Incidence and predictors of tuberculosis among HIV-positive adults on antiretroviral therapy at Debre Markos Referral Hospital, Northwest Ethiopia: A retrospective record review

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Belisty Temesgen
Debre Markos Referral Hospital

Getiye Dejenu Kibret
Debre Markos University

Nakachew Mekonnen Alamirew
Debre Markos University

Animut Alebel animut.a23@gmail.com
Debre Markos University
Corresponding Author
ORCiD: 0000-0003-2822-2062

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Abstract

Background: Tuberculosis (TB) is the leading cause of morbidity and mortality among people living with human immunodeficiency virus. Almost one-third of deaths among people living with human immunodeficiency virus (PLHIV) are attributed to tuberculosis. Despite this fact, in Ethiopia, particularly in our study area there is a scarcity of information regarding the incidence and predictors of TB among people living with HIV. Thus, this study aimed to assess the incidence and predictors of tuberculosis among HIV-positive adults on antiretroviral therapy (ART). Methods: A retrospective record review was conducted among 544 HIV-positive adults on ART at Debre Markos Referral Hospital from January 1, 2012 to December 31, 2017. The study participants were selected using a simple random sampling technique. The data extraction format was adapted from ART intake and follow-up forms. Cox-proportional hazards regression model was fitted and Cox-Snell residual test was used to assess the goodness of fit. Model with the least value of Akaike's information criteria was selected as the best model. Tuberculosis free survival time was estimated using the Kaplan-Meier survival curve. Both the bi-variable and multivariable Cox-proportional hazard regression models were used to identify predictors of TB. Results: Among 492 HIV-positive adults included in the final analysis, 16.9% developed TB at the time of follow-up. The incidence rate of TB was found to be 6.5 (95%CI: 5.2, 8.0) per 100-person-years of observation. Advanced WHO clinical disease stage (III and IV) (AHR: 2.1, 95% CI: 1.2, 3.2), being ambulatory and bedridden (AHR: 1.8, 95% CI: 1.1, 3.1), baseline opportunistic infections (AHR: 2.8, 95% CI: 1.7, 4.4), low hemoglobin level (AHR: 3.5, 95% CI: 2.1, 5.8), and not taking IPT (AHR: 3.9, 95% CI: 1.9, 7.6) were found to be the predictors of TB. Conclusion: The study found that there was a high rate of TB occurrence as compared to previous studies. Baseline opportunistic infections, being ambulatory and bedridden, advanced disease stage, low hemoglobin
level, and not taking IPT were found to be the predictors of TB. Therefore, early detection and treatment of opportunistic infections like TB should get a special attention. Keywords: Debre Markos, HIV, Incidence, Predictors, TB

Background

Tuberculosis (TB) is the leading cause of morbidity and mortality among People Living with Human Immunodeficiency Virus (PLHIV) [1]. PLHIV are 20 times more likely to develop TB as compared to those without HIV [2, 3]. In 2017, an estimated 10 million people developed TB disease and 1.6 million died from TB. Of whom, 9% were among PLHIV. In the same year, approximately 300,000 people died due to Acquired Immunodeficiency Syndrome (AIDS) related TB worldwide. Of whom, 72% of the deaths were occurred in Africa [4]. Sub-Saharan Africa (SSA) shared the highest (74%) burden of all TB cases [5, 6]. Ethiopia is one of the SSA countries with the highest prevalence of TB/ HIV co-infection and ranked the seventh among the world 30 high TB burden countries. In 2017, according to the Centers for Diseases control and prevention (CDC) report, the incidence rate of TB in Ethiopia was 164 cases per100, 000 population. Of whom, about 7% were among HIV-positive individuals. In the same year, the mortality rate of TB patients in Ethiopia was 24 deaths per 100, 000 population [7, 8]. To tackle this problem, different interventions have been implemented at the global and local levels. For example, integrated management of TB/HIV co-infection in a single health facility by a single health care provider to deliver integrated therapy and managing both diseases efficiently. In addition, a scale-up of Antiretroviral Therapy (ART), which mainly aimed to reduce HIV-related morbidity and mortality as well as to increase the survival of HIV-infected patients [9-12]. The Ethiopian government has adapted and implemented different strategies to reduce TB related morbidity and mortality among PLHIV. For example, the Ministry of Health (MOH)
decentralized TB/HIV co-infection care services from hospitals to health centers and strengthen the referral systems to improve the level of TB care and treatment at the community level [13]. In addition, early initiation of ART and early screening of TB, prior provision of Isonized Preventive Therapy (IPT) [14, 15] and Co-trimoxazole Prophylactic Therapy (CPT) were some of the strategies that have been implemented to reduce the incidence of TB among PLHIV [16-20].

Despite the incidence of TB among HIV-positive adults in Ethiopia has been improved due to different interventions, still it’s the top cause deaths among PLHIV. The previous Ethiopian studies have documented that the incidence of TB among HIV-positive adults ranged from 3.3 per 100-person years of observation in Addis Ababa [21] to 8.6 per 100-person years of observation in Afar Region [22]. Regarding factors affecting the occurrence of TB, previous studies conducted in Ethiopia have identified that household family size between 3 to 4 individuals, cigarette smoking, not taking IPT, not taking CPT, low baseline CD4 counts, advanced WHO clinical disease stages (stage II and IV), and having a history of diabetic mellitus were the most commonly factors increased the risk of developing TB among HIV-positive adults [22-24].

The Ethiopian government targeted to reduce TB related deaths by 90 % and TB incidence by 80% by 2030, as compared with levels in 2015 [25]. To evaluate this ambitious plan, current and up-to-date information in related to the occurrence of TB is vital. Therefore, we conducted this retrospective record review to explore the incidence of TB among HIV-positive adults at Debre Markos Referral Hospital. Results obtained from this study will have a paramount input for policy makers and program planners working at various levels of TB control programs. Besides, it will be an input for health care professionals working in the area of TB control and prevented.

Methods
Study design, area, and period

A retrospective record review was conducted at Debre-Markos Referral Hospital from January 1, 2012 to December 31, 2017. Debre Markos Referral Hospital is found in Debre Markos Town which is located 299 km far from Addis Ababa, the capital city of Ethiopia and 265 km from Bahir-Dar, the main city of Amhara Regional State. The hospital serves for more than 3.5 million people in East Gojjam Zone and neighboring areas. Apart from other services, the hospital has been providing ART follow-up care services since 2005. In the hospital, the recorded number of HIV-positive people ever started ART was 3,716. Of whom, about 1,569 HIV-positive adults started ART care from January 1, 2012 to December 31, 2017.

Population

All HIV-positive adults who had ART follow-up at Debre Markos referral hospital from January 1, 2012 to December 31, 2017 were the target population for this study. All HIV-positive adults started ART from January 1, 2012 to December 31, 2017, and who had at least one month of ART follow-up were included. However, HIV-positive adults on ART who had TB or started anti-TB treatment at the beginning of the follow-up as well as who had incomplete baseline data for important variables (WHO stage, CD4 counts, Hgb, IPT, CPT and level of ART adherence) were excluded from the study.

Sample size determination and sampling procedures

The minimum required sample size was calculated using a sample size determination formula for survival analysis using Stata Version 13 statistical software by considering CD4 count, functional status, and WHO clinical staging as major exposure variables. It was calculated by considering the following statistical assumptions: two-sided significant level (α) of 5 %, power 80 %, \( Z_{a/2} \) = value at 95 % CI =1.96, \( q_1 \): proportion of subjects that are in group 1 (exposed), \( q_0 \): proportion of subjects that are in group 2 (unexposed); 1-\( q_1 \), HR:
hazard ratio, and probability of event (E) for functional status were taken from a study conducted at the University of Gondar Teaching Hospital (0.33) [23]. Then, the final sample size for this study was 544. To select the study participants, the records of all HIV-positive adults started ART and registered from January 1, 2012 to December 31, 2017 were sorted. Then, the study participants were selected using a simple random sampling technique through computer-generated numbers. We selected this follow-up period in order to have a nearest six years of follow up. In addition, during this time, the hospital adapted a standardized ART documentation and reporting formats at this time.

**Data collection tool and procedures**

The data extraction tool was prepared from the ART entry and follow-up forms. Trained health professionals (BSc Nurses) who have been working in the ART clinic of Debre Markos Referral Hospital collected the data. The most recent laboratory test results before starting ART were considered as a baseline value. If there were no pre-treatment laboratory test results, obtained at the time of ART initiation, test results done within one month of ART initiation were used as a baseline data. In case of two results obtained within a month, the mean value was computed and taken as a baseline. At the time of data collection, to assure data quality, the data extraction tool was prepared carefully from a standardized ART intake and follow up forms. In addition, as a data collector, we recruited staff nurses who have been working in ART clinic and, preferably, who had comprehensive ART care training certificate. Moreover, training was given for both data collectors and supervisor concerning the data collection tool and data collection process for two days. Furthermore, before the beginning of data collection, the consistency in the recording was checked by taking few charts and few amendments were done on the data collection tool. The supervisor and principal investigators performed a strict follow up and supervision throughout the entire data collection period.
Variables of the Study

The dependent variable was the time to develop TB.

The predictor variables were: Socio demographic characteristics (age, sex, marital status, residence, family size, level of education, and occupation), Baseline clinical and laboratory characteristics (WHO clinical stage, CD4 cell count, hemoglobin level, history of TB, and history of OI and body mass index (BMI), and ART and other medications related characteristics (ART regimen, presence of regimen change, ART side effects, taking IPT, ART adherence and taking CPT).

Operational definitions

In this study, the study participants were classified as event (the occurrence of TB), if they had any documented history of TB and took ant-TB medications during the follow-up time (from January 1, 2012 to December 31, 2017). This was ascertained by reviewing patient records.

In this study, the study participants were classified as censored in either of the following conditions: If the study participants lost from follow-up or died before developing TB or if the study participants who were alive at the end of the study, but they didn’t develop TB and took anti-TB medications. This was ascertained by reviewing patient records.

Lost was defined as when the patient missed his or her appointment for three months.

Adherence was classified as good, fair and poor, according to the percentage of drug dosage calculated from a monthly total dose of ART drugs. Describe as good (equal to or greater than 95% or ≤ 3 dose missing per months), fair (85-94% or 4-8 dose missing per months), or poor (less than 85% or ≥ 9 dose missing per months [26]).

Low hemoglobin level was defined as HIV-positive adults who had Hgb level less than to 10 g/dl.

OIs were diagnosed if HIV-positive adults developed any morbidities after starting ART, as
documented by health care professionals.

**Data processing and analysis**

Data were entered using EPI-data Version 4.2, and analyzed using STATA Version 13 statistical software. Patients’ follow-up characteristics for continuous data were described in terms of central tendency, dispersion, and frequency distribution for categorical data. At the end of follow up, the outcome of each study participant was dichotomized into censored or event. The necessary assumption of Cox proportional hazard regression model was checked using Schoenfeld residual and Log-Log plot tests. In addition, the model goodness of fit was assessed using Cox-Snell residual test and model with the least value of Akaike's information criteria was selected as the best model. The Kaplan Meier survival curve was used to estimate the TB free survival time of HIV-positive adults on ART. Log rank test was used to compare the survival curves of different categorical explanatory variables. Bi-variable Cox-proportional hazard regression model was used to screen variables for the final model. Variables having p-value ≤ 0.25 in the bivariable analysis were fitted into the multivariable Cox-proportional hazard regression model. Finally, adjusted hazard ratio with its corresponding 95% confidence interval was reported to declare the presence of significant association between the explanatory and outcome variables.

**Results**

**Socio-demographic Characteristics of the Study Participants**

After removal of fifty-two (52) incomplete records, 492 HIV-positive adult charts were included in the final analysis. The median age of the entire cohort was 33.0 years (IQR: 27, 40 years). More than half (53.6%) of the study participants were female and more than three fourth (78.86%) of the participants disclosed their HIV status (Table 1).

**Baseline clinical, laboratory, ART, and other medication related information**
Clinically, more than half (61.8%) of the study participants were classified as WHO clinical stage I/II. The mean baseline CD4 cell count of the study participants was 252.7 cell /mm$^3$ (SD: 9.5 cell /mm$^3$). In addition, the majority (90.43%) of study participants had a hemoglobin level of 10gm/dl and more. Almost, one-third (32.93%) of the participants had baseline opportunistic infections. Regarding functional status, the majority (81.2%) of study participants classified as working functional status. At baseline, less than one-third (29.47%) of the participants were undernourished (BMI < 18.5). About 5% of the participants had a history of initial regimen change during their follow-up time. The majority (95.53%) of participants had a history of good adherence. Moreover, the majority (85.98%) of participants took CPT; however, only 36.38% of the participants received IPT (Table 2).

**Incidence of Tuberculosis**

In this study, a total of 492 study participants were followed for a different period, contributing a cohort of 1285.54-person-years of observation. During the follow-up time, about 83 (16.9%) of the study participants experienced TB. The overall incidence rate of TB was found to be 6.5 (95%CI: 5.2, 8.0) per 100-person-years of observation. The incidence rate (14.5, 95%CI: 11.3, 18.7 per 100 PY) of TB was highest in the first year of follow-up and then, decreasing in subsequent years of follow-up. The cumulative probability of TB free survival at the end of one year, two, three, four, five and six years were 0.87, 0.84, 0.82, 0.80, 0.79, and 0.78 respectively. The mean TB free survival time of the entire follow up was 60.8 months (95% CI: 58.2, 63.1 months) (Figure 1).

**Bi-variable and Multivariable Cox-regression Analysis**

In the multivariable Cox-regression analysis, advanced WHO clinical stages (III and IV), baseline OIs, being ambulatory and bedridden, low hemoglobin level (<10g/dl), and not
taking IPT were found to be significant predictors of TB. In this study, the hazard of developing TB among HIV-positive adults on ART who were classified as WHO clinical stage III and IV at baseline was 2.1 (95%CI: 1.2, 3.2) times higher as compared to those who were classified as WHO stage I and II. Similarly, the hazard of developing TB among HIV-positive adults classified as ambulatory and bedridden at baseline was 1.8 (95%CI: 1.1, 3.1) times higher as compared to those who were classified as working functional status. In addition, the hazard of developing TB among patients who had OIs at baseline was 2.8 times (95% CI: 1.7, 4.4) higher as compare to those who hadn’t OIs at baseline. Furthermore, the hazard of developing TB among patients presented with hemoglobin level less than 10g/dl during ART initiation was 3.5 (95%CI: 2.1, 5.8) times higher as compared to those who had hemoglobin level greater than or equal to 10g/dl. Lastly, HIV-positive adults on ART who didn’t take IPT were 3.9 (95% CI: 1.9, 7.6) times more likely to develop TB as compared to those who took IPT (Table 3). The goodness of fit for the model was assessed using Cox-Snell residual test (Figure 2).

Discussion

Tuberculosis is a major public health challenge and remained the most commonly diagnosed opportunistic infection among PLHIV [3]. Therefore, we conducted this retrospective record review to determine the incidence and predictors of TB among HIV-positive adults at Debre Markos Referral Hospital. In this study, the overall incidence of TB among HIV-positive adults at Debre Markos Referral Hospital was 6.5 (95% CI: 5.2, 8.0) per 100-person-years of observation. This finding is in line with previous Ethiopian studies conducted in Gondar (7.89 cases per 100-person years) [23] and Arba Minch (5.36 cases per 100-person years) [24]. On the other hand, this finding is higher than studies reported from developed as well as developing countries included: Brazil (2.28 cases per 100 PY) [27], Nigeria( 0.57 cases per 100 PY) [28] and Tanzania (4.4 cases per 100 PY)
The higher incidence of TB in this study could be attributed to the differences in follow-up period, sample size, characteristic of study participants, and the difference in the prevalence of tuberculosis [20]. For example, the median follow-up period for a study conducted in Tanzania was 2-years whereas, in this study we followed the study participants for 6-years. It is well understood that as the follow-up period increases, the number of events also increases. Additional possible explanation for the above variations could be due to the differences in characteristic of study participants. In this regard, a study done in Tanzania included all HIV-positive patients-initiated ART in all health facilities. However, our study was conducted at a referral hospital, which provides tertiary level services for patients referred from health centers or general hospitals that are often experiencing advanced disease stage. It is well known that HIV-positive patients with advanced disease stage are at higher risk of developing TB [30].

However, the incidence rate of TB obtained from this study is lower than a study conducted in Afar region, Northeast Ethiopia (8.6 cases per 100 PY [22]. The variation could be explained by the difference in study settings, since this study was conducted at one referral hospital whereas, a study conducted in Afar region was done in three hospitals and two health centers. As we know, the Ethiopian TB care strategy currently becomes decentralized due to that, patients commonly visited health centers before referred to hospitals. Therefore, including health centers as a study stetting will increases the case detection rate, which ultimately increases the incidence of TB [22]. Another possible explanation for this variation could be due to the difference in characteristics of study participants during ART initiation. In this study, about 38.2% of the study participants were classified as WHO clinical stage III or IV, but in a study conducted in Afar health facilities more than half (53.4%) of the study participants were classified as
WHO stage III and stage IV [18]. As the WHO clinical disease stage become more advanced, the risk of developing and recurrence of opportunistic infections including TB also simultaneously increased.

Regarding the time to develop TB, about 60% of TB cases developed TB in the first six months of follow-up. This finding in line with studies conducted in different parts of Ethiopia and studies conducted elsewhere [20, 22-24, 27-29]. The higher incidence of TB in early phase of ART could be associated with the progression of the disease from latent to active TB could be remained undetectable during early phase of ART [31]. Besides, IRIS was very common in the first 2-12 weeks of ART. It highly increases the protective responses of the immune system which, leads a typical inflammatory condition this may create a high chance of latent TB infection to active TB [32]. Moreover, the main actions of HAART are increasing CD4 cell counts and decreasing viral load, which ultimately improves the immune function and reduces the occurrence of opportunistic infections including TB [33].

In this study, advanced WHO clinical disease stages (III and IV) was found to be an important predictor of TB among HIV-positive adults on ART. This finding is consistent with studies previously conducted in different regions of Ethiopia [23, 29, 30, 34-36], and South Africa [31]. as WHO clinical disease staging become more advanced, the risk of developing and recurrence of opportunistic infections including TB also simultaneously increased [30].

Being ambulatory and bedridden was also another predictor of tuberculosis among HIV positive adults. Accordingly, those who were classified as ambulatory and bedridden were more likely to develop TB as compared to those who were classified as working. This finding is consistent with different studies conducted in Ethiopia [22, 23, 35]. Being bedridden and ambulatory functional status are more prone to develop TB because
patients become bedridden and ambulatory due to advanced disease stage and more immune compromised stage of HIV [23]. The other possible explanation could be due to restriction from physical activities and unable to perform daily tasks which, indirectly devastating the immune system [22]. This may also increase the risk of any other opportunistic infections and TB.

This study also found that patients who had baseline opportunistic infections were more likely to develop TB as compared with those who hadn’t baseline opportunistic infections. The possible explanation may be due to the presence of opportunistic infections during ART initiation will increases piles burden, which resulted from drug-rug interaction and side effects which, resulted synergic effects with HIV. This leads to more weakening of the immune system [31].

Moreover, patients who had a low baseline hemoglobin level (Hgb<10g/dl) were more likely to develop TB as compared to who had a high hemoglobin level (Hgb>=10g/dl).

Supportive findings were reported from previous studies conducted in different regions of Ethiopia [22-24, 35]. Anemia and TB could be indirectly associated. It is well known that as the WHO disease stage become more advanced anemia also increased as a result of Immunosuppression and reduction of bone marrow cell production [35].

Lastly, taking IPT was another independent predictor of tuberculosis among HIV positive adults on ART. Patients who hadn’t taken IPT were more likely to develop TB as compared to those who took IPT. This finding is congruent with previous studies conducted in different parts of Ethiopia [17, 18, 22, 35]. This may be because of the role of IPT in reducing the occurrence of TB among PLHIV [16, 37]. Currently, all HIV positive individuals who have no evidence of active TB infection recommended taking INH preventive therapy (IPT) to prevent TB infection.

**The Public Health implication of this study**
The results of this study be an input for policy makers and program planners working at various levels of TB control programs. Besides, results obtained from this study will be helpful for health care professionals working in the area of TB/HIV control and prevention unit of Debre Markos referral hospital. Additionally, the study will be an input for further interventional studies.

Limitations of the study

This study has some limitations that must be considered before interpreting results. As the study was conducted through reviewing of records, it didn’t include important predictors of TB like housing condition, household income, viral load, and substance use due to incomplete recording system. In addition, study subjects who had incomplete data were excluded from the study. This could undermine or overestimate the incidence of TB. Furthermore, since this study was a facility-based study it may not capture HIV-positive individuals who are out of care (at the community level).

Conclusions

The study found that there was a high rate of TB occurrence as compared to previous studies. Baseline opportunistic infections, being ambulatory and bedridden, advanced disease stage, low hemoglobin level, and not taking IPT were found to be the predictors of TB. Besides, a high rate of TB occurrence was observed in the first six months of ART follow-up. Therefore, based on our findings, we forwarded the following recommendations. A special emphasis and close follow-up should be given for the first six months of ART follow-up. Moreover, early detection and treatment of opportunistic infections like TB should get a special attention. Furthermore, provision of IPT for HIV positive patients should be strengthened.

List Of Abbreviations
AIDS: Acquired Immune Deficiency Syndrome, ART: Antiretroviral Therapy, CDC: Centers for Diseases control and prevention, CPT: Co-trimoxazole Preventive Therapy, HAART: Highly Active Antiretroviral Therapy, HIV: Human Immunodeficiency Virus, Hgb: Hemoglobin, IRIS: Immune Reconstitution Inflammatory Syndrome, TB: Tuberculosis, PLHIV: People Living with Human Immunodeficiency Virus, WHO: World Health Organization.

Declarations

**Ethics approval and consent to participate**

Ethical clearance was obtained from an Institutional Review Committee of Debre Markos University, College of Health Science, Department of Public Health. Besides, a permission letter was also secured from Debre Markos Referral Hospital. As the study was conducted by reviewing medical records of HIV-positive adults, informed oral or written consent from the participants was not feasible. Therefore, the Ethics committee formally waived the consent. To maintain confidentiality, names or unique ART numbers were not included in the data extraction format. Moreover, collected data were not disclosed to anyone other than principal investigators.

**Consent for publication**

Not applicable

**Availability of data and material**

The data sets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

**Competing interests**

The authors have declared that they have no competing interests.

**Authors’ contribution**

**BT:** conception of the research idea, study design, data collection, analysis and
interpretation, and manuscript write-up. GDK, NMA, and AA: analysis and interpretation, and manuscript write-up. All authors have read and approved the final manuscript.

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Tables

Table 1. Socio-demographic characteristics of patients on chronic HIV care at Debre-Markos Referral Hospital, Northwest Ethiopia

| Characteristics         | Frequency |
|-------------------------|-----------|
| Age                     |           |
| 15-24 year              | 62        |
| 25-34 year              | 199       |
| 35-44 year              | 151       |
| >45 year                | 80        |
| Sex                     |           |
| Male                    | 228       |
| Female                  | 264       |
| Single                  | 66        |
| Marital status          |           |
| Married                 | 268       |
| Divorced                | 126       |
| Widowed                 | 32        |
| Religion                |           |
| Orthodox                | 477       |
| Others                  | 15        |
| Educational status      |           |
| No formal education     | 145       |
| Primary                 | 115       |
| Secondary               | 144       |
| Tertiary                | 86        |
| Not recorded            | 2         |
| Occupation              |           |
| Employed                | 110       |
| Unemployed              | 376       |
| Residence               |           |
| Within catchment area   | 464       |
| Out of catchment area   | 28        |
| Disclosure status       |           |
| Disclosed               | 388       |
| Not disclosed           | 104       |
| Family size             |           |
| <=3                     | 389       |
| >3                      | 85        |
Table 2. Baseline clinical, Laboratory, ART and other medication related information of HIV patients on chronic HIV care at Debre-Markos Referral Hospital, Northwest Ethiopia

| Characteristics                  | Frequency (N) |
|----------------------------------|---------------|
| **WHO clinical staging**         |               |
| I / II                           | 304           |
| III / IV                         | 188           |
| < 100                            | 113           |
| **CD4 count**                    |               |
| 100-200                          | 123           |
| 201-350                          | 140           |
| >= 351                           | 115           |
| **Functional status**            |               |
| Working                          | 418           |
| Ambulatory / bed redden          | 73            |
| **Hemoglobin level**             |               |
| < 10gm/dl                        | 44            |
| >= 10gm/gl                       | 416           |
| **BMI/MUAC**                     |               |
| Underweight                      | 145           |
| Not Underweight                  | 347           |
| **Eligible criteria**            |               |
| CD4 cell count                   | 199           |
| WHO stage                        | 49            |
| Both                             | 116           |
| Test & treat                     | 89            |
| Not recorded                     | 38            |
| **Initial regimen**              |               |
| 1d = ZDV-3TC EFV                 | 11            |
| 1c = ZDV-3TC- NVP                | 36            |
| 1e = TDF-3TC-EFV                 | 423           |
| 1f = TDF-3TF-NVP                 | 15            |
| Other                            | 6             |
| **Past TB history**              |               |
| Yes                              | 7             |
| No                               | 483           |

Table 3. Bi-variable and multivariable Cox-regression analysis to identify the predictors of tuberculosis among HIV positive adults on ART care at Debre-Markos Referral Hospital, Northwest Ethiopia
| Variables                      | Survival status | CHR (95%CI) |
|--------------------------------|-----------------|-------------|
|                                | Event | Censored |                  |
| Sex                            |        |          |                  |
| Male                           | 47     | 181      | 1.6 (1.1, 2.5)   |
| Female                         | 36     | 228      | 1               |
| CD4 cell count                 |        |          |                  |
| <200 cell/mm³                  | 55     | 180      | 2.2 (1.4, 3.4)   |
| >=200 cell/mm³                 | 28     | 228      | 1               |
| WHO clinical staging           |        |          |                  |
| Stage I and II                 | 26     | 278      | 1               |
| Stage III and IV               | 57     | 131      | 4.0 (2.5, 6.4)   |
| Functional status              |        |          |                  |
| Working                        | 51     | 367      | 1               |
| Ambulatory & bedridden         | 32     | 41       | 5.0 (3.2, 7.8)   |
| BMI / MUAC                     |        |          |                  |
| Underweight                    | 32     | 113      | 1.6 (1.1, 2.6)   |
| Not Underweight                | 51     | 296      | 1               |
| Hemoglobin level               |        |          |                  |
| <10 g/dl                       | 27     | 20       | 6.7 (4.2, 10.7)  |
| ≥10 g/dl                       | 56     | 383      | 1               |
| Opportunistic infection        |        |          |                  |
| Yes                            | 51     | 111      | 3.7 (2.4, 5.7)   |
| No                             | 32     | 298      | 1               |
| CPT                            |        |          |                  |
| Yes                            | 69     | 354      | 1               |
| No                             | 14     | 55       | 1.6 (0.9, 2.8)   |
| IPT                            |        |          |                  |
| Yes                            | 10     | 169      | 1               |
| No                             | 73     | 240      | 4.8 (2.5, 9.3)   |

**Significant predictors**

**Figures**
Figure 1

The overall Kaplan-Meier survival curve with 95% confidence interval of TB free survival time of HIV positive adults on ART car at Debre-Markos Referral Hospital, Northwest Ethiopia
Goodness of fit test for Cox-proportional hazard regression model.