TREATMENT OUTCOMES OF GENE XPERT POSITIVE TUBERCULOSIS PATIENTS IN KWAMASHU COMMUNITY HEALTH CENTRE, KWAZULU NATAL SOUTH AFRICA A RETROSPECTIVE REVIEW

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As the candidate's supervisor I have/have not approved this thesis for submission.

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Overview

Tuberculosis (TB) poses a huge burden of disease management in South Africa. The World Health Organisation (WHO) in 2018 estimated an incidence of 322000 cases of active TB. Furthermore, in 2014 the South African Department of Health estimated that 73% of TB patients were HIV co-infected. It is estimated that in the KwaMashu district of Durban alone, 39% of patients are HIV positive. The introduction of GeneXpert (GXP) testing in 2011 greatly improved the screening and prompt diagnosis of TB. This study serves as a quality improvement project, which will help identify predictors for a successful treatment outcome as outlined by the WHO case definitions. The number of patients co-infected with HIV at the KwaMashu Community Health Centre will also be reviewed, and further to this the proportion of patients who are on Anti-Retro Viral Therapy assessed.

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PART 1: BACKGROUND AND SIGNIFICANCE

Mycobacterium Tuberculosis Complex is a group of acid-fast bacilli belonging to the Mycobacterium genus. The Mycobacterium genus includes the Mycobacterium tuberculosis complex and Non-tuberculosis Mycobacteria. Mycobacterium tuberculosis (MTB) is the most common cause for disease within the Mycobacterium Tuberculosis complex. Other organisms within this group include Mycobacterium Bovis, Microti and Africanum. The Non-tuberculosis Mycobacteria include M. Kansasii, M Marinum and the Mycobacterium avium complex. (1)

M. Tuberculosis is a rod-shaped aerobic bacterium. It is considered an acid-fast bacillus as it is not decolourised by acid alcohol. This is due to its high content of mycolic acids and long chained cross-linked fatty acids. In the cell wall these mycolic acids are linked to peptidoglycan and arabinogalactan which results in low permeability of the cell wall, reducing the potency of antibiotics.

Lipoarabinomannan, another content of the cell wall, is involved in the pathogen – host interaction and aids with the survival of Mycobacterium Tuberculosis within macrophages. (1) Tests looking at the presence of mycobacterial lipoarabinomannan (LAM) antigen in urine have emerged as a possible diagnostic test in the fight against Mycobacterium Tuberculosis. (2) Mycobacterium Tuberculosis is transmitted predominantly via airborne droplet spread. Particles are 1-5 microns in diameter. (3) MTB most commonly affects the lungs. Extra-pulmonary disease can also occur. Common extrapulmonary sites of involvement include the central nervous system (CNS), lymphatics, pleura, pericardium and bones. Isolated extrapulmonary TB is non-contagious. (4) This study will focus on pulmonary tuberculosis.

In 2018 TB cases in South Africa were amongst the top two thirds of the global total with a 3% prevalence. (5) The disease continues to spread at an alarming rate. World Health Organization (WHO) statistics show that the incidence of TB has increased by 400% in 15yrs, with an estimated 322000 cases of active TB in 2018. (6) 193000 of the 322000 confirmed cases were co-infected with Human Immunodeficiency Virus (HIV). Latest South African government statistics have revealed TB HIV co-infection to be as high as 73 %. (7)

Provincially, in 2017 KwaZulu-Natal had an incidence of 58117 TB cases. There were 32855 cases of new smear positive and 9527 cases of recurrent TB. The incidence of pulmonary TB per 100000 patients was 907. This was the second highest incidence in South Africa that year. Western Cape recorded the highest incidence with 911 cases. However, KwaZulu-Natal had the highest incidence of all TB cases with 1076 per 100000 patients. (7)

In 2018 the WHO revealed that 10 million people worldwide were diagnosed with TB. Of these patients 1.2 million (11%) were co-infected with HIV. The worldwide TB mortality rate that year was 1.2 million individuals. 251000 of these patients were HIV positive. (5) In South Africa TB was the leading cause of death between 2013 to 2015. (8)

Furthermore, in South Africa there is an increased risk of infection due to household overcrowding, poor living conditions and migration. (9) As Andreas Diacon a pulmonologist at Tygerberg Hospital states, "*Our TB patients are practically living on top of each other, and many of them are malnourished, HIV positive and prone to alcohol abuse. Not only does crowding make it more likely that you'll be exposed to TB, but substance abuse also weakens your immune system.*" (10)

South Africa finds itself in a unique position due to the fact that many people migrated from rural areas and settled in areas known as townships across the country. One such township is Khayelitsha in the Western Cape. The population is estimated at 450-500000. (9) Forty five percent of the population is unemployed and approximately 30% live in informal housing. (11) The effects of poverty and overcrowding are evident if one looks at the TB statistics for this township. In 2005 Khayelitsha had 1283 per 100000 newly reported TB cases. (9)

This study will focus on patients from the KwaMashu area, a township similar to Khayelitsha in the Western Cape in certain respects. KwaMashu falls under the Northern central district of the eThekwini municipality in KwaZulu-Natal, South Africa. This district has a population of 476727 people. It includes the suburbs of Ntuzuma, Inanda, Newlands East, Newlands West, Lindilani, and Parlock. In 2012-2013 the Northern district was considered a 'hot spot' for the prevalence of HIV, which was estimated at 39 %. (12) (13)

The diagnosis of TB begins with good health education to recognise the symptoms of the disease. Patients presenting to primary health care facilities to screen for TB require accurate

diagnostic tests with good sensitivity and specificity. The KwaMashu Community Health Centre serves as the focal primary health care centre for many of the patients in this area. The community health centre serves an estimated population of 750000 people and also serves as a referral point for six satellite clinics and eleven mobile points. (14) The Ngubane Clinic within the KwaMashu health centre deals specifically with HIV patients on a daily basis. This study will focus on the predictors of a successful treatment outcome within this community.

The National Guidelines focus on the following diagnostic tests: sputum microscopy, sputum culture and Polymerase chain reactions (PCR) based assays namely XPERT-MTB RIF and line probe assay (LPA). (12) (Figure:1)

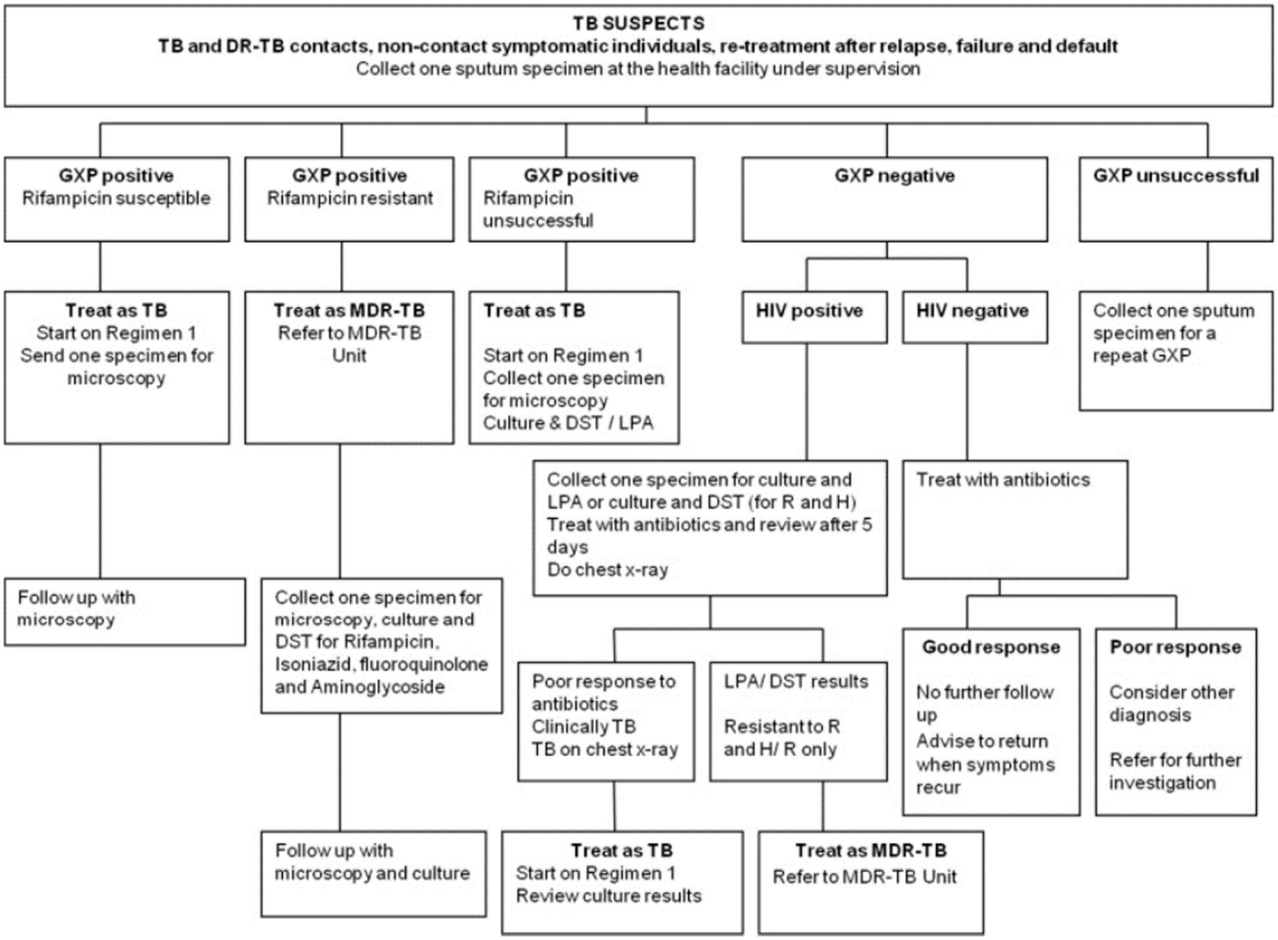

Figure:1 Gene Xpert MTB/RIF Algorithm (12)

With regard to microscopy the two staining methods are the Ziehl-Neelsen and the Fluorescent Auramine staining. Sputum microscopy demonstrates good specificity for TB. In HIV positive patients with non-cavitatary pulmonary disease or in patients with low bacillary load it

demonstrates a low sensitivity. Smear microscopy requires 10000 TB bacilli per ml of sputum to be detected positive. (15) Sputum microscopy does not distinguish between MTB complex and non-tuberculosis mycobacteria.

There are currently two molecular tests available to diagnose TB. The Gene- Xpert MTB/RIF and the line probe assay. Both are PCR based tests. The GeneXpert MTB/RIF is used to rapidly diagnose TB and to demonstrate rifampicin resistance. It detects resistance by targeting specific mutations in the rpoBgene mutation. Results may be available within two hours (15)

In 2013 the WHO guidelines recommend Gene-Xpert MTB-RIF to be used in all adults with suspected TB. In South Africa Gene-Xpert has replaced sputum microscopy as the initial diagnostic test for Tuberculosis. The South African MTB-RIF programme is the largest in the world, accounting for more than half of all GXP cartridges procured globally in 2013. (16)

GXP is more sensitive than smear microscopy. Only 150 bacilli per millilitre of sputum are needed to detect MTB. Smear microscopy will detect acid fast bacilli (AFB's) in 30% of HIV positive MTB complex, culture positive patients and 60-70% of HIV negative MTB complex culture positive patients. The Gene-Xpert will detect 98% of smear positive, culture positive MTB complex cases and 60-70% of smear negative, culture positive patients. Importantly the GXP will also detect only MTB complex and not non tuberculosis mycobacteria. (17) The test also has a short turnover time of 2 hours and it can be processed on the following specimens: cerebral spinal fluid, sputum, body fluids and tissue samples. There is also a decreased risk of cross contamination as the test is carried out within a closed system (15)

There are however, certain limitations of the GXP test. It cannot distinguish between live or dead bacilli and therefore cannot be used for follow up of patients on treatment. The test may be unsuccessful due to laboratory errors, test failure or invalid results. GXP is a molecular test which detects rifampicin resistance by testing for RPOB gene mutation. Rifampicin resistance detected may not correlate with physiological resistance leading to a disturbance between Xpert and culture results (15) (17)

South Africa was the first country to replace smear microscopy with Xpert MTB/RIF. (16) Churchyard *et al* looked at Xpert MTB/RIF versus sputum microscopy as the initial diagnostic test for tuberculosis. Xpert MTB/RIF resulted in a 50% increase in the number of

bacteriological confirmed cases of tuberculosis. This resulted in more patients assessing treatment at an earlier stage. (16) Internationally, Sachdeva *et al* looked at the utilisation of Xpert MTB/RIF in rural public health settings and its effect on pulmonary TB, and MDR case findings in India. (18) The study found that the use of Xpert MTB/RIF resulted in greater notification rates of bacteriologically confirmed TB cases and importantly the implementation of the Xpert MTB/RIF resulted in an over fivefold increase in the detection rate of rifampicin resistant TB cases. (18)

By April 2015 a total of 5 793 307 specimens were processed. The TB positivity rate has been shown to be 16-18% in the first year, 13-14% in the second and third year and 11% in the fourth year. Therefore, the GeneXpert test has a higher sensitivity compared to microscopy with a TB positivity rate of only 8%. In April 2015 KwaZulu-Natal had performed the greatest number of tests. In 2015 GeneXpert MTB/RIF statistics in KZN showed that 18284 tests confirmed MTB (8.45% total detected), 190800 specimens were undetected by the test and 7206 specimens were unsuccessful. A total of 216290 sputum samples were sent for analysis. This large total in comparison to other provinces is most likely as a result of the number of GXP testing instruments that are placed in KwaZulu-Natal. (19) A further reason could be the higher burden of disease in KwaZulu-Natal.

The LPA is the second molecular test used to diagnose TB. It also detects resistance to rifampicin and isoniazid. It can therefore reduce the time needed to diagnose MDR TB. It is also specific for MTB complex. However, like the Gene Xpert the test can only be used for diagnosis and not monitoring patients on treatment as it does not distinguish between live and dead bacilli. Also as mentioned with the Gene Expert, resistance detected may not correlate with physiological resistance. The test is also dependent on smear results and can only be performed on smear positive or culture positive sputum specimens. The test itself is also labour intensive and contamination and human error can occur. (15)

Even with advent of molecular based tests to detect MTB there still remains an important role for sputum culture results in the national diagnostic guidelines. Sputum culture is more sensitive than smear microscopy. It allows you to distinguish Mycobacterium tuberculosis from non-Mycobacterium Tuberculosis and to perform drug susceptibility testing. However, it is expensive and can only be reported as negative at the end of 6 weeks of incubation. Important indications for culture include the diagnosis of paucibacillary TB disease, drug susceptibility

testing in patients at high risk for MDR TB and in patients who remain smear positive at the end of the intensive or continuation phase of TB treatment.

Culture is still required for HIV positive TB suspects who have a negative GXP test. It is also required for those patients diagnosed as rifampicin resistant on GXP who require drug susceptibility testing (DST) of other drugs, and in patients diagnosed as rifampicin sensitive TB on GXP who are failing treatment despite good adherence and therefore resistance to drugs other than rifampicin is suspected. (15)

The National Tuberculosis management guidelines require patients to present at two months and five months to assess sputum microscopy for smear conversion (Figure 2). Reasons for non-conversion at the end of the intensive phase of TB treatment include the fact that non-viable bacteria may remain visible by microscopy. Other potential explanations for non-conversion of sputum smear at the end of the intensive phase of TB treatment are: poor supervision of the initial phase of therapy, poor patient adherence, poor quality of anti-TB drugs, under dosing of drugs, co-morbid conditions, drug-resistant *M. tuberculosis* that is not responding to first-line treatment and heavy initial bacillary load.(20) Singla *et al* reported that, "patients with numerous bacilli on pre-treatment sputum smear examination had an almost six times greater risk of persistent sputum positivity than patients with few bacilli". (21)(22) A further study also found that a higher pre-treatment smear grading and bilateral radiographic involvement were associated with the delay of smear conversion. (21) HIV status does not seem to influence sputum smear conversion rates. (23)

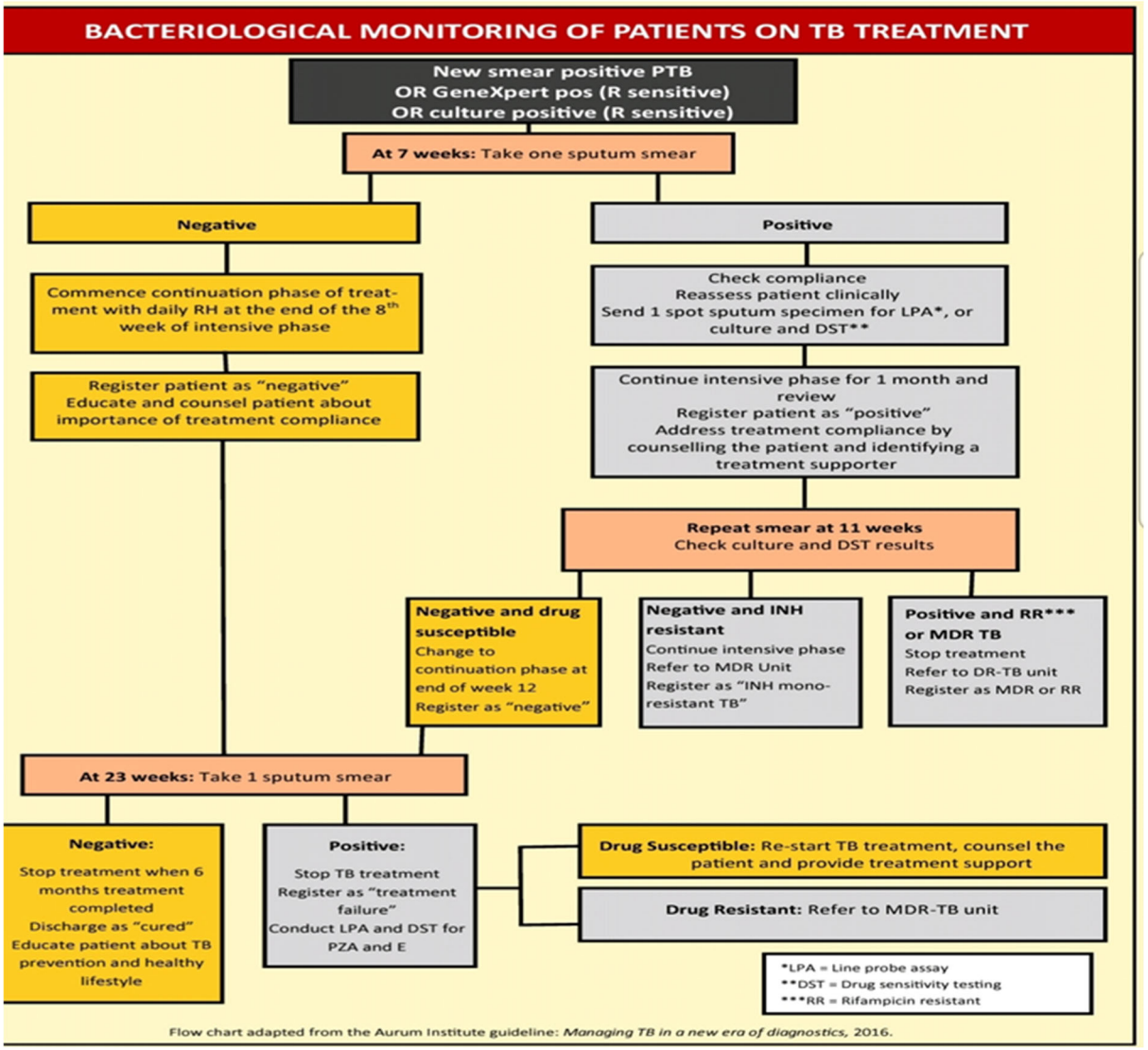

Figure:2 New Smear Positive, Drug sensitive TB Management (24)

The WHO has defined six treatment outcomes which have been adopted into the South African National Tuberculosis Guidelines. (Figure:3) (25). It has been argued that these treatment outcomes are best suited for countries with a high incidence of Tb. (26) Ditah *et al* further state that some of the outcomes are non- inclusive of patient care where treatment management needs to be individualised. (26) This could result in patients being misclassified as per the guidelines. This is a limitation that would need to be addressed in future guidelines. This study will be using the six treatment outcomes as per the WHO.

All bacteriologically confirmed and clinically diagnosed TB cases should be assigned an outcome from this list **except** those with RR-TB or MDR-TB, who are placed on a second-line drug regimen (see section A.2.2).

Outcome	Definition
Cured	A pulmonary TB patient with bacteriologically confirmed TB at the beginning of treatment who was smear- or culture-negative in the last month of treatment and on at least one previous occasion.
Treatment completed	A TB patient who completed treatment without evidence of failure BUT with no record to show that sputum smear or culture results in the last month of treatment and on at least one previous occasion were negative, either because tests were not done or because results are unavailable.
Treatment failed	A TB patient whose sputum smear or culture is positive at month 5 or later during treatment.
Died	A TB patient who dies for any reason before starting or during the course of treatment.
Lost to follow-up	A TB patient who did not start treatment or whose treatment was interrupted for 2 consecutive months or more.
Not evaluated	A TB patient for whom no treatment outcome is assigned. This includes cases "transferred out" to another treatment unit as well as cases for whom the treatment outcome is unknown to the reporting unit.
Treatment success	The sum of *cured* and *treatment completed*.

Figure: 3 WHO Treatment outcomes for TB patients (excluding Rifampicin resistance or MDR-TB) (25)

The WHO has also set a treatment success rate of at least 90% for persons diagnosed with TB. However, current data for new bacteriologically confirmed PTB cases indicates a decrease in treatment success rate from 86% in 2014 to 83% in 2017. (7,27) This study will focus on the predictors of successful treatment outcomes.

Establishing reasons for unsuccessful treatment outcomes is important for reducing morbidity and mortality and for implementing more effective treatment strategies. (27) Plans for distributing clinical guidelines are often dependent on access to information and teaching of the guidelines. Initiatives that audit and provide feedback to individuals regarding their own performance are found to be more effective in implementing guidelines. (28) This would assist in promoting compliance to national TB guidelines.

There are currently challenges faced in achieving successful treatment outcomes in TB patients in South Africa. One of the concerns is the lack of education among health care workers, regarding the treatment algorithm. The lack of education and training in many state facilities has severely hampered adherence to compliance. As Wondale *et al* state "*treatment outcomes are fundamentally dependant on the adherence to the treatment protocol which is also dependant on the knowledge and commitment of patients and health care workers.*" Patients living in poorly accessible and remote places could have a low level of knowledge that may contribute to poor treatment outcomes, (29) This is also relevant in a South African setting

where many patients live in remote, resource poor areas with a lack of education and health promotion. Furthermore, the lack of compliance to the TB algorithms and poor treatment outcomes has been compounded by the high frequency of staff rotations in hospital wards. (19)

There are also many other factors that contribute to unsuccessful treatment outcomes. Frederick *et al* quoted a study done in Lusaka where 45% of the TB patients were non-complaint with drug treatment for various reasons such as poor transportation to the hospital and lack of family support. (30) Other patient factors identified included low socioeconomic class, poor accessibility to health care facilities, stigma attached to TB and associated illness. (30) Another South African study conducted in the Eastern Cape by Cramm *et al* in 2010 found that the stigma associated with a TB diagnosis may hinder a patients decision to seek medical assistance as well as remain compliant to TB treatment. The study also showed that TB/HIV co-infection may result in further stigmatization. (31)(32) Another important factor resulting in non-adherence is an initial improvement after commencing TB treatment. This results in patients having a misconception that they have been cured and not continuing their course of treatment and follow up visits. (30)

In a South African context, further challenges as highlighted by Wendy Stevens include improving linkages to care and focusing on populations at high risk. This includes patients from correctional services, miners and those diagnosed with MDR TB. (33) Ditah *et al* also found that male sex, the elderly and sputum + PTB patients had worse treatment outcomes. (26) Another study conducted in Harar Town, Ethiopia also found that male sex and age > 65 was associated with unsuccessful treatment outcomes. (34) This was further supported by a study conducted in Adis Adaba that showed that older age groups were associated with worse outcomes. (35)

Possible reasons for poor outcomes in the elderly could include associated comorbidities in the elderly, physical deterioration due to the ageing process and less accessibility to health care facilities in the elderly as compared to the younger age groups. (35) Improving accessibility to health care for the elderly could be an important means of improving treatment outcomes.

TB/HIV co-infection has also been associated with worse treatment outcomes. HIV predisposes to TB infection and also worsens outcomes. HIV/TB co-infection resulted in an increased incidence of treatment failure in a study done in Eastern Ethiopia. (36). This was

also supported by other studies from Nairobi, Gambella Region, Dire Dare, Assela and Harar Town were TB/HIV co-infection resulted in worse treatment outcomes. (37,38,39,40,41). This could be due to the increased pill burden associated with HIV/TB co-infection as well as the increased mortality associated with the two conditions. (42). Strengthening health education and improving adherence to treatment with possible directly observed treatment regimens in this patient population could assist with improving treatment outcomes in a South African setting where we have a large population of patients that are co-infected with HIV and TB.

Improving technical and clinical training among health care workers would also be important. Stevens also points out that the GeneXpert MTB/RIF diagnostic algorithm may require simplification. The diagnostic arm for HIV-positive patients found to be Xpert MTB/RIF negative may need to be reviewed. A simplified algorithm may result in better compliance to guidelines. (33)

This study will aim to assess treatment outcomes as per the National Tuberculosis GeneXpert MTB/RIF guidelines. There is currently limited data regarding treatment outcomes as per the guidelines. It is hoped that this study will also serve as a quality improvement project by identifying the possible reasons for non-compliance and proposing possible further areas for developments within the guidelines.

Quality Improvement projects can help improve the health care system in South Africa. As Muller states, "*A person's health is one of the most important assets -therefore health care delivery should be of the highest quality*." He also states, "*Quality in health care can be based largely on the quality of professional training and education*." (43) An example of a quality improvement project was undertaken by Scott *et. al.* that helped improve the diagnosis and management of TB patients in the Western Cape, South Africa. Data was collected for the study by conducting interviews with facility managers, auditing available equipment at various facilities and through the review of patient folders. The data was then reviewed and action plans were then formulated to address key problem areas. Successful strategies and lessons learnt were then shared to other health care workers. (44)

It is hoped that the data from this study will improve TB management and treatment outcomes at the local community health centre in KwaMashu a township in Durban, South Africa. This area is currently a hotbed for TB and HIV co-infection. This study will help identify factors

associated with poor treatment outcomes. This would then improve the diagnosis and management of patients with TB and therefore aid with the fight against the Tuberculosis epidemic in the country. This study could then serve as a quality improvement project that can hopefully be extrapolated onto a bigger scale and promote similar studies to be undertaken at other institutes in South Africa.

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PART 2: A SUBMISSION READY MANUSCRIPT

Treatment outcomes of Gene Xpert positive Tuberculosis patients in KwaMashu Community Health Centre, KwaZulu Natal South Africa-A retrospective review

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Abstract

Background.

Understanding the clinical reasons for unsuccessful treatment outcomes for patients presenting with Tuberculosis (TB) is important for evaluating the effectiveness of TB control programs. Unsuccessful treatment outcomes for TB patients in this study is defined according to the World Health Organization (WHO) treatment outcome definitions as patients who died, failed treatment, were lost to follow up, or not evaluated[1]. Here, we sought to investigate the relationship between TB treatment outcomes and its predictors in the KwaMashu region in Kwazulu-Natal (KZN). This area is currently a hotbed for TB and HIV co-infection.

Method

A retrospective study design was adopted to characterise adult patients diagnosed with Gene Expert (GXP) positive pulmonary TB at KwaMashu Community Health Centre from 1 January 2016- 31 December 2017. TB treatment outcomes were assessed according to the WHO guidelines. Multiple logistic regression was used to explore determinants of unsuccessful treatment outcomes.

Results

Among the 596 TB patients diagnosed, the successful outcomes included 51.01% (n = 304) of cases cured, 6.38 % (n = 38) completed treatment. The overall treatment success rate was 57.38% whereas unsuccessful treatment outcomes were evident by 0.50% (n = 3) patients who died, 22.32% (n = 133) who were lost to follow-up and 10.91% (n = 65) who were unaccounted for. Sputum conversion at two months [AOR = 1.94 (1.27 – 2.96)] was significantly associated with unsuccessful treatment outcomes.

Conclusion

Treatment success rate was 57.38% which was below the success target set by the WHO. This proportion may be increased by regular follow-up of patients with poor treatment outcomes, by strengthening treatment adherence strategies and the provision of health information on TB treatment to patients from rural areas. This study also highlights the high rates of loss to follow up and unaccounted for patients during the six months of treatment follow up. This underscores the urgent need to aggressively follow-up treatment defaulters and design interventions to improve retention in care to improve treatment outcomes.

Keywords: *Tuberculosis, Sputum conversion, unsuccessful treatment outcomes*

INTRODUCTION

What is known?

In 2018, an estimated 10 million people globally were diagnosed with TB with the burden being heterogenous among countries. Of these patients 1.2 million (11%) were co-infected with Human Immunodeficiency Virus (HIV). The worldwide TB mortality was 1.2 million among HIV negative individuals and in addition 251000 deaths in HIV positive patients[2]. The highest TB burden was reportedly in men (aged ≥ 15 years) with 57% being diagnosed in 2018. Comparatively women accounted for 32% of the cases while children (aged < 15 years) accounted for 11%.[2] Geographically, 30 high TB burden countries collectively account for 87% of the word cases in 2018.[3] South Africa has featured amongst the top two thirds of the global total with a 3% prevalence rate.[2]

Considerable efforts have been mounted in the past decade to improve TB treatment outcomes and cure rates in South Africa. However, South Africa's national treatment's success rate of 76% is still below the WHO success rate of 90%. The country did not achieve the highly ambitious millennium development goals (MDG) target of halving its prevalence rate and mortality rate[4]. In 2017, South Africa reported an incidence of 322000 TB cases, of these cases 193000 (60%) were HIV positive. This highlights the need to continually strengthen existing TB control initiatives and also address patient comorbidities in the country.

What is unknown?

Over a 5-year period (2011-2015) there has been a steady decline in the incidence rate of TB in South Africa, with 690 per 100 000 cases reported in 2012 compared to the 520 per 100 000 in 2015[5]. In 2015 the province of KwaZulu Natal out of all 9 provinces ranked as having the second highest incidence rate of TB with 685 per 100 000 population, however the most notable decline in the incidence rate has been in KwaZulu Natal over 5 years with a decrease from 1185 to 685 per 100 000 population between 2011 and 2015 respectively[6]. In 2017 the incidence cases in KwaZulu Natal were 58117 with almost half, 23059 cases reported from eThekwini municipality.

Despite a notable decline in the TB incidence rate both globally and within South Africa, TB still ranks in the top 10 causes of death worldwide[7]. Between 2014 and 2016 TB was the leading cause of death in South Africa[8]. Being a curable disease, it still claims 4400 lives daily. In an attempt to control the global burden of disease in 2000, the United Nations Millennium Development Goals (MDGs) aimed to "Stop the spread and reverse the incidence of the global TB epidemic by 2015", This goal was achieved between 2000-2013 and an estimated 37 million lives were saved[9]. Between 2000 and 2014 the annual incidence rate of TB fell by 1.5%. The Stop TB Partnership which aimed by 2015 to reduce the TB prevalence and mortality rates by 50% compared to 1990 were not achieved worldwide[10].

As per the WHO, TB treatment outcomes should be assessed annually at both national and district levels[11]. We sought to evaluate treatment outcomes in a high-risk population group and identify reasons for defaulting follow up. This will assist in achieving the Stop TB 90/90/90 targets and also assist South Africa in achieving a 90% success rate. The 90/90/90 target 'Is to identify at least 90% of all TB patients in the population that require treatment and place them on appropriate therapy, it aims to reach at least 90% of the key population groups and reach at least 90% treatment success through affordable treatment services, promoting adherence and social support'.[12]

METHODS

Study Setting

This was a facility based retrospective study conducted in KwaMashu Community Health Centre. KwaMashu Community Health Centre is situated in KwaMashu township ward 45 of the eThekwini district, KwaZulu Natal province in South Africa. The CHC offers health services to the community of Kwamashu. It has a total of 25 beds. Currently the centre serves mainly the KwaMashu community and surrounding areas, with a catchment population of approximately 750 000 people. It is also a referral centre for six satellite clinics, eleven mobile clinics and other facilities in Phoenix, Inanda, Ntuzuma, Newlands East and Newlands West, Lindelani, and Parlock. In 2012-2013 the Northern district was considered a 'hot spot' for the prevalence of HIV, which was estimated at 39 %[13,14].

Study design and data collection

A retrospective study design of adult patients (from 12 years and above) presenting at the KwaMashu community Health Center. Demographic and clinical data were retrieved from files of patients that presented between January 2016 to December 2017. Other data sources included provincial TB registers, patient treatment cards and laboratory registers. Individual patient notes were reviewed to supplement missing data or resolve discrepancies. TB treatment outcomes were reported and recorded according to the defined World Health Organization (WHO) outcome categories.

De-identified patient data including socio-economic and clinical characteristics were collected on a pretested standardized form and entered in an Excel 2013 (Microsoft Corporation, Redmond, USA) spreadsheet. Two individuals, independently cross-checked each entry for logical inconsistencies, invalid codes, omissions and improbable data by tabulating, summarizing and plotting variables with missing observations being excluded systematically.

Operational definitions of key terms as defined by the WHO[1]

Cured: An initially sputum smear-positive patient who is sputum smear/culture negative at or one month prior to, the completion of TB treatment and on at least one previous occasion at least 30 days prior

Treatment completed: A patient who's baseline sputum was positive and who has completed anti-TB treatment without evidence of failure but for whom sputum smear or culture results are not available in the last month of treatment and on at least one previous occasion.

Treatment success: The sum of patients who were declared 'cured' and those who had 'completed' treatment.

Treatment failure: A patient whose sputum smear or culture is positive at the fifth month of treatment or later during the course of treatment. Excluded in this definition are patients found to have multi-drug resistant tuberculosis at any point of time during the treatment.

Treatment defaulter/Lost to follow up: A patient who has been on treatment for at least four weeks and whose treatment was interrupted for two consecutive months or more.

Died: A patient who died for any reason during the course of treatment.

Transfer out: A patient who started treatment and was transferred to another treatment unit and for whom the treatment outcome is not known at the time of evaluation of treatment results.

Reporting of treatment outcomes/Operational definition

Treatment outcomes among patients were reported as recommended by the WHO and the International Union Against Tuberculosis and Lung Disease (IUATLD)[15]. Six outcomes categories defining the treatment outcomes were used. Successful outcomes were; cured and treatment completed whereas unsuccessful outcomes were treatment failure, loss to follow-up, death, and absence of evaluation.

Cured **(**Patient completing full course treatment with negative bacteriology result in the last treatment month), treatment completed (PTB positive patient who has completed treatment), treatment failure (PTB positive whose bacteriology result remains positive at six months), loss to follow-up (PTB positive patient whose treatment is interrupted for two consecutive months or more after registration), death (A PTB positive patient who died due to TB or other course during TB treatment)

Cured and treatment completed were summarized as treatment success whereas unsuccessful treatment outcome was represented by treatment failure, loss to follow-up, died and unaccountable.

Statistical Analysis

Data was analyzed in STATA 15 (Stata Corp LP, College Station, TX, USA). Summary statistics were presented, with continuous variables summarized with their mean and standard deviation (SD) whereas categorical variables summarized as counts and proportions (%). Simple logistic regression models were used to evaluate the relationship between unsuccessful treatment outcome (dependent variable) and the selected demographic and clinical variables. To determine the effect of predictors of unsuccessful treatment, unadjusted and adjusted odds ratios (AOR), 95% CI and p value were estimated for each predictor with a two-sided p value < 0.05 deemed statistically significant.

Ethical Statement

Ethical clearance and approval for the study was provided by the Biomedical Research Committee (BREC) in association with the University of KwaZulu Natal (BREC No BE509/16). Patients records were anonymized and de-identified before analysis with strict confidentiality of patient information prioritized.

RESULTS

Demographic and clinical characteristics

A total of 596 patients records were considered over the study period. Out of these cases 381 (63.9%) were males and 215 (36.1%) were females. A total of 360 (60.4%) of the patients examined were HIV positive with 250 (42%) recorded as being on antiretroviral treatment (ART). The 30 – 39 age range had the highest percentage (34.2%) of TB cases, followed by the 20 – 29 age range with (32.2%), 40 – 49 age range with 15.9%, 50 – 59 range with 7.6%, below 20 with 6.0% and above 60 with 4.0%. (Table 1 and Table 2)

Treatment outcomes

Treatment outcomes of new smear positive pulmonary tuberculosis patients as per the standard criteria are shown in Table 3. Among the 596 patients included in the study 51.01% (n = 304) were cured, 6.38% (n = 38) completed their treatment, 8.89% (n = 53) had treatment failure at five months, 22.32% (n = 133) were lost to follow-up, 0.50% (n = 3) died and 10.91% (65/596) of the patients treatment outcomes could not be accounted for.

Table 1: Demographic characteristics

Patient's Characteristics		Patients: n (%)
Gender	Male	381 (63.9)
	Female	215 (36.1)
HIV Status	Positive	360 (60.4)
	Negative	168 (28.2)
	Unknown	68 (11.41)
ART	Yes	250 (42.0)
	No	326 (54.7)
	Unknown	20 (3.36)
Age (years)	Below 20	36 (6.0)
	20 – 29	192 (32.2)
	30 – 39	204 (34.2)
	40 – 49	95 (15.9)
	50 – 59	45 (7.6)
	Above 60	24 (4.0)

Abbreviations used: HIV – Human immunodeficiency virus; ART - Antiretroviral therapy

Table 2: Clinical characteristics of participants by gender (n = 596)

Patient's Characteristics		Patients		
		Total: n (%)	Male, % (95% CI)	Female: % (95% CI)
Age	Below 20	36 (6.0)	3.4 (2.0 – 5.8)	10.7 (7.2 – 15.6)
	20 – 29	192 (32.2)	29.4 (25.0 – 34.2)	37.2 (31.0 – 43.9)
	30 – 39	204 (34.2)	37.0 (32.3 – 42.0)	29.3 (23.6 – 35.8)
	40 – 49	95 (15.9)	17.8 (14.3 – 22.0)	12.6 (8.7 – 17.7)

	50 – 59	45 (7.6)	7.9 (5.6 – 11.1)	7.0 (4.2 – 11.3)
	Above 60	24 (4.0)	4.5 (2.8 – 7.1)	3.2 (1.6 – 6.7)
HIV Status	Positive	360 (60.4)	54.1 (49.0 – 59.0)	71.6 (65.2 – 77.3)
	Negative	168 (28.2)	31.8 (27.3 – 36.6)	21.9 (16.8 – 27.9)
	Unknown	68 (11.41)	14.2 (11.0 – 18.1)	6.5 (3.9 – 10.7)
ART	Yes	250 (42.0)	36.7 (32.0 – 41.7)	51.2 (44.5 – 57.8)
	No	326 (54.7)	59.6 (54.5 – 64.4)	46.0 (39.5 – 52.8)
	Unknown	20 (3.36)	3.7 (2.2 – 6.1)	2.8 (1.3 – 6.1)
Diabetes mellitus	No	529 (96.5)	97.2 (94.8 – 98.5)	95.4 (91.4 – 97.6)
	Yes	18 (3.3)	2.9 (1.5 – 5.2)	4.1 (2.0 – 7.9)
	Unknown	1 (0.2)	0	0.5 (0.1 – 3.5)
Smear Microscopy result	Negative	236 (39.6)	37.8 (33.0 – 42.8)	42.8 (36.3 – 49.5)
	Positive	251 (42.1)	45.1 (40.1 – 50.2)	36.7 (30.5 – 43.4)
	Unknown	109 (18.3)	17.1 (13.6 – 21.2)	20.5 (15.6 – 26.4)

Abbreviations used: HIV – Human immunodeficiency virus; ART - Antiretroviral therapy

Table 3: Treatment outcomes of new smear positive pulmonary tuberculosis patients as per the standard criteria

Treatment outcomes	Patients n (%)	Total n (%)
Successful		342 (57.38)
- Cure	304 (51.01)	
- Treatment completed	38 (6.38)	
Unsuccessful		254 (42.62)
- Treatment failure	53 (8.89)	
- Treatment Defaulter	133 (22.32)	
- Died	3 (0.50)	
- Unaccountable	65 (10.91)	

World Health Organization and International Union Against Tuberculosis and Lung Disease Criteria

In univariate analysis, unknown HIV status [OR = 2.60 (1.32 – 5.14)] and sputum conversion at two months [OR = 1.88 (1.27 – 2.78)] were associated with unsuccessful treatment outcome.

Multivariate logistic regression analysis was used to explore treatment outcomes in the cohort study. The explanatory variables used in the regression model were gender, HIV status, ART, age, diabetes, and sputum conversion at two months.

After adjusting for possible confounding factors such as gender, ART, age and diabetes, both unknown HIV status [aOR = 4.94 (1.83 – 13.36)] and sputum conversion at two months [aOR = 1.94 (1.27 – 2.96)] were significantly associated with increased odds of unsuccessful treatment outcomes (Table 4)

Table 4: Predictors of Unsuccessful treatment outcomes - Multiple regression analysis

	Unadjusted Odds Ratio (95% CI)	P-value	Adjusted Odds Ratio	P-value
Gender				
Female *(Ref)*				
Male	1.04 (0.73, 1.49)	0.814	1.02 (0.66, 1.57)	0.941
HIV Status				
Negative *(Ref)*				
Positive	1.25 (0.85, 1.82)	0.257	1.59 (0.86, 2.97)	0.142
Unknown	2.60 (1.32, 5.14)	0.006	4.94 (1.83, 13.36)	0.002
ART				
No *(Ref)*				
Yes	0.84 (0.59 – 1.19)	0.333	0.70 (0.39, 1.23)	0.213
Unknown	0.67 (0.27 – 1.70)	0.402	0.35 (0.08, 1.42)	0.140
Age				
Below 20 *(Ref)*				
20 – 29	0.98 (0.46, 2.08)	0.952	1.09 (0.43, 2.77)	0.864
30 – 39	1.07 (0.50, 2.27)	0.862	1.11 (0.42, 2.93)	0.829
40 – 49	0.94 (0.42, 2.11)	0.880	0.96 (0.34, 2.72)	0.943
50 – 59	1.00 (0.39, 2.53)	1.000	1.23 (0.39, 3.93)	0.723
Above 60	1.50 (0.47, 4.76)	0.491	2.30 (0.46, 11.4)	0.309
Diabetes				
No *(Ref)*				
Yes	0.99 (0.37, 2.70)	0.996	0.72 (0.21, 2.46)	0.602
Sputum conversion 2 months				
No *(Ref)*				
Yes	1.88 (1.27, 2.78)	0.002	1.94 (1.27, 2.96)	0.002

Abbreviations used: HIV – Human immunodeficiency virus; ART - Antiretroviral therapy

DISCUSSION

In this retrospective study we assessed TB treatment outcomes and the plausible determinants of unsuccessful outcomes. The study findings revealed a higher percentage of TB cases among the age groups of 20-29 and 30-39. This is consistent with studies done in Mpumalanga South Africa, Northeast and Central Ethiopia[16,17,18]. In our study the disproportionate burden in the age groups 20-29 and 30-39 could be as a result of greater mobility attendant to this demographic group occasioned by social and economic ambitions. A further contributing factor within the South African population could be due to the high prevalence of HIV co-infection among this age groups[19]. This is in contrast to studies in China, Cambodia and Vietnam where patients were older than 55 years [20,21]. Diabetes, concomitant malignancies and other co-morbidities in the elderly may predispose the older population to TB infection, Similarly there may be an increase in reactivation TB in the elderly[22].Evidence alludes age to be an important factor in determining TB treatment outcomes[23,24,25,26]. However, no significant relationship was found between age and unsuccessful treatment outcome in our study.

The majority of patients in our study were male (63.9%). This is consistent with other international studies conducted in Malaysia (70.24%)[27], Cambodia, China, Vietnam

(69.1%)[21], Ethiopia (61.3%)[28] and Pakistan (51.7%)[29] which have noted a similar trend. This could be attributed to differential susceptibility to TB due to biological orientation, lower female notification rates as a result of socio-economic and cultural barriers in health care access and higher risk in males due to their high-risk exposure, substance abuse and social engagement[30].

A large proportion of the patients in this study (60.4%) were HIV positive, consistent with HIV and TB coinfection rates in South Africa[2]. CD4 cell counts and viral loads were not known in many patients. Of note, only 40% of the HIV positive patients were on ART. This is of concern as according to The Joint United Nations Programme on HIV/AIDS (UNAIDS) strategy to end HIV as a public health threat by 2030, 90% of all people living with HIV should know their HIV status, 90% of all patients diagnosed with HIV infection should receive sustained antiretroviral therapy and 90% of all people receiving antiretroviral therapy should have viral suppression by 2020[31]. With the institution of the "test and treat" campaign in 2016 together with the national TB guidelines it is of concern that there is a large number of patients who are not on ART[32,33]. Our study also revealed that 11% of patients were also unaware of their HIV status.

One of the determinants of an unsuccessful treatment outcome in this study was patients who did not know their HIV status. An opt out approach for HIV testing were HIV testing becomes a routine procedure as opposed to an opt in approach may result in less patients with HIV/TB co-infection being missed and allow for earlier diagnosis and treatment[34,35]. Patients diagnosed and initiated on treatment during the advanced stages of HIV could also have affected treatment outcomes[36].

Patients with higher CD4 cell counts and who are on ART have been shown to have more successful outcomes[37]. TB/HIV treatment in combination has been shown to improve treatment failure rates[38]. For patients who are HIV/TB coinfected and on ART the national rates have improved from 28% in 2011 to 89.1% in 2017[6]. In comparison to the national standards, our study showed a large proportion of HIV positive patients who were not on treatment. Stronger initiatives aimed at HIV testing and commencement of treatment especially in TB/HIV high risk areas will need to be employed to improve TB treatment outcome rates.

It is important to achieve and sustain acceptable levels of treatment success rates among TB patients[39]. The overall treatment success rate based on sputum smear positive TB cases was 57.38%. The cure rate was 51.01%. The treatment success rate obtained in our study is relatively higher than 40.6% in Uganda[40]. However, this was still low compared to the WHO successful target rate of 90%[12.] Countries which have succeeded in making this target are Ethiopia (91.8%)[41] and China (95.02%,93,9%)[20,42]. A systemic review and meta-analysis done in 7 Sub Saharan Africa countries showed a total TB success rate of 76%[43]. Two studies in Gauteng Province found success rates of 80%[44] and 83.48%[23]. The low TB success rate within our study is an indication of generally under performing and failing TB programme in resource constrained areas.

Other contributing factors might be our study's sample size, the study period, HIV status and health care quality. A possible reason for the higher success rates obtained in the Gauteng studies may be the inclusion of all TB patients regardless of smear status, extrapulmonary TB and children. Patients who were transferred out were also excluded from the Gauteng study.

There was also a large default group in our cohort. A large pill burden associated with HIV and TB coinfection as well as patients starting to feel better after initial treatment commencement may have resulted in patients defaulting treatment. The KwaMashu district remains an impoverished community with a high rate of unemployment. Financial factors in terms of accessing health care facilities and attending follow up visits may have also contributed to patients defaulting treatment.

A deeper understanding of factors associated with unsuccessful TB treatment outcomes can encourage appropriate interventions intended to reduce morbidity and mortality[45]. In this study, loss to follow-up 22.32% (n = 133) comprised a major portion of the unsuccessful outcome. Significantly lower rates were noted in a primary health care facility in Johannesburg (11%)[44], Gauteng province (5.4%)[23] and Ethiopia (8.5%)[18] Age, gender and not being on ART has shown to increase the risk for lost to follow up.[23] Several reasons related to our study participants and the health center may have contributed to the outcomes reported. It was noted in this study that patients were lost to follow up due to patient relocation, attempts were made by health care workers to trace patients through home visits and telephonic consultations. Social issues including alcohol and drug abuse as well as psychiatric conditions also contributed to patients being lost to follow up.

Sputum conversion at two months was significantly associated with unsuccessful TB treatment outcomes. These findings are inconsistent with studies widely reported in Western Cape, South Africa[46], Pakistan[29] and India[47]. A possible reason for this could be that a large proportion of the unsuccessful outcomes in our study were due to patients who were lost to follow up. Patients who had achieved sputum conversion at two months may have believed that they have been cured and thereafter defaulted further treatment and follow up. Future treatment and monitoring programs and strategies should aim to ensure that patients are followed up for the entire six months and that patients adhere strictly to treatment regimes.

Conclusion

Tuberculosis continues to be a serious health concern both in South Africa and internationally. The study findings showed the treatment success rate to be below the WHO target of 90%. Information about determinants of unsuccessful treatment outcomes is important for TB control initiatives. Findings have implications for TB programmes and future studies. KwaMashu a township in Durban, South Africa is currently a hotbed for TB and HIV co-infection. It is hoped that this data will help improve TB management in resource constraint settings. This study will help identify factors affecting unsuccessful treatment outcomes and would then improve the management of patients with TB. It could also then serve as a quality improvement project that can hopefully be extrapolated onto a bigger scale and promote similar studies to be undertaken at other TB endemic areas and regions.

Study limitations

Study results should be applied with caution, due to inherent limitations of registry-based data. Information on important variables such as HIV risk factors, hospitalization history was not identified.

Authors' contributions:

All authors contributed to the conception and design of the study. SP was responsible data collection and data entry. SP wrote the first draft of the paper under supervision by NPM. All authors revised and approved the final manuscript.

Conflict of interest

No conflict of interest

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Appendices

Appendix: 1 The final study protocol:

A RETROSPECTIVE REVIEW OF COMPLIANCE TO THE NATIONAL TUBERCULOSIS MANAGEMENT GUIDELINES: GENE XPERT MTB/RIF ALGORITHIM IN A PRIMARY HEALTH CARE CENTRE IN KWA-ZULU NATAL, SOUTH AFRICA

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CONTENTS

ABSTRACT

Background

Tuberculosis (TB) poses a huge burden of disease management in South Africa. The World Health Organisation (WHO) in 2013 estimated an incidence of 450,000 cases of active TB. Furthermore, in 2014 the South African Department of Health estimated that 73% of TB patients were HIV co-infected. It is estimated that in the KwaMashu district of Durban alone, 39% of patients are HIV positive (10). The introduction of GeneXpert (GXP) testing in 2011 greatly improved the screening and prompt diagnosis of TB. However, little is known of the compliance to these management guidelines and the GXP algorithm. This study aims to test compliance to the GeneXpert sputum guidelines. The number of patients co-infected with HIV at the KwaMashu Community Health Centre will also be reviewed

Methods

In this retrospective descriptive study the following categorical variables have been identified: age, gender, baseline sputum sample, two month sputum sample, five month sputum sample, HIV status, Diabetic status, compliance to sputum guidelines (Gene Xpert MTB RIF algorithm).

Independent variables include age, gender, baseline sputum sample, two month sputum sample, and five month sputum sample, HIV status and Diabetic status. The Dependent variable is compliance to sputum guidelines. Possible confounding variables are gender and age. Due to the source and nature of the data collection it is expected that missing values due both to patients who are lost to follow- up and human error will arise. To account for these values occurring not at the baseline level we will conduct imputation. A logistic regression using the aforementioned variables will be used to predict compliance.

Results

Discussion and Conclusion

PROBLEM STATEMENT

Overview

This study serves as a quality improvement project. As an initial step a hypothesis test will be conducted. This will form a clinical audit. The data will be collected by means of a question survey which will be completed by the staff at KwaMashu CHC who are involved in the TB sputum collections and data recording. This survey will test the staffs' knowledge of the GXP sputum guidelines. If the hypothesis test is found true it will serve as motivation for conducting this study and further quality improvement at KwaMashu CHC.

If however, the hypothesis test is found to be false and that in fact the staff at KwaMashu CHC are well educated on the GXP sputum guidelines, if required, further investigation should be undertaken to evaluate the reasons for non-compliance to guidelines.

Research Question/Hypothesis

The Staff at KwaMashu CHC lack the knowledge of the Gene Xpert MTB/RIF algorithm and are therefore not compliant to the National tuberculosis GXP guidelines.

SPECIFIC AIM AND OBJECTIVES

Specific Aims

To evaluate compliance to the National Tuberculosis Management Guidelines: Gene Xpert MTB/RIF Algorithm for patients presenting with GXP sputum positive Tuberculosis.

This Aim will be investigated by evaluating the following objectives:

- The number of patients who are Gene Xpert Positive who get a smear at base.
- The proportion of patients who have sputum collected at two months and 5 months.
    - The proportion of patients who have sputum collected at two months and 5 months who undergo smear conversion or develop drug resistance Tuberculosis.
- The proportion of patients diagnosed GXP positive Tuberculosis who are co-infected with HIV.
    - The number of HIV co-infected patients who achieve smear conversion or develop drug resistant Tuberculosis.
- To evaluate the knowledge of the GXP guidelines by the staff at KwaMashu Community Health Centre.
    - To Correlate staff knowledge with patient management at KwaMashu CHC

BACKGROUND AND SIGNIFICANCE

Mycobacterium Tuberculosis Complex is a group of acid fast bacilli belonging to the Mycobacterium genus. The Mycobacterium genus includes the Mycobacterium tuberculosis complex and Non-tuberculosis Mycobacteria. Mycobacterium tuberculosis (MTB) is the most common cause for disease within the Mycobacterium Tuberculosis complex. Other organisms within this group include Mycobacterium bovis, microti and africanum. The Non-tuberculosis Mycobacteria include M. Kansasii, M Marinum and the Mycobacterium avium complex. (1)
M. Tuberculosis is a rod shaped aerobic bacterium. It is considered an acid fast bacillus as it is not decolourised by acid alcohol. This is due to its high content of mycolic acids and long chained cross linked fatty acids. In the cell wall these mycolic acids are linked to peptidoglycan and arabinogalactan which results in low permeability of the cell wall, reducing the potency of antibiotics.

Lipoarabinomannan, another content of the cell wall, is involved in the pathogen – host interaction and aids with the survival of Mycobacterium Tuberculosis within macrophages. (1) Tests looking at the presence of mycobacterial lipoarabinomannan (LAM) antigen in urine have merged as a possible diagnostic test in the fight against Mycobacterium Tuberculosis. (2) Mycobacterium Tuberculosis is transmitted predominantly via airborne droplet spread. Particles are 1-5 microns in diameter. (3) MTB most commonly affects the lungs. Extra-pulmonary disease can also occur. Common extrapulmonary sites of involvement include the central nervous system (CNS), lymphatics, pleura, pericardium and bones. Isolated extrapulmonary TB is non-contagious. (4) This study will focus on pulmonary tuberculosis.

In 2013 South Africa had the third highest incidence of TB internationally. The disease continues to spread at an alarming rate. WHO statistics show that the incidence of TB has increased by 400% in 15yrs, with an estimated 450000 cases of active TB in 2013. 270000 of the 450000 cases were co-infected with HIV. Latest South African government statistics have revealed TB HIV co-infection to be as high as 73 %.(9)

Provincially, in 2006 KwaZulu-Natal had a total of 104705 cases of TB. Of that total 88271 were PTB cases. There were 32855 cases of new smear positive and 9527 cases of recurrent TB. The incidence of pulmonary TB per 100000 patients was 907. This was the second highest incidence in South Africa that year. Western Cape recorded the highest incidence with 911 cases. However, KwaZulu-Natal had the highest incidence of all TB cases with 1076 per 100000 patients. (9)

In 2014 the World Health Organization (WHO) revealed that 9.6 million people worldwide were diagnosed with TB. Of these patients 1.2 million were co-infected with Human Immunodeficiency Virus (HIV). The worldwide TB mortality rate that year was 1.5 million individuals. 400000 of these patients were HIV positive. (8) In South Africa TB was the leading cause of death between 2010 to 2012 for the population group 15 to 49. (9)

Furthermore, in South Africa there is an increased risk of infection due to household overcrowding, poor living conditions and migration. (5) As Andreas Diacon a pulmonologist at Tygerberg Hospital states, "Our TB patients are practically living on top of each other, and many of them are malnourished, HIV positive and prone to alcohol abuse. Not only does crowding make it more likely that you'll be exposed to TB, but substance abuse also weakens your immune system." (6)

South Africa finds itself in a unique position due to the fact that many people migrated from rural areas and settled in areas known as townships across the country. One such township is Khayelitsha in the Western Cape. The population is estimated at 450-500000. (5) Forty five percent of the population is unemployed and approximately 30% live in informal housing. (7) The effects of poverty and overcrowding are evident if one looks at the TB statistics for this township. In 2005 Khayelitsha had 1283/100000 population of newly reported TB cases. (5)

This study will focus on patients from the KwaMashu area, a township similar to Khayelitsha in the Western Cape in certain respects. KwaMashu falls under the Northern central district of the Ethekwini municipality in KwaZulu-Natal, South Africa. This district has a population of 476727 people. It includes the suburbs of Ntuzuma, Inanda, Newlands East and Newlands West, Lindilani, and Parlock. In 2012-2013 the Northern district was considered a 'hot spot' for the prevalence of HIV, which was estimated at 39 %. (10) (11)

The diagnosis of TB begins with good health education to recognise the symptoms of the disease. Patients presenting to primary health care facilities to screen for TB require accurate diagnostic tests with good sensitivity and specificity. The KwaMashu Community Health Centre serves as the focal primary health care centre for many of the patients in this area. The community health centre serves a population of about 750000 people and also serves as a referral point for six satellite clinic and eleven mobile points. (28) The Ngubane Clinic within the KwaMashu health centre deals specifically with HIV patients on a daily basis. This study will focus on compliance to national TB treatment guidelines from this focal point.

The National Guidelines focus on the following diagnostic tests: sputum microscopy, culture and Polymerase chain reactions (PCR) based assays namely XPERT-MTB RIF and line probe assay (LPA). (12) Once these diagnostic tests have been used the study will hope to ascertain whether the compliance thereafter to national guidelines is being adhered to.

With regard to microscopy the two staining methods are the Ziel-Neelsen and the Fluorescent Auramine staining. Sputum microscopy demonstrates good specificity for TB. In HIV positive patients with non-cavitatory pulmonary disease or in patients with low bacillary load it demonstrates a low sensitivity. Smear microscopy requires 10000 TB bacilli per ml of sputum to be detected positive. (12) Sputum microscopy does not distinguish between MTB complex and non-tuberculosis mycobacteria.

There are currently two molecular tests available to diagnose TB. The Gene- Xpert MTB/RIF and the line probe assay. Both are PCR based tests. The GeneXpert MTB/RIF is used to rapidly diagnose TB and to demonstrate rifampicin resistance. It detects resistance by targeting specific mutations in the rpoBgene mutation. Results may be available within two hours (12)

In 2013 the WHO guidelines recommend Gene-Xpert MTB-RIF to be used in all adults with suspected TB. In South Africa Gene-Xpert has replaced sputum microscopy as the initial diagnostic test for Tuberculosis. The South African MTB-RIF programme is the largest in the world, accounting for more than half of all GXP cartridges procured globally in 2013(13)

GXP is more sensitive than smear microscopy. Only 150 bacilli per millilitre of sputum are needed to detect MTB. Whereas smear microscopy will detect acid fast bacilli (AFB's) in 30% of HIV positive MTB complex, culture positive patients and 60-70% of HIV negative MTB complex culture positive patients. The Gene-Xpert will detect 98% of smear positive, culture positive MTB complex cases and 60-70% of smear negative, culture positive patients. Importantly the GXP will also detect only MTB complex and not non tuberculosis mycobacteria. (14) The test also has a short turnover time of 2 hours and it can be processed on the following specimens: cerebral spinal fluid, sputum, body fluids and tissue samples. There is also a decreased risk of cross contamination as the test is carried out within a closed system (12)

There are, however, certain limitations of the GXP test. It cannot distinguish between live or dead bacilli and therefore cannot be used for follow up of patients on treatment. The test may be unsuccessful due to laboratory errors, test failure or invalid results. GXP is a molecular test

which detects rifampicin resistance by testing for RPOB gene mutation. Rifampicin resistance detected may not correlate with physiological resistance leading to a disturbance between Xpert and culture results (12) (14)

South Africa was the first country to replace smear microscopy with Xpert MTB/RIF. (13) Churchyard *et al* looked at Xpert MTB/RIF versus sputum microscopy as the initial diagnostic test for tuberculosis. Xpert MTB/RIF resulted in a 50% increase in the number of bacteriological confirmation of tuberculosis. This resulted in more patients assessing treatment at an earlier stage. (13) Internationally, Sachdeva *et al* looked at the use of Xpert MTB/RIF in decentralized public health settings and its effect on pulmonary TB, and MDR case finding in India. (15) The study found that the implementation of Xpert MTB/RIF resulted in greater notification rates of bacteriologically confirmed TB cases and importantly the implementation of the Xpert MTB/RIF resulted in over fivefold increase in the detection rate of rifampicin resistant TB case detection. (15)

The LPA is the second molecular test used to diagnose TB. It also detects resistance to rifampicin and isoniazid. It can therefore reduce the time needed to diagnose MDR TB. It is also specific for MTB complex. However, like the Gene Xpert the test can only be used for diagnosis and not monitoring patients on treatment as it does not distinguish between live and dead bacilli. Also as mentioned with the Gene Expert, resistance detected may not correlate with physiological resistance. The test is also dependent on smear results and can only be performed on smear positive or culture positive sputum specimens. The test itself is also labour intensive and contamination and human error can occur. (12)

Even with advent of molecular based tests to detect MTB there still remains an important role for sputum culture results in the national diagnostic guidelines. Sputum culture is more sensitive than smear microscopy. It allows you to distinguish Mycobacterium tuberculosis from non-Mycobacterium Tuberculosis and to perform drug susceptibility testing. However it is expensive and can only be reported as negative at the end of 6 weeks of incubation.
Important indications for culture include the diagnosis of paucibacillary TB disease, drug susceptibility testing in patients at high risk for MDR TB and in patients who remain smear positive at the end of the intensive or continuation phase of TB treatment.

Culture is still required for HIV positive TB suspects who have a negative GXP test. It is also required for those patients diagnosed as rifampicin resistant on GXP who require drug suscessability testing (DST) of other drugs, and in patients diagnosed as rifampicin sensitive

TB on GXP who are failing treatment despite good adherence and therefore resistance to drugs other than rifampicin is suspected. (12)

The National tuberculosis management guidelines require patients to present at two months and five months to assess sputum microscopy for smear conversion. Reasons for non-conversion at the end of the intensive phase of TB treatment include the fact that non-viable bacteria may remain visible by microscopy. Other potential explanations for non-conversion of sputum smear at the end of the intensive phase of TB treatment are: poor supervision of the initial phase of therapy, poor patient adherence, poor quality of anti-TB drugs, under dosing of drugs, co-morbid conditions, drug-resistant *M. tuberculosis* that is not responding to first-line treatment and heavy initial bacillary load.(24) Singla *et al* reported that, "patients with numerous bacilli on pre-treatment sputum smear examination had an almost six times greater risk of persistent sputum positivity than patients with few bacilli". (25)(27) A further study also found that a higher pre-treatment smear grading and bilateral radiographic involvement were associated with the delay of smear conversion. (25) HIV status does not seem to influence sputum smear conversion rates. (26)

This study will focus on the compliance to sputum guidelines as set out in the National Tuberculosis Guidelines. There are many challenges faced in implementing national health guidelines. As Davis and Taylor-Vaisey described in a systematic review, "the characteristics of health professionals, practice setting, regulatory environment, incentives and patient factors play a role in converting guidelines into practice".(16)(17) Similarly, Cabana *et al* also found that the ignorance of the existence and content of guideline's existence common reasons for noncompliance. (17) (18)

This study also intends to serve as a quality improvement project. Plans for distributing clinical guidelines are often dependent on access to information and teaching of the guidelines. Initiatives that audit and provide feedback to individuals regarding their own performance are found to be more effective in implementing guidelines. (17) This would assist in promoting compliance to national TB guidelines.

There are currently challenges faced in implementing the GXP guidelines in South Africa. One of the concerns is the lack of education among health care workers, regarding the GXP testing algorithm. The lack of education and training in many state facilities has severely hampered adherence to compliance. Furthermore, the lack of compliance to the TB algorithms has been compounded by the high frequency of staff rotations in hospital wards. (19)

There is currently a lack of data on patient factors for non-compliance to GXP sputum guidelines. However, if one looks at patient factors responsible for non-compliance to TB treatment guidelines one would expect the reasons to be similar. Frederick *et al* quoted a study done in Lusaka where 45% of the TB patients are non-complaint with drug treatment for various reasons such as poor transportation to the hospital and lack of family support. (20) Other Patient factors identified include low socioeconomic class, poor accessibility to health care facilities, stigma attached to TB and associated illness. (20) Another South African study conducted in the Eastern Cape by Cramm *et al*. (2010) found that the associated stigma might influence TB patients' behaviour in seeking help and adhering to TB treatment. In the same study, the findings showed that people infected with TB had a tendency to hide their TB status out of fear of being stigmatised. This might be influenced by its association with HIV infection. (21)(22) Another important factor resulting in non-adherence is an initial improvement after commencing TB treatment. This results in patients having a false belief that they have been cured and not continuing their course of treatment and follow up visits. (20)

In a South African context, further challenges as highlighted by Wendy Stevens include improving linkages to care, and focusing on populations at high risk. This includes patients from correctional services, miners and those diagnosed with MDR TB. Improving technical and clinical training would also be important. Stevens also points out that the GeneXpert MTB/RIF diagnostic algorithm may require simplification. The diagnostic arm for HIV-positive patients found to be Xpert MTB/RIF negative may need to be reviewed. A simplified algorithm may result in better compliance to guidelines. (23)

Despite the challenges faced there has been great progress with the GeneXpert MTB/RIF programme. By April 2015 a total of 5 793 307 specimens were processed. The TB positivity rate has been shown to be 16-18% in the first year, 13-14% in the second and third year and 11% in the fourth year. This result shows the GeneXpert tests' higher sensitivity over microscopy with a TB positivity rate of only 8%. In April 2015 KwaZulu-Natal had performed the greatest number of tests. In 2015 GeneXpert MTB/RIF statistics in KZN showed that 18284 tests confirmed MTB (8.45% total detected), 190800 specimens were undetected by the test and 7206 specimens were unsuccessful. A total of 216290 sputum samples were sent for analysis. This large total in comparison to other provinces is most likely as a result of the number of GXP testing instruments that are placed in KwaZulu-Natal. (19) A further reason could be the higher burden of disease in KwaZulu-Natal.

This study will aim to test compliance to the national tuberculosis GeneXpert MTB/RIF guidelines. There is currently a paucity of data regarding compliance to these guidelines. It is hoped that this study will also serve as a quality improvement project by identifying the possible reasons for non-compliance and proposing possible further areas for developments within the guidelines.

Quality Improvement projects can help improve the health care system in South Africa. As Muller states, “A person's health is one of the most important assets -therefore health care delivery should be of the highest quality.” He also states, “Quality in health care can be based largely on the quality of professional training and education.” (30) An example of a quality improvement project was undertaken by Scott *et a*l that helped improve the diagnosis and management of TB patients in the Western Cape, South Africa. Data was collected for the study by conducting interviews with facility managers, auditing available equipment at various facilities and through the review of patient folders. The data was then reviewed and action plans were then formulated to address key problem areas. Successful strategies and lessons learnt were then shared to other health care workers. (31) It is hoped that this study will serve as a quality improvement project to help improve the compliance to the GXP sputum guidelines and therefore aid with the fight against the Tuberculosis epidemic in South Africa.

RESEARCH DESIGN AND METHODS

Overview

The study is a retrospective descriptive study. In this section, a brief overview of the population and study sample will be outlined. Then a sample size calculation will take place, which serves to motivate the current sample size used. The source of the data for the study will be described. The data management will be reviewed, before finally describing the data analysis strategies to be employed in the paper. In concluding this section the ethical considerations will be outlined and a general timeline will be advised for the duration of the study.

Population and Study Sample

For the purpose of this research study, the population group is restricted to adult patients (from 12 years and above) who have been diagnosed with sputum positive pulmonary Tuberculosis at KwaMashu Community Health Centre (Site 1). The sample period is inclusive of 1 January-31 December 2015. The population is filtered by a 2 week follow at the HIV/TB clinic (Ngobani Clinic, Site 2). This community has an estimated HIV population of 39%(10).

Sample Size and Selection of Sample

All patients from 1 January-31 December 2015 will be used. To test if this sample size would suffice for this study, a brief sample size calculation is utilised for each of the objectives. Different sample size calculations are necessary as the sample size requirements differ per type of variable (qualitative and quantitative).

For studies that will utilise proportions, a qualitative power calculation is necessary. Displayed below, a qualitative sample size formula is presented:

$$\frac{z^2{}_{1-\frac{\alpha}{2}} p(1-p)}{d^2}$$

- $z_{1-\frac{\alpha}{2}}$ is the standard normal variate where α is the probability of a type I error. For the purpose of this calculation, α = 0.05 will be used where Z = 1.96.
- P represents the expected proportion based on empirical evidence.
- “d” Represents the required precision or absolute error of the study.

For this study we can assume P = 0.4 and d = 0.05. Hence the required sample size for the is:

$$\frac{1.96^2 * 0.40 * (1 - 0.40)}{0.05^2} = 368.79 \cong 369\ patients$$

Sources of Data

The primary source of data consists of notebooks and patient files recorded by the attending nurses at the two sites.

At KwaMashu Community Health Centre initial sputum samples are collected and patients are screened for tuberculosis. These screening data books contain patient demographics (patients name; cell phone number; date of birth), HIV status, diabetic status, date of initial sputum sample, date patient followed up results and if commenced on treatment. These data books form sample one.

After receiving two weeks of treatment the patients move to the second site, the HIV/TB Clinic. Here the patient's folder will be used as data sample two. The data within these folders contain some of the information from sample one but also details the follow up visits, compliance to treatment, further sputum results and discharge information.

Data Management

A primary feature of a medical study is the use of paper records as the source data. The inherent risk introduced from this feature can introduce both bias and incompleteness to the sample data set. To reduce the bias and incompleteness due to human error; a well-defined data management plan is necessary. This plan needs to detail the controls to be exercised when capturing the manual records, reviewing the captured information and cleaning the final dataset for analysis.

In the following sections, the discussion of the data controls, treatment of incomplete records and cleaning of the dataset will be discussed.

Data Entry

The process of data entry is typically conducted by data capturers who are not cognisant of the purpose of the study or intended use of the data. As such the quality of the data captured can be adversely affected due to incorrect understanding of the required data types. Thus it is

imperative that a clear guideline is set up with respect to the capturing process. This is summarised below;

- Two data capturers need to be utilised
- One to transcribe the data and the other to check the transcribed data for errors
- All missing information needs to be typed as NULL
- The variable fields need to be clearly explained and labelled in the spread sheets.
- Formatting rules need to be applied to ensure only correct data types are captured.
- Uncertainty regarding records need to be highlighted and escalated to the researcher.
- Once all data is transcribed, random samples need to be drawn and rechecked by both the researcher and two data capturers to identify any errors or omissions.
- Once the researcher is content with the data capturing, a data signoff can occur.

Data Cleaning

The aim for the data cleaning protocol is to ensure that the raw data is consistent with the predefined variable types. This is to ensure occurrences of data type mismatch do not occur. Data cleaning has two procedural methods namely; correction (through direct editing) and deletion of the whole record.

Correction of specific categories can include recoding of characters as numbers such as “two” to “2”, “malee” to “male” etc. These errors could occur both from source and through data capturing. The aim of the data entry protocol is to ensure these errors are corrected on entry. A secondary error that could incur would be invalid records such as negative ages or ages beyond a designated band.

To identify these secondary entries, it is prudent to conduct descriptive analysis of the data. This would include take means of the data for numerical data types, medians and modes for categorical data types, and in addition, the creation of five number summaries for each variable. This basic summary of the data will allow for an immediate overview of available data and assist in the identification of any outliers in the data set. These outliers will include the secondary errors.

Data deletion, the complete removal of secondary error records, ensures that the data is internally consistent and can be correctly analysed without introducing bias and spurious results.

Missing/Incomplete Data

An inherent feature of manual case records is the occurrence of missing or incomplete records. As highlighted by Worster, two methods are typically employed in response to this phenomenon. The first is that of case deletion where the record is deleted from the dataset. The disadvantage from this method, is the sample size is reduced (the power as well) and bias may be introduced into the population. The alternative method frequently used (and the one employed in this study) is multiple imputation. This method utilises the existing data points to estimate the variance and covariances of the missing observations to generate parameter estimates and confidence intervals (29).

Data Analysis Strategies

The analysis of the data is required to be subdivided into two separate areas of focus. The necessity of this division stems from the underlying objectives forming two separate groups; the first covers the compliance of the clinics with Clinical Guidelines while the second deals with HIV and TB proportions.

The general analysis for a medical study consists of the analysis of categorical and numerical information. The inherent nature of these data types, lead to the calculation of proportions. To test if significant differences exist between proportions, a Chi Squared test is typically utilised. In conjunction to this test, to identify if there are differences in the means of the sample populations, a T-Test is typically employed. The combination of these two types of Hypothesis tests is sufficient to cover the scope of this study.

If the interest extends beyond proportional and mean comparison, and instead focuses on generating models that allow for the prediction of compliance; a regression model can be fitted. The regression model, models the relationship between a dependent variable and a list of independent variables in an attempt to explain the dependent variable. A multivariable regression model is termed a multiple regression model. This term is typically applied when the dependent variable is non-categorical or numeric. In a medical study however the variable of interest tends to be binary in nature. A regression model where the dependent variable is binary or categorical is termed a Logistic Regression Model.

Logistic Regression

One of the principal methods to be employed for the data analysis section is that of regression analysis. The intent is to develop a model that will allow for functional classification of sites in

terms of their compliance with clinic guidelines. To predict this binary response, a logistic model is necessary.

We have a dependent variable Y = compliance status
Y = 1 if compliant
Y = 0 if non-compliant
We are interested in the P(compliance) = P(Y=1) = p. Of particular interest to us, is how this dependent variable relates to the independent variables in the study. A typical linear regression model of form:

$$p = \beta_0 + \beta_1 x$$

Is not appropriate as for β values can lie between (-∞,∞) where as we want p to be between 0 and 1; the data that is analysed is not normally distributed and as such the normal theory underlying linear models is not appropriate and the variance for each individual is not constant. These reasons motivate the use of a logistic regression model where a transformation to "p" is applied:

$$logit(p) = \log(\frac{p}{1-p})$$

Our model is now represented by:

$$logit(p_i) = \log\left(\frac{p_i}{1-p_i}\right) = \sum_{k=1}^{k} \beta_k x_{ki} + \beta_0$$

Where the "i" subscript refers to each individual. The logistic regression model forms part of the generalized linear model family. The underlying distribution for this model is the binomial distribution.

After fitting the model and estimating the beta parameters, the significance can be tested. Either a confidence interval approach or standard T-Test can be used. With the null hypothesis of $\beta_j = 0$, the ratio of $(\beta_j)/se(\beta_j)$ can be computed and compared the relevant critical value. To compute a confidence interval at the 95% interval;

$$\hat{\beta}_j \mp 1.96 \times se(\hat{\beta}_j)$$

Finally if the interest is in the odds ratio rather than the $\hat{\beta}_j$, this can be computed as below:

$$\hat{\beta}_j = \log(OR)$$

$$OR = e^{\hat{\beta}_j}$$

Point-Biserial Correlation:

A hypothesis question has been formulated, 'The Staff at KwaMashu CHC lack the knowledge of the Gene Xpert MTB/RIF algorithm and are therefore not compliant to the National tuberculosis GXP guidelines.' This hypothesis will allow for the scope of the study to be correctly defined. The results from the questionnaires will permit motivation for conducting the study and aid in proving the specific aims. The hypothesis result would either be confirmatory or investigative. The correlation with the study results will help verify the study aims and form part of the quality improvement project. The hypothesis results will be correlated to the study results, this is to be tested by investigating the linear relationship between a questionnaire form (numeric variable) and the compliance factor (dichotomous variable).

A typical correlation cannot be used as it measures the relationship between two continuous variables. To allow for the presence of a binary variable, the adjusted correlation coefficient of the Point-Biserial Correlation is warranted. We will term this coefficient as r_{pb}. In a typical correlation format, -1 and 1 represent the range of values the coefficient can take. Where -1 and 1 represent perfect negative and positive correlation (and 0 represents no association).

The Point-Biserial Correlation coefficient like typical Pearson Correlation has two assumptions which need to be tested before the application of the technique namely; the continuous variable is normally distributed and homoscedasticity. It should be noted that an alternative to test the relationship between the above mentioned variables is a univariant logistic regression.

$$r_{bp} = ((M_1 - M_2) * p_1 p_2)/ZS_y$$

- Where $M_1$and M_2 are the means of the two groups.
- Where $p_1$and p_2 are the proportions of the two groups of the total.
- Where S_y is the standard deviation of the continuous variable as a whole.
- Where Z is the Z-score for p_1 or p_2 whichever is smaller.

Ethics and Human Subjects Issues

1. Scientific validity.

There is a paucity of data concerning the compliance to sputum guidelines, this study is not only scientifically valid but also a means of quality improvement.

2. Confidentiality

This is a retrospective chart review study. There will be no patient contact. Patients will be captured on the data collection tool using only their registration numbers.

The questionnaire conducted is also anonymous.

3. Informed Consent

Informed consent was not obtained for the study as it is a retrospective chart review. Informed consent was however obtained at the time of HIV testing.

4. Conflict of Interest

There is no conflict of interest.

Timelines:

- The 2 year degree of the MMED SCI was registered in March 2016.
- Proposal completion March 2016-August 2016
- Project Converted to MMED January 2017 (Registrar Post Internal Medicine)
- Submission to Biomedical Research Ethics Committee (BREC) for Ethics review February 2017
- Data Collection: June 2017-February 2018
- Data Analysis March 2018
- Write up of Articles March-June 2018

LIMITATIONS OF THE STUDY

Data limitations are imposed from censored data points. This will involve both patients who are lost to follow up and due to human error through documentation and record keeping. Bias can be introduced into the data from the fact that only one clinic is examined-this constricts the sample size and demographics of the population.

PUBLIC HEALTH SIGNIFICANCE

Tuberculosis continues to be a serious health concern both locally in South Africa and internationally. Many studies have been published with regard to the compliance to Tuberculosis treatment guidelines, however little is known about compliance to the GeneXpert sputum guidelines. Sputum collection forms the corner stone of TB diagnosis and further management. According to the South African guidelines, Gene-Xpert forms the initial investigation for the diagnosis of TB with South Africa having the largest Gene-Xpert rollout programme in the world. However, there currently is a paucity of data regarding compliance to the national Gene-Xpert sputum guidelines. Further research is required on this topic to help improve the diagnosis and management of patients with suspected TB. It is hoped that the data from this study will improve TB diagnosis and management at the local community health centre in KwaMashu a township in Durban, South Africa. This area is currently a hotbed for TB and HIV co-infection. This study will help identify compliance to the GeneXpert algorithm by staff at the health centre. This would then improve the diagnosis and management of patients with TB. This study could then serve as a quality improvement project that can hopefully be extrapolated onto a bigger scale and promote similar studies to be undertaken at other institutes in South Africa.

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APPENDICES

Appendix 1: Questionnaire

PLEASE CIRCLE THE CORRECT ANSWER

1. What is the initial sputum test you order for patients suspected to have Tuberculosis (TB)?

   (**A.** GXP or **B.** AFB's)

2. If your specimen for GXP is unsuccessful what sputum specimen do you send?

   (A. GXP or **B.** AFB's)

3. If the initial sputum test is GXP positive what is the second sputum test you send?

   (A. GXP or **B**. AFB'S)

4. Resistance to which drug/s can GXP pick up?

   (A. Rifampicin or **B**. Isoniazid or **C.** Both)

5. At which intervals do you repeat sputum tests while on treatment?

   (A. 2 months or **B**. 5 months or **C**. Both or **D**. 3 months)

6. With regards to follow up sputum, while on treatment, which sputum test do you order?

   (A. GXP or **B**. AFB's)

7. In a HIV positive patient who is suspected of having TB and the GXP sputum test is negative, what is the next test to be ordered?

   (**A**. GXP or **B**. AFB'S or **C**. Culture + LPA/DST)

8. If a patient is GXP positive and resistant to rifampicin, which sputum tests do you order?

   (**A**. GXP or **B**. AFB'S or **C**. Culture + LPA/DST or **D**. Both **B** and **C**)

*GXP (Gene Xpert); AFB (Acid Fast Bacilli); LPA/DST (Line Probe Assay/Drug Sensitivity Testing)

Information Sheet and Consent to Participate in Research

Date:

Hello/Sawubona

My name is Dr. S Pillay. I am a medical doctor working in the department of internal medicine at King Edward VIII Hospital. My contact number is 0313603111, Email: sarush.pillay@gmail.com .

You are being invited to consider participating in a study that involves in part a research questionnaire, based on your knowledge of the sputum Gene Xpert Algorithm. The aim of this research is to evaluate the compliance to the Gene Xpert algorithm at your clinic. The study is expected to enroll 30 staff members from the KwaMashu Community Health Centre. It will involve an 8 question questionnaire. It is an anonymous questionnaire. The questionnaire will take a few minutes of your time to complete and thereafter there is no further involvement on your part which is required.

We hope that this study will improve compliance to the sputum Gene Expert guidelines. This will help improve the diagnosis and management of patients suspected of having tuberculosis (TB). This study could then serve as a quality improvement project that can be implemented in other health facilities in South Africa.

This study has been ethically reviewed and approved by the UKZN Biomedical research Ethics Committee (approval number_____).

In the event of any problems or concerns/questions you may contact the researcher at Tel: 031 360 3111, Email: sarush.pillay@gmail.com or the UKZN Biomedical Research Ethics Committee, contact details as follows:

BIOMEDICAL RESEARCH ETHICS ADMINISTRATION
Research Office, Westville Campus
Govan Mbeki Building
Private Bag X 54001
Durban
4000
KwaZulu-Natal, SOUTH AFRICA
Tel: 27 31 2604769 - Fax: 27 31 2604609
Email: BREC@ukzn.ac.za

Your participation in this research is voluntary; you may withdraw your participation at any point. In the event of refusal/withdrawal of participation you will not incur any penalty or loss. Participants who are found to have duplicated other participants' answers to the questionnaire will be excluded from the study. No costs will be incurred by participants as a result of participation in this study.

The questionnaire is anonymous with no participant identifiers. The answers to the questions will be captured in an excel document with no participant identifiers. This data will then be analysed. Confidentiality will be maintained.

CONSENT

I_____have been informed about the study entitled: *A Retrospective review of compliance to the national Tuberculosis management guidelines: Gene Xpert MTB/RIF algorithm in a primary health care center in Kwa-Zulu Natal, South Africa* by Dr. S Pillay.

I understand the purpose of the study.

I have been given an opportunity to ask questions about the study and have had answers to my satisfaction.

I declare that my participation in this study is entirely voluntary and that I may withdraw at any time without any loss.

If I have any further questions/concerns or queries related to the study I understand that I may contact the researcher at Tel: 031 360 3111, Email: sarush.pillay@gmail.com.

If I have any questions or concerns about my rights as a study participant, or if I am concerned about an aspect of the study or the researchers then I may contact:

BIOMEDICAL RESEARCH ETHICS ADMINISTRATION
Research Office, Westville Campus
Govan Mbeki Building
Private Bag X 54001
Durban
4000
KwaZulu-Natal, SOUTH AFRICA
Tel: 27 31 2604769 - Fax: 27 31 2604609
Email: BREC@ukzn.ac.za

_____ _____
Signature of Participant **Date**

_____ _____
Signature of Witness **Date**
(Where applicable)

_____ _____
Signature of Translator **Date**
(Where applicable)

Appendix 2: Data Collection Tool

					HIV POPULATION						
1. DEMOGRAPHICS											
	Patient Registration number	Race	Gender	Age	HIV Positive	CD4 (cells/uL)	On HAART	HIV Negative	HIV Unknown	Diabetis Mellitus	
Legends		Black: 1	Male 1		Yes: 1	Blank: Not applicable		Yes: 1	Yes: 1	Yes: 1	
		Indian: 2	Female: 2		No: 0	0: Unknown		No: 0	No: 0	No: 0	
		Coloured: 3						Unknown:2		Unknown:2	
		White: 4									
		Unknown: 5									

2. INITIAL SPUTUM COLLECTION				
Date sputum collected	Result Date	GXP Result	Smear Microscopy result	Rifampicin resistant
		Detected:1	Pos:1	Yes: 1
		Undetected:2	Neg:0	No: 0
		Unsuccessful:0		Unsuccessful:2

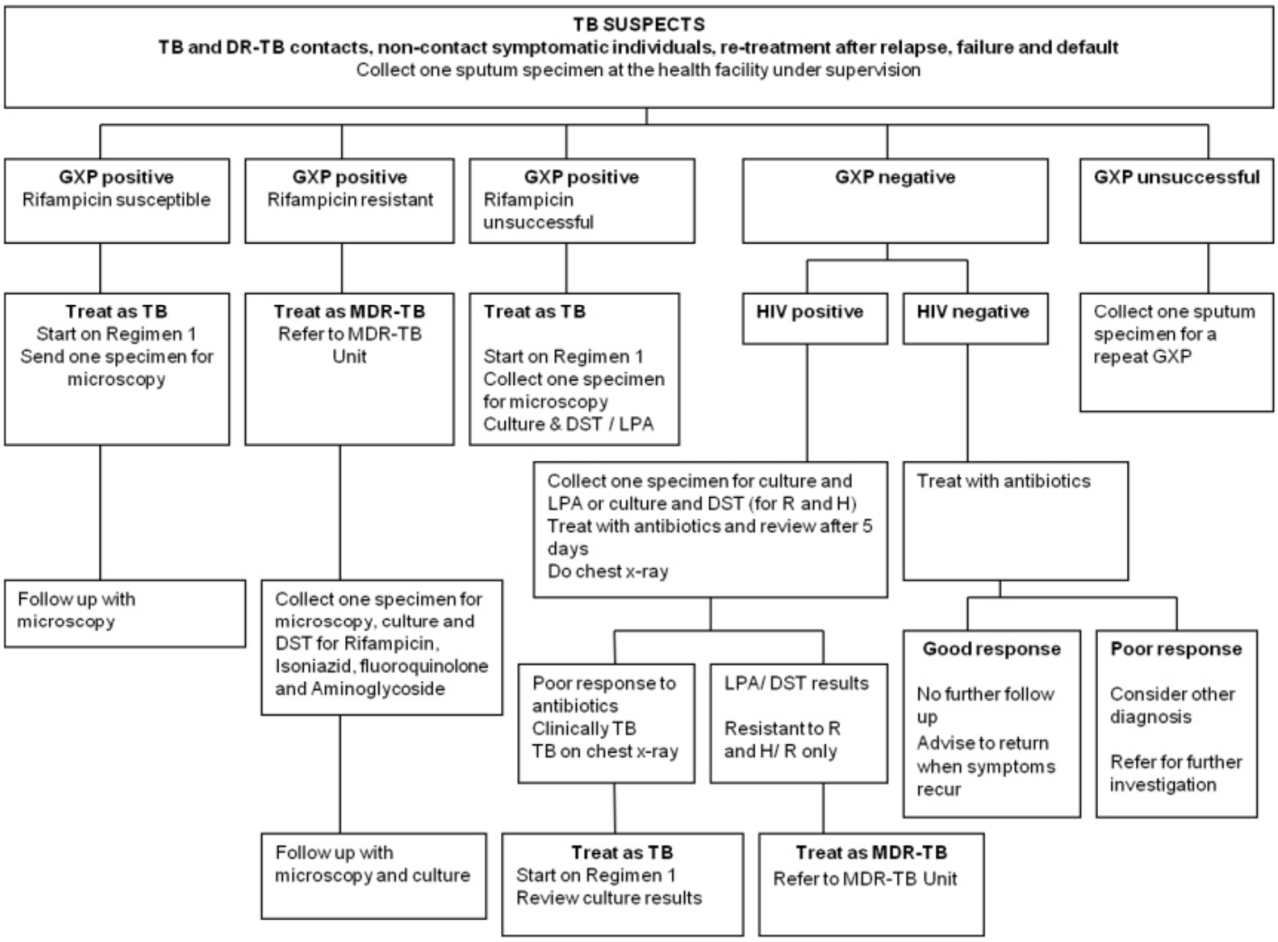
3. SPUTUM CULTURE			
Date Culture taken	TB Culture Result	Resistance INH/RIF	LPA/DST done
	Pos:1	RIF:1	LPA:1
	Neg:0	INH:0	DST:0
	Contaminated:2		

4 TUBERCULOSIS TREATMENT STARTED	
Treatment Started	**Lost to follow up**
Yes:1	Yes:1
No:0	No:0

5. FOLLOW UP SPUTUM	
Smear Microscopy taken at 2 months	**Smear Microscopy taken at 5 months**
Yes:1	Yes:1
No:0	No:0

6. OUTCOMEs				
Sputum Conversion 2/12	**Sputum Conversion 5/12**	**Defaulted follow up**	**Died**	**MDR TB**
Yes:1	Yes:1	Yes:1	Yes:1	Yes:1
No:0	No:0	No:0	No:0	No:0

Appendix 3: GeneXpert MTB/RIF Algorithm



Appendix 2: Ethics Approval

UNIVERSITY OF KWAZULU-NATAL
INYUVESI YAKWAZULU-NATALI

06 February 2016

Dr S Pillay (216076058)
Department of Medicine
School of Clinical Medicine
NRMSM
sarush.pillay@gmail.com

Dear Dr Pillay

Title: A retrospective review of the compliance to the National Tuberculosis Management guidelines: Gene Xpert MTB/RIF algorithm in a primary health care centre in KwaZulu-Natal, South Africa. Degree: MMedSc **BREC REF NO: BE509/16**

EXPEDITED APPLICATION

A sub-committee of the Biomedical Research Ethics Committee has considered and noted your application received on 08 September 2016.

The study was provisionally approved pending appropriate responses to queries raised. Your response received on 03 February 2017 to BREC letter dated 28 September 2016 have been noted by a sub-committee of the Biomedical Research Ethics Committee. The conditions have now been met and the study is given **full ethics approval** and may begin as from 06 February 2017.

This approval is valid for one year from **06 February 2017.** To ensure uninterrupted approval of this study beyond the approval expiry date, an application for recertification must be submitted to BREC on the appropriate BREC form 2-3 months before the expiry date.

Any amendments to this study, unless urgently required to ensure safety of participants, must be approved by BREC prior to implementation.

Your acceptance of this approval denotes your compliance with South African National Research Ethics Guidelines (2015), South African National Good Clinical Practice Guidelines (2006) (if applicable) and with UKZN BREC ethics requirements as contained in the UKZN BREC Terms of Reference and Standard Operating Procedures, all available at http://research.ukzn.ac.za/Research-Ethics/Biomedical-Research-Ethics.aspx.

BREC is registered with the South African National Health Research Ethics Council (REC-290408-009). BREC has US Office for Human Research Protections (OHRP) Federal-wide Assurance (FWA 678).

The sub-committee's decision will be **RATIFIED** by a full Committee at its next meeting taking place on **14 March 2017.**

We wish you well with this study. We would appreciate receiving copies of all publications arising out of this study.

Yours sincerely

Professor Joyce Tsoka-Gwegweni
Chair: Biomedical Research Ethics Committee

cc supervisor: [illegible] cc postgraduate officer: [illegible]

UNIVERSITY OF KWAZULU-NATAL
INYUVESI YAKWAZULU-NATALI

17 August 2020

Dr S Pillay (216076058)
Department of Medicine
School of Clinical Medicine
NRMSM
sarush.pillay@gmail.com

Dear Dr Pillay

Title: A retrospective review of the compliance to the National Tuberculosis Management guidelines: Gene Xpert MTB/RIF algorithm in a primary health care centre in KwaZulu-Natal, South Africa.
Degree: MMed
BREC REF NO: BE509/16
New Title: TREATMENT OUTCOMES OF GENE XPERT POSITIVE TUBERCULOSIS PATIENTS IN KWAMASHU COMMUNITY HEALTH CENTRE, KWAZULU NATAL SOUTH AFRICA-A RETROSPECTIVE REVIEW

We wish to advise you that your correspondence received on 07 August 2020 submitting an application for amendments to change the title to the new title above for the above study has been **noted and approved** by a subcommittee of the Biomedical Research Ethics Committee.

The committee will be notified of the above at its next meeting taking place on 08 September 2020.

Yours sincerely

Ms A Marimuthu
(for) Prof D Wassenaar
Chair: Biomedical Research Ethics Committee

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Website http://research.ukzn.ac.za/Research-Ethics/Biomedical-Research-Ethics.aspx

07 February 2019

Dr S Pillay (216076058)
Department of Medicine
School of Clinical Medicine
NRMSM
sarush.pillay@gmail.com

Dear Dr Pillay

Title: A retrospective review of the compliance to the National Tuberculosis Management guidelines: Gene Xpert MTB/RIF algorithm in a primary health care centre in KwaZulu-Natal, South Africa. Degree: MMed
BREC REF NO: BE509/16

We wish to advise you that your application for amendments dated 22 January 2019 for the above study has been **noted and approved** by a subcommittee of the Biomedical Research Ethics Committee.

The committee will be advised of the above at its next meeting to be held on 12 March 2019.

Yours sincerely

Prof V Rambiritch
Chair: Biomedical Research Ethics Committee

health
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PROVINCE OF KWAZULU-NATAL

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DIRECTORATE:
Health Research & Knowledge Management

HRKM Ref: 14/16
NHRD Ref: KZ_2016RP2_906

Date: 23 January 2017
Dear Dr S. Pillay

Approval of research

1. The research proposal titled **'A retrospective review of compliance to the National Tuberculosis Management Guidelines: Gene Xpert MTB?RIF algorithm in a primary health care centre in KZN, South Africa'** was reviewed by the KwaZulu-Natal Department of Health.

   The proposal is hereby **approved** for research to be undertaken at KwaMashu CHC.

2. You are requested to take note of the following:
   a. Make the necessary arrangement with the identified facility before commencing with your research project.
   b. Provide an interim progress report and final report (electronic and hard copies) when your research is complete.

3. Your final report must be posted to **HEALTH RESEARCH AND KNOWLEDGE MANAGEMENT, 10-102, PRIVATE BAG X9051, PIETERMARITZBURG, 3200** and e-mail an electronic copy to hrkm@kznhealth.gov.za

For any additional information please contact Mr X. Xaba on 033-395 2805.

Yours Sincerely

Dr E Lutge
Chairperson, Health Research Committee
Date: 27/01/17

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11 January 2017

Dear Dr Sarusha Pillay

RE: Permission to conduct research at KwaMashu CHC

Please note that permission has been granted for you to conduct your research at KwaMashu Community Health Centre on the study titled: *A retrospective review of the compliance to the National Tuberculosis Management Guildlines: Gene Xpert MTB/RIF algorithm in a Primary Health Care Centre in KwaZulu-Natal, South Africa.*

Please note that this permission is conditional on you acquiring full ethical clearance and approval from the Department of Health – Health Research and Knowledge Unit.

You are kindly advised to liaise with Ms. M.L. Dowdall (Acting Nursing Manager as well as M&E, 031 504 9100, extension 9212) to facilitate your research.

Wishing you all the best on your research study.

Yours sincerely

Dr B Badripersad
CEO KwaMashu CHC

Appendix: 3 Additional statistical analysis

A. DESCRIPTIVE STATISTICS

Demographic Characteristics – Complete dataset (N = 596)

Variable	Category	Frequency – n (%)
Age	Below 20	36 (6.04)
	20 - 29	192 (32.21)
	30 - 39	204 (34.23)
	40 - 49	95 (15.94)
	50 - 59	45 (7.55)
	Above 60	24 (4.03)
Gender	Male	381 (63.93)
	Female	215 (36.07)
HIV Status	Positive	360 (60.40)
	Negative	168 (28.19)
	Unknown	68 (11.41)
On HAART	No	326 (54.70)
	Yes	250 (41.95)
	Unknown	20 (3.36)

Demographic Characteristics – Defaulted Cohort (N = 162)

Variables	Category	Frequency – n (%)
Age	Below 20	10 (6.17)
	20 – 29	58 (35.80)
	30 – 39	57 (35.19)
	40 – 49	24 (14.81)
	50 – 59	10 (6.17)
	Above 60	3 (1.85)
Gender	Male	100 (66.67)
	Female	54 (33.33)
HIV Status	Positive	109 (67.28)
	Negative	36 (22.22)
	Unknown	17 910.49)
On HAART	No	87 (53.70)
	Yes	68 (41.98)

	Unknown	7 (4.32)
GXP Procedure	Done	156 (96.30)
	Not done	6 (3.70)

B. RESULTS BASED ON THE OBJECTIVES

- *The number of patients who are Gene Xpert Positive who get a smear at base.*

Gene Xpert	**Category**	**Frequency – n (%)**
Procedure (n =596)	Done	572 (95.97)
	Not done	24 (4.03)
Results (n = 572)	Unsuccessful	4 (0.70)
	Detected	558 (97.55)
	Undetected	10 (1.75)

		Smear Microscopy result			
Gene Xpert	**Category**	**Negative**	**Positive**	**Unknown**	**Total**
Procedure (n =596)	Not done	4	19	1	24 (4.03)
	Done	232	232	108	572 (95.97)
Results (n = 572)	Unsuccessful	2	0	2	4 (0.70)
	Detected	222	231	105	558 (97.55)
	Undetected	8	1	1	10 (1.75)

- *The proportion of patients who have sputum collected at two months and 5 months.*
  - *The proportion of patients who have sputum collected at two months and 5 months who undergo smear conversion or develop drug resistance Tuberculosis*

Smear Microscopy	**Category**	**Frequency – n (%)**
2 Months (n = 596)	No	208 (34.90)
	Yes	388 (65.10)
5 Months (n = 596)	No	337 (56.54)
	Yes	257 (43.12)
	Unknown	2 (0.34)

Sputum conversion	Category	Frequency – n (%)
2 Months (n = 546)	No	162 (29.67)
	Yes	384 (70.33)
5 Months (n = 458)	No	59 (12.88)
	Yes	399 (87.12)

		Smear Microscopy (2 Months)		
Sputum Conversion	**Category**	**No**	**Yes**	**Total**
2 Months	Yes	195	189	384 (70.33)
	No	0	162	162 (29.67)

		Smear Microscopy (2 Months)		
Sputum Conversion	**Category**	**No**	**Yes**	**Total**
5 Months	Yes	198	201	399 (87.12)
	No	10	49	59 (12.88)

		Smear Microscopy (5 Months)			
Sputum Conversion	**Category**	**No**	**Yes**	Unknown	**Total**
5 Months	Yes	206	192	1	399 (87.12)
	No	2	57	0	59 (12.88)

		MDR TB		
Sputum Conversion	**Category**	**No**	**Yes**	**Total**
2 Months	Yes	338	46	384 (70.33)
	No	152	10	162 (29.67)

		MDR TB		
Sputum Conversion	**Category**	**No**	**Yes**	**Total**
5 Months	Yes	355	44	399 (87.12)
	No	50	9	59 (12.88)

- *The proportion of patients diagnosed GXP positive Tuberculosis who are co-infected with HIV.*
    - *The number of HIV co-infected patients who achieve smear conversion or develop drug resistant Tuberculosis.*

	GXP Procedure		
HIV Status	**Not Done**	**Done**	**Total (%)**
Positive	12	348	360 (60.40)
Negative	10	158	168 (28.19)
Unknown	2	66	68 (11.41)
Total	24	572	596 (100.00)

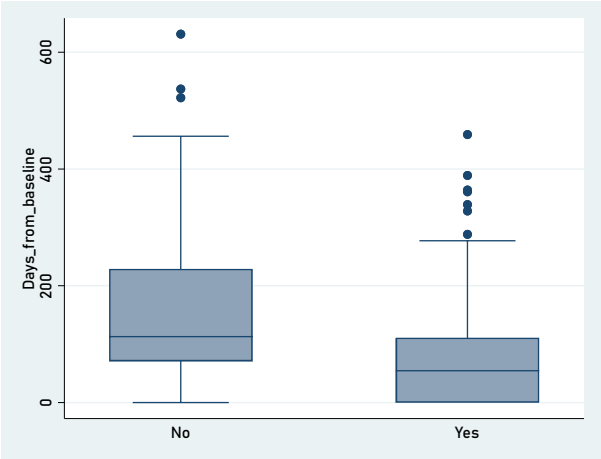
	GXP Result			
HIV Status	**Unsuccessful**	**Detected**	**Undetected**	**Total (%)**
Positive	4	335	9	348 (60.84)
Negative	0	158	0	158 (27.62)
Unknown	0	65	1	66 (11.54)
Total	4	558	10	572 (100.00)

	Sputum conversion – 2 Months		
HIV Status	**Yes**	**No**	**Total (%)**
Positive	244	89	333 (60.99)
Negative	90	62	152 (27.84)
Unknown	50	11	61 (11.17)
Total	384	162	546 (100.00)

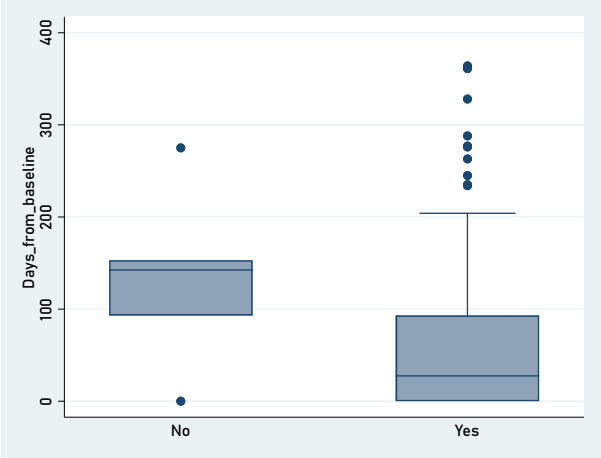
	Sputum conversion – 5 Months		
HIV Status	**Yes**	**No**	**Total (%)**
Positive	240	30	270 (58.95)
Negative	104	22	126 (27.51)
Unknown	55	7	62 (13.54)
Total	399	59	458 (100.00)

	MDR TB		
HIV Status	**Yes**	**No**	**Total (%)**
Positive	42	318	360 (60.40)
Negative	14	154	168 (28.19)
Unknown	2	66	68 (11.41)
Total	58	538	596 (100.0)

THE DEFAULTED COHORT - (N = 162)



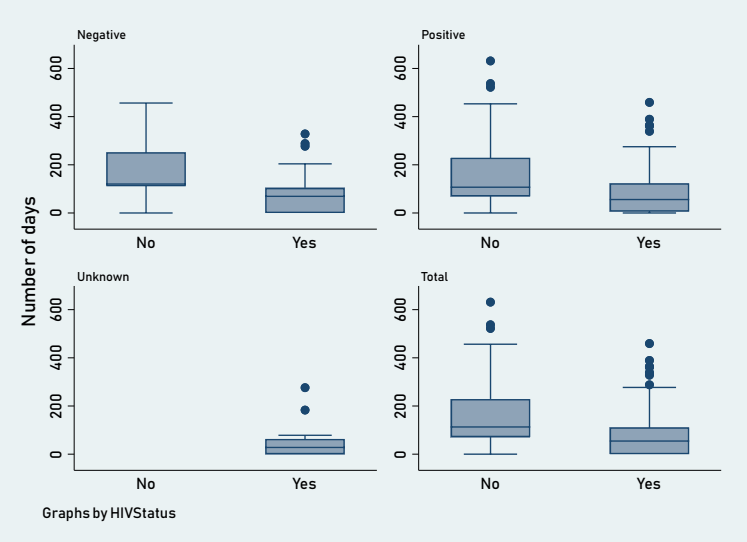
Sputum conversion- 2 months



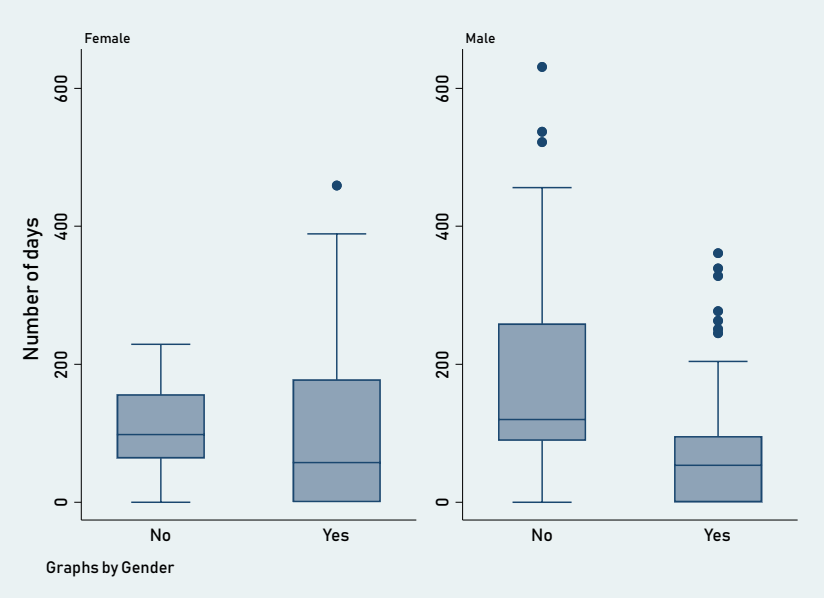
Sputum conversion- 5 months

C. SPUTUM CONVERSION – 2 MONTHS

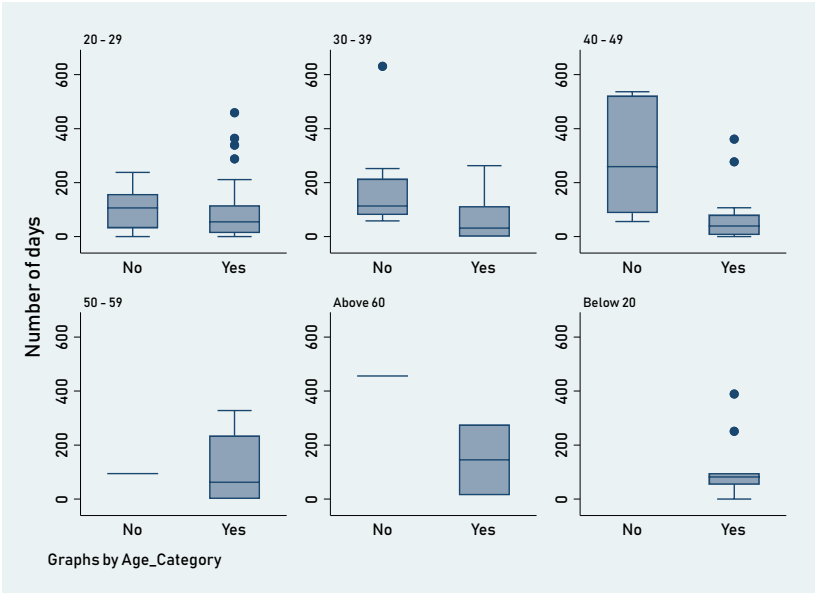
a. HIV Status



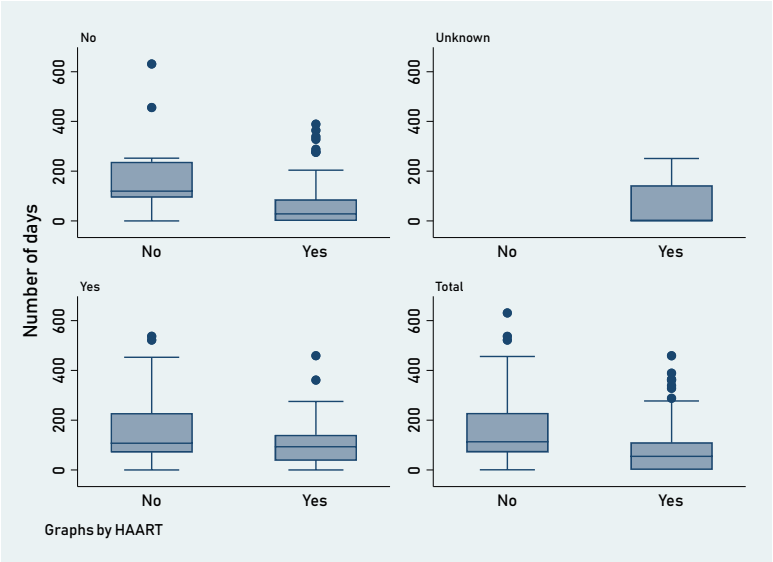
b. Gender



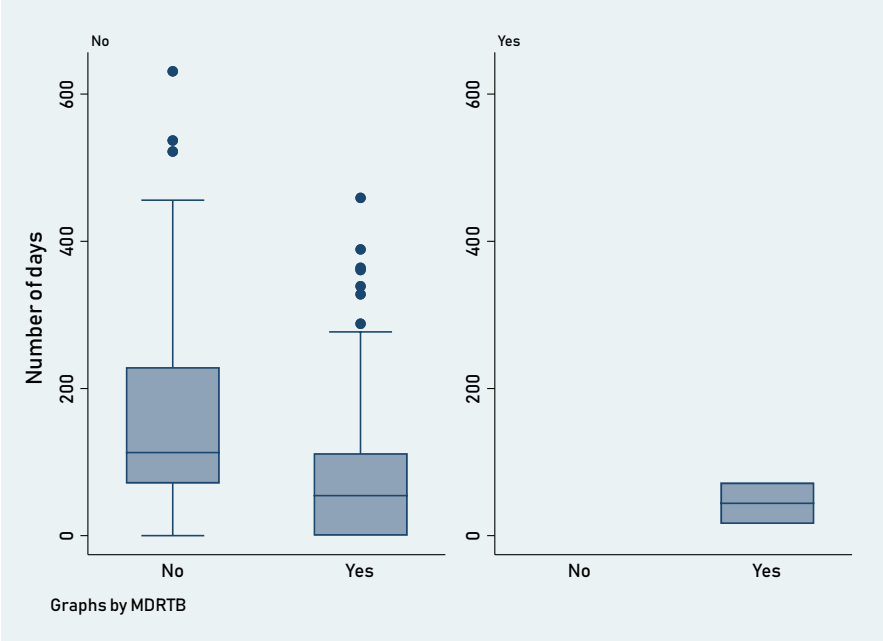
c. Age group



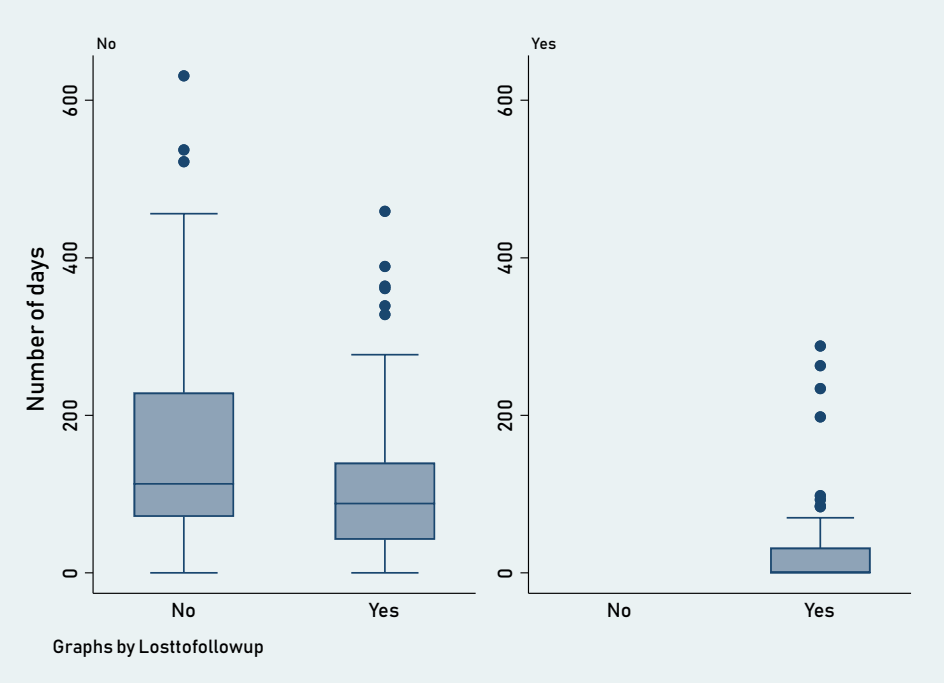
d. HAART



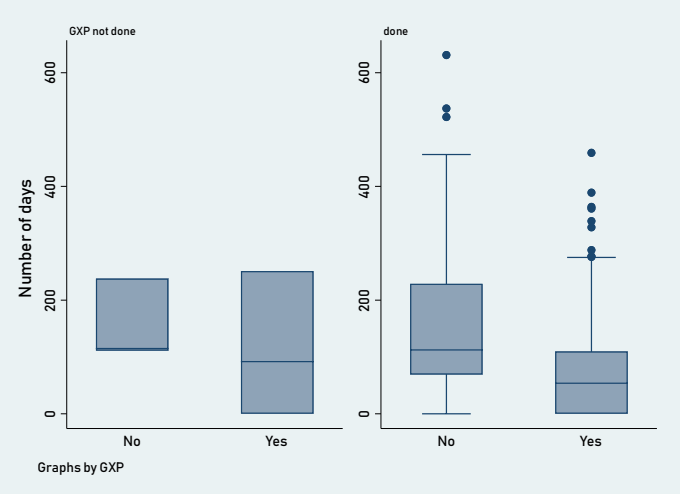
e. MDR-TB



f. Loss to follow-up

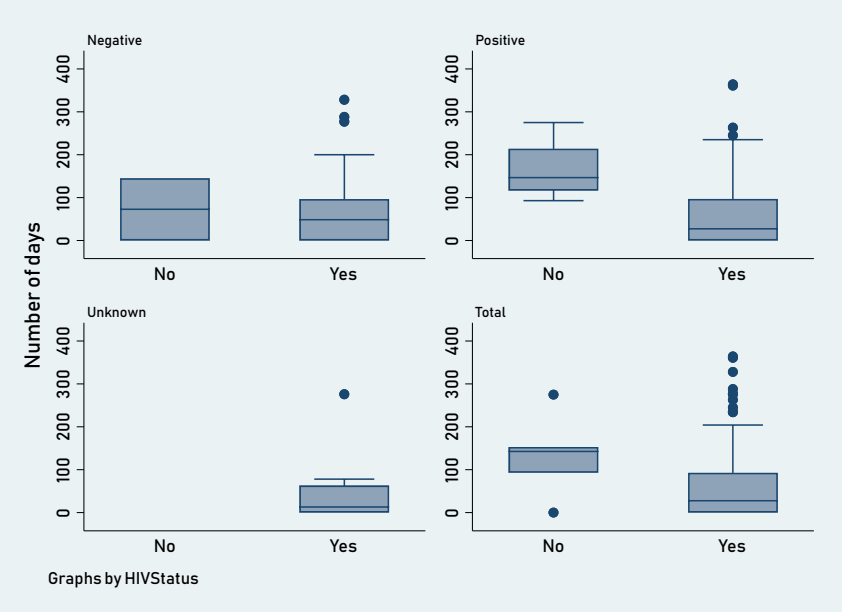


g. GXP

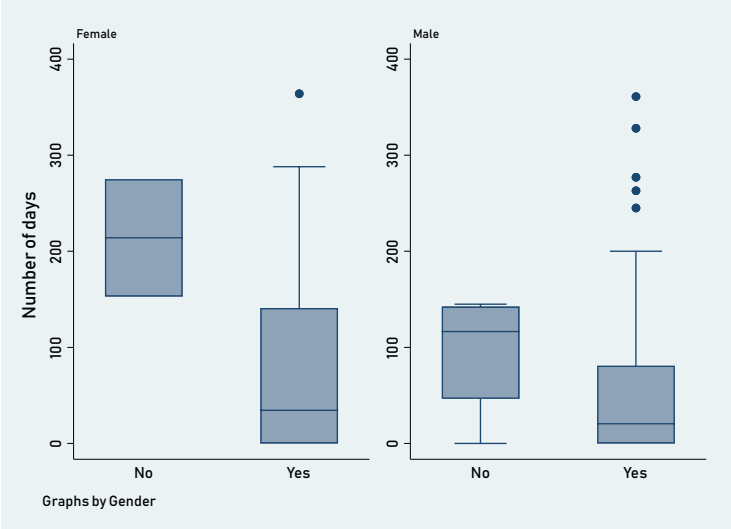


D. SPUTUM CONVERSION – 5 MONTHS

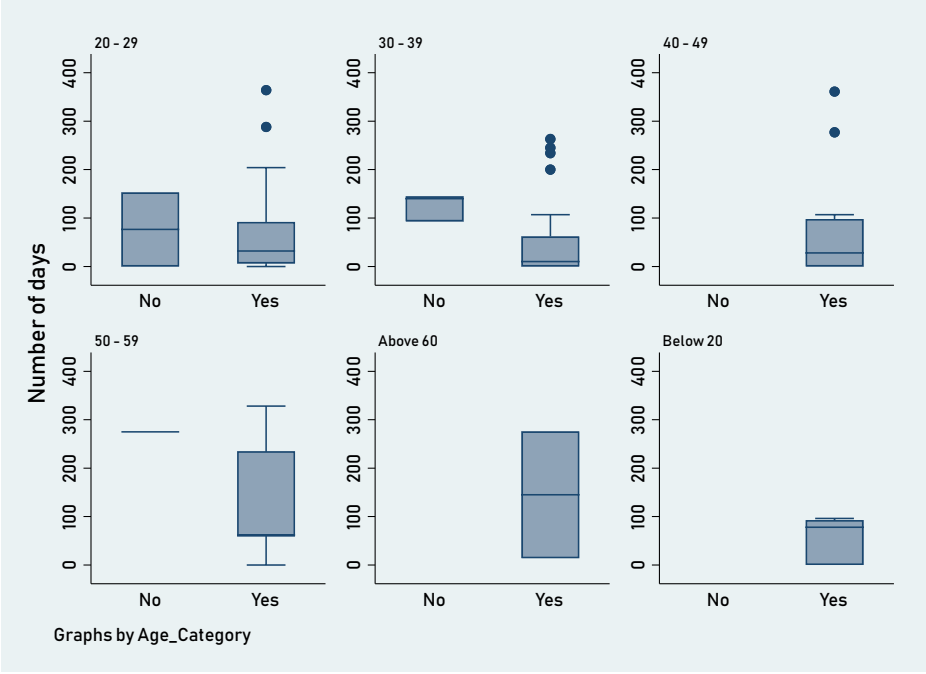
a. HIV Status



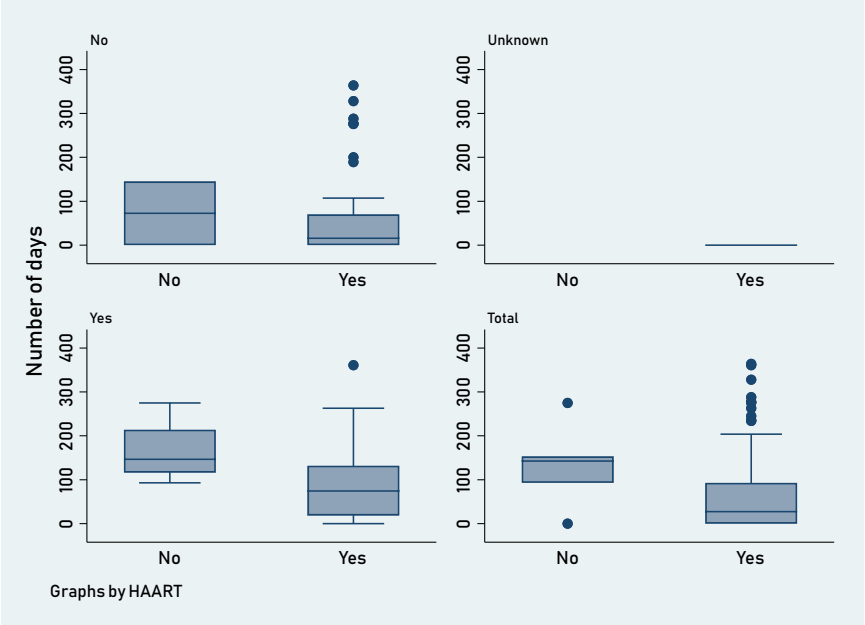
b. Gender



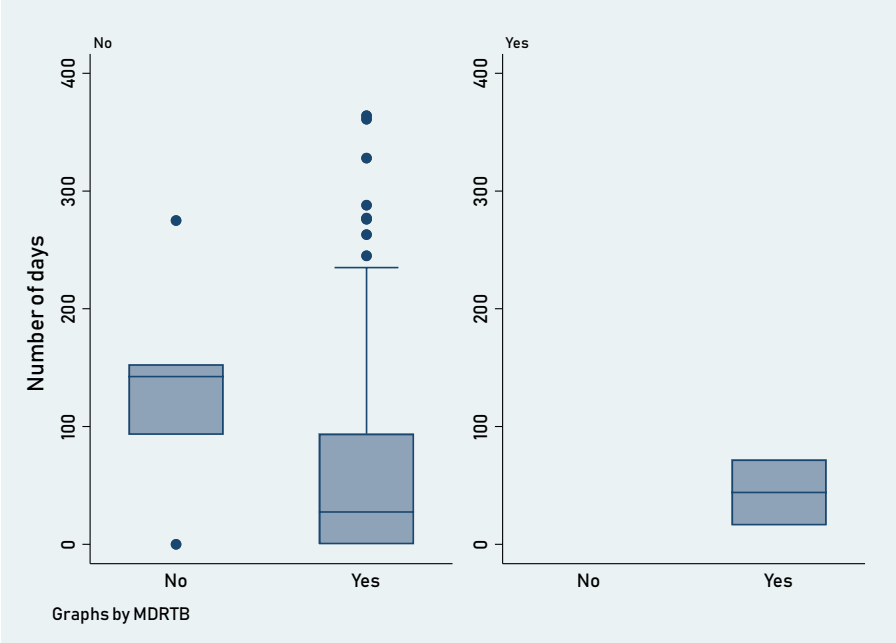
c. Age group



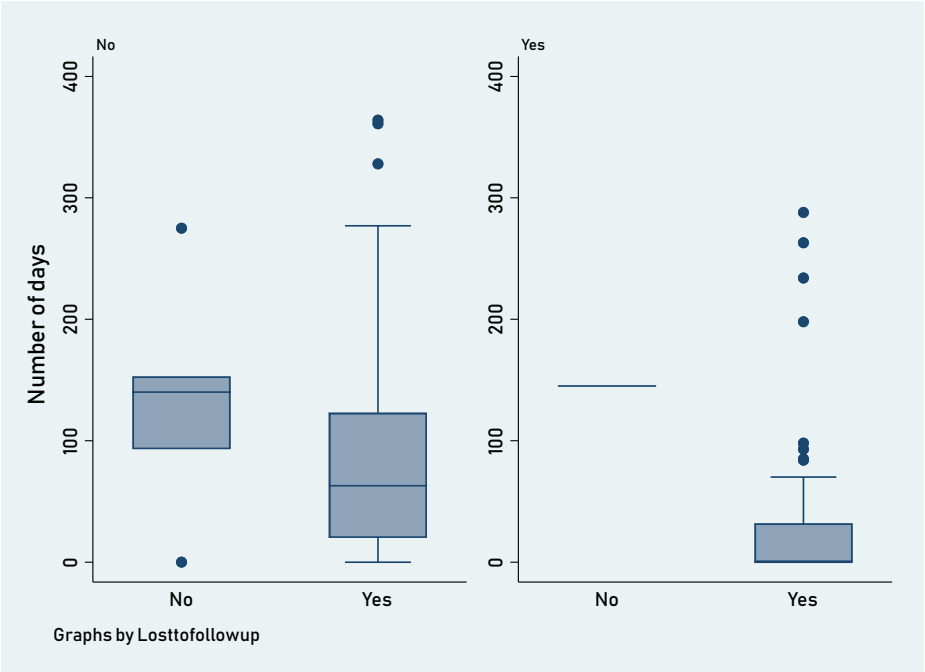
d. HAART



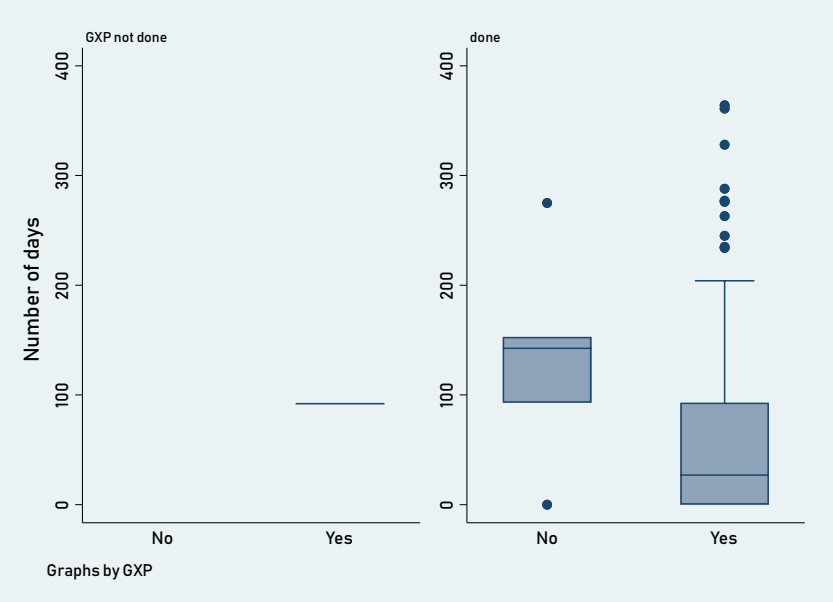
e. MDR-TB



f. Loss to follow-up

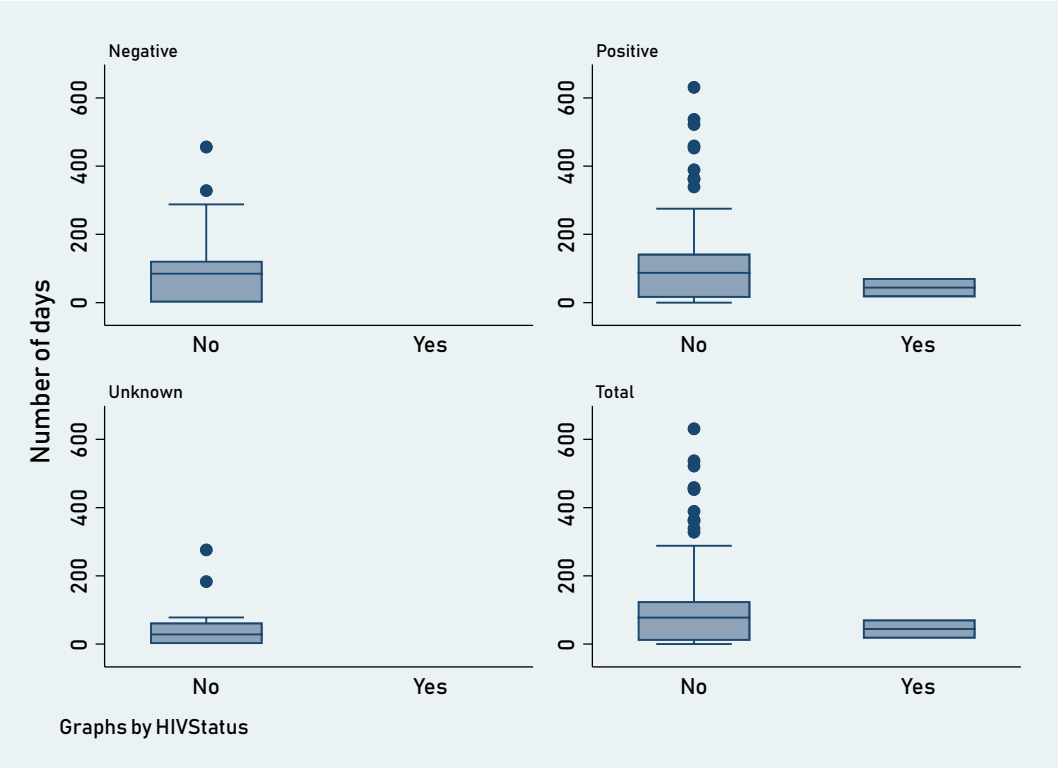


g. GXP



E. MULTI DRUG RESISTANT- TB

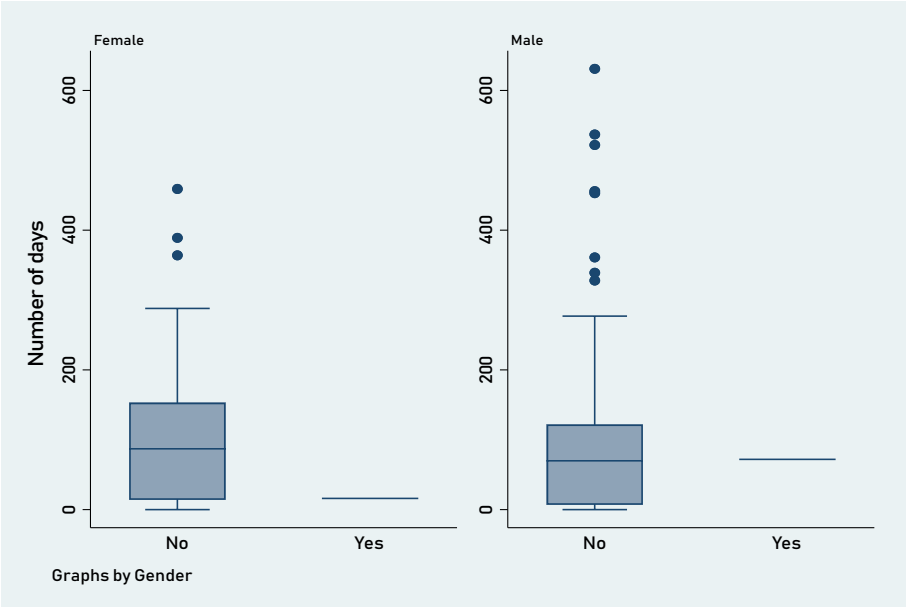
a. By HIV Status



MDR – TB grouped by HIV Status, based on the number of days from baseline.

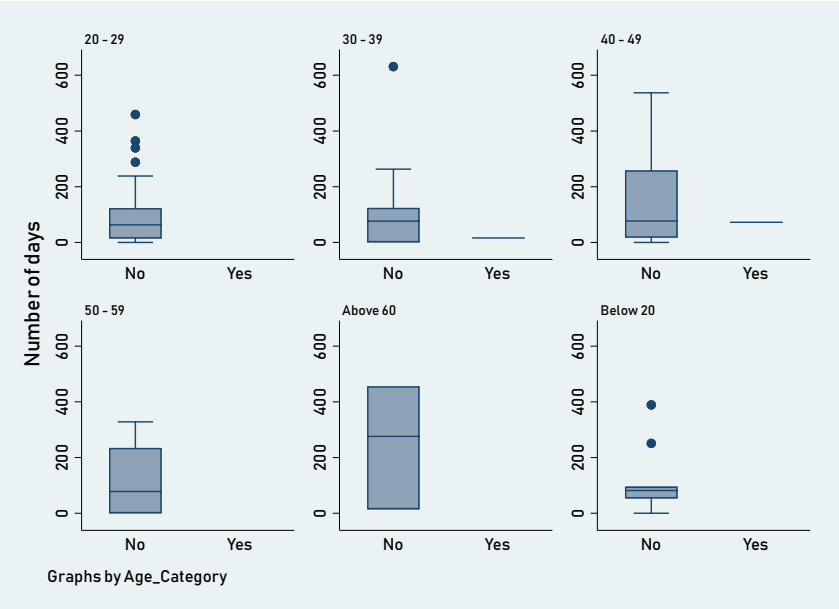
- Evidently, it's only patients who were HIV+ that developed MDR-TB, from the baseline day.

b. By Gender



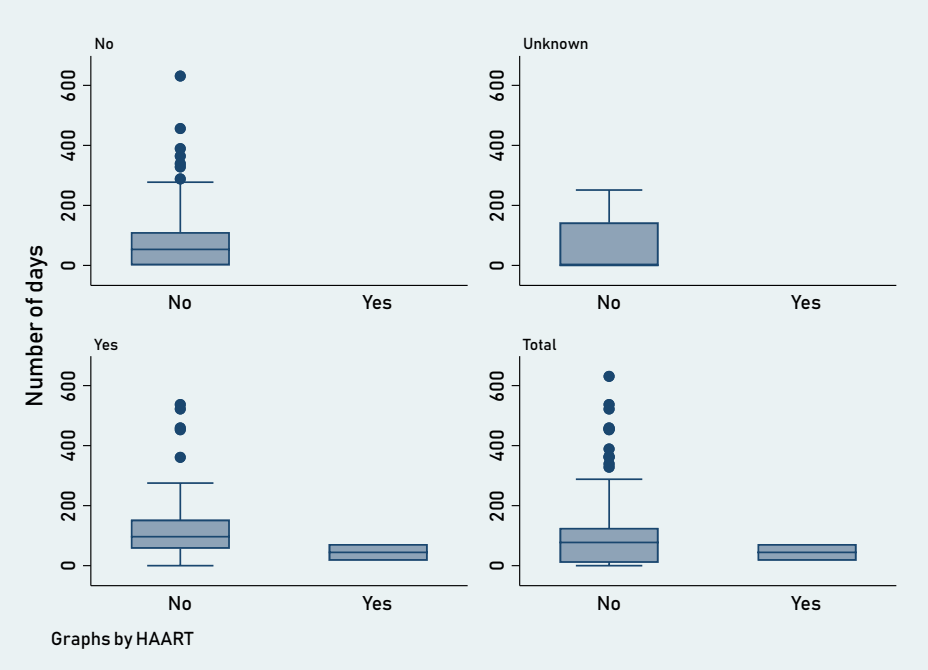
- It takes males more days to develop MDR – TB. Are males more compliant than the females?

c. Age-group



➢ The trend is unique to the ages group of (30 – 39) and (40 – 49).

d. HAART



e. GXP Procedure