical presentation of leprosy, since these patients were diagnosed BB, BL and BT.

The histopathological correlations are prominent vascular alterations (endothelial hyperplasia with luminal narrowing and red cell spillage) and tissue alterations suggestive of reactive phenomena (interstitial dermal edema and nuclear fragmentation), besides the granulomatous reaction characteristic of leprosy. Those prominent vascular alterations indicate the installation of a reactive picture, since the habitual histological picture of leprosy does not contemplate them. The initial presentation as BT type and the favorable evolution, reinforces the knowledge that AIDS does not interfere with the spectrum nor with the course of leprosy<sup>1</sup>.

The clinical exuberance of the reactive picture was controlled with the use of systemic corticosteroids, in the usual dosis for leprosy reactions. The occurrence of ulcers<sup>11</sup> and necrosis on the cutaneous reaction lesions without systemic symptoms points out to the possibility of IRIS. Although there are no established protocols, it is also recommended that systemic corticosteroids be used for the control of the manifestations in certain clinical cases of immunological restoration syndrome<sup>8, 16</sup>.

Although AIDS has not caused a specific impact on the incidence / prevalence of leprosy in Brazil, it can modify the form of presentation of this mycobacteriosis in the context of the immunological restoration syndrome induced by HAART<sup>17, 18</sup>. The immunological improvement induced by the ARV therapy is favorable both for the infection by HIV and for leprosy; thus it can be inferred that immunological restoration syndrome is for AIDS is similar to what reverse reaction is for leprosy.

**Table1** Cases Summary

Case	Gender /age	HAART	Leprosy	Clinical features and diagnosis	IRS	CD4		Hystopathological findings	Others findings
						before	after		
1	M / 31	Jan / 04	May / 04	Erythematous-infiltrated plaques on the trunk and limbs; swollen right ulnar nerve. BB, type I reaction	60 days	40	130	Granulomatous inflammatory infiltration, in vascular, neural and adnexial dermis; fragmented AFB were seen focally.	Skin smears positive
2	M / 33	Dec / 03	Feb / 04	Erythematous-edematous plaques and nodules in the legs, trunk; large erythematous-edematous plaque with a clear center and satellite on the left thigh, with isolated small necrotic crusts. Sensitive impairment. BB, type I reaction	40 days	47	643	Granulomatous inflammatory infiltration, in vascular, neural and adnexial dermis. AFB negative.	Skin smears negative
3	F / 30	Jun / 03	Jul / 03	Infiltrated erythematous-violet plaques on the right upper limb with superficial desquamation and necrotic crusts; satellite lesions, in her thigh and right buttock. BT, type I reaction	20 days	52	475	Granulomatous inflammatory infiltration with sparce AFB structures.	Skin smears negative

4	M / 33	Jul /04	May / 04 (IL) Aug / 04 (BT)	Infiltrated erythematous plaques, in the trunk, with foveolar aspect and similar smaller lesions on the righth arm, thighs and buttocks. Impairment of the sensitivity. BT, type I reaction	90 days	-	-	A-Mild lymphohystiocitic infiltration, favoring I. B-Granulomatous inflammatory infiltration, AFB negative.	Skin smears negative
5	M / 50	Jan / 05	Mar / 05	Eritemato-violaceous macules and papules, on the lower limbs, mild eritematous lesion on the righth elbow. A week after, worsenig of the established lesions and intense necrosis and ulceration. Edema of the lower righth limb, and palpable peripheral nerves. BB, type I reaction	60 days	19	288	Chronic granulomatous infiltration, AFB negative.	Serology anti-PGL-I positive
6	M / 32	Jun / 04	Sep / 05	Erythematopapulous and painful lesions disseminated on the trunk and limbs; infiltrated auricular lobes, enlarged ulnar nerves and swollen wrists and hands. BL, multiforme erythema	120 days	232	383	Fragmented AFB in focal distribution.	Skin smears +; Serology anti-PGL-I negative
7	F / 54	May / 02	jun / 02	Erythematous violaceous irregular plaques with marked limits, on the legs. These lesions were infiltrated, anesthetic and some of them showed necrosis and ulcerated areas. BT, type I reaction	-	461	813	Chronic granulomatous infiltration.	Skin smears positive

- CD4.** cell count (Th lymphocytes / mm<sup>3</sup>) before starting HAART and at the moment of leprosy reaction (during HAART).  
**IRS** period between starting HAART and beginning of leprosy reaction / immune reconstitution syndrome  
**HAART** highly active antiretroviral therapy  
**IL** Indetermined leprosy  
**BT** Borderline tuberculoid leprosy  
**BB** Borderline borderline leprosy



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