

WHO consolidated guidelines on tuberculosis

Module 4: Treatment

**Drug-resistant
tuberculosis treatment**

Online annexes



World Health
Organization

WHO consolidated guidelines on tuberculosis. Module 4: treatment - drug-resistant tuberculosis treatment. Online annexes

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Design by Inis Communication.

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Module 4: Treatment

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Abbreviations and acronyms

ACSM	advocacy, communication and social mobilization
ACTG	AIDS Clinical Trials Group
ATS	American Thoracic Society
CDC	United States Centers for Disease Control and Prevention
DALY	disability-adjusted life year
DoI	declaration of interest
DR-TB	drug-resistant tuberculosis
DSMB	Data and Safety Monitoring Board
DST	drug-susceptibility testing
EFPIA	European Federation of Pharmaceutical Industries and Associations
ERG	Evidence Review Group
EtD	evidence-to-decision (framework)
EU	European Union
FDC	fixed-dose combination
FIND	Foundation for Innovative New Diagnostics
FTE	full-time equivalent
GDG	Guideline Development Group
GRADE	Grading of Recommendations Assessment, Development and Evaluation
GRC	WHO Guideline Review Committee
GSK	Glaxo SmithKline
HALT	Hepatitis and Latent TB infection
HIV	human immunodeficiency virus
Hr-TB	isoniazid (H)-resistant tuberculosis
IDSA	United States Infectious Diseases Society of America
IPD	individual patient data
KNCV	KNCV Tuberculosis Foundation
LAM	lipoarabinomannan assay
LSHTM	London School of Hygiene & Tropical Medicine
LTBI	latent tuberculosis infection
MDR-TB	multidrug-resistant tuberculosis

MDR/RR-TB	multidrug- or rifampicin-resistant tuberculosis
MSF	Médecins Sans Frontières
NIAID	United States National Institutes of Allergy and Infectious Disease
NIH	United States National Institutes of Health
Opti-Q	Efficacy and safety of levofloxacin for the treatment of MDR-TB (study)
PICO	population, intervention, comparator and outcomes
PMDT	programmatic management of drug-resistant TB
PK/PD	pharmacokinetics/pharmacodynamics
TB-PRACTECAL	Pragmatic clinical trial for more effective, concise and less toxic MDR-TB treatment regimen(s)
RCT	randomized controlled trial
RECRU	Respiratory Epidemiology and Clinical Trials Unit (McGill University)
RR-TB	rifampicin-resistant TB
SAE	serious adverse event
SIAPS	Systems for Improved Access to Pharmaceuticals and Services
STREAM	Evaluation of a standardised treatment regimen of anti-tuberculosis drugs for patients with MDR-TB (trial)
TAG	Treatment Action Group
TB	tuberculosis
TBTC	Tuberculosis Trials Consortium
UNION	International Union Against Tuberculosis and Lung Disease
UNITAID	Global investment initiative for TB, HIV, malaria and Hepatitis C
USAID	United States Agency for International Development
WHO	World Health Organization
WHO/GTB	World Health Organization Global TB Programme
XDR-TB	extensively drug-resistant tuberculosis

Annex 1: Methods and expert panels

A1 Methods

Since 2007, the guideline development process within the World Health Organization (WHO) has been overseen by the WHO Guidelines Review Committee (GRC), which follows internationally recognized standards such as the GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach, to support to a structured and transparent methodology for policy-making. The policy recommendations presented here were developed following the standards and updated procedures described in the *WHO handbook for guideline development*.¹

Initially, a WHO Guideline Steering Group was established to determine specific areas requiring up-to-date evidence, and to bring together experts to synthesize and independently review new evidence and develop recommendations (see **Annex 2** and **Annex 4**). Also, an external review group was assembled to review the updated recommendations based on the input of the Guideline Development Group (GDG; see **Annex 4**). The GDG comprised researchers, epidemiologists, end-users (clinicians and national tuberculosis [TB] control programme officers), community representatives and experts in evidence synthesis. In compliance with the procedures and practices established by the GRC, declarations of interest (DOI) were managed according to the WHO Conflict of Interest Policy, including review of curricula vitae and critical evaluation of DOI. Additionally, contingent to the assessment of competing interests, the full list of members of the GDG and their biographies were published on the WHO website on 30 September 2019. This was followed by a public notice and comment period, during which WHO allowed members of the public to provide comments pertinent to any interests that might have gone unnoticed or unreported during earlier assessments.

During the face-to-face GDG meeting held in Geneva, Switzerland on 12–14 November 2019, the members of the GDG reached decisions through a process of discussion and consensus. Where consensus could not be reached through discussion, the GDG voted on decisions – these decisions were noted in GRADEpro and were made based on the vote of the majority.

A1.1 Preparation for evidence assessment

The GRADE approach was used to rate the certainty in the estimate of effect (quality of evidence) as high, moderate, low or very low, and to determine the strength of the recommendations (as strong or conditional). A scoping proposal was submitted and approved by the WHO GRC in September 2019. Details about the preparatory work ahead of the update were released to the public through a public comment that focused on the following: the rationale for providing up-to-date guidance, including the scope of the updates; prioritization and formulation of key questions; and the list, affiliations and constituencies of potential members of the GDG undergoing conflict of interest assessments, as per the policies of the WHO Office of Compliance, Risk Management and Ethics policies.

¹ WHO handbook for guideline development – 2nd edition Geneva, Switzerland World Health Organization; 2014 (<https://apps.who.int/iris/handle/10665/145714>, accessed 20 March 2020).

In preparation for the GDG meeting, four webinars were held with the group to finalize the scoping and PICO (patients, intervention, comparator and outcomes) questions, score outcomes of interest and discuss preliminary data analysis results. The PICO questions – inclusive of subpopulations, treatment regimen composition and duration, and outcomes – were agreed on by members of the GDG. The questions were framed to capture the effect of novel treatment regimens for specific populations and the value (in terms of effectiveness and safety) of adding, prolonging and combining specific anti-TB agents (see **Box A1**).

Box A1. PICO questions

- In MDR/RR-TB patients, does an all-oral treatment regimen lasting <12 months safely improve outcomes when compared with other regimens conforming to current WHO guidelines?
- In XDR-TB patients or patients who are treatment intolerant or with non-responsive MDR-TB, does a treatment regimen lasting 6–9 months composed of bedaquiline, pretomanid and linezolid safely improve outcomes when compared with other regimens conforming to current WHO guidelines?
- In MDR/RR-TB patients, does treatment with bedaquiline for more than six months safely improve outcomes when compared with treatment up to six months as part of regimens otherwise conforming to current WHO guidelines?
- In MDR/RR-TB patients, does concurrent use of bedaquiline and delamanid safely improve outcomes when compared with other treatment regimen options otherwise conforming to current WHO guidelines?

MDR/RR-TB: multidrug-resistant or rifampicin-resistant tuberculosis; MDR-TB: multidrug-resistant tuberculosis; PICO: patients, intervention, comparator and outcomes; XDR-TB: extensively drug-resistant tuberculosis; WHO: World Health Organization.

The PICO questions looked at the following eight distinct outcomes: successful completion of treatment; bacteriological cure by end of treatment; adherence to treatment (or treatment interruption by non-adherence); treatment failure or relapse; death during treatment; adverse reactions caused by anti-TB medicines; acquisition (amplification) of drug resistance; and sustained bacteriological cure at least 6 months after successful treatment.

Members of the GDG were invited to score the outcomes as “critical”, “important” or “not important” for making recommendations on the use of specific regimens under evaluation. The scores are shown in Table A1.

Table A1. Scoring of outcomes considered relevant by the GDG for the evidence review

Outcomes (as outlined in scoping proposal)	Rating
Survival (or death)	8.33
Relapse-free cure	8.22
Bacteriological cure by end of treatment	8.19
Successful completion of treatment (or lack of successful completion)	7.96
Treatment failure or relapse	7.93
Adherence to treatment (or treatment interruption due to non-adherence)	7.48
Acquisition (amplification) of drug resistance	7.33
Adverse events from anti-TB medicines	7.19

GDG: Guidelines Development Group; TB: tuberculosis.

Note: Relative importance was rated on an incremental scale, as follows: 1–3 points: not important for making recommendations; 4–6 points: important but not critical for making recommendations; and 7–9 points: critical for making recommendations on the evaluated interventions.

A1.2 Evidence gathering and analysis

The evidence to inform the update and development of recommendations resulted from a cooperative effort between WHO, national TB programmes (NTPs) and partner organizations, and close collaboration with a not-for-profit product development partnership (TB Alliance). For this particular update, the following data sources were used:

- Programmatic data of multidrug- or rifampicin-resistant TB (MDR/RR-TB) patients from South Africa treated with all-oral bedaquiline-containing shorter regimens, provided by the National TB Control and Management Cluster of the Department of Health of the Republic of South Africa.
- Data from a single-arm study [Nix-TB] containing records on patients receiving a novel all-oral regimen consisting of bedaquiline, pretomanid and linezolid, provided by the TB Alliance.
- Data for patients with MDR/RR-TB and extensively drug-resistant TB (XDR-TB) from 17 epidemiologically diverse countries treated with bedaquiline or delamanid-containing regimens, from the observational study of the EndTB project provided by the EndTB Consortium (Partners in Health, Médecins Sans Frontières, Interactive Research & Development and Unitaid).
- Data from a cohort study that included records of women treated during pregnancy for MDR/RR-TB using bedaquiline-containing regimens, provided by the South African Medical Research Council.
- Data resulting from a public call for records on patients from India, Republic of Belarus and Uzbekistan, treated according to WHO-recommended regimens.

Only individual patient data (IPD) was used for purposes of this update. Comparator data was assembled as part of an IPD database containing records of more than 13 000 patients with MDR/RR-TB, from 53 individual datasets from 40 countries. Sample sizes varied according to the availability of IPD for each analysable outcome. Analysable sample sizes are presented in **Annex 4**.

The methods used to minimize bias and confounding, and to make the intervention and comparator groups as similar as possible were exact matching (HIV coinfection or antiretroviral therapy [ART] use, TB treatment history and total number of drugs the strain was resistant to) and propensity score-based matching (on age, sex, and baseline sputum acid-fast bacilli [AFB] smear result). This process was conducted with replacement using a caliper distance of 0.02 during the propensity score-based matching, to estimate the adjusted odds ratios (aORs) of outcomes and their 95% confidence intervals

(CI). In addition, the distribution of the matched covariates within the intervention and comparator groups was further examined to assess the fidelity of the matching process.

The decision process that informs and leads to the making of any recommendations goes beyond the understanding of the magnitude of the desirable and undesirable effects resulting from the implementation of a particular intervention, and beyond the certainty of the evidence assessed. It also takes into account how people who are directly affected value a given intervention in terms of the main outcomes, resource implications, cost–effectiveness, impact on equity, feasibility and acceptability. For this update, the magnitude of the desirable and undesirable effects of the interventions was evaluated through the analysis methods already described. Other critical factors that could help to inform the judgements of the GDG for making an evidence-informed assessment were considered. The evidence reviews on cost–effectiveness, values, preferences and acceptability described below were commissioned to help inform the decision-making process and the conclusions drawn on the interventions under evaluation.

Evidence on cost–effectiveness

Costs could be affected, for example, through changes in duration of a regimen, use or replacement of newer agents, health care delivery costs, duration of follow-up visits and safety monitoring (and type of monitoring required; e.g. electrocardiography and audiometry). Therefore, a decision analytic model, together with estimates of the efficacy and safety differences between regimens, was used to help inform any considerations for the implementation of these recommendations. The model aimed to assess the cost of changes to recommended regimens for drug-resistant TB; estimate cost–effectiveness; and identify parameters and set specific characteristics that could influence cost or cost–effectiveness, focusing² on the use of an all-oral bedaquiline-containing shorter regimen of 9–12 months' duration, and on the use of bedaquiline for longer than 6 months and its concurrent use with delamanid. The modelling approach used projections from existing models, incorporated into certain individual parameter estimates (e.g. transmission models for secondary cases prevented by more effective treatment, and Markov cost–effectiveness models for total costs of MDR-TB cases). Costs were evaluated from a health system perspective (see Annex 4).

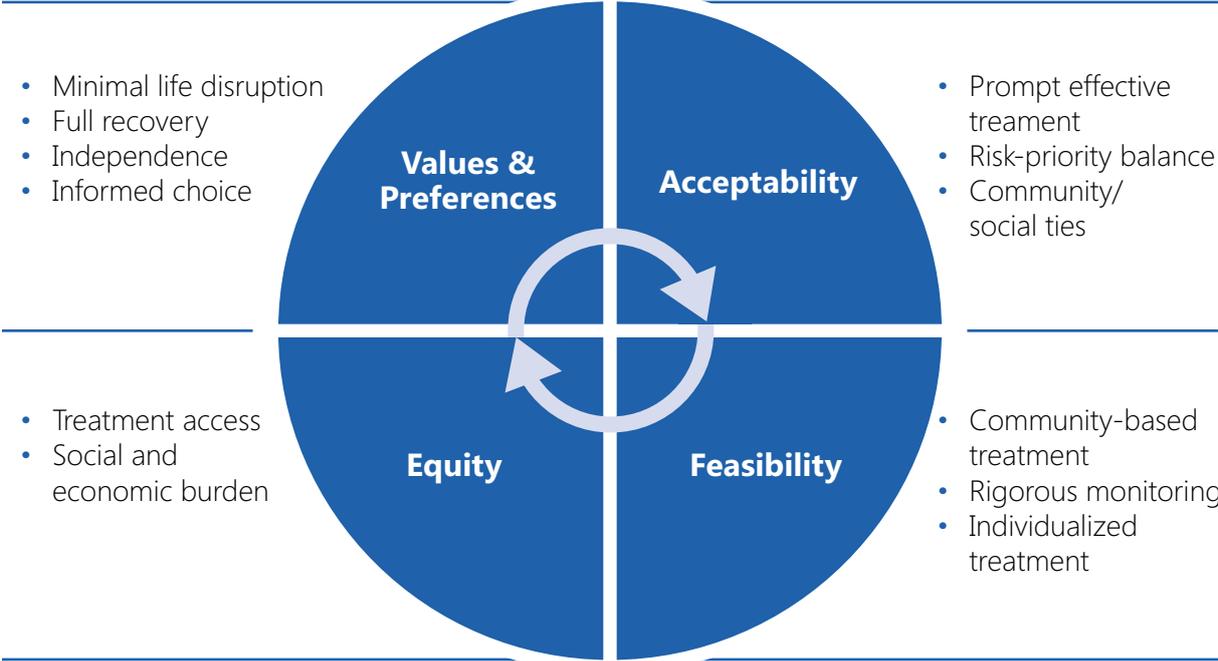
In addition, an economic evaluation was carried out to estimate the cost–effectiveness of a new regimen containing bedaquiline, pretomanid, and linezolid (BPaL), compared with the standard of care for patients who have XDR-TB, or have failed or are intolerant to their MDR-TB treatments, in three epidemiological settings at a given price. A Markov model was developed to follow a cohort of the intended population for the BPaL regimen. This provided the advantage of modelling both disease and treatment processes, where timing of events was important. Clinical data from the Nix-TB study were used to inform clinical efficacy of the intervention, and costing estimates were obtained through data available in the Global Health Costing Consortium database and from Value-TB (a multicounty TB costing study funded by the Bill & Melinda Gates Foundation).

Evidence on values and preferences

A qualitative study was undertaken to provide better understanding of the values and preferences for treatment, and perspectives on treatment acceptability, feasibility and equity. Although the goal was to gather evidence representing all individuals who would either use or be affected by the recommendations on each intervention – including policy-makers, health professionals, patients and other key stakeholders – this qualitative study was only able to capture data on patient representatives and MDR/RR-TB survivors. The methodology used to capture relevant data focused on in-depth interviews with stakeholders from high TB burden countries in Asia, Africa, Eastern Europe and South America. Fig. A1 provides an overview of the qualitative themes that reflect the values, preferences and perspectives regarding acceptability, feasibility and equity of the treatment of drug-resistant TB.

² A separate evaluation of the BPaL regimen for the treatment of patients who have XDR-TB, or have failed or are intolerant to their MDR-TB treatments, was commissioned by the manufacturer and presented to the GDG.

Fig. A1. Overview of the main qualitative themes



A1.3 Certainty of evidence and strength of recommendations

In assessing the quality of evidence, several factors can increase or decrease the quality of evidence. The highest quality rating is usually assigned to evidence gathered from randomized, controlled trials (RCTs), whereas evidence from observational studies, including programmatic data, is usually assigned a value of low or very low quality. The higher the quality of evidence, the more likely it is that a strong recommendation can be made (Table A2). The criteria used by the GDG to determine the quality of available evidence are summarized in **Annex 4**. The certainty in the estimates of effect (quality of evidence) was assessed and rated either down or up on the basis of risk of bias, inconsistency or heterogeneity, indirectness, imprecision and other considerations.

Table A2. Certainty of evidence and strength of recommendations

Certainty in the evidence	Definition
High (⊕⊕⊕⊕)	Further research is very unlikely to change our confidence in the estimate of effect.
Moderate (⊕⊕⊕○)	Further research is likely to have an important impact on our confidence in the effect and may change the estimate.
Low (⊕⊕○○)	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low (⊕○○○)	Any estimate of effect is very uncertain.

Through the GRADE system, the strength of a recommendation is classified as “strong” or “conditional”. The strength of a recommendation is determined by the balance between desirable and undesirable effects, values and preferences, resource use, equity considerations, acceptability and feasibility to implement the intervention. For *strong* recommendations, the GDG is confident that the desirable

effects of adherence to the recommendation outweigh the undesirable effects. For *conditional* recommendations, the GDG considers that the desirable effects probably outweigh the undesirable effects. The strength of a recommendation has implications for the individuals affected by these guidelines (Table A3).

Table A3. Perspective taken, and description of strength and conditionality of recommendations

Perspective	Strong recommendation	Conditional recommendation
From patients	Most individuals in this situation would want the recommended course of action and only a small proportion would not. Formal decision aids are not likely to be needed to help individuals make decisions consistent with their values and preferences.	The majority of individuals in this situation would want the suggested course of action, but many would not.
From clinicians	Most individuals should receive the intervention. Adherence to this recommendation according to the guidelines could be used as a quality criterion or performance indicator.	Recognize that different choices will be appropriate for individual patients, and that patients must be helped to arrive at a management decision consistent with their values and preferences. Decision aids may be useful in helping individuals to make decisions consistent with their values and preferences.
From policy-makers	The recommendation can be adopted as policy in most situations.	Policy-making will require substantial debate and involvement of various stakeholders.

A1.4 Assessment of the quality of the evidence

The WHO guideline development process uses specific criteria to assess the characteristics of a body of evidence, such as within-study bias (methodological quality), consistency, precision, and directness or applicability of the evidence. The evidence reviewed at the November 2019 GDG meeting was primarily programmatic data or data from cohort studies, although one dataset was from an RCT. These data were assessed as having low or very low certainty, based on an assessment of the criteria described above. The low or very low certainty of the evidence reinforced the need for additional high-quality evidence (from carefully executed research studies, including RCTs) to inform policy-making. To ensure proper assessment of the quality of the evidence, quality assurance procedures were performed by the Research Institute of the McGill University Health Centre, assisted by a GRADE methodologist.

Analysis of IPD data from studies or programmatic cohorts described in Section A1.1 was used to inform the development of specific recommendations. The IPD-based analyses help to reduce between-study heterogeneity; they also allow the examination of patient-level characteristics, harmonization of outcomes and exploration of variability in effectiveness. Although double-adjustment in propensity score matching analyses was carried out to remove the effects of confounding, there was still potential for bias in the effect estimates to have occurred through residual or unmeasured

confounding. Residual confounding could also have arisen from unknown factors, associated with both the exposure and the outcome, for which data were not collected.

A1.5 Publication, implementation, evaluation and expiry

These guidelines were prepared in accordance with the requirements of the GDG.³ They will be published on the WHO website and made freely available to download, as part of a comprehensive set of WHO consolidated guidelines on TB. They will also be communicated widely at international and regional conferences, and at meetings of programme managers in all regions. In 2020, WHO will also release an operational guide with more practical details, to support programmatic implementation of the revised recommendations. National programmes will be supported by WHO and technical and funding partners, to prepare a national plan for the programmatic management of drug-resistant TB. Implementers should create a conducive policy and programmatic environment – including national and local policies, and standard operating procedures – to facilitate implementation of the recommendations in these guidelines. This should include promoting universal health coverage and offering public financing for management of drug-resistant TB. Furthermore, dedicated resources should be allocated, including for staff development and service delivery in the community. It is important to train frontline health care staff and students in critical areas such as diagnosis, designing a regimen, patient support, monitoring response to treatment and management of adverse reactions. National programmes should ensure meaningful engagement with affected populations, their communities, the private sector, other relevant health programmes and ministries in both planning and implementing the recommendations. The uptake of these WHO recommendations will be monitored in the annual data collection of WHO Global TB Data Monitoring. WHO will update the guidelines 5 years after their publication, or earlier if new evidence becomes available that necessitates a revision.

³ WHO handbook for guideline development – 2nd edition Geneva, Switzerland World Health Organization; 2014 (<https://apps.who.int/iris/handle/10665/145714>, accessed 20 March 2020).

A2 Expert panels

This section lists the participants at GDG meetings for various updates of the drug-resistant TB treatment guidelines.

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A2.2 WHO treatment guidelines for rifampicin- and multidrug-resistant tuberculosis, 2018 update

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A2.3 WHO treatment guidelines for isoniazid-resistant tuberculosis, 2018 update

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63. Soleil LABELLE, TSC/GTB

64. Christian LIENHARDT, PSI/GTB

65. Knut LÖNNROTH, PSI/GTB

66. Alberto MATTEELLI, THC/GTB

67. Fuad MIRZAYEV, LDR/GTB

68. Linh Nhat NGUYEN, LDR/GTB

69. Marco Antonio VITORIA, TAC/HIV

70. Fraser WARES, LDR/GTB

71. Diana WEIL, PSI/GTB

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73. Matteo ZIGNOL, TME/GTB

WHO Consultant

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* Affiliated with McGill University for the evidence reviews done for these guidelines

A2.6 WHO guidelines for the programmatic management of drug-resistant tuberculosis, 2011 update

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6. **Timothy H. HOLTZ**
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7. **Joël KERAVEC**
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9. **Aamir J. KHAN**
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17. **Sarah ROYCE**
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21. **Holger SCHÜNEMANN**
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22. **Elena SKACHKOVA**
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- 28. Haileyesus GETAHUN
- 29. Malgorzata GRZEMSKA
- 30. Christian GUNNEBERG
- 31. Ernesto JARAMILLO
- 32. Christian LIENHARDT
- 33. Fuad MIRZAYEV
- 34. Paul NUNN
- 35. Mario C. RAVIGLIONE
- 36. Delphine SCULIER
- 37. Fraser WARES
- 38. Karin WEYER
- 39. Matteo ZIGNOL

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- 40. Chris DUNCOMBE
- 41. Marco Antonio DE AVILA VITORIA

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- 48. Lindiwe MVUSI
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- 52. Katsunori OSUGA
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Annex 2: Declarations of interest

A2.1 WHO treatment guidelines for multidrug- and rifampicin-resistant tuberculosis, 2020

In conformity with WHO guidelines for declaration of interests for WHO experts issued by the WHO Office for Compliance and Risk Management and Ethics, members of the Guideline Development Group, External Review Group and evidence reviewers were requested to submit completed WHO Declaration of Interest forms (DOIs) and declare in writing any competing interest (whether academic, financial or other) which could be deemed as conflicting with their role in the development of this guideline. In order to ensure the neutrality and independence of experts, an assessment of the DOI forms, curricula vitae, research interests and activities was conducted by the WHO Guideline Steering Committee. For cases in which potential conflicts were identified, the WHO Office for Compliance and Risk Management and Ethics was consulted for further clarification and advice as to how to manage competing interests. If any declared interests were judged significant, individuals were not included as members of the Guideline Development Group.

As per WHO rules, the objectives of the guideline development process and the composition of the GDG, including member biographies, were made public ahead of the meeting (<https://www.who.int/tb/areas-of-work/drug-resistant-tb/treatment/drug-resistant-tb-gdg/en/>). This public notice was conducted to allow the public to provide comments pertinent to any competing interests that may have gone unnoticed or not reported during earlier assessments.

Guideline Development Group

The following Guideline Development Group members declared no conflicts of interest: Holger Schünemann (Chair); Rafael Laniado-Laborin (Co-Chair); Erlina Burhan; Fernanda Dockhorn Costa Johansen; Bernard Fourie; Elmira Gurbanova; Muhammad Amir Khan; Marian Loveday; Mahshid Nasehi; Ben Marais; Beatrice Mutayoba; Maria Rodríguez; Debrah Vambe; and Nguyen Viet Nhung. One member of the Guideline Development Group submitted additional information, which required no further action as this did not result in any conflict.

- **Ingrid Schoeman:** As an XDR-TB survivor, she went through the side-effects of being on treatment for 2 years. She works at TB Proof, and advocacy organisation which is often invited to attend key stakeholder meetings where they share the experiences of DR-TB survivors and advocated for high-quality TB care. She has been employed by TB Proof since 2017. She is certain that better evidence-based guidelines for treating DR-TB would benefit her colleagues, friends and local communities.

Six members of the Guideline Development Group declared interests that were judged non-significant and were believed not to affect the independence and impartiality of the experts during the guideline development process. Therefore, no restrictions to their participation applied:

- **Charles Daley:** Participation in the Data Monitoring Committee (DMC) for delamanid. A total of 5000 USD by Otsuka Pharmaceutical for services rendered in 2016 as the Chairman of the Committee. Participation in the DMC for pediatric trials of delamanid (Role Member). A total of 4000 USD by Otsuka Pharmaceutical for current services as a member of the Committee.

- **Gerry Davies:** Participation in the PreDiCT-TB consortium, a public-private partnership funded by the European Union Innovative Medicines Initiative and the European Federation of Pharmaceutical Industries and Associations (EFPIA). Role as academic coordinator (2012–2017) led to engagement with industrial partners in pre-competitive areas of research into TB drug development. All of these activities were fully supported by public funding from the European Union. No financial support was received from EFPIA. Current collaborator on pharmacokinetic sub-studies deriving from the STREAM Stage 1 trial. Funding support will be provided through research institution [University of Liverpool] to support analysis of pharmacokinetic samples and data later in late 2019/early 2020. This work focuses on evaluating clofazimine and fluoroquinolones. Academic co-supervisor of PhD candidate who is currently involved in the TB-PRACTECAL trial (chief investigator) at the London School of Hygiene and Tropical Medicine. Funding support will be provided through research institution [University of Liverpool] from Médecins Sans Frontières to support analysis of pharmacokinetic samples in early 2020. This work will involve bedaquiline, pretomanid, clofazimine, linezolid and moxifloxacin.
- **Yuhong Liu:** China's New Drug Introduction and Protection Program (NDIP) was supported by the Bill & Melinda Gates Foundation (BMGF) and Janssen Pharmaceutica. Bedaquiline was provided by Janssen Pharmaceutica through the global donation project (4000 patients). BMGF and Janssen Pharmaceutica also project support to doctors' training, project activity implementation, quality control, etc. A total of 500 000 USD were provided for project implementation by BMGF including training, data collection, project supervision, between 2016–2020. Financial interests (resulting from funding source) that could directly affect, or could appear to affect, the professional judgment of the expert were not identified.
- **Iqbal Master:** Non-monetary support provided by Janssen Pharmaceutica to attend the 2016 International Lung conference in Liverpool. Only flights and accommodation were sponsored. No direct or indirect payments were made. As a manager in the MDR unit, I provide a link for the implementation of research studies, including STREAM 1 and the Nix-TB trial from 2013 onwards. I received no monetary support or remuneration for involvement in these studies. My involvement was purely from an altruistic wish to facilitate research in order to improve treatment regimens and outcomes in MDR patients in general. As a Government official, working in at a public health hospital, participation in the roll-out of bedaquiline and delamanid through a Clinical access programme, launched by the National TB programme. Member of the Provincial and National MDR-TB Advisory Committee of South Africa which makes recommendations and advises Government sites on clinical management.
- **Payam Nahid:** Federal CDC contract to support clinical trial units in San Francisco and Hanoi, Vietnam United States Centers for Disease Control and Prevention University of California, San Francisco Federal contract to support clinical trial units in San Francisco and Hanoi, Vietnam. Participation as a member of the DSMB for an MDR-TB clinical trial, TB-PRACTECAL. All DSMB related materials are obviously kept confidential. Discussions are underway with Médecins Sans Frontières (MSF) for future potential participation of Vietnam clinical trial units in Hanoi and HCMC in EndTB MDR-TB clinical trials. No contracts or agreements have been offered, signed or formalized. If agreements are formalized, enrolments into the EndTB trials would be anticipated to begin in 2020.
- **Carrie Tudor:** Grant from Eli Lilly Foundation – Lilly MDR-TB Partnership for TB Project managed by the International Council of Nurses. Award of approximately USD 1 000 000 from 2013–2019.

The below-mentioned members of the Guideline Development Group declared interests which were judged to be significant and which required further discussion and assessment by the WHO Office for Compliance and Risk Management and Ethics to outline a management plan:

- **Susan Abdel-Rahman:** (Significant) Research Support from the Thrasher Foundation for an amount of 197 000 USD. Funding ended on 30 October 2017. The Thrasher Research Fund provides grants for paediatric medical research. The Fund is currently supporting over 150 projects, including but not limited to research on childhood blindness, nutritional deficiencies, brain injuries, diabetes, asthma, cancer, genetic diseases and a number of infections including HIV, malaria, TB, schistosomiasis, cytomegalovirus and otitis media. Employment & Consultancies: WHO Agreement

for performance of work to conduct a summary review of preclinical and EBA data on pretomanid use. Financial interests (resulting from research support) that could directly affect, or could appear to affect, the professional judgment of the expert were not identified. Financial interest resulting from WHO Agreement for performance of work may be perceived to compromise the expert's objectivity or independent professional judgment in the discharge of GDG duties and responsibilities led to partial exclusion from decision-making and voting limited to BPAL regimen.

- **Daniela Cirillo:** Research grant to measure minimum inhibitory concentrations (MIC) for bedaquiline. Work sponsored through the Ospedale San Raffaele by Janssen Therapeutics. The amount granted was 50 000 USD in 2018. Research grant to study MIC distributions for new TB drugs. Work sponsored through the Ospedale San Raffaele by the TB Alliance. The amount granted was 30 000 USD in 2018. Payment for MIC work for new TB drugs was done through Ospedale San Raffaele and not direct to the individual. Although these interests are tangentially related to the subject of the current guideline development meeting (i.e. diagnostics), a significant conflict of interest was identified for participation in the decision-making process and voting related to funding from the TB Alliance, leading to partial exclusion from decision-making and voting limited to BPAL regimen.
- **Kelly Dooley:** Participation as PI of the "Assessing Pretomanid for TB (APT)" trial, assessing pretomanid for treatment of drug-sensitive TB. Support and funding is from the U.S. FDA. Drug donation from TB Alliance (pretomanid) and Pfizer (rifabutin). No salary support. Participation as investigator on trials sponsored by the NIH, FDA, the U.S. CDC or UNITAID, assessing: Use of rifapentine for TB infection in pregnant women, young children, patients with HIV co-infection; use of rifapentine for treatment shortening in patients with pulmonary TB (rifapentine donated by Sanofi); use of high-dose rifampin and levofloxacin for pediatric TB meningitis (NIH funded); use of high-dose isoniazid for MDR-TB (NIH funded, ACTG A5312); delamanid for MDR-TB in children with HIV infection (NIH funded, IMPAACT 2005; drug donation by Otsuka); bedaquiline for children with MDR-TB and HIV infection (NIH Funded, IMPAACT 1108); meropenem/amox/clav for drug-sensitive- and MDR-TB (FDA funded). No salary support. Protocol Co-Chair ACTG study A5343 assessing use of delamanid and bedaquiline among patients with MDR-TB. Drug donation by Otsuka, Janssen and ViiV Healthcare. Support and funding for this trial are provided by the U.S. NIH, Division of AIDS (DAIDS); no salary support. Involvement in the DELamanId BEdaquiline for ResistAnt Tuberculosis study (A53439) led to partial exclusion limited to discussions and voting processes related to the combined use of bedaquiline and delamanid.
- **Agnes Gebhard:** Research grant provided to KNCV by the TB Alliance to conduct a situational analysis in 3 countries (Indonesia, Kyrgyzstan, Nigeria) to understand the current infrastructure, resources, and practices for management of all forms of TB, and potential hurdles for integrating regimens (BPAL, BPAMZ, separately and together as a comprehensive solution to TB treatment). Research grant provided by the TB Alliance (305 000 USD – Between 2018 and 2019) to develop a country roadmap for introduction of new regimens. Four countries were chosen as examples (Kazakhstan, Kyrgyzstan, Uzbekistan and Indonesia). These roadmaps are flexible for use with any new (DR) TB regimen. Public support for the approval of Pretomanid in combination with bedaquiline and linezolid submitted to the U.S. FDA Antimicrobial Drugs Advisory Committee in response to a request for comments. The letter is in the public domain (<https://www.regulations.gov/docketBrowser?rpp=25&so=DESC&sb=commentDueDate&po=0&dct=PS&D=FDA-2019-N-1317>). Financial interest (Institutional) resulting from research grants provided by the TB Alliance led to partial exclusion from decision-making and voting limited to BPAL regimen.
- **Alberto Piubello:** Involvement in the Union-sponsored study "Treatment Regimen of Anti-tuberculosis Drugs for Patients With Multi-Drug-Resistant TB (STREAM), Stage 2" led to partial exclusion from decision-making and voting limited to the all-oral bedaquiline-containing shorter regimen.
- **Alena Skrahina:** Principal Investigator in the Pragmatic Clinical Trial for a More Effective Concise and Less Toxic MDR-TB Treatment Regimen(s) (TB-PRACTECAL) led to partial exclusion from decision-making and voting limited to BPAL regimen.

- **Andrew Vernon:** Work in the Division of TB Elimination at CDC which involved collaboration with NIH and Sanofi on the conduct of a multinational phase 3 trial of TB treatment using daily rifapentine. Sanofi provided medications for the trial, and has supported costs of PK testing. Total contribution to CDC Foundation was ~\$3million (from 2007–17). No payment was received through these funds. Moreover, these funds were only a small proportion of overall trial costs, the vast majority of which were borne by CDC as the trial sponsor. In his capacity as a TB researcher and clinician at CDC, Andrew participated in meetings, both internal and external, concerned with the development of guidelines for the treatment of active TB and of LTBI in the United States. Role of the U.S. CDC as temporary voting members within the U.S. FDA's Antimicrobial Drugs Advisory Committee Meeting. The latter interest led to partial exclusion from decision-making and voting limited to BPaL regimen.

External Review Group

The following External Review Group members declared no conflicts of interest: Heather ALEXANDER, Sarabjit Singh CHADHA, Lisa CHEN, Edwin H HERRERA-FLORES, Anna Marie Celina GARFIN, Mathilde JACHYM, Giovanni Battista MIGLIORI, Thato MOSIDI, Welile SIKHONDZE, Bhabana SHRESTHA, Ivan SOLOVIC, Carlos TORRES, Zarir UDWADIA.

The following ERG member declared interests that were judged not to be in conflict with the objectives of the guidelines:

- **Amanullah FARHANA:** Declared that she has been employed and undertaken consultancy work for WHO and that she has had research activities funded by WHO and the Global Fund.
- **Guy MARKS:** Is the President of The Union (IUATLD), which undertakes projects and work in the field of MDR-TB. He is an investigator on the VQUIN trial, an investigated-initiated, publicly funded study on preventive therapy for contacts of patients with MDR-TB.
- **Andrei MARYANDYSHEV:** Declared research undertaken on MDR/RR-TB. The new TB drugs were investigated in the clinical trials in the hospital where Dr Maryandyshev works, i.e. Arkhangelsk clinical antituberculosis dispensary, Russian Federation where he was a main investigator. He participated in the clinical trials of new TB drugs: TMC207-TiDP13-C209 and TMC207TBC3001 phase II-III from 1.02.2012 to 3.10.2016; "An international, multicenter, prospective, randomized, double-blind, controlled study evaluating the efficacy and tolerability of a chemotherapy regimen including SQ 109 in pulmonary tuberculosis patients with multiple drug-resistant M. tuberculosis (phase IIc-III) from 19.08.2014 to 13.07.2016; PBTZ169-A15-C2b-1 "An international multicenter, double-blind, placebo-controlled, randomized trial to evaluate the efficacy, safety, and pharmacokinetics of PBTZ169 when used in combination therapy for patients with respiratory tuberculosis with bacterial excretion and drug resistance, phase IIb-III" from 13.12.2016 to 29.05.2017; Compassionate use of Delamanid (OPC-6768) for patients MDR TB, 6.12.2016 his hospital has received Delamanid for 5 patients from Otsuka company.
- **Lawrence MBUAGBAW:** Undertook a biostatistical consultation to support FDA reporting requirements for the use of bedaquiline, for Janssen Pharmaceuticals for which he received payment.
- **Anuj K BHATNAGAR:** Is the Co-Principal investigator for the STREAM 2 trial (Medical Research Council Clinical Trials Unit, London), for the Rajan Babu Institute of Pulmonary Medicine and Tuberculosis (RBIPMT) site, Delhi in India. The trial was initiated in this site in March 2019. The monetary aspects of the trial are being looked after by Vital Strategies as an affiliate of IUATLD for refurbishment of the ward, equipment, hiring of staff, upgrading laboratory facilities, access to all laboratory tests and patient support including monetary compensation. No money has been transferred to the institute for this trial. In addition, the National Institute for Research in Tuberculosis, Chennai (NIRT), an organization of the Indian Council of Medical Research (ICMR), Ministry of Health and Family Welfare, Government of India has initiated a Phase 3 trial – called BEAT TB, to study the efficacy and tolerability of a combination of newer drugs for shortening the treatment for pre-XDR and XDR-TB in 5 sites of India. At the RBIPMT site, of which Dr Bhatnagar is the Principal Investigator for this trial, they have just completed a site initiation visit and recruitment of personnel.

The first instalment of the grant for the initiation of this trial by NIRT Chennai has been given for recruitment of staff, equipment, laboratory reagents and patient and DOT provider support.

Evidence reviewers:

The following experts who conducted the evidence for to inform the revision of the recommendations declared the below interests, which require no action beyond reporting for transparency purposes.

- **Amrita Daftary:** Columbia University Consultancy (2016–2021) – This is an ongoing consultancy to provide qualitative expertise to the design and evaluation of an adherence intervention in people with XDRTB-HIV in KwaZulu Natal, South Africa. Commissioned qualitative research for current GDG meeting. IC-IMPACTS funded grant (2015 – 2018) – study has been completed at McGill University; this was an intervention to engage pharmacy providers in Patna, India, to screen and refer TB symptomatic persons for a chest x-ray and doctor for timely TB detection. BMGF funded grant (2017–2020) – This study is held at McGill University where she was based until June 2019; this is an observational study using standardized patients to assess quality of clinical care for TB diagnosis in Cape Town and Durban, South Africa. NIH funded grant (2018 – 2020) – study is based at CAPRISA and Columbia University; this is an intervention to reduce XDRTB-HIV stigma in coinfecting patients in KwaZulu Natal, South Africa.
- **David Dowdy:** Research grant Bill and Melinda Gates Foundation Grant to Institution (not owned by me) approx \$300,000 current year interest, approximately \$50,000. Travel to meetings Bill and Melinda Gates Foundation Travel paid for me to attend, approx. \$10,000.
- **Gabriela Gomez:** Consultant providing modelling results for an investment case on a universal drug regimen for TB. Direct funding granted through BMGF for an amount of USD 40000. Funding concluded in 2018. Managed research grant to LSHTM for an economic evaluation of TB-PRACTECAL. Funding provided through MSF to research unit. Approximately £ 150 000. Her involvement stopped August 2019, although the project continues. In addition, a second grant from TB Alliance was granted to conduct an economic evaluation of the BPAL regimen. Approximately £ 60 000. Since 12 August 2019, she has been employed by Sanofi Pasteur. She is the lead for Europe in Vaccine Epidemiology and Modelling. There is no TB vaccine in the commercial pipeline of Sanofi Pasteur to her knowledge currently. She was not representing Sanofi Pasteur at this meeting, but only presenting work done as part of her previous position as Associate Professor at LSHTM.
- **Richard Menzies:** Commissioned WHO evidence reviews (2016-current) to identify, assess and synthesize the evidence for the development of guidelines for treatment of MDR-TB.
- **Rada Savic:** She received research funding from NIH, UNITAID and BMGF. Research funding to her institution (UCSF) where she is a principal investigator. She serves on Scientific Advisory Committee for TB Alliance, but receives no income for that role. She is a member of Core Science Group for NIH clinical trial network (ACTG) and for CDC clinical trial consortia (TBTC).

A2.2 WHO treatment guidelines for multidrug- and rifampicin-resistant tuberculosis, 2018

Guideline Development Group

The scope of the guidelines update and the composition of the Guidelines Development Group (GDG), including the biographies of the members, were made public for comment ahead of the meeting, in line with WHO requirements (<https://www.who.int/tb/areas-of-work/drug-resistant-tb/treatment/gdg-meeting-mdr-rr-tb-treatment-2018-update/en/>). All GDG members completed the WHO Declaration of interest (DoI) form and agreed to the confidentiality undertaking. The WHO Guideline Steering Committee reviewed the completed forms.

The following GDG members declared no interests conflicting with the objectives of the guidelines: Eden ABADIANO MARIANO, Sarabjit S CHADHA, Fernanda DOCKHORN COSTA JOHANSEN, Edwin

HERRERA-FLORES, Ayuko HIRAI, Alexander KAY, Rafael LANIADO-LABORIN, Lawrence MBUAGBAW, Austin Arinze OBIEFUNA, Cristina POPA, Wipa REECHAIPICHITKUL, Maria RODRIGUEZ, Holger SCHÜNEMANN, Adman Skirry SHABANGU and Sabira TAHSEEN.

The following GDG members declared interests that were judged not to be in conflict with the objectives of the guidelines:

Susan ABDEL-RAHMAN declared that a research grant (US\$ 196 356) was received by her institution from the Thrasher Foundation in September 2017 for her role as Principal Investigator to study whether second-line TB medicines can be accurately quantified from dried blood spots (funding ongoing). Daniela CIRILLO declared that a grant (US\$ 26 000) was provided to her research unit by the Foundation for Innovative New Diagnostics (FIND) to evaluate new TB diagnostics (funding ongoing). In 2014, she received funding from Janssen (US\$ 10 000) and Otsuka (US\$ 25 000) for work on drug-susceptibility testing (DST) of new drugs. In 2014, Janssen Italy funded her participation in an expert working group on the use of bedaquiline in Italy (US\$ 1000). Geraint (Gerry) Rhys DAVIES declared that he was until November 2017 the academic coordinator of the PreDiCT-TB consortium, a public-private partnership funded by the European Union Innovative Medicines Initiative and the European Federation of Pharmaceutical Industries and Associations (EFPIA). Although this role involved engagement with industrial partners (GSK, Sanofi, Janssen) in pre-competitive areas of research into TB drug development, these activities were fully supported by public funding from the European Union (EU) and neither he nor his research institution have received any funding from EFPIA or from the individual industrial partners. He has been asked and intends to provide advice to the STREAM study team on possible PK studies, which may be carried out in future using existing or further prospectively collected samples (no payment or research support has been offered for this activity). In 2017, he was paid fees by WHO for expert consultancies (US\$ 5000). He is a member of a steering group convened by Critical Path to TB Regimens to advise on development of the lipoarabinomannan (LAM) biomarker developed by Otsuka in the context of adaptive clinical trials (receives no payment for this activity). Bernard FOURIE declares receiving US\$ 16 000 per year (ongoing) to act as a non-executive director and member of the Board of the National Bioproducts Institute in South Africa, which is exclusively involved in the production and marketing of blood- and plasma-derived products. Payam NAHID declares an ongoing Federal US Centers for Disease Control and Prevention (CDC) contract to the University of California San Francisco to support clinical trial units in San Francisco and Viet Nam (total amount not specified). Carrie TUDOR declares that her employer receives funding from the Eli Lilly Foundation (~US\$ 1000 000 for 2013–2017; ongoing at US\$ 243 000 in 2018) to run the International Council of Nurses' TB/MDR-TB project. The project focuses on building the capacity of nurses and allied professionals on TB and DR-TB care through training and currently operates in China, Eswatini, Ethiopia, Lesotho, Malawi, the Russian Federation, Uganda and Zambia. She also received US\$ 20 000 from the KwaZulu Natal Research Institute for TB & HIV (South Africa) and Fogarty/NIH (US) for her dissertation and postdoctoral research on TB until 2014. Zarir UDWADIA declares that he has supported about 40 patients to access bedaquiline and three patients to access delamanid through the compassionate use programmes of Janssen and Otsuka, respectively. He declares that he did not charge fees to the patients involved and there were no financial transactions with the manufacturers. Andrew VERNON declares that he heads a clinical research group at US CDC (Tuberculosis Trials Consortium [TBTC]) doing TB trials. TBTC often collaborates with pharmaceutical companies, which may provide modest support, e.g. drug supplies, funding for PK sub-studies. Sanofi Aventis awarded ~US\$ 2.8 million in six unrestricted grants to CDC Foundation in 2007–2015 to facilitate or support TBTC work on rifapentine (e.g. PK studies, staff contracts, travel for invited speakers, preparation of data to support regulatory filings). These funds have not otherwise benefited the research group. TBTC has studies under way with rifapentine (TBTC Study 31) and levofloxacin (Opti-Q, TBTC Study 32). He declares that his branch has supported studies of drug-susceptible TB that have included moxifloxacin (TBTC Study 27, Study 28 and Study 31). His branch has also supported enrolment at two of the three sites involved in the Opti-Q Study. This study evaluates different doses of levofloxacin in the treatment of DR-TB and has no comparator arm. There is no involvement with drug procurement. The principal investigator and management of the study, including data handling, analysis and drug

procurement, are at Boston University. The Opti-Q outcomes are not yet known and the final analysis has yet to start. The majority of the study was funded by the US NIH (National Institutes of Allergy and Infectious Diseases [NIAID]).

The following GDG member declared an interest that was judged to conflict with the objectives of the guidelines (funding for new medicines for use in MDR-TB regimens). He therefore withdrew from the GDG panel and participated as a technical resource. Gary MAARTENS declared that his laboratory will receive US\$ 2 184 608 from the US NIH (NIAID) to undertake drug assays for a trial on the safety, tolerability and PK of bedaquiline and delamanid, alone and in combination, among patients on MDR-TB treatment (AIDS Clinical Trials Group study A5343). He will receive no salary support.

External Review Group (ERG)

The following ERG members declared no interest conflicting with the objectives of the guidelines: Essam ELMOGHAZI, Mildred FERNANDO-PANCHO, Anna Marie Celina GARFIN, Barend (Ben) MARAIS, Andrei MARYANDYSHEV, Alberto MATTEELLI, Giovanni Battista MIGLIORI, Nguyen Viet NHUNG, Rohit SARIN, Welile SIKHONDZE, Ivan SOLOVIC, Pedro SUAREZ and Carlos TORRES.

The following ERG member declared interests that were judged not to be in conflict with the objectives of the guidelines:

Thato MOSIDI declares that she represents people affected by and living with TB on the Global Fund Country Coordinating Mechanism in South Africa. She is also an active member of TB Proof, a not-for-profit organization that advocates for patient access to TB medicines.

The following evidence reviewers were from McGill University, Montréal, Canada – Syed ABIDI, Jonathon CAMPBELL, Zhiyi LAN and Dick MENZIES. They declared no interest conflicting with the objectives of the guidelines.

The following evidence reviewer declared interests that were judged not to be in conflict with the objectives of the guidelines: Faiz Ahmad KHAN declared payment by WHO to collect data and carry out a meta-analysis on the shorter MDR-TB regimens for the 2016 guidelines (CAD\$ 4080) and travel fees to present these findings at a GDG meeting in 2015. He also declares undertaking an update of the same analysis in 2016–2018 for the ATS guidelines for which he receives no remuneration.

A2.3 WHO treatment guidelines for isoniazid-resistant tuberculosis, 2018

In conformity with the WHO guidelines for declarations of interest¹ for WHO experts issued by the WHO Compliance, Risk Management and Ethics Office, members of the Guideline Development Group (GDG), Evidence Review Group (ERG) and evidence reviewers were requested to submit completed WHO Declaration of Interest forms (DoIs) and declare in writing any competing interest (whether academic, financial or other) that could be deemed as conflicting with their role in the development of this guideline. In order to ensure the neutrality and independence of experts, an assessment of the DoI forms, curricula vitae, research interests and activities was conducted by the WHO Guideline Steering Committee. For cases in which potential conflicts were identified, the WHO Compliance, Risk Management and Ethics Office was consulted for further clarification and advice as to how to manage competing interests. If any declared interests were judged significant, individuals were not included in the GDG.

ERG members were also requested to declare interests and these were also assessed for potential conflict. As per WHO rules, the objectives of the guideline development process and the composition of the GDG, including member biographies, were made public 4 weeks ahead of the meeting (<https://www.who.int/tb/areas-of-work/drug-resistant-tb/treatment/gdg-meeting-isoniazid-resistant-tb/en/>).

This public notice was conducted to allow the public to provide comments pertinent to any competing interests that may have gone unnoticed or not reported during earlier assessments.

Guideline Development Group

The following GDG members declared no interests: Daniela CIRILLO, Kelly DOOLEY (Co-Chair), Gustavo DO VALLE BASTOS, Raquel DUARTE, Christopher KUABAN, Rafael LANIADO-LABORIN, Gary MAARTENS, Andrei MARYANDYSHEV, Ignacio MONEDERO-RECUERO, Maria Imelda Josefa QUELAPIO, Wipa REECHAIPICHITKUL, Nancy SANTESSO (Co-Chair), Welile SIKHONDZE and Armand VAN DEUN.

Five GDG members declared interests that were judged non-significant and not affecting the neutrality of the guideline development process. Therefore, no restrictions to their participation applied:

Farhana AMANULLAH: (1b) paediatric expert for WHO TB monitoring mission in Indonesia (value US\$ 600/day, 14–27 January 2017); (2a) paediatric TB expert for Harvard Medical School Global Health Delivery grant (20% full-time equivalent [FTE]; June 2016–June 2018); (2b) paediatric TB expert for Global Fund grant (20% FTE; June 2016–December 2017).

Tsira CHAKHAIA: (1b) Research coordinator for TB Alliance NC-006 clinical trial (2016); community engagement project coordinator for TB Alliance (current); research coordinator for NiX-TB (from May 2017).

Philipp DU CROS: (2a) Member of the protocol writing committee and steering committee of the TB-PRACTECAL Clinical Trial, which has received a grant of €6.8 million from the Dutch Postcode Lottery to Médecins Sans Frontières, Operational Centre Amsterdam (currently active).

Michael RICH: (1a) employed by Partners in Health to work on clinical care guidelines and in the programmatic management of DR-TB; (1a) WHO consultancies on treatment of drug-resistant TB to national TB programmes; (2a) conduct research and develop regimens for drug-resistant tuberculosis (DR-TB) as a recipient of the UNITAID's Expand new drug markets for TB [EndTB] grant (all active during the development of the present recommendations).

Rada SAVIC: (1b) Member of the panel of the WHO Meeting on Target Regimen Profiles (value US\$ 2500); grant reviewer for European and Developing Countries Clinical Trials Partnership (value US\$ 1000); (2a) principal investigator or co-principal investigator of research grants by United States National Institutes of Health (NIH) and Gates Foundation on improving TB treatment options (all currently active).

External Review Group

The following ERG members declared no interests related to the objectives of this meeting: Essam ELMOGHAZI, James JOHNSTON, Enos MASINI, Rohit SARIN, Kitty VAN WEEZENBEEK, Irina VASILYEVA and Piret VIKLEPP.

The below-mentioned ERG members declared interests that were judged not to be significant to the topic of the guideline. Some of the ERG members were involved in clinical trials not related to the treatment of Hr-TB and therefore no restrictions applied to their participation as expert reviewers.

Charles L. DALEY: (1b) Chair and member of data monitoring committees for delamanid studies (US\$ 45 000 provided by Otsuka Pharmaceutical over 8 years; ongoing); Chair of data monitoring committee for clofazimine studies (US\$ 2500 provided by Novartis; finished in 2016).

Ingrid OXLEY: (5b) at the Union Conference 2015 in Cape Town, TB Proof campaigns advocated for treatment of latent TB infection (LTBI) among health care workers. She is a health care worker and has had two episodes of TB. Many members of TB Proof who are health care workers may have benefited

from the WHO guidelines for the treatment of LTBI or received funding for LTBI treatment. This was not the focus of the current guideline.

Simon SCHAAF: (2a) research support to employer for pharmacokinetics work on second-line TB medicines in children from the NIH and Otsuka Pharmaceutical (approximately ZAR 5 million/year). NIH grant ceased in 2015; Otsuka Pharmaceutical grant is still active.

Helen STAGG: (1b) grant to employer for consultancy work on MDR-TB clinical pathways in eastern Europe (Otsuka Pharmaceutical: £59 925; 2013–2015); (2a) grant to employer for Hepatitis and Latent TB Infection (HALT) study (Department of Health of the United Kingdom; National Institute for Health Research, United Kingdom; £86 000 for HALT study (2014); £315 265 for fellowship, salary, research costs; 2015–2017); (2b) non-monetary support for HALT study (Sanofi provides free rifapentine to the research study participants; 2014–2017); (6d) received International Trainee Scholarship Award (US\$ 1000 value) at the American Thoracic Society (ATS) conference 2016 where she presented the results of a review she conducted (1).

Carlos A. TORRES-DUQUE: (5a) & (5b) as member of the National Advisory Committee for Tuberculosis (Ministry of Health of Colombia) participates in the updates of national TB treatment guidelines. His expert opinion is based upon evidence and local/international experience and does not generate any profits for him.

Evidence reviewers

The independent experts who undertook the systematic reviews of evidence for this revision declared no interests related to the topic of the policy guideline objectives.

This information is included in the Declaration of interest section in the WHO treatment guidelines for isoniazid-resistant tuberculosis, pages ix–xi, available at: <https://apps.who.int/iris/bitstream/handle/10665/260494/9789241550079-eng.pdf>

A2.4 WHO guidelines for the treatment of drug-susceptible tuberculosis and patient care, 2017 update

The scope for the update of the Guidelines for treatment of drug-susceptible tuberculosis and patient care and the composition of the Guideline Development Group (GDG), as well as the External Review Group, were established in line with WHO's policy on conflict of interest. All contributors completed a WHO Declaration of Interest form. All stated declarations of interest were evaluated by three members of the steering group for the existence of any possible financial or intellectual conflict of interest. In some cases there was possible conflict of interest justifying the exclusion from membership of the GDG, and the Director of the WHO Global TB Programme, the WHO Guideline Review Committee and the WHO Legal Office were consulted on this and a decision was made. Diversity and broad representation in the GDG were sought in an effort to address and overcome any potential intellectual conflicts of interest. The GDG was composed of representatives of technical partners and academia, a GRADE methodologist, national TB programme managers from different WHO regions, representatives of civil society organizations, experts from WHO collaborating centres, professional organizations and a representative from the International Organization for Migration (see web Annex 1). The biographies of the GDG members were made public ahead of the meeting, and the WHO Guidelines Steering Committee, which was formed in preparation for the update of the guidelines, reviewed the completed forms at the beginning of the meeting with everyone present.

Guideline Development Group

The following members declared no interests: Si Thu AUNG; Frank BONSU; Jeremiah CHAKAYA; Lucy CHESIRE; Daniela CIRILLO; Poonam DHAVAN; Kathy FIEKERT; Andrei MARYANDYSHEV; Nguyen Viet NHUNG; Ejaz QADEER; Abdul Hamid SALIM; Holger SCHÜNEMANN; Pedro SUAREZ; Justin Wong Yun YAW.

The following GDG members declared interests that were judged not to be in conflict with the policy of WHO, or the objectives of the meeting:

Kelly DOOLEY declared that she did not receive any salary support from drug companies for her work in the following roles and activities: Co-chair of the AIDS Clinical Trials Group (ACTG) study assessing bedaquiline and delamanid for MDR-TB; principal investigator, assessing pretomanid for tuberculosis trial, assessing pretomanid (PA-824, investigational drug) for treatment of drug-sensitive TB; investigator on trials assessing rifapentine for pregnant women with latent TB infection, rifapentine for treatment shortening in patients with pulmonary TB, high-dose rifampicin and levofloxacin for paediatric TB meningitis, high-dose isoniazid for MDR-TB, and delamanid for MDR-TB in children with and without HIV. Mike FRICK declared that his organization received non-commercial support (1) to track investment made in TB research and development; (2) to host a symposium at the UNION meeting; (3) advocate for increased funding for TB research and development, research and access to evidence-based interventions; and (4) management of community research advisors group. Simon SCHAAF declared receiving grants for pharmacokinetic drug studies in children of second-line drugs and for studying preventive therapy in MDR-TB. Carrie TUDOR declared that her organization receives funding from Eli Lilly Foundation for activities related to TB and MDR-TB projects.

External Review Group

The following External Review Group members declared no interest related to the objectives of this meeting: Riitta DLODLO, Celine GARFIN, Lee REICHMAN, Vaira LEIMANE, Rohit SARIN, Dalene VON DELFT and Fraser WARES. The following WHO staff from the regional offices reviewed the final draft of the guideline document: Masoud DARA (Europe), Mirtha DEL GRANADO (Americas), Daniel KIBUGA (Africa), Hyder KHURSHID (South-East Asia), Mohamed AZIZ (Eastern Mediterranean), and Nobuyuki NISHIKIORI (Western Pacific).

Evidence Reviewers

The researchers who undertook the systematic reviews of evidence for this revision were the following:

Narges ALIPANAH, Cecily MILLER, Payam NAHID (team leader for PICO 1, 2 & 7–10), University of California, San Francisco, United States of America; and Lelia CHAISSON, Johns Hopkins Bloomberg School of Public Health, Baltimore, United States of America.

Richard MENZIES, McGill University, Montreal, Canada (team leader for PICO 3, 4 & 6); and James JOHNSTON, University of British Columbia, Vancouver, Canada.

Gregory FOX (team leader for PICO 11) and Jennifer HO, University of Sydney, Sydney, Australia.

The evidence reviewers did not participate in the formulation of the policy recommendations.

The following reviewers declared no interest related to the objectives of and their attendance at the meeting: Narges ALIPANAH, Jennifer HO and James JOHNSTON. The following reviewer declared interests that were judged not to be in conflict with the policy of WHO, or the objectives of the meeting: Payam NAHID declared that his research unit received support from the United States Centers for Disease Control and Prevention through a federal contract to support clinical trial units in San Francisco, USA, and in Hanoi, Viet Nam.

This information is included in the Declaration and management of conflict of interest section in the Guidelines for treatment of drug-susceptible tuberculosis and patient care, 2017 update, pages 6–7, available at: <https://apps.who.int/iris/bitstream/handle/10665/255052/9789241550000-eng.pdf>

A2.5 WHO treatment guidelines for drug-resistant tuberculosis, 2016 update

Guideline Development Group

The scope of the guidelines update, and the composition of the GDG, including their biographies, were made public for comment ahead of the meeting in line with WHO's conflict of interest policy. All GDG members completed the WHO Declaration of Interest forms. The WHO Guideline Steering Committee, in preparation for the update of the guidelines and the GDG meeting, reviewed the completed forms. The following GDG members declared no conflicting interests: Luis Gustavo do

Valle BASTOS, José A CAMINERO, Tsira CHAKHAIA, Michel GASANA, Armen HAYRAPETYAN, Antonia KWIECIEN, Sundari MASE, Nguyen Viet NHUNG, Maria RODRIGUEZ, Holger SCHÜNEMANN, James SEDDON and Alena SKRAHINA.

The following GDG members declared interests that were judged not to be in conflict with the objectives of the meeting: Farhana AMANULLAH declared having received funding for consultancies (US\$ 500/ day) and travel from WHO; and grants from the Global Fund and TB-REACH to cover her salary (10% full-time equivalent).

Daniela CIRILLO declared having received funding from FIND to conduct evaluation of drug-susceptibility testing (DST) for new drugs (US\$ 16 000), and from Otsuka to evaluate DST for delamanid (US\$ 25 000). She also declared being the head of a supranational TB reference laboratory in Italy involved in country capacity-building in DST technologies for second-line drugs and new diagnostics for drug-resistant TB; and being a member of the Italian national committee for the use of bedaquiline. Charles L. DALEY declared having received funding from Otsuka to serve as chair of the data monitoring committee for trials of delamanid (US\$ 47 000 over 7 years–current). Kelly DOOLEY declared having received funding to provide expert advice on a trial design for TB/HI (US\$ 2000/ year paid to the university/ employer); she also declared the following activities and roles: co-chair AIDS Clinical Trials Group (ACTG) study assessing bedaquiline and delamanid; principal investigator for adjuvant paclitaxel and trastuzumab (APT) trial assessing pretomanid (PA-824); and investigator in trials assessing high-dose isoniazid for MDR-TB, rifapentine for pregnant women and children with latent TB infection (LTBI), high- dose rifampicin and levofloxacin for paediatric TB meningitis, as well as bedaquiline and delamanid for children with MDR-TB and HIV infection.

Agnes GEBHARD declared that she works for the KNCV TB Foundation, which has two projects funded by the Eli Lilly and Company Foundation: (i) engaging the private sector in diagnosis and treatment of TB and MDR-TB with quality-assured second-line TB drugs, and (ii) the roll-out of QuanTB (a drug forecasting tool) in countries not supported by the Systems for Improved Access to Pharmaceuticals and Services (SIAPS) implemented by Management Sciences for Health. In addition, she declared that the KNCV TB Foundation has a collaborative project with Cepheid in two countries (Nigeria, Viet Nam), with KNCV providing services for the installation and initial training on the use of GeneXpert machines. Carlos TORRES-DUQUE declared having received honoraria from Janssen Pharmaceuticals for presentations on TB prevention and WHO policy on bedaquiline at a Latin American Meeting on MDR-TB held in 2014 (US\$ 2000). Tom SHINNICK declared being an employee of the United States Centers for Disease Control and Prevention (CDC). CDC supports his travel and research related to his work on laboratory services needed for TB control. He declared having often represented CDC's position on laboratory services needed for TB diagnosis, treatment and control. As part of his official duties for CDC, he served on the Data and Safety Monitoring Board (DSMB) organized by Otsuka

for the clinical trial of delamanid. He did not receive any remuneration for serving on the DSMB nor for travel expenses (CDC paid for all travel expenses related to serving on the DSMB). The DSMB has completed its work for the trial.

The following GDG members declared interests that were judged to be in conflict with some of the objectives of the meeting and were thus recused from some of the discussions: Lindsay MCKENNA declared non-commercial support to Treatment Action Group (TAG), her employer, from Stop TB Partnership; Bill & Melinda Gates Foundation; the US Department of Veteran Affairs (on behalf of CDC); Janssen Therapeutics for Hepatitis C and HIV projects and the Global Alliance for TB Drug Development (a public–private entity developing new drugs and regimens for TB treatment). She was thus recused from participating in the 9 November 2015 meeting session on Patients, Intervention, Comparator and Outcomes (PICO) question 1 on MDR-TB regimen composition for adults and children. José A CAMINERO stated in his biosketch that he is a staff consultant of the International Union Against Tuberculosis and Lung Disease (UNION), an agency directly involved in the implementation and evaluation of programmes using shorter MDR-TB regimens. He was therefore recused from the 10 November 2015 meeting session on PICO question 3 on shorter regimens for MDR-TB.

External Review Group

The following ERG members declared no interest related to the objectives of this meeting: Chen-Yuan CHIANG, Celine GARFIN, Michael KIMERLING, Vaira LEIMANE, Gao MENGQIU, Norbert NDJEKA, Ejaz QADEER, Lee REICHMAN, Rohit SARIN and Irina VASILYEVA.

The following two ERG members declared interests which were judged not to be in conflict with the objectives of the guidelines. Guy MARKS declared research support from AERAS (US\$ 450 000) related to the evaluation of latent TB infection and the rate of recurrence of TB after initial treatment in Viet Nam. He also declared being the Vice-President (and a board member) of the UNION and Editor-in-Chief of the International Journal of Tuberculosis and Lung Disease (for which he receives an honorarium). Dalene VON DELFT declared having received support from TAG, USAID, UNITAID, Janssen Pharmaceuticals, Critical Path to TB Drug Regimens (CPTR) and AERAS to cover travel costs and accommodation to give presentations/speeches on drug-resistant TB. She declared that in 2011 she received bedaquiline as part of her MDR-TB treatment through a compassionate use access programme.

Evidence Reviewers

The following reviewers declared interests that were judged not to be in conflict with the objectives of the meeting:

Gregory J FOX declared having received research and non-monetary support from the UNION (sponsored by Otsuka) valued at about US\$ 5000 to attend the 2015 International UNION Conference and to receive the Young Innovator Award (he declares no work for Otsuka or any relationship of this award with any commercial or research activities with Otsuka).

Katherine FIELDING declared that her employer (LSHTM) was a recipient of an award from Médecins Sans Frontières (MSF) (£26 890) for the period February–December 2015 to provide statistical support for the TB-PRACTECAL study on which she is a co-investigator. The study is a Phase II–III randomized controlled trial (RCT) to evaluate the efficacy and safety of shorter MDR-TB regimens for adults.

Rebecca HARRIS declared she is consulting for a clinical research organization (Cromsource) working for Glaxo SmithKline (GSK) vaccines (~£90 000 in 2013); and on GSK vaccines not related to TB (~£10 000 since 2013) for Manpower Solutions.

David MOORE declared receiving research support from the Wellcome Trust Research Training Fellowship Programme to supervise a PhD student to study MDR-TB in Peru (£207 056 in 2014).

Anneke HESSELING declared that her employer (Stellenbosch University) is a recipient of an award from Otsuka Pharmaceutical (~US\$ 70 000 to date) for her work on the Phase III delamanid clinical trials in children.

This information is included in the Declaration of interest section in the WHO treatment guidelines for drug-resistant tuberculosis, 2016 update, pages 2–5, available at: https://www.who.int/tb/areas-of-work/drug-resistant-tb/Annexes_8-10.pdf

A2.6 WHO guidelines for the programmatic management of drug-resistant tuberculosis, 2011 update

Funding for the meetings and reviews involved in the updating of the guidelines came entirely from the United States Agency for International Development (USAID). The experts on the Guideline Development Group (GDG) and the institutions where they work contributed time for the various discussions and other activities involved in the update process.

The Declaration of interest forms were completed by all non-WHO members of the GDG and the External Review Group, as well as the members of the academic centres who were involved in the reviews. Four members of the GDG declared interests that were judged to represent a potential conflict and were excused from the sessions of the meeting on 25–27 October 2010 during which recommendations relating to the drug regimens were discussed. Jaime BAYONA was a consultant for the development of clinical trial design for studies of an anti-tuberculosis drug manufactured by Otsuka Pharmaceutical Co. Ltd (OPC-67683). Charles L. DALEY was chairperson of drug-safety monitoring for two trials conducted by Otsuka Pharmaceutical Co. Ltd. Carole D. MITNICK served as a member of the Scientific Advisory Board of Otsuka Pharmaceutical Co. Ltd and had an advisory role on drug OPC-67683. Ma. Imelda QUELAPIO received support (monetary and non-monetary) for research from Otsuka Pharmaceutical Co. Ltd.

The following members of the academic centres, who performed the reviews of evidence from which the recommendations contained in these guidelines are derived, presented their findings at the meeting: Matthew ARENTZ, Melissa BAUER, Richard MENZIES, Carole D. MITNICK, Olivia OXLADE, Patricia PAVLINAC and Judd L. WALSON. They did not participate in the formulation of recommendations related to the respective reviews of evidence that they performed.

This information is included in the Funding and declarations of interest section in the Guidelines for the programmatic management of drug-resistant tuberculosis, 2011 update, page 2, available at: https://apps.who.int/iris/bitstream/handle/10665/44597/9789241501583_eng.pdf

Annex 3: GRADE evidence summary tables

A3.1 WHO treatment guidelines for multidrug- and rifampicin-resistant tuberculosis, 2020 update

Author(s): Research Institute of the McGill University Health Centre

Question: Should an all-oral shorter regimen of 9–12 months' duration including bedaquiline vs a shorter regimen recommended by WHO (with injectable) be used for MDR/RR-TB patients to safely improve outcomes?

Setting: International

Date: April 2020

№ of studies	Certainty assessment				№ of patients		Effect		Certainty	Importance		
	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	All-oral bedaquiline-containing shorter regimen of 9–12 months duration	Shorter regimen recommended by WHO (with injectable)			Relative (95% CI)	Absolute (95% CI)
1	observational studies	serious ^a	not serious	not serious	not serious	none	631/653 (96.6%)	573/621 (92.3%)	OR 2.1 (1.1 to 4.0)	3 more per 100 (from 1 more to 6 more) ^{b,c}	⊕○○○ VERY LOW	CRITICAL
Success vs. Failure/Recurrence (follow up: mean 18 months)												
1	observational studies	serious ^a	not serious	not serious	not serious	none	631/791 (79.8%)	573/792 (72.3%)	OR 1.6 (1.2 to 2.1)	8 more per 100 (from 3 more to 13 more) ^{b,c}	⊕○○○ VERY LOW	CRITICAL
Success vs. Death (follow up: mean 18 months)												
1	observational studies	serious ^a	not serious	not serious	not serious	none	631/813 (77.6%)	573/840 (68.2%)	OR 1.7 (1.3 to 2.2)	10 more per 100 (from 5 more to 15 more) ^{b,c}	⊕○○○ VERY LOW	CRITICAL
Success vs. Failure/Recurrence/Death (follow up: mean 18 months)												

Certainty assessment				№ of patients		Effect				
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Effect			
							Relative (95% CI)	Absolute (95% CI)		
Success vs. All Unfavorable (follow up: mean 18 months)										
1	observational studies	serious ^a	not serious	not serious	none	631/891 (70.8%)	573/987 (58.1%)	OR 1.9 (1.6 to 2.4) 14 more per 100 (from 9 more to 19 more) ^{bc}	⊕○○○ VERY LOW	CRITICAL
Lost vs. All Other Outcomes (follow up: mean 18 months)										
1	observational studies	serious ^a	not serious	not serious	none	88/891 (9.9%)	171/987 (17.3%)	OR 0.5 (0.4 to 0.7) 7 fewer per 100 (from 11 fewer to 4 fewer) ^{bc}	⊕○○○ VERY LOW	CRITICAL
AFB Smear Positive: Success vs. Failure/Recurrence (follow up: mean 18 months)										
1	observational studies	serious ^a	not serious	not serious	none	267/274 (97.4%)	197/221 (89.1%)	OR 4.4 (1.6 to 11.9) 8 more per 100 (from 3 more to 13 more) ^b	⊕○○○ VERY LOW	CRITICAL
AFB Smear Positive: Success vs. Death (follow up: mean 18 months)										
1	observational studies	serious ^a	not serious	not serious	none	267/341 (78.3%)	197/269 (73.2%)	OR 1.3 (0.8 to 2.1) 5 more per 100 (from 3 fewer to 12 more) ^b	⊕○○○ VERY LOW	CRITICAL
AFB Smear Positive: Success vs. Failure/Recurrence/Death (follow up: mean 18 months)										
1	observational studies	serious ^a	not serious	not serious	none	267/348 (76.7%)	197/293 (67.2%)	OR 1.7 (1.1 to 2.6) 10 more per 100 (from 2 more to 17 more) ^b	⊕○○○ VERY LOW	CRITICAL
AFB Smear Positive: Success vs. All Unfavorable (follow up: mean 18 months)										
1	observational studies	serious ^a	not serious	not serious	none	267/378 (70.6%)	197/345 (57.1%)	OR 2.3 (1.6 to 3.3) 16 more per 100 (from 9 more to 24 more) ^b	⊕○○○ VERY LOW	CRITICAL

Certainty assessment			№ of patients		Effect		Certainty	Importance				
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			All-oral bedaquiline-containing shorter regimen of 9–12 months duration	Shorter regimen recommended by WHO (with injectable)	Relative (95% CI)	Absolute (95% CI)
AFB Smear Positive: Lost vs. All Other Outcomes (follow up: mean 18 months)												
1	observational studies	serious ^a	not serious	not serious	not serious	none	33/378 (8.7%)	63/345 (18.3%)	OR 0.4 (0.2 to 0.6)	11 fewer per 100 (from 16 fewer to 5 fewer) ^b	⊕○○○ VERY LOW	CRITICAL
HIV-Positive on ART: Success vs. Failure/Recurrence (follow up: mean 18 months)												
1	observational studies	serious ^a	not serious	not serious	not serious	none	429/446 (96.2%)	346/368 (94.0%)	OR 1.4 (0.7 to 2.9)	2 more per 100 (from 2 fewer to 5 more) ^b	⊕○○○ VERY LOW	CRITICAL
HIV-Positive on ART: Success vs. Death (follow up: mean 18 months)												
1	observational studies	serious ^a	not serious	not serious	not serious	none	429/541 (79.3%)	346/492 (70.3%)	OR 1.6 (1.2 to 2.3)	8 more per 100 (from 3 more to 14 more) ^b	⊕○○○ VERY LOW	CRITICAL
HIV-Positive on ART: Success vs. Failure/Recurrence/Death (follow up: mean 18 months)												
1	observational studies	serious ^a	not serious	not serious	not serious	none	429/558 (76.9%)	346/514 (67.3%)	OR 1.6 (1.2 to 2.2)	9 more per 100 (from 3 more to 15 more) ^b	⊕○○○ VERY LOW	CRITICAL
HIV-Positive on ART: Success vs. All Other Unfavorable (follow up: mean 18 months)												
1	observational studies	serious ^a	not serious	not serious	not serious	none	429/613 (70.0%)	346/599 (57.8%)	OR 1.9 (1.4 to 2.4)	14 more per 100 (from 8 more to 19 more) ^b	⊕○○○ VERY LOW	CRITICAL
HIV-Positive on ART: Lost vs. All Other Outcomes (follow up: mean 18 months)												
1	observational studies	serious ^a	not serious	not serious	not serious	none	63/613 (10.3%)	97/599 (16.2%)	OR 0.6 (0.4 to 0.8)	6 fewer per 100 (from 10 fewer to 2 fewer) ^b	⊕○○○ VERY LOW	CRITICAL

Certainty assessment				№ of patients		Effect		Certainty	Importance			
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	All-oral bedaquiline-containing shorter regimen of 9–12 months duration			Shorter regimen recommended by WHO (with injectable)	Relative (95% CI)	Absolute (95% CI)
HIV Negative: Success vs. Failure/Recurrence (follow up: mean 18 months)												
1	observational studies	serious ^a	not serious	not serious	not serious	none	195/199 (98.0%)	205/228 (89.9%)	OR 6.5 (1.4 to 29.5)	7 more per 100 (from 2 more to 12 more) ^b	⊕○○○ VERY LOW	CRITICAL
HIV Negative: Success vs. Death (follow up: mean 18 months)												
1	observational studies	serious ^a	not serious	not serious	not serious	none	195/234 (83.3%)	205/254 (80.7%)	OR 1.9 (1.1 to 3.5)	10 more per 100 (from 1 more to 18 more) ^b	⊕○○○ VERY LOW	CRITICAL
HIV Negative: Success vs. Failure/Recurrence/Death (follow up: mean 18 months)												
1	observational studies	serious ^a	not serious	not serious	not serious	none	195/238 (81.9%)	205/277 (74.0%)	OR 2.1 (1.3 to 3.6)	13 more per 100 (from 4 more to 21 more) ^b	⊕○○○ VERY LOW	CRITICAL
HIV Negative: Success vs. All Other Outcomes (follow up: mean 18 months)												
1	observational studies	serious ^a	not serious	not serious	not serious	none	195/255 (76.5%)	205/327 (62.7%)	OR 2.7 (1.7 to 4.3)	20 more per 100 (from 11 more to 29 more) ^b	⊕○○○ VERY LOW	CRITICAL
HIV Negative: Lost vs. All Other Outcomes (follow up: mean 18 months)												
1	observational studies	serious ^a	not serious	not serious	not serious	none	18/255 (7.1%)	61/327 (18.7%)	OR 0.3 (0.2 to 0.7)	10 fewer per 100 (from 17 fewer to 4 fewer) ^b	⊕○○○ VERY LOW	CRITICAL

AFB: acid-fast bacilli; aOR: adjusted odds ratio; ART: antiretroviral therapy; CI: confidence interval; HIV: human immunodeficiency virus; MDR/RR-TB: multidrug- or rifampicin-resistant TB; OR: odds ratio; WHO: World Health Organization.

Explanations

- For some patients, information was missing on AFB smear result and culture result in the analysis. Patients with unknown age, sex, or HIV status were excluded from all analyses.
- Outcomes and costs are simulated using a model that draws parameter estimates from multiple sources, including the aORs for success versus death/failure described above.
- The absolute effect is calculated after matching intervention and comparator populations, and performing binomial regression with an identity link.

Author(s): Research Institute of the McGill University Health Centre

Question: Should an all-oral shorter regimen of 9–12 months' duration including bedaquiline vs longer regimens without new TB drugs be used for MDR/RR-TB patients to safely improve outcomes?

Setting: International

Date: April 2020

№ of studies	Certainty assessment					№ of patients		Effect		Certainty	Importance	
	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	All-oral bedaquiline-containing shorter regimen of 9–12 months duration	Longer regimens without new TB drugs	Relative (95% CI)			Absolute (95% CI)
1	observational studies ^a	serious ^a	not serious	not serious	not serious	none	631/653 (96.6%)	679/771 (88.1%)	OR 3.7 (2.2 to 6.3)	8 more per 100 (from 5 more to 11 more) ^{b,c}	⊕○○○ VERY LOW	CRITICAL
Success vs. Failure/Recurrence (follow up: mean 18 months)												
1	observational studies	serious ^a	not serious	not serious	not serious	none	631/791 (79.8%)	679/1044 (65.0%)	OR 2.3 (1.8 to 3.0)	15 more per 100 (from 10 more to 19 more) ^{b,c}	⊕○○○ VERY LOW	CRITICAL
Success vs. Death (follow up: mean 18 months)												
1	observational studies	serious ^a	not serious	not serious	not serious	none	631/813 (77.6%)	679/1136 (59.8%)	OR 2.6 (2.0 to 3.3)	18 more per 100 (from 14 more to 23 more) ^{b,c}	⊕○○○ VERY LOW	CRITICAL
Success vs. Failure/Recurrence/Death (follow up: mean 18 months)												
1	observational studies	serious ^a	not serious	not serious	not serious	none	631/891 (70.8%)	679/1437 (47.3%)	OR 2.8 (2.3 to 3.5)	23 more per 100 (from 18 more to 27 more) ^{b,c}	⊕○○○ VERY LOW	CRITICAL
Success vs. All Unfavorable (follow up: mean 18 months)												

No of studies		Certainty assessment					No of patients		Effect		Certainty	Importance
		Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	All-oral bedaquiline-containing shorter regimen of 9–12 months duration	Longer regimens without new TB drugs	Relative (95% CI)		
1		observational studies	serious ^a	not serious	not serious	none	88/891 (9.9%)	368/1437 (25.6%)	OR 0.4 (0.3 to 0.5)	14 fewer per 100 (from 17 fewer to 10 fewer) ^{b,c}	⊕○○○ VERY LOW	CRITICAL
Lost vs. All Other Outcomes (follow up: mean 18 months)												
1		observational studies	serious ^a	not serious	not serious	none	267/274 (97.4%)	248/288 (86.1%)	OR 8.9 (3.4 to 23.7)	12 more per 100 (from 7 more to 17 more) ^b	⊕○○○ VERY LOW	CRITICAL
AFB Smear Positive: Success vs. Failure/Recurrence (follow up: mean 18 months)												
1		observational studies	serious ^a	not serious	not serious	none	267/341 (78.3%)	248/378 (65.6%)	OR 2.1 (1.5 to 3.1)	13 more per 100 (from 6 more to 20 more) ^b	⊕○○○ VERY LOW	CRITICAL
AFB Smear Positive: Success vs. Death (follow up: mean 18 months)												
1		observational studies	serious ^a	not serious	not serious	none	267/348 (76.7%)	248/418 (59.3%)	OR 3.0 (2.1 to 4.4)	19 more per 100 (from 12 more to 26 more) ^b	⊕○○○ VERY LOW	CRITICAL
AFB Smear Positive: Success vs. Failure/Recurrence/Death (follow up: mean 18 months)												
1		observational studies	serious ^a	not serious	not serious	none	267/378 (70.6%)	248/529 (46.9%)	OR 2.9 (2.1 to 4.0)	24 more per 100 (from 17 more to 31 more) ^b	⊕○○○ VERY LOW	CRITICAL
AFB Smear Positive: Success vs. All Unfavorable (follow up: mean 18 months)												
1		observational studies	serious ^a	not serious	not serious	none	33/378 (8.7%)	131/529 (24.8%)	OR 0.3 (0.2 to 0.6)	15 fewer per 100 (from 20 fewer to 9 fewer) ^b	⊕○○○ VERY LOW	CRITICAL
AFB Smear Positive: Lost vs. All Other Outcomes (follow up: mean 18 months)												

No of studies		Certainty assessment				No of patients		Effect		Certainty	Importance	
		Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	All-oral bedaquiline-containing shorter regimen of 9–12 months duration	Longer regimens without new TB drugs			Relative (95% CI)
HIV-Positive on ART: Success vs. Failure/Recurrence (follow up: mean 18 months)												
1	observational studies	serious ^a	not serious	not serious	not serious	none	429/446 (96.2%)	432/491 (88.0%)	OR 4.5 (2.4 to 8.4)	8 more per 100 (from 4 more to 11 more) ^b	⊕○○○ VERY LOW	CRITICAL
HIV-Positive on ART: Success vs. Death (follow up: mean 18 months)												
1	observational studies	serious ^a	not serious	not serious	not serious	none	429/541 (79.3%)	432/689 (62.7%)	OR 2.7 (2.0 to 3.7)	18 more per 100 (from 12 more to 23 more) ^b	⊕○○○ VERY LOW	CRITICAL
HIV-Positive on ART: Success vs. Failure/Recurrence/Death (follow up: mean 18 months)												
1	observational studies	serious ^a	not serious	not serious	not serious	none	429/558 (76.9%)	432/748 (57.8%)	OR 2.9 (2.2 to 3.9)	21 more per 100 (from 15 more to 26 more) ^b	⊕○○○ VERY LOW	CRITICAL
HIV-Positive on ART: Success vs. All Unfavorable (follow up: mean 18 months)												
1	observational studies	serious ^a	not serious	not serious	not serious	none	429/613 (70.0%)	432/919 (47.0%)	OR 2.7 (2.1 to 3.5)	23 more per 100 (from 17 more to 28 more) ^b	⊕○○○ VERY LOW	CRITICAL
HIV-Positive on ART: Lost vs. All Other Outcomes (follow up: mean 18 months)												
1	observational studies	serious ^a	not serious	not serious	not serious	none	63/613 (10.3%)	214/919 (23.3%)	OR 0.4 (0.3 to 0.6)	11 fewer per 100 (from 15 fewer to 7 fewer) ^b	⊕○○○ VERY LOW	CRITICAL
HIV Negative: Success vs. Failure/Recurrence (follow up: mean 18 months)												
1	observational studies	serious ^a	not serious	not serious	not serious	none	195/199 (98.0%)	227/258 (88.0%)	OR 6.7 (2.2 to 20.8)	12 more per 100 (from 6 more to 18 more) ^b	⊕○○○ VERY LOW	CRITICAL

No of studies		Certainty assessment					No of patients		Effect		Certainty	Importance
		Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	All-oral bedaquiline-containing shorter regimen of 9–12 months duration	Longer regimens without new TB drugs	Relative (95% CI)		
1		observational studies	serious ^a	not serious	not serious	none	HIV Negative: Success vs. Death (follow up: mean 18 months)					CRITICAL
							195/234 (83.3%)	227/302 (75.2%)	OR 2.1 (1.2 to 3.8)	13 more per 100 (from 5 more to 21 more) ^b	⊕○○○ VERY LOW	
1		observational studies	serious ^a	not serious	not serious	none	HIV Negative: Success vs. Failure/Recurrence/Death (follow up: mean 18 months)					CRITICAL
							195/238 (81.9%)	227/333 (68.2%)	OR 2.5 (1.6 to 3.8)	17 more per 100 (from 9 more to 26 more) ^b	⊕○○○ VERY LOW	
1		observational studies	serious ^a	not serious	not serious	none	HIV Negative: Success vs. All Other Outcomes (follow up: mean 18 months)					CRITICAL
							195/255 (76.5%)	227/440 (51.6%)	OR 3.5 (2.4 to 5.2)	28 more per 100 (from 20 more to 37 more) ^b	⊕○○○ VERY LOW	
1		observational studies	serious ^a	not serious	not serious	none	HIV Negative: Lost vs. All Other Outcomes (follow up: mean 18 months)					CRITICAL
							18/255 (7.1%)	130/440 (29.5%)	OR 0.2 (0.1 to 0.4)	21 fewer per 100 (from 28 fewer to 14 fewer) ^b	⊕○○○ VERY LOW	

AFB: acid-fast bacilli; aOR: adjusted odds ratio; ART: antiretroviral therapy; CI: confidence interval; HIV: human immunodeficiency virus; MDR/RR-TB: multidrug- or rifampicin-resistant TB; OR: odds ratio; WHO: World Health Organization.

Explanations

- For some patients, information was missing on AFB smear result and culture result in the analysis. Patients with unknown age, sex, or HIV status were excluded from all analyses.
- Outcomes and costs are simulated using a model that draws parameter estimates from multiple sources, including the aORs for success versus death/failure described above.
- The absolute effect is calculated after matching intervention and comparator populations, and performing binomial regression with an identity link.

Author(s): Research Institute of the McGill University Health Centre

Question: Should an all-oral shorter regimen of 9–12 months' duration including bedaquiline vs longer regimens containing bedaquiline be used in MDR/RR-TB patients to safely improve outcomes?

Setting: International

Date: April 2020

№ of studies	Certainty assessment					№ of patients		Effect		Certainty Importance		
	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	All-oral bedaquiline-containing shorter regimen of 9–12 months duration	Longer regimens containing bedaquiline	Relative (95% CI)		Absolute (95% CI)	
1	observational studies	serious ^a	not serious	not serious	not serious	none	631/653 (96.6%)	268/292 (91.8%)	OR 3.9 (1.7 to 9.1)	5 more per 100 (from 1 more to 9 more) ^{b,c}	⊕○○○ VERY LOW	CRITICAL
Success vs. Failure/Recurrence (follow up: mean 18 months)												
1	observational studies	serious ^a	not serious	not serious	not serious	none	631/791 (79.8%)	268/338 (79.3%)	OR 1.0 (0.6 to 1.5)	4 fewer per 100 (from 10 fewer to 3 more) ^{b,c}	⊕○○○ VERY LOW	CRITICAL
Success vs. Death (follow up: mean 18 months)												
1	observational studies	serious ^a	not serious	not serious	not serious	none	631/813 (77.6%)	268/362 (74.0%)	OR 1.4 (0.9 to 2.0)	2 more per 100 (from 4 fewer to 9 more) ^{b,c}	⊕○○○ VERY LOW	CRITICAL
Success vs. Failure/Recurrence/Death (follow up: mean 18 months)												
1	observational studies	serious ^a	not serious	not serious	not serious	none	631/891 (70.8%)	268/440 (60.9%)	OR 1.6 (1.2 to 2.2)	7 more per 100 (from 1 more to 14 more) ^{b,c}	⊕○○○ VERY LOW	CRITICAL
Success vs. All Unfavorable (follow up: mean 18 months)												

Certainty assessment				№ of patients		Effect						
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	№ of patients		Effect			
							All-oral bedaquiline-containing shorter regimen of 9–12 months duration	Longer regimens containing bedaquiline	Relative (95% CI)	Absolute (95% CI)		
Lost vs. All Other Outcomes (follow up: mean 18 months)												
1	observational studies	serious ^a	not serious	not serious	not serious	none	88/891 (9.9%)	88/440 (20.0%)	OR 0.5 (0.4 to 0.8)	8 fewer per 100 (from 13 fewer to 3 fewer) ^{b,c}	⊕○○○ VERY LOW	CRITICAL
AFB Smear Positive: Success vs. Failure/Recurrence (follow up: mean 18 months)												
1	observational studies	serious ^a	not serious	not serious	not serious	none	267/274 (97.4%)	133/148 (89.9%)	OR 4.1 (1.4 to 12.2)	6 more per 100 (from 1 fewer to 12 more) ^b	⊕○○○ VERY LOW	CRITICAL
AFB Smear Positive: Success vs. Death (follow up: mean 18 months)												
1	observational studies	serious ^a	not serious	not serious	not serious	none	267/341 (78.3%)	133/171 (77.8%)	OR 0.8 (0.5 to 1.4)	4 fewer per 100 (from 13 fewer to 5 more) ^b	⊕○○○ VERY LOW	CRITICAL
AFB Smear Positive: Success vs. Failure/Recurrence/Death (follow up: mean 18 months)												
1	observational studies	serious ^a	not serious	not serious	not serious	none	267/348 (76.7%)	133/186 (71.5%)	OR 1.5 (0.9 to 2.5)	4 more per 100 (from 5 fewer to 13 more) ^b	⊕○○○ VERY LOW	CRITICAL
AFB Smear Positive: Success vs. All Unfavorable (follow up: mean 18 months)												
1	observational studies	serious ^a	not serious	not serious	not serious	none	267/378 (70.6%)	133/223 (59.6%)	OR 2.0 (1.3 to 3.1)	12 more per 100 (from 3 more to 21 more) ^b	⊕○○○ VERY LOW	CRITICAL
AFB Smear Positive: Lost vs. All Other Outcomes (follow up: mean 18 months)												
1	observational studies	serious ^a	not serious	not serious	not serious	none	33/378 (8.7%)	41/223 (18.4%)	OR 0.3 (0.2 to 0.6)	11 fewer per 100 (from 17 fewer to 5 fewer) ^b	⊕○○○ VERY LOW	CRITICAL

Certainty assessment				№ of patients		Effect						
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	№ of patients		Effect			
							All-oral bedaquiline-containing shorter regimen of 9–12 months duration	Longer regimens containing bedaquiline	Relative (95% CI)	Absolute (95% CI)		
HIV-Positive on ART: Success vs. Failure/Recurrence (follow up: mean 18 months)												
1	observational studies	serious ^a	not serious	not serious	not serious	none	429/446 (96.2%)	191/205 (93.2%)	OR 2.8 (1.0 to 8.2)	4 more per 100 (from 0 fewer to 8 more) ^b	⊕○○○ VERY LOW	CRITICAL
HIV-Positive on ART: Success vs. Death (follow up: mean 18 months)												
1	observational studies	serious ^a	not serious	not serious	not serious	none	429/541 (79.3%)	191/244 (78.3%)	OR 1.0 (0.6 to 1.6)	1 fewer per 100 (from 9 fewer to 6 more) ^b	⊕○○○ VERY LOW	CRITICAL
HIV-Positive on ART: Success vs. Failure/Recurrence/Death (follow up: mean 18 months)												
1	observational studies	serious ^a	not serious	not serious	not serious	none	429/558 (76.9%)	191/258 (74.0%)	OR 1.2 (0.8 to 1.9)	1 more per 100 (from 6 fewer to 9 more) ^b	⊕○○○ VERY LOW	CRITICAL
HIV-Positive on ART: Success vs. All Unfavorable (follow up: mean 18 months)												
1	observational studies	serious ^a	not serious	not serious	not serious	none	429/613 (70.0%)	191/311 (61.4%)	OR 2.1 (1.4 to 3.1)	12 more per 100 (from 5 more to 20 more) ^b	⊕○○○ VERY LOW	CRITICAL
HIV-Positive on ART: Lost vs. All Other Outcomes (follow up: mean 18 months)												
1	observational studies	serious ^a	not serious	not serious	not serious	none	63/613 (10.3%)	62/311 (19.9%)	OR 0.3 (0.2 to 0.6)	12 fewer per 100 (from 18 fewer to 7 fewer) ^b	⊕○○○ VERY LOW	CRITICAL
HIV Negative: Success vs. Failure/Recurrence (follow up: mean 18 months)												
1	observational studies	serious ^a	not serious	not serious	not serious	none	195/199 (98.0%)	73/82 (89.0%)	OR 3.5 (0.8 to 15.4)	8 more per 100 (from 1 fewer to 16 more) ^b	⊕○○○ VERY LOW	CRITICAL

Certainty assessment				№ of patients		Effect			
№ of studies	Study design	Risk of bias		All-oral bedaquiline-containing shorter regimen of 9–12 months duration	Longer regimens containing bedaquiline	Relative (95% CI)	Absolute (95% CI)	Certainty	Importance
		Inconsistency	Indirectness						
HIV Negative: Success vs. Death (follow up: mean 18 months)									
1	observational studies	not serious	not serious	not serious	none	OR 1.3 (0.5 to 3.3)	1 more per 100 (from 11 fewer to 13 more) ^b	⊕○○○	CRITICAL
HIV Negative: Success vs. Failure/Recurrence/Death (follow up: mean 18 months)									
1	observational studies	not serious	not serious	not serious	none	OR 1.7 (0.8 to 3.7)	6 more per 100 (from 7 fewer to 18 more) ^b	⊕○○○	CRITICAL
HIV Negative: Success vs. All Unfavorable (follow up: mean 18 months)									
1	observational studies	not serious	not serious	not serious	none	OR 1.8 (0.9 to 3.4)	11 more per 100 (from 1 fewer to 24 more) ^b	⊕○○○	CRITICAL
HIV Negative: Lost vs. All Other Outcomes (follow up: mean 18 months)									
1	observational studies	not serious	not serious	not serious	none	OR 0.4 (0.2 to 0.9)	11 fewer per 100 (from 20 fewer to 2 fewer) ^b	⊕○○○	CRITICAL

AFB: acid-fast bacilli; aOR: adjusted odds ratio; ART: antiretroviral therapy; CI: confidence interval; HIV: human immunodeficiency virus; MDR/RR-TB: multidrug- or rifampicin-resistant TB; OR: odds ratio.

Explanations

- For some patients, information was missing on AFB smear result and culture result in the analysis. Patients with unknown age, sex, or HIV status were excluded from all analyses.
- Outcomes and costs are simulated using a model that draws parameter estimates from multiple sources, including the aORs for success versus death or failure described above.
- The absolute effect is calculated after matching intervention and comparator populations, and performing binomial regression with an identity link.

Author(s): Research Institute of the McGill University Health Centre

Question: Should an all-oral shorter regimen of 9–12 months duration including bedaquiline vs longer regimens containing bedaquiline and linezolid be used in MDR/RR-TB patients to safely improve outcomes?

Setting: International

Date: April 2020

№ of studies	Certainty assessment					№ of patients		Effect		Certainty	Importance	
	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	All-oral bedaquiline-containing shorter regimen of 9–12 months duration	Longer regimens containing bedaquiline and linezolid	Relative (95% CI)			Absolute (95% CI)
1	observational studies	serious ^a	not serious	not serious	not serious	none	631/653 (96.6%)	103/110 (93.6%)	OR 1.8 (0.5 to 6.3)	3 more per 100 (from 3 fewer to 9 more) ^{b,c}	⊕○○○ VERY LOW	CRITICAL
Success vs. Failure/Recurrence (follow up: mean 18 months)												
1	observational studies	serious ^a	not serious	not serious	not serious	none	631/791 (79.8%)	103/118 (87.3%)	OR 1.1 (0.5 to 2.6)	1 fewer per 100 (from 10 fewer to 8 more) ^{b,c}	⊕○○○ VERY LOW	CRITICAL
Success vs. Death (follow up: mean 18 months)												
1	observational studies	serious ^a	not serious	not serious	not serious	none	631/813 (77.6%)	103/125 (82.4%)	OR 0.9 (0.5 to 1.8)	5 fewer per 100 (from 15 fewer to 5 more) ^{b,c}	⊕○○○ VERY LOW	CRITICAL
Success vs. Failure/Recurrence/Death (follow up: mean 18 months)												
1	observational studies	serious ^a	not serious	not serious	not serious	none	631/891 (70.8%)	103/157 (65.6%)	OR 2.1 (1.2 to 3.7)	13 more per 100 (from 3 more to 23 more) ^{b,c}	⊕○○○ VERY LOW	CRITICAL
Success vs. All Unfavorable (follow up: mean 18 months)												
1	observational studies	serious ^a	not serious	not serious	not serious	none	88/891 (9.9%)	36/157 (22.9%)	OR 0.4 (0.1 to 0.6)	15 fewer per 100 (from 23 fewer to 7 fewer) ^{b,c}	⊕○○○ VERY LOW	CRITICAL
Lost vs. All Other Outcomes (follow up: mean 18 months)												

No of studies		Certainty assessment					No of patients		Effect		Certainty	Importance
		Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	All-oral bedaquiline-containing regimen of 9–12 months duration	Longer regimens containing bedaquiline and linezolid	Relative (95% CI)		
1		observational studies	serious ^a	not serious	not serious	none	429/446 (96.2%)	80/85 (94.1%)	OR 2.6 (0.5 to 13.8)	4 more per 100 (from 2 fewer to 10 more) ^b	⊕○○○ VERY LOW	CRITICAL
HIV-Positive on ART: Success vs. Failure/Recurrence (follow up: mean 18 months)												
1		observational studies	serious ^a	not serious	not serious	none	429/541 (79.3%)	80/91 (87.9%)	OR 0.6 (0.2 to 1.4)	9 fewer per 100 (from 20 fewer to 2 more) ^b	⊕○○○ VERY LOW	CRITICAL
HIV-Positive on ART: Success vs. Death (follow up: mean 18 months)												
1		observational studies	serious ^a	not serious	not serious	none	429/558 (76.9%)	80/96 (83.3%)	OR 1.0 (0.4 to 2.3)	3 fewer per 100 (from 14 fewer to 8 more) ^b	⊕○○○ VERY LOW	
HIV-Positive on ART: Success vs. Failure/Recurrence/Death (follow up: mean 18 months)												
1		observational studies	serious ^a	not serious	not serious	none	429/613 (70.0%)	80/119 (67.2%)	OR 1.8 (0.9 to 3.6)	11 more per 100 (from 0 fewer to 23 more) ^b	⊕○○○ VERY LOW	CRITICAL
HIV-Positive on ART: Lost vs. All Other Outcomes (follow up: mean 18 months)												
1		observational studies	serious ^a	not serious	not serious	strong association	63/613 (10.3%)	26/119 (21.8%)	OR 0.3 (0.1 to 0.7)	15 fewer per 100 (from 24 fewer to 6 fewer) ^b	⊕○○○ VERY LOW	CRITICAL

aOR: adjusted odds ratio; ART: antiretroviral therapy; CI: confidence interval; HIV: human immunodeficiency virus; MDR/RR-TB: multidrug- or rifampicin-resistant TB; OR: odds ratio.

Explanations

- For some patients, information was missing on AFB smear result and culture result in the analysis. Patients with unknown age, sex, or HIV status were excluded from all analyses.
- Outcomes and costs are simulated using a model that draws parameter estimates from multiple sources, including the aORs for success versus death or failure described above.
- The absolute effect is calculated after matching intervention and comparator populations, and performing binomial regression with an identity link.

Author(s): TB Alliance

Question: Should treatment regimen lasting 6–9 months composed of bedaquiline, pretomanid and linezolid vs. longer regimens containing bedaquiline and linezolid in addition to other anti-TB drugs be used for XDR-TB patients or patients who are treatment intolerant or with non-responsive MDR-TB?

Setting: Five sites in South Africa

Bibliography: Conradie F, Diacon AH, Ngubane N et al. Treatment of highly drug-resistant pulmonary tuberculosis, New England Journal of Medicine. 2020; 382(10): 893–902.

№ of studies	Certainty assessment				№ of patients	Effect		Certainty	Importance	
	Study design	Risk of bias	Inconsistency	Indirectness		Imprecision	Other considerations			Relative (95% CI)
1 ^a	observational studies	very serious ^b	serious ^c	serious ^d	none	Success vs. Failure/Recurrence (follow up: mean 24 months)	OR 3.3 (0.8 to 13.7)	6 more per 100 (from 2 fewer to 14 more) ^g	⊕○○○ VERY LOW	CRITICAL
						Success vs. Failure/Recurrence (follow up: mean 24 months)	OR 3.3 (0.8 to 13.7)	6 more per 100 (from 2 fewer to 14 more) ^g	⊕○○○ VERY LOW	CRITICAL
1 ^a	observational studies	very serious ^b	serious ^c	serious ^d	none	Success vs. Death (follow up: mean 24 months)	OR 1.0 (0.1 to 8.2)	1 more per 100 (from 7 fewer to 8 more) ^g	⊕○○○ VERY LOW	CRITICAL
						Success vs. Death (follow up: mean 24 months)	OR 1.0 (0.1 to 8.2)	1 more per 100 (from 7 fewer to 8 more) ^g	⊕○○○ VERY LOW	CRITICAL
1 ^a	observational studies	very serious ^b	serious ^c	serious ^d	none	Success vs. Failure/Recurrence/Death (follow up: mean 24 months)	OR 1.8 (0.7 to 4.4)	6 more per 100 (from 4 fewer to 16 more) ^g	⊕○○○ VERY LOW	CRITICAL
						Success vs. Failure/Recurrence/Death (follow up: mean 24 months)	OR 1.8 (0.7 to 4.4)	6 more per 100 (from 4 fewer to 16 more) ^g	⊕○○○ VERY LOW	CRITICAL
1 ^a	observational studies	very serious ^b	serious ^c	serious ^d	none	Success vs. All Unfavorable (follow up: mean 24 months)	OR 1.2 (0.5 to 3.1)	2 more per 100 (from 7 fewer to 12 more) ^g	⊕○○○ VERY LOW	CRITICAL
						Success vs. All Unfavorable (follow up: mean 24 months)	OR 1.2 (0.5 to 3.1)	2 more per 100 (from 7 fewer to 12 more) ^g	⊕○○○ VERY LOW	CRITICAL

Certainty assessment					Effect		Certainty	Importance	
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			No of patients
							treatment regimen lasting 6–9 months composed of bedaquiline, pretomanid and linezolid	longer regimens containing bedaquiline and linezolid in addition to other anti-TB drugs	Relative (95% CI)
1 ^h	observational studies	very serious ⁱ	not serious	serious	very serious ^j	none	BPaL regimen: 1 (0.9%) patient died, 27 (25%) patients experienced other serious adverse events including hospitalizations and life threatening events, and 53 (49%) patients experienced at least one Grade 3–4 adverse events. Drug discontinuation for adverse events: related to all three drugs in 1 patient, and related to linezolid (initial dose 1200 mg/day) discontinued in another 35 (32%) patients. Only 20 (18%) patients completed a full course of 1200 mg/day. In the IPD studies (90% received 600 mg/day or less), the pooled rate of LZD permanent discontinuation was 17.9%, and in the EndTB study (all patients received 600mg/day or less), the rate of LZD discontinuation was 13.1%. In EndTB: 9 persons out of 1094 (0.8%) died of a possibly/probably drug related AE, including two persons with sudden cardiac death and QT prolongation.	⊕○○○	CRITICAL
Adverse events									

AE: adverse event; BPaL: bedaquiline, pretomanid and linezolid; CI: confidence interval; IPD: individual patient data; LZD: linezolid; MDR/RR-TB: multidrug- or rifampicin-resistant TB; OR: odds ratio.

Explanations

- One cohort study compared with IPD meta-analysis of 55 studies.
- This was a small and one-armed unblinded cohort study with substantial selection into the cohort; follow-up data to 24 months were not available for all patients, so end-points of clinical failure may be underestimated.
- There were major differences between the intervention and comparator groups (in selection, characteristics and intensity of care), all of which could have affected the comparison.
- This was a small, well-resourced, one-armed, unblinded cohort study that was compared with cohorts and routinely collected programmatic data in the IPD. All comparisons between the intervention and the comparator were indirect.
- This was a small study (108 patients in total in modified intention-to-treat analysis). It was difficult to perform adequate matching in the analysis, so some secondary analyses were even more limited by small numbers.
- Outcomes and costs were simulated using a model that draws parameter estimates from multiple sources, including the adjusted odds ratios for success versus death or failure described above.
- The absolute effect is calculated after matching intervention and comparator populations, and performing binomial regression with an identity link.
- One cohort study (compared with IPD meta-analysis of 30 studies containing adverse event information and the EndTB observational study)
- Within the IPD, adverse event data are only consistently reported for individuals who permanently stopped the drug of interest; also, certain drugs may be more closely monitored for toxicities (e.g. bedaquiline and linezolid).
- This was a small study (109 patients in the safety analysis) compared with 30 different studies in the IPD, which may vary in the intensity and completeness of adverse event reporting.

Author(s): Research Institute of the McGill University Health Centre

Question: Should bedaquiline for more than six months vs. bedaquiline for up to six months be used in MDR/RR-TB patients as part of the longer treatment regimens?

Setting: International

Bibliography: Unpublished data from the individual patient dataset, 2019 (held by McGill University)

№ of studies	Certainty assessment				№ of patients bedaquiline for more than six months	Effect Relative (95% CI)	Certainty	Importance
	Study design	Risk of bias	Inconsistency	Indirectness				
1	observational studies	very serious ^a	not serious	not serious	none	OR 1.4 (0.7 to 2.7)	⊕○○○ VERY LOW	CRITICAL
Success vs. Failure (follow up: mean 21 months)								
					188/212 (88.7%)	235/255 (92.2%)		
1	observational studies	very serious ^a	not serious	not serious	none	OR 0.8 (0.2 to 2.4)	⊕○○○ VERY LOW	CRITICAL
Success vs. Death (follow up: mean 21 months)								
					188/200 (94.0%)	235/242 (97.1%)		
1	observational studies	very serious ^a	not serious	not serious	none	OR 1.0 (0.5 to 1.7)	⊕○○○ VERY LOW	CRITICAL
Success vs. Failure/Death (follow up: mean 21 months)								
					188/224 (83.9%)	235/262 (89.7%)		
1	observational studies	very serious ^a	not serious	not serious	none	OR 0.8 (0.5 to 1.2)	⊕○○○ VERY LOW	CRITICAL
Success vs. All Unfavorable (follow up: mean 21 months)								
					188/242 (77.7%)	235/273 (86.1%)		

CI: confidence interval; MDR/RR-TB: multidrug- or rifampicin-resistant tuberculosis; OR: odds ratio.

Explanations

- a. Data from a single cohort study with excellent quality of information, but reasons for bedaquiline extension varied by provider and site, with many decisions individualized. Some sites rarely gave bedaquiline for more than 6 months and others rarely gave bedaquiline for less than or equal to 6 months. In most sites, however, duration appeared to be based at least partly on poor response to therapy, creating substantial selection bias.
- b. Study involved relatively small numbers with bedaquiline extension, with limited events.
- c. Outcomes and costs are simulated using a model that draws parameter estimates from multiple sources, including the adjusted odds ratios for success versus death/failure described above.
- d. The absolute effect is calculated after matching intervention and comparator populations, and performing binomial regression with an identity link.

Author(s): Research Institute of the McGill University Health Centre and Professor Kelly Dooley, Johns Hopkins University

Question: Should concurrent use of bedaquiline and delamanid vs. no concurrent use of bedaquiline and delamanid be used in MDR/RR-TB patients as part of the longer treatment regimens?

Setting: International (for the dataset from McGill University) and South Africa and Peru for the dataset from Johns Hopkins University

Bibliography: Unpublished data from the individual patient dataset, 2019 (held by McGill University) and unpublished data from the DELamanId BEdaquiline for ResistAnt Tuberculosis (DELIBERATE) trial, Johns Hopkins University

No of studies	Study design	Certainty assessment				No of patients		Effect		Certainty	Importance	
		Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	concurrent use of bedaquiline and delamanid	no concurrent use of bedaquiline and delamanid	Relative (95% CI)			Absolute (95% CI)
4	observational studies	very serious ^a	serious ^b	not serious	serious ^c	none	52/58 (89.7%)	285/306 (93.1%)	OR 1.6 (0.5 to 5.4)	6 more per 100 (from 6 fewer to 18 more) ^{d,e}	⊕○○○ VERY LOW	CRITICAL
Success vs. Failure (follow up: mean 17.5 months)												
4	observational studies	very serious ^a	serious ^b	not serious	serious ^c	none	52/69 (75.4%)	285/333 (85.6%)	OR 0.8 (0.3 to 2.1)	1 fewer per 100 (from 15 fewer to 12 more) ^{d,e}	⊕○○○ VERY LOW	CRITICAL
Success vs. Death (follow up: mean 17.5 months)												
4	observational studies	very serious ^a	serious ^b	not serious	serious ^c	none	52/75 (69.3%)	285/354 (80.5%)	OR 1.2 (0.6 to 2.5)	5 more per 100 (from 10 fewer to 20 more) ^{d,e}	⊕○○○ VERY LOW	CRITICAL
Success vs. Failure/Death (follow up: mean 17.5 months)												
4	observational studies	very serious ^a	serious ^b	not serious	serious ^c	none	52/84 (61.9%)	285/401 (71.1%)	OR 0.6 (0.3 to 1.1)	11 fewer per 100 (from 25 fewer to 2 more) ^{d,e}	⊕○○○ VERY LOW	CRITICAL
Success vs. All Unfavorable (follow up: mean 17.5 months)												

No of studies	Certainty assessment				Other considerations	No of patients		Effect		Certainty	Importance	
	Study design	Risk of bias	Inconsistency	Indirectness		Imprecision	Other considerations	concurrent use of bedaquiline and delamanid	no concurrent use of bedaquiline and delamanid			Relative (95% CI)
1	randomised trials	not serious	not serious	serious	serious ^f	none					⊕⊕○○ LOW	CRITICAL
<p>Sudden cardiac death (follow up: mean 24 weeks; assessed with: QTcF prolongation measured in milliseconds change from baseline)</p> <p>The primary aim of the DELIBERATE trial was to compare the mean change from baseline (averaged over weeks 8–24) in QTcF when bedaquiline and delamanid are co-administered to the mean change observed when each drug is administered alone. At week 24, in 28 patients who received bedaquiline as part of their MDR-TB treatment regimen the mean increase in QTcF was 11.9 ms (95% CI 7.4–16.4 ms). For 28 patients who received delamanid as part of their MDR-TB treatment regimen the mean increase in QTcF was 8.6 ms (95% CI 4.0–13.2 ms). When 28 patients received concurrent bedaquiline and delamanid as part of their MDR-TB treatment regimen the mean increase in QTcF was 20.7 ms (95% CI 16.1–25.4 ms). The additive effect of adding delamanid to a regimen that already contained bedaquiline was determined to be a mean of 8.8 ms (95% CI 2.3–15.3 ms), whereas the additive effect of adding bedaquiline to a regimen that already contained delamanid was a mean of 12.1 ms (95% CI 5.6–18.6 ms). There were no Grade 3 or Grade 4 QT adverse events recorded in all three patient groups, including among those who received bedaquiline and delamanid concurrently.</p>												

CI: confidence interval; MDR-TB: multidrug-resistant tuberculosis; MDR/RR-TB: multidrug- or rifampicin-resistant tuberculosis; OR: odds ratio.

Explanations

- For the two cohort studies with the intervention, the small number of patients represents less than 3% of all patients in one cohort study with excellent quality of information; hence, there is a possibility of substantial selection bias. The second cohort also had small numbers, but the patients represent almost half of all cohort members; hence, there is less possibility of selection bias.
- Patients for the intervention were treated in two very different cohort studies, with different centres or providers and protocols. Patients for the comparator were treated in four very different cohort studies.
- There are serious concerns about this study, given that small numbers received bedaquiline and delamanid concomitantly ($n=84$).
- Outcomes and costs are simulated using a model that draws parameter estimates from multiple sources, including the adjusted odds ratios for success versus death/failure described above.
- The absolute effect is calculated after matching intervention and comparator populations, and performing binomial regression with an identity link.
- Imprecision is secondary to the small number of individuals enrolled. Typically, for continuous outcomes, a sample size of 400 makes it possible to draw conclusions with confidence, although this is a general rule.

A3.2 WHO treatment guidelines for isoniazid-resistant tuberculosis, 2018

Refer to Annex 5: GRADE evidence summary tables in the *WHO treatment guidelines for isoniazid-resistant tuberculosis* (https://www.who.int/tb/publications/2018/WHO_treatment_guidelines_isoniazid_resistant_TB_Online_GRADE_tables_Annexes.pdf, accessed 2 March 2019).

A3.3 WHO treatment guidelines for multidrug- and rifampicin-resistant tuberculosis, 2018 update

Refer to Annex 8: GRADE evidence summary tables in the *WHO treatment guidelines for multidrug- and rifampicin-resistant tuberculosis, 2018 update* (https://www.who.int/tb/areas-of-work/drug-resistant-tb/Annexes_8-10.pdf, accessed 2 March 2019).

A3.4 Guidelines for the programmatic management of drug-resistant tuberculosis, 2011 update

Refer to Annex 2: GRADE glossary and summary of evidence tables (questions 6 and 7) in the *Guidelines for the programmatic management of drug-resistant tuberculosis, 2011 update* (https://apps.who.int/iris/bitstream/handle/10665/70677/WHO_HTM_TB_2011.6b_eng.pdf, accessed 2 March 2019).

A3.5 WHO treatment guidelines for drug-resistant tuberculosis, 2016 update

Refer to Annex 4: GRADE tables (question 4) in the *WHO treatment guidelines for drug-resistant tuberculosis, 2016 update* (<https://apps.who.int/iris/bitstream/handle/10665/250125/9789241549639-webannexes-eng.pdf>, accessed 2 March 2019).

A3.6 Guidelines for treatment of drug-susceptible tuberculosis and patient care, 2017 update

Refer to Annex 3: GRADE evidence profiles (questions 10 and 11) in the *Guidelines for treatment of drug-susceptible tuberculosis and patient care, 2017 update* (https://www.who.int/tb/publications/2017/dstb_guidance_2017/en/, accessed 2 March 2019).

Annex 4: GRADE evidence-to-decision tables

A4.1 WHO treatment guidelines for multidrug- or rifampicin-resistant tuberculosis, 2020 update

Should an all-oral shorter regimen of 9–12 months' duration including bedaquiline vs a shorter regimen recommended by WHO (with injectable) be used for MDR/RR-TB patients to safely improve outcomes?

POPULATION:	MDR-/RR-TB patients to safely improve outcomes
INTERVENTION:	All-oral bedaquiline-containing shorter regimen of 9–12 months duration (BDQ-LFX/MFX-ETO-E-Z-H ^r -CFZ)
COMPARISON:	Shorter regimen recommended by WHO (with an injectable agent)
MAIN OUTCOMES:	Success vs. Failure/Recurrence; Success vs. Death; Success vs. Failure/Recurrence/Death; Success vs. All Unfavourable; Lost vs. All Other Outcomes; AFB Smear Positive; Success vs. Failure/Recurrence; AFB Smear Positive; Success vs. Death; AFB Smear Positive; Success vs. Failure/Recurrence/Death; AFB Smear Positive; Success vs. All Unfavourable; AFB Smear Positive; Lost vs. All Other Outcomes; HIV-Positive on ART; Success vs. Failure/Recurrence; HIV-Positive on ART; Success vs. Death; HIV-Positive on ART; Success vs. Failure/Recurrence/Death; HIV-Positive on ART; Success vs. All Other Unfavourable; HIV-Positive on ART; Lost vs. All Other Outcomes; HIV Negative; Success vs. Failure/Recurrence; HIV Negative; Success vs. Death; HIV Negative; Success vs. Failure/Recurrence/Death; HIV Negative; Success vs. All Other Outcomes; HIV Negative; Lost vs. All Other Outcomes.
SETTING:	South Africa.
PERSPECTIVE:	Public health and health systems perspective
BACKGROUND:	Multidrug-resistant (MDR-) and rifampicin-resistant tuberculosis (MDR-/RR-TB) is emerging as a major problem due to poor management of drug-sensitive as well as drug-resistant TB. MDR-/RR-TB is treatable, but has required the use of longer treatment regimens which contain potentially toxic drugs. The interest in reducing the duration of treatment for MDR-TB motivated a number of initiatives in recent years to treat patients with shorter regimens under programmatic as well as trial conditions. In 2016, on the basis of data from observational studies of the shorter regimens in different Asian and African countries, WHO started to recommend a standardized shorter MDR-TB regimen, containing an injectable agent, based on the ones under study for eligible patients. In 2018, further modifications were made to the earlier recommended shorter regimen, replacing kanamycin by amikacin (based on evidence from the comparative effectiveness of these two injectable agents). Evidence of permanent effects attributed to the toxicity of injectable agents, have prompted further advances in the development of new treatments such as shorter injectable-sparing regimens. In particular, observational data on an all-oral bedaquiline-containing shorter regimen of 9–12 months duration became available. This is of particular importance given that the regimen may offer patients the likelihood of better tolerating treatment without significant toxicity.
CONFLICT OF INTERESTS:	Alberto Piubello.

Assessment

Problem		
Is the problem a priority?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> <input type="radio"/> No <input type="radio"/> Probably no <input type="radio"/> Probably yes <input checked="" type="radio"/> Yes <input type="radio"/> Varies <input type="radio"/> Don't know 	<p>Tuberculosis (TB) remains a threat to global public health and is the topmost infectious cause of death in the world. In 2018, an estimated 10 million people developed TB and 1.4 million died from the disease. About 500 000 new cases of multidrug- or rifampicin-resistant TB (MDR/RR-TB) were estimated to emerge in 2018. Although all of these would have been eligible for a second-line TB treatment regimen, only 156 071 enrolments on treatment were reported by countries in 2018 – about 30% of the estimated caseload. Despite this, significant improvements in the availability of enhanced diagnostics and more effective medicines have occurred in recent years and have led to earlier detection and higher success rates among patients with MDR/RR-TB in a number of national programmes. However, these successes have not been reproduced in the rest of the world, and the overall treatment success rate worldwide reached only 56% for patients with MDR/RR-TB who started on treatment in 2016, and only 39% for patients with extensively drug-resistant TB (XDR-TB).</p>	

Desirable Effects

How substantial are the desirable anticipated effects?

- JUDGEMENT**
- Trivial
 - Small
 - Moderate
 - Large
 - Varies
 - Don't know

RESEARCH EVIDENCE

Outcomes	Relative	Effect
		Absolute
Success vs. Failure/Recurrence (follow up: mean 18 months)	OR 2.1 (1.1 to 4.0)	3 more per 100 (1 more to 6 more)
Success vs. Death (follow up: mean 18 months)	OR 1.6 (1.2 to 2.1)	8 more per 100 (3 more to 13 more)
Success vs. Failure/Recurrence/Death (follow up: mean 18 months)	OR 1.7 (1.3 to 2.2)	10 more per 100 (5 more to 15 more)
Success vs. All Unfavorable (follow up: mean 18 months)	OR 1.9 (1.6 to 2.4)	14 more per 100 (9 more to 19 more)
Lost vs. All Other Outcomes (follow up: mean 18 months)	OR 0.5 (0.4 to 0.7)	7 fewer per 100 (11 fewer to 4 fewer)
AFB Smear Positive: Success vs. Failure/Recurrence (follow up: mean 18 months)	OR 4.4 (1.6 to 11.9)	8 more per 100 (3 more to 13 more)
AFB Smear Positive: Success vs. Death (follow up: mean 18 months)	OR 1.3 (0.8 to 2.1)	5 more per 100 (3 fewer to 12 more)
AFB Smear Positive: Success vs. Failure/Recurrence/Death (follow up: mean 18 months)	OR 1.7 (1.1 to 2.6)	10 more per 100 (2 more to 17 more)
AFB Smear Positive: Success vs. All Unfavorable (follow up: mean 18 months)	OR 2.3 (1.6 to 3.3)	16 more per 100 (9 more to 24 more)
AFB Smear Positive: Lost vs. All Other Outcomes (follow up: mean 18 months)	OR 0.4 (0.2 to 0.6)	11 fewer per 100 (16 fewer to 5 fewer)
HIV-Positive on ART: Success vs. Failure/Recurrence (follow up: mean 18 months)	OR 1.4 (0.7 to 2.9)	2 more per 100 (2 fewer to 5 more)
HIV-Positive on ART: Success vs. Death (follow up: mean 18 months)	OR 1.6 (1.2 to 2.3)	8 more per 100 (3 more to 14 more)
HIV-Positive on ART: Success vs. Failure/Recurrence/Death (follow up: mean 18 months)	OR 1.6 (1.2 to 2.2)	9 more per 100 (3 more to 15 more)
HIV-Positive on ART: Success vs. All Other Unfavorable (follow up: mean 18 months)	OR 1.9 (1.4 to 2.4)	14 more per 100 (8 more to 19 more)
HIV-Positive on ART: Lost vs. All Other Outcomes (follow up: mean 18 months)	OR 0.6 (0.4 to 0.8)	6 fewer per 100 (10 fewer to 2 fewer)

ADDITIONAL CONSIDERATIONS

Results from the data assessment commissioned to inform these recommendations show that favourable outcomes were significantly better for the all-oral shorter bedaquiline-containing shorter regimen than for a shorter regimen recommended by WHO (with injectable).

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT

- Large
- Moderate
- Small
- Trivial
- Varies
- Don't know

RESEARCH EVIDENCE

The Guideline Development Group (GDG) discussed earlier results of the individual-patient data (IPD) meta-analysis conducted to assess the overall balance between benefits and harms of individual agents. In the analysis, 1995 patients received kanamycin and 268 (13.4%) experienced an adverse event causing permanent drug discontinuation; 4106 patients received amikacin, of whom 235 (5.7%) experienced an adverse event causing permanent drug discontinuation; additionally, 1932 received capreomycin and 161 (8.3%) experienced an adverse event causing permanent drug discontinuation. In contrast, 464 patients received bedaquiline, of whom 9 (1.9%) experienced an adverse event causing permanent drug discontinuation.

ADDITIONAL CONSIDERATIONS

Though no major signals of risk were observed with the use of the all-oral bedaquiline-based shorter regimen, the GDG acknowledged that some uncertainties remained given the lack of systematic collection of data, and lack of clarity as to any changes in the regimen that could have been informed by the presence of adverse events. However, the GDG recognized that the analysis was not completely agnostic about safety, in particular the balance between desirable versus undesirable effects, and the group was somewhat reassured that earlier signals attributed to the use of bedaquiline were not observed, presenting no additional safety concerns. The group re-emphasized that although 1.9% of patients using bedaquiline experience an adverse event that leads to the discontinuation of the drug, this consequence is not to be considered as "trivial", and that for now, safety data are needed to better understand [safety] aspects of the all-oral bedaquiline-containing shorter regimen. Safety data are needed to better understand [safety] aspects of the all-oral bedaquiline-containing shorter regimen.

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT

- Very low
- Low
- Moderate
- High
- No included studies

RESEARCH EVIDENCE

The GDG pointed out that, on the basis of the evidence assessed – namely, observational data and potential residual confounding – the overall certainty regarding the estimates of effect based was judged to be *very low*, with the effects for all outcomes also rated as “very low”. Although double-adjustment in propensity score matching analyses was carried out to remove the effects of confounding, members of the GDG further discussed that although these efforts compensated for some potential confounders, residual bias is likely to be present. The group acknowledged that although the use of programmatic data holds great promise because they better reflect real practice, some considerations in terms of the extent to which these findings could be applied to other settings are to be contemplated. For instance, specific clinical characteristics of the population (e.g. HIV prevalence and drug-resistance patterns) as well as quality of health care services, models of care, and treatment adherence strategies.

Values	
Is there important uncertainty about or variability in how much people value the main outcomes?	
JUDGEMENT	RESEARCH EVIDENCE
<input type="radio"/> Important uncertainty or variability <input type="radio"/> Possibly important uncertainty or variability <input type="radio"/> Probably no important uncertainty or variability <input checked="" type="radio"/> No important uncertainty or variability	<p>A qualitative study undertaken to highlight the perspectives of key stakeholders, mainly, patient and civil society representatives (n = 16) looked at general preferences and values regarding different aspects of treatment regimens for drug-resistant TB, such as duration, pill burden, use of injectable agents and potential for experiencing adverse events.</p> <p>Participants had the opportunity to discuss important adverse effects, including permanent sensorineural hearing loss, nephrotoxicity, electrolyte abnormalities, injection pain and local injection-site complications. From a patient perspective, adverse events such as optic neuritis, hearing impairment, mental status changes due to uremia, and electrolyte abnormalities are late effects among others associated with the use of specific second-line agents, including injectable agents, and were deemed unacceptable..</p>
ADDITIONAL CONSIDERATIONS	
<p>Preferences about treatment appeared to be rooted in core values, including minimal disruption to normal life. Relatively few patients seemed to prefer a short regimen that was tied to more serious side-effects, but only if the side-effects were rare or reversible. In addition, in terms of the duration of treatment, preferences seemed to be guided first by side-effects and second by efficacy of treatment regimens.</p>	
Balance of effects	
Does the balance between desirable and undesirable effects favor the intervention or the comparison?	
JUDGEMENT	RESEARCH EVIDENCE
<input type="radio"/> Favors the comparison <input type="radio"/> Probably favors the comparison <input type="radio"/> Does not favor either the intervention or the comparison <input type="radio"/> Probably favors the intervention <input checked="" type="radio"/> Favors the intervention <input type="radio"/> Varies <input type="radio"/> Don't know	<p>The GDG considered whether the balance between desirable and undesirable effects favoured the intervention. Data assessment showed that the overall rate of adverse events attributed to bedaquiline as compared with injectable agents was two times less. At the same time, the GDG noted a 50% reduction in death, attributing this effect to the addition of bedaquiline. However, the group emphasized the potential harms if this bedaquiline-containing regimen were to be implemented without ensuring proper drug-susceptibility patterns. When deciding on whether or not the balance of effects favoured the intervention or the comparator, the group proceeded to vote. Total voting members present: 29 experts (plus 1 conflict of interest). Voting proceeded as follows: Probably, 13; favours the intervention, 14; varies, 1; abstention, 1; plus one voting member who abstained due to conflict of interest.</p>
ADDITIONAL CONSIDERATIONS	
<p>The GDG considered whether the balance between desirable and undesirable effects favoured the intervention. Data assessment showed that the overall rate of adverse events attributed to bedaquiline as compared with injectable agents was two times less. At the same time, the GDG noted a 50% reduction in death, attributing this effect to the addition of bedaquiline. However, the group emphasized the potential harms if this bedaquiline-containing regimen were to be implemented without ensuring proper drug-susceptibility patterns. When deciding on whether or not the balance of effects favoured the intervention or the comparator, the group proceeded to vote. Total voting members present: 29 experts (plus 1 conflict of interest). Voting proceeded as follows: Probably, 13; favours the intervention, 14; varies, 1; abstention, 1; plus one voting member who abstained due to conflict of interest.</p>	

Resources required	
How large are the resource requirements (costs)?	
JUDGEMENT	ADDITIONAL CONSIDERATIONS
<p>RESEARCH EVIDENCE</p> <p>Compared with the injectable-containing shorter regimen, the 9–12-month all-oral regimen is projected to be both cost-saving and more effective than the injectable-containing shorter regimen under nearly all modelled conditions. The projected cost savings average US\$ 1000 (2019) in South Africa and depend primarily on the extent to which higher drug costs are outweighed by the reduced costs of delivering injectable agents, and treating recurrent and secondary cases (about US\$ 2000 per patient is saved in settings with two-times-higher health care costs, versus <US\$ 100 saved in settings with high drug costs but low health care costs).</p> <p> <input type="radio"/> Large costs <input type="radio"/> Moderate costs <input type="radio"/> Negligible costs and savings <input checked="" type="radio"/> Moderate savings <input type="radio"/> Large savings <input type="radio"/> Varies <input type="radio"/> Don't know </p>	<p>An important issue acknowledged by the GDG was that although the all-oral bedaquiline-containing regimen seemed to be both cost-saving and more effective as compared with the shorter regimen recommended by WHO (with an injectable), costs are not expected to automatically eliminated or decreased. Several other key factors must also be considered, including the existing stock of second-line medications while transitioning from an injectable-based regimen to an all-oral one, diagnostic capacity to identify eligible individuals into currently recommended regimens (based on drug-susceptibility patterns, etc.), and capacity to conduct regular active TB drug safety monitoring and management. However, there were no data for determining the exact resources that would be consumed with the implementation of this all-oral bedaquiline-containing regimen.</p> <p>The GDG did agree that, overall, savings can be considered in terms of future retreatments prevented, as well as reduced hospitalization rates resulting from less adverse reactions.</p>
 certainty of evidence of required resources	 certainty of evidence of resource requirements (costs)?
JUDGEMENT	ADDITIONAL CONSIDERATIONS
<p>RESEARCH EVIDENCE</p> <p>The cost savings relative to a short injectable-containing regimen are also robust, except at extremes with drug costs, health care costs or the cost of bedaquiline and other companion drugs.</p> <p> <input type="radio"/> Very low <input type="radio"/> Low <input checked="" type="radio"/> Moderate <input type="radio"/> High <input type="radio"/> No included studies </p>	<p>Though the uncertainty around the estimates of effect was acknowledged, the GDG agreed that there seemed to be moderate cost savings, because of reduced hospitalization rates resulting from fewer adverse reactions, less monitoring/visits (for injectable use), and fewer treatment interruptions because of better adherence.</p>

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT

- Favors the comparison
- Probably favors the comparison
- Does not favor either the intervention or the comparison
- Probably favors the intervention
- Favors the intervention
- Varies
- No included studies

RESEARCH EVIDENCE

A cost-effectiveness model was developed, incorporating estimated health system costs with drug procurement, health care delivery, adverse events, retreatments, secondary cases, and morbidity and mortality associated with TB mortality and recurrence, treatment duration, drug toxicity and TB transmission. Costs and cost-effectiveness were evaluated in South Africa, with sensitivity analyses representing a range of drug and health care costs, high and low HIV co-prevalence, 95% CIs for estimates of relative efficacy derived from statistical analysis of patient cohort data, and uncertainty in the values of parameters representing the natural history of TB.

Compared with the injectable-containing shorter regimen, the 9–12-month all-oral regimen is projected to be **both cost saving and more effective** than the injectable-containing shorter regimen under nearly all modelled conditions. The projected cost savings average US\$ 1000 (2019) in South Africa and depend primarily on the extent to which higher drug costs are outweighed by reduced costs of delivering injectable agents, and treating recurrent and secondary cases (about US\$ 2000 saved per patient is saved in settings with two-times-higher health care costs, versus <US\$ 100 saved in settings with high drug costs but low health care costs). In a scenario where the all-oral regimen was no longer cost-saving because bedaquiline prices were fourfold higher than current pricing in South Africa or via the GDF, the incremental cost-effectiveness ratio of the all-oral regimen was US\$ 400 per disability adjusted life-year averted (range: US\$ 100–US\$ 900 across 95% CI for relative regimen efficacy).

ADDITIONAL CONSIDERATIONS

Equity

What would be the impact on health equity?

JUDGEMENT

- Reduced
- Probably reduced
- Probably no impact
- Probably increased
- Increased
- Varies
- Don't know

RESEARCH EVIDENCE

A qualitative study undertaken to highlight the perspectives of key stakeholders, mainly, patient and civil society representatives ($n=16$) looked at general preferences and values regarding different aspects of treatment regimens for drug-resistant TB treatment, such as duration, pill burden, use of injectable agents and potential for experiencing adverse events.

Participants considered anything less than universal and immediate access to new treatments to be unethical, but when prompted to consider this preference against a limited supply of drugs, a few would prioritize the youngest and sickest, as well as those who are adherent and could be monitored for adverse events. Patients who face socioeconomic challenges to adherence, or who live in remote, rural or poorer communities that lack technical skill or equipment for treatment monitoring, could then be disproportionately and unjustly placed at a disadvantage

ADDITIONAL CONSIDERATIONS

The GDG agreed that injectable-sparing regimens would be easier to decentralize and, therefore, in remote and underserved settings and disadvantaged populations, would help to alleviate health inequities, without anticipating differences in outcomes in specific populations. Further, the group also noted that because audiometry would not be required, it might be easier to monitor individuals in spite of increased requirements for electrocardiography, which is a prerequisite for the use of bedaquiline-containing regimens. However, the group stressed that the use of electrocardiography should not be a differentiating element between these two regimens, because patients receiving injectable agents such as amikacin should also have regular cardiac monitoring. The group acknowledged that it is possible that, in some settings, not all patients will be able to undergo electrocardiographic monitoring; however, it was also noted that the increasing access to electrocardiography at periphery levels might improve equity.

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT

- No
- Probably no
- Probably yes
- Yes
- Varies
- Don't know

RESEARCH EVIDENCE

A qualitative study undertaken to highlight the perspectives of key stakeholders, mainly patient and civil society representatives ($n = 16$), looked at general preferences and values regarding different aspects of treatment regimens for drug-resistant TB, such as duration, pill burden, use of injectable agents and potential for experiencing adverse events. The results of this qualitative analysis suggested that most patients would prioritize a regimen with fewer and less-severe side-effects above all else, because it would allow them to continue routine activities. Of note, survivors of drug-resistant TB remarked that they would accept a longer treatment that promised **fewer severe adverse effects** over a shorter regimen tied to more severe side-effects, even if treatment was experimental or efficacy was unclear. This contrasted with comparatively few participants who prioritized rapid return to normal life and would rather assume the risk of more serious side-effects within a shorter regimen, even if treatment was experimental and efficacy unclear.

ADDITIONAL CONSIDERATIONS

The GDG noted that patients recognize that their experiences and perceptions are highly person- and context-dependent, though preference for this [shorter] regimen seemed to be conditional upon adverse events being rare or reversible. Nevertheless, overall, a short, injection-free regimen with few to no physical and mental health side-effects and a low pill burden appeared to be the most acceptable.

Feasibility

Is the intervention feasible to implement?

JUDGEMENT

- No
- Probably no
- Probably yes
- Yes
- Varies
- Don't know

RESEARCH EVIDENCE

A qualitative study undertaken to highlight the perspectives of key stakeholders, mainly patients and civil society representatives ($n = 16$) looked at general preferences and values regarding different aspects of treatment regimens for drug-resistant TB, such as duration, pill burden, use of injectable agents and potential for experiencing adverse events.

This study revealed that as the regimen, in particular the expansion of bedaquiline access to all patients, is held back in some settings as a result of restrictive eligibility (i.e. prioritization of specific groups) criteria, lack of funding, or lack of adequate infrastructure in place (e.g. diagnostics), the operationalization and immediate rollout of the all-oral bedaquiline-containing regimen may be hampered.

ADDITIONAL CONSIDERATIONS

One important requirement highlighted by the GDG was that of ensuring the careful selection of patients who are to benefit from this regimen, conducting rapid and accurate DST, and the monitoring of bedaquiline resistance. The implementation of the regimen may be limited by the need for improved laboratory infrastructure. Although countries are implementing rapid molecular tests to identify rifampicin resistance, laboratory capacity needs to be effectively established to conduct genotypic and phenotypic testing for other important agents in the regimen. Also, although the prevalence of identified mutations conferring low-level drug resistance is very low, countries are to strengthen laboratory capacity and to monitor the acquisition of resistance to bedaquiline through their national reference laboratories or TB supranational reference sites. This is especially important given the pipeline of new anti-TB regimens that are relying on bedaquiline as a backbone.

The removal of injectable agents, as discussed by the GDG, also pointed towards the convenience (for health care workers) of not having to deliver daily injections, and more so, for patients not having to endure the pain and other significant adverse events.

The implementation of the regimen is perceived to go beyond securing of funding, but it further requires making long-term, sustainable systems change to ensure rapid transition, considering the registration of bedaquiline and other new agents, uninterrupted supply of quality-assured drugs and active TB drug safety monitoring and management system in coordination with existing pharmacovigilance structures at the country level.

Also, the implementation of this regimen (and any other novel regimen) will require decision-making towards multisectoral policies, tailoring patient-centred programmes which also consider aspects such as mental health and management of other comorbidities, facilitating counselling and support during treatment, and after completion, facilitating full recovery.

Summary of judgements

PROBLEM	JUDGEMENT						Don't know
					Yes	Varies	
DESIRABLE EFFECTS	Trivial	Small	Moderate		Large	Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small		Trivial	Varies	Don't know
CERTAINTY OF EVIDENCE VALUES	Very low Important uncertainty or variability	Low	Moderate	Moderate	High	Varies	Don't know No included studies
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability	Varies	Don't know
RESOURCES REQUIRED	Large costs	Moderate costs	Moderate costs	Does not favor either the intervention or the comparison	Favors the intervention	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	Negligible costs and savings	Moderate savings	Varies	Don't know
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Varies	No included studies
EQUITY	Reduced	Probably reduced	Probably no	Probably no impact	Probably increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	Probably yes	Probably yes	Yes	Varies	Don't know
FEASIBILITY	No	Probably no	Probably yes	Probably yes	Yes	Varies	Don't know

Type of recommendation

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input checked="" type="radio"/>	<input type="radio"/>

Conclusions

Recommendation

A shorter, all-oral, bedaquiline-containing regimen of 9–12 months' duration is recommended in eligible patients with confirmed MDR/RR-TB who have not been exposed to treatment with second-line TB medicines used in this regimen for more than 1 month and in whom resistance to fluoroquinolones has been excluded. (Conditional recommendation, very low certainty in the evidence)

Justification

Overall, the GDG noted that the certainty of the evidence on the efficacy of the all-oral shorter regimen was very low, attributable namely to concerns of serious risk of bias, despite efforts to balance baseline covariates. However, the group recognized that the current evidence assessment of the all-oral, bedaquiline-containing shorter regimen showed a better ratio of success versus unfavourable outcomes and a significant reduction in loss to follow-up. When deciding on the strength of the recommendation, the GDG reached a unanimous decision on the conditionality of the recommendation, mainly attributed to the very low certainty in the evidence and requirements to build laboratory capacity and ensure DST.

Other grounds for the strength and direction of this recommendation are as follows:

- The analysis conducted to inform the development of this recommendation was based on observational programmatic data from South Africa where the standardized shorter, all-oral, bedaquiline-containing regimen (BDQ-LFX/MFX-ETO-E-Z-Hⁿ-CFZ) was used for patients with MDR/RR-TB.
- Though no major signals of risk were observed with the use of the all-oral bedaquiline-based shorter regimen, there also remained some uncertainties, given the lack of systematic collection of data, and given the lack of clarity as to any changes in the regimen that could have been informed by the presence of adverse events.
- Cost-effectiveness modelling of the all-oral, shorter, bedaquiline-containing regimen showed robust cost savings relative to either a longer oral regimen or a short injectable-containing regimen.
- The GDG judged that many eligible patients would prefer the all-oral, bedaquiline-containing regimen of 9–12 months' duration. This is supported by limited observations involving 16 survivors of drug-resistant TB. In addition, this regimen may help promote health equity or mitigate the worsening of health inequities. Although the panel recognized that implementation and scale-up of this regimen may be slow due prerequisites on laboratory capacity and monitoring.

Subgroup considerations

The analysis attempted to describe the balance of effects and considerations for various subgroups or special populations. However, the evidence reviewed supported the use of this on the following, with specific caveats:

- People living with HIV infection: The data evaluated corresponded to a setting with a high prevalence of HIV, and of particular significance, most PLHIV (>95%) who started the all-oral bedaquiline-containing regimen were receiving antiretroviral therapy (ART). In view of the treatment outcomes described in the analysis, there were no grounds to believe that the regimen would perform any differently in PLHIV. It is necessary to consider significant clinical interactions that may increase bedaquiline exposure or that of other agents with potential for cardiotoxicity when these are co-administered with antiretrovirals.
- Children: Although no direct outcome estimations could be drawn for this population, extrapolation was deemed reasonable. However, because bedaquiline is currently recommended for children and adolescents aged 6–17 years, the GDG concluded that the all-oral bedaquiline-containing regimen may be used in eligible children within this age group, taking into account specifications for regimen companion drugs – in particular, bedaquiline.
- Pregnant and lactating women: More evidence is needed to better inform the use of the all-oral, bedaquiline-containing shorter regimen (BDQ-LFX/MFX-ETO-E-Z-Hⁿ-CFZ). One of the agents in this all-oral shorter regimen, ethionamide, is usually contraindicated in pregnancy, and withholding this agent or replacing it with another one could seriously compromise the effectiveness of the regimen. In the case of pregnant and lactating women, it is therefore recommended that an individualized, all-oral longer regimen (with inclusion of bedaquiline) is used in this population (see Recommendations on the use of longer regimens for MDR/RR-TB).
- Extrapulmonary disease: In view of the unavailability of evidence on surrogates for severity or extent of disease, clinical judgement is advised to decide on the use of this regimen in patients with extensive TB disease or severe forms of extrapulmonary TB.

Implementation considerations

The interest in reducing the duration of treatment for MDR/RR-TB has motivated a number of studies in recent years to treat patients with shorter regimens under programmatic as well as trial conditions. Following experiences in various settings, [eligible] patients now have an option to be treated with a shorter, injectable-sparing regimen of 9–12 months' duration. To ensure that the regimen achieves its desirable effects, prevent the acquisition (or amplification) of additional drug resistance, while regimen components are protected, countries are to consider the following:

- Patient selection and decisions to start the all-oral shorter regimen: Patients with confirmed MDR/RR-TB and with resistance to fluoroquinolones ruled out are expected to benefit the most from this regimen. Proper patient selection would not only lead to improved treatment outcomes but will also contribute to protecting against the development of bedaquiline resistance. In this respect, the regimen is to only be implemented in settings where routine DST for rifampicin and fluoroquinolones can be guaranteed.

It is very important that the implementation of these recommendations is accompanied by continued efforts to increase access to DST for all medicines for which reliable methods exist, as well as for the development and rollout of DST methods for newer medicines. In the absence of a drug-susceptibility test, assays specific for bedaquiline resistance should be monitored through assessment of MICs of bedaquiline.

- Resistance to other anti-TB drugs should be monitored in accordance to WHO recommendations.
- Use of linezolid: The evidence made available to inform this recommendation focused on the assessment of a regimen composed of bedaquiline, levofloxacin/moxifloxacin, ethionamide, ethambutol, pyrazinamide, high-dose isoniazid, clofazimine and pyrazinamide. However, secondary analyses (only in longer regimens containing bedaquiline and bedaquiline plus linezolid) showed favourable outcomes when treatment regimens included both linezolid and bedaquiline. The basis for the addition of linezolid was to protect the regimen – in particular, bedaquiline – while awaiting susceptibility results on additional resistance to fluoroquinolones and other drugs. The GDG decided that, until new evidence is available on shorter regimens that include both of these agents, the all-oral bedaquiline-containing shorter regimen advised herein should not include linezolid. However, the group encouraged countries to consider the use of a *modified all-oral bedaquiline- and linezolid-containing regimen only under operational research until new evidence becomes available*.
- Patient-centred approach: Efforts are required to provide patient support to enable full adherence to treatment.

Monitoring and evaluation

- The implementation of this regimen requires the use of routine DST not only for patient selection but also to monitor the acquisition of resistance.
- Although the data assessed did not unearth any major signals of risk, active TB drug safety monitoring and management systems must be functional in order to conduct rigorous active monitoring of adverse events and to detect, manage, and report suspected or confirmed drug toxicities in a timely manner.

Research priorities

Members of the GDG discussed the research gaps to inform the development of public health recommendations for the management and care of patients with MDR/RR-TB, and highlighted the following priorities:

- studies assessing comparisons of all-oral shorter regimens which include both bedaquiline and linezolid, in addition to other companion drugs;
- studies assessing comparisons of all-oral shorter regimens among different subgroups and special populations, including pregnant and lactating women;
- randomized, controlled trials or operational research of the effectiveness and safety of all-oral shorter regimens, increasing the certainty in the evidence;
- studies exploring mechanisms of acquisition of resistance to bedaquiline and genetic markers to identify resistance; and
- efforts to determine best ways to standardize data collection so that countries can contribute to development of global recommendations.

ART: antiretroviral therapy; DST: drug-susceptibility testing; GDF: Global Drug Facility; GDG: Guideline Development Group; MDR/RR-TB: multidrug-resistant or rifampicin-resistant tuberculosis; MIC: minimum inhibitory concentration; WHO: World Health Organization.

Should an all-oral shorter regimen of 9–12 months' duration including bedaquiline vs longer regimens containing bedaquiline be used for MDR/RR-TB patients to safely improve outcomes?

POPULATION:	MDR-/RR-TB patients to safely improve outcomes
INTERVENTION:	All-oral bedaquiline-containing shorter regimen of 9–12 months duration (BDQ-LFX/MFX-ETO-E-Z-H ^h -CFZ)
COMPARISON:	Longer bedaquiline-containing regimen
MAIN OUTCOMES:	Success vs. Failure/Recurrence; Success vs. Death; Success vs. Failure/Recurrence/Death; Success vs. All Unfavourable; Lost vs. All Other Outcomes; AFB Smear Positive; Success vs. Failure/Recurrence; AFB Smear Positive; Success vs. Death; AFB Smear Positive; Success vs. Failure/Recurrence/Death; AFB Smear Positive; Success vs. All Unfavourable; AFB Smear Positive; Lost vs. All Other Outcomes; HIV-Positive on ART; Success vs. Failure/Recurrence; HIV-Positive on ART; Success vs. Death; HIV-Positive on ART; Success vs. Failure/Recurrence/Death; HIV-Positive on ART; Success vs. All Other Unfavourable; HIV-Positive on ART; Lost vs. All Other Outcomes; HIV Negative; Success vs. Failure/Recurrence; HIV Negative; Success vs. Death; HIV Negative; Success vs. Failure/Recurrence/Death; HIV Negative; Success vs. All Other Outcomes; HIV Negative; Lost vs. All Other Outcomes.
SETTING:	South Africa.
PERSPECTIVE:	Public health and health systems perspective
BACKGROUND:	Multidrug-resistant (MDR-) and rifampicin-resistant tuberculosis (MDR-/RR-TB) is emerging as a major problem due to poor management of drug-sensitive as well as drug-resistance TB. MDR-/RR-TB is treatable, but has required the use of longer treatment regimens which contain potentially toxic drugs. The interest in reducing the duration of treatment for MDR-TB motivated a number of initiatives in recent years to treat patients with shorter regimens under programmatic as well as trial conditions. In 2016, on the basis of data from observational studies of the shorter regimens in different Asian and African countries, WHO started to recommend a standardised shorter MDR-TB regimen, containing an injectable agent, based on the ones under study for eligible patients. In 2018, further modifications were made to the earlier recommended shorter regimen, replacing kanamycin by amikacin (based on evidence from the comparative effectiveness of these two injectable agents). Evidence of permanent effects attributed to the toxicity of injectable agents, have prompted further advances in the development of new treatments such as shorter injectable-sparing regimens. In particular, observational data on an all-oral bedaquiline-containing shorter regimen of 9–12 months duration became available. This is of particular importance given that the regimen may offer patients the likelihood of better tolerating treatment without significant toxicity.
CONFLICT OF INTERESTS:	Alberto Piubello.

Assessment

Problem		ADDITIONAL CONSIDERATIONS
Is the problem a priority?		
JUDGEMENT	RESEARCH EVIDENCE	
<input type="radio"/> No <input type="radio"/> Probably no <input type="radio"/> Probably yes <input checked="" type="radio"/> Yes <input type="radio"/> Varies <input type="radio"/> Don't know	<p>TB remains a threat to global public health and is the top infectious cause of death in the world. In 2018, an estimated 10 million people developed TB and 1.4 million died from the disease. About 500 000 new cases of multidrug- or rifampicin-resistant TB (MDR/RR-TB) were estimated to emerge in 2018. Although all of these would have been eligible for a second-line TB treatment regimen, only 156 071 enrolments in treatment were reported by countries in 2018 – about 30% of the estimated caseload. Despite this, significant improvements in the availability of enhanced diagnostics and more effective medicines have occurred in recent years, and have led to earlier detection and higher success rates among patients with MDR/RR-TB in a number of national programmes. However, these successes have not been reproduced in the rest of the world, and the overall treatment success rate worldwide reached only 56% for patients with MDR/RR-TB who started treatment in 2016, and only 39% for patients with extensively drug-resistant TB (XDR-TB).</p>	

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT

- Trivial
- Small
- Moderate
- Large
- Varies
- Don't know

RESEARCH EVIDENCE

The analysis also suggested that when the all-oral shorter regimen was compared with an injectable-free longer⁴ regimen containing bedaquiline, there seemed to be no marked differences in the outcomes observed earlier; however, relatively modest beneficial effects were noted in the direction of the intervention; in particular, success vs failure/recurrence (aOR 3.9, 95% CI 1.7–9.1), success vs all unfavourable outcomes (aOR 1.6, 95% CI 1.2–2.2) and loss to follow up (aOR 0.5, 95% CI 0.4–0.8), all favouring the use of the all-oral shorter regimen.

ADDITIONAL CONSIDERATIONS

The GDG judged the desirable anticipated effects to be small. The group argued that when a drug such as bedaquiline is included in a regimen – as seen in the analysis – the outcomes in the intervention and comparison groups are not too distant. In actuality, the data evaluated seemed to indicate that the all-oral bedaquiline-containing shorter regimen of 9–12 months' duration was just as good as all-oral longer regimens containing bedaquiline. The main advantages of the all-oral shorter regimen as observed in the analysis was mostly in terms of decreased rates of loss to follow-up.

Outcome	n/N (Bdq short)	n/N (Long, new drugs)	Number of Pairs	aOR (95% CI)	aRD (95% CI)
Success vs. Failure/Recurrence	631/653	268/292	285	3.9 (1.7, 9.1)	5 (1, 9)
Success vs. Death	631/791	268/338	328	1.0 (0.6, 1.5)	-4 (-10, 3)
Success vs. Failure/Recurrence/ Death*	631/813	268/362	352	1.4 (0.9, 2.0)	2 (-4, 9)
Success vs. All Unfavorable	631/891	268/440	427	1.6 (1.2, 2.2)	7 (1, 14)
Lost vs. All Other Outcomes	88/891	88/440	427	0.5 (0.4, 0.8)	-8 (-13, -3)

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT

- Large
- Moderate
- Small
- Trivial
- Varies
- Don't know

RESEARCH EVIDENCE

In past years, the increased use of bedaquiline has reassured the TB community of the potential for adverse events associated with this agent.

The GDG anticipated that the undesirable anticipated effects on the use of regimens may not be so different between an all-oral shorter and an all-oral longer regimen when both contain bedaquiline. However, these effects may vary, depending on, for example, the selection or allocation of patients into regimens containing bedaquiline, severity of disease, drug-resistance patterns, quality of care and monitoring.

⁴ Recommendations released by WHO in December 2018 emphasized that fully oral [longer] regimens should be prioritized and become the preferred option for most patients, and that injectable agents were no longer among the priority medicines to consider when designing longer MDR-TB regimens.

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT

- Very low
- Low
- Moderate
- High
- No included studies

RESEARCH EVIDENCE

ADDITIONAL CONSIDERATIONS

The GDG pointed out that on the basis of the evidence assessed – namely, observational data and potential residual confounding – the overall certainty in the estimates of effect was judged to be *very low*, with the effects for all outcomes also rated as “very low”. Although double adjustment in propensity score matching analyses was carried out to remove the effects of confounding, members of the GDG further noted that although these efforts compensated for some potential confounders, residual bias is likely to be present. The group acknowledged that although the use of programmatic data holds great promise because they better reflect real practice, some considerations in terms of the extent to which these findings could be applied to other settings are to be contemplated. For instance, specific clinical characteristics of the population (e.g. HIV prevalence and drug-resistance patterns) may have an effect, as may quality of health care services, models of care, and treatment adherence strategies.

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT

- Important uncertainty or variability
- Possibly important uncertainty or variability
- Probably no important uncertainty or variability
- No important uncertainty or variability

RESEARCH EVIDENCE

A qualitative study undertaken to highlight the perspectives of key stakeholders, mainly patient and civil society representatives ($n=16$) looked at general preferences and values regarding different aspects of drug-resistant TB treatment regimens, such as duration, pill burden, use of injectable agents and potential for experiencing adverse events.

Participants had the opportunity to discuss important adverse effects including permanent sensorineural hearing loss, nephrotoxicity, electrolyte abnormalities, injection pain and local injection-site complications. From a patient perspective, adverse events (e.g. optic neuritis, hearing impairment and mental status changes due to uremia or electrolyte abnormalities) associated with the use of specific second-line agents, including injectable agents, were deemed unacceptable.

ADDITIONAL CONSIDERATIONS

Preferences regarding treatment appeared to be rooted in core values, including minimal disruption to normal life. Relatively few patients seemed to prefer a short regimen that is tied to more serious side-effects, and then only if the side-effects were rare or reversible. In addition, in terms of treatment duration, preferences seemed to be guided first by side-effects and second by efficacy of treatment regimens.

Balance of effects	
Does the balance between desirable and undesirable effects favor the intervention or the comparison?	
JUDGEMENT	ADDITIONAL CONSIDERATIONS
<input type="radio"/> Favors the comparison <input type="radio"/> Probably favors the comparison <input type="radio"/> Does not favor either the intervention or the comparison <input checked="" type="radio"/> Probably favors the intervention <input type="radio"/> Favors the intervention <input type="radio"/> Varies <input type="radio"/> Don't know	
Resources required	
How large are the resource requirements (costs)?	
JUDGEMENT	ADDITIONAL CONSIDERATIONS
<input type="radio"/> Large costs <input type="radio"/> Moderate costs <input type="radio"/> Negligible costs and savings <input checked="" type="radio"/> Moderate savings <input type="radio"/> Large savings <input type="radio"/> Varies <input type="radio"/> Don't know	The projected cost saving is nearly US\$ 3000 (2019 US\$) in South Africa, and varies across settings, largely in proportion to health care and drug costs (with savings of >US\$ 2000 even in a low-income setting and after reduction in drug costs to half of current Global Drug Facility [GDF] prices). Smaller if linezolid is not included.
Certainty of evidence of required resources	
What is the certainty of the evidence of resource requirements (costs)?	
JUDGEMENT	ADDITIONAL CONSIDERATIONS
<input type="radio"/> Very low <input type="radio"/> Low <input type="radio"/> Moderate <input type="radio"/> High <input checked="" type="radio"/> No included studies	

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<input type="radio"/> Favors the comparison <input type="radio"/> Probably favors the comparison <input type="radio"/> Does not favor either the intervention or the comparison <input checked="" type="radio"/> Probably favors the intervention <input type="radio"/> Favors the intervention <input type="radio"/> Varies <input type="radio"/> No included studies	<p>A cost-effectiveness model was developed, incorporating estimated health system costs with drug procurement, health care delivery, adverse events, retreatments, secondary cases, and morbidity and mortality associated with TB mortality and recurrence, treatment duration, drug toxicity, and TB transmission. Costs and cost-effectiveness were evaluated in South Africa, with sensitivity analyses representing a range of drug and health care costs, high and low HIV co-prevalence, 95% confidence intervals (CIs) for estimates of relative efficacy derived from statistical analysis of patient cohort data, and uncertainty in the values of parameters representing TB natural history.</p> <p>Compared an 18–20-month all-oral regimen (modelled as containing WHO group A drugs including bedaquiline and linezolid), a 9–12-month all-oral, bedaquiline-containing regimen is projected to be both cost saving and effective under all modelled scenarios. Because the shorter oral regimen dominated over the longer regimen in all scenarios modelled, cost-effectiveness was not calculated.</p>	

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<input type="radio"/> Reduced <input type="radio"/> Probably reduced <input type="radio"/> Probably no impact <input type="radio"/> Probably increased <input checked="" type="radio"/> Increased <input type="radio"/> Varies <input type="radio"/> Don't know	<p>A qualitative study undertaken to highlight the perspectives of key stakeholders, mainly patients and civil society representatives ($n = 16$), looked at general preferences and values regarding different aspects of treatment regimens for drug-resistant TB, such as duration, pill burden, use of injectable agents, and potential for experiencing adverse events.</p> <p>Participants considered anything less than universal and immediate access to new treatments to be unethical, but when prompted to consider this preference against a limited supply of drugs, a few would prioritize the youngest and sickest, as well as those who were adherent and could be monitored for adverse events. Patients who face socioeconomic challenges to adherence or who live in remote, rural or poorer communities that lack technical skill or equipment for treatment monitoring, could then be disproportionately and unjustly placed at a disadvantage.</p>	<p>The GDG agreed that injectable-sparing regimens would be easier to decentralize and therefore to use in remote and underserved settings and disadvantaged populations, helping to alleviate health inequities, without anticipating differences in outcomes in specific populations. The group also noted that because audiometry would not be required, it might be easier to monitor individuals, in spite of increased requirements for electrocardiography, which is a prerequisite for the use of bedaquiline-containing regimens. However, the group stressed that the use of electrocardiography should not be a differentiating element between these two regimens, because patients receiving injectable agents such as amikacin should also have regular cardiac monitoring. The group acknowledged that it is possible that in some settings not all patients would be able to undergo electrocardiographic monitoring; however, the group also noted that the increasing access to electrocardiography at peripheral levels might improve equity.</p>

Acceptability	
Is the intervention acceptable to key stakeholders?	
JUDGEMENT	ADDITIONAL CONSIDERATIONS
<input type="radio"/> No <input type="radio"/> Probably no <input type="radio"/> Probably yes <input checked="" type="radio"/> Yes <input type="radio"/> Varies <input type="radio"/> Don't know	<p>The GDG noted that patients recognize that their experiences and perceptions are highly person- and context-dependent, though preference for this [shorter] regimen seemed to be conditional upon adverse events being rare or reversible.</p> <p>Nevertheless, overall, a short, injection-free regimen with few to no physical and mental health side-effects and a low pill burden appeared to be the most acceptable.</p>
	<p>A qualitative study undertaken to highlight the perspectives of key stakeholders, mainly patients and civil society representatives ($n = 16$), looked at general preferences and values regarding different aspects of treatment regimens for drug-resistant TB, such as duration, pill burden, use of injectable agents, and potential for experiencing adverse events. The results of this qualitative analysis suggested that most patients would prioritize a regimen with fewer and less severe side-effects above all else, because it would allow them to continue routine activities. Of note, survivors of drug-resistant TB remarked that they would accept a longer treatment that promised less severe adverse effects over a shorter regimen tied to more severe side-effects, even if treatment was experimental or efficacy unclear. This contrasted with the comparatively few participants who prioritized rapid return to normal life and would rather assume the risk of more serious side-effects within a shorter regimen, even if treatment was experimental and efficacy unclear.</p>

Feasibility

Is the intervention feasible to implement?

JUDGEMENT

- No
- Probably no
- Probably yes
- Yes
- Varies
- Don't know

RESEARCH EVIDENCE

A qualitative study undertaken to highlight the perspectives of key stakeholders, mainly patients and civil society representatives ($n=16$) looked at general preferences and values regarding different aspects of drug-resistant TB treatment regimens, such as duration, pill burden, use of injectable agents and potential for experiencing adverse events.

This study revealed that as the regimen, in particular the expansion of bedaquiline access to all patients is held back is some settings as a result of restrictive eligibility (i.e. prioritization of specific groups) criteria, lack of funding or lack of adequate infrastructure in place (e.g. diagnostics); therefore, the operationalization and immediate roll-out of the all-oral bedaquiline-containing regimen may be hampered.

ADDITIONAL CONSIDERATIONS

One important requirement highlighted by the GDG was that of ensuring the careful selection of patients who are to benefit from this regimen, conducting rapid and accurate DST, and monitoring bedaquiline resistance. The implementation of the regimen may be limited by the need for improved laboratory infrastructure. Although countries are implementing rapid molecular tests to identify rifampicin resistance, laboratory capacity needs to be effectively established to conduct genotypic and phenotypic testing for other important agents in the regimen. Also, although the prevalence of identified mutations conferring low-level drug resistance is very low, countries are to strengthen laboratory capacity and to monitor the acquisition of resistance to bedaquiline through their national reference laboratories or TB supranational reference network sites. This is especially important given the pipeline of new anti-TB regimens that are relying on bedaquiline as a backbone.

The removal of injectable agents, as discussed by the GDG, also pointed towards the convenience (for health care workers) of not having to deliver daily injections, and more so, for patients not having to endure pain and other significant adverse events.

The implementation of the regimen is perceived to go beyond securing of funding, but it further requires making long-term, sustainable systems changes to ensure rapid transition, considering the registration of bedaquiline and other new agents, uninterrupted supply of quality-assured drugs, and active TB drug safety monitoring and management system in coordination with existing pharmacovigilance structures at the country level.

Also, the implementation of this regimen (and any other novel regimen) will require decision-making towards multisectoral policies, tailoring patient-centred programmes that also consider aspects such as mental health and management of other comorbidities, facilitating counselling and support during treatment, and after completion, facilitating full recovery.

Summary of judgements

PROBLEM	JUDGEMENT					
	No	Probably no	Probably yes	Yes	Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	Moderate	Large	Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	Trivial	Varies	Don't know
CERTAINTY OF EVIDENCE VALUES	Very low	Low	Moderate	High		No included studies
	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability		
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High		No included studies
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Varies	No included studies
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	Probably yes	Yes	Varies	Don't know
FEASIBILITY	No	Probably no	Probably yes	Yes	Varies	Don't know

Type of recommendation

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input checked="" type="radio"/>	<input type="radio"/>

Conclusions

Recommendation

A shorter, all-oral, bedaquiline-containing regimen of 9–12 months duration is recommended in eligible patients with confirmed MDR/RR-TB who have not been exposed to treatment with second-line TB medicines used in this regimen for more than one month and in whom resistance to fluoroquinolones has been excluded.

(Conditional recommendation, very low certainty in the evidence)

Justification

Overall, the GDG noted that the certainty of the evidence regarding the efficacy of the all-oral shorter regimen was “very low”, attributable to concerns of serious risk of bias, despite efforts to balance baseline covariates. However, the group recognized that the current evidence assessment of the all-oral, bedaquiline-containing shorter regimen has some additional advantages as compared with all-oral longer regimens, namely in terms of lower loss to follow-up (desirable effect) and obvious shorter duration (acceptability).

When deciding on the strength of the recommendation, the GDG reached a unanimous decision on the conditionality of the recommendation, mainly attributed to the very low certainty in the evidence and requirements to build laboratory capacity and ensure DST.

Other grounds for the strength and direction of this recommendation are as follows:

- The analysis conducted to inform the development of this recommendation was based on observational programmatic data from South Africa where the standardized shorter, all-oral, bedaquiline-containing regimen (BDQ-LFX/MFX-ETO-E-Z-Hⁿ-CFZ) was used for patients with MDR/RR-TB.
- Though no major signals of risk were observed with the use of the all-oral bedaquiline-based shorter regimen, there also remained some uncertainties given the lack of systematic collection of data, and the lack of clarity as to any changes in the regimen that could have been informed by the presence of adverse events.
- Cost-effectiveness modelling of the all-oral, shorter, bedaquiline-containing regimen showed robust cost savings relative to either a longer oral regimen or a short injectable-containing regimen.
- The GDG judged that many eligible patients would prefer the all-oral, bedaquiline-containing regimen of 9–12 months' duration. This is supported by limited observations involving 16 survivors of drug-resistant TB. In addition, this regimen may help promote health equity or mitigate the worsening of health inequities. However, the panel recognized that implementation and scale-up of this regimen might be slow because of prerequisites regarding laboratory capacity and monitoring.

Subgroup considerations

The attempted to describe the balance of effects and considerations for various subgroups or special populations. However, the evidence reviewed supported the use of this in the following settings, with specific caveats:

- People living with HIV infection (PLHIV): The data evaluated corresponded to a setting with a high prevalence of HIV, and of particular significance, most PLHIV (>95%) who started the all-oral bedaquiline-containing regimen were receiving antiretroviral therapy (ART). In view of the treatment outcomes described in the analysis, there were no grounds to believe that the regimen would perform any differently in PLHIV. It is necessary to consider significant clinical interactions that may increase bedaquiline exposure or that of other agents with potential for cardiotoxicity when these are co-administered with antiretrovirals.
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- Extrapulmonary disease: In view of the unavailability of evidence regarding surrogates for severity or extent of disease, it is advisable to use clinical judgement to decide on the use of this regimen in patients with extensive TB disease or severe forms of extrapulmonary TB.

Implementation considerations

The interest in reducing the duration of treatment for MDR/RR-TB has motivated a number of studies in recent years of treating patients with shorter regimens under programmatic as well as trial conditions. Because of experiences in various settings, [eligible] patients now have an option to be treated with a shorter, injectable-sparing regimen of 9–12 months' duration. To ensure that the regimen achieves its desirable effects and to prevent the acquisition (or amplification) of additional drug resistance (while protecting regimen components), countries are to consider the following:

- Patient selection and decisions to start the all-oral shorter regimen: Patients with confirmed MDR/RR-TB and with resistance to fluoroquinolones ruled out are expected to benefit the most from this regimen. Proper patient selection will not only lead to improved treatment outcomes, but will also contribute to avoiding the development of resistance to bedaquiline. In this respect, the regimen is to only be implemented in settings where routine DST for rifampicin and fluoroquinolones can be guaranteed.
 - It is very important that the implementation of these recommendations is accompanied by continued efforts to increase access to DST for all medicines for which reliable methods exist, as well as for the development and rollout of DST methods for newer medicines. In the absence of a drug-susceptibility test, assays specific for bedaquiline resistance should be monitored through assessment of minimum inhibitory concentrations (MICs) of bedaquiline.
 - Resistance to other anti-TB drugs should be monitored in accordance with WHO recommendations.
- Use of linezolid: The evidence made available to inform this recommendation focused on the assessment of a regimen composed of bedaquiline, levofloxacin/moxifloxacin, ethionamide, ethambutol, pyrazinamide, high-dose isoniazid, clofazimine, and pyrazinamide. However, secondary analyses (only in longer regimens containing bedaquiline and bedaquiline plus linezolid) showed favourable outcomes when treatment regimens included both linezolid and bedaquiline. The basis for the addition of linezolid was to protect the regimen, in particular, bedaquiline, while awaiting susceptibility results on additional resistance to fluoroquinolones and other drugs. The GDG decided that until new evidence is available on shorter regimens that include both of these agents, the all-oral bedaquiline-containing shorter regimen advised herein should not include linezolid. However, the group encouraged countries to consider the use of a *modified all-oral bedaquiline- and linezolid-containing only under operational research until new evidence becomes available*.
- Patient-centred approach: Efforts are required to provide patient support to enable full adherence to treatment.

Monitoring and evaluation

- The implementation of this regimen requires the use of routine DST not only for patient selection, but also for monitoring of the acquisition of resistance.
- Although the data assessed did not unearth any major signals of risk, active TB drug safety monitoring and management systems must be functional in order to conduct rigorous active monitoring of adverse events and to detect, manage and report suspected or confirmed drug toxicities in a timely manner.

Research priorities

Members of the GDG discussed the research gaps to inform the development of public health recommendations for the management of MDR/RR-TB, and highlighted the following priorities:

- studies assessing comparisons of all-oral shorter regimens which include bedaquiline and linezolid, in addition to other companion drugs;
- studies assessing comparisons of all-oral shorter regimens among different subgroups and special populations, including pregnant and lactating women;
- randomized-controlled trials or operational research of the effectiveness and safety of all-oral shorter regimens, increasing the certainty of the evidence;
- studies exploring mechanisms of acquisition of resistance to bedaquiline and genetic markers to identify resistance; and
- efforts to determine best ways to standardize the collection of data so that countries can contribute to the development of global recommendations.

aOR: adjusted odds ratio; ART: antiretroviral therapy; drug-susceptibility testing; GDF: Global Drug Facility; GDG: Guideline Development Group; MDR/RR-TB: multidrug- or rifampicin-resistant TB; MIC: minimum inhibitory concentration; PLHIV: people living with human immunodeficiency virus; TB: tuberculosis; WHO: World Health Organization.

Should an all-oral shorter regimen of 9–12 months' duration including bedaquiline vs longer regimens without new TB drugs be used for MDR-/RR-TB patients to safely improve outcomes?

POPULATION:	MDR-/RR-TB patients to safely improve outcomes
INTERVENTION:	All-oral bedaquiline-containing shorter regimen of 9–12 months duration (BDQ-LFX/MFX-ETO-E-Z-H ⁿ -CFZ)
COMPARISON:	Longer regimens without new TB drugs
MAIN OUTCOMES:	Success vs. Failure/Recurrence; Success vs. Death; Success vs. Failure/Recurrence/Death; Success vs. All Unfavourable; Lost vs. All Other Outcomes; AFB Smear Positive; Success vs. Failure/Recurrence; AFB Smear Positive; Success vs. Death; AFB Smear Positive; Success vs. Failure/Recurrence/Death; AFB Smear Positive; Success vs. All Unfavourable; AFB Smear Positive; Lost vs. All Other Outcomes; HIV-Positive on ART: Success vs. Failure/Recurrence; HIV-Positive on ART: Success vs. Failure/Recurrence/Death; HIV-Positive on ART: Success vs. All Other Unfavourable; HIV-Positive on ART: Lost vs. All Other Outcomes; HIV Negative: Success vs. Failure/Recurrence; HIV Negative: Success vs. Death; HIV Negative: Success vs. Failure/Recurrence/Death; HIV Negative: Success vs. All Other Outcomes; HIV Negative: Lost vs. All Other Outcomes.
SETTING:	South Africa.
PERSPECTIVE:	Public health and health systems perspective
BACKGROUND:	Multidrug-resistant (MDR-) and rifampicin-resistant tuberculosis (MDR-/RR-TB) is emerging as a major problem due to poor management of drug-sensitive as well as drug-resistant TB. MDR-/RR-TB is treatable, but has required the use of longer treatment regimens which contain potentially toxic drugs. The interest in reducing the duration of treatment for MDR-TB motivated a number of initiatives in recent years to treat patients with shorter regimens under programmatic as well as trial conditions. In 2016, on the basis of data from observational studies of the shorter regimens in different Asian and African countries, WHO started to recommend a standardized shorter MDR-TB regimen, containing an injectable agent, based on the ones under study for eligible patients. In 2018, further modifications were made to the earlier recommended shorter regimen, replacing kanamycin by amikacin (based on evidence from the comparative effectiveness of these two injectable agents). Evidence of permanent effects attributed to the toxicity of injectable agents, have prompted further advances in the development of new treatments such as shorter injectable-sparing regimens. In particular, observational data on an all-oral bedaquiline-containing shorter regimen of 9–12 months duration became available. This is of particular importance given that the regimen may offer patients the likelihood of better tolerating treatment without significant toxicity.
CONFLICT OF INTERESTS:	Alberto Piubello.

Assessment

Problem

Is the problem a priority?

JUDGEMENT

- No
- Probably no
- Probably yes
- Yes
- Varies
- Don't know

RESEARCH EVIDENCE

Tuberculosis (TB) remains a threat to global public health and is the topmost infectious cause of death in the world. In 2018, an estimated 10 million people developed TB and 1.4 million died from the disease. About 500 000 new cases of multidrug- or rifampicin-resistant TB (MDR/RR-TB) were estimated to emerge in 2018. Although all of these would have been eligible for a second-line TB treatment regimen, only 156 071 enrolments in treatment were reported by countries in 2018 – about 30% of the estimated caseload. Despite this, significant improvements in the availability of enhanced diagnostics and more effective medicines has occurred in recent years and has led to earlier detection and higher success rates among patients with MDR/RR-TB in a number of national programmes. However, these successes have not been reproduced in the rest of the world, and the overall treatment success rate worldwide reached only 56% for patients with MDR/RR-TB who started treatment in 2016, and only 39% for patients with extremely drug-resistant TB (XDR-TB).

ADDITIONAL CONSIDERATIONS

Desirable Effects

How substantial are the desirable anticipated effects?

- JUDGEMENT**
- Trivial
 - Small
 - Moderate
 - Large
 - Varies
 - Don't know

RESEARCH EVIDENCE

The primary analysis also illustrated the effect of an all-oral shorter bedaquiline-based regimen as compared with long regimens that did not contain any new drugs. The shorter regimen performed significantly better across all outcomes and all subgroups as compared with treatment outcomes when longer regimens without new drugs were implemented.

ADDITIONAL CONSIDERATIONS

Outcome	n/N (Bdq short)	n/N (Long, no new drugs)	Number of Pairs	aOR (95% CI)	aRD (95% CI)
Success vs. Failure/ Recurrence	631/653	679/771	580	3.7 (2.2, 6.3)	8 (5, 11)
Success vs. Death	631/791	679/1044	747	2.3 (1.8, 3.0)	15 (10, 19)
Success vs. Failure/Rec./ Death	631/813	679/1136	771	2.6 (2.0, 3.3)	18 (14, 23)
Success vs. All Unfavorable	631/891	679/1437	859	2.8 (2.3, 3.5)	23 (18, 27)
Lost vs. All Other Outcomes	88/891	368/1437	859	0.4 (0.3, 0.5)	-14 (-17, -10)

Undesirable Effects

How substantial are the undesirable anticipated effects?

- JUDGEMENT**
- Large
 - Moderate
 - Small
 - Trivial
 - Varies
 - Don't know

RESEARCH EVIDENCE

The GDG discussed earlier results of the individual-patient data (IPD) meta-analysis conducted to assess the overall balance between benefits and harms of individual agents. In the analysis, 1995 patients received kanamycin and 268 (13.4%) experienced an adverse event causing permanent drug discontinuation; 4106 patients received amikacin, of whom 235 (5.7%) experienced an adverse event causing permanent drug discontinuation; additionally, 1932 received capreomycin and 161 (8.3%) experienced an adverse event causing permanent drug discontinuation. In contrast, 464 patients received bedaquiline, of whom nine (1.9%), nine (1.9%) experienced an adverse event causing permanent drug discontinuation.

ADDITIONAL CONSIDERATIONS

The GDG agreed that there is evidence of patients experiencing adverse events after the use of bedaquiline. However, it was emphasized that compared with the alternative, and on the basis of the IPD meta-analysis, these events seem to be significantly fewer.

Some members of the GDG did emphasize that although the undesirable effects of the all-oral bedaquiline-containing shorter regimens seemed to be trivial compared with those of longer regimens without new TB drugs, there were still adverse events associated with the drugs used in the all-oral regimen.

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT RESEARCH EVIDENCE

- Very low
- Low
- Moderate
- High
- No included studies

ADDITIONAL CONSIDERATIONS

The GDG pointed out that on the basis of the evidence assessed – namely observational data and potential residual confounding – the overall certainty of the estimates of effect was judged to be “very low”, with the effects for all outcomes also rated as “very low”.

Although double adjustment in propensity score matching analyses was carried out to remove the effects of confounding, members of the GDG further noted that although these efforts compensated for some potential confounders, residual bias was likely to be present. The group acknowledged that although the use of programmatic data holds great promise because they better reflect real practice, some considerations in terms of the extent to which these findings could be applied to other settings are to be contemplated, such as specific clinical characteristics of the population (e.g. HIV prevalence; drug-resistance patterns), as well as quality of health care services, models of care, and treatment adherence strategies.

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT RESEARCH EVIDENCE

- Important uncertainty or variability
- Possibly important uncertainty or variability
- Probably no important uncertainty or variability
- No important uncertainty or variability

ADDITIONAL CONSIDERATIONS

Preferences regarding treatment appeared to be rooted in core values, including minimal disruption to normal life. Relatively few patients seemed to prefer a short regimen that was tied to more serious side-effects, and then only if the side-effects were rare or reversible. In addition, in terms of the duration of treatment, preferences seemed to be guided first by side-effects and second by efficacy of treatment regimens.

A qualitative study undertaken to highlight the perspectives of key stakeholders, mainly patients and civil society representatives ($n = 16$), looked at general preferences and values regarding different aspects of treatment regimens for drug-resistant TB, such as duration, pill burden, use of injectable agents, and potential for experiencing adverse events.

Preferences for treatment duration seemed to be guided first by side-effects and second by efficacy. The qualitative study, though small, highlighted how most patients would prefer a longer regimen with less severe side-effects over a shorter regimen with more severe side-effects.

Balance of effects	
Does the balance between desirable and undesirable effects favor the intervention or the comparison?	
JUDGEMENT	RESEARCH EVIDENCE
<input type="radio"/> Favors the comparison <input type="radio"/> Probably favors the comparison <input type="radio"/> Does not favor either the intervention or the comparison <input type="radio"/> Probably favors the intervention <input checked="" type="radio"/> Favors the intervention <input type="radio"/> Varies <input type="radio"/> Don't know	<p>The discussed whether the balance between desirable and undesirable effects favoured the intervention. Data assessed showed that the overall rate of adverse events attributed to bedaquiline as compared with injectable agents was two time less. At the same time, the GDG noted a 50% reduction in deaths, attributing this effect to the addition of bedaquiline. However, the group emphasized the potential harms if this bedaquiline-containing regimen were to be implemented without ensuring proper DST, and the potential for amplification of resistance patterns.</p>
Resources required	
How large are the resource requirements (costs)?	
JUDGEMENT	RESEARCH EVIDENCE
<input type="radio"/> Large costs <input type="radio"/> Moderate costs <input type="radio"/> Negligible costs and savings <input checked="" type="radio"/> Moderate savings <input type="radio"/> Large savings <input type="radio"/> Varies <input type="radio"/> Don't know	<p>The GDG did agree that, overall, savings can be considered in terms of future retreatments prevented, as well as reduced hospitalization rates resulting from fewer adverse reactions.</p>
Certainty of evidence of required resources	
What is the certainty of the evidence of resource requirements (costs)?	
JUDGEMENT	RESEARCH EVIDENCE
<input type="radio"/> Very low <input type="radio"/> Low <input checked="" type="radio"/> Moderate <input type="radio"/> High <input type="radio"/> No included studies	<p>The GDG anticipated the cost savings to be robust, with savings on drugs, health care delivery, fewer adverse events and lower retreatment and loss-to-follow-up rates.</p>

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT

- Favors the comparison
- Probably favors the comparison
- Does not favor either the intervention or the comparison
- Probably favors the intervention
- Favors the intervention
- Varies
- No included studies

RESEARCH EVIDENCE

No cost-effectiveness analysis was performed only for currently recommended comparator regimens. A longer regimen containing no new TB drugs was not separately modelled.

ADDITIONAL CONSIDERATIONS

Although the analytic-decision model did not focus on comparing cost savings and cost-effectiveness relative to longer regimens without the use of any new drugs, the GDG did acknowledge that the shortening of the regimen and the switch from injectables to oral drugs are estimated to be resource saving as a result of savings on drugs, health care delivery, and reduced rates of adverse events.

Equity

What would be the impact on health equity?

JUDGEMENT

- Reduced
 - Probably reduced
 - Probably no impact
 - Probably increased
 - Increased
 - Varies
 - Don't know
- A qualitative study undertaken to highlight the perspectives of key stakeholders, mainly patients and civil society representatives ($n = 16$), looked at general preferences and values regarding different aspects of treatment regimens for drug-resistant TB, such as duration, pill burden, use of injectable agents, and potential for experiencing adverse events.
- Participants considered anything less than universal and immediate access to new treatments to be unethical, but when prompted to consider this preference against a limited supply of drugs, a few would prioritize the youngest and sickest, as well as those who were adherent and could be monitored for adverse events. Patients who face socioeconomic challenges to adherence or who live in remote, rural, or poorer communities that lack technical skill or equipment for treatment monitoring could then be disproportionately and unjustly placed at a disadvantage.

ADDITIONAL CONSIDERATIONS

The GDG agreed that the all-oral shorter regimen would be easier to decentralize and therefore make available to remote and underserved settings and disadvantaged populations, helping to alleviate health inequities, without anticipating differences in outcomes in specific populations. Further, the group noted that because audiometry would not be required, it might be easier to monitor individuals, in spite of increased requirements for electrocardiography, which is a prerequisite for the use of bedaquiline-containing regimens. However, the group stressed that the use of electrocardiography should not be a differentiating element between these two regimens, because patients receiving injectable agents such as amikacin should also have regular cardiac monitoring. The group acknowledged that it is possible that, in some settings, not all patients will be able to undergo electrocardiographic monitoring; however, members also noted that the increasing access to electrocardiography at peripheral levels might improve equity.

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT

- No
- Probably no
- Probably yes
- Yes
- Varies
- Don't know

RESEARCH EVIDENCE

A qualitative study undertaken to highlight the perspectives of key stakeholders, mainly patients and civil society representatives ($n = 16$), looked at general preferences and values regarding different aspects of treatment regimens for drug-resistant TB, such as duration, pill burden, use of injectable agents, and potential for experiencing adverse events. The results of this qualitative analysis suggested that most patients would prioritize a regimen with fewer and less severe side-effects above all else, because it would allow them to continue routine activities. Of note, survivors of drug-resistant TB remarked that they would accept a longer treatment that promised **less severe adverse effects** over a shorter regimen tied to more severe side-effects, even if treatment was experimental or efficacy was unclear. This contrasted with comparatively few participants who prioritized a rapid return to normal life and would rather assume the risk of more serious side-effects within a shorter regimen, even if treatment was experimental and efficacy was unclear.

ADDITIONAL CONSIDERATIONS

The GDG noted that patients recognize that their experiences and perceptions are highly person- and context-dependent, though preference over this [shorter] regimen seemed to be conditional upon adverse events being rare or reversible. Nevertheless, overall, a short, injection-free regimen with few to no physical and mental health side-effects and a low pill burden appeared to be the most acceptable.

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<input type="radio"/> No <input type="radio"/> Probably no <input type="radio"/> Probably yes <input type="radio"/> Yes <input checked="" type="radio"/> Varies <input type="radio"/> Don't know	<p>A qualitative study undertaken to highlight the perspectives of key stakeholders, mainly patients and civil society representatives (n = 16), looked at general preferences and values regarding different aspects of treatment regimens for drug-resistant TB, such as duration, pill burden, use of injectable agents, and potential for experiencing adverse events.</p> <p>This study revealed that because the regimen – in particular the expansion of bedaquiline access to all patients – is held back in some settings as a result of restrictive eligibility (i.e. prioritization of specific groups) criteria, lack of funding, or lack of adequate infrastructure in place (e.g. diagnostics), the operationalization and immediate rollout of the all-oral bedaquiline-containing regimen might be hampered.</p>	<p>One important requirement highlighted by the GDG was that of ensuring the careful selection of patients who are to benefit from this regimen, conducting rapid and accurate DST, and monitoring bedaquiline resistance. The implementation of the regimen may be limited by the need for improved laboratory infrastructure. Although countries are implementing rapid molecular tests to identify rifampicin resistance, laboratory capacity needs to be effectively established to conduct genotypic and phenotypic testing for other important agents in the regimen. Also, although the prevalence of identified mutations conferring low-level drug resistance is very low, countries are to strengthen laboratory capacity and to monitor the acquisition of resistance to bedaquiline through their national reference laboratories or TB supranational reference network sites. This is especially important given the pipeline of new anti-TB regimens that are relying on bedaquiline as a backbone.</p> <p>The removal of injectable agents, as discussed by the GDG, also pointed towards the convenience (for health care workers) of not having to deliver daily injections, and more so, for patients not having to endure pain and other significant adverse events.</p> <p>The implementation of the regimen is perceived to go beyond securing of funding, but it further requires making long-term, sustainable systems changes to ensure rapid transition, considering the registration of bedaquiline and other new agents, uninterrupted supply of quality-assured drugs, and active TB drug safety monitoring and management system in coordination with existing pharmacovigilance structures at the country level.</p> <p>Also, the implementation of this regimen (and any other novel regimen) will require decision-making towards multisectoral policies, tailoring patient-centred programmes that also consider aspects such as mental health and management of other comorbidities, facilitating counselling and support during treatment, and after completion, facilitating full recovery.</p>

Conclusions

Recommendation

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- Patient selection and decisions to start the all-oral shorter regimen: Patients with confirmed MDR/RR-TB and with resistance to fluoroquinolones ruled out are expected to benefit the most from this regimen. Proper patient selection will not only lead to improved treatment outcomes, but will also contribute to avoiding the development of resistance to bedaquiline. In this respect, the regimen is to only be implemented in settings where routine DST for rifampicin and fluoroquinolones can be guaranteed.

It is very important that the implementation of these recommendations is accompanied by continued efforts to increase access to DST for all medicines for which reliable methods exist, as well as for the development and rollout of DST methods for newer medicines. In the absence of a drug-susceptibility test, assays specific for bedaquiline resistance should be monitored through assessment of minimum inhibitory concentrations (MICs) of bedaquiline.

Resistance to other anti-TB drugs should be monitored in accordance with WHO recommendations.

- Use of linezolid: The evidence made available to inform this recommendation focused on the assessment of a regimen composed of bedaquiline, levofloxacin/moxifloxacin, ethionamide, ethambutol, pyrazinamide, high-dose isoniazid, clofazimine, and pyrazinamide. However, secondary analyses (only in longer regimens containing bedaquiline and bedaquiline plus linezolid) showed favourable outcomes when treatment regimens included both linezolid and bedaquiline. The basis for the addition of linezolid was to protect the regimen – in particular, bedaquiline – while awaiting susceptibility results on additional resistance to fluoroquinolones and other drugs. The GDG decided that until new evidence is available on shorter regimens that include both of these agents, the all-oral bedaquiline-containing shorter regimen advised herein should not include linezolid. However, the group encouraged countries to consider the use of a *modified all-oral bedaquiline- and linezolid-containing only under operational research until new evidence becomes available*.

- Patient-centred approach: Efforts are required to provide patient support to enable full adherence to treatment.

Monitoring and evaluation

- The implementation of this regimen requires the use of routine DST not only for patient selection, but also for monitoring of the acquisition of resistance.
- Although the data assessed did not unearth any major signals of risk, active TB drug safety monitoring and management systems must be functional in order to conduct rigorous active monitoring of adverse events and to detect, manage and report suspected or confirmed drug toxicities in a timely manner.

Research priorities

Members of the GDG discussed the research gaps to inform the development of public health recommendations for the management and care of patients with MDR/RR-TB, and highlighted the following priorities:

- studies assessing comparisons of all-oral shorter regimens which include bedaquiline and linezolid, in addition to other companion drugs;
- studies assessing comparisons of all-oral shorter regimens among different subgroups and special populations, including pregnant and lactating women;
- randomized-controlled trials or operational research of the effectiveness and safety of all-oral shorter regimens, increasing the certainty of the evidence;
- studies exploring mechanisms of acquisition of resistance to bedaquiline and genetic markers to identify resistance; and
- efforts to determine best ways to standardize the collection of data so that countries can contribute to the development of global recommendations.

aOR: adjusted odds ratio; ART: antiretroviral therapy; drug-susceptibility testing; GDF: Global Drug Facility; GDG: Guideline Development Group; MDR/RR-TB: multidrug- or rifampicin-resistant TB; MIC: minimum inhibitory concentration; PLHIV: people living with human immunodeficiency virus; TB: tuberculosis; WHO: World Health Organization.

Should a treatment regimen lasting 6–9 months composed of bedaquiline, pretomanid and linezolid vs longer regimens containing bedaquiline and linezolid in addition to other anti-TB drugs be used for XDR-TB patients or patients who are treatment intolerant or with non-responsive MDR-TB?

POPULATION:	XDR-TB patients or patients who are treatment intolerant or with non-responsive MDR-TB
INTERVENTION:	Treatment regimen lasting 6–9 months composed of bedaquiline, pretomanid and linezolid
COMPARISON:	Longer regimens containing bedaquiline and linezolid in addition to other anti-TB drugs
MAIN OUTCOMES:	Success vs. Failure/Recurrence/Death; Success vs. All Unfavorable; Adverse events;
SETTING:	Treatment of MDR-TB patients with additional fluoroquinolone resistance and / or MDR-TB patients who are treatment intolerant or who had not responded to previous MDR-TB treatment, using a shorter regimen composed of bedaquiline, pretomanid and linezolid (BPAL) of 6–9 months duration in a combination of hospital and ambulatory care settings in South Africa. The data were derived from the Nix-TB study, with 108 patients included for analysis (the whole study population was 109 patients; however one patient withdrew consent and this person was not included in the efficacy analyses)
PERSPECTIVE:	Public health and health systems
BACKGROUND:	<p>Treatment of extensively drug-resistant forms of TB presents multiple challenges to clinicians and national TB programmes both due to the limited range of medicines available and the life-threatening nature of the disease. Patients with MDR/RR-TB and additional fluoroquinolone resistance have typically experienced poor treatment outcomes since the description of XDR-TB was first used in 2006.⁵ Based on data reported by Member States to WHO, for the cohort of XDR-TB patients who started treatment in 2016 (and for whom treatment outcomes were available in 2018), only 39% completed treatment successfully, while 26% died, treatment failed for 18% and an additional 18% were lost to follow up or were not evaluated.⁶ The pressing need for more effective treatment regimens for patients with extensive drug resistance, including fluoroquinolone resistance and more extensive drug resistance profiles, has motivated a number of studies and initiatives to test more effective and novel treatment regimens, inclusive of newer and repurposed medicines.</p> <p>One such study is the Nix-TB study,⁷ conducted by TB Alliance. The Nix-TB study was a one arm, phase three, open label prospective cohort study that assessed the safety, efficacy, tolerability and pharmacokinetic properties of a 6 month treatment regimen composed of bedaquiline, pretomanid⁸ and linezolid (BPAL), extendable to 9 months for those who missed doses or for patients who remained culture positive or reverted from culture negative to positive between months 4 to 6 of treatment. The study was conducted between 2014 and 2019 at three study sites, all in South Africa, with the first patient enrolled in April 2015. Eligible patients were aged 14 years and above, weighed ≥ 35kg, had a documented HIV result and had bacteriologically confirmed sputum culture positive XDR-TB or bacteriologically confirmed MDR/RR-TB but who were treatment intolerant or non-responsive to previous MDR/RR-TB treatment. A number of other inclusion criteria were applied. Patients were followed up for a period of up to 24 months post treatment completion. The primary outcome measure was the incidence of bacteriologic failure or relapse or clinical failure through follow up until 6 months after the end of treatment (TB Alliance, Nix-TB study protocol, available at: https://clinicaltrials.gov/ct2/show/NCT02333799). Secondary outcome measures comprised:</p> <ol style="list-style-type: none"> 1. Incidence of bacteriologic failure or relapse or clinical failure through follow up until 24 months after the end of treatment (as a confirmatory analysis). 2. Time to sputum culture conversion to negative status through the treatment period. 3. The proportion of subjects with sputum culture conversion to negative status at 4, 6, 8, 12, 16 and 26 or 39 weeks. 4. Linezolid dosing (actual) and efficacy. 5. Change from baseline in TB symptoms. 6. Change from baseline in Patient Reported Health Status. 7. Change from baseline in weight (TB Alliance, Nix-TB study protocol, available at: https://clinicaltrials.gov/ct2/show/NCT02333799). <p>The Nix-TB study regimen comprised pretomanid administered at 200mg once daily, bedaquiline administered at 400mg once daily for the first two weeks of treatment (days 1 to 14) and then 200mg three times a week thereafter, and linezolid commenced at 1200mg per day (additional information on linezolid dosing is included under Implementation considerations, below). Close microbiologic, clinical and adverse event monitoring were features of the Nix-TB study.</p>

⁵ Emergence of XDR-TB [website]. Geneva, Switzerland World Health Organization 2006 (<https://www.who.int/mediacentre/news/notes/2006/np23/en>, accessed 28 February 2020).

⁶ WHO consolidated guidelines on drug resistant tuberculosis treatment. Geneva, Switzerland: World Health Organization; 2019 (<https://apps.who.int/iris/bitstream/handle/10665/311389/9789241550529-eng.pdf?ua=1>, accessed 20 March 2020).

⁷ The Nix-TB study protocol is available at: <https://clinicaltrials.gov/ct2/show/NCT02333799>. A publication on the results of the study is available at: <https://www.nejm.org/doi/full/10.1056/NEJMoa1901814>.

⁸ Pretomanid is a new chemical entity and a member of a class of compounds known as nitroimidazo-oxazines, which possess significant anti-TB activity and a unique mechanism of action.

The evidence to inform this PICO question was derived from the Nix-TB study and included information on 108 patients. The total study population was 109 patients; however, one patient withdrew informed consent to participate in the study and this person was included in safety analyses but not in the analyses for effectiveness. These data were compared to a subset of data from the individual patient dataset (IPD) which overall includes 13 273 individual patient records from 55 different studies/centres in 38 countries. For the primary analyses, the comparator group included patients from the IPD on longer treatment regimens (with a mean duration of treatment of 21.0–25.5 months), who received both bedaquiline and linezolid as part of the regimen (no patients received pretomanid in the IPD). This comparison group included 456 patients who were treated in Belarus, India, France, Russia and in countries in Asia. The intervention and comparison groups were matched exactly for XDR, MDR and fluoroquinolone resistance and HIV status, with propensity score matching for the variables of age, sex, baseline culture result, extent of disease (determined by baseline AFB smear or chest x-ray findings of cavitation or bilateral disease if AFB smear result was missing) and country income level (World Bank Atlas method). Treatment outcomes used in these analyses comprised the investigator defined outcomes for the intervention group (for the Nix-TB study) and treatment outcomes largely defined according to WHO definitions (Laserson KF et al., 2005; World Health Organization, 2013: <https://www.who.int/tb/publications/definitions/en/>) for the comparator group (for the patients included in the IPD). In order to allow an equal opportunity for treatment outcomes to occur from the start of treatment when comparing the two groups, all outcomes were included from the start of treatment to 24 months post treatment start. This meant that in the intervention group these outcomes occurred post treatment completion and for the comparator group the outcomes were end of treatment outcomes (as patients in the IPD received a longer regimen and were not followed up post treatment completion). Three other comparator groups from the IPD included patients on longer treatment regimens who received a regimen which included bedaquiline, or a regimen which included linezolid, or a regimen with neither bedaquiline or linezolid included. The initial intention of the GDG was to assess the intervention regimen against all three comparison groups however, during their deliberations the panel agreed that the judgements should be based on the comparison group who received bedaquiline and linezolid as part of their regimen, as these patients most closely resemble patients who would receive currently recommended longer regimens composed with medicines from Groups A, B and C. However, a direct comparison of BPaL with all-oral longer regimens constructed according to the most recent WHO recommendations issued in May 2019 was not possible as these regimens may have only been in use since mid-2019, and treatment outcomes for these patients are not yet available. Additional data reviewed by the Guideline Development Group relevant to this PICO question were a cost effectiveness analysis, a study on the acceptability and likelihood of implementation of the BPaL regimen, modelled pharmaco-kinetic data based on the development of a pharmaco-kinetic toxicodynamic model and a summary review of preclinical and early clinical data on pretomanid. The cost effectiveness analysis, acceptability study and modelled pharmacokinetic studies were conducted as part of the Nix-TB study and were sponsored by TB Alliance.

Susan ABDEL-RAHMAN, Daniela CIRILLO, Agnes GEBHARD, Alena SKRAHINA, Andrew VERNON

**CONFLICT
OF INTERESTS:**

Assessment

Problem		ADDITIONAL CONSIDERATIONS
Is the problem a priority?		
JUDGEMENT	RESEARCH EVIDENCE	
<input type="radio"/> No <input type="radio"/> Probably no <input type="radio"/> Probably yes <input checked="" type="radio"/> Yes <input type="radio"/> Varies <input type="radio"/> Don't know	<p>Tuberculosis (TB) remains a threat to global public health and is the top infectious cause of death in the world. In 2018, an estimated 10 million people developed TB and 1.4 million died from the disease. About 500 000 new cases of multidrug- or rifampicin-resistant TB (MDR/RR-TB) were estimated to emerge in 2018. While all of these would have been eligible for a second-line TB treatment regimen, only 156 071 enrolments on treatment were reported by countries in 2018 – about 30% of the estimated caseload. In addition, the average proportion of MDR-TB cases with extensively drug-resistant TB (XDR-TB) is approximately 6.2% (95% confidence interval [CI]: 4.4–8.2%). Despite this, significant improvements in the availability of enhanced diagnostics and more effective medicines has occurred in recent years, and has led to earlier detection and higher success rates among patients with MDR/RR-TB in a number of national programmes. However, these successes have not been reproduced in the rest of the world, and the overall treatment success rate worldwide reached only 56% for MDR/RR-TB patients who started on treatment in 2016, and only 39% for patients with XDR-TB.</p>	

Desirable Effects

How substantial are the desirable anticipated effects?

- JUDGEMENT**
- Trivial
 - Small
 - Moderate
 - Large
 - Varies
 - Don't know

RESEARCH EVIDENCE

Outcomes	With longer regimens containing bedaquiline and linezolid in addition to other anti-TB drugs	With treatment regimen lasting 6–9 months composed of bedaquiline, pretomanid and linezolid	Difference	Relative effect (95% CI)
Success vs. Failure/ Recurrence follow up: mean 24 months	92 per 100	97 per 100 (90 to 99)	6 more per 100 (2 fewer to 8 more)	OR 3.3 (0.8 to 13.7)
Success vs. Death follow up: mean 24 months	92 per 100	92 per 100 (53 to 99)	0 fewer per 100 (39 fewer to 7 more)	OR 1.0 (0.1 to 8.2)
Success vs. Failure/ Recurrence/ Death follow up: mean 24 months	85 per 100	91 per 100 (80 to 96)	6 more per 100 (5 fewer to 11 more)	OR 1.8 (0.7 to 4.4)
Success vs. All Unfavorable follow up: mean 24 months	82 per 100	85 per 100 (70 to 93)	3 more per 100 (12 fewer to 11 more)	OR 1.2 (0.5 to 3.1)

Adverse events BPaL regimen: 1 (0.9%) patient died, 27 (25%) patients experienced other serious adverse events including hospitalizations and life-threatening events, and 53 (49%) patients experienced at least one Grade 3–4 adverse events. Drug discontinuation for adverse events: related to all three drugs in 1 patient, and related to linezolid (initial dose 1200 mg/day) discontinued in another 35 (32%) patients. Only 20 (18%) patients completed a full course of 1200 mg/day. In the IPD studies (90% received ≤ 600 mg/day), the pooled rate of linezolid permanent discontinuation was 17.9%, and in the EndTB study (all patients received 600 mg/day or less), the rate of linezolid discontinuation was 13.1%. In EndTB: 9 out of 1094 participants (0.8%) died of a possibly or probably drug-related adverse event, including two participants with sudden cardiac death and QT prolongation.

ADDITIONAL CONSIDERATIONS

The GDG panel noted that the evidence was uncertain, reflected in the certainty rating of “very low”. They also acknowledged the overall high success rates in the Nix-TB study.

The panel voted on the magnitude of the desirable effects, with 17 voting “small” and 7 voting “trivial”. One abstained, and 5 reported conflicts of interest.

The panel then re-evaluated the differential desirable effects of the shorter regimen with regard to burden (which is a desirable effect if is reduced by the intervention). This re-evaluation was brought up when the balance of the effects was found to be inconsistent with the criteria noted under desirable and undesirable effects.

Patient representatives raised the issues of other consequences of a longer duration of treatment; these include a larger pill burden and may include depression and other undesirable effects. The panel noted that loss to follow-up does not capture all of the burden of differing MDR/RR-TB regimens on patients. After these additional discussions, the GDG came to consensus (through voting) that the difference in the desirable effects were moderate. The votes were tallied as 5 for “small” and 18 for “moderate”. One member abstained and 5 members reported conflicts of interest; another GDG member was not present at the meeting by this point.

Additional evidence presented included modelled pharmacokinetic data based on the development of a pharmacokinetic–toxicodynamic model designed to quantify the relationship between pharmacokinetic and toxic qualities of linezolid as part of a 6-month BPaL regimen. These analyses were sponsored by the TB Alliance and were based on data from the Nix-TB study. Information on modelled data from 88 patients who received linezolid in the Nix-TB study was presented. This patient population included information on 7 patients who had died; 21 individuals from the Nix-TB study were excluded from these analyses because 16 had incomplete dosing histories (i.e. they were receiving ongoing treatment at the time of analysis) and 5 had unverifiable dosing histories. Among the 109 patients in the Nix-TB study, anaemia was reported in 37% and peripheral sensory neuropathy was reported in 69%. On the basis of the modelled data, it was concluded that the pharmacokinetics related to linezolid are nonlinear in patients with XDR-TB and that individual linezolid concentration times are the best predictor of toxicity. Higher toxicity rates were observed at higher total daily doses, with comparable toxicity rates for BID and QD dosing schedules. Anaemia can be managed by closely monitoring changes in haemoglobin over the first 4 weeks of treatment (in particular, changes in haemoglobin that represent a >10% increase from baseline should trigger a reduction in the dose of linezolid – haemoglobin levels recover well after dose reductions). Peripheral neuropathy should be closely monitored; when it does occur, it is reversible for most patients within 3 months. Thrombocytopenia is potentially not a major concern with high-dose linezolid for patients with XDR-TB.

The GDG considered the desirable effect of treatment success, which was higher in the intervention groups than in the comparator groups, for all four treatment outcomes that were assessed. Overall, when comparing treatment success with failure/recurrence, the treatment success rate in the Nix-TB study was 97.0%, compared with 91.7% in the comparator group (resulting in 6 more treatment successes per 100 patients). For treatment success versus death, treatment success was 93.2% in the Nix-TB study compared with 91.9% in the comparator group (resulting in 1 more treatment success per 100 patients). The GDG considered rates of loss to follow-up to be a desirable effect; the proportion of patients who were lost to follow-up was lower in the intervention group (1.8%) compared with the comparison group (3.1%). The uncertainty in the evidence was acknowledged by the panel when making their judgement on the desirable (and undesirable) effects.

The BPAL regimen was associated with a high rate of adverse events, considered to be related to the study drugs. This included the death of 1 (0.9%) participant; other serious adverse events (including hospitalizations and life-threatening events) in 27 (25%) participants and at least one Grade 3–4 adverse event in 53 (49%) participants. This led to discontinuation of all three drugs for 1 patient, and discontinuation of linezolid (initial dose 1200 mg/day) for another 35 (32%) patients. Only 18 (17%) patients completed a full course of linezolid at 1200 mg/day.

The GDG noted that it is difficult to compare these adverse event rates with other studies because of major and important differences in adverse event ascertainment, assessment, and reporting. However, in the IPD studies (where 90% of patients received a linezolid dose of ≤ 600 mg/day), the pooled rate of permanent discontinuation of linezolid was 17.9%, and in the EndTB trial (where all patients received ≤ 600 mg/day of linezolid), the rate of linezolid discontinuation was 13.1%. In both of these studies, >80% of patients received a starting dose of linezolid of 600 mg/day. In the EndTB study, preliminary analyses suggested that 9 of 1094 participants (0.8%) died of a possibly or probably drug-related adverse event, including 2 participants with sudden cardiac death

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT

- Large
- Moderate
- Small
- Trivial
- Varies
- Don't know

RESEARCH EVIDENCE

Outcomes	With longer regimens containing bedaquiline and linezolid in addition to other anti-TB drugs	With treatment regimen lasting 6–9 months composed of bedaquiline, pretomanid and linezolid	Difference	Relative effect (95% CI)
Success vs. Failure/ Recurrence follow up: mean 24 months	92 per 100	97 per 100 (90 to 99)	6 more per 100 100 (2 fewer to 8 more)	OR 3.3 (0.8 to 13.7)
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Success vs. All Unfavorable follow up: mean 24 months	82 per 100	85 per 100 (70 to 93)	3 more per 100 100 (12 fewer to 11 more)	OR 1.2 (0.5 to 3.1)

ADDITIONAL CONSIDERATIONS

The issue of serious adverse events, particularly those related to linezolid, and potential safety signals related to male infertility observed in animal (murine) models, were of concern to the panel. The GDG highlighted the potential difficulties in monitoring of infertility in a programmatic setting. Additional human sperm studies recommended by the US Food and Drug Administration will be carried out by the TB Alliance; however, these data were not available for the GDG to consider at the time of the meeting (and they will not be available for a few years). The GDG determined that infertility is a serious issue because it affects not only patients but also their families. The GDG also acknowledged that, at the time the Nix-TB study started, there were few treatment options for patients and there was a high case fatality rate, which means that patients might have placed a different value on potential male infertility than they might now. Additional evidence presented included modelled pharmacokinetic data based on the development of a pharmacokinetic–toxicodynamic model designed to quantify the between pharmacokinetics and toxicity of linezolid as part of a 6-month BPal regimen. These analyses were sponsored by the TB Alliance and were based on data from the Nix-TB study. Information on modelled data from 88 participants who received linezolid in the Nix-TB study was presented. The information on this population included data on 7 patients who had died. Twenty-one individuals from the Nix-TB study were excluded from these analyses because 16 had incomplete dosing histories (i.e. they were receiving ongoing treatment at the time of analysis) and 5 had unverifiable dosing histories. Among the 109 patients in the Nix-TB study, anaemia was reported in 37% of patients and peripheral sensory neuropathy was reported in 69%. On the basis of the modelled data, it was concluded that the pharmacokinetics related to linezolid are nonlinear in patients with XDR-TB and that individual linezolid concentration times are the best predictor of toxicity. Higher toxicity rates were observed at higher total daily doses, with comparable toxicity rates for BID and QD dosing schedules. Anaemia can be managed by closely monitoring changes in haemoglobin over the first 4 weeks of treatment (in particular, increases in haemoglobin of > 10% over baseline should trigger a reduction in the dose of linezolid; haemoglobin levels recover well after dose reductions). Peripheral neuropathy should be closely monitored; when it does occur, it is reversible for most patients within 3 months. Thrombocytopenia is potentially not a major concern with high-dose linezolid for patients with XDR-TB.

Adverse events BPaL regimen: 1 (0.9%) patient died, 27 (25%) patients experienced other serious adverse events including hospitalizations and life-threatening events, and 53 (49%) patients experienced at least one Grade 3–4 adverse events. Drug discontinuation for adverse events: related to all three drugs in 1 patient, and related to linezolid (initial dose 1200 mg/day) discontinued in another 35 (32%) patients. Only 20 (18%) patients completed a full course of 1200 mg/day. In the IPD studies (90% received 600mg/day or less), the pooled rate of LZD permanent discontinuation was 17.9%, and in the EndTB study (all patients received 600mg/day or less), the rate of LZD discontinuation was 13.1%. In EndTB: 9 persons out of 1094 (0.8%) died of a possibly/probably drug related AE, including two persons with sudden cardiac death and QT prolongation.

The GDG considered the desirable effect of treatment success, which was higher in the intervention groups than in the comparator groups, for all four treatment outcomes that were assessed. Overall, when comparing treatment success with failure/recurrence, the treatment success rate in the Nix-TB study was 97.0%, compared with 91.7% in the comparator group (resulting in 6 more treatment successes per 100 patients). For treatment success versus death, treatment success was 93.2% in the Nix-TB study compared with 91.9% in the comparator group (resulting in 1 more treatment success per 100 patients). The GDG considered rates of loss to follow-up to be a desirable effect; the proportion of patients who were lost to follow-up was lower in the intervention group (1.8%) compared with the comparison group (3.1%). The uncertainty in the evidence was acknowledged by the panel when making their judgement on the desirable (and undesirable) effects.

The BPaL regimen was associated with a high rate of adverse events, considered to be related to the study drugs. This included the death of 1 (0.9%) participant; other serious adverse events (including hospitalizations and life-threatening events) in 27 (25%) participants and at least one Grade 3–4 adverse event in 53 (49%) participants. This led to discontinuation of all three drugs for 1 patient, and discontinuation of linezolid (initial dose 1200 mg/day) for another 35 (32%) patients. Only 18 (17%) patients completed a full course of linezolid at 1200 mg/day.

The GDG noted that it is difficult to compare these adverse event rates with other studies because of major and important differences in adverse event ascertainment, assessment, and reporting. However, in the IPD studies (where 90% of patients received a linezolid dose of ≤600 mg/day), the pooled rate of permanent discontinuation of linezolid was 17.9%, and in the EndTB trial (where all patients received ≤600 mg/day of linezolid), the rate of linezolid discontinuation was 13.1%. In both of these studies, > 80% of patients received a starting dose of linezolid of 600 mg/day. In the EndTB study, preliminary analyses suggested that 9 of 1094 participants (0.8%) died of a possibly or probably drug-related adverse event, including 2 participants with sudden cardiac death

Another undesirable effect that the GDG considered was the inconsistency of evidence on the reversibility of peripheral neuropathy; the evidence suggested either complete or incomplete reversibility of peripheral neuropathy. Both patients and clinicians who were panel members described the potentially debilitating effects of irreversible peripheral neuropathy, which were of concern. GDG members also considered the fact that longer regimens for MDR/RR-TB carry a substantially higher pill burden, which may be viewed as undesirable for many patients.

Risk of bias with regard to the comparison was mentioned by panel members (monitoring of adverse effects was more frequent in the Nix-TB study than in the comparison group, which includes programmatic data). This was not necessarily a problem with the IPD cohorts, but posed a problem with the lack of a control group in the study that tested the intervention.

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT

- Very low
- Low
- Moderate
- High
- No included studies

RESEARCH EVIDENCE

The primary source of evidence for this PICO question is the Nix- TB study, which was composed of 109 patients recruited in a one-arm, phase III, open-label study that assessed the safety, efficacy, tolerability, and pharmacokinetic properties of a 6-month treatment regimen composed of bedaquiline, pretomanid and linezolid (BPaL) in South Africa. The evidence was generated, in the context of thorough monitoring and follow-up, at baseline, throughout treatment, and for 24 months after treatment completion. There were 109 patients in the intention-to-treat population and 108 in the modified intention-to-treat population. These data were compared with the data from the IPD because the study was not a randomized, controlled trial. Overall, the certainty of the evidence was classified as “very low”. The chair of the GDG panel noted that confidence intervals (CIs) around the estimates of effect have limited application in the context of very low evidence.

ADDITIONAL CONSIDERATIONS

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT

- Important uncertainty or variability
- Possibly important uncertainty or variability
- Probably no important uncertainty or variability
- No important uncertainty or variability

RESEARCH EVIDENCE

No research evidence was identified.

ADDITIONAL CONSIDERATIONS

Although no research evidence was identified, the panel felt that there was possibly important uncertainty or variability in how much people would value the main outcomes. Fertility was raised as an outcome for which there is less information. The panel thought that this would increase the complexity of the judgement about how much people would value the outcomes. The GDG determined that infertility is a serious issue because it affects not only patients but also their families. The panel noted that there are other safety outcomes (e.g. other adverse events, including peripheral neuropathy) that may vary and that people may value differently.

Indirect evidence was considered by the panel in the form of a separate qualitative study conducted among 16 patients with drug-resistant TB who were from high TB burden countries (which informed the judgements on PICO 1). The aim of the study was to determine the most acceptable treatment regimen for drug-resistant TB. On the basis of the results of this study, the preferred regimen was short and injection-free with few to no physical or mental health side-effects and with a low pill burden. Ranked preferences for treatment of drug-resistant TB included (1) adverse events, (2) duration, (3) injection (free) and (4) pill burden.

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT

- Favors the comparison
- Probably favors the comparison
- Does not favor either the intervention or the comparison
- Probably favors the intervention
- Favors the intervention
- Varies
- Don't know

RESEARCH EVIDENCE

The panel noted the moderate desirable effects and the moderate undesirable effects (and the low certainty of the evidence overall), and took this into account when making their judgement about the balance of effects, which were felt to not favour either the intervention or the comparison.

ADDITIONAL CONSIDERATIONS

The panel considered at length the desirable and undesirable effects and the balance of these effects, noting the very low certainty of the evidence and acknowledging the efforts to match patients in the intervention and comparator groups (through exact and propensity score-based matching). The GDG noted that randomized, controlled trials are needed in the future, which may allow for a more closely aligned comparison group with less potential for residual confounding. Through a voting process, the panel concluded that the balance of effects does not favour either the intervention or the comparison. Fifteen panel members voted that the balance of effects does not favour either the intervention or the comparison, 5 voted that the balance of effects probably does favour the comparison and 4 voted that they did not know. One member abstained, and 5 reported conflicts of interest.

Resources required

How large are the resource requirements (costs)?

JUDGEMENT

- Large costs
- Moderate costs
- Negligible costs and savings
- Moderate savings
 - Large savings
- Varies
- Don't know

RESEARCH EVIDENCE

No research evidence was identified.

ADDITIONAL CONSIDERATIONS

The GDG considered evidence from a cost-effectiveness analysis study which was conducted by staff from the London School of Hygiene & Tropical Medicine on behalf of the TB Alliance. The GDG noted that the analysis was not done for this –evidence to decision framework – that is, undesirable effects were not considered according to the GDG's judgements. This made the cost-effectiveness analyses informative but not directly based on the evidence that the GDG was assessing.

The analyses were based on Georgia, the Philippines, and South Africa. The aims of the research were to estimate the cost-effectiveness of a new regimen containing bedaquiline, pretomanid, and linezolid (BPaL) compared with the standard of care at a given price, and to estimate the maximum drug price at which the BPaL regimen could be considered cost-effective or cost-neutral in each setting. The perspective taken was a health service one, and the study assumed BPaL to be effective. When assessing the potential cost-effectiveness of BPaL for the treatment of XDR-TB, the GDG observed that in all three settings this regimen has the potential to be cost-saving at a given drug price of US\$ 364 per treatment course for pretomanid. The study found that cost-savings are a function of the cost of care and the magnitude of XDR-TB burden, and are about US\$ 4490 – not including antiretroviral therapy (ART) costs – in South Africa; US\$ 4060 in Georgia and US\$ 3860 in the Philippines. In high HIV-TB prevalence settings such as South Africa, related future costs such as those from the HIV programme (ART costs) reduce the magnitude of expected cost savings to US\$ 1400 per patient. Overall, when BPaL is introduced to a larger population (including those with MDR-TB treatment failure and those with treatment intolerance), the GDG observed an increase in the incremental benefits, both in terms of deaths and disability adjusted life-years averted and incremental costs.

Food costs were not included in the cost-effectiveness analysis and would need to be considered when BPaL is implemented. During the Nix-TB study, all study medications were administered with food (because of the administration of bedaquiline, which will also now feature as a core medicine in longer treatment regimens for MDR/RR-TB). The cost of the BPaL regimen is US\$ 1040 according to the Global Drug Facility (GDF), based on GDF-weighted average tablet price.

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT

- Very low
- Low
- Moderate
- High
- No included studies

RESEARCH EVIDENCE

No research evidence was identified.

ADDITIONAL CONSIDERATIONS

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT

- Favors the comparison
- Probably favors the comparison
- Does not favor either the intervention or the comparison
- Probably favors the intervention
- Favors the intervention
- Varies
- No included studies

RESEARCH EVIDENCE

No research evidence was identified.

ADDITIONAL CONSIDERATIONS

The GDG considered evidence from a cost-effectiveness analysis study that was conducted by staff from the London School of Hygiene & Tropical Medicine on behalf of the TB Alliance. The GDG noted that the cost-effectiveness analysis was not done for this evidence to decision framework – that is, undesirable effects were not considered according to the GDG's judgements. This made the cost-effectiveness analyses informative but not directly based on the evidence that the GDG was assessing.

The analyses were based on Georgia, the Philippines, and South Africa. The aims of the research were to estimate the cost-effectiveness of a new regimen containing bedaquiline, pretomanid and linezolid (BPaL) compared with the standard of care at a given price, and to estimate the maximum drug price at which the BPaL regimen could be considered cost-effective or cost-neutral in each setting. The perspective taken was a health service one, and the study assumed BPaL to be effective. When assessing the potential cost-effectiveness of BPaL for the treatment of XDR-TB, the GDG observed that in all three settings, this regimen has the potential to be cost saving at a given drug price of US\$ 364 per treatment course for pretomanid. The study found that cost savings are a function of the cost of care and the magnitude of XDR-TB burden, and are about US\$ 4490 – not including antiretroviral therapy (ART) costs – in South Africa; US\$ 4060 in Georgia and US\$ 3860 in the Philippines. In high HIV-TB prevalence settings, such as South Africa, related future costs such as those from the HIV programme (ART costs) reduce the magnitude of expected cost savings to US\$ 1400 per patient. Overall, when BPaL is introduced to a larger population (including patients with failure of MDR-TB treatment and those who cannot tolerate treatment), the GDG observed an increase in the incremental benefits, both in terms of deaths and disability adjusted life years averted and incremental costs.

Food costs were not included in the cost-effectiveness analysis and would need to be considered when BPaL is implemented. During the Nix-TB study, all study medications were administered with food (because of the administration of bedaquiline, which will also now feature as a core medicine in longer treatment regimens for MDR/RR-TB).

Equity

What would be the impact on health equity?

JUDGEMENT

- Reduced
- Probably reduced
- Probably no impact
- Probably increased
- Increased
- Varies
- Don't know

RESEARCH EVIDENCE

No research evidence was identified.

ADDITIONAL CONSIDERATIONS

Although no research evidence was identified, the GDG panel felt that the impact on health equity would be a probable increase, given the option of a shorter regimen that could be available globally (i.e. available to all patients). The GDF has identified a price for pretomanid and stated that it will make the BPaL regimen available to national TB programmes, dependent upon the recommendation from the panel. The GDF representative noted that two bottles of bedaquiline will need to be ordered for anyone who is receiving the BPaL regimen. Children and pregnant women were ineligible for inclusion in the Nix-TB study and therefore will not be an eligible population for BPaL if it is recommended, which may be an equity issue.

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT

- No
- Probably no
- Probably yes
- Yes
- Varies
- Don't know

RESEARCH EVIDENCE

The GDG panel thought that the judgement was *probably yes* because the concerns regarding reproductive toxicities were not discussed as part of the acceptability study conducted by KNCV (because this was not known to the study investigators at the time) and the comparator used in this study was not the same as that for the evidence that was assessed.

ADDITIONAL CONSIDERATIONS

The GDG considered evidence from an acceptability and feasibility study conducted by KNCV on behalf of the TB Alliance. The objectives of the study were to assess the acceptability and likelihood of implementation of the BPaL regimen as anticipated by key stakeholders and based on a number of criteria (including the perceived benefits and challenges of implementation of BPaL and longer individualized treatment regimens, and other practical requirements of implementation). The study was a mixed-methods, multicountry, cross-sectional investigation conducted in –2018–2019 among stakeholders in Indonesia, Kyrgystan and Nigeria. Views were offered by a total of 188 participants, including caregivers, programmatic stakeholders (including national and international programmatic stakeholders and patient-advocacy groups) and public and private laboratory stakeholders. On the basis of seven assessment categories (ranging from patient friendliness to treatment safety monitoring), the acceptability of BPaL when compared with a longer treatment regimen for MDR-TB was higher for every category. Acceptability was higher for BPaL than for the longer MDR-TB regimens in six of the seven categories assessed, with the exception of treatment safety monitoring, where the difference was negligible. The main drivers of acceptability of BPaL were the shorter duration, absence of injectables, lower pill burden, anticipated higher treatment success, lower costs for the burden for patients, anticipated higher treatment success, lower costs for the health system, minimal additional requirements for diagnostic processes, and a lower anticipated per-patient burden to the TB laboratory for bacteriological treatment monitoring. Indirect evidence was considered by the panel in the form of a separate qualitative study conducted among 16 patients with drug-resistant TB who were from high burden countries (which informed the judgements on PICO 1). The aim of the study was to determine the most acceptable treatment regimen for drug-resistant TB. On the basis of the results of this study, the preferred regimen was short and injection-free with few to no physical or mental health side-effects and a low pill burden. Ranked preferences for drug resistant TB treatment were as follows: (1) adverse events, (2) duration, (3) injection (free) and (4) pill burden.

Feasibility

Is the intervention feasible to implement?

JUDGEMENT

- No
- Probably no
- Probably yes
- Yes
- Varies
- Don't know

RESEARCH EVIDENCE

The GDG considered evidence from an acceptability and feasibility study conducted by KNCV on behalf of the TB Alliance. The objectives of the study were to assess the acceptability and likelihood of implementation of the BPaL regimen as anticipated by key stakeholders and on the basis of a number of criteria, including the perceived benefits and challenges of implementation of BPaL and longer individualized treatment regimens, and other practical requirements of implementation. The study was a mixed-methods, multicountry, cross-sectional investigation conducted in 2018–2019 among stakeholders in Indonesia, Kyrgyzstan and Nigeria. A total of 188 participants offered their views, including caregivers, programmatic stakeholders (including national and international programmatic stakeholders and patient-advocacy groups), and public and private laboratory stakeholders. On the basis of seven assessment categories (ranging from friendliness for patients to treatment safety monitoring), the acceptability of BPaL when compared with a longer treatment regimen for MDR-TB was higher for every category. Acceptability was higher for BPaL than for the longer MDR-TB regimens in six of the seven categories assessed, with the exception of treatment safety monitoring, where the difference was negligible. In line with the overall high acceptability of the BPaL regimen, the overall likelihood of implementing the BPaL regimen as a standard of care for the treatment of patients with XDR-TB and MDR-TB treatment failure/intolerance scored at 88; only 1% of the 166 participants scored that implementation as “unlikely” and 11% had a neutral opinion. The likelihood of implementation was similar (84%) to that for the BPaL regimen as a standard of care for patients with MDR-TB with fluoroquinolone resistance, regardless of additional resistance to second-line injectables. This indicated that the regimen may be feasible to implement from the perspective of those interviewed.

ADDITIONAL CONSIDERATIONS

Summary of judgements

PROBLEM	JUDGEMENT					Don't know
	No	Probably no	Probably yes	Yes	Varies	
DESIRABLE EFFECTS	Trivial	Small	Moderate	Large	Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	Trivial	Varies	Don't know
CERTAINTY OF EVIDENCE VALUES	Very low Important uncertainty or variability	Low Possibly important uncertainty or variability	Moderate Probably no important uncertainty or variability	High No important uncertainty or variability	Varies	No included studies
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High	Varies	No included studies
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Varies	No included studies
EQUITY	Reduced	Probably reduced	Probably no impact	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	Probably yes	Yes	Varies	Don't know
FEASIBILITY	No	Probably no	Probably yes	Yes	Varies	Don't know

Type of recommendation

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
<input type="radio"/>	<input type="radio"/>	<input checked="" type="radio"/>	<input type="radio"/>	<input type="radio"/>

Conclusions

Recommendation

A treatment regimen lasting 6–9 months composed of bedaquiline, pretomanid and linezolid (BPAL) may be used under operational research conditions in MDR-TB patients with TB that is resistant to fluoroquinolones who have had no previous exposure to bedaquiline and linezolid for more than two weeks (conditional recommendation, very low certainty in the estimates of effect).

Justification

Treatment of patients with forms of extensively drug-resistant TB (XDR-TB) presents multiple challenges to clinicians and national TB programmes, both because of the limited range of medicines available and the life-threatening nature of the disease. Patients with MDR/RR-TB and additional fluoroquinolone resistance have typically experienced poor treatment outcomes since the description of XDR-TB was first used in 2006.⁹ The data reported by member states to WHO, for the cohort of patients with XDR-TB who started treatment in 2016 (and for whom treatment outcomes were available in 2018) show that only 39% completed treatment successfully, whereas 26% died, 18% experienced treatment failure, and an additional 18% were lost to follow-up or were not evaluated.¹⁰ The pressing need for more effective treatment regimens for patients with extensive drug resistance, including fluoroquinolone resistance and more extensive drug resistance profiles, has motivated a number of studies and initiatives to test more effective and novel treatment regimens, including newer and repurposed medicines.

One such study is the Nix-TB study, conducted by the TB Alliance. The Nix-TB study was a one-arm, phase III, open-label prospective cohort study that assessed the safety, efficacy, tolerability, and pharmacokinetic properties of a 6-month treatment regimen composed of bedaquiline, pretomanid and linezolid (BPAL), extendable to 9 months for those who missed doses or for patients who remained culture positive or reverted from culture negative to culture positive between months 4 and 6 of treatment. The study was conducted between 2014 and 2019 at three study sites, all in South Africa, with the first patient enrolled in April 2015. Eligible patients were aged 14 years or older, weighed ≥ 35 kg, had a documented HIV result, and had bacteriologically confirmed sputum culture positive XDR-TB or bacteriologically confirmed MDR/RR-TB but could not tolerate treatment or had disease that did not respond to previous MDR/RR-TB treatment. A number of other inclusion criteria were applied.

Patients were followed up for a period of up to 24 months after completion of treatment. The primary outcome measure was the incidence of bacteriological failure or relapse or clinical failure through follow-up until 6 months after the end of treatment.¹¹ Secondary outcome measures were as follows:

1. Incidence of bacteriological failure or relapse or clinical failure through follow up until 24 months after the end of treatment (as a confirmatory analysis).
2. Time to sputum culture conversion to negative status through the treatment period.
3. Proportion of subjects with sputum culture conversion to negative status at 4, 6, 8, 12, 16 and 26 or 39 weeks.
4. Linezolid dosing (actual) and efficacy.
5. Change from baseline in TB symptoms.
6. Change from baseline in patient reported health status.
7. Change from baseline in weight (TB Alliance, Nix-TB study protocol, available at: <https://clinicaltrials.gov/ct2/show/NCT02333799>).

The Nix-TB study regimen comprised pretomanid administered at 200 mg/day, bedaquiline administered at 400 mg/day for the first 2 weeks of treatment (days 1–14) and 200 mg three times a week thereafter, and linezolid commencing at 1200 mg/day (additional information on linezolid dosing is included under “Implementation considerations”). Close microbiologic, clinical and adverse event monitoring were features of the Nix-TB study.

⁹ Emergence of XDR-TB. Geneva, Switzerland World Health Organization 2006 (<https://www.who.int/mediacentre/news/notes/2006/np23/en>, accessed 28 February 2020).

¹⁰ Global tuberculosis report 2019 (WHO/CDS/TB/2019.15). Geneva, Switzerland World Health Organization; 2019 (https://www.who.int/tb/publications/global_report/en/, accessed 29 May 2020).

¹¹ 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) [website]. Maryland, United States of America U.S. National Library of Medicine; 2017 (<https://clinicaltrials.gov/ct2/show/NCT03086486>, accessed 20 March 2020).

The evidence to inform this PICO question was derived from the Nix-TB study and included information on 108 patients. The total study population was 109 patients; however, 1 patient withdrew informed consent to participate in the study and was included in safety analyses but not in analyses for effectiveness. These data were compared with a subset of data from the IPD, which overall includes 13 273 individual patient records from 55 different studies or centres in 38 countries. For the primary analyses, the comparator group included patients from the IPD receiving longer treatment regimens (with a mean duration of treatment ranging between 21.0–25.5 months), who received both bedaquiline and linezolid as part of the regimen (no patients received pretomanid in the IPD). This comparison group included 456 patients who were treated in Belarus (Republic of), France, India, and Russia, and in countries in Asia. The intervention and comparison groups were matched exactly for XDR-TB status, MDR-TB status, fluoroquinolone resistance, and HIV status, with propensity score matching for the variables of age, sex, baseline culture result, extent of disease (determined by baseline AFB smear or chest X-ray findings of cavitation or by bilateral disease if AFB smear result was missing) and country income level (World Bank Atlas method). Treatment outcomes used in these analyses comprised the investigator-defined outcomes for the intervention group (for the Nix-TB study) and treatment outcomes largely defined according to WHO definitions¹² for the comparator group (for the patients included in the IPD). To allow an equal opportunity for treatment outcomes to occur from the start of treatment when comparing the two groups, all outcomes were included from the start of treatment to 24 months after the start of treatment. This meant that, in the intervention group, these outcomes occurred after completion of treatment, and for the comparator group, the outcomes were end-of-treatment outcomes (because patients in the IPD received a longer regimen and were not monitored after treatment completion). Three other comparator groups from the IPD included patients receiving longer treatment regimens which included bedaquiline, or a regimen which included linezolid, or a regimen with neither bedaquiline or linezolid included. The initial intention of the GDG was to assess the intervention regimen against all three comparison groups; however, during their deliberations the panel agreed that the judgements should be based on the comparison group who received bedaquiline and linezolid as part of their regimen, because these patients most closely resembled patients who would receive currently recommended longer regimens composed of medicines from Groups A–C. However, a direct comparison of BPaL with all-oral longer regimens constructed according to the most recent WHO recommendations issued in May 2019 was not possible, because these regimens might have been in use only since mid-2019, and treatment outcomes for these patients are not yet available.

Additional data reviewed by the GDG relevant to this PICO question were a cost-effectiveness analysis, a study on the acceptability and likelihood of implementation of the BPaL regimen, modelled pharmacokinetic data based on the development of a pharmacokinetic–toxicodynamic model, and a summary review of preclinical and early clinical data on pretomanid. The cost-effectiveness analysis, acceptability study, and modelled pharmacokinetic studies were conducted as part of the Nix-TB study and were sponsored by the TB Alliance.

The GDG considered the desirable effect of treatment success, which was higher in the intervention group when compared with the comparator, for all four treatment outcomes that were assessed. Overall, when comparing treatment success versus failure/recurrence, the treatment success rate in the Nix-TB study was 97.0% compared with 91.7% in the comparator group (resulting in 6 more outcomes of treatment success per 100 patients). For the comparison of treatment success versus death, treatment success was 93.2% in the Nix-TB study compared with 91.9% in the comparator group (resulting in 1 more outcome of treatment success per 100 patients). For the comparisons of treatment success versus failure/recurrence/death and treatment success versus all unfavourable outcomes combined (i.e. failure/relapse/death and loss to follow-up), the proportions of patients with treatment success in the intervention and comparator groups were 90.5% versus 84.8% (6 more outcomes of treatment success per 100 patients) and 88.9% versus 82.2% (2 more outcomes of treatment success per 100 patients), respectively. On the basis of these figures, the primary analysis yielded adjusted odds ratios (aORs) of 3.3 for treatment success (versus the combined outcome of failure and recurrence; 95% CI: 0.8–13.7), 1.0 for success versus death (95% CI: 0.1–8.2), 1.8 for success versus failure/relapse/death (95% CI: 0.7–4.4), and 1.2 for success versus all unfavourable outcomes (95% CI: 0.5–3.1), with a mean duration of follow-up of 24 months (range, 21–25.5 months), when BPaL was compared with longer regimens containing bedaquiline and linezolid. The GDG considered rates of loss to follow-up to be a desirable effect; the proportion of patients who were lost to follow-up was lower in the intervention (BPaL) group (1.8%) than in the comparator group (3.1%); however, this difference was not considered by the panel to be large. The panel also considered a shortened duration of treatment and less drug exposure to be desirable effects of the intervention, and noted that these were both components of the overall burden of a given MDR/RR-TB treatment regimen, which may not be wholly reflected in rates of loss to follow-up alone. Specified subgroup analyses were unable to be undertaken because of limitations in the sample size.

¹² Laserson KF, Thorpe LE, Leimane V, Weyer K, Mitnick CD, Rieklstina V et al. Speaking the same language: treatment outcome definitions for multidrug-resistant tuberculosis. *Int J Tuberc Lung Dis.* 2005;9(6):640–5. and Definitions and reporting framework for tuberculosis – 2013 revision (updated December 2014) [WHO/HTM/TB/2013.2]. Geneva, Switzerland: World Health Organization; 2013 (https://apps.who.int/iris/bitstream/handle/10665/79199/9789241505345_eng.pdf?sequence=1, accessed 20 March 2020).

The BPaL regimen was also associated with a high rate of adverse events, considered to be related to the study drugs, which was a concern for GDG members. Of the 109 patients in the Nix-TB study, 28 (25.7%) experienced at least one serious adverse event. This included 1 death (0.9%) related to acute haemorrhagic pancreatitis, 27 (25%) other serious adverse events including hospitalizations and life-threatening events, and 2 (1.8%) adverse events that resulted in persistent or significant disability or incapacity. Fifty-three participants (49%) experienced at least one Grade 3–4 adverse event considered to be related to the study drugs, comprising 25 with peripheral neuropathy (resolved in 11), 16 with increased hepatic transaminases (resolved in 13), 9 with haematological adverse events (resolved in all), 8 who had increased pancreatic enzymes (resolved in 7), and 2 with optic neuritis (resolved in both). This led to drug discontinuation of all three drugs for 1 participant, and linezolid (initial dose: 1200 mg/day) was discontinued in another 35 participants (32%). Only 18 participants (17%) completed a full course of linezolid at 1200 mg/day. The GDG noted that it is difficult to compare these adverse event rates with other studies because of major and important differences in ascertainment, assessment, and reporting of adverse events. However, in the IPD studies (where 90% of participants received a linezolid dose of \leq 600 mg/day), the pooled rate of permanent discontinuation of linezolid was 17.9%, and in the EndTB observational study (where all patients received \leq 600 mg/day of linezolid), the rate of linezolid discontinuation was 13.1%. In both of these studies, >80% of participants received a starting dose of linezolid of 600 mg/day. In preliminary analyses of the EndTB observational study, 9 of 1094 participants (0.8%) died of a possibly or probably drug-related adverse event, including 2 participants with sudden cardiac death; these patients were receiving bedaquiline, clofazimine, capreomycin, and *p*-aminosalicylic acid (PAS) and had hypokalaemia.

Information presented from the independent review of the preclinical data and early-phase clinical data highlighted that pretomanid possesses activity against replicating and nonreplicating bacilli that is both concentration and dose dependent. A comprehensive description of the safety signals was reported, many of these signals were observed at exposures that are higher than would be used in humans; however, safety signals of note include liver toxicities (hypertrophy of hepatocytes, transaminase elevation, and increased liver weight, observed at higher doses in rodents and lower doses in monkeys) and reproductive toxicities in males observed in animal (murine and simian) models, which appear to be both time and dose dependent. These observations in monkeys might have been attributed to the general decline of health in these animals; however, the same signals were observed in rodent models with some evidence that these effects might be irreversible. In mouse models, these effects were observed at exposures that would be used in humans. Reproductive toxicities were also observed in females.

Additional information on adverse events presented to the GDG included the results of a pharmacokinetic–toxicodynamic model (Savic R, unpublished data, University of California San Francisco, November 2019). On the basis of these data, it was concluded that the pharmacokinetics related to linezolid are nonlinear in patients with XDR-TB and that individual linezolid concentration times are the best predictor of toxicity. Higher toxicity rates were observed at higher total daily doses, with comparable toxicity rates for BID and QD dosing schedules. The results of the modelled data highlighted that anaemia can be managed by closely monitoring changes in haemoglobin over the first 4 weeks of treatment (in particular, changes in haemoglobin that represent a >10% decrease from baseline should trigger a reduction in the dose of linezolid; haemoglobin levels recover well after dose reductions). Thrombocytopenia was potentially not a major concern. The study investigators recommended that peripheral neuropathy be closely monitored, and noted that the modelled data showed that, when it did occur, it was reversible for most patients, within 3 months.

Subgroup considerations

Children. Children (aged 0–13 years) were excluded from the Nix-TB study; therefore, no analysis specific to this subgroup of patients could be performed. It is recommended that children with pulmonary MDR/RR-TB with additional resistance to fluoroquinolones be given the same consideration for longer treatment regimens as adults, to include components with a safety profile that is better established. Bedaquiline is currently recommended only for children aged 6 years or older. It is acknowledged that additional data on the use of BPaL in children, when eligible, would be useful; this may be a feature of carefully planned and monitored future research.

PLHIV: PLHIV represented half of those enrolled in the Nix-TB study; however, it was impossible to perform any adjusted stratified analyses for PLHIV because of the sample size. PLHIV were eligible to enrol in the Nix-TB study if they had a CD4 count of >50 cells/ μ L and if they were using permitted antiretroviral medications.¹³ It is important to note drug–drug interactions when administering TB and HIV medications in combination, including the documented interactions between bedaquiline and efavirenz.¹⁴ Efavirenz also reduces pretomanid exposures significantly; therefore, an alternative antiretroviral agent should be considered if pretomanid or the BPaL regimen is to be used.¹⁵ Regimens including zidovudine should be used with special caution because zidovudine and linezolid may both cause peripheral nerve toxicity and are known to have myelosuppression cross-toxicity.

Pregnant and lactating women were excluded from the Nix-TB study; therefore, no analysis specific to this subgroup of patients could be performed. For such patients, it is recommended that a longer regimen be individualized to include components with a safety profile that is better established. When this is the case, the outcomes of treatment and pregnancy (including infant characteristics), and postpartum surveillance for congenital anomalies, should be documented to help inform future recommendations for MDR-TB treatment during pregnancy. The use of bedaquiline in pregnancy has been shown to be associated with infants born with a lower mean birth weight, when compared with infants whose mothers who did not take bedaquiline; however, this did not appear to be a clinically significant finding when infants were followed up over time. Breastfeeding is not recommended for women taking BPaL.¹⁶

Extrapulmonary TB: Participants with extrapulmonary TB were excluded from the Nix-TB study; therefore, no analysis specific to this subgroup of patients could be performed. The WHO recommendations for longer MDR-TB regimens apply to patients with extrapulmonary disease, including those with TB meningitis. There are few data on the central nervous system penetration of bedaquiline or pretomanid.

Patients with very limited treatment options: In some instances, patients will have extensive drug resistance profiles that may make it difficult (or impossible) to construct a regimen based on existing WHO recommendations. In such situations, the patient's life may be endangered. Therefore, for individual patients for whom the design of an effective regimen based on existing recommendations is not possible,¹⁷ the BPaL regimen may be considered a last resort under prevailing ethical standards. For such patients, the use of BPaL should be accompanied by individual patient informed consent, adequate counselling on the potential benefits and harms, and active monitoring and management of adverse events. Patients should also be advised that reproductive toxicities have been observed in animal studies, and that the potential effects on human male fertility have not been adequately evaluated at this time.

¹³ The permitted antiretroviral treatments were as follows: (1) nevirapine in combination with any NRTIs; (2) lopinavir/ritonavir in combination with any NRTIs; (3) tenofovir/lamivudine/abacavir (if normal renal function); (4) triple NRTI therapy consisting of zidovudine, lamivudine, and abacavir (noting the increased risk of peripheral nerve toxicity with zidovudine and linezolid); and (5) raltegravir in combination with NRTIs.

¹⁴ HIV drug interactions [website]. Liverpool, United Kingdom University of Liverpool 2020 (<https://www.hiv-druginteractions.org/checker>, accessed 11 March 2020).

¹⁵ Drug approval package: Pretomanid [website]. Maryland, United States of America: U.S. Food and Drug Administration; 2019 (https://www.accessdata.fda.gov/drugsatfda_docs/nda/2019/212862Orig1s000TOC.cfm, accessed 28 February 2020).

¹⁶ Drug approval package: Pretomanid [website]. Maryland, United States of America: U.S. Food and Drug Administration; 2019 (https://www.accessdata.fda.gov/drugsatfda_docs/nda/2019/212862Orig1s000TOC.cfm, accessed 28 February 2020).

¹⁷ Usually this group of patients would include those with an extensive drug resistance profile who have very limited treatment options as part of a longer treatment regimen.

Implementation considerations

Given the paucity of evidence on the use of BPaL, and the concerns mentioned above, members of the GDG suggested that its use should be conditional upon implementation in the context of operational research only. The GDG emphasized that, despite the promising treatment success rates observed in the Nix-TB study, the regimen may not be considered for programmatic use worldwide until additional evidence on efficacy and safety has been generated. The GDG members emphasized the need for this research to take the form of randomized, controlled trials as well as observational studies. Given the conditionality of this recommendation in the context of additional research, certain standards and principles are prerequisites for the implementation of BPaL. Further, the GDG emphasized that in any operational research study involving BPaL, the principles of good clinical practice should apply. Overall, to reproduce the treatment success rates observed in the Nix-TB study, all efforts need to be made to carefully select eligible patients and then, once they are enrolled, to provide effective patient support to enable adherence to treatment, as well as close monitoring for adverse events, response to treatment, and emerging drug resistance. All efforts should be made to do the following:

- Ensure proper patient inclusion (use is not advised in pregnant and lactating women and in children, noting the other inclusion and exclusion criteria of the Nix-TB study). Although DST is an important component of patient selection for the BPaL regimen (described below), another key implementation consideration is prior TB treatment history. Patients are eligible for the BPaL regimen only if they have not received bedaquiline or linezolid for 2 weeks or more previously, and this was an eligibility criterion of the Nix-TB study. Given that the current WHO recommendation for longer treatment regimens for MDR/RR-TB includes bedaquiline and linezolid as priority medicines in Group A, some patients who have previously started treatment with a longer MDR/RR-TB regimen may in fact be ineligible for BPaL should they later develop fluoroquinolone resistance. This reaffirms previous statements by WHO on the need to carefully select eligible patients for longer or shorter MDR/RR-TB treatment regimens, and then, once patients are receiving a regimen, to ensure patient support and close monitoring and follow-up, including monitoring for treatment failure and relapse, and emerging drug resistance, with DST performed when indicated. If resistance is suspected during treatment and DST is not available, the strains should be conserved and referred to a WHO supranational TB reference laboratory for further testing. Each operational research protocol on the use of BPaL in a given setting will need to include detailed inclusion and exclusion criteria.
- Obtain signed patient informed consent after detailed explanations on the novel nature of the regimen and pretomanid, including the risks and benefits of the regimen. The GDG members thought that although individual patient informed consent is necessary, it should not be overly burdensome for patients; therefore, consent forms should be adapted, contextualized, streamlined and provided in the local language(s) so that they are easy for patients to understand. Nevertheless, the GDG also noted that patients should be fully informed about the regimen, given that it also includes a new compound, pretomanid. As part of the informed consent process, patients should be offered sufficient information on potential adverse events, including low blood cell counts (e.g. anaemia, thrombocytopenia, neutropenia), liver toxicities, and peripheral and optic neuropathy. Patients should also be advised that reproductive toxicities have been observed in animal studies and that the potential effects on human male fertility have not been adequately evaluated at this time. Patients should also be informed that pretomanid is excreted in breast milk, and its safety in infants and children has not been adequately evaluated.¹⁸ A medication guide is available as part of the pretomanid product label that may be used when informing patients about the BPaL regimen as part of a research study.
- Treatment must be administered under closely monitored conditions, to enable optimal drug effectiveness and safety, and to monitor for the acquisition of emerging drug resistance, should it arise. Given that the regimen is shorter, that it includes a new compound (pretomanid), and that its implementation is in the context of research, it may be especially important that clinical progress is monitored after completion of treatment, to ensure relapse free cure. Other design features of the Nix-TB study have implications for its implementation under operational research conditions. In the Nix-TB study, all medications were administered with food throughout, and study medications were supervised according to local site practices, as a form of patient support. Preventing treatment interruption is important for increasing the likelihood of treatment success. Measures to support patient adherence, either by facilitating patient visits to health care facilities or home visits by health care staff, or by using digital technologies for daily communication, may be important for retention of patients in treatment, even though the regimen is comparatively short.¹⁹ WHO recommendations on the care and support of patients with MDR/RR-TB are provided in the WHO consolidated guidelines on drug-resistant TB treatment.²⁰
- Active pharmacovigilance and proper management of adverse drug reactions and prevention of complications from drug–drug interactions. The national TB programme should actively monitor drug safety to ensure proper patient care, to report any adverse drug reactions to the responsible drug safety authority in the country, and to inform national and global policy.

¹⁸ Drug approval package: Pretomanid [website]. Maryland, United States of America: U.S. Food and Drug Administration; 2019 (https://www.accessdata.fda.gov/drugsatfda_docs/nda/2019/212862Orig1s000TOC.cfm, accessed 28 February 2020).

¹⁹ Guidelines for treatment of drug-susceptible tuberculosis and patient care, 2017 update (WHO/HTM/TB/2017.05). Geneva, Switzerland: World Health Organization; 2017 (<https://apps.who.int/iris/bitstream/handle/10665/255052/9789241550000-eng.pdf?sequence=1>, accessed 20 March 2020).

²⁰ WHO consolidated guidelines on drug resistant tuberculosis treatment. Geneva, Switzerland: World Health Organization; 2019 (<https://apps.who.int/iris/bitstream/handle/10665/311389/9789241550529-eng.pdf?ua=1>, accessed 20 March 2020).

The implementation of the BPAL regimen in the context of operational research implies that:

- a study protocol has been developed by appropriately skilled and experienced researchers;
- this research protocol is submitted to a national ethics board or other ethical approval committees;
- there are pre-specified inclusion and exclusion criteria in place (noting the criteria used for the Nix-TB study);²¹
- there is an appropriate schedule of safety monitoring and reporting in place, including active drug safety monitoring (aDSM) – usually overseen by a data safety monitoring board or similar independent research governance committee);
- there is a predefined schedule of clinical and microbiological monitoring in place, preferably including follow-up after completion of treatment;
- individual patient informed consent is obtained;
- patient support is provided; and
- standardized reporting and recording is used, including for adverse events.

Review of treatment and management protocols by an independent group of experts in clinical management and public health, such as the national MDR-TB advisory group, is recommended.

Drug-susceptibility testing is an important implementation consideration that will need further enhancement in many countries, given the increasing potential use of bedaquiline and linezolid (even for longer regimens for MDR/RR-TB) and the inclusion of new medicines – such as pretomanid – in MDR-TB treatment regimens. Baseline DST will confirm eligibility for the BPAL regimen; therefore, the establishment and strengthening of drug-susceptibility testing services will be a vital implementation consideration. In patients with bacteriologically confirmed MDR/RR-TB;²² the MTBDRs assay may be used as the initial test, in preference to culture and phenotypic DST, to detect resistance to fluoroquinolones (conditional recommendation; certainty of evidence for direct testing of sputum from low to moderate.²³ In settings in which laboratory capacity for DST to fluoroquinolones is not yet available, or cannot be accessed, it will be difficult to carry out operational research on BPAL. If testing for susceptibility to bedaquiline or linezolid is available, it is highly desirable that this is also carried out at baseline; however, this need not be a prerequisite for treatment initiation, nor need it be so in the absence of culture conversion during treatment. DST for pretomanid is not yet available. Currently, there is limited capacity globally to carry out DST for bedaquiline and linezolid; however, laboratory capacity should be strengthened in this area as these medicines and regimens become more widely used. National and reference laboratories will need to have the medicine powders available to enable DST to be carried out and will need data on the minimum inhibitory concentration (MIC) distribution of all *Mycobacterium tuberculosis* lineages that are circulating globally. If resistance to any of the component medicines in the BPAL regimen is detected, the patient should commence treatment with a longer MDR-TB regimen. WHO Supranational Reference Laboratory Network is available to support national TB reference laboratories in performing quality-assured DST. A WHO technical consultation in 2017 established critical concentrations for DST for the fluoroquinolones, bedaquiline, delamanid, clofazimine and linezolid.²⁴ Methods for testing pretomanid susceptibility are currently under development.

²¹ The protocol for the Nix-TB study is available at: <https://clinicaltrials.gov/ct2/show/NCT02333799>

²² MDR/RR-TB is usually confirmed by rapid molecular tests that detect resistance to rifampicin and *M. tuberculosis*. Current WHO recommendations state that the Xpert MTB/RIF assay should be used rather than conventional microscopy, culture, and DST as the initial diagnostic test in adults suspected of having MDR-TB or HIV-associated TB (strong recommendation; high-quality evidence). The Xpert MTB/RIF assay should be used rather than conventional microscopy, culture, and DST as the initial diagnostic test in children suspected of having MDR-TB or HIV-associated TB (strong recommendation; very low-quality evidence) – Automated real-time nucleic acid amplification technology for rapid and simultaneous detection of tuberculosis and rifampicin resistance: Xpert MTB/RIF assay for the diagnosis of pulmonary and extrapulmonary TB in adults and children (WHO/HTM/TB/2013.16). Geneva, Switzerland: World Health Organization; 2013 (https://apps.who.int/iris/bitstream/handle/10665/112472/9789241506335_eng.pdf?sequence=1, accessed 20 March 2020). A recent WHO rapid communication reinforced the high diagnostic accuracy and improved patient outcomes of rapid molecular diagnostic tests such as Xpert MTB/RIF, Xpert MTB/RIF Ultra, and TrueNat – Rapid communication: molecular assays as initial tests for the diagnosis of tuberculosis and rifampicin resistance. Geneva, Switzerland World Health Organization 2020 (<https://apps.who.int/iris/bitstream/handle/10665/330395/978924000339-eng.pdf>, accessed 20 March 2020).

²³ The use of molecular line probe assays for the detection of resistance to second-line anti-tuberculosis drugs: policy guidance [WHO/HTM/TB/2016.07]. Geneva, Switzerland: World Health Organization; 2016 (<https://apps.who.int/iris/bitstream/handle/10665/246131/9789241510561-eng.pdf?sequence=1>, accessed 20 March 2020).

²⁴ Automated real-time nucleic acid amplification technology for rapid and simultaneous detection of tuberculosis and rifampicin resistance: Xpert MTB/RIF assay for the diagnosis of pulmonary and extrapulmonary TB in adults and children (WHO/HTM/TB/2013.16). Geneva, Switzerland: World Health Organization; 2013 (https://apps.who.int/iris/bitstream/handle/10665/112472/9789241506335_eng.pdf?sequence=1, accessed 20 March 2020).

Dosing of linezolid: The linezolid dosage used in the Nix-TB study was 1200 mg/day. Initially, all study participants received 600 mg of linezolid BD because that was the approved dose used to treat bacterial infections for up to 28 days at the time the study commenced. However in May 2018, the protocol was changed to a dosing of 1200 mg OD. According to the protocol, dose reduction to 600 mg daily and further to 300 mg daily or temporary cessation of linezolid was permitted for up to 35 consecutive days, for any known linezolid adverse reactions of myelosuppression, peripheral neuropathy and optic neuropathy. If toxicity prohibited further treatment with linezolid, then patients could continue to take bedaquiline and pretomanid, provided that they had received the 1200 mg/day dose for at least the first 4 consecutive weeks, were sputum smear-negative and were responding to treatment as indicated by clinical monitoring and follow-up. Missed doses of linezolid were not made up during the Nix-TB study, and dose modifications for bedaquiline and pretomanid were not allowed. Overall, 18 patients (17.3%) in the Nix-TB study completed a full course of linezolid at the 1200-mg dose, 38 (36.5%) completed with a 600-mg dose, 16 (15.4%) completed with a 300-mg dose, and 32 (30.7%) stopped linezolid early because of an adverse event. In view of the experience of the Nix-TB study, it may be necessary to modify the dose of linezolid during treatment on the basis of adverse events, highlighting the importance of close monitoring, patient follow-up and aDSM. Additional studies – such as the ZeNix study (TB Alliance) – are underway to assess the optimal dosing and duration of linezolid for the treatment of drug-resistant TB; however, the results of these studies are not yet available for review. To date, the BPaL regimen has been studied as a standardized course of treatment. Modification of the regimen through early discontinuation or replacement of any of the component medicines may result in poor treatment outcomes. The pretomanid product label recommends that if either bedaquiline or pretomanid tablets are discontinued, the entire BPaL regimen should also be discontinued. If linezolid is permanently discontinued during the initial 4 consecutive weeks of treatment, then bedaquiline and pretomanid should also be discontinued. If linezolid is discontinued after the initial 4 weeks of consecutive treatment, clinicians should continue administering bedaquiline and pretomanid, consistent with the Nix-TB study protocol. In the Nix-TB study, it was necessary for patients to complete 6 months of the regimen (i.e. 26 weeks of prescribed doses) within 8 months, and for those who had treatment extended, it was necessary for patients to complete 9 months of treatment (i.e. 39 weeks of prescribed doses) within 12 months. Patients who remained culture positive or who reverted to being culture positive between months 4 and 6, and whose clinical condition suggested they might have ongoing TB infection, had treatment extended to a total of 9 months.

Monitoring and evaluation

Patients who receive BPaL (or any shorter regimen for the treatment of MDR/RR-TB) need to be tested at baseline and then monitored during treatment using schedules of relevant clinical and laboratory testing. According to the product label for pretomanid, baseline assessments before initiation of the BPaL regimen include assessments for symptoms and signs of liver disease (e.g. fatigue, anorexia, nausea, jaundice, dark urine, liver tenderness and hepatomegaly) and the conduct of laboratory tests (alanine aminotransferase [ALT], aspartate aminotransferase [AST], alkaline phosphatase, and bilirubin, complete blood count and serum potassium, calcium, and magnesium, which should be corrected if abnormal). Treating clinicians should also obtain an electrocardiogram before initiation of treatment. The baseline monitoring schedule of the Nix-TB study was much more comprehensive than this, and included a thorough baseline clinical assessment, followed by a schedule of weekly patient monitoring until week 20 and then monitoring every 4 to 6 weeks thereafter, partly dependent on whether the patient had treatment for 6 months in total or whether treatment was extended by another 3 months (to 9 months in total).

Given that the BPaL regimen is new and is being implemented under operational research conditions, it is also important to follow up with patients after the completion of treatment for possible relapse. In the Nix-TB study, monitoring after completion of treatment was carried out monthly for months 1 to 3, and then every 3 months thereafter. Follow-up after treatment completion was for a total of 24 months; however, at the time of data analysis, about half of the patients had been followed up for this period. The analysis of the Nix-TB study data indicated that there was treatment failure or recurrence in 3 patients (2.8% of patients overall), taking into account the period of post-treatment completion follow-up.

Detailed schedules of baseline and follow-up monitoring, including post-treatment completion, should be developed for any BPaL operational research protocol, with standardized measures for recording adverse events. The WHO framework for aDSM needs to be applied to patients receiving any type of MDR-TB regimen, to ensure appropriate action and an acceptable level of monitoring for and prompt response to adverse events – alongside monitoring for treatment failure. Additional evidence generated on adverse events will be important for building the evidence base on the safety of the BPaL regimen in varied settings. Monitoring of changes in dosing and duration of linezolid in particular (when needed) will also be important for informing the future evidence base on the wider use of the BPaL regimen and the tolerability of linezolid in this regimen.

Research priorities

- Research on the use of BPaL to compare efficacy, safety and tolerability to other all-oral regimens.
- Data from other regions and countries (beyond South Africa).
- Description of the mechanism and molecular markers of pretomanid resistance. Surveillance for the development of resistance, with adequate consideration paid to the impact of selected mutations.
- Documenting of the full adverse effect profile of pretomanid, and the frequency of relevant adverse effects, with a focus on hepatotoxicity and reproductive toxicity in humans. Reproductive toxicities of pretomanid have been signalled in animal studies but potential effects of this medicine on human fertility have not been adequately evaluated and require appropriate research.
- Exploring the relative efficacy (and added value in multidrug regimens) of pretomanid and delamanid.
- Research on optimal dose and duration of linezolid use in drug-resistant TB regimens (ZeNix study).

AFB: acid-fast bacillus; ART: antiretroviral therapy; BID: Twice a day (dosing); BPaL: bedaquiline, pretomanid and linezolid; CI: confidence interval; GDF: Global Drug Facility; GDG: Guideline Development Group; HIV: human immunodeficiency virus; IPD: individual patient data; KNCV: KNCV Tuberculosis Foundation; MDR-TB: multidrug-resistant tuberculosis; MDR/RR-TB: multidrug- or rifampicin-resistant tuberculosis; MDR-TB: multidrug-resistant tuberculosis; MIC: minimum inhibitory concentration; NRTI: nucleoside reverse-transcriptase inhibitors; PLHIV: people living with human immunodeficiency virus; PICO: patients, intervention, comparator and outcomes (questions); QD: once a day (dosing); TB: tuberculosis; WHO: World Health Organization; XDR-TB: extensively drug-resistant tuberculosis.

A4.2 WHO treatment guidelines for isoniazid-resistant tuberculosis, 2018

Refer to Annex 6: GRADE evidence-to-decision tables in the *WHO treatment guidelines for isoniazid-resistant tuberculosis* (https://www.who.int/tb/publications/2018/WHO_treatment_guidelines_isoniazid_resistant_TB_Online_GRADE_tables_Annexes.pdf, accessed 2 March 2019).

A4.3 WHO treatment guidelines for multidrug- and rifampicin-resistant tuberculosis, 2018 update

Refer to Annex 9: GRADE evidence-to-decision tables in the *WHO treatment guidelines for multidrug- and rifampicin-resistant tuberculosis, 2018 update* (https://www.who.int/tb/areas-of-work/drug-resistant-tb/Annexes_8-10.pdf, accessed 2 March 2019).

A4.4 Guidelines for the programmatic management of drug-resistant tuberculosis, 2011 update

Refer to Annex 2: GRADE glossary and summary of evidence tables (questions 6 and 7) in the *Guidelines for the programmatic management of drug-resistant tuberculosis, 2011 update* (https://apps.who.int/iris/bitstream/handle/10665/70677/WHO_HTM_TB_2011.6b_eng.pdf, accessed 2 March 2019), where the content of the evidence-to-decision process was summarized in the remarks relating to each recommendation.

A4.5 WHO treatment guidelines for drug-resistant tuberculosis, 2016 update

Refer to Annex 5: Evidence-to-decision tables (question 4) in the *WHO treatment guidelines for drug-resistant tuberculosis, 2016 update* (<https://apps.who.int/iris/bitstream/handle/10665/250125/9789241549639-webannexes-eng.pdf>, accessed 2 March 2019).

A4.6 Guidelines for treatment of drug-susceptible tuberculosis and patient care, 2017 update

Refer to Annex 4: Evidence-to-decision tables (questions 10 and 11) in the *Guidelines for treatment of drug-susceptible tuberculosis and patient care, 2017 update* (https://www.who.int/tb/publications/2017/dstb_guidance_2017/en/, accessed 2 March 2019)

Annex 5: Summaries of unpublished data

A5.1 WHO treatment guidelines for multidrug- and rifampicin-resistant tuberculosis, 2020 update

A5.1.1: Summary review for the GDG of preclinical and early clinical data on pretomanid for use in MDR and XDR-TB: CPMT Project No.: 19010

By Professor Susan M Abdel-Rahman

Overview:

Pretomanid (Pa) was granted approval by the U.S. FDA in August 2019 to be used as part of a bedaquiline, pretomanid, linezolid (BPaL) regimen. This document summarizes a broader report to WHO detailing background information on Pa including pre-clinical data and early phase clinical safety and efficacy.

Chemistry:

Pa represents a class of nitroimidazopyrans arising from the naturally occurring nitroimidazole, azomycin, and its synthetic derivative metronidazole. It bears structural similarity to the nitroimidazooxazole, delamanid.[1–4]

Putative mechanisms of action for Pa include; 1) reductive activation to reactive nitro radical anion intermediates, 2) nitric oxide release, 3) ketomycolic acid depletion, and 4) toxic methylglyoxal accumulation.[1, 5–7] The cofactor F₄₂₀ mediated redox system is integral to the activity of Pa and sequence variations in MTb proteins that are involved with the synthesis, oxidation or reduction of this cofactor are linked to resistance. These include Ddn (Rv3547), Fgd (Rv0407), fbiA (Rv3261), fbiB (Rv3262), fbiC (Rv1173), and fbiD (Rv2983).[1, 8–14] With limited exception, these proteins are not required for the growth/survival of MTb and their disruption does not limit mycobacterial fitness. [15–19]

The frequency of spontaneous Pa resistance in vitro (10^{-5} to 10^{-7}) is influenced by the concentration to which the isolates are exposed and the starting mycobacterial inoculum. Estimates are greater than that of rifampin but comparable to other agents including isoniazid, ethambutol, and pyrazinamide. [20] Spontaneous resistance rates in vivo are variable ($\sim 10^{-3}$ – 10^{-5}) and increase in direct proportion with dose; however, they drop in combination with INH.[13, 21–23]

Cross resistance to other antimycobacterial agents is rare with the exception of delamanid for which it is common but incomplete.[24] Cross resistance has also been documented with the more recently discovered nitrofuranylamides and 5-nitrothiophenes which share structural features with Pa and delamanid.[25,26]

Microbiology:

MIC for Pa against drug-susceptible, monoresistant, MDR, and XDR isolates of MTb (0.005–0.48 µg/mL) suggest that resistance phenotype has limited impact on Pa activity.[24] MICs against MTb increase in low oxygen conditions and in the presence of human albumin/serum.[24, 27–28] Pa demonstrates activity against other species in the Mycobacterium tuberculosis complex including *M. bovis*, *M. africanum*, and *M. pinnipedii* (MIC range <0.0312 to 0.125 µg/mL); however, there is little to no activity in other mycobacterial and non-mycobacterial species.[24]

In vitro, Pa appears to exhibit both concentration- and time-dependent bactericidal activity.[24] Intracellular potency appears comparable to INH and inferior to delamanid and rifampin, though intracellular to extracellular ratios vary by drug and incubation condition.[29–31]

Murine models support a dose-response relationship for Pa with a minimum effective dose of 12.5 mg/kg and a minimum bactericidal dose of 100 mg/kg. At this dose, CFU reductions in the lung and spleen comparable to INH (25 mg/kg), gatifloxacin (100 mg/kg) and moxifloxacin (100 mg/kg).[1, 21, 32]. Monotherapy with Pa at 50 mg/kg fails to achieve a sterile cure, though combinations with bedaquiline and an oxazolidinone achieve CFU reductions that are a full order of magnitude lower than achieved with Pa alone.[26, 33–35] The combination PaMZ is similarly effective in the guinea pig model.[1, 36] Dose fractionation studies in these animal models suggest that %T>MIC demonstrates the strongest association with CFU count reduction.[37]

In humans, 14-day single-dose studies suggest no appreciable increase in EBA above 200 mg.[38–39] When administered in combination, EBA observed in regimens containing Pa did not appear inferior to combinations without this agent. Pa-based regimens also outperformed standard HRZE treatment regimens in select studies, though none of the combinations tested reflect the FDA approved BPaL regimen.[40–43]

Pharmacology/Toxicology:

Information relevant to understanding the disposition of Pa and its drug-interaction potential derives largely from the CDER review [44] and are summarized as follows:

- Absolute bioavailability in non-human primate is less than 50%
- Protein binding ranges from 86.3 to 86.5% with a low potential for partitioning into red blood cells.
- Pa undergoes biotransformation by multiple P450 and non-P450 pathways with CYP3A4 the only relevant P450 accounting for up to 20% the drugs metabolism.
- In vitro studies demonstrate the potential for Pa to inhibit CYP3A4/5, though at concentrations in excess of those observed with routine dosing. Recorded IC₅₀ values suggest DDI mediated via other P450 isoforms is unlikely.
- The potential for pretomanid to induce CYP3A4 appears to be negligible.
- Pa does not appear to be a substrate for transporters evaluated to date; however, it does inhibit the renal tubular uptake transporter OAT3 at clinically relevant concentrations.
- Clinically relevant in vivo DDI observed in humans are limited to a drop in Pa exposure when co-administered with CYP3A inducers (e.g. rifampin, efavirenz, lopinavir/ritonavir).[45–48]
- Pa does appear to increase in moxifloxacin exposures in rats; however, the mechanism and relevance to humans is unclear.
- Drug-food interactions are marked by an increase in Pa exposures (C_{max} and AUC) when co-administered with a high-fat meal. The relative increase in bioavailability gets disproportionately larger with increasing dose.[49]
- Cardiac toxicity mediated by hERG inhibition (IC₅₀ was 17.3 µM) is not likely to be relevant at labeled doses.
- Carcinogenicity and mutagenicity risk also appear low.[24, 44] However, safety signals in animals have been observed in various organ systems the most relevant of which is hepatotoxicity at labeled

doses.[24, 44] Testicular toxicity has also been observed at lower exposures and the uncertain human implications have lead the FDA to require additional post-marketing studies.

Clinical Pharmacokinetics:

In healthy volunteers, Pa concentrations peak between 4–5 hours post-dose with a less-than proportional relationship between dose and exposure through 600 to 1000 mg after which point increasing dose produces no corresponding increase in exposure.[50–51] Mean Pa half-life ranges from 15–20 hours explaining a doubling in the extent of exposure at steady state.[50]

Efficacy/Safety:

Nix-TB [24]: This non-comparative study of BPaL in 109 individuals reported favorable outcomes in 89%, 91% and 92% of their ITT, MITT, and PP populations respectively. No appreciable differences in response were observed as a function of HIV status, linezolid regimen (BID vs. QD), age, gender, race, cavitation, or time to positivity at baseline. All participants (100%) experienced at least 1 treatment emergent adverse event (TEAE), 99% of which were considered related to study regimen. The most frequently reported AE can be identified in the clinicaltrials.gov URL referenced above. Those most likely associated with Pa based on preclinical data include: dermatitis/eczema (53.2%), non-infective gastrointestinal upset (48.6%), hepatic disorder (38.5%), headache (29.4%), lens disorder (13.8%), severe cutaneous reaction (6.4%), and convulsions (1.8%). There were 8 deaths in the trial 7 of which led to premature discontinuation of the study and TEAE in an additional 5 patients that led to treatment discontinuation.

STAND [52]: In this trial of PaMZ, the rate of unfavorable outcomes for the primary measure exceeded those of the standard HRZE treatment group. At the point of analysis, the Pa containing regimens failed non-inferiority criterion prompting early discontinuation of the trial. Note that this was preceded by a clinical hold from the FDA owing to 3 hepatotoxicity associated deaths. TEAE rates ranged from 87–94% in the Pa containing arms compared with 91% in standard treatment arm. The only SAE observed in more than 1 individual across all pretomanid containing regimens include increases in ALT/AST and seizures. Additional AE observed with more than a 2-fold higher rate in the Pa groups (vs. HRZE) were gastrointestinal (nausea, vomiting, diarrhea) and pulmonary (pleuritic pain, hemoptysis, URI).

ZeNix [53]: In this ongoing trial of BPaL, 83.6% of 61 participants have experienced at least one TEAE, 55.7% of which were considered related to study drug. The most frequently reported AE parallel those reported in Nix-TB. To date, TEAE have led to permanent discontinuation in 2 participants.

Early Clinical Trials [38–43]: In the 14-day EBA monotherapy studies, reported SAE were restricted to complications of the underlying disease (pneumonia, pneumothorax, hemoptysis). The only non-serious AE experienced by more than one individual across all treatment arms was nausea, vomiting, headache, pruritis, rash, and iron deficiency anemia. In the 8-week BA studies, TEAE rates approximated those of the efficacy studies described above. When the regimens are broadly combined, and non-serious AE are evaluated against the standard HRZE regimen, neurologic and hepatic disturbances appeared to be more prevalent in the Pa containing regimens. Early clinical studies also identified a relationship between trough Pa concentrations and an increase in circulating serum creatinine levels which resolved after discontinuation of the drug.[50] Subsequent exploratory studies suggests that these changes are likely the result of inhibition of creatinine secretion at the level of the renal proximal tubule.[51]

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A5.1.2: Model-based projections of costs and cost effectiveness of changes in MDR/RR-TB regimens

By Dr Emily A Kendall, MD PhD

Background:

Changes in recommended MDR/RR-TB treatment are likely to have economic consequences, through their effects on drug costs, drug delivery (for example, injections), safety monitoring requirements, numbers of follow-up visits, or (via changes in treatment outcomes) the number of TB patients who will require treatment in the future. Changes to recommended regimens might be cost-saving under common conditions, or might result in cost increases and potential access concerns that need to be weighed against clinical advantages. We developed a model to estimate the costs and cost-effectiveness of three potential changes to recommended treatments for MDR/RR TB.

Methods:

A single decision analytic modeling framework was developed to evaluate multiple regimen comparisons that were under consideration by the Guidelines Development Group (GDG). For PICO question 1, the costs and effectiveness of a shorter (9–12 month), all-oral, bedaquiline-containing regimen (modeled as based on South African guidelines) were compared to two types of currently recommended MDR/RR-TB regimens: (a) a longer (18–20 month), bedaquiline-containing oral regimen (modeled as consisting of WHO class A and B drugs bedaquiline, linezolid, levofloxacin, clofazimine, and terizidone), or (b) a 9–12 month, injectable-containing regimen (modeled as evaluated in STREAM). For PICO 3 (use of bedaquiline for longer than 6 months in longer oral regimens), use of bedaquiline for 6 months in the 18–20 month regimen described above was compared to use for the duration of treatment. For PICO 4 (concurrent use of delamanid and bedaquiline), use of delamanid was modeled in two ways: (a) as an addition to the 18–20 month oral regimen (thus potentially increasing efficacy while adding cost) or (b) as a replacement for linezolid (with main goal to reduce toxicity).

Each pair of regimens was compared in a population of adult patients with MDR/RR (not pre-XDR/XDR) pulmonary TB. Modeled differences in TB outcomes between regimens (differences in relapse/failure, mortality, and loss to follow up) were based on the statistical analyses of individual patient data performed for the GDG by Drs. J Campbell and R Menzies. Differences in cost, in 2019 US dollars, were evaluated from a health system perspective, accounting for resources required to manage current and future TB (including drugs, office visits and hospitalizations, safety monitoring, recurrences and secondary cases) and adverse events. Future non-TB health care costs (e.g. of ART) incurred as a result of preventing deaths were excluded. Serious adverse event risks were estimated per drug-month using data from a global surveillance project. Differences in effectiveness, in disability-adjusted life years (DALYs) averted, accounted for estimated morbidity and mortality during and after treatment (with disability weights¹³ for TB disease, drug side effects, treatment burden, and health status, and with 3%/year discounting of DALYs and costs). Primary analyses were based in South Africa, and sensitivity analyses explored the range of health care costs, drug costs, and HIV co-prevalence expected across low- and middle-income countries.

Results:

PICO 1: A shorter, all-oral, bedaquiline-containing regimen was projected to be cost-saving relative to either comparator regimen: by nearly \$3,000 per patient when compared to a longer, all-oral regimen, and by \$1,000 per patient when compared to a short, injectable-containing regimen (both in South Africa). Compared to the longer oral regimen, the majority of the resource savings associated with the shorter all-oral regimen were due to reduced costs of drugs, but savings were also projected in costs of health care delivery, adverse events, and future retreatments and secondary cases. Compared to the short, injectable-containing regimen, the shorter all-oral regimen did not reduce drug costs, but it provided similar projected resources savings in other categories. The shorter all-oral regimen was also projected to be more effective than either comparator.

In sensitivity analyses, the resource savings of the shorter all-oral regimen relative to a longer all-oral regimen appeared extremely robust to country setting and underlying assumptions. The greatest variations in (cost savings) were seen with a two-fold decrease or increase in drug costs (cost savings \$2000 and \$4600, respectively) and with a two-fold decrease or increase in all non-drug healthcare costs (cost savings \$2300 and \$4000). The resource savings of the shorter all-oral regimen relative to the shorter injectable-containing regimen were nearly as robust, with the shorter all-oral regimen ceasing to be cost-saving (but remaining cost-effective, at < \$400 per DALY averted) only when we assumed a large (four-fold) isolated increase in the cost of the drug bedaquiline.

PICO 3: Extending the duration of bedaquiline treatment, from six months to the full 18–20 month duration of a longer all-oral regimen, was expected to add approximately \$500 per patient to health system costs (at current drug prices). Cost-effectiveness depended heavily on the magnitude of the clinical benefit of extending treatment, and a sufficiently large benefit to achieve cost-effectiveness when used for all patients could not be observed in available data. If patients could be identified who would derive a clinically meaningful efficacy benefit (e.g. odds ratio of 0.6 for treatment success), then extending the duration of bedaquiline might be cost effective for those patients, at an estimated incremental cost effectiveness ratio in South Africa of \$1,200 per DALY averted.

PICO 4: Current high delamanid prices made cost-effectiveness difficult to achieve, whether delamanid was considered for inclusion in MDR/RR-TB treatment regimens in order to enhance efficacy (analysis a) or to prevent toxicity from another drug through substitution (assuming no significant loss of efficacy, analysis b). When adding delamanid to an otherwise-optimized longer all-oral regimen that already contained bedaquiline, the best-case incremental cost effectiveness ratio was \$2,000 per DALY averted in South Africa, at the most optimistic data-consistent estimate of the efficacy benefit that delamanid might provide to patients. Data also supported an outcome of additional cost with no benefit, if true efficacy gains were minimal. When delamanid replaced a more toxic drug (e.g. linezolid) without changing regimen efficacy, then at current drug prices, the most optimistic incremental cost effectiveness ratio achievable in sensitivity analyses was \$16,000 per DALY averted; this required assuming a serious adverse event rate of 0.7%/month for the drug that was replaced by delamanid (at the high end of the uncertainty range supported by data for linezolid), and high acute DALY impact per serious adverse event (0.4 DALYs each, similar to one full year with symptomatic active TB), and a high management cost of \$17,000 per averted serious adverse event.

Conclusions:

A 9–12 all-oral regimen was projected to be both cost-saving and effective, relative to either a longer all-oral regimen or a shorter injectable-containing regimen, and cost savings were robust to setting-dependent variables and parameter uncertainty.

On the other hand, extending the duration of bedaquiline or adding delamanid within longer MDR/RR-TB regimens added substantial cost, and these changes were unlikely to be cost-effective at current prices when implemented for all patients, because of the relatively small effectiveness benefits

expected. However, moderate cost effectiveness was possible when used for select patients for whom effective regimens could not otherwise be composed.

A5.1.3: Patient perspectives on DR-TB treatment: a summary report prepared for the November 2019 WHO GDG Meeting

Introduction

Patient values and preferences for treatment, and perspectives on treatment acceptability, feasibility and equity are key to the World Health Organization's Evidence to Decision framework for drug-resistant tuberculosis (DR-TB) treatment interventions. A qualitative study was undertaken to illuminate patient perspectives and inform discussions for a November 2019 Guidelines Development Group (GDG) meeting for updated DR-TB treatment guidelines. A summary of the study is provided here.

Methods

Private in-depth interviews were held with persons who had received M/XDR-TB treatment in or after 2012, and were at least 18 years old and not receiving any form of TB treatment at the time of the study. They were recruited by referral from non-governmental organizations, as well as former patients with public profiles, from high DR-TB burden countries. Representation was sought from women, men, and people who had received newer or repurposed drugs for DR-TB. Interviews were conducted by phone in English, Russian, Mandarin or Spanish, and audio-recorded. Interview topics included: experiences with DR-TB treatment; preferences for treatment regimens; and the real or perceived acceptability of newer regimens, including perspectives on access and delivery. Recordings were transcribed, translated and identifiers removed. Data were thematically analyzed using OneNote to develop insights on patient values and preferences (characteristics, concerns and expectations of treatment that are considered to be most important); acceptability (appropriateness of treatment based on anticipated or experienced physical, cognitive and emotional effects); feasibility (practical considerations related to taking treatment); and equity (perceived or potential impacts on health and social inequalities). Ethics approval was granted by the Office of Research Ethics, York University, Canada.

Findings

Sixteen participants (44% female) of median age 29.5 years (range 22–64) were interviewed over two weeks in Oct 2019, from Africa (4), Asia (5), Eastern Europe (5) and South America (2). Nine (56%) participants began treatment for MDR-TB and 7 (44%) for pre-XDR or XDR-TB between 2011 to 2017. All had received longer regimens, from 1.5 up to 3 years. Most (96%) participants had experience with a second-line injectable and 40% with at least one of the new or repurposed drugs. One participant received bedaquiline as first-line therapy. Two participants were treated when they were adolescents. Few participants reported a co-morbidity: HIV (1), diabetes (2), chronic kidney illness (1).

Participants' acceptability and preferences for DR-TB treatment were rooted in the following core values: minimal disruption to normal life and independence during treatment, and full physical and mental recovery post treatment. A short, injection-free regimen with few to no side effects and a low pill burden was considered to be the most acceptable treatment for DR-TB. Barring the fulfillment of all these characteristics, a regimen with least side effects was prioritized, as side effects were considered to be the most disruptive aspect of treatment. This was followed by a shorter regimen, no injections, and fewer pills, in that order.

Side effects that tended to resolve themselves over the course of a day or over the course of treatment (nausea, mild vomiting, body aches and pains, fatigue, and ringing in the ears) were disliked but tolerated. By contrast, severe and persistent vomiting, intense mental health effects (severe depression including suicidal ideation, and severe anxiety including delusional thoughts), and any side effect that

could result in organ or sensory damage (hearing or vision loss, major damage to organs such as the kidney or heart, jaundice, and severe neuropathy or burning) were all considered unacceptable, even if they were short-term and reversible. Severe mental health problems and any loss of hearing and vision were described as the worst side effects. Skin pigmentation and injection pain were highly undesirable; they were accepted in the short-term only if there was no other treatment choice.

There were caveats and nuances to participants' priorities, as well as important differences in acceptability, based on personal experiences with treatment, and the environment and context in which DR-TB care was received. Consequently, informed patient choice was considered a highly valuable component of the treatment decision-making process. Other elements valued by participants and considered crucial to acceptability of DR-TB treatment regimens were tight monitoring of serious adverse events, mental health counselling and support, ability to receive treatment in one's own community (e.g., decentralized care), and universal access to new drugs and regimens.

These values and preferences have implications for the feasibility of new DR-TB treatment interventions. Some patient values may conflict due to feasibility challenges, for example if treatment monitoring cannot be reasonably provided in the community. Feasibility issues give way to equity considerations if patient preferences are not upheld across all communities, or place certain populations at a disadvantage, such as those living in remote or rural locations where provision of new drugs or treatment monitoring may be difficult.

Study attributes and limitations

Open ended in-depth inquiry was key to uncovering the dynamic subjectivity of patient values and preferences. Saturation was likely not achieved with regards to the perspective of people with co-morbidities, permanent clinical sequelae, and experience with shorter, non-injectable regimens as first-line treatment. The sample was enriched by the voices of several participants who were TB peer educators and patient advocates and brought the experience of current patients into their narratives.

Conclusion

The study, rooted in the recent lived experience of people who were treated for DR-TB in a number of high burden countries, illuminates novel insights into patients' core values, ranked preferences, and comparative risk perceptions and acceptability related to DR-TB treatment. Insights gained may inform patient-centred treatment guidelines for DR-TB.

Acknowledgements

The study was conducted by Amrita Daftary and Stephanie Law in preparation for the WHO GDG for updated DR-TB treatment in November 2019. AD is based at the School of Global Health & Daedaleh Institute of Global Health Research, York University, Canada, and appointed to the Centre for the AIDS Programme of Research in South Africa (CAPRISA). SL is postdoctoral fellow at the Department of Global Health and Social Medicine, Harvard Medical School, Boston, USA. The researchers wish to acknowledge and sincerely thank the people who participated in this study, as well as referring organizations and persons.

Annex 6: Statistical analysis plans

A6.1 WHO treatment guidelines for multidrug- and rifampicin-resistant tuberculosis, 2020 update

A6.1.1: PICO question 1: In MDR/RR-TB patients, does an all-oral treatment regimen lasting 9-12 months safely improve outcomes when compared with other regimens conforming to WHO guidelines?

Effectiveness of an all-oral MDR/RR-TB regimen lasting 9–12 months in South Africa: Statistical Analysis Plan (draft)

Prepared by Jonathon Campbell & Dick Menzies, McGill University: April 15, 2020

Overarching PICO Question (PICO 1)

In MDR/RR-TB patients, does an all-oral, bedaquiline-containing regimen lasting 9–12 months safely improve outcomes when compared with other regimens conforming to current WHO guidelines?

Population	Intervention	Comparator	Outcomes
MDR/RR-TB patients a. without additional drug resistance b. with additional drug resistance patterns (for FLDs and/or SLDs; if specific mutation data is available in dataset). c. with FQ resistance d. with severe disease (i.e. cavitary disease on radiography or SS+) e. previously treated with 2nd line drugs or not f. children (0–14y) / adults (adolescents 10–19y if available) g. persons with HIV (+/- ARVs) h. pregnant women i. with extrapulmonary disease j. with comorbidities (e.g. diabetes mellitus; malnutrition; mental disorders)	– An all-oral shorter regimen of 9–12 months duration including bedaquiline	1. Shorter regimen recommended by WHO 2. Old longer regimens without new drugs in the IPD dataset 3. Longer regimens with new TB drugs from the IPD dataset 4. Longer regimens with use of new drugs from the EndTB dataset.	<ul style="list-style-type: none"> • Successful completion of treatment (or lack of successful completion) • Bacteriological cure by end of treatment • Adherence to treatment (or treatment interruption due to non-adherence) • Treatment failure or relapse • Survival (or death) • Adverse reactions from anti-TB medicines • Acquisition (amplification) of drug resistance • Relapse free cure

Research Questions

Primary – intervention and comparator populations from South Africa data

1. Relative to the WHO recommended short-regimen lasting 9–12 months, does a bedaquiline-containing all-oral regimen lasting 9–12 months have the same or better outcomes?
2. Relative to a regimen lasting ≥ 18 months without the use of new TB drugs (e.g. **does not contain** bedaquiline, linezolid, delamanid, or carbapenems), does a bedaquiline-containing all-oral regimen lasting 9–12 months have the same or better outcomes?
3. Relative to a regimen lasting ≥ 18 months with new TB drugs (e.g. **contains** bedaquiline), does a bedaquiline-containing all-oral regimen lasting 9–12 months have the same or better outcomes?

Secondary – intervention population from South Africa data, and comparator populations are from IPDinMDR – 2019 or the EndTB observational study

1. Relative to people in the IPDinMDR – 2019 data set receiving a regimen lasting ≥ 18 months without the use of new TB drugs (e.g. **does not contain** bedaquiline, linezolid, delamanid, or carbapenems), does a bedaquiline-containing all-oral regimen lasting 9–12 months have the same or better outcomes?
2. Relative to people in the IPDinMDR – 2019 data set receiving a regimen lasting ≥ 18 months with new TB drugs (e.g. **contains** bedaquiline), does a bedaquiline-containing all-oral regimen lasting 9–12 months have the same or better outcomes?
3. Relative to people in the EndTB data set receiving a regimen lasting ≥ 18 months with bedaquiline and/or delamanid (for a maximum of 6-months), does a bedaquiline-containing all-oral regimen lasting 9–12 months have the same or better outcomes?

Background and Rationale

The use of shorter (9–12 months) regimens, in particular the new all-oral regimens for MDR/RR-TB, is presumed to have more benefits as compared to longer regimens lasting ≥ 18 months; as well as to other shorter injectable-containing regimens. Primarily, the shorter duration puts a lower burden on patients and reduces the direct and indirect costs (both to the patient and the healthcare system) associated with treatment since MDR/RR-TB treatment is usually delivered through directly observed therapy. Secondly, injectable-agents are among the most toxic drugs used for MDR/RR-TB, have poor efficacy against TB and can lead to irreversible adverse events. While treatment & care delivery for TB²⁵, including patients with drug-resistant TB can be community-based, usually injection-containing regimens must be administered at health facilities, adding travel and waiting time to the discomfort and inconvenience, and potentially contributing to poor treatment adherence in some cases. Thus, there are several advantages to a shorter all-oral regimen if they are as effective as regimens that (a) last longer and/or (b) contain an injectable.

To date, shorter regimens have only been recommended for individuals who have not been exposed to second-line TB drugs (i.e. are new patients or have only received first-line TB drugs) and whose TB isolates have proven susceptibility to fluoroquinolones and second-line injectables. Given the nature of programmatic data, this latter criterion often simplifies to “not proven resistant” – i.e., their drug susceptibility test result is ‘susceptible’ or ‘not performed’ for these two classes of drugs, although in ideal settings, drug susceptibility results would be available. However, generally this means that patients with MDR/RR-TB that qualify for a shorter regimen are much less “complex”, than patients with MDR-TB with additional resistance patterns²⁶ and XDR-TB, or that have been previously treated with second-line TB drugs. This makes comparisons of treatment of these two groups at very high-risk

²⁵ *Treatment & care delivery for TB* is used in this context to refer to the administration of “Directly Observed Therapy [DOT]”.

²⁶ *MDR-TB with additional resistance patterns* refers to MDR-TB cases which present MDR-TB plus resistance to fluoroquinolones (MDR-TB+*FQ*) or additional resistance to injectable agents (MDR-TB+*SLI*). This term does NOT mean MDR with resistance to PZA, EMB, Ethionamide Cycloserine or other similar and commonly used second-line drugs.

of bias. Thus, for the purposes of this PICO question, we will exclude patients from all data sources (detailed below in Section 3.1) who have been exposed to second line drugs previously or who are MDR-TB with additional resistance to a second-line injectable and/or a fluoroquinolone. The number of patients excluded will be quantified, but are expected to be minimal, with only 4% and 1.5% of patients treated with a short regimen in South Africa previously receiving second-line drugs and having MDR -TB with additional resistance patterns or XDR, respectively, in a prior analysis of 2014–2015 data.

Within South Africa, over 10,000 people initiate MDR/RR-TB treatment each year. Both shorter (9–12 months) and longer (≥ 18 months) regimens have been used and, over the last 2–3 years, there has been a transition from the WHO recommended short, injectable-containing regimen, to one that has replaced the injectable with bedaquiline. Thus, the data from South Africa presents a unique opportunity to compare patient important outcomes with four different types of regimens²⁷ delivered concurrently in the same settings, by the same providers, faced with the same health system resources and constraints. The comparisons within the South Africa data set are thus considered the primary analysis.

In addition to comparison within South Africa, use of patients from the IPDinMDR – 2019 database and/or from the EndTB observational study allow comparisons between settings and patients with different characteristics. If findings are similar, we can be more confident in their generalizability. Due to many potentially confounding differences between health systems and patients with MDR/RR-TB, within South Africa, and other settings, the comparisons between South African cohorts and other cohorts will be considered secondary.

Data Sources

South Africa

All data for MDR/RR-TB patients who initiated treatment within South Africa is housed within the Electronic Drug Resistant TB register (EDRWeb). This register includes information such as age, sex, facility of treatment, previous treatment history, HIV co-infection, ART use, every drug received during treatment, individual culture and smear results during treatment, drug-resistance testing (both genotypic and phenotypic), regimen type (short or long), and end-of-treatment outcomes.

We plan to use data from every individual in South Africa who initiated any short-regimen between Jan 1 and Dec 31, 2017 (N=3772) and data from every individual in South Africa who initiated a “long”-regimen in Q1 and Q2 2017 (Jan 1 to June 30, 2017) (N=3722). We selected the year 2017 for the short, injectable-free regimen as this was the first year this short-regimen had been widely used throughout the country. As well, regardless of the date a person started treatment that year, every individual should have at least 6 months of post treatment follow-up for possible relapse (data extraction for relapse is being performed in August 2019). We selected the first two quarters of 2017 (1 January to 30 June) for the long regimen as these patients would be receiving treatment concurrently with the short regimen patients and 95% of patients initiating therapy within this interval should have had an end of treatment outcome by 31 December 2018, allowing at least 6 months of follow-up for possible relapse. There may be concerns regarding selection of individuals to a short or long regimen when both were systematically offered in 2017. To examine this, we will also compare outcomes with the BDQ short regimen received in 2017 with outcomes among patients who received the conventional (long) regimen in 2016 for a second comparison. In 2016 only 213 of 13,193 (1.6%) persons starting RR/MDR-TB treatment received a short regimen, suggesting that selection bias should have been minimal in 2016, compared to 2017.

As many of the regimens being compared are significantly different in duration, accounting for relapse and death non-differentially presents a challenge. For example deaths during treatment may occur up to 18 or even 24 months after initiation of a conventional ‘long’ regimen, but only up to 12 months with

²⁷ All-oral 9–12 month regimen; WHO recommended 9–12 month regimen; Longer regimen without new drugs; Longer regimen with new drugs.

the short regimen. Therefore, death in Months 12–24 will be counted as ‘deaths during TB treatment’ with the long regimen, even if unrelated to TB, whereas they would not be classified as such with the short regimen. Similarly, a patient could have culture reversion at month 15 of a long regimen and be classified as a treatment failure, but such a late reversion would not be detected with the short regimen (unless relapse was carefully measured). In both situations, knowledge of post-treatment relapse and death outcomes is crucial to minimize differential outcome ascertainment. We plan to detect relapses within EDRWeb by cross-matching all names of those treated in 2016 and 2017 with EDRWeb to ascertain if any patients who are classified as treatment success are subsequently restarted on MDR/RR treatment. We will detect these relapses by probabilistically matching patients within EDRWeb. However, as deaths following treatment completion are not recorded with EDRWeb (treatment must be initiated to be entered in this system), we will link all patients who started treatment in Jan 1 to June 30 2017, and those who started the short regimen from July 1 to Dec 31 2017 and successfully completed treatment with the South African MRC using their South Africa ID number to see if death occurred after treatment completion. Information about the South Africa ID within EDRWeb is ~90% complete, so we expect this should result in a fairly complete capture of deaths post-treatment.

IPDinMDR – 2019

In 2018 an IPD was assembled of 53 data sets from 40 countries/regions containing records for more than 13,000 patients with MDR-TB. This IPD-2018 data set was analyzed to answer a number of PICO questions developed by a WHO MDR-TB guidelines development group (GdG). These guidelines have since been published. This IPD-2018 itself was based on an IPD data set assembled in 2016–17 to answer questions of a GdG of the CDC/ATS/IDSA/ERS. These guidelines have not yet been published, but the analyses that informed this set of guidelines were published in the *Lancet* in Sept 2018. This database contains records of ~150 patients from the EndTB study, who will be removed and updated with the more complete data set (see below). Further, the IPD-2018 contains about 3,500 records from South Africa, which we will exclude for the purposes of the secondary analyses.

Within this iteration of the IPD – 2019, we anticipate adding data from a public call executed by the WHO, however at the time of writing we are unsure of the type, number, and treatment regimens of patients who might be added.

EndTB Observational Study

The EndTB observational study includes 1094 patients with MDR-TB who were treated with bedaquiline- and/or delamanid-containing long regimens between 1 April 2015 and 31 March 2017 in 17 countries²⁸. They were followed as part of an observational study – executed by three institutions – PIH, MSF and IRD. There is comprehensive data capture on all important variables within the data set, including detailed information on treatment associated adverse events.

Considerations for the IPDinMDR – 2019 and EndTB Observational Study Data Sets

Within the IPDinMDR – 2019 and EndTB data sets, there are important differences when compared to the South Africa cohorts from 2016 and 2017 that will be analyzed. Firstly, these data sets contain patients treated from 2000–2017. We will only include patients initiating treatment from 1 January 2013 onwards to ensure comparability with the patients treated in 2016 and 2017 in South Africa. Further, it is important to compare patients treated in similar resource settings. The primary analysis will include patients treated in all settings, and in sensitivity analyses we will restrict the comparators to patients treated in other World Bank classified upper-middle-income countries, as is this the category South Africa belongs to. We will quantify how many patients this represents and compare them to those we included from both studies.

²⁸ Armenia, Bangladesh, Belarus, Democratic People's Republic of Korea (DPRK), Ethiopia, Georgia, Haiti, Indonesia, Kazakhstan, Kenya, Kyrgyzstan, Lesotho, Myanmar, Pakistan, Peru, South Africa and Vietnam; (<http://endtb.org/about>)

Defining Regimens

As the treatment trajectory of MDR/RR-TB represents the complex interaction of patient, provider and health system capacities and constraints, there may be deviations from intended durations of therapy and number of drugs used. We will examine descriptively the distribution of treatment duration for all persons who received long or short regimens, as well as the distribution of treatment duration for persons with successful treatment who received a long or a short regimen. Based on these descriptive analyses, we will select cut-points (ideally using inter-modal points) that appear to best define the duration of treatment that can be called 'short' and 'long' (e.g. how far before or after the 'planned' duration of 'short' treatment do we accept as still meeting the definition of a short regimen to include in this analysis?).

Therefore, we propose to establish criteria to classify people within regimen types. For data from South Africa, we plan to classify people who received a long-regimen as those who: (i) were classified as receiving a long-regimen within EDRWeb; (ii) had treatment duration not exceeding 24 months; (iii) received ≥ 4 TB drugs (any drugs, regardless of susceptibility for this definition) during treatment, regardless of whether they were effective and; (iv) if given an outcome of cure or complete, had a treatment duration ≥ 17.5 months. For data from IPDinMDR – 2019 and the EndTB data set, all patients received a long regimen, therefore we will include people conforming to criteria (ii), (iii), and (iv).

We plan to classify people who received a short-regimen as those who: (i) were classified as received a short-regimen within EDRWeb; (ii) had a treatment duration not exceeding 12 months; (iii) received ≥ 6 drugs during treatment and; (iv) if given an outcome of cure or complete, had a treatment duration ≥ 8.5 months. These duration cut-points are subject to change pending the distribution of treatment durations we find. The short regimen target duration is 9 months, but a 3-month (33%) extension is permissible by PICO definition, similarly, a long regimen target duration is 18 months, so the equivalent extension permissible is 24 months. Further, for the minimum treatment durations for success in the 2018 MDR Guideline Update, the 17.5 month cut-point for the long-regimen was used. A similar two-week period should be used for the short-regimen, which may reflect simply differences in dispensation of prescriptions (e.g. 36 weeks of meds vs. 270 days) or deviations in timing of visits and pills dispensed. We will describe any patients excluded because their treatment duration does not fall within these limits.

Regimen Classifications

Intervention Regimen

All-Oral Short Bedaquiline-Containing Regimen: The intervention in each analysis will be individuals who receive a short regimen (lasting 9–12 months) who did not receive any injectable during treatment and received bedaquiline.

Comparator Regimens

1. **WHO Recommended Short-Regimen:** The first comparator is the WHO recommended short-regimen, which consists of pyrazinamide, ethambutol, moxifloxacin/levofloxacin, and clofazimine given for 9–11 months with high-dose isoniazid, amikacin (if given kanamycin or capreomycin – these will be included), and ethionamide or prothionamide given in the first 4–6 months of treatment.
2. **Long Regimen Without New TB Drugs:** The second comparator is a long regimen given for a duration of 18–20 months, which does not contain one of the new TB drugs: bedaquiline, delamanid, linezolid, clofazimine, or carbapenems. The target duration of the regimen may not be reached due to treatment non-response, death, or loss to follow-up. Hence, we refer to long regimens as those intended to be given for ≥ 18 months in our analysis plan.
3. **Long Regimen Containing New TB Drugs:** The third comparator is a long regimen given for a duration of 18–20 months, which contains at least one of the new TB drugs: bedaquiline,

delamanid, linezolid, clofazimine, or carbapenems. The target duration of the regimen may not be reached due to treatment non-response, death, or loss to follow-up. Hence, we refer to long regimens as those intended to be given for ≥ 18 months in our analysis plan.

Regimens Excluded from Analysis

- a. **Short-Regimen without Bedaquiline and Not Conforming to WHO Recommendations:** It is possible patients are treated with a regimen lasting 9–12 months that does not conform to the WHO recommended regimen and does not contain bedaquiline. Individuals receiving a regimen falling into this category will be classified uniquely. We will compare characteristics and outcomes of these patients to others receiving a short regimen descriptively, but they will be excluded from analysis.
- b. **Short-Regimen with Bedaquiline and an Injectable:** It is possible patients began a short-regimen with an injectable, only to have it stopped and replaced with bedaquiline. Individuals receiving a regimen falling into this category will be classified uniquely. We will compare characteristics and outcomes of these patients to others receiving a short regimen descriptively, but they will be excluded from analysis.

Analysis of Outcomes

The PICO lists eight distinct outcomes: (i) Successful completion of treatment, (ii) Bacteriological cure by end of treatment, (iii) Adherence to treatment (or treatment interruption due to non-adherence)²⁹; (iv) Treatment failure or relapse, (v) Death during treatment, (vi) Adverse reactions from anti-TB medicines, (vii) Acquisition (amplification) of drug resistance, and (viii) Sustained bacteriological cure at least 6 months after successful treatment

We will combine failure and relapse, and also combine completion and cure as success. We will estimate odds of relapse free treatment success vs several combinations of poor outcomes, and also examine loss to follow-up (LTFU) vs other outcomes – as summarized below. Adverse reactions from anti-TB medicines, and acquisition of drug resistance during treatment can NOT be analyzed using South Africa data as this information is not routinely captured in South Africa's EDRWeb.

Comparisons analyzed:

1. Relapse free treatment success (cure + treatment completion) up to 24* months post treatment initiation vs. failure/relapse
2. Relapse free treatment success (cure + treatment completion) up to 24* months post treatment initiation vs. failure/relapse and death during treatment.
3. Relapse free treatment success (cure + treatment completion) up to 24* months post treatment initiation vs. all other outcomes (fail/relapse, death, and loss to FU).
4. Lost to follow-up during treatment vs. all other outcomes.

* The follow-up periods were selected as this will give follow-up times that are comparable for both regimens. A key consideration is that the first patient in our analysis initiates treatment in January 2017 and follow-up ends in June 2019 (30 months elapsing from the time of the first patient recruited until follow-up ends). This time elapsed necessarily shrinks as the year progresses. Thus, setting a limit of 24 months post-treatment initiation for follow-up, and censoring events occurring beyond this period, maximizes the study population for comparison. As this limitation necessarily excludes all patients initiating treatment beyond June 2017, we will conduct sensitivity analyses, examining outcomes 18-months post treatment initiation and 21-months post treatment initiation. Therefore, we will have three comparisons described in the table below:

²⁹ This correlates with loss to follow-up

Months of Follow-up Post-Treatment Initiation	Dates of Patients Included Receiving Short Regimen	Dates of Patients Included Receiving Long Regimen
18 months	January to December 2017	January to June 2017
21 months	January to September 2017	January to June 2017
24 months	January to June 2017	January to June 2017

Outcomes are clinician defined within South Africa and from our experience largely reflect Laserson (WHO 2005) criteria; this is how the majority of outcomes have been defined in IPDiNMDR – 2019 (44/53 studies). Within EndTB, outcomes are coded as per WHO 2013 outcomes, however we will also create outcomes based on microbiologic data to align with WHO 2005 for comparability.

Summary of Approach for Each Research Question

We will conduct all main analyses described in sections 5.1.1, 5.2.1, and 5.3.1 using the concurrent long regimen controls (from Q1 and Q2 2017) and the historical long regimen controls (from all of 2016). These estimates will be shown separately. We will only conduct sensitivity analyses in these sections on the concurrent long regimen controls. For the outcomes described in section 4.0, we will conduct sensitivity analyses examining outcomes up to 18-months and 21-months post-treatment initiation in addition to those at 24 months post-treatment initiation.

Overall Descriptive Analysis

Before analysis of each research question, we will conduct a descriptive analysis for each of the reference and exposure group (detailed below), looking at key characteristics including: age (continuous and 0–14 vs. 14+ and 10–19 vs. 19+), sex, previous treatment history (drugs received and outcome), baseline acid-fast bacilli smear result, number of drugs received during treatment, total number and type of drugs resistant to (not double-counting ‘similar’ drugs of ethionamide/prothionamide and cycloserine/terizidone, for example), presence of specific drugs in the regimens (e.g. bedaquiline, linezolid, clofazimine, moxifloxacin/levofloxacin, delamanid), and province of treatment. This will help clarify if there are systematic differences between the people who received each regimen, possible differences in **where** each regimen was used, and provincial differences in overall treatment outcomes. The information elicited from this analysis will be used to inform further variables for matching and/or adjustment described below – for example, addition of a random-effect for province of treatment (or exact matching within the province). Thus, within the approach for each question, the listed variables are an *a priori* list for inclusion, but may be modified based on data completeness and availability, and further sensitivity analyses including/excluding other variables may be developed based on the results of the descriptive analyses.

The descriptive analysis is also intended to determine how many individuals would be excluded due to regimen composition. We will see if there are any important differences between those included and excluded from analysis.

Primary Analysis (within South Africa only)

Primary Analysis Question 1

Relative to the WHO recommended short-regimen lasting 9–12 months, does a bedaquiline-containing all-oral regimen lasting 9–12 months have the same or better outcomes?

Intervention: All-Oral Short Bedaquiline-Containing Regimen 9–12 months in duration
Comparator: WHO Recommended Short-Regimen

Approach

Our approach will be to use a combination of exact matching and propensity score-based matching on several covariates to create two groups that are as comparable as possible, and thereby minimize bias and confounding. Between the intervention and comparator groups, we will perform exact matching on HIV co-infection/ART-use, previous TB treatment history (a 2 level variable – never and prior 1st line [recall, all people who previously received 2nd line TB treatment will be excluded]), and total number of drugs the strain was resistant to – this latter covariate is key to ensure the groups are comparable with regard to the full resistance patterns. We will further perform propensity score-based matching on age, sex, and baseline sputum AFB smear result. This matching process will be conducted with replacement using a caliper distance of 0.02 during the propensity score-based matching. We will examine the distribution of the matched covariates within the intervention and comparator groups to assess the fidelity of the matching process.

For each outcome described in section 4.0, within our ‘matched’ population we will conduct logistic regression using mixed-models including random-intercepts for each matched ‘pair’ and, depending on what we find for the descriptive analysis, for province of treatment. We will not include random-slopes as our experience is that there are significant model convergence issues when these random-effects are included. The logistic regression analysis will calculate adjusted odds ratios and associated 95% confidence intervals. We will further conduct binomial regression, using only fixed effects, on the matched population to calculate adjusted risk differences and their associated 95% confidence intervals.

Primary Analysis Question 2

Relative to a regimen lasting ≥ 18 months without the use of new TB drugs (e.g. **does not contain** bedaquiline, linezolid, delamanid, or carbapenems), does a bedaquiline-containing all-oral regimen lasting 9–12 months have the same or better outcomes?

Intervention: All-Oral Short Bedaquiline-Containing Regimen 9–12 months in duration
Comparator: Long Regimen Without New TB Drugs

Approach

We will utilize the same approach described in section 5.1.1 to compare outcomes among people receiving the intervention and comparator regimens.

Primary Analysis Question 3

Relative to a regimen lasting ≥ 18 months with new TB drugs (e.g. **contains** bedaquiline), does a bedaquiline-containing all-oral regimen lasting 9–12 months have the same or better outcomes?

Intervention: All-Oral Short Bedaquiline-Containing Regimen 9–12 months in duration
Comparator: Long Regimen Containing New TB Drugs

Approach

We will utilize the same approach described in section 5.1.1 to compare outcomes among people receiving the intervention and comparator regimens.

If there are enough patients, we will conduct sensitivity analyses within sub-groups defined by use of specific drugs, or combinations of drugs. For example, the sub-group of patients who received, or did not receive linezolid, or delamanid, or bedaquiline, or carbapenems, as part of a long regimen. If any of the subgroup analyses result in < 100 patients being included in the analysis population, we will not conduct analyses. We will further conduct a sensitivity analysis repeating the approach in section 5.1.1 for other new or repurposed drugs: delamanid, linezolid, and carbapenems.

Secondary Analysis (Comparing to IPDinMDR – 2019 or EndTB Data Sets)

Secondary Analysis Question 1

Relative to people in the IPDinMDR – 2019 data set receiving a regimen lasting ≥ 18 months without the use of new TB drugs (e.g. **does not contain** bedaquiline, linezolid, delamanid, or carbapenems), does a bedaquiline-containing all-oral regimen lasting 9–12 months have the same or better outcomes?

Intervention: All-Oral Short Bedaquiline-Containing Regimen 9–12 months in duration
Comparator: Long Regimen Without New TB Drugs

Approach

We will utilize the same approach as described in section 5.1.1 to compare outcomes among people receiving the intervention and comparator regimens. Recall that we will only include people from the IPDinMDR – 2019 data set who began treatment from the year 2013 onward and who were treated in an upper-middle income country. We will conduct a sensitivity analysis relaxing the criteria for country-level income and report the outcomes.

Secondary Analysis Question 2

Relative to people in the IPDinMDR – 2019 data set receiving a regimen lasting ≥ 18 months with new TB drugs (e.g. **contains** bedaquiline), does a bedaquiline-containing all-oral regimen lasting 9–12 months have the same or better outcomes?

Intervention: All-Oral Short Bedaquiline-Containing Regimen 9–12 months in duration
Comparator: Long Regimen Containing New TB Drugs

Approach

We will utilize the same approach as described in section 5.1.1 to compare outcomes among people receiving the intervention and comparator regimens. Recall that we will only include people from the IPDinMDR – 2019 data set who began treatment from the year 2013 onward and who were treated in an upper-middle income country. We will conduct a sensitivity analysis relaxing the criteria for country-level income and report the outcomes.

If there are enough patients, we will conduct further sensitivity analyses within sub-groups defined by use of specific drugs, or combinations of drugs. For example, the sub-group of patients who received, or did not receive linezolid, or clofazimine, or delamanid, or bedaquiline, or carbapenems, as part of a long regimen. If any of the subgroup analyses result in < 100 patients being included in the analysis population, we will not conduct analyses. We will further conduct a sensitivity analysis repeating the approach in section 5.1.1 for other new or repurposed drugs: delamanid, linezolid, and carbapenems.

Secondary Analysis Question 3

Relative to people in the EndTB data set receiving a regimen lasting ≥ 18 months with bedaquiline and/or delamanid (for a maximum of 6-months), does a bedaquiline-containing all-oral regimen lasting 9–12 months have the same or better outcomes?

Intervention: All-Oral Short Bedaquiline-Containing Regimen 9–12 months in duration
Comparator: Long Regimen Containing New TB Drugs

Approach

We will utilize the same approach as described in section 5.1.1 to compare outcomes among people receiving the intervention and comparator regimens. Recall that we will only include people from the EndTB observational study data set who began treatment from the year 2013 onward and who

were treated in an upper-middle income country. We will conduct a sensitivity analysis relaxing the criteria for country-level income and report the outcomes.

As all patients in EndTB observational study data set received bedaquiline and/or delamanid, we will conduct further sensitivity analyses within sub-groups defined by use of these specific drugs. These will include patients who received, or did not receive, bedaquiline, or delamanid, or both bedaquiline and delamanid. If any of the subgroup analyses result in <100 patients being included in the analysis population, we will not conduct analyses.

Limitations

Within the South Africa cohorts, drug resistance testing is reflexive and generally relies solely on genotypic drug resistance tests: Xpert MTB/RIF for rifampicin and line probe assays for isoniazid and rifampicin (GenoType MTBDRplus) and fluoroquinolones and second-line injectables (GenoType MTBDRs). Because of this, resistance to drugs commonly used in short regimens (pyrazinamide, clofazimine, ethambutol, and ethionamide/prothionamide) is likely **not available** for most patients. As we are matching patients exactly on previous treatment history and pre-XDR/XDR phenotypes are excluded (as they would not be eligible for a short-regimen), we expect these unknown resistances to be similar between the groups being compared.

We do not have chest radiographic results at baseline which may have influenced a clinician's decision to treat patient with a short or long regimen. Hence this must be considered an unmeasured confounder.

Adverse events and acquisition (or amplification) of drug resistance are not reported in the South Africa cohorts, so analyses of these important outcomes are not possible.

Co-morbidities of diabetes, mental health disorders, and others are not routinely captured within EDRWeb, so the potential impact of these disorders on treatment outcomes cannot be analyzed. Extrapulmonary TB is not included in the IPDinMDR – 2019 data set and represents only 2% of patients receiving a short regimen in a previous extract of EDRWeb, so they cannot be analyzed as a subgroup as well. However bacteriologic confirmation of cure or failure/relapse is rarely obtained, which makes analysis of these outcomes more subject to observer bias. And, in drug sensitive TB results of RCT in pulmonary TB have been successfully applied to treatment of extra-pulmonary TB.

A6.1.2: PICO question 2: In XDR-TB patients or patients who are treatment intolerant or with non-responsive MDR-TB, does a treatment regimen lasting 6-9 months composed of bedaquiline, pretomanid and linezolid safely improve outcomes when compared with other regimens conforming to WHO guidelines?

Comparative analysis of outcomes and safety between current XDR-TB treatments and a new regimen of bedaquiline, pretomanid, and linezolid.

Statistical Analysis Plan, Draft.

Prepared by Dick Menzies, Nicholas Winters and Jonathon Campbell, McGill University.

PICO Question (WHO):

In XDR-TB patients or patients who are treatment intolerant or with non-responsive MDR-TB, does a treatment regimen lasting 6–9 months composed of bedaquiline, pretomanid and linezolid safely improve outcomes when compared with other regimens conforming to current WHO guidelines?

Population	Intervention	Comparator	Outcomes
XDR/TB patients or and/ or those who are treatment intolerant or with non-responsive MDR-TB: a. with additional drug resistance patterns b. with severe disease (i.e. cavitory disease on radiography or SS+) c. previously treated with 2nd line drugs or not persons with HIV (+/- ARVs) d. adults (adolescents 10–19y if available) e. With comorbidities (e.g. diabetes mellitus; malnutrition; mental disorders)	– Nix-TB trial regimen containing bedaquiline, pretomanid and linezolid given for 6 to 9 months	– Using matched controls from the individual patient dataset (*current WHO recommendations) ^[1]	<ul style="list-style-type: none"> • Successful completion of treatment (or lack of successful completion) • Bacteriological cure by end of treatment • Adherence to treatment (or treatment interruption due to non-adherence) • Treatment failure or relapse • Survival (or death) • Adverse reactions from anti-TB medicines • Acquisition (amplification) of drug resistance

Research Questions:

1. Do patients receiving BPAL have the same or better outcomes 24 months post treatment start compared to patients receiving non-pretomanid regimens containing BDQ/LZD, with total duration of treatment of 24 months (*within an allowed range of 22.5 to 25.5 months*)
2. Do patients receiving BPAL have the same or better outcomes 18 months post treatment start compared to patients receiving non-pretomanid regimens containing BDQ/LZD for with total duration of treatment of 18 months (*within an allowed range of 17 to 19 months – see Page 6*)

3. What is the occurrence of Grade 3–5 adverse events (AE), serious AE, and AE resulting in permanent discontinuation of at least one of the three component drugs of the Nix-TB regimen. (*This is descriptive only, and ideally these rates of AE would be compared to rates with a WHO recommended BDQ/LZD containing regimen, but the comparator would have to come from a data set with equally careful and thorough ascertainment of treatment associated AEs.*)

Rationale:

Despite global advances in controlling Tuberculosis (TB), this remains one of the most important communicable diseases in the world, accounting for an estimated 10 million cases and 1.6 million deaths in 2017 [WHO TB Report 2018]. Treatment of drug sensitive TB is highly effective in randomized controlled trials, however, treatment is much less effective for drug resistant strains of TB, particularly multidrug resistant TB (MDR-TB), defined as TB that is resistant to both rifampicin (Rif) and Isoniazid (INH). As TB strains become more resistant, the treatment is increasingly difficult. MDR-TB patients with additional resistance to at least one fluoroquinolone and one second-line injectable, termed extensively drug resistant TB (XDR-TB), are an increasing public health concern. There were an estimated 600,000 cases of MDR-TB in 2016, of which approximately 6.2% were XDR-TB [WHO TB report 2018].

Currently, for treatment of XDR-TB the WHO recommends the use of at least five drugs in the intensive phase and four in the continuation phase, with durations ranging from 18–24 months. In the XDR-TB patients notified to the WHO in 2015, only 34% completed treatment and 26% died. These poor outcomes are in large part due to a lack of novel drugs, as well as lengthy treatment duration and frequent drug toxicity that result in low adherence. In order to combat XDR-TB and prevent possible devastating epidemics, new drugs as well as shorter regimens that increase the likelihood of adherence are needed.

A novel, all-oral, treatment regimen consisting of bedaquiline, pretomanid and linezolid (BPaL) for 6 months has been assessed in an open-label trial. However, the trial had no comparison group. To adequately assess the efficacy and safety of this new regimen in the context of current XDR-TB treatment, it is essential to compare outcomes in NIX-TB trial patients with similar patients who received different regimens. To do this we plan to use an individual patient dataset, contributed over the past 3 years by more than 55 centres. This data now includes more than 13,000 patients with MDR and more than 3,000 patients with pre-XDR and XDR TB.

Data Sources:

Intervention group: the Nix-TB study was a one arm, phase 3, open labeled trial assessing the safety and efficacy of BPaL in patients > 14 years of age with confirmed sputum culture-positive XDR-TB or treatment intolerant/non-responsive MDR-TB. The trial was conducted between 2014 and 2019 in South Africa. The data from this trial that will be used in our analyses includes, but is not limited to: age, sex, race, medical history (BMI, diabetes, alcohol), TB treatment history, AFB smear microscopy results, Gene Xpert results, HIV and ART use, chest x-ray results, sputum culture result, patient reported severity of TB symptoms and health status, hematology/CBC/FBC, clinical chemistry, urinalysis, DST results (phenotypic), adverse events (AE) and serious AE based on DMID severity scale.

Control or comparison group: Patients included in an individual patient data meta-analysis (IPD-MA) study, that included MDR/XDR-TB patients from 53 studies/centres in 40 countries. The included patients began treatment between 1993 and 2016, but we will select patients treated after BDQ was approved for treatment of MDR-TB in 2013 (of the XDR or pre-XDR patients there were 1007 on Bdq and 956 on Lzd). These patients will be matched to patients in the Nix-TB trial, on the basis of patients' characteristics, DST, drugs used, and other factors that will affect treatment propensity (described in detail below).

Regimens:

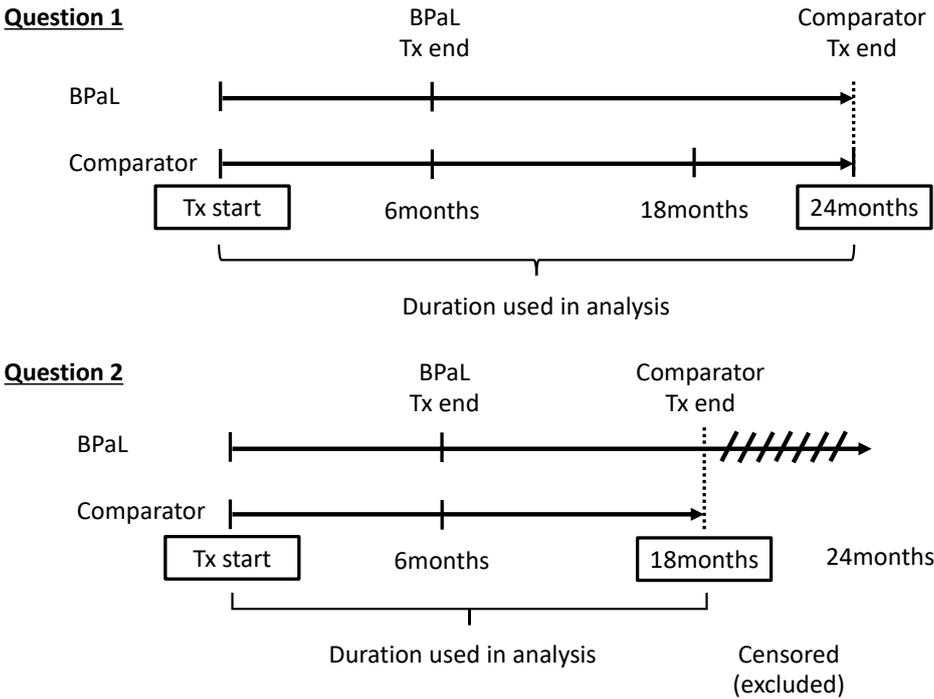
Intervention: The Nix-TB regimen consists of bedaquiline (Bdq, at a 400 mg once daily for 2 weeks then 200 mg 3 times per week), pretomanid (200 mg once daily) and linezolid (Lzd, at a daily dose of 1200 mg/day) for 6–9 months (9 months if sputum culture positive at 4 months). These patients were followed for up to 24 months after treatment end.

Comparison (control): 4 comparator regimens will be assessed. Patients receiving regimens for up to 25.5 months (Q1) or 19.0 months (Q2) that contained:

- Bdq plus Lzd plus other anti-TB drugs,
- Bdq plus others,
- Lzd plus others,
- Neither Bdq nor Lzd, but other drugs.

No patients in the IPD received pretomanid. In the Nix-TB trial there are treatment start and stop dates, and in the MDR IPD we have precise total/planned treatment duration until outcome. Thus, analyses will be conducted comparing patients in both regimens from time of treatment start to outcome or end of the specified analytical duration.

The regimens used in the IPD-MA for XDR-TB are significantly longer than the 6–9mo BPaL regimen in the Nix-TB study. This will present difficulties in comparing end-of-treatment outcomes, particularly failure and death. Patients treated with the conventional longer regimens have a much longer time during which they could die (of TB or other causes) or fail. Patients treated with conventional 18 or 24 months regimens may have sputum culture conversion at 6 months, but later revert to culture positivity. If treatment had been only 6 months, they would have been considered a ‘cure’, and then a relapse. Similarly, if a patient dies in the 15th month of conventional XDR treatment, that is, by definition a ‘death during treatment’ whereas if the regimen had been only 6 or 9 months, this would not have been a death during treatment. It is therefore necessary to assess outcomes from treatment start to a specified duration of time where after any events that occur in the comparator groups are censored, as diagramed below (Tx = treatment). Therefore in our analyses of treatment outcomes, all relapses or deaths (regardless of cause) occurring post-treatment in NIX-TB patients, up to 25.5 months (Question 1) or up to 19.0 months (Question 2) post treatment start, will be considered to have the outcomes of failure/relapse, or death and considered equivalent to “during treatment” failure or deaths with conventional regimens.



Outcome Definitions:

The PICO lists seven distinct outcomes: (i) Successful completion of treatment, (ii) Bacteriological cure by end of treatment, (iii) Adherence to treatment (or treatment interruption due to non-adherence); (iv) Treatment failure or relapse, (v) Death during treatment, (vi) Adverse reactions from anti-TB medicines, and, (vii) Acquisition (amplification) of drug resistance

In the analyses, we will combine failure and relapse, and also combine completion and cure as success. We will estimate odds of relapse free treatment success vs several combinations of poor outcomes, and also examine LTFU vs other outcomes – as summarized below.

Adverse reactions from anti-TB medicines, and Acquisition of drug resistance during treatment can NOT be analyzed using the IPD data as this information is not routinely captured in many data sets. These two outcomes were measured in the NixTB study carefully, so can be described. As discussed below a different source of comparator data would be ideal. This has been discussed and agreed upon in principle by investigators with the EndTB and the Alliance, and is now described briefly in the sensitivity analyses.

The outcomes are defined in the Nix-TB protocol as follows:

Bacteriologic failure: during the treatment period = failure to attain culture conversion to negative; bacteriologic relapse: during the follow-up period = failure to maintain culture conversion to negative status in culture, with culture conversion to positive status with a *Mycobacterium tuberculosis* (M.tb.) strain that is genetically identical to the infecting strain at baseline;

Clinical failure: a change from protocol-specified TB treatment due to treatment failure, retreatment for TB during follow up, or TB-related death.

In the IPD cohorts treatment outcomes were defined according to the WHO guidelines, summarized below:

WHO 2005 (Laserson) Outcome Definitions (44/53 studies in our IPD used these definitions or definitions based on bacteriologic criteria)

Outcome	Definition
Cure	Completed treatment according to program protocol and has at least five consecutive negative cultures from samples collected at least 30 days apart in the final 12 months of treatment. If only one positive culture is reported during that time, and there is no concomitant clinical evidence of deterioration, a patient may still be considered cured, provided that this positive culture is followed by a minimum of three consecutive negative cultures taken at least 30 days apart.
Complete	Completed treatment according to program protocol but does not meet the definition for cure because of lack of bacteriological results (i.e. fewer than five cultures were performed in the final 12 months of treatment).
Failure	Treatment will be considered to have failed if two or more of the five cultures recorded in the final 12 months of therapy are positive, or if any one of the final three cultures is positive. (Treatment will also be considered to have failed if a clinical decision has been made to terminate treatment early because of poor clinical or radiological response or adverse events).
Death	A patient who dies for any reason during the course of MDR/RR-TB treatment
Lost to Follow-up	A patient whose treatment was interrupted for two or more consecutive months for any reason without medical approval.

WHO 2013 Outcome Definitions: 9/53 studies in our IPD used these definitions

Outcome	Definition
Cure	Treatment completed as recommended by the national policy without evidence of failure AND three or more consecutive cultures taken at least 30 days apart are negative after the intensive phase (or Month 8 if no intensive phase).
Complete	Treatment completed as recommended by the national policy without evidence of failure BUT no record that three or more consecutive cultures taken at least 30 days apart are negative after the intensive phase (or Month 8 if no intensive phase).
Failure	Treatment terminated or need for permanent regimen change of at least two anti-TB drugs because of: (1) lack of conversion by the end of the intensive phase, or (2) bacteriological reversion in the continuation phase after conversion to negative, or (3) evidence of additional acquired resistance to fluoroquinolones or second-line injectable drugs, or (4) adverse drug reactions.
Death	A patient who dies for any reason during the course of treatment
Lost to Follow-up	A patient whose treatment was interrupted for 2 consecutive months or more.

For our analysis, we will use different outcome definitions for patients in the Nix-TB trial from patients in the IPD-2019. For Nix-TB, the detailed clinical and microbiologic data will be used to verify the investigator defined end-of-treatment outcomes. Assuming they match their definition outlined in their protocol, we will use their investigator defined end-of-treatment outcomes, plus account for relapse during up to 18 months of post-treatment follow-up. For the EOT outcomes in the IPD-2019, we will use the investigator defined outcomes as well. In the data set we have now, 44/53 data sets used 2005 WHO guidelines to define these outcomes, and 9/53 stated they used WHO2013, but all data sets contained sufficient information to verify that almost all patients met microbiologic outcome definitions (ie fit WHO2005). Therefore we have already redefined the outcomes of the nine studies that used the 2013 guidelines to conform to the 2005 WHO criteria. In summary, within the IPD-2019 data set, we will verify investigator defined outcomes, reclassify if applicable to meet microbiologic criteria (WHO 2005 criteria) and compare these end-of treatment outcomes in the analysis to the NixTB investigator defined outcomes (including relapse as above). The coding of all information from the Nix-TB study will be verified with Alliance staff, and all discordant outcomes will also be verified manually (ie if a specific patient is classified as having treatment success in the original data set but does not meet that definition using the data we have – this will be manually checked)

Analytic approach:

Descriptive statistics:

Treatment outcomes: as described above, the treatment outcomes assigned to patients in the NixTB trial will be reclassified (potentially) according to WHO 2005 definitions, using the detailed clinical and microbiological information available from the Alliance. The concordance of these outcome swill be verified as a first step. Any discordance will be verified manually and the data and programming may also be verified with the Alliance.

Duration: As the treatment trajectory of MDR/RR-TB represents the complex interaction of patient, provider and health system capacities and constraints, there may be deviations from intended durations of therapy and number of drugs used. In the IPD data, we will examine descriptively the

distribution of treatment duration for persons with successful treatment who received one of the four comparator regimens. Based on these descriptive analyses, we will select cut-points (ideally using inter-modal points) that appear to best define the duration of treatment that can be called '18 months' and '24 months' (e.g. how far before or after the exact duration of 18 or 24 months do we accept as still meeting the definition of a regimen of 18 or 24 months to include in this analysis?). A second issue is the planned duration in persons who die, or are lost to follow-up ('default'), or fail and therapy is stopped early. These patients will not have an actual treatment duration of 18 or 24 months, but of course must be included in the analyses to avoid bias. To identify persons with these outcomes we will use the planned duration (listed in many data sets). In some data sets planned duration is not given. In these we will examine the frequency distribution of duration in those patients treated *successfully* at the same centres. If this is unimodal, then the mode will be considered the planned duration. If this is a more complex distribution then we will predict the duration based on key predictors of duration (age, extent of resistance, extent of disease and specific drugs used) at that centre.

Patient populations Before analysis of each research question, we will conduct a descriptive analysis for the BPAL and four comparator groups (detailed below), looking at key characteristics including: age (continuous and 0–14 vs. 14+ and 10–19 vs. 19+), sex, previous treatment history (drugs received and outcome), baseline acid-fast bacilli smear result, number of drugs received during treatment, total number and type of drugs resistant to (not double-counting 'similar' drugs of ethionamide/prothionamide and cycloserine/terizidone, for example), presence of specific drugs in the regimens (e.g. bedaquiline, linezolid, clofazimine, moxifloxacin/levofloxacin, delamanid), and country of treatment. This will help clarify if there are systematic differences between the people who received each regimen, and possible differences in characteristics and outcomes where each regimen was used. The information elicited from this analysis will be used to inform further variables for matching and/or adjustment described below, and addition of a random-effect for country of treatment (or exact matching by country). Thus, within the approach for each question, the listed variables are an a priori list for inclusion, but may be modified based on data completeness and availability, and further sensitivity analyses including/excluding other variables may be developed based on the results of the descriptive analyses. The descriptive analysis is also intended to determine how many individuals would be included, and excluded due to regimen composition. In addition, for non-Nix-TB patients we will include the number of drugs received during treatment and presence of specific drugs in the regimens (e.g. Bdq, Lzd, clofazimine, moxifloxacin/levofloxacin, delamanid).

Comparing efficacy of regimens::

Q1: Do patients receiving BPAL have the same or better outcomes 24 months post treatment start compared to patients receiving one of 4 comparator non-pretomanid containing regimens, with total duration of treatment of 24 months (*within an allowed range of 22.5 to 25.5 months*). These four comparators are: (1) Bdq+Lzd+others, (2) Bdq+others, (3) Lzd+others, and (4) neither Bdq or Lzd containing regimens.

Comparisons:

1. Relapse free treatment success (defined as cure or treatment completion) vs. bacteriological/clinical failure or relapse.
2. Relapse free treatment success vs. death
3. Relapse free treatment success vs. clinical/bacteriological failure or relapse, or death.
4. Relapse free treatment success vs. clinical/bacteriological failure or death or relapse or lost to follow-up/default.

Our approach will use a combination of exact matching and propensity score-based matching on several covariates to select comparator groups from the IPD-MA that are as comparable as possible to the patients who received BPAL, and thereby minimize bias and confounding. All patient matching

will be performed by an algorithm in our statistical software that will randomly select from the best patient matches. This algorithm will not include outcome. The variables used for exact matching will depend on the distribution of characteristics in the Nix-TB data and will be finalized once we are able to explore this in detail. For exact matching, we anticipate matching on two variables we consider critical: (1) XDR vs non-responsive/intolerant MDR-TB; and, (2) HIV infection and ART-use. Once we have matched on these two critical variables, we intend to further match exactly, if possible, based on the following important variables: (3) number of drugs to which the patient's isolate is resistant, and, (4) previous FLD/SLD use, and if the data allows, also (5) disease severity (indicated by one of: AFB smear, cavitory and/or Bilateral disease). These variables will ensure that patients with clinical profiles which predict their treatment outcomes will be compared. There may be issues with identifying patients in the IPD cohort who have non-responsive/intolerant MDR-TB. If so, we will select IPD patients who have previous SLD use. In addition, we will match patients based on PS, calculated using age, sex, and remaining variables of the three important variables listed above which could not be used for exact matching (AFB smear, Cavitation, number of drugs resistant to, etc). We will allow a calliper distance equal to 0.2 of the standard deviation of the logit of the propensity score. Matching will be done with replacement. If no potential matches fall within the calliper distance, the next closest match to 0.2 of the standard deviation will be selected. We will assess the success of matching by assessing the balance of confounders between the two groups. Additionally, we will determine how many patients were matched more than once to different patients in Nix-TB. This will indicate the need for consideration of methods to control for the effects of independence and increased variance on model fit, from having multiple matches.

The power of this analysis is limited by the small number of patients in the NixTB study. To enhance power, we will match up to 4 controls from the IPD to each Nix-TB patient, depending on whether there are sufficient numbers of suitable matches to each NixTB patient (Four is considered the optimal number to enhance power, after which little added power is gained by matching further controls).

For each outcome, we will conduct logistic regression using mixed-models including random-intercepts for each matched 'pair' and, depending on what we find for the descriptive analysis, for country of treatment. We will not include random-slopes as our experience is that there are significant convergence issues when these random-effects are also included. Outcomes will be dichotomous (i.e. the outcome occurred during the specified analysis duration = 1 vs. the outcome not occurring = 0). The logistic regression analysis will calculate adjusted odds ratios and associated 95% confidence intervals. We will further conduct binomial regression, using fixed effects, on the 'matched' group to calculate adjusted risk differences and their associated 95% confidence intervals.

For post-treatment relapse, we will first determine in which data sets of IPD-2019 this outcome was assessed. Then we will obtain information from the study authors on the methods of ascertainment, the intensity of follow-up visits, and the duration of follow-up. This will give us an idea of the comparability of this outcome with that of the NixTB study. In addition duration of follow-up and timing of relapse may not be available for all individuals or centres. Therefore we will present cumulative incidence of relapse in each study as the proportion of patients relapsing out of the total number of patients that successfully completed treatment.

This analysis will be repeated for each of the four comparisons listed above.

Q2: Do patients receiving BPAL have the same or better outcomes 18 months post treatment start compared to patients receiving non-pretomanid regimens containing BDQ/LZD for with total duration of treatment of 18 months (*within an allowed range of 17 to 19 months*)

We will use the same methods outlined in Q1, except that duration used in the analyses will be 18 months, and any event occurring in post treatment follow-up of the BPAL group after this period will be censored.

Q3: Descriptive analysis of the occurrence of Grade 3–5 adverse events (AE), serious AE, and AE resulting in permanent discontinuation of at least one of the three component drugs of the Nix-TB regimen. Three separate but related outcomes.

We will describe the occurrence of any of the secondary outcomes listed above to present results on the safety related measures recorded in the Nix-TB data. Permanent discontinuation of each component drug of the BPAL regimen will be analysed, and the stoppage of one drug but continuation of the others will be considered a drug associated AE for the drug that was stopped. In addition, we will also investigate the effects of dose reduction. We will use proportions or mean (standard deviations) where appropriate. This will not be compared to any of the comparator groups in our IPD listed above.

Comparator: As noted earlier, this safety analysis is limited by the lack of an adequate comparator population, as AEs were not ascertained with the same methods in the IPD-MA studies. Ideally these rates of AE would be compared to rates with a WHO recommended BDQ/LZD containing regimen, but the comparator would have to come from a data set with equally careful and thorough ascertainment of treatment associated AEs. The only data set to which we have access with comparable methods of systematically assessing AEs is the EndTB data set. We suggest that the AEs' reported – in patients who received one of the 4 types of regimens listed above in the EndTB study, would be compared with the AEs reported in NixTB. Note that this suggestion would require the agreement of the EndTB investigators as well as the Alliance)

Sensitivity analyses:

We will conduct the same analyses outlined in Q1 and 2 using different subpopulations of patients to select comparators:

(1) Match patients in the Nix-TB trial to patients in IPD-2019, using ONLY South African cohorts. By limiting to South African cohorts, we will match to patients from the same region, which may account for unique characteristics of the patient populations.

(2) Match patients in the Nix-TB trial to patients who received treatment ONLY in high income countries. This may result in a better match on the basis of resources available for follow-up.

(3) Limit comparisons to patients from studies where relapse was ascertained for at least 6 months of follow-up post treatment end. We will contact authors from these studies to obtain any additional information re definition and methods for ascertainment for relapse.

(4) to compare AE between Nix-TB and a suitable comparator group, we need to ensure we have patient populations that are comparable, but also that AE are ascertained in a similar way. In the IPD-2019 we did not have systematic methods to detect, define, investigate manage or report AEs. Thus, we will match patients in the Nix-TB trial to those from the EndTB data, as AE were collected and documented with similar intensity of monitoring to Nix-TB.

Limitations:

There may have been substantial selection bias into the Nix-TB trial, as there was no randomization. Hence participation could have been influenced by physician selection of patients judged better able to tolerate the regimen, or that were sicker, with fewer treatment options (i.e. selection bias could go either way). There is also the potential for bias in the comparison of patients in NixTB with the IPD patients due to differences in loss to follow up. We can lessen, but not eliminate the impact of these biases, by exact and propensity score matching patients in the Nix-TB study to patients in the MDR IPD. This matching should result in patient groups that are balanced with respect to measured confounding factors, which should enhance clinical utility of the results. There may also be limitations in achieving four exact matches on all variables for each NixTB patient. This is why we have listed variables in order of their importance, and PS matching on the same variables will be used if exact

matching cannot be achieved. In addition, we will use PS matching with a wider caliper distance to achieve matching, if necessary.

Additionally, as noted above, the data on safety is limited in our IPD, and so we will be unable to compare the secondary safety outcomes between patients in NixTB and the IPD.

Relapse was not measured systematically in most studies included in the IPD-2019. Hence this may have been under-estimated. As well for patients treated for 24 months, they finish treatment at the same time as post treatment follow-up ends for the NIXTB patients. So to include post-treatment follow-up will bias results as different lengths of Follow-up can lead to differences in outcomes due to other events. Relapse can be measured for 6 months if treatment is only 18 months, but early relapse rates tend to be highest – so this may overestimate cumulative relapse rates.

Sept 6, 2019

A6.1.3: PICO questions 3: In MDR/RR-TB patients, does a treatment regimen containing bedaquiline for more than six months safely improve outcomes when compared with bedaquiline for up to six months as part of longer regimens otherwise conforming to WHO guidelines? and 4: In MDR/RR-TB patients, does concurrent use of bedaquiline and delamanid safely improve outcomes when compared with other treatment regimen options otherwise conforming to WHO guidelines?

Statistical Analysis Plan (draft) for PICO 3 & 4 using the EndTB observational study and the IPD2019 data: prepared by Dick Menzies & Jonathon Campbell, McGill University: Sept. 6, 2019

WHO Guidelines group – PICO questions

Question 3. In MDR/RR-TB patients, does treatment with bedaquiline for more than six months safely improve outcomes when compared with treatment up to six months as part of regimens otherwise conforming to current WHO guidelines?

Population	Intervention	Comparator	Outcome
<p>MDR/RR-TB patients:</p> <p>a. Simple MDR-TB (no additional resistance, risk factors)-</p> <p>b. with additional drug resistance patterns, but not XDR</p> <p>c. with XDR-TB</p> <p>d. with severe disease (i.e. cavitory disease on radiography or SS+)</p> <p>e. previously treated with 2nd line drugs or not</p> <p>f. children (0–14y) / adults (adolescents 10–19y if available)</p> <p>g. persons with HIV (+/- ARVs)</p> <p>h. pregnant women</p> <p>i. people with diabetes mellitus</p> <p>j. extrapulmonary disease</p> <p>k. malnutrition</p>	<p>- Use of bedaquiline as part of the treatment regimen beyond six months of treatment</p>	<p>- A regimen containing bedaquiline for six months of treatment only</p>	<ul style="list-style-type: none"> • Successful completion of treatment (or lack of successful completion) • Bacteriological cure by end of treatment • Adherence to treatment (or treatment interruption due to non-adherence) • Treatment failure or relapse • Survival (or death) • Adverse events with anti-TB medicines • Acquisition (amplification) of drug resistance

(PICO 3) Effectiveness of prolongation of bedaquiline beyond 24 weeks:

Three specific questions – related to use of different information sources

1. Relative to bedaquiline (BDQ) use for 24 weeks (6 months), does prolongation of bedaquiline beyond 24 weeks (within properly designed regimens) result in improved treatment outcomes for patients with RR-TB in the EndTB observational study?
2. In the IPD-2019 data set, are treatment outcomes improved in patients who take more than 6 months of BDQ compared to BDQ for 6 months, and to no BDQ?
3. In the combined IPD-2019 and EndTB data sets, are treatment outcomes improved in patients who take more than 6 months of BDQ compared to BDQ for 6 months, and to no BDQ?

Five Outcomes of interest for the Proposed Analyses:

End of treatment:

1. Relapse free treatment success (or simply success, if relapse not assessed) vs fail/relapse
2. Relapse free treatment success (or simply success if relapse not assessed) vs fail/relapse/death
3. Relapse free treatment success (or simply success if relapse not assessed) vs death alone
4. Relapse free treatment success (or simply success if relapse not assessed) vs fail/relapse/death/LTFU (i.e. good vs all bad combined)

During therapy:

5. Adverse events (AE) – defined as serious AEs that resulted in permanent discontinuation of that medication.
 - This information is available in considerable detail in the EndTB data following the MSF severity scale – definitions provided at the end of the document. It is less consistently available [~8000 patients in 30 datasets] and defined as grade 3–5 or serious AE that resulted in permanent discontinuation of that medication and may be differentially ascertained in the IPD2019. This may confound comparisons of AE rates – particularly for drugs that are used more, or less in the two datasets.
 - If permission granted from all parties, we will also compare AE in EndTB data set with AE detected in NixTB study. These two studies had more comparable intensity of AE detection, although different definitions, and methods for AE.

N.B. Adherence (as % doses taken or other measure) is available in the EndTB data set, but not the IPD2019. Thus, this will only be described for the EndTB data set.

DATA SETS to be used in PICO 3 analyses:

IPD2019

In 2018 an IPD was assembled of 53 data sets from 40 countries/regions containing records for 13,000 patients with MDR-TB. This IPD-2018 data set was analyzed to answer a number of PICO questions developed by a WHO MDR-TB guidelines development group (GdG). These guidelines have since been published. This IPD-2018 was itself based on an IPD data set assembled in 2016–17 to answer questions of a GdG of the CDC/ATS/IDSA/ERS. These guidelines have not yet been published, but the analyses that informed this set of guidelines were published in the Lancet in Sept 2018.

Hence the IPD-2019 represents an update of the IPD-2018. We anticipate adding data from one national surveillance programs – in South Africa. We will delete the previous records of patients treated in the EndTB observational study, that were included in the IPD-2018, to avoid duplication and overlap with the new data set from EndTB. We may also add two other data sets – provided in response to a public call for data contributions.

EndTB:

1094 patients with MDR-TB were treated with bedaquiline- and/or delamanid-containing regimens between 1 April 2015 and 31 March 2017. They were followed as part of an observational study – executed by three NGO’s – PIH, MSF and IRD.

Rationale

Why the question of optimal duration of BDQ is challenging.

There are several important potential sources of bias in analysis of duration of therapy in observational studies. We note 2 examples here:

i) Patients who live longer on RR-TB treatment can be treated longer with bedaquiline. Simply comparing the outcomes among people who survive to receive the longer treatment to those who didn’t receive the longer treatment can result in an overestimate of the benefits of the longer treatment. This bias is called “immortal time bias”.

ii) Bedaquiline prolongation varied by patient factors and by country and time. Bedaquiline was prolonged most often in patients with baseline and on-treatment risk factors for poor outcome, i.e., patients whose initial response to treatment was poor, whose regimens without bedaquiline were considered weak, or whose resistance profile or treatment-emergent toxicities limited treatment options. Simply comparing the outcomes among people who got prolonged bedaquiline to those who did not could underestimate the benefits of prolonged bedaquiline. This bias is called (time-varying) confounding by indication.

In the EndTB study, across countries and over time, the use of prolonged bedaquiline varied. Some countries prolonged bedaquiline in nearly all patients, while in other countries, bedaquiline prolongation was not permitted by national guidance. At other sites, bedaquiline prolongation became more common over time as clinicians became more comfortable with the drug.

It’s important to acknowledge the focus on bedaquiline (and delamanid) duration is exceptional, as other drugs (i.e. linezolid) have analogous issues in that people can receive them longer if they don’t experience treatment-limiting toxicity, which in linezolid’s case is ~1 in 5 people. Thus, while the analysis approach that we propose attempts to minimize many sources of bias, we acknowledge it may not be possible to manage all biases.

Defining ‘margins’ in duration analyses:

Since start dates and end-dates of specific drugs are available in the EndTB dataset the duration can be defined to the precise number of days. But, in reality, the precise duration depends on timing of visits, and events such as missed visits, cancelled clinics, holidays or even just bad weather can result in variation of up to a month around the time when a specific drug is stopped. Hence we will first define a frequency distribution of duration for BDQ, in order to define the optimal cut-points for each duration. *As an example, from recent analysis of one data set – the frequency of actual duration in days of one drug is plotted (see Annex 1). This plot shows a large number of persons with duration centred around 6 months, but we would conclude that for our purposes “6 months” duration should include patients with duration of 150 to 200 days.*

Therefore, in this SAP when we refer to duration of “24 weeks”, or “36 weeks”, or “52 weeks” we mean **N weeks + NN weeks**, with the value of NN to be determined from the initial descriptive analysis.

Challenges in comparing results using the EndTB data, and the IPD2019 data:

There are several important potential differences between the patient populations, treatment, and other factors between these two sources of individual patient data.

i) The EndTB study was conducted by agencies and at centres with different patient populations, as well as resources and clinical expertise, from those in the IPD-2019. The IPD-2019 contains data from a greater variety of settings including samples of patients included in national MDR surveillance systems. Hence outcomes may be different in the IPD data-set – independent of measured clinical and treatment characteristics due to unmeasured confounding. While for some datasets in the IPD there may also be differences in outcomes, we will quantify differences between the IPD and EndTB descriptively. As we have done in the past, mixed models will be used to account for heterogeneity between datasets.

ii) There is a perception that the EndTB sites have more complicated patients who have comorbidities and other challenges (homelessness, hx of incarceration, IV drug and alcohol use) that make developing an effective regimen especially difficult;

iii) the extent and quality of data, particularly on-treatment, longitudinal observations; follow-up for recurrent disease (ie for relapse);

iv) methods for collection and reporting of safety data;

v) extent of prolongation of Bdq;

vi) In the EndTB data set all patients received DLM or BDQ or both. But none got *neither* of these drugs – in contrast to large numbers of patients in the IPD data set who received neither. If DLM is very effective, this could substantially affect comparisons of the no BDQ group in the IPD2019 cohort to the no BDQ group in the EndTB data set since all these patients received DLM. We will, therefore, control for exposure to DLM in all analyses.

vii) overall willingness to use Bdq/Dlm;

viii) outcome classification.

Some of these differences are sources of variability within the IPD as well (e.g., bdq use, outcome classification, safety, etc). However, the IPD2019 data set includes data from over 13,000 patients, treated in 53 studies in 40 countries/regions. The diversity of patients, disease, providers, and treatments provides an excellent opportunity to compare and contrast treatment related covariates in very different settings and should result in more generalizable findings.

The results from Questions 1 and 2 will see if the effect of bedaquiline use beyond six-months is similar in EndTB and the IPD, after accounting for numerous possible confounders. Any confounding effect of DLM will be managed by controlling for delamanid in all analyses. The analysis for Question 3 will analyze the benefit of BDQ for 6 months, vs longer vs a group that did not receive BDQ while adjusting for use of delamanid as well as the data source or study (ie EndTB or IPD2019) and other covariates. In other words, in this analysis the reference group (comparator) will be the group who received BDQ for 6 months. While the IPD2019 data set has important limitations, compared to the EndTB data set, we believe there are important advantages of conducting the analyses of BDQ duration using both the IPD2019 data set and the EndTB dataset. These advantages include the greater diversity of settings and patients in which this question can be addressed – enhancing the generalizability of results. As well the diversity of settings increases the likelihood of diversity in patients receiving longer duration of BDQ – potentially reducing unmeasured confounding relative to actual differences in detectable treatment benefits. Finally, this should increase the number of patients who received any single regimen/combination of medications/duration of BDQ, so simply enhancing power.

Overview of the analyses for the three specific Questions (end of treatment outcomes)

Q1: Relative to bedaquiline (BDQ) cessation at 24 weeks, does prolongation of bedaquiline result in improved treatment outcomes for patients with RR-TB in the EndTB observational study?

Comparator: use of bedaquiline for 24 weeks **in EndTB**

Intervention: use of bedaquiline for >24 weeks **in EndTB**

Sensitivity analysis comparator: use of bedaquiline for 24–36 weeks in EndTB

Sensitivity analysis Intervention: use of bedaquiline for >36 weeks in EndTB

Defining a Time Cut-Off for Bedaquiline Use

As discussed above, it seems likely that BDQ use will not be precisely 24 weeks in many patients, due to the vagaries of dates of visits, drug supply, delays in starting, or stopping, or missed doses. We want to know, as best as we can, if 6 months, or 9 months is planned – what, in reality is the duration? If we restricted analysis to those who got exactly 180 or 270 days – we would have about 20 people. So, we need to account for some variation in actual duration. Hence, we propose to examine the frequency distribution of duration of BDQ to attempt to find ‘inter-modal’ cut-points that best discriminate patients treated with BDQ for ‘24 weeks’, or 36 weeks, or 52 weeks. **ONLY TO DEFINE THIS CUT-POINT**, we will exclude patients who died or were lost to follow-up to ensure that the population assessed are only those who *could have* received the drug to this point. This will also be done for the sensitivity analysis population. It should be recognized that any selected timepoint will necessarily dichotomize some patients who received only a few days difference of bedaquiline treatment, however by selecting the inter-modal points, this problem should be minimized. The rest of this plan below is written assuming 24 weeks is selected but will be adjusted based on our findings here and may represent a range (e.g., 20–26 weeks of bedaquiline).

Step 1: Descriptive Analysis of the Population Subgroups

We will then undertake descriptive analysis to characterize those who did not receive BDQ, those who received BDQ for at least one month, but <6 months, and those who received at least 24 weeks – divided into two groups: (BDQ for 24 weeks; and BDQ for >24 weeks). We will also sub-divide the group with BDQ for >24 weeks into persons who were treated with BDQ for 24–36 weeks, and those who received BDQ for >36 weeks. The description will include: site where treated, baseline/pre-treatment characteristics: sex, age, HIV and ART treatment, other comorbidities, prior TB treatment, AFB smear, CXR results, DST results (both in terms of resistance patterns and total number of drugs resistant to), year of starting treatment, and number of likely effective drugs used initially. Consideration of the total number of drugs resistant warrants further explanation. It is possible that for drugs with DST that is perceived to be unreliable (e.g. cycloserine, PAS), in the event they were found susceptible, they were reinforced, or in the event they were found resistant, the drug was used anyways. Likewise, there may be reasons some drugs had DST done on them, perhaps due to previous exposure or a regimen was failing. Thus, for these reasons it is important to consider the total number of drugs a patient is resistant to, as well, the more drugs a person is resistant to, the more limited treatment options are, and the more probable it is that bedaquiline is extended. So, we plan to adjust for this covariate in statistical analysis. Because of this, we propose to count the number of drugs individuals are resistant to drugs other than fluoroquinolones and second-line injectables (which will be accounted for in the composite resistance pattern of MDR, pre-XDR, and XDR) – we will assume cross-resistance to similar drugs (e.g. ethionamide and prothionamide or cycloserine and terizidone, or amikacin and kanamycin – unless there is DST for both drugs). There are also sensitivity analyses surrounding this, detailed in the appropriate section below. We are also interested in events during treatment that would affect clinical decisions at the time points of interest – meaning at 6, 9 and 12 months. These would include: culture and DST results indicating any newly detected drug resistance from cultures

of samples collected prior to the end of week 16 (we assume that at the time of the 6-months evaluation, that cultures and DST would be available only for samples collected prior to weeks 16 and 12 respectively). We would examine AFB smear and CXR results from 24 weeks, as well as number of drugs permanently stopped due to intolerance / AEs up to 24 weeks – all of which information would be available at the 6-month evaluation and could be indications for extension of BDQ. This descriptive analysis will be further stratified by site to determine if there are unique site characteristics. We will further describe exact resistance patterns of all drugs (Resistant, Susceptible, Not Done/Unknown) to see how common testing was and prevalent resistances were when testing was done. We will repeat the descriptive analysis using appropriate time-points for the proposed sensitivity analysis.

Step 2: Exploring the use of delamanid – descriptively

In the same way as bedaquiline, we will descriptively examine the characteristics of people who received delamanid (no BDQ) or did not receive delamanid, and compare those to patients who received DLM and BDQ and to patients who received BDQ alone. One issue that will be explored is whether delamanid was used from the start, or introduced after, since many patients received DLM after several months of therapy. This raises the possibility of indication bias, since those who had DLM added are likely to have been responding poorly, but on the other hand, also immortal time bias since patients had to survive longer to have a chance of later introduction of delamanid. (This is where separate analyses of failure, and death may be especially helpful). Thus we will describe median (IQR) time of delamanid start after treatment start and also how many started within 0–3 months, 4–6 months, 7–9 months, or 9+ months after treatment start. We will also look at these characteristics by site, as policies regarding use may vary between sites, and could be an important potential determinant of use. We will examine whether characteristics of patients was ‘balanced’ between the treatment groups as defined above. Even if there is no evidence of substantial confounding of patient characteristics with DLM use, we will consider delamanid as a unique drug given and adjust for its use in the multivariable analyses described below (like LZD or later generation FQN, for example).

Step 3: Analysis of duration of BDQ

To assess the benefit of bedaquiline extension beyond 24 weeks, we plan two analytical methods and will compare the results. We will do this for each of the **four** outcomes defined above each method will be repeated for sensitivity analysis.

Method 1: Exact and Propensity score matching. Patient characteristics at baseline that are missing will be imputed using multivariate imputation via chained equations. Note – exposure and outcome data will never be imputed. We will match persons who received bedaquiline for 24 weeks to those who received it longer using a combination of exact and propensity score based matching for covariates that are likely to influence treatment extension at week 24. These covariates include: Baseline characteristics: Resistance to FQ or SLI, total Number of drugs resistant to, AFB smear, Cavitation on CXR, HIV-coinfection and ART use, previous treatment history (first-line drugs only or also second-line), age and sex. During-treatment characteristics: culture status at 12 and 16 weeks (ie culture conversion or non-conversion), number of acquired/new resistances at 16 weeks (0, 1, or 2+), cumulative number of drugs stopped due to adverse events at week 24 (0,1 or 2+), radiologic findings at week 24, treatment at Week 24 including use of receipt of fluoroquinolone, linezolid, and delamanid and number of other likely effective medications. As we have done in past analyses, we attempt to match exactly on as many covariates as possible (recognizing that within the EndTB data set this may be challenging), and propensity score match on the remainder. The covariates selected for exact matching are those with strongest association with the outcomes of interest for that analysis. We will propensity score match on the remaining covariates listed above. We again will consider clustering by site and further adjustment by year of treatment start and/or country level income. We will estimate adjusted odds ratios and associated 95% CI. For each analysis, the matched groups will be examined in standard reports looking at the improvement (or not) in balance of characteristics between the two groups from the matching algorithm.

Method 2: Survival Analysis using inverse probability of treatment weighting (IPTW) and inverse probability of censor weighting (IPCW). The survival analysis will begin with everyone included in the analysis population who received treatment with bedaquiline for at least six months (i.e., baseline=month 6). We will examine exposure in two ways. (1) Dichotomous: received only six-months of BDQ vs. received more than six-months of BDQ; (2) Continuous: treating months of BDQ beyond six as a continuous variable. The outcome of interest will be failure/relapse/death (composite). We will treat loss to follow-up as a censoring event. We will include patient time until the end of follow-up for relapse. We will construct a baseline patient profile based on what would be clinically known at month 6, including time-fixed covariates of age, sex, previous treatment history, etc. From here, we will update information each month for patients that is time-varying: receipt of concomitant drugs (type and number), number of AE requiring drugs to be stopped, culture status, radiologic findings. Using these time-fixed and time-varying covariates, we will estimate the IPCW for the population (i.e., for LTFU). We will also estimate the IPTW based on timing of BDQ stop (i.e, for people stopping BDQ at month 6, IPTW will be estimated for all time points; for people continuing to receive BDQ beyond month 6, IPTW will be estimated until the time of BDQ stop, then considered constant). We will then run a survival analysis, clustering by patients and centre and incorporating the calculated IPCW and IPTW weights. This analysis will be run for both dichotomous and continuous outcome. For the continuous outcome, please see sensitivity analyses where we consider the benefit of bedaquiline to be non-linear and we describe alternate analytic methods to be explored (e.g. g-formula).

Q2: In IPD-2019 data set, are treatment outcomes improved in patients who take more than 6 months of BDQ compared to no BDQ and BDQ for 6 months?

Exposure 1: No use of Bedaquiline (defined as <30 days) in IPD2019

Reference (comparator) 1: Use of bedaquiline for 24 weeks in IPD2019 (exact duration based on descriptive analysis as in Q1).

Exposure 2: Use of bedaquiline for >24 weeks in IPD2019 (exact duration based on descriptive analysis as in Q1).

We propose three analyses: No BDQ to 24 weeks, and 24 weeks to BDQ to >24 weeks, plus a combined – where BDQ use is a 3-level categorical variable (none, 24 weeks, and >24 weeks). Since this is all within IPD2019 – We propose to match patients exactly on the **baseline** characteristics of fluoroquinolone and second line injectable resistance, HIV co-infection and ART use, and country-level income (using World Bank categories). We will match patients further using propensity score matching on age, sex, previous TB treatment (first line and second line drugs), extent of disease (AFB smear and/or cavitation on CXR), use of linezolid, use of fluoroquinolones, use of delamanid, BMI (dichotomized as underweight or not), and number of other effective drugs used in the initial regimen. Because of limitations of lack of detailed information about changes and events during therapy, we cannot include these variables in this analysis.

Q3: In the combined IPD-2019 and EndTB data sets, are treatment outcomes improved in patients who take more than 6 months of BDQ compared to no BDQ and BDQ for 6 months?

Exposure 1: No use of Bedaquiline (defined as <30 days) in IPD2019

Reference (comparator) 1: Use of bedaquiline for 24 weeks in IPD2019 (exact duration considered 24 weeks based on descriptive analysis as in Q1).

Exposure 2: Use of bedaquiline for >24 weeks EndTB and in IPD2019

In the analysis strategy deployed, the “exposure” will be BDQ use for 24 weeks or >24 weeks, as treatment in the combined data set of EndTB and IPD2019. The comparator will be BDQ use for <30

days in IPD2019. Our analytic approach will follow the same approach as described in Q2 comparing the reference to exposure 1 and exposure 2, and when comparing exposure 1 to exposure 2.

Outcome 5: Analysis of adverse events:

The analysis plan for adverse events is made somewhat difficult by the fact that we are not yet certain of the data available from the EndTB study. In the IPD2019 we have information on type of adverse events, and the drug considered responsible by the treating team, as well as whether that drug was permanently stopped – in 30 studies with >8000 patients. We did not have much information on the severity of the AE (i.e. few studies provided information on the Grade), so the analysis was simply the cumulative percent of patients who received at least 1 month of the drug, and the drug was stopped permanently because of an AE, as well as type of AE in most of these studies. Using this we calculated a proportion stopping each drug in each study.

We propose to try three approaches to analyze the occurrence of AE. First, we will perform standard aggregate data meta-analysis for proportions. The estimated proportion of patients within each cohort in whom each specific drug was stopped permanently (out of all patients in the cohort receiving that drug) because of an AE (AE incidence). Then AE proportion for each drug from each cohort will be estimated using generalized linear mixed model with random effects at cohort level using the “metaprop” function within R package “meta”, then pooled using standard aggregate data random effects meta-analysis. To address the PICO question, we will sub-divide each cohort into ‘comparator = 6 months BDQ’ and ‘intervention = BDQ longer’. This analysis will be conducted without adjustment for confounders, then we will assess the relationship of covariates (especially age, sex, HIV status, and extent of disease indicators) to AE, and repeat the analysis with adjustment for these confounders.

Second, we can perform an arm-based network meta-analysis using the “nma.ab.bin” function within R package “pcnetmeta” (ref). In this approach, drugs not used in a study or cohort will be considered as missing at random. The use of a multivariate Bayesian mixed model allows estimation of the population averaged treatment specific event proportions. This model will account for the correlation between different treatments within each cohort as compared to the above approach that estimated drug-specific event proportions based solely on cohorts that used the particular drug. Absolute risk of AE for each drug will be estimated using a random effects model within the Bayesian framework, and the median value with 95% credible interval and mean value with standard deviation reported.

A third approach is to use a ranking-based non-parametric method, as this should more accurately assess the relative toxicity of shorter and longer BDQ vs other drugs in different studies (i.e. if comparing AE in IPD2019 and EndTB. In the first step, within each cohort the drugs used were ranked in the order of observed AE incidence of each drug, from one to N (representing the total number of distinct drugs prescribed). If more than one drug was stopped, they received a proportion of a point (e.g. if two drugs stopped 0.5, if three drugs stopped 0.33, etc.) Note that ‘incidence’ refers to cumulative incidence in the IPD2019 – as we may not have adequate information on drug duration, so we have used the proportion who stopped among those who received the drug for at least 1 month. If two or more drugs had the same AE incidence in a study, the drugs were assigned tied ranks. Next, the raw ranks were adjusted by the maximum distinct number of drugs of all cohorts. In a third step, the unweighted average rank for each drug was calculated across all cohorts using the drug, with equal weight ascribed to each cohort. The weighted average rank for each drug will be estimated in the same way except a weight will be assigned for each cohort based on the number of patients using the drug in that cohort; however, cohorts with large sample size will have a dominant influence on the average ranks; therefore, the unweighted ranking will be considered the primary approach. For this PICO, we will assess the ranking of BDQ in those who received BDQ for 6 months (reference or comparator), vs more than 6 months. A change in ranking would imply greater or lesser AE in the intervention group. An improved AE ranking might suggest selection – since those who tolerate a drug are more likely to continue it.

Limitations (PICO 3 analysis)

As noted above, patients may receive prolonged bedaquiline, because they were sicker, or had fewer treatment options (AE, or more resistance). Indeed, information from the investigators indicates that all EndTB countries initiated BDQ use in the patients with the worst MDRTB and the least treatment options – many after prior treatment failures. Early in the EndTB project, countries were very conservative to use BDQ therefore it was included only when cases were desperate and late in the treatment. Second, across countries and over time, the use of prolonged bedaquiline may have varied. However, this is in fact an advantage, as some differences in bedaquiline prescription and duration may have had less to do with patient characteristics, and more to do with local policy, physicians' beliefs, and BDQ availability – creating a quasi-experimental situation – with less confounding due to patient characteristics. We will use two methods to control for confounding; however, we will not be able to completely control all possible confounding, especially unmeasured confounding. But we expect that if unmeasured confounding is related to indication, then this will act to underestimate the benefit of bedaquiline if sicker patients or those with fewer effective drugs are more likely to receive prolonged bedaquiline.

Potential Sensitivity analyses

1. Analyses repeated but accounting for missed doses (due to non-adherence) from the 24 weeks of initial bedaquiline exposure in EndTB.
2. Assess time to loss-to FU/dropout/default, inpatients who take no BDQ, 6 months BDQ and >6 months BDQ. Compare time to LTFU in EndTB and IPD2019 in same sub-groups based on BDQ duration.
3. Examine whether the effect of prolongation depends on specific other drugs used in the treatment regimen (eg, Dlm, clofazimine, PZA or cycloserine).
4. Assess whether Bdq prolongation is more effective than no Bdq prolongation in patients with an indication for prolongation, i.e., patients whose regimen would be compromised if Bdq were withdrawn (resistance, toxicity, culture positivity, etc). It's very possible that Bdq prolongation is not helpful in patients who don't need it after 6 months. Including these patients in an analysis of effectiveness of Bdq prolongation could underestimate the contribution of prolongation. To analyze the effect of prolongation in those who need prolongation would require establishing the risk group based on patient characteristics after 6 months of Bdq, not only those at baseline.
5. For Question 1, Method 2: We will consider modelling time non-linearly using a spline or by including a second quadratic term for duration. Further, we will also use g-formula to calculate the expected probabilities of our outcome, which would reduce biases introduced due to people surviving longer can receive bedaquiline longer. Finally, we will consider LTFU an outcome, and not a censoring event, since LTFU may be due to undetected, clinically important reasons of long duration and/or toxicity.
6. For Question 1: We will not consider the number of drugs a person is resistant to, but instead consider drugs with perceived unreliable DST (notably E, Z, PAS, Eto/Pto, Cs/Trd) as (a) susceptible regardless of result and (b) resistant regardless of result.
7. For AE: Compare frequency of specific drug related AE in EndTB and NixTB studies.

Adverse Event Definitions in EndTB

EndTB AEs are classified using severity grades 1–5 according to the **MSF severity scale**. They use the commonly-accepted (ICH-GCP among others) criteria to classify events as serious: results in death; is life-threatening (places the subject at immediate risk of death from the event as it occurred); results in inpatient hospitalization or prolongation of existing hospitalization; results in a persistent or significant disability/incapacity; results in a congenital anomaly/birth defect; or is otherwise medically significant: based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition.

Question 4. In MDR/RR-TB patients, does concomitant use of bedaquiline and delamanid safely improve outcomes when compared with other treatment options in regimens otherwise conforming to current WHO guidelines?

Population	Intervention	Comparator	Outcomes
MDR/RR-TB patients a. with additional drug resistance patterns b. with XDR-TB c. with severe disease (i.e. cavitory disease on radiography or SS+) d. previously treated with 2nd line drugs or not e. children (0–14y) / adults (adolescents 10–19y if available) f. persons with HIV (+/- ARVs) g. pregnant women h. people with diabetes mellitus i. extrapulmonary disease j. malnutrition	– Concomitant use of bedaquiline and delamanid, given for six months of treatment	– A regimen without concomitant use of bedaquiline and delamanid for six months of treatment	<ul style="list-style-type: none"> • Successful completion of treatment (or lack of successful completion) • Bacteriological cure by end of treatment • Adherence to treatment (or treatment interruption due to non-adherence) • Treatment failure or relapse • Survival (or death) • Adverse events with anti-TB medicines • Acquisition (amplification) of drug resistance

(PICO 4) Adding Delamanid to bedaquiline: specific questions

1. In the EndTB data set are treatment outcomes improved with concomitant use of BDQ and DLM compared to use of BDQ without DLM (in addition to other components of an adequate MDR regimen)?
2. In the combined IPD-2019 and EndTB data sets, are treatment outcomes improved with concomitant use of BDQ and DLM compared to use of other treatment options?

Challenges in this analysis:

In the EndTB study, DLM use varied between sites, and may have been started at beginning, or given later in therapy, even given as ‘salvage therapy’. If added later, DLM may have been added because of local or individual preference/protocol, or based on response to therapy to that point. Hence, we will begin this analysis with a careful descriptive analysis (as described above as Step 2 for PICO 3) – comparing those who received DLM to those who did not – separately within the EndTB data set. We will also perform the same descriptive analyses for the IPD2019 (where same problems likely applied). This will include an assessment of timing of DLM start, and duration of use.

Study population/data sources (PICO 4):

IPD-2019.

In 2018 an IPD was assembled of 53 data sets from 40 countries/regions containing records for 13,000 patients with MDR-TB. This IPD-2018 data set was analyzed to answer a number of PICO questions developed by a WHO MDR-TB guidelines development group (GdG). These guidelines have since been published. This IPD-2018 was itself based on an IPD data set assembled in 2016–17 to answer questions of a GdG of the CDC/ATS/IDSA/ERS. These guidelines have not yet been published, but the analyses that informed this set of guidelines were published in the Lancet in Sept 2018.

Hence the IPD-2019 represents an update of the IPD-2018. We anticipate adding data from one national surveillance programs – in South Africa. We will delete the previous records of patients treated in the EndTB observational study, that were included in the IPD-2018, to avoid duplication and overlap with the new data set from EndTB. We may also add two other data sets – provided in response to a public call for data contributions.

EndTB:

1094 patients with MDR-TB were treated with bedaquiline- and/or delamanid-containing regimens between 1 April 2015 and 31 March 2017. They were followed as part of an observational study – executed by three NGO's – PIH, MSF and IRD.

Approach

As with PICO 3, the approach here will have the same outcomes. We will again observe the distribution of 'duration' for people receiving BDQ and DLM to define cut-points to call the duration six-months. We will perform the same descriptive analyses described in Question 1 of PICO 3 for the intervention population receiving BDQ and DLM to six months and perform the same statistical analyses comparing it to the comparator populations of (1) people who received only Bdq; (2) people who received only Dlm; (3) people who received BDQ and Dlm for <6 months and; (4) people who received BDQ and Dlm for more than 6 months. We will limit analyses within EndTB as this data set is the only one with enough detail to adequate control for the numerous time-varying confounders that may influence which patients fell into the intervention group or one of the four comparator groups.

Limitations – PICO 4

Many of the same limitations apply to PICO 4 as PICO 3, except that in addition there were fewer patients treated – in IPD2019 or end-TB data sets – limiting ability to match on key confounding covariates and limiting power as well to detect small benefits (or harms). In addition, there may have been even greater selection biases (and immortal time bias) affecting estimates of effect of DLM on outcomes.

A6.2 WHO treatment guidelines for multidrug- and rifampicin-resistant tuberculosis, 2018 update

Refer to Annex 10: Summaries of unpublished data and analysis plans used for the recommendations in the *WHO treatment guidelines for multidrug- and rifampicin-resistant tuberculosis, 2018 update* (https://www.who.int/tb/areas-of-work/drug-resistant-tb/Annexes_8-10.pdf, accessed 2 March 2019).

A6.3 Guidelines for treatment of drug-susceptible tuberculosis and patient care, 2017 update

Refer to Annex 5: Reports of the systematic reviews (reports on systematic reviews for: adherence interventions in tuberculosis treatment and decentralized treatment and care for multidrug-resistant tuberculosis patients) in the *Guidelines for treatment of drug-susceptible tuberculosis and patient care, 2017 update* (https://www.who.int/tb/publications/2017/dstb_guidance_2017/en/, accessed 2 March 2019). The systematic reviews have subsequently been published (37,38)



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