Incidence and Predictors of tuberculosis among HIV patients after initiation of ART treatment in Ethiopia: A systematic review and Meta-analysis

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Abstract

Background: Tuberculosis is the oldest infectious disease and it is still the leading cause of morbidity and mortality worldwide. Even though, several primary studies have been conducted on incidence of tuberculosis among HIV infected individuals in Ethiopia, national level TB incidence is unknown. Therefore, this systematic review and meta-analysis study is aimed to study TB incidence rate and its predictors among HIV infected individuals in Ethiopia.

Methods: We conducted extensive search of literature as indicated in the guideline of reporting systematic review and meta-analysis (PRISMA). The databases used were PubMed, Google Scholar, HINARI and Scopus literature. Searching terms used were “incidence”, “predictors”, “Tuberculosis”, “HIV infected patients”, and “Ethiopia”. We used Joanna Briggs Institute (JBI) Meta-Analysis of Statistics Assessment and Review Instrument for critical appraisal of studies. The meta-analysis and Meta regressions were conducted using STATA 14 software. The pooled meta-analysis and Meta regression were computed to present the pooled incidence rate and predictors of tuberculosis among HIV infected patients after initiation of ART therapy with a 95% confidence interval

Results: Among a total of 189 studies, 11 studies were included in this analysis. The estimated pooled incidence rate of TB per 100-person year observation (PYO) among HIV infected patients after initiation of ART therapy was 4.8(95% CI: 3.69–5.83). In subgroup analysis, the estimated pooled incidence of tuberculosis showed a slightly difference between Adults and children after initiation of ART treatment, which was 4.3 (95% CI: 2.96, 5.71) and 5.0 (95% CI: 3.51, 6.50), respectively. Significant predictor of pooled estimate of meta-analysis showed that being anemic patients (2.30, 95% CI: 1.75, 3.02); on WHO clinical stage III & IV (2.26, 95% CI (1.70, 3.02); and not on CPT (2.16, 95% CI: 1.23, 3.72) and a Meta regression revealed that CD4 <200 cells/mm³ (2.12, 95% CI: 1.17, 3.86) was positively significant predictors among Adults.

Conclusions: The current systematic review and meta-analysis showed that the pooled incidence of TB among HIV patients was found to lower than WHO 2018 national estimate. Being anemic, WHO stage III& IV, not on CPT, CD4 <200cells/μl and being male were significant predictors of Tuberculosis. Therefore, the existing strategies to decrease TB should be strengthening.

1. Background

Tuberculosis (TB) is the oldest infectious disease and it is still the leading cause of morbidity and mortality worldwide (1). HIV infected people are at the highest risk for developing TB in which 22 times more likely to fall ill with TB than those without HIV. HIV infection is the main risk factor for active tuberculosis disease (2) and 10% higher rates of progression from latent to active TB that leads to more severe disseminated disease presentation and increased mortality. An estimated 862, 000 people with HIV fell ill TB in 2018 and 251,000 deaths (3).

Despite the widespread use of ART and Isoniazid preventive therapy (IPT), intensified case finding and infection control (WHO) 3 I's strategy among HIV patients in Ethiopia, Tuberculosis is the common cause of morbidity and mortality. According to the WHO global TB report, 2018, Ethiopia had an estimated 12000 incident TB per 100, 000 population among HIV infected individuals(1).

Although HIV itself is the main risk factor for active TB disease, there are possible additional aggravating factors. Based on previous studies, low CD4 count, advanced WHO clinical stage, ambulatory or bedridden, being anemic, under nutrition, OIs, DM, high viral load and increased family size in adults and the above plus delayed motor development, inappropriate vaccination for BCG were the predictors of incident TB cases among individuals on ART(4–9), while, both Cotrimoxazole preventive Therapy (CPT) and IPT reduced TB incidence(7, 10–15).

Although several primary studies have been conducted on the incidence of TB among HIV infected individuals in Ethiopia, there are no aggregated national-level studies after ART initiation. Therefore, this systematic review and meta-analysis aimed to estimate the pooled incidence and predictors of tuberculosis among HIV infected individuals after ART initiation in Ethiopia so as important to design interventions and prevention mechanisms for further improvement of quality of life among PLHIV.

2. Methods

2.1 Searching strategy

We conducted an extensive search of literature as indicated in the guideline of reporting systematic review and meta-analysis (PRISMA) (16). We used search engines like PubMed, HINARI, Scopus, Google scholar, and free google databases in parallel using search strings adapted to the requirements of each database. We conducted search for PubMed/Medline search engine by using the entry term as: incidence [titles/abstract] AND predictors [titles/abstract] OR determinants [titles/abstract] OR "risk factors" [titles/abstract] and "mycobacterium" next "tuberculosis" next "infection" [titles/abstract] OR tuberculosis [titles/abstract] OR TB [titles/abstract] OR PTB [titles/abstract] OR "pulmonary tuberculosis positive"[titles/abstract] OR "bacteriologically confirmed pulmonary tuberculosis"[titles/abstract] AND "OR "acquired immune deficiency syndrome virus" [titles/abstract] OR "acquired immunodeficiency syndrome virus" [titles/abstract]OR "human immunodeficiency virus" [titles/abstract]OR "human immunodeficiency viruses" [titles/abstract] AND Ethiopia[all fields]. We used specific-subject headings for the other databases (HINARI, Cochrane library, Google scholar and Scopus) Besides, to identify other relevant articles, we manually searched the reference lists of eligible articles.

2.2 Eligibility criteria

Three independent reviewers (MM, NM, and GS) screened all titles and abstracts of the articles prior full-text review. Full texts were then screened by the same reviewers according to the pre-specified inclusion and exclusion criteria. The majority (two-thirds) of the reviewers' agreement was been taken for screened paper and eligibility for systematic review and Meta-analysis.

Inclusion criteria

We included only people who took ART as study population, reporting as TB incidence rate and predictors among HIV patients, articles published in English language, studies done in Ethiopia and articles published between 1st January 2010 and 31st October 2019

Exclusion Criteria

We excluded reviewed papers for the same objectives, those papers exclusively reporting multi-drug or extensively drug-resistant (MDR/XDR), TB as outcomes and studies other than in humans

2.3 Extraction of data from eligible papers

Data were extracted for each included study as name of first author, date of publication, study setting, target population, study region, study area, study design, sample size, diseased (new TB case), person year observation, incidence rate per 100-person year observation, predictors (risk estimate (HR) and their 95% confidence interval) by using standardized data extraction form (Table 1). Data extraction from selected articles was done independently by three reviews. Disagreements were resolved by 2/3 of the reviewers' consensus.

2.4 Assessment of study quality

Study quality was assessed using a standardized tool adapted from the JBI tool for cohort studies. The tool was considering the following study characteristics: sampling representative and size, exclusion of TB at cohort entry, outcomes ascertainment during follow up, duration of follow up. Studies with fulfilling the required criteria as score 1 and studies with scores 0 were considered to be of poor quality for specified criteria. No studies were excluded from the reviews on the basis of their quality scores(17).

2.5 Data management and processing

The outputs from the searching engines were imported into Endnote Version 7.1 software and duplicate removed. Data were recorded on the abstraction forms and entered into an Excel 2013 sheet (Microsoft Corporation, Washington, USA) and then exported to Stata version 14 for analysis.

2.6 Data synthesis and analysis

Both systematic review and Meta-analysis were done by using STATA 14 software. In the qualitative part of the review, all eligible articles reporting as TB incidence rate among HIV positive individuals were summarized according to the target age group, study regions and by study setting. Where studies only reported the number of TB cases and person-years of follow up for the different strata in the cohort, the incidence rates, and confidence intervals were computed in Stata 14.

Meta-analyses (quantitative reviews) were conducted to determine the overall pooled incidence rate of TB among HIV infected individuals across different categories or strata. Heterogeneity was evaluated using the Cochran statistic and the I^2 statistics(18). The magnitude of statistical heterogeneity between studies was assessed using I^2 statistics and values of 25, 50 and 75% were considered to represent low, medium and high, respectively. The random-effects model was used for the data identified as heterogeneous during analysis. Meta-analyses and Meta-regression were performed using Stata software version 14.1. For the incidence of tuberculosis with data from ≥ 15 studies, we performed meta-regression analyses to calculate the Hazard ratio (HR). In addition, we carried out a leave-one-out sensitivity analysis to evaluate the key studies that exert a major impact on between-study heterogeneity. The small study effect was assessed by a funnel plot and Egger's regression tests (18–20).

3. Results

3.1 Studies identification and retrieval

The combined literature search strategy retrieved a total of 189 potential studies, of which 32 were screened for full-text review and 11 studies were eligible to be included in the systematic and meta-analysis (Fig. 1)

3.2 Systematic review

Characteristics of included studies

Eleven articles found in different parts of Ethiopia published from 2010 to 2019 from international peer-reviewed and national journals included to estimate incidence and predictors of tuberculosis among HIV infected patients. A total sample size of 8,875 participants were involved in the final analysis. Among this, 1, 036 new tuberculosis cases were found among HIV patients from 2010 to 2019 published years. The sample size of included studies ranged from 271 (13) to 4210 (21) subjects. All of the reviewed studies were retrospective follow-up studies with a follow-up duration for assessing the outcome ranging from 42 months to 84 months (11-15, 21-26)

Findings from a review of studies showed that the highest and lowest incidence rate of tuberculosis among HIV patients was in Afar region (12) and in the Amhara region (23) which was 8.64 and 2.22 per 100 person-year observation

respectively (12, 23) (see Table 1). The majority of the studies reported that positively significant predictors for the incidence of tuberculosis were ambulatory and Bedridden vs. working, being anemic individuals, WHO clinical staging III and IV, being males, CD4 less than 200 cells/mm³, past history of tuberculosis, not on CPT and IPT.

Table 1: Characteristics of included studies with the outcome of the studies (n = 11)

The author with the publication year	Study region	Study design	Study population	Follow-up time(months)	Sample size	Total PY(O)	IR per 100 PYO	Study quality
Ayalaw et al,2015	Amhara	Retrospective follow-up study	Children	72	271	1100.5	4.73	Good
Endalamaw et al,2018	Amhara	Retrospective follow-up study	Children	60	352	1294.7	2.63	Good
Beshir MT et al,2019	Oromia	Retrospective follow-up study	Children	60	428	1109.6	6.04	Good
Alemu YM. Et al,2016	Amhara	Retrospective follow-up study	Children	60	645	1854.0	4.26	Good
Jerene et al,2017	AA&SNNP	Retrospective follow-up study	Adults	84	660	2843.5	2.25	Good
Ahmed A, et al,2017	Afar	Retrospective follow-up study	Adults	84	451	1377.4	8.64	Good
Temesgen,2017	Amhara	Retrospective follow-up study	Adults	60	492	1285.5	6.46	Good
Tamiso,2016	SNNP	Retrospective follow-up study	Adults	72	496	1977.6	5.36	Good
Assefa et al,2014	Amhara	Retrospective follow-up study	Adults	42	400	1181.8	2.20	Good
Alene et al,2013	Amhara	Retrospective follow-up study	Adults	60	470	1724.1	7.89	Good
Kassa et al, 2012	AA	Retrospective follow-up study	Adults	60	4210	8792.3	3.07	Good

3.3 Meta-analysis

Given a considerable heterogeneity of the outcome across eleven included studies, this meta-analysis aims to determine the incidence of tuberculosis and identify different predictor factors of active TB among HIV positive patients taking ART in Ethiopia.

3.3.1 Pooled incidence of active TB among HIV positive patients

All eleven articles provided information on the incidence of tuberculosis among PLHIV in Ethiopia (11-15, 21-26). Based on the results of random-effects method, the overall pooled incidence rate of TB per 100-person year observation among HIV infected patients was 4.8 (95% CI: 3.69–5.83) and the heterogeneity was considerable ($I^2 = 94.1\%$, $Q=170$, $DF=10$, $variance= 2.97$, $z=8.7$, $p < 0.0001$). Fig (2).

3.3.2 Subgroup analyses of the incidence rate of tuberculosis in people living with HIV (PLWHIV)

We conducted subgroup analysis based on the pre-defined category of study setting, year of publication, study population, length of Follow-up time and sample size classification used to assess the incidence of tuberculosis (Table 2).

In our subgroup analysis of the incidence of tuberculosis among PLWHIV in Ethiopia with studies in Hospital-based was slightly lesser than facility-based studies (4.7; 95% CI: 3.46, 5.97 Vs 5.0; 95% CI: 1.92, 8.01).

Furthermore, we conducted a subgroup analysis based on the year of publication date used to assess the incidence of tuberculosis. The pooled incidence rate estimates of tuberculosis for the studies conducted within 2010 – 2014 was significantly lesser than studies in 2015-2019 (4.3; 95 % CI: 1.95, 6.66) Vs 5.0; 95% CI: 3.54, 6.40) (Table 2).

We also performed a subgroup analysis based on the total sample size which the studies were conducted. The pooled incidence of tuberculosis among people living with HIV in Ethiopia was significantly higher for sample size less than 500 (5.4; 95% CI: 3.80, 7.08) compared to those articles with a sample size of greater than or equal to 500 (3.1; 95% CI: 2.23, 4.00).

Finally, we conducted subgroup analysis based on the follow-up period for sampled population. so that the pooled incidence of tuberculosis among HIV infected ART user individuals was significantly higher for the follow-up period less than sixty months (5.1; 95%CI: 3.64,6.46) compared to longer period of follow-up time (4.1; 95% CI: 1.87,6.27) (Table 2).

In the analyses stratifying summary estimates of TB incidence rates in the above categories, heterogeneity remained high for each stratum. This implied that these variables did not explain most of the heterogeneity observed in the TB incidence rate (Table 2.)

Table 2: Incidence of tuberculosis in people with HIV in Ethiopia: Subgroup meta-analysis and heterogeneity analysis

Subgroup types	Observation(N)	IR per 100 PY(O)	95%CI	I ² (%)	Q-statistic	Tau ²	Df	P value
Year of publication								
2010_2014	3	4.3	[1.95,6.66]	96.3	53.9	4.11	2	P<0.0001
2015_2019	8	5.0	[3.54, 6.40]	93.6	109.5	3.88	7	P<0.0001
Study Setting								
Hospital based	8	4.7	[3.46,5.97]	93.3	104.9	2.95	7	P<0.0001
Facility based	3	5.0	[1.92,8.01]	96.8	63.4	6.95	2	P<0.0001
Study population								
Children	4	4.3	[2.96,5.71]	83.7	18.5	1.61	3	P<0.0001
Adults	7	5.0	[3.51,6.50]	95.9	148.1	3.77	6	P<0.0001
Sample size range								
Less than 500	8	5.4	[3.80,7.08]	93.8	112.6	5.20	7	P<0.0001
Greater than/equal 500	3	3.1	[2.23,4.00]	85.8	14.1	0.51	2	P=0.001
Follow-up period(months)								
Less than or equal to 60	8	5.1	[3.64,6.46]	94.7	132.8	5.80	7	P<0.0001
Greater than 60	3	4.1	[1.87,6.27]	94.1	34.0	3.53	2	P<0.0001

We also performed a subgroup analysis based on the Study population used to determine the incidence rate of tuberculosis among HIV patients. Four studies were in children and the rest were about adult people. The pooled incidence rate tuberculosis in people living with HIV was 4.3 (95% CI: 2.96, 5.71) and 5.0 (95% CI: 3.51, 6.50) for the studies conducted children and adults respectively (see Fig 3)

3.3.3 Sensitivity analysis

We performed a leave-one-out sensitivity analysis for the sake of further investigating the potential sources of heterogeneity in the analysis of the incidence rate of tuberculosis in PLWHIV. Our sensitivity analysis showed that our findings were not influenced by a single study that all the point estimates of the leave-one-out are within the confidence interval of the combined estimate and it is stable. Our pooled estimated incidence varied between 4.4 (3.39-5.38) and 5.0 (3.85–6.23) after the deletion of a single study (see Table 3 and fig 4).

Table 3: sensitivity analysis for the incidence of tuberculosis among HIV infected patients in Ethiopia.

Study omitted	Estimate [95% CI]
Ayalaw et al (2015)	4.8 (3.63, 5.90)

Endalamaw et al (1)	5.0 (3.82, 6.16)
Beshir MT et al (2019)	4.6 (3.53, 3.74)
Alemu YM. Et al (2016)	4.8 (3.65, 5.99)
Jerene et al (2017)	5.0 (3.85, 6.23)
Ahmed A, et al (2017)	4.4 (3.39, 5.38)
Temesgen et al (2017)	4.6 (3.51, 5.68)
Dalbo M. Tamiso A (2016)	4.7 (3.57, 5.82)
Assefa et al (2014)	5.0 (3.87, 6.19)
Alene et al (2013)	4.4 (3.43, 5.43)
<u>A. Kassa et al (2012)</u>	<u>5.0 (3.63, 6.32)</u>
Combined	4.8 (3.69, 5.83)

3.3.4 Publication bias

The funnel plot and Egger's regression tests showed that there is no evidence of substantial publication bias for the incidence of tuberculosis among HIV infected patients in Ethiopia (see additional files 1 and 2).

3.3.5 Pooled estimated effects of predictors on the incidence of Tuberculosis among HIV patients

Meta-analysis was conducted to identify pooled estimates of predictors for the incidence of tuberculosis among HIV infected individuals after the initiation of ART in Ethiopia. Among pooled estimates of predictors Bedridden functional status, anemia status, WHO clinical staging, cotrimoxazole preventive therapy, Isoniazid, preventing therapy, CD4 cell count and Gender were found to be significant predictors for the incidence of tuberculosis whereas Ambulatory Functional status, previous history of tuberculosis, past opportunistic infections and family size were not statistically significant pooled predictors estimates for the incidence of tuberculosis among HIV infected individuals in Ethiopia.

The hazard of developing tuberculosis among HIV infected individuals for the pooled estimates of four observations for anemia was 2.3 times more likely as compared to those who had no anemia (HR:2.30; 95%CI:1.75,3.02; I^2 (p-value) =31.2%(0.18); Publication bias: β (p-value) =0.82(0.60)).

Incidence of tuberculosis among HIV infected individuals was higher for those on WHO clinical staging III and IV than I and II by meta-analysis of 10 studies (HR: 2.26; 95%CI: 1.70, 3.02; I^2 (test) = 47.2 % (p=0.048); publication bias: β (p-value) =-0.13(0.90)).

The Hazard of developing tuberculosis among HIV infected individuals for those not using CPT was 2.16 times more likely than CPT users for five articles (HR: 2.16; 95%CI:1.23,3.72; I^2 (test)= 55.3%(p= 0.062); publication bias: β (p-value) = -1.37 (0.54)).

The hazard of developing TB among male HIV infected individuals was 37% higher among combined of five articles by meta-analysis compared to those female patients (HR: 1.37; 95%CI:1.16,1.63; $I^2(\text{test}) = 0(P=0.59)$; publication bias: $\beta(\text{p-value}) = -2.88 (0.01)$).

Since the heterogeneity of the variables not using IPT and CD4 count was high, further analysis by Meta-regression required to manage it (see table 5).

Table 5: a meta-analysis of predictors of incidence of tuberculosis among HIV positive patients in Ethiopia (2010-2019)

Variables	Observation	HR	95%CI	p-value of Q	I ² (%)	Tau ²	Q-statistic	P value of estimate
Functional status								
Working(ref)	4	1						
Ambulatory		1.46	[0.84,2.51]	p=0.001	78.8	0.29	18.83	P=0.18
Bedridden		2.01	[1.21,3.35]	p= 0.137	42.7%	0.13	6.98	p = 0.007
Anemia status								
Not anemic(ref)	8	1						P<0.001
Anemic		2.30	[1.75,3.02]	P=0.179	31.2	0.05	10.17	
WHO clinical staging								
Stage I/II(ref)	10	1						P<0.001
Stage III/IV		2.26	[1.70,3.02]	p= 0.048	47.2	0.09	17.05	
Cotrimoxazole preventive therapy								
Yes(ref)	5	1						p = 0.007
No		2.16	[1.23,3.72]	p= 0.062	55.3	0.20	8.95	
Isoniazid preventing therapy								
Yes(ref)	7	1						P=0.001
No		3.67	[1.73,7.76]	P<0.001	79.1	0.74	28.7	
CD4 cell count								
Greater than 200	6	1						P=0.002
Less than or equal to 200		2.12	[1.31,3.43]	P<0.001	90.8	0.32	54.38	
Previous history of Tuberculosis								
No	3	1						
Yes		1.49	[0.77,2.89]	p= 0.004	73.5	0.39	15.11	P=0.24
Gender								
Female	5	1						
Male		1.37	[1.16,1.63]	p =0.588	0	0	2.82	P<0.001
Family size								
Small family size(<5)		1						
Large family size(≥5)	3	1.18	[0.89,1.56]	p = 0.29	19.0	0.01	2.47	P= 0.26

Meta-regression for High heterogeneity variables.

Isoniazid preventive therapy was a statistically significant predictor for the incidence of tuberculosis among HIV infected individuals for seven articles. The risk of developing tuberculosis among HIV infected individuals for those not using IPT was 3.47 times more likely than IPT users ((HR: 3.67; 95%CI:1.73,7.76; I^2 (test)= 79.1%($p<0.001$); publication bias: β (p -value) =3.47(0.14)). Meta-regression revealed that not using IPT in adults' study group was higher than children for the incidence of tuberculosis (HR: 2.12; 95% CI: 1.17, 3.86).

CD4 count at baseline of ART initiation was a significant pooled factor for developing tuberculosis among six articles. The risk of tuberculosis incidence among HIV infected individuals was 2.12 times more likely for those who had less than 200 cells/ mm³ at baseline than greater CD4 cell count (HR: 2.12; 95%CI:1.31,3.43; I^2 (test)= 90.8%($P<0.001$); publication bias: β (p -value) = -3.16 (0.57)).

Table 6: Meta-regression of selected predictors to the incidence of tuberculosis among HIV positive patients in Ethiopia (2010-2019)

Study level variables	Low CD4 count				Not using IPT			
	HR with 95% CI	I^2	Tau ²	Adj.R ²	HR with 95% CI	I^2	Tau ²	Adj.R ²
Study population								
Children	Ref.							
Adults	2.12[1.17,3.86]	90.6%	0.28	0	2.94[0.50,17.02]	71.4%	0.52	25.97%
Study setting								
Health facility based	Ref.							
Hospital based	0.96[0.21,4.44]	92.6%	0.36	26.5%	0.31[0.06,1.63]	69.2%	0.44	37.93%
Follow-up time								
Less/equal to 5 years	Ref.							
Greater than 5 years	2.18[0.73,6.50]	78.4%	0.15	46.05%	0.53[0.06,5.08]	68.4%	0.68	3.61%

4. Discussion

Studies with tuberculosis incidence conducted among HIV patients in different regions of Ethiopia were included and carried out to determine the pooled incidence of tuberculosis among HIV infected patients after ART initiation using eleven studies, which were published in scientific and reputable journals between 2010 and 2019.

Findings from a systematic review of included studies showed that the highest and lowest incidence rate of tuberculosis among HIV patients was observed in studies conducted in the Afar region and in the Amhara region which was 8.64 and 2.2 per 100 PYO respectively (12).

The pooled TB incidence among HIV infected patients of this study revealed that 4.76 (95% CI; 3.69–5.83) per 100 PYO which was in line with the primary studies done in India in 2019, and Tanzania in 2015 which were 4.39 cases, and 4.4 cases per 100 PYO, respectively (27, 28). The current finding of pooled incidence was higher than studies conducted in higher-income countries in 2012, in Asia in 2019, in Brazil, Nigeria in 2017 and South Africa 2005 which were 0.3,

0.99, 1.90 and 0.57 and 2.44 per 100 person-years, respectively (29-33). This difference might be because progressive development of latent TB to active TB disease due to the high incidence of HIV compared with higher-income countries (34) and this study also incorporated both children and adults. The other might be a better case-finding strategy in Ethiopia. This study was lower than prospective community-based study done in South Africa in 2012 that was 7.4 per 100 PYO (5). This difference might be all included primary studies in this paper were retrospective cohort studies and health facility-based studies.

Subgroup analysis by study population of this study showed that the pooled TB incidence among adults and children was slightly different which were 5.01 (95% CI: 3.51, 6.50) and 4.34 (95% CI 2.96, 5.71) respectively. This finding was consistent with studies done in India in 2019, and Tanzania in 2015 which were 4.39 cases, and 4.4 cases per 100 PYO, respectively (27, 28). This might be the same socioeconomic status between these countries.

The current meta-analysis of the predictors showed that being anemic patients were 2.30 higher risk for incidence of tuberculosis among HIV infected individuals than non-anemic (HR 2.30, 95% CI: 1.75, 3.02). This might be due to the reason that anemia leads to the development of infections including tuberculosis by impairing the function of hemoglobin.

Our findings also showed that patients on advanced WHO clinical stages (III & IV) were 2.26 times greater risk of developing TB (HR:2.26, 95% CI (1.70, 3.02). This was supported by several studies (6, 28,35). This is due to the fact that being stage III and IV will have low CD4 cell count and ultimately unable to defend infections including tuberculosis.

This finding also revealed that patients with severe immunosuppression (CD4% <200 cell/mm³) were 2.12 times higher risk of developing TB than those with higher CD4 in adults. This was consistent with various studies (28, 29, 32, 35, 36) in which severe immune suppression fastened the progression of latent TB to active disease (2). This is because HIV kills TB protective immune cells among HIV patients. A prospective cohort study done in South Africa showed that TB incidence was nearly 7 times higher risk observed with person-time at CD4 cell counts, 100 cells/mL compared with person-time at CD4 cell counts 700 cells/mL(5).

This meta-analysis study revealed that HIV patients without taking IPT were 3.67 times more risk of developing new active TB than those taking IPT despite lifelong HAART (HR: 3.67, 95% CI: 1.73, 7.76). Our study was consistent with the study done in Brazil in 2007(30) which revealed that TB incidence with no IPT was higher. It was also supported by a meta-analysis study done in Ethiopia in which using IPT reduced TB incidence by 74% (37) and another study done in Ethiopia in 2014 (38). Several studies also showed that TB incidence among those patients on IPT prophylaxis was reduced compared with none-IPT groups (39).

This study also showed that HIV patients without CPT were 2.16 times more hazards of developing TB than their counterparts [HR 2.2, 95% CI: 1.23,3.72]. This was supported by a study done in Asia in 2019 which revealed CPT reduced TB incidence by 28% (31). This may be due to the fact that CPT protects at least five types of opportunistic disease among HIV patients that worsened immunosuppression and progression of the disease.

This study identified that previous TB treatment was not a significant predictor for TB incidence. This was in line with the cohort national study conducted in South Africa (33).

Strengths and Limitations of this study

More than one reviewers were involved in this systematic review and meta-analysis, and we used a comprehensive searching strategy. Moreover, during this review, we had also strictly followed the PRISMA guideline. This systematic review and meta-analysis study of TB incidence among HIV infected after ART initiation was the first at national by combining both children and adults

In this systematic review and meta-analysis, we encountered some limitations. For example, the number of studies that are included is limited, which might affect the pooled estimate of Tuberculosis incidence and predictors among HIV infected individuals in Ethiopia. The retrospective nature of the designs restricts the assessment of all possible predictors that affect the incidence of TB.

Conclusions

The qualitative part of this review showed that TB incidence ranges from 2.2 to 8.64 per 100-person year observation (PYO), after initiation of ARTT in Ethiopia.

The pooled estimate of this TB incidence was higher than in several African and Asian countries. The pooled TB incidence among adults and children was 5.0 and 4.3 per 100 PYO respectively

This meta-analysis indicated that Anemia, WHO clinical staging of three and four, low CD4 cell counts were significant effects for the high incident of TB among HIV positive patients receiving ART. However Isoniazid preventive therapy in reducing the incidence of tuberculosis among HIV infected patients. Besides, the incidence of tuberculosis has a significant difference between children and adults. Moreover, this study also identified the high incidence of active TB among HIV infected patients at facility-based areas compared to Hospitals. Thus, The Ethiopian government should strengthen WHO three is a strategy to reduce the high TB incidence among HIV patients. Clinicians should strengthen ART adherence

Abbreviations

ART: Antiretroviral Treatment; BCG: Bacillus Calmette–Guerin; CPT: Cotrimoxazole preventive Therapy; DM Diabetes Mellitus; HIV Human Immunodeficiency Virus; IPT Isoniazid Preventive Therapy; OI: Opportunistic infections; PLHIV: People living with Human Immune Virus; PY (O): Person year Observation; TB: Tuberculosis; WHO: World Health Organization.

Declarations

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Data will be available from the corresponding author upon request other than the included articles.

Authors' contributions

MM, NM, GS, and DA: Designed the study, reviewed literature, selecting the study, quality assessment, extracted and analyzed data, interpreted results, drafted the manuscript and reviewing the manuscript for its scientific content. All authors have read and approved the manuscript

Ethics approval and consent to participate

Not applicable

Consent for publication

Not applicable

Competing interests

The authors declare that they have no conflicts of interest

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Supplementary Files

additional file 1- Egger test for publication bias for incidences of tuberculosis in Ethiopia

additional file 2- The funnel plot and Egger's regression tests

Figures

Diagrammatic representation of selection of Eligible articles

Figure 1

RISMA flow chart for the studies screened, reviewed and included

Tuberculosis among HIV patients

Figure 2

The forest plots of the incidence rate of tuberculosis among HIV infected patients in Ethiopia.

Tuberculosis among HIV patients by study population

Figure 3

Forest plot of Subgroup analysis of the incidence of tuberculosis among HIV infected patients by study population in Ethiopia.

Figure 4

Sensitivity analysis for the incidence of tuberculosis among HIV infected patients in Ethiopia.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [additionalfile2funnelplot.docx](#)
- [additionalfile1eggertest.docx](#)