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) co-infected 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/mm^3 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/mm^3 (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.

Received on 5 February 2007; revised 6 August 2007.
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This study was supported by Rede-TB Milenio I (CNPq) and PAPES 3, Fiocruz. These programs are public institutions and there are no conflicts of interest involved that could compromise the results.

The Brazilian Journal of Infectious Diseases 2007;11(5):462-465.
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Patient Recruitment

All patients with TB/HIV diagnosis followed at IPEC-FIOCRUZ from January 2000 to January 2003 were reviewed throughout TB therapy. Only one patient for whom other opportunistic disease was diagnosed was excluded. All subjects signed informed consent forms to participate in this study, approved by the Evandro Chagas Research Institute Institutional Review Board.

Tuberculosis Diagnosis

All IRS cases had their TB diagnoses confirmed by the isolation of *Mycobacterium tuberculosis*. The IRS-negative TB patients were diagnosed by a positive culture or a positive therapeutic test in patients without other concomitant opportunistic diseases. The identification of *M. tuberculosis* was based on biochemical testing.

HIV Infection

This was defined as a positive ELISA test in two different blood specimens, confirmed by immunofluorescence or Western Blot.

TB and Antiretroviral Therapies

Antiretroviral therapy was initiated at least 30 days after the introduction of standard short-course (six months) TB therapy in naïve patients, based on our experience and local recommendations [11]. All nucleoside analogs were Brazilian generic. The original laboratories supplied other classes of ARV. TB chemotherapy products were produced by Brazilian Federal Laboratories. TB therapy was not directly observed. All patients were followed through the end of TB therapy (at 15, 30, 60, 120, and 180 days after treatment), and a follow-up visit was routinely scheduled after one year after the end of TB therapy. At each clinical-examination visit, CBC, biochemical evaluation and radiological procedures were

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/mm^3; 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, hepatoesplenomegaly and anemia with a positive Coombs test. These 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/mm^3 in 50% of them. After introduction of antiretroviral therapy, 50% of the patients reached CD4+ counts >200 cells/mm^3. 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 1.5cm, 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/mm^3 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 naive and a baseline CD4 count <100 cell/mm^3 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

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

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

*Miliary pattern.

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

Patient	ARV		IRS		Time interval#	CD4+1	CD4+2	CD8+1	CD8+2
	Drug used	Data	Clinical form	Data					
1	AZT+ddI+EFV	08.24.00	Lymph nodes enlargement	11.10.00	78	177	328	NA	550
2	d4T+3TC+EFV	04.24.01	Lymph nodes enlargement + fever	06.13.01	50	140	168	412	440
3	d4T+3TC+RTV+SQV	04.05.02	Lymph nodes enlargement	05.02.02	27	34	269	1359	860
4	AZT+ddI+EFV	11.29.01	Lymph nodes enlargement + fever + chills	03.01.02	92	NA	NA	NA	NA
5	AZT+3TC+EFV	11.27.00	Lymph nodes enlargement	06.04.01	189	166	233	NA	900
6	AZT+3TC+RTV+SQV	07.06.01	Lymph nodes enlargement	10.05.01	91	30	142	757	513
7	AZT+3TC+EFV	09.05.00	Lymph nodes enlargement	10.05.01	30	38	62	NA	289
8	AZT+3TC+RTV+SQV	07.19.02	Lymph nodes enlargement + hepatosplenomegaly + fever + weakness + hemolytic anemia	07.22.02	03	21	561	644	603
9	AZT+3TC+RTV+SQV	08.17.01	Lymph nodes enlargement	10.11.01	55	7	41	NA	329
10	AZT+3TC+EFV	08.14.00	Lymph nodes enlargement + fever	09.04.00	21	178	444	510	1,181

NA=not available, CD4[1] and CD8 counts in mm^3, pre-TB, [2]After TB CD4 and CD8 counts in mm^3, [#]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.

Acknowledgements

We thank Dr. Amina Jindani, St. George's, University of London, United Kingdom, for her critical review and suggestions on the manuscript, Dr. Carla Vorsatz for translation review and Ministry of Science and Technology Milenio I – REDE-TB for the financial support.

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