Immune Reconstitution Syndrome in Patients Treated for HIV and Tuberculosis in Rio de Janeiro

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We made a retrospective longitudinal study from January 2000 to January 2003 to examine cases of immune reconstitution syndrome (IRS) and its incidence rate in tuberculosis (TB)-human immunodeficiency virus (HIV) coinfected patients. The incidence rate (IR) was calculated using a Poisson regression. The confidence interval (CI) that was stipulated was 95%. IRS occurred in 10/84 HIV and TB-positive patients; nine of them were on highly active anti-retroviral therapy (HAART) during a mean of 61.7 (±59) days following the introduction of antiretrovirals. Lymph-node enlargement was the sole clinical manifestation. CD4 counts were <100 cells/mm³ in 50% of the patients, at the time of TB diagnosis. All but two patients were treated with prednisone, and recovered from TB within a mean of 91 days (±30 days). One relapse of TB was observed, but there were no IRS-related deaths. The incidence rate was higher (IR=11.18; CI, 1.41-88.76) in patients that had superficial lymph node enlargement at the moment of TB diagnosis (not associated with TB), extrapulmonary TB (IR=1.97; CI, 0.44-8.79), were antiretroviral naive (IR=1.85; CI, 0.48-7.16), and CD4 counts <100 cells/mm³ (IR=1.50; CI, 0.40-5.59), although with a wide CI. IRS was frequent in our sample, occurred more frequently in HIV-naive patients with lymph-node enlargement and extrapulmonary TB. No cases of new pulmonary lesions or worsening of pulmonary infiltrates were observed.

Key-Words: AIDS, immune reconstitution syndrome, tuberculosis, HAART, lymph node enlargement, paradoxical reaction.

A paradoxical worsening of preexisting lesions or the appearance of new lesions in patients with tuberculosis (TB) during appropriate anti-TB therapy was first reported more than four decades ago [1]. The development or worsening of lymphadenopathy has been the most-commonly-reported exacerbation [2-4]. Other manifestations include recurrent fever, enlargement of pulmonary lesions, and/or the appearance of new lesions [2,5-7]. More recently, a similar phenomenon was observed in Human Immunodeficiency Virus (HIV) positive patients that achieved an undetectable viral load after Highly Active Anti-retroviral Therapy (HAART) introduction, allowing a subclinical disease to manifest its symptoms as a result of the improvement of the immune response. In these cases pathogens other than M. tuberculosis can be detected [8,9]. Autoimmune disorders, like Graves disease and Sarcoidosis, were also reported to appear as an Immune Reconstitution Syndrome (IRS) manifestation [10].

Our objective was to describe IRS in HIV-TB patients during specific therapy for TB, and estimate the incidence rate.

Materials and Methods

Study Design

This is a retrospective and longitudinal study with review of cases included in a survival study.

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performed. CD4 and CD8 counts and viral load were obtained each four to six months, as recommended by the Brazilian Ministry of Health [11].

Definition Criteria for IRS
The criteria were worsening of TB symptoms during appropriate therapy, excluding resistance, lack of adherence, or other differential diagnoses [3,12].

Incidence Rate Calculation
The IRS incidence rate was calculated as the number of IRS cases over the total amount of person-years. Person-years were calculated as the time that the patient was under observation in the study.

A Poisson-regression model was used to estimate IRS incidence in groups of the following indicator variables: I) naïve for ARV; II) CD4 cell count ≤ 100/mm³; III) presence of adenomegaly during TB diagnosis, excluding ganglionar TB; and IV) TB clinical presentation, defined as pulmonary, extrapulmonary, and disseminated.

Results
IRS occurred in 10/84 cases selected for this study (12%), including seven males and three females. Table 1 shows TB clinical forms and demographic data in IRS patients.

All but one patient in this group were treated with HAART during tuberculosis therapy, and among them six patients were ARV naïve. The regimens used and IRS characteristics are listed in Table 2.

IRS-related lymph-node enlargements varied in location and size (from 3 to 9 cm in diameter). Most were located in the cervical region (seven cases), and the remaining in the cervical plus mediastinal (1), multiple superficial (1), cervical and femoral regions (1). The latter case was complicated by deep venous thrombosis. One patient presented an atypical manifestation with general signs such as fever, hepatosplenomegaly and anemia with a positive Coombs test. The findings were not observed in other patients.

IRS occurred within a mean of 61.7±59 days after initiating HAART and 80.5±43 days after initiating TB treatment. CD4+ counts in IRS patients are shown in Table 2. Baseline values were <100 cells/mm³ in 50% of them. After introduction of antiretroviral therapy, 50% of the patients reached CD4+ counts >200 cells/mm³. CD8+ counts did not change significantly following anti-TB and antiretroviral treatment (Table 2).

Eight of 10 patients with IRS were treated with prednisone (1 mg/kg/day) until improvement of clinical symptoms. The other two cases were treated with nonsteroidal anti-inflammatory drugs. Recovery occurred in all cases in a mean of 91±30 days. One case of TB relapse was observed, but no IRS-related deaths occurred after two years of follow-up.

The general incidence rate of IRS was 25.93/100 person-years (pp/y), CI=25.77-26.09; the incidence rates grouped by relevant clinical presentation show that the patients with superficial adenomegaly at the time that TB diagnosis was made (not associated with ganglionar TB) had an incidence rate 11 fold (IR=11.18; CI, 1.41-88.76) greater than individuals not presenting adenomegaly. The lymph nodes were generally slightly tender, firm, mobile, multiple and of small size, varying from 0.5 to 1.5 cm, mostly found in the cervical region and did not decrease in size after TB therapy.

In ARV-naïve patients, the incidence rate was 85% (IR:1.85; CI, 0.48-7.16), which was higher compared to experienced patients, being 50% (IR:1.50; CI, 0.40-5.59) higher among patients with CD4+ <100 cells/mm³ compared to the others. Patients presenting extrapulmonary TB had an IRS incidence rate approximately two-fold higher (IR=1.97; CI, 0.44-8.79) compared to patients presenting pulmonary and disseminated TB.

Discussion
IRS increased significantly in incidence since antiretroviral therapy became available in most countries. Such reactions are more frequent and severe in TB/HIV co-infected patients than in non HIV-infected patients with TB [2,13].

The incidence rate of IRS in our group (25%) was similar to the incidence rate reported in Thailand [4], but it was two-fold higher than found in India [14]. Factors that were associated with a higher incidence rate, such as extrapulmonary TB, such as ARV naïve and a baseline CD4 count <100 cell/mm³ were also observed in other studies, but none of them included the variable superficial lymph-node enlargement at the moment of TB diagnosis in the model [3,4,12]. This finding was associated with a higher incidence rate in our study (11 fold).

In our patients, IRS occurred at a mean of eight weeks after initiating HAART. The strategy of initiate HAART after 30 days of TB therapy could have contributed to the identification of a temporal relationship between IRS and HAART as opposed to anti-TB therapy.

The sole form of TB-related IRS observed in our study was lymph node enlargement, which was previously reported by other authors [14,15], although many of them also observed transient worsening of pulmonary infiltrates, pleural effusions, or miliary infiltrates [13,16-18], which we did not detect.

In our study, the mean time between worsening and improvement of IRS was 90 days, which was similar to other author’s findings [7,13,16], while other reports showed a trend towards longer duration and greater severity [15], requiring hospitalization in some cases [4,12]. Only one patient with IRS in our series required hospitalization. Deep venous thrombosis was a complication reported in another patient. The use of corticosteroids may have helped to stabilize IRS in our series. TB relapse was observed in only one patient, one year after end of treatment, but no deaths were registered. The duration of the phenomenon and the multiple resulting scars in some cases were a major cosmetic problem.

The higher incidence rate of IRS associated with lymph-node enlargement during TB diagnosis could mean immune system response to the new infection.
Table 1. Clinical data of Tuberculosis-HIV co-infected patients that presented immune reconstitution syndrome (IRS) from January 2000 to January 2003 at IPEC – FIOCRUZ

<table>
<thead>
<tr>
<th>Patient</th>
<th>Gender</th>
<th>Age at TB diagnosis (yrs)</th>
<th>PPD (mm)</th>
<th>Sites infected by TB</th>
<th>TB diagnosis date due to IRS</th>
<th>Hospitalization</th>
<th>Relapse of TB</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Female</td>
<td>37</td>
<td>55</td>
<td>Lymph Nodes</td>
<td>08.10.00</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>2</td>
<td>Female</td>
<td>26</td>
<td>0</td>
<td>Lymph Nodes</td>
<td>04.24.01</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>3</td>
<td>Male</td>
<td>25</td>
<td>0</td>
<td>Lymph Nodes</td>
<td>03.01.02</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>4</td>
<td>Male</td>
<td>54</td>
<td>0</td>
<td>Lung + Lymph Nodes</td>
<td>01.04.02</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>5</td>
<td>Male</td>
<td>37</td>
<td>63</td>
<td>Lymph Nodes</td>
<td>12.04.00</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>6</td>
<td>Male</td>
<td>33</td>
<td>0</td>
<td>*Disseminated</td>
<td>06.06.01</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>7</td>
<td>Male</td>
<td>27</td>
<td>0</td>
<td>Lung + Lymph Nodes</td>
<td>07.13.00</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>8</td>
<td>Male</td>
<td>30</td>
<td>NA</td>
<td>Lung + Lymph Nodes</td>
<td>06.17.02</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>9</td>
<td>Female</td>
<td>48</td>
<td>0</td>
<td>*Disseminated</td>
<td>07.19.01</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>10</td>
<td>Male</td>
<td>37</td>
<td>68</td>
<td>Pulmonary</td>
<td>06.30.00</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

*Miliary pattern.

Table 2. Laboratory and immune reconstitution syndrome (IRS) characteristics of Tuberculosis-HIV co-infected patients that presented IRS from January 2000 to January 2003 at IPEC – FIOCRUZ

<table>
<thead>
<tr>
<th>Patient</th>
<th>ARV Drug used</th>
<th>Time interval</th>
<th>Data</th>
<th>Clinical form</th>
<th>IRS Drug used</th>
<th>Data</th>
<th>Clinical form</th>
<th>Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>AZT+ddI+EFV</td>
<td>08.24.00</td>
<td>11.10.00</td>
<td>Lymph nodes enlargement</td>
<td></td>
<td>78</td>
<td>177</td>
<td>328</td>
</tr>
<tr>
<td>2</td>
<td>d4T+3TC+EFV</td>
<td>04.24.01</td>
<td>06.13.01</td>
<td>Lymph nodes enlargement + fever</td>
<td></td>
<td>50</td>
<td>140</td>
<td>168</td>
</tr>
<tr>
<td>3</td>
<td>d4T+3TC+RTV+SQV</td>
<td>04.05.02</td>
<td>05.02.02</td>
<td>Lymph nodes enlargement</td>
<td></td>
<td>27</td>
<td>34</td>
<td>269</td>
</tr>
<tr>
<td>4</td>
<td>AZT+ddI+EFV</td>
<td>11.29.01</td>
<td>03.01.02</td>
<td>Lymph nodes enlargement + fever + chills</td>
<td></td>
<td>92</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>5</td>
<td>AZT+3TC+EFV</td>
<td>11.27.00</td>
<td>06.04.01</td>
<td>Lymph nodes enlargement</td>
<td></td>
<td>189</td>
<td>166</td>
<td>233</td>
</tr>
<tr>
<td>6</td>
<td>AZT+3TC+RTV+SQV</td>
<td>07.06.01</td>
<td>10.05.01</td>
<td>Lymph nodes enlargement</td>
<td></td>
<td>91</td>
<td>30</td>
<td>142</td>
</tr>
<tr>
<td>7</td>
<td>AZT+3TC+EFV</td>
<td>09.05.00</td>
<td>10.05.01</td>
<td>Lymph nodes enlargement</td>
<td></td>
<td>30</td>
<td>38</td>
<td>62</td>
</tr>
<tr>
<td>8</td>
<td>AZT+3TC+RTV+SQV</td>
<td>07.19.02</td>
<td>07.22.02</td>
<td>Lymph nodes enlargement + hepatosplenomegaly + fever + weakness + hemolytic anemia</td>
<td></td>
<td>03</td>
<td>21</td>
<td>561</td>
</tr>
<tr>
<td>9</td>
<td>AZT+3TC+RTV+SQV</td>
<td>08.17.01</td>
<td>10.11.01</td>
<td>Lymph nodes enlargement</td>
<td></td>
<td>55</td>
<td>7</td>
<td>41</td>
</tr>
<tr>
<td>10</td>
<td>AZT+3TC+EFV</td>
<td>08.14.00</td>
<td>09.04.00</td>
<td>Lymph nodes enlargement + fever</td>
<td></td>
<td>21</td>
<td>178</td>
<td>444</td>
</tr>
</tbody>
</table>

NA=not available, CD41 and CD8 counts in mm³, pre-TB, 2After TB CD4 and CD8 counts in mm³, *Time interval between initiation of ARV and development of IRS (days).

activation, probably a result of HIV infection in TB patients. This is the first evidence of a clinical marker for IRS, easily identified by clinicians at bedside, although further prospective studies may be necessary to better determine the relevance of this finding as a marker for IRS.

In spite of the fact that most of the variables that we analyzed did not achieve a statistical significance of 5% for the incidence rate, we considered the results clinically relevant. It is important to register these findings as possible risk factors to be included in future analyses with larger series.

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References


