Incidence of tuberculosis among HIV-positive adults on antiretroviral therapy at Debre Markos Referral Hospital, Northwest Ethiopia: A retrospective cohort study

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Abstract
Background: Tuberculosis 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 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 peoples living with HIV. Thus, this study aimed to assess the incidence and predictors of tuberculosis among HIV positive adults. Methods: An institution based retrospective cohort study 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. Data were entered using Epi-Data version 4.2 and analyzed using STATA Version 13. 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 the time to develop TB.
Results: Among 492 HIV-positive adults included in the final analysis, 16.9% of them 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. 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 predictors of the time to develop TB. Conclusion: In this study, a high incidence rate of TB was observed among HIV-positive adults. Advanced HIV disease stage (III and IV), being ambulatory and bedridden, having opportunistic infections, having a low hemoglobin level, and not taking IPT were found to be predictors of the time to develop TB. Keywords: HIV, Incidence, Predictors, TB

Background
Tuberculosis is the leading cause of morbidity and mortality among People Living with Human Immunodeficiency Virus (PLHIV) [1]. Those population are five times at higher risk to develop TB compared to the general population [2, 3]. According to the United Nation AIDS (UNAIDS) 2016 global report, about 1.2 million (11%) of all TB, cases were among PLHIV. Around 390,000 PLWHIV people were died due to TB worldwide. Of which, about 75% of the deaths were occurred in Africa in 2015.
Africa accounted for 26% of all TB cases of which, Sub-Saharan Africa shared the higher burden (74%) of all TB cases [5, 6].

Ethiopia is one of the sub-Saharan African countries with the highest prevalence of TB/HIV co-infection and it ranked seventh among the world 30 high TB burden countries. According to the World Health Organization (WHO) 2016 TB report, Ethiopia had an estimated number of 137,960 TB cases in 2015, with an incidence rate of 192 cases per100,000 populations. Of whom, about 8% were among HIV positive individuals with an estimated incidence rate of 16/100,000 population [6, 7]. 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 improving quality of life finally increase the survival of HIV patients [8-11].

Likewise, the Ethiopian government has also 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 [12]. In addition, early initiation of ART and early screening of TB, prior provision of Isonized Preventive Therapy (IPT) [13] [13, 14] and Co-trimoxazole Prophylactic Therapy (CPT) were some of the strategies that have been implemented to reduce the incidence of TB among PLHIV [15-19].

Despite the incidence of TB among HIV positive adults in Ethiopia has been improved due to the expanded access of ART services, still TB is a major cause of morbidity and mortality among PLHIV. Regarding factors contributing to TB incidence among PLHIV, different factors have been reported from previous studies, which have been conducted in Ethiopia and different parts of Africa [19-24]. These studies identified that socio-demographic characteristics, baseline clinical and laboratory characteristic, and follow-up characteristics were the most common contributing factors to develop TB among HIV positive adults on ART [19-24].

The Ethiopian government targeted to reduce TB related deaths by 90% and TB incidence by 80% by 2030, as compared with levels in 2015. To evaluate this plan, data regarding the incidence of TB are crucial. Therefore, we conducted this retrospective cohort study to explore the incidence and predictors of TB among HIV positive adults at Debre Markos Referral Hospital, Northwest Ethiopia. The results of this study will have a paramount input for policy makers and program planners working at various levels of TB control programs. It will also have an input for health care professionals working
in the area of TB control and preventions.

Methods

Study design, area, and period

An institution based retrospective cohort study 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 of the East Gojjam administrative Zone and neighboring areas. Apart from other services, the hospital has provided ART follow-up care services since 2005. Currently, about 3,716 PLHIV are on care and follow up in this hospital. More than 1569 HIV positive adults were enrolled to HIV care to this Hospital 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. 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 were excluded from the study.

Sample size determination and sampling procedures

The minimum sample size was calculated using a sample size determination formula for survival analysis 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 ($\alpha$) of 5 %, power 80 %, $Z_{\alpha/2}= value at 95 \% CI = 1.96$, $q_1$: 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 taken from a study conducted at University of Gondar Teaching Hospital was 0.33 [20]. The final sample size was 544. To select the study participants, all HIV positive adults who had ART follow up 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.

Variables of the Study

The primary interest of outcome was the time to develop TB.

The explanatory variables include:: 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 medication related characteristics (ART regimen, presence of regimen change, ART side effect, IPT, last ART adherence and CPT).

Operational definitions

Event was defined as the occurrence of any type of TB confirmed by physician among PLHIV from ART initiation.

Censored was defined as the study participants either lost, drop out, transfer out, died before developing TB or still TB free at the end of the follow up.

Lost was defined as patients missing their appointment for follow up or drug pick up at least for one to 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 [25].

Data collection tool and procedure

Before data collection, we prepared the data extraction tool 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.

Data processing and analysis

Data were entered into EPI-data Version 4.2, and analysis was done 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, participants were dichotomized into censored or event. The necessary assumption of Cox proportional hazard regression model was checked by using Schoenfeld residual and Log-Log plot tests. In addition, the model fitness was assessed by using Cox-Snail residual test. The Kaplan Meier survival curve was used to estimate the TB free survival time of HIV positive adults on ART. Log rank tests were estimated to compare the survival curves for different categorical explanatory variables. Bi-variable Cox-proportional hazard regression model was used to screen variables for the final model. Variables having p-value \( \leq 0.25 \) 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 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 them 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 year observations. About 83 (16.9 %) of the study participants experienced TB. The overall incidence rate of TB was 6.5 (95%CI: 5.2, 8.0) per 100-person year observations. 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 bi-variable Cox-regression analysis, variables having p-value < 0.25 were screened for multivariable Cox-regression analysis. In this regard, variables including, being male, presence of baseline OIs, BMI<18.5kg/m2 or MUAC < 23cm, baseline Hgb level <10g/dl, baseline CD4 cell count < 200 cell/mm³, WHO clinical stage III and IV, being ambulatory and bedridden, didn’t take IPT, and didn’t take CPT were screened for the final multivariable Cox-regression model. Accordingly, HIV positive adults on ART who were classified as WHO clinical stage III and IV at baseline were 2.1 (95%CI: 1.2, 3.2) times more likely to develop TB as compared to those who were classified as WHO stage I and II. Similarly, HIV positive adults classified as ambulatory and bedridden at baseline were 1.8 (95%CI: 1.1, 3.1) times more likely to develop TB as compared to working functional status. In addition, patients who had OI’s at baseline were 2.8 times (95% CI: 1.7, 4.4) more likely to develop TB as compare to those who hadn’t OI’s at baseline. Moreover, patients presented with hemoglobin level of less than 10g/dl during ART initiation were 3.5 (95%CI: 2.1, 5.8) times more likely to develop TB as compared to those who had hemoglobin level greater than or equal to 10g/dl. Furthermore, HIV positive adults on ART who did not 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).

**Discussion**

Tuberculosis is a major public health challenge and remained the most commonly diagnosed opportunistic infection among PLHIV [3]. Therefore, we conducted this retrospective cohort study 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. This finding is in line with previous Ethiopian studies conducted in Gondar (7.89 cases per 100 person year) [20] and Arba Minch (5.36 cases per 100 person years) [21]. 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) [26], Nigeria( 0.57 cases per 100 PY) [27] and Tanzania (4.4 cases per 100 PY) [22]. The higher incidence of TB in this study could be attributed to the difference in study period, sample size, characteristic of study participants, and the difference in the prevalence of tuberculosis [19]. Another possible explanation for the higher incidence of TB in this study as compared to other developing countries could be due to the difference in socioeconomic characteristics among study participants of the respective countries [7].
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[28]. The variation could be explained by the difference in study settings, since this study was conducted at one referral hospital whereas the 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 setting will increases the case detection rate, which ultimately increases the incidence of TB [28]. 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 [17]. 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 is consistent with studies conducted in different parts of Ethiopia and different studies conducted elsewhere [19-22, 26-28]. 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[29]. 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 [30]. 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 [31].

In this study, advanced WHO clinical disease stage (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 [20, 22-24, 32, 33], and South Africa [29]. as WHO HIV clinical staging become more advanced, the risk of developing and recurrence of opportunistic infections including TB also simultaneously increased [24]. 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 [20, 28, 32]. 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 [20].
other possible explanation could be due to the restriction from physical activities and unable to perform daily tasks which, indirectly devastating the immune system [28]. 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 the initiation of ART increases pile burden, which results from drug interaction and side effect which, resulted synergic effect with HIV. This leads to more weaken the immune system [29].

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 [20, 21, 28, 32]. 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 [32].

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 [16, 17, 28, 32]. This may be because of the role of IPT in reducing the occurrence of TB among PLHIV [15, 34]. Currently, all HIV positive individuals who have no evidence of active TB infection recommended taking INH preventive therapy (IPT) to prevent TB infection.

Limitations
This study has some limitations that must be considered before interpreting the results. As the study was conducted through the reviewing of records retrospectively, 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.

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 predictors of TB. Therefore, a special emphasis and close follow-up should be given for the first six months of ART follow-up since this is the period of
high TB occurrence. In addition, early detecting and treating opportunistic infections should get a special attention. Moreover, provision of IPT for HIV positive patients should be strengthened.

Abbreviations
AIDS: Acquired Immune Deficiency Syndrome, ART: Antiretroviral Therapy, 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 Sciences department of public health. Besides, permission letter was also secured from Debre Markos Referral Hospital. As the study was retrospective follow up, the individual patients may not be subjected to harm as much as the confidentiality was kept. Therefore, to maintain confidentiality, names or unique ART numbers were not included in the data extraction format. Moreover, no data were 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: data collection, 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 (N=492)**        |               |
| I / II                                  | 304           |
| III / IV                                | 188           |
| < 100                                   | 113           |
| **CD4 count (N=491)**                   |               |
| 100-200                                 | 123           |
| 201-350                                 | 140           |
| >= 351                                  | 115           |
| **Functional status (N= 491)**          |               |
| Working                                 | 418           |
| Ambulatory / bed redden                 | 73            |
| **Hemoglobin level (N= 460)**           |               |
| < 10gm/dl                               | 44            |
| >=10gm/gl                               | 416           |
| **BMI/MUAC**                            |               |
| Underweight                             | 145           |
| Not Underweight                         | 347           |
| **Eligible criteria (N = 491)**         |               |
| CD4 cell count                          | 199           |
| WHO stage                               | 49            |
| Both                                    | 116           |
| Test & treat                            | 89            |
| Not recorded                            | 38            |
| **Initial regimen (N=491)**             |               |
| 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 (N= 490)**            |               |
| 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 (N= 492)                   |       |          |            |
| Male                           | 47    | 181      | 1.6(1.1, 2.5) |
| Female                         | 36    | 228      | 1          |
| CD4 cell count (N=491)         |       |          |            |
| <200 cell/mm³                  | 55    | 180      | 2.2 (1.4, 3.4) |
| >=200 cell/mm³                 | 28    | 228      | 1          |
| WHO clinical staging (N=492)   |       |          |            |
| Stage I and II                 | 26    | 278      | 1          |
| Stage III and IV               | 57    | 131      | 4.0 (2.5, 6.4) |
| Functional status (N=491)      |       |          |            |
| Working                        | 51    | 367      | 1          |
| Ambulatory & bedridden         | 32    | 41       | 5.0 (3.2, 7.8) |
| BMI / MUAC (N=492)             |       |          |            |
| Underweight                    | 32    | 113      | 1.6 (1.1, 2.6) |
| Not Underweight                | 51    | 296      | 1          |
| Hemoglobin level (N=486)       |       |          |            |
| <10 g/dl                       | 27    | 20       | 6.7 (4.2, 10.7) |
| ≥10 g/dl                       | 56    | 383      | 1          |
| Opportunistic infection (N=492)|       |          |            |
| Yes                            | 51    | 111      | 3.7 (2.4, 5.7) |
| No                             | 32    | 298      | 1          |
| CPT (N= 492)                   |       |          |            |
| Yes                            | 69    | 354      | 1          |
| No                             | 14    | 55       | 1.6 (0.9, 2.8) |
| IPT (N =492)                   |       |          |            |
| Yes                            | 10    | 169      | 1          |
| No                             | 73    | 240      | 4.8 (2.5, 9.3) |

** Significant predictors

**Figures**
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