Anemia and its determinants among TB-HIV co-infected adults of ART naïve in two public hospitals of Mekelle, Ethiopia: a facility based cross-sectional study

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Research article

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Abstract

Background Anemia has up to 87% prevalence in high Tuberculosis (TB) and HIV burden settings of the Sub-Saharan Africa (SSA) including Ethiopia. It increases Lost to follow up (LTFU) rate, reduces quality of life and shortens the life expectancy of TB-HIV patients. Despite these facts, there is limited information on anemia and its determinants among TB-HIV adults of ART naïve in Ethiopia in general. Hence, the current study will partly fill the gap in the setting particularly.

Methods A facility based cross-sectional study was conducted among 305 TB-HIV co-infected patients of ART naïve who have been started treatment from January, 2009 to December, 2017 in two public hospital of Mekelle, Ethiopia by reviewing an ART register and patient medical charts. A Generalized Linear Model (GLM) of binomial family with link function logit (logit model) was fitted to identify the statistically significant determinants of anemia. Finally, the decision was made based on the 95% Confidence Interval (95% CI) and the magnitude of association was measured based on the Adjusted Odds ratio (Adj. OR).

Results At baseline, the cumulative prevalence of anemia was 59.0% (95% CI: 53.3% – 64.6%) where the prevalence of mild, moderate and severe anemia's 24.6%, 28.2% and 6.2%, respectively. Female sex ((Adj.OR = 0.379; 95% CI: 0.226 – 0.635) and Body Mass Index (Adj. OR = 0.897, 95% CI: 0.823 - 0.977) reduces the odds of developing anemia whereas baseline ambulatory functional status (Adj. OR = 2.302; 95% CI: 1.293 - 4.097), Bedridden functional status (Adj. OR = 2.352; 95% CI: 1.074 - 5.149), HIV Clinical stage III (Adj. OR = 2.987; 95% CI: 1.226-7.279) and HIV Clinical stage IV (Adj. OR = 3.056; 95% CI: 1.219 - 7.657) increases the odds of anemia in TB-HIV co-infected adults of ART naïve in the current study.

Conclusion Six in every ten TB-HIV co-infected adults of ART naïve developed anemia at baseline. Therefore, curious attention has to be given to undernourished, advanced clinical stage (III and IV) and non-working functional status TB-HIV adults to reducing anemia associated bad consequences.

Background

According to the World Health Organization (WHO), anemia is defined as hemoglobin levels <12.0 g/dl in women and <13.0 g/dl in men though other factors such as race, altitude, physiological status, and pregnancy status has taking in to consideration [1]. Anemia is a global public health problem that affects an estimated one-fourth of the world’s population, with an inconsistent discrimination of cases occurring in sub-Saharan Africa [2, 3]. The burden of anemia increase the morbidity and mortality, decreased quality of life and negatively affects productivity of women particularly [4].

Though etiology of anemia is multifactorial, studies showed that HIV and tuberculosis (TB) are both strongly significantly associated with anemia. Several studies indicated that factors contributing to anemia in adults living with Human Immunodeficiency Virus (HIV) including nutritional deficiencies of iron, folate and vitamin B$_{12}$ as well as co-morbidities such as malaria, helminthes infections and opportunistic infections and also adverse drug effects. HIV and its viral proteins as well as immune suppressions during the course of HIV infection were found to be responsible for bone marrow suppression which leads to anemia [5, 6]. Furthermore, Tuberculosis (TB) plays a significant role in causing HIV-related anemia in Sub-Saharan Africa (SSA) region including Ethiopia [7-9].
Anemia is frequently manifested among HIV patients of Antiretroviral Therapy (ART)-naïve in Sub-Saharan Africa (SSA), with a prevalence ranging from 45-87% [10-13]. Anemia is one of the leading cause and frequent clinical complications of both HIV and TB disease and is associated with substantial morbidity and mortality in TB-HIV co-infected patients [14-16]. It is also related with markedly increased Lost to Follow up (LTFU) rate of up to 23% in anemic TB-HIV co-infected adults as compared to near 10% among non-anemic adults at baseline in a study conducted in Mekelle, Ethiopia (i.e. same setting) indicating that anemia results in high incidence of LTFU rate among adults co-infected with TB and HIV dually [17]. Though the relationship between anemia and HIV associated TB has not yet been well described, anemia may serve as a useful biomarker for the improved HIV associated TB diagnosis and clinical management of such patients [18]. On the other hand, dissemination of TB to the gastrointestinal tract mucosa may result in iron deficiency anemia, while bone marrow involvement may cause impairment of all hematopoietic cell lines and anemia had reported to be strongly and consistently associated with HIV disease progression, suggesting the need for routine screening and treatment of anemia in HIV patients on Highly Active Antiretroviral Therapy (HAART) [19-21].

Studies conducted in different area showed that an increased prevalence of anemia in female HIV-infected persons compared to male HIV-infected persons, which is often, documented the reason due to blood loss during menstruation, pregnancy, and delivery. In addition, it is greatly transpired in HIV infected individuals with low number of CD4 T-cell count, high erythrocyte sedimentation rate and vitamin D insufficiency as main predictors of anemia in HIV- seropositive individuals [22, 23]. Another study revealed that the risk of death to be up to 70% or greater in HIV-infected anemic patients compared with non-anemic patients and that with anemia, the need for transfusions is greater and quality of life is poorer manly due to fatigue [24].

To the level of our understanding, only few studies were conducted in Ethiopia regarding anemia and its determinants among HIV infected adults regardless of their TB status. These studies revealed the overall prevalence of anemia was varying from 23.0% - 42.9% with the highest proportion among patients of ART naive than on HAART. Male sex, rural place of residence, WHO clinical stage III/IV, presence of TB co-infection and low baseline CD4 cell count were reported as positive predictors of anemia at baseline in one or more of the studies [25-28]. However, none of the studies were assessed the magnitude of anemia in TB-HIV co-infected adults. Thus, this study was aimed to filling the gap partly by determining baseline determinants of anemia among TB-HIV co-infected adults of ART naive in the current study so as to help in clinical care of anemic patients, evidence based decision making on the prevention of anemia and giving base line information for further study on Anemia longitudinally by clinicians, decision makers and researchers, respectively.

Methods

Study setting and design
A hospital based cross-sectional study was conducted among TB/HIV co-infected persons who started ART from September, 2009 – December, 2016 at two governmental hospitals - Mekelle Hospital and Ayder Comprehensive Specialized Hospital - Mekelle, Ethiopia. Mekelle is the capital city of the national regional state of Tigray which is 783 kilometers far from Addis Ababa, the capital of Ethiopia. All active TB and HIV co-infected adults who fulfilled the eligibility criteria were included in the study. ART service has been begun since September, 2004 in Mekelle Hospital and since September, 2009 in Ayder comprehensive specialized hospital. Collectively, above 12,000 HIV patients initiated ART since their foundations.

**Sample size determination and sampling proportion**

In the current study, participants were ascertained their active TB and HIV co-infection status by reviewing ART logbook and patient medical charts. We used the single population proportion formula to estimate the minimum sample size considering the following underlining assumptions - 95% confidence level, 5% acceptable level of precision (margin of error), and overall prevalence of anemia (23%) among HIV patients irrespective their ART conducted in Debre-tabor, Ethiopia which is [28]. (see Equation 1 in Supplementary Files)

Study variables, tool, data quality and data collection procedure

A well-organized data abstraction sheet (checklist) was prepared and then, modified considering the most important baseline socio-demographic and clinical characteristics of the target participants. After training on how to review data was given to data collectors, the following data elements were collected from the ART registers and patient medical charts using a well standardized checklist:

1. Baseline Socio-demographic characteristics of TB-HIV co-infected patients (i.e. sex, age, educational status, marital status, religion, place of residence and ART follow up site)
2. Baseline clinical and laboratory characteristics of the participants (i.e. functional status, WHO clinical stage, Body Mass Index (BMI in kg/m\(^2\)), CD4+ cell count (cells/mm\(^3\)), and TB infection site).
3. Hemoglobin concentration (g/dl) of TB-HIV co-infected adults. In the current study, hemoglobin was considered as the proxy indicator of anemia to classify the participants as normal (hemoglobin >=12 g/dl for women and >=13 g/dl for men) or anemic (hemoglobin <12.0 g/dl for men versus <13.0 g/dl for men). Anemia is further classified in adult males as: mild anemia (11.0 – 12.9 g/dl), Moderate anemia (8.0 – 10.9 g/dl) and Severe anemia (<8.0 g/dl). On the other hand, the classification of anemia is slightly different in adult females (i.e. mild anemia (11.0 – 11.9 g/dl), Moderate anemia (8.0 – 10.9 g/dl) and Severe anemia (<8.0 g/dl) [1]. Thus, anemia status is the outcome variable labeled as 1 if anemic (success) and 0 else (i.e. normal (failure)).

**Statistical methods of data analysis**

First, data were entered, exported and then cleaned in STATA version 14.2 statistical tool. The participants were described using frequency (percent) and Median (Interquartile Range (IQR) by taking in to account
the categorical and numeric variables included in the study, respectively and the adequacy of cell counts was also checked using cross-tabulation so as to fit a Generalized Linear Model (GLM) of binomial family with logit link function. Both interaction and multicollinearity were checked. Hence, none of the interaction terms were statistically significant and collinearity was not problematic in the study. Multiple GLM models (logit model and robust Poisson model) were run separately and the best model was selected based on the Akaike Information Criterion (AIC) and consequently, the logit model was fitted explaining the data well. Finally, the strength of association of each statistically significant predictor was measured and interpreted based on the Adjusted Odds Ratio (Adj. OR) and its corresponding 95% Confidence Interval (CI). For the categorical predictors, the estimate (Adj.OR) was interpreted in comparison to the reference category for the odds of developing anemia (i.e. collectively mild, moderate or severe). On the other hand, for the numeric (i.e. continuous predictor), the estimate was interpreted as a unit increase in the continuous predictor decreases/increases the odds of developing of anemia depending on the magnitude of the Adj.OR.

Results

Socio demographic characteristics of TB-HIV co-infected adults by anemia status

Regarding the baseline socio-demographic characteristics, 148 of 305 (48.5%) of the participants were males with a median (IQR) age and hemoglobin of 35 (IQR: 29 - 40 years), and 11.9 (IQR: 10.3-13.5 g/dl), respectively. Moreover, 69 of 305 (22.6%) had single marital status, 65 of 305 (21.5%) were with no education, 293 of 305 (96.1%) were orthodox followers, 222 of 305 (72.8%) were residents of Mekelle city, and 172 of 305 (56.4 %) had initiated ART service in Mekelle hospital. Based on their anemia status, 65 of 157 (41.4%) females, 43 of 129 (33.3%) married adults, 40 of 129 (33.6%) with secondary educational status, and 9 of 12 (75.0%) Muslims were anemic at baseline (Table 1).

Table 1: Baseline Socio-demographic characteristics and anemia status of TB-HIV co-infected adults of ART naïve from September, 2009 to December, 2016 in Mekelle, Ethiopia (n = 305)
| Socio-demographic characteristic | Baseline level of Anemia Status | Prevalence rate (number of anemia cases per 100 TB-HIV adults) | P-value |
|----------------------------------|---------------------------------|---------------------------------------------------------------|---------|
|                                  | Normal (n=125)                  |                                |         |
|                                  | Mild anemia (n=75)              |                                |         |
|                                  | Moderate anemia (n=86)          |                                |         |
|                                  | Severe anemia (n=19)            |                                |         |
| Baseline level of Anemia Status  | Number of TB-HIV cases (%)      |                                |         |
|                                  | Count (%)                       | Count (%)                      | Count (%)| Count (%)| |
| x                                 | Male                            | 47 (37.6)                      | 57 (76.0)| 37 (44.0)| 7 (36.8)| 148 (48.5) | 68.2 |
|                                  | Female                          | 78 (62.4)                      | 18 (24.0)| 49 (56.0)| 12 (63.2)| 157 (51.5) | 50.2 |
| Baseline Age (Median & IQR)      | 35 (29-40) years                |                                | 0.320   |
| Educational Status               |                                 |                                | 0.194   |
| No education                     |                                 | 25 (20.0)                      | 15 (20.0)| 21 (24.4)| 4 (21.1)| 65 (21.3) | 61.5 |
|                                 | Primary                         | 30 (24.0)                      | 24 (32.0)| 31 (36.0)| 5 (26.3)| 90 (29.5) | 66.7 |
|                                 | Secondary                       | 57 (45.6)                      | 24 (32.0)| 28 (32.6)| 10 (52.6)| 119 (39.0) | 52.1 |
|                                 | Tertiary                        | 13 (10.4)                      | 12 (16.0)| 6 (7.0)   | 0 (0.0) | 31 (10.2) | 58.1 |
| Marital Status                   |                                 |                                | 0.639   |
| Single                           |                                 | 30 (24.0)                      | 14 (18.7)| 21 (24.4)| 43 (22.5)| 69 (22.6) | 56.5 |
| Married                          |                                 | 55 (44.0)                      | 34 (45.3)| 30 (34.9)| 86 (45.0)| 129 (42.3) | 57.4 |
| Othersa                          |                                 | 40 (32.0)                      | 27 (36.0)| 35 (40.7)| 62 (32.5)| 107 (35.1) | 62.6 |
| Religion                         |                                 |                                | 0.251   |
| Orthodox                         |                                 | 122 (97.6)                     | 72 (96.0)| 83 (96.5)| 16 (84.2)| 293 (96.1) | 58.4 |
| Muslim                           |                                 | 3 (2.4)                        | 3 (4.0)   | 3 (3.5)   | 3 (15.8) | 12 (3.9) | 75.0 |
| Race of residence                |                                 |                                | 0.797   |
| Mekelle                          |                                 | 90 (72.0)                      | 51 (68.0)| 69 (80.2)| 12 (63.2)| 222 (72.8) | 59.5 |
| Outside Mekelle                  |                                 | 35 (28.0)                      | 24 (32.0)| 17 (19.8)| 7 (36.8) | 83 (27.2) | 57.8 |
| TB follow up site                |                                 |                                | 0.003   |
| ACSH                             |                                 | 42 (33.6)                      | 42 (56.0)| 39 (45.4)| 10 (52.6)| 133 (43.6) | 68.4 |
| Mekelle hospital                 |                                 | 83 (66.4)                      | 33 (44.0)| 47 (54.6)| 9 (47.4) | 172 (56.4) | 51.7 |

Othersa: Widowed/Divorced/Separated
ACSH: Ayder Comprehensive Specialized Hospital
IQR: Interquartile Range
Clinical characteristics of TB-HIV co-infected adults by anemia status

Based on the clinical characteristics, 141 (46.2%) and 142 (46.6%) of TB-HIV co-infected adults had baseline working functional status, and WHO clinical stage. In addition, 132 (43.3%) of TB cases were involved the lung (diagnosed with PTB) where the median baseline BMI (kg/m$^2$), and CD4+ cell count (cells/mm$^3$) were kept at 17.4 and 86, respectively. Regarding the outcome status, 49 of 110 (45.5%) TB-HIV adults with baseline ambulatory functional status, 61 of 142 (43.3%) adults with baseline clinical stage IV and 69 of 173 (39.9%) EPTB or mixed – HIV co-infected adults had anemia at the time of ART initiation (Table 2).

Table 2: Baseline clinical characteristics and anemia status of TB-HIV co-infected adults of ART naïve from September, 2009 to December, 2016 in Mekelle, Ethiopia (n = 305)
## Baseline clinical characteristics

| Status                          | Count (n=125) | Count (n=75) | Count (n=86) | Count (n=19) | Number of TB-HIV cases (%) | Prevalence rate (number of anemia cases per 100 TB-HIV adults) | P-value |
|---------------------------------|---------------|--------------|--------------|--------------|--------------------------|------------------------------------------------------------------|---------|
| Normal                          | 76 (60.8)     | 33 (44.0)    | 28 (32.6)    | 4 (21.1)     | 141 (46.2)               | 46.1                                                             | <0.001  |
| Mild anemia                     | 34 (27.2)     | 30 (40.0)    | 39 (45.3)    | 7 (36.8)     | 110 (36.1)               | 69.1                                                             |         |
| Moderate anemia                 | 15 (12.0)     | 12 (16.0)    | 19 (22.1)    | 8 (42.1)     | 54 (17.7)                | 72.2                                                             |         |
| Severe anemia                   |               |              |              |              |                         |                                                                  |         |
| Number of TB-HIV cases (%)      |               |              |              |              |                         |                                                                  |         |

### Functional status

| Status | Count (n=125) | Count (n=75) | Count (n=86) | Count (n=19) | Number of TB-HIV cases (%) | Prevalence rate (number of anemia cases per 100 TB-HIV adults) | P-value |
|--------|---------------|--------------|--------------|--------------|--------------------------|------------------------------------------------------------------|---------|
| Working| 76 (60.8)     | 33 (44.0)    | 28 (32.6)    | 4 (21.1)     | 141 (46.2)               | 46.1                                                             | <0.001  |
| Ambulatory | 34 (27.2)   | 30 (40.0)    | 39 (45.3)    | 7 (36.8)     | 110 (36.1)               | 69.1                                                             |         |
| Bedridden | 15 (12.0)   | 12 (16.0)    | 19 (22.1)    | 8 (42.1)     | 54 (17.7)                | 72.2                                                             |         |

### HO clinical stage

| Stage | Count (n=125) | Count (n=75) | Count (n=86) | Count (n=19) | Number of TB-HIV cases (%) | Prevalence rate (number of anemia cases per 100 TB-HIV adults) | P-value |
|-------|---------------|--------------|--------------|--------------|--------------------------|------------------------------------------------------------------|---------|
| I/II  | 30 (24.0)     | 14 (18.7)    | 3 (3.5)      | 0 (0.0)      | 30 (10.5)                | 28.1                                                             |         |
| III   | 55 (44.0)     | 34 (45.3)    | 38 (44.2)    | 6 (31.6)     | 131 (42.9)               | 57.3                                                             |         |
| IV    | 40 (32.0)     | 27 (36.0)    | 45 (52.3)    | 13 (68.4)    | 142 (46.6)               | 67.6                                                             |         |

### WBC count

| WBC count | Count (n=125) | Count (n=75) | Count (n=86) | Count (n=19) | Number of TB-HIV cases (%) | Prevalence rate (number of anemia cases per 100 TB-HIV adults) | P-value |
|-----------|---------------|--------------|--------------|--------------|--------------------------|------------------------------------------------------------------|---------|
| <=200 Cells/mm³ | 90 (72.0) | 64 (85.3)    | 79 (91.9)    | 17 (89.5)     | 250 (82.0)               | 64.0                                                             |         |
| >200 Cells/mm³  | 35 (28.0)    | 11 (14.7)    | 7 (8.1)      | 2 (10.5)      | 55 (18.0)                | 36.4                                                             |         |

### Infection

| Infection | Count (n=125) | Count (n=75) | Count (n=86) | Count (n=19) | Number of TB-HIV cases (%) | Prevalence rate (number of anemia cases per 100 TB-HIV adults) | P-value |
|-----------|---------------|--------------|--------------|--------------|--------------------------|------------------------------------------------------------------|---------|
| PTB       | 62 (49.6)     | 29 (38.7)    | 36 (41.9)    | 5 (26.3)     | 132 (43.3)               | 53.0                                                             |         |
| EPTB/Mixed type | 63 (50.4) | 46 (61.3)    | 50 (58.1)    | 14 (73.7)    | 173 (56.7)               | 63.6                                                             |         |

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ALT: Alanine Transferase  
AST: Aspartate Transferase  
PTB: Pulmonary Tuberculosis  
EPTB: Extra Pulmonary Tuberculosis  
BMI: Body Mass Index  
IQR: Interquartile range

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**Prevalence of Anemia among TB-HIV co-infected adults**

Based on the baseline hemoglobin measurement (g/dl or %) of TB-HIV co-infected adults, 180 of 305 (prevalence rate = 59.0%; 95% CI: 53.3 – 64.6%) were anemic. Furthermore, the prevalence’s of mild, moderate and severe anemia were 24.6%, 28.2% and 6.2%, respectively at baseline (Fig.1). Comparatively,
the prevalence of anemia was varying across the different categories of the baseline socio-demographic and clinical characteristics of adults co-infected with dual burdens of TB and HIV co-infections (Tables 1 and 2).

**Determinants of anemia among TB-HIV co-infected adults**

Upon running the final multiple logit regression analysis, the baseline determinants of anemia were: Sex, functional status, WHO clinical stage, and BMI ($\text{kg/m}^2$). Keeping other variables constant, female TB-HIV co-infected adults of ART naïve were 0.379 (Adj.OR = 0.379; 95% CI: 0.226 – 0.635) times less likely to develop anemia than male adults (i.e. being a male TB-HIV co-infected adult protects approximately 62% against anemia). Like wisely, the changes in odds of developing anemia among TB-HIV co-infected adults with baseline ambulatory functional status, bedridden functional status, WHO clinical stage III and IV were approximately 130%, 140%, 200% and 210%, respectively as compared to their reference categories. However, a unit increase in BMI ($1 \text{ kg/m}^2$) reduces the occurrence of anemia by 10% (Adj. OR = 0.897, 95% CI: 0.823 - 0.977) in TB-HIV co-infected adults (Table 3).

**Table 3:** statistically significant determinants of anemia among TB-HIV co-infected adults of ART naïve from September, 2009 to December, 2016 in Mekelle, Ethiopia (n = 305)

| Independent variables | Category     | Adj.OR | Standard Error | 95% CI         | P-value |
|-----------------------|--------------|--------|----------------|----------------|---------|
|                       |              |        |                | 2.5% (LL) | 97.5% (UL) |                     |
| Sex                   | Male         | 1.000  |                |              |          |                     |
|                       | Female       | 0.379  | 0.100          | 0.226        | 0.635    | <0.001**            |
| BMI (kg/m$^2$)        |              | 0.897  | 0.039          | 0.823        | 0.977    | 0.013*              |
| Functional status     | Working      | 1.000  |                |              |          |                     |
|                       | Ambulatory   | 2.302  | 0.677          | 1.293        | 4.097    | 0.005**             |
|                       | Bedridden    | 2.352  | 0.940          | 1.074        | 5.149    | 0.032*              |
| WHO Clinical stage    | I or II      | 1.000  |                |              |          |                     |
|                       | III          | 2.987  | 1.358          | 1.226        | 7.279    | 0.016*              |
|                       | IV           | 3.056  | 1.432          | 1.219        | 7.657    | 0.017*              |
| Intercept             |              | 3.980  | 3.782          | 0.618        | 25.626   | 0.146               |

Adj. OR: Adjusted Odds Ratio BMI: Body Mass Index CI: Confidence Interval LL: lower Limit UL: Upper Limit 1.000: Reference category *: significant at 5% level of significance **: significant at 1% level of significance

**Discussion**

The current study was conducted to investigate the prevalence of anemia and its socio-demographic and clinical determinants among TB/HIV co-infected adults in two public hospitals, Mekelle, Ethiopia. Thus, the current study has revealed that 59% (95% CI: 53.3 – 64.6%) of adults co-infected with TB and HIV were anemic at the time of ART initiation. Moreover, female sex, baseline ambulatory functional status,
baseline bedridden functional status, WHO clinical stage III, WHO clinical stage IV and BMI were identified as statistically significant determinants of anemia among TB - HIV co-infected adults in the current study.

In this study, the overall prevalence of anemia at baseline was found to be 59.0% (24.6% mild, 28.2% moderate and 6.2% severe anemia) which almost exactly in line to a study conducted across Europe where the target groups HIV patients of HAART naïve [29]. The overall prevalence of anemia in the current study was higher than other different studies that ranges from 18.9% in Uganda to 49.6% in Indonesia [25-28, 30-34]. To the contrary, the baseline prevalence was lower than other studies conducted among ART Naïve HIV or TB patients in Ghana, Nigeria and Gambia that had been reported 63.0%, 69.2% and 67%, respectively [11, 35, 36]. The reasons for the high prevalence of anemia at baseline in the current study is in fact possibly related to the contribution tuberculosis in speeding up the occurrence of HIV associated anemia as the participants in almost all the studies used for comparison are either HIV Patients with or without TB co-infection [7-9]. On the other hand, the low prevalence when compared to the other three studies could be the difference in operationalizing anemia using hemoglobin level and difference in ethnicity, geographic location, stage of the HIV infection, presence of other opportunistic infection and feeding style of the population contributing a lot for the discrepancy.

In the current study, female sex is negatively statistically associated with the anemia occurrence of anemia among adult TB-HIV co-infected patients of HAART naïve. The finding was in agreement with other studies conducted in Benin city (Nigeria) and Zewidtu Memoral Hospital (Ethiopia) which had been revealed that being a female is an opportunity to protect anemia as compared to male HIV patients HAART naïve or HAART experienced [11, 25]. However, it is in-consistent with other similar studies that had been reported the harmful effect of female sex against anemia [26, 32, 33, 35] which all have reported that the prevalence of anemia was higher among females than males. The main reason for the inconsistency findings as compared to the current study might be the difference in definitions of anemia that used different cutoff values of hemoglobin for males and females. Of course, logically the prevalence of anemia was expected to be higher on adult HIV and/or TB co-infected women because of the contributions of blood loss during menstruation, pregnancy and delivery that aggravates the prevalence of anemia [22, 23]. Despite that fact, the prevalence of anemia was higher among adult TB-HIV women than Men mainly due to: - 1) the cutoff point for anemia classification used for both sexes was not uniform (i.e. a woman with hemoglobin level of 12 g% and above is considered as normal where as a man with hemoglobin level of only 13 g% and above was considered as normal) 2) there were other important but uninvestigated variables that may confounded with sex such as altitude, and feeding style revealing that most females might be from highlands with low oxygen tension so that their hemoglobin concentration was increased to compensate that and females might have also better feeding practice than males that developed from nutritional counseling during pregnancy from their doctors. All these might contribute to the significant proportion of women to have normal baseline anemia despite the probability of blood loss as a result of menstruation, pregnancy and delivery.

BMI (kg/m$^2$) also significantly negatively predicting the odds of developing anemia among TB-HIV co-infected adults. A unit increase in baseline anemia protects the occurrence of by approximately 10% Adj.
OR = 0.897, 95% CI: 0.823 - 0.977) keeping the effect of other covariates on the logit model. This finding was consistent with other studies conducted in South Africa, Uganda and Rwanda which all have supported the inverse relationship between baseline BMI and anemia revealing that the risk of developing anemia was higher among underweight adult HIV patients as compared to normal or overweight once [30, 33, 37]. However, the socio-demographic variable sex was fixed in the Rwandan study where the participants were only adult women. It is obvious that nutritional deficiencies including iron, folic acid and vitamin B_{12} plays a major role in causing nutrition related anemia in HIV and/or TB infected adults [5, 6]. Thus, a low BMI is an indication poor nutritional status (i.e. under nutrition) that may increases the risk of developing of TB-HIV associated anemia in the current study.

Both baseline ambulatory and bedridden functional status of adult HIV patients were statistically positive associated with the likelihood of developing anemia TB/HIV co-infected adults of ART naïve indicating that adult TB/HIV co-infected adults with baseline ambulatory and bedridden functional stat were approximately 2.3 and 2.4 times more likely to develop anemia than those with working functional status counterpart. Though literatures on this part were scarce, it is clear that patients with these two functional statues have extra burdens that might lost their appetite to take foods of adequate diversity score including iron, folic acid and Vitamin B_{12} speeds up the development of anemia.

Similarly, HIV adults of ART Naïve with WHO Clinical stage III and IV were more likely to develop anemia than those with clinical stage I/II collectively. The result of current study was supported with the findings other similar studies conducted in Uganda and south Africa which had been reported that the odds of developing anemia was increasing as patients clinical stage advanced from stage I/II to III and then IV [32, 33]. The key reasons could be as HIV infections was advanced from the early stages (I or II): 1) to III - there would be marked weight loss (>10% of total weight), consistent diarrhea, PTB, systematic bacterial infections (i.e. pneumonia, meningitis, bone and joint infections), oral candidiasis and others and 2) stage IV- it includes all the AIDS defining illnesses mainly the clinical findings such as HIV wasting syndrome, Pneumocystis Pneumonia (PCP), EPTB, HIV encephalopathy, CNS toxoplasmosis, chronic herpes simplex virus infection, Cytomegalic Virus (CMV) and other complications [38]. Thus, all additional infections and complications in stages III and IV of HIV adults might lead to anemia because of excessive fluid loss due to prolonged diarrhea as result of different opportunistic infections of bacterial and viral origins that causes immune suppression.

Despite an appropriate study designed using robust statistical methods, the current study was not completely free of limitations. The study populations were considered as TB-HIV co-infected of ART naïve (i.e. prior ART initiation) regardless of the exact time of TB development. The pregnancy status of women at baseline was not known and thus, the anemia classification for pregnant women was not applied that may underestimate the prevalence of anemia among Adult women in the study. Some variables which are assumed to be confounded with anemia such as geographic distribution and wealth index (socio-economic status) were not retrieved from the record.

**Conclusions**
Approximately six in ten TB-HIV co-infected adults of ART naïve were anemic at enrollment. Male sex, low baseline BMI, ambulatory functional status, bedridden functional status, WHO HIV clinical stage III and IV increasing the prevalence of anemia in adults with TB and HIV co-infections. Therefore, adult patients with under nutrition, more advanced clinical stages, and non-working functional status have to be assessed for anemia and given appropriate interventions so as to limit anemia associated bad consequences of TB and HIV in adults.

**Abbreviations**

- **AIC**: Akaike Information Criterion
- **Adj. OR**: Adjusted Odds Ratio
- **AIDS**: Acquired Immunodeficiency Virus
- **ART**: Antiretroviral Therapy
- **BMI**: Body Mass Index
- **CI**: Confidence Interval
- **GLM**: Generalized Linear Model
- **HAART**: Highly Active Antiretroviral Therapy
- **HIV**: Human Immunodeficiency Virus
- **IQR**: Interquartile Range
- **TB**: Tuberculosis
- **WHO**: World Health Organization

**Declarations**

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**Ethics approval and consent to participate**

Ethics approval was issued by the Institutional Review Board (IRB) of Mekelle University-College of Health Sciences and the consent to participate from the participants was fully waived since patients were not directly involved. However, data were kept confidentially and no personal identifiers were used.

**Availability of data and materials**

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

**Author Contribution**

KEG is participated in proposing, designing, analyzing data and drafting the manuscript, acts as the principal author of the manuscript. KHM and AY are participated in drafting the manuscript.

**Consent for publication**
Not applicable

**Competing interests**

The authors have declared that no financial and non-financial conflict of interest. The final draft of the manuscript has read and approved by all authors.

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Figures

Figure 1

Prevalence of mild, moderate and severe anemia in TB-HIV co-infected adults of ART naïve from September, 2009 to December, 2016 in two public hospitals of Mekelle, Ethiopia (n = 305)

Supplementary Files

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- Equation1.jpg