REVIEW OF OUTCOMES FOR ISONIAZID

PREVENTIVE THERAPY AMONG HIV

INFECTED CLIENTS AT A CLINIC IN

SWAZILAND

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A mini-thesis submitted in partial fulfilment of the requirements for the degree of Master in Public Health at the School of Public Health, University of the Western Cape

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DECLARATION

I, Normusa Musarapasi declare that, “Review of Outcomes for Isoniazid Preventive Therapy Among HIV Infected Clients at A Clinic in Swaziland” is my own work, that it has not been submitted for any degree or examination in any university and that all the sources I have used or quoted have been indicated and acknowledged by complete references.

Signed

Date: 13 March 2019

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DEDICATION

I dedicate this work to my children.

Helen, “my shining light”

And

Nigel, “my champion”
ACKNOWLEDGEMENTS

Finally, I made it! I am grateful to the following people and institutions who made it possible.

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KEYWORDS
Swaziland
Tuberculosis in HIV
Tuberculosis prevention
Antiretroviral therapy
Latent TB infection
Isoniazid preventive therapy
TB screening
Outcomes
Treatment completion
Adverse events
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<tr>
<td>AHF</td>
<td>AIDS Healthcare Foundation</td>
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<td>AIDS</td>
<td>Acquired Immune Deficiency Syndrome</td>
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<td>ART</td>
<td>Antiretroviral therapy</td>
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<td>CD4</td>
<td>Cluster of differentiation 4</td>
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<td>CDC</td>
<td>Centers for Disease Control and Prevention</td>
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<td>HIV</td>
<td>Human Immune-deficiency Virus</td>
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<td>IPT</td>
<td>Isoniazid Preventive Therapy</td>
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<td>LTBI</td>
<td>Latent tuberculosis infection</td>
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<td>LTFU</td>
<td>Lost to follow up</td>
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<td>MSF</td>
<td>Medecins Sans Frontieres (Doctors without borders)</td>
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<td>NHRRBS</td>
<td>National Health Research Review Board of Swaziland</td>
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<td>PTB</td>
<td>Pulmonary tuberculosis</td>
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<td>SHIMS</td>
<td>Swaziland HIV Incidence Measurement Survey</td>
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<td>SPSS</td>
<td>Statistical package for social sciences</td>
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<td>TB</td>
<td>Tuberculosis</td>
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<td>TCR</td>
<td>Treatment completion rate</td>
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<td>THRio</td>
<td>TB/HIV study in Rio de Janeiro</td>
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<td>UNAIDS</td>
<td>Joint United Nations Programme on HIV and AIDS</td>
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<td>UWC</td>
<td>University of the Western Cape</td>
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<td>WHO</td>
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DEFINITIONS OF KEY TERMS

A case on IPT is a patient who has accepted IPT and has received a dose of at least one month of isoniazid (Swaziland Ministry of Health, 2012).

Adverse effect: A symptom produced by a drug or therapy that is injurious to the patient (Miller-Keane Encyclopaedia and Dictionary of Medicine, Nursing, and Allied Health, 2003). In this study only adverse effects which led to the discontinuation of IPT were recorded.

Latent tuberculosis: This is when one is infected with Mycobacterium tuberculosis but do not have symptoms and is non-infectious (CDC, 2014).

Definition of outcomes (Swaziland Ministry of Health, 2012)

❖ Completed: A person who received a full course of isoniazid (6 months/180 doses) in a period of 6-9 months.
❖ Defaulted: If a patient has taken isoniazid for one or more months, then interrupted for 60 days or more.
❖ Died: A person on IPT who is reported to have died of any cause during treatment (based on information gathered and recorded by a responsible health worker).
❖ Failed: If a person develops active TB disease while on IPT.
❖ Transferred out: A person who has been transferred to another site or region to continue treatment.
❖ Treatment discontinued: A person for whom the IPT has been discontinued by a healthcare worker due to adverse effects or any other reason.
❖ Lost to follow up (LTFU) on TB treatment: A patient who is LTFU on TB treatment is one who did not start treatment or whose treatment was interrupted for 2 consecutive months or more (WHO, 2014a). This definition is difficult to apply to IPT as has been done with other IPT outcomes because a patient may stop taking IPT and still come to the clinic for other services and still refuse to resume IPT. In this study a LTFU patient was defined as one who did not present to the clinic for more than two months and efforts to trace them were fruitless. Patients who still came to the clinic but stopped IPT for at least two months were classified under the defaulter category.
**Tuberculosis:** Tuberculosis (TB) is defined as an infectious disease which is caused by the bacillus Mycobacterium tuberculosis that mainly affects the lungs PTB (pulmonary tuberculosis) although it also affects other sites of the body (extra pulmonary tuberculosis) (WHO, 2014b).
ABSTRACT

Background: TB is one of the most common opportunistic infections in the HIV infected population. In 2014, of the 9.6 million people estimated to have TB globally, 1.2 million were also infected with HIV. In the same year WHO reported 400,000 TB deaths in HIV infected people worldwide. TB Prevention strategies include ensuring HIV infected people take ART, TB infection control, treatment of TB cases and pharmacological prevention of primary TB infection or progression of latent TB into active TB. Isoniazid preventive therapy for a minimum of six months has been recommended to reduce the risk of TB in people living with HIV.

Aim: The study’s aim was to determine the programmatic outcomes of isoniazid preventive therapy (IPT) and factors associated with treatment completion among people living with HIV aged 15 years and above at the AIDS Healthcare Foundation LaMvelase clinic in Manzini Swaziland, who were enrolled for IPT during the period March to December 2014.

Methodology: This was a quantitative retrospective analytical cohort study that reviewed 3642 patient care records. IBM SPSS 20 was used for descriptive and statistical analysis of the data. Descriptive statistics were calculated and reported as frequencies and percentages. Bivariate statistics were carried out to test independent associations between socio-demographic and clinical characteristics, and IPT completion. Further multiple logistic regression analysis was done to determine the nature of association between the dependent and independent variables which had p < 0.1.

Results: A high treatment completion rate (93.8%) was demonstrated in clients who received IPT at AHF LaMvelase clinic. Hepatotoxicity was the commonest side effect (1.6%) leading to treatment interruption. Occurrence of gynaecomastia was found to be more common (0.73%) than previously reported elsewhere. Residing in the rural area was found to be associated with lower IPT completion rates (p=0.046; OR 0.75 (95% CI 0.56-1.00)). Having a higher CD4 count was associated with higher IPT completion rates (p=0.005; OR 1.75 (95% CI 0.56-1.00)).

Conclusion: Differentiated care is necessary to improve outcomes in the rural population and those with severe immune suppression. Further studies are required to: determine reasons for high IPT completion rates (qualitative), determine the duration of the effectiveness of the six-month IPT regimen in this population, assess implementation of early TB preventive therapy uptake for clients who have been on ART for at least a month in line with the recent WHO guidelines, and to explore shorter TB preventive therapy regimens in Swaziland.
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1. BACKGROUND

1.1 Introduction

Tuberculosis (TB) is a disease that is caused by the bacillus mycobacterium tuberculosis. Although in most cases it affects the lungs, the disease can affect many other parts of the body including the bones, lymph nodes, liver, meninges and bladder (WHO, 2016a). It is highly communicable and spreads through droplets produced when a person with active pulmonary TB disease coughs or sneezes (WHO, 2016a). One person infected with TB can spread the disease to many people and this makes it a disease of public health importance (Escombe et al., 2007).

A third of the world’s population is infected with latent TB (Dye et al., 1999). Latent TB infection (LTBI) refers to the state where one’s immune system is continuously activated by the TB bacilli but they are clinically not sick (Escombe et al., 2007). Prevention of the development of active TB in people living with the Human Immune-deficiency Virus (HIV) is important since they have a 10% yearly risk of developing active TB as compared to 10% lifetime risk in the HIV negative population (WHO, 2008). Screening of people living with HIV for TB and the provision of preventive treatment are components of the first pillar of the World Health Organisation’s (WHO) End TB Strategy (WHO, 2016a). It is hoped that by the year 2025 at least 90% of eligible People living with HIV would be receiving treatment for LTBI (WHO, 2016a).

This study reviews the programmatic outcomes for isoniazid preventive therapy (IPT) among HIV infected clients at the AHF LaMvelase clinic in Swaziland. Isoniazid is one of the drugs that can be used in the treatment of LTBI (Akolo et al., 2010). IPT also decreases the risk of recurrence of TB disease in people living with HIV (Fitzgerald et al., 2000). While IPT has been used mainly to benefit the individual, mathematical models have shown that it can decrease the incidence of TB in high prevalence HIV/TB settings (WHO, 2008).

The first part of this chapter explores the burden of HIV and TB globally, the synergistic effects of HIV/TB co-infection, strategies for managing HIV/TB co-infection, isoniazid for TB prevention, global IPT implementation, the Swaziland HIV and TB burden, and the IPT programme in Swaziland. The problem statement and significance of this study are then
presented. The chapter concludes by providing an overview of the contents of the rest of the thesis.

1.2 The global HIV and TB burden

Tuberculosis (TB) is one of the most common opportunistic infections in people living with HIV. TB and HIV are also leading causes of death in the world. TB is now killing more people in the world compared to HIV (UNAIDS, 2016). In 2014, of the 9.6 million people estimated to have TB 1.2 million were also infected with HIV (WHO, 2015). In the same year the WHO reported 1.5 million deaths due to TB of which 400 000 were people living with HIV (WHO, 2015).

In 2015 estimated TB cases were on the rise compared to 2014. The estimated number of TB cases was 10.4 million (11% of these had HIV co-infection) and 1.8 million (390 000 HIV positive) people died from TB (WHO, 2016a). Figure 1.1 below shows the global distribution of new TB cases in 2015. Sub-Saharan Africa is amongst those areas with incidence of TB greater than 300 cases per 100 000 population per year.

Figure 1.1: Worldwide estimated TB incidence rates 2015 (WHO, 2016a)

1.3 HIV and TB co-infection

People living with HIV have a 20-37 times chance of developing TB as compared to the general population (WHO, 2011). TB is associated with significant morbidity and mortality and
outcomes are worse if co-morbid with HIV. According to Mayer and Hamilton (2010), HIV and TB work in synergy to weaken the body’s defence system. Both these diseases accelerate the progress of each other. TB significantly decreases survival in people living with HIV (Kwan & Ernst, 2011). HIV is the most common risk factor for the advancement from latent TB to active TB (Swaziland Ministry of Health, 2012). TB also speeds up viral replication and the development of full blown Acquired Immune Deficiency Syndrome (AIDS) from HIV infection (Toossi et al., 2001). HIV causes challenges in diagnosing TB in the severely immune suppressed as the typical signs and symptoms are absent (Raviglione, Narain and Kochi, 1992).

1.4 Strategies for managing HIV/TB co-infection

Strategies to manage HIV/TB co-infection as proposed by the Swaziland Ministry of Health include; initiation of antiretroviral therapy (ART), improving diagnosis of TB in people living with HIV through screening and active case finding, improved TB infection prevention control, and isoniazid prophylaxis to prevent progression of latent infection to active disease (Swaziland Ministry of Health, 2012). Starting ART in the early stages of HIV infection for People living with HIV ensures that the immune system is preserved thereby protecting them from opportunistic infections like TB which result in increased morbidity and mortality (Suthar et al., 2012). HIV positive TB patients benefit from early detection and treatment of TB because their health outcomes are improved (Varma et al., 2009). Early detection and treatment of TB is important as it protects the public from contracting the disease from infected individuals (Kranzer et al., 2013).

1.5 Isoniazid as prophylaxis for TB prevention

Isoniazid kills and reduces bacterial growth through the inhibition of the production of mycolic acid which is needed for the formation of the mycobacterial cell wall. It is one of the first line drugs used for the prevention and treatment of TB (CDC, 2016) in people living with HIV. Isoniazid mono-therapy has been found to be the least toxic option for TB prevention in People living with HIV and is therefore the drug of choice (WHO, 2011). Woldehanna and Volmink (2004) in their review of 11 trials that offered TB preventive therapy to 8,130 randomized participants who are HIV infected, found that preventive therapy, irrespective of choice of anti-TB drug compared to placebo, resulted in a lower incidence of active TB. In this review

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isoniazid was found to be favourable as it was associated with fewer side-effects regardless of the duration of therapy. Churchyard et al. (2003), in their study on secondary prophylaxis for TB in mine workers in South Africa, found that the overall incidence of TB relapse dropped by 55% in those who took IPT as compared to controls. These studies show that IPT can reduce the burden of TB in those with HIV. Reducing the burden of TB in People living with HIV is important to reduce deaths due to TB. A minimum of six months treatment with a 300mg daily dose of isoniazid for adults is recommended for treatment of LTBI (WHO, 2014c). Isoniazid is co-administered with pyridoxine at an adult dose of 25mg daily to prevent peripheral neuropathy.

1.6 Global isoniazid preventive therapy implementation

A cross-sectional study on national policy and implementation of cotrimoxazole and IPT recommendations in 41 high HIV and TB burden countries was conducted by the World Health Organisation (WHO) through HIV/AIDS programme officers in 2007 (Date et al., 2010). It revealed that only 51% of the countries had an IPT policy in place and of these only 28% had a nationwide implementation of the policy. In this survey 17 countries were from the African Region of which 47% had a national IPT policy, yet only 13% were implementing the policy at national level. At this juncture there were concerns about potential isoniazid mono-resistance, inadequate skills to diagnose LTBI and ruling out of active TB disease (Date et al., 2010). Gupta et al. (2014) while reviewing the policy and implementation status of collaborative HIV-TB activities in 23 high-burden countries (16 African, 6 Asian and 1 South American) in 2013, found that 70% (16) of the countries included IPT in their policy and this represented 67% of the global burden of HIV-TB. This was an improvement from the previous assessment by Date et al. (2010). Of these countries, 12 endorsed the use of the symptom screening tools only to identify patients eligible for IPT. The remainder of the countries prescribed the use of the tuberculin skin test (TST) or symptom screening and TST or symptom screening and chest radiography. Of these countries, 15 were found to be compliant with the WHO guidelines that recommend a minimum of six months of IPT. While six countries strictly adhered to the six months, the rest varied from six to 36 months for specific subpopulations. Countries that did not have a clear policy on IPT included Zimbabwe, Democratic Republic of Congo (DRC), Cote d’Ivoire, Myanmar, China, Indonesia and India.
These assessments show the incremental adoption of the use of IPT in the prevention of TB but do not evaluate treatment completion.

1.7 Swaziland HIV and TB burden

Nearly a quarter of Swaziland’s population is infected with HIV (UNAIDS, 2014); hence are at higher risk of developing TB than the general population. Swaziland has a high HIV and TB burden with an HIV prevalence of almost 31% in the 18-49 year age group in 2011 (UNAIDS, 2014). In 2014, 73% of TB patients were HIV co-infected and the incidence rate of TB in this population was 464 per 100 000 population which was much higher than the entire Africa region (90 per 100 000) and the global estimate of 16 per 100 000 (WHO, 2016). Deaths attributable to TB in people living with HIV in 2014 in Swaziland were 135 per 100 000 population compared to 32 per 100 000 and 5.3 per 100 000 for Africa and globally respectively. The WHO considers Swaziland to be one of the countries with a high burden of TB/HIV co-infection that needs to be reduced through preventive and treatment measures.

1.8 IPT programme in Swaziland

The Swaziland Ministry of Health IPT Guidelines (Swaziland Ministry of Health, 2012) identify all people living with HIV who screen negative for TB as eligible for IPT. Other people eligible for IPT are healthcare workers, children under 5 years who are exposed to TB, and people in congregate settings for example prisoners. This is in line with the WHO recommendations for management of LTBI (WHO, 2015b). The Swaziland protocol for TB prevention recommends administering IPT for six months every two years in people with HIV who are TB negative and therefore at risk of developing TB (Swaziland Ministry of Health, 2012).

According to the Swaziland Ministry of Health (2012) possible IPT outcomes are: treatment completed, defaulted, treatment failed, death, transferred out, lost to follow up and treatment discontinuation at health facility. A client is considered to have completed treatment if they take IPT for six months. If treatment is interrupted for less than two months the client is allowed to resume treatment and complete it within nine months of the initial starting date. If they miss at least two consecutive months of treatment during the first nine months of initiating IPT after initially taking treatment for at least one month, they are classified as a defaulter. IPT failure is
considered if patients develop active TB whilst on therapy. Death due to any cause while on IPT is also recorded as an outcome. Some patients may also transfer out to continue treatment at other health facilities. Those who do not present to the clinic for scheduled IPT refills for more than two months and efforts to trace them are futile are classified as lost to follow up. The decision to discontinue IPT for a patient can be taken at the health facility in the presence of severe adverse effects or poor adherence. While Swaziland has listed causes of non-completion as outcomes, other guidelines such as those in South Africa have summarised the outcomes to completion, non-completion and treatment failure (South African Department of Health, 2010). The definitions for these outcomes are similar to the Swaziland ones.

IPT was introduced in Swaziland as a pilot in 2009 for people living with HIV and expansion of IPT services for these people in more health facilities was started in 2011 (Calnan et al., 2017). Although the IPT programme was introduced in Swaziland in 2011 (Swaziland Ministry of Health, 2012), it was rolled out at the AIDS Healthcare Foundation (AHF) LaMvelase clinic, the study site, in 2014. The introduction of IPT in Swaziland provided a great opportunity for the primary and secondary prevention of drug sensitive TB in the country for people living with HIV. Reviewing IPT outcomes is important to gauge the success of the IPT programme and to guide interventions for clients who develop adverse events. Swaziland will significantly benefit from a functional TB prevention programme that can reduce the incidence of TB disease.

1.8.1 Screening for active TB before IPT

All clients presenting at Swaziland health facilities are screened for active TB. Those who screen negative are eligible to be given IPT if they do not meet the exclusion criteria. Exclusion criteria include known allergy to isoniazid, active hepatitis, regular and excessive alcohol intake, at least grade two peripheral neuropathy, current active TB treatment, on work up for ART within the next four weeks and if the client received IPT within the past two years (Swaziland Ministry of Health, 2012).

1.9 Problem Statement

IPT benefits the individual taking it as they are protected from developing active TB (South African Department of Health, 2010). It also reduces TB transmission in the community therefore completion of the course of IPT is important for this benefit to be achieved (Churchyard et al., 2007). A lot of emphasis has been put on enrolling as many people living with
HIV as possible on IPT in Swaziland but evaluation of whether they complete the treatment has not been done systematically (Pasipamire et al., 2016). Evaluation of the outcomes of the IPT programme and factors associated with IPT completion is important in monitoring programme performance. The Global TB Report (WHO, 2015) shows only the number of people initiated on IPT in Swaziland without mention of outcomes. It is important for patients to complete IPT for the population to gain from its protective effect against TB disease and to prevent negative individual outcomes. IPT programmes that have low completion rates and high defaulter or lost to follow up rates are a waste of resources (Aït-Khaled et al., 2009) therefore there is a need to determine the different outcomes in people living with HIV in Swaziland who take IPT and to determine whether these outcomes are affected by patient or clinical characteristics. Although high IPT completion rates of 89.4% have been reported in Swaziland (Adams et al., 2017), these were measured under a prospective study. This study involved interventions to actively track clients who missed appointments through home visits which is not the norm in a programmatic context. There is a need to measure the outcomes in a normal routine service delivery context.

1.10 Significance of the study

The purpose of this research was to determine the programmatic IPT outcomes among people living with HIV receiving care at the AHF LaMvelase clinic. First and foremost, this data will be useful to provide relevant and important information to clinicians, program designers and implementers, to improve their records and knowledge of the outcomes, side-effects or factors related to these. The clinicians in the facility will be able to put in place measures to improve completion rates and to look out for and manage side-effects more effectively while at the same time tracking defaulters and lost to follow ups. The IPT programme is intended to complement other TB prevention strategies hence it is necessary to determine the level of completion for this treatment. Treatment completion is necessary for this intervention to be effective. Side-effects affect adherence to treatment and completion hence there is a need to anticipate the extent to which patients may develop these. This data is also useful at national level to estimate expected IPT toxicity which will guide future programmatic interventions. TB incidence outcomes are useful for planning of resources used in the prevention, diagnosis and management of TB.
1.11 Study outline

This study is presented in six chapters. The first chapter introduced the study by discussing the burden of HIV and TB globally; synergistic effects of HIV/TB co-infection; strategies for managing HIV/TB co-infection; isoniazid as prophylaxis for TB prevention; implementation of IPT worldwide; the TB/HIV burden and the IPT programme in Swaziland. The problem statement and significance of this study will also be discussed in this chapter.

The second chapter reviews literature on the global situation for IPT, LTBI treatment options, secondary prophylaxis, benefits of IPT, the duration of the protective effect of IPT, the TB screening tool specificity and sensitivity, IPT outcomes, factors associated with IPT outcomes and the adverse events related to use of IPT.

The third chapter focuses on the methodology employed in conducting the study by first introducing the aim, objectives and setting of the study. The study approach, study design, population and sample selection, data collection and analysis, validity and reliability, limitations and ethical issues in conducting the study are discussed at length. The fourth chapter presents results from the study. The socio-demographic and clinical characteristics are presented as well as other findings linked to the study objective. The fifth chapter provides an in-depth discussion of the findings, in relation to the existing relevant literature. In the last chapter, conclusions are drawn and recommendations made, based on the study findings.
2. LITERATURE REVIEW

Treatment of latent tuberculosis infection (LTBI) in People living with HIV is one way of reducing morbidity and mortality in this population (WHO, 2012). This study aimed to determine the outcomes of isoniazid preventive therapy (IPT) and patient factors associated with IPT completion in HIV-positive clients at the AHF LaMvelase clinic Swaziland. The literature review covers the evidence for choosing IPT for TB prevention, the impact of IPT on TB morbidity and mortality and use of IPT in patients previously treated for TB. A review of studies that showed IPT outcomes for clients given IPT and completion rates across studies was conducted. Studies that showed factors associated with IPT outcomes and the adverse events related to use of IPT, especially those leading to treatment discontinuation were reviewed. The literature review helped to contextualise the study, to see how others conducting similar studies carried them out, the outcomes and associated factors that have been found.

2.1 The choice of IPT for TB prevention

Treatment of active drug sensitive TB infection is usually by use of four drugs whereas LTBI treatment involves use of one (isoniazid or rifampicin) or two (rifapentine and isoniazid or rifampicin and isoniazid) drugs (Fox et al, 2017). Isoniazid six month regimen was found to be safe and efficacious in people living with HIV (Person & Sterling, 2012). This regimen was also associated with better treatment adherence compared to the longer isoniazid regimens. Standard therapy with IPT (six to 12 months) has been found to be equally effective compared to combination of rifampin and isoniazid short therapy in the treatment of LTBI (Ena & Valls, 2005). This meta-analysis compared progression to TB, severe adverse events and death as end points for patients in Hongkong, Spain and Uganda. Isoniazid mono-therapy was also found to be associated with less probability of discontinuation due to side-effects compared to multi-drug regimens for the prevention of TB disease (Akolo et al., 2010). The benefit of TB preventive therapy was more pronounced in those with a positive tuberculin skin test. A tuberculin skin test is done on the skin through injecting proteins derived from the TB bacillus and observing the reaction on the skin (CDC, 2016b). A positive test means a person has been exposed to TB infection. Akolo et al. (2010), concluded that the type of regimen chosen for TB prevention is dependent on market availability price, side-effects, compliance and drug resistance patterns.
2.2 Impact of IPT on TB morbidity and mortality

Zar et al. (2007) in their prospective double-blind placebo-controlled trial to determine the effect of IPT on TB incidence and mortality due to TB in children living with HIV in South Africa, found that IPT reduced morbidity and mortality from TB.

A systematic review of 12 randomised controlled trials conducted across the globe on the effectiveness of TB preventive therapy in people living with HIV found IPT to reduce incidence and mortality of TB disease (Akolo et al., 2010). Akolo et al. (2010) conducted a systematic review of randomised controlled trials that quantified the effect of IPT versus placebo in which they found that IPT reduced mortality in people living with HIV, particularly in children where early mortality was reduced by 50% and TB incidence was reduced by 70%.

Golub et al. (2007) in their retrospective medical record review on the impact of ART and IPT on TB incidence in HIV infected patients in Rio de Janeiro Brazil (the THRio study), found that ART and IPT reduced the risk of TB independently and those that were given both were at significantly lower risk of getting TB compared to those who did not get either therapy. In this study 76.1% of the 1096 patients who received IPT completed six months of treatment.

Badje et al. (2017) in the Temprano ANRS 12136 Cote d'Ivoire 2008 to 2015 trial of adult HIV patients on IPT found that the six-month IPT regimen had a mortality protective effect that lasted up to six years in clients with high CD4 count and on ART. Reduction in mortality was estimated to be 37%. The extended effect of IPT in patients on ART was attributed to synergistic effects of both IPT and ART in the same patient. The study also showed IPT to be beneficial in patients who had no evidence of latent TB infection and the benefit was independent of CD4 cell count. Assessing IPT completion in this study was important to estimate the population that is potentially protected from TB for the specified duration of the protective effect of the treatment.

The studies presented in this section demonstrate that IPT by itself or combined with ART is highly effective in reducing morbidity and mortality in people infected with HIV.

2.3 IPT as secondary prophylaxis for TB prevention

Churchyard et al. (2004) in their observational study on the efficacy of secondary IPT in HIV positive gold miners in South Africa found that IPT after TB treatment reduced recurrence of TB due to relapse or new infection by 55% as compared to the control group which did not receive
any type of TB preventive therapy. The protective effect of secondary IPT has been documented in Haiti (Fitzgerald et al., 2000) and in Abidjan (Haller et al., 1999). Secondary IPT is beneficial in high TB/HIV burden areas (Churchyard et al., 2004).

### 2.4 IPT outcomes

Durovni et al. (2010) conducted a cluster randomised trial in Brazil to determine whether routine screening for and treatment of latent TB in HIV clinic patients with access to ART will reduce TB incidence at the clinic level. Of the 1670 people living with HIV who started IPT 85% completed the therapy. IPT completion was higher among patients receiving ART (87%) than those not yet on ART (79%). Adverse reactions requiring discontinuation of treatment occurred in 1.2% of patients followed up. IPT was shown to decrease the incidence of TB disease in the people living with HIV with latent TB infection (Durovni et al., 2010). This study is important in showing that ART status may influence IPT outcomes.

Studies in Botswana, South Africa and Uganda showed moderate to high treatment completion rates (TCRs) of 47 – 88% (Uyei et al., 2011). In the studies the integration of HIV and TB services resulted in higher TCR in several settings. In this systematic review, TCR was defined as the percentage of patients who took at least 80% of prescribed doses within a nine month period (Adams et al., 2014).

A high IPT completion rate of 91%, 1% failure rate and 8% defaulter rate (due to poor adherence or side-effects) was reported by Medecins Sans Frontieres for 292 patients on ART in four sites in Shiselweni region in Swaziland (MSF, 2010). The methodology used to obtain the data in this pilot was not stated. The high completion rate recorded was in contrast to the low one reported by Cronin et al. (2015). The high completion rate can be attributed to the fact that only patients on ART were given IPT and this was under a study setting rather than programmatic. Another factor is that MSF as an organisation has rigorous measures put in place for patient support and follow up. The report on the pilot did not elaborate on the type of side-effects observed which would be useful in comparing the side effect profiles in different populations.

Varying treatment completion rates for IPT have been found in HIV infected individuals in different sites (Adams et al., 2014). This is similar to the two studies from Swaziland cited previously.
Adams et al. (2017) in their prospective cohort study on completion and adherence to treatment using different IPT delivery models in people living with HIV in public HIV/TB clinics in Swaziland, found adherence to be as high as 94.8%. In this study completion was defined as having taken at least 80% of the expected six-month doses. The completion rate in this study was 89.4%. The IPT discontinuation rate was 6.3% whereas patients who were lost to follow up comprised 4.1% of the sample.

### 2.5 Factors associated with IPT outcomes

Shayo et al. (2015) conducted a prospective multi-centre cohort study on IPT acceptance, adherence and completion in people living with HIV in Tanzania. They found that age affected outcomes as children less than 18 years were less likely to complete treatment as compared to adults. They found no association between IPT outcomes and sex, occupation, duration of HIV infection, being on ART and duration of ART.

Namuwenge et al. (2011) in their study on lost to follow up on IPT in people living with HIV at a non-governmental Voluntary Counselling and Testing sites in Uganda documented factors associated with lost to follow up. They found that people less than 30 years of age, those who had primary school level education or less and those who were widowed, separated, or divorced were at high risk of being lost to follow up compared to other people in the study. Those below 30 years of age were believed to possibly have considered themselves to have minimal risk of getting TB (Namuwenge et al., 2011), or they could not afford the frequent clinic visits due to high levels of unemployment in Uganda (Uganda Ministry of Gender, Labour and Social Development, 2006). People who spent less time in school have been found to have less knowledge on health issues hence they may not be aware of the benefits of TB preventive therapy. The lost to follow up (LTFU) in the widowed, separated and divorced was attributed to lack of social and emotional support as well as the possibility of increased workload after losing a partner who used to be responsible for other family or household activities (Namuwenge et al., 2011).

Adverse effects are part of outcomes of IPT which can lead one to default the therapy or have it discontinued at the health facility, yet they also affect other outcomes. A cross-sectional multicentre study in Ethiopia on adherence to IPT in people with HIV showed that adverse effects resulted in patients being 93% less likely to adhere to the prescribed doses (Mindachew et
al., 2011). This showed that adverse events reduce adherence to treatment as they make clients uncomfortable and clients fail to complete the course.

Oni et al. (2012) in their Khayelitsha, South Africa prospective cohort study of ART naive patients who had CD4 counts above 200 cells/mm³, found that patients who have a recent diagnosis of HIV, smoke or drink alcohol are more likely not to complete IPT. Although not statistically significant, they also found out that males and recent migrants to Khayelitsha appeared more likely to discontinue treatment. The TCR in this group was 69%. This was a small sample though, so results cannot be confidently generalised outside the study population.

According to The Aurum Institute (2012), potential serious side-effects of IPT in people living with HIV include hepatotoxicity, hypersensitivity rash, psychosis, convulsions and moderate to severe peripheral neuropathy. Rarely death may occur if there is a delay in stopping IPT in the event of hepatotoxicity and the risk of death associated with IPT has been found to range from 0.001% to 0.004% (Nolan et al., 1999; Salpeter, 1993; Churchyard et al., 2007, Grant et al., 2010 & The Aurum Institute, 2012). Grant et al. (2010) in their large cluster randomised study of community wide IPT among 24221 (95% males) gold miners in South Africa (Thibela TB study) which included those infected with HIV, reported hypersensitivity rash in 0.25%, peripheral neuropathy in 0.21%, clinical hepatotoxicity in 0.07%, convulsions in 0.02% of the study participants. In this study hepatotoxicity was found to be associated with consumption of alcohol but not with sex, age, weight or concurrent antiretroviral therapy.

### 2.6 Summary

This chapter reviewed the existing evidence on adopting IPT for TB prevention, its effect on morbidity and mortality. The IPT outcomes, factors associated with the outcomes were reviewed. Adverse events leading to IPT discontinuation were also discussed.

The next chapter describes the methods that were used in carrying out this study.
3. METHODOLOGY

This chapter states the aim and objectives of this study. It also gives an in-depth description of the study setting, approach and design. The study population is defined and sample selection discussed. Data extraction and the variables considered are described. The statistical analyses conducted on the data and the ethical considerations considered during this study are also explained.

3.1 Study Aim and Objectives

3.1.1 Aim of the study

The aim of this study was to determine the programmatic outcomes of isoniazid preventive therapy (IPT) and factors associated with treatment completion among people living with HIV aged 15 years and above at the AIDS Healthcare Foundation LaMvelase clinic in Manzini Swaziland, who were enrolled for IPT during the period March to December 2014.

3.1.2 Study objectives

1. To describe the socio-demographic and clinical characteristics of the clients
2. To describe the IPT outcomes in clients
3. To describe the range of side effects experienced whilst on IPT that led to treatment discontinuation by clients
4. To determine socio-demographic and clinical factors associated with IPT completion in clients

3.2 Description of study setting

The study was carried out during August and September 2017 at the AHF LaMvelase clinic in Swaziland. The clinic is run by the non-governmental organisation AIDS Healthcare Foundation (AHF) in partnership with the town council of Manzini. The clinic opened in 2007 to provide HIV testing, care, treatment and prevention services in a highly accessible area of the Manzini region.

In 2014 the clinic expanded its services to include TB services (screening, testing, treatment and prevention), sexual and reproductive health services. The clinic also recently started offering care
for non-communicable diseases. The clinic offers all services free of charge and is exclusively for people living with HIV and currently has about twelve thousand clients on treatment. The clinic boasts a 100% uptake of ART for HIV-TB patients as compared to the country average of 80% (WHO, 2015).

The clinic is centrally located and easily accessible as it is placed in the heart of the Manzini town near the public bus rank. The catchment area for the clinic is not just restricted to the city of Manzini. It serves people from other towns, peri-urban and rural areas. It has a reputation for quality service and good customer care and thus has attracted many people. It is currently the second largest HIV clinic in the Manzini region.

IPT services were introduced at the AHF LaMvelase Clinic in 2014 and nearly 3800 patients had been enrolled by the end of that year according to the clinic IPT register. A simple five question TB symptom screening tool (attached in appendix 6) is used to select patients for enrolment on IPT if they screen negative for TB (Swaziland Ministry of Health, 2012). The tool is used by TB screening officers and is administered to the clients as they wait to be seen by clinicians. Patients commenced on IPT are registered in the IPT register. The IPT register contains patient IPT serial number, patient names, chronic/HIV care number, date of starting IPT, date of completing or stopping IPT, the IPT outcome and a column for comments. The patient file contains details about demographic and clinical information. Patients are initiated on IPT by the doctors and nurses. Outcomes are regularly checked and updated by the TB screening officer and clinicians in the register and patient files.

### 3.3 Study Approach

A quantitative approach was applied in this study. This approach was chosen because the information required (outcomes) was already pre-formulated, many patient records had to be reviewed, a highly structured technique needed to be applied for data collection, and data needed to be quantified to allow generalisations to the population under study. Characteristics of groups rather than individuals are described (Robson, 2011) in this type of study. Previous studies on IPT outcomes have used this approach (Cronin et al., 2015; Medecins Sans Frontieres, 2010; Adams et al., 2014; Mindachew et al., 2011; Gust et al., 2011; Nolan et al. 1999; Oni et al., 2012; Diaz et al., 2010).
3.4 Study Design

A retrospective cohort study was conducted to describe the programmatic outcomes and factors associated with treatment completion in patients given IPT in an HIV/TB clinic setting. In this study IPT is the exposure and outcomes occur after the exposure. Data analysis was done retrospectively on exposure and outcomes (Bonita, Beaglehole and Kjellstrom, 2006). The focus of the study was on the range of programmatic outcomes namely treatment completion, treatment defaulting, treatment failure, death, transfer out, lost to follow up and treatment discontinuation at health facility. Socio-demographic and clinical characteristics recorded when the clients were enrolled for ART or Pre-ART were used in the analysis. A retrospective record review of the IPT register and patient file was conducted.

The retrospective cohort study was appropriate because data on people living with HIV who received IPT and their outcomes is available from the client records. The choice of the study method was also based on the limited time available to complete the thesis and this methodology was well aligned to the objectives.

3.5 Population and sampling

The IPT register was used to identify patients who were registered for IPT within the defined period. Treatment records for all people living with HIV 15 years and older who were initiated on IPT at the AHF clinic between March and December 2014 were reviewed. The cut off age for inclusion in the study was 15 years because the clinic is mainly an adult care treatment facility with low numbers of children as there is a paediatric clinic run by Baylor in the same town. The cohort of patients who received IPT in 2014 was chosen because this was the first batch of clients to ever receive IPT at this clinic, therefore would not have experienced side effects from the treatment warranting exclusion. This means that if the analysis had been done on a later cohort, chances are they would have received IPT previously since it is given every two years. So those who previously got IPT and developed side-effects that required the stopping of the drug would not have a repeat course thus the true occurrence of side-effects in the repeat IPT cohort would be lower. All records (whole population) of these clients were used to derive information required for the study. All records were used to improve the power to detect all outcomes and the factors associated with the outcomes. It was also reasonable to use all IPT cases in this age group as clinicians have tended to administer IPT to more ART patients.
compared to pre-ART patients. Inclusion of all clients who received IPT also ensured that all side effects that were observed are documented. There were initially 3801 records of patients who were given IPT and recorded in the year 2014 register. Table 3.1 below shows reasons for exclusion of some records from the study. In the final analysis only 3642 records were included.

Table 3.1: Reasons for exclusion of some records from the study

<table>
<thead>
<tr>
<th>Reason</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Records identified in the IPT register</td>
<td>3801</td>
</tr>
<tr>
<td>Records without final outcomes</td>
<td>110</td>
</tr>
<tr>
<td>Records of clients who took IPT home but never consumed it</td>
<td>26</td>
</tr>
<tr>
<td>Records of 2015 clients wrongly put in 2014 register</td>
<td>18</td>
</tr>
<tr>
<td>Staff members given IPT</td>
<td>5</td>
</tr>
<tr>
<td>Records eventually used for the study</td>
<td>3642</td>
</tr>
</tbody>
</table>

**Inclusion criteria**

1. IPT register records and chronic care files for all people living with HIV aged 15 years and above who received IPT at AHF LaMvelase clinic during the period March to December 2014
2. IPT register records and chronic care files for people living with HIV aged 15 years and above who received IPT soon after completing drug sensitive TB treatment
3. IPT register records and chronic care files for clients aged 15 years and above who transferred into care at LaMvelase clinic from other facilities but had been initiated on IPT within the defined period

**Exclusion criteria**

1. Records of people living with HIV who were registered for IPT and received the drug but were recorded in the register as ‘never used IPT’
2. Records of children less than 15 years
3. Records without documented final outcomes
3.6 Data Collection

A data extraction sheet (attached in Appendix 1) was used to extract the relevant data from the IPT register and patient files. Two research assistants (a data clerk and a nurse in the clinic) were hired to assist the researcher with the data abstraction. The researcher was also responsible for overseeing and double checking the work done by the research assistants. The IPT register was used to identify patients who were registered for IPT, their file numbers (to track the file), age, gender, date of starting IPT, date of stopping IPT and reasons for stopping IPT (if applicable), and this information was recorded on the data extraction sheet.

The patient file was then used to populate the rest of the information on the data abstraction sheet. The file was also useful in obtaining information missing from the IPT register. The socio-demographic variables recorded were age, gender, place of residence, employment status and marital status. These were collected to describe the study population and ascertain if there was an association between these and the study outcomes. Those who stayed in the rural and peri-urban area were jointly both grouped under rural for the purposes of this study because some rural/peri-urban areas are poorly demarcated.

Clinical variables were: time since HIV diagnosis, cotrimoxazole or dapsone use, on ART or pre-ART, duration of IPT, type of ART regimen, CD4 count at IPT initiation and type of IPT prophylaxis. These variables described the clinical characteristics of the study population and there was also need to find if there were associations between these and the outcomes. The Swaziland National IPT guidelines recommend six months (180 doses) of IPT within a nine month period (Swaziland Ministry of Health, 2012). The duration of IPT was measured to compare with the programmatic recommendation of six months. Interruption details of IPT were useful in the calculation of the actual IPT duration.

The types of ART drug regimens currently in use in Swaziland are first line, second line and third line. The US Department of Health and Human Services website AIDSinfo (2018) defines first line therapy as:

A treatment that is accepted as best for the initial treatment of a condition or disease. The recommended first-line HIV treatment regimens include antiretroviral (ARV) drugs that
are safe, effective, and convenient for most people with HIV who have never taken ARVs before.

Second line therapy is given to clients who have failed first line ART, while third line is given to clients who fail second line. Second and third line drug regimens tend to have higher pill loads compared to first line and this may affect consumption of IPT.

The CD4 count categories were divided into less than or equal to 200 copies per microliter and above 200 cells per microliter. Those with CD4 count below 200 are at high risk of life-threatening illnesses like TB.

A further dissection of the reasons for not completing IPT provided further clarification on non-completion outcomes.

According to the Swaziland Ministry of Health (2012) outcomes for IPT are completion, treatment failure, defaulting, death, transfer out, discontinuation at the clinic due to adverse effects and lost to follow up. A patient is considered to have completed treatment if they have received at least six months (180 doses) of isoniazid in a period of six to nine months. Treatment failure occurs if a person develops active TB disease whilst taking IPT. A defaulted outcome is given to a patient who has taken isoniazid for at least one month and then interrupts treatment for 60 days or more. The deceased category comprised of any person who died due to any cause whilst on IPT. A transfer out outcome is assigned to a person who has been transferred to another ART site or region to continue treatment. A person for whom the IPT has been discontinued by a healthcare worker due to adverse effects or any other reason is categorised under treatment discontinued. A patient who is lost to follow up (LTFU) on TB treatment is a TB patient who did not start treatment or whose treatment was interrupted for 2 consecutive months or more (WHO, 2014). This definition is difficult to apply to IPT as has been done with other IPT outcomes because a patient may stop taking IPT and still come to the clinic for other services and still refuse to resume IPT. In this study a LTFU patient was defined as one who did not present to the clinic for more than two months and efforts to trace them were fruitless. Patients who still came to the clinic but had stopped IPT for at least two months were classified under the defaulter category. These definitions of outcomes are similar to those used in a
Swaziland study on implementation of 36 months IPT in people living with HIV in Shiselweni region (Müller, 2016).

The health care workers mainly nurses are responsible for updating the IPT register and the chronic care patient file with the outcomes. When they see a client who has come for consultation they check if the client was given IPT and calculate if the duration of taking IPT has been adequate (six months) then they record a completed outcome. They also record other outcomes as they occur before the six months. It is worth noting that clients whose outcomes were not recorded were excluded from the study.

3.7 Data management
Data collected on the abstraction sheet was entered into the Statistical Package for Social Sciences (SPSS) for analysis. Numerical data was grouped into categories and frequencies recorded. Numerical variables were age, time between HIV diagnosis and starting IPT, time between starting ART and starting IPT and CD4 count at the time of starting IPT. Categorical variables were created to simplify data analysis for numerical variables.

3.8 Data Analysis
Descriptive statistics
The analysis of age was important to see the age distribution of the clients who received IPT. The time between HIV diagnosis and starting IPT was important to see how long the programme took to offer IPT to clients who were enrolled into HIV care. Some clients were also initiated on ART soon after HIV diagnosis and it was important to see the time the programme took to put clients on IPT after they started ART. Measurement of CD4 count was included as a proxy assessment of the clinical status of the client at IPT initiation.

Categorical data was summarised using frequencies and proportions. The variables were gender, place of residence, employment status, marital status, cotrimoxazole or dapsone use, ART status, ART regimen, IPT completion, IPT non-completion (defaulted, died, lost to follow up, transferred out, and discontinued at health facility) and type of IPT prophylaxis. Analysing these variables was important to see what proportions of clients who took IPT fell into the different categories.
Frequencies for the different outcomes were recorded to see if there were gaps between the expected or what has been seen before and this particular study population. The actual duration of IPT for clients whose outcomes were recorded as completed in the IPT register or chronic care file was calculated to ascertain if clients received adequate doses and to note any programme inefficiencies that may happen due to prolonged duration of IPT. The result was recorded in months.

The different side-effects that occurred in clients who took IPT which led to treatment discontinuation and the frequencies of these side-effects were recorded. Determining the frequencies of these side-effects was important for comparison with other populations.

**Analytical statistics**

The chi-squared test was used to test if there was an association between exposure (independent) variables (age, gender, place of residence, employment status, marital status, time since HIV diagnosis, cotrimoxazole or dapsone use, ART status, ART regimen, duration on ART before starting IPT, and CD4 count at IPT initiation, type of IPT and completion of an IPT course (dependent variable). The chi-square values and p-values were recorded. For the chi-squared test, the outcomes were grouped into a binary completion and non-completion variable. Completion was taken as is but the rest of the outcomes were put into the non-completion category.

Uni-variate logistic regression was conducted for the independent variables (age, gender, place of residence, employment status, marital status, time since HIV diagnosis, cotrimoxazole or dapsone use, ART status, duration on ART, and CD4 count at IPT initiation) versus IPT completion to determine if there were significant associations. The test was run for each variable independently without controls. Variables with p values less than 0.1 were used to conduct the multiple logistic regression analysis.

Multiple logistic regression was conducted for the variables: place of residence, ART status and CD4 count at IPT initiation to determine how these were related to IPT completion. The odds ratios, 95% confidence intervals and p-values were determined.
3.9 Validity and Reliability

Validity is the ability of an instrument to measure what it is supposed to measure (Bolarinwa, 2015). To ensure validity there were clear definitions of the outcomes (completed, defaulted, died, transferred out, lost to follow up and discontinued at health facility) in order to correctly categorise clients. The inclusion and exclusion criteria were clearly defined to determine the records which were to be included in the study. The data extraction tool was standardised to ensure that the same information was collected for each patient record. It was pre-tested on twenty patient records. Question 13 was changed from date of completing IPT to date of stopping IPT because some clients stopped IPT without necessarily completing the course. The research assistants were trained to ensure that they followed the standard operating procedure for data abstraction.

Reliability is the ability of the measuring tool to give the same result after repeated assessments (Heale and Twycross, 2015). The data extraction tool was based on data that is available and routinely recorded in patient files and registers hence repeat assessments would still give the same information.

3.10 Ethical Considerations

Approval for conducting this study was provided by the Bio-Medical Research Ethics Committee at the University of the Western Cape (attached in appendix 4), and the National Health Research Review Board of Swaziland (NHRBS) formerly the Scientific and Ethics Committee of Swaziland (attached in appendix 5). Further permission to conduct the study at LaMvelase clinic was obtained from the Medical Director of AIDS Healthcare Foundation in Swaziland (letter attached in appendix 3).

The information was extracted from the IPT register and patient files. Personal identifying information specifically the names was not used or captured (Cash et al., 2009) in the data extraction sheets. A study serial number was assigned to each record in addition to the IPT number and ART number that were on the patient record. The IPT and ART numbers were useful where cross checking became necessary during the data cleaning process.
Obtaining consent from patients whose records were used was not deemed necessary as this study analysed secondary data which would be disseminated in aggregated format that would not infringe on the privacy of the patients.

All the data extraction sheets were kept in a locked drawer at the clinic where the study was conducted and the electronic records were kept on the researcher’s password protected computer. The hard copy data extraction sheets were destroyed soon after the study as this information was entered on a spreadsheet and stored as electronic copies. The researcher kept the electronic copies thereafter.

Results obtained from the study were presented in an aggregated form which did not identify individual patients and were shared with the Medical Director at AHF clinic, the School of Public Health, University of the Western Cape and the NHRRBS.

3.11 Summary

The study aimed at determining programmatic outcomes of IPT and factors associated with IPT completion among people living with HIV aged at least 15 years, receiving care at the AHF clinic in Manzini Swaziland. A quantitative retrospective cohort analysis was conducted for all records that met the inclusion criteria. Information collected using a pre-tested data extraction tool was entered in SPSS and analysed to describe the IPT outcomes, the range of side-effects, and to determine socio-demographic and clinical factors associated with IPT completion. Approval for conducting the study was sought from relevant authorities. Findings from the study are presented in the next chapter.
4. RESULTS

This chapter presents the findings from the study and is aligned with the key objectives as outlined in the beginning of the methods chapter. The socio-demographic and clinical characteristics of the study population are initially summarised to describe the sample and its characteristics. This is followed by a presentation of the treatment outcomes for patients who took isoniazid preventive therapy (IPT); which are presented according to the pre-determined categories as described in the methods chapter and defined by the Swaziland National Guidelines. A summary of the IPT duration (from start to completion) for clients who were assigned the completed status is presented. A sub-analysis of patients who were classified as having discontinued their IPT at the health facility is completed to show the reasons for discontinuation other than treatment failure. The results from chi-squared tests to assess the associations between patient characteristics and outcomes is presented. The final section of this chapter outlines the results of the regression analysis which shows the variables that were associated with IPT completion.

4.1 Socio-demographic characteristics

Table 4.1 below gives the socio-demographic characteristics of the clients who took IPT. Most of the clients (83.1%) were in the greater than or equal to 30 years age group. Females comprised the majority (70%) of the clients. About half (50.6%) of the study population stay in the urban area. A good proportion (41.7%) of the clients were unemployed according to the record on the patient file. People who were identified as single accounted for 39.5% and the married comprised 36.7%. The divorcees and widows or widowers comprised 7.2% of the study under study.

Table 4.1: Socio-demographic characteristics of HIV infected clients aged 15 years and above who received IPT at the AHF LaMvelase clinic in 2014 N=3642

<table>
<thead>
<tr>
<th>Variable</th>
<th>Frequency</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;30</td>
<td>617</td>
<td>16.9</td>
</tr>
<tr>
<td>≥30</td>
<td>3025</td>
<td>83.1</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>1092</td>
<td>30</td>
</tr>
<tr>
<td>Female</td>
<td>2546</td>
<td>69.9</td>
</tr>
<tr>
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<td>4</td>
<td>0.1</td>
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</table>
**Place of residence**

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<thead>
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<th></th>
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</tr>
</thead>
<tbody>
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</tr>
<tr>
<td>Urban</td>
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**Employment status**

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</thead>
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<td>Unemployed</td>
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<tr>
<td>Employed</td>
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<td>Missing</td>
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<td>15</td>
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</table>

**Marital Status**

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</thead>
<tbody>
<tr>
<td>Single</td>
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</tr>
<tr>
<td>Married</td>
<td>1335</td>
<td>36.7</td>
</tr>
<tr>
<td>Divorced / Widowed</td>
<td>262</td>
<td>7.2</td>
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<tr>
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<td>607</td>
<td>16.7</td>
</tr>
</tbody>
</table>

### 4.2 Clinical characteristics

In Table 4.2 below, the clinical characteristics of clients who took IPT at the AHF clinic are presented. Most clients (73.8%) were diagnosed with HIV more than a year prior to commencement of IPT. A minority of 5.3% did not have the date of HIV diagnosis hence they could not be classified in the two previous categories.

**Table 4.2**: Clinical characteristics of HIV infected clients aged 15 years and above who received IPT at the AHF LaMvelase clinic in 2014 N = 3642

<table>
<thead>
<tr>
<th>Variable</th>
<th>Frequency</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time between HIV diagnosis and starting IPT (years)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 1 year</td>
<td>762</td>
<td>20.9</td>
</tr>
<tr>
<td>&gt;1 year</td>
<td>2687</td>
<td>73.8</td>
</tr>
<tr>
<td>Missing</td>
<td>193</td>
<td>5.3</td>
</tr>
<tr>
<td>On cotrimoxazole or dapsone</td>
<td>Yes</td>
<td>3642</td>
</tr>
<tr>
<td>On ART</td>
<td>Yes</td>
<td>3509</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>133</td>
</tr>
<tr>
<td>Time between starting ART and starting IPT (years)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 1 year</td>
<td>1131</td>
<td>31</td>
</tr>
<tr>
<td>&gt;1 year</td>
<td>2294</td>
<td>63</td>
</tr>
<tr>
<td>Missing</td>
<td>217</td>
<td>6</td>
</tr>
</tbody>
</table>
Type of ART regimen

<table>
<thead>
<tr>
<th>Type of ART regimen</th>
<th>Count</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>1&lt;sup&gt;st&lt;/sup&gt; line</td>
<td>3505</td>
<td>96.2%</td>
</tr>
<tr>
<td>2&lt;sup&gt;nd&lt;/sup&gt; line</td>
<td>4</td>
<td>0.1%</td>
</tr>
<tr>
<td>Missing</td>
<td>133</td>
<td>3.7%</td>
</tr>
</tbody>
</table>

CD4 count (cells per microliter)

<table>
<thead>
<tr>
<th>CD4 count (cells per microliter)</th>
<th>Count</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤200 cells per microliter</td>
<td>342</td>
<td>9.4%</td>
</tr>
<tr>
<td>&gt;200 cells per microliter</td>
<td>3229</td>
<td>88.7%</td>
</tr>
<tr>
<td>Missing</td>
<td>71</td>
<td>1.9%</td>
</tr>
</tbody>
</table>

Duration of IPT (months)

<table>
<thead>
<tr>
<th>Duration of IPT (months)</th>
<th>Count</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;six months</td>
<td>495</td>
<td>13.6%</td>
</tr>
<tr>
<td>Six to nine months</td>
<td>2974</td>
<td>81.7%</td>
</tr>
<tr>
<td>&gt;nine months</td>
<td>94</td>
<td>2.6%</td>
</tr>
<tr>
<td>Missing</td>
<td>79</td>
<td>2.2%</td>
</tr>
</tbody>
</table>

Type of IPT

<table>
<thead>
<tr>
<th>Type of IPT</th>
<th>Count</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary prophylaxis</td>
<td>3606</td>
<td>99.01%</td>
</tr>
<tr>
<td>Secondary prophylaxis</td>
<td>35</td>
<td>0.96%</td>
</tr>
<tr>
<td>Missing</td>
<td>1</td>
<td>0.03%</td>
</tr>
</tbody>
</table>

All the clients who took IPT were taking either cotrimoxazole or dapsone for the prevention of opportunistic infections like Pneumocystis Jiroveci Pneumonia (PCP/PJP), malaria, diarrhoea and severe bacterial infections. Cotrimoxazole or dapsone was being offered to all clients who are HIV infected in 2014 in Swaziland (Swaziland Ministry of Health, 2010).

Of those clients who were given IPT, the majority (96.3%) were on ART and the remainder were in pre-ART care. Almost two thirds (63%) of clients had been on ART for more than a year before they were introduced to IPT. Close to one third (31%) of clients started IPT within a year of starting ART.

The first line ART regimen was the most common amongst these IPT clients with 96.2% in this category and there were no patients on third line treatment.

About 9.4% of the clients had CD4 counts of 200 cells per millilitre or below. The majority of clients (88.7%) had a CD4 count of above 200 cells per millilitre.

Clients who took IPT for less than six months comprised 13.6%. These included those whose outcome was recorded as completed and the ones that did not complete treatment for various reasons. Those who took the number of recommended doses six to nine months were 81.7%. Only 2.6% took IPT beyond nine months.
A majority (99%) of the sample were taking IPT as primary prophylaxis as they had no documented history of TB in the IPT register and chronic care file.

### 4.3 IPT outcomes

Table 4.3 below shows IPT outcomes as assigned in the IPT register or patient file. Most clients (93.8%) completed their IPT course. The defaulter rate for IPT was 2.7%. Those who developed TB whilst taking IPT were classified under treatment failure and comprised 0.2%. The transfer out rate was 0.5% and lost to follow up rate was even lower at 0.2%. Treatment was stopped at the health facility in 2.5% of clients because of adverse effects or adherence issues. Clients who were defaulting on their treatment at least two times had their treatment stopped by the nurses or doctors to address adherence issues.

**Table 4.3: IPT outcomes for HIV infected clients aged 15 years and above who received IPT at the AHF LaMvelase clinic in 2014 N=3642**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Frequency</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Completed</td>
<td>3417</td>
<td>93.8</td>
</tr>
<tr>
<td>Defaulted</td>
<td>98</td>
<td>2.7</td>
</tr>
<tr>
<td>Treatment failure</td>
<td>8</td>
<td>0.2</td>
</tr>
<tr>
<td>Transferred out</td>
<td>20</td>
<td>0.5</td>
</tr>
<tr>
<td>Lost to follow up</td>
<td>7</td>
<td>0.2</td>
</tr>
<tr>
<td>Treatment discontinued at health facility</td>
<td>92</td>
<td>2.5</td>
</tr>
</tbody>
</table>

### 4.4 Actual duration of IPT for clients who were reported to have completed IPT

From the pie graph in Figure 4.1 below it is evident that of those who were reported as completing IPT, 89.2% received at least a minimum of six months (180) doses. Of note is that 10.6% took IPT for less than less months.
Figure 4.1: Actual duration of IPT for HIV infected clients aged 15 years and above who received IPT at the AHF LaMvelase clinic in whose outcomes were recorded as completed $N=3417$

4.5 Treatment discontinuation at health facility

Previously in Table 4.3 it was shown that 92 (2.5%) clients had their treatment stopped at the health facility. Figure 4.2 below shows the reasons for IPT discontinuation at health facility for HIV infected clients who received IPT at the clinic. This figure shows the percentages of clients whose treatment was stopped in relation to all clients who had treatment stopped at the health facility. Hepatotoxicity was the major reason for stopping treatment and contributed 63% of treatment discontinuations. This category included patients who came to the clinic complaining of jaundice, nausea, vomiting, abdominal pain and those whose liver enzymes were found to be elevated. Neuropsychiatric side-effects occurred in 9.8% of those whose treatment was discontinued and these included dizziness, confusion and psychosis. Clients who were poorly adherent to IPT and ART had their IPT discontinued at the facility and these contributed 7.6%. Breast tissue enlargement in males each contributed to 5.4% of discontinuations. Gastrointestinal disturbances contributed to 4.3% of discontinuations and this category comprised of clients who presented with persistent vomiting yet the liver enzyme tests were normal. Of note is that there were clients who had combinations of two side effects that led to treatment being stopped and
these contributed 3.3%. In 2.2% of clients there was no reason recorded for the treatment discontinuation.

**Figure 4.2: Reasons for IPT discontinuation at health facility for HIV infected clients aged 15 years and above who received IPT at the AHF LaMvelase clinic in 2014 N=92**

Table 4.4 below shows the range and frequency of side-effects observed in the study namely hepatotoxicity, neuropsychiatric, gynaecomastia, gastrointestinal disturbances, peripheral neuropathy and skin rash. Mosby (2012), defined gynaecomastia as abnormal breast tissue growth in males. Hepatotoxicity was commonest affecting 1.62% of the study population, followed by neuropsychiatric side-effects which occurred in 0.27% of the clients. Gynaecomastia occurred in 0.73% of the male clients. Gastrointestinal disturbances, peripheral neuropathy and skin rash occurred in 0.11%, 0.08% and 0.05% of clients respectively. Figure 4.2 illustrates frequencies and percentages of different reasons for stopping treatment among participants that
stopped treatment; which included non-side-effects. Table 4.4 provides the range of side effects in relation to the whole study population.

Table 4.4: Frequency and percentage of side-effects in HIV infected clients aged 15 years and above who received IPT at the AHF LaMvelase clinic in 2014 N=3642

<table>
<thead>
<tr>
<th>Side effects</th>
<th>Frequency</th>
<th>Percentage of study population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatotoxicity</td>
<td>59</td>
<td>1.62%</td>
</tr>
<tr>
<td>Neuropsychiatric side-effects (8 dizziness, 1 confusion, 1 psychosis)</td>
<td>10</td>
<td>0.27%</td>
</tr>
<tr>
<td>Gynaecomastia</td>
<td>8</td>
<td>*0.73%</td>
</tr>
<tr>
<td>Gastrointestinal disturbances</td>
<td>4</td>
<td>0.11%</td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td>3</td>
<td>0.08%</td>
</tr>
<tr>
<td>Skin rash</td>
<td>2</td>
<td>0.05%</td>
</tr>
</tbody>
</table>

*N= 1092 males only

4.6 Cross tabulations

Table 4.5 below shows the tests for association between socio-demographic and clinical factors and IPT completion. The Fischer’s Exact Test (FET) was used where cell counts were five or below. For cell counts above five, the chi-squared test was used. A p-value below 0.05 is significant. Of note is that statistically significant associations were found between place of residence (p=0.042) and CD4 count (p=0.004) versus IPT completion. A higher number of participants in the urban area and higher number of participants with higher CD4 counts completed treatment.

Table 4.5: Associations between socio-demographic and clinical characteristics with outcomes (Chi-squared and Fischer’s Exact tests) for HIV infected clients aged 15 years and above who received IPT at the AHF LaMvelase clinic in 2014 N=3642

<table>
<thead>
<tr>
<th>Completed IPT</th>
<th>Did not complete IPT</th>
<th>Total</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years) (n=3642)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;30</td>
<td>576</td>
<td>41</td>
<td>617</td>
</tr>
<tr>
<td>≥30</td>
<td>2841</td>
<td>184</td>
<td>3025</td>
</tr>
<tr>
<td>Gender (n=3638)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>1017</td>
<td>75</td>
<td>1092</td>
</tr>
<tr>
<td>Female</td>
<td>2396</td>
<td>150</td>
<td>2546</td>
</tr>
</tbody>
</table>
Place of residence (n=3513)

<table>
<thead>
<tr>
<th>Place of residence</th>
<th>Count</th>
<th>Rural</th>
<th>Urban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rural</td>
<td>1670</td>
<td>1584</td>
<td>86</td>
</tr>
<tr>
<td>Urban</td>
<td>1843</td>
<td>1718</td>
<td>125</td>
</tr>
</tbody>
</table>

Employment status (n=3095)

<table>
<thead>
<tr>
<th>Employment status</th>
<th>Count</th>
<th>Rural</th>
<th>Urban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unemployed</td>
<td>1518</td>
<td>1447</td>
<td>71</td>
</tr>
<tr>
<td>Employed</td>
<td>1577</td>
<td>1498</td>
<td>79</td>
</tr>
</tbody>
</table>

Marital status (n=3035)

<table>
<thead>
<tr>
<th>Marital status</th>
<th>Count</th>
<th>Rural</th>
<th>Urban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single</td>
<td>1438</td>
<td>1361</td>
<td>77</td>
</tr>
<tr>
<td>Married /Divorced</td>
<td>1335</td>
<td>1277</td>
<td>58</td>
</tr>
<tr>
<td>Divorced</td>
<td>262</td>
<td>250</td>
<td>12</td>
</tr>
</tbody>
</table>

Time between HIV diagnosis and starting IPT (n=3642)

<table>
<thead>
<tr>
<th>Time between HIV diagnosis and starting IPT</th>
<th>Count</th>
<th>Rural</th>
<th>Urban</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 1 year</td>
<td>762</td>
<td>709</td>
<td>53</td>
</tr>
<tr>
<td>&gt;1 year</td>
<td>2687</td>
<td>2525</td>
<td>162</td>
</tr>
</tbody>
</table>

On ART (n=3642)

<table>
<thead>
<tr>
<th>On ART</th>
<th>Count</th>
<th>Rural</th>
<th>Urban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>3509</td>
<td>3287</td>
<td>222</td>
</tr>
<tr>
<td>No</td>
<td>133</td>
<td>130</td>
<td>3</td>
</tr>
</tbody>
</table>

ART regimen (n=3509)

<table>
<thead>
<tr>
<th>ART regimen (1st line)</th>
<th>Count</th>
<th>Rural</th>
<th>Urban</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st line</td>
<td>3505</td>
<td>3283</td>
<td>222</td>
</tr>
<tr>
<td>2nd line</td>
<td>4</td>
<td>4</td>
<td>4</td>
</tr>
</tbody>
</table>

Time between starting ART and starting IPT (n=3425)

<table>
<thead>
<tr>
<th>Time between starting ART and starting IPT</th>
<th>Count</th>
<th>Rural</th>
<th>Urban</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 1 year</td>
<td>1131</td>
<td>1061</td>
<td>70</td>
</tr>
<tr>
<td>&gt;1 year</td>
<td>2294</td>
<td>2155</td>
<td>139</td>
</tr>
</tbody>
</table>

CD4 count (cells per microliter) (n=3571)

<table>
<thead>
<tr>
<th>CD4 count</th>
<th>Count</th>
<th>Rural</th>
<th>Urban</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤200</td>
<td>342</td>
<td>309</td>
<td>33</td>
</tr>
<tr>
<td>&gt;200</td>
<td>3229</td>
<td>3045</td>
<td>184</td>
</tr>
</tbody>
</table>

Type of IPT (n=3641)

<table>
<thead>
<tr>
<th>Type of IPT</th>
<th>Count</th>
<th>Rural</th>
<th>Urban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary prophylaxis</td>
<td>3606</td>
<td>3381</td>
<td>225</td>
</tr>
<tr>
<td>Secondary prophylaxis</td>
<td>35</td>
<td>35</td>
<td>35</td>
</tr>
</tbody>
</table>

4.7 Logistic regression analysis

Table 4.6 shows multivariate logistic regression analysis done on socio-demographic and clinical characteristics in relation to IPT completion for variables whose p value was less than 0.1. The first category for each variable was used as the reference category hence its assigned odds ratio (OR) was one. These variables were chosen after running a univariate logistic analysis of each independent variable without controls.

There was no statistically significant association between being on ART and IPT completion. The odds of completing IPT treatment were 25% less for rural dwelling clients compared to their urban counterparts. The odds of completing IPT were 75% higher for clients with CD4 count above 200 compared to those who had a lower CD4 count.
Table 4.6: Multiple logistic regression analysis of place of residence, ART status and CD4 count versus completion of IPT for clients aged 15 years and above who received IPT at the AHF LaMvelase clinic in 2014

<table>
<thead>
<tr>
<th>IPT completion</th>
<th>Multiple logistic regression analysis N=3501</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number of clients</td>
</tr>
<tr>
<td><strong>Place of residence</strong></td>
<td></td>
</tr>
<tr>
<td>Urban</td>
<td>1666</td>
</tr>
<tr>
<td>Rural</td>
<td>1835</td>
</tr>
<tr>
<td><strong>On ART</strong></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>3384</td>
</tr>
<tr>
<td>No</td>
<td>117</td>
</tr>
<tr>
<td><strong>CD4 count (cells per microliter)</strong></td>
<td></td>
</tr>
<tr>
<td>≤200</td>
<td>329</td>
</tr>
<tr>
<td>&gt;200</td>
<td>3172</td>
</tr>
</tbody>
</table>

4.8 Summary

Major findings from the study were: the greater than or equal to 30 years age group had the highest percentage (83.1%) of clients receiving IPT, women comprised 70% of those who received IPT, 73.8% of clients receiving IPT had been diagnosed with HIV for more than a year, 63% of clients had been on ART for more than a year, 100% of clients were taking cotrimoxazole or dapsone, 96.3% were on antiretroviral therapy (ART), a recorded high treatment completion rate of 93.8% and 89.2% of these received at least six months (180 doses) treatment. Side effects that led to treatment discontinuation at the clinic were hepatotoxicity, neuropsychiatric side effects, gynaecomastia, gastrointestinal disturbances, peripheral neuropathy and skin rash. Hepatotoxicity was the main side effect and accounted for 63% of treatment discontinuations. The odds of clients staying in rural areas completing were 25% less than their urban counterparts. Clients with higher CD4 counts had 75% higher odds of completing treatments compared to those with lower CD4 counts.
5. DISCUSSION

The main objective of this study was to determine the programmatic outcomes of isoniazid preventive therapy (IPT) and factors associated with treatment completion among people living with HIV aged 15 years and above at the AIDS Healthcare Foundation LaMvelase clinic in Manzini Swaziland, who were enrolled for IPT during the period March to December 2014. Specific objectives were to:

- To describe the socio-demographic and clinical characteristics of the clients
- To describe the IPT outcomes in clients
- To describe the range of side effects experienced whilst on IPT that led to treatment discontinuation by clients
- To determine socio-demographic and clinical factors associated with IPT completion in clients

5.1 Socio-demographic characteristics

Most of clients (83.1%) who were HIV-infected who received IPT at the clinic in 2014 were in the 30 years and above age group. This pattern corresponds well with the HIV prevalence in Swaziland which peaks at age 30-34 in women (54%) and 35-39 in men (47%) as reported in the Swaziland HIV Incidence Measurement Survey (SHIMS) First Finding Report (Swaziland Ministry of Health, 2012).

The percentage of women in the study was 70%. In 2014 women comprised 62.2% of the HIV infected population of Swaziland (The World Bank, 2018). The bigger proportion of women compared to men in this study can be partially attributed to the fact that there are more females in Swaziland compared to males (94 males per 100 females) as shown by the 2017 Swaziland Population and Housing Census Preliminary results (Central Statistical Office, 2017) and there is a higher prevalence of HIV in women in Swaziland (UNAIDS, 2018). In Canada it was demonstrated that women have better health-seeking behaviour compared to men (Thompson et al., 2016). The higher proportion of women on IPT found in this study was similar to findings by Pasipamire et al. (2016) where 59% of HIV infected clients on IPT were women in an evaluation of TB collaborative activities study done in Swaziland.
5.2 Clinical characteristics

The AHF LaMvelase clinic started operating in Swaziland in 2007 and IPT services started in 2014. The majority of clients (73.8%) had been diagnosed with HIV for more than a year and that 63% of clients had been on ART for more than a year prior to initiating IPT. This shows a delayed IPT initiation for clients as only 26.2% of clients received IPT within a year of HIV diagnosis and 37% received IPT within a year of starting ART. This finding shows that many clients who were given IPT had been enrolled into pre-ART and ART care for quite some time before the introduction of IPT at the facility. The time of enrolment into the IPT programme depended on the clinic rolling out this service. The health facility started IPT provision in 2014. IPT enrolment was also guided by the national guidelines which stated that a client had to be on ART for at least three to six months before starting IPT. A systematic review and meta-analysis by Gupta et al. (2011) on early mortality in adults initiating ART in low and middle-income countries showed the highest 12-month pooled mortality probability of 0.17 (95% CI 0.11–0.24) in Sub-Saharan Africa compared to other regions and TB was one of the commonest causes of mortality. In a study by Charalambous et al. (2010) clients were given IPT prior to or within three months of starting ART and this resulted in less advanced HIV disease at ART initiation for those who took IPT before ART, and reduced mortality for those who took it before or with ART (3.7-person years) compared to those who never took IPT (11.1-person years) with a hazard ratio of 0.34 (95% CI:0.24–0.49). These studies show that starting IPT early in people living with HIV reduces morbidity and mortality related to TB.

In this study cotrimoxazole or dapsone uptake was 100%. According to the Swaziland National HIV guidelines in use in 2014 all people living with HIV were supposed to receive cotrimoxazole or dapsone (Swaziland Ministry of Health, 2010). The high uptake of cotrimoxazole and dapsone shows good adherence to the guidelines and good recording of administering of these at the health facility.

Patients who were already taking antiretroviral therapy (ART) comprised 96.3%. A study by Mulissa, Jerene and Lindtjørn (2010) showed 25% percent of clients enrolled in a pre-ART programme became lost to follow up before starting ART. Lower rates of retention in pre-ART care (34.8-44.9%) have also been reported in several studies (Evangeli, Newell and McGrath, 2016; Lessells et al., 2011; du Toit et al., 2014). The higher lost to follow up in pre-ART clients
could explain why in the study at hand most clients who took IPT were on ART. A study from Ethiopia on the benefits of IPT and ART on tuberculosis incidence in HIV-infected people showed that clients in pre-ART group were less likely to be initiated on IPT (Yirdaw et al., 2014) as only 44% took the treatment. This figure is higher than findings at the AHF LaMvelase clinic where only 3.7% of clients receiving IPT were in the pre-ART group. The proportion of pre-ART clients being followed up at the AHF LaMvelase clinic was also less than that of those on ART as seen in the pre-ART registers in the health facility. Both ART and pre-ART clients were eligible for IPT although those recently starting ART had to wait at least three months before IPT enrolment.

5.3 IPT outcomes

Most clients (93.8%) had an outcome of IPT completion recorded. This is a high treatment completion rate (TCR) in programmatic set-up compared to the one of 47% obtained in Swaziland by Cronin et al. (2015). This study also had a high completion rate compared to those of 89.4% (Adams et al., 2017) and 91% obtained under study settings in Swaziland (MSF, 2010). Studies in Botswana, South Africa and Uganda showed moderate to high TCRs of 47 – 88% (Uyei et al., 2011). The achievement of a high treatment completion rate in this study can be attributed to harmonisation of ART and IPT refill appointments for clients which has been recommended by other researchers (Thindwa et al., 2018). Golub et al. (2007) in their retrospective medical record review on the impact of ART and IPT on TB incidence in HIV infected patients in Rio de Janeiro Brazil (the THRio study), found that ART and IPT reduced the risk of TB independently and those that were given both were at significantly lower risk of getting TB. Badje et al. (2017), in the Temprano ANRS 12136 Cote d’Ivoire 2008 to 2015 trial of adult HIV patients on IPT found that the six-month IPT regimen had a mortality protective effect that lasted up to six years in clients with high CD4 count and on ART. This extended effect of IPT in patients on ART was attributed to synergistic effects of both IPT and ART in the same patient.

The defaulter rate of 2.7% in this study was three times lower than findings by MSF (2010). This lower defaulter rate could be attributed to the fact that many clients (96.3%) were on ART hence their IPT refills were combined with ART refills. The treatment failure rate in the MSF pilot study was 1% which was much higher than the finding of 0.2% in this study. The clients who
developed or were diagnosed with tuberculosis (TB) while on IPT at the AHF LaMvelase clinic did not have isoniazid resistance as shown by the culture results in their follow up. Reduction in the IPT failure rate can be achieved through intensified pre-treatment screening for TB (Thailand Ministry of Public Health, 2000). Findings of a low treatment failure rate from this study could mean that there was thorough screening of clients for TB before IPT initiations thereby detecting most clients with TB.

5.4 Actual duration of IPT for clients who were reported to have completed IPT

In this study, IPT completion was taken to be the outcome recorded in the patient records or IPT registers. Comparison of this completion status versus actual duration of IPT given to clients showed some differences. Of the clients who had been recorded to have completed treatment, 10.6% received IPT for less than six months. Clients who received at least six months of treatment were 89.2%. The Swaziland country guidelines recommend six months of IPT and accommodates completion up to nine months. The programme is guided by this to procure isoniazid so there is a risk of stock outs and reduced cost effectiveness if clients are receiving the drug for a longer duration compared to the programme recommendation. A study by Pina et al. (2012) showed that while IPT for six months was comparable to the nine months in terms of cost effectiveness, the 12 months course was the least cost effective. Clinicians at times continue to refill IPT for a client without reviewing the duration leading to clients receiving the treatment for longer than the recommended period.

5.5 IPT side-effects

Findings from the study showed that side effects associated with treatment discontinuation were hepatotoxicity, neuropsychiatric disturbances, gynaecomastia, gastrointestinal disturbances, peripheral neuropathy and hypersensitivity skin rash. This side effect profile is related to IPT intake and has been found in South Africa, Mexico, Haiti, the United States, Zambia, Uganda and Kenya (The Aurum Institute, 2012; Bucher et. al., 1999).

Clients who developed hepatotoxicity constituted 1.62% of those given IPT at AHF LaMvelase clinic and this was quite high compared to findings from other studies namely 0.07% in a community wide IPT randomised controlled trial in South Africa (Grant et al., 2010), 0.75% in a
Ugandan randomised controlled trial for IPT in adults living with HIV (Whalen et al., 1997) and 0.13% in South African HIV-infected gold miners (Grant et al., 2005). These other studies mainly reported on clinical hepatotoxicity but in the study at hand clients had liver enzyme tests done at one month after initiation of IPT and at any other point if they became symptomatic. The tests done at month also detected those clients who had elevated liver enzymes but were asymptomatic so this is a possible reason for the higher prevalence of hepatotoxicity reported in this study. A meta-analysis involving 38257 clients who received isoniazid prophylaxis showed a risk of clinical hepatotoxicity ranging from 0% to 2.9% (Steele, Burk and DesPrez, 1991).

Findings at the AHF LaMvelase clinic fall within this range.

Clients who developed neuropsychiatric disturbances (dizziness, confusion, psychosis) comprised 0.27% of those who took treatment. Only one client (0.03%) developed psychosis. A study in Swaziland on the different models of IPT delivery showed that 0.2% (2) of 908 clients developed psychosis whilst taking IPT (Adams et al., 2017). This was seven times higher than findings at the AHF LaMvelase clinic hence it is possible that there were other contributing factors to the development of psychosis in these clients. Isoniazid induced psychosis is a rare side effect and has mainly been reported in case studies (Menon et al., 2017; Masood et al., 2011; Herrag, Sajiai and Alaoui Yazidi, 2011), and these findings are consistent with the current study’s findings.

Isoniazid associated breast enlargement is a rare side-effect (Khan and Agarwal, 2012; Morrone et al., 2008). It has been reported mainly as case studies and a systematic review of the Pubmed database by Khan and Agarwal (2012) reviewed five cases of isoniazid induced gynaecomastia. In the study at LaMvelase clinic 0.73% of males who took IPT developed gynaecomastia which resolved upon stopping isoniazid. Masuka et al. (2018) in their comparison of adverse events in patients on ART and TB found that gynaecomastia was more common in patients on ART. In patients taking TB treatment isoniazid has been found to be the drug causing abnormal breast enlargement in men (Kyung Lee et al., 2009; Manjunatha Goud et al., 2012). Efavirenz has been found to be the commonest ART drug to cause abnormal breast enlargement in males (Njuguna et al., 2016; Mayo Clinic, 2018). The 0.73% clients who developed gynaecomastia had also been on efavirenz for some time prior to being given isoniazid. The fact that gynaecomastia developed after introduction of isoniazid and fully resolved after stopping the drug suggests that the
isoniazid could have been the cause or the administering of both efavirenz and isoniazid put the clients at higher risk of developing the side effect. Gynaecomastia was found to be more common than previously reported elsewhere. The high prevalence of gynaecomastia in this population compared to literature may be because a big number of clients were exposed to isoniazid preventive therapy compared to the usual lower numbers of people treated for TB.

While the WHO (2015) has identified vomiting coupled with elevated liver enzymes under hepatotoxicity, in this study 0.11% of clients had severe vomiting which was not associated with elevated liver enzymes and were classified under gastrointestinal disturbances. In a Brazilian study by Durovni et al. (2010), 0.41% of clients developed gastrointestinal disturbances that led to treatment discontinuation and this is comparatively higher than the one at AHF LaMvelase clinic. This could be because those who presented with gastrointestinal symptoms at AHF LaMvelase clinic and were confirmed to have elevated liver enzymes were classified under those who developed hepatotoxicity.

Peripheral neuropathy leading to treatment discontinuation occurred in 0.08% of clients given IPT and this was lower than the 0.21% found by Grant et al. (2010). Clients receiving IPT were also routinely given pyridoxine 25mg to prevent peripheral neuropathy hence the occurrence of peripheral neuropathy was possibly lower than what would have been obtained without the use of pyridoxine. It is also important to note that only severe peripheral neuropathy leading to treatment discontinuation was reported in this study.

Clients who developed hypersensitivity rash leading to stopping of treatment comprised 0.05% of those who took IPT. This was five times lower than findings from a South African study which evaluated side effects due to isoniazid preventive therapy (Grant et al., 2010). The difference in the findings from these studies is because Grant et al. (2010) reported all cases of hypersensitivity skin rash yet at the AHF LaMvelase clinic only cases in whom IPT was discontinued were reported. A study in Malawi also showed a high prevalence of skin rash (1.8%) in clients who took IPT and had to have the drug stopped due to this side effect (Thindwa et al., 2018).
5.6 Factors associated with IPT completion

Apart from place of residence and CD4 count, all the other socio-demographic and clinical factors were not significantly associated with IPT completion. Another study by Namuwenge et al. (2012) showed that younger people below 30 years of age were less likely to complete IPT compared to the older age groups. In this study the chi squared test p value was 0.597 showing no statistically difference in IPT completion between those below the age of 30 and the older group.

Clients staying in the rural area had 25% less odds of completing treatment in comparison to those residing in the urban area. Urban dwellers had higher chances of completing treatment compared to their rural counterparts probably because they were nearer the clinic hence, they did not face financial constraints related to travel. The rural folk may also face challenges of the long distance to travel to health facilities and also limited availability of public transport. Similar findings were observed in a Tanzanian study which assessed completion of IPT in HIV-infected patients (Munseri et al. 2008).

Those with CD4 counts greater than 200 cells per micro millilitre had a higher chance of completing treatment compared to those with CD4 counts of 200 cells per millilitre and below. This is similar to observations made in Malawi where a low CD4 count (100-350 copies per millilitre) was associated with non-completion of IPT. Non-completion in patients with lower CD4 counts at the LaMvelase clinic study may possibly due to the fact that these clients are severely immune-compromised and too sick to come to the clinic on a regular basis. The other explanation maybe that due to the compromised immune system, they have many concurrent opportunistic infections for which they might be receiving treatment thereby increasing the pill burden and the risk of stopping treatment increases.

5.7 Limitations

The retrospective nature of the study does not permit measurement of the incidence of TB and the extent of TB prevention derived from use of IPT in the population under study because of the short period covered by the study. A prospective cohort study would have been more suitable but due to time and cost constraints this was not practical.
The use of secondary data is a challenge as it may be incomplete. Secondary data may have been collected only for service management and is not specifically tailored to the needs of this research. In selecting records to include in the study 4% (159) were discarded because they did not have IPT outcomes. According to IBM (2009) problems that can arise because of missing data include automatic deletion of cases with incomplete information by the statistical procedure, statistically insignificant data because of low input data and results may be equivocal if the cases included in the analysis do not represent a random sample of the dataset. Variables which had missing data of at least 5% were employment status (15%), marital status (16.7%), time between HIV diagnosis and starting IPT (5.3%) and time between ART initiation and starting IPT (6%). Records which have incomplete data were automatically excluded from the statistical procedures namely chi-squared test, Fischer’s exact test and regression analysis. To minimise the effect of missing data on the multi-variate logistic regression model, uni-variate logistic regression was done first and variables with significant p-values were then computed into the multiple logistic regression model.

Socio-economic factors for example level of education or income levels, associated with adherence were not measured in this study because this information was not recorded in the IPT register or on patient files.

The patients who took IPT were not specifically selected or randomised therefore they could be different from those who did not take IPT but access services in the clinic. The AHF LaMvelase clinic is exclusive for people living with HIV and at the time of the study had about 12 000 clients in care and approximately 30% of these were enrolled in the study. This 30% represents 96% of clients on IPT in the health facility hence one can safely say the sample representative of all adult clients on IPT in the facility but not children. The sample has patients with different clinical and socio-demographic characteristics hence it can also be considered to be representative of the people living with HIV on IPT in Swaziland.

The employment status was recorded at the time the patient was registered for ART and pre-ART and may not have been the actual one at the time of taking IPT.

Recording of outcomes in the IPT register and chronic care files need the healthcare worker to actively check if the client has completed the six months treatment or has stopped treatment for
any reason and document. A good number of clients did not have their outcomes updated in both the IPT register and the chronic care file. There were also computation errors as evidenced by the assignment of the completed outcome to clients who received IPT for less than six months.

Only side effects leading to treatment discontinuation at the health facility were reported in this study. There is possibly an underestimate of the reported side effects because clients who stopped treatment on their own may have experienced side effects but did not report them. Minor side effects that did not result in stopping of treatment were not reported or recorded in the IPT register.

5.8 Generalisability

The results of this study apply mainly to the study population but may have wider relevance to people in Swaziland who are infected with HIV and receiving HIV care and IPT services at public institutions that have set up effective TB/HIV collaborative activities. This sample has a good representation of clients aged 15 years and above who are on ART and receiving IPT. The findings can be generalised to countries in Sub-Saharan Africa as they are faced with a similar TB/HIV epidemic.
6. CONCLUSION AND RECOMMENDATIONS

6.1 Conclusions
A high treatment completion rate was demonstrated in clients who received IPT at AHF LaMvelase, most likely due to harmonisation of ART and IPT refills. Hepatotoxicity, neuropsychiatric effects, gynaecomastia, gastrointestinal disturbances, peripheral neuropathy and skin rash continue to be important side effects to monitor for in clients receiving IPT. Hepatotoxicity was the commonest side effect leading to treatment interruption. Occurrence of gynaecomastia was found to be more common than previously reported elsewhere. Residing in the rural area was found to be associated with lower IPT completion rates. Having a higher CD4 count was associated with higher IPT completion rates.

6.2 Recommendations
❖ The best practices done at this clinic to achieve high IPT completion rates need to be shared so that other health facilities within the country and worldwide can adopt and improve patient care. Harmonisation of ART and IPT drug refills have been found to improve IPT completion in people living with HIV (Thindwa et al., 2018)
❖ Implications/areas for future research
  o Reasons for high IPT completion rates (mixed methods study)
  o Follow up studies to determine the duration of the effectiveness of the six-month IPT regimen in this population are required since Swaziland is a HIV/TB high burden country.
  o Case studies for the hepatotoxicity cases
  o Case studies for the gynaecomastia cases
  o Assessing implementation of early TB preventive therapy uptake for clients who have been on ART for at least a month in line with the recent WHO guidelines
  o Exploring shorter TB preventive therapy regimens in Swaziland
❖ Implications for future practice
  o Close monitoring of clients to detect hepatotoxicity as it is a potentially life-threatening side effect if not adequately managed
The lower completion rates for the rural population call for a differentiated approach to service delivery for this population. Intensified community mobilisation and education on TB preventive. Community outreach services for IPT refills in conjunction with other services may also be helpful. Swaziland is currently in the process of scaling up differentiated service delivery for ART patients and this may be an opportunity to integrate several services in one package.

The association of lower CD4 count with lower treatment completion rates could imply that we are losing these clients to opportunistic infections or they have pill burden due to comorbidities which is affecting their adherence to treatment. Clients with advanced disease need close monitoring to identify and promptly treat opportunistic infections and comorbidities to reduce morbidity and mortality.
REFERENCES


Durovni, B. et al. (2010) ‘The implementation of isoniazid preventive therapy in HIV clinics: the


http://etd.uwc.ac.za/


http://etd.uwc.ac.za/
Appendix 1: Data extraction sheet

REVIEW OF OUTCOMES FOR IPT AMONG HIV INFECTED CLIENTS AT A CLINIC IN SWAZILAND

| Study serial number: ……………… IPT number……………………. File number …………………… |

SECTION A: SOCIO-DEMOGRAPHIC INFORMATION

1. Age (in years) …………
2. Gender  
   - □ Male
   - □ Female
3. Residence  
   - □ Urban
   - □ Rural
4. Employment status  
   - □ Formally employed
   - □ Self employed
   - □ Unemployed
5. Marital Status  
   - □ Single
   - □ Married
   - □ Divorced
   - □ Widowed

SECTION B: CLINICAL INFORMATION

6. Time since HIV diagnosis……………Years…………Months
7. Patient on cotrimoxazole or dapsone  
   - □ Yes
   - □ No
8. Patient on ART  
   - □ Yes
   - □ No (Go to question 11)
9. Time since starting ART …………Years…………Months
10. ART regimen  
    - □ First line
    - □ Second line
    - □ Third line
11. CD4 count at IPT initiation (cells per micro-millilitre) ……………
12. Date of starting IPT…………………………
13. Date of stopping IPT………………..
14. Duration of IPT…………………
15. Duration of interruption (if any) …………
16. Outcomes  
   - □ Completed
   - □ Defaulted
   - □ Treatment failure
   - □ Died
   - □ Transferred out
   - □ Lost to follow up
   - □ Treatment discontinued at health facility
   - □ Side-effects (Specify)
   - □ Poor adherence
17. Type of IPT  
   - □ Primary prophylaxis
   - □ Secondary prophylaxis

For research assistant only: I confirm that the information above is correct and has not been fabricated or falsified. Signature……………………………………… Date…………………………
Appendix 2: Permission Request letter to clinic Medical Director

Flat FE1 Extension 7
Manzini
Swaziland
16 August 2016

The Medical Director
AHF-Swaziland
Corner Nkoseluhlaza and Sandlane Streets
Manzini,
Swaziland

Dear Sir

Re: Request to access patient data for the purpose of a study on “Review of outcomes for isoniazid preventive therapy among HIV infected clients at a clinic in Swaziland”

I am a Master in Public Health student at the University of the Western Cape, South Africa and also a clinician at the AHF-LaMvelase Clinic. I am requesting for your permission to access patient information in carrying out the above said study as you are in charge of AHF clinics in Swaziland. The study is a requirement for the partial fulfilment for the completion of my Master in Public Health degree.

The aim of this study is to determine outcomes of IPT and their associated factors among HIV-infected clients receiving care at AHF LaMvelase clinic for the period March 2014 to December 2015. This data will be useful primarily for clinicians in the facility to put in place measures to improve completion rates and also to look out for and manage side-effects more effectively while at the same time tracking defaulters and lost to follow ups. This data will also be useful at national level to estimate expected IPT toxicity and also adoption of best practices to improve IPT uptake and completion. TB incidence outcomes are useful for planning of resources used in the prevention, diagnosis and management of TB.
All records of patients who took IPT between March 2014 and December 2015 will be used in the proposed study and information collected on a data extraction sheet (attached to this letter). Data collection will be done at AHF-LaMvelase Clinic over one to two months. I am requesting to use my consulting room and TB room during the free hours for the data collection period to ensure safety and confidentiality of patient records. IPT serial numbers will be the only code used on data extraction sheets. I am also requesting to engage the services of two clinic staff members (data clerk and TB screening officer or TB nurse) during their free time to assist in retrieval of patient records and data collection. The use of internal people will further enhance confidentiality of patient information. Information collected on data extraction sheets will be kept in a locked cabinet until the end of the study when it will be destroyed. Electronic records will be kept on the researcher’s password protected computer. The final report will be in form of aggregated information about prevalence of outcomes and factors affecting outcomes, without characteristics that link records to the actual patient.

The study findings will be shared with the AHF organisation. Approval to conduct the study is also being sought from the University of the Western Cape Ethics Committee and Swaziland National Health Research Review Board.

For any questions with regard to the research study please contact me Dr Normusa Musarapasi on cell phone number +26876397782, email: normusamg@gmail.com or my Supervisor: Dr. Lucia Knight, University of the Western Cape, Private Bag X17, Bellville, 7535, Telephone: +27 21 959 2243, Email address: lnknight@uwc.ac.za.

Yours faithfully,

Dr Normusa Musarapasi
Appendix 3: Permission letter from clinic’s medical director

18 August 2016

To: School of Public Health
   University of the Western Cape

Dear Sir/Madam

**RE: Permission to Conduct Research at LaMvelase Help Centre**

I have reviewed Dr Normusa Musarapazi’s research concept paper/protocol and understand what the study titled: “Review of outcomes for isoniazid preventive therapy (IPT) among HIV infected clients at a clinic in Swaziland” entails.

I have the authority to and hereby grant her permission to conduct this research at the AIDS Healthcare Foundation’s LaMvelase Help Centre Clinic in Manzini.

**Dr Nkululeko Dube**
Medical Director
AIDS Healthcare-Swaziland
Phone: +268 76969451(Mobile)
+268 25059183(Office)
E-mail: nkululeko.dube@aidshealth.org
Appendix 4: UWC Ethics approval

OFFICE OF THE DIRECTOR: RESEARCH
RESEARCH AND INNOVATION DIVISION

Private Bag X17, Bellville 7535
South Africa
T: +27 21 916 1988/2948
F: +27 21 916 2170
E: research_etd@uwc.ac.za

http://etd.uwc.ac.za/

19 January 2017

Dr N Munyapazi
School of Public Health
Faculty of Community and Health Sciences

Ethics Reference Number: BM/1/1/7

Project Title: Review of outcomes of tenofovir emtricitabine therapy among HIV infected clients at a clinic in Swaziland

Approval Period: 15 December 2016 – 15 December 2017

I hereby certify that the Biomedical Science Research Ethics Committee of the University of the Western Cape approved the scientific methodology and ethics of the above mentioned research project.

Any amendments, extension or other modifications to the protocol must be submitted to the Ethics Committee for approval. Please remember to submit a progress report in good time for annual renewal.

The Committee must be informed of any serious adverse event and/or termination of the study.

[Signature]

Ms Patricia giants
Research Ethics Committee Officer
University of the Western Cape

PROVISIONAL REC NUMBER: 120416-010

http://etd.uwc.ac.za/
Appendix 5: Swaziland NHRRB Ethics approval

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**Research Protocol clearance certificate**

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<td>Name of contact officers</td>
<td>Ms Slibange le Tjuma</td>
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<td><a href="mailto:kalxamasi@gmail.com">kalxamasi@gmail.com</a></td>
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<td>Telephone no.</td>
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Page 1 of 2
Appendix 6: Swaziland Ministry of Health tuberculosis screening tool

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**ACTION TAKEN**

Note: If a case satisfies the instructions in (a) to (d) then select POSITIVE; but if it does not, then select NEGATIVE.

System collected for Lab Investigation: Yes / No

Referral to Doctor for Clinical Assessment: Yes / No

---

Name of Facility: Ministry of Health TB Screening Tool

| Date: / / /       |                                     |
| Patient Data:     |                                     |
| Age:              |                                     |
| Sex: M / F        |                                     |
| Weight (in Kgs):  |                                     |
| Height (m):       |                                     |
| Entry Point:      |                                     |
| Patient ID:       |                                     |
| Patient Category: |                                     |
| Pre-ART/ART R. No.|                                     |
| Question 1:       |                                     |
| Current Cough? (a)| Fever for 2 weeks or more?          |
| Question 2:       |                                     |
| Poor weight gain/loss to 10% History of contact with a TB case |
| Question 3:       |                                     |
| SCREEN RESULT:    |                                     |
| POSITIVE (Presumptive TB) | NEGATIVE |

**ACTION TAKEN**

Note: If a case satisfies the instructions in (a) to (d) then select POSITIVE; but if it does not, then select NEGATIVE.

System collected for Lab Investigation: Yes / No

Referral to Doctor for Clinical Assessment: Yes / No

---

Name of Facility: Ministry of Health TB Screening Tool

| Date: / / /       |                                     |
| Patient Data:     |                                     |
| Age:              |                                     |
| Sex: M / F        |                                     |
| Weight (in Kgs):  |                                     |
| Height (m):       |                                     |
| Entry Point:      |                                     |
| Patient ID:       |                                     |
| Patient Category: |                                     |
| Pre-ART/ART R. No.|                                     |
| Question 1:       |                                     |
| Current Cough? (a)| Fever for 2 weeks or more?          |
| Question 2:       |                                     |
| Fever for 2 weeks or more? | Night Sweats for 2 weeks or more?  |
| Question 3:       |                                     |
| Poor weight gain/loss to 10% History of contact with a TB case |
| Question 4:       |                                     |
| SCREEN RESULT:    |                                     |
| POSITIVE (Presumptive TB) | NEGATIVE |

**ACTION TAKEN**

Note: If a case satisfies the instructions in (a) to (d) then select POSITIVE; but if it does not, then select NEGATIVE.

System collected for Lab Investigation: Yes / No

Referral to Doctor for Clinical Assessment: Yes / No

---

Name of Facility: Ministry of Health TB Screening Tool

| Date: / / /       |                                     |
| Patient Data:     |                                     |
| Age:              |                                     |
| Sex: M / F        |                                     |
| Weight (in Kgs):  |                                     |
| Height (m):       |                                     |
| Entry Point:      |                                     |
| Patient ID:       |                                     |
| Patient Category: |                                     |
| Pre-ART/ART R. No.|                                     |
| Question 1:       |                                     |
| Current Cough? (a)| Fever for 2 weeks or more?          |
| Question 2:       |                                     |
| Fever for 2 weeks or more? | Night Sweats for 2 weeks or more?  |
| Question 3:       |                                     |
| Poor weight gain/loss to 10% History of contact with a TB case |
| Question 4:       |                                     |
| SCREEN RESULT:    |                                     |
| POSITIVE (Presumptive TB) | NEGATIVE |

**ACTION TAKEN**

Note: If a case satisfies the instructions in (a) to (d) then select POSITIVE; but if it does not, then select NEGATIVE.

System collected for Lab Investigation: Yes / No

Referral to Doctor for Clinical Assessment: Yes / No

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