CAUSES OF DEATH AND STRATEGIES TO IMPROVE LINKAGE TO HIV AND TB CARE IN ADULTS BEING-INVESTIGATED FOR TB IN SOUTH AFRICA

Mosehle Noriah Maraba

(Student no: 0505275F)

Supervisors:

Dr Violet Chihota

Professor Kathleen Kahn

Professor Alison Grant

A thesis completed by published work,
Submitted to the School of Public Health, Faculty of Health Sciences,
University of the Witwatersrand,
In fulfilment of the requirements for the degree of
Doctor of Philosophy

Johannesburg, 2020

DECLARATION

This thesis is submitted in the integrative narrative format, approved by the Faculty of Health sciences.

I, Mosehle Noriah Maraba, declare that this thesis is my original work. Where there has been contribution from other people, this has been duly acknowledged. It is being submitted for the degree of Doctor of Philosophy in Public Health in the University of the Witwatersrand, Johannesburg, South Africa. It has not been submitted before for any degree or examination at this or any other University.

I have read the sections on referencing and plagiarism in the WITS Plagiarism Policy and I understand that plagiarism can lead to the suspension or permanent expulsion of students in serious cases. I confirm that the work submitted for assessment for the above degree is my own unaided work except where I have explicitly indicated otherwise. I have followed the required conventions in referencing the thoughts and ideas of others. I understand the University of the Witwatersrand may take disciplinary action against me if there is a belief that this is not my own unaided work or I have failed to acknowledge the source of the ideas or words in my writing.

Signature: 

Date: 21 September 2020

DEDICATION

I dedicate this thesis to my family (grandmother, aunt, sisters, brother, husband and son).

To my grandmother (Maggie Mphahlele), I am so grateful that God has granted you long life so you could see me achieve this. To my aunt thank you for constantly cheering me on. To my sisters and brother (Motlatšo, Basetsana, Itumeleng and Lesedi) pursue what you love and do not forget the value of processes.

To my parents (Joyce and Thomas Matabane), I am grateful that God made you my parents (the differences in characters brought so much balance to me). The constant support and love you provided me throughout my academic life mean the world to me. Thank you for instilling the value of education from a young age and for allowing me to pursue what I love.

To my husband (Jacob Maraba), thank you for your continuous love and support. Thank you for pushing me to do my best. Thank you for enduring those lonely weekends.

To my son, God gave you to me at the right time, and you became my retreating place during these last months of this journey. I love you.

Lastly, I would like to thank God Almighty for strengthening me throughout this journey. This journey would not be possible without His enduring Grace. I am eternally grateful.

PRESENTATIONS ARISING FROM THIS POSTGRADUATE RESEARCH

- ***Maraba N***, Alison Grant, Kerrigan McCarthy, Gavin J Churchyard, and Violet Chihota. Mortality and pre-treatment loss to follow-up in patients being investigated for TB in a pilot case manager intervention. 46th Union World Conference on Lung Health Cape Town, South Africa 6 Dec 2015. *Oral presentation*

- ***Maraba N***, Hoffmann CJ, Chihota VN, Chang LW, Ismail N, Candy S, Madibogo E, Katzwinkel M, Churchyard GJ and McCarthy K. Using mHealth to improve TB case identification in South Africa: Results from a pilot study. South Africa TB conference, Durban, 12-15 June 2018. *Poster presentation*

PUBLICATIONS ARISING FROM THIS POSTGRADUATE RESEARCH

- ***Maraba N***, Karat AS, McCarthy K, Churchyard GJ, Charalambous S, Kahn K, Grant AD and Chihota V. Verbal autopsy-assigned causes of death among adults being investigated for TB in South Africa. Transactions of the Royal Society of Tropical Medicine and Hygiene 2016; 110: 510–516

- ***Maraba N***, Chihota V, McCarthy K, Churchyard G, Grant AD. Linkage to care among adults being investigated for tuberculosis in South Africa: pilot study of a case manager intervention. BMJ Open 2018; 8:e021111.

- ***Maraba N***, Hoffmann CJ, Chihota VN, Chang LW, Ismail N, Candy S, Madibogo E, Katzwinkel M, Churchyard GJ, McCarthy K. Using mHealth to improve tuberculosis case identification and treatment initiation in South Africa: Results from a pilot study. PLoS ONE 2018; 13(7): e0199687.

Manuscript ready for submission

- ***Maraba N***, Chihota V, Nieuwoudt S, McCarthy K, Churchyard GJ, and Grant AD. Experiences of patients, providers and case managers in linking adults into TB and HIV care: a qualitative study.

The student role and contribution in each paper are shown in appendix A

ABSTRACT

Introduction

There is high mortality amongst adults being investigated for tuberculosis (TB) in primary health care (PHC) facilities in South Africa, but the causes of death (CoDs) are not clearly defined. Patient and health system-related factors such as diagnostic delays, delays in delivery of laboratory results and treatment start delays exist and prevent this population from linking into care. Innovative interventions are needed to assist with linkage to HIV and TB care. This is important as the first two goals of the South African National Strategic Plan are to hasten the development of interventions to prevent new infections, and to reduce morbidity as well as mortality by providing treatment and adherence support. The first target of the global STOP TB plan is to reach 90% of all people with TB and place them on appropriate treatment. The national tuberculosis guidelines also recommend that everyone undergoing TB investigation should be tested for HIV, a recommendation that links to the Joint United Nations Programme on HIV/AIDS (UNAIDS) targets to ensure that 90% of people living with HIV know their status.

The aim of this PhD was to determine the causes of death amongst adults being investigated for TB, and pilot two interventions in PHC facilities to improve linkage into HIV and TB care, a case manager and mobile health (mHealth) intervention.

A study investigating causes of death in people being investigated for TB and two studies piloting interventions to improve linkage to care form the basis of this thesis:

(i) Determining causes of death amongst people undergoing TB investigation using verbal autopsy in South Africa
(ii) A pilot study to evaluate the feasibility and acceptability of using a case manager to improve linkage to TB and HIV care amongst people investigated for TB in primary health care facilities in South Africa
(iii) Development and implementation of mHealth-based clinical decision support messaging for health care workers and patients in the initial investigation of tuberculosis in primary health care facilities in South Africa.

This thesis comprises of these three studies and is presented in two parts: an integrative narrative which synthesises the studies, followed by three published papers and one unpublished manuscript presenting the studies.

Methods

The first study determined the CoDs in people being investigated for TB and was a sub-study of the XTEND Trial, a cluster-randomized trial comparing Xpert MTB/RIF versus smear microscopy as the initial test for diagnosing TB. The study was done amongst caregivers of the 231 deceased participants who were enrolled in the XTEND study. The caregivers were aged 18 years and above and lived in four provinces (Gauteng, Free State, Eastern Cape and Mpumalanga) of South Africa. For the sub-study, all contactable caregivers of deceased XTEND participants were interviewed using the World Health Organization (WHO) approved verbal autopsy (VA) tool. The VA tool has a quantitative section with questions requiring 'Yes' or 'No' responses and a narrative section which allows for detailed documentation of events leading to death. Cause of death (CoD) was determined using physician certified verbal autopsy (PCVA) and InterVA 4.3 software with comparison of the CoD profile between the two methods. Responses from the narrative section of VA were used to ascertain perceived barriers of care as described by caregivers of the decedents.

The second study piloted a case manager intervention, where a lay counsellor supported patients undergoing TB investigations for three months by encouraging HIV testing, calling them to return for results, following up on their laboratory results, and assisting with treatment initiation if confirmed to have TB. The study was done amongst people undergoing TB investigation aged 18 years and above, in six PHC facilities in Mpumalanga and Gauteng provinces of South Africa. Linkage to TB care was defined as starting TB treatment within 28 days of having sputum taken for TB investigation. HIV linkage to care for HIV positive people was defined as having blood taken for CD4 count test and, for those eligible, starting antiretroviral therapy within three months. The feasibility of implementing the intervention was assessed by attempts made through telephonic calls or participants visiting the clinic. Qualitative interviews were conducted to assess the acceptability of the intervention and explore barriers and facilitators of linkage to HIV care and TB treatment initiation.

The third study developed and piloted an mHealth application to capture patients' TB investigation data and deliver laboratory test results directly to patients via text messaging.

The study was done amongst people undergoing TB investigation aged 18 years and above in two clinics in the Gauteng Province of South Africa. Data were collected over two periods: pre-implementation period and implementation period. The pre-implementation period involved facility health care workers recording TB investigation data in the paper-based TB identification register, and the implementation period involved the facility health care workers recording TB investigation data in an electronic register while research staff recorded the data in paper-based TB investigation registers. The feasibility of using the mHealth application was assessed in the implementation period by comparing proportions of patients with complete personal details and documented results using mHealth application versus paper. TB indicators (turn-around time from sample collection to when a patient gets sputum results, time to TB treatment initiation and proportion on treatment within a specific period) were compared in the pre-implementation and implementation periods to assess the potential effectiveness of the mHealth application. Qualitative interviews were conducted to assess the acceptability of the intervention.

Results

Amongst the 231 who died during the XTEND trial, caregivers of 137 decedents were interviewed as part of the study on causes of death. Of the 137 deceased, 76 (55.4%) were males, median age was 41 years (interquartile range [IQR] 33-50 years). PCVA assigned 70 (51.1%) deaths to TB; 21(15.3%) to HIV and 46 (33.5%) to other CoD. InterVA 4.3 software assigned 48 (35.0%) deaths to TB, 49 (35.7%) to HIV and 40 (29.1%) to other CoD. Delays in accessing health-care, treatment delay and clinic organisation were perceived to challenge the health-seeking journey of decedents.

Amongst 562 participants enrolled in the case manager study, 307(54.6%) were females with a median age 36 years (IQR 29-44). A total of 189/562 (33.6%) participants needed linkage to care: 132 needed only HIV care, 35 needed TB treatment initiation only, 22 needed both HIV care and TB treatment initiation. Of the 57 participants who needed TB treatment, 53 (93%) were initiated on treatment. By the end of three months follow-up, 40 participants (29/132 [22%] needing HIV care, 4/35 [11.4%] needing TB treatment and 7/ 22 [31.8%] needing HIV linkage to care and TB treatment initiation) had not linked to care. Patient (fear and competing priorities) and health system (poor implementation of updated TB and HIV management guidelines as well as the way facilities booked patients for ART initiation)

related factors were highlighted as barriers to HIV linkage. Patients' ill-health and clinic experience were the main facilitators of initiating TB treatment.

In the mHealth study, 457 patients were recorded in the register during the pre-implementation period (195 [42.7%] males, median age 34 years [IQR 28-40]). During implementation period, 319 patients were recorded in paper register and mHealth application (131 [41.1%] males, median age 32 years [IQR 27-38]). Implementation of the mHealth intervention in PHC facilities showed no difference in proportion with complete personal details: (mHealth 95% versus paper register 94.0%, [p=0.54]) and proportion with documented results: (mHealth 97.4% versus paper 97.8%, [p=0.8]). The intervention improved the proportion of patients with results available within 48 hours from sample collection, (pre-implementation 68.6% versus implementation period 96.8%; [p>0.001]) but did not improve time to TB treatment initiation (pre-implementation, median = 4 days interquartile range [IQR] 2-6; implementation median = 3 days IQR [2-5]; p=0.5). The delivery of results via text message did not infringe on patients' privacy.

Conclusion

TB and HIV are leading CoDs amongst adults being investigated for TB in primary health care clinics in South Africa, as determined by VA. This points to the importance of integrated TB and HIV care and linkage into care for both diseases in this group. InterVA-underestimates TB associated deaths and needs to be refined to be able to include extrapulmonary TB as a CoD.

Support interventions using lay workers as case managers to link adults undergoing TB investigation into HIV and TB care might help improve TB treatment initiation. However, this kind of support is not adequate to assist HIV positive patients' to link into HIV care, showing the complexity of the HIV linkage to care process. Future support interventions to be piloted should address both patient and health system factors.

Finally, mHealth applications could take the place of current paper-based TB care programme case-finding tools, and could substantially improve results turn-around time and management of TB within the programme. These applications may empower patients with direct receipt of TB results. Implementation of mHealth interventions to support and improve TB care has the potential to improve patient-level outcomes, and large-scale evaluations of these technologies are urgently required. Additionally, future interventions to improve TB treatment initiation

need to focus on how to improve patients' clinic experience and empower patients to seek care.

ACKNOWLEDGEMENTS

This thesis would not have been possible without the continuous guidance and motivation provided by my supervisors—Violet for believing in me, encouraging me, and guiding me throughout this journey. Kathy, for allowing me to grow under your wing by supervising both my masters and this postgraduate study. Alison, thank you for demanding nothing but quality.

I am grateful to the Xpert for TB-Evaluating a New Diagnostic trial investigators, for providing me with a fellowship opportunity to support my studies. I would also like to thank my employer for providing me the time to write throughout my PhD journey, and all my colleagues from the Aurum Institute, who assisted with data collection for all the three studies. Thank you to Sibuse Ginindza and Katherine Fielding for providing me with statistical support. I would also like to extend a hand of appreciation to all the participants who took part in all the three studies that contributed to this body of work. I would like to thank the health facilities, and staff were enrolments took place. Thank you to Nish, Candice, Tonderai, and colleagues for the encouragement and support you provided.

I would also like to extend my gratitude to The National Institutes for Health and The Bill and Melinda Gates Foundation, who financially supported the studies that contributed to this thesis. To Gavin Churchyard, Violet Chihota, Alison Grant, Salome Charalambous, and Kerrigan McCarthy, who acquired funding for the studies and allowed me to use the data for my studies.

TABLE OF CONTENTS

DECLARATION i
DEDICATION ii
PRESENTATIONS ARISING FROM THIS POSTGRADUATE RESEARCH iii
PUBLICATIONS ARISING FROM THIS POSTGRADUATE RESEARCH iv
ABSTRACT v
ACKNOWLEDGEMENTS x
TABLE OF CONTENTS xi
LIST OF ABBREVIATIONS xiv
LIST OF FIGURES xvi
LIST OF TABLES xvi
CHAPTER 1: BACKGROUND 1
1.1 Introduction 1
1.2 Global TB status 1
1.3 Historical overview of TB and HIV epidemic in South Africa 2
1.4 TB in South Africa 3
1.5 The relationship between HIV and TB 4
1.6 TB and HIV management policy changes in South Africa 5
1.7 Mortality in those undergoing TB investigation 6
1.8 Mortality in people with TB disease on TB treatment 7
1.9 Barriers along the TB care cascade 8
1.10 Barriers along the HIV care cascade 11
1.11. Justification for undertaking this postgraduate research 13
1.12 Research question 14
1.13 Hypotheses 14
1.14 Thesis Aim 15
1.15 Thesis Objectives 15
CHAPTER 2: LITERATURE REVIEW 17
2.1 Counting deaths 17
2.2 Determining causes of death 17
2.2.1 Pathological autopsy 17
2.2.2 Prevalence of TB related mortality using pathological autopsy 18
2.2.3 Using chart reviews to determine the cause of death 18
2.2.4 Verbal autopsy 19

2.3 Strategies to reduce TB morbidity and mortality 20
2.3.1 Finding TB 21
2.3.2 Treating TB 23
2.3.3 Prevention of TB disease 24
2.4 Strategies to improve linkage to care 26
2.4.1 Task shifting 26
2.4.2 Support interventions 27
2.4.3 mHealth interventions 28
2.5 Thesis Framework 29
CHAPTER 3: METHODOLOGY 32
3.1 Linkage of the three studies to XTEND trial 32
3.2 Brief overview of XTEND trial 33
3.3 Data sources 34
3.4 Verbal autopsy – methodology for paper I 34
3.4.1 Study aim: 34
3.4.2 Setting 35
3.4.3 Study design 36
3.4.4 Study population 37
3.4.5 Study procedures 37
3.4.6 Data management and assessment 38
3.4.7 Study Outcomes 39
3.4.8 Statistical analysis 39
3.5 Case manager study – Methodology for papers II and III 40
3.5.1 Study aim 40
3.5.2 Setting 40
3.5.3 Study design 40
3.5.4 Study population 40
3.5.5 Sample size 41
3.5.6 Description of intervention 41
3.5.7 Recruitment and study procedures 44
3.5.8 Study outcomes 44
3.5.9 Qualitative data collection 45
3.5.10 Quantitative data analysis 45
3.5.11 Qualitative data analysis 46
3.6 mHealth application –Methodology for paper IV 46
3.6.1 Study aim 46
3.6.2 Setting 46

3.6.3 Study design 47
3.6.4 Study population and sampling 48
3.6.5 Development of mHealth application 48
3.6.6 Study procedures 49
3.6.7 Study outcomes 50
3.6.8 Acceptability of the mHealth application data collection 50
3.6.9 Statistical analysis 51
3.7 Ethical considerations 51
CHAPTER 4: RESULTS SECTION 53
4.1 Mortality and cause of death: verbal autopsy study 53
4.1.1 Decedent demographic characteristics 53
4.1.2 Cause of death 53
4.1.3 Perceived barriers to linkage to care 56
4.2 Linkage to HIV care and TB treatment initiation: Case manager study 57
4.2.1 Supporting linkage to HIV care using case manager intervention 57
4.2.2 Supporting TB treatment initiation using the case manager intervention 61
4.3 Initiation of TB treatment: mHealth application 62
4.3.1 Supporting TB treatment initiation using the mHealth intervention 62
CHAPTER 5: DISCUSSION 66
5.1 Introduction 66
5.2 Key findings 66
5.2.1 Verbal Autopsy 66
5.2.2 Case manager intervention 68
5.2.3 mHealth intervention 72
5.3 Questions arising during the postgraduate research? 74
5.4 Limitations of the postgraduate research 75
5.5 Strengths of the postgraduate research 76
5.6 Recommendations 77
5.7 Recommendations for future research 78
5.8 Conclusion 78
6. REFERENCES 80
APPENDIX A: ROLE OF STUDENT 93
APPENDIX B: PUBLICATIONS 95

LIST OF ABBREVIATIONS

AIDS	Acquired Immunodeficiency syndrome
ART	Antiretroviral therapy
BCG	Bacilli Calmette Guerin
BMI	Body Mass Index
CCC	Concordance correlation coefficient
CCVA	Computer coded verbal autopsy
CoD	Cause of death
EPTB	Extra pulmonary Tuberculosis
HDSS	Health demographic surveillance system site
HIV	Human Immunodeficiency Virus
ICD-10	International classification of disease version 10
InterVA	Interpreting Verbal Autopsy software
IPT	Isoniazid Preventive Therapy
IQR	Interquartile range
IRIS	Immune Reconstitution Inflammatory Syndrome
LBTI	Latent TB Infection
LMIC	Low- and Middle-Income Countries
MDR/RR-TB	Multidrug-resistant TB or rifampicin-resistant TB
mHealth	mobile Health
MMDS	Mortality medical data system
MTB	Mycobacterium tuberculosis
NDoH	National Department of Health
NHLS	National Health Laboratory Services
NSP	National Strategic Plan
PCVA	Physician certified verbal autopsy
PHC	Primary health care
PTB	Pulmonary Tuberculosis
SMS	Short Message Service
TB	Tuberculosis
TB-IRIS	Tuberculosis immune reconstitution inflammatory syndrome
WHO	World Health Organization
UNAIDS	Joint United Nations Programme on HIV/AIDS
USA	United States of America

VA	Verbal Autopsy
XDR-TB	Extensively drug-resistant TB
XPERT	Xpert MTB/RIF
XTEND	Xpert for TB-Evaluating a New Diagnostic

LIST OF FIGURES

Figure 1: Description of TB care pathway from MacPherson et al. 2013. 9
Figure 2: Description of HIV care pathway from Kranzer K et al. 2012..... 12
Figure 3: Thesis framework adapted from Corbett EL 2013 on TB Screening in high HIV prevalence settings. 29
Figure 4: Relationship of the three thesis studies to the XTEND trial. 32
Figure 5: Map showing the provinces of South Africa (Gauteng, Mpumalanga, Free State and Eastern Cape), with TB incidence rates for 2012 and location of XTEND study indicated in the different shades of grey. 35
Figure 6: Identification of deceased XTEND trial participants and recruitment into verbal autopsy study. 37
Figure 7: TB and HIV algorithm used to guide case managers, from paper II: Maraba et al. BMJ Open 2018. 43
Figure 8: Regional demarcations of the city of Johannesburg metropolitan municipality. 47
Figure 9: Flow of participants through linkage to HIV care pathway, from paper II: Maraba et al. BMJ Open 2018. 60

LIST OF TABLES

Table 1: Relationship between thesis objectives, the 3 studies and the 4 papers 16
Table 2: Immediate cause of death assigned by physician-certified verbal autopsy compared with "most probable" cause of death assigned by InterVA-4 (n=137). 55
Table 3: Comparison of cause-specific mortality fractions as assigned by physician certified verbal autopsy and InterVA-4 56
Table 4: Total expected number of participants and actual numbers of participants enrolled per clinic 58
Table 5: Process indicators assessing potential effectiveness of using mHealth application compared to paper register 63

CHAPTER 1: BACKGROUND

1.1 Introduction

This section provides an overview of the global TB status, historical overview of TB and HIV epidemic in South Africa, TB as a public health problem in South Africa, the relationship between TB and HIV, as well as the barriers that exist along the TB and HIV care cascade. It also provides a justification for undertaking the postgraduate study.

1.2 Global TB status

The incidence of tuberculosis (TB) worldwide was estimated to be 10 million cases, and about 1.7 billion people were estimated to have latent TB infection in 2017(1). The majority of these estimated number of cases occurred in regions of South-East Asia and Africa (1). The World Health Organization (WHO) has identified 30 countries that are considered to be high TB burden, and these countries were reported to have accounted for the majority of the estimated incident cases. Within these 30 high burden countries, six countries from Asia and two from Africa accounted for close to 70% of the total global incident cases (1). When looking at countries annual number of incident TB cases relative to population size, most (24) of the 30 high burden countries had an incident rate of between 150-400 cases per 100 000 population (1). Only six countries, including South Africa, had an incident rate of above 500 cases per 100 000 population (1). An estimated 9% of TB incidence (920 000 cases) occurred in people living with human immunodeficiency virus (HIV), most of which were in Africa, particularly Southern Africa (1).

TB was ranked the tenth leading cause of death worldwide in 2017, with the majority of deaths occurring in Africa and South-East Asia (1). The estimated TB mortality rate amongst HIV negative people was 17 per 100 000 population and 21 per 100 000 population amongst HIV positive people. Countries in Southern Africa, including Lesotho, South Africa and Mozambique had the highest TB mortality rates of 206, 99 and 90 deaths per 100 000 population, respectively (1).

There were an estimated 558 000 incident cases of multidrug-resistant or rifampicin-resistant (MDR/RR-TB) with an estimated 3.5% occurring in new cases and 18% in previously treated cases (1). Although Europe had a relatively low overall TB incidence, it had higher

proportions of TB cases with RR or MDR/RR-TB compared to the other regions. An estimated 230 000 deaths were due to MDR/RR-TB in 2017. The WHO reported a 2.3% increase in the average proportion of MDR cases with extensively drug-resistant TB (XDR-TB) in 2017 compared to 2016 (1).

1.3 Historical overview of TB and HIV epidemic in South Africa

Historically, TB in South Africa was driven by the mining industry from the late 1800s. Miners were living in hostels that were overcrowded and poorly ventilated. They also worked in poorly ventilated underground tunnels and interacted with other TB infected individuals. These living and working conditions promoted the transmission of the disease within the mining communities, and oscillating migration promoted the transmission of TB disease from miners to their communities (2). From that period on, TB incidence increased steadily until the 1990's. Thereafter, it started to increase steeply due to the maturing HIV epidemic (3). The disease was then declared a public health emergency in the country in 2003, and a crisis management plan was launched to address it. It was previously believed that the TB epidemic in the country was driven by the mining industry. However, a recent modelling study suggests that gold miners who make up 1% of the South African population contributed to 4% of new infections in the country annually (4).

The introduction of HIV in the country occurred in the 1980s, and the epidemic became established around the late 1990s. The government's responses to combatting the disease have not been without challenges, as it started with a slow or no response period after the first democratic elections in 1994. The slow response period evolved into a period of denialism that HIV caused acquired immunodeficiency syndrome (AIDS) that continued from 1998 to 2003. By 2004, the country's policies eventually changed after pressure from civil society, and funding to help control the disease was allowed into the country. Antiretroviral therapy (ART) became available in the public sector in 2004, and by 2013 over two million people were on ART (5). By mid-2017, it was estimated that the HIV incidence rate was around 0.9% and 7 million (12.6%) of South Africans were living with HIV (6).

1.4 TB in South Africa

In 2017, South Africa was amongst the 30 countries identified by the WHO as having a high burden of TB. It had the eighth highest TB incidence with an estimated 322 000 cases in 2017, of which 193 000 cases were amongst HIV positive people. When accounting for population size, the country had the second-highest TB case notification rate of 567 per 100 000 population (1). Apart from people living with HIV, other vulnerable populations that were at high risk of having TB in the country in 2017 were the elderly, incarcerated individuals, and children under five years with an estimated TB prevalence of between 190 to 511 per 100 000 population in each risk group. Miners, migrants, and refugees, as well as health care workers, had an estimated prevalence of 1056 to 1470 per 100 000 population in each risk group. Lastly, communities living in informal settlements, diabetics, pregnant women and household contacts had an estimated prevalence of between 2703 to 3500 per 100 000 population (7). The treatment success rate for new and relapse cases of drug-susceptible TB for 2016 was 82% and 80% amongst HIV positive TB cases. Previously treated cases, excluding relapse cases, were reported to be 62% for 2016 (1). The country was also reported to be amongst the 30 high MDR-TB burden countries, with an incidence rate of 25 per 100 000 population. An estimated 3.4% MDR/RR-TB cases were new, while 7.1% were previously treated TB cases. The treatment success rate for 2015 for MDR/RR-TB cases started on the second line regimen was 55% and 48% for XDR TB cases (1). TB mortality rate is also high, with 39 deaths per 100 000 population in HIV negative and 99 deaths per 100 000 population in HIV positive people (1).

At the provincial level in 2015, six of the nine provinces in the country had incidence rates of above 500 per 100 000 population (8). The Eastern Cape had an incidence rate of 692 per 100 000 population; Kwa-Zulu Natal 685 per 100 000 population, Western Cape 681 per 100 000 population, Northern Cape 645 cases per 100 000 population, Free State 545 per 100 000 population and North West 528 per 100 000 population (8). Kwa-Zulu Natal and Mpumalanga had the highest TB rifampicin resistance rates with 8.3% and 8.6%, respectively (8). TB was a leading cause of death in six of the nine provinces, with proportions of 11.2% reported in Kwa Zulu Natal, 9.8% in Mpumalanga, 9.0% in Eastern Cape, 8.9% in North West, 8.4% in Free State and 7.4% in Limpopo. Gauteng province, Mpumalanga, and Kwa-Zulu Natal had the highest proportions of TB patients living with HIV at 68.4%, 68.1% and 63.6%, respectively (8).

1.5 The relationship between HIV and TB

TB infection occurs when a person harbours mycobacterium tuberculosis in the lungs, and latent TB infection (LTBI) is defined as a state when a person is infected but is not presenting with symptoms of TB disease because the bacteria are in a dormant state (9, 10). A person may progress from LTBI to active TB disease, at which point they present with signs and symptoms of the disease and can transmit to susceptible hosts (9). Though treatment is available for active TB disease, recurrent TB disease may occur when a person who was previously treated for TB, declared cured or completed their treatment falls ill with a new episode of TB either due to reinfection or relapse (11). TB relapse is the reactivation of an original strain, while reinfection is an infection of a new strain of *Mycobacterium Tuberculosis* (MTB) bacilli in an individual (12).

HIV infection in an individual leads to progressive immunosuppression and increased susceptibility to infections (13, 14). Infection with TB in these individuals also accelerates the progression to immunosuppression (13, 14). HIV increases the risk of rapid progression to TB disease after primary infection or reactivation of LTBI and recurrence of TB disease. The presence of HIV in an individual who has latent TB infection also increases the risk of progression of TB disease (15, 16). The risk of developing TB disease also doubles in the first year post-HIV infection (17). The annual risk of developing TB disease after TB infection in people living with HIV ranges between 5 to 15% compared to a lifetime risk of between 5 to 10% amongst HIV negative individuals (18). HIV positive patients also have a higher risk of having recurrent TB disease due to reinfection (19, 20). Although TB relapse is reported to be rare amongst HIV positive patients, TB relapse rate was reported to be 5% amongst severely immunocompromised HIV positive people who withdraw their TB treatment compared to 0.4% in HIV negative patients (13). TB increases the risk of AIDS-related deaths, while having HIV is a risk factor for developing TB disease (14, 20).

HIV infection modifies the clinical presentation of TB, and this varies with the extent of immunosuppression making it more challenging to diagnose and treat (13). The presentation of TB disease in people living with HIV may be different from that in HIV uninfected individuals as classic symptoms such as fever, weight loss, night sweats, haemoptysis, and cough may be atypical, few or not present (20, 21). Following recommendations by WHO, the TB screening tool has been modified for PLHIV such that if they present with any of the four symptoms; cough of any duration, fever, weight-loss and night sweats, they are presumed to

have TB and are eligible for further investigations to confirm active disease. People with HIV presenting with current cough are suspected of having TB compared to a cough lasting longer than two weeks in HIV negatives (22, 23). People living with HIV have a shorter mean duration of TB infectiousness, defined as smear positivity, compared to HIV negative patients, although this is dependent on whether they are in care and are diagnosed rapidly (24).

For many years, smear-microscopy has been used as a first-line diagnostic tool for TB. However, the use of smear-microscopy alone in the diagnosis of TB in HIV positive patients is more challenging as most patients present with smear-negative disease because such individuals are likely to have paucibacillary disease with the majority having extra-pulmonary TB (25, 26). In severely immunocompromised patients, the disease may present as both pulmonary and extra-pulmonary TB disease (20). The ability of chest X-ray (CXR) to screen or diagnose TB in people co-infected with HIV also presents challenges as it is largely dependent on HIV disease staging, which in turn affects the presentation of TB disease (21). In patients with high CD4 count, CXR has the classical findings of upper lobe disease, cavitation, or pulmonary fibrosis. However, in severely immunosuppressed patients, CXR has atypical findings (21). All these challenges result in delayed diagnosis leading to continuous transmission and delays in initiating treatment in these individuals, producing poor outcomes in those co-infected with HIV (13, 27).

1.6 TB and HIV management policy changes in South Africa

In 2011, South Africa started using a rapid and sensitive test called Xpert MTB/RIF as a first-line diagnostic tool for TB investigation (28). Challenges in diagnosing TB in HIV positive individuals persisted as the sensitivity of the test was 60% in smear-negative patients (29). To address this challenge, an Xpert algorithm was developed to guide health care workers in the management of patients undergoing TB investigation. The algorithm recommended that if an initial Xpert MTB/RIF test result of an HIV positive patient is negative, an additional sample should be taken for culture, and a chest X-ray should also be done. Additionally, the patient should be given antibiotics and reviewed after five days (30).

Over the years, the timing of when to initiate ART after TB diagnosis has also needed to be modified. By 2006, uncertainties of when to start ART in HIV positive patients with a confirmed diagnosis of TB still persisted. These uncertainties were driven by fears related to

drug toxicity, pill burden, and need to avoid paradoxical immune reconstitution inflammatory syndrome (IRIS) in these patients. During that period, WHO recommended that ART be given to HIV positive patients with extra-pulmonary TB (EPTB) as well as those with pulmonary TB (PTB) and a CD4 <350 cells/mm^3. The initiation of ART in those with a CD4 count above 350 cells/mm^3 was deferred to after completion of TB treatment. ART initiation was also only prioritised for patients with a CD4 <200 cells/mm^3 (31). A South African trial (SAPiT) conducted in 2008 amongst HIV and TB positive patients, showed that initiation of ART during the course of TB treatment improved survival in this population (32). Following the SAPIT trial, WHO changed the recommendations so that all HIV positive TB patients be started on ART regardless of the CD4 count. It also recommended that ART be started in HIV positive patients with a CD4 count <350 cells/mm^3 (33). However, in 2009 the South African government updated TB management guidelines and recommended that ART be provided only to HIV positive TB patients with CD4 count <200 cells/mm^3 and that ART should be deferred after completion of treatment for those who have a CD4 >200 cells/mm^3 (34). Only in 2013 did the country's guidelines change to recommend that ART be provided to all HIV positive TB patients regardless of the CD4 count; this was incorporated into the 2014 national TB management guidelines (30).

1.7 Mortality in those undergoing TB investigation

An individual is regarded as having symptoms suggestive of TB if they have any of four symptoms including; a cough for more than two weeks, fever, night sweats, unintentional weight loss or haemoptysis (22). Around 35.2% of primary health clinic attendees in South Africa come to the clinic because they have symptoms suggestive of TB (35). Even though people are attending health facilities to seek care in South Africa, it is estimated that 13% of TB cases are lost at the point of providing sputum for TB testing and getting a diagnosis (36). A high HIV prevalence has also been reported in this group, ranging between 34.6% and 62% (37-41).

High mortality in adults having symptoms suggestive of TB in community and health care facilities has also been reported. In sub-Saharan African countries, mortality at 12 months from the time of TB investigation is between 4.1% and 11.6% (37, 38). Even with the availability of the newer more rapid and sensitive diagnostic tools such as Xpert MTB/RIF, sub-Saharan African mortality of around 4.0% to 11.0% has been reported at six months from the time patients present at health care facilities with symptoms suggestive of TB (39, 40, 42).

Risk factors for mortality in this population include lower body mass index (BMI), an increasing number of TB symptoms, and people not knowing their HIV status. In people living with HIV, not knowing one's CD4 count, having a low CD4 count, not being on ART, and not receiving antibiotics were associated with mortality (39, 40, 42).

Furthermore, one post mortem study has shown that 31.8% of people with TB had died before a diagnosis was made (43). Other post mortem studies show that infectious and undiagnosed TB at the time of death ranged between 31.8% to 42.0% amongst those dying in hospitals and those dying at home (43, 44). A similar high prevalence of infectious and undiagnosed TB, ranging from 13.4% to 84.6%, has also been reported among hospitalised decedents in other low-and middle-income countries (LMIC) (45-47), suggesting the presence of barriers along the TB care cascade.

1.8 Mortality in people with TB disease on TB treatment

Mortality in those on TB treatment is also high. Post mortem studies in LMIC countries including South Africa, conducted in hospitals amongst people on TB treatment, the majority of whom were HIV positive, reported that TB was a leading cause of death ranging from 27% to 68% (48-50). However, TB is not always the leading cause of death in TB patients living with HIV. A South African study conducted in people living with HIV but who died at home and in communities, showed 68% had pathogenic bacterial infections, 47% had TB and 12% cryptococcal disease (51). In a study conducted in Brazil amongst TB patients living with HIV, the leading cause of death in this population was an invasive bacterial disease (46.9%) (52). In another study done in China amongst those on TB treatment, TB was the third leading cause of death contributing to 17% of deaths, while cancer contributed 19.5% of deaths and respiratory system diseases 36.4% of deaths (53).

Risk factors for death in this group are previous TB, unknown HIV status, being HIV positive and not on ART, lower CD4 count, and diagnostic uncertainty (52, 54, 55).

1.9 Barriers along the TB care cascade

The pathway of TB diagnosis and care starts with the onset of TB symptoms, leading to presentation at the health care facility, symptom screen, further investigations with laboratory-based tests and treatment initiation with the final step being TB cured or treatment completed. Along this pathway, patients can be lost, or delays could be incurred at each step. These areas can be categorised into: 1) non-initiation of care-seeking; 2) non-identification of patient as a tuberculosis patient; 3) loss to follow-up during the diagnostic process; 4) pre-treatment loss to follow-up, and 5) loss to follow-up while on treatment (Figure 1) (56, 57).

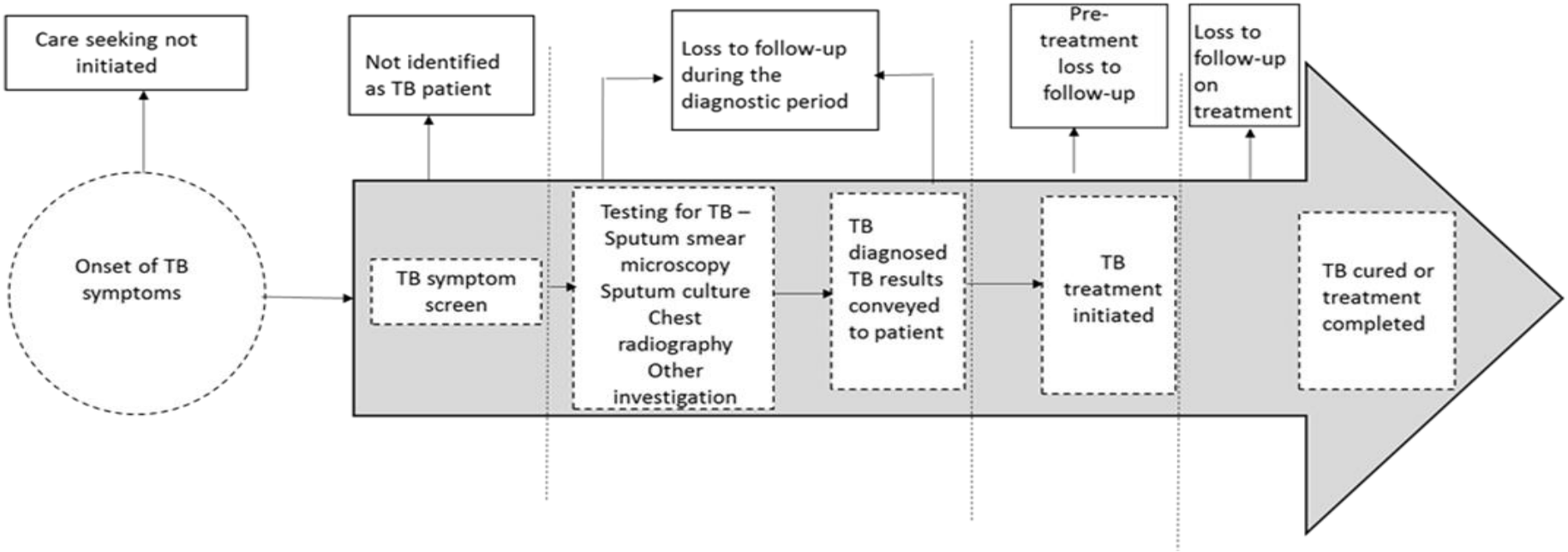


Figure 1: Description of TB care pathway from MacPherson et al. 2013.

Delayed TB diagnosis results in delayed TB treatment initiation, promoting ongoing TB transmission which results in poor treatment outcomes (58). Delays in diagnosis could be due to a patient presenting late for care or health system-related delays or both (59). In sub-Saharan Africa, patients presenting late for care were more likely to: have low levels of education; lack awareness of causes and transmissions of TB; believe themselves at low risk for contracting TB infection; live more than 5km from a health care facility, first seek care at religious, traditional and private practitioners; self-medicate; have traditional and cultural beliefs about the source of illness; fear stigma and discrimination associated with TB (60-65). Health system factors associated with delayed diagnosis were: providers degree of suspicion for TB, patients having multiple visits to a health facility before the diagnosis of TB, medical expenditure of TB related symptoms, non-satisfaction with service received by health providers, lost results and long turn-around time for obtaining results (64, 66-70), (57).

Pre-treatment loss to follow-up, defined as not starting on TB treatment after a diagnosis is made, ranges between 8-25% in some of the sub-Saharan countries, including South Africa (39, 40, 68, 71-73). Some barriers to starting TB treatment in South Africa were: patients not feeling well enough to return to the clinic; clinic appointments conflicting with work commitments; transport and distance challenges in accessing health facilities; desire to continue drinking and smoking (74). Another patient-related factor reported in a systematic review was lack of TB knowledge, while health system-related factors included: repeated health facility visits, delays in receiving results, and dissatisfaction with facility waiting times (56).

Loss to follow-up on TB treatment occurs when a TB patient has been started on TB treatment, but their treatment is interrupted for 2 consecutive months or more (11). Treatment interruption has been associated with structural, social, health service, and personal factors. These four factors have been shown to be equally important and interact, therefore affecting patients' adherence to treatment (75). Structural factors include poverty and financial burden of having TB (75, 76), while social factors include lack of support from family and community as well as fear of stigma (76, 77). Health service factors include the distance of health facility from patients' home, waiting period in the facility, patients' relationship with the health provider and patients' ability to communicate with providers about side effects experienced or providers asking about side effects of taking medication (75, 78). Personal factors include alcohol and tobacco use by patients, pill burden and patients knowledge of TB disease (75-77).

1.10 Barriers along the HIV care cascade

Despite the high HIV prevalence reported amongst those undergoing TB investigation (37-41), linkage into HIV care in this group was low (40, 79), a finding that might be linked to existing barriers along the HIV care cascade.

Prior to 2016, the HIV care cascade consisted of three stages: 1) HIV testing, 2) retention in pre-ART care until treatment initiation, and 3) retention on ART. Stage 1 involved getting a test for HIV and, if positive getting a CD4 count test done. Stage 2 was the period between enrolment into care, ART eligibility assessment, and the period until the patient met the ART eligibility criteria for initiating ART. Stage 3 involved patients retained in care after ART initiation (80). Attritions that could occur along this pathway included: individuals not enrolled in care after testing HIV positive, individuals lost from care before initiation on ART, and individuals lost from care after initiating ART (Figure 2) (80). A systematic review of studies in sub-Saharan Africa showed that 61.0% of individuals living with HIV did not know their HIV status; 43.0% of recently diagnosed HIV positive individuals did not complete an assessment for ART eligibility; 34.0% of those who were ART eligible did not start treatment, and only 35.0% of those initiated on ART were retained on ART (80). The recent changes in the HIV treatment guidelines where everyone who tests HIV positive should be initiated on treatment (81), have made the pre-ART stage obsolete.

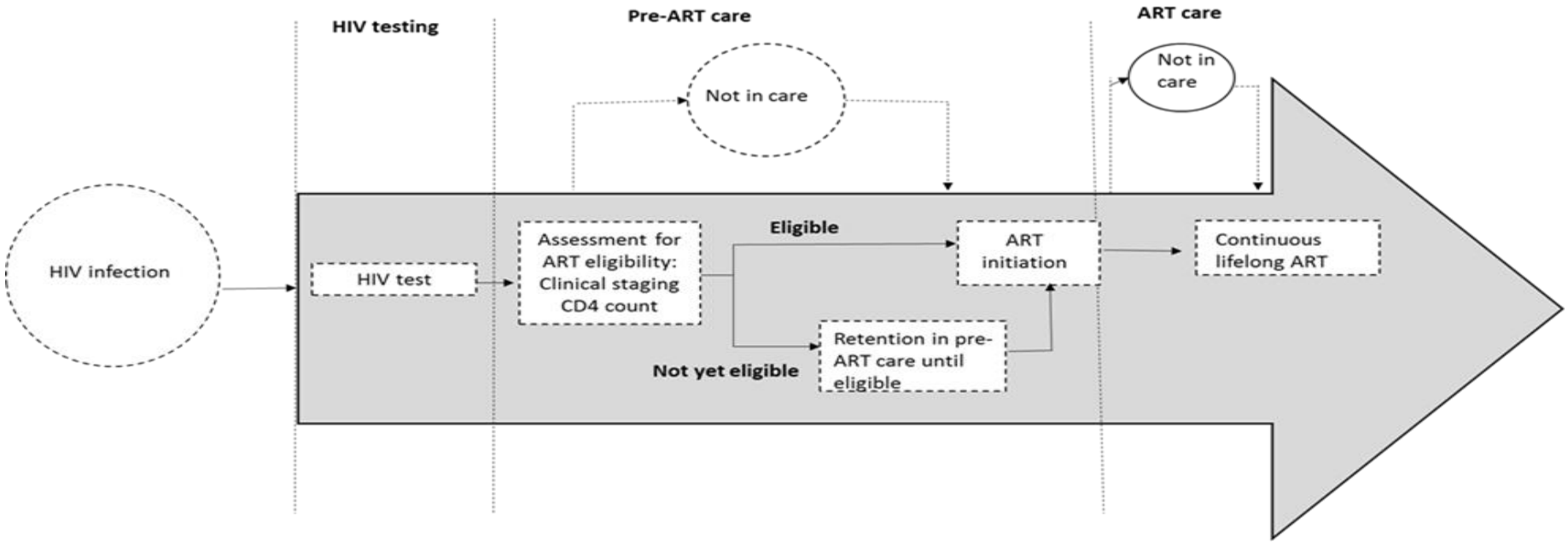


Figure 2: Description of HIV care pathway from Kranzer K et al. 2012.

1.11. Justification for undertaking this postgraduate research

The South African national strategic plan (NSP) for responding to HIV, TB, and sexually transmitted infections (STIs) has eight goals (82). The first goal seeks to accelerate prevention interventions to ensure the reduction of new HIV and TB infections as well as STIs. The second goal seeks to provide treatment, care and adherence support for all patients with HIV, TB, and STIs to reduce morbidity and mortality (82). These two goals also support the STOP TB targets of reaching 90% of everyone with TB and placing them on appropriate treatment. The NSP goals also subscribe to the UNAIDS treatment targets of ensuring that 90% of HIV positive patients know their status and 90% of these patients are on TB treatment (83). The work in this thesis contributes to these two NSP goals.

This thesis was based on work done amongst adults being investigated for TB. There is high mortality in those undergoing investigations for TB and those with infectious undiagnosed TB. The *Xpert for TB-Evaluating a New Diagnostic (XTEND)* study, implemented in 2012-2013, examined the trajectory that adults being investigated for TB undergo when seeking care in South African PHC facilities. The study reported not only high early mortality but an increased risk of death among HIV positive participants and those with an unknown HIV status (40). Understanding the causes of death in patients being investigated for TB is needed to help identify effective interventions to reduce mortality. There is currently limited data available in South Africa on causes of death in patients being investigated for TB in PHC facilities.

Existing challenges of diagnosing TB in PHC facilities were shown to be lengthy laboratory turn-around time and loss of laboratory results at clinics before being communicated to patients, (68) resulting in patients not starting on appropriate treatment timeously (pre-treatment loss to follow-up). Similarly, the XTEND study showed that though the use of Xpert MTB/RIF to investigate TB increased the proportion of patients with a positive TB test, this did not result in an increase in the proportion of patients starting TB treatment (40). The results suggested a gap in the South African health care system in supporting patients who are being investigated for TB to receive their test results on time and start appropriate treatment. Mobile Health (mHealth) interventions have been used in HIV and sexually transmitted infections (STI) management to communicate results via short message service (SMS) to

clinics and patients (84, 85). Case manager interventions to identify and address patients' needs, reduce barriers to accessing care, and encourage contact with health professionals at clinics, have been piloted. The intervention improved linkage to HIV care in patients that were supported through their health-seeking journey compared to those not supported (86, 87). Neither the mHealth intervention to relay results directly to patients nor the case manager intervention have been evaluated amongst adults being investigated for TB in South Africa.

WHO strategic priorities for TB are to achieve universal access to TB prevention, treatment, and care services (1). Furthermore, the South African NSP plans to reduce pre-treatment loss to follow-up rates in order to successfully treat 90% of those diagnosed with TB, and to ensure that 90% of all HIV positive patients are initiated on ART. These targets were adopted from the UNAIDS report (83).

This thesis will add to limited information on causes of death amongst people undergoing TB investigations in South Africa. It will further contribute to knowledge by piloting and evaluating the use of a case management strategy and mHealth application in supporting patients to initiate on TB treatment, so reducing pre-treatment loss to follow–up, and linking these patients into HIV care.

1.12 Research question

What are adults undergoing TB investigations dying from, and what interventions could be implemented to help reduce mortality?

1.13 Hypotheses

Amongst adults with symptoms suggestive of TB and who are undergoing TB investigations at primary health care facilities in South Africa:

1. TB is a leading cause of death, among people being investigated for TB
2. Support provided by a lay worker case manager to link into HIV care and initiate on TB treatment is feasible and acceptable to patients.
3. Those who receive their positive sputum test results via text messages will start on TB treatment sooner compared to those who return to the clinic to access their results.

1.14 Thesis Aim

To establish causes of death and pilot primary health care strategies to improve linkage to HIV care and initiation into TB treatment in adults being investigated for TB.

1.15 Thesis Objectives

1. To describe cause-specific mortality in a cohort of adults being investigated for TB using verbal autopsy.
2. To determine the feasibility and acceptability of a case-manager strategy to improve linkage to TB treatment and HIV care for adults being investigated for TB in primary health care facilities.
3. To explore the barriers and facilitators of TB treatment initiation and linkage to HIV care in primary health care facilities.
4. To assess the feasibility and acceptability of using an mHealth application to improve case identification and treatment initiation in adults being investigated for TB in primary health care facilities.

Table 1: Relationship between thesis objectives, the 3 studies and the 4 papers

	Studies			
	Verbal Autopsy (nested in XTEND trial)	Case manager study		mHealth study
Objectives		Papers		
	I **Cause-specific mortality using Verbal Autopsy (Appendix B)**	II **Case manager intervention - Quantitative study (Appendix B)**	III **Case manager intervention - Qualitative study (Appendix B)**	IV **mHealth application -Quantitative -Qualitative (Appendix B)**
To describe cause-specific mortality in a cohort of adults being investigated for TB using verbal autopsy *(Objective 1*)	X			
To determine the feasibility and acceptability of a case manager strategy to improve linkage to TB treatment and HIV care for adults being investigated for TB in primary health care facilities. *(Objective 2)*		X		
To explore the barriers and facilitators of TB treatment initiation and linkage to HIV care in primary health care facilities. *(Objective 3)*			X	
To assess the feasibility and acceptability of using an mHealth application to improve case identification and treatment initiation in adults being investigated for TB in primary health care facilities. *(Objective 4)*				X

CHAPTER 2: LITERATURE REVIEW

This section provides a literature review on how deaths are counted and types of methodologies for determining causes of death, strategies that are currently used to reduce TB morbidity and mortality, and strategies to improve linkage to HIV care as well as TB treatment initiation. The framework for this thesis is also presented.

2.1 Counting deaths

Keeping a record of which diseases cause most deaths in a population is crucial for a country's health department. This data assists governments to: monitor the burden of disease and plan for service provision, as well as distribute resources based on this evidence in order to have the greatest possible impact on improving people's lives. South Africa has a civil registration and vital statistics system. The United Nations defines civil registration as the continuous, permanent, compulsory recording of the occurrences and attributes of vital statistics pertaining to a country. A major advantage is that it is a legal requirement, and it provides legal documents for people to use, however, the system has incomplete data (88). In the South African context, which has a high HIV prevalence, the system underreports HIV-associated deaths (89, 90).

2.2 Determining causes of death

2.2.1 Pathological autopsy

The most accurate way of determining causes of death in individuals is by conducting a pathological autopsy. This process can be minimally invasive where samples of organs are collected from a deceased individual and then tested for disease or invasive where there is removal of whole organs from a deceased body. Not only does pathological autopsy allow the determination of CoD from tissue samples, it also enables the creation of a tissue sample repository for use in future research (91). However, performing pathological autopsy is limited by the costs as it requires medically trained staff, specialised laboratories with well-equipped storage facilities, and transportation of the corpse (91). Another limitation of pathological autopsy is the low rate of consenting from family members (91). A qualitative study reported that socio-cultural factors influencing consenting for autopsy were gendered

power relations, traditional and religious beliefs, and communication and trust. However, the study did not report on which of these three factors was more important than the rest (92).

2.2.2 Prevalence of TB related mortality using pathological autopsy

Studies performing pathological autopsies have been done in HIV positive and TB positive patients to understand the broad spectrum of disease present at the time of death. A study using minimally invasive autopsy in HIV positive patients with advanced HIV disease from primary health care clinics, showed 47.0% of the population had TB at time of death, and 38.0% of those with TB had not been initiated on TB treatment prior to death (51). Amongst adults with TB disease who were also HIV infected, pulmonary TB (68.0%), disseminated TB (60.0%) and bacterial pneumonia (26.0%) were among the leading CoD (49). South African studies using non-invasive autopsies and chart reviews to determine CoD amongst HIV positive patients on ART dying in hospital have shown that TB deaths ranged from 18.0-33.0% (93, 94). Another study using invasive autopsy amongst hospitalised HIV positive patients reported post mortem tuberculosis to be 38.0% (95). Studies amongst hospitalised patients who were mostly HIV positive in other LMICs, reported the leading cause of death determined by invasive or non-invasive autopsy and chart reviews to be TB, ranging from (28.4% -58.0%) (48, 96-100).

2.2.3 Using chart reviews to determine the cause of death

As it is not always possible to perform pathological autopsies, if a death occurs in a medical facility, chart reviews can be done to determine the causes of death. The advantage of chart reviews is that it is inexpensive, while the major disadvantage is that records might lack important data (101). Studies using this methodology in LMICs amongst HIV positive patients have also reported high TB-related mortality of between 6.6%-21.0% (102-104).

2.2.4 Verbal autopsy

An alternative method to ascertain the cause of death if a pathological autopsy cannot be performed or a death did not occur in a health facility is by conducting a verbal autopsy (VA). This method is used in settings where civil registration and vital statistics coverage is inadequate, and people are dying at home, situations that still prevail in LMICs. Verbal autopsy is used to determine causes of death based on interviews with carers of deceased patients at the time of death, using a World Health Organization (WHO) standardised VA tool. The tool extracts information about the deceased's signs, symptoms, and medical circumstances preceding death (105). The advantages of VA are that it describes the cause of death profile in a population, it is reproducible, does not require handling of a corpse and specialised medical staff (91). The disadvantages are that VA is not designed to determine the cause of death for individuals as cause-specific mortality fractions are determined using total population. The diagnostic specificity of this approach depends on the prevalence of the disease in a population, age of the deceased and their gender, and is dependent on the skill of the interviewer to extract data from the respondents, ability and willingness of respondent to recall events, as well as time from death to the date of interview (91).

The verbal autopsy questionnaire comprises of closed questions with "yes", "no" or "do not know" responses and an open narrative section. Interviewers, usually lay workers, administer the questionnaire to caregivers of the deceased. The caregiver gives a detailed account of the signs, symptoms, medical history of the deceased, and circumstances leading to their death (105).

The most widely used method for interpretation of VA data is physician-certified verbal autopsy (PCVA). PCVA involves physicians reviewing each interview and assigning causes of death according to the International Classification of Diseases, Tenth Revision (ICD-10) (106), (107). Disadvantages of using PCVA to assign causes of death are that the process is time-consuming and expensive in terms of physician remuneration, inter-and intra-observer variability amongst physicians is a problem as it depends on their training, experience and perception of local disease epidemiology, and repeatability of the process may be difficult to achieve (107). To overcome these challenges, computer-coded verbal autopsy (CCVA) methods were developed that use algorithms or Bayesian probabilities to assign cause of death. Methods using Bayesian probabilistic theory include interpreting verbal autopsy software (InterVA), which is expert-driven and generates up to three likely CoD (108-110).

Other CCVA methods include: Tariff (111), InSilicoVA (112), SmartVA (113), random forest (114), King-Lu (115), Simplified Symptom Pattern (116).

Validation of VA to determine CoD compared to hospital diagnoses as a reference showed that VA has a sensitivity of 89%, specificity 93%, and positive predictive value of 76% when assigning communicable diseases (117). A systematic review of data from LMIC assessing the performance of PCVA and five CCVA methods (tariff, InterVA, random forest, King-Lu and Simplified Symptom Pattern) with hospital based-deaths as a reference standard, reported that PCVA had a consistently higher specificity versus hospital assigned CoD (106). Data from five African countries validating the use of InterVA for measuring HIV/AIDS mortality showed that InterVA had a specificity of 90.1% (95% CI 88.7-91.4%) in identifying HIV/AIDS-related deaths (118). When comparing the interpretation of VA data using PCVA and InterVA in Africa and Asia, the overall concordance correlation coefficient (CCC) between the two methods was 0.83 (95% CI 0.75-0.91). The CCC improved to 0.97 (95% CI 0.96 -0.99) when PTB deaths and HIV/AIDS deaths were combined as a single cause (119).

Longitudinal studies in sub-Saharan Africa, using VA to ascertain CoDs in adults and adolescents in health and demographic surveillance system sites (HDSS) from data collected over one to four year periods, have shown that TB and HIV were leading CoD ranging from 9.4%-19.7% when using PCVA (120-123). Other studies interpreting VA data using InterVA in adults showed that TB attributed between 6.4% and 26.9% of deaths from data collected over two to 10 year periods (124, 125).

2.3 Strategies to reduce TB morbidity and mortality

WHO has been leading the fight against TB since 1993, launching strategies such as the DOTS in 1995, STOP TB in 2006, and END TB in 2015 in response to the epidemic. The END TB strategy includes TB prevention, care and control targets beyond 2015. The targets for 2035 are to reduce the 2015 projected 1.3 million TB deaths by 95% and reduce the 2015 projected 110 per 100 000 population TB incidence rate by 90% (126). The strategy comprises three pillars: 1) integrated, patient-centred care and prevention, 2) bold policies and supportive documents, and 3) intensified research and innovation. To achieve integrated, patient-centred care and prevention, four components need to be addressed: a) early diagnosis of TB and systematic screening of contacts, b) treatment of all people with TB and patient

support, c) collaborative TB/HIV activities and management of comorbidities, and d) preventive treatment of persons at high risk and vaccination against TB (126).

The current South African NSP for STIs, HIV, and TB aims to implement the 90-90-90 strategy for TB, adopted from the Stop TB partnership's Global TB Plan. The strategy entails finding 90% of all those with TB and initiating them on TB treatment, finding 90% of TB cases in key populations and starting them on appropriate treatment, and lastly successfully treating at least 90% of those diagnosed with drug-susceptible TB and 75% of those with drug-resistant TB (127).

2.3.1 Finding TB

Screening for TB

Currently, the initial step in finding active TB is screening patients for symptoms suggestive of TB. WHO defines systematic TB screening as the identification of people with suspected active TB in a predetermined target group, using tests, examinations or other procedures that can be applied rapidly (22). This process initially involves a symptom screen asking a patient if they have any of four symptoms including; a cough for more than two weeks or current cough in HIV positives, fever, night sweats, unintentional weight loss, or haemoptysis. The presence of any one of these four symptoms suggests a possibility of active TB and requires that further diagnostic tests be conducted. WHO recommends that anyone presenting at health facilities for TB screening should be offered an HIV test. In people living with HIV, it is recommended that screening for active TB should be done at each of their visits to a health facility (22). However, the performance of this four-screening rule in excluding TB amongst people living with HIV that are on ART has not been good. A systematic and meta-analysis assessing the sensitivity and specificity of the WHO four-symptom screening rule among people living with HIV found that it had a lower sensitivity amongst people on ART (51% , 95% CI 28.4-73.2) compared to ART naïve patients (89.4%,95% CI 83.0-93.5). The specificity of the screening rule was higher for those on ART (70.7%, 95% CI 47.8-86.4%) compared to those ART naïve patients (28.1%, 18.6%-40.1%) (128).

Diagnostic tools

Once an individual is suspected of having TB, a number of diagnostic tests can be done. For over 100 years, smear microscopy has been used to detect *Mycobacterium tuberculosis*.

Smear microscopy is cheap and has a relatively fast turnaround time, but the sensitivity of acid-fast bacilli (AFB) detection is low as the test requires 5000 - 10 000 organisms/ml of sputum to be positive (129). The sensitivity is further reduced in persons co-infected with HIV as these patients often release fewer numbers of organisms in sputum. Sputum culture test, which has traditionally been done on solid media such as Löwestein Jensen is more sensitive than smear, requires fewer bacilli per ml (10 -100) and is able to test for drug susceptibility. However, it has the disadvantage of requiring 2 - 6 weeks to grow the organisms (129). Radiological methods such as chest X-rays are also used to diagnose TB. The process is fast and has high sensitivity in HIV negatives (129). However, chest X-rays require specialised equipment and skilled physicians to interpret them, are non-specific to TB when used alone as a diagnostic tool and are unreliable in settings with HIV (129). The need to reduce TB-related morbidity and mortality has led to the development of new diagnostics tools that are more sensitive and rapid.

Over the past 20 years, WHO has endorsed the use of several new tools, which include 1) liquid culture with rapid speciation as the reference standard for bacteriological confirmation and 2) nucleic acid amplification tests. Liquid culture, mycobacterial growth indicator tubes (MGIT) have a shorter time to positivity but are more likely to be contaminated (130, 131). Nucleic acid amplification tests such as line probe assay and Xpert MTB/RIF increase DNA and RNA segments to rapidly identify the microorganisms in a specimen and can detect *MTB* within hours (129). Xpert MTB/RIF assay is currently used as a first-line diagnostic tool for TB in South Africa. Xpert MTB/RIF is a fully automated, cartridge-based, nucleic acid amplification test for rapid detection of *MTB* and rifampicin resistance with the results available in two hours (132). The test's sensitivity ranges from 70.0% to 100% in culture-positive disease and 60% in smear negatives. Specificity ranged from 91.0% to 100% (29). In HIV positive patients enrolling on antiretroviral therapy (ART), case detection increased by 45.0% with a sensitivity of 73.0%, compared to the 28.0% in microscopy (133). However, Xpert MTB/RIF assay is not good as an early sputum biomarker of monitoring response to TB treatment. A study showed that 27% of microbiologically cured patients after 6 months treatment were still Xpert positive, compared to 3% Lowenstein-Jensen and 4% MGIT cultures(134). The test is also more likely to generate false-positive results in patients being retreated for TB compared to those being treated for the first time, with a previous study reporting Xpert positive being 14% in retreatment cases and 8% in new cases (135). This is due to Xpert detecting the presence of non-viable mycobacterium bacilli. A new generation of Xpert called the Xpert MTB/RIF Ultra assay showed an additional sensitivity of 5.0%

compared to its predecessor. The greatest gains in sensitivity were amongst HIV positive patients and smear negative culture positive patients (136). This tool is currently being rolled out in South Africa.

Contact tracing

Contact tracing is done to enable people who have been exposed to potentially infectious cases of TB to undergo screening for TB disease. This process ensures that people who are at an increased risk of acquiring TB would be provided with preventive therapy or started on TB treatment if they have active TB. South Africa requires that contact tracing for all households or close contacts of an index case be conducted as recommended by WHO. An index case is defined as anyone who had smear–positive pulmonary TB, multi-drug resistant TB, and is living with an HIV positive person or a child under five years of age (137). The recommendation was made as a result of a systematic review and meta-analysis showing a TB prevalence of 3.1% (95% CI 2.2-4.4%) amongst household contacts, microbiologically proven TB of 1.2% (95% CI 0.9-1.8%) and latent infection of 51.5% (95% CI 47.1-55.8%) (138).

2.3.2 Treating TB

Drug susceptible TB treatment

Anti-TB treatment is provided with the aim of curing TB in patients, decreasing TB transmission to others, and preventing deaths from TB or complications linked to having TB. The drugs that are currently used in treating drug-susceptible TB, are rifampicin, isoniazid, pyrazinamide, ethambutol and streptomycin. TB treatment is taken over a period of six months with two months intensive phase and four months continuation phase. Currently, the South African National Department of Health (NDOH) requires that anyone with susceptible TB be started within two days of diagnosis. However, there is no published data on how often this occurs (30).

Treating TB in HIV positive people

Initiation of TB treatment in TB patients living with HIV cannot be done in isolation of ART as ART plays an important part in reducing mortality in this group (139, 140). The current TB management guidelines recommend that if an HIV positive person develops TB while they

are already on ART, they should continue taking their ART and should be initiated on TB treatment (30). For those HIV positive patients who get diagnosed with TB before starting on ART, their CD4 count is an important measure of when they start taking ART after initiating TB treatment. Patients with CD4 < 50 cells/mm^3 should be started on ART within 2 weeks of starting TB treatment and those with CD4 count ≥ 50 cells/mm^3 within 2-8 weeks after starting TB treatment. These guidelines on the timing of ART initiation in this population were produced as an effort to reduce the development of TB-IRIS and death (30, 141-143).

2.3.3 Prevention of TB disease

Vaccination

Bacilli Calmette Guerin (BCG) is the only TB vaccine available for use to prevent TB. BCG has efficacy of between 0-80% and offers protection against death, TB meningitis and disseminated TB when given after birth (144, 145). BCG is given to all children except those with signs of AIDS, living in countries with high TB prevalence. Although BCG prevents TB disease in children, its protective effect seems to wane with time and therefore, does not prevent the development of TB in adulthood. Recently, an ongoing phase 2b trial showed that M72/$AS01_E$ vaccine provided 54% protection against active TB disease in adults infected with *MTB* (146).

HIV diagnosis and treatment

HIV prevention is important for TB control. Regular testing for HIV leads to early diagnosis of HIV and early ART initiation in those who have tested HIV positive. Early ART initiation leads to a decreased risk of developing AIDS-related illnesses and reduces the risk of *MTB* infection and active TB. Receiving an HIV negative test result for those testing for HIV might lead to behavioural change and uptake of precautionary measures such as consistent condom use to prevent HIV infection. The SA government launched a national HIV counseling and testing campaign in 2010 to increase the uptake of HIV testing (147). This shifted HIV testing from being patient-initiated to provider-initiated and resulted in 13 million people knowing their HIV status and approximately two million HIV positive people on ART by 2012 (148). By 2014, South Africa adopted the UNAIDS 90-90-90 treatment targets which aim to have 90% of people living with HIV knowing their HIV status, 90% of HIV positive people on treatment, and 90% of those on treatment with an undetectable viral load by 2020 (83, 148). ART eligibility in the country changed from all HIV positive TB patients or a CD4 count ≤

350 cells/mm^3 in 2013, to having CD4 count ≤ 500 cells/mm^3 in 2015. The country took further steps to curb the HIV epidemic by adopting universal test and treat in 2016 where everyone testing positive for HIV is expected to start on ART regardless of CD4 count (148).

Effects of ART on TB disease

The provision of ART for all HIV-positive people regardless of CD4 count, decreases the risk of incidence of TB (149). ART reduces the risk of TB incidence by 65% (hazard ratio =0.35, [95% CI 0.28-0.44]) in people living with HIV. The protective effect of ART on TB incidence was also present irrespective of the CD4 count that a person had when starting ART (149). TB incidence is high in patients who have just started ART compared to those receiving ART for longer (150, 151). A modelling study has predicted that with the adoption of universal test and treat and a coverage of 95%, starting ART as soon as people test HIV positive will further decrease HIV-related TB by 98.4% (97.8%-98.9%) (152). ART also reduces mortality in HIV positive patients on TB treatment by between 44% and 71% (153).

TB preventive therapy

Isoniazid preventive therapy (IPT) is provided to individuals who are unlikely to have active TB but are at increased risk of developing TB. These include HIV positive patients as well as children younger than 5 years who are contacts of a TB positive patient. In HIV positive patients, IPT reduces the risk of developing TB disease (154) and of recurrent TB (155). IPT was reported to offer 35% TB risk reduction (relative risk = 0.65, 95% CI [0.51-0.84]) in HIV positives and a larger 52% TB risk reduction (relative risk = 0.48, 95% CI [0.29-0.82]) in HIV positives with a positive tuberculin skin test (TST) (154). However, in miners, the mass provision of IPT for nine months regardless of HIV status did not reduce either the incidence or prevalence of TB or the rate of death from any cause (156). In studies done among HIV infected individuals in Ivory Coast, Ethiopia and Brazil, IPT was shown to have an impact on mortality, with the risk of death reduced in patients on IPT compared to those not on IPT (157-159). Initiating HIV positive patients without TB on IPT and ART further reduces the risk of developing TB disease and death (160, 161). In settings where TB incidence is high, the protective effect of IPT once a patient has stopped taking the therapy wears off quickly and therefore, longer durations are recommended (156). This led to WHO recommending that in high TB incidence settings, people living with HIV who do not have TB be provided with IPT for at least 36 months (162). Recently, WHO has recommended that a weekly dose of a combination of rifapentine and isoniazid for three months (3HP) may be used as an alternative

to IPT (10). Other preventive therapy regimens that are being considered are a daily dose of rifapentine and isoniazid for one month (163) and a daily dose of rifampin therapy for four months (164). Rifamycin based regimens have greater sterilizing activity, are less hepatotoxic, and have shorter treatment courses compared to isoniazid only regimens (165, 166). These short treatment courses have led to high treatment adherence and completion rates compared to taking isoniazid for six months or longer (166). A modelling study suggested that 3 months rifamycin-based regimens cured 19% to 100% of latent TB infection in HIV positive people compared to 0% with an interquartile range of 0 to 39% for isoniazid (167). The study also suggested that the curative effect of rifamycin-based regimens would have durable patient benefit in HIV individuals in settings where risk of reinfection is low but in high HIV settings, the effect might not be evident due to the high risk of TB reinfection (167).

TB infection control

Infection control involves several measures that together aim to reduce the risk of TB transmission in populations (168). These include managerial, administrative, environmental, and personal protective equipment controls. Managerial measures involve the development of financial plans, policies, assessment of the appropriateness of existing structures or need for new ones, and surveillance of TB disease. Administration measures control the spread of bacteria within health facilities by prompt identification and attendance of patients with TB symptoms, teaching them cough etiquette, and separating them from other patients. Environmental controls reduce the number of bacteria in the air by use of ventilation systems (natural or mechanical) or ultraviolet germicidal irradiation lights if ventilation cannot be achieved. The use of personal protective equipment occurs when health care workers use N95 masks to prevent the inhalation of bacteria (168).

2.4 Strategies to improve linkage to care

2.4.1 Task shifting

Task shifting is defined as the redistribution of appropriate tasks from more highly qualified health care workers to less qualified individuals requiring less training for the efficient use of available staff (169). This strategy is used in PHC facilities to address human resource constraints and relieve overloaded health care workers. In HIV care in PHC settings, community health workers / lay counsellors have been given responsibility such as health

promotion (170), HIV counselling and testing (171), and treatment support (172). People living with HIV can also be trained on disease self-management, and to provide HIV support, treatment adherence, and psychosocial support to fellow patients (173). The task-shifting strategy was shown to provide cost-effective and high quality care to people living with HIV (174). The strategy has also been used in TB care where a lower cadre of staff has been used to: screen for TB and provide counselling and treatment adherence support in PHC facilities (175).

2.4.2 Support interventions

Support interventions such as case management are defined as the facilitation or coordination of a patient by health care staff to ensure that the patient obtains and continues to receive appropriate medical care (176). The strategy, coupled with strength-based counselling technique – counselling that identifies a patient's strengths and focuses on those strengths to improve linkage to care – has been adopted in the United States of America to assist with linkage to care of people living with HIV (177).

The use of case managers amongst people living with HIV has been associated with increased ART usage, viral suppression, higher CD4 count, decreased sexual risk behaviours and unmet support needs (86, 87, 178-180). Few studies have assessed the acceptability of these support interventions by health providers and patients. One study done in South Africa amongst people living with HIV and using peers (fellow HIV positive people) as case managers showed that the intervention was well-received by patients (181). Another study done in Rwanda amongst people living with HIV, using either a social worker or nurse as case managers, reported that patients appreciated the emotional and social support they received from case managers. The study also reported that the health providers appreciated what the case managers did as they followed up on patients' needs (182). In TB care, the use of case managers to support TB patients to seek care were evaluated in a hospital setting. These case managers were responsible for: providing TB education to patients and their families; follow-up of patients to check for treatment adherence and side effects of treatment; and tracking of patients who missed appointments (183). Patients supported by this hospital-based case manager had higher rates of successful treatment outcomes – either being cured or completing treatment – compared to those without case managers (183).

2.4.3 mHealth interventions

Mobile health (mHealth) is the use of mobile devices in the delivery of medical care. mHealth technologies have been used as: i) communication tools between individuals and health services, ii) health monitoring and surveillance tools, iii) consultation tools between health care professionals, and iv) to access information for health care professionals at point of care (184). Implemented interventions within HIV care have either been: i) patient-centered focusing on behavioural changes, ii) health system inclined focusing on data collection and reporting tools, and iii) populations inclined focusing on disease awareness campaigns (185). In studies in sub-Saharan Africa, mHealth interventions have been tested as communication tools sending reminders via text messages to patients needing linkage to care. The interventions improved adherence to ART and were perceived as useful by patients (186, 187) (84, 85), were used to communicate with higher-level professionals, (188) as a support intervention for lower cadre staff to communicate with higher-level professionals, (188) and for health promotion by assisting with education and motivation for treatment adherence (189). In TB, mHealth interventions sending text messages have only been used to support patients by promoting adherence to TB treatment. However, there is poor quality data on the effect of text messages on TB treatment adherence (190) as well as for health promotion by assisting with education and motivation for treatment adherence (189).

The literature review reveals several gaps which this postgraduate research aims to address.

- While causes of death are well described for hospitalised HIV positive and TB positive patients, little is known on causes of death in those undergoing TB investigation in PHC facilities.
- While a case manager support intervention for HIV positive patients has been well documented, there is limited information on this strategy to support an individual seeking care for TB.
- mHealth interventions have been used in HIV care for communication, results delivery, support, health promotion and treatment adherence. However, there is limited data on use of this technology in the delivery of results to patients attending for TB care in PHC facilities.

2.5 Thesis Framework

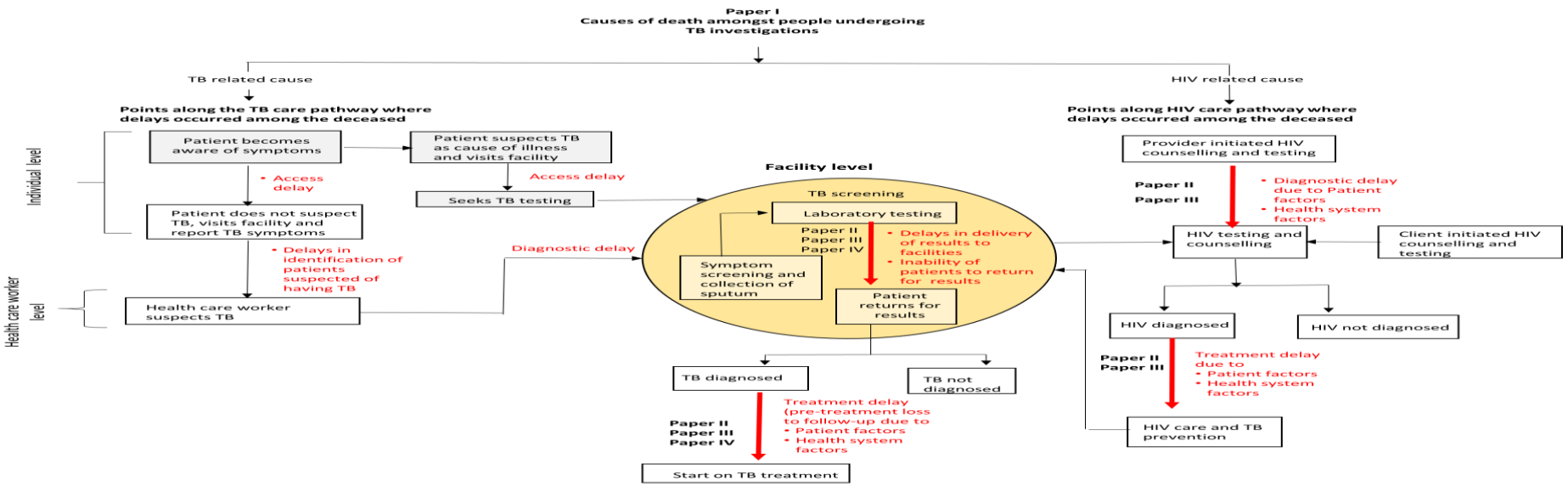


Figure 3: Thesis framework adapted from Corbett EL 2013 on TB Screening in high HIV prevalence settings.

The grey boxes indicate pathways where patient seeks TB care. The individual level parenthesis shows areas in the TB care pathway that are dependent on the patient. The health care worker parenthesis shows an area in the pathway that is dependent on the health care worker. The yellow circle indicates that the enclosed activities occur at facility level. The red arrows indicate areas along the TB care and HIV care pathways where delays could occur and also which delays are addressed by papers included in the thesis.

Paper I: determines causes of death in people being investigated for TB; Paper II: addresses HIV diagnostic delay, ART delay, and TB treatment delay; Paper III: describes barriers and facilitators of HIV and TB care using the case manager intervention; Paper IV: addresses delays of patients receiving TB test results and treatment start delay using the mHealth intervention.

This thesis began with ascertaining causes of death in adults being-investigated for TB using verbal autopsy methodology. In an effort to understand possible reasons for these deaths, patient and health system delays were identified along the TB and HIV care pathways affecting the care-seeking behaviour and quality of care of adults being-investigated for TB. In response, two interventions aiming to address identified delays occurring at the facility level, where patients seek care, were piloted.

Figure 3 is a framework adapted for this thesis from Corbett EL et al. 2013 (191). The framework shows where delays can occur along the TB and HIV care pathways with patient entry points into TB and HIV care pathways occurring at the facility level. For the TB care pathway, the framework shows that the entry point could either be patients being aware of their symptoms and visiting facilities to seek care, due to suspicion of TB as the cause of illness or patients being aware of their symptoms and visiting facilities to seek care with lack of suspicion of TB disease. Both these entry points would lead them to be screened for TB, tested for TB, and started on TB treatment if found to be TB positive. The delays that exist in this pathway are access delay, diagnostic delay, delays in receiving results, and treatment delays. Access delay is due to patient-related factors linked to seeking timely care at health facilities, diagnostic delays due to health system-related factors linked to the diagnosis of TB, and treatment delays due to patient and health system-related factors linked to TB treatment initiation.

For the HIV care pathway, the framework shows that HIV testing and counselling could be initiated by a client or a provider. It also shows that once a patient tests HIV positive, they are linked to HIV care and provided with TB prevention medication in those who do not have TB. The delays highlighted in the HIV care pathway are diagnostic and treatment delays. Diagnostic delays are due to health system and patient-related factors linked to the diagnosis of HIV; treatment delays are due to patient and health system-related factors linked to ART initiation.

Although patient-related access delays were highlighted as barriers for TB and HIV care, this thesis specifically examines interventions addressing delays occurring at PHC level when patients are already seeking care. PHC level was chosen as it presented an opportunity to influence processes to initiate TB treatment and link patients to HIV care.

Two interventions (an mHealth and case manager intervention) were piloted to attempt to address the delays that occurred at PHC level along the TB and HIV care pathways. Points at which the different delays occur along the pathway are highlighted in red in the framework and pathways that the two interventions aim to address have red coloured arrows (Figure 3). The case manager intervention aimed to address delays in getting an HIV diagnosis, initiating ART and TB treatment (papers II and III). Furthermore, paper III explored barriers and facilitators to testing and initiating of TB and HIV treatment. Paper IV reported on the mHealth intervention, addressing delays in patients receiving TB test results, and initiating TB treatment.

CHAPTER 3: METHODOLOGY

This section includes a description of how the three studies that constitute this thesis link to a preceding large pragmatic trial; as well as the settings, populations, specific procedures, and analyses undertaken for each of the studies.

For this thesis, linkage to TB care is defined as TB treatment initiation.

3.1 Linkage of the three studies to XTEND trial

This thesis comprises of three studies: a cause of death study and two pilot intervention studies (case manager and mHealth interventions). The cause of death investigation was a sub-study of a parent study called XTEND (Xpert for TB-Evaluating a New Diagnostic trial), while the two pilot studies were conceptualised based on the findings of high pre-treatment loss to follow up and mortality from the XTEND trial (Figure 4) in order to address challenges identified in the TB and HIV care pathways during the trial.

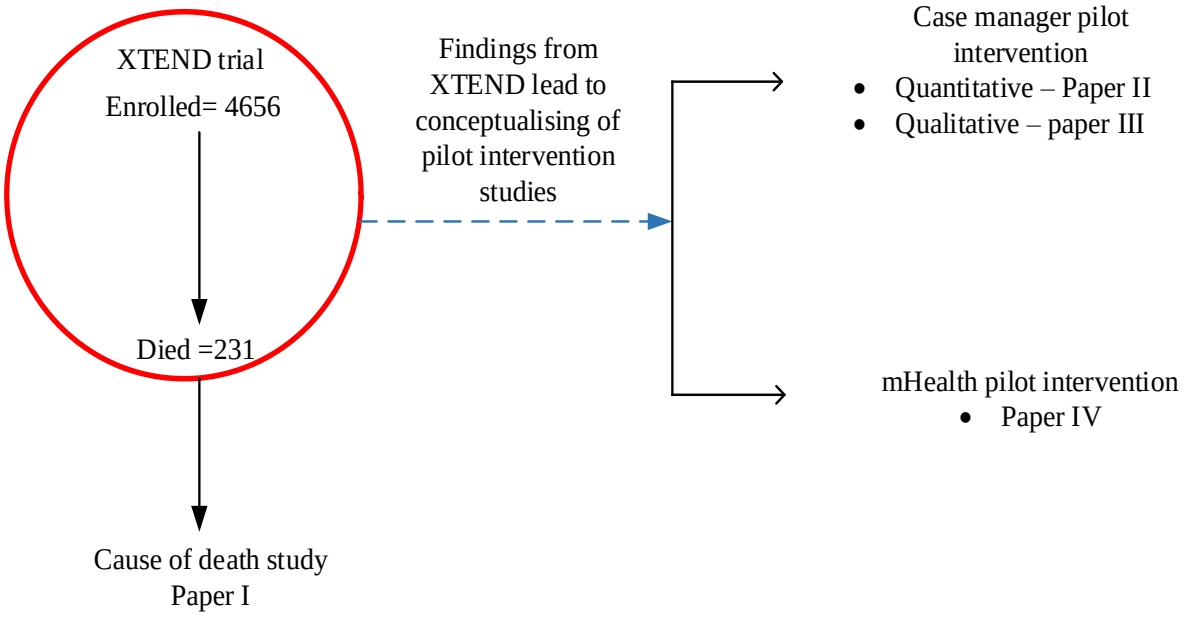


Figure 4: Relationship of the three thesis studies to the XTEND trial.

The red circle shows the population enrolled in the XTEND study and those who died during the study's follow-up period. The blue arrow indicates that the two pilot studies were conceptualised from the XTEND findings.

3.2 Brief overview of XTEND trial

XTEND was embedded in the Phase 3 national roll-out of Xpert MTB/RIF across national health laboratory system (NHLS) networks. Xpert MTB/RIF was used as the first-line diagnostic tool in place of smear microscopy for the diagnosis of tuberculosis (40). The aim of the trial was to evaluate the use of Xpert MTB/RIF compared to smear microscopy in TB investigation and its impact on patient outcomes. This was a pragmatic cluster randomized trial, conducted from June–November 2012, where a laboratory was a unit of randomization. A cluster comprised of one laboratory and two PHC clinics selected from high burden districts in four provinces (Eastern Cape, Gauteng, Free State, and Mpumalanga). Intervention laboratories received the GeneXpert platform, with one specimen submitted for Xpert MTB/RIF analysis, replacing the two specimens submitted for smear microscopy at diagnosis according to the NHLS algorithm for the diagnosis of TB. Based on the results of an Xpert MTB/RIF assay conducted on a single sputum, persons were started on TB treatment if positive for MTB and rifampicin sensitive. Drug susceptibility testing was done on MGIT culture if Xpert MTB/RIF result was rifampicin resistant. In alignment with South African guidelines, individuals were also investigated further for TB with chest X-Ray/culture if HIV-positive, Xpert MTB/RIF negative or requested to submit a second specimen for Xpert MTB/RIF if the Xpert MTB/RIF test was unsuccessful. In the XTEND study, control laboratories received standard of care, as per the South African national guidelines which was doing two smears for all individuals suspected of having TB. A culture would be done if any of the following criteria were met: smear-negative, and symptomatic which included persons living with HIV; persons at risk of multi-drug resistant TB (MDR-TB); or persons with prior history of TB. The study was conducted in 40 clinics in the four provinces. Patients were eligible to take part in the XTEND study if they were aged ≥ 18 years; identified by the clinic staff as needing TB investigations and had provided sputum specimen for TB investigation; were resident in the clinic catchment area and not planning on relocating from that area within eight months. XTEND study staff recruited consecutive patients presenting in facilities with less than five patients undergoing TB investigation per day, or every second or third patient in

facilities with 6-15 patients undergoing TB investigation per day. The XTEND study enrolled 4656 participants (40).

To address the postgraduate research objectives, different methodologies from the three studies employed in the thesis were used. These methodologies are described in papers I–IV.

3.3 Data sources

This postgraduate research uses data from the following sources:

- Verbal autopsy (August - November 2013) nested within the XTEND study

  This involved interviews using WHO VA tool with caregivers aged 18 years and above of deceased XTEND study participants.

- Evaluation of a case manager intervention (September 2014 - March 2015)

  This involved piloting a case management intervention for patients being investigated for TB aged 18 years and above, to improve linkage into TB and HIV care. The study also included a qualitative component with in-depth interviews conducted with patients, health providers, and case managers.

- Evaluation of an mHealth intervention (September 2015 - April 2016)

  This involved piloting an mHealth intervention that captured TB case identification data and relayed results via text messages to patients being investigated for TB aged 18 years and above. The study also included a qualitative component with interviews conducted with patients and health care providers.

3.4 Verbal autopsy – methodology for paper I

3.4.1 Study aim:

To assign the cause of death using verbal autopsy methodology, amongst adults being investigated for TB.

3.4.2 Setting

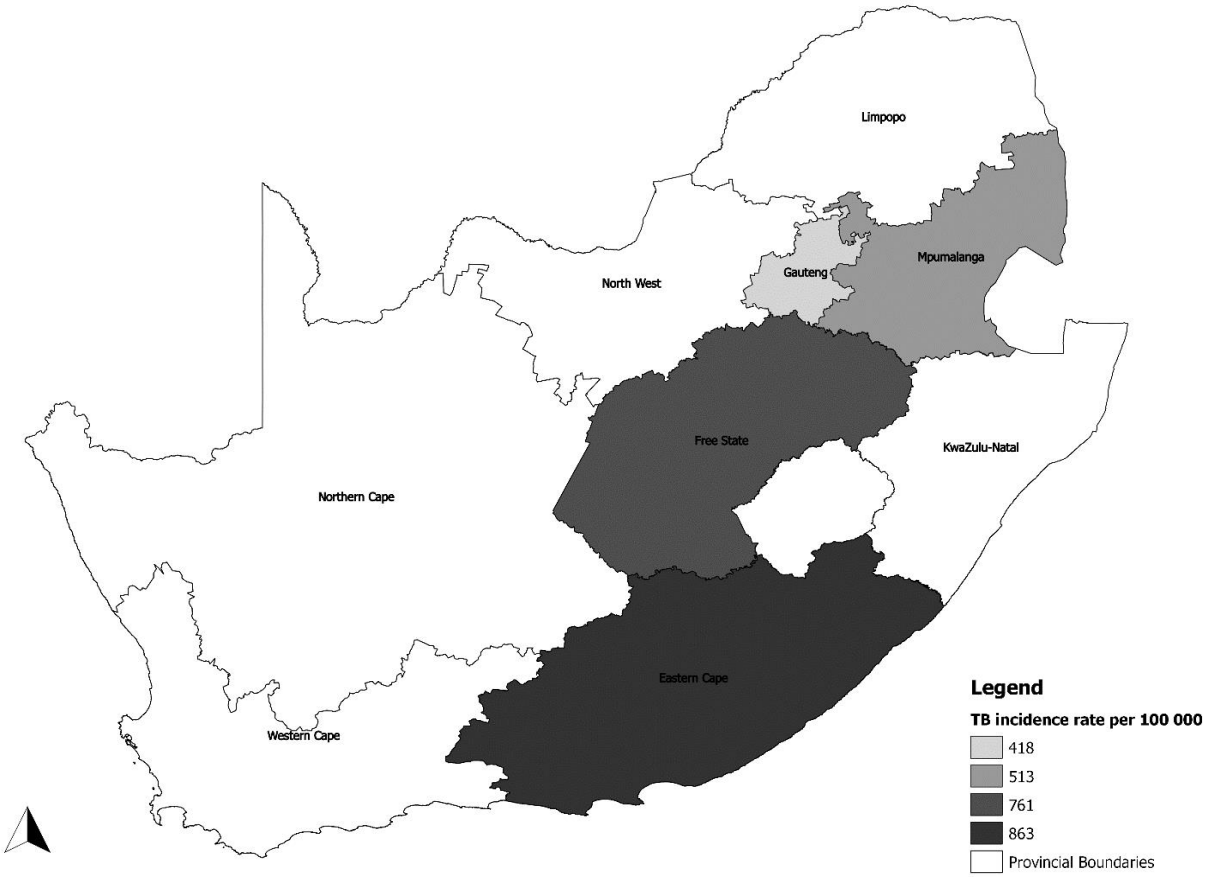


Figure 5: Map showing the provinces of South Africa (Gauteng, Mpumalanga, Free State and Eastern Cape), with TB incidence rates for 2012 and location of XTEND study indicated in the different shades of grey.

The study was undertaken in Mpumalanga, Gauteng, Free State, and Eastern Cape (Figure 5). Mpumalanga province is made up of three districts, Gert Sibanda, Nkangala, and Ehlazeni. It is the second smallest province but ranks as the sixth most populous province in the country. The province had a TB incidence rate of 513 cases per 100 000 population (8). Gauteng province has five districts namely: Ekurhuleni Johannesburg, Tshwane, West rand and Sedibeng. Data collection excluded Sedibeng district. The province is the smallest in the country but densely populated and referred to as the economic hub of South Africa. The TB incidence rate within the province was 418 cases per 100 000 population in 2012 (8). The Free State is the third-largest province with second-lowest population density and is found at the center of the country. It is divided into five districts, namely: Xhariep, Lejweleputswa,

Thabo Mofutsanyane, Fezile Dabi and Mangaung. It had a TB incidence rate of 761 cases per 100 000 population in 2012 (8). Eastern Cape Province is the second largest province with the third-largest population in the country but is one of the poorest provinces in the country. The province is made up of 7 districts namely: Alfred Nzo, Joe Gqabi, Chris Hani, Sarah Baartman, OR Tambo, Amathole, Buffalo city, and Nelson Mandela bay (192). It had a TB incidence rate of 813 per 100 000 population in 2012 (8).

3.4.3 Study design

This was a cross-sectional study nested within the XTEND trial.

3.4.4 Study population

The population was all participants who died during the XTEND trial.

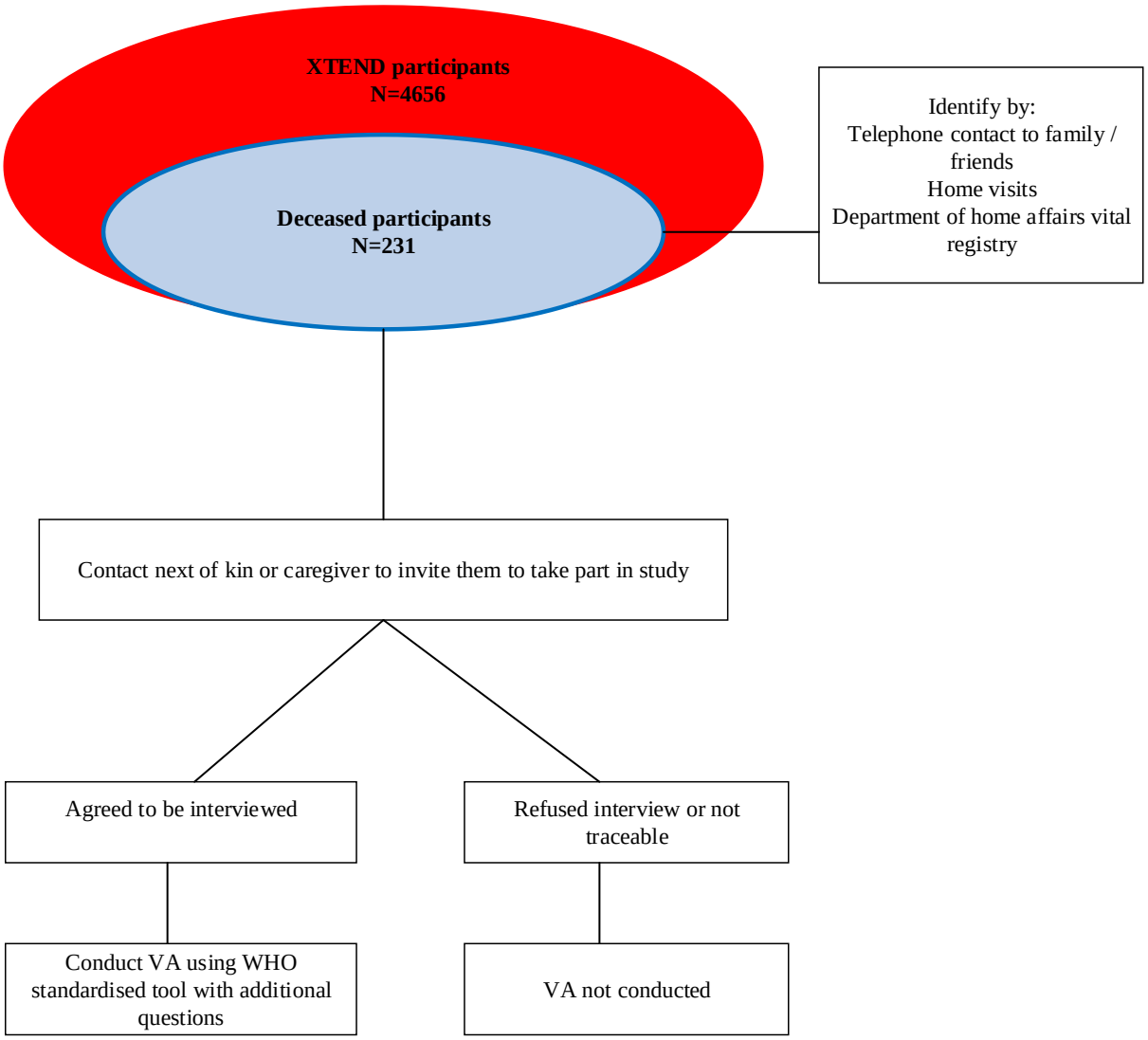


Figure 6: Identification of deceased XTEND trial participants and recruitment into verbal autopsy study.

The red oval (Figure 6) represents the XTEND trial participants, and the blue oval represents deceased XTEND trial participants.

3.4.5 Study procedures

During the XTEND trial, participants provided the study team with contact details of their family members or close friends to assist with their follow-up if they could not be located. The identification of the deceased participants is shown in Figure 6 above. Caregivers of identified deceased participants across the four provinces were telephonically contacted by

research staff to invite them to participate in the study and set up an interview date. If they could not be contacted telephonically, a home visit was done. Research staff were trained in administering the 2012 WHO standardised verbal autopsy tool, which focused on signs and symptoms of the terminal illness; they were also trained on bereavement counselling. Training on the administration of the WHO VA tool was done by staff from a health and socio-demographic surveillance site who had extensive experience in administering the tool, while the bereavement counselling training was done by a trained clinical psychologist. The VA tool comprised of an open narrative section and closed questions on signs and symptoms. The additional questions asked included whether the deceased had started TB treatment and ART. Caregivers were interviewed in either Xhosa, Zulu, siSwati, Sotho or Sepedi and this was done at a place of their convenience (Paper I).

3.4.6 Data management and assessment

The cause of death assessment was done in two ways: using the verbal autopsy interpretation software InterVA-4.3 (http://www.byass.uk/interva/products.htm) and physician certified verbal autopsy (PCVA). Questionnaires were excluded from the process of assigning a cause of death if the entire quantitative or narrative sections were incomplete. The PCVA methodology involved two physicians independently assigning an immediate and underlying cause of death for each decedent using ICD-10 codes. If the physicians assigned different causes of death for a decedent, they would meet to discuss and try to reach consensus. If consensus was not achieved, the case was referred to a third independent physician. If consensus was not achieved, the cause of death was classified as indeterminate or ill-defined. Individual CoD assigned by PCVA were processed further using mortality medical data system (MMDS) software, which generates underlying CoD from multiple CoD. The output generated by MMDS was categorised into WHO 2012 VA cause of death groups; cause-specific mortality fractions (CSMFs) were calculated by dividing the number of deaths assigned to a group by the total number of deaths.

The same VA data used to determine the cause of death using PCVA methodology was imported into the InterVA-4.03 software. The model was programmed to have low malaria and high HIV prevalence and detected only “Yes” responses to determine the cause of death. It also provided up to three probable causes of death for a deceased individual and categorised a cause of death as indeterminate if it was unable to reach a conclusion. InterVA-4 assigns

only PTB as a TB-related cause of death, classifying all extra-pulmonary TB as “other unspecified infectious diseases”.

3.4.7 Study Outcomes

The cause of death study firstly reported on proportions of causes of death assigned to HIV, TB and other groups of diseases as determined by PCVA and InterVA methodologies. Secondly, cause-specific mortality fractions, calculated by dividing the number of deaths assigned to a group of disease by the total number of deaths, were generated for PCVA and InterVA methods.
Thirdly, a comparison of percentages of the cause of deaths for the different disease groups and cause-specific mortality fractions generated for the two methods was done.

3.4.8 Statistical analysis

Demographics were described using proportions for categorical variables such as gender, nationality, number of TB symptoms, as well as medians and interquartile ranges for continuous variables such as age. For PCVA individual CoD analysis, the following ICD-10 codes were considered to be HIV-related deaths: B20 (HIV resulting in infectious and parasitic diseases), B21 (HIV disease resulting in malignant neoplasms), B22 (HIV disease resulting in other specified diseases), B23 (other conditions associated with HIV), and B24 (unspecified HIV disease). ICD-10 codes A15 (respiratory tuberculosis, bacteriologically and histologically confirmed) and A16 (respiratory tuberculosis, not confirmed bacteriologically or histologically) were categorized as pulmonary TB, while A17 (TB of the nervous system), A18 (TB of other organs), and A19 (miliary TB) were categorized as extra-pulmonary TB. InterVA-4 assigns only PTB as a TB-related cause of death, classifying all EPTB as “other unspecified infectious diseases”. Individual CoD assigned by PCVA were processed further using mortality medical data system (MMDS) software, which generates underlying CoD from multiple CoD. The output generated by MMDS was categorised into WHO 2012 VA cause of death groups; cause-specific mortality fractions (CSMFs) were calculated by dividing the number of deaths assigned to a group by the total number of deaths. At the individual level, the focus was on the most probable CoD assigned by InterVA-4, compared with the underlying CoD generated by MMDS for PCVA. For TB deaths, PTB deaths assigned by PCVA and by InterVA-4 were compared. For HIV deaths, ICD-10 codes (B20-

24) assigned by physicians were grouped together and compared with HIV/AIDS related deaths assigned by InterVA-4. For population-level comparisons, CSMF from PCVA and InterVA methodologies were generated (Paper I).

3.5 Case manager study – Methodology for papers II and III

3.5.1 Study aim

To pilot an intervention to determine if support from a case manager would assist adults being investigated for TB adults to link into TB treatment and HIV care.

3.5.2 Setting

By the end of the XTEND trial, a number of clinics from three of the four provinces which are Eastern Cape, Gauteng and Mpumalanga had high proportions of pre-treatment loss to follow up throughout the trial. However, we could not include all the clinics in the case manager study due to budget constraints and distance from the study management team who were located in Gauteng. Only six primary health clinics in Gauteng and Mpumalanga provinces, that had high proportions of pre-treatment loss to follow up during the XTEND trial, were selected to be part of the case manager intervention pilot study. These six clinics were chosen purposively across rural, urban, and peri-urban communities, offering a diversity between living conditions and socio-economic status of participants enrolled in the study.

3.5.3 Study design

This was a pilot interventional cohort study with quantitative and qualitative data collection components.

3.5.4 Study population

The study population was adults that came to the clinic for care and were identified by the clinic staff as needing investigation for TB, using the TB symptom screening tool (22). These patients were referred from other consultation rooms to the TB consultation room to produce sputum for TB investigation and be recorded in the TB identification register. The study aimed to enrol 1200 participants from six primary health care facilities across two provinces

(Gauteng and Mpumalanga). The eligibility criteria were adults aged 18 years and above, not planning to leave the study area in the next eight months, providing sputum for TB investigations, able to provide adequate locator information, and gave consent.

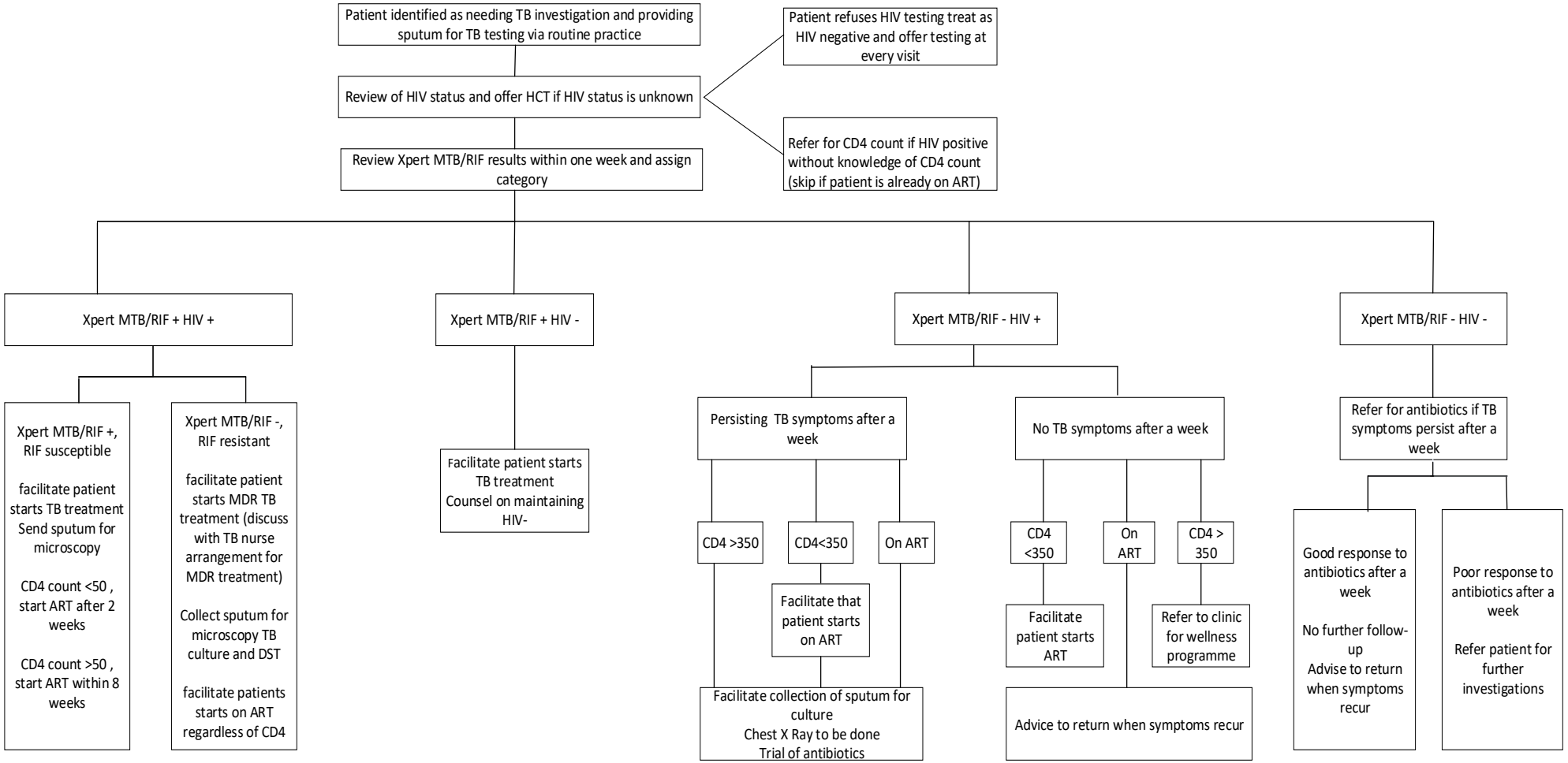
3.5.5 Sample size

We anticipated enrolling 200 patients from each of the six clinics in three months as previously achieved in the XTEND trial, totalling 1200 participants. This pilot study was not powered to show differences in study outcomes. The sample size calculation was based on two outcomes: the first was uptake of ART among those who were HIV positive and ART eligible, as well as those enrolled not knowing their HIV status. Using XTEND findings, we assumed 20% of patients would not know their HIV status, and 60% of those would test HIV positive. A further 50% of those who tested HIV positive would be eligible for ART.
The second outcome was pre-treatment loss to follow-up in those who tested TB positive. Using XTEND study findings, we assumed that 8% of participants would test TB positive, and 21% of those would not start TB treatment. The XTEND findings were used to calculate the sample sizes for these outcomes as they showed TB treatment and HIV linkage to care rates amongst people undergoing TB investigations. The TB outcome was selected because the intervention was designed to assist those who would not start on TB treatment after testing TB positive. For HIV outcomes, the intervention was also designed to assist those who did not know their HIV status to do an HIV test, and further assist those HIV positive patients eligible for ART to start ART.

3.5.6 Description of intervention

Lay counsellors referred to as case managers were trained by investigators on TB and HIV education as well as on the national TB management and ART guidelines at the time (Paper II). One case manager was placed at each of the six clinics. The case managers were selected on the basis that they had previous training in HIV counselling and testing. Case managers were responsible for encouraging and conducting an HIV test amongst those with an unknown HIV status, facilitate CD4 count tests, as well as actively follow up on laboratory results and ART initiation in ART eligible (CD4 count ≤ 350 cells/mm^3 or TB positive) HIV positive patients. They also actively following-up on TB results from the laboratory, informed patients of result /availability, and facilitated initiation of TB treatment amongst those who had a positive TB test. A study algorithm, based on the national TB management and ART

guidelines, was developed to assist the study staff in guiding patients through the health system in seeking appropriate care (Figure 7). Case managers contacted participants who needed to be initiated on TB treatment or linked into HIV care weekly (in-person or telephonically) and recorded these contacts into log sheets. The work of the case managers was supervised by a study coordinator and the study project manager.



At the time of the study, a CD4 count of ≤350 cells/mm^3 was criteria for ART eligibility in South Africa

Figure 7: TB and HIV algorithm used to guide case managers, from paper II: Maraba et al. BMJ Open 2018.

3.5.7 Recruitment and study procedures

Consecutive patients presenting themselves at clinics, and identified by facility nurses as needing TB investigations were referred to research staff. Patients were included in the study if they met the following eligibility criteria: age ≥18 years, will be living in the catchment area for the next eight months, able to provide sputum for TB investigations, able to provide adequate locator information, and gave consent. Data on basic demographics (gender, age, nationality, marital status, level of education), current symptoms, TB history, and health care-seeking behaviour as well as HIV history were collected.

Three months after enrolment to the study, participants who either needed to be initiated on TB treatment or linked into HIV care were contacted and interviewed either telephonically or in-person to find out if they were initiated on the relevant treatment since enrolment. This was done by collecting self-reported data on HIV testing, TB and ART treatment start dates, health-seeking behaviour and current TB symptoms. Additional data on HIV data (such as HIV testing dates, HIV results, CD4 count testing dates, CD4 count results and ART start dates) and TB data (TB testing dates, TB test results, and TB treatment start dates) were abstracted from patient medical records by research nurses.

3.5.8 Study outcomes

Quantitative outcomes

Linkage into HIV care was defined as at three months after enrolment, i) if HIV status unknown at enrolment: testing HIV-positive, having done a CD4 count and being started on ART if eligible (CD4 count ≤ 350 cells/mm3 or testing Xpert MTB/RIF positive); ii) if HIV-positive with an unknown CD4 count and not on ART at enrolment: having done a CD4 count test; and being started on ART if eligible; iii) if last CD4 count done more than six months previously and not on ART at enrolment: having a CD4 count done; and being started on ART if eligible. Failure to initiate ART after three months when ART eligible at initial assessment was defined as non-linkage to HIV care.

Linkage into TB care (TB treatment initiation) was defined as TB treatment start within 28 days of sputum submission among patients with a positive sputum test result. Non-linkage to

TB treatment (pre-treatment loss to follow up) was defined as not starting TB treatment within 28 days of sputum collection among people with a positive TB test result.

Qualitative study outcomes

A priori themes that were assessed were acceptability of the intervention, facilitators and barriers to TB treatment initiation and HIV linkage to care. Data collection methods are described below.

3.5.9 Qualitative data collection

At the end of three months follow-up period, patients from Gauteng and Mpumalanga provinces were purposively sampled depending on whether they linked or did not link into TB or HIV care. The aim was to interview 12 participants: 10 that did not link into care and two that successfully linked into care. Research staff attempted to contact all those participants telephonically to arrange an appointment. If the participant was reached telephonically, then a date and time was scheduled with them to meet at the clinic to conduct an in-depth interview in a language of their preference by research staff; participants were reimbursed with R50 for transport costs. The study's project manager, who was trained by a qualitative researcher, conducted all the participants' in-depth interviews. In order to reduce moderator acceptance bias, an independent consultant conducted interviews with all five case managers as well as health care workers who either initiated patients on TB treatment or ART at the facilities and worked closely with the case manager during implementation of the intervention. These interviews were conducted in English. Questions included in the interview guides for the patients were on their experiences of being supported by a case manager, what facilitated or inhibited their TB treatment initiation and HIV linkage to care. In addition to these questions, the case manager and healthcare worker interview guides included questions on working relationship with each other, and future changes to be made to the strategy. The interviews lasted between 20 to 30 minutes for patients and 30 to 45 minutes for health care workers as well as case managers.

3.5.10 Quantitative data analysis

The sample enrolled was described according to demographic variables (age, gender, nationality, marital status, TB symptoms. Continuous variables were described in medians

and interquartile ranges. Categorical variables were described according to percentages. Contact attempts were described according to medians and interquartile ranges.

3.5.11 Qualitative data analysis

Data collected through interviews were transcribed and then translated into English. Transcribed files were imported into NVIVO 10 QSR International Pty Ltd and coded using a codebook. To ensure data validity, the codebook was discussed with a qualitative researcher. Data were analyzed using themes identified a priori on the acceptability of the intervention, barriers and facilitators of TB treatment initiation, as well as HIV linkage to care. Thematic analysis involved organisation of data according to patterns.

3.6 mHealth application –Methodology for paper IV

3.6.1 Study aim

To pilot an intervention to assess the feasibility and acceptability of using a mHealth application to improve case identification and treatment initiation.

3.6.2 Setting

The study took place in the Johannesburg metropolitan municipality in Gauteng province. The municipality is made of seven regions from A to G (Figure 8). The population in these sub-districts are served by 111 PHC clinics and 10 community health centres. The study was conducted in two primary health care facilities in region F, which includes the Johannesburg Central Business District. For the purpose of this study, clinics were selected on the basis of having > 100 patients presenting with symptoms suggestive of TB per month.

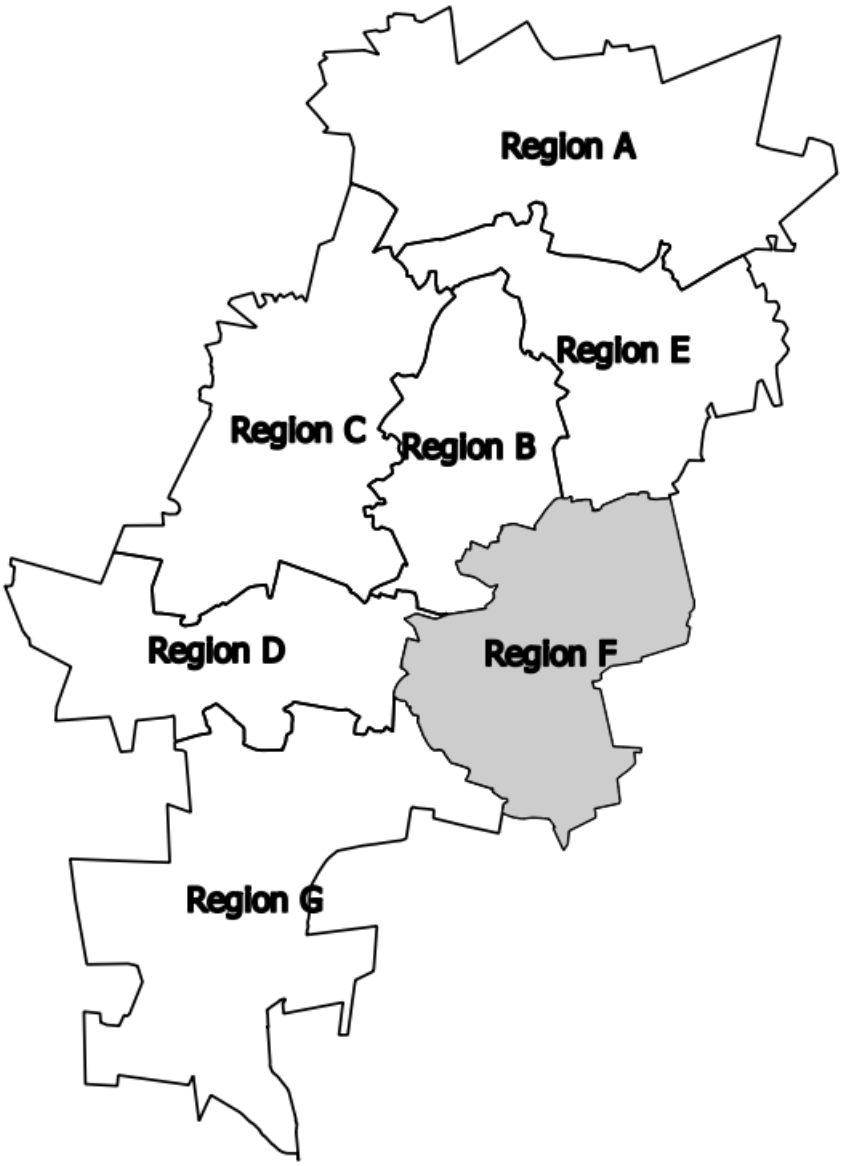


Figure 8: Regional demarcations of the city of Johannesburg metropolitan municipality.

The grey area in the figure indicates the location of Region F where the two clinics piloting the mHealth study are located.

3.6.3 Study design

This was a pilot interventional study with quantitative and qualitative data collection components.

3.6.4 Study population and sampling

The study population were people undergoing TB investigation. Patients were recruited into the study if they were adults aged 18 years or older, being investigated for TB at the two health care facilities in Gauteng province and submitting sputum for TB investigation. These individuals were identified by health care workers as needing further investigations for TB. The study did not have a pre-determined sample size of patients to recruit and was dependant on the number identified at those facilities as needing TB investigation.

There was no sample size calculation for this study as it did not aim to show the effectiveness of the intervention but rather the feasibility and acceptability of using an mHealth application to replace the traditional paper register within the PHC facility.

3.6.5 Development of mHealth application

A software application to be used on a mobile handheld device (tablet) was developed. The application allowed for: i) capturing and storage of data including patient identifiers, contact details, HIV and TB data which are normally captured onto a traditional paper TB identification register; ii) integration between the software application and the national health laboratory system (NHLS) central data warehouse; iii) retrieval of results from the NHLS data warehouse; iv) sending of TB results via pin code protected bi-directional text messages to patients and alerts to health care workers; and v) overall view of TB programme data per clinic by clinic manager and TB coordinator. A workshop was held with TB nurses at participating clinics, district TB coordinator, and DOT supporters to discuss and agree on the content of the text messages that would be sent to patients. The group agreed that for TB positive patients, the message should advise patients to return to the clinic to start treatment. Patients with negative sputum results received the following text message: ‘Your result is “MTB negative”, please visit the clinic if symptoms persist’. Patients with positive sputum results received the message ‘Your result is “MTB positive”, please visit the clinic to start TB treatment’. Patients with a rejected or invalid sputum result received the following text message ‘Your result is “rejected specimen”, please visit the clinic to provide further specimens’. Participants in the study were able to choose if they wanted to receive results via text or get a text message informing them of results availability. Those who opted to receive results via text were required to choose a four-digit secret pin code to access their results.

3.6.6 Study procedures

Research staff were placed at the clinics to support the health care worker responsible for TB care. Research staff and facility health care workers were trained in the application by the software developers. Each of the two facilities was assigned two tablets to which the TB professional nurse and the facility data capturer had access. However, only one of the tablets was in use at any one time. Adults aged ≥18 years who were providing sputum for TB investigation were approached by research staff to participate in the study. If patients agreed to participate, the health care workers captured their data in the application using tablets while the research staff captured the same data into the traditional paper-based register. Participants were not provided with any study-related tool, but the study relied on patients' personal cell-phones. Once TB results were available in the NHLS data warehouse, they were retrieved by the application data warehouse and were automatically sent to participants' phones via text messages. The study coordinator and project manager were able to monitor if text messages were successfully sent or not to participants through the application dashboard. Data were collected over two phases. First, the pre-implementation phase, which was a three-month period during which data were collected using the paper register only. Second, the implementation phase, which was for a three-month period during which data was collected by both mHealth application and paper registers. The study did not have a follow-up period. Data from paper registers were transcribed into a Microsoft Excel spreadsheet for both periods.

The feasibility of the application was assessed by comparing TB indicators for the same individuals collected using the paper TB identification register and mHealth application during the implementation period. We decided a priori that the mHealth application would be feasible if we observed no difference between key indicators generated from the paper and mHealth applications as follows: (i) successful collection by the mHealth application of all data elements usually collected by the paper TB register; (ii) successful and more rapid receipt of electronic laboratory results at the clinic using the mHealth application; and (iii) success in automatic sending of text notifications and results to patients. The potential effectiveness of the application was assessed by comparing indicators in the pre-implementation and implementation periods. This was done to (1) identify slower and faster processes delivered by the mHealth application and parallel paper register; and (2) to identify specific indicators that could be improved by mHealth (such as time to TB treatment initiation) by comparing implementation period with pre-implementation period data.

3.6.7 Study outcomes

Quantitative components

A comparison of proportions of the following indicators generated from data in the mHealth application and on the paper register during implementation: 1) the proportion of patients with specimen results; 2) the proportion of results received within 48 hours; 3) proportion with positive Xpert MTB/Rif results; 4) the proportion of patients with positive Xpert MTB/RIF results who were initiated on TB treatment within 48 hours and within 28 days; and 5) the proportion of patients with a positive Xpert MTB/Rif result who also had a subsequent smear result recorded, was done.

Qualitative outcomes

Acceptability of the intervention described health care providers' experiences of implementing the intervention and patient's experiences of using the application to receive their results. The themes were categorised according to the three normalisation theory domains described below.

3.6.8 Acceptability of the mHealth application data collection

After three months of running the application at the clinics, qualitative interviews to assess the acceptability of the intervention were conducted with patients who took part in the study and with health care workers at the participating clinics. The interviews were done by two people independent from the study team, with extensive experience in conducting qualitative research. A purposive sample of 20 patients was drawn, including 10 that had tested TB negative and 10 TB positive. We further categorised each of the TB positive and negatives into two groups of five patients each, with one group having received sputum results and the other group having not received results via text messages. Patient interviews were conducted either in Zulu, Tswana, or English and lasted between 20-30 minutes. Health care workers who used the application were also interviewed, and their interviews were conducted in English. All transcripts were transcribed into English.

Acceptability of the application was assessed using the normalization theory. The theory assessed the implementation of, and factors which facilitated uptake of a new technology into

routine health care settings. We focused on three domains of the theory, namely reflexive monitoring, collective action and cognitive participation (193, 194). *Collective action* was defined as the ease of use of the application by health care workers as well as patients and how the application integrates within existing systems. *Cognitive participation* was defined as the patients' willingness to use the application to retrieve results, and health care workers' willingness to capture patients' data into the system and search for results. *Reflexive monitoring* was the ability of the mHealth application to deliver results by text to patients and health care workers. The domain also assessed the experiences that a patient had after using the application to retrieve results and get initiated on TB treatment as well as the feeling a health care worker had after receiving results and starting TB patients on treatment. An additional domain was *confidentiality,* which was defined as the patient's belief that the method of results delivery (application) did or did not promote confidentiality of the results.

3.6.9 Statistical analysis

Demographic characteristics of the population were described according to age, gender and HIV status. Medians and interquartile range were used for continuous variables, and proportions and percentages used for categorical variables. For feasibility, McNemar test was used to compare TB indicators; the proportion with specimen results, proportion with positive Xpert MTB/RIF results and proportion with a positive Xpert MTB/RIF result who had a subsequent smear result recorded. This comparison was done with data for the same patients collected during the implementation period using the two methods. For potential effectiveness, the proportion test for two samples was used to compare the proportion started on TB treatment within two days and 28 days of sputum submission for TB investigation between paper register data from the pre-implementation period and mHealth data in the implementation period. Stata version 14 (StataCorp LP, Texas) was used to analyse the quantitative data. Nvivo version 10 (QSR international Pty software) was used to organise the qualitative data into themes.

3.7 Ethical considerations

The verbal autopsy study was approved by the ethics committee of the University of the Witwatersrand (M130381) and London School of Hygiene and Tropical Medicine (6394). Permission to undertake the case manager study was obtained from the University of the

Witwatersrand (M131143) and London School of Hygiene and Tropical Medicine (7124). Additional permission was also obtained from Gauteng and Mpumalanga provincial government and the sub-districts. The implementation of the mHealth study was approved by the Human Research Ethics Committees of John Hopkins (IRB00071530) and Witwatersrand (M141008) universities.

The research teams were trained in good clinical practice to ensure they did not infringe on the ethical rights of the participants. All the participants and caregivers of decedents who took part in the three studies provided written informed consent to be interviewed as well as to use their data for publications. Interviews were done in an environment where the respondent felt safe and comfortable. Respondents were advised to stop the interviews at any time if they did not feel comfortable continuing and that there would be no negative consequences. Enrolled participants could also withdraw from the studies at any point without affecting the care they received at clinics.

CHAPTER 4: RESULTS SECTION

This section highlights key findings: causes of death from verbal autopsy study, linkage into HIV care and initiation of TB treatment from case manager pilot, and initiation of TB treatment using mHealth intervention. This section also makes reference to the four thesis papers listed in Table 1.

4.1 Mortality and cause of death: verbal autopsy study

This section describes the causes of death amongst deceased participants who had undergone TB investigation, and barriers to linkage to care.

4.1.1 Decedent demographic characteristics

From 1 August to 29 November 2013, a total of 231 verbal autopsy (VA) interviews were attempted with caregivers. Of these, 138 (59.8%) were completed, 68 (29.4%) caregivers could not be traced, and 25 (10.8%) refused to be interviewed. Interviews were conducted within a median time of 11 months (interquartile range [IQR] 8-12 months) after deaths had occurred. Descriptive data for the deceased were collected during the enrolment period in the XTEND trial. Verbal autopsy interviews were conducted with caregivers of 138 decedents, but 137 were included in the analysis because one of the VA questionnaires administered did not have a narrative section. The 137 decedents included 76 males (55.4%), 61 females (44.5%) with a median age of 41 years (IQR 33-50). Seventy percent of decedents had self-reported being HIV positive at the time of enrolment into the XTEND trial. The results in this section have been presented in paper I (195). A comparison of the individual causes of death assigned by PCVA and the most probable cause of death assigned by InterVA 4.3 are shown in Table 2, while the comparison of cause-specific mortality fractions between the two methodologies is shown in Table 3.

4.1.2 Cause of death

Using the PCVA methodology, TB was the leading cause of death identified in 70/137 (51.1%) of decedents. Of the 70 TB deaths, 44 (63%) were attributed to PTB and 26 (37%) to EPTB. The second leading cause of death was HIV/AIDS 21/137 (15.3%) and the third, gastrointestinal disease 7/137 (5.1%). The InterVA 4.3 methodology assigned HIV/AIDS

with 49/137 (35.7%) cases, followed by TB with 48/137 (35%), and then malignant neoplasm with 14 deaths (10.2%) (Table 2). Cause-specific mortality fractions calculated after PCVA CoD were processed by MMDS software showed that HIV/AIDS-related deaths accounted for 66.4% of PCVA deaths; PTB for 9.5%; cardiac disease for 2.9%; and malignant neoplasms, gastrointestinal diseases and accident/self-harm for 2.2% each (Table 3). InterVA-4 cause-specific mortality fractions (CSMFs) were calculated using all assigned CoD, and these showed that PTB accounted for 33.2% of deaths; HIV/AIDS for 32.8%; malignant neoplasms for 9.6%; and respiratory ailments for 4.9% (Table 3).

Table 2: Immediate cause of death assigned by physician-certified verbal autopsy compared with "most probable" cause of death assigned by InterVA-4 (n=137).

Cause of death	**Physician-certified verbal autopsy**	**InterVA-4**
	N (%)	**N (%)**
Pulmonary tuberculosis	44 (32.1)	48 (35.0)
Not bacteriologically-confirmed	*36 (26.0)*	NA
Bacteriologically-confirmed	*8 (6.0)*	NA
Extrapulmonary tuberculosis	26 (19.0)	NA
Tuberculosis of nervous system	*11 (8.0)*	NA
Miliary tuberculosis	*10 (7.0)*	NA
TB of other organs	*5 (4.0)*	NA
HIV/AIDS-related deaths	21 (15.3)	49 (35.7)
Gastrointestinal diseases	7 (5.1)	4 (3.0)
Pneumonia	5 (3.6)	4 (3.0)
Cardiac disease/ failure	4 (3.0)	5 (3.6)
Respiratory ailments	4 (3.0)	2 (1.5)
Renal failure	3 (2.0)	1 (0.7)
Malignant neoplasm	3 (2.0)	14 (10.2)
Liver diseases	2 (1.5)	1 (0.7)
Intentional self-harm/poisoning	2 (1.5)	1 (0.7)
Meningitis	1 (0.7)	0 (0.0)
Indeterminate/unspecified	4(3.0)	1 (0.7)
Other	11 (8.0)	7 (5.1)
Total	137	137

From Paper I (Maraba et al. Trans R Soc Trop Med Hyg 2016). Not Applicable (NA) for InterVA as the software can only assign pulmonary TB deaths and not extra-pulmonary TB.

Table 3: Comparison of cause-specific mortality fractions as assigned by physician certified verbal autopsy and InterVA-4

Cause of death	PCVA CSMF %	InterVA-4 CSMF %
HIV/AIDS-related death	66.4	32.8
Pulmonary tuberculosis	9.5	33.2
Cardiac diseases	2.9	2.9
Malignant neoplasm	2.2	9.6
Gastrointestinal diseases	2.2	0.5
Accident/self-harm	2.2	0.7
Diabetes Mellitus	1.5	1.0
Respiratory ailments	1.5	4.9
Liver diseases	1.5	1.0
Other diseases	8.0	6.2
Unknown cause of death	2.2	7.4
Total	100	100

CSMF: cause specific mortality fractions; PCVA: physician-certified verbal autopsy
Concordance correlation coefficient: 0.67 (95% CI 0.38 - 0.97)

4.1.3 Perceived barriers to linkage to care

The narrative sections of the VA interviews highlighted some difficulties experienced by the deceased in seeking TB and HIV care. The barriers were related to both patient and health system. Patient-related barriers included: use of traditional medicines for TB symptoms, presenting with advanced disease, patients not returning to the clinic for results because of ill health, fear of testing for HIV, refusing to start ART, lost to follow-up while on either ART or TB treatment, and non-disclosure of their HIV status. Identified health service barriers included: lost patient files, missing test results, diagnostic delay due to difficulty of microbiologically identifying TB as a cause of illness in some patients, and health system delays in initiating patients on ART.

The two interventions piloted as part of this postgraduate research aimed to address the observed barriers to improve linkage to HIV care and initiation of TB treatment using case managers (Section 4.2), and initiation of TB treatment using mHealth intervention (Section 4.3).

4.2 Linkage to HIV care and TB treatment initiation: Case manager study

This section reports on TB treatment initiation and linkage to HIV care using a case manager intervention amongst adults who were undergoing TB investigation. These results have been reported in paper II (196) and paper III of the thesis.

4.2.1 Supporting linkage to HIV care using case manager intervention

A total of 562 participants were enrolled from five clinics. The anticipated 1200 participants could not be enrolled as the study experienced delays in obtaining local approvals which resulted in a reduction in enrolment period, and also that enrolments from our clinics were much slower than was anticipated (Table 3). The slow enrolments could have been due to facility staff identifying low numbers of patients as needing TB investigations or that our research staff could have missed some patients and so not invited them to take part in the study. We also had ill health preventing one research staff member from following all study-specific procedures in one of the selected clinics resulting in enrolments being stopped in that facility and the 23 participants enrolled being excluded from the analysis. Despite this, we were able to report on the findings as this pilot study was neither designed nor powered to show any effectiveness of the intervention.

Table 4: Total expected number of participants and actual numbers of participants enrolled per clinic

Clinics	Province	Expected number	Actual numbers
A	Gauteng	200	59
B	Gauteng	200	94
C	Gauteng	200	150
D	Mpumalanga	200	160
E	Mpumalanga	200	99
F	Mpumalanga	200	23*

*All participants enrolled in that clinic (23) were excluded from analysis and additional enrolments were not done.

The case manager intervention supported 562 patients, 307 (54.6%) females, 255 (45.4%) males. The population had a median age of 36 years (IQR 29-44), over half (328 [69.1%]) self–reported being HIV positive, with 157/328 (47.8%) having had a CD4 count test previously. A median CD4 count of 315 cells/mm^3 (IQR 164-471) was calculated for those who had a CD4 count test in the past, but nearly two-thirds (209 [63.9%]) had never received ART.

Additionally, semi-structured interviews were conducted with 22 participants (five case managers, nine patients, and eight health care providers). Of the five case managers, four were females, and only one had tertiary education. Of the nine patients, five were from Gauteng, seven were male, and eight had secondary level education. Of the eight providers, six were female, and all were professional nurses. Five of the providers were from clinics in Gauteng province. Seven of the nine patients interviewed did not link to HIV care successfully three months post enrolment into the main study. The majority of those who did not link to HIV care and were approached to participate in this study were male. All three groups perceived the role of the case managers to be important with patients particularly appreciating their patience and the respect they received from the case managers. Health care providers reported that the case managers assisted them by performing duties such as the collection of sputum, follow-up with patients who needed to start on TB or HIV treatment by calling them,

telephonically encouraging patients who still had TB symptoms even after testing TB negative and also those who had side effects to medication to return to the clinic for further management.

Of the 562 participants enrolled, 132 people needed linkage to HIV care only at enrolment (Figure 9); 407 contact attempts were made to these individuals with a median of 3 (IQR 2-4) attempts per individual. By the end of three months follow-up, 29 of 132 (22.0%) people had still not linked to HIV care and a total of 111 contact attempts, with a median of four attempts (IQR 2- 4) per individual, had been made to these individuals.

A further 22 of 562 enrolled participants needed to both initiate TB treatment and link into HIV care. Seventy contact attempts with a median of three (IQR 2-4) attempts were made. By the end of the follow-up period, 15/22 (63.8%) participants were linked into HIV care and started on TB treatment, while 7/22 (31.8%) had started on TB treatment but not completely linked into care because they had not initiated ART. Twenty-seven contact attempts with a median of two attempts (IQR 4-5) per individual were made to these seven individuals.

Figure 9 shows the different stages of the HIV linkage pathway at which patients were when case manager support started. Patients entered and exited the pathway at any stage depending on their stage at enrolment into the study: 94 with unknown HIV status, 132 needing a CD4 count and 135 with a CD4 count. The figure also shows how some patients exited the pathway because they did not complete or meet the criteria to move to the next stage. Twenty-six of the 94 (27.7%) with unknown HIV status refused an HIV test, 13/132 (9.8%) who needed a CD4 count did not test, 44/135 (32.6%) with a CD4 count result did not meet the ART initiation eligibility criteria at the time, and 24/91 (26.4%) of those ART eligible did not initiate on ART.

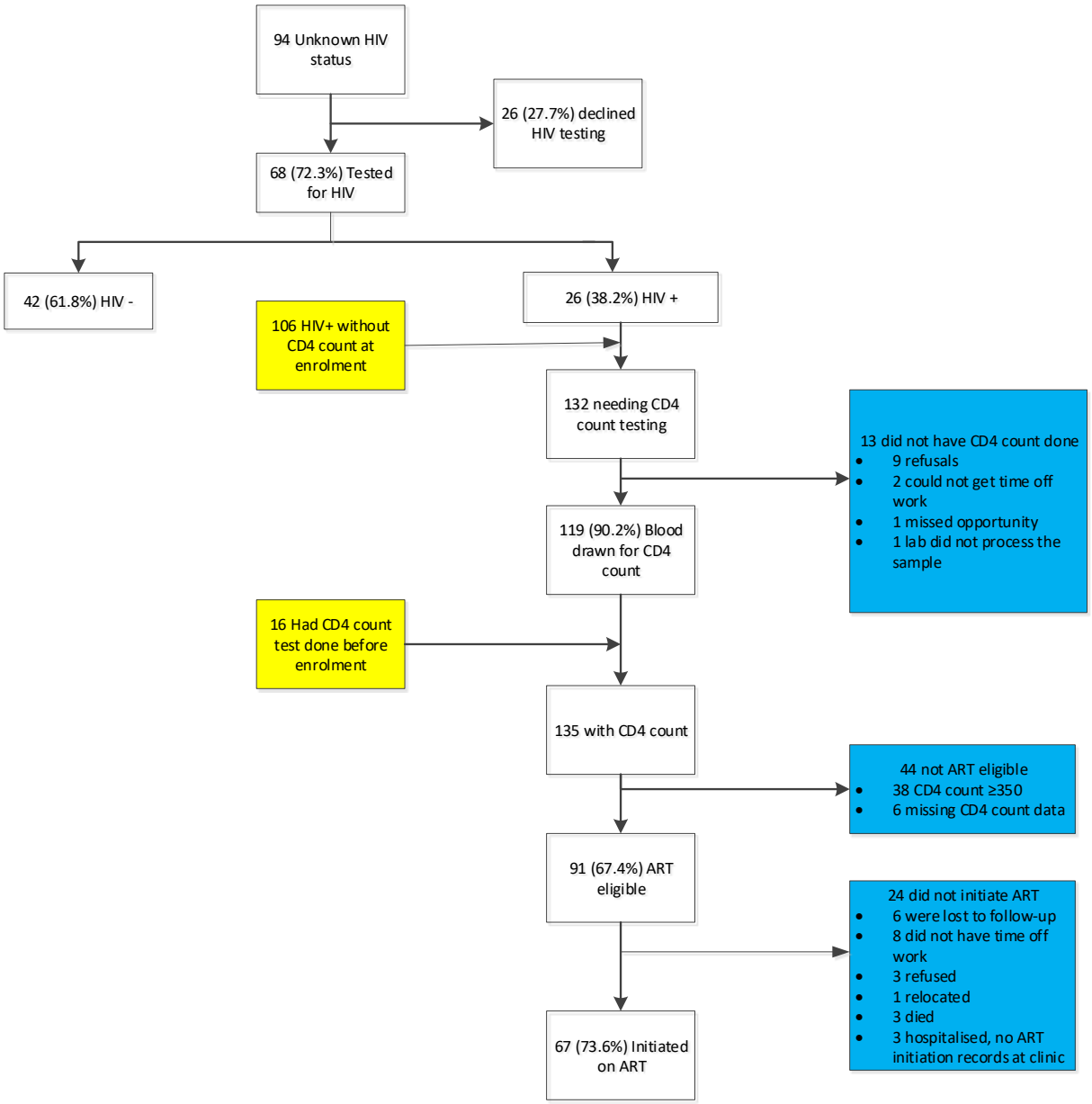


Figure 9: Flow of participants through linkage to HIV care pathway, from paper II: Maraba et al. BMJ Open 2018.

The yellow squares in the figure indicate the groups of patients that entered the pathway and blue squares the patients that exited the pathway at that stage of linkage to care.

The semi-structured interviews showed that barriers to HIV care in this context could be grouped into patient and health system factors. Patient-level barriers were fear, competing priorities, and refusal to start ART. Competing priorities, such as work commitments or looking for employment, prevented patients from returning to the clinic for further HIV management. TB patients living with HIV refused to start ART while still taking TB

treatment, and those who were HIV positive only delayed returning to the clinic for ART initiation. The reason why TB patients living with HIV refused to start ART while still taking TB treatment was because they wanted to finish their TB treatment first before initiating on ART. Fear of stigma also played a role in patients avoiding care for HIV.

Health system factors included the way facilities booked patients for ART initiation and long queues, poor implementation of updated HIV and TB management guidelines and lost patient files or missing results. Lost patient clinic files or results prevented providers from managing patients well. The way facilities booked patients for ART initiation did not allow prioritising patients with low CD4 counts that needed to be fast-tracked to start ART and therefore delayed these patients from linking into care. Long queues discouraged patients from seeking care. There also seemed to be a reluctance amongst health providers in terms of initiating ART between 2-8 weeks after starting a person on TB treatment resulting in the poor implementation of the updated HIV and TB management guidelines. This reluctance was due to fears that patients will develop IRIS.

4.2.2 Supporting TB treatment initiation using the case manager intervention

Of the 562 participants supported by a case manager to test for TB, 57 (10.1%) had a positive index Xpert MTB/RIF result, and 53 (93.0%) started TB treatment within 28 days of testing positive for TB. The median time to TB treatment initiation was five days (IQR 2-7). Four participants did not initiate treatment, two died before starting treatment, and two participants started treatment more than 28 days after sputum was taken. Of the two deceased participants, one died within five days, and the other within one day of taking sputum for TB investigation.

Thirty- five of the 57 (61.4%) with positive index Xpert MTB/RIF results only needed to initiate TB treatment and did not need HIV linkage to care. The case manager made 78 contact attempts (median two attempts [IQR 1-3] per individual) to this group. By the end of the follow-up period, four participants had not initiated TB treatment, and 10 contact attempts were made (median one attempt [IQR 1-4] per individual).

The semi-structured interviews revealed that facilitators of TB testing and initiating on TB treatment were the type of reception at the health facilities and ill health. Type of reception at facilities included health care worker's attitude towards patients seeking care and patients feeling that they get assisted when they go to the facilities. Ill-health or having the desire to

get better also encouraged patients to seek care. One patient described seeking care because he had a desire to live.

> "*For me …. I wanted to live. I could not continue coughing forever. I was not gaining weight and I was thinking a lot. I even stopped working for a while, now am better, I could not walk totally. Now am better I have energy, I can walk, clean and cook for myself*." **Male patient, struggled to get a TB diagnosis and to initiate on TB treatment.**

One barrier to testing and initiating TB treatment was non-referral of patients for chest X-ray. This barrier was reported specifically by case managers who indicated that in some facilities, health care workers did not refer people living with HIV with an initial Xpert MTB/RIF result for chest X-ray.

4.3 Initiation of TB treatment: mHealth application

This section reports on supporting TB treatment initiation amongst those undergoing TB investigations using the mHealth intervention. These results are reported in paper IV (197).

4.3.1 Supporting TB treatment initiation using the mHealth intervention

Evaluation of the mHealth intervention was conducted during two time-periods: pre-implementation and implementation period. The pre-implementation period involved data for 457 patients, 195 (42.7%) were male with a median age of 34 years (IQR 28-40). Implementation period involved 319 participants: 131 (41.1%) were male, median age 32 years (IQR 27-38), 259 (81.2%) self-reported being HIV positive. The results of this study are reported in paper IV.

Of the 319 patients, 286 (89.6%) asked to receive results by text message, 31 (9.7%) did not wish to receive any text message, and 2 (0.6%) opted to receive a text message indicating the availability of results at the clinic. Of those who requested to receive their results via text message, 59 (20.6%) did not receive them because: 1) participants did not understand how to respond with a secret pin (49/59; 83.1%); 2) the application server did not receive results from laboratory server (5/59; 8.4%); 3) the application did not send results to patients even though these patients responded with the correct pin (5/59; 8.4%).

The proportion of TB results documented at the clinic within 48 hours was 68.6% during the pre-implementation period compared to 96.8% during the implementation period, and this was statistically significant (Table 5). There was no significant reduction in the time to TB treatment initiation four days (IQR 2-6) in the pre-implementation period and three days (IQR 2-5) in the implementation period (p=0.5). Although there was no significant increase in the number on treatment within 28 days of testing RIF susceptible TB positive, there was a trend towards an association with 68.2% in the pre-implementation period and 84.8% in the implementation period (p-value =0.08). Similar findings were also observed for the number lost to follow-up which was not significant but showed a trend to association with 31.8% in the pre-implementation period and 15.2% in the implementation period (p-value =0.08)

Table 5: Process indicators assessing potential effectiveness of using mHealth application compared to paper register

	Pre-implementation	**Implementation**	
Source of data	**Paper register**	**mHealth**	**P-value**
Process indicators	**N (%)**	**N (%)**	
Number with turn-around time for sputum results within 48 hours	293/427 (68.6)	309/319 (96.8)	<0.001
Time to TB treatment initiation, median (IQR)	4 (2 - 6)	3 (2 -5)	0.50
Number on treatment within 48 hours of testing Rif susceptible TB positive	14/44 (31.8)	10/33 (30.3)	0.85
Number on treatment within 28 days of testing Rif susceptible TB positive	30/44 (68.2)	28/33 (84.8)	0.08
Number lost to follow-up (not on treatment within 56 days)	14/44 (31.8)	5/33 (15.2)	0.08

Table from Maraba et al. PloS One 2018

The acceptability of the application assessed through four domains (cognitive participation, collective action, reflexive monitoring, and confidentiality are discussed below.

Cognitive participation: The application brought convenience to patients allowing them to access results anywhere without the need to return to the clinic. Providers perceived that the application assisted patients in starting TB treatment early.

Collective action: In the initial phase of implementation, providers had technical difficulties using the mobile devices, but this improved with experience. Once providers gained experience using the application, they felt that it assisted them to initiate patients on TB treatment more quickly as patients returned to the clinic after receiving results on their cell phones.

> *"Most of the patients were coming back before I call them or send a tracer, if their results were positive."* **TB nurse, Clinic B**

Patients also experienced technical challenges, preventing them from retrieving their results.

> "*Yes I got the text message, ….the sister said when I get a text message, she gave me these other numbers* [the pin code], [and] *she said I must send to that number. She showed me how. I did what she said,* [but] *I did not get* [result], *so I never got the result."* **Male TB negative patient 3, clinic B.**

This was due to either software malfunction, where patients' results were not delivered even though they correctly followed the retrieval instructions, or due to individuals not understanding the steps required to retrieve results.

> *"They sent them* [results*] but I was not responding in a good way until I came to the clinic and they assisted me in getting the results, I pressed wrongly on my phone."* **Male TB positive patient no 3, clinic B.**

Reflexive monitoring: Providers and patients were satisfied with the intervention. Providers perceived that the mHealth application saved patients' time.

> *"Patients were satisfied because some of them did not have to ask for permission [*from work*] to come to the clinic more especially the ones that the results come back negative."* **Facility manager, Clinic B**

Confidentiality: Patients believed that receiving results through text messaging did not infringe on their privacy and they appreciated receiving results via pin-protected text message.

> *"Sister like I know my phone it's mine… even if I get a text I will open it and see it myself, and no one will know what is happening on my phone, I think it's a good way to receive your result through text through the phone. Than to come to the clinic sister, and for the sister to see it.* **Male TB negative patient no 2, clinic B**

CHAPTER 5: DISCUSSION

5.1 Introduction

In this thesis, causes of death in adults undergoing TB investigation were identified, and interventions to address the top causes of death found (TB and HIV) were explored to improve linkage to HIV care and/or TB treatment initiation.
The section also discusses thesis findings in relation to findings from other settings as well as the strengths, limitations, recommendations, and conclusions.

5.2 Key findings

5.2.1 Verbal Autopsy

TB was the leading cause of death in adults undergoing TB investigations in PHC facilities, with 51.1% attributed to it by PCVA and 35% by InterVA-4. The second leading cause of death was HIV, with 15.3% of deaths attributed to it by PCVA and 35.7% by InterVA. TB and HIV specific barriers exist, preventing this population from linking into HIV care and initiating TB treatment. Caregivers reported specific barriers to TB treatment initiation to be delays in accessing health care, diagnostic delays and loss of results. Reported specific barriers for HIV linkage to care were access delays (delayed presentation to seek care), loss of laboratory results, and treatment delays.

Studies ascertaining causes of death using pathological and VA data amongst those seeking care in primary health care facilities are limited. One study, using minimally invasive autopsy conducted in SA amongst HIV positive patients with advanced disease attending PHC facilities, reported that TB was the leading CoD contributing 47% of the deaths (51). Although this population was from PHC facilities, it differed from ours in that all patients were HIV positive**.** Majority of studies using pathological autopsy to determine CoD were undertaken in hospital settings. Previous work conducted in hospitalised populations of predominately HIV-infected individuals showed TB to be the leading cause of death (48, 96-100). Determination of CoD using VA has also not been done in populations in PHC facilities but rather in populations living in health demographic surveillance system sites. In Kenya, Ethiopia, South Africa, and Angola, TB was shown to be the leading cause of death when using PCVA ranging from 9.4%-19.7%, and HIV ranged from 8.9%-32.0% (120-123, 198).

These findings are lower than those found in this study. In the current study, it was not surprising that TB was the leading cause of death because the study population was identified as having symptoms suggestive of TB and were already undergoing TB investigation. Further, physicians interpreting the data may have selected TB as a CoD because they knew that the population was being investigated for TB. However, it is surprising that despite the availability of diagnostics tests and treatment, large proportions of people die while being investigated for TB, which suggests that people do not get offered TB testing at facilities as they should be (35). In studies done in Côte d'Ivoire, Kenya, and Ethiopia, interpreting VA data using InterVA showed that HIV-related deaths ranged from 3.8%-12.6% (125, 199, 200) and TB deaths from 6.0% -36.0% (125, 200-202). TB-related mortality was similar compared to that found in this postgraduate study (35.0%) while the HIV-related deaths reported in the previous study (35.7%) were higher. The high HIV-related deaths in the current study could be because of the higher HIV prevalence in South Africa compared to those in the three countries. Even though HIV-related mortality in this study was higher compared to that found in other studies, the reported level could still be underestimated as some of the caregivers responding to the interviews did not know if the deceased was HIV positive or not. In this study, PCVA methods assigned more TB-related deaths compared to InterVA, possibly because InterVA software can only assign pulmonary TB as a cause of death and classifies extra-pulmonary TB under 'other infectious disease'.

In this study, people living with HIV delayed seeking care because of fear of being stigmatised or were in denial of their HIV status, resulting in patients refusing ART initiation or being lost to follow-up while on ART treatment. Clinics were also responsible for delaying ART initiation in some cases. Similar findings were reported in a study using verbal and social autopsies where stigma, denial, and health system challenges were perceived by caregivers of deceased HIV positive women in Kenya to be barriers to seeking care in the population (203). Delayed presentation for TB care was due to patients' first using traditional medicine prior to seeking care or seeking care when their symptoms had progressed. A study in Malawi amongst newly diagnosed HIV positive patients showed those who sought care from traditional healers or pharmacists had an increased odds of diagnostic delays (204). A South African study also reported that patients who sought care from traditional healers took longer to be initiated on TB treatment and were more likely to die (205). Patients not returning for their results at the clinic because of ill health was consistent with findings from a study done in India (206). Lost results was also reported as a barrier for TB treatment initiation in this study. Similar findings were also reported in a systematic review on pre-

treatment loss to follow-up, which showed that delays in receiving laboratory results was a contributor to patients not initiating on TB treatment on time (56).

The two interventions - the case manager and mHealth application- were piloted in an attempt to address facility-level challenges of linkage to HIV care and TB treatment initiation in this population. The case manager intervention attempted to address the diagnostic delays, including the delivery of or receipt of laboratory results, and treatment delays linked to HIV care and TB treatment initiation. The mHealth intervention aimed to address delivery or access to laboratory results and treatment delays linked to TB treatment initiation.

5.2.2 Case manager intervention

The case manager intervention was piloted in an attempt to address facility-level challenges, with a particular interest in diagnostic and treatment delays linked to linkage to HIV care and TB treatment initiation in this population. These delays were addressed by facilitating patients' HIV and TB health-seeking journey by providing education and support to address patient-related diagnostic delays for both HIV and TB, such as refusal for testing. Attempts to address diagnostic delays were made by interceding on health system barriers such as delays in the delivery of laboratory results. The intervention also provided communication between patients and the provider. Attempts to address treatment delays for both TB and HIV treatment were made by providing education and ongoing follow-up with laboratory, providers, and patients.

The intervention was implemented by placing an additional person, who was a trained lay counsellor, at the clinic to assist patients in navigating the health system. The majority of patients with TB started on TB treatment with ease (93.0%). Facilitators to TB treatment initiation were spread across patient and health system-related factors. The quality of reception received at the facilities motivated patients to seek care. Ill-health, linked to a desire to get better when sick, persuaded patients to seek care. Despite high TB treatment initiation rates, people living with HIV did not link into HIV care sufficiently; 73.6% of ART eligible patients linked into care while 26.4% did not. This was regardless of numerous successful contacts and failed contact attempts made to provide support to these patients. For those patients that did not link into care after the follow-up period, the perceived barriers to HIV linkage to care were patient and health system-related. Patient barriers were: refusal to start ART, fear linked to knowing one’s HIV status and being on lifelong treatment, as well as

competing priorities such as seeking employment. Health system barriers included: poor clinic booking system for ART initiation and long queues, poor implementation of updated HIV and TB management guidelines, and lost patient files or results.

Patients refusing to be initiated on ART while still taking TB treatment was surprising as one might assume that if a patient was willing to start on TB treatment, they would be willing to start on ART. The reason for the refusal in the case manager study was that patients wanted to finish the TB medication first before starting on ART. This refusal could be due to fear of side effects or pill burden of taking both medications (76). This indicates that this population may require personalised counselling in an attempt to address these fears. As in this study, fear of being on lifelong treatment, difficulties scheduling appointments, long queues and poor clinic booking system, were reported barriers to ART initiation in other studies in Kenya, Uganda and South Africa (207-210). Although updated South African TB management guidelines had just been published in mid-2014, during the implementation of the case manager study which occurred from September 2014 to March 2015, health care providers were still reluctant to initiate TB patients living with HIV on ART early as these patients needed to be initiated between 2-8 weeks after TB treatment initiations. This reluctance by health care providers was due to concerns of patients developing IRIS. One way of addressing this poor implementation of updated HIV and TB management guidelines can be by retraining on updated guidelines as done in Nigeria and Kyrgyzstan (211). However, it would still be up to the health care providers to adhere to these updated HIV and TB management guidelines once training was provided.

The barriers to HIV linkage to care highlighted above show the complexity of linking an individual into care. For an HIV positive individual to link into care, a balance between perceived value and costs of seeking care is required. This perceived value and cost to link to care is influenced by: individual perception of their health status, interpersonal interactions, clinic experiences, community and social norms, and type of policies adopted by the government to promote linkage to care (212)**.** As shown in the case manager study, some patients chose to seek employment or go to work rather than attend the clinic for further HIV management, while others avoided care because of fear of being stigmatized.

Reported facilitators to TB treatment initiation (quality of reception at the facility and ill health) in this study were found to be similar to those found in a Kenyan study identifying barriers and facilitators of linkage into TB care (208). These facilitators show the importance

of patients' clinic experience and patients' need to get better in seeking care. The case manager study showed that patients appreciated the patience and respect received from case managers, further improving patients' clinic experience.

Studies that have used case managers trained in strength-based counselling in the USA (86, 87, 178-180) have shown an improvement in linkage to HIV care amongst HIV positive patients. The effect of a case manager on linkage to HIV care in the South African context has been inconsistent: it improved linkage to care in a randomized trial in two provinces (Gauteng and Limpopo) amongst newly HIV positive diagnosed from mobile HIV counselling and testing units (213), but failed to show an improvement in HIV linkage to care amongst newly HIV diagnosed patients from hospital outpatient departments and primary health care facilities in Kwazulu-Natal (214). Both studies differed from this study in that all the case managers were trained in strength-based counselling while case managers in this study were not. Case manager interventions in the African context might need to address more than personal support to encourage linkage to care as the health system barriers impeding linkage to care efforts also exist.

One intervention that managed to improve ART initiation was from a cluster randomised controlled trial study conducted in Uganda (215). The intervention study evaluated an intervention that addressed health system barriers by providing: 1) health provider behavioural training; and 2) point of care CD4 count test; modified counselling approach and feedback to facilities about ART initiation rates compared to other facilities. The intervention study showed an improvement in linkage to HIV care (215). Perhaps for the current case manager intervention to successfully link HIV positive patients into care, a health system component that targets both patient and health system barriers needs to be integrated into it. Another intervention that seemed to work used a combination of peer support and mHealth intervention. This was a cluster randomized controlled trial in primary health care clinics in South Africa, testing if two SMS interventions – SMS reminders and SMS reminders plus peer navigation to address barriers to HIV – could improve linkage to care amongst adults followed for 12 months. The study showed that retention in care over a 12 month period was higher in patients assigned to SMS plus peer navigation compared to standard of care with an odds ratio of 1.83 (95% CI: 1.01-3.33) (216).

A strength of the case manager intervention was that it relieved the health providers of responsibilities such as patient and laboratory results follow-up as indicated by health care

providers. It provided personal support, encouragement and guidance to patients in terms of seeking care for TB and HIV. It enhanced communication between patients and the facility. The intervention was intended to help improve the adherence to Xpert MTB/RIF algorithm by health care workers for HIV positive patients who initially had a negative Xpert MTB/RIF result. The role of the case managers in this instance was to ensure that additional diagnostic tests were done as per the Xpert MTB/RIF testing algorithm. This was important as adherence to this algorithm was shown to be as low as 24% in South African PHC facilities (217).

Weaknesses of the case manager intervention were that attempts to achieve timeous initiation of ART and TB treatment in patients were challenged by the differences in how the five facilities delivered TB and HIV care. In the provision of HIV care, these differences were firstly, the required number of days (3) that ART adherence counselling had to take place before a patient could be initiated on ART. The standard number of days for adherence counselling is three days. Adherence counselling in this study was either done over 2 days in some clinics or 3 days in other clinics and after this patients would still need to wait for weeks or more before they were initiated on ART. Secondly, facilities differed in the way that patients were booked for ART initiation, which depended on the number of people that a facility could initiate per week and how many days in week ART initiations took place. This decision by facilities to have maximum number of people that can start on ART each week was concerning as it meant that patients were turned away. This also led to patients with lower CD4 count not getting prioritised to start on ART or even TB patients living with HIV still had to wait for a month or so to be initiated on ART after TB treatment initiation. Lastly, the timing of ART initiation after TB treatment initiation in TB positive patients living with HIV also differed between facilities. This was due to health care workers further delaying the ART initiation for TB patients living with HIV to longer than the recommended two weeks even though patients' CD4 counts were above 50 cells/mm^3 because of fear of patients developing IRIS.

One of the differences in the provision of TB care in the five facilities was that health care workers did not follow the TB diagnostic algorithm in referring patients for chest X-ray if they were HIV positive and had a negative Xpert MTB/RIF result as observed by case managers in this study. This meant that TB diagnosis in HIV positive patients with TB was delayed resulting in a delay in TB treatment initiation. The same findings were reported in a study assessing the adherence of health care workers to the TB diagnostic algorithm after a negative sputum result in South African PHCs (217). In the current study, case managers had

to push that these HIV positive patients got referrals to hospitals for chest X-rays. Another difference was that one of the five clinics referred patients with negative initial Xpert MTB/RIF test results to a provincial referral hospital to collect sputum specimens for culture testing. This decision did not align with national guidelines as primary health care clinics were expected to collect sputum for culture. This meant that TB diagnosis for some patients was delayed as these patients would only be able to travel to the hospital if they had money or the time to do so.

New policies adopted might address some of the delays in ART initiation experienced during the implementation of this intervention. The case manager intervention was implemented at a time when the ART eligibility criterion in the country was CD4 count ≤ 350 cells/mm^3. Since then, the eligibility criterion changed to CD4 count ≤ 500 cells/mm^3 in 2015, with the adoption of the universal test and treat policy in 2016 whereby all HIV positive people are eligible to initiate on ART. The current policy adopted is fast track initiation counselling which has reduced adherence counselling prior to ART initiation from three days to only one day (218).

5.2.3 mHealth intervention

The mHealth intervention attempted to address the treatment delay and delivery of or access to TB results. Implementation of the intervention by PHC facility staff did not interfere with facility routine practices. Both providers and patients appreciated the intervention, and the delivery of laboratory results to both patient and clinic staff improved with the implementation of the intervention.

The mHealth intervention removed the need for results to be physically delivered to the clinic, minimising the possibility of results getting lost while being transported from laboratory to clinic, when being filed or when SMS printers malfunction (68). This reduced the delay in receipt of laboratory results, contributing to a reduction in pre-treatment loss to follow-up (56, 68). It also removed the need for patients with negative results and no symptoms suggestive of TB to return to facilities to access their results. This minimised the burden of taking time off work and reduced costs of unnecessary travel to a clinic. In South Africa, people undergoing TB investigation were shown to incur the highest income losses compared to people already on TB treatment (219). The intervention aimed to reduce the waiting period

from specimen submission to delivery of results by sending the results directly to the patient's phone, potentially reducing the time to TB treatment start.

Strengths of the intervention are that it provided real-time data capturing of TB investigation data and real-time access of laboratory results to both patients and providers. It also provided real-time monitoring of TB treatment initiation data by facility managers. The pin-protected method of results delivery protected patient's data confidentiality and did not infringe on their privacy.

Weaknesses of the mHealth intervention are that in the initial phases of implementation of the intervention, there was resistance from the providers to use the technology. Facility management would relocate staff from the designated TB consultation rooms to consultation rooms where assistance was most needed. This left the TB consultation room without an mHealth-trained provider. Use of the mHealth application requires patients to be literate or able to use cell phones. There needed to be constant monitoring to check if the application was delivering results and that there were no technical glitches; if results were not transmitted from the laboratory server to the application server, then patients would not receive their results. The use of a secret pin to access laboratory results prevented some patients from accessing the results as they forgot their secret pin.

Within TB research, this intervention is the only study that sent laboratory results directly to patients. Another study done in South Africa looking to improve pre-treatment loss to follow-up, evaluated the effect of two SMS interventions that served as reminders to patients undergoing TB investigation to return to the clinic for their TB test results. The study showed that patients that received SMS reminders encouraging them to return for TB test results were more likely to return to the clinic compared to the control group (220). Other previously tested interventions to improve TB treatment initiation and adherence include 1) provision of incentives and reminders to patients, 2) providing once-off incentives by calling patients before their appointments to return to collect their test results, and 3) the use of medication monitors and video-observed therapy (221, 222). These were shown to improve patient adherence to TB clinic appointments for diagnosis and treatment (222). A pilot study in India evaluated the feasibility of providing rural health care providers with an mHealth application to refer people with presumptive TB to microscopy centers for TB investigation. The study showed that health care providers that used the mHealth application referred more people for testing compared to those not using the application (223). Providing once-off incentives also

promoted the return of patients to collect their TB test results and initiate on TB prophylaxis treatment, or to continue taking TB treatment in special populations such as the homeless or drug users (224).

In HIV research, a study in Swaziland tested whether the delivery of HIV laboratory results to remote clinics via text messaging improved turnaround time compared to delivery of paper reports to clinics but did not report on whether the intervention improved any patient outcomes (85). The study showed that sending results via text messaging shortened turnaround time. The findings are consistent with those of the mHealth intervention study as it showed an improvement in results turnaround time compared to recording in paper registers. In a Ugandan study, laboratory results were sent directly to patients. The study showed how literacy at enrolment was a predictor of whether a patient received their laboratory result or not and that patients receiving pin-protected results were less likely to receive their results (84). The difficulty in patients accessing their results when using a pin-protected method was similar to this study. Patients perceived that delivery of their laboratory results via text did not infringe on their privacy (225). This is also consistent with the findings of this study. A future possibility could be to include interactive voice recognition software in the application so people that forget their pin-codes could call in and the software would recognise their voice, therefore, providing them with test results. This future concept would need to be piloted first to ensure it does not infringe on participants rights or their privacy.

5.3 Questions arising during the postgraduate research?

A number of questions have surfaced during the course of this postgraduate research. Firstly, given that VA is designed to estimate the relative frequency of different causes of death at a population level rather than to identify the cause of death in an individual, what are the individual causes of death for people undergoing TB investigation? Secondly, would a modified case manager intervention that includes personalised counselling that identifies individuals barriers of linkage to HIV care and strengths that could overcome these be effective in improving linkage to care in this population? Thirdly, would continuous training of health workers on current management guidelines and providing managerial training to facility managers on adapting facilities to changing guidelines be effective in improving linkage to care in this population? Fourthly, would the mHealth intervention be effective in reducing time to TB treatment initiation, and would it be cost-effective to manage the software? Fifthly, would the implementation of the mHealth intervention be successful in

rural setting facilities? Lastly, would there be added value in integrating support from a case manager and using the mHealth application to provide TB results to patients?

5.4 Limitations of the postgraduate research

The causes of death sub-study used VA to determine CoD which is not as accurate as using pathological autopsy. The VA interpretations are stronger at describing the CoD profile at population-level data through cause-specific mortality fractions and not at individual-level. We were not able to conduct a VA for everyone who died and could thus have missed other causes of death which have implications on the profile of causes reported in this population. The cause of death sub-study was started at the end of the XTEND trial, and the two studies did not run concurrently. If these studies ran simultaneously, it could have assisted with conducting a lot more verbal autopsies with caregivers than what is currently reported.

A limitation of the case manager study is that as a pilot study, it did not have a "standard of care" comparison group and could not therefore formally determine if the strategy made a difference or not. The study also did not collect baseline data from the six clinics which could have allowed for a pre- and post-intervention implementation comparison. The findings of this study cannot be generalised to the entire country but only to settings with similar living conditions. We also were unable to enrol all the patients to reach the planned sample size target, but were nevertheless able to report the findings. The study had a short implementation period which also contributed to low enrolment numbers. The limitations of the qualitative interviews conducted after implementation of the case manager intervention were that we could not interview all of the sampled patients that did not link into care even after multiple attempts to schedule an appointment. This translated into the study not reaching theme saturation. Participants did not vary sufficiently by gender to explore gender differences which are known to impact care-seeking in South Africa, nor did the sample distribution enable comparison by provincial context.

A limitation of the mHealth intervention was that it was conducted in two clinics only in an urban setting which means results cannot be generalised to rural settings. The study did not collect data about where a phone was shared or not. This information could have assisted in understanding our study population better for future research. The study had a short implementation period where the application was running with only a few system glitches. This resulted in the low number of data used for analysis. The application was not able to send results to everyone who requested their results via text messaging either because: 1)

patients had forgotten their secret pin codes; 2) patients were not able to follow the instructions previously provided by the research team to access their results and; 3) the laboratory server did not send results into the application server. The application also required an individual to be literate in order to access their results which meant illiterate people could not access their results without help from other people. The application was not utilised optimally by facility managers to review daily facility TB statistics which was due to lack of internet connectivity in the facilities. Finally, the text messages were only available in English which meant that some people did not understand the content of the messages sent.

5.5 Strengths of the postgraduate research

A major strength of the cause of death study is that it was nested within a larger pragmatic trial. The population was a large systematic sample of adults being investigated for TB in a real-world setting conducted across rural, urban and peri-urban settings, making our results likely to represent causes of death in adults being investigated for TB in similar settings. The study also managed to perform the majority of VA interviews within one year of death which made it easier for respondents to recall exact events leading to a participant's death.

Strengths of the case manager study included prospectively enrolling a representative sample of adults being investigated for TB from five clinics in two provinces of the country which are diverse in living conditions and population and likely to be representative of urban and peri-urban practices in South Africa. The intervention was implemented as intended with 555 contact attempts made to participants needing linkage to care. The qualitative interviews conducted with interviewed patients, case managers and providers after implementation of the case manager intervention, provided an overview of perspectives of the facilitators and barriers of implementing a case management strategy in the primary health care clinics in South Africa.

One of the strengths of the mHealth intervention study was that it was tested in primary health care settings in the country and was fully operated by public health care providers. An additional strength of the mHealth application was that it was able to document TB evaluation data and provide in real-time TB test results to health care providers in two busy public sector primary care clinics. The qualitative interviews conducted after implementation of the mHealth application provided overall perspectives of the intervention by patients and providers.

5.6 Recommendations

Adults undergoing TB investigation need to be aware of their HIV status as previous research has shown that people were more likely to die if they did not know their HIV status or were HIV positive and not on ART. Intensified TB screening also needs to be improved as the sensitivity of the current screening tool is suboptimal, and a diagnostic test for TB with high sensitivity and specificity that could be used in primary health care settings is a priority. The current VA assessment methodology needs to be improved to be able to categorise TB deaths correctly and include EPTB. This is important as previous research has reported that 88% of HIV-positive individuals with autopsy evidence of TB have disseminated disease and if VA methods do not classify EPTB as TB, a large number of TB deaths will be missed.

Implementation of new support interventions that include placing an additional person in facilities should consider how this person will work with existing health providers. It is also important to consider that the presence of additional people to assist with intervention activities in health facilities might seem to facility staff that additional assistance has been provided to assist with facility duties. These people will therefore end up performing facility related duties in addition to their intervention related duties. Additionally, it should be taken into account that facilities provide care in different ways and different challenges will be encountered in different facilities and any additional person placed in facilities will need to navigate these challenges in order to perform their daily duties. Case manager support interventions for linkage to HIV care should address both patient and health-system level factors in order to succeed in addressing the challenge of linkage to HIV care.

Implementation of mHealth interventions to facilitate TB treatment initiation of adults being investigated for TB within the health system will bring new challenges that would need to be addressed. When implementing mHealth interventions in a facility, it is important to take into account the behavioural aspect of the providers who will use the technologies as some providers might not want to use such interventions. These providers will need additional support for them to warm up to these new technology interventions. Implementation of such interventions should also take into account how facilities are run in order to integrate these technologies into routine settings and processes. These interventions would include retraining of, and ongoing refresher training for health providers to allow for technophobic health providers to adapt to the new technologies. Implementation also requires ongoing monitoring to check if these systems are working properly and to quickly identify technical glitches that

prevent them from delivering what they were designed to do. The most important aspect of developing or implementing mHealth interventions is that they should ultimately be suitable for integration into already existing TB programme systems; hence relevant stakeholders within TB programmes should be involved when they are developed and tested. Future interventions to improve TB treatment initiation need to focus on how to improve patients' clinic experience and empower patients to seek care.

5.7 Recommendations for future research

Additional research on identifying a more sensitive and specific TB screening tool is needed. A CoD study using pathological autopsy on adults being investigated for TB attending PHCs to identify causes of death at an individual level would help confirm or refute these findings. Additional work on how to modify the InterVA software to identify and classify extra-pulmonary TB as a CoD is needed. Additional work is needed on whether using support interventions, lay workers for example, with ongoing training of facility staff on updated HIV and TB management guidelines, managerial training to facility managers to enable facilities to adapt to changing guidelines as well as providing longitudinal counselling to patients in order to identify their personal barriers of linkage to care and strengths to overcome these, will be effective in linking patients into HIV care. Feasibility studies of these enhanced support interventions should be done initially to test the ideas before efficacy studies are conducted. For mHealth interventions, research is required to determine if providing TB results to patients could include interactive voice recognition or biometric software to assist illiterate patients to access their results. Larger trials are needed to assess the effectiveness of mHealth intervention that provide TB results via text messages on time to treatment initiation, as well as the cost-effectiveness of such interventions within the health system. Lastly, the feasibility and acceptability of using mHealth interventions in rural settings need to be tested.

5.8 Conclusion

This research has determined CoD amongst adults being investigated for TB in PHC clinics in South Africa using verbal autopsy. These findings indicate that TB is the leading CoD based on verbal autopsy data using either PCVA or InterVA-4 for adults being investigated for TB. The findings indicate that the current TB diagnostic pathway is inadequate as people with TB disease may still be missed or commenced on treatment too late. HIV was identified as the

second most common CoD, pointing to the importance of integrated TB and HIV care and linkage into care for both diseases. The health service through implementation science research needs to find ways to facilitate access to TB and HIV care for persons who need to navigate both services.

The findings from this thesis also suggest that support interventions using lay case managers to link adults undergoing TB investigation into HIV care and TB treatment initiation might improve TB treatment initiation. However, this kind of support alone is not adequate to assist HIV positive patients in linking to HIV care. The successful linkage to care for people living with HIV is a complex process and is dependent on patient and health system factors. Hence, future support interventions should address both patient and health system factors.

Finally, mHealth applications could take the place of current paper-based TB care programme case-finding tools, and may substantially improve results turn-around time and management of TB within the programme. These applications may empower patients with direct receipt of TB results. Implementation of mHealth interventions to support and improve TB care has the potential to improve patient-level outcomes, and large-scale evaluations of this technology are urgently required.

6. REFERENCES

1. World Health Organization. Global Tuberculosis Report 2018. http://apps.who.int/iris/bitstream/handle/10665/274453/9789241565646-eng.pdf?ua=1. [Accessed 23 November 2018].
2. Lurie MN, Williams BG. Migration and Health in Southern Africa: 100 years and still c irculating. Health Psychol Behav Med. 2014 Jan 1;2(1):34-40.
3. Abdool Karim SS, Churchyard GJ, Karim QA, Lawn SD. HIV infection and tuberculosis in South Africa: an urgent need to escalate the public health response. Lancet. 2009 Sep 12;374(9693):921-33.
4. Chang ST, Chihota VN, Fielding KL, Grant AD, Houben RM, White RG, et al. Small contribution of gold mines to the ongoing tuberculosis epidemic in South Africa: a modeling-based study. BMC Med. 2018 Apr 12;16(1):52.
5. Simelela NP, Venter WD. A brief history of South Africa's response to AIDS. S Afr Med J. 2014 Mar;104(3 Suppl 1):249-51.
6. Statistics South Africa. Statistical release. Mid-year population estimates 2017. http://www.statssa.gov.za/publications/P0302/P03022017.pdf. [Accessed 4 April 2018].
7. South African National Department of Health. Burden of TB Disease in South Africa. http://www.google.co.za/url?sa=t&rct=j&q=&esrc=s&source=web&cd=1&ved=2ahUKEwi6mOHwy4_lAhUaRRUIHRuDBREQFjAAegQIBBAC&url=http%3A%2F%2Fwww.health.gov.za%2Findex.php%2F2014-03-17-09-09-38%2Fstrategic-documents%2Fcategory%2F392-nepad-regional-meeting-midrand-2017%3Fdownload%3D2253%3Aburden-of-tb-disease-in-south-africa&usg=AOvVaw1_EJg2-FAe9oYOxdOlMhvf. [Accessed 9 October2019].
8. Massyn N, Peer N, English R, Padarath A, Barron P, Day C. District Health Barometer 2015/16. Durban: Health Systems Trust; 2016. http://www.hst.org.za/publications/Pages/-District-Health-Barometer-201516.aspx. [Accessed 9 September 2018].
9. . Stop TB Partnership. END TB UNOPS. United to end TB, every word counts, suggested language and usage for tuberculosis communications. First edition. http://www.stoptb.org/assets/documents/resources/publications/acsm/LanguageGuide_ForWeb20131110.pdf. Accessed 27 September 2019.
10. World Health Organization. Latent tuberculosis infection. Updated and consolidated guidelines for programmatic management. 2018. http://apps.who.int/iris/bitstream/handle/10665/260233/9789241550239-eng.pdf;jsessionid=85777A81EAE0C7486D9A7A32CF94484D?sequence=1. [Accessed 8 September 2018].
11. World Health Organization.Definitions and reporting framework for tuberculosis-2013 revision. https://apps.who.int/iris/handle/10665/79199 . [Accessed 27 September 2019].
12. Guerra-Assuncao JA, Houben RM, Crampin AC, Mzembe T, Mallard K, Coll F, et al. Recurrence due to relapse or reinfection with Mycobacterium tuberculosis: a whole-genome sequencing approach in a large, population-based cohort with a high HIV infection prevalence and active follow-up. J Infect Dis. 2015 Apr 1;211(7):1154-63.
13. Aaron L, Saadoun D, Calatroni I, Launay O, Memain N, Vincent V, et al. Tuberculosis in HIV-infected patients: a comprehensive review. Clin Microbiol Infect. 2004 May;10(5):388-98.
14. Pawlowski A, Jansson M, Skold M, Rottenberg ME, Kallenius G. Tuberculosis and HIV co-infection. PLoS Pathog. 2012 Feb;8(2):e1002464.
15. Bucher HC GL, Guyatt GH, Sudre P, Naef M, Sendi P, Battegay M. Isoniazid prophylaxis for tuberculosis in HIV infection: a meta-analysis of randomised controlled trials. AIDS. 1999;13:501-7.
16. Daley CL, Small PM, Schecter GF, Schoolnik GK, McAdam RA, Jacobs WR, Jr., et al. An outbreak of tuberculosis with accelerated progression among persons infected with the human immunodeficiency virus. An analysis using restriction-fragment-length polymorphisms. N Engl J Med. 1992 Jan 23;326(4):231-5.

17. Sonnenberg P, Glynn JR, Fielding K, Murray J, Godfrey-Faussett P, Shearer S. How soon after infection with HIV does the risk of tuberculosis start to increase? A retrospective cohort study in South African gold miners. J Infect Dis. 2005 Jan 15;191(2):150-8.
18. Raviglione MC, Harries AD, Msiska R, Wilkinson D, Nunn P. Tuberculosis and HIV: current status in Africa. AIDS. 1997;11 Suppl B:S115-23.
19. Chaisson RE, Churchyard GJ. Recurrent tuberculosis: relapse, reinfection, and HIV. J Infect Dis. 2010 Mar;201(5):653-5.
20. Kwan CK, Ernst JD. HIV and tuberculosis: a deadly human syndemic. Clin Microbiol Rev. 2011 Apr;24(2):351-76.
21. Reid MJ, Shah NS. Approaches to tuberculosis screening and diagnosis in people with HIV in resource-limited settings. Lancet Infect Dis. 2009 Mar;9(3):173-84.
22. World Health Organization. Systematic Screening for active Tuberculosis. Principles and Recommendations. 2013. http://www.who.int/tb/publications/Final_TB_Screening_guidelines.pdf. [Accessed 4 February 2017].
23. Getahun H, Kittikraisak W, Heilig CM, Corbett EL, Ayles H, Cain KP, et al. Development of a standardized screening rule for tuberculosis in people living with HIV in resource-constrained settings: individual participant data meta-analysis of observational studies. PLoS Med. 2011 Jan 18;8(1):e1000391.
24. Dye C, Williams BG. The population dynamics and control of tuberculosis. Science. 2010 May 14;328(5980):856-61.
25. Banda H, Kang'ombe C, Harries AD, Nyangulu DS, Whitty CJ, Wirima JJ, et al. Mortality rates and recurrent rates of tuberculosis in patients with smear-negative pulmonary tuberculosis and tuberculous pleural effusion who have completed treatment. Int J Tuberc Lung Dis. 2000 Oct;4(10):968-74.
26. Schutz C, Meintjes G, Almajid F, Wilkinson RJ, Pozniak A. Clinical management of tuberculosis and HIV-1 co-infection. Eur Respir J. 2010 Dec;36(6):1460-81.
27. Hargreaves NJ, Kadzakumanja O, Whitty CJ, Salaniponi FM, Harries AD, Squire SB. 'Smear-negative' pulmonary tuberculosis in a DOTS programme: poor outcomes in an area of high HIV seroprevalence. Int J Tuberc Lung Dis. 2001 Sep;5(9):847-54.
28. South African National Health Laboratory Services. Implementation of GeneXpert MTB/Rif. http://www.nhls.ac.za/priority-programmes/tb-genexpert/implementation/. [Accessed 27 September 2019].
29. World Health Organization. Rapid Implementation of the Xpert MTB/RIF diagnostic test. Technical and operational 'How to' practical considerations. WHO 2011. 2011. http://apps.who.int/iris/bitstream/handle/10665/44593/9789241501569_eng.pdf?sequence=1. [Accessed 8 March 2016]
30. Department of Health: South Africa. National tuberculosis management guidelines. 2014. http://www.hst.org.za/sites/default/files/NTCP_Adult_TB-Guidelines-27.5.2014.pdf. [Accessed 19 February 2017]
31. World Health Organization. HIV/AIDS programme. Antiretroviral therapy for HIV infection in adults and adolescents: recommendations for a public health approach. 2006 revision. http://www.who.int/hiv/pub/guidelines/artadultguidelines.pdf?ua=1. [Accessed 25 April 2018].
32. Abdool Karim SS, Naidoo K, Grobler A, Padayatchi N, Baxter C, Gray A, et al. Timing of initiation of antiretroviral drugs during tuberculosis therapy. N Engl J Med. 2010 Feb 25;362(8):697-706.
33. World Health Organization. Rapid advice. Antiretroviral therapy for HIV infection in adults and adolescents. 2009. Accessed 4 April 2018. http://www.who.int/hiv/pub/arv/rapid_advice_art.pdf.
34. Department of Health: South Africa. National tuberculosis management guidelines.2009. http://familymedicine.ukzn.ac.za/Libraries/Guidelines_Protocols/TB_Guidelines_2009.sflb.ashx. [Accessed 28 September 2018]

35. Chihota VN, Ginindza S, McCarthy K, Grant AD, Churchyard G, Fielding K. Missed Opportunities for TB Investigation in Primary Care Clinics in South Africa: Experience from the XTEND Trial. PLoS One. 2015;10(9):e0138149.
36. Naidoo P, Theron G, Rangaka MX, Chihota VN, Vaughan L, Brey ZO, et al. The South African Tuberculosis Care Cascade: Estimated Losses and Methodological Challenges. J Infect Dis. 2017 Nov 6;216(suppl_7):S702-S13.
37. Nliwasa M, MacPherson P, Mukaka M, Mdolo A, Mwapasa M, Kaswaswa K, et al. High mortality and prevalence of HIV and tuberculosis in adults with chronic cough in Malawi: a cohort study. Int J Tuberc Lung Dis. 2016 Feb;20(2):202-10.
38. Macpherson P, Dimairo M, Bandason T, Zezai A, Munyati SS, Butterworth AE, et al. Risk factors for mortality in smear-negative tuberculosis suspects: a cohort study in Harare, Zimbabwe. Int J Tuberc Lung Dis. 2011 Oct;15(10):1390-6.
39. Theron G, Zijenah L, Chanda D, Clowes P, Rachow A, Lesosky M, et al. Feasibility, accuracy, and clinical effect of point-of-care Xpert MTB/RIF testing for tuberculosis in primary-care settings in Africa: a multicentre, randomised, controlled trial. Lancet. 2014 Feb 01;383(9915):424-35.
40. Churchyard GJ, Stevens WS, Mametja LD, McCarthy KM, Chihota V, Nicol MP, et al. Xpert MTB/RIF versus sputum microscopy as the initial diagnostic test for tuberculosis: a cluster-randomised trial embedded in South African roll-out of Xpert MTB/RIF. Lancet Glob Health. 2015 Aug;3(8):e450-7.
41. Adjei AA, Adiku TK, Ayeh-Kumi PF, Hesse IF. Prevalence of human immunodeficiency virus infection among tuberculosis suspect patients in Accra, Ghana. West Afr J Med. 2006 Jan-Mar;25(1):38-41.
42. van Lettow M, Bedell R, Maosa S, Phiri K, Chan AK, Mwinjiwa E, et al. Outcomes and Diagnostic Processes in Outpatients with Presumptive Tuberculosis in Zomba District, Malawi. PLoS One. 2015;10(11):e0141414.
43. Omar T, Variava E, Moroe E, Billioux A, Chaisson RE, Lebina L, et al. Undiagnosed TB in adults dying at home from natural causes in a high TB burden setting: a post-mortem study. Int J Tuberc Lung Dis. 2015 Nov;19(11):1320-5.
44. Cohen T MM, Wallengren K, Alvarez GG, Samuel EY, Wilson D. The Prevalence and Drug Sensitivity of Tuberculosis among Patients Dying in Hospital in KwaZulu-Natal, South Africa: A Postmortem Study. PLoS Med. 2010;7(6). Epub e1000296.
45. Bates M, O'Grady J, Mwaba P, Chilukutu L, Mzyece J, Cheelo B, et al. Evaluation of the burden of unsuspected pulmonary tuberculosis and co-morbidity with non-communicable diseases in sputum producing adult inpatients. PLoS One. 2012;7(7):e40774.
46. Kilale AM, Kimaro GD, Kahwa AM, Chilagwile M, Ngowi BJ, Muller W, et al. High prevalence of tuberculosis diagnosed during autopsy examination at Muhimbili National Hospital in Dar es Salaam, Tanzania. Tanzan J Health Res. 2013 Jul;15(3):171-7.
47. Punia RS, Mundi I, Mohan H, Chavli KH, Harish D. Tuberculosis prevalence at autopsy: a study from North India. Trop Doct. 2012 Jan;42(1):46-7.
48. Bates M, Mudenda V, Shibemba A, Kaluwaji J, Tembo J, Kabwe M, et al. Burden of tuberculosis at post mortem in inpatients at a tertiary referral centre in sub-Saharan Africa: a prospective descriptive autopsy study. Lancet Infect Dis. 2015 May;15(5):544-51.
49. Martinson NA, Karstaedt A, Venter WD, Omar T, King P, Mbengo T, et al. Causes of death in hospitalized adults with a premortem diagnosis of tuberculosis: an autopsy study. AIDS. 2007 Oct 01;21(15):2043-50.
50. Kantipong P, Murakami K, Moolphate S, Aung MN, Yamada N. Causes of mortality among tuberculosis and HIV co-infected patients in Chiang Rai, Northern Thailand. HIV AIDS (Auckl). 2012;4:159-68.
51. Karat AS, Omar T, von Gottberg A, Tlali M, Chihota VN, Churchyard GJ, et al. Autopsy Prevalence of Tuberculosis and Other Potentially Treatable Infections among Adults with Advanced HIV Enrolled in Out-Patient Care in South Africa. PLoS One. 2016;11(11):e0166158.

52. da Silva Escada RO, Velasque L, Ribeiro SR, Cardoso SW, Marins LMS, Grinsztejn E, et al. Mortality in patients with HIV-1 and tuberculosis co-infection in Rio de Janeiro, Brazil - associated factors and causes of death. BMC Infect Dis. 2017 May 30;17(1):373.
53. Wang WB, Zhao Q, Yuan ZA, Jiang WL, Liu ML, Xu B. Deaths of tuberculosis patients in urban China: a retrospective cohort study. Int J Tuberc Lung Dis. 2013 Apr;17(4):493-8.
54. Field N, Lim MS, Murray J, Dowdeswell RJ, Glynn JR, Sonnenberg P. Timing, rates, and causes of death in a large South African tuberculosis programme. BMC Infect Dis. 2014 Dec 21;14:3858.
55. Adamu AL, Gadanya MA, Abubakar IS, Jibo AM, Bello MM, Gajida AU, et al. High mortality among tuberculosis patients on treatment in Nigeria: a retrospective cohort study. BMC Infect Dis. 2017 Feb 23;17(1):170.
56. MacPherson P, Houben RM, Glynn JR, Corbett EL, Kranzer K. Pre-treatment loss to follow-up in tuberculosis patients in low- and lower-middle-income countries and high-burden countries: a systematic review and meta-analysis. Bull World Health Organ. 2014 Feb 01;92(2):126-38.
57. Krishnan L, Akande T, Shankar AV, McIntire KN, Gounder CR, Gupta A, et al. Gender-related barriers and delays in accessing tuberculosis diagnostic and treatment services: a systematic review of qualitative studies. Tuberc Res Treat. 2014;2014:215059.
58. Gebreegziabher SB, Bjune GA, Yimer SA. Total Delay Is Associated with Unfavorable Treatment Outcome among Pulmonary Tuberculosis Patients in West Gojjam Zone, Northwest Ethiopia: A Prospective Cohort Study. PLoS One. 2016;11(7):e0159579.
59. Storla DG, Yimer S, Bjune GA. A systematic review of delay in the diagnosis and treatment of tuberculosis. BMC Public Health. 2008 Jan 14;8:15.
60. Nyasulu P, Phiri F, Sikwese S, Chirwa T, Singini I, Banda HT, et al. Factors Influencing Delayed Health Care Seeking Among Pulmonary Tuberculosis Suspects in Rural Communities in Ntcheu District, Malawi. Qual Health Res. 2016 Jul;26(9):1275-88.
61. Wandwalo ER, Morkve O. Delay in tuberculosis case-finding and treatment in Mwanza, Tanzania. Int J Tuberc Lung Dis. 2000 Feb;4(2):133-8.
62. Mesfin MM, Newell JN, Walley JD, Gessessew A, Madeley RJ. Delayed consultation among pulmonary tuberculosis patients: a cross sectional study of 10 DOTS districts of Ethiopia. BMC Public Health. 2009 Feb 09;9:53.
63. Njau IW, Karanja SM, Wanzala P, Omolo JO. Factors associated with late presentation of suspected tuberculosis cases to tuberculosis management facilities: The case in Dagoretti district, Nairobi, Kenya. Pan Afr Med J. 2012;12:93.
64. Takarinda KC, Harries AD, Nyathi B, Ngwenya M, Mutasa-Apollo T, Sandy C. Tuberculosis treatment delays and associated factors within the Zimbabwe national tuberculosis programme. BMC Public Health. 2015 Jan 29;15:29.
65. Said K, Hella J, Mhalu G, Chiryankubi M, Masika E, Maroa T, et al. Diagnostic delay and associated factors among patients with pulmonary tuberculosis in Dar es Salaam, Tanzania. Infect Dis Poverty. 2017 Mar 24;6(1):64.
66. Osei E, Akweongo P, Binka F. Factors associated with DELAY in diagnosis among tuberculosis patients in Hohoe Municipality, Ghana. BMC Public Health. 2015 Jul 29;15:721.
67. Meintjes G, Schoeman H, Morroni C, Wilson D, Maartens G. Patient and provider delay in tuberculosis suspects from communities with a high HIV prevalence in South Africa: a cross-sectional study. BMC Infect Dis. 2008 May 25;8:72.
68. Davids M, Dheda K, Pant Pai N, Cogill D, Pai M, Engel N. A Survey on Use of Rapid Tests and Tuberculosis Diagnostic Practices by Primary Health Care Providers in South Africa: Implications for the Development of New Point-of-Care Tests. PLoS One. 2015;10(10):e0141453.
69. World Health Organisation. Regional Office for the Eastern Mediterranean. (2006). Diagnostic and treatment delay in tuberculosis. https://apps.who.int/iris/handle/10665/116501 . [Accessed 1October 2019].

70. Kiwuwa MS, Charles K, Harriet MK. Patient and health service delay in pulmonary tuberculosis patients attending a referral hospital: a cross-sectional study. BMC Public Health. 2005 Nov 24;5:122.
71. Botha E, Den Boon S, Verver S, Dunbar R, Lawrence KA, Bosman M, et al. Initial default from tuberculosis treatment: how often does it happen and what are the reasons? Int J Tuberc Lung Dis. 2008 Jul;12(7):820-3.
72. Claassens MM, du Toit E, Dunbar R, Lombard C, Enarson DA, Beyers N, et al. Tuberculosis patients in primary care do not start treatment. What role do health system delays play? Int J Tuberc Lung Dis. 2013 May;17(5):603-7.
73. Mwansa-Kambafwile J, Maitshotlo B, Black A. Microbiologically Confirmed Tuberculosis: Factors Associated with Pre-Treatment Loss to Follow-Up, and Time to Treatment Initiation. PLoS One. 2017;12(1):e0168659.
74. Skinner D, Claassens M. It's complicated: why do tuberculosis patients not initiate or stay adherent to treatment? A qualitative study from South Africa. BMC Infect Dis. 2016 Nov 25;16(1):712.
75. Munro SA, Lewin SA, Smith HJ, Engel ME, Fretheim A, Volmink J. Patient adherence to tuberculosis treatment: a systematic review of qualitative research. PLoS Med. 2007 Jul 24;4(7):e238.
76. Gebremariam MK, Bjune GA, Frich JC. Barriers and facilitators of adherence to TB treatment in patients on concomitant TB and HIV treatment: a qualitative study. BMC Public Health. 2010 Oct 28;10:651.
77. Tola HH, Tol A, Shojaeizadeh D, Garmaroudi G. Tuberculosis Treatment Non-Adherence and Lost to Follow Up among TB Patients with or without HIV in Developing Countries: A Systematic Review. Iran J Public Health. 2015 Jan;44(1):1-11.
78. Zegeye A, Dessie G, Wagnew F, Gebrie A, Islam SMS, Tesfaye B, et al. Prevalence and determinants of anti-tuberculosis treatment non-adherence in Ethiopia: A systematic review and meta-analysis. PLoS One. 2019;14(1):e0210422.
79. Ndudzo C, Tripathy JP, Tauro F, Sibanda C, Chiramba M, Shamu A, et al. HIV care among patients with presumptive tuberculosis in Masvingo district of Zimbabwe, 2017: how well are we doing? Pan Afr Med J. 2019;33:158.
80. Kranzer K, Govindasamy D, Ford N, Johnston V, Lawn SD. Quantifying and addressing losses along the continuum of care for people living with HIV infection in sub-Saharan Africa: a systematic review. J Int AIDS Soc. 2012 Nov 19;15(2):17383.
81. Fox MP, Rosen S. A new cascade of HIV care for the era of "treat all". PLoS Med. 2017 Apr;14(4):e1002268.
82. South African National AIDS Council. South Africa's National Strategic Plan for HIV, TB and STIs 2017-2022. http://sanac.org.za/wp-content/uploads/2017/05/NSP_FullDocument_FINAL.pdf [Accessed 21 November 2018].
83. The Joint United Nations Programme on HIV/AIDS. 90-90-90 An ambitious treatment target to help end the AIDS epidemic. 2014. . http://www.unaids.org/sites/default/files/media_asset/90-90-90_en_0.pdf. [Accessed 24 February 2017].
84. Siedner MJ, Santorino D, Haberer JE, Bangsberg DR. Know your audience: predictors of success for a patient-centered texting app to augment linkage to HIV care in rural Uganda. J Med Internet Res. 2015 Mar 24;17(3):e78.
85. Jian WS, Hsu MH, Sukati H, Syed-Abdul S, Scholl J, Dube N, et al. LabPush: a pilot study of providing remote clinics with laboratory results via short message service (SMS) in Swaziland, Africa. PLoS One. 2012;7(9):e44462.
86. Gardner LI, Metsch LR, Anderson-Mahoney P, Loughlin AM, del Rio C, Strathdee S, et al. Efficacy of a brief case management intervention to link recently diagnosed HIV-infected persons to care. AIDS. 2005 Mar 4;19(4):423-31.

87. Craw JA, Gardner LI, Marks G, Rapp RC, Bosshart J, Duffus WA, et al. Brief strengths-based case management promotes entry into HIV medical care: results of the antiretroviral treatment access study-II. J Acquir Immune Defic Syndr. 2008 Apr 15;47(5):597-606.
88. United Nations. Principles and Recommendations for a Vital Statistics System. Revision 3 (2014). https://unstats.un.org/unsd/demographic/standmeth/principles/M19Rev3en.pdf. [Accessed 10 June 2018].
89. Yudkin PL, Burger EH, Bradshaw D, Groenewald P, Ward AM, Volmink J. Deaths caused by HIV disease under-reported in South Africa. AIDS. 2009 Jul 31;23(12):1600-2.
90. Birnbaum JK, Murray CJ, Lozano R. Exposing misclassified HIV/AIDS deaths in South Africa. Bull World Health Organ. 2011 Apr 1;89(4):278-85.
91. Fligner CL, Murray J, Roberts DJ. Synergism of verbal autopsy and diagnostic pathology autopsy for improved accuracy of mortality data. Popul Health Metr. 2011 Aug 01;9:25.
92. Banyini AV, Rees D, Gilbert L. "Even if I were to consent, my family will never agree": exploring autopsy services for posthumous occupational lung disease compensation among mineworkers in South Africa. Glob Health Action. 2013 Jan 24;6:19518.
93. Wong EB, Omar T, Setlhako GJ, Osih R, Feldman C, Murdoch DM, et al. Causes of death on antiretroviral therapy: a post-mortem study from South Africa. PLoS One. 2012;7(10):e47542.
94. Karstaedt AS. Profile of cause of death assigned to adults on antiretroviral therapy in Soweto. S Afr Med J. 2012 Aug;102(8):680-2.
95. Garcia-Jardon M, Bhat VG, Blanco-Blanco E, Stepian A. Postmortem findings in HIV/AIDS patients in a tertiary care hospital in rural South Africa. Trop Doct. 2010 Apr;40(2):81-4.
96. Lartey M, Asante-Quashie A, Essel A, Kenu E, Ganu V, Neequaye A. Causes of Death in Hospitalized HIV Patients in the Early Anti-Retroviral Therapy Era. Ghana Med J. 2015 Mar;49(1):7-11.
97. Ansari NA KA, Kenyon TA, Hone NM, Tappero JW, Nyirenda ST, Binkin NJ,Lucas SB. Pathology and causes of death in a group of 128 predominantly HIV-positive patients in Botswana, 1997–1998. International journal of tuberculosis and lung disease. 2002;6(1):55-63.
98. Cox JA, Lukande RL, Nelson AM, Mayanja-Kizza H, Colebunders R, Van Marck E, et al. An autopsy study describing causes of death and comparing clinico-pathological findings among hospitalized patients in Kampala, Uganda. PLoS One. 2012;7(3):e33685.
99. Rana FS, Hawken MP, Mwachari C, Bhatt SM, Abdullah F, Ng'ang'a LW, et al. Autopsy study of HIV-1-positive and HIV-1-negative adult medical patients in Nairobi, Kenya. J Acquir Immune Defic Syndr. 2000 May 01;24(1):23-9.
100. Peonim V, Sujirachato K, Srisont S, Udnoon J. Pathology of HIV seropositive: forensic autopsy study in a tertiary care hospital, Bangkok, Thailand. J Med Assoc Thai. 2012 Aug;95(8):1059-65.
101. Hess DR. Retrospective studies and chart reviews. Respir Care. 2004 Oct;49(10):1171-4.
102. Stepchenkova T, Martynenko O, Yurchenko O. Analysis of causes of death among HIV-infected patients of Kiev Regional AIDS Center during 2013. J Int AIDS Soc. 2014;17(4 Suppl 3):19617.
103. Chkhartishvili N, Sharvadze L, Chokoshvili O, Bolokadze N, Rukhadze N, Kempker RR, et al. Mortality and causes of death among HIV-infected individuals in the country of Georgia: 1989-2012. AIDS Res Hum Retroviruses. 2014 Jun;30(6):560-6.
104. Saraceni V, King BS, Cavalcante SC, Golub JE, Lauria LM, Moulton LH, et al. Tuberculosis as primary cause of death among AIDS cases in Rio de Janeiro, Brazil. Int J Tuberc Lung Dis. 2008 Jul;12(7):769-72.
105. World Health Organization.Verbal Autopsy instrument. 2012. http://www.who.int/healthinfo/statistics/WHO_VA_2012_RC1_Instrument.pdf. [Accessed 28 September 2018].
106. Leitao J, Desai N, Aleksandrowicz L, Byass P, Miasnikof P, Tollman S, et al. Comparison of physician-certified verbal autopsy with computer-coded verbal autopsy for cause of death

assignment in hospitalized patients in low- and middle-income countries: systematic review. BMC Med. 2014;12:22.
107. Fottrell E, Byass P. Verbal autopsy: methods in transition. Epidemiol Rev. 2010;32:38-55.
108. Fantahun M, Fottrell E, Berhane Y, Wall S, Hogberg U, Byass P. Assessing a new approach to verbal autopsy interpretation in a rural Ethiopian community: the InterVA model. Bull World Health Organ. 2006 Mar;84(3):204-10.
109. Byass P, Fottrell E, Dao LH, Berhane Y, Corrah T, Kahn K, et al. Refining a probabilistic model for interpreting verbal autopsy data. Scand J Public Health. 2006;34(1):26-31.
110. Byass P, Huong DL, Minh HV. A probabilistic approach to interpreting verbal autopsies: methodology and preliminary validation in Vietnam. Scand J Public Health Suppl. 2003;62:32-7.
111. James SL, Flaxman AD, Murray CJ, Population Health Metrics Research C. Performance of the Tariff Method: validation of a simple additive algorithm for analysis of verbal autopsies. Popul Health Metr. 2011 Aug 4;9:31.
112. McCormick TH, Li ZR, Calvert C, Crampin AC, Kahn K, Clark SJ. Probabilistic Cause-of-death Assignment using Verbal Autopsies. J Am Stat Assoc. 2016;111(515):1036-49.
113. Serina P, Riley I, Stewart A, James SL, Flaxman AD, Lozano R, et al. Improving performance of the Tariff Method for assigning causes of death to verbal autopsies. BMC Med. 2015 Dec 8;13:291.
114. Flaxman AD, Vahdatpour A, Green S, James SL, Murray CJ, Population Health Metrics Research C. Random forests for verbal autopsy analysis: multisite validation study using clinical diagnostic gold standards. Popul Health Metr. 2011 Aug 4;9:29.
115. King GL, Y. Verbal autopsy methods with multiple causes of death. Statistical Science. 2008;23:78-91.
116. Murray CJ, James SL, Birnbaum JK, Freeman MK, Lozano R, Lopez AD, et al. Simplified Symptom Pattern Method for verbal autopsy analysis: multisite validation study using clinical diagnostic gold standards. Popul Health Metr. 2011 Aug 4;9:30.
117. Kahn K, Tollman SM, Garenne M, Gear JS. Validation and application of verbal autopsies in a rural area of South Africa. Trop Med Int Health. 2000 Nov;5(11):824-31.
118. Byass P, Calvert C, Miiro-Nakiyingi J, Lutalo T, Michael D, Crampin A, et al. InterVA-4 as a public health tool for measuring HIV/AIDS mortality: a validation study from five African countries. Glob Health Action. 2013;6:22448.
119. Byass P, Herbst K, Fottrell E, Ali MM, Odhiambo F, Amek N, et al. Comparing verbal autopsy cause of death findings as determined by physician coding and probabilistic modelling: a public health analysis of 54 000 deaths in Africa and Asia. J Glob Health. 2015 Jun;5(1):010402.
120. van Eijk AM, Adazu K, Ofware P, Vulule J, Hamel M, Slutsker L. Causes of deaths using verbal autopsy among adolescents and adults in rural western Kenya. Trop Med Int Health. 2008 Oct;13(10):1314-24.
121. Melaku YA, Sahle BW, Tesfay FH, Bezabih AM, Aregay A, Abera SF, et al. Causes of death among adults in northern Ethiopia: evidence from verbal autopsy data in health and demographic surveillance system. PLoS One. 2014;9(9):e106781.
122. Pronyk PM, Kahn K, Hargreaves JR, Tollman SM, Collinson M, Hausler HP, et al. Undiagnosed pulmonary tuberculosis deaths in rural South Africa. Int J Tuberc Lung Dis. 2004 Jun;8(6):796-9.
123. Rosario EV, Costa D, Timoteo L, Rodrigues AA, Varanda J, Nery SV, et al. Main causes of death in Dande, Angola: results from Verbal Autopsies of deaths occurring during 2009-2012. BMC Public Health. 2016 Aug 04;16:719.
124. Mberu B, Wamukoya M, Oti S, Kyobutungi C. Trends in Causes of Adult Deaths among the Urban Poor: Evidence from Nairobi Urban Health and Demographic Surveillance System, 2003-2012. J Urban Health. 2015 Jun;92(3):422-45.
125. Weldearegawi B, Melaku YA, Spigt M, Dinant GJ. Applying the InterVA-4 model to determine causes of death in rural Ethiopia. Glob Health Action. 2014;7:25550.

126. World Health Organization. The END TB strategy: Global strategy and targets for Tuberculosis prevention, care and control for 2015. http://www.who.int/tb/strategy/End_TB_Strategy.pdf?ua=1. [Accessed 23 February 2017].
127. Department of Health: South Africa .The National Strategic Plan on HIV, STIs and TB(2017-2022). 2017. http://sanac.org.za/wp-content/uploads/2017/05/NSP_FullDocument_FINAL.pdf. [Accessed 25 May 2018]
128. Hamada Y, Lujan J, Schenkel K, Ford N, Getahun H. Sensitivity and specificity of WHO's recommended four-symptom screening rule for tuberculosis in people living with HIV: a systematic review and meta-analysis. Lancet HIV. 2018 Sep;5(9):e515-e23.
129. World Health Organization. Diagnostics for tuberculosis. Global demand and market potential. 2006. www.who.int/tdr/publications/documents/tbdi.pdf.Accessed. [Accessed 8 March 2016]
130. Chihota VN, Grant AD, Fielding K, Ndibongo B, van Zyl A, Muirhead D, et al. Liquid vs. solid culture for tuberculosis: performance and cost in a resource-constrained setting. Int J Tuberc Lung Dis. 2010 Aug;14(8):1024-31.
131. Phillips PPJ, Mendel CM, Nunn AJ, McHugh TD, Crook AM, Hunt R, et al. A comparison of liquid and solid culture for determining relapse and durable cure in phase III TB trials for new regimens. BMC Med. 2017 Nov 24;15(1):207.
132. World Health Organization. Global tuberculosis control:WHO report 2011. 2011. http://www.who.int/iris/handle/10665/44728. [Accessed 8 March 2018].
133. Lawn SD, Brooks SV, Kranzer K, Nicol MP, Whitelaw A, Vogt M, et al. Screening for HIV-associated tuberculosis and rifampicin resistance before antiretroviral therapy using the Xpert MTB/RIF assay: a prospective study. PLoS Med. 2011 Jul;8(7):e1001067.
134. Friedrich SO, Rachow A, Saathoff E, Singh K, Mangu CD, Dawson R, et al. Assessment of the sensitivity and specificity of Xpert MTB/RIF assay as an early sputum biomarker of response to tuberculosis treatment. Lancet Respir Med. 2013 Aug;1(6):462-70.
135. Theron G, Venter R, Calligaro G, Smith L, Limberis J, Meldau R, et al. Xpert MTB/RIF Results in Patients With Previous Tuberculosis: Can We Distinguish True From False Positive Results? Clin Infect Dis. 2016 Apr 15;62(8):995-1001.
136. World Health Organization. WHO Meeting Report of a Technical Expert Consultation: Non-inferiority analysis of Xpert MTB/RIF Ultra compared to Xpert MTB/RIF. 2017. http://www.who.int/tb/publications/2017/XpertUltra/en/. [Accessed 5 May 2018].
137. World Health Organization. Recommendations for investigating contacts of persons with infectious tuberculosis in low and middle income countries. 2012. http://apps.who.int/iris/bitstream/10665/77741/1/9789241504492_eng.pdf?ua=1. [Accessed 19 February 2017].
138. Fox GJ, Barry SE, Britton WJ, Marks GB. Contact investigation for tuberculosis: a systematic review and meta-analysis. Eur Respir J. 2013 Jan;41(1):140-56.
139. Manosuthi W, Chottanapand S, Thongyen S, Chaovavanich A, Sungkanuparph S. Survival rate and risk factors of mortality among HIV/tuberculosis-coinfected patients with and without antiretroviral therapy. J Acquir Immune Defic Syndr. 2006 Sep;43(1):42-6.
140. Nglazi MD, Bekker LG, Wood R, Kaplan R. The impact of HIV status and antiretroviral treatment on TB treatment outcomes of new tuberculosis patients attending co-located TB and ART services in South Africa: a retrospective cohort study. BMC Infect Dis. 2015 Nov 19;15:536.
141. Abdool Karim SS, Naidoo K, Grobler A, Padayatchi N, Baxter C, Gray AL, et al. Integration of antiretroviral therapy with tuberculosis treatment. N Engl J Med. 2011 Oct 20;365(16):1492-501.
142. Havlir DV, Kendall MA, Ive P, Kumwenda J, Swindells S, Qasba SS, et al. Timing of antiretroviral therapy for HIV-1 infection and tuberculosis. N Engl J Med. 2011 Oct 20;365(16):1482-91.

143. Yan S, Chen L, Wu W, Fu Z, Zhang H, Li Z, et al. Early versus Delayed Antiretroviral Therapy for HIV and Tuberculosis Co-Infected Patients: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. PLoS One. 2015;10(5):e0127645.
144. Colditz GA, Brewer TF, Berkey CS, Wilson ME, Burdick E, Fineberg HV, et al. Efficacy of BCG vaccine in the prevention of tuberculosis. Meta-analysis of the published literature. JAMA. 1994 Mar 02;271(9):698-702.
145. Brewer TF. Preventing tuberculosis with bacillus Calmette-Guerin vaccine: a meta-analysis of the literature. Clin Infect Dis. 2000 Sep;31 Suppl 3:S64-7.
146. Van Der Meeren O, Hatherill M, Nduba V, Wilkinson RJ, Muyoyeta M, Van Brakel E, et al. Phase 2b Controlled Trial of M72/AS01E Vaccine to Prevent Tuberculosis. N Engl J Med. 2018 Sep 25.
147. South African National AIDS Council Secretariat. The national HIV counseling and testing campaign strategy. 2010. https://www.westerncape.gov.za/Other/2010/6/hct_campaign_strategy_2_3_10_final.pdf. [Accessed 24 February 2017].
148. The Joint United Nations Programme on HIV/AIDS.Turn Around: The story of South Africa's HIV response. 2016. http://www.health.gov.za/index.php/component/phocadownload/category/319. [Accessed 24 February 2017]
149. Suthar AB, Lawn SD, del Amo J, Getahun H, Dye C, Sculier D, et al. Antiretroviral therapy for prevention of tuberculosis in adults with HIV: a systematic review and meta-analysis. PLoS Med. 2012;9(7):e1001270.
150. Liu E, Makubi A, Drain P, Spiegelman D, Sando D, Li N, et al. Tuberculosis incidence rate and risk factors among HIV-infected adults with access to antiretroviral therapy. AIDS. 2015 Jul 17;29(11):1391-9.
151. Gupta A, Wood R, Kaplan R, Bekker LG, Lawn SD. Tuberculosis incidence rates during 8 years of follow-up of an antiretroviral treatment cohort in South Africa: comparison with rates in the community. PLoS One. 2012;7(3):e34156.
152. Williams BG, Granich R, De Cock KM, Glaziou P, Sharma A, Dye C. Antiretroviral therapy for tuberculosis control in nine African countries. Proc Natl Acad Sci U S A. 2010 Nov 09;107(45):19485-9.
153. Odone A, Amadasi S, White RG, Cohen T, Grant AD, Houben RM. The impact of antiretroviral therapy on mortality in HIV positive people during tuberculosis treatment: a systematic review and meta-analysis. PLoS One. 2014;9(11):e112017.
154. Ayele HT, Mourik MS, Debray TP, Bonten MJ. Isoniazid Prophylactic Therapy for the Prevention of Tuberculosis in HIV Infected Adults: A Systematic Review and Meta-Analysis of Randomized Trials. PLoS One. 2015;10(11):e0142290.
155. Churchyard GJ, Fielding K, Charalambous S, Day JH, Corbett EL, Hayes RJ, et al. Efficacy of secondary isoniazid preventive therapy among HIV-infected Southern Africans: time to change policy? AIDS. 2003 Sep 26;17(14):2063-70.
156. Churchyard GJ, Fielding KL, Lewis JJ, Coetzee L, Corbett EL, Godfrey-Faussett P, et al. A trial of mass isoniazid preventive therapy for tuberculosis control. N Engl J Med. 2014 Jan 23;370(4):301-10.
157. Ayele HT, van Mourik MS, Bonten MJ. Effect of isoniazid preventive therapy on tuberculosis or death in persons with HIV: a retrospective cohort study. BMC Infect Dis. 2015 Aug 13;15:334.
158. de Pinho AM, Santoro-Lopes G, Harrison LH, Schechter M. Chemoprophylaxis for tuberculosis and survival of HIV-infected patients in Brazil. AIDS. 2001 Nov 09;15(16):2129-35.
159. Group TAS, Danel C, Moh R, Gabillard D, Badje A, Le Carrou J, et al. A Trial of Early Antiretrovirals and Isoniazid Preventive Therapy in Africa. N Engl J Med. 2015 Aug 27;373(9):808-22.

160. Rangaka MX, Wilkinson RJ, Boulle A, Glynn JR, Fielding K, van Cutsem G, et al. Isoniazid plus antiretroviral therapy to prevent tuberculosis: a randomised double-blind, placebo-controlled trial. Lancet. 2014 Aug 23;384(9944):682-90.
161. Yirdaw KD, Jerene D, Gashu Z, Edginton ME, Kumar AM, Letamo Y, et al. Beneficial effect of isoniazid preventive therapy and antiretroviral therapy on the incidence of tuberculosis in people living with HIV in Ethiopia. PLoS One. 2014;9(8):e104557.
162. World Health Organization. Guidelines for intensified tuberculosis case-finding and isoniazid preventive therapy for people living with HIV in resource constrained settings. 2011. http://apps.who.int/iris/bitstream/handle/10665/44472/9789241500708_eng.pdf?sequence=1. [Accessed 8 September 2018].
163. Swindells, S.; Ramchandani R.; Gupta A.; Benson C.A.;Leon-Cruz J.T.; Omoz-Oarhe A et al. One month of rifapentine/isoniazid to prevent TB in people with HIV: BRIEF-TB/A5279. Conference on Retroviruses and Opportunistic Infections, 4-7 March 2018. Late breaker oral abstract 37LB.
164. Menzies D, Adjobimey M, Ruslami R, Trajman A, Sow O, Kim H, et al. Four Months of Rifampin or Nine Months of Isoniazid for Latent Tuberculosis in Adults. N Engl J Med. 2018 Aug 2;379(5):440-53.
165. Dutta NK, Karakousis PC. Latent tuberculosis infection: myths, models, and molecular mechanisms. Microbiol Mol Biol Rev. 2014 Sep;78(3):343-71.
166. Pease C, Hutton B, Yazdi F, Wolfe D, Hamel C, Quach P, et al. Efficacy and completion rates of rifapentine and isoniazid (3HP) compared to other treatment regimens for latent tuberculosis infection: a systematic review with network meta-analyses. BMC Infect Dis. 2017 Apr 11;17(1):265.
167. Houben RM, Sumner T, Grant AD, White RG. Ability of preventive therapy to cure latent Mycobacterium tuberculosis infection in HIV-infected individuals in high-burden settings. Proc Natl Acad Sci U S A. 2014 Apr 8;111(14):5325-30.
168. World Health Organization. WHO policy on TB infection control in health care facilities, congregate settings and households. 2009. [Accessed 21 February 2017]. http://apps.who.int/iris/bitstream/10665/44148/1/9789241598323_eng.pdf.
169. . World Helath Organization. Task shifting. Global recommendation and guidelines. 2008. http://www.who.int/healthsystems/TTR-TaskShifting.pdf?ua=1. [Accessed 5 April 2018].
170. Kipp W, Konde-Lule J, Saunders LD, Alibhai A, Houston S, Rubaale T, et al. Antiretroviral treatment for HIV in rural Uganda: two-year treatment outcomes of a prospective health centre/community-based and hospital-based cohort. PLoS One. 2012;7(7):e40902.
171. Mwisongo A, Mehlomakhulu V, Mohlabane N, Peltzer K, Mthembu J, Van Rooyen H. Evaluation of the HIV lay counselling and testing profession in South Africa. BMC Health Serv Res. 2015 Jul 22;15:278.
172. Torpey KE, Kabaso ME, Mutale LN, Kamanga MK, Mwango AJ, Simpungwe J, et al. Adherence support workers: a way to address human resource constraints in antiretroviral treatment programs in the public health setting in Zambia. PLoS One. 2008 May 21;3(5):e2204.
173. Zachariah R, Ford N, Philips M, Lynch S, Massaquoi M, Janssens V, et al. Task shifting in HIV/AIDS: opportunities, challenges and proposed actions for sub-Saharan Africa. Trans R Soc Trop Med Hyg. 2009 Jun;103(6):549-58.
174. Callaghan M, Ford N, Schneider H. A systematic review of task- shifting for HIV treatment and care in Africa. Hum Resour Health. 2010 Mar 31;8:8.
175. Rich ML, Miller AC, Niyigena P, Franke MF, Niyonzima JB, Socci A, et al. Excellent clinical outcomes and high retention in care among adults in a community-based HIV treatment program in rural Rwanda. J Acquir Immune Defic Syndr. 2012 Mar 1;59(3):e35-42.
176. Lukersmith S, Millington M, Salvador-Carulla L. What Is Case Management? A Scoping and Mapping Review. Int J Integr Care. 2016 Oct 19;16(4):2.
177. Brun C, Rapp RC. Strengths-based case management: individuals' perspectives on strengths and the case manager relationship. Soc Work. 2001 Jul;46(3):278-88.

178. Brennan-Ing M, Seidel L, Rodgers L, Ernst J, Wirth D, Tietz D, et al. The Impact of Comprehensive Case Management on HIV Client Outcomes. PLoS One. 2016;11(2):e0148865.
179. Kenya S, Chida N, Cardenas G, Pereyra M, Del Rio C, Rodriguez A, et al. Case Management: Steadfast Resource for Addressing Linkage to Care and Prevention with Hospitalized HIV-Infected Crack Users. J HIV AIDS Soc Serv. 2014;13(4):325-6.
180. Katz MH, Cunningham WE, Fleishman JA, Andersen RM, Kellogg T, Bozzette SA, et al. Effect of case management on unmet needs and utilization of medical care and medications among HIV-infected persons. Ann Intern Med. 2001 Oct 16;135(8 Pt 1):557-65.
181. Steward WT, Sumitani J, Moran ME, Ratlhagana MJ, Morris JL, Isidoro L, et al. Engaging HIV-positive clients in care: acceptability and mechanisms of action of a peer navigation program in South Africa. AIDS Care. 2018 Mar;30(3):330-7.
182. Thurman TR, Haas LJ, Dushimimana A, Lavin B, Mock N. Evaluation of a case management program for HIV clients in Rwanda. AIDS Care. 2010 Jun;22(6):759-65.
183. Lin RL, Lin FJ, Wu CL, Peng MJ, Chen PJ, Kuo HT. Effect of a hospital-based case management approach on treatment outcome of patients with tuberculosis. J Formos Med Assoc. 2006 Aug;105(8):636-44.
184. World Health Organization. mHealth:New horizons for health through mobile technologies:second global survey on eHealth. 2011. http://www.who.int/goe/publications/goe_mhealth_web.pdf. [Accessed 10 April 2018]
185. Forrest JI, Wiens M, Kanters S, Nsanzimana S, Lester RT, Mills EJ. Mobile health applications for HIV prevention and care in Africa. Curr Opin HIV AIDS. 2015 Nov;10(6):464-71.
186. Mbuagbaw L, van der Kop ML, Lester RT, Thirumurthy H, Pop-Eleches C, Smieja M, et al. Mobile phone text messages for improving adherence to antiretroviral therapy (ART): a protocol for an individual patient data meta-analysis of randomised trials. BMJ Open. 2013 May 28;3(5).
187. Georgette N, Siedner MJ, Zanoni B, Sibaya T, Petty CR, Carpenter S, et al. The Acceptability and Perceived Usefulness of a Weekly Clinical SMS Program to Promote HIV Antiretroviral Medication Adherence in KwaZulu-Natal, South Africa. AIDS Behav. 2016 Nov;20(11):2629-38.
188. Chang LW, Kagaayi J, Arem H, Nakigozi G, Ssempijja V, Serwadda D, et al. Impact of a mHealth intervention for peer health workers on AIDS care in rural Uganda: a mixed methods evaluation of a cluster-randomized trial. AIDS Behav. 2011 Nov;15(8):1776-84.
189. Nhavoto JA, Gronlund A, Klein GO. Mobile health treatment support intervention for HIV and tuberculosis in Mozambique: Perspectives of patients and healthcare workers. PLoS One. 2017;12(4):e0176051.
190. Nglazi MD, Bekker LG, Wood R, Hussey GD, Wiysonge CS. Mobile phone text messaging for promoting adherence to anti-tuberculosis treatment: a systematic review protocol. Syst Rev. 2013 Jan 16;2:6.
191. Corbett EL, MacPherson P. Tuberculosis screening in high human immunodeficiency virus prevalence settings: turning promise into reality. Int J Tuberc Lung Dis. 2013 Sep;17(9):1125-38.
192. The Local Government Handbook: South Africa 2018. . www.municipalities.co.za. [Accessed 7 July 2018].
193. May C, Finch T, Mair F, Ballini L, Dowrick C, Eccles M, et al. Understanding the implementation of complex interventions in health care: the normalization process model. BMC Health Serv Res. 2007 Sep 19;7:148.
194. Murray E, Treweek S, Pope C, MacFarlane A, Ballini L, Dowrick C, et al. Normalisation process theory: a framework for developing, evaluating and implementing complex interventions. BMC Med. 2010 Oct 20;8:63.
195. Maraba N, Karat AS, McCarthy K, Churchyard GJ, Charalambous S, Kahn K, et al. Verbal autopsy-assigned causes of death among adults being investigated for TB in South Africa. Trans R Soc Trop Med Hyg. 2016 Sep;110(9):510-6.

196. Maraba N, Chihota V, McCarthy K, Churchyard GJ, Grant AD. Linkage to care among adults being investigated for tuberculosis in South Africa: pilot study of a case manager intervention. BMJ Open. 2018 May 24;8(5):e021111.
197. Maraba N, Hoffmann CJ, Chihota VN, Chang LW, Ismail N, Candy S, et al. Using mHealth to improve tuberculosis case identification and treatment initiation in South Africa: Results from a pilot study. PLoS One. 2018;13(7):e0199687.
198. Kebede Y, Andargie G, Gebeyehu A, Awoke T, Yitayal M, Mekonnen S, et al. Tuberculosis and HIV are the leading causes of adult death in northwest Ethiopia: evidence from verbal autopsy data of Dabat health and demographic surveillance system, 2007-2013. Popul Health Metr. 2017;15:27.
199. Kone S, Furst T, Jaeger FN, Esso EL, Baikoro N, Kouadio KA, et al. Causes of death in the Taabo health and demographic surveillance system, Cote d'Ivoire, from 2009 to 2011. Glob Health Action. 2015;8:27271.
200. Sifuna P, Otieno L, Ogwang S, Ogutu B, Andagalu B, Owuoth J, et al. Cause-specific mortality in the Kombewa health and demographic surveillance systems site, rural Western Kenya from 2011-2015. Glob Health Action. 2018;11(1):1442959.
201. Tadesse S, Tadesse T. Evaluating the performance of interpreting Verbal Autopsy 3.2 model for establishing pulmonary tuberculosis as a cause of death in Ethiopia: a population-based cross-sectional study. BMC Public Health. 2012 Nov 29;12:1039.
202. Karat AS, Tlali M, Fielding KL, Charalambous S, Chihota VN, Churchyard GJ, et al. Measuring mortality due to HIV-associated tuberculosis among adults in South Africa: Comparing verbal autopsy, minimally-invasive autopsy, and research data. PLoS One. 2017;12(3):e0174097.
203. Njuki R, Kimani J, Obare F, Warren C. Using verbal and social autopsies to explore health-seeking behaviour among HIV-positive women in Kenya: a retrospective study. BMC Womens Health. 2014 Jun 27;14:77.
204. Ngwira LG, Dowdy DW, Khundi M, Barnes GL, Nkhoma A, Choko AT, et al. Delay in seeking care for tuberculosis symptoms among adults newly diagnosed with HIV in rural Malawi. Int J Tuberc Lung Dis. 2018 Mar 1;22(3):280-6.
205. Barker RD, Millard FJ, Malatsi J, Mkoana L, Ngoatwana T, Agarawal S, et al. Traditional healers, treatment delay, performance status and death from TB in rural South Africa. Int J Tuberc Lung Dis. 2006 Jun;10(6):670-5.
206. Gopi PG, Subramani R, Santha T, Chandrasekaran V, Kolappan C, Selvakumar N, et al. Estimation of burden of tuberculosis in India for the year 2000. Indian J Med Res. 2005 Sep;122(3):243-8.
207. Loeliger KB, Niccolai LM, Mtungwa LN, Moll A, Shenoi SV. Antiretroviral therapy initiation and adherence in rural South Africa: community health workers' perspectives on barriers and facilitators. AIDS Care. 2016 Aug;28(8):982-93.
208. Rachlis B, Naanyu V, Wachira J, Genberg B, Koech B, Kamene R, et al. Identifying common barriers and facilitators to linkage and retention in chronic disease care in western Kenya. BMC Public Health. 2016 Aug 8;16:741.
209. Bogart LM, Chetty S, Giddy J, Sypek A, Sticklor L, Walensky RP, et al. Barriers to care among people living with HIV in South Africa: contrasts between patient and healthcare provider perspectives. AIDS Care. 2013;25(7):843-53.
210. Nakigozi G, Atuyambe L, Kamya M, Makumbi FE, Chang LW, Nakyanjo N, et al. A qualitative study of barriers to enrollment into free HIV care: perspectives of never-in-care HIV-positive patients and providers in Rakai, Uganda. Biomed Res Int. 2013;2013:470245.
211. Awofeso N, Schelokova I, Dalhatu A. Training of front-line health workers for tuberculosis control: lessons from Nigeria and Kyrgyzstan. Hum Resour Health. 2008 Sep 29;6:20.
212. Hoffmann CJ, Mabuto T, McCarthy K, Maulsby C, Holtgrave DR. A Framework to Inform Strategies to Improve the HIV Care Continuum in Low- and Middle-Income Countries. AIDS Educ Prev. 2016 Aug;28(4):351-64.

213. Hoffmann CJ, Mabuto T, Ginindza S, Fielding KL, Kubeka G, Dowdy DW, et al. Strategies to Accelerate HIV Care and Antiretroviral Therapy Initiation After HIV Diagnosis: A Randomized Trial. J Acquir Immune Defic Syndr. 2017 Aug 15;75(5):540-7.
214. Bassett IV, Coleman SM, Giddy J, Bogart LM, Chaisson CE, Ross D, et al. Sizanani: A Randomized Trial of Health System Navigators to Improve Linkage to HIV and TB Care in South Africa. J Acquir Immune Defic Syndr. 2016 Oct 1;73(2):154-60.
215. Amanyire G, Semitala FC, Namusobya J, Katuramu R, Kampiire L, Wallenta J, et al. Effects of a multicomponent intervention to streamline initiation of antiretroviral therapy in Africa: a stepped-wedge cluster-randomised trial. Lancet HIV. 2016 Nov;3(11):e539-e48.
216. Steward W.T.; Agnew E.; DeKadt J.; Gilmore H.; Ratlhangana M.;Grignon J.; et al. Peer navigation enhances HIV care retention: an RCT in South African primary clinics. Conference on Retroviruses and Opportunistic Infections. Seattle, February 13-16, 2017. Abstract 111.
217. McCarthy KM, Grant AD, Chihota V, Ginindza S, Mvusi L, Churchyard GJ, et al. Implementation and Operational Research: What Happens After a Negative Test for Tuberculosis? Evaluating Adherence to TB Diagnostic Algorithms in South African Primary Health Clinics. J Acquir Immune Defic Syndr. 2016 Apr 15;71(5):e119-26.
218. Department of Health: South Africa. Adherence guidelines for HIV, TB and NCDs.Policy and service delivery guidelines for linkage to care, adherence to treatment and retention in care. 2016. . https://www.nacosa.org.za/wp-content/uploads/2016/11/Integrated-Adherence-Guidelines-NDOH.pdf. [Accessed 28 September 2018].
219. Foster N, Vassall A, Cleary S, Cunnama L, Churchyard G, Sinanovic E. The economic burden of TB diagnosis and treatment in South Africa. Soc Sci Med. 2015 Apr;130:42-50.
220. Wagstaff A, van Doorslaer E, Burger R. SMS nudges as a tool to reduce tuberculosis treatment delay and pretreatment loss to follow-up. A randomized controlled trial. PLoS One. 2019;14(6):e0218527.
221. Ngwatu BK, Nsengiyumva NP, Oxlade O, Mappin-Kasirer B, Nguyen NL, Jaramillo E, et al. The impact of digital health technologies on tuberculosis treatment: a systematic review. Eur Respir J. 2018 Jan;51(1).
222. Liu Q, Abba K, Alejandria MM, Sinclair D, Balanag VM, Lansang MA. Reminder systems to improve patient adherence to tuberculosis clinic appointments for diagnosis and treatment. Cochrane Database Syst Rev. 2014 Nov 18(11):CD006594.
223. Chadha S, Trivedi A, Nagaraja SB, Sagili K. Using mHealth to enhance TB referrals in a tribal district of India. Public Health Action. 2017 Jun 21;7(2):123-6.
224. Lutge EE, Wiysonge CS, Knight SE, Sinclair D, Volmink J. Incentives and enablers to improve adherence in tuberculosis. Cochrane Database Syst Rev. 2015 Sep 3(9):CD007952.
225. Siedner MJ, Haberer JE, Bwana MB, Ware NC, Bangsberg DR. High acceptability for cell phone text messages to improve communication of laboratory results with HIV-infected patients in rural Uganda: a cross-sectional survey study. BMC Med Inform Decis Mak. 2012 Jun 21;12:56.

APPENDIX A: ROLE OF STUDENT

I have been involved in all aspects of the three studies that comprise this thesis: Verbal autopsy study (*Causes of death);* a pilot study to evaluate the feasibility and acceptability of using a case manager to improve linkage to TB and HIV care amongst people investigated for TB in South Africa, (*Case manager);* and Development and implementation of mHealth-based clinical decision support messaging for health care workers and patients in the initial investigation of tuberculosis (*mHealth).* My role in each of the studies is summarized in the table below.

Study Name	**Study design**	**Aim**	**Objectives**	**Study sites**	**Student Role in studies and manuscript development**
Determining causes of death amongst people undergoing TB investigation using verbal autopsy in South Africa	Cross-sectional	Determining all-cause mortality amongst adults being investigated for TB	To determine causes of death using verbal autopsy amongst cohort of patients being investigated for TB. (Paper I)	Communities across four provinces Eastern Cape, Gauteng, Free state and Mpumalanga	Developed data collection tools, database design, submissions to ethics, engaging stakeholders, data collection, data cleaning, analysis, training of research teams and supervision. Analysed data, wrote first draft of the manuscript and revised the manuscript.
A pilot study to evaluate the feasibility and acceptability of using a case manager to improve linkage to TB and HIV care amongst people investigated for TB in	Prospective cohort study design	Determining the feasibility and acceptability of a case-manager to improve linkage to TB and HIV care for people being investigated for TB.	To assess the feasibility and acceptability of a case-manager strategy to improve linkage to TB and HIV care in patients being investigated for TB at	Six primary health care facilities across two provinces [Mpumalanga and Gauteng]	Developed protocol, informed consent forms, data collection tools, database design, submissions to ethics. Engaged stakeholders. Conducted data collection, data cleaning, analysis, training of research teams and supervision. Contributed to the development of final report to funder. Wrote first draft of the manuscript, revised the manuscript.

primary health care facilities in South Africa			primary health care facilities. (Paper II)		
Development and implementation of mHealth-based clinical decision support messaging for health care workers and patients in the initial investigation of tuberculosis in primary health care facilities in South Africa.	Prospective cohort study	Determining feasibility and acceptability of a mHealth-intervention that relays sputum TB results with tailored clinical decision support messaging from laboratory to health care workers and patients.	• To develop software (mobile applications, data interface and backend database) to ensure rapid delivery of sputum results from laboratory services • To develop text messaging (SMS) strategies by which patients will be informed of their sputum results. (Paper III)	Two primary health care facilities across in Johannesburg	Assisted with mhealth application design, submissions to ethics, engaging stakeholders. Conducted training of research teams and supervision, data collection, data cleaning and analysis. , Developed final report to funder. Wrote first draft of the manuscript, revised the manuscript.

APPENDIX B: PUBLICATIONS

PAPER I

Trans R Soc Trop Med Hyg 2016; **110**: 510–516
doi:10.1093/trstmh/trw058 Advance Access publication 7 October 2016

ORIGINAL ARTICLE

Verbal autopsy-assigned causes of death among adults being investigated for TB in South Africa

Noriah Maraba[a,b,*], Aaron S Karat[c], Kerrigan McCarthy[d], Gavin J Churchyard[a,b,c,e], Salome Charalambous[a,b], Kathleen Kahn[f,g,h], Alison D Grant[b,c,i] and Violet Chihota[a,b]

[a]The Aurum Institute, Parktown, Johannesburg, South Africa; [b]School of Public Health, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa; [c]London School of Hygiene & Tropical Medicine, UK; [d]Division of Public Health Surveillance and Response, National Institute for Communicable diseases of the National Health Laboratory Service, Johannesburg, South Africa; [e]Advancing Treatment and Care for TB and HIV, South African Medical Research Council Collaborating Centre for HIV/TB; [f]MRC/Wits Rural Public Health and Health Transitions Research Unit (Agincourt); School of Public Health, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa; [g]Umeå Centre for Global Health Research, Division of Epidemiology and Global Health, Department of Public Health and Clinical Medicine, Umeå University, Umeå 90187, Sweden; [h]INDEPTH Network, Accra, Ghana; [i]School of Nursing, Public Health, Africa Center for Population Health, University of Kwa-Zulu Natal

*Corresponding author: Present address: Aurum Institute, Post Net Suite 300, Private Bag X30500, Houghton 2041, South Africa; Tel: +2710 590 1300; E-mail: nmaraba@auruminstitute.org

Received 13 May 2016; revised 12 August 2016; accepted 6 September 2016

Background: Adults being investigated for TB in South Africa experience high mortality, yet causes of death (CoD) are not well defined. We determined CoD in this population using verbal autopsy (VA), and compared HIV- and TB-associated CoD using physician-certified verbal autopsy (PCVA) and InterVA-4 software.

Methods: All contactable consenting caregivers of participants who died during a trial comparing Xpert MTB/RIF to smear microscopy were interviewed using the WHO VA tool. CoD were assigned using PCVA and InterVA-4. Kappa statistic (K) and concordance correlation coefficient (CCC) were calculated for comparison.

Results: Among 231 deaths, relatives of 137 deceased were interviewed. Of the 137 deceased 76 (55.4%) were males, median age 41 years (IQR 33–50). PCVA assigned 70 (51.1%) TB immediate CoD (44 [62.8%] pulmonary TB; 26 [37.1%] extra-pulmonary TB); 21 (15.3%) HIV/AIDS-related; and 46 (33.5%) other CoD. InterVA-4 assigned 48 (35.0%) TB deaths; 49 (35.7%) HIV/AIDS-related deaths; and 40 (29.1%) other CoD. Agreement between PCVA and InterVA-4 CoD was slight at individual level (K=0.20; 95% CI 0.10–0.30) and poor at population level (CCC 0.67; 95% CI 0.38–0.99).

Conclusions: TB and HIV are leading CoD among adults being investigated for TB. PCVA and InterVA agreement at individual level was slight and poor at population level. VA methodology needs further development where TB and HIV are common.

Keywords: Causes of death, InterVA, Physician assigned verbal autopsy, Tuberculosis, Verbal autopsy

Introduction

TB is a leading cause of death in South Africa[1] and is a public health priority, with an estimated 380 000[2] cases in 2013, among whom 62% were also living with HIV.[3] WHO has set global targets to reduce TB mortality by 75% in 2025 compared to 2015 figures as a baseline.[2] To track the reduction in TB mortality, accurate data on numbers of TB deaths are needed. Cause of death is most accurately assigned using pathological autopsy.[4] However, pathological autopsies are logistically difficult and rarely performed. In areas where not all deaths occur in health facilities and causes of death are not determined, poor vital statistics, as well as the need to better understand the distribution of cause of death at population level, have led to verbal autopsy (VA) being used to estimate cause of death. This involves interviewing caregivers about the signs, symptoms, medical history and circumstances surrounding an individual's death.[5] VA interview data can be interpreted to estimate cause of death using methods such as

physician-certified verbal autopsy (PCVA) and computer-coded verbal autopsy (CCVA), with PCVA being the most widely used method. CCVA uses software that employs algorithms and probabilistic methods (including InterVA-4 [http://www.interva.net/]), while the PCVA method involves at least two physicians examining each record and attempting to reach a consensus on cause of death using codes from the 10th version of the International Classification of Diseases (ICD-10).[6,7]

The XTEND trial, a pragmatic cluster-randomised trial embedded in the South African national roll-out of Xpert MTB/RIF, compared mortality over six months among adults investigated for TB using Xpert MTB/RIF vs smear microscopy as the initial diagnostic test.[8] XTEND found high mortality in adults being investigated for TB, with no difference in mortality at 6 months between the study arms.[8] The cohort of XTEND participants who died, presented a unique opportunity to evaluate VA methodologies in a cohort with high TB/HIV prevalence. The aim of this paper was to use VA to assign cause of death, among adults being investigated for TB with a particular interest in TB, and to compare cause of death assigned by PCVA to that assigned by a CCVA method (InterVA-4).

Methods

XTEND study

The parent XTEND trial is described in detail elsewhere.[8] Between June and November 2012, a representative sample of 4656 consenting participants who were ≥18 years, planning to live in the study catchment area for more than 8 months, identified by clinic staff as needing investigation for TB and providing sputum for TB testing were enrolled into the study. At enrolment, participants provided contact details and those of close relatives or friends. Vital status was ascertained by contacting participants, their next of kin or friends by telephone and, if necessary, conducting home visits. Vital status of participants was further ascertained by reviewing the Department of Home Affairs vital statistics register.

Verbal autopsy

All XTEND participants who died during the study were eligible for the VA sub-study, including some who died more than 6 months post-enrolment and hence did not contribute to the XTEND primary outcome. Demographic details and past medical history of deceased participants were extracted from the XTEND database, but were not available to staff doing VA interviews nor to physicians assigning cause of death. The XTEND database also included case note reviews where TB treatment start dates and antiretroviral treatment (ART) start dates were obtained. Caregivers, defined as a relative or friend closely associated with the participant at time of death, were invited to participate by telephonic contact, or if unsuccessful, home visit. Lay counsellors, trained in administering the standardized 2012 WHO VA tool and in grief counselling, administered the questionnaire. The tool comprised of closed questions with 'yes', 'no', or 'don't know' responses and a narrative section. The caregiver recounted the events leading up to the participant's death, detailing information about the deceased's signs, symptoms, medical history, and circumstances preceding death in the narrative section.[5] Time from enrolment to death was defined as period from enrolment to date of death. Time from enrolment to TB treatment initiation was the period from enrolment to date of TB treatment initiation and time from enrolment to ART initiation was the period from enrolment to date of ART initiation.

Interpretation of verbal autopsies using PCVA

PCVA involved two physicians independently assigning immediate and underlying cause of death using ICD-10 guidelines, based on VA data, including the caregiver's narrative for each decedent. Where different immediate or underlying causes of death were assigned by the physicians, a consensus meeting was held; if no consensus was reached, the case was referred to a third independent physician. If still no consensus was reached, the case was classified 'indeterminate'. Physicians were aware that all decedents were participants in the XTEND trial and had been investigated for TB. For individual cause of death analysis, the following ICD-10 codes were considered to be HIV-related deaths: B20 (HIV resulting in infectious and parasitic diseases), B21 (HIV disease resulting in malignant neoplasms), B22 (HIV disease resulting in other specified diseases), B23 (other conditions associated with HIV) and B24 (unspecified HIV disease). ICD-10 codes A15 (respiratory TB, bacteriologically and histologically confirmed) and A16 (respiratory TB, not confirmed bacteriologically or histologically) were categorised as pulmonary TB (PTB) while A17 (TB of nervous system), A18 (TB of other organs) and A19 (miliary TB) as extra-pulmonary TB (EPTB).[9] Individual cause of death assigned by PCVA were processed further using mortality medical data system (MMDS) software, which generates underlying cause of death from multiple causes of death.[10] The output generated by MMDS was categorised into WHO 2012 VA causes of death groups; cause specific mortality fractions were calculated by dividing the number of deaths assigned to a group by the total number of deaths.[5,10]

Interpretation of verbal autopsies using InterVA-4

InterVA version 4.03 RC1 is software that uses Bayesian probabilistic theory to assign cause of death. The software generates up to three probable causes of death for each case based on a predetermined algorithm with the cause of death assigned the highest likelihood being referred to as the most probable cause of death.[11–13] VA data were imported into InterVA-4, set at high HIV and low malaria prevalence for our study setting. InterVA-4 assigns only PTB as a TB-related cause of death, classifying all EPTB as 'other unspecified infectious diseases'. Specificity of InterVA-4 in assigning HIV-related cause of death has previously been reported to be 90.1% (95% CI 88.7–91.4%).[14] The probable cause of death generated for each individual were further processed to generate population cause specific mortality fractions.

All respondents gave written informed consent, or witnessed verbal consent if unable to read and write.

Comparing InterVA-4 and PCVA

The two methods assign a wide range of cause of death but for this study we concentrated on HIV/AIDS- and TB-related deaths. At individual level, we focused on the most probable cause of death assigned by InterVA-4, compared with underlying cause of death generated by MMDS for PCVA. For TB deaths, we compared PTB deaths assigned by PCVA and by InterVA-4. For HIV

deaths, ICD-10 codes (B20–24) assigned by physicians were grouped together and compared with HIV/AIDS-related deaths assigned by InterVA-4. For individual causes of death assigned, the level of agreement between the two methods was estimated using Cohen's kappa (K) statistic with a 95% CI. K=1 would indicate perfect agreement, and K=0 would indicate agreement no better than chance.[15] Cause specific mortality fractions generated by the two methods were compared using Lin's concordance correlation coefficient (CCC) which ranges from −1 to +1 with +1 being perfect agreement and 0 showing no agreement.[16] All analyses were done using Stata (version 13, Stata Corp LP, College Station, TX, USA).

Results

A total of 231 XTEND participants died between 8 June 2012 and 31 June 2013. From 1 August to 29 November 2013, 231 interviews were attempted with caregivers. Of these 138 (59.8%) were completed; 68 (29.4%) caregivers could not be traced and 25 (10.8%) refused to be interviewed. Interviews were conducted within a median time of 11 months (IQR 8–12 months) after deaths had occurred. One interview was excluded due to a missing narrative section leaving 137 for analysis. Among the 137 decedents, 76 (55.4%) were male and the median age was 41 years (IQR 33–50). Ninety-seven (70.8%) had self-reported being HIV-positive with median self-reported CD4 count 118 (IQR 52–290) cells/μL. Baseline characteristics of those who were included were similar to those who were not included except for number of TB symptoms reported at enrolment (Table 1). Furthermore there was no difference in time from enrolment to death between the two groups. A total of 41 participants were started on TB treatment and 28 (20.4%) had a VA done. Median time from enrolment to TB treatment was 11 days (IQR 7–33) in those with a VA vs 15 days (IQR 5–30) in those without a VA; this did not differ between the two groups. A total of 162 participants self-reported being HIV-positive in

Table 1. Characteristics of deceased participants who had verbal autopsy vs those who did not

Variables Characteristics at baseline	Verbal autopsy done n=137	Verbal autopsy not done n=94	p-value
Male gender, n (%)	76 (55.4)	57 (60.6)	NS
Age, years (median, IQR)	41 (33–50)	37 (31–48)	NS
Country of origin, n (%)[a]			
South Africa	128 (93.4)	84 (89.4)	
Non-South African	9 (6.5)	9 (9.6)	NS
Self-reported HIV status at enrolment, n (%)[a]			
Positive	97 (70.8)	65 (69.1)	
Negative	15 (10.9)	11 (11.7)	
Unknown	25 (18.2)	17 (18.1)	NS
Self-reported CD4 count (median, IQR)[a]	118 (52–290)	199 (103–253)	NS
No. of TB symptoms reported at enrolment, n (%)[a]			
0	0 (0)	2 (2.1)	
1	15 (10.9)	4 (4.3)	
2	34 (24.8)	16 (17.0)	
3	38 (27.7)	36 (38.3)	
4	50 (36.5)	35 (37.2)	0.05
Body mass index (kg/m2)[a]			
<18.5	26 (18.9)	22 (23.4)	
18.5–24.9	74 (54.0)	56 (59.5)	
25–29.9	20 (14.6)	8 (8.5)	
30+	17 (12.4)	7 (7.4)	NS
HIV and TB treatment initiation, death			
Time from enrolment to death, days (median, IQR)[b]	64 (31–115)	57 (28–113)	NS
No. started on TB treatment, n (%)			
Overall n=41 (17.7%)	28 (20.4)	13 (13.8)	NS
Time from enrolment to TB treatment initiation, days (median, IQR)	11 (7–33)	15 (5–30)	NS
No. started on ART after enrolment, n=35 (%)	23 (65.7)	12 (34.2)	NS
Time from enrolment to ART initiation, days (median, IQR)	25 (9–48)	15 (8–40)	NS

ART: antiretroviral therapy; NS: not significant.
[a] Data missing for one participant in the group without a verbal autopsy.
[b] Data missing for 12 participants.

the study and 61 (37.6%) had evidence of being initiated on ART. Of the 61, 35 (57%) started ART after enrolment into XTEND. Median time from enrolment to ART initiation was not different between the groups (Table 1).

PCVA assigned cause of death

PCVA assigned immediate and underlying cause of death for 134 (98.0%) VAs; three (2.2%) VAs were indeterminate (Table 2). Of the 134 with a cause of death, 95 (70.9%) were assigned without requiring a consensus meeting and 39 (28.5%) after a consensus meeting. Among the 137 decedents, the most common immediate cause of death assigned was TB (70 decedents, 51.1%). Of these 70 TB deaths, 44 (63%) were attributed to PTB, of which eight (18%) were classified as bacteriologically confirmed as reported on VA. EPTB was assigned as cause of death in 26/70 (37%) TB deaths. Of these, 11 (42%) were TB of the nervous system, 10 (38%) miliary TB and 5 (19%) TB of other organs; 57/70 (81%) of those assigned an immediate TB cause of death were assigned an underlying HIV cause of death by the physicians. HIV/AIDS-related immediate cause of death were assigned in 21/137 (15.3%) decedents; gastrointestinal diseases in seven (5.1%) decedents; pneumonia in five (3.6%); cardiac disease and respiratory ailments in four (3.0%) each; renal failure and malignant neoplasm in three (2.0%) each; while liver disease and intentional self-harm were in two (1.5%) each (Table 2). Cause specific mortality fractions were calculated after PCVA causes of death were processed by MMDS software: HIV/AIDS-related deaths accounted for 66.4% of PCVA deaths; PTB for 9.5%; cardiac disease for 2.9%; and malignant neoplasms, gastrointestinal diseases and accident/self harm for 2.2% each (Table 3).

InterVA-4 assigned cause of death

InterVA-4 assigned cause of death to 136 (99.2%) decedents; one (0.7%) was classified as indeterminate. Of the 137 decedents, 48 (35.0%) were assigned a most probable cause of death of PTB, 49 (35.7%) an HIV/AIDS-related cause, and 14 (10.2.%) a malignancy-related cause of death. Only one decedent was assigned an 'other unspecified infectious diseases' cause of death by InterVA-4 (Table 2). InterVA-4 assigned 16 decedents with more than one cause of death, 13 were assigned two, and three were assigned three causes of death. Of the 16 with more than one cause of death, three (18.7%) had HIV as a less probable cause and four (25.0%) had TB as less probable cause of death. Only one decedent with a most probable cause of death of PTB had HIV assigned as a less probable cause and also one with HIV as a most probable cause of death had PTB assigned as a less probable cause. InterVA-4 cause specific mortality fractions were calculated using all assigned causes of death: PTB accounted for 33.2% of deaths; HIV/AIDS for 32.8%; malignant neoplasms for 9.6%; and respiratory ailments for 4.9% (Table 3).

Table 2. Immediate cause of death assigned by physician-certified verbal autopsy compared with 'most probable' cause of death assigned by InterVA-4 (n=137)

	Physician-certified verbal autopsy	InterVA-4
Cause of death	n (%)	n (%)
Pulmonary TB	44 (32.1)	48 (35.0)
Not bacteriologically-confirmed	36 (26.0)	NA
Bacteriologically-confirmed	8 (6.0)	NA
Extrapulmonary TB	26 (19.0)	NA
TB of nervous system	11 (8.0)	NA
Miliary TB	10 (7.0)	NA
TB of other organs	5 (4.0)	NA
HIV/AIDS-related deaths	21 (15.3)	49 (35.7)
Gastrointestinal diseases	7 (5.1)	4 (3.0)
Pneumonia	5 (3.6)	4 (3.0)
Cardiac disease/failure	4 (3.0)	5 (3.6)
Respiratory ailments	4 (3.0)	2 (1.5)
Renal failure	3 (2.0)	1 (0.7)
Malignant neoplasm	3 (2.0)	14 (10.2)
Liver diseases	2 (1.5)	1 (0.7)
Intentional self-harm/poisoning	2 (1.5)	1 (0.7)
Meningitis	1 (0.7)	0 (0.0)
Indeterminate/unspecified	4 (3.0)	1 (0.7)
Other	11 (8.0)	7 (5.1)
Total	137	137

NA: not applicable.

Comparing InterVA-4 and PCVA cause of death

A direct comparison of the single underlying cause of death assigned by MMDS for PCVA and the most probable cause of death assigned by InterVA-4 showed agreement in 65/137 (47.4%) decedents with kappa statistic 0.20 (95% CI 0.10–0.30); representing slight agreement (Table 4). Comparison of cause specific mortality fractions assigned by PCVA and InterVA showed a CCC of 0.67 (95% CI 0.38–0.97), which was poor (Table 3).

Discussion

The XTEND study is the largest cohort to date of adults being investigated for TB. In this sub-study, we used VA to investigate cause of death, which showed that about half (51% based on PCVA and 35% based on InterVA-4) the deaths were attributed to TB. These findings might be surprising as these were people accessing health care who had investigation for TB initiated and who had submitted at least one sputum specimen for smear microscopy or Xpert MTB/RIF. Though one might hope that people who had TB investigations initiated should not die of TB, some patients may have already been very sick at the time TB investigation was initiated, as illustrated by the 18.9% with BMI <18.5 and the 64.2% reporting three or four TB symptoms. If these cause of death data are correct, it suggests that persons are presenting for care too late, or that the current health system is failing to identify and treat persons who have TB, or both. It could also be that the health system is too slow to diagnose TB, resulting in delays in TB treatment initiation. This latter possibility was suggested by data from the XTEND trial which showed median time to starting TB treatment of 7 days[8] which is a little longer than the Department of Health recommended 2–5 days.[17] HIV-related disease was the second most common cause of death, consistent with absence of ART at enrolment being a risk factor for death among XTEND participants.[8]

Adults being investigated for TB have been studied far less often than those starting TB treatment, and where cause of death data exist, they are generally from hospitals rather than primary health care clinics. The high proportion of deaths attributable to TB was similar to studies using pathological autopsy to assign cause of death. An autopsy study in South Africa among hospitalised HIV-positive adults either on, or eligible for, ART showed that 66% died of TB, while only 27% were on TB treatment at time of death and 33% had never been treated for TB prior to death.[18] In Zambia, a study amongst hospitalised adults, mostly HIV-positive (81%), reported that 62% of deaths were attributed to TB and 26% were never treated for TB prior to death.[19] A recent systematic review among HIV-positive adults and children reported that TB was a primary cause of death in 91.4% (95% CI 85.5–97) of those diagnosed at autopsy.[20] Another study in South Africa seeking to understand cause of death among ART initiators dying in hospital using VA and hospital case reviews also reported similar findings where mortality attributable to TB was 44.3%.[21]

Our study compared PCVA and InterVA-4 methods of assigning cause of death at individual and population level. The majority of studies comparing these methodologies have been done in community settings in health and demographic surveillance system sites where VAs are done for all persons who die. In our study, when comparing immediate and most probable cause of death, PCVA assigned more deaths to TB than InterVA-4. This could be because InterVA-4 can only assign PTB as a TB-related death and assigns EPTB to other infectious diseases, while PCVA allows deaths to be assigned as either PTB or EPTB, so EPTB deaths are not misclassified. PCVA and InterVA-4 models have been compared in other populations and have shown fair to moderate agreement.[22–24] A study conducted in a health and demographic surveillance system in Kenya, collecting data on cause of death over a 6 year period amongst children <5 years and adults aged ≥18 years, showed that PCVA assigned 9.9% of deaths to PTB and 34% to HIV/AIDS while InterVA assigned 31% to PTB and 16% to HIV/AIDS (K=0.27, 95% CI 0.25–0.30).[22] In Ethiopia, data on cause of death collected over a 2 year period from adults aged ≥14 years in a health and demographic

Table 3. Comparison of cause specific mortality fractions as assigned by physician certified verbal autopsy and mortality medical data system and InterVA-4

Cause of death	PCVA CSMF (%)	InterVA-4 CSMF (%)
HIV/AIDS related	66.4	32.8
Pulmonary TB	9.5	33.2
Cardiac diseases	2.9	2.9
Malignant neoplasm	2.2	9.6
Gastrointestinal diseases	2.2	0.5
Accident/self-harm	2.2	0.7
Diabetes mellitus	1.5	1.0
Respiratory ailments	1.5	4.9
Liver diseases	1.5	1.0
Other diseases	8.0	6.2
Unknown	2.2	7.4
Total	100	100

CSMF: cause specific mortality fractions; PCVA: physician-certified verbal autopsy.
Concordance correlation coefficient: 0.67 (95% CI 0.38–0.97).

Table 4. Agreement between 'most probable' cause of death assigned by InterVA-4 and single underlying cause of death assigned by physician-certified verbal autopsy and mortality medical data system for 137 deceased XTEND participants

	Physician-certified verbal autopsy				
InterVA-4		TB	HIV	Other	Total
	TB	10	32	6	48
	HIV	1	38	10	49
	Other	2	21	17	40
	Total	13	91	33	137

Cohen's kappa: 0.20; 95% CI 0.10–0.30.

surveillance system showed that PCVA assigned 23% to PTB and InterVA-3 assigned 36% deaths to PTB (K=0.5, 95% CI 0.4–0.6).[23] When comparing cause specific mortality fractions assigned by PCVA and InterVA, InterVA assigned more TB than PCVA. This is largely because ICD-10 coding rules require that assignment of a single cause of death in individuals with immediate cause of death of TB and underlying cause of death of HIV be classified as an HIV/AIDS-related death.[9] This resulted in 57 (81%) of immediate TB deaths assigned at individual level being classified as HIV/AIDS-related deaths after processing by the MMDS software. A recent study done in Asia and Africa comparing VA cause of death as assigned by PCVA and InterVA-4 also reported a CCC of 0.83 (95% CI 0.75–0.91) between the methods which was higher than the 0.67 found in our study.[25]

PCVA assigned more immediate PTB cause of death in our study compared to health and demographic surveillance system studies, most likely because our study included people with symptoms suggestive of TB who were identified by clinic staff as needing TB investigation. It is also possible that, because the physicians who interpreted the VAs knew that all study participants were being investigated for TB, this could have biased them to choose TB as a cause of death.

A major strength of our study is that our study population was a large systematic sample of adults being investigated for TB in a real-world setting. Our results can be generalised to adults being investigated for TB in similar settings and also to people with TB symptoms severe enough to need investigation. We also managed to perform the majority of VA interviews within one year of death which made it easier for respondents to recall exact events leading to a participant's death.

A study limitation is that we could not conduct a VA for everyone who died, and could thus have missed other causes of death which has implications on the profile of causes reported in this population. A higher proportion of decedents who had VA done had started TB treatment compared to those who died but did not have a VA done. Those who were on TB treatment would have been easier to contact because they were already in care, therefore overestimating TB as a cause of death in the study.

Our findings show that when interpreting VA data using either PCVA or InterVA-4 for adults being investigated for TB, TB is a leading cause of death. These results also suggest that the current TB diagnostic pathway is inadequate as people with TB disease may still be missed or commenced on treatment too late. The fact that HIV was identified as the second most common cause of death points to the importance of integrated TB and HIV care and linkage into care for both diseases. The health service through implementation science research needs to find ways to facilitate access to TB and HIV care for persons who need to navigate both services. We recommend that adults being investigated for TB need to be aware of their HIV status, as data from XTEND also showed that people were more likely to die if they were HIV-positive and not on ART or if their HIV status was unknown.[8] Intensified TB screening also needs to be improved as the sensitivity of the current screening tool is suboptimal and a diagnostic test for TB with high sensitivity and specificity that could be used in primary health care settings is a priority. We also recommend that current CCVA methods should be improved to include EPTB. Research has shown that 88% of HIV-positive individuals with autopsy evidence of TB have disseminated disease[20]; if VA methods do not classify EPTB as TB, a large number of TB deaths will be missed.

Authors' contribution: The study was designed by ADG, KM, GJC, SC, KK and VC. NM, KM, SC, VC, ADG and ASK were responsible for data collection. NM and ASK were responsible for the analysis. NM drafted the first draft and all other authors provided guidance on revision of the manuscript. All authors read and approved the final manuscript. NM is the guarantor of the paper.

Acknowledgements: We thank all the participants who consented to taking part in the study. We appreciate the commitment of the study team in interviewing next of kin of deceased participants, Drs Evan Shoul and Sarah Stacey for assigning the cause of death from the verbal autopsies, and Sizzy Ngobeni for training the fieldworkers who conducted the verbal autopsy interviews.

Funding: This work was supported by Bill & Melinda Gates Foundation [Grant Number: OPP1034523] for funding the study.

Competing interests: None declared.

Ethical approval: The study was approved by the ethics committees of the University of Witwatersrand and the London School of Hygiene & Tropical Medicine.

References

1 Statistics South Africa. Mortality and causes of death in South Africa 2013: Findings from death notification. Pretoria: Statistics South Africa; 2014. http://beta2.statssa.gov.za/publications/P03093/P03093201 3.pdf [accessed 2 April 2015].

2 WHO. Global Tuberculosis Report 2014. Geneva: World Health Organization; 2014. http://apps.who.int/iris/bitstream/10665/137094/1/9789241564809_eng.pdf [accessed 2 April 2015].

3 Shisana O, Rehle T, Simbayi LC et al. South African National HIV Prevalence, Incidence and Behaviour Survey, 2012. Cape Town: HSRC Press; 2014.

4 Burton JL, Underwood J. Clinical, educational and epidemiological value of autopsy. Lancet 2007;369:1471–80.

5 WHO. Verbal autopsy standards: ascertaining and attributing causes of death. The 2014 WHO verbal autopsy instrument. Geneva: World Health Organization; 2014. http://www.who.int/healthinfo/statistics/verbalautopsystandards/en/ [accessed 10 August 2014].

6 Leitao J, Desai N, Aleksandrowicz L et al. Comparison of physician-certified verbal autopsy with computer-coded verbal autopsy for cause of death assignment in hospitalized patients in low- and middle-income countries: systematic review. BMC Med 2014;12:22.

7 Fottrell E, Byass P. Verbal autopsy: methods in transition. Epidemiol Rev 2010;32:38–55.

8 Churchyard G, Stevens W, Mametja LD et al. Xpert MTB/RIF versus sputum microscopy as the initial diagnostic test for tuberculosis: a cluster-randomized trial embedded in South Africa roll-out of Xpert MTB/RIF. Lancet Glob Health 2015;3:e450–7.

9 WHO. International Statistical Classification of Diseases and Related Health Problems [ICD-10]. 10th Revision. Geneva: World Health Organization; 2015. http://apps.who.int/classifications/icd10/browse/2015/en/ [accessed 26 July 2016].

10 CDC/National Center for Health Statistics, National Vital Statistics System. Mortality Medical Data System. Atlanta: Centers for Disease Control and Prevention; 2012. http://www.cdc.gov/nchs/nvss/mmds.htm [accessed 20 July 2016].

11 Byass P, Huong DL, Minh HV. A probabilistic approach to interpreting verbal autopsies: methodology and preliminary validation in Vietnam. Scand J Public Health 2003;31(Suppl 62):32–7.

12 Byass P, Fottrell E, Huong DL et al. Refining a probabilistic model for interpreting verbal autopsy data. Scand Public Health 2006;34:26–31.

13 Fantahun M, Fottrell E, Berhane Y et al. Assessing a new approach to verbal autopsy interpretation in a rural Ethiopian community: the InterVA model. Bull World Health Organ 2006;84:204–10.

14 Byass P, Calvert C, Miiro-Nakiyingi J et al. InterVA-4 as a public health tool for measuring HIV/AIDS mortality: a validation study from five African countries. Glob Health Action 2013;6:22448.

15 Viera AJ, Garrett JM. Understanding interobserver agreement: The Kappa statistic. Fam Med 2005;37:360–3.

16 Lin L I-Kuei. A concordance correlation coefficient to evaluate reproducibility. Biometrics 1989;45:255–68.

17 South Africa. National Department of Health. National Tuberculosis Management Guidelines 2014. Pretoria: Department of Health 2014. http://sahivsoc.org/Files/NTCP_Adult_TB%20Guidelines%2027.5.2014.pdf [accessed 21 January 2016].

18 Wong EB, Omar T, Setlhako GJ et al. Causes of death on antiretroviral therapy: a post-mortem study from South Africa. PLoS One 2012;7:e47542.

19 Bates M, Mudenda V, Shibemba A et al. Burden of tuberculosis at post mortem in patients at a tertiary referral centre in sub-Saharan Africa: a prospective descriptive autopsy study. Lancet Infect Dis 2015;15:544–51.

20 Gupta RK, Lucas SB, Fielding KL, Lawn SD. Prevalence of tuberculosis in post-mortem studies of HIV-infected adults and children in resource-limited settings: a systematic review and meta-analysis. AIDS 2015;29:doi:10.1097/QAD.0000000000000802.

21 MacPherson P, Moshabela M, Martinson N, Pronyk P. Mortality and loss to follow-up among HAART initiators in rural South Africa. Trans R Soc Trop Med Hyg 2009;103:588–93.

22 Oti OS, Kyobutungi C. Verbal autopsy interpretation: a comparative analysis of the InterVA model versus physician review in determining causes of death in the Nairobi DSS. Popul Health Metr 2010;8:21.

23 Tadesse S , Tadesse T. Evaluating the performance of interpreting Verbal Autopsy 3.2 model for establishing pulmonary tuberculosis as a cause of death in Ethiopia: a population-based cross-sectional study. BMC Public Health 2012;12:1039.

24 Byass P, Kahn K, Fottrell E et al. Moving from data on deaths to public health policy in Agincourt, South Africa: approaches to analyzing and understanding verbal autopsy findings. PLoS Med 2010;8:e10003251–8.

25 Byass P, Herbst K, Fottrell E et al. Comparing verbal autopsy cause of death findings as determined by physician coding and probabilistic modelling: a public health analysis of 54 000 deaths in Africa and Asia. J Glob Health 2015;5:010402.

PAPER II

BMJ Open

Linkage to care among adults being investigated for tuberculosis in South Africa: pilot study of a case manager intervention

Noriah Maraba,[1,2] Violet Chihota,[1,2,3] Kerrigan McCarthy,[2,4] Gavin J Churchyard,[1,2,5,6] Alison D Grant[2,7,8]

To cite: Maraba N, Chihota V, McCarthy K, *et al*. Linkage to care among adults being investigated for tuberculosis in South Africa: pilot study of a case manager intervention. *BMJ Open* 2018;**8**:e021111. doi:10.1136/bmjopen-2017-021111

► Prepublication history for this paper is available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2017-021111).

Received 12 December 2017
Revised 26 March 2018
Accepted 26 April 2018

For numbered affiliations see end of article.

Correspondence to
Noriah Maraba;
nmaraba@auruminstitute.org

ABSTRACT

Objectives We piloted an intervention to determine if support from a case manager would assist adults being investigated for tuberculosis (TB) to link into TB and HIV care.

Design Pilot interventional cohort study.

Participants and setting Patients identified by primary healthcare clinic staff in South Africa as needing TB investigations were enrolled.

Intervention Participants were supported for 3 months by case managers who facilitated the care pathway by promoting HIV testing, getting laboratory results, calling patients to return for results and facilitating treatment initiation.

Outcomes measured Linkage to TB care was defined as starting TB treatment within 28 days in those with a positive test result; linkage to HIV care, for HIV-positive people, was defined as having blood taken for CD4 count and, for those eligible, starting antiretroviral therapy within 3 months. Intervention implementation was measured by number of attempts to contact participants.

Results Among 562 participants (307 (54.6%) female, median age: 36 years (IQR 29–44)), most 477 (84.8%) had previously tested for HIV; of these, 328/475 (69.1%) self-reported being HIV-positive. Overall, 189/562 (33.6%) participants needed linkage to care (132 HIV care linkage only; 35 TB treatment linkage only; 22 both). Of 555 attempts to contact these 189 participants, 407 were to facilitate HIV care linkage, 78 for TB treatment linkage and 70 for both. At the end of 3-month follow-up, 40 participants had not linked to care (29 of the 132 (22.0%) participants needing linkage to HIV care only, 4 of the 35 (11.4%) needing to start on TB treatment only and 7 of the 22 (31.8%) needing both).

Conclusion Many people testing for TB need linkage to care. Despite case manager support, non-linkage into HIV care remained higher than desirable, suggesting a need to modify this intervention before implementation. Innovative strategies to enable linkage to care are needed.

Strengths and limitations of this study

- ► The study had a representative sample of adults being investigated for TB from five clinics in two provinces with diverse living conditions and representative of urban as well as periurban setting.
- ► The intervention was well implemented with 555 contact attempts made to participants needing linkage to care.
- ► The lack of a 'standard of care' comparison group meant we could not formally determine if the strategy made a difference or not.

BACKGROUND

People being investigated for tuberculosis (TB) are not linking into TB and HIV care. Studies done in South Africa have shown that 11%–25% people with positive sputum results have 'pre-treatment loss to follow-up', defined as not starting on TB treatment either at all, or within a month of sputum submission.[1–3] More recently the XTEND (Xpert for TB-Evaluating a New Diagnostic) trial, a pragmatic cluster-randomised controlled trial comparing smear microscopy versus Xpert MTB/RIF (a rapid and more sensitive assay) among adults being investigated for TB showed pretreatment loss to follow-up of 17%, not reduced by use of Xpert MTB/RIF.[4] Mortality at 3 and 6 months of sending sputum for microbiological investigation was 3.2% and 5.0%, respectively.[4 5] South Africa's guidelines recommend that all patients with a positive diagnosis for TB as well as those being investigated for TB be tested for HIV.[6] The XTEND trial also showed that not being on ART and not knowing one's HIV status were associated with an increased risk of death,[4] suggesting that for persons being investigated for TB and not already on antiretroviral treatment (ART), linkage to HIV care is a priority.

Linking people with a positive HIV test result into HIV care has traditionally involved multiple steps, including undertaking a CD4 count to determine eligibility for ART initiation, with losses at each step.[7] Furthermore,

TB and HIV care are not fully integrated, making it difficult for patients needing treatment for TB and HIV to access care for both conditions. In an attempt to improve linkage into HIV care among HIV-positive patients, strategies such as case management or health system navigation, using strengths-based case management, where patients identify their strengths and use them to improve their circumstances, have been evaluated.[8–10] One such study, a randomised control trial in the USA among recently diagnosed HIV-positive people supported by a case manager, showed that 78% in the intervention arm linked into care successfully compared with the 60% in the control arm.[8] Task-shifting of duties such as TB counselling, HIV counselling and testing and ART adherence counselling to lay counsellors has been used as a strategy to relieve short-staffed and overwhelmed healthcare workers in primary healthcare clinics (PHCs).[11] In this study, we pilot tested an intervention using lay counsellors to provide support to adults being investigated for TB by following up with patients to ensure that they returned to clinic (1) to receive their TB and HIV-related test results; (2) to do follow-up tests and (3) to start appropriate treatment. This was intended to overcome obstacles such as nurses not having enough time to follow-up patients and the difficulties of making contact with patients. The study objectives were to determine feasibility of implementing the intervention (determined by number of interactions made) and acceptability of the intervention (determined by a qualitative study, reported separately) and to estimate linkage to TB and HIV care.

METHODS

Study design

An interventional cohort study was designed to pilot-test case manager support at PHCs for adults being investigated for TB to link them into HIV care and initiate TB treatment where these were clinically indicated. The study was conducted from September 2014 to April 2015 in six PHCs in Mpumalanga and Gauteng provinces, South Africa, which had previously participated in the XTEND trial and were selected on the basis of their high proportions of pretreatment loss to follow-up during that trial. At the time of implementing the case manager study, South Africa's criteria for ART initiation were a CD4 count of ≤350 cells/mm^3 or active TB at any CD4 count. Guidelines also suggested that following a TB diagnosis, ART should be initiated in HIV-positive persons within 2 weeks after TB treatment initiation.

Description of case manager intervention

Case managers were lay counsellors, trained by investigators on basic TB and HIV education and national ART and TB management guidelines at the time. One case manager was placed at each of the six clinics. The roles of the case managers were: (1) to follow-up on sputum test results from the laboratory; (2) to call all patients to return to the clinic for their results; (3) to facilitate TB treatment start in patients with a positive sputum test result; (4) to encourage those with unknown HIV status or negative HIV test results older than 3 months at enrolment to test for HIV; and (5) for those who tested HIV-positive or knew themselves to be HIV-positive but did not know their CD4 count at enrolment, to facilitate CD4 count testing, follow-up on CD4 results from laboratory and to facilitate ART initiation if eligible. A study algorithm, based on the national TB management and ART guidelines, was developed to assist the study staff in guiding patients through the health system in seeking appropriate care (figure 1). Case managers attempted to contact participants at least once a week and continued with contact attempts until linkage to care was complete, or the end of study follow-up, 3 months after enrolment. Lists for weekly follow-ups of enrolled participants that needed linkage to care were maintained through the automated release of weekly follow-up case report forms by a smart phone application that was used to collect study data. Contact attempts were made to inform participants of the availability of their results as soon as they were received at the clinics, to remind participants of clinic appointments and to check if patients had returned to clinic for appropriate care. These attempts included inperson meetings at the clinic or telephonic calls. Contacts were categorised as successful if the case manager was able to meet with the participant or speak to the participant telephonically. All decisions about clinical management of participants were made by PHC staff according to their routine practice. Case managers were not actively involved in arranging any additional investigations for TB after enrolment.

Study population and data collection

Participants were eligible for inclusion in the study, based on the criteria previously used in the XTEND trial: if they were aged ≥18 years, identified by PHC staff as needing investigation for TB through TB symptom screen as having any of the four TB symptoms, provided a sputum specimen for TB investigation, able to give informed consent, likely to remain in the study catchment area for 8 months and able to provide adequate locator information, including an alternative contact number for either a friend of family member. Case managers recruited participants who met the inclusion criteria. Data on demographics, current TB symptoms, TB and HIV history and healthcare-seeking behaviour was collected at enrolment. Contact attempts and participants' progress in linkage into appropriate care was recorded on log forms.

At the end of the follow-up period, the case managers conducted a telephonic or clinic interview with the participant to ascertain if linkage into appropriate care had taken place by collecting self-reported data on HIV testing, TB and ART treatment start dates, health-seeking behaviour and current TB symptoms. Additional data were collected by professional nurses abstracting from clinic records HIV data (such as HIV testing, CD4 count testing and ART start dates) and TB data (TB testing and treatment start dates). Case report forms were completed

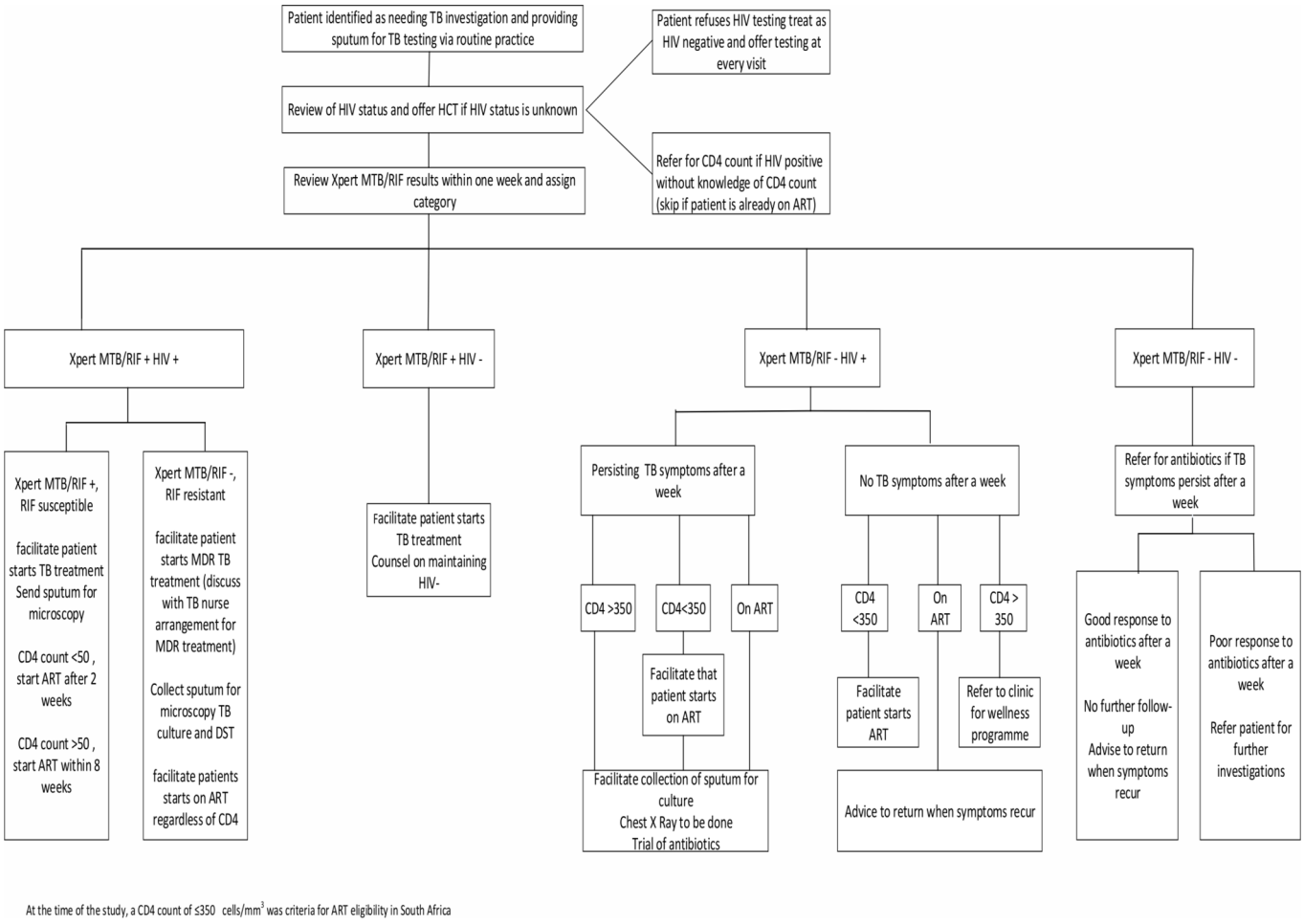


Figure 1 TB and HIV algorithm used to guide case managers. ART, antiretroviral treatment; DST, Drug-susceptibility testing; HCT, HIV Counselling and Testing; MDR, Multi-Drug-resistant; TB, tuberculosis.

on a study-specific smartphone application and data submitted in an encrypted format to a central database.[4]

Description of outcomes and analysis

Linkage into HIV care was defined as at 3 months after enrolment: (1) if HIV status unknown at enrolment: testing HIV-positive, having done a CD4 count and being started on ART if eligible (CD4 count ≤350 cells/mm^3 or testing Xpert MTB/RIF positive); (2) if HIV-positive with an unknown CD4 count and not on ART at enrolment: having done a CD4 count test and being started on ART if eligible; (3) if last CD4 count done more than 6 months previously and not on ART at enrolment: having a CD4 count done and being started on ART if eligible. Failure to initiate ART after 3 months when ART eligible at initial assessment was defined as non-linkage to HIV care.

Linkage into TB care (TB treatment initiation) was defined as TB treatment start within 28 days of sputum submission among patients with a positive sputum test result. Non-linkage to TB treatment (pretreatment loss to follow-up) was defined as not starting TB treatment within 28 days of sputum collection among people with a positive TB test result, consistent with definitions in previous studies.[2 4]

Linkage to HIV care or TB treatment initiation was confirmed by record of ART or TB treatment start date as reported by the participant and documented in study documents or from patient clinic files. Mortality was ascertained by reports by close relatives or friends indicating the death of a participant. Participants were defined as lost to follow-up if at 3 months linkage status was unknown and the participant could not be contacted by case managers.

Contacts attempts were defined as any effort (successful or unsuccessful), done either telephonically or inperson meeting, made by case managers to interact with a patient. The total number of contact attempts per patients was counted, and median attempts needed for linkage into TB and HIV care or both were calculated.

Sample size calculation

This was a pilot study aiming to determine feasibility of implementing the intervention and to estimate linkage to TB and HIV care. The sample size calculation was based on two binary outcomes: (1) uptake of ART among those who were HIV positive and ART eligible; (2) pretreatment loss to follow-up among those who tested TB positive. We had planned to enrol 1200 participants (200 per clinic as

in XTEND) with the assumption that 96 (8%) of those tested for TB would test TB positive and need to initiate TB treatment.[4] We also assumed that 20 (21%) of people with a sputum testing positive for TB would experience pretreatment loss to follow-up.[4] For patients needing linkage to HIV care, the assumption was that 240 (20%) of patients enrolled would not know their HIV status. It was also assumed that 576 (60%) of patients who knew their HIV status would self-report being HIV positive.[4] Two hundred and eighty-eight (50%) of those who were HIV positive would not know their CD4 count and would be ART eligible once a CD4 count test was done.[4]

Risk factor analysis for mortality

Univariable logistic regression analysis was used to assess risk factors for mortality. Due to the small proportion of participants who died by end of 3-month follow-up, categories per predictor variable in the univariable model were restricted to three and a multivariable logistic regression model was not built as a minimum of 10 events per predictor variable is required.[12] All statistical analyses were done using Stata V.14.

Patient and public involvement

Patients or public were not involved in the development of research question, outcome measures, study design, recruitment to and conduct of the study. Copies of the study report will be sent to participants who contact the investigators about an interest to receive the study results.

RESULTS

Baseline characteristics

From September to December 2014, 800 adults having a sputum taken for TB investigations in six PHCs were screened and 585 were enrolled. Of these 585, 23 from one site were excluded from analysis because ill health prevented the case manager from undertaking study procedures correctly, leaving 562 from five clinics for analysis. Of the 562 participants, 307 (54.6%) were female, and the median age was 36 years (IQR 29–44) (table 1). The majority of participants (477, 84.8%) self-reported having had an HIV test in the past and of these 328/475 (69.1%) reported being HIV-positive. Of the 328 HIV-positive participants, 156/327 (47.7%) reported having a CD4 count done within the previous 6 months and self-reported median CD4 count was 315 cells/mm^3 (IQR 164–471). Over half of the HIV-positive participants with a known CD4 count (209/327 (63.9%)) had never received ART. Ninety-six of 562 (17.1%) of the enrolled participants were previously treated for TB. Five hundred and fourteen of 543 (94.7%) participants reported having at least one TB symptom to the study team, and the majority 452/514 (87.9%) reported having cough (table 1).

Implementation of the intervention

Overall, 189/562 (33.6%) participants required linkage into HIV care or TB treatment initiation or both. Of the

Table 1 Baseline characteristics of the study population

Variable	n (%) n=562
Gender	
Female	307 (54.6)
Age (median, IQR)	36 (29–44)
Country of birth	
South Africa	447 (79.5)
Ethnic group	
Black	556 (98.9)
Highest education completed	
No schooling	23 (4.0)
Preschool–Grade 7	124 (22.0)
Grades 8–12	377 (67.1)
University/technical qualification	38 (6.8)
Marital status	
Single never married	250 (44.5)
Married	108 (19.2)
Cohabitating	159 (28.3)
Divorced/widowed/separated	45 (8.0)
Main income source	
Formal employment	250 (44.5)
Self-employment/odd jobs	134 (23.8)
No income	88 (15.7)
Grant/dependence	90 (16.0)
Average monthly income	
<ZAR 600	34 (6.0)
ZAR 601–1000	73 (13.0)
ZAR 1001–2000	120 (21.4)
ZAR 2001–4000	167 (29.7)
Greater than ZAR 4000	58 (10.3)
Don't know	110 (19.6)
Ever had HIV test	
Yes	477 (84.9)
Self-reported HIV status (n=475)*	
Negative	143 (30.1)
Positive	328 (69.1)
Unknown	4 (0.8)
CD4 count known (n=327)†	
Yes	156 (47.7)
Self-reported CD4 count, median (IQR)	315 (164–471)
Ever been on ART (n=327)	
Never	209 (63.9)
Currently	116 (35.5)
Previously	2 (0.6)
Time on ART in years, median (IQR) n=118	2 (0–4)
Ever treated for TB	

Continued

Table 1 Continued

Variable	n (%) n=562
Yes	96 (17.1)
TB symptoms reported (n=543)‡	
Yes	514 (94.7)
Symptoms reported (n=514)	
Cough	452 (87.9)
Unintentional weight loss	311 (60.5)
Night sweats	218 (42.4)
Fever	186 (36.2)

*Two participants refused to disclose their HIV status.
†Data missing for one participant.
‡Data missing for 19 participants.
ART, antiretroviral treatment; TB, tuberculosis.

189, 132/189 (69.8%) participants required linkage into HIV care only, 35/189 (18.5%) required TB treatment initiation only and 22/189 (11.6%) required both TB treatment initiation and linkage to HIV care. A total of 555 contact attempts were made by the case managers to these participants: 310/555 (55.9%) were telephonic, 243/555 (43.8%) were contacts at clinic and 2/555 (0.4%) were home visits. Of the 310 telephonic contacts, 211/310 (68.1%) were successful. Of the 99 unsuccessful telephone contact attempts, 98 were due to numbers ringing without an answer and in one the call went to voicemail.

Contact attempts for linkage to HIV care only

Of the 132 people needing linkage to HIV care only, 407 contact attempts in total were made to these individuals with a median of 3 (IQR 2–4) attempts per individual. At the end of the follow-up, 29/132 (22.0%) people had still not linked into HIV care, and a total of 111 contact attempts, with a median of four attempts (IQR 2–4) per individual, had been made to these individuals.

Contact attempts for linkage to TB care only

For people needing to initiate TB treatment only (35), 78 contact attempts with a median of 2 (IQR 1–3) attempts were made. Four (11.4%) of the 35 participants did not initiate TB treatment by end of follow-up period. Ten contact attempts with median of 1 (IQR 1–4) were made to these individuals.

Contact attempts for linkage to TB and HIV care

Seventy contact attempts with median of 3 (IQR 2–4) attempts were made to the 22 participants that needed both to initiate TB treatment and link into HIV care. At end of follow-up, seven (31.8%) of the 22 participants had not completely linked into care as they had started on TB treatment but had not initiated ART. Twenty-seven contact attempts with a median of 2 (IQR 4–5) attempts per individual were made to these seven individuals.

Linkage into HIV care

Participant flow through the steps of linkage to HIV care is shown in figure 2. At enrolment, 94 participants had unknown HIV status or a negative HIV test results older than 3 months and were offered an HIV test. Among the 94, 26 (27.7%) declined to test. Of those who tested, 26/68 (38.2%) were HIV positive. A total of 132 (26 newly tested HIV positive and 106 not on ART with unknown CD4 count) needed a CD4 count, of whom 119/132 (90.2%) had blood taken for a CD4 count by the end of the study. Of the 135 with a CD4 count result (119 who had a new CD4 count and 16 who already knew their CD4 count), 91/135 (67.4%) were ART eligible and 67/91 (73.6%) of those initiated for ART. Of those needing a CD4 count, 13/132 (9.8%) did not have a CD4 count done and 24/91 (26.4%) ART eligible did not initiate ART. The highest proportion of HIV-positive patients were lost at the ART initiation stage (figure 2).

TB treatment initiation

A total of 57/562 (10.1%) participants had a positive index Xpert MTB/RIF result. Of the 57, 53 (93.0%) started TB treatment within 28 days of testing positive for TB with median time to TB treatment initiation of 5 days (IQR 2–7). Of the four that were not initiated on TB treatment, two died before starting TB treatment and two started TB treatment more than 28 days after sputum was taken. An additional of 22 participants were started on TB treatment after being diagnosed by follow-up tests.

We could not do a risk factor analysis for non-linkage into care because of the complexity of differing denominators at different stages of HIV linkage into care and the low numbers for those who did not initiate TB treatment.

Mortality and loss to follow-up

At the end of the 3-month follow-up, 27/562 (4.8%) participants had died and loss to follow-up was 49/535 (9.2%). Of the 27 participants who died, 18 had self-reported being HIV positive, and 14/18 (77.8%) of them were on ART. Only four of the deceased participants had a TB positive index Xpert MTB/RIF result.

Risk factors of mortality at 3 months after enrolment

Univariable analysis for mortality (table 2) showed weak evidence for an association between having more than one TB symptom (OR 2.4, 95% CI 0.89 to 6.45) and increased risk of death, but a chance finding cannot be excluded.

DISCUSSION

In our study, 33.6% of people being investigated for TB at PHCs in South Africa required linkage into HIV care or TB treatment initiation. A high proportion of people with positive TB test results started TB treatment with 78 contact attempts made to them. However, despite support with 477 contact attempts from a case manager, a total of 21.9% of those needing HIV care only and 31.8%

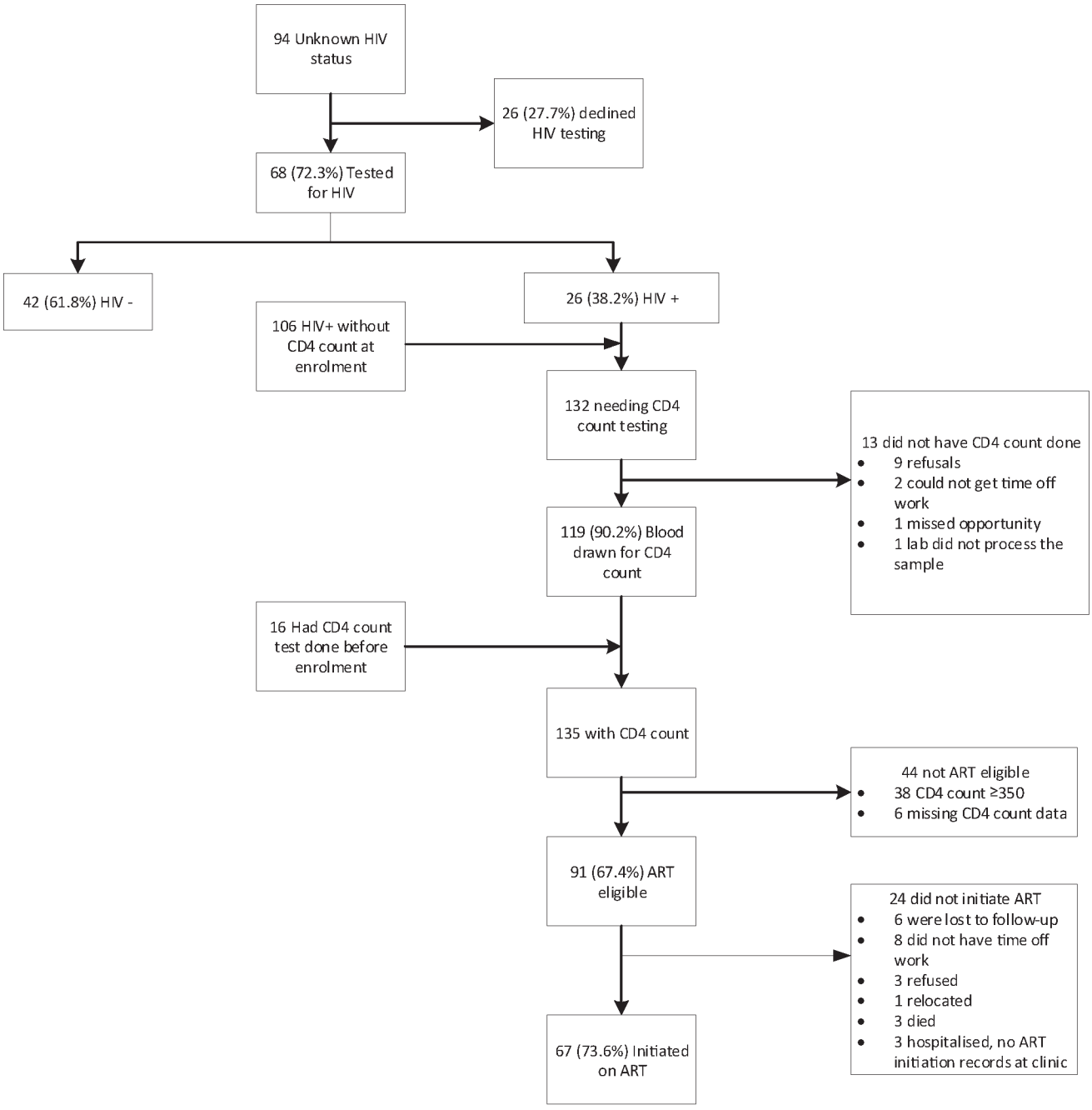


Figure 2 Flow diagram of linkage into HIV care after 3-month follow-up. ART, antiretroviral treatment.

needing TB and HIV care did not link into HIV care at the end of the 3-month follow-up period with the highest proportion lost at the ART initiation step. By piloting this intervention, we had hoped to overcome obstacles such as nurses not having enough time to follow-up patients and difficulties of making contact with the patients such as clinic phones not working or people having not given their contact numbers. The processes of the intervention largely worked as intended, with multiple contacts to people needing linkage into care. However, HIV linkage care was still suboptimal, suggesting that this intervention as implemented for HIV was insufficient. It also suggests that linkage to HIV care compared with initiation of TB treatment is harder to achieve. This is probably due to the larger number of steps that were necessary for a person to start ART at the time of the study, which included CD4 count testing for ART eligibility assessments, attendance at ART adherence classes and baseline blood tests for assessment of contraindications to specific antiretroviral drugs. This resulted in patients needing to visit the clinic multiple times. South African guidelines now recommend ART for all HIV-positive people regardless of CD4 count. This may reduce losses along the linkage pathway by reducing the number of visits needed.

Some of our study participants refused HIV testing, but the proportions (27.7%) in our study were lower than that found in a South African study done in 2007 comparing uptake of HIV test between provider-initiated

Table 2 Univariate analysis for risk factors for mortality

Variable	Proportion died (%)	OR (95% CI)	P values
Gender			
Male	10/255 (3.9)	1	
Female	17/307 (5.5)	1.43 (0.65 to 3.19)	0.37
Age group			
>30	5/144 (3.5)	1	
30–39.9	14/210 (6.7)	1.99 (0.69 to 5.64)	
≤40	8/208 (3.8)	1.11 (0.36 to 3.47)	0.29
Self-reported HIV status			
Negative	5/130 (3.8)	1	
HIV-positive on ART	4/120 (3.3)	0.86 (0.23 to 3.28)	
HIV-positive not on ART	14/205 (6.8)	1.83 (0.64 to 5.21)	0.29
Number of TB symptoms			
≤1	5/194 (2.6)	1	
2 and more	22/368 (6.0)	2.4 (0.89 to 6.45)	0.05
BMI			
<18.5	4/78 (5.1)	0.88 (0.29 to 2.68)	
18.5–24.9	18/311 (5.8)	1	
25+	5/173 (2.9)	0.48 (0.18 to 1.32)	0.33

ART, antiretroviral treatment; BMI, body mass index; TB, tuberculosis.

testing and counselling and provider referral to voluntary HIV testing among patients attending community health centres.[13] The study reported that 45% of patients in the provider-initiated testing group, versus 69% of patients in voluntary HIV testing group, refused HIV testing.[13] In a 2012 study, among HIV non-testers from South Africa, barriers to testing included fear of knowing one's HIV status and fear of what people may say.[14] Linkage to care (HIV and TB) in our study was higher compared with Sizanani, a randomised control trial in South Africa done between 2010 and 2013 using health navigators sending short messaging service reminders to newly diagnosed HIV-positive people to link into TB and HIV care.[10] This difference is probably because linkage to care was defined differently in Sizanani compared with our study. Standardised definitions of linkage to care would facilitate making comparisons and setting standards.[10]

A number of participants in our study declined to start on ART because they could not get time off work. This could be because the health system is too difficult or time-consuming for working people to navigate; it could also be that participants not wanting to start ART for other reasons gave this as an excuse for not returning to the clinic. A study determining rates and predictors of declining to start ART in treatment-eligible HIV-positive individuals in South Africa in 2009 showed that 20% refused to start ART and 37% of those reported feeling healthy as a reason for non-initiation.[15] Another study, from South Africa in 2010, showed that stigma was the main barrier to initiating ART.[16] The limited information available around the reasons for non-linkage to HIV care suggest that the problem is not simply a failure of clinic staff to communicate results but rather a multifactorial challenge with health system, individual and structural components.[10]

Some interventions have had successes in improving linkage to care. A study in Uganda focusing on improving processes within clinics showed an improvement in ART initiation among HIV-positive patients.[17] Another study done in Zambia and Tanzania that combined clinic-based care plus community support showed a reduction in mortality in HIV-positive patients compared with standard of care.[18] It is hard to know what exactly made these interventions work, but the Ugandan study differed from our study in that it targeted multiple number of components within the clinic such as staff training, coaching and facility feedback. However, the Zambian and Tanzanian study differed in that community support was provided by a lay worker with a higher qualification than a lay counsellor and trained on monitoring of patients for disease progression as well as drug toxicity. Our intervention tried to address challenges of communication between clinic and patients as well as provide support and encouragement to patients.

Our data showed that among adults with a positive Xpert MTB/RIF sputum result, 93.0% were started on TB treatment with 148 contact attempts made to them. The median time to TB treatment start in our study was 5 days, which is within the recommended national department of health target of 2–5 days.[6] We could not quantify the total number of participants who were diagnosed with TB using follow-up tests in our study, as some may have started TB treatment after our follow-up ended. Pretreatment loss to follow-up was lower than the 11%–25% found in previous studies in South Africa, although comparisons are limited by the relatively small numbers in our study.[1–4]

Mortality was high in our study at 4.8% by 3 months suggesting that people are presenting with advanced disease or when already severely ill. This underscores the importance of early diagnosis and linkage to care.

Strengths of our study include prospectively enrolling a representative sample of adults being investigated for TB from five clinics in two provinces of the country that are diverse in living conditions and population and likely to be representative of urban and periurban practice in South Africa. A limitation of our study is that this was a pilot study and as such had no 'standard of care' comparison group; therefore, we cannot formally determine if the strategy made a difference or not. Another limitation is that we did not keep record of TB treatment started after the follow-up period.

CONCLUSION

In our pilot study assessing the potential effect of a case manager to support linkage into HIV care and TB

treatment initiation among adults being investigated for TB, we report a higher than desirable rate of non-linkage into HIV care. This is an indication that the piloted strategy lacks components that are crucial to the successful engagement of patients into HIV care. A qualitative evaluation of the intervention (in progress) may give insights into how this intervention could be improved. This pilot study was planned with the intention to conduct a larger trial afterwards, but our findings suggest that further work be done before the intervention is further evaluated. We recommend that more innovative approaches be explored to find strategies that will improve linkage to HIV care and TB treatment initiation in this population to reduce mortality.

Author affiliations
[1]The Aurum Institute, Johannesburg, Gauteng, South Africa
[2]School of Public Health, Faculty of Health Science, University of Witwatersrand, Johannesburg, Gauteng, South Africa
[3]Foundation for Innovative New Diagnostics, Geneva, Switzerland
[4]National Institute for Communicable Diseases, Sandringham, South Africa
[5]Advancing Treatment and Care for TB and HIV, South African Medical Research Council Collaborating Centre for HIV/TB, Cape Town, South Africa
[6]London School of Hygiene and Tropical Medicine, London, UK
[7]TB Centre, London School of Hygiene & Tropical Medicine, London, UK
[8]School of Nursing and Public Health, Africa Health Research Institute, University of Kwazulu-Natal, Durban, South Africa

Acknowledgements We would like to acknowledge all the participants enrolled in the study, the study team who assisted with data collection and clinic staff were data collection occured.

Contributors All authors contributed in the design of the study. NM, ADG, VC and KM supervised data collection. NM analysed the data and wrote the first draft of the manuscript. AG, VC, KM and GC provided comments for the revision of the manuscript.

Funding The study was funded by the Bill & Melinda Gates Foundation grant number OPP1034523.

Disclaimer The funder did not play a part in the design, collection, analysis or interpretation and the writing of the manuscript.

Competing interests None declared.

Patient consent Not required.

Ethics approval Ethical clearance was obtained from the Human Research Ethics Committee of the University of the Witwatersrand reference number M131143 and the London School of Hygiene & Tropical Medicine, UK reference number 7124. Participants in the study gave written consent, or witnessed oral consent for participants who could not read or write.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement Data used for this study can be accessed from the London School of Hygiene & Tropical Medicine repository.

REFERENCES

1. Botha E, den Boon S, Lawrence KA, *et al*. From suspect to patient: tuberculosis diagnosis and treatment initiation in health facilities in South Africa. *Int J Tuberc Lung Dis* 2008;12:936–41.
2. Claassens MM, du Toit E, Dunbar R, *et al*. Tuberculosis patients in primary care do not start treatment. What role do health system delays play? *Int J Tuberc Lung Dis* 2013;17:603–7.
3. Bristow CC, Dilraj A, Margot B, *et al*. Lack of patient registration in the electronic TB register for sputum smear-positive patients in KwaZulu-Natal, South Africa. *Tuberculosis* 2013;93:567–8.
4. Churchyard GJ, Stevens WS, Mametja LD, *et al*. Xpert MTB/RIF versus sputum microscopy as the initial diagnostic test for tuberculosis: a cluster-randomised trial embedded in South African roll-out of Xpert MTB/RIF. *Lancet Glob Health* 2015;3:e450–57.
5. McCarthy K, Fielding K, Grant A, *et al*. High risk of early mortality among persons suspected of TB in South Africa. *Poster 834 session 145 Conference on retroviruses and opportunistic infections*; March, 2013.
6. *National tuberculosis management guidelines*. South Africa: National Department of Health, 2014. http://sahivsoc.org/Files/NTCP_Adult_TB%20Guidelines%2027.5.2014.pdf. (accessed 12 Mar 2017).
7. Bassett IV, Regan S, Chetty S, *et al*. Who starts antiretroviral therapy in Durban, South Africa?… not everyone who should. *AIDS* 2010;24(Suppl 1):S37–44.
8. Gardner LI, Metsch LR, Anderson-Mahoney P, *et al*. Efficacy of a brief case management intervention to link recently diagnosed HIV-infected persons to care. *AIDS* 2005;19:423–31.
9. Craw JA, Gardner LI, Marks G, *et al*. Brief strengths-based case management promotes entry into HIV medical care: results of the antiretroviral treatment access study-II. *J Acquir Immune Defic Syndr* 2008;47:597–606.
10. Bassett IV, Coleman SM, Giddy J, *et al*. Sizanani: a randomized trial of health system navigators to improve linkage to HIV and TB care in South Africa. *J Acquir Immune Defic Syndr* 2016;73:154–60.
11. Languza N, Lushaba T, Magingxa N, *et al*. *Community health workers: a brief description of the HST experience*: Health System Trust, 2011. http://www.hst.org.za/sites/default/files/CHWs_HSTexp022011.pdf (accessed 12 Mar 2017).
12. Peduzzi P, Concato J, Kemper E, *et al*. A simulation study of the number of events per variable in logistic regression analysis. *J Clin Epidemiol* 1996;49:1373–9.
13. Dalal S, Lee CW, Farirai T, *et al*. Provider-initiated HIV testing and counseling: increased uptake in two public community health centers in South Africa and implications for scale-up. *PLoS One* 2011;6:e27293.
14. Mohlabane N, Tutshana B, Peltzer K, *et al*. Barriers and facilitators associated with HIV testing uptake in South African health facilities offering HIV counselling and testing. *Health SA Gesondheid* 2016;21:86–95.
15. Katz IT, Essien T, Marinda ET, *et al*. Antiretroviral refusal among newly diagnosed HIV-Infected adults in Soweto, South Africa. *AIDS* 2011;25:2177–81.
16. Bogart LM, Chetty S, Giddy J, *et al*. Barriers to care among people living with HIV in South Africa: contrasts between patient and healthcare provider perspectives. *AIDS Care* 2013;25:843–53.
17. Amanyire G, Semitala FC, Namusobya J, *et al*. Effects of a multicomponent intervention to streamline initiation of antiretroviral therapy in Africa: a stepped-wedge cluster-randomised trial. *Lancet HIV* 2016;3:e539–48.
18. Mfinanga S, Chanda D, Kivuyo SL, *et al*. Cryptococcal meningitis screening and community-based early adherence support in people with advanced HIV infection starting antiretroviral therapy in Tanzania and Zambia: an open-label, randomised controlled trial. *Lancet* 2015;385:2173–82.

PAPER III

Title: Experiences of patients, providers and case managers in linking adults into TB and HIV care: a qualitative study

Suggested authors: N Maraba[1,2*], V Chihota[1,2,3], S J Nieuwoudt[2], K McCarthy[2,4], G.J Churchyard[1,2,5,6], and A D Grant[2,6,7]

Affiliations:

1 The Aurum Institute, Queens Road Parktown, Johannesburg, South Africa

2 School of Public Health, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa

4 National Institute of Communicable Disease

5 Advancing Treatment and Care for TB and HIV, South African Medical Research Council Collaborating Centre of HIV/TB

6 TB Centre, London School of Hygiene & Tropical Medicine, UK

7 Africa Health Research Institute, School of Nursing and Public Health, University of Kwazulu-Natal, South Africa

*Corresponding author

Email: nmaraba@auruminstitute.org

Tel: 010 590 1446

Abstract

Background:
Gaps in linkage to HIV care and TB treatment initiation exist amongst those undergoing TB investigations. The aim of this qualitative study was to understand care providers', case managers' and patients' experiences of a lay case manager intervention to initiate patients on TB treatment and/or link them into HIV care.

Methods:
Care providers that worked closely with case managers and case managers that implemented the intervention were interviewed. Purposive sampling was used to recruit patients including those who did and did not successfully link into care. Thematic analysis was applied.

Results:
Twenty two participants were recruited for in-depth interviews: eight providers, five case managers and nine patients. Seven of the nine patients interviewed did not link into HIV care successfully three months post enrolment into main study. The role of a case manager was perceived to be important by case managers, patients and providers. Barriers and facilitators to TB and HIV care were analysed at patient and health-system levels. Patient barriers to TB care were competing priorities while health systems struggled to contact patients after sputum submission linked to delayed laboratory results. Clinic experiences and personal drive facilitated patient care. Patient-level barriers to HIV care were fear, competing priorities and ART refusal. Health-system factors included facility-specific ART initiation scheduling systems and long queues; poor provider understanding of HIV and TB management guidelines; and lost patient files or results. Patient readiness to know their HIV status or start ART and receipt of education facilitated linkage to care.

Conclusion:
While the intervention was acceptable, providing support to patients is insufficient to link patients to care. Additional health-system and patient barriers preventing linkage into TB and HIV care need to be addressed.

Introduction

Adults being investigated for tuberculosis (TB) in South Africa have a high HIV (human immunodeficiency virus) prevalence (1). There are also gaps in linkage both to TB treatment and to HIV care leading to high mortality rates within this group (1-4).

Previous studies exploring barriers of linkage to HIV care and TB treatment initiation have been done specifically amongst HIV positive patients or TB patients only. Barriers of linkage to care for these two groups can be categorized into patient and health-system factors. Patients with TB and those living with HIV share difficulties in getting time of work to attend facilities for care. HIV specific patient related barriers were stigma, fear of knowing ones HIV status and refusal to test (5-7). TB specific patient related barriers were lack of understanding of TB its severity or potential benefits of treatment. Health-system barriers that are common between patients with TB and those with HIV were the dissatisfaction with waiting times, distance from health care centres, costs to travel to health care centres (8). Health-system barriers specific to HIV were perceived poor quality of health care also contribute to failure of patients starting antiretroviral therapy (ART) (9). Health-system barriers that were specific to TB care were long costly TB diagnostic and care pathways, and long processes for registration of suspected and confirmed TB cases (10). With all of these barriers, innovative strategies are needed to initiate patients on TB treatment and link those who are HIV positive patients into HIV care. There is paucity of data on the exploration of barriers to linkage to HIV care and TB treatment initiation amongst people undergoing TB investigation, majority of whom are HIV positive.

A pilot study of a case manager strategy was undertaken to assist with linkage into HIV care and initiation of TB treatment amongst adults being investigated for TB in South Africa (11) . The strategy involved the use of trained lay counsellors as case managers to provide support to patients to help navigate the care pathway by facilitating testing and treatment initiation for both HIV and TB. Through communication at the clinic or telephone contact, case managers advised patients on the next steps following an investigation for TB (11). The study showed that the majority of those supported for TB treatment initiation successfully started treatment, while linkage into HIV care was suboptimal (11). To better understand experiences of the strategy by care providers, case managers and patients, a qualitative sub-study was undertaken. We report here the barriers and facilitators of linkage into HIV care and initiation of TB treatment as perceived by care providers, case managers and patients.

Methods

This qualitative study was part of a pilot study, determining if support from a case manager would assist adults being investigated for TB to initiate TB treatment and/or HIV care. The study was conducted from September 2014-March 2015 in five primary health care clinics in Gauteng and Mpumalanga provinces. Five lay case managers (three in Gauteng and two in Mpumalanga) were placed at the clinics. Details of the case manager strategy are described elsewhere (11) .

In-depth interviews were conducted with case managers, providers and patients. Providers were TB and ART nurses, purposively sampled on the basis that they worked closely with the case managers during the implementation of the intervention. All case managers that implemented the intervention were also interviewed. Purposive sampling was used to recruit a mix of patients who successfully linked into relevant HIV or TB care (n=2) and those who did not link into care (n=7) by the end of three months' follow-up across the two provinces. For patients who did not link into care, interviews were done with those who could be located and were available to return to the clinics where they were enrolled into the study across the two provinces. Furthermore, those who did not link into care were intentionally oversampled to better understand barriers of linkage to care in this group.

To reduce moderator acceptance bias, a qualitative consultant who was not part of the study team conducted interviews with the case managers and providers, while patient interviews were conducted by NM in Zulu, Isiwati and Sepedi languages. They lasted for 30 - 40 minutes. Interview guides for the patients included questions on acceptability, facilitators and barriers to TB treatment initiation and HIV linkage to care. The case manager and healthcare worker interview guides included questions on acceptability, facilitators and barriers of linkage into TB and HIV care, working relationship, and future changes to be made to the strategy. To assess acceptability, we explored how the case manager strategy affected the work of providers and the compatibility of the strategy to their routine work. For patients, we looked at how the strategy affected how they sought care. We also assessed how patients and providers perceived the strategy. All interviews were audio recorded with participant consent.

Data management and analysis

Provider and case manager audio recorded interviews were transcribed by the consultant while NM simultaneously transcribed and translated patient interviews into English. The first transcripts were

used to identify common phrases or themes inductively from the data. These, along with the study objectives, were then used to develop a coding framework for coding of the rest of the data. NM identified major themes for thematic content analysis. The major themes on acceptability, facilitators and barriers to TB treatment initiation and HIV linkage to care from the data were discussed and refined with SN. QSR international's NVIVO 10 software was used to support data analysis.

Ethics

Ethical Approval was provided by the Human research ethics committees of the London School of Hygiene and Tropical Medicine (reference number 7124) and University of Witwatersrand (M131143). Written consent was obtained from all who participated in the study. Participants also provided consent to be audio-recorded and quoted. Interviews were done in a private place at the clinics.

Results

Participant characteristics

A total of 22 interviews were conducted between January to March 2015; eight with providers, five case managers and nine patients. Of the eight providers, six were females and all were professional nurses. Five of the providers were from clinics in Gauteng province. Four of the four case managers were females and only one had a tertiary education (Table 1). Twelve patients were contacted to schedule an appointment to take part in the study and three did not present themselves to be interviewed on the appointment date. Of the nine patients, five were from Gauteng, seven were males and eight had secondary level education. Seven of the nine patients interviewed did not link into HIV care successfully three months post enrolment into main study.

The case manager's role

Patients, providers and case managers all perceived the role of the case managers to be important, but described their roles in slightly different ways. Of the many roles played by case managers, some patients particularly appreciated the patience and respect they received from the case managers. One patient emphasized that being treated well makes a sick person feel better.

> [from what the case manager did, I liked] *the way she understands, the way she respects people and the way she treats people.… She is very patient with people. It makes a sick person feel very satisfied inside and even the disease gets reduced inside because they*

become free inside. If you find that they are not treating you nicely, the disease keeps you down. (Male patient, unsuccessful in linking into HIV care)

The majority of the providers indicated that they knew what the case managers were doing at the clinics. They reported that the case managers assisted them by performing duties such as collection of sputum, follow-up with patients who needed to start on TB or HIV treatment by calling them, telephonically encouraging patients who still had TB symptoms even after testing TB negative and also those who had side effects to medication to return to clinic for further management. They also said case managers provided HIV counselling to some patients.

The majority of the case managers reported that they assisted with service provision for clinic attendees by performing additional duties such as completing TB identification registers, provision of results to TB patients, performing HIV counselling and testing (HCT) and opening clinic files for patients on days the clinic was busy.

All three respondent groups felt that if the strategy is to be implemented in the future, case managers should provide TB and HIV education. Patients and case managers emphasized that case managers need to have a good attitude towards patients. Providers (and some case managers) focused more on qualifications, suggesting that the individual needs to be trained as a professional nurse to be able to start patients on treatment without relying on overloaded facility staff.

Patient linkages to TB and HIV testing and care

Reported facilitators and barriers of linkages to testing and care differed between TB and HIV. When relevant, facilitators and barriers are discussed as being located at a patient or health-system level.

Facilitators to care

Patient related facilitators for linkage into HIV care were reported by all the three groups to be readiness to know one's HIV status or start ART and provision of education. All of the groups felt provision of education about HIV leads to individuals being ready to know their HIV status as this brings understanding of the disease. They also felt that readiness to test for HIV was a facilitator as once a patient is ready to know their HIV status, it leads to them wanting to conduct an HIV test. They associated this with a willingness to accept whatever the outcome of the test and start on ART if HIV positive. One patient indicated that he compared himself with other patients that were also on ART and that motivated him to start and stay on ART as shown in the quote below.

Yes, I am brave. Sometimes most people get hurt because they are afraid and they end up stressing themselves. They end up thinking because they are like this [HIV positive], they are the only ones in the world, while we are a lot. You compare yourself with other people, just because am sick does not mean am not human anymore. Because am getting treatment am supposed to use the treatment. (Male patient, unsuccessful in linking into HIV care)

Motivation to seek care was an important TB facilitator for patients, where their ill health and having the desire to get better pushed them to seek care. For other patients this motivation came from having witnessed family members being sick with TB or getting encouragement from friends and family to test for TB. One patient described why he sought care:

For me …. I wanted to live. I could not continue coughing forever. I was not gaining weight and I was thinking a lot. I even stopped working for a while. Now am better. I could not walk totally. Now am better. I have energy. I can walk, clean and cook for myself. (Male patient, struggled in getting a TB diagnosis and TB treatment initiation)

Health-system facilitator for TB was type of reception at facilities which comprised of provider attitudes towards those patients coming to seek care and patients feeling assisted when they went to the facilities. Both patients and providers felt that having providers that treat patients in a good manner motivated patients to return to facilities.

TB patients, sometimes they come here with an attitude, sometimes they do not understand why they have TB… but if you smile to them, and have good relationship with them and I do give them my phone number sometimes my cell number to contact me at home. (TB and HIV nurse, Mpumalanga province)

Barriers to care

Fears linked to testing for HIV were common between TB treatment initiation and HIV linkage to care. One provider felt that fear of testing for HIV was the reason why some TB positive patients were not returning to the facility for further management of TB as elaborated in the quote below:

They may come and start [TB treatment] *and then when you tell them please can you test for HIV because it is important to know your* [HIV] *status and to be given the treatment that is due to you. They would say next time, and next time when they supposed to come they would not come just because they are afraid of testing* [for HIV]. (Provider, Gauteng)

However, case managers and patients did not say anything regarding this point. Some patients talked about fearing knowing their HIV status as it meant they would have to be on life-long treatment.

Another barrier for linkage to HIV care highlighted by the three groups was refusal to test for HIV. One of the reasons why patients refused to test was lack of readiness to test as described by case manager:

> *He was tested for TB and was positive. We had to go and look for him to start [TB] treatment. The other tenant at the house said this guy only comes back on weekends. I called and called. I asked him to do an HIV test, he [said he] was not ready. He refused to be tested for HIV. Even in the file it is written that he said he was not ready to be tested [for HIV].* (Case manager, Gauteng)

Patient-level barriers were fear, competing priorities, and refusal to start ART. Patients described competing priorities like work commitments or looking for work as preventing them from returning to clinic for further HIV management. Some case managers and one provider perceived refusal to take ART as a barrier among both TB/ HIV co-infected patients as well as HIV positive patients. Providers and case managers perceived that TB and HIV co-infected patients were not willing to take ART while still taking TB treatment. Patients who were HIV positive only, seemed to delay returning to the clinic for ART initiation. This was perceived by providers and one case manager as stemming from patients' fear of being stigmatised.

Providers and case managers perceived that patient-related barriers to TB testing and treatment initiation included lack of time or money for further tests, relocation or providing incorrect contact details to the clinic. They perceived that no time or money to return to clinic was a barrier because patients could not get time off work to return to clinic or they did not have transport money. They felt that patients were responsible for challenges faced with tracing them after submitting sputum for TB tests. Case managers and providers also perceived patients relocation to a different place due to work commitments or providing incorrect contact details when the TB identification registers were being completed was another barrier for initiating on TB treatment. This led to not being able to inform patients about their results or the health facility staff not being able to trace patients to start TB treatment if they were confirmed to have TB.

Health-system barriers to HIV linkage to care included health facility ART booking system, long queues, poor provider understanding of HIV and TB management protocols, and lost patient files or results.

Case managers perceived losing of patient's clinic files or results at the clinics was a barrier as it made it difficult for providers to manage patients further. Case manager perceived that the facility booking systems for ART initiation and long queues was another barrier as some of the patients that needed to be started on ART quickly were given return dates far ahead in the future. This was because facilities were initiating only a specific number of patients on a weekly basis. Some case managers perceived that the long queues that HIV patients had to stand in to access HIV treatment could discourage patients to seek care. One case manager emphasized the large number of patient accessing HIV care in a facility as a reason for long queues.

> *That there are too many people at the waiting area and they do not want to wait a long time at the clinic. They know the TB room has a few people, but the ARV room sees about 80 people a day. So they do not want to wait here.* (Case manager, Gauteng)

Another barrier mentioned by some providers was the lack of clarity on the timing of ART initiation after TB treatment initiation in TB and HIV positive patients. This meant that some patients were delayed in initiating on ART after starting on TB treatment.

The only health-system barrier for TB testing was delay in delivery of laboratory results. Case managers perceived that delay of laboratory results was a barrier because clinic staff did not receive results on time and patients did not find the results when they returned on their return date. This was not mentioned by the providers or patients.

Discussion

Our study found that the pilot intervention to link adults being investigated for TB into TB and HIV care was accepted by providers and patients. We analysed TB and HIV related barriers into patient related and health-system related, in keeping with the broader literature (8, 12-16). Reported TB related facilitators were type of reception received at facilities and motivation to seek care. Facilitators to HIV linkage to care were readiness to know HIV status or start ART and provision of education. A majority of those who did not link into HIV care and were approached to participate in this study were males. This is similar to what was reported by a study characterizing the engagement of HIV care in South Africa in 2012; the report showed that less men were in care compared to women (17).

Although the intervention was reported to be acceptable, case managers and providers agreed that in the future the role should be implemented by a professional nurse. This view was not shared by the patients. In our study, the role of the case manager was carried out by a lay counsellor as we wanted to shift this task away from professional nurses in order to relieve their workload. Lay counsellors have been widely used to provide counselling and education for TB and HIV in primary health care settings in South Africa (18). A study evaluating the effect of an intervention to optimize TB and HIV integration in primary health care facilities found that nurses who were hired to integrate TB and HIV services spent the majority of their time managing patients(19) . It is unclear, from this study, how a similar situation could be averted if professional nurses were asked to apply a case management approach.

Facilitators and barriers for TB and HIV linkage to care in our study were categorized as health-system or patient related factors. While there was no overlap of facilitators, fear of HIV testing emerged as a common patient related barrier for TB and HIV linkage to care. Fears of knowing their HIV status and of being stigmatized reported in our study were also documented in a study describing barriers and facilitators of HIV counselling and testing (HCT) done in health facilities in South Africa (6). That study showed that the reason why most patients (73%) did not test for HIV was because they were afraid of finding their HIV status, with 33% reporting a fear of death (33%) and 11% citing fear of stigma (6). Refusal to initiate ART while on TB treatment by some patients, indicating the preference to finish TB treatment, first could be due to the fear of pill burden and side effects of taking both treatments, as shown in study in Ethiopia (20).

HIV specific patient related barriers such as competing priorities linked to job hunting or going to work preventing patients from linking into HIV care were similar to a study done in South Africa amongst newly HIV diagnosed patients. The study showed how burdensome health-system linked to multiple visits to clinics promoted the disengagement of care by patients (12). The patient related challenge of time for TB patients or health-system challenge of delayed results at facilities and lack of transport money were also highlighted in a study exploring why TB patients do not initiate or adhere to TB treatment in South Africa (8) . The study reported that newly diagnosed TB patients would not start on TB treatment because their TB results would not be available at the facilities on the day they had returned to check on them (8). TB patients found it hard to stay adherent on treatment if they had to pay a bus or taxi fare to get to a facility to collect treatment (8). Delay of receipt of sputum result was also highlighted as a health-system barrier for starting TB treatment in another study in Malawi exploring why smear positive TB cases were not starting on treatment. The study showed that sputum results were sometimes only available at a time of death of a patient (14). The poor understanding of TB and HIV management protocols by providers in our study shows the importance of re-training of facility staff on updated TB and HIV management guidelines to improve the management of patients. A study reviewing the quality, quantity and distribution of providers within TB programs in Nigeria and Kyrgyzstan highlighted the importance of re-training in order to control TB (15).

The relocation of patients after submitting sputum specimens to another area before receiving their results shows that the population that was served by primary health clinic in our context was a migrant one. This suggests that perhaps the health system should be moving towards point of care TB testing where patients would leave a facility already knowing their TB results and initiated on TB treatment on the same day if they are diagnosed (21).

The observation that education and readiness to test for HIV or start ART were facilitators for linkage into HIV care was expected as the two are connected. A study in Swaziland, examining individuals experiences of HIV testing and linkage to care showed that a person's acceptance of their HIV status encouraged them to seek care and therefore be more willing to start treatment (13). A South African study done in health facilities also showed that provision of education was the leading facilitator for uptake of HIV testing at 32% (6). In our intervention, case managers provided education to patients, but the existence of other barriers prevented individuals to test or start ART.

Motivation to seek care and type of reception as (patient and health-system related) facilitators to TB testing and treatment found in our study were similar to findings in a study done in Kenya between 2012 and 2013 which was identifying barriers and facilitators of linkage and retention in chronic care for HIV, TB and hypertension(16). The study reported that personal initiative and good provider-patient relationship were important facilitators of linkage to care for TB and HIV (16). The good provider-patient relationship was also highlighted by studies that showed improvement of treatment outcomes in patients if they were supported (22, 23), which is consistent with what our study found.

The strength of the study is that we interviewed patients, case managers and providers providing a complete overview of perspectives of the facilitators and barriers of implementing a case manager strategy in the primary health care clinics in South Africa. The inclusion of patients and providers in our sample. Our limitations were that we could not interview all of the sampled patients that did not link into care even after multiple attempts of trying to schedule an appointment. This could have introduced some selection bias to our study. Participants did not vary sufficiently by gender to explore gender differences, which are known to impact care seeking in South Africa (17), nor did the sample distribution enable comparison by provincial context.

Conclusion

Our study showed that the use of lay case managers providing support to patients being investigated for TB was acceptable to patients and providers. However, providing support to patients only is not enough, as additional health-system and patient barriers are preventing linkage into TB and HIV care. We recommend that interventions that assist with TB treatment initiation and linkage to HIV should address both patients and health-system level factors in order to succeed in addressing this challenge. Additionally, we recommend that interventions for facility management be piloted to facilitate access to HIV care services.

Reference

1. Churchyard GJ, Stevens WS, Mametja LD, McCarthy KM, Chihota V, Nicol MP, et al. Xpert MTB/RIF versus sputum microscopy as the initial diagnostic test for tuberculosis: a cluster-randomised trial embedded in South African roll-out of Xpert MTB/RIF. The Lancet Global health. 2015 Aug;3(8):e450-7. PubMed PMID: 26187490.
2. Botha E, den Boon S, Lawrence KA, Reuter H, Verver S, Lombard CJ, et al. From suspect to patient: tuberculosis diagnosis and treatment initiation in health facilities in South Africa. The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease. 2008 Aug;12(8):936-41. PubMed PMID: 18647454.
3. Claassens MM, du Toit E, Dunbar R, Lombard C, Enarson DA, Beyers N, et al. Tuberculosis patients in primary care do not start treatment. What role do health system delays play? The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease. 2013 May;17(5):603-7. PubMed PMID: 23575324.
4. Bristow CC, Dilraj A, Margot B, Podewils LJ. Lack of patient registration in the electronic TB register for sputum smear-positive patients in KwaZulu-Natal, South Africa. Tuberculosis. 2013 Sep;93(5):567-8. PubMed PMID: 23769141. Pubmed Central PMCID: 4616016.
5. Dalal S, Lee CW, Farirai T, Schilsky A, Goldman T, Moore J, et al. Provider-initiated HIV testing and counseling: increased uptake in two public community health centers in South Africa and implications for scale-up. PloS one. 2011;6(11):e27293. PubMed PMID: 22114668. Pubmed Central PMCID: 3219659.
6. Mohlabane N TB, Peltzer K, Mwisongo A. Barriers and facilitators associated with HIV testing uptake in South Africa health facilities offereing HIV counselling and testing Health SA Gesondheid. 2016;2I:86-95.
7. Bogart LM, Chetty S, Giddy J, Sypek A, Sticklor L, Walensky RP, et al. Barriers to care among people living with HIV in South Africa: contrasts between patient and healthcare provider perspectives. AIDS care. 2013;25(7):843-53. PubMed PMID: 23061894. Pubmed Central PMCID: 3552028.
8. Skinner D, Claassens M. It's complicated: why do tuberculosis patients not initiate or stay adherent to treatment? A qualitative study from South Africa. BMC infectious diseases. 2016 Nov 25;16(1):712. PubMed PMID: 27887646. Pubmed Central PMCID: 5124309.
9. Katz IT, Bangsberg DR. Cascade of Refusal-What Does It Mean for the Future of Treatment as Prevention in Sub-Saharan Africa? Current HIV/AIDS reports. 2016 Apr;13(2):125-30. PubMed PMID: 26894487. Pubmed Central PMCID: 5233714.
10. MacPherson P, Houben RM, Glynn JR, Corbett EL, Kranzer K. Pre-treatment loss to follow-up in tuberculosis patients in low- and lower-middle-income countries and high-burden countries: a systematic review and meta-analysis. Bulletin of the World Health Organization. 2014 Feb 01;92(2):126-38. PubMed PMID: 24623906. Pubmed Central PMCID: 3949536.
11. Maraba N, Chihota V, McCarthy K, Churchyard GJ, Grant AD. Linkage to care among adults being investigated for tuberculosis in South Africa: pilot study of a case manager intervention. BMJ open. 2018 May 24;8(5):e021111. PubMed PMID: 29794100. Pubmed Central PMCID: 5988070.
12. Mabuto T, Charalambous S, Kennedy C, Hoffmann CJ. Perceptions of Value and Cost of HIV Care Engagement Following Diagnosis in South Africa. AIDS and behavior. 2018 Mar 19. PubMed PMID: 29556834.
13. Horter S, Thabede Z, Dlamini V, Bernays S, Stringer B, Mazibuko S, et al. "Life is so easy on ART, once you accept it": Acceptance, denial and linkage to HIV care in Shiselweni, Swaziland. Social science & medicine. 2017 Jan 06;176:52-9. PubMed PMID: 28129547.
14. Squire SB, Belaye AK, Kashoti A, Salaniponi FM, Mundy CJ, Theobald S, et al. 'Lost' smear-positive pulmonary tuberculosis cases: where are they and why did we lose them? The

international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease. 2005 Jan;9(1):25-31. PubMed PMID: 15675546.

15. Awofeso N, Schelokova I, Dalhatu A. Training of front-line health workers for tuberculosis control: lessons from Nigeria and Kyrgyzstan. Human resources for health. 2008 Sep 29;6:20. PubMed PMID: 18822179. Pubmed Central PMCID: 2569065.

16. Rachlis B, Naanyu V, Wachira J, Genberg B, Koech B, Kamene R, et al. Identifying common barriers and facilitators to linkage and retention in chronic disease care in western Kenya. BMC public health. 2016 Aug 08;16:741. PubMed PMID: 27503191. Pubmed Central PMCID: 4977618.

17. Takuva S, Brown AE, Pillay Y, Delpech V, Puren AJ. The continuum of HIV care in South Africa: implications for achieving the second and third UNAIDS 90-90-90 targets. Aids. 2017 Feb 20;31(4):545-52. PubMed PMID: 28121668.

18. Petersen I, Fairall L, Egbe CO, Bhana A. Optimizing lay counsellor services for chronic care in South Africa: a qualitative systematic review. Patient education and counseling. 2014 May;95(2):201-10. PubMed PMID: 24629835.

19. Kufa T, Fielding KL, Hippner P, Kielmann K, Vassall A, Churchyard GJ, et al. An intervention to optimise the delivery of integrated tuberculosis and HIV services at primary care clinics: results of the MERGE cluster randomised trial. Contemporary clinical trials. 2018 Jul 25;72:43-52. PubMed PMID: 30053431.

20. Gebremariam MK, Bjune GA, Frich JC. Barriers and facilitators of adherence to TB treatment in patients on concomitant TB and HIV treatment: a qualitative study. BMC public health. 2010 Oct 28;10:651. PubMed PMID: 21029405. Pubmed Central PMCID: 2978153.

21. Stime KJ, Garrett N, Sookrajh Y, Dorward J, Dlamini N, Olowolagba A, et al. Clinic flow for STI, HIV, and TB patients in an urban infectious disease clinic offering point-of-care testing services in Durban, South Africa. BMC health services research. 2018 May 11;18(1):363. PubMed PMID: 29751798. Pubmed Central PMCID: 5948731.

22. Wouters E, Van Damme W, van Rensburg D, Meulemans H. Impact of baseline health and community support on antiretroviral treatment outcomes in HIV patients in South Africa. Aids. 2008 Nov 30;22(18):2545-8. PubMed PMID: 19005281.

23. Ong'ang'o JR, Mwachari C, Kipruto H, Karanja S. The effects on tuberculosis treatment adherence from utilising community health workers: a comparison of selected rural and urban settings in Kenya. PloS one. 2014;9(2):e88937. PubMed PMID: 24558452. Pubmed Central PMCID: 3928331.

450 Table 1 : Qualitative sample overview n=22

	N (%)
Health providers (n=8)	
gender	
Male	2 (25 %)
Female	6 (75 %)
Health provider clinic role	
TB nurse	3 (38 %)
HIV nurse	3 (38 %)
HIV and TB nurse	2 (25 %)
Cadre of staff	
Professional nurse	8 (100 %)
Province	
Gauteng	6 (75 %)
Mpumalanga	3 (25 %)
Patients (n=9)	
Gender	
Male	7 (78 %)
Females	2 (22 %)
Education level	
Primary school	0
Secondary (Grade 8-12)	8 (89 %)
Tertiary (degree)	1 (11 %)
Province	
Gauteng	5 (56 %)
Mpumalanga	4 (44 %)
Case managers (n=5)	
Gender	
Male	1 (20 %)
Female	4 (80 %)
Education level	
Primary school	-
secondary (matric level)	4 (80 %)
Tertiary	1 (20 %)
Province	
Gauteng	3 (60 %)
Mpumalanga	2 (40 %)

451

PAPER IV

PLOS ONE

RESEARCH ARTICLE

Using mHealth to improve tuberculosis case identification and treatment initiation in South Africa: Results from a pilot study

Noriah Maraba[1,2]*, Christopher J. Hoffmann[1,3], Violet N. Chihota[1,2¤], Larry W. Chang[3], Nazir Ismail[4], Sue Candy[4], Edwin Madibogo[5], Marc Katzwinkel[6], Gavin J. Churchyard[1,2,7,8], Kerrigan McCarthy[1,2,4]

1 The Aurum Institute, Johannesburg, South Africa, **2** School of Public Health, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa, **3** John Hopkins University School of Medicine, Baltimore, MD, United States of America, **4** National Institute of Communicable Disease, Johannesburg, South Africa, **5** Department of Health and Social Development, City of Johannesburg, Johannesburg, South Africa, **6** Mobenzi, Cape Town, South Africa, **7** Advancing Treatment and Care for TB and HIV, South African Medical Research Council Collaborating Center for HIV/TB, Johannesburg, South Africa, **8** London School of Tropical and Hygiene Medicine, London, United Kingdom

¤ Current address: Foundation for Innovative New diagnostics, Geneva, Switzerland
* nmaraba@auruminstitute.org

OPEN ACCESS

Citation: Maraba N, Hoffmann CJ, Chihota VN, Chang LW, Ismail N, Candy S, et al. (2018) Using mHealth to improve tuberculosis case identification and treatment initiation in South Africa: Results from a pilot study. PLoS ONE 13(7): e0199687. https://doi.org/10.1371/journal.pone.0199687

Editor: Petros Isaakidis, Médecins Sans Frontières (MSF), SOUTH AFRICA

Received: February 28, 2018

Accepted: June 12, 2018

Published: July 3, 2018

Data Availability Statement: All relevant data are within the paper and its Supporting Information files.

Funding: Research reported in this publication was supported by the Fogarty International Center of the National Institutes of Health (5R21TW009894) https://www.fic.nih.gov/Pages/Default.aspx. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. The funders had no role in study design, data collection

Abstract

Background

Tuberculosis (TB) incidence in South Africa is among the highest globally. Initial loss to follow-up (ILFU), defined as not starting on TB treatment within 28 days of testing positive, is undermining control efforts. We assessed the feasibility, acceptability, and potential of a mHealth application to reduce ILFU.

Methods

An mHealth application was developed to capture patients TB investigation data, provide results and monitor treatment initiation. This was implemented in two primary health clinics (PHC) in inner-city Johannesburg. Feasibility was assessed by comparing documentation of personal details, specimen results for same individuals during implementation period (paper register and Mhealth application). Effectiveness was assessed by comparing proportion of patients with results within 48 hours, and proportion started on treatment within 28 days of testing TB positive during pre- implementation (paper register) and implementation (mHealth application) periods. In-depth interviews with patients and providers were conducted to assess acceptability of application.

Results

Pre-implementation, 457 patients were recorded in paper registers [195 (42.7%) male, median age 34 years (interquartile range IQR (28–40), 45 (10.5%) sputum Xpert positive]. During implementation, 319 patients were recorded in paper register and the mHealth application [131 (41.1%) male, median age 32 years (IQR 27–38), 33 (10.3%) sputum Xpert

and analysis, decision to publish, or preparation of the manuscript. KM received funding for this research. M. Katzwinkel is employed by Mobenzi, South Africa who were contracted and paid as a vendor to develop and maintain the mHealth application. Mobenzi, South Africa provided support in the form of salary for author MK, but did not have any additional role in the study design, data collection and analysis, decision to publish, or preparation of the manuscript. The specific role of this author is articulated in the 'author contributions' section.

Competing interests: MK was employed by Mobenzi during the period of the study. There are no patents, products in development or marketed products to declare. This does not alter our adherence to all PLOS ONE policies on sharing data and materials.

positive]. The proportion with complete personal details: [mHealth 95.0% versus paper register 94.0%, (p = 0.54)] and proportion with documented results: [mHealth 97.4% versus paper register 97.8%, (p = 0.79)] were not different in the two methods. The proportion of results available within 48 hours: [mHealth 96.8% versus paper register 68.6%), (p <0.001)], and the proportion on treatment within 28 days [mHealth 28/33 (84.8%) versus paper register 30/44 (68.2%), (p = 0.08)] increased during implementation but was not statistically significant. In-depth interviews showed that providers easily integrated the mHealth application into routine TB investigation and patients positively received the delivery of results via text message. Time from sputum collection to TB treatment initiation decreased from 4 days (pre-implementation) to 3 days but was not statistically significant.

Conclusions

We demonstrated that implementation of the mHealth application was feasible, acceptable to health care providers and patients, and has potential to reduce the time to TB treatment initiation and ILFU in PHC settings.

Introduction

There are an estimated 834 cases of tuberculosis (TB) per 100 000 population diagnosed annually in South Africa [1]. Without appropriate initiation of treatment, people with pulmonary TB may transmit TB to others and suffer from TB associated morbidity and mortality [2]. Initial loss to follow-up (ILFU) is defined as not starting TB treatment within 28 days of a microbiologically confirmed TB test. ILFU is estimated to occur among 17–25% of all persons diagnosed with TB in South Africa [3–5].

Common reasons for ILFU in TB patients include health system-, patient- and disease-related factors [6]. Health system-related reasons for ILFU include: delays in clinics receiving results or failure to receive results from laboratories; the need for patients to return repeatedly to clinics to enquire about results, and long waiting periods to receive care in health facilities. Patient-related factors include the need to take time off work to return to the clinic, and being prevented through illness from returning to clinic [6]. Optimal strategies to reduce ILFU will likely need to address both clinic-and patient-level factors.

Mobile technology use in health care, often referred to as mHealth, has potential to address both clinic and patient-level factors related to ILFU. mHealth has been used for communication with both providers and patients and has been reported to be acceptable and effective in diverse settings including during pre-natal screening, sexually transmitted disease care and HIV management [7–9]. mHealth innovations may help close patient- and health system-related gaps that contribute to ILFU. We therefore aimed to assess, using mixed methods, the feasibility, acceptability, and potential for addressing TB ILFU of a mHealth application to support and improve the TB care continuum.

Methods

Study setting

This study was based at two primary health clinics (PHC) serving high-TB-burden communities located in Johannesburg, South Africa.

mHealth application development

The mHealth application was developed by the study team in collaboration with the District TB Control Program (TCP), PHC managers and the National Health Laboratory services (NHLS). The mHealth application was designed to (1) replace the data collection and reporting function of a TB register through direct data entry onto a mobile application at the point of care of TB case identification data, (2) automate TB laboratory result delivery to PHC clinic by directly pulling results from a central lab (NHLS) into the mHealth system, (3) provide a dashboard display of the status of all patients in the TB testing and care continuum, (4) provide electronic notification of TB sputum results to clinic TB staff, and (5) provide pin-protected electronic TB sputum result notification to patients. The goal was to produce an application that would reduce the time and effort required for TB data reporting, provide rapid and automatic access to Xpert MTB/Rif TB test results and empower patients by directly providing results via cell phone messaging. The TB result-reporting component allowed health care workers to track patient progress to treatment initiation, prompt TB nurses to submit baseline smear microscopy on patients with positive Xpert MTB/Rif results and identify as well as remediate patients with a break in care (e.g. initiation of TB treatment for those with TB positive sputa) (Fig 1).

The content of results messages sent to patients was developed and refined during a workshop with the district TB coordinator, clinic TB nurses, and facility DOT supporters. Patients were notified by text of result availability, and were then required to access the results using a four-digit secret pin which patients chose at initial clinic visit. Patients who requested to receive an electronic result received the message 'Please reply to this message with your secret pin in order to receive your MTB results'. If the participant entered the correct pin, one of the following messages were provided: 1) 'Your result is MTB negative, please visit clinic <name> if symptoms persist'; 2) 'Your result is MTB positive, please visit clinic <name> in order to start TB treatment'; or 3) 'Your result is unsuccessful specimen, please visit clinic <name> to provide further specimens'. Patients who did not want to receive the results via text message but wanted to be notified of results availability received the message 'Your MTB results are ready for collection at the clinic'.

Study participants and procedures

The study was divided into two periods. The pre-implementation period occurred from January to March 2015. The clinic staff received training updates on use of the standard mHealth application and continued to use the paper register for all TB-related data collection. Prior to the implementation period, there was a 'run-in' period for training of study staff and to allow for troubleshooting of operational challenges encountered with the mHealth application. The implementation period occurred between February and April 2016. During the implementation period, study staff recruited sequential adults $\geq$18 years of age who had been referred for TB investigation including sputum testing. Patients were allowed to select whether to receive sputum results directly on their phone via text message or to get a text message informing them that their results were available at the clinic. Reasons for participant refusal to receive text messages were not collected. During the implementation period, clinic staff used the mHealth application for recording all patient data while in parallel; study staff captured the same data onto the paper registers. Simultaneous data collection on mHealth and paper registered allowed for comparison of data collection methodology whilst ensuring that the clinic adhered to TB control programme recording and reporting practice regarding the use of paper registers.

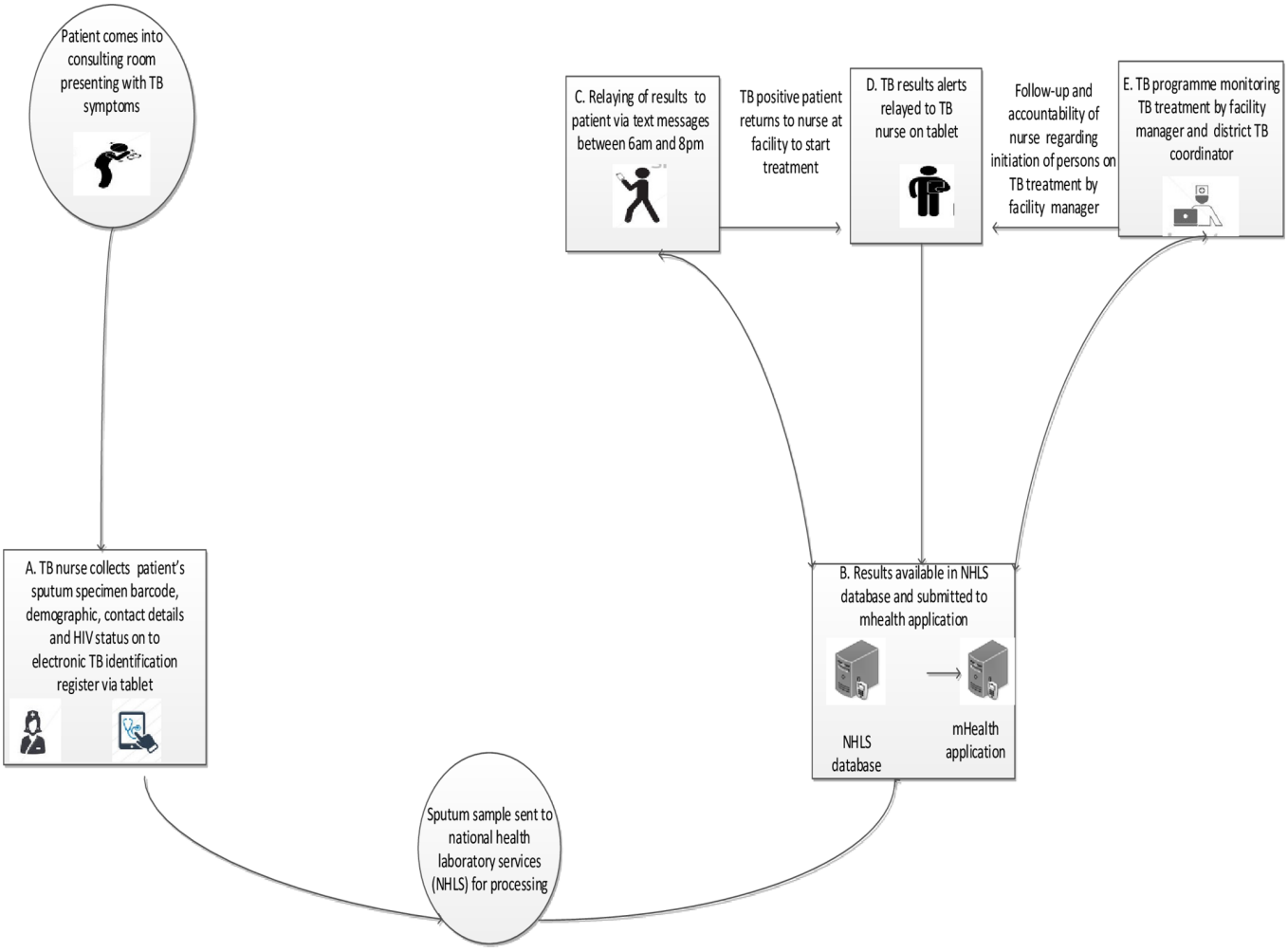


Fig 1. Illustration of the direction of communication between laboratory, health care worker and patient during TB case investigation. NHLS: National Health Laboratory Services; TB: Tuberculosis.

https://doi.org/10.1371/journal.pone.0199687.g001

Feasibility analysis

Data collection. Feasibility was assessed by evaluating the concordance of data captured in both the mHealth application by clinic staff and the paper-based register by research staff for the same set of patients in the implementation period. We decided *a priori* that the mHealth application would be feasible if we observed no difference between key indicators generated from the paper and mHealth applications as follows: in (i) successful collection by the mHealth application of all data elements usually collected by the paper TB register, (ii) successful and more rapid receipt of electronic laboratory results at the clinic using the mHealth application (iii) success in automatic sending of text notifications and results to patients. We compared the following indicators generated from data in the mHealth application and on the paper register during implementation: 1) the proportion of patients with specimen results; 2) proportion with positive Xpert MTB/Rif results; 3) the proportion of patients with a positive Xpert MTB/Rif result who also had a subsequent smear result recorded.

Data analysis. A McNemar test was used to compare indicators generated from mHealth and paper registers in implementation period. A statistically significant difference in indicators

(as evidenced by a p-value <0.05) suggested a difference in data collection accuracy, thus allowing inferences to be made regarding feasibility of the mHealth application to support TCP monitoring and evaluation requirements.

Acceptability

Data collection. Acceptability of the mHealth application to patients and healthcare providers was assessed using semi-structured interviews. At seven months post- implementation of the mHealth application, structured interviews were conducted with purposively selected patient participants who (1) tested TB negative and received the result via a text message, (2) tested TB negative and did not receive the result via text message, (3) tested TB positive and received the result via text message, or (4) tested TB positive and did not receive results via text message. Interviews were conducted in English, isiZulu, Sesotho or Setswana and lasted approximately 30 minutes. Structured interviews were conducted with providers who used the mHealth application at each clinic and the regional TB coordinator. All provider interviews were conducted in English. All interviews were recorded and transcribed and, when required, translated into English for analysis. Data were uploaded and analysed in Nvivo version 10 (QSR international Pty software).

Data analysis. We adapted Normalization Process Theory (NPT) [10], to frame our analysis of patient and provider interviews [10] [11]. We specifically focused on NPT domains of: (1) 'cognitive participation' which we defined as the provider's willingness to capture patient's data into the application and search for results, or the patient's willingness to use the application to retrieve and receive results, (2) 'collective action' which we defined as: a) the usability of the mHealth application and how it integrates within existing systems; b) the ease of use of the mHealth application by providers and patients, and (3) 'reflexive monitoring' which we defined as the patient's or providers' experience in using of the device to retrieve results [12,13]. To the existing NPT domains, we added 'confidentiality' which we defined as patients' confidence in the system's ability to disclose their results appropriately. Using these domains, transcripts were coded by NM. Specific passages were discussed among the investigative team to resolve discrepancies in coding and identify key themes.

Potential effectiveness

Data collection. Potential effectiveness was assessed through comparing specific indicators collected during the pre-implementation and implementation period data. We calculated TB treatment initiation within 48 hours. We chose TB treatment initiation within 48 hours as it is the cut-off point that the national TB programmes uses to describe ILFU [14] while a cut-off point of 28 days was chosen to allow comparison with prior studies from South Africa regarding ILFU [3–5,15].

Data analysis. Change in specific indicators related to timing of return of sputum results to clinic, proportion started on TB treatment within two and 28 days was assessed and proportion lost to follow-up. The proportion test for two samples was used to compare indicators generated from mHealth data in implementation period and from paper registers in the pre-implementation period. A statistically significant difference in indicators (p value <0.05) suggested that a real difference in proportions between the two methods exists. A Mann-Whitney test was done to compare for time to TB treatment in the pre-implementation and implementation periods.

Ethical considerations

Approval to implement the study was provided by the institutional review boards for human subjects research of the University of the Witwatersrand (HREC certificate no: M141008) and

Johns Hopkins University (IRB certificate no: IRB00071530). All participants provided written informed consent to take part in the study.

Results

Demographic characteristics

In pre-implementation period, 457 patients were recorded in the TB register. Of these patients, 195 (42.7%) were male, median age was 34 years (interquartile range [28–40]), and 353 (77.2%) patients self-reported being HIV positive (Table 1). In the implementation period, 319 persons were enrolled and registered on the mHealth application and paper register of whom 131 (41.1%) were male, median age 32 years (IQR 27–38), 259 (81.2%) self-reported being HIV positive. Of 319, 286 (89.6%) requested to receive results by text message, 31 (9.7%) did not wish to receive any text message and two (0.6%) opted to receive a text message indicating availability of results at the clinic. Of the 286 TB patients who requested to receive results via text messages, 59 (20.6%) failed to receive their results. This was due to:1) user failure for 49 (83.1%) patients who did not understand how to respond with a secret pin code; 2) data interface failure (the application did not receive results from the laboratory) for five (8.4%) patients; and 3) application failure (mHealth did not send results after patients responded with a correct pin) for five (8.4%) patients.

Feasibility

During the implementation period we sought to determine if there was any loss in data quality through electronic data collection compared to paper registers. We found no statistically significant difference between indicators derived from the mHealth application versus those obtained from paper-based registers as follows: 1) the proportion with complete personal data (mHealth 95% versus 94% paper register); 2) the proportion with a recorded specimen result (mHealth 97.4% versus 97.8% paper register); 3) the proportion with Xpert MTB/RIF positive result (mHealth 10.3% versus 10.6% paper register). (Table 2). The proportion of Xpert MTB/RIF positive TB results with a subsequent sputum smear result (mHealth 84.8% versus paper register 52.9%) was significantly higher with the mHealth application (Table 2).

Acceptability

Qualitative interviews were conducted with 21 TB patients (11 with positive sputum for TB and 10 with negative TB sputum results) and eight healthcare workers.

Table 1. Baseline characteristics of patients in pre-implementation and implementation period.

	Pre-implementation period	Implementation period
Variables	**N (%)**	**N (%)**
	N = 457	**N = 319**
Gender		
Male	195 (42.7%)	131 (41.1%)
Age (median, IQR)	34 (28–40)	32 (27–38)
HIV status (self-reported)	353 (77.2%)	259 (81.2%)
Opted to receive results via text		
Yes	N/A	286 (89.6%)
No	N/A	31 (9.7%)
Text for availability of results	N/A	2 (0.6%)

IQR: Interquartile range; N/A: not applicable

https://doi.org/10.1371/journal.pone.0199687.t001

Table 2. Feasibility of documenting data using the mHealth application compared to paper register.

	Implementation period		
	Paper register	mHealth	P value
Process indicators	**N (%)**	**N (%)**	
Total population screened by health care workers at clinics using TB screening tool	N = 319	N = 319	
Number with complete personal details	300/319 (94.0)	303/319 (95.0)	0.54
Number with a recorded specimen result	312/319 (97.8)	311/319 (97.4)	0.79
Number with Xpert® MTB/RIF positive result	34/319 (10.6)	33/319(10.3)	0.89
Number of positive, Rif sensitive Xpert® MTB/RIF results with a baseline specimen submitted for smear microscopy	18/34 (52.9)	28/33 (84.8)	<0.001

TB: Tuberculosis; Rif: Rifampicin

https://doi.org/10.1371/journal.pone.0199687.t002

Cognitive participation: The majority of patients (n = 13) valued the convenience of the mHealth application allowing them to access results without having to visit the clinic (Table 3, Quote 1). The majority of providers believed that the mHealth application assisted patients to start TB treatment earlier (Table 3, Quote 2 and 3).

Collective action: Some providers (n = 4) expressed concerns about technical difficulties experienced while using the mobile devices during the initial phase of implementation. However, they indicated that the use of technology improved with experience (Table 3, Quote 4). Once providers gained experience using the application they reported that it assisted them to start patients on TB treatment because patients returned to the clinic promptly after receiving results on their cell phones (Table 3, Quote 8). Some patients (n = 6) also reported that they encountered technical challenges that prevented them from retrieving their results (Table 3, Quote 5). At times, this arose through software malfunction that failed to deliver results despite patients correctly following retrieval instructions. Individual comprehension of steps also interfered with retrieving results (Table 3, Quotes 6 and 7). Patients who received results reported that it facilitated their return clinic visit (Table 3, Quote 9).

Reflexive monitoring: Overall, the majority of interviewed providers (n = 7) and patients (n = 14) were satisfied with the intervention. Providers perceived that the mHealth application assisted with patients returning to the clinic faster to start on TB treatment and saved patients' time (Table 3, Quote 10 and 11).

Confidentiality: Some patients (n = 7) raised the matter of confidentiality of receiving results through text messaging and six of them appreciated receiving results via pin-protected text message (Table 3, Quote 12). There were no reports of inadvertent disclosure of results.

Potential effectiveness

The largest improvement we observed in implementing the mHealth application was the proportion of TB results documented at the clinic within 48 hours when comparing the observation period immediately prior to mHealth use and the mHealth implementation period. During the pre-implementation period 68.6% of TB results were documented at the clinic within 48 hours compared to 96.8% in the implementation period (Table 4). Time to TB

Table 3. Patients and provider experiences of the mHealth intervention for TB case investigation.

Evaluation domains	Quote
Cognitive participation	***QUOTE 1***:*"Yes I would recommend it, at least it saves you time than you coming to the clinic standing in a queue and you will get the same result as the one you will get on your phone. When you get it on your phone, you at home, you do not leave, or when you are at work, and sometime at work you cannot get day offs just to come and collect results. And when you come to the clinic to collect your result you must come in the morning. You see, it clashes with the time to work. When you get via a text message it is easy, you can go to work and still get your result."* ***Female*** **TB negative patient no 5, clinic B**
	QUOTE 2: *"I strongly recommend it because we have a community that moves around a lot, so it will help because people leave the sputum then go to KZN* [Kwazulu Natal Province]. *If they have this system in place, they would go to the nearest clinic and show them the result and start them on treatment".* **Female, facility manager clinic B** ***QUOTE 3***: *"Yes* [I would recommend it]. *It will make TB rooms work much easier. If it can be something that is used permanently in all the clinics it can make everything easier. It really makes things easier; we do not have to wait for hard copy because the printing of results delays sometimes and you can get the results after 2 days. But this one* [text message intervention] *you get your results within 24hrs like I send a sputum today and tomorrow morning the results are back I initiate the patient without me waiting for hardcopy which can take even 3 days because a human error happens there courier takes the results to another or wrong clinic then it delays the process of starting TB treatment".* **TB nurse, Clinic A**
Collective action	***QUOTE 4:*** *"we did experience challenges in the beginning because the tablet scanner was not able to capture barcode and it was delaying us. Then we reported it to the research team leader who acted fast and they got us a manual scanner and . . ...capturing of barcode was faster".* **TB nurse, clinic B**
	QUOTE 5: "*yes I got the text message, ...the sister said when I get a text message, she gave me these other numbers* [the pin code], [and] *she said I must send to that number. She showed me how. I did what she said*, [but] *I did not get* [result], *so I never got the result."* **Male TB negative patient 3, clinic B**
	QUOTE 6: *"They sent them* [results] *but I was not responding in a good way until I came to the clinic and they assisted me in getting the results, I pressed wrongly on my phone."* **Male TB positive patient no 3, clinic B**
	QUOTE 7: *"text message I got it, but, I am not well educated, I asked the ones that are, they said I did not have TB, but I may have it, they will follow on it."* **Male TB negative patient no 3, clinic B**
	QUOTE 8: *"Most of the patients were coming back before I call them or send a tracer, if their results were positive."* **TB nurse, Clinic B**
	QUOTE 9: *"The person I saw here when I arrived treated me well a nurse that work here in TB room, I told her I have received the results and the text saying I have got TB then she said I must wait next to Tb room since there was someone in the room then I will get in when they leave, I did not even take long maybe ±20 to 30 minutes to finish, I got helped very quickly."* **Male TB positive patient 5, Clinic A**
Reflexive monitoring	***QUOTE 10***: *"It* [the text message intervention] *help that client came quicker to start treatment, they didn't delay in coming, others even before we could think they would be here they were already in the clinic to start treatment and those who were lost to follow-up we could immediately see that these need to be contacted so that they can come and start treatment."* **Facility manager, Clinic A**
	QUOTE 11: *"Patients were satisfied because some of them did not have to ask for permission* [from work] *to come to the clinic more especially the ones that the results come back negative."* **Facility manager, Clinic B**
Confidentiality	***QUOTE 12***: *"sister like I know my phone it's mine, it's my private inside, even if I get a text I will open it and see it myself, and no one will know what is happening on my phone, I think it's a good way to receive your result through text through the phone. Than to come to the clinic sister, and for the sister to see it.* **Male TB negative patient no 2, clinic B**

https://doi.org/10.1371/journal.pone.0199687.t003

treatment was decreased from 4 days (IQR 2–6) in the pre-implementation period to 3 days (IQR 2–5) in the implementation period; this was not statistically significant (p = 0.5).

Table 4. Process indicators assessing potential effectiveness of using mHealth application compared with paper register.

	Pre-implementation	Implementation	
Source of data	**Paper register**	**mHealth**	**P value**
Process indicators	**N (%)**	**N (%)**	
Number with turn-around time for sputum results within 48 hours	293/427 (68.6)	309/319 (96.8)	<0.001
Time to TB treatment, median (IQR)	4 (2–6)	3 (2–5)	0.50
Number on treatment within 48 hours of testing Rif susceptible TB positive	14/44 (31.8)	10/33 (30.3)	0.85
Number on treatment within 28 days of testing Rif susceptible TB positive	30/44 (68.2)	28/33 (84.8)	0.08
Number lost to follow-up (not on treatment within 56 days)	14/44 (31.8)	5/33 (15.2)	0.08

TB: Tuberculosis, Rif: Rifampicin, IQR: Interquartile range

https://doi.org/10.1371/journal.pone.0199687.t004

Discussion

This pilot study demonstrated that our mHealth intervention to improve the TB care was feasible, acceptable and appeared to offer advantages over the paper based register. The study showed that the mHealth TB evaluation and treatment management application effectively supported all paper register functions while appearing to improve data quality and to decrease time to TB treatment initiation.

One of the reasons why the mHealth application reduced the time for patients to start TB treatment is that patients returned to the clinic when they were notified of result availability. This eliminated the time required by the laboratory to hand-deliver printed sputum results to the clinic, and the time required for TB nurses to sort the paper results and call patients with positive results. The fact that patients did not need to return to clinic until notified that results were available also has potential to considerably lessen the financial and time burden on those who test TB negative. It has potential to reduce the workload on TB nurses as fewer patients with negative results would need to return to the clinic. Further, we observed that patient's knowledge of their sputum results enhanced their self-efficacy: for example, patients who tested positive for TB arrived at the clinic requesting TB treatment. An additional reason for improved time to receipt of results and TB treatment initiation is that our mHealth application eliminated the administrative work required to locate patients' register entries and file their paper-based results as healthcare workers could rapidly locate patient's results on the tablet. Our findings are similar to a study done in Swaziland that delivered sputum TB results via text message to clinics and showed an improved turnaround time to TB treatment initiation compared to receiving results via paper reports [16].

Improvements in indicators when comparing the mHealth application to the paper-based register likely represents valid and meaningful changes. For example, the mHealth application obtained TB lab results through a direct data download from the national laboratory system server through a matching process based on the specimen identification barcode. Therefore the mHealth register contained the "true" result reported in the national database and eliminated potential for human transcription error. In contrast, sputum results were written into the paper register by a health care worker after: (1) a hard copy of the laboratory results were received at the clinic, AND (2) the health care worker appropriately filed the results, AND (3) the health care worker correctly transcribed the data into the register. Each of these three steps was open to system or human error. Regarding the proportion of TB positive patients on treatment by 28 days after testing, this reflects the date of treatment commencement as recorded by health care worker in either the register or the mHealth application. Data entry into the register or the mHealth application was subject to same risk of error, however, the mHealth

application date entry field included inbuilt validity checks to reduce incorrect date entry (E.g. selecting today's date as the date of visit; and preventing visit dates out of a set range).

Implementation of the application was not without challenges. Patient-level challenges were related to lack of proficiency in receiving text messages, in understanding the content of the messages and in replying to text messages with their secret pin. Patient-level challenges with retrieving laboratory results through mobile applications have been reported in other studies and were ascribed to literacy levels and familiarity with using a mobile phone [17]. In a study done in Uganda, persons who were not concerned about confidentiality of receiving results via text message and who were illiterate approached a person they trusted to read their results for them [18]. However, these patient-level challenges may be overcome with improved patient instruction or instructional aids. In addition, proficiency in the use of mobile phone applications will improve as society increasingly adopts mobile technology. This, along with the qualitative satisfaction in the use of the application by the majority of our participants, suggests that the added value of the application outweighs obstacles created by patient-level challenges.

This was a pilot study in two clinics using the mHealth application in parallel with the TCP paper case investigation register. Thus, the generalizability to wider use and to system deployment in the absence of a paper-based register cannot be directly inferred from the study. However, we believe that dispensing with the paper register will increase efficiency without compromising care or programmatic TB reporting. Notably, the mHealth application was able to sustain TB evaluation and management in two busy public sector primary care clinics whilst simultaneously being fully operational by public sector staff.

In conclusion, we have demonstrated that the mHealth application tested in this study may take the place of current paper-based TCP case-finding tools, and may have potential to substantially reduce the time to TB treatment initiation, improve TCP management, identify persons with delay in TB treatment initiation and empower patients with direct receipt of TB results. Implementation of an mHealth application to support and improve the TB care has the potential to substantially improve treatment indicators and patient-level outcomes and large-scale evaluations of this technology are urgently required.

Supporting information

S1 Table. Minimal dataset for variables reported in the pre-implementation period.
(CSV)

S2 Table. Minimal dataset for variables reported in the implementation period.
(CSV)

S1 Text. Data dictionary–Variable names, description and value labels for pre-implementation period.
(TXT)

S2 Text. Data dictionary–Variable names, description and value labels for implementation period.
(TXT)

Acknowledgments

We would like to thank Simphiwe Ntshuntshe, Lebohang Masia and Fikile Khoza for assisting with the data collection during the study. We would also like to thank all the clinic staff and the participants of the study.

Author Contributions

Conceptualization: Christopher J. Hoffmann, Violet N. Chihota, Larry W. Chang, Nazir Ismail, Gavin J. Churchyard, Kerrigan McCarthy.

Data curation: Noriah Maraba, Christopher J. Hoffmann, Violet N. Chihota, Kerrigan McCarthy.

Formal analysis: Noriah Maraba.

Funding acquisition: Christopher J. Hoffmann, Violet N. Chihota, Larry W. Chang, Gavin J. Churchyard, Kerrigan McCarthy.

Methodology: Noriah Maraba, Christopher J. Hoffmann, Violet N. Chihota, Kerrigan McCarthy.

Project administration: Noriah Maraba.

Resources: Edwin Madibogo.

Software: Noriah Maraba, Nazir Ismail, Sue Candy, Edwin Madibogo, Marc Katzwinkel, Kerrigan McCarthy.

Supervision: Christopher J. Hoffmann, Violet N. Chihota, Kerrigan McCarthy.

Writing – original draft: Noriah Maraba.

Writing – review & editing: Noriah Maraba, Christopher J. Hoffmann, Violet N. Chihota, Larry W. Chang, Nazir Ismail, Sue Candy, Edwin Madibogo, Marc Katzwinkel, Gavin J. Churchyard, Kerrigan McCarthy.

References

1. World Health Organization. Global Tuberculosis Report. (2015). [cited 30 September 2016]. Available from: http://www.who.int/tb/publications/global_report/gtbr15_main_text.pdf.
2. Wood R, Johnstone-Robertson S, Uys P, Hargrove J, Middelkoop K, Lawn SD, et al. (2010) Tuberculosis transmission to young children in a South African community: modeling household and community infection risks. Clin Infect Dis 51: 401–408. https://doi.org/10.1086/655129 PMID: 20604716
3. Botha E, Den Boon S, Verver S, Dunbar R, Lawrence KA, Bosman M, et al. (2008) Initial default from tuberculosis treatment: how often does it happen and what are the reasons? Int J Tuberc Lung Dis 12: 820–823. PMID: 18544210
4. Claassens MM, du Toit E, Dunbar R, Lombard C, Enarson DA, Beyers N, et al. (2013) Tuberculosis patients in primary care do not start treatment. What role do health system delays play? Int J Tuberc Lung Dis 17: 603–607. https://doi.org/10.5588/ijtld.12.0505 PMID: 23575324
5. Mwansa-Kambafwile J, Maitshotlo B, Black A. (2017) Microbiologically Confirmed Tuberculosis: Factors Associated with Pre-Treatment Loss to Follow-Up, and Time to Treatment Initiation. PLoS One 12: e0168659. https://doi.org/10.1371/journal.pone.0168659 PMID: 28068347
6. MacPherson P, Houben RM, Glynn JR, Corbett EL, Kranzer K. (2014) Pre-treatment loss to follow-up in tuberculosis patients in low- and lower-middle-income countries and high-burden countries: a systematic review and meta-analysis. Bull World Health Organ 92: 126–138. https://doi.org/10.2471/BLT.13.124800 PMID: 24623906
7. Gurol-Urganci I, de Jongh T, Vodopivec-Jamsek V, Car J, Atun R. (2012) Mobile phone messaging for communicating results of medical investigations. Cochrane Database Syst Rev: CD007456. https://doi.org/10.1002/14651858.CD007456.pub2 PMID: 22696369
8. Menon-Johansson AS, McNaught F, Mandalia S, Sullivan AK. (2006) Texting decreases the time to treatment for genital Chlamydia trachomatis infection. Sex Transm Infect 82: 49–51. https://doi.org/10.1136/sti.2004.014381 PMID: 16461603
9. Hirsch-Moverman Y, Daftary A, Yuengling KA, Saito S, Ntoane M, Frederix K, et al. (2017) Using mHealth for HIV/TB Treatment Support in Lesotho: Enhancing Patient-Provider Communication in the START Study. J Acquir Immune Defic Syndr 74 Suppl 1: S37–S43. https://doi.org/10.1097/QAI.0000000000001202 PMID: 27930610

10. May C, Finch T, Mair F, Ballini L, Dowrick C, Eccles M, et al. (2007) Understanding the implementation of complex interventions in health care: the normalization process model. BMC Health Serv Res 7: 148. https://doi.org/10.1186/1472-6963-7-148 PMID: 17880693

11. Murray E, Treweek S, Pope C, MacFarlane A, Ballini L, Dowrick C, et al. (2010) Normalisation process theory: a framework for developing, evaluating and implementing complex interventions. BMC Med 8: 63. https://doi.org/10.1186/1741-7015-8-63 PMID: 20961442

12. Asiimwe C, Kyabayinze DJ, Kyalisiima Z, Nabakooza J, Bajabaite M, Counihan H, et al. (2012) Early experiences on the feasibility, acceptability, and use of malaria rapid diagnostic tests at peripheral health centres in Uganda-insights into some barriers and facilitators. Implement Sci 7: 5. https://doi.org/10.1186/1748-5908-7-5 PMID: 22269037

13. Ansbro EM, Gill MM, Reynolds J, Shelley KD, Strasser S, Sripipatana T, et al. (2015) Introduction of Syphilis Point-of-Care Tests, from Pilot Study to National Programme Implementation in Zambia: A Qualitative Study of Healthcare Workers' Perspectives on Testing, Training and Quality Assurance. PLoS One 10: e0127728.

14. South Africa National Department of Health. Tuberculosis Management Guidelines. 2014. [cited 1 July2017]. Available from: https://www.idealclinic.org.za/docs/National-Priority-Health-Conditions/National%20TB%20management%20guidelines%202014.pdf.

15. Churchyard GJ, Stevens WS, Mametja LD, McCarthy KM, Chihota V, Nicol MP, et al. (2015) Xpert MTB/RIF versus sputum microscopy as the initial diagnostic test for tuberculosis: a cluster-randomised trial embedded in South African roll-out of Xpert MTB/RIF. Lancet Glob Health 3: e450–457. https://doi.org/10.1016/S2214-109X(15)00100-X PMID: 26187490

16. Jian WS, Hsu MH, Sukati H, Syed-Abdul S, Scholl J, Dube N, et al. (2012) LabPush: a pilot study of providing remote clinics with laboratory results via short message service (SMS) in Swaziland, Africa. PLoS One 7: e44462. https://doi.org/10.1371/journal.pone.0044462 PMID: 23028543

17. Siedner MJ, Santorino D, Haberer JE, Bangsberg DR (2015) Know your audience: predictors of success for a patient-centered texting app to augment linkage to HIV care in rural Uganda. J Med Internet Res 17: e78. https://doi.org/10.2196/jmir.3859 PMID: 25831269

18. Siedner MJ, Haberer JE, Bwana MB, Ware NC, Bangsberg DR. (2012) High acceptability for cell phone text messages to improve communication of laboratory results with HIV-infected patients in rural Uganda: a cross-sectional survey study. BMC Med Inform Decis Mak 12: 56. https://doi.org/10.1186/1472-6947-12-56 PMID: 22720901

0505275f:Intergrative_narrative_re_exam_23Jan2020_clean.doc.

ORIGINALITY REPORT

20%	18%	16%	%
SIMILARITY INDEX	INTERNET SOURCES	PUBLICATIONS	STUDENT PAPERS

PRIMARY SOURCES

1	researchonline.lshtm.ac.uk Internet Source	3%
2	act4tbhiv.org Internet Source	3%
3	journals.plos.org Internet Source	3%
4	academic.oup.com Internet Source	1%
5	apps.who.int Internet Source	1%
6	hdl.handle.net Internet Source	1%
7	www.ncbi.nlm.nih.gov Internet Source	1%
8	Noriah Maraba, Violet Chihota, Kerrigan McCarthy, Gavin J Churchyard, Alison D Grant. "Linkage to care among adults being investigated for tuberculosis in South Africa:	<1%

R14/49 Ms Noriah Matabane et al

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M140847

NAME: (Principal Investigator)	Ms Noriah Matabane et al
DEPARTMENT:	School of Public Health Johannesburg, Mpumalanga and Gauteng PHCs
PROJECT TITLE:	Identifying Causes of Death and Piloting a Case Manager Strategy to Link Patients being Investigated for TB into HIV and TB Care in South Africa
DATE CONSIDERED:	29/08/2014
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Violet Chihota
APPROVED BY:	Professor P Cleaton-Jones, Chairperson, HREC (Medical)
DATE OF APPROVAL:	16/01/2015

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 Secretary in Room 10004, 10th floor, Senate House, University.
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**.

Principal Investigator Signature Date

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

Declaration: Student's contribution to articles and agreement of co-author(s)

I, [Noriah Maraba], student number [0505275F], declare that this Thesis is my own work and that I contributed adequately towards research findings published in the articles stated below which are included in my Thesis.

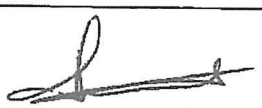
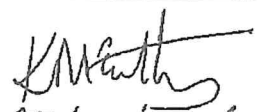
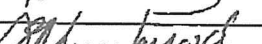
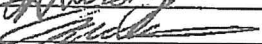
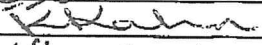
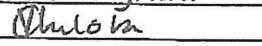
Signature of Student.....Maraba.....Date.....14 December 2018.....

Name of primary supervisor.....VIOLET CHIHOTA.....

Signature of primary supervisor .....Date.....23 November 2018.....

Agreement by co-authors: By signing this declaration, the co-authors listed below agree to the use of the article by the student as part of her Thesis. In cases where the student is not the 1st author of a published article, the primary supervisor must explain (under comments) why the student is entitled to use the paper for her degree purposes.

Article 1: Title: Verbal autopsy-assigned causes of death among adults being investigated for TB in South Africa. Transactional Royal Society of Tropical Medicine Hygiene 2016; 110: 510–516

Authors	Name	Signature	Date
1st Author	Noriah Maraba		
2nd Author	Aaron S Karat		25 October 2018
3rd Author	Kerrigan McCarthy		
4th Author	Gavin J Churchyard		
5th Author	Salome Charalambous		23 Nov 2018
6th Author	Kathleen Kahn		6December 2018
7th Author	Alison D Grant	Alison Grant	19 November 2018
8th Author	Violet Chihota		23 November 2018

Comments by primary supervisor:

.....

.....

Article 2: Title: Linkage to care among adults being investigated for tuberculosis in South Africa: pilot study of a case manager intervention BMJ Open 2018;8:e021111.

Authors	Name	Signature	Date
1st Author	Noriah Maraba		
2nd Author	Violet Chihota		23 November 2018
3rd Author	Kerrigan McCarthy		
4th Author	Gavin J Churchyard		
5th Author	Alison D Grant		19 November 2018

Comments by primary supervisor:

.....

.....

Article 4: Title: Experiences of patients, providers and case managers in linking adults into TB and HIV care: a qualitative study.

Authors	Name	Signature	Date
1st Author	Noriah Maraba		
2nd Author	Violet Chihota		23 November 2018
3rd Author	Sara Nieuwoudt		12 December, 2018
4th Author	Kerrigan McCarthy		
5th Author	Gavin J Churchyard		
6th Author	Alison D Grant		19 November 2018

Comments by primary supervisor:

.....

.....

5th Author	Alison D Grant		

Comments by primary supervisor:

.....

.....

Article 3: Title: Using mHealth to improve tuberculosis case identification and treatment initiation in South Africa: Results from a pilot study. PLoS ONE 13(7): e0199687.

Authors	Name	Signature	Date
1st Author	Norlah Maraba		
2nd Author	Christopher J Hoffmann		7 NOV 18
3rd Author	Violet Chihota		23 NOV 2018
4th Author	Larry W Chang		2 Nov 2018
5th Author	Nazir Ismail		2 November 2018
6th Author	Sue Candy		2 NOVEMBER 2018
7th Author	Edwin Madibogo		31 October 2018
8th Author	Marc Katzwinkel		01 NOVEMBER 2018
9th Author	Gavin J Churchyard		
10th Author	Kerrigan McCarthy		

Comments by primary supervisor:

.....

.....

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

FACULTY OF HEALTH SCIENCES

PLAGIARISM DECLARATION TO BE SIGNED BY ALL HIGHER DEGREE STUDENTS

SENATE PLAGIARISM POLICY: APPENDIX ONE

I Mosehle Noriah Maraba (Student number: 0505275F) am a student registered for the degree of Doctor of philosophy in the academic year 2020.

I hereby declare the following:

- I am aware that plagiarism (the use of someone else's work without their permission and/or without acknowledging the original source) is wrong.
- I confirm that the work submitted for assessment for the above degree is my own unaided work except where I have explicitly indicated otherwise.
- I have followed the required conventions in referencing the thoughts and ideas of others.
- I understand that the University of the Witwatersrand may take disciplinary action against me if there is a belief that this is not my own unaided work or that I have failed to acknowledge the source of the ideas or words in my writing.
- I have included as an appendix a report from "Turnitin" (or other approved plagiarism detection) software indicating the level of plagiarism in my research document.

Signature:  Date: 20-09-2020