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Systematic Review / Meta-analysis

Treatment outcomes of multi-drug resistant tuberculosis patients with or without human immunodeficiency virus co-infection in Africa and Asia: Systematic review and meta-analysis

Violet Dismas Kajogoo [a,*], Julieth Lalashowi [b], Willyhelmina Olomi [b], Mary Gorret Atim [c], Dawit Getachew Assefa [d], Issa Sabi [b]

[a] Mafia District Hospital, Mafia Islands, Tanzania
[b] Mbeya Medical Research Centre, National Institute for Medical Research (NIMR), Tanzania
[c] Department of Public Health, Faculty of Health Sciences, Busitema University, Mbale, Uganda
[d] Department of Nursing, Dilla University College of Health Science and Medicine, Dilla, Ethiopia

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ABSTRACT

Background: Treatment outcomes of multidrug resistant tuberculosis (MDRTB) is a challenge, especially in resource limited settings. The aim of this study was to compare whether Human Immune Virus (HIV) has influence on the treatment outcomes of MDRTB among patients in Africa and Asia.

Methods: Studies were searched from PubMed, Google scholar, African Journals online, EBSCOhost and CENTRAL from year 2000 until January 2021. The participants in the studies were reported of using MDRTB treatment regimen and also included those with HIV. Studies published before 2000 were excluded. Quality of the review was assessed by AMSTEL 2 criteria. The Mantel- Haenszel random effects method was used for the analysis, with risk ratio (RR) as an effect estimate, with 95% confidence interval and using Stata 14 software.

Results: Nine studies were included in the meta-analysis. Treatment success was low in HIV negative participants (RR 0.62, 95% CI 0.58–0.67). However, death was higher in the HIV co-infected participants. (RR 1.35, 95% CI 1.25–1.45). There was no significant difference in treatment failure among patients with or without HIV. (RR 1.08, 95% CI 0.97–1.20). Consistently, no significant difference was found in lost to follow up (LTF) between the two groups (RR 1.07, 95% CI 0.93–1.20).

Conclusion: Treatment success was lower for the MDRTB and HIV co-infections. No significant difference has been found on other outcomes like failure and lost to follow up between patients with HIV co-infected and HIV negative group. The study limitations are that we had only 2 studies representing Asia, and this could have affected the outcome of results. There is need for interventions to improve treatment success in the HIV co-infected group.

Other: The protocol was registered in International prospective register of systematic reviews (PROSPERO), ID: CRD42021247883. There was no funding for the review.

1. Introduction

Tuberculosis (TB) remains the largest infectious disease killer worldwide [1]. Tuberculosis causes an estimated 1.8 million case fatalities yearly, with approximately 80% of these deaths coming from 22 high-burden countries [2]. Multidrug-resistant (MDR)-TB, defined as resistance to rifampicin (RIF) and isoniazid (INH), continues to be a public health problem [3,4]. In 2019 about half a million people developed rifampicin Resistant Tuberculosis (RR-TB) globally, of which 78% had MDR-TB [4]. Of the estimated MDR-TB cases in 2019, 206,030 and 177,099 cases were notified and reported to have started second-line treatment respectively [4] (see Tables 1 and 2, Figs. 3–5).

MDR-TB treatment takes about 9–20 months and often is associated with drug adverse events and hence poor treatment outcomes [5,6]. Although treatment success for MDR-TB has improved globally (up to 57%), poor outcomes defined as high rates of failure, loss to follow-up,

* Corresponding author. Mafia District Hospital, P.O. Box 51 Mafia Island, Tanzania.
E-mail addresses: vkajogoo@rocketmail.com (V.D. Kajogoo), jlalashowi@nimr-mmrc.org (J. Lalashowi), wolomi@nimr-mmrc.org (W. Olomi), atimgoretti@gmail.com (M.G. Atim), dawitgetachewa@gmail.com (D.G. Assefa), isabi@nimr-mmrc.org (I. Sabi).

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Table 1
Characteristics of included studies.

Author and year of publication	Country	Study design	year of data collection	Participants	Participant's status	Follow up	Treatment outcomes (event of total)
Sam S et al., 2017	Cambodia	Cohort	2006–2016	486	TBHIV positive (+ve) = 117 TBHIV negative (-ve) = 369	24 months	Rx success (cure and complete) 65 of 117 309 of 369 Died 32 of 117 45 of 369 Failed 1 of 117 2 of 369 LTF 8 of 117 20 of 369
Mugabo et al., 2015	South Africa	Retrospective cohort	January 2004 and December 31, 2006	363	TBHIV + ve = 95 TBHIV -ve = 268	Final 12 months of treatment	Rx success (cure and complete) 45 of 95 147 of 268 Died 16 of 95 29 of 268 failed 5 of 95 24 of 268 LTF 24 of 95 52 of 268 Transfer out 5 of 95 16 of 268
van der Walt et al., 2016	South Africa	Retrospective Cohort	2000–2008	671	TBHIV + ve = 393 TBHIV -ve = 278	24 months	Rx success (cure and complete) 224 of 393 212 of 278 Died 123 of 393 35 of 278 Failed 8 of 393 2 of 278 LTF 18 of 393 14 of 278
Farley JE et al., 2011	South Africa	Cohort	2000–2004	757	TBHIV + ve = 287 TBHIV -ve = 470	post treatment of the 12–18 months regimen.	Rx success (cure and complete) 115 of 287 233 of 470 Died 101 of 287 76 of 470 Failed 12 of 287 62 of 470 LTF 59 of 287 99 of 470
Satti H et al., 2012	Lesotho	Retrospective cohort	January 2008 and September 2009.	134	TBHIV + ve = 94 TBHIV -ve = 40	Post treatment completion	Rx success (cure and complete) 62 of 94 21 of 40 Died 29 of 94 17 of 40 Failed 1 of 94 0 of 40 LTF 0 of 94 1 of 40 Transfer out 2 of 94 1 of 40 (page 5)
Satti H et al., 2012	Lesotho	Retrospective cohort	July 2007 and January 2011	17	TBHIV + ve = 3 TBHIV -ve = 14	Post treatment completion	Rx success (cure and complete) 12 of 14 3 of 3 Died

(*continued on next page*)

relapse and death are still reported in majority of those who are being initiated on MDR-TB treatment [4,7].A study in South Africa revealed thirty-six (24%) children were cured, 101 (68%) probably cured, 1 (1%) [8]. Another study in Karakalpakstan, Uzbekistan, reported treatment success of 71.9% (92 out of 128) among patients who were treated with a shorter MDRTB regimen [9].

Comorbid conditions including Human immunodeficiency Virus (HIV), are among the factors attributable to poor treatment outcomes in MDRTB patients [7]. HIV co-infected MDRTB has been described by Wells et al. as the "Perfect storm" [10].HIV has been reported to increase the rate of recurrent Tuberculosis among individuals with recently acquired infection [11]. The effects of HIV on treatment outcomes among drug sensitive Tuberculosis cases have been described, and multiple studies have shown that Tb–HIV Co-infection is associated with negative TB-treatment outcomes [12,13]. In MDRTB cases there are limited number of studies that have shown the association of HIV on MDR-TB treatment outcomes even in areas with high MDR-burden as well as those areas with high burden of HIV-Tuberculosis Co-infection like Sub-Saharan Africa [7]. Knowing the association of HIV on MDR-TB treatment outcomes in these areas with high burden of MDR-TB as well as TB-HIV co-infection will enable to strengthen the existing preventive tuberculosis modalities on the HIV infected population.

We performed a systematic review of published, peer-reviewed literature examining the association between HIV and MDRTB treatment outcomes [14–17]. We aimed to examine the relationship between HIV and standardized treatment outcomes including death, default, failure and Treatment success. If HIV influences the treatment outcomes of MDRTB, and how.

2. Methodology

This is a study registered by PROSPERO number CRD42021247883. The study followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [18,19]**Data sources**.

Search was done in PubMed, Medline via PubMed and google scholar for published articles from year 2000 to present date 2021. For PubMed, MeSH terms like " Tuberculosis [Text Word]' OR ″ Multidrug-Resistant Tuberculosis "[MeSH Terms] OR ("Resistant Tuberculosis "[Mesh]), AND ″ People living with HIV "[MeSH Terms] OR People with HIV [Text Word], AND HIV/TB co-infection [Text Word] OR ″ drug resistant tuberculosis/HIV coinfection "[Mesh] OR ″ Multidrug resistant tuberculosis HIV coinfection "[Mesh], AND ″ Treatment outcome "[Text Word] OR ″ Treatment "[Mesh] OR ″ Success "[Mesh] OR ″ Failure "[Mesh] OR ″ loss to follow up "[Mesh] OR ″ default "[Mesh] OR ″ died "[Mesh] AND "Asia"[Text word] OR ″ Pacific region "[Mesh] AND Antiretroviral therapy [All Fields] OR ″ Antiretroviral medication "[Mesh] OR ″ Antiretroviral regimen "[Mesh] OR ″ Antiretroviral administration "[Mesh] OR ″ Highly active antiretroviral "[Mesh] were used.

2.1. Eligibility criteria

2.1.1. Inclusion criteria

2.1.1.1. Population. Cohort studies with participants of any age group, diagnosed with MDR-TB clinically, culture and by drug susceptibility testing.

Table 1 (*continued*)

Author and year of publication	Country	Study design	year of data collection	Participants	Participant's status	Follow up	Treatment outcomes (event of total)
Brust et al., 2017	South Africa	prospective, observational study	2011–2013	191	TB HIV + ve = 138 TB HIV -ve = v 53	Post treatment completion	2 of 14 0 of 3 Treatment success 97 of 138 43 of 53 Died 19 of 138 3 of 53 Failed 5 of 138 1 of 53 LTF 17 of 138 6 of 53
Meressa et al., 2015	Ethiopia	cohort	February 2009 to December 2014	612	TB HIV + ve = 133 TB HIV -ve = 479	post treatment of the 12–18 months regimen	Treatment success 93 of 133 388 of 479 Died 27 of 133 58 of 479 Failed 4 of 113 6 of 479 LTF 9 of 133 6 of 479
Le Hong Van et al., 2020	China	cohort	January 2011 to December 2015	2240	TBHIV + ve = 204 TBHIV -ve = 2036	post treatment of the 12–18 months regimen	Rx success (cure and complete) 105 of 204 1537 of 3 Died 49 of 204 177of 2036 Failed 8 of 204 105 of 2036 LTF 42 of 204 217 of 2036

2.1.1.2. Intervention. Report of using MDR treatment regimen.

2.1.1.3. Comparator. Participants with HIV co infection by using confirmatory tests.

2.1.1.4. Outcomes. Reports of at least 2 treatment outcomes. The outcomes include treatment success, death, failure and LTF.

2.1.1.5. Settings. Published studies from year 2000 in African and Asian settings, of English language.

2.1.1.6. Exclusion criteria. We excluded studies published before year 2000, those without HIV participants, and those with mono resistance.

2.1.1.7. Operational definitions. MDR - MDR was defined as infection with *M. tuberculosis* resistant to isoniazid (INH) and RIF as detected by DST [20].

Treatment outcomes were defined and reported according to WHO definitions for MDR-TB [21].

2.1.1.8. Study selection. Electronic databases were extensively searched, and duplicates were removed using the Mendeley software. Started by screening of titles and abstracts, and those studies that were not relevant were removed. Full texts of the remaining studies were read, and using the inclusion and exclusion criteria's, the remaining studies were removed with justifications. Quality of studies and risk of bias assessments were done. The study selection process was done by two authors independently, and any disagreements was resolved by consensus.

2.1.1.9. Data extraction. A data extraction form was used to extract data from our studies, that was designed in Ms Excel. Data extraction was done by 2 authors independently, and double checked later. When additional data was required, authors of the studies were contacted when necessary. In case of disagreements, it was discussed and a consensus reached. Extracted data included name of the first author and publication year, country of study, design, year of data collection, number of participants, participants statuses in relation to HIV, treatment outcomes.

2.1.1.10. Quality assessment. Our cohort studies were assessed by the Newcastle-Ottawa quality assessment scale [22,23]. For a good study quality, it ought to have the following characteristics: Standardized methods confirming MDR-TB and HIV, sample size that was large enough, multicenter study, appropriate statistical methods that report outcomes, accounting for confounders (demographics, socioeconomic status, previous treatment history), clear methodology for the selection of participants, and representativeness of both MDR-TB and HIV co-infected population.

In addition, use of a valid source for retrieving outcomes and participant information; adequate treatment duration; reporting less than 1/3 missing data at final analysis compared to original population recruited, and proof of ethical review of the study were also considered [23]. Quality of the review was assessed by AMSTEL 2 criteria [24].

2.1.1.11. Data analysis and synthesis. Stata version 14 was used for the meta-analysis. Heterogeneity was calculated using chi square and I square, with a 95% CI. All of our results were binary outcomes, that included treatment success, failure, death, and default/lost to follow up. Studies were included if they contained at least 3 of the outcomes. The Mantel- Haenszel random effects method was used in our analysis, with RR as our effect estimate.

3. Results

We identified 519 studies from different databases, and 11 from other additional sources. (forward and backward search). After removal of duplicates by the Mendeley reference manager, we remained with 174 articles. Titles and articles were screened and we removed 150 articles. The remaining 24 full text articles were read, and we were left with 9 studies for the final review. (Fig. 1). This was done by 2 authors independently. We requested for additional data from 1 author, and the response was positive (see Fig. 2).

3.1. Study characteristics

The studies were published from the year 2000. The total sample size of participants was 5471. We included studies with both the adult and children population, so we didn't have a range of ages for the participants. Participants with MRTB alone were 3996 and those with both MDRTB and HIV co infection was 1475. The study duration for most of our studies was between 18 months and 10 years. Studies conducted in Africa were 7 And those in Asia were 2. Countries include South Africa, Lesotho, Ethiopia, Cambodia and China. All of the studies were cohorts. We were not specific about the type of MDR treatment that was received or the methods of diagnosis.

Table 2
The risk of bias in each particular studies.

	Standardized methods confirming MDR-TB and HIV	large enough sample size	multicenter study	appropriate statistical methods that report outcomes	Accounting for confounders	clear methodology for the selection of participants	Representativeness of both MDR-TB and HIV co-infected population.
Sam S et al 2017 [20]							
Mugabo et al 2015 [16]							
Van der walt et al 2016 [17]							
Farley JE et al 2011 [15]							
Satti H et al 2012 [25]							
Satti H et al 2012 [26]							
Brust et al 2017 [1]							
Meressa et al 2015 [14]							
Van et al 2020 [27]							

Green cells = low risk; Blank cells = unclear risk; Red cells = high risk

Green cells=low risk; Blank cells=unclear risk; Red cells=high risk.

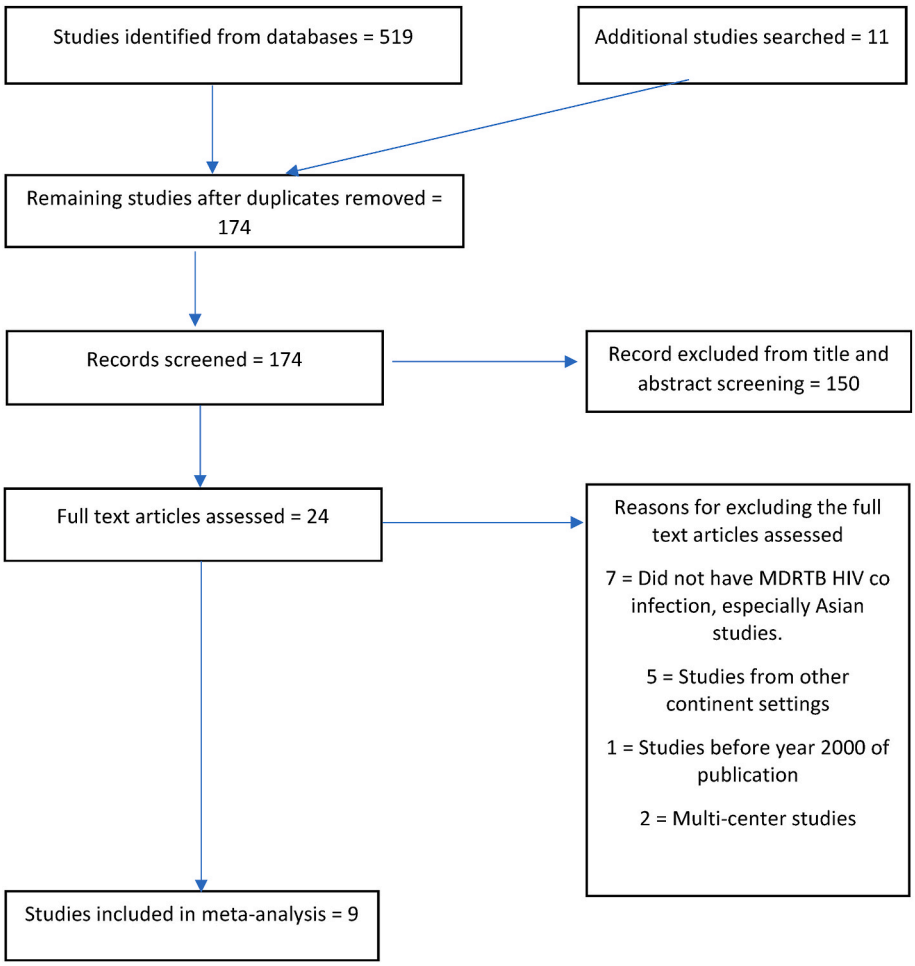

Fig. 1. The PRISMA study selection flow diagram.

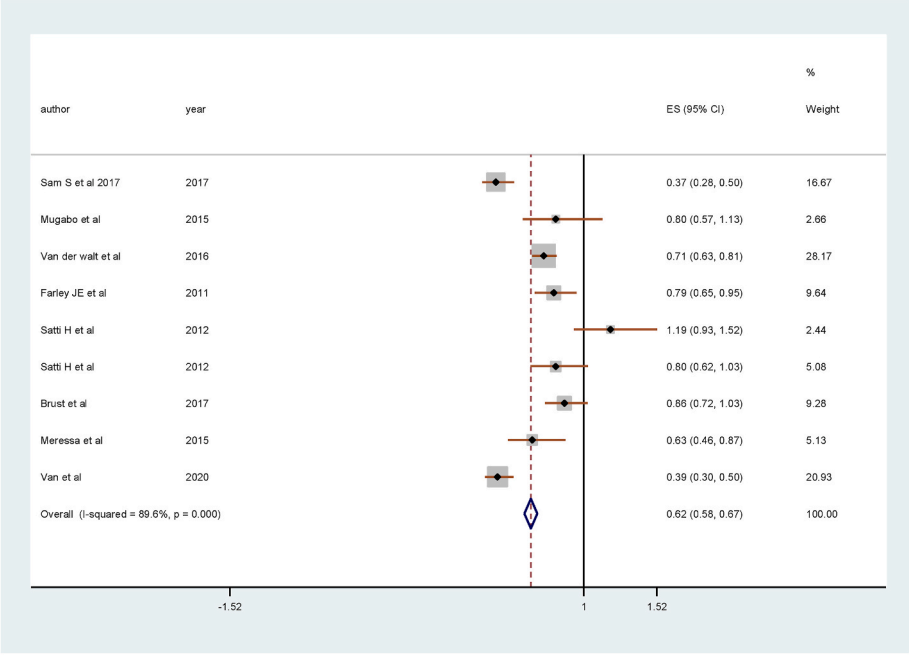

Fig. 2. Treatment success comparison between MDRTB and MDRTB-HIV co-infection.

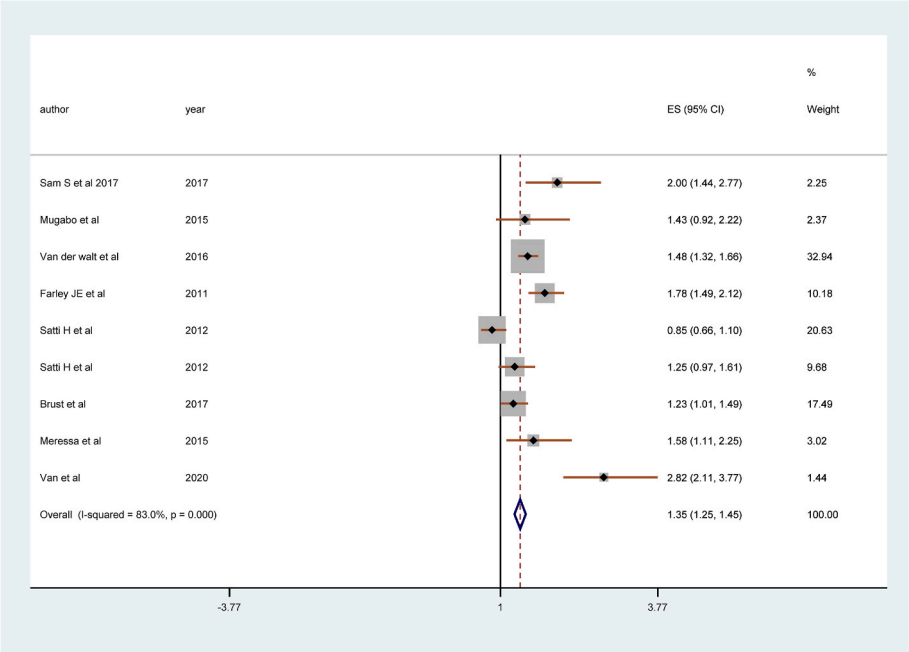

Fig. 3. Death outcomes between MDRTB and MDRTB-HIV co-infection.

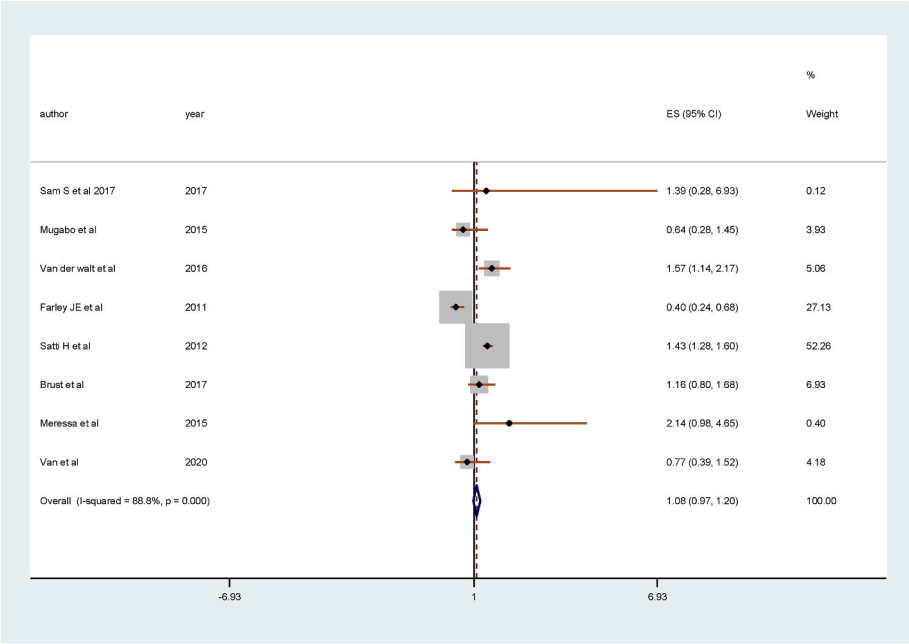

Fig. 4. Outcomes of failure between MDRTB and MDRTB-HIV co-infection.

3.2. Treatment outcomes

3.2.1. Treatment success

There were 9 studies with a population of 5471 that compared treatment success outcomes in patients with MDRTB and MDRTB-HIV co-infection. The pooled result shows that the treatment success was 38% lower in patients with HIV co-infection (RR 0.62, 95% CI 0.58–0.67, $I^2 = 89.65$, p = 0.000).

3.2.2. Death

There were 9 studies with a population of 5471 that compared death outcomes in patients with MDRTB and MDRTB-HIV co-infection. The pooled result showed that the risk of death was higher by 35% in patients with HIV co-infection (RR 1.35, 95% CI 1.25–1.45, $I^2 = 83.0\%$, P = 0.000).

3.2.3. Treatment failure

There were 8 studies with a population of 5454 that compared treatment failure outcomes in patients with MDRTB and MDRTB-HIV co-infection. There was no significant difference in treatment failure among patients with or without HIV co-infection (RR 1.08, 95% CI 0.97–1.20, $I^2 = 88.8\%$, P = 0.000).

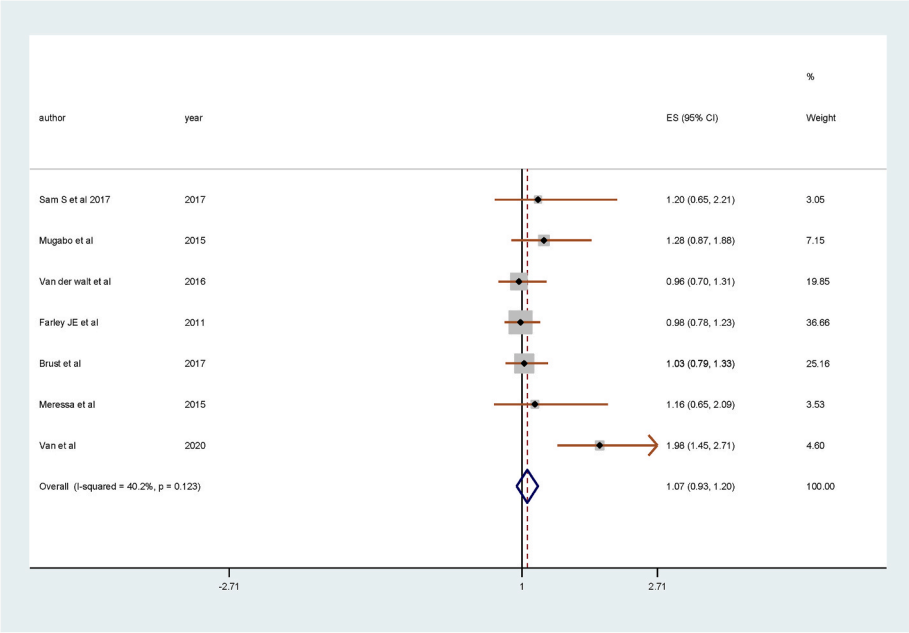

Fig. 5. LTF outcomes in MDRTB and MDRTB-HIV co-infection.

3.2.4. Loss to follow up

There were 7 studies with a population of 5320 that compared LTF outcomes in patients with MDRTB and MDRTB-HIV co-infection. No significant difference has been found in los to follow up between patients with or without HIV co-infection (RR 1.07, 95% CI 0.93–1.20, I^2 = 40.2%, P = 0.123).

4. Discussion

Nine studies were included in the review [1,14–17,20,25–27]. The treatment outcomes that were reported are treatment success, death, treatment failure and lost to follow up. The most common outcomes across all the studies were treatment success and death. Lost to follow up was the least common outcome found in 7 studies. The overall findings of the meta-analysis show that the outcomes of success and death were high among MDR-TB cases with HIV. The other outcomes of failure and lost to follow up were without significant difference in both treatment groups. Treatment success was significantly higher in MDR-TB co-infected cases as compared to those with MDRTB only. The heterogeneity within the studies could be due to different settings (Africa and Asia), and also participants ages as we included studies with all age groups. Reasons for higher treatment success in the co-infected arm could be attributed to good adherence of the HIV clients to the antiretrovirals. On the flip side, there was also more deaths on the co-infected arm maybe due to pill burdens.

Treatment failure and lost to follow up had equal significance in individuals with HIV co-infection and those with MDR-TB only. Heterogeneity in the studies could be attributed to different study settings, age groups as we included studies with adult and children. It could also be due to the different MDR-TB regimens, and the times of completion. The results could also have been skewed by the few numbers of MDR-TB and HIV co-infection, especially in Asian studies. With the above findings, we need to find regimens that effective and friendly, with a less pill burden and time of completion. Screening and early diagnosis for TB and also index tracing of MDRTB cases is necessary.

Different findings were observed in Chem et al. [23] whereby low treatment success were observed in MDRTB patients coinfected with HIV than those without HIV, while a study by Isaakidis et al. [28] revealed similar treatment success in both groups of MDR-TB and MDR-TB and HIV co-infections. In T. A. Umanah et al. the Cure was higher in males on ART prior to initiating MDR-TB treatment compared with males on ART after initiating MDR-TB treatment. The inverse was the case among females [29]. A study in Haiti HIV-positive patients tended to have a lower survival than HIV-negative patients, but they were no less likely to be lost to follow-up [30].

Limitations to the study include the fact that randomized controlled studies (RCTs) were not included. This was because it was hard to find RCTs that analyzed MDR-TB and HIV co-infection treatment outcomes, especially in the Asian setting. The study limitations are that we had only 2 studies representing Asia, and this could have affected the outcome of results. None of the studies was a multicenter study and could affect the inclusiveness of participants. Only one study included children and it had 17 participants, this could have led to small study bias. On the other hand, the review was inclusive of children.

5. Conclusion

It can be concluded from the meta-analysis that treatment success and survival is higher in individuals with MDR-TB and no HIV co-infection. There was no difference observed in the other outcomes of death, treatment failure and lost to follow up. Emphasis of care in the TB-HIV care nd treatment clinics is needed, especially in adherence and follow up, as the results reveal that those with co-infection have lower treatment success and survival. Existing practice and policy on adherence could be modified to become treatment friendly for both care givers and patients. More research to improve treatment success and survival of patients is needed in TB-HIV co-infection.

Ethical approval

No ethical approvals were required for the review.

Sources of funding

There was no funding for the review.

Authors contribution

VDK, JL and IS conceived and developed the protocol. VDK and WO were responsible for data collection, analysis and construction/plotting

summary of findings tables, and evaluated the quality of evidence. VDK, MGA and JL –wrote the draft of the manuscript. DGA and IS provided expert advice on data interpretation. All authors contributed to the revisions and approved the final manuscript.

VDK - Violet Dismas Kajogoo.
JL - Julieth Lalashowi.
WO - Willyhelmina Olomi.
MGA - Mary Gorret Atim.
DGA - Dawit Getachew Assefa.
IS – Issa Sabi.

Trial registry number

1.Name of the registry:
2.Unique Identifying number or registration ID:
3.Hyperlink to your specific registration (must be publicly accessible and will be checked):
The review was registered in International prospective register of systematic reviews (PROSPERO), ID: CRD42021247883.

Guarantor

There was no guarantor for the review.

Consent

No consent forms were required for the review.

Funding

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Declaration of competing interest

The authors declare no conflict of interest.

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Provenance and peer review Not commissioned, externally peer reviewed.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.amsu.2022.103753.

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