Clinicodemographic profile and outcome of tuberculosis treatment in TB-HIV co-infected patients receiving daily ATT under a single window TB-HIV services delivery initiative

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Abstract

The risk of death in HIV-TB coinfected individuals is far greater than in HIV-only patients. It is critical to provide timely and appropriate therapy in HIV-TB coinfected patients in order to reduce morbidity and mortality. The purpose of this study was to evaluate the clinical presentation and outcome of TB treatment in HIV-TB co-infected patients receiving daily anti-tubercular therapy (ATT) and concurrent antiretroviral therapy (ART) at a tertiary respiratory care centre in New Delhi, India. The research was cross-sectional, observational, and hospital-based A. From September 2018 to August 2019, a total of 53 patients with HIV-TB coinfection were enrolled at the Institute's ART centre. Patients were evaluated with a structured proforma. Data were evaluated using SPSS version 23.0 and a p-value of less than 0.05 was considered statistically significant. Among the patients enrolled, the mean age was 35.98 years. Among the patients enrolled, 56.6% patients had EPTB, 32% had PTB and 11.3% had both PTB and EPTB. The majority of the enrolled patients (n=46, 86.7%) had favourable TB treatment outcomes, while 13.3% (n=7) had unfavourable outcome [including death (n=5) and loss to follow-up (n=2)]. During the study and follow-up period, no patients were transferred out or relapsed. In univariate analysis, low SES, bedridden functional status, low BMI, anaemia, hypoalbuminemia, and a low CD-4 cell count (<100 cells/mm^3) were significantly associated with an unfavourable outcome. Bedridden functional status (p=0.002), anaemia (p=0.040), and low BMI (p<0.001) were independently associated with a poor outcome. Adequate disease knowledge and health education can be very beneficial in reducing morbidity and mortality. Early ART in combination with ATT can reduce mortality in TB-HIV co-infected patients.

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Key words: tuberculosis; TB-HIV co-infection; risk factors; outcome.

Contributions: DM, UA, LK, VV, AS, study concept; DM, UA, LK, AS, definition of intellectual content; DM, VV, literature research; DM, VV, UA, manuscript preparation; DM, UA, VV, LK, AS, manuscript editing; Manuscript review and final approval: all author's

Conflict of interest: the authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Ethics approval and consent to participate: ethical approval was obtained from Institutional Research and Ethical Committee (Office letter no: NITRD/PGEC/2018/6617). Informed written consent was obtained from the patients included in this study.

Patient consent for publication: not applicable.

Availability of data and materials: all data generated or analysed during this study are included in this article.

Received: 11 August 2022.
Accepted: 27 September 2022.
Early view: 5 October 2022.

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Monaldi Archives for Chest Disease 2023; 93:2405
doi: 10.4081/monaldi.2022.2405

Introduction

As one of the leading causes of morbidity and mortality worldwide, tuberculosis remains a significant threat. In 2020, 1.5 million people died of tuberculosis (TB) all over the world, including 0.21 million HIV-TB coinfected deaths [1]. In India, the incidence of TB cases in 2021 was 1.93 million and of them, 53,000 were HIV-TB coinfected [2]. In 2020, there were 0.49 million deaths from TB in India. The number of deaths among HIV-TB coinfected patients was 11,000 in 2021 [2]. HIV-TB coinfected individuals have a higher death rate than HIV-infected patients without TB. HIV infection has the strongest known effect on the progression of latent TB infection to TB disease. It is 26-31 times more likely for people who live with HIV to develop TB infection than people who do not live with HIV [2]. The risk of recurrence of TB infections is also high in HIV-infected patients.

It is important to note that many of the countries affected by these two diseases are resource-poor settings. Providing timely and appropriate therapy is crucial to reducing morbidity and mortality

in HIV-TB coinfected patients. Moreover, this approach helps prevent the transmission of TB within the population [3].

HIV-infected people with TB present with different clinical presentations depending on their level of immunosuppression. An upper lobe predominant disease and positive sputum smear for acid-fast bacilli (AFB) are characteristic of patients with relatively preserved immune function (CD4 counts >200 cells/mm3) whereas patients with severe immunosuppression are more likely to manifest with atypical clinical and radiographic features. EPTB is also more common in severe HIV infection [4].

The Revised National Tuberculosis Control Programme (RNTCP) rolled out daily anti-tubercular therapy (ATT) regimen for HIV-TB cases in January 2017 and for all TB patients throughout India in the 2nd-3rd quarter of 2017 [5]. There are some studies in the past from India using alternate day ATT regimen in HIV TB coinfection cases, recent studies show better outcomes of TB with daily short course ATT regimen of 6 months duration in comparison to the alternate regimen [6,7]. Therefore, we undertook this study with the aim to assess the clinical presentation and outcome of TB treatment in HIV co-infected patients who receive daily ATT and are concurrently treated with ART under a single window TB/HIV services delivery initiative.

Materials and Methods

Study design

It is a single centre-based, cross-sectional observational study carried out among patients with PLHIV who attended the Anti-Retroviral Therapy (ART) centre of the institute from September 2018 to August 2019. Ethical approval was obtained from Institutional Ethical Committee (Office letter no: NITRD/PGEC/ 2018/6617). The study aimed to assess clinical presentation, outcome and risk factors associated with the outcome of TB treatment in HIV-TB co-infected patients receiving daily ATT (Under the RNTCP) and concurrently treated with ART under a single window TB/HIV services delivery initiative at a tertiary respiratory care centre in New Delhi, India.

Sample size

This was a study done between September 2018 to August 2019. According to a study by Sinshaw *et al*. [8], the prevalence of favourable outcome is 77%, hence p=0.77.

Hence sample size:

$$N = \frac{(Z_{\alpha/2})^2 \times P \times (1-P)}{E^2} = \frac{(1.96)^2 \times 0.77 \times (1-0.77)}{(0.05)^2} = 272$$

$Z_{\alpha/2}$=Z statistic at 95% confidence interval=1.96
P=Prevalence
E=Precision assumed to be 0.05

According to hospital records in the previous year, among 326 HIV patients receiving treatment at NITRD, 73 patients (including 6 multi-drug resistant (MDR) tuberculosis patients and 4 patients <18 years of age) were diagnosed to have HIV-TB co-infection in one year. Hence, we applied the finite population correction to the sample:

$n_0 = \frac{n \times N}{n+(N-1)}$ where, n=63 (excluding MDR patients and age <18 years) and N=272

=51.3≈52. After applying the formula, the resulting sample size obtained was 52 and it was rounded up to 53.

Study subject

Following patients were included in the study with the necessary inclusion and exclusion criteria after taking informed written consent.

Inclusion/exclusion criteria

All patients between 18-70 years with PLHIV including both ART-naïve and those already on ART diagnosed with active TB disease (including patients who were newly diagnosed with TB and those who were previously treated for TB) were recruited in the study at the time of anti-tubercular therapy (ATT) initiation (we defined these patients as HIV-TB coinfected); and TB cases included pulmonary TB (PTB), extrapulmonary TB (EPTB) and patients with a combination of the two were included in the study. Exclusion criteria were patients aged <18 years and PLHIV patients with microbiologically confirmed drug-resistant TB.

Methods

Patients enrolled in the study were evaluated using a structured clinical evaluation proforma. Their demographic details including socio-economic status (SES) [9], functional status [10], clinical presentation, type of TB disease, chest radiography, sputum examination, haemoglobin levels, serum albumin and CD4 cell counts were documented. Every enrolled patient was followed up for a period of 6 months from the diagnosis for documenting the outcome (except in the cases of CNS TB and TB psoas abscess where they were followed up for 12 months). Treatment completed and cured were considered as favourable outcomes while lost to follow up (LTFU) and death were considered as unfavourable outcomes. Diagnosis of HIV was done as per the National AIDS Control Programme (NACP) guidelines. Diagnosis of TB disease was done using sputum microscopy for AFB and GeneXpert MTB/Rif for suspected PTB cases. Other corroborative tests like USG abdomen, pleural fluid analysis, CT scan of thorax, FNAC and GeneXpert MTB/Rif of cervical or inguinal lymph nodes, MRI of brain and spinal cord were done depending on the site of TB disease. Only rifampicin sensitive tuberculosis (PTB and EPTB) cases were included except in situations like abdominal TB and pleural effusion where GeneXpert MTB/Rif was not feasible; clinico-radiological, cytological and biochemical study aided us in diagnosing these cases. Daily, supervised ATT comprising of fixed dose combinations (FDC) of isoniazid, rifampicin, pyrazinamide and ethambutol was given for 6 months in all cases except CNS TB and TB psoas abscess where the treatment was prescribed for 12 months according to NTEP guidelines. ART in the form of FDC of tenofovir, lamivudine and efavirenz and alternate second-line regimen including FDC of zidovudine, lamivudine and efavirenz as a once-daily dose was given as treatment for HIV as per National AIDS Control Organization (NACO) guidelines. HIV viral load determination was not available under the national programmes and hence was not assessed.

Statistical analysis

The collected data were transformed into variables, coded, and entered in Microsoft Excel. The data were analysed and statistically evaluated using SPSS (Statistical Package for Social Studies) Windows version 23.0. Quantitative data were expressed in mean and standard deviation while qualitative data were expressed in

percentage and compared using *t*-test. The differences between the proportions were tested using Chi-square test, Fischer's exact test, and multiple linear regression analysis. A p-value <0.05 was considered statistically significant.

Results

A total of 60 newly diagnosed patients with HIV-TB coinfection were enrolled during the study period among a total of 305 HIV patients screened for TB. Of these, 7 patients were excluded (4 patients were diagnosed with multi-drug resistant (MDR) tuberculosis and 3 patients did not provide consent) and the rest 53 patients who met the inclusion criteria were enrolled for the study.

Among the enrolled patients, the mean age of the study participants was 35.98±11.37, and 84.9% (n=45) were male. The majority (66%, n=35) belonged to lower socio-economic status (SES) according to the modified Kuppuswamy scale. The functional status of the enrolled patients (defined as per validated and accepted WHO criteria) revealed 86.7% (n=46) of patients were from the working class, 3.7% (n=2) were ambulatory and 9.4% (n=5) were bedridden. BMI <18.5 kg/m^2 was seen in 44 patients (83.1%).

Among the patients enrolled, 56.6% patients had EPTB, 32% had PTB and 11.3% had both PTB and EPTB. The majority of the patients, 98.12% (n=52) were ART naïve and one patient (1.88%) was already on ART. Cavities in chest radiographs were present in 30.2% of patients. Sputum microscopy for AFB showed smear 3+ in 34.7% of patients while in the rest 65.3% bacillary load was <3+ (includes 2+,1+, scanty and smear-negative patients). The distribution of the enrolled patients is shown in Figure 1. Among presenting symptoms of active TB, fever (n=47, 88.6%) was the most common clinical finding in our study followed by weight loss (n=43, 81.1%), cough (n=32, 60.3%), chest pain (n=20, 37.7%), night sweats (n=17, 32%), diarrhoea (n=7, 13.2%), shortness of breath (n=7, 13.2%), and abdominal pain (n=5, 9.4%). Presenting symptoms are shown in Figure 2.

Anaemia (Hb <12 g/dl) was seen in 60.3% of patients. Among the patients with anaemia, 56.2% had Hb levels between 9 to 11 g/dl. Mean Hb level with favourable outcomes was 11.3±2.3 while among unfavourable outcome was 10.0±2.35. Serum albumin level <3.5 g/dl was seen in 52.8% of the patients. All unfavourable outcome patients had low serum albumin levels (<3.5 g/dl) with a mean value of 2.77±0.35. Seventy-one percent (71%) of them with unfavourable outcomes had a CD4 cell count of less than 100 cells/mm^3. The mean CD4 count (n=46, 87%) at TB diagnosis was 190±137.03 while that at the completion of TB treatment (excluding patients with unfavourable outcome, n=7) was 277±190.12. Among the patients enrolled, 81.1% of patients were new cases of TB, while 18.9% were previously treated TB cases. Patient characteristics associated with the outcome is depicted in Table 1.

Among the enrolled patients, the majority (86.7%) had favourable TB treatment outcomes [including cured (n=22) and treatment completed (n=24)] while 13.3% of the patients had unfavourable outcomes [including death (n=5) and lost to follow-up (n=2)]. None of the patients had transfer out or relapse during treatment and follow-up. In univariate analysis, low SES (p=0.002), bedridden functional status (p=0.001), low BMI (<0.001), hypoalbuminemia (p=0.010), anaemia (p=0.015) and low CD-4 cell count (<100 cells/mm^3) (p=0.015) had a statistically significant association with unfavourable outcome. Univariate analysis of the factors associated with the

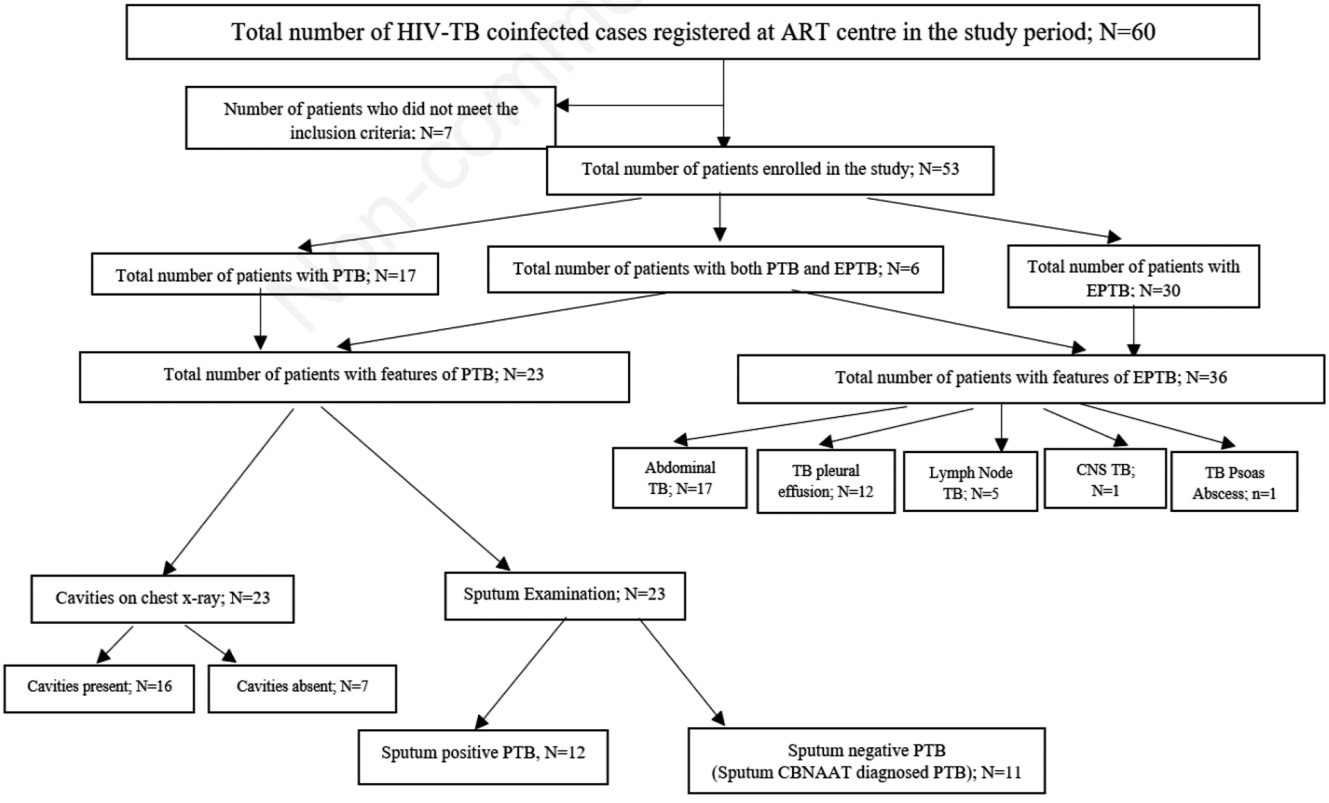

Figure 1. Distribution of the enrolled patients in the study.

outcome is shown in Table 1. Multiple logistic regression analysis was carried out on the factors that were statistically significant in the univariate analysis. Variables including Low SES, bedridden functional status, hypoalbuminemia, anaemia and low CD-4 cell count (<100 cells/mm^3) were analysed for the unsuccessful outcome. Bedridden functional status [OR: 16.50 (2.100-129.629), p=0.002], low BMI [OR: 86.00 (7.654-966.212), p<0.001] and anaemia [OR: 10.23 (1.134-92.380), p=0.040] were independently associated with unfavourable outcome. Multivariate analysis of the factors associated with the outcome is shown in Table 2.

Discussion

Before the advent of ART, HIV infection carried a very high mortality rate [11]. The Indian government made ART freely accessible in 2004 after introducing it in 1996. But at this point, ATT was given as alternate-day dosing regimen. From 2006 onwards, the anti-tubercular therapy for drug-sensitive TB became a daily FDC regimen under the single window TB/HIV services delivery system, wherein TB treatment for PLHIV was provided from HIV clinics (ART Centres) instead of Directly Observed Treatment Short Course (DOTS) Centres. Data related to TB treatment outcomes when ATT is provided in this setting is still sparse. Hence, we conducted this study in a tertiary care hospital running a specialized HIV clinic for the last 15 years.

In our study, the majority (57%) of patients in our study had EPTB similar to the findings in the studies by Chennaveerappa *et*

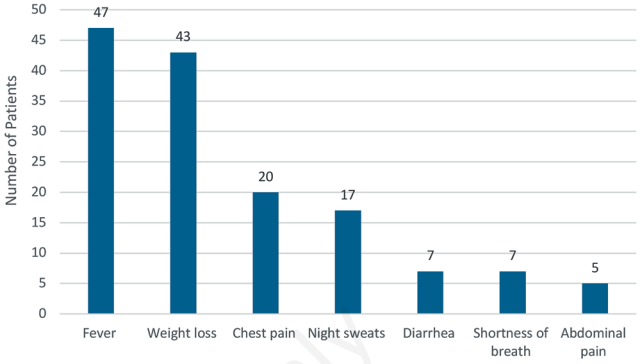

Figure 2. Presenting symptoms of active tuberculosis among the enrolled patients.

Table 1. Patient characteristics with the outcome of tuberculosis.

Parameters	Subgroups	Favourable outcome n=46 (%)	Unfavourable outcome n=7 (%)	Univariate analysis p-value
Age (years)	≥35	22 (47.8)	4 (57.1)	0.478
	<35	24 (52.2)	3 (42.9)	
Sex	Males	39 (84.7)	6 (85.7)	1
	Females	7 (15.3)	1 (14.3)	
Marital status	Unmarried	13 (28.2)	0 (0)	0.174
	Married	33 (71.7)	7 (100)	
Socio-economic status	Upper middle	4 (8.6)	0 (0)	0.002
	Lower middle	14 (30.4)	0 (0)	
	Upper lower	23 (50)	2 (28.5)	
	Lower	5 (10.8)	5 (71.5)	
Functional status	Working	43 (93.4)	3 (42.8)	0.001
	Ambulatory	1 (2.1)	1 (14.2)	
	Bedridden	2 (4.3)	3 (42.8)	
BMI	≤18.5 kg/m^2	3 (6.5)	6 (85.7)	<0.001
	>18.5 kg/m^2	43 (93.4)	1 (14.2)	
Type of tuberculosis	PTB	15 (32.6)	2 (28.5)	0.954
	EPTB	26 (56.5)	4 (57.1)	
	PTB with EPTB	5 (10.8)	1 (14.2)	
Previously treated with ATT	Yes	9 (19.5)	1 (14.2)	1
	No	37 (80.4)	6 (85.7)	
Chest X-ray laterality	Unilateral	5 (10.8)	1 (14.2)	0.954
	Bilateral	15 (32.6)	2 (28.5)	
	Normal	26 (56.6)	4 (57.1)	
Cavity in chest X-ray	Yes	14 (30.4)	2 (28.5)	0.920
	No	32 (69.5)	5 (71.4)	
Anaemia (Hb <12 g/dl)	Yes	17 (37)	6 (85.7)	0.015
	No	29 (63)	1 (14.2)	
Hypoalbuminemia(<3.5 g/dl)	Yes	21 (45.6)	7 (100)	0.010
	No	25 (54.3)	0 (0)	
CD4 cell count at TB diagnosis (<100 cells/mm^3)	Yes	10 (21.7)	5 (71.4)	0.015
	No	36 (78.2)	2 (28.5)	

BMI, body mass index in kg/m^2.

al. [12], and Sharma *et al*. [13] where a greater number of patients had EPTB than PTB. Predominant USG abdomen findings in our study were ascites, abdominal lymph node enlargement and hepatomegaly which was similar to the study by Sinkala *et al*. [14]. The abdomen is a frequent site for tuberculosis in PLHIV who present with non-specific symptoms. As ultrasound of the abdomen has high specificity for diagnosing abdominal TB [15], it should be an integral part of intensified case finding for HIV-infected individuals living in countries with high TB burden.

Lower SES, bedridden functional status, low BMI, anaemia, low serum albumin levels, and CD-4 count <100 cells/mm^3 were the factors found to be significantly associated with unfavourable outcomes in our study. The majority of the enrolled patients (61%) in our study belonged to lower SES as per the modified Kuppuswamy Scale. All patients with lower SES had an unfavourable outcome and the association was significant. Lower SES is a proven risk factor for unfavourable outcomes in TB [16,17] and in HIV [18,19] as shown by a few studies in the past. Lower socio-economic status patients are more prone to have unfavourable outcome due to various factors like low nutrition, low awareness, poor living conditions, less access to healthcare and overcrowding. In our study, a significant and independent association was seen between bedridden functional status and unfavourable outcomes, similar to the studies by Gesesew *et al.* [20], and Sinshaw *et al*. [8]. Bedridden patients are probably more exposed to opportunistic infections and have poor outcome due to impaired immunity, which in turn makes them susceptible to more opportunistic infections [21]. In the study, underweight (BMI ≤18.5 kg/m^2) was significantly and independently associated with unfavourable outcomes. Being underweight is a well-known risk factor for unfavourable outcomes in TB [22]. Similarly, the studies by Damtew *et al*. [23] and others [8,24] showed a higher chance of mortality among underweight HIV-TB patients. A malnourished TB patient has lower levels of immunoglobulins, interleukin-2 receptors, and T-cell subsets (helper, suppressor-cytotoxic, and natural killer cells) [25]. This along with HIV infection probably works as a synergy to further lower the immunity thereby making HIV-TB coinfected patients prone to opportunistic infections which increases their chances of having unfavourable outcomes.

The majority of patients in our study who had poor outcomes (85.7%) had anaemia. Anaemia was also found to be significantly and independently linked to poor outcomes. In a study by Kerkhoff *et al.* [26] anaemia was found to be an independent predictor for TB in HIV-infected patients. Anaemia is also a known risk factor for mortality in HIV-TB coinfected patients [27,28]; hence, the management of anaemia in this subgroup of patients needs special attention. Our study showed the majority of patients (52.8%) had low serum albumin levels (<3.5 g/dl) and all patients with unfavourable outcomes had hypoalbuminemia. Low serum albumin is known to be a predictor of mortality in TB [29] and in HIV patients [30]. Similarly, hypoalbuminemia was also associated with poor outcomes in a study by Tabarsi *et al*. [31]. Low albumin level is indicative of poor nutritional status which renders the body susceptible to infections like TB, and HIV coinfection further decreases the chances of survival.

In our study, median baseline CD4 cell count was 163 (IQR: 83-239) and that at TB treatment outcome was 260 (IQR: 150-351); 71.4% of patients with unfavourable outcome had a CD4 count of <100 cells/mm^3. Similar findings were seen in studies done by Teklu *et al*. [32,33] and Vashishtha *et al*. [33]. A baseline CD4 count of <250 was found in 77% of the patients in our study, a finding which is also echoed in the study by Kapadiya *et al*. [34]. As per WHO recommendations, HIV programmes should perform baseline CD4 cell counts as it is the best indicator of immune status, opportunistic infections, and supports diagnostic decision-making, particularly in patients with advanced HIV disease [35].

In our study, the majority (87%) of patients had a favourable outcome (including cured and treatment completed) in comparison to unfavourable outcomes which were seen only in 13% of the patients. A study by Agarwal *et al*. [36] which was based on alternate-day ATT regimen, showed only 67.2% favourable outcomes, much lower than our study. A study by Jenks *et al*. [6] showed more individuals achieved a better clinical outcome in the daily ATT group in comparison to the intermittent ATT group (73.0% *vs* 44.1%). A metanalysis done by Khan *et al*. [37] comparing daily *vs* thrice weekly ATT regimens inferred that compared to daily therapy, thrice-weekly therapy was associated with higher rates of failure and relapse. Hence with the advent of daily ATT by the RNTCP, we can expect an increase in the number of HIV-TB patients with favourable outcomes in comparison to that during the alternate day regimen that was previously followed by the programme.

Table 2. Multivariate analysis of the factors associated with the outcome of tuberculosis.

Parameters	Subgroups	Favourable outcome n=46 (%)	Unfavourable outcome n=7 (%)	Multivariate analysis p-value	Multivariate analysis OR (95% CI)
Socio-economic status	Upper middle	4 (8.6)	0 (0)	0.772	20.50
	Lower middle	14 (30.4)	0 (0)		(3.114- 134.945)
	Upper lower	23 (50)	2 (28.5)		
	Lower	5 (10.8)	5 (71.5)		
Functional status	Working	43 (93.4)	3 (42.8)	0.002	16.50
	Ambulatory	1 (2.1)	1 (14.2)		(2.100-129.629)
	Bedridden	2 (4.3)	3 (42.8)		
BMI	≤18.5 kg/m^2	3 (6.5)	6 (85.7)	<0.001	86.00
	>18.5 kg/m^2	43 (93.4)	1 (14.2)		(7.654-966.212)
Anaemia(Hb <12 g/dl)	Yes	17 (37)	6 (85.7)	0.040	10.23
	No	29 (63)	1 (14.2)		(1.134-92.380)
Hypoalbuminemia (<3.5 g/dl)	Yes	21 (45.6)	7 (100)	0.588	17.790
	No	25 (54.3)	0 (0)		(0.958-329.768)
CD4 cell count at TB diagnosis (<100 cells/mm^3)	Yes	10 (21.7)	5 (71.4)	0.898	9.00
	No	36 (78.2)	2 (28.5)		(1.512-53.542)

There were a few limitations in our study: as this study was conducted in a tertiary care hospital which caters to referred patients from different states of the country, the results do not represent the local population. HIV-TB coinfection in patients below 18 years of age was not included in the study. This study did not take into account opportunistic infections other than TB which may influence unfavourable outcomes.

To summarize, our study was based on the 99DOTS program's daily ATT regimen combined with concurrent ART. The majority of patients in our study had positive outcomes. As a result, a daily ATT-ART regimen is the best way to effectively treat HIV-TB coinfected patients. Appropriate knowledge of the disease and factors associated with poor outcome, early screening for anaemia, adequate health education, and nutrition are all essential for optimal management and help to reduce mortality and morbidity. All patients seeking HIV treatment require tuberculosis screening and the prompt implementation of appropriate treatment regimens for dual diseases.

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