Corticosteroid therapy in borderline tuberculoid leprosy patients co-infected with HIV undergoing reversal reaction: a clinical study

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Summary

Background: Mycobacterium leprae and HIV cause infectious diseases of great concern for the public health care sector worldwide. Both are especially worrisome diseases when patients become co-infected and exhibit the expected clinical exuberance. The objective of this study was to evaluate episodes of reversal reaction (RR) and the effect of the use of corticosteroids on the treatment of borderline tuberculoid leprosy patients co-infected with the human immunodeficiency virus (HIV).

Methods: This is a retrospective cohort study in which the clinical manifestations of the patients and their responses to corticosteroid therapy were observed. Variables were analysed during and after multidrug therapy between the first and last days of prednisone, which occurred up to a maximum of 6 months after initiating corticosteroid therapy.

Results: A total of 22 HIV-positive and 28 HIV-negative cases were included. Loss of sensitivity and neural thickening were statistically significant while clinically ulcerated lesions were only observed in the co-infected group. Most patients were diagnosed with leprosy in the presence of RR and six patients manifested RR as an immune reconstitution inflammatory syndrome. On average, both groups received similar doses of corticosteroids (difference of 0·1 mg/kg/day).
Conclusions: It is of special interest that the clinical manifestations in both groups were found to be similar and that overall improvement occurred as a result of corticosteroid therapy.

Trial registration
This work was submitted to and approved by the Ethics Committee on Research of the Oswaldo Cruz Institute on August 8, 2011 (registration 616/11).

Keywords: Infectious Diseases, Leprosy, Co-infection, HIV, Corticosteroids

Background
Leprosy, caused by *Mycobacterium leprae*, and the human immunodeficiency virus (HIV) infection are two diseases that present major public health challenges. In 2013, there were 215,656 new leprosy cases detected worldwide. In Brazil alone, there were 31,064 new cases in the following year. In that same year internationally about 37 million people were infected by HIV approximately 734,000 of whom were in Brazil. The sheer magnitude of these stable detection rates for both diseases in recent years underscores the importance of more closely monitoring the occurrence of this co-infection.

According to the World Health Organization (WHO), Brazil is one of the few countries in which leprosy and AIDS are endemic. The Brazilian Ministry of Health offers free treatment for both diseases and plays an important role in the study of co-infected individuals. Unfortunately, there are still no available data from any previous studies regarding the prevalence and overall incidence of this kind of co-infection.

During the clinical course of leprosy, patients may present with episodes of acute inflammation associated with altered immune responses. Referred to as reactional episodes, there are two distinct types: reversal reactions (RR) and erythema nodosum leprosum (ENL). Such reactions may occur before, during or after leprosy treatment. Reversal reactions are the leading cause of hospitalisation and are known to provoke the onset of life-long neurological sequelae. While little is known about the influence of HIV infection on leprosy, it is believed that HIV infection may be the singular major risk factor in the development of reactional episodes, especially among paucibacillary patients.

Some studies have recently demonstrated that after the introduction of highly active antiretroviral therapy (HAART), RR occurred as a manifestation of a new clinical presentation, called the immune reconstitution inflammatory syndrome (IRIS), characterised by a high HIV viral load reduction and an increase in CD4 T cells. It has been surmised that HIV infection could exacerbate the pathogenesis of leprosy lesions, making them more severe, as shown in many case reports of co-infected patients presenting ulcerations during reversal reaction. At the same time, it was likewise expected that HIV/ *M. leprae* patients would present a more exuberant neurological clinical condition since the use of HAART and other medications commonly administered to HIV patients have been known to also lead to the development of peripheral neuropathy.

Treatment of RR is aimed at controlling acute inflammation, relieving pain, and avoiding nerve damage. The use of corticosteroids to treat RR was first reported in 1952 and, at that time, recommendations were made to start treatment as soon, and as cautiously, as possible, noting the potential for the development of opportunistic diseases and metabolic alterations.
A number of later studies suggested that corticosteroid therapy might also benefit patients co-infected with HIV.\textsuperscript{15,16,20,21} However, to date, there have been no published clinical studies on the co-infected. As a result, there is still no consensus on the optimal use of corticosteroids as to dosage, duration, and treatment safety with these patients.

In this study, we analysed HIV comorbidity with the \textit{borderline tuberculoid} (BT) clinical form of leprosy (according to the classification of Ridley and Jopling\textsuperscript{22}), which is the most prevailing clinical manifestation in co-infected patients in Brazil, as described in many reports.\textsuperscript{7,10–12,16} Although the association between \textit{M. leprae} and HIV infection may not have a direct impact on public health,\textsuperscript{23} the clinical management and proper care of reactional states are extremely important to those most involved in this issue, and the community itself. The goal of this study is to evaluate and compare the epidemiological and clinical characteristics of BT patients with RR in HIV-positive and HIV-negative groups.

### Methods

An analytical retrospective cohort study was carried out between January 1996 and September 2012 on the available medical records at the Souza Araújo Clinic (ASA) / Leprosy Laboratory (LAHAN)/Fiocruz, in the city of Rio de Janeiro.

Both male and female patients 15 years of age or older and undergoing regular multidrug therapy (MDT) for leprosy were included in the study. An analysis was made of the first RR episode (confirmed by histopathology) among the BT patients, who were divided up into two groups according to their serologic status for HIV infection: 1) an HIV/\textit{M. leprae} co-infected group; and 2) an HIV-negative control group. HIV-infected patients were defined according to current Brazilian Ministry of Health guidelines.\textsuperscript{24}

Epidemiological and clinical data were evaluated in two stages: the first involved the RR diagnosis itself; and the second was at the end of corticosteroid therapy (considering a cutoff of 6 months for those patients who had been administered corticosteroid therapy for a longer period of time) (Figure 1).

As the location of the research at hand is a national reference centre for the treatment of leprosy, the staff physicians are highly experienced and qualified in carrying out a rigorously thorough history and physical examination while being sensitive about detecting significant alterations in the development of the disease. As such, the following signs and symptoms were clinically and qualitatively assessed: loss of sensitivity (evaluated with anesthesiometer), lymphadenopathy, arthralgia, nerve pain, edema, weight loss, neural thickening, fever, malaise, myalgia, orchitis, paresthesia, hyperesthesia, and nasal and visual complaints. Furthermore, the number of affected body segments (head, anterior chest, posterior chest, right arm, left arm, abdomen, back, right leg, and left leg) was assayed; and the averages of these numbers were calculated for each group. Type of skin lesion, neuritis, degree of disability, and the Mitsuda test results (Figure 1) were also analysed.

Moreover, immunological status and the use of HAART and IRIS (according to the hallmarks described by Deps and Lockwood\textsuperscript{12}) (Figure 1) were likewise evaluated. IRIS was defined as the presence of reaction at any time during the first 6 months of HAART together with a decrease of more than 1 log in the HIV-1 viral load and if a reaction occurs during the first 6 months of HAART in association with an undetectable HIV-1 viral load among naive patients with no laboratory test data.
Corticosteroid therapy was administered if a patient had begun prednisone at the beginning and/or end of MDT. Whether a patient needed corticosteroid therapy beyond the 6 months of the study (Figure 1) was also evaluated. For such patients, the observed dose was the one given during the sixth month of corticosteroid therapy, which was subdivided into three dosage groups, as follows: 0 mg; from 5 mg to 15 mg; and 20 mg or more. Moreover, the total dosage averages (mg/kg/day) were calculated for both co-infected and non-co-infected groups and compared. Finally, the need for pulse therapy and/or hospitalisation was also reviewed.

Statistical analyses were performed using SPSS® version 16.0 software based on information regarding the variables stored on the above-mentioned database. Categorical variables were analysed using the chi-square test for Person or Fisher (to expected values of less than 5); and continuous variables were examined via the t-Student test, with a 5% statistically significant rate. Furthermore, analyses were performed by the logistic regression model to compare group variables in order to keep track of any interference of possibly confounding factors.

Results

Epidemiological and Clinical Characteristics

During the study period, 50 borderline tuberculoid patients were diagnosed with RR, 28 of whom were HIV-negative and 22 HIV-positive. A majority of patients in both groups was male (53% of the HIV-negative and 54% of the HIV-positive subjects). The average age of the control group was 38 (SD = 11.12) and that of the co-infected group was 40 ($P = 0.657$;
SD = 12.33). Seventeen of the co-infected patients (77%) were on HAART, four (18%) were not in HIV treatment; and in one case (5%), this information was not registered. Most patients had CD4 > 200 cell/mm.³ It is worth noting that six of the co-infected patients (27%) manifested RR as IRIS.

Upon a RR diagnosis, a great majority of patients presented skin lesion plaques (88%) followed by macules (14%) with no significant differences between the groups (P = 0.683 and P = 0.444 for plaque skin lesions and macules, respectively). Among the HIV-positive, ulcerated skin lesions were only observed in two IRIS patients (9%; P = 0.189). At the second stage of the RR evaluation, i.e., at the 6th month, macular lesions were more prevalent within the HIV-negative group (21%; P = 0.438) while plaque lesions were the most frequently found among the co-infected (17%; P = 0.915).

Neuritis was present in four within the control group (14%) and six among the co-infected patients (27%), P = 0.254 while most subjects in both groups had a disability grade of zero: 75% at baseline and 70% at the end of the review.

The average number of body segments affected by skin lesions was five (SD = 3.271) in the HIV-negative and four (SD = 3.075) in the HIV-positive groups at baseline (P = 0.157). In the end, the average was one segment in each group (SD = 2.231 among the controls and SD = 2.625 in the HIV/M. leprae group; P = 0.673).

The Mitsuda test results in both groups of patients were greater than or equal to 3 mm (67% HIV-negative and 77% HIV-positive patients; P = 0.462).

All variables had been considered in the statistical analysis, in Figure 2 are shown only the most prevalent clinical manifestations observed in both groups.

Among the signs and symptoms analysed at the end of the assessment, neural thickening (P = 0.024) and loss of sensitivity (P = 0.029) were considered statistically significant (Figure 2).

**Analyses of Variables Related to the Use of Corticosteroids**

It was observed that the majority of patients in both groups initiated MDT while undergoing reversal reaction (P = 0.919). At the end of MDT, about 62% of all patients were still using corticosteroids (Table 1).

![Figure 2. Initial and final evaluation of the main signs and symptoms of RR.](image-url)
The majority of both groups required an extension of the 6-month period; and no patient underwent pulse therapy for RR. Of the total 50 patients, only two HIV-positive ones required hospitalisation for RR clinical treatment.

Corticosteroid dosage at the 6th month of treatment did not differ between the groups, as can be seen in Table 1. The average total corticosteroid dosage within the HIV-negative and HIV-positive groups, respectively, was 0·4 mg/kg/day (SD = 0·12) and 0·5 mg/kg/day (SD = 0·19), $P = 0·102$.

**Discussion**

To date, there have been few published studies related to HIV- *M. leprae* co-infection. It was perhaps ultimately possible to gather together these 50 patients because both diseases are endemic in Rio de Janeiro. And ASA/LAHAN, a national reference centre for the treatment of co-infected patients, has a readily-available population at its disposal along with an extensive research database.

Some demographic characteristics described here such as average age and the higher proportion of men than women are similar to those examined in a number of other epidemiological studies conducted with co-infected patients in Brazil.\(^7,11,12,16,21,25,26\)

Since the HIV virus affects cellular immunity and causes deficiencies in granuloma formation, a reduction in the response to the Mitsuda antigen in HIV-positive patients was expected, as demonstrated by other authors.\(^27\) In the present work, among the HIV/*M. leprae* patients, the test remained positive, a fact also previously reported by other authors,\(^28\) which is perhaps explicable by the preservation of a specific cellular immunity against *M. leprae*.

As treatment progressed, a cutback in the number of lesions in both groups was observed. Despite being uncommon in RR, in the present study, ulcerated lesions were only found among IRIS patients, also observed in other reports.\(^10,12,14,15\) A reminder that detecting this kind of lesion is a procedure that must be conducted with caution; and the decision as to whether or not to extend the use of corticosteroid therapy should be taken with care.

It is assumed that HIV infection may aggravate the nerve damage caused by the bacillus in association with antiretroviral drug toxicity by causing a synergistic effect among these

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### Table 1. Evaluation of the use of corticosteroids

| Characteristics                                    | HIV                |
|----------------------------------------------------|--------------------|
|                                                    | Negative N/Nn (%)  | Positive N/Np (%) | Total N/Nt (%) | $P$ value |
| MDT initiated with corticosteroids                 | 20/28 (71·4)       | 16/22 (72·7)      | 36/50 (72)     | 0·919     |
| MDT ending with corticosteroids                    | 17/28 (60·7)       | 14/22 (63·6)      | 31/50 (62)     | 0·833     |
| Corticosteroids used for more than 6 months        | 18/28 (64·3)       | 14/22 (63·6)      | 32/50 (64)     | 0·962     |
| Dosage of corticosteroid at the 6th month          |                   |                   |                |           |
| 0 mg                                               | 10/28 (35·7)       | 8/22 (36·4)       | 18/50 (36)     | 0·858     |
| 5 mg to 15 mg                                      | 12/28 (42·9)       | 8/22 (36·4)       | 20/50 (40)     |           |
| 20 mg or more                                      | 6/28 (21·4)        | 6/22 (27·3)       | 12/50 (24)     |           |

(*%) Percentage of the valid total. N: number of patients; Nn: total number of HIV-negative patients; Np: total number of HIV-positive patients; Nt: total number of patients.

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factors. This phenomenon has also been observed in other viral co-infections with leprosy, such as HTLV-1 and hepatitis B and C, and can change the host immunity, generating more severe neurological damage.²⁹

In the present study, it is likewise noteworthy that most of the signs and symptoms of RR did not appear to be more severe among the co-infected patients. There did not seem to be any significant worsening in comparison to the uninfected, which has been verified by a number of other reports.¹¹,¹⁵,¹⁸,³⁰–³² However, the neural thickening and loss of sensitivity detected in the final group evaluation were statistically significant. Nonetheless, some aspects of the immunopathological mechanisms involved in the interaction between M. leprae and HIV infection remain nebulous.

Overall, it was found that RR among the HIV-positive patients appeared to be slightly more neurologically compromised than the RR in their non-co-infected counterparts even though neuritis and degree of disability were similar in both groups. It is, of course, quite difficult to separate the synergy between the peripheral nerve involvement caused by M. leprae and the neuropathy associated with HIV and/or the effects of HAART.

After initiating HAART followed by the subsequent increase in CD4 T cells, RR may manifest as IRIS among the HIV-positive,¹⁰–¹²,³⁴,³⁵ as was seen in the present study in which most patients were on HAART and had CD4 > 200 cell/mm.³ In defining the moment this phenomenon takes place, Deps and Loockwood¹² suggested considering four different classifications. Nonetheless, immunological studies remain rare. Pires et al.¹¹ have found that 75% of BT patients developed RR as a manifestation of IRIS while, interestingly, our study found this same result in only six (27%) patients.

The major goals of any RR treatment are to control acute inflammation, relieve pain, and reverse nerve damage. Prednisone, which remains the drug of choice, including for co-infected patients,¹⁰,¹¹,¹⁶,³⁵ must be administered immediately to avoid sequelae.³⁶–³⁸ It is initially given in doses of 1–2 mg/kg/day and should be withdrawn only very gradually in all patients.³⁶–³⁸

Again, in the present study, both groups received similar doses of corticosteroids (an additional 0·1 mg/kg/day for the HIV-positive patients); and no statistically significant differences were found between the groups.

Pulse therapy is indicated for patients with an uncontrolled reactional condition.³⁷ In our cohort, no patient showed a need for pulse therapy. In some cases, a higher level of care is necessary such as hospitalisation to better control the effects of reaction, which in our case only occurred in two co-infected patients.

Sarno et al. (2008) showed that the HIV/M. leprae group manifested more reactions at diagnosis than the control group although both groups have had similar cumulative rates over time. The reason behind the increased frequency of reaction in co-infected patients is not yet clear but may be explained by the characteristic dysregulation of the immune system as a result of HIV infection. However, in the present study, most patients in both groups presented RR at the moment of diagnosis.

Regarding the duration of corticosteroid therapy, WHO recommends treating RR and neuritis for from 3–6 months in a specialised reference centre.³⁹ Again, most patients in the two groups continued corticosteroid therapy beyond the WHO-recommended 6 month period, indicating the need for continuity in treatment monitoring. It has been demonstrated that patients receiving a high initial dose of corticosteroid have fewer relapses and less nerve damage.⁴⁰ Nevertheless, it is important to emphasise that despite the high dosages still in use at the end of the present study, the need for a larger dose and prolonged treatment in some
cases may have been influenced by the fact that ASA/LAHAN is a referral centre for the treatment of severe cases of reversal/neuritis reaction. Moreover, while corticosteroid is considered a mainstay in treating leprosy reaction, caution should be exercised so as to prevent any negligence or abuse. Prolonged use of these drugs may predispose patients to adverse events, opportunistic infections, and illnesses like diabetes, arterial hypertension, osteoporosis, glaucoma, and dermatological diseases.\textsuperscript{15,41–44}

The major contribution of the present study was its novel approach to analysing a variety of data that made it possible to simultaneously compare RR in HIV-positive and HIV-negative patients. Most importantly, the results showed that corticosteroid therapy was effective in both these groups with major improvements in their cutaneous, systemic, and neural manifestations, particularly in comparison to their initial evaluations.

To conclude, it is our conviction that leprosy and HIV control programmes should be integrated to optimise the diagnosis, treatment, and care of co-infected patients. For this purpose, serologic tests for HIV could also be offered to RR patients. In addition, it should be emphasised that further studies aiming to better understand the epidemiological and clinical associations of these patients are a priority.

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Authors’ contributions

PJSA participated in the design of the study, carried out data acquisition, and drafted the manuscript. MAVBH performed the statistical analysis. AMS, JACN and VMM reviewed the medical content of the text. FDG helped draft the manuscript; and ENS participated in its design and coordination. All authors contributed to the writing of the final manuscript; and all have read and approved it.

The author(s) declare that they have no competing interests.

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