

# Incidence and risk factors of immune reconstitution inflammatory syndrome in HIV-TB coinfecting patients

## ABSTRACT

Tuberculosis is one of the leading causes of development of Immune reconstitution inflammatory syndrome (IRIS) in HIV patients receiving antiretroviral therapy (ART). **Objective:** To determine the incidence of IRIS in HIV-TB coinfecting patients, and to find out the possible risk factors associated with IRIS. **Materials and Methods:** Study commenced with 96 patients adhered to standard antitubercular therapy (ATT) and ART without defaulting, and followed up for six months. **Result:** The mean ( $\pm$  SD) CD4 count and CD4 percentage at baseline was 59.16 ( $\pm$  24.63) per mm<sup>3</sup> and 4.59% ( $\pm$  1.73) respectively. Only 18.75% developed IRIS after 57.05 ( $\pm$  14.12) days of initiation of ART. Extrapulmonary tuberculosis was the most significant factor associated with IRIS (83.33%) than those without IRIS (44.87%) ( $p = 0.0032$ ). Specifically, tubercular lymphadenitis (38.88%,  $p = 0.0364$ ) and disseminated tuberculosis (33.33%,  $p = 0.0217$ ) were significantly associated with IRIS. The other risk factors associated with appearance of IRIS were higher CD4 count ( $p = 0.0212$ ) at three months after initiation of ART and increment of CD4 count ( $p = 0.0063$ ) and CD4 percentage ( $p = 0.0016$ ) during this period. The major manifestations of IRIS were fever (40%), followed by lymphadenitis (38%). The mortality rate in IRIS was not higher than those without IRIS. **Conclusion:** Patients with extrapulmonary tuberculosis, especially tubercular lymphadenitis, were more likely to develop IRIS and fever was associated in most of them. Higher increment of CD4 count may indicate development of IRIS in presence of new or worsening tuberculosis lesion.

**Keywords:** HIV; tuberculosis; immune reconstitution inflammatory syndrome; CD4 lymphocyte count.

## INTRODUCTION

Human immunodeficiency virus (HIV) infection today is one of the major causes of mortality and morbidity globally. Association of tuberculosis (TB) coinfection with HIV poses greater therapeutic challenge. In developing nations, patients often present late with advanced HIV infection along with different opportunistic infections, most commonly tuberculosis.<sup>1</sup> Tuberculosis in HIV-infected patients often presents with diagnostic difficulties, with increased chance of negative sputum smear results, atypical chest X-ray findings, negative tuberculin skin test, lack of classical granuloma formation in late stage and also presence of more frequent extrapulmonary tuberculosis. With the advent of highly active antiretroviral therapy (HAART), incidence rate of immune reconstitution inflammatory syndrome

(IRIS) also raised significantly. Classically IRIS is defined as “occurrence or manifestation of new or existing opportunistic infection within six weeks to six months after initiation of antiretroviral therapy (ART), with associated increase in CD4 count”.<sup>2</sup> Any opportunistic infection may present with IRIS though tuberculosis (TB) is the major cause. Other important manifestations include CMV retinitis, *Pneumocystis jiroveci* pneumonia, herpes simplex infection, varicella zoster virus infection, cryptococcal meningitis, hepatitis B, hepatitis C infection and even some auto-immune diseases.<sup>3</sup> The main features of IRIS with TB are increasing pneumonitis, development of pleural effusion, occurrence of new radiographic lesions, painful and enlarged lymphadenopathy, often with discharging sinus, persistent fever, development of meningitis, expanding intracranial

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space occupying lesions etc.<sup>4,5</sup> It is hypothesized that pro-inflammatory cytokines produced excessively in response to systemic bacterial lipopolysaccharide, non-specifically act on latent mycobacterial antigens leading to clinical deterioration and paradoxical worsening of inflammatory responses.<sup>6</sup> In most of the cases, IRIS regress spontaneously without any significant mortality but sometimes it may cause worsening clinical scenario with respiratory failure and tracheal compression by enlarged lymph nodes resulting in death. It should be differentiated from exacerbation of tuberculosis due to drug resistance or non-compliance, appearance of new tubercular lesion or other opportunistic infection due to advancement of HIV. Till date, there is lack of clinical data about occurrence of IRIS in HIV and TB coinfecting patients in Indian population. Therefore, we conducted a cross-sectional study in a tertiary care set-up to find out prevalence and risk factors of IRIS in HIV-TB coinfecting patients.

## MATERIAL AND METHODS

Recently diagnosed HAART naive HIV-infected patients, who had clinical, radiological or microbiological evidence of active TB, were selected for our study. Inclusion criteria were as follows:

Recently diagnosed HIV positive by ELISA method. (According to NACO guideline, a symptomatic suspected HIV-infected person is diagnosed HIV positive when the serum sample is reactive with at least two out of three different ELISA kit).<sup>2</sup>

Patient having active tuberculosis diagnosed by clinical features, radiological appearances, presence of granuloma in aspiration material, or microscopy and/or culture positive acid-fast bacilli (AFB).

Receiving antitubercular therapy (ATT) from Revised National Tuberculosis Control Programme (RNTCP).

Started ART after 15 days of ATT as per protocol followed in the institution.

All the patients were followed up for the period of six months. The patients with non-compliance with either ATT or ART during the follow-up period were excluded from the study. The diagnosis of IRIS was done using the pre-set criteria as follows:

The patient had to be on ART with rising CD4 count.

Prior to starting ART, the patient must have documented radiological, histological or microbiologically confirmed tuberculosis.

Prior to starting ART, patient must have improvement of tuberculosis by antitubercular therapy.

Following initiation of ART, the patients must have appearance of new symptoms or re-appearance of previous symptoms.

The patients must have spontaneous resolution of symptoms with continuation of same treatment.

Our primary objective was to determine the incidence of IRIS in HIV-TB coinfecting patients. Secondly we tried to find out the possible risk factors for emergence of IRIS. The patients were divided into two groups according to development of IRIS or not. The demographic, clinical features, site of tuberculosis, presence of other opportunistic infection, baseline and follow-up CD4 count were measured and compared between the two groups. The statistical analysis was done, using chi-square test and Student's *t* test using SPSS ver-16 to determine the significance of the variables. A *p*-value < 0.05 was taken to be statistically significant. A total of 96 patients, who were attending Medicine outdoor and indoor of Medical College Kolkata from May 2009 to April 2010, who met the eligibility criteria, were included in this study. The study was approved by the institutional ethical committee. The necessary informed consent was taken from all the patients.

## RESULTS

Out of 96 patients suffering from both HIV and tuberculosis, 84 (87.5%) of them male, only 18 (18.75%) patients developed IRIS (Table 1). The initial mean ( $\pm$  SD) CD4 count of these patients was 59.16 ( $\pm$  24.63) per mm<sup>3</sup> and initial mean CD4 percentage was 4.59% ( $\pm$  1.73). The baseline parameters of the patients developing IRIS and those who did not develop IRIS were compared (Table 1). The male:female ratios of both groups were comparable. There was no significant difference between the two groups in respect of mode of transmission of HIV. But the distribution of tuberculosis is strikingly different between the two groups. Those, who developed IRIS had significantly higher incidence of extrapulmonary tuberculosis (83.33%) than those who did not develop IRIS (44.87%) (*p* = 0.0032). Of the various forms of extrapulmonary tuberculosis in IRIS positive patients, most had tubercular lymphadenitis (38.88%). None of the IRIS positive patient had CNS tuberculosis. The initial CD4 count in both groups were comparable, but the patients with IRIS experienced significantly higher increments of mean CD4 count (45.22  $\pm$  18.17 per mm<sup>3</sup>) than those without IRIS (31.37  $\pm$  14.88 per mm<sup>3</sup>), and this was statistically significant (*p* = 0.0063) (Table 1). Also after three months, the mean CD4 count in patients with IRIS (105.56  $\pm$  23.76 per mm<sup>3</sup>) were significantly higher than those without IRIS (90.26  $\pm$  24.23 per mm<sup>3</sup>) (*p* = 0.0212). The symptoms during development of IRIS are described in Table 2 and Table 3. Among the various systemic symptoms developed with IRIS, fever was predominant involving 40% patients of IRIS. The second most common symptom was generalized lymphadenopathy (38%). The incidence of flare up of pulmonary tuberculosis was 18%, while that of abdominal tuberculosis manifested by tubercular ascites and enlargement of abdominal lymph nodes was 27 percent. Only five patients required hospital admission for the severe manifestation of IRIS and intra-venous hydrocortisone was administered as a life-saving measure. Two of them died

**Table 1. Baseline characteristics of all HIV-TB coinfecting patients**

	IRIS pos (n = 18)	Iris neg (n = 78)	p value	Total (n = 96)
Sex				
Male	16 (88.88%)	68 (87.18%)	0.8433	84 (87.5%)
Female	2 (11.12%)	10 (12.82%)		12 (12.5%)
Mode of infection				
Sexual	16 (88.88%)	72 (92.31%)	0.6362	88 (91.67%)
Blood transfusion	2 (11.12%)	6 (7.69%)		8 (8.33%)
Site of tuberculosis				
Pulmonary TB	3 (16.66%)	43 (55.13%)	0.0032	46 (47.92 %)
Extrapulmonary TB	15 (83.33%)	35 (44.87%)	0.0032	50 (52.08 %)
TB lymphadenitis	7 (38.88%)	13 (16.67%)	0.0364	20 (20.83%)
Abdominal TB	2 (11.12%)	8 (10.26%)	0.5374	10 (10.42%)
CNS TB	0 (0%)	5 (6.41%)	0.8926	5 (5.21%)
Disseminated TB	6 (33.33%)	9 (11.54%)	0.0217	15 (15.625%)
CD4 counts				
CD4 baseline	60.33 ± 24.13	58.88 ± 24.89	0.8213	59.16 ± 24.63
CD4 % baseline	4.59 ± 1.64	4.59 ± 1.76	0.9938	4.59 ± 1.73
CD4 after 3 months	105.56 ± 23.76	90.26 ± 24.23	0.0212	93.13 ± 24.76
CD4 % after 3 months	8.67 ± 2.28	7.01 ± 1.99	0.0091	7.33 ± 2.14
CD4 increments	45.22 ± 18.17	31.37 ± 14.88	0.0063	33.97 ± 16.37
CD4 % increments	4.08 ± 1.85	2.42 ± 1.20	0.0016	2.73 ± 1.49
Death rate	2 (11.11%)	7 (8.97%)	0.3896	9 (9.375%)

**Table 2. Distribution of symptoms in the patients of TB-IRIS**

Symptoms during development of IRIS	Frequency
Fever	7 (38.89 %)
Fever with cough & expectoration	1 (5.56 %)
Fever with cough & haemoptysis	1 (5.56 %)
Fever with ascites	2 (11.11 %)
Fever with lymph node enlargement	2 (11.11 %)
Fever only	1 (5.56 %)
Cough & expectoration only	1 (5.56 %)
Abdominal lymphadenopathy only	3 (16.67 %)
Lymph node enlargement only	7 (38.89 %)
Total	18
Mean duration of development of IRIS	57.05 ± 14.12

in hospital. ART was continued in all of the patients. The patients who did not develop IRIS mostly improved clinically with resolution of their symptoms. Only 11 of 78 non-IRIS patients (14.1%) had clinical deterioration, of which three had pulmonary tuberculosis, and the others had extrapulmonary tuberculosis. These patients did not show any initial improvement. The mortality rates in both TB-IRIS and non-IRIS groups were comparable. The cause of death in one of the two persons suffering from IRIS was the compression of trachea by enlarged cervical lymph nodes, while the other died due to disseminated tuberculosis leading to multi-organ failure. Out of seven non-IRIS patients who died during the study, three had CNS tuberculosis, mostly meningitis, and four had disseminated tuberculosis. None of the patient with pulmonary tuberculosis died during the study. The mean duration of development of IRIS after initiation of ART was 57.05 (± 14.12) days (Table 2). The ART followed was according to the NACO guideline and was similar in both groups. ART was started in all patients after 15 days of ATT.

Table 3. Patient profiles of HIV-TB coinfecting patients who developed IRIS

Serial no.	Age (yrs.)	Sex	Mode of infection	Symptoms during IRIS	CD4 count (per mm <sup>3</sup> ) baseline	CD4 % baseline	CD4 count (per mm <sup>3</sup> ) after 3 months	CD4 % after 3 months	CD4 (per mm <sup>3</sup> ) increment	CD4 % increment	Duration of IRIS (day)	Death
1	28	Male	Sexual	Fever and cough	78	5.6	92	7.5	14	1.9	45	Not occurred
2	26	Male	Sexual	Fever with generalized LN enlargement	26	2.1	72	6.2	46	4.1	75	Not occurred
3	42	Male	Sexual	Cough and expectoration	110	7.4	126	9.4	16	2	60	Not occurred
4	32	Male	Sexual	Abdominal lymphadenopathy	55	4.6	84	6.8	29	2.2	68	Not occurred
5	45	Female	Blood transfusion	Generalized lymphadenopathy	86	6.7	140	11.5	54	4.8	45	Not occurred
6	35	Male	Sexual	Generalized lymphadenopathy	37	3.9	76	6.4	39	2.5	30	Not occurred
7	29	Male	Sexual	Fever with ascites with hepatosplenomegaly	48	3.6	110	8.9	62	5.3	66	Not occurred
8	40	Male	Sexual	Fever with cough and haemoptysis	82	6.4	126	10.5	44	4.1	50	Not occurred
9	36	Male	Sexual	Generalized lymphadenopathy	96	7.1	108	9.8	12	2.7	75	Not occurred

cont.

Table 3. Patient profiles of HIV-TB coinfecting patients who developed IRIS (Cont.)

Serial no.	Age (yrs.)	Sex	Mode of infection	Symptoms during IRIS	CD4 count (per mm <sup>3</sup> ) baseline	CD4 % baseline	CD4 count (per mm <sup>3</sup> ) after 3 months	CD4 % after 3 months	CD4 (per mm <sup>3</sup> ) increment	CD4 % increment	Duration of IRIS (day)	Death
10	28	Male	Sexual	Generalized lymphadenopathy	28	2.1	86	7.4	58	5.3	45	Occurred
11	42	Male	Blood transfusion	Fever with generalized LN enlargement	78	4.3	146	12.4	68	8.1	70	Not occurred
12	26	Male	Sexual	Generalized lymphadenopathy	38	2.7	92	6.4	54	3.7	55	Not occurred
13	36	Male	Sexual	Fever only	48	3.2	108	7.8	60	4.6	60	Not occurred
14	35	Female	Sexual	Generalized lymphadenopathy	52	4	96	6.8	44	2.8	45	Not occurred
15	47	Male	Sexual	Generalized lymphadenopathy	46	3.8	94	6.4	48	2.6	45	Not occurred
16	52	Male	Sexual	Abdominal lymphadenopathy	78	6.1	152	13.7	74	7.6	66	Not occurred
17	27	Male	Sexual	Abdominal lymphadenopathy	48	4.3	104	10.4	56	6.1	82	Not occurred
18	39	Male	Sexual	Fever with ascites with hepatosplenomegaly	52	4.7	88	7.8	36	3.1	45	Occurred

LN, lymph node.

## DISCUSSION

The incidence of IRIS varies throughout the world. In pre-HAART era, incidence of IRIS in developed countries was reported to be about 36%.<sup>7</sup> In developing countries, due to higher prevalence of tuberculosis, the incidence of IRIS is also higher, though remains largely under reported. The incidence in developing countries ranges from 11% to 43%, whereas in India it was reported as 8%.<sup>6,8</sup> In our study, incidence of TB-IRIS was 18.75%. As HAART is now widely available in India, the incidence of IRIS is likely to be increasing. The IRIS appears mostly within first three months of initiating ART. In our study the mean duration of appearance of IRIS was 57.05 days. The early appearance of IRIS may be due to early initiation of ART, after 15 days of ATT, in all patients. Other studies from developing countries like Brazil also documented similar result.<sup>9</sup> Shelburne et al.<sup>10</sup> showed that IRIS is more likely to develop earlier if HAART is initiated earlier. Most of the IRIS patients experienced an exacerbation of extrapulmonary tuberculosis, tubercular lymphadenitis being most common. Significantly 27% of the patients presented with intra-abdominal flaring up of tuberculosis. Various previous studies also showed similar result though occurrence of intra-abdominal tuberculosis was not high.<sup>11-13</sup> This highlights that one must look out for the enlargement of abdominal lymph nodes as a marker of IRIS. Interestingly, in our study, none had CNS tubercular manifestation. This may be because CNS involvement in TB-IRIS usually occurs late with median interval being 5-10 months.<sup>14</sup> The risk factor emerged from the study was presence of extrapulmonary tuberculosis, of which tubercular lymphadenitis and disseminated tuberculosis predominates. These findings corroborates with the findings of previous western studies, though they did not show disseminated tuberculosis as a risk factor.<sup>15</sup> This may be due to the fact, that exposure to high load of mycobacterium and their interaction with the immune system in disseminated form of tuberculosis increases the risk of IRIS.<sup>16</sup> The baseline CD4 count was not a risk factor for emergence of IRIS. Although previous studies, including those from different developing countries with high prevalence of HIV, postulated that CD4 counts less than 100 per mm<sup>3</sup> are associated with increased incidence of IRIS, this was not present in our study.<sup>9,17</sup> Rather, the increase in absolute as well as percentage of CD4 count was significantly higher in IRIS group of patients than the other. Similar result was shown by Breton G et al.<sup>12</sup> This may be due to the inherent pathophysiology of IRIS development. With the initiation of ART, there is partial restoration of immune response, which causes increase in CD4 count. As IRIS occurs due to excessive effect of various inflammatory mediators liberated from activated lymphocytes, so increment of CD4 count is related with occurrence of IRIS and it may act as a surrogate marker of development of IRIS, though

more detailed studies need to be done to know the actual predictive value. The major limitation of the study was exclusion of subclinical tuberculosis patients who may develop IRIS after initiation of ART. Also all the patients were given standard ATT and ART, so effect of variation of therapy with emergence of IRIS was not evaluated. In addition, because ART was started after 15 days of ATT in all patients, any effect of delay of ART with appearance of IRIS could not be studied. All the patients recruited in the study were in advanced HIV. Further study is needed to know the variation of incidence of IRIS at different stages of HIV. Although most of our patients recovered spontaneously without requiring any deviation from their treatment protocol, large prospective study will guide us about proper management of IRIS.

## CONCLUSION

In conclusion, IRIS in HIV-TB coinfecting patients is an important entity, 12% of the patients developed IRIS in our study within two months of starting ART. Patients with extrapulmonary tuberculosis, especially tubercular lymphadenitis are more prone to develop IRIS. Fever is associated in most of these patients. Higher increment of CD4 count may give warning for development of IRIS in presence of new or worsening tuberculosis lesion.

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