

## **Leprosy presenting as immune reconstitution inflammatory syndrome: proposed definitions and classification**

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HIV infection has been strongly associated with mycobacterial infections such as tuberculosis (TB) and *M. avium-intracellulare* infection. In the early stages of the HIV epidemic it was predicted that leprosy might be worsened in the presence of HIV infection. It was anticipated that having HIV infection might be a risk factor for developing leprosy, and that more patients would develop the anergic, lepromatous type. However, paradoxically, leprosy in HIV infection seems to be associated with immunologically active types of disease and now may present as an immune reconstitution syndrome. Here we review the ways in which HIV and leprosy interact at the time of presentation and propose four different ways in which leprosy may present in this setting.

Highly antiretroviral active therapy (HAART) is now widely used for the treatment of HIV infection in many countries, including those endemic for leprosy. HAART suppresses HIV multiplication and so permits both quantitative and functional reconstitution of the immune system. However, a dysregulated recovery of pathogen-specific immune responses may occur, especially in the first months of HAART, with the development of unusual and strong inflammatory response against pathogens, the so-called immune reconstitution inflammatory syndrome (IRIS).<sup>1</sup> The most common pathogens implicated in IRIS are *M. tuberculosis*, cytomegalovirus, B and C hepatitis viruses.

In 2003, the first case report of leprosy presenting as an IRIS in an HIV infected patient newly started on HAART was published<sup>2</sup> and subsequently other numerous case reports have been published. Most of those cases have used the following diagnostic criteria: HIV infected patients who developed leprosy or Type 1 leprosy reaction (T1R) within 6 months of starting HAART, accompanied by a significant increase in CD4+ T cells. These different case reports have highlighted different aspects of this interaction. A systematic review of these

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case reports is therefore needed so that common features of this presentation can be identified and important aspects are illustrated.

Before these data can be presented it was necessary to review the case definitions and discussion on the features of IRIS and particularly leprosy occurring as an IRIS since this informs our own definition for this review. IRIS is a clinical deterioration occurring as a direct consequence of rapid and dysregulated restoration of antigen specific immune response during HAART,<sup>3</sup> and diagnostic criteria should identify three aspects: clinical presentation, immune restoration and timing of onset.

In 2004, major and minor diagnostic criteria for IRIS in AIDS were proposed.<sup>4</sup> Major criteria are: an atypical presentation of opportunistic infections or tumour in patients responding to HAART, and decrease in viral load at least 1 log<sub>10</sub> copies/ml; the minor criteria are: an increase in CD4+ cell count after HAART, an increase in immune response specific to a relevant pathogen and spontaneous resolution of infection without specific antimicrobial therapy or tumour with continuation of HAART.

Some authors have suggested that, for a diagnosis of IRIS to be made, including for leprosy as IRIS, either the clinical presentation and/or clinical course of the disease should be atypical and be consistent with an intense inflammatory response.<sup>4-6</sup> In leprosy this would pertain in the case of a T1R. We therefore concluded that an appropriate case definition for leprosy associated with IRIS in AIDS should include: leprosy and/or T1R and ENL developing within 6 months of starting HAART; advanced HIV infection; low CD4+ count before starting HAART and, CD4+ count increasing after HAART.<sup>7</sup> Ideally, both viral load and CD4+ cell count should be used as diagnostic criteria. If data on viral load is not available then there should be an increase in CD4+ count associated with starting HAART.

We then used these case definitions to define all the published cases of HIV leprosy which were then analysed and are presented here. The different clinical and laboratory aspects of the data are presented and discussed in the context of other published data relating to both leprosy and HIV infection. We also propose that four subgroups of leprosy IRIS can be distinguished.

## **Methods**

### DATA SOURCES AND SEARCH STRATEGY

MEDLINE and PUBMED databases were searched in January 2009 to identify all case reports of leprosy as IRIS in HIV infected patients. The following search terms were used: immune reconstitution phenomenon, immune reconstitution inflammatory syndrome (IRIS) and immune reconstitution disease (IRD). Key words were leprosy, Hansen' disease, IRIS, immune reconstitution phenomenon, IRD, HIV and AIDS. Manuscripts in English, Spanish, French and Portuguese were considered.

### CASE DEFINITION FOR IRIS IN LEPROSY

Leprosy and/or T1R and ENL developing within 6 months of starting HAART; advanced HIV infection; low CD4+ count before starting HAART, and CD4+ count increasing after HAART.

## DATA SYNTHESIS

Twenty three cases were identified in 14 publications. Nineteen cases met the inclusion criteria and were included in the analysis. Data was collected on the clinical and laboratory manifestations, with particular focus on HIV related data such as CD4+ count and viral load.

**Results**

## CLINICAL PRESENTATION OF LEPROSY ASSOCIATED WITH IRIS IN AIDS PATIENT

Of the 21 published cases 17 (81%) were men and four (19%) women with a mean age 36.7 years-old (range 25–54 years) (Table 1).<sup>2,8–18</sup>

Out of 19 IRIS cases, 13 (62%) were from Brazil, four (19%) from India, two from French Guiana (9.5%), one from Martinique (4.75%) and one (4.75%) from Uganda.

From those 21 IRIS cases, at the moment of leprosy diagnosis 17 (89.5%) had a histopathological diagnosis of TT or BT leprosy. Pignataro *et al.*<sup>8</sup> described a patient who was clinically diagnosed as having BL, but had a Mitsuda skin test response of 10 mm. Talhari *et al.*<sup>19</sup> describe two patients diagnosed as BL and upgraded to BT after some weeks of continuing HAART. We therefore classified the patients as having BT type leprosy, so giving 18 (85.7%) IRIS cases (Table 1).

Atypical leprosy lesions were reported in a few cases. Nearly all of them had evidence of T1R. T1R plus neuritis (NT) were clearly described in eight (42%). One patient was described presenting NT without T1R (5.2%).<sup>16</sup> Six (28.5%) cases were reported with ulcerated lesions and an intense inflammatory process on histological examination (Table 1).<sup>8,9,17,19</sup>

Two leprosy patients reported as having IRIS by Martiniuk *et al.*<sup>20</sup> did not meet our diagnostic criteria for leprosy presenting as IRIS. In patient 1, the authors did not make any comments about immune recovery (increasing T CD4+ count or decreasing viral load after HAART) and in patient 2, the authors considered leprosy occurring as IRIS 2 years after starting HAART (we have considered within 6 months).

## EVIDENCE OF IMMUNE RESTORATION

The mean CD4+ count (pre-HAART) in these patients was 91 cells/ml (ranged 6–299 cells/ml). Twelve patients (57.2%) had CD4+ counts less than 100 cell/ml, seven (33.3%) between 100 and 200 cell/ml, and only two (9.5%) had CD4+ counts between 201–300 cell/ml (Table 1).

Nineteen patients had a CD4+ count at the time of diagnosis of leprosy as IRIS with a mean of 248 cells/ml (ranged 70–504 cell/ml). There was a more than two fold (2.63 increasing) in the CD4+ counts between diagnosis of leprosy and the diagnosis of IRIS, and CD4+ count during IRIS. The increment of the CD4+ during IRIS was calculated as the value of CD4+ count at the moment of IRIS minus the CD4+ count at baseline for each patient, the mean of those differences was 4.34 fold (ranged from 1.5 to 12.6).

## TIMING OF ONSET

The onset of IRIS in these leprosy patients had a mean and median of 8.7 weeks (range 4–24 weeks). Most of the patients (57%) developed leprosy as IRIS between 8–12 weeks (2–3 months) after initiating HAART (Table 1).

**Table 1.** Clinical and laboratorial aspects of the 21 IRIS cases

| Origin of patient/reference | Clinical manifestation | Age | RJ/IRIS classification | Sex | No. weeks HAART | CD4 × 10 <sup>6</sup> /L |      | VL copies/ml |        |
|-----------------------------|------------------------|-----|------------------------|-----|-----------------|--------------------------|------|--------------|--------|
|                             |                        |     |                        |     |                 | Baseline                 | IRIS | Baseline     | IRIS   |
| Uganda (2)                  | SL/T1R                 | 37  | BT/IRIS 1              | M   | 4               | 10                       | 70   | 120 000      | 1000   |
| Brazil (8)                  | SL/U/T1R               | 48  | BT/IRIS 1              | M   | 8               | 147                      | 499  | –            | –      |
| Brazil (8)                  | SL/U/T1R               | 32  | BL/IRIS 3              | F   | 4               | 37                       | 200  | –            | –      |
| French Guiana (9)           | SL/U/T1R/NT            | 54  | BB/IRIS 1              | M   | 6               | 87                       | 257  | 19 000       | < 650  |
| French Guiana (9)           | SL/U/T1R/NT            | 40  | TT/IRIS 4              | M   | 8               | 130                      | 278  | 40 701       | 68     |
| Martinique (9)              | SL/T1R/NT              | 39  | BT/IRIS 4              | F   | 12              | 31                       | 171  | 62 700       | 50     |
| Brazil (10)                 | SL/T1R                 | 38  | BT/IRIS 1              | F   | 8–24            | 73                       | 270  | –            | –      |
| Brazil (10)                 | SL/T1R                 | 25  | BT/IRIS 1              | M   | 8–24            | 35                       | 100  | –            | –      |
| Brazil (11)                 | SL/NT/T1R?             | 32  | TT/IRIS 1              | M   | 8               | 7                        | 90   | –            | –      |
| India (14)                  | SL/T1R/NT              | 28  | BT/IRIS 1              | M   | 4               | 125                      | 280  | 150 000      | 1750   |
| Brazil (12)                 | SL/T1R                 | 40  | BT/IRIS 3              | F   | 8?              | 223                      | 436  | 23 000       | < 50   |
| India (13)                  | SL/T1R/NT              | 32  | B ?/IRIS 2             | M   | 4               | 108                      | 224  | –            | –      |
| Brazil (16)                 | SL/NT                  | 35  | BT/IRIS 1              | M   | 14              | 92                       | 426  | –            | 8300   |
| India (15)                  | SL/T1R/NT              | 35  | BT/IRIS 1              | M   | 12              | 299                      | 504  | –            | –      |
| India (15)                  | SL/T1R/NT              | 42  | BT/IRIS 1              | M   | 8               | 114                      | 184  | –            | –      |
| Brazil (17)                 | SL/U/T1R               | 28  | BT/IRIS 4              | M   | 10              | 33                       | –    | 6310         | –      |
| Brazil (17)                 | SL/T1R                 | 27  | BT/IRIS 4              | M   | 4               | 170                      | –    | 9230         | –      |
| Brazil (18)                 | SL/T1R                 | 32  | BT/IRIS 1              | M   | 8               | 14                       | 172  | 213 000      | 69 000 |
| Brazil (18)                 | SL/T1R                 | 53  | TT/IRIS 2              | M   | 8               | 104                      | 235  | –            | –      |
| Brazil (19)                 | SL/U/T1R               | 32  | BL/BT/IRIS 1           | M   | 4               | 71                       | 257  | –            | –      |
| Brazil (19)                 | SL/T1R                 | 25  | BL/BT/IRIS 4           | M   | 24              | 6                        | 77   | 100 000      | IND    |

Legend: RJ – Ridley-Joplin; SL – skin lesion; U – ulceration; T1R – type 1 reaction; NT – neuritis.

**Table 2.** Distribution of the 21 IRIS cases within leprosy IRIS classification

|                       |                         | IRIS Classification |   |   |   | Total |
|-----------------------|-------------------------|---------------------|---|---|---|-------|
|                       |                         | 1                   | 2 | 3 | 4 |       |
| Origin of the patient | <i>Brazil</i>           | 7                   | 1 | 2 | 3 | 13    |
|                       | <i>French Guiana</i>    | 1                   | 0 | 0 | 1 | 2     |
|                       | <i>India</i>            | 3                   | 1 | 0 | 0 | 4     |
|                       | <i>Martinique</i>       | 0                   | 0 | 0 | 1 | 1     |
|                       | <i>Uganda</i>           | 1                   | 0 | 0 | 0 | 1     |
| Sex                   | <i>Female</i>           | 1                   | 0 | 2 | 1 | 4     |
|                       | <i>Male</i>             | 11                  | 2 | 0 | 4 | 17    |
| Ulceration            | <i>No</i>               | 9                   | 2 | 1 | 2 | 14    |
|                       | <i>Yes</i>              | 3                   | 0 | 1 | 2 | 6     |
| Leprosy reaction      | <i>T1R</i>              | 8                   | 1 | 2 | 3 | 14    |
|                       | <i>T1R + Neuritis</i>   | 4                   | 1 | 0 | 2 | 7     |
| Ridley-Joplin Class   | <i>TT</i>               | 1                   | 1 | 0 | 1 | 3     |
|                       | <i>BT</i>               | 9                   | 1 | 1 | 3 | 14    |
|                       | <i>BB</i>               | 1                   | 0 | 0 | 0 | 1     |
|                       | <i>BL</i>               | 1                   | 0 | 1 | 1 | 3     |
| CD4+ baseline         | <i>0–100</i>            | 8                   | 0 | 1 | 3 | 12    |
|                       | <i>101–200</i>          | 3                   | 2 | 0 | 2 | 7     |
|                       | <i>201–300</i>          | 1                   | 0 | 1 | 0 | 2     |
| CD4+ IRIS*            | <i>0–100</i>            | 3                   | 0 | 0 | 1 | 4     |
|                       | <i>101–200</i>          | 2                   | 0 | 1 | 1 | 4     |
|                       | <i>201–300</i>          | 4                   | 2 | 0 | 1 | 7     |
|                       | <i>&gt; 300</i>         | 3                   | 0 | 1 | 0 | 4     |
| HAART Scheme*         | <i>2 NRTI + 1 PI</i>    | 3                   | 0 | 1 | 1 | 5     |
|                       | <i>2 NRTI + 1 NNRTI</i> | 4                   | 2 | 1 | 0 | 7     |
|                       | <i>1 NRTI + 2 PI</i>    | 1                   | 0 | 0 | 0 | 1     |
|                       | <i>3 NRTI</i>           | 1                   | 0 | 0 | 1 | 2     |

\*There are some missing information about CD4+ IRIS and HAART Scheme.

Legend: NRTI – Nucleoside reverse transcriptase inhibitors: zidovudine (ZDV), stavudine (d4T), lamivudine (3TC), ddI (didanosine), abacavir, tenofovir.

PI – Protease inhibitors: atazanavir, indinavir, Kaletra (lopinavir + ritonavir), nelfinavir, saquinavir. NNRTI – Non-nucleoside reverse transcriptase inhibitors: efavirenz, nevirapine.

#### ANTIRETROVIRALS AND IRIS

Data was available on anti-retroviral treatment for 15 (71.4%) cases, in 12 (80%) AZT was used. Some combination such as AZT + lamivudine (3TC) was used in eight patients (53%) and AZT + 3TC + abacavir was used in three (20%). However, efavirenz, nelfinavir, didanosine, nevirapine, kaletra, indinavir also were used in combinations (Table 2). There was no apparent relationship between the development of leprosy as IRIS and any particular antiretroviral.

#### Discussion

It is a little surprising that there appears to be so few cases of leprosy presenting as IRIS. This is in contrast to tuberculosis where there are substantial numbers of cases being reported. However, there may be an ascertainment bias and we were only able to look at published cases. Thus there are probably many more cases. Some will not be recognised as leprosy, many will not be reported and only a small number will be published as case reports. It is

therefore important that surveillance studies should be set up to document this phenomenon. These would probably have to be set up at regional level to ensure the adequate recruitment of leprosy cases and then identify those who had leprosy as IRIS.

The clinical picture in this case series is of patients with highly immunologically active leprosy who present after immune reconstitution. Nearly all the cases had the tuberculoid type of the disease, with very active, florid skin lesions. By comparison when TB occurs as IRIS most cases have had a typical clinical presentation.<sup>21–23</sup> Most patients also had a leprosy reaction, a further episode of immunological activity. Making comparisons about the frequency of T1R in HIV and non HIV infected patients is difficult because T1R is the commonest complication of borderline leprosy, occurring in at least 30% of patients in most cohort studies, and only very small numbers of patients with leprosy as IRIS have been described.

However, an increase to 90 or 100% having reactions would be highly significant. This again needs to be tested with larger numbers of patients. The reactions also appear to be atypical with florid skin lesions and frequently prolonged and paradoxically needing prolonged immunosuppression.

Probably, HIV infected patients with poor immune recovery after initiations of HAART have subclinical leprosy and those patients with an intermediate rate of immune recovery develop leprosy with normal presentation. Occurrence of atypical clinical presentation with florid lesions or intense T1R and neuritis occur in those patients with a dysregulated immune recovery.

#### IMMUNE MECHANISMS

The factors that determine the CD4+ T cells responses to antiretroviral treatment are only partly known and depend on both the host and the virus. Considerable individual variation in the reconstitution of CD4+ T cells has been noted.<sup>24</sup> An early increase in both CD4+ and memory CD4+ cells is noted 4 weeks after starting HAART (an increase of 1.42 times compared to the baseline for the memory CD4+) and this increase persists through 16 weeks (1.56 times) and up to 48 weeks (1.89 times). However, significant increases in naïve CD4+ lymphocytes and percentage of activated CD4+ and CD8+ T cells have been noted within 48 weeks of starting HAART.<sup>25</sup> This early rise (4–12 weeks) of CD4+ lymphocytes probably results from a redistribution of CD4+ cells from lymphoid tissue.<sup>26</sup> This would also fit with the reported timing of presentation of leprosy lesions.

Following the stoppage of HIV replication after the initiation of HAART, a very rapid increase in peripheral CD4+ cell that were trapped in the lymphoid tissue, is noted particularly in the first 3–6 months. The second phase, memory CD4+ count present a slower increase at 4–6 years, with contribution of naïve CD4+ cells from thymus.<sup>24,26</sup>

Apart from those unmasking cases described originally as leprosy associated with IRIS, when both leprosy and T1R developed after starting HAART,<sup>2,8,10,14,15</sup> a few IRIS cases presented with other timings. Leprosy as IRIS has also occurred as T1R in pre-existing leprosy or skin lesions suggestive of leprosy before starting HAART.<sup>8,13,18</sup> One case of probable leprosy relapse after starting HAART was also published.<sup>17</sup>

Two published cases as leprosy in HIV positive patients were considered to be mimicking IRIS because they had not started HAART at the time T1R was diagnosed.<sup>27</sup>

Immune restoration in leprosy as IRIS might be demonstrated either by an increase in circulating CD4+ T cells (most usual) or by detecting CD4+ T cells in the skin lesions. Demonstrating an increase in CD4+ T cells in lesions is only possible when the early lesion

is visible and has been biopsied. Furthermore, doing counts of CD4+ cells in skin lesions has not been standardised.

Sarno *et al.*<sup>28</sup> have reported that a lower CD4+ cell count at the time of HIV diagnosis is associated with a shorter time to developing leprosy.

#### LEPROSY REACTIONS

It is striking that many of these patients had clinical evidence of T1R, often with unusually florid clinical features.

HIV infection does not appear to alter the histological appearance of leprosy lesions. These remain typical across the spectrum with or without HIV infection. Further analysis of the leprosy lesions at the time of IRIS is needed to establish whether there are any unique features in this setting.<sup>29,30</sup> Typically there are low numbers of T cells (most CD8+ T cells) in lepromatous lesions and parasitised macrophages cells; and in tuberculoid lesions, normal granuloma formation and T cells infiltrate (most CD4+ T cells). In this timing set, HIV infection before leprosy, cellular immune response represented by lepromin reaction, lymphoproliferation and INF-gamma release were relatively affected in both lepromatous and tuberculoid forms. However, during the T1R, those who had a tuberculoid type, had a positive lepromin response.<sup>30</sup> Associated to an unresponsiveness of BT/HIV patients to the lepromin skin test, a failure on T cells to proliferate in response to *M. leprae* has been also demonstrated.<sup>31</sup>

In leprosy lesions from co-infected patients, tissue production of IFN-gamma has been presumed since HLA-DR is expressed as are ICAM-1 and TNF-alfa.<sup>30,31</sup> During the immune restoration due to HAART the CD4+ and CD8+ lymphocytes expressing activation antigen HLA-DR decrease significantly during the first 16 weeks.<sup>25</sup> The decrease in activation marker expression supports the hypothesis that viral replication drives immune activation.<sup>32</sup>

The Mitsuda skin reaction may change from negative to positive after starting HAART therapy,<sup>12,18,33</sup> however this changed from 10mm to 7mm in case 2 reported in Pignataro *et al.*<sup>8</sup>

#### PROPOSAL OF A NEW CLASSIFICATION FOR LEPROSY ASSOCIATED WITH IRIS IN AIDS

We used the current IRIS definition of leprosy as IRIS to identify two forms of leprosy as IRIS occurring in the first few months of HAART. The first type is an inflammatory 'unmasking' of a previously untreated infection, in this case by *M. leprae*.<sup>3</sup> The second type is as a paradoxical clinical deterioration in pre-existing leprosy when the patients has a HAART associated T1R. It is also possible that co-infected patients diagnosed with leprosy before starting HAART or starting MDT could develop a leprosy reaction after HAART and this might also be an IRIS.

Using data on timing and clinical presentation of those 21 published cases of leprosy as IRIS we have identified four possible situations when a case of leprosy and/or T1R can be called IRIS in AIDS patients.

Type 1. Unmasking – when patients develop leprosy or T1R after starting HAART (Figure 1). These patients have not been diagnosed with leprosy. They are probably incubating leprosy and the disease is only manifest after the immune restoration that occurs caused by HAART. Of the 21 published cases, 12 (57%) were in the unmasking group (Table 2).<sup>2,8–11,14–16,18–19</sup>

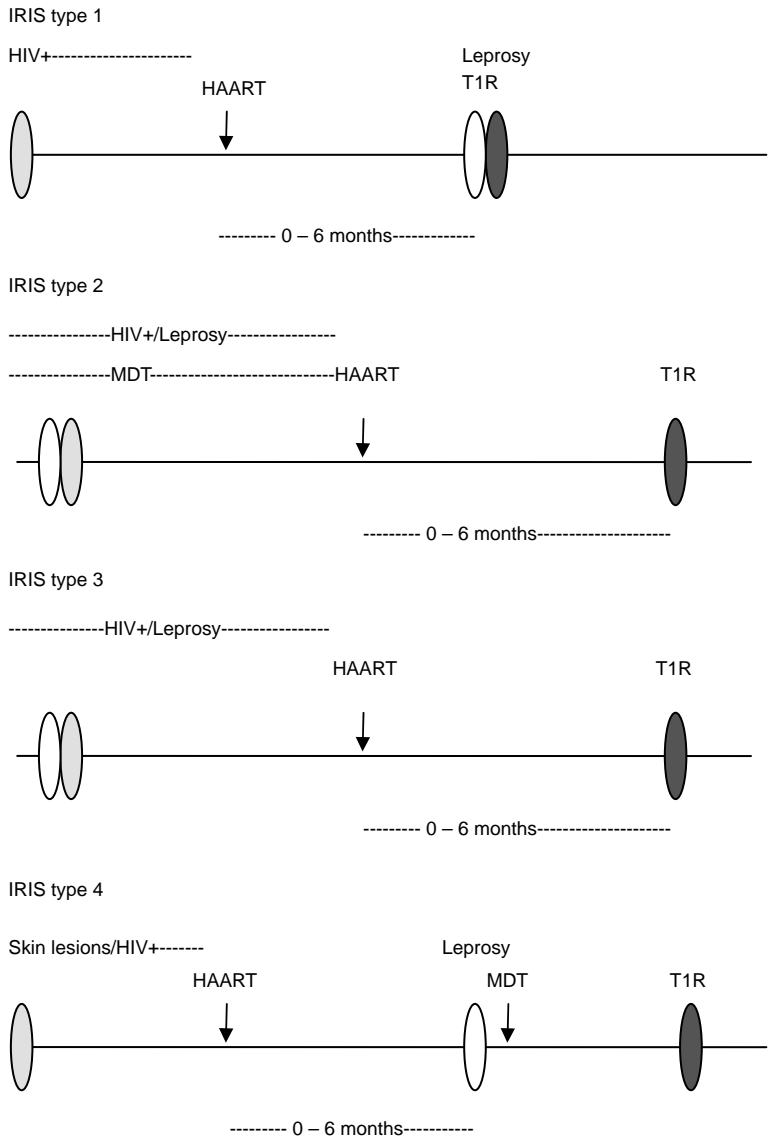


Figure key

|         |      |     |
|---------|------|-----|
| Leprosy | HIV+ | T1R |
|         |      |     |

Leprosy – leprosy infection; HIV+ – HIV infection; MDT – Multi-drug therapy; HAART – Highly Active Anti-retroviral Therapy; T1R – Type 1 Reaction; ----- - period of time; \_\_\_\_\_ - time life.

Figure 1. Types of IRIS occurring in leprosy and HIV co-infection.



Type 2 – Overlap of immune restoration (paradoxical) – when leprosy has already been diagnosed before starting HAART. When MDT and HAART are started within 3 months, T1R occurs as a paradoxical reaction (Figure 1). Two (10.5%) of 21 leprosy as IRIS published cases, are in this category (Table 2).<sup>13,18</sup> T1R represents an exacerbated immune-inflammatory response against *M. leprae* and is related to reactivation of the cell-mediated immune (CMI) response.<sup>34</sup>

Type 3 – Undiagnosed leprosy or previously treated leprosy occurring at least 6 months before HAART. When HAART is introduced, T1R occurs (Figure 1). Two (10.5%) published cases were in this category (Table 2).<sup>8,1</sup>

Type 4 – Unmasking followed by overlap of immune restoration after HAART and MDT. When within 6 months after start HAART, leprosy has been diagnosed and MDT started. Later the patient develops T1R (Figure 1). From the 21 leprosy as IRIS published cases, five (23.8%) fell into this classification (Table 2).<sup>9,17,19</sup>

## Conclusions

The most common IRIS classification among the published cases was IRIS category 1 in 12 patients (57%), unmasking leprosy from a subclinical *M. leprae* infection.

The development of leprosy as an IRIS appears to be associated with a 1.6 increase in the CD4+ count from the initial pre-HAART count.

The CD4+ count can help doctors to identify leprosy as IRIS in AIDS is CD4+ count, but clinical situations should be interpreted carefully to avoid misdiagnosis. Clinical and immunological data are still lacking to explain the whole phenomenon.

Reactions are very common in this group of patients so the optimal way of giving immunosuppression to already immune-suppressed patients needs to be carefully tested and evaluated.

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