

ORIGINAL ARTICLE

INCIDENCE OF TUBERCULOSIS AND ASSOCIATED FACTORS AMONG PATIENTS ATTENDING THE HIV CLINIC AT FELEGE-HIWOT REFERRAL HOSPITAL, BAHR DAR, NORTHWEST ETHIOPIA

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ABSTRACT

Background: Although a highly active anti retroviral therapy (HAART) reduces the incidence of tuberculosis in the developed world, it remains poorly documented in resource-poor settings including the Amhara Region of Ethiopia.

Objectives: The objective was to assess the incidence and associated risk factors of TB among HIV clients under follow up at Felege Hiwot Referral Hospital (FHRH)

Methods: A retrospective cohort study with comparison groups of Pre-ART and ART was conducted at FHRH HIV Clinic at Bahir Dar, north-west Ethiopia. The charts of 219 Pre-ART and 219 ART patients were reviewed. The required sample was selected by the systematic sampling technique and was collected from April 1 to 30, 2010. Incidence rates of TB and relative risks were computed for the different comparison groups

Results: The cumulative incidence of TB was 9.6% among patients on pre-ART chronic HIV care and 3.2% among those receiving HAART (RR =0.33). Patients at the lower WHO clinical stages (Stage I-III) had lesser risk of developing TB compared to patients at WHO clinical stage IV (AOR=0.08). Patients with a baseline CD4 cell count of <200 (AOR= 11.54) and hematocrit level of less than 30 (AOR=18.12) were at higher risk of developing TB. Those who didn't take Cotrimoxazole prophylaxis had higher risk of developing TB (AOR= 36.24)

Conclusion: Incidence of TB was high among HIV patients who were not receiving ART. Low baseline CD4 cell count, low HCT, advanced WHO clinical stage, and not receiving cotrimoxazole preventive therapy were found to be at a higher risk of developing TB. An early initiation of ART may be considered to reduce the incidence of TB. Frequent checking for anaemia and maximizing the cotrimoxazole preventive therapy is also recommended.

Key words: Incidence of tuberculosis, Pre-ART, ART, Risk factors of tuberculosis.

INTRODUCTION

Tuberculosis is the most important infectious cause of adult deaths after HIV/AIDS in low and middle income countries. The situation is worse in regions with poor socioeconomic status where poverty is both the cause and effect of high HIV/AIDS prevalence (1). Tuberculosis (TB) remains a common opportunistic infection (OI) and a major cause of death among patients with HIV, especially in sub-Saharan African and Asian countries. The HIV pandemic presents a massive challenge to the control of TB at all levels in people living with HIV/AIDS (PLWHA) (2-5). The major challenge facing ART programs is TB-HIV co-infection, particularly in Africa. Findings

of different studies reemphasize that TB incidence and recurrence rates, even if reduced by ART, remain very high in HIV-infected patients accessing life-prolonging antiretroviral drugs. Various studies in sub-Saharan Africa have shown that mortality is highest in the first 3 months in patients with disseminated TB and/or CD4 count below 50cells/ μ l (6-10).

According to a study conducted in South Africa, TB incidence is highest among patients with baseline CD4 cell counts of less than 100 cells/ml and those with WHO clinical stage III and IV. Despite similar virological responses to HAART, blood CD4 cell count increases were much smaller among patients who developed TB than among those who remained free of TB (4). A previous study in South Ethiopia revealed tuberculosis incidence rate of 3.7 per 100 person years of observation in the HAART group

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and 11.1 per 100 person years of observation in the pre-HAART group (2).

HAART is one element within the framework aimed at a functional integration of control programs for TB and HIV/AIDS (11, 12), but in Ethiopia there was scarce evidence on the effect of HAART on TB control, and that was what made this research necessary. This research was conducted with the objective of assessing TB incidence rates and associated risk factors among Pre ART and ART patients at Felege Hiwot Referral Hospital, Bahir Dar, Amhara National Regional State, northwest Ethiopia.

METHODS

Study design: This was a retrospective cohort study on pre-ART and ART clients at Felege Hiwot Referral Hospital (FHRH).

Study area and period: The study was conducted at Felege Hiwot Referral Hospital found in Bahir Dar town (capital city of the Amhara National Regional State) and serves about 1,000,000 to 1,500,000 people in the catchment. Felege Hiwot Referral Hospital is one of the five-referral hospitals in the Amhara National Regional State and provides all services, including chronic HIV care, ART treatment, and screening and treatment of TB. Health professionals in the hospital apply the WHO recommendation to initiate ART for HIV/AIDS cases (13). Data was collected from April 1 to 30, 2010, among Pre-ART and ART clients enrolled between Jan 01, 2008, and Jan.1, 2010.

Source and Study population: All clients aged 15 years and above and received chronic HIV care and HAART in the ART clinics of FHRH were the source population, and clients selected from the source population by a systematic sampling method served as the study population.

Inclusion criteria: Patients 15 years and above enrolled at the pre-ART chronic HIV follow up care clinic at FHRH, Bahir Dar, from Jan.01, 2008, to Jan 01, 2010, were included.

Exclusion criteria: Patients transferred-in from other health institutions to FHRH with TB diagnosis and patients transferred from the pre-ART to ART clinic with treatment of TB were excluded.

Sample size and sampling technique: In this study, patients in pre-ART were taken as unexposed cohort,

and patients in ART were taken as exposed cohort. Epi Info 2002 was used to calculate the sample size. Accordingly, a sample size of 219 patients in the pre-ART and 219 patients on ART was required based on the assumptions of 95% confidence level, 80% power, 1:1 ratio of exposed to unexposed, 11.1% expected frequency of TB in the unexposed group, and RR of 0.33 (2). A sampling frame was developed by using the unique patient identifier number for patients on pre-ART and ART Register. Study units for the chart review were identified by using systematic sampling and the first sample was selected randomly by the lottery method. If the selected patient record didn't fulfill the inclusion criteria, the next immediate record was included.

Variables of the study:

Outcome variable of the study: Presence of TB

Independent variables:

- Received ART
- Age
- Sex
- Religion
- Marital status
- Educational status
- Occupation
- Functional status
- WHO clinical stage
- CD4 count
- Hematocrit (HCT)
- INH prophylaxis
- CPT prophylaxis
- Duration of ART initiation (for those on ART)

Operational definitions: ART patients- People Living with HIV/ AIDS enrolled for ARV therapy.
Pre ART patients- People Living with HIV/ AIDS enrolled for HIV chronic care.

Data collection: Medical records of sampled patients enrolled between Jan 01, 2008, and Jan 01, 2010, were collected from the pre-ART and ART record-room of the hospital from April 1 to 30, 2010. Data was extracted using a checklist from patient records by two trained nurses supervised by one health officer and the principal investigator.

Data processing and analysis: Extracted data were checked for completeness and entered into SPSS version 16 statistical package for analysis. Incidences of TB among the pre-ART and ART groups were calculated. For all statistical significance tests, the cut-off value set was $p < 0.05$. Relative Risk (RR) with 95% confidence interval was used to measure

the magnitude of association between the presence of TB and the different independent variables. Multiple logistic regression was applied to control confounding effects.

Ethical consideration: Ethical clearance was obtained from the School of Public Health of the University of Gondar. The necessary permission to undertake the study was obtained from Bahr Dar Town Administration Health Office and the chief executive officer of FHRH. To insure confidentiality, names were not written on the data extraction form.

RESULTS

Socio-demographic and clinical characteristics of study subjects: Records of 219 clients (80 men and 139 women) in the pre-ART cohort and 219 (82 men and 137 women) in the ART cohort were reviewed. The median age of the study subjects was 30.69 [IQR, (25-36)] and 32 [IQR, (32-40)] years in the pre-ART and ART groups, respectively. Among the study subjects, 48.4% of the pre-ART and 38.4% of the ART fell in the age range of 25-34 years. The majority of the clients, 93.6%, in the Pre-ART and 86.3% in the ART cohort, were Orthodox Christians. One hundred and nine (49.8%) in the pre-ART and 100 (45.7%) in the ART were married. In terms of occupation, 19.6% of the pre-ART and 27.4% of the ART were civil servants (Table 1).

One hundred ninety-seven (90%) in the pre-ART and 173(79%) in the ART groups were working. The predominant WHO clinical stage was stage III, 36.1% in Pre-ART and 68.1% in ART cohort. At baseline determination, clients had a median CD4 cell count of 350 cells / μ l [IQR (213-499)] in Pre-ART and 159 [IQR (75-204)] in ART (Table 2).

Incidence of Tuberculosis: Out of the total 438 HIV patients who were followed from records, 28 developed tuberculosis during the follow up period, making the overall cumulative incidence 6.4%. During the one-year follow-up period, 21 patients in the pre-ART cohort (9.6%) and 7 patients in the ART cohort (3.2%) acquired TB (Table 3). Of the patients who developed TB in the ART group, 4(57%) developed the disease within three months of ART initiation (Fig 1).

Table 1: Socio-demographic characteristics of HIV/AIDS patients at FHRH, Bahir Dar, April 2010

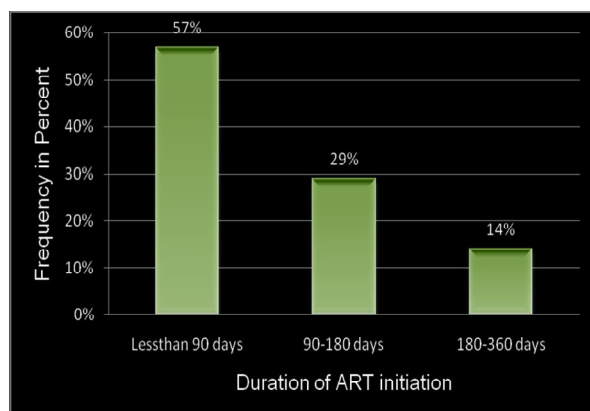
Socio-demographic Characteristics	Pre-ART (Total N=219)	ART (Total N=219)
	No (%)	No (%)
Sex		
Female	139 (63.5)	137 (62.6)
Male	80 (36.5)	82 (37.4)
Age category		
15-24	50 (22.8)	36 (16.4)
25+	169 (77.2)	183 (83.6)
Educational status		
No education	103 (47.0)	76 (34.7)
Primary	38 (17.4)	47 (21.5)
Secondary	54 (24.7)	63 (28.8)
Tertiary	25 (11.0)	33 (15.1)
Religion		
Orthodox	205(93.6)	189(86.3)
Muslim	11(5.0)	20(9.1)
Protestant	2(0.9)	6(2.7)
Other	1(0.5)	2(0.9)
Not documented	0(0.0)	2(0.9)
Marital status		
Single	35(16.0)	32(14.6)
Married	109(49.8)	100(45.7)
Divorced	50(22.8)	57(26.0)
Widowed	22(10.0)	23(10.5)
Separated	3(1.7)	7(3.2)
Occupation		
Civil servant	43(19.6)	60(27.4)
House wife	31(14.2)	39(17.8)
Daily laborer	17(7.8)	36(16.4)
Merchant	28(12.8)	28(12.8)
Construction worker	20(9.1)	12(5.4)
Farmer	15(6.8)	7(3.2)
FCSW	4(1.8)	4(1.8)
Others	16(7.3)	10(4.6)
Not documented	45(20.5)	23(10.5)

Table 2: Clinical characteristics of HIV/AIDS patients at FHRH, Bahir Dar, April 2010

Clinical Characteristics	Pre-ART	ART
	(Total N=219) No (%)	(Total N=219) No (%)
Functional status		
Bed ridden	1(0.5)	3(1.4)
Ambulatory	21(9.6)	42(19.4)
Working	197(90.0)	173(79.0)
WHO clinical stage		
Stage I	76(34.7)	20(9.1)
Stage II	56(25.6)	29(13.2)
Stage III	79(36.1)	150(68.1)
Stage IV	8(3.7)	20(9.1)
CD4 cell count		
<200	48(21.9)	84(38.4)
≥200	171(78.1)	135(61.6)
Hematocrit level		
Less than 30	25(11.4)	68(31.1)
≥30	194(88.6)	151(68.9)
Cotrimoxazol prophylaxis therapy		
Yes	105(47.9)	218(99.5)
No	114(52.1)	1(0.5)
INH prophylaxis		
Yes	7(3.2)	6(2.7)
No	212(96.8)	213(97.3)

Table 3: Incidence of TB among Pre- ART and ART clients, FHRH, Bahr Dar, Ethiopia, June, 2010.

Cohorts	Tuberculosis		
	Yes(%)	NO (%)	RR (95% CI)
Pre-ART	21 (9.6)	198 (90.4)	1
ART	7 (3.2)	212 (96.8)	0.33 (0.14,0.77)

**Figure 1:** Percentage of HIV patients who developed TB among ART cohorts at different times of follow up at FHRH, Bahir Dar, Ethiopia, June 2010**Factors Associated with Presence of Tuberculosis:**

Compared to pre-ART cohorts the cumulative incidence of TB was significantly lower in ART cohorts. HAART reduces the risk of developing TB by 67% compared to those who were only on chronic HIV care (RR =0.33, 95% CI=0.14-0.77).

When the Pre-ART and ART groups were considered separately, baseline hematocrit and CD4 cell count were found to be predictors of developing active TB during the follow-up period in both cohorts. WHO clinical stage and Cotrimoxazol prophylactic therapy predicted the incidence of TB only among patients in the Pre-ART cohort. INH prophylaxis therapy predicted incidence of TB neither in the pre-ART nor in the ART cohorts.

The Pre ART follow-up: In the multivariate analysis, the incidence of tuberculosis showed an independent association with WHO clinical stage, baseline CD4 cell count, baseline hematocrit level, and Cotrimoxazol prophylaxis. Patients at the lower WHO clinical stage had less risk of developing TB compared to patients at WHO clinical stage IV ((AOR=0.08, 95% CI 0.02, 0.61). Patients with a baseline CD4 cell count of <200 were found to be at higher risk of developing TB (AOR= 11.54, 95% CI 2.97, 44.96). Similarly, patients with a baseline hematocrit level of less than 30 were found to have about 18 times more risk of developing TB compared to those who had a hematocrit of greater or equal to 30 (AOR=18.12, 95% CI 4.57, 64.20). Those who didn't take Cotrimoxazol prophylaxis had a higher risk of developing TB compared to those who took it (AOR= 36.24, 95% CI=5.72, 87.02) (Table 4)

The HAART cohort: In the multivariate analysis, baseline CD4 cell count and HCT level showed a significant association with the development of TB. Patients with a CD4 count of less than 200 had about 8 times more risk of developing TB compared to those with a CD4 count of greater than or equal to 200 (AOR= 8.07, 95% CI 1.03, 69.83). Similarly, those with low level of HCT had higher risk of TB (AOR= 4.34 95% CI 1.09, 23.62) (Table 5)

Table 4: Association of factors with development of TB among HIV patients in the Pre-ART follow up at Felege Hiwot Referral Hospital, June 2010

Variable	Category	Tuberculosis		COR (95% CI)	AOR (95% CI)
		Yes (%)	No (%)		
Age group	15-24	6 (2.7)	44 (20.1)	1	1
	25+	15 (6.9)	154 (70.3)	0.67 (0.22,2.08)	0.94(0.17,7.32)
Sex	Male	12 (5.5)	68 (31.1)	2.55(1.03,6.35)	3.08(0.81,11.67)
	Female	9 (4.1)	130 (59.4)	1	1
WHO clinical stage	IV	5 (2.3)	3 (1.4)	1	1
	III, II and I	16 (7.3)	195(89.0)	0.05(0.01,0.22)	0.08(0.02,0.61)
CD4 cell count	Less than 200	15 (3.4)	31 (6.8)	15.06(4.85,37.40)	11.54(2.97,44.96)
	Greater than or equal to 200	6 (2.7)	187 (76.3)	1	1
HCT level	Less than 30	13 (5.9)	12 (5.5)	25.19 (8.77,72.46)	18.12 (4.5,64.20)
	Greater than or equal to 30	8 (3.7)	186 (84.9)	1	1
CPT	Yes	7 (3.20)	96 (43.8)	1	1
	No	14 (6.4)	102 (46.6)	1.88 (0.73,4.83)	36.24 (5.72,87.02)

CPT, Cotrimoxazol preventive therapy

Table 5: Association of factors with development of TB among HIV patients at the ART follow up in FHRH, Bahr Dar, Ethiopia, June 2010

Variable	Category	Tuberculosis		COR (95%CI)	AOR (95% CI)
		Yes (%)	No (%)		
Sex	Male	4 (1.8)	78 (35.6)	2.29(0.50,10.50)	2.59 (0.53,12.95)
	Female	3 (1.3)	134 (61.2)	1	1
WHO clinical stage	IV	2 (0.9)	17 (7.8)	1	1
	III, II and I	5 (2.3)	195 (89.0)	0.22 (0.04,1.62)	4.43 (0.97,12.90)
CD4 cell count	Less than 200	6 (2.7)	78 (35.6)	10.31 (1.22,87.20)	8.07 (1.03, 69.83)
	Greater than or equal to 200	1 (0.5)	134 (61.2)	1	1
HCT level	Less than 30	5 (2.3)	63 (28.8)	5.92 (1.12,31.29)	4.34 (1.09,23.62)
	Greater than or equal to 30	2 (0.9)	149 (68.0)	1	1

DISCUSSION

In this study, the incidence of tuberculosis among Pre-ART clients was 9.6% which is similar with a research finding in South Africa (9.7%) (7), but slightly lower than the incidence found at Arba

Minch Hospital in Ethiopia (11.1%). In the ART cohort, the incidence of TB was 3.2% which is again slightly lower than the incidence at Arba Minch Hospital (3.7%) (2). This difference may be attributed to time, study population, and sample size differences between the current study and the study conducted in Arba Minch. Additionally, the improvement in the implementation of HIV/TB con-

trol could have resulted in a lower incidence of TB in the current study. Greater than half (57%) of the HIV/AIDS case developed TB during the first 3 months of the ART initiation. A similar finding in South Africa demonstrated that the incidence of TB was 22.1/100 person-years during the first 3 months of ART and decreased to an average of 4.5/100 person-years during the second and third years (9). The possible explanation for this high rate of TB in the first 3 months can be immune reconstitution inflammatory syndrome (IRIS) (14).

In this study, patients who Initiated HAART had less risk of developing TB by 68% as compared to those who were under HIV chronic care. The result is more or less similar to the finding of a study done at Arba Minch Hospital (70-90%) (2). Patients with a low baseline CD4 cell count were found to have a higher risk of developing TB in both pre-ART and ART cohorts which is in agreement with results of studies done in other countries like Brazil, Korea, Europe, and North America (15,16,17). When the CD4 count is low, there will be a suppression of cellular immunity, which leads to either a fast progression of active TB infection or a progression of latent infection to active TB (18).

In both pre-ART and ART groups, clients with a low level of baseline hematocrit are found to have more chance of developing TB than a higher hematocrit level. Those with a baseline hematocrite of less than 30 had eighteen times in pre-ART and four times in ART cohorts have the risk of developing TB as compared to those who had base line hematocrit of greater than 30. A similar finding was obtained in Brazil and Addis Ababa where high rates of TB were observed in Anaemic patients (15,19).

Also, as demonstrated in a study conducted in Addis Ababa (19), WHO clinical stage (Pre-ART) clients were found to be significantly associated with the incidence of tuberculosis. Those who were in advanced WHO clinical stage (Stage IV) were found to have higher risk of developing TB compared to those who had lower WHO clinical stages (I-III). The immune suppression in the advanced clinical stage might have contributed to the high incidence of TB (18). Cotrimoxazol preventive therapy has also shown effectiveness in reducing TB incidence. A similar result was obtained in a study conducted in Addis Ababa, Ethiopia (19).

In conclusion, the incidence of TB was high among HIV patients who were not receiving ART. Low baseline CD4 cell count, low HCT, advanced WHO

clinical stage, and not receiving cotrimoxazole preventive therapy were found to be risk factors for developing TB. Hence, early initiation of ART might be considered to reduce the incidence of TB. Additionally, HIV patients need to be checked frequently for anaemia and treated accordingly. Maximizing the cotrimoxazole preventive therapy is also recommended.

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