Tuberculosis and its association with CD4+ T cell count among adult HIV positive patients in Ethiopian settings: a systematic review and meta-analysis

Demeke Geremew1*, Mulugeta Melku2, Aklilu Endalamaw3, Berhanu Woldu2, Alebachew Fasil4, Markos Negash1, Habtamu Wondifraw Baynes4, Habtamu Geremew5, Takele Teklu1, Tekalign Deressa6, Belay Tessema7 and Ulrich Sack8

Abstract

Background: Tuberculosis (TB) and HIV have been intertwined and makeup a deadly human syndemic worldwide, especially in developing countries like Ethiopia. Previous studies have reported different TB incidences and its association with CD4+ T cell counts among HIV positive patients in Ethiopia. Thus, the goal of this meta-analysis was, first, to determine pooled incident TB among adult HIV positive patients, and second, to assess the association between incident TB and baseline CD4+ T cell count strata.

Methods: We searched PubMed, Cochrane library, Science Direct and Google scholar databases from June 1 to 30, 2018. The I² statistics and Egger’s regression test was used to determine heterogeneity and publication bias among included studies respectively. A random effects model was used to estimate pooled incident TB and odds ratio with the respective 95% confidence intervals using Stata version 11.0 statistical software.

Results: A total of 403 research articles were identified, and 10 studies were included in the meta-analysis. The pooled incident TB among adult HIV infected patients in Ethiopia was 16.58% (95% CI; 13.25–19.91%). Specifically, TB incidence in Pre-ART and ART was 17.16% (95% CI; 7.95–26.37%) and 16.24% (95% CI; 12.63–19.84%) respectively. Moreover, incident TB among ART receiving patients with baseline CD4+ T cell count < and ≥ 200 cells/mm³ was 28.86% (95% CI; 18.73–38.98%) and 13.7% (95% CI; 1.41–25.98%) correspondingly. The odds of getting incident TB was 2.88 (95% CI; 1.55–5.35%) for patients with baseline CD4+ T cell count < 200 cells/mm³ compared to patients with baseline CD4+ T cell count ≥ 200 cells/mm³.

Conclusion: High incident TB among adult HIV positive patients was estimated, especially in patients with CD4+ T cell count < 200 cells/mm³. Therefore, Early HIV screening and ART initiation, as well as strict compliance with ART and increasing the coverage of TB preventive therapy to more risky groups are important to prevent the problem.

Trial registration: Study protocol registration: CRD42018090802.

Keywords: Tuberculosis, HIV, CD4+ T cell, Meta-analysis, Ethiopia

* Correspondence: deme2112@gmail.com
1Department of Immunology and Molecular Biology, School of Biomedical and Laboratory Sciences, University of Gondar, P.O.Box: 196, Gondar, Ethiopia

Full list of author information is available at the end of the article

© The Author(s). 2020 Open Access This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article’s Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article’s Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit http://creativecommons.org/licenses/by/4.0/. The Creative Commons Public Domain Dedication waiver (http://creativecommons.org/publicdomain/zero/1.0/) applies to the data made available in this article, unless otherwise stated in a credit line to the data.
Background

Tuberculosis (TB) is one of the major problems of mankind worldwide, especially after the emergence of HIV pandemic, TB is resurging mainly in resource limited areas of sub-Saharan Africa [1]. Even with the advancement of TB/HIV control programs, the twin widespread emergence of HIV and TB makes them the deadly syndemic of mankind. Many epidemiological studies showed that HIV is a driving force for TB incidence, and people living with HIV (PLWH) have higher risk of developing incident TB [2, 3]. It has been reported that TB is the most common opportunistic infection among HIV positive patients, and recently 12% of the 9.6 million new TB cases were among HIV infected patients [4]. The risk of getting incident TB in PLWH is 21 times greater than the population without HIV comorbidity [5].

Previous studies clearly demonstrated that HIV causes immunosuppression directly by depletion of host CD4+ T lymphocytes. As a result of lymphocytopenia and downregulation of these immune cells, vulnerability to TB diseases is increased in HIV positive patients [6, 7]. Moreover, HIV infected patients with decreased CD4+ T cell count is associated with increased risk of TB, especially CD4+ T lymphocyte count < 200 cells/mm3 is much more accompanied with higher TB incidence [8, 9].

Therefore, CD4+ T lymphocyte count remains the best indicator of a patient’s immunological and clinical status, the risk of opportunistic infections like TB, and supports diagnostic decision making, particularly for patients with advanced HIV disease [10]. In Ethiopia, individual studies showed inconsistent TB incidence among adult HIV infected patients ranging from 8.3 [11] to 29.06% [12]. Besides, although CD4+ T cell count in PLWH impacts TB risk, the quantitative connection between CD4+ T cell count and TB risk is not well documented in our country. Thus, we sought to provide a meta-analysis estimate of pooled incident TB among adult HIV positive patients and its association with baseline CD4+ T cell counts for better planning and execution of screening programs, regular follow ups and prevention approaches.

Methods

Definitions

We have used the following terms in this meta-analysis; incident TB defined as all new TB cases from the beginning to the last day of observation. It was calculated by dividing the number of new TB cases by total number of study participants at risk at the beginning of observation, and times by 100. Further, the term “incident TB” and “TB incidence” was used interchangeably throughout this manuscript as it was also evidenced elsewhere [13, 14]. Pooled incident TB described as an estimate considered from reported TB incidences of all included studies. Nevertheless, this proportion does not adjust whether the study cohorts were within 6 or > 6 months of follow up for HIV infected patients on pre-ART.

Reporting and protocol registration

This review was conducted based on Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement guideline [15]. This study was registered in International Prospective Register of Systematic Reviews (PROSPERO) database with protocol number, CRD42018090802.

Search strategy

An inclusive literature search was made using PubMed, Cochrane library, Science Direct and Google scholar databases from June 1 to 30, 2018. The search term used for retrieving records in PubMed on 07/08/2018 was: “human immunodeficiency virus” OR “HIV” AND “CD4” T cell count” OR “CD4 count” AND (Tuberculosis OR TB) AND (infection OR incidence) AND (“Ethiopia”). The PubMed search string was developed in accordance with the Medical Subject Headings thesaurus, (Additional file 1). Moreover, grey literature was also searched in google and from reference lists of pertinent articles to retrieve additional studies. Endnote version 7 (Thomson Reuters, London) reference manager software was used to remove duplicate entries and manage the citation process.

Inclusion and exclusion criteria

All original research articles conducted in Ethiopian settings that fulfill the following criteria were included in this meta-analysis. Articles with cohort study design, studies reporting TB incidence among adult HIV positive patients conducted only in Ethiopia, articles with a clear participants’ ART status and incident TB report, and studies published in English were considered in this meta-analysis. However, studies with participants below the age of 15 years were excluded from our analysis due to their differences in TB and HIV natural history from adults.

However, review articles, conference abstracts and proceedings, editorials and case reports, studies without full-text access, and studies that investigated patterns of drug resistance only without incidence were excluded. Likewise, studies that reported prevalence of TB among adult HIV positive patients were also excluded.

Outcome of interest

The primary outcome of interest was the proportion of incident TB among adult HIV infected patients in Ethiopia. Moreover, the results have been stratified by ART status (Pre-ART versus ART), ART follow up time (6 months versus > 6 months) and baseline CD4+ T cell counts (baseline CD4+ T cell counts < 200 versus ≥ 200...
cells/mm³). Secondly, we have also determined the odds ratio of developing incident TB among adult HIV infected patients receiving ART with baseline CD4⁺ T cell counts < 200 versus ≥200 cells/mm³.

**Data extraction and quality assessment**

Two reviewers (DG and AE) independently examined the identified studies for inclusion and extracted relevant data. Disagreement between the two reviewers was resolved by discussion and articles were included after consensus was reached. Moreover, if the discrepancy could not be fixed, a third author (MM) was involved to examine the article and resolve the inconsistency. The following parameters were extracted from each included study: study author and year of publication, study area/region, study design, study period, participants’ ART status and age, laboratory methods employed to diagnose TB whenever reported, sample size, ART follow up time to report incident TB, number of participants with incident TB, number of participants with baseline CD4⁺ T cell count less 200 cells/mm³ and with or without incident TB, number of participants with baseline CD4⁺ T cell count ≥200 cells/mm³ and with or without incident TB.

The quality of included studies was verified by using Joanna Brigg’s Institute (JBI) quality assessment checklist for cohort studies [16] by two independent authors (DG, AE) and a third review author (MM) was also involved whenever necessary. That is, each study data was cleared based on the research design and study population (adult HIV positive patients in Ethiopia on pre-ART or ART), reported data quality (incident TB data, and incident TB report based on baseline CD4⁺ T cell count status). Namely, there were 188 incident TB cases among HIV infected patients on ART based on participants baseline CD4⁺ T cell count < 200 versus 200 cells/mm³ and with or without incident TB.

**Statistical analysis**

Data was extracted using Microsoft Excel, then it was exported into Stata version 11.0 (StataCorp, College Station, TX, USA) for further analysis. The random effects model (DerSimonian-Laird method) [17] was used for pooled incidence analysis and odds ratio (OR) with the respective 95% confidence intervals (95% CIs). Nevertheless, for studies with small or large prevalence, near 0 or 1, the inverse variance method adds disproportionately large weight, variance becomes small, and the calculated CI may lie outside of the 0 to 1 range [18]. Thus, we used Freeman Tukey arcsine methodology to address stabilizing variances [19].

Heterogeneity between included studies was determined using the I² statistics. The I² values of 25, 50 and 75% was considered as low, medium and high heterogeneity, respectively [20]. Although the use of I² in assessing heterogeneity may mislead, studies with relatively large I² may be pooled when the clinical heterogeneity is acceptable [21]. Clinical heterogeneity could be partly patient baseline characteristics but not on the outcome measurement scale, statistical heterogeneity. Egger’s test (a statistical analogue for funnel plot) was used to assess publication bias [22]. The robustness of the pooled estimate and the impact of a single study on aggregate result was figured out by sensitivity analysis. Based on the JBI checklist, all studies involved in this analysis were having a quality score of 50% and above.

**Results**

**Identification and documentation of studies**

The overall literature search yielded a total of 403 potential articles, of which 28 were selected for detailed full text review and 10 studies were found to be appropriate and included in the quantitative analysis (Fig. 1).

**Characteristics of included studies**

All the studies included were cohort studies and were published from 2012 to 2017. Among the 10 studies subjected to the meta-analysis, 2 articles [11, 23] reported incident TB on pre-ART, 6 studies on ART [24–29] and 2 studies [12, 30] in both pre-ART and ART receiving HIV positive patients. On the other hand, 2 articles [11, 23] reported incident TB among pre-ART HIV infected patients within 6 months of follow up, whereas 2 studies [12, 30] didn’t indicate the follow up time clearly. In the meantime, 2 articles [24, 25] and 4 studies [26–29] reported incident TB within 6 and above 6 months of ART follow up respectively. Of the 10 studies, 7 articles [11, 12, 23–26, 29] reported incident TB regardless of the baseline CD4⁺ T cell count while 3 studies [27, 28, 30] stated incident TB data on ART in both baseline CD4⁺ T cell count < 200 and ≥200 cells/mm³.

The age of the participants were ranging from 15 to 64 years old. The studies considered in the meta-analysis have provided incident TB data among a total of 10,074 (1904 on pre-ART and 8170 on ART) HIV infected patients. Of the total 10,074 participants, 1309 (328 on pre-ART and 981 on ART) participants developed incident TB. Moreover, three studies [27, 28, 30] exclusively reported incident TB data on 1290 HIV positive patients on ART based on participants baseline CD4⁺ T cell count status. Namely, there were 188 incident TB cases among HIV infected patients on ART with CD4⁺ T cell count < 200 cells/mm³ and 91 incident TB cases with CD4⁺ T cell count ≥200 cells/mm³ (Table 1).

**Meta-analysis**

**Heterogeneity and publication bias**

The existence of heterogeneity and publication bias was determined within included studies. Consequently, there
was considerable heterogeneity across ten included studies in this meta-analysis ($I^2 = 95.6\%$). The Egger’s test for publication bias was marginally insignificant ($p = 0.07$), indicating no evidence of publication bias within included studies. Besides, funnel plot was also depicted to illustrate the presence/absence of publication bias (Fig. 2).

**Sensitivity analysis**

Sensitivity analysis showed that the effect of individual studies on pooled estimate was insignificant, suggesting the robustness of aggregated estimate. Therefore, the pooled incident TB among HIV infected patients was steady and reliable when examined by neglecting one study at a time (Table 2).

**Pooled incident TB among HIV positive patients**

The overall pooled incident TB among adult HIV positive patients in this meta-analysis from the random effects model was 16.58% (95% CI; 13.25–19.91%). Subgroup analysis based on patients ART status showed that 17.16% (95% CI; 7.95–26.37%) and 16.24% (95% CI; 12.63–19.84%) TB incidence on pre-ART and ART taking patients respectively (Fig. 3).

Moreover, subgroup analysis was done based on ART follow up time (6 months versus > 6 months) and baseline CD4$^+$ T cell counts (< 200 versus ≥ 200 cells/mm$^3$). Accordingly, the pooled TB incidence among adult HIV infected patients on ART within 6 and > 6 months of follow up was 14.15% (95% CI; 7.01–21.28%; $I^2 = 87.3\%$) and 14.59% (95% CI; 10.06–19.13%; $I^2 = 96.4\%$) correspondingly. Likewise, the pooled incidence TB among adult HIV positive patients on ART with baseline CD4$^+$ T cell count < 200 and ≥ 200 cells/mm$^3$ was 28.86% (95% CI; 18.73–38.98%; $I^2 = 88.5\%$) and 13.7% (95% CI; 1.41–25.98%; $I^2 = 95.8\%$) respectively (Table 3).

**Association between CD4$^+$ T cell count and the risk of incident TB**

Among 3 studies [27, 28, 30] reporting incident TB data in HIV positive patients on ART with both strata of baseline CD4$^+$ T cell counts, we have determined incident TB among HIV positive patients with CD4$^+$ T cell count < 200 cells/mm$^3$ compared to HIV infected patients with CD4$^+$ T cell count ≥ 200 cells/mm$^3$. Consequently, the odds ratio for incident TB among HIV positive patients with CD4$^+$ T cell count < 200 cells/mm$^3$ was 2.88 (95% CI; 1.55–5.35%; $I^2 = 70.7\%$: Egger’s test, $p = 0.27$) compared to HIV infected patients with CD4$^+$ T cell count ≥ 200 cells/mm$^3$. In clinical perspectives, it means that HIV positive patients with CD4$^+$ T

![Fig. 1 PRISMA flow chart for the studies screened, reviewed and included](image-url)
| Study author | Study region | Study design | Study period | Age (years) | Specimen | Methods employed | ART status | Sample size | TB incidence follow up time | Incident TB (%) | Participants' with CD4+ T cell counts < 200 cells/mm³ | Events | Total | Events | Total |
|--------------|--------------|--------------|--------------|-------------|----------|-----------------|------------|-------------|----------------------------|---------------|--------------------------------------------------|---------|-------|--------|-------|
| Balcha et al., 2014 [23] | Oromia | PCS | Oct2011-Mar2013 | ≥ 18 | Sputum, Urine | Microscopy, Culture, Xpert and LAM | Pre-ART | 757 | 6 months | 16.91 | – | – | – | – |
| Assebe et al., 2015 [11] | Oromia | RCS | Jan2008-Feb2012 | 15–64 | Sputum | Microscopy and CXR | Pre-ART | 588 | 6 months | 8.33 | – | – | – | – |
| Bekele et al. 2017 [12] | SNNP | RCS | Sep2009-Aug2010 | > 15 | N/S | N/S | Pre-ART | 422 | Not clearly stated | 31.99 | – | – | – | – |
| Ahmed et al. 2015 [27] | Afar | RCS | July2010-May2015 | ≥ 15 | N/S | N/S | ART | 132 | > 6 months | 19.70 | – | – | – | – |
| Dalbo et al. 2016 [30] | SNNP | RCS | Dec 2014-Jan2015 | ≥ 15 | Sputum | Microscopy and culture | Pre-ART | 451 | Not clearly stated | 11.68 | – | – | – | – |
| Abossie et al. 2017 [24] | SNNP | RCS | Sep2010-Aug2011 | 25–34 | Sputum | Microscopy and culture | ART | 359 | 6 months | 25.07 | 29 | 159 |
| Edessa et al. 2014 [25] | Addis Ababa | RCS | Feb2013-May2013 | ≥ 18 | N/S | N/S | ART | 742 | 6 months | 10.78 | – | – | – | – |
| Semu et al. 2017 [26] | Addis Ababa | RCS | Jul2012-Aug2012 | Adult | N/S | N/S | ART | 2524 | > 6 months | 10.97 | – | – | – | – |
| Nigussie et al. 2015 [28] | Addis Ababa | RCS | Aug2014-May2015 | ≥ 15 | Sputum | Microscopy and CXR | ART | 480 | > 6 months | 14.58 | 323 | 5 | 157 |
| Kassa et al. 2012 [29] | Addis Ababa | RCS | 2005–2009 | ≥ 15 | N/S | N/S | ART | 3211 | > 6 months | 8.41 | – | – | – | – |

**Keys:** ART Antiretroviral therapy, CXR Chest x-ray, N/S Not specified, PCS Prospective cohort study, RCS Retrospective cohort study, SNNP Southern nations nationalities and peoples of Ethiopia
cell count < 200 cells/mm$^3$ have 2.88 times more likely to develop incident TB compared with patients who have CD4$^+$ T cell count $\geq$ 200 cells/mm$^3$ (Fig. 4).

**Discussion**

HIV fueled incident TB is resurging in developing countries, especially in sub-Saharan Africa where HIV prevalence is rampant. CD4$^+$ T lymphocytes has a crucial role in both HIV and TB infection, and a decreased CD4$^+$ T cell count has been implicated as a strong predictor of TB risk in HIV infected patients [31]. Thus, this meta-analysis was aimed to determine pooled incident TB and its association with baseline CD4$^+$ T cell count among adult HIV infected patients in Ethiopia.

Based on this meta-analysis, the overall pooled incident TB was 16.58% (95% CI; 13.25–19.91%). This study demonstrated higher incident TB among adult HIV positive patients compared to the Ethiopian national population based TB prevalence survey, 261 per 100,000 person incident TB [32] among the general population of Ethiopia. This could be because of the difference in the study population. Our review summarized the finding in HIV positive patients who are at higher risk of developing TB [2] unlike the national population based survey that predominantly included HIV uninfected population. Partly, it may be due to national TB prevalence survey reports are rough estimates, and may underestimate the actual picture of TB incidence in the country.

As indicated in subgroup analysis, TB incidence in Pre-ART and ART taking patients was 17.16% (95% CI; 7.95–26.37%) and 16.24% (95% CI; 12.63–19.84%) respectively. However, previous studies revealed 21.63 and 14.27% in India [33], 7.9 and 4.4% in Tanzania [34] and 10.64 and 3.41% in South Africa [35] incident TB among pre-ART and ART receiving patients respectively. Therefore, except pre-ART incident TB reported in India, this study revealed higher incident TB report relative to other high TB burden settings, including South Africa [5, 36, 37]. This might be because of the clinical picture of the diseases may vary in different countries due to socio-economic or socio-cultural variations. Moreover, this study also demonstrated higher incident TB among HIV positive patients receiving ART in Ethiopia compared to previous studies established.

**Table 2** Sensitivity analysis of pooled incident TB among adult HIV positive patients on pre-ART and ART in Ethiopia

| Study omitted                  | Estimate | 95% CI          |
|-------------------------------|----------|-----------------|
| Balcha et al. 2014 [23]       | 16.554401| 13.042163, 20.066639 |
| Assebe et al. 2015 [11]       | 17.416502| 13.771809, 21.061195 |
| Bekele et al. 2017a [12]      | 15.120082| 12.209677, 18.030487 |
| Dalbo et al. 2016a [30]       | 16.986979| 13.485174, 20.488785 |
| Ahmed et al. 2015 [27]        | 15.636593| 12.475107, 18.798079 |
| Abossie et al. 2017 [24]      | 16.450867| 12.984303, 19.917431 |
| Edessa et al. 2014 [25]       | 17.186029| 13.488454, 20.883606 |
| Semu et al. 2017 [26]         | 17.243677| 13.042066, 21.445288 |
| Bekele et al. 2017a [12]      | 16.354092| 12.918216, 19.789968 |
| Dalbo et al. 2016a [30]       | 15.805243| 12.532356, 19.078131 |
| Nigussie et al. 2015 [28]     | 16.78417 | 13.223361, 20.34498  |
| Kassa et al. 2012 [29]        | 17.459826| 13.627331, 21.29232  |
| Combined                      | 16.580467| 13.251581, 19.909352 |

*the author reported incident TB in both pre-ART and ART patients in a single study*
elsewhere. This sustained susceptibility to TB regardless of ART status in Ethiopia may be due to ongoing community level TB transmission, or possibly nosocomial TB transmission. As it is shown in this study, incident TB in pre-ART, 17.16% (95% CI; 7.95–26.37%), and ART, 16.24% (95% CI; 12.63–19.84%), was almost the same. This could be partially explained by the immune reconstitution inflammatory syndrome (IRIS), that can increase incident TB within the first one to 2 months following ART initiation among severe immunodeficiency patients [38], thereby mystifying the efficacy of ART to avert TB. On the other hand, it might be because of delayed HIV diagnosis and ART initiation, or due to poor ART adherence.

Further, the aggregate TB incidence among adult HIV positive patients within 6 and > 6 months of ART follow up was also determined as 14.15% (95% CI; 7.01–21.28%) and 14.59% (95% CI; 10.06–19.13%) respectively. This study suggests slightly increasing in TB incidence with increasing ART follow up time. However, previous studies indicated that incident TB was higher within the first 6 months of ART initiation than those who have been on ART for more than 6 months and longer [39]. This might be because of poor ART adherence and less concomitant use of TB preventive therapy in this study participants than previously established studies.

In addition, the pooled incident TB among adult HIV positive patients on ART with baseline CD4⁺ T cell counts < and ≥ 200 cells/mm³ was also measured in this meta-analysis. Thus, this study revealed 28.86% (95% CI; 18.73–38.98%) and 13.7% (95% CI; 1.41–25.98%) incident TB among adult HIV infected patients on ART with baseline CD4⁺ T cell counts < and ≥ 200 cells/mm³ respectively. Nevertheless, earlier studies demonstrated...
1.90 and 1.52% in South Africa [35], 4.98 and 0.63% in Uganda [40], and 0.6 and 0.0% in Brazil [41] incident TB among HIV positive patients on ART with baseline CD4+ T cell counts < and > 200 cells/mm³ respectively. Thus, this study revealed higher incident TB compared to previous studies reporting incidence TB among HIV infected patients receiving ART with both baseline CD4+ T cell counts < 200 and/or > 200 cells/mm³. This might be due to higher TB transmission rate at the community level in Ethiopia compared to other study settings. Moreover, as ruling out TB in HIV positive patients on ART is challenging due to poor sensitivity of the sputum smear and also WHO symptom screening [42], the actual burden of incidence TB might be even higher than the stated one in our study. High incident TB was demonstrated in adult HIV infected patients on ART with baseline CD4+ T cell counts < 200 cells/mm³ relative to patients with CD4+ T cell counts > 200 cells/mm³ in this study. Consistent to our finding, previous meta-analysis study in South Africa indicated that the proportion of incident TB cases were increased as the baseline CD4+ T cell count decreased, especially when it was below 200 cells/mm³ [43]. There are enormous evidences that noted that baseline CD4+ T cell counts < 200 cells/mm³ is associated with increased incidence TB [8, 40, 41, 44]. This might happen for two reasons. First, this could be partly due to impaired restoration of TB specific immunity when patients are severely immunocompromised (baseline CD4+ T cell counts < 200 cells/mm³) at ART initiation [36]. Second, it might be because of primary infection or re-infection with the bacilli or re-activation of the existing latent TB as a result of severe immunosuppression.

Besides, the quantitative correspondence between baseline CD4+ T cell count and TB risk was measured in this meta-analysis. Consequently, adult HIV positive patients on ART with baseline CD4+ T cell count < 200 cells/mm³ were 2.88 times more likely to develop incident TB compared to patients with CD4+ T cell count > 200 cells/mm³. A comparable result was also reported in previous study from rural South Africa, three fold [36] and Tanzania, 5 to 20% higher risk of TB among HIV infected patients with CD4+ T cell count < 200 cells/mm³.
mm$^3$ [34]. There are a large number of evidences that showed baseline CD4$^+$ T cell count < 200 cells/mm$^3$ as a risk factor for development of incident TB in HIV positive patients [8, 36, 40, 41, 44]. This could be because of HIV induced depletion of CD4$^+$ T lymphocytes leads to impaired cellular immunity and increased vulnerability to opportunistic infections like TB or reactivation of the latent TB [7] even in the presence of ART. Besides CD4$^+$ T lymphocytes, HIV has also effects on antigen presenting cells like macrophages, and affects antigen processing and presentation as well cytokine production, which might also prevent the host from having an initial or latent TB infection [45]. Therefore, the result of this study indicates Ethiopian Federal Ministry of Health and HIV program managers in the country to increase the coverage of TB preventive therapy, adherence to ART and TB preventive therapy for HIV positive patients as per the recently recommended treatment guideline [46].

Limitations of the study
Although the binomial distribution of meta-analysis was preferred to model within-study variability of the proportion [47], we used the usual DerSimonian and Laird random effects model to meta-analyze the proportion of incident TB. Repeated CD4$^+$ T cell count measurement and the corresponding incident TB was not determined in this meta-analysis due to lack of report in included studies. CD4$^+$ T cell counts and the risk of incident TB among pre-ART patients was not evaluated due to lack of CD4$^+$ T cell count in the original studies. Besides, incident TB and duration of ART is not characterized in this study due to lack of clear evidence in the original studies. Although IRIS associated incident TB might be one of the factors for higher TB incidence among ART receiving patients, IRIS related incident TB was not documented in this study due to lack of information in the included studies. To report incidence rate, we were unable to find the details of each individual data, how many days/months/years spent each study participant in the observation. Therefore, in the absence of each participant’s detailed data in the observation, we reported incidence proportion rather than incidence rate in this study.

Conclusions
This meta-analysis demonstrated that incident TB was considerably high in Ethiopia, especially in HIV positive patients with baseline CD4$^+$ T cell count < 200 cells/mm$^3$. Therefore, early HIV screening and ART initiation, as well as strict compliance with ART and increasing the coverage of TB preventive therapy to the more risky groups are important to overcome the problem in Ethiopia.

Supplementary information

Abbreviations
ART: Antiretroviral therapy; CD4: Cluster of differentiation 4; CI: Confidence interval; FMH: Federal Ministry of Health; HIV: Human immunodeficiency virus; OR: Odds ratio; PLWH: People living with HIV; TB: Tuberculosis; WHO: World health organization.

Acknowledgements
Not applicable.

Authors’ contributions
DG: Conceived and designed the study, reviewed literatures, extracted and analyzed data, interpreted results and drafted the manuscript. MM, AE, BW, AF, MN, HWB and HG: involved in study selection, data collection, extraction, quality assessment and reviewing the manuscript. TT, TD, BT and US: Supervision, analysis and interpretation, reviewed the manuscript thoroughly for its scientific content. All authors have read and approved the manuscript.

Funding
None.

Availability of data and materials
All data pertaining to this study are contained and presented in this manuscript.

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

Author details
1Department of Immunology and Molecular Biology, School of Biomedical and Laboratory Sciences, University of Gondar, P.o.Box: 196, Gondar, Ethiopia. 2Department of Hematology and Immunohematology, School of Biomedical and Laboratory Sciences, University of Gondar, Gondar, Ethiopia. 3Department of Pediatrics and Child Health Nursing, School of Health Sciences, College of Medicine and Health Sciences, Bahir Dar University, Bahir Dar, Ethiopia. 4Department of Clinical Chemistry, School of Biomedical and Laboratory Sciences, University of Gondar, Gondar, Ethiopia. 5Department of Reproductive Health, School of Public Health, Debre Markos University, Debre Markos, Ethiopia. 6Ethiopian Public Health Institute, HIV/AIDS and TB Research Directorate, Addis Ababa, Ethiopia. 7Institute of Clinical Immunology, Medical Faculty, University of Leipzig, Leipzig, Germany.

Received: 12 November 2019 Accepted: 16 April 2020
Published online: 07 May 2020

References
1. Sulis G, Roggi A, Matteelli A, Ravignone MC. Tuberculosis: epidemiology and control. Mediter J Hematol Infect Dis. 2014;6(1):e2014070. https://doi.org/10.4086/MJHID.2014.070.
2. Kwan CK, Ernst JD. HIV and tuberculosis: a deadly human syndemic. Clin Microbiol Rev. 2011;24(2):351–76.
3. USAID. USAID report on the twin epidemics: HIV AND TB co-infection. 2014. https://www.usaid.gov/news-information/fact-sheets/twin-epidemics-hiv-and-tb-co-infection (accessed 31/10/2018).
4. WHO. Global tuberculosis report 2016. Geneva: WHO; 2016.
5. WHO. Global tuberculosis report 2017. Geneva: WHO; 2017.
