

“Universal test and treat” program reduced TB incidence by 75% among a cohort of adults taking antiretroviral therapy (ART) in Gurage zone, South Ethiopia

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Abstract

Background: Tuberculosis (TB) remains the leading cause of morbidity and mortality in peoples living with HIV. At least 25% of deaths are attributed to TB. It is believed that, Universal test and treat (UTT) program for HIV reduces incidence of TB and most countries implement the program. However, there is limited study conducted to evaluate the impact of UTT on TB incidence. Therefore, by recruiting a cohort of ART users in the “UTT” and “differed treatment” programs we aimed to measure the effect of the UTT program on incidence of TB.

Objective: To measure the effect of “UTT” program on TB incidence among a cohort of adults taking antiretroviral therapy (ART) in Gurage zone, South Ethiopia.

Methods: Health facility based retrospective cohort study through record review of 5 year (2014-2019) cohort was conducted in public facilities of Gurage Zone. Randomly selected 384 records were reviewed by using standardized structured checklist. Data was entered by Epi info version 7 and analyzed by STATA. Generalized Linear Model with binomial link function was fitted to measure adjusted incidence density/Incidence rate ratio and identify predictors of incidence difference between the two programs.

Results: During the follow up period, 39 incident TB cases were occurred, and making the overall incidence rate of 4.79/100 person-year (PY). It is significantly lower in the UTT (IR=2.10/100 PY) than the differed program (IR=6.23/100 PY). The adjusted Incidence Rate Ratio (AIRR) of TB among patients enrolled in the UTT program was; 0.25 (95% CI=0.08-0.70) compared to patients enrolled in the differed program. Thus, UTT program reduce TB incidence by 75% compared to differed program. In addition to the program, IPT (isoniazid preventive therapy) use (AIRR= 0.35 (95% CI=0.22-0.48)), WHO Stage I and II (AIRR=0.70 (95% CI=0.61-0.94)) and higher Base line CD4 count (AIRR=0.96 (95% CI=.94-0.99)) significantly reduce incidence of TB. Whereas, treatment failure increase the incidence (AIRR=5.8 (95% CI=1.93-8.46)).

Conclusion: TB incidence was significantly reduced by 75% after UTT. Therefore, intervention to further reduce the incidence has to focus on strengthening UTT program and IPT.

Background

Tuberculosis (TB) is a major global public health problem (1, 2). It is the ninth leading cause of death worldwide and the leading cause from a single infectious agent (2, 3). In 2018, 10 million new cases of TB was occurred, of which 8.6% of the incident TB cases were among people living with HIV. Thus, the risk of developing active TB in people living with HIV (PLWH) is 19 times higher than others (2, 4, 5). In the same year, TB infection caused 1.45 million deaths (2), including 251,000 deaths occurred among HIV positive people. The African region accounts the largest share of this death (5-7).

The risk of developing TB increase as the CD4 count decreases and altered immune status (7-9). At least 25% of deaths among PLWHA are attributed to TB and many of these deaths occur in developing African

countries (10). HIV positive people with latent TB infection have a 10% annual and 50% lifetime risk of developing active TB disease, compared to a 10% life time risk among HIV negative individuals (10, 11). In areas where an HIV infection rate is higher, TB continues to be a major public health problem (1-3).

By considering this relationship, HIV and TB management programs are provided in integrated approaches at clinical and public health system level (1, 2). WHO has changed the differed program which has been implemented since HIV treatment program was started, by the UTT program. Differed program used CD4 count and/or WHO clinical stage as criteria for initiating HIV treatment. While the UTT recommend initiation of HIV treatment regardless of CD4 level and WHO clinical stage (1, 5, 10). Thus, UTT facilitates early initiation of treatment and have an impact on TB epidemiology, particularly in reducing the incidence of active TB (1, 2, 12).

Previous studies reported that ART reduces the incidence of TB (13-18). One of these researches reported that the risk of TB is reduced by 65% through ART initiation (13). ART also reduced mortality from TB by 95% (18). Other studies have also consistently shown the benefit of ART on TB outcomes, particularly when ART is initiated early (17-20). One of the observational research reported that early initiation of ART in HIV-infected TB patients reduces TB incidence rates by 90% at individual level (18) and by 60% at population level (19). ART also reduces TB recurrence rates by 50% (20).

Ethiopia is one of the SSA countries with the highest prevalence of TB/HIV co-infection and ranked seventh among the world's 30 highest TB burden countries (6). In 2017, according to the Centers for Diseases Control (CDC) and Prevention report, the incidence rate of TB in Ethiopia was 164 cases per 100,000 population including approximately 7% who were PLHIV. In the same year, the mortality rate of TB patients in Ethiopia was 24 per 100,000 population (2, 21).

Ethiopia has started the UTT program in 2016 in order to alter the epidemiology of HIV infection. It is believed that, the program facilitates early initiation of ART, hence, reduce incidence of TB and other opportunistic infections (2). However, there is no study conducted to evaluate the impact of UTT on incidence of TB. Therefore, by recruiting a cohort of ART users in the new (UTT) and previous (differed treatment) programs we aimed to assess the effect of UTT program in incidence of TB among PLWHA. The evidence will be used as base line information for planners, implementers and aid organizations.

Methods And Materials

Study design and settings

Health facility based retrospective cohort study was conducted in ART clinics found in Gurage Zone, Southern Ethiopia between May and June 2019 by reviewing a five year (2014-2019) cohorts. Gurage zone is one of the 13 zones available in SNNPRs. Wolkite is the capital of the zone located 158 Km south of the capital city Addis Ababa. The zone has 16 districts and 5 town administrations. There are 76 health centers and 6 hospitals. Of these 20 facilities provide HIV care and treatment in the area.

Study population, sample size and sampling technique

The source population of this study was all adults (age 15+) diagnosed to have HIV infection and enrolled to the treatment program in ART clinics found in Gurage zone. Of the 20 facilities, 5 facilities were randomly selected and the sample size was proportionally allocated to the facilities based on patient load. The sample size was calculated based on double population proportion formula by using Epi Info version 7 computer program considering the following assumptions: a 0.5 risk ratio within 95% confidence level, power of 80%, ratio of unexposed to exposed 2:1 and outcome in unexposed =28.9% (22). Finally by adding 20% for incompleteness the sample size became 392 (131 exposed and 261 unexposed).

Data collection procedure and data quality control

The Pre-ART register, ART register, patients' ART follow up and medical charts were sources of information. In those registers and follow up charts, clients' socio demographic, clinical and laboratory information, treatments being provided, the follow up status of each client and incidence of tuberculosis were recorded. Data was collected using a structured checklist for records review developed from the registers and follow up charts. Five data collectors and three supervisors working in ART clinics were recruited for data collection.

Study variables

The outcome variable is incidence of tuberculosis after enrolment with in the HAART program. It is measured as the number of incident cases per person year of follow up.

The two groups (exposed and unexposed) are program of enrolment (UTT Vs Differed) and the outcome is development of TB which is found from records. Declaration of outcome (TB development) is ascertained by 4 criteria according to the national guide line. 1. Sputum smear test, 2. Chest X-Ray, 3. Culture and 4. By clinical (physician) decision (when other tests are reported negative and sign and symptoms clearly indicated). Both the exposure status and outcome status are retrospectively reviewed from records.

Data processing and analysis

The data was entered into Epi-info version 7 and exported to STATA version 11 for statistical analysis. After exploratory data analysis and assumption test, Generalized Linear Model with binomial link function was fitted to measure adjusted incidence density and identify predictors of incidence difference. Crude and adjusted Incidence rate ratio was measured and reported with 95% confidence interval.

Results

Socio-demographic characteristics

A total of 392 randomly selected patients' charts were reviewed with structured check list and eight were found to be incomplete for main outcome. Out of the final 384 records fully reviewed 128 (33.3%) were among clients enrolled in the UTT program. Nearly two third (68.7%) of the patients enrolled into the study were females and 214 (55.7%) were urban residents. Half (51%) of the clients were married and more than one third (37%) of has no formal education. Regarding their occupational status, 30% of them were unemployed. The mean age at time of diagnosis was 34.8 (SD=9.1) years with no difference between the two programs (**Table 1**).

Table 1: socio-demographic characteristics of HIV infected patients enrolled in UTT and differed programs in Gurage Zone, 2019.

bles	Outcome by Program				Total (N, %)
	UTT (N, %)		CD4 based (N, %)		
	TB	NO TB	TB	NO TB	
age at DX	34.7± 8.8		35.1± 9.2		34.8± 9.1
Sex					
Male	2 (33.3)	47(38.5)	12 (36.4)	59 (26.5)	120 (31.2)
Female	4 (66.7)	75 (61.5)	21 (63.6)	164 (73.5)	264 (68.7)
Residence					
Rural	4 (66.7)	38 (31)	22 (66.6)	106(47.5)	170 (44.3)
Urban	2 (33.3)	84(69)	11 (33.4)	117(52.5)	214 (55.7)
Marital status					
Single	1 (16.7)	17(14)	5 (15)	40(18)	63 (16.4)
Married	2 (33.3)	69(56.5)	21 (63.6)	104(46.6)	196 (51)
Divorced	3 (50)	36(29.5)	7 (21.4)	79(35.4)	125 (32.6)
Education status					
Illiterate	4 (66.7)	44(36)	12 (36.4)	82(36.8)	142 (37)
Literate	2 (33.3)	78(64)	21 (63.6)	141(63.2)	242 (63)
Occupation status					
Employed	3 (50)	92(75.4)	18 (54.5)	156(70)	269 (70)
Unemployed	3 (50)	30(24.6)	15 (45.5)	67(30)	115 (30)

UTT-Universal test and treat DX-Diagnosis TB-Tuberculosis

Baseline and clinical characteristics

The median time from diagnosis to initiation of treatment was 0.7 (IQR=0.2-1.2) year. The average weight of participants was 52.3 kg (SD=11.3Kg), patients in the UTT program have slightly higher weight (52.5± 2 Kg) than patients in the differed program (51 ± 9 Kg). The median CD4 count during the initiation of ART was 201 (IQR: 126-303), it was higher among patients in the UTT program 262.4 (IQR: 130-568) than the differed treatment 181 (IQR: 110-235) (**Table 2**).

During initiation of ART 51.7% of the patients were in WHO clinical stage III and IV in either group. Specifically on the UTT program, only 39.8% of patients were in WHO clinical stage III and IV, whereas in the deferred treatment program nearly 57.4% of patients were in WHO clinical stage III and IV. More than two third of patients received IPT (isoniazid preventive therapy- a prophylaxis which is given to prevent active TB). Half of patients were diagnosed to have at least one opportunistic infection before ART initiation. Also 5.2% of clients developed treatment failure in the course of ART treatment (**Table 2**).

Table 2: Baseline clinical characteristics of HIV infected patients enrolled in UTT and differed programs in Gurage Zone, 2019.

bles	Outcome by Program				
	UTT (N, %)		CD4 based (N, %)		Total (N, %)
	TB	NO TB	TB	NO TB	
Stage					
Stage I	0 (0)	38(31.1)	3 (9.1)	48(21.5)	89 (23.1)
Stage II	1 (16.7)	38(31.1)	5 (15.3)	53(23.8)	97 (25.2)
Stage III	3 (50)	40(32.8)	22 (66.7)	115(51.5)	180 (47)
Stage IV	2 (33.3)	6(4.9)	3 (9)	7(3.2)	18 (4.7)
an CD4 count	262.4 (IQR: 130-568)		181 (IQR: 110-235)		201 (IQR: 126-303)
. weight	52.5± 2		51 ± 9		52.3±11.3
an time to Rx	0.3 (IQR=0.1-4.2)		0.9 (IQR=0.6-1.6)		0.7 (IQR=0.2-1.2)
efore ART					
Yes	3 (50)	49(40.2)	22 (66.7)	116(52)	190 (49.5)
No	3 (50)	73(59.8)	11 (33.3)	107(48)	194 (50.5)
Yes	4(66.7)	113(92.6)	11(33.3)	155(69.5)	283(73.7)
No	2(33.3)	9(7.4)	22(66.7)	68(30.5)	101(26.3)
ment Failure					
Yes	3 (50)	9(7.4)	2 (6)	6(2.7)	20 (5.2)
No	3 (50)	113(92.6)	31 (94)	217(97.3)	364 (94.8)

IPT-Isoniazid preventive therapy RX-Treatment

Incidence rate of Tuberculosis

Among the 384 HIV-infected patients who were followed for a total of 9766 person-month, 39 incident TB cases were occurred, and making the overall incidence of 4.79/100 PY. The overall incidence density rate (IDR) of TB was significantly different for the two comparison groups, where the incidence was 2.10/100 PY of observation in the UTT and 6.23/100 PY of observation in the differed treatment program with a p.value of 0.003. After adjusting for the effect of other variables the adjusted Incidence Rate Ratio (AIRR) of Tuberculosis among patients enrolled in the UTT program compared to patients enrolled in the differed program was; AIRR= 0.25(0.08-0.70). Thus, UTT program reduce TB incidence by 75% compared to the differed treatment program (**Table 3**).

Also, incidence deference was observed between different groups. Males have incidence of 5.36/100-person-year compared to 4.52/100-person-year incidence among females. Rural residents have by far greater risk of developing TB, 7.6/100-person-year than rural residents which is 2.75/100-person-year. Also, the incidence of TB was higher for unemployed patients, advanced clinical stage patients and those experienced treatment failure (**Table 3**).

Factors associated with TB incidence among HIV infected patients

In bivariate analysis, program of enrolment, residence, employment status, marital status, sex, base line weight, history of IPT, base line CD4 count and treatment failure were associated with TB incidence at the cut of p.value less than 0.25. By using these variables multivariate analysis was conducted. After controlling the effect of other variables program of enrolment, WHO clinical stage, IPT, treatment failure and base line CD4 count were significantly associated with TB incidence among HIV/AIDS infected patients in the course of treatment (**Table 3**).

After controlling the effect of other variables, patients enrolled in the UTT program were 75% less likely to develop TB than patients enrolled in the differed program; where AIRR=0.25 (95 % CI [0.08-0.70], p.value <0.001). Likewise, patients who were in WHO clinical stage one and two were 30% less likely to develop TB than patients in clinical stage three and four; AIRR=0.70 (95 % CI [0.61-0.94], p.value <0.001). Meanwhile, having IPT reduces the risk of developing TB by two-third; AIRR=0.35 (95 % CI [0.22-0.48], p.value <0.001). The Risk of developing TB was 5.80 (95 % CI [1.93-8.46], p.value <0.001) times higher for patients who have treatment failure than their counter parts, who don't have failure history. Also the increment of base line CD4 count by one unit reduces the risk of developing TB by four percent (**Table 3**).

Table 3: Univariate and multivariate analysis of Incidence rate of TB among clients enrolled in UTT and differed programs in Gurage Zone, 2019

Factors	Event/p-M	IR/100P-Y	CIRR(95%CI)	p.value	AIRR(95%CI)
Total	39/9766	4.79	-	-	-
Program					
UTT	6/3417	2.10	0.33(0.11-0.81)	0.003	0.25(0.08-0.70)*
Differed	33/6349	6.23	1		1
	-	-	1.01(0.97- 1.04)	0.622	-
Sex					
Male	14/3134	5.36	1.18(0.56- 2.37)	0.230	1.33(0.64-2.75)
Female	25/6632	4.52	1		1
Residence					
Rural	26/4094	7.6	2.77(1.42-5.38)	0.001	1.58(0.82- 3.05)
Urban	13/5672	2.75	1		
Employment					
Employed	21/6999	3.60	1		1
Unemployed	18/2767	7.80	2.16(1.34-5.10)	0.001	2.2(0.82-4.54)
Marital status					
Married	23/4920	5.60	1.41(0.71- 2.86)	0.14	1.73(0.88-3.40)
Unmarried	16/4846	3.96	1		1
Educational status					
Illiterate	16/3680	5.22	1.15(0.56-2.27)	0.33	
Literate	23/6086	4.53	1		
Age					
	-	-	0.97(0.94- 1.00)	0.110	0.97(0.94- 1.01)
CD4 Stage					
Stage I/II	9/3600	3.00	0.51(0.26-0.96)	0.018	0.70(0.61-0.94)*
Stage III/IV	30/6166	5.84	1		1
Smoking					
Yes	15/6800	2.64	0.27(0.18-0.56)	0.001	0.35(0.22-0.48)*
No	24/2966	9.71	1		1
Treatment Failure					
Yes	5/422	14.2	3.25(1.10-8.36)	0.015	5.80(1.93-8.46)*
No	34/9344	4.37	1		1
Baseline CD4 count					
	-	-	0.99(0.98-1.00)	0.050	0.96(.94-0.99)*

*AIRR-Adjusted Incidence Rate Ratio *IRR-Incidence Rate Ratio *CIRR-Crude Incidence Rate Ratio

Discussion

This retrospective cohort study assessed the effect of UTT program on TB incidence among a cohort of HIV infected patients enrolled in the HAART program between 2014 and 2019 in public health facilities of Gurage Zone, South Ethiopia. Accordingly, the overall incidence rate (IR) was 4.79/100 person-year. This level of incidence is by far lower than previous studies conducted in Hawassa (8.79/100PY) (23), Gondar (7.88 per 100PY) (22), and from the finding of a meta-analysis conducted in Ethiopia (10.5/100PY) (24). On the other hand, this finding is slightly lower than the finding of a recent research conducted in Debre

Markos referral hospital North Ethiopia (6.5 per 100PY) (25). Such difference may have been occurred due to time difference in initiation of treatment, overall TB prevention program and service difference (23-25).

The IR among patients enrolled in the UTT program was lower than patients enrolled in the differed program (2.10/100-Person-Year Vs. 6.23/100-Person-Year). Thus, UTT program significantly reduced TB incidence by 75% when compared to the differed program. This may be as a result of early initiation and strong follow up (19, 24, 25). In addition to this, patient enrolled in the UTT program were initiated ART at higher CD4 level which helps to prevent TB. Also previous studies evidenced that early initiation of ART in HIV-infected TB patients reduces TB incidence rates by 90% at individual level (18).

Although, overall incidence and life time risk of TB among HIV infected patients has been reduced in the last subsequent years in high burden countries like Ethiopia, such a remarkable reduction due to the effect of UTT program and overall reduction of HIV epidemics is a promising finding (1, 2, 11, 26). Hence, expanding and strengthening the program to the level of 90-90-90 target along with early initiation, drug adherence and implementation of overall TB prevention program have the potential to further enhance the impact of UTT program on reducing TB incidence.

According to this study, in addition to the type of program which patients were enrolled, provision of IPT significantly reduces the incidence of TB. Patients who received IPT have 65% lower risk of developing TB than those patients who don't received IPT. In line with this research many researchers reported the preventive effect of IPT in different settings (13, 16, 22, 24, 25, 27). A pooled estimate from Ethiopia reported that IPT reduces the incidence of active TB among HIV positive patients by 74% (24). Also the national guide lines and WHO guide line recommends implementation of IPT as mainstay to reduce incidence of TB among HIV infected patients particularly in high TB/HIV burden countries (10, 11, 27).

The other most important factors found to reduce the risk of developing TB among HIV infected patients were WHO clinical stage and base line CD4 count. Being in WHO clinical stage one and two reduce the incidence of TB by 30% compared to advanced stages (stage three and four). Similarly, a unit increase in base line CD4 count found to reduce incidence of TB by 4% among HIV infected patients. This is in line with previous studies, where clinical stages and bases line CD4 counts were the most important factors for TB development (22, 23, 25). This is because, TB develops at advanced stages of HIV when CD4 count is getting lower and results in immune compromisation (2, 11, 24, 27)

On the other hand development of treatment failure increases the risk of TB incidence by six fold. Treatment failure and drug resistance increases viral load and reduces CD4 count; as a consequence, it increases risk of opportunistic infection including TB. It is a well-recognized evidences that incidence of treatment failure results in multiples of adverse outcomes in HIV treatment (1, 9, 11, 22, 23, 25). Most commonly it is associated with incidence of fatal opportunistic infections like Tuberculosis (2, 11, 18, 23).

Strength and Limitation of the Study

To the extent of the researcher's knowledge there is no research that assessed the impact of UTT on TB incidence among HIV infected patient since the program was started in Ethiopia. Therefore, this research will bring a new clue on the impact of UTT in clinical setups. The findings of this study might suffer from the fact that it is retrospective study and based on record review; incompleteness of information and reliability of the recorded data remains a major concern.

Conclusion And Recommendations

We found that UTT program significantly reduced TB incidence by 75% when compared to the differed program among HIV-infected patients. The overall incidence density rate (IDR) of death in the cohort is lower than most of other national studies. In addition to the program of enrolment being in early WHO clinical stage, having IPT exposure and having higher base line CD4 count significantly reduces incidence of TB. Whereas, the risk of developing TB increases as patients develop treatment failure. Therefore, intervention to further reduce TB incidence has to focus on strengthening UTT program to initiate treatment as early as possible and prevention of treatment failure. The finding of this research may provide necessary information in areas of improvement; however further research is needed to give policy level recommendations.

List Of Abbreviations

AIRR: Adjusted Incidence Rate Ratio; **ART:** Antiretroviral therapy, **HAART:** Highly Active Antiretroviral therapy; **HIV:** Human immunodeficiency virus, **IDR:** Incidence density rate, **IPT:** isoniazid preventive therapy; **IRR:** Incidence Rate Ratio; **OIs:** Opportunistic infections, **TB:** Tuberculosis; **UTT:** universal test and treat, **WHO:** World Health organization

Declarations

Ethics approval and consent:

Ethical clearance was obtained from institutional review board of Wolkite University and permission letter was obtained from Gurage zone and district health departments. All data obtained from records were kept confidential by using codes instead of any personal identifiers. The finding of the study is believed to benefit the clients indirectly through improvement of health care system; which will maximize the benefit and minimize the harm.

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