ORIGINAL ARTICLE

Clinical Profile of Patients with Immune Reconstitution Inflammatory Syndrome in Human Immunodeficiency Virus/Tuberculosis Coinfection and their Outcome: A Prospective Observational Study

Madhanmohan Kalyanasundaram[1], Sivaraja Subramaniam[2], Allwyn Vijay Gowrishankar[3]

Received on: 06 April 2022; *Accepted on:* 07 December 2022; *Published on:* 14 March 2023

Abstract

Introduction: Antiretroviral therapy (ART) is a life-saving treatment for the human immunodeficiency virus (HIV). However, the starting of ART is often complicated by immune reconstitution inflammatory syndrome (IRIS) in tuberculosis (TB). This study was done to examine the clinical profile of patients with IRIS in HIV-TB coinfection and their outcomes.

Materials and methods: A prospective observational study was conducted at the Government Hospital of Thoracic Medicine, Chennai, Tamil Nadu, India, from January to December 2013. Patients diagnosed to have HIV and TB coinfection, those on anti-tuberculosis therapy (ATT) and ART, patients with paradoxical IRIS, and ART-naïve patients were included in the study. A total of 230 patients were studied and followed up for 1 year. Clinical examination and chest X-rays, sputum smear for acid-fast bacillus (AFB), baseline CD4 count, ultrasonogram of the abdomen, routine blood investigations, and other necessary parameters required to determine IRIS TB in HIV/TB coinfected patients were taken.

Results: Among the 230 HIV patients studied, 74.3% were males, and the mean age was 39.01 ± 9.60 years. The incidence of IRIS was 20.9%, and the mortality rate was 25% among them. Oral candidiasis was the most common opportunistic infection (37.8%). Among IRIS patients, 62.5% had stage III clinical disease.

Conclusion: The time of starting ART is critical to reducing IRIS-associated morbidity. Improved knowledge of the pathophysiology of IRIS will enable better diagnostic modalities and targeted treatments to be developed.

Keywords: Acquired immunodeficiency syndrome, Acquired immunodeficiency syndrome-related opportunistic infections, Immune reconstitution inflammatory syndrome, Tuberculosis.

Indian Journal of Respiratory Care (2023): 10.5005/jp-journals-11010-1001

Introduction

Human immunodeficiency virus (HIV)—associated TB is common, with an estimated 1.4 million cases and 374,000 deaths annually.[1] ART is an essential, life-saving treatment for HIV. Still, HIV-infected patients initiating ART are at increased risk of TB-associated IRIS (TB-IRIS) in TB-endemic places. TB-IRIS is an acute inflammatory condition that causes worsening of TB in HIV patients on ATT after initiating ART (paradoxical TB-IRIS) or new onset of TB with the acute inflammatory response after starting ART (unmasking TB-IRIS).[2] This is often attributed to the restoration of host immunity after ART initiation, which causes exaggerated inflammatory responses to *Mycobacterium tuberculosis* antigens.[3]

Symptoms of IRIS include fever and new or increased lymph node enlargement, often accompanied by reddening and inflammation of the overlying skin of enlarged lymph nodes, which can rupture to form sinuses. Other manifestations comprise pleural and pericardial effusion, psoas abscess, ascites, cutaneous lesions, new or increasing central nervous tuberculoma, and worsening of pulmonary lesions. Corticosteroid therapy is used to reduce the symptoms of IRIS.[4]

A previous study from India reported that IRIS was seen in 7.6% of patients who started on ART.[5] In another prospective study, using consensus case definitions criteria, the incidence of paradoxical TB associated with IRIS was 4%, and highly active ART (HAART)—associated TB was 7.5%.[6]

One of the critical risk factors for IRIS is an opportunistic infection at the time of starting ART. Another important risk factor

[1]Department of T.B. & Chest, Dhanalakshmi Srinivasan Medical College and Hospital, Perambalur, Tamil Nadu, India

[2]Department of Pulmonology, Delta Care Hospital, Thanjavur, Tamil Nadu, India

[3]Department of T.B & Respiratory Medicine, Madras Medical College, Chennai, Tamil Nadu, India

Corresponding Author: Madhanmohan Kalyanasundaram, Department of T.B. & Chest, Dhanalakshmi Srinivasan Medical College and Hospital, Perambalur, Tamil Nadu, India, Phone: +91 9789517650, e-mail: dr86madhan@gmail.com

How to cite this article: Kalyanasundaram M, Subramaniam S, Gowrishankar AV. Clinical Profile of Patients with Immune Reconstitution Inflammatory Syndrome in Human Immunodeficiency Virus/Tuberculosis Coinfection and their Outcome: A Prospective Observational Study. Indian J Respir Care 2023;12(1):8–11.

Source of support: Nil

Conflict of interest: None

for the development of IRIS is the disseminated disease before starting HAART in patients with the cryptococcal disease and *M. tb*.[7] This study was conducted with the objective of studying the clinical profile of patients with IRIS in HIV-TB coinfection and their outcomes.

Materials and Methods

A prospective observational study was conducted at the Government Hospital of Thoracic Medicine, Chennai, Tamil Nadu, India from January to December 2013. The Institutional Ethics Committee clearance was obtained. Patients diagnosed to have HIV and TB coinfection, patients started on ATT and ART, patients diagnosed with paradoxical IRIS, and ART naïve patients were included in the study. Patients started on ART previously, and severely ill patients were excluded. With signed informed written consent, the patients were followed up for 1 year. Clinical examination and chest X-rays, sputum smear for AFB, baseline cluster of differentiation 4 (CD4) count, ultrasonogram of the abdomen, routine blood investigations, and other necessary parameters required to determine IRIS TB in HIV/TB coinfected patients were taken. Diagnosis of IRIS TB was made, based on the definition proposed by Colebunders et al.[8] Patients were followed up to find the incidence of IRIS.

Sample Size Calculation

The sample size was calculated based on the proportion of IRIS in HIV/TB patients as 18%, as per the study by Quinn et al.[9] The absolute precision of 5 and 95% confidence level were considered. The formula by Daniel et al. was used for sample size calculation.[10] The required sample size as per the formula was 227. Another three subjects were included in addition to counter the nonparticipation rate of 1%. Hence, the total sample size was 230.

Statistical Methods

IRIS TB was considered the primary outcome variable. Outcome (alive, died) was regarded as a secondary outcome variable. Demographic variables (age, gender, smoking, and alcohol status), World Health Organization (WHO) clinical staging, sputum smear for AFB, disseminated TB, and ART regimen were considered primary explanatory variables. Mean and standard deviation was used for representing descriptive statistics in continuous variables, and frequency and proportion for categorical variables. Univariate binary logistic regression analysis was performed to test the association between the explanatory variables and outcome variables. An unadjusted odds ratio along with a 95% confidence interval (CI) is presented. Statistical significance was considered when the *p*-value was <0.05. Data was analyzed by using coGuide software, V.1.[11]

Table 1: Summary of baseline parameters (N = 230)

Parameter	*Summary*
Age (in years)	39.01 ± 9.60
Duration of ATT before ART	19.84 ± 9.34
Gender	
Female	57 (24.8%)
Male	171 (74.3%)
Transgender	2 (0.9%)
WHO clinical staging	
Stage III	143 (62.2%)
Stage IV	87 (37.8%)
Incidence of IRIS	48 (20.9%)
Sputum smear for AFB	47 (20.4%)
ART regimen	
TLE	102 (44.3%)
ZLE	128 (55.7%)

Results

A total of 230 subjects were included in the final analysis.

The mean age was 39.01 years. Out of the 230 patients, 171 were male, 57 were female, and two were transgender. Out of 230, 143 (62.2%) were in WHO clinical stage III, and 87 (37.8%) were in WHO clinical stage IV. Diagnosis of IRIS TB (paradoxical IRIS) was made in 48 (20.9%) patients. In this study, 47 (20.4%) were sputum smear-positive for AFB, 128 (55.7%) were on zidovudine + lamivudine + efavirenz (ZLE) regimen and 102 (44.3%) were on tenofovir + lamivudine + efavirenz regimen (TLE) (Table 1).

Among 230 patients, 72 (31.3%) had extrapulmonary TB, 142 (61.7%) had pulmonary TB, and 16 (7%) had both pulmonary and extrapulmonary TB, that is, disseminated TB. Other coinfections in these patients were oral candidiasis 87 (36.1%), oro-esophageal candidiasis 38 (16.5%), cryptococcal meningitis 13 (5.7%), pneumocystis pneumonia (PCP) seven (3%), and herpes zoster two (0.9%) (Table 2).

Of these 48 patients diagnosed with IRIS TB, 39 (81.2%) were male and nine (18.8%) were female, and the mean age was 39.54 years. The mean duration of a symptom of IRIS was 13.94 days. The mean duration of ATT before HAART initiation was 18.71 days. The mean duration of HAART therapy before the diagnosis of IRIS TB in these 48 patients was 68.33 days. Among these 48 patients, 23 (47.9%) had alcohol disorders and 28 (58.3%) were smokers. The mean rise in CD4 + T cell count, hemoglobin level, and weight were 143.44, 0.38% gm, and 3.67 kg, respectively. The mean duration of hospital stay was 13.08 days. Among 48 patients, 30 (62.5%) were in WHO clinical stage III and 18 (37.5%) were in WHO clinical stage IV with 16 (33.3%) sputum smear-positive for AFB and 32 (66.7%) sputum smear-negative for AFB. Within IRIS TB patients, 13 (27.1%) had extrapulmonary TB, 29 (60.4%) had pulmonary TB, six (12.5%) had both pulmonary and extrapulmonary TB; 28 (58.3%) were started on a ZLE regimen and 20 (41.7%) were started on TLE regimen among 48 patients diagnosed to be TB IRIS in HIV seropositive (Table 3).

Out of 39 males, 11 (28.21%) died whereas in females 11.11% (one out of nine) died and the relative risk of males for mortality compared to females was 2.54 (0.37–17.22). Out of 30 stage III participants, 20% (six out of 30) died and in stage IV 33.33% (six

Table 2: Summary of TB classification and coinfection (N = 230)

Parameter	*Summary*
TB classification	
Extrapulmonary	72 (31.3%)
Pulmonary	142 (61.7%)
Pulmonary and extrapulmonary	16 (7%)
Coinfection	
Oral candidiasis	87 (37.8%)
Oro-esophageal candidiasis	38 (16.5%)
Cryptococcal meningitis	13 (5.7%)
PCP	7 (3%)
Herpes zoster	2 (0.9%)
Nil	83 (36.1%)
IRIS TB	48 (20.9%)

Table 3: Summary of baseline parameters in patients diagnosed with IRIS TB (N = 48)

Parameter	*Summary*
Age	39.54 ± 8.64
Female	9 (18.8%)
Male	39 (81.2%)
Duration of symptom (in days)	13.94 ± 4.295
Duration of ATT before ART (in days)	18.71 ± 7.131
Duration of ART	68.33 ± 31.94
Rise in CD4 + count	143.44 ± 103.96
The rise in weight (in kg)	3.67 ± 2.85
The rise in hemoglobin level (gm %)	0.38 ± 0.802
Number of days of hospital stay	13.08 ± 4.635
WHO clinical staging	
Stage III	30 (62.5%)
Stage IV	18 (37.5%)
ART regimen	
TLE	20 (41.7%)
ZLE	28 (58.3%)
Sputum smear for AFB	16 (33.3%)
Smoking	28 (58.3%)
Alcohol disorder	23 (47.9%)
Outcome	
Alive	36 (75%)
Died	12 (25%)
Pulmonary/extrapulmonary	
Extrapulmonary	13 (27.1%)
Pulmonary	29 (60.4%)
Pulmonary and extrapulmonary	6 (12.5%)
Disseminated TB	7 (14.6)

out of 18) died. Compared to stage IV relative risk of mortality was 0.6 (0.23–1.58) in stage III. Sputum smear AFB positive cases reported 0.67 (0.21–2.13) relative risk of mortality compared to negative cases since the proportion of mortality was 18.75% in positive cases. Disseminated TB cases had 28.57% (two out of seven) deaths with 1.17 (0.32–4.25) relative risk of mortality compared to nondisseminated TB cases. The proportion of death was more in ART regimen TLE (50%) compared to 7.14% in ZLE and the relative risk of mortality was seven (1.72–28.55) for TLE. Smoking and alcohol habits showed a high relative risk of mortality 3.57 (0.87–14.56) and 2.17 (0.75–6.26), respectively. There was a statistically significant association with the outcome only for ART regimen and smoking since the *p*-value <0.05 (Table 4).

Discussion

With increasing access to ART worldwide, many patients still start ART with low CD4 counts. Among them, IRIS remains a common complication. It is an assorted condition with numerous case definitions in use.[12] The major findings of this prospective observational study are the incidence of IRIS among HIV-TB coinfected patients was 20.9%. Among them, 81.2% were males, and the duration of ATT before starting ART was 18.71 ± 7.131 days. Among patients with IRIS, 75% survived. A history of smoking was present in 58.3% and alcohol intake in 47.9%. These can also act as predisposing factors to the development of IRIS.

Past literature has shown a similar incidence of IRIS. A meta-analysis of 54 studies done between 1998 and 2009 showed that 13% of the cases had IRIS among 13,103 HIV-infected patients on ART.[13] The epidemiology of IRIS mirrors the epidemiology of HIV-related opportunistic infections. Various risk factors for IRIS include low CD4 count and disseminated opportunistic infection at the start of ART. In the current study, 20.4% of the patients had sputum positive for AFB. The most common opportunistic infection next to TB was oral candidiasis (37.8%). Cryptococcal meningitis,

Table 4: Comparison of demographic and clinical parameters with outcome (alive/died) in patients diagnosed to be having IRIS TB (N = 48)

	Outcome		*Relative risk*	*Fisher's exact*
Parameter	*Alive*	*Died*	*95% CI*	*p-value*
Sex				
Male (N = 39)	28 (71.79%)	11 (28.21%)	2.54 (0.37–17.22)	0.416
Female (N = 9) (reference)	8 (88.89%)	1 (11.11%)		
WHO clinical staging				
Stage III (N = 30)	24 (80%)	6 (20%)	0.6 (0.23–1.58)	0.325
Stage IV (N =18) (reference)	12 (66.67%)	6 (33.33%)		
Sputum smear for AFB				
Positive (N = 16)	13 (81.25%)	3 (18.75%)	0.67 (0.21–2.13)	0.725
Negative (N = 32) (reference)	23 (71.88%)	9 (28.13%)		
Disseminated TB (reference = no)	5 (71.43%)	2 (28.57%)	1.17 (0.32–4.25)	1.00
ART regimen				
TLE (N = 20)	10 (50%)	10 (50%)	7 (1.72–28.55)	<0.001
ZLE (N = 28) (reference)	26 (92.86%)	2 (7.14%)		
Smoking (reference = no)	18 (64.29%)	10 (35.71%)	3.57 (0.87–14.56)	0.043
Alcohol (reference = no)	15 (65.22%)	8 (34.78%)	2.17 (0.75–6.26)	0.13

herpes, and PCP were other opportunistic infections in the study patients. The mortality in the current study among patients with IRIS was 25%. Previous studies report varying mortality between 0 and 15%.[13–15] This variation in mortality is attributed to geographic distribution, associated opportunistic infection, baseline morbidity, and the level of immunosuppression. The majority, 62.2%, of the patients had stage III as per WHO clinical staging. Previous literature also indicates that the incidence of IRIS is relatively high among stage III and above status.[16]

The onset of IRIS symptoms is inconstant but is characteristically from a few days to 6 months after ART initiation. In the current study, at 18.71 ± 7.131 days, the IRIS patients were on ATT before starting ART, and the mean duration of ART before the onset of IRIS was 68.33 ± 31.94 days. While ART initiation causes IRIS, it is key to recovering immune function and improving health outcomes. Therefore, delay or discontinuation of ART due to IRIS is not usually recommended.[12] Among the patients studied, 58.3% were on the ZLE ART regimen. The type of regimen and its influence on IRIS was not studied in the current study, but it can be considered a comparison factor in future studies. The present study's limitation is that it is an observational study. Future studies on large populations with various types of IRIS are recommended.

Conclusion

The incidence of TB IRIS in the current study was 20.9%. The various factors associated with IRIS were immunosuppression, opportunistic infection, and duration of ART and ATT. The mortality caused by IRIS was 25%. Future studies should focus on better diagnostic techniques and new therapeutic interventions.

Acknowledgments

We acknowledge the technical support in data entry, analysis, and manuscript editing by Evidencian Research Associates.

References

1. WHO. Global Tuberculosis Report 2017 [Internet]. World Health Organisation. 2017. [Cited 2021 May25]. Available from: https://www.who.int/tb/publications/global_report/gtbr2017_main_text.pdf
2. Breton G. Immune reconstitution inflammatory syndrome. Bull Acad Natl Med 2011;195(3):561–575. DOI: 10.1016/S0001-4079(19)32064-3
3. Mutnal MB, Schachtele SJ, Hu S, et al. T-cell reconstitution during murine acquired immunodeficiency syndrome (MAIDS) produces neuroinflammation and mortality in animals harboring opportunistic viral brain infection. J Neuroinflammation 2013;10(1):98. DOI: 10.1186/1742-2094-10-98
4. Pozniak AL, Coyne KM, Miller RF, et al. British HIV Association guidelines for the treatment of TB/HIV coinfection 2011. HIV Med 2011;12(9):517–524. DOI: 10.1111/j.1468-1293.2011.00954.x
5. Kumarasamy N, Chaguturu S, Mayer KH, et al. Incidence of immune reconstitution syndrome in HIV/tuberculosis-coinfected patients after initiation of generic antiretroviral therapy in India. J Acquir Immune Defic Syndr 2004;37(5):1574–1576. DOI: 10.1097/00126334-200412150-00007
6. Karmakar S, Sharma SK, Vashishtha R, et al. Clinical characteristics of tuberculosis-associated immune reconstitution inflammatory syndrome in North Indian population of HIV/AIDS patients receiving HAART. Clin Dev Immunol 2011;2011:239021. DOI: 10.1155/2011/239021
7. Lortholary O, Fontanet A, Mémain N, et al. Incidence and risk factors of immune reconstitution inflammatory syndrome complicating HIV-associated cryptococcosis in France. AIDS 2005;19(10):1043–1049. DOI: 10.1097/01.aids.0000174450.70874.30
8. Colebunders R, John L, Huyst V, et al. Tuberculosis immune reconstitution inflammatory syndrome in countries with limited resources. Int J Tuberc Lung Dis 2006;10(9):946–953.
9. Quinn CM, Poplin V, Kasibante J, et al. Tuberculosis iris: Pathogenesis, presentation, and management across the spectrum of disease. Life (Basel) 2020;10(11):262. DOI: 10.3390/life10110262
10. Daniel W. Determination of sample size for estimating proportions. Biostat A Found Anal Heal Sci 1999;8:189–190.
11. BDSS Corp. Released 2020. coGuide Statistics software, Version 1.0, India: BDSS corp. Available from: https://www.coguide.in. [Last accessed on 2021 Apr 5]
12. Walker NF, Scriven J, Meintjes G, et al. Immune reconstitution inflammatory syndrome in HIV-infected patients. HIV/AIDS (Auckl) 2015;7:49–64. DOI: 10.2147/HIV.S42328
13. Müller M, Wandel S, Colebunders R, et al. Immune reconstitution inflammatory syndrome in patients starting antiretroviral therapy for HIV infection: a systematic review and meta-analysis. Lancet Infect Dis 2010;10(4):251–261. DOI: 10.1016/S1473-3099(10)70026-8
14. Letang E, Lewis JJ, Bower M, et al. Immune reconstitution inflammatory syndrome associated with Kaposi sarcoma: higher incidence and mortality in Africa than in the UK. AIDS 2013;27(10):1603–1613. DOI: 10.1097/QAD.0b013e328360a5a1
15. Ablanedo-Terrazas Y, Alvarado-De La Barrera C, Reyes-Terán G. Towards a better understanding of Kaposi sarcoma-associated immune reconstitution inflammatory syndrome. AIDS 2013;27(10):1667–1669. DOI: 10.1097/QAD.0b013e328360106b
16. Balkhair A, Ahamed S, Sankhla D. Unmasking immune reconstitution inflammatory syndrome (IRIS): a report of five cases and review of the literature. Sultan Qaboos Univ Med J 2011;11(1):95–103.