Evaluation of the costs of managing cutaneous adverse drug reactions to first-line TB therapy in South African TB patients

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DECLARATION

I, Lauren Kerry Knight (KNGLAU005) hereby declare that the work on which this dissertation/thesis is based is my original work (except where acknowledgements indicate otherwise) 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.

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LIST OF ABBREVIATIONS

3TC	lamivudine
ABC	abacavir
ADR	adverse drug reaction
ALT	alanine aminotransferase
ART	antiretroviral therapy
AST	aspartate aminotransferase
BDQ	bedaquiline
BPaMZ	bedaquiline, pretomanid, moxifloxacin, pyrazinamide
BPaZ	bedaquiline, pretomanid, pyrazinamide
CADR	cutaneous adverse drug reaction
CP	continuation phase
CT	computerised tomography
CXR	chest radiograph
d4T	stavudine
DALY	disability adjusted life year
DILI	drug-induced liver injury
DLM	delamanid
DOTS	Directly Observed Treatment, Short-Course
DPT	drug provocation test
DRESS	drug rash with eosinophilia and systemic symptoms
DR-TB	drug-resistant tuberculosis
DS-TB	drug-sensitive tuberculosis
DST	drug sensitivity testing
E	ethambutol
EMB	ethambutol
ETO	ethionamide
FBC	full blood count
FTC	emtricitabine
GSH	Groote Schuur Hospital

H	isoniazid
HIV	Human Immunodeficiency Virus
INH	isoniazid
IP	intensive phase
IRIS	immune reconstitution inflammatory syndrome
LDR	lichenoid drug reaction
LFX	levofloxacin
LTBI	latent tuberculosis infection
M. tuberculosis	Mycobacterium tuberculosis
MDR-TB	multi-drug resistant tuberculosis
MFX	moxifloxacin
MSF	Medécins Sans Frontières
NHLS	National Health Laboratory Services
NNRTI	non-nucleoside reverse transcriptase inhibitor
NRTI	nucleoside reverse transcription inhibitor
NTP	National TB Programme
PaMZ	pretomanid, moxifloxacin, pyrazinamide
PCR	polymerase chain reaction
PTB	pulmonary tuberculosis
PZA	pyrazinamide
QALY	quality adjusted life year
R	rifampicin
RFB	rifabutin
RIF	rifampicin
RR-TB	rifampicin-resistant tuberculosis
Rx	treatment
SJS	Stevens-Johnson syndrome
STREAM	Standardised Treatment Regimen of Anti-Tuberculosis Drugs for Patients with MDR- TB
TB	tuberculosis
TDF	tenofovir

UCT	University of Cape Town
USD	United Stated dollars
UT	unnecessarily treated for TB
TEN	toxic epidermal necrolysis
WCC	white cell count
WHO	World Health Organization
XDR-T	extensively drug-resistant
Xpert® MTB/RIF	Xpert mycobacterium/rifampicin
Z	pyrazinamide
ZAR	South African rand

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ABSTRACT

Background

Optimal tuberculosis (TB) treatment remains the backbone of effective TB control programmes. However, TB drugs are often associated with adverse drug reactions (ADR) that affect treatment adherence and cure. Cutaneous adverse drug reactions (CADR) are more commonly associated with Human Immunodeficiency Virus (HIV)/TB co-infection, occurring in up to 7% of patients. If severe, CADR require treatment interruption and hospitalisation. There are no standardised guidelines for managing CADR to TB therapy. Current practice in South Africa involves drug rechallenge, a process, which aims to identify the offending drug and modify the treatment regimen. This practice can carry significant risks that need to be weighed against the benefits.

Despite significant resources required to manage CADR, there is no available data regarding their economic impact. Alternate strategies to manage TB therapy-associated CADRs and their cost have never been evaluated. The purpose of this study is to evaluate the economic impact of TB therapy-associated CADRs in South Africa and compare the cost of drug rechallenge with alternative strategies.

Methods

Data was obtained from 97 patients, admitted to the Groote Schuur Hospital dermatology ward with TB therapy-associated CADR. Clinical data pertaining to hospitalisation, diagnostic/monitoring tests and drug prescriptions was extracted from patient medical records. Healthcare and patient-related costs were obtained from financial department records, interviews and hospital admission records. Alternative drug regimens for CADR management were derived from literature and expert clinical advice. Costs were estimated using an ingredient's approach in 2016 US dollars. A cost-comparative analysis was performed comparing the cost of the current practice with alternative options. Univariate sensitivity analysis was used to investigate the uncertainties around cost components.

Results

The cost of managing a TB therapy-associated CADR was $6,525 per patient. Within this population the average cost of managing a CADR in a patient with DS-TB was $5,831 (95% CI: 8438; 10727). The main contributor of CADR costs was hospitalisation amounting to $3,638/patient (62% of total cost). Alternative CADR management strategies using outpatient-initiated second-line regimens containing rifabutin, bedaquiline and delamanid cost 44-55% less than drug rechallenge depending on the drug regimen used ($2,651/patient to $3,276/patient). Sensitivity analyses indicated that drug rechallenge was most sensitive to hospitalisation costs, whereas second-line treatment strategies were sensitive to TB drug costs. The average total loss experienced by patients as a result of the CADR was $530 (25% of their annual income), as compared to an estimated loss in the alternate regimens of $154 (10% of their annual income). Societal costs with alternate regimens were also lower at 46-66% that of current cost of $6,134.

Conclusion

CADR to TB treatment represent a significant economic burden to the healthcare system and affected patient. The alternate strategy of outpatient-initiated second-line therapy provides an economically feasible option by implementing an ambulatory practice of care despite using more expensive drugs. Shorter hospitalisation reduces patient and healthcare costs. This data should inform policy makers on optimal resource use within the healthcare system. Once the effectiveness and risk of drug-resistance of these strategies has been determined, further research should estimate their cost-effectiveness.

1. INTRODUCTION

Tuberculosis (TB) remains a major disease burden, particularly in the developing world where human immunodeficiency virus (HIV) co-infection is a major driver of the TB epidemic. While the World Health Organization (WHO) millennium development goals have promoted better case detection and access to treatment with great success, the number of individuals still affected is substantial [1]. These affected individuals account for significant healthcare expenditure and suffer considerable personal loss. South Africa, where the research was conducted, has one of the highest per year incidence rates of TB at 834 cases per 100 000 population, with HIV co-infection rates being as high as 50% in parts of the country [2].

First-line TB drugs; rifampicin, isoniazid, pyrazinamide and ethambutol, are both highly effective and affordable for the treatment of TB [3-5]. However, these drugs carry a risk of serious adverse drug reactions (ADR) such as hepatotoxicity and cutaneous adverse drug reactions (CADR) that often require treatment interruption and hospitalisation with significant mortality. To ensure optimal treatment and cure, patients often have to be rechallenged with the same drugs to identify and eliminate the offending drug [6-9]. Early withdrawal of the offending drug is necessary and associated with favourable patient outcomes in CADR [10]. Yet, TB treatment interruption is associated with significant mortality, especially if occurring during the intensive phase (initial 2 months) of therapy [3, 11]. With longer interruptions resulting in poorer outcomes. Thus, re-initiation and optimisation of TB treatment as soon as possible, balancing the risk of death from ADR and that from progressively worsening TB, is critical. Oral rechallenge, defined as a controlled administration of a drug in order to diagnose the offending drug in a hypersensitivity reaction, is the gold standard. *In vitro* methods like the lymphocyte transformation tests have low specificity and after being used for many years are still considered experimental and not widely used [6]. Oral rechallenge carries a significant risk of recurrence of a life-threatening ADR. It is for this reason historically that many authors were against rechallenging with any drug in severe CADR like Stevens Johnson

syndrome (SJS), toxic epidermal necrolysis (TEN) and drug rash with eosinophilia and systemic symptoms (DRESS).

In support of rechallenge there have been scattered reports in the literature of patients with severe CADR successfully rechallenged with first-line TB drugs to eliminate the offending drug from the regimen [12-15]. Rechallenge protocols differ between countries and centres without any general consensus on a method of rechallenge [6, 16, 17]. At Groote Schuur Hospital (GSH), hundreds of patients with TB-associated CADR have been successfully rechallenged using the framework outlined below.

Once hospitalised, all potential offending drugs are stopped and patients are allowed to reach biochemical and clinical baseline. Following this the potential offending first-line TB drugs are introduced sequentially and additively while clinical and biochemical parameters are monitored for rechallenge reactions. This allows identification of the causative drug [18, 19]. Typically, the most effective TB drugs, isoniazid and rifampicin are rechallenged first [6, 16, 17, 20, 21]. Based on patient sensitivities, co-morbidities and drug availability, the most effective and appropriate individualised TB drug regimen is derived. This process typically requires a protracted hospital stay placing substantial financial burdens on the patient and the healthcare service. Following drug rechallenge, patients are often subjected to prolonged treatment courses, specifically in cases where regimens exclude the first-line drugs, resulting in further personal burden.

The development of newer TB therapies has not kept up with the rate at which the TB epidemic has escalated. Alternate first-line drugs such as rifabutin in South Africa, are being shown to be as, if not more, effective as their primary first-line counterparts [22, 23]. The newer second-line drugs bedaquiline and delamanid, have passed phase 2b trials and have shown promising results in terms of rate of and time to sputum conversion [24, 25]. Phase 3 trials for bedaquiline are currently underway with phase 3 trial results of delamanid expected to be available in 2018. In South Africa access to these drugs is limited requiring approval from the TB advisory boards. These highly effective second-line drugs offer the option of an all-oral alternative for those who cannot use standard first-line drugs for any reason. Thus, avoiding the use of second-line

injectables, which are not only painful, but require daily clinic visits for the drugs to be administered if used in an outpatient setting.

With these newer effective treatment options in mind, we proposed an alternative therapy using mainly second-line drugs, avoiding drug rechallenge to optimise therapy while reducing costs associated with the rechallenge process. Patients would be admitted after the onset of CADR to allow for stabilisation, after which a regimen to which they have never been exposed would be started and they would be discharged for follow up in the community as per the National TB Programme (NTP) guidelines [26, 27]. Although second-line TB drugs are more costly than the first-line drugs [28, 29], the cost of hospitalisation associated with second-line therapy and ADR has been shown in many studies to be the greatest driver of treatment cost [26-28, 30].

TB and poverty have been shown to be on a perpetual cycle. TB more commonly affects poor people. TB disease and patient costs then result in a further loss of income and economy, perpetuating poverty. Patient level costs in the form of lost income (30-40% of annual income while on TB treatment) and disease related bills are higher during hospitalisation compared to treatment as an outpatient [31, 32]. Decentralised models of continuing optimum TB therapy may therefore also reduce patient level costs.

In resource-poor settings where budget constraints dictate practice, an evaluation of available treatment options is necessary to optimise expenditure while maintaining adequate patient access to health care. Cost-analyses often focus on the cost to the healthcare system with few studies considering the cost to the patient. Diseases are dynamic and this is highlighted by the TB/HIV pandemic and emergence of drug-resistant TB. Management strategies therefore too need to be adaptive and newer TB drugs need to be trialed. Once proven effective, they should be incorporated into treatment regimens. This will result in increased demand, reduction in cost of distribution and ultimately cost to the consumer. Patients should be offered the most effective and tolerable regimens to afford them the best outcomes while maintaining optimal quality of life.

1.1 Rationale and justification for research

In South Africa, despite widely implemented TB control programmes, an overburdened healthcare system has failed to adequately curb the TB epidemic resulting in a persistently high incidence of TB. Resources, both financial and otherwise need to be allocated to areas where they will yield maximum benefits for the patients and the healthcare system. Economic analyses, as part of a broader strategy, are needed to provide data on optimisation of resource management and patient treatment.

The occurrence of CADR to first-line TB drugs that requires interruption of treatment can be as high as 20% in HIV-infected populations [6]. This is particularly concerning in countries such as South Africa with high HIV and TB burdens. The cost of managing CADR to first-line TB drugs in South Africa is likely to be high due to the prolonged hospital stay, monitoring tests and drug substitutions that are required. However, these costs have never been fully determined. With newer second-line drugs that have better side effect profiles, becoming more available, alternative treatment regimens are not only feasible, but also more appealing. Furthermore, it is unknown whether first-line drug rechallenge or immediate second-line therapy is a more economically feasible approach to managing TB patients who develop CADR to first-line TB drugs. These data will be important to policy makers for rational planning, allocation of resources, determination of optimal prevention and management strategies, prioritization of funding for competing healthcare issues as well as inform future cost effectiveness analyses.

1.2 Objectives of the study

- To determine the individual cost per patient of TB therapy-associated cutaneous adverse drug reactions (CADR) using the current practice of drug rechallenge with first-line TB drugs.
- To compare the overall cost of drug rechallenge with first-line TB drugs to a hypothetical strategy of the immediate use of second-line drugs for the management of DS-TB patients who develop CADRs to first-line therapy.

- To determine the effect of varying specific component parameters on the cost of drug rechallenge and the alternative treatment regimens in a sensitivity analysis.
- To determine the costs incurred directly by patients who suffer from a TB therapy associated CADR and subsequent rechallenge in terms of lost income and medical expenses.

1.3 The research questions

- What is the current cost to the healthcare system and to the patient of managing TB-therapy associated CADR in South Africa?
- Is it more affordable to manage a CADR to first-line TB therapy in DS-TB patients by in-hospital drug rechallenge with first-line TB drugs, or immediate second-line outpatient therapy?

1.4 Thesis outline

This study presents the costs related to managing a CADR to TB therapy in a predominantly HIV-infected population in South Africa. Costs are calculated based on the current practice of drug rechallenge to optimise an individual patient's TB therapy. Chapter 1 provides an introduction to the thesis topic and outlines briefly the rationale for undertaking the cost analysis. The literature review is found in Chapter 2. Chapter 3 offers an explanation of the study design and methodology. Findings of the study are presented in Chapter 4 as costs of current rechallenge practice as well as alternative treatment options. Within this chapter a comparison of costs of available options is presented along with a sensitivity analysis of the main contributors to overall cost. A discussion of the study findings in the context of South Africa and in relation to the available literature is found in Chapter 5. Chapter 6 concludes the main study finding and provides recommendations for future analyses.

2. LITERATURE REVIEW

2.1 Epidemiology of Tuberculosis

TB is one of the most prevalent infectious diseases globally. In some countries, predominantly in the developing world, TB has reached epidemic status making it a public health emergency. According to the WHO, TB is one of the top 10 causes of death worldwide by a single infectious agent. South Africa, where this work was conducted, together with India, Indonesia, China, Nigeria and Pakistan account for 60% of the world's TB infections [2]. South Africa has one of the highest number of annual incident cases at 834 per 100 000 population (Figure 2.1), with 50% of these cases co-infected with HIV in parts of South Africa [1].

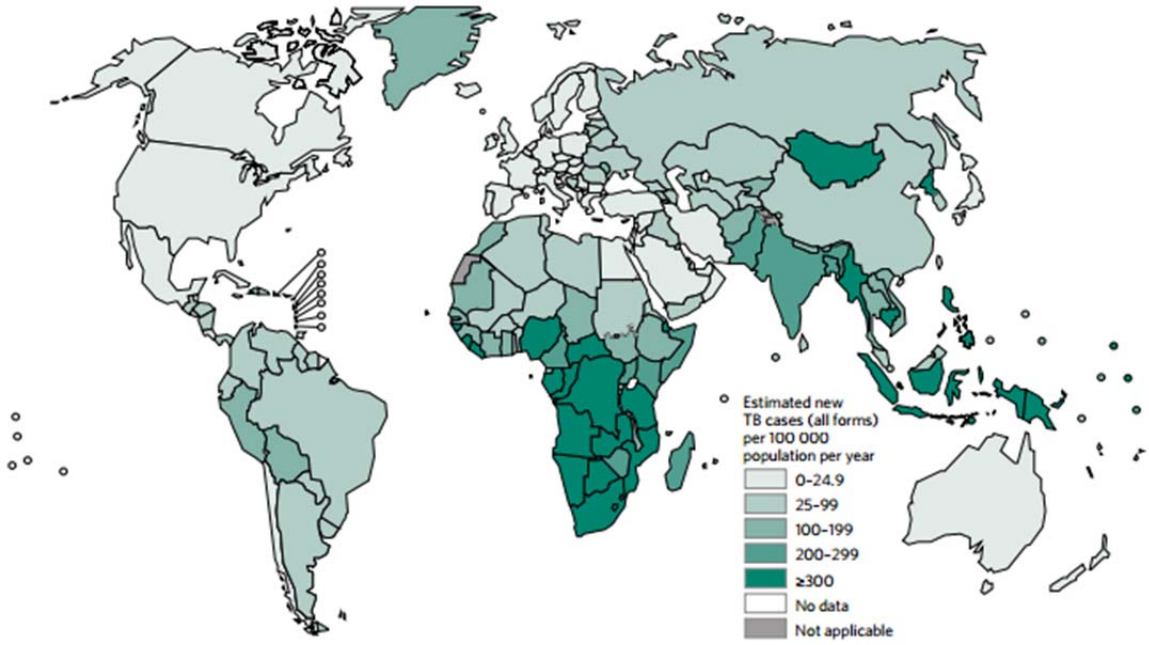

Figure 2.1: Global estimated TB incidence for 2015 [1].

In 2015, 10.4 million people were infected worldwide and there were 1.8 million deaths due to the disease; 0.4 million of these deaths occurred in individuals with HIV [2]. TB was the cause of death in 35% of people infected with HIV in 2015. The vast majority

(95%) of TB related deaths occurred in low- and middle-income countries and 60-80% of these individuals are co-infected with HIV [2, 19] (Figure 2.2). In South Africa, the TB epidemic is further fueled by poor socio-economic circumstances associated with overcrowding, hostel living among migrant workers, use of congested public transport systems and a high rate of HIV co-infection, all promoting the spread of TB by smear-positive patients. The typical clinical course of TB, characterised by prolonged latency and asymptomatic period, often delays treatment-seeking efforts by infected individuals resulting in disease transmission. It is estimated that a single infected person could infect up to 15 people per year [2].

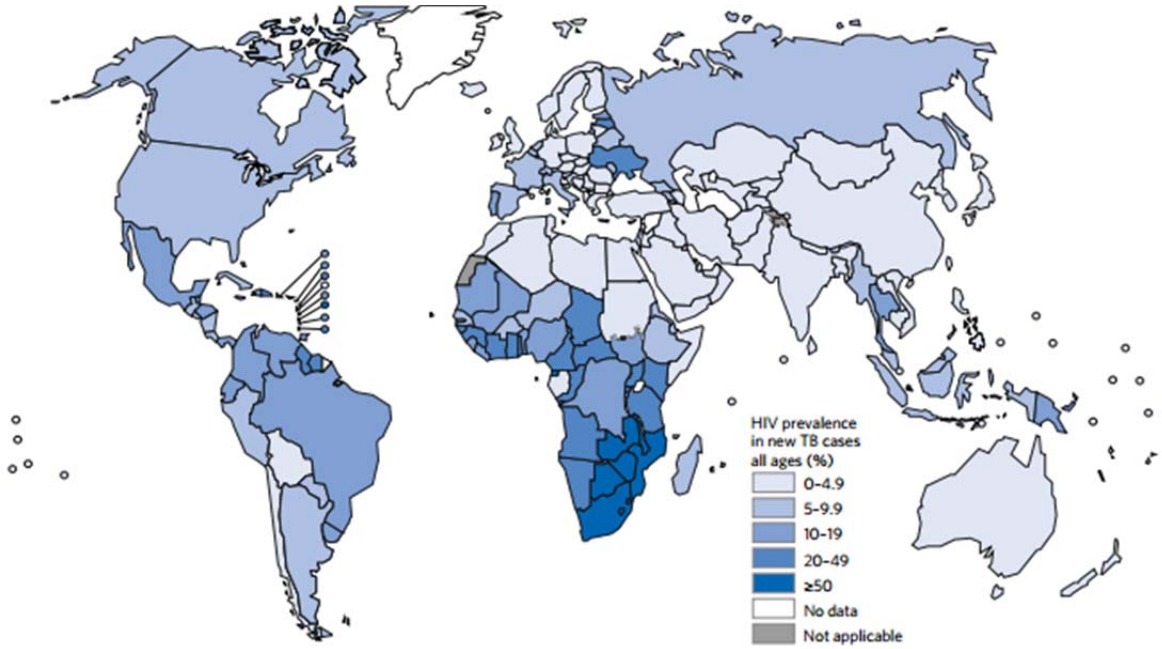

Figure 2.2: Estimated HIV prevalence in new and relapse TB cases in 2015 [1].

Multi-drug resistant TB (MDR-TB) is defined as resistance to at least rifampicin and isoniazid. MDR-TB can either be acquired, typically through treatment interruption or non-adherence (acquired resistance), or via transmission of MDR strains, known as primary MDR-TB [33]. The incidence of MDR-TB was estimated by the WHO to be 480,000 in 2015, with a further 100,000 people being diagnosed with rifampicin-resistant TB (RR-TB), who are also treated with MDR-TB regimens (Figure 2.3) [1].

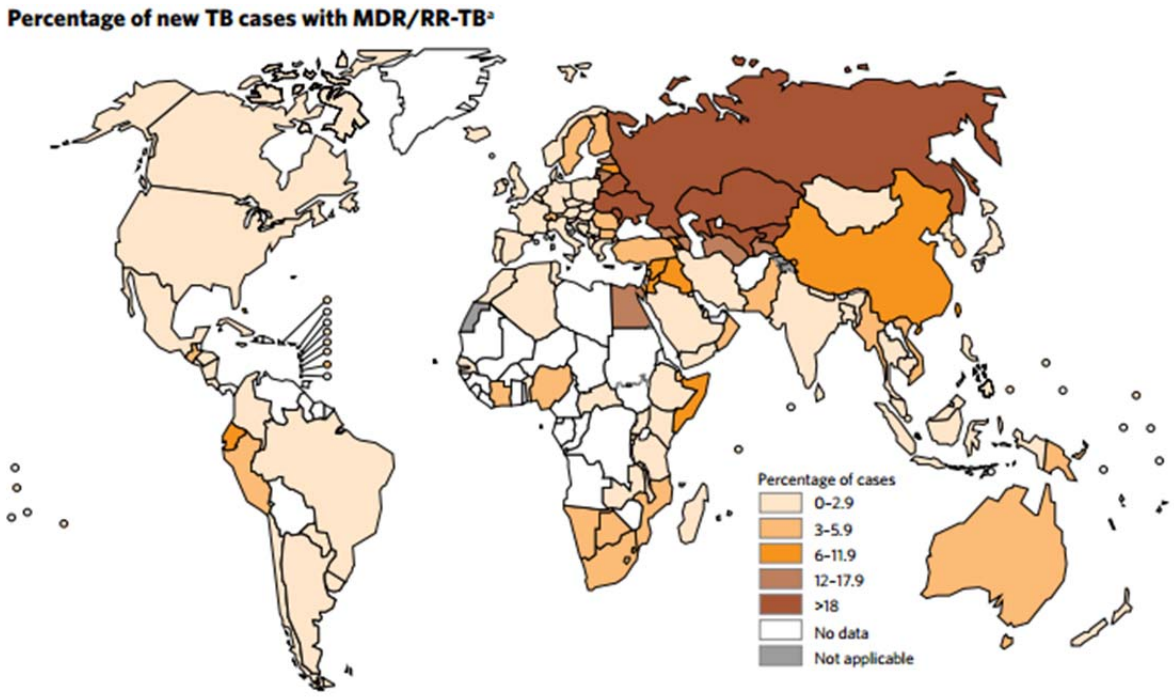

Figure 2.3: Global percentage of new cases with MDR/RR-TB in 2015 [1].

2.2 Pathogenesis of Tuberculosis

Mycobacterium tuberculosis (M. tuberculosis) is the causative agent of TB. The main site of infection is the lung (pulmonary TB), but *M. tuberculosis* can also affect other organs (extra- pulmonary TB) or spread to multiple organs via the peripheral blood (disseminated TB). Transmission of the bacilli is typically airborne, spread via cough aerosols from infected individuals, but can also occur through direct inoculation. Inhaled bacilli travel through the respiratory tract and eventually end up in the terminal alveoli where resident cells such as alveolar macrophages and neutrophils engulf the bacilli [34]. These cells function as the first-line of defense against *M. tuberculosis*. Once the bacilli are engulfed, additional cell types of the adaptive immune system, such as activated T lymphocytes, are recruited and interact to form a granuloma. A granuloma is a concentration of immune cells that effectively contains the *M. tuberculosis* [35].

In the majority of infected individuals, *M. tuberculosis* bacilli are contained within the granuloma in a non-replicating state known as latent TB infection (LTBI). The WHO estimates that about one third of the world's population, which could be up to 80% of the population in developing countries, has LTBI [2]. However, in a small proportion of individuals, when the balance between host immunity and the bacterial response is altered, the bacilli undergo replication. If the immune system is no longer able to contain the infection, this results in primary active disease [36]. A small number of latently infected individuals may develop active TB, known as reactivation TB, particularly if their immune system becomes compromised. Immunocompetent people have a 10% lifetime risk of developing active TB [37]. However, those with compromised immune status from malnutrition, diabetes, malignancy and, most notably, HIV, have a 20-30 times increased risk of developing TB at a rate of 8-10% per year [37].

2.3 Relationship between HIV and Tuberculosis

TB is the most common opportunistic infection affecting HIV-infected individuals, with 50-80% of patients with TB being HIV co-infected in Southern Africa [1, 38]. It has been well documented that HIV is one of the major drivers of the TB epidemic. Defective alveolar macrophages as well as a lack of CD4 T cells are thought in part to contribute to the increased susceptibility to TB in HIV-infected individuals [38]. HIV increases the risk of progression from latent to active TB, as impaired host immunity results in inadequate containment of the disease [37]. Lawn et al. clearly showed that the TB notification rate increased concurrently with the rate of HIV prevalence within the peri-urban population in the Western Cape province of South Africa [39]. Over the study period of 1996-2004, the TB notification rate increased 2.5-fold from 32 to 188, with the HIV prevalence increasing from 6% to 22%. The TB notification rate for HIV-infected participants was calculated to be 4,381 cases per 100,000 persons (95% CI, 3570-5313 cases per 100,000 persons) and 656 cases per 100,000 persons in the HIV-uninfected population (95% CI, 486–866 cases per 100,000 persons (Table 2.1) [39].

Table 2.1: Tuberculosis (TB) notification rates and the prevalence of HIV infection in a peri-urban community in the Western Cape, South Africa, 1996–2004 [39].

Table 1. Tuberculosis (TB) notification rates and the prevalence of HIV infection in a peri-urban community in the Western Cape, South Africa, 1996–2004.

Year	No. of TB notifications	Population size	TB notification rate, cases/100,000 persons[a]	TB re-treatment rate, %[b]	Estimated prevalence of HIV infection, %
1996	32	5518	580	3	6.3
1997	42	6429	653	21	8.9
1998	67	7339	913	7	11.6
1999	74	8250	897	20	14.2
2000	90	9161	982	17	16.5
2001	142	10,071	1410	15	18.4
2002	150	10,982	1366	18	19.9
2003	175	11,892	1472	22	21.1
2004	188	12,803	1468	24	21.9

[a] $P = .007$, by test for trend.
[b] $P = .073$, by test for trend.

The risk of TB is greatest within the first year of HIV infection [40, 41]. TB is often one of the first opportunistic infections heralding the individual being infected with HIV, but can occur at any stage with the risk increasing as CD4 count decreases [41]. Furthermore, the stage of HIV infection often has an effect on clinical presentation of TB, which can affect the ease of TB diagnosis. At greater degrees of immunosuppression with correspondingly lower CD4 counts, the radiological manifestations become less typical and disseminated TB becomes more common [42].

TB is also known to advance HIV progression, possibly due to increased immune activation, accelerating eventual death, especially in case of untreated HIV infection [43, 44].

2.4 Diagnosing Tuberculosis

Diagnosis of TB, though at times challenging, is an important aspect TB control programmes. Conventional methods of direct sputum smear microscopy examination by auramine fluorescent microscopy, sputum culture, chest radiograph (CXR) and tuberculin skin test have their own various limitations [45]. Typically, patients are

screened for symptoms including: cough, fever, weight loss and night sweats lasting more than 3 weeks. Symptom screening for TB has a sensitivity of 93%, but specificity is very low (36%) [46]. An absence of these symptoms has a negative predictive value of 97.7% to exclude TB [47]. Smear microscopy is still used in many developing country laboratories but suffers from low sensitivity and in a high HIV prevalence setting, patients with active TB, are often smear-negative. In a Kenyan study of 1,389 participants with an overall HIV prevalence of 45%, 66% of the participants with TB were smear-negative [48]. Sputum culture is considered the gold standard of TB diagnosis but availability of results can take up to 6 weeks. CXR as a diagnostic tool for TB, also has limitations, as it is subject to both inter- as well as intra-provider variability. In HIV co-infection radiological findings often differ from typical features of cavitation and upper lobe infiltrates, to more atypical features of non-cavitatory infiltration and consolidation in the mid and lower lung zones dependent on the patient's immune status [49]. More typical CXR features often correspond to smear-positive TB, with sensitivity of the CXR being up to 68% [48]. However, specificity is low (67%) resulting in patients being frequently started on TB treatment despite having negative smears (45%) [48].

Although not available at the onset of this study, the Xpert® MTB/RIF assay has greatly improved diagnosis accuracy and efficiency leading to its large scale roll out as the primary tool for TB diagnosis in South Africa [50]. In a sample population of 1,730 patients in 4 countries the test accurately diagnosed TB in 98.2% of smear-positive TB cases and 72.5% of smear-negative TB cases [50]. Specificity was reported to be 99.2% in these participants. The Xpert® MTB/RIF assay can diagnose TB as well as rifampicin-resistance as a surrogate marker for MDR-TB to aid in distinguishing patients from those with DS-TB. The assay is a polymerase chain reaction (PCR) based platform that probes regions of the gene responsible for the development of rifampicin resistance as a surrogate marker for drug resistance [45]. Within Boehme et al.'s population, MTB/RIF testing accurately identified 97.6% of rifampicin-resistance by phenotypic drug-susceptibility testing and 98.1% of rifampicin-susceptible bacilli [50].

As a result of the significant personal and public health consequences of untreated TB, a high index of suspicion and clinical judgment are often used as the basis upon which to initiate empiric TB therapy while investigations are still pending [3]. Empiric TB therapy is often itself a key factor in the delay of accurately diagnosing TB. This is particularly important in cases of disseminated or extra-pulmonary TB where CXR and sputum investigation aimed at detecting pulmonary TB are likely to be negative, yet patients still have the TB symptomatology.

Diagnosis of disseminated and extra-pulmonary TB provides a significant challenge. Investigations are often more costly and require the patient to be seen at a hospital as compared to diagnostic tools for pulmonary TB (PTB) that can be implemented at the primary health care level. Diagnostic methods range from less invasive radiology such as sonography of the abdomen and computerised tomography (CT) scans; to more invasive tissue histopathology of lymph nodes or any available affected tissues, bronchoscopy, and/or lumbar puncture to detect TB of the central nervous system. As with CXR, radiological investigations often have suggestive features such as intra-abdominal lymph nodes, splenic micro-abscesses and free fluid. Once again, tissue diagnosis and culture is the only definitive way of confirming TB infection [51]. In advanced HIV abdominal TB, which is relatively common, has characteristic features making abdominal sonography a reliable diagnostic tool as shown by Heller et al. [52].

2.5 Treatment of drug-sensitive Tuberculosis

Prompt and appropriate initiation of TB treatment limits not only transmission, but also potential life-threatening complications of the disease. There are 3 main objectives of TB treatment: (1) to rapidly reduce the number of actively growing bacilli; (2) to reduce disease transmission and disease severity by targeting populations of persistent bacilli allowing for durable cure after treatment completion; and (3) to prevent the development of drug resistance [3]. To meet these objectives, the TB treatment regimen of a prolonged course with combination chemotherapy was developed. DS-TB treatment is divided into two phases; the intensive and continuation phase. The intensive phase, which spans the initial 2 months of therapy, comprises a 4-drug regimen of rifampicin,

isoniazid, pyrazinamide and ethambutol. The continuation phase includes the final 4 months of therapy and, comprises only rifampicin and isoniazid. This combination therapy has been shown to decrease the risk of drug resistance while allowing for a shorter duration of therapy [4]. Rifampicin and pyrazinamide, through their sterilizing activity, are the key drugs that allow for the shortening of the duration to 6 months [22, 53]. Regimens containing a rifamycin (in this case rifampicin) throughout the treatment course are superior [5].

Current TB therapies and treatment strategies have proven to be highly effective with the WHO stating that 49 million lives were saved through accurate diagnosis and treatment of TB over the last 15 years and the global incidence of TB has fallen by 1.5% since 2000 [2].

Despite the efficacy of TB treatment, many barriers to completion and cure still exist. With the protracted course of treatment, significant patient responsibility is required. There has been a shift to a more patient-centered approach to the management of TB with emphasis being placed on educating the patient and the community as well as tailoring treatment to suit the individual. Despite this improved ‘‘treatment literacy” where patients are educated about treatment, side effects and potential complications, adverse effects are most commonly the reason patients default from any medication [3].

2.6 Treating Tuberculosis in the context of HIV

Due to the increased risk of mortality with concomitant HIV and TB infection (estimated between 10-50%), South African guidelines currently recommend that TB treatment is initiated first followed by antiretroviral therapy (ART) 2-8 weeks later [54]. Delay in ART initiation allows for a decline in the TB bacterial load. With initiation of ART, the immune system is boosted with risk of immune reconstitution system (IRIS), an exaggerated immune response to the TB bacilli [6, 38, 54]. The severity of IRIS is associated with the bacilli load. This approach in the majority of patients is associated with improved survival, but also reduces the risk of drug interactions and overlapping toxicities. All patients who are HIV/TB co-infected irrespective of CD4 cell count

became eligible for ART with the update of South African TB guidelines in 2013, although this was not the case when this study was initiated [55]. Individuals co-infected with HIV and TB between 2009 and 2013 were only eligible for ART based on the guidelines outlined in Table 2.2 below [56].

Table 2.2: Eligibility guidelines for ART and ideal first-line regimens with their associated adverse events during the course of the study.

South African ART Guidelines	Eligibility Criteria	1st line Regimen	Special considerations	Potential adverse drug reactions
2010	CD4 count <200 cells/mm^3 **OR** CD4 count <350 cells/mm^3 -In patients with TB/HIV -Pregnant women **OR** WHO stage IV irrespective of CD4 count **OR** MDR/XDR irrespective of CD4 count.	**Newly diagnosed:** TDF + 3TC/FTC + EFV/NVP **Stable on d4T regimen:** d4T + 3TC + EFV	EFV preferred to NVP in patients with TB. Contra-indications to TDF (renal disease) use AZT	TDF: renal impairment NVP: hepatitis and **CADR** AZT: anaemia, neutropaenia D4T: peripheral neuropathy and pancreatitis EFV: **CADR,** hepatitis
2013	CD4 count <350 cells/mm^3 **OR** All types of TB **OR** WHO stage 3 or 4 disease	**Newly diagnosed** TDF + FTC (or 3TC) +EFV FDC preferred **Currently on d4T regimen** TDF + FTC/3TC + EFV FDC preferred	Contraindication to TDF and AZT (renal disease and anaemia) use d4T Problem with TDF, AZT and d4T use ABC	TDF: renal impairment FTC: hyperlactaemia 3TC: anaemia, hyperlactaemia EFV: **CADR** hepatitis ABC: **CADR** NVP: **CADR**, hepatitis
2015	CD4 <500 cells/mm^3 **OR** Clinically stage 3 or 4 disease **OR** Active TB Pregnant/breastfeeding Hepatitis B virus co-infection	**Newly diagnosed** TDF + FTC (3TC) + EFV FDC preferred **If on d4T** Change to TDF if virologically suppressed and Cr clearance >50mL/min	Contraindication to EFV use NVP Contraindication to EFV and NVP use LPV/r Contraindication to TDF use ABC	TDF: renal impairment FTC: hyperlactaemia 3TC: anaemia, hyperlactaemia EFV: **CADR**, hepatitis NVP: **CADR**, Hepatitis

Key: 3TC=lamivudine, ABC=abacavir, Cr= creatinine, CADR=cutaneous adverse drug reaction, d4T=stavudine, EFV=efavirenz, FTC= emtricitabine, LPV/r=lopinavir/ritonavir, NVP=nevirapine, TDF=tenofovir

2.7 Drug related toxicities

The concomitant initiation and use of ART and TB treatment has significant drawbacks. Not only do clinicians managing these individuals have to deal with the significant risk of IRIS, there is also a high risk of drug-drug interactions and overlapping adverse drug reactions (ADR); the most notable being hepatotoxicity and CADR. Adverse drug reactions have been defined by the WHO as ‘‘A response to a drug which is noxious and unintended, and which occurs at doses normally used in man for the prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function’’ [57].

2.7.1 ADR related to TB therapy

The incidence of ADR to first-line TB therapy varies widely from 8-85% largely due to variation in definitions, study design and population based factors [58]. Major adverse events, defined as those requiring hospitalisation or interruption of therapy, overall seem to be less common than the milder reactions at 12.8% compared to 41.1%, which was noted at a teaching hospital in Brazil [58, 59].

Literature reports an incidence of 53% of individuals on TB therapy experiencing adverse events. In a study by Michael et al. in a Nigerian population, 30% of whom were HIV co-infected, the majority of adverse events to TB drugs was mild and resolved within 2 weeks of starting therapy [60].

Hepatotoxicity and CADR are two of the more serious ADR related to TB treatment. They are often the primary reason of treatment interruption; hospitalisation; prolonged illness; inadequate treatment and potential life-threatening events further increasing morbidity and mortality [6-8]. Studies have shown that the majority of cases of hepatotoxicity and CADR occur during the intensive phase of therapy [19, 37, 61].

2.7.1.1 Hepatotoxicity

Studies have reported up to 28% of patients on TB treatment experiencing hepatotoxicity with Hassen et al. reporting that 11.5% of patients developed hepatotoxicity while receiving TB treatment [37]. Of the four first-line TB drugs, rifampicin, isoniazid and pyrazinamide are known hepatotoxins.

The definition of hepatotoxicity varies in the literature, but comprises both clinical as well as serological manifestations that occur as a result of exposure to a hepatotoxin. The definition favoured in the South African context is: (1) an alanine transaminase (ALT) level>120IU/l with nausea, vomiting, abdominal pain or jaundice, or (2) ALT>200 IU/l and asymptomatic or (3) total serum bilirubin concentration >40µmol/l [37, 62].

Despite slightly varied cut offs of raised levels of liver enzymes, aspartate transaminase (AST) and ALT for the diagnosis of hepatotoxicity, the literature reports an incidence of hepatotoxicity of between 6.9% and 11.5% [9, 37, 63]. TB drug induced hepatotoxicity was found to occur in the first 6 weeks of initiation of therapy in 93% of cases, but occurring sooner, within 14 days (range 4-60) of treatment initiation in HIV/TB co-infected patients [37]. Various risk factors have been identified for the development of hepatotoxicity. Hassen et al. found disseminated TB (p=0.001) and malnutrition (body mass index <18.5kg/m^2) (p=0.010) were independent risk factors for the development of hepatotoxicity [37].

Hepatotoxicity can occur both independently, as an ADR, or in conjunction with CADR. Liver function abnormalities are not commonly associated with TEN, but occur in up to 50% of cases of DRESS. Involvement can range from a mild hepatitis to fulminant necrosis with an associated increase in mortality and is frequently related to prolonged periods of hospitalisation [64]. Hepatotoxicity also influences rechallenge practice with pyrazinamide not being rechallenged due to its direct association as a hepatotoxin [65].

2.7.1.2 Cutaneous adverse drug reactions

CADR is defined as an undesirable change to structure or function of the skin, the appendages or the mucous membranes due to administration of a drug [64]. Studies report variable incidences (5.7% to as high as 23% in some populations) of CADRs to TB therapy, largely due to differences in study design, populations as well as a lack of consistent case definitions and disease severity grading [6, 11, 61, 66, 67].

All first-line TB drugs (rifampicin, isoniazid, pyrazinamide and ethambutol) can potentially cause CADR [65]. However, the extent to which each of the first-line drugs

is implicated remains unclear. Some authors suggest that pyrazinamide is the most common offending drug [11, 68]. Conversely, Yee et al. found that rifampicin was most commonly implicated in CADR occurring in HIV-infected patients (hazard ratio: 2.4–2.9, isoniazid; hazard ratio: 8.0, rifampicin; and hazard ratio: 2.1, for pyrazinamide) [68]. In a study conducted at Groote Schuur hospital, rifampicin was found to be the most common offender [65].

These cutaneous manifestations can vary from; mild, requiring no intervention, to those requiring topical or mild systemic therapy, to severe and life-threatening. Although the majority of patients will have milder forms of CADR such as morbilliform rashes and urticaria, up to 17% can develop more severe forms associated with an epidermal necrolysis and systemic involvement [11]. A third of patients require hospitalisation and up to 75% of patients will need to have their drug regimen modified either as an inpatient or outpatient following development of CADR.

2.7.1.2.1 Clinical phenotypes of TB-associated CADR

There is a wide range of CADR associated with TB drugs (Table 2.3). These vary from the milder forms such as drug exanthems, which are usually self-limiting requiring only supportive management, to the more severe forms of SJS (Figure 2.4), SJS/TEN overlap and TEN (Figure 2.5)[11]. These are associated with epidermal and mucosal necrosis (10% epidermal detachment in SJS, 10-30% in SJS/TEN overlap and >30% in TEN), occasionally systemic involvement and may progress to skin failure if not managed correctly [6]. Mortality in these cases can be up to 40% specifically in the more severe forms of TEN, even with optimal care in tertiary specialist departments and intensive care units [69]. In patients with active TB, the development of SJS and TEN is associated with increased mortality [70]. Notably, the more severe reactions often initially resemble the milder forms of drug exanthems, so the reaction does need to be monitored for potential progression [6]. Drug rash with eosinophilia and systemic symptoms (DRESS) (Figure 2.6) has a latency period of up to 3 weeks. Systemic symptoms are described in Table 2.3, but commonly include hepatitis.

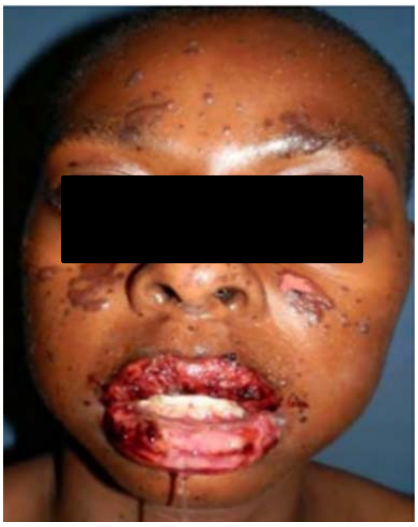

Figure 2.4: Mucosal ulceration characteristic of SJS [71].

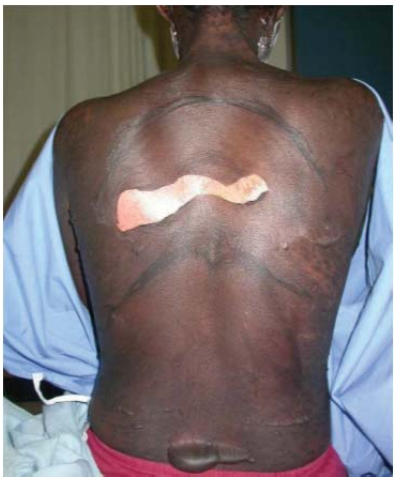

Figure 2.5: TEN with characteristic blistering and stripping of the epidermis [6].

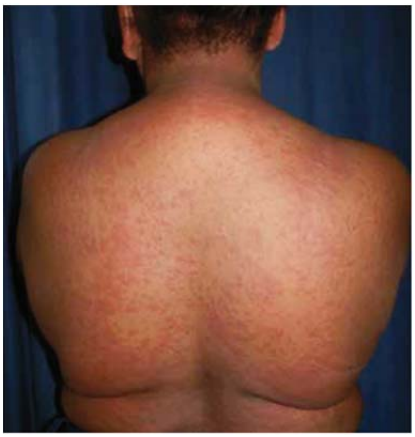

Figure 2.6: DRESS Syndrome with visible urticarial papules [16].

Table 2.3: Clinical phenotypes and associated features of cutaneous adverse drug reactions occurring as a result of TB therapy.

REACTION	FEATURES OF RASH	% BSA	LATENT PERIOD	SYSTEMIC FEATURES	SEVERITY	MANAGEMENT
Drug Exanthem	Erythematous macules and/or papules, start centrally becoming generalized +/- confluent.	<50%	7–14 days*	Low-grade fever, pruritus.	Mildest form CADR, but commonest (95%).	Usually self-limiting, requiring supportive management.
SJS/TEN	Painful dusky macular erythema, blisters, Nikolsky sign, erosive mucositis in ≥2 surfaces, palmoplantar tender erythema.	SJS <10% SJS/TEN overlap 10-30% TEN >30%	4-21 days	Prodrome of flu-like symptoms, high fever, malaise, rarely pneumonitis.	Up to 40% mortality [69, 70].	Treatment interruption and avoidance of offending drug.
DRESS	Itchy exanthem or urticarial papules/plaques, erythroderma, non-erosive mucositis.	N/A	2-6 weeks*	Fever, oedema lymphadenopathy, eosinophilia and most commonly hepatitis.	10% mortality [6, 70]	Treatment interruption and avoidance of offending drug.
LDR	Itchy symmetrical flat-topped purplish papules or macules becoming confluent, scale, may be photodistributed [72], longstanding lesions may hyperpigment or depigment, may have oral lesions.	N/A	Months to more than a year.	None	Mild	No interruption of offending agent as no acute markers on rechallenge [73, 74].

* The "Latent period" could be shorter in already sensitized patients

Key: BSA=body surface area, CADR=cutaneous adverse drug reactions, DRESS=drug reaction with eosinophilia and systemic symptoms, LDR= lichenoid drug reaction, SJS=Steven's Johnson syndrome, TEN= toxic epidermal necrolysis

2.7.2 ADR related to ART

ADR due to ART is also a common occurrence. In a Swiss cohort of 1000 patients receiving combination ART, 47% of patients were reported to have clinical adverse events [75]. Furthermore, the risk of drug hypersensitivity in HIV-infected individuals is thought to be much greater as compared with HIV-uninfected individuals [70, 76, 77].

CADR have been described in varying frequency and with varying clinical manifestations with all classes of ART. Cutaneous manifestations range from hyperpigmentation and hair loss to SJS and TEN [78]. As is the case with CADR due to TB therapy, exact incidence is often difficult to estimate due to differing study designs and disease definitions. However, in a study conducted in a tertiary hospital in India, 16,5% of mucocutaneous manifestation in HIV-infected individuals using ART were CADR, the severity of which was not defined [76].

The non-nucleoside reverse transcriptions inhibitors (NNRTI) class, of which nevirapine (NVP) and efavirenz are commonly used in South African Treatment guidelines, are the most commonly associated with CADR occurring in up to 26% of patients [78]. In a study of 27 consecutive pregnant women with SJS/TEN, NVP was found to be the offending agent in 95% of the women [79]. CADR associated with nucleoside reverse transcription inhibitors (NRTI), such as tenofovir and protease inhibitors (PI) lopinavir/ritonavir, occur less frequently in about 5% of exposures [78].

2.7.3 Drug-drug interactions between TB therapy and ART

Even in cases where treatment is well tolerated, the high pill burden associated with the two concomitant diseases, impacts on patients' adherence to therapy. Added to this is the impact of increased risk of ADR. Adverse events occur more commonly in HIV-infected individuals (26.7%) as compared to HIV-uninfected individuals on TB therapy (13.3%) [80]. Furthermore, there is a 1.7 fold increase of serious ADR related to TB therapy in individuals with HIV co-infection [60].

Hoffmann et al. found that TB therapy, when used concurrently with ART, resulted in an 8.5 fold increase in the risk of developing hepatotoxicity [81]. This is likely due to IRIS, causing hepatic inflammation and elevated transaminase levels in the liver whether ART was started prior to or following TB therapy initiation [81].

CADR are also more commonly associated with HIV infection, with HIV being one of the clinical characteristics related to the development of CADR (p=0.001), along with polypharmacy (p=0.003) and autoimmune disorders (p=<0.001) [11]. The role of HIV in CADR development is further supported by a UK study where the CADR was severe enough to warrant treatment interruption in 13% of HIV-infected patients as compared to 8% in the HIV-uninfected population [7]. Thioacetazone is an example of a drug used historically to treat TB, which was found to have such a strong association with SJS/TEN and mortality thereof in HIV/TB co-infected patient that WHO recommended that its continued use be abandoned [6, 7, 82, 83].

With HIV co-infection predisposing individuals to the risk of CADR to TB therapy as well as ART being an independent cause of CADR, it is often difficult to determine which drug is the causative agent. In addition, IRIS in itself could present a picture suggestive of an ADR adding to the diagnostic conundrum [62]. In many cases identifying the causative agent may be easier based on treatment durations; i.e. the last introduced being the most likely to have caused the reaction. The Naranjo ADR probability scale (see appendix 1), a widely accepted questionnaire used to establish a

temporal relationship between exposure to a drug and the subsequent ADR, further supports this notion [84]. Rechallenge reactions enable clinician to prove causality and subsequently add to this score resulting in a higher Naranjo probability.

2.7.4 IRIS as a confounder in the diagnosis of ADR

There is no diagnostic test to confirm the presence of IRIS, with diagnosis being based on the clinical presentation and exclusion of other causes for the patient's symptoms [62, 85]. Typical IRIS is associated with mycobacterial, fungal and viral infections. Unrecognised infections may be unmasked or in cases where patients have already been diagnosed with an opportunistic infection, there may be recurrence or worsening of the symptoms despite effective treatment [85]. Diagnosis of IRIS relies on; 1) an improvement of symptoms on treatment for the opportunistic infection before ART; 2) worsening clinical condition suggestive of an opportunistic infection soon after starting ART; and demonstration of a response to ART (improving CD4 count and suppressed viral load) as well as 3) exclusion of alternative causes for deterioration (bacterial or additional opportunistic infection, ADR, poor adherence, or resistance to treatment) [85]. TB-IRIS typically presents with fever, lymphadenitis, pulmonary infiltrates and effusions [86]. These symptoms could therefore be associated with the systemic features prior to CADR or with hepatitis.

2.8 Management of TB drug associated toxicities

In cases of severe reactions, patients are usually hospitalised and all potential offending drugs (TB drugs and ART) are withdrawn. The clinical symptoms and biochemistry are closely monitored, as these are early indicators of worsening condition of the patient. The same parameters typically improve on withdrawal of the offending drug. Less severe reactions, defined as those, with rash and pruritis, without systemic or mucosal involvement, requiring supportive therapy are managed at a clinic level according to the South African National TB guidelines [87].

Withdrawal of the offending drug has been shown to be associated with a more favourable outcome in the cases of CADR, which is used to justify treatment interruption [10]. This practice is supported by both the American Thoracic Society as

well as British Thoracic Society guidelines which recommend stopping therapy in cases of severe hepatitis until there is a resolution of the biochemical disturbance and improvement in symptoms [88]. Drug withdrawal could be associated with increased mortality for affected patients in the intensive phase and, particularly, in the first two weeks of therapy. Furthermore, interruptions can lead to drug resistance, especially if patients remain on mono- or dual-drug therapy. Such sub-optimal regimens can result in impaired action against rapidly dividing bacilli leading to disease progression and transmission to other susceptible or exposed individuals [6, 62]. In a multivariate analysis of 820 individuals, interruption of treatment was associated with increased risk of death in the intensive phase (hazard ratio: 3.20; p=0.001) [11]. Similarly, the San Francisco Tuberculosis Control Programme found that treatment interruption in the intensive phase was associated with increased mortality (hazard ratio: 3.15; 95% CI: 1. 52–6 .52; p = 0.002). Mortality was even higher when reviewed in the HIV-infected population (hazard ratio: 3.47; 95% CI: 1. 27– 9.50; p = 0.02) [3].

Based on the literature, it is clear that treatment needs to be interrupted, or at least the offending drug withdrawn, to allow for recovery and a more favourable patient outcome in terms of the adverse reaction. However, treatment needs to be reinitiated promptly to prevent excessive patient morbidity and mortality. One of the more widely used methods of ensuring this is drug rechallenge, which is discussed below.

2.9 Principles of rechallenge of first-line TB Therapy

The gold standard to diagnose drug hypersensitivity is a drug provocation test (DPT), in which there is controlled administration of the drug to prove causality [18]. The European Network for Drug Allergy and the European Academy of Allergology and Clinical Immunology interest group on hypersensitivity has developed guidelines for DPT (Figure 2.7) [18].

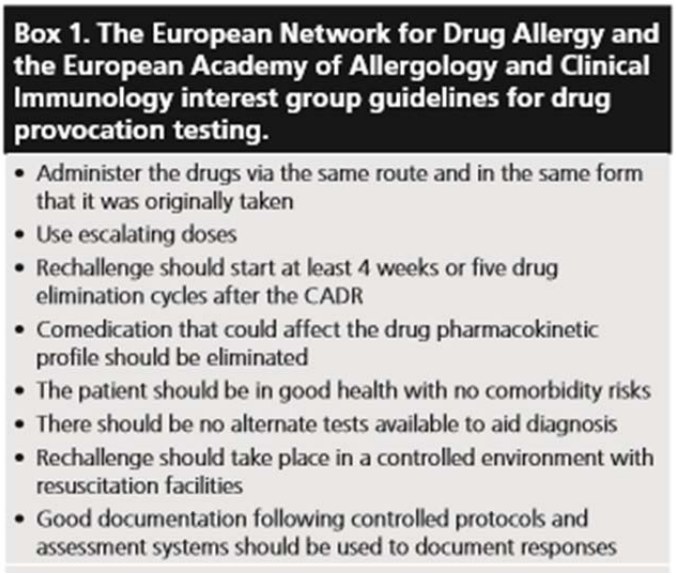

Figure 2.7: Guidelines for DPT [18].

Various methods of rechallenge have been debated in the literature. Current practice at Groote Schuur hospital involves using a full dose of the TB drugs sequentially and additively in keeping with guidelines of 'administering the drugs via the same route and in the same form that it was originally taken' [18]. Sharma et al. showed that full dose rechallenge compared to dose escalation is not associated with increased risk of reintroduction reactions [17]. Full regimen reintroduction allows for treatment to be optimised more rapidly, but has the disadvantage in that individual causative drugs can't be identified should a rechallenge reaction occur. This method is also associated with an increased risk of hepatotoxicity [89]. The order in which the drugs should be rechallenged is still contentious. Some strategies suggest rechallenge with the least likely offending drug first [6]. Whereas others favour reintroduction of rifampicin and isoniazid, the most effective drugs, first to optimise the treatment regimen [6]. Consensus as to which of the currently used drugs is the most likely implicated in the CADR has not been reached. Rifampicin has been identified as the most common offending drug in a predominantly HIV-infected population by both Yee et al. and Lehloenya et al. who found that reintroduction reactions were caused by rifampicin in 35% of their study population [6, 68]. At Groote Schuur hospital, the rechallenge sequence follows the hypothesis that isoniazid has the highest early bactericidal activity,

followed sequentially by rifampicin, pyrazinamide and ethambutol [20, 21]. This theoretically minimises the risk of developing resistance during the early phases of rechallenge by eliminating highest number of viable bacilli.

Upon presentation with CADR, all patients with severe reactions are typically admitted for inpatient stabilisation and monitoring. All potential offending drugs are withdrawn and patients receive supportive therapy while clinical and biochemical parameters are monitored. Once the patient is clinically and biochemically normalized, 3 second-line anti-TB drugs to which the patient has not previously been exposed are initiated as 'bridge' therapy (Figure 2.8). Literature largely reports that duration on bridge therapy can vary widely based on the extent of systemic involvement and hepatic injury [90]. In a population of 175 patients undergoing TB drug rechallenge the average time to stabilisation before rechallenge could be initiated was between 17-21days [17]. The use of bridge therapy aims to minimize the risk of developing mycobacterial resistance during the prolonged rechallenge period with the individual first-line drugs, by avoiding periods of mono- or dual-drug therapy. Lehloenya et al. in Cape Town, South Africa have reported using a combination of aminoglycosides (streptomycin, amikacin or kanamycin), quinolones (ofloxacin or moxifloxacin), terizidone, ethionamide, linezolid, clofazimine or para-amino-salicylic acid dependent on the hospital's treatment guidelines, drug availability and toxicity profile in relation to the patient's co-morbidities [6]. Sharma et al. in an Indian study used a similar bridge therapy in their population combining ethambutol, streptomycin and one of the fluoroquinolones [17]. Though stabilisation periods in CADR are typically managed as inpatients, consensus statements on management of drug-induced liver injury (DILI) to TB therapy provide guidelines for outpatient management, which provide the possibility that the same could be applied to CADR [62]. According to these guidelines moderate DILI (ALT>200), in a clinically well patient, can be managed as an outpatient with TB therapy being stopped, a bridging regimen of streptomycin, moxifloxacin and ethionamide started and ALT monitored every 7 days [62].

Following withdrawal of the offending drug but prior to reinitiating therapy, patients are either desensitized (in the case of IgE mediated reactions) to the offending drug or a suitable alternative drug(s) is added in their existing regimen [65]. It is well documented that there is a limit to effective TB therapy and many alternatives to the first-line combined chemotherapy are inferior, have different and potentially more adverse effects resulting in a need for a longer treatment course of up to 24 months [6]. To further support the preferred use of first-line drugs, there is compelling evidence that rifampicin-based regimens are superior to those which exclude rifampicin in terms of a favourable outcome of TB and disease relapse [17, 91, 92]. The concept of drug rechallenge has been developed to identify and exclude the offending drug and subsequently modify the treatment regimen rather than removing all first-line TB drugs. This strategy aims to create the most effective and safe patient specific regimen. Thus, once on bridge therapy first-line TB drugs are then sequentially and additively rechallenged. This typically takes about 30 days as reported by Lehloenya et al. who rechallenged TB treatment in TB/HIV co-infected patients at a tertiary centre in Cape Town, South Africa [65]. A drug is considered an offender if a rechallenge reaction occurs on repeat exposure then reversed upon its withdrawal [6, 84].

The interval between introducing drugs during rechallenge is also contentious and in some studies has been found to be too short to exclude overlapping toxicities of drugs [19]. These studies have found that with too short an interval between rechallenge, it is difficult to establish causality based on the rechallenge reactions occurring upon re-exposure to the offending drugs [19]. However, in a predominantly HIV-infected population in Cape Town, 22 of the 23 reactions occurred within 72 hours of reintroducing the offending drug supporting the 3-4 day interval between drug reintroduction [65].

Figure 2.8: Overview of drug rechallenge process in CADR.

With first-line TB therapy being more effective, rechallenge to build regimens based on first-line therapies seems prudent. However, rechallenge can carry a significant risk to the affected patient. Lehloenya et al. reported that 50% of their predominantly HIV-infected (91%) population developed rechallenge reactions. Although the majority of the reactions were mild and resolved spontaneously, there were 6/23 (26%) moderate and 4/23 (17%) severe reactions upon re-introduction of the offending drug [65]. The authors concluded that although rechallenge is feasible and frequently successful, the process is not entirely benign and requires close inpatient monitoring. In this study, the mean hospital stay was 30 days (range 24-47) for inpatient stabilisation, with a further 18 days (range 14-33) needed to complete the rechallenge process [65].

2.10 Alternatives to drug rechallenge

In instances of severe drug reactions, some authors recommend ensuring the patient is never re-exposed to the offending drugs and an alternative regimen is devised [14, 15]. A potential alternative to rechallenge involves initiating patients directly onto second-line therapy. This is typically the case in drug-resistant TB (DR-TB), or in cases where there are significant contra-indications to rechallenge such as severe comorbidities, pregnancy and in those where there is an unacceptable risk of life threatening rechallenge reactions [6, 88].

Second-line regimens are less effective (48-60% success rate), have a greater risk of adverse effects, require a longer duration of treatment (18-24 months) and are

significantly more expensive than first-line alternatives [26, 27, 30]. These regimens are generally reserved for cases of MDR-TB.

2.10.1 Second-line TB therapy regimens

In patients with rifampicin-resistant TB (RR-TB), or MDR-TB, the WHO guidelines recommend a regimen that comprises at least 5 anti-TB drugs known to be effective [93]. This regimen should include pyrazinamide (PZA) along with 4 other drugs comprising:

- 1 drug from group A
- 1 from group B
- and at least 2 from group C (see Table 2.4).

Table 2.4: Medicines recommended for the treatment of rifampicin-resistant and multidrug-resistant TB [93].

A. Fluoroquinolones[2]		Levofloxacin Moxifloxacin Gatifloxacin	Lfx Mfx Gfx
B. Second-line injectable agents		Amikacin Capreomycin Kanamycin (Streptomycin)[3]	Am Cm Km (S)
C. Other core second-line agents[2]		Ethionamide / Prothionamide Cycloserine / Terizidone Linezolid Clofazimine	Eto / Pto Cs / Trd Lzd Cfz
D. Add-on agents (not part of the core MDR-TB regimen)	**D1**	Pyrazinamide Ethambutol High-dose isoniazid	Z E H[h]
	D2	Bedaquiline Delamanid	Bdq Dlm
	D3	*p*-aminosalicylic acid Imipenem-cilastatin[4] Meropenem[4] Amoxicillin-clavulanate[4] (Thioacetazone)[5]	PAS Ipm Mpm Amx-Clv (T)

If the minimum number of drugs cannot be comprised using the above formula, it is recommended that a drug from group D2 and other drugs from D3 may be added to make the 5 drugs in the regimen.

In confirmed DR-TB cases, the regimen should be further strengthened with high dose isoniazid (INH) and, or ethambutol (EMB) [93]. In cases of INH-resistance, resistance is either to the *kat*G or *inh*A promoter gene [94]. Mutations result in TB bacilli being resistant to low dose INH, with higher doses 0,4ug/ml as compared to 0,1ug/ml being effective. The efficacy is thought to be as a result of not all the population of bacilli being resistant to INH, thus resulting in death of those that are not, and those with low dose resistance being susceptible to higher doses [95]. A South African study has shown that more than 10% of MDR-TB may benefit from high-dose INH [94].

The shorter MDR-/RR-TB regimen should be 4-6 months of kanamycin, moxifloxacin, prothionamide, clofazimine, pyrazinamide and high dose ethambutol followed by 5 months of moxifloxacin, clofazimine, pyrazinamide and ethambutol [96]. Therefore, there is now an intensive phase of 4-6 months consisting of 4 second-line drugs compared with 8 months of ≥4 second-line drugs in the conventional regimen. This is followed by a 5-month continuation phase of 2 second-line drugs compared to ≥12 months of ≥3 second-line drugs. Until early 2016, treatment for RR-TB and MDR-TB could be up to 20 months, costing $2,000-$5,000 per patient. This shortened regimen results in an overall cost saving with an estimated cost of $1,000 per patient [1]. Despite the reduction in per patient cost, there is risk for worsening drug resistance if used inappropriately, thus highlighting the importance of appropriate patient selection [96]. This regimen has been suggested for cases of pulmonary MDR-TB/RR-TB that is not resistant to second-line drugs, but excludes pregnant women. An understanding of the construction of such second-line regimens is necessary in contemplating and developing alternatives to the rechallenge process.

Options of shortening second-line drug regimens, in the context of DR-TB, have been evaluated in the literature. The Bangladesh regimen has been heralded as a successful 9-month regimen for patients with MDR-TB achieving an 84% cure rate [97]. This

regimen comprises a minimum 4-month intensive phase with gatifloxacin, ethambutol, pyrazinamide, clofazimine, kanamycin, prothionamide and isoniazid, which is extended if sputum smears were positive after the initial 4 months. The continuation phase was started once sputum smears were negative and was only 5 months long. The continuation phase comprised gatifloxacin, ethambutol, pyrazinamide and clofazimine [97]. However, this study excluded HIV-infected individuals and patients had optimal personal and family support through trial centres. The STREAM study (Standardised Treatment Regimen of Anti-Tuberculosis Drugs for Patients with MDR-TB) is an ongoing trial to evaluate the use of shorter regimes and compare efficacies of WHO regimens with the Bangladesh regimen. Additionally, some of the regimens being evaluated will attempt to exclude injectables [98].

Development of new and alternate drugs has expanded the treatment options with some second-line drugs, as well as some alternative first-line drugs, having benefits over the conventional 4-drug first-line regimen. For example, rifabutin a first-line line drug is favoured over rifampicin when patients are on protease inhibitors as part of ART as there is less induction of cytochrome P3A [22]. Furthermore, rifabutin may be associated with a lower incidence of severe adverse effects than its rifamycin counterpart while retaining the effectiveness of rifampicin [22, 23, 99]. In 80% of cases where rifampicin is not tolerated, the literature has shown that rifabutin can be tolerated [22]. Caution must be exercised in CADR related to rifampicin, as rifabutin use carries a 9-fold increased risk of adverse reaction (CI 1.6–55) [22]. CADR occurred in 23.2% ($p<0.01$) of Chien et al.'s population, but were mild requiring only symptomatic support [100]. However, Lehloenya et al. in a study of rifabutin use following DRESS to rifampicin, now totaling 14 consecutive patients, found that rifabutin is well tolerated and there was no cross reactivity between the two drugs in this specific population (personal communication) [99].

Due to its unique mechanism of action by binding subunit C of the enzyme necessary for energy generation in *M. tuberculosis*, bedaquiline interferes with energy metabolism [101-103]. Thus bedaquiline has proven to be promising in cases of MDR-TB where regimens can't easily be constructed [24]. Bedaquiline based regimens including

kanamycin, ofloxacin, ethambutol, pyrazinamide, and cycloserine or terizidone were found to have a 48% rate of sputum-culture conversion when compared to placebo as well as a faster time to conversion of 83 days compared with 125 days ($p<0.001$) [24]. Yet, in a phase II randomized control trial by Diacon et al. there was increased mortality in the bedaquiline group. No mechanism of causality was identified and deaths occurred a median of 329 days after the last dose [104]. Bedaquiline is known to cause QT prolongation and may be associated with a risk of hepatotoxicity. Despite these risks, the WHO still recommends the use of bedaquiline for treating DR-TB and it is likely to be useful as part of an alternative regimen for managing CADRs to first-line TB drugs [105].

Delamanid, another new second-line TB drug, has been granted approval by the European Medicines Agency (EMA) based on a phase II study that involved 481 individuals with DR-TB over a 2 month period [25]. Delamanid was found to increase the proportion of patients who achieved sputum culture conversion when given for 2 months (45.4% vs. 29.6%, $p=0.008$)[106]. Skripconoka et al. showed that delamanid improved survival rates with only a 1% mortality in the delamanid group compared to 8% mortality in the population not receiving delamanid ($P<0.001$) [107]. Delamanid in these trials was used alongside pyrazinamide and 4 other second-line drugs known to be effective. As with bedaquiline, there is also an increased risk of QT prolongation, but no studies to date have reported prolongation as an adverse event due to delamanid [25]. Furthermore, in the 2-month trial by Gler et al. there were no more adverse events in the group receiving delamanid than those receiving placebo [106].

2.10.2 ADR to second-line TB therapy

ADR to second-line TB drugs are common ranging from mild to severe, with up to 25% of patients experiencing ADR requiring the offending agent to be permanently discontinued [108]. Within the commonly used second-line regimens the most common adverse reaction has been shown to be ototoxicity at 41%, with CADR accounting for 5% in a study of 263 Turkish patients [109]. Tinnitus (40%) and hearing loss (23%) were 2 of the 4 commonest side effects reported in a Namibian study with a high HIV prevalence of 53% [110]. In South Africa through the DOTS-Plus cohort of 2079

patients, 7% of patients experience ADR to second-line TB therapy, 39% of which is ototoxicity [111].

2.10.3 The use of second-line TB therapy for DS-TB

There is a paucity of robust data as to the effectiveness of second-line TB therapy in the treatment of DS-TB. It is not clear whether the efficacy of second-line agents in the treatment of DR-TB can be extrapolated to cases of DS-TB.

Many studies have evaluated the use of second-line drugs in addition, or as substitutes to one or more of the first-line drugs in the standard regimen as a means of shortening treatment duration [112]. Merle et al. substituted ethambutol for gatifloxacin in the intensive phase and continued the drug along with rifampicin and isoniazid for a 2-month continuation phase for total treatment duration of 4 months. While the shortened regimen resulted in increased compliance and a lower treatment failure rate, there was a higher rate of relapse as compared to the standard regimen [113]. The REMoxTB study evaluated the substitution of ethambutol with moxifloxacin in the standard regimen as well as moxifloxacin with isoniazid in the comparator arm with regard to the possibility of a shortened treatment regimen for DS-TB. Although both moxifloxacin-containing regimens produced a more rapid decline in bacterial load than the standard treatment regimen, noninferiority for these regimens was not shown, thus not allowing for a shortened duration of TB therapy [114]. Conde et al. found the use of rifapentine; moxifloxacin, isoniazid and pyrazinamide used in the intensive phase of TB therapy were at least as bactericidal as the standard intensive phase regimen with equivalent adverse events [115].

The TB Alliance's STAND trial is a novel 3-drug regimen comprising both first- and second-line TB therapy in the form of pretomanid, moxifloxacin and pyrazinamide (PaMZ) for the treatment of both DS-TB as well as MDR-TB. The purpose of this study was to assess the efficacy, safety and tolerability of the drugs in patients with DS-TB and selected patients with MDR-TB. In phase 2b of the clinical trial (known as NC-002) which enrolled more than 200 patients in South Africa and Tanzania the new

combination therapy was shown to be safe, well tolerated as well as having an overall superior bactericidal activity when compared to first-line therapy during the trial period (0·155, 95% Bayesian credibility interval 0·133–0·178 compared to 0·112, 0·093–0·131) [116]. Upon 2 month follow up 71% of patient on PaMZ had negative sputum cultures for TB as compared to 38% of patients on original first-line TB regimens. Of importance is that PaMZ was found to be effective independent of HIV status [117]. Phase 3 of this trial was discontinued in light of the even more promising results seen in phase 2b clinical trials (NC-005) with bedaquiline, pretomanid and pyrazinamide (BPaZ) as well as bedaquiline, pretomanid, moxifloxacin and pyrazinamide (BPaMZ). BPaz was found to kill 99% of TB bacteria over 14 days and has the potential to decrease TB treatment to 3 months in clinical trial completed in 2014 [117]. The NC-005 trial is still being carried out and results are as yet not available.

Despite promising trial results, with potential future treatment options, the lack of robust data results in a delay of these options being included in standard management guideline of ADR. However, the above trials demonstrate the possibility of second-line drugs being used as alternative to successfully treat of DS-TB as well as improve DR-TB therapy.

2.10.4 ART and second-line TB therapy

As in patients on first-line TB therapy and ART, drug-drug interactions may be problematic with second-line drugs and ART. There is no debate as to the benefit of treating both TB and HIV with this benefit outweighing the risk of drug-drug interactions. Medécins Sans Frontières (MSF) conducted a study on 67 HIV/MDR-TB co-infected patients in Mumbai India between 2007 and 2011 [118]. Eleven patients required hospitalisation for their ADR, but none were severe enough to warrant stopping the entire MDR or ART regimen. Within this population ADR included gastrointestinal upset (45%), peripheral neuropathy (38%), hypothyroidism (32%), psychiatric symptoms (29%) and hypokalaemia (23%). Commonly implicated drugs included traditional second-line therapy of streptomycin, kanamycin and the fluoroquinolones as well as efavirenz, zidovudine, nevirapine and lopinavir [118]. Shean et al. looked at

ADR in 115 patients with XDR-TB [119]. Within this population, although ADR were common (68% of the population), the type frequency and severity of the ADR was not influenced by the HIV status [119]. Furthermore, in a systematic review of 10 observational studies with a total of 217 patients with DR-TB on ART, overlapping side effects of ART and TB therapy were found, but there was insufficient data to determine whether ART increased adverse drug reactions when used with TB therapy [120].

Rifabutin is preferred to rifampicin in higher-income settings as rifampicin is a potent inducer of drug metabolism resulting in lower concentrations of protease inhibitors [121]. However, concomitant use of rifabutin and nevirapine or lopinavir/ritonavir can result in increased levels of rifabutin due to the inhibition of cytochrome P450 metabolism, with risk of rifabutin toxicity [122]. The same increase in exposure has been identified with bedaquiline, yet the clinical significance is still to be determined [123]. Ethionamide with ART therapy may result in increased incidence of gastro-intestinal intolerance and neuropsychiatric side effects [121]. Although no published evidence exists for the use of delamanid and ART in HIV-infected individuals with DR-TB, studies in healthy individuals suggest than there are no additional dose adjustments required [124]. Table 2.5 below outlines the overlapping toxicities due to ART and TB therapy and the commonest offending agents.

Table 2.5: Toxicities related to ART and TB therapy and the offending agents [120].

Potential Toxicity	Antiretroviral Therapy	Antituberculosis Therapy
peripheral neuropathy	stavudine	cycloserine
	didanosine	isoniazid
		ethambutol
		flouroquinolones
		streptomycin
		kanamycin
		amikacin
		capreomycin
		viomycin
		ethionomide/prothionomide
		linezolid
psychiatric symptoms	efavirenz	cycloserine
		isoniazid
		flouroquinolones
		ethionomide/prothionomide
hepatitis	nevirapine	pyrazinamide
	ritonovir/protease inhibitors	isoniazid
	efavirenz	rifampin/rifabutin
	etravirine	para-aminosalicylic acid
	maraviroc	ethionomide/prothionomide
		flouroquinolones
renal toxicity	tenofovir	streptomycin
	indinavir	kanamycin
		capreomycin
		amikacin
		viomycin
		rifampin
gastro-intestinal intolerance	zidovudine	ethionomide/prothionomide
	protease inhibitors	para-aminosalicylic acid
	stavudine	pyrazinamide
	didanosine	isoniazid
		rifampin
		ethambutol
		clofazimine
bone marrow toxicity	zidovudine	linezolid
		rifampin (thrombocytopenia)
lactic acidosis	stavudine	linezolid
	didanosine	
	zidovudine	
stevens-johnson syndrome	nevirapine	thioacetazone
	efavirenz	cycloserine
	etravirine	linezolid
		ethambutol
		streptomycin
arrhythmias/Qt prolongation	atazanavir	flouroquinolones
	saquinavir/ritonavir	
	Kaletra	
rash/pruritus	nevirapine	rifampin/rifabutin
	efavirenz	pyrazinamide
	etravirine	
	abacavir	

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2.10.5 Obstacles in second-line TB therapy

Although these factors are associated mainly with MDR-TB treatment, they also need to be considered when developing an alternative regimen containing second-line drugs for CADR management.

In cases of MDR-TB, delayed diagnosis of drug-resistance often results in inadequate treatment with first-line drugs. In more resource poor settings, such as found in the Lesotho cohort, the absence of initial drug sensitivity testing (DST) meant that 97% of patients with MDR-TB had previously been treated for presumed DS-TB. Furthermore, 65% of these had been treated twice or more for DS-TB [125]. During this suboptimal therapy, higher bacillary loads can cause parenchymal destruction, cavitation and walled off areas limiting drug penetration and leading to increased transmission and chronic disease [29].

Another factor resulting in delayed initiation of second-line therapy is the reliance on inpatient initiation of treatment. In many countries, and many parts of South Africa, this is standard practice. Inpatient initiation of second-line TB therapy is thought to improve mostly clinical outcomes for patients and limit disease transmission to the greater community [125]. With the ever-increasing incidence of MDR-TB this practice has many of its own drawbacks. The shortage of hospital beds translates to patients being diagnosed, but having to wait months for admission to a MDR-TB hospital to be initiated on treatment [125]. This then results in an increased risk to the community as patients aren't admitted at diagnosis and are often maintained within the community on suboptimal therapy. Furthermore the practice of inpatient management increases the risk of nosocomial transmission due to poor infection control measures, especially in resource-poor settings [125]. The need for inpatient treatment places significant economic pressure on not only the healthcare system, but also patients themselves.

One of the influential factors hindering efficacy of treatment are patients who default (0%-44%) from treatment due to long duration of expected treatment, adverse effects or poor provider-patient relationships [29, 126]. Shean et al. found that default rates were up to 29% in MDR-TB patients treated in the West Coast/Winelands of South Africa

[126]. Adverse events associated with drugs are known to be obstacles to adherence. Nathanson et al. reviewed adverse events from the DOTS-plus initiative (programme specific to MDR-TB) in 818 patients from 5 study sites [127]. The most common adverse effects were nausea/vomiting (32.8%), diarrhoea (21.1%), arthralgia (16.4%), dizziness/vertigo (14.3%) and hearing disturbances (12%). Despite these adverse events, only 2.1% of patients stopped treatment. However, 30% of patients required removal of the suspected agent. This highlights the importance of patient follow-up to proper management of adverse events that would otherwise result in treatment interruption or cessation.

2.11 Cost of adverse drug reactions

With the evident number of cases of ADR, a substantial cost is associated with the management and treatment of these reactions. Marques et al. carried out a systematic review of 31 observational studies that evaluated to the costs of ADR [128]. Cutaneous events as an adverse event of a single type constituted 13% of reactions reported in 4 of the 13 studies [128]. Only a single study, by Noize et al. reported on CADR that was not related to treatment used in therapy for malignancies, which was ketoprofen, a non-steroidal anti-inflammatory drug [129]. Within this study ADR amounted to €316 per case with serious ADR costing 9 times that [129]. Eleven percent of the population required hospitalisation for their ADR [129]. Within the remaining studies in the review, the cost of adverse reactions occurring in hospital ranged from €943.40 to €5,972.74 [130-135].

All studies reported costs relating to the management of the ADR. Costs including the hotel cost, medications and personnel cost. Within the populations reported to exhibit CADR, the costs were between $1,920 and $6,325 [136, 137]. Costs in the Gyllensten et al. population, that comprised 4970 adults included from a population-based observational retrospective cohort study, encompassed the societal cost of illness, which included both direct and indirect costs (average of $6,325). Direct costs referred to cost of healthcare services as well as dispensed medications, whereas the indirect costs

included the individuals' loss to productivity [136]. The Borovicka et al. cost of CADR, related only to the direct costs of treating the ADR [137]. This population was made up of 132 adults managed at the department of Dermatology, Northwestern University. Noize et al. found that the cost of severe CADR, was nine times higher than the less severe forms at €3,383.56 compared to €373.33 [129]. Most studies are reported from America and Europe. Of note is that above studies range from 1999-2016, costs would therefore need to be adjusted to USD and inflated to reflect current costs, resulting in potentially higher than reported estimates. A recent study published in the journal of rheumatology assessed the cost of severe CADR (SJS, TEN and DRESS) to allopurinol as a means of establishing cost effectiveness for genotyping prior to allopurinol use. CADR cost in this population spanned 10 years and included costs related to hospitalisation. The mean cost for managing CADR was $8,452 in the total population and $2,947 per patient if those who demised are excluded [138]. Within the reviewed literature a study by Mehta et al. was the only South African study describing the contribution of ADR to patient morbidity, hospitalisation and mortality in 665 patients admitted to hospital. TB drugs were reported as causing renal complications, but not CADR and costs of ADR were not estimated [139]. None of the studies report on costs of CADR attributed to first-line TB therapy, which is one of the aims of our study.

2.12 Cost of second-line TB therapy

A costing analysis by Pooran et al. comparing the costs of DS-TB, MDR-TB and extensively drug-resistant TB (XDR-TB), found that DR-TB cases placed a disproportionate burden on the national TB budget. Drug-resistant cases accounted for 2.2% of the TB cases, yet cost 32% of the estimated 2011, national TB budget [28]. A smear-positive DS-TB case in 2011 cost $191.66, with smear-negative ($252.54) and retreatment cases ($455.50) being more expensive, with an overall estimated cost per case of $256.61 [28]. Within this study MDR-TB treatment was found to be twenty-six times greater at $6,771.92 (inpatient = $5,930.02, outpatient =$14,348.94), of which 49% is attributed to TB drugs (Figure 2.9) [28].

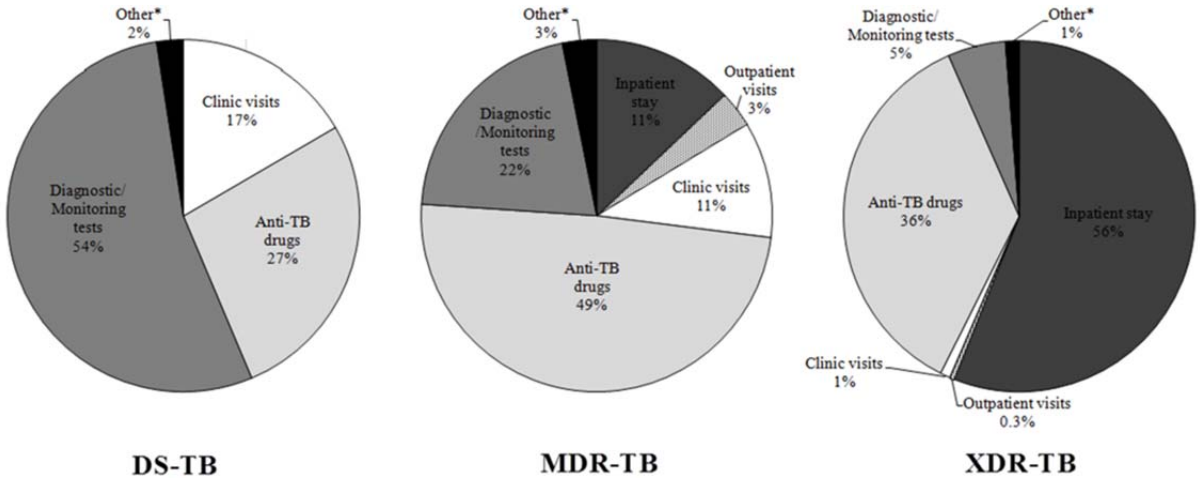


Figure 2.9: Parameters contributing to the total cost per patient for DS-TB, MDR-TB and XDR-TB [28].

It was previously thought that MDR-TB was too expensive to treat, but drugs have become more affordable through the general decrease in drug costs and various funding opportunities in low-income countries [29]. In Pooran et al.'s study drug costs accounted for 45% of the spending in DR-TB [28]. Suárez et al. carried out a feasibility and cost-effectiveness analysis in Peru of MDR-therapy, which comprised 18 months of kanamycin, ciprofloxacin, ethionamide, pyrazinamide and ethambutol [140]. Within their analysis they found that their programme cost US$0.6million per year equating to 8% of the National Tuberculosis Programme Budget. The cost per disability adjusted life year (DALY) saved was US$21, with the average treatment cost per patient being US$2,381. The cost per DALY saved was lower than the per-person gross domestic product of many countries proving the intervention cost-effective [140].

Despite treatment with more costly drugs being deemed cost-effective, treatment of MDR-TB can cost thousands of dollars per patient for their treatment course. Alternative strategies need to be devised to ensure sustainability of treatment programmes. Generic treatments options of antiretroviral medications, as was seen in HIV/AIDS, allowed for a rapid price decrease and an up-scale of treatment [141]. Gotham et al. in their estimate of generic pricing of new TB drugs found that costs of regimens could be reduced in some

case by up to 97% (41-97%). Novel regimens comprising these generic drugs could allow for 5-10 times more patients to be treated within the current budgets [141].

Cost of MDR-TB treatment has many contributing factors with many centres favouring inpatient therapy. Schnippel et al. found that the cost of inpatient treatment for DR-TB was 40 times more than that of treating DS-TB in South Africa with 95% of this cost attributed to prolonged inpatient therapy [30]. These authors noted that the South African National TB Programme has adopted a greater move to more outpatient therapy. However, only 30-40% of drug-resistant patients would qualify for outpatient therapy based on current guidelines, which require specifically that patients are smear-negative and in good clinical condition. Cox et al. explored this approach to treatment and also found that hospitalisation, along with treatment failure, were the greatest drivers of cost [26]. They also noted that facility costs for decentralised services might be greater due to economics of scale. This model benefits the patients in seemingly less out-of-pocket expenditure for themselves and their families. Sinanovic et al. found that a fully decentralised model of care was 42% less costly than a treatment plan involving full hospitalisation, with the reduced number of days in hospital being the key-contributing factor [27]. Pooran et al. with their sensitivity analysis, found that inpatient day costs had the most significant influence on XDR-TB costs. Similarly the MDR-TB group analysis was most sensitive to changes in proportion hospitalised and duration of treatment [28]. While decentralised treatment may improve the patient experience in this regard, it still remains unclear how it would affect patient wellbeing.

Seung et al. found a community-based model of MDR-TB care to be feasible and effective by creating a working relationship between hospital-based and community-based care in order to maximise resources and ensure close follow up of patients [125]. Within their population only patients requiring high level of care or those unable to ambulate were hospitalised for initiation of treatment. During the course of treatment, if patients became ill or suffered adverse effects they too were hospitalised, but discharged back to community-based care as soon as possible [125].

By reducing duration of therapy to the WHO approved shortened regimen for MDR-TB, there is a potential to further reduce cost attributed to second-line therapies being more expensive than their first-line counterparts [93].

2.13 Indirect costs of TB therapy

In calculating expenditure, one often focuses on the cost to the healthcare system, and the associated economic impact, while overlooking the affected individual. The relationship between poverty and TB has been mentioned previously, with poor socio-economic circumstances being a risk factor for contracting TB and hindering treatment completion. Numerous studies and strategies to enhance adherence and treatment completion are often centered on social support of patients.

This relationship is two-fold and it is also well documented that TB exacerbates poverty. The loss of income due to illness, which is approximately 3-4 months and 20-30% of annual household incomes for patients, results in an overwhelming economic burden [32].

TB patient costs typically include out-of-pocket medical costs (tests, administration fees and costs associated with hospitalisation), cost of travel to hospital or healthcare sites, as well as other treatment related costs such as meals while at clinic visit or supplementary foods recommended by healthcare providers and can be substantial. Gospodarevskaya et al. found that patient costs related to continuation phase (US$74 in Tanzania and US$56 in Bangladesh) were lower than the intensive phase (US$150 in Tanzania and US$111 in Bangladesh). However, even the lower continuation phase costs represented a significant proportion of the annual national income (89% and 77%) [31].

Ramma et al. reported in their cohort of MDR-TB patients, a drop in proportion of income earners from 37%-3% while on treatment [32]. Productivity loss due to hospitalisation was the main contributor to patient cost. Furthermore, 81% of the population reported MDR-TB social grants being their primary source of income. Decentralisation and outpatient TB treatment therefore seems to reduce health sector costs and may potentially reduce patient costs. Yet Ramma et al. also noted that patient

costs in terms of transport, nutritional supplements and healthcare visits are greater in the outpatient model. Within this population 81% reported being dependent on social grants to cover the additional burden the disease places on households [32]. This dependence on social grants places a further strain on a country's general economy.

It is clear that TB treatment is associated with significant direct and indirect costs. Even in uncomplicated treatment cases, patients often experience significant income loss. Although, in cases of CADR, the facility and treatment costs become even more substantial, raised by the protracted hospital stay required in carrying out the rechallenge process. Second-line treatment alternatives can also incur significant costs. As an alternative to current in hospital practice of CADR management, a new outpatient approach with second-line therapy could potentially be cost saving.

2.14 The value of our study

In South Africa, TB control programmes and an overburdened healthcare system have failed to curb the TB epidemic. Despite effective TB therapy, the incidence of TB and new infections remains high. Furthermore, the prevalence of HIV within South Africa not only fuels the TB epidemic, but also places its own burden on the healthcare system and health expenditure. With the increasing demand on healthcare services, resources and funds need to be allocated to where they are most needed. Healthcare needs to be both effective in treating the patient and preventing spread to the community, but should also be sustainable. Thus, economic analyses are needed to provide data on optimal strategies of patient management and treatment.

ADR can have significant effects on morbidity and mortality. Nevertheless, it is important that patients remain on optimum treatment. Rechallenge, to reinitiate first-line TB therapy, or changing a patient to second-line alternatives, need to be comparatively studied to determine efficacy. Comparisons need to be drawn as to which practice has the best overall impact on the patient's wellbeing by limiting treatment interruption, improving cure rates, reducing disease relapse and curbing the TB epidemic.

Rechallenge is not a benign process and the risks and benefits of rechallenge need to be evaluated on an individual patient basis. In cases of severe adverse drug reactions due to first-line TB drugs, where there is no drug resistance and treatment failure is less likely to occur, it is unclear what the most economical treatment option is. It remains unknown, if lengthy hospitalisation and patient monitoring during the rechallenge period in an attempt to resume treatment with first-line TB therapy is an economically optimal strategy. Furthermore, the cost and cost-effectiveness of an alternative treatment strategy using second-line therapy has yet to be adequately evaluated. Although prolonging treatment with more expensive second-line drugs does at first sight seem to naturally be the more expensive approach, outpatient approaches with ambulatory MDR-TB care seem promising and an excellent potential for cost saving. This saving is not only to the healthcare system but to the patient in terms of an improved quality of life with a shorter hospital stay and a more community or patient-centered approach to care.

The lower efficacy, toxicity and cost of second-line therapies seem to be a deterrent to their favoured use over first-line treatments. However, in a population with uncomplicated TB who could potentially have a shorter course of therapy on an outpatient basis, the feasibility of such a strategy needs to be determined. This study will attempt to evaluate the cost of current practices comparing them to a potential alternative strategy of outpatient second-line therapy for patients with DS-TB who are intolerant to first-line TB drugs.

In our analysis, we hope to provide answers as to what is the most economically feasible way to limit treatment interruption and achieve treatment completion. The strategy, when faced with this unique subset of the population, should be one that allows for optimisation of patient health and wellbeing while reducing the strain on already stretched healthcare budgets.

3. METHODOLOGY

3.1 Study design:

A comparative cost analysis was performed to 1) estimate the overall cost of CADR to TB therapy, following which 2) the traditional practice of sequential and additive drug rechallenge using first-line TB drugs was compared with an alternative strategy of immediately initiating second-line TB therapy in patients with DS-TB who develop a CADR to first-line TB treatment.

Costing of the current rechallenge strategy for patients with CADR to TB therapy and the second-line treatment strategy was performed from the perspective of the healthcare system as well as patient loss in the primary analysis. Data was collected from a study cohort comprising of patients with probable or confirmed TB that were admitted to the Dermatology ward of Groote Schuur Hospital (GSH), a tertiary hospital in Cape Town South Africa, during the period from May 2010-July 2015 with a CADR and at least one first-line TB drug in their current treatment regimen. Medical records were retrospectively reviewed and relevant clinical information was extracted. Cost data relating to the management of each individual patient suffering from a CADR was collected from appropriate sources and used to calculate the total and per patient cost of managing the CADRs. This data provided the source for our first objective of determining the cost of CADR to first-line TB therapy using the current rechallenge process.

Based on extensive literature review regarding principles of second-line therapies used for MDR-TB treatment and in conjunction with clinical advice from Professor Gary Maartens (Head of the Division of Clinical Pharmacology, University of Cape Town, UCT and previous head of Infectious Diseases and HIV Medicine, University of Cape Town, UCT) and Associate Professor Helen Cox (Division of Medical Microbiology, UCT), whom are both experts regarding development of TB drug regimens for DS-TB and DR-TB, we constructed alternative TB drug regimens as a substitute to drug

rechallenge. This was done, as there is a lack of data regarding alternatives to the commonly used primary TB drugs for DS-TB. Second-line TB drug costs and dosage recommendations were obtained from the relevant literature and clinical sources.

Costs directly incurred by CADR patients were determined for the study cohort and hypothetical population. Patients' annual salaries were collected and used to determine out-of-pocket expenses due to lost income from hospitalisation. In cases where patients were unemployed, standard minimum wage values were used as a proxy for income as was performed in previous studies [32, 142]. These out-of-pocket expenses were expressed as a percentage of annual income. Direct costs included fees for medical expenses but excluded transportation, food and guardian costs. Based on annual income patients were further classified according to the Western Cape government payment schedule, which classifies patients according to their ability to pay for healthcare services. Using this classification, the cost to patient for the treatment course was determined (Appendix 4) [143].

Although the cohort recruitment time frame ranged from May 2010-July 2015, costs were expressed in 2016 US Dollars ($), so as to ensure relevancy in the current economic landscape. In all cases, costs were inflated to 2016 costs in South African Rand (ZAR) using the South African consumer price index [144]. Costs were then converted to USD at an exchange rate of US$1=R14,69 (average exchange rate for 2016; Currency Converter/Foreign Exchange Rates/OANDA) [145]. In cases where drug costs were not available in South Africa, costs were taken from the literature and converted to USD using the above mentioned method [146, 147].

3.2 Study population

Medical records of CADR patients who presented at the dermatology ward in GSH from the period of May 2010 to July 2015 were evaluated. All patients who were suspected of having a CADR related to TB treatment in this cohort were included as the study

population. Due to the retrospective nature of the study a convenience method of sampling was employed.

Patients included those with TB on at least one first-line drug in their treatment regimen. Patients within the population could also have been on ART and/or prophylaxis or treatment for opportunistic infections commonly associated with HIV e.g. co-trimoxazole. In cases of patients only being on TB therapy, first-line TB drugs were rechallenged, and second-line drugs were rechallenged or replaced based on the Naranjo probability score for the individual drugs. An example is terizidone, which has hardly if ever been documented to cause CADR, with notoriety of a drug being a key component to the Naranjo score [84]. In cases where patients were on ART or other potential offending drugs and TB therapy at the time of presentation the Naranjo score was used to assess probability of the drug having caused the CADR. Based on the Naranjo score, as to whether an ART drug was a possible, probable or definite offender, the regimen was changed to exclude that drug and alternative ART and treatment/prophylaxis for opportunistic infections were initiated and no rechallenge was performed for these drugs. Thus, patients were only rechallenged with first-line drugs to exclude TB drugs as the offending drug and potentially establish alternate therapy as the more likely offending drug.

In cases of an unconfirmed diagnosis of TB, further investigations were carried out in an attempt to confirm TB. Those who were diagnosed with definite or probable TB after consultation with infectious disease specialists were then rechallenged. Those with improbable or unlikely TB did not undergo rechallenge [148].

The TB population was further divided into 4 subgroups (Figure 3.1). Those with confirmed DS-TB in the intensive phase (first two months) of TB therapy on all 4 first-line TB drugs. Those in the continuation phase (last four months) of TB therapy on rifampicin and isoniazid, as well as those unnecessarily treated for TB who were found to not have TB [148]. The last group was those with DR-TB on second-line TB therapy that included at least one first-line TB drug. Within the DR-TB population there is a

wide variety of sensitivities, which could also include first-line drugs. Although these drugs are not necessary for the successful treatment of DR-TB, isoniazid, pyrazinamide and ethambutol are valuable add on components in second-line regimens and thus first-line drugs were rechallenged in these patients.

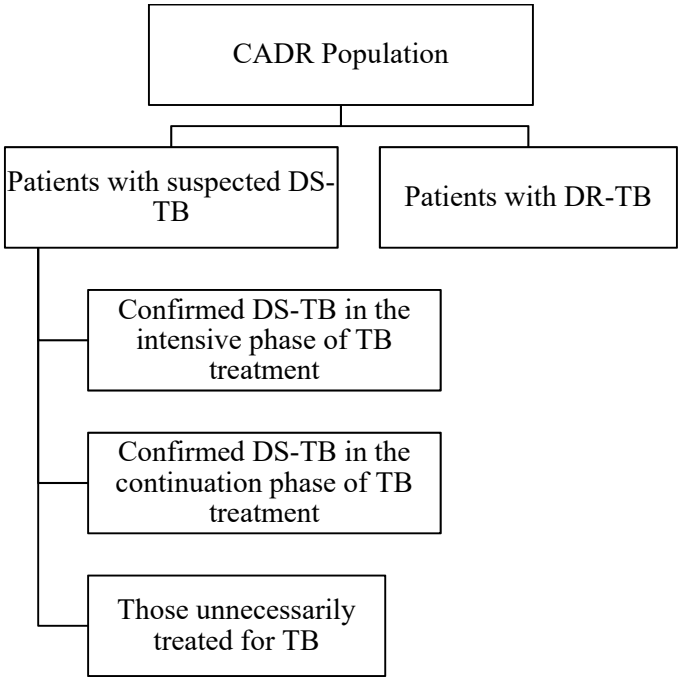


Figure 3.1: Breakdown of the subgroups of the study population.

All costs incurred by these subgroups of the TB population were calculated. Totals and averages were calculated for each period of the rechallenge process for the DS-TB population as a whole, for the 3 subgroups of patients within the DS-TB group and those with DR-TB. Breaking down the costs to reflect the proportion each group contributed to the total allowed for a more accurate cost comparison with the hypothetical cohort who would only have DS-TB. In the cost comparison the DR-TB cost would be excluded as it is near to impossible to derive a regimen based on the same principle of excluding all agents to which the patient had been exposed while creating an effective regimen as was applied to those with DS-TB.

3.3 CADR management strategies

Various methods of rechallenge have been debated in the literature [65]. However, the method of drug rechallenge used in our study cohort was standardised and reflects the current practice employed at GSH.

3.3.1 Rechallenge to first-line TB drugs

In our study cohort, once a CADR was diagnosed, all suspected offending drugs were withdrawn from the patient's' treatment. Various investigations are then carried out and the patient is supportively managed and monitored until all clinical and laboratory parameters have returned to the patient's expected baseline. This period is defined as the period of stabilisation (Figure 3.2).

Once baseline is reached, an alternative regimen consisting of second-line TB medications, to which the patient has never been exposed, are used as a 'bridge' therapy for at least 2 weeks. This reduces the risk of developing drug resistance, as a result of monotherapy, while drugs are reintroduced. First-line drugs from the initial regimen are reintroduced sequentially and additively. This is done to identify the causative drug and subsequently tailor a treatment regimen for each patient that is the most effective and least toxic. The Naranjo ADR probability scale was used to guide need for rechallenge with first-line TB therapy (Appendix 1) [84]. The rechallenge period is defined as the period from which 'bridge' therapy was initiated until the patient was either discharged from hospital on optimal therapy with normal clinical and biochemical parameters or had a less favourable outcome.

Following discharge from hospital, patients continued on their individualised drug regimen as an outpatient until treatment was completed (optimised treatment period). The treatment period varied for each patient and was dependent on the particular drug regimen that was implemented. For a small percentage of patients, data on their post discharge management was available and in these cases real patient data was used in the costing for the post discharge (optimised treatment) period. In cases where this information was not available, the frequency of clinic visits and laboratory investigations

during the outpatient treatment period was guided by the National TB Programme (NTP) management guidelines as well as clinical expertise. It was assumed that patients were compliant on their treatment and completed the total duration of the prescribed course and attended all clinic follow-ups. Follow-up after discharge consisted of specialist dermatologist visit at 6 weeks, which is the current practice at GSH. We included more regular, weekly visits for the first month following discharge then monthly follow up at the TB clinic with a medical officer as we assumed these patients were at a higher risk of developing adverse drug reactions or defaulting from treatment. Sputum culture was performed every 6 months and following treatment completion. Additionally, screening liver function serological tests and differential cell counts were done initially weekly then at monthly intervals. For alternative regimens using bedaquiline, delamanid and fluoroquinolones (moxifloxacin, levofloxacin), we included appropriate screening tests to account for risk of cardiac abnormalities and other side effects commonly associated with these drugs (discussed under the specific regimens, Section 3.2.2).

In some instances, CADR patients were admitted to other referral centres before being admitted to GSH where they may have even been started on the rechallenge process or the rechallenge process attempted. In these cases where patients were already on appropriate bridging therapy, the rechallenge period was determined from the point of admission to GSH. In other instances where patients were either inappropriately rechallenged or not tolerating the rechallenge drugs, they were managed as a new patient upon admission to GSH where all medication was stopped.

3.3.2 Alternative treatment regimens

As there is no literature addressing the proposed alternative management, optimal therapies were derived based on data from current drug trials and clinical advice from experts in the field. Alternative treatment strategies were devised for DS-TB patients only. In those with DR-TB there is no possibility of an effective alternative regimen that would exclude all TB drugs to which the patients were exposed. In the alternative treatment strategy, patients were assumed to skip the rechallenge process and immediately initiate treatment using a combination of second-line TB drugs. The alternative regimen was devised in order to develop an optimal therapeutic regimen

while limiting the time spent in hospital and avoiding rechallenge. This was achieved by using drugs to which the patient had never been exposed, thereby avoiding rechallenge with potential of reactions and the associated inpatient monitoring. As our alternate regimens were only devised for patients known to have DS-TB, they avoided full MDR-TB based treatment regimens that include drugs likely to be unnecessary in DS-TB that are associated with more frequent and severe ADR and higher costs [26, 27, 30].

A number of alternative drug regimens were proposed including an option for patients who developed CADR during the intensive phase of TB therapy and those who developed their CADR in the continuation phase of therapy (Figure 3.2).

If a patient developed a CADR after the intensive treatment phase, they were initiated on rifabutin and ethionamide for an additional 4 months from the time of CADR stabilisation.

Traditional continuation phase therapy comprises rifampicin and isoniazid for 4 months. Rifabutin has sterilizing activity, which has been shown to be comparable if not better than rifampicin, with earlier sputum smear and culture conversion [23, 149]. Rifabutin has potentially better tolerability with increased treatment adherence and completion making it an appropriate substitute for rifampicin in cases of rifampicin intolerance [22, 23, 100]. In 80% of cases where rifampicin is not tolerated, the literature has shown that rifabutin can be tolerated [22]. Furthermore, Lehloenya et al. have reported on 6 consecutive HIV-infected patients who developed DRESS to rifampicin and tolerated rifabutin, with a further 10 cases having been added to their cohort since publication of the initial data [99]. Side effects of rifabutin are usually mild; gastro-intestinal upset, headaches and arthralgia occur commonly. Monitoring is required for more severe adverse events such as hepatitis, neutropenia and thrombocytopenia. For these a regular AST, ALT and bilirubin with a white cell and platelet count are recommended [150]. Acquired rifampin resistance amongst HIV-infected patients has also been shown to be equivalent between the two rifamycins, dependent rather on the rifampin-dosing schedule [151].

Ethionamide is a structural analog of isoniazid and the two drugs are thought to share a common mode of action being potent inhibitors of mycolic acid synthesis [152, 153]. For this reason, there has always been a concern that the two drugs might have overlapping hypersensitivity reactions as well as the risk of cross-resistance, in that patients with INH-resistant TB may also be resistant to ethionamide resulting in poorer outcomes for patients with DR-TB [154]. Fortunately Lehloenya et al. have recently shown that hypersensitivity does not overlap in cases of CADR [155]. Potential activators of ethionamide have been identified which may enhance its efficacy but these have not been studied in as much detail as isoniazid [152, 156]. The use of ethionamide is based on specialist advice supported by research showing that the use of ethionamide in MDR-TB regimens is associated with treatment success as a surrogate for its efficacy [157]. Common side effects include gastro-intestinal upset and headaches with drowsiness and low mood, but do not require specific monitoring. Gastro-intestinal upset occasionally makes the drug intolerable and may require a regimen change to terizidone [150].

If a CADR developed during the intensive phase then a number of different treatment regimens were assessed. These include:

1) Regimen 1: moxifloxacin, rifabutin and ethionamide for 9 months.
2) Regimen 2: rifabutin, levofloxacin and bedaquiline for 6 months followed by rifabutin and levofloxacin for a further 3 months.
3) Regimen 3: delamanid, levofloxacin and rifabutin for 6 months followed by rifabutin and levofloxacin for a further 3 months.

As previously mentioned, both rifabutin and ethionamide can be considered feasible alternatives for DS-TB treatment. However, in constructing our regimen for those developing a reaction in the intensive phase using second-line drugs, we were faced with the potential of having to develop longer regimens. The potency of rifabutin in this instance has enabled us to argue for a 9-month treatment course. In further support, a shorter 9 month course of TB therapy has also been validated by the WHO as well as the Bangladesh regimen, which is an alternative to the WHO shortened TB therapy for patients with MDR-TB [96, 97].

Moxifloxacin and levofloxacin are drugs from the group known as fluoroquinolones. Fluoroquinolones are thought to have effective activity against intracellular mycobacteria due to their wide distribution throughout the body [158, 159]. Moxifloxacin is one of the fluoroquinolones that has the potential to shorten TB therapy as it has the greatest bactericidal activity with the shortest minimum inhibitory concentration (the lowest concentration of a chemical that prevents detectable bacterial growth) [159, 160]. Moxifloxacin activity has been shown to be comparable to that of isoniazid with the time to kill 50% of viable bacteria being lower in isoniazid than rifampicin and moxifloxacin [161, 162]. It was therefore used in our regimen as a valuable substitute for isoniazid. Moxifloxacin is generally well tolerated, but does have propensity to cause gastro-intestinal upset as well as mild drug hypersensitivity. Standard monitoring as is employed for rifabutin was thought to detect possible adverse events related to moxifloxacin [159]. Levofloxacin provides an alternative to moxifloxacin with similar effect when bedaquiline is used due to the lower rate of QT prolongation (discussed later) with this combination [163, 164]. Levofloxacin is well tolerated with a study showing equivalent, and in some cases, lower rates of adverse events as compared to first-line treatment regimens [165].

Bedaquiline is a relatively new TB drug associated with enhanced and rapid sputum conversion rates [104]. It has been approved by the WHO and is now used in patients with pre-XDR and XDR-TB. Use of bedaquiline in other instances is protected through advisory committee permission. Patients are granted use in situations where no other substitutes are available to protect against the development of drug resistance. Bedaquiline is associated with an increased risk of QT interval prolongation. The QT interval is the measure of the time between the start of the Q wave and the end of the T wave in the heart's electrical cycle (seen on electrocardiograph-ECG), representing electrical depolarization and repolarization of the ventricles [166, 167]. Prolongation represents delayed ventricular repolarisation predisposing to re-entrant tachycardia such as torsades de Pointes [166]. This risk is further exacerbated when used in conjunction with moxifloxacin. The long half-life of bedaquiline (5 months) typically results in it being prescribed for the first 6 months of therapy, yet monitoring is required after the

drug is discontinued to cover the presence of any circulating residual drug that may result in adverse events [167]. The Centres for Disease Control recommends baseline ECG, potassium, calcium and magnesium monitoring with ECG being repeated at 2, 12 and 24 weeks. AST, ALT, bilirubin and alkaline phosphatase should be monitored at baseline and monthly to screen for potential hepatotoxicity [168].

Although trials show delamanid to have excellent treatment potential it is currently only available in South Africa through MSF and use requires both MSF and government regulatory approval [25]. WHO guidelines on delamanid use report the only drug specific side effects to be QT prolongation ($p=0.048$ for the dose of 100mg compared with placebo and $p=0.005$ in use of 200mg compared with placebo) [124]. This risk is only notable when used in conjunction with regimens containing a fluoroquinolone such as ours (levofloxacin). To this end monitoring of ECG as well as electrolytes that can contribute to cardiac abnormalities such as potassium is recommended [25, 124].

In instances where rifabutin is not tolerated, a regimen would have to be devised excluding the rifabutin but then lasting 18 months. However, use of the NIX regimen, which comprises bedaquiline, pretomanid and linezolid for 9 months could be an alternative [169]. The NIX regimen is an all oral regimen which is currently in phase 3 of clinical trials providing an all oral alternative regimen for patients with XDR-TB predicted to be able to cure TB in 6-9 months [169]. However, due to pretomanid not being readily available with costs largely unknown an evaluation for the cost of this regimen as an alternative was not undertaken.

We assumed that patients in the alternative treatment arm would undergo standard monitoring tests most commonly associated with the drugs used in each of the proposed regimens. The frequency of monitoring tests was based on NTP guidelines related to monitoring for development of specific drug-induced adverse reactions in patients on MDR-therapy and included the parameters discussed above [168]. Assuming that the stabilisation period prior to rechallenge would be equivalent using both strategies, we compared the cost of using these alternative treatment strategies with the rechallenge

strategy up to treatment completion. It was assumed that treatment in the alternative strategy was outpatient initiated as the literature provides substantial evidence for ambulatory care of MDR-TB cases [26, 27, 32].

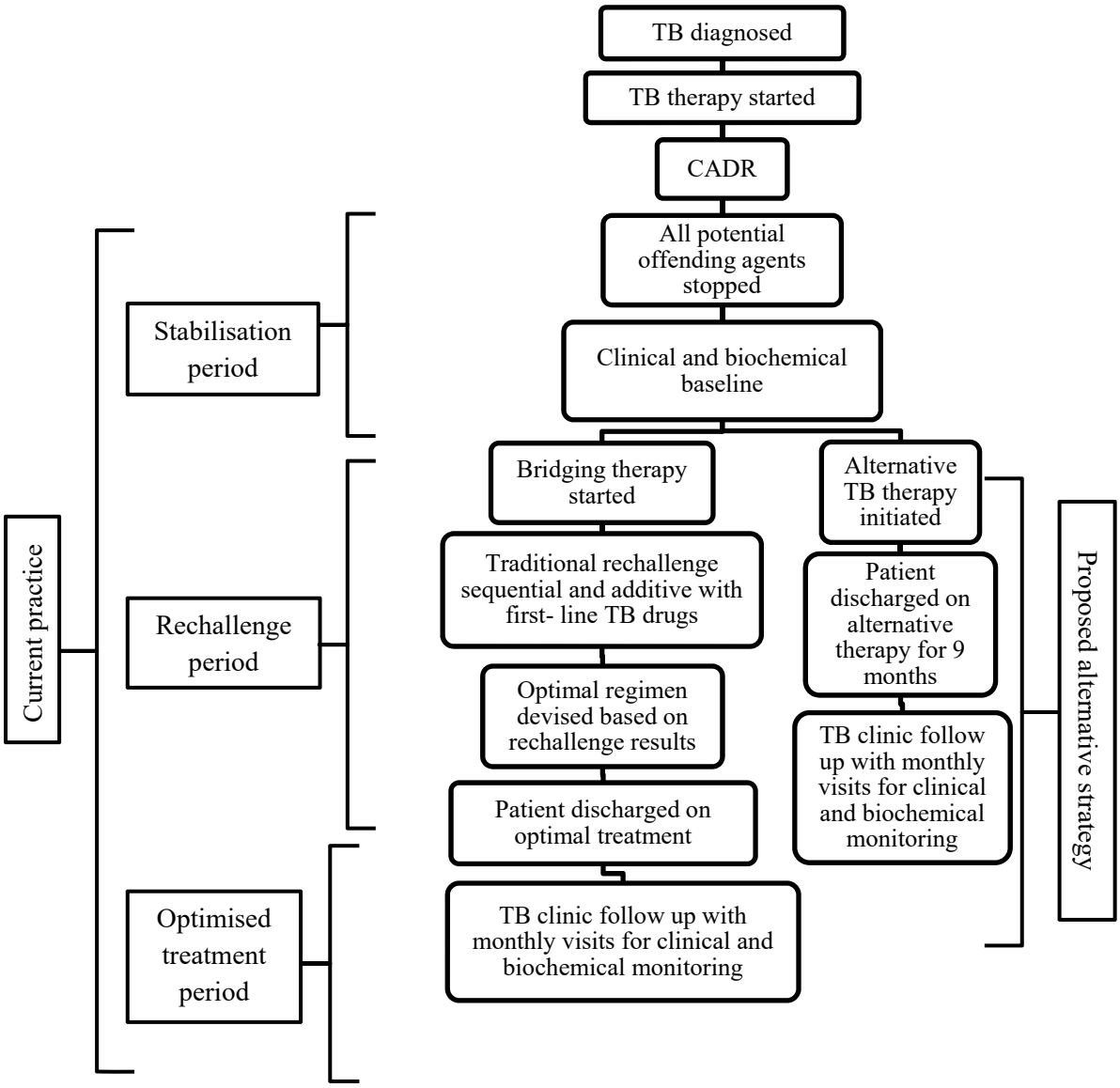


Figure 3.2: Flow chart illustrating the arms of the study model.

3.4 Data sources

Actual clinical information and, in most cases, costs directly incurred by the healthcare-system were used in this analysis thus representing 'real-world' data. Cost data was obtained from relevant sources including review of financial records and interviews with financial administrative staff. When actual cost data was unavailable, in cases of second-line drug costs, estimates from the literature were used. The costs of each resource item were used to calculate per patient and overall cost of managing TB patients who develop a CADR to TB drugs at GSH. The main analysis was performed from the perspective of the healthcare provider as well as the patient. Details of the clinical data and cost components used in the analysis are given below.

3.4.1 Clinical data

Hospital records of the patients' admission to the GSH Dermatology ward as well as clinic and referral records were reviewed. Relevant clinical data pertaining to the period from diagnosis of CADR to treatment completion was extracted. Data included; patient HIV status, CD4 count, ART information, TB diagnosis and treatment details, date of admission and discharge to determine duration of hospitalisation, additional inpatient dressings, investigations, specialist consults that patients may have required and data pertaining to rechallenge and ultimately their discharge treatment prescription. Completion of TB treatment was defined as a completion of the determined treatment period, which was decided upon discharge. The majority of patients are discharged to the community with their care transferred to primary level clinics. Unfortunately, clinic records of patients completing treatment were not readily available and many patients were lost to follow up. As such we did not have outcome data after treatment completion for all patients in the study cohort. In cases where post discharge management was known, this was extracted and patient specific costs were calculated. Where not available, we assumed monitoring and investigations were carried out according to standard South African NTP treatment guidelines.

3.4.2 Study periods

For the current practice of rechallenge, the costs were divided into 3 different periods shown below:

3.4.2.1 Stabilisation Period:

This period was defined from the time of onset of CADR, through the period of in hospital stabilisation until the point at which clinical and biochemical markers had normalised. This period was assumed to be the same for the alternative treatment strategy.

3.4.2.2 Rechallenge Period:

The rechallenge period was defined as the time from initiation of bridge therapy, after the patient's baseline had been reached, up to the point of the patient being discharged. During this period, first-line therapies were re-introduced sequentially to identify the potential offending drug.

3.4.2.3 Optimised Treatment Period:

After the rechallenge period, an individualised treatment regimen was defined for each patient based on suspected offending drug/s, duration of treatment prior to CADR and expert opinion. This period referred to the time from discharge up to completion of the individualised treatment.

3.4.3 Hospitalisation costs

Hospitalisation cost refers to the daily cost of a patient admitted to hospital. This included bed, food, and basic nursing. The hospital cost accounts for the existing hospital infrastructure as well as overhead costs such as electricity, water and maintenance. Both tertiary and secondary hospitalisation costs were obtained. GSH and Victoria Hospital finance departments provided per day costs for tertiary and secondary level hospitals, respectively. These costs represented the actual cost incurred by the hospital. Primary care clinic visit costs were obtained from two TB clinics located in the Cape Town Metro region, Langa Clinic and Chapel Street Clinic.

3.4.4 Medical and allied health professionals staff costs

Medical consultations by specialist physicians and registrars (specialists in training), as well as allied health professionals, were included in the costing analysis. Allied health professionals referred to individuals integral to the management of this cohort of patients such as; physiotherapists, occupational therapists, speech therapists, dieticians, social workers and ART counselors. Health professional costs were calculated using the Provincial Government of the Western Cape (PGWC) 2016 circular of annual salaries and included basic salaries and benefits. The average (mid-range) salary in each personnel category was applied in the analysis to account for the varying levels of experience of the staff treating the patient. The hourly salary was then calculated (annual salary/days worked per year/8-hour day). The time spent for each consultation was variable and not recorded in the patients' medical records. We assumed this time to be 15 minutes per consult based on interviews with consultants from the different departments. The admitted patients were seen by dermatology registrars daily ($7.00/15min consult) and the consultant dermatologist ($8.00/15min consult) three times a week in the ward. Consults with other specialists were calculated at the same rate, allied health professionals were $3.00/consult, with social worker or ART counselor consults being $2.00/consult. These consults were on a referral basis and cost was calculated according to the number and length of the consults noted in the medical records of each patient.

3.4.5 Diagnostic tests, pathology and laboratory investigations

Laboratory and radiological investigation costs were calculated for each patient per investigation multiplied by the number of times each investigation was carried out according to hospital and National Health Laboratory Services (NHLS) records. Costs of radiological investigations including X-rays, CT scans and ultrasound were obtained directly from the GSH finance department. Laboratory and pathology test costs were obtained from the NHLS 2016 state price list. The NHLS is the laboratory service servicing government healthcare facilities, from clinic level to tertiary hospitals in South Africa. As such these prices directly reflect the cost incurred by the healthcare system.

Other studies have also directly used NHLS test costs in their cost analyses [28, 170, 171].

3.4.6 TB drug costs

Currently used first- and second-line TB drug costs were obtained from the GSH pharmacy drug order lists and represent state tender prices (PGWC: Metropole Region, Western Cape). These costs represent costs to the NTP in South Africa. Costs were calculated per patient from inpatient treatment charts while in hospital, with only administered doses being included in costing as well as doses according to the discharge prescription. As delamanid is currently not freely available, drug costs were obtained from published literature [25, 146, 147]. Outpatient costs for discharge medications were calculated according to the issued discharge prescription. It was assumed that all doses were taken and the treatment course completed.

3.4.7 Dressings and ancillary medications

Ancillary medications in the case of TB therapy typically refer to therapy used to prevent side effects of the drugs; for example, pyridoxine to prevent peripheral neuropathy and vitamin D and calcium to counteract the side effects of steroid use. However, use of these drugs is standard practice when prescribing the drugs with known adverse effects. This cost was therefore not included in the cost of our management. Within our study population ancillary medications and dressings referred rather to medications other than TB therapy required by the patients admitted as a result of the CADR for the management of the CADR and associated symptoms. These medications included largely analgesics and antibiotics used to manage symptoms and complications of the CADR. Chronic medications that the patients may have been taking as well as ART for associated co-morbidities was not included in the definition or costing of the ancillary medication. Only medications and dressing directly related to the CADR, or hospitalisation as a result of the CADR were included in the costing. Ancillary medication costs were also obtained from the GSH pharmacy drug order lists (PGWC: Metropole Region, Western Cape). Inpatient medication and dressing cost was calculated per dosage or administration as recorded in the in-patient treatment and

dressing charts. Costs were therefore only applied to medication and dressings signed off as having been given in order to account for missed, or doses not given. Dressings used commonly included paraffin gauze (Jelonet™) dressings for excoriated mucous membranes such as the lips, steroid dressings of varying strengths for the body, as well as non-adherent dressings like Mepitel™, Natural tears and fluocinolone gel to prevent adhesions in affected mucous membranes. Included under dressing costs were the entities of Sitz and betadine baths, which were used in various cases for washing of the affected areas. All dressing and their associated costs are included in the table of costs (Appendix 3).

3.4.8 Patient level costs

Patient level costs were determined in a secondary analysis. Costs incurred directly by patients were calculated according to the expected loss of income due to hospitalisation as well as their expected medical bill for the treatment period. This cost was based on their employment status and annual income. In cases where patients were unemployed or earning close to minimum wage, they were assigned a proxy of income equivalent to the lowest minimum wage earner in South Africa. This was an entry-level worker at the city council earning $97/month (working 8 hours per day and 22 days/month) [142]. Patients making use of government subsidised healthcare facilities are assigned to a level of payment subsidy according to their ability to contribute to the cost of their healthcare (Appendix 4) [143, 172]. According to their payment bracket, personal treatment related expenses were allocated and calculated. These out-of-pocket expenses were then expressed as a percentage of their annual income. As data was collected retrospectively, there was no information available on other expenses (transport, food etc.) or guardian costs they might have incurred related to the course of their illness and accessing of treatment. Patient loss in our population refers only to the loss of income from days of work missed due to hospitalisation as well as the expected medical expenses that the patient would be liable for during the treatment course as per their income category [143].

Patient level costs were also estimated for the alternative regimens. This estimate was based on the percentage of the costs that the hypothetical patient would be liable for as per the proportions of patients in the original study population and their classification in the payment subsidy structure.

3.5 Data cost collection

A bottom-up ingredient's approach was used to calculate the total cost (for the study period) and the cost per patient based on the unit costs for each defined period of the rechallenge process. Within the analysis CADR patients with TB were considered as the total population, following which patients with DS-TB and DR-TB were separated with the DS-TB group being further divided into those in the continuation phase of treatment, those in the intensive phase of treatment and those unnecessarily treated for TB and calculations were made accordingly. Costs were only assigned to data relating to each patient's care that was administered or experienced as noted on the various data sources (clinical folders, NHLS systems) for each period of the rechallenge process. Assumptions of costs were made for the periods of stabilisation during which the patient may have been given a pass-out in that it was assumed they would use all the prescribed medication. Similarly, in the optimised treatment phase in cases of missing data, costs were applied according to the discharge treatment prescription as well as the standard NTP guidelines on monitoring and patient follow up. It was assumed that all treatment was completed and all appointments attended with all monitoring tests carried out. Totals and averages were calculated for DS-TB population and DR-TB population as a whole as well as for the 3 separate subgroups of the DS-TB population.

3.6 Analysis

A decision-analytic model was used to determine the cost estimates of drug rechallenge compared to immediate initiation onto second-line therapy in DS-TB patients. The cost data collected for the study population was used to determine the cost of first-line drug rechallenge in cases of CADR. The cost of second-line therapy was determined

separately using an ingredients approach for a theoretical cohort based on literature and clinical advice. Patient level costs that applied to the actual study population and estimated costs for the hypothetical cohort were determined in a separate analysis.

The primary outcomes included (i) the total and per patient cost of managing CADR cases to first-line TB treatment (ii) the comparative and/or incremental per patient cost of first-line drug rechallenge versus immediate second-line treatment initiation in DS-TB patients. The timeframe of the analysis was from onset of the CADR to TB treatment completion. Secondary analyses included (i) a univariate sensitivity analysis and a multivariate scenario analysis to determine the key cost drivers in managing CADRs in all strategies and (ii) a patient-perspective cost analysis to determine out-of-pocket expenses incurred by patients suffering from a CADR to TB therapy.

3.6.1 Analysis packages

Analysis and calculations, as well as figures where necessary, were done using Microsoft Office (2015) Excel and column statistics were performed using GraphPad Prism version 6.0 (GraphPad Software, La Jolla California USA). The decision tree was constructed using TreeAge Pro 2015, R1.0. (TreeAge Software, Williamstown, MA).

3.7 Sensitivity analyses

A univariate sensitivity analyses were carried out to explore the implications of uncertainty around the cost variables used in the analysis. Additionally, specific parameters were varied to determine how pragmatic changes in the model affected the cost of each strategy.

These included:

- Hospital costs: Costs of hospital stay were doubled and halved. Duration of hospitalisation was also increased (doubled in the rechallenge period of the study population) and an extra month of inpatient therapy included in the alternate arms of therapy. The effect of outpatient stabilisation was also included.

Severe drug reactions are typically referred to tertiary level hospitals where patients are seen by treating dermatologists as well as other specialist units. Hospital costs are likely to vary between provinces and countries. To account for this variation, we analysed changes in total daily cost by halving as well as doubling the per day hospital cost. Practically in our data set current cost refers to tertiary hospitalisation cost, whereas hospitalisation at a secondary level hospital would be equivalent to half this cost. Furthermore initiation of each drug can be done at 4-8 day intervals in the literature [6, 16]. Within our population this is typically done at 4-day intervals but an alternative cost was analysed using introduction at 8-day intervals. For the alternate regimens, we analysed the impact of a month-long period of hospitalisation after starting the second-line drugs to monitor for the potential development of an ADR. The impact of outpatient stabilisation on total cost was also evaluated. Based on literature approach to outpatient stabilisation with DILI, we extrapolated that patients with DRESS and an ALT<100 at presentation would be a lower risk population, eligible for outpatient stabilisation [62].

- Laboratory and radiological investigations: Costs of laboratory investigations and radiology were increased by 50% and halved within the population.

  When patients are unwell and when clinically indicated, laboratory investigations need to be carried out. However, daily-screening investigations can be of little benefit. More specific tests may have a greater sensitivity and a substantial impact on overall cost. The sensitivity analysis was carried out to see how the unit cost per patient was affected through the use of less frequent and more specific screening protocols.

- Category of personnel: The time spent by personnel attending to study patients was doubled and halved. Increased and reduced frequency of consultations by specialist dermatologists at current cost was also evaluated.

  The cost analysis was performed incorporating double the estimated time for the consultation with current staff (30 minutes) and half (7 minutes) instead of current

15-minute consultations. Furthermore, the baseline frequency of consultant review was 3 times a week, but this was varied from daily consults to weekly consults to determine the impact on overall cost.

- Drug pricing: Costs of TB and ancillary medication used was doubled as well as halved.

  Sensitivity analysis of drug costs was done to determine the effect of a reduction of the cost of drug therapies has on the overall cost of rechallenge as well as the alternative arm of therapy. Drug costs were halved and doubled to account for the range of costs as described in the literature [28, 173, 174].

- Fluctuation of the ZAR/USD exchange rate: Lowest and highest rates recorded for 2016.

  The exchange rate of South African rand to US dollar fluctuated substantially during 2016. In order to explore the implication of using the average exchange rate for this period we also calculated overall costs based on the lowest (1USD=R13.26) as well as highest (1USD= R16.86) exchange rate recorded for this period [145]. This is important as in cases where drugs are internationally sourced fluctuations in exchange rate may have significant implications in the various costs of the regimens.

- Patient costs in terms of societal costs: Patients annual incomes doubled and halved. As many of the study population were classified as being unemployed an income proxy of a general worker earning the minimum wage was assigned in order to estimate the patient loss in terms of loss of annual income. Higher patient costs ultimately result in higher societal costs. To account for the potential under-estimation of patient incomes, in cases were the data may have been captured incorrectly or they may be informally employed, annual incomes were doubled. To contrast this in instances where patient may in fact be casually employed and

earning less than the minimum wage due to fewer days of employment or completely unemployed with no subsidised income, annual incomes were halved.

In addition, a scenario analysis was undertaken in which multiple variables were altered simultaneously in order to determine their effect on overall cost. This was done for both "best" and "worst" case scenarios. In the "best" case scenario hospital costs were halved to model those of secondary level hospitals ($32.06 per day). Patients were assumed to be healthier or more tolerant of the rechallenge and alternative therapies requiring fewer monitoring tests. Furthermore, daily management was by training dermatologists with weekly specialist dermatologist review. TB drug costs were halved to model a situation where they are affordable and readily available, especially in the case of the newer second-line drugs of bedaquiline and delamanid.

To contrast the "best" case, the cost of a "worst" case scenario was determined to model a situation where patients were very sick and costs were higher. Specifically, the length of hospitalization was increased in the rechallenge period, amounting to 8 days between each drug being reintroduced as opposed to 4 days. In the alternate arms an additional 30-day in-patient monitoring period was included before patients were discharged on the hypothetical alternative treatment regimens to allow for monitoring of potential development of ADRs. As the patients were seemingly less tolerant, they were seen daily by specialist dermatologists and lab investigation costs were increased by 50% to account for the potential increase in tests these patients would warrant. Within this scenario TB drug costs were also doubled making for a situation in which drugs are costly and hard to come by.

The total per patient cost of each strategy in these two scenarios were estimated and compared to determine the most influential factor that affected these costs.

3.8 Ethical considerations:

Ethics approval was granted by the University of Cape Town, Faculty of Health Sciences, Human Research and Ethics Committee on the 22 April 2016 (HREC REF: 240/2016) (see Appendix 2). The study posed no risk to any of the participants. All

identifying particulars of patients were removed from the database. Furthermore, the database was stored, password protected with access limited only to authors and supervisors. All participants had given consent during their hospital stay for their records to be used for clinical research.

4. RESULTS

The main study findings will be presented in this chapter. Firstly, the baseline characteristics of the study population will be reported. In section 4.2 the resources required for the process of rechallenge will be identified and valued for a total cost of the CADR with standard procedure in currently practiced at Groote Schuur Hospital. Section 4.3 presents the estimated costs of the alternative drug regimens that would be used in place of the rechallenge process. Section 4.4 comprises a comparison and cost consequence of the alternate arms of the study and section 4.5 presents the results of the sensitivity analyses. Lastly section 4.6 will look at patient related costs attributed to by the CADR.

4.1 Baseline characteristics

Data was obtained from a cohort of 97 patients admitted to the dermatology ward at GSH with a CADR to TB drugs, at least one of which was a first-line drug, during the period from May of 2010 to July of 2015. Based on microbiological and drug sensitivity testing as well as clinical and radiological evidence, the majority of patients, 89 (92%) were suspected of having DS-TB, 4 (4%) MDR-TB, 2 (2%) had rifampicin mono-resistant TB and the other 2 (2%) had isoniazid mono-resistant TB (Table 4.1). Within this population, the prevalence of DR-TB was 8.5%.

Table 4.1: Baseline characteristics of the study population that developed a CADR to TB therapy admitted to the Dermatology ward at Groote Schuur Hospital.

	Study Population (97 patients)
Sex (%)	
Male	47 (48)
Female	50 (52)
Median Age	36
(IQR)	(30, 42)
HIV Status (%)	
Infected	85 (88)
Uninfected	12 (12)
Median CD4 Count	130
cell/mm^3 (IQR)	(46, 236)
On ART	29 (34)
ART naïve	56 (66)
Type of TB (%)	
Pulmonary	68 (70)
Disseminated	27 (28)
INH prophylaxis	2 (2)
TB Sensitivity (%)	
DS-TB	89 (92)
MDR-TB	4 (4)
RR-TB	2 (2)
INH mono-resistant TB	2 (2)
CADR (%)	
DRESS	60 (62)
SJS	22 (23)
SJS/TEN overlap	4 (4)
TEN	10 (10)
LDR	1 (1)
Days to onset of CADR	26
IQR	(17, 43)

Key: ART=anti-retroviral therapy, CADR=cutaneous adverse drug reaction, DRESS=drug reaction with eosinophilia with systemic symptoms, DS-TB=drug-sensitive TB, HIV=Human immunodeficiency virus, INH=isoniazid, IQR= interquartile range, LDR=lichenoid drug reaction, MDR-TB=multi-drug resistant TB, RR-TB=rifampicin-resistant TB, SJS=Stevens Johnson syndrome, TB=tuberculosis, TEN=toxic epidermal necrolysis

Within the HIV-infected population, 29/85 (34%) were on ART, 19 of the 85 patients (22%) were within 2 weeks of starting TB therapy and 37/85 (44%) had been on TB treatment for longer than 2 weeks and should have been on ART.
Sixty-eight of the patients had PTB, with the remainder (27) having extra-pulmonary TB and in 2 instances the patient was only on INH prophylaxis used for the prevention of TB in HIV-infected patients as well as those who may be immuno-compromised as a result of another systemic illness or as a result of immuno-suppressive therapy, such as corticosteroids used in the treatment of many systemic illnesses.

DRESS was diagnosed in the majority (60/97, 62%) of cases while SJS was the second most commonly occurring CADR (22/97, 23%) (Table 4.1). All CADR occurred a median of 26 days (IQR 17; 43) after the initiation of TB therapy in the study population.

4.1.1 Rechallenge population outcomes

Of the 97 patients admitted with CADR to TB drugs, 85 (88%) were rechallenged with first-line TB drugs. Twelve patients were not rechallenged. One patient was admitted with a lichenoid drug reaction (LDR) and treatment was continued under supervision, a further 2 patients had been on INH prophylaxis which was discontinued upon presentation with CADR and in the remaining 8 patients there was insufficient evidence to support the TB diagnosis thus rechallenge was deemed unnecessary. Seventy-six of the 85 patients undergoing rechallenge (78% of the study population) were discharged on TB therapy, 34 of which were discharged on first-line TB therapy, with 42/76 (55%) requiring regimen adjustment to include second-line TB drugs. Four patients were rechallenged to various degrees before the decision was taken that they had been unnecessarily treated for TB. Three patients absconded from the hospital ward after a weekend pass-out and were lost to follow up. Two patients died due to conditions unrelated to the CADR (Addisonian crisis due to high dose steroid use for chronic obstructive pulmonary disease; diarrhoea complicated by hypokalaemia after discharge) (Table 4.2).

Table 4.2: Population rechallenged and outcomes of the rechallenge process for the study population.

Patient group	**Number of patients (% of study population)**
Number of patients admitted with CADR	97 (100)
Number of patients rechallenged	85 (88)
Patients not undergoing rechallenge	
LDR	1 (1)
Insufficient evidence for TB	8 (8)
INH prophylaxis	2 (2)
Absconded	1 (1)
Number of patients discharged on TB therapy	
After rechallenge	76 (78)
Continued treatment under observation	1 (1)
Discharge TB Treatment regimens	
First-line therapy	34 (35)
Adapted regimens	42 (43)
Final Outcomes	
Discharge	92 (95)
Death	2 (2)
Lost to follow up	3 (3)

Key: CADR=cutaneous adverse drug reaction, INH= isoniazid, LDR=lichenoid drug reaction, TB=tuberculosis

4.1.2 Causative drugs

Causative drugs of the CADR were confirmed with rechallenge in 64 of the 85 cases undergoing rechallenge (75%) (Table 4.3). A single drug was implicated in 46/64 patients (72%). In 18/64 (28%) of patients there was more than one possible offending drug and in the remaining 22/86 patients (26%) a causative drug was not identified. Three of the population with DR-TB was found to have reacted to first-line TB drugs (2 to pyrazinamide and 1 to isoniazid).

Twenty-one of the 22 patients (95%), in whom a causative drug was not identified, were HIV-infected. Seven of these patients were on ART (tenofovir, lamivudine and efavirenz). In 3/7 cases the ART initiation was within 2 weeks of starting TB treatment

and the CADR developing. In a single case, ART was started a month after TB therapy, but 4 months before CADR. In 2/7 cases, ART had been started more than a year before the diagnosis and treatment of TB. In the remaining case, the patient reported symptoms of CADR before ART was initiated at the TB clinic. In a further 2 of the cases where the offending agent could not be identified the patients were known to be epileptic and on treatment for their epilepsy.

Table 4.3: The frequency of first-line drugs identified as the causative drug of CADR in the study population.

Suspected offending drug	**Number of cases identified (%)**
Rifampicin	11 (18)
Isoniazid	11 (18)
Pyrazinamide	10 (16)
Ethambutol	9 (15)
Rifampicin/Isoniazid	5 (8)
Pyrazinamide/Ethambutol	4 (6)
Rifampicin/Ethambutol	2 (3)
Isoniazid/Pyrazinamide/Ethambutol *	1 (2)
Rifampicin/Ethambutol/Pyrazinamide *	2 (3)
Rifampicin/Isoniazid/Pyrazinamide *	1 (2)
Rifampicin/Isoniazid/Ethambutol *	1 (2)

* Multiple drug hypersensitivity

Exclusion of the offending drug resulted in a regimen adjustment in 45/76 (59%) patients discharged onto TB therapy. Four patients were rechallenged successfully with the four first-line drugs and discharged on a regimen containing all four drugs with no further documented reaction. Pyrazinamide and ethambutol was the suspected causative agent in 2 each of these 4 cases.

In the 22 patients where the causative drug was not known, 17 patients tolerated all the first-line TB drugs that were rechallenged. Fifteen of which had DS-TB and were restarted on first-line TB therapy (comprising 2 or more of the original 4 first-line drugs) without further reactions thus no additional investigations were required to identify the

offending drug. Three absconded from hospital during the rechallenge process and 2 died before a drug could be identified and had not reacted to the any of the drugs during rechallenge.

Overall, 34/76 (45%) patients were discharged on a regimen containing first-line TB drugs. Seventeen were discharged on a regimen comprising all 4 first-line drugs for various durations. The other 17 (22%) were discharged on various combinations of 2 or 3 first-line drugs only. The remaining 42/76 patients (55%) were discharged on regimens of TB therapy that included both first- as well as second-line TB therapy.

4.1.3 Duration of hospitalisation and treatment

Duration in each stage of the rechallenge process was calculated for all individuals of the study population. The average patient in the study population spent a median of 48 days in hospital (IQR 33; 73), the majority of hospitalisation, 41 days, was for the period of rechallenge. It would take the average patient in the study population a median of 255 days (IQR 172; 342) from diagnosis of CADR, through management to final treatment completion (Table 4.4)

Table 4.4: Duration in days that the study population spent in each stage of the rechallenge process.

	Duration median days (IQR)
Stabilisation period	8 (3;12)
Rechallenge period	41 (28; 63)
Optimised treatment period	180 (120; 270)
Total days hopistalised	48 (33; 73)
Duration from diagnosis to treatment completion	255 (172; 342)

4.1.4 Study population for cost comparison

As our hypothetical alternate regimens would only be costed for use in patients with DS-TB, the study population was separated into those with DS-TB (89 patients) and those

with DR-TB (8 patients) to allow for a more accurate cost comparison. Within the group of the population that had DS-TB, 2 were on INH prophylaxis and not rechallenged, while 12 lacked sufficient evidence for TB and thus were deemed to have been inappropriately treated for TB. Among those with confirmed DS-TB, there was a further division between those in the intensive phase and those in the continuation phase of treatment. Number of days in each stage of the process as well as days in hospital would be important for comparison and eventual costing. The differences in each group are shown in Table 4.5 below. Within the group of patients with DS-TB the average patient spent a median of 52 days in hospital (IQR 38; 79), the majority of hospitalisation being for the period of rechallenge. Within each population it is important to note that at various points during the rechallenge period patient were allowed a temporary discharge pass-out during which they could return home for a pre-determined period. This was typical done after patients were started on bridge therapy prior to the rechallenge period. In the DS-TB group patients were discharged for a median of 12 days (IQR 9; 14), and within the DR-TB group only 1 patient was allowed home for 20 days (Table 4.5).

Table 4.5: Duration in days spent in each stage of the rechallenge process in DS-TB and DR-TB patients in the study population.

Duration (median days)	**DS-TB days (IQR)**	**DR-TB days (IQR)**
Stabilisation period	11 (7, 19)	24 (11, 63)
Rechallenge period	45 (32, 66)	42 (34, 64)
Optimised Treatment Period	217 (180, 270)	437 (270, 591)
Total Duration of hospitalisation	52 (38, 79)	100 (62, 113)

Key: DS-TB=drug-sensitive TB, IQR=inter-quartile range, DR-TB=drug resistant TB, TB=tuberculosis

Following discharge, the average patient with DS-TB would need to complete a further 217 (IQR 180; 270) days of TB therapy, with DR-TB patients still having 437 (IQR 270; 591) days of therapy after discharge. From presentation to completion of TB treatment, the average patient with DS-TB would have been in the CADR management programme for a median 239 days (IQR 159; 335), comparable with a regimen of second-line drugs for 9 months. DR-TB patients were in the programme for a median 537 days (IQR 310; 710).

4.2 Cost of current drug rechallenge process

The 3 periods of the rechallenge process include; stabilisation, rechallenge and optimised treatment, which all contributed to the overall cost in varying degrees. In terms of the first aim of the study, calculating the total cost of CADR to first-line TB therapy, a total for the entire study population was calculated. Thereafter, the population was divided into those with DS-TB and those with DR-TB. Within these 2 subsets of the population totals and various results were presented to allow for a more accurate point of comparison for the hypothetical cohort for the second aim of the study.

4.2.1 Total and per-patient cost of CADR management

The total cost of managing CADR to first-line TB therapy in our population of 97 patients admitted to GSH was $632,918 ($6,525 per patient).

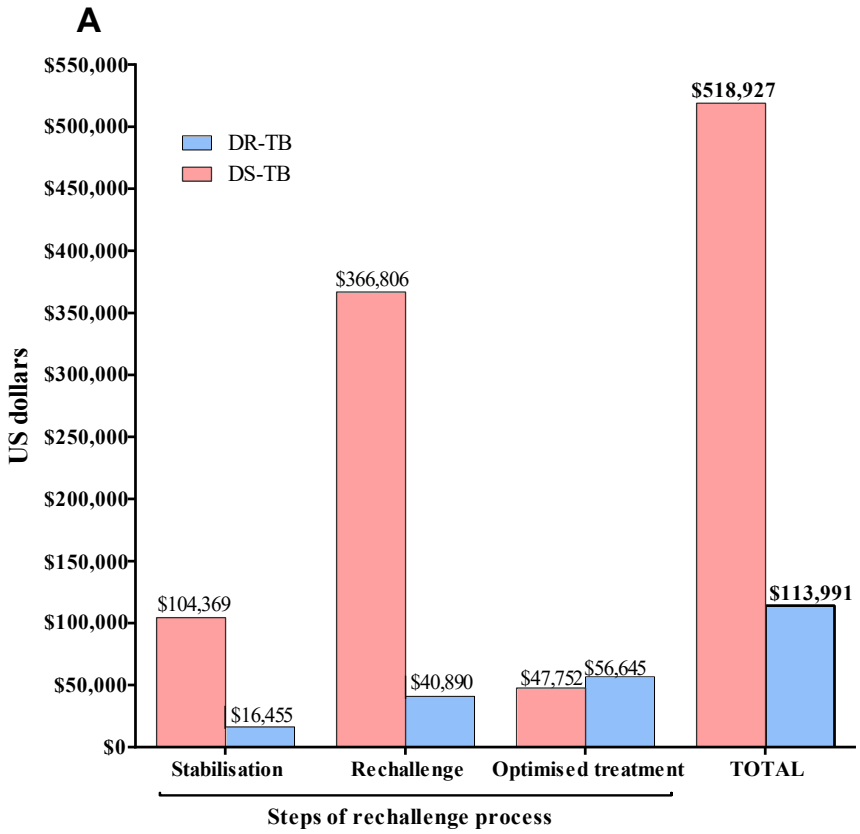
The majority of this total, $518,927 (82%) was made up from the cost of managing the CADR in the DS-TB patients in the CADR population. Within this group of the population the period of rechallenge was the most costly ($366,806; 71% of the total DS-TB cost). However, the period of initial stabilisation and optimised treatment also contributed significantly to the overall cost $104,369 (20% of the total DS-TB cost) and $47,752 (9% of the total DS-TB cost) respectively.

The remaining $113,991 amounted to the cost of managing the CADR in the patients with DR-TB. Within this group of the population the majority of the cost was made up by the optimised treatment period ($56,646; 50% of the total DR-TB cost). Within this population the initial stabilisation and rechallenge contributed $16,455 (14% of the total DR-TB cost) and $40,890 (36% of the total DR-TB cost) respectively (Figure 4.1 A).

The average cost per patient was also determined for each group within the study population. The cost of managing a single patient with DS-TB and CADR was $5,831 (95% CI 5134; 6527). Once again, the major contributor was the rechallenge period at

$4,121 (95% CI 3521; 4722). The management of a single patient with DR-TB and CADR was more than double that of the DS-TB at $14,249 (95% CI 7257; 21240).

The average cost per patient in the DR-TB population was greatest in the optimised treatment phase at $7,081 (95% CI 2305; 11856) (Figure 4. 1 B).


A
$550,000
$500,000
$450,000
$400,000
$350,000
$300,000
$250,000
$200,000
$150,000
$100,000
$50,000
$0
US dollars
DR-TB
DS-TB
$104,369
$16,455
$366,806
$40,890
$47,752
$56,645
$518,927
$113,991
Stabilisation
Rechallenge
Optimised treatment
TOTAL
Steps of rechallenge process

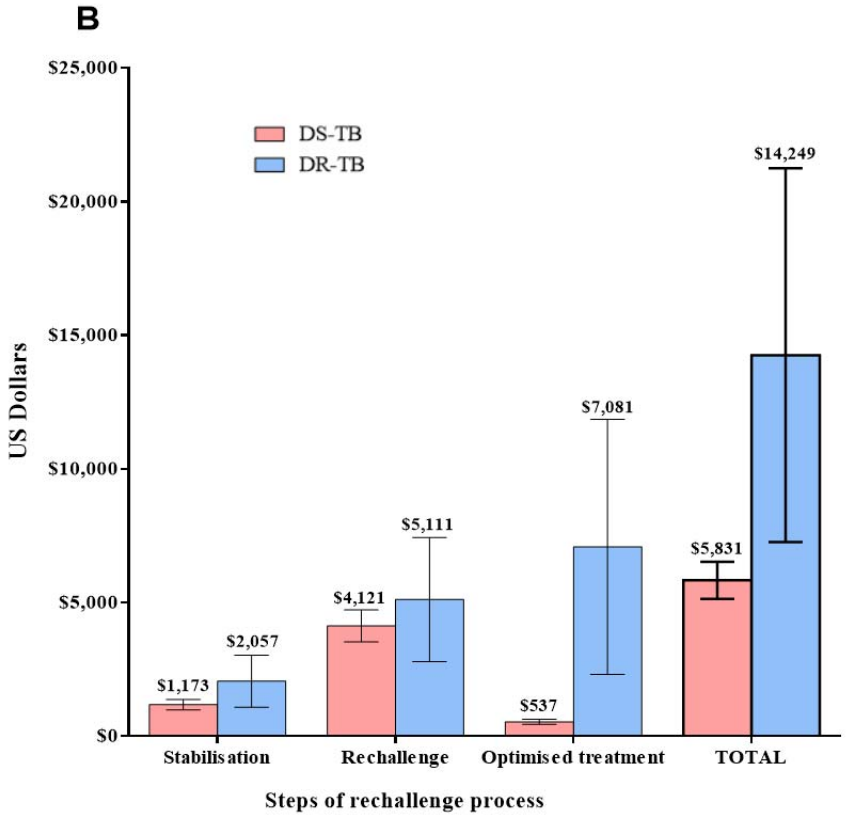

B
$25,000
$20,000
$15,000
$10,000
$5,000
$0
US Dollars
DS-TB
DR-TB
$1,173
$2,057
$4,121
$5,111
$537
$7,081
$5,831
$14,249
Stabilisation
Rechallenge
Optimised treatment
TOTAL
Steps of rechallenge process

Figure 4.1. Graphs showing (A) the total cost and (B) the average cost per patient of managing a CADR for the entire phase and for each stage of the rechallenge process in the patients with DS-TB and DR-TB. In (A), values above each bar represent the total cost. In (B), values above each bar represent the mean cost and error bars show the 95% confidence interval. Values expressed in 2016 US $.

4.2.2 Cost per subset within the DS-TB population

The DS-TB patients within the study population could be further broken down into those who developed their CADR in the intensive phase of TB therapy (68; 76%), those in the continuation phase of TB therapy (7; 8%) and those unnecessarily treated for TB (14; 16%).

Patients in the intensive phase of TB therapy contributed $439,761 (85%) to the total CADR cost in DS-TB patients with 72% ($316,884) of this cost attributed to the rechallenge period. Patients in the continuation phase contributed $46,782 (9%), with the majority ($36,309; 78%) of this total also due to the rechallenge period. Those who were unnecessarily treated for TB, contributed a total of $32,383 (6%) to the overall cost. In this group the period of stabilisation was the greatest contributor to total cost for this group at $18,657 (58%) (Figure 4.2). The majority of this cost in the unnecessary treatment group (a total of $13,612; $3,403 per patient) was attributed to the 4 of the 14 that underwent rechallenge to various degrees before the decision was made to discontinue TB treatment.

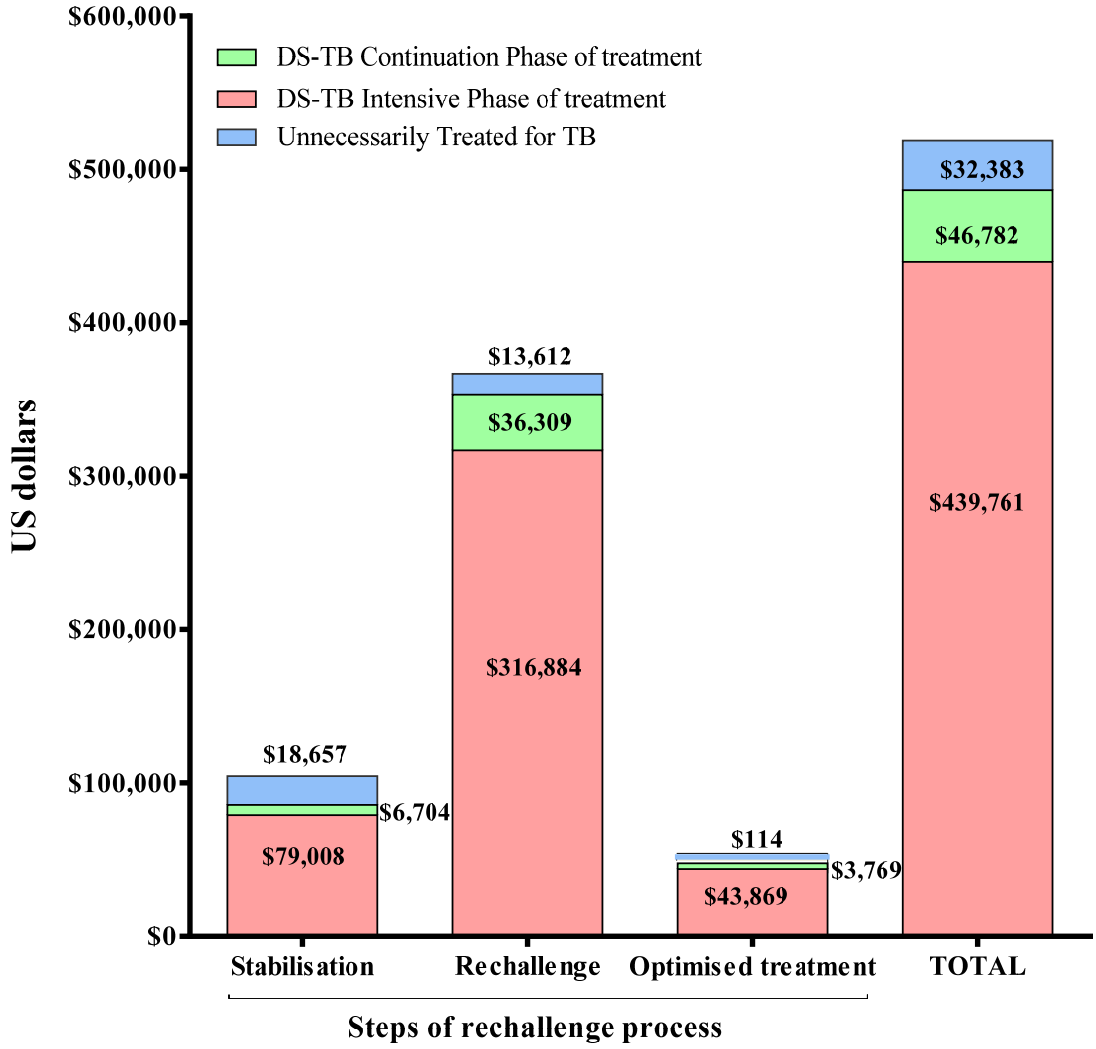


Figure 4.2: Proportions of total cost of CADR in patients with DS-TB in the study population contributed to by the 3 different groups within the DS-TB group for each step of the rechallenge process. Costs are expressed in 2016 US $.

The average cost of CADR for patients with DS-TB in the intensive phase of treatment was $6,467 (SD of mean 3,048) this is compared with $6,683 (SD of the mean 3,968) in the continuation phase and $2,313 (SD of mean 1,738) in those unnecessarily treated for TB. Of the patients who should have been in the continuation phase of treatment, 3 of the 7 underwent a more extensive rechallenge with pyrazinamide and ethambutol. In the confirmed TB groups, the greatest cost was incurred in the rechallenge period ($5,187

per patient in the continuation phase and $4,660 per patient in the intensive phase). The cost of rechallenging individuals in the continuation phase of TB therapy accounted for 10% of the total cost for the whole DS-TB population (Figure 4.3).

In those who were found to be unnecessarily treated for TB, 48% of the total cost was incurred in the stabilisation period at $1,333 per patient (SD of mean 617). In the optimised treatment period, these patients did not undergo TB treatment but were followed up at 6 weeks by a dermatologist to ensure resolution of the CADR symptoms, as is standard practice in the unit and ensure that they had not since developed TB. This amounted to a total cost of $114 ($8 per patient), equivalent to 0.2% of the study total for DS-TB at this stage (Figure 4.3).

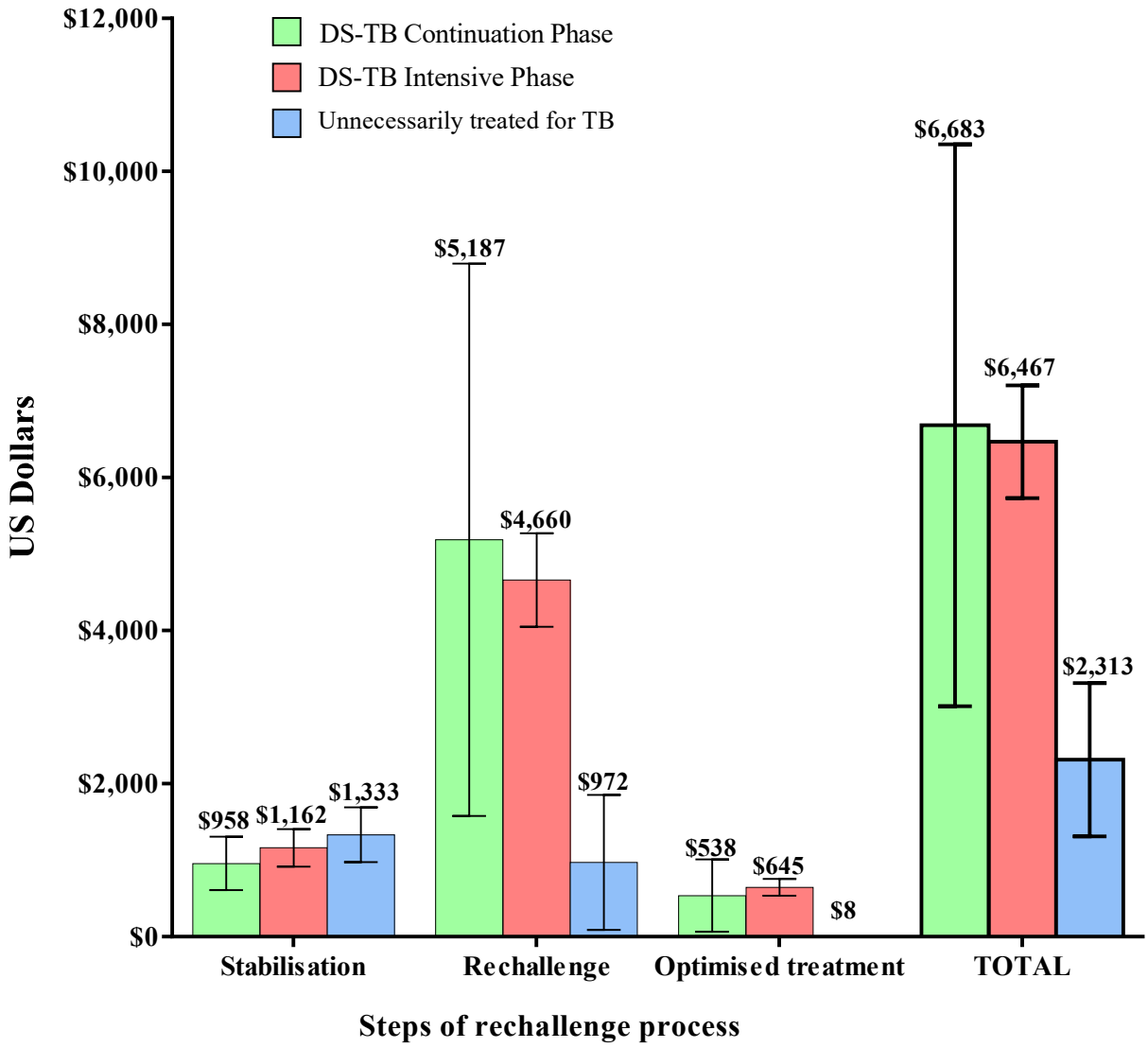


Figure 4.3: Average per patient cost for the 3 different groups within the group of patients with DS-TB for each step of the rechallenge process. Values are expressed in 2016 US $.

4.2.3 Components contributing to cost of CADR management

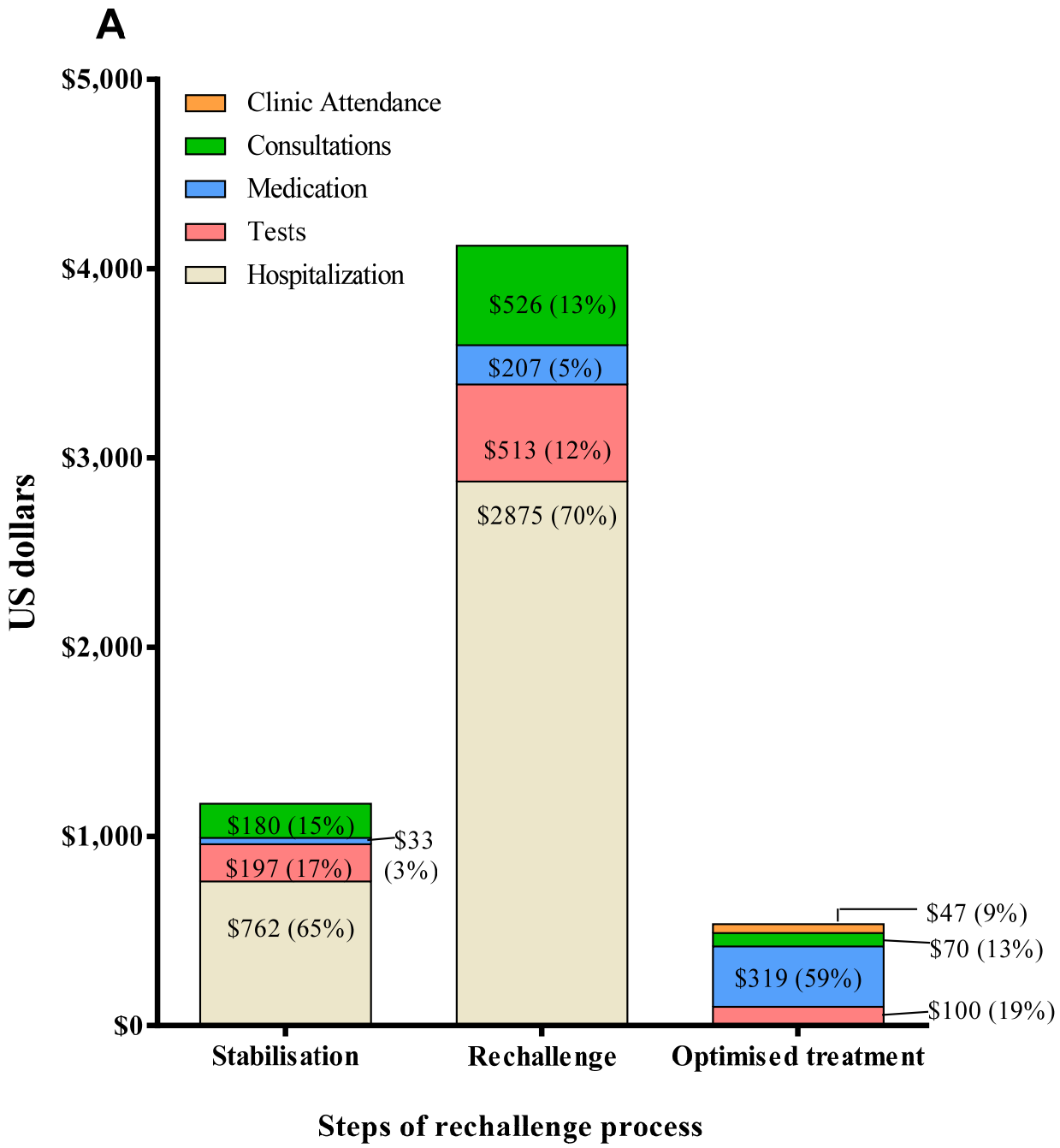
Within the 3 periods of the rechallenge process several parameters influenced overall cost to varying extents. Within the period of stabilisation and rechallenge the greatest driver of cost was hospitalisation in the DS-TB patients in the study population. During stabilisation, the average cost per patient for hospitalisation amounted to $762 (65% of total stabilisation cost) whereas the cost of hospitalisation was $2,875 for the rechallenge

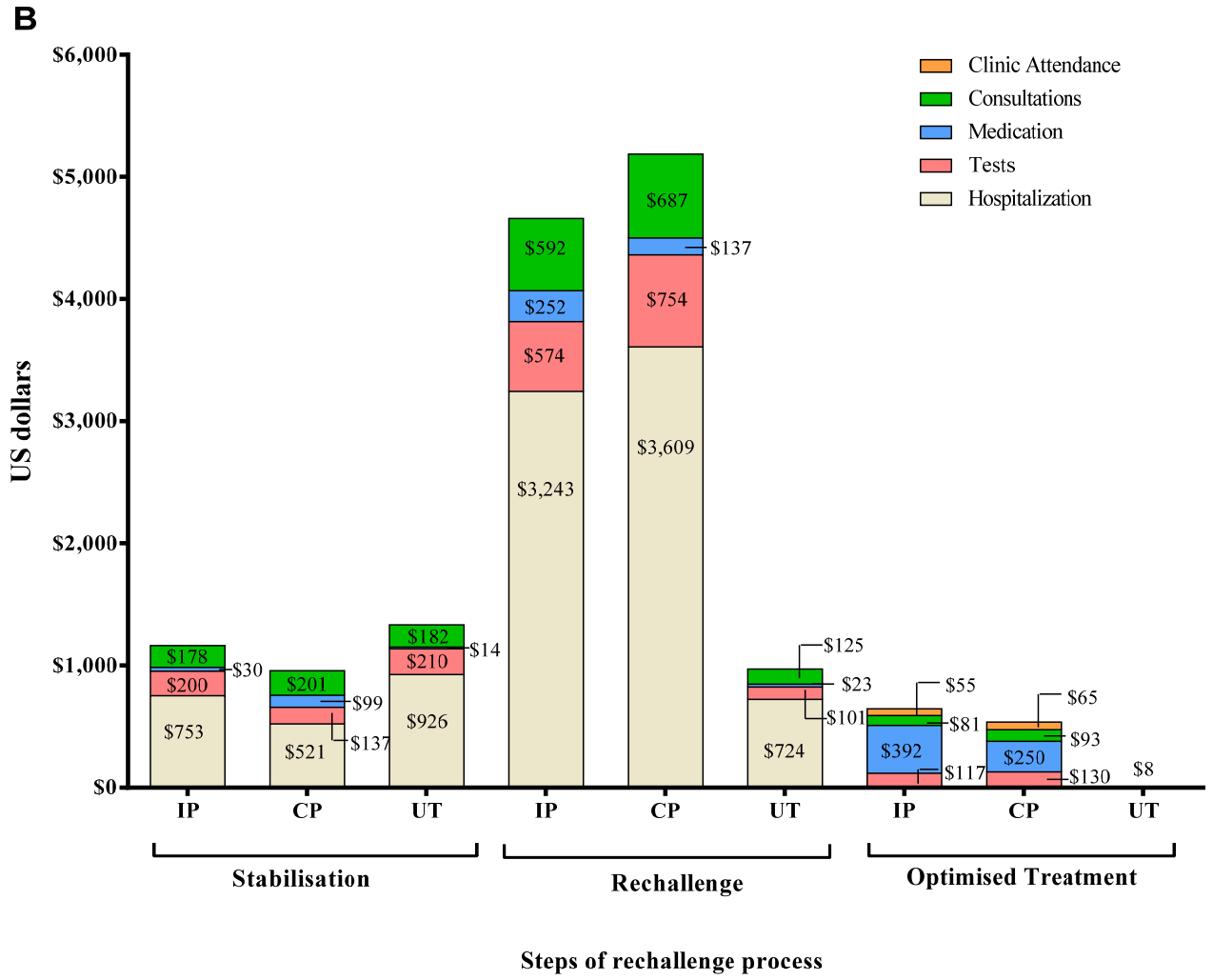
period (70% of the total cost for this period). Both consultations and investigations contributed almost equally during these 2 stages and were the second major contributors to total cost.

After discharge, the main contributor to total cost became that of medication at $28,412 ($319/patient). Tests in this stage contributed to 19% of the total cost, more than they had in previous stages (10 % and 13% respectively) (Figure 4.4A).

Within the group of patients with DS-TB, the influence of the various parameters on cost could also be seen amongst the 3 subgroups of this population subset. The group that was unnecessarily treated for TB had the highest average per patient cost for the stabilisation period with hospitalisation having the greatest contribution at $926. Patients in the intensive phase of TB treatment had the second highest per patient cost in the stabilisation period, with hospitalisation being $753 per patient and investigations being the second biggest contributor at $200. However, within the rechallenge period, the per patient cost was higher for the group in the continuation phase of treatment. In the optimised treatment phase, the average patient cost was again greater in the intensive phase group, with medication costs being the greatest contributor to overall cost at $392 per patient (Figure 4.4B).

In the group of patients with DR-TB, hospitalisation was the main contributor of total cost in the stabilisation ($1,381 per patient) and rechallenge period ($3,462 per patient,). Optimised treatment after discharge from hospital was largely influenced by the combination of TB drugs used with drugs costs amounting to a total of $51,872 or $6,484 per patient in this stage (Figure 4.4C).


A
$5,000
$4,000
$3,000
$2,000
$1,000
$0
US dollars
Clinic Attendance
Consultations
Medication
Tests
Hospitalization
$180 (15%)
$33
(3%)
$197 (17%)
$762 (65%)
$526 (13%)
$207 (5%)
$513 (12%)
$2875 (70%)
$47 (9%)
$70 (13%)
$319 (59%)
$100 (19%)
Stabilisation
Rechallenge
Optimised treatment
Steps of rechallenge process


B
$6,000
$5,000
$4,000
$3,000
$2,000
$1,000
$0
US dollars
Clinic Attendance
Consultations
Medication
Tests
Hospitalization
$178
$30
$200
$753
$201
$99
$137
$521
$182
$14
$210
$926
$592
$252
$574
$3,243
$687
$137
$754
$3,609
$125
$23
$101
$724
$55
$81
$392
$117
$65
$93
$250
$130
$8
IP
CP
UT
IP
CP
UT
IP
CP
UT
Stabilisation
Rechallenge
Optimised Treatment
Steps of rechallenge process

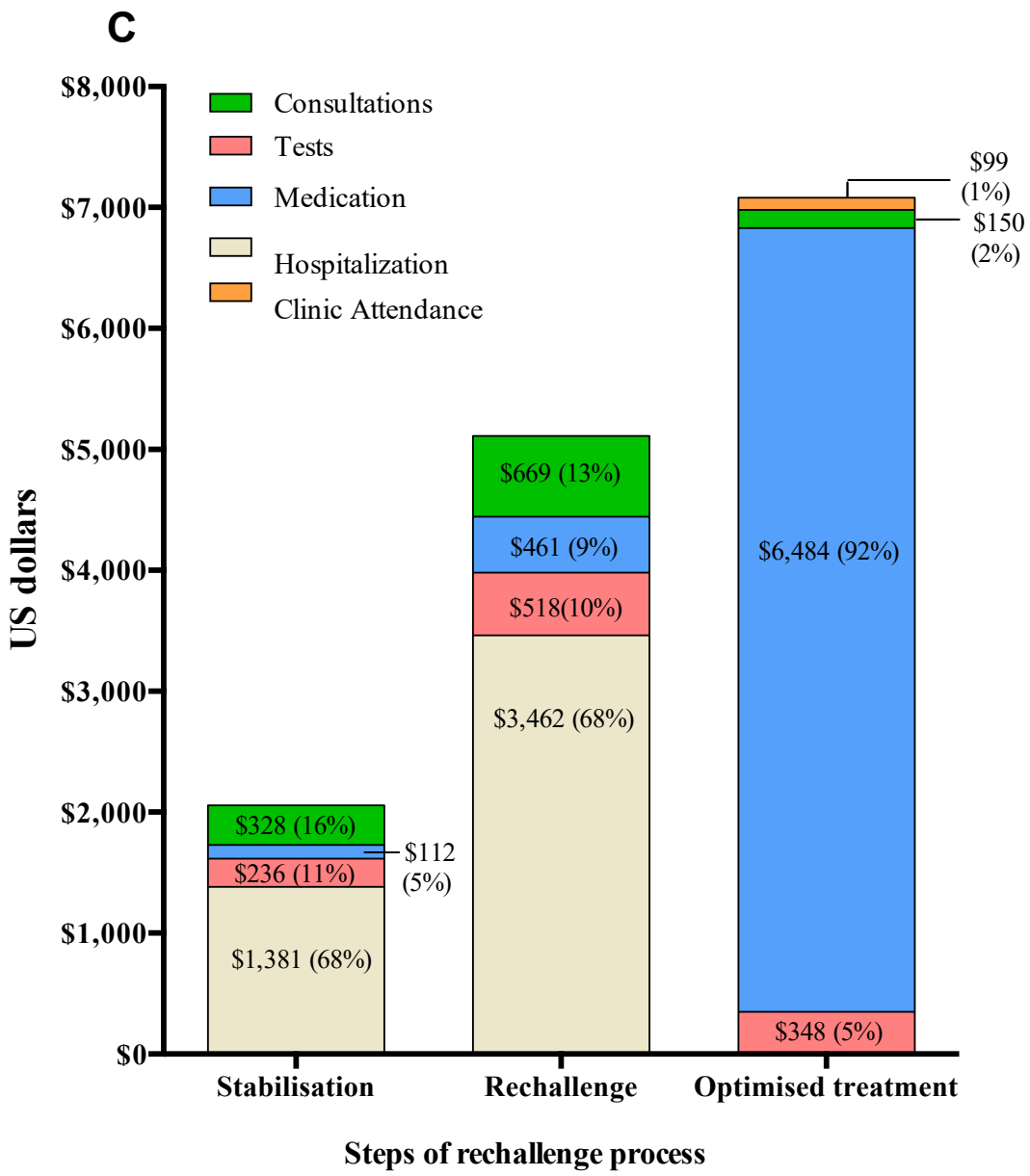


Figure 4.4: Breakdown of the per patient cost components contributing to each step of the rechallenge process in (A) the patients with DS-TB in the study population and (B) in the different 3 groups within the DS-TB population and (C) the patients with DR-TB in the study population. The cost values in each bar represent the cost of a particular component with the percentage representing the proportion contributed to the total cost in each step of the rechallenge process. Values expressed in 2016 US $. CP: DS-TB in the continuation phase of treatment, IP: DS-TB in intensive phase of treatment, UT; population unnecessarily treated for TB.

4.2.4 Medication cost breakdown

Medication costs were further broken down for the entire rechallenge process into dressing costs, ancillary medications and TB drug costs. In patients with DS-TB total medication costs amounted to $18,431 and $207 per patient (95% CI: 126.7; 287.5). The greatest contributor to this total was the cost of TB drugs at $111 per patient (95% CI 75.51; 146.3). Ancillary medications contributed $71 per patient (95% CI 0.46; 141.6). Dressings were the least costly at $26 per patient (95% CI: 19.04; 32.17).

Medication cost was more than double in patients with DR-TB as compared to those with DS-TB ($461 per patient; 95% CI: 232.2; 690.5). TB drugs were, by far, the greatest cost contributor at $429 per patient (95% CI: 192.6; 664.4). This cost comprised 93% of the total medication cost compared to the 54% in those with DS-TB. Dressing and ancillary drugs only amount to $28 (95% CI: 6.256; 49.83) and $5 (95% CI: 1.369; 11.02) per patient, respectively (Figure 4. 5).

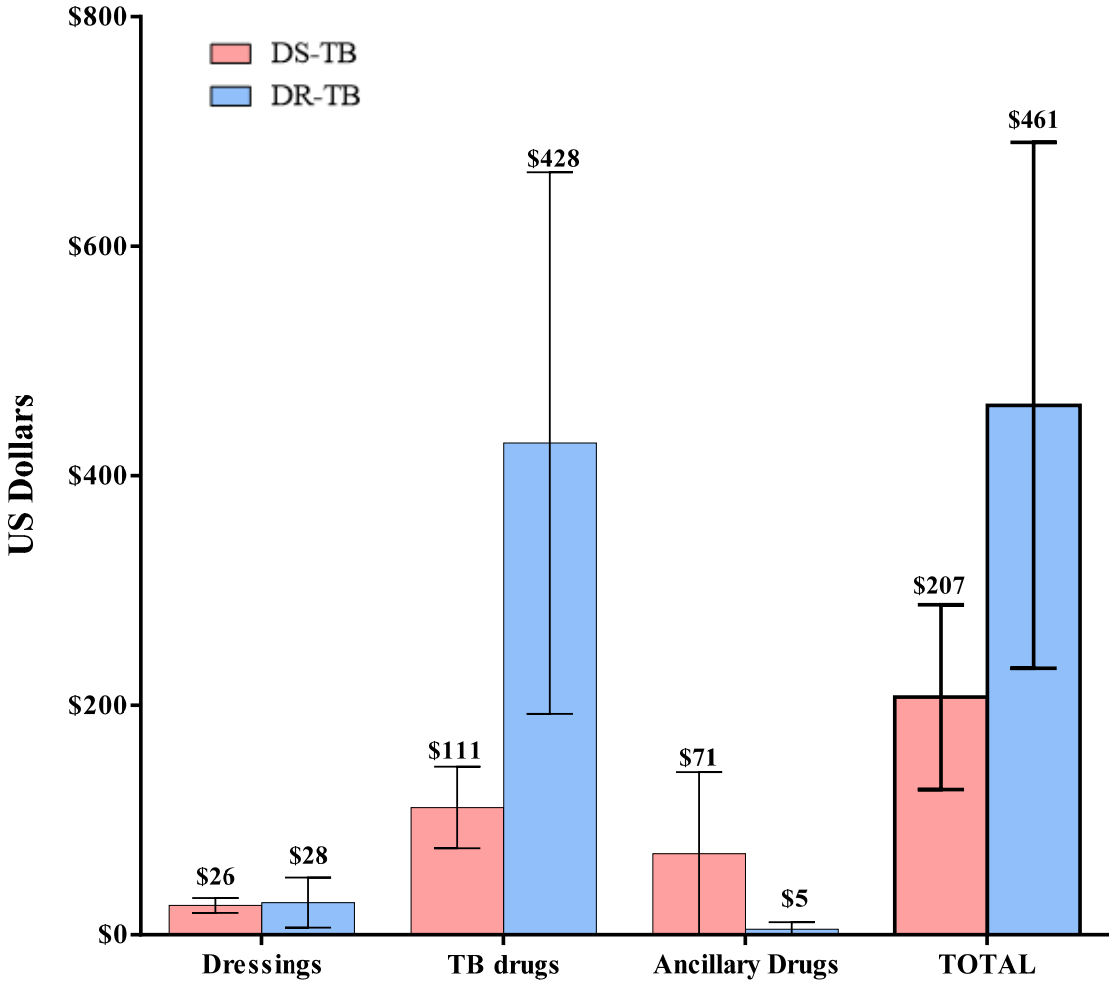


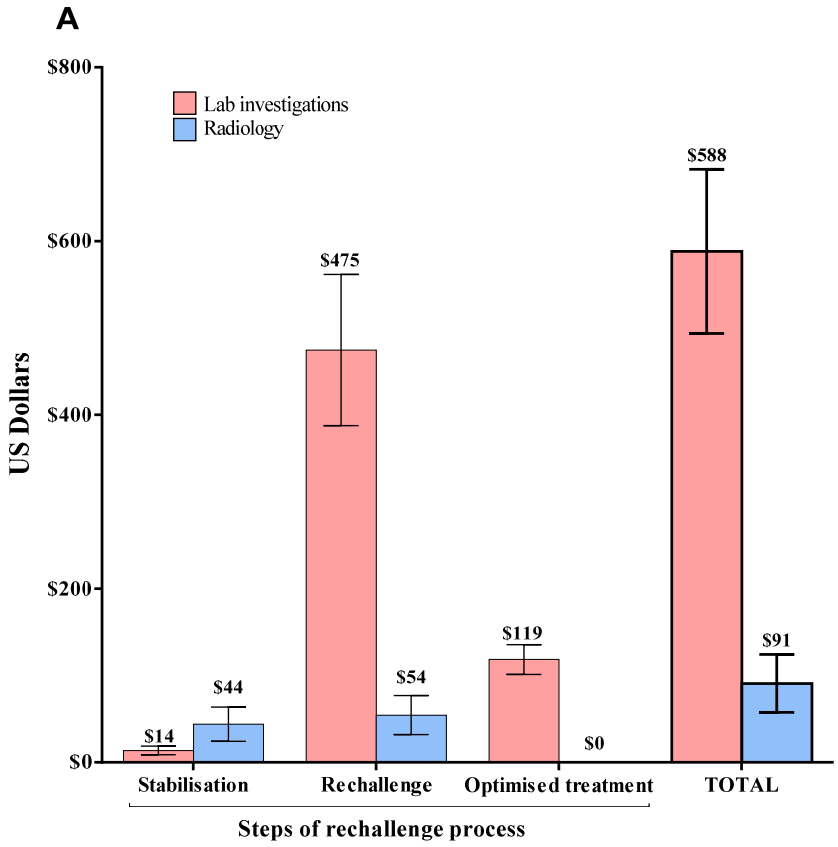
Figure 4.5: Breakdown of the total drug and dressing cost for the rechallenge period in patients with DS-TB and DR-TB. Values above each bar represent the mean cost and error bars show the 95% confidence interval. Values expressed in 2016 US $.

4.2.5 Test cost breakdown

Within the study population test costs, comprising laboratory investigations and radiological examinations, contributed to a substantial proportion throughout the entire process. Radiological examinations were more commonly used in the diagnosis of extra-pulmonary TB and had higher unit costs amongst the investigations carried out in the study population. CXR cost on average $13, with abdominal sonographs being $38, CT scans were by far the most expensive investigation at $182. Within the group of patients

with DS-TB the total cost of tests amounted to $588 per patient (95% CI 494; 682.7) and a total of $52,360. This contributed to 10% of the overall total cost (Figure 4.6A). Laboratory investigation costs for commonly used individual tests ranged from a white cell count (WCC) and haemoglobin at $1 to $4 for an AST or ALT. Less frequently used tests such as CD4 count cost $17. These less frequently used tests were used predominantly in the stabilisation period when evaluating a patient for all their baseline characteristics. Despite radiological examinations having higher unit costs as compared to typical laboratory investigations, the frequency at which the laboratory investigations were done contributed to a greater overall cost (86% of the total test cost). The greatest laboratory investigation costs were recorded during the rechallenge period ($475; 95% CI 387.9; 561.4).

Amongst the patients with DR-TB the cost of tests per patient was higher at $827 (95% CI 601.6; 1052) for a total cost of $6,614 (6% of overall total cost). The highest laboratory investigation cost was incurred in the rechallenge period ($471 per patient; 95% CI: 219.5; 723.1), but these costs were also significant in the optimised treatment period at $348 (95% CI: 249.4; 446.1) (Figure 4.6B).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US Dollars
Lab investigations
Radiology
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$475
$54
$119
$0
$588
$91
Stabilisation
Rechallenge
Optimised treatment
TOTAL
Steps of rechallenge process

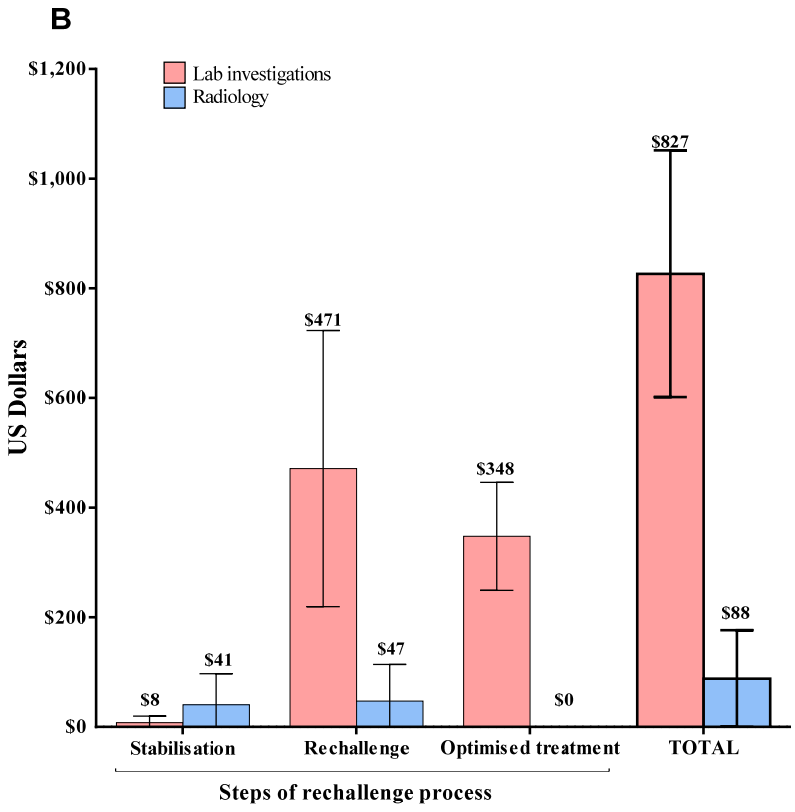

B
$1,200
$1,000
$800
$600
$400
$200
$0
US Dollars
Lab investigations
Radiology
$8
$41
$471
$47
$348
$0
$827
$88
Stabilisation
Rechallenge
Optimised treatment
TOTAL
Steps of rechallenge process

Figure 4.6: Breakdown of the cost of investigations carried out in the patients with DS-TB (A) and patients with DR-TB (B) at the various stages of the rechallenge procedure for the average patient. Values above each bar represent the mean cost and error bars show the 95% confidence interval. Values expressed in 2016 US $.

4.3 Estimated cost of the proposed alternative regimens

The cost of a strategy where patients with DS-TB suffering from a CADR were immediately placed on second-line treatment as an alternative to rechallenge with first-line TB drugs was determined. Patients with DR-TB with a CADR were not assessed in this model.

It was assumed that the cost per patient for the stabilisation period in the hypothetical alternate regimen would be equivalent to that of a patient with DS-TB undergoing the rechallenge process ($1,173 per patient). All patients with CADR would be admitted and stabilised and then immediately initiated on specific second-line TB regimens rather than backbone therapy and avoid rechallenge. After therapy is started, patients would be discharged and continue treatment as outpatients with standard monitoring tests and follow up as per the South African NTP.

4.3.1 Patients developing a CADR in the continuation phase of treatment

For patients who had already completed the intensive phase (first 2 months) of first-line therapy at the onset of a CADR, we modeled a continuation phase regimen that would require an additional 4-month treatment period using the drugs rifabutin and ethionamide. This accounted for 7/75 (9%) patients with DS-TB in the rechallenge study cohort. Within this hypothetical population, the cost per patient was $681 from the period of stabilisation to treatment completion. TB drug costs accounted for 61% of this total cost. Rifabutin can be associated with hepatitis; neutropenia and thrombocytopenia thus screening tests included regular AST, ALT, and bilirubin with a white cell and platelet count. Ethionamide commonly causes gastrointestinal upset and does not require more specific monitoring. Investigations were the second greatest contributor to overall

cost with a total of $170 (25% of total cost). The cost breakdown is shown in Table 4.6 below.

Table 4.6: Component and total costs of a hypothetical alternative CADR management strategy using rifabutin and ethionamide for an average DS-TB patient who develops a CADR during the continuation phase of first-line treatment. The period of costings stated here includes from the end of stabilisation to treatment completion. Costs are expressed in 2016 US $.

Component		**Unit cost (US $)**	**Total cost/patient (US $)**
Drug	**Dosage/Treatment length**		
Rifabutin	300mg daily/4 months	1.71	205.20
Ethionamide	750mg daily/4 months	1.77	212.40
Follow up visits	**Frequency (total # of visits for treatment period)**		
Dermatologist follow up visit	6 weeks from treatment initiation (1)	8.16	8.16
Clinic visit (Facility cost)	Weekly for the first month then monthly (7)	5.27	36.89
Appointment with doctor at clinic	Weekly for the first month then monthly (7)	6.94	48.58
Tests	**Frequency (total # of tests for treatment period)**		
Sputum culture	At 3 months and end of treatment (2)	12.49	24.98
Aspartate transaminase (AST)	Monthly (7)	4.31	30.17
Alanine transaminase (ALT)	Monthly (7)	4.31	30.17
Alkaline phosphatase (ALP)	Monthly (7)	4.31	30.17
Total bilirubin	Monthly (7)	3.85	26.95
White cell count (WCC)	Monthly (7)	1.30	9.10
Eosinophil count	Monthly (7)	1.30	9.10
Platelet count	Monthly (7)	1.30	9.10
TOTAL COST			**680.97**

4.3.2 Patients with CADR within 2 months of starting first-line therapy

In DS-TB patients who develop a CADR during the intensive phase of first-line treatment, we modeled 3 different regimens comprising second-line drugs to which the patients had never been exposed to be taken for 9 months. These regimens were developed based on clinical evidence from the literature and in consultation with experts in the field. With regard to laboratory investigations outlined in the methods chapter, some of the selected drugs required more specific monitoring as detailed in Table 4.7-4.9 below.

1) **REGIMEN 1 comprised moxifloxacin, rifabutin and ethionamide for 9 months.**

The total treatment period cost for regimen 1 was $1,478 per patient. TB drug costs accounted for the majority of this cost at $1,050 per patient (71% of the total cost). Monitoring is required for more severe adverse events such as hepatitis, neutropenia and thrombocytopenia and included regular AST, ALT, and bilirubin with a white cell and platelet count. These side effects are most commonly associated with rifabutin use. Moxifloxacin and ethionamide are generally well tolerated, but can cause gastro-intestinal upset. These side effects are generally benign and don't require any specific monitoring. Monitoring tests in this regimen was the second greatest contributor to overall cost at $273 per patient (18% of the total cost). The cost breakdown is shown in Table 4.7.

Table 4.7: Component and total costs of a hypothetical alternative CADR management strategy using rifabutin, ethionamide and moxifloxacin for an average DS-TB patient who develops a CADR during the intensive phase of first-line treatment. The period of costings stated here includes from the end of stabilisation to treatment completion. Costs are expressed in 2016 US $.

Component		**Unit cost (US $)**	**Total cost/patient (US $)**
Drug	**Dosage/Treatment length**		
Rifabutin	300mg daily/9 months	1.71	461.70
Ethionamide	750mg daily/9 months	1.77	477.90
Moxifloxacin	400mg daily/9 months	0.41	110.70
Follow up visits	**Frequency (total # of visits for treatment period)**		
Dermatologist follow up visit	6 weeks from treatment initiation (1)	8.16	8.16
Clinic visit (Facility cost)	Weekly for the first month then monthly (12)	5.27	63.24
Appointment with doctor at clinic	Weekly for the first month then monthly (12)	6.94	83.28
Tests	**Frequency (total # of tests for treatment period)**		
Sputum culture	At 3 months and end of treatment (2)	12.49	24.98
Aspartate transaminase (AST)	At each clinic visit (12)	4.31	51.72
Alanine transaminase (ALT)	At each clinic visit (12)	4.31	51.72
Alkaline phosphatase (ALP)	At each clinic visit (12)	4.31	51.72
Total bilirubin	At each clinic visit (12)	3.85	46.20
White cell count (WCC)	At each clinic visit (12)	1.30	15.60
Eosinophil count	At each clinic visit (12)	1.30	15.60
Platelet count	At each clinic visit (12)	1.30	15.60
TOTAL COST			**1,478.12**

2) **REGIMEN 2 comprised rifabutin, levofloxacin and bedaquiline all for 6 months then rifabutin and levofloxacin for a further 3 months.**

Along with investigations included in Regimen 1, bedaquiline requires additional monitoring tests due to the increased risk of QT interval prolongation. These tests include; an ECG as well as potassium, calcium and magnesium monitoring. ECG is performed at baseline and repeated at 2, 12 and 24 weeks while lab tests should be done at each visit. Bilirubin, AST, ALT, and alkaline phosphatase should be monitored at baseline and monthly to screen for potential hepatotoxicity.

The overall cost of the treatment period used in this regimen was $1,746 per patient. The need for additional monitoring resulted in investigation costs being greater than in Regimen 1 at $339 per patient (19% of total cost). However, drugs still contributed the majority to the cost of this regimen at $1,252 (72% of total cost of Regimen 2; Table 4.8).

Table 4.8: Component and total costs of a hypothetical alternative CADR management strategy using rifabutin, levofloxacin and bedaquiline for an average DS-TB patient who develops a CADR during the intensive phase of first-line treatment. The period of costings stated here includes from the end of stabilisation to treatment completion. Costs are expressed in 2016 US $.

Component		**Unit cost (US $)**	**Total cost/patient (US $)**
Drug	**Dosage/Treatment length**		
Rifabutin	300mg daily/9 months	1.71	461.70
Levofloxacin	500mg twice daily/9 months	0.42	113.40
Bedaquiline (BDQ)	400mg daily for 2 weeks then 200mg 3xweek for 22 weeks	3.60	677.17
Follow up visits	**Frequency (total # of visits for treatment period)**		
Dermatologist follow up visit	6 weeks from treatment initiation (1)	8.16	8.16
Clinic visit (Facility cost)	Weekly for the first month then monthly (12)	5.27	63.24
Appointment with doctor at clinic	Weekly for the first month then monthly (12)	6.94	83.28
Tests	**Frequency (total # of tests for treatment period)**		
Sputum culture	At 3 months and end of treatment (2)	12.49	24.98
Aspartate transaminase (AST)	At each clinic visit (12)	4.31	51.72
Alanine transaminase (ALT)	At each clinic visit (12)	4.31	51.72
Alkaline phosphatase (ALP)	At each clinic visit (12)	4.31	51.72
White cell count (WCC)	At each clinic visit (12)	1.31	15.60
Eosinophil count	At each clinic visit (12)	1.31	15.60
Platelet count	At each clinic visit (12)	1.31	15.60
Creatinine	Monthly while on BDQ (6)	2.93	17.58
Potassium	Monthly while on BDQ (6)	2.93	17.58
Calcium	Monthly while on BDQ (6)	2.18	13.08
Magnesium	Monthly while on BDQ (6)	2.18	13.08
Electrocardiograph (ECG)	At weeks 2, 12 and 22 from starting BDQ (3)	16.88	50.64
TOTAL COST			**1,745.85**

3) **REGIMEN 3 comprised delamanid, levofloxacin and rifabutin for 6 months, followed by levofloxacin and rifabutin for an additional 3 months.**

Similarly, to bedaquiline, delamanid carries the risk of QT prolongation. As such, the same monitoring tests used in Regimen 2 should also be used in Regimen 3 including liver function tests, ECGs and electrolytes that can contribute to cardiac abnormalities (sodium, potassium and magnesium). Intervals for tests were the same as those used for Regimen 2. Test costs in this regimen still accounted for the second highest component cost at $339 per patient (16% of total cost). The higher drug cost of delamanid reduced the proportion of test contribution in this regimen. TB drug costs were $1,610 per patient, which was 77% of the total cost for Regimen 3 (Table 4.9). The total cost of this regimen from stabilisation to treatment completion was $2,103 per patient.

Table 4.9: Component and total costs of a hypothetical alternative CADR management strategy using rifabutin, levofloxacin and delamanid for an average DS-TB patient who develops a CADR during the intensive phase of first-line treatment. The period of costings stated here includes from the end of stabilisation to treatment completion. Costs are expressed in 2016 US $.

Component		**Unit cost (US $)**	**Total cost/patient (US $)**
Drug	**Dosage/Treatment length**		
Rifabutin	300mg daily/9 months	1.71	461.70
Levofloxacin	500mg twice daily/9 months	0.42	113.40
Delamanid	100mg twice daily/6months	5.74	1034.44
Follow up visits	**Frequency (total # of visits for treatment period)**		
Dermatologist follow up visit	6 weeks from treatment initiation (1)	8.16	8.16
Clinic visit (Facility cost)	Weekly for the first month then monthly (12)	5.27	63.24
Appointment with doctor at clinic	Weekly for the first month then monthly (12)	6.94	83.28
Tests	**Frequency (total # of tests for treatment period)**		
Sputum culture	At 3 months and end of treatment (2)	12.49	24.98
Aspartate transaminase (AST)	At each clinic visit (12)	4.31	51.72
Alanine transaminase (ALT)	At each clinic visit (12)	4.31	51.72
Alkaline phosphatase (ALP)	At each clinic visit (12)	4.31	51.72
White cell count (WCC)	At each clinic visit (12)	1.30	15.60
Eosinophil count	At each clinic visit (12)	1.30	15.60
Platelet count	At each clinic visit (12)	1.30	15.60
Creatinine	Monthly while on delamanid (6)	2.93	17.58
Potassium	Monthly while on delamanid (6)	2.93	17.58
Calcium	Monthly while on delamanid (6)	2.18	13.08
Magnesium	Monthly while on delamanid (6)	2.18	13.08
Electrocardiograph (ECG)	At weeks 2, 12 and 22 from starting delamanid (3)	16.88	50.64
TOTAL COST			**2,103.12**

4.3.3 Total cost estimates of alternate arm options

The treatment period costs for each of the alternative regimens are provided in Tables 4.6-4.9 above. In order to determine the total cost of each regimen, the period of stabilisation, the per-patient cost of which is assumed to be the same as in the rechallenge process, was added to the treatment costs of each regimen. This total cost then reflects the cost of each regimen from the period of CADR diagnosis to treatment completion. Management of CADR occurring in the continuation phase would be $1,854 per patient. Intensive phase regimens remain more costly and are reflected below (Table 4.10).

Regimen 3 was the most costly ($3,276 per patient) due to the higher cost of delamanid. Both Regimen 1 and 2 had similar costs at $2,651 and $2,919 per patient respectively. In the next section, the cost per patient of the rechallenge process was compared to each of the alternative regimens

Table 4.10: Total costs of the hypothetical alternative CADR management strategies for an average DS-TB patient who develops a CADR during the intensive phase of first-line treatment. The period of costings stated here includes from the start of stabilisation to treatment completion. Costs are expressed in 2016 US $.

	Regimen 1	**Regimen 2**	**Regimen 3**
Stabilisation Period	$1,172.69	$1,172.69	$1,172.69
Optimised Treatment Period	$1,478.12	$1,745.85	$2,103.12
Total cost/ patient (US $)	$2,650.81	$2,918.54	$3,275.81

4.4 Cost comparison of the drug rechallenge strategy to alternative treatment strategies

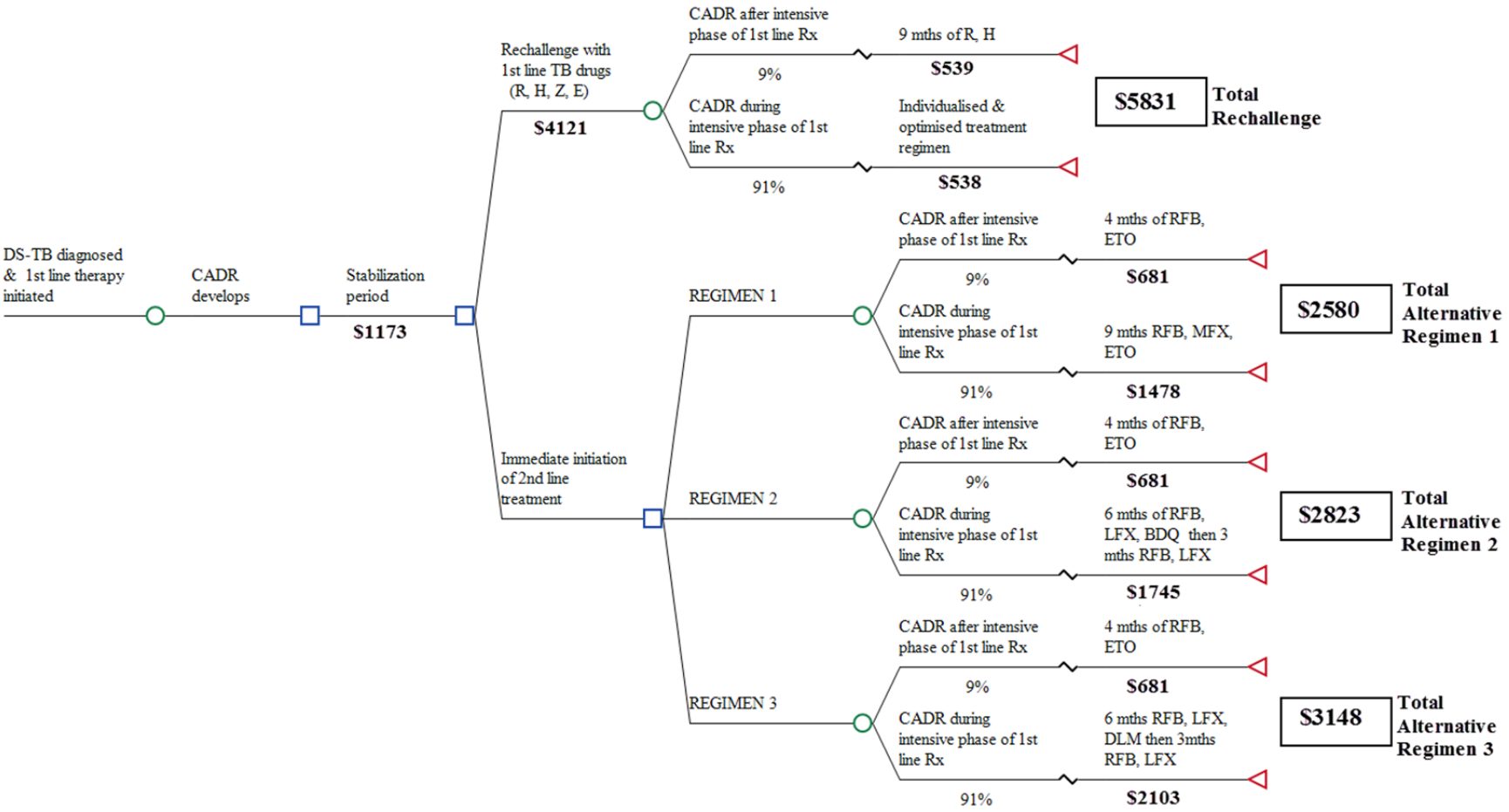
A cost comparative analysis was performed to compare the per patient cost of managing a first-line TB therapy-associated CADR in patients with DS-TB using the current strategy of drug rechallenge to the proposed alternative second-line treatment regimens.

In the rechallenge strategy, and assumed to be the same with the alternative strategies, all patients were admitted to the GSH Dermatology ward upon presentation with their CADR. Following admission, patients were offered supportive therapy and symptomatic management until all clinical and biochemical parameters had stabilised (stabilisation period). In the rechallenge strategy, this initial period of stabilisation cost $1,172.69 per patient with DS-TB and was assumed to be equivalent in each of the alternative strategies. However, CADR patients undergoing rechallenge in terms of current practice incurred a cost of $4,121.41 for the rechallenge phase and $536.54 for optimised treatment and follow up.

Following stabilisation, our hypothetical cohort was assumed to initiate treatment on the alternative regimens immediately and subsequently be discharged to continue treatment and follow up as outpatients (Figure 4.7). All patients were assumed to complete a full course of the prescribed treatment in both strategies.

In the current drug rechallenge process, 9% of patients presented with a CADR in the continuation phase of treatment and were subsequently discharged on rifampicin and isoniazid only. The cost when using the proposed alternate continuation phase regimen in this population subset cost $1,854 per patient compared with $10,983 per patient in the current rechallenge process (83% and $9,130 per patient saving). When estimating the costs of the alternate arms, the same proportion of patients (9%) was assumed to only require continuation phase therapy (Figure 4.7).

The total cost of the drug rechallenge strategy was $5,831 per patient. In the alternative strategy, the cost per patient for Regimen 1 was $2,651 (45% less than current practice) with an incremental saving of $3,180. Although Regimens 2 and 3 were more costly at $2,919 and $3,276 per patient respectively, they were also associated with significant saving compared to drug rechallenge, with an incremental cost of $2,912 (Regimen 2) and $2,555 (Regimen 3).



Key: BDQ=bedaquiline, CADR=cutaneous adverse drug reaction, DLM=delamanid, DS-TB=drug-sensitive TB, E=ethambutol, ETO=ethionamide, H=isoniazid, LFX=levofloxacin, MFX=moxifloxacin, R=rifampicin, RFB=rifabutin, Rx=treatment, TB=tuberculosis, Z=pyrazinamide.

Figure 4.7: A decision tree comparing the cost of the various alternative second-line treatment regimens to the cost of the current practice of drug rechallenge.

Hospitalisation was the primary driver of costs in drug rechallenge at $2,875 per patient (49% of total cost). Despite TB drug costs being much higher in our proposed alternatives compared to drug rechallenge, these costs still remained lower than that of hospitalisation. TB drug costs amounted to $1,050 per patient (40% of total cost) in Regimen 1, whereas these costs were higher in Regimen 2 at $1,252 per patient (43% of the total cost). Regimen 3, which included delamanid, incurred the highest drug cost at $1,610 per patient (49% of the total cost). Healthcare personnel and test costs were also much lower in the alternative regimen strategies as these patients were primarily treated as outpatients. The cost breakdown of each strategy is shown in Table 4.11.

Table 4.11: Breakdown of parameters contributing to total cost per patient in the drug rechallenge strategy and the alternative treatment strategies. Costs were expressed in 2016 US $.

	Current practice	**Alternative treatment strategies**		
Component	**Drug rechallenge**	**Regimen 1**	**Regimen 2**	**Regimen 3**
Stabilisation period	$1,172.69	$1,172.69	$1,172.69	$1,172.69
Hospitalisation	$2,875.18	$0.00	$0.00	$0.00
Clinic visit	$47.13	$60.91	$60.91	$60.91
Healthcare personnel	$596.12	$88.37	$88.37	$88.37
Tests	$613.19	$264.00	$323.85	$323.84
TB drugs	$526.32	$993.77	$1,177.57	$1,502.68
TOTAL COST (US $)	**$5,831**	**$2,580**	**$2,824**	**$3,148**

4.5 Patient costs

The cost incurred directly by patients in the study cohort suffering from a CADR to TB therapy was also determined. The majority of patients, (61/97, 63% of the study population), were classified as being unemployed, or being employed in jobs earning close to minimum wage. Unemployed patients were assigned an income of $221/month. Conversely, thirty patients were employed and their specific annual incomes were obtained from hospital records. The average annual income was $2,057 ($2,087 in patients with DS-TB and $1,716 in patients with DR-TB) with a daily income of $8 and $6.50 in the DS-TB and DR-TB patients, respectively. Patients admitted with DS-TB and a CADR spent a mean of 54 days in hospital with 39 of those days being working days, while patients with DR-TB and a CADR spent a mean of 65 days in hospital of which 46 days were determined to be working days.

4.5.1 Medical expenses

Patients accessing government healthcare services are liable to pay a portion of their medical bills based on their annual individual or household income. Within the study population, the majority of patients fell into the H1 category of partial subsidisation with an annual income of less than $2,450 (single income) or $3,403 (family income). Five individuals (4 DS-TB, 1 DR-TB) had an income of more than $3,403 but less than $4,900 falling into the H2 category. Within the study population there were 6 individuals who earned more than $4,900 per year and they were classified as H3. This group incurred higher hospitalization costs of $54/day and was liable for 75% of the total cost of laboratory tests and ancillary medications. As TB services in South Africa are free, all costs related to TB diagnosis and treatment was not included in the patient costs.

The average patient in the H1 category incurred a mean cost of $38 up to the point of treatment completion (95% C1 17.74; 58.40). H2 patients incurred a mean cost of $420 (95% CI 171.4; 667.9), while H3 patients incurred the greatest cost of $3,058 (95% CI 1117; 5000) (Figure 4.8).

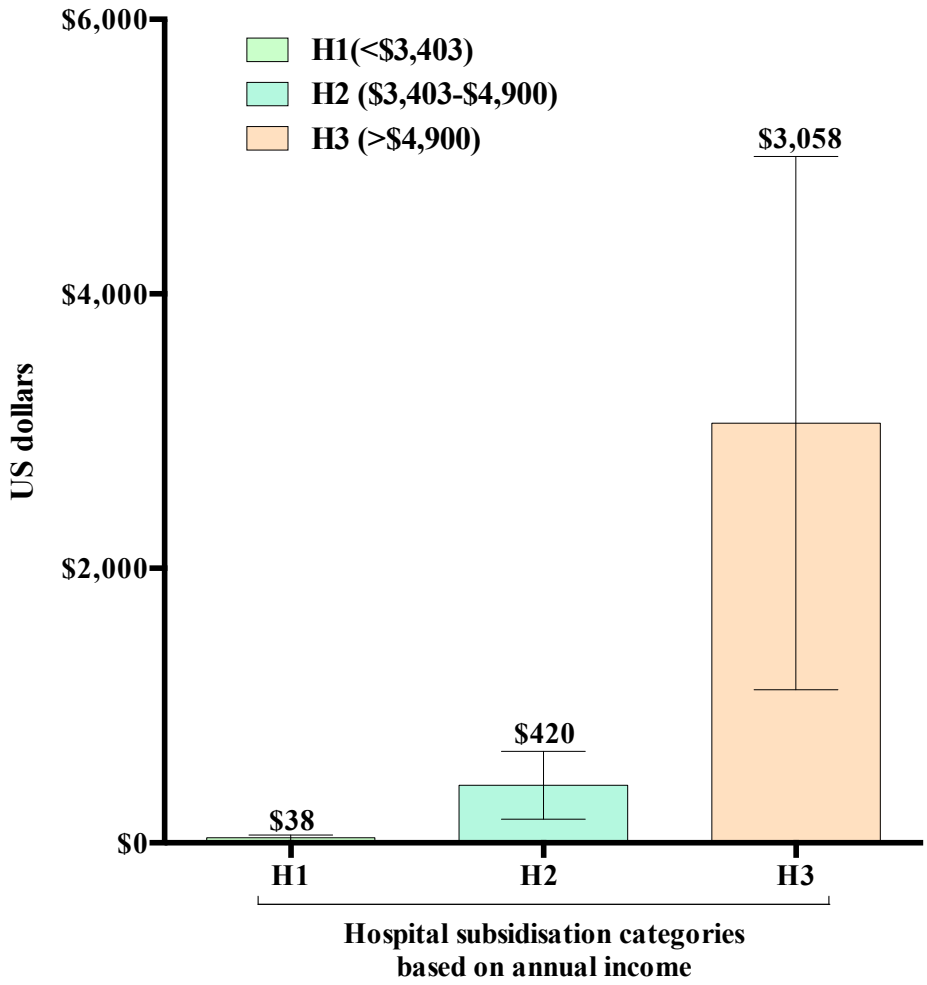


Figure 4.8: Medical expenses incurred by each patient being managed for a CADR by drug rechallenge stratified by the hospital subsidization categories, which were based on the patient's annual income. Values above the graph represent the mean cost per patient with error bars representing the 95% confidence intervals. Values are expressed in 2016 US $.

4.5.2 Patient loss and expenses

The average loss of income due to hospitalisation was $303 (15% of total annual income) in the patients with DS-TB in the study population (95% CI: 228.2; 377.9) and $308 (18% of total annual income) in those patients with DR-TB (95% CI 137; 479.7). In the study population the loss of income due to hospitalisation contributed to the greatest proportion of overall loss of annual income (Figure 4.9).

Overall patients not only lost a substantial portion of their annual income due to hospitalisation, but also were further subject to a debt of $227 in the patients with DS-TB (95% CI 48.64; 405.9) and $154 in the patients with DR-TB (95% CI 108; 416.6) as a result of medical expenses that were incurred due to the CADR. The majority of these expenses in were incurred in the rechallenge phase. In those with DS-TB, the mean patient expense for this phase was $148 (68% of total expenses) and $77 (50% of total expenses) in the DR-TB patients in the study population. The stabilisation period was the second most expensive period for the patients with DS-TB in terms of expenses at a mean of $71, whereas in those with DR-TB the optimised treatment phase was the second most expensive period at a mean of $41 per patient.

By the time of treatment completion an average patient with DS-TB in the study population would have lost 25% of their annual income, equating to a mean of $530 (95% CI 288.3; 772.3). An average patient with DR-TB experienced a loss of $462 (95% CI 74.26; 851.1), 27% of their annual income (Figure 4.9).

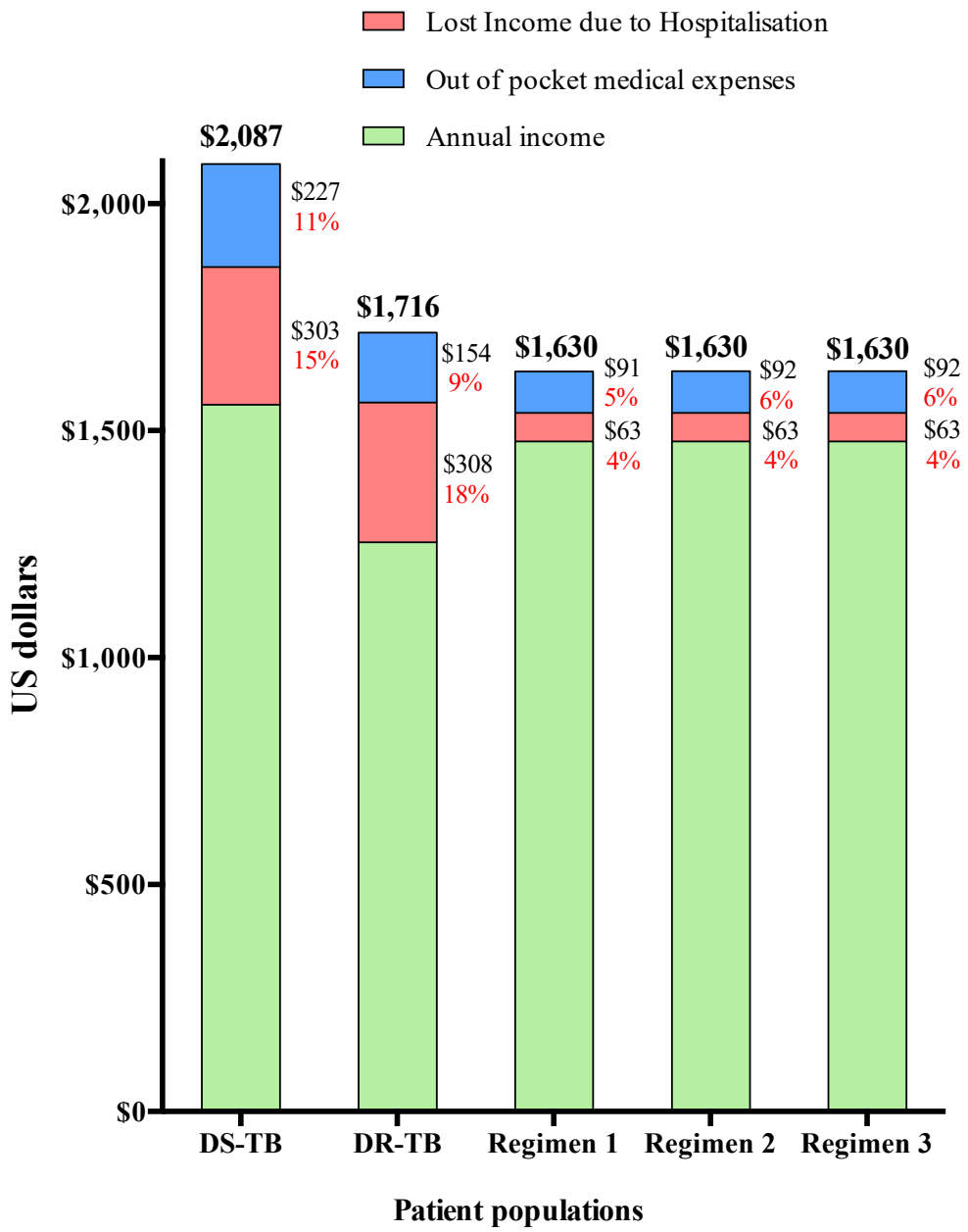


Figure 4.9: Costs incurred by study and hypothetical patients using alternate regimens suffering from a CADR and expressed as a percentage of their annual income. Values above the graph represent the mean annual salary per patient within each group. Percentages shown in red represent the proportion of the annual patient income that is assigned to each component. Values are expressed in 2016 US $.

4.6 Estimated patient costs for alternate regimens

Using the same proportions of patients employed and their average annual incomes. As well as the proportion on each payment subsidy of the patients with DS-TB within the study population (89% H1, 4% H2, 7% H3), an estimate of the loss of annual income and costs for the alternate regimens was calculated. Costs included the costs incurred in the original period of stabilisation and the optimised treatment phase as per the alternate treatment regimens outlined earlier in this chapter.

The annual income for this population amounted to $1,630 ($5.72/day). Loss of income due to hospitalisation for a total of 11 days (equivalent to that of patients with DS-TB in the study population) in the period of stabilisation was $63. Patient costs relating to each regimen are shown in Figure 4.9 above.

Overall the alternate regimens therefore resulted in a total patient loss of $154 for Regimen 1 and $155 for Regimen 2 and 3. This amounted to 10% of the total annual income in both groups.

4.7 Societal costs

The rechallenge process amounted to a total societal cost of $545,898 equivalent to $6,134 per patient with DS-TB who developed a CADR to first-line TB therapy (95% CI 5401; 6866). This cost was lower in the alternate regimens. Regimen 1 cost $2,643 (43% of current practice) per patient, with regimen 2 and 3 costing $2,982 (47% of current practice) and $3,339 (52% of current practice) per patient respectively (Table 4.12).

Table 4.12: Breakdown of the societal costs for the rechallenge practice and alternate regimens.

	Rechallenge	**Regimen 1**	**Regimen 2**	**Regimen 3**
Healthcare Provider costs	$5,831	$2,580	$2,823	$3,148
Patient costs	$303	$63	$63	$63
Total	$6,134	$2,643	$2,886	$3,211

4.8 Sensitivity analysis

A univariate sensitivity analysis was performed to determine the uncertainty around the assumptions and values of each variable used to estimate the costs of drug rechallenge and alternative treatment strategies. Hospitalisation, TB drugs and ancillary drug costs were either doubled or halved and test costs were increased or reduced by 50%. Additionally, the influence of outpatient stabilisation for eligible patients was considered and the consultation times (halved and doubled) and frequency (daily and weekly) was varied as well as the percentage of patients who developed a CADR during the continuation phase of treatment. Figure 4.10A-D shows the effects of changing these parameters on the overall cost per patient of each strategy.

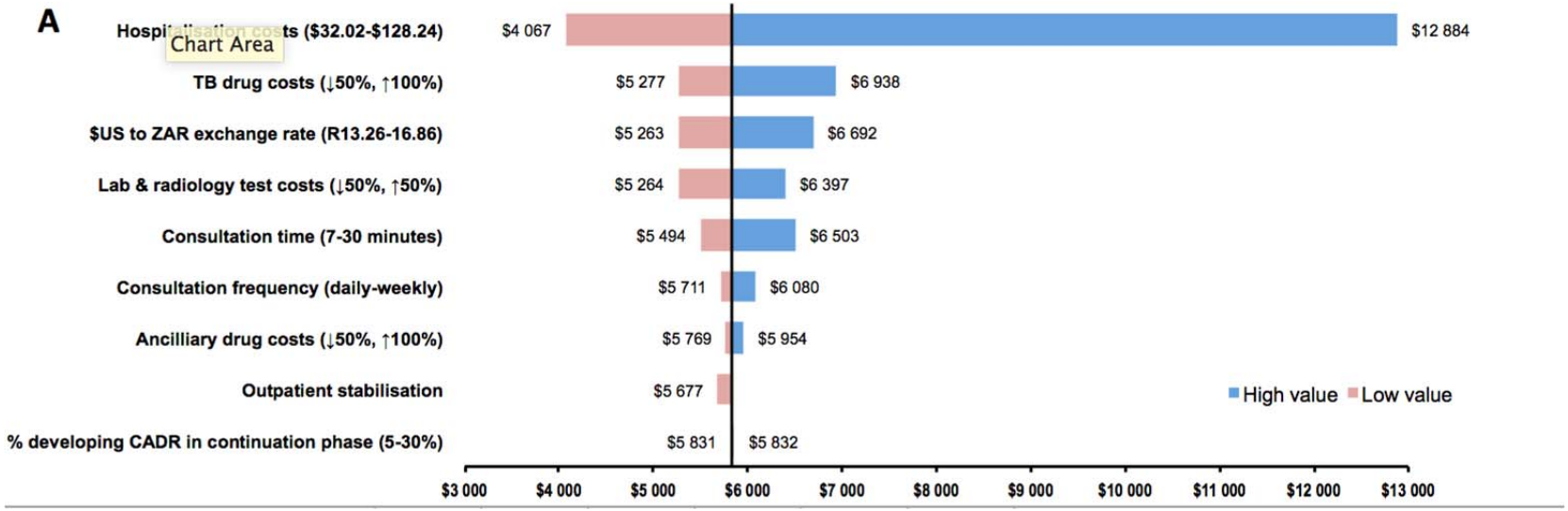
In the drug rechallenge strategy; variation in hospitalisation costs had, by far, the greatest influence on the overall cost likely due to extensive length of hospitalisation that is required for these patients. When costs were halved, this resulted in a 30% reduction in overall cost, with rechallenge costing $4,067 per patient. Doubling these costs brought the total per patient to $12,884 (2,2 times more than current cost). Outpatient stabilisation resulted in a $154 saving per patient, which was an overall saving of between 2.6% in current practice to 5.9% in Regimen 1 (5.4% Regimen 2 and 4.8% Regimen 3). Alternatively, if this period were carried out at a secondary level it would result in a $145 saving equivalent to 2.8% in current practice and up to 5.5% in Regimen 1. Consultation time and TB drug costs also had a significant influence on overall cost within the rechallenge population. Longer consults with patients while admitted resulted in a 12% increase in cost per patient. Conversely, when consultation time was halved, cost was reduced by 6% ($5,494). TB drug costs when doubled resulted in a 19%

increase in rechallenge total per patient at $6,938, when halved the cost was reduced by 9% to $5,277 per patient. Due to the similar cost of the optimised treatment period, whether patients develop a CADR either in the intensive or continuation phase, altering the percentage of patients developing a CADR in the continuation phase had very little impact on the overall cost per patient in this strategy ($1, Figure 4.10A).

Conversely, the biggest impact on overall cost per patient in the alternative treatment strategies was TB drug costs. Doubling the costs of TB drugs resulted in a substantial increase in the alternative regimen costs ($3,630; 41%, $4,076; 44% and $4,758; 51% for Regimens 1-3, respectively). Halving theses costs resulted in a reduction of costs from 20-26% for the alternate regimens as seen in Figures 4.10 B-D. Within the alternate regimens, hospitalisation still had a significant influence on overall cost. Doubling the cost of hospitalisation resulted in a 16-19% increase in overall cost, whereas halving this cost resulted in an 8-10% saving on the total cost. Implementing an additional month of inpatient hospitalisation in alternate regimens increased costs by 61-75%. Regimen 1 cost $4,504 per patient with Regimen 2 and 3 costing $4,747 and $5,072 per patient. Test costs also impacted overall costs due to the more intensive monitoring required for the second-line drugs. This increase and decrease in the cost in all alternate regimens was between 9 and 10%. Varying the percentage of patients developing a CADR in the continuation phase had a greater impact on overall costs in these strategies, particularly at the higher estimate, as the continuation phase treatment regimen (rifabutin & ethionamide) were much cheaper than the full second-line treatment regimens (Regimens 1-3). Regimens 1-3 exhibited sensitivity to similar components in the sensitivity analysis.

Using the lowest reported ZAR to USD exchange rate for the period of R13.26=1USD resulted in a 10% decrease in the overall costs of the current as well as the alternate regimens with current rechallenge practice costing $5,263 per patient with Regimen 1, 2 and 3 costing $2,329, $2,549 and $2,842 per patient respectively. However, using the higher rate of R16.86=1USD reported for the 2016 period resulted in a 15% increase in

the overall per patient cost. Rechallenge practice would then cost $6,692 with alternate regimens costing $2,962, $3,241 and $3,614 per patient respectively.


A
Chart Area
Hospitalisation costs ($32.02-$128.24)
TB drug costs (↓50%, ↑100%)
$US to ZAR exchange rate (R13.26-16.86)
Lab & radiology test costs (↓50%, ↑50%)
Consultation time (7-30 minutes)
Consultation frequency (daily-weekly)
Ancilliary drug costs (↓50%, ↑100%)
Outpatient stabilisation
% developing CADR in continuation phase (5-30%)
$4 067
$12 884
$5 277
$6 938
$5 263
$6 692
$5 264
$6 397
$5 494
$6 503
$5 711
$6 080
$5 769
$5 954
$5 677
$5 831
$5 832
High value
Low value
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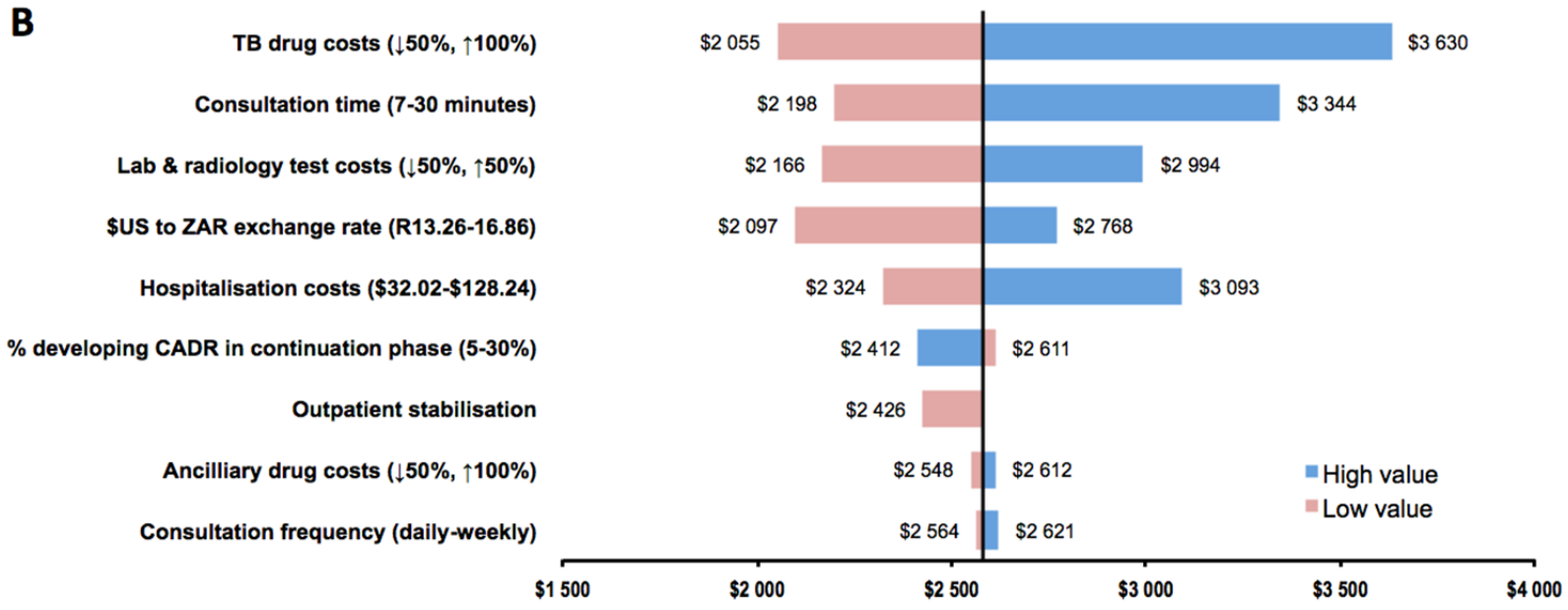
$11 000
$12 000
$13 000


B
TB drug costs (↓50%, ↑100%)
Consultation time (7-30 minutes)
Lab & radiology test costs (↓50%, ↑50%)
$US to ZAR exchange rate (R13.26-16.86)
Hospitalisation costs ($32.02-$128.24)
% developing CADR in continuation phase (5-30%)
Outpatient stabilisation
Ancilliary drug costs (↓50%, ↑100%)
Consultation frequency (daily-weekly)
$2 055
$3 630
$2 198
$3 344
$2 166
$2 994
$2 097
$2 768
$2 324
$3 093
$2 412
$2 611
$2 426
$2 548
$2 612
$2 564
$2 621
High value
Low value
$1 500
$2 000
$2 500
$3 000
$3 500
$4 000

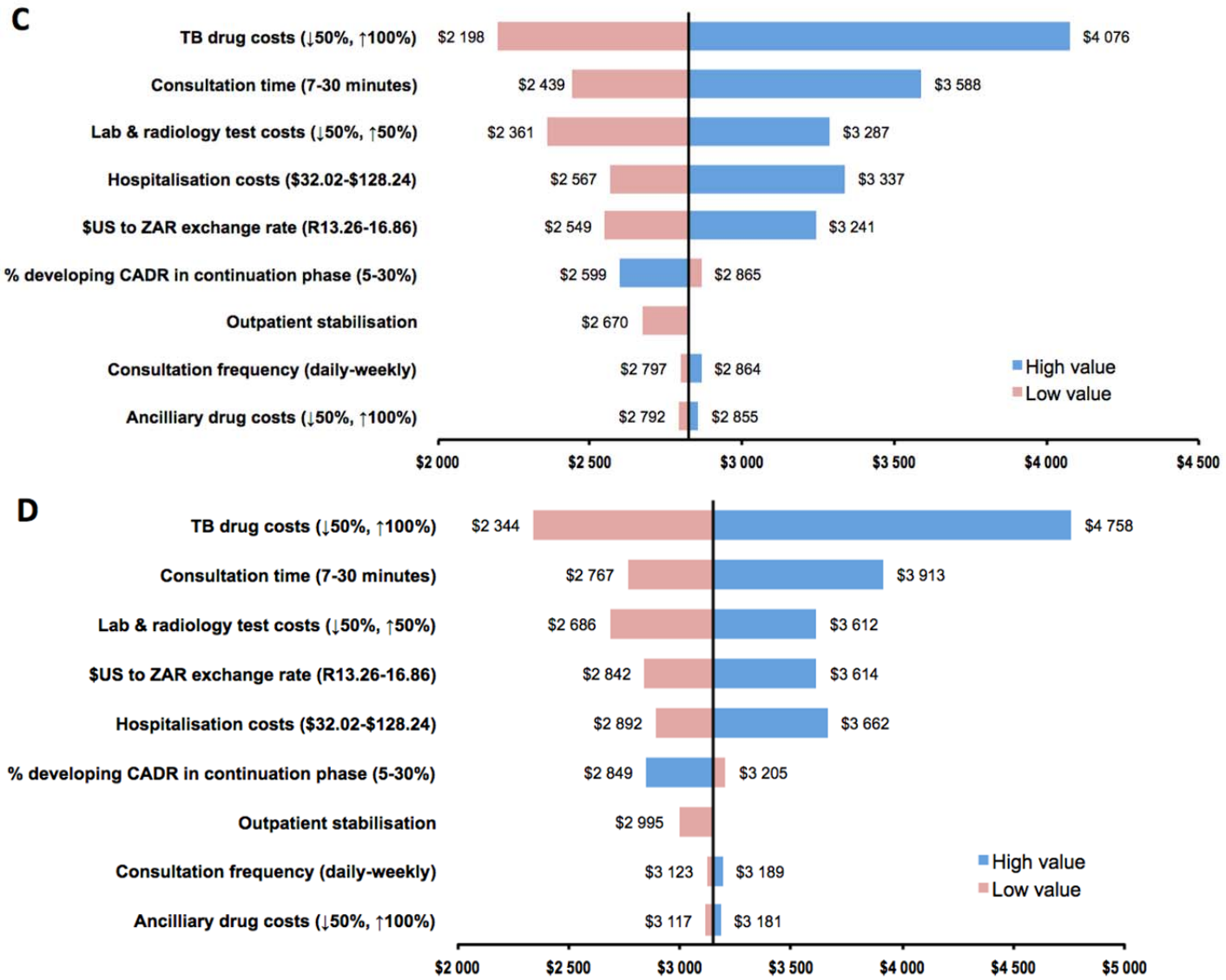


Figure 4.10: Tornado diagram showing the effect of changing specific parameters on the cost per patient for managing a CADR case in (A) the current practice of drug rechallenge and in (B) regimen 1, (C) regimen 2 and (D) regimen 3 of the alternative second-line treatment strategies. Costs are expressed in 20

4.8.1 Sensitivity analysis of patient costs

By doubling the annual incomes of the study population societal costs were also increased due to the higher patient costs. Societal costs for the rechallenge process were $6,407 (5% higher), with Regimen 1, 2 and 3 costing $2,706, $2,949 and $3,274 per patient respectively (2% greater than current costs). Should patient have a lower than estimated annual income, societal costs would decrease accordingly. Halving the annual income resulted in a 5% decrease to $5,801 per patient in the rechallenge group and a 2% decrease in the alternate regimens at $2,508, $2,823 and $3,148 respectively.

4.8.2 Scenario analysis

A scenario analysis was also performed where a number of variables were varied simultaneously to determine the effect on the overall cost of each strategy. The specific variables that were altered in the "best" and "worst" case scenarios have been described in detail in the methods chapter (Chapter 3).

The cost per patient in the "best" case scenario ranged from $1,640 to $3174, with savings from 54% (in the current strategy) to 37% (in the alternative second-line treatment strategies) compared to the baseline. Conversely, the "worst" case scenario almost doubled the cost of each strategy compared to the baseline ($5,981- $8,027). When the "best" and "worst" case scenarios were compared between the different strategies, the alternative treatment option was cheaper than drug rechallenge strategy. However, "worst case" scenario for the alternative treatment options was more costly than baseline rechallenge strategy cost, but still cheaper than the worst case of the baseline (Figure 4.11).

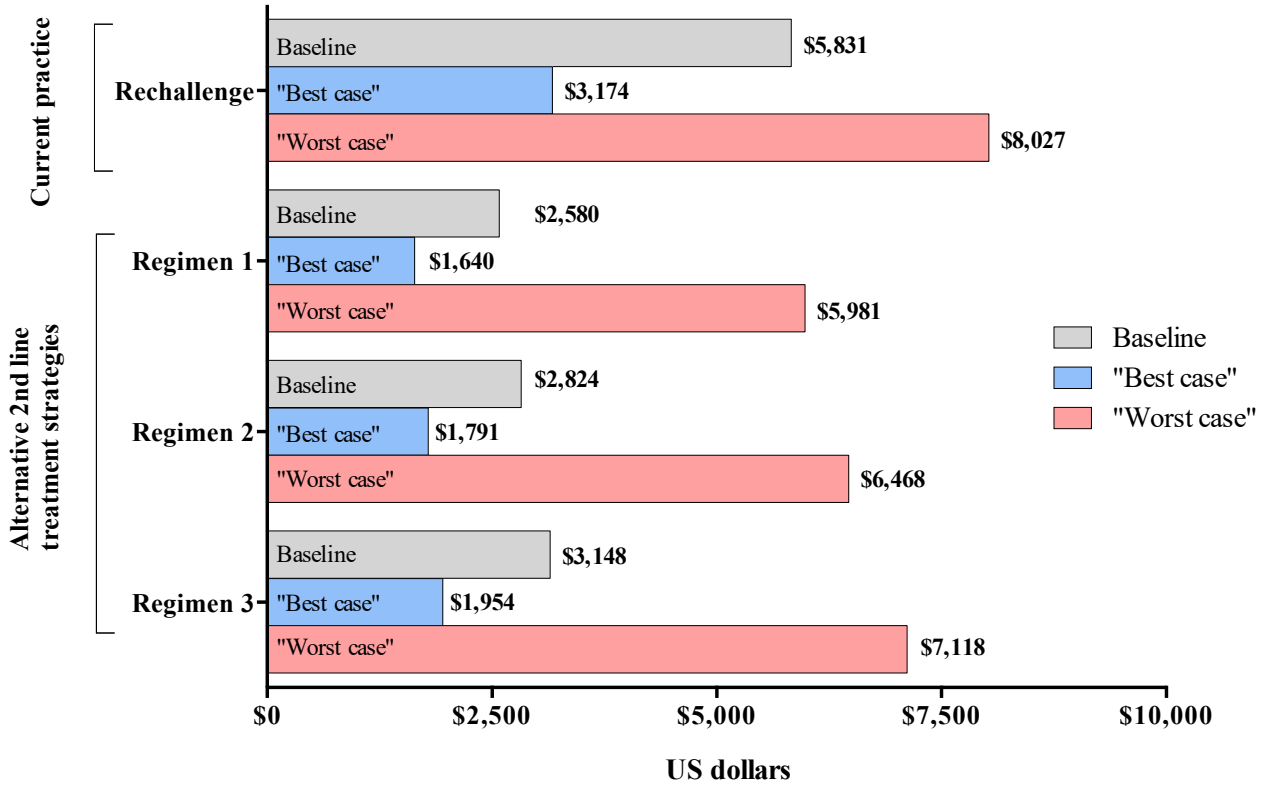


Figure 4.11: Scenario analysis showing the cost per patient of the "best" and "worst" case scenarios for managing a CADR case in the current practice of drug rechallenge and regimens 1, 2 and 3 of the alternative second-line treatment strategies. Values are expressed in 2016 US $.

When costs were broken down into their components, hospitalisation was again the greatest cost driver for the drug rechallenge strategy. This was also the case in the alternative treatment strategies, but to a lesser extent. Drug costs had the greatest influence on the overall cost of Regimens 1-3. A full breakdown of costs in the "best" and "worst" case scenarios for each strategy are shown in Table 4.13.

Table 4.13: Scenario analysis showing the cost breakdown per patient of the "best" and "worst" case scenarios for managing a CADR case in the current practice of drug rechallenge and regimens 1, 2 and 3 of the alternative second-line treatment strategies. Values are expressed in 2016 US $.

		Component	Baseline	Best case	Worst case
Current practice	**Rechallenge**	Hospitalisation	$3,637.55	$1,763.30	$5,257.84
		Clinic visits	$47.13	$47.13	$47.13
		Tests	$809.98	$465.42	$809.98
		Specialist consultations	$776.16	$553.29	$921.85
		TB drugs	$430.15	$215.08	$860.30
		Ancillary drugs	$129.67	$129.67	$129.67
		TOTAL	**$5,830.64**	**$3,173.89**	**$8,026.77**
Alternative second-line treatment strategies	**Regimen 1**	Hospitalisation	$762.37	$381.19	$2,685.97
		Clinic visits	$60.91	$60.91	$60.91
		Tests	$460.89	$409.39	$921.78
		Specialist consultations	$268.51	$257.66	$291.20
		TB drugs	$993.87	$496.94	$1,987.74
		Ancillary meds	$33.49	$33.49	$33.49
		TOTAL	**$2580.05**	**$1,639.58**	**$5,981.09**
	Regimen 2	Hospitalisation	$762.37	$381.19	$2,685.97
		Clinic visits	$60.91	$60.91	$60.91
		Tests	$520.73	$469.23	$1,041.26
		Specialist consultations	$268.51	$257.66	$291.20
		TB drugs	$1,177.68	$588.84	$2,355.36
		Ancillary Meds	$33.49	$33.49	$33.49
		TOTAL	**$2,823.69**	**$1,791.32**	**$6,468.19**
	Regimen 3	Hospitalisation	$762.37	$381.19	$2,685.97
		Clinic visits	$60.91	$60.91	$60.91
		Tests	$520.73	$469.23	$1,041.26
		Specialist consultations	$268.51	$257.66	$291.20
		TB drugs	$1,502.38	$751.19	$3,004.76
		Ancillary meds	$33.49	$33.49	$33.49
		TOTAL	**$3,148.39**	**$1,953.67**	**$7,117.59**

5. DISCUSSION

5.1 Study objective

Tuberculosis remains an epidemic in South Africa with a reported annual incidence of 834 per 100,000 in 2016, with up to 50% of patients being co-infected with HIV [1]. Fortunately, the implementation of TB and HIV management programmes has enabled infected individuals access to effective, affordable care with resultant improved case detection and treatment initiation rates. However, first-line TB therapy can be associated with severe adverse events requiring treatment interruption and even cessation. As a result, a balance of appropriate, effective treatment while preventing patient exposure to potentially toxic therapy must be maintained.

Until now, drug rechallenge has been the method of choice for identifying the offending drug/s in cases of CADR to TB drugs. Drug regimens are then subsequently modified to exclude offending drug/s while providing effective treatment. No standard guidelines exist as to how the rechallenge process should be carried out. Current practice within the study population required prolonged hospitalisation imposing a financial burden on both the healthcare system and the patient. The extent of which has not previously been quantified. Alternative strategies using second-line drugs for the treatment of DS-TB have only been used experimentally and too have not been completely evaluated in terms of their efficacy or estimated costs. Parameters contributing to the cost of CADR management have varying influences on the overall total and highlight potential areas for adjustments that could result in cost saving. Aspects affecting healthcare and patient costs, though evaluated in other literature, have not been analysed in the context of CADR to first-line TB drugs. Within our study we not only estimated healthcare costs, but also estimated patient level costs in terms of loss of income and medical expenses as well as the societal cost attributed to CADR.

5.2 Key study findings

Estimated costs of the current practice of rechallenge in cases of CADR to TB drugs are significant amounting to $6,525 (95% CI 5612; 7438) per patient. The majority of this cost (82%) was contributed to by CADR management in patients with DS-TB, $5,831 (95% CI 5134; 6527) per patient. This total includes the cost of the rechallenge process, as well as subsequent outpatient management up to the point of treatment completion. Patient level costs place a substantial personal burden on affected individuals amounting to 25-27% of their annual income. With the proposed hypothetical alternative strategy, using newer second-line drugs, we have shown a more affordable option for CADR management and subsequent treatment. All three of the alternative treatment regimens are associated with significant estimated provider and patient cost saving. Alternative regimens were estimated to cost between 45% and 55% of the current practice, despite the higher TB drug costs, which were found to have the greatest influence on overall cost. Patients experienced a lower 10% loss of annual income in the alternative treatment strategy as compared to the current drug rechallenge strategy. Savings to both the patient and provider in the alternative regimens was attributed to the shorter period of hospitalisation.

5.3 Study findings in view of the current literature

5.3.1 Study population

Among our population of 97 individuals admitted to the GSH dermatology ward in Cape Town, with a significant HIV prevalence (88%), 87 (89%) were assumed to have DS-TB at presentation, 14 of which were later determined to have been unnecessarily treated for TB. Of the remaining 10 patients, 2 were receiving only INH prophylaxis and 8 were classified as having DR-TB (4 MDR-TB and 2 each INH- and rifampicin (RIF) mono-resistance). Within this population, the prevalence of DR-TB amongst patients with TB was 8.5%, much higher than the National Institute for Communicable Diseases estimated prevalence of 2.8% for South Africa [175]. This is likely due to selection bias as the study cohort consisted of inpatients in a tertiary hospital, thus not a true representation of the general population affected by TB who are typically managed at community-based

TB clinics. Tertiary hospitals are referral centres for more complicated medical cases and the higher number of DR-TB cases is therefore expected. Furthermore, this population consists of individuals with an ADR. The management of milder ADR may be attempted at TB clinics, but ADR in cases with MDR-TB are more likely to be referred onto specialist referral centres such as GSH.

Despite low CD4 counts (median of 130 cell/mm^3) only a third (29 patients) of the total HIV-infected population was on ART. Regardless of changing ART guidelines within the period spanned by the study, all HIV-infected individuals were eligible for ART [54-56]. In most of the cases in the study, as is commonly reported; TB diagnosis was the indication for HIV testing. TB is often the initial opportunistic infection heralding HIV-seroconversion [38, 41]. ART in this subset of HIV-infected individuals is therefore delayed to reduce the risk of TB-IRIS, as was seen in 19 patients who were within the 2 weeks of starting TB treatment [6, 38, 40]. However, 37 patients (44%) had been on TB therapy for more than 2 weeks and should have been initiated on ART. The delay in initiation of ART has been shown to further negatively impact treatment outcomes related to TB and HIV [43, 44]. It is not clear why the ART was not yet started in these eligible individuals.

Despite the low median CD4 count, the majority of patients had PTB and not the disseminated form of disease, as would be expected [42]. Within our population, the type of TB (pulmonary vs. extra-pulmonary or disseminated) was based on the first diagnostic test used that produced a positive result, i.e. a positive sputum smear, a CXR or abdominal ultrasound suggestive of TB or a positive culture from a biopsied sample. As such, not all patients were screened for further sites of TB resulting in cases of extra-pulmonary or disseminated TB perhaps being missed and classified as PTB.

In all cases of CADR, the diagnosis of TB needs to be definitive before patients undergo rechallenge. Following this, within our study population if TB was unconfirmed prior to rechallenge, more extensive investigations were undertaken to prove TB. In cases where TB could not be proven, infectious diseases specialists were consulted to advise if there

were enough grounds to treat for TB. In 14 individuals (16%) in our study population who were assumed to have DS-TB, their opinion was that there were insufficient grounds to re-initiate TB treatment. However, four patients within this group still underwent drug rechallenge according to standard rechallenge practice before treatment was discontinued as a result of differing opinions by consulting specialists. These individuals highlight the challenges experienced in diagnosing TB in a high HIV prevalence setting including; atypical CXR features of multi-lobar as compared to apical consolidation, and negative smears for microscopy [40, 48]. As a result, diagnosis of TB in HIV-infected persons is usually more costly. Of the 14 patients, 6 (43%) were started on treatment based on CXR findings thought to be suggestive of TB, whereas 2 had been initiated on TB treatment based on clinician opinion alone. The practice of "empiric" TB treatment is commonplace in high incidence setting of HIV and TB co-infection [19, 176]. HIV not only increases the risk of developing TB, but also alters the clinical course of TB, with co-infected patients having an increased mortality [40]. South African TB guidelines include the practice of empiric therapy or rather treatment initiation based on suggestive symptoms and radiological features without the more sensitive bacteriological confirmation in order to avert the morbidity and mortality associated with untreated TB [40] [87].

Smear microscopy has a high specificity for TB, but low sensitivity in patients who have non-cavitatory pulmonary disease or low sputum bacillary load [40]. Within the HIV-infected population, especially at lower CD4 counts, sputum smear results are often negative [40]. The more sensitive Xpert® MTB/RIF assay was not yet available at periods during the study [45]. Xpert® MTB/RIF still has a lower sensitivity in HIV-infected compared to HIV-uninfected individuals but is more sensitive than smear microscopy [40, 177].

5.3.2 CADR

In the study cohort, CADR occurred a median of 26 days after initiating TB therapy. This is comparable to other studies reporting that majority of CADR and hepatotoxicity to first-line TB drugs occurs during the intensive phase of treatment [19, 37, 61].

The majority of patients (60/97, 62%) were diagnosed as having DRESS, with the remaining patients having SJS (22/97, 23%), SJS/TEN overlap (4/97, 4%) and TEN (10/97, 10%) and a single patient diagnosed with LDR (1%). Literature reports that >90% of TB-associated CADR in HIV-infected patients are classified as being DRESS, SJS and TEN as was the finding in our population [65, 178]. All our patients were admitted to hospital as no standard guidelines exist for the management of CADR and South African TB guidelines recommend hospital admission for all severe CADR, defined as those with erythematous rash and fever, blistering, mucosal involvement or hepatitis, for expert rechallenge [40]. Milder pruritic rashes without blistering, mucosal or systemic involvement are managed supportively at TB clinics with antihistamines [40].

5.3.3 Offending TB drug

The decision to rechallenge drugs was based on the Naranjo probability scale with offending drugs being identified through the rechallenge process [84]. Only first-line TB drugs were rechallenged. In cases where patients were on second-line TB therapy or ART, based on the Naranjo probability score, these drugs were changed to appropriate alternatives as needed and if using therapy for opportunistic infections this was discontinued. The offending drug was identified in 64/86 (74%) cases undergoing rechallenge. First-line drugs were implicated in 57/64 (89%) cases, with 16/57 cases developing a rechallenge reaction to more than one of the first-line TB drug. First-line drugs were identified as the offending drug in 3/8 cases of DR-TB. Although not key to the second-line drug regimens for DR-TB, this finding highlights the value of rechallenging first-line drugs. If identified as the offending drug, regimen adjustments to exclude the drug are straightforward, but if not, it allows for the use of an effective, well tolerated more affordable agent as compared with the D2 and D3 options of bedaquiline and delamanid (D2) and meropenem, imipenem, PAS and amoxicillin-clavulanate (all D3) in the DR-TB regimen. In one case within the population co-trimoxazole was identified as being the offending drug rather than first-line TB therapy following successful rechallenge with all four first-line drugs.

The causative drug was not identified in 22 patients. This was a result of a number of reasons including; 1) drug rechallenge with only rifampicin and isoniazid in those who had already completed or were about to complete intensive phase of therapy, 2) pyrazinamide not being rechallenged in individuals with severe hepatitis due to the drug's direct liver toxicity, 3) patients absconding from the hospital before completion of rechallenge or 4) successful rechallenge of the TB drugs in those only on TB therapy or in those on another drug that was concurrently taken with TB drugs e.g. anti-epileptics or ART that could have been the offender.

Seven patients in the group who developed a CADR to more than one drug, or where the drug could not be identified were on ART. In 3 of the 7 cases the ART had been started within 2 weeks of the TB therapy and the subsequent CADR. The incidence of ADRs in HIV-infected individuals is 26.7% higher than uninfected individuals. It is well established that ART and co-trimoxazole are associated with CADR in their own right [80, 111]. It is therefore possible that the individuals could have developed their CADR to ART rather than first-line TB therapy where these individuals were successfully rechallenged. In the case of one HIV-infected patient in the cohort, who was later deemed to have been unnecessarily treated; nevirapine or TB therapy was thought to have been equally likely to be the causative drug. ART was only stopped or changed within our population if the Naranjo probability score indicated a high probability of it being the offending drug at presentation. Thus if not stopped or changed and CADR improved with the withdrawal of TB therapy, the TB drug/s was the more likely causative agent.

No consensus as to the most common offending TB drug has been reached with all four first-line TB drugs having the potential to result in CADR. Authors have reported various likelihoods of pyrazinamide and rifampicin being the most common culprits [11, 65, 68]. In this study, we found that all 4 drugs were implicated almost equally in cases where a single offending drug was identified (11 for rifampicin and isoniazid, 10 for pyrazinamide and 9 for ethambutol). This finding highlights the danger of assuming that

any one of the 4 drugs is benign. All drugs need to be treated equally as potential offenders in first-line TB drug-associated CADR. First-line drug regimens cannot be altered without going through the rechallenge process, as even if there is a high index of suspicion of a causative drug with the Naranjo score, one is never sure if the patient may have multiple drug hypersensitivities as was seen in our population (11/64 reaction to more than 1 first-line drug and 5/64 having multiple drug hypersensitivities, 8%).

5.3.4 Rechallenge

In South Africa, drug rechallenge ensures infection control and prevents monotherapy through the use of bridging therapy, comprising three second-line drugs to which the patient has never been exposed for 2 weeks [65]. The first-line TB drugs are then rechallenged, sequentially and additively every 4 days, with rifampicin and isoniazid being the most effective drugs, rechallenged first [6, 17, 65]. The 4-day interval between subsequent drug introductions is used based on the premise that most rechallenge reactions will occur within 72 hours of repeat exposure [16, 65].

5.3.4.1 Rapidity of rechallenge

Interruption of TB treatment in the intensive phase is associated with a three times increased risk of mortality. This risk increases to an almost 4 times higher risk of mortality in those who are TB/HIV co-infected [3, 6, 11, 16]. Re-initiation of TB therapy should therefore happen as soon as possible. Limiting the length of the rechallenge process ensures that patients begin an optimal TB treatment regimen sooner thereby reducing the mortality risk [6]. However, the 96-hour interval between drug rechallenge cannot be shortened.

The duration of bridging therapy has the potential to be shortened, regardless of the severity of the index CADR. Two weeks was reported as the duration in Lehloenya et al.'s population whereas 17-21 days was reported in the Sharma et al. population [17, 65]. Our population had comparable average time to stabilisation in the DS-TB population with the literature (11 days; IQR 7; 19). The possibility of a shorter stabilisation period was not assessed in this study. Further studies are needed to

determine the optimum duration of the bridging therapy considering the relatively high frequency of multiple drug hypersensitivity in this setting [179].

The most easily implementable cost-reducing change to the rechallenge process would be the use of an outpatient stabilisation period. No clear guidelines exist as to what would make a patient eligible for outpatient management and this option would need to be assessed on an individual patient basis. However, we estimated, based on specialist clinical opinion and literature that patients with DRESS and ALT of <100U/L could potentially be stabilized as outpatients and this would therefore apply to 26 (29%) of the study population [62]. Within our population 45 of the patients were given temporary discharge pass-outs, with a median of 12 days in the stabilisation period, further highlighting the possibility of outpatient management in this stage for patients with DS-TB. As duration of stabilisation is patient dependent, measures could be put in place for regular assessment of these patients to allow for a perhaps sooner initiation of rechallenge.

The period of rechallenge was associated with a significant duration of hospitalisation with the average patient spending a median of 41 days (IQR 28; 63) in hospital. Those with DS-TB had an expected longer median of 45 days, as compared to those with DR-TB (42 days) as a result of more drugs needing to be rechallenged in cases where second-line drugs were suspected as causing the CADR. The duration of hospitalisation was comparable with Lehloenya et al.'s experience with a median of 50 inpatient days [6]. The extensive hospitalisation period was attributed to the practice of rechallenge employed. Hospitalisation was further prolonged in patients that developed rechallenge reactions to reintroduced TB drugs. Following a rechallenge reaction, the patient would be allowed to once again reach their baseline before the process could continue. In addition, some patients developed more severe reactions upon rechallenge where the causative drug was not apparent, resulting in all drugs having to be stopped and the rechallenge process restarted.

Outpatient based rechallenge is employed in specialised community TB clinics in cases of less severe CADR that require only supportive therapy [87]. This practice would result in the greatest cost saving. However, with the documented mortality associated with CADR reported in our typical population, a more appropriate alternative could be the use of secondary level hospitals for rechallenge. The lower level of hospitalisation would result in the daily cost of hospitalisation being halved ($27 per day compared to current cost of $64 per day). In order to ensure patient safety, clear guidelines would have to be developed based on current knowledge and the staff in these hospitals trained appropriately. As estimated previously about 30% of the population could be eligible for this alternative, but this estimate is based on expert opinion.

Upon discharge, an average treatment course of 217 days (IQR 180; 270) was anticipated in the patients with DS-TB, which is comparable to a 9-month course of second-line TB therapy. In the patients with DR-TB the expected duration to completion of treatment was a median of 437 days (IQR 270; 591).

5.3.5 Patient outcomes

The majority of patients (85) were rechallenged. Most patients (76/85, 89%) were discharged on TB therapy. TB treatment was continued in the patient with the LDR throughout the resolution of the reaction and upon discharge. Thirty-four of the 85 patients (40%) were successfully rechallenged and discharged onto regimens comprising first-line TB drugs. Four of the individuals were discharged on a regimen comprising all four first-line drugs. Forty-two of the rechallenged patients (49%) required individualised regimens comprising both first and second-line therapy to optimise their treatment. The remaining 9 patients, who were rechallenged, were not discharged onto TB therapy as 4 were deemed to have been unnecessarily treated for TB, 3 absconded and the other 2 died. Drug regimens as well as expected durations of treatments in this population cannot be standardised. Regimens are built around suspected offending drug/s, duration of treatment prior to CADR, drug sensitivities, potential drug interactions and patient co-morbidities [16]. In our population, discharge drug regimens

were devised based on expert opinion of both the treating dermatologists and infectious disease specialists with extensive experience in managing TB.

5.3.5.1 Morbidity and mortality associated with rechallenge

The majority of patients were discharged successfully. Three individuals in the study population failed to return to the dermatology ward during the study period following a temporary discharge pass. In these individuals, we have no information as to whether they received further treatment. In hospital mortality associated with rechallenge was 2%. Unfortunately, patients were not followed up beyond the 6-week dermatologist review post discharge. Patients continued their treatment at local clinics and did not usually return to the hospital. Attempts were made to follow up information after discharge via clinics. This was largely unsuccessful due to changing contact details and migration to other provinces or areas of the Western Cape. As such, it is unknown if patient completed treatment, absconded or demised. This missing patient information could potentially contribute to a higher overall morbidity as well as mortality rate for the overall population. The rate of treatment completion and subsequent cure, or the potential number of inadequately treated and relapsed patients as well as those who potentially developed drug-resistance is not known.

5.3.6 Cost of CADR

According to cost analysis studies in the literature, treatment of DS-TB costs $257 per patient ($334.85 once inflated to 2016 cost) in South Africa [28]. Costs of treating DS-TB vary greatly in the literature due to different geographic regions as well as differences in clinical practice. Health service related costs are usually dependent on GNI per capita. Costs are thought to be less in lower income countries such as Zimbabwe where the average cost per patient was $45-$57.60 per patient in a US study [173, 180, 181].

Within our population the average cost for treating a CADR to TB treatment was $6,525 per patient (25 times greater than an uncomplicated case). The higher cost is not surprising, as uncomplicated cases are managed as outpatients, with initially weekly than

monthly appointments at community-based primary care clinics requiring only standard monitoring and investigations. Costing within the study population was analysed in terms of the 4 subgroups mentioned previously. The authors wished to determine the cost of CADR to TB therapy in all patients regardless of sensitivities. However, development of an alternate regimen was only possible for cases with DS-TB. The alternate regimen was derived on the premise that only drugs to which the patient had never been exposed would be used thus avoiding the need for rechallenge. This same principle could not be applied to DR-TB patients who represent a unique subset of the population, with regimens containing a wide variety of combinations based on sensitivities. It is therefore impossible to derive a regimen that avoids all drugs that patients DR-TB could potentially be on. After the initial costing of the whole population, the population was divided into those with DS-TB and DR-TB. Costing of the separate groups allowed for a more accurate comparison of costs with the alternate regimens. It is well documented that costs of managing DR-TB are much greater and thus we anticipated that complicated cases would have an even greater cost thus overinflating our estimate of current practice.

Patients in our population with DS-TB that were managed for CADR cost $5,831 per patient (95% CI 5,134; 6,537) (23 times greater than an uncomplicated case). MDR-TB case treatment costs $6,772 ($8,836 once inflated to 2016 cost), with our patients with DR-TB cost being $14,249 (95% CI 7,257; 21,240) per patient (double that of an uncomplicated case) [28]. This relatively smaller increase is likely due to the fact that TB drug costs in DR-TB have the greatest influence on cost, which remains high whether or not the patient develops a CADR. Hospitalisation and in-patient investigations contribute in this instance to the greater cost in light of the CADR.

A wide range of costs of CADR management is reported in the literature from $1,920-$8,452 [128, 129, 136-138]. Although the cost within our study population falls within this range it is difficult to make meaningful comparisons as studies not only span a range of periods, but also have been conducted in varying geographical locations, with varying management practices and various costs being included in the different totals. Many

include just the direct medical costs, whereas the Gyllensten et al. population included the societal cost as their average cost per patient ($6,325) [136].

CADR was associated with significant cost to the healthcare system. Costs within each period varied greatly with the period of rechallenge clearly being the most costly (71% of the total cost) in the patients with DS-TB, and the optimised treatment period (50% of the total cost) in the patients with DR-TB.

5.3.7 Cost of CADR amongst subgroups of patients with DS-TB

As can be expected patients in the intensive phase of TB therapy (68 patients) at the time of CADR contributed the majority (85%) of the total cost for the patients with DS-TB. This was equivalent to $6,467 per patient. The greatest cost within this group was encountered during the rechallenge period at $4,660 per patient ($316,884 total for the rechallenge period). The individuals who demised and those who did not return following their temporary discharge pass-outs may lower the total cost per patient in this group as there is incomplete data for these patients related to the varying periods of the rechallenge process.

For those in the continuation phase of TB therapy at the time of CADR (7 patients), the cost of the rechallenge process was $446,782 ($6,683 per patient). As this group of patients only needs to tolerate rifampicin and isoniazid, this higher average is unexpected. Four of the patients were only rechallenged with rifampicin and isoniazid, resulting in a very affordable rechallenge and optimised treatment phase. However, 3 of these individuals underwent a prolonged rechallenge. One individual was rechallenged with ethambutol for 4 days before it was discontinued, with another 2 patients rechallenged with both ethambutol and pyrazinamide contributing to an additional 17 and 121 days in hospital respectively. However, some of these patients had not sputum-converted at the end of the intensive phase of treatment and would benefit from treatment with four drugs beyond the two months should the drugs not be the offending drug. Others had interrupted therapy during the intensive phase and it was felt they had not had enough treatment. These 7 patients were in the minority in terms of the

population yet contributed to 9% of the total cost for the DS-TB group. Much like those in the intensive phase of therapy, the rechallenge period was the greatest contributor to overall cost at $5,187 per patient ($36,309 total for rechallenge period).

At the outset of rechallenge individuals need to be assessed in terms of how far they are in to their treatment regimen to prioritise which agents need to be available for continued use. This assessment needs to consider whether the patient was compliant to medication and whether sputum conversion has occurred qualifying the patient for the continuation phase of TB therapy. Provided parameters are met, rechallenging these individuals with only rifampicin and isoniazid could result in cost saving through reduced number of days in hospital as well as fewer drugs used.

Another group within the DS-TB patients were the 14 who were admitted with CADR and managed to various degrees before it was decided that they had been incorrectly diagnosed and unnecessarily treated for TB. Four of the 14 were rechallenged for a total of $972 per patient for the rechallenge period, which contributed to 4% of the total cost of the rechallenge period in the patients with DS-TB. Despite 4% being a relatively small proportion, this cost becomes significant on a population level and detracts from the budget available for treating confirmed TB cases. Not only is there an increased cost with empiric TB, but also a danger with these individuals having developed potentially life-threatening reactions to treatment that was unnecessary. On the other hand, this has to balance against the need for empiric TB treatment, a strategy recommended by the WHO in settings of high HIV prevalence. The strategy has been shown to improve survival in severely ill HIV-infected person with presumed TB [182]. The practice of initiation of TB therapy based on clinical symptoms and radiology without biological evidence is also supported as a recommended approach by the South African TB guidelines and as such cannot be faulted by the clinicians treating the study population [40]. Within this group the stabilisation period expectedly made the largest contribution to the total cost $18,657 ($1,333 per patient). This is due to the more extensive investigations that were carried out to determine whether or not the patients had TB prior to initiating the rechallenge process.

5.3.8 Components contributing to costs

Hospitalisation, personnel costs, TB drugs and ancillary medication as well as laboratory investigations and radiology contributed in varying degrees to the total cost of the periods of the rechallenge process. Parameters influence varied amongst periods of the process as well as between the 3 subgroups (intensive, continuation and unnecessary treatment) of the patients with DS-TB, highlighting the absence of standardised management guidelines for CADR.

5.3.8.1 Hospitalisation

Among the patients with DS-TB, the greatest contributor to cost was hospitalisation in both the stabilisation (65% of total stabilisation period cost, $762/patient) and rechallenge period (70% of total rechallenge period cost, $2,875/patient). In all 3 subgroups of the DS-TB patients, hospitalisation was the greatest contributor in the stabilisation period. In the case of the unnecessary treatment group, the per patient hospitalisation cost ($926 per patient) was higher than those who had proven TB. Within the stabilisation period, hospital costs are substantial considering that the study population had temporary pass-outs for a median of 12 days. Hospitalisation costs in the rechallenge period for patients with proven TB accounted for 70% of the rechallenge period cost in both subgroups. A similar trend was observed in the patients with DR-TB where hospitalisation was the main cost contributor in the stabilisation (67% of total stabilisation period cost, $1,381/patient) and rechallenge period (68% of total rechallenge period cost, $3,462/patient). The rechallenge period was also associated with a significant duration of hospitalisation due to the 72-hour interval between subsequent first-line TB drug reintroduction. With the identification of causative drugs, alternative treatment options were derived which too contributed to the duration as patients were observed ensuring tolerance of the new regimens.

The significant contribution to total cost by the cost of hospitalisation is in keeping with literature findings. Pooran et al. demonstrated in a cost analysis that cost of hospitalisation had the most significant influence on XDR-TB costs [28]. A fully decentralised model of care was found to reduce treatment costs in MDR-TB by 42%,

with the reduced number of days in hospital being the key contributor [26, 27]. Costs of ADR vary in literature reports likely related to prolonged hospitalisation, with one study reporting a cost of $2,262/ADR [134]. Within the USA in 1997 Cullen et al. found inpatient costs related to ADRs to be as high as $19,685 in an ICU setting and $13,994 in a non-intensive care unit [183]. In a systemic review by Laurence et al. of 59 studies related to DS-TB costs, hospitalisation was found to contribute to 74% of the total cost ($11,283 in high income countries and $128 in low income countries) [173].

Within our population the cost of hospitalisation could once again be reduced through the use of a step-down approach in which patients are transferred to secondary or district level hospitals to complete rechallenge. Patients could be managed in conjunction with specialist dermatologists and referred back should they once again become unstable. This option offers potential further benefit to patients, as secondary or district hospitals are often closer to areas in which they live resulting in lower transport costs incurred by the patient household.

5.3.8.2 TB drugs

TB drugs comprised the majority of medication costs in the study population and were the greatest contributor to overall cost within the patients with DR-TB. Drug costs are determined by a number of prices including customs duties, registration fees as well as local and international taxes [174]. DR-TB patients were discharged on regimens comprising second-line therapy for much longer periods compared to those with DS-TB, the longest being 36 months with a median of 437 days (IQR 270; 591) of treatment post discharge. The costs of many of the second-line drugs are much greater than first-line drugs. Cost of the first-line drugs range from $0.02-$0.10, with the combination drug Rifafour™ costing $0.05/tablet. In comparison second-line drugs have an average cost of $4 (range $0.09-$22/tablet). Overall drug costs are reported to account for about 5% of the total cost of treating DS-TB, though this can vary greatly [173]. In a study by Burman et al. drug costs were shown to account for $311 per DS-TB patient, but could be as high as $654 [184, 185].

In an analysis by Laing et al. it was found that costs of TB therapy were generally higher in the developed as compared to the developing world, with the average price of first-line drugs increasing by 10.7% per year in the private sector and 4.1% in the public sector [174]. Whereas in the developing world prices rise at a rate of 2% per year [174]. A systemic review illustrated these differences with average costs of treating DS-TB patients in high-income countries at $14,659 (SD 13,594) as a result of these drug costs, compared with $258 (SD 352) in the low-income countries [173].

Within Pooran et al.'s cost analysis, TB therapy contributed to 49% of the total cost of treatment in MDR-TB. MDR-TB treatment costs were found to be 26 times greater than those for DS-TB [28]. Furthermore, DR-TB cases accounted for only 2.2% of total TB cases, yet the treatment of these cases cost 32% of the annual TB budget. This is comparable to our study population where patients with DR-TB made up 8% of the total study population but contributed to 18% of the total cost. However, the average cost per patient in the DR-TB group was only 2.5 times greater than the cost per patient in the DS-TB group. The relative similarity in cost is likely accounted for by the prolonged hospitalisation that occurred in the groups (DS-TB median 56, DR-TB median 69), with the greater number of DS-TB patients, which diluted out the effects of the higher drug costs in the DR-TB group.

TB drug cost reductions will have a substantial impact on the overall cost of potential alternative regimes. The affordability of currently used first-line drugs enhances the appeal of the rechallenge process to re-establish conventional first-line treatment. However, within our population in many instances the cost of hospitalisation outweighed the cost saving achieved through the use of first-line TB drugs.

5.3.8.3 Investigations

Investigations made up of both laboratory investigations as well as radiological examinations contributed significantly throughout the drug rechallenge procedure (11% of total cost in DS-TB and 6% in DR-TB patients). The higher per patient costs amongst those with DR-TB was mainly due to the higher drug costs, which diminished the % of

costs that were attributable to investigations in these patients. Costs of investigations prior to rechallenge in the patients with DS-TB include tests needed to confirm TB in cases where the diagnosis was not evident. This is highlighted by the higher cost of investigations in the group unnecessarily treated for TB where stabilisation phase investigation costs were the highest at $210 per patient.

There is no standard protocol for how frequently investigations should be carried out in individuals who develop a CADR. Laboratory investigations as well as radiological examinations, particularly tests relating to detection of hepatic dysfunction or eosinophilia (a rise in the eosinophil count associated with DRESS), are generally done as screening. In instances where patients are symptomatic i.e.; a rash develops, gastrointestinal upset ensues or they develop another systemic symptom, investigations are likely to be more specific and guided by the clinical presentation or complaint [6, 65]. In our population, screening tests were done at varying intervals, particularly during the period of rechallenge to detect possible rechallenge reactions. Although all individuals were managed within the same unit, differences in the practice of treating dermatologists, as well as inter-patient variability influenced the frequency and the extent to which investigations were carried out. Having a standardised guideline as to the use of screening tests would not only limit the cost in our population, but also contribute to the development of management guidelines for CADR, which would assist in the implementation of decentralised management.

The selection of laboratory investigations ordered by the treating clinician also has a potential for cost saving. For example, liver function tests include a combination screen of AST and ALT. Both aminotransferases are highly concentrated in the liver but, ALT is more liver-specific with elevated serum levels being more indicative of liver damage [186]. Use of ALT alone could enable detection of hepatotoxicity and potentially decrease investigation cost. The same could be said for ordering combination tests of a full blood count (FBC) ($8) and differential count ($5) when assessing for an elevated eosinophil count as is commonly seen in DRESS. The FBC provides the white cell count (WCC), haemoglobin, mean cell volume and platelets, when one only needs the WCC

($1.30) to determine the eosinophil count. This amounts to a 50% reduction in cost of this test alone at $6.30 rather than $13.

5.3.9 Alternatives to rechallenge

Drug rechallenge can be contra-indicated in cases of severe comorbidities, pregnancy and in those where there is an unacceptable risk of life threatening rechallenge reactions [6, 14, 15, 88]. As such, a set of alternative regimens was devised using second-line therapies based on the needs of these groups, but applicable to an average population with DS-TB that develop CADR enabling the rechallenge process to be avoided. Disadvantages of using second-line drugs are attributed to their presumed lower efficacy (47-60% success rate), greater rate of adverse events, longer treatment duration (18-24months) and greater cost of medications [26, 27, 30].

Nonetheless, there are new second-line drugs becoming available. Based on clinical trial data, these drugs have efficacies that seem to match their first-line counterparts translating to improved treatment outcomes and shorter durations of therapy for DR-TB. Regimens using these drugs have been trialed further demonstrating the efficacy of these agents in the treatment of DS-TB [113, 117]. The proposed regimen consists only of drugs taken orally avoiding the use of typical second-line injectable drugs. This further reduces not only patient discomfort in receiving a daily injection, but also cost in terms of daily clinic visits for both the healthcare services and patients. In addition, avoidance of daily clinic appointments does not limit patients in their ability to continue or seek employment. A further benefit is that proposed alternate regimens have monitoring based on the current NTP, thus placing no additional burden on the healthcare system. Furthermore, with the use of drugs for DS-TB one could argue that the duration of treatment could be shorter at 9 months matching regimens in the literature [96, 97].

Perhaps of greatest concern with use of traditional as well as newer second-line TB therapy for DS-TB, is the risk of resistance to these drugs developing as a result of increased use. This not only translates to a greater individual as well as community risk, with increased numbers of drug-resistant strains of TB, but also a further decrease in

available treatment options for individual patients should they develop or contract DR-TB requiring treatment with second-line drugs. Acquired drug resistance occurs when the patient does not take or absorb the medication thus selecting for a bacterial population, which is now resistant to the drug as a result of prior exposure [187]. Although the risk or rate of development of resistance can't be determined, mechanisms of development of resistance for the various drugs are being explored. A study by Li et al. found that the rate of acquired rifampin resistance was equivalent with rifampicin and rifabutin [151]. Resistance to fluoroquinolones (moxifloxacin) occurs as a result of mutations of genes in the quinolone resistance-determining region [187]. The risk of acquiring a primarily resistant strain in cases of fluoroquinolones is marginally further increased as a result of prior exposure with fluoroquinolones commonly being used to treat community acquired pneumonia or urinary tract infections [188]. Literature has shown a potential cross-resistance between isoniazid and ethionamide. Patients who have isoniazid-resistant TB may also have resistance to ethionamide making DR-TB regimens less effective [154]. What is not clear is whether increased ethionamide exposure with risk of resistance will result in increased isoniazid resistance by the same mechanism. Delamanid and bedaquiline, have longer half-lives. If there is premature continuation of the accompanying drugs there is an increased risk of development of resistance due to the residual low plasma levels of drug [189].

In modeling our alternative regimens, newer drugs were used based on clinical evidence from literature as well as personal meetings with experts in the field including Professor Gary Maartens and Associate Professor Helen Cox. Second-line drugs were used for DS-TB CADR cases based on the assumption that fewer drugs in combination would be effective to eliminate the disease while avoiding unnecessary side effects of multiple second-line therapies as well as the overwhelming drug costs.

By using rifabutin as a tolerable substitute for rifampicin, we were able to cost shorter durations of therapy, while still maintaining regimen strength of a rifamycin, with potentially fewer adverse events [5, 22, 23, 53, 190]. Furthermore, despite being from

the same drug class, 80% of individuals who react to rifampicin are documented to be able to tolerate rifabutin [22, 99, 100].

Newer second-line alternatives in bedaquiline and delamanid have been shown to have great potential. Bedaquiline has shown a 48% rate of sputum-culture conversion when compared to placebo as well as a faster time to conversion of 83 days compared with 125 days ($p<0.001$), while delamanid showed increased rate and proportion (45.4% vs. 29.6%, $p=0.008$) of sputum culture conversion in the population receiving delamanid compared to placebo [24, 106, 117]. Both these new drugs have been documented to cause QT prolongation, adding not only to the risk of use, but also to the increased cost of monitoring that is necessary [106, 191]. Despite this proven efficacy, use in South Africa requires regulatory approval and confined to MDR-TB cases.

These alternatives like their first-line counterparts have the potential to cause ADR resulting in hospitalisation and interruption of treatment, which would increase the estimated costs. Drug-drug interaction with ART, much like was described in the index population with first-line TB therapy, is also a possibility. Complications of further CADR to second-line alternatives or ART in this population was not accounted for and would need to be evaluated as not only a contributor to cost, but as a risk to use.

5.3.10 Costs of alternative arms of therapy

5.3.10.1 CADR in the continuation phase

Within our study cohort, 7/75 (9%) individuals with DS-TB had already completed the intensive phase of first-line 4-drug therapy at the time their reaction occurred. They therefore only required tolerance to rifampicin and isoniazid to complete their treatment. An alternate 2-drug regimen using rifabutin and ethionamide was derived to account for this proportion of the population. From onset of CADR to treatment completion using the devised regimen, the cost was $1,854 per patient. This equates to 17% of the actual cost in current rechallenge practice for a total cost saving of $9,130 per patient. The significant savings in this group is attributed to the avoidance of hospitalisation costs during the rechallenge period as well as investigation costs that were included as part of

the management of the 3 patients within this group that underwent rechallenge with more than just rifampicin and isoniazid.

5.3.10.2 CADR within the intensive phase

The majority of the study population, compatible with literature findings developed their CADR within the first 2 months of TB therapy. Three alternative regimens were derived, comprising various combinations of second-line TB drugs. The first alternative made use of drugs commonly used in the treatment of MDR-TB, moxifloxacin and ethionamide, combined with rifabutin as a new alternative. Regimen 1 required less intensive monitoring (for a cost of $273/patient) and had lower TB drug costs ($1,050) than the alternatives that used newer drugs. The total cost per patient in this regimen combining the initial stabilisation cost was $2,651. Although rifabutin was a newer addition it has relatively lower drugs costs compared to other newer drugs employed for the treatment of drug resistant TB ($1.71 compared with $3.60 for bedaquiline and $5.74 for delamanid). Moxifloxacin and ethionamide, already fairly widely used, are very affordable options for treatment, $0.41 and $1.77 per dose respectively. This regimen is one that is not only potentially effective, but is also the most affordable and readily available. Making use of already circulating freely available medications makes access to this regimen unrestricted.

For the second and third option, we elected to use drugs that have been approved and are in clinical use, though requiring regulatory approval for use. These newer TB drugs are proving to be promising and should be incorporated into protocols for use to not only improve patient outcomes, but also potentially increase use, decreasing costs of the individual drugs [24]. Often increased use and demand can result in decreased costs of individual drugs with increased competition for tenders, which drive costs, as well as development of generic drugs as was seen in the HIV epidemic with rollouts resulting in decreased costs of ART [141]. In using bedaquiline there are serious concerns about adverse events related to QT prolongation leading to sudden cardiac death [104]. Use therefore requires more intense electrolyte and cardiac monitoring accounted for in the costing of this regimen ($339/ patient for investigations). Drug cost in this regimen was

$1,252, making up 43% of the total cost ($2,919). Although only used for the first 6 of the total 9 months of treatment the cost of bedaquiline, at $3.60 per dose, is substantial and almost double that of the cost of the other drugs used in this regimen, which were only $2.13.

The final alternative option made use of delamanid with rifabutin and levofloxacin. Like bedaquiline, delamanid is associated with the risk of QT prolongation [25, 191]. Monitoring in this population was therefore equivalent to Regimen 2, with the difference in drug costs driving the difference in cost between these two regimens. The higher cost of delamanid, $5.74 per dose, contributed significantly to the overall drug cost of $1,610 in this regimen. The total cost for Regimen 3 was estimated at $3,276 per patient, 48% of which was TB drug cost.

All 3 of the alternative regimens were found to cost less than the current drug rechallenge practice despite higher second-line drug costs and more intense drug specific monitoring required. The first regimen comprising rifabutin and ethionamide was the most affordable of the 3 alternate regimens. This is due to the use of more readily available and affordable second-line drugs. Moreover, these drugs had relatively few side effects making fewer screening investigations during the course of treatment necessary, for a lower overall cost of investigations at $273 ($66 less than Regimen 2 and 3 per patient). This regimen cost 45% of that of the current rechallenge practice with an incremental cost saving of $3,180 per patient.

Regimen 2 and 3 made use of newer TB drugs. Nevertheless, both regimens, which included more expensive drugs in bedaquiline ($3.60 per dose), levofloxacin ($0.42 per dose) and delamanid ($5.74 per dose), proved to be more affordable that the traditional rechallenge practice (50% and 56% of the cost of current practice respectively). Even with the more intensive monitoring required, the costs of monitoring were still lower than those encountered in the drug rechallenge process ($339 per patient compared with $810).

Regimen 3 using delamanid, levofloxacin and rifabutin was estimated to account for an incremental cost saving of $2,555 per patient, with drug cost accounting for 48% of the total regimen cost. This was comparable with literature reports of the large proportion that second-line drugs typically contribute to overall cost [26, 27, 30]. Delamanid is not yet freely available and pricing is therefore not well established. We costed delamanid in our alternative regimen based on literature reported costs at which the drug will be made available by the Japanese pharmaceutical company Otsuka [146, 147]. It is anticipated that costs should be lower in the developing world as has been the reported trend of drug costs and developing countries are unlikely to pay the exorbitant amounts that the drug is costing in more developed countries [25]. Furthermore, once trials have completed and drugs are more readily available one would expect this cost to decrease making this regimen more feasible. A cost-effectiveness analysis by Diel et al. reported a course of delamanid (168 days) to be €25 200 [192]. Despite the high drugs costs and the contribution added to the total overall cost of treating MDR-TB, delamanid use was deemed cost-effective. The efficacy of the drug resulted in cost savings that outweighed the increased drug costs in terms of incremental cost per quality adjusted life year (QALY) and disability adjusted life year (DALY) avoided [192].

Regimens containing the newer drugs are seemingly more expensive based on drug costs. Hospitalisation costs in our study population and in the literature have been shown to be the major contributor to cost of TB treatment [26-28]. Outpatient use and monitoring of these drugs, with the avoidance of hospitalisation seems to negate the additional expected drug costs.

It is well documented that second-line TB drugs carry a high risk of ADR [16, 65, 80]. All the above hypothetical regimens could at any time be complicated by the development of an ADR, which would potentially result in hospitalisation and increased cost of the regimen. The frequencies of reactions are not well established and using new combinations and regimens makes this estimation problematic. All estimates of costs in the hypothetical populations using the new regimens are based on uncomplicated well-tolerated cases.

5.3.11 Patient costs

TB and HIV are for the most part diseases of the developing world, with poverty playing an integral role in the disease momentum [1]. Poverty and poor socio-economic circumstances are risk factors for contracting TB and hindering treatment completion. While TB exacerbates poverty by limiting the affected individuals' ability to work as well as increasing out-of-pocket expenditure with hospital visits, as well as transport and nutritional supplementation costs. Poverty often delays health seeking and ultimately diagnosis resulting in poorer disease outcomes.

Within our population of largely unemployed individuals or those earning minimum wage the average loss of income due to hospitalisation was 15% in patients with DS-TB and 18% in those with DR-TB. The Western Cape government payment schedule classifies healthcare users according to their annual income in terms of their ability to contribute to the cost of their healthcare. The majority of our population fell into the H1 category making the vast majority of their care subsidised with patients being responsible for $4 per 30 days hospitalised which included all tests, medications and procedures the patient may have required. Following discharge, patients would be billed $1.22 per clinic visit. All individuals received TB medication for free, with the cost being carried by the NTP. Despite the seemingly small individual burden the total billed amount for the period cost the average patient $227 (DS-TB) and $154 (DR-TB). This combined with the income lost for the period of hospitalisation meant that patients with DS-TB would have lost 25% of their annual income and 27% in those with DR-TB. Literature estimates that while on TB therapy patients can lose up to 30-40% of their annual income [32].

Estimated loss using the alternate regimens amounted to 10% of patients' annual income in all 3 of the alternate regimens. This is likely due to the shorter period of hospitalisation (11 days in the period of stabilisation), theoretically enabling patients to have very little time away from work as compared with the traditional process. Although these regimens make use of more expensive drugs, most of the expense in these regimens is related to TB treatment and will be borne by the NTP. However, what is not

clear is whether the regimens, which depart from standard treatment guidelines, would be covered under the NTP, potentially resulting in greater patient costs if they were not included.

Due to the retrospective nature of the study we were unable to account for more specific patient level costs attributed to transport, nutritional supplementation as well as potential employment finding difficulty and the cost beyond the period of hospitalisation. Taking all this into account it is likely that our estimates of patient loss are likely to be much higher.

Gospodarevskaya et al. within their populations in Tanzania and Bangladesh found patient costs, although lower in the continuation phase than the intensive phase, represented a significant proportion of annual income (89% and 77% respectively) [31]. Within our population during the optimised treatment phase patients would be liable for a further $25 (DS-TB) and $43 (DR-TB) up until completion of treatment. This cost would only be related to clinic visits and ongoing investigations, with the higher cost in patients with DR-TB group being attributed to the longer proposed duration of TB treatment until completion.

It is expected that in the further treatment phase that there would be ongoing loss of income as monthly clinic visits and disease place a strain on individuals trying to find permanent employment. Ramma et al. who reported a drop in proportion of income earners from 37%-3% while on treatment in their MDR-TB treatment cohort support this assumption [32]. Within a population earning largely minimum wage, with many households reliant on a single income, a 15-17% higher loss of the annual income is substantial. This loss is even more catastrophic as it is likely to be higher due to the inability to commit to employment in the optimised treatment phase. Society helps these individuals by providing temporary disability grants. Although this provides personal respite, this burden is then carried by governmental sources.

Within both the rechallenge process and alternative regimens, the societal cost incurred was significant. The cost of rechallenge amounted to $6,134 per patient. The alternate regimens were more economical as costs were 46-56% lower than that of the current practice. This substantial saving allows for resources to be made available to other areas of social importance.

5.3.12 Sensitivity analysis

Within our population hospitalisation was found to have the greatest influence on overall cost. The effect of hospitalisation on the overall cost was demonstrated by increasing both hospital cost and the duration of hospitalisation. These findings are consistent with literature reports of hospitalisation being the main contributor to cost in the case of TB therapy and drug reactions [26, 27, 30]. A variation of hospital cost, i.e. half and double enables the cost to be viewed in terms of the effect secondary level hospitalisation (half the cost, 30% reduction in total cost) as well as perhaps cost at a more costly centre (private, 2.2X increase in total cost) would have on the overall cost of the rechallenge procedure. In addition, increasing the current 4-day interval between rechallenge of subsequent TB drugs to a more conservative interval of 8 days (as reported in the literature) significantly increased the per patient cost of the rechallenge process [6, 19, 65]. Furthermore, making use of outpatient stabilisation for eligible patients (DRESS with ALT <100U/L) resulted in cost saving despite these patients being in the minority (2.6% reduction in total cost). These findings are consistent with literature reports of inpatient day costs having the greatest influence on cost of treatment of XDR-TB [28]. Regimen 1, with lower drug costs, was largely influenced by the cost of hospitalisation. This was highlighted in the worst case where an additional month of hospitalisation after initiation of alternate regimen was added prior to discharge (discussed later).

It is well documented that second-line TB drugs are more costly than first-line alternatives [28]. Pooran et al. found treatment of MDR-TB to be 26 times greater than the treatment of DS-TB with 49% of this cost being due to TB drugs [28]. Potential generic options of second-line TB drugs were found to decrease overall treatment costs by 41-97% [141]. Current practice cost increased by 19% when drug costs were doubled

and as Regimen 1 starts to make use of more costly second-line drugs the effect of increased costs in increased with a 41% increase in total per patient cost. This is even more pronounced in Regimen 2 (44% increase in total cost) and 3 (51% increase in total cost), which make use of newer, even more costly, second-line drugs.

The impact of drug costs, as well as hospitalisation to various extents as shown by the sensitivity analysis was further demonstrated through the scenario analysis. In changing multiple variables simultaneously, the overall costs increased and decreased as expected. Within the current rechallenge process hospitalisation costs have been a major contributor to the total cost in all stages. This influence was further highlighted in the "best" scenario, where reduced component costs resulted in a 56% decrease in total costs at $3,174 per patient. In the alternate regimens, the length of hospitalisation was minimal and drug costs are the greatest driver of costs. Making the drugs more affordable, along with the reduction in the aforementioned parameters contributed to a 36% reduction in Regimen 1 ($1,640 per patient) and 2 ($1,790 per patient) and a 38% reduction in Regimen 3 ($1,954 per patient).

Conversely, in the "worst" case scenario where costs of drugs and hospitalisation were doubled, patients were seen more frequently and lab tests done more regularly, there was a 38% increase in the total cost per patient for the drug rechallenge strategy ($8,027 per patient). Interestingly, increasing drug costs in the alternative strategies has a more profound influence on regimen costs than reducing them. Higher drug costs increased regimens costs by 1,3 times on average (Regimen 1; $5,981 Regimen 2; $6,468 and Regimen 3; $7,118 per patient respectively). In the "worst" case scenario, the increase is not solely due to the drug costs, but also contributed to by the additional hospitalisation. This again highlights the influence of inpatient management on cost.

The $US to ZAR exchange rate fluctuated widely in 2016. In order to account for this fluctuation, the impact of the lowest as well as the highest 2016 rate on overall cost per patient was assessed. Using the higher rate of R16.86=1USD resulted in a 15% increase in rechallenge as well as alternate regimen total costs. Conversely, the lowest period rate

of R13.26 resulted in a 10% decrease in costs across all regimens. Fluctuations are particularly important when drugs are internationally sourced, with higher rates resulting in greater costs and vice versa with lower rates. The higher rate (weaker ZAR) is likely to reflect the more appropriate rate.

Patient annual incomes were recorded as per hospital records. In cases where annual incomes were unknown or patients were classified as being unemployed, a proxy income equivalent to a minimum wage general worker was assigned. With this assumption, it is possible to both under- as well as overestimate patient incomes. Patients who were informally employed or earning more than estimated would be under-estimated, whereas those who were perhaps employed casually (working fewer days or not receiving any income or subsidy) would be over-estimated. To account for this, annual incomes were doubled and halved to assess their impact on societal cost. Within the rechallenge practice where patients spent more days in hospital with resultant higher loss of income doubling and halving their annual income increased and decreased societal costs by 5%. This was marginally higher than the 2% increase and decrease seen with the alternate regimens. This relatively small influence of patient costs on overall societal costs is likely to be due to the provider costs being substantial higher and thus a greater contributor.

5.4 Study significance

TB remains a major health concern with the sheer number of patients on treatment resulting in a higher incidence of adverse events as compared to other conditions. Extensive health economic evaluations on the cost of TB treatment exist, yet costing studies of adverse events are less frequent. To our knowledge this is the first piece of work that not only assesses the cost of the current practice of rechallenge in individuals developing CADR to first-line TB drugs, but also assesses potential alternatives. These hypothetical alternatives were evaluated not only in terms of what the best drug composition for treatment would be, but also where they would best fit into the treatment regimen and the estimated costs of these alternatives. Furthermore, patient and society costs were estimated for both current practice and alternate regimens, demonstrating the

significant impact CADR have on patients' annual income and society as a whole. Through this analysis we have not only highlighted areas which contribute significantly to overall cost, particularly hospitalisation and drug costs, but proposed potential cost saving alternatives. This saving in the alternate regimens translates to both healthcare services and the patient. In the current economic climate with an overburdened healthcare system, analysis of the costs of current practice and potential cost saving alternatives are critical. More appropriate use of resources allows for optimal budget expenditure. This study provides more affordable hypothetical treatment regimens that need to be further studied in terms of their clinical efficacy. However, should alternative regimen use be delayed, study findings support the development of standardised rechallenge guidelines to assist with the management of CADR in terms of current rechallenge procedure to allow for decentralised cost saving options at secondary level hospitals or community based clinics. Results of this study are potentially generalizable to other populations with high HIV/TB co-infection that manage CADR to first-line TB drugs.

5.5 Limitations

Although our study provides a novel option for the management of CADR to first-line TB therapy occurring in a predominantly HIV-infected population there are several limitations. These include those inherently associated with a retrospective review as well as those arising as a result of the proposed novel management. As there is no current protocol governing drug rechallenge, in cases of CADR or alternate treatment options, evidence was derived and based on expert opinion.

The tertiary setting of the study results in a population selection bias, in that we were only able to evaluate patients referred to the dermatology unit. One could assume that the population is representative of the severe cases of CADR seen at the local clinics, where they manage the milder cases. The data on the proportion of patients with CADR that are referred was not available. Management of adverse reactions is largely based on literature guidance and personal experience of treating physicians. It is assumed that

specialist inpatient management is safer, but once alternate facilities have adequately trained staff it is feasible that these patients could be managed at lower levels of care. Following on this study we would hope to develop guidelines to assist in the development of management protocols to be implemented at a clinic level. This will not only improve patient outcomes, but also standardise management allowing for a comparison of outcomes at varying levels of care.

Due to the retrospective nature of the study, clinical outcomes were not included, yet this has significant implications on the proposed regimens. Efficacy of the regimens in terms of cure are not known, as well as additional acquired resistance and ongoing transmission which are likely to increase the cost of rechallenge were not accounted for. As the proposed regimens in combination are novel, implications of cure, relapse and further complications with each regimen can only be based on literature and outcomes known for individual drugs. Combinations are proposed based on evidence that cure and relapse levels should be comparable to current practice, but this needs to be evaluated. Work conducted and under investigation by the TB Alliance with the REMoxTB and STAND trial are specific examples that provide evidence to the benefit of the proposed regimens and why we should continue to question the use of standard drug-regimens [116, 117].

Furthermore, the authors acknowledge that in exposing DS-TB patients to traditionally DR-TB therapies, there may be increased development of drug-resistance with a resultant reduced efficacy of these drugs should patients subsequently acquire or develop DR-TB. Mechanisms and rates of development of resistance for the proposed drugs were discussed in the preceding sections.

Possible drug-drug interactions of TB drugs and TB drugs and ART of the proposed alternative regimens, as discussed in the literature review, were not accounted for which could result in adverse events potentially increasing costs of the alternate regimens. With the lack of clinical outcomes for the proposed regimens it was not possible to carry out a cost-effectiveness analysis. Our aim was to report on the cost of current practice as well

as cost potential alternatives to provide a basis for future research, which could evaluate potential outcomes of the alternate treatment strategies.

The use of cost data from GSH and local clinics and the NHLS is representative of healthcare services in the Western Cape. These costs may not be reflective of the rest of South Africa as hospitalisation and treatment facility costs, treatment regimens and rechallenge policies for CADR are likely to vary between provinces and countries. However, in the case of costing the CADR with current rechallenge practice, data to which costs were applied was collated from a substantial population at a single centre where the practice was standardised. The small population number of those with DR-TB do not allow for any significant analysis to be applied to this specific subset of the population.

The costs of chronic medications, based on patient co-morbidities, including HIV and ART, was not included in the overall costing as they were not directly related to the management of the CADR and were continued in all patients where appropriate. In addition, the cost of any additional monitoring investigations required for HIV and ART were not included. Upon presentation where HIV status was unknown, testing and CD4 counts were carried out. If HIV-infection was confirmed then CD4 counts were performed. This was common practice in the population and these investigations were carried out in the stabilisation phase, which is therefore accounted for in the alternate regimens.

Patients were assumed to have completed treatment courses as outlined on discharge prescriptions, which results in an over-estimation of optimised treatment phase costs in cases of patients missing doses and not completing the treatment course. Monitoring costs included in the NTP were also included, further over-estimating these costs in patients who discontinue treatment or are lost to follow up. Statistical methods such as imputations were not used to evaluate missing data, with these costs rather being explored in the sensitivity analysis.

There is a paucity of data on the use of second-line drugs for DS-TB. Alternate regimens are based on available literature and expert opinion. Alternative drug therapies postulated are based on drugs that although have strong supporting clinical trial data have limited and restricted availability. Bedaquiline although currently available, is restricted to use in cases of XDR-TB and those not tolerant the other regimens of TB therapy. However, with time it is expected to become more readily available. Delamanid is unfortunately not available in South Africa other than through MSF and the DR-TB regulatory board approval. Costs were estimated based on literature, which may have resulted in costs of regimens based on delamanid being under- or overestimated.

Within our population all alternative regimens comprised rifabutin with the assumption that the majority of individuals (80%) who react to rifampicin would be able to tolerate rifabutin. These options did however not account for the 20% who may react to rifabutin and those with multiple drug hypersensitivity syndromes. We do however feel that based on Lehloenya et al.'s experience on the successful use of rifabutin after rifampicin these options are validated [99].

Individual costs for both current practice and the alternate regimens, were not estimated beyond loss of income due to days of work missed and expected patient expense liability as per the governmental hospital payment subsidy schedule. Patient specific information with regard to travel and other medical and nutritional expenses were not known. Loss in the optimised treatment phase did not include lost income as a result of not returning to work, but rather patient expenses incurred during this period. As patients may or may not have returned to work during this period, this loss could be under-estimated in those who did not return to work. Furthermore, potential complications resulting in a longer treatment period would further compound this unaccounted loss. Societal costs did not include the cost to the state of potential disability grants that may be accessed by this population.

Despite the above limitations costing estimates are robust and fairly present the costs of the current practice and alternative strategies. Although carried out in a tertiary institute,

this study is generalizable to other developing settings with a high HIV prevalence where CADR are commonplace and management places a significant burden on healthcare as well as patient resources.

Future research should focus on measuring health related outcomes of the alternate regimens in order to establish their efficacy and ultimately cost-effectiveness as well as influence on patient loss and wellbeing. Newer drugs should be incorporated into regimens to drive demand and hopefully reduce costs.

6. CONCLUSION

Despite worldwide decreasing incidence of TB in line with millennium development goals, the incidence in developing countries such as South Africa still accounts for a significant disease burden. HIV continues to fuel the epidemic. Despite TB treatment being highly effective, there are significant adverse events affecting treatment outcomes and attrition rates. These adverse events place significant burden on the suffering individual and the healthcare system. In resource-poor countries, expenditure needs to focus on optimal care. Money spent on treating adverse events could better be spent on treating more individuals in order to optimise health care expenditure.

Newer drugs need to be considered and alternative options must be explored to allow the healthcare system to adapt to the continuing epidemic of TB. Research allows these options to be critically evaluated to determine their feasibility and potential benefits. Although research and innovation can be initially costly, the increasing demands and indications for drugs can result in subsequent long-term decrease in costs.

Individual cost in terms of income loss and expenses needs to be prioritized. Patients are typically affected at the height of their earning potential, likely to be heads of households and often the sole source of income. This increases need for social support, placing further burdens on government departments and budgets.

The study results demonstrated that second-line alternative regimens for managing a CADR to first-line TB therapy in patients with DS-TB are not only plausible, but also potentially more affordable for patients and providers. These alternative treatment options result in shorter periods of hospitalisation with subsequent reduction in cost and personal patient loss. A large proportion of the cost of alternative regimens is related to costs of newer drug therapies. With time and increasing use, these drugs too should become more affordable. However, it remains important to determine the outcomes of using these alternatives in the context of CADR to first-line TB therapy. One needs to balance the risk of resistance and future treatment failure should patients develop DR-

TB, with the efficacy and cost-saving in instituting these drugs in the management of CADR to first-line TB therapy.

6.1 Policy recommendations

Based on the findings of this study the following policy recommendations can be made:

- *Government should take steps to increase availability of second-line TB drugs*

  Efforts should be made to negotiate with suppliers and patent holders to gain access to these newer drugs at costs that are sustainable within our resource-limited setting. This study has clearly shown that in the alternate treatment options, drug costs are the major driver of total cost, as has been shown in the literature. Furthermore, these drugs should be made available in cases of severe CADRs to first-line TB therapy where rechallenge may be life-threatening.

- *Hospitalisation should be limited or transferred to the lowest suitable level of care*

  The cost of hospitalisation has been shown to have the biggest influence on the cost of the rechallenge procedure. Outpatient based therapy at tertiary hospitals, or even transfer of management to secondary level hospitals (half daily bed cost as compared to tertiary hospitals) once patients have been stabilised would result in significant cost saving.

- *Community based partnerships should be forged*

  Service provision in terms of the optimised treatment phase at the community level is an essential component in ensuring adequate management of patients having experienced CADR. Patients need to be appropriately referred to community TB clinics for follow up and ongoing management. TB clinics in turn should have easy access to tertiary hospitals for ongoing support and advice in managing the patients, as well as referral should problems occur. Relationships are integral to maintaining the feasibility of the decentralised model.

6.2 Suggestions for further research

Through this study the following areas for further research have been highlighted;

- *Study to assess the cost-effectiveness of alternative treatment options*

  Although the alternate treatment regimens have been shown in this study to be more affordable and literature provides good evidence of efficacy of individual drugs, a study should be undertaken to follow up true outcomes of the regimens in the context of CADR development in DS-TB. Outcomes of interest would include; cure rate, time to sputum conversion, risk of drug-resistance as well as patient adherence to treatment and time to return to work for individual patients.

- *Standardised protocol for rechallenge*

  A set method for rechallenge should be established detailing the order in which drugs should be re-introduced and guides to appropriate investigations. This would not only decrease costs due to inter-provider variability in ordering tests, but allow for more specific tests to be used as well as enable rechallenge to be adequately undertaken outside of specialist centres.

6.3 Main conclusion

This study has shown that the current cost of managing a CADR to first-line TB therapy is expensive. Alternatives strategies are not only feasible, but also more affordable, with the cost saving being due to the shortened period of hospitalisation. Based on these findings, it is economically feasible for alternatives to rechallenge to be employed in individuals who experience CADR to first-line TB therapy. Importantly clinical outcome data is required to determine the effectiveness of alternate regimens. Risk of development of drug-resistance to second-line drugs with increased use needs to be considered and accounted for. While second-line drug availability as per the alternative regimens can't be ensured, the current practice should be decentralised to a lower level of care or outpatient management to reduce the healthcare and patient costs associated with hospitalisation.

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8. APPENDICES

8.1 Naranjo ADR probability scale

Naranjo adverse drug reaction probability scale is the tool used to establish causality of an offending agent in the case of ADR [84].

Naranjo Adverse Drug Reaction Probability Scale				
Question	Yes	No	Do Not Know	Score
1. Are there previous *conclusive* reports on this reaction?	+1	0	0	
2. Did the adverse event appear after the suspected drug was administered?	+2	-1	0	
3. Did the adverse reaction improve when the drug was discontinued or a *specific* antagonist was administered?	+1	0	0	
4. Did the adverse event reappear when the drug was re-administered?	+2	-1	0	
5. Are there alternative causes (other than the drug) that could on their own have caused the reaction?	-1	+2	0	
6. Did the reaction reappear when a placebo was given?	-1	+1	0	
7. Was the drug detected in blood (or other fluids) in concentrations known to be toxic?	+1	0	0	
8. Was the reaction more severe when the dose was increased or less severe when the dose was decreased?	+1	0	0	
9. Did the patient have a similar reaction to the same or similar drugs in *any* previous exposure?	+1	0	0	
10. Was the adverse event confirmed by any objective evidence?	+1	0	0	
TOTAL SCORE:				

8.2 Ethics Approval

UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee

Room ES2-24 Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 406 6492
Email: sumayah.arieldien@uct.ac.za
Website: www.health.uct.ac.za/fhs/research/humanethics/forms

22 April 2016

HREC REF: 240/2016

Dr A Pooran
Department of Medicine
H46.51
OMB

Dear Dr Pooran

PROJECT TITLE: THE COST AND COST EFFECTIVENESS OF MANAGING CUTANEOUS ADVERSE DRUG REACTIONS TO 1ST LINE TB THERAPY IN TB PATIENTS IN SOUTH AFRICA (MSc Candidate - Dr L Knight)

Thank you for submitting your study to the Faculty of Health Sciences Human Research Ethics Committee (HREC) for review.

It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned study.

Approval is granted for one year until the 30 April 2017.

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.
(Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanethics/forms)

Please quote the HREC REF in all your correspondence.

We acknowledge that the student, Dr Lauren Knight will also be involved in this study.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please note that for all studies approved by the HREC, the principal investigator **must** obtain appropriate institutional approval before the research may occur.

Yours sincerely

pp T Burgess

PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN RESEARCH ETHICS COMMITTEE

Federal Wide Assurance Number: FWA00001637.
Institutional Review Board (IRB) number: IRB00001938

HREC 240/2016

8.3 Table of costs related to the study population

PARAMETER	UNIT COST US$
Hospitalisation (per day)	
• Tertiary	64,12
• Secondary	27,23
Consultation (per 15min)	
• Specialist	8,16
• Registrar	6,94
• Allied Health professional	2,75
• Social Worker/ARV Counsellor	2,22
Radiology	
• Xray	13,48
• Ultrasound	38,05
• CT Scan	182,14
• EEG	28,75
Investigations	
• FBC	8,50
• Differential Count	5,02
• Haemoglobin	1.30
• White cell count	1.30
• Urea and creatinine	6,13
• Full liver function tests	26,95
• Sodium	2,93
• Potassium	2,93
• Urea	2,93
• Creatinine	2,93
• Total bilirubin	3,85
• Conjugated bilirubin	2,93
• Alanine transaminase	3,85
• Aspartate transaminase	3,85
• Alkaline phosphatase	3,85
• Gamma-glutamyltransferase	3,85
• Calcium	2,18
• Magnesium	2,18
• HIV serology	3,97
• CD4 count	17,07
• Sputum geneXpert®	11,75
• Sputum TB culture	12,49
• ECG	16,88
First-line TB drugs (per dose)	
• Rifampicin	0,10
• Isoniazid	0,04
• Pyrazinamide	0,02
• Ethambutol	0,04
• Rifafour™	0,05/tablet

Bridging therapy TB drugs • Streptomycin • Ethionamide • Ofloxacin • Terizidone • Moxifloxacin	 0,44 0,35 0,95 1,03 0,41
Alternate regimen TB drugs • Rifabutin • Levofloxacin • Bedaquiline • Delamanid	 0,86 1,68 3,60 6,42
Dressings • Acqeous cream • Emulsifying ointment • Cetomacrogol • Dovate • Mylocort • Natural tears • Lacrilube • Paraffin gauze (Jelonet™) • 20%steroid/glycerine/H20 • Betadine baths • Glycothymol mouthwash • Non-adherent dressings (Mepitel ™) • Fluocinolone gel • Flamazine • Benzac Gel • Betamethasone 10% • Sitz Baths • UEA	 0,14 1,40 0,53 1,52 1,55 0,20 3,14 0,67 0,59 0,57 0,16 68,06 0,97 1,78 0,97 0,98 0,26 0,14

8.4 Hospital subsidy categories and expected expenses

Subsidisation classification	Hospital stay (tertiary)	Hospital stay (secondary)	Hospital Outpatients visit	Clinic Visit	Laboratory investigations	Radiological tests	Medications
H1 (<$3,403 per annum)	$5 up to 30 days	$3 up to 30 days	$2	$1,50	Included in the consultation or inpatient fee		
H2 ($3,403-$4,900 per annum)	$5/day	$3/day	$7	$4	50% of the full cost (actual cost +30% overheads)		
H3 ($4,900-$6,807 per annum)	$34/day	$18/day	$9	$4	75% of the full cost average		
Full paying (>$6,807 per annum)	$56/day	$30/day	$13	$6	Unsubsidised		