Does the inclusion of the cost and burden of adverse drug reactions associated with drug-resistant TB treatment affect the incremental cost-effectiveness of new treatment regimens? A case study from the introduction of bedaquiline in South Africa National TB Programme

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Statement of Intent

I, Kathryn Lou Bistline, hereby declare that this thesis is presented in fulfilment of the requirements for the degree of Doctor of Philosophy (PhD) in the School of Public Health and Family Medicine, Faculty of Health Sciences, University of Cape Town. The contents of this thesis and the work on which this thesis is based is my original work and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university. The degree candidate personally conducted all of the work presented here. For multi-authored, published papers, the degree candidate designed and conducted the analyses and led the writing. The contribution of the degree candidate to multi-authored papers is outlined in detail in the synopsis prior to each manuscript. Further, where co-authorships are involved, my co-authors have agreed that I may include the publications.

Signed by candidate

Kathryn Lou Bistline

BSTKAT003

Date: 13 February 2018

ABSTRACT

Does the inclusion of the cost and burden of adverse drug reactions associated with drug-resistant TB treatment affect the incremental cost-effectiveness of new treatment regimens? A case study from the introduction of bedaquiline in South Africa National TB Programme

Kathryn Lou Bistline

South Africa has one of the world's highest burdens of TB, HIV/TB co-infection, and drug-resistant TB. Second-line TB treatment is less effective, more expensive, and more toxic than treatment for drug-sensitive TB. Nearly 1 in every 5 persons who starts treatment for drug-resistant TB in South Africa will die; 1 in every 3 persons who survives treatments experiences permanent, profound hearing loss. For decades there was little progress in TB research, however, and so treatment with old regimens continued despite safety concerns. In 2012 the US and European regulatory authorities approved a new drug, bedaquiline, but only for treatment in cases with no other options. In 2015, the South African Medicines Control Council approved bedaquiline for drug-resistant TB, but only a limited number of doses were approved in the 2016/2017 annual budget and the focus, again, was only for the patients who had no other options. In order to inform policy makers in planning and budgeting for drug-resistant TB treatment, the aim of this thesis was to determine whether the simple calculation that bedaquiline was too expensive relative to standard regimens using kanamycin was too simple. Particularly, given the high burden of adverse drug reactions (ADR) associated with kanamycin, would the inclusion of the cost and burden of ADR affect the incremental cost effectiveness ratio of a new treatment regimen where bedaquiline replaces kanamycin?

Analysis of the national drug-resistant TB case register showed that mortality during second-line treatment was early, primarily in the first 6 months of treatment, even when patients do not have extensive drug resistance. HIV-positive patients not on anti-retroviral therapy (ART) at initiation of drug-resistant TB treatment have the highest risk of mortality. The high early mortality is a real risk that clinicians have to balance when deciding to initiate ART and effective second-line TB treatment both as quickly as possible. Daily injections coupled with taking more than 10 pills each day are a heavy burden for patient compliance, but also pose concerns in terms of overlapping and compounding toxicities; this burden was confirmed through a meta-analysis of the pooled frequency of adverse events among cohorts with at least 25% of the patients HIV-positive. A competing risk analysis of a cohort of drug-resistant TB patients from Johannesburg – addressing the reality that patients may not have experienced an ADR because they died rather than because they were at lower risk – indicated that HIV-infected patients who are not yet stable on ART and second-line TB treatment are at the highest risk of ADR.

A Markov model built and parameterized using the data from the South African national TB programme indicates that bedaquiline for all drug-resistant TB led to a small gain in effectiveness at a cost that was under the costs of the drug itself, due to savings from daily injection visits. While cost-effective, it was not clear that South African policy makers needed to move beyond the offer of bedaquiline for patients with extensive drug resistance. However, the calculation, and the decision point, were different once the costs and disability associated with ADRs was included in the analysis. Bedaquiline-based regimens offer a cost-saving and more effective alternative to an injection-based regimen for drug-resistant TB patients treated in the public sector in South Africa.

Dedication and acknowledgements

For anyone who has never visited or worked at an M/XDR-TB hospital or met a survivor of this disease, the passion and commitment of the patient advocates, clinicians and policy makers working in this field may seem unexplainable. At the end of 2017, a published review included the words and photos of patients, calling out for attention and action.[1]

"During my treatment period, I lost my hearing. It started with the right ear. Both ears were affected by July— just 2 months after I started treatment. I felt so lost and isolated because I couldn't communicate with my family. I preferred to be alone, that way I felt like I was coping. Meanwhile I was dying inside because all my dreams and the fun I used to have with my loved ones were shattered." Ntokozo Nkosi, South Africa [1]

I dedicate this work to the women who have taught me to see, listen, and serve. When there is suffering, we are called to truly see it, truly listen to those who need our help, and act.

I would like to express my sincere gratitude for the following people, organizations, and funders:

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My brother, Greg Schnippel, for not letting me give up and always helping out when I needed it.

And finally, most importantly, my two boys, Marcus and Christopher Bistline, for all the nights that I spent on the computer and with piles of papers. I hope to share with you the commitment to others that keeps me working through the night. And I pray that you will have healthy, long lives.

Preface

As per general provisions 6.7 in the General Rules for the Degree of Doctor of Philosophy (PhD) of the University of Cape Town, and with the approval of the University Doctoral Degrees Board on 29 January 2018, this thesis includes the full-text of manuscripts that have been published in or submitted for publication in peer-reviewed journals.

I confirm that I have been granted permission by the University of Cape Town's Doctoral Degrees Board to include the following publications in my PhD thesis, and where co-authorships are involved, my co-authors have agreed that I may include the publications:

1. Schnippel K, Firnhaber C, Ndjeka N, Conradie F, Page-Shipp L, Berhanu R, Sinanovic E. Persistently high early mortality despite rapid diagnostics for drug-resistant tuberculosis cases in South Africa. *The International Journal of Tuberculosis and Lung Disease*. 2017 Oct 1;21(10):1106-11.

2. Schnippel K, Berhanu RH, Black A, Firnhaber C, Maitisa N, Evans D, Sinanovic E. Severe adverse events during second-line tuberculosis treatment in the context of high HIV Co-infection in South Africa: a retrospective cohort study. *BMC Infectious Diseases*. 2016 Oct 21;16(1):593.

3. Schnippel K, Firnhaber C, Berhanu R, Page-Shipp L, Sinanovic E. Adverse drug reactions during drug-resistant TB treatment in high HIV prevalence settings: a systematic review and meta-analysis. *Journal of Antimicrobial Chemotherapy*. 2017 Apr 16. doi: 10.1093/jac/dkx107.

4. Schnippel K, Firnhaber C, Conradie F, Ndjeka N, Sinanovic E. Incremental cost effectiveness of bedaquiline for the treatment of rifampicin-resistant tuberculosis in South Africa: model-based analysis. *Applied Health Economics and Health Policy.* 4 Oct 2017. doi: 10.1007/s40258-017-0352-8.

5. Schnippel K, Firnhaber C, Berhanu R, Page-Shipp L, Sinanovic E. Direct costs of managing adverse drug reactions during rifampicin-resistant tuberculosis treatment in South Africa. *The International Journal of Tuberculosis and Lung Disease*, 2018. *In press.*

6. Schnippel K, Firnhaber C, Page-Shipp L, Sinanovic E. Impact of adverse drug reactions on the incremental cost effectiveness of bedaquiline for drug-resistant tuberculosis. *The International Journal of Tuberculosis and Lung Disease*, 2018. *In press.*

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ABBREVIATIONS

ADR	Adverse drug reaction
AE	Adverse event
aHR	Adjusted Hazard Ratio (aHR)
ALT	Alanine aminotransferase, a liver function laboratory test
AM	Amikacin
ART	Antiretroviral (ARV) therapy for HIV
BCAP	Bedaquiline Clinical Access Programme
BDQ	Bedaquiline
BMI	Body mass index
CFZ	Clofazimine
CI	95% confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CM	Capreomycin
CPI	Consumer Price Index
DALY	Disability adjusted life year
DOH	Department of Health
DR-TB	Drug resistant tuberculosis
DST	Drug susceptibility testing
DW	Disability weight
E, EMB	Ethambutol
ECG	Electrocardiogram (machine or test)
EDRweb	Electronic drug resistant TB case register
EFV	Efavirenz
ETO	Ethionamide
GBD	Global Burden of Disease study
GFR	Glomerular Filtration Rate, a kidney function laboratory measure
GXP	GeneXpert machine
H, INH	Isoniazid
Hb	Haemoglobin
HIV	Human Immunodeficiency Virus
HR	Hazard ratio
IA	Injectable agents for anti-TB treatment, e.g. kanamycin, capreomycin, amikacin
ICER	Incremental cost-effectiveness ratio
inhA	inhA protein (result of genotypic test for INH resistance)
IQR	Interquartile range
katG	Mycobacterial catalase-peroxidase (result of genotypic test for INH resistance)
KM	Kanamycin
LFX	Levofloxacin
LPV/r	Lopinavir/ritonavir
LPA, PCR	Line probe assay or polymerase chain reaction (e.g. HAIN Genotype MTBDR®)
LYS	Life years saved
LZD	Linezolid
MCC	South African Medicines Control Council

MDR-TB	Multidrug-resistant tuberculosis
MDR/RR-TB	Multidrug-resistant or rifampicin-resistant tuberculosis
MFX	Moxifloxacin
NDOH	National Department of Health
NHLS	National Health Laboratory Services
NTP	National Tuberculosis Programme
NVP	Nevirapine
OBR	Optimized background regimen
OFX	Ofloxacin
PAS	p-aminosalicylic acid
preXDR-TB	Pre-extensively drug-resistant TB, either FLQ or SLD resistance
QALY	Quality adjusted life years
QT	Interval between start of Q wave and end of T wave
QTcF	QT interval corrected using Fridericia formula
R, RIF	Rifampicin
RR-TB	Rifampicin resistant TB
SA	South Africa, South African
sd	Standard deviation
sHR	Sub-hazard ratio
SOC	Standard of care
TB	Tuberculosis
TDF	Tenofovir
TZD	Terizidone
USD, US$	United States dollar
WHO	World Health Organisation
WTP	Willingness to pay
XDR-TB	Extensively drug-resistant TB
Xpert MTB/RIF	Xpert MTB/RIF® test on GXP platform
Z, PZA	Pyrazinamide
ZAR	South African Rand

Glossary of Terms

Adverse drug reactions	or *adverse events* that occur during treatment which are believed to be related to a drug or combination of drugs rather than the underlying disease can range in *severity* and may affect different systems of the body.
Cost-effectiveness	analysis is used to answer questions about how much the effect (of the new policy or treatment or product) costs to adopt. The *incremental cost-effectiveness ratio* (ICER) is one measure to compare two different interventions, where the difference in cost and effectiveness is presented as a ratio
Decision-analysis	modelling is a method to represent the complex choices in a simplified form where expected values such as costs and outcomes can be estimated for different options and compared. Options are often outlined as trees, with each branch representing the outcome of different possible paths.
Disability adjusted life years	is one measure used in health economics to allow for comparability across diseases, injury, and interventions. DALYs are the sum of life years lost and years of life lived with disability. An intervention that resulted in a year more of perfect health than the base case would be said to avert 1 DALY. The measure is an alternative approach for the same purpose of common outcome assessment as a *quality-adjusted life year* (QALY).
Disability weighting	is the measure used to reduce the comparable value of a year of life according to the extent of disability. While subjective, the intent is to measure the difference between interventions where the same number of persons survive but that not all persons return to (or attain) perfect health. The *Global Burden of Disease* study is a large-scale, repeated attempt to have consensus on the weights assigned to different disabilities.
Injectable agents	Second-line injectable drugs for TB treatment include the aminoglycosides (kanamycin, amikacin) and cyclic peptides (capreomycin). Streptomycin is a first-line injectable anti-TB drug.
Markov modelling	is one type of *decision-analysis modelling*. For health economics, patients are represented as being in one health state and then have a probability of transitioning to a different health state in a time step. Markov models have no history, so that each transition probability is independent of the time spent in (a) previous health state(s).
Provider perspective	for cost studies, it is important to indicate whose costs are being included in the equation as some decisions may involve a trade-off where an intervention is cheaper for one part of society but more expensive for another.

Rifampicin-resistant TB	or RR-TB, is TB that is at least resistant to the core first-line drug. If a patient with RR-TB is also resistant to isoniazid with or without any other first-line drug resistance, it is known as multi-drug resistant (MDR-) TB. A patient with MDR-TB resistant also to either (a) fluoroquinolone(s) or (a) second-line injectable(s) is described throughout this thesis as preXDR-TB, although this terminology is not used by the WHO. MDR-TB patients with resistance to both (a) fluoroquinolone(s) and (a) second-line injectable(s) are said to have extensively drug resistant (XDR-) TB.
Treatment regimens	MDR/RR-TB is treated with a multi-drug regimen; no single-drug treatment is approved for use. In 2016, the WHO recommended a standardized *short-course regimen* of 9-12 months in addition to the *standard long-course regimen* of 18-24 months recommended in 2011. When a new drug is added to the standard regimens, and the other drugs in the regimen are unchanged, the standard drugs are sometimes referred to as *background regimen*. When drugs are removed for intolerance or resistance or added to strengthen the regimen, it is said to be *individualized* and no longer the standard offered to all patients.

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1 INTRODUCTION AND OVERVIEW

1.1 INTRODUCTION

Tuberculosis (TB) is the leading cause of infectious disease globally.[2] In 2016, there were an estimated 10.4 million incident cases and nearly 1.7 million deaths from TB.[2] In 2014, the World Health Assembly adopted a 20-year strategy to end TB with a vision of zero TB deaths, disease or suffering. However, resistance to rifampicin, one of the core first line treatments for TB has been growing over time and threatens progress in ending the TB epidemic. In 2016, there were an estimated 600,000 incident cases of multi-drug resistant or rifampicin-resistant TB (MDR/RR-TB) across the world and an estimated 240,000 persons with MDR/RR-TB died.[2] Resistance to TB drugs can be acquired during TB treatment, for example during treatment interruptions or if inadequately dosed for weight or concomitant medication. TB is an airborne disease and drug-resistant strains of the TB bacteria can also be transmitted. In 2016, 4.1% (95%CI: 2.8-5.3%) of new TB cases (no prior history of having TB) were estimated to have MDR/RR-TB as well as 19% (95%CI: 9.8-27%) of previously treated TB cases.[2] Second-line TB treatment is complicated to administer, with potential for severe and permanently disabling adverse drug reactions (ADR) [1,3–5] and success rates of 52 to 62%.[2,5–8]

"Patients with drug-resistant TB face agonising, prolonged suffering and often permanent disability while on second-line treatment, together with devastating economic hardship, stigma and discrimination. On top of the clinical toll taken by M/XDR-TB treatment, patients often face catastrophic economic repercussions, pushing them into extreme poverty."[9]

The WHO estimates that only 1 in 4 persons with MDR/RR-TB are diagnosed and 1 in 5 persons with drug-resistant TB are initiated on appropriate treatment. Evidence from countries with repeated drug-resistance surveillance [2] as well as modelling shows that, because of the limited diagnosis and effectiveness of second-line treatment that the proportion of drug-resistant TB among all TB will increase over time.[10,11] By 2050, 2.59 million additional people are projected to die every year from MDR-TB, in excess of current United Nations mortality projections and MDR-TB is estimated to have a global cost of $15.7 trill from 2015 to 2050.[11]

Although updated modelling and analysis by the World Health Organization (WHO) presented in the 2017 Global Tuberculosis Report shows a declining trend in TB incidence and prevalence for South Africa since 2008, the WHO also estimates that South Africa has among the worst rates of TB incidence and prevalence per 100,000 population in the world, at 781 / 100,000 (95% confidence interval (CI): 543–1 060).[2] Perhaps of more concern is that South Africa ranks in the top 10 countries for the absolute number of RR-TB cases diagnosed in 2016, with 19,073.[2] For the 2014 South African cohort, only 54% of MDR/RR-TB patients were cured or successfully completed treatment.[2]

Adding to the burden, an estimated 59% of TB patients in South Africa are co-infected with the human immunodeficiency virus (HIV).[2] TB/HIV co-infected patients, especially those not on antiretroviral therapy (ART), have higher mortality than HIV-negative patients.[12,13] A 2015 meta-analysis reported a pooled proportion of 38% (95%CI: 28 to 48.1%) mortality for HIV co-infected adults with MDR/RR-TB.[12] In 2016, the WHO estimated that the mortality rate for TB/HIV was 181/100,000 population (95%CI: 120-254), 4-times the rate of mortality among TB excluding HIV-positive patients (41/100,000 population, 95%CI: 31-52).[2] TB, and particularly RR-TB, represents a major challenge to public health in South Africa.

RR-TB treatment models

Currently, RR-TB requires 12-24 months of anti-TB second-line treatment.[14–17] RR-TB can be mono-RIF resistant TB, MDR-TB that is resistant to both RIF and isoniazid (INH), extensively drug resistant (XDR) TB which is MDR-TB plus resistance to second-line drugs from the fluoroquinolone and injectable drug classes, or preXDR-TB which is MDR-TB plus resistance to either a fluoroquinolone *or* a second-line injectable drug.[18] The standard of care for MDR/RR-TB treatment in South Africa from 2011 through the end of 2016 was to use a standardized regimen for all RR-TB patients until further resistance was either confirmed or ruled-out. The regimen consists of 6 months (intensive phase) of 5 drugs (a second-line injectable, a fluoroquinolone, ethionamide or ethambutol, terizidone, and pyrazinamide) followed by 12 to 18 months (continuation phase) of 4 drugs, excluding the injectable. Patients with additional drug resistance were eligible for individualized second-line TB regimen (if preXDR-TB or XDR-TB, pre/XDR-TB) and INH may be added to the regimen (if mono-RIF resistant).[15,17,19] In 2016, the WHO recommended a 'short-course' regimen, where the intensive phase can be limited to 3-4 months and the continuation phase to 6-9 months for patients with no prior exposure to second-line anti-TB drugs or in whom resistance to second-line anti-TB drugs had been excluded.[14,20] The South African National TB Program (NTP) adopted these guidelines for a shorter regimen in 2017, after the period of analysis for this thesis.

RR-TB treatment costs

The STOP TB Global Plan 2016 to 2020 estimated that, at current levels, approximately US$7 billion is spent each year on prevention, diagnosis, and management of TB.[21] The South African TB budget for 2017 was reported as US$244 million.[2] Evaluations of both costs and effectiveness of interventions to manage TB are essential for improved planning and investment in TB control, and where possible, these need to be specific to the context and country in which it will be implemented.[22] However, there is insufficient evidence of real-world, contextualized cost and effectiveness evaluations for even the most commonly implemented TB interventions.[23] While drug-resistant TB treatment is more expensive than drug-sensitive TB treatment, globally, there is evidence that MDR/RR-TB treatment is cost-effective.[24] In South Africa, MDR/RR-TB treatment, including the cost of clinical care in out-patient or in-patient facilities, laboratory monitoring, and anti-TB drugs, is estimated to cost US$3,894 [25] to US$4,925 [26] per person adjusted to 2016 USD.[27,28]

New treatments for RR-TB, bedaquiline

Results of a pilot clinical trial where 8 weeks of bedaquiline (manufactured by Janssen Pharmaceuticals under the name brand Sirturo) or placebo was added to the standard of care regimen in South Africa, showed a dramatic increase, from 9 to 48%, in the proportion of MDR-TB patients who converted to a negative sputum culture at 8 weeks without significant increase in the frequency or severity of adverse drug reactions (ADR).[29] Use of bedaquiline significantly reduced the time to culture conversion (hazard ratio(HR): 2.253, 95%CI: 1.08 to 4.71).[29] Building on this successful pilot, a Phase 2b clinical trial of 24 weeks of bedaquiline or placebo in addition to the standard of care regimen, was implemented. Culture conversion on bedaquiline was also significantly higher (HR: 2.44; 95%CI: 1.57 to 3.80) and there was a higher rate of cure.[30] However, final treatment outcomes of the Phase 2b clinical trials were not as promising and there were more deaths in the bedaquiline arm.[30] The authors indicated it was a statistically significant imbalance in mortality with more deaths occurring in the patients on bedaquiline compared to placebo (12.7% and 2.5%, respectively).[30]

In 2013 the WHO issued interim guidelines which reviewed available evidence on the benefits and risks of bedaquiline use for the treatment of RR-TB.[31] The revised guidance indicated the Phase 2b findings had potentially “very serious bias” for imprecision from the small patient numbers and also “serious bias” for indirectness; none of the deaths in the bedaquiline arm were attributed to bedaquiline.[31] However, because of the statistically significant imbalance in mortality, the recommendation in both 2013 and 2017 was cautious.[31,32] As per the guidelines:

> *“Bedaquiline may be added to a WHO-recommended regimen in adult MDR-TB patients under the following conditions (conditional recommendation, very low confidence in estimates of effect, i.e. very low quality of evidence):*
>
> - *when an effective treatment regimen containing four second-line drugs in addition to pyrazinamide according to WHO recommendations cannot be designed;*
> - *when there is documented evidence of resistance to any fluoroquinolone in addition to multidrug resistance.”* [31]

The phase 2b trial for bedaquiline included South African public-sector drug-resistant TB sites; thus, some South African clinicians had experience with and familiarity with bedaquiline before the results of the clinical trial were completed. However, the clinical trial had strict inclusion and exclusion criteria, so that only 5 of the 66 bedaquiline patients (8%) were HIV-positive. To increase access to bedaquiline for drug-resistant TB patients for whom an effective treatment regimen could not be constructed, the South African Medicines Control Council (MCC) approved a compassionate use programme for bedaquiline in December 2012.[33] The Bedaquiline Clinical Access Programme (BCAP) also increased the body of evidence for use of bedaquiline in HIV-infected patients and the experience of clinicians in the South Africa public sector drug-resistant TB programme. Interim results among patients with pre/XDR-TB indicated a high rate of culture conversion.[34] In October 2014, the MCC approved the use of Sirturo (bedaquiline) for treatment of MDR/RR-TB.[19]

An exploratory cost-effectiveness analysis of bedaquiline was used for the 2013 WHO recommendations, but was completed prior to final results of the Phase 2b study being available and with uncertainty around whether bedaquiline would increase cure by reducing loss to treatment follow-up, death or failure.[31] The WHO’s guideline development group’s 2016 systematic review of updated evidence on the use of bedaquiline prior to issuing 2017 revisions to the guidelines did not update the cost effectiveness analysis.[32] In the first (2013) version of the WHO guidance, one of the concerns about the cost-effectiveness analysis was the simplifying assumptions of the model: “While the cost-effectiveness modelling showed overall benefit, there were concerns about the simplifying assumptions used (e.g. no accounting for the difference in serious adverse events, no accounting for effect on transmission, uncertainty about application of trial outcomes – including deaths – to routine programmatic conditions, etc.).”[31] According to a review by Reuter et al (2017), these simplifying assumptions may have excluded significant societal costs:

“Moreover, the ongoing use of [injectable agents, (IA)] requires a significant amount of logistical support and likely contributes to the difficulties faced by persons who are unable to return to work, school, or perform other activities of normal life while on treatment. These attributes of IA treatment most certainly contribute to costs incurred by persons living with MDR-TB, and are not compatible with the WHO’s End TB Strategy, which has pledged to eliminate catastrophic costs to MDR-TB patients by 2020. The WHO has also highlighted the ethical duty to address all forms of suffering associated with TB, through appropriate access to care and to the management of adverse drug reactions.”[1]

1.2 Aims and objectives

This study aims to use the introduction of bedaquiline within the South African National TB Programme (SA NTP) as a case study to determine whether the inclusion of the cost and burden of ADR associated with MDR/RR-TB treatment affects the incremental cost-effectiveness ratio (ICER) of new treatment regimens. In order to complete this analysis, the costs and burden of ADR, in addition to the costs and effectiveness of MDR/RR-TB treatment in South Africa will need to be estimated.

Objectives

1. To describe the types, frequency, and severity of ADRs experienced during MDR/RR-TB treatment.
2. To evaluate the provider cost of prevention, monitoring, and management of ADRs incurred during MDR/RR-TB treatment, including drugs, hospitalization, laboratory monitoring, and clinic visits.
3. To estimate the ICER of bedaquiline treatment regimen compared to the long-course, standard of care (SOC) MDR/RR-TB treatment regimen in SA, having included the cost and burden of ADR during MDR/RR-TB treatment.

Thus, the objectives of this study are listed in the order in which they were answered. Before costs of ADR management could be added to the cost-effectiveness model, they needed to be estimated. Before the costs of ADR management could be estimated, the types and frequencies of ADR experienced had to be described.

The results of this study were intended inform comparison of new treatment regimens for MDR/RR-TB and assist policy makers in planning and budgeting for MDR/RR-TB treatment within the SA NTP and the HIV/TB programme of the South African public health sector. While use of health technology assessment is not a required or consistently used approach to health policy decision making within the South Africa, it does have a role particularly in the HIV and TB sector. The 2012-2016 and 2017-2022 South African HIV and TB national strategic plans (NSP) have been 'costed', including estimates of the cost of the proposed interventions.[35,36] The 2012-2016 NSP [35] could be critiqued as mostly a presentation of the costs for the interventions selected already by policy makers, i.e. regardless of relative cost effectiveness.[37] In comparison, the 2017-2022 NSP was intended to have an investment approach and decisions were to have been informed by the work of the investment case that combined disease modelling and cost-effectiveness analysis of packages of HIV and TB interventions.[36,38,39] Thus, while routine use of health technology assessment is still nascent in South Africa, there is a willingness and interest by the policy makers within the National Department of Health and the South African National AIDS Council to consider evidence such as this thesis aims to generate.

1.3 OVERALL STRUCTURE AND CONCEPTUAL FRAMEWORK

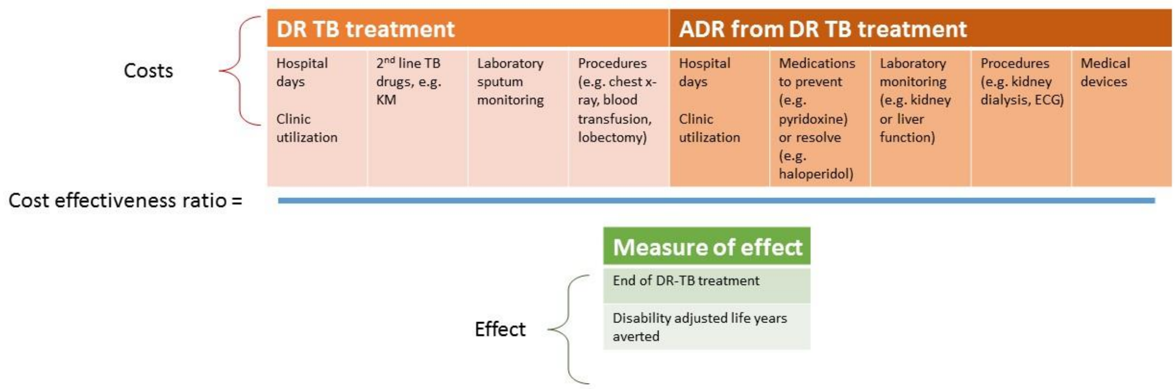
This thesis includes an introduction, background and literature review, six results chapters which are also manuscripts, and a discussion and conclusions chapter. Manuscripts are included word-for-word as the final submitted version. As per guidance on the inclusion of the manuscripts, these have been reformatted to be consistent with the overall formatting of the thesis. Page, table, and figure numbering as well as citation number and referencing style in each manuscript have been updated to be consistent with the overall thesis, but no other editing has been done to the final version of the manuscripts as submitted. Thus, the index of tables, index of figures, and the references are consistent throughout the document. Supplemental materials from the manuscripts and other appendices constitute the final section of the document.

Conceptual framework

Overall, the research presented aims to use cost-effectiveness analysis to inform policy, treatment guidelines and decisions as to the inclusion of bedaquiline for the treatment of RR-TB. The conceptual framework introduced in therefore on how cost-effectiveness analysis can inform this particular policy. An overview of the framework is provided below; more detailed review of the concepts of cost-effectiveness and their application to RR-TB treatment guidelines can be found in Chapter 2.

Cost effectiveness ratios are a means of comparing both the costs and the effectiveness of an intervention at the same time, so that decision makers are not limited to the one dimension or the other.

Figure 1-1 Cost-effectiveness ratio of bedaquiline regimens for MDR/RR-TB treatment

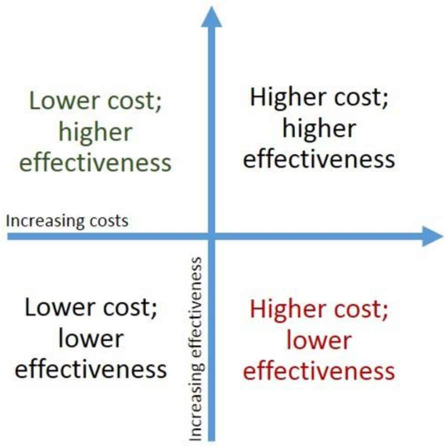


Focusing in on only cost, for example, bedaquiline and the other drugs in the background regimen are more costly than the standard injection-based regimen drugs. As the Figure 1-1 shows, the costs of ADR monitoring, prevention, and management will be added to the typical cost categories of MDR/RR-TB treatment, including hospital and clinic utilization, 2nd line TB drugs, laboratory sputum monitoring and procedures such as chest x-ray. Similarly, the effectiveness of the bedaquiline regimens (i.e. increased cure) will be calculated using the end of treatment results, the final outcome of treatment. These results will be adjusted to account for the ADR associated with the second-line MDR/RR-TB treatment.

Incremental cost-effectiveness analysis is based upon calculating the incremental cost, the difference between the cost of the new intervention and the SOC, and incremental effectiveness of two alternatives. The results are presented as a ratio of the incremental costs divided by the incremental effectiveness. Incremental cost-effectiveness rations (ICERs) are most appropriate when there is an existing intervention that is already shown to be cost effective relative to a 'do nothing approach'. As a result, the question for decision makers has shifted from 'why should I do anything?' to 'what would it cost to do achieve more health?' or 'could I minimize costs without losing any health?'. These are questions on the marginal, or or incremental cost and benefits of two alternatives. Therefore, the base case can be taken as the current standard of care compared to the new intervention or health technology. For this thesis study, the resulting adjusted ICERs from the proposed analysis will be compared to those estimated without ADR costs and disability burden to determine whether the increased complexity of considering ADRs affects the overall cost-effectiveness determination and placement on a cost-effectiveness plane.

Estimated ICERs and uncertainty around the ICERs can be visualized if plotted on a cost-effectiveness plane that is typically divided into quadrants. Interventions that are higher cost and lower effectiveness (lower right quadrant) than an alternative are said to be dominated – the decision to avoid high costs and low effectiveness is straightforward. The converse, lower costs and higher effectiveness (upper left quadrant), similarly is an easier decision if money can be saved and better outcomes obtained. Higher cost and higher effectiveness (upper right quadrant) typically requires additional information to make the decision, such as affordability of the higher costs and willingness (of the payer) to pay the higher costs. The lower left quadrant, with lower costs but also lower effectiveness, is sometimes chosen because of affordability reasons.

Figure 1-2 Cost-effectiveness plane



In addition to placement on a quadrant, cost-effectiveness acceptability curves provide information on the probability that an intervention either meets a certain threshold for cost-effectiveness (such as a willingness to pay threshold, described in Chapter 2) or is more cost-effective than the alternative intervention.[40] This presentation of cost-effectiveness results can assist decision makers in understanding the underlying uncertainty in the results as well as whether further research is needed prior to making a decision. For example, if, despite a high level of uncertainty in effectiveness or cost input parameters, there is a high probability that the new intervention or health technology will be cost-effective, this is important to communicate to decisions makers.

1.4 SUMMARY OF METHODS

A mixed methods approach was used, including literature review, patient-file review, ingredients-based guidelines costing, and decision-analysis modelling. Methods for each of the major results are described below.

ADR experienced during MDR/RR-TB treatment.

A retrospective, de-identified analysis of a clinical file review was used to describe the frequency, duration, and severity of ADR experienced during MDR/RR-TB treatment at two sites in Johannesburg, South Africa. Results are presented in Chapter 4.2. Additionally, a systematic review and meta-analysis describing the frequency and severity of ADR during MDR/RR-TB treatment in the context of high HIV prevalence settings is presented as Chapter 5.2.

Provider cost of prevention, monitoring, and management of ADRs

The resources required for ADR prevention and monitoring, because applicable to all patients on treatment, are included in the standard of care and bedaquiline treatment costs in Chapter 6. ADR management costs based on guidelines and clinician input were estimated by extracting ingredients costs from public sector databases and literature to estimate the bottom-up provider costs for ADR including hospital and clinic utilization, medications, and laboratory investigations. These costs were multiplied expected frequencies of each type of ADR and results are presented in Chapter 7.

ICER of bedaquiline treatment regimen compared to SOC MDR/RR-TB treatment regimen in South Africa, having included the cost and burden of ADR during MDR/RR-TB treatment.

In order to estimate the ICER of bedaquiline for all MDR/RR-TB compared to the injection-based regimens, a Markov health state model that represents MDR/RR-TB treatment in South Africa, including appropriate health states for HIV/TB co-infection was built. Transition probabilities for the health states, disaggregated by HIV and ART status were generated from the national drug-resistant TB register for South Africa. Results on the timing of mortality were described in . Provider costs of ingredients for MDR/RR-TB in South Africa are provided as input parameters. The model and results of the analysis are presented through Chapter 6.

The model expanded on and parameterized using the frequencies of ADR estimated in Objective 1 and the costs of these ADR estimated in Objective 2. Thus, the costs of RR-TB treatment were increased by the expected average ADR costs (expected incidence of ADR multiplied by the unit cost of the ADR) associated with the regimen. The expanded model and results, including the results of probabilistic sensitivity analysis are presented in Chapter 8.

It should be noted that three of the results chapters (Chapter 6, Chapter 7, and Chapter 8) are built from a Markov model in TreeAge. Unit costs anti-TB drugs, laboratory monitoring, and common procedures (e.g. audiology and ECG) for SOC and bedaquiline treatment are common throughout all three models, as are the monthly transition probabilities for MDR/RR-TB and XDR-TB for loss from treatment, culture conversion (the inverse of treatment failure), and death. However, during the analysis for the costing of ADR management, it was recognized that use of average costs added to the total cost per patient did not sufficiently account for the differences in frequencies and severity of events that had been established through the analyses in Chapters 4-5 and that these should be added to the model as health states. With additional health states, the point estimates and one-way sensitivity analysis was not sufficient for the complexity of the possible patient outcomes. More specifically, prior to the introduction of an calculated cost of moderate ADR and severe ADR, the cost inputs to the model were ingredients based and therefore could be represented as point estimates. However, the costs of ADR management vary according to event experienced, duration, and clinical management. Further, there was likely correlation between input parameters – patients with HIV newly initiating on ART were more likely to die during treatment and more likely to experience costly severe ADR. In these cases (input parameter uncertainty or imprecision and correlation), probabilistic sensitivity analysis, rather than deterministic sensitivity analysis is recommended.[40–42] Thus, between Chapter 6 and Chapter 7, unit costs and transition probabilities were converted to distributions (normal and beta, respectively) and the ADR management costs were added using a gamma distribution. At this point, Chapter 6 had already been published using the initial model and thus, there are differences in the estimate for the cost per patient of the SOC from Chapter 6 to Chapter 8.

Additionally, while there have been some studies indicating the patient costs associated with TB and MDR/RR-TB diagnosis and treatment, similar information is not available for patient costs associated with ADR experienced during MDR/RR-TB treatment. Thus, in order to maintain the same perspective for the costs of both treatment and ADR, a provider perspective was chosen for the analysis. Patient costs of TB, including direct costs incurred for medical expenditure (for example, seeking over the counter or private sector care prior to accessing the public health clinic), direct costs for non-medical expenditure (for example, transport to the clinic) and indirect costs associated with loss of income while ill or hospitalized, can be catastrophic to the patient and family.[43–45] In one study from South Africa, the proportion of patients who were employed dropped from 37% before illness to 3% during MDR/RR-TB treatment; this loss of income and productivity was associated with 44% of the study participants relying on social grants as their primary source of income during treatment.[44] Especially in contexts like South Africa where the costs of medication and clinical care is provided free of charge, the indirect costs of illness are the largest component of patient costs for TB and MDR/RR-TB.[43–45] Exclusion of patient costs by the use of a provider perspective therefore does not represent the societal costs and this limitation will be noted in results chapters (6-8) as well as in the discussion (Chapter 9).

Interventions compared

No MDR/RR-TB treatment.
As a comparator to the standard, long-course, IA-based MDR/RR-TB treatment regimen, no MDR/RR-TB treatment was modelled. The situation may represent undiagnosed or undetected active TB disease, which does occur. The mortality rate for this intervention (no MDR/RR-TB treatment) was assumed to be the same as the mortality rate during early MDR/RR-TB treatment (e.g. weeks 0-12).

MDR/RR-TB treatment without bedaquiline (injectable agent-based regimen).
The standard of care regimen for both MDR/RR-TB treatment and XDR-TB treatment was modelled as the comparison scenario. However, this regimen is no longer in use in South Africa. Roll-out of bedaquiline for patients with additional drug-resistance began in March 2015 [19], and as of late 2016 bedaquiline was available across all provinces for patients who have additional resistance and therefore are eligible for individualized treatment regimens. While not in use, this scenario was used as a base-case scenario for comparison as bedaquiline use within the SA NTP was adopted without cost-effectiveness analysis.[19] Additionally, this scenario is still in accordance with the WHO guidelines for MDR/RR-TB treatment long-course regimens, where bedaquiline is considered as an alternative to the core drugs.[14]

- MDR/RR-TB treatment consisting of 6 months of kanamycin (IA), moxifloxacin (fluoroquinolone), terizidone, ethionamide, and pyrazinamide, followed by 12 months of moxifloxacin, terizidone, ethionamide, and pyrazinamide.
- XDR-TB treatment consisting of 6 months of capreomycin (IA), moxifloxacin (fluoroquinolone), terizidone, ethionamide, pyrazinamide, and para-aminosalicylic acid followed by 12 months of moxifloxacin (fluoroquinolone), linezolid, terizidone, ethionamide, pyrazinamide, clofazimine and para-aminosalicylic acid.

Bedaquiline for XDR-TB only

Another comparator was established that better represents the regimens in place in the SA NTP throughout 2016. The model was based on standard of care, long-course IA-based regimen for MDR/RR-TB and an individualized, bedaquiline containing regimen for patients who fail treatment and require XDR-TB treatment. Treatment interventions modelled here represent the guidelines issued by the SA NTP in June 2015.[19]

- MDR/RR-TB treatment consisting of 6 months of kanamycin (IA), moxifloxacin (fluoroquinolone), terizidone, ethionamide, and pyrazinamide, followed by 12 months of moxifloxacin, terizidone, ethionamide, and pyrazinamide.
- XDR-TB treatment consisting of 6 months of bedaquiline, levofloxacin (fluoroquinolone), terizidone, ethionamide, pyrazinamide, and para-aminosalicylic acid followed by 12 months of moxifloxacin (fluoroquinolone), linezolid, terizidone, ethionamide, clofazimine and pyrazinamide.

Bedaquiline for all MDR/RR-TB

This fourth comparison arm was built using a bedaquiline-based regimen for both MDR/RR-TB and XDR-TB. This proposed regimen is not currently in use in the SA NTP or reported to be in use by mid-2017. Tiberi *et al* and Caminero and Scardigli (2015) suggested a re-grouping of the WHO classification of MDR/RR-TB treatment which would promote bedaquiline to be used rather than the IA; and that kanamycin would only be used if an insufficient number of drugs could be otherwise used.[46,47] This proposed regimen was also implicitly recommended in the 2015 SA NTP guidelines for the roll-out of bedaquiline, where bedaquiline could be used to replace kanamycin (single-drug substitution) in the case of toxicity to kanamycin.[19]

- MDR/RR-TB treatment consisting of 6 months of bedaquiline, levofloxacin (fluoroquinolone), terizidone, ethionamide, and pyrazinamide, followed by 12 months of moxifloxacin, terizidone, ethionamide, and pyrazinamide.
- XDR/RR-TB treatment consisting of 6 months of bedaquiline, levofloxacin (fluoroquinolone), terizidone, ethionamide, pyrazinamide, and para-aminosalicylic acid followed by 12 months of moxifloxacin (fluoroquinolone), linezolid, terizidone, ethionamide, clofazimine and pyrazinamide.

Ethical Considerations

The study protocol was approved by the Human Research Ethics Committee of the University of Cape Town (490/2015, July 2015). Portions of the study protocol were also submitted to and approved by the Human Research Ethics Committee of the University of Witwatersrand: #M150340, March 2015 for analysis of EDRweb and #M131128 in November 2013 for the ADR clinical file review.

Outline of chapters

Chapter 1 provides an introduction to the research, based upon the approved proposal for the PhD research. Chapter one also describes the aims and objectives, the overall structure of the thesis, and the conceptual framework.

Chapter 2 presents a comprehensive literature review covering the basis for using cost-effectiveness analysis for health policy decision making, the state of the MDR/RR-TB epidemic in South Africa, the current treatment guidelines and new drug regimens, and the burden of ADR during MDR/RR-TB treatment. The chapter summarizes current literature and presents unanswered questions that framed the PhD research.

Chapter 3 describes the timing of mortality during MDR/RR-TB treatment based upon analysis of the SA national electronic drug-resistant TB case register, the EDRweb. The timing and risk factors for mortality, including the differential risks of mortality for HIV-negative, HIV-infected patients on ART, and HIV-infected patients not on ART, were used for the development and parameterization of the Markov health state model used for the analysis in Chapters 6-8.

Chapter 4 reports on the results of a ADR-focused clinical file review of two out-patient MDR/RR-TB clinic cohorts in Johannesburg, South Africa. Although a retrospective review, the clinical data captured provided more in-depth understanding of the ADR experienced by MDR/RR-TB patients.

Chapter 5 presents the results of a systematic review and meta-analysis on the types, frequency, and severity of ADR during MDR/RR-TB treatment in cohorts where at least 20% of the patients were HIV-infected.

Chapter 6 is the first of three results chapters using a newly established Markov model for MDR/RR-TB treatment. This model includes separate health states for initiation of MDR/RR-TB treatment, intensive phase, continuation phase, and completion. The model was parameterized using the cohort analysed and described in Chapter 3, bottom up ingredients costing from the perspective of the provider – the SA NTP – and uses separate transition probabilities from all health based upon HIV and ART status.

Chapter 7 describes the direct, provider costs of managing the most frequently occurring moderate to severe ADR associated with the current standard of care MDR/RR-TB treatment regimen in the SA public health sector. Using guidelines for the management of ADR, resource use was extracted and multiplied by ingredient unit costs from South Africa; the same ingredient costs were used to parameterize the cost-effectiveness model in Chapter 6 and Chapter 8.

Chapter 8 builds upon the Markov model first presented in Chapter 6 and modified in Chapter 7 to include the disability weighting for patients who survive and complete MDR/RR-TB treatment but who experienced ototoxicity associated with the use of the second-line injectable agents.

2 LITERATURE REVIEW

"I have to take them [medicines and injections] daily. And I cry every day. Every day I cry for an hour … the place where they give the injection becomes stone hard. When I take the injection, I can't lift my legs, my legs hurt a lot and I am unable to walk. If you give me pills, I will eat them. As many as you want me to [eat]. I have no problems with that. The injections are very painful." – Female patient, aged 37 years [48]

2.1 INTRODUCTION

The aim of this chapter is to review the literature on the question of the incremental cost-effectiveness of bedaquiline for the treatment of MDR/RR-TB in South Africa. The chapter starts by reviewing the literature first to understand whether the question has been previously answered. Is the incremental cost-effectiveness of bedaquiline in the South African context already known? Is the cost-effectiveness known for a similar-enough context that the findings can be applied and used for decision making?

Second, the chapter starts back at the beginning – is the question itself a useful one for decision makers? The role of health economics and outcomes research, especially the use of decision-analytical models and analysis to inform decisions on the adoption of new health technologies is reviewed. Then, the chapter follows the logic of health economic evaluation and reviews existing literature to answer 'so what?' Next, the burden of MDR/RR-TB in South Africa is reviewed. Concerns around the current standard of care and potential new drugs that may be able to improve health outcomes are summarized. Measurements of effectiveness are reviewed for appropriateness in answering the overall topic. The next part of the chapter goes into more detail to unintended consequences of some drugs – adverse drug reactions (ADR) – and what impact these ADR might have on clinical and policy level decisions to use new drugs.

Finally, the chapter provides a summary of findings and highlights the outstanding questions that need to be answered for evidence-based decision making.

2.2 Costs and cost-effectiveness of MDR/RR-TB treatment

First, literature on the cost-effectiveness of MDR/RR-TB was reviewed to determine whether the research question had already been answered. A growing body of work on MDR/RR-TB captures the costs of the medications that make up the treatment regimen, the clinic or hospital visits 'consumed' for administering and monitoring treatment, and the laboratory testing for monitoring treatment.[24] Measures of effectiveness have tracked the standard definitions now used for MDR/RR-TB: successfully treated (cured or completed), failed, or died. While drug-resistant TB treatment is more expensive than drug-sensitive TB treatment, globally, there is evidence that MDR/RR-TB treatment is cost-effective.[24]

Drummond et al summarizes key factors that might affect the applicability of a cost-effectiveness analysis to a new setting, including population demography and disease epidemiology, variations in clinical practice, and relative prices and costs.[40] Because of the high rates of HIV co-infection and differences in treatment regimens, prevalence of second-line drug resistance, models of care, and relative costs of health care services compared to internationally procured pharmaceuticals and diagnostics, preference was given to cost-effectiveness evidence from South Africa. A Google Scholar search of "South Africa" AND "MDR" OR "Rifampicin resistant" AND "cost" identified multiple studies that described the costs of MDR/RR-TB treatment in South Africa.[24–26,49,50] An article published in 2001 analysing the cost-effectiveness of directly observed treatment in the USA and South Africa[51] was excluded from the review because of the major changes to HIV and MDR/RR-TB treatment guidelines since 2009 in South Africa. Analyses focusing solely on diagnosis of drug resistant TB, for example the roll-out of Xpert MTB/RIF, were excluded as the MDR/RR-TB costs used were either citing other studies or were presented with insufficient detail to evaluate. Published costs of MDR/RR-TB treatment which may be comparable to the current standard of care in South Africa were reviewed and costs extracted. As inpatient admission for MDR/RR-TB treatment was found to be a major component of the total cost [24,50], many of the studies have been focused on the comparison of inpatient vs outpatient models of care. MDR/RR-TB treatment using an ambulatory (outpatient) model of care for South Africa is estimated range from US$3,894 [25] to US$4,925 [26] cost per patient for the 24 months of treatment when adjusted to 2016 USD.[27,28]

Table 2-1 Literature of costs of standard, long-course, injection-based MDR/RR-TB treatment

Model of RR-TB treatment; Cost method	Setting, period	Included cost components	Point estimate, range	Reference
Ambulatory (outpatient) RR-TB treatment for all stable patients Costs by treatment outcomes Bottom-up provider costs	MSF, Khayelitsha, South Africa 2009-2011	Hospitalization TB drug regimen Primary health care (outpatient) visits Diagnosis and TB treatment monitoring ADR monitoring: kidney function, liver function, thyroid function, and hearing tests	Successfully treated, 2013 USD: 8,359 (range: 2,585 – 32,506)	[26,49]
Inpatient treatment for all RR-TB patients until culture conversion Costs by treatment outcomes Bottom-up provider costs	Klerksdorp, North West province 2009-2011	Hospitalization TB drug regimen Diagnosis and treatment monitoring ADR monitoring: kidney function, liver function, thyroid function, and hearing tests/ECG? ADR drugs (concomitant medications)	6-month successful outcome (discharge to outpatient), 2011 USD: 17,327 (sd: 6, 572)	[50]
Ingredients-based guidelines cost Outpatient per patient treated Inpatient per patient treated	Western Cape, South Africa	Hospital inpatient stay (if inpatient) Hospital outpatient visit Clinic visits TB drug regimen Diagnostic / monitoring tests ADRs Surgery (e.g. lobectomy if required) Death	Average unit cost, 2011 USD: 5,930 (outpatient) 14,349 (inpatient)	[25]

Costs and cost-effectiveness of bedaquiline

More recently, the cost and cost effectiveness of new drugs has been the focus of economic evaluations. The initial WHO 2013 guidance for the use of bedaquiline included results of an exploratory cost-effectiveness analysis. According to the published guidance, the bedaquiline was determined to be cost-effective in many settings, when compared to a willingness to pay threshold (WTP) of the gross national income per capita.[31] Because of the much lower assumed WTP threshold for low-income countries (including for the modelled context of Nepal at US$540), the cost-effectiveness of bedaquiline was considered to be 'uncertain' or 'ambiguous' in low-income settings.[31] Also, the expert group indicated that it was uncertain about the affordability of the treatment (even if cost-effective) in many high-burden MDR/RR-TB settings. Additionally, the expert group concluded: "While the cost-effectiveness modelling showed overall benefit, there were concerns about the simplifying assumptions used (e.g. no accounting for the difference in serious adverse events, no accounting for effect on transmission, uncertainty about application of trial outcomes – including deaths – to routine programmatic conditions, etc.).”[31]

Evidence has been growing on the cost-effectiveness of bedaquiline in different settings. As of August 2017, five studies were identified that analysed the cost-effectiveness of bedaquiline [52–57], in addition to the original analysis included in the WHO recommendations.[31] The studies were identified using a Google Scholar search for “bedaquiline” AND “cost”. Review articles summarizing other studies but not presenting original research or articles providing only a unit cost were excluded from the analysis. All of the identified studies assumed that the mortality imbalance in the Phase 2b trial was an anomaly and assumed no difference in mortality for the bedaquiline regimen versus standard regimen in the base case analysis.[52–57] The analyses similarly made assumptions so that the concerns of the expert group about no accounting for difference in serious adverse events was not answered. Similar to the initial exploratory analysis and the Phase 2b trial, all identified reviews considered bedaquiline added on to the standard regimen rather than replacing the injection.

Key findings of the cost-effectiveness analyses for bedaquiline were extracted from literature and summarized below (Table 2.2). A previously published cost-effectiveness analysis established that bedaquiline could actually be cost saving compared to the standard regimens when patients who are sputum culture positive are hospitalized until sputum negative.[53] However, South Africa adopted ambulatory, outpatient care for MDR/RR-TB in 2011 and therefore was unlikely to realize this cost saving. Similarly, like the adaptation of the model for Italy, surgery for MDR/RR-TB patients who have failed treatment is very rare in South Africa and the use of bedaquiline could not avert surgical costs.[56]

Table 2-2 Cost effectiveness analysis of introduction of bedaquiline

Regimens compared	**Setting, period**	**Result**	**Reference**
Standard regimen vs standard regimen + bedaquiline including XDR-TB	Korea, 2014	ICER = 1,300 KRW/QALY over 10 years	[52]
Background regimen vs background regimen + bedaquiline	United Kingdom, 2014	ICER = -11,434 GBP/QALY over 10 years (cost saving, dominated background regimen)	[53]
Background regimen vs background regimen + bedaquiline for MDR/RR-TB and XDR-TB separately	Germany, 2014	ICER MDR = 22,118EUR/QALY ICER XDR = 5,472 EUR/QALY over 10 years	[54,57]
Background regimen vs background regimen + bedaquiline including transmission	South Africa, 2013	ICER = 14,576 USD/DALY averted over 10 years, if bedaquiline at ½ lowest range price	[55]
Background regimen vs background regimen + bedaquiline including transmission, societal and provider payer perspectives	Italy, 2014	ICER = 16,639 EUR/LYG	[56]

The Markov model initially built for analysing the use of bedaquiline in the United Kingdom was also used to estimate the cost-effectiveness of bedaquiline in multiple low and middle-income countries, including South Africa. South Africa does benefit from a very discounted price to access bedaquiline, at ZAR 9,950 (US$675) for a complete course of treatment. Bedaquiline was projected to be cost effective, even at costs for bedaquiline 30- to 70-times what it is priced at for South Africa.[55] However, this finding was driven by a very low treatment success rate for the standard regimens and therefore a large reduction in the number of patients requiring XDR-TB treatment once regimens included bedaquiline [55]. Additionally, while the rates of HIV/TB co-infection in South Africa are among the highest in the world [58] the model did not account for the higher mortality of MDR/RR-TB patients with HIV co-infection [13] or the on-going costs of ART after MDR/RR-TB treatment completion. Thus, it is uncertain whether the modelled results would be appropriate for decision makers to apply in the South African context.

2.3 HEALTH AND OUTCOMES RESEARCH

With the understanding that the research question remains unanswered, the next review considered the appropriateness of a question of cost-effectiveness. Is it useful and appropriate for decision makers to consider the cost-effectiveness of new treatment regimens? Cost-effectiveness analysis (CEA) is a type of economic evaluation that compares both the monetary costs and the effectiveness of two different interventions. CEA of health care programs is a method for helping decision makers to optimize finite resources in the achievement of population health. As Drummond *et al* lay out in their text on economic evaluation in healthcare, questions around the comparative costs of two different health programs or interventions should be preceded by questions of efficacy and effectiveness.[40] If a new treatment is not efficacious in improving the outcome of interest in a tightly controlled setting such as a Phase 2 randomized, controlled clinical trial, no one would want to buy the new treatment, making questions of its cost less relevant. The efficacy from controlled trials must be replicated in 'real world' conditions or settings with broader inclusion categories and less control over outside factors, such as during Phase 3 clinical trials, for the new drug to be declared effective. Similarly, there is less interest in purchasing new treatments that are known to be ineffective, and therefore economic evaluations such as CEA on these ineffective treatments would be less likely. As indicated in Chapter 1.3 in introducing the cost-effectiveness plane, for cost minimization, at times a less effective but lower cost intervention would be the preferred option. The United Kingdom's National Institute for Health Care Excellence summarizes the decision point in its guidelines.[41] Health economists are encouraged to recommend consideration by the guidelines development group of interventions that either 1) "increase clinical effectiveness at an acceptable level of increased cost" or 2) "are less effective than current practice but free up a substantial amount of resources".[41]

There is no formal definition for what level of efficacy or effectiveness is efficacious or effective, the levels are often presented in relation to another value which is known. For example, new treatments are often compared to the natural history of disease, i.e. what was observed to have happened to patients with a disease prior to treatment options being available. New treatments might also be compared to the currently accepted standard of care, where the comparative effectiveness of achieving cure is more of interest than the absolute effectiveness relative to no treatment at all. In CEA, this is defined as the difference between an intervention mix constrained CEA and a generalized CEA.[42] Evaluation and decisions on the relative efficacy and effectiveness of different healthcare interventions can happen at many different levels, including the patient choosing to go to a clinic when s/he coughs; the clinician choosing whether to order expensive diagnostic tests or to send the coughing patient home with cough syrup; and the government health department choosing to launch a TB symptom screening campaign or an infant immunization campaign. Integrating the use of systematic review, clinical trial results, and other evidence as to the efficacy and effectiveness of healthcare into the clinical decision making progress is now known as evidence based medicine.[59]

In South Africa, MDR/RR-TB is primarily treated in the public sector, at government supported facilities. All patients are offered services free of charge. Medical aid funds are not required to offer treatment for TB or drug resistant TB; the prescribed minimum benefits reference "Diagnosis and acute medical management; successful transfer to maintenance therapy in accordance to DOH guidelines."[60] Thus, decisions made at the public health level, in terms of setting the DOH guidelines, tenders, and approach are the most relevant and impactful on MDR/RR-TB outcomes in South Africa. Public health decision making, as with clinical decision making, also does not start with questions of cost. Before asking about efficacy and effectiveness, for public health policy and budget making, the first questions are often about burden and impact. Essentially, the first question is 'So what? Why should (we) care?'. Diseases or health problems that only affect a small proportion of the society or that have a relatively small impact on even a large proportion of the society, seldom rise to the level of priority for public health policy. Thus, for public health, the first evidence considered is a quantification of the mortality and morbidity from different causes. Quantification of mortality and morbidity at the global or national context can help to focus policy and decision makers on the diseases and issues that are having (and will have in the future) the most impact on the population.[61] For example, applying the burden of disease methodology to South Africa in the early 2000's identified that South Africa was facing a quadruple 'burden of disease': HIV/AIDS, 'pre-transitional diseases linked to under development', non-communicable diseases, violence and injury.[62,63] Measurement of the burden of different diseases does not mean that public health decision makers will only or should only consider the results of a quantification exercise. Additionally, decision makers need to consider societal values and preferences, especially with regards to the distribution of health across different population groups.[63,64] However, the quantification provides a starting point for prioritization and evidence to use in the debates.

Evidence as to effectiveness of an available intervention is still essential to public health policy making as it is for clinical management of individuals.[65] There is a re-enforcing loop – research needed to develop effective interventions or to build the evidence base that existing interventions are (not) effective – often only happens after the 'so what?' question has been answered.[61,65] The World Bank 1993 report on investing in health established the case for why health is essential to development and then defined the major failures with previous investments in health: misallocation of resources (not allocating towards interventions that are most cost-effective), inequity, inefficiency, and 'exploding' costs. With this diagnosis of the problem, the three-pronged recommendation for investing in health was to 1) foster an environment that enables households to improve health; 2) improve government spending on health; and 3) promote diversity and competition.[66] While information on the comparative or incremental cost-effectiveness of an intervention is not the only evidence that is or should be considered; its importance for public health decision making is now well established.[40,42,64]

DALYs and QALYs

As we can see above, CEA starts first with measurement of effectiveness. Using a measurement common across multiple diseases, injuries and disabilities can assist in optimizing resource allocation for population health and not just optimizing treatment of any one disease. Thus, there is a need to define how (how much) alleviating the mortality or morbidity of a particular disease or injury contributes to the overall population health. The disability adjusted life years (DALYs) approach measures both years of life lost and years lived in a state of reduced health (disability). Life years saved are directly calculated using the deaths occurring as a result of the disease or injury using the age of the patient at death subtracted from the life expectancy at that age of that specific population.

Quality-adjusted life years (QALYs) are an alternative outcome to DALYs which are also commonly used. QALYs are gained while DALYs are averted, and sometimes the two terms are used as the mathematical reflection of the other (e.g. 1 - disability weight = quality adjusted year). However, there are difference in the methodology for calculating QALYs compared to DALYs. QALYs are most commonly used for resource-rich settings.[67] QALYs use utility measurements, where the disutility of being in hospital or having a disease is considered to be less than 1(perfect utility) but greater than 0 (no utility, or death). QALYs incorporate hospitalization, loss of productivity, and disability as a whole [68]; this makes it challenging to disentangle one effect from the other when modelling a new treatment that potentially has a difference in one of these factors. The QALYs therefore are also specific to the setting and expectations of that setting. For example, in low-burden, resource-rich settings with low mortality and little drug resistance, active TB is considered to have a very low disutility and therefore little incentive to avoid active TB through preventative interventions.[69] There is little evidence from limited-resource settings as to the disutility of having TB, especially when combined with HIV infection or with additional drug resistance.[68] One of the first cost-effectiveness analyses for the treatment of MDR/RR-TB in Peru used a QALY of 0.58 [70] based upon a study from India.[71] This lack of evidence on the disutility of a disease or disability within limited-resource settings is not limited to TB; most studies measuring utility (or disutility) are from resource-rich settings, e.g. Europe, the USA, and Australia.[67]

Disability weightings

Disability weighting, in contrast to utility, is intended to have a more limited scope and measure disability only; loss of welfare is excluded from the measurement.[72] A disability weight is a measure between 0 and 1 where 0 represents full health and 1 represents death; the higher the disability weight, the more DALYs add up. Disability weights were constructed in order to provide a way to consider non-fatality outcomes across multiple health conditions and interventions.[72] Disability weights are more subjective than mortality, but attempt to at least transparently describe and quantify for debate different weights. DALYs are based on two principles: "Principle 1. The burden calculated for like health outcomes should be the same." and "Principle 2. The non-health characteristics of the individual affected by a health outcome that should be considered in calculating the associated burden of disease should be restricted to age and sex."[72] The first principle attempts to exclude issues of stigma or temporality of the disability. The second principle attempts to exclude issues such as whether the person affected is a wage earner or 'contributes to society' in some way.

In absence of a specific study from the context being analysed, the disability weights of reference are those from the Global Burden of Disease (GBD) study. The methodology underlying the disability weights reported in the GBD 2013 has evolved substantially from the origin of the DALYs in 1996. Initially, disability weights were assigned to classes ranked according to loss of welfare and function (Table 2.3).[73] The different health states were assigned a disability weighting by a group of experts from around the world met at the WHO (e.g. persons from the US were from the U.S. Centres for Disease Control) who were asked to weigh the social preference for time spent in one state versus another.[72,73] It was recognized, although left to future work, that there was outstanding debate over how to elicit utility or preference for one health state over another and whether the relative weights of disability would differ across the globe.[72,73] Newer states reflect not only improved statistical analysis and methodology for collecting valuation; especially for HIV/AIDS, the prognosis and understanding of the prognosis for a person living with HIV who is on ART has also changed over time. The 2004 value for an AIDS cases on ART represented a disability weight nearly 2-times that of the value used in 2013 (0.167 compared to 0.078, respectively)[74] in part because of the additional 10-years of experience and understanding that ART is a very effective treatment.

Table 2-3. Definitions of disability weighting in the 1996 DALY construct [73]

Class	Description	Weight
Class 1	Limited ability to perform at least one activity in one of the following areas: recreation, education, procreation or occupation	0.096
Class 2	Limited ability to perform most activities in one of the following areas: recreation, education, procreation or occupation	0.220
Class 3	Limited ability to perform most activities in two or more following areas: recreation, education, procreation or occupation	0.400
Class 4	Limited ability to perform most activities in all of the following areas: recreation, education, procreation or occupation	0.600
Class 5	Needs assistance with instrumental activities of daily living such as meal preparation, shopping or housework.	0.810
Class 6	Needs assistance with activities of daily living such as eating, personal hygiene or toilet use.	0.920

In 2015, weights for 220 disabilities were published as part of the GBD 2013.[74] Each of the disabilities had been mapped as a sequela of a disease, e.g. hearing loss could occur as a result of congenital abnormality, ear infection, or meningitis.[75] As part of the GBD 2010 study, more than 40,000 persons were surveyed through face-to-face, telephone, or web-based questions comparing pairs of different health states. Thus, the weights were calculated from repeated measurements comparing one health states to another, rather than asking for participants to assign a score or rank the 220 conditions individually.[74] The pairwise comparisons were anchored to a ranking between 0 and 1 using a public health evaluation approach – participants in the web survey were asked to choose whether to allocate resources to one disability or to a group of another disability to determine how many people would have to be helped for the two disabilities to be considered equal (e.g. whether curing 100 cancers is equivalent to 10, 100 or 1,000 TB cases).[74,75]

Although Salomon et al concluded from the GBD 2010 study that there is a significant level of consistency across different contexts (e.g. Peru compared to the USA) [74], this conclusion has continued to be questioned.[75–78] A South African team replicated many of the methods from the GBD 2010 in Cape Town, South Africa to investigate whether the weightings would be similar in the SA context.[79] A total of 671 persons, mostly younger than 50 years and 79.3% without having matriculated from secondary school were interviewed.[79] The differences in weighting found is not only due to cultural differences, but may also be because of the anchoring done where persons were asked how many years of healthy life were equivalent to 10 years in the disabled state (a time trade-off approach).[79] In 2013, the weights were revised again in order to 1) incorporate additional sequelae; 2) revising the lay description of certain health states to improve consistency of wording across different levels of severity; and 3) to assess whether weighting is insensitive to the duration of disability.[75]

Co-morbid conditions

Co-morbid conditions, such as HIV and TB, are more challenging to assess. The loss of health due to TB/HIV co-infection was a specific trade off that interviewees were asked to consider for the GBD study. However, other less common co-morbidities or additional co-morbid conditions while TB/HIV co-infected do not have published disability weights. For example, HIV-infected patients may experience one or more ADR during MDR/RR-TB treatment. These patients may have a higher disability weight than those without ADR. When there are co-morbid conditions that were not grouped for the ranking questions (e.g. diabetes and TB), the scores can be adjusted to determine the overall burden of the co-morbidity.[80–82]

As Haagsma et al describe, when there are co-morbidities, sometimes the higher of the morbidities is used only (the one with the greater disability weight); sometimes the two disability weights are added; and sometimes they are multiplied.[82] Haagsma et al found that highest correlation between observed disability weights for certain combinations of conditions and the calculated comorbidity weight was highest for additive approach and the multiplicative approach.[82] A separate study of multiplicative approach also found high correlation to observed values for certain combinations of comorbidities.[80] The two or more disability weightings can be converted to scores (1-disability weight) and then multiplied to determine the overall burden of the co-morbidity[80,83], similar to methods used for calculating the utility in a cost-utility analysis.[80] Thus, a person who has TB without HIV infection (disability weight (dw) = 0.331, converted score = .669) who has severe hearing loss with ringing (GBD 2010 disability weight=0.065, converted score=0.935[74]) would have a combined score of 0.626 or equivalent disability weight of 0.374.

$1 - dw_{TBHIV} = score_{TBHIV}$	$1 - dw_{hearing} = score_{hearing}$	
$1 - 0.331 = 0.669$	$1 - 0.065 = 0.935$	
$score_{TBHIV} \times score_{hearing}$	$= score_{TBHIV\ hearing}$	$1 - score_{TBHIV\ hearing} = dw_{TBHIVhearing}$
0.669×0.935	$= 0.626$	$1 – 0.626 = 0.374$

Costs

Once (relative or incremental) effectiveness is established, the question of costs must be addressed. Again, the text by Drummond et al offers a useful framing, asking: 'Which costs should be considered?' and 'How should costs be estimated?'[40] For the proposed analysis comparing two different drug regimens for the treatment of MDR/RR-TB, an incremental costing rather than a full costing is appropriate. Further, the costs can be narrowly defined to those that would likely differ between the two options. For example, the management and operations of the district health system is unlikely to differ based upon different drug regimens administered and therefore can safely be kept outside the scope of the incremental costing. For where possible, the bottom-up costing methods to be implemented for the study are consistent with the "Guidelines for cost and cost-effectiveness analysis of tuberculosis control" [84], in order to facilitate comparison to other studies and to non-DR tuberculosis costing control. An ingredients-based approach building up provider costs is a recommended method for costing studies [84] and has been used for the many of the economic evaluations of MDR/RR-TB reviewed above.[26,49,50,85–87]

Cost effectiveness thresholds

Estimated cost effectiveness ratios and ICERs can also be compared against a theoretical threshold below which an intervention is considered to be cost-effective. In some countries that routinely use health technology assessments to evaluate new interventions (e.g. the UK), WTP thresholds may be explicitly set.[41,88,89] Use of a WTP threshold assists decision makers in understanding whether any of the interventions being analysed are worthwhile. For example, if the decision maker is willing to pay a $500 for a life saved and the cost of the intervention is $400 per life saved, that intervention would be considered 'cost-effective' (CER < WTP). However, in many contexts, the WTP is not an expressed; policy makers do not explicitly state that they are willing to pay a certain dollar amount for a life saved. Initially, the World Bank defined interventions that cost $50 or less per DALY in low-income settings or $150 or less per DALY in middle-income settings as highly cost-effective.[66,90] In middle-income countries such as South Africa, less than $500 per DALY averted would be considered cost effective by this standard.[90] The WHO CHOICE project (Choosing Interventions that are Cost-Effective) set a standard based upon the per capita income for a country. Interventions are considered cost effective if they cost less than three times the average per capita income per DALY averted; interventions are considered very cost effective if they cost less than the average per capita income per DALY averted.[42,91] For South Africa, with a gross national income (GNI) per capita of $3,320 in 1993 (https://data.worldbank.org/country/south-africa), the difference between these two thresholds ($500 vs $9,960) is nearly 20-fold. However, there is growing recognition that while the simplicity of a global formula for a threshold based on per capita income and a pass/fail assessment of interventions is attractive, it provides insufficient information for informing decisions and may lead to decisions that are unaffordable or inefficient.[37,88,90]

Cost-effectiveness models

Modelling is one method for extending the costs or effectiveness beyond the limitations of a particular study. For example, many clinical trials have interim markers or intermediate outcomes which are used to compare interventions while the differential effectiveness may be realized outside of the time limits of the study. Modelling helps to extend the expected results beyond what was demonstrated or observed in a study. Drummond et al explains the key objectives of economic evaluation that modelling provides: 1) structure of health states and alternate outcomes); 2) framework for analysing evidence by selection and use of input parameters; 3) evaluation of alternative options; 4) consideration of uncertainty and variability; and 5) identification of priority unanswered questions for further research.[40] Modelling is an appropriate form of economic evaluation when there is need to bring together various sources of evidence on costs and effectiveness in order to inform decisions about health care policy [48]. Markov models are a form of health-state transition models. They are appropriate for closed cohorts where transitions occur at specific states. The more simplified decision tree models, in contrast, neither reflect time nor can they reflect time-dependent parameters.[92] Best practice recommendations are that cycle length should reflect clinical events.[92]

Literature was reviewed to identify existing models for estimating the cost-effectiveness of MDR/RR-TB treatment. Three basic approaches were identified: 1) average cohort costs multiplied by expected outcomes; 2) state transition model starting from TB infection; and 3) Markov health state model. A cost-effectiveness model used to analyse the introduction of bedaquiline has been applied and adapted to many contexts. However, none of the models identified allowed for both the contextualization of high prevalence HIV setting and alternative MDR/RR-TB treatment strategies. HIV health states were common in state transition and population models of infection, but not for MDR/RR-TB treatment. Multiple cost-effectiveness models exist which include, but do not focus on, the health state of MDR/RR-TB active disease or the phases of MDR/RR-TB treatment. For example, cost-effectiveness models for new TB diagnostics include the possibility that undiagnosed and untreated TB could be drug-resistant TB and that this leads to higher treatment costs (e.g. see Menzies *et al* [93]). However, these models that included but were not developed for MDR/RR-TB led to simplifying assumptions on the MDR/RR-TB stages or states that precluded use of the models for understanding differences between MDR/RR-TB treatment regimens.

One of the earliest cost-effectiveness analyses of MDR-TB treatment was from Peru, based on a pilot project from 1997 to 1999. The authors built an Excel model where the ingredients-based average costs were multiplied by the expected treatment outcomes of different strategies.[85] Results were presented as cost per

DALY averted (the equivalent of an ICER) for providing the second-line drugs. This type of Excel model where the average cost of treatment strategies was multiplied by the different patient outcomes was also used for an analysis in the Philippines.[86] A systematic review of the cost-effectiveness of MDR-TB treatment applied the same approach globally, adjusting the bottom-up cost components according to model of care (outpatient or hospitalized) and WHO CHOICE inputs (e.g. cost per day in hospital), in order to provide a range of estimated costs for MDR-TB across different regions.[24]

The Peru cohort was also the starting point for a dynamic state transition model (Figure 2.1). The state transition model started from a population who was susceptible to TB infection, followed them through latent TB infection, active TB and chronic TB or MDR-TB. MDR-TB costs and effectiveness were taken as average based on the same total costs and cohort outcomes as used in the Excel model (above). A similar approach of starting with TB infection but not going into detail on MDR-TB treatment was used for modelling the roll-out of Xpert MTB/RIF (e.g. Menzies et al, [93]). The different health states included in the model reflect a different prioritization of the questions being asked. The Peru model is useful for understanding what would happen in absence of MDR/RR-TB treatment, showing on-going transmission to an uninfected population and also the lag in time (latent TB or latent MDR health states) between infection and active disease. However, treatment for MDR/RR-TB is one health state for two populations (acquired MDR or primary MDR), a limitation when assessing differences in the effectiveness of MDR/RR-TB treatment.

Figure 2-1 State transition model, Peru model [70]

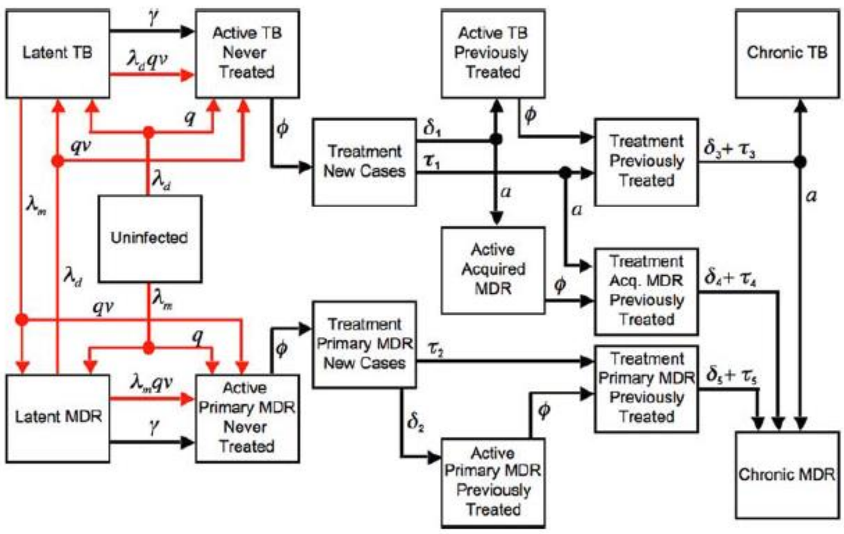
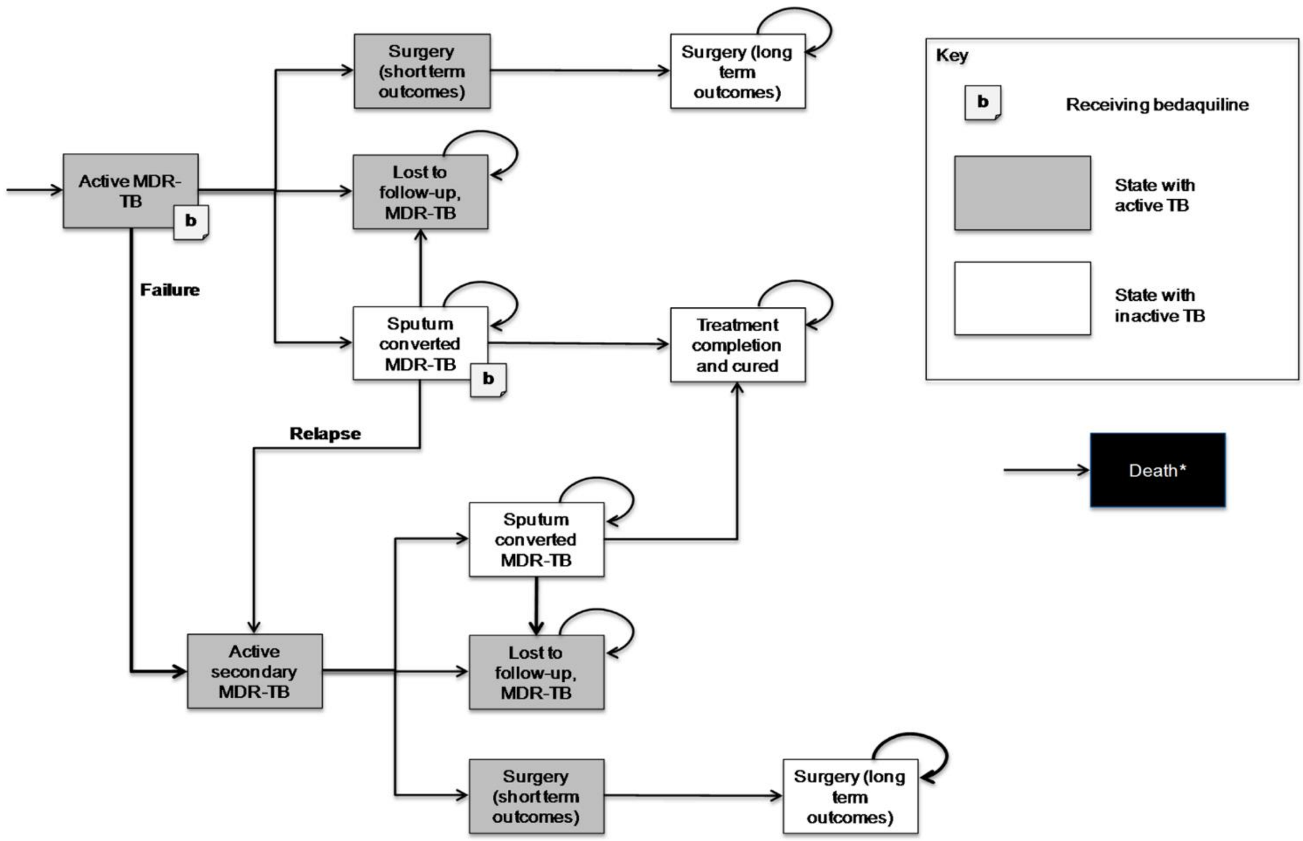


Figure 1. Structure of the TB Treatment Model
Boxes represent health states, arrows represent population flow between health states, red arrows represent infection and re-infection. λ_d is the force of non-MDR infection, λ_m is the force of MDR TB infection, q is the proportion of new infections that break down rapidly, v is the immunity factor, γ is the rate of delayed progression from latent to active disease, φ_i is the case detection rate, δ_i is the treatment dropout rate, τ is the treatment failure rate, and a is the fraction of uncured patients acquiring MDR. Death can occur from any state (not shown). Cure can occur from any diseased state. Cured patients transition to the latent infection health state (not shown).
DOI: 10.1371/journal.pmed.0030241.g001

A more recently published cost-effectiveness model for MDR-TB used a decision-tree analysis to estimate the ICER of delamanid plus background regimen in Germany.[94] There were only five possible outcomes modelled: cure, treatment completed, failure, loss from treatment, or death. The time step was yearly and the time horizon 10 years.

Wolfson et al developed a cost-effectiveness model of MDR/RR-TB treatment for the UK (Figure 2-2), which was subsequently applied to Germany [54] as well as Estonia, Russia, South Africa, Peru, China, the Philippines, and India [55]; it was also adapted to Korea [52] and Italy [56]. The model has six health states, where patients transition from having newly diagnosed MDR-TB, to sputum converted MDR-TB, to treatment completion and cure. Patients could also relapse, have surgery for MDR-TB, be lost from treatment or die.[53] Time to sputum conversion and rates of relapse are important drivers of cost in the model. The time step was monthly (28 days) and the time horizon 10 years. This model starts after diagnosis, at treatment initiation, which is the same starting point for the patient level data within EDRweb. Risk of transmission or the impact of undiagnosed or untreated MDR/RR-TB therefore cannot be assessed using the UK model. For the South African context, the inclusion of surgery as health states (surgery, short term surgery outcomes, long term surgery outcomes) adds complexity for a very small proportion of patients. While surgery for chronic MDR/RR-TB, i.e. lobectomy, is expensive (estimated at $5,549 per event [25]), it is very rare in the SA NTP and is reserved for patients in whom individualized and extended chemotherapy has failed. Availability may be at certain treatment sites but is estimated at less than 5% of the XDR-TB cohort.[95] Conversely, the UK model does not include separate health states or transition probabilities for patients co-infected with HIV. While this simplification may be appropriate for low-prevalence settings such as the UK, it may not be appropriate for South Africa.

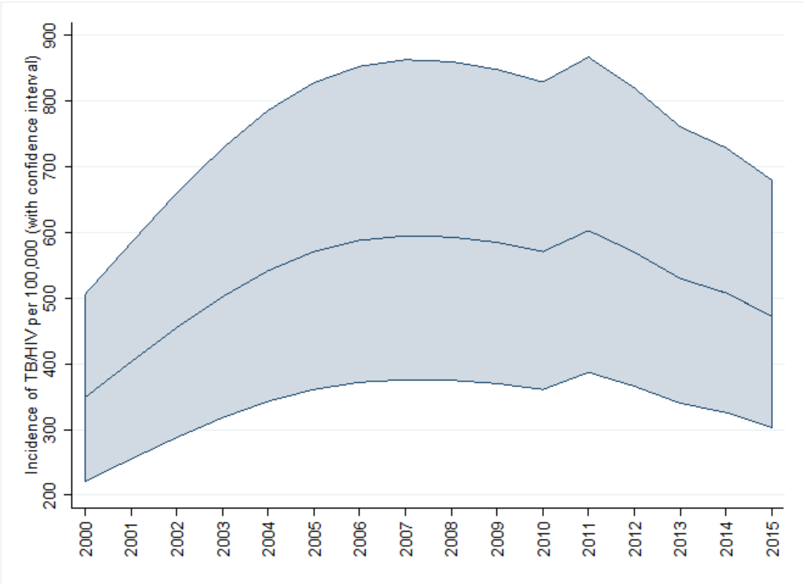
Figure 2-2 Markov model, MDR-TB treatment UK model [53]



2.4 MDR/RR-TB

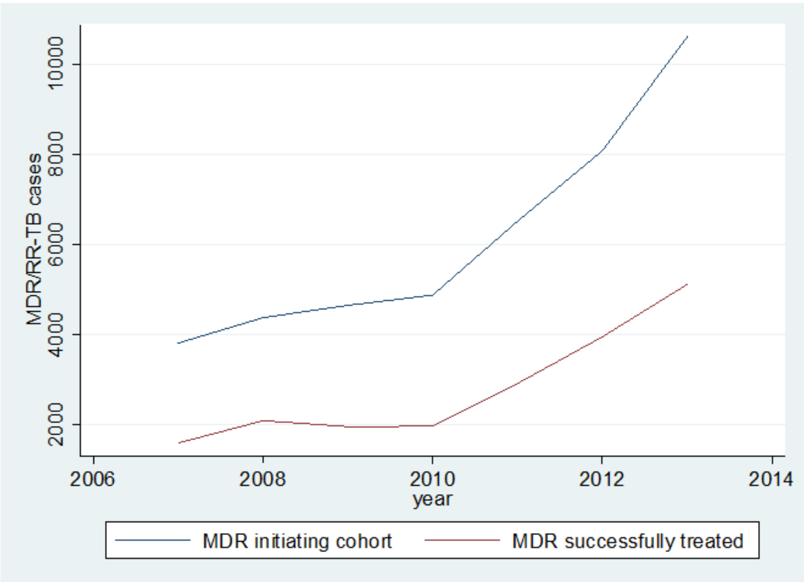
As established in the introductory chapter (Introduction), MDR/RR-TB represents a significant public health problem for South Africa. According to the Global Tuberculosis Report 2016, only 6 countries accounted for 60% of the new TB cases globally: India, Indonesia, China, Nigeria, Pakistan and South Africa. The report concludes "Global progress depends on major advances in TB prevention and care in these countries."[58] Improved modelling of incidence in South Africa shows a declining trend in the incidence and prevalence rates over time [58] (Figure 2-3), likely a result in increased access to ART.[96]

Figure 2-3 TB/HIV incidence in South Africa, per 100,000 population, 2000 to 2015



Data source: WHO Global TB database http://www.who.int/tb/data/en/

Figure 2-4 Number of MDR/RR-TB cases initiating and successfully treated, South Africa 2007 to 2013



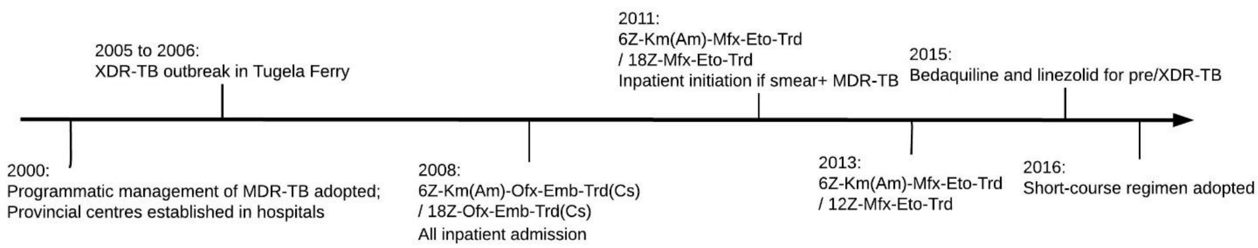
Data source: WHO Global TB database http://www.who.int/tb/data/en/

In 2015, there were 19,613 laboratory confirmed cases of MDR/RR-TB and 1,024 laboratory confirmed XDR-TB. [58] More than 1/3 (36%) of diagnosed cases were not registered as having started on MDR/RR-TB treatment (2015 cohort of 12,527 initiating).[58] Of the 10,614 patients who started treatment in 2013, only 48% were successfully treated (Figure 2-4).[58] According to Stats SA, there were 1,115 deaths due to MDR-TB and 162 deaths due to XDR-TB in 2015.[97] TB, including both drug resistant and drug sensitive forms, accounted for 33,063 deaths in 2015. Although the number of deaths has been declining over time, TB has been the leading cause of death in South Africa for multiple years.[97]

Standard of care treatment regimens and duration

In line with WHO 2011 treatment guidelines [16], through mid-2016, the standard of care for newly diagnosed MDR/RR-TB treatment in South Africa was to use a standardized regimen, unless documented resistance or intolerance to the drugs in the regimen requires an individualized regimen (Figure 2-5).[17,19] The initial diagnostic test for most TB patients is the Xpert MTB/RIF, which detects both TB and resistance to rifampicin. Patients can also be diagnosed on TB culture. Specimens that are culture positive are tested using line probe assay (LPA), which can detect both rifampicin and isoniazid resistance and therefore diagnose MDR-TB. All patients who are at least rifampicin resistant are initiated on MDR/RR-TB treatment regardless of whether a test for isoniazid resistance has been performed.

Figure 2-5 Drug-resistant TB treatment guidelines, 2000 to 2016 in South Africa



As of 2016, WHO-recommended standardized regimens for MDR/RR-TB are now categorized as either short-course (9 to 12 months) or long-course (18 to 24 months).[14] Standard long-course MDR/RR-TB treatment is divided into two phases: 6 months (intensive phase) of 5 drugs (kanamycin, moxifloxacin, ethionamide, terizidone, and pyrazinamide) followed by 12 to 18 months (continuation phase) of 4 drugs (moxifloxacin, ethionamide, terizidone, and pyrazinamide). The intensive phase is set at 6 months in order that the average patient receives at least 4 months of treatment following culture conversion, where patients who were culture positive convert to a negative culture. The continuation phase similarly is based upon the length of the intensive phase, patients are expected to have at least 12 months of treatment with the continuation drugs while culture negative. Reversion of culture status (from negative back to positive) during treatment or interruptions in treatment may lead a clinician to extend the length of either the intensive or continuation phases.

Patients with at least either preXDR- or XDR-TB are treated with individualized regimens which may include high-dose isoniazid, para-aminosalicylic acid (PAS), clofazimine, and/or capreomycin. Linezolid has been available but in a very limited way due to the cost prior to registration of a generic version and inclusion of linezolid in a public tender in 2016.[98] Although capreomycin is a cyclic peptide and therefore has a different means of action against TB than the aminoglycides kanamycin and amikacin, it is not as commonly used as before [19] due to increasing evidence of cross resistance with the other second line injectables (SLD).

As indicated above, surgery for drug-resistant TB is very rare in South Africa and is reserved for patients in treatment has failed. It is estimated that less than 30 patients would have received surgery out of the more than 11,000 who initiated MDR/RR-TB treatment in 2014 in South Africa .[2,95]

According to the WHO 2016 updated guidelines for the treatment of drug-resistant TB [14], core drugs were re-prioritized in terms of creating standard regimens (Table 2-4). In order to design an effective regimen, clinicians are first asked to 1) choose 1 later-generation fluoroquinolone (group A); 2) add one second-line injectable agent (group B); 3) add two or more from the other core second-line agents (group C); and 4) add pyrazinamide and any first line drug that may strengthen the regimen (group D1). Drugs from group D2 or D3 *could be added if an otherwise effective regimen* could not be composed.[20]

Table 2-4 Standard regimens for long-course MDR/RR-TB treatment

<table>
<tr><th colspan="2">WHO 2011 Classification [16]</th><th colspan="3">WHO 2016 Classification [14]</th></tr>
<tr><td>Group 1
First-line oral anti-TB drugs</td><td>Isonaizid
Rifampicin
Ethambutol
Pyrazinamide</td><td>Group A
Fluoroquin-olones</td><td colspan="2">Levofloxacin
Moxifloxacin
Gatifloxacin</td></tr>
<tr><td>Group 2
Injectable anti-TB drugs</td><td>Streptomycin
Kanamycin
Amikacin
Capreomycin</td><td>Group B
Second-line injectable agents</td><td colspan="2">Kanamycin
Amikacin
Capreomycin</td></tr>
<tr><td>Group 3
Fluoroquin-olones</td><td>Levofloxacin
Moxifloxacin
Gatifloxacin
Ofloxacin</td><td>Group C
Other core second-line agents</td><td colspan="2">Ethionamide/Prothionamide
Cycloserine/Terizidone
Linezolid
Clofazimine</td></tr>
<tr><td>Group 4
Oral bacteri-ostatic sec-ond-line</td><td>Ethionamide/Prothionamide
Cycloserine/Terizidone
p-aminosalicylic acid</td><td rowspan="3">Group D
Add-on agents</td><td>D1</td><td>High-dose isoniazid
Ethambutol
Pyrazinamide</td></tr>
<tr><td rowspan="2">Group 5
Anti-TB drugs with limited data on efficacy and safety</td><td rowspan="2">Linezolid
Amoxicillin/Clavulanate
Imipenem/Cliastatin
Meropenem
Thiocetazone
Clarithromycin</td><td>D2</td><td>Bedaquiline
Delamanid</td></tr>
<tr><td>D3</td><td>Amoxicillin/Clavulanate
p-aminosalicylic acid
Imipenem/Cliastatin
Meropenem</td></tr>
<tr><td>New drugs</td><td>Not included in 2011 classification, but with separate recommenda-tions, e.g. Bedaquiline [31]; Delamanid [99]</td><td>New drugs</td><td colspan="2">N/A in 2017</td></tr>
</table>

New drugs and drug regimens

In January 2013, pre/XDR-TB patients were able to access bedaquiline under BCAP at five centralized M/XDR-TB hospitals in South Africa.[33,34] Following approval from the national regulatory authority at the end of 2014, in March 2015 bedaquiline was expanded to more sites nationally. Current indications for bedaquiline [19] in South Africa include at least rifampicin-resistant patients with resistance to a fluoroquinolone or/and a second-line injectable drug (pre-XDR/XDR- TB), MDR/RR-TB with both *inhA* and *katG* mutations, or toxicity to drug(s) in the standardized MDR/RR-TB regimen. As per labelling, bedaquiline treatment is for 24 weeks, during the intensive phase of second-line TB treatment. Patients with HIV infection are eligible for bedaquiline; appropriate ART regimen changes are made to either lopinavir/ritonavir or nevirapine as clinically indicated if the patient is on efavirenz.

The WHO 2016 update to the treatment guidelines [14] preceded the meeting of the guidelines development group and the issuance of updated recommendations for both bedaquiline [32] and delamanid [100]. As a result, some policy makers have recommended an updated classification to the 2016 WHO version, upgrading the use of the new drugs (Table 2-5).[46,47] Importantly, under the new proposal, effective drug regimens could now be composed without second-line injectables. According to the authors of the proposal, "moreover having an oral Group B could mean that shortly it may be possible to have an injectable free-regimen to treat MDR-TB patients meaning potentially less toxicity, monitoring, and reduced hospital stay and visits, and possibly better adherence."[46] A further call for use of an injection-free regimen was published in late 2017, which concluded that continued use of second-line injections without explaining the potential effects and offering alternatives would contravene ethical standards and human rights.[1] While not yet policy in South Africa, the SA NTP guidelines for bedaquiline allow for an injection-free regimen for patients that have experienced or at risk of toxicity to the injections.[19]

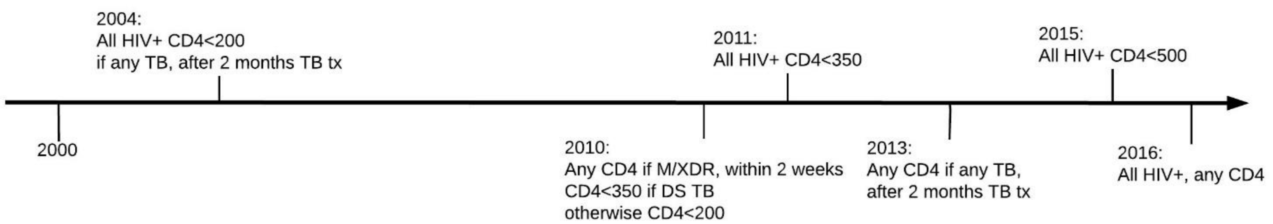
Table 2-5 Proposed regimens for long-course MDR/RR-TB treatment

WHO 2016 Classification [14]			**Proposed Future Classification** [46]	
Group A Fluoroquin-olones	Levofloxacin Moxifloxacin Gatifloxacin		Group A Fluoroquin-olones	Levofloxacin Moxifloxacin Gatifloxacin
Group B Second-line injectable agents	Kanamycin Amikacin Capreomycin		Group B Other core second-line agents	Bedaquiline Delamanid Ethionamide/Prothionamide Cycloserine/Terizidone Linezolid Clofazimine
Group C Other core second-line agents	Ethionamide/Prothionamide Cycloserine/Terizidone Linezolid Clofazimine		Group C Second-line injectable agents	Kanamycin Amikacin Capreomycin
Group D Add-on agents	D1	Pyrazinamide High-dose isoniazid Ethambutol	Group D Add-on agents (not core MDR-TB regimen com-ponents)	High-dose isoniazid Ethambutol Pyrazinamide Amoxicillin/Clavulanate p-aminosalicylic acid Imipenem/Cliastatin Meropenem Rifabutin
	D2	Bedaquiline Delamanid		
	D3	Amoxicillin/Clavulanate p-aminosalicylic acid Imipenem/Cliastatin Meropenem		

HIV testing and treatment

Access to HIV testing and treatment for MDR/RR-TB patients has improved rapidly in the last two decades in South Africa (Figure 2-6). In April 2010, the SA guidelines for antiretroviral therapy (ART) were updated to indicate that all M/XDR-TB patients, regardless of CD4 count were eligible for ART initiation.[101] In 2013, these guidelines were updated to include any TB, regardless of CD4 count. As of 2016, clinical providers initiate (encourage) HIV testing to all clinic visitors, especially to all TB patients. ART is fast-tracked for patients who are ART-naïve when starting MDR/RR-TB treatment, regardless of CD4 count.

Figure 2-6 ART eligibility guidelines for TB patients in South Africa, 2004 to 2016



Data collection

The South African Electronic Drug Resistant Tuberculosis Register (EDRWeb) is a reporting database that collects non-aggregated, patient-level data from drug-resistant TB treatment sites. Access to this central database is granted to authorized users who can capture data for units dealing with RR-TB. This system is intended to act as tool for providing quality data for program management, surveillance, monitoring and evaluation and supervision. It collects information on patient-level demographic data, case registration, Xpert MTB/RIF, line probe assay, sputum smear results, culture results, and drug sensitivity testing (DST), treatment details, treatment outcome, adverse events and HIV information from facility TB registers. In South Africa this system has been implemented in all nine provinces and is being used in more than 50 units providing RR-TB treatment. It is the most complete dataset of RR-TB treatment (MDR/RR-TB, preXDR-TB, and XDR-TB) and outcomes in South Africa and is the cohort reported to the WHO.

While EDRweb is the most complete dataset, there is evidence of substantial underreporting, particularly at the decentralized sites that began initiating MDR/RR-TB patients after 2012. A 2012 review of paediatric clinical records in Cape Town, Western Cape found that 1/3 of patients were not recorded in EDRweb.[102] A national analysis for a sample of 2011 and 2013 adults initiating MDR/RR-TB treatment, only 62% and 53%, respectively, were reported in EDRweb.[103] The study had started by looking at diagnosis of MDR/RR-TB records from NHLS and then attempting to trace patients to treatment sites.

The dataset also does not include all clinical factors of interest for RR-TB treatment. Aside from HIV status and sputum smear positivity, few other indicators of physical condition or mortality risk factors are included in EDRweb, such as hospitalization (for initiation or ADR), other comorbidities (such as diabetes), body mass index, serum albumin, haemoglobin, liver function or kidney function. For HIV-positive patients, the date of ART initiation and information on CD4 count at baseline or at any point during MDR/RR-TB treatment is not routinely captured. Out of the more than 90,000 records in EDRweb, there are fewer than 10,000 records with CD4 count or ART initiation date, despite more than 65% of the patients known to be infected with HIV. Other patient characteristics which are not reported but known to be clinically relevant are extent of damage to the lungs, return to care after interruption, relapse, development of new resistance, HIV viral suppression, intolerance and toxicity to treatment regimens. Additionally, resource use is not captured and the EDRweb cannot be used to estimate the number of days hospitalized, visits to a clinic, or laboratory monitoring tests done.

In mid-2016, with support from Janssen Pharma, a new version of EDRweb was implemented with additional fields for data collection. Efforts began in 2017 to link EDRweb to the vital statistics register maintained by the Department of Home Affairs and to the laboratory information system of the NHLS. For bedaquiline patients in particular, EDRweb also serves as the monitoring system required for the regulatory review of bedaquiline by the US FDA. However, the data used in this thesis was exported in May 2016 and represents the version of EDRweb which predated these amendments.

2.5 Estimating the effectiveness of MDR/RR-TB treatment

The most common outcome reported for RR-TB treatment is the end of treatment. This may be at 18-24 months for the long-course regimen, or in some cases with extensive drug resistance, as long as 36 months. 24-month outcomes sometimes include the category 'still on treatment' which is an indication that the reporting period (24-months) censored the end of treatment outcome. End of treatment outcomes that will be considered for this analysis, at the earliest reporting date, are indicated below (Table 2-6). Note that the terms reference the treatment course and not the patient, i.e. the treatment course failed to cure the MDR/RR-TB, not that the patient is failed or has failed.[104] For similar reasons, although the definitions of the 'lost to follow-up' or 'lost from treatment' or 'lost from care' are not different in content from previous definitions of 'default' or 'defaulter' the language defining the term has been revised.[104]

Table 2-6 Table RR-TB patient outcomes

OUTCOME	DEFINITION OF CRITERIA
Cured	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, i.e. at least three consecutive cultures after month 6.
Completed	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.
Died	A patient who dies for any reason during the course of treatment.
Failed	Treatment terminated or need for permanent regimen change of at least two anti-TB drugs because of: − lack of conversion by the end of the intensive phase, or − bacteriological reversion in the continuation phase after conversion to negative, or evidence of additional acquired resistance to fluoroquinolones or second-line injectable drugs, or − adverse drug reactions (ADRs).
Lost to follow-up	A patient whose treatment was interrupted for 2 consecutive months or more.
Not evaluated	A patient for whom no treatment outcome is assigned. (This includes cases "transferred out" to another treatment unit and whose treatment outcome is unknown)
Culture conversion (interim outcome)	The terms "conversion" and "reversion" of culture as used here are defined as follows: Conversion (to negative): culture is considered to have converted to negative when two consecutive cultures, taken at least 30 days apart, are found to be negative. In such a case, the specimen collection date of the first negative culture is used as the date of conversion. Reversion (to positive): culture is considered to have reverted to positive when, after an initial conversion, two consecutive cultures, taken at least 30 days apart, are found to be positive. For the purpose of defining Treatment failed, reversion is considered only when it occurs in the continuation phase.

Table reference: [18]

Culture conversion

Short-term outcomes for RR-TB focus on 6 months, which is the time where most patients should be finishing the intensive phase of treatment and starting the continuation phase. At 6 months, patients should still be in care, especially as the injectable drugs require daily visits to or by a healthcare worker. And, at 6 months, patients should be culture negative. For those who were culture positive at the start of treatment, the indicator of proportion culture converted is tracked as well as the number of days from treatment initiation to culture conversion. Culture conversion is defined as the first two consecutive negative cultures taken one month apart, when patient was initially sputum culture positive. The date of culture conversion is taken as the date of the sputum collection for the first negative culture. Therefore, culture conversion can only be measured retrospectively and also requires that the person remain in care for at least three culture sputa to be collected. Many of the cost-effectiveness models established for MDR/RR-TB are driven by the rates and time to culture conversion, as hospitalization is required in many contexts until culture negative.[53–55]

Phase 2b randomized clinical trial evidence for the use of bedaquiline in addition to the standard treatment regimen for MDR-TB showed promising results in terms of efficacy with higher rates of culture conversion and cure compared to standard regimen plus placebo. An interim cohort analysis of the first 91 patients from the South African BCAP published in 2015 76% culture conversion among XDR-TB and preXDR-TB, however many patients had 6 months or less follow-up time.[34] Another interim cohort from a compassionate access program in France (2015) reported that at 6 months, 97% (28 of 29) of culture positive patients had culture converted.[105]

Mortality

The Phase 2b trial of bedaquiline reported a statistically significant imbalance in mortality 10/79 deaths occurring patients exposed to bedaquiline (12.7%) and 2 deaths (2/81, 2.5%) in the placebo arm.[30] As a result, interim WHO guidelines recommend limited use of bedaquiline only in RR-TB when there is resistance to fluoroquinolones and when there are no other treatment options.[31] An interim cohort analysis of the first 91 patients from the South African BCAP published in 2015 reported 3 (3.3%) deaths among XDR-TB and preXDR-TB, however many patients had 6 months or less follow-up time.[34] At 120 weeks, the open-label trial TMC207-C209 reported 16 deaths out of 233 enrolled patients (6.9%), all of which were considered not related to bedaquiline.[106] Another interim cohort from a compassionate access program in France (2015) reported that at 6 months, 1/35 patients had died (3%) and 97% (28 of 29) of culture positive patients had culture converted.[105] Each were single arm, non-randomized studies, however, and without a control group the signal of excess mortality from the Phase 2b bedaquiline trial could not be confirmed or refuted.

In March 2017 [32], the WHO updated its 2013 conditional recommendations [31] for the use of bedaquiline for the treatment of MDR/RR-TB. Encouraging results from the compassionate use program [34] and the public sector roll-out of bedaquiline in South Africa was among the evidence considered by the guidelines development group in revising the recommendations.[32] These results included a rate of deaths for patients on bedaquiline of 7.9%, similar to previous reports. In comparison, the Phase 2b TMC207-C208 trial where the placebo arm reported 2.5% mortality had restricted enrolment of those with second-line resistance or use of ARVs; only 19 of the 132 patients in the study were HIV-infected (14·4%).[30] The 19.8% mortality for patients with second-line resistance receiving bedaquiline through compassionate use access [34] reported in the revised WHO recommendations for bedaquiline is therefore encouraging.[32] Additionally, the revised recommendations included observational reporting from the EDRweb where the mortality rates on bedaquiline were lower than for the patients not on bedaquiline.[32]

Disability from TB

The disability of having active TB disease (and being in hospital or in regular care) as well co-infection with HIV and TB, was a specific ranking of health states for persons to consider in the GBD 2010 study (Table 2-7).[74] The disability may persist for years after cure, especially if extensive damage to the lung prior to cure, e.g. bronchiectasis or if an adverse drug reaction caused permanent disability, e.g. profound hearing loss. One study of the lung impairment following drug-sensitive TB cure calculated that most of the disutility of having active TB is not the acute, symptomatic period, but rather the life-long chronic lung impairment *after cure*.[69] The analysis drew on studies of lung function of TB cases and controls, which showed that approximately 10% of TB cases had severe lung function impairment after cure.[69] Disability from MDR/RR-TB may have also started prior to diagnosis and initiation of MDR/RR-TB, e.g. if the patient was already in very poor health at the time of diagnosis.

The disability weight of MDR/RR-TB was not specified in the 2010 GBD reference or the 2013 update.[74,75] It may be that the burden of having TB is an appropriate applicable weight. In the 2016 GBD study, disability weights for TB with HIV/AIDS were estimated for drug-susceptible, MDR/RR, and XDR-TB without anaemia and with mild, moderate or severe anaemia. Weights and confidence intervals differed by the status of anaemia, but not whether the TB was drug-susceptible, resistant or extensively resistant.[107] However, MDR/RR-TB is usually more disabling than TB – patients are often hospitalized, there is greater stigma attached because of greater fear, the treatment duration is longer, and the mortality is higher. DALYs were intended to be neutral of duration, so that the duration of disability could be adjusted according to the specific conditions being compared.[73] This assumption was investigated in the 2013 revision of disability weightings and it was noted that for HIV, the fact that it was a chronic disease with no cure lead to it having a higher disability weighting than the regression co-efficient to adjust for the temporary symptoms.[75] A similar difference may occur with MDR/RR-TB or XDR-TB given the poor prognosis compared to drug-sensitive TB. Further, it is unclear from the weighting whether the active TB infection period should be applied throughout treatment (the full 18 to 24 months) or only during the sputum culture positive intensive phase. The health states described are based on symptoms, which are alleviated before the course of anti-TB antibiotics are completed.

For the 2010 GBD assessment, TB without HIV was described as “has a persistent cough and fever, is short of breath, feels weak, and has lost a lot of weight” and TB with HIV was described as “has a persistent cough and fever, shortness of breath, night sweats, weakness and fatigue and severe weight loss.”[74] Thus, the difference between having TB or TB with HIV/AIDS was in effect described as having night sweats and ‘severe weight loss’ rather than a ‘lot of’ weight loss. The 2016 GBD study indicated a definition of “has a persistent cough and fever, shortness of breath, night sweats, weakness and fatigue and severe weight loss” for patients with TB and HIV co-infection; no difference in the description was made for drug-resistant TB. [107]A South African household survey using the GBD 2010 methodology concludes there was a ‘moderate correlation’ between the local study and the 2010 GBD study, and reports a Pearson’s correlation coefficient of 0.44 (p=0.0015).[79] The authors also concluded that the South African population from Cape Town seemed to value physical mobility over cognitive functioning.[79] The conclusion from the 2010 GBD study that the disability weights from different contexts are similar therefore was in question based upon this local study. The main reason for using disability weights from a different context is non-availability; therefore, where weights are available for South Africa, these should parameterize a cost-effectiveness model for South Africa. For TB and HIV (Table 2-7), the South African weights were the highest (greatest disability) among reviewed disability studies for TB without HIV infection (0.368) and symptomatic, pre-AIDS HIV (0.417).[79] GBD 2013 had the 2nd highest weights for TB without HIV and symptomatic HIV and the highest weights for TB with HIV and HIV not on ART and therefore the GBD 2013 values are the closest to the local ranking.

Table 2-7 HIV/TB disability weights from using the Global Burden of Disease methodology

Description^	**Value (95% CI)**	**Source**
TB without HIV infection: has a persistent cough and fever, is short of breath, feels weak, and has lost a lot of weight"	0.333 (0.224-0.454)	GBD 2013, [75]
TB without HIV infection	0.331 (0.222-0.450)	GBD 2010, [74]
TB without HIV infection	0.308 (0.264-0.353)	Europe, [77]
TB cases	0.271	GBD 2004, as cited in [75]
TB without HIV infection	**0.368 (0.260-0.430)**	**South Africa,** [79]
TB with HIV infection: has a persistent cough and fever, shortness of breath, night sweats, weakness and fatigue and severe weight loss.	**0.408 (0.274-0.549)**	**GBD 2013,** [75]
TB with HIV infection	0.399 (0.267-0.547)	GBD 2010, [74]
TB with HIV infection	0.383 (0.345-0.435)	Europe, [77]
TB with HIV infection (mapped to AIDS, not on ARVs)	0.505	GBD 2004, as cited in [75]
HIV infection, on ART: has occasional fevers and infections. The person takes daily medication that sometimes causes diarrhea	**0.078 (0.052-0.111)**	**GBD 2013,** [75]
HIV infection, on ART	0.053 (0.034-0.079)	GBD 2010, [74]
HIV/AIDS cases, receiving ART	0.108 (0.089-0.132)	Europe, [77]
HIV/AIDS – AIDS cases on ART	0.167	GBD 2004, as cited in [75]
HIV infection, AIDS, not on ART: has severe weight loss, weakness, fatigue, cough and fever, and frequent infections, skin rashes and diarrhoea	**0.582 (0.406-0.743)**	**GBD 2013,** [75]
HIV infection, AIDS, not on ART	0.547 (0.382-0.715)	GBD 2010, [74]
AIDS cases, not receiving ART	0.574 (0.518-0.635)	Europe, [77]
AIDS cases: not on ARV	0.505	GBD 2004, as cited in [75]
HIV infection, symptomatic, pre-AIDS: has weight loss, fatigue, and frequent infections	0.274 (0.184-0.377)	GBD 2013, [75]
HIV infection, symptomatic, pre-AIDS	0.221 (0.146-0.310)	GBD 2010, [74]
HIV/AIDS - HIV cases	0·135	GBD 2004, as cited in [75]
HIV infection, symptomatic, pre-AIDS	**0.417 (0.285-0.502)**	**South Africa,** [79]

^ Bolding indicates value selected to be used in analysis.

2.6 Adverse drug reactions during MDR/RR-TB

In the Phase IIb randomized control trial for bedaquiline where bedaquiline or placebo was added to a standard background regimen, 99% of participants in the treatment arm and 98% of the participants in the placebo arm experienced one or more adverse events. Most of these events were categorized as being related to the treatment, 70% (bedaquiline) and 69% (placebo) for the two arms, respectively.[30] The duration of drug-resistant TB treatment is longer (usually 9-24 months) than for drug-sensitive TB (usually 6-9 months) . The standard treatment regimens for MDR/RR-TB are complicated and include 4 to 7 drugs with different[16] mechanisms of action, including oral bacteriostatic drugs such as cycloserine, terizidone, ethionamide; aminoglycoside and cyclic peptide injectables; fluoroquinolones (e.g. moxifloxacin, ofloxacin, gatifloxacin, and levofloxacin); and newer agents such as bedaquiline (a diarylquinoline) and delamanid (a nitroimidazole). See Table 2-10. Many of the drugs have known toxicities, especially at the doses and durations required to treat resistant strains of TB. There is limited clinical trial data on dosage and related side effects, particularly among drugs which have been repurposed for MDR/RR-TB and therefore were approved without specific clinical trials for their use in MDR/RR-TB, e.g. clofazimine and linezolid. As a result, ADR are very common during drug-resistant TB treatment. A systematic review and meta-analysis of published literature through October 2012 found that 57.3% of included patients had experienced at least one type of AE, including mild to severe events.[3] For example, in the South African study indicated above with 99% incidence of AE, injection site pain was the second most commonly reported clinical AE. Injection site pain was only reported in this cohort in patients refusing to continue with the injections for reason of pain.

The most common ADR during MDR/RR-TB treatment in the SA NTP are indicated in the treatment guidelines from 2013 [17] and 2015 [19], along with suspected drugs and guidelines on prophylaxis (if available), screening or laboratory monitoring, and management. The list (see Table 2-8), while helpful to keep track of all the different possibilities, does not indicate the varying severity or duration that the ADR impact on the patient's health state and ability to function. Psychosis and severe depression, associated with the use of terizidone or the related drug cycloserine, could lead to violence against others or the patient, including suicide.[34,108–110] The temporary, drug-induced thyroid dysfunction often needs to be treated – more pills to take – and the effects persist for the duration of the ethionamide, typically 18-24 months.[111–114] Hearing loss from the aminoglycoside IAs is permanent and disabling.[1,115,116]

> *"I thought I was going to die because of the medicines…it was that bad."* – 40-year-old male patient in India.[48]

Table 2-8 Literature on ADR associated with MDR/RR-TB treatment (based upon [17,19]*)*

Adverse reaction	**Associated TB drugs**
Arthralgia/arthritis	Pyrazinamide, Fluoroquinolones
Bone marrow toxicity	Linezolid
Electrolyte disturbances (hypokalaemia, hypomagnesemia)	Second-line injectables
Gastro-intestinal intolerance, including gastritis, nausea, and vomiting	Ethionamide, Para-aminosalicylic acid, Pyrazinamide, Ethambutol, Clofazimine
Hepatitis and hepatoxicity	Pyrazinamide, Para-aminosalicylic acid, Ethionamide, Fluoroquinolones
Hypothyroidism	Ethionamide, Para-aminosalicylic acid
Optic neuritis	Ethambutol, Linezolid
Ototoxicity, including hearing loss and tinnitus	Second-line injectables
Peripheral neuropathy	Cycloserine/Terizidone, Ethambutol, Fluoroquinolones, Second-line injectables, Ethionamide, Linezolid
Psychiatric symptoms, including psychosis and depression	Cycloserine/Terizidone, Fluoroquinolones, Ethionamide, Capreomycin
Renal failure and nephrotoxicity	Second-line injectables
Seizures	Cycloserine/Terizidone, Fluoroquinolones

ADR can lead to the clinician or patient interrupting, stopping, or reducing the dosage of treatment before completion, and therefore may increase the risk of mortality, resistance, or treatment failure.[117] In qualitative studies, patients cite side effects as a major reason for why they stopped treatment.[118,119]

> *"I took fewer drugs, but the effect was terrible. Better I die than going again through all this. . . . I felt I was dying because of prothionamide . . . because of cycloserine, I was having hallucinations . . . I had ulcer due to PAS . . . I didn't want to continue."* - MDR/RR-TB patient who was lost from care [118]

Either sequelae from the ADR or the untreated TB disease may lead to reduced quality of life.[120] However, the high mortality, risk of transmission, and limited alternatives mean that clinicians and patients with drug-resistant TB are left with little choice. On average, each patient experiences 3 to 8 ADR during the course of MDR/RR-TB treatment.[108,121,122] ADR are most frequent during the first 6 months of treatment [108,122], which also coincides with the intensive phase using injectables.

ADR experienced during RR-TB treatment may be underreported if relying on routine reporting; only serious adverse events are required to be reported to the MCC. The National Pharmacovigilance Centre in South Africa recommends use of its new forms for ADR experienced during RR-TB treatment and encourages reporting of all ADR, however, these forms are not well known or used at RR-TB treatment centres. ADR which led to a treatment change or a serious outcome (e.g. hospitalization or death) are therefore documented more commonly than those that the patient complains of but did not affect treatment outcome (e.g. headaches, gastro-intestinal complaints). Reports of ADRs therefore are usually from clinical trials of new and re-purposed drugs or file reviews rather than routine reporting. Even among peer-reviewed published observational cohorts, reporting of ADR is inconsistent. Of 74 studies included in a recent systematic review of MDR/RR-TB treatment, only 44 reported on adverse events, and only 26 of these indicated a drug related to the ADR.[5] During the monthly visits to the outpatient clinics for MDR/RR-TB treatment, treatment guidelines do not require that patients be prompted to self-report AE. In some cases, patients may have discussed AE with the counsellor, nurse, or clinician but if the healthcare worker did not note the discussion in the medical file. This may result in an under-reporting of AEs, particularly those are mild to moderate (grade 1-2). A South African study where patients were prompted in their local language and with visual aids to identify AEs found that, on average the clinicians had noted 1.4 AE per patient while patients reported 8.6 AE each.[123] Also, while guidelines indicate monitoring for certain AEs, implementation may differ from intended practice. Facilities may not have the staff, equipment, or budget required for the recommended monitoring schedule.[116] This is especially true for audiology (e.g. a study reporting ADR from Ethiopia [124]), which, until recently, required a special sound proof room for testing. A qualitative study published in 2009 found that while 63% of the MDR/RR-TB patients interviewed reported having symptoms of ototoxicity – either tinnitus or hearing loss – none (0%) had been referred to a specialist for care.[125]

Clinicians cannot actively screen for symptoms or document patient complaints when the patient is not in care. Loss to follow-up is also high during MDR/RR-TB treatment. A global meta-analysis reported 23% as lost from treatment or with unknown outcomes.[8] And, it is high in the SA NTP, with rates in excess of 25%.[13,126,127] A study of a cohort in Johannesburg reported 13.5% loss to follow-up within the first 6 months of treatment.[128] From the same clinic, 53.5% of MDR/RR-TB patients missed at least one appointment.[129] A counselling toolkit for decentralized treatment programmes provides guidance to patients on dealing with the side-effects of treatment in order to improve adherence and completion of the course.[127]

Further, ADR can occur even after treatment has been stopped or completed. For hearing loss, the aminoglycosides persist in the ear for long after treatment has been completed or discontinued [130]; ototoxicity is known to occur even after treatment discontinuation.[125,131]

ADR grading

For record keeping, clinical trials and pharmacovigilance, it is important to have some understanding of the severity of the ADR experienced by the patient. While mild nausea may not require medical intervention, does not persist, and does not interfere with a patient's daily activities, severe nausea may require hospitalization. Thus, naming of the ADR is not sufficient to determine its (potential) impact on patient well-being and costs of treatment. Unfortunately, grading of ADR is subjective according to patient report and clinician experience for many ADR. For laboratory abnormalities, there are now extensive tables, often specific to the patient population and/or indicated disease which help to assign a grading to the ADR.[132–135] For example, anaemia is considered mild (grade 1) when 9.5 gm/ dL < Hb < 10.5 gm/dL and life threatening (grade 4) when Hb < 6.5 gm/dL.[132] For ADR that are not as quantifiably measured as laboratory tests or which are not included in the tables being referenced, a more general grading based upon impairment of patient functionality and activities is assessed by the clinician (Table 2-9). Clinicians may monitor mild reactions and continue TB treatment, but at grade 4 hospitalization, medical interventions, and interruption of TB therapy and other actions are immediately taken.

Table 2-9 ADR severity grading, based upon DAIDS toxicity table[133]

Severity Grading	**Explanation**
Mild (1)	Awareness of the symptoms, but does not interfere with daily activities, limited duration, no medical intervention indicated.
Moderate (2)	Interferes with some daily activities. Minimal medical intervention indicated
Severe (3)	Prevents normal functioning; significant impairment of functioning. Requires medical intervention, including possible hospitalization.
Life threatening (4)	Immediate significant medical intervention or therapy, including probable hospitalization, is required to prevent death or disability.
Death (5)	Death

ADR and HIV

In some settings, particularly sub-Saharan Africa, TB and HIV are inextricably linked. Treatment of HIV and TB co-infection results in high pill burden and potentially increased toxicity. Effective ART regimens include three drugs, usually two nucleoside reverse transcriptase inhibitors (NRTIs) with either a non-nucleoside reverse transcriptase inhibitor or protease inhibitor (PI) in resource-limited countries. Toxicities can be overlapping, such as potential renal impairment from antiretrovirals including tenofovir and anti-TB medications kanamycin/amikacin; peripheral neuropathy from stavudine and zidovudine, ethionamide and linezolid; bone marrow suppression from zidovudine and linezolid; nausea and vomiting potentially from zidovudine and ethionamide and para-aminosalicylic acid; or psychiatric symptoms associated with efavirenz and cycloserine and terizidone.[16,136] HIV infection, even for the ART naïve, and particularly for those who have advance HIV disease or immunosuppression may also pose its own risk for ADR. For example, thioacetazone was removed from TB treatment recommendations early in the HIV epidemic because of an increased risk of Stevens-Johnson syndrome in HIV-infected patients.[137] Table 2-10 below highlights the overlapping toxicities of ART and second-line TB treatment regimens.

Table 2-10 ADR associated TB and HIV drugs (based upon [17,136]*)*

Adverse reaction	**TB drugs**	**Antiretrovirals**
Arthralgia/arthritis	Pyrazinamide Fluoroquinolones	
Bone marrow toxicity	Linezolid Rifampicin	Zidovudine
Electrolyte disturbances (hypokalaemia, hypomagnesemia)	Second-line injectables	
Gastro-intestinal intolerance	Ethionamide/Prothionamide Para-aminosalicylic acid Pyrazinamide Isoniazid Rifampicin Ethambutol Clofazimine	Zidovudine Protease inhibitors Stavudine Didanosine
Hepatitis and heptatoxicity	Pyrazinamide Isoniazid	Nevirapine Ritonavir/protease inhibitors

	Rifampicin /rifabutin Para-aminosalicylic acid Ethionamide/Prothionamide Fluoroquinolones	Efavirenz Etravirine Maraviroc
Hypothyroidism	Ethionamide/Prothionamide Para-aminosalicylic acid	
Lactic acidosis	Linezolid	Stavudine Didanosine
Optic neuritis	Ethambutol Linezolid	
Ototoxicity (hearing loss and tinnitus)	Second-line injectables	
Peripheral neuropathy	Cycloserine/Terizidone Isoniazid Ethambutol Fluoroquinolones Second-line injectables Ethionamide/Prothionamide Linezolid	Stavudine Didanosine
Pyschiatric symptoms, including psychosis and depression	Cycloserine/Terizidone Isoniazid Fluoroquinolones Ethionamide/Prothionamide Capreomycin	Efavirenz
Renal failure and nephrotoxicity	Second-line injectables Rifampicin	Tenofovir Indinavir
Seizures	Cycloserine/Terizidone Fluoroquinolones	
Stevens-Johnson syndrome	Thiocetazone Cycloserine/Terizidone Linezolid	Nevirapine Efavirenz Etravirine

Bedaquiline-associated ADR

The Phase 2b clinical trial of bedaquiline noted no statistically significant difference in the frequency or severity of ADR in the bedaquiline arm or placebo arm.[30] Among the 79 treated with bedaquiline, 5% (n=4) experienced an event leading to treatment discontinuation; 43% (n=34) experienced a grade 3 or 4 event; 70% (n=55) experienced an event related to treatment (ADR); and 99% (n=78) experienced any adverse event. Among the 81 treated with placebo plus background regimen, 6% (n=5) experienced an event leading to treatment discontinuation; 36% (n=29) experienced a grade 3 or 4 event; 69% (n=56) experienced an event related to treatment (ADR); and 98% (n=79) experienced any adverse event.[30] In a large, multi-centre observational study, bedaquiline was interrupted for 11.9% (n=51/428), but only 5.8% (n=5.8%) experienced an interruption due to adverse events.[138] An interim cohort analysis of the first 91 patients from the South African BCAP published in 2015 reported few severe adverse events among XDR-TB and preXDR-TB, however only severe or serious events were reported.[34]

As per the full prescribing information for Sirturo, bedaquiline is associated with QT prolongation, especially when used with other drugs that prolong the QT interval.[139] As a result, both initial ECG screening and monthly monitoring are recommended while on bedaquiline treatment. Bedaquiline is contraindicated in patients with a QTcF (QT interval corrected using Fridericia's formula) over 500ms at baseline or who have a history of QT prolongation (e.g. congenital QT prolongation).[19,31,139] Bedaquiline may be interrupted if QTcF increases by more than 50ms from baseline or if it exceeds 500ms during treatment [19,31,139]; ECGs should be repeated prior to interrupting treatment as readings may vary with each measurement.[139] QT prolongation is monitored as it is associated with *Torsade de Pointes* (TdP), a type of ventricular tachycardia which could lead to sudden cardiac death. In the multi-centre study referenced above, of the 33 deaths (33/428), only one had ECG abnormalities, the patient also had severe hypokalaemia and this was found to be the cause of the cardiac arrest.[138]

Bedaquiline is one of many drugs that is associated with QT interval prolongation. Other classes of drugs which are known to prolong the QT interval include fluoroquinolones[140–143]an which core drugs for the treatment of MDR/RR-TB and XDR-TB. Protease inhibitors, used in second-line ART, can also lead to drug-induced QT prolongation.[142] Not all patients who experience drug-induced QT prolongation develop TdP, although the risk exponentially increases with each increase of 10ms for patients with QTcF intervals >500ms or who have an increase in more than 60ms from baseline.[140,143] In one review article, it was noted that the incidence of TdP with moxifloxacin use was between 1:100,000 to 1:1,000,000 exposures.[140] Additionally, not all episodes of TdP are fatal, it may self-resolve and the symptoms of dizziness and tachycardia also resolve.[140] Management of drug-induced QT prolongation is thus focused on prevention of QT prolongation and TdP, early detection, and stopping of the suspected drug.[140–142] Prevention and monitoring are built into the treatment guidelines for the use of bedaquiline, such as excluding patients who have a history of congenital QT prolongation syndrome or baseline QTcF exceeding 450ms.[19,31,139] The costs of managing QT prolongation once experienced are therefore limited (stop bedaquiline).[19,31,139]

Bedaquiline also has drug-drug interactions that need to be considered, especially for patients who are on ART. Co-administration of bedaquiline and efavirenz is contraindicated in the South African treatment guidelines.[19] In South Africa at the time of this study (2016), the recommended first line ART regimen in the public sector was a fixed dose combination of tenofovir, efavirenz, and lamivudine. Thus, the standard first-line ART regimen is contra-indicated during bedaquiline treatment. HIV-positive patients in South Africa The need to modify the ART regimen during bedaquiline treatment could potentially add to the costs of the treatment regimen.

Because of how bedaquiline is metabolized, the protease inhibitor lopinavir/ritonavir significantly increases the exposure to bedaquiline.[144,145] Potentially, the increased exposure could increase the risk of QT prolongation or other safety concerns. Thus, the researchers recommended a reduced dosing regimen for bedaquiline when used with lopinavir/ritonavir.[145] However, at the time of this study (2016), the bedaquiline dosing was common across ART and non-ART patients, regardless of the ART regimens. Additionally, with the roll-out of dolutegravir in South Africa as the preferred ART regimen[146], the continued role for lopinavir/ritonavir during bedaquiline treatment is unknown.

Disability from ADR

ADR, whether permanent or temporary, can also lead to disability. Weights of relevance to common ADR during MDR/RR-TB are presented below (Table 2-11, Table 2-12). The commonality of the value or preference for different health states across contexts (e.g. Peru compared to the USA) [74] continues to be questioned, particularly for contexts where coping mechanisms may be less available.[75–78] It is important to recognize that differences across contexts or cultures or even test-retest within the same participants may be different for different disabilities.[71] Mahapatra, Salomon and Nanda (2000) describe this as whether the community being sampled has 'crystallized' it's values or preferences for a particular health state.[71] They note that some health states are considered 'universally' bad and there is a high degree of consistency, while others change with the valuation method, the description of the condition, or even from test to retest checks for consistency.[71] For example, use of a wheel chair in a context where well-designed wheel-chairs are affordable and where public transport, schools, shops, housing and other buildings are accessible to persons in wheel chairs may result in less limitation of functioning than in a context where none of these conditions apply.

As can be seen in the table below (Table 2-11), the disability weights for hearing loss are inconsistent across studies. Profound hearing loss in the GBD 2010 was valued at 0.031 and then in the GBD 2013 at 0.204, nearly a 7-fold increase. Complete hearing loss in the GBD 2013 was weighted as 0.215, but in a South African study it was weighted as 0.405, nearly a 2-fold difference. The difference in disability weighting within the GBD 2013 for profound hearing loss (always has great difficulty hearing in any situation and is not able to use a phone) compared to complete hearing loss (cannot hear at all) was only a difference of 0.011, or 5%. The disability weight assigned to moderate hearing loss in the South African study was 10-times the weight assigned to complete hearing loss in the GBD 2010.

Table 2-11 Disability weights for hearing loss using the Global Burden of Disease methodology

Description	**Value (95% CI)**	**Source**
Hearing loss, moderate: has difficulty hearing a normal voice and great difficulty following a conversation in a noisy environment	0.023 (0.013-0.038)	GBD 2010, [74]
Hearing loss, moderate: is unable to hear and understand another person talking in a noisy place (for example, on an urban street), and has difficulty hearing another person talking even in a quiet place or on the phone	.037 (0.028-0.045)	Europe, [77]
Hearing loss, moderate	**0.357 (0.240-0.437)**	**South Africa,** [79]
Hearing loss: severe has great difficulty hearing in any situation or in using a phone.	0.032 (0.018 – 0.051)	GBD 2010, [74]
Hearing loss, severe	0.158 (0.105-0.227)	GBD 2013, [75]
Hearing loss, untreated	0.213-0.233	GBD 1996, as cited in [76]
Hearing loss, severe	0.152 (0.125-0.187)	Europe, [77]
Hearing loss: profound always has great difficulty hearing in any situation and is not able to use a phone.		GBD 2010, [74]
Hearing loss, profound	0.031 (0.018 – 0.49)	GBD 2010, [74]
Hearing loss, profound	0.204 (0.134-0.288)	GBD 2013, [75]
Hearing loss, profound: is unable to hear and understand another person talking, even in a quiet place, is unable to take part in a phone conversation, and has great difficulty hearing anything in any other situation. Difficulties with communicating and relating to others often cause worry, depression or loneliness.	0.235 (0.197-0.274)	Europe, [77]
Hearing loss: complete cannot hear at all, even loud sounds.	0.033 (0.020-0.052)	GBD 2010 [74]
Hearing loss, complete	0.215 (0.144-0.307)	GBD 2013, [75]
Hearing loss, complete	**0.405 (0.282-0.479)**	**South Africa,** [79]

^ Bolding indicates value selected to be used in analysis.

Disability weights for other ADR that are frequent during MDR/RR-TB were also reviewed. Few weights were available from the South African study, but again the differences between the SA study and the global and European contexts were marked. For major depressive disorder Table 2-12, which may occur during MDR/RR-TB treatment, either because of the disease and its poor outcomes or as an adverse drug reaction to the terizidone, the SA disability weightings were the lowest among reviewed weights (0.344 for severe episode).[79] A meta-analysis of the safety of cycloserine and terizidone included reports of 450 patients treated with terizidone across 10 studies, 72% of the patients were from South Africa.[147] Three-quarters of the reports of ADR were psychiatric, including psychoses (14%), depression (7%), suicidal ideation (2%), and suicide (1%).[147]

Table 2-12 Disability weights for major depressive disorder using the Global Burden of Disease methodology

Description	**Value (95% CI)**	**Source**
Major depressive disorder: mild episode has constant sadness and has lost interest in usual activities. The person can still function in daily life with extra effort, but sleeps badly, feels tired, and has trouble concentrating.	0.159 (0.107 – 0.223)	GBD 2010, [74]
Major depressive disorder: moderate episode has constant sadness and has lost interest in usual activities. The person has some difficulty in daily life, sleeps badly, has trouble concentrating, and sometimes thinks about harming himself (or herself).	0.406 (0.276-0.551)	GBD 2010, [74]
Major depressive disorder: moderate episode	0.294 (0.248 – 0.341)	Europe [77]
Major depressive disorder: moderate episode	**0.270 (0.192 – 0.317)**	**South Africa** [79]
Major depressive disorder: severe episode has overwhelming, constant sadness and cannot function in daily life. The person sometimes loses touch with reality and wants to harm or kill himself (or herself).	0.655 (0.469 – 0.816)	GBD 2010, [74]
Major depressive disorder: severe episode	0.571 (0.509 – 0.635)	Europe [77]
Major depressive disorder: severe episode	0.344 (0.224 – 0.436)	South Africa [79]

^ Bolding indicates value selected to be used in analysis.

In contrast, the SA disability weights for moderate anaemia (0.298, [79]) were nearly 2-times greater than the 0.149 value of the GBD 2013.[75] Linezolid is associated with anaemia (low red blood cell count) during MDR/RR-TB treatment, as well as leukopenia (low white blood cell count) and thrombocytopenia (low platelet count).[148] In a systematic review of linezolid for the treatment of MDR/RR-TB, 58.9% of the 107 patient reports reviewed experienced ADR associated with linezolid use, of which 68.4% had major ADR, defined as requiring interruption or cessation of linezolid. Most common were anaemia (38.1%) and peripheral neuropathy (47.1%), but also thrombocytopenia (11.8%).[148] In South Africa, now that linezolid is available on public tender, it is commonly prescribed alongside bedaquiline for pre/XDR-TB.[19] in the most recent GBD study (2016) disability weights for TB with HIV/AIDS were estimated for drug-susceptible, MDR/RR, and

XDR-TB according to the occurrence and severity of anaemia.[107] The combined disability weights used for HIV/TB co-infection in the 2016 GBD ranged from 0.408 (95% CI: 0.274–0.549) for disease without anaemia to 0.495 (95%CI 0.353–0.64) for HIV/TB disease with severe anaemia, a difference in weight of 0.087.[107] Thus, the combined disability weights of the 2016 GBD are equivalent to the 2013 GBD disability weights combined for the co-morbidity using a the multiplicative method described previously [80,83]. For example, person who has TB with HIV infection (2013 dw = 0.408, converted score = .592) who has severe anaemia (2013 dw=0.149, converted score=0.851) would have a combined score of 0.504 or disability weight of 0.496.[75]

Table 2-13 Disability weights for anaemia disorder using the Global Burden of Disease methodology

Description	**Value (95% CI)**	**Source**
Anaemia, moderate feels moderate fatigue, weakness, and shortness of breath after exercise, making daily activities more difficult.	0.058 (0.038-0.086)	GBD 2010, [74]
Anaemia, moderate	0.052 (0.034-0.076)	GBD 2013, [75]
Anaemia, moderate	0.045 (0.035-0.054)	Europe [77]
Anaemia, moderate	0.298 (0.189-0.388)	South Africa [79]
Anaemia, severe feels very weak, tired and short of breath, and has problems with activities that require physical effort or deep concentration.	0.164 (0.112-0.228)	GBD 2010, [74]
Anaemia, severe	0.149 (0.101-0.209)	GBD 2013, [75]
Anaemia, severe	0.118 (0.098-0.145)	Europe [77]

Note: in the analysis presented in Chapter 8, disability weights from anaemia and other ADR experienced during MDR/RR-TB treatment were not added to the model

Other conditions that are associated with ADR during MDR/RR-TB treatment are listed below (Table 2-14). Ethionamide, one of the core drugs for MDR/RR-TB treatment standard of care in South Africa and para-aminosalicylic acid, used in individualized XDR-TB regimens [17,19], are both associated with hypothyroidism. The 2010 GBD did not include the condition; in the European disability weight study and the 2013 GBD, it was described as has a person who has 'low energy and feels cold'.[75,77] Other symptoms are dry skin, constipation, hair loss, and slow heart rate although the diagnosis in South Africa is usually made through routine testing of the thyroid stimulating hormone (TSH).during MDR/RR-TB treatment. Half of a cohort of patients from Lesotho experienced elevated TSH levels [111], for example, and other studies in Southern Africa show similar high rates.[108,112,149] Moderate to severe hypothyroidism requires treatment with levothyroxine (assuming that the ethionamide cannot be interrupted).[17]

Table 2-14 Disability weights other ADR associated with MDR/RR-TB treatment using the Global Burden of Disease methodology

Description	**Value (95% CI)**	**Source**
Chronic kidney disease (stage IV) tires easily, has nausea, reduced appetite and difficulty sleeping	0.105 (0.069-0.154)	GBD 2010, [74]
Chronic kidney disease (stage IV)	0.108 (0.09-0.132)	Europe [77]
End-stage renal disease: on dialysis sometimes feels tired and down, and has some difficulty with daily activities.	0.573 (0.397 – 0.749)	GBD 2010, [74]
Diarrhoea: severe has diarrhoea three or more times a day with severe belly cramps. The person is very thirsty and feels nauseous and tired.	0.281 (0.184-0.399)	GBD 2010, [74]
Diarrhoea: severe	0.247 (0.164–0.348)	GBD 2013, [75]
Diarrhoea: severe	0.239 (0.202–0.285)	Europe [77]
Hypothyroidism	0.019 (0.010-0.032)	GBD 2013, [75]
Hypothyroidism has low energy and feels cold.	0.022 (0.017-0.028)	Europe [77]

Note: in the analysis presented in Chapter 8, disability weights from anaemia and other ADR experienced during MDR/RR-TB treatment were not added to the model

2.7 CONCLUSION AND UNANSWERED QUESTIONS

This chapter reviewed existing literature with regards to the proposed CEA of the use of bedaquiline for MDR/RR-TB treatment. There are both conclusions that can be made from this review that will inform the methods and input parameters for the CEA and a set of unanswered questions that will be further investigated through the remainder of the thesis.

First, this chapter began by reviewing previously published CEA on MDR/RR-TB treatment and bedaquiline for MDR/RR-TB treatment. While these studies provided important insights, parameters, assumptions and model structures did not fit well with the current context and intervention mix and therefore it was not clear that it would be appropriate to use the results of the previously published literature. Thus, having reviewed the existing literature, the overall question of the thesis remains unanswered.

- What is the incremental cost-effectiveness of a MDR/RR-TB treatment regimen inclusive of bedaquiline compared to an injection-based regimen in the South African context?

It is noted here and will be discussed again in the limitations to the study (Chapter 9) that there is an unanswered question and continued uncertainty regarding the imbalance in mortality observed in the Phase 2b randomized clinical trial of bedaquiline.[30] This question cannot be completely resolved using observational data such as what is presented here from the SA NTP roll-out of bedaquiline and will require reporting from the Phase 3 trial (underway) as well as active pharmacovigilance. Within the Phase 2b study, the placebo arm experienced mortality of 2.5% compared to bedaquiline at 12.7%.[30] Both arms of the study had mortality rates that were substantially lower than the approximately 20% mortality within the SA NTP MDR/RR-TB cohort, as is routinely reported to the WHO [2] and described in Chapter 3. If the relative risk from the Phase 2b study was applied to the SA mortality from the IA-based regimens (approximately 5 x higher for bedaquiline), the expected mortality from bedaquiline would be 100% mortality. This has not aligned to the experience with the roll-out in South Africa and thus was not used. Observational data from South Africa (2014 to 2016) was submitted to the WHO for its revision of the recommendations for bedaquiline.[32] Additionally, the guidelines development group assessed multiple studies that were similarly observational, mostly compassionate use access programmes such as the BCAP implemented in South Africa.[32–34] While the consistency of the reported results from the observational studies was encouraging, "the panel emphasized that due to limitations in the design of these observational studies, potential serious biases could have been introduced, especially for outcome assessment."[32]

Secondly, the chapter reviewed the underlying assumption of the analysis; that CEA of the two interventions should be used to inform health policy. Thus, the second part of the chapter presented a review of the use of cost-effectiveness analysis for decision making with regards to health interventions. It is appropriate to conclude that CEAs are useful and important, although not sufficient, for policy making. For the context of South Africa and the interventions being compared, an ICER approach from a provider (the government of South Africa through the public health facilities) perspective which uses DALYs as the effectiveness will provide meaningful information for decision makers. With this conclusion, existing cost-effectiveness models and structures were reviewed to determine if appropriate for use in the South African context. It was found that while the health state models generally offered a useful framework for comparing MDR/RR-TB policies, that previously published model structures did not include health states for ambulatory (out-patient) MDR/RR-TB treatment or HIV/TB co-infection.

- What is the impact of including HIV specific health states and costs in the cost effectiveness model for MDR/RR-TB in the context of a high burden of HIV/TB co-infection?

This chapter also reviewed the state of MDR/RR-TB in SA and the issues around HIV co-infection. It is clear that MDR/RR-TB is significant public health problem that consumes a high level of resources and represents a disease burden for the population. With the chapter, the context for the current standard of care and the proposed new intervention, a bedaquiline-based regimen, was also reviewed. The evidence that bedaquiline is an effective treatment for MDR/RR-TB has been reconfirmed by a WHO systematic review.[32] Remaining questions to be answered:

- What is the timing of outcomes that occur before 18-24 months?
- Do transition probabilities differ by HIV and ART status?
- How does the interim effectiveness of bedaquiline for improved culture conversion translate into final MDR/RR-TB treatment outcomes?

There is also strong evidence that ADR are common during MDR/RR-TB treatment. Although there is much evidence that ADR are frequent during MDR/RR-TB treatment, specification of the costs of ADR prevention, monitoring, and management during MDR/RR-TB treatment has not been the focus of the MDR/RR-TB cost analyses. This is in part due to the limited information about the costs of ADR management in particular; monitoring is often done according to guidelines and is included in many costs. Additionally, even where there is information about the costs of ADR management, it is difficult to apply across settings as management depends on availability of services which may be quite specialized and expensive during treatment of MDR/RR-TB (e.g. dialysis and cochlear implants). Disability weights were also reviewed, and a local study was identified measuring the valuation of a South African community for different health states. The disability weights from the SA study [79] were found to be much different than those from the global [74,75] and European contexts.[77] The following unanswered questions would need to be resolved for the inclusion of ADR impact within a cost-effectiveness model:

- What is the frequency of specific ADR at specific severity during MDR/RR-TB treatment?
- Do ADR occur at similar frequency, duration, and severity when HIV-infected or when on HIV treatment?
- What is the cost of ADR management, as a function of the expected costs and the expected frequencies of ADR during MDR/RR-TB treatment?

Finally, the literature review concludes that the overall question of the thesis is still unanswered.

- Does the inclusion of the cost and burden of ADR associated with MDR/RR-TB treatment affect the incremental cost-effectiveness of bedaquiline treatment regimen compared to the current kanamycin-based treatment?

3 RESULTS: TIMING OF MORTALITY DURING MDR/RR-TB TREATMENT

3.1 SYNOPSIS

Formal citation: Schnippel K, Firnhaber C, Ndjeka N, Conradie F, Page-Shipp L, Berhanu R, Sinanovic E. Persistently high early mortality despite rapid diagnostics for drug-resistant tuberculosis cases in South Africa. The International Journal of Tuberculosis and Lung Disease. 2017 Oct 1;21(10):1106-11.

A 2015 meta-analysis which reported adult mortality in TB/HIV MDR/RR-TB patients of 1.8 to 87.8% (pooled proportion of 38%; 95%CI: 28 to 48.1%) indicated that the cohorts with the lower rates of mortality were likely to be more recent [12]. Older cohorts, with no or limited access to ART, had higher rates of mortality [12]. As ART eligibility criteria have expanded over time in South Africa, moving from a low CD4 (< 200 cells/ mm3) threshold in 2010 to ART for all HIV-positive regardless of CD4 by the end of 2016, this would be expected to improve survival of MDR/RR-TB patients co-infected with HIV. Other guidelines changes have also been implemented since 2011 in an effort to improve MDR/RR-TB treatment outcomes, including rapid molecular diagnostics and decentralized, deinstitutionalized treatment for MDR/RR-TB. This chapter consists of a manuscript which describes mortality in the national, public-sector 2012 to 2014 cohort (covering patients on treatment from 2012 to 2016).

The study is limited by its use of the national, routinely captured treatment database, the EDRweb. Importantly, EDRweb begins at the point of MDR/RR-TB treatment initiation rather than diagnosis. Patients who died or never initiated after diagnosis are likely different from those that did initiate treatment. The more limited cohort of survivors of the period from diagnosis to treatment initiation were not at risk of death, by the definition of the cohort (sometimes described as an 'immortal bias'). The discussion and conclusions of this chapter address other limitations of the routinely captured data.

Contribution to the thesis and novelty

The TB and HIV epidemics in South Africa are both rapidly changing and diverse across the provinces. By analysing and presenting the most recent complete national cohorts for MDR/RR-TB, the results of this chapter improve the fit of the cost-effectiveness model and the generalizability of the results to the SA NTP. This paper was the first to match the EDRweb dataset to the vital statistics register to validate the vital status of patients and to more precisely measure the timing of mortality. The finding that the mortality rates differ so substantially over the period of treatment has implications for cost-effectiveness and budgeting for the program. For example, if mortality is within the first weeks, the expected cost saving from adoption of short-course treatment may not be realized if it was assumed that most MDR/RR-TB patients incurred the full costs of long-course treatment.

Role of the candidate

Based upon the background and literature review, the candidate identified that it was necessary to extract transition probabilities for the MDR/RR-TB health state model from a dataset rather than from published literature. She received the national case register from the NDOH, merged the data with the vital statistics from the Department of Home Affairs, and created an analytic dataset. The candidate also designed and implemented the statistical analysis, using tests of the Cox proportional hazards model to diagnose the change in hazards of mortality over time. She wrote the first draft of the manuscript and revised based on comments from co-authors and from reviewers. The co-authors approved the final version.

3.2 MANUSCRIPT 1

Title: Persistently high early mortality despite rapid diagnostics for drug-resistant tuberculosis cases in South Africa

Short title: MDR/RR-TB treatment early mortality

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Abstract

Objective

To describe timing and predictors of mortality of multi-drug and rifampicin-resistant tuberculosis (MDR/RR-TB) patients reported from the South African electronic drug-resistant TB register 2012 - 2014.

Design

We present time to event survival analysis and Cox proportional hazards regression. Identity numbers were matched to the national vital statistics register.

Results

A total of 20,653 patients were included in the analysis, with a median age of 35 (IQR: 28, 43). Over half were male (53.0%, n=10,944). Most were HIV-positive (68.9%, n=14,174), most of whom were on antiretroviral therapy (ART, 88.0%, n=12,471).

At 24 months, 4,689 patients had died (22.9%); 2,072 deaths (42.6%) were reported within 12 weeks of MDR/RR-TB treatment initiation. From week 12-24, there were 717 deaths/18,048 persons; 59.5% of the mortality occurred within the first 24 weeks.

During the first 12 weeks, adjusted hazard of mortality was highest for patients missing a baseline culture result (aHR: 3.78, 95%CI: 2.94, 4.86) and HIV-positive, ART naïve (aHR: 3.40, 95%CI: 2.90, 3.99). Patients initiating MDR/RR-TB treatment within 4 weeks of diagnosis had higher mortality compared to those with delayed initiation (aHR: 1.57, 95%CI: 1.41, 1.75).

Conclusion

Within the South African case register, mortality is highest in the first weeks after MDR/RR-TB treatment initiation.

Background

Rifampicin-resistant (RR) tuberculosis (TB), and multi-drug resistant (MDR-TB) that is resistant to both rifampicin and isoniazid is a growing public health concern. In 2015, there were 580,000 cases of MDR/RR-TB across the world and an estimated 190,000 persons with MDR/RR-TB died.[58] Globally, only 52% of MDR/RR-TB patients (2013 cohort) successfully completed treatment or were cured.[58]

According to the WHO, South Africa has among the world's highest burdens of MDR/RR-TB as well as drug-sensitive TB and TB/HIV co-infection.[58] In 2015, there were 19,613 laboratory confirmed MDR/RR-TB cases diagnosed in South Africa.[58] UNAIDS estimates that 7.0 million South Africans are infected with HIV;[150] 57% of the 294,603 reported TB cases in South Africa in 2015 were are HIV positive.[58]

Prior to 2011, drug-resistance testing in South Africa was primarily phenotypic and targeted towards patients who were known contacts of MDR/RR-TB, had a prior history of TB treatment (any outcome), or who were failing first-line treatment (persistent smear positive). Genotypic testing for rifampicin and isoniazid resistance using the Genotype MTBDRplus line probe assay (LPA, Hain Lifescience, Germany) became available from the National Health Laboratory Services (NHLS) in 2010. In 2011, NHLS implemented Xpert MTB/RIF (GeneXpert, Cepheid, USA) as the first-line test for TB in South Africa, replacing smear microscopy. In 2011, the South African National TB Programme (NTP) updated its treatment guidelines in alignment with the 2011 WHO recommendations[16] and adopted a policy framework for decentralized, out-patient treatment initiation for smear-negative MDR/RR-TB patients without additional drug resistance.[151] However, the routine recording and reporting mechanism, EDRweb, remained unchanged.

Despite these policy changes, there were only modest gains in treatment success as reported in the EDRweb and deaths remained high. In the 2013 MDR/RR-TB cohort in South Africa (n=10,614), 48% were successfully treated and 22% died; compared to 45% success and 18% mortality for the 2011 MDR/RR-TB cohort (n=6,523).[58] The persistently high mortality is described by presenting survival analyses of routinely reported data from the SA NTP for patients initiating MDR/RR-TB treatment from 2012 to 2014.

Methods

Standard of care

Through 2016, the standard of care for MDR and RR-TB patients in South Africa was a standardized regimen: 6 months of 5 drugs (kanamycin, moxifloxacin, ethionamide, terizidone, and pyrazinamide) followed by 12 to 18 months of 4 drugs (moxifloxacin, ethionamide, terizidone, and pyrazinamide).[17,19] Since 2011, provider-initiated HIV counselling and testing for all MDR/RR-TB patients is standard of care in South Africa. As per guidelines, antiretroviral therapy (ART) should be fast tracked in ART-naïve HIV-positive MDR/RR-TB patients regardless of CD4 count.

Inclusion and exclusion

All drug-resistant TB cases registered within the South African electronic drug-resistant TB register (EDRweb) was exported on 5 May 2016. Cases initiating treatment before 1 January 2012 or after 30 April 2014 were excluded. Each patient contributed at least 24 months of follow-up time prior censoring at 30 April 2016.

Patients reported as transferred in or out; with missing or invalid treatment initiation dates; without documented rifampicin resistance; with XDR-TB or had documented resistance to fluoroquinolones (e.g. ofloxacin or moxifloxacin) or second-line injectable drugs (e.g. amikacin, kanamycin, or capreomycin); or who died on or before day of treatment initiation were excluded from the analysis (Figure 3-1). Starting from 6 months prior to the analysis period (i.e. from 1 July 2011), where two or more cases had identical SA identity (ID) numbers and/or combination of surname, date of birth, and sex, the initial case record was maintained and subsequent case records excluded.

Time to event

The primary outcome for analysis was all-cause mortality. Final treatment outcomes (cure, treatment completion, treatment failure, and loss from treatment) including death from any cause are reported in EDRweb as per WHO definitions.[18] Valid patient SA ID numbers from EDRweb were matched to the national vital statistics register (through April 2016) to ascertain any additional report of deaths during the 24 months of follow-up. Deaths from either the EDRweb or the vital statistics register were combined.

Time to event analysis started from the date of MDR/RR-TB treatment initiation. The date of death was obtained from the vital statistics register, otherwise the EDRweb date of final treatment outcome was used. Deaths from the vital statistics register were censored at 24 months, according to cohort reporting standards. For patients missing an outcome, data was censored at 24 months and patient assumed to be alive.

Definitions and statistical analysis

HIV status was categorized as HIV negative, HIV-positive on ART, HIV-positive and no ART reported (ART naïve), or HIV status unknown. Characteristics of the TB disease included method of diagnosis (phenotypic, LPA, Xpert MTB/RIF, or could not be determined), extrapulmonary or pulmonary TB, history of previous TB treatment or no TB history reported, initial sputum smear microscopy results (negative, positive, or not reported), and initial sputum culture results (negative, positive, or contaminated or not reported).

All analyses were done in Stata v14 (College Station, TX). Cox proportional hazards were estimated, adjusted by co-variates, and results presented with 95% confidence intervals (CI). Proportional hazards assumption was tested using scaled Schoenfeld residuals. Based on the non-proportionality of the entire 24 months, analysis was split into 0 to 12 weeks, 12 to 24 weeks, and 24 to 104 weeks.

Ethics

The study protocol was approved by the Human Research Ethics Committees of the University of Witwatersrand (#M150340, March 2015) and the University of Cape Town (490/2015, July 2015). The requirement to obtain informed patient consent for individual patients was waived for this retrospective analysis of routinely reported data.

Results

Baseline characteristics of the 20,653 patients contributing follow-up time are presented in Table 3-1. The median age at initiation was 35 (IQR: 28, 43) and 53.0% were male (n=10,944). Most were HIV-positive (68.9%, n=14,174), most of whom were on ART (88.0%, n=12,471/14,174). Nearly half (45.2%, n=9,481) did not have history of prior TB treatment documented in the register.

Vital status was ascertained for 46.0% (n=9,503) of the cohort. HIV-positive patients on ART (48.9%, n=6,100/12,471) and HIV-positive, ART naïve patients (48.7%, n=829/1,703) were more likely to have been matched to the vital statistics register compared to HIV-negative (40.0%, n=2,236/5,596) and HIV status unknown (38.3%, n=338/883); Pearson chi-squared test p-value<0.000. There were 4,980 deaths from any source (Table 3-2). These included 4,199 deaths reported in EDRweb, 490 deaths ascertained from the vital statistics register and included in the analysis, and 291 deaths reported only in the vital statistics register which were censored at 24 months and patients analysed as alive. Nearly all (89.6%, n=4,199) of the 4,689 deaths (22.7% of the cohort) were reported in EDRweb. The majority (57.1%, n=280/490) of newly ascertained deaths were among EDRweb patients reported as lost from treatment; this represented 6.3% of the total loss from treatment (n=280/4,478). Patients missing an EDRweb treatment outcome accounted for 19.4% (n=95/490) of the newly ascertained deaths.

There were 2,072 deaths reported within 12 weeks (44.2% of 4,689), an incidence rate of 8.99 deaths per 1,000 person-weeks. From week 12 to 24, 18,048 persons remained and experienced 717 deaths; the incidence rate was 3.46 deaths per 1,000 person-weeks. From week 24 to 104, the 16,615 persons remaining experienced 1,790 deaths, an incidence rate of 1.78 per 1,000 person-weeks.

Figure 3-2 and Figure 3-3display the Kaplan-Meier survival curves for all MDR/RR-TB patients and for patients disaggregated according to their HIV status. HIV-positive ART naïve and HIV-unknown patients experienced the worst survival rates (p<0.000, log-rank test). Cox proportional hazards analysis results are presented in Table 3-3 separately for the initial 12 weeks, week 12 to 24, and week 24 to 104. During the first 12 weeks, patients with a missing or contaminated baseline culture result (aHR: 3.78, 95%CI: 2.94, 4.86) and ART naïve HIV-positive (aHR: 3.40, 95%CI: 2.90, 3.99) had the highest reported adjusted hazard of mortality. During this period, patients initiating MDR/RR-TB treatment within 4 weeks of diagnosis had a higher adjusted hazard of mortality compared to those with delayed initiation (aHR: 1.57, 95%CI: 1.41, 1.75).

Baseline characteristics less strongly predicted mortality or survival after the initial 24 weeks. While the patients who were ART naïve HIV-positive at baseline were still at the highest risk of mortality during the period 24 to 104 weeks (aHR: 1.56, 95%CI: 1.28, 1.89), this risk was similar to patients on ART (aHR: 1.51, 95%CI: 1.34, 1.69). Adjusted hazards of mortality increased for males, for patients with a history of prior TB treatment, for patients initiating in 2013, and for patients missing a diagnosis date after the initial 24 weeks but were lower for other baseline characteristics tested.

Discussion

In 2011, South Africa updated its standardized treatment regimen for MDR/RR-TB, adopted rapid genotypic testing for TB and rifampicin resistance, and increased access to MDR/RR-TB treatment with the decentralization of care and introduction of outpatient initiation of second-line treatment.[152] Yet, mortality during MDR/RR-TB treatment has remained persistently high, at 18% in the 2011 cohort and 22% in the 2013 cohort.[58] We analysed cases reported in EDRweb from 2012 to 2014 and found 44.2% of the deaths occurred within the first 3 months of the 24 months of MDR/RR-TB treatment. The estimated incidence rate was 8.99 deaths/1,000 person-weeks before week 12 compared to 1.78/1,000 person-weeks after week 24.

The persistent high mortality in the SA NTP treatment cohort may reflect improved linkage to care (reduction in initial loss to follow up) - as fewer are dying prior to treatment initiation (e.g. at home or in community) but are instead dying while on treatment and, thus, now recorded. One study from South Africa demonstrated that mortality immediately following sputum collection for the diagnosis of MDR-TB was high[153], but the time period from sputum collection until treatment initiation is not captured within

EDRweb's *treatment* cohort. Another study on the linkage to treatment after diagnosis showed that 17.5% of a South African cohort died before initiation in the period 2011-2012 when the median days to initiation was 33; in 2013-2014, 5.8% died before initiation with median of 14 days to initiation.[154] Multiple studies in South Africa have confirmed that the introduction of decentralized, outpatient care[155] and rapid molecular diagnosis reduced the time to treatment initiation from months to days.[103,156,157] The cohort analysed here does show approximately ½ of the patients initiated MDR/RR-TB treatment within 4 weeks of diagnostic sputum collection. However, the earlier initiation was associated with a higher mortality hazard, suggesting that the more ill patients with a higher risk of death are now able to start on treatment prior to death, but are still at high risk of death.

While there was significant non-reporting of the SA identity number (53.6%) required for ascertaining vital status, nearly all of the deaths identified in the vital statistics register were also reported within EDRweb (89.6%). HIV-positive patients were more likely to have had an SA ID recorded and therefore an opportunity to ascertain the additional mortality from the vital statistics register. The number of patients lost to follow-up as per EDRweb now found to have died was low--6.3% of all patients (n=280/4,478), or 16.1% of patients with valid ID (n=280/1,744). These findings were different compared to the over 30% mortality among HIV-positive patients lost to follow-up from an ART clinic in Johannesburg, South Africa.[158] Further research is needed to understand whether these surviving patients are truly no longer in treatment and doing well or if the case register was not able to identify that patients have returned to treatment, changed treatment sites within South Africa, or emigrated from South Africa.

Limitations

The large cohort size and real-world experience captured in EDRweb are strengths of this analysis, however, routinely collected data also has limitations in its completeness. A 2012 review of paediatric clinical records in one province found that 1/3 of patients were not recorded in EDRweb.[102] A national analysis for a sample of 2011 and 2013 adults initiating MDR/RR-TB treatment, only 62% and 53%, respectively, were reported in EDRweb.[103] Reasons why patients were included or not included in EDRweb was not explored In this analysis. If SA NTP MDR/RR-TB patients not reported in EDRweb differ in terms of baseline characteristics or treatment outcomes from those in the EDRweb, the analysis presented here would provide more understanding of the treatment cohorts reported to the WHO, but may not reflect the SA NTP as a whole.

Another limitation of this study is that aside from HIV status and sputum smear positivity, few other indicators of physical condition or mortality risk factors are included in EDRweb, such as hospitalization, other comorbidities, body mass index, serum albumin, or haemoglobin. For HIV-positive patients, the date of ART initiation and information on CD4 count at baseline or at any point during MDR/RR-TB treatment is not routinely captured, so the mortality observed here could not be analysed by CD4 strata. Given the high mortality for ART naïve, HIV/TB co-infected patients[159] and guidelines for immediate ART initiation[17], it is possible that the HIV-positive not on ART who survived the full 104 weeks were initiated on ART but EDRweb was not updated. Inclusion of persons on ART in the category would underestimate the risk of mortality for these patients. Similarly, mortality for HIV-positive patients newly initiating ART (<6 months) is higher than for patients who are stable on ART treatment[159], but without start date or ART duration this could not be differentiated in the current analysis. Published cohorts from South Africa indicate approximately 40% of patients 'on ART' during MDR/RR-TB treatment initiated ART after initiating MDR/RR-TB.[127,128] In light of the very high and rapid mortality reported here, additional monitoring, more frequent visits, or access to in-patient or step-down care until stabilized on MDR/RR-TB treatment, including patients who are HIV-positive and not virally suppressed, may be required for some patients. It is important to note that the association of HIV with early mortality shown here cannot indicate direction or causality. ART naïve, HIV-positive patients shown to have higher mortality are unlikely to have been in care for their HIV prior to the MDR/RR-TB diagnosis and therefore more likely to have been in poorer health. Similarly, the high adjusted hazard of mortality for patients missing their baseline sputum culture result may have been because patients died prior to providing sputum for testing.

While 59% deaths occurred within the first 24 weeks from initiation of MDR/RR-TB treatment, mortality continues throughout the 24 months of follow-up and following treatment completion (as evidenced by censoring of deaths identified through the vital statistics register). Baseline characteristics analysed here did not help in identifying who was at highest risk for this later mortality. Extent of damage to the lungs, relapse, development of new resistance, poor adherence to second-line TB treatment, poor adherence or inadequate viral suppression on ART for HIV-positive patients, intolerance and toxicity to treatment regimens, and other medical or social predictors of this late mortality need to be further explored to improve survival.

Conclusions

Processes and data collection tools to link diagnosed TB patients with TB treatment initiation have important limitations which need to be addressed to optimally inform policy recommendations. Persistently high mortality during MDR/RR-TB treatment in South Africa was highest in the first 12 weeks following treatment initiation.

Acknowledgements

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Conflict of interest statement

The authors declare no conflicts of interest.

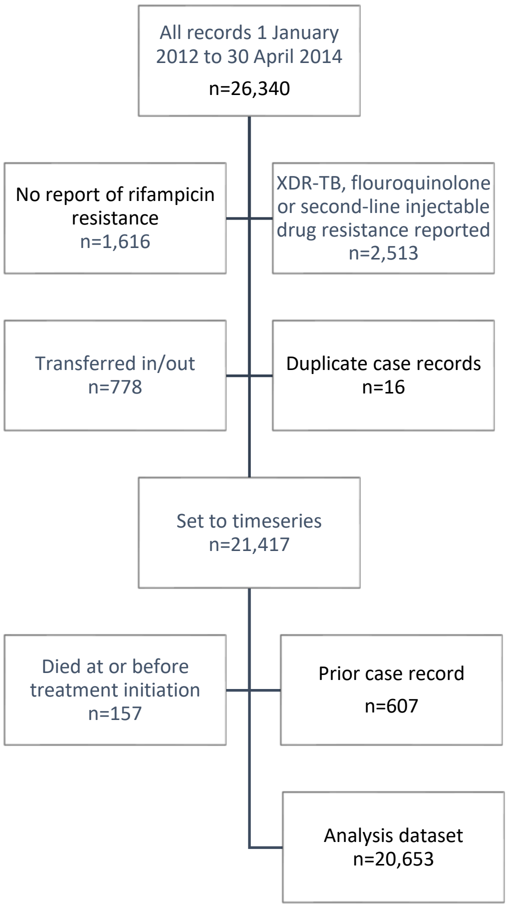
NN is an official at the South African National Department of Health and therefore has responsibility for establishing and implementing national treatment guidelines for drug-resistant TB.

References

(At end of thesis)

Figures

Figure 3-1 Cohort inclusion



Duplicate case record: Same date of treatment initiation, treatment site and either SA ID number or combination of surname, date of birth, and sex

Prior case record: Same SA ID number or combination of surname, date of birth, and sex as a case record with different treatment initiation date during the period 1 July 2011 to 30 April 2014. Initial case record in period was maintained and subsequent record(s) excluded.

Figure 3-2 Kaplan-Meier survival estimates, all MDR/RR-TB (n=20,653)

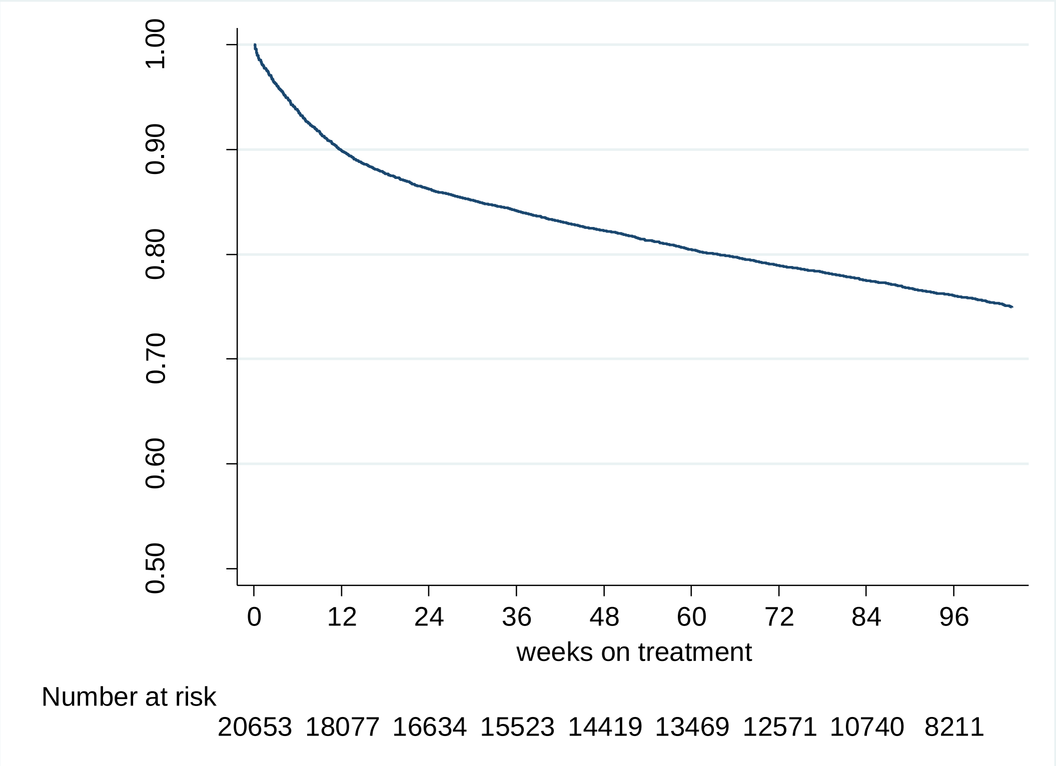
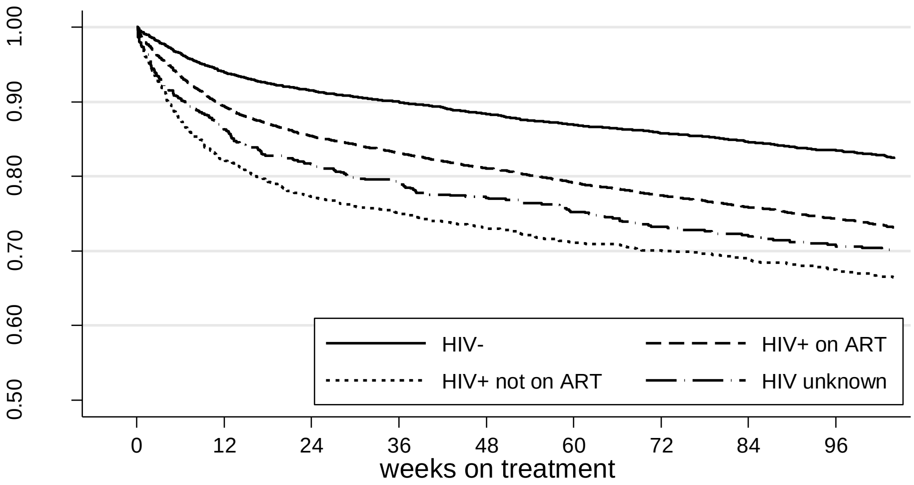


Figure 3-3 Kaplan-Meier survival estimates, by HIV and ART status (n=20,653)



Number at risk

HIV-	5596	5118	4764	4462	4139	3848	3562	2983	2165
HIV+ on ART	12471	10897	10040	9383	8722	8169	7672	6593	5089
HIV+ not on ART	1703	1339	1186	1091	1009	939	875	752	612
HIV unknown	883	723	644	587	549	513	462	412	345

Tables

Table 3-1 MDR/RR- TB case outcomes, change in outcomes once matched to vital status registry (n=20,653)

		All MDR/RR-TB
		n=20,653
Sex	Male	10,944 (53.0%)
	Female	9,709 (47.0%)
Age	Median (IQR)	35 (IQR: 28, 43)
HIV status	HIV-negative	5,596 (27.1%)
	HIV+, on ART	12,741 (60.4%)
	HIV+, not on ART	1,703 (8.2%)
	HIV unknown	883 (4.3%)
History of TB treatment	No history or missing	9,329 (45.2%)
	Prior TB	11,324 (54.8%)
ID number	Vital status ascertained	9,503 (46.0%)
	South African ID missing or invalid	11,150 (54.0%)
Site of TB	Pulmonary	17,169 (83.1%)
	Extrapulmonary	281 (1.4%)
	Missing	3,203 (15.5%)
Diagnostic method^	Phenotypic	1,418 (6.9%)
	Line probe assay	10,521 (50.9%)
	Xpert MTB/RIF	7,391 (35.8%)
	Could not be determined	1,323 (6.4%)
Base or initial smear	Negative	6,250 (30.3%)
	Positive	9,937 (48.1%)
	Missing	4,466 (21.6%)
Base or initial culture	Negative	2,202 (10.7%)
	Positive	13,361 (64.7%)
	Contaminated or missing	5,090 (24.6%)
Year treatment start	2012	7,308 (35.4%)
	2013	9,710 (47.0%)
	2014 (January – April)	3,635 (17.6%)
Time to initiation	$\leq$ 4 weeks from diagnosis sputum date	9,907 (48.0%)
	After 4 weeks	7,250 (35.1%)
	Could not be determined	3,496 (16.9%)

ART: Anti-retroviral therapy; ID: identity number; IQR: inter-quartile range; Xpert MTB/RIF: GeneXpert for mycobacterial tuberculosis and rifampicin resistance

^ Calculated using earliest sputum date for a rifampicin resistant result. Could not be determined includes patients who were categorized as “Laboratory confirmed MDR-TB” but without a reported rifampicin resistant laboratory test date.

Table 3-2 MDR/RR-TB case outcomes, updated vital status (n=20,653)

	EDRweb	**Change (% difference from EDRweb)**	**Vital status updated**
All patients (n=20,653)			
Died	4,199 (20.3%)	+490 (11.7%)	4,689 (22.7%)
Lost from treatment	4,478 (21.7%)	-280 (6.3%)	4,198 (20.3%)
Missing results	1,550 (7.5%)	-95 (6.1%)	1,455 (7.0%)
Failed treatment	559 (2.7%)	-50 (8.9%)	509 (2.5%)
Treatment success	9,867 (47.8%)	-65 (0.7%)	9,802 (47.5%)

Table 3-3 Cox proportional hazards with 95% confidence (CI) intervals for mortality during MDR/RR-TB, adjusted by baseline patient characteristics

		aHR (95%CI)	aHR (95%CI)	aHR (95%CI)
All patients		0 to 12 weeks N=20,653	12 to 24 weeks N=18,048	24 to 104 weeks N=16,615
	Deaths	2,072	717	1,790
Sex	Female	Referent	Referent	Referent
	Male	**0.89 (0.81, 0.97)**	0.98 (0.85, 1.14)	**1.15 (1.04, 1.26)**
Age	Years	**1.03 (1.03, 1.03)**	**1.02 (1.02, 1.03)**	**1.02 (1.01, 1.02)**
History	No history reported	Referent	Referent	Referent
	Prior TB treatment	**0.90 (0.81, 0.97)**	1.01 (0.86, 1.17)	**1.32 (1.20, 1.46)**
HIV status	HIV negative	Referent	Referent	Referent
	HIV+, on ART	**1.95 (1.73, 2.21)**	**1.76 (1.44, 2.14)**	**1.51 (1.34, 1.69)**
	HIV+, not on ART	**3.40 (2.90, 3.99)**	**2.50 (1.88, 3.32)**	**1.56 (1.28, 1.89)**
	HIV unknown	**2.08 (1.69, 2.57)**	**2.08 (1.45, 2.98)**	**1.49 (1.16, 1.92)**
Site of TB	Pulmonary TB*	Referent	Referent	Referent
	Extrapulmonary TB	**1.08 (1.04, 1.12)**	**1.09 (1.02, 1.16)**	1.01 (0.96, 1.05)
Diagnostic method	Phenotypic	Referent	Referent	Referent
	Line probe assay	1.15 (0.95, 1.39)	1.25 (0.89, 1.77)	0.90 (0.75, 1.08)
	Xpert MTB/RIF	0.97 (0.80, 1.19)	1.14 (0.80, 1.63)	0.89 (0.73, 1.08)
	Not reported	1.11 (0.87, 1.41)	1.52 (0.99, 2.34)	0.91 (0.72, 1.18)
Base or initial smear	Negative	Referent	Referent	Referent
	Positive	**1.18 (1.05, 1.33)**	**1.21 (1.00, 1.46)**	**1.12 (1.00, 1.26)**
	Missing or unknown	**1.56 (1.35, 1.79)**	**1.37 (1.07, 1.76)**	1.02 (0.87, 1.20)
Base or initial culture	Negative	Referent	Referent	Referent
	Positive	**2.34 (1.85, 2.97)**	1.32 (0.99, 1.77)	**1.31 (1.10, 1.56)**
	Contaminated or unknown	**3.78 (2.94, 4.86)**	**1.59 (1.14, 2.22)**	**1.52 (1.24, 1.86)**
Vital status	No valid South African ID	Referent	Referent	Referent
	Confirmed in register	**0.71 (0.65, 0.77)**	1.00 (0.86, 1.16)	1.06 (0.96, 1.16)
Year initiate	2012	Referent	Referent	Referent
	2013	0.98 (0.88, 1.09)	0.93 (0.78, 1.11)	**1.15 (1.03, 1.29)**
	2014	0.87 (0.76, 1.00)	0.83 (0.66, 1.05)	0.87 (0.75, 1.01)
Time to initiation	after 4 weeks	Referent	Referent	Referent
	within 4 weeks of diagnosis	**1.57 (1.41, 1.75)**	**1.52 (1.27, 1.81)**	**1.29 (1.16, 1.44)**
	Could not be determined	1.02 (0.88, 1.20)	0.96 (0.73, 1.25)	**1.28 (1.10, 1.50)**

Bolded text indicates statistical significance at $p<0.05$

aHR: adjusted proportional hazard ratio; ART: Anti-retroviral therapy; ID: identity number; Xpert MTB/RIF: GeneXpert for mycobacterial tuberculosis and rifampicin resistance

* Pulmonary TB includes cases with both extrapulmonary sites and pulmonary TB and those cases with no extrapulmonary sites reported

4 RESULTS: TYPES AND SEVERITY OF ADR DURING MDR/RR-TB TREATMENT

4.1 SYNOPSIS

Formal citation: Schnippel K, Berhanu RH, Black A, Firnhaber C, Maitisa N, Evans D, Sinanovic E. Severe adverse events during second-line tuberculosis treatment in the context of high HIV Co-infection in South Africa: a retrospective cohort study. *BMC Infectious Diseases*. 2016 Oct 21;16(1):593.

This chapter presents data collected through a retrospective, patient-level medical file review at two Johannesburg MDR/RR-TB clinics. The frequency, types, severity and outcomes of adverse events documented in the files are described. The published manuscript also reports on patient characteristics and treatment characteristics associated with the most frequent and most severe events with the intent that if adverse events can be predicted they can be prevented or mitigated. The retrospective clinical file review was designed to address the first objective of the overall thesis, to describe the overall frequency, type, and severity of ADR experienced during MDR/RR-TB treatment. The cohort consists of a census of all eligible patients who initiated treatment at one of two large, public-sector MDR/RR-TB outpatient clinics located within the Helen Joseph and Charlotte Maxeke Academic Hospitals, respectively, in Johannesburg, South Africa.

Contribution to the thesis and novelty

Previous observational studies and meta-analysis of ART during MDR/RR-TB treatment had not been satisfying in establishing whether initiation of treatment for both HIV and MDR/RR-TB within weeks of each other was the safest course of action. This chapter presents a novel analysis which could help to explain why even the direction of the evidence as to the impact of ART initiation on ADR during MDR/RR-TB treatment was uncertain: competing risks. The methodology for competing risks analysis is now common to studies on cancer recurrence; it is now standard practice to adjust the risk of cancer recurrence having accounted for the possibility that the cancer did not recur because the patient died. This manuscript was the first publication to use the methodology to adjust the incidence of ADR: patients with the highest risk of mortality (those who are HIV-positive and not stable on ART prior to MDR/RR-TB treatment initiation) also have the highest risk of ADR.

Role of the candidate

The candidate worked with the clinicians to design a case record form and database to extract relevant fields from the medical records and reviewed and queried data captured. She designed and implemented the statistical analysis, and explained the importance of its use both to the co-authors and through the methods section for reviewers and readers. The candidate wrote the first draft of the manuscript and revised based on comments from co-authors and from reviewers. The co-authors approved the final version.

4.2 Manuscript 2

Title: Severe Adverse Events during Second-Line Tuberculosis Treatment in the Context of High HIV Co-infection in South Africa: a Retrospective Cohort Study

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Key words: HIV, antiretroviral therapy, multi-drug resistant TB, tuberculosis, adverse drug reactions

Abstract

Background:

According to the World Health Organization, South Africa ranks as one of the highest burden of TB, TB/HIV co-infection, and drug-resistant TB (DR-TB) countries. DR-TB treatment is complicated to administer and relies on the use of multiple toxic drugs, with potential for severe adverse drug reactions. We report the occurrence of adverse events (AEs) during a standardised DR-TB treatment regimen at two outpatient, decentralized, public-sector sites in Johannesburg, South Africa.

Methods:

We reviewed medical records of the six-month intensive treatment phase for rifampicin-resistant (RR) TB patients registered May 2012 - December 2014. Patients contributed follow-up time until death, loss from treatment, censoring (6 months) or data extraction. A standardized regimen of kanamycin, moxifloxacin, ethionamide, terizidone, and pyrazinamide was used according to national guidelines. AEs were graded using the AIDS Clinical Trial Group scale. We present subhazard ratios from competing risk analysis for time to severe AE, accounting for mortality and loss from treatment.

Results:

Across the two sites, 578 eligible patient files were reviewed. 36.7% were categorized as low weight ($\leq$50 kg) at DR-TB initiation. 76.0% had no history of TB treatment prior to the current episode of RR-TB. 26.8% were diagnosed with RR-TB while hospitalized, indicating poor clinical condition. 82.5% of patients were also HIV positive, of whom 43.8% were on ART prior to RR-TB treatment and 32.1% initiated ART with or after RR-TB treatment. Median CD4 count was 114.5 (IQR: 45-246.5). Overall, 578 reports of AEs were captured for 204 patients (35.3%) and 110 patients (19.0%) had at least one severe AE reported. Patients with at least one AE experienced a median of 3 (IQR: 2-4) AEs per patient. HIV-positive patients with CD4 counts $\leq$100 cells/mm^3 and those newly initiating ART were more likely to experience a severe AE (sHR: 2.76, 95% CI: 1.30 – 5.84 and sHR: 3.07, 95% CI: 1.46 – 6.46, respectively).

Conclusion:

Severe AE are common during the first 6 months of RR-TB treatment and HIV-positive patients newly initiating ART have the highest subdistribution hazard ratio for severe AE, accounting for the competing risks of death and loss from treatment.

Introduction

South Africa has made progress in controlling the TB epidemic; the 2015 Global Tuberculosis Report highlights a declining incidence and prevalence of TB for South Africa [160]. Despite the progress seen tuberculosis has been the most common cause of death in South Africa from 2005-2014 [161] and the, number of persons diagnosed with drug-resistant (DR-TB) TB has increased significantly over the last decade from 2,000 patients in 2005 to 18,734 in 2014 [160].

In 2011, South Africa adopted a policy of universal rifampicin (RIF) resistance testing using Xpert MTB/RIF (Cepheid, USA) as the first-line TB diagnostic in the country. Reporting of DR-TB now focuses on RIF resistant TB (RR-TB), which includes RIF resistance with unknown or pending sensitivities to other drugs, mono-RIF resistant TB, multi-drug resistant (MDR) TB that is resistant to both RIF and isoniazid (INH), extensively drug resistant (XDR) TB which is MDR TB plus resistance to second-line drugs from the fluoroquinolone and injectable aminoglycoside or cyclic peptide classes, or preXDR TB which is MDR TB plus resistance to either a fluoroquinolone *or* a second-line injectable drug [18]. The South African National TB Programme (NTP) treatment guidelines for RR-TB indicate 18-24 months of treatment [17]. All RR-TB patients are started on the standardized second-line MDR TB regimen until further resistance is either confirmed or ruled-out at which point the patient may be switched to an individualized second-line TB regimen (if preXDR or XDR TB) or INH may be added to the regimen (if mono-RIF resistant) [17].

Second-line TB treatment is complicated to administer, with frequent and potentially severe adverse drug reactions (ADR) [3,117]. Adding to the complexity of treatment, an estimated 60% of all TB patients [160] and up to 80% of RR-TB patients in South Africa [13] are also HIV-infected and therefore eligible for antiretroviral therapy (ART). RR-TB treatment and ART present overlapping toxicities which may be worsened by concomitant use, for example both kanamycin and tenofovir may cause renal dysfunction [136].

ADR can negatively impact the effectiveness of RR-TB treatment in many ways. Patients or clinicians may interrupt, reduce dosage, or stop treatment in an attempt to alleviate side effects. This results in an increased risk of acquiring additional drug resistance, failing treatment, or dying from TB. ADR themselves may also result in hospitalization, permanent disability, or death. Only 49% of the 2012 cohort of MDR TB patients in South Africa were cured or successfully completed treatment, below both the global average (50%) and targets (75%) [160]. Thus, evidence of the burden and risks of ADR during RR-TB treatment is important for both patients and clinicians to manage this complexity. In order to quantify the burden of ADR during outpatient RR-TB treatment in the context of high co-infection with HIV, we present the results of a medical file review of routinely reported adverse events (AE) from two decentralised public-sector sites within South Africa.

Methods

The study was conducted at the TB Focal Point clinics at Helen Joseph and Charlotte Maxeke Academic Hospitals in Johannesburg, South Africa. Patients with laboratory diagnosis of pulmonary or extrapulmonary RR-TB are referred to these NGO-supported, outpatient, public-sector facilities for initiation of second-line TB treatment and further drug resistance testing. Patients are referred from surrounding primary health care centres, private facilities, Helen Joseph and Charlotte Maxeke inpatient wards, and surrounding hospitals. A census of medical files for patients who enrolled for second-line TB treatment at Helen Joseph (May 2012 to June 2014) or Charlotte Maxeke (May 2012 to December 2014) were reviewed retrospectively in September 2014 and April 2015, respectively. Only patients with documentation of at least rifampicin resistance, i.e. RIF resistance detected by Xpert, RIF mono-resistance or MDR-TB diagnosed by LPA, poly resistance, or XDR TB were included in the study.

Standard of care treatment

Upon referral the patient undergoes HIV counselling and testing, patients are educated about the length and toxicities of RR-TB treatment, and given resources for screening of exposed family members. Patients are then examined and evaluated by a medical officer. All RIF resistance diagnosed by Xpert is treated presumptively as MDR-TB as per the South African National TB Programme (NTP) guidelines [17]. The intensive phase of treatment (approximately 6 months) consists of a five-drug regimen including the second-line injectable kanamycin, moxifloxacin, ethionamide, terizidone, and pyrazinamide [16,17]. The continuation phase of treatment (18 to 24 months) includes moxifloxacin, ethionamide, terizidone, and pyrazinamide. Treatment dose is adjusted for patient weight, with patients 33 to 50 kg receiving smaller doses of kanamycin (500 - 750 mg vs. 1000 mg), ethionamide (500 mg vs. 750 mg), and pyrazinamide (1000 – 1750 mg vs. 2000 – 2500 mg) than patients weighing 51 to 70 kg [17]. Linezolid and bedaquiline were not available at the study sites during the study period [19].

Since 2010, all HIV-positive patients with RR-TB in South Africa are eligible for antiretroviral therapy (ART) initiation regardless of CD4 count [101] within two weeks of RR-TB treatment initiation. The 2010 South African ART guidelines also indicated eligibility for HIV-infected patients with TB co-infection at CD4 $\leq$350 cells mm^3 and for any patient with CD4 $\leq$200 cells mm^3 [101]. Eligibility was expanded in 2013 to include all patients with any TB to include all patients with CD4 count $\leq$350 cells mm^3 [162]. Patients not currently on ART are initiated at the RR-TB site and patients currently on ART can receive ART from the RR-TB site for the duration of second-line TB treatment. From 2010, most South African ART patients in the public sector are initiated on a standard, first-line three-drug regimen of tenofovir, efavirenz or nevirapine, and lamivudine or emtricitabine. From 2013, a fixed-dose combination of tenofovir, efavirenz, and emtricitabine has been the preferred first-line ART regimen [162].

Patients are asked to return at two weeks and subsequently reviewed monthly by a TB nurse or medical officer for adherence to therapy, evaluation of side effects and treatment response. Sputum samples for smear microscopy and TB culture are collected monthly in pulmonary TB patients to assess for sputum smear and culture conversion. As per NTP treatment guidelines, baseline laboratory tests are conducted prior to treatment initiation to assess for anaemia and renal, thyroid and liver function. If HIV co-infected, laboratory tests to monitor HIV treatment (CD4 count and HIV viral load) or ART toxicities are integrated. Every two months during the six-month intensive phase of treatment blood work is repeated. Additional or more frequent laboratory testing may be ordered if clinically indicated. Audiology testing for hearing loss is conducted monthly during the six month intensive phase due to the high rates of aminoglycoside induced hearing dysfunction [116]. Electrocardiograms for monitoring were not included in the guidelines for the standard RR-TB regimen at the time of the study.

Adverse events and drug reactions

For most of the period under review, pharmacovigilance requirements were for targeted spontaneous reporting to the national regulatory agency, the Medicines Control Council. Programmatic pharmacovigilance for HIV and TB, including RR-TB was in the process of being rolled out by the National Pharmacovigilance

Centre [163]. According to the regulatory form which is separate from the medical file, 'advice about voluntary reporting' requests clinicians to please report all 'serious reactions and interactions with all products' to the Medicines Control Council.

Most of the AEs identified in this file review were found in the clinical progress notes section of the medical files. Causality was not routinely documented. AEs such as weight loss could be related to adverse drug reactions from second-line TB treatment or ART, or HIV or TB morbidity. Pre-existing conditions at the time of RR-TB treatment initiation were noted under patient medical history and co-morbidities and therefore not included in the adverse events. However, if pre-existing conditions worsened during treatment it would be reported.

AEs of interest were those most likely to be adverse drug reactions and defined prior to the review as including renal dysfunction, hypokalaemia, ototoxicity, vestibular dysfunction, severe anaemia, psychosis and depression, peripheral neuropathy, seizures, hypothyroidism, nausea and/or vomiting, and joint pain. Other AEs identified during the review were recorded and categorized during data analysis. Standard of care does not include routine screening for gastro-intestinal disorders such as nausea or vomiting or mental health such as depression, insomnia, or insomnia; AEs captured were as reported by patients with during routine visits.

AEs were graded either at the time of the event (in the clinical notes) or during the file review by the treating clinician as mild (grade 1), moderate (grade 2), severe (grade 3), potentially life-threatening (grade 4), or fatal (grade 5) according to the AIDS Clinical Trials Group grading system [164]. AEs included those detected clinically and through laboratory testing. Where outcome of the AE (e.g. death, hospitalization, permanent disability, drug discontinuation, and/or drug dose reduction) was available in the file it was also captured. Deaths that were not reported as an outcome of an AE, i.e. those thought to be from TB, were not re-categorised as an AE.

Statistical analysis

We present descriptive analysis of the number of AEs by patient, types of AE reported, and severity of AEs identified from the medical record review, including frequencies and proportions.

We used time to event analysis to present the mean time from second-line TB treatment initiation to (first) severe adverse event (grade 3 or higher). Follow-up is censored at 6 months after second-line TB treatment initiation, final outcome (i.e. death or loss from treatment for at least 2 months), transfer to another site, or data extraction (September 2014 for Helen Joseph and April 2015 for Charlotte Maxeke). We used competing risk regression method from Fine and Gray [165] to determine if occurrence of a severe AE was associated with *a priori* identified patient demographic and clinical characteristics. Because loss from treatment may represent unreported mortality, both death and loss from treatment were considered to be the risks competing with report of a severe AE. Univariate (crude) subdistribution hazard ratios (sHR) with 95% confidence intervals (CI) are presented. All analysis was completed in Stata v14 (College Station, TX).

Characteristics considered included: HIV status (HIV negative, HIV-positive on ART prior to RR-TB diagnosis and initiation defined as at least 30 days prior to RR-TB treatment start, HIV-positive initiated on ART at or after RR-TB initiation, or HIV positive not on ART or ART unknown); age category (10-24, 25-39, 40-54, 55 years or older), and sex. We also examined markers of severity of illness: report of cough, fever, weight loss, or night sweats, low weight at treatment initiation ($\leq$50 kg), diagnosed with RR-TB during hospitalization for any cause, and CD4 count at RR-TB treatment initiation as documented in the patient file (HIV negative, HIV-positive with CD4 >100 cells/ mm^3, or HIV-positive with CD4 $\leq$100 cells/mm^3). Information on pre-existing conditions or self-reports of prior TB treatment (none, first-line regimen, or regimen that included streptomycin) were also considered. All patients were on standardized treatment regimens for RR-TB; patients diagnosed with XDR TB were transferred out to initiate individualized treatment at another site and therefore exposure was censored.

Ethics, consent and permissions

Ethical approval without patient informed consent for this de-identified medical record review was obtained from the Human Research Ethics Committees of the University of the Witwatersrand and the University of Cape Town.

Results

Across the two sites, 578 files were available for review and patients eligible for the study, patient characteristics are reported in Table 4-1. Patients presented with RR-TB at a median age of 35 (IQR: 29-42 years) and 49.0% were male. One-third of the patients (36.7%) were categorized as low weight (<50 kg) at initiation of second-line TB treatment, the median weight at initiation was 54 kg (IQR: 47.9-61.5). Only 1.2% reported a history of TB treatment with an injectable drug (streptomycin) and the majority (76.0%) had no history of any TB treatment prior to the current episode of RR-TB. Approximately one-quarter (26.8%) of the patients were diagnosed with RR-TB while hospitalized, indicating poor clinical condition.

Table 4-1 Characteristics of patients at initiation of second-line TB treatment (n=578)

Characteristic	Description	Count	Proportion
Sex	Male	283	49.0%
	Female	295	51.0%
Age	10-24 years	56	9.7%
	25-39 years	338	58.5%
	40-54 years	163	28.2%
	55+ years	21	3.6%
Weight (kg)	Low weight ($\leq$50 kg)	195	36.7%
	>51 kg	337	63.3%
	Missing	46	8.0%
TB foci	Pulmonary	541	93.6%
	Extrapulmonary only	37	6.4%
Prior TB	No history of TB treatment	439	76.0%
	Prior first-line TB treatment	119	20.6%
	Prior TB treatment with streptomycin	7	1.2%
	Unknown	13	2.2%
Current TB diagnosis	MDR-TB (INH and RIF resistance)	182	31.5%
	RIF mono-resistant TB	198	34.3%
	RIF resistant, sensitivities unknown	191	33.0%
	XDR TB (second-line resistance)	7	1.2%
Presenting symptoms	Cough	281	65.9%
	Any of cough, weight loss, fever, night sweats	453	78.4%
Sputum smear microscopy	Positive (scanty or higher)	284	49.1%
	Negative or unknown	294	50.9%
Level of care at TB diagnosis	Outpatient, ambulatory	406	70.2%
	Inpatient, hospitalized	155	26.8%
	Missing	17	2.9%

MDR-TB: Multi-drug resistant tuberculosis; RIF: rifampicin; INH: isoniazid; XDR TB: extensively drug-resistant tuberculosis

HIV infection was the most common co-morbidity reported as 82.5% (n= 477/578) were HIV positive (Table 4-2). Of those who were HIV positive, 43.8% were on ART at least 30 days prior to RR-TB treatment initiation with a median 332 days on ART (IQR: 160, 991) and 31.9% initiated ART with or after RR-TB treatment with a median time to ART initiation of 26 days after RR-TB treatment (IQR: 14, 42). Of the 77.8% of HIV-positive patients with CD4 counts reported at RR-TB treatment initiation, the median CD4 was 114.5 (IQR: 45-246.5). Half (50.2%) were on the standard first-line regimen for the public sector ART program (tenofovir, efavirenz, and lamivudine or emtricitabine). Few other co-morbidities were reported, with no one co-morbidity affecting 10 or more patients. Diabetes mellitus (1.9%), renal insufficiency (1.4%), and hepatitis or liver dysfunction (1.2%) were the three most common co-morbidities other than HIV. Seven women (2.4% of women) were pregnant during RR-TB treatment.

Table 4-2 Co-morbidities, clinical conditions and chronic medications (n=578)

Characteristic	Description	Count	Proportion
HIV status	Negative	95	16.4%
	Positive	477	82.5%
	Unknown	6	1.0%
CD4 count^ (n=477)	Low ($\leq$100 cells/mm^3)	173	36.3%
	>100 cells/mm^3	198	41.5%
	Missing	106	22.2%
ART status (n=477)	Not on ART	116	24.3%
	Median CD4 count	156.5	IQR: 65, 255
	Initiated ART with or after RR-TB	153	32.1%
	Median CD4 count	100.5	IQR: 42.5, 221.5
	Median days RR-TB at ART initiation	26	IQR: 14, 42
	On ART prior to RR-TB initiation	209	43.8%
	Median CD4 count	101	IQR: 41, 253
	Median days on ART at RR-TB initiation	332	IQR: 160, 991
ART regimen (n=362)	TDF + 3TC or ETC + EFV	182	50.23%
	D4T or AZT + 3TC + EFV	34	9.4%
	TDF + 3TC + LPV/r	3	0.8%
	D4T or AZT + 3TC + LPV/r	46	12.7%
	Other regimen	53	14.6%
	Missing	44	12.2%
Reported co-morbidities	Hepatitis or liver disorder	7	1.2%
	Epilepsy	6	1.0%
	Psychiatric disorder	5	0.9%
	Diabetes mellitus	9	1.6%
	Renal dysfunction	8	1.4%
Pregnancy (n=295)	Pregnant	7	2.4%
Contraception (n=295)	Using hormonal contraceptive	16	5.4%

ART: antiretroviral therapy; TDF: tenofovir; 3TC: lamivudine; EFV: efavirenz; LPV/r: lopinavir/ritonavir
^ CD4 count at RR-TB treatment initiation

Adverse events

Overall, 578 reports of AEs were captured for 204 patients (35.3%) and 110 patients (19.0%) had at least one severe AE (grade 3+). Patients with at least one reported AE experienced a median of 3 AEs (IQR: 2-4) per patient.

Gastro-intestinal AEs were the most common, with 138 reports of vomiting, nausea, abdominal pain, epi-gastric discomfort, diarrhoea, constipation, loss of appetite, or weight loss. Although most nausea and vom-iting reported (67.1% of 70 reports) was mild to moderate (Figure 4-1), it was the second most commonly reported severe AEs (11.8% of all the severe AEs). The most common severe AE reported was hearing loss or ototoxicity (Figure 4-2). In total, 114 reports of hearing loss were noted affecting 17.3% of patients (n=100/578). Of the hearing loss AEs reported, 61 (53.5%) were categorised as grade 3+. Renal dysfunction or failure accounted for 10.3% of all severe AEs, with 20 episodes reported. Psychosis (6.7%), neuropathy

(6.1%) and hepatitis or liver dysfunction (5.6%) were also among the most frequent severe AEs reported. Rare severe AE reports included deep vein thrombosis (n=2), sepsis (n=1), miscarriage (n=1), suicidal thoughts (n=1), and neuroleptic malignant syndrome (n=1).

Figure 4-1 Counts of most frequent mild or moderate adverse events by HIV and ART status (n=204)

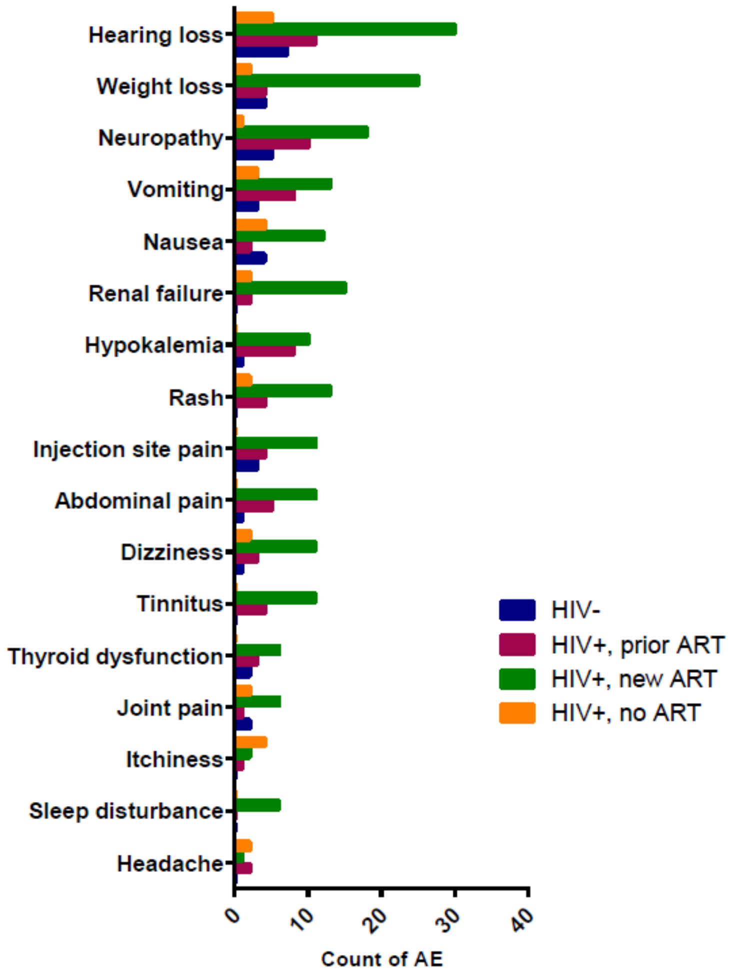
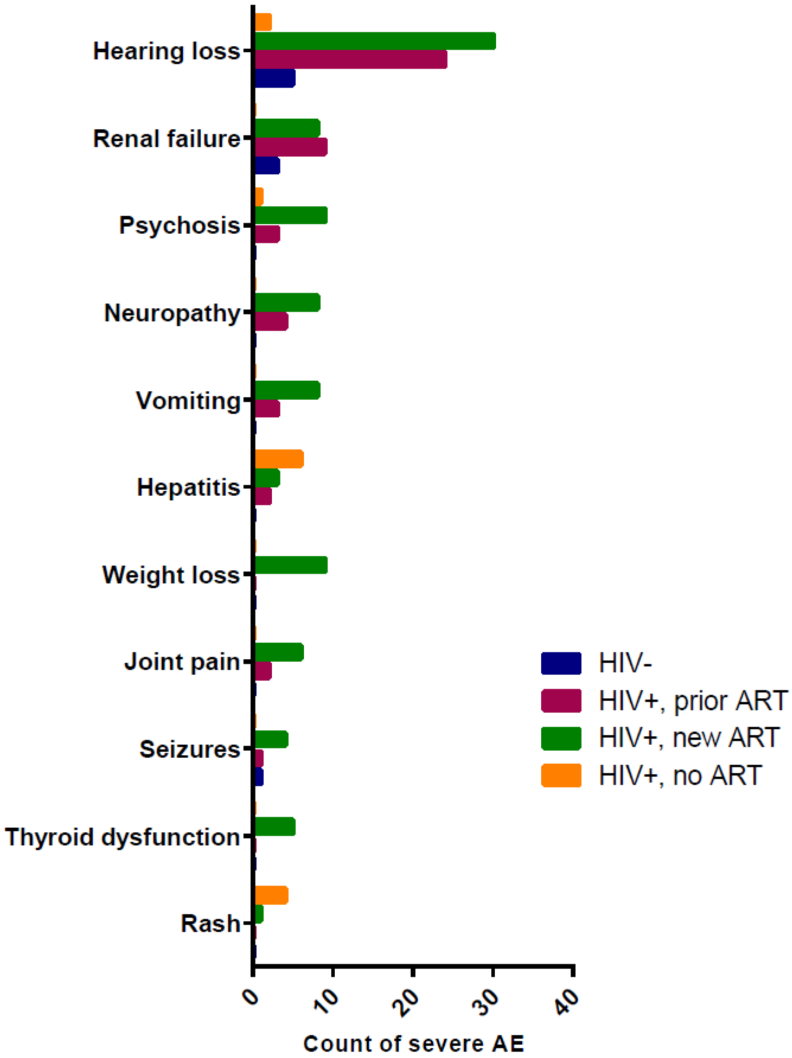


Figure 4-2 Counts of most frequent severe adverse events by HIV and ART status (n=110)



Kanamycin was listed as the suspected drug causing AE or severe AE for 54.4% (111/204) of patients experiencing an AE. Among the 309 AEs with at least one suspected drug listed, kanamycin was listed 175 times (56.6%). Of the severe AEs with at least one suspected drug listed, terizidone was listed 32/126 times (25.4%). Less than 5% (n=26) of the AEs had hospitalization documented as an outcome of the AE. Nearly 20% (n=109) of identified AEs resulted in the suspected drug being discontinued and an additional 10% (n=57) resulted in the dose of the suspected drug being reduced.

Subdistribution hazard ratios of severe AE

Of the 578 patient files reviewed, 18 did not contribute to the time-to-event analysis as patient either died or were transferred out prior to returning to the clinic after RR-TB treatment initiation. The 560 that were included contributed 52,684 person-days of follow-up with a median exposure of 70 days. There were 107 severe AEs analysed, giving an incidence rate for severe AE of 0.74 per person year.

HIV-positive patients with low CD4 counts ($\leq$100 cells/mm^3) and those who initiated ART with RR-TB treatment both were approximately 3 times more likely to experience a severe AE with crude sHR: 2.76 (95% CI:

1.30 – 5.84) and sHR: 3.07 (95% CI: 1.46 – 6.46), respectively (Table 4-3). Patients previously treated for TB with a regimen including streptomycin were also more likely to experience a severe AE, sHR: 3.49 (95% CI: 1.52 – 8.02), all were ototoxicity. Subdistribution hazard ratios for categorized age, low weight at treatment initiation, smear microscopy positive, recent hospitalization, sex, cough at initiation, or pre-existing renal, liver, or psychiatric conditions were not statistically different.

Table 4-3 Risks of severe (grade 3+) adverse events during first 6 months of RR-TB treatment

Characteristic	Description	sHR^	95% CI
Age category	10–24 years	0.70	0.31 – 1.58
	25–39 years	Referent	
	40–54 years	0.92	0.61 – 1.39
	55 years +	1.93	0.85 – 4.37
HIV and CD4 status	HIV negative	Referent	
	HIV+, CD4>100 cells/mm^3	1.81	0.84 – 3.89
	HIV+, CD4≤100 cells/mm3	**2.76**	**1.30 – 5.84**
HIV and ART status	HIV negative	Referent	
	HIV+, initiated ART prior to RR-TB	1.77	0.83 – 3.77
	HIV+, initiated ART with or after RR-TB	**3.07**	**1.46 – 6.46**
	HIV+, not on ART	1.15	0.43 – 3.10
Weight (kg)	Weight >51 kg	Referent	
	Low weight (≤50 kg)	1.43	0.97 – 2.10
Prior TB treatment	No TB history reported	Referent	
	History of first-line TB treatment	1.33	0.85 – 2.07
	History of streptomycin for TB treatment	**3.49**	**1.52 – 8.02**
Referring site	Outpatient facility	Referent	
	Inpatient facility	1.11	0.74 – 1.70
Sex	Female	Referent	
	Male	0.83	0.57 – 1.22
Smear microscopy	Sputum smear negative or not reported	Referent	
	Sputum smear positive (scanty or higher)	1.00	0.69 – 1.47
Presenting symptom	No cough	Referent	
	Any cough	1.37	0.90 – 2.08
Co-morbidities	No reported pre-existing renal insufficiency, liver or psychiatric disorder	Referent	
	Pre-existing renal, liver, or psychiatric condition	0.47	0.11 – 1.93

ART: antiretroviral therapy; RR-TB: Rifampicin resistant tuberculosis; sHR: subdistribution hazard ratio;
^sHR crude analysis from competing risk regression accounting for death and loss from treatment

Competing risk regression sHR can be displayed as a graph of the cumulative incidence (of the risk analysed) function over the time at risk. Figure 4-3shows patients initiating ART with or after RR-TB treatment had the highest sHR of experiencing a severe AE versus HIV-negative patients, HIV-positive patients who had been on ART prior to RR-TB diagnosis, and HIV-positive patients never on ART. As a comparison, the cumulative incidence function of death during RR-TB treatment, accounting for the competing risk of loss from treatment, is shown for the same HIV and ART categories (Figure 4). HIV-positive patients who did not initiate ART either before or at RR-TB initiation were more than 3 times more likely to die during RR-TB treatment than HIV-negative patients (sHR: 3.25, 95% CI: 1.17 – 9.02). Figure 4-4shows the cumulative incidence function for mortality during second-line TB treatment was highest for HIV-positive patients never on ART versus HIV-negative, HIV-positive patients who had been on ART prior to RR-TB diagnosis, and HIV-positive patients initiating ART along with or after RR-TB treatment.

Figure 4-3 Cumulative incidence function after competing risk regression of any severe adverse event

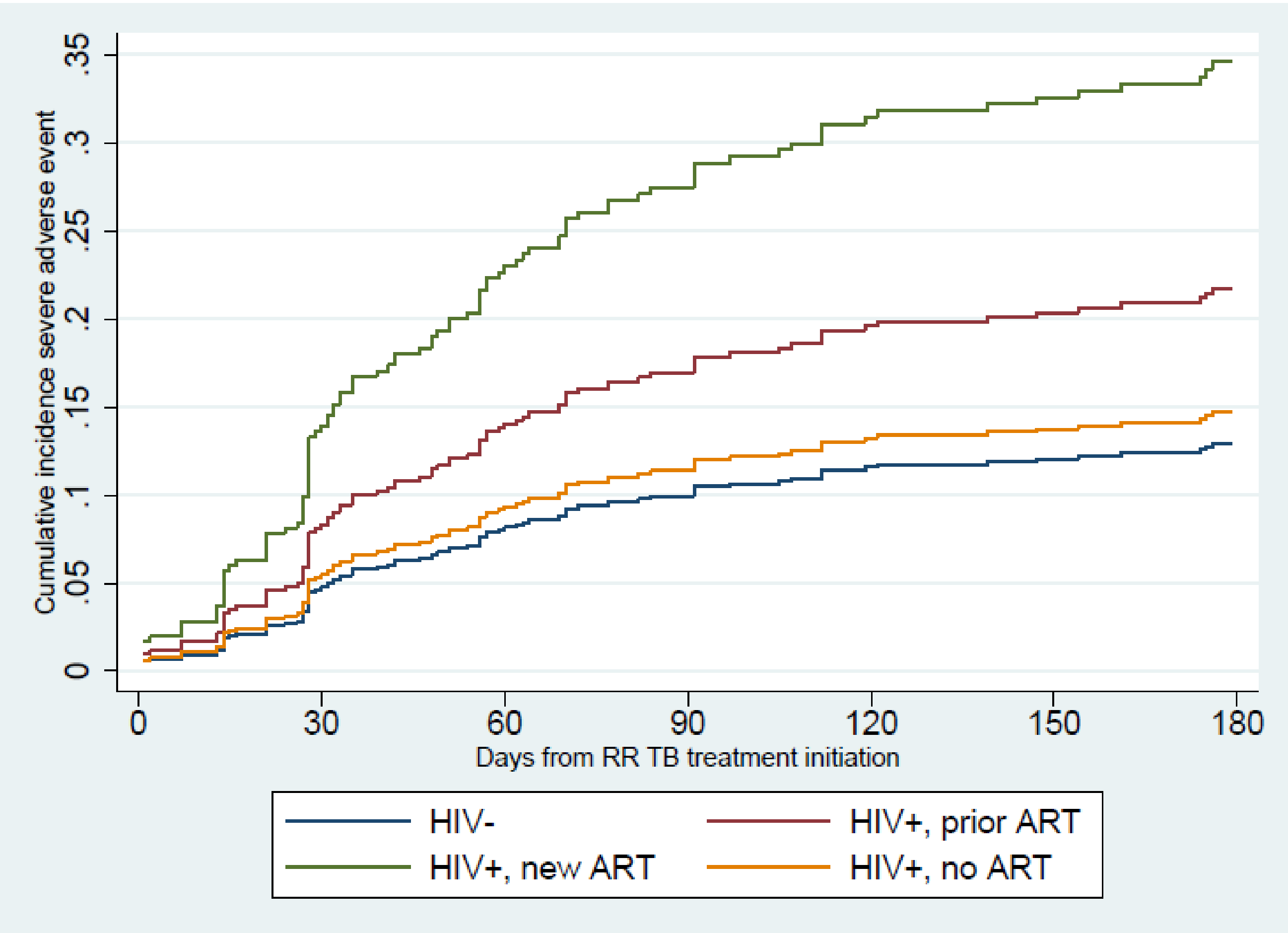


Figure 3 Legend: Competing risk accounting for loss from treatment and death during treatment, by HIV and ART status

Figure 4-4 Cumulative incidence function after competing risk regression of death during RR-TB treatment

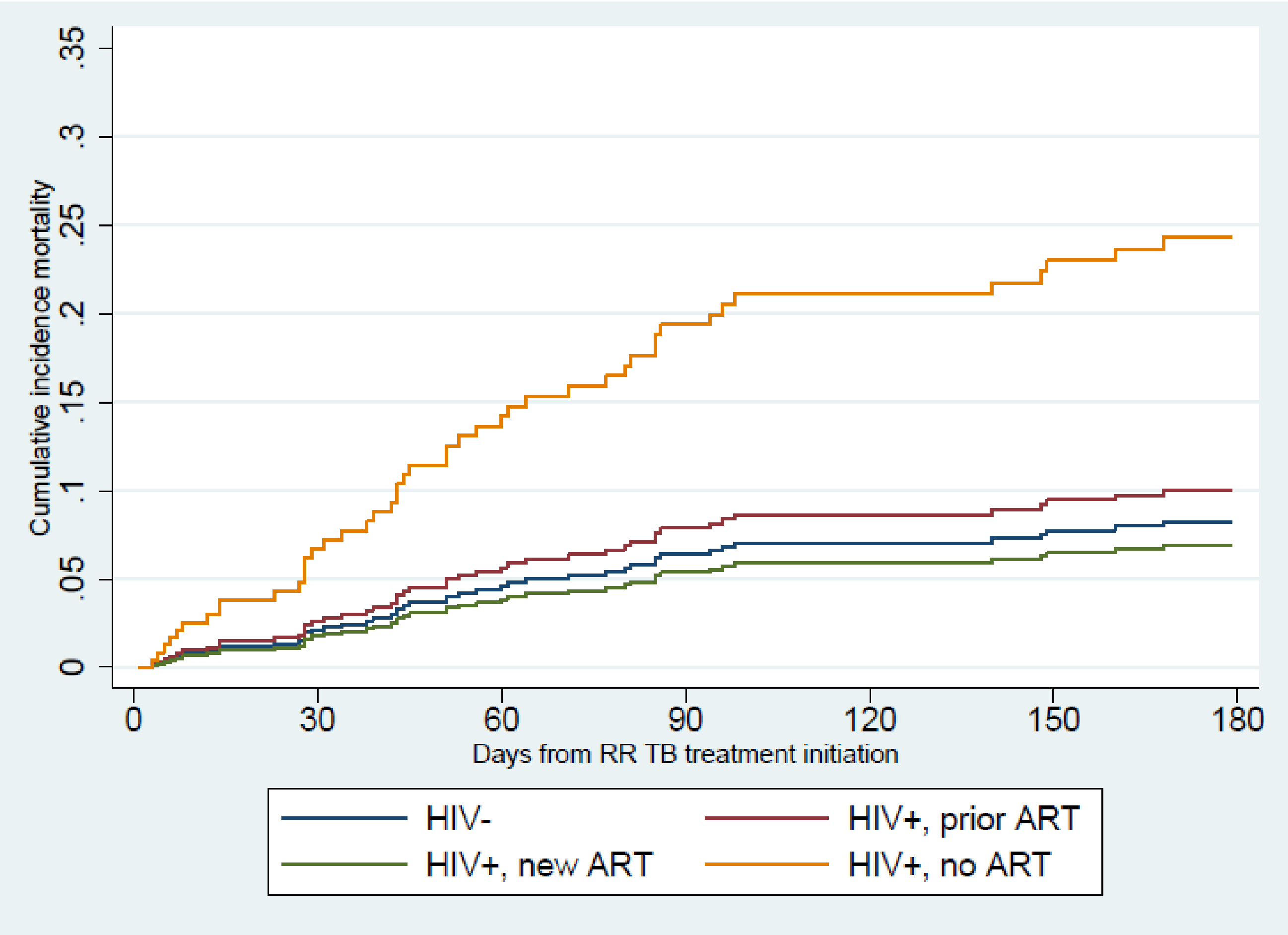


Figure 4 Legend: Competing risk accounting for loss from treatment, by HIV and ART status

Discussion

During the first six months of RR-TB treatment in a context where 82.5% of patients were also infected with HIV, 35.3% of patients experienced at least 1 AE. This incidence was less than reported in a meta-analysis of adverse drug events during the 18 to 24 months of treatment of MDR-TB, which found 57.3% of patients (260/534) experienced at least one AE [3]. One of the included studies, from a similar context in South Africa, reported that 99% of the 71 patients in that cohort experienced at least one AE [108]. The meta-analysis did not report whether the AEs were mild, moderate, severe, life threatening, or fatal [3]. In our cohort, the incidence of severe AEs during the first 6 months of treatment was 19.0%, far higher than the 6.9% reported in a large cohort of HIV positive, ART naïve MDR TB patients also from South Africa [109].

Kanamycin was listed as the suspected drug causing AE or severe AE for 54.4% of cohort patients experiencing an AE. Kanamycin, along with other aminoglycosides, is associated with ototoxicity (hearing loss and vestibular dysfunction) and renal dysfunction [17,109,116,166]. While an effective agent against drug-resistant TB [16], multiple trials are underway to develop an injection-free regimen for treating RR-TB in an attempt to reduce the overall burden of ADR and improve adherence to long-term therapy [167].

Our finding that patients recently initiating both ART and RR-TB treatment have an increased sHR for severe AE during the first 6 months (sHR: 3.07) has not been previously reported. The WHO recommendation to immediately initiate ART was based upon lower risk of death but found that there was 'very low quality of evidence' as to whether concomitant use of ART and RR-TB treatment led to more severe AE or drug interactions [16]. A previous systematic review of the use of ART during second-line TB treatment concluded there was insufficient data as to whether concomitant use of ART and RR-TB treatment increased the risk of ADR [136]. A study of XDR TB patients in South Africa found that there was no difference in the proportion of patients (using chi-squared test) with a severe AE reported for HIV-positive patients on ART compared to HIV-negative patients [168]. Our finding of the higher sHR for severe AE may be because other studies did not differentiate the grade of AE, had insufficient numbers of patients on ART, or did not differentiate the time on ART. Additionally, using the competing risk methodology to calculate sHR accounting for the competing risk of death and loss from treatment was useful in the context of very high early mortality for patients not on ART. The increased sHR point to a need for additional or more frequent monitoring for AE for patients initiating both ART and RR-TB treatment at the same time. These patients may also benefit from inpatient treatment initiation where they can be more closely monitored and managed.

The cumulative incidence function for mortality accounting for the competing risk of loss to treatment indicated that patients not on ART are most at risk of death and therefore our results are consistent with studies and guidelines that indicate early initiation of ART for patients with TB [169–171] and drug-resistant TB [16,136]. This reversal of risk (patients with highest relative sHR of mortality have the lowest relative sHR of severe AE) also highlights the need for greater access to ART and initiation at higher CD4 counts. In our study, there was a high proportion of patients with very low CD4 counts not on ART despite increasing access to ARVs in South Africa; patients with CD4$\leq$100 cells/mm^3 also had a higher sHR of severe AE (sHR: 2.76). Further, a quarter of the patient files reviewed in this study were diagnosed with RR-TB while hospitalized although testing for RIF resistance is available at the lowest levels of the public health system in South Africa. Again, this represents delays in diagnosis and case finding at the primary health care level leading to hospitalization and late diagnoses.

While most nausea and vomiting were reported as mild to moderate (67.1% of 70 reports) this AE can impact on both adherence and effectiveness of treatment. Because of AEs, the treating clinicians discontinued or reduced the dosage of the suspected drug for 17.3% of patients (100/578), a similar proportion to the 21% calculated from a patient-level meta-analysis of MDR-TB studies [8]. Because of overlapping toxicities, a patient who experienced an AE during RR-TB treatment may no longer be eligible for standard ART or second-line TB treatment regimens, for example because of drug-induced liver or kidney injuries. Fewer effective drugs in the second-line TB regimen is associated with lower probability of treatment success [8] and consequently higher risk of acquired additional resistance.

Prior exposure to streptomycin may be a risk factor for ototoxicity during RR-TB treatment with increased aminoglycoside cumulative dose [116]. In our cohort, although the numbers of patients with prior exposure were small (1.2%), this was the strongest predictor of a severe AE (sHR: 3.30), with all severe AEs related to ototoxicity. With the introduction of Xpert MTB/RIF diagnosis, the 'retreatment' regimen containing streptomycin was phased out and as of end 2013 is no longer in use in the South African NTP [172]. While the lack of history of prior TB treatment may reduce the risk of some types of ADR, from a public health perspective the 76.0% of patients in this cohort without any prior TB history is concerning as it indicates primary transmission of RR-TB.

Limitations

The lower rates of ADR in this cohort may be a result of both the lack of routine reporting and retrospective study design. During the monthly visits to the outpatient clinic, patients are not prompted to self-report AE. In some cases, patients may have discussed AE with the counsellor, nurse, or clinician but if the healthcare worker did not note the discussion in the medical file it would not have been counted in this review. This may have resulted in an under-reporting of AEs, particularly those that were mild to moderate (grade 1-2). Also, while guidelines indicate monitoring for certain AEs, implementation may differ from intended practice. One challenge that both sites noted during the study was that it was difficult to access audiology screening for patients due to concerns about infection control as audiology services were not co-located within the TB clinic. Additionally, this study focused on the first 6 months of treatment, the intensive phase, which includes kanamycin. It is possible that some patients who did not experience an ADR during the first 6 months would be affected in subsequent months or that an ADR would be detected in subsequent months, specifically aminoglycoside ototoxicity is known to occur even after treatment discontinuation [131].

Another limitation of this study which is the inability to distinguish between the AE and ADR. For this reason, events described in this analysis were described as AE rather than the more specific term ADR. This limitation is common to studies describing ADR and AE and must be taken into consideration when trying to draw conclusions across studies. For example, in the South African study indicated above with 99% incidence of AE, injection site pain was the second most commonly reported clinical AE. Injection site pain was only reported in this cohort for patients refusing to continue with the injections for reason of pain. This study also did not try to distinguish whether the AE was related to the ART or second-line TB treatment.

Finally, the study period preceded the roll-out of bedaquiline and linezolid in the South African NTP. These two drugs are now available for patients who experience toxicity to one of the drugs of the standard regimen [19] and use of the new and re-purposed drugs may affect the profile of ADR experienced by patients with drug-resistant TB in South Africa.

Conclusions

Severe adverse events are common during the first 6 months of second-line treatment and HIV-positive patients on ART have the highest relative subdistribution hazard ratio of experiencing a severe AE, accounting for the competing risk of death and loss from treatment. Patients whose clinical condition requires immediate initiation of ART and RR-TB treatment may benefit from intensive monitoring or even inpatient treatment initially to watch for severe AEs.

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NM is an employee of GlaxoSmithKline (GSK); however, the study was conducted prior to her employment with GSK. GSK has not sponsored or funded the study in any way. The contents are the responsibility of the authors and not of GSK.

Competing interests

The authors declare no competing interests.

REFERENCES

(At end of thesis)

5 RESULTS: META-ANALYSIS OF ADR DURING MDR/RR-TB TREATMENT

5.1 SYNOPSIS

Formal citation: Schnippel K, Firnhaber C, Berhanu R, Page-Shipp L, Sinanovic E. Adverse drug reactions during drug-resistant TB treatment in high HIV prevalence settings: a systematic review and meta-analysis. Journal of Antimicrobial Chemotherapy. 2017 Apr 16. doi: 10.1093/jac/dkx107.

Supplemental materials appended (Annex – Supplemental materials for meta-analysis of ADR in HIV settings)

This chapter presents a systematic review and meta-analysis of studies reporting on adverse drug reactions or adverse events during treatment for MDR/RR-TB. Articles could be from any period, but the treatment regimens needed to be aligned to the WHO recommended standard long-course regimens 2011 to 2016; therefore, most articles were during this period. In order to be included, articles had to report on the HIV status of included patients. Only those cohorts where at least 20% of the patients were known to be HIV-infected were included. The intent was to capture the frequency, types, severity and outcomes of adverse events documented. However, because of inconsistencies in reporting and descriptions of the reported ADR, the meta-analysis was limited to the prevalence of the ADR, disaggregated by whether severe to serious or mild to moderate. The published manuscript also reports on a systematic review of comparisons presented between HIV-infected and HIV-negative patients with regards to frequency, types, or outcomes of ADR reported.

Contribution to the thesis and novelty

Based on both the clinical file review (Manuscript 2) and Literature Review, the question of whether HIV-infected patients experience the same rates of ADR during MDR/RR-TB treatment had not been answered. Most MDR/RR-TB studies are observational and relatively small, which led to uncertainty and imprecision in the estimates of ADR prevalence. In order to include a burden of ADR in the cost-effectiveness model, it was important to first understand whether estimates for HIV-negative populations could be applied in a high HIV prevalence setting such as South Africa. This analysis was novel in limiting the focus to settings with a high proportion of HIV-infected patients rather than grouping all settings together. Because all studies found were observational and the question was prevalence (frequency of) ADR rather than treatment effect or relative risk, the *metaprop* command in Stata was used. Metaprop manages the variance of a meta-analysis, but relies on a binomial distribution appropriate for binary questions such as whether a patient experienced an ADR or not.

Role of the candidate

The candidate wrote the protocol for the systematic review and revised based on review of results from initial searches. The candidate screened all titles and abstracts if needed for duplicates and inclusion criteria (700+), retrieved and screened articles that could not be excluded based on abstract review. She also retrieved and hand searched the reference lists for articles identified as reviews. The candidate extracted relevant fields from the articles, designed and performed the statistical analysis on captured fields. The candidate wrote the first draft of the manuscript and revised based on comments from co-authors and from reviewers. The co-authors approved the final version.

5.2 MANUSCRIPT 3

Title: Adverse drug reactions during drug-resistant tuberculosis treatment in high HIV prevalence settings: a systematic review and meta-analysis

Short title: Adverse drug reactions during drug-resistant TB treatment: meta-analysis

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Abstract
Objective

To estimate the prevalence of adverse drug reactions or events (ADR) during drug-resistant tuberculosis (DR-TB) treatment in the context of settings with high HIV prevalence (at least 20% of patients) by conducting a systematic review and meta-analysis of articles in PubMed and Scopus. Pooled proportions of patients experiencing adverse events and relative risk with 95% confidence intervals (CI) were calculated.

Results

The search yielded 24 studies, all observational cohorts. Ten reported on number of patients experiencing ADR and were included in the meta-analysis representing 2,776 study participants of which 1,981 were known to be HIV-infected (71.4%). An average of 83% (95%CI: 82%, 84%) of patients experienced one or more ADR. Among the 7 articles (n=664 study participants) with information on occurrence of severe ADR, 24% (95%CI: 21%, 27%) patients experienced at least 1 severe ADR during DR-TB treatment. Sixteen of the 24 studies analysed the relative risk of ADR by HIV infection, nine of which found no statistically significant association between HIV-infection and occurrence of drug-related ADR. There was insufficient information to disaggregate risk by concomitant treatment with HIV antiretrovirals or by immunosuppression (CD4 count).

Conclusions

No randomized clinical trials were found for WHO-recommended treatment of DR-TB treatment where at least 20% of the cohort was co-infected with HIV. Nearly all patients (83%) experience ADR during DR-TB treatment. While no significant association between ADR and HIV co-infection was found, further research is needed to determine whether concomitant antiretrovirals or immunosuppression increases the risks for HIV-infected patients.

Introduction

The World Health Organization (WHO) estimates that in 2015, 580,000 of the 6.1 million persons who were notified as tuberculosis (TB) cases had a drug-resistant strain of the disease. Only 20% were diagnosed and initiated on treatment of which 52% had successful outcomes.[58] Access to drug-resistant TB treatment is limited by timely diagnosis of resistance, availability of treatment, staff capacity, high early mortality, and cost.

Patients resistant to rifampicin alone or in combination with any other first-line or second-line drugs require second-line treatment. Rifampicin resistant (RR-) TB includes multi-drug resistant (MDR-) TB, resistant to both isoniazid and rifampicin, and extensively drug resistant (XDR-) TB, MDR-TB that is also resistant to both a fluoroquinolone and a second-line injectable drug. The duration of drug-resistant TB treatment is longer than for drug-sensitive TB (typically 9-24 months) and standard regimens for MDR/RR-TB include 4 to 7 drugs with different[16] mechanisms of action, including oral bacteriostatic drugs; aminoglycoside and cyclic peptide injectables; fluoroquinolones; and newer agents such as bedaquiline and delamanid.

Many of the drugs have known toxicities, especially at the doses and durations required to treat resistant strains of TB and there is limited clinical trial data on dosage and related side effects. As a result, adverse drug reactions (ADR) are very common during drug-resistant TB treatment. A systematic review and meta-analysis of published literature through October 2012 found that 57.3% of included patients had experienced at least one type of ADR, including mild to severe events.[3] ADR can lead to the clinician or patient interrupting, stopping, or reducing the dosage of treatment before completion, and therefore may increase the risk of mortality, treatment failure, or death.[117] Either sequelae from the ADR or the untreated TB disease may lead to reduced quality of life.[120] However, the high mortality, risk of transmission, and limited alternatives mean that clinicians and patients with drug-resistant TB are left with little choice.

Within the last decade, there has been escalated progress for drug-resistant TB drug development; new treatments are being developed and multiple drugs are entering or in clinical trials.[167,173] Knowing whether the rates of ADR experienced in clinical trials for new drugs are of concern requires a better understanding of the base case scenario. Additionally, in efforts to improve treatment outcomes existing drugs such as linezolid (an oxazolidinone) and clofazimine are being re-purposed for drug-resistant TB treatment. Because the drugs have existing regulatory approval for other indications, randomized controlled trials are not required in many settings and available understanding of the potential side effects and optimal doses for the regimens are limited to observational cohorts.[98,174] Additionally, the sickest patients or those with HIV, advanced HIV, or other comorbid conditions are often excluded from clinical trials. For high prevalence HIV-settings, this can limit applicability of clinical trial data to patients co-infected with HIV and other comorbid conditions. Yet, in some settings, particularly sub-Saharan Africa, TB and HIV are inextricably linked. Treatment of HIV and TB co-infection results in high pill burden and potentially increased toxicity. Effective ART regimens include three drugs, and toxicities can be overlapping.[16,136] HIV infection, even for the ART naïve, and particularly for those who have advance HIV disease or immunosuppression may also pose its own risk for ADR.

To understand the association between HIV infection and treatment and the prevalence of ADR during drug-resistant TB treatment, we systematically reviewed and conducted a meta-analysis of peer-reviewed published literature to identify the types, frequencies, severity and seriousness of ADRs associated with the pre-2016 WHO-recommended regimens for drug-resistant TB in settings with HIV co-infection of at least 20%.

Methods

Literature search was done in PubMed (inclusive of MEDLINE) and Scopus. The title, abstract, and full text were searched for adverse or toxicity or side effects or safety or tolerability AND drug-resistant or multi-drug resistant or second-line treatment or rifampicin-resistant AND tuberculosis or TB AND human immunodeficiency virus or HIV or acquired immune deficiency syndrome or AIDS. No date ranges were set; the search was initially done on 11 February 2016 and then updated on 4 August 2016. Retrieved results were de-duplicated. Conference proceedings and conference abstracts were not included in the search because of limited presentation of results in abstract format. Manuscripts in languages other than English were excluded.

Titles and abstracts were screened and the following excluded from the articles to be retrieved: opinion pieces, editorials; guidelines; case reports; and studies with no reports of drug-resistant TB treatment, e.g. drug-sensitive TB treatment, laboratory testing, bench research, pharmacokinetic studies, and diagnostic tools, methods, or algorithm. Systematic reviews and meta-analyses identified during the screening were not included in this systematic review, but were retrieved and a manual search done of the references.

If from the title or abstract it was clear that the article did not meet inclusion criteria or if an exclusion criteria was present, the article was excluded from further review. For any abstracts which met inclusion criteria or for which the abstract was not sufficiently detailed to determine eligibility, the full text was retrieved and reviewed. Retrieved full texts were reviewed for inclusion and exclusion criteria (Table 11-1). Based on the articles retrieved, the included articles were further classified according to whether they reported on only severe (i.e. events that were severe in intensity[133]) or serious ADR (i.e. death or a life-threatening experience; hospitalization or prolongation of hospitalization; persistent significant disability; or congenital anomaly[117]), only on one ADR (e.g. hearing loss), or only on the ADR probably related to one drug (e.g. clofazimine). These more limited sub-analyses were analysed separately from studies reporting on multiple drugs, events, and of different severity gradings.

If the same cohort was reported in multiple eligible manuscripts, the article with the most information on ADR (if treatment outcome and ADR described separately) or the most complete follow-up (if interim results and final results) was included. In one case, each article separately reported on one specific ADR and both papers were included in the analyses for those two individual ADRs.

Analysis

Available data was extracted related to the number of severe ADR or AE during treatment, disaggregated by type of ADR, suspected drug, grading of ADR severity, HIV and ART status of the patient, and whether the ADR led to the drug being stopped, hospitalization, or death. Severity was extracted as per categorization within the articles as severe or worse (severe, life threatening or fatal or grades of 3 to 5) or non-severe (mild or moderate or grades of 1 to 2). Extracted ADRs included categories for ADRs that have known associations to the anti-TB drugs in the WHO pre-2016 regimens,[16,117] including: gastrointestinal symptoms, ototoxicity, psychiatric disorder, electrolyte imbalance, anaemia, thyroid dysfunction, liver dysfunction, kidney dysfunction, dermatologic problems, peripheral neuropathy, arthralgia, cardiac (e.g. QT prolongation), systemic symptoms (e.g. fatigue, general malaise), and seizures. Other reactions were captured and described as reported. Bias was not explicitly assessed as intention was to include observational studies.

Extracted data was captured in MS Access 2013 and then imported to Stata v14 (College Station, TX) for analysis. The Stata function *metaprop*[175] was used to create forest plots and analysis of the point and confidence interval estimates for the prevalence of ADR out of all patients, as well as disaggregates when possible (sub-analyses). *Metaprop* was used as it is based on binomial distribution appropriate for analysing proportions and is less likely to produce unallowable intervals even when the proportions are close to 0 or 1.[176] The Stata function *metan* was used for sub-analyses to estimate the relative risk of HIV infection for experiencing an ADR.[177]

Results

Across PubMed, Scopus, and reference searches, 727 citations were identified (Figure 5-1), of which 137 were found to be duplicates. Titles and abstracts of the remaining 590 citations were screened for inclusion and exclusion criteria. Fifty-four articles were retrieved for full-text review, at which point 30 more were excluded.

Data was extracted from the remaining 24 articles (Table 11-2 Included articles, reporting on multiple ADR and suspected drugsTable 11-2 and Table 11-3), all of which were not randomized and only 7 of which were prospective. Analysis was limited by the reported data which was not consistent across all studies; the studies were further classified as having a diverse scope of ADR included in the reporting (12 studies, n=2,941 patients[108,114,123,124,168,178–184]). Within the articles that had a diverse coverage, eight reported on both the numbers of patients experiencing ADR and the total number of ADR experienced and two provided only a count of patients who had experienced an ADR; these ten[108,114,123,124,168,178–181,184] were included in the meta-analysis of the proportion of patients experiencing an ADR. Two other diverse coverage studies reported on the count of ADR but not the count of patients and were included in sub-analyses. A further 12 studies included only in sub-analyses were those that described only severe (4 studies, n=421 patients[34,185–187]) or serious ADR (1 studies, n=1,390 patients[109]); only the ADR related to a drug of interest (1 studies, n=85 patients[188]); or only a particular type of ADR of interest—hypothyroidism (3 studies, n=468 patients[111–113]), hearing loss (2 studies, n=588 patients[115,189]), and peripheral neuropathy (1 study, n=246 patients[190]).

Cohorts from eight countries were included (five African countries: Botswana, Ethiopia, Lesotho, Namibia, and South Africa; Haiti; India; and the United States). Sixty percent (15/25) were from South Africa. The median proportion of HIV-infected patients within the studies was (unweighted) 63.4% (IQR: 39.1%, 74.4%) of the 4,682 participants. Of the 22 studies reporting patients on HIV treatment, the ART coverage of HIV-infected patients was high (median 90.2%, IQR: 70.8% to 100%). ART was usually reported as binary (on ART or not on ART). Six studies further classified ART as having been initiated prior to or during MDR/RR-TB treatment, including two that estimated the number of months prior to MDR/RR-TB treatment. Eighteen studies indicated a median CD4 count; the median CD4 count reported was 202 (IQR: 90 to 329).

Of the total 6,139 drug-resistant TB patients, 10.1% (n=622) had second-line drug resistance in addition to rifampicin resistance, including XDR-TB. All 10 studies that were not limited to a specific drug or ADR described a drug regimen which included cycloserine or terizidone. The most commonly reported other drugs were pyrazinamide (8/10 studies), amikacin or kanamycin (8/10 studies), ethionamide (8/10), para-aminosalicylic acid (6/10), moxifloxacin (5/10), levofloxacin (3/10) and ofloxacin (2/10).

Patients experiencing ADR

For the 10 studies (n=2,776 patients) included in the main meta-analysis (of which 1,943 were HIV-infected), 1,725 experienced at least one ADR, with a pooled proportion of 83% (95%CI: 82% to 84%) out of all patients (Figure 5-2). Seven studies (n=664) reported on the number of patients who experienced at least 1 severe (or worse) ADR during treatment (Figure 5-3).[34,114,168,180,183,185,186] The proportion of patients experiencing at least 1 severe or worse ADR ranged from 13% to 43%, with an overall estimate of 24% (95%CI: 21% to 27%).

Reported ADRs by type

As shown in Figure 5-4, gastrointestinal related ADR, including vomiting, nausea, and diarrhoea, were the most commonly reported ADR overall 837/4,498 (18.6%) events disaggregated by ADR type. Of the severe events, gastrointestinal-related ADR (151/743 severe events, 20.3%) were also the most commonly reported. Ototoxicity, including hearing loss and tinnitus, was the second most common for all ADR (n=746, 16.6%) and severe ADR (n=139, 18.7%) as well. Psychiatric events including depression, suicidal ideation and suicide accounted for 13.7% of all ADR reported. For severe ADR, hypothyroidism (n=118, 15.9%), peripheral neuropathy (n=69, 9.3%), psychiatric disorders (n=61, 8.2%), arthralgia (n=57, 7.7%), and dermatologic symptoms (n=56, 7.5%) were the next most commonly reported events.

Ten studies[108,115,123,168,178,179,181,182,189,191] reported on hearing loss believed to be a result of treatment with aminoglycosides amikacin and kanamycin; an additional study indicated that hearing was not routinely tested and was therefore excluded from this sub-analysis[124] (Figure S1). The estimated proportion of all patients experiencing any hearing loss across these studies was 36% (95%CI: 34% to 38%).

Reported ADR by suspected drug

None of the included studies systematically reported on drug(s) suspected to cause the ADR described with the exception of studies addressing a single ADR of interest, e.g. the papers describing hypothyroidism ascribed whether its occurrence was related to the use of para-aminosalicylic acid and/or ethionamide. While there was one paper focused on clofazimine, the described ADR were not attributed to clofazimine. Across the 628 ADR from 12 papers covering 3,326 patients which had counts of any, severe or serious ADR associated with (a) specific drug(s), the second-line injectables combined (kanamycin, amikacin, and capreomycin) had 273 reports. Para-aminosalicylic acid and/or ethionamide (the studies indicated that it was unknown which of the two was more likely) were implicated in 235 events, and cycloserine/terizidone were mentioned 92 times.

Relative risk of ADR by HIV infection and HIV treatment

Sixteen[109,111,112,123,124,178,180,181,185,186,189] of the reviewed studies included information about the relative risk of ADR by HIV infection, most used the Pearson chi-squared test for difference of proportions (Table 1). Nine studies found no statistically significant association between the proportion of patients experiencing any ADR by HIV status.[109,111,112,123,124,178,180,185,189] One study found that HIV-infected patients were at a 4-fold higher cumulative hazard of moderate-to-severe ADR (95%CI: 1.5 to 10.5) compared to HIV-negative patients.[181] A single study reported that HIV-negative patients experienced more severe ADR.[186] Disaggregation of counts of patients experiencing any ADR by HIV status was limited to 2 studies, and therefore was not tested through the meta-analysis.

There were more differences by HIV status found in individually reported ADR. Two studies found that HIV was associated with an increased odds of experiencing hearing loss[179,192] for patients on amikacin or kanamycin; two others found an association with peripheral neuropathy and either HIV or HIV treatment (e.g. stavudine).[124,179] An association with HIV was also noted for psychosis and hypothyroidism (suspected drugs not indicated).[179] In contrast, no association was found with 17/18 reported ADR statistically tested and 21/21 ADR statistically tested in two studies.[108,193] In one study that focused on peripheral neuropathy, risk was differentiated by incident or prevalent ADR at the start of drug-resistant TB treatment. There was no association with HIV for incident peripheral neuropathy, but prevalent peripheral neuropathy was much more likely for patients who were HIV-infected and the risk was increased for those with prolonged prior exposure to stavudine.[190] Disaggregation of ototoxicity by HIV status was available for 4 studies,[108,181,189,192] the pooled relative risk by HIV infection across these studies was not statistically significant (RR: 1.17, 95%CI: 0.93 to 1.47).

Discussion

Many of the drugs currently used for drug-resistant TB treatment have not undergone robust clinical trials and optimal dosage and side effects are poorly described. This is exacerbated for HIV-Infected patients where HIV and ART interactions have not been thoroughly investigated and resulting in inadequate evidence as to the impact of these treatments in the context of high prevalence of HIV co-infection. To understand the prevalence of adverse drug reactions associated with drug-resistant TB treatment, we searched for studies reporting on ADR during drug-resistant TB treatment where at least 20% of the patients were known to be infected with HIV. Data was extracted from 24 studies for the systematic review, but quantitative meta-analysis was limited by inconsistent definitions and reporting categories. No randomized control trials with at least 20% of the patient population HIV-infected were identified; this clearly creates a gap in knowledge. Of the 24 studies, 10 counted the patients who experienced at least 1 ADR and could be included in the main meta-analysis (n=2,776 of which there were n=1,943 HIV-infected); for these studies the pooled proportion of patients experiencing an ADR was 83% (95%CI: 82% to 84%).

The 83% experiencing at least one ADR is significantly higher than a previous systematic review and meta-analysis that did not focus on high-burden HIV settings, where 57% of included patients experienced at least one type of ADR, including mild to severe events.[3] HIV could increase the number of ADR due to overlapping toxicities from treatment, but also because of poor clinical condition and advanced disease at presentation, including low CD4 count and low body mass index. Although the observational studies reviewed here presented a larger cohort of HIV-infected patients on drug-resistant TB treatment, there was limited analysis of why or how HIV co-infected drug-resistant TB patients may have had a higher number of reported ADR. There was insufficient disaggregation of the data presented in the included studies to estimate a pooled relative risk by HIV-status so as to know whether the difference in pooled proportions (83% vs 57%) was due to chance or statistically significant. Of the studies that tried to look at ADR by HIV status, more than half found that there was no association or increased risk, but the statistical methods used were not adjusted for potential confounders. One study remarked that while HIV-infected patients experienced fewer ADR, they experienced more death;[168] this may be an indication that the competing risk of death for patients not on ART is the reason that they do not (live long enough to) experience ADR. A study published after the search and systematic review found that HIV-infected patients newly on ART are at increased risk of ADR, if the competing risk of early mortality from not being on ART is accounted for in the analysis.[194]

Fewer than 10 of the studies disaggregated reported ADR by severity, among them, the pooled proportion of patients experiencing at least one severe or worse ADR was 24% (95%CI: 21% to 27%). While additional reports would have improved the analysis, severity of the ADR does not always correlate with impact on quality of life and adherence: i.e. pain from injections and nausea from ethionamide although both considered to be ‘mild’ in severity are likely to have outsize impact on adherence and loss from care due to the significant impact on patient’s quality of life.

Meta-analysis was limited by non-standard definitions of ADRs, severity of ADRs, and outcomes of the ADR. For example, sometimes the number of patients was reported and in other cases the number of events. Prospective studies sometimes indicated a standard definition of ADR that was defined in advance, such as those required for clinical trials.[132,133] However, in addition to the potential biases of observational cohorts, few of the studies were prospectively or explicitly designed to report on ADR. Thus, within patient records, ADR that were more severe or more frequent or more surprising may have been more likely to be recorded by the clinician. Within observational reporting, again, those ADR that seemed more interesting may have been more likely to have been included in the write up of the cohort. As noted in many of the studies, ADR which led to a treatment change or a serious outcome (e.g. hospitalization or death) are documented more commonly than those that the patient complains of but did not affect treatment outcome (e.g. headaches, gastrointestinal complaints). And finally, in choosing whether to publish, again there might have been bias. The retrieval and review of studies that summarized only ADR from one particular drug (e.g. clofazimine) or only a specific type of ADR (e.g. hypothyroidism, ototoxicity, and peripheral neuropathy) or only those that were serious or severe are examples of how the publication bias potentially affected the availability of evidence related to the prevalence of ADR during DR-TB treatment. In 2016, the WHO recommended a shorter 9-to 12-month regimen for patients who are unlikely to have second-line drug resistance, despite indicating "very low certainty in the evidence", anticipating that reduced exposure time would reduce the burden of ADR.[14] Studies of the shorter regimen were excluded from the meta-analysis and the comparable burden of ADR for the short-course treatment was not evaluated.

Given the high toxicity associated with drug-resistant TB new drugs will be needed to replace the currently recommended regimens. New drug classes like bedaquiline and delamanid, the first new anti-TB drugs approved in 40 years, offer promise for a well-tolerated, injection free, effective drug-resistant TB regimen. Bedaquiline and delamanid use is recommended where there is either resistance or toxicity to older treatment.[14] Current research priorities include trials of new regimens (rather than adding new drugs to old regimens) where the intention is to both shorten exposure time and to replace the injectables (e.g. kanamycin, amikacin, and capreomycin) and all its associated higher risks of ADR.[173] However, it is crucial that these trials include those who are infected with HIV. There is a clear imperative for programmes and countries to develop and implement robust pharmacovigilance systems with standardized reporting at minimum of the number of patients affected, the number of events experienced, the severity of events, and the suspected causative agent to allow for meta-analysis and review; particularly as new drugs are rapidly introduced into patient care.

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TRANSPARENCY DECLARATION

All authors: no conflict of interests to declare.

REFERENCES

(At end of thesis)

Figure 5-1 Included articles

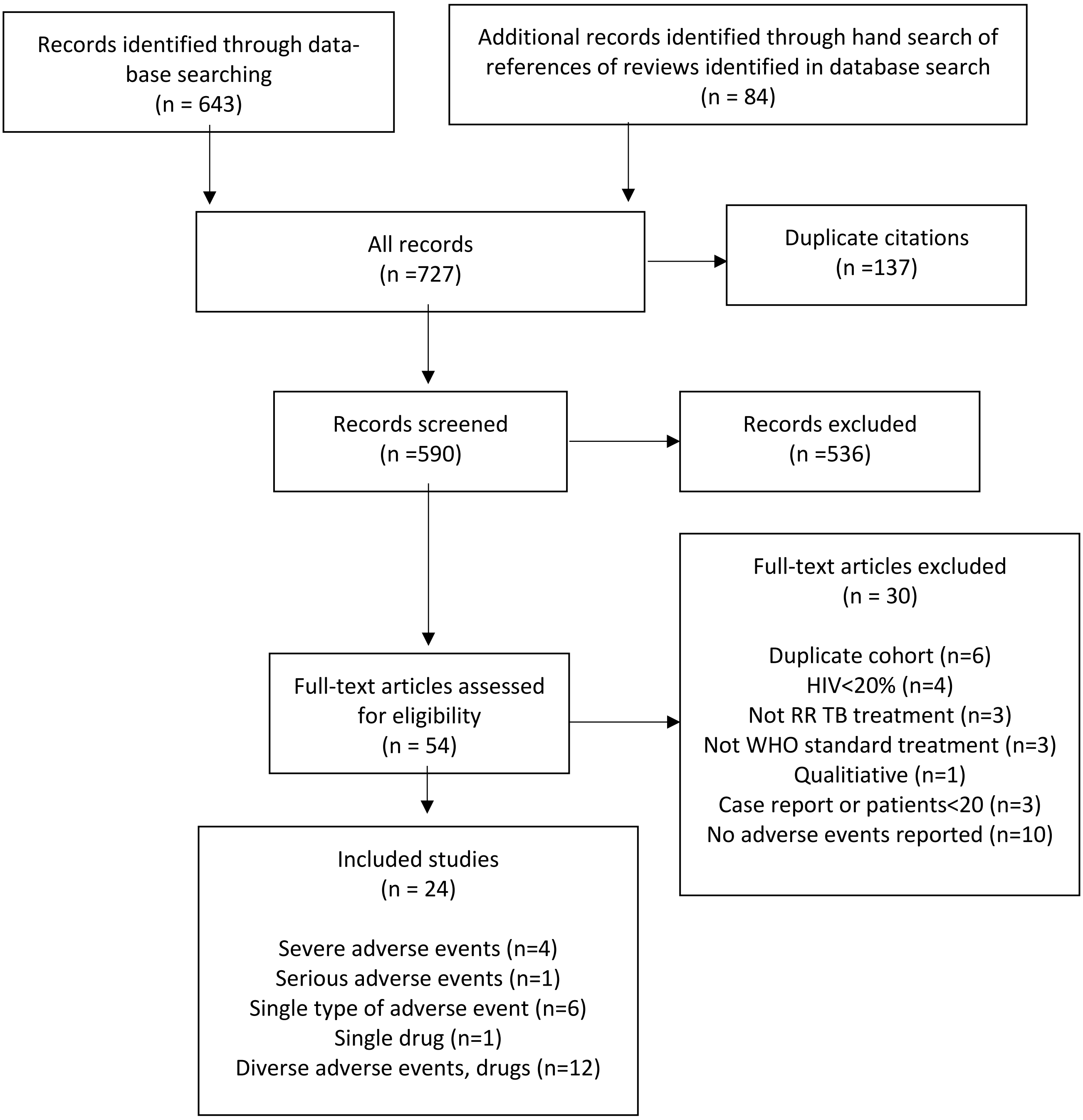


Figure 5-2 Forest plot of estimate of overall proportion of patients experiencing one or more adverse drug reactions during drug-resistant TB treatment (10 articles, n=2,776 study participants)

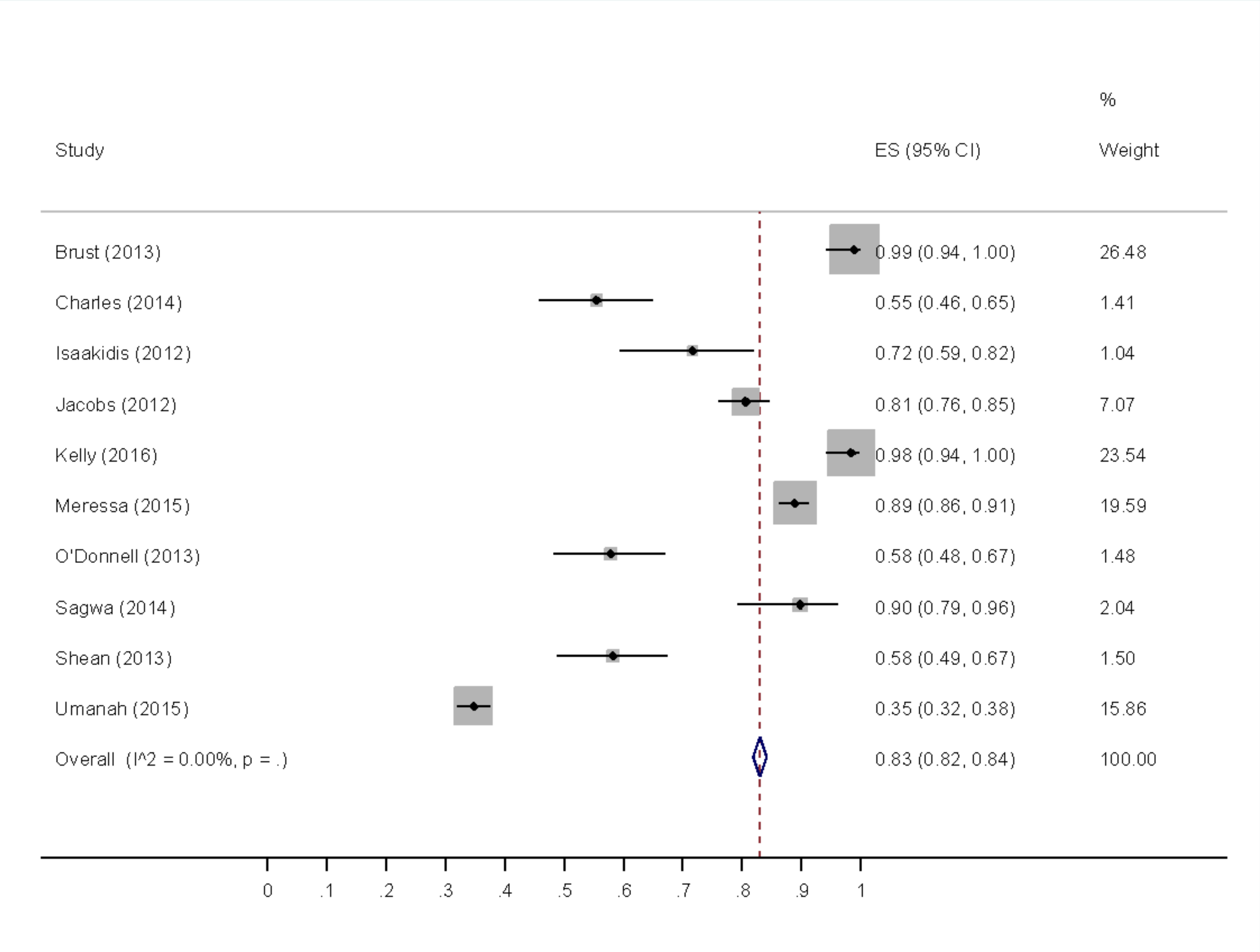


Figure 5-3 Forest plot of estimate of proportion of patients experiencing one or more severe, life threatening, or fatal adverse drug reactions (7 articles, n=664 study participants)

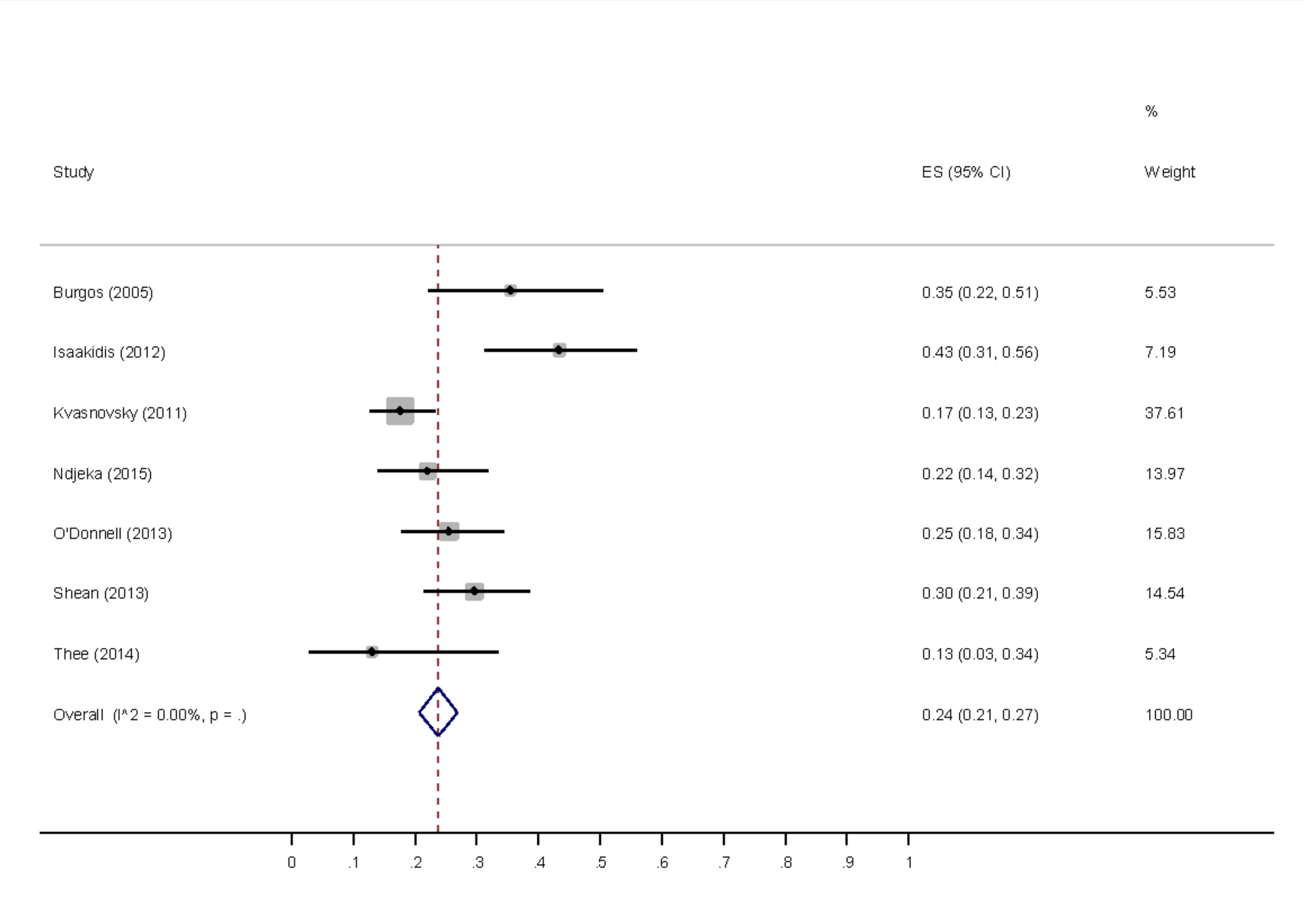


Figure 5-4 Frequency of all adverse drug reactions and severe adverse drug reactions reported by type.

All ADR: 4,498 events across 4,274 patients from 18 studies with counts of ADR by type

At least severe ADR: 743 events across 3,284 patients from 11 studies with counts of severe ADR by type

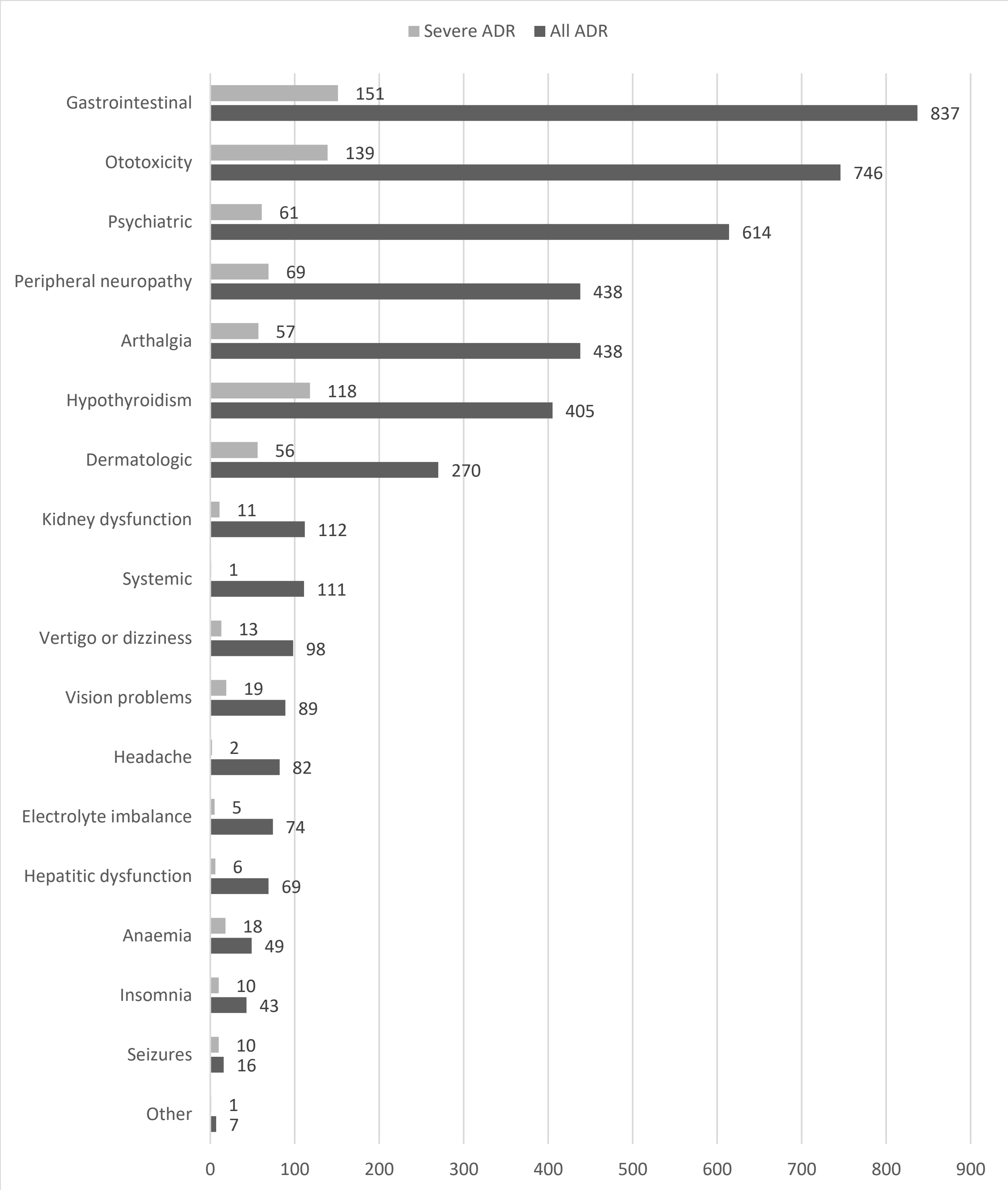


Table 5-1 Relative risk of ADR by HIV status

First author	Year	% HIV	Relative risk of ADR by HIV status
Brust[108]	2013	81.3%	Difference in proportions ADR experienced not statistically significant for 21 individual ADR tested.
Charles[178]	2014	24.5%	Difference in proportions ADR experienced not statistically significant, p=0.185.
Jacobs[179]	2012	72.6%	HIV-infected patients more likely to have had peripheral neuropathy (p<0.001); psychosis and confusion (p=0.04); hearing loss (p=0.047); thyroid dysfunction (p<0.001). Difference in proportions ADR experienced by HIV-infected on ART or not on ART not statistically significant, p=0.432.
Kelly[123]	2016	74.4%	Difference in number of ADR experienced not statistically significant as recorded in interviews (p=0.277) and medical records (p=0.098).
Meressa[124]	2015	21.7%	Difference in proportions ADR experienced not statistically significant. HIV-infected had higher incidence peripheral neuropathy (p<0.001).
O'Donnell[180]	2013	71.9%	Difference in proportions ADR experienced not statistically significant. Difference in proportions severe ADR experienced not statistically significant. Difference in proportions ADR experienced by HIV-infected on ART or not on ART not statistically significant. Difference in proportions severe ADR experienced by HIV-infected on ART or not on ART not statistically significant.
Sagwa[181]	2014	52.5%	Cumulative hazard of moderate-to-severe ADR, HIV-infected HR: 4.0, 95%CI: 1.5 to 10.5. Additional analysis reported in 2013 [193] no statistically significant difference of proportions for 17 ADR tested, only abdominal pain associated with HIV p=0.02. Effect modification from HIV in adjusted relative risk analysis for nausea and joint pain.
Shean[168]	2013	41.7%	Difference in proportions ADR experienced not statistically significant, p=0.26. Difference in number of ADR experienced not statistically significant, p=0.15. Difference in number of severe ADR experienced not statistically significant, 0.01. Patients who died were more likely to be HIV-infected (p=0.01)
Burgos[185]	2005	22.9%	Difference in proportions severe ADR experienced not statistically significant, p=0.520
Kvasnovsky[186]	2011	52.4%	HIV negative experienced more severe ADR than HIV-infected, difference in proportions p<0.01. Difference in proportions ADR experienced not statistically significant for HIV-infected on ART or not on ART, p=0.33
Van der Walt[109]	2013	39.1%	Difference in proportions of serious ADR experienced by ART naïve HIV-infected not statistically significant, p=0.083.
Conradie[190]	2014	80.9%	Incident peripheral neuropathy not associated with HIV, HR: 1.00 (95%CI: 0.35 to 2.91). Prevalent peripheral neuropathy associated with HIV, HR: 3.21 (95%CI: 1.25 to 8.22), risk was also associated with duration of exposure to stavudine.
Harris[192]	2012	57.0%	HIV-infected patients were more likely to experience hearing loss, OR 3.25 (95% CI: 1.65 to 6.37).

Mo-dongo[112]	2012	63.4%	Difference in proportions experiencing hypothyroidism not statistically significant.
Mo-dongo[189]	2014	65.9%	Difference in proportions experiencing hearing loss not statistically significant.
Satti[111]	2012	67.6%	Difference in proportions experiencing hypothyroidism not statistically significant, p=0.172

^ Excluded as all patients were HIV-infected: Issakidis 2012[114], Umanah 2015[184], Andries 2013[113]

Did not disaggregate ADR by HIV status: Ndjeka 2015[34], Seung 2009[187], Thee 2014[183], Padayatchi 2014[188], Seddon 2013[182]

ADR: Adverse drug reaction; ART: Antiretroviral therapy; CI: Confidence interval; HR: Hazard ratio; OR: Odds ratio

6 RESULTS: CEA BEDAQUILINE

6.1 SYNOPSIS

Formal citation: Schnippel K, Firnhaber C, Conradie F, Ndjeka N, Sinanovic E. Incremental Cost Effectiveness of Bedaquiline for the Treatment of Rifampicin-Resistant Tuberculosis in South Africa: Model-Based Analysis. *Applied Health Economics and Health Policy*. 2017 Oct 4:1-2.

In order to assess the cost-effectiveness of a bedaquiline-based regimen for MDR/RR-TB treatment in a high-HIV prevalence setting from the perspective of the South African public health sector, we established a Markov model for ambulatory treatment of MDR/RR-TB parameterized using clinical outcomes from the South African National TB Programme (SA NTP) before (2012 - 2014) and after (2015 – 2016) bedaquiline roll-out. The results indicate that providing bedaquiline for all MDR/RR-TB patients costs less than the cost of procurement for the drug because of savings from an injection-free treatment regimen. The ICER of US$1,242 per additional DALY averted is below the 2015 per capita GDP for South Africa of US$5,718, which is considered very cost effective.[42,91] Further, providing bedaquiline for all MDR/RR-TB patients could increase the treatment success rate in South Africa from 56.3% on a non-bedaquiline regimen to 60.6% and is affordable in the South African context (cost USD 2.6 million over a 10-year horizon).

Contribution to the thesis and novelty

As of August 2017, the five studies identified that analysed the cost-effectiveness of bedaquiline [52–56], in addition to the original analysis included in the WHO recommendations [31] considered bedaquiline added on to the standard regimen rather than replacing the injection. This analysis was the first to use evidence from programmatic roll out to show what may happen using a new regimen. Additionally, Although South Africa has one of the highest burdens of MDR/RR-TB in terms of total incident cases, most cost-effectiveness models for MDR-TB have been built for Europe and other settings with low HIV prevalence and hospital-based treatment.

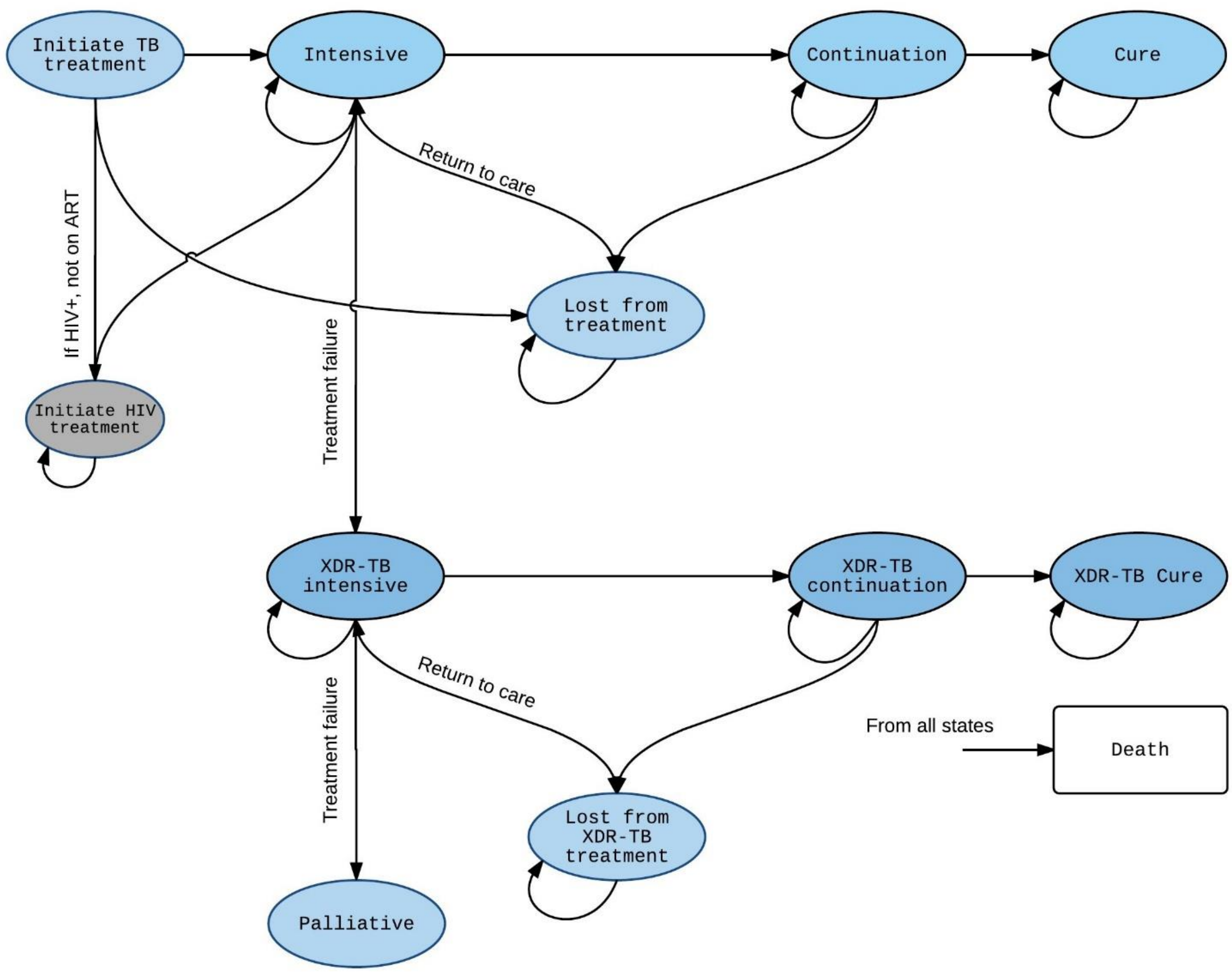
Role of the candidate

The candidate designed the Markov health state model and built the decision tree within TreeAge. She ran different versions to balance the availability of data, the complexity of the model, and the reasonableness of the outputs for the base case outputs. The candidate also collected ingredients costs from public sector price lists and calculated transition probabilities from the EDRweb cohort. The candidate wrote the first draft of the manuscript and revised in response to inputs from co-authors. She revised the article based upon suggestions from the editor and reviewers.

6.2 TREE STRUCTURE CEA BEDAQUILINE

For this analysis, a Markov model with monthly steps was built in TreeAge Pro 2015 (TreeAge Software, Williamstown, MA) The model was structurally the same for all treatment Markov nodes (i.e. SOC for all MDR/RR-TB, SOC for MDR/RR-TB and bedaquiline for patients who failed MDR/RR-TB treatment, and bedaquiline for all MDR/RR-TB patients), but transition probabilities and costs were different for each of the modelled regimens. Markov health states were constructed to represent initiation MDR/RR-TB treatment (with the possibility of hospitalization), intensive phase, and culture negative continuation phase of treatment. Tunnel states for treatment were created to ensure that patients receive at least 6 months of intensive phase regimen and at least 12 months in the continuation phase of treatment for MDR/RR-TB patients and 18 months in the continuation phase of treatment for XDR-TB, as per current SA NTP treatment guidelines.[17] If the patient fails to sputum culture convert after 6 months of treatment, the patient would transition in the model to XDR-TB treatment. Failure during XDR-TB treatment transitions to palliative care.

Figure 6-1 State transition diagram

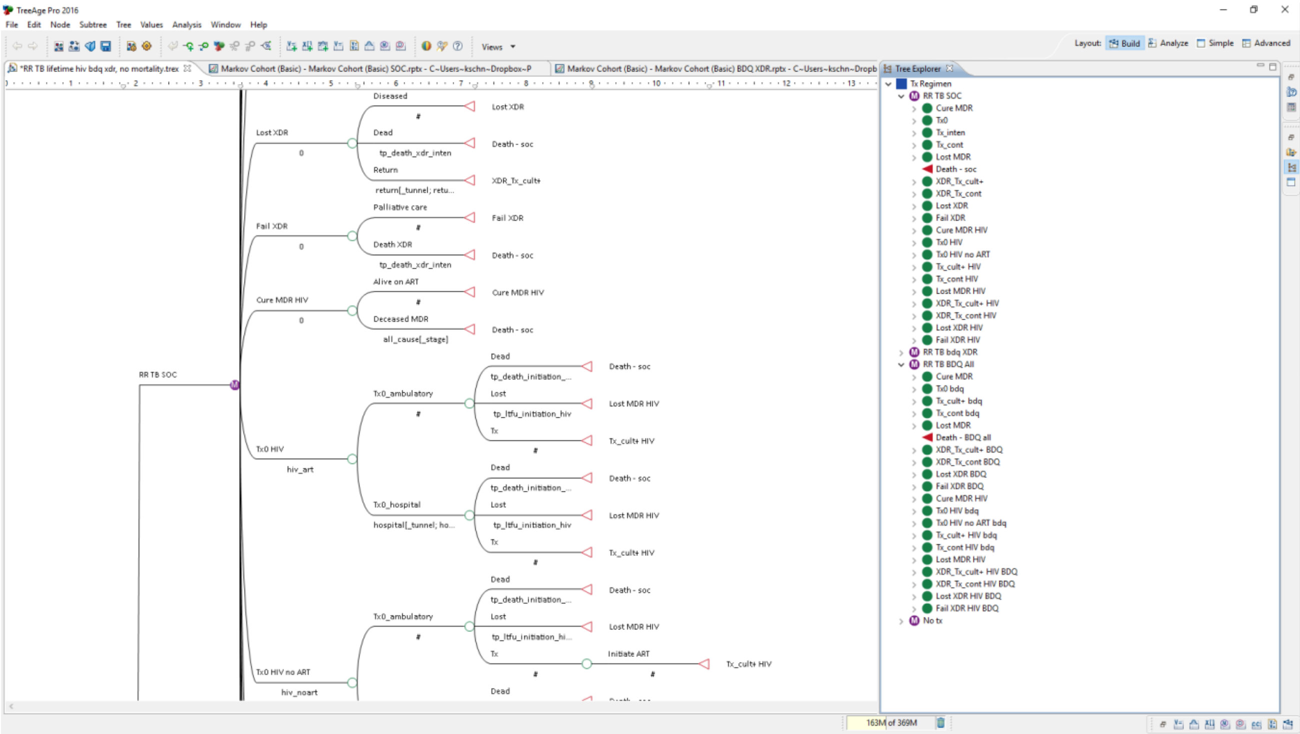


Model overview

The Markov model was parameterized using South African data where available. The costs are presented from the perspective of the South African public health sector, which includes both costs that are part of the South African National TB Programme as well as the costs of hospitalization or utilization of primary health care clinics. Monthly costs for drugs, laboratory tests, procedures and investigations, clinic visits and hospital inpatient days, were extracted from public sector databases.

Transition probabilities for the South African context standard of care were calculated using Stata v14.1 based on the dataset described in Chapter 3which excluded patients on bedaquiline. Separate transition probabilities were estimated for patients known to be HIV-negative, HIV-positive on ART, and HIV-positive not on ART. Differences in effectiveness of culture conversion for bedaquiline were extracted from published literature. The model and probabilities can also be represented as a tree.

Figure 6-2 Overview, decision tree all Markov nodes



Sensitivity of the results to the model inputs was tested using one-way sensitivity analysis.

Although not described in the manuscript, the assumption regarding the assumed discount rate of 3% was also tested as per recommended methods for cost-effectiveness analysis.[40,195] Results are presented in the table below.

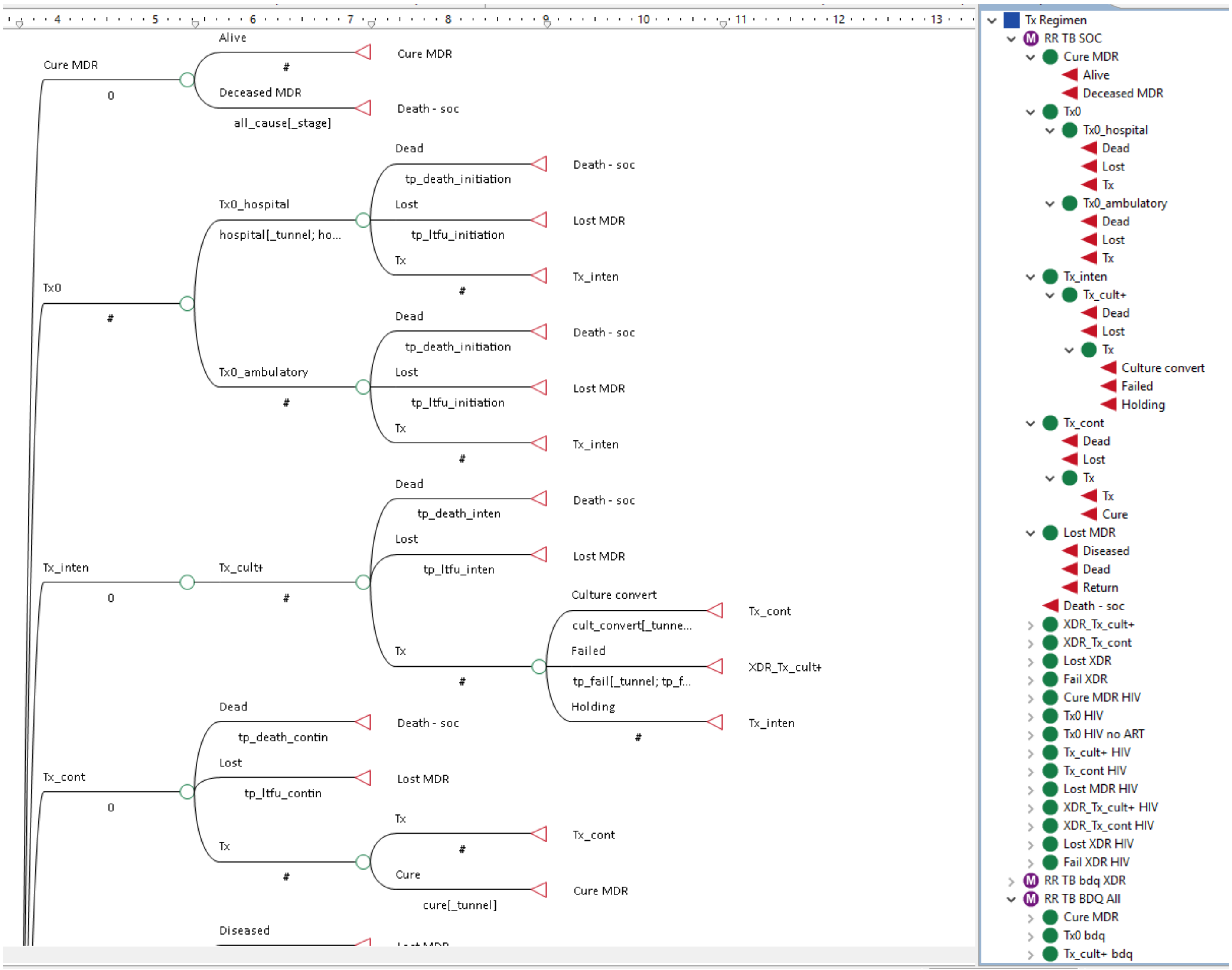
Table 6-1 Incremental cost-effectiveness ratios compared standard of care for MDR/RR TB regimens, differing discount rate assumptions

		0% discount rate	3% discount rate (base case)	6% discount rate
SOC (injection-based)				
	Cost	$4,641	$4,439	$4,267
	Effect	5.91	5.12	4.48
Bedaquiline for XDR-TB				
	Cost	$4,556	$4,356	4187
	Effect	5.94	5.14	4.50
	ICER	More effective, cost saving	More effective, cost saving	More effective, cost saving
Bedaquiline for all MDR/RR TB				
	Cost	$4,867	$4,648	$4,489
	Effect	6.11	5.29	4.63
	ICER	$226 / 0.20 = $1,130	$209 / 0.17= $1,229	$222 / 0.15 =$1,480

HIV-negative treatment states

For HIV-negative populations, treatment states included initiation (Tx0), intensive phase (Tx_inten), continuation phase (Tx_cont), cure (Cure MDR), death (Death – Soc), lost from MDR/RR-TB treatment (Lost MDR), failed and intensive phase for XDR-TB treatment (XDR_Tx_cult+), continuation phase XDR TB treatment (XDR_Tx_cont), failed XDR-TB treatment, or lost from XDR-TB treatment.

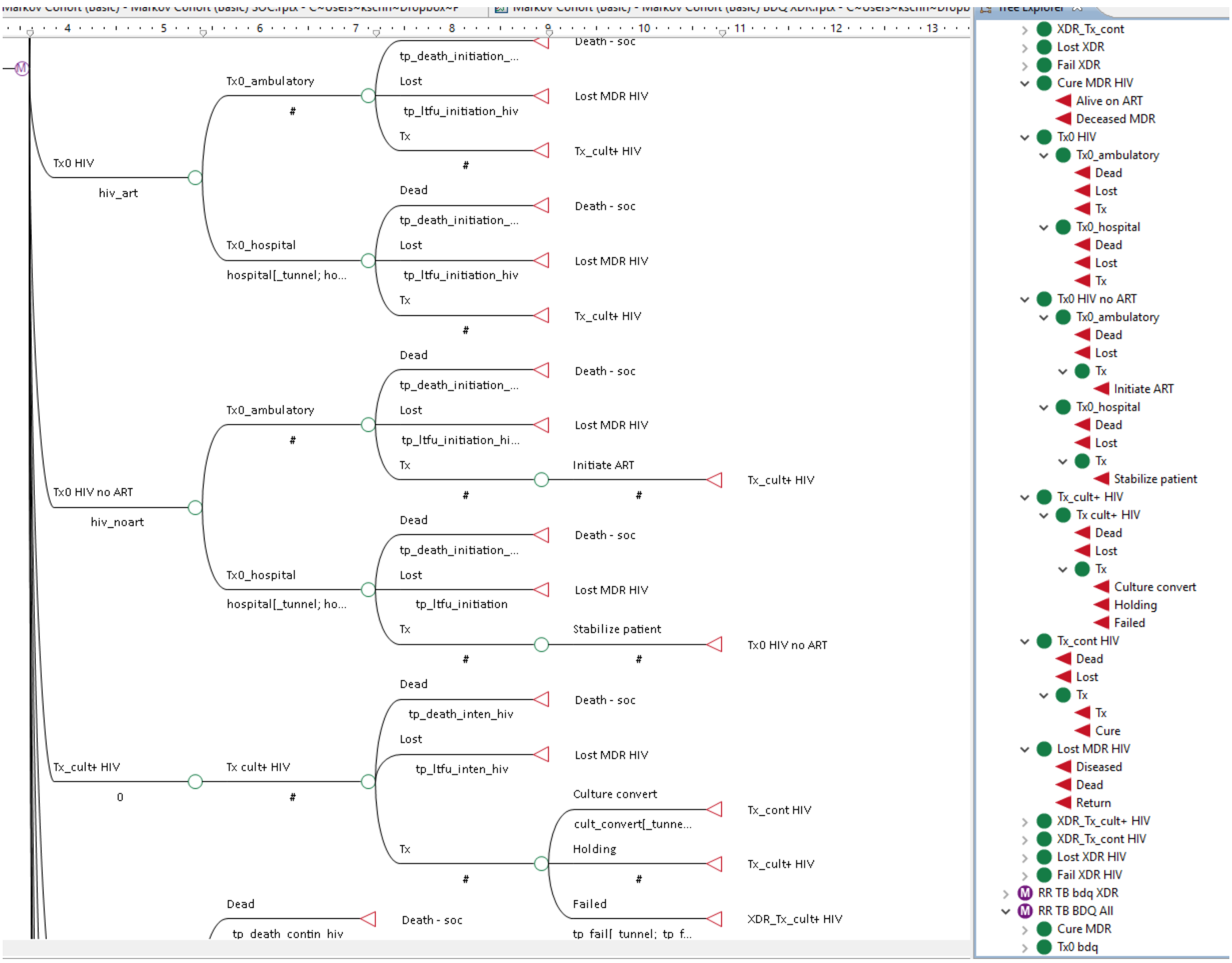
Figure 6-3 Decision tree: details of HIV negative nodes



HIV-positive treatment states

For HIV-positive populations, treatment states included initiation (Tx0) as either HIV on ART (Tx0 HIV) or ART naïve (Tx0 HIV no ART), intensive phase (Tx_cult+ HIV), continuation phase (Tx_cont HIV), cure (Cure MDR HIV), death (Death – Soc), lost from MDR/RR-TB and HIV treatment (Lost MDR HIV), failed and intensive phase for XDR-TB treatment (XDR_Tx_cult+ HIV), continuation phase XDR TB treatment (XDR_Tx_cont HIV), failed XDR-TB treatment, or lost from XDR-TB and HIV treatment treatment (Lost XDR HIV).

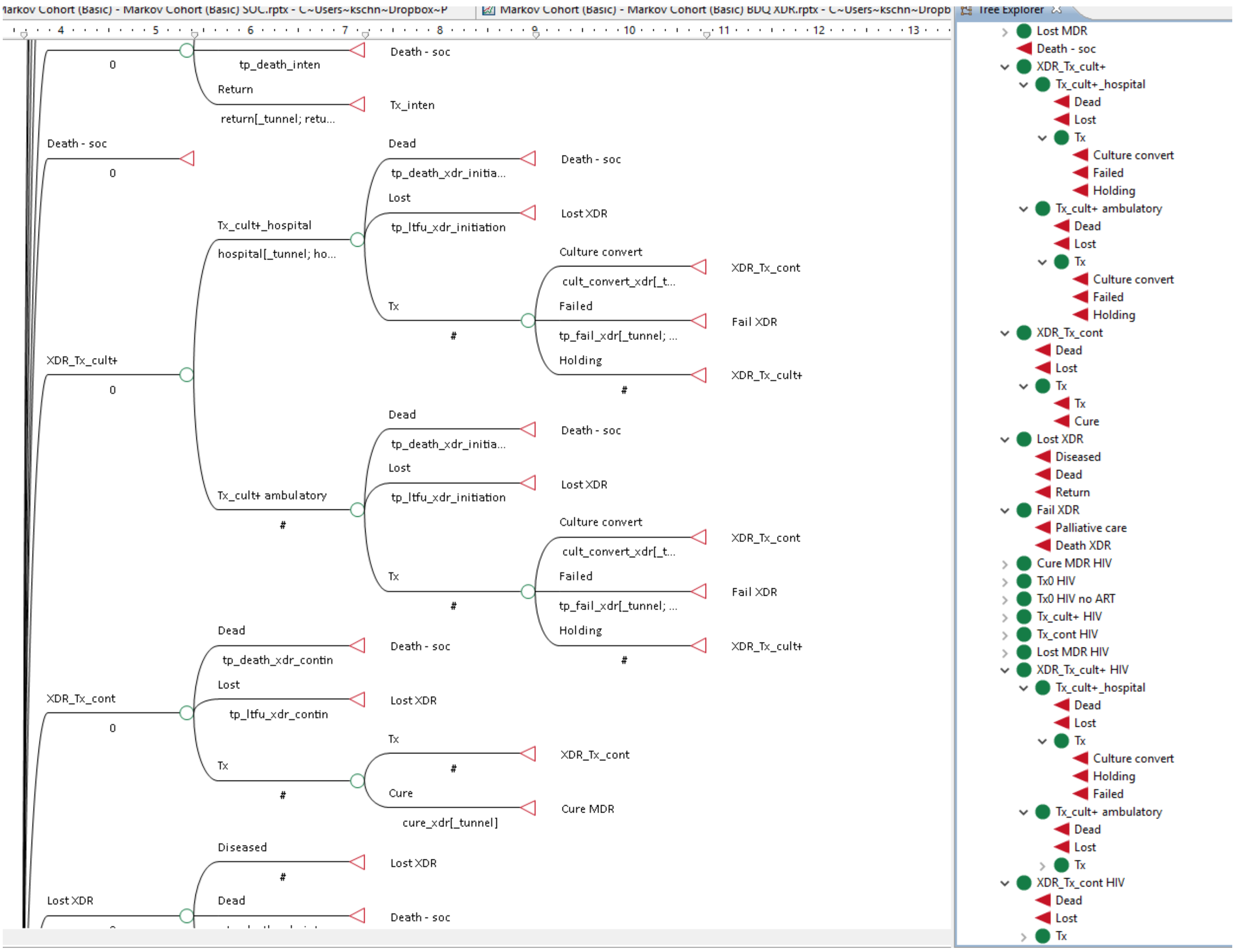
Figure 6-4 Decision tree: details of HIV-positive nodes



XDR-TB treatment states

Because all patients with XDR-TB at initiation were excluded from the analysis, the XDR-TB treatment states start with the intensive phase (XDR_Tx_cult+ HIV or XDR_Tx_cult+). Similarly, because of the model structure that to complete the intensive phase of MDR/RR-TB treatment – either transitioning to MDR/RR-TB continuation phase or as treatment failure to XDR-TB intensive phase – an HIV-patient must be initiated on ART, all HIV-positive patients who have survived and transitioned to the XDR-TB health states are assumed to be on ART. In the model, patients can transition to the continuation phase XDR-TB treatment (XDR_Tx_cont HIV or XDR_Tx_cont), failed XDR-TB treatment (Fail XDR), or lost from XDR-TB (Lost XDR) and lost from XDR-TB and HIV treatment (Lost XDR HIV).

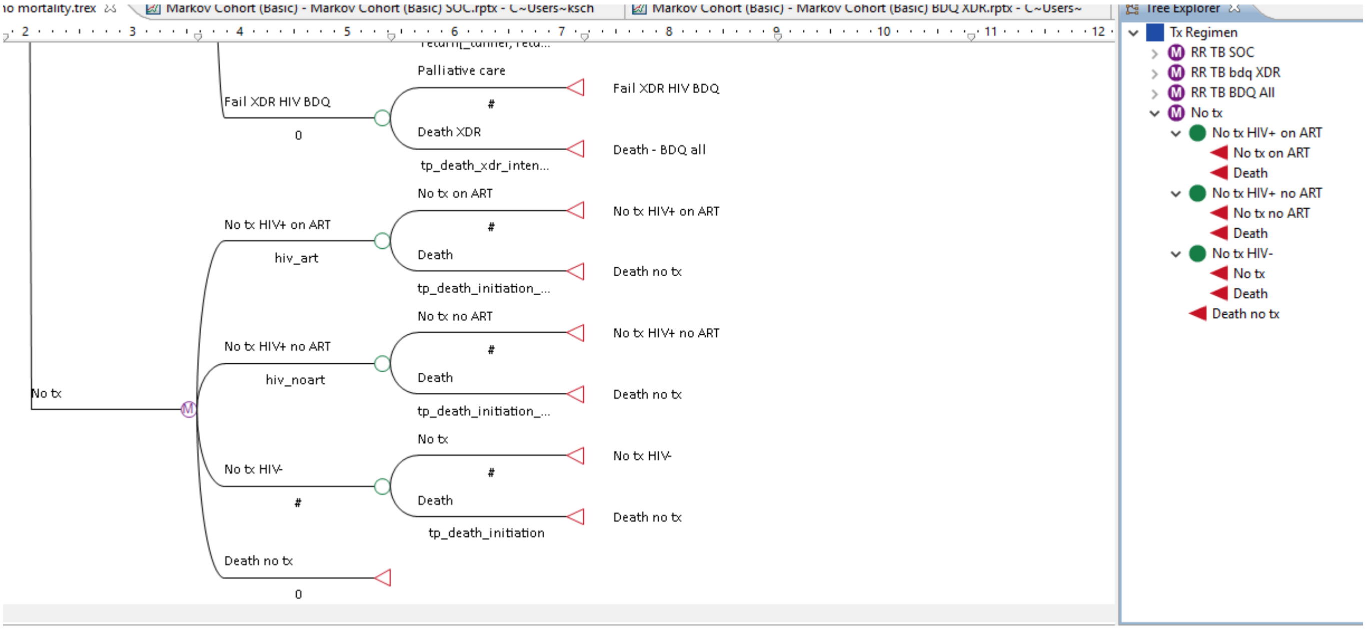
Figure 6-5 Decision tree: Details of XDR-TB nodes



No treatment comparison arm

For the no treatment arm, initial distribution was to either HIV-positive on ART or HIV-positive ART naïve, or HIV-negative. Patients could continue in that initial distribution until death.

Figure 6-6 Decision tree: No treatment



6.3 Manuscript 4

Title: Incremental cost effectiveness of bedaquiline for the treatment of rifampicin-resistant tuberculosis in South Africa: model-based analysis

RUNNING TITLE: Cost effectiveness of bedaquiline for MDR-TB treatment

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Abstract

Background

Nearly 20,000 people were diagnosed with multi-drug and rifampicin-resistant (MDR/RR-TB) in South Africa in 2015; yet, only ½ of the patients who start treatment are expected to have a successful outcome. There is increasing evidence of the effectiveness and safety of new drug regimens containing bedaquiline for MDR/RR-TB; however, it is uncertain whether they are affordable for high burden, limited-resource settings.

Methods

We established a Markov model for ambulatory treatment of MDR/RR-TB in a high-HIV prevalence setting, parameterized using clinical outcomes from the South African National TB Programme (SA NTP) before (2012 - 2014) and after (2015 – 2016) bedaquiline roll-out. The effectiveness of treatment was evaluated in disability adjusted life years (DALYs). Ingredient costs from the provider perspective were collected in 2016 South African Rand and converted to US$, including bedaquiline at US$675.23 per 6-month treatment course. Culture conversion rates were derived from the Phase 2b trial of bedaquiline and disability adjustments were adapted from published literature. Costs and effectiveness were discounted at 3%.

Results

For non-bedaquiline regimens, the total expected cost over the 10-year time horizon for a MDR/RR-TB patient was US$4,439 and disability-adjusted survival of 5.1 years. Replacing capreomycin with bedaquiline for patients who failed MDR/RR-TB treatment and required XDR-TB treatment resulted in cost savings ($4,356, 1.8% less) and similar effectiveness (0.02 DALYs averted). As a result, the standard regimen (no bedaquiline) was dominated. Replacing kanamycin with bedaquiline so that all MDR/RR-TB patients access bedaquiline cost US$4,647 (4.3% more) and averted 0.17 DALYs compared to the no bedaquiline regimen. The incremental cost effectiveness ratio was US$1,242 / DALY averted.

Conclusion

Markov modelling indicates providing bedaquiline for all MDR/RR-TB patients could increase the 24-month treatment success rate in South Africa from 56.3% using the current regimen to 60.6%, at an incremental cost of $2.6 million over a 10-year horizon, less than 1% of the estimated US$425 million SA NTP annual budget.

Key points for decision makers

Providing bedaquiline for all MDR/RR-TB patients costs less than the cost of procurement for the drug because of savings from an injection-free treatment regimen.

Providing bedaquiline for all MDR/RR-TB patients could increase the treatment success rate in South Africa from 56.3% on a non-bedaquiline regimen to 60.6%, at an incremental cost of US$2.6 million over a 10-year horizon.

Introduction

According to the World Health Organization (WHO), globally in 2015, there were 580,000 incident cases of rifampicin-resistant (RR) TB. In the same year, an estimated 190,000 persons died from RR-TB and multi-drug resistant (MDR) TB, RR-TB that is also resistant to isoniazid. Across all countries reporting to the WHO, among patients initiating treatment, only 52% of MDR/RR-TB patients (2013 cohort) were successfully treated [58].

Results from the Phase 2b clinical trials of bedaquiline, a novel agent for the treatment of RR TB, demonstrated significant benefits in terms of both the proportion of patients who sputum culture converted and the time to culture conversion [30]. In March 2017, the WHO updated its 2013 conditional recommendations for the use of bedaquiline [32] based upon a growing body of evidence including observational results from public-sector use of bedaquiline in South Africa. While further evidence is still needed to resolve uncertainty around the safety of bedaquiline use [32]; results such as those from a 15-country multi-centre study [138] are encouraging enough that policy makers [46,47] and clinical researchers [196] are considering whether bedaquiline could replace second-line injectables as a core MDR/RR-TB drug.

South Africa is categorized by the WHO as being a high TB, high HIV/TB, and high MDR/RR-TB burden country [58]. Approximately 295,000 TB cases initiated treatment in South Africa in 2015, of which 57% were known HIV-positive and 19,613 were diagnosed as MDR/RR-TB [58]. In October 2014, the South African Medicines Control Council regulatory authority approved the use of bedaquiline for treatment of MDR/RR-TB. Starting in March 2015, the SA NTP began the process of rolling out bedaquiline as an additional drug to strengthen the existing regimens for MDR/RR-TB, particularly where there was either resistance to or intolerance of fluoroquinolones and/or second-line injectable drugs.

Despite the revised WHO recommendations, encouraging treatment outcomes and concessional pricing for high-burden countries, further roll-out of bedaquiline in South Africa and other resource-limited settings is uncertain where the drug is priced at ZAR 9,950 (US$675.23) per 6-month treatment course. An exploratory cost-effectiveness analysis of bedaquiline was used for the 2013 WHO recommendations, but with uncertainty around whether bedaquiline would increase cure by reducing loss to treatment follow-up, death or failure [197]. Cost-effectiveness studies published since then have been largely for cohorts where, unlike in South Africa, MDR/RR-TB patients are hospitalized until culture conversion. In these settings, the high culture conversion rates of bedaquiline and therefore shorter duration of hospitalization lead it to be cost-effective [52,54] or even cost saving compared to the standard regimen [53]. A Markov model established for the United Kingdom [53] was applied to seven countries with a high burden of MDR/RR-TB, including South Africa [55]. For South Africa, the analysis indicated that bedaquiline could be cost saving relative to the standard regimen because of a large reduction in the number of persons requiring extensively drug-resistant (XDR)-TB treatment (having failed MDR/RR-TB treatment). However, the model assumed a very low rate of treatment success on the standard regimen (23.6%) compared to the routinely reported success rate for MDR/RR-TB treatment in South Africa (49% [58]) and did not have separate costs or transition probabilities for HIV infection.

In order to estimate the incremental cost-effectiveness of a bedaquiline-based regimen for the treatment of MDR/RR-TB, we established a novel Markov model for ambulatory treatment of MDR/RR-TB in a high-HIV prevalence setting, parameterized using evidence from the SA NTP.

Methods

2.1 Setting and standard of care

Since 2011, patients without extensive drug resistance (XDR-TB) in South Africa are eligible for ambulatory treatment [17]. If hospitalized for treatment initiation, treatment guidelines indicate that patients can be discharged once sputum smear microscopy negative if MDR/RR-TB (e.g. within two weeks) and once sputum culture negative if XDR-TB. From 2011 through 2016, the standard of care for both MDR- and RR-TB patients in South Africa was a standardized regimen: 6 months (intensive phase) of 5 drugs including both a second-line injectable and a fluoroquinolone followed by 12 to 18 months (continuation phase) without the injectable drug [17,19]. Patients with resistance to or intolerance of fluoroquinolones and/or second-line injectable drugs are treated with individualized regimens. Roll-out of bedaquiline and linezolid started in March 2015, other drugs for individualized regimens include the injectable capreomycin, para-aminosacylic acid (PAS), and/or clofazimine [19]. The individualized regimens follow the principles of ensuring at least two core effective second-line drugs; thus, where patients do not have second-line drug resistance, bedaquiline can be added in single-drug substitution. Evidence from the SA NTP's large-scale use of bedaquiline, including in an individualized, all-oral long-course regimen for MDR/RR-TB patients (i.e. if the patient had experienced toxicity or resistance to kanamycin) was used to parameterize a cost-effectiveness model.

In South Africa, since 2011, HIV testing is offered to all MDR/RR-TB patients and antiretroviral therapy (ART) is initiated once a patient has stabilized on TB treatment (typically after 2-8 weeks) in ART-naïve HIV-positive patients, regardless of CD4 count [17]. The standard first-line ART regimen for adults and adolescents in South Africa is a fixed dose combination of tenofovir, lamivudine or emtricitabine, and efavirenz. Eligibility for ART has been increasing over time in South Africa, first for those with very low CD4, then for pregnant women and TB patients, and as of 2016 all patients are eligible to initiate ART regardless of CD4 count. As a result, a significant proportion of HIV-positive patients starting MDR/RR-TB treatment are already on ART [128,198].

2.2 Health states for MDR/RR-TB treatment

A Markov model with monthly steps was built in TreeAge Pro 2015 (TreeAge Software, Williamstown, MA) to analyse the incremental cost-effectiveness of two different strategies for the inclusion of bedaquiline within the long-course MDR/RR-TB treatment regimens for South Africa: 1) XDR only: standard of care for MDR/RR-TB and bedaquiline containing regimen for patients who fail treatment and require XDR-TB treatment or 2) All MDR/RR-TB: bedaquiline containing regimen for both MDR/RR-TB and XDR-TB. The bedaquiline strategies were compared with: 3) MDR/RR-TB treatment without bedaquiline and 4) No MDR/RR-TB treatment.

Markov health states were constructed to represent initiation of MDR/RR-TB treatment (with the possibility of hospitalization), intensive phase, and culture negative continuation phase of treatment (Figure 6-7). Tunnel states for treatment were created to ensure that patients receive at least 6 months of intensive phase regimen and at least 12 months in the continuation phase of treatment for MDR/RR-TB patients and 18 months in the continuation phase of treatment for XDR-TB, as per current SA NTP treatment guidelines [17]. If the patient fails to sputum culture convert after 6 months of treatment, the patient would transition in the model to XDR-TB treatment. In this analysis, patients initiating as XDR-TB (i.e. already have extensive resistance at diagnosis) were excluded. Failure during XDR-TB treatment transitions to palliative care. Surgery for RR-TB is very rare in the SA NTP and therefore was not included as a Markov health state in the model. From any treatment state, patients could be lost from treatment or die. Patients lost from treatment could return to treatment with either MDR/RR-TB or XDR-TB within the first 12 months or remain lost from care until death, but incur no further costs. After successful treatment completion, simulated patients experience background mortality and die from other causes.

2.3 HIV and ART status

Initially, patients are distributed in the model to the initiation of MDR/RR-TB treatment according to whether HIV-negative or HIV-positive. If HIV-positive, the model further differentiates as to whether the patient is on ART or not. Based on previous South African studies indicating more than 50% of patients on ART at initiation [128,198], 60% of the HIV-positive cohort was assumed to be on ART and 40% not on ART at MDR/RR-TB treatment initiation. In South Africa, HIV-positive patients, including those on ART, are also eligible for bedaquiline but the efavirenz is replaced by either lopinavir/ritonavir or nevirapine during bedaquiline treatment. After successful MDR/RR-TB treatment completion, patients continue to incur costs for ART.

2.4 Transition probabilities and effectiveness of bedaquiline

Monthly transition probabilities during treatment (Table 6-2) were derived from the observational cohort of public sector SA NTP patients as reported in the national electronic drug-resistant TB case register (EDRweb), as exported on 5 May 2016. MDR/RR-TB treatment is a notifiable disease in South Africa and public sector hospitals and clinics managing MDR/RR-TB treatment have used EDRweb since 2009 [13,103,199]. For the non-bedaquiline regimens, transition probabilities are based on the cohort starting treatment between 1 January 2012 and 30 April 2014, in order that each patient could contribute at least 24 months of follow-up time prior to the censor date of 30 April 2016. Valid patient South African identity (ID) numbers, if available within the dataset, were matched to the national vital statistics register. Any additional report of deaths during the 24 months MDR/RR-TB treatment were combined with the deaths in EDRweb; thus, the mortality rate in this cohort are higher than EDRweb reporting alone. Patient and treatment characteristics of the cohort, as well as survival analysis and proportional hazards ratios have been separately reported[199]. Rates of loss from treatment and death were derived using the *ltable* command within Stata version 14 (College Station, TX, USA) for months 0 to 2, months 3 to 5, and months 6 to 11 and converted to the monthly transition probabilities. Rates were derived separately for MDR/RR-TB and XDR-TB and for HIV-negative and HIV-positive on ART for all three periods. Rates for HIV-positive not on ART were only derived for months 0 to 2, in accordance with treatment guidelines for fast-tracked initiation of ART. Culture conversion for MDR/RR-TB patients at 6 months(88%) was also extracted from the EDRweb cohort.

Use of bedaquiline was modelled as increasing the proportion of patients who culture converted by the end of 6 months by a hazard ratio of 2.44 (95%CI: 1.57, 3.80) [30] for both MDR/RR-TB and XDR-TB patients. Similar to previous cost-effectiveness analyses [52–54], the model did not include the mortality imbalance found in the Phase 2b clinical trial as the deaths were not attributed to bedaquiline [30]. Mortality from all other causes was calculated from standardized life tables for South Africa 2013 [200], starting from age 35, the median age of the cohort.

2.5 Costs, disability adjustments and model inputs

Ingredients costs were collected from a provider perspective, in this case the SA NTP within the public health sector (Table 6-3). All costs were collected in ZAR. Average monthly exchange rate for 2016, 14.74 ZAR/USD was applied to ZAR costs.[27] Costs were inflated to 2016 ZAR if applicable using the consumer price index for medical services [28].

Costs for laboratory services [201] and TB and HIV drugs were accessed from the public sector price lists for these cost components [202]. For ART, first-line treatment regimens were assumed, with drug substitutions as per guidelines in the case of drug-drug interactions [17,19]. Chest x-ray, pure tone audiometry, and electrocardiogram (ECG) testing were categorized as other investigations required for monitoring treatment or screening for adverse drug reactions. Costs of these ambulatory procedures were extracted from the public sector uniform schedule of patient fees for unsubsidized patients [203], including both facility and health professional costs. Monthly resource utilization for laboratory services, medications, and other investigations were based upon SA NTP MDR/RR-TB-TB guidelines updated Jan 2013 for standard of care regimen for the adult weight band 55-70 kg [17]. Bedaquiline guidelines version June 2015 was used for bedaquiline containing regimen laboratory services, medications, and other investigations [19]. At the time of the study, the full 6 months of bedaquiline was dispensed for individual patients and therefore the full ZAR 9,950 was modelled for all initiating patients.

The proportion of patients hospitalized at treatment initiation [26,128] was extracted from South African studies and applied to both bedaquiline and standard MDR/RR-TB regimens. For the 2nd month of treatment, the proportion hospitalized was reduced by the proportion expected to culture convert, with fewer patients expected to be hospitalized in the 2nd month if on bedaquiline.

Costs for either a medical officer or nurse-supported drug collection visits at a primary health care centre were also extracted from a South African study [26]. Based on this study and the treatment guidelines, it was assumed that for both standard of care and bedaquiline regimens there was a medical consultation at initiation, two weeks, and monthly thereafter. Injection regimens (standard of care) were assumed to require a drug collection visit daily during intensive phase; continuation phase treatment and bedaquiline regimens were assumed to require a weekly drug collection visit. Costs for an inpatient hospital stay at a sub-acute facility and a specialized M/XDR-TB hospital were extracted from the same study [26,49] and averaged with the national per hospital day equivalent expenditure reported for South Africa [204]. US dollar costs from literature were converted to ZAR using the exchange rate provided by the study authors [26,49], and then inflated to 2016 values using the medical consumer price inflation index [28].

The effectiveness of treatment was evaluated in disability adjusted life years (DALYs). Disability weights (

Table 6-4) were extracted from the Global Burden of Disease (GBD) 2010 study [74]. The GBD 2010 was a large-scale, multi-country assessment of the pairwise ranking by the 'general public' (rather than medical experts) of the impact on health for different conditions such as infectious diseases, non-communicable disease, and injuries [74]. . Future costs and effectiveness were discounted at 3% as per international standards [205] and a time horizon of 10 years was assumed. Results were multiplied by a cohort of 12,527 patients (the number who initiated MDR/RR-TB treatment in South Africa in 2015 [58]).

2.6 Sensitivity analysis

For parameters extracted from literature, i.e. bedaquiline effectiveness and the disability weights, associated confidence intervals from literature were used in one-way sensitivity analysis. For transition probabilities and initial population distributions estimated from the SA NTP, a percentage adjustment of +25% and -25% was used rather than calculated confidence intervals in order to introduce more uncertainty in the parameters than was reported for analysed cohort. Similarly, for costs, point estimates were collected from the South African public-sector price lists and therefore a percentage adjustment of +25% and -25% was considered to understand the impact of possible future changes in costs rather than observed variation. One-way sensitivity analysis is presented as a tornado diagram. The resulting expected values were multiplied by the number of patients for the 2015 cohort of MDR/RR-TB patients to estimate the total budgetary impact for the SA NTP of the different treatment strategies.

Results

3.1 Base case results

At 24 months, the standard cohort reporting period for long-course MDR/RR-TB, the modelled standard regimen was associated with 28.0% mortality and 56.3% successful treatment outcome. Adding bedaquiline for MDR/RR-TB patients who failed treatment and needed to access individualized XDR-TB treatment did not change the treatment success rate at 24 months as XDR-TB treatment was still continuing. Providing bedaquiline for all MDR/RR-TB patients from initiation was associated with an improved treatment success rate of 60.6% and reduced mortality of 26.2%.

For non-bedaquiline regimens, the total expected cost over the 10-year time horizon for a MDR/RR-TB patient was US$4,439 and average disability-adjusted survival of 5.1 years. Compared to no treatment, MDR/RR-TB treatment without bedaquiline averted 3.7 DALYs. Replacing capreomycin with bedaquiline for patients who failed MDR/RR-TB treatment and required XDR-TB treatment resulted in cost savings (US$4,356, 1.8% less) and similar effectiveness with 0.02 DALYs averted (Table 6-5). As a result, the no bedaquiline (standard) regimen for all was dominated (less effective and more expensive). Replacing kanamycin with bedaquiline so that all MDR/RR-TB patients access bedaquiline cost US$4,647 (4.3% more) and averted 0.17 DALYs compared to the no bedaquiline regimen. The incremental cost of providing bedaquiline for all MDR/RR-TB (an increase of US$209) was less than the cost of bedaquiline at US$675 for the full 6-month course of treatment, as the cost savings from an all-oral therapy offset the higher drug costs. The incremental cost effectiveness ratio (ICER) of bedaquiline for all MDR/RR-TB was US$1,242 per additional DALY averted compared to the standard regimen.

In 2015, 12,527 patients initiated MDR/RR-TB treatment in South Africa [58]. The total estimated cost of the cohort for the standard regimen was US$55.6 million over the 10-year horizon of the analysis (Table 4). Providing bedaquiline for all MDR/RR-TB was estimated to cost US$58.2 million, or an incremental cost of US$2.6 million (4.7% increase), in order to avoid 2,109 DALYs (3.3%) over the 10 years. The incremental cost is less than the estimated cost of US$8.5 million to procure the recommended 6-month course of bedaquiline for the entire annual cohort.

3.2 Sensitivity analysis

Robustness of the findings was explored in one-way sensitivity analysis. The estimated ICERs of bedaquiline for all MDR/RR-TB compared to the non-bedaquiline standard regimen were calculated and plotted using a tornado diagram (Figure 6-8). Variables tested which resulted in a variance of less than ±5% from the expected value (±US$62.02/DALY averted; 2/3 of all variables tested) are not shown in Figure 2. Overall, the analysis was most sensitive to the proportion of patients who culture convert on the standard regimen: a 25% increase culture conversion on standard regimens led to a 2.3-fold increase in the ICER for bedaquiline for all (US$3,908/DALY averted). Results were also sensitive to a 25% increase in the cost of bedaquiline, which led to a 90% increase in the ICER (US$2,242/DALY).

Discussion

In March 2017 [32], the WHO updated its 2013 conditional recommendations [31] for the use of bedaquiline for the treatment of MDR/RR-TB. Encouraging results from the compassionate use program [34] and the public sector roll-out of bedaquiline in South Africa was among the evidence considered by the guidelines development group in revising the recommendations [32]. Yet, in high-burden, limited resource settings like South Africa, the uncertainty around the affordability of providing bedaquiline to all MDR/RR-TB patients rather than just those with no other option has delayed wider implementation. Using a Markov model for ambulatory treatment of MDR/RR-TB in a high-HIV prevalence setting, parameterized using evidence from the SA NTP, we estimate that the incremental total cost of a long-course MDR/RR-TB regimen where bedaquiline replaces kanamycin for a cohort of patients to be US$2.6 million over 10 years. The incremental cost effectiveness ratio of US$1,242 per additional DALY averted is below the 2015 per capita GDP for South Africa of US$5,718 (data.worldbank.org). This amount also represents less than 1% of the total SA NTP budget estimated at US$425 million for 2015 [58] and is less than the annual cost of procurement for bedaquiline of US$8.5 million because of cost savings from an all-oral therapy compared to an injection-based regimen. Additionally, with fewer bedaquiline patients failing MDR/RR-TB treatment and therefore requiring XDR-TB treatment, the SA NTP could potentially avert 2,109 DALYs when this one cohort is followed over 10 years.

The results of this incremental cost-effectiveness analysis are consistent with previous analyses of bedaquiline regimens [52,54,197], despite significant differences in the model structure derived from the standard treatment regimens for MDR/RR-TB in South Africa compared to other contexts. A previously published cost-effectiveness analysis established that bedaquiline could actually be cost saving compared to the standard regimens when patients who are sputum culture positive are hospitalized until sputum negative [53]. However, South Africa adopted ambulatory, outpatient care for MDR/RR-TB in 2011 and therefore was unlikely to realize this cost saving. Similarly, like the adaptation of the model for Italy, surgery for MDR/RR-TB patients who have failed treatment is very rare in South Africa and the use of bedaquiline could not avert surgical costs [56]. The Markov model initially built for analysing the use of bedaquiline in the United Kingdom was also used to estimate the cost-effectiveness of bedaquiline in multiple low and middle-income countries, including South Africa. South Africa does benefit from a very discounted price to access bedaquiline, at ZAR 9,950 (US$675) for a complete course of treatment. Bedaquiline was projected to be cost effective, even at costs for bedaquiline 30- to 70-times what it is priced at for South Africa [55]. However, this finding was driven by a very low treatment success rate for the standard regimens and therefore a large reduction in the number of patients requiring XDR-TB treatment once regimens included bedaquiline [55]. Additionally, while the rates of HIV/TB co-infection in South Africa are among the highest in the world [58] the model did not account for the higher mortality of MDR/RR-TB patients with HIV co-infection [13] or the on-going costs of ART after MDR/RR-TB treatment completion.

The average cost for standard regimens modelled here (US$3,863 at 24 months and US$4,439 across the 10 years) are similar to costs previously estimated for the SA NTP when adjusted to 2016 USD ($4,925 [26] and US$3,894 [25]). Costs have dropped since 2011 as a result of increasing decentralization and deinstitutionalization of the SA NTP as well as devaluation of the local currency. Additionally, the cohort was limited to patients who did not have resistance to either fluoroquinolones or second-line injectable medicines at the initiation of treatment. SA NTP guidelines still recommend hospital-based initiation of treatment and individualized regimens for patients with second-line drug resistance in South Africa, inclusion of patients with additional resistance would have increased the average costs of the cohort. Previous costing studies for MDR/RR-TB in South Africa have limited the time horizon to the 2 years, in line with the guidelines for reporting cohort outcomes. The 10-year horizon in the model established here may be more appropriate as it captured extended treatment for patients who failed MDR/RR-TB treatment initially as well as treatment interruptions when patients were lost from care but then returned. Additionally, the longer time horizon captures the costs of chronic care for HIV-positive patients who successfully complete MDR/RR-TB treatment within the 2 years but then need to continue lifelong ART.

4.1 Study limitations

Similar to other cost-effectiveness analyses that have been published for bedaquiline [53–56], we did not use findings from the Phase 2b clinical trial with regards to mortality. The Phase 2b trial showed a statistically significant imbalance in mortality in the two treatment arms with more deaths occurring in the patients exposed to bedaquiline (10/79, 12.7%) than in the placebo arm (2/81, 2.5%) [30]. However, none of the deaths in the bedaquiline arm were attributed to bedaquiline by the clinical trial investigators. Prior to the roll-out of bedaquiline for patients with XDR-TB in South Africa, more than 40% of patients died before completing treatment [13,58,206]. The 19.8% mortality for patients with second-line resistance receiving bedaquiline through compassionate use access [34] reported in the revised WHO recommendations for bedaquiline is therefore encouraging [32]. Additionally, the revised recommendations included observational reporting from the EDRweb where the mortality rates on bedaquiline were lower than for the patients not on bedaquiline [32]. If the observational data described in the WHO systematic review is confirmed, the analysis presented here with the same mortality for standard and bedaquiline regimens would underestimate the DALYs that could be averted by adoption of bedaquiline for all MDR/RR-TB patients.

This incremental cost-effectiveness analysis also did not include a measure of on-going transmission. TB, including RR-TB, is an infectious disease. RR-TB treatment costs and complexity increases with the degree of resistance, and treatment with a 'failing' regimen can lead to increased resistance. Therefore, successful MDR/RR-TB treatment can avert future costs of treating XDR-TB. These (averted) costs of transmission and development of further drug resistance are excluded from this analysis as transmission modelling is outside the scope of this study. However, this may result in an underestimate of the benefits of a more effective regimen.

Finally, the direct provider costs estimated here, while a significant component of health care costs, do not reflect the cost to society. Direct and indirect costs incurred by patients to access MDR/RR-TB treatment while on treatment are excluded from this analysis and therefore the costs presented here will be an underestimate of the societal costs of MDR/RR-TB treatment. In this analysis, it was assumed that injections were provided at a health care facility and not by an injection team travelling to visit a patient in his or her home. Patients on an injection-based regimen (e.g. kanamycin) are likely to incur higher out-of-pocket expenses for the increased frequency of clinic visits required for injections.

Conclusions

Markov modelling indicates providing bedaquiline for all MDR/RR-TB patients could increase the treatment success rate in South Africa for MDR/RR-TB patients without additional second-line drug resistance from 56.3% on a non-bedaquiline regimen to 60.6%, at an incremental cost US$2.6 million over a 10-year horizon. This amount is far less than US$8.5 million to procure bedaquiline for the initiating treatment cohort and is affordable, at less than 1% of the estimated US$425 million SA NTP annual budget.

ACKNOWLEDGEMENTS:

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Compliance with Ethical Standards:

Funding: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflict of interest statement: KS, CF, FC, NN, and ES declare no conflicts of interest.

NN is an official at the South African National Department of Health and therefore has responsibility for establishing and implementing national treatment guidelines for drug-resistant TB.

Ethics statement:

All procedures performed in the study involving human participants (i.e. analysis of transition probabilities from the EDRweb case register) were in accordance with the 1964 Helsinki declaration and its later amendments and the ethical standards the Human Research Ethics Committee of the University of Cape Town (#490/2015, July 2015) and the Human Research Ethics Committee of the University of Witwatersrand (#M150340, March 2015). For this type of secondary, retrospective analysis of routinely collected data, formal consent is not required. A data sharing agreement was submitted to the Research Information Monitoring, Evaluation and Surveillance Directorate within the South African National Department of Health for access to the EDRweb. Methods and results are presented according to the CHEERS checklist for economic evaluations [195].

Author Contributions:

KS conceptualized the analysis, built and parameterized the cost-effectiveness model, drafted the manuscript and incorporated all author comments and revisions. CF and ES advised on the analysis design and methods, reviewed the analysis results, and reviewed and critically revised the manuscript. FC and NN assisted in providing access to the data, supported interpretation and understanding of the model parameters, and reviewed the manuscript. All authors approved the manuscript submitted for publication.

REFERENCES: (At end of thesis)

Tables

Table 6-2. Markov model monthly transition probabilities

RR-TB diagnosis	HIV, ART status	Phase	
Mortality during treatment			**Transition probability[a]**
MDR/RR-TB	HIV-negative	Initiation	0.0184
		Intensive	0.0101
		Continuation	0.0061
	HIV-positive, on ART	Initiation	0.0325
		Intensive	0.0167
		Continuation	0.0086
	HIV-positive, no ART	Initiation	0.0547
XDR-TB	HIV-negative	Intensive	0.0220
		Continuation	0.0215
	HIV-positive, on ART	Intensive	0.0368
		Continuation	0.0261
Loss from treatment			**Transition probability[a]**
MDR/RR-TB	HIV-negative	Initiation	0.0103
		Intensive	0.0159
		Continuation	0.0155
	HIV-positive, on ART	Initiation	0.0087
		Intensive	0.0159
		Continuation	0.0129
	HIV-positive, no ART	Initiation	0.0157
XDR-TB	HIV-negative	Intensive	0.0103
		Continuation	0.0107
	HIV-positive, on ART	Intensive	0.0045
		Continuation	0.0078
All RR-TB	Return after loss	Month 3-12 of loss	.05[b]
Mortality after treatment			**Transition probability**
All RR-TB	All HIV status		0.0005 to 0.0010 [200]
Culture conversion			**Proportion**
MDR/RR-TB	All HIV status	Intensive	88.4%[a]
XDR-TB	All HIV status	Intensive	76.8% [30,34]
Hospitalization			
MDR/RR-TB	All HIV status	Initiation	20.6% [128]
Initial distribution			**Proportion[a]**
	HIV-negative	Initiation	28.3%
	HIV-positive	Initiation	71.7%
	HIV-positive, no ART	Initiation	Assumption 40% HIV+ not on ART [128,198]
Bedaquiline effectiveness			**Hazard ratios**
All RR-TB	All HIV status	Culture conversion	2.44 (95%CI: 1.57, 3.80) [30]

MDR/RR-TB: Multi-drug resistant or rifampicin-resistant tuberculosis; XDR-TB: extensively drug resistant TB; HIV: human immunodeficiency virus; ART: anti-retroviral therapy

[a] Initial patient distribution and transition probabilities generated from South African EDRweb cohort 2012-2014
[b] Calibrated assumption

Note: Patients that do not culture convert at 6 months (end of intensive phase) are considered as treatment failures and, in the model, transition to intensive phase of XDR-TB treatment.

Table 6-3. Monthly unit costs in 2016 USD

Diagnosis	Phase	Regimen	Monthly cost[a]	Source
Drugs [b]				
MDR/RR-TB	Intensive	standard of care	$ 100.96	[202]
	Intensive	bedaquiline [c]	$ 93.40	[202]
	Continuation	All	$ 83.79	[202]
XDR-TB	Intensive	standard of care	$ 520.77	[202]
	Intensive	bedaquiline [c]	$ 451.67	[202]
	Continuation	All	$ 301.67	[202]
HIV ART	Intensive	standard of care	$ 11.92	[202]
	Intensive	bedaquiline [c]	$ 10.92	[202]
	Continuation	All	$ 9.88	[202]
All RR-TB	Intensive (full 6 months)	bedaquiline [c]	$ 675.23	SA NTP
Laboratory testing [b]				
All RR-TB	Initiation	standard of care	$ 54.40	[201]
	Initiation	bedaquiline [c]	$ 52.50	[201]
	Intensive	standard of care	$ 14.12	[201]
	Intensive	bedaquiline [c]	$ 10.32	[201]
	Continuation	All	$ 12.53	[201]
HIV ART	ART initiation (CD4)	All	$ 3.90	[201]
	ART monitoring (Viral load)	All	$19.92	[201]
Other investigations [b]				
All RR-TB	Initiation	standard of care	$ 19.60	[203]
	Initiation	bedaquiline [c]	$ 19.34	[203]
	Intensive	standard of care	$ 10.56	[203]
	Intensive	bedaquiline [c]	$ 10.30	[203]
	Continuation	All	Not required	
Care [b]				
All RR-TB	Hospitalized	All	$ 2,882.52	[26,49,204]
	Initiation	standard of care	$ 98.12	[49]
	Initiation	bedaquiline	$ 31.35	[49]
	Intensive	standard of care	$ 89.86	[49]
	Intensive	bedaquiline	$ 23.09	[49]
	Continuation	All	$ 23.09	[49]

MDR/RR-TB: Multi-drug resistant or rifampicin-resistant tuberculosis; XDR-TB: extensively drug resistant TB; HIV: human immunodeficiency virus; ART: anti-retroviral therapy; SA NTP: South African National TB Programme

[a] All costs: All costs collected in ZAR. Average monthly exchange rate for 2016, 14.74 ZAR/US$ was applied to ZAR costs [27].

[b] Assumed resource utilization as per guidelines for each month patient in care.

[c] Bedaquiline guidelines version June 2015 used for bedaquiline containing regimen laboratory and investigations clinical monitoring requirements [19].

Note 1: bedaquiline costs are in addition to other MDR/RR-TB or XDR-TB treatment drugs, i.e. the total cost for MDR/RR-TB treatment per month in the intensive phase for someone completing the full 6 months of treatment would be \$93.40 + \$675.23/6 = \$205.94, nearly twice as expensive as the kanamycin-based regimen cost of \$100.96 / month.

Note 2: Monthly ART costs differ according to whether bedaquiline or SOC regimen as per Sirturo prescribing guidance indicating that patients should be switched from efavirenz to nevirapine or lopinavir/ritonavir.

Table 6-4. Disability weights, extracted from the Global Burden of Disease 2010 study [74]

HIV status	Value (confidence interval)	Applicable model states
HIV-negative		
	Tuberculosis: without HIV infection 0.331 (95%CI: 0.222– 0.450)	Initiation, Intensive phase, Continuation phase, Lost from treatment, Palliative care
	No adjustment (assumed full health)	Cure
HIV-positive, on ART		
	Tuberculosis: with HIV infection 0.399 (95%CI: 0.267–0.547)	Initiation, Intensive phase, Continuation phase, Palliative care
	HIV/AIDS: receiving antiretroviral treatment 0.053 (95%CI: 0.034–0.079)	Cure
HIV-positive, not on ART		
	Calculated[a] from product of two co-morbid-itiesas 0.697 (95%CI: 0.470 – 0.843)	Initiation, Lost from treatment

HIV: human immunodeficiency virus; ART: anti-retroviral therapy; AIDS: acquired immune deficiency syndrome

[a]A multiplicative model for computing co-morbid conditions was used [80]. Scores (1 - disability weight) of two co-morbid conditions. AIDS: not receiving ART, 0.547 (95%CI: 0.382–0.715) and TB: without HIV infection 0.331 (95%CI: 0.222– 0.450) were multiplied to create a disability weight for patients not on HIV or TB treatment [74].

Table 6-5. Sensitivity analysis, incremental cost effectiveness ratio of adding bedaquiline, 10-year horizon

Strategy	Cost, 2016 USD ± standard deviation	Effectiveness (disability-adjusted years)	Incremental Cost	Incremental Effectiveness (DALYs averted)	ICER
MDR/RR-TB standard regimen (dominated)[a]					
Average	$ 4,439	5.12	Reference	Reference	Reference
Total	$ 55.60 million	64,128	Reference	Reference	Reference
MDR/RR-TB standard regimen + bedaquiline for XDR-TB[b]					
Average	$ 4,356	5.14	- $ 82.42	0.02	
Total	$54.57 million	64,499	- $ 1.03 million	271	- $ 3,804
MDR/RR-TB bedaquiline for all[c]					
Average	$ 4,648	5.29	$ 208.99	0.17	
Total	$ 58.22 million	66,237	$ 2.62 million	2,109	$ 1,242

MDR/RR-TB: Multi-drug resistant or rifampicin-resistant tuberculosis; XDR-TB: extensively drug resistant TB; HIV: human immunodeficiency virus; ART: anti-retroviral therapy

[a] MDR/RR-TB patients access standard regimen of kanamycin (injectable, 6 months), moxifloxacin, terizidone, ethionamide, and pyrazinamide for 18 months. If fail MDR/RR-TB treatment, treated with XDR-TB regimen consisting of capreomycin (injectable, 6 months), linezolid, moxifloxacin, terizidone, ethionamide, clofazimine, para-aminosacylic acid, and pyrazinamide for 24 months

[b] MDR/RR-TB patients access standard regimen of kanamycin (injectable, 6 months), moxifloxacin, terizidone, ethionamide, and pyrazinamide for 18 months. If fail MDR/RR-TB treatment, treated with XDR-TB regimen consisting of bedaquiline (oral, 6 months), linezolid, levofloxacin, terizidone, ethionamide, clofazimine, para-aminosacylic acid, and pyrazinamide for 24 months.

[c] MDR/RR-TB patients access bedaquiline regimen of bedaquiline (oral 6 months), levofloxacin, terizidone, ethionamide, and pyrazinamide for 18 months. If fail MDR/RR-TB treatment, treated with XDR-TB regimen consisting of bedaquiline (oral, 6 months), linezolid, levofloxacin, terizidone, ethionamide, clofazimine, para-aminosacylic acid, and pyrazinamide for 24 months.

Figures

Figure 6-7. State transition diagram

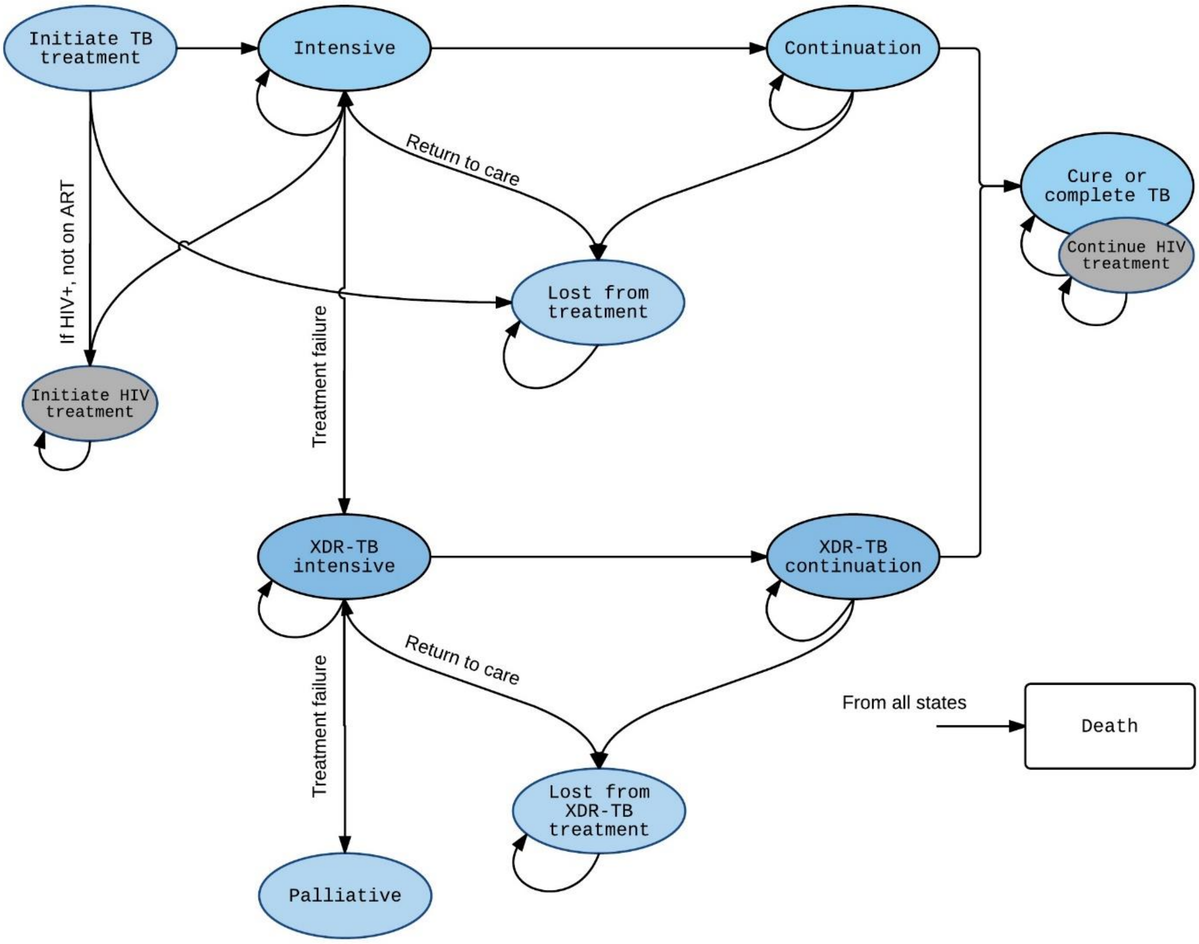
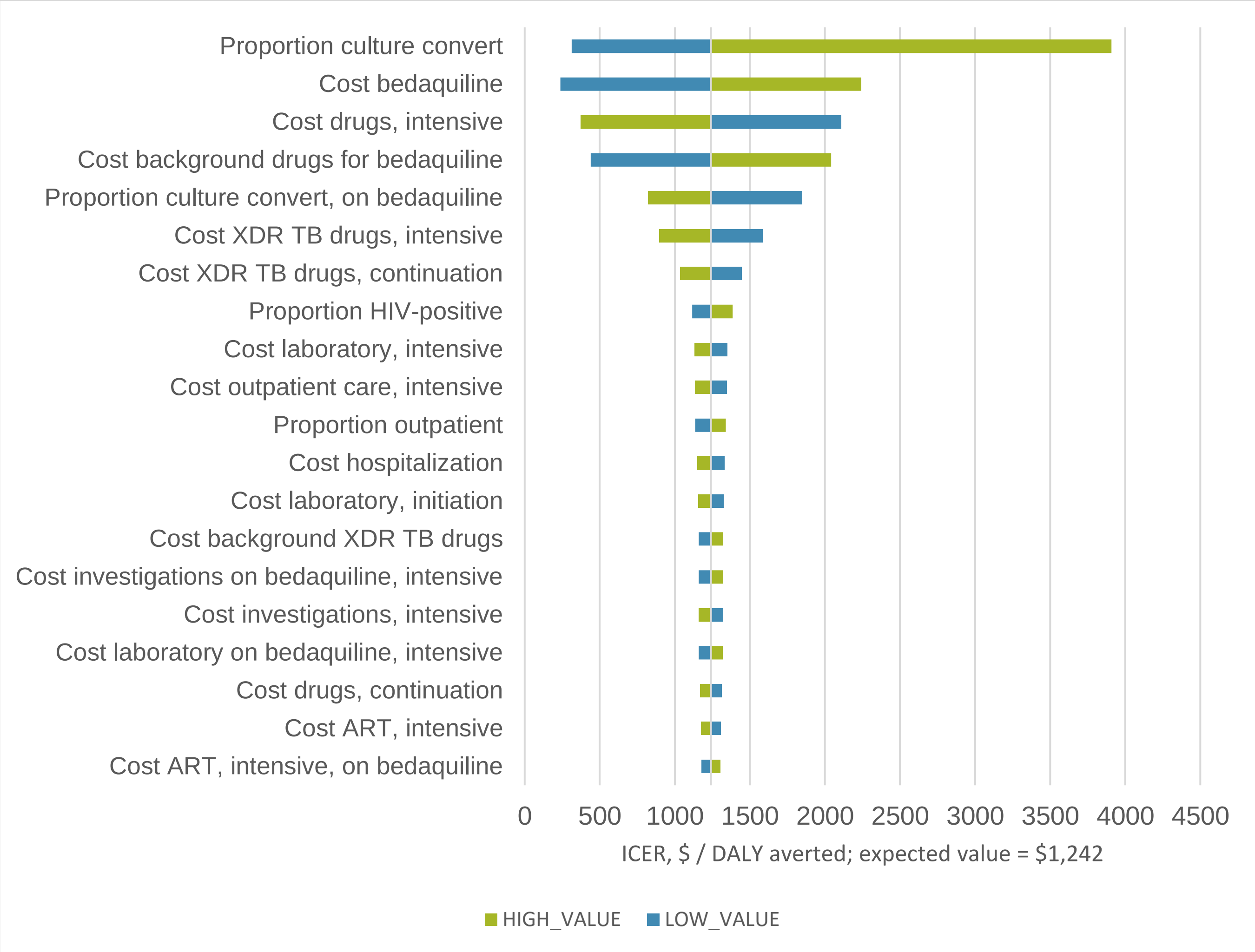


Figure 6-8. Tornado analysis of the incremental cost-effectiveness ratio of bedaquiline for all MDR/RR-TB patients compared to standard regimen



Note: Proportion culture converting refers to the baseline rate of culture conversion on the SOC regimen. A higher proportion of SOC patients converting (and therefore not experiencing treatment failure and requiring individualized treatment regimens) would lower the incremental effect of bedaquiline and therefore increase the ICER/DALY averted, as while bedaquiline improves the rate of culture conversion, the proportion of patients who have culture converted cannot exceed 100%.

7 RESULTS: PROVIDER COSTS OF ADR MANAGEMENT

7.1 SYNOPSIS

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Supplemental materials appended (Annex - Supplemental materials ADR cost model)

This chapter was written to achieve the second overall objective of the thesis research; namely, to evaluate the provider cost of management of ADRs incurred during RR-TB treatment, including drugs, hospitalization, laboratory monitoring, and clinic visits for the most frequently occurring moderate to severe ADR associated with the current standard of care MDR/RR-TB treatment regimen in the SA public health sector. Resource use was extracted from clinical guidelines for MDR/RR-TB treatment in the public sector. Ingredient costs collected from the same public sector sources as for Chapter 6 were multiplied by the expected resource use in a cost worksheet (attached as supplemental materials, Annex - Supplemental materials ADR cost model). Weighted average costs for moderate ADR and for severe and serious ADR were multiplied by the expected frequency of each of the different events, as extracted from literature identified during the systematic review Chapter 5. Based upon the analysis presented inChapter 4, where the competing risk of mortality can affect the observed prevalence of the ADR, the Markov model for MDR/RR-TB treatment introduced in Chapter 6 was used to evaluate the expected costs of ADR management. Distributions were added for all model parameters, so that instead of one-way sensitivity analysis, probabilistic sensitivity analysis could be used. For an average cohort of MDR/RR-TB patients such as the 12,527 who initiated treatment in the SA NTP in 2015, including ADR management costs increased the estimated cost of MDR/RR-TB treatment in South Africa from $57.55 million over 10 years to $62.31 million.

Contribution to the thesis and novelty

Cost-effectiveness analyses of MDR/RR-TB treatment have sometimes applied an average cost for ADR management to all patients, but have not specified the type, frequency, cause, or specific management for the ADR in the details. This analysis was a guidelines-based cost for the management of all common ADR included in the SA MDR/RR-TB treatment guidelines. A frequency for each of the ADR was estimated from literature review (as presented inChapter 5) and multiplied by the cost of managing the ADR estimated from the bottom-up ingredients approach. The costing workbook indicates the suspected drugs for each of the included ADR, and thus also can be used to estimate the costs of ADR for different regimens (as it was for Chapter 8).

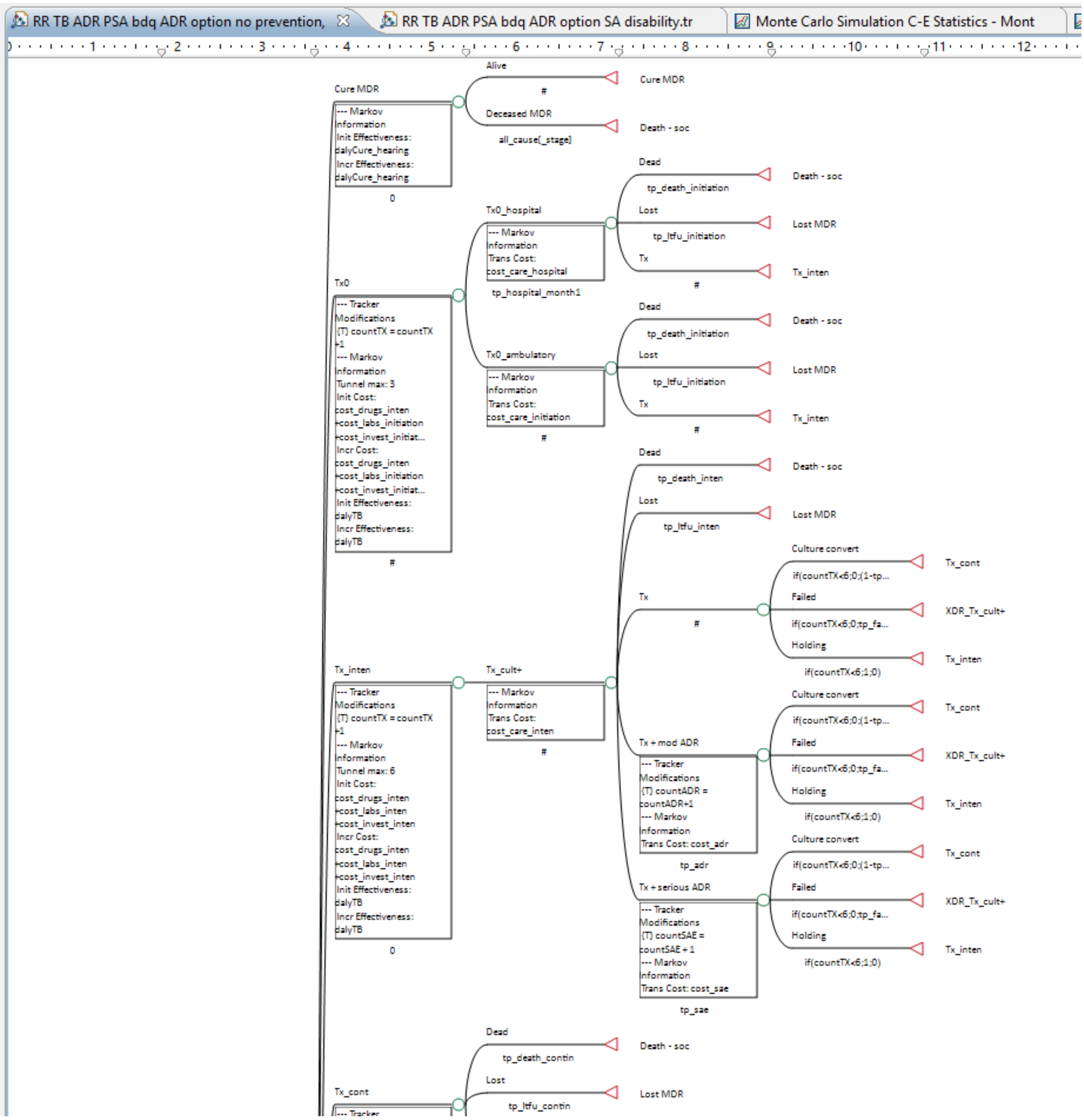
Role of the candidate

The candidate worked with the clinicians to interpret the guidelines for treatment of ADR during MDR/RR-TB treatment and to identify and quantify the resources required for management of ADR. She then extracted unit costs from public sector databases and consulted with the clinicians in ensuring that the costs were appropriately matched to the required resources. She built an Excel-based cost worksheet for the most frequently occurring serious or severe ADR and the most frequent mild, moderate and severe ADR as reported in M3. The candidate wrote the first draft of the manuscript and revised in response to inputs from co-authors. She made revisions based on comments from reviewers. All authors approved the final manuscript.

7.2 Tree structure ADR costing

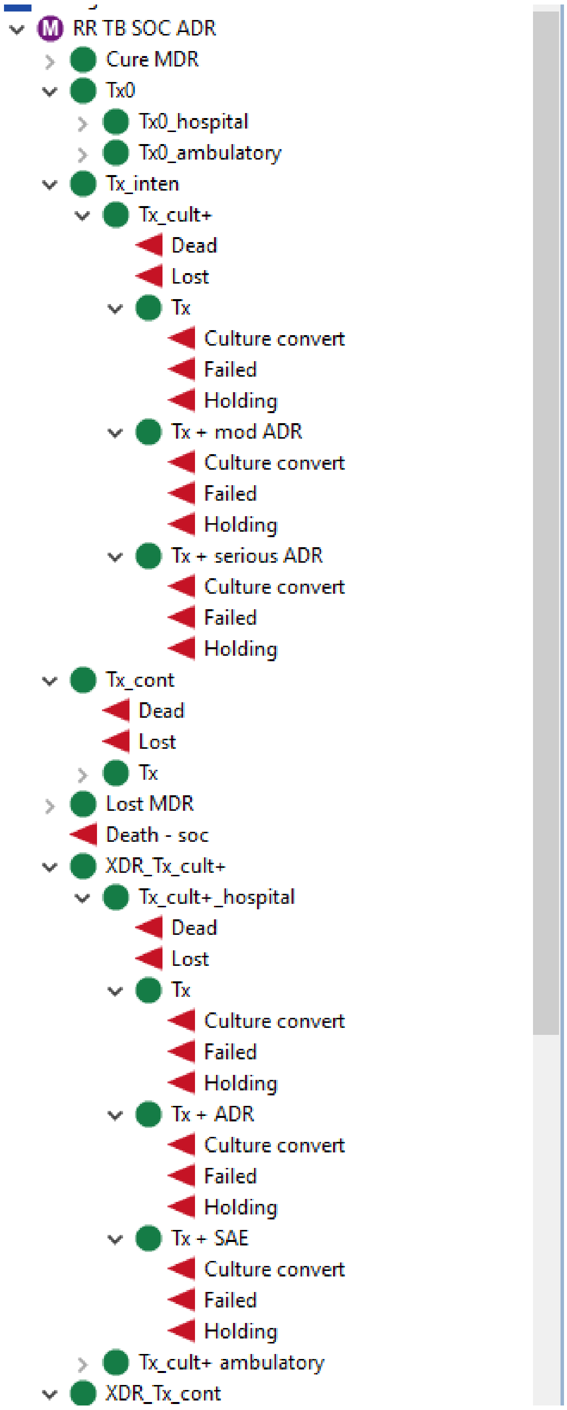
The model described above was modified in order to include the costs of ADR and to estimate the expected costs per MDR/RR-TB patient. In order to account for additional uncertainty with regards to the frequency and timing of the ADR, probabilistic sensitivity analysis method was adopted. This meant that all parameters (costs, transition probabilities, and initial patient distributions) had to be sampled from appropriate distributions rather than using point estimates and one-way variance.

Figure 7-1 Decision tree: Modifications for ADR



In the above diagram, unlike the initial Markov model, trackers have been added to be able to count the ADR or SAE experienced. Since some patients experience none and other patients experience more than one ADR, the tracker counts are important to estimate the cost for an 'average' patient.

Figure 7-2 Decision tree: Tree explorer for ADR model



In the above diagram, unlike the initial Markov model, additional health states have been added during the intensive phase of MDR/RR-TB and XDR-TB treatment. Patients in the model can transition from initiation to one of three health states for intensive treatment (Tx_cult+): treatment (Tx), treatment and experiencing a moderate ADR (Tx + mod ADR), or treatment and experiencing a serious ADR (Tx + serious ADR).

7.3 MANUSCRIPT 5

Title: Direct costs of managing adverse drug reactions during rifampicin-resistant tuberculosis treatment in South Africa

SHORT TITLE: Costs of MDR-TB treatment adverse drug reactions

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Key words: multi-drug resistant tuberculosis; Markov model; budget impact; adverse events

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Summary
Word count: 190

Objective

To estimate the provider costs of managing adverse drug reactions (ADR) to standard long-course treatment for multi-drug and rifampicin-resistant tuberculosis (MDR/RR-TB) according to South African guidelines.

Methods

We parameterized a previously published Markov health state model for MDR/RR-TB with guidelines-based, bottom-up public-sector provider costing of ADR management. Frequency of ADR was extracted from literature. Costs were estimated over 10 years, discounted 3% annually, and tested using probabilistic sensitivity analysis.

Results

On average, the guidelines-based costing of moderate ADRs weighted by frequency of occurrence was US$135.76 (standard deviation (sd): US$17.18) and the cost of serious ADRs was US$521.29 (sd: US$55.99) per patient. We estimated the incremental costs of ADR management are $380.17 per patient initiating MDR/RR-TB treatment annually. The incremental costs of ADR management for the public health sector in South Africa was US$4.76 million; 8.3% of the estimated cohort costs of MDR/RR-TB treatment ($57.55 million) for the 2015 cohort of 12,527 patients.

Conclusions

Management of multiple ADR and serious ADR, common during the first 6 months of standard, long-course MDR/RR-TB treatment, substantially increases provider treatment costs. These results add to need to account for the cost of adverse events in comparing regimen costs and the urgency for identifying drug regimens with improved safety profiles.

Introduction

Patients resistant to the core first-line drug for treatment of tuberculosis (TB), rifampicin, alone or in combination with any other first-line or second-line drugs require second-line TB treatment. The World Health Organization (WHO) estimates that globally in 2015 there were 580,000 new rifampicin-resistant (RR-) TB cases. In South Africa, there were 19,613 laboratory-confirmed diagnoses and 12,527 MDR/RR-TB cases initiated treatment, with an estimated HIV co-infection rate of 57%.[58]The average cost of treating a MDR/RR-TB patient in South Africa, assuming implementation of guidelines for ambulatory, outpatient standardized long-course treatment, is estimated at US$3,863 to US$4,926 per patient (converted to 2016 USD).[25,26,207] Not only are the drugs expensive; many of the second-line TB drugs have known toxicities. According to a meta-analysis of cohorts where at least 20% of the patients were known to be HIV-positive, 83% (95% confidence interval (CI): 82%,84%) of all patients experienced at least one adverse event (AE) during treatment and 24% (95%CI: 21%, 27%) experienced a severe or serious AE during MDR/RR-TB treatment.[208] On average, each patient experiences 3 to 8 AE during the course of MDR/RR-TB treatment.[122,123,194] Although there is much evidence that many of the AE are related to drugs, i.e. are adverse drug reactions (ADR), specification of the costs of ADR management has not been a focus of the MDR/RR-TB cost analyses.

To improve planning, budgeting, and policy decision making, we collected the costs of provider (payer) costs of managing ADR during MDR/RR-TB treatment in South Africa and used a previously established Markov model [207] to estimate the incremental cost of ADR management.

Methods

Setting

All MDR/RR-TB patients in South Africa receive treatment free of charge at public sector (government) facilities. Treatment for MDR/RR-TB was both de-institutionalized and decentralized in 2011; most patients do not receive facility-based directly observed treatment. As of 2015, most patients without second-line drug resistance initiate treatment on an out-patient basis at a nearby hospital or community health centre and receive daily injections during the initial phase at a primary health clinic. Through the end of 2016, South African National TB Programme (SA NTP) guidelines recommended a long-course (18-24 month), standardized regimen, including an injectable aminoglycoside (kanamycin) during the first 6 months 4 oral drugs: a fluoroquinolone (moxifloxacin), terizidone, ethionamide and pyrazinamide).[17] MDR/RR-TB patients in whom treatment fails are able to access individualized regimens similar to those for extensively drug-resistant (XDR-) TB, which in South Africa prior to the introduction of bedaquiline in 2015 included capreomycin, moxifloxacin, linezolid, clofazimine, ethionamide, para-aminosalicylic acid, terizidone, and pyrazinamide.

Guidelines-based costing of ADR management

An ingredients costing approach was built from the estimated resources use for guidelines-based management of ADR and serious ADR included in the SA NTP guidelines [17] or WHO guidelines for the standard regimen.[209] The costing work book and details are attached as supplemental materials. Resource use for ADR management, e.g. quantity and duration of required medications, laboratory tests, investigations, fluids, additional clinic visits, or hospitalization, was based on indications in the MDR/RR-TB SA NTP guidelines, or WHO or SA primary health care guidelines where there was insufficient details.[17,209,210] Costs for each ADR was then multiplied by the expected frequency of each ADR during MDR/RR-TB [108,123,179,194,211] and extensively drug resistant (XDR-) TB [148,168] treatment which was extracted from literature [108,115,123,148,168,179,194] in order to create weighted average costs. Prevention and screening for early AE detection, e.g. screening for symptoms or monitoring for laboratory abnormalities, are applicable to all patients who initiate treatment, included in guidelines-based costing of MDR/RR-TB treatment [25,26,207] and therefore are excluded here.

All unit costs were collected from the perspective of the public sector in South Africa in the local currency (ZAR) using public sector databases and price lists.[202,212–214] If needed, costs were inflated to 2016 ZAR using the medical component of the consumer price index (CPI) and converted to USD at the average exchange rate for 2016, 14.74 ZAR to USD.[27,28] Capital investment in infrastructure, pre-service education, vehicles or medical equipment was not separately estimated as assumed to be considered in the listed prices. No patient costs were included in this analysis. Patient transport, including emergency transport to hospital, was also not included in the analysis.

Cost per treatment episode and budget impact

Having calculated a weighted average cost per ADR and serious ADR, the total cost of ADR management per MDR/RR-TB treatment episode was modelled using a previously published Markov model for ambulatory, long-course standard MDR/RR-TB treatment parameterized for South Africa.[207] Only patients without second-line resistance at the initiation of MDR/RR-TB treatment are included in the analysis. The health state model (Figure 7-3) was built in TreeAge Pro 2015 (TreeAge Software, Williamstown, MA). Patients are initially distributed in the model according to whether HIV-negative (28.3%) or HIV-infected (71.7%); HIV-infected patients are differentiated as to whether already on anti-retroviral therapy (ART, 60.0%) or ART naïve at initiation of MDR/RR-TB (40.0%).[207] Patients progress through monthly steps from initiation of treatment, intensive phase (first six months), continuation (following 12-18 months) phase of treatment, to treatment completion (cure). Patients may be hospitalized at initiation of MDR/RR-TB treatment (20.6%).[11] From any treatment state, patients could be lost from treatment or die. Patients failing to sputum culture convert by 6 months transition in the model to XDR-TB treatment; patients failing to sputum culture convert after 6 months of XDR-TB treatment transition to palliative care. Transition probabilities for loss from care, treatment failure, and death for HIV-negative and HIV-infected patients with either MDR/RR-TB or XDR-TB were as reported in the original model analysis [207] derived from the SA drug-resistant TB case register (January 2012 - April 2014 cohort).[199] Provider costs for ART, MDR/RR-TB treatment, prevention of and monitoring for ADR were already included in the model and not adjusted for this analysis.[207]

Based on the frequency of ADR reported in literature, it was assumed that during months 1 to 5, a patient could experience either a moderate ADR (mean transition probability 0.183)[208] or a serious ADR (mean transition probability 0.052).[194] ADRs were not included in the first month of treatment (month 0) or after intensive phase (months 6 to 18). Patients who failed MDR/RR-TB treatment and needed to initiate XDR-TB treatment regimen were modelled as possibly experiencing ADR or serious ADR in months 1 to 5 of XDR-TB treatment. Patients can experience one, none, or multiple ADR or serious ADR. HIV-infected patients naïve to ART at MDR/RR-TB initiation experienced a relative increase in risk of ADR and serious ADR (sub-hazard ratio: 3.07 relative to HIV-negative patients).[194]

Frequency and costs of ADR and serious ADR for MDR/RR-TB and XDR-TB health states, initial population distributions of HIV-infected and HIV-infected on ART, and the relative risk of ADR if ART naïve, were varied using probabilistic sensitivity analysis through Monte Carlo simulation. ADR costs were sampled from a gamma distribution with variances as estimated; transition probabilities and HIV proportions were sampled from a beta distribution with variance of 25%. A time horizon of 10 years was assumed and future costs were discounted 3% annually as per international standards.[18] Potential impact on the SA health budget was summed from the 12,527 trials, based upon the 2015 SA initiating cohort.

Ethics and reporting

No patient-level data or information was collected, reviewed, or analysed for this study. Description of methods and reporting of results is in alignment with the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement.[195]

Results

Management of ADR

The costs, frequency, and weighted costs of management of the most frequently occurring ADR during MDR/RR-TB treatment are presented in Table 7-1(cost components and XDR-TB frequencies are presented in supplemental materials). The weighted average for moderate ADR was US$135.76. The costs ranged US$2.51 for diarrhoea (ancillary medicine provided during regular MDR/RR-TB visit) to US$208.23 for temporary drug-induced hypothyroidism, which requires ancillary treatment from onset to completion of MDR/RR-TB treatment. Hypothyroidism was also the most frequent moderate ADR at 36% [108] and therefore contributed the most to the weighted average.

Nine of the 10 severe or serious ADR (Table 7-2) include hospitalization and the duration of hospitalization was the most significant cost component. Severe systemic allergic reaction (e.g. Stevens–Johnson syndrome) require ICU care and, as a result, were the most expensive of all the ADR costed, at $5,461, although it was also the most infrequent. The most frequently experienced severe ADR was permanent and profound hearing loss, at 40% of patients on the kanamycin-based regimen [115], which was estimated to cost the provider $50.76. The weighted average for serious ADR experienced during MDR/RR-TB treatment was US$521.29.

Cost per MDR/RR-TB treatment episode

In 2015, according to the WHO, 12,527 patients initiated MDR/RR-TB treatment in South Africa (63.9% of the 19,613 diagnosed).[58] On average, the standard, long-course regimen in South Africa was estimated to cost $4,594 (95%CI: 3,950 to 5,283) over the 10-year horizon of the model. Having adjusted the model to account for the costs of ADR management in the MDR/RR-TB and XDR-TB health states, including moderate (US$135.76 and $156.05, respectively) and serious ADR (US$521.29 and $1,039, respectively), increased the average cost to US$4,974 (95%CI: 4,280 to 5,714). The average cost of managing ADR was an additional US$381.17 per patient, an 8.3% increase. For the 2015 MDR/RR-TB cohort, ADR management increased the costs of MDR/RR-TB treatment from US$57.55 million to US$62.31 million, an additional $4.76 million per year (95%CI: 4.13 to 5.40 million).

Discussion

For South Africa, a high-burden TB/HIV and high-burden MDR/RR-TB country, the incremental costs of each ADR and serious ADR are estimated to add up to US$4.76 million annually. These substantial cost estimates highlight that ADR represent not only a burden on the patient experiencing the event(s), but also a measurable cost to the public health system. While the standard deviations presented here indicate uncertainty in an average cost based upon the nature, frequency and severity of the ADR that occur during the standardized, long-course MDR/RR-TB treatment, nearly all patients experience at least one ADR. We added the average calculated weighted cost of managing ADR to a Markov health state model in order to estimate an expected cost per MDR/RR-TB patients sampling from the wide distribution of possible outcomes. Thus, until a better tolerated regimen is available, even an uncertain estimate of the costs is important for planning, budgeting, and analysis of MDR/RR-TB treatment regimens.

The 2016 SA NTP budget, as reported to the WHO, was $425 million for 2016 including $68 million for drug-resistant TB, including patients with MDR/RR-TB and XDR-TB.[58] The budget is built from expected patient cohorts, multiplied by the drug costs per patient and expected days of hospitalization as per treatment guidelines [58] and excludes the costs of management of moderate to serious ADR. ADR management costs estimated here exceed previously reported estimates from South Africa ($190 [25]), at least in part because of longer duration of hospitalization(s) associated with serious ADR. Neither the SA NTP budget nor this analysis included the increased costs for individualized regimens (drug substitution) for patients after ADR, and thus is still a conservative estimate. Adding the incremental costs of ADR management estimated here as well would increase the estimated resources required for MDR/RR-TB treatment. Similar analysis should be done for those patients initiating as XDR-TB; the costing of the ADRs included here can serve as a starting point.

While the resources used and unit costs presented here were calculated for South Africa, the frequency of the ADR during MDR/RR-TB treatment are common across multiple settings [208] and the relative incremental resource requirement (8.3% increase for ADR management) could improve estimation. Similarly, this analysis drew on evidence from the SA NTP prior to the 2017 roll-out of short-course (9 to 12 month) regimens for MDR/RR-TB, however, the methods and costing reported here are useful for the short-course as well, as most ADR during MDR/RR-TB treatment occur in the first 6 months [26] and the long and short-course regimens are based on the same core and additional drugs.[14] Although treatment regimens and guidelines are changing; these results remain relevant as they are indicative of the need for taking into account the costs of medication as well as managing adverse events when comparing regimens.

Limitations

The provider perspective for costs excludes patient direct and opportunity costs and, therefore, underestimates the societal burden of the ADR experienced. Hospitalization often results in increased transportation costs for patients and family members, as well as patient and caregiver loss of income. On average, a month of hospitalization for MDR/RR-TB cost SA patients US$211 (converted to USD 2016), mostly from lost productivity.[44] For patients experiencing profound hearing loss, the use of a provider-payer perspective, especially in a context where rehabilitative surgery (cochlear implants) is rare, greatly underestimates the societal costs for this treatment. Yet, ototoxicity (ranging from mild to severe) is one of the most frequent ADR experienced by MDR/RR-TB patients.[115] Similarly, the most serious ADR may result in death, the burden of which is not considered in an analysis limited to provider costs.

We also did not measure the non-monetary effects of ADR including increased stress and distress for patients experiencing these events. Patients who experience an ADR may be reluctant to continue treatment that they associate with the adverse reactions resulting in poor adherence, loss from care and sub-optimal outcomes.[215,216] Patient-perceived toxicity may also not be aligned to the culprit drug and patients may associate ADR with a drug that was unlikely to have caused the ADR. If patients interrupt or reduce prescribed dosing, they could be at risk of increased resistance and transmission of a highly resistant strain of TB. A study of MDR/RR-TB patients found that risk of acquired resistance increased by 20% for each month where less than 80% of the prescribed doses were taken.[217]

Finally, this guidelines-based costing assumed that only the guideline-indicated minimum treatment was used; this may underestimate clinical care received. In cases where a patient experiences multiple ADR concurrently, additional drug/drug interactions and contraindications may be experienced which require more complex or higher cost treatments. Conversely, guidelines-based costing may also overestimate the costs if, for any reason, treatment is not completed, laboratory tests not done, or medication not prescribed. The appropriate management of patients after ADR is limited by the availability of alternatives, when clinicians have to weigh the risks of the ADR with the risks of untreated or undertreated disease.[192,218,219] Additionally, this analysis did not consider the costs of on-going transmission of MDR/RR-TB, including transmission while hospitalized for ADR, or acquired resistance as a result of ADR.

Conclusions

Each year, management of multiple moderate to severe adverse drug reactions during the standardized, long-course MDR/RR-TB treatment requires US$4.76 million in additional medications, laboratory tests, procedures, and clinic and hospital utilisation – compared to the budgeted estimates of US$57.55 million which exclude ADR management. This represents a measurable and substantial cost to the South African public health system, underlines the need to account for the cost of adverse events in comparing regimen costs, and adds to the urgency of identifying a better tolerated regimen for the treatment of MDR/RR-TB, especially in resource-limited settings.

TRANSPARENCY DECLARATION

All authors: no conflict of interests to declare.

REFERENCES

(at end of thesis)

Tables

Table 7-1 South African public sector guidelines-based provider costs [17,209,210] *of managing the most commonly experienced moderate ADR during MDR/RR-TB treatment (2016 USD)*

Moderate adverse events	**Description, severity**	**Total cost, 2016 USD**	**Frequency MDR/RR-TB (% patients experiencing)**	**Weighted cost, 2016 USD**
Thyroid dysfunction, hypothyroidism	e.g. requiring supplementation	**$ 208.23**	36% [108]	**$ 74.96**
Hepatitis, liver dysfunction	e.g. elevated ALT < 5 x upper limit of normal	**$ 155.01**	7% [108]	**$ 10.85**
Hearing loss	Permanent, high frequency hearing loss	**$ 50.76**	18% [115]	**$ 9.14**
Psychiatric disorder	e.g. depression, confusion	**$ 43.20**	10% [108]	**$ 4.32**
Sleep disturbance, insomnia		**$ 31.57**	10% [179]	**$ 3.16**
Peripheral neuropathy		**$ 28.89**	18% [123]	**$ 5.20**
Visual disturbance		**$ 23.73**	Not associated	**$ -**
Tinnitus	without hearing loss	**$ 23.68**	12% [123]	**$ 2.84**
Dizziness, vertigo		**$ 19.49**	8% [123]	**$ 1.56**
Hypersensitivity, allergic reaction	Rash, dermatologic reaction (moderate)	**$ 15.97**	16% [123]	**$ 2.56**
Nausea, vomiting	Vomiting or nausea limiting oral intake	**$ 15.72**	18% [123]	**$ 2.83**
Joint pain, arthralgia		**$ 11.09**	12% [123]	**$ 1.33**
Tendonitis		**$ 3.06**	0.5%, Assumption	**$0.02**
Headache		**$ 2.52**	3% [123]	**$0.08**
Diarrhoea		**$ 2.51**	15% [108]	**$0.38**
	Average cost	**$ 42.36**	Weighted average	**$119.22 (sd: 18.81)**

Description of laboratory tests, medications, investigations, and specialist consultations and the frequencies and averages for XDR-TB is included in each unit cost is provided the ADR cost workbook, attached as supplemental materials.

^ An MDR/RR-TB patient may experience none, one or multiple ADR during treatment.

Table 7-2. South African public sector guidelines-based provider costs [17,209,210] *of managing most commonly experienced serious adverse drug reactions during MDR/RR-TB treatment (2016 USD)*

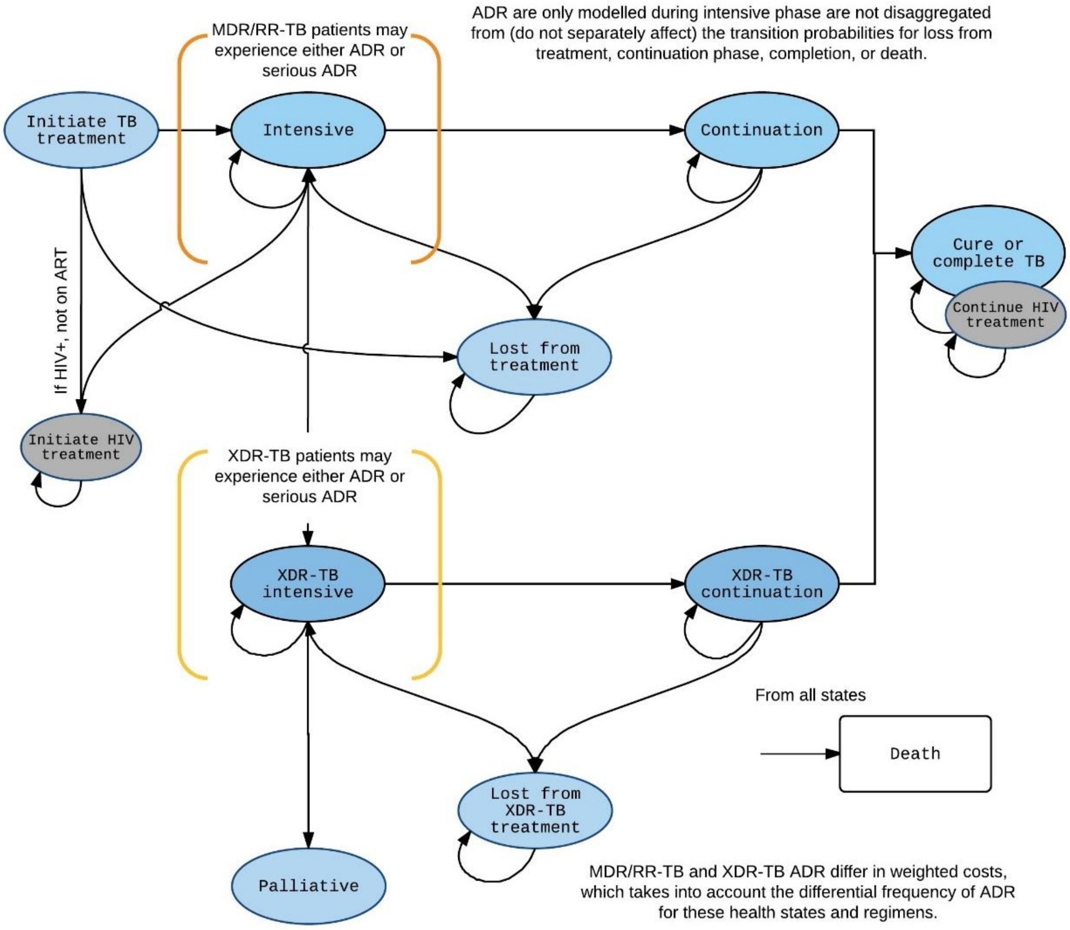
Severe or serious adverse events	**Description, severity**	**Total cost, 2016 USD**	**Frequency MDR/RR-TB (% patients experiencing)**	**Weighted cost, 2016 USD**
Hypersensitivity, allergic reaction	e.g. Stevens-Johnson Syndrome and Toxic epidermal necrolysis	**$ 5,461.05**	0.5% [194]	**$ 27.31**
Hepatitis, liver dysfunction	e.g. ALT > 5 x the upper limit of normal	**$ 2,703.45**	6% [194]	**$ 162.21**
Anemia	Thrombocytopenia, <50,000 cells/mm3	**$ 1,943.75**		**$ -**
Psychiatric disorder	e.g. suicidal or pyschosis (harm to self or others)	**$ 1,824.41**	8% [194]	**$ 145.95**
Renal dysfunction	Globular filtration rate < 30 ml/min	**$ 1,807.88**	2% [194]	**$ 36.16**
Seizures	New onset, severe	**$ 1,120.21**	3% [194]	**$ 33.61**
Anemia	Hemoglobin <8 g/dL	**$ 928.93**	2% [194]	**$ 18.58**
Hypokalemia, electrolyte imbalance	e.g. Magnesium 0.6 to < 0.9 mEq/L or Potassium 2.0 to < 2.5 mEq/L	**$ 891.99**	2% [194]	**$ 17.84**
Nausea, vomiting	Persistent vomitting or nausea resulting in minimal oral intake	**$ 847.65**	7% [194]	**$ 59.34**
Renal dysfunction	Glomerular filtration rate < 60 to 30 ml/min	**$ 100.65**	8% [194]	**$ 8.05**
Anemia	Hemoglobin <11 g/dL and >8 g/dL	**$ 84.41**	28% [108]	**$ 23.63**
Hypokalemia, electrolyte imbalance	e.g. Magnesium 0.9 to < 1.2 mEq/L or Potassium 2.5 to < 3.0 mEq/L	**$ 70.75**	12% [108]	**$ 8.49**
Hearing loss	Permanent, profound deafness (with or without tinnitus)	**$ 50.76**	40% [115]	**$ 20.31**
	Average cost	**$1,371.99**	Weighted average	**$561.46 (sd: 50.51)**

Description of laboratory tests, medications, investigations, and specialist consultations and the frequencies and averages for XDR-TB is included in each unit cost is provided the ADR cost workbook, attached as supplemental materials.

^ An MDR/RR-TB patient may experience none, one or multiple serious ADR during treatment.

Figures

Figure 7-3 Markov health state model of ambulatory standard long-course MDR/RR-TB treatment, modified to adjust for adverse drug reactions



8 RESULTS: COST-EFFECTIVENESS ANALYSIS ADJUSTED FOR TOXICITY

8.1 SYNOPSIS

Formal citation: Schnippel K, Firnhaber C, Page-Shipp L, Sinanovic E. Impact of adverse drug reactions on the incremental cost effectiveness of bedaquiline for drug-resistant tuberculosis. *The International Journal of Tuberculosis and Lung Disease*, 2018. *In press.*

In this manuscript, the decision-analysis model established under Objective 3 was adjusted in order to adjust the incremental cost effectiveness of bedaquiline RR-TB treatment regimen compared to the SOC RR-TB treatment regimen, including the costs and burden of ADR. Bedaquiline for all MDR/RR-TB compared to bedaquiline reserved for treatment failure after injection-based regimen was found to have a mean ICER of $567 per DALY averted using the standard Markov model. Costs for both regimens increased and effectiveness decreased for the injection-based regimen once the model was adjusted for the toxicity. The resulting ICER of a bedaquiline for all was cost saving ($96 / patient) and more effective (0.96 DALYs averted).

Contribution to the thesis and novelty

This final results chapter pulls together findings presented in earlier chapters, including timing of mortality during MDR/RR-TB treatment by HIV and ART status Chapter 3, proportion of persons experiencing ADR and serious ADR in HIV settings Chapter 5, and the increased relative risk of ADR for HIV-infected patients newly initiating ART Chapter 4. Ingredients costs first used in the Markov model established in Chapter 6 and average costs for ADR management as estimated in Chapter 7 are also used. Disability weights for hearing loss (Table 2-11) are added to the model. As identified in Chapter 2, indicated management of drug-induced QT prolongation, which is associated with bedaquiline use, is interruption of treatment and therefore does not have a cost for management beyond the clinic visit already incorporated in the cost of treatment. The result is a cost-effectiveness analysis that is based upon real-world implementation of an injection-free regimen in South Africa and that quantifies the provider costs and disability of permanent, profound hearing loss from the MDR/RR-TB injection-based regimens.

Role of the candidate

The candidate conceived the initial research question, and revised the Markov health state model according to findings from the objectives of the thesis (i.e. differential transition probabilities by time on treatment and HIV and ART status, differential risk of ADR for HIV-infected newly initiating on ART, and differential costs of ADR management during MDR/RR-TB or XDR-TB). All model revisions, including use of trackers for counts of ADRs and months on ART, were built in TreeAge. She ran different versions to balance the availability of data, the complexity of the model, and the reasonableness of the outputs for the base case outputs. The candidate wrote the first draft of the manuscript and revised in response to inputs from co-authors. She revised the article based upon suggestions from the editor and reviewers.

8.2 MANUSCRIPT 6

Title: Impact of adverse drug reactions on the incremental cost effectiveness of bedaquiline for drug-resistant tuberculosis
RUNNING TITLE: Drug toxicity affects cost analysis of MDR/RR-TB

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Ethics statement: The study protocol, including retrospective analysis of a routinely collected public health dataset, was approved by the Human Research Ethics Committee of the University of Cape Town (#490/2015, July 2015) and the Human Research Ethics Committee of the University of Witwatersrand (#M150340, March 2015). Methods and results are presented according to the CHEERS checklist for economic evaluations [24].

Summary
Background

Adverse drug reactions (ADR) are frequent during standard, long-course treatment for multi-drug and rifampicin-resistant tuberculosis (MDR/RR-TB). In particular, the second-line injectable agents (IA) are associated with permanent hearing loss, acute renal injury and electrolyte imbalance. We adapted an established Markov model for ambulatory treatment to estimate the impact of the toxicity profile on the incremental cost-effectiveness ratio (ICER) for a proposed MDR/RR-TB regimen replacing the IA with bedaquiline.

Methods

Treatment effectiveness was evaluated in disability adjusted life years (DALYs). Clinical outcomes and ingredient costs from a provider perspective were derived from the South African public-sector treatment programme or extracted from literature. Costs and effectiveness were discounted at 3%/year over 10 years.

Results

A bedaquiline-based MDR/RR-TB regimen compared to the IA regimen had a mean ICER of $516 per DALY averted using the standard Markov model. Costs for both regimens increased and effectiveness decreased for the IA regimen once adjusted for toxicity. The resulting ICER for bedaquiline-based regimen was cost saving ($96/patient) and more effective (0.96 DALYs averted) after adjusting for ADR.

Conclusion

Decision analysis models of treatment for MDR/RR-TB, including new drug regimens, should consider the costs of managing ADR and their sequalae.

Key words:

bedaquiline; cost-effectiveness; rifampicin-resistant TB; DALYs; Monte Carlo simulation

Introduction

According to the World Health Organization's (WHO), in 2016, there were 600,000 incident cases and 240,000 deaths from rifampicin-resistant (RR-) and multi-drug resistant (MDR-) tuberculosis (TB).[2] South Africa has the world's largest epidemic of HIV, and one of the world's largest epidemics of TB, TB/HIV and MDR/RR-TB. In 2016, the South African National TB Programme (SA NTP) initiated 11,192 MDR/RR-TB cases on treatment.[2] Through the end of 2016, the SA NTP implemented a standard, long-course regimen for MDR/RR-TB without additional second-line drug resistance (6 months of kanamycin, moxifloxacin, ethionamide, terizidone and pyrazinamide followed by 12 months excluding kanamycin).[19] In March 2015, the SA NTP approved bedaquiline as an additional drug to strengthen the existing regimens, where there was either resistance to or intolerance of fluoroquinolones and/or second-line injectable agents (IA).[19]

Fluoroquinolones and IA are considered core drugs for constructing effective MDR/RR-TB regimens.[14] Yet, even among MDR/RR-TB patients initiating recommended regimens, globally only 54% to 60% patients are successfully treated [2,5]; for the South African 2014 cohort 54% were successfully treated.[2] More recently registered drugs such as bedaquiline [30,32] have shown promise in terms of improved efficacy and there are hopes for an all-oral regimen where IA are replaced by more effective and safer drugs.[1] However, the costs of the newly developed drugs may pose a barrier to adoption in resource-limited settings. A cost-effectiveness analysis for ambulatory treatment of MDR/RR-TB parameterized using SA NTP data estimated that IA-based long-course MDR/RR-TB regimens cost US$4,439 per patient over the 10-year horizon. Replacing IAs with bedaquiline cost US$4,647 and averted 0.17 disability adjusted life years (DALYs) for an incremental cost effectiveness ratio (ICER) of US$1,242 per DALY averted.[207]

The poor efficacy of current IA-based regimens is not the only concern: a meta-analysis of adverse drug reactions (ADR) during MDR/RR-TB treatment in high HIV prevalence settings reported 83% (95%CI: 82-84) of all patients experienced at least one event.[208] Second-line IAs are thought to be the cause of many of the known toxicities, including high rates of nephrotoxicity and electrolyte imbalance (e.g. hypokalaemia).[1,130] Additionally, IAs are associated with high rates of ototoxicity including tinnitus, vertigo, and hearing loss.[1,116,130,192] Hearing loss, which affects between 2.6 to 61.5% of patients, ranges from loss of high frequency tones to profound deafness and can be permanent.[116]

To understand how the disability from hearing loss and the costs of managing other ADR impact the ICER calculations for an injection-free regimen based on bedaquiline, we adapted a previously established Markov model[207,220] to include the toxicity profile of both regimens.

Methods

The model was parameterized with costs, transition probabilities, and initial populations distributions for the South African public health sector[207,220] and built in TreeAge Pro 2015 (TreeAge Software, Williamstown, MA). Although patients may incur costs for transport, food or lodging, all MDR/RR-TB treatment in South Africa is provided free of charge through the public-sector health facilities. A provider perspective, that of the SA public health sector, was assumed. Future costs and effectiveness were discounted at 3%.[205] A time horizon of 10 years was assumed to capture the full length of treatment for patients plus some impact of permanent disability.

Two MDR/RR-TB treatment strategies were modelled: 1) IA-based regimen for MDR/RR-TB (6 months kanamycin, 18 months moxifloxacin, terizidone, ethionamide, and pyrazinamide) and 2) bedaquiline-based regimen for all MDR/RR-TB, where bedaquiline replaces kanamycin. Patients with initial intolerance or additional second-line drug resistance including extensively drug resistant (XDR) TB at initiation were excluded in all scenarios.

MDR/RR-TB Markov model

Monthly transition probabilities (Table 8-1) for 11,192 HIV-negative and HIV-infected patients (the SA 2015 MDR/RR-TB initiating cohort[2]). for eachz health state were based upon the original model analysis[207] derived from the SA NTP drug-resistant TB case register[199] using Stata version 14 (College Station, TX, USA). Markov health states (Figure 8-1) represent initiation of MDR/RR-TB treatment (Month 0), intensive phase (Months 1-5), and culture negative continuation phase of treatment (Months 6-18). In the model, patients failing to sputum culture convert after 6 months of MDR/RR-TB treatment transition to XDR-TB treatment; XDR-TB patients failing to culture convert after 6 months of treatment transition to palliative care. It was assumed that patient could experience either a moderate ADR or a severe or serious ADR during months 1 to 5.[122] HIV-infected patients naïve to ART at MDR/RR-TB initiation experienced a relative increase in risk of ADR and severe ADR (sub-hazard ratio: 3.07 relative to HIV-negative).[194] From any state, patients can be lost from treatment or die. After successful treatment completion, patients experience background mortality. HIV-infected patients continue to incur the costs of ART after completion of MDR/RR-TB treatment. In the model, it was assumed bedaquiline increased the proportion culture converting by a hazard ratio of 2.44 (95%CI: 1.57, 3.80).[30] Bedaquiline regimens were modelled to have 28% fewer moderate and 60% fewer severe, or serious ADR than IA-based regimens[220]; the assumption was tested in sensitivity analysis. Based upon a South African study, IA-based MDR/RR-TB regimens were assumed to have 40% permanent profound hearing loss from month six.[192]

Ingredients costing

Provider costs (Table 8-2) for MDR/RR-TB treatment, derived from public-sector price lists for medicines, laboratory tests, and procedures or from literature for clinic visits and hospitalization were also as reported in the original model.[207] Costs were collected in ZAR and converted to USD using the average monthly exchange rate for 2016, 14.74 ZAR/USD.[27] Costs were inflated to 2016 ZAR if applicable using the consumer price index for medical services.[28] The full 6 months' course of bedaquiline at US$675 was modelled for all bedaquiline-initiating patients. The distribution of ADR management costs during IA regimens was extracted from a separate study.[220] For the bedaquiline-based regimen, the costs of IA-associated ADR were excluded from the weighted average.

Disability weighting

Disability weights for TB (0.368, 95%CI: 0.260 to 0.430) were extracted from a South Africa study based on the Global Burden of Disease (GBD) methodology.[79] TB/HIV co-infection (0.408, 95%CI: 0.274 to 0.549), AIDS with no ART (0.582, 95%CI: 0.406 to 0.743), and HIV-infected on ART (0.078, 95%CI: 0.052 to 0.111) were extracted from the 2013 GBD study.[75] For hearing loss, effectiveness was adjusted using the disability weighting for moderate hearing loss estimated from the South African survey (0.357, 95%CI: 0.240 to 0.437).[79] To avoid double counting, disability from all other

ADR, e.g. anaemia, peripheral neuropathy, kidney or liver injury that overlapped completely with MDR/RR-TB treatment, was not included in the model. Disability from co-morbidity, e.g. profoundly deaf and HIV-infected on ART, was calculated using a multiplicative model.[80] DALYs were calculated as 1- the sum of time spent in each health state after weighting for disability.

Sensitivity analysis

Incorporation of the toxicity profile into the model increased the number of input parameters and increased the variability of outcomes for an individual patient in terms of what ADR would be experienced, at what frequency and severity. In line with recommendations for managing parameter uncertainty[221], the Markov model was adapted in order to use probabilistic uncertainty analysis where model parameters are sampled from distributions through running 100 Monte Carlo simulations for the cohort.

Results

Without adjustments made for the toxicity profile, i.e. without including costs of ADR management and disability burden, the mean expected value of sampled trials for the IA regimen was a cost of US$4,614 (95%CI: 3,821-6,496) and resulted in 4.88 DALYs (95%CI: 4.18-5.61) over the 10-year horizon (Table 8-3). The mean expected bedaquiline regimen cost was $4,739 (95%CI: 4,077-5,463) and resulted in 4.64 DALYs (95%CI: 3.96-5.36), for an ICER of US$516 per DALY averted. Incorporating the cost of ADR management increased the cost of the IA regimen by US$381 per patient and the bedaquiline regimen by US$161 per patient, a reduction of $221 in the incremental cost of using bedaquiline. Incorporating permanent hearing loss resulted in 0.72 more DALYs for the IA regimen, for a total of 5.60 DALYs. As a result, the bedaquiline regimen absolutely dominated the IA regimen, saving $96 and averting 0.96 DALYs per patient over the modelled period.

The resulting ICERs of the probabilistic uncertainty analysis were plotted on cost-effectiveness plane (Figure 8-2). The distribution of the incremental cost of bedaquiline regimens shifted right (more effective) and incremental costs shifted down (less costly) relative to the IA regimens once toxicity profile was added. The toxicity profile also increased results dispersion. Figure 8-3 shows the cost-effectiveness acceptability curves, 80% of the sampled distributions resulted in an ICER of <$2,100 per DALY averted when the ADR costs and disability were not considered. Once adjusted for toxicity, 80% of the sampled distributions resulted in an ICER below $150 per DALY averted and 62% of the distributions resulted in an ICER that was cost saving (below $0) and more effective.

Discussion

The public sector roll-out of bedaquiline in South Africa was among the evidence considered by the WHO's guidelines development group in issuing revised recommendations for bedaquiline in 2017.[32] No update was provided for the cost-effectiveness analysis initially done for the 2013 interim recommendations.[32] Cost-effectiveness studies published since the initial exploratory analysis have focused on savings achieved from the high rates of culture conversion using bedaquiline and therefore shorter duration of hospitalization lead it to be cost-effective or even cost saving compared to the standard regimen.[52,53,55,56] The high rate of ADR during MDR/RR-TB treatment is well established [1,14,208], yet cost-effectiveness analyses of new treatment regimens have not explicitly modelled the costs or disability associated with toxicity profiles.[52,53,55,56]

Previous cost-effectiveness analyses also did not explicitly model bedaquiline replacing the IA. With growing evidence that bedaquiline is both effective and safe, including in the WHO guidelines review [32], a 15-country multi-centre study[138], clinical researchers[196], policy makers[46] and advocates[1] are considering whether bedaquiline or delamanid should replace second-line IA as core MDR/RR-TB drugs. As of 2015 in South Africa, patients with either second-line drug resistance or demonstrated toxicity to the standard MDR/RR-TB injection-based treatment are eligible for bedaquiline regimens.[19] The analysis presented here demonstrates that toxicity profile of the IAs can significantly impact the calculation of the ICER for new regimens. Once the toxicity profile was included in the analysis, a bedaquiline regimen is both cost saving ($96 per patient) and more effective (averted 0.96 DALYs). For the sake of understanding, this model simplified into distinct regimens what has become a more fluid and incremental choice. Within the SA NTP, bedaquiline can be initiated once either resistance or intolerance, such as ototoxicity, is detected. For ototoxicity, however, this change may be too late as hearing loss can progress even after the IA is withdrawn.[1,192] Thus, the more conservative use of bedaquiline only after other options have been exhausted may not realize the cost savings or DALYs averted estimated here.

This analysis built upon a previously established Markov model, where the ICER for a bedaquiline for all approaches was reported as $1,242 per DALY averted[207], more than twice the ICER of $516 reported here. The major difference for the base models (i.e. not adjusted for ADR) was the use of probabilistic uncertainty analysis, which resulted in a smaller incremental cost and more DALYs averted.[207] The inclusion of ADR management, where the frequency, severity, and costs of ADR experienced are not easily measured or included in an analysis increased the model uncertainty further. WHO-recommended standard long- and short-course regimens for MDR/RR-TB were not established via prospective, randomized clinical trial but rather rely on observational studies.[1,14] Reporting of adverse events and ADR in observational and retrospective studies may reflect a reporting bias, where only serious or severe events are noted or only events associated with a particular drug of interest. Meta-analysis of the observational studies is further limited by a lack of common terminology and definitions to determine whether variability was due to differences in measurement and study design or differences in regimen or patient characteristics.[5,130,199] In the prospective Phase 2b trial where bedaquiline was added to the standard IA regimen the bedaquiline and placebo arms had statistically similar rates of adverse events (99% and 98%, respectively) and similar rates of ADR (70% and 69%), which suggests that bedaquiline did not add to the already high ADR burden.[30]

The higher relative effectiveness for an all oral regimen estimated in this analysis is because IAs are associated with the high levels of ototoxicity.[1,115,130] Permanent and profound hearing loss reduces the overall effectiveness of the IA treatments when disability weightings are applied beyond the completion of the MDR/RR-TB treatment. The profound hearing loss disability weighting used here was from a South African survey; the weighting was nearly twice as high as the global study.[75,79] The preference or value of a health state such as hearing loss may differ across contexts (e.g. South Africa compared to Europe), particularly for resource-limited contexts where coping mechanisms may be less available. Both the potential underestimation of effects of hearing loss on quality of life and the inclusion of only guidelines-based provider costs suggest that the ICER for a safer, more tolerated treatment regimen for MDR/RR-TB presented here is a conservative estimate.

Study limitations

Similar to other cost-effectiveness analyses that have been published for bedaquiline[52,53,55,56], we used the same mortality rates for bedaquiline regimens as for IA regimens even though the Phase 2b trial showed a statistically significant imbalance in mortality with more deaths occurring in the patients on bedaquiline compared to placebo (12.7% and 2.5%, respectively).[30] The revised 2017 WHO bedaquiline guidance indicated the Phase 2b findings had potentially very serious bias for imprecision from the small patient numbers and also serious bias for indirectness; none of the deaths in the bedaquiline arm were attributed to bedaquiline.[32] The revised WHO guidance also reported on promising observational results from South Africa (the same cohort used for this analysis) indicating that use of bedaquiline may result in reduced, rather than increased, mortality.[32] However, until completion of the phase 3 study for bedaquiline, the uncertainty of the mortality is a limitation of this and other cost-effectiveness analyses for bedaquiline. Other limitations are common to the initially established model: we did not include a measure of either on-going transmission or increased resistance profile due to ADR and excluded patient direct and opportunity costs.[207]

Finally, in order to use data from implementation and roll-out, the analysis presented here is comparison of the long-course (18 to 24 months) IA regimen and the bedaquiline regimen used in South Africa prior to the end of 2016. SA NTP MDR/RR-TB patients without second-line resistance are now eligible for the short-course regimen, which was recommended by the WHO in 2016.[14] While waiting for the results of studies using short-course bedaquiline and delamanid regimens[1], the results of this cost-effectiveness analysis adds more weight to the urgency to re-evaluate the use of IA in the treatment of MDR/RR-TB.

Conclusion

Current injection-based long-course standard treatment for MDR/RR-TB is associated with high rates of adverse drug reactions, including the possibility of permanent hearing loss. Based on this modelling of bedaquiline regimens in South Africa, new drugs that can allow for an all oral MDR/RR-TB treatment regimen may be cost saving and more effective than current injection-based regimens, if cost-effectiveness analyses incorporate the costs and burden of the expected adverse drug reactions.

Tables

Table 8-1. Markov model monthly transition probabilities and proportions

Model inputs	Patients	Mean values
Mortality		**Transition probability[a]**
	MDR/RR-TB, HIV-negative	0.006 to 0.018[c]
	MDR/RR-TB, HIV-infected, on ART	0.009 to 0.033 [c]
	MDR/RR-TB, HIV- infected, no ART	0.055
	XDR-TB[d], HIV-negative	0.022 to 0.022 [c]
	XDR-TB[d], HIV- infected, on ART	0.026 to 0.037 [c]
After treatment	All patients	0.0005 to 0.001[200]
Loss from treatment		**Transition probability[a]**
	MDR/RR-TB, HIV-negative	0.010 to 0.016
	MDR/RR-TB, HIV- infected, on ART	0.009 to 0.016 [c]
	MDR/RR-TB, HIV- infected, no ART	0.016
	XDR-TB[d], HIV-negative	0.010 to 0.011[c]
	XDR-TB[d], HIV- infected, on ART	0.005 to 0.008 [c]
Return after loss	Month 3-12	.05 [b]
Culture conversion		**Proportion**
Cumulative at 6 months	MDR/RR-TB, All HIV status	88.4%
Cumulative at 6 months	XDR-TB[d], All HIV status	76.8% [30,34]
Relative effectiveness	Bedaquiline regimens	2.44 (95%CI: 1.57, 3.80) [30]
Initial distribution		**Proportion[a]**
HIV status	HIV-negative	28.3%
	HIV-positive	71.7%
	HIV-positive, no ART	40% of the 71.7%
Hospitalization	All RR-TB, All HIV status	20.6% [128]
Adverse drug reactions		**Transition probability**
Any moderate to severe	All RR-TB	0.183, excluding severe [208]
Any severe or serious	All RR-TB	0.052 [208]
Relative risk of ADR	All RR-TB, if HIV+, newly on ART (<6 months)	Sub-hazard ratio: 3.07 (95%CI: 1.46,6.46) relative to HIV-negative patients [194]
Reduction of ADR if no kanamycin/amikacin	MDR/RR-TB, All HIV status	28%, assumption based on relative frequency ADR attributed to second-line injectables [220]
Profound hearing loss	All RR-TB, All HIV status	40% [192]

MDR/RR-TB: Multi-drug resistant or rifampicin-resistant tuberculosis; XDR-TB: extensively drug resistant TB; HIV: human immunodeficiency virus; ART: anti-retroviral therapy; 95%CI: 95% confidence interval

[a] Initial patient distribution and transition probabilities generated from South African EDRweb cohort 2012-2014. Initial patient distribution and transition probabilities are the same as previously published model.[207]

[b] Calibrated assumption

[c] Value dependent on treatment phase

[d] All XDR-TB in model is among patients in whom MDR/RR-TB treatment failed; patients diagnosed with XDR-TB from onset are excluded from the model.

Table 8-2. Monthly unit costs in 2016 USD provider (payer) perspective and sampled distribution

Treatment strategy	Patients	Mean monthly cost [a]	Distribution
TB components			
Medications (anti-TB, antiretroviral therapy, and pyridoxine)			
Injection-based[b]	MDR/RR-TB, HIV-negative	\$83.79 to \$100.96[d]	Normal, +/- 25%
	MDR/RR-TB, HIV-infected, on ART	\$93.67 to \$112.88[d]	Normal, +/- 25%
	XDR-TB, HIV-negative	\$301.67 to \$520.77[d]	Normal, +/- 25%
	XDR-TB, HIV-infected, on ART	\$311.55 to \$532.69[d]	Normal, +/- 25%
Bedaquiline-based[c]	MDR/RR-TB, HIV-negative	\$83.79 to \$205.94[d]	Normal, +/- 25%
	MDR/RR-TB, HIV-infected, on ART	\$93.67 to \$216.86[d]	Normal, +/- 25%
	XDR-TB, HIV-negative	\$301.67 to \$564.21[d]	Normal, +/- 25%
	XDR-TB, HIV-infected, on ART	\$311.55 to \$575.13[d]	Normal, +/- 25%
TB monitoring (sputum smear microscopy, sputum culture, resistance testing, and chest x-ray)			
All strategies	All RR-TB, all HIV status	\$9.76 to \$36.82[d]	Normal, +/- 25%
		Clinic visits and hospital inpatient days	
Injection-based[b]	Hospitalized, all RR-TB, all HIV status	\$ 2,882.52	Normal, +/- 25%
	All RR-TB, all HIV status	\$23.09 to \$98.12[d]	Normal, +/- 25%
Bedaquiline-based[c]	Hospitalized, all RR-TB, all HIV status	\$ 2,882.52	Normal, +/- 25%
	All RR-TB, all HIV status	\$23.09 to \$31.35[d]	Normal, +/- 25%
ADR components			
ADR monitoring (guidelines-based laboratory screening, audiology, and electrocardiograms)			
Injection-based[b]	All RR-TB, all HIV status	\$2.84 to \$28.14[d]	Normal, +/- 25%
Bedaquiline-based[c]	All RR-TB, all HIV status	\$2.84 to \$25.99[d]	Normal, +/- 25%
Mean estimated costs of ADR management (ancillary medication for ADRs, clinic and hospitalization for ADR, laboratory tests and investigations required for managing and resolving ADR)			
Injection-based[b]	MDR/RR-TB, moderate ADR	\$135.76 [220]	Gamma, std dev
	MDR/RR-TB, severe or serious ADR	\$521.29 [220]	Gamma, std dev
	XDR-TB, moderate ADR	\$156.05 [220]	Gamma, std dev
	XDR-TB, severe or serious ADR	\$1,039.06 [220]	Gamma, std dev
Bedaquiline-based[c]	MDR/RR-TB, moderate ADR	\$105.68[e] [220]	Gamma, std dev
	MDR/RR-TB, severe or serious ADR	\$464.83[e] [220]	Gamma, std dev
	XDR-TB, moderate ADR	\$130.42[e] [220]	Gamma, std dev
	XDR-TB, severe or serious ADR	\$946.44[e] [220]	Gamma, std dev

MDR/RR-TB: Multi-drug resistant or rifampicin-resistant tuberculosis; XDR-TB: extensively drug resistant TB; HIV: human immunodeficiency virus; ART: anti-retroviral therapy; SA NTP: South African National TB Programme; std dev: standard deviation

[a] Ingredient costs were collected in ZAR and converted to USD using the average monthly exchange rate for 2016, 14.74 ZAR/USD.[27] Costs were inflated to 2016 ZAR if applicable using the consumer price index for medical services.[28] Drug costs from the Master Procurement Catalogue of the Essential Drug Programme, South African National Department of Health (2016). Laboratory test costs from the South African National Health Laboratory Service State Price List (2015). Procedures and investigation costs from the South African National Department of Health Uniform Patient Fee Schedule (2016). Ingredient costs were previously published with the original model.[207]

[b] MDR/RR-TB patients access standard regimen of 6 months kanamycin, moxifloxacin, terizidone, ethionamide, and pyrazinamide and 12 months moxifloxacin, terizidone, ethionamide, and pyrazinamide. If fail MDR/RR-TB treatment, treated with XDR-TB regimen consisting of 6 months capreomycin, linezolid, moxifloxacin, terizidone, ethionamide, clofazimine, para-aminosacylic acid, and pyrazinamide and 18 months linezolid, moxifloxacin, terizidone, ethionamide, clofazimine, para-aminosacylic acid, and pyrazinamide.

[c] MDR/RR-TB patients access bedaquiline regimen consisting of 6 months bedaquiline, levofloxacin, terizidone, ethionamide, and pyrazinamide and 12 months moxifloxacin, terizidone, ethionamide, and pyrazinamide. If fail MDR/RR-TB treatment, treated with XDR-TB regimen consisting of 6 months bedaquiline, linezolid, levofloxacin, terizidone, ethionamide, clofazimine, para-aminosacylic acid, and pyrazinamide and 18 months linezolid, moxifloxacin, terizidone, ethionamide, clofazimine, para-aminosacylic acid, and pyrazinamide.

[d] Value dependent on treatment phase

[e] Excluding ADR associated with injectables

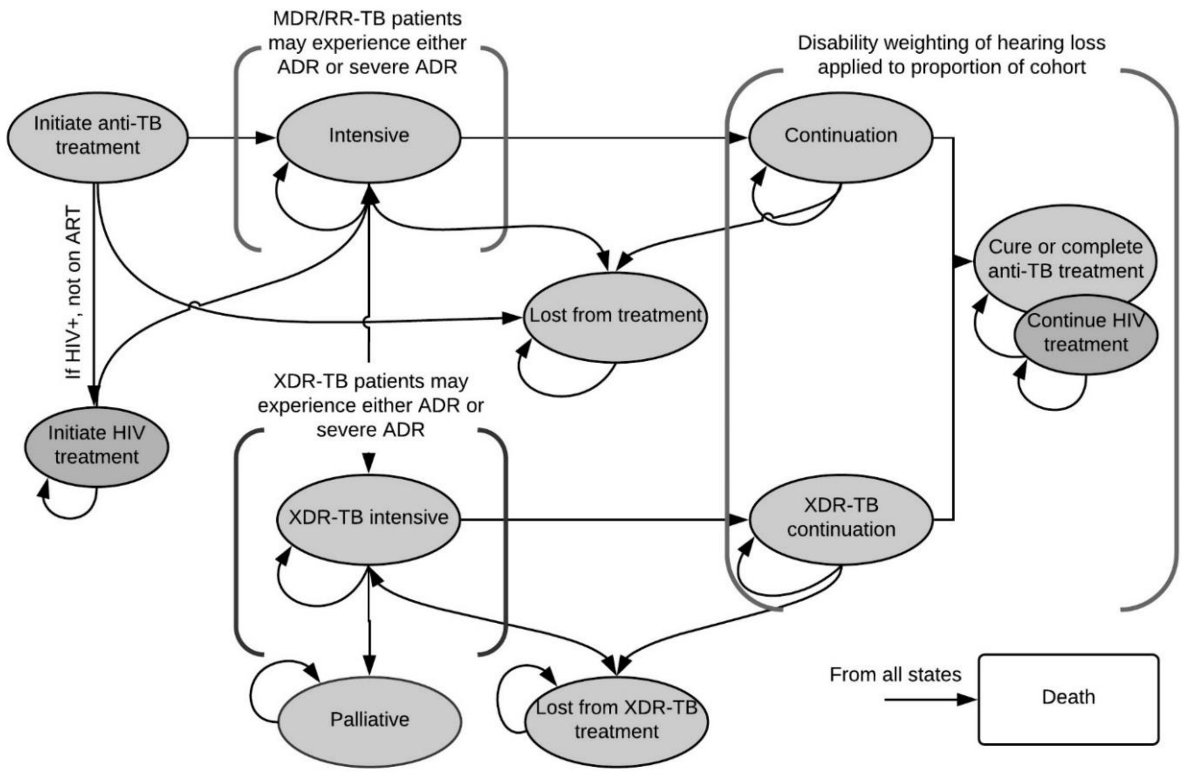
Table 8-3. Impact of including toxicity profile in the incremental cost effectiveness ratio of replacing kanamycin with bedaquiline for MDR/RR-TB treatment, 10-year horizon

	Cost 2016 USD (sd)	Incremental cost (sd)	Disability adjusted life years (sd)	DALYs averted (sd)	Cost per DALY averted
No toxicity profile					
Injection-based	$4,614 ($435)	Reference	4.88 (0.36)	Reference	
Bedaquiline-based	$4,738 ($358)	$124 ($267)	4.64 (0.36)	0.24 (0.12)	$516
Adjusted for toxicity					
Injection-based	$4,996 ($453)	Reference	5.60 (0.34)	Reference	Dominated
Bedaquiline-based	$4,899 ($365)	- $96 ($281)	4.64 (0.36)	0.96 (0.18)	

ADR: adverse drug reaction; XDR-TB: extensively drug resistant TB; sd (standard deviation)

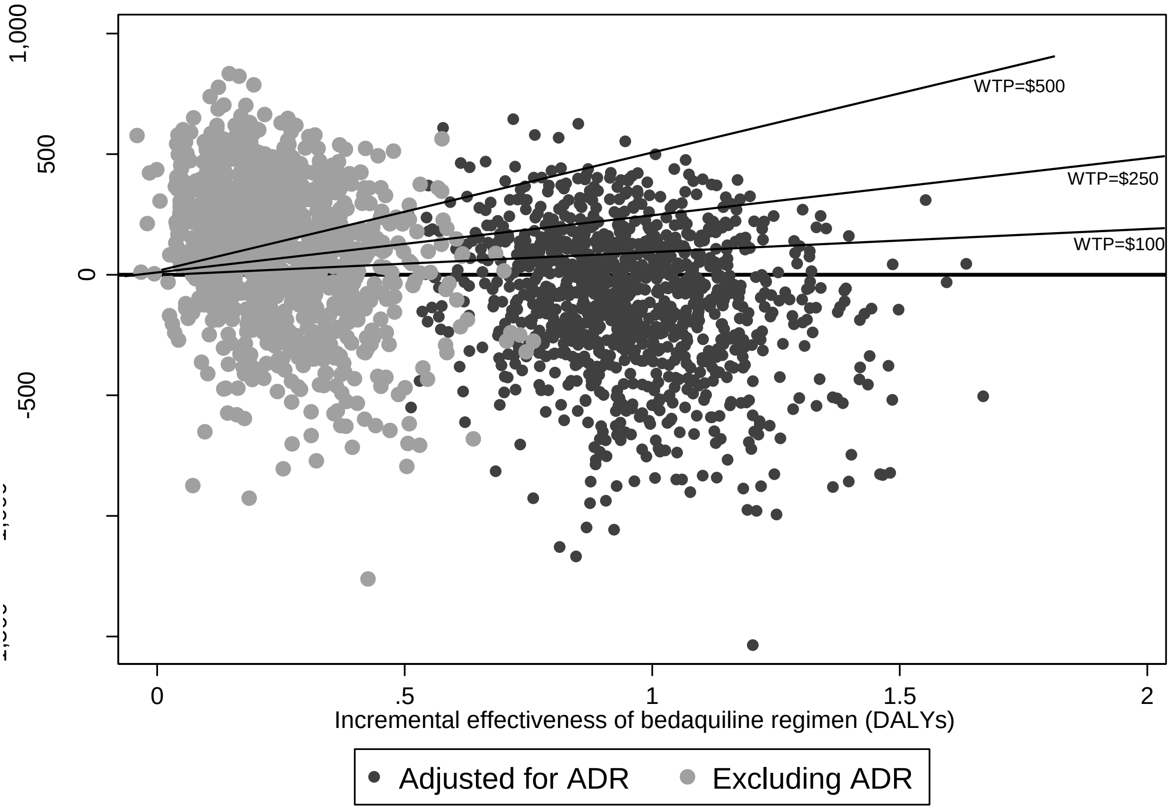
Figures

Figure 8-1. MDR/RR-TB state transition diagram of Markov health state model adjustments for toxicity profile



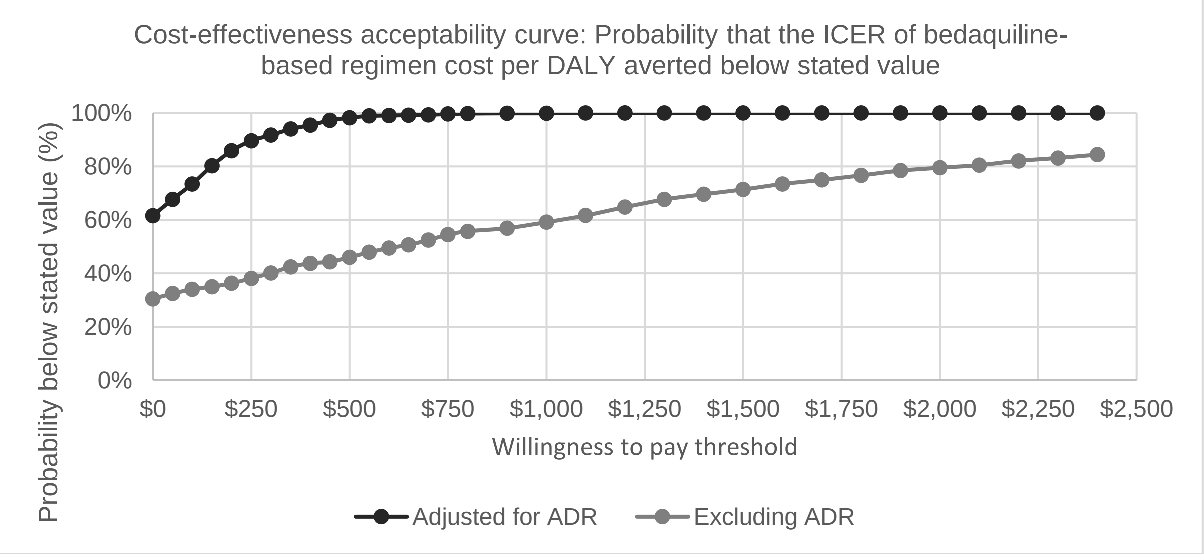
ADR: adverse drug reaction; MDR/RR-TB: Multi-drug resistant or rifampicin-resistant tuberculosis; XDR-TB: extensively drug resistant TB; HIV: human immunodeficiency virus; ART: anti-retroviral therapy

Figure 8-2. Cost-effectiveness plane, incremental cost effectiveness of bedaquiline-based regimen compared to injection-based regimen in DALYs averted, before and after adjusting for toxicity



WTP: Willingness to pay; ADR: Adverse drug reaction; DALY: Disability adjusted life years

Figure 8-3 Cost-effectiveness acceptability curve: probability that incremental cost effectiveness of bedaquiline-based regimen compared to injection-based regimen was below stated value, before and after adjusting for toxicity



ADR: Adverse drug reaction; DALY: Disability adjusted life years; ICER: Incremental cost-effectiveness ratio

9 DISCUSSION AND CONCLUSIONS

9.1 DISCUSSION

The aim of this thesis was to understand whether the inclusion of the costs and burden of ADR associated with MDR/RR-TB treatment regimens would impact the incremental cost-effectiveness of a bedaquiline-based regimen compared to the injectable-agent based regimen. A bedaquiline-based regimen for all MDR/RR-TB patients compared to an IA-based regimen was found to have a mean ICER of $516 Chapter 8, using probabilistic sensitivity analysis) to $1,242 (Chapter 6), estimated at means) per DALY averted using the standard Markov model. This finding, set in the context of the SA NTP's ambulatory model of care for MDR/RR-TB, expanded the body of evidence that bedaquiline-based regimens are cost-effective beyond the previously described settings where MDR/RR-TB patients are hospitalized until culture conversion.[31,52–56] Costs for both regimens increased and effectiveness decreased for the injection-based regimen once the model was adjusted for toxicity. The resulting ICER of a bedaquiline-based regimen was cost saving ($96/patient) and more effective (0.96 DALYs averted) after adjusting for ADR, as described in Chapter 8. The analysis presented here demonstrates that toxicity profile of the IAs can significantly impact the calculation of the incremental cost-effectiveness ratio of adopting new MDR/RR-TB treatment regimens.

The public sector roll-out of bedaquiline in South Africa was among the evidence considered by the WHO's guidelines development group in issuing revised recommendations for bedaquiline in 2017.[32] However, no update was provided for the cost-effectiveness analysis initially done for the 2013 interim recommendations, even though the guidelines noted that the simplifying assumptions of how the cost-effectiveness analysis addressed the burden of ADR was a limitation.[31,32] The high rate of ADR during MDR/RR-TB treatment is well established [1,3,14,208] and was confirmed in this thesis research (Chapters 4 and 5), yet cost-effectiveness analyses of bedaquiline have not explicitly attempted to measure the incremental costs or effectiveness of the different toxicity profiles.[52–55,94] The pilot trial of an 8-week dose of bedaquiline versus placebo added onto the standard injection-based regimen to test the tolerability of bedaquiline found no statistically significant differences in the frequency or severity of adverse events in the bedaquiline arm with the exception of mild to moderate nausea.[29] In the prospective Phase 2b trial where bedaquiline was added to the standard IA regimen the bedaquiline and placebo arms had statistically similar rates of adverse events (99% and 98%, respectively) and similar rates of ADR (70% and 69%), also suggesting that bedaquiline did not add to the already high ADR burden.[30] In the BCAP compassionate access programme implemented by the SA NTP from 2012 to 2015, severe adverse events reported were not attributed to bedaquiline.[34] Rates of severe or serious adverse events in the BCAP cohort were noted to be similar to other compassionate treatment access programmes and in line with high rates known to be associated with the standard of care regimens.[34,105,222] There is growing evidence that bedaquiline is both effective and safe, including in the WHO guidelines review [32] and a 15-country multi-centre study [138]. With evidence of safety and effectiveness clinical researchers [196], policy makers [46,47] and advocates [1] are considering whether bedaquiline and delamanid should replace second-line IA as core MDR/RR-TB drugs. This advocacy for use of bedaquiline was despite the WHO finding that the cost-effectiveness of bedaquiline was "ambiguous in low-income settings" and possibly unaffordable beyond a donation program to low-income countries.[32] The finding that a bedaquiline-based regimen is both more effective and cost-saving therefore removes an important barrier to further roll-out of an injection-free regimen for treatment of MDR/RR-TB, not just in South Africa.

Discussion points and conclusions relevant to the results of each of the analyses were presented in the specific manuscripts which were presented in the results chapters (Chapters 3 to 8, Manuscript 1 to 6, respectively). The following summary and discussion provides a cumulative summary of the thesis findings in respect to the objectives above as well as the unanswered questions from the literature review (Chapter 2, Literature Review). For each of the main findings, a discussion of the generalizability of these findings to other contexts outside of South Africa or beyond the specific comparison of drug regimens is also included.

Aims of the research

Chapter 1, the Introduction and Overview, provided an introduction to the overall aims and objectives of this research, based upon the approved proposal for the PhD research.

As noted in Chapter 1.2 the objectives of this thesis were to:

1. To describe the types, frequency, and severity of ADRs experienced during MDR/RR-TB treatment.
2. To evaluate the provider cost of prevention, monitoring, and management of ADRs incurred during MDR/RR-TB treatment, including drugs, hospitalization, laboratory monitoring, and clinic visits.
3. To estimate the ICER of bedaquiline treatment regimen compared to standard of care (SOC) MDR/RR-TB treatment regimen in SA.
4. To estimate the ICER of bedaquiline compared to SOC regimen having included the cost and burden of ADR during MDR/RR-TB treatment.

Each of the objectives builds on the previous, in that the estimated ICER of a bedaquiline-based regimen compared to an IA-based regimen for the treatment of MDR/RR-TB having adjusted for the toxicity of the regimens requires first to describe the expected toxicity and costs. Thus, if each of the objectives is achieved, the overall aim of the study would also be reached. The overall aim of the research was to use the introduction of bedaquiline within the SA NTP as a case study to determine whether the inclusion of the cost and burden of ADR associated with MDR/RR-TB treatment affects the ICER of new treatment regimens.

Literature review

Chapter 2 presented a comprehensive literature review covering the basis for using cost-effectiveness analysis for health policy decision making (Chapter 2.3), the state of the MDR/RR-TB epidemic in South Africa, including standard of care, long-course, IA-based MDR/RR-TB treatment guidelines and the introduction of bedaquiline (Chapter 2.4), measurements of effectiveness of MDR/RR-TB treatment (Chapter 2.5), and the burden of ADR during MDR/RR-TB treatment (Chapter 2.6). The chapter summarized current literature and presented unanswered questions that framed the PhD research.

- Do ADR occur at similar frequency, duration, and severity when HIV-infected or when on HIV treatment?

- What is the cost of ADR management, as a function of the expected costs and the expected frequencies of ADR during MDR/RR-TB treatment?
- What is the cost-effectiveness of a bedaquiline-based regimen rather than an injection-based regimen?
- What is the timing of outcomes that occur before 18-24 months? Do transition probabilities differ by HIV and ART status?
- Does the inclusion of the cost and burden of ADR associated with MDR/RR-TB treatment affect the incremental cost-effectiveness of bedaquiline treatment regimen compared to the current kanamycin-based treatment?

Timing of mortality during MDR/RR-TB treatment

Chapter 3 described the timing of mortality during MDR/RR-TB treatment based upon analysis of the SA national electronic drug-resistant TB case register, the EDRweb. The timing and risk factors for mortality, including the differential risks of mortality for HIV-negative, HIV-infected patients on ART, and HIV-infected patients not on ART, were used for the development and parameterization of the Markov health state model used for the analysis in Chapters 6-8. This statistical analysis was published in the International Journal of Tuberculosis and Lung Disease in October 2017 (doi: 10.5588/ijtld.17.0202). The results of this analysis was presented as the first of the results chapters because of the unanswered questions identified through the literature review (Chapter 2). Additionally, the reviewed literature left unanswered whether the risk of mortality over time would differ by HIV and ART status, or whether the increased risk of mortality for HIV-infected patients [13,186,223] was a proportional hazard. These questions needed to be resolved in order to build a Markov health state model that reflected the South African context of a high prevalence of HIV/TB co-infection.

The statistical analysis, a retrospective review of routinely captured data in the South African national drug-resistant TB case register (EDRweb) and matched to the vital statistics register, found that mortality is highest during the first weeks of MDR/RR-TB treatment. Approximately 1 in every 5 patients who starts MDR/RR-TB treatment in South Africa dies during treatment.[2,58] As reported in Manuscript 1, across the national cohort registered in the EDRweb, nearly half (44.2%) of the deaths occurred within the first 3 months of the 24 months of MDR/RR-TB treatment. The estimated incidence rate for all patients was 8.99 deaths per 1,000 person-weeks before week 12, 5-times the 1.78 deaths per 1,000 person-weeks after week 24.

The findings of this analysis of the EDRweb led to the structure of the Markov model built and reported on in Chapters 6 to 8 reflecting three health states while on MDR/RR-TB treatment – initiation, intensive phase, and continuation phase – with monthly time steps. The findings of this analysis also led to the a population distribution in the Markov model that reflected patients who are HIV-negative, HIV-positive on ART at MDR/RR-TB initiation, and HIV-positive ART naïve at MDR/RR-TB initiation. Because the risks and timing of death during MDR/RR-TB treatment in South Africa differ by HIV status, inclusion of separate health states and transition probabilities for HIV-infected was important to be able to generate estimates for the context.

Based upon this model structure, the cohort described in Chapter 3 was also used to create the monthly transition probabilities for each of the three sub-populations for each of the three treatment phases. Although the manuscript reported only on the results of mortality over time, transition probabilities were also extracted from this cohort for other health states of loss from treatment and treatment failure.

Risk of severe ADR during MDR/RR-TB treatment

Chapter 4 reports on the results of a ADR-focused clinical file review of two out-patient MDR/RR-TB clinic cohorts in Johannesburg, South Africa. Although a retrospective review, the clinical data captured provided more in-depth understanding of the ADR experienced. This analysis was designed to address the first objective of the overall research, namely: To describe the types, frequency, and severity of ADRs experienced during MDR/RR-TB treatment.

The statistical analysis presented in used competing risk analysis to separate out the sub-hazard ratio of severe ADR after accounting for the very high early mortality of HIV-infected patients newly initiating ART (as described in chapter 3). This statistical analysis was published in *BMC Infectious Diseases* in October 2016 (doi: 10.1186/s12879-016-1933-0). Similarly to the national cohort described in Chapter 3, for the Johannesburg MDR/RR-TB treatment cohorts analysed in Chapter 4, the risk of death was highest in the first 90 days, especially for HIV-positive patients not on ART at the initiation of MDR/RR-TB treatment.

For these two Johannesburg-based out-patient (ambulatory) MDR/RR-TB cohorts described in Chapter 4, 19.0% of patients had at least one severe adverse event. After accounting for the competing risk of high early mortality for HIV-positive patients not on ART at the start of MDR/RR-TB treatment, the analysis presented in Chapter 4 found that HIV-positive patients who initiated ART with MDR/RR-TB treatment were approximately 3 times more likely to experience a severe ADR (sHR: 3.07, 95% CI: 1.46 to 6.46).

Prevalence of moderate and severe ADR during MDR/RR-TB treatment

Chapter 5 presents the results of a systematic review and meta-analysis on the types, frequency, and severity of ADR during MDR/RR-TB treatment in cohorts where at least 20% of the patients were HIV-infected. As found during the overarching literature review in Chapter 2, the prevalence of ADR during MDR/RR-TB treatment varies across different cohorts and settings. Additionally, it was unknown whether patients co-infected with HIV were at a higher risk of ADR during MDR/RR-TB treatment. The review was published in the Journal of Antimicrobial Chemotherapy in April 2017 (doi: 10.1093/jac/dkx107). Similar to Chapter 4, this analysis was designed to address the first objective of the overall research, namely: To describe the types, frequency, and severity of ADRs experienced during MDR/RR-TB treatment. A meta-analysis approach was chosen in order to test the generalizability of the findings from the Johannesburg cohorts presented in Chapter 4 and to expand the analysis to include moderate ADR, which were not routinely noted in the medical files reviewed for the analysis presented in Chapter 4.

The systematic review and meta-analysis found that ADR are frequent during MDR/RR-TB treatment in high prevalence HIV settings, especially for HIV-infected patients who are newly initiating ART. In the systematic review presented as Chapter 5, of the 24 included studies, 10 counted the patients who experienced at least 1 ADR and could be included in the main meta-analysis; for these studies the pooled proportion of patients experiencing an ADR was 83% (95%CI: 82% to 84%). Among the studies which disaggregated reported ADR by severity, the pooled proportion of patients experiencing at least one severe or worse ADR was 24% (95%CI: 21% to 27%). Similar to previously published meta-analyses on ADR during MDR/RR-TB treatment, the meta-analysis of the observational studies was limited by a lack of common terminology and definitions to determine whether variability was due to differences in measurement and study design or differences in regimen or patient characteristics.[3,5,130,208] Although the lack of consistency in reporting limited the meta-analysis of specific events to the two most commonly described in specific studies – ototoxicity and hypothyroidism – the systematic review process did identify studies with sufficient detail in reporting to be used for extracting the frequencies of events which were used in Chapter 7 to created weighted average costs.

Cost-effectiveness of bedaquiline compared to injection-based regimen

Chapter 6 is the first of three results chapters using a newly established Markov model for MDR/RR-TB treatment. This model includes separate health states for initiation of MDR/RR-TB treatment, intensive phase, continuation phase, and completion. The model was parameterized using the cohort analysed and described in Chapter 3, bottom up ingredients costing from the perspective of the provider – the SA NTP – and uses separate transition probabilities from all health based upon HIV and ART status. The Markov model and analysis presented in Chapter 6 was designed to meet the third objective of the overall thesis research, namely: To estimate the ICER of bedaquiline treatment regimen compared to standard of care (SOC) MDR/RR-TB treatment regimen in SA.

In Chapter 6, the use of bedaquiline as a replacement for the injectable agents is found to be cost-effective and affordable, but more expensive than the injection-based standard of care regimen and for a relatively modest gain in effectiveness. One-way sensitivity analysis indicated that the results were sensitive to a significant increase or reduction in the cost of bedaquiline or the assumption of the proportion of patients who culture convert on the standard regimen. Results of this cost-effectiveness analysis were published in the journal Applied Health Economics and Health Policy in October 2017 (doi: 10.1007/s40258-017-0352-8).

The incremental cost effectiveness ratio (ICER) of bedaquiline for all MDR/RR-TB was US$1,242 per additional DALY averted compared to the standard regimen. Markov modelling indicates providing bedaquiline for all MDR/RR-TB patients could increase the treatment success rate in South Africa for MDR/RR-TB patients without additional second-line drug resistance from 56.3% on a non-bedaquiline regimen to 60.6%, at a cost US$2.8 million over a 10-year horizon. This amount is far less than US$8.5 million to procure bedaquiline for the initiating treatment cohort due to cost savings from replacement of the injections.

Direct provider costs of ADR management

Chapter 7 describes the direct, provider costs of managing the most frequently occurring moderate to severe ADR associated with the current standard of care MDR/RR-TB treatment regimen in the SA public health sector. This analysis presented in this chapter was designed in order to achieve the second objective of the overall thesis, namely: To evaluate the provider cost of prevention, monitoring, and management of ADRs incurred during MDR/RR-TB treatment, including drugs, hospitalization, laboratory monitoring, and clinic visits.

While all patients should receive prophylaxis to prevent ADR – i.e. pyridoxine for peripheral neuropathy – and screening for the early detection of ADR – e.g. audiometry or ECG monitoring or kidney and liver function laboratory tests – only patients experiencing ADR incur the costs of ADR management. Therefore, the Markov model for MDR/RR-TB treatment introduced in Chapter 6 was used to evaluate the expected costs of ADR management when there is the competing risk of mortality. Using guidelines for the management of ADR, resource use was extracted and multiplied by ingredient unit costs from South Africa; the same ingredient costs were used to parameterize the cost-effectiveness model in Chapter 6 and Chapter 8. The model used the frequencies of the ADR as calculated in the meta-analysis (Chapter 5) and the higher relative risk of ADR for HIV-infected patients newly initiated ART as presented in Chapter 3. Distributions were added for all model parameters, so that instead of one-way sensitivity analysis, probabilistic sensitivity analysis could be used. For an average cohort of MDR/RR-TB patients such as the 12,527 who initiated treatment in the SA NTP in 2015, including ADR management costs increased the estimated cost by $4.76 million from $57.55 million total. The provider cost analysis was accepted at the International Journal of Tuberculosis and Lung Disease in December 2017 and is currently in press.

The costs of managing the most frequently occurring ADR during MDR/RR-TB treatment are presented in Chapter 7. For moderate ADR with clinical management, the costs ranged US$2.51 for diarrhoea to US$208.23 for temporary drug-induced hypothyroidism. Severe systemic allergic reaction (e.g. Stevens–Johnson syndrome) require ICU care and, as a result, were the most expensive of all the ADR costed, at $5,461. Frequency of occurrence affected the weighted averages. The weighted average for moderate ADR was US$135.76, pulled up because the most expensive ADR (hypothyroidism), was also the most frequent moderate ADR at 36%.[108] Conversely, the weighted average for severe or serious ADR was pulled down to US$521.29 per episode because the most frequently experienced severe ADR was permanent and profound hearing loss, which standard guidelines for the public sector in South Africa do not indicate hearing aids or cochlear implants. An estimated 40% of patients on the kanamycin-based regimen [115] experience this severe ADR, which was estimated to cost the provider $50.76. While the costs of ADR management were described for the standard of care regimen, the management of bedaquiline-based regimen could be derived from the same analysis (see Chapter 8). As indicated in Chapter 2, the indication for management of QT interval prolongation once detected is to interrupt (if QT prolongation resolves) or stop bedaquiline, which does not add further to the costs of ADR management.[19]

Management of ADR from MDR/RR-TB treatment was found to represent significant financial cost to the South African public-sector health services. For each patient treated for MDR/RR-TB the average cost of managing ADR was an additional US$381.17 per patient, an 8.3% increase. For the 2015 SA public sector MDR/RR-TB cohort, ADR management increased the costs of MDR/RR-TB treatment from US$57.55 million to US$62.31 million, an additional $4.76 million per year (95%CI: 4.13 to 5.40 million). Similar to most of the TB treatment costs in South Africa, this additional cost is not incurred by the SA NTP or included in the HIV/TB conditional grant, rather, most of the cost is required for additional primary health care services and hospital utilization.

Cost-effectiveness of bedaquiline having adjusted for toxicity

Chapter 8 builds upon the Markov model first presented in Chapter 6 and modified in Chapter 7 to include the disability weighting for patients who survive and complete MDR/RR-TB treatment but who experienced ototoxicity associated with the use of the second-line injectable agents. Disability weights, as reviewed in Chapter 2, are a means to discount years of life that are not lived at full health. Disability from having TB, TB/HIV on ART, TB/HIV not on ART, and HIV on ART (for persons who completed TB treatment) as reported in the Global Burden of Disease study in 2013 had been incorporated in initial version of the model. In Chapter 8, the disability weight discounting years of life lived with profound deafness were used to discount the effectiveness of surviving the standard of care regimen, for an expected proportion of patients, as found through the systematic review (Chapter 5). The disability weight for hearing loss was extracted from a study implemented in South Africa using the Global Burden of Disease methodology; as described in the literature review (Chapter 2) the South African respondents weighed hearing loss as a much more severe disability and loss of health than in other settings. Results of this incremental cost-effectiveness analysis were submitted in December 2017 for peer review and publication.

This final results chapter pulls together findings presented in each of the previous chapters, including timing of mortality during MDR/RR-TB treatment by HIV and ART status Chapter 3, proportion of persons experiencing ADR and serious ADR in HIV settings Chapter 5, and the increased relative risk of ADR for HIV-infected patients newly initiating ART Chapter 4. Ingredients costs and the Markov model established in Chapter 6 and average costs for ADR management as estimated in Chapter 7 are also used. Disability weights for hearing loss (Table 2-11) are added to the model. The result is a cost-effectiveness analysis that is based upon real-world implementation of an injection-free regimen in South Africa and that quantifies the provider costs and disability of permanent, profound hearing loss from the MDR/RR-TB injection-based regimens.

With the probabilistic sensitivity analysis estimating a range of possible combinations of parameters, the relatively higher ADR management costs associated with the injection-based regimens, and the decreased effectiveness of the injection-based regimens once discounted for the hearing loss, a bedaquiline-based MDR/RR-TB regimen dominated the standard of care regimen. Bedaquiline for all MDR/RR-TB, not just the patients with extensive drug-resistance, was more effective (DALYs averted) and cost saving.

9.2 GENERALIZABILITY OF FINDINGS

Timing of mortality during MDR/RR-TB treatment

The timing of MDR/RR-TB treatment outcomes was not previously described for the South African context, although the findings are consistent with previously published analyses of timing of mortality from initial sputum collection [224], as well as Kaplan-Meier and cumulative incidence function graphs from South African cohorts which showed sharp drops in survival in first weeks followed by a levelling off.[186,223–225] The South African context may be most generalizable to other contexts implementing a standardized, long-course regimen where there is a high prevalence of HIV/TB co-infection. The early timing of mortality during treatment may be related to the time development of active disease to diagnsosis and to the time from diagnosis to initiation on treatment. Understanding of the natural history of the disease progression (i.e. in absence of medical interventions) is limited. Additionally, most studies, like this one, focus only on one part of the continuum from active disease to death from any cause. As a result, there is bias introduced in both the right censoring (e.g. starting at treatment initiation rather than sputum collection for diagnosis) and left censoring (e.g. stopping at 72 or 104 weeks rather than 120 weeks or longer) of the analysis period which limits generalizability to analysis periods with different right or left censoring.

Increased risk of ADR for MDR/RR-TB patients newly initiating ART

The systematic review presented in Chapter 5 confirmed the novelty of the major finding from Chapter 4, that patients newly initiating ART at the same time as initiating MDR/RR-TB treatment are at the highest relative risk of ADR. Although the experiences of the specific cohorts from Johannesburg may be a limitation of the study (see below, Chapter 0), the novelty of the finding is a strength of the specific data collection and analysis methods, rather than a limitation of the generalizability. As noted in the chapter, many other studies which described AE during MDR/RR-TB in high HIV prevalence settings did not differentiate the grade of AE [184], had insufficient numbers of patients on ART [109], or did not differentiate the time on ART [108]. Most commonly, when analysis was presented, it was a difference in proportions.[111,122] Other studies analysed difference in outcomes such as death, culture conversion, or treatment success by HIV and ART status, but did not provide the analysis for ADR by HIV and ART status.[183,188] For the current study, this differential risk for ADR was both statistically significant and clinically significant and, therefore, was used to parameterize the Markov models used in Chapters 7 and 8.

Applicability to the short-course regimen

The use of robust statistical techniques to calculate pooled proportions across the observational studies strengthen the generalizability of these findings to similar standardized MDR/RR-TB long-course treatment regimens. Further, because the newer short-course treatment regimens rely on the same drugs[14] and because the ADR typically occur during the initial months of treatment, the findings should be generalizable to the short-course regimens as well. The short-course regimen being implemented in South Africa since the end of 2016 is still based upon an intensive phase using kanamycin. Although the Bangladesh study that pioneered the short-course regimen reported hearing loss of 7%, it is not clear that this low rate is a benefit of the short-course regimen as the measurement of hearing loss is not described.[226] A subsequent report from the same centre of a larger cohort (n=515) did not report the proportion of patients who had hearing loss even in the section on

ADR and indicated that ADR "were not systematically recorded, and recording of most events (except for glycosuria) was mostly based on spontaneous reporting by the patient".[227] As discussed in Chapter 2.6, this could lead to under-reporting of ADR, especially hearing loss at high frequencies. A more recent study from Bangladesh designed to measure differences in hearing loss at baseline, 2, 3, 6, and 8 months after treatment initiation reported 77.8% of the 36 MDR/RR-TB patients tested using pure tone audiometry acquired hearing loss, 1/3 of which occurred by 2 months.[228] Implementation of the short-course regimen in other settings has also led to high rates of permanent hearing loss, even though the duration of the intensive phase is shortened to 4 months. In Niger, 20% of patients experienced hearing loss and in Cameron, 43% of patients had a documented deterioration in their hearing during the short-course treatment that is now standard of care.[229,230] While waiting for the results of studies using short-course bedaquiline and delamanid regimens [1], the results of this cost-effectiveness analysis adds more weight to the urgency to re-evaluate the use of IA in the treatment of MDR/RR-TB.

Inclusion of ADR in cost-effectiveness analysis of TB interventions

While the specific dollar amounts estimated for South Africa are unlikely to be generalizable to other settings, the overall finding that the costs of ADR management should not be excluded from budget estimations is likely to hold true across all settings implementing MDR/RR-TB treatment. Particularly in contexts where treatment guidelines for managing hearing loss indicate expensive rehabilitation such as cochlear implants, unlike in the SA NTP, exclusion of ADR management costs could result in under-estimation of required resources. This finding is important beyond cost-effectiveness analyses of MDR/RR-TB treatment, for example, prevention of TB transmission and acquired drug-resistance also needs to have an accurate estimation of the costs of MDR/RR-TB treatment.

Disability weighting of permanent profound hearing loss

The increased effectiveness for an all oral regimen estimated in this analysis is because IAs are associated with the high levels of ototoxicity.[1,115,130] Permanent and profound hearing loss reduces the overall effectiveness of the IA treatments when disability weightings are applied beyond the completion of the MDR/RR-TB treatment. The profound hearing loss disability weighting used here was from a South African survey; the weighting was nearly twice as high as the global study.[75,79] The commonality of the value or preference for different health states across contexts (e.g. South Africa compared to Europe) [33] continues to be questioned, particularly for resource-limited contexts where coping mechanisms may be less available.[34–37] While the disability may be less in higher-income settings, the costs may be higher. In countries with more coping mechanisms, the costs to providers or patients for accessing rehabilitative services or devices such as hearing aids and cochlear implants, would be much higher than the South African context. Although the disability weighting may not be generalizable across different contexts, again, the significance of considering the burden of ADR even after MDR/RR-TB treatment is appropriate for any settings implementing the IA-based drug-resistant TB drug regimens.

South African health care costs

As was noted in Chapter 2, generalizing cost-effectiveness analyses to other settings in part depends on whether the cost structures and relative prices and costs are common across settings.[40] The major ingredients of the service delivery cost of MDR/RR-TB treatment are clinical care (hospitalization or primary health care visits), anti-TB drugs, laboratory tests, and procedures. Of these, clinical care and procedures are not internationally traded; they are costs of services built from the underlying wages of health care workers in South Africa. In this analysis, a detailed original costing study of hospital stays, clinic visits, or procedures was not done. The published, unsubsidized charges that are applied to foreigners or persons of high income were used in absence of more detailed information. The SA Department of Health's Uniform Patient Fee Schedule (Revised April 2016)[3], which is based on the Reference Price List for medical services, was used as a proxy for estimating the costs of investigations, procedures, consultations, facility utilization, phlebotomy, and pharmacy dispensing. These charges include assumptions about allocation of shared and overhead expenses, capitalization and annuitization of buildings and equipment, staffing levels, and utilization rates. Where the analysis used to generate the patient fee schedule is out of date, too simplistic or not granular, or simply where assumptions and actual experience differ, the charges and actual costs will differ. Further studies are needed to understand the cost to charge ratio in South Africa. Further, health care costs, whether actual costs or based on charges are affected greatly by utilization rates. South Africa has one of the world's largest MDR/RR-TB treatment cohorts and is ranked even higher in terms of the treatment cohort size relative to its population.[2] Specialized doctors, nurses, and facilities may therefore have a lower cost per patient because of the patient volumes than would be applicable to other settings.

The large treatment cohort also has an impact on internationally traded goods such as anti-TB drugs and laboratory cartridges, reagents, and equipment. For example, South Africa has been able to negoitiate discounted rates for ARVs, Xpert MTB/RIF, and bedaquiline because it is a significant portion of the market. Because of its market size, South Africa does not participate in the Global Drug Facility (GDF) (http://www.stoptb.org/gdf/) a procurement system of the Stop TB partnership which pools orders from smaller programs to WHO-recommended anti-TB drugs. There is uncertainty as to how long South Africa will be able to procure bedaquiline at the $675 for a 6 month supply. In 2014, Janssen announced a partnership with the GDF where bedaquiline prices would be tiered: $30,000/treatment course for high-income countries, $3,000 for middle-income countries, and $900 for low-income countries. Although South Africa is not a low-income country, Janssen supplied bedaquiline to the SA public health sector at the $900/per treatment course. The $675 used in this analysis was not separately negotiated, it was the result of the procurement being set in ZAR and deflation in the value of the ZAR to the USD that occurred subsequent to procurement agreements. If the prices are below market value, they may be only temporary in nature, and the findings of this analysis that bedaquiline is cost-saving relative to the standard of care regimen may not be applicable.

9.3 STUDY LIMITATIONS

The study design applied and analysis presented have limitations which were noted in the presentation of the results Chapters (3 to 8). Major limitations are further examined here.

ADR experienced during MDR/RR-TB treatment

Two different methods were combined to estimate the types, frequency, and severity of ADR experienced by MDR/RR-TB patients. A retrospective, de-identified analysis of a clinical file review was used to describe the frequency, duration, and severity of ADR experienced during MDR/RR-TB treatment at two sites in Johannesburg, South Africa; results are presented in Chapter 4. As noted above (Chapter 9.1), one of the major limitations of the data may be the generalizability of two public-sector clinics located within Academic Hospitals in Johannesburg to other contexts. Further, while the data extraction forms for the clinical file review were designed to capture details for clinical factors determined, a priori, to be relevant to the study, the study itself was a retrospective review of routinely captured data. Symptoms or ADR that were not reported could not be analysed.

To improve the generalizability of the findings from the Johannesburg MDR/RR-TB treatment cohorts, a systematic review and meta-analysis describing the frequency and severity of ADR during MDR/RR-TB treatment in the context of high HIV prevalence settings was presented as Chapter 5. The 'true' frequency of ADR during MDR/RR-TB treatment depends on many factors, from patient characteristics to health services and systems issues. The systematic review and meta-analysis reported in Chapter 5 did not find any publications from randomized, clinical trials including where at least 20% of the treatment cohort was HIV-positive. The limitations of the observational data are worsened (generally) by inconsistency in definitions and reporting standards, as further described in Chapter 5.

The limitations of observational data are more pronounced for the secondary analysis of routinely captured, implementation data such as the EDRweb. Transition probabilities for the modelling were based upon data as routinely documented in the SA NTP electronic case register, the EDRweb. As is elaborated on in Chapter 3, the large cohort size and real-world experience captured in EDRweb are strengths of this analysis, however, routinely collected data also has limitations in its completeness. Few indicators of physical condition or mortality risk factors are included in EDRweb, such as hospitalization, other comorbidities, body mass index, serum albumin, or haemoglobin. Fields that should be captured in EDRweb, including reporting of ADR or start date for ART and CD4 count if HIV-infected were poorly completed and so not used in the analysis despite the importance of this information.

Provider cost of prevention, monitoring, and management of ADRs

Limitations regarding the reporting of ADR were carried into the direct provider cost analysis (presented as Chapter 7, as the expected frequency of each ADR was used to create a weighted average. Additionally, the ADR management costs based on guidelines are limited by the use of a guidelines-based approach. Where clinicians provide additional services, drugs, or procedures beyond those indicated or where clinicians are unable to provide all indicated resources, the actual costs would differ from the guidelines-based approach.

All of the cost results – Chapter 6-8 – reported include the limitation of the provider cost perspective. Provider costs, while a significant component of health care costs in the South African public sector, do not reflect the cost to society. Direct and indirect costs incurred by patients to access

MDR/RR-TB treatment or to manage ADRs while on treatment were excluded and therefore the costs presented here are an underestimate of the societal costs. Further, this analysis effectively ignored programme costs above the patient or service-delivery level. At least in the short-term as a bedaquiline-based regimen is rolled out in South Africa the costs of district, provincial or SA NTP training, coordination and management may be important costs to consider.[22,231]

More broadly, and therefore not elaborated on in the results chapters, the focus of this thesis on the cost-effectiveness of bedaquiline-based MDR/RR-TB treatment regimens can be viewed as a limitation. There are ethical and human rights reasons for adopting new treatments if more effective and more tolerated, even if more costly. A court in India ruled that the public health system had to allow for a girl with XDR-TB to receive bedaquiline, even though more costly and not available in her region of the country.[232] Recently, there have been high-profile editorials and reviews calling to end the use of IAs for children [233] and adults [1], even assuming a higher cost associated with new regimens. However, this type of analysis also provides a systematic process for decision making that can help to balance the different competing needs in a society. There is risk in making commitments that a society cannot afford [37], even if there is a strong advocacy for a particular group in society and desire to protect life. The challenges of and need for multi-criteria decision making does not negate the value of cost-effectiveness analyses, but does emphasize that the finding that something is cost-effective is not sufficient for decision makers.

ICER of bedaquiline-based regimens

For both of the results chapters presenting the ICER of bedaquiline-based regimens compared to IA-based regimens, the most significant limitation is the uncertainty with regards to the mortality imbalance reported in the Phase 2b trial.[30] As the WHO noted in both its 2013 and 2017 guidance on the use of bedaquiline, the evidence from the Phase 2b trial had potentially “very serious bias” for imprecision from the small patient numbers and also “serious bias” for indirectness; none of the deaths in the bedaquiline arm were attributed to bedaquiline.[31,32] Because of this potential for serious bias, similar to previously published cost-effectiveness analyses for bedaquiline [53–56], this thesis used the same mortality rates for bedaquiline regimens as for IA regimen. Data presented to the WHO during the guidelines review from the EDRweb cohort suggest that bedaquiline regimens have *lower* mortality than standard of care.[32] Thus, the uncertainty remains a limitation until Phase 3 clinical trial results are available.

9.4 Summary of thesis contributions

Detail on the contribution of this thesis to the field of study is included in the Synopsis section prior to each manuscript chapter (3-8). In summary:

Chapter 3

In this analysis, the EDRweb dataset was matched to the vital statistics register to validate the vital status of patients and to more precisely measure the timing of mortality. This matching had not been previously done for the national cohort. The finding that the mortality rates differ so substantially over the period of treatment has implications for treatment policy and practice as well as budgeting and planning for the program, including whether there is sufficient clinical capacity to increase the intensiveness of clinical monitoring with the current patient volumes.

Chapter 4

As was confirmed through a systematic literature review and meta-analysis (Manuscript 3), previous observational studies and meta-analysis of ART during MDR/RR-TB treatment had not established whether patients on ART and second-line treatment were at higher risk for ADR, even with known overlapping toxicities. By using competing risk analysis to adjust the incidence of ADR for the competing risk of mortality, this manuscript provided evidence that patients with the highest risk of mortality (those who are HIV-positive and not stable on ART prior to MDR/RR-TB treatment initiation) also have the highest risk of ADR.

Chapter 5

This analysis was novel in using a relatively new statistical method for managing the variance of a meta-analysis, but relies on a binomial distribution, appropriate for binary questions such as whether a patient experienced an ADR or not. Using meta-analysis with pooled proportions provided more clarity as to the frequency of ADR during MDR/RR-TB treatment, as the literature was entirely from observational studies from varied settings.

Chapter 6

As of August 2017, the five studies identified that analysed the cost-effectiveness of bedaquiline [52–56], in addition to the original analysis included in the WHO recommendations [31] considered bedaquiline added on to the standard regimen rather than replacing the injection. This analysis was the first to use evidence from programmatic roll out to show what may happen using a new regimen where bedaquiline replaced the injection. Additionally, this was the first cost-effectiveness model for MDR/RR-TB with separate health states and transition probabilities for HIV co-infection.

Chapter 7

Previously published cost-effectiveness analyses of MDR/RR-TB treatment, if including the costs for ADR management, used an average which did not specify the type, frequency, cause, or specific management for the ADR in the details. Therefore, these analysis could not be used when the expected ADR differed by the comparison treatment regimens. The costing workbook indicates the suspected drugs for each of the included ADR, and thus also can be used to estimate the costs of ADR for different regimen than the standard of care injection-based regimen costed, as it was used for Chapter 8.

Chapter 8

Bringing together the estimated costs of ADR management Chapter 7and the burden of permanent disability from hearing loss, this manuscript is the first to find that overall, a bedaquiline-based regimen is likely to be cost saving compared to an injection-based regimen, even in an low-resource setting with ambulatory, decentralized treatment of MDR/RR-TB. The inclusion of the costs and disability weighting of ADR for cost-effectiveness analysis of MDR/RR-TB treatment regimens is novel addition to the literature that is necessary to more closely determine the cost of MDR care in analysis and policy decisions around new MDR treatment.

9.5 FUTURE DIRECTIONS

This thesis set out to evaluate whether the inclusion of the costs of adverse drug reaction management and the disability burden affected the incremental cost-effectiveness ratio of a bedaquiline-based MDR/RR-TB treatment regimen. Prior to adjusting for the toxicity of the standard of care regimen, the use of bedaquiline in the SA NTP was affordable, but more expensive for moderate gains in effectiveness. Compared with other health priorities or other societal priorities, expanded use of bedaquiline did not dominate the standard of care injectable-agent based regimen. However, once the costs of managing ADR, including electrolyte imbalance and renal dysfunction and the permanent disability of profound hearing loss associated with the use of the second-line injectable drugs, the results changed. Bedaquiline-based treatment for MDR/RR-TB is cost-saving and more effective than regimens using the less expensive injections.

Recommendations for future directions

Beyond the importance of the findings of Chapter 3 for the analysis of the cost-effectiveness of bedaquiline, the high rates of early mortality during MDR/RR-TB treatment presents an urgency to identify the associated risk factors. With more research into the clinical risk factors – e.g. low CD4 count, poor HIV viral suppression, low BMI, pre-existing or incident anaemia, hepatitis, or kidney dysfunction – MDR/RR-TB treatment guidelines can be updated to allow for triaging of patients and differentiated care for those that are in greatest need. These clinical risk factors for poor treatment outcomes overlap with ADR common to MDR/RR-TB treatment and HIV treatment (as noted in Chapters 2, 5) and may also increase the risk for ADR during MDR/RR-TB or HIV treatment (Chapter 4). Again, better understanding of the clinical markers during MDR/RR-TB treatment beyond sputum culture positivity will assist in more targeted monitoring for ADRs or treatment regimens individualized to avoid toxicities. Further, the early mortality presents a compelling motivation for more research into treatment guidelines that start from a perspective of assuming second-line resistance and reducing the number of active drugs over time, rather than starting with the standard regimen and adding active drugs after the initial regimen fails to lead to clinical improvement, if the burden of ADR from the additional drugs is does not outweight the benefits.

The increased risk of ADR for HIV-positive, ART naïve patients described in Chapter 4 point to a need for additional or more frequent monitoring for AE for patients initiating both ART and RR-TB treatment at the same time, beyond the current guidelines indications of monthly visits.[17] The cumulative incidence function for mortality accounting for the competing risk of loss to treatment indicating that HIV-infected MDR/RR-TB patients who were ART naïve have the highest risk of mortality is consistent with studies and guidelines that indicate early initiation of ART for patients with TB [169–171] and drug-resistant TB [16,136]. With the 2015 WHO recommendation that all persons living with HIV initiate ART, regardless of CD4 count, this differential risk for the HIV-positive, ART naïve MDR/RR-TB patient will hopefully become a less important factor over time as the population of HIV-infected patients not on ART declines. Until that time, routine monitoring such as that captured in the EDRweb, should capture information on CD4 count, duration of time on ART, and other clinical factors such as BMI, laboratory monitoring for ADR, and extent of damage to the lungs, none of which are currently routinely reported or monitored at a national level in South Africa.

Given the findings of the systematic review and meta-analysis presented in Chapter 5, clinical guidelines should encourage active symptom screening and improved reporting of ADR during MDR/RR-TB treatment. Patients whose clinical condition requires immediate initiation of ART and RR-TB treatment may benefit from intensive monitoring or even inpatient treatment initially to watch for severe AEs. This additional monitoring may require additional clinic capacity and resources and should be reflected in the SA NTP budget. The systematic review Chapter 5 highlighted that ADR are not always noted in patient files, and grading of severity and identification of suspected drugs is not even less frequency. Yet, if the symptoms go unnoticed by the clinicians, management of the symptoms or reaction, including changes to the treatment regimen, cannot be done. Active screening, by asking patients if they have had a set of symptoms using a standardized form for reporting, rather than passive screening by waiting for patients to report a complaint, could improve the evidence base for the effects of current or new treatment regimens. Further studies on the quality of life or the disability experienced during MDR/RR-TB treatment in high burden settings are also warranted, given the assumptions and uncertainty in the estimates of disability weighting. The disability weights from the South African GBD study [79] were very different than the global weights [74,75,77,107], should the weights be re-evaluated with more input from the contexts with the highest burden? It may also be that the description of MDR/RR-TB (i.e. "has a persistent cough and fever, shortness of breath, night sweats, weakness and fatigue and severe weight loss" [107]) should be re-evaluated given new evidence of the impact on patients, and that in doing so, the relative weight assigned to the disability, no matter what context is considering it, would differ.

Finally, future MDR/RR-TB guidelines, policy considerations and recommendations should consider the differential impact of proposed treatment regimens on the costs of ADR prevention, monitoring, and management as well as any associated disability or morbidity that continues after treatment completion. Even while new trial results and guideline revisions are pending, MDR/RR-TB patients in South Africa should be given the opportunity to make an informed choice between an 18-month regimen using bedaquiline for 6 months or a 12-month regimen using injectable agents for 4 months. Risks of both regimens, including success rates and expected ADR, should be discussed between the health care provider and patient.

9.6 CONCLUSION

Bedaquiline-based treatment for MDR/RR TB is cost-saving and more effective than regimens using the less expensive injections. Based on these findings, it is important to modify policy guidelines to specifically recommend bedaquiline for all long-course MDR/RR-TB treatment from the start of treatment. Current guidelines still give preference for kanamycin before use of bedaquiline, for example by waiting until a patient experiences hearing loss before switching.

Additionally, the findings of this thesis suggest an urgent re-evaluation of the recommended short-course regimen to determine whether bedaquiline can replace kanamycin for the short-course regimens that also rely on IA. In order to use evidence from implementation and roll-out of bedaquiline, the analysis presented here is comparison of the long-course (18 to 24 months) IA regimen and the bedaquiline regimen used in South Africa prior to the end of 2016. SA NTP MDR/RR-TB patients without second-line resistance are now eligible for the short-course regimen, which was recommended by the WHO in 2016. While waiting for the results of studies using short-course bedaquiline and delamanid regimens, the results of this cost-effectiveness analysis adds more weight to the urgency to re-evaluate the use of IA in the treatment of MDR/RR-TB. Until evidence is sufficient to adapt the regimen, patients should be given the opportunity to make an informed choice between an 18-month regimen using bedaquiline for 6 months or a 12-month regimen using injectable agents for 4 months. Risks of both regimens, including success rates and expected ADR, should be communicated to patients.

Current injection-based long-course standard treatment for MDR/RR-TB is associated with high rates of adverse drug reactions, including permanent hearing loss. Based on this modelling of bedaquiline regimens in South Africa, new drugs that can allow for an all oral MDR/RR-TB treatment regimen may be cost saving and more effective than current injection-based regimens, if cost-effectiveness analyses incorporate the costs and burden of the expected adverse drug reactions.

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11 ANNEXES

1 Supplemental materials, Manuscript 3

2 Supplemental materials, Manuscript 5

11.1 Annex – Supplemental materials for meta-analysis of ADR in HIV settings

Supplemental Materials

Adverse drug reactions during drug-resistant tuberculosis treatment in high HIV prevalence settings: a systematic review and meta-analysis

Kathryn Schnippel, Cynthia Firnhaber, Rebecca Berhanu, Liesl Page-Shipp, and Edina Sinanovic

Additional background:

The duration of drug-resistant TB treatment is longer than for drug-sensitive TB (typically 9-24 months) and standard regimens for MDR/RR-TB include 4 to 7 drugs with different[16] mechanisms of action, including oral bacteriostatic drugs such as cycloserine, terizidone, ethionamide; aminoglycoside and cyclic peptide injectables; fluoroquinolones (e.g. moxifloxacin, ofloxacin, gatifloxacin, and levofloxacin); and newer agents such as bedaquiline (a diarylquinoline) and delamanid (a nitroimidazole).

In some settings, particularly sub-Saharan Africa, TB and HIV are inextricably linked. Treatment of HIV and TB co-infection results in high pill burden and potentially increased toxicity. Effective ART regimens include three drugs, usually two nucleoside reverse transcriptase inhibitors (NRTIs) with either a non-nucleoside reverse transcriptase inhibitor or protease inhibitor (PI) in resource-limited countries. Toxicities can be overlapping, such as potential renal impairment from antiretrovirals including tenofovir and anti-TB medications kanamycin/amikacin; peripheral neuropathy from stavudine and zidovudine, ethionamide and linezolid; bone marrow suppression from zidovudine and linezolid; nausea and vomiting potentially from zidovudine and ethionamide and para-aminosalicylic acid; or psychiatric symptoms associated with efavirenz and cycloserine and terizidone.[16,136] HIV infection, even for the ART naïve, and particularly for those who have advance HIV disease or immunosuppression may also pose its own risk for ADR. For example, thioacetazone was removed from TB treatment recommendations early in the HIV epidemic because of an increased risk of Stevens-Johnson syndrome in HIV-infected patients.[137]

Within the last decade, there has been escalated progress for drug-resistant TB drug development; new treatments are being developed and multiple drugs are entering or in clinical trials.[167,173] In the Phase IIb randomized control trial for bedaquiline where bedaquiline or placebo was added to a standard background regimen, 99% of participants in the treatment arm and 98% of the participants in the placebo arm experienced one or more adverse events. Most of these events were categorized as being related to the treatment, 70% (bedaquiline) and 69% (placebo) for the two arms, respectively.[30] Knowing whether the rates of ADR experienced in clinical trials for new drugs are of concern requires a better understanding of the base case scenario. Additionally, in efforts to improve treatment outcomes existing drugs such as linezolid (an oxazolidinone) and clofazimine are being repurposed for drug-resistant TB treatment. Because the drugs have existing regulatory approval for other indications, randomized controlled trials are not required in many settings and available understanding of the potential side effects and optimal doses for the regimens are limited to observational cohorts.[98,174]

References for Annex:

References for entire thesis combined as Chapter 10.

Table 11-1 Study inclusion and exclusion criteria

Inclusion criteria:	**Exclusion criteria:**
Patients were diagnosed as at least rifampicin (RIF) resistant by any World Health Organization (WHO) approved method (e.g. Xpert MTB/RIF, phenotypic drug-sensitivity testing, or line probe assay).	Fewer than 20 RIF-resistant TB patients were included in the published cohort.
At least 20% of the cohort was known to be HIV-infected.	Information on RIF-TB treatment regimen was not available.
Results were available in English language.	Information on HIV status of patients was not available.
Patients described were on a second-line TB treatment regimen that was in alignment with the WHO 2011 Programmatic guidelines[2] or subsequent updated recommendations in 2013 and 2014 for bedaquiline[14] and delamanid[15], respectively.	Information on adverse drug reaction (ADR) or adverse event (AE) suspected to be related or known to be associated with second-line TB treatment experienced by cohort not reported.
Alignment was defined as meaning treatment for 18-24 months with 4-6 drugs from the WHO recommendations: ● Second-line injectable agent: kanamycin, amikacin, or capreomycin ● Fluoroquinolones: levofloxacin, moxifloxacin, gatifloxacin, ofloxacin ● Oral bacteriostatic: ethionamide, prothionamide, cycloserine, terizidone, para-aminosalicylic acid ● Additional drugs (previously known as 'Group 5 drugs'): clofazimine, linezolid, amoxicillin/clavulanate, thioacetazone, clarithromycin, imipenem ● New agents: bedaquiline, delamanid	Reports of a trial of a non-WHO recommended treatment regimen or method as of 2015, i.e. short course, surgery, herbal treatments, or immunotherapy.

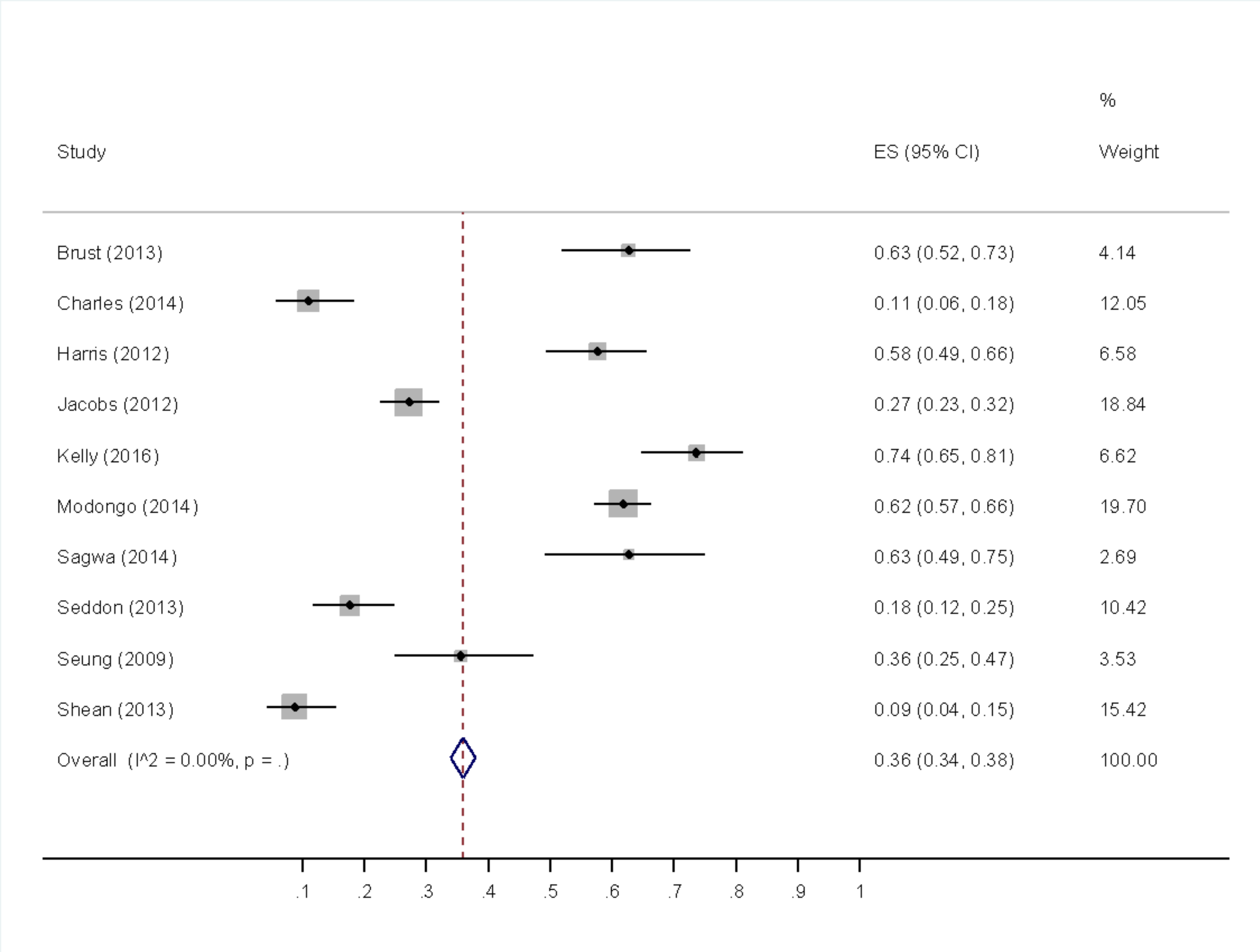
Table 11-2 Included articles, reporting on multiple ADR and suspected drugs

First author	Year	Citation	Country	All patients	HIV+ patients	% HIV	Year start	Year finish	Notes
All ADR									
Brust	2013	[108]	South Africa	91	74	81.3%	2008	2011	
Charles	2014	[178]	Haiti	110	27	24.5%	2010	2013	
Isaakidis	2012	[114]	India	67	67	100%	2007	2011	
Jacobs	2012	[179]	South Africa	350	254	72.6%	2010	2011	
Kelly	2016	[123]	South Africa	121	90	74.4%	2014	2014	
Meressa	2015	[124]	Ethiopia	612	133	21.7%	2009	2014	
O'Donnell	2013	[180]	South Africa	114	82	71.9%	2006	2007	XDR TB only
Sagwa	2014	[181]	Namibia	59	31	52.5%	2008	2010	
Seddon	2013	[182]	South Africa	142	32	22.5%	2009	2011	
Shean	2013	[168]	South Africa	115	48	41.7%	2002	2008	XDR TB only
Thee	2014	[183]	South Africa	23	6	26.1%	2012	2014	
Umanah	2015	[184]	South Africa	1,137	1,137	100%	2007	2010	

Table 11-3 Included articles, reporting on only severe ADR, one type of ADR, or one suspected drug

First author	Year	Citation	Country	All patients	HIV+ patients	% HIV	Year start	Year finish	Notes
Severe ADR									
Burgos	2005	[185]	United States	48	11	22.9%	1982	2000	Severe only
Kvasnovsky	2011	[186]	South Africa	206	108	52.4%	2006	2008	XDR TB; Severe only
Ndjeka	2015	[34]	South Africa	91	54	59.3%	2013	2014	Severe only
Seung	2009	[187]	Lesotho	76	56	73.7%	2007	2008	Severe only
Serious ADR									
Van der Walt	2013	[109]	South Africa	1,390	544	39.1%	2000	2004	Serious only
ADR specific									
Andries	2013	[113]	India	69	69	100%	2006	2013	Hypothyroidism
Conradie	2014	[190]	South Africa	246	199	80.9%	2009	2011	Peripheral neuropathy
Harris	2012	[192]	South Africa	151	86	57.0%			Hearing loss
Modongo	2012	[112]	Botswana	213	135	63.4%	2007	2011	Hypothyroidism
Modongo	2014	[189]	Botswana	437	288	65.9%	2007	2012	Hearing loss
Satti	2012	[111]	Lesotho	186	125	67.6%	2007	2009	Hypothyroidism
Drug specific									
Padayatchi	2014	[188]	South Africa	85	73	85.9%	2009	2011	XDR TB; Clofazamine

*Figure 11-1 Forest plot of estimate of proportion of patients experiencing hearing loss (ototoxicity)^*



^Excluding Meressa as noted in study that no hearing screening or tests performed.

Metaprop was used as it is based on binomial distribution appropriate for analysing proportions and is less likely to produce unallowable intervals even when the proportions are close to 0 or 1[176]

11.2 ANNEX - SUPPLEMENTAL MATERIALS ADR COST MODEL

Table 11-4 Definitions and methodology for calculating unit costs

Unit costs

All unit costs were collected from the perspective of the public sector in South Africa in the local currency (ZAR) using public sector databases. Costs were either collected in 2016 ZAR or inflated to 2016 using the medical component of the consumer price index (CPI).[1] Costs were converted to USD at the average exchange rate for 2016, 14.74 ZAR to USD.[2]

Uniform patient fee schedule

The SA Department of Health's Uniform Patient Fee Schedule (Revised April 2016)[3], which is based on the Reference Price List for medical services, was used as a proxy for estimating the costs of investigations, procedures, consultations, facility utilization, phlebotomy, and pharmacy dispensing. The Schedule includes a detailed list of different procedures and investigations for patients and indicates costs groupings.

Based on the cost grouping, a facility fee plus a general medical officer or specialist fee was extracted. The highest (unsubsidized, full cost) fee was assumed to be representative of the full cost of the health facility utilization for the provider.

The Schedule for South Africa also includes a standard fee for 12 hours in either a general medical ward or an intensive care unit.

Additionally, the standard fee for an outpatient consultation was used for outpatient monitoring of mild to moderate ADR or follow-up after hospital discharge for serious ADR.

The standard pharmacy dispensing fee was added to all ADR with prescribed medications or IV fluids.

The standard fee for a blood draw was added to all ADR with laboratory tests requiring phlebotomy. The charge was only added once per set of tests on the same day.

National Health Laboratory Services state price list

Indicated laboratory tests were matched to items on the 2015/16 state (public sector) price list from the National Health Laboratory Services [4] and inflated to 2016 ZAR.

Essential medicines procurement

The Master Procurement Catalogue March 2016 [5] was downloaded from the National Department of Health website and public sector prices for medications at the indicated doses and quantities were extracted.

National blood service state price list

Costs for blood products and related services were extracted from the state price list of the South African National Blood Service for 2016.[6]

Excluded costs

Costs of antiretroviral therapy (ART) for HIV, the standard MDR/RR-TB regimen, and monitoring for TB sputum conversion were excluded from the analysis as these are included in the costs of HIV and/or MDR/RR-TB treatment. Capital investment in infrastructure, pre-service education, vehicles or medical equipment was not separately estimated. No patient costs were included in this analysis.

References

1. Statistics South Africa. Consumer Price Index. Pretoria: 2016. http://www.statssa.gov.za

2. USForex Inc. dba OFX. Historical Exchange Rates 2016. https://www.ofx.com/en-us/forex-news/historical-exchange-rates/ (accessed March 5, 2017).

3. National Department of Health. UPFS Fee Schedule for Full Paying Patients 2016. http://www.health.gov.za/index.php/shortcodes/2015-03-29-10-42-47/2015-04-30-09-10-23/uniform-patient-fee-schedule/category/282-u2016

4. National Health Laboratory Service. NHLS State Price list 2015-2016.

5. Essential Drug Programme. Master Procurement Catalogue. National Department of Health 2016. http://www.health.gov.za/index.php/component/phocadownload/category/196 (accessed March 25, 2016).

6. South African National Blood Service. State Patients Price List 2016. https://sanbs.org.za/wp-content/uploads/2016/09/2016-SANBS-State-Price-List-1.pdf

Table 11-5 Resource estimation notes and methodology

Resource use estimation

Overall note

Resource use was extracted from guidelines for the purposes of costing only; clinical screening or activities without an identified additional cost were excluded. Minimum or essential standard treatment was assumed for a conservative provider costing perspective. Resource use described below is not meant to be or replace clinical guidelines or to be interpreted as recommended practice. Also see limitations section in main article.

Management of ADR

Management of ADR and their sequalae may include additional clinic consultations, investigations, laboratory tests, medications, and/or hospitalization. Resource utilization for each of the most frequently experienced ADR and serious ADR were extracted from the SA guidelines for primary healthcare treatment [2] or the SA guidelines for the treatment of MDR/RR-TB [1] if described, and compared for consistency against guidelines for the management of ADR in the WHO companion handbook, chapter 11 [3].

Additional clinical consultations were assumed for each month (4 weeks) duration of the ADR episode if moderate and requiring either prescription medication, laboratory follow-up or specialist referral.

1 week of hospitalization was assumed for serious ADR unless guidelines indicated additional duration of stay.

All hospitalization was assumed to be in the general medical ward except ICU for Stevens-Johnsons Syndrome.

Clinical follow-up was assumed for all hospitalized ADR episodes, at least at level required for moderate episode or 1 x visit.

Severity or details listed are extracted from the DAIDS grading tables [4], but are used only to be descriptive and illustrative that different levels of severity may require different resource utilization.

References

1. Directorate Drug-Resistant TB. Management of Drug-Resistant TB: Policy Guidelines. Pretoria: National Department of Health; 2013.

2. The South African National Department of Health. Standard Treatment Guidelines and Essential Medicines List for South Africa: Primary Health Care Level; 2014.

3. World Health Organization. Companion handbook to the WHO guidelines for the programmatic management of drug-resistant tuberculosis; 2014.

4. Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.0; 2014.

Table 11-6 Costed ingredients of SAE

Costed ingredients of (S)AE, 2016 USD, by component category and % of total cost

Adverse events	Description, severity	Hospitalization costs	%	Additional clinic visit costs	%	Laboratory costs	%	Investigations and procedures costs	%	Medication and fluids costs	%	Total cost per patient experiencing
Severe or serious AE												
Hypersensitivity, allergic reaction	e.g. Stevens-Johnson Syndrome and Toxic epidermal necrolysis	$ 4,827.77	88%	$ 13.17	0%	$ 101.16	2%	$ 488.19	9%	$ 30.76	1%	**$ 5,461.05**
Hepatitis, liver dysfunction	e.g. ALT > 5 x the upper limit of normal	$ 2,438.35	90%	$ 39.50	1%	$ 167.00	6%	$ 46.42	2%	$ 12.19	0%	**$ 2,703.45**
Thrombocytopenia	<50,000 cells/mm3	$ 812.78	42%	$ 52.66	3%	$ 63.49	3%	$ 534.59	28%	$ 480.23	25%	**$ 1,943.75**
Psychiatric disorder	e.g. suicidal or pyschosis (harm to self or others)	$ 1,625.57	89%	$ 26.33	1%	$ 87.77	5%	$ 76.25	4%	$ 8.50	0%	**$ 1,824.41**
Renal dysfunction	Globular filtration rate < 30 ml/min	$ 1,625.57	90%	$ 52.66	3%	$ 111.05	6%	$ -	0%	$ 18.60	1%	**$ 1,807.88**
Seizures	New onset, severe	$ 812.78	73%	$ 78.99	7%	$ 48.56	4%	$ 155.47	14%	$ 24.40	2%	**$ 1,120.21**
Anemia	Hemoglobin <8 g/dL	$ 812.78	87%	$ 52.66	6%	$ 63.49	7%	$ -	0%	$ -	0%	**$ 928.93**
Hypokalemia, electrolyte imbalance	e.g. Magnesium < 0.9 mEq/L or Potassium < 2.5 mEq/L	$ 812.78	91%	$ 26.33	3%	$ 23.80	3%	$ -	0%	$ 29.08	3%	**$ 891.99**
Nausea, vomiting	Persistent vomitting or nausea resulting in minimal oral intake	$ 812.78	96%	$ 13.17	2%	$ 9.66	1%	$ -	0%	$ 12.04	1%	**$ 847.65**
Hearing loss	Permanent, profound deafness (with or without tinnitus)	$ -	0%	$ 13.17	26%	$ -	0%	$ 37.60	74%	$ -	0%	**$ 50.76**

Notes: hospital	Notes: clinic visits	Notes: laboratory tests
1 week ICU, 1 week medical ward	x 1 follow-up	4 x full blood count; 4x liver function panel; 4 x kidney panel
3 weeks medical ward	Monthly x 3	4 x liver function panel; full blood count; kidney function panel; hepatitis B surface antigen; hepatitis C serology; hepatitis A serology; and follow-up tests as per moderate (below)
1 week medical ward	Monthly x 4	Full blood count; ferritin; PT/INR, reticulocyte count; iron; thyroid stimulating hormone; and follow-up tests as per moderate (below)
2 weeks medical ward	Monthly x 2	Full blood count; kidney function panel; thyroid stimulating hormone; cryptococcal antigen; serum magnesium, cerebral spinal fluid (CSF) culture, CSF gram stain, CSF cryptococcal antigen, CSF HSV PCR; CSF protein; CSF gluclose; and follow-up tests as per moderate (below)
2 weeks medical ward	Monthly x 4	Urinalysis, liver function panel, full blood count, creatinine; 7 x kidney function panel; and follow-up tests as per moderate (below)
1 week medical ward	Monthly x 6	Full blood count; kidney panel; thyroid stimulating hormone; cerebral spinal fluid (CSF) culture, CSF gram stain, CSF cryptococcal antigen, CSF HSV PCR; CSF protein; CSF gluclose ; liver function panel
1 week medical ward	Monthly x 4	Full blood count; ferritin; PT/INR, reticulocyte count; iron; thyroid stimulating hormone; and follow-up tests as per moderate (below)
1 week medical ward	Monthly x 2	Serum magnesium; serum potassium; serum calcium
1 week medical ward	x 1 follow-up	Full blood count; serum magnesium; serum potassium
None standard	x 1 for referral	None standard

Notes: procedures and investigations	Notes: medications and fluids
Dressings, debridement, specialized care	14 x liter IV fluid; 1 x week prednilosone
Abdominal ultrasound	6 x liter IV fluid
Transfusion	1 x unit platelets
Lumbar puncture; 1/3 of patients brain CT (non-contrast)	14 x tablets haloperdal; 30 x tablets risperdal; 2 x months fluoxetine
	6 x liters IV fluid; 3 x days metoclopromide; 4 x months enalapril; furosemide
CT brain (contrast); chest x-ray; lumbar puncture	6 x months valproate
None standard	6 x liters IV fluid; spironolactone; 6 x months potassium, magnesium, and/or calcium supplement as applicable
None standard	5 x Metoclopromide IV; 10 x liter IV fluid
Evaluation by audiologist; 1/3 of patients ear, nose, throat specialist evaluation; 1/10 patients CT brain with contrast	None standard

Table 11-7 Costed ingredients of AE

Adverse events	Description, severity	Hospitalization costs	%	Additional clinic visit costs	%	Laboratory costs	%	Investigations and procedures costs	%	Medication and fluids costs	%	Total cost per patient experiencing
Moderate AE												
Renal dysfunction	Glomerular filtration rate < 60 to 30 ml/min	$ -	0%	$ 52.66	52%	$ 36.81	37%	$ -	0%	$ 11.18	11%	**$ 100.65**
Anemia	Hemoglobin <11 g/dL and >8 g/dL	$ -	0%	$ 52.66	62%	$ 31.75	38%	$ -	0%	$ -	0%	**$ 84.41**
Hypokalemia, electrolyte imbalance	e.g. Magnesium 0.9 to < 1.2 mEq/L or Potassium 2.5 to < 3.0 mEq/L	$ -	0%	$ 26.33	37%	$ 15.86	22%	$ -	0%	$ 28.56	40%	**$ 70.75**
Thyroid dysfunction, hypothyroidism	e.g. requiring supplementation	$ -	0%	$ 78.99	38%	$ 89.16	43%	$ -	0%	$ 40.08	19%	**$ 208.23**
Hepatitis, liver dysfunction	e.g. elevated ALT < 5 x upper limit of normal	$ -	0%	$ 39.50	25%	$ 69.10	45%	$ 46.42	30%	$ -	0%	**$ 155.01**
Hearing loss	Permanent, high frequency hearing loss (with or without tinnitus)	$ -	0%	$ 13.17	26%	$ -	0%	$ 37.60	74%	$ -	0%	**$ 50.76**
Psychiatric disorder	e.g. depression, confusion	$ -	0%	$ 26.33	61%	$ 10.95	25%	$ -	0%	$ 5.92	14%	**$ 43.20**
Sleep disturbance, insomnia		$ -	0%	$ 26.33	83%	$ -	0%	$ -	0%	$ 5.24	17%	**$ 31.57**
Peripheral neuropathy		$ -	0%	$ 13.17	46%	$ -	0%	$ -	0%	$ 15.73	54%	**$ 28.89**
Visual disturbance		$ -	0%	$ 13.17	55%	$ -	0%	$ 10.56	45%	$ -	0%	**$ 23.73**
Tinnitus	without hearing loss	$ -	0%	$ 13.17	56%	$ -	0%	$ 10.52	44%	$ -	0%	**$ 23.68**
Dizziness, vertigo		$ -	0%	$ 13.17	68%	$ 3.37	17%	$ -	0%	$ 2.96	15%	**$ 19.49**
Hypersensitivity, allergic reaction	Rash, dermatologic reaction (moderate)	$ -	0%	$ 13.17	82%	$ -	0%	$ -	0%	$ 2.80	18%	**$ 15.97**
Nausea, vomiting	Vomitting or nausea limiting oral intake	$ -	0%	$ 13.17	84%	$ -	0%	$ -	0%	$ 2.56	16%	**$ 15.72**
Joint pain, arthralgia		$ -	0%	$ -	0%	$ 8.03	72%	$ -	0%	$ 3.06	28%	**$ 11.09**
Tendonitis		$ -	0%	$ -	0%	$ -	0%	$ -	0%	$ 3.06	100%	**$ 3.06**
Headache		$ -	0%	$ -	0%	$ -	0%	$ -	0%	$ 2.52	100%	**$ 2.52**
Diarrhoea		$ -	0%	$ -	0%	$ -	0%	$ -	0%	$ 2.51	100%	**$ 2.51**

Notes: hospital	Notes: clinic visits	Notes: laboratory tests
None standard	Monthly x 4	4 x kidney function panel; 4 x urinalysis
None standard	Monthly x 4	Full blood count; ferritin; PT/INR, reticulocyte count; iron; thyroid stimulating hormone
None standard	Monthly x 2	Serum magnesium; serum potassium; serum calcium; and follow-up tests as per moderate (below)
None standard	Monthly x 6	4 x thryroid function panel
None standard	Monthly x 3	Liver function panel; 3 x hepatitis antigen tests; 4 x alanine aminotransferase; 4 x billirubin
None standard	x 1 for referral	None standard
None standard	Monthly x 2	Thryoid stimulating hormone
None standard	Monthly x 2	None standard
None standard	x 1 to prescribe ancillary medications	None standard
None standard	x 1 for referral	None standard
None standard	x 1 for referral	None standard
None standard	x 1 to prescribe ancillary medications	Hemoglobin
None standard	x 1 to prescribe ancillary medications	None standard
None standard	x 1 to prescribe ancillary medications	None standard
None standard	None standard	Serum magnesium; serum potassium; uric acid
None standard	None standard	None standard
None standard	None standard	None standard
None standard	None standard	None standard

Notes: procedures and investigations	Notes: medications and fluids
None standard	4 x months enalapril; furosemide
None standard	None standard
None standard	6 x months potassium, magnesium, and/or calcium supplement as applicable
None standard	14 x months thyroxine (from onset to completion of MDR/RR-TB treatment)
Abdominal ultrasound	None standard
Evaluation by audiologist; 1/3 of patients ear, nose, throat specialist evaluation; 1/10 patients CT brain with contrast	None standard
None standard	2 x months fluoxetine
None standard	2 x months amitriptyline
None standard	6 x months amitriptyline
Referral to opthamologist	None standard
Evaluation by audiologist	None standard
None standard	Promethazine
None standard	Calamine lotion; cetirizine
None standard	Metoclopramide
None standard	4 x weeks ibuprofen; methyl salicylate ointment
None standard	4 x weeks ibuprofen; methyl salicylate ointment
None standard	Paracetomol
None standard	24 hours x loperamide

Table 11-8 Weighted average costs of SAE, 2016 USD

Adverse events	Description, severity	Associated MDR/RR-TB drug	Associated XDR-TB drug	Frequency (% patients experiencing) MDR/RR-TB	Source, notes
Severe AE					
Hypersensitivity, allergic reaction	e.g. Stevens-Johnson Syndrome and Toxic epidermal necrolysis	Any	Any	0.5%	Schnippel et al
Hepatitis, liver dysfunction	e.g. ALT > 5 x the upper limit of normal	pyrazinamide, ethi	pyrazinamide, ethi	6%	Schnippel et al
Thrombocytopenia	e.g. Platelets <50,000 cells/mm3		linezolid		Not associated with current treatment regimen
Psychiatric disorder	e.g. suicidal or pyschosis (harm to self or others)	terizidone	terizidone	8%	Schnippel et al
Renal dysfunction	Globular filtration rate < 30 ml/min	kanamycin	capreomycin	2%	Schnippel et al
Seizures	New onset, severe	terizidone, moxiflo	terizidone, moxiflo	3%	Schnippel et al
Anemia	Hemoglobin <8 g/dL		linezolid	2%	Schnippel et al
Hypokalemia, electrolyte imbalance	e.g. Magnesium < 0.9 mEq/L or Potassium < 2.5 mEq/L	kanamycin	capreomycin	2%	Schnippel et al
Nausea, vomiting	Persistent vomitting or nausea resulting in minimal oral intake	ethionamide	ethionamide, para-	7%	Schnippel et al
Hearing loss	Permanent, profound deafness (with or without tinnitus)	kanamycin	capreomycin	40%	Harris et al
Summary stats	Resulting SAEs / MDR/RR-TB patient	0.71	Resulting SAEs / XDR-TB patient	1.09	Average per patient

Frequency (% patients experiencing) XDR-TB	Source, notes	Total cost per patient experiencing	Weighted MDR/RR-TB costs	Weighted XDR-TB costs
1%	Assumption 2 x MDR/RR-TB because of number of drugs used	$ 5,461.05	$ 27.31	$ 54.61
6%	Assumption same as MDR/RR-TB as same drugs	$ 2,703.45	$ 162.21	$ 162.21
12%	Sotgiu et al	$ 1,943.75	$ -	$ 233.25
8%	Assumption same as MDR/RR-TB as same drugs	$ 1,824.41	$ 145.95	$ 145.95
4%	Shean et al	$ 1,807.88	$ 36.16	$ 72.32
3%	Assumption same as MDR/RR-TB as same drugs	$ 1,120.21	$ 33.61	$ 33.61
26%	Sotgiu et al	$ 928.93	$ 18.58	$ 243.57
2%	Shean et al	$ 891.99	$ 17.84	$ 13.92
7%	Shean et al	$ 847.65	$ 59.34	$ 59.34
40%	Assumption similar profile to kanamycin	$ 50.76	$ 20.31	$ 20.31

$ 1,758.01		Weighted average MDR/RR-TB	$ 521.29	Weighted average XDR-TB	$ 1,039.06

Table 11-9 Weighted average costs of AE, 2016 USD

Moderate AE					
Renal dysfunction	Glomerular filtration rate < 60 to 30 ml/min	kanamycin	capreomycin	8%	Schnippel et al
Anemia	Hemoglobin <11 g/dL and >8 g/dL		linezolid		Not associated with current treatment regimen
Hypokalemia, electrolyte imbalance	e.g. Magnesium 0.9 to < 1.2 mEq/L or Potassium 2.5 to < 3.0 mEq/L	kanamycin	capreomycin	12%	Brust et al, grade 3 or higher
Thyroid dysfunction, hypothyroidism	e.g. requiring supplementation	ethionamide	ethionamide, para-	36%	Brust et al
Hepatitis, liver dysfunction	e.g. elevated ALT < 5 x upper limit of normal	pyrazinamide, ethi	pyrazinamide, ethi	7%	Brust et al
Hearing loss	Permanent, high frequency hearing loss (with or without tinnitus)	kanamycin	capreomycin	18%	Harris et al
Psychiatric disorder	e.g. depression, confusion	terizidone	terizidone	10%	Brust et al
Sleep disturbance, insomnia		terizidone	terizidone	10%	Jacobs and Ross
Peripheral neuropathy		terizidone	terizidone, linezoli	18%	Kelly et al (provider reported)
Visual disturbance			linezolid		Not associated with current treatment regimen

Tinnitus	without hearing loss	kanamycin	capreomycin	12%	Kelly et al (provider reported)
Dizziness, vertigo		kanamycin	capreomycin	8%	Kelly et al (provider reported)
Hypersensitivity, allergic reaction	Rash, dermatologic reaction (moderate)	Any	Any	16%	Kelly et al (provider reported)
Nausea, vomiting	Vomitting or nausea limiting oral intake	ethionamide	ethionamide, para-	18%	Kelly et al (provider reported)
Joint pain, arthralgia		pyrazinamide	pyrazinamide	12%	Kelly et al (provider reported)
Tendonitis		moxifloxacin	moxifloxacin	0.5%	Assumption, not reported in cited studies but is listed in guidelines
Headache		terizidone	terizidone	3%	Kelly et al (provider reported)
Diarrhoea			para-aminosacylic	15%	Brust et al

Summary stats	Resulting AEs / MDR/RR-TB patient	2.04	Resulting AEs / XDR-TB patient	2.73	Average per patient

3% Shean et al	$ 100.65	$ 8.05	$ 3.02
12% Sotgiu et al	$ 84.41	$ -	$ 9.94
12% Assumption at least as high as MDR/RR-TB as capreomycin has worse profile than kanamycin	$ 70.75	$ 8.49	$ 8.49
36% Assumption at least as high as MDR/RR-TB	$ 208.23	$ 74.96	$ 74.96
7% Assumption same as MDR/RR-TB as same drugs	$ 155.01	$ 10.85	$ 10.85
18% Assumption similar profile to kanamycin	$ 50.76	$ 9.14	$ 9.14
10% Assumption same as MDR/RR-TB as same drugs	$ 43.20	$ 4.32	$ 4.32
10% Assumption same as MDR/RR-TB as same drugs	$ 31.57	$ 3.16	$ 3.16
58% Sotgiu et al	$ 28.89	$ 5.20	$ 16.76
13% Sotgiu et al	$ 23.73	$ -	$ 3.08

12%	Assumption similar profile to kanamycin	$ 23.68	$ 2.84	$ 2.84
11%	Shean et al	$ 19.49	$ 1.56	$ 2.14
6%	Shean et al	$ 15.97	$ 2.56	$ 0.96
30%	Shean et al	$ 15.72	$ 2.83	$ 4.72
9%	Shean et al	$ 11.09	$ 1.33	$ 1.00
0.5%	Assumption same as MDR/RR-TB as same drugs	$ 3.06	$ 0.02	$ 0.02
7%	Shean et al	$ 2.52	$ 0.08	$ 0.18
19%	Shean et al	$ 2.51	$ 0.38	$ 0.48
$ 42.36	Weighted average MDR/RR-TB	$ 135.76	Weighted average XDR-TB	$ 156.05

Costed standard long-course regimen for South Africa MDR/RR-TB:

6 months kanamycin, moxifloxacin, terizidone, ethionamide, and pyrazinamide and 12 months moxifloxacin, terizidone, ethionamide, and pyrazinamide.

Costed indivdiualized regimen for South Africa XDR-TB, injection-based (pre-bedaquiline):

6 months capreomycin, linezolid, moxifloxacin, terizidone, ethionamide, clofazimine, para-aminosacylic acid, and pyrazinamide and 18 months linezolid, moxifloxacin, terizidone, ethionamide, clofazimine, para-aminosacylic acid, and pyrazinamide.

Associated ADR are those that were indicated (first listed or bolded as most likely drug) in:

World Health Organization. Companion handbook to the WHO guidelines for the programmatic management of drug-resistant tuberculosis; 2014.
Directorate Drug-Resistant TB. Management of Drug-Resistant TB: Policy Guidelines. Pretoria: National Department of Health; 2013.

Frequencies of ADR during MDR/RR-TB treatment were sourced according to severity from South African studies using current regimen that reported patient counts:

SAE (except hearing):	Schnippel K, Berhanu RH, Black A, et al. Severe adverse events during second-line tuberculosis treatment in the context of high HIV Co-infection in South Africa: a retrospective cohort study. BMC Infect Dis 2016; 16: 593.
Hearing:	Harris T, Bardien S, Schaaf HS, et al. Aminoglycoside-induced hearing loss in HIV-positive and HIV-negative multidrug-resistant tuberculosis patients. South African Med J 2012; 102: 363–6.
AE (if reported):	Brust JCM, Shah NS, van der Merwe TL, et al. Adverse events in an integrated home-based treatment program for MDR-TB and HIV in KwaZulu-Natal, South Africa. J Acquir Immune Defic Syndr 2013; 62: 436–40.
	Kelly AM, Smith B, Luo Z, et al. Discordance between patient and clinician reports of adverse reactions to MDR-TB treatment. Iternational J Tuberc Lung Dis 2016; 20: 442–7.
	Jacobs TQ, Ross A. Adverse effects profile of multidrug-resistant tuberculosis treatment in a South African outpatient clinic. South African Fam Pract 2012; 54: 531–9.

Frequencies of ADR during XDR-TB treatment:

AE associated with capreomycin or PAS:	Shean K, Streicher E, Pieterson E, et al. Drug-associated adverse events and their relationship with outcomes in patients receiving treatment for extensively drug-resistant tuberculosis in South Africa. PLoS One 2013; 8: e63057.
AE associated with linezolid:	Sotgiu G, Centis R, D'Ambrosio L, et al. Efficacy, safety and tolerability of linezolid containing regimens in treating MDR-TB and XDR-TB: Systematic review and meta-analysis. Eur Respir J 2012; 40: 1430–42.