



The Impact of HIV Status on Anti-tuberculous Therapy: A Systematic Review and Meta-Analysis

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Abstract

Background: The global health challenge of tuberculosis (TB) and human immunodeficiency virus (HIV) co-infection demands an in-depth evaluation of TB treatment's safety and efficacy in individuals, regardless of their HIV status.

Objective: This study critically examines the literature to determine the effectiveness of anti-TB therapies among HIV-positive and HIV-negative patients.

Methods: We conducted a systematic review of the literature by searching databases such as Web of Science, SCOPUS, PubMed, and the Cochrane Central Register up to 30 August 2023. Using RAYYAN.AI for initial screening and the R programming language for meta-analysis, we extracted and analysed outcome data, focusing on treatment success and mortality rates. The analysis included heterogeneity assessment via the I^2 test and bias risk evaluation via the Newcastle-Ottawa Scale.

Results: Our meta-analysis incorporated five observational studies with a total of 28,607 TB patients under treatment. Findings revealed that HIV-positive patients had a significantly lower likelihood of TB treatment success and a higher risk of mortality compared to HIV-negative patients, indicating the detrimental impact of HIV on TB treatment outcomes.

Conclusion: The study highlights a significant association between HIV-positive status and adverse TB treatment outcomes, emphasising the urgent need for targeted interventions to enhance treatment success and reduce mortality among HIV-positive TB patients.

Keywords: Anti-tuberculosis drugs, HIV, Safety, Effectiveness, Meta-analysis.

Introduction

Tuberculosis (TB) and human immunodeficiency virus (HIV) co-infections present a complex and challenging scenario for healthcare systems worldwide, particularly affecting people living with HIV (PLHIV).^{1,2} TB remains a leading cause of death among PLHIV, especially in regions with high HIV prevalence such as sub-Saharan Africa and Southeast Asia, where co-infection rates are significantly elevated.^{3,4,5} In 2022, the World Health Organization (WHO) estimated that 1.5 million people died of TB, a substantial proportion of whom were co-infected with HIV.⁶

HIV significantly increases the risk of TB reactivation in individuals with latent TB infections and accelerates the progression of both diseases. The weakened immune system caused by HIV predisposes patients to TB and complicates the treatment of co-infected individuals, as TB treatment can accelerate the progression of HIV, resulting in more severe complications, including AIDS-related outcomes.^{7,8,9,10} Moreover, PLHIV are at greater risk for multidrug-resistant TB (MDR-TB), complicating treatment further.¹¹

Management of TB-HIV co-infections requires addressing overlapping toxicities between TB and HIV treatments, which are particularly relevant for antiretroviral therapy (ART) and anti-tuberculous drug regimens.^{12,13} These overlapping toxicities can lead to treatment interruptions or modifications, which reduce treatment efficacy and increase the likelihood of drug resistance.^{12,13} Furthermore, adherence to treatment regimens is a major challenge for PLHIV, particularly in advanced stages of HIV, where patients may face multiple complications and side effects from dual therapy.¹⁴ This necessitates specialised treatment strategies and close monitoring.

The development and evaluation of vaccines and therapies for TB are key to reducing the burden of co-infection. However, differences in immune responses between PLHIV and HIV-negative individuals must be considered to optimise treatment outcomes.^{15,16} Understanding the comparative safety and efficacy of anti-tuberculosis therapies between HIV-positive and HIV-negative patients is crucial for guiding clinical decisions and public health strategies aimed at controlling TB-HIV co-infections.^{17,18}



The emergence of drug-resistant TB strains, combined with drug interactions between TB and HIV medications, underscores the urgent need for effective co-infection management strategies.^{19,20,21,22} It is essential to develop interventions that address the unique challenges faced by this vulnerable population.

In this review, we aim to critically assess the impact of HIV status on the safety and efficacy of anti-tuberculosis therapy in PLHIV. By analysing available data, we hope to inform clinical decision-making, guide policy development, and contribute to improving outcomes for PLHIV with TB, ultimately supporting efforts to reduce the global burden of both TB and HIV/AIDS.

Research methods and design

Protocol Registration

The protocol for this review was registered in PROSPERO under the ID: CRD42023463986. We performed a systematic review and meta-analysis following the guidelines set out by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement and adhering to the methodology outlined in the Cochrane Handbook of Systematic Reviews and Meta-Analysis.^{23,24}

Amendments to the Protocol: Since the initial protocol registration, substantial amendments have been made, including a modification to the research question. These changes were introduced to refine the scope and to address emerging evidence related to TB and HIV co-infection. Although the searches were conducted in August 2023, the search strategy has been reassessed to ensure that it aligns with the updated research question and remains relevant to the aims of this study.

Data Sources and Search Strategy

We systematically searched the Web of Science, SCOPUS, PubMed (MEDLINE), and Cochrane Central Register of Controlled Trials (CENTRAL) databases from their inception until 30 August 2023. The full search strategy and search results are detailed in **Table 1**.

Eligibility Criteria

Primary research articles were included based on the following (PICO) criteria: Population (P): Patients with tuberculosis infection confirmed by bacteriological studies using sputum examination and sputum cultures. Intervention (I): Standard anti-tuberculosis therapy, regardless of the regimen or treatment duration. Comparator (C): HIV-positive patients compared to HIV-negative patients. Outcomes (O): The primary outcome was treatment success rate, while the secondary outcome was all-cause mortality during treatment.

We excluded secondary research articles (systematic reviews, meta-analyses, editorials), case reports, case series, animal studies, and any primary research articles that did not report at least one of our outcomes of interest.

Definition of Outcomes

Primary Outcome: Treatment success rate, defined as the proportion of HIV-positive patients who achieved complete resolution of tuberculosis following anti-tuberculosis therapy, reflecting the effectiveness of the treatment.

Secondary Outcome: All-cause mortality during treatment, defined as the rate of death from any cause among HIV-positive patients undergoing anti-tuberculosis treatment, highlighting the potential risks in immunocompromised individuals. In our study, all-cause mortality during anti-tuberculosis treatment was used to evaluate the overall treatment outcome in HIV-positive patients, rather than as a direct measure of treatment safety. This reflects the broader impact of HIV on patient vulnerability to mortality during treatment, and the importance of reducing mortality in this high-risk population.

Study Selection

Search results were uploaded into RAYYAN.AI, where duplicates were removed.²⁵ The remaining records underwent independent screening by four authors (A.O., E.A.B., A.R., M.E.Q.), with a fifth author (K.E.) resolving any conflicts. The screening process included an initial review of titles and abstracts to assess relevance, followed by a full-text screening to confirm eligibility based on the inclusion criteria.

Relevance of Study Selection: Given the modifications to the research question, all previously selected studies were re-evaluated to ensure alignment with the revised focus of the systematic review.

Data Extraction



Four authors (A.O., E.A.B., A.R., and M.E.Q.) independently extracted data and recorded the information in a standardised Excel sheet. Extracted data included the following:

- Author name, year of publication, study design, and location.
- Total number of participants, group size, participants' demographics (age, sex).
- Methods of tuberculosis and HIV diagnosis, anti-tuberculosis treatment regimens and duration.
- Follow-up duration and results for the primary and secondary outcomes.

Risk of Bias Assessment

The risk of bias was evaluated using the Newcastle-Ottawa Scale (NOS)²⁶ by two independent reviewers (A.O. and E.B.), focusing on three domains: selection, comparability, and outcomes. Studies were rated as follows:

- Good quality: ≥ 7 stars.
- Fair quality: 2 to 6 stars.
- Poor quality: ≤ 1 star.

Statistical Analysis

Statistical analyses were performed using the R statistical programming language and the meta package. We calculated odds ratios (ORs), risk differences (RDs), and corresponding 95% confidence intervals (CIs) for all outcomes.^{27,28} Heterogeneity was assessed using the I² test, with values above 60% indicating substantial heterogeneity. When significant heterogeneity was present, a random-effects model was applied to the meta-analysis. A p-value of less than 0.05 was considered statistically significant.

Amendments to Statistical Analysis: The statistical methods were applied consistently throughout, despite the protocol amendments. This approach ensured that the results of the meta-analysis remained robust and aligned with the revised research question.

Results

Search Results and Study Selection

The initial search identified 5775 articles from PubMed, Cochrane, SCOPUS, and Web of Science (WOS) databases. After removing 453 duplicates and screening 5319 titles and abstracts for relevance, 353 full-text articles were assessed for eligibility. Of these, 348 were excluded due to reasons such as study design not meeting the criteria, lack of relevant outcome data, and non-compliance with the inclusion criteria. As a result, five studies met the inclusion criteria for the systematic review and meta-analysis. The study selection process is detailed in the PRISMA flow diagram (Figure 1).²⁹

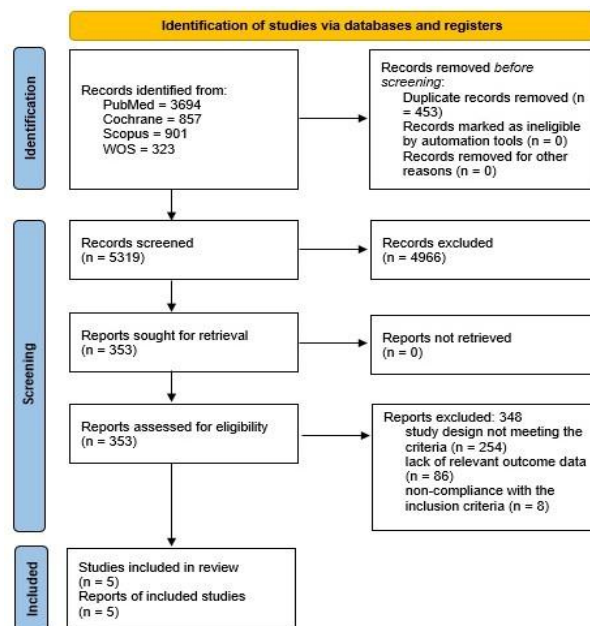


Figure 1. PRISMA flow chart of the studies screened, reviewed, and included.



Characteristics of Included Studies and Participants

The five observational studies included a total of 28,607 patients undergoing anti-tuberculosis therapy. Among these, 8365 patients were HIV-positive, and 20,242 were HIV-negative. The included studies varied in terms of geographical region, patient age, TB diagnosis methods, and treatment regimens. A summary of the baseline characteristics is provided in **Table 2**.

Risk of Bias Assessment

The quality of the included studies was assessed using the Newcastle-Ottawa Scale (NOS). Four studies were rated as "good" quality, while one was rated as "fair" quality due to limited follow-up duration (**Table 3**).²⁶

Primary Outcome: Treatment Success Rate

Four studies, comprising 27,815 patients, reported on treatment success rates. HIV-positive patients had significantly lower odds of achieving treatment success compared to HIV-negative patients (OR, 0.62; 95% CI [0.58, 0.67]; $P < 0.01$) (**Figure 2**). Additionally, the pooled risk difference was -0.07 (95% CI [-0.08, -0.06]; $P < 0.01$), indicating that HIV-positive patients had a lower success rate in anti-tuberculosis therapy (**Figure 3**).

Note on Treatment Success Definitions: The definition of treatment success varied between studies, with some relying on microbiological cure, while others used clinical resolution of symptoms. This variation could introduce some heterogeneity into the analysis.

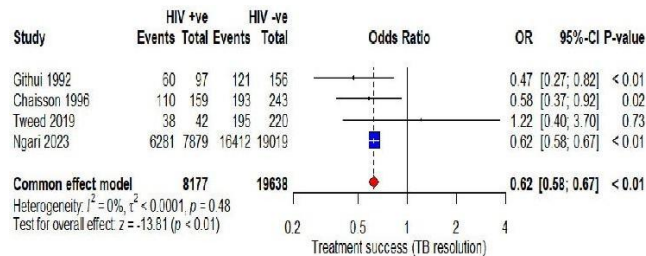


Figure 2. Forest plot for the outcome of tuberculosis treatment success rate.

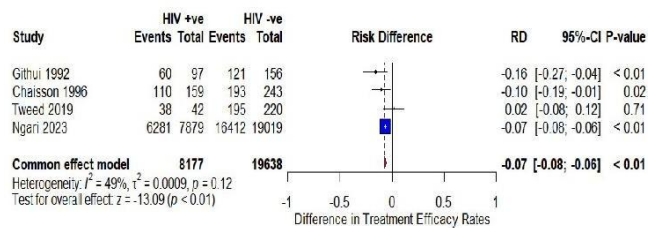


Figure 3. Forest plot of risk differences for tuberculosis treatment success rate

Secondary Outcome: Mortality During Anti-Tuberculosis Treatment

Four studies, comprising 28,209 patients, reported on mortality during anti-tuberculosis treatment. HIV-positive patients had significantly higher odds of mortality compared to HIV-negative patients (OR, 5.14; 95% CI [2.38, 11.12]; $P < 0.01$) (**Figure 4**). The analysis showed high heterogeneity ($I^2 = 90\%$, $P < 0.01$), which might be due to differences in the stages of HIV infection or variations in ART coverage across the included studies. A risk difference analysis also revealed a pooled risk difference of 0.14 (95% CI [0.05, 0.23]; $P < 0.01$) (**Figure 5**), further confirming the association between HIV-positive status and increased mortality risk during treatment.

Considerations for Population Differences and Bias

The included studies exhibited significant variability in key characteristics such as ART coverage, treatment duration, and stage of HIV infection. Additionally, 95% of the patient population came from a single study (Ngari et al., 2023), which may have introduced bias into the overall results.

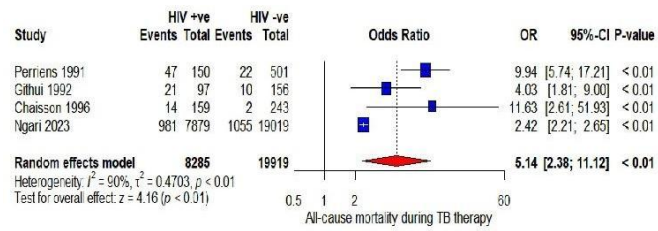


Figure 4. Forest plot for the outcome of all-cause mortality during tuberculosis treatment.

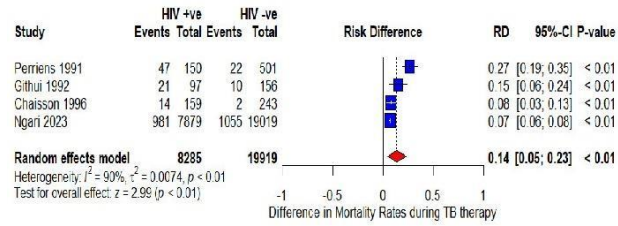


Figure 5. Forest plot of risk differences for mortality rates during tuberculosis treatment



Database	Search strategy	Results	Search date
PubMed	((tuberculosis[Title/Abstract] OR mycobacterium tuberculosis[Title/Abstract] OR TB[Title/Abstract])) AND ((Acquired Immunodeficiency Syndrome[Title/Abstract] OR AIDS[Title/Abstract] OR HIV[Title/Abstract])) AND ((vaccine[Title/Abstract] OR vaccination[Title/Abstract] OR BCG[Title/Abstract] OR Bacille Calmette-Guérin[Title/Abstract] OR M72/AS01[Title/Abstract] OR chemoprophylaxis[Title/Abstract] OR isoniazid[Title/Abstract] OR pyrazinamide[Title/Abstract] OR rifampin[Title/Abstract] OR ethambutol[Title/Abstract]))	3694	30/8/2023
Cochrane Library	((tuberculosis OR mycobacterium tuberculosis OR TB) AND (Acquired Immunodeficiency Syndrome OR AIDS OR HIV) AND (vaccine OR vaccination OR BCG OR Bacille Calmette-Guérin OR M72/AS01 OR chemoprophylaxis OR isoniazid OR pyrazinamide OR rifampin OR ethambutol))	857	30/8/2023
Scopus	(TITLE-ABS-KEY (tuberculosis OR (mycobacterium AND tuberculosis) OR tb) AND TITLE-ABS-KEY ((acquired AND immunodeficiency AND syndrome) OR aids OR hiv) AND TITLE-ABS-KEY (vaccine OR vaccination OR bcg OR (bacille AND calmette-guérin) OR m72/as01 OR chemoprophylaxis OR isoniazid OR pyrazinamide OR rifampin OR ethambutol))	901	30/8/2023
Web of Science	(tuberculosis OR "mycobacterium tuberculosis" OR TB (Title) AND "Acquired Immunodeficiency Syndrome" OR AIDS OR HIV (Title) AND vaccine OR vaccination OR BCG OR "Bacille Calmette-Guérin" OR "M72/AS01" OR chemoprophylaxis OR isoniazid OR pyrazinamide OR rifampin OR ethambutol (Title))	323	30/8/2023

Table 1. Data bases search approach



Table 2. Baseline characteristics of the included studies

Study ID	Study design	Region	Groups	No. of participants	Age	Male, n	TB diagnosis	HIV testing	Intervention regimen	Duration of treatment	Definition of therapy failure	Follow up
Perriens 1991	Prospective observational study	Democratic Republic of the Congo	HIV +ve	170	31.8 (8.4) ^a	448	Sputum microscopy of freshly-expectorated sputum sample and sputum cultures on Lowenstein-Jensen medium	HIV serology was done using an ELISA test and confirmed by indirect immunofluorescence	Daily IM streptomycin (1 gm), oral thiacetazone (150 mg), and oral isoniazid (300 mg) for 2 months followed by oral thiacetazone (150 mg), and oral isoniazid (300 mg) for 10 months	12 months	Smear and culture positive for M. tuberculosis after 12 months from starting the chemotherapy	1 year
			HIV -ve	597	29.8 (10.7) ^a							
Githui 1992	Prospective observational study	Kenya	HIV +ve	97	NA	NA	Acid-fast bacilli were detected on direct smear by fluorescence microscopy or by Ziehl-Neelsen staining and cultures on Lowenstein-Jensen media	All serum samples were tested by two enzyme-linked immunosorbent assay (ELISA) tests	Daily oral thiacetazone (150 mg) and oral isoniazid (300 mg) for 12 months supplemented by daily IM streptomycin (1 gm) in the first month, or a combined preparation of rifampicin, isoniazid, and pyrazinamide for 2 months with streptomycin for the first month only, and thiazina from the third to the eighth month inclusive	12 months	At least 2 specimens taken after 6 months of therapy and at least 2 weeks apart contained at least 10 colonies each	1 year
			HIV -ve	156								
Chaisson 1996	Prospective observational study	Haiti	HIV +ve	177	30 ^b	99	Sputum microscopy of freshly-expectorated sputum sample and sputum cultures on Ogawa media	Serologic testing was performed with an enzyme-linked immunosorbent assay	Isoniazid and rifampin were given for 26 weeks, and pyrazinamide with ethambutol were given for the first 8 wk. Drug doses were	6 months	Consistently positive sputum smears and cultures or a lack of resolution of symptoms	2.5 years
			HIV -ve	250	29 ^b	107						3 years



Author	Study Design	Country	HIV Status	n	Age Group	n	Diagnosis	Assay	Treatment	Duration	Outcome	Follow-up
Tweed 2019	Prospective observational study	UK	HIV +ve	42	<25: 4, 25-30: 17, >35: 21	23	NA	NA	2 months of isoniazid, rifampicin, pyrazinamide, and ethambutol followed by 4 months of isoniazid and rifampicin alone	6 months	Failing to achieve microbiological cure at the end of 18 months	1.5 years
			HIV -ve	220	<25: 40, 25-30: 84, >35: 96	154						
Ngari 2023	Retrospective observational study	Kenya	HIV +ve	7879	18-30: 1700, 31-40: 2974, 41-50: 2125, >50: 1080	3930	TB was diagnosed bacteriologically using smear microscopy, culture or molecular TB diagnostics (Xpert MTB/RIF) or clinically by a medical practitioner based on clinical symptoms, X-ray abnormalities, and suggestive histology	NA	Rifampicin, Isoniazid, Pyrazinamide and Ethambutol for 2 months followed by Rifampicin and Isoniazid for 4 months	6 months	Remaining smear-positive after 5 months of treatment	9 years
			HIV -ve	19019	18-30: 6853, 31-40: 4629, 41-50: 7280, >50: 4757	13253						

^a data is in mean (SD) form ^b data is in median form Abbreviations: *TB* Tuberculosis, *HIV* Human Aids Virus, *ELISA* Enzyme Linked Immuno-sorbent Assay, *IM* intra muscular, *NA* not available.



Table 3. Results of quality assessment by Newcastle-Ottawa Scale for the included studies

Study	Selection			Demonstration that outcome of interest was not present at start of study	Comparability		Outcome		Total score
	Representativeness of exposed cohort	Selection of non exposed cohort	Ascertainment of exposure		Control for important or additional factors	Assessment of outcome	Follow-up long enough for	Adequacy of follow up of cohorts	
Perriens 1991	*	*	*	*		*	*	*	7
Githui 1992	*	*	*	*		*	*	*	7
Chaisson 1996	*	*	*	*			*	*	6
Tweed 2019	*	*	*	*	**	*	*	*	9
Ngari 2023	*	*	*	*	*	*	*	*	8

The NOS included 3 categorical criteria with a maximum score of 9 points. The quality of each study was rated using the following scoring algorithms: ≥ 7 points were considered as “good”, 2 to 6 points were considered as “fair”, and ≤ 1 point was considered as “poor” quality.



Discussion

Tuberculosis (TB) remains one of the leading global public health challenges, particularly in regions with low- and middle-income economies where access to healthcare services is often constrained¹². Despite advancements in diagnosis and treatment, TB continues to claim millions of lives each year, with the World Health Organization (WHO) reporting an estimated 10 million new cases and 1.5 million deaths annually³³. The rise of drug-resistant strains such as multidrug-resistant TB (MDR-TB) and extensively drug-resistant TB (XDR-TB) further complicates global control efforts, as these strains are harder to treat and result in poorer outcomes³⁴. The challenges of co-infection, drug resistance, and evolving diagnostic tools require innovative approaches to TB control^{30,31}. Innovative strategies for prevention, diagnosis, and treatment, including research on point-of-care diagnostics and novel treatment regimens, remain critical in addressing the evolving nature of TB^{32,35}.

The intersection of TB and HIV exacerbates the global burden of both diseases. HIV weakens the immune system, making individuals more susceptible to TB infection and significantly increasing the risk of TB reactivation³⁶. TB is a leading cause of mortality among people living with HIV, contributing substantially to the global burden of both diseases^{37,38}. In turn, TB accelerates the progression of HIV by inducing systemic inflammation and immune activation, further compromising immune function⁵. The symbiotic relationship between TB and HIV, therefore, poses a significant challenge to global health and underscores the importance of integrated care models for co-infected individuals.

Our systematic review is the first to systematically investigate the impact of HIV status on the clinical outcomes of standard anti-tuberculosis treatments in patients with active TB. The pooled results from our analysis demonstrated that HIV-positive patients had significantly lower odds of achieving treatment success (OR, 0.62; 95% CI [0.58, 0.67]; $p < 0.01$) and faced a higher risk of mortality during TB treatment (OR, 5.14; 95% CI [2.38, 11.12]; $p < 0.01$). These findings highlight the challenges that HIV-positive individuals face in achieving favourable TB treatment outcomes and reinforce the need for more robust, integrated approaches to TB and HIV care^{3,4,6}.

The variability in outcomes observed in the analysis, including the substantial heterogeneity in mortality results ($i^2 = 90\%$), suggests that patient characteristics such as antiretroviral therapy (ART) coverage, stage of HIV infection, and treatment regimens could influence outcomes. For example, studies have shown that ART can significantly reduce mortality in HIV-positive TB patients by enhancing immune function and improving overall treatment success^{11,39}. However, the lack of consistent reporting on ART usage across the studies in this review limits our ability to fully understand its impact. One study did exclude patients on ART, but the absence of detailed information on ART use in the remaining studies presents a notable gap in the literature. This lack of reporting may have confounded the results and reduced the ability to draw firm conclusions about the interaction between ART and TB treatment outcomes^{12,13}.

Another limitation of this review is the reliance on observational studies, which, while valuable for exploring associations in real-world settings, are inherently susceptible to biases such as confounding and selection bias²⁶. Unlike randomised controlled trials (RCTs), observational studies lack randomisation and control over confounding factors, making it more difficult to establish causality. The dominance of one large study (Ngari et al., 2023), which accounted for 95% of the patient population in this review, also raises concerns about potential bias. Future meta-analyses should apply weighting or conduct sensitivity analyses to ensure that the pooled results are not disproportionately influenced by single, large studies^{26,29}.

Beyond these methodological limitations, the review also highlights important gaps in the literature regarding specific populations. For example, there is a lack of research focused on vulnerable groups such as children, pregnant individuals, and those with drug-resistant TB. These populations present unique challenges, such as differing pharmacokinetics, treatment tolerability, and disease manifestations, that require tailored diagnostic and treatment approaches. Future research must prioritise the inclusion of these populations to inform evidence-based guidelines that better address their needs^{20,21,34}.

Recent studies have made strides in the development of new TB vaccines that could provide long-term protection to both HIV-positive and HIV-negative individuals. For example, the study by Kumarasamy et al.⁴⁰ reported promising safety and immunogenicity results for the M72/AS01E candidate TB vaccine in HIV-positive and HIV-negative populations, marking an important step forward in TB prevention strategies. These advancements underscore the need for ongoing research into novel therapeutic and preventative interventions for TB, particularly in the context of HIV co-infection.

Despite these limitations, our review represents an important contribution to the existing literature by synthesising evidence on the impact of HIV status on TB treatment outcomes. The large sample size, which includes a diverse range of observational studies from different geographical regions, enhances the generalisability of our findings and provides valuable insights into the complex interplay between TB and HIV¹⁸. However, further research is needed to explore the impact of ART on TB treatment outcomes, as well as to investigate the specific challenges faced by vulnerable populations such as children and pregnant individuals.

Moving forward, it is crucial to address these gaps in the literature and prioritise the development of integrated care models that account for the unique needs of HIV-positive individuals. By advancing our understanding of the clinical outcomes of TB treatment in the context of HIV co-infection, we can develop more effective strategies for reducing mortality and improving treatment success



rates^{6,7,14}. Furthermore, the development of new vaccines and treatment regimens, particularly for MDR-TB and XDR-TB, remains critical to mitigating the global burden of these diseases¹⁹.

Conclusion

In conclusion, our systematic review and meta-analysis highlight the clinical challenges of anti-tuberculosis treatment in HIV-positive individuals, revealing a significant association between HIV-positive status and reduced treatment success rates, alongside increased mortality during TB treatment. These findings underscore the heightened vulnerability of HIV-positive individuals to TB and emphasise the critical need for targeted interventions to improve outcomes in this population.

The prevalent omission of antiretroviral therapy (ART) usage data across the reviewed studies presents a substantial barrier, hindering the clear interpretation of treatment outcomes. Future research should prioritise the meticulous documentation and analysis of ART usage in conjunction with TB treatment, to better understand how these interventions interact.

Further research is essential to address the complexities of TB-HIV co-infection. By advancing our understanding through collaborative global research and focusing on specific areas such as ART integration and the treatment of vulnerable populations, we can work towards reducing the morbidity and mortality associated with this dual epidemic and improving health outcomes worldwide.

Statements and declarations

Authors contribution

AO: Led the project design, manuscript writing, and data interpretation, contributing significantly across all stages of the review.

Y.A: contributed significantly in analyzing the study's results for insightful conclusions and selecting key references to enrich and support the manuscript's arguments.

A.R: Focused on the systematic literature search and initial screening of articles, ensuring a comprehensive and rigorous selection process.

M.EQ: Was pivotal in managing the data extraction process and ensuring the integrity of the data used in our analysis.

K.E: Assisted in selecting articles for inclusion and played a key role in manuscript revision for clarity and coherence.

EA.B: Handled the statistical analysis and revised the articles for accuracy, also assisting in manuscript refinement.

All authors approved the final manuscript for submission.

Conflict of interest

The authors of this review declare no conflict of interest.

Funding

This research was conducted with the support of the CNRST under the 'PhD-Associate Scholar-ship – PASS' program.

Ethical approval

Not applicable.

Availability of data and material

Not applicable.

Acknowledgment

None.

References

1. Getahun H, Gunneberg C, Granich R, Nunn P. HIV Infection–Associated Tuberculosis: The Epidemiology and the Response. *Clin Infect Dis*. 2010 May;50(suppl_3):S207. doi: 10.1086/651492.
2. Corbett EL, Watt CJ, Walker N, Maher D, Williams BG, Raviglione MC, et al. The Growing Burden of Tuberculosis. *Arch Intern Med*. 2003 May;163(9):1009–1021. doi: 10.1001/archinte.163.9.1009.
3. Bruchfeld J, Correia-Neves M, Källenius G. Tuberculosis and HIV Coinfection. *Cold Spring Harb Perspect Med*. 2015 Jul;5(7). doi: 10.1101/cshperspect.a017871.
4. Lelisho ME, Gelaw YA, Teferi M, Tessema GA, Yimer G, Gashu Z, et al. Survival rate and predictors of mortality among TB/HIV co-infected adult patients: retrospective cohort study. *Sci Rep*. 2022 Nov;12(1):18360. doi: 10.1038/s41598-022-23316-4.
5. Walker NF, Meintjes G, Wilkinson RJ. HIV-1 and the immune response to TB. *Future Virol*. 2013 Jan;8(1):57–80. doi: 10.2217/fvl.12.123.



6. Ndiaye BP, Thienemann F, Ota M, Landry B, Camara M, Dieye S, et al. Safety, immunogenicity, and efficacy of the candidate tuberculosis vaccine MVA85A in healthy adults infected with HIV-1: a randomised, placebo-controlled, phase 2 trial. *Lancet Respir Med*. 2015 Mar;3(3):190–200. doi: 10.1016/S2213-2600(15)00037-5.
7. Minassian AM, Rowland R, Beveridge NE, Poulton ID, Satti I, Harris SA, et al. A Phase I study evaluating the safety and immunogenicity of MVA85A, a candidate TB vaccine, in HIV-infected adults. *BMJ Open*. 2011 Nov;1(2). doi: 10.1136/bmjopen-2011-000223.
8. Whalen C, Horsburgh CR, Hom D, Lahart C, Simberkoff M, Ellner J. Accelerated course of human immunodeficiency virus infection after tuberculosis. *Am J Respir Crit Care Med*. 1995 Jan;151(1):129–135. doi: 10.1164/ajrccm.151.1.7812542.
9. Sonnenberg P, Glynn JR, Fielding K, Murray J, Godfrey-Faussett P, Shearer S. How Soon after Infection with HIV Does the Risk of Tuberculosis Start to Increase? A Retrospective Cohort Study in South African Gold Miners. *J Infect Dis*. 2005 Jan;191(2):150–158. doi: 10.1086/426827.
10. Tornheim JA, Dooley KE. Tuberculosis Associated with HIV Infection. *Microbiol Spectr*. 2017 Feb;5(1). doi: 10.1128/microbiolspec.TNMI7-0028-2016.
11. Meintjes G, Brust JCM, Nuttall J, Maartens G. Management of active tuberculosis in adults with HIV. *Lancet HIV*. 2019 Jul;6(7):e474. doi: 10.1016/S2352-3018(19)30154-7.
12. Manosuthi W, Wiboonchutikul S, Sungkanuparph S. Integrated therapy for HIV and tuberculosis. *AIDS Res Ther*. 2016 Dec;13(1):22. doi: 10.1186/s12981-016-0106-y.
13. Esmail A, Sabur NF, Okpechi I, Dheda K. Management of drug-resistant tuberculosis in special sub-populations including those with HIV co-infection, pregnancy, diabetes, organ-specific dysfunction, and in the critically ill. *J Thorac Dis*. 2018 May;10(5):3102–3118. doi: 10.21037/jtd.2018.05.11.
14. Cobelens F, Sculier D, McKinney B, van Wyk S, Jaramillo E, Migliori GB, et al. Accelerating research and development of new vaccines against tuberculosis: a global roadmap. *Lancet Infect Dis*. 2022 Apr;22(4):e120. doi: 10.1016/S1473-3099(21)00810-0.
15. Nachega JB, Kapata N, Sam-Agudu NA, Masekela R, Declodt EH, Ntakwinja M, et al. Minimizing the impact of the triple burden of COVID-19, tuberculosis and HIV on health services in sub-Saharan Africa. *Int J Infect Dis*. 2021 Dec;113(Suppl 1):S21. doi: 10.1016/j.ijid.2021.03.038.
16. Korencak M, Byrne M, Richter E, Schultz BT, Juszczak P, Edgil D, et al. Effect of HIV infection and antiretroviral therapy on immune cellular functions. *JCI Insight*. 2019 Jun;4(12). doi: 10.1172/jci.insight.126675.
17. Nyström S, Govender M, Yap SH, Kamarulzaman A, Rajasuriar R, Larsson M. HIV-Infected Individuals on ART With Impaired Immune Recovery Have Altered Plasma Metabolite Profiles. *Open Forum Infect Dis*. 2021 Jul;8(7). doi: 10.1093/ofid/ofab288.
18. Nuttall JJC, Eley BS. BCG Vaccination in HIV-Infected Children. *Tuberc Res Treat*. 2011;2011:712736. doi: 10.1155/2011/712736.
19. Sharan R, Kaushal D. Vaccine strategies for the Mtb/HIV copandemic. *NPJ Vaccines*. 2020 Oct;5(1):95. doi: 10.1038/s41541-020-00245-9.
20. Vila Torres SG, Fullmer J, Berkowitz L. A Case of Multidrug-Resistant (MDR) Tuberculosis and HIV Co-Infection. *Cureus*. 2023 Apr. doi: 10.7759/cureus.37033.
21. Sultana ZZ, Hasan MT, Rahman F, Hossain MG. HIV infection and multidrug resistant tuberculosis: a systematic review and meta-analysis. *BMC Infect Dis*. 2021 Dec;21(1):51. doi: 10.1186/s12879-020-05749-2.
22. Naidoo K, Theron G, Rangaka MX, Chihota VN, Vaughan L, Brey ZO, et al. Recurrent tuberculosis among HIV-coinfected patients: a case series from KwaZulu-Natal. *Infect Drug Resist*. 2018 Sep;11:1413–1421. doi: 10.2147/IDR.S150644.
23. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ*. 2021 Mar;372. doi: 10.1136/bmj.n71.
24. Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA, editors. *Cochrane Handbook for Systematic Reviews of Interventions* version 6.4 (updated August 2023). Cochrane; 2023.
25. Ouzzani M, Hammady H, Fedorowicz Z, Elmagarmid A. Rayyan—a web and mobile app for systematic reviews. *Syst Rev*. 2016 Dec;5(1):210. doi: 10.1186/s13643-016-0384-4.
26. Lo CKL, Mertz D, Loeb M. Newcastle-Ottawa Scale: comparing reviewers' to authors' assessments. *BMC Med Res Methodol*. 2014 Dec;14(1):45. doi: 10.1186/1471-2288-14-45.
27. R Core Team. *R: A Language and Environment for Statistical Computing*. Vienna, Austria: R Foundation for Statistical Computing; 2022.
28. Balduzzi S, Rücker G, Schwarzer G. How to perform a meta-analysis with R: a practical tutorial. *Evid Based Ment Health*. 2019;22(4):153–160. doi: 10.1136/ebmental-2019-300117.
29. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. PRISMA 2020 explanation and elaboration: updated guidance and exemplars for reporting systematic reviews. *BMJ*. 2021 Mar;372. doi: 10.1136/bmj.n160.
30. Heidary M, Goudarzi M, Eslami G, Soleimani S, Khoshnood S, Rezaei S. Tuberculosis challenges: Resistance, co-infection, diagnosis, and treatment. *Eur J Microbiol Immunol (Bp)*. 2022 Apr;12(1):1–17. doi: 10.1556/1886.2021.00021.
31. Shah HD, Shah N, Doshi P, Vyas H, Singh P, Prajapati A. Gaps and interventions across the diagnostic care cascade of TB patients at the level of patient, community and health system: A qualitative review of the literature. *Trop Med Infect Dis*. 2022 Jul;7(7):136. doi: 10.3390/tropicalmed7070136.
32. Nahid P. Advances in the Diagnosis and Treatment of Tuberculosis. *Proc Am Thorac Soc*. 2006 Mar;3(1):103–110. doi: 10.1513/pats.200511-119JH.
33. World Health Organization. WHO Global tuberculosis report 2023 | 7 November 2023 [Internet]. Geneva: World Health Organization; 2023 [cited 2024 Feb 20]. Available from: <https://www.who.int/teams/global-tuberculosis-programme/tb-reports>.
34. Chowdhury K, Ahmad R, Sinha S, Dutta S, Haque M. Multidrug-Resistant TB (MDR-TB) and Extensively Drug-Resistant TB (XDR-TB) among Children: Where We Stand Now. *Cureus*. 2023 Feb. doi: 10.7759/cureus.35154.
35. Gill CM, Dolan L, Piggott LM, McLaughlin AM. New developments in tuberculosis diagnosis and treatment. *Breathe (Sheff)*. 2022 Mar;18(1):210149. doi: 10.1183/20734735.0149-2021.
36. Bhatt A, Quazi Syed Z, Singh H. Converging Epidemics: A Narrative Review of Tuberculosis (TB) and Human Immunodeficiency Virus (HIV) Coinfection. *Cureus*. 2023 Oct. doi: 10.7759/cureus.47624.
37. Cheng SL, Wang HC, Yang PC. Paradoxical response during anti-tuberculosis treatment in HIV-negative patients with pulmonary tuberculosis. *Int J Tuberc Lung Dis*. 2007 Dec;11(12):1290–1295.
38. Mollel EW, Todd J, Mahande MJ, Msuya SE. Effect of tuberculosis infection on mortality of HIV-infected patients in Northern Tanzania. *Trop Med Health*. 2020 Dec;48(1):26. doi: 10.1186/s41182-020-00212-z.



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39. Akksilp S, Karnkawinpong O, Wattanaamornkiat W, Viriyakitjar D, Tonklai K, Prempee P. Antiretroviral Therapy during Tuberculosis Treatment and Marked Reduction in Death Rate of HIV-Infected Patients, Thailand. *Emerg Infect Dis.* 2007 Jul;13(7):1001–1007. doi: 10.3201/eid1307.061506.
 40. Kumarasamy N, Vanitha N, Pooranagangadevi N, Swaminathan S, Britto MP, Immuthala S, et al. Long-term safety and immunogenicity of the M72/AS01E candidate tuberculosis vaccine in HIV-positive and -negative Indian adults. *Medicine (Baltimore).* 2018 Nov;97(45). doi: 10.1097/MD.00000000000013120.