Original Article

Effect of IRIS development on survival in HIV-TB patients on antiretroviral therapy among north Indian population

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Abstract:

Background: The survival of people with HIV-associated TB has not been extensively studied. The objective of this present study was to explore the association of Immune reconstitution inflammatory syndrome (IRIS) development and mortality in HIV patients initiated on antiretroviral therapy (ART).

Methods: This was a prospective cohort study of 400 HIV positive patients who initiated antiretroviral therapy and followed up for one year. Baseline clinical and immunological parameters were assessed.

Results: A total of 38 (9.5%, 95%CI=6.6-12.4) patients developed IRIS within one year of follow-up. The mean duration of development of IRIS was 2.87 months (95%CI=2.08-3.67). The mortality was almost two times significantly higher in those patients who developed IRIS (21.1%) as compared to those who did not develop (9.7%) (RR=2.18, 95%CI=1.09-4.35, p=0.03). The average survival was significantly lower in those patients who developed IRIS (10.43 months) as compared to those who did not developed IRIS (11.5 months) (Log rank test p=0.03).

Conclusion: Appropriate use of ART to preserve immunity and treat HIV infection, ensuring high levels of coverage and compliance is required to prevent TB. The DOTS strategy is useful to ensure cure of TB in patients with HIV/AIDS. A strong coordination between the national TB and the AIDS control programs is required for effective management of HIV-TB patients.

Key words: HIV/AIDS, Survival, Antiretroviral therapy, TB, IRIS

Introduction:

Human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS), since the time of its initial description more than two decades ago, has relentlessly spread all around the globe showing no sign of abatement. According to the data from World Health Organization (WHO), there were at least 1.37 million cases of HIV/tuberculosis (TB) co-infection globally in the year 2007 (1).

The survival of people with HIV-associated TB (TB-HIV) has not been studied extensively. In sub-Saharan Africa mortality of people with TB-HIV is significantly greater than that of HIV-uninfected groups (2), but the data describing survival are scarce. In developed countries, prior to the introduction of antiretroviral therapy (ART), a wide range of survival times in people with TB-HIV was reported (3). Some of these reports showed associations between immuno-suppression, history of AIDS and TB location with risk of death (4).

Over the past two decades, symptomatic deterioration in patients on ART has been described in relation to a number of pre-existing subclinical infections, inflammatory disorders and autoimmune diseases. This phenomenon is known by multitude of names including, "immune reconstitution inflammatory syndrome (IRIS)", "immune reconstitution" or "restoration disease (IRD)", and "immune reconstitution syndrome (IRS)". Although IRIS is now a well established entity, uncertainty exists with regards to its pathogenesis and management, and research in the field is hampered by lack of a consistent definition of the syndrome.

Not many studies had been done on the association of IRIS and mortality, therefore, the present study was conducted to find out the effect of IRIS development on survival in HIV-TB patients on antiretroviral therapy.

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Methods:

Study population:

In a prospective cohort study, 400 HIV positive patients were included from July 2008 to August 2010. The study subjects were recruited from ART centre, Department of Medicine, CSM Medical University, Lucknow. The inclusion criteria used for the selection of the subjects were: 1) Patients diagnosed having HIV infection, 2) ART eligibility according to National AIDS Control Organization (NACO Guidelines, 2009) (5) , 3) ART naive, 4) HIV positive patients already on ATT and 5) Willingness to participate in the study and exclusion criteria: 1) Patient not willing to give consent, and 2) Patients who were already on ART.

Clinical data measurements:

All patients were diagnosed as HIV positive using ELISA according to NACO guidelines (2009). A pre-designed pre-structured proforma was used to collect socio-demographic characteristics and relevant clinical data of the patients, and their information related to risk factors for acquiring IRIS. All patients were subjected to thorough clinical history and examinations. The data particularly included age, sex, mode of transmission, symptoms suggestive of presence of OIs, TB history collected included: history of contact in the tuberculous family and the history of prior TB treatment or anti-tubercular treatment (ATT), prior TST, cough, night sweats, loss of weight and appetite and swelling of glands anywhere on the body. We asked patients if they had ever taken ARV drugs for any length of time. Body Systems examination was conducted for the presence of signs of TB: signs of pulmonary consolidation, pleural effusion, wheezing. We looked for presence of ascitis, abdominal tenderness, enlarged liver and spleen. Other physical examination findings were recorded as and when found.

Diagnosis of active tuberculosis:

Patients were considered to have active tuberculosis when they had two positive sputum smears by AFB, positive mycobacterium culture on Lowenstein Jensen media and if they had TB symptoms (any one of cough of more than 2 weeks, fever, loss of appetite, night sweats or loss of weight), *M. tb* polymerase chain reaction (PCR) positive in various body fluids or classical pulmonary infiltrates with no response to antibiotics or USG/Chest X-ray/MRI/CT findings highly suggestive of tuberculosis. Sputum tests were performed at enrolment and during follow up visits as indicated by the clinical presentation of the patients.

IRIS development:

Minimum follow up period for the development of IRIS was one year. Patients were followed on monthly basis and their clinical characteristics were recorded. End point of study was the development of IRIS. IRIS was diagnosed on the basis of published criteria (6).

Statistical analysis:

Continuous data are presented as mean ± standard deviation (for normally distributed variables). Categorical data are presented as numbers with proportions. The categorical data were compared between groups by the Chi square or Fisher's exact test. The relative risk with its 95% confidence interval (CI) was calculated. Kaplan-Meir survival curves were drawn to compare the survival of patients with IRIS and without IRIS. All tests were two-sided and $p<0.05$ was considered statistically significant. All analyses were using a statistical software package by SPSS (version 15.0).

Ethics:

The study experiment was conducted with the understanding and the consent of the human subject and responsible ethical committee, CSM Medical University, Lucknow, India has approved the experiments after obtaining institutional ethical clearance.

Results:

Socio-demographic profile

A total of 400 patients were included in the study. The mean age was 33.79 years ranging from 21-51 years. More than half of the patients were males (73%) and literates (57.2%). Majority of the patients were married (78.3%) and belonged to low socio-economic status (94.8%) (Table-1).

Prevalence of IRIS

A total of 38 (9.5%, 95% CI=6.6-12.4) patients developed IRIS within one year of follow-up. The mean duration of development of IRIS was 2.87 months (95% CI=2.08-3.67). More than one third (39.5%) developed IRIS between 1-2 month and 21.1% each developed within one and 3-4 month. About one tenth (10.5%) developed after 6 month and 7.9% developed IRIS between 5-6 month (Fig.1).

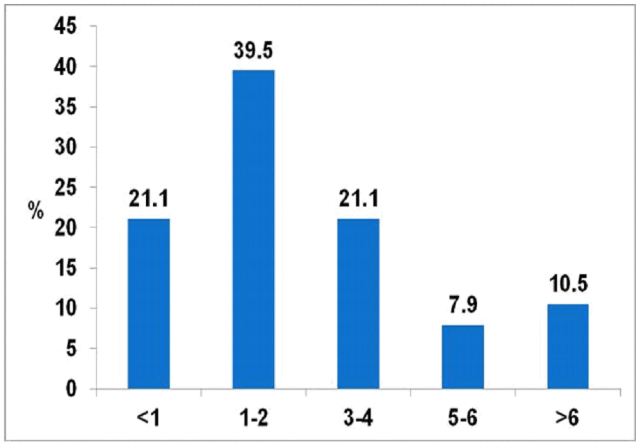
Effect of IRIS on survival

The mortality was almost two times significantly higher in those patients who developed IRIS (21.1%) as compared to those who did not develop (9.7%) (RR=2.18, 95% CI=1.09-4.35, p=0.03) (Table-2). The average survival was significantly lower in those patients who developed IRIS (10.43 months) as compared to those who did not develop IRIS (11.5 months) (Log rank test p=0.03).

Table-1: Socio-demographic characteristics of the study participants

Socio-demographic characteristics	No. (n=400)	%
Age in years		
<30	94	23.5
30-40	234	58.5
41-50	58	14.5
>50	14	3.5
Mean±SD, Median, (Min.-Max)	33.79±7.20, 31.50, 21-51	
Sex		
Male	292	73.0
Female	108	27.0
Education		
Illiterate	171	42.8
Literate	229	57.2
Marital status		
Married	313	78.3
Unmarried	36	9.0
Divorced/Separated	6	1.5
Widowed	45	11.3
Socio-economic status		
Low	379	94.8
Middle	14	3.5
High	7	1.8

Fig. 1: Duration of IRIS development in months



Overall prevalence of IRIS= 9.5% (95% CI= 6.6-12.4)
Mean duration (95% CI)= 2.87 (2.08-3.67)

Fig.2: Kaplan-Meir survival curves according to (i) development of IRIS and (ii) not development of IRIS

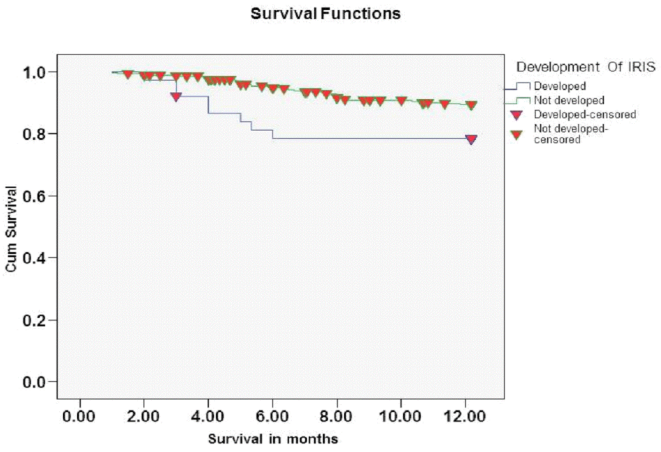


Table-2: Effect of development of IRIS on Mortality

IRIS	No. of patients	Dead		Alive		RR (95%CI) p-value
		No.	%	No.	%	
Developed	38	8	21.1	30	78.9	2.18 (1.09-4.35) 0.03*
Not developed	362	35	9.7	327	90.3	

*Significant

Discussion:

In our study, we found the prevalence of IRIS being 9.5%. However, most of the literature on epidemiology comes from the developed countries. In a series from southern India TB-IRIS was reported in 7.6% of patients (7). In a retrospective study, incidence rates of 7.5% for paradoxical TB-IRIS and 3% for ART-associated TB had been reported using consensus case-definitions (8). In a prospective study, using stringent case-definitions criteria (9), paradoxical TB-IRIS was seen in 4% of patients and ART associated TB in 7.5% of patients. No cases of ART-associated TB fulûlling the criteria of unmasking TB-IRIS were identified in either of the studies. The higher incidence of TB-IRIS reported, particularly in the western literature, may be explained by leniency of clinical diagnostic criteria.

Majority of patients with IRIS have a self-limiting disease course. Mortality associated with IRIS is relatively uncommon; however, associated high morbidity places considerable burden on the healthcare system (10, 11). In our study, the mortality was 21.1% among those who developed IRIS. However, morbidity and mortality rates vary according to the pathogen and organs involved. IRIS in the setting of opportunistic infections involving the CNS has high mortality rates. The heightened immune response in a relatively closed space leads to raised intracranial pressures, with potentially irreversible damage leading to increased morbidity and mortality. High mortality rates are reported for cryptococcal meningitis (12). Overall mortality rate of TB-IRIS is low; however, significant morbidity and mortality may be seen with ARDS and CNS involvement in TBIRIS (13).

It is expected that IRIS will become more common in resource-constrained settings like India, where access to ART is increasing. The underlying prevalence of opportunistic infections like *M. tuberculosis* is high in this setting and the patients initiating ART are more likely to have advanced immunosuppression (14).

So, we concluded that appropriate use of ART to preserve immunity and treat HIV infection, ensuring high levels of coverage and compliance is required to prevent TB. The DOTS strategy is useful to ensure cure of TB in patients with HIV/AIDS. A strong coordination between the national TB and the AIDS control programs is required for effective management of HIV-TB patients.

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