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

CURRENT STATUS: UNDER REVIEW

Tropical Diseases, Travel Medicine and Vaccines  ■ BMC

Tadele Girum
Wolkite University

girumtadele@yahoo.com Corresponding Author

Fedila Yasin
Wolkite University

Samuel Dessu
Wolkite University

Bereket Zeleke
Wolkite University

Mulugeta Geremew
Wolkite University

DOI: 10.21203/rs.3.rs-17983/v1

SUBJECT AREAS
Health Economics & Outcomes Research  Infectious Diseases

KEYWORDS
Universal test and treat, differed treatment, Tuberculosis, incidence
Abstract

Background: Tuberculosis (TB) remains the leading cause of morbidity and mortality in peoples living with HIV. At least twenty five percent 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 no 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/CD4 based” 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 by trained professionals. 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. It is significantly lower in the UTT (IR=2.10/100 person-year) than the differed program (IR=6.23/100 person-year). 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%. In addition to the program, IPT 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 that affects millions of people around the
globe, predominantly in low- and middle-income countries (1, 2). TB is the ninth leading cause of death worldwide and the leading cause from a single infectious agent (2, 3). In 2018, there were an estimated 10 million new cases of TB, with incidence of 132 cases per 100,000 population (2, 4). An estimated 8.6% of the incident TB cases were among people living with HIV. The risk of developing active TB in people living with HIV (PLWH) is 19 times higher than the risk in the rest of the world population (1–5).

In the same year, TB infection caused 1.45 million deaths (2), off which 251,000 deaths occurred among HIV positive people. It is 33% of the total number of deaths caused by HIV/AIDS. World Health Organization (WHO) African Region and the WHO South-East Asia Region accounted for 85% of the combined total of TB deaths in HIV-negative and HIV-positive people (2, 3). Also, 72% of all Acquired Immunodeficiency Syndrome (AIDS)-related TB death reported worldwide occurred in Africa (6). The Sub-Saharan Africa (SSA) countries carry the highest burden of all TB cases related to high prevalence of HIV infection (2, 6, 7).

HIV infection remains the greatest risk factor for acquiring Mycobacterium tuberculosis infection and developing active tuberculosis (TB) (2), as well as the risk of death during TB treatment (2, 8). Altered immune state associated with low CD4 + T lymphocyte counts during the late stage of HIV infected patients favor the development and progression of TB infection (7). Also, TB is the most frequently incident opportunistic infection (OI) and disease in people living with HIV/AIDS (PLWHA), world-wide (7, 9).

TB remains the leading cause of morbidity and mortality in PLWHA (9). At least twenty five percent 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). Thus, early initiation of ART is important.
among HIV-infected TB patients (11, 12). Moreover, the WHO universal test and treat program may have impact on tuberculosis epidemiology, particularly in reducing the incidence of active TB infection in the course of HIV treatment (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 reduce mortality from TB by 95% (18). Other studies have also consistently shown a 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 universal test and treat 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/CD4 based) programs we aimed to assess the effect of the 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. 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 exposed = 28.9% (22). Finally by adding 20% for incompleteness the sample size became 392 (131 exposed and 261 unexposed). The sample was allocated proportionally for the five selected facilities and records were selected randomly.

Data Collection Procedure And Data Quality Control
The Pre-ART register, ART register, patients’ ART follow up and medical charts were sources of information for the research. 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.

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 universal test and treat 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 patients 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.

| Variables          | UTT (N, %) | CD4 based (N, %) | Total (N, %) |
|--------------------|------------|------------------|--------------|
|                    | TB         | NO TB            | TB           | NO TB      |
| Mean age at DX     | 34.7 ± 8.8 | 35.1 ± 9.2       | 34.8 ± 9.1   |
| Sex                |            |                  |              |
| Male               | 2 (33.3)   | 12 (36.4)        | 59 (26.5)    | 120 (31.2) |
| Female             | 4 (66.7)   | 21 (63.6)        | 164 (73.5)   | 264 (68.7) |
| Residence          |            |                  |              |
| Rural              | 4 (66.7)   | 22 (66.6)        | 106 (47.5)   | 170 (44.3) |
| Urban              | 2 (33.3)   | 11 (33.4)        | 117 (52.5)   | 214 (55.7) |
| Marital status     |            |                  |              |
| Single             | 1 (16.7)   | 5 (15)           | 40 (18)      | 63 (16.4)  |
| Married            | 2 (33.3)   | 21 (63.6)        | 104 (46.6)   | 196 (51)   |
| Divorced           | 3 (50)     | 7 (21.4)         | 79 (35.4)    | 125 (32.6) |
| Educational status |            |                  |              |
| Illiterate         | 4 (66.7)   | 12 (36.4)        | 82 (36.8)    | 142 (37)   |
| Literate           | 2 (33.3)   | 21 (63.6)        | 141 (63.2)   | 242 (63)   |
| Employment status  |            |                  |              |
| Employed           | 3 (50)     | 18 (54.5)        | 156 (70)     | 269 (70)   |
| Unemployed         | 3 (50)     | 15 (45.5)        | 67 (30)      | 115 (30)   |

UTT-Universal test and treatDX-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 at start 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).
Table 2
Baseline clinical characteristics of HIV infected patients enrolled in UTT and differed programs in Gurage Zone, 2019.

| Variables          | Outcome by Program | UTT (N, %) | CD4 based (N, %) | Total (N, %) |
|--------------------|--------------------|------------|------------------|-------------|
|                    |                    | TB | NO TB | TB | NO TB |
| WHO 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) |
| Median CD4 count   | 262.4 (IQR: 130–568) | 181 (IQR: 110–235) | 201 (IQR: 126–303) |
| Mean weight        | 52.5 ± 2           | 51 ± 9 | 52.3 ± 11.3 |
| Median time to Rx  | 0.3 (IQR = 0.1-4.2) | 0.9 (IQR = 0.6-1.6) | 0.7 (IQR = 0.2-1.2) |
| OIS before 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) |
| IPT                |                    |    |       |    |       |
| 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) |
| Treatment 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) |

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. 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).

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 person-year. The overall incidence density rate (IDR) of TB was significantly different for the two comparison groups, where the incidence was 2.10/100 person year of observation in the UTT and 6.23/100 person-year 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).
Table 3: Univariate and multivariate analysis of Incidence rate of TB among clients enrolled in UTT and differed programs in Gurage Zone, 2019

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

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

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, 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).

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 (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 may have been prevented TB incidence. 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 may 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 researches have been 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, it is observed that a unit increase in base line CD4 count 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 increased 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.

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.
Consent for publication:
Not applicable
Availability of data and materials:
lease contact author for data requests
Competing interests:
The author declare no conflict of interest
Funding:
Not applicable
Authors Contributions:
All authors have made substantial intellectual contributions to conception, design, and acquisition of data, analysis and interpretation of data to this study. They also have been involved in drafting the manuscript, approved the final manuscript and agreed to be accountable for all aspects of the work
Acknowledgements:
The authors would like to sincerely thank Head of the health department, data collectors, and others who ever contributed for this work. We would also like to acknowledge Wolkite University for facilitating the study.
References
1. Moscow Declaration to End TB; First WHO global ministerial conference on ending TB in the sustainable development era: a multisectoral response. Geneva: World Health Organization and the Ministry of Health of the Russian Federation; 2017 (https://www.who.int/tb/features_archive/Moscow_Declaration_to_End_TB_final_ENGLISH.pdf?ua=1, accessed 20 December 2019).
2. Global tuberculosis report 2019. Geneva: World Health Organization; 2019.
3. Sulis G, Roggi A, Matteelli A, Raviglione MC. Tuberculosis: epidemiology and control. Mediterr J Hematol Infect Dis. 2014;6(1).
4. Sustainable development goals [website]. New York: United Nations; (https://sustainabledevelopment.un.org/topics/sustainabledevelopmentgoals, accessed 20 December 2019).
5. Uplekar M, Weil D, Lönnroth K, Jaramillo E, Lienhardt C, Dias HM, et al. WHO's new End TB strategy. Lancet. 2015;385(9979):1799–801. https://www.ncbi.nlm.nih.gov/pubmed/25814376. accessed 20 December 2019).
6. World Health Organization: Global Tuberculosis Report 2018. 2018. Available from https://www.who.int/tb/publications/global_report/gtbr2018_main_text_28Feb2019.pdf?ua1. accessed 20 December 2019.
7. Beauté J, Dara M, Pc D, Ehsani S, Gozalov O, Hovanessian A, Ködmön C, Molnárová B, Boom M, van der Werf M. Tuberculosis surveillance and monitoring in Europe 2017; 2017.
8. Narain JP, Raviglione MC, Kochi A. HIV-associated tuberculosis in developing countries: epidemiology and strategies for prevention. Tuber Lung Dis. 1992;73(6):311–21.
9. Reid A, et al., “Towards universal access to HIV prevention, treatment, care, and support: the role of tuberculosis/HIV collaboration,” Lancet Infect Dis., vol. 6, pp. 483 – 95, 2006.
10. WHO. “Priority research questions for TB/HIV in HIV-prevalent and resource-limited settings,” vol. 3, 2010.
11. MOH. “National comprehensive HIV care and treatment training manual for health providers,” Ethiopia, 2014.
12. Joint United. Nations Programme on HIV/AIDS (UNAIDS). UNAIDS Data 2017.
13. Suthar AB, Lawn SD, del Amo J, Getahun H, Dye C, et al. Antiretroviral therapy for prevention of tuberculosis in adults with HIV: a systematic review and meta-analysis. PLoS Med. 2012;9:e1001270.
14. Curran A, Falco V, Pahissa A, Ribera E. Management of tuberculosis in HIV-infected patients. AIDS Rev. 2012;14:231–46.
15. Abdool Karim SS, Naidoo K, Grobler A, Padayatchi N, Baxter C, et al. Timing of initiation of antiretroviral drugs during tuberculosis therapy. N Engl J Med. 2010;362:697–706.
16. Blanc FX, Sok T, Laureillard D, Borand L, Rekacewicz C, et al. Earlier versus later start of antiretroviral therapy in HIV-infected adults with tuberculosis. N Engl J Med. 2011;365:1471–81.
17.
Havlir DV, Kendall MA, Ive P, Kumwenda J, Swindells S, et al (2011) Timing of antiretroviral therapy for HIV-1 infection and tuberculosis. N Engl J Med 365: 1482–1491. Manosuthi W, Mankatitham W, Lueangniyomkul A, Thongyen S, Likanonsakul S, et al. (2012) Time to initiate antiretroviral therapy between 4 weeks and 12 weeks of tuberculosis treatment in HIV-infected patients: results from the TIME study. J Acquir Immune Defic Syndr 60: 377–383.

18. Lawn SD, Kranzer K, Wood R. Antiretroviral therapy in the control of HIV associated tuberculosis in resource-limited settings. Clinics in Chest Medicine. 2009.

19. Middelkoop K, Wood R, Myer L, Whitelaw A, Kaplan g, McIntyre j, Bekker LG Widespread ART is associated with decline in TB prevalence. 5th IAS conference on HIV Pathogenesis, Prevention and Treatment. Cape Town, South Africa; 2009.

20. Golub JE, Durovni B, King BS, Cavalcante SC, Pacheco AG, Moulton LH, et al. Recurrent tuberculosis in HIV-infected patients in Rio de Janeiro, Brazil. AIDS. 2008 Nov 30;22(18):2527–33.

21. Centers for Diseases control and prevention (CDC). Global HIV & Tuberculosis Ethiopia Country Profile available at https://www.cdc.gov/globalhivtb/where-we-work/ethiopia/ethiopia.html. In.; last reviewed: August 29, 2019. Accessed December 20, 2019.

22. Alene KA, Nega A, Taye BW. Incidence and predictors of tuberculosis among adult people living with HIV at the university of Gondar referral hospital, northwest Ethiopia. BMC infectious disease. 2013;13:292.

23. Henok B, Mesfin K, Aman Y, Girum T. Incidence and Predictors of Tuberculosis among Adult PLWHA at Public Health Facilities of Hawassa City. International Journal of Public Health Science (IJPHS). 2017;6:3.

24. Demeke G, Aklilu E, Markos N, Setegn E, Belay T. The protective effect of isoniazid preventive therapy on tuberculosis incidence among HIV positive patients receiving ART in Ethiopian settings: a meta-analysis. BMC Infect Dis. 2019;19:405.

25. Belisty T, Getiye D, Nakachew M, Mamaru W, Yitbarek T, Pammla P, et al. Incidence and predictors of tuberculosis among HIV-positive adults on antiretroviral therapy at Debre Markos referral hospital, Northwest Ethiopia: a retrospective record review. BMC Public Health. 2019;19:1566.

26. Girum T, Abebaw W, Abdulsemed W. Trend of HIV/AIDS for the last 26 Years and Predicting Achievement of the 90-90-90 HIV Prevention Targets by 2020 in Ethiopia: A Time Series Analysis. BMC infectious disease. 2018;18:320.

27. Mahlet S, Teferi G, Girmay M, Dawit A. Effectiveness of isoniazid preventative therapy in reducing incidence of active tuberculosis among people living with HIV/ AIDS in public health facilities of Addis Ababa, Ethiopia: a historical cohort study. BMC Infect Dis. 2017;17:5.