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Retrospective analysis of time to smear and culture conversion and treatment outcomes of rifampicin resistant tuberculosis patients treated with long and short course regimen at Tshepong Hospital (2015 –2018)

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RETROSPECTIVE ANALYSIS OF TIME TO SMEAR AND CULTURE CONVERSION AND TREATMENT OUTCOMES OF RIFAMPICIN RESISTANT TUBERCULOSIS PATIENTS TREATED WITH LONG AND SHORT COURSE REGIMEN AT TSHEPONG HOSPITAL (2015 – 2018)

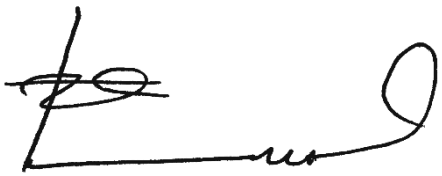
Petudzai Muchichwa

A research write-up submitted to the Faculty of Health Sciences at the University of Witwatersrand, Johannesburg, in partial fulfilment of the requirements for the degree of Master of Medicine in the branch of Internal Medicine

Johannesburg 2021

I. DECLARATION

I, Petudzai Muchichwa, do hereby declare that this research report is my unaided work. It is being submitted for the degree of Master of Medicine in the division of Internal Medicine. This research report is submitted in the submissible format as recognized by the Faculty of Health Science at the University of Witwatersrand, Johannesburg. I further declare that this work has not been submitted for any other examination or degree at this or any other University.



The 2nd day of September 2021

II. DEDICATION

Thank you to Patrick and Lucy Lehmann for taking my kids, Tanaka and Tinotenda, to and from school for the 3 years of my studies following the tragic loss of my wife Tafadzwa E. Mubeda.

III. PRESENTATIONS ORIGINATING FROM THIS RESEARCH

Nil.

IV. ETHICAL CONSIDERATIONS

Permission for this retrospective study was obtained from Tshepong Hospital, Department of Health Northwest Province, Faculty of Health Sciences, University of the Witwatersrand, and the Human Research Ethics Committee of the University of Witwatersrand (clearance certificate number – M181128).

V. ABSTRACT

Background: Shortened treatment regimens and novel therapies have become available for programmatic adoption due to toxicities and the prolonged duration of treatment required for drug resistant (DR) TB. Sputum smear and culture conversion to negative and successful treatment outcomes are important parameters to assess treatment effectiveness.

Objective: To compare responses and outcomes between short and long course DR TB treatment regimens at Tshepong Hospital, Klerksdorp, South Africa.

Methods: A retrospective review was conducted of patients diagnosed with rifampicin resistance and who were also smear and culture positive for *Mycobacterium tuberculosis* between January 2015 and June 2018. We compared patients receiving short course regimens and long course regimens using historical controls.

Results: Data from 285 of 1399 DR TB patients' records was analysed; 39.2% were on short course DR treatment, 61.8% on long course. Short course participants were less likely to smear convert at 2 months (42.2%), compared to those on long regimen (31.8%, *p=0.0209*) but culture conversion at 2 months was similar (45.9% v 47.2%, *p=0.7682*). A higher proportion of patients receiving short course treatment were cured or completed treatment (71.6% vs. 58.0%, *p=0.021*), and short course patients were less likely to have died (7.3% vs 22.7%, *p=0.0007*).

Conclusion: There was no statistical difference in time to culture conversion between the two treatment groups, however, short DR TB regimen was associated with better outcomes and significantly lower mortality. Thus, advent of shorter and injection free regimens is a welcome development in the global fight against drug resistant TB.

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MDR TB Unit, Tshepong Hospital for availing medical records.

IX. LIST OF ABBREVIATIONS

AAFB	Acid-Alcohol Fast Bacilli
AIDS	Acquired Immune Deficiency Syndrome
ARV	Antiretroviral Therapy
BCG	Bacille Calmette - Guérin
CD4	Cluster of Differentiation 4
DOH	Department of Health
DOT	Directly Observed Treatment
DST	Drug Susceptibility Testing
E	Ethambutol
ECG	Electrocardiogram
GXP Test	Xpert MTB/RIF Test
H	Isoniazid
HIV	Human Immunodeficiency Virus

HR	Isoniazid/ Rifampicin
HRZE	Isoniazid/ Rifampicin/ Pyrazinamide/ Ethambutol
LPA	Line Probe Assay (Genotype MTBDR)
MDR TB	Multidrug-Resistant Tuberculosis
MGIT	Mycobacterial Growth Indicator Tube
MTB	Mycobacterium Tuberculosis
P	Pyrazinamide
PCR	Polymerase Chain Reaction
Pre-XDR	Pre-Extensively Drug Resistant Tuberculosis
R	Rifampicin
Reflex test	AAFB, first-line LPA for susceptibility to rifampicin and isoniazid and to identify the two INH mutations (inhA and katG). Second-line LPA for susceptibility to fluoroquinolones and injectables, TB culture and phenotypic DST
RR	Resistance to at least rifampicin, with or without resistance to other drugs
RSA	Republic of South Africa
TB	Tuberculosis
WHO	World Health Organization
XDR TB	Extensively Drug-Resistant TB

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CHAPTER 1: PROTOCOL WITH EXTENDED LITERATURE REVIEW

1.1 Introduction and Justification of the Study

Mycobacterium tuberculosis (MTB) has co-existed with humans for millennia. It is largely spread through air droplets issued by an infected individual, and once inside the host, evades the immune system by lying dormant in the lungs as latent TB. MTB typically affects the lungs, causing pulmonary tuberculosis (TB), but can also be extra-pulmonary, affecting any organ system.[1] However, progression to disease is largely determined by the interplay between host's immune system, and the virulence of the bacilli.[2]

Ever since *Mycobacterium tuberculosis* infected humans, it has presented multiple genomic mutations, some of which affect the genes against which anti-tuberculous drugs work, resulting in these mutated MTB phenotypically showing resistance to TB medication.[3, 4]

Rifampicin resistance (RR) TB is defined as resistance to at least rifampicin, with or without resistance to other drugs.[5] Multidrug-resistant TB (MDR TB), is defined as any mycobacterium infection resistant to the two main first line drugs, rifampicin and isoniazid. Conventionally, treatment of RR is lengthy, costly, and presents both a high pill burden, and more side effects.[6]

In 2016, the World Health Organization (WHO) recommended the adoption of short treatment regimen for selected RR patients.[7] However, even though publications on the outcomes of short course have primarily relied on observational studies, very limited data is as yet available on the treatment outcomes under programmatic settings. Moreover, there is paucity of data were outcomes of short and long-term regimens are compared in settings with high TB and HIV burden. As such, a review of drug resistant TB outcomes and HIV co-infection under programmatic settings will provide information on the effectiveness of the short course treatment roll out.

1.2 Disease Burden

A third of the world's population is estimated to be infected with the bacillus, 5 - 15% of which will subsequently develop TB. However, immune-suppressive states put infected patients at a far higher risk of developing TB.[1]

Globally, 4.1% of new cases, and 19% of previously treated drug susceptible patients, have MDR TB. While in South Africa (2016), 3.4% of new cases and 7.1% of previously treated cases had RR TB.[1]

Drug resistant TB consumes about 40% of the resources allocated to TB in South Africa, hence prevention, early diagnosis, and effective treatment should be prioritised.[8, 9]

1.2.1 TB and HIV Co-infection

Approximately 70% of adults with RR TB in South Africa are co-infected with the *human immunodeficiency virus* (HIV), often complicating treatment.[10, 11] Drug resistant TB patients co-infected with HIV and on treatment have similar culture conversion times compared to HIV non-infected individuals.[12, 13] [14] However, a study done in Ethiopia suggested that being HIV negative is associated with delayed culture conversion,[15] while treatment outcomes remain similar between the two groups. [13, 14, 16] In contrast, another meta-analysis also done in Sub-Saharan Africa concluded that MDR TB patients with co-infected with HIV have less favourable outcomes.[17]

In this study, we aim to determine the effect of HIV co-infection on the time to smear and culture conversion.

1.3 TB Treatment

Treatment of drug sensitive TB is with rifampicin, isoniazid, ethambutol and pyrazinamide for 2 months, followed by rifampicin and isoniazid for 4 months.[18] A 4 months fluroquinolone comprising regimen for drug sensitive TB showed treatment success in about 80% of patients, however it failed to achieve non inferiority compared to the standard treatment.[19]

Rifampicin resistance (RR) makes TB treatment difficult, and often with poorer outcomes. [10]

In South Africa, 2015, the standardised long MDR TB treatment comprised a 6 month intensive phase of moxifloxacin, kanamycin, ethionamide, terizidone and pyrazinamide, followed by a continuation phase with other four drugs excluding kanamycin for 18 to 24 months.[20]

In 2016, the WHO recommended that short course treatments consist of 4 to 6 months of kanamycin, moxifloxacin, ethionamide, clofazimine, pyrazinamide, a high dose isoniazid, and ethambutol followed by a 5 months continuation phase of moxifloxacin, clofazimine, pyrazinamide and ethambutol.[7] For this regimen, bedaquiline was substituted for kanamycin if the latter was contraindicated or intolerable.

Patients excluded from short course include those who exhibit resistance to fluoroquinolones and or second line injectable drugs (SLID); those who should be treated as pre-extensively drug resistant (Pre-XDR) or XDR; who are pregnant; who have extra pulmonary TB; who had exposure to second line drugs in the short course for more than a month; and those who are intolerant to any drug in the short course.[21] These recommendations were constantly being reviewed as data from randomised control studies was being available.

In 2019, guidelines for short course treatment consist of linezolid for 2 months, a high dose INH for 4 to 6 months, bedaquiline for 6 to 9 months, and 9 months of levofloxacin, clofazimine, pyrazinamide and ethambutol.[5] The long course regimen comprises 6 to 8 months of linezolid, bedaquiline, levofloxacin, clofazimine and terizidone, followed by 12 months of levofloxacin, clofazimine and terizidone.[5] Even short, affordable and well tolerated regimens for MDR and XDR TB namely BPaL (bedaquiline, pretomanid and linezolid) and BPaMZ (bedaquiline, pretomanid, moxifloxacin and pyrazinamide) have be sanctioned by TB Alliance in April 2019, but are yet to be adopted widely.[22]

Clofazimine is a key drug in the 2016 short course regimen in part because it has been shown to reduce the length of treatment in MDR TB regimen.[23] Due to toxicity and limited data on efficacy, terivalidin, which was used in the standardised long course regimen, has been replaced by Clofazimine.[24]

1.4 Outcomes of TB Treatments

As can be expected, the treatment success rate for treating drug sensitive TB is better compared to that of drug resistant TB, 83% vs 48 - 68% respectively.[10, 25] Poor compliance and adherence are important factors in the surge of drug resistant TB, which is associated with increase in morbidity and mortality.[26] Short course regimens are designed to improve adherence and attain better outcomes. Recent data suggests that there is a potential cure rate of 83.7% with the short course compared to 50% on the conventional treatment.[8] This has seen at least 35 countries, including South Africa, adopting the new guidelines and the use of the novel drugs, bedaquiline and delamanid.[6] According to a retrospective study done in South Africa, use of bedaquiline in MDR and XDR TB regimen was associated with a 3-fold decrease in mortality compared to regimens without.[9]

1.4.1 Smear and culture conversion

The time to culture conversion is a useful marker in the prediction of therapeutic efficacy in drug resistant TB patients, this is because non-conversion at the end of the intensive phase is strong indication of unfavourable outcomes.[27] Initial smear burden is the most important predictor of time to culture conversion.[28] However, for the purposes of both monitoring and predicting possible outcomes, using both smear and culture conversion is recommended.[29] Delayed smear and culture conversion in drug resistant TB is associated with resistance to fluoroquinolones, resistant to both R and H, cigarette smoking, ethanol use, initial smear burden, underweight, low creatinine level, HIV negative and previous history of TB.[15, 27] Cavitation on a chest radiograph is an independent predictor of time-to-culture conversion in drug resistant TB patients and a separate risk factor for adverse outcomes.[30] A Portuguese study demonstrated delayed in smear and culture conversion on older patients above 50 years, male gender and bilateral chest x-rays changes.[31]

The introduction of bedaquiline, a diarylquinoline that inhibits MTB ATP synthase, to the background long MDR treatment regimen is associated with early culture conversion compared with placebo.[25] In a programmatic assessment in India of effects of bedaquiline containing regimen smear conversion was 51% and 91% patients at the end of 1st week and 3rd month respectively. Culture conversion was 93% and 98% at the end of 3rd and 6th months respectively[32] Bedaquiline has a long half-life so discontinuation of companion drugs with short half-lives could result in emergence of resistance through Rv0678 mutations which compromise its use.[8]

1.5 Evidence for Adoption of Short Course

The recommendations for short MDR TB regimen was based on observational studies in Bangladesh, Uzbekistan, Swaziland, Cameroon, Niger and 7 other sub-Saharan African countries.[6, 7] A meta-analysis of MDR TB patients treated with short course in 32 observational studies done in 23 countries demonstrated a success rate of 54%.[33] A multi-country prospective observational study in West and Central Africa showed 72.4% patients were declared cured, and 9.2% treatment completed, giving a success rate of 81.6%.[34] Results from the stage 1 STREAM study (Standardised Treatment Regimen of Anti-Tuberculosis Drugs for Patients with MDR TB) has shown that short regimen is as close in effectiveness as the conventional treatment.[5, 33, 35]

1.6 Limitations of Short Course

The medium- and long-term effects on the implementation of short course regimen are uncertain, in the optimistic projection it is expected by 2024 to reduce the incidence of MDR TB by 23% compared to continued use of long regimens.[36] The durability of the effectiveness of short course is obscure as it is uncertain that there are no additional drug resistance patterns generated and more patients being excluded.[36] Treatment outcomes on programmatic settings are still being evaluated.

In this manuscript, we summarize the outcomes obtained from a programmatic setting comparing short term regimen and long-term regimen.

1.7 Research Question

Is the short course MDR TB regimen non-inferior to conventional long regimen at Tshepong hospital in treating rifampicin resistant TB?

1.8 Objectives

1. To compare differences in time to smear and culture conversion of drug resistant TB patients on short and long course treatments.
2. To determine the proportion of patients that used either kanamycin or bedaquiline or both in the intensive phase.
3. To report the effect of HIV status on smear and culture conversion on the two groups.
4. To ascertain factors associated with time to smear and culture conversion in the two groups.
5. To report treatment outcomes in the two groups.

1.9 Methods

1.9.1 Study design

Retrospective cohort study conducted at Tshepong Hospital comparing the short-course treatment (January 2017 to June 2018) to that of the long previous treatment regimen (January 2015 to December 2016).

1.9.2 Setting

Klerksdorp/Tshepong Hospital complex MDR TB unit which is a referral site for MDR/XDR TB patients in North West Province, South Africa. The MDR TB unit has medical officers, nursing staff, physiotherapist, audiologist, social worker and psychologists. In this study the investigator was responsible for all data collection.

1.9.3 Sample size and sampling

The study population were adult MDR and rifampicin mono-resistant TB patients (above 18yrs of age) admitted to Tshepong MDR-TB Unit between 2015 and 2018. Rifampicin mono-resistant TB patients were included in this study as they were treated with the same regimen as MDR TB patients. Drug resistant TB records of adult patients who fulfilled the inclusion and exclusion criteria were stratified into subgroup A and B for those admitted from 2015 to 2016 and 2017 to 2018 respectively.

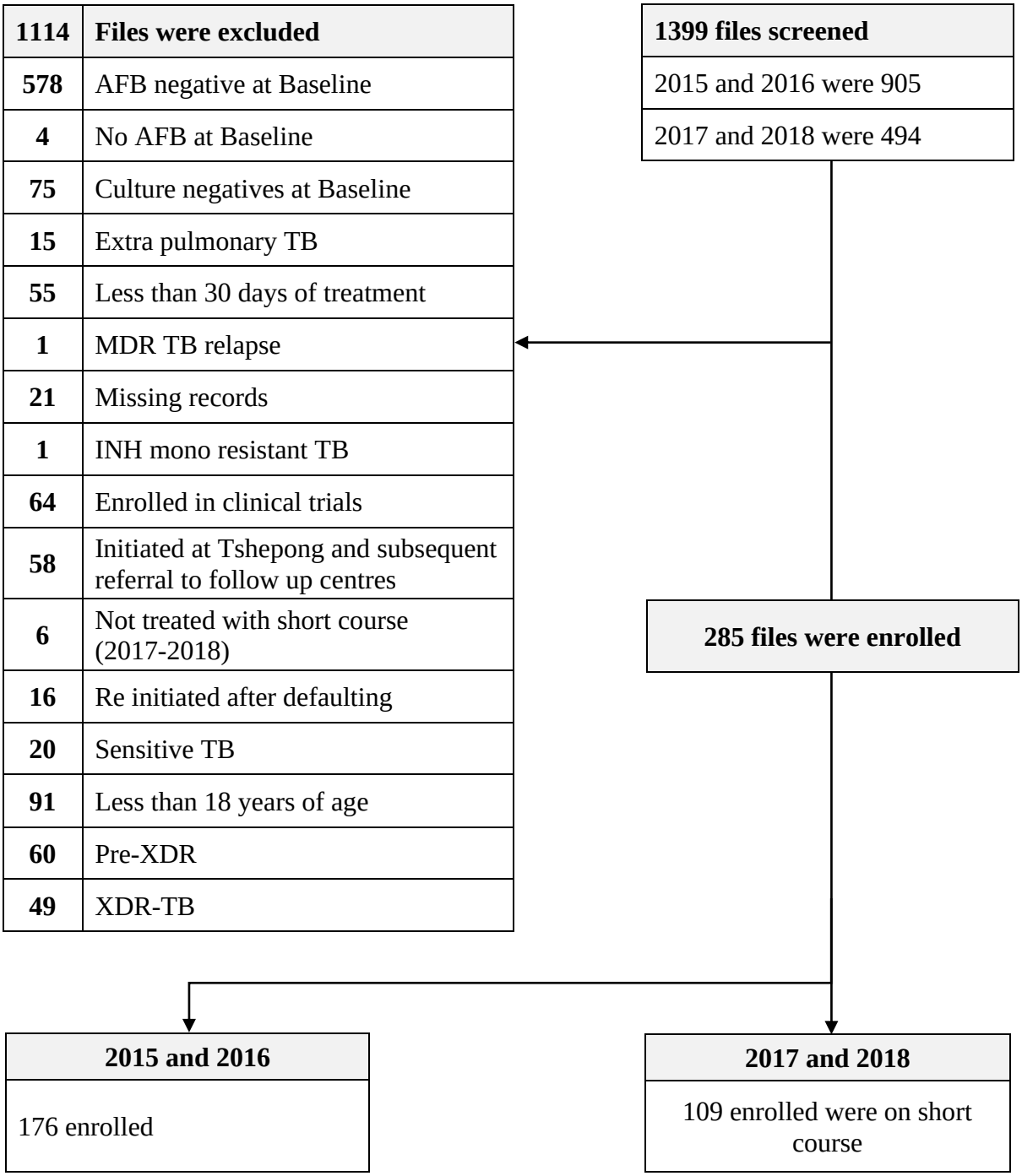

Fig. 1.1 - Flow diagram showing enrolled patients after applying inclusion and exclusion criteria

1.9.4 Participant selection

Inclusion criteria

1. MDR TB and rifampicin mono-resistant patients on Tshepong Hospital drug resistant register for the years 2015 to 2016 and 2017 to 2018
2. At least scanty positive and culture positive at baseline as this will be required to determine time to smear and culture conversion

3. DR TB Treatment received for at least 30 days
4. HIV status known with CD4 and viral load at base line or within six months prior to or one month after initiating therapy
5. Laboratory confirmed rifampicin resistance ascertained on initial GXP and or LPA

Exclusion criteria

1. Patients on the register aged less than 18 years
2. Patients re initiated after defaulting TB therapy for long than 2 months
3. Laboratory confirmation of resistance to 2nd line drugs (pre-XDR or XDR)
4. Patients enrolled in clinical trials
5. Patients only initiated at Tshepong and subsequent referral to follow up centres

1.9.5 Data collection

A questionnaire was used to tabulate data extracted from patient's hospital records which included demographics, baseline TB diagnosis, TB history, background medical history, and admission medical data.

Subgroup A had data collected up to 18-24 months or till outcome was recorded and for subgroup B data had collected for 9 months or till outcome was documented. Patients in subgroup 2 were categorized on whether they received bedaquiline or kanamycin short course or initially kanamycin then changed to bedaquiline short course.

Treatment outcomes were determined as per WHO 2013 guidelines for the two subgroups as stated on Table 1.[37] Cured includes patients with treatment completed as recommended by the national policy without evidence of failure and three or more consecutive cultures taken at least 30 days apart are negative after the intensive phase. Treatment completed subgroups have treatment completed as recommended by the national policy without evidence of failure but no record that three or more consecutive cultures taken at least 30 days apart are negative after the intensive phase. Treatment failed category have treatment terminated or need for permanent regimen change of at least two anti-TB drugs because of lack of conversion by the end of the intensive phase or bacteriological reversion in the continuation phase after conversion to negative, or evidence of additional acquired resistance to fluoroquinolones or second-line injectable drugs, or adverse drug reactions (ADRs). Lost to follow-up are patients whose treatment was interrupted for 2 consecutive months or more. Not evaluated includes patients for whom no treatment outcome is assigned. This includes cases transferred out to

another treatment unit and whose treatment outcome is unknown. Treatment success is sum of cured and treatment completed. [37]

1.10 Statistical Analysis

Categorical data was analysed and presented as frequencies and percentages for overall and stratified by short course and long course treatments respectively. Descriptive statistics described baseline demographics and clinical characteristics stratified by treatment group. The statistical comparison between short course and long course treatments was assessed using Pearson's Chi-Square test and Fisher's exact for sparse data. Continuous measures were assessed using medians and inter-quartile ranges (IQR) stratified by the two groups and statistically compared non-parametrically using Kruskal-Wallis test.

Time to smear and culture conversion of patients on short course and long course treatments were evaluated using Kaplan-Meier survival curves. To compare the differences in time to smear and culture conversion between the two groups using the curves evaluated, logrank test was used. The curves were compared at 2, 4 and 6 months of TB treatment between the two groups.

Cox proportional hazard regression was used to determine factors associated with time to smear and culture conversion between the two groups at 2, 4 and 6 months of TB treatment for all patients and for those who are HIV infected. Risk factors were determined in both univariate and multivariate level. A backward selection procedure was used to determine the final multivariate model adjusting for covariates. Entire statistical assay was done in SAS Enterprise Guide 7.1.

1.11 Ethics

Ethics was sought from the Human Research Ethics Committee of the University of the Witwatersrand and permission was granted from Northwest province and Klerksdorp Tshepong hospital. Patient identifications numbers were used on the data collection sheet to safeguard the identity of the study participants. Findings will be availed to Tshepong hospital and published in academic journals for improved care of patients nationally and internationally.

1.12 Limitations, Bias, Reliability, and Validity

1. For this retrospective study, the data used was originally collected for clinical care, therefore not all the relevant information was available for analysis.
2. Missing data was encountered for files that qualified for analysis.
3. This study was retrospective, allowing no control over the way interventions were administered.
4. Two groups from two different time frames were compared, therefore there might have been different characteristics, conditions and clinicians.
5. There is also the possibility of contamination bias, that is, patients who may have been recorded as having had short course treatment whilst they got drugs for conventional treatment.
6. Patients who were on the short course may have been more carefully monitored due to the use of new drugs, resulting in an attention bias.
7. Patients on bedaquiline required monthly Electrocardiograms (ECG), resulting in closer and more frequent monitoring that further reinforced an attention bias.
8. Patients analysed were smear and culture positive at baseline thus findings of CXR cavities may been over presented.
9. The short regimen patients were treated with 2016 guidelines and has since changed with the use of more novel drugs like linezolid.

1.13 Funding

This project was self-funded. Costs incurred include stationary, printing, internet access and transportation.

1.14 Time Frame

Gantt chart showing the timeline of the study:

2018	May	June	July	August	Sept	Oct	Nov	Dec
Literature review								
Preparing protocol								
Protocol Assessment								

2019	Jan	Feb	March	April	Aug	Sep	Oct	Nov	Dec
Ethics Application									
Data collection									

2020	Jan	Feb	March	April	May	June	July	Aug
Data collection								
Analysis								
Write up								

1.15 References - Chapter 1

1. Global tuberculosis report 2017 [Internet]. WHO. [Date accessed 10/04/2020]. Available from: https://www.who.int/tb/publications/global_report/gtbr2017_main_text.pdf.

2. Fox GJ, Schaaf HS, Mandalakas A, Chiappini E, Zumla A, Marais BJ. Preventing the spread of multidrug-resistant tuberculosis and protecting contacts of infectious cases. Clin Microbiol Infect. 2017;23(3):147-53.

3. Forrellad MA, Klepp LI, Gioffre A, Sabio y Garcia J, Morbidoni HR, de la Paz Santangelo M, et al. Virulence factors of the Mycobacterium tuberculosis complex. Virulence. 2013;4(1):3-66.

4. Dookie N, Rambaran S, Padayatchi N, Mahomed S, Naidoo K. Evolution of drug resistance in Mycobacterium tuberculosis: a review on the molecular determinants of resistance and implications for personalized care. J Antimicrob Chemother. 2018;73(5):1138-51.

5. Global Tuberculosis report 2019 [Internet]. WHO. 2019 [Date accessed 10/04/2020]. Available from: https://apps.who.int/iris/bitstream/handle/10665/329368/9789241565714-eng.pdf?ua=1.

6. Falzon D, Schunemann HJ, Harausz E, Gonzalez-Angulo L, Lienhardt C, Jaramillo E, et al. World Health Organization treatment guidelines for drug-resistant tuberculosis, 2016 update. Eur Respir J. 2017;49(3).

7. Global Tuberculosis Programme. WHO treatment guidelines for drug-resistant tuberculosis : 2016 update. [Internet]. WHO. 2016 [Date accessed 10/04/2020]. Available from: http://apps.who.int/iris/bitstream.

8. Dheda K, Cox H, Esmail A, Wasserman S, Chang KC, Lange C. Recent controversies about MDR and XDR-TB: Global implementation of the WHO shorter MDR-TB regimen and bedaquiline for all with MDR-TB? Respirology (Carlton, Vic). 2018;23(1):36-45.

9. Schnippel K, Ndjeka N, Maartens G, Meintjes G, Master I, Ismail N, et al. Effect of bedaquiline on mortality in South African patients with drug-resistant tuberculosis: a retrospective cohort study. Lancet Respir Med. 2018;6(9):699-706.

10. Farley JE, Ndjeka N, Kelly AM, Whitehouse E, Lachman S, Budhathoki C, et al. Evaluation of a nurse practitioner-physician task-sharing model for multidrug-resistant tuberculosis in South Africa. PLoS One. 2017;12(8):e0182780.

11. Farley JE, Ram M, Pan W, Waldman S, Cassell GH, Chaisson RE, et al. Outcomes of multi-drug resistant tuberculosis (MDR-TB) among a cohort of South African patients with high HIV prevalence. PLoS One. 2011;6(7):e20436.

12. Brust JC, Lygizos M, Chaiyachati K, Scott M, van der Merwe TL, Moll AP, et al. Culture conversion among HIV co-infected multidrug-resistant tuberculosis patients in Tugela Ferry, South Africa. PLoS One. 2011;6(1):e15841.

13. Mohr E, Cox V, Wilkinson L, Moyo S, Hughes J, Daniels J, et al. Programmatic treatment outcomes in HIV-infected and uninfected drug-resistant TB patients in Khayelitsha, South Africa. Transactions of the Royal Society of Tropical Medicine and Hygiene. 2015;109(7):425-32.

14. Magis-Escurra C, Günther G, Lange C, Alexandru S, Altet N, Avsar K, et al. Treatment outcomes of MDR-TB and HIV co-infection in Europe. Eur Respir J. 2017;49(6).

15. Shibabaw A, Gelaw B, Wang SH, Tessema B. Time to sputum smear and culture conversions in multidrug resistant tuberculosis at University of Gondar Hospital, Northwest Ethiopia. PLoS One. 2018;13(6):e0198080.

16. Isaakidis P, Casas EC, Das M, Tseretopoulou X, Ntzani EE, Ford N. Treatment outcomes for HIV and MDR-TB co-infected adults and children: systematic review and meta-analysis. Int J Tuberc Lung Dis. 2015;19(8):969-78.

17. Chem ED, Van Hout MC, Hope V. Treatment outcomes and antiretroviral uptake in

multidrug-resistant tuberculosis and HIV co-infected patients in Sub Saharan Africa: a systematic review and meta-analysis. BMC Infect Dis. 2019;19(1):723.

18. National Tuberculosis Management Guidelines 2014 South Africa [Internet]. 2014 [Date accessed 10/04/2020]. Available from: https://aidsfree.usaid.gov/sites/default/files/tb_south-africa_adult_2014.pdf.

19. Imperial MZ, Nahid P, Phillips PPJ, Davies GR, Fielding K, Hanna D, et al. A patient-level pooled analysis of treatment-shortening regimens for drug-susceptible pulmonary tuberculosis. Nat Med. 2018;24(11):1708-15.

20. Management of Drug-Resistant Tuberculosis 2013 [Internet]. WHO. 2013 [Date accessed 10/04/2020]. Available from: https://www.idealhealthfacility.org.za/docs/National-Priority-Health-Conditions/Management%20of%20Drug-Resistant%20Tuberculosis%202013.pdf.

21. Trauer JM, Achar J, Parpieva N, Khamraev A, Denholm JT, Falzon D, et al. Modelling the effect of short-course multidrug-resistant tuberculosis treatment in Karakalpakstan, Uzbekistan. BMC Med. 2016;14(1):187.

22. Keam SJ. Pretomanid: First Approval. Drugs. 2019;79(16):1797-803.

23. Padayatchi N, Gopal M, Naidoo R, Werner L, Naidoo K, Master I, et al. Clofazimine in the treatment of extensively drug-resistant tuberculosis with HIV coinfection in South Africa: a retrospective cohort study. J Antimicrob Chemother. 2014;69(11):3103-7.

24. Hwang TJ, Wares DF, Jafarov A, Jakubowiak W, Nunn P, Keshavjee S. Safety of cycloserine and terizidone for the treatment of drug-resistant tuberculosis: a meta-analysis. Int J Tuberc Lung Dis. 2013;17(10):1257-66.

25. Diacon AH, Pym A, Grobusch MP, de los Rios JM, Gotuzzo E, Vasilyeva I, et al. Multidrug-resistant tuberculosis and culture conversion with bedaquiline. N Engl J Med. 2014;371(8):723-32.

26. Chauke T, Netshikweta L, Netshandama VO, Nyathi L, Tshitangano TG and Olanivi FC. Proposed Guidelines to Minimise Multi-Drug Resistant Tuberculosis Treatment Default in a Multi-Drug Resistant Unit of Limpopo Province, South Africa. Afr J Infect Dis. 2018;12(2):55-65.

27. Liu Q, Lu P, Martinez L, Yang H, Lu W, Ding X, et al. Factors affecting time to sputum culture conversion and treatment outcome of patients with multidrug-resistant tuberculosis in China. BMC Infect Dis. 2018;18(1):114.

28. Musteikiene G, Miliauskas S, Zaveckiene J, Zemaitis M, Vitkauskiene A. Factors associated with sputum culture conversion in patients with pulmonary tuberculosis. Medicina (Kaunas). 2017;53(6):386-93.

29. Alene KA, Viney K, Yi H, McBryde ES, Yang K, Bai L, et al. Comparison of the validity of smear and culture conversion as a prognostic marker of treatment outcome in patients with multidrug-resistant tuberculosis. PLoS One. 2018;13(5):e0197880.

30. Te Riele JB, Buser V, Calligaro G, Esmail A, Theron G, Lesosky M, et al. Relationship between chest radiographic characteristics, sputum bacterial load, and treatment outcomes in patients with extensively drug-resistant tuberculosis.
Int J Infect Dis. 2019;79:65-71.

31. Caetano Mota P, Carvalho A, Valente I, Braga R, Duarte R. Predictors of delayed sputum smear and culture conversion among a Portuguese population with pulmonary tuberculosis. Portuguese journal of pulmonology 2012;18(2):72-9.

32. Sarin R, Singla N, Vohra V, Singla R, Puri MM, Munjal S, et al. Initial experience of bedaquiline implementation under the National TB Programme at NITRD, Delhi, India. The Indian journal of tuberculosis. 2019;66(1):209-13.

33. Moodley R, Godec TR, Team ST. Short-course treatment for multidrug-resistant tuberculosis: the STREAM trials. Eur Respir Rev. 2016;25(139):29-35.

34. Trebucq A, Decroo T, Van Deun A, Piubello A, Chiang CY, Koura KG, et al. Short-Course Regimen for Multidrug-Resistant Tuberculosis: A Decade of Evidence. Journal of clinical medicine. 2019;9(1).

35. Nunn AJ, Rusen ID, Van Deun A, Torrea G, Phillips PP, Chiang CY, et al. Evaluation of a standardized treatment regimen of anti-tuberculosis drugs for patients with multi-drug-resistant tuberculosis (STREAM): study protocol for a randomized controlled trial. Trials journal. 2014;15:353.

36. Sotgiu G, Migliori GB. Effect of the short-course regimen on the global epidemic of multidrug-resistant tuberculosis. Lancet Respir Med. 2017;5(3):159-61.

37. Definitions and reporting framework for tuberculosis – 2013 revision (updated December 2014 and January 2020) [Internet]. WHO. 2013 [Date accessed 27/04/2020]. Available from: https://apps.who.int/iris/bitstream/handle/10665/79199/9789241505345_eng.pdf?sequence=1&isAllowed=y.

CHAPTER 2: SUBMISSIBLE ARTICLE

2.1 Title:

Retrospective analysis of time to smear and culture conversion and treatment outcomes of rifampicin resistant tuberculosis patients treated with long and short course regimens at Tshepong Hospital

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2.1.3 Short title:

Comparison of short and long rifampicin resistant TB treatment regimens in a programmatic setting

2.1.4 Conflict of interest:

Nil

2.1.5 Keywords:

MDR TB, short course, long course, smear conversion, culture conversion, treatment outcomes, bedaquiline

2.1.6 Word count:

3778

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248

2.2 Abstract

2.2.1 Background:

Shortened treatment regimens and novel therapies have become available for programmatic adoption due to toxicities and the prolonged duration of treatment required for drug resistant (DR) TB. Sputum smear and culture conversion to negative and successful treatment outcomes are important parameters to assess treatment effectiveness.

2.2.2 Objective:

To compare responses and outcomes between short and long course DR TB treatment regimens at Tshepong Hospital, Klerksdorp, South Africa.

2.2.3 Methods:

A retrospective review was conducted of patients diagnosed with rifampicin resistance and who were also smear and culture positive for *Mycobacterium tuberculosis* between January 2015 and June 2018. We compared patients receiving short course regimens and long course regimens using historical controls.

2.2.4 Results:

Data from 285 of 1399 DR TB patients' records was analysed; 39.2% were on short course DR treatment, 61.8% on long course. Short course participants were less likely to smear convert at 2 months (42.2%), compared to those on long regimen (31.8%, *p=0.0209*) but culture conversion at 2 months was similar (45.9% v 47.2%, *p=0.7682*). A higher proportion of patients receiving short course treatment were cured or completed treatment (71.6% vs. 58.0%, *p=0.021*), and short course patients were less likely to have died (7.3% vs 22.7%, *p=0.0007*).

2.2.5 Conclusion:

There was no statistical difference in time to culture conversion between the two treatment groups, however, short DR TB regimen was associated with better outcomes and significantly lower mortality. Thus, advent of shorter and injection free regimens is a welcome development in the global fight against drug resistant TB.

2.3 Introduction

Mycobacterium tuberculosis (MTB) has co-existed with humans for millennia and typically affects the lungs causing pulmonary tuberculosis (TB), but can also be extra pulmonary, affecting any organ system.(1) One third of the world's population is estimated to be infected with the bacillus, 5 - 15% of which will subsequently develop TB, and those in immunosuppressive states are at a far higher risk of developing the disease.[1]

After evading the immune system, MTB lies dormant in the lungs as latent TB, and progression to the disease is largely controlled by the interplay amongst individual immune system and the pathogenicity of the bacilli.[2] Ever since infecting humans, MTB has presented multiple genomic mutations, some of which affect the genes against which anti-tuberculous drugs work, thereby showing phenotypic resistance to them.[3, 4] Resistance to at least rifampicin, with or without resistance to other drugs defines rifampicin resistance (RR) TB. Multidrug-resistant TB (MDR TB), is defined as any mycobacterium infection resistant to the two main first line drugs, rifampicin and isoniazid. Worldwide, 4.1% of index cases, and 19% of prior treated drug susceptible cases, have MDR TB. In 2016, 3.4% of index cases and 7.1% of prior treated cases had MDR TB in South Africa.[1] Treatment of drug sensitive TB employs rifampicin, ethambutol, isoniazid, and pyrazinamide for 2 months, followed by rifampicin and isoniazid for 4 months[5], with a success rate of 83%.[6]

However, RR makes TB treatment more difficult, with low treatment success rates that range between 49 and 68%.[6, 7] Conventionally, RR TB treatment is lengthy, costly, and presents patients with both a high pill burden, and potential toxicities.[8] Approximately 70% of adults with MDR TB in South Africa are co-infected with HIV, complicating treatment [6, 9]. Due to the costly nature of RR TB treatments, they account for approximately 40% of the resources allocated to controlling TB in South Africa. This necessitates the prioritisation of prevention, early diagnosis, and effective treatment.[10, 11] As a result, a combination of novel and repurposed drugs have been included in novel short course regimens to improve adherence and attain better outcomes. But as yet, there is a paucity of data on the real-world effectiveness of short course regimens in South Africa.

In 2016, the World Health Organization (WHO) recommend the adoption of short treatment regimens for selected drug resistant TB patients.[12] This has prompted at least 35 countries, South Africa included, to adopt the new guidelines which use the novel drugs, bedaquiline and

delamanid. Higher treatment success, and lower relapse rates were seen in patients on short regimens as compared to the conventional long course regimens.[8] Standardised, long course drug resistant TB treatment in South Africa (2016) was composed of a 6 months intensive phase of moxifloxacin, kanamycin, ethionamide, terizidone and pyrazinamide, followed by a continuation phase with four other drugs that exclude kanamycin, for 18 to 24 months.[13] Current guidelines for short course regimens consist of linezolid for 2 months, high doses of INH for 4 to 6 months, bedaquiline for 6 to 9 months, and 9 months of levofloxacin, clofazimine, pyrazinamide and ethambutol.[14] Whereas, long course regimens comprise 6 to 8 months of linezolid, bedaquiline, levofloxacin, clofazimine and terizidone, followed by 12 months of levofloxacin, clofazimine and terizidone.[14]

Even short, affordable and well tolerated regimens for MDR and XDR TB namely bedaquiline, pretomanid and linezolid (BPAL) and bedaquiline, pretomanid, moxifloxacin and pyrazinamide (BPaMZ) were proposed by the TB Alliance in April 2019, but are yet to be widely adopted.[15]

Patients excluded from short course regimens include those who exhibit resistance to fluoroquinolones and/or second line injectable drugs (SLID); those who should be treated as pre-extensively drug resistant (Pre-XDR) or XDR; those who are pregnant; who have extra pulmonary TB; who had exposure to second line drugs in the short course for more than a month; and those who are intolerant to any drug in the short regimen.[16]

Recommendations for the short MDR TB regimen was based on observational studies in Bangladesh, Uzbekistan, Swaziland, Cameroon, Niger and 7 other sub-Saharan African countries.[8, 12] The medium and long-term effects of implementing short course regimens are uncertain, but the incidence of MDR TB is optimistically projected to decrease by as much as 23% by the year 2024, compared to projections with the continued use of long term regimens.[17, 18]

Time to culture conversion is a useful marker in the prediction of therapeutic efficacy in drug resistant TB patients, because non-conversion at the end of the intensive phase is strong indication of unfavourable outcomes.[19] The initial smear burden is a vital predictor of culture conversion time.[20] However, for the purposes of both monitoring and predicting possible outcomes, using sputum smear and culture conversion together is recommended.[21]

Data available on measures of success of the short course compared to long course under programmatic settings are limited, and publications on the outcomes of the short course have

primarily relied only on observational studies. The objective of this analysis was to evaluate and compare outcomes of short and long DR TB treatment regimens in a programmatic setting at Tshepong Hospital, including smear and culture conversion.

2.4 Methods

A retrospective hospital-based cohort study was conducted, abstracting data from the records of eligible patients who were both diagnosed with rifampicin mono-resistant or MDR-TB, and met other inclusion criteria at Tshepong Hospital in Klerksdorp, between January 2015 and June 2018. (Fig. 2.1 shows the participant disposition flow chart)

The main outcome measures, times to smear and culture conversion, were measured from the date of drug resistant TB treatment initiation, to the date of sputum collection of the first of two successive negative smear and culture conversions respectively. Patients with negative initial smear and culture conversions were excluded from the study since these values would have been necessary for the calculation of conversion times. Treatment outcomes were as per the hospital records made by the treating clinicians at the hospital. South Africa also has a high TB and HIV coinfection burden (70%), and so analysed the effect of HIV on the two treatment regimens.

The study was sanctioned by the University of Witwatersrand Medical Human Research Ethics Committee (Ethics authorisation number - M181128).

2.5 Statistical Measurements

2.5.1 Demographic and clinical data

Demographic data collected consisted of sex, age (in years) and weight. Four age categories were created, (18-24, 25-34, 35-44 and 45+ years). Clinical data included HIV status, CD4 count, baseline viral load, and viral load at the end of drug resistant TB treatment, albumin, haemoglobin and creatinine. Microbiological data included baseline sputum Gene Xpert, smear density, and culture results. Initial chest x-rays findings were characterised as either cavitary or non-cavitary.

2.5.2 TB treatment

TB treatment was categorised as either long course or short course. Long course treatment included patients who were initiated on drug resistant TB treatment between 2015 and 2016, whereas short course comprised patients treated between 2017 and 2018. Patients treated with long course between 2017 and 2018 were excluded as outcomes were not available at the time the data was abstracted.

2.6 Data Analysis

Categorical data was analysed and presented as frequency and percentages for overall and stratified by short course and long course treatments respectively. Descriptive statistics construed baseline demographics and clinical characteristics stratified by treatment group. The statistical comparison between short course and long course treatments was assessed using Pearson's chi-squared test, while Fisher's exact test assessed sparse data. Continuous measures were assessed using medians and inter-quartile ranges (IQR) stratified into the two groups and compared both statistically and non-parametrically using the Kruskal-Wallis test. Time to smear and culture conversion of patients on both short course and long course treatments were evaluated using Kaplan-Meier survival curves. To compare the differences in time to smear and culture conversion between the two groups, a log-rank test was used on the evaluated curves. The two groups' curves were compared at 2, 4 and 6 months of TB treatment. Cox proportional hazard regression was used to determine factors associated with time to smear and culture conversion between the two groups at 2, 4 and 6 months of TB treatment for all patients, and for those with HIV. Risk factors were determined at both univariate and multivariate levels. A backward selection procedure was used to determine the final multivariate model, adjusting for covariates. Entire statistical assay was done in SAS Enterprise Guide 7.1.

2.7 Results

2.7.1 Participant Disposition

1399 files were screened, 905 patients who received long course from 2015 to 2016, and 494 short course from 2017 to 2018. A total of 1114 files were excluded, leaving a final enrolment of 285 files:176 on long course (2015-2016) and 109 on short course (2017-2018).

Of the 1114 files excluded, 578 were AFB negative at baseline, 4 had no AFB at baseline, 75 had culture negatives at baseline, 15 had extra pulmonary TB, 55 were on fewer than 30 days of treatment, 1 had relapsed MDR TB, 21 had missing records, 1 had INH mono resistant TB, 64 were enrolled in clinical trials, 58 had started treatment at Tshepong but subsequently referred to follow centres, 6 were treated between 2017 and 2018 but under the long course regimen, 16 were reinitiated after defaulting on treatments, 20 had drug sensitive TB, 91 were under 18 years of age, 60 had Pre-XDR TB and 49 had XDR-TB. (Fig. 2.1). Of the patients analysed who were taking long course, none was switched to the shorter regimen.

2.7.2 Demographic characteristics

Data from 285 patients was analysed, 38.2% (*n=109/285*) were on short course treatment, 61.8% (*n=176/285*) were on long course treatment. Overall, the majority of patients were male (65.3%, n=186/285), and between 35 - 44 years of age (32.6%, *n=93/285*). (Table 2.1) Those on short course treatment were significantly older than patients of the long course treatment (median [IQR] age 39.0 [IQR: 34.0-50.0] years vs. median [IQR] age 36.0 [IQR: 31.0-44.0] years; *p=0.0021*).

2.7.3 Clinical characteristics

Rifampicin resistance on Xpert MTB/RIF was detected in 90.9% (*258/285*). HIV coinfection was 77.2% (*220/285)*, 77.1% (84/109) for short course and 77.3% (136/176) for long course. CXR cavitation was seen in 63.3% (*n=174/285*) and 50.5% (*n=144/285*) received bedaquiline. (Table 2.2.1-3). Patients on short course treatment had higher CD4 counts (median [IQR] 212 cells/ml^3 [110-330 cells/ml^3] vs. median [IQR] 148 cells/ml^3 [41-290 cells/ml^3], *p=0.0049*), higher levels of albumin (median [IQR] 31.0 g/l [27.0-36.0 g/l] vs. median [IQR] 27.0 g/l [23.0-34.0 g/l], *p=0.0001*) and higher haemoglobin (median [IQR]

11.5 g/dl [10.4-13.5 g/dl] vs. median [IQR] 10.7 g/dl [8.8-12.3 g/dl], *p=0.0007*) when compared to those receiving long course DR TB treatment. In addition, those on short course treatment were more likely to have CXR cavitation (80.2% vs. 53.5%, *p<0.0001*), more received bedaquiline (99.1% vs. 20.5%, *p<0.0001*) and more were switched from kanamycin to bedaquiline (81.5% vs. 13.9%, *p<0.0001*) when compared to long course treatment. Conversely, long course patients were more likely to have received kanamycin (44.9% vs. 24.8%, *p=0.0006*). (Table 2.3)

2.7.4 Time to smear and culture conversion of drug resistant TB patients on short course and long course treatments

Figure 2.2.1-3 shows that participants in the short course treatment were less likely to smear convert earlier, at 2 months, compared to those in long course treatment (42.2% vs 31.8%, *p=0.0209*) but at 4 months no statistically significant difference was noted (12.8% vs 12.5%, *p=0.2695)*. There was no difference in culture conversion between short course and long course treatments at 2 months (45.9% v 47.2%, *p=0.7682*) and at 4 months (20.2 vs 27.8, *p=0.2329*) (Figure 2.3). Culture reversion was noted in 7% (*n=6/85*) of patients treated with short course, vs 13.5% (*n=20/148*) of those treated with the long course.

2.7.5 Treatment outcomes

Overall, in this cohort, treatment success (cured and completed treatment) was observed in 63.2% (*n=180/285*); 16.8% (*n=48/285*) died; 13.3% (*n=38/285*) were lost to follow-up, 4.9% (*n=14/285*) were not evaluated, and 1.8% (*n=5/285*) were treatment failures.

Short course treatment had significantly a higher proportion of patients with treatment success (71.6% vs. 58.0%, *p=0.021*) when compared to the long course. Patients in short course treatment were less likely to die (7.3% vs 22.7%, *p=0.0007*) compared to those on long course treatment. There were no statistical differences in those who were lost to follow up, not evaluated and with treatment failures. (Table 2.4)

2.7.6 Effect of HIV status on smear and culture conversion on the two groups

There was no significant statistical difference between HIV positive and HIV negative patients in smear (37.5% vs 30.1%, *p=0.2632*) and culture (45.0% vs 47.8%, *p=0.6583*) conversion at

2 months in both short course and long course treatments (Fig. 2.4 and 2.5). No difference was also noted at 4 and 6 months of TB treatment.

2.7.7 Patients that used either kanamycin or bedaquiline or both in long course and short course treatments

Patients who received bedaquiline only, kanamycin only, and both bedaquiline and kanamycin were 36.5% (*n=104/285*), 22.8% (*n=65/285*), and 14.4% *(n=41/285*) respectively. Short course patients were more likely to have received bedaquiline only (75.2% vs. 12.5%; *p<0.0001*), and both bedaquiline and kanamycin (23.9% vs. 8.5%, *p=0.0003*), compared to long course. (Table 2.3)

2.7.8 Factors associated with time to smear and culture convert at 2, 4 and 6 months of TB treatment

Females (HR: 1.471, 95% CI: 1.053-2.056; *p=0.0236*) were more likely to smear convert by 2 months of treatment. (Table 2.5) The presence of 2+ and 3+ initial AAFB positivity was associated with being smear positive at 2 months of treatment (HR: 0.414, 95% CI: 0.239-0.715; *p=0.0016*) and (HR: 0.339, 95% CI: 0.208-0.552; *p<0.0001*) respectively. Similarly, being culture positive at 2 months of treatment was associated with the presence of 2+ (HR: 0.352, 95% CI: 0.167-0.741; *p=0.0060*) and 3+ (HR: 0.482, 95% CI: 0.264-0.879; *p=0.0173*) initial AAFB positivity (Table 2.5). Those who were on short course treatment (HR: 1.432, 95% CI: 1.1014-2.022, *p=0.0414*) were associated with culture conversion at 4 months of TB treatment whereas age (HR: 0.984, 95% CI: 0.969-0.999; *p=0.0387*), 1+ (HR: 0.550, 95% CI: 0.319-0.947*; p=0.0312*) and 2+ (HR: 0.494, 95% CI: 0.277-0.882; *p=0.0171*) initial AAFB positivity were associated with prolonged culture conversion at 4 months of treatment (Table 2.6).

Figure 2.6 shows that participants who were on bedaquiline were more likely to smear convert at 2 and 4 months (53.8% vs 39.8%, *p=0.0134* and 17.3% vs 9.9%, *p=0.0149* respectively) compared to those not on bedaquiline. Those who were on kanamycin were also more likely to smear covert at both 2 and 4 months compared to those not on kanamycin (48.2% vs 33.8%, *p=0.0248* and 14.5% vs 6.25%, *p=0.0087*). Bedaquiline based, kanamycin based as well as bedaquiline and kanamycin based regimen had no effect on culture conversion.

2.8 Discussion

This retrospective study was conducted to determine the effectiveness of short regimens in the treatment of drug resistant TB under programmatic settings. We analysed and noted that times to culture conversion were similar for patients treated with short- and long-term regimens. Additionally, HIV status did not appear to affect smear and culture conversion times in both treatment groups. Expectedly, outcomes were more favourable in the short course group as compared to the long course group with treatment success at 71.6% vs 58%, and deaths at 7.3% vs 22.7% respectively.

We found no significant statistical difference in culture conversion between the two treatment groups (*p=0.076*). These findings suggest that the two regimens are similar in early treatment efficacy. Results from the stage 1 *STREAM* study also noted that the short regimen is as close in effectiveness as the conventional treatment.[14, 22, 23] These similarities support the adoption of short course treatments in national TB programs. Possible explanations for the similarity in outcomes of smear and culture conversion include the fact that the practice setup did not change in-between the two treatment groups. The introduction of bedaquiline in our analysis seems not to have had an effect on time to culture conversion. In our study, patients who were on bedaquiline had 2-month smear and culture conversion rates of 60% and 47.6% respectively. 2-month sputum smear and culture conversion rates of 81.1% and 56.7% respectively were noted in regimens containing bedaquiline. In the study by Borisov *et al* [24], bedaquiline was part of the regimens together with other potent anti-TB drugs such as linezolid and carbapenems, this was not the case with the patients in our study. Diacon *et al* showed 6 months culture conversion times of 79.9% in patients where bedaquiline had been added to the baseline treatment.[7] However, none of these studies was comparative.

HIV status alone did not appear to have an effect on time to smear and culture conversion in the two treatment groups. Adjusted log rank p values showed no significant statistical difference in time to smear and culture conversion between the two groups after controlling for the HIV status of patients. The data is comparable to the James C. *et al* and Mohr *et al* studies, both of which concluded that MDR TB patients co-infected with HIV had similar culture conversion rates to HIV negative individuals.[25, 26] Magis-Escurra *et al* also had similar findings [27], but Shibabaw *et al* suggested that being HIV negative was associated with delayed culture conversion.[28] The data provides reassurance that the introduction of short regimens to national TB guidelines will not have an adverse impact on HIV infected individuals, while

concerns of drug interactions affecting outcomes of TB treatment can also be allayed. HIV viral load at the end of treatment would be of interest for further inquiry in order to prove that the short treatment regimens have no impact on it.

On the effect of gender on smear and culture conversion, Caetano *et al* postulated that the delays seen in males may largely be due to greater use of alcohol and tobacco amongst men.[29] We were able to demonstrate in the univariate analysis that women were more likely to smear convert earlier than men (*p=0.044*), however this was not the case with culture conversion, where there was no statistical difference. Body weight in the range 50 - 59kg was associated with early smear conversion (*p=0.027*) but not culture conversion. That was in contrast to other manuscripts which suggest that being underweight is associated with delayed culture conversion.[30] In Shibabaw *et al's* study, being underweight and resistant to both RIF and INH with low creatinine was statistically significant for delayed sputum culture conversion.[28] According to Liu *et al*, delayed smear and culture conversion in drug resistant TB is associated with resistance to fluoroquinolones, cigarette smoking, ethanol use, and initial smear burden.[19] Caetano *et al* demonstrated delays in smear and culture conversions in patients that were above 50 years, male, and who had bilateral chest x-rays changes.[29]

Cavitation on chest radiographs is an independent predictor of time to culture convert in MDR-TB patients, and a separate risk factor for adverse outcomes.[31] In our analysis, cavitary CXR was associated with delayed smear and culture conversion at 2 months under univariate analysis, (*p=0.02* and *p=0.06* for smear and culture conversions respectively). There was no statistically significant difference in time to smear and culture conversion between cavitary and non-cavitary TB under multivariate analysis (*p=0.54* and *p=0.251*). However, the fact that only smear positive patients were included in this study may have skewed the data in favour of cavitary TB.

Higher proportions of patients with successful treatments were from the short course group (71.6% vs 58%). Patients in the short course treatment were also less likely to have died (7.34% vs 22.73%). This is comparable to global treatment success rates for long course treatment, which range between 49 and 68%.[6, 7] WHO touts a potential short course treatment cure rate of 83.7% in comparison to 50% for the conventional long course treatment.[10] The Ahuja *et al* meta-analysis of MDR TB patients treated under long course in 32 observational studies done in 23 countries, demonstrated a success rate of 54%.[32] Trebucq *et al*, a multi-country prospective observational study done in West and Central Africa had 72.4% of short course

patients declared cured, 9.2% of them completing treatment, and a success rate of 81.6% for the course.[33] Similarly Harouna *et al*, carried out under programmatic settings, reported a treatment success rate of 88% in adults treated with the short course (*n=110*).[34]

Better outcomes observed with short regimens could be explained in part by the introduction of bedaquiline and clofazimine; the former is associated with early culture conversion, and the latter with reductions in treatment length.[7, 35] Due to toxicity concerns and limited data on efficacy, terivalidin was replaced by Clofazimine in the short regimen.[36] In a retrospective study done in South Africa, the use of bedaquiline in MDR and XDR TB regimen was associated with a 3-fold decrease in mortality compared to regimens without.[37] In a separate study, bedaquiline introduction contributed to earlier culture conversions in patients treated with short regimens.[34] Another contributing factor to better outcomes in short regimens is the requirement for monthly ECGs. This likely facilitated closer monitoring which may have improved adherence. Patients on injectables as outpatient were required to attend the local clinic on a daily basis and it is uncertain how this affected compliance and outcomes. Also, we note that 42.6% patients of patients on long course regimens did not receive either kanamycin or bedaquiline as part of their treatment. This could have either been an omission in the data capturing process, or simply common practice at the treating hospital to abstain from injectables.

2.9 Limitations of the Study

For this retrospective study, the data used was originally collected for clinical care, and as such, not all the information relevant to the study was available for analysis. Files that qualified for analysis often had missing data. There was no control over the way interventions were administered. The two groups studied were from two different eras, possibly resulting an underlying secular trend, confounding the results we report, and irrespective of receipt to short course, patients may have improved outcomes in later eras. Short course cohort compared to long course had higher baseline CD4 counts, higher baseline albumin and higher baseline creatinine thus at baseline better outcomes would be expected in the former. Patients who were on the short course may have been monitored more carefully due to the introduction of novel drugs resulting in a selection and attention biases. Patients on bedaquiline required monthly electrocardiograms (ECG), giving rise to attention bias. Despite these limitations, this is the

first and largest study of its kind in South Africa, i.e., a study comparing the short- and long-term regimens in the treatment of drug resistant TB. Its findings therefore reassure the health sector about the adoption short course regimens in the national treatment guidelines.

2.10 Conclusion

There was no statistical difference in time to culture conversion between the two treatment groups. However, short regimen was associated with better treatment success and significantly fewer deaths. HIV status alone did not appear to have an effect on the time to smear and culture conversion. The study supports adoption of short regimens into nationwide treatment guidelines. Shorter, injection free regimen is a welcome development to patients with drug resistant TB.

2.11 References – Chapter 2

1. Global tuberculosis report 2017 [Internet]. WHO. [date accessed 10/04/2020]. Available from: https://www.who.int/tb/publications/global_report/gtbr2017_main_text.pdf.

2. Fox GJ, Schaaf HS, Mandalakas A, Chiappini E, Zumla A, Marais BJ. Preventing the spread of multidrug-resistant tuberculosis and protecting contacts of infectious cases. Clin Microbiol Infect. 2017;23(3):147-53.

3. Forrellad MA, Klepp LI, Gioffre A, Sabio y Garcia J, Morbidoni HR, de la Paz Santangelo M, et al. Virulence factors of the Mycobacterium tuberculosis complex. Virulence. 2013;4(1):3-66.

4. Dookie N, Rambaran S, Padayatchi N, Mahomed S, Naidoo K. Evolution of drug resistance in Mycobacterium tuberculosis: a review on the molecular determinants of resistance and implications for personalized care. J Antimicrob Chemother. 2018;73(5):1138-51.

5. National Tuberculosis Management Guidelines 2014 South Africa [Internet]. 2014 [date accessed 10/04/2020]. Available from: https://aidsfree.usaid.gov/sites/default/files/tb_south-africa_adult_2014.pdf.

6. Farley JE, Ndjeka N, Kelly AM, Whitehouse E, Lachman S, Budhathoki C, et al. Evaluation of a nurse practitioner-physician task-sharing model for multidrug-resistant tuberculosis in South Africa. PLoS One. 2017;12(8):e0182780.

7. Diacon AH, Pym A, Grobusch MP, de los Rios JM, Gotuzzo E, Vasilyeva I, et al. Multidrug-resistant tuberculosis and culture conversion with bedaquiline. N Engl J Med. 2014;371(8):723-32.

8. Falzon D, Schunemann HJ, Harausz E, Gonzalez-Angulo L, Lienhardt C, Jaramillo E, et al. World Health Organization treatment guidelines for drug-resistant tuberculosis, 2016 update. Eur Respir J. 2017;49(3).

9. Farley JE, Ram M, Pan W, Waldman S, Cassell GH, Chaisson RE, et al. Outcomes of multi-drug resistant tuberculosis (MDR-TB) among a cohort of South African patients with high HIV prevalence. PLoS One. 2011;6(7):e20436.

10. Dheda K, Cox H, Esmail A, Wasserman S, Chang KC, Lange C. Recent controversies about MDR and XDR-TB: Global implementation of the WHO shorter MDR-TB regimen and bedaquiline for all with MDR-TB? Respirology (Carlton, Vic). 2018;23(1):36-45.

11. Schnippel K, Rosen S, Shearer K, Martinson N, Long L, Sanne I, et al. Costs of inpatient treatment for multi-drug-resistant tuberculosis in South Africa. Tropical Medicine & International Health. 2013;18(1):109-16.

12. Global Tuberculosis Programme. WHO treatment guidelines for drug-resistant tuberculosis : 2016 update. [Internet]. WHO. 2016 [date accessed 10/04/2020]. Available from: http://apps.who.int/iris/bitstream.

13. Management of Drug-Resistant Tuberculosis 2013 [Internet]. WHO. 2013 [date accessed 10/04/2020]. Available from: https://www.idealhealthfacility.org.za/docs/National-Priority-Health-Conditions/Management%20of%20Drug-Resistant%20Tuberculosis%202013.pdf.

14. Global Tuberculosis report 2019 [Internet]. WHO. 2019 [date accessed 10/04/2020]. Available from: https://apps.who.int/iris/bitstream/handle/10665/329368/9789241565714-eng.pdf?ua=1.

15. Keam SJ. Pretomanid: First Approval. Drugs. 2019;79(16):1797-803.

16. Trauer JM, Achar J, Parpieva N, Khamraev A, Denholm JT, Falzon D, et al. Modelling the effect of short-course multidrug-resistant tuberculosis treatment in Karakalpakstan, Uzbekistan. BMC Med. 2016;14(1):187.

17. Sotgiu G, Migliori GB. Effect of the short-course regimen on the global epidemic of multidrug-resistant tuberculosis. Lancet Respir Med. 2017;5(3):159-61.

18. Kendall EA, Fojo AT, Dowdy DW. Expected effects of adopting a 9 month regimen for multidrug-resistant tuberculosis: a population modelling analysis. Lancet Respir Med. 2017;5(3):191-9.

19. Liu Q, Lu P, Martinez L, Yang H, Lu W, Ding X, et al. Factors affecting time to sputum culture conversion and treatment outcome of patients with multidrug-resistant tuberculosis in China. BMC Infect Dis. 2018;18(1):114.

20. Musteikiene G, Miliauskas S, Zaveckiene J, Zemaitis M, Vitkauskiene A. Factors associated with sputum culture conversion in patients with pulmonary tuberculosis. Medicina (Kaunas). 2017;53(6):386-93.

21. Alene KA, Viney K, Yi H, McBryde ES, Yang K, Bai L, et al. Comparison of the validity of smear and culture conversion as a prognostic marker of treatment outcome in patients with multidrug-resistant tuberculosis. PLoS One. 2018;13(5):e0197880.

22. Moodley R, Godec TR, Team ST. Short-course treatment for multidrug-resistant tuberculosis: the STREAM trials. Eur Respir Rev. 2016;25(139):29-35.

23. Nunn AJ, Rusen ID, Van Deun A, Torrea G, Phillips PP, Chiang CY, et al. Evaluation of a standardized treatment regimen of anti-tuberculosis drugs for patients with multi-drug-resistant tuberculosis (STREAM): study protocol for a randomized controlled trial. Trials. 2014;15:353.

24. Borisov SE, Dheda K, Enwerem M, Romero Leyet R, D'Ambrosio L, Centis R, et al. Effectiveness and safety of bedaquiline-containing regimens in the treatment of MDR- and XDR-TB: a multicentre study. Eur Respir J. 2017;49(5).

25. Brust JC, Lygizos M, Chaiyachati K, Scott M, van der Merwe TL, Moll AP, et al. Culture conversion among HIV co-infected multidrug-resistant tuberculosis patients in Tugela Ferry, South Africa. PLoS One. 2011;6(1):e15841.

26. Mohr E, Cox V, Wilkinson L, Moyo S, Hughes J, Daniels J, et al. Programmatic

treatment outcomes in HIV-infected and uninfected drug-resistant TB patients in Khayelitsha, South Africa. Transactions of the Royal Society of Tropical Medicine and Hygiene. 2015;109(7):425-32.

27. Magis-Escurra C, Günther G, Lange C, Alexandru S, Altet N, Avsar K, et al. Treatment outcomes of MDR-TB and HIV co-infection in Europe. Eur Respir J. 2017;49(6).

28. Shibabaw A, Gelaw B, Wang SH, Tessema B. Time to sputum smear and culture conversions in multidrug resistant tuberculosis at University of Gondar Hospital, Northwest Ethiopia. PLoS One. 2018;13(6):e0198080.

29. Caetano Mota P, Carvalho A, Valente I, Braga R, Duarte R. Predictors of delayed sputum smear and culture conversion among a Portuguese population with pulmonary tuberculosis. 2012;18(2):72-9.

30. Putri FA, Burhan E, Nawas A, Soepandi PZ, Sutoyo DK, Agustin H, et al. Body mass index predictive of sputum culture conversion among MDR-TB patients in Indonesia. Int J Tuberc Lung Dis. 2014;18(5):564-70.

31. Te Riele JB, Buser V, Calligaro G, Esmail A, Theron G, Lesosky M, et al. Relationship between chest radiographic characteristics, sputum bacterial load, and treatment outcomes in patients with extensively drug-resistant tuberculosis. Int J Infect Dis. 2019;79:65-71.

32. Ahuja SD, Ashkin D, Avendano M, Banerjee R, Bauer M, Bayona JN, et al. Multidrug resistant pulmonary tuberculosis treatment regimens and patient outcomes: an individual patient data meta-analysis of 9,153 patients. PLoS Med. 2012;9(8):e1001300.

33. Trebucq A, Decroo T, Van Deun A, Piubello A, Chiang CY, Koura KG, et al. Short-Course Regimen for Multidrug-Resistant Tuberculosis: A Decade of Evidence. Journal of clinical medicine. 2019;9(1).

34. Harouna SH, Ortuno-Gutierrez N, Souleymane MB, Kizito W, Morou S, Boukary I, et

al. Short-course treatment outcomes and adverse events in adults and children-adolescents with MDR-TB in Niger. Int J Tuberc Lung Dis. 2019;23(5):625-30.

35. Padayatchi N, Gopal M, Naidoo R, Werner L, Naidoo K, Master I, et al. Clofazimine in the treatment of extensively drug-resistant tuberculosis with HIV coinfection in South Africa: a retrospective cohort study. J Antimicrob Chemother. 2014;69(11):3103-7.

36. Hwang TJ, Wares DF, Jafarov A, Jakubowiak W, Nunn P, Keshavjee S. Safety of cycloserine and terizidone for the treatment of drug-resistant tuberculosis: a meta-analysis. Int J Tuberc Lung Dis. 2013;17(10):1257-66.

37. Schnippel K, Ndjeka N, Maartens G, Meintjes G, Master I, Ismail N, et al. Effect of bedaquiline on mortality in South African patients with drug-resistant tuberculosis: a retrospective cohort study. Lancet Respir Med. 2018;6(9):699-706.

2.12 List of Tables

Table 1 Treatment outcomes for RR-TB/MDR-TB/XDR-TB patients treated using second-line treatment

Outcome	Definition
Cured	Treatment completed as recommended by the national policy without evidence of failure and three or more consecutive cultures taken at least 30 days apart are negative after the intensive phase
Treatment completed	Treatment completed as recommended by the national policy without evidence of failure but no record that three or more consecutive cultures taken at least 30 days apart are negative after the intensive phase
Treatment failed	Treatment terminated or need for permanent regimen change of at least two anti-TB drugs because of: lack of conversion by the end of the intensive phase or bacteriological reversion in the continuation phase after conversion to negative, or evidence of additional acquired resistance to fluoroquinolones or second-line injectable drugs, or adverse drug reactions (ADRs)
Died	A patient who dies for any reason during treatment.
Lost to follow-up	A patient whose treatment was interrupted for 2 consecutive months or more.
Not evaluated	A patient for whom no treatment outcome is assigned. This includes cases "transferred out" to another treatment unit and whose treatment outcome is unknown.
Treatment success	The sum of cured and treatment completed

Culture conversion is considered when two consecutive cultures, taken at least 30 days apart, are found to be negative, in which case the specimen collection date of the first negative culture is noted. Adapted from: https://apps.who.int/iris/bitstream/handle/10665/79199/9789241505345_eng.pdf?sequence=1&isAllowed=y.

Table 2.1 Demographic characteristics by short course and long course treatments

Variable	Overall	Short Course	Long Course	P-Value
Number of enrolment (n)	285	109	176	-
Gender				
Male (%)	186/285 (65.26)	72/109 (66.06)	114/176 (64.77)	
Age (years)				
18-24	26/285 (9.12)	7/109 (6.42)	19/176 (10.80)	0.2127
25-34	83/285 (29.12)	21/109 (19.27)	62/176 (35.23)	0.0039
35-44	93/285 (32.63)	40/109 (36.70)	53/176 (30.11)	0.2493
45+	83/285 (29.12)	41/109 (37.61)	42/176 (23.86)	0.0130
Median (IQR)	37.0 (32.0-46)	39.0 (34.0-50)	36.0 (31.0-44)	0.0021
Weight (kg)				
Median (IQR)	50.0 (43.0-57)	49.0 (43.0-58.5)	50.0 (43.0-57)	0.9272

Table 2.2.1 Clinical characteristics by short course and long course

Variable	Overall	Short Course	Long Course	P-Value
No. of enrolment (n)	285	109	176	-
Gene Xpert				
Negative (%)	2/284 (0.70)	1/109 (0.92)	1/175 (0.57)	0.7345
Not Available (%)	24/284 (8.45)	13/109 (11.93)	11/175 (6.29)	0.0965
Positive Rif Resistant (%)	258/284 (90.85)	95/109 (87.16)	163/175 (93.14)	0.0889
HIV Status				
Positive (%)	220/285 (77.19)	84/109 (77.06)	136/176 (77.27)	
CD4 Count (cells/ml^3)				
<200	124/220 (56.36)	38/84 (45.24)	86/136 (63.24)	0.0089
200 - <350	51/220 (23.18)	26/84 (30.95)	25/136 (18.38)	0.0318
≥350	45/220 (20.45)	20/84 (23.81)	25/136 (18.38)	0.3323
HIV VL Baseline (copies/ml)				
<20	42/185 (22.70)	14/72 (19.44)	28/113 (24.78)	0.4919
20 - <1000	39/185 (21.08)	18/72 (25.00)	21/113 (18.58)	
≥1000	104/185 (56.22)	40/72 (55.56)	64/113 (56.64)	
HIV VL at end of MDR TB treatment (copies/ml)				
<20	49/133 (36.84)	19/57 (33.33)	30/76 (39.47)	0.4675
20 - <1000	35/133 (26.32)	22/57 (38.60)	13/76 (17.11)	0.0053
≥1000	49/133 (36.84)	16/57 (28.07)	33/76 (43.42)	0.0693
Albumin (g/l)				
Median (IQR)	29.0 (24.0-35)	31.0 (27.0-36)	27.0 (23.0-34)	0.0001
Haemoglobin (g/dl)				
Median (IQR)	11.1 (9.35-12.7)	11.5 (10.4-13.5)	10.7 (8.80-12.3)	0.0007
Creatinine (µmol/L)				
Median (IQR)	62.0 (51.0-81)	64.5 (51.0-81)	61.0 (52.0-79)	0.8785

Table 2.2.2 Clinical characteristics by short course and long course

Variable	Overall	Short Course	Long Course	P-Value
CXR				
Features of Tb (%)	276/285 (96.84)	101/109 (92.66)	175/176 (99.43)	0.0015
No Features of Tb (%)	7/285 (2.46)	6/109 (5.50)	1/176 (0.57)	0.0089
Not Available (%)	2/285 (0.70)	2/109 (1.83)	0/176 (0.00)	-
Cavitary (%)	174/275 (63.27)	81/101 (80.20)	93/174 (53.45)	<.0001
Bedaquiline received?				
Yes (%)	144/285 (50.53)	108/109 (99.08)	36/176 (20.45)	<.0001
Kanamycin received				
Yes (%)	106/285 (37.19)	27/109 (24.77)	79/176 (44.89)	0.0006
Kanamycin changed to Bedaquiline				
Yes (%)	33/106 (31.13)	22/27 (81.48)	11/79 (13.92)	<.0001
Reasons for Kanamycin to Bedaquiline switch				
Hearing loss (%)	21/33 (63.63)	15/22 (68.18)	6/11 (54.55)	0.0028
Completed 6 months (%)	2/33 (6.06)	1/22 (4.55)	1/11 (9.09)	0.7818
Defaulted (%)	1/33 (3.03)	0/22 (0.00)	1/11 (9.09)	-
Unknown (%)	3/33 (9.09)	0/22 (0.00)	3/11 (27.27)	-
Not captured (%)	6/33 (18.18)	6/22 (27.27)	0	-
HAART prior to MDR TB treatment				
Defaulted (%)	43/241 (17.84)	20/106 (18.87)	23/135 (17.04)	0.7125
No (%)	32/241 (13.28)	6/106 (5.66)	26/135 (19.26)	0.0020
Not Applicable (%)	21/241 (8.71)	21/106 (19.81)	0/135 (0.00)	-
Yes (%)	145/241 (60.17)	59/106 (55.66)	86/135 (63.70)	0.2055
HAART on MDR TB treatment				
Defaulted (%)	29/238 (12.18)	14/104 (13.46)	15/134 (11.19)	0.5958
No (%)	5/238 (2.10)	0/104 (0.00)	5/134 (3.73)	-
Not Applicable (%)	22/238 (9.24)	22/104 (21.15)	0/134 (0.00)	-
Yes (%)	182/238 (76.47)	68/104 (65.38)	114/134 (85.07)	0.0004

Table 2.2.3 Clinical characteristics by short course and long course

Variable	Overall	Short Course	Long Course	P-Value
Gene Xpert				
Negative (%)	3/284 (1.06)	2/109 (1.83)	1/175 (0.57)	0.1807
Not Done (%)	27/284 (9.51)	14/109 (12.84)	13/175 (7.43)	
Positive (%)	254/284 (89.44)	93/109 (85.32)	161/175 (92.00)	
If Gene Xpert positive				
Resistant (%)	235/254 (92.52)	86/93 (92.47)	149/161 (92.55)	0.6586
Rifampicin inconclusive (%)	8/254 (3.15)	2/93 (2.15)	6/161 (3.73)	
Sensitive (%)	11/254 (4.33)	5/93 (5.38)	6/161 (3.73)	
Initial AAFB positivity				
Scanty (%)	34/283 (12.01)	8/108 (7.41)	26/175 (14.86)	0.0611
+ (%)	72/283 (25.44)	25/108 (23.15)	47/175 (26.86)	0.4865
++ (%)	54/283 (19.08)	27/108 (25.00)	27/175 (15.43)	0.0465
+++ (%)	123/283 (43.46)	48/108 (44.44)	75/175 (42.86)	0.7936
Culture				
Negative (%)	1/285 (0.35)	1/109 (0.92)	0/176 (0.00)	-
Not Done (%)	23/285 (8.07)	22/109 (20.18)	1/176 (0.57)	<.0001
Positive (%)	261/285 (91.58)	86/109 (78.90)	175/176 (99.43)	<.0001
Reflex test done				
Yes (%)	282/284 (99.30)	109/109 (100.0)	173/175 (98.86)	
AAFB				
Negative (%)	24/282 (8.51)	13/109 (11.93)	11/173 (6.36)	0.1027
Positive (%)	258/282 (91.49)	96/109 (88.07)	162/173 (93.64)	
If AAFB positive				
+ (%)	69/258 (26.74)	22/96 (22.92)	47/162 (29.01)	0.1919
++ (%)	49/258 (18.99)	19/96 (19.79)	30/162 (18.52)	
+++ (%)	111/258 (43.02)	48/96 (50.00)	63/162 (38.89)	
Scanty (%)	29/258 (11.24)	7/96 (7.29)	22/162 (13.58)	
Culture				

Variable	Overall	Short Course	Long Course	P-Value
Contaminated (%)	6/282 (2.13)	4/109 (3.67)	2/173 (1.16)	0.1127
Negative (%)	4/282 (1.42)	3/109 (2.75)	1/173 (0.58)	
Positive (%)	272/282 (96.45)	102/109 (93.58)	170/173 (98.27)	

Table 2.3 To determine the proportion of patients that used either kanamycin or bedaquiline or both in short course and long course

Variable	Overall	Short Course	Long Course	P-value
MDR TB Drug				
None (%)	75/285 (26.32)	0/109 (0.00)	75/176 (42.61)	-
Bedaquiline (%)	104/285 (36.49)	82/109 (75.23)	22/176 (12.50)	<.0001
Kanamycin (%)	65/285 (22.81)	1/109 (0.92)	64/176 (36.36)	<.0001
Kanamycin + Bedaquiline (%)	41/285 (14.39)	26/109 (23.85)	15/176 (8.52)	0.0003

Table 2.4 Treatment outcomes by short course and long course

Variable	Overall	Short Course	Long Course	P-value
Treatment Outcome - Overall				
Treatment success (%)	180/285 (63.16)	78/109 (71.56)	102/176 (57.95)	0.0207
Cured (%)	148/285 (51.92)	70/109 (64.22)	78/176 (44.32)	0.0011
Treatment completed (%)	32/285 (11.22)	8/109 (7.34)	24/179 (13.41)	0.1018
Died (%)	48/285 (16.84)	8/109 (7.34)	40/176 (22.73)	0.0007
Lost to follow-up (%)	38/285 (13.33)	18/109 (16.51)	20/176 (11.36)	0.2139
Not evaluated (%)	14/285 (4.91)	4/109 (3.67)	10/176 (5.68)	0.4450
Treatment failure (%)	5/285 (1.75)	1/109 (0.92)	4/176 (2.27)	0.3970
Treatment Outcome - Rif Mono (n=160)				
Treatment success (%)	102/160 (64.15)	41/57 (71.93)	61/103 (59.22)	0.1093
Died (%)	26/160 (16.35)	3/57 (5.26)	23/103 (22.33)	0.0051
Lost to follow-up (%)	20/160 (12.58)	10/57 (17.56)	10/103 (9.71)	0.1513
Not evaluated (%)	10/160 (5.66)	3/57 (5.26)	7/103 (6.80)	0.7013
Treatment failure (%)	2/160 (1.26)	0/57 (0.0)	2/103 (1.94)	-
Treatment Outcome - MDR (n=116)				
Treatment success (%)	71/116 (61.21)	33/48 (68.75)	38/68 (55.88)	0.1613
Died (%)	20/116 (17.24)	5/48 (10.42)	15/68 (22.06)	0.1021
Lost to follow-up (%)	18/116 (15.52)	8/48 (16.67)	10/68 (14.71)	0.7739
Not evaluated (%)	4/116 (3.45)	1/48 (2.08)	3/68 (4.41)	0.4985
Treatment failure (%)	3/116 (2.59)	1/48 (2.08)	2/68 (2.94)	0.7743

Treatment success = cured + treatment completed.

Table 2.5 Factors associated with time to smear and culture conversion at the end of months 2 of treatment

	Smear Conversion				Culture Conversion			
	Univariate		Multivariate		Univariate		Multivariate	
Variables	**HR 95% (CI)**	**P-Value**	**HR 95% (CI)**	**P-Value**	**HR 95% (CI)**	**P-Value**	**HR 95% (CI)**	**P-Value**
Gender								
Female	1.310 (0.950-1.805)	0.0995	1.471 (1.053-2.056)	0.0236	1.064 (0.712-1.59)	0.7611	-	-
Male	(ref)	-	-	-	(ref)	-	-	-
Age	0.992 (0.978-1.006)	0.2581	-	-	0.987 (0.969-1.006)	0.1765	0.985 (0.965-1.005)	0.1357
Weight	1.009 (0.996-1.022)	0.1809	1.009 (0.995-1.023)	0.1933	1.006 (0.991-1.022)	0.4186	-	-
TB treatment								
Long Course	1.465 (1.053-2.038)	0.0234	-	-	1.062 (0.711-1.586)	0.7699	-	-
Short Course	(ref)	-	-	-	(ref)	-	-	-
Gene Xpert								
Negative	(ref)	-	-	-	1.220 (0.170-8.755)	0.8430	-	-
Positive Rif Resistant	1.430 (0.200-10.21)	0.7213	-	-	(ref)	-	-	-
HIV Status								

	Smear Conversion				Culture Conversion			
	Univariate		Multivariate		Univariate		Multivariate	
Variables	**HR 95% (CI)**	**P-Value**	**HR 95% (CI)**	**P-Value**	**HR 95% (CI)**	**P-Value**	**HR 95% (CI)**	**P-Value**
Negative	(ref)	-	-	-	1.102 (0.714-1.7)	0.6609	-	-
Positive	1.263 (0.853-1.871)	0.2434	-	-	(ref)	-	-	-
Albumin	0.996 (0.980-1.013)	0.6452	-	-	0.989 (0.969-1.01)	0.3011	-	-
Haemoglobin	0.999 (0.989-1.009)	0.8160	-	-	1.004 (0.988-1.02)	0.6268	-	-
Creatinine	1.000 (0.998-1.002)	0.9490	-	-	1.300 (0.968-1.747)	0.0814	1.324 (0.988-1.775)	0.0606
CXR								
Cavitary	(ref)	-	-	-	(ref)	-	-	-
Non Cavitary	1.467 (1.064-2.023)	0.0193	-	-	1.466 (0.983-2.185)	0.0605	1.364 (0.897-2.074)	0.1461
Initial AAFB positivity								
Scanty	(ref)	-	-	-	(ref)	-	-	-
+	0.620 (0.382-1.006)	0.0530	0.650 (0.394-1.071)	0.0910	0.615 (0.344-1.099)	0.1009	0.546 (0.288-1.036)	0.0640
++	0.411 (0.240-0.703)	0.0012	0.414 (0.239-0.715)	0.0016	0.336 (0.167-0.677)	0.0023	0.352 (0.167-0.741)	0.0060
+++	0.323 (0.200-0.521)	<.0001	0.339 (0.208-0.552)	<.0001	0.439 (0.252-0.768)	0.0039	0.482 (0.264-0.879)	0.0173

HR: Hazard Ratio
CI: Confidence Intervals

Table 2.6 Factors associated with time to smear and culture conversion at the end of months 4 of treatment

	Smear Conversion				Culture Conversion			
	Univariate		Multivariate		Univariate		Multivariate	
Variables	**HR 95% (CI)**	**P-Value**	**HR 95% (CI)**	**P-Value**	**HR 95% (CI)**	**P-Value**	**HR 95% (CI)**	**P-Value**
Gender								
Female	1.007 (0.770-1.318)	0.9574	-	-	(ref)	-	-	-
Male	(ref)	-	-	-	1.140 (0.838-1.551)	0.4046	1.215 (0.877-1.683)	0.2424
Age	0.998 (0.987-1.01)	0.7297	-	-	0.991 (0.977-1.005)	0.1906	0.984 (0.969-0.999)	0.0387
Weight	1.004 (0.993-1.015)	0.4955	-	-	1.003 (0.992-1.015)	0.5914	-	-
TB treatment								
Long Course	1.156 (0.891-1.499)	0.2763	-	-	(ref)	-	-	-
Short Course	(ref)	-	-	-	1.196 (0.889-1.61)	0.2370	1.432 (1.014-2.022)	0.0414
Gene Xpert								
Negative	(ref)	-	-	-	1.497 (0.371-6.048)	0.5709	-	-
Positive Rif Resistant	3.099 (0.434-22.14)	0.2595	-	-	(ref)	-	-	-
HIV Status								

	Smear Conversion				Culture Conversion			
	Univariate		Multivariate		Univariate		Multivariate	
Variables	**HR 95% (CI)**	**P-Value**	**HR 95% (CI)**	**P-Value**	**HR 95% (CI)**	**P-Value**	**HR 95% (CI)**	**P-Value**
Negative	(ref)	-	-	-	1.224 (0.882-1.699)	0.2270	-	-
Positive	1.085 (0.801-1.47)	0.5969	-	-	(ref)	-	-	-
Albumin	0.996 (0.982-1.01)	0.5562			1.000 (0.986-1.014)	1.0000	-	-
Haemoglobin	1.001 (0.993-1.009)	0.8245	-	-	1.005 (0.995-1.016)	0.3404	-	-
Creatinine	1.000 (0.998-1.002)	0.9092	-	-	1.002 (0.999-1.005)	0.1970	1.002 (0.999-1.005)	0.1047
CXR								
Cavitary	(ref)	-	-	-	(ref)	-	-	-
Non Cavitary	1.336 (1.022-1.747)	0.0341	1.264 (0.964-1.658)	0.0901	1.123 (0.826-1.526)	0.4604	1.254 (0.896-1.754)	0.1865
Initial AAFB positivity								
Scanty	(ref)	-	-	-	(ref)	-	-	-
+	0.610 (0.394-0.943)	0.0261	0.552 (0.344-0.884)	0.0135	0.682 (0.415-1.119)	0.1300	0.550 (0.319-0.947)	0.0312
++	0.439 (0.275-0.7)	0.0005	0.400 (0.245-0.653)	0.0002	0.567 (0.334-0.964)	0.0362	0.494 (0.277-0.882)	0.0171
+++	0.407 (0.269-0.616)	<.0001	0.392 (0.253-0.609)	<.0001	0.728 (0.461-1.149)	0.1723	0.666 (0.405-1.098)	0.1112

2.13 List of Figures

Figure 2.1 Participant disposition flow chart

1114	Files were excluded
578	AFB negative at Baseline
4	No AFB at Baseline
75	Culture negatives at Baseline
15	Extra pulmonary TB
55	Less than 30 days of treatment
1	MDR TB relapse
21	Missing records
1	INH mono resistant TB
64	Enrolled in clinical trials
58	Initiated at Tshepong and subsequent referral to follow up centers
6	Not treated with short course (2017-2018)
16	Re initiated after defaulting
20	Sensitive TB
91	Less than 18 years of age
60	Pre-XDR
49	XDR-TB

1399 files screened
2015 and 2016 were 905
2017 and 2018 were 494

285 files were enrolled

2015 and 2016
176 enrolled

2017 and 2018
109 enrolled were on short course

Treatment Outcome	
78	Cured
24	Treatment completed
40	Died
20	Lost to follow-up
10	Not evaluated
4	Treatment failure

Treatment Outcome	
70	Cured
8	Treatment completed
8	Died
18	Lost to follow-up
4	Not evaluated
1	Treatment failure

Figure 2.2 Time to smear conversion between short and long course TB treatment

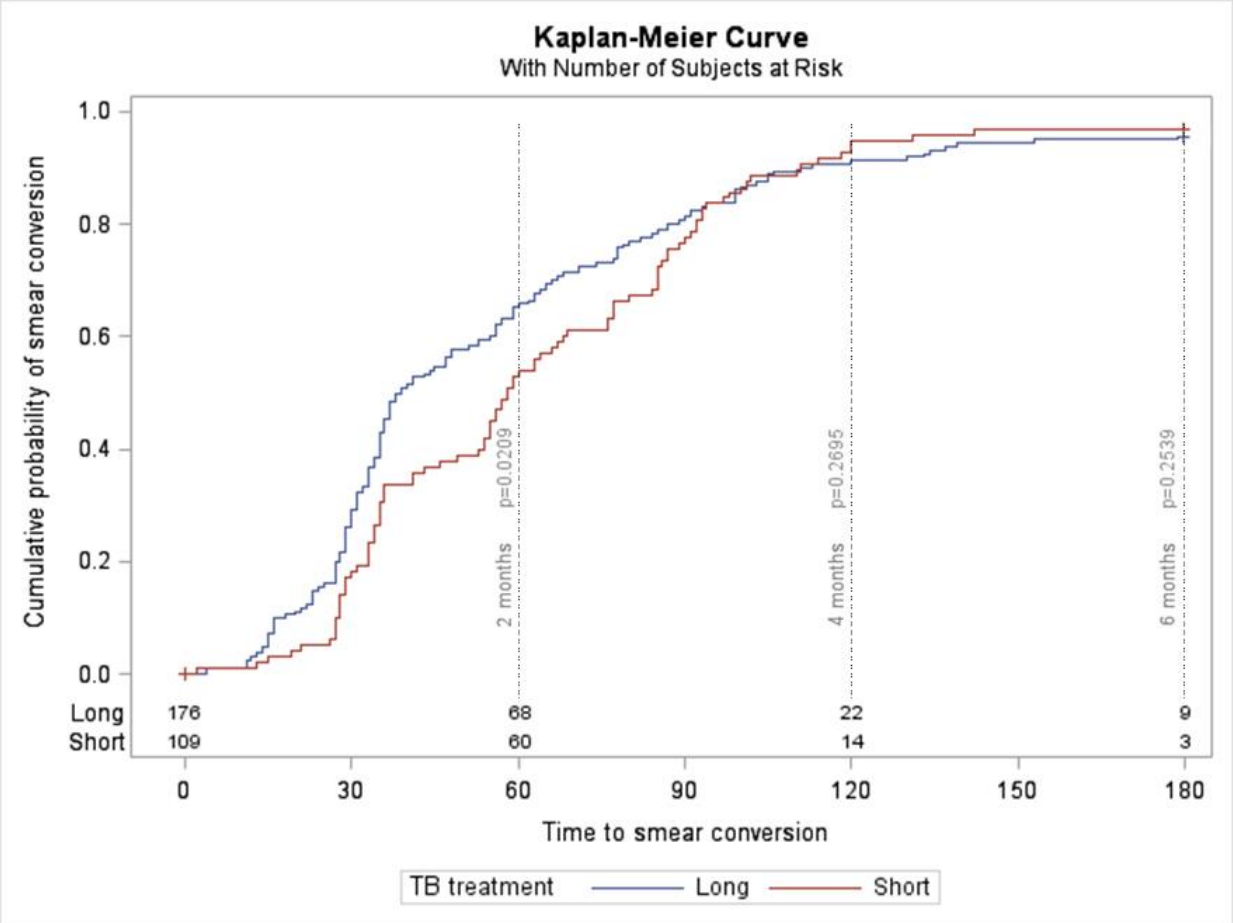


Figure 2.3 Time to culture conversion between short and long course TB treatment

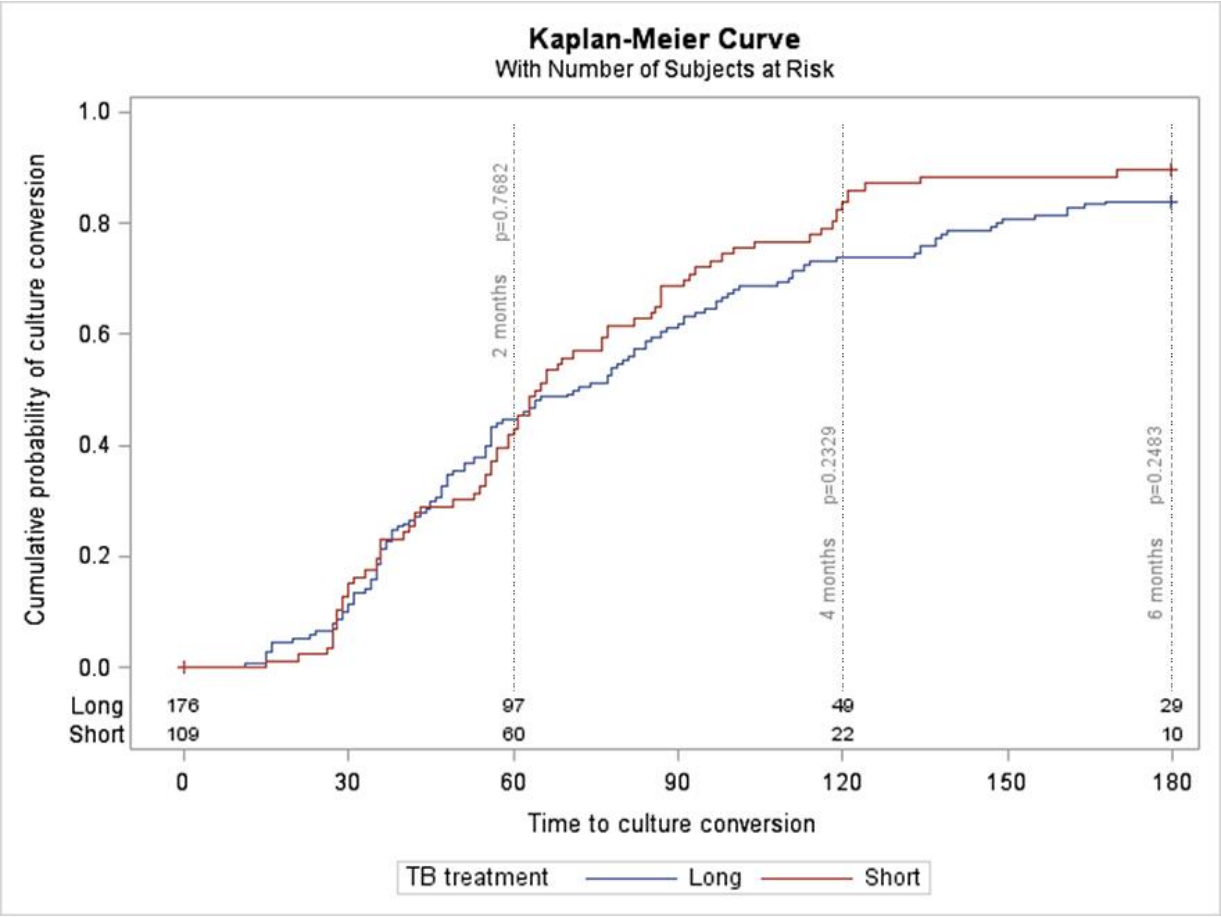


Figure 2.4 Effect of HIV status on smear conversion

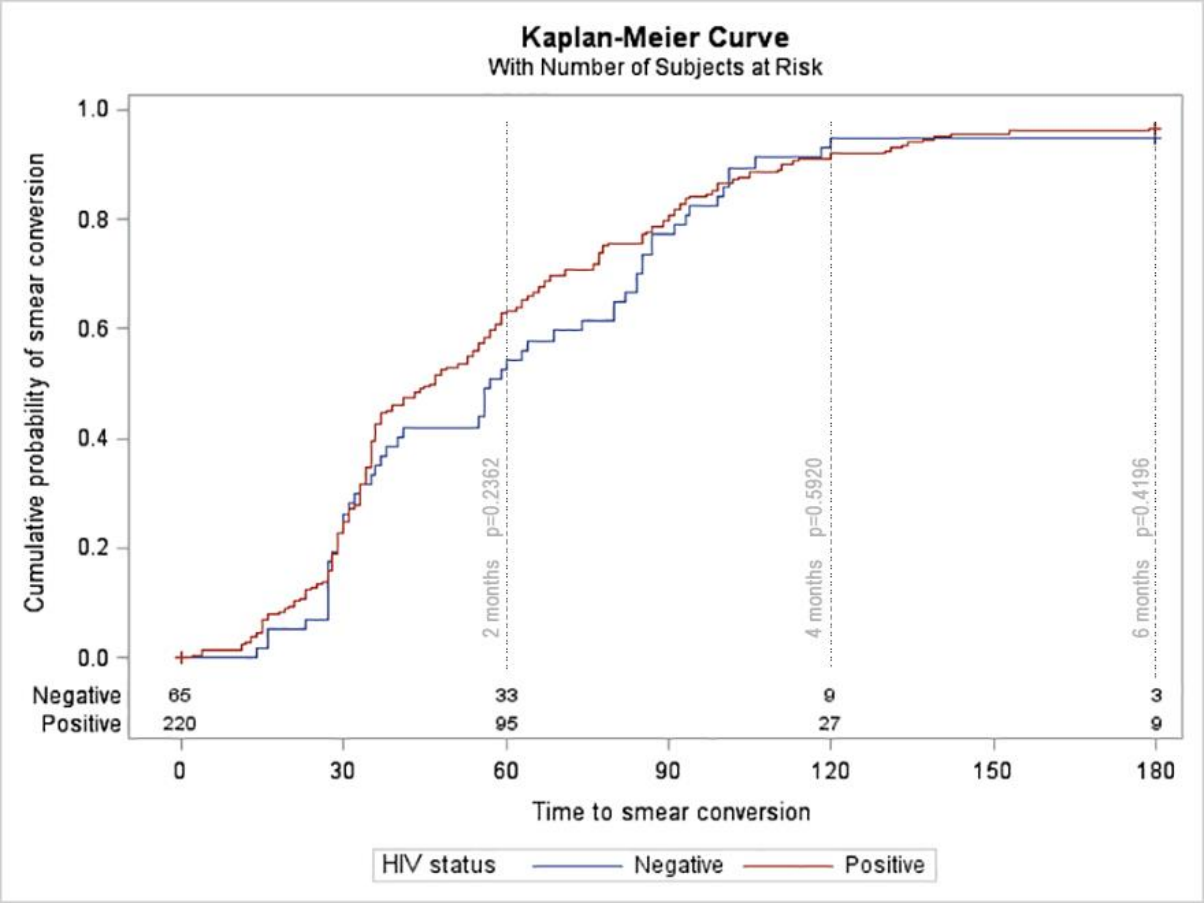


Figure 2.5 Effect of HIV status on culture conversion

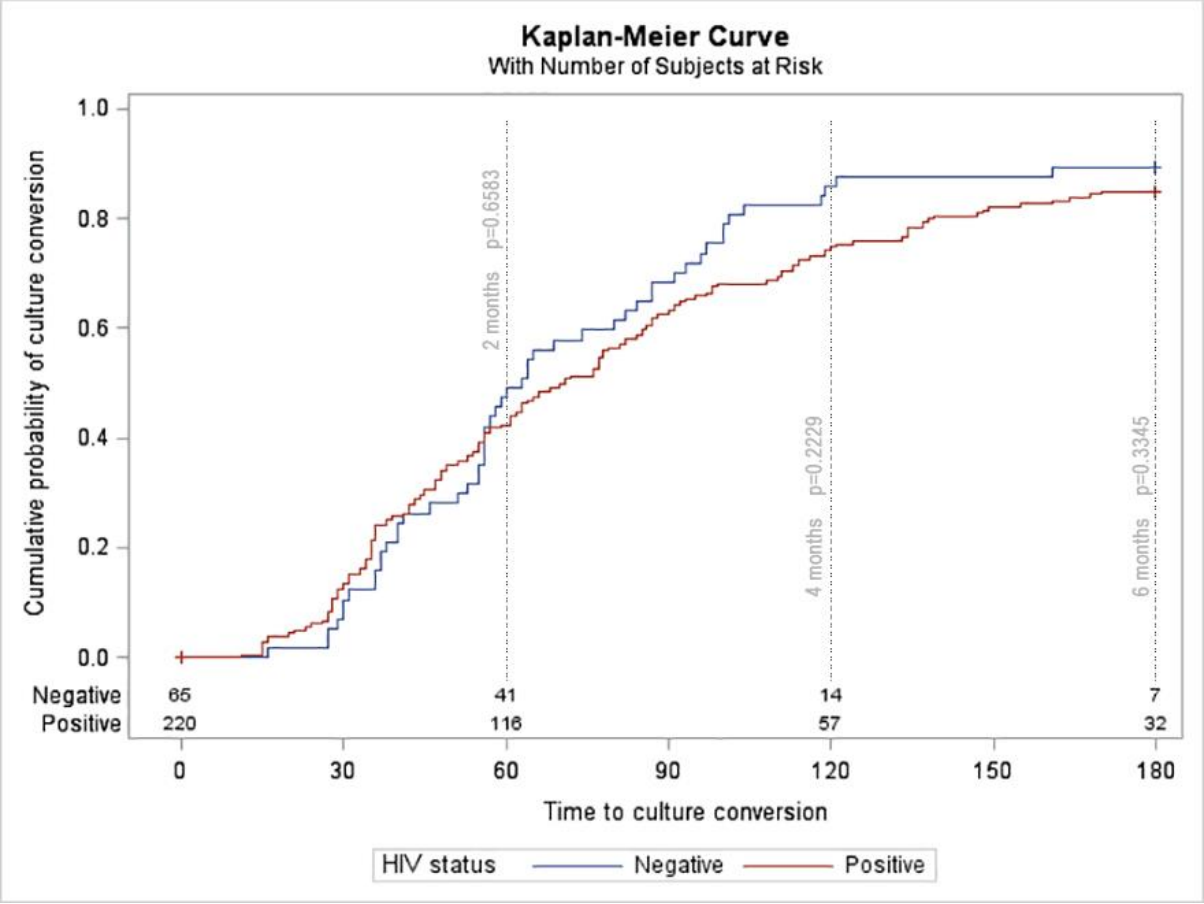
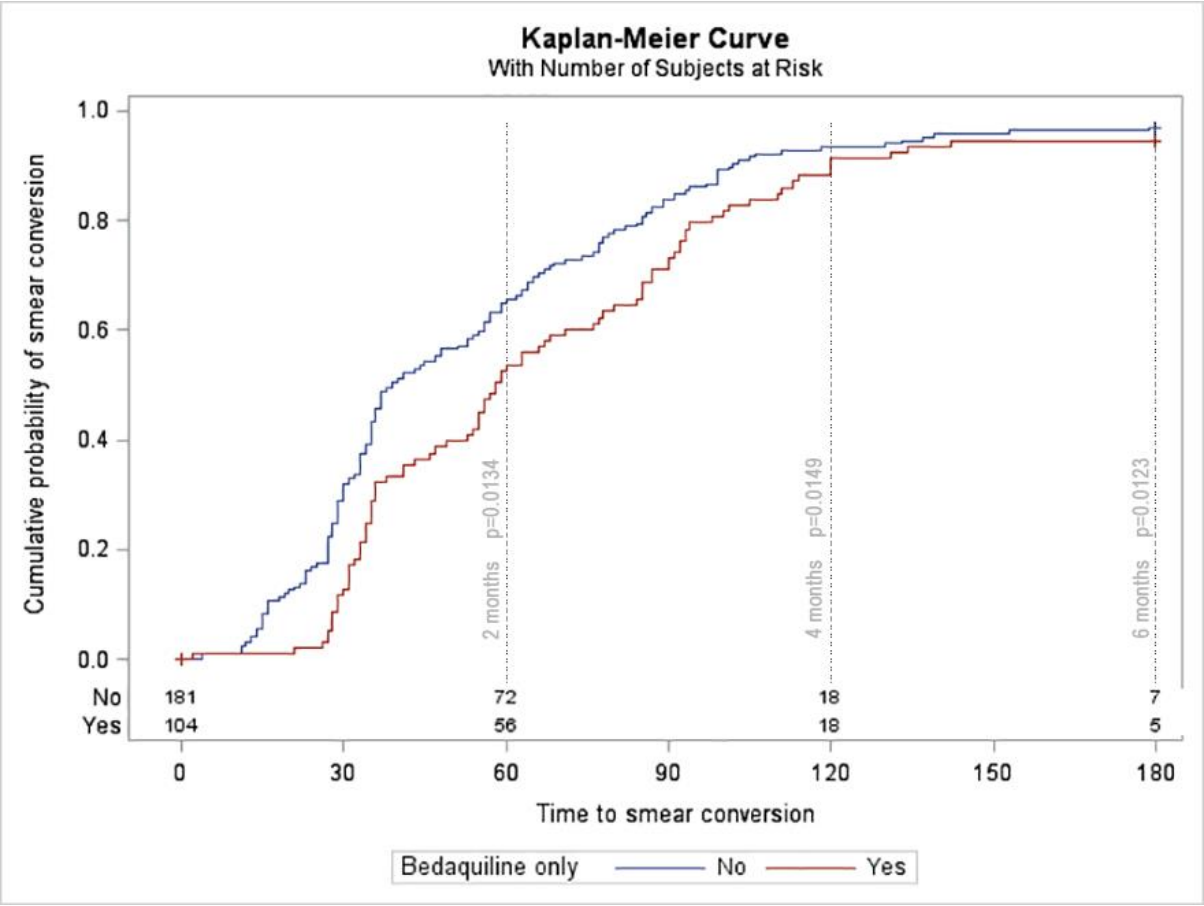


Figure 2.6 Effect of bedaquiline on smear conversion



CHAPTER 3: APPENDIX

3.1 Appendix A: Data Collection Sheet

Retrospective analysis of time to smear and culture conversion and treatment outcomes of rifampicin resistant tuberculosis patients treated with long and short course regimens at Tshepong Hospital

Demographics			
Sex	Male	Female	
Age			
Weight			
Baseline Investigations			
Gene X pert	Positive Rif resistant	Negative	Not available
Time to treatment	Date of diagnosis	Date of treatment initiation	Duration in weeks
	/ /	/ /	wks
Length of hospital stay	Date of admission	Date of discharge	
	/ /	/ /	
HIV status	Positive	Negative	Unknown
CD4 count		Date	Not available
		/ /	
HIV VL Baseline		Date	Not available
		/ /	
HIV VL at end of MDR TB treatment Albumin		Date	Not available
		/ /	
Haemoglobin		Date	Not available

		/ /	
Creatinine		Date	Not available
		/ /	
CXR	Features of TB	No features of TB	Not available
	Cavitary		
	Non-Cavitary		
Bedaquiline received	Yes	No	

Kanamycin Received	Yes				No	
	Start date / /				Reason	
	Stop date / /				Hearing	
	Reason	Hearing loss	Renal	Complete 6 months	Renal	

Kanamycin changed to Bedaquiline	Yes		No	
HAART prior to MDR TB treatment	Yes		No	Default
	Regimen	AZT/TDF/ABC		
		3TC/FTC		
		EFV/LPVr		
HAART on MDR TB Treatment	Regimen	AZT/TDF/ABC		Default
		3TC/FTC		
		EFV/NVP/Rilpivirine/LPVr		

Sputum Tracking Sheet								
Date	Test		Result					
	Gene Xpert		Positive	Negative	Rif	R	S	I
	AAFB							
	Culture							
	Reflex Test	AAFB						
		Culture						
		First Line LPA	Rif S R		INH S R inhA katG			
		Second Line LPA	Fq S R		SLI S R			
		MGIT DST						
	AAFB Baseline							
	Culture							
	AAFB M1							
	Culture							
	AAFB M2							
	Culture							
	AAFB M3							
	Culture							
	AAFB M4							
	Culture							
	AAFB M5							
	Culture							
	AAFB M6							
	Culture							

	AAFB M7		
	Culture		
	AAFB M8		
	Culture		
	AAFB M9		
	Culture		
	AAFB M10		
	Culture		
	AAFB M11		
	Culture		
	AAFB M12		
	Culture		
	AAFB M13		
	Culture		
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	AAFB M17		
	Culture		
	AAFB M8		
	Culture		
	AAFB M19		

	Culture		
	AAFB M20		
	Culture		
	AAFB M21		
	Culture		
	AAFB M21		
	Culture		
	AAFB M22		
	Culture		
	AAFB M23		
	Culture		
	AAFB M24		
	Culture		

Treatment Outcomes				
Cured or treatment completed	Died	Lost to_follow up	Treatment failure	Not_evaluated
Time to smear conversion in weeks				
Time to culture conversion in weeks				

3.2 Appendix B: Ethics Approval

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

R14/49 Dr Petudzai Muchichwa et al

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M181128

NAME: (Principal Investigator)	Dr Petudzai Muchichwa et al
DEPARTMENT:	Internal Medicine Klerksdorp Tshepong Hospital, MDR TB Unit
PROJECT TITLE:	Retrospective analysis of time to smear and culture conversation and treatment outcomes of Multi drug resistant tuberculosis patients treated with longer and short course regimens at Tshepong Hospital
DATE CONSIDERED:	30/11/2018
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Prof Ebrahim Variava
APPROVED BY:	CB Penny Dr CB Penny, Chairperson, HREC (Medical)
DATE OF APPROVAL:	05/03/2019

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary on the Third Floor, Faculty of Health Sciences, Phillip Tobias Building, 29 Princess of Wales Terrace, Parktown, 2193, University of the Witwatersrand. I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit the application to the Committee. **I agree to submit a yearly progress report**. The date for annual re-certification will be one year after the date of convened meeting where the study was initially reviewed. In this case, the study was initially reviewed in **November** and will therefore be due in the month of **November** each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

Principal Investigator Signature Date

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

3.3 Appendix C: Turnitin Reports – Excluding matches below 5%

1856389:P_Muchichwa_Mmed_10.pdf

ORIGINALITY REPORT

9%	3%	9%	1%
SIMILARITY INDEX	INTERNET SOURCES	PUBLICATIONS	STUDENT PAPERS

PRIMARY SOURCES

1	Platon Eliseev, Grigory Balantcev, Elena Nikishova, Anastasia Gaida et al. "The Impact of a Line Probe Assay Based Diagnostic Algorithm on Time to Treatment Initiation and Treatment Outcomes for Multidrug Resistant TB Patients in Arkhangelsk Region, Russia", PLOS ONE, 2016 Publication	2%
2	journals.plos.org Internet Source	1%
3	Boubacar Djelo Diallo, Alhassane Diallo, Lansana Mady Camar, Gladys Djuiga Fotso et al. "Risk Score to Predict Time-to Sputum Smear and Culture Conversions in Patients Treated with Shorter MDR Tuberculosis Regime in Guinea: A Retrospective Cohort Study", Central African Journal of Public Health, 2020 Publication	1%
4	I. Wrohan, L. Redwood, J. Ho, K. Velen, G. J. Fox. "Ototoxicity among multidrug-resistant TB patients: a systematic review and meta-	1%

analysis", The International Journal of Tuberculosis and Lung Disease, 2021
Publication

5	David J. Horne, Catherine O. Johnson, Eyal Oren, Christopher Spitters, Masahiro Narita. "How Soon Should Patients with Smear-Positive Tuberculosis Be Released from Inpatient Isolation?", Infection Control & Hospital Epidemiology, 2015 Publication	<1%
6	"Physicians Poster Sessions", Bone Marrow Transplantation, 03/2009 Publication	<1%
7	Shinkyo Yoon, Byung Woog Kang, Su Yeon Park, Hye Jin Kim, Jun Seok Park, Gyu Seog Choi, Jong Gwang Kim. "Prognostic relevance of genetic variants involved in immune checkpoints in patients with colorectal cancer", Journal of Cancer Research and Clinical Oncology, 2016 Publication	<1%
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10	S. Tiberi, M. Muñoz-Torrico, R. Duarte, M. Dalcolmo, L. D'Ambrosio, G.-B. Migliori. "New	<1%

drugs and perspectives for new anti-tuberculosis regimens", Revista Portuguesa de Pneumologia (English Edition), 2018
Publication

11	Simon Tiberi, Marie-Christine Payen, Giovanni Sotgiu, Lia D'Ambrosio et al. "Effectiveness and safety of meropenem/clavulanate-containing regimens in the treatment of MDR- and XDR-TB", European Respiratory Journal, 2016 Publication	<1%
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14	Pedro F. Dalberto, Eduardo V. de Souza, Bruno L. Abbadi, Christiano E. Neves et al. "Handling the Hurdles on the Way to Anti-tuberculosis Drug Development", Frontiers in Chemistry, 2020 Publication	<1%
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	Roshen Erasmus, N Olga Siwisa, Khulile Thomas, Martie L van der Walt. "Extensively Drug-Resistant TB in Eastern Cape, South Africa: High Mortality in HIV-Negative and HIV-Positive Patients", JAIDS Journal of Acquired Immune Deficiency Syndromes, 2011 Publication	<1%
18	Chi C. Leung, Wing W. Yew, Chi K. Chan, Chi H. Chau, Cheuk M. Tam, Chak W. Lam, Wai O. Tam, Kam S. Lau, Wai T. Liu. "Tuberculosis in Older People: A Retrospective and Comparative Study from Hong Kong", Journal of the American Geriatrics Society, 2002 Publication	<1%
19	Matthew W. Carroll, Doosoo Jeon, James M. Mountz, Jong Doo Lee et al. "Efficacy and Safety of Metronidazole for Pulmonary Multidrug-Resistant Tuberculosis", Antimicrobial Agents and Chemotherapy, 2013 Publication	<1%
20	Simon Tiberi, Ruaridh Buchanan, José A. Caminero, Rosella Centis et al. "The challenge of the new tuberculosis drugs", La Presse Médicale, 2017 Publication	<1%

Exclude quotes	On	Exclude matches	< 5 words
Exclude bibliography	On		

3.4 Appendix D: Hospital Approval

health
Department of
Health
North West Province
REPUBLIC OF SOUTH AFRICA

All correspondence to be directed to:
The Clinical Manager
Dr. David Leburu
K/T Hospital Complex
Private Bag A14
KLERKSDORP
2570

Tel: (018) 406 4740
Fax: (018) 462 1923
DLeburu@nwpg.gov.za
Enq: Sbooi@nwpg.gov.za

CLINICAL MANAGER'S OFFICE

10th December 2018

To : Dr. Muchichwa

Dear Sir/ Madam

RE : Retrospective analysis of time to smear and culture conversion and treatment outcomes of Multi drug resistant tuberculosis patients treated with longer and short course regiments at Tshepong hospital

Presenter – Dr. Muchichwa
Date – 13th November 2018

This letter serves to confirm that permission has been granted by K/T Hospital Complex Patient Safety Group (PSG) for study approval letter for study title: Retrospective analysis of time to smear and culture conversion and treatment outcomes of Multi drug resistant tuberculosis patients treated with longer and short course regiments at Klerksdorp/Tshepong Hospital Complex. The researcher is requested to submit regular study progress reports and final study report upon completion of the project.

Kind Regards

.....
Dr. N.D. Leburu
Clinical Manager
K/T Hospital Complex

GESONDHEIDS DIENSTE
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Privaatsak/Private Bag A14
2018 -12- 10
KLERKSDORP 2570
KLERKSDORP/TSHEPONG
HOSPITAL COMPLEX
HEALTH SERVICES

Healthy Living for All

1

3.5 Appendix E: Provincial Clearance

health
Department of
Health
North West Province
REPUBLIC OF SOUTH AFRICA

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New Office Park
MAHIKENG, 2735

Enq: Nthabiseng Mapogo
Tel: 018 391 4504
NMapogo@nwpg.gov.za
www.nwhealth.gov.za

POLICY, PLANNING, RESEARCH, MONITORING AND EVALUATION

Name of researcher : Dr. P. Muchichwa
University of the Witwatersrand

Physical Address (Work/ Institution) Klerksdorp/Tshepong Hospital complex P. Bag A14

LEPAPHA LA BOITEKANELO
DEPARTMENT OF HEALTH
Kgetsana Poso /Private Bag X2068
Mmabatho,2735
1 JUL 2019
NORTH WEST PROVINCE
REPUBLIC OF SOUTH AFRICA

Subject: Research Approval Letter- Retrospective analysis of time to smear and culture conversion and treatment outcomes of Multi Drug Resistant Tuberculosis patients treated with long and short course regimens at Tshepong Hospital.

This letter serves to inform the Researcher that permission to undertake the above-mentioned study has been granted by the North West Department of Health. The Researcher is expected to arrange in advance with the chosen facilities and issue this letter as proof that permission has been granted by the Provincial office.

This letter of permission should be signed, and a copy returned to the department. By signing, the Researcher agrees, binds him/herself and undertakes to furnish the Department with an electronic copy of the final research report. Alternatively, the Researcher can also provide the Department with electronic summary highlighting recommendations that will assist the Department in its planning to improve some of its services where possible. Through this the Researcher will not only contribute to the academic body of knowledge but also contributes towards the bettering of health care services and thus the overall health of citizens in the North West Province.

Kindest regards

Dr. F.R.M. Reichel
Director: PPRM&E

01/07/2019
Date

Researcher

7/2019
Date

Healthy Living for All

3.6 Appendix F: University Approval

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

Private Bag 3 Wits, 2050
Fax: 027117172119
Tel: 02711 7172076

Reference: Mrs Sandra Benn
E-mail: sandra.benn@wits.ac.za

06 February 2019
Person No: 1856389
PAG

Dr P Muchichwa
P O Box 7136
Flamewood
2572
South Africa

Dear Dr Petudzai Muchichwa

Master of Medicine in Internal Medicine: Approval of Title

We have pleasure in advising that your proposal entitled *Retrospective analysis of time to smear and culture conversion and treatment outcomes of multi drug resistant tuberculosis patients treated with longer and short course regimens at Tshepong Hospital.* has been approved. Please note that any amendments to this title have to be endorsed by the Faculty's higher degrees committee and formally approved.

Yours sincerely

Mrs Sandra Benn
Faculty Registrar
Faculty of Health Sciences