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HIV infection and unknown HIV status among tuberculosis patients in Ethiopia: a systematic review and meta-analysis

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SUMMARY

BACKGROUND and OBJECTIVE: Each case of human immunodeficiency virus (HIV) infection worsens the global HIV situation, leads to the failure to achieve tuberculosis (TB) control targets worldwide, and impacts on the use of health service resources. We determined the prevalence of HIV infection among TB patients and the proportion of TB patients with unknown HIV status in Ethiopia.

METHODS: We searched PubMed, EMBASE, Google Scholar and Web of Science electronic databases. Heterogeneity of the included studies was checked using the I^2 statistic and publication bias was assessed using funnel plots and Egger's regression statistical test. We employed a random-effects model to determine the pooled prevalence of HIV infection and unknown HIV status. A sensitivity analysis was also conducted to examine the effect of possible outliers on the overall estimate.

RESULTS: The prevalence of HIV infection among TB patients and the proportion of TB patients with unknown HIV status was respectively 23.4% (95%CI 19.6–27.2) and 6.4% (95%CI 1.7–11.0). Based on geographical location, the prevalence of HIV infection was 31.4% (95%CI 19.2–43.6) in Amhara Region, 23.2% (95%CI 9.9–36.5) in Oromia, 20.9% (95%CI 17.8–24.0) in Addis Ababa and 16.5% (95%CI 12.0–21.0) in Southern Nations, Nationalities and Peoples' Region (SNNPR).

CONCLUSION: In Ethiopia, almost one in four TB patients is infected with HIV. Given the epidemiological variation of Ethiopia, responsive, integrated sustainable programmes for HIV and TB are essential to minimise the epidemics of HIV infection and TB.

KEY WORDS: human immunodeficiency virus infection; TB; Ethiopia

ACCORDING TO THE 2017 World Health Organization (WHO) global tuberculosis (TB) report, the annual incidence of TB was 10.4 million cases, 10 million of which were from sub-Saharan African countries.[1] Of those new cases of TB in 2016, an estimated 2.1 million were among human immunodeficiency virus (HIV) positive individuals.[1] HIV remains to be one of the deadliest infectious diseases; in 2017, there were 36.9 million new cases and 2 million deaths due to HIV and TB-HIV co-infection.[1] Ethiopia is also one of the world's 41 high HIV-TB burden countries.[2]

Each case of HIV worsens the global HIV situation and leads to a failure to achieve TB control targets worldwide. Nationally[3–6] and internationally,[7–11] the TB burden among HIV patients is usually reported as the prevalence and/or incidence of HIV-TB co-infection among HIV-infected patients.

The WHO has established a global policy for joint prevention, diagnosis, and treatment of TB and HIV, as well as routine HIV testing for TB patients, people with TB symptoms, and their partners or family members.[12] HIV testing is the first step for people living with HIV to begin treatment, which can keep them healthy. Moreover, HIV testing of high-risk populations can be a gateway to strategies that can protect them from HIV. The Stop TB Strategy recommends that 100% of TB patients be tested for HIV.[13] Despite this noble aim, many HIV-infected persons do not get tested even late in their infection. HIV screening among TB patients in different studies in Ethiopia has shown that the prevalence of unknown HIV status ranges between 1.8%[14] and 14.9%.[15] A wide distribution of HIV infection and unknown HIV status constitutes a challenge for implementation of collaborative TB-HIV interventions. The HIV status of TB patients in Ethiopia has been reported in various studies conducted in different geographical areas and time periods.[14–26] The distribution of HIV in those studies was highly

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heterogeneous, ranging from 9.5%[21] to 52.1%.[23] In addition, not all studies were representative of the national burden.

HIV surveillance among TB patients could be a sensitive indicator of whether HIV continues to be a national epidemic.[27] National-level information about the HIV status of TB patients would facilitate planning, resource utilisation and appropriate choice of treatment modality for comprehensive HIV/acquired immune-deficiency syndrome (AIDS) care. Furthermore, it would help the Government of Ethiopia to achieve the UNAIDS 90-90-90 targets for sustained HIV epidemic control, and target the national HIV response to at-risk populations to ensure sustainable HIV/AIDS control and prevention.

The present systematic review and meta-analysis aimed to determine the prevalence of HIV infection among TB patients and the proportion of TB patients with unknown HIV status in Ethiopia.

METHODS

Protocol registration and reporting

This systematic review was conducted based on a protocol registered in the PROSPERO database (registration number CRD42018086428) in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analysis.[28]

Search strategy

PubMed, EMBASE (Excerpta Medical Data Base), Google Scholar and Web of Science electronic databases were searched for studies published between 2003 and 2018. Digital repositories of the online library databases of the University of Gondar and Addis Ababa University were accessed to search for unpublished articles. Cross-references were further screened for additional publications.

The key terms used were 'tuberculosis', 'TB', 'HIV', 'AIDS', 'human immunodeficiency virus' and 'acquired immunodeficiency syndrome'. The search strategy for PubMed was as follows: [(Tuberculosis OR TB [MeSH Terms]) AND (HIV OR AIDS [MeSH Terms] OR HIV/AIDS [MeSH Terms] OR 'Human immunodeficiency virus' [MeSH Terms] OR 'Human immunodeficiency syndrome' [MeSH Terms]) AND (Ethiopia)].

Inclusion and exclusion criteria

Original cross-sectional or cohort studies on the HIV status of TB patients and those published in the English language were included; articles that did not report HIV prevalence among TB patients, editorials and conference abstracts were excluded. When duplicate studies were found, the version that was published first or the one with the complete data set were included.

Study quality and risk of bias assessment

The Joanna Briggs Institute (JBI) quality appraisal criteria were employed to assess the risk of bias of the studies included;[29] two of the authors assessed the quality of the studies independently. Studies included were weighed based on the following criteria: 1) appropriate sample frame, 2) appropriate sampling technique, 3) adequacy of sample size, 4) description of study subjects and setting, 5) sufficient coverage of data analysis, 6) validity of the method for identification of condition, 7) standard, reliable measurement for all participants, 8) appropriateness of statistical analysis, and 9) adequacy and management of response rate. For each criterion, 'Yes' or 'No' were possible responses. If the article fulfilled the evaluation criteria, a 'yes' answer received 1 point, if not it received 0 points. If the paper fulfilled more than half of the evaluation criteria, it was considered to be of high quality and included in the analysis.

Data extraction and synthesis

Two authors extracted the following data: names of authors, year of publication, geographical location of the study, study design, sample size, study population based on age and TB type, prevalence of HIV and the proportion of TB patients with unknown HIV status. When discrepancies arose between two reviewers, a second round of data extraction was undertaken to reach a consensus. Any further discord was resolved by a third reviewer.

Outcome measurement

Prevalence of HIV infection among TB patients was estimated based on the response to the question 'how many TB patients were diagnosed as being HIV-positive?' The proportion of TB patients with unknown HIV status was estimated based on the response to the question 'how many TB patients did not know their HIV status?'

Data analysis

A meta-analysis based on the DerSimonian and Laird random effects model was carried out to calculate the prevalence of HIV among TB patients in Ethiopia. Heterogeneity (I^2) between studies was checked: values of respectively 25%, 50% and 75% indicated low, moderate and high degrees of heterogeneity.[30] Statistical analysis was carried out using Stata v 14 (Stata Corporation, College Station, TX, USA).

Publication bias was assessed using a funnel plot and Egger's regression statistical test. A sensitivity analysis was conducted to show how each individual study affected the overall estimate based on other studies.

Ethics approval was not required because primary data were not collected.

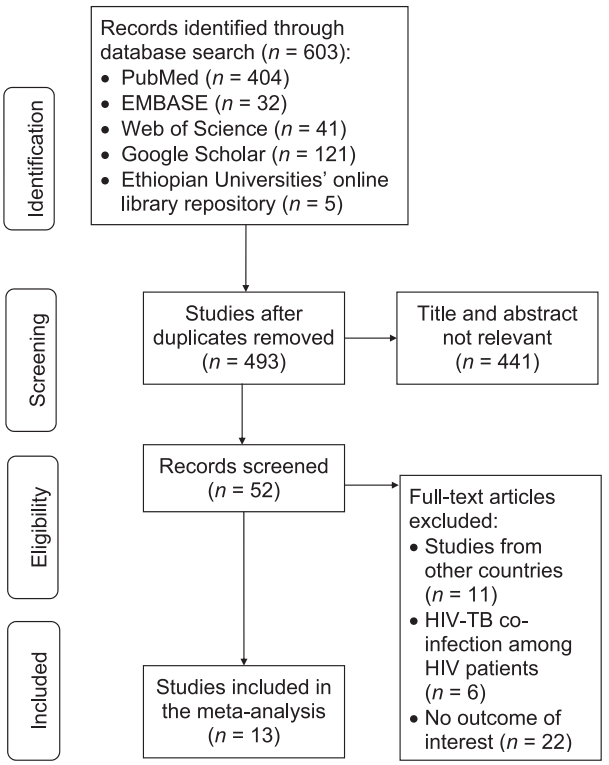

Figure 1 Preferred reporting items for systematic reviews and meta-analyses diagram for the systematic review and meta-analysis.

RESULTS

Literature search and selection of eligible articles

A total of 603 articles was found using Medical Subject Headings[31] and key terms and/or phrases. After removing duplicates and irrelevant articles, we reviewed 52 full-text articles. Of the 52 studies, 13 were used for the quantitative analysis (Figure 1).[14–26]

Characteristics of studies

The studies included in the meta-analysis were found between 2003 and 2018. Thirteen hospital-based studies reported on the prevalence of HIV infection among 19 212 TB patients. The largest sample size was from Addis Ababa (n = 8690), followed by Southern Nations, Nationalities and Peoples' Region (SNNPR) (n = 3769); 3343 were from Amhara, and respectively 3123 and 287 from Oromia and Afar. Six studies reported on the prevalence of unknown HIV status of TB patients.[14–16,19,21] The minimum and maximum sample sizes were respectively 257[23] and 8272.[15] Four studies were conducted in only adult populations;[17,23,25,26] the remaining nine studies were conducted in all age groups. Three studies[17,18,26] were conducted among pulmonary TB (PTB) patients, whereas the remaining 10 studies were conducted among all types of TB patients. Four studies were conducted in Oromia,[16,21,25,26] three in Amhara,[14,20,23] three in SNNPR[19,22,24] and one in the Afar[17] Region. The remaining two studies were from Addis Ababa,[15,18] the capital city (Table 1).

Quality of the included studies

All studies included were assessed using the JBI Critical Appraisal Checklist for Studies Reporting Prevalence checklist. Based on the assessment, none of the included studies was deemed poor quality and excluded (Table 1).

Meta-analysis

Publication bias

A funnel plot for the prevalence of HIV infection was not completely symmetrical (Figure 2). However, we did not find evidence of publication bias using Egger's test ($P = 0.211$).

Human immunodeficiency virus infection among tuberculosis patients

Thirteen studies were included for the meta-analysis of the prevalence of HIV infection. The overall pooled estimates for HIV infection was 23.4% (95% confidence interval [CI] 19.6–27.2; $I^2 = 97.6\%$, $P < 0.001$) (Figure 3).

Table 1 Characteristics of studies included

Author, year, reference	Region	Study population	Type of TB patient	Sample size *n*	HIV-positive %	Unknown HIV status %	Quality
Yadeta, 2013[16]	Oromia	All age groups	All TB	681	31.6	1.9	High
Mekonnen, 2015[14]	Amhara	All age groups	All TB	990	24.3	1.8	High
Assfaw, 2011[15]	Addis Ababa	All age groups	All TB	8272	19.8	14.9	High
Simieneh, 2017[19]	SNNPR	All age groups	All TB	1961	12.5	10	High
Tarekegn, 2016[20]	Amhara	All age groups	All TB	2096	19.3	4.3	High
Gebremariam, 2016[21]	Oromia	All age groups	All TB	1649	9.5	5.3	High
Datiko, 2008[22]	SNNPR	All age groups	All TB	1308	18	—	High
Mihret, 2014[18]	Addis Ababa	All age groups	PTB	418	23.2	—	High
Wajisso, 2003[25]	Oromia	Adults	All TB	419	37.2	—	High
Kassu, 2007[23]	Amhara	Adults	All TB	257	52.1	—	High
Yassin, 2004[24]	SNNPR	All age groups	All TB	500	19.4	—	High
Mengesha, 2015[26]	Oromia	Adults	PTB	374	14.97	—	High
Belay, 2015[17]	Afar	Adults	PTB	287	28.6	—	High

TB = tuberculosis; HIV = human immunodeficiency virus; SNNPR = Southern Nations, Nationalities and Peoples' Region; PTB = pulmonary TB.

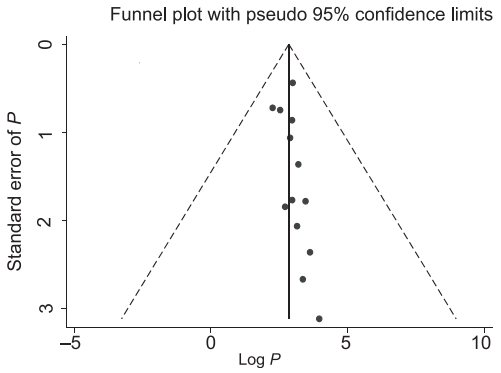

Figure 2 Funnel plot in which the vertical line provides an estimate of the effect size and the diagonal line indicates the precision of individual studies with 95% confidence intervals.

Subgroup analysis

The pooled prevalence of HIV infection by region was 31.4% (95%CI 19.2–43.6) in Amhara, 23.2% (95%CI 9.9–36.5) in Oromia, 20.9% (95%CI 17.8–24.0) in Addis Ababa and 16.5% (95%CI 12.0–21.0) in SNNPR (Figure 4). The prevalence of HIV infection among patients with all types of TB patients was 23.8% (95%CI 19.4–28.2) and 22.1% (95%CI 14.4–29.8) among PTB patients (Figure 5). The prevalence of HIV infection among all age groups of TB patients was 19.6% (95%CI 15.9–23.2), and 33.1% (95%CI 17.8–48.5) among adults (Figure 6).

Unknown human immunodeficiency virus status among tuberculosis patients

Of the 13 studies, only six reported on the number of TB patients with unknown HIV status. The prevalence of unknown HIV status was 6.4% (95%CI 1.7–11.0; $I^2 = 99.3\%$, $P < 0.001$) (Figure 7).

Sensitivity analysis

To assess the robustness of the prevalence of HIV infection, we conducted a leave-one-out sensitivity analysis. No study dominated the overall estimation because all of the studies were in the 95%CIs of the overall estimation (Table 2).

DISCUSSION

Our meta-analysis aimed to assess the prevalence of HIV infection among TB patients and the proportion of TB patients with unknown HIV status. The prevalence of HIV infection among TB patients was 23.4% and the proportion of TB patients who did not know their HIV status was 6.4%.

Our study findings are comparable with those from a study conducted in Ghana.[32] In 2016, respectively 57% and 82% of TB patients worldwide and in the WHO African region had a known HIV test result.[13] Patients with unknown HIV status may have HIV infection and infect their partners and/or communities, leading to an increase in HIV-associated TB costs. This also indicates that the number of HIV-infected people may have been underreported, which

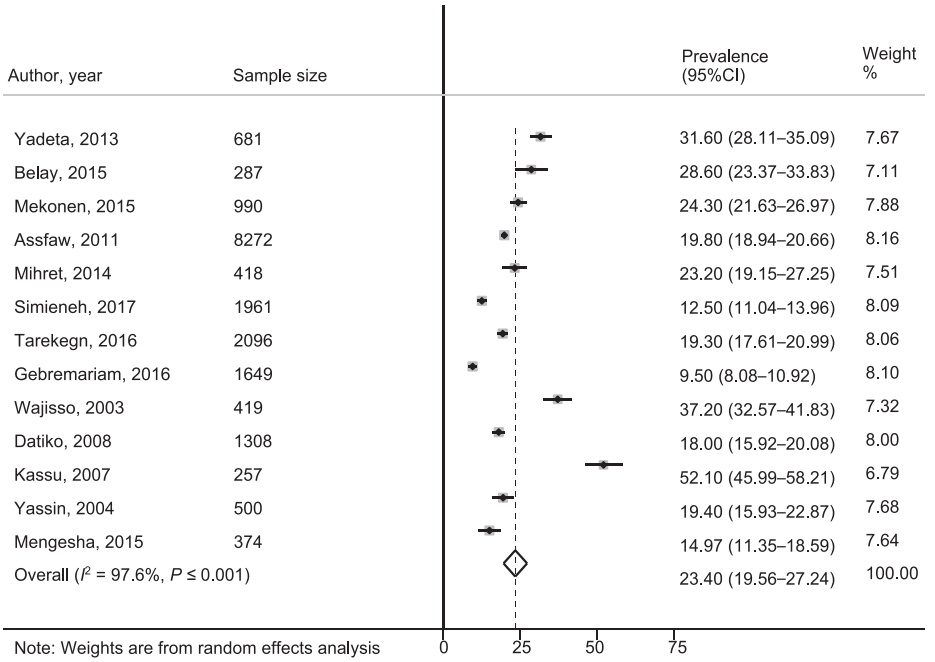

Figure 3 Forest plots of the pooled prevalence of HIV positivity among TB patients. The midpoint and length of each segment indicates prevalence and 95%CIs, whereas the diamond shows the combined prevalence of all studies. CI = confidence interval; HIV = human immunodeficiency virus; TB = tuberculosis.

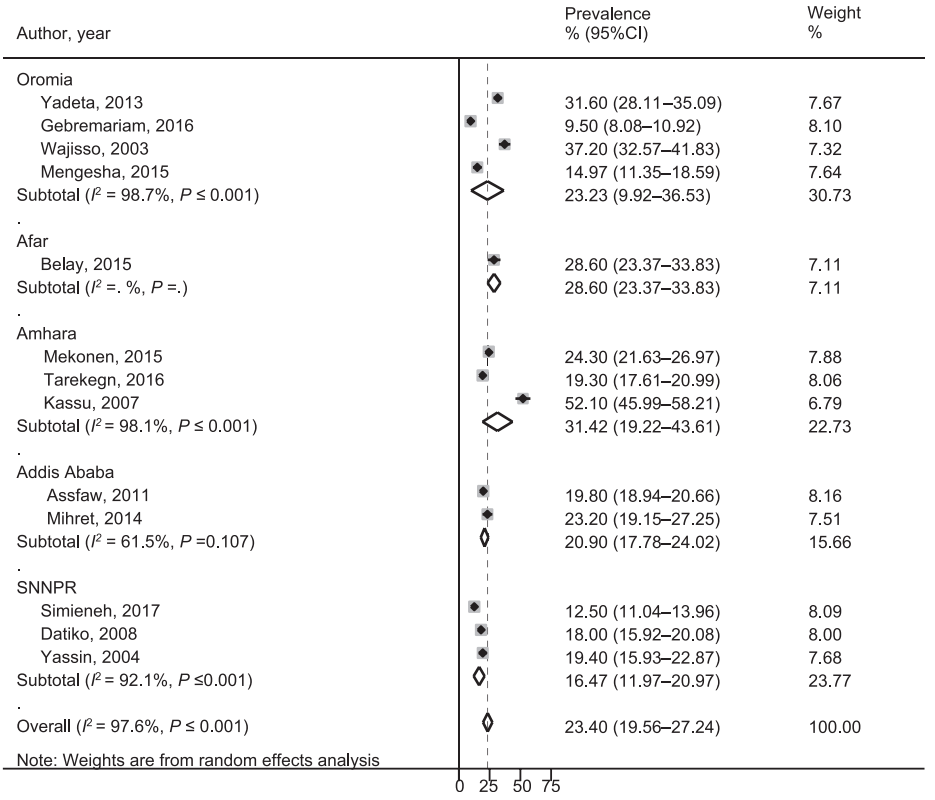

Figure 4 Forest plots showing subgroup analysis of the prevalence of HIV positivity among TB patients based on the region of Ethiopia. The midpoint and length of each segment indicates the prevalence and 95%CIs, whereas the diamond shape shows the combined prevalence of all studies. CI = confidence interval; SNNPR = Southern Nations, Nationalities and Peoples' Region; HIV = human immunodeficiency virus; TB = tuberculosis.

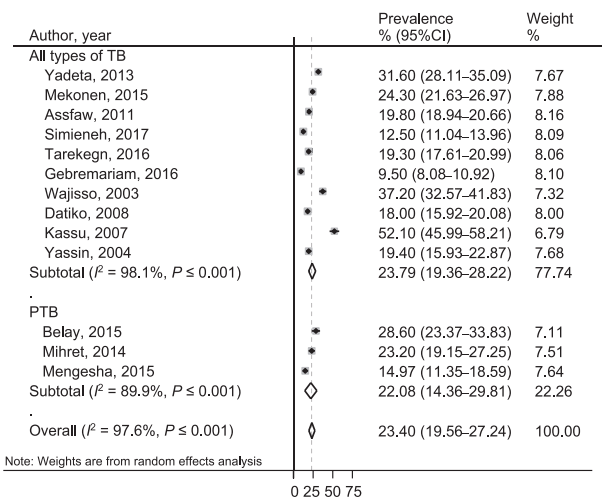

Figure 5 Forest plots showing subgroup analysis of the prevalence of HIV positivity among TB patients based on the types of TB patients included in the study. The midpoint and length of each segment indicates the prevalence and 95%CIs, whereas the diamond shows the combined prevalence of all studies. CI = confidence interval; TB = tuberculosis; PTB = pulmonary TB; HIV = human immunodeficiency virus.

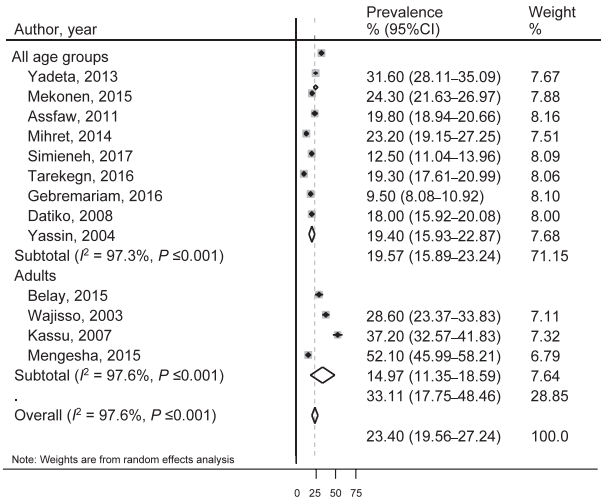

Figure 6 Forest plots showing subgroup analysis of the prevalence of HIV positivity among TB patients by age of the study population. The midpoint and length of each segment indicates the prevalence and 95%CIs, whereas the diamond shows the combined prevalence of all studies. CI = confidence interval; HIV = human immunodeficiency virus; TB = tuberculosis.

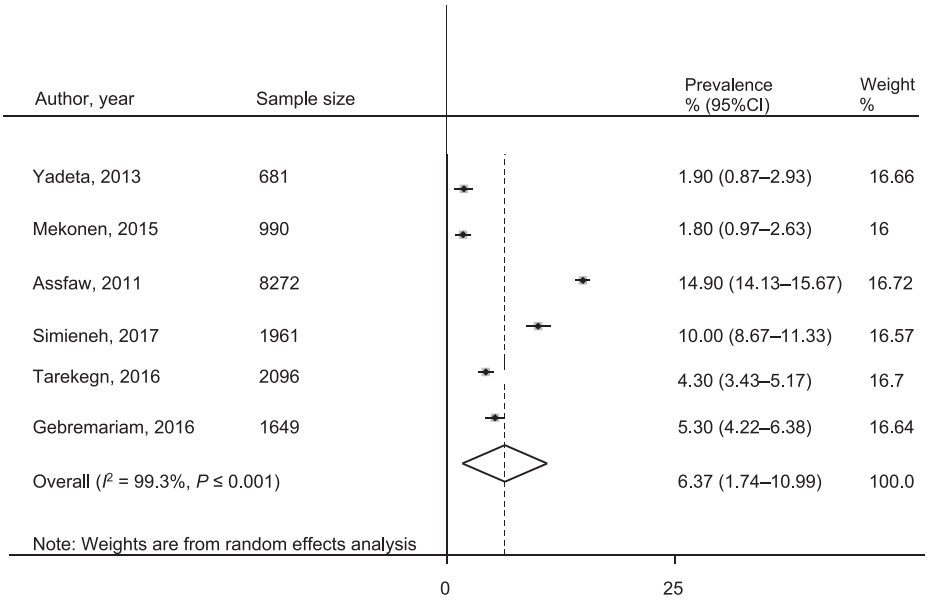

Figure 7 Forest plots of the pooled prevalence of unknown HIV status among TB patients. The midpoint and length of each segment indicates the prevalence and 95%CIs, whereas the diamond shows the combined prevalence of all studies.

makes it difficult to provide collaborative TB-HIV interventions, management of other comorbidities and the best HIV prevention activities. This problem might be due to a weak health care system or rural-based HIV testing and counselling, home-based care, lack of education and health service support, poor access to testing information, lack of comprehensive knowledge of and perception of self-risk to HIV infection, lack of interest and unpreparedness, lack of previous testing and fear of the lack of confidentiality.[33,34]

The prevalence of HIV infection among TB patients was 23.4% (23.8% among all types of TB patients and 22.1% among PTB patients only). This finding is lower than the WHO estimate for Africa (34%)[13] but higher than the 2016 worldwide prevalence (13%),[13] WHO European region (15%),[13] Asia-Pacific Region (6.3%),[10] Brazil (19%)[35] and Ghana (18.2%).[32] Overall findings indicate that in Ethiopia the burden of HIV infection is high, which signifies slow progress in reaching the country's 2020 targets. Evidence suggests that inadequate utilisation of basic HIV prevention services, decreasing attention to AIDS education, low media coverage, higher prevalence of mother-to-child transmission, weak youth-friendly interventions, higher prevalence of unwanted pregnancies among infected mothers and higher mixed infant feeding practices may result in an increase in the prevalence of HIV infection in Ethiopia.[36–39]

Table 2 Sensitivity analysis of the prevalence of HIV positivity and unknown HIV status among TB patients

Studies omitted Author, year, reference	HIV infection Prevalence % (95%CI)	Unknown HIV status Prevalence % (95%CI)
Yadeta, 2013[16]	22.7 (18.8–26.5)	7.3 (2.0–12.5)
Mekonnen, 2015[14]	23.3 (19.3–27.4)	7.3 (2.2–12.4)
Assfaw, 2011[15]	23.9 (19.1–28.7)	4.6 (2.1–7.2)
Simieneh, 2017[19]	24.4 (20.3–28.5)	5.6 (0.4–10.9)
Tarekegn, 2016[20]	23.8 (19.5–28.1)	6.8 (1.1–12.4)
Gebremariam, 2016[21]	24.5 (20.9–28.2)	6.6 (1.1–12.1)
Belay, 2015[17]	23.0 (19.0–26.9)	—
Wajisso, 2003[25]	22.3 (18.5–26.0)	—
Mihret, 2014[18]	23.4 (19.4–27.4)	—
Datiko, 2009[22]	23.9 (19.7–28.1)	—
Kassu, 2007[23]	21.2 (17.7–24.8)	—
Yassin, 2004[24]	23.7 (19.7–27.8)	—
Mengesha, 2015[26]	24.1 (20.1–28.2)	—
Combined	23.4 (19.6–27.2)	6.4 (1.7–11.0)

HIV = human immunodeficiency virus; TB = tuberculosis; CI = confidence interval.

The prevalence of HIV infection in our study was higher among adults (33.1%) than among all age groups of TB patients (19.6%). This result may have been due to a high HIV prevalence among adults in the general population of Ethiopia. Children may have been infected by their mothers, would become adults after 15 years of age, thereby leading to an increase in the HIV burden among adults on attaining 15 years of age.

Based on regional subgroup analysis, the prevalence of HIV infection was 31.4% in the Amhara Region, which was higher than estimates for other regions. This result might have been due to the higher prevalence of HIV in the general population in Amhara Region (28.5%) than in other regions.[40] Second, based on population size, coverage of health services packages such as HIV care was low.[41] As the number of health facilities increase, it is possible that each segment of the population will receive health information on HIV transmission, prevention, diagnosis and treatment from nearby hospitals. Finally, the unemployment rate is high,[42] which could expose

adolescents to substance abuse and unsafe sex, and therefore, HIV infection.[43,44]

As the prevalence of HIV infection among TB patients in Ethiopia exceeded the 5% threshold set by the WHO, strong interventions must be taken.[44] This is a wake-up call for the Ethiopian TB and HIV control programme, which plans to create a HIV-free generation by 2020. Given the epidemiological variations in HIV infection in Ethiopia, a strong political commitment, integrated sustainable programmes for HIV and the reinforcement of established official institutional policies for HIV care and prevention are essential to prevent further HIV transmission. To implement HIV screening among all TB patients, culturally appropriate HIV testing efforts must be continued and strengthened.

CONCLUSION

This study provides the first national-level data on HIV status among TB patients. HIV is a major public health problem in many countries, including Ethiopia, where almost one in four TB patients are infected with HIV. Given the epidemiological variations in Ethiopia, integrated sustainable programmes for HIV and TB are essential to minimise the epidemic of HIV infection.

Conflicts of interest: none declared.

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RÉSUMÉ

CONTEXTE et OBJECTIF : La survenue de chaque cas de virus de l'immunodéficience humaine (VIH) pèse sur la situation du VIH dans le monde qui aboutit à un échec de l'objectif mondial de lutte contre la tuberculose (TB) et pourrait avoir un impact sur l'utilisation des ressources des services de santé. Dans cette étude, a été déterminée la prévalence de l'infection à VIH parmi les patients TB et la proportion de patients TB dont le statut VIH est inconnu en Ethiopie.

MÉTHODE : Nous avons fait une recherche des bases de données électroniques de PubMed, EMBASE (Excerpta Medical Data Base), Google Scholar et Web of Science. L'hétérogénéité des études incluses a été mise en évidence par le test I^2 et les biais de publication ont été évalués grâce à une visualisation du graphique en entonnoir et du test de régression statistique d'Egger. Nous avons utilisé le modèle à effets aléatoires afin de déterminer la prévalence groupée de l'infection à VIH et du statut VIH inconnu. L'analyse de sensibilité a également été réalisée pour examiner l'effet d'éventuels résultats aberrants sur l'estimation d'ensemble.

RÉSULTATS : La prévalence de l'infection à VIH parmi les patients TB et la proportion de patients TB de statut VIH inconnu a été de 23,4% (IC95% 19,6–27,2) et 6,4% (IC95% 1,7–11,0), respectivement. En termes de localisation, la prévalence de l'infection à VIH a été de 31,4% (IC95% 19,2–43.6) dans la région d'Amhara, de 23,2% (IC95% 9,9–36,5) dans celle d'Oromia, de 20,9% (IC95% 17,8–24,0) à Addis Ababa et de 16,5% (IC95% 12,0–21,0) dans les Regions des Nations, des Nationalites et des Peuples du Sud (SNNPR).

CONCLUSION : En Ethiopie, près d'un patient tuberculeux sur quatre est infecté par le VIH. En raison des variations épidémiologiques en Ethiopie, des programmes intégrés VIH et TB réactifs et durables sont essentiels pour minimiser les épidémies d'infection à VIH et à la TB.

RESUMEN

MARCO DE REFERENCIA y OBJETIVO: La aparición de cada caso de infección por el virus de la inmunodeficiencia humana (VIH) pone en la balanza la situación mundial del VIH que lleva al incumplimiento de la meta de control mundial de la tuberculosis (TB) y puede tener repercusiones en la utilización de los recursos de los servicios de salud. En el presente estudio se determinó la prevalencia de infección por el VIH en los pacientes con TB y la proporción de pacientes tuberculosos que desconocen su situación frente al VIH en Etiopía.

MÉTODOS: Se llevó a cabo una búsqueda en las bases de datos electrónicas PubMed, EMBASE (Excerpta Medical Data Base), Google Scholar y Web of Science. La heterogeneidad de los estudios incluidos se evaluó con la estadística I^2 y el sesgo de publicación se analizó con la visualización del gráfico en embudo y la prueba de regresión estadística de Egger. Se aplicó el modelo de efectos aleatorios con el fin de determinar la prevalencia combinada de infección por el VIH y el desconocimiento de la situación frente al virus. Mediante un análisis de sensibilidad se examinó el efecto de posibles valores atípicos sobre una estimación global.

RESULTADOS: La prevalencia de infección por el VIH en los pacientes con TB fue 23,4% (IC95% 19,6–27,2) y la proporción de pacientes tuberculosos que desconocía su situación frente al VIH fue 6,4% (IC95% 1,7–11,0). Según la localización geográfica, la prevalencia de infección por el VIH fue 31,4% (IC95% 19,2–43,6) en la región Amhara; 23,2% (IC95% 9,9–36,5) en Oromia; 20,9% (IC95% 17,8–24,0) en Adís Abeba; y 16,5% (IC95% 12,0–21,0) en la Región de las Naciones, Nacionalidades y Pueblos Meridionales (SNNPR).

CONCLUSIÓN: En Etiopía, cerca de un cuarto de los pacientes con TB presentan coinfección por el VIH. Dadas las variaciones epidemiológicas observadas en el país, es primordial contar con programas integrados de atención de la infección por el VIH y la TB que sean sostenibles y respondan a las necesidades, con el objeto de reducir a un mínimo las epidemias de infección por el VIH y por la TB.