INT J TUBERC LUNG DIS 19(8):969–978

http://dx.doi.org/10.5588/ijtld.15.0123

Treatment outcomes for HIV and MDR-TB co-infected adults and children: systematic review and meta-analysis

P. Isaakidis,*† E. C. Casas,‡ M. Das,* X. Tseretopoulou,† E. E. Ntzani,† N. Ford§

***Médecins Sans Frontières, Mumbai, India; †Clinical and Molecular Epidemiology Unit, Department of Hygiene and Epidemiology, University of Ioannina School of Medicine, Ioannina, Greece; ‡Operational Center Amsterdam, Médecins Sans Frontières, Amsterdam, The Netherlands; §Centre for Infectious Disease Epidemiology and Research, University of Cape Town, Cape Town, South Africa**

SUMMARY

BACKGROUND: The incidence of multidrug-resistant tuberculosis (MDR-TB) is increasing in high human immunodeficiency virus (HIV) prevalence settings, with high associated mortality. Treatment outcomes in HIV-co-infected adults and children are poorly documented.

OBJECTIVE: To systematically assess treatment outcomes among HIV–MDR-TB co-infected patients.

METHODS: We searched two databases and the proceedings of an annual international conference up to November 2014 for studies reporting on major clinical outcomes among HIV–MDR-TB-co-infected adults and children, and pooled the results using random-effects meta-analysis.

RESULTS: Of 4812 abstracts and articles screened, 30 studies providing data on 2578 adults and 147 children were included. Overall pooled treatment success was 56.9% (95% confidence interval [CI] 46.2–67.6), 49.9% (95%CI 38.5–61.2) among adults and 83.4% (95%CI 74.7–92) among children. Mortality was 38% in adults (95%CI 28–48.1) and 11.4% (95%CI 5.8–17.1) in children. Loss to follow-up was higher among adults (16.1%, 95%CI 9–23.2) than among children (3.9%, 95%CI 0.9–6.9). Adverse events were experienced by the majority of patients; however, this was inconsistently documented. The use of fluoroquinolones, aminoglycosides and Group IV drugs appeared to be associated with treatment success.

CONCLUSION: The proportion of HIV–MDR-TB-co-infected patients achieving treatment success was similar to success rates reported among MDR-TB patients in general, regardless of HIV status; however, mortality was higher, particularly among adults, highlighting the need for early diagnosis and more effective treatment regimens.

KEY WORDS: human immunodeficiency virus/AIDS; multidrug-resistant tuberculosis; meta-analysis; mortality; treatment success

MULTIDRUG-RESISTANT TUBERCULOSIS (MDR-TB, defined as tuberculosis [TB] resistant to both isoniazid and rifampicin [RMP]) is an escalating problem worldwide. In 2013, the World Health Organization (WHO) estimated that there were 480 000 new MDR-TB cases globally.[1] According to the WHO, progress towards targets for diagnosis and treatment of MDR-TB is off track in several countries, and overall less than half of patients initiating MDR-TB treatment have successful outcomes;[2] however, treatment success rates appear to be higher among children.[3]

TB and human immunodeficiency virus (HIV) co-infection is a global health priority. TB is a major cause of death among people living with HIV (PLHIV), and HIV is the main reason for the failure to meet TB control targets in many settings. Of the 27 high MDR-TB burden countries (defined as having >4000 MDR-TB cases and/or with MDR-TB cases representing at least 10% of newly registered TB cases), seven are classified as having a generalised HIV epidemic (HIV firmly established in the general population) and 10 as having a concentrated HIV epidemic (HIV concentrated in sub-populations).[4] There is evidence that TB patients living with HIV are at greater risk of harbouring and acquiring MDR-TB strains,[5] and that HIV-related immunodeficiency is a risk factor for poor outcomes in MDR-TB patients.[6–8]

Current guidance for the use of antiretroviral therapy (ART) in HIV–MDR-TB co-infected patients is largely the same as for HIV–drug-susceptible TB co-infected patients,[9] but treatment of MDR-TB in HIV-infected patients is more challenging: in addition to the long and difficult treatment associated with MDR-TB treatment, HIV–MDR-TB co-infected pa-

Correspondence to: Petros Isaakidis, Médecins Sans Frontières/Doctors Without Borders, Chandni Bungalow, Union Park, Off Carter Road, Khar (West), Mumbai 400 052, India. Tel: (+91) 99305 34211. e-mail: msfocb-asia-epidemio@brussels.msf.org

Article submitted 6 February 2015. Final version accepted 28 March 2015.

tients may have additional comorbidities and opportunistic infections, a higher pill burden resulting from the co-administration of anti-tuberculosis and ART drugs, and the potential for additive side effects and drug interactions.[10]

We conducted a systematic review and meta-analysis of the available evidence on treatment outcomes among MDR-TB adult and paediatric patients co-infected with HIV, and assessed characteristics of studies and patients that may influence outcomes, particularly treatment success.

METHODS

This study was conducted according to the PRISMA (preferred reporting items for systematic reviews and meta-analyses) guidelines for the reporting of systematic reviews.[11] As this was a retrospective analysis of data, informed consent from participants was not required.

Eligibility criteria

We sought studies reporting major clinical outcomes in MDR-TB adult and paediatric patients co-infected with HIV. The primary outcome of interest was treatment success, defined as a combination of cure and treatment completion according to WHO definitions. Secondary outcomes were death, loss to follow-up (LFU), transfer, relapse, failure and adverse events. Studies were eligible regardless of language, design and setting, provided they reported any outcomes of at least five HIV-infected patients and described MDR-TB treatment with second-line anti-tuberculosis drugs. We did not restrict the selection to culture-confirmed MDR-TB cases, as bacteriological confirmation was not always possible among HIV-infected patients, particularly children.[12] However, papers focusing on a single presentation of TB, such as MDR-TB meningitis with higher rates of mortality, were excluded to prevent skewing the results for the most relevant question of treatment outcomes across all populations studied. When there were multiple reports from the same cohort, the study with the longest follow-up period was selected.

Information sources and search strategy

We searched Medline via PubMed and Embase from inception to November 2014 using the following search terms as MESH headings and free-text terms: human immunodeficiency, HIV, AIDS, HIV/AIDS, tuberculosis, TB, drug-resistant tuberculosis, multidrug resistance, multidrug-resistant, MDRTB, MDR TB, MDR-TB, treatment, outcome. We further screened all abstracts of the International Union Against Tuberculosis and Lung Disease's World Conferences on Lung Health from 2011 to 2014 to identify studies that had been completed but not yet published as full text. Four investigators (PI, ECC, MD, XT) performed the initial title and abstract screening independently, and relevant abstracts were assessed in full text. Final inclusion was decided through consensus, with disagreements resolved by a fifth investigator (EEN). Bibliographies of full-text articles and previous meta-analyses of treatment outcomes among MDR-TB patients were examined for eligible studies.[3,13–15] Authors of relevant studies were contacted for clarification and additional data when necessary.

Data extraction

Information was collected about patients (adults, children), studies (study design, cohort size, setting), treatment protocols (number and type of second-line anti-tuberculosis drugs; individualised or standardised), treatment duration and study outcome definitions. Data on ART initiation were also extracted. All data were extracted independently and in duplicate using a standardised extraction form. We assessed the methodological quality of the included studies and the risk of bias conferred by using elements from the RTI (Research Triangle Institute, Research Triangle Park, NC, USA) item bank.[16]

Data analysis

Point estimates and 95% confidence intervals (95%CIs) were calculated for all primary and secondary outcomes. The denominator for all outcomes was the proportion of patients enrolled and those initiating treatment. The variance of raw proportions was stabilised using a Freeman-Tukey type arc sine square-root transformation;[17] proportions were then pooled using a DerSimonian and Laird random effects model[18] stratified by age. We calculated the τ^2 statistic using DerSimonian and Laird's method of moments estimator[18] to assess between-study heterogeneity.[19] Studies reporting single outcomes contributed data to that outcome such that different studies contributed data for different outcomes; however, we also ran an analysis restricted to studies reporting all four major outcomes (treatment success, death, LFU and transfer out). We ran a sensitivity analysis on our primary outcome using a Bayesian random-effects model with Monte Carlo Markov chain simulations of variability. Sources of heterogeneity were explored through pre-planned univariate subgroup analyses to assess the potential influence of the following covariates: study setting, study design, regimen (individualised vs. standardised), duration, number of Group IV drugs (<2 vs. $\geqslant 2$), use of aminoglycosides (any aminoglycoside vs. no use of aminoglycoside or not reported), use of fluoroquinolones (FQs) (no use of FQ or not reported vs. use of ofloxacin or non-specified use of FQ vs. use of a later generation of FQ), and use of ART drugs. All analyses were conducted using Stata, version 12 (Stata Corp LP, College Station, TX, USA)

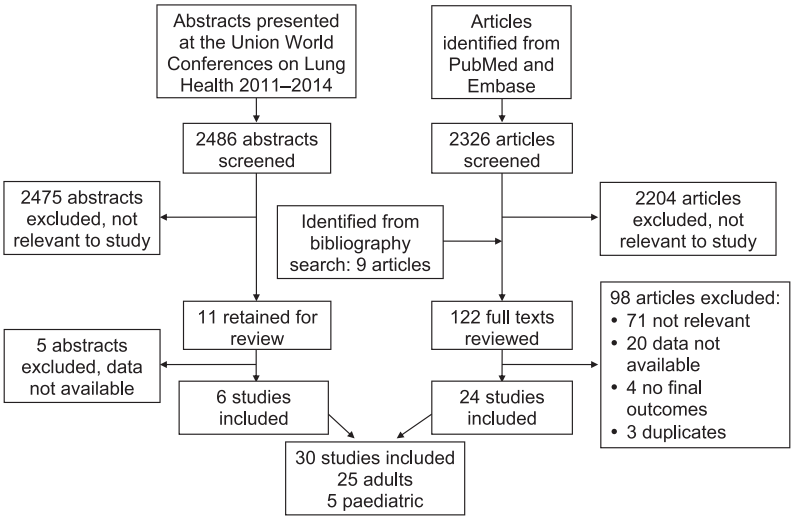

Figure 1 Study selection flow chart.

and Open MetaAnalyst (http://www.cebm.brown.edu/open_meta/download); $P \leqslant 0.05$ was considered significant.

RESULTS

Characteristics of included studies

A flow chart of the study selection is shown in Figure 1. Of 4812 abstracts screened, 30 abstracts with data on outcomes on 2578 adults[20–43] and 147 children[44–48] between 1990 and 2014 (Table 1) were included in the final review. Characteristics of studies, populations and treatment are given in Table 1. Cohort size ranged from 7 to 440 patients with HIV and MDR-TB (median 43, interquartile range [IQR] 13–87). Six studies were from high-income settings (United States and Europe), 14 from upper middle-income settings (Argentina, South Africa, Peru, Azerbaijan and Botswana), six from lower middle-income settings (India, Lesotho, Swaziland and Georgia) and three from low-income settings (Haiti, Cambodia and Ethiopia); paediatric studies were from two countries in southern Africa: South Africa and Lesotho. Nine studies did not report use of ART, one reported no use, 10 reported use of ART in all patients (including three paediatric studies) and eight studies reported mixed use. All studies reported some degree of microbiological confirmation of MDR-TB, with 23 studies reporting microbiological confirmation for the entire cohort. Two studies did not provide information on treatment regimen. Treatment duration, as reported by 23 studies, ranged from 8.3 months to 33 months.

Methodological characteristics

All studies used an appropriate study design to answer the research question, and inclusion and exclusion criteria were clearly stated by most studies and were implemented consistently across study participants. Outcome definitions were not clearly stated, and time points for the measurement of the primary outcomes were not consistently defined due to the retrospective nature of the majority of the studies. Finally, it was judged that the investigators assessed outcomes using valid and reliable measures, and the length of follow-up was sufficient to support the conclusions of the study regarding primary outcomes. The main limitations were the retrospective study design of the majority of the studies ($n = 19$) and the small sample size, which prevent any valid conclusions being drawn regarding the accuracy and precision of the observed estimates.

Primary and secondary outcomes

Treatment success, regardless of reporting of other clinical outcomes, was reported by 23 studies, and overall the pooled proportion of patients achieving treatment success was 56.9% (95%CI 46.2–67.6). Among adults, treatment success varied from 12.2% to 98.2%, with a pooled proportion of 49.9% (95%CI 38.5–61.2). Among children, overall success was 83.4% (95%CI 74.8–92) (Figure 2). These pooled estimates were the same if a Bayesian approach was taken (successful treatment in 56.6% of patients overall, 95% credible interval 45.9–67.1).

Adult mortality, regardless of the reporting of other clinical outcomes, varied from 1.8% to 87.8%, with a pooled proportion of 38% (95%CI 28–48.1). Child mortality varied from 3.2% to 19%, with a pooled proportion of 11.5% (95%CI 5.9–17.1); overall mortality was 33.5 (95%CI 24.5–42.6) (Figure 3).

When analyses were restricted to adult studies reporting all outcomes (treatment success, mortality, LFU and transfer out), results were as follows: 43.4% (95%CI 31.3–65.4) of adults (10 studies) achieved treatment success, 29.4% (95%CI 18.1–40.7) died,

Table 1 Characteristics of patients, and studies in 28 reports of HIV–MDR-TB treatment outcomes, 1990–2014

Study	Country	Setting income	Study years	Study design	Total cohort	ART	Treatment regimen	Treatment duration months
Adult cohorts								
Flament-Saillour[20]	France	High	1994	Case control	8	NR	Not reported	8.3
Gonzalez Montaner[21]	Argentina	Upper middle	1995–1997	Retrospective cohort	440	NR	STR, use of quinolones not reported	NR
Telzak[22]	USA	High	1993–1997	Prospective cohort	12	NR	STR	12
Burgos[23]	USA	High	1982–2000	Retrospective cohort	11	Mixed	ITR with 5 drugs, including quinolones and aminoglycosides	33
Ferrara[24]	Italy	High	1995–1999	Retrospective cohort	15	NR	ITR, use of quinolones and aminoglycosides not reported	18+
Munsiff[25]	USA	High	1992–1997	Prospective cohort	352	NR	STR	NR
Eker[26]	Germany	High	2004–2006	Retrospective cohort	7	NR	ITR including use of quinolones and aminoglycosides	NR
Shean[27]	South Africa	Upper middle	1992–2002	Retrospective cohort	15	NR	ITR including use of aminoglycosides; use of quinolones not reported	18+
Isaakidis[28]	India	Lower middle	2007–2011	Prospective cohort	23	Yes	ITR including use of aminoglycosides; use of quinolones not reported	18+
Farley[29]	South Africa	Upper middle	2000–2004	Prospective cohort	287	No	STR	18+
Kvasnovsky[30]	Multicentric	Lower middle	2005–2008	Prospective cohort	153	Mixed	NR	NR
Palacios[31]	Peru	Upper middle	1996–2005	Retrospective cohort	51	Mixed	ITR and STR, use of quinolones and aminoglycosides not reported	18+
Brust[32]	South Africa	Upper middle	2008–2010	Prospective cohort	56	Yes	STR	24
Satti[45]	Lesotho	Lower middle	2008–2009	Retrospective cohort	94	Yes	STR	22.9
Mdluli[34]	Swaziland	Lower middle	2009	Retrospective cohort	65	Mixed	STR	24
Cox[35]	South Africa	Upper middle	2008–2010	Prospective cohort	351	Yes	ITR including use of quinolones and aminoglycosides	18+
Khan[36]	Cambodia	Low	2007–2011	Retrospective cohort	42	Mixed	STR	22+
Mikiashvili[37]	Georgia	Lower middle	2009–2010	Retrospective cohort	43	NR	STR	20+
Kokebu[38]	Ethiopia	Low	2009–2013	Retrospective cohort	46	NR	STR	NR
Charles[39]	Haiti	Low	2010–2013	Retrospective cohort	15	Yes	STR	15+
Zetola[40]	Botswana	Upper middle	2005–2011	Retrospective cohort	328	Mixed	STR	22+
Padayatchi[41]	South Africa	Upper middle	2005–2010	Prospective cohort	8	Yes	STR	NR
Mugabo[48]	South Africa	Upper middle	2004–2006	Prospective cohort	88	Mixed	STR	18+
Post[42]	Multicentric	Upper middle	2004–2006	Prospective cohort	55	Mixed	NR	NR
Mekhdiyev[43]	Azerbaijan	Upper middle	2007–2010	Retrospective cohort	13	NR	ITR	18+
Paediatric cohorts								
Seddon[44]	South Africa	Upper middle	2003–2009	Retrospective cohort	43	Yes	ITR including use of quinolones and aminoglycosides	19
Satti[33]	Lesotho	Lower middle	2007–2011	Retrospective cohort	12	Yes	STR	24
Mugabo[48]	South Africa	Upper middle	2004–2006	Retrospective cohort	7	Mixed	STR	18+
Seddon[46]	South Africa	Upper middle	2009–2010	Prospective cohort	32	Yes	ITR including use of quinolones and aminoglycosides	16
Hicks[47]	South Africa	Upper middle	2009–2010	Retrospective cohort	53	Yes	ITR including use of quinolones and aminoglycosides	18+

HIV = human immunodeficiency virus; MDR-TB = multidrug-resistant tuberculosis; ART = antiretroviral therapy; NR = not reported; STR = standard treatment regimen; ITR = individualised treatment regimen.

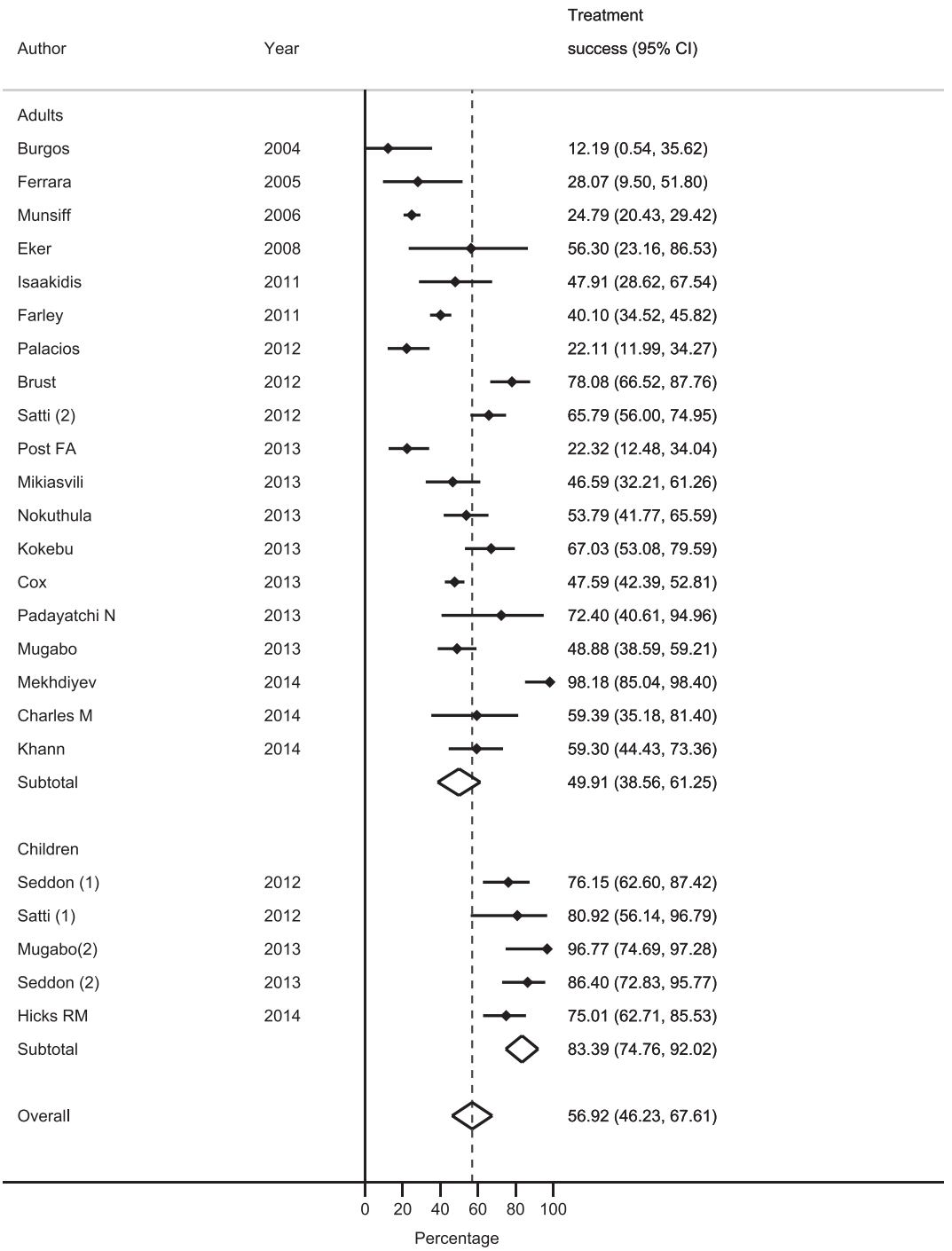

Figure 2 Proportion of MDR-TB–HIV-co-infected patients achieving treatment success, weighted according to random-effects analysis. CI = confidence interval; MDR-TB = multidrug-resistant tuberculosis; HIV = human immunodeficiency virus.

16.1% (95%CI 6.8–25.4) were lost to follow-up and 5.2% (95%CI 2.3–8.0) were transferred; 83.4% (95%CI 74.8–92.0) of children (5 studies) achieved treatment success, 11.5% (95%CI 5.9–17.1) died, 3.9% (95%CI 0.9–7.0) were lost to follow-up and 1.7% (95%CI 0–4.1) were transferred.

The results of the subgroup analyses (Table 2) suggested that the proportion of patients successfully treated did not differ significantly according to design or regimen (individualised vs. standardised). Treatment success did appear to be greater in low- and lower-middle-income countries, when two or more Group IV drugs, aminoglycosides and older or newer generation FQs were included in the regimen. Data were insufficient to explore the potential influence of treatment duration or concomitant ART use.

LFU (20 studies) was significantly higher among adults (16.1%, 95%CI 9–23.2) than among children

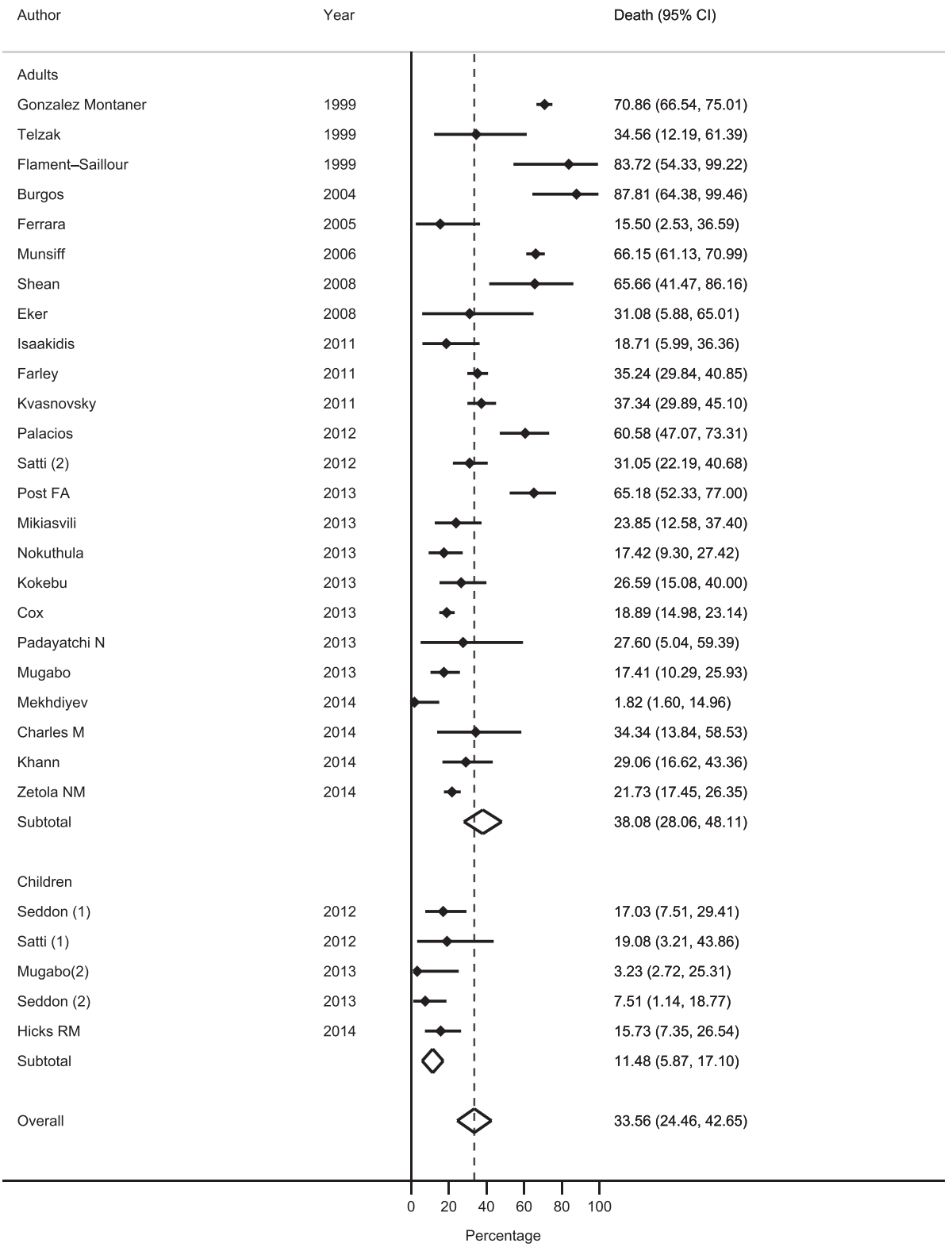

Figure 3 Proportion of MDR-TB–HIV-co-infected patients who died. CI = confidence interval; MDR-TB = multidrug-resistant tuberculosis; HIV = human immunodeficiency virus.

(3.9%, 95%CI 0.9–6.9) (Figure 4). The proportion of patients relapsing (11 studies) was low in both adults (1.2%, 95%CI 0.4–2) and children (0.7%, 95%CI 0–2.4), with relatively low proportions of patients failing treatment (adults 4.9%, 95%CI 3.2–6.4; children 1.8%, 95%CI 0–4.2). Few patients were transferred (adults 5.1%, 95%CI 2.3–8; children 1.6%, 95%CI 0–4.1; 18 studies).

Table 2 Pooled treatment success among subgroups of adult studies for MDR-TB and HIV co-infected patients

	Studies reporting treatment success *n*	Treatment success % (95%CI)	*P* value	τ^2
Study setting				
Upper-middle-income/high-income	12	40.8 (32.6–49.0)	—	0.06
Low-income/lower-middle-income	7	64.6 (43.0–86.2)	0.04*	0.24
Study design				
Prospective	6	42.7 (32.1–53.4)	—	0.06
Retrospective	13	53.0 (37.5–68.6)	0.28	0.17
Regimen				
Individualised	5	48.9 (16.8–81.0)	—	0.35
Standardised	12	54.6 (43.4–65.9)	0.74	0.13
<2 Group IV drugs	2	27.4 (0.2–54.7)	—	0.17
⩾2 Group IV drugs	12	62.2 (49.9–74.5)	0.02*	0.06
Aminoglycosides: yes	16	54.8 (42.4–67.2)	—	0.12
Aminoglycosides: no/not reported	2	23.4 (13.5–33.3)	<0.01*	0
Fluoroquinolones: no/not reported	2	23.4 (13.5–33.3)	—	0
Fluoroquinolones: OFX and yes/not specified	7	46.2 (30.6–61.9)	0.02*	0.14
Fluoroquinolones: all, LVX, MFX	9	61.0 (45.8–76.2)	<0.01*	0.06

* Statistically significant.
MDR-TB = multidrug-resistant tuberculosis; HIV = human immunodeficiency virus; CI = confidence interval; OFX = ofloxacin; LVX = levofloxacin; MFX = moxifloxacin.

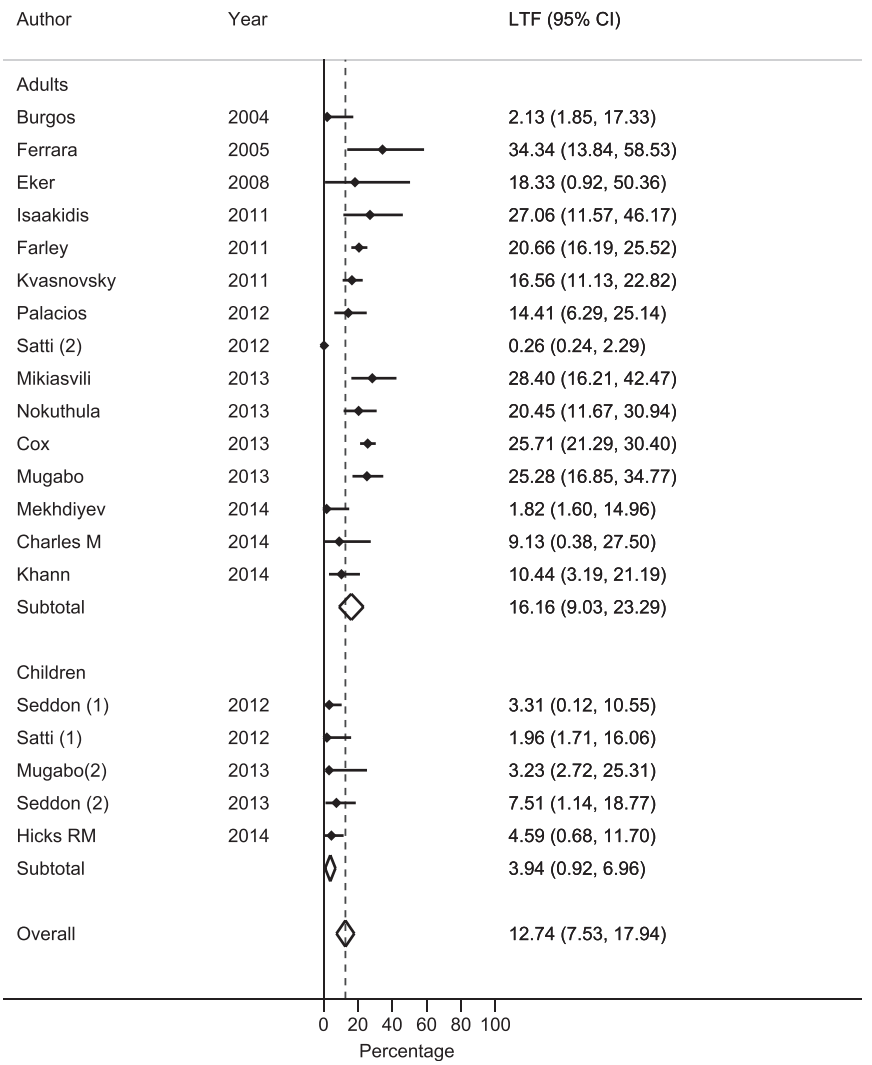

Figure 4 Proportion of MDR-TB–HIV-co-infected patients lost to follow-up. LTF = lost to follow-up; CI = confidence interval; MDR-TB = multidrug-resistant tuberculosis; HIV = human immunodeficiency virus.

Finally, adverse events were experienced by the majority of adult (83.1%, 95%CI 73.3–92.9) and paediatric (92.5%, 95%CI 83.7–100) patients; however, only five studies provided adequate data to assess the frequency of adverse events.

DISCUSSION

This systematic review of data for 2725 HIV co-infected adult and paediatric patients treated for MDR-TB found that only around half of the patients achieved treatment success. Treatment outcomes were better in children than in adults, consistent with findings reported for non-HIV-co-infected patients.[3] However, mortality among adults was four times higher than reported for HIV-negative populations (38% vs. 11%), while mortality among children was twice as high (11.5% vs. 6%).[13,15,49]

Among adults, the highest success rates were reported in Azerbaijan[43] and South Africa.[32] The success of these programmes may be attributable to three factors: ensuring adherence with direct observation and/or adherence support; provision of intensive adverse event monitoring; and, in the case of the southern African countries, providing decentralised home-based care and access to ART for all or most co-infected patients. More than 70% of patients in the South African cohorts and 95% of patients in Lesotho were receiving ART during MDR-TB treatment. In children, early identification of patients with presumed MDR-TB through contact tracing,[44] early empiric treatment while waiting for confirmation from drug susceptibility testing (DST) in community-based programmes, and early ART initiation as soon as patients tolerated MDR-TB treatment were described and were likely to be related to low mortality.[42] Programmes using FQs, especially later-generation FQs, aminoglycosides and more than two Group IV drugs, showed better success rates. This is similar to reports in the general population, regardless of HIV status.[49]

Cohorts reporting the worst outcomes[23,25] and higher mortality[23] were mainly the early cohorts of HIV–MDR-TB co-infected patients when the use of ART was limited. The high mortality among HIV-co-infected individuals underlines the pressing need to improve early diagnosis of both diseases, with access to rapid diagnosis of TB and identification of RMP-resistant TB, and to improve the efficacy and safety of drugs to treat MDR-TB. Two new drugs—bedaquiline and delamanid—have been approved for the management of MDR-TB but are not yet widely available for patients in need; other promising drugs are in the research and development pipeline. However, clinical data on the safety, efficacy and drug-drug interactions in co-infected patients, particularly among severely immunocompromised patients and those on concomitant ART, are limited, as co-infected patients are generally excluded from clinical trials.[50–52] Efforts are needed to ensure that HIV-infected adults and children are included in future clinical trials and observational cohorts.

Adverse events were reported inconsistently, underscoring the need for standardisation of reporting adverse events. As studies reporting only adverse events but no other outcomes were not included, it is not possible to draw major conclusions. However, there is a need to better understand the risks associated with co-administration of MDR-TB treatment and ART, as the high mortality reported by this review supports current recommendations to treat HIV and MDR-TB concomitantly, similar to drug-susceptible TB.

A detailed analysis of the impact of ART was not possible due to the variability in the reporting of access to ART; this was due to the inclusion of cohorts from the pre-ART era, differing recommendations regarding ART use in co-infected patients and poor study reporting. Microbiological confirmation was often not possible in HIV-infected patients and young children; also, the inclusion of unconfirmed cases in the studies included in this meta-analysis might have introduced bias. Another limitation of the evidence base was that most studies did not differentiate between the inclusion/exclusion of patients with second-line drug resistance, mostly due to the lack of access to second-line DST, either because cohorts were from earlier periods or because settings currently lacked access to second-line DST. This might partly explain the heterogeneity in treatment success rates across studies.

We used a broad search strategy that allowed the identification of studies reporting outcomes across populations and settings; however, despite the high disease burden very few data are available, particularly among paediatric patients. The inclusion of data from a range of settings resulted in considerable heterogeneity, which was compensated for by using random-effects analysis and undertaking subgroup analyses; however, such analyses were also limited by the inconsistent reporting of important study characteristics, in particular baseline immune status, type of MDR-TB treatment regimen and concomitant ART. In this review, we chose to include any reported outcomes to prevent loss of information, as can be appreciated from the fact that the analysis was restricted to studies reporting all outcomes. This review summarises published outcomes, which may not be representative of all outcomes achieved in routine programme settings. Finally, the review only considers outcomes among patients who initiated MDR-TB treatment; MDR-TB treatment coverage remains inadequate in most high-burden countries,[2] and substantial mortality occurs among people who have not been able to start treatment.

In conclusion, the findings of this systematic review

and meta-analysis indicate high mortality in HIV–MDR-TB co-infected patients, underscoring the urgent need to improve on current approaches to diagnosis and treatment. Early identification of HIV to allow early initiation of ART, early diagnosis of MDR-TB with improved access to resistance testing for HIV-TB co-infected patients, and access to second-line anti-tuberculosis drugs, are critical to increase the likelihood of treatment success and survival among HIV–MDR-TB co-infected populations. HIV-infected adults and children should be included in future clinical trials and observational cohorts to ensure that the necessary data are generated to allow these vulnerable populations to benefit from advances in treatment.

Acknowledgements

The authors thank the following authors who responded to our request and shared data and/or provided suggestions: M R O'Donnel (USA), K Sokhan (Cambodia), C Auer (Switzerland), N Zetola (Botswana), M Charles (Haiti), F Post (UK), F Palmieri (Italy), E Nathanson (Myanmar), C Mitnick (USA), R Centis (Italy), G B Migliori (Italy), M Burgos (USA), J Robert (France), C Lange (Germany), N Mdluli (Swaziland), A Shapiro (USA), L Mikiashvili and M Kikvidze (Georgia), J Furin (USA), J Seddon (South Africa), J Brust (South Africa), B Eker (Germany), G Ferrara (Italy), H Cox (SA), R Mekhdiyev (Azerbaijan).

Conflicts of interest: none declared.

References

1 World Health Organization. Global tuberculosis report 2014. WHO/HTM/TB/2014.08. Geneva. Switzerland: WHO, 2014.
2 Falzon D, Jaramillo E, Wares F, Zignol M, Floyd K, Raviglione M C. Universal access to care for multidrug-resistant tuberculosis: an analysis of surveillance data. Lancet Infect Dis 2013; 13: 690–697.
3 Ettehad D, Schaaf H S, Seddon J A, Cooke G S, Ford N. Treatment outcomes for children with multidrug-resistant tuberculosis: a systematic review and meta-analysis. Lancet Infect Dis 2012; 12: 449–456.
4 World Health Organization. Towards universal access to diagnosis and treatment of multidrug-resistant and extensively drug-resistant tuberculosis by 2015. WHO progress report 2011. WHO/HTM/TB/2011.3. Geneva, Switzerland: WHO, 2011.
5 Mesfin Y M, Hailemariam D, Biadglign S, Kibret K T. Association between HIV/AIDS and multidrug resistance tuberculosis: a systematic review and meta-analysis. PLOS ONE 2014; 9: e82235.
6 Quy H T, Cobelens F G, Lan N T, Buu T N, Lambregts C S, Borgdorff M W. Treatment outcomes by drug resistance and HIV status among tuberculosis patients in Ho Chi Minh City, Viet Nam. Int J Tuberc Lung Dis 2006; 10: 45–51.
7 Wells C D, Cegielski J P, Nelson L J, et al. HIV infection and multidrug-resistant tuberculosis: the perfect storm. J Infect Dis 2007; 196 (Suppl 1): S86–S107.
8 Gandhi N R, Nunn P, Dheda K, et al. Multidrug-resistant and extensively drug-resistant tuberculosis: a threat to global control of tuberculosis. Lancet 2010; 375: 1830–1843.
9 World Health Organization. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach. Geneva, Switzerland: WHO, 2013.
10 Arentz M, Pavlinac P, Kimerling M E, et al. Use of antiretroviral therapy in tuberculosis patients on second-line anti-TB regimens: a systematic review. PLOS ONE 2012; 7: e47370.
11 Moher D, Liberati A, Tetzlaff J, Altman D G, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Ann Intern Med 2009; 151: 264–269.
12 Pearce E C, Woodward J F, Nyandiko W M, Vreeman R C, Ayaya S O. A systematic review of clinical diagnostic systems used in the diagnosis of tuberculosis in children. AIDS Res Treat 2012; 2012: 401896.
13 Orenstein E W, Basu S, Shah N S, et al. Treatment outcomes among patients with multidrug-resistant tuberculosis: systematic review and meta-analysis. Lancet Infect Dis 2009; 9: 153–161.
14 Toczek A, Cox H, du Cros P, Cooke G, Ford N. Strategies for reducing treatment default in drug-resistant tuberculosis: systematic review and meta-analysis. Int J Tuberc Lung Dis 2013; 17: 299–307.
15 Johnston J C, Shahidi N C, Sadatsafavi M, Fitzgerald J M. Treatment outcomes of multidrug-resistant tuberculosis: a systematic review and meta-analysis. PLOS ONE 2009; 4: e6914.
16 Viswanathan M, Berkman N D, Dryden DM, Hartling L. Assessing risk of bias and confounding in observational studies of interventions or exposures: further development of the RTI item bank. Methods Research Report. AHRQ Publication No. 13 EHC106-EF. Rockville, MD, USA: Agency for Healthcare Research and Quality, 2013.
17 Freeman M F, Tukey J W. Transformations related to the angular and the square root. Ann Math Statist 1950; 21: 607–611.
18 DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986; 7: 177–188.
19 Higgins J P, Thompson S G, Deeks J J, Altman D G. Measuring inconsistency in meta-analyses. BMJ 2003; 327: 557–560.
20 Flament-Saillour M, Robert J, Jarlier V, Grosset J. Outcome of multi-drug-resistant tuberculosis in France: a nationwide case-control study. Am J Respir Crit Care Med 1999; 160: 587–593.
21 Gonzalez Montaner L J, Alberti F, Palmero D. Multidrug-resistant tuberculosis associated with AIDS. Bull Acad Natl Med 1999; 183: 1085–1096.
22 Telzak E E, Chirgwin K D, Nelson E T, et al. Predictors for multidrug-resistant tuberculosis among HIV-infected patients and response to specific drug regimens. Terry Beirn Community Programs for Clinical Research on AIDS (CPCRA) and the AIDS Clinical Trials Group (ACTG), National Institutes for Health. Int J Tuberc Lung Dis 1999; 3: 337–343.
23 Burgos M, Gonzalez L C, Paz E A, et al. Treatment of multidrug-resistant tuberculosis in San Francisco: an outpatient-based approach. Clin Infect Dis 2005; 40: 968–975.
24 Ferrara G, Richeldi L, Bugiani M, et al. Management of multidrug-resistant tuberculosis in Italy. Int J Tuberc Lung Dis 2005; 9: 507–513.
25 Munsiff S S, Ahuja S D, Li J, Driver C R. Public-private collaboration for multidrug-resistant tuberculosis control in New York City. Int J Tuberc Lung Dis 2006; 10: 639–648.
26 Eker B, Ortmann J, Migliori G B, et al. Multidrug- and extensively drug-resistant tuberculosis, Germany. Emerg Infect Dis 2008; 14: 1700–1706.
27 Shean K P, Willcox P A, Siwendu S, et al. Treatment outcome and follow-up of multidrug-resistant tuberculosis patients, West Coast/Winelands, South Africa, 1992–2002. Int J Tuberc Lung Dis 2008; 12: 1182–1189.
28 Isaakidis P, Cox H S, Varghese B, et al. Ambulatory multi-drug resistant tuberculosis treatment outcomes in a cohort of HIV-infected patients in a slum setting in Mumbai, India. PLOS ONE 2011; 6: e28066.
29 Farley J E, Ram M, Pan W, et al. Outcomes of multi-drug resistant tuberculosis (MDR-TB) among a cohort of South African patients with high HIV prevalence. PLOS ONE 2011; 6: e20436.

30 Kvasnovsky C, Kurbatova E V, Odendaal R, Wolfgang M, Ershova J, Cegielski J P. HIV infection in patients with multidrug-resistant tuberculosis from the Preserving Effective TB Treatment Study. Am J Respir Crit Care Med 183; 2011: A1821.
31 Palacios E, Franke M, Muñoz M, et al. HIV-positive patients treated for multidrug-resistant tuberculosis: clinical outcomes in the HAART era. Int J Tuberc Lung Dis 2012; 16: 348–354.
32 Brust J C, Berman A R, Zalta B, et al. Chest radiograph findings and time to culture conversion in patients with multidrug-resistant tuberculosis and HIV in Tugela Ferry, South Africa. PLOS ONE 2013; 8: e73975.
33 Satti H, McLaughlin M M, Hedt-Gauthier B, et al. Outcomes of multidrug-resistant tuberculosis treatment with early initiation of antiretroviral therapy for HIV co-infected patients in Lesotho. PLOS ONE 2012; 7: e46943.
34 Mdluli N. MDR-TB treatment outcomes among HIV and non-HIV infected patients in Swaziland: a review of routinely collected data. 44th World Conference on Lung Health, Paris, France, 30 October–3 November 2013. Int J Tuberc Lung Dis 2013: 17 (12 Suppl 2): S431 [Abstract PC-799-03].
35 Cox H, Hughes J, Daniels J, et al. Community-based treatment of drug-resistant tuberculosis in Khayelitsha, South Africa. Int J Tuberc Lung Dis 2014; 18: 441–448.
36 Khann S, Mao T E, Tan K, Rajendra Y. Using community-based care to achieve low defaulter rates among MDR-TB patients of Cambodia. 45th World Conference on Lung Health, Barcelona, Spain, 28 October–1 November 2014. Int J Tuberc Lung Dis 2014: 18 (Suppl 1): S499. [Abstract PD-1174-01].
37 Mikiashvili L Kikvidze, M. Impact of comorbidities on multidrug-resistant tuberculosis outcomes: a cohort study. 44th World Conference on Lung Health, Paris, France, 30 October–3 November 2013. Int J Tuberc Lung Dis 2013: 17 (12 Suppl 2): S372 [Abstract PC-724-02].
38 Kokebu D, Hurtado R, Ejara E, et al. Treatment outcomes from a collaborative multidrug-resistant tuberculosis treatment programme in Ethiopia. 44th World Conference on Lung Health, Paris, France, 30 October–3 November 2013. Int J Tuberc Lung Dis 2013: 17 (12 Suppl 2): S237 [Abstract OP-180-02].
39 Charles M, Vilbrun S C, Koenig S P, et al. Treatment outcomes for patients with multidrug-resistant tuberculosis in post-earthquake Port-au-Prince, Haiti. Am J Trop Med Hyg 2014; 91; 715–772.
40 Zetola N M, Modongo C, Moonan P K, et al. Clinical outcomes among persons with pulmonary tuberculosis caused by *Mycobacterium tuberculosis* isolateswith phenotypic heterogeneity in results of drug-susceptibility tests. J Infect Dis 2014; 209: 1754–1763.
41 Padayatchi N, Abdool Karim S S, Naidoo K, Grobler A, Friedland G. Improved survival in multidrug-resistant tuberculosis patients receiving integrated tuberculosis and antiretroviral treatment in the SAPiT Trial. Int J Tuberc Lung Dis 2014; 18: 147–154.
42 Post F A, Grint D, Werlinlurd A M, et al. Multidrug-resistant tuberculosis in HIV positive patients in Eastern Europe. J Infect 2014; 68: 259–263.
43 Mekhdiyev R, Auer C, Gurbanova E, et al. Good treatment outcomes among prisoners with DRTB: hope from Baku, Azerbaijan and challenge to the TB world. 45th World Conference on Lung Health, Barcelona, Spain, 28 October–1 November 2014. Int J Tuberc Lung Dis 2014: 18 (Suppl 1): S346. [Abstract PD-952-31]
44 Seddon J A, Hesseling A C, Willemse M, Donald P R, Schaaf H S. Culture-confirmed multidrug-resistant tuberculosis in children: clinical features, treatment, and outcome. Clin Infect Dis 2012; 54: 157–166.
45 Satti H, McLaughlin M M, Omotayo D B, et al. Outcomes of comprehensive care for children empirically treated for multidrug-resistant tuberculosis in a setting of high HIV prevalence. PLOS ONE 2012; 7: e37114.
46 Seddon J A, Hesseling A C, Godfrey-Faussett P, Schaaf H S. High treatment success in children treated for multidrug-resistant tuberculosis: an observational cohort study. Thorax 2014; 69: 458–464.
47 Hicks R M, Padayatchi N, Shah N S, et al. Malnutrition associated with unfavorable outcome and death among South African MDR-TB and HIV co-infected children. Int J Tuberc Lung Dis 2014; 18: 1074–1079.
48 Mugabo P, Adewumi A, Theron D, Burger A, Van Zyl L. Do HIV infection and antiretroviral therapy influence multidrug-resistant tuberculosis treatment outcomes? Acta Clinica Belgica 2013; 68: 456.
49 Ahuja S D, Ashkin D, Avendano M, et al. Multidrug resistant pulmonary tuberculosis treatment regimens and patient outcomes: an individual patient data meta-analysis of 9,153 patients. PLOS MED 2012; 9: e1001300.
50 Clayden P, Collins S, Daniels C, et al. HIV, HCV, and TB. Pipeline Report. Drugs, diagnostics, vaccines, preventive technologies, research toward a cure, and immune-based and gene therapies in development. New York, NY, USA & London, UK: HIV i-Base/Treatment Action Group, 2014.
51 Gler M T, Skripconoka V, Sanchez-Garavito E, et al. Delamanid for multidrug-resistant pulmonary tuberculosis. N Engl J Med 2012; 366: 2151–2160.
52 Diacon A H, Pym A, Grobusch M, et al. The diarylquinoline TMC207 for multidrug-resistant tuberculosis. N Engl J Med 2009; 360: 2397–2405.

RESUME

CONTEXTE : L'incidence de la tuberculose multirésistante (TB-MDR) est en augmentation dans les zones de prévalence élevée du virus de l'immunodéficience humaine (VIH), avec une lourde mortalité associée. Les résultats du traitement des adultes et des enfants co-infectés par le VIH sont peu documentés.

OBJECTIF : Evaluer systématiquement le devenir des patients co-infectés par la TB-MDR et le VIH.

MÉTHODE : Nous avons fait des recherches dans deux bases de données et les livres d'abstract d'une conférence internationale annuelle jusqu'à novembre 2014 pour des études rapportant les résultats cliniques principaux concernant des adultes et des enfants co-infectés par une TB-MDR et par le VIH et nous avons regroupé les résultats en utilisant une méta-analyse à effets aléatoires.

RÉSULTATS : Sur 4812 résumés et articles revus, 30 études, fournissant des données sur 2578 adultes et 147 enfants, ont été incluses. Dans l'ensemble, le taux de réussite du traitement a été de 56,9% (IC95% 46,2–67,6), 49,9% (IC95% 38,5–61,2) parmi les adultes et de 83,4% (IC95% 74,7–92) parmi les enfants. La mortalité a été de 38% pour les adultes (IC95% 28–48,1) et de 11,4% (IC95% 5,8–17,1) chez les enfants. Les perdus de vue ont été plus nombreux chez les adultes (16,1%, IC95% 9–23,2) comparés aux enfants (3.9%, IC95% 0,9–6,9). La majorité des patients a connu des effets indésirables ; cependant, ceux-ci n'ont pas été documentés de façon cohérente. L'utilisation de fluoroquinolones, d'aminosides et de médicaments du Groupe IV semblent avoir été associée avec le succès du traitement.

CONCLUSIONS : La proportion de patients co-infectés par une TB-MDR et par le VIH dont le traitement a réussi est similaire au taux de succès rapporté pour les patients TB-MDR, quel que soit leur statut VIH, mais la mortalité est plus élevée, surtout parmi les adultes, ce qui souligne le besoin de diagnostic précoce et de protocoles de traitement plus efficaces.

RESUMEN

MARCO DE REFERENCIA: La incidencia de tuberculosis multidrogorresistente (TB-MDR) está aumentando en los entornos con alta prevalencia de infección por el virus de la inmunodeficiencia humana (VIH) y se asocia con una alta mortalidad. Existe poca documentación sobre los desenlaces terapéuticos en los adultos y los niños coinfectados por el VIH.

OBJETIVO: Evaluar de manera sistemática los desenlaces de pacientes coinfectados por el VIH y la TB-MDR.

METODOS: Se llevó a cabo una búsqueda en dos bases de datos y en las comunicaciones de una conferencia internacional anual hasta noviembre del 2014, de estudios sobre los principales desenlaces clínicos de los adultos y los niños coinfectados por el VIH y la TB-MDR y se agregaron los resultados mediante un análisis de efectos aleatorios.

RESULTADOS: De los 4812 resúmenes y artículos examinados, se retuvieron 30 estudios con datos sobre 2578 adultos y 147 niños. El éxito terapéutico global agregado fue 56,9% (IC95% 46,2–67,6), 49,9% en los adultos (IC95% 38,5–61,2) y 83,4% en los niños (IC95% 74,7–92). Se observó una mortalidad de 38% en los adultos (IC95% 28–48,1) y 11,4% en los niños (IC95% 5,8–17,1). La pérdida durante el seguimiento fue más alta en los adultos (16,1 %; IC95% 9–23,2) que en los niños (3,9%; IC95% 0,9–6,9). La mayoría de los pacientes presentó reacciones adversas; sin embargo, la documentación de este acontecimiento fue inconstante. El uso de fluoroquinolonas, aminoglucósidos y medicamentos del Grupo IV resultó asociado con el éxito terapéutico.

CONCLUSION: La proporción de pacientes coinfectados por el VIH y la TB-MDR que alcanzó el éxito terapéutico fue equivalente a las tasas de éxito notificadas en los pacientes TB-MDR sin consideración de su situación frente al VIH, pero la mortalidad fue más alta, sobre todo en los adultos, lo cual destaca la necesidad de un diagnóstico temprano y de regímenes terapéuticos más eficaces.