Epidemiological and clinical patterns of 92 patients co-infected with HIV and *Mycobacterium leprae* from Rio de Janeiro State, Brazil

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**Background:** Many articles have shown that HIV infection can modify the clinical course of leprosy, but very scant epidemiological and clinical data about this co-infection are available in the peer-reviewed literature.

**Methods:** We herein describe the geographical distribution and demographic characteristics of 92 HIV/*M. leprae* co-infected patients assisted in a Brazilian Leprosy referral center. A multivariate analysis was performed in order to establish clinical factors associated with type 1 reaction.

**Results:** Co-infected patient admissions have steadily increased over the last years at this referral center. Most patients were men, with a mean age of 32.3 years and presenting with the paucibacillary form of leprosy. The use of antiretroviral therapy (ART) was the only factor associated with type 1 reaction. Most patients were living in the metropolitan area and the north sub area of Rio de Janeiro City.

**Conclusion:** Co-infected patients receiving ART have a greater chance to develop type 1 reaction. Patients living with both HIV and leprosy are likely to live in regions characterized by a high density impoverished population.

**Keywords:** Brazil, Leprosy and HIV co-infection, Social geography of leprosy, Type 1 reaction

**Introduction**

Several studies have documented the complex relation between socioeconomic context and the spread of infectious diseases. Such a relation may help to explain geographic and socio-demographic overlapping and eventual clustering of different infectious diseases on a single geographic area or affected population. Such superimposed burdens may include different tropical diseases and HIV/AIDS in contexts of poverty and pronounced socioeconomic and geographic heterogeneity.

Since the beginning of the AIDS epidemic, in the early eighties, the role of co-infections with major tropical diseases like tuberculosis, leishmaniasis and malaria has been studied in Brazil.1,2

As recently highlighted by an editorial in *Lancet Infectious Diseases*, in years to come the proper management of different co-infections will be one of the key battlegrounds in the worldwide effort to curb the epidemic and provide optimal care for those already living with HIV/AIDS.3

Despite the evidence that HIV infection can modify the natural history of leprosy,4–5 little epidemiological data on HIV/*M. leprae* co-infection have been published in the literature.5

Leprosy is primarily found in countries situated in tropical and subtropical regions of the world. According to WHO reports, 105 countries reported 219 075 new cases during 2011.6 Although there has been a declining trend in overall prevalence and new-case detection in recent years, leprosy remains a relevant public health care problem in Brazil, yet to be satisfactorily curbed. In 2011, the prevalence rate of the disease was 1.54 cases per 10 000 habitants and 33 955 new cases of leprosy were detected all over the country.9

By the same token, HIV infection remains one of most serious health care problems due to its pandemic nature and high morbidity and mortality rates in areas where potent therapies remain elusive. WHO estimates that 2.5 million people became HIV infected in 2011 and 34 million people were living with HIV at the end of 2011.10 In Brazil, the AIDS epidemic has been stabilized within the last 10 years. In 2011, the incidence rate was 20.2 per 100 000 inhabitants with 38 776 new cases of AIDS being registered throughout the country.11

To the best of our knowledge, no reliable estimates of the number of AIDS/leprosy co-infected individuals have been published to date. However, analyses documenting the superimposed burden...
of both diseases in the same impoverished areas and estimates clinical cases of co-infection overall show that both diseases overlap to some extent in Brazil as well as in Sub-Saharan Africa and Southeastern Asia.

In the last decade, leprosy and HIV co-infection gained the attention of the scientific community due to the possibility of type 1 reaction after the initiation of combined antiretroviral therapy (ART). Patients with leprosy who are co-infected with HIV seem to be at higher risk of developing type 1 reaction. It is broadly accepted that reaction is the result of a shift in the patient’s level of inflammation and/or cell-mediated immunity which, in turn, may lead to accelerated nerve damage and serious physical disabilities.

In order to evaluate the clinical and epidemiological patterns of HIV/M. leprae co-infected patients in Brazil, data from a major leprosy referral center located in the City of Rio de Janeiro, were compiled and analyzed. Thematic maps were used to assess the geographical distribution of co-infected patients, according to the address of their household. In addition, factors associated with the type 1 reaction were evaluated, profiling from socio-demographic and clinical data from their medical records.

**Material and methods**

**Study site**

The City of Rio de Janeiro is the major and most important municipality in the state of the same name with a population of roughly 6,320,446 people. Despite being the second wealthiest city in the country (the first being Sao Paulo), Rio de Janeiro has been affected by entrenched socioeconomic inequalities. A substantial proportion of its population still lives in precarious living conditions. The city has 160 neighborhoods and is historically divided into four regions referred to as southern, northern, western and central areas or zones.

According to the last Brazilian Census in 2010, Rio de Janeiro State had a population of 15,989,929 people, the vast majority of whom (96.7%) were living in urban areas, especially in the Greater Metropolitan Area of Rio de Janeiro capital city. Rio de Janeiro State is subdivided in 5 meso-regions, namely metropolitan, southern, northern, northwest, and central.

The Leprosy Outpatient Clinic at FIOCRUZ is a center of excellence for leprosy diagnosis, management and care, as well as contact tracing. Under the auspices of the Brazilian Ministry of Health, it has been responsible for evaluating HIV/leprosy co-infected patients since 1989. As a referral center, the clinic’s coverage is not limited to any specific geographical area. Notwithstanding, most of its clientele consists of individuals from the Metropolitan region of Rio de Janeiro City due to their easy access to the Clinic, but also includes patients from other cities located in the State of Rio de Janeiro, and a sizeable minority of patients from all over the country. Patients may be referred to the Clinic by any health service (public or private) nationwide, may spontaneously seek care, or may have been appointed to the Clinic after diagnosis of their index cases (contact tracing).

**Study design**

An analysis of socio-demographic, clinical and geographical data from the Leprosy Outpatient Clinic cohort of patients living with HIV/M. leprae was carried out in order to evaluate the clinical and epidemiological profile of this population. Patient information is systematically collected at the time of leprosy diagnosis at Fiocruz and it is maintained in a dedicated database over time. Data from all co-infected patients included in the present study were then retrieved from this database.

**Definitions and the clinical routine**

All patients were evaluated according to standardized clinical and dermatological procedures. For diagnosis and classification, skin lesion biopsies were obtained and samples were stained with hematoxylin and eosin. Detection of acid-fast bacilli was performed via Wade’s modification of the Ziehl-Nielsen method. Slit skin smears were obtained from six body sites and stained for acid-fast bacilli detection by Ziehl-Nielsen technique. The bacilloscopic index was calculated by way of the Ridley and Jopling logarithmic scale. The lepromin test was measured 28 days after the intradermal injection of 0.1 mL of heat-killed M. leprae in the anterior forearm. The result was scored as either negative if ≤5 mm, or positive if ≥5 mm. Leprosy was then diagnosed and classified according to Ridley-Jopling criteria, including pure neural (PN) and indeterminate (I). The WHO disability grading was evaluated. Grade 0 corresponded to the absence of all anesthesia, visible deformity, and neurological damage.

Type 1 reaction was clinically defined by the presence of inflammatory skin lesion (new lesion or preexisting skin lesion which becomes inflamed) or by the presence of acute neuritis associated or not with skin lesion. Dermatopathological diagnosis criteria for type 1 reaction were based on the presence of epithelioid cells granuloma. This study identified two main patterns of type 1 reaction depending on the severity of the tissue inflammatory changes: 1. mild acanthosis and exocytosis; well developed cohesive epithelioid granulomas intermingled with few lymphocytes; blood vessels, arrector pili muscles, adnexa and nerve bundles; sparse multinucleated cells and small foci of red blood cell leakage; and 2. Exuberant changes such as moderate to severe acanthosis, spongiosis and exocytosis; epithelial apoptosis and basal epidermal erosion; severe dermal inflammatory infiltration, including granulomas dissociated by marked edema or centered by necrosis in addition to numerous giant cells and red blood cell extravasation.

Diagnosis of HIV infection included the performance of two tests; the immuno-enzymatic method (ELISA) and immunofluorescence or western blot.

The variables under analysis refer to patients’ information at diagnosis and comprise gender, age, education, marital status, leprosy clinical form, data from the WHO operational classification, disability grade, bacilloscopic index, reaction to the lepromin test, use of ART and CD4 lymphocyte count.

**Geoprocessing and mapping**

Information on patients’ household addresses from 1989 until 2011 were georeferenced in order to build dot density thematic maps showing the geographical distribution of leprosy cases included in the present study in the cities within the geographical perimeters of the State of Rio de Janeiro as a whole and in the neighborhoods located within the city of Rio de Janeiro. Maps were built using the ArcMap 9.3 program (ESRI, Redlands, CA,
USA). Each dot represented one randomly-distributed case within Rio de Janeiro State and Rio de Janeiro City.

Different maps were built in order to illustrate the geographical distribution of new leprosy cases and AIDS cases in the State of Rio de Janeiro reported to the respective national notification systems. Reported cases of leprosy retrievable from the respective national notification system were only available from 2001. As the length of time covered by the present study was long, even for chronic infectious diseases, maps were divided in two time periods: 2001–2005 and 2006–2010. Epidemiological changes that occurred during this long period may have caused modifications in geographical and temporal patterns.

To take into account differences in population size and number of cases, average incidence rates of AIDS and leprosy were calculated for those given periods, for each municipality under analysis, using standardized population sizes as denominators.21

Statistical analysis

Bivariate analyses were performed to compare reactional vs non-reactional patients via the χ² test. Multivariate analysis was performed using logistic regression to assess factors associated with type 1 reaction. A significance level of 5% was adopted.

Results

Patient characteristics at diagnosis

From January 1989 to December 2011, 92 leprosy patients with an HIV positive serology were referred to the FIOCRUZ Leprosy Clinic. Most of these patients (83/92; 90%) had the diagnosis of HIV established prior to the leprosy diagnosis and for 9 (10%) the diagnosis of HIV was made during leprosy follow-up.

Out of the 92 patients, fifty two (57%) were male and the mean age at diagnosis was 32.3 (18–72) years old. The marital status and the time of schooling were available for 86 of the 92 patients included. The great majority of them (70/86; 81%) were unmarried (single or divorced). Most (66/86; 77%) had had 1–8 years of formal schooling, whereas 21% (18/86) had attended school for more than 8 years and 2% (2/86) had never been to school.

Although a great majority of the patients were classified as paucibacillary (71/92; 77%), because they had a bacilloscopic index equal to zero, almost half (41/92; 45%) had a negative lepromin test (<5 mm). We were able to identify the disability grade of 90 patients and most of them (62/90; 69%) had a disability grade equivalent to zero at leprosy diagnosis, whereas for 21% (19/90) it was grade 1, and for 10% (9/90), grade 2.

Out of the 92 patients included in the study, 33 (36%) patients were undergoing leprosy reaction at the time of the diagnosis, of whom 32 (97%) had type 1 and one patient a type 2 reactions.

The patient characteristics at the first visit and cross-comparisons between the characteristics of those patients with type 1 reaction with those without reaction are summarized in Table 1 (exception made to the single patient with type 2 leprosy reaction).

Ridley and Jopling criteria were used to classify the 59 patients who did not present leprosy reaction at diagnosis, as follows: two (3%) were classified as having tuberculosis; 33 (56%), as borderline tuberculoid; four (7%) as borderline borderline; five (8%) as lepromatous borderline; two (3%) as lepromatous lepromatous; 11 (19%) as indeterminate, and two (3%) as having the pure neural clinical form.

More than two-thirds (65/91; 71%) of the patients under analysis were receiving ART before being diagnosed with leprosy. For one patient data on the use of ART was missing, CD4 lymphocyte counts were available for this first visits for 62 (67%) patients and their mean CD4 lymphocyte count was 371.3 cells/ mm³. HIV viral load count was available for 58 of the 92 (63%) patients at leprosy diagnosis and it was undetectable in 28 from the 58 (48%) patients. We were able to identify the past medical history of 68 (74%) patients from the 92 included in the study. Out of these 68 patients, 17 (25%) patients presented tuberculosis prior to leprosy diagnosis and 15 (22%) had presented others opportunistic infections: neurotoxoplasmosis, pneumocystosis, Cytomegalovirus retinitis, Kaposi sarcoma, isosporiasis, esophageal candidiasis and Mycobacterium Avium intracellulare infection.

Factors associated with type 1 reaction

In bivariate analyses, a low CD4 lymphocyte count and the use of ART at the time of leprosy diagnosis were found to be associated

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<tr>
<th>Table 1. Characteristics of the patients at leprosy diagnosis</th>
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<tr>
<td>Characteristics</td>
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<tr>
<td>Male sex</td>
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<tr>
<td>Mean age (min-max)</td>
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<tr>
<td>IB:0</td>
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<td>Using ART</td>
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<td>Negative LT</td>
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<tr>
<td>Mean CD4 count</td>
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<td>Undetectable HIV viral load</td>
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IB: bacilloscopic index; LT: lepromin test; NS: not significant.

<sup>a</sup> CD4 count and HIV viral load data were not available for 1 and 5 patients, respectively.

<sup>b</sup> CD4 count and HIV viral load data were not available for 28 patients.
with the development of type 1 reaction. Such findings were further assessed using logistic regression, as summarized in Table 2. The use of ART remained as the single independent factor associated with the outcome (type 1 reaction). The high proportion of patients without a valid CD4 for this initial visit precluded any further analysis of this covariate.

Temporal and spatial distribution of co-infected patients

The number of co-infected patients referred to Fiocruz Leprosy Clinic has increased over the last few years (1989–2011; Figure 1). In contrast, the prevalence and incidence rates of leprosy have been decreasing in Rio de Janeiro State as reported by the national notification systems: 24.9/10 000 and 21.8/100 000 inhabitants in 1990, respectively, versus 0.9/10 000 habitants and 10.6/100 000 habitants in 2011.

The general reduction in the detection rate of leprosy and incidence rate of AIDS in the cities and time period under analysis are visualized in Figure 2. The rates of leprosy and AIDS were higher in some regions of the State, particularly the metropolitan area and the northern area of Rio de Janeiro City, and in some municipalities on the coastal plains and the southern part of the Rio State.

The AIDS map for the second period shows a more homogeneous epidemic accompanied by rates reductions in the metropolitan region of the City of Rio de Janeiro and no great variation among Rio State cities.

Almost all of the 92 co-infected patients included in the present study were living in the metropolitan region of Rio de Janeiro City by the time they were diagnosed with leprosy (Figure 3). Half (46/92) of the patients were living in the City of Rio de Janeiro, 41 (45%) were living in other cities within the Metropolitan area of Rio de Janeiro City, and only five (5%) patients were referred to Fiocruz from others cities of the Rio de Janeiro State outside the metropolitan area of Rio de Janeiro City.

Among the 46 patients living in the City of Rio de Janeiro, 24 (52%) were from the northern area of the City, 15 (33%) from the western area, five (11%) from the central area, and two (4%) from the southern area of the City (Figure 4).

Most of patients (71/92; 77%) were natives of the State of Rio de Janeiro, Fifteen (16%) patients had migrated to Rio de Janeiro from the Brazilian northeast, and six patients (7%) came from other States in the Brazilian southeast. The majority of the patients (81/92; 88%) were referred to the Clinic by other public health care services.

Discussion

The findings from our work are by no means representative of all cases of HIV/ M. leprae co-infection living in Rio de Janeiro as the study was based on a non probability haphazard sample from a single center for leprosy treatment in the city of Rio de Janeiro. As a referral center, the clinic receives more frequently patients with severe presentations of the disease such as type 1 reaction. Still, the amount of missing data, especially related with the characteristics of the HIV infection, made further analysis difficult.

However, up to 2013, the 92 co-infected patients in the present work make up the largest HIV/M. leprae cohort under analysis in the international literature. We strongly believe that the majority of the patients co-infected with HIV/M. leprae in the state of Rio de Janeiro have been followed up at Fiocruz.

The present study shows that an increasing number of co-infected patient have been admitted over the last 15 years at the leprosy outpatients Clinic. In contrast, the burden of leprosy and AIDS has declined in Rio de Janeiro over the same period of time.

One possible explanation for this recent increase is that since 1997 ART has become available for all patients with AIDS in Brazil. Some authors have suggested that the initiation of ART is associated with clinical presentation of leprosy. Thus, the appearance of clinical signs of leprosy in individuals with HIV does not seem to be a manifestation of immune suppression but rather of immune reconstitution.

Although it was expected that HIV infection would lead to an increase in the frequency of multibacillary forms of leprosy, the present study shows that HIV/M. leprae co-infected patients can present all clinical forms of leprosy. Actually, our findings documented a higher percentage of patients presenting paucibacillary leprosy. Paucibacillary leprosy is characterized by a strong cellular immune response with skin lesions containing a well organized

Figure 3. Spatial distribution of HIV/Mycobacterium leprae co-infected patients followed up at Fiocruz per city of leprosy diagnosis, Rio de Janeiro State, 1989–2011. Source: Brazilian National System of Disease Notification and Brazilian Institute of Geography and Estatistics.
We may hypothesize that the underlying antigenic stimulus associated with the progressive restoration of the immune competence after the initiation of ART may be associated with granuloma formation and the subsequent appearance of tuberculoid skin and nerve lesions.

Type 1 reactions are secondary to an enhancement of cellular immunity and delayed hypersensitivity to M. leprae. It is well known that ART is associated with a dramatic HIV viral load reduction and a subsequent increase in CD4 T cells, a key marker of the partial recovery of the immune function. To fully elucidate whether the high frequency of type 1 reaction observed at diagnosis, as documented by our study, is a consequence of immunological recovery triggered by the use of ART is not within the scope of the present study. However, initiation of ART has been reported to be associated with activation of sub-clinical M. leprae infection and exacerbation of pre-existing leprosy lesions. As such, the use of ART was the only independent factor associated with the presence of type 1 reaction at diagnosis (Table 2).

The socio-demographic characteristics of the co-infected patients at their first visit to the referral center presented herein were similar to the ones observed among cases notified in Brazil nationwide. National databases related to both diseases show a higher concentration of male patients between 30 and 59 years old, as was also observed in the present study. Interestingly, no patients under 15 years of age were admitted to the Clinic even though this category accounted for 3.4% of all new leprosy cases in the State of Rio de Janeiro in 2010. This must due to the low incidence of AIDS cases in children in Brazil (8.1/100,000 in 2010).

In the present study, the preponderance of single or divorced patients was noteworthy. It proved impossible to identify the HIV transmission patterns of these patients. However, national data indicate that HIV transmission is mainly concentrated in and around sexual networks, especially among men who have sex with men. Most of the patients in our study had 1–8 years of schooling. Neglected diseases, particularly leprosy, are often found in poor, marginalized sections of the population with restricted access to formal education.

The maps visualizing the distribution of leprosy and AIDS cases throughout the state documented a preponderance of co-infected patients living in the metropolitan area of Rio de Janeiro City. Few co-infected patients have come from other areas of the state, such as the eastern and northeastern, despite the high AIDS incidence and leprosy detection rates in these areas. This may be due to many causes, such as the low number of co-infected individuals and the less than optimal quality of local health care services.

We did not demonstrate any association between the distribution of the patients in the City of Rio de Janeiro and the Rio de Janeiro State with the prevalence rates of leprosy and AIDS in each City subarea and state regions. Most of the patients were living in the metropolitan area of the City and the northern region of the Rio de Janeiro City, closely followed by those from the western zone. Regions such as the metropolitan area and the northern and western regions of Rio de Janeiro City are characterized by a great number of favelas (slums), with high density population, which may be a major contributor to the spread of leprosy. However, as Fiocruz referral center is located in the northern region of Rio de Janeiro City, it is not possible to attribute the distribution of the
co-infected patients demonstrated in the present study as an actual pattern or rather a consequence of inclusion bias.

Leprosy distribution is characterized by its heterogeneity. Factors such as rapid city growth, migration, access to health services, high population density, as well as impoverishment and non-hygienic living conditions are among the determinants that most influence the high geographic endemicity of leprosy.26–29

Authors’ contributions: The study was planned and supervised by ENS and MH and executed by VMM and MH. AM performed the histopathologic analysis. AMS, MCGG, JACN and VMM were treating physicians of the patients. VMM wrote the first draft and ENS, MH and FIB critically reviewed the manuscript. All authors approved the final version. ENS is guarantor of the paper.

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Ethical approval: The Oswaldo Cruz Institute ethics committee granted ethical approval for this study. All the patients gave informed written consent.

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