Safety of treatment regimens containing bedaquiline and delamanid in the endTB cohort

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Summary: Systematic adverse events reporting during the endTB observational study found that adverse events related to linezolid and injectable drugs were frequent during MDR-TB treatment containing bedaquilline and delamanid, whereas QT prolongation was uncommon. Adverse event monitoring should be adapted accordingly.

ABSTRACT

Rationale: Safety of treatment for multidrug-resistant tuberculosis (MDR/RR-TB) can be an obstacle to treatment completion

Objectives: Evaluate safety of longer MDR/RR-TB regimens containing bedaquiline and/or delamanid.

Methods: Multicentre (16 countries), prospective, observational study, reporting incidence and frequency of clinically relevant adverse events of special interest (AESI) amongst patients who received MDR/RR-TB treatment containing bedaquiline and/or delamanid. The AESIs were defined *a priori* as important events caused by bedaquiline, delamanid, linezolid, injectables, and other commonly used drugs. Occurrence of these events was also reported by exposure to the likely causative agent.

Results: Among 2296 patients, the most common clinically relevant AESIs were: peripheral neuropathy in 26.4%, electrolyte depletion in 26.0%, and hearing loss in 13.2% of patients. Per 1000 person-months of treatment, the incidence of these events was 21.5 (95% confidence interval [CI]: 19.8-23.2), 20.7 (95% CI: 19.1-22.4), and 9.7 (95% CI: 8.6-10.8), respectively. QT interval was prolonged in 2.7% or 1.8 (95% CI: 1.4-2.3)/1000 person-months of treatment. Patients who received injectables (N=925) and linezolid (N=1826) were most likely to experience events during exposure: Hearing loss, acute renal failure, or electrolyte depletion occurred in 36.8% or 72.8 (95%CI: 66.0-80.0) times/1000 person-months of injectable drug exposure. Peripheral neuropathy, optic neuritis and/or myelosuppression occurred in 27.8% or 22.8 (95% CI: 20.9-24.8) times/1000 patient-months of linezolid exposure.

Conclusions: Adverse events often related to linezolid and injectable drugs were more common than those frequently attributed to bedaquiline and delamanid. MDR-TB treatment monitoring schedules and individual drug durations should reflect expected safety profiles of drug combinations.

Keywords: MDR-TB, adverse events, new drugs, QT prolongation, linezolid

INTRODUCTION

The treatment for rifampin-resistant/multi-drug resistant tuberculosis (MDR/RR-TB) has been notorious for its toxicity, long duration and poor effectiveness. Whilst the adverse events (AEs) experienced by patients receiving these multiple combinations of drugs are common and well known to clinicians, they have often been poorly documented and frequently considered as unavoidable. Many drugs. such as the injectables (kanamycin, amikacin and capreomycin), ethionamide/ prothionamide, cycloserine/terizidone and para-aminosalicylic acid (PAS), have been used for decades; patients have rarely been offered choices despite the knowledge that patients would suffer AEs. However, with the increased use of bedaquiline and delamanid and the so called “re-purposed drugs”, such as linezolid and clofazimine, the experience of treating MDR/RR-TB has changed for patients and clinicians alike. The UNITAID funded endTB project, comprising an observational study and two randomized controlled clinical trials (ClinicalTrials.gov Identifier: NCT02754765 and NCT03896685), was established to increase access to and optimize the use of these drugs. Starting in April 2015, the endTB Observational Study systematically collected information on the safety and effectiveness of MDR/RR-TB regimens containing bedaquiline and/or delamanid used according to World Health Organisation (WHO) guidance in place[1,2]. This investment was pivotal: In 2019, WHO updated its Guidelines, recommending bedaquiline, linezolid and clofazimine as top choices for regimen composition and demoting the injectable drugs, PAS and ethionamide.[3] These recommendations are largely informed by an individual patient data (IPD) analysis of MDR/RR-TB treatment. Effectiveness data was much more readily available than safety data. The latter comprised fewer studies and was limited only to data on AEs leading to permanent drug changes. The present study reports the

frequency and incidence of clinically relevant adverse events of special interest (AESIs) amongst patients with MDR/RR-TB receiving longer bedaquiline and/or delamanid-containing regimens.

METHODS

Study design and population

This multi-centre prospective observational study included consecutively all patients who started a bedaquiline- or delamanid-containing MDR/RR-TB regimen between 1 April 2015 and 30 June 2018 through the endTB project in 16 countries (Armenia, Bangladesh, Belarus, Ethiopia, Georgia, Haiti, Indonesia, Kazakhstan, Kenya, Kyrgyzstan, Lesotho, Myanmar, Pakistan, Peru, South Africa, and Vietnam). Patients from the Democratic People's Republic of Korea were excluded due to incomplete and inconsistent monitoring and reporting of adverse events in this site. More details of the study protocol and methods are described elsewhere[4] and in the supplementary material.

Procedures

Patients were identified as requiring bedaquiline and/or delamanid in a longer MDR/RR-TB multi-drug regimen according to WHO interim guidance and local standards at the time[1,2,5,6]. In general, eligibility was based on lack of four effective drugs to construct an effective regimen (due to resistance or adverse events) and/or fluoroquinolone resistance. These standards and the regularly updated versions of the endTB Clinical Guide[7], also guided the treatment regimen composition and follow-up schedule including systematic monitoring for safety (see supplement, Table

S1 for monitoring schedule). The endTB Clinical Guide also provided detailed advice on the management of AEs with additional practical support from the endTB medical committee when required. Treatment was provided under routine programmatic conditions by National TB Programs (NTPs) and partners.

Data collection, reporting and definitions

Table 1 displays the classification of all adverse events that were recorded for all patients irrespective of severity level. The subgroup of AESIs were defined *a priori* as important events caused by bedaquiline, delamanid, linezolid, injectables, and other commonly used drugs (see supplement, Table S2 for corresponding severity scale terms). Information recorded for each AE included AE term, severity grade (see supplement, Table S3), causality assessment, contributing factors (co-morbidities, other drugs) and AE outcomes. More details can be found in the supplement and at endTB.org/resources/pharmacovigilance. Data was recorded in the endTB electronic medical record[4]. In addition, serious adverse events (SAEs) were reported to the MSF pharmacovigilance (PV) unit and local authorities and entered into the PV unit database in Geneva. Quality control was performed[4].

Table 2 shows the severity grade at which an AESI is deemed to be clinically relevant for this study i.e., the severity grade at which a change in TB regimen or supplementation would be indicated according to the endTB Clinical Guide[7].

All recorded events deemed to be clinically relevant, including those classified as serious, are included in the present analysis.

Analysis

Patient and treatment characteristics were summarized using frequencies and percentages for categorical variables, and median and interquartile ranges (IQRs) for continuous variables.

For each clinically relevant AESI, we calculated the number of patients with at least one occurrence of the event, the median number of months to the first occurrence of the event (interquartile range, IQR); and the incidence of the event /1000 person-months of treatment and its 95% confidence interval (CI).

Incidence rates were calculated in two ways: Firstly, overall incidence of each clinically relevant AESI amongst the entire cohort, regardless of the drugs received when the clinically relevant AESI occurred. Person-months of exposure were counted from the start of treatment containing bedaquiline and/or delamanid until the event or until the end of the analyses period. Secondly, we calculated the incidence of each clinically relevant AESI only during exposure to the drug of interest (bedaquiline, delamanid, linezolid or injectable). Person-months of exposure were counted from the start of the treatment containing the drug(s) of interest until the event, a change in regimen or until the end of the analysis period.

In light of the special interest in cardiac toxicity, we draw on prior work[8] (http://endtb.org/resources/endtb-fatal-and-life-threatening-sae-report) to identify QT prolongation occurring amongst serious adverse events reported as “deaths”, “sudden deaths” and “arrythmias”.

Ethics considerations

The endTB observational study protocol was approved by local ethics review boards in all participating countries as well as by the institutional international ethics review boards. Written informed consent was obtained from all patients. The endTB observational study is registered at www.clinicaltrials.gov (NCT02754765).

RESULTS

In total, 2296 consented to participate in the endTB observational study in one of the study sites (Figure 1).

Patient and disease characteristics are shown in table 3 (additional information supplement table S4). Known risk factors for poor outcomes were common including cavitary disease on X-ray (60.9%) and fluoroquinolone resistance (53.6%).

The composition of the baseline regimen (regimen at start of bedaquiline or delamanid) is shown in table 4. At baseline, more patients received bedaquiline (1630, 71.0%) than delamanid (904, 39.4%) and 238 (10.4%) patients received both. Linezolid was commonly given (79.5%). The median time of follow-up was 16.5 months (IQR 11.5 - 19.9). For dosing see supplement, table S5.

Table 5 shows the frequency, time to first occurrence and incidence rate of clinically relevant AESI experienced by the 2296 patients in this cohort regardless of regimen composition. Incidence rates of clinically relevant AESI during exposure to a drug of interest are shown in table 6. The most common clinically relevant adverse events of special interest were: peripheral neuropathy in 26.4%, electrolyte depletion in 26.0%, and hearing loss in 13.2% of patients. QT interval was prolonged in 2.7%.

Patients who received injectables (N=925) and linezolid (N=1826) were most likely to experience events during exposure.

The subset of clinically relevant AESI that were reported as SAEs are presented in the supplement Table S6. From a total of 2296 patients, 273 patients experienced SAEs of any type with fatal outcomes[8]. We identified two patients who had an arrythmia or sudden death and in whom QT prolongation may have contributed to the event but had not previously been reported as a separate event.

DISCUSSION

Here, we report on the relative safety of bedaquiline and delamanid used in drug-resistant TB regimens in the largest, prospective observational study to date, with a particular emphasis on safety reporting. Despite a heterogeneous study population from 16 countries, monitoring and reporting were highly uniform. Distinct from prior observational reports[9–14], the present study deployed a single, externally-supported monitoring schedule including monthly electrocardiograms and audiometry; reported solicited and unsolicited adverse events; used standardized *a priori* definitions of adverse events of interest; graded events according to a single severity scale; and received support from a central pharmacovigilance unit[4,15,16].

In the endTB observational study, peripheral neuropathy was the most frequent clinically relevant adverse event of interest, experienced by over a quarter of patients (26.4% of patients), consistent with frequencies reported elsewhere [17–20]. Other toxicities often associated with linezolid occurred less often than reported in other studies; myelosuppression in only 6.0% of patients compared to 18-55% reported

elsewhere, optic neuropathy in only 3.1% compared to 13-23% reported elsewhere [12,17,18] This may be due in part to dosing strategies, which heeded experience showing that much of linezolid toxicity is driven by trough concentrations, particularly myelosupression[19]. Starting doses of linezolid were limited to 600 mg or less, doses which have been previously reported to reduce linezolid-related toxicity[18].

Most initial peripheral neuropathy events were reported as one or two on the severity scale, corresponding to mild to moderate impairment or discomfort (91%). The high proportion of low severity grade events could reflect frequent monitoring and early detection. Use of the standardized brief peripheral neuropathy screening tool, regular hematology tests, and optical screening, coupled with clear management recommendations may have resulted in dose changes, or suspension of all possibly causative drugs (cycloserine, high-dose isoniazid and linezolid) at the first sign of a clinically relevant AESI[7].

Peripheral neuropathy appears in the first 4 months for half of patients, consistent with previous studies.[21] In the context of an otherwise potent regimen, and after an initial exposure of several months, linezolid dose changes may have safety benefits with limited impact on efficacy. This question is ripe for additional research and several recently completed or ongoing trials [22–24] will inform linezolid dose optimization. In the interim, continued vigilance and active management of linezolid-related events are warranted to avert permanent disability and deaths.

Although these adverse events are commonly associated with linezolid, we do not establish causality in this report. Indeed, peripheral neuropathy causes are multiple, including pre-existing co-morbidities, concomitant TB and non-TB drugs, and other

conditions (such as excessive alcohol consumption). Myelosuppression is also linked to other conditions, including HIV co-infection.

Electrolyte depletion (hypokalemia or hypomagnesemia) was frequent, experienced by over a quarter of patients. This is especially concerning given that electrolyte depletion is a risk factor for QT prolongation and can also be aggravated by vomiting, another frequent adverse event experienced by MDR/RR-TB patients[25]. The present results support the 2019 WHO Guidelines' demotion of the aminoglycosides and polypeptides among recommended drugs for MDR/RR-TB treatment. In the rare occasions when one of these agents needs to be used, it demands systematic monitoring of electrolytes, and the possibility of replacement.

Other clinically relevant AESIs commonly associated with aminoglycosides and polypeptides, were also common. Hearing loss, of particular concern, occurred among almost 20% of patients who started a regimen with an injectable drug. Unlike many other toxicities associated with RR/MDR-TB treatment, to date, this serious disability has proved difficult to prevent despite active monitoring.[26,27] The majority of hearing loss was low grade, however, nearly a third of patients, had severe impairment (grade 3 or 4) when detected. Other studies and programs have reported higher rates of severe hearing loss[28]. In our study, systematic and regular audiometry was implemented for patients receiving injectables, which can explain early detection of low-grade hearing loss. Audiometry, early discontinuation in the presence of change, and access to otology services and devices are required to minimize the often-devastating impact of hearing loss[29,30].

In this context where ECGs were performed monthly, clinically relevant QT interval prolongation was detected in a low proportion of patients (3%), occurring only 2.6 times per 1000 patient-months of exposure to bedaquiline or delamanid. This low event rate is especially noteworthy since 96% of patients received at least one other QT-prolonging anti-TB drug (moxifloxacin, levofloxacin, clofazimine).

Initial guidance on the use of bedaquiline and delamanid emphasized potential safety risks, implying that these drugs were more toxic than drugs used previously[1,2]. QT interval prolongation, previously reported among patients who had received bedaquiline and/or delamanid[13,31–35], as well as with exposure to clofazimine[36,37] or fluoroquinolones[38–40], was feared because of its association with potentially fatal arrhythmias. Our results show QT interval prolongation is one of the least frequently reported clinically relevant AESI. One patient with this event was reported to have had a fatal outcome. Two additional patients died of unknown causes, where an arrythmia possibly related to QT prolongation are potential causes. Common factors amongst these cases, were multiple QT prolonging drugs including non-TB drugs and the use of beta blocker cardiac drugs. Although these events remain uncommon, attention is required to avoid polypharmacy and the use of beta-blockers as prevention for QT prolongation. Patients at risk for QT-prolongation require increased monitoring.[16]

Clinically relevant events commonly associated with the aminoglycosides/polypeptides (hearing loss, renal injury and electrolyte imbalances) and linezolid (peripheral neuropathy, optic neuritis, or myelosuppression) occurred almost 30 and 10 times more often, respectively. Our QT-prolongation results

(frequency of 2.7%) are consistent with those reported in a systematic analysis of cardiac safety of bedaquiline reported by Pontali et al. (3.2%),[41] the phase III delamanid trial (7/341, 2.1%)[35] and other cohort studies[9,11,33,34]. Comparison between studies is challenging due to the differences in endpoints (some reported only discontinuation of study drugs due to AE) and/or small sample sizes[10,13]. The reported frequency of important QTc prolongation in the present study is higher than in the bedaquiline phase II trial (1/79, 1.2%)[31], possibly due to endTB including patients with comorbidities and concomitant drugs (TB and non-TB) that increase the risk of QT prolongations; these were excluded from the pivotal trial of bedaquiline[31]. Despite these minor differences, it is clear from endTB and other studies that major QTc prolongation is uncommon compared to other clinically important events. However due to the seriousness of potential arrythmias and complex pharmaceutical regimens, these results highlight the importance of developing evidence-based monitoring and management strategies.

We note that the ECG monitoring and management strategy, including immediate investigation and management of other risk factors for QT prolongation (i.e., concomitant drugs, electrolyte imbalance, thyroid disorder) may have averted larger numbers of events. This strategy was feasible in routine, programmatic conditions in 16 highly diverse countries. Nevertheless, these results support suggestions that perhaps such a vigilant strategy of systematic monthly QT interval monitoring for all patients in routine care is not warranted, rather a schedule informed by individual risk may be more appropriate.[38,42]

Strengths and limitations:

The strengths of this analysis are multiple. Although not a clinical trial, the endTB Observational Study produced one of the largest prospective, systematically collected, multi-country datasets of safety data in a cohort of patients receiving new and repurposed drugs, collected with an emphasis on comprehensive, standardized drug safety monitoring, recording, and reporting. Data quality has been verified throughout the study. We report frequency and incidence to account for variability in exposure. These features permitted confident aggregation of data across countries and comparison across AESIs. Distinct from other publications on safety of bedaquiline and delamanid, the present study also included AESIs linked to repurposed and older drugs. These results are representative of safety issues that can be expected in programs throughout the world introducing similar regimens.

However, this report shares some of the limitations of other safety analyses of multidrug regimens, including the difficulty of attributing causality to a single drug. Many anti-TB drugs have toxicity profiles that overlap with other anti-TB drugs and with drugs used commonly for other indications in TB patients. Other contributing factors include comorbidities, nutritional deficiencies and substance use disorders. As an acknowledgment, we include both overall frequency of each reported event as well as incidence during exposure to the drug (class) of interest. Although neither measure attributes causality, the incidence provides a reasonable estimate of the events that can be expected with the use of the drug of interest, whether or not that drug is responsible for the event. Overestimates may occur when missing baseline safety data result in reporting of an adverse event that is actually a pre-existing condition. And, although monitoring was frequent, certain toxicities (e.g., QT

prolongation) are transient and may not be detected with the standard monitoring schedule.

Limitations specific to the present analysis also exist. We report only the first clinically relevant episode of each AESI in order to reduce bias that could result from increased risk of a subsequent event or decreased risk due to regimen change. This may underestimate the total number of events, although does not impact on the frequency of patients experiencing each event. This study does not report outcomes of the adverse events and reports only on selected AEs; this was motivated by their importance and the value of being able to make valid comparisons, rather than inducing bias by comparing fully reported events to those that may be underreported. These estimates are useful for programs planning for the number of patients who might require management of a particular event or regimen changes. A full explanation of the management strategies and repeated events is beyond the scope of the present paper.

In conclusion, this study reveals that adverse events associated with drugs commonly used in MDR/RR-TB such as linezolid, and the injectable drugs, are common. However, clinically relevant QT prolongation is uncommon when using MDR/RR-TB regimens containing bedaquiline and/or delamanid consistant with current WHO recommendations on regimen composition. Monitoring strategies should reflect the safety profiles of the drugs within these regimens. This includes brief peripheral neuropathy screening, visual assessments and blood tests for patients receiving linezolid, as well as systematic, formal hearing assessments and electrolyte monitoring for all patients receiving injectables, and targeted use of ECG.

Given that bedaquiline and linezolid are now both prioritised for the treatment of MDR/RR-TB, this data may guide clinicians when constructing MDR/RR-TB regimens, monitoring and managing adverse events, and informing patients of what to expect.

The safety data presented are relevant to both longer and shorter injectable-sparing regimens, however many questions remain on the duration and combinations that optimize efficacy and safety of MDR/RR-TB treatment. Whilst awaiting the outcomes of clinical trials underway to answer some of these questions, using shorter regimens with more effective and better tolerated drugs should be encouraged under correct monitoring conditions.

NOTES

Authors contributions:

Conceived and designed the activity: CH, HH, MB, CM, KS, MR, MF, UK, PK, FV

Acquired data: MA, LL, MN, AK, GL, SI, ND, OK, BK, HK, PT, MKK, SA, SM, AJ, AK, SP, NM, NL, SC, EO, SA

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Wrote the paper: CH

Critically revised the manuscript: CH, MB, HH, CDM, FV, MF

All authors agree with the manuscript's results and conclusions.

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Conflicts of interest

Bedaquiline donations made from Janssen to the Global Drug Facility were used for patients in the endTB observational study. Donations of delamanid from Otsuka were used for initial patients enrolled in the endTB Observational Study. Carole Mitnik declared to be a member of Akagera, Scientific Advisory Board for development of lipidbased, nano-particle delivery of anti-TB drugs (started December 2020). One payment of ~$1500 has been made to Partners In Health as honorarium for this work. Michael Rich declared 5% of time is spent on the National Institute of

Allergy and Infectious Diseases (NIAID) sponsored grant “Strengthen Evidence for Multidrug-resistant (MDR) Tuberculosis (TB) Treatment through Improved Epidemiologic Methods (STEM-TB) an observational study of MDR-TB treatment regimens and 5% of time is spent as an Expert Consultant on Operational Research in the WHO EURO project “Intercountry research on shorter all-oral treatment regimens for MDR-TB of the European TB Research Initiative”.

Other authors declare that they have no competing interests.

Conflicts of interest and funding

The endTB project, including the Observational Study, is funded by Unitaid. Payments were made to one of the three participating organisations Médecins Sans Frontières, ¨Partners In Health and Interactive Research and Development and paid for drugs, staff, medical equipment, medical consultations, data base development.

Bedaquiline donations made from Janssen to the Global Drug Facility were used for patients in the endTB observational study. Donations of delamanid from Otsuka were used for initial patients enrolled in the endTB Observational Study. Carole Mitnik declared to be a member of Akagera, Scientific Advisory Board for development of lipidbased, nano-particle delivery of anti-TB drugs (started December 2020). One payment of ~$1500 has been made to Partners In Health as honorarium for this work. Michael Rich declared 5% of time is spent on the National Institute of Allergy and Infectious Diseases (NIAID) sponsored grant “Strengthen Evidence for Multidrug-resistant (MDR) Tuberculosis (TB) Treatment through Improved Epidemiologic Methods (STEM-TB) an observational study of MDR-TB treatment regimens and 5% of time is spent as an Expert Consultant on Operational Research in the WHO EURO project “Intercountry research on shorter all-oral treatment regimens for MDR-TB of the European TB Research Initiative”. Shrivani Padayachee reports being a sub-investigator on the TB-PRACTECAL (NCT02589782) trial, sponsored by Médecins Sans Frontières, as an employee of Tuberculosis & HIV investigative Network (THINK). Other authors declare that they have no competing interests.

REFERENCES

1. World Health Organization. The use of bedaquiline in the treatment of multidrug-resistant tuberculosis interim policy guidance. WHO/HTM/TB/2013.6; 2013. 1–64. p.

2. World Health Organization. The use of delamanid in the treatment of multidrug-resistant tuberculosis: Interim policy guidance [Internet]. 2014. 1–65 p. Available from: http://apps.who.int/iris/bitstream/10665/137334/1/WHO_HTM_TB_2014.23_eng.pdf?ua=1

3. World Health Organisation. WHO consolidated guidelines on drug-resistant tuberculosis treatment. WHO/CDS/TB. 2019. 1–99 p.

4. Khan U, Huerga H, Khan AJ, Mitnick CD, Hewison C, Varaine F, et al. The endTB observational study protocol: treatment of MDR-TB with bedaquiline or delamanid containing regimens. BMC Infect Dis [Internet]. 2019 Dec 20;19(1):733. Available from: https://bmcinfectdis.biomedcentral.com/articles/10.1186/s12879-019-4378-4

5. World Health Organization. WHO treatment guidelines for drug-resistant tuberculosis. Geneva, Switz [Internet]. 2016;1–56. Available from: https://apps.who.int/iris/bitstream/handle/10665/250125/9789241549639-eng.pdf?sequence=1

6. World Health Organisation. Companion handbook to the WHO guidelines for the programmatic management of drug-resistant tuberculosis [Internet]. 2014. 1–447 p. Available from:

http://apps.who.int/iris/bitstream/10665/130918/1/9789241548809_eng.pdf?ua=1&ua=1

7. The endTB Project. endTB Clinical and Programmatic Guide for Patient Management with New TB Drugs. 3.3. 2016. 1–63 p.

8. endTB consortium. Report of fatal and life-threatening adverse events during endTB post-marketing safety surveillance of new and repurposed TB drugs [Internet]. 2021. Available from: http://endtb.org/resources/endtb-fatal-and-life-threatening-sae-report

9. Guglielmetti L, Tiberi S, Burman M, Kunst H, Wejse C, Togonidze T, et al. QT prolongation and cardiac toxicity of new tuberculosis drugs in Europe: A Tuberculosis Network European Trialsgroup (TBnet) study. Eur Respir J. 2018;52(2).

10. Lan Z, Ahmad N, Baghaei P, Barkane L, Benedetti A, Brode SK, et al. Drug-associated adverse events in the treatment of multidrug-resistant tuberculosis: an individual patient data meta-analysis. Lancet Respir Med. 2020;8(4):383–94.

11. Borisov S, Danila E, Maryandyshev A, Dalcolmo M, Miliauskas S, Kuksa L, et al. Surveillance of adverse events in the treatment of drug-resistant tuberculosis: first global report. Eur Respir J [Internet]. 2019;54(6):1–14. Available from: http://www.ncbi.nlm.nih.gov/pubmed/31601711

12. Olayanju O, Esmail A, Limberis J, Dheda K. A regimen containing bedaquiline and delamanid compared to bedaquiline in patients with drug-resistant tuberculosis. Eur Respir J [Internet]. 2020;55(1). Available from:

http://www.ncbi.nlm.nih.gov/pubmed/31619478

13. Ferlazzo G, Mohr E, Chinmay L, Hewison C, Hughes J, Jonckheere S, et al. Early safety and efficacy of the combination of bedaquiline and delamanid for the treatment of drug-resistant tuberculosis patients in Armenia, India and South Africa: a retrospective cohort study. Lancet Infect Dis [Internet]. 2018;In press(18):1–9. Available from: http://dx.doi.org/10.1016/S1473-3099(18)30100-2

14. Das M, Dalal A, Laxmeshwar C, Ravi S, Mamnoon F, Meneguim AC, et al. One step forward: Successful end-of-treatment outcomes of drug-resistant TB patients who received concomitant bedaquiline and delamanid in Mumbai, India. Clin Infect Dis [Internet]. 2020 Oct 20; Available from: http://www.ncbi.nlm.nih.gov/pubmed/33079176

15. Seung KJ, Khan U, Varaine F, Ahmed S, Bastard M, Cloez S, et al. Introducing new and repurposed TB drugs: the endTB experience. Int J Tuberc Lung Dis [Internet]. 2020 Oct 1;24(10):1081–6. Available from: http://www.ncbi.nlm.nih.gov/pubmed/33126943

16. Lachenal N, Hewison C, Mitnick C, Lomtadze N, Coutisson S, Osso E, et al. Setting up pharmacovigilance based on available endTB Project data for bedaquiline. Int J Tuberc Lung Dis [Internet]. 2020 Oct 1;24(10):1087–94. Available from: http://www.ncbi.nlm.nih.gov/pubmed/33126944

17. Singh B, Cocker D, Ryan H, Dj S. Linezolid for drug-resistant pulmonary tuberculosis (Review) SUMMARY OF FINDINGS FOR THE MAIN COMPARISON. 2019;(3).

18. Cox H, Ford N. Linezolid for the treatment of complicated drug-resistant tuberculosis: A systematic review and meta-analysis. Vol. 16, International Journal of Tuberculosis and Lung Disease. 2012. p. 447–54.

19. Agyeman AA, Ofori-Asenso R. Efficacy and safety profile of linezolid in the treatment of multidrug-resistant (MDR) and extensively drug-resistant (XDR) tuberculosis: A systematic review and meta-analysis. Ann Clin Microbiol Antimicrob. 2016;15(1):1–17.

20. Borisov SE, Dheda K, Enwerem M, Leyet RR, D'Ambrosio L, Centis R, et al. Effectiveness and safety of bedaquiline containing regimens in the treatment of MDR- and XDR-TB: A multicentre study. Eur Respir J [Internet]. 2017;49(5). Available from: http://dx.doi.org/10.1183/13993003.00387-2017

21. Tang S, Yao L, Hao X, Zhang X, Liu G, Liu X, et al. Efficacy, safety and tolerability of linezolid for the treatment of XDR-TB: a study in China. Eur Respir J. 2015 Jan;45(1):161–70.

22. ClinicalTrials.gov. Evaluating Newly Approved Drugs for Multidrug-resistant TB (endTB) [Internet]. identifier: NCT02754765. [cited 2019 Aug 22]. Available from: https://clinicaltrials.gov/ct2/show/NCT02754765?term=endTB&rank=2

23. ClinicalTrials.gov. Safety and Efficacy of Various Doses and Treatment Durations of Linezolid Plus Bedaquiline and Pretomanid in Participants With Pulmonary TB, XDR-TB, Pre- XDR-TB or Non-responsive/Intolerant MDR-TB (ZeNix) [Internet]. identifier: NCT03086486. [cited 2019 Aug 22]. Available from: https://clinicaltrials.gov/ct2/show/NCT03086486?term=zenix&rank=1

24. ClinicalTrials.gov. Pragmatic Clinical Trial for a More Effective Concise and

Less Toxic MDR-TB Treatment Regimen(s) (TB-PRACTECAL) [Internet]. Identifier: NCT02589782. [cited 2021 Dec 21]. Available from: https://clinicaltrials.gov/ct2/show/NCT02589782

25. Nathanson E, Gupta R, Huamani P, Leimane V, Pasechnikov a D, Tupasi TE, et al. Adverse events in the treatment of multidrug-resistant tuberculosis: results from the DOTS-Plus initiative. Int J Tuberc Lung Dis [Internet]. 2004 Nov;8(11):1382–4. Available from: http://www.ncbi.nlm.nih.gov/pubmed/15581210

26. Nunn AJ, Phillips PPJ, Meredith SK, Chiang C-Y, Conradie F, Dalai D, et al. A Trial of a Shorter Regimen for Rifampin-Resistant Tuberculosis. N Engl J Med [Internet]. 2019;NEJMoa1811867. Available from: http://www.nejm.org/doi/10.1056/NEJMoa1811867

27. Reuter A, Tisile P, von Delft D, Cox H, Cox V, Ditiu L, et al. The devil we know: is the use of injectable agents for the treatment of MDR-TB justified? Int J Tuberc Lung Dis [Internet]. 2017 Nov 1;21(11):1114–26. Available from: http://www.ingentaconnect.com/content/10.5588/ijtld.17.0468

28. Seddon JA, Godfrey-faussett P, Jacobs K, Ebrahim A, Hesseling AC, Schaaf HS. Hearing loss in patients on treatment for drug-resistant tuberculosis. 2012;40(5):1277–86.

29. World Health Organization (WHO). Global costs of unaddressed hearing loss and cost-effectiveness of interventions: a WHO report, 2017 [Internet]. 2017. 1–48 p. Available from: https://apps.who.int/iris/handle/10665/254659

30. Hong H, Budhathoki C, Farley JE. Increased risk of aminoglycoside-induced

hearing loss in MDR-TB patients with HIV coinfection. Int J Tuberc Lung Dis [Internet]. 2018 Jun 1;22(6):667–74. Available from: http://www.ingentaconnect.com/content/10.5588/ijtld.17.0830

31. Diacon AH, Pym A, Grobusch MP, de Los Rios JM, Gotuzzo E, Vasilyeva I, et al. Multidrug-Resistant Tuberculosis and Culture Conversion with Bedaquiline. N Engl J Med. 2014;371(8):723–32.

32. Skripconoka V, Danilovits M, Pehme L, Tomson T, Skenders G, Kummik T, et al. Delamanid improves outcomes and reduces mortality in multidrug-resistant tuberculosis. Eur Respir J. 2013;41(6):1393–400.

33. Mbuagbaw L, Guglielmetti L, Hewison C, Bakare N, Bastard M, Caumes E, et al. Outcomes of Bedaquiline Treatment in Patients with Multidrug-Resistant Tuberculosis. Emerg Infect Dis [Internet]. 2019 May;25(5). Available from: http://wwwnc.cdc.gov/eid/article/25/5/18-1823_article.htm

34. Guglielmetti L, Jaspard M, Dû D Le, Lachâtre M, Marigot-outtandy D, Bernard C, et al. Long-term outcome and safety of prolonged bedaquiline treatment for multidrug-resistant tuberculosis. Eur Respir J. 2017;49(1601799).

35. von Groote-Bidlingmaier F, Patientia R, Sanchez E, Balanag V, Ticona E, Segura P, et al. Efficacy and safety of delamanid in combination with an optimised background regimen for treatment of multidrug-resistant tuberculosis: a multicentre, randomised, double-blind, placebo-controlled, parallel group phase 3 trial. Lancet Respir Med [Internet]. 2019 Mar;7(3):249–59. Available from: https://linkinghub.elsevier.com/retrieve/pii/S2213260018304260

36. Yoon HY, Jo KW, Nam GB, Shim TS. Clinical significance of QT-prolonging drug use in patients with MDR-TB or NTM disease. Int J Tuberc Lung Dis. 2017;21(9):996–1001.

37. Wallis RS. Cardiac safety of extensively drug-resistant tuberculosis regimens including bedaquiline, delamanid and clofazimine [Internet]. Vol. 48, European Respiratory Journal. 2016. p. 1526–7. Available from: http://dx.doi.org/10.1183/13993003.01207-2016

38. Monedero-Recuero I, Hernando-Marrupe L, Sánchez-Montalvá A, Cox V, Tommasi M, Furin J, et al. QTc and anti-tuberculosis drugs: a perfect storm or a tempest in a teacup? Review of evidence and a risk assessment. Int J Tuberc Lung Dis [Internet]. 2018 Dec 1;22(12):1411–21. Available from: https://www.ingentaconnect.com/content/10.5588/ijtld.18.0423

39. Briasoulis A PW. QT Prolongation and Torsade de Pointes Induced by Fluoroquinolones: Infrequent Side Effects from Commonly Used Medications. Cardiol . 2011;120(22):103–10.

40. Harausz E, Cox H, Rich M, Mitnick CD, Zimetbaum P, Furin J. QTc prolongation and treatment of multidrug-resistant tuberculosis. Int J Tuberc Lung Dis. 2015;19(4):385–91.

41. Pontali E, Sotgiu G, Tiberi S, D'Ambrosio L, Centis R, Migliori GB. Cardiac safety of bedaquiline: A systematic and critical analysis of the evidence. Eur Respir J [Internet]. 2017;50(5). Available from: http://dx.doi.org/10.1183/13993003.01462-2017

42. Dooley KE, Rosenkranz SL, Conradie F, Moran L, Hafner R, von Groote-

Bidlingmaier F, et al. QT effects of bedaquiline, delamanid, or both in patients with rifampicin-resistant tuberculosis: a phase 2, open-label, randomised, controlled trial. Lancet Infect Dis [Internet]. 2021 Jul;21(7):975–83. Available from: http://www.croiwebcasts.org/p/2019croi/84

Table 1: Definitions of the adverse events recorded in the endTB observational study[a]

Serious Adverse Events (SAEs)	Adverse Events of special interest (AESIs)	Adverse Events (AEs) leading to a treatment change	Adverse Events (AEs) judged as otherwise clinically significant
- Fatal - Immediately life-threatening - Leading or prolonging hospitalization - Permanent/significant disability or incapacity - Birth defect or congenital anomaly - Otherwise serious (intervention required to prevent one of the above outcomes)	- Prolonged QT interval (Fridericia correction) - Peripheral neuropathy (paraesthesia) - Myelosuppression (anaemia, thrombocytopenia, neutropenia) - Optic nerve disorder - Hearing impaired - Acute kidney injury - Electrolyte depletion - Hepatitis - Hypothyroidism	AEs leading to a discontinuation of TB treatment, including permanent and temporary treatment interruption, or changes in drug(s) dosage(s) or drug regimen as decided by the clinician	Not pertaining to one of the other categories but considered of clinical significance by the treating physician

[a] Adverse events listed here were recorded irrespective of severity level

Table 2: Severity scale threshold and definition for clinically relevant adverse events of special interest in the endTB observational study

Adverse events of special interest	Threshold grade for clinically relevant adverse events of special interest and definitions	
	Grade(s)	**Definition(s), by grade**
QT prolongation	≥3	Grade 3: QTcF >= 501 msec, no symptoms Grade 4: QTcF >=501 or 60 msec increase AND symptoms[a]
Peripheral neuropathy	All grades	Impairment or discomfort/BPNS subjective sensory neuropathy score: Grade 1: Mild/BPNS 1-3 on any side Grade 2: moderate/BPNS 4-6 Grade 3: severe/BPNS 7-10 Grade 4: sensory loss, incapacitating
Optic neuritis	All grades	Grade 1: Clinical diagnosis, no symptoms; ≥Grade 2: Limiting vision (20/40 or worse)
Myelosuppression	Anemia ≥ 3	Grade3: < 7.9 g/dL
	Thrombocytopenia ≥ 3	Grade3: Platelets decreased <50,000/mm^3
	Leukopenia ≥ 3	Grade3: White blood cell decrease <2000/mm^3
	Lymphocytopenia ≥ 3	Grade3: Lymphocyte decrease <500/mm^3
	Neutropenia ≥ 2	Grade 2: Absolute neutrophil count <750/mm^3
	Pancytopenia ≥ 2	Grade 2: Any combination of the above
Hearing loss	All grades	Grade 1:Threshold shift of >=15-25 dB at >=2 frequencies or with patients with no baseline, an adverse event was declared if abnormal hearing was identified during treatment
Acute renal failure	≥ 2	Grade 2 Creatinine: ≥ 2-3 times above baseline or in absence of baseline, 1.6-3 times above the upper limit of normal creatinine Grade 2 Creatinine clearance: <90 - 60 mL/min OR 10 to <30% decrease from baseline
Electrolyte depletion	All grades	Grade 1: K < 3.4 mmol/l requiring K replacement Grade 1: Mg < 0.7 mmol/l requiring Mg

		replacement
Hepatotoxicity	≥ 3	Grade 3: ALT and/or AST > 5 times the upper limit of normal
Hypothyroidism	≥ 2	Grade 2: Symptomatic requiring thyroxin replacement

Abbreviations: QTcF: corrected QT interval by Fredericia formula; msec: milli-seconds; BPNS: Brief Peripheral Neuropathy Screen, Hb: Haemoglobin, dL: deci-litres, AST: aspartate aminotransferase, ALT; Alanine aminotransferase; K: potassium, Mg: magnesium

[a]: Symptoms include one of the following: Torsade de pointes or polymorphic ventricular tachycardia or signs/symptoms of serious arrhythmia

Table 3 Baseline patient characteristics of the endTB Observational Study cohort enrolled 1 April 2015 - 30 June 2018 (N=2296)

Patient characteristics	Total
	n (%)
Median age at registration [interquartile range]	36 [27-46]
Age (range)	(9-88)
Male	1480 (64.5)
Co-morbidities	
Diabetes mellitus (N=2277)	343 (15.3)
HIV infection (N=2296)	316 (13.8)
Hepatitis B surface antigen positivity (N=2269)	104 (4.6)
Hepatitis C antibody positivity (N=2274)	259 (11.4)
At least one other co-morbidity[c]	229 (10.0)
Body mass index <18.5 (N=1899)	592 (31.2)
Disease characteristics	
Past TB treatments (N=2294)	
No prior TB treatment	306 (13.3)
Received prior TB treatment only with first line TB drugs	251 (15.3)
Received prior TB treatment with second line TB drugs	1637 (71.4)
Extra-pulmonary disease only	18 (0.8)
Radiographic findings	
Bilateral disease (N=2026)	1355 (66.9)
Cavitary disease (N=1968)	1198 (60.9)
Smear 2+ and cavitary disease (N=1894)	345 (18.2)
Resistance profile	
RR/MDR-TB without injectable or fluoroquinolone resistance	464 (20.2)
RR/MDR-TB without second-line drug susceptibility results	274 (11.9)
RR/MDR-TB with injectable resistance	292 (12.7)
RR/MDR-TB with fluoroquinolone resistance	548 (23.9)
XDR-TB	683 (29.7)
No results for RR/MDR	35 (1.5)

Abbreviations: RR: rifampicin resistant, MDR-TB: Multidrug resistant tuberculosis - tuberculosis resistant to rifampicin and isoniazid, XDR-TB: extensively drug resistant tuberculosis - MDR-TB resistant to both a fluoroquinolone and at least one injectable drug (capreomycin, amikacin or kanamycin)

Table 4: Frequency of individual drugs in the baseline treatment regimen at time of initiation of bedaquiline or delamanid in the endTB Observational Study cohort, 1 April 2015 - 30 June 2018 (N=2296)

Drugs comprising the baseline treatment regimen	
Bedaquiline	1630 (71.0)
Delamanid	904 (39.4)
Bedaquiline and Delamanid	238 (10.4)
Linezolid	1826 (79.5)
Clofazimine	1606 (69.9)
Cycloserine	1520 (66.2)
Moxifloxacin or Levofloxacin	1456 (63.4)
Prothionamide / Ethionamide	1015 (44.2)
Kanamycin, Capreomycin or Amikacin	925 (40.3)
P-Aminosalicylic Acid	619 (27.0)
Imipenem/Cilastatin or Meropenem	376 (16.4)
Pyrazinamide	1338 (58.3)
Median number of drugs included in baseline regimen [IQR]	6 [5-6]
Median number of likely effective drugs included in baseline regimen [IQR][a]	5 [4-5]
Number with bedaquiline or delamanid and at least one QT prolonging drugs[b]	2197 (95.7)

[a] Likely effective drugs were either drugs for which all reported testing (genotypic or phenotypic) showed drug susceptibility (for those drugs with reliable testing i.e. fluoroquinolones, amikacin, kanamycin and capreomycin) or drugs with no resistance reported and that the patient had not previously received for more than 1 month.

[b] QT prolonging drugs: levofloxacin, moxifloxacin or clofazimine

Table 5: Frequency, months to first occurrence and incidence rate of clinically relevant adverse events of special interest[a] in the endTB Observational Study cohort (N=2296)

Clinically Relevant Adverse Event of Special Interest (AESI)	Patients with at least one occurrence of clinically relevant AESI[a] N (%)	Months to first occurrence of clinically relevant AESI[a] Median [IQR]	Incidence of clinically relevant AESI[a] / 1000 person-months (95% CI)
QT prolongation	63 (2.7)	2.5 [0.9-5.1]	1.8 (1.4-2.3)
Peripheral neuropathy[b]	606 (26.4)	3.9 [1.8-7.1]	21.5 (19.8-23.2)
Optic neuritis	72 (3.1)	7.6 [4.2-11.5]	2.1 (1.6-2.6)
Myelosuppression	138 (6.0)	2.5 [0.9-5.2]	4.0 (3.4-4.7)
Hearing loss[c]	304 (13.2)	4.0 [2.0-6.9]	9.7 (8.6-10.8)
Acute renal failure	174 (7.6)	2.6 [0.9-6.2]	5.1 (4.4-5.9)
Hepatotoxicity	127 (5.5)	3.1 [1.0-7.0]	3.6 (3.0-4.3)
Electrolyte depletion	596 (26.0)	3.0 [1.0-7.2]	20.7 (19.1-22.4)
Hypothyroidism	155 (6.7)	4.0 [2.8-7.3]	4.6 (3.9-5.4)

Abbreviations: AESI; adverse event of special interest.

[a]Adverse events of special interest occurring at or above the clinically relevant severity threshold as defined in table 2, includes those reported as serious adverse events.

[b]Peripheral neuropathy maximum severity of first event: grade 1: 347 (57.3%); grade 2: 204 (33.7%); grade 3: 50 (8.2); grade 4: 5 (0.8%)

[c]Hearing loss maximum severity of first event: grade 1: 135, 44.4%; grade 2: 71, 23.4%; grade 3: 87, 28.6%; grade 4: 9, 3.0%; unknown: 2, 0.7 %

Table 6: Incidence rate of clinically relevant adverse events of special interest* among patients during exposure to a drug of interest

Clinically relevant[a] adverse event of interest	Drug of interest	Person months of exposure to drug of interest	Patients with at least one occurrence of a clinically relevant[a] AESI, N (%)	Incidence of clinically relevant[a] AESI / 1000 person-months (95% CI)
QT prolongation	Bedaquiline or delamanid	19,543	50/2296 (2.2)	2.6 (1.9-3.4)
Hearing loss	Kanamycin Amikacin Capreomycin	4,936	182/925 (19.7)	36.9 (31.9-42.6)
Hearing loss OR acute renal failure OR electrolyte depletion	Kanamycin Amikacin Capreomycin	5,864	340/925 (36.8)	72.8 (66.0-80.0)
Peripheral neuropathy OR optic neuritis OR myelosuppression	Linezolid	23,660	507/1826 (27.8)	22.8 (20.9-24.8)

[a]Events occurring at or above the clinically relevant severity threshold as defined in table 2, includes those reported as serious adverse events.

Abbreviations: AESI: Adverse event of special interest

Figure Legend:

EndTB study sites chart

Figure 1