Original Article

Incidence and Outcomes of Tuberculosis-Associated Immune Reconstitution Inflammatory Syndrome (IRIS) Following Antiretroviral Therapy (ART) in HIV-Infected Patients

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Background: The incidence and outcomes of paradoxical immune reconstitution inflammatory syndrome (IRIS) and unmasking tuberculosis-associated IRIS (TB-IRIS) after antiretroviral therapy (ART) initiation is not well defined.

Objective: To determine the cumulative incidence and outcomes of paradoxical and unmasking TB-IRIS after ART initiation

Materials and Methods: The authors performed a retrospective cohort study of HIV-infected patients starting ART at Siriraj Hospital between January 2010 and December 2013. The outcomes obtained were mortality, rate of hospitalization, the increment of CD4 cell count, and the proportion of virologic suppression six months and one year after ART initiation.

Results: Three hundred seventy HIV-infected patients were included, with a median CD4 cell count at baseline of 44 cells/mm^3. Of the 120 patients who were diagnosed with TB before starting ART, 21 (17.5%) developed paradoxical TB-RIS at a median time of 24 days. Of the 250 patients who were not receiving TB treatment when ART was initiated, 18 (7.2%) experienced ART-associated TB, with a median time of 47.5 days and 13 cases (5.2%) identified as unmasking TB-IRIS. No significant differences were found in the increments of the CD4 cell count and the proportions of virologic suppression at 6- and 12-month. Four patients who died did not develop TB-IRIS. Those with paradoxical TB-IRIS or ART-associated TB were hospitalized within six months after ART more frequently than those without TB-IRIS (33.3% and 33.3% versus 8.2%, respectively; p=0.001) and required more diagnostic procedures than those without TB-IRIS (42.9% and 55.6% versus 3.3%, respectively; p<0.001).

Conclusion: Patients with TB-IRIS were hospitalized and underwent a diagnostic procedure far more frequently than those without TB-IRIS, but none of the TB-IRIS patients died. ART should be provided early, and fear of any type of IRIS should not be a reason to defer ART in HIV-TB co-endemic areas.

Keywords: Tuberculosis-associated immune reconstitution inflammatory syndrome, TB-IRIS, HIV

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Highly active antiretroviral therapy (HAART) dramatically reduces the incidence of opportunistic infections (OIs) and mortality as a result of HIV viral suppression and increased CD4 cell count[1,2]. Tuberculosis (TB) is the most common OI and the leading cause of death affecting HIV-infected individuals[3,4]. A previous systematic review and meta-analysis demonstrated that early antiretroviral therapy (ART) substantially reduces the incidence of TB across all CD4 cell counts[5]. However, in resource-limited settings, many people learn of their HIV status at a late stage of the disease, and TB is frequently the first-recognized presenting disease of an underlying HIV infection[4]. Many studies have supported the recommendation of starting ART as soon as possible, ideally within the first two to eight weeks of initiation of TB treatment, depending on the CD4 cell count[6,7]. Nevertheless, marked restoration

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of the immune system may result in either the clinical deterioration of a previously treated OI, the so-called paradoxical immune reconstitution inflammatory syndrome (IRIS), or the unmasking of a subclinical infection, known as unmasking IRIS. The incidence of TB-IRIS in the previous studies has varied widely and mainly focused on paradoxical TB-IRIS[8]. Very few studies have reported the incidence of unmasking TB-IRIS or the outcomes in terms of the morbidity and immunological response of those with TB-IRIS. The authors conducted the present study to determine the cumulative incidence and outcomes of paradoxical and unmasking TB-IRIS after ART initiation.

Materials and Methods

A retrospective cohort study was conducted at Siriraj Hospital, the largest university hospital in Bangkok, Thailand. The patients aged 18 years or older who were diagnosed with HIV between January 2001 and December 2014 were identified. The authors enrolled those patients who had been prescribed highly active antiretroviral therapy (HAART), had a measurement of the baseline CD4 cell count, had at least one measurement of the CD4 cell count or HIV viral load following HAART initiation, and were followed up for at least one year. All available records of the patients who met the inclusion criteria were reviewed.

Diagnosis of active TB, either by clinical or microbiological criteria and either before or after introducing HAART, were examined. Definite TB was defined as a positive culture or positive molecular assay for *Mycobacterium tuberculosis* complex from any clinical specimen. Probable TB was defined as patients who were started on anti-TB treatment with a subsequent documented clinical improvement at the 2-month follow-up without bacteriological confirmation. The diagnosis of TB-IRIS, either paradoxical or unmasking, was based on a previously published definition[9]. In brief, paradoxical TB-IRIS was suspected in patients who were diagnosed with active TB before HAART initiation and a response to anti-TB treatment. After initiation of ART, these patients developed recurrent, new, or worsening symptoms or signs of TB (such as fever, worsening cough, lymph node enlargement, or recurrent, new, or deteriorating radiographic findings), typically within three months. TB that was diagnosed after ART initiation was defined as ART-associated TB. Active TB that was diagnosed within three months of starting ART was defined as unmasking TB-IRIS[10].

The incidences of paradoxical and unmasking TB-IRIS were determined. The outcomes of patients with paradoxical TB-IRIS or ART-associated TB, including unmasking TB-IRIS, were compared with those without TB-IRIS. The outcomes of interest included rate of hospitalization, mortality, the increment of CD4 cell counts, and the proportion of patients with virologic suppression six months and one year after HAART initiation.

Sample size calculations

According to previous studies, the incidences of paradoxical and unmasking TB-IRIS are 12.6% and 15%, respectively[11,12]. The authors calculated the sample size required to estimate the proportion, with a precision of 5% and confidence interval of 95%. The sample sizes required for paradoxical and unmasking TB-IRIS were 174 and 196 cases, respectively, using the nQuery Advisor program. Therefore, 370 patients were examined.

Statistical analysis

The categorical variables, which include the cumulative incidence of paradoxical and unmasking TB-IRIS, the mortality and hospitalization rates, and the proportion of patients with HIV-RNA of less than 40 copies/mL, are presented in percentages. The continuous variables will be presented in mean with standard deviation (SD) or median with interquartile range (IQR) as appropriate. The authors combined patients with paradoxical TB-IRIS and ART-associated TB in the group of TB-IRIS. The categorical outcomes of those with and without TB-IRIS were compared using chi-square or Fisher's exact test, as appropriate. The changes in the CD4 cell counts and the corresponding percentages six and twelve months from the baseline CD4 were compared using the Mann-Whitney U test. A p-value of less than 0.05 was considered statistically significant. Statistical calculations were performed using PASW Statistics 18.0 (SPSS Inc., Chicago, IL, USA).

Results

Of the 370 patients enrolled in the study, 120 were receiving TB treatment prior to HAART initiation and 250 were not receiving TB treatment when HAART was initiated. The mean (SD) age of all patients was 40.02 (SD 10.36) years, and 60.8% were male. The median (IQR) baseline CD4 cell count was 44 (17.5 to 91.5) cells/mm^3, and the median (IQR) baseline HIV-RNA was 310,000 (116,000 to 646,000) copies/mL. Ninety-seven percent and 54% of patients had baseline CD4 cell counts of less than 200 cells/mm^3 and less

Table 1. Baseline characteristics of patients with and without TB-IRIS

Characteristics	TB-IRIS (n=39)	No TB-IRIS (n=331)	p-value
Age (years), Mean (SD)	37.8 (9.2)	40.3 (10.5)	0.161
Body weight (kg) at ART initiation, Mean (SD)	55.6 (11.9)	55.1 (10.9)	0.797
Sex: male, n (%)	27 (69.2)	198 (59.8)	0.255
ART regimen, n (%)			
NVP-based	7 (17.9)	76 (22.9)	0.478
EFV-based	32 (82.1)	244 (73.7)	0.228
PIs-based	0 (0.0)	11 (3.3)	0.248
CD4 cell count (cells/mm^3), Median (IQR)	33 (16 to 75)	45 (18 to 94)	0.484
HIV-RNA (copies/mL), Median (IQR)	579,000 (47,700 to 1,350,000)	287,000 (116,000 to 638,000)	0.680

TB=tuberculosis; IRIS=immune reconstitution inflammatory syndrome; ART=aniretroviral therapy; NVP=nevirapine; EFV=efavirenz; PIs=protease inhibitors; SD=standard deviation; IQR=interquartile range

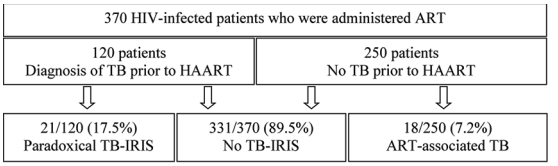

Figure 1. Schematic representation of patients in each group.

than 50 cells/mm³, respectively. Approximately 75% of patients received an efavirenz (EFV)-based regimen, followed by a nevirapine (NVP)-based regimen (22.4%) and a protease inhibitor (PI)-based regimen (3%). Diagnosis of TB in 120 patients who were diagnosed TB prior to HAART initiation were as follows, 76 patients (63.3%) had pulmonary TB with culture proven in 43 patients (35.8%), 88 patients (73.3%) had extrapulmonary TB, with culture proven in 57 patients (47.5%), and 44 patients had disseminated TB (36.7%). As to those patients receiving TB treatment prior to ART, HAART was initiated at a median duration of 62.5 days (IQR 31 to 120.5) following the commencement of the TB treatment.

A schematic representation of the patients in each group is shown in Figure 1. Of the 120 patients for whom TB was diagnosed prior to ART initiation, 21 (17.5%) developed paradoxical TB-IRIS at a median interval of 24 days (IQR 14 to 49) after the HAART initiation. Only two patients who developed paradoxical IRIS received TB treatment within 14 days. The proportions of extra-pulmonary TB in those developing IRIS and no IRIS were similar (81% versus 72.4%; p=0.420). Eighteen out of the 250 patients (7.2%) who had no TB prior to the ART initiation were diagnosed with ART-associated TB at a median interval of 47.5 days (IQR 23 to 98) after the HAART initiation. There were no significant differences in the timings from HAART initiation to the occurrence of paradoxical TB-IRIS or ART-associated TB (24 days versus 47.5 days; p=0.204). Thirteen out of those 18 patients developed TB-IRIS within three months, giving an incidence of unmasking TB-IRIS of 5.2%. A comparison of the baseline characteristics of the patients with and without TB-IRIS is presented in Table 1. Overall, there were no significant differences in the ages, body weights, baseline CD4 cell counts, plasma HIV-RNAs, or HAART regimens of the patients with and without TB-IRIS.

The presenting features of the paradoxical TB-IRIS and ART-associated TB were similar. Constitutional symptoms such as fever, night sweats, or weight loss, were the most frequent presenting symptoms, accounting for 76.2% and 72.2% of the symptoms in the paradoxical TB-IRIS and ART-associated TB, respectively. These were followed by new or enlarging lymph nodes or cold abscesses for 57.1% of the paradoxical IRIS and 38.9% of the ART-associated TB cases. The clinical manifestations of the paradoxical and ART-associated TB cases are detailed in Table 2.

The clinical outcomes of the patients with paradoxical TB-IRIS or ART-associated TB, and of those without TB-IRIS, are summarized in Table 3. Those with and without TB-IRIS demonstrated no significant differences in the increments of the CD4 cell counts, percentage of CD4, or the proportion of patients with virologic suppression. However, following the ART initiation, patients with paradoxical

Table 2. Clinical manifestations of paradoxical TB-IRIS and ART-associated TB

Clinical events	Paradoxical TB-IRIS (n=21) n (%)	ART-associated TB (n=18) n (%)	p-value
Major criteria			
New or enlarging LN, cold abscesses	12 (57.1)	7 (38.9)	0.256
New or worsening radiological features	6 (28.6)	10 (55.6)	0.088
New or worsening CNS tuberculosis	3 (14.3)	3 (16.7)	0.837
New or worsening serositis	1 (4.8)	1 (5.6)	0.911
Minor criteria			
New or worsening constitutional symptoms	16 (76.2)	13 (72.2)	0.777
New or worsening respiratory symptoms	4 (19.0)	6 (33.3)	0.308
New or worsening abdominal pain	3 (14.3)	4 (22.2)	0.520

TB=tuberculosis; IRIS=immune reconstitution inflammatory syndrome; ART=aniretroviral therapy; LN=lymph node; CNS=central nervous system

Table 3. Clinical outcomes of patients with and without TB-IRIS

Clinical outcomes	TB-IRIS		No TB-IRIS (n=331) (C)	p-value	
	Paradoxical (n=21) (A)	ART-associated (n=18) (B)		A vs. C	B vs. C
Increment of CD4 cell count (cells/mm^3), Median (IQR)					
At 6 months	94 (71.5 to 130)	104 (58 to 202)	114 (68 to 184)	0.365	0.430
At 12 months	142 (82 to 251)	143.5 (79 to 222)	185 (124.5 to 276)	0.245	0.108
Increment of % CD4 count (cells/mm^3), Median (IQR)					
At 6 months	4.32 (2.42 to 7.30)	5.61 (4.42 to 6.88)	4.34 (2.55 to 7.01)	0.798	0.158
At 12 months	5.95 (1.55 to 8.47)	5.88 (3.63 to 9.21)	6.23 (4.37 to 9.66)	0.249	0.457
HIV RNA <40 copies/mL at 12 months, n (%)	16 (88.9)	14 (93.3)	261 (88.8)	1.000	1.000
Hospitalization after ART, n (%)					
Within 6 months	7 (33.3)	6 (33.3)	27 (8.2)	0.001	0.001
Within 12 months	7 (33.3)	7 (38.9)	29 (8.8)	0.001	<0.001
Invasive procedure within 12 months, n (%)	9 (42.9)	10 (55.6)	11 (3.3)	<0.001	<0.001
Death at 1 year*, n (%)	0 (0.0)	0 (0.0)	4 (1.2)	1.000	1.000

TB=tuberculosis; IRIS=immune reconstitution inflammatory syndrome; ART=aniretroviral therapy; IQR=interquartile range

* Death at 1 year after ART; increment of CD4 cell count means the difference of CD4 cell count at 6 and 12 months after ART which increased from baseline CD4

TB-IRIS or ART-associated TB were hospitalized more frequently than those without TB-IRIS within six months (33.3%, 33.3% versus 8.2%, respectively; p=0.001) and within 12 months (33.3%, 38.9% versus 8.2%; p=0.001). Those with paradoxical TB-IRIS or ART-associated TB also required more diagnostic procedures within 12 months than those without TB-IRIS (42.9%, 55.6% versus 3.3%, respectively; p<0.001). Lymph node biopsies or aspirations were the most frequent diagnostic procedures, followed by lumbar punctures and bone marrow aspirations or biopsies.

All patients with ART-associated TB were treated with anti-TB drugs. Among the 21 patients with paradoxical TB-IRIS, 10 (47.6%) were clinically subsided without treatment, six (28.6%) received NSAIDs, and five (23.8%) improved with corticosteroids. Four out of the 370 (1.08%) patients died within one year of the HAART initiation. Two patients died from septic shock without an identified organism. The third patient died from cryptococcal meningitis 100 days after the ART initiation. The

fourth died from TB meningitis 347 days after the HAART initiation. Those who died did not have any type of TB-IRIS.

Discussion

In the present study, the cumulative incidences of paradoxical and unmasking TB-IRIS were 17.5% and 5.2%, respectively. A previous systematic review of 16 studies that had been conducted between 1998 and 2009 reported an overall incidence of TB-IRIS of 15.7%, varying between 8% and 43%[8]. Another recent meta-analysis of 40 studies that had been carried out between 1998 and 2014 included 1,048 patients who had developed TB-IRIS among 7,789 at-risk patients, giving a pooled TB-IRIS incidence of 18% (95% CI 16 to 21%)[13]. The incidence of paradoxical TB-IRIS found by the present study was very similar to previous findings and to those reported in Thailand (13% to 18%)[12,14]. The incidence of paradoxical TB-IRIS can vary, depending on the baseline CD4 cell count, the diagnostic criteria used for IRIS, and the income of countries[8]. The incidence of ART-associated TB in the present study was 7.2%, and 5.2% of the study cohort were defined as unmasking TB-IRIS. Likewise, previous studies found that 3% to 14% of HIV-infected patients developed TB during HAART, and a significant proportion of patients (1.4% to 8.8%) developed unmasked TB early, within three months of HAART initiation[11]. Several studies reported a very low mortality rate (less than 4%) in patients with paradoxical TB-IRIS. Unlike paradoxical TB-IRIS, the risk of death from unmasked TB has been found to be higher and may exceed 25%, particularly in low-income countries, which is partly due to missed or delayed diagnoses and treatment[8,11]. However, none of the present patients who developed any type of TB-IRIS died. In the current study, the authors did not find significant differences for the patients in the TB-associated IRIS and non-IRIS groups in their increment of CD4 cell counts, their increment of % CD4, or the proportions of patients with virologic suppression at 6- and 12-months.

Similar to previous studies in Thailand[12,15] and the United States[16], the authors found that patients with paradoxical TB-IRIS and ART-associated TB were more frequently hospitalized and required more diagnostic procedures than those without TB-IRIS. This implies that the occurrence of TB-associated IRIS required intensive attempts to differentiate the causes of worsening symptoms.

The limitations of the present study included its retrospective character, and some of the clinical symptoms of patients may have been underreported. The authors minimized this issue by using the case definition of TB-associated IRIS in resource-limited settings. Another consideration is that the CD4 cell counts and HIV RNA levels were not determined at the time of the IRIS event; therefore, it is not possible to confirm the hypothesis of immune reconstitution process.

Conclusion

The present study has demonstrated that the occurrence of paradoxical TB-IRIS is not uncommon, whereas that of ART-associated TB, including unmasking TB-IRIS, was relatively lower, even in a high-TB burden country like Thailand. Even though patients with these two conditions had a higher morbidity in the first year of HAART initiation and experienced more frequent hospitalization and diagnostic procedures than those without TB-IRIS, a very low mortality was observed. Therefore, ART should be provided early, and fear of TB-IRIS should not be the reason to defer ART, even in areas co-endemic for HIV and TB.

What is already known on this topic?

The occurrence of paradoxical TB-IRIS is not uncommon in areas co-endemic for HIV and TB. The incidence of paradoxical TB-IRIS has varied between 15% and 18%, which is quite similar to the finding observed in the present study (17.5%).

What this study adds?

Although paradoxical TB-IRIS was found in 17.5% of cases, ART-associated TB was found in only 7%. Although patients with any type of TB-IRIS had more frequent hospitalization and diagnostic procedures than those without TB-IRIS, a very low mortality was observed.

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Conflicts of interest

The authors declare that there are no conflicts of interest.

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