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Impact of HIV coinfection on tuberculosis treatment outcomes in Ethiopia: a systematic review and meta-analysis

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ABSTRACT

Objectives Despite the implementation of a short-term direct observation treatment programme, HIV coinfection is one of the main determinants of tuberculosis (TB) treatment success. This meta-analysis was conducted to report the impact of HIV on TB treatment outcomes using inconsistent and variable study findings.

Design Systematic review and meta-analysis was performed.

Data sources The PubMed/Medline, Web of Science and Google Scholar databases were used to access the articles. The Joanna Briggs Institute (JBI) Meta-Analysis of Statistics Assessment and Review Instrument was used for the critical appraisal.

Eligibility criteria All observational studies conducted in Ethiopia and reporting TB treatment outcomes in relation to HIV coinfection were included in the final analysis.

Data extraction and synthesis Two independent reviewers extracted the data using a standardised data extraction format. The JBI critical appraisal tool was used to assess the quality of primary studies. Stata V.14 was used for the data analysis. Cochran's Q statistic with inverse variance (I^2) and funnel plot are used to assess the presence of heterogeneity (I^2=94.4%, p<0.001) and publication bias, respectively. A random effect model was used to estimate TB treatment outcomes with a 95% CI.

Results The overall success rate of TB treatment was 69.9% (95% CI 64% to 75%). The cure rate of TB among patients living with HIV was 19.3%. Furthermore, the odds of unsuccessful treatment among TB-HIV coinfected patients were 2.6 times greater than those among HIV nonreactive patients (OR 2.65; 95% CI 2.1 to 3.3).

Conclusion The success of TB treatment among patients living with HIV in Ethiopia was lower than the WHO standard threshold (85%). HIV coinfection hurts TB treatment success. Therefore, collaborative measurements and management, such as early treatment initiation, follow-up and the management of complications, are important.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ A strict, standardised methodological approach, wide inclusion criteria and the inclusion of diverse experts were among this review's strong points.
⇒ This review was also performed based on extensive search and planned reviews, and two reviewers were engaged to minimise all possible risk of bias.
⇒ Although this meta-analysis is the first study conducted in Ethiopia to report the impact of HIV coinfection on tuberculosis treatment outcomes, data were available for only 8 regional states of the country (not including all the 13 regional states found in Ethiopia).
⇒ Variation in methodological approaches across the included studies may compromise the result of the study.
⇒ In addition, the included studies did not report the treatment outcomes of transferred-out patients.

BACKGROUND

Tuberculosis (TB) continues to cause ill health and death across many populations worldwide. It has been 25 years since the WHO declared the disease a global emergency.[1] Globally, TB is the 13th leading cause of death and the leading cause of infection (above HIV). In 2020, an estimated 10 million people worldwide were ill with TB, and 1.5 million people died from this disease.[2] Over 95% of TB cases and deaths are in developing countries. The WHO regions of Southeast Asia, Africa and the Western Pacific had the most cases of TB. In 2020, 43% of new TB cases occurred in the Southeast Asian Region, followed by the African Region, with 25% of new cases.[1] Ethiopia is the second most common TB-diseased country in Africa and among the 30 countries with the highest number of TB cases in the world.[3 4]

Even though ending the TB epidemic by 2030 is among the health targets of the United Nations Sustainable Development Goals (SDGs), progress towards achieving this target remains slow.[5] If current trends in TB incidence continue, few countries are likely

to meet the SDG target. An estimated 66 million lives were saved through TB diagnosis and treatment between 2000 and 2020.[6] Directly observed treatment short course (DOTS) is one of the strategies adopted by the WHO to achieve a 70% case detection rate and an 85% treatment success rate.[7] Despite the implementation of different strategies, such as the DOTS programme, massive involvement of health extension workers in TB prevention and control activities, the USAID-designed and USAID-funded Help Ethiopia Address Low TB Performance programme, Guidelines for Clinical Management and Programmatic Management of TB, Leprosy and TB/HIV, TB and Leprosy control programme, and integrated TB/HIV activities,[8 9], different reports across the country have indicated the existence of challenges in improving TB treatment outcomes.[10]

Although the success of TB treatment is affected by different factors, HIV coinfection is considered the leading one.[11 12] TB-HIV coinfection is considered a double-burden disease worldwide.[13 14] TB is the leading cause of death among people living with HIV, accounting for one in three of these disease-related deaths.[15] According to a recent report, 10 million people are ill with TB, and 1.6 million people die from the disease, 26% of whom are infected with HIV-TB.[4 10] Among low-income and middle-income countries, the African continent accounts for the greatest share (74%) of the 1.2 million HIV-TB cases worldwide.[10 16] Ethiopia is one of the low-income countries with the highest number of HIV-TB cases and deaths reported.[17 18] HIV coinfection is one of the main determinants of TB treatment success. HIV and TB form a lethal combination, each speeding the other's progress. A systematic review and meta-analysis reported in Africa showed that the risk of unsuccessful TB treatment was 1.53 times greater among people living with HIV than among their counterparts.[19] Thus, coinfection is associated with a significantly increased risk of morbidity and mortality, treatment failure, loss to follow-up and a low success and cure rate.[20]

In Ethiopia, a number of primary studies have reported on the impact of HIV on TB treatment outcomes. However, inconsistent and variable results have been reported across studies. In addition, there is a lack of rigorous evidence generated based on large population sizes on the treatment outcomes of coinfected patients with active TB disease receiving anti-TB treatment in Ethiopia. It is essential and timely to better understand how and why HIV coinfected TB patients have unfavourable treatment outcomes and to understand the severity of the problem. Therefore, a recent concrete and meagre scientific report at the national level is mandatory for policymakers to meet the SDGs on TB. Accordingly, this review addresses the following research question: 'Does HIV coinfection influence TB treatment outcomes?' Thus, this systematic review and meta-analysis was conducted in Ethiopia to determine the impact of HIV coinfection on TB treatment outcomes. Assessing TB treatment outcomes and contributing factors specifically related to HIV through continued research can assist policy-makers and healthcare providers in planning interventions to overcome these barriers and improve patient treatment response. Moreover, it can serve as an indicator of the quality of TB treatment provided.

METHODS

Search strategies and tools

This is the first systematic review and meta-analysis conducted in Ethiopia to explore the impact of HIV coinfection on TB treatment outcomes using available equivocal and variable primary studies. This systematic review and meta-analysis was reported using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses checklist[21] (online supplemental file 1). Published articles were searched using major medical electronic databases such as PubMed/Medline, Web Science and Google Scholar. Keywords or phrases such as impact of HIV coinfection on TB treatment outcomes, TB treatment outcomes, multidrug-resistance tuberculosis treatment outcomes, unsuccessful TB treatment outcome and Ethiopia with respective Medical Subject Heading terms (MeSH terms) combined with Boolean operators ('AND' and 'OR') were applied to access available articles (online supplemental file 2). Furthermore, unpublished studies were accessed using cross-references of identified articles, local academic institution libraries and repositories. The overall article search was conducted through April 2023.

The eligibility criteria

EndNote citation manager software V.X-7 for Windows was used to exclude duplicate studies. All observational studies (cross-sectional, case–control and cohort) conducted in Ethiopia on TB patients receiving treatment (bacteriologically, clinically confirmed TB, new or recurrent TB) were included in this meta-analysis. In addition, studies published only in the English language and reporting TB treatment outcomes in relation to HIV coinfection were considered for the final analysis. No restrictions were applied in terms of publication status, study and publication year, study setting or sampling technique. However, papers that were not fully accessible at the time of our search process were excluded after contacting the principal investigator via email at least two times. Finally, after reviewing their full texts, studies of poor quality according to the established criteria for reviewing the articles were excluded from the final analysis.

Outcome variable and data extraction

The main aim of this study was to explore the impact of HIV coinfection on TB treatment outcomes. First, this meta-analysis aimed to determine the success of TB treatment among people living with HIV coinfection. Second, the pooled effect estimate of the impact of HIV coinfection among confirmed TB patients on treatment was also explored. National Tuberculosis and Leprosy Control Programme (NTLCP) of Ethiopia and WHO guideline

on TB infection prevention and control have settled a standard definition for TB treatment outcomes and were divided into cured, treatment completed, defaulter/lost to follow-up, treatment failure, death and transferred out.[22 23] Accordingly, a successful treatment was considered when TB patients were cured and/or completed the treatment. A cure was defined as treatment completed without evidence of failure and with negative bacteriology results. Treatment completed was defined as a TB patient who finished treatment without evidence of failure, with no records of sputum smear or culture results in the last month of treatment and on at least one previous occasion were negative. An unsuccessful treatment outcome was considered if TB treatment resulted in treatment failure, defaulter or death. Treatment failure was considered when a patient remained smear-positive at 5 months or later during treatment, despite the patient taking medications correctly. Whereas, defaulter was defined as a patient who lost to follow-up or interrupted their treatment for ≥2 consecutive months for any reason without medical approval. Death was defined as a patient who died during the treatment from any cause.[11 22 23]

Two authors extracted the data using a standardised data extraction format developed according to the 2014 Joanna Briggs Institute (JBI) Reviewers' Manual.[24] From each primary study, study setting or region, publication year, study design, sampling technique, response rate, sample size, proportion of TB treatment success, proportion of unsuccessful TB treatment outcome and odds ratio (OR) showing the impact of HIV coinfection on unsuccessful TB treatment outcome were extracted. Disagreements between the authors were resolved by face-to-face discussion and consensus.

Quality assessment

Two independent reviewers evaluated all the primary studies. The JBI critical appraisal tool adapted for observational studies (cross-sectional, case–control and cohort) was used to assess the quality of the primary studies.[24] The following JBI criteria were applied for evaluating cross-sectional studies: (1) inclusion criteria, (2) study subject and setting description, (3) valid and reliable exposure measurements, (4) objective and standard criteria, (5) confounding identification, (6) strategies to address confounding factors; (7) reliable and valid outcome measurement and (8) the appropriate statistical analysis was performed. The following criteria were used to evaluate the quality of the cohort studies: (1) similar groups were recruited from the same population; (2) similar exposure measurements, (3) valid and reliable exposure measurements, (4) confounding identification, (5) strategies to address confounding factors, (6) selection of participants at the start of the study, (7) reliable and valid outcome measurement, (8) appropriate follow-up time, (9) completeness of follow-up, (10) strategies to deal with incompleteness and (11) the appropriate statistical analysis was performed. Any disagreements between the reviewers were resolved via discussion and a census; if not, a third reviewer was involved. Accordingly, those articles scoring at least half of the predefined quality measurement criteria were included in the final meta-analysis.

Patient and public involvement

Not applicable, since a systematic review and meta-analysis study.

Data analysis

First, the extracted data were computed in an Excel spreadsheet and imported into STATA V.14 software. Cochran's Q statistic with inverse variance (I^2) was used to assess the existence of heterogeneity and to quantify it. Low, moderate and high heterogeneity were considered at 25%, 50% and 75%, respectively.[25] In addition, a $p<0.05$ was used to confirm the presence of statistically significant heterogeneity across studies. Based on the test, statistically significant heterogeneity was detected (I^2=94.4%, $p<0.05$). TB treatment outcome measures were evaluated as the proportion of successful (cured plus completed treatment) versus unsuccessful treatment outcome (defaulter plus failure plus death) as defined by WHO criteria[23] and NTLCP of Ethiopia.[22] A random effect meta-analysis model, because of heterogeneity of the study, was run using metaprop command of STATA V.14 that was used to estimate the pooled proportion of treatment success and treatment unsuccessful with their corresponding 95% CI. To estimate the pooled impact of HIV coinfection on unsuccessful TB treatment outcome, a random effect meta-analysis using metan command was fitted and quantified through OR with 95% CI. Subgroup analysis using regions was also performed, and the results were presented. Publication bias was assessed using Egger's regression test and funnel plots.[26]

RESULTS

Characteristics of the included studies

A total of 485 studies were retrieved from PubMed/Medline, the Cochrane Library and Google Scholar. Among these, 367 articles were excluded because of duplication. After title and abstract screening, 52 articles were excluded because they were not related to this study. The full texts of the remaining 66 studies were assessed, and 32 articles were removed because they did not report our outcome of interest. Moreover, 34 full articles were critically appraised using the JBI-MAStARI critical appraisal tool.[24] Finally, 34 studies were included in this meta-analysis to evaluate the pooled success of TB treatment among HIV coinfected patients and its impact (online supplemental figure 1).

Among the included studies, 11 were from the Amhara region,[27–37] 6 were from Oromia,[38–43] 5 were from the South Nationality and People,[44–48] 3 were from Tigray,[49–51] 2 were from Harari,[52 53] 3 were from Addis Ababa,[54–56] 1 was from Gambella,[57] 1 was from Afar,[58] and from the remaining two studies, 1 was from Addis Ababa and Amhara[59] and the other one was from Amhara and Oromo.[60] All the included studies

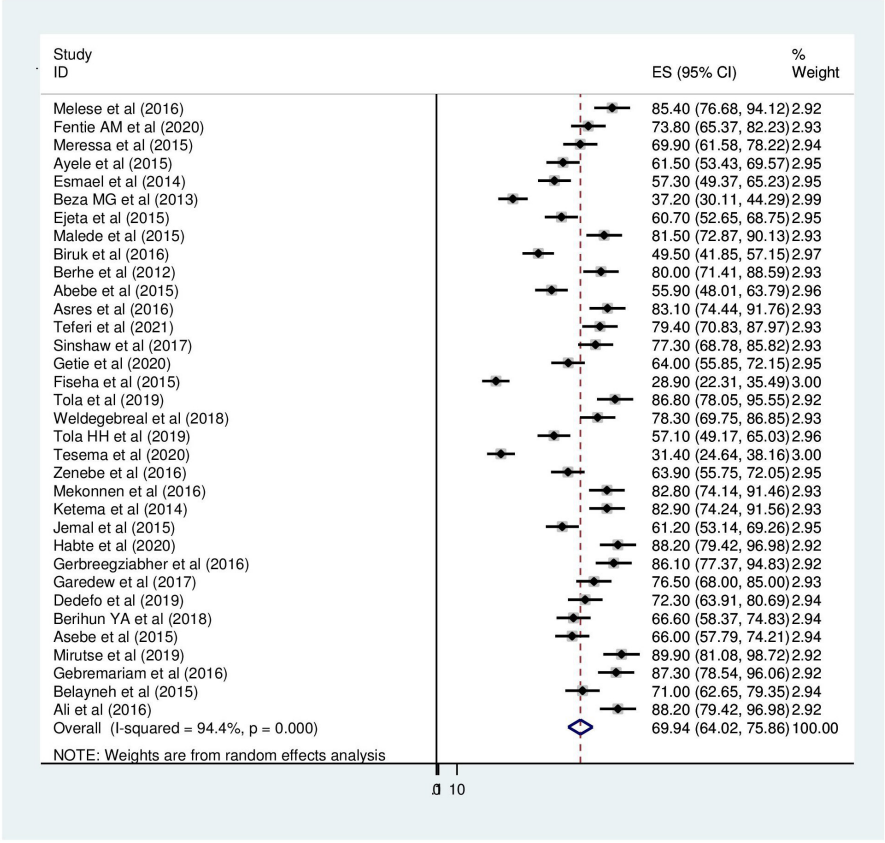

Figure 1 Pooled success of TB treatment among patients living with HIV coinfection in Ethiopia. TB, tuberculosis.

documented successful TB treatment outcomes among HIV/TB coinfected patients. Regarding the study design, more than half[19] of the articles were cross-sectional studies, and the remaining 15 articles used retrospective cohort designs. Nearly all included studies were published across known international journals from 2012 to 2021. A total of 7909 TB patients living with HIV were included to estimate the pooled prevalence of successful TB treatment and its impact. The prevalence of TB treatment success among patients living with HIV ranged from 28.9% to 89.9% (online supplemental table 1).

Meta-analysis

TB treatment success among HIV patients

According to the pooled meta-analysis of 34 primary studies and 7909 patients living with HIV and receiving TB treatment, the overall success rate of TB treatment was 69.94% (95% CI 64% to 75%) (figure 1). The forest plot showed that there was significant heterogeneity across the included primary studies (I^2=94.4%, p<0.001). Hence, subgroup analysis was based on study setting or region. In addition, a symmetrical funnel plot (figure 2) and Egger's test suggested no publication bias (p=0.564).

Success of TB treatment among regions

11 studies in the Amhara region reported HIV/TB coinfection treatment success, with minimum and maximum rates of 37.2%[29] and 86.1%,[36] respectively. According to the subgroup analysis, the pooled success rates of TB treatment among patients living with HIV in the Amhara region were 67.9%, 67.9% in the South Nation, Nationality and People Region and 63.18% in the Oromia Region. The pooled success of TB treatment in Addis Ababa was 72.9%, in Tigray was 80.2% and in Harari was 82.5%. In addition, 63.9% and 66% TB treatment success rates were reported in the Afar and Gambella regions, respectively (figure 3).

Cure rate of TB treatment among patients living with HIV

A total of 19 studies reported the cure rate of TB treatment among HIV/TB patients. Among these, seven studies were in the Amhara region,[27–30 32 34] four from the South Nation, Nationality and People[45–48] and People, two from Addis Ababa,[54–56] two from Oromia,[38 43] two from Harar,[52 53] one from Tigray[50] and one each from the Addis Ababa and Amhara regions.[59] In addition to estimating the pooled success of TB treatment (cured plus completed) among patients living with HIV, this

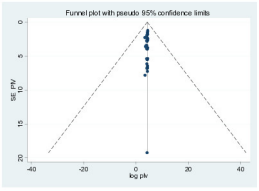

Figure 2 Funnel plot of primary studies included in estimating the impact of HIV coinfection on TB treatment outcomes in Ethiopia. TB, tuberculosis.

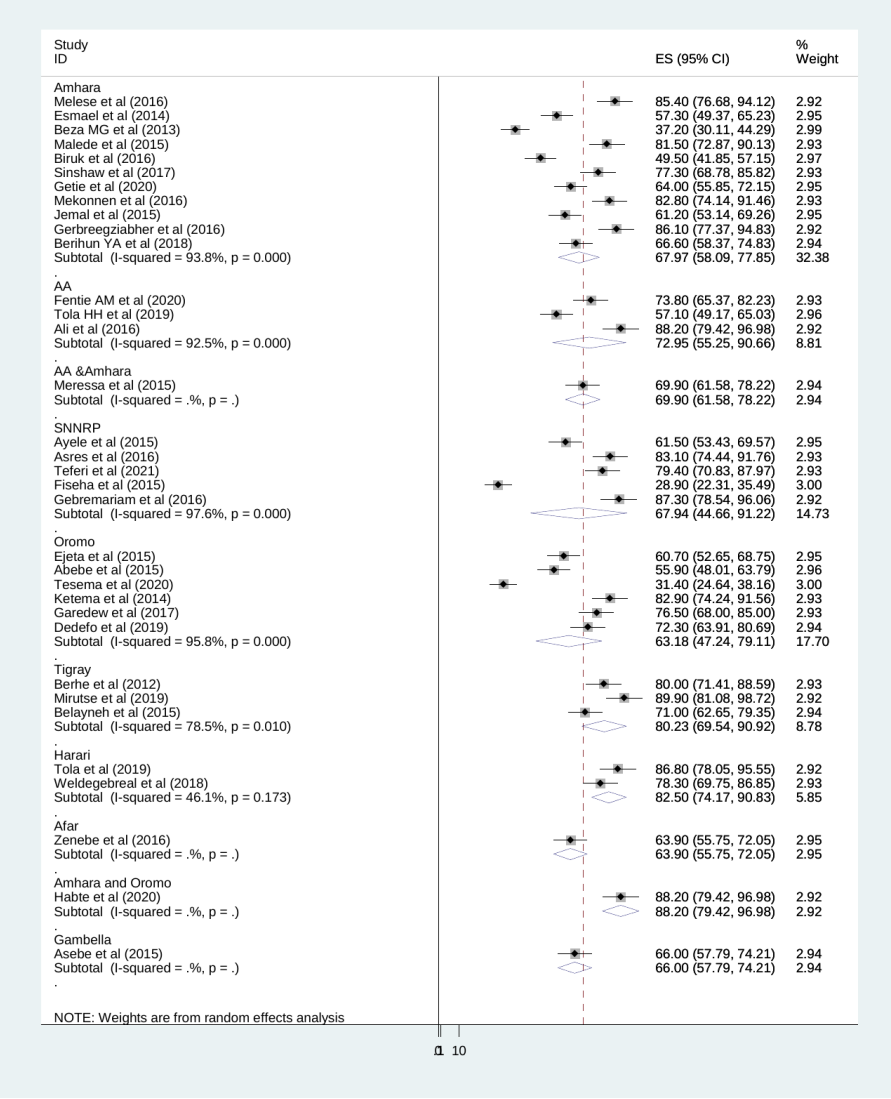

Figure 3 Subgroup analysis of TB treatment success among patients with HIV coinfection using regions. TB, tuberculosis. **SNNP: Southern Nation, Nationalities, Regions and People**

meta-analysis aimed to estimate the pooled cure rate of treatment among these patients. A total of 19 primary studies were eligible for this meta-analysis. Accordingly, the pooled cure rate of TB treatment among HIV patients was only 19.29% (95% CI 14% to 24%) (figure 4).

The impact of HIV coinfection on TB treatment outcomes

A total of 27 primary studies were eligible and included to estimate the pooled impact of HIV coinfection on TB treatment outcomes in Ethiopia. Based on the meta-analysis of these studies, the odds of unsuccessful TB treatment (loss to follow-up plus failure plus death) were 2.65 times greater among patients living with HIV than among HIV nonreactive patients (OR 2.65; 95% CI 2.1 to 3.3) (figure 5).

DISCUSSION

Ethiopia is a country with a high HIV/TB burden in which treatment success is highly limited and remains low. According to the present meta-analysis, the overall TB treatment success rate among patients living with HIV was 69.9%. This implies that the TB treatment success rate among patients living with HIV was lower than the WHO threshold of 85%.[61] The low treatment success rate of this study may be attributed to the fact that all the studies included in this meta-analysis were from a country, Ethiopia, with high TB/HIV coinfection and a weak health system. In addition, other reasons for this low TB treatment success rate may be the late diagnosis and treatment of TB patients and poor healthcare-seeking behaviour in the community.[54–56] The difficult nature of TB diagnosis and poor initiation of HIV testing may also contribute to the low TB treatment success rate among HIV coinfected TB patients. In fact, the HIV pandemic poses a great challenge to the control of the TB epidemic by changing the natural progression of latent TB to active TB, in turn influencing its clinical outcomes. The management of HIV-TB coinfection is complicated by several factors,

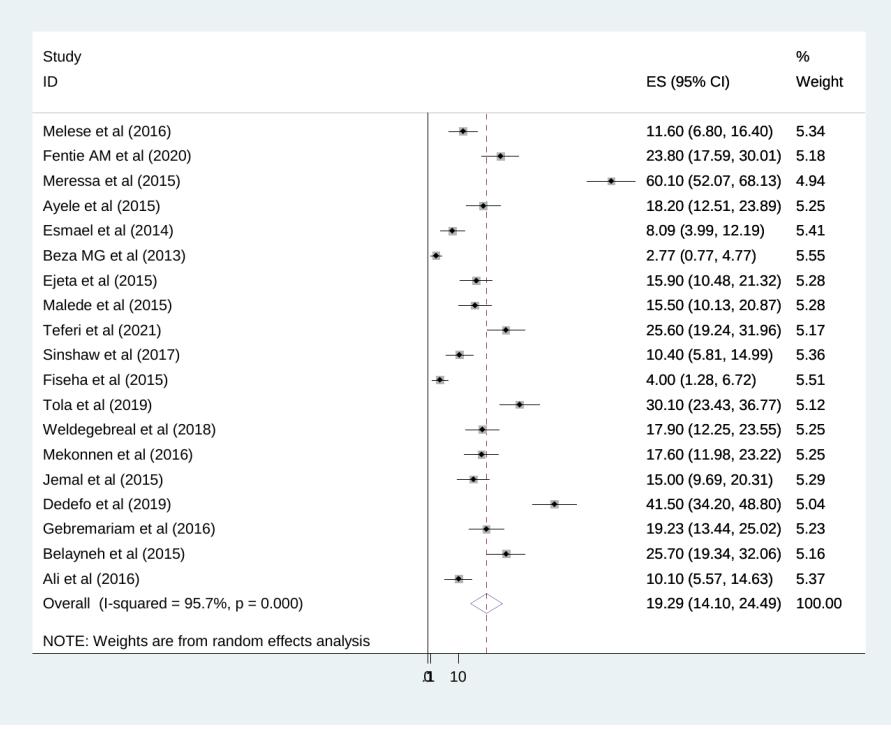

Figure 4 Forest plot showing the pooled cure rate of TB treatment among HIV patients in Ethiopia. TB, tuberculosis.

including drug interactions, overlapping drug toxicities, exacerbation of side effects, concerns about adherence and immune reconstitution inflammatory syndrome.[62–64] HIV-TB coinfection places an immense burden on healthcare systems, poses particular diagnostic and therapeutic challenges and has become a major challenge for achieving SDGs, particularly in low-income and middle-income countries such as Ethiopia.[65] This result is in line

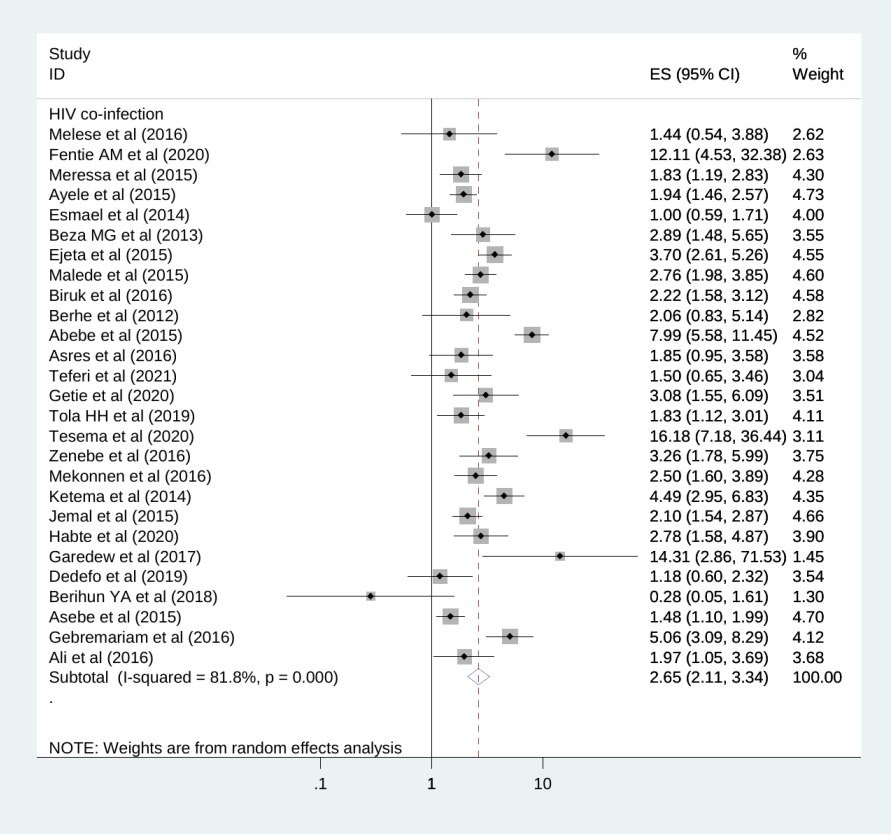

Figure 5 Forest plot showing the impact of HIV coinfection on TB treatment outcomes in Ethiopia. TB, tuberculosis.

with and supported by the findings of studies reported in India[66] and Ghana.[67]

However, the current finding regarding the proportion of TB treatment success was lower than the results of a systematic review and meta-analysis performed in Ethiopia among general TB patients (83.7%).[68] In addition, this percentage is lower than that reported in similar studies conducted in Cameroon (78.6%)[69] and South Africa (82.2%).[70] On the other hand, the results of this meta-analysis are greater than the findings of studies reported in Nigeria (48.8%)[71] and Malaysia (53.4%).[72] This variation might be due to socioeconomic differences across countries, differences in the quality and accessibility of HIV-TB health services and variations in health education and community services. Furthermore, the average cure rate of TB treatment among patients coinfected with HIV was only 19.3%. Despite the availability of effective drugs for treating both HIV and TB, the comanagement of TB and HIV has proven very difficult largely because of nonadherence due to the high pill burden and other double burdens. This finding is much lower than that of studies reported in India, which reported a 72% cure rate.[73] The possible explanation for this low cure rate of TB among HIV coinfected patients may be due to late presentation and diagnosis of HIV and not being on ART. Furthermore, simultaneous administration of anti-TB and Anti-retroviral therapy (ART)drugs can lead to default from a greater pill burden and poor patient compliance, and the presence of other opportunistic diseases in HIV coinfected TB patients may also contribute to this low cure rate. HIV lowers immunity against TB, leading to increased active TB infection, reinfection or reactivation. It also increases the risk of TB progression from latent TB to active TB disease, the risk of TB treatment failure and TB loss to follow-up.[74]

The odds of unsuccessful TB treatment among patients living with HIV were 2.6 times greater than that of unsuccessful TB treatment among patients with HIV non-reactive individuals. This evidence is supported by a similar study conducted in Africa.[19] HIV and TB are two major public health problems that have synergistic effects on each other.[75] HIV coinfected TB patients have significantly greater adverse treatment outcomes than HIV-non-reactive TB patients.[76] The reasons for the adverse treatment outcome may be immunosuppression,[77] drug interactions between anti-TB drugs and antiretroviral agents,[78] suboptimal concentrations of anti-TB drugs[79] and malabsorption of anti-TB drugs.[80] In fact, the HIV pandemic poses a great challenge to the control of the TB epidemic by changing the natural progression of latent TB to active TB, in turn influencing its clinical outcomes. Many HIV/TB coinfected patients are uncomfortable with the long duration of treatment, the frequency of drug administration and unregulated immunological responses.[65 70] In addition, it has been difficult for HIV/TB coinfected patients to receive the prescribed drugs via routine treatments. Low knowledge about latent TB infection, fear of side effects and the cost of medication may contribute to unsuccessful TB treatment. Furthermore, delayed healthcare seeking and the choice of TB treatment regimen may aggravate loss to follow-up among patients with TB.[81 82] Reasonably, HIV-TB coinfected individuals are being treated for two infectious diseases, and therefore, the goals of treatment for both diseases must be harmonised through therapy integration, management of HIV-related clinical problems and control of drug toxicity.[83]

Conclusion

The findings of this meta-analysis confirmed that the success of TB treatment among patients living with HIV in Ethiopia was lower than the WHO-declared standard threshold (85%). This study also revealed that the cure rate of TB among HIV coinfected patients was much lower than usual expectations and targets. Furthermore, the odds of unsuccessful TB treatment among patients living with HIV were greater than that among non-reactive patients. Thus, HIV coinfection has a great negative impact on TB treatment success, and it will be difficult to achieve the SDGs for TB by 2030. Therefore, important attention and measurements should be taken on coinfected patients, such as early treatment initiation, careful follow-up and management of complications and toxicity.

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Contributors HM and TG developed the protocol and design. HM, TG and AN were involved in quality assessment. HM, TG, AN, GD, MD, GTM, YDT and TMK were involved in the selection of the study, data extraction, statistical analysis, development of the initial drafts of the manuscript, preparation and revision of subsequent drafts, as well as preparation of the final draft of the manuscript. All the authors have read and approved the final draft of the manuscript. Overall, HM is the guarantor and takes full responsibility for the work and/or the conduct of the study.

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