e-ISSN: 0975-1556, p-ISSN:2820-2643

Available online on www.ijpcr.com

International Journal of Pharmaceutical and Clinical Research 2023; 15(3); 580-586

Original Research Article

Early versus Delayed Initiation of Anti-Retroviral Therapy in HIV–TB Co- Infected Patients on Anti Tuberculosis Treatment

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Received: 26-10-2022 / Revised: 30-11-2022 / Accepted: 20-12-2022
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Conflict of interest: Nil

Abstract

Introduction: The optimal time to initiate antiretroviral therapy (ART) in HIV-TB coinfection is challenging due to the higher incidence of TB-Immune Reconstitution Inflammatory Syndrome (IRIS) and other adverse effects. HIV-TB coinfection poses a challenge of drug interaction between ART and antitubercular treatment (ATT) and higher mortality in this subgroup. Previous research has shown that early ART initiation increases the chance of TB-IRIS but decreases HIV-TB-associated mortality.

Aim: To assess the proportion of TB-IRIS, CD4 cell count, HIV disease progression and TB treatment outcome during early vs. delayed ART initiation in HIV-TB coinfected patients on ATT.

Materials and Methods: The present study was a unicentric prospective comparative clinical trial conducted at the Tertiary care hospital in collaboration with the institutional ART centre from January-2013 to January-2014. After initial screening of HIV-TB coinfected patients, 60 eligible participants were enrolled in the study and further randomly divided into two groups using a simple randomization technique. Group-A (n=30) received ART within 2-8 weeks of ATT initiation and Group-B (n=30) received ART after 8 weeks of ATT initiation. These patients were assessed to compare the proportion of TB-IRIS, CD4 cell count (at baseline, 6- and 12-month interval), HIV disease progression, and TB treatment outcome. The data was statistically analysed using the Student's T test for baseline parameters and the chi-square test for treatment comparisons between the two groups. A p-value of less than 0.05 was considered statistically significant.

Results: There was no statistically significant difference in baseline characteristics and laboratory parameters. Among the 60 patients with HIV-TB coinfection who were initiated on ART, there was no significant difference in proportion of TB-IRIS, tuberculosis treatment outcome or mortality in either of the groups. There was a significant improvement in 6-month (p=0.016) and 12-month (p=0.001) CD4 cell counts in early ART initiation group.

Conclusion: The CD4-cell count improvement which is statistically significant in Group-A denotes slower HIV disease progression. With a statistically non-significant rate of increased TB-IRIS in Group-A, it is preferred to initiate ART before 8 weeks (early) in HIV-TB coinfection patients who were on ATT.

Keywords: CD4-cell, TB-IRIS, HIV disease, Immune Reconstitution Inflammatory Syndrome.

Introduction

Human Immunodeficiency virus (HIV) and Tuberculosis (TB) persist as public health challenges on a national and global platform. According to the Global TB Report 2021, the estimated incidence of all forms of TB in India for the year 2020 was 188 per 1,00,000 people (129-257), while HIV-positive TB incidence and mortality were 3.8 (2.6-5.2) and 0.78 (0.71-0.84) per 1,00,000 people, respectively. Compared to people living without HIV infection residing in the same country, people living with HIV (PLHIV) have a 29-fold increased risk of developing tuberculosis disease. [1]. The notified TB patients should know their HIV status and treatment should be initiated accordingly. The potential risks of starting ART early in TB treatment may include drug toxicity, drug–drug interactions, a perceived high pill burden for patients and immune reconstitution inflammatory syndrome (IRIS), all of which may affect adherence and retention in care [2,3].

The present question of when to initiate ART in HIV-TB co-infection patients at the time of TB diagnosis is seems to be controversial in spite of having previous published systemic reviews and meta-analysis reports in the literature. Early initiation is dooming patients with TB-IRIS and other adverse effects. In this study, the early ART initiation group (2 to 8 weeks after initiation of ATT) and the late ART initiation group (after 8 weeks of initiation of ATT) were compared for the proportion of TB-IRIS, CD4 cell count, progression of HIV and tuberculosis treatment outcome. This study will help us determine the optimal time to initiate ART in HIV-TB co-infection patients.

Materials and Methods

The Unicentric prospective comparative study was conducted at Tertiary care hospital in collaboration with the institutional ART centre after obtaining approval from the Institutional Ethics Committee for Human Studies. The study was conducted from January 2013 to January 2014. All HIV-TB coinfected patients who were not on ART were thoroughly examined physically along with baseline laboratory investigations and further categorised according to RNTCP guidelines for initiating ATT.

Inclusion Criteria:

- Age ≥18 years
- Confirmed Pulmonary or Extra Pulmonary Tuberculosis on ATT
- HIV positive Patients not started on ART

Exclusion Criteria:

- Age < 18 years
- Patients with comorbidities namely diabetes mellitus, Systemic hypertension and chronic kidney disease
- HIV positive patients who were already on ART

Written informed consent was obtained from only those patients who met the above criteria, and confidentiality was maintained throughout the study period. Sixty eligible patients were randomly assigned into Group-A (2 to 8 weeks:

n=30) and Group-B (more than 8 weeks: n=30) according to time of ART initiation. Here we considered Group-A as an early ART initiation group and Group-B as a late ART initiation group. NACO provided the antiretroviral drugs free of cost, which were dispensed through the institutional ART center. Patients were followed up periodically for 12 months to assess the frequency of TB-IRIS, CD4 count (baseline, 6 months, and 12 months), HIV progression, and TB outcome.

Statistical Methods:

Descriptive statistics were used to compare baseline characteristics. Proportion of TB-IRIS, CD4 cell count, progression of HIV and TB treatment outcomes over time were summarized as proportions and medians and comparison tested using the chi-square.

Results

There were no statistically significant differences in the distribution of age, sex, and laboratory parameters (haemoglobin, total blood count, CD4 cell count, ESR, urea, creatinine, AST, and ALT) in the trial participants. The median age of enrolled patients was 39 years (18–58 years). Among 36 (60%) males, 20 (33%) were enrolled in early and 16 (27%) were enrolled in delayed ART initiation group. Among 24 (40%) females, 10 (17%) were enrolled in early and 14 (23%) were enrolled in delayed ART initiation group. Pulmonary TB was diagnosed in 54 patients, and among them, 49 were sputum smear-negative and 5 were sputum smear-positive for AFB. The remaining 6 patients had extra pulmonary manifestations with lymphadenopathy in 2, pleural effusion in 2, TB meningitis and abdominal TB in one each. CAT-1 ATT was initiated in 58 patients, and CAT-2 was initiated in 2 patients, who also belonged to the early ART-initiated group. TB-IRIS was manifested in 4 patients of the early group (13.3%) and in 1 (3.3%) patient of the late group, and the difference was not statistically significant. Of those 5 patients, 3 had pulmonary TB and 2 had extra pulmonary TB. Among the TB-IRIS manifested patients, 4 had received CAT-1 and 1 had received CAT-2 ATT. All 60 patients had completed ATT and among them, 1 from each group died. Patients were also monitored for drug-related adverse effects and were managed appropriately. This doesn't affect the participation of patients in the trial. All 60 patients adhered to the treatment schedule, and there were no dropouts in our study.

Table 1: Baseline characteristics of TB-HIV coinfected patients

Characteristics	n (60)	% (100)
Gender		
Male	36	60
Female	24	40
Age (years)		
18-20	2	3.3
21-30	9	15
31-40	23	38.3
Above 40	26	43.3
TB-related information		
Pulmonary TB	54	90
Extrapulmonary TB	6	10
• Lymphadenopathy • Pleural effusion • Tuberculosis meningitis • Abdominal TB	2 2 1 1	

Sputum test		
No sputum	6	10
AFB positive	5	8.3
AFB negative	49	81.7
TB treatment regimen		
CAT-1 regimen	58	96.7
CAT-2 regimens	2	3.3
ART initiation		
2-8 weeks	30	50
More than 8 weeks	30	50

Table 2: Comparison of TB-IRIS and outcome of tuberculosis treatment in early and late ART initiation groups.

IRIS	**2 to 8 weeks (n=30)**	**More than 8 weeks (n=30)**	**Total (n=60)**	**Statistical inference**
Nil	26(87%)	29(96.7%)	55(91.7%)	X^2=2.071 df=3 0.344 > 0.05 Not Significant
Fever	1(3.3%)	1(3.3%)	2(3.3%)	
INC NODE	1(3.3%)	0	1(1.7%)	
INC PLU	1(3.3%)	0	1(1.7%)	
INC PUL	1(3.3%)	0	1(1.7%)	
IRIS- Immune Reconstitution Inflammatory Syndrome, INC NODE- Increased lymphadenopathy, INC PLU- increased pleural effusion, INC PUL- increased pulmonary infiltrates				
Outcome of TB				
Complete	29(96.7%)	29(96.7%)	58(96.7%)	X^2=0.000 df=1 1.000 > 0.05 Not Significant
Died after ATT	1(3.3%)	1(3.3%)	2(3.3%)	

Table 3: CD4 cell counts before, after 6 & 12 months of ART therapy

Baseline CD-4 cell counts before starting ART	**Mean**	**S.D**	**Statistical Inference**
2 to 8 weeks (n=30)	170.33	77.064	T=0.988 df=58 0.327 > 0.05 Not Significant
More than 8 weeks (n=30)	152.17	64.815	
CD-4 cell count after 6 months starting ART			
2 to 8 weeks (n=30)	211.93	101.137	T=2.477 df=58 0.016 < 0.05 **Significant**
More than 8 weeks (n=30)	158.37	61.640	
CD-4 cell count after 12 months starting ART			
2 to 8 weeks (n=30)	264.93	133.098	T=3.367 df=58 0.001 < 0.05 **Significant**
More than 8 weeks (n=30)	174.60	62.243	

Discussion

In our study, we found a male preponderance (60%) in ART initiation, indicating that barriers to ART for females exist (Table/Fig 1). Grouping of patients with respect to age revealed that majority of subjects (43.3%) belonged to above 25-44 years age group which indicates that most patients affected by HIV/AIDS are in the sexually active group similar to a study conducted in Karnataka around 2012 with

also showed higher prevalence among males (75.3%), in the sexually active age group 31-45 years (61.3%) [4]. In a retrospective cohort study conducted in Pune, it was reported that the earlier administration of ART irrespective of the CD4 cell counts reduced the rate of incident TB, and there was a higher prevalence of baseline TB among male patients [5]. A Chinese meta-analysis reported that males were found to be at a 73% higher risk of advanced HIV disease at their first clinic visit as compared to females [6].

Immune Reconstitution Inflammatory Syndrome (IRIS) is an exaggerated inflammatory response after ART initiation. Many retrospective and prospective studies have reported that 7–43% of patients with HIV-TB co-infection develop IRIS within 5 days of starting ART, with the most common time of IRIS presentation being 2 to 6 weeks, but it can occur at 1 to 4 years also [7]. The frequency of TB-IRIS was 12.6% when ART and ATT were started concomitantly [8]. A similar frequency of TB-IRIS in the early ART-initiated group (13.3%) was noted in this present study without mortality.

A retrospective study in Capetown has shown a decrease in TB mortality with an increase in CD4 count and was most strongly associated with the initiation of ART during TB treatment [9]. In a study from Tanzania, an increase in CD4 count was strongly associated with the initiation of ART [10]. Prospective Ethiopian research reported an increasing CD4 count in TB patients on ATT irrespective of their HIV positive or negative status. The continuous increase of CD4 cell counts during treatment for TB strongly suggests that TB per se contributes to subnormal CD4 cell levels in peripheral blood. Other researchers have reported similar findings in HIV-negative TB patients, both in Africa and elsewhere, but the reasons for this phenomenon, as well as its clinical significance, are not well understood [11]. In our recent study, a significant improvement in CD4 cell counts in the early initiation group at 6th and 12th months indicated that HIV disease progression was slower in the early ART group than in the late ART group amidst a non-significant higher frequency of IRIS in the early ART group.

Research done in Northern Tanzania analysed mortality trends from 2012 to 2017 for HIV and HIV-TB subpopulations over the 6-year period and reported a 40% higher mortality rate in HIV-TB coinfected patients when compared with PLHIV who don't have TB after adjusting for age, sex, residence, WHO stage, and bodyweight [2]. The death rate noted in our present study was 3.3%, which happened after the completion of ATT, and no significant differences in tuberculosis treatment outcomes among the two groups were noted.

A recent systematic review and meta-analysis which was done comparing early ART (≤4 week) versus later ART (>4 week) initiation in HIV-TB coinfection reported no difference in mortality and a non-significant slight increase in incidence of IRIS in people with all CD4 counts. When they stratified the analysis with respect to the CD4 counts, IRIS was slightly higher when ART was initiated less than 4 weeks in patients with CD4 counts of 50 cells/mm^3, but there was a reduced risk of death. Our research has also shown a similar trend in IRIS frequency, and it is the correct recommendation included in the March 2021WHO guidelines [3]. Another systemic review and meta-analysis call for clinical judgement as early ART was associated with a lower risk of overall mortality and TB treatment failure compared with late ART. This major concern of the early initiation of ART was due to overlapping toxicity profiles like hepatotoxicity, cutaneous reactions, renal impairment, neuropathy, and neuropsychiatric adverse

effects, drug interactions, and high pill burden. However, delayed ART initiation may be associated with an increased risk of AIDS-related illness and death. [12,13]

Conclusion

In our study, even though there is a non-significant increase in TB-IRIS in the early ART group compared to the delayed ART group, early ART initiation is preferred in view of delaying HIV disease progression based on the improvement in CD4 counts in those patients and not affecting tuberculosis treatment outcome.

The limitations of the study were smaller sample size, shorter study duration, simple random allocation of participants to the treatment arms, lack of blinding, and lack of assessment of quality of life, disability grading and HIV-RNA plasma viral quantitative assessment.

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