ISONIAZID PREVENTIVE THERAPY FOR TUBERCULOSIS OCCURRENCE IN HIV-POSITIVE PATIENTS IN LESOTHO

by

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DECLARATION WITH REGARD TO INDEPENDENT WORK

I, ELTONY MUGOMERI, identity number , and student number , do hereby declare that this research project submitted to the Central University of Technology, Free State for the Degree DOCTOR OF HEALTH SCIENCES: BIOMEDICAL TECHNOLOGY, is my own independent work; and complies with the Code of Academic Integrity, as well as other relevant policies, procedures, rules and regulations of the Central University of Technology, Free State; and has not been submitted before to any institution by myself or any other person in fulfilment (or partial fulfilment) of the requirements for the attainment of any qualification.

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SUMMARY

Tuberculosis (TB) remains a main public health problem, particularly in people living with HIV (PLHIV) in sub-Saharan Africa (SSA). This persistent problem may be an indication of underlying problems in national health policies, and their implementation in SSA. The Southern African country of Lesotho, with one of the highest TB incidences in the world, is facing a catastrophic syndemic of HIV and tuberculosis (TB). The effectiveness of isoniazid preventive therapy (IPT), which has the potential to reduce the incidence of TB in PLHIV, has not been adequately evaluated since its introduction in 2011. This study evaluated the uptake of IPT, its effectiveness and the associated factors in Lesotho, with the aim of establishing the necessary policy changes required to prevent the occurrence of TB in PLHIV.

To determine the effectiveness of IPT and the factors underpinning the implementation of this intervention in Lesotho, a quantitative evaluation as well as a qualitative study of the implementation of IPT was used. The study was therefore based on a triangulation of quantitative and qualitative research methods in two phases.

The qualitative phase of the study identified health system challenges affecting the implementation of IPT, based on a cross-sectional qualitative analysis of interview responses of healthcare workers and stakeholders of the TB/HIV programmes, which included the Ministry of Health officials and support partners, purposively selected for their roles in IPT implementation in Lesotho. The rationale of this study phase was based on the premise that the rate of initiation of IPT and its effectiveness is largely dependent on the quality of implementation of the IPT programme.

The qualitative study phase revealed that seven factors in the health system were affecting the implementation of IPT in the country, namely poorly decentralised HIV services; inefficient monitoring and evaluation systems; ineffective service delivery; interrupted supply chains; an undertrained and inadequate health workforce; insufficient health system financing; and inefficient health information systems. The implementation of IPT was therefore a complex task which needed certain sectors of the health system to change. The most important lesson from this is that key health interventions need a 'health system approach' for success.

The quantitative phase of the study was a quasi-experimental review of HIV-positive medical records randomly selected from eight health institutions in six districts of Lesotho. This study phase selected two patient groups, one enrolled into antiretroviral therapy (ART) before (2004-2010 cohort), and the other one after the launch of IPT (2011-2016 cohort), to establish the rate of initiation of IPT and its effectiveness in preventing the occurrence of TB in the country. IPT uptake and its effectiveness were evaluated using an analytical model based on Cox's proportional hazards regression analysis, an approach often used to determine the relative risk of contracting a disease and the associated factors.

The quantitative study phase included 2 955 randomly selected records that met the inclusion criteria set for the study. Overall, 68.8% of the 2 955 patients had received IPT over a course of six years (2011-2016), which translated to a sluggish IPT uptake rate of 20.6 per 100 person-years over the six-year period. Notably, only 135 (6.6%) patients defaulted IPT, which is a small proportion. Comparatively, the 2011-2016 cohort had a significantly (p=0.000) higher rate of IPT initiation (27.0 per 100 person-years) than the

2004-2010 cohort, (15.8 per 100 person-years), implying that patients newly enrolled into ART had a higher rate of IPT initiation. Findings indicated that the most significant predictors for initiation of IPT were age group, district category and duration of ART. Furthermore, based on odds ratios (OR), patients in the sparsely populated districts (OR=1.6) and males (OR=2.1) had significantly (p<0.05) higher odds of defaulting IPT, compared to those in the densely populated districts and females, respectively. Whereas higher defaults in the sparsely populated districts were associated with long distance from hospitals and the mountainous terrain associated with these districts, higher rates of defaulting by males were most likely due to migrant work in South Africa.

The TB incidence rate reduced from 2.3 per 100 person-years in 7 985 person-years in the 2004-2010 cohort, to 1.6 per 100 person-years in 4 223 person-years in the 2011-2016 cohort, implying that the IPT intervention had considerably reduced the occurrence of TB. However, the use of IPT was not without adverse effects. By proportion, the most common side effects to IPT were skin rash (37.2%), peripheral neuropathy (25.4%) and liver toxicity (9.4%). In addition, out of 246 patients who had developed TB and were discovered during a follow-up, 15.9% of the patients developed TB after exposure to IPT. Further findings indicated that prescribing IPT within one year of ART commencement, which reduced TB incidences to only 1.3 incidences per 100 person-years, was the most effective intervention for preventing the occurrence of TB, compared to other commencement timing of IPT intervention. Other TB incidences per 100 person-years by timing of IPT were as follows – IPT before ART (1.7), IPT after ART (1.8), no IPT (2.6), and IPT 3-5 years after ART initiation (2.3). Gender, baseline WHO clinical stage, district category and time to IPT relative to ART commencement emerged as significant predictors of TB occurrence. Notably, increasing commencement time for IPT by one six-

month interval increased the risk of contracting TB by between 6% and 59%, depending on the cohort, with the 2011-2016 cohort having a higher risk compared to the 2004-2010 cohort.

The findings of this study indicate that the implementation of IPT in Lesotho has notable challenges. Clearly, there is a need to improve the rate of IPT initiation in the patient groups with the most sluggish rate of IPT uptake, and to improve retention of some patient groups with poor adherence to IPT. The findings of this study also indicate that delayed IPT commencement after ART initiation significantly affects the effectiveness of IPT. Furthermore, the study reveals that IPT is a complex health intervention, and its implementation therefore needs a health sector-wide or 'health systems' approach.

KEYWORDS: Effectiveness of IPT; implementation of health interventions; IPT uptake; isoniazid preventive therapy; timing of isoniazid preventive therapy; tuberculosis

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ACRONYMS

3TC	lamivudine
ABC	abacavir
ACP	acid phosphatase
AIDS	acquired immunodeficiency syndrome
ALT	alanine aminotransferase
ANC	antenatal care
ART	antiretroviral therapy
ARV	antiretroviral
ATV/r	atazanavir boosted with Ritonavir
AZT	zidovudine
BCG	Bacillus Calmette–Guérin
BOS	Bureau of Statistics
CFP-10	culture filtrate protein 10
CI	confidence interval
CS	cycloserine
DC	dendritic cell
DDI	didanosine
DNA	deoxyribonucleic acid

DOTS	directly observed treatment, short-course
DTH	delayed-type hypersensitivity
EGPAF	Elizabeth Glaser Pediatric AIDS Foundation
ELISPOT	enzyme-linked immunospot
EMB	ethambutol
ESAT-6	early secretory antigenic target–6
ETH	ethionamide
FTC	emtricitabine
GalN	non-N-acetylated galactosamine
GoL	Government of Lesotho
GOVT	government
HBsAg	Hepatitis B surface antigens
HBV	Hepatitis B virus
HC	health centre
HCW	healthcare worker
HIV	human immunodeficiency virus
HOSP	hospital
HTC	HIV testing and counselling
IC	infection control
ICF	intensive case finding

IFN	interferon
IL	interleukin
INH	isonicotinic acid hydrazide or isoniazid
IPT	isoniazid preventive therapy
IQR	interquartile range
IU/L	international unit per litre
KAPs	knowledge, attitudes and practices
LFT	liver function test
LPV/r	lopinavir boosted with Ritonavir
MCH	mother and child health
MDR	multi-drug resistant
mm^3	cubic millimetre (1 $mm^3 = 10^{-9}$ m^3)
MoH	Ministry of Health
MTB	*Mycobacterium tuberculosis*
NAD	nicotinamide adenine dinucleotide
NAG	N-acetyl glucosamine
NAM	N-acetyl muramic acid
NNRTI	non-nucleoside reverse transcriptase inhibitors
NRTI	nucleoside reverse transcriptase inhibitors
OPD	outpatient department

OR	odds ratio
PEPFAR	President's Emergency Plan for AIDS Relief
PI	protease inhibitor
PLHIV	people living with HIV
PN	peripheral neuropathy
PPD	purified protein derivative
PTH	prothionamide
PZA	pyrazinamide
RIF	rifampicin
RNA	ribonucleic acid
RNI	reactive nitrogen intermediates
ROI	reactive oxygen intermediates
ROS	reactive oxygen species
SADC	Southern African Development Community
SM	streptomycin
SSA	sub-Saharan Africa
TB	tuberculosis
TLR2	toll-like receptor 2
Tnd	target not detected
TST	tuberculin skin test

USA	United States of America
VL	viral load
WHO	World Health Organisation
XDR	extra-drug resistant

CHAPTER ONE

CHAPTER 1: INTRODUCTION

1.1 BACKGROUND TO THE RESEARCH PROBLEM

Global statistics released by the World Health Organisation (WHO) reveal that one-third of the world population had tuberculosis (TB) infection in 2014, making TB the leading infectious disease (WHO 2016). Furthermore, TB is the most frequent life-threatening opportunistic disease in people living with human immunodeficiency virus (HIV). Of the 1.5 million people who died from TB in 2013 alone, 360 000 were HIV-positive (WHO 2014). The sub-Saharan region accounts for 74% of the annual 1.2 million people living with HIV who develop TB globally (Hermans, Grant, Chihota, Lewis, Vynnycky, Churchyard & Fielding 2016). People living with HIV (PLHIV) in the sub-Saharan region therefore constitute the largest reservoir of TB globally. Thus, the control of latent TB infection is an important step towards reducing HIV/TB-associated deaths, and ultimately TB elimination (Sandgren, Noordegraaf-Schouten, Van Kessel, Stuurman, Oordt-Speets & Van der Werf 2016).

TB, which is caused by a bacterium known as *Mycobacterium tuberculosis* (MTB), is an ancient contagious disease, known to the early Greeks as phthisis and to the Romans as tabes (Boslaugh 2012). TB usually attacks the lungs but can also attack the brain, spine, and other parts of the body (Gengenbacher & Kaufmann 2012). The finding of evidence of TB infection in Egyptian mummies and the remains of Neolithic man in Germany (Bartels, 1907), France (Maczel, 2001), Italy (Formicola, 1987), and Denmark (Boslaugh 2012) is empirical evidence that the prevention and control of TB has eluded mankind for millennia, thus making this disease an important example for studying the failure and effectiveness of public health interventions.

MTB, which has one of the most reinforced cell walls of all known pathogenic bacteria genera (Gengenbacher & Kaufmann 2012), is one of the most difficult organisms to cure, thus making preventive interventions critical to the success of TB control. Due to their capacity to remain dormant and avoid host defences, MTB pose a threat to HIV-positive people. The organism is known to reactivate and cause tuberculosis when the immune system is weakened by HIV (Gengenbacher & Kaufmann 2012).

Empirical evidence of the effectiveness of isoniazid preventive therapy (IPT), which was recommended by the WHO (2004) as part of its Three I's strategy for the prevention of TB in PLHIV, remains so scarce that it is difficult to judge the success or failure of this intervention. Notwithstanding the initial empirical evidence of the success of IPT in eradicating MTB from the body and in reducing the risk of progression to active TB disease in high TB burden settings (WHO 2004), the initiation and completion rates for IPT are frequently suboptimal and vary greatly within and across different populations, including those with high TB incidence rates (Sandgren *et al*. 2016). The variation in outcomes therefore necessitates more population studies of this intervention.

Besides the safety concern for IPT, particularly liver toxicity (Woldehanna & Volmink, 2004; Rangaka, Wilkinson, Boulle, Glynn, Fielding, Van Cutsem, Wilkinson, Goliath, Mathee & Goemaere 2014), the unknown optimal treatment duration and the durability of its protection are the most critical concerns with IPT. The optimal treatment duration, which has not been established for a very long time (Comstock 1999; Fitzgerald, Morse, Pape & Johnson 2000), remains a contentious issue. Several treatment durations have been tried, including nine months (Comstock 1999), six months (Johnson, Okwera, Hom, Mayanja, Mutuluuza Kityo, Nsubuga, Nakibali, Loughlin, Yun, Mugyenyi, Vernon,

Mugerwa, Ellner & Whalen 2001); and 36 months (Fitzgerald *et al.* 2000; Martinson, Barnes, Msandiwa, Moulton, Gray, McIntyre, Hausler, Ram & Chaisson 2009; Samandari, Agizew, Nyirenda, Tedla, Sibanda, Shang, Mosimaneotsile, Motsamai, Bozeman, Davis, Talbot, Moeti, Moffat, Kilmarx, Castro & Wells 2011). These authors warned that the duration of protection depends on the background TB prevalence and infection control strategies. Among gold miners in a high TB burden setting in South Africa, the durability of protection by IPT is reportedly lost within 6 to twelve months, with the loss being conceptually attributed to reactivation of persistent latent infection (Hermans *et al*. 2016). Houben, Sumner, Grant and White (2014) emphasised the need for more evidence of the effectiveness of IPT in different settings, including limited resource settings.

The efficacy of IPT when used concurrently with antiretroviral drugs also needs more empirical evidence, particularly in countries with a high HIV and TB burden (Charalambous, Grant, Innes, Hoffmann, Dowdeswell, Pienaar, Fielding & Churchyard 2010; Lawn, Wood, De Cock, Kranzer, Lewis & Churchyard 2010; Fielding, Grant, Hayes, Chaisson, Corbett & Churchyard 2011). Lawn *et al.* (2010) and Golub, Saraceni, Cavalcante, Pacheco, Moulton, King, Efron, Moore, Chaisson and Durovni (2007) note that the risk of tuberculosis reinfection remains several times higher in patients with a lower CD4 count level, compared to those with higher CD4 levels. Noting that poor immune recovery is common in countries where HIV patients start ART at very low levels of CD4 counts due to late diagnosis of HIV, there is still a need for further research in these settings to determine patient groups in need of extended IPT or other interventions. In addition, given that IPT has been demonstrated to be more effective in patients with a positive tuberculin skin test compared to those with a negative tuberculin skin test (Churchyard, Scano, Grant & Chaisson 2007), more evidence of the effectiveness of IPT

in settings without tuberculin screening tests (TST) for latent tuberculosis, such as in Lesotho, is therefore crucial.

Poor implementation strategies may be negatively affecting IPT efficacy in developing countries. Apparently, ineffective implementation of health interventions at national scale is not uncommon in developing countries, despite the availability of theoretical and conceptual frameworks for effective and sustainable implementation of health interventions (Barker, Reid & Schall 2016; Iwelunmor, Blackstone, Veira, Nwaozuru, Airhihenbuwa, Munodawafa, Kalipeni, Jutal, Shelley & Ogedegbe 2016; MacDonald, Pauly, Wong, Schick-Makaroff, Van Roode, Strosher, Kothari, Valaitis, Manson & O'Briain 2016). Of note, Iwelunmor *et al.* (2016) and Yellappa, Lefèvre, Battaglioli, Devadasan and Van der Stuyft (2017) postulate that the prevailing healthcare worker shortages, weak health systems and limited resources in sub-Saharan Africa call for careful implementation of health interventions, prioritising sustainability as a core component of health interventions in this region.

Thus, the critical evaluation of health interventions such as IPT requires reliable guiding frameworks (WHO 2009). The evaluation of the implementation of the IPT intervention in this study is based on two theoretical frameworks which are often used for evaluating the effectiveness of health interventions: firstly, the WHO framework for evaluating interventions (WHO 2007), and secondly, a framework for evaluating the implementation of best practices in health interventions by Spencer, Schooley, Anderson, Kochtitzky, DeGroff, Devlin and Mercer (2013).

The investigation of the effectiveness of IPT in high TB/HIV settings, based on sound scientific methodologies, thus remain critical for purposes of providing more evidence to

support its continued use or the need for a policy shift. Without evaluations of health interventions, the possibility of inappropriate use of resources remains ever present. Also, given that the failure of the IPT intervention may emanate from poor implementation strategies of an otherwise effective intervention, such investigations should therefore also include the evaluation of the implementation strategies themselves.

1.2 STUDY RATIONALE

The uptake and effectiveness of IPT, which was recommended by the WHO (2004) for the prevention of TB in PLHIV, is not well studied in the high HIV/TB-burden setting of Lesotho, where it was introduced in 2011 (Government of Lesotho 2013). By mid-2017, only one study on the use of IPT among pregnant HIV-positive women in Lesotho appeared in the literature (Tiam, Machekano, Gounder, Maama-Maime, Ntene-Sealiete, Sahu, Isavwa, Oyebanji, Ahimbisibwe, Mokone, Barnes, Chaisson, Guay & Kassaye 2014). Lesotho is one of ten countries in the world which did not provide data for this indicator in 2014 (WHO 2014). Furthermore, given that the country has the second highest adult HIV prevalence rate in the world - estimated at 23.5% (UNAIDS 2016), and the third highest TB incidence rates globally, which is estimated at 852 per 100 000 population (WHO 2015), Lesotho remains an important research and knowledge gap for this health intervention. The need to address these knowledge gaps is therefore imperative.

This study sought to answer the following research questions: (1) What is the rate of IPT initiation and retention in PLHIV, and what factors influence this rate in Lesotho? (2) How effective is IPT in preventing the occurrence of tuberculosis and reducing the prevalence of TB in the context of Lesotho? (3) What contextual factors within the health system of Lesotho affect the implementation of IPT as a health intervention?

1.3 AIM AND OBJECTIVES

1.3.1 Aim

The overarching aim of the study was to investigate the rate of initiation and retention on IPT, its effectiveness and the health system challenges affecting its implementation in Lesotho.

1.3.2 Study objectives

The specific objectives of this study were:

- To assess the rate of initiation and retention of patients on IPT, and to determine the predictors of poor uptake of the drug.
- To evaluate the effectiveness of IPT in preventing the occurrence of TB in PLHIV, the occurrence of adverse reactions, and to determine the factors associated with poor outcomes of IPT.
- To investigate the health system challenges that are affecting the implementation of IPT intervention in PLHIV in Lesotho.

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CHAPTER TWO

CHAPTER TWO: LITERATURE REVIEW

2.1 *MYCOBACTERIUM TUBERCULOSIS* AND ITS PATHOGENICITY

Tuberculosis (TB) remains one of the world's deadliest communicable diseases, and the most frequent life-threatening opportunistic disease in people living with human immunodeficiency virus (HIV). In 2014, about 9.0 million people developed TB, and 1.5 million died from this disease worldwide, 360 000 of whom were HIV-positive (WHO 2014).

TB is caused by *Mycobacterium tuberculosis* (MTB), a slow growing, non-spore-forming bacterium that belongs to the genus *Mycobacterium* (Gengenbacher & Kaufmann 2012). The genus includes other pathogenic mycobacteria such as *Mycobacterium leprae*, which causes leprosy, *Mycobacterium africanum*, which causes less virulent forms of TB, and *Mycobacterium bovis*, which is another human pathogen contracted mainly from cattle.

MTB has a mean generation time of 18 to 24 hours at 37°C under optimal conditions of oxygen and nutrients, implying that the organism can form visible colonies much longer than other bacteria (Gengenbacher & Kaufmann 2012). The organism forms white to light yellow pigmented colonies on Löwenstein-Jensen medium within three to four weeks under aerobic-to-facultative anaerobic conditions.

The organism has a Gram positive cell wall (see Figure 2.1) that is reinforced by peptidoglycans, polysaccharides, glycolipids and lipids (Kieser & Rubin 2014). The lipids are unusual and are characterised by long-chain fatty acids such as mycolic acids, which reinforce the cell wall. Mycolic acids are long chains of β-unsaturated, branched fatty acids, which contribute to the non-permeability and rigidity of the cell envelope. The cell envelope, being the most distinctive feature of this organism, has been extensively studied

for drug targets. Isoniazid, ethionamide, ethambutol and cycloserine are all drugs whose mechanisms of action are dependent on interfering with the synthesis of the cell wall components (Kieser & Rubin 2014).

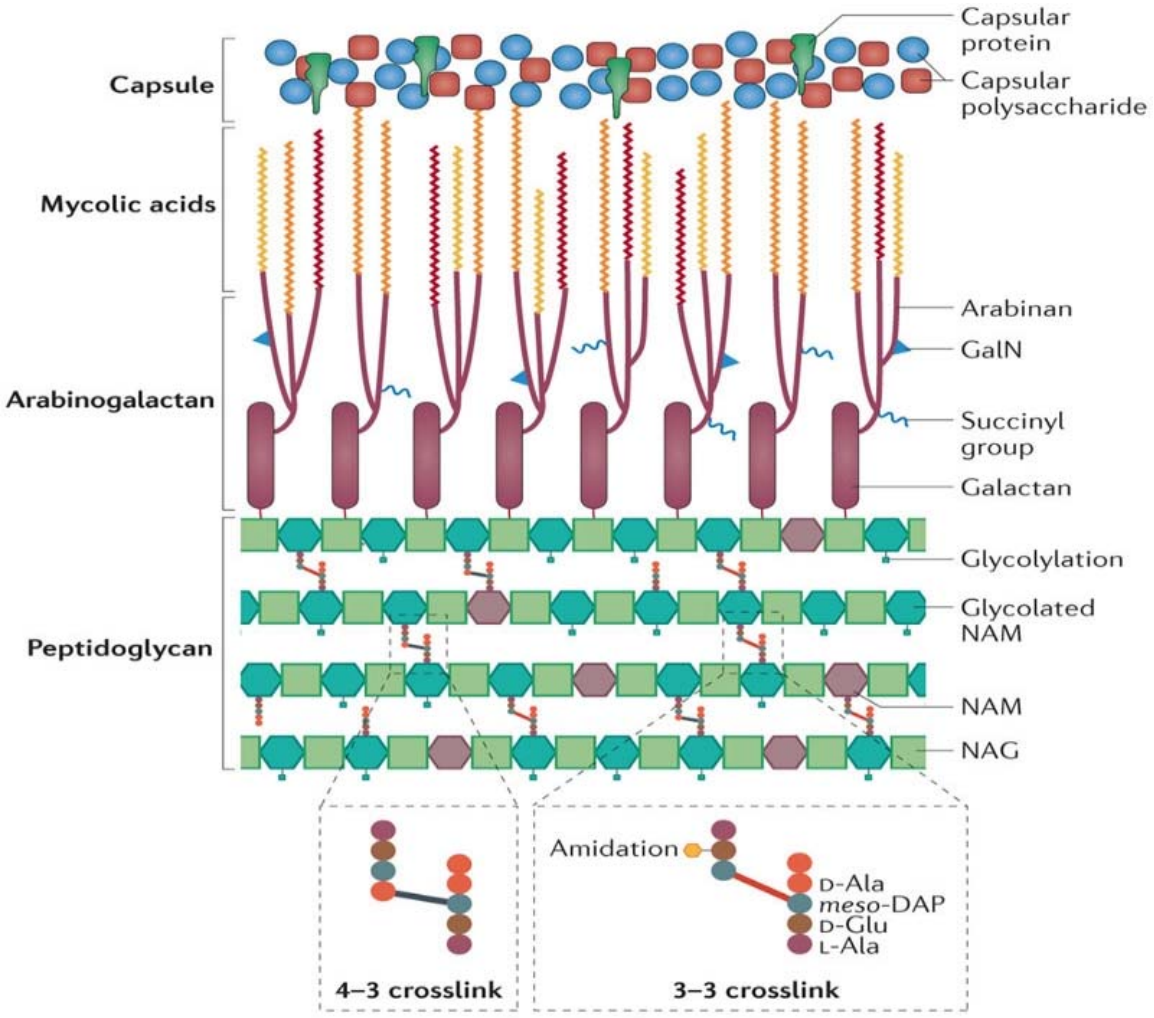

Figure 2.1 The ultrastructure of *Mycobacterium tuberculosis* cell wall
NAG=N-acetyl glucosamine; NAM=N-acetyl muramic acid; GalN=non-N-acetylated galactosamine; Source (Kieser & Rubin 2014).

The various virulence factors of MTB, which are critical for its pathogenicity, are either protein in nature or glyconjugate cell wall components. Although work on unravelling the molecular mechanisms underlying these processes is still in progress, understanding these mechanisms is a crucial step towards finding anti-tuberculosis drugs and reliable

biomarkers for TB diagnosis. Table 2.1a and 2b present the virulence factors of MTB and their pathogenicity mechanisms.

Table 2.1a Virulence factors of *Mycobacterium tuberculosis* and their pathogenicity

Factor (Gene)	Mechanism of pathogenicity
Proteins	
	Immunomodulation
ESAT-6 (esxA) and CFP-10 (esxB)	T cell stimulation, elicitation of DTH Downregulate ROS production in macrophages. Block TLR2-mediated signaling
	Pore formation, apoptosis, cytolysis
α-crystallin (acr)	Antigenic; potential role in triggering latency
Antigen 85 complex (fbpA, fbpB, fbpC)	Antigenic; mediates attachment to macrophages
	Intracellular survival/metabolism
Erp (erp)	Required for intracellular growth
Cholesterol transporter (Mce4)	Main cholesterol uptake system, important for survival during chronic phase
Enzymes and lipid carriers (Igr locus)	Cholesterol metabolism; important for growth
Isocitrate lyase (Icl1)	Allows shift to use of fatty acids as main carbon source; important for chronicity and persistence
	Protection against ROI and RNI
Catalase-peroxidase-peroxynitritase (KatG)	
Alkyl-hydroperoxide reductase (ahpC)	
Superoxide dismutases (sodA, sodC)	
Nitric oxide reductase (noxR3)	

CFP-10=culture filtrate protein–10; DC=dendritic cell; DTH=delayed-type hypersensitivity; ESAT-6=early secretory antigenic target–6; IFN=interferon; IL=interleukin; NAD=nicotinamide adenine dinucleotide; RNI= reactive nitrogen intermediates; ROI=reactive oxygen intermediates; ROS=reactive oxygen species; TLR2=Toll-like receptor 2; Source (Sakamoto 2012).

Table 2.1b Virulence factors of *Mycobacterium tuberculosis* and their pathogenicity (continued)

Factor (Gene)	Mechanism of pathogenicity
	Intracellular survival, protective granulomas and host cell damage
Cell wall components	
Lipoarabinomannan Mannose-capped	Inhibition of DC maturation; induction of IL-10. Inhibition of phagolysosomal fusion Protection against ROI; inhibition of protein kinase C activity; block transcription of IFN-g-inducible genes
Mycolic acids	Role in granuloma formation, macrophage activation. Required for mycobacterial survival Biofilm formation
Table 2.1 (continued)	
Glycopeptidolipids	Biofilm formation
Trehalose dimycolate	Granuloma formation, pro-inflammatory, cachexia, Decrease in NAD Damage to host cell membranes Damage to mitochondria induction of apoptosis Inhibition of phagosomal-lysosomal fusion
Phenolic glycolipids	Immunosuppression
Sulpholipids	Increase macrophage infectivity, impair macrophage activation by inhibiting phagosomal maturation, blocking priming by IFN-g

CFP-10=culture filtrate protein–10; DC=dendritic cell; DTH=delayed-type hypersensitivity; ESAT-6=early secretory antigenic target–6; IFN=interferon; IL=interleukin; NAD=nicotinamide adenine dinucleotide; RNI=reactive nitrogen intermediates; ROI=reactive oxygen intermediates; ROS=reactive oxygen species; TLR2=Toll-like receptor 2; Source (Sakamoto 2012).

MTB's pathogenicity success, as noted by Sakamoto (2012) and Gengenbacher and Kaufmann (2012), is based on three important capacities, namely: (1) immunomodulation – its capacity to re-program macrophages after initial phagocytosis to prevent its destruction; (2) intracellular survival/metabolism – the capacity to protect itself against reactive nitrogen intermediates (RNI) and reactive oxygen intermediates (ROI), and its

capability to minimise metabolism and terminate replication allows the bacterium to remain dormant and avoid host defences and drug treatment; and (3) MTB's cell wall components – which initiate the formation of protective granulomas and cause damage to host cells.

2.2 PROPERTIES AND MECHANISM OF ACTION OF ANTI-TUBERCULOSIS DRUGS

2.2.1 History of anti-tuberculosis drugs and current treatment practices

Mycobacterium tuberculosis is one of the most difficult bacteria to treat. For generations, TB treatment has required prolonged combination chemotherapy with several drugs working in synergy (see Figure 2.2 for the chemical structures of the common anti-tuberculosis drugs). The order of these discoveries puts the discovery of isoniazid, an important drug used to treat or prevent the occurrence of TB, into perspective. Of note is the fact that the drug isoniazid has been in use for the treatment of TB for more than 60 years. The discovery of INH was a significant milestone, as INH was highly active, inexpensive, and less prone to side effects.

Chronologically, anti-tuberculosis drugs were discovered beginning with streptomycin (1944); para-aminosalicylic acid (PAS) (1946); isoniazid (INH) and pyrazinamide (PZA) (1952); ethionamide (ETH) and Prothionamide (PTH) (1956); and ethambutol (EMB) (1961). More anti-tuberculosis drugs were discovered in the 1960s, including cycloserine; kanamycin; amikacin; capreomycin; and rifampicin (RIF), which is the drug of choice for treatment of TB since the 1970s. Fluoroquinolones, important second-line drugs for the treatment of drug-resistant TB, were developed in the 1980s.

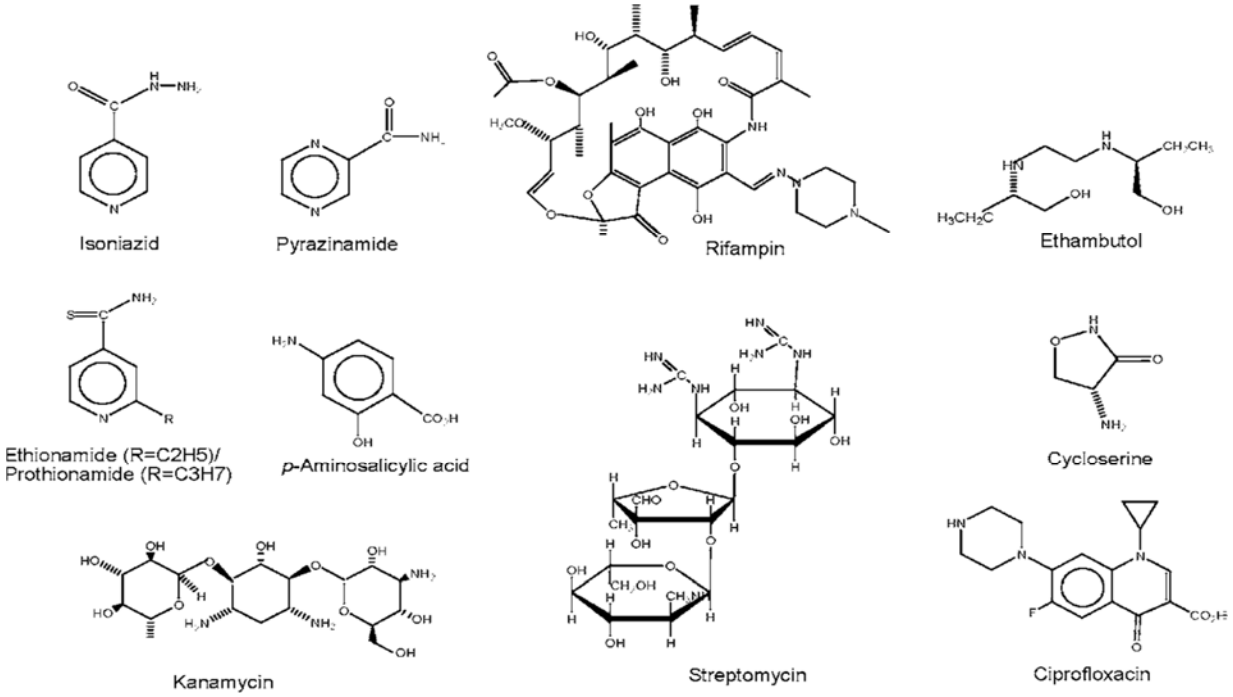

Figure 2.2 Chemical structures of some common anti-tuberculosis drugs Source (Zhang 2005).

The current six-month TB chemotherapy recommended by the WHO, known as the directly observed treatment short-course (DOTS), comprises an intensive two-month treatment phase with four drugs, namely INH, RIF, PZA and EMB, followed by a continuation phase with INH and RIF for another four months (WHO 2010). For multi-drug resistant TB (MDR-TB), the WHO recommends DOTS-Plus, which means DOTS plus second-line TB drugs such as aminoglycosides, polypeptides and fluoroquinolones, among others (WHO 2010). While amikacin and kanamycin are most effective, aminoglycosides capreomycin is the most commonly used polypeptide drug, and likewise, ciprofloxacin is the most common fluoroquinolone used to treat TB (Hu, Zhang, Zhao, Gao, Feng, Lv, Xu & Wu 2017).

2.2.2 Properties and mechanism of action of common anti-tuberculosis drugs

Table 2.2 presents the properties, mechanisms of action and targets of common anti-tuberculosis drugs. Isonicotinic acid hydrazide (INH) or isoniazid, is a synthetic drug of which the primary target of inhibition is the synthesis pathway of cell wall mycolic acids (Zhang 2005). Specifically, the drug targets the enoyl ACP reductase enzyme in this pathway. The loss of acid fastness in MTB exposed to INH has been demonstrated as the most critical laboratory evidence of the effect of INH on mycolic acid synthesis, and MTB can only kill actively-dividing mycobacteria (Hu *et al.* 2017). INH being a prodrug, its active form, isonicotinic acyl radical, reacts with NAD to form INH-NAD composite, which not only inhibits the enoyl ACP reductase enzyme, but also damages DNA, carbohydrates, and lipids, and inhibit NAD metabolism in mycobacteria (Zhang 2005). It is therefore not surprising that significant changes in the NADH/NAD ratio due to mutations in NAD dehydrogenase II may cause resistance to INH, although mutations in the gene KatG, which is involved in INH activation, is the main mechanism of INH resistance (Hu *et al.* 2017).

Ethionamide (ETH) is a prodrug that is activated by a monooxygenase enzyme EtaA. It inhibits the same target InhA as INH in the mycolic acid synthesis pathway (Vale, Gomes & Santos 2013). Ethambutol (EMB) interferes with the biosynthesis of arabinogalactan, a major polysaccharide of mycobacterial cell wall, specifically inhibiting the polymerization of cell wall arabinan of arabinogalactan and of lipoarabinomannan (Chakraborty & Rhee 2015). Cycloserine (CS) inhibits the synthesis of cell wall peptidoglycan by blocking the action of D-alanine racemase (Alr), an enzyme involved in the conversion of L-alanine to an important substrate, D-alanine (Kolyva & Karakousis 2012).

Table 2.2 Properties, mechanisms of action and targets of anti-tuberculosis drugs

Drug (year of discovery)	MIC[a] (g/ml)	Effect on bacterial cell	Mechanisms of action	Targets
Isoniazid (1952)	0.01–0.2	Bactericidal	Inhibition of mycolic acid synthesis and other effects on DNA, lipids, carbohydrates, and NAD metabolism	Multiple targets, including acyl carrier protein reductase (InhA)
Rifampicin (1966)	0.05–0.5	Bactericidal	Inhibition of RNA synthesis	RNA polymerase β subunit
Pyrazinamide (1952)	20–100 pH 5.5 or 6.0	Bacteriostatic/ Bactericidal	Disruption of membrane transport and energy depletion	Membrane energy metabolism
Ethambutol (1961)	1–5	Bacteriostatic	Inhibition of cell wall arabinogalactan synthesis	Arabinosyl transferase
Streptomycin (1944)	2–8	Bactericidal	Inhibition of protein synthesis	Ribosomal S12 protein and16S rRNA
Kanamycin (1957)	1–8	Bactericidal	Inhibition of protein synthesis	16S rRNA
Quinolones (1963)	0.2–4	Bactericidal	Inhibition of DNA synthesis	DNA gyrase
Ethionamide (1956)	0.6–2.5	Bacteriostatic	Inhibition of mycolic acid synthesis	Acyl carrier protein reductase (InhA)
PAS (1946)	1–8	Bacteriostatic	Inhibition of folic acid and iron metabolism?	Unknown
Cycloserine (1952)	5–20	Bacteriostatic	Inhibition of peptidoglycan synthesis	D-alanine racemase[c]

[a]MIC=minimum inhibitory concentration; PAS=para-aminosalicylic acid; *Source* (Zhang 2005).

Rifampicin (RIF) is a broad-spectrum anti-TB drug that impedes RNA synthesis through binding to DNA-dependent RNA polymerase of MTB (Kolyva & Karakousis 2012). Of note is the fact that RIF can inhibit both actively growing and dormant MTB. Fluoroquinolones, particularly nalidixic acid, ciprofloxacin, ofloxacin, levofloxacin, and sparfloxacin, are important MDR-TB second-line drugs that inhibit DNA synthesis by targeting the DNA gyrase enzyme (Zhang 2005).

Aminoglycoside anti-TB drugs, particularly streptomycin (SM), interfere with protein synthesis through inhibiting initiation of mRNA translation, resulting in misreading of the genetic code (Zhang 2005).

Pyrazinamide (PZA), a prodrug that requires conversion to its active form, pyrazinoic acid, has no clear activity against MTB at normal culture conditions, but is important for shortening the duration of TB therapy to six months (Kolyva & Karakousis 2012). Nevertheless, PZA is believed to facilitate the reduction of the membrane potential in MTB, thus de-energising the membrane and affecting membrane transport (Zhang 2005).

2.3 EPIDEMIOLOGY OF TB IN LESOTHO AND TREATMENT GUIDELINES

2.3.1 The prevalence and incidence of TB in Lesotho

In 2015, Lesotho, with a TB incidence rate in the general population estimated at 852 per 100 000 population (WHO 2015), was amongst the top three nations with the highest rates of TB worldwide, with the two other nations, South Africa and Swaziland, having TB incidence rates above 700 per 100 000 population. By 2018, despite improvement in the incidence rate from 852 to 665 per 100 000 population (WHO 2018), Lesotho continued to have the highest TB incidence in the regional grouping of countries in Southern Africa

known as Southern African Development Community (SADC). According to latest WHO (2018) figures, other countries with high TB incidence rate per 100 000 population in the SADC region were South Africa (567), Mozambique (551), Namibia (423) and Zambia (361). Of note, TB incidences per 100 000 population in Swaziland (308), Botswana (300), Zimbabwe (221) and Malawi (133) depict significant improvement in these countries (WHO 2018).

Government of Lesotho (GoL) (2013b) attributes the high magnitude of TB in Lesotho to the high HIV prevalence, which is estimated at 23% among adults. Notably, TB is most prevalent in correctional institutions in the country, in migrant mineworkers and factory workers who live in overcrowded settings (GoL 2013b). About 75% of patients with TB in Lesotho are co-infected with HIV (WHO 2014). The main drivers of the high TB infection rate include poverty, poor nutrition, overcrowding and poor ventilation in the homes (GoL 2013b).

2.3.2 ART and TB guidelines in Lesotho: rationale and challenges

The current ART guidelines in Lesotho recommend a combination of three antiretroviral (ARV) drugs in all HIV-positive patients. the first line treatment for adults consists of two nucleoside reverse transcriptase inhibitors (NRTI) and one non-nucleoside reverse transcriptase inhibitor (NNRTI) used according to a rationale shown in Table 2.3 (GoL 2013a).

Selecting regimens that are compatible with TB therapy in HIV-positive people co-infected with TB presents several challenges, particularly in Lesotho where the number of treatment options is severely limited. For example, for children younger than three years, regimens based on protease inhibitor (PI) are the preferred first line option, but

interactions between rifampicin and LPV/r or NVP mean that co-treatment in children under three years is challenging (GoL 2013a). Rifampicin reduces concentrations of LPV/r or NVP since it induces the cytochrome P450 enzymes (Wilson, Cotton, Bekker, Meyers, Venter & Maartens 2008). HIV patients co-infected with TB therefore may need to be given other regimens at an added expense.

Table 2.3 Current first-line and second-line ART drugs recommended for adults in Lesotho

First-line ART	Preferred first-line regimens	Alternative first-line regimens
Adults including pregnant and breastfeeding women and adults with TB and HBV coinfection	**TDF + 3TC + EFV**	AZT + 3TC + EFV AZT + 3TC + NVP TDF + 3TC + NVP *ABC + 3TC + EFV (or NVP)
Adolescents (10 to 19 years) ≥35 kg		AZT+3TC+EFV AZT+3TC+NVP TDF+3TC+NVP *ABC+3TC+EFV(or NVP)
Children (3 to 9 years) and **Adolescents** <35 kg	**ABC + 3TC + EFV**	AZT + 3TC + EFV ABC + 3TC + NVP AZT + 3TC + NVP
Children < 3 years	**ABC + 3TC + LPV/r**	AZT + 3TC + LPV/r ABC+3TC+NVP AZT + 3TC + NVP

ABC=abacavir; AZT=zidovudine; 3TC=lamivudine; LPV/r=lopinavir/ritonavir; NVP=nevirapine; EFV=efavirenz; TDF=tenofovir; Source (GoL 2013a).

Switching to second-line ART drugs is recommended in cases where treatment failure as assessed by clinical and CD4 count is suspected or confirmed by viral load tests. Table 2.4 outlines the second-line drug options available in Lesotho. However, both access to viral load tests and access to second-line ARVs in Lesotho is limited (GoL 2013a). These

limitations imply that the capacity to prove explicitly that a patient needs second-line therapy before switching to second- and third-line drugs is greatly curtailed. Third-line drugs for Lesotho include darunavir, ritonavir, raltegravir and etravirine (GoL 2013a).

Table 2.4 Recommended second-line drug options for Lesotho

	Children	First-line ART regimen	Second-line ART regimen
LPV/r-based first-line regimen	Younger than 3 years	ABC + 3TC + LPV/r	No change
		AZT + 3TC + LPV/r	
	3 years and older	ABC + 3TC + LPV/r	AZT + 3TC + EFV
		AZT + 3TC + LPV/r	ABC + 3TC + EFV
NNRTI-based first-line regimen	All ages	ABC + 3TC + EFV (or NVP)	AZT + 3TC + LPV/r
		TDF + 3TC + EFV (or NVP)	
		AZT + 3TC + EFV (or NVP)	ABC + 3TC + LPV/r

ABC=abacavir; AZT=zidovudine; 3TC=lamivudine; LPV/r=lopinavir/ritonavir; NVP=nevirapine; EFV=efavirenz; TDF=tenofovir; Source (GoL 2013a).

2.3.3 IPT guidelines

Isoniazid preventive therapy (IPT) was launched in Lesotho in 2011 (GoL 2013b) as part of the WHO's Three I's programme, which comprised intensified case finding (ICF), Isoniazid preventive therapy (IPT) and tuberculosis infection control (IC), (Kranzer, Houben, Glynn, Bekker, Wood & Lawn 2010). According to the national IPT guidelines, a six-month course of IPT is recommended in all HIV-positive persons over one year of age in whom active TB and other contraindications have been excluded (GoL 2013a). These contraindications include active hepatitis, alcoholism and severe peripheral neuropathy. Other contraindications include epilepsy and kidney failure. The main aim of this recommendation is to treat latent TB infection and reduce the risk of progression to active TB. The rationale behind the recommendation by the GoL (2013a) is based on the fact

that the risk of contracting TB is particularly high during the first six months after ART initiation. However, the screening of active TB is based on symptoms, clinical signs and X-rays. Tuberculin skin tests are not available to diagnose latent TB infection.

The Lesotho guidelines for IPT also recommend that IPT be given to all eligible HIV-positive patients, irrespective of CD4 counts, WHO clinical status, ART status and ART regimen (GoL 2013a).

With respect to liver function, IPT is recommended in patients with alanine aminotransferase (ALT) levels up to two to five times the upper limit of the normal range, with monthly monitoring of liver function. Of note, in Lesotho, is that ALT is regarded as normal if the level is below 40 IU/L in males and below 31 IU/L in females (GoL 2013a). However, IPT is contraindicated if ALT is more than five times the upper limit of the normal range, that is, ALT levels greater than 200 IU/L. However, recommendations stipulate that routine laboratory monitoring of liver function tests, including ALT, without indications for liver disease, is not mandatory.

IPT is regarded to be safe during pregnancy, including during breastfeeding. In addition, all HIV-positive infants <12 months and children with possible exposure to TB in the households should also be initiated on IPT after ruling out contraindications, and with relevant dosage titrations applied (GoL 2013a).

IPT dosages as stated by GoL (2013a) should not be more than 300mg/day in adults and children for six months. However, in children, a dosage of 10 mg/kg body weight is recommended. In addition, the IPT recommendation stipulates that an IPT treatment course has to be restarted if there is a treatment interruption of three months or less. Pyridoxine phosphate or vitamin B6 has to be given concurrently with IPT to prevent the

occurrence of peripheral neuropathy. The effectiveness of the six-month treatment duration without further IPT is not clear in Lesotho, the main challenge being that the threat of reinfection may continue after IPT, particularly in patients with low immune recovery (Lawn, Wood, De Cock, Kranzer, Lewis & Churchyard 2010).

2.4 EARLY EVIDENCE OF IPT EFFECTIVENESS IN PEOPLE LIVING WITH HIV

2.4.1 Optimum duration of IPT treatment

Early evidence of IPT treatment in HIV-infected patients with latent tuberculosis proved that IPT reduces their lifetime risk of active tuberculosis to 4% or less (Fitzgerald, Morse, Pape & Johnson 2000). However, Fitzgerald *et al.* (2000), one of the earliest research teams on IPT efficacy, note that the protection was dependent on the duration of therapy, with longer durations of IPT treatment up to 36 months associated with protection for up to 40 months on average. Short treatment durations of six months were only associated with short protection for six months on average. Comstock (1999) reviewed the data from clinical trials conducted mostly in the United States of America (USA), and found inconclusive evidence for the efficacy of the six-month course of IPT; and recommended that the optimal protection from IPT appears to be obtained by at least nine months of treatment (Figure 2.3).

It is also important to note that historically, trials included other curative anti-tuberculosis drugs such as rifampicin and pyrazinamide. However, six-month treatment with IPT alone proved to have a better effect, though less sustained than other regimens containing rifampicin or pyrazinamide (Johnson, Okwera, Hom, Mayanja, Mutuluuza Kityo, Nsubuga, Nakibali, Loughlin, Yun, Mugyenyi, Vernon, Mugerwa, Ellner & Whalen 2001).

Contrastingly, the rifampicin and pyrazinamide regimens provided less efficacious and narrower therapeutic-to-safety indices. Of note, the term “therapeutic index” refers to the therapeutic window relative to the safety window, and, in practice, the therapeutic index is obtained by comparing the amount of a therapeutic agent required to achieve therapeutic effect to the amount that causes toxicity.

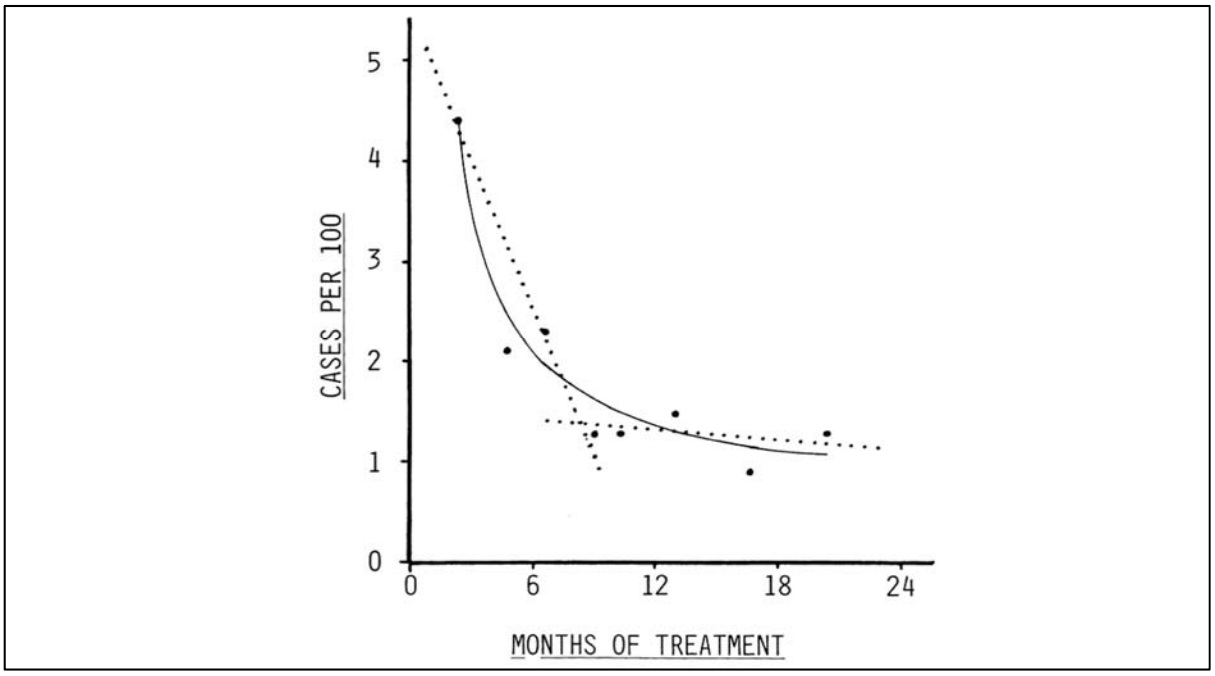

Figure 2.3 Tuberculosis case rates by duration of IPT treatment in the clinical trials

The tuberculosis case rates are in per cent (%); Dots represent observed whilst the continuous line represents the fitted line. Source: (Comstock 1999).

Based on these and possibly other studies, the WHO (2004) recommended routine use of IPT for prophylaxis against TB for prophylaxis in 2004. However, the WHO (2004) recommendation did not state the maximum period that IPT was to be taken due to a lack of evidence, but only recommended that IPT may be used for six up to nine months. In addition, the WHO (2004) acknowledged that the effectiveness of this therapy in developing countries is less clear because, at that time, there was inconclusive evidence about its effectiveness. However, the WHO (2004) believed that the results of upcoming

studies assessing the effectiveness of concurrent IPT and ART needed to be monitored closely in order to inform the adopted policy on IPT. To date, the duration for IPT has remained contentious, with some authors recommending six, nine or twelve months (Getahun, Granich, Sculier, Gunneberg, Blanc, Nunn & Raviglione 2010). Two trials from Botswana and South Africa have recommended durations of up to 36 months (Martinson, Barnes, Msandiwa, Moulton, Gray, McIntyre, Hausler, Ram & Chaisson 2009; Samandari, Agizew, Nyirenda, Tedla, Sibanda, Shang, Mosimaneotsile, Motsamai, Bozeman, Davis, Talbot, Moeti, Moffat, Kilmarx, Castro & Wells 2011); although the protection has since been seen to decline rapidly (Samandari, Agizew, Nyirenda, Tedla, Sibanda, Mosimaneotsile, Motsamai, Shang, Rose & Shepherd 2015).

2.4.2 The effectiveness of IPT in the African setting

Notable studies of historical importance prior to general acceptance in routine use in African settings include the one by Grant, Charalambous, Fielding, Day, Corbett, Chaisson, De Cock, Hayes and Churchyard (2005) and Rangaka, Wilkinson, Boulle, Glynn, Fielding, Van Cutsem, Wilkinson, Goliath, Mathee and Goemaere (2014) in South Africa. IPT reduced tuberculosis incidence by between 38%, and by 60% in HIV-infected adults with no history of tuberculosis. However, tuberculosis incidence remained high despite IPT. By the end of the study, IPT had reduced the incidence of tuberculosis from 11.9 to 9.0 per 100 person-years.

Further studies reflected in a review by Churchyard, Scano, Grant and Chaisson (2007) further motivated researchers to accept IPT for routine use, including during ART (Figure 2.4). However, Churchyard *et al.* (2007) warned that reinfection is an important problem in African settings, having noticed disappointing results in a Zambian IPT trial (Quigley,

Mwinga, Hosp, Lisse, Fuchs, Porter & Godfrey-Faussett 2001). This review by Churchyard *et al.* (2007) also demonstrates that the benefits of IPT are much better for patients who have had a positive tuberculin skin sensitivity test, which is based on purified protein derivative (PPD), compared to those whose PPD results are negative or unknown.

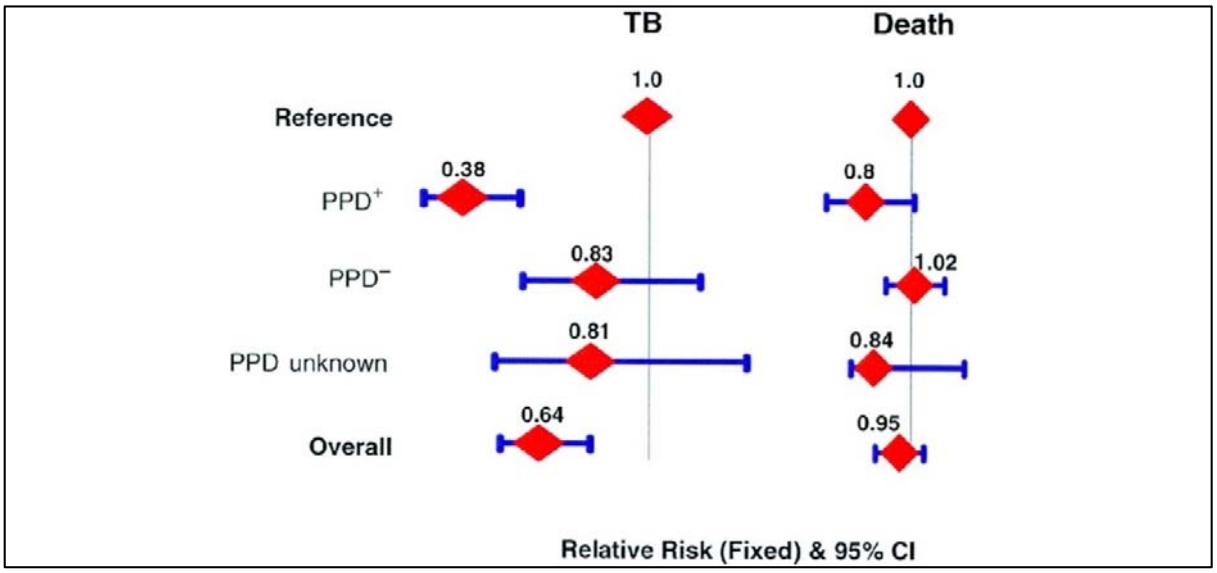

Figure 2.4 Efficacy of IPT: Results of meta-analysis review

PPD = purified protein derivative; Source: (Churchyard *et al.* 2007).

2.4.3 The problem of short-term protection against tuberculosis

The main challenge facing IPT is that it provides short-lived protection. Randomised controlled trials have shown IPT provides short-term protection against tuberculosis, which is quickly lost after cessation of therapy, because IPT does not effectively cure *Mycobacterium tuberculosis* infection, and also does not prevent reinfection (Houben, Sumner, Grant & White 2014). Therefore, there is a need to find a better prophylactic drugs for preventing TB in PLHIV.

2.4.4 The joint effect of ART and IPT

The joint effect of ART and IPT on the risk of contracting tuberculosis is an interesting phenomenon. Generally, the risk of tuberculosis has an antithetical relationship to the level of immunity, as depicted in Figure 2.5 (Havlir, Getahun, Sanne & Nunn 2008). The use of antiretroviral drugs, with the main purpose of limiting HIV replication, increases the CD4 count levels, and reduces the risk of tuberculosis infection. However, it is important to note that, although ART significantly reduces the risk of tuberculosis, it does not reduce the risk entirely (Getahun *et al.* 2010). Havlir *et al.* (2008) reviewed the effect of ART on the risk of tuberculosis infection, and concluded from nine studies that ART reduces the risk of tuberculosis infection, but not entirely.

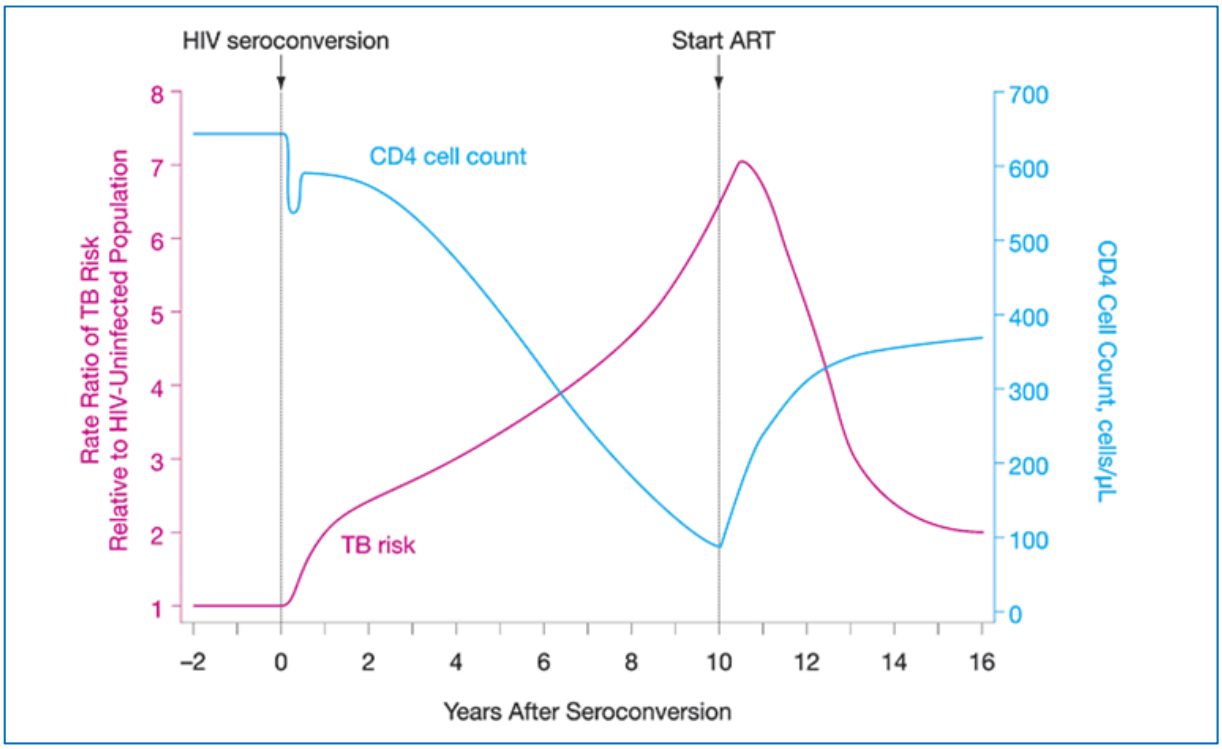

Figure 2.5 The risk of tuberculosis infection relative to CD4 count
Source: (Havlir *et al.* 2008).

In recent times, more researchers have continued to study the joint effect of IPT and ART. From the studies, it is now generally accepted that antiretroviral therapy used concurrently

with IPT further reduces the incidence of TB compared to ART alone, due to restoration of immunity (Charalambous, Grant, Innes, Hoffmann, Dowdeswell, Pienaar, Fielding & Churchyard 2010; Lawn *et al.* 2010; Fielding, Grant, Hayes, Chaisson, Corbett & Churchyard 2011). Charalambous *et al.* (2010) and Fielding *et al.* (2011) observed that mortality was significantly lower in cohorts taking IPT and ART concurrently. However, as Lawn *et al.* (2010) note, in HIV-positive patients presenting with advanced immunodeficiency with very low CD4 counts, it is necessary to delay concurrent IPT until completion of the first few months of antiretroviral therapy, when active tuberculosis has been excluded. Lawn *et al.* (2010) further note that the risk of tuberculosis infection remains several times higher in those with poor immune recovery than in patients with higher CD4 levels. Golub, Saraceni, Cavalcante, Pacheco, Moulton, King, Efron, Moore, Chaisson and Durovni (2007) confirm this theory, and also note that the reduction in the relative risk of infection with TB is dependent on the CD4 count level at which IPT is given together with ART. Patients with better immunity levels as indicated by CD4 counts had better outcomes compared with patients with low CD4 counts (below 350 cells/cm^3). These observations raise a concern in many limited resource settings, including Lesotho, where a significant proportion of patients still start ART at very low levels of CD4 counts due to late diagnosis of HIV. Therefore, further evaluations of antiretroviral treatment outcomes following the use of IPT in limited resource settings is important.

2.4.5 The effectiveness of IPT in settings without access to the tuberculin skin test and other biomarkers

It is important to note that in resource-limited settings such as Lesotho, IPT is given without prior screening for latent TB using tuberculin skin test (TST) such as the purified

protein derivative (PPD) test. This may be due to many factors, including scarcity of resources and the need to confirm the results with more reliable tests. However, the effectiveness of this approach is still unclear.

In practice, positive PPD tests have to be confirmed by other tests that are less influenced by previous Bacillus Calmette–Guérin (BCG) vaccination such as the QuantiFERON-TB Gold™ which is based on quantifying interferon-gamma released by T-lymphocytes when exposed to certain *Mycobacterium tuberculosis* antigens (Altet, Dominguez, De Souza-Galvao, Jimenez-Fuentes, Mila, Solsona, Soriano, Latorre, Lara, Cantos, Ferrer, Orcau, Ruiz-Manzano & Cayla 2015), and the T-SPOT.TB™ test, which is a type of Enzyme-Linked ImmunoSpot (ELISPOT) assay which enumerates anti-mycobacterial T-cells that produce interferon-gamma in a sample of blood (Leung, Yam, Ho, Yew, Chan, Law, Lee, Chang, Tai & Tam 2015). Thus, the PPD test in limited resource settings remains unavailable for routine use until other cheaper and more accurate tests become available. Meanwhile, the proportion of latent tuberculosis in limited resource settings remain speculative, and opportunities to halt the spread of TB continue to be missed.

In recent years, researchers have tried other options to confirm latent TB diagnosis. For example, Kasempimolporn, Thaveekarn, Kerdpanich, Skulpichetrat, Saekhow, Boonchang, Bharnthong and Sitprija (2015) compared the diagnostic performance of the strip test with the tuberculin skin test and interferon-gamma release assay. The strip test did not appear to be useful for the diagnosis of active TB in comparison with the interferon-gamma release assay. Further efforts in this regard are therefore required.

Chegou, Heyckendorf, Walzl, Lange and Ruhwald (2014) also reviewed some of the markers that are currently being tested, including recent advances in the development of

other antigens specific to *Mycobacterium tuberculosis* such as ESAT-6 and CFP-10 (Weldingh & Andersen, 2008; Wu, Zhang, Zhang, Zhang, Zhu & Shi 2008). It is not clear which of these markers will eventually prove to be useful in humans. Limited understanding of pathogenic mechanisms through which *Mycobacterium tuberculosis* causes disease may be one reason for the delayed success in finding better markers (Gengenbacher & Kaufmann 2012). Consequently, more research on the mechanisms that cause mycobacterial latency and activation is necessary.

Molecular screening of tuberculosis is perhaps one of the recent successes in the diagnosis of latent tuberculosis. The GeneXpert molecular technique couples rapid confirmation of *Mycobacterium tuberculosis* with a sensitivity test for rifampicin (Walters, Goussard, Bosch, Hesseling & Gie 2014). This technique is particularly important in children where prior confirmation of *Mycobacterium tuberculosis* infection and rifampicin sensitivity is invaluable. Therefore, molecular techniques offer a glimmer of hope for the diagnosis of latent tuberculosis in settings with a high TB burden in the future, as the technology becomes more affordable.

2.5 THE SAFETY OF IPT

2.5.1 Liver toxicity

The safety of IPT is another ongoing debate, with liver toxicity being the most serious concern. The source of INH hepatotoxicity is believed to be the acetylation of INH by the liver enzyme N-acetyltransferase 2 (NAT2), which produces two hepatotoxic metabolites, acetylhydrazine and isonicotinic acid (Tostmann, Boeree, Aarnoutse, De Lange, Van Der Ven & Dekhuijzen 2008).

Early clinical trials in HIV-positive patients indicate that IPT is less hepatotoxic than other regimens based on rifampicin and pyrazinamide (Woldehanna & Volmink 2004). Saukkonen, Cohn, Jasmer, Schenker, Jereb, Nolan, Peloquin, Gordin, Nunes, Strader, Bernardo, Venkataramanan and Sterling (2006) recommend that patients on INH should have liver function tests such as ALT monitored, particularly in chronic alcohol consumers, patients on concomitant hepatotoxic drugs, active viral hepatitis such as hepatitis B sufferers, and other pre-existing liver disease. Daily alcohol consumption increases the risk of hepatitis by more than four times (Saukkonen *et al.* 2006). It is also important to note that active hepatitis B, but not quiescent hepatitis B, is a significant factor to IPT hepatotoxicity (Saukkonen *et al.* 2006). However, this finding needs to be verified in other settings.

IPT toxicity poses a risk in African settings due to limited laboratory tests for monitoring toxicity of the drug. Notwithstanding that ALT and hepatitis B screening tests for liver function are available in rural settings of African countries, the tests are sometimes not performed due to cost constraints. Viral hepatitis is rampant in these settings. For example, Mugomeri *et al*. (2015) found that in one cohort of 304 HIV-positive patients in Lesotho, 10.5% had HBV/HIV coinfection by laboratory values. Therefore, hepatitis B screening and liver function tests are important to reduce IPT toxicity.

Studies of the dynamics of IPT toxicity during IPT treatment have noted that about 60% of toxicity cases are reported in the first three months of treatment, with about 80% of the cases occurring in the first six months (Saukkonen *et al.* 2006). Additional risk factors to IPT toxicity include older age (above 50). However, more adverse drug reaction profiles and their risk factors need to be reviewed in limited resource settings.

Another safety concern related to hepatotoxicity, is the potential effect of INH on cytochrome P450 isoenzymes. Given that INH inhibits several cytochrome P450 isoenzymes, which metabolise many antiretroviral drugs (Wen, Wang, Neuvonen & Backman 2002), Rangaka *et al.* (2014) warns that increased antiretroviral drug concentrations reaching toxic proportions are highly possible in patients taking ARVs and IPT concurrently.

2.5.2 Peripheral neuropathy and other concerns

INH is associated with peripheral neuropathy (PN), a condition which affects the sensory and motor nerves leading to loss of nerve function (Mafukidze, Calnan & Furin 2016). However, it is important to note that TB itself, comorbid conditions such as HIV disease, malnutrition, or diabetes mellitus and their treatment, and anti-TB drugs such as ethambutol, may also cause PN. ARVs, particularly stavudine, didanosine and zidovudine and drugs for drug-resistant TB namely, cycloserine, high-dose INH, ethionamide and linezolid have also been associated with PN (Mafukidze *et al.* 2016).

While withdrawal of the offending agent is the most effective treatment for PN, use of analgesics and serotonin reuptake inhibitors may also reverse the effects of PN. Fortunately, vitamin supplementation is known to prevent the occurrence of PN in patients on INH (Lawn *et al.* 2010). In the African setting, vitamin supplementation with pyridoxine phosphate or vitamin B6 given has become the standard practice for preventing PN in HIV-positive patients taking IPT (Rangaka *et al.* 2014).

INH is also associated with skin rash typical of drug-induced hypersensitivity (Rangaka *et al.* 2014). Furthermore, INH may be a cause of cutaneous ichthyosis, characterised by keratinization and generalised scaly lesions (Kouismi, Bourkadi & Iraqi 2013).

2.5.3 Safety of IPT in children

As IPT became standard treatment in HIV-positive patients, its use was extended to children where safety concerns had delayed its use for some years. Gray, Zar and Cotton (2009), Frigati, Kranzer, Cotton, Schaaf, Lombard and Zar (2011) and Schaaf, Cotton, Boon and Jeena (2013) found IPT to be significantly (p<0.05) associated with low incidence of TB among children on ART. However, their recommendations came with warnings. IPT was only justifiable in cases where there was evidence of prior exposure to TB. According to the same authors, screening of active TB is therefore mandatory before IPT is used in children. However, it is also important to note that, whereas the PPD test is useful in adults, the same test has limited utility in children. Gray *et al.* (2009) report that the PPD test may not be useful in children as it is not sufficiently sensitive in children.

Recently, Lala, Parbhoo, Verwey, Khan, Dangor, Moore, Pettifor and Martinson (2014) evaluated the effect of topical calcipotriol or zinc as enhancers on the tuberculin skin tests in hospitalised South African children. Topical calcipotriol or zinc did not significantly improve the performance of the tuberculin skin test in children. Therefore, the screening of active tuberculosis remains the most important test before administering IPT in children.

2.6 IPT AND THE THREAT OF DRUG RESISTANCE

One of the early stumbling blocks to the widespread use of IPT was the potential to develop drug resistance. However, a review by Balcells, Thomas, Godfrey-Faussett and Grant (2006) revealed that the overall relative risk for developing drug resistance was 1.45%, with a 95% confidence interval between 0.85 and 2.47. Van Halsema, Fielding, Chihota, Russell, Lewis, Churchyard and Grant (2010) studied the characteristics of TB

in gold miners previously exposed to IPT in South Africa. The authors report that, although the occurrence of IPT drug resistance is relatively more common among patients pre-exposed to IPT, tuberculosis has similar prevalence of drug resistance to background treatment outcomes. However, as Balcells *et al.* (2006) note, numerous limitations in the studies - including small sample sizes and incomplete data - limit the generalisation of the findings. Therefore, the risk of developing drug resistance to IPT remains possible.

The emergence of multidrug-resistant tuberculosis (MDR-TB) and extensively drug-resistant tuberculosis (XDR-TB) pose a threat, particularly in high TB-burden settings such as Lesotho. Fortunately, new affordable molecular diagnostic methods to detect this resistance are now available (N'guessan, Assi, Ouassa, Ahui-Brou, Tehe, Keita Sow, Guei, Kouakou & Dosso 2014). These methods detect mutations in the rpoB and inhA genes of *Mycobacterium tuberculosis* - changes that are attributed to rifampin. INH resistance, on the other hand, is usually due to mutations in the *katG* gene (N'guessan *et al.* 2014).

The sensitivity of GeneXpert™ molecular assays for INH resistance detection is generally lower than for the detection of rifampicin resistance. While the sensitivity for INH ranges from 73% to 92%, the sensitivity for rifampicin ranges from 92% to 99% (N'guessan *et al.* 2014). For this reason, the GeneXpert™ technique is generally used to detect resistance to rifampicin.

Adherence to preventive drugs is much more complicated than adherence to curative drugs. When patients are asked to take a preventive drug, their adherence is likely to depend on their level of loyalty and understanding of the condition they are preventing. It is therefore possible that some patients may see additional drugs (e.g. INH) to their other

antiretroviral drugs as extra inconvenience. According to Churchyard *et al.* (2007), rates of adherence to IPT in South Africa, Zambia and Malawi ranged between 24% and 59%. Most patients cited adverse effects of the drug INH, lack of money for transport to collect the IPT and a perception that IPT was not effective.

2.7 THEORETICAL FRAMEWORKS FOR EVALUATING THE EFFECTIVENESS OF HEALTH INTERVENTIONS

2.7.1 The WHO framework for evaluating the effectiveness of health interventions

Empirical evaluation of the effectiveness of health interventions is integral to evidence-based practice. Such evaluations are also meant to ensure that treatment outcomes meet quality of care standards (Long 2011). Further, the evaluation of health interventions is key to health sector reforms, particularly to address policy concerns such as health disparities. However, the implementation of health interventions in developing countries is often poor due to poor consideration of service delivery strategies, infrastructure and technology during conceptualisation and early stages (Hickey, Odeny, Petersen, Neilands, Padian, Ford, Matthay, Hoos, Doherty & Beryer 2017).

The need for evaluations is critical throughout the implementation stages of health interventions. Barker, Reid and Schall (2016) emphasise that health interventions should be implemented in four sequential steps, namely: (1) setting-up – prepare the ground for introduction and testing of the intervention that will be taken to full scale; (2) developing the scalable unit – early testing phase; (3) testing of scale-up – tests the intervention in different settings and contexts where the intervention will be implemented in full scale;

and (4) full scale implementation – rapid unfolding or replicating the intervention to a full number of sites.

It is therefore not surprising that the implementation of IPT, which is a complex TB/HIV collaborative activity, needs to be carefully conceptualised and requires constant monitoring of its effectiveness. According to the WHO (2009), such monitoring and evaluation of health interventions:

"…provides the means to assess the quality, effectiveness, coverage and delivery of services and promotes a learning culture within programmes to ensure continual health improvement."

Evaluation is defined as a rigorous, scientifically-based collection of information about intervention activities, characteristics, and outcomes that determine the merit or worth of the intervention (WHO 2009). Therefore, evaluation studies provide empirical evidence for improving programmes or interventions.

The monitoring and evaluation of TB/HIV activities have to ensure that patients receive optimal care from both programmes (WHO 2009). Nevertheless, impact evaluation of interventions in TB/HIV programmes can rarely be attributed to a single intervention. Therefore, the evaluation of particular interventions requires rigorous designs that assess the combined effects of a number of interventions (WHO 2009).

The process of evaluating the effectiveness of interventions has to be based on a reliable theoretical framework. The WHO health system framework for evaluating the effectiveness of health interventions is such a framework (WHO 2007). The framework is invaluable for evaluating the extent to which the set goals of a community or country are being met, based on the locally defined core values of a health system.

Notably, the framework of the WHO (2007) takes into account local perceptions of what should constitute the health system of the local community. In basic terms, a health system is defined as the aggregate of commitments or resources which any national society invests in the health concerns of its inhabitants (Field 1973). However, the WHO (2007) goes on to define health system goals as defined targets for improving health and health equity, in a responsive, financially sound and resource-efficient way. Moreover, the need to increase greater access to and coverage of effective health interventions without compromising the quality and safety of the interventions are other goals listed as desirable attributes for any health system (WHO 2007).

These attributes constitute what is known as the “six building blocks of a health system”, as depicted in Figure 2.6. The WHO (2007) stresses the need to ensure the existence of multiple, dynamic relationships within the health framework. To improve the outcomes of any health intervention, all the six building blocks should be addressed proportionately in terms of four indicators, namely access, coverage, quality and safety. Therefore, the art of evaluating health interventions is based on evaluating the dynamic relationships and equilibrium among these indicators. In addition, to evaluate these four indicators objectively, there is need to review the theoretical frameworks that are important for developing and implementing best practices in health interventions.

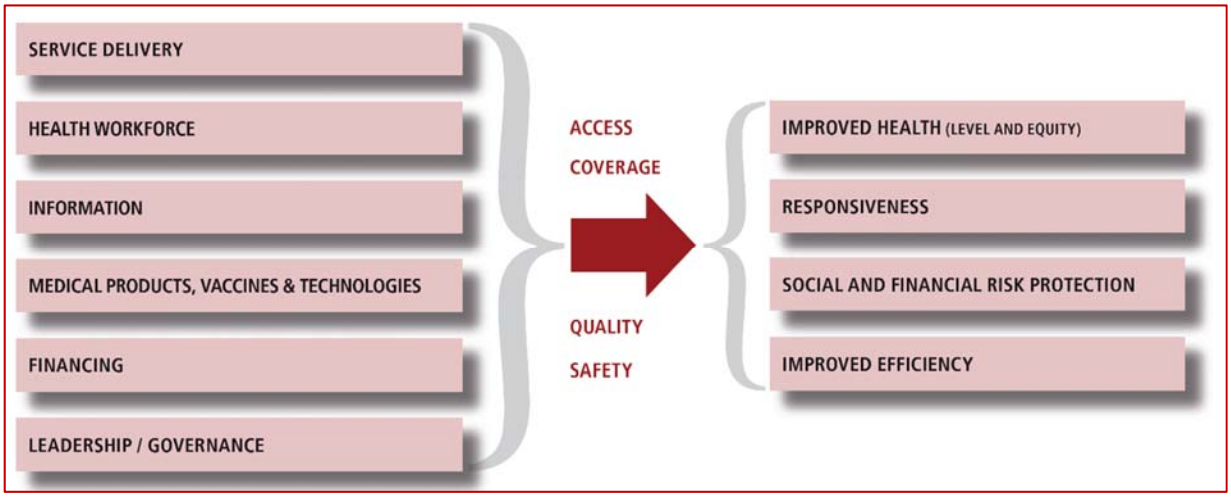

Figure 2.6 Theoretical framework for evaluating the effectiveness of health interventions

Source: (WHO 2007).

2.7.2 Framework for evaluating the implementation of best practices in health interventions

To understand how best practice frameworks are developed, it is important to review the theories that guide such missions. Historically, the evaluation of drug interventions has been carried out in 4 phases beginning with evaluation of safe dosages in phase 1 and efficacy in phase 2. If a drug is deemed safe for human trials, it is then evaluated for efficacy on a wider scale in phase 3, and finally for effectiveness through surveillance in phase 4 (Chen 2010). To ensure validity of these evaluations, methodical approaches have to be adopted. The model proposed by Campbell and Stanley (1963) over 50 years ago for evaluating health interventions based on internal and external validity is still in use today. Internal validity asks whether, in specific experimental instances, the intervention can make a significant difference, whilst external validity on the other hand, asks whether an experimental effect is capable of generalisation, and if so, to what populations, settings, or treatment and measurement variables (Spencer, Schooley, Anderson, Kochtitzky, DeGroff, Devlin & Mercer 2013).

The evaluation of health interventions is critical to their success or failure. Aarons, Sklar, Mustanski, Benbow and Brown (2017) discuss conceptual conditions critical for success of health interventions when scaled out to contexts that are different from the setting where the intervention was originally tested, and concludes that, although shorter timeframes of "translation" to new contexts is possible, the implementation of health interventions needs to be critically evaluated whenever they are transferred to new environments.

Internal and external validity of health interventions are equally important. However, Spencer *et al.* (2013) argues that, internal validity being the fundamental basis of developing best practices for health interventions, seems to be more important. The implications of this argument is that the development of best practice frameworks should consider, first and foremost, what adaptations are needed for the intervention in question to make a significant difference in local settings. Thereafter, the process should review how best to generalise the findings to other populations with similar clinical and demographic variables.

The process of determining a particular framework of best practice requires continual development and refinement throughout the implementation of the intervention. Of note, the term "best practice" refers to a particular practice that gives maximum efficiency and effectiveness. As Spencer *et al.* (2013) note, the process of developing best practices also needs a critical review of better practices in use. By definition, better practices are those practices that have been tried and tested and have good chances of making a better public health impact within a particular setting (Spencer *et al.* 2013). It is against this background that Spencer *et al.* (2013) presents an alternative framework for developing best practices for implementing health interventions.

The hallmark of the approach put forward by Spencer *et al.* (2013) is the evaluation of qualitative and quantitative evidence of better practices in local settings. More importantly, Spencer *et al.* (2013) classifies the qualitative and quantitative evidence into five groups of elements, namely: effectiveness, reach, feasibility, sustainability, and transferability. Transferability refers to the extent to which the practice can be applied to or adapted to various contexts. Figure 2.7 shows the conceptual framework for developing best practices as put forward by Spencer *et al.* (2013).

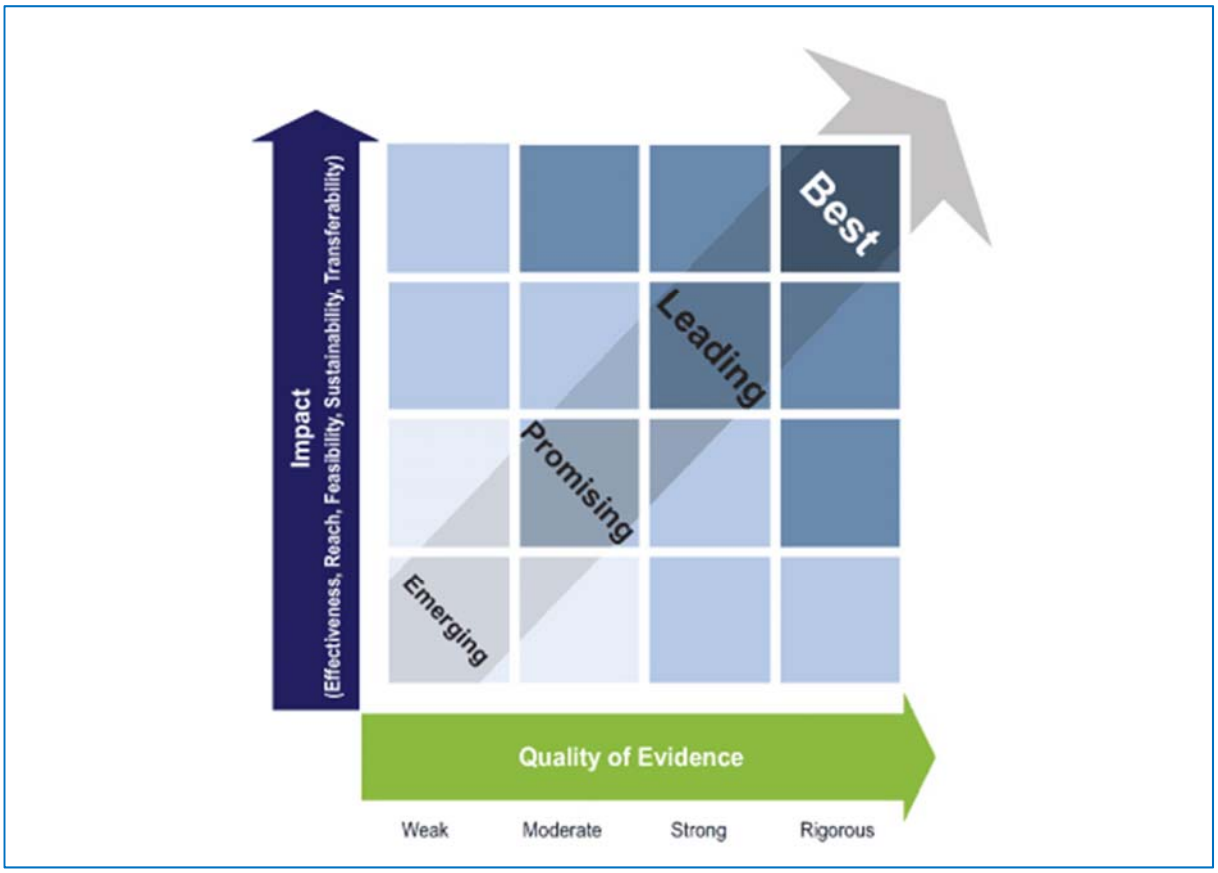

Figure 2.7 Theoretical framework for developing and implementing best practices in health interventions

Source: (Spencer *et al.* 2013).

Note that the order in which these elements appear in the conceptual framework is important. According to Spencer *et al.* (2013), the relative order of the elements implies

that other issues such as sustainability and transferability are not only more important but challenging to resolve during the development of best practice frameworks. Villeval, Bidault, Shoveller, Alias, Basson, Frasse, Génolini, Pons, Verbiguié and Grosclaude (2016) also concur that, unless health interventions are well evaluated and described, they are difficult to transfer to new contexts or country regions. Importantly, Spencer *et al.* (2013) recommend that the quality of evidence from the evaluation be ranked into 4 levels, ranging from weak to rigorous.

The strength of the framework by Spencer *et al.* (2013) is that it is based on multiple frameworks of evaluation. These include the integrative validity model; the systematic evaluation framework; and sound assessment methods. Systematic evaluation refers to consistent evaluation of the existing health interventions. The integrative validity model is an evaluation framework which prioritises the stakeholders' views and concerns during the evaluation process (Chen 2010). In addition, the integrative validity model includes elements such as the reach, effectiveness, adoption, and implementation during evaluation.

It is also important to note that this conceptual framework of developing best practices brings together aspects of impact and quality to formulate reliable criteria for evaluating public health interventions. In addition, the conceptual framework by Spencer *et al.* (2013) simplifies the process of formulating research questions that can be used for collecting evidence during the evaluations.

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CHAPTER THREE

CHAPTER THREE: METHODS

3.1 STUDY SETTING

Lesotho, located 29.6100° South and 28.2336° East, is completely surrounded by South Africa with about 2.2 million people, and an estimated gross domestic product (GDP) per capita of US$1 000, which puts the country into the low-income countries tier (BOS 2017). The country is divided into ten administrative districts, five of which are considered scale-up districts for HIV/TB programmes, due to the fact that these districts are densely populated and have the highest rates of HIV and TB. The scale-up districts occupy the densely populated lowlands of the country, while the other five districts occupy the mountainous sparsely populated highlands (PEPFAR Lesotho 2016). The government of Lesotho, through the Ministry of Health (MoH) and in partnership with implementing partners, adopted and implemented the 6-month IPT guidelines of the WHO in 2011 (GoL 2013).

Study participants were sampled from three district hospitals in three sparsely populated (non-scale-up) districts, and five district hospitals from three densely inhabited (scale-up) districts of the country (Figure 3.1). Of the eight hospitals selected, six started giving IPT in 2011, while the remaining two hospitals each commenced in 2012 and 2014 respectively.

3.2 STUDY DESIGN

The study was based on a triangulation of quantitative and qualitative research methods, an approach often adopted to improve the reliability of the study findings (Rehle, Saidel,

Mills & Magnani 2001). The overall conceptual framework of the study is presented in Figure 3.2.

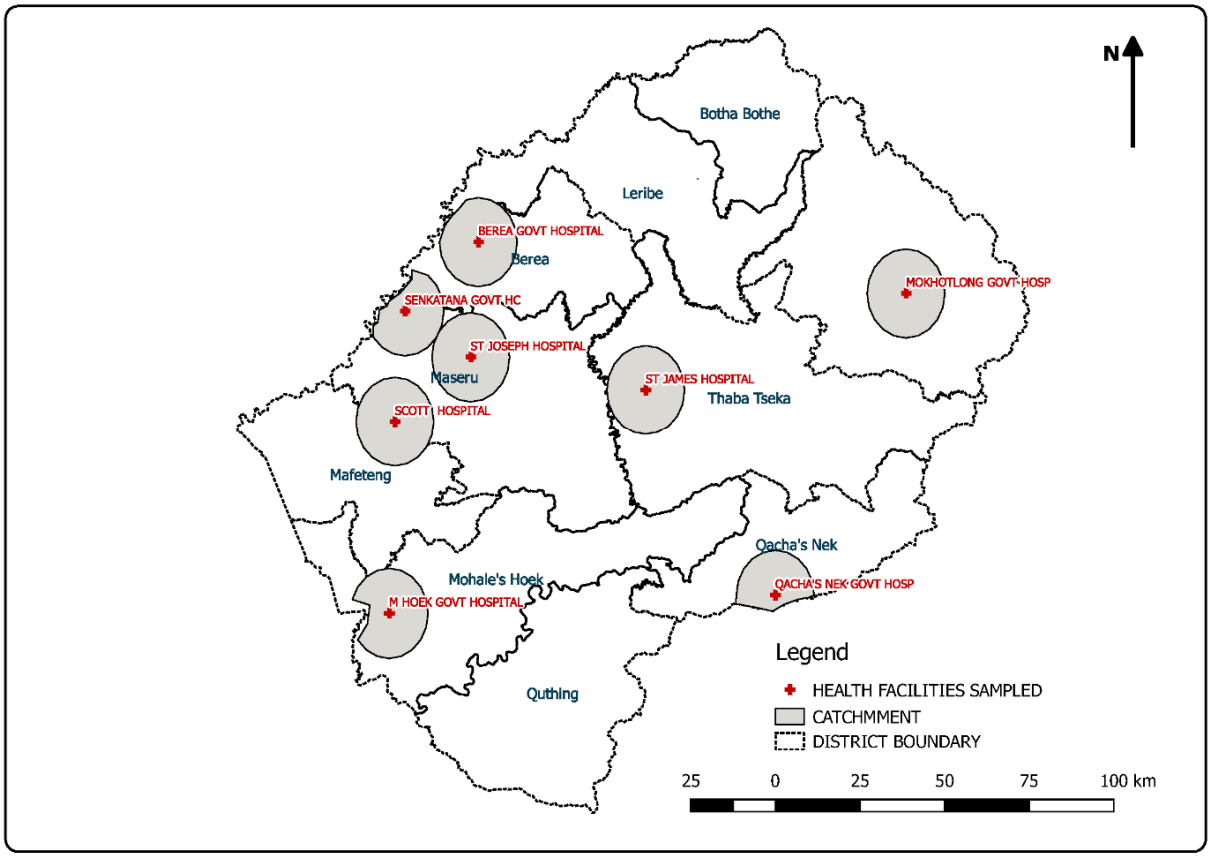

Figure 3.1 Data collection sites

Densely populated districts included in the study were Maseru, Berea and Mohale's Hoek, while sparsely populated districts sampled were Mokhotlong, Thaba Tseka and Qacha's Nek; GOVT=government; HC=health centre; HOSP=hospital; M. HOEK= Mohale's Hoek.

The study was conducted in two phases. Phase 1, which was based on in-depth cross sectional qualitative interviews with key informants involved in the implementation of IPT in Lesotho, identified contextual constraints within the national health system that affected the implementation of IPT in PLHIV within Lesotho. Key informants were sampled from among health workers and stakeholders of the TB/HIV programmes which included the Ministry of Health officials and support partners.

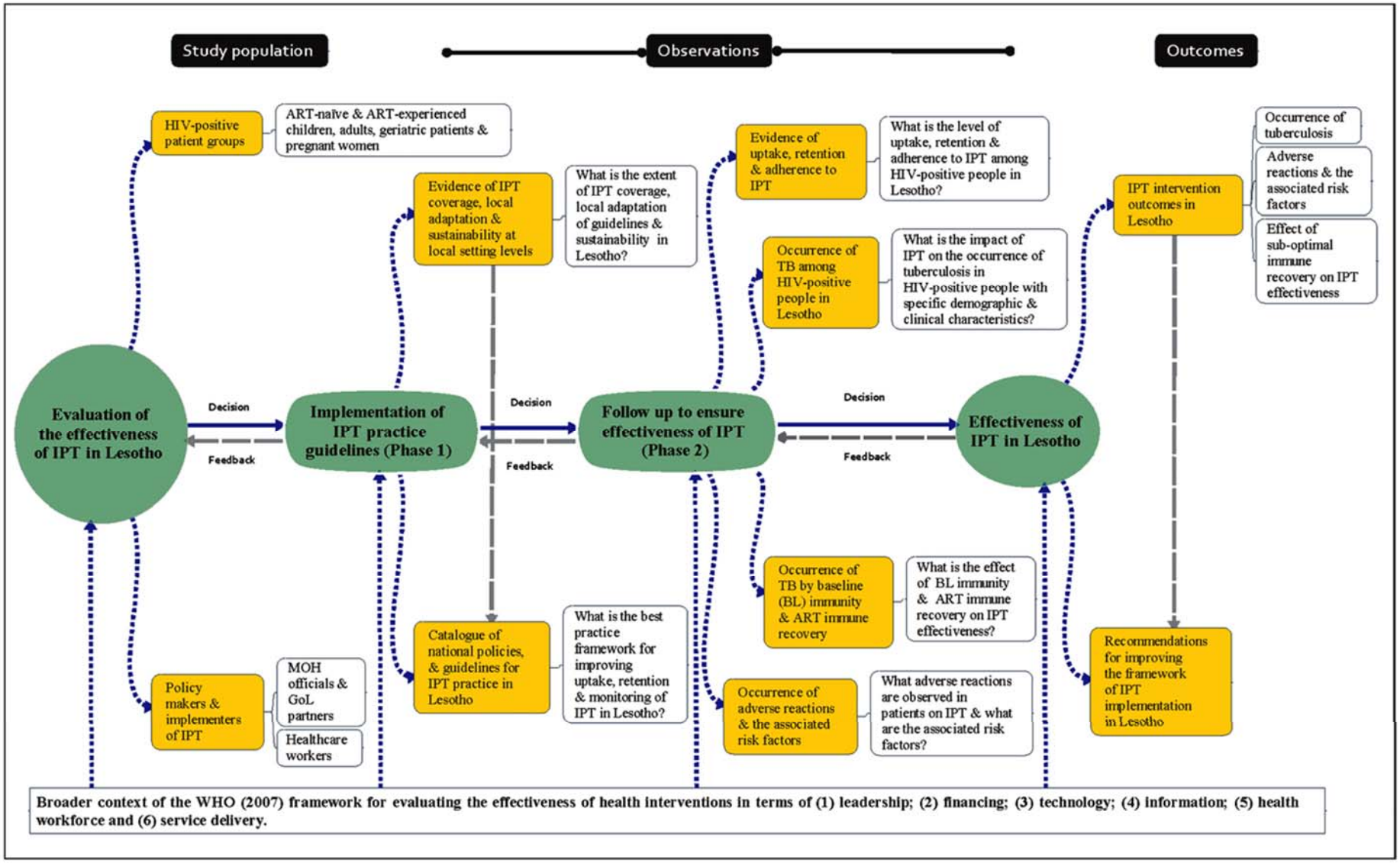

Figure 3.2 Conceptual framework for evaluating the effectiveness of IPT

Phase 2, which was based on a retrospective cohort analyses of patient records randomly selected from the register of ART patients at eight purposively selected health institutions, evaluated the rate of initiation and retention of PLHIV on IPT and the effectiveness of IPT in preventing the occurrence of TB. Figure 3.3 outlines the overall study design and the procedures followed in the study.

3.3 STUDY POPULATION AND SAMPLING

3.3.1 Phase 1

Phase 1 was based on interviews with key informants purposively sampled for their roles in the provision of HIV/TB services and their knowledge about the subject in question from among health workers at the health institutions, officials at the Ministry of Health of Lesotho and implementing partners involved in TB/HIV programmes.

The healthcare workers targeted in this phase included all those involved in the implementation of IPT in the ART centres, TB wards, pharmacies, laboratories, and administrative staff at each health institution. The target population at each of the eight health institutions was estimated at about five, implying that the total target population in the health institutions was 40.

3.3.2 Phase 2

3.3.2.1 Target population

The target population for the study was HIV-positive people enrolled in HIV care between 2004 and 2016 in the selected eight health institutions. Patients were categorised into two groups, with the first group comprising patients enrolled on ART before IPT was launched in Lesotho (2004-2010 cohort), and the second group consisting of the patients enrolled on ART from 2011 onwards (2011-2016 cohort).

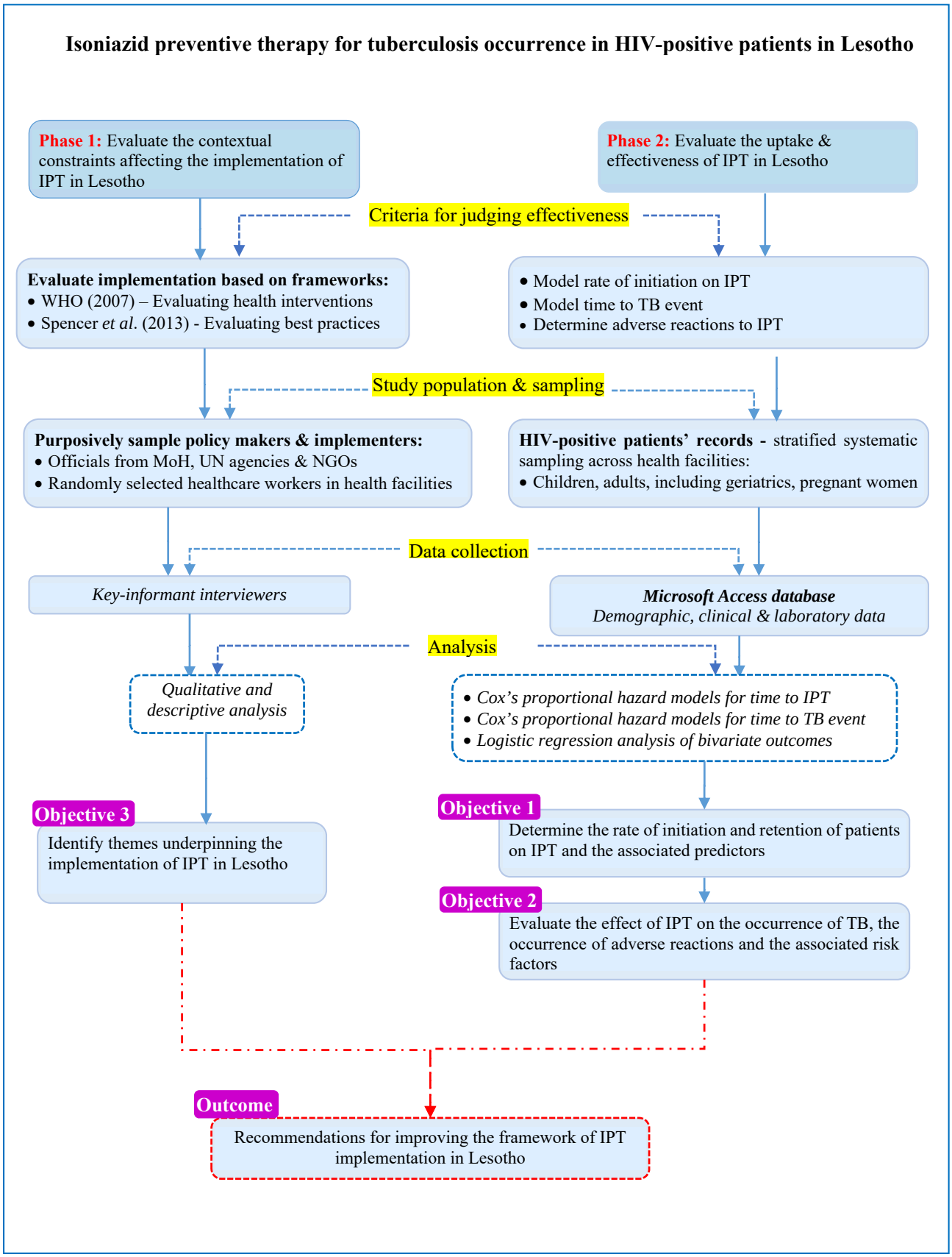

Figure 3.3 Study design schematic layout

3.3.2.2 Sample size calculation

This study phase, which required an acceptable minimum sample size of patients' records to reconstruct the occurrence of TB with or without exposure to IPT, was determined based on three criteria, namely: (1) the target population, (2) the minimum relative precision acceptable for the study, and (3) the confidence interval of the estimated occurrence. The minimum sample size was calculated following standard WHO guidelines for estimating incidences of disease conditions with a specified relative precision (Lwanga & Lemeshow 1991).

The calculated minimum number of patients' records, based on a minimum relative precision of 10% and a significance level of 5% (Lwanga & Lemeshow 1991) was 385 at each hospital, or 3 080 in the eight hospitals. However, more patient records were required to account for losses due to exclusion criteria and incomplete records, and this was estimated at 40%, implying that at least 4 620 patient files were required.

3.3.2.3 Sampling technique

Patient records were sampled based on a sampling frame, with the list of all patient records representing the sampling frame. Patients' records were then selected using a stratified random sampling technique from the sampling frame to ensure proportional representation of all patient groups, including gender and age groups, and to avoid bias, as noted by Lohr (2010).

3.4 INCLUSION AND EXCLUSION CRITERIA

3.4.1 Phase 1

3.4.1.1 Inclusion criteria

The inclusion criteria for phase 1 of the study were:

(i) key informants included nurses, doctors, pharmacists, laboratory personnel, HIV counsellors and administrators involved in TB/HIV treatment at the selected health centres;

(ii) Ministry of Health officials involved in TB/HIV programmes;

(iii) officials working with support partners and non-governmental organisations who were involved in TB/HIV interventions in Lesotho.

3.4.1.2 Exclusion criteria

(i) The study excluded health workers, officials working at Government support partner organisations, and Government officials not involved in TB/HIV programmes.

3.4.2 Phase 2

3.4.2.1 Inclusion criteria

(i) Records of all HIV-positive patients, exposed or unexposed to IPT;

(ii) the study included children and infants, adult men and women, geriatric patients and pregnant women; and

(iii) the study also included participants with any duration of antiretroviral treatment for HIV, implying that no participants were to be excluded on the grounds of treatment duration.

3.4.2.2 Exclusion criteria

(i) Patients contraindicated for IPT, and who were therefore not supposed to be initiated on IPT, were excluded from the study, including HIV-positive patients with acute or chronic liver disease; those with signs and symptoms suggestive

of active hepatitis and kidney failure; patients known to be heavy alcohol consumers; those with symptoms of severe peripheral neuropathy; and patients with a history of epilepsy or convulsions; and

(ii) patient-initiated antiretroviral treatment outside the time frames set for the study, that is, before January 2004, and those with less than six months' follow-up data, were also excluded.

3.5 DATA COLLECTION

Phase 1 of the study collected data through semi-structured questionnaires shown in Appendices A1 and A2, and data were captured into the Microsoft Access® database (see Appendix A3). A data capture form for phase 2 is presented in Appendix B. Phase 2 data was also captured in the database to improve the quality of data entry.

The data collection forms and the questionnaires for phases 1 and 2 were pilot-tested with 10 individuals who were not to be included in the final data analysis. Data were collected from January 2016 to October 2016 from the paper-based ART, IPT and TB registers, with the assistance of data collectors who were trained during the piloting phase.

3.6 DATA ANALYSIS

3.6.1 Phase 1

Data for phase 1 were analysed according to standard guidelines for analyzing qualitative data. With the help of two native speakers of the vernacular language (Sesotho) who were also competent to communicate in English language, data were manually transcribed from Sesotho to English using open coding before analysis. Thematic coding was carried out manually, and the barriers to the effective implementation of the IPT intervention were tallied and classified into four theme

categories according to the adopted conceptual framework for developing and implementing best practices in health interventions by Spencer, Schooley, Anderson, Kochtitzky, DeGroff, Devlin and Mercer (2013). Each main theme was further classified into six theme categories or typologies according to the WHO criteria for benchmarking the effectiveness of the implementation of health interventions (WHO 2007).

3.6.2 Phase 2

Data analyses for phase 2, whose main aim was to determine the rate of initiation for IPT and its effectiveness, was based on statistical modelling in Stata version 13.1 (StataCorp, Texas, USA), with the modelling being based on Cox's proportional hazard regression. Firstly, the probability of IPT initiation was modelled, considering time to IPT as the dependent variable. Secondly, the relative risk of developing TB with or without IPT were also modelled, with time to TB as the dependent variable. In both models, patient characteristics associated with the dependent outcome were factored into the model to identify the most influential factors.

The justification of the model used in the analyses was based on theoretical guidelines commonly applied in the modelling of event occurrences (Singer & Willett 2003). Kleinbaum and Klein (2005) define and explain the advantages of using Cox's proportional hazard model, noting that Cox's model estimates the hazard (*ht*) at a specified time for an individual *i* with certain characteristics:

$$h(t_{ij}) = \frac{n\ events\ j}{n\ at\ risk\ j}$$

where "*n events j*" represents the number of individuals who experience the target event in time period j, and "*n at risk j" represents* the number of individuals at risk during time period j.

Patient characteristics constituted predictor variables that were modeled to predict an individual's hazard of having an 'event'. In this study, the hazard was the initiation of the IPT event, and in the second, the hazard was the occurrence of TB, while in both

instances, time to event referred to the duration in months from the initial time of observation for each patient. The overall duration of observation in this study was subdivided into constantly spaced six-month intervals (Singer & Willett 2003), to study the effect of time on the rate of initiation for IPT and the occurrence of TB.

It is important to note that, although Cox's hazard regression model is somewhat similar to logistic regression models (Kleinbaum & Klein 2005), Cox's model is often preferred over logistic models because it works better in cases where the baseline hazard is not specified. The key difference between these models is that logistic regression estimates odds ratio, while Cox's model estimates relative risks of occurrence for given phenomena.

3.7 ETHICAL ASPECTS

The study was approved by the Ministry of Health of Lesotho prior the collection of data (see Appendix E). In addition, the study was approved by the Ethical Review Board for the Central University of Technology. To safeguard patient information privacy, the researchers observed standard ethical principles (World Medical Association 2015), including informing key informants about the purpose of the study (Appendix C1 and C2), and obtaining written consent from key informants (Appendix D1 and D2). To maintain privacy, all information collected from the medical records was treated as confidential, and fictitious patient identifier codes were used to identify the patients.

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CHAPTER FOUR

This chapter is under peer review for potential publication.

CHAPTER FOUR: MODELLING THE RATE OF INITIATION OF ISONIAZID PREVENTIVE THERAPY IN A HIGH HIV/TB-BURDEN SETTING OF LESOTHO

ABSTRACT

Background: Tuberculosis (TB) remains a public health problem, particularly in people living with HIV (PLHIV). Efforts to reduce TB incidence using isoniazid preventive therapy (IPT) have been curtailed by a poor rate of uptake of this intervention. This study modelled the rate of initiation of IPT and the associated factors in the sub-Saharan country of Lesotho, which has one of the highest TB incidences in the world. The aim was to identify patient groups that need IPT scale-up in the country.

Methods: This longitudinal retrospective study modelled the rate of initiation of IPT in randomly sampled medical records of PLHIV based on Cox's proportional hazards function. Differences in the periods of enrollment into HIV care were controlled by considering 2011, the year when IPT was launched, as the base year for follow up, and stratifying the medical records into the 2004-2010 cohort (before the launch of IPT) and the 2011-2016 cohort (after the launch of IPT).

Results: Out of 2 955 patients included in the final analysis, 68.8% had received IPT by the study exit time. The overall rate of IPT initiation was 20.6 per 100 person-years, with 135 (6.6%) defaults. Compared to the 2004-2010 cohort, the 2011-2016 had a significantly (p=0.000) higher rate of initiation (15.8 versus 27.0 per 100 person-years, respectively). Age group, district category and duration of ART emerged as the most significant predictors of IPT initiation. Patients in the sparsely populated districts [Odds ratio (OR)=1.6; p=0.000] and males [OR=2.1; p=0.006] had higher rates of defaulting IPT compared to those in the densely populated districts, and females, respectively.

Conclusion: These findings indicate a slow rate of implementation of a key health intervention for TB in PLHIV. Significant factors associated with disparities in the initiation and defaulting of IPT in this study are important for policy review.

Keywords: Cox's proportional hazards function; isoniazid preventive therapy; Lesotho; PLHIV; tuberculosis; uptake of health interventions

4.1 INTRODUCTION

4.1.1 Background

Human immunodeficiency virus (HIV) and tuberculosis (TB) have become a global syndemic responsible for nearly 25% of all HIV-associated deaths (WHO 2018). Of the 1.3 million people who died from TB in 2017 alone, 300 000 were HIV-positive (WHO 2018). In addition, the WHO (2018) notes that the incidence of TB in 2013 was about 133 cases per 100 000 global population. Despite the effectiveness of isoniazid, also known as isonicotinylhydrazine (INH), recommended by the WHO (2004) for the prevention of TB in people living with HIV (PLHIV), having been demonstrated to be effective when given in combination with antiretroviral therapy (ART) in many countries including, but not limited to Ethiopia, Brazil, Cambodia, Botswana and South Africa, the rate of initiation of IPT has generally been slow (Dowdy, Golub, Saraceni, Moulton, Cavalcante, Cohn, Pacheco, Chaisson & Durovni 2014; Tedla, Nguyen, Sibanda, Nyirenda, Agizew, Girde, Rose & Samandari, 2015; Ayele, Mourik & Bonten 2016; Sumner, Houben, Rangaka, Maartens, Boulle, Wilkinson & White 2016). This includes developing countries categorised by the World Health Organization (WHO 2015) as high TB-burden settings.

The reasons for the slow implementation vary from country to country (Temprano ANRS 12136 Study Group 2015). In some countries, poor healthcare delivery systems and a lack of adequate means to exclude a pre-existing TB infection prior to treatment initiation are some of the most cited reasons for the slow rate of initiation of IPT (Assebe, Reda, Wubeneh, Lerebo & Lambert, 2015; Tadesse, Gebre, Daba, Gashu, Habte, Hiruy, Negash, Melkieneh, Jerene, Haile, Kassie, Melese & Suarez 2016). Jena and Harinath (2015) also cited skepticism by healthcare professionals about potential drug resistance. In addition, underestimation of the potential public health impact of IPT by HIV/TB programme managers has also been reported as a barrier to IPT uptake

(Guwatudde, Debanne, Diaz, King & Whalen 2004; Ayele, Van Mourik & Bonten 2015). Furthermore, some countries were not convinced of the benefits of IPT, and deferred the implementation of IPT altogether for many years. For example, the Ivory Coast had not implemented IPT by 2014 (Temprano ANRS 12136 Study Group 2015).

The uptake of health interventions, preventive therapies included, particularly in developing countries, are often sluggish (Ostermann, Brown, De Bekker-Grob, Mühlbacher & Reed 2017). It is important to note that barriers to scaling up health interventions in developing countries are diverse, and studies on these barriers have recently become a significant mini-branch of science known as implementation science (Yamey, 2012; Bragge, Grimshaw, Lokker & Colquhoun 2017). Realising the challenge of translating knowledge into policy and practice, the main focus within this science has been on studying the "know-do gap" – the gap between what is known and what gets implemented (Pablos-Mendez & Shademani 2006). As such, some causes of the know-do gap applicable to the sluggish IPT uptake in developing countries include inexperience in evidence-based problem-solving and learning approaches among programme leaders; lack of ownership of knowledge by potential adopters; lack of evaluation; and continuous improvement strategies (Pablos-Mendez & Shademani 2006). The slow uptake of IPT in developing countries is therefore a symptom of a range of problems in the health systems of these countries. Therefore, assessments of barriers to IPT uptake in developing countries are an important proxy for gaging the efficiency of the respective national health systems.

Lesotho is a small country completely surrounded by the Republic of South Africa, with a territory of only about 30 000 square kilometres, and a population of about 2.2 million (GoL, 2013). The United Nations (2009) notes that Lesotho is a poor country, with 40% of its population living below the official poverty line of US$1.25 per day. The country, with a 23.5% adult HIV prevalence rate, has the second highest prevalence rate of HIV

worldwide (UNAIDS 2016), and with the TB incidence rate in the general population estimated at 852 per 100 000 population (WHO 2015), the country is amongst the top three nations with the highest rates of TB worldwide.

INH preventive therapy (IPT) was introduced to Lesotho in 2011 (GoL 2013). However, since the programme was launched, information on the rate of initiation of IPT and the associated factors has remained obscure (GoL 2013). To put this obscurity into perspective, the country is one of the ten countries in the world which did not provide data for the IPT indicator to the WHO repository in 2014 (WHO 2014).

This study assessed the rate of initiation of IPT and retention in HIV-infected patients in the high TB-burden setting of Lesotho since its launch. The study also determined the predictors of poor uptake of this intervention, with the aim of identifying patient groups that need IPT scale-up in the country.

4.2 METHODS

4.2.1 Study design

This longitudinal retrospective cohort study modelled the probability of IPT initiation associated with characteristics of PLHIV in Lesotho, considering time to IPT as the dependent variable. The study made recourse to statistical principles of the Cox's proportional hazard regression, based on data extracted from randomly sampled ART records of patients enrolled into ART between 2004 and 2016.

The study fitted Cox's proportional hazards regression to the probability of IPT initiation, assuming a fairly constant rate of IPT initiation over the study follow-up time. One previous study reports that, with minimal calibrations, data on time to IPT initiation generally fits an exponential curve which can be modeled by Cox's proportional hazards function (Dowdy *et al.* 2014).

4.2.2 Study population

The target population for the study was HIV-positive people enrolled in HIV care between 2004 and 2016 in the selected eight health institutions, all of which were district hospitals with at least 2 000 patients on ART. For purposes of analysing the effect of the duration of ART on IPT initiation, patients were categorised into two groups, with the first group comprising patients enrolled on ART before IPT was launched in Lesotho (2004-2010 cohort), while the second group consisted of patients enrolled on ART from 2011 onwards (2011-2016 cohort). In addition, the study population was divided into sparsely and densely populated district categories, based on population density. ART records of HIV-positive children, adolescents and adults, including geriatric patients and pregnant women were selected using stratified systematic random sampling across eight health facilities, to ensure proportional representation of all patient categories including gender, age groups and period of enrolment.

4.2.3 Sample size calculation

The minimum sample size was calculated following standard guidelines for estimating incidence with a specified relative precision (Lwanga & Lemeshow 1991). The minimum number of patients' records, based on a minimum relative precision of 10% and a significance level of 5% (Lwanga & Lemeshow 1991), was 385 at each hospital, or 3 080 in the eight hospitals. However, more patient records were required to account for losses due to exclusion criteria and incomplete records. An ample buffer for this loss was estimated at 40%, implying that at least 4 620 patient files were required. In addition, the minimum sample size per hospital was proportionally adjusted for slight differences in the study populations at the hospitals following statistical rules for stratified systematic random sampling.

Data were collected from January to October 2016 from the paper-based ART, IPT and TB registers. To improve the quality of data entry, a Microsoft Access database application tool was used to capture data from the files. Data were captured into the database tool in six-month discrete intervals.

4.2.4 Patient sampling and data collection

File selection was based on a sampling frame. The sampling frame was prepared from the ART attendance registers by drawing a list of all the patients enrolled into HIV care since 2004. The total number of files to be sampled per hospital was obtained by dividing the total number of patients enrolled in HIV care by the proportional target sample size for the hospital. For example, in a hospital with 2 000 patients enrolled and a target sample size of 350, one in six patients was systematically selected by sampling every 6^{th} patient from the patient register.

4.2.5 Final sample selection criteria

Overall, 4 122 patient files were collected. Of the 4 122 patients, 1 167 were excluded according to the following exclusion criteria: transfer-in (118), past TB cases (337); on TB treatment at enrolment, or were diagnosed with TB within one month of enrolment (482); less than six months of follow-up time, or died before the IPT programme was launched (131); or insufficient information (99) (see Figure 4.1). Therefore, the final sample size was 2 955.

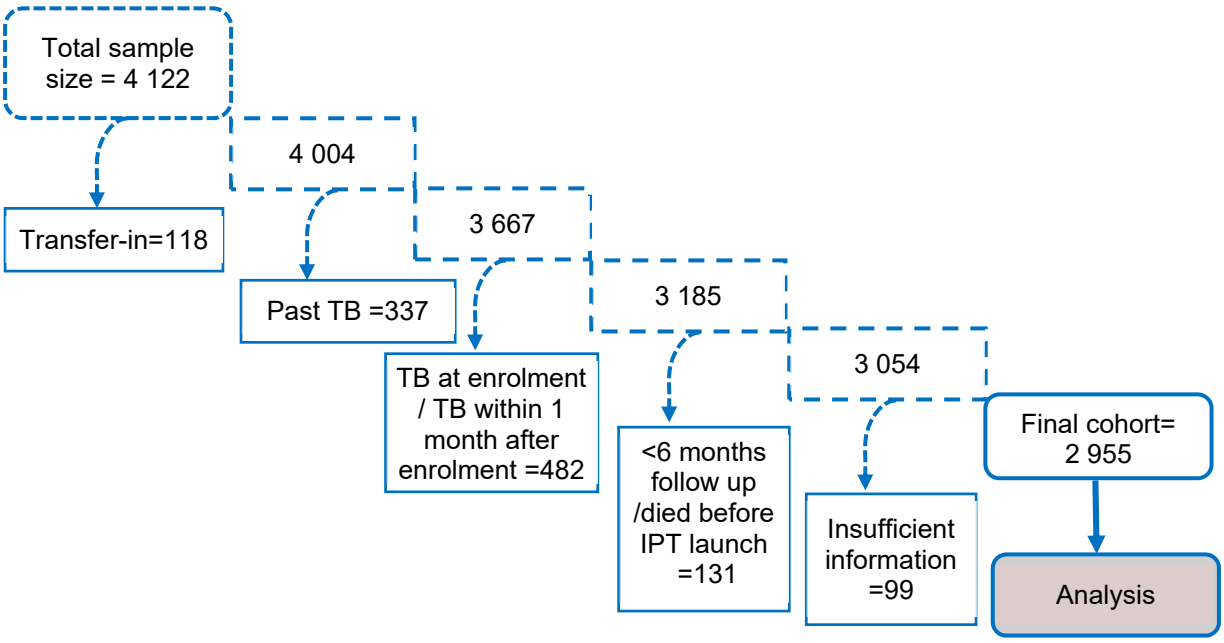

Figure 4.1 Exclusion criteria for the patients

Insufficient information referred to patient files with grossly missing data; past TB= having a diagnosis of TB before enrolment into HIV care; TB=tuberculosis.

4.2.6 Patient data and outcome measures

For purposes of evaluating the associations between patient characteristics and time to IPT (in months), which was the main outcome variable, demographic, baseline clinical data and ART follow-up information were needed. Thus, demographic information including gender, date of birth and marital status of the patients meeting the selection criteria were collected from the records. Their clinical data, including dates of HIV diagnosis, enrolment into HIV care, ART and IPT initiation; baseline indicators including CD4 count, viral load, patient ART status and WHO clinical staging; ART and IPT regimens and check-up information at each visit; adherence records; and laboratory monitoring data were also extracted from the records. Time-variant variables, including age, were calculated according to the time at enrolment into HIV care. Patients late for their scheduled appointments by more than a month, and those who did not return for ART services were classified as drop-outs.

Time to IPT was calculated by subtracting the date of enrolment into HIV care from the date that IPT was prescribed. Patient treatment outcomes were assessed by median

CD4 and viral load values. The duration of the period before ART commencement (in years), known as the Pre-ART period, was calculated by subtracting the date of HIV diagnosis from that of ART commencement.

Furthermore, the proportion of patients who defaulted IPT was calculated, and the factors associated with the defaulting were assessed using logistic regression analysis.

4.2.7 Data preparation

Data for IPT initiation in the Microsoft Access database were verified and exported to Stata version 13.1 for further cleaning and analysis (StataCorp, Texas, USA). Data were formatted for survival analysis as discrete-time survival data, with the interval date as the time variable. The occurrence of IPT event defined the 'failure' outcome, and the scale for the time variable was set in years. To obtain comparable follow-up times, patients enrolled before IPT were declared to have entered the risk set in 2011, the year that IPT was launched in the country. For purposes of calculating Cox's proportional hazards ratios, entry times into the risk set were delayed by one month for all the patients to calibrate for inconsistencies at first entry into the risk set. The date of enrolment into HIV care, and the exit date, marked the left and right censoring times respectively.

4.2.8 Modelling patient characteristics associated with IPT initiation

This analysis modelled the rate of IPT initiation and identified patient characteristics associated with IPT initiation through the Cox's hazard regression function (Kleinbaum & Klein 2005). The method was applied taking the hazard as a probability that an individual with certain characteristics would receive IPT in a specified time.

Breslow's correction for tied data was used to correct the assumption that survival times in the study were distinct (Kleinbaum & Klein 2005). Follow-up times were

subdivided into six-month discrete intervals due to observation gaps for the patients (Singer & Willett 2003).

To assess the patient characteristics associated with IPT initiation, descriptive statistics of the data were summarised by cross-tabulating the patient characteristics with IPT initiation outcome with the Chi-square values, indicating the significance of the differences. Patient characteristics were further analysed using cumulative probability distribution plots and univariate Kaplan-Meier curves to determine their suitability in the model of IPT initiation. Further, Wilcoxon's log-rank test and Cox's regression analysis were used to determine equality across strata for categorical variables and continuous variables, respectively. Predictors with *p*-values <0.2 were included in the IPT initiation model.

The variable "period of enrolment" was selected *a priori* as a strata variable to control for differences in the periods of enrollment into HIV care. The year 2011, when IPT was launched, was set as the base year for follow up, and medical records were stratified into the 2004-2010 cohort (before the launch of IPT) and the 2011-2016 cohort (after the launch of IPT). Nine predictors, namely, age, gender, baseline CD4 count, duration of pre-ART, patient ART status, baseline WHO clinical stage, duration of ART, adherence to ART, and district category were selected into the model and excluded using the stepwise method. Three variables, namely age group, district category, and duration of ART remained in the model.

The model was tested for predictor interaction, and two variables, duration of ART and district category had significant interactions (p<0.005). The models with and without the interaction variables were compared using the likelihood ratio (Lrtest), and the difference was found to be significant (Chi (3)=10.0; p=0.006), implying that the bigger model with the interaction terms was superior to the one without.

The unstratified model was checked for proportionality using the Schoenfeld and scaled Schoenfeld residuals (Phtest) test. One categorical variable, duration of ART, significantly (p=0.032) violated the proportionality assumption. However, this variable was retained in the model, and the anomaly was corrected by the subsequent stratified analysis.

4.2.9 Ethical aspects

The study was approved by the Ministry of Health of Lesotho (see Appendix E). To safeguard patient information privacy, the researchers observed standard ethical principles (World Medical Association 2015). To maintain privacy, all information collected from the medical records was treated as confidential, and fictitious patient identifier codes were used to identify the patients.

4.3 RESULTS

4.3.1 Patient characteristics by IPT initiation

In total, 2 955 patients were included in the final analysis. By proportion, 68.8% of the patients received IPT during follow up, while 31.2% had not received the drug at the exit time for the study. Tables 4.1a – 4.1c present the characteristics of the patients and their IPT initiation outcomes.

Females had a higher rate of IPT initiation compared to males (71.8% females versus 63.1% males; t=23.5; p<0.001) (See Table 4.1a). The rate of initiation of IPT varied significantly (t=30.8; p<0.001) by age groups. The 65-84 (75.0%) and 0-9 (40.4%) age groups had the highest and the least rates of IPT initiation, respectively. IPT initiation rates differed significantly (t=24.7; p<0.001) by marital status, with the widowed (74.5%) and the single (62.3%) having the highest and least rates, respectively.

Overall, the densely populated districts, which constituted 64.7% patients, had significantly (t=28.1; p<0.001) higher rates (72.1%) of IPT initiation, compared to the sparsely inhabited ones (62.8%). Two densely populated districts, Berea (87.6%) and Maseru (70.2%), had the highest initiation rates, while Mohale's Hoek (44.7%), a densely populated district, and two sparsely populated districts, Qacha's Nek (54.3%), and Thaba Tseka (55.0%), had the least rates (Table 4.1a).

Of note, the cohort enrolled into HIV care from 2011 to 2016 (59.1%) significantly (p<0.001) outnumbered that of the period from 2004 to 2010 (Table 4.1b). The total IPT initiation in the 2004-2010 period (73.7%) was significantly higher (t=23.1; p<0.001) than in the latter period (65.4%). The majority (58.6%) of the patients were prescribed with Tenofovir/ lamivudine/ efavirenz for baseline ART.

Patients who entered into HIV care through the Adolescents Department (100%) and the HIV Testing and Counselling Department (89.8%) had the highest proportion of IPT initiation, while the proportion initiated was below 60% in the self-refer (55.6%) and the under-five (50.0%) entry points (Table 4.1b).

At the time the study was terminated (Table 4.1b), 84.4% patients were still continuing ART; the other patients were drop-outs (9.0%), had died (4.1%), or had transferred out (2.6%). Patients with poor adherence had slightly higher overall initiation of IPT (73.0%) compared to those with good adherence (70.5%).

Table 4.1a Associations between patient characteristics and IPT initiation in PLHIV in Lesotho

		Received IPT while in HIV care		
	Total Column% (*n*)	No Row% (*n*)	Yes Row% (*n*)	Chi-square (*p*-value)
Total	100 (2 955)	31.2 (922)	68.8 (2 033)	
Gender				
Female	65.7 (1 942)	28.2 (548)	71.8 (1 394)	23.5 (0.000)
Male	34.3 (1 013)	36.9 (374)	63.1 (639)	
Age (years)				
0-9	1.8 (52)	59.6 (31)	40.4 (21)	30.8 (0.000)
9-18	1.3 (38)	42.1 (16)	57.9 (22)	
18-25	9.1 (269)	33.5 (90)	66.5 (179)	
25-35	34.8 (1 027)	32.7 (336)	67.3 (691)	
35-45	27.9 (824)	27.4 (226)	72.6 (598)	
45-55	16.1 (477)	29.1 (139)	70.9 (338)	
55-65	7.6 (224)	32.6 (73)	67.4 (151)	
65-84	1.5 (44)	25 (11)	75 (33)	
Marital status				
Married	59.3 (1 752)	32.2 (564)	67.8 (1188)	24.7 (0.000)
Divorced	0.4 (11)	27.3 (3)	72.7 (8)	
Separated	6.5 (193)	26.9 (52)	73.1 (141)	
Widowed	15.5 (458)	25.5 (117)	74.5 (341)	
Cohabiting	0.2 (6)	33.3 (2)	66.7 (4)	
Single	14.9 (440)	37.7 (166)	62.3 (274)	
(-)	3.2 (95)	18.9 (18)	81.1 (77)	
District				
Berea	18.3 (540)	12.4 (67)	87.6 (473)	235.9 (0.000)
Maseru	38.7 (1 145)	29.8 (341)	70.2 (804)	
Mohale's Hoek	7.7 (228)	55.3 (126)	44.7 (102)	
Mokhotlong	11.4 (336)	20.2 (68)	79.8 (268)	
Qacha's Nek	10.2 (302)	45.7 (138)	54.3 (164)	
Thaba Tseka	13.7 (404)	45 (182)	55 (222)	
District category				
Dense	64.7 (1 913)	27.9 (534)	72.1 (1 379)	27.3 (0.000)
Sparse	35.3 (1 042)	37.2 (388)	62.8 (654)	

(-)=missing information; *n*=number of patients;

Table 4.1b Associations between patient characteristics and IPT initiation in PLHIV in Lesotho (continued)

		Received IPT while in HIV care		
	Total Column% (*n*)	No Row% (*n*)	Yes Row% (*n*)	Chi-square (*p*-value)
Total	100 (2 955)	31.2 (922)	68.8 (2 033)	
Period of enrolment into HIV care				
2011-2016	59.1 (1 745)	34.6 (604)	65.4 (1 141)	23.1 (0.000)
2004-2010	40.9 (1 210)	26.3 (318)	73.7 (892)	
Entry point				
Adolescent clinic	0.4 (12)	0 (0)	100 (12)	50 (0.000)
HTC	4 (118)	10.2 (12)	89.8 (106)	
MCH	9.1 (268)	29.5 (79)	70.5 (189)	
OPD	77.7 (2 295)	31.2 (717)	68.8 (1 578)	
Self-refer	7.9 (232)	44.4 (103)	55.6 (129)	
Under-five clinic	0.2 (6)	50 (3)	50 (3)	
Hospital ward	0.8 (24)	33.3 (8)	66.7 (16)	
Baseline regimen				
TDF+3TC+EFV	58.6 (1 732)	30.2 (523)	69.8 (1 209)	22.2 (0.005)
AZT+3TC+EFV	23.8 (704)	35.1 (247)	64.9 (457)	
AZT+3TC+NVP	5.9 (173)	27.2 (47)	72.8 (126)	
D4T+3TC+NVP	4.1 (120)	24.2 (29)	75.8 (91)	
D4T+3TC+EFV	2.8 (84)	27.4 (23)	72.6 (61)	
TDF+3TC+NVP	2.2 (65)	26.2 (17)	73.8 (48)	
ABC+3TC+NVP	1.1 (32)	37.5 (12)	62.5 (20)	
ABC+3TC+EFV	1 (29)	55.2 (16)	44.8 (13)	
ABC+3TC+kaletra	0.5 (16)	50 (8)	50 (8)	
Patient status				
Drop-out	9 (265)	48.7 (129)	51.3 (136)	185.9 (0.000)
Dead	4.1 (121)	78.5 (95)	21.5 (26)	
Transfer out	2.6 (76)	35.5 (27)	64.5 (49)	
ART continuing	84.4 (2 493)	26.9 (671)	73.1 (1 822)	

ART=antiretroviral therapy; ABC=abacavir; AZT=zidovudine; 3TC=lamivudine; kaletra=lopinavir/ritonavir; NVP=nevirapine; EFV=efavirenz; TDF=tenofovir; BL=baseline; HTC=HIV testing and counselling; MCH=mother and child health; OPD=outpatient department.

Table 4.1c Associations between patient characteristics and IPT initiation in PLHIV in Lesotho (continued)

		Received IPT while in HIV care		
	Total Column% (*n*)	No Row% (*n*)	Yes Row% (*n*)	Chi-square (*p*-value)
Total	100 (2 955)	31.2 (922)	100 (2 955)	
Adherence to ART				
Good	79.1 (2 336)	32.3 (755)	67.7 (1 581)	6.5 (0.011)
Poor	20.9 (619)	27 (167)	73 (452)	
Treatment failure				
No	98.4 (2 909)	31.5 (916)	68.5 (1 993)	7.2 (0.007)
Yes	1.6 (46)	13 (6)	87 (40)	
BL CD4 count				
1-100	21.6 (639)	35.1 (224)	64.9 (415)	19.5 (0.000)
101-350	58 (1 714)	28.1 (481)	71.9 (1 233)	
351-500	12.1 (357)	37.3 (133)	62.7 (224)	
501-1512	8.3 (245)	34.3 (84)	65.7 (161)	
BL WHO Clinical stage				
I	35.5 (1 049)	30.1 (316)	69.9 (733)	46.5 (0.000)
II	41.3 (1 219)	30.9 (377)	69.1 (842)	
III	17.5 (516)	26.6 (137)	73.4 (379)	
IV	5.8 (171)	53.8 (92)	46.2 (79)	
Median viral load				
Tnd*	9.1 (268)	24.3 (65)	75.7 (203)	14.7 (0.005)
Low	1.3 (38)	34.2 (13)	65.8 (25)	
High	2.1 (61)	31.1 (19)	68.9 (42)	
Very high	2.8 (84)	17.9 (15)	82.1 (69)	
(-)	84.7 (2 504)	32.3 (810)	67.7 (1 694)	
Length of pre-ART (years)				
<1	72 (2 127)	29.9 (636)	70.1 (1 491)	28.8 (0.000)
01-2	9.1 (269)	26.4 (71)	73.6 (198)	
03-5	11.6 (344)	33.4 (115)	66.6 (229)	
>5	7.3 (215)	46.5 (100)	53.5 (115)	

ART=antiretroviral therapy; *Tnd=target not detected; WHO= World Health Organization; *n*=number of patients; CD4 counts are in cells/mm^3; viral load ranges in copies/mm^3 are as follows: tnd (0-50); low (50-500); high (500-10 000); and very high (>10 000).

Only 1.6% of the patients had treatment failure (Table 4.1c). Patients with treatment failure had significantly (t=7.2; *p*=0.007) higher initiation of IPT, compared to those with no regimen change due to treatment failure (87.0% versus 68.5%).

IPT initiation significantly (t=28.4; *p*<0.001) varied with the length of pre-ART time, with the highest initiation (73.6%) occurring in those exposed to ART 1-2 years of testing positive, and the least (53.5%) occurring in those with a pre-ART time of more than five years (Table 4.1c). Baseline stage III had the highest initiation of IPT (73.4%); the least was baseline stage IV with an initiation of 46.2%. The 101-350 CD4 count category had the highest initiation of IPT (71.9%), while the 351-500 category had the least. Overall, IPT initiation varied significantly (t=19.4; *p*<0.001).

IPT initiation significantly (t=14.7; *p*=0.005) varied with median viral load categories (Table 4.1c). Patients with very high median viral load had the highest initiation (82.1%) of IPT, while those with low median viral load had the least (65.8%). However, 84.6% patients had missing data for the median viral load.

4.3.2 Associations between incident IPT initiation and predictor variables

Tables 4.2a and 4.2b present the overall incident IPT cases, and the cases stratified by period of enrolment. Overall, 2,033 incident IPT cases in 9 728 person-years of observation occurred out of the 2 955 patients in the study. The overall rate of IPT initiation was 20.6 per 100 person-years. The effective follow-up time since IPT was launched in 2011 ranged from 0.5 to 5.8 years (mean=3.5; median=4.1; interquartile range (IQR): 1.4–5.6). With the data stratified by period of enrolment, the median time to IPT for the patients enrolled before 2011 was higher than that of the patients enrolled on ART after 2011 (4.8 versus 2.5 years, respectively). Compared to patients enrolled before 2011, patients enrolled after 2011 had a significantly (*p*=0.000) higher initiation rate (15.8 versus 27.0 per 100 person-years, respectively).

Table 4.2a Associations between predictors and IPT initiation stratified by period of enrolment into HIV care

	Overall		Enrolment period 2004-2010					Enrolment period 2011-2016				
	%IPT cases (*n*)	IPT cases/ 100 PYs*	Total (*n*)	IPT cases Row % (*n*)	Person -years	IPT cases/ 100 PYs*	Chi-square; *p*-value	Total (*n*)	IPT cases Row % (*n*)	Per-son-years	IPT cases/ 100 PYs*	Chi-squared; *p*-value
Total	69 (2 033)	20.6	1210	74 (892)	5 641	15.8		1 745	65 (1141)	4 223	27.0	300 (0.000)*
Gender												
Female	72 (1 394)	21.1	798	77 (613)	3 740	16.4	1.5 (0.226)	1 144	68 (781)	2 856	27.3	1.8 (0.176)
Male	63 (639)	19.6	412	68 (279)	1 901	14.7		601	60 (360)	1367	26.3	
Age												
Children	40 (21)	10.7	31	42 (13)	135	9.6	3.1 (0.373)	21	38 (8)	61	13.2	4.3 (0.23)
Adolescents	60 (33)	28.2	12	42 (5)	43	11.7		43	65 (28)	74	37.6	
Adult	69 (1 876)	20.7	1116	75 (839)	5 217	16.1		1 587	65 (1 037)	3 849	26.9	
Elderly	71 (103)	21.2	51	69 (35)	246	14.2		94	72 (68)	239	28.4	
District category												
Dense	72 (1 379)	20.5	922	75 (691)	4 266	16.2	0.9 (0.336)	991	69 (688)	2 452	28.1	2.9 (0.091)
Sparse	63 (654)	20.8	288	70 (201)	1 375	14.6		754	60 (453)	1772	25.6	
Patient status												
Drop-outs	51 (136)	17.4	146	53 (77)	540	14.3	9.5 (0.024)	119	50 (59)	239	24.6	8.1 (0.045)
Dead	21 (26)	15.0	73	23 (11)	116	9.5		48	31 (15)	57	26.3	
Transfer out	64 (49)	18.2	29	93 (21)	135	15.5		47	60 (28)	133	21.0	
ART cont.	73 (1 822)	21.1	962	81 (783)	4 848	16.2		1531	68 (1 039)	3 794	27.4	
Adherence												
Good	68 (1 581)	21.7	843	75 (620)	3 864	16.0	0.2 (0.642)	1 493	68 (961)	3 420	28.1	1.1 (0.29)
Poor	73 (452)	17.5	367	74 (272)	1 777	15.3		252	71 (180)	802	22.4	

*100 PYs = 100 person years; ART=antiretroviral therapy; BL=baseline; IPT=isoniazid preventive therapy; *n*=number of patients; TB=tuberculosis;

Table 4.2b Associations between predictors and IPT initiation stratified by period of enrolment into HIV care (continued)

	Overall		Enrolment period 2004-2010					Enrolment period 2011-2016				
	%IPT cases (*n*)	IPT cases/ 100 PYs*	Total (*n*)	IPT cases Row % (*n*)	Person -years	IPT cases/ 100 PYs*	Chi-square; *p*-value	Total (*n*)	IPT cases Row % (*n*)	Per-son-years	IPT cases/ 100 PYs*	Chi-squared; *p*-value
Total	69 (2 033)	20.6	1210	74 (892)	5 641	15.8		1 745	65 (1141)	4 223	27.0	300 (0.000)*
Treatment failure												
No	69 (1 993)	19.1	1176	73 (860)	5 471	18.9	2.1 (0.144)	1 733	65 (1 133)	4 184	27.1	0.2 (0.649)
Yes	87 (40)	20.6	34	94 (32)	169	15.7		12	67 (8)	40	20.2	
BL CD4												
1-100	65 (413)	18.9	321	71 (229)	1 449	15.8	2.4 (0.515)	318	59 (186)	757	24.6	2.7 (0.313)
101-350	72 (1 232)	19.9	757	76 (567)	3 582	15.8		957	70 (666)	2 602	25.6	
351-500	60 (214)	26.2	81	76 (62)	379	16.3		276	59 (162)	477	34.0	
501-1572	66 (161)	26.0	51	67 (34)	231	14.6		194	65 (127)	387	32.8	
BL WHO stage												
I	70 (733)	24.4	246	80 (196)	1 192	16.4	4.2 (0.240)	803	67 (537	1 813	29.6	12.4 (0.006)
II	69 (842)	18.7	609	71 (430)	2 848	15.1		610	67 (412)	1 664	24.7	
III	73 (379)	19.6	295	76 (224)	1 355	16.5		221	70 (155)	577	26.8	
IV	46 (79)	19.1	60	70 (42)	245	17.1		111	33 (37)	169	21.9	
Duration of pre-ART												
<1	70 (1 491)	20.7	892	74 (663)	4 151	15.9	1.9 (0.602)	1 235	67 (828)	3 050	27.2	4.5 (0.213)
1-2	74 (198)	21.1	121	76 (92)	561	16.4		148	72 (106)	377	28.1	
3-5	67 (229)	19.2	135	76 (102)	654	15.6		209	56.4 (127)	538	23.6	
>5	53 (115)	21.6	62	56 (35)	273	12.8		153	46.6 (80)	258	31.0	
Duration of ART (Years)												
0-2	45 (329)	59.4	59	2 (1)	40	2.4	24 (0.000)	678	48.4 (328)	514	63.8	9.4 (0.024)
3-4	67 (479)	23.7	63	32 (20)	191	10.4		654	70.2 (459)	1830	25.1	
5-6	81 (570)	17.6	313	76 (239)	1 499	15.9		388	85.3 (331)	1 745	19.0	
>6	82 (655)	16.2	775	81 (632)	3 909	16.1		25	92.0 (23)	134	17.1	

*100 PYs = 100 person years; tnd=target not detected; WHO= World Health Organization; CD4 counts are in cells/mm^3

Five variables, namely gender, patient status, antiretroviral treatment failure, baseline WHO clinical stage and duration on ART, had considerable association (p<0.300) with IPT initiation in the patients enrolled on ART before 2011 (see Tables 4.2a and 4.2b). However, for the patients enrolled on ART after 2011, more variables namely, gender, age, district category and patient status had substantial influence (p<0.300) on IPT initiation. Other variables with sizable effect (p<0.300) on IPT initiation for the patients enrolled on ART after 2011 were adherence, baseline WHO clinical stage, duration on pre-ART and duration on ART.

Figures 4.2 and 4.3 depict the predictive effect of selected variables in Table 4.2 on IPT initiation, based on the Kaplan-Meier failure function of time to IPT initiation per predictor variable. Period of enrolment and district category displayed disproportionate distribution attributes contraindicated for the use of Cox's proportional hazards function, which justified the need for stratified analysis with period of enrolment as the strata variable to correct this anomaly.

Significant (p<0.2) categorical predictor variables that had distinct plots were: (1) gender; (2) marital status; (3) district; (4) geographic location; (5) period of enrolment into HIV care; (6) baseline WHO clinical stage; (7) adherence to ART; (8) patient status at exit time of the study; and (9) history of past TB infection on first visit. For continuous predictors, significant (p<0.2) predictors (in Table 4.2) that also had distinct plots (Figures 4.2 and 4.3) were: (1); age (2) baseline CD4 count; (3) median CD4 count; (4) median viral load; and (5) duration of pre-ART.

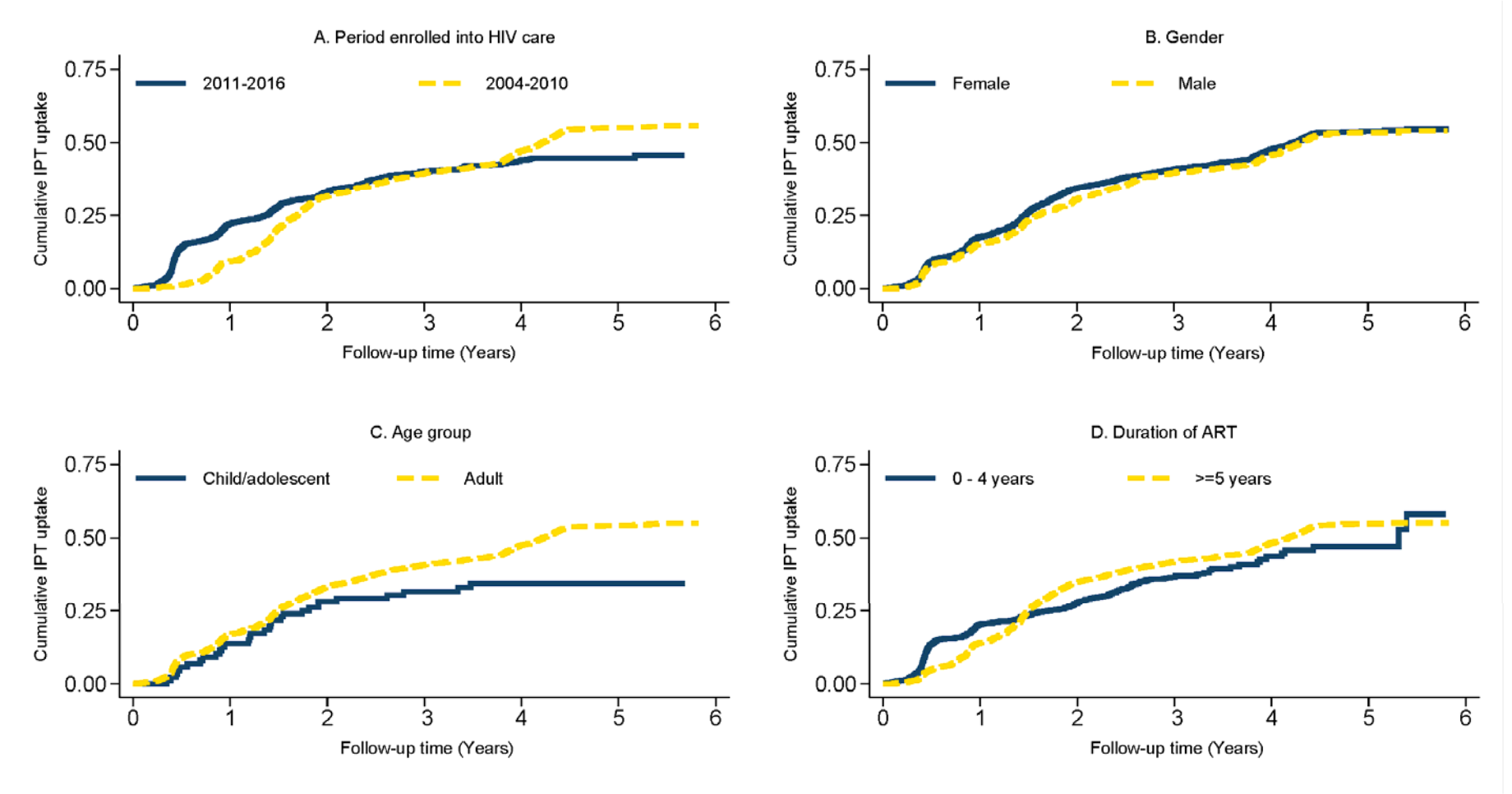

Figure 4.2 Kaplan-Meier function of time to IPT initiation by predictor variables (A-D)

Age group (C) and duration of ART (D) were important determinants of IPT initiation, while gender (B) was not. Note that period of enrolment was disproportionate, which justified the need for stratified analysis.

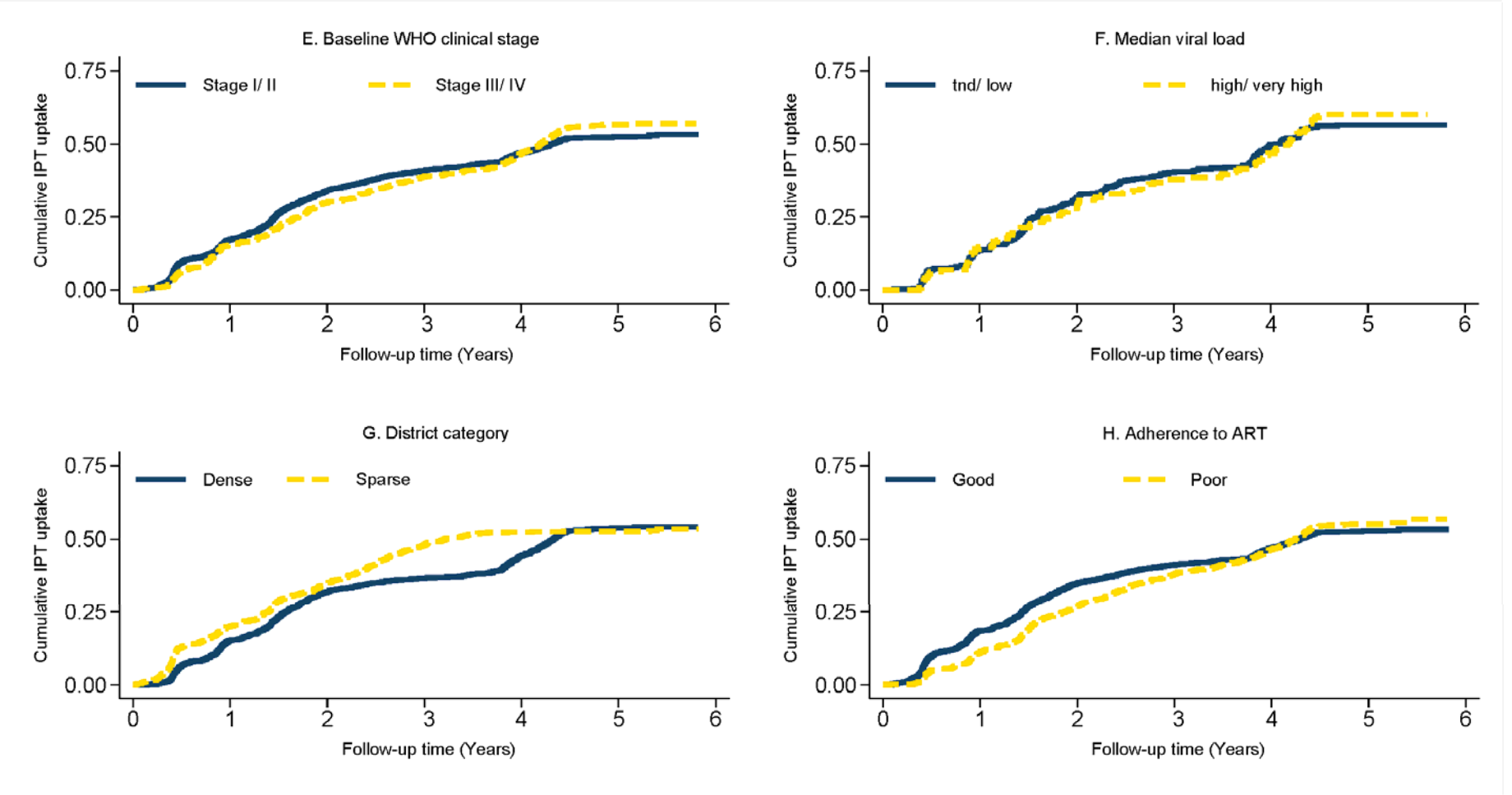

Figure 4.3 Kaplan-Meier function of time to IPT initiation by predictor variables (E-H)

Baseline WHO clinical stage (E), Median viral load (F), District category (G) and adherence (H) were all important predictors of IPT initiation; tnd=target not detected; viral load ranges in copies/mm^3 are as follows; tnd (0-50); low (50-500); high (500-10000); and very high (>10000).

4.3.3 Associations between patient characteristics and defaulting IPT

Table 4.3 presents the associations between patient characteristics and defaulting IPT. The gender, and district density categories were significantly (p<0.050) associated with defaulting IPT by Chi-square test. The baseline CD4 count was only marginally significant (t=7.6; p=0.056). However, in univariate logistic regression analysis (see Table 4.4), males [OR: 1.7; 95% CI: 1.2-2.4; p=0.006] and the sparsely populated district category [OR: 2.1; 95% CI: 1.5-3.0; p=0.000] had significantly higher odds of defaulting IPT compared to females and densely populated geographic location, respectively. In addition, baseline CD4 count category 351-500 cells/mm3 [OR: 2.1; 95% CI: 1.2-3.8; p=0.010] and baseline WHO clinical stage IV [OR: 2.4; 95% CI: 1.2-4.8; p=0.016] also had significantly higher odds of defaulting IPT, compared to baseline CD4 count category 1-100 cells/mm3 and baseline WHO clinical stage I. However, in multiple logistic regression analysis, the sparsely populated district category [adjusted OR: 1.6; 95% CI: 1.1-2.3; p=0.000] and gender [adjusted OR: 2.1; 95% CI: 1.5-3.0; p=0.006] were the most influential in determining defaulting of IPT. Baseline CD4 count category 351-500 cells/mm3 [OR: 2.2; 95% CI: 1.2-4.0; p=0.013] and baseline WHO clinical stage IV [OR: 2.5; 95% CI: 1.2-5.1; p=0.015] were also significant in multiple logistic regression analysis.

Table 4.3 Association between patient characteristics and IPT defaulting

Patient Characteristic & Subcategory		Total (*n*)	Defaulted IPT: No. Row% (*n*)	Defaulted IPT: Yes Row% (*n*)	Chi-square; *p*-value
Total		2,033	93.4 (1898)	6.6 (135)	
Age	0-9	21	100 (21)	0 (0)	4.1; 0.765
	9-18	22	90.9 (20)	9.1 (2)	
	18-25	179	94.4 (169)	5.6 (10)	
	25-35	691	93.8 (648)	6.2 (43)	
	35-45	598	92.6 (554)	7.4 (44)	
	45-55	338	92.3 (312)	7.7 (26)	
	55-65	151	94 (142)	6 (9)	
	65-84	33	97 (32)	3 (1)	
Gender					
	Female	1,394	94.4 (1316)	5.6 (78)	7.8; 0.005
	Male	639	91.1 (582)	8.9 (57)	
Geographic location					
	Dense	1,379	95 (1310)	5 (69)	18.5; 0.000
	Sparse	654	89.9 (588)	10.1 (66)	
Period enrolled into HIV care					
	2011-2016	1,141	93.2 (1063)	6.8 (78)	0.2; 0.689
	2004-2010	892	93.6 (835)	6.4 (57)	
Baseline WHO clinical stage					
	1	733	93.6 (686)	6.4 (47)	7.6; 0.056
	2	842	93.3 (786)	6.7 (56)	
	3	379	94.5 (358)	5.5 (21)	
	4	79	86.1 (68)	13.9 (11)	
BL CD4 count					
	1-100	415	94.2 (391)	5.8 (24)	13.1; 0.004
	101-350	1,233	94.3 (1163)	5.7 (70)	
	351-500	224	88.4 (198)	11.6 (26)	
	501-1512	161	90.7 (146)	9.3 (15)	

IPT=isoniazid preventive therapy; ART=antiretroviral therapy; BL=baseline; *n*=number of patients; WHO= World Health Organization; CD4 are in cells/mm^3.

Table 4.4 Logistic regression of predictors associated with IPT defaulting

Patient Characteristic		Defaulted IPT	Chi-square	Univariate		Multivariate	
Subcategory	Total (*n*)	Row% (*n*)	*p*-value	Unadjusted OR (95% CI)		Adjusted OR (95% CI)	*p*-value
Gender							
Female	1 394	5.6 (78)	7.8; 0.005	base (1)		base (1)	
Male	639	8.9 (57)		1.7 (1.2-2.4)	0.006	1,7 (1.5-3.0)	0.006
Geographic location							
Dense	1 379	5 (69)	18.5; 0.000	base (1)		base (1)	
Sparse	654	10.1 (66)		2.1 (1.5-3.0)	0.000	1.6 (1.1-2.3)	0.000
Period enrolled into HIV care							
2011-2016	1 141	6.8 (78)	0.2; 0.689	base (1)			
2004-2010	892	6.4 (57)		1.1 (0.8-1.5)	0.689	Excluded	-
Baseline WHO clinical stage							
1	733	6.4 (47)	7.6; 0.056	base (1)	base (1)		
2	842	6.7 (56)		1.0 (0.7-1.6)	0.848	1.3 (0.9-2.1)	0.174
3	379	5.5 (21)		0.9 (0.5-1.5)	0.566	1.1 (0.6-2.0)	0.688
4	79	13.9 (11)		2.4 (1.2-4.8)	0.016	2.5 (1.2-5.1)	0.015
BL CD4 count							
1-100	415	5.8 (24)	13.1; 0.004	base (1)	base (1)		
101-350	1 233	5.7 (70)		0.9 (0.6-1.6)	0.936	1.1 (0.6-1.7)	0.828
351-500	224	11.6 (26)		2.1 (1.2-3.8)	0.010	2.2 (1.2-4.0)	0.013
501-1512	161	9.3 (15)		1.7 (0.9-3.3)	0.133	2.0 (2.0-3.9)	0.060

IPT=isoniazid preventive therapy; *n*=number of patients; ART=antiretroviral therapy; BL=baseline; WHO= World Health Organization; CD4 counts are in cells/mm^3.

4.3.4 Modelling the rate of initiation of IPT

Out of ten variables considered for inclusion in the model, three predictors - district category, age group and duration on ART - emerged as significant (p<0.050) predictors (Table 4.5a and 4.5b). Two predictors, duration on ART and district category, had significant (p=0.000) interactions (shown as: Duration on ART # District category in Table 4.5b). Based on the likelihood-ratio test, the model with the interactions was superior to the one without interactions (t=19.7; p<0.001).

In the tests of proportional-hazards assumption using the Schoenfeld and scaled Schoenfeld residuals (phtest) test, one predictor, duration of ART, was not proportional. However, the variable was retained in the model after stratified analysis to correct for this anomaly.

Table 4.5a Cox's proportional hazards model for initiation of IPT by PLHIV in Lesotho

Predictor	Outcome		Unstratified model				Model stratified by period of enrolment	
			2004-2016				2004-2010	2011-2016
	Total (*n*)	Initiation rate per 100 PY	Unadjusted HR (95% CI)	*p*-value	Adjusted HR (95% CI)	*p*-value	Adjusted HR (95% CI)	Adjusted HR (95% CI)
Enrolment period								
2011-2016	1 745	27.0	1 (base)		1 (base)			
2004-2010	1 210	15.8	0.60 [0.54-0.68]	0.000	0.63 [0.55-0.72]	0.000		
Duration of pre-ART								
<1	2 127	20.7	1 (base)		1 (base)			
1-2	269	21.1	1.02 [0.86-1.20]	0.851	1.01 [0.85-1.20]	0.909		
3-5	344	19.2	1.06 [0.91-1.23]	0.491	0.99 [0.85-1.16]	0.905		
>5	215	21.6	0.96 [0.76-1.20]	0.706	0.84 [0.66-1.06]	0.137		
Baseline WHO stage								
I	1 049	24.4	1 (base)		1 (base)			
II	1 219	18.7	0.81 [0.72-0.91]	0.000	0.87 [0.77-0.98]	0.023		
III	516	19.6	0.83 [0.72-0.96]	0.011	0.92 [0.79-1.06]	0.255		
IV	171	19.1	0.88 [0.68-1.13]	0.333	0.92 [0.72-1.19]	0.538		
Adherence								
Good	2 219	21.7	1 (base)		1 (base)			
Poor	615	17.5	0.96 [0.85-1.07]	0.432	0.96 [0.85-1.07]	0.462		
District category								
Sparse	1 042	16.9	1 (base)		1 (base)		1 (base)	1 (base)
Dense	1 913	15.4	0.77 [0.69-0.86]	0.000	0.58 [0.42-0.78]	0.000	1.03 (0.46-2.30)	0.59 [0.38-0.94]
Duration on ART*								
0-4	1 454	16.0	1 (base)		1 (base)		1 (base)	
>=5	1 501	15.8	0.76 [0.67-0.86]	0.000	1.40 [1.16-1.70]	0.001	3.34 [2.06-5.43]	1.33 [1.00-1.76]

*Predictors insignificant when controlled for baseline WHO clinical stage, duration of ART, district category and adherence to ART; WHO=World Health Organization, ART= Antiretroviral therapy; *n*=number of patients; PLHIV=People living with HIV; # denotes interaction of terms.

Table 4.5b Cox's proportional hazards model for initiation of IPT by PLHIV in Lesotho (continued)

Predictor	Outcome		Unstratified model				Model stratified by period of enrolment	
			2004-2016				2004-2010	2011-2016
	Total (*n*)	Initiation rate per 100 PY	Unadjusted HR (95% CI)	*p*-value	Adjusted HR (95% CI)	*p*-value	Adjusted HR (95% CI)	Adjusted HR (95% CI)
Geographic location # Duration of ART					1 (base)		1 (base)	
Sparse	1 042	16.9			0.81 [0.83-0.95]	0.000	0.86 [0.77-0.96]	0.95 [0.85-1.06]
Dense	1 913	15.4			0.86 [0.79-0.89]	0.000	0.86 [0.81-0.90]	1.01 [0.89-1.14]
Gender*								
Female	1 942	16.1	1 (base)		1 (base)			
Male	1 013	15.4	0.97 [0.87-1.08]	0.568	0.97 [0.88-1.07]	0.579		
Age*								
Child/ Adolescent	107	9.7	1 (base)		1 (base)		1 (base)	1 (base)
Adult	2 848	16.1	1.63 [1.13-2.33]	0.008	1.71 [1.20-2.47]	0.003	1.64 [1.02-2.61]	1.78 [1.00-3.15]
Baseline CD4 count*								
1-100	639	15.9	1 (base)		1 (base)			
101-350	1 714	15.9	1.10 [0.98-1.25]	0.116	1.08 [0.95-1.22]	0.231		
351-500	357	17.3	1.25 [1.03-1.52]	0.024	1.11 [0.91-1.35]	0.316		
501-1572	245	14.6	1.07 [0.85-1.36]	0.553	1.02 [0.81-1.30]	0.841		
Patient status*								
Drop-out	265	14.6	1 (base)		1 (base)			
Dead	121	14.2	0.83 [0.54-129]	0.416	0.79 [0.51-1.22]	0.288		
Transfer out	76	15.1	1.19 [0.83-1.70]	0.355	1.16 [0.81-1.67]	0.417		
Art cont.	2 493	16.1	1.28 [1.06-1.55]	0.012	1.27 [1.05-1.55]	0.014		
Treatment failure*								
No	2 909	18.2	1 (base)		1 (base)			
Yes	46	15.9	0.74 [0.53-1.04]	0.083	0.79 [0.56-1.11]	0.176		

*Predictors insignificant when controlled for baseline WHO clinical stage, duration of ART, district category and adherence to ART; Patient status=patient status at study exit time; *n*=number of patients; PLHIV=People living with HIV; # denotes interaction of terms.

In the final model stratified by period of enrolment into HIV care (Table 4.5a and 4.5b), considering the patients enrolled on ART before 2011, the following findings were noted: (1) adults had 64% higher probability of receiving IPT (HR=1.64; 95% CI: 1.02-2.61) relative to children and adolescents; (2) The likelihood of receiving IPT did not statistically differ between patients in the densely populated districts (HR = 1.03; 95% CI: 0.46–2.30) and those in the sparsely populated regions; and (3) longer durations on ART were associated with higher chances of IPT uptake. For example, patients on ART for five or more years were three times more likely to receive IPT, compared to patients on ART for less than five years (HR=3.34; 95% CI: 2.06-5.43). However, comparing two subjects on ART for five or more years in the densely populated districts, and considering the interaction terms, having five or more years of ART was 20% more likely to receive IPT compared to patients on ART for less than five years.

Considering patients enrolled in the 2011-2016 period, notable trends were as follows (1) adults had 78% higher probability of receiving IPT (HR=1.78; 95% CI: 1.00-3.15) relative to children and adolescents; (2) patients in the densely populated districts had 59% lower likelihood of receiving IPT (HR=0.59; 95% CI: 0.38-0.94) compared to the sparsely populated districts; and (4) longer durations on ART were still associated with higher chances of IPT initiation. For instance, patients on ART for five or more years were 33% more likely to receive IPT, compared to patients on ART for less than five years (HR=1.33; 95% CI: 1.00-1.76). However, comparing two subjects on ART for five or more years in the densely populated districts, and taking into account the interaction terms, having five or more years of ART was 34% more likely to receive IPT, compared to patients on ART for less than five years.

These results may be summarised as follows: (1) children and adolescents in the 2004-2010 and the 2011-2016 cohorts had lower chances of receiving IPT; (2) while IPT

initiation did not differ much by district category in the 2004-2010 cohort, IPT initiation in the densely populated districts was much lower in the 2004-2010 cohort; and (3) longer durations on ART were associated with a higher chance of receiving IPT in the 2004-2010 and the 2011-2016 cohorts, with the effect of duration being more influential in the 2004-2010 cohort.

4.4 DISCUSSION

The study found a fairly high IPT uptake (68.8%), but generally a slow initiation rate of 20.6 per 100 person-years. The slow initiation, even among patients enrolled into HIV care after IPT was launched in the country, indicates a slow scale-up exercise for this programme considering the high TB burden in this setting, which is estimated at 852/100,000 in Lesotho (WHO 2015). The 20.6 per 100 person-years rate of IPT initiation in this study is comparable to the one reported in Brazil, where IPT initiation was 20.0 per 100 person-years (Dowdy *et al.* 2014).

One model of the impact of tuberculosis incidence on IPT effectiveness projects that IPT is more effective in high TB-burden countries, given an optimum initiation of the IPT intervention (Ragonnet, Trauer, McBryde, Houben, Denholm, Handel & Sumner 2017). This study highlights that the rate of IPT initiation is slow in Lesotho despite the high TB-burden status which places the country in the top three nations with annual incidences exceeding 700 cases/100,000 alongside South Africa and Swaziland (Ragonnet *et al.* 2017). Therefore, this study suggests that, while current scale-up efforts need to be appreciated, intensification of the scale-up efforts is needed.

The median time to IPT for the 2004-2010 cohort was almost twice as high as that of the 2011-2016 cohort, implying that the patients enrolled on ART after IPT was launched have a higher initiation rate in this setting. Possible explanations of this

finding as cited in the literature include resistance by patients enrolled on ART before IPT was launched. The challenge of reviewing the files for patients enrolled on ART before IPT was launched to identify those qualifying for IPT may be another contributing factor.

The fact that children and adolescents had a lower chance of IPT initiation compared to adults in both the 2004-2010 and 2011-2016 cohorts, emphasises the need for scale-up efforts for this patient group. Tadesse *et al.* (2016) and Triasih, Padmawati, Duke, Robertson, Sawyer and Graham (2016) in Ethiopia and Indonesia, respectively, note that children in resource-limited high TB-burden settings have a low initiation rate of IPT, despite the fact that a six-month course of IPT reduces the risk of childhood TB by the same margin of about 60% as adults. The same authors attribute the problem to poor access to HIV and TB diagnostic tools in these countries, particularly for early HIV detection. Lesotho therefore needs to scale up TB contact screening as recommended by the WHO (2015). Deficiencies for the identification of children in need of IPT have been noted by other authors, including in Brazil, Benin and Indonesia (Mendonca, Kritski & Sant'Anna 2015; Adjobimey, Masserey, Adjonou, Gbenagnon, Schwoebel, Anagonou & Zellweger 2016; Triasih *et al.* 2016). Triasih *et al.* (2016) observe that barriers to IPT initiation and adherence to this intervention among children in limited-resource settings also include healthcare worker and health facility-related factors, including social support and access.

IPT initiation in the densely populated districts was much lower in the 2004-2010 cohort, compared to the 2011-2016 cohort. Access to HIV/TB services, including IPT, in the densely populated districts have generally been slow due to a number of reasons, including resource limitations for scale-up efforts in these areas, which have an estimated 72% of the country's population (PEPFAR Lesotho 2016). The lower

initiation rates in the densely populated districts indicate that IPT initiation scale-up efforts, currently supported by PEPFAR Lesotho (2016), need to be intensified in these districts.

It is important to note that IPT initiation in this setting is expected to improve, following the adoption and implementation of the new HIV treatment guidelines for the intensified 'Test and Treat' programme of the WHO in Lesotho (WHO 2016). However, studies are required to assess the effect of the new guidelines on IPT initiation. Although Nachega, Uthman, Del Rio, Mugavero, Rees and Mills (2014) affirm the benefits of the 'Test and Treat' programme, the authors reiterate that this new programme can only improve IPT initiation if linkage to care, acceptability of HIV/TB services, retention and monitoring strategies are well taken care of.

Defaulting of IPT was associated with staying in the sparsely populated districts, being male, having baseline CD4 count category 351-500 cells/mm^3 and baseline WHO clinical stage IV. Patients in the sparsely populated districts, particularly those who are bed ridden and in WHO clinical stage IV, may be defaulting due to long distances from the hospitals and the mountainous terrain associated with these geographic locations. Upscaling healthcare delivery in these areas is therefore needed to reduce defaulting. In South Africa, Jacobson, Niccolai, Mtungwa, Moll and Shenoi (2017) report that inefficient health service delivery, ineffective communication with healthcare workers, and the financial burden of obtaining transport to clinics were among the most important determinants for defaulting IPT. These factors point to the need for interventions to address these challenges. Higher rates of defaulting among males emphasise the need for intensified patient education in this group. In Botswana, males also defaulted IPT more than females (Mokwena & Motsamai 2015).

A qualitative assessment of the factors contributing to low IPT initiation is required in this setting - particularly for assessing factors contributing to the low IPT initiation of healthcare workers. It is also important to note that barriers to IPT implementation in some areas have included healthcare workers themselves (Lester, Hamilton, Charalambous, Dwadwa, Chandler, Churchyard & Grant 2010). Lack of knowledge and experience, unawareness of the benefits of IPT, a lack of clarity about the IPT guidelines, and the belief that TB screening tools are inaccurate in HIV-infected people were the main barriers among the healthcare workers (Lester *et al.* 2010). Thus, there is a need to assess the effect of healthcare worker factors on the implementation of IPT.

It is important to note that in some African countries such as the Ivory Coast, the national guidelines had not recommended the use of IPT by 2014, citing that IPT could lead to resistant TB bacilli in patients with undiagnosed TB (Temprano ANRS 12136 Study Group 2015). This highlights the magnitude of the challenge of scaling up health interventions in developing countries.

This study is not without limitations, one of which is the lack of data on patient views. As Ostermann *et al.* (2017) note, interventions must factor in the preferences of the intended target populations to improve initiation and adherence to the intervention. Therefore, investigations on patient preferences and concerns about IPT are needed in Lesotho. However, the main strength of this study is the reporting of IPT initiation in person-years, which allows comparisons with other settings outside of Lesotho. This study also demonstrates that routine data in ART programmes of developing countries can be assembled into useful datasets for inferential modelling.

4.5 CONCLUSION

This study investigated the rate of IPT initiation since the IPT progamme was launched in 2011 in a high TB-burden setting of Lesotho. A fairly high overall coverage, but with a slow initiation rate, was observed. Clearly, Lesotho's efforts to implement the IPT programme is commendable considering its economic challenges. However, the slow initiation of IPT, particularly for children, patients leaving in sparsely populated districts and those enrolled before the intervention was launched, remains a concern given the scale of the TB burden the country faces. Furthermore, the slower initiation of IPT in the densely populated districts compared to the sparsely populated districts evokes debates on the need to further decentralise health service delivery. The high rates of defaulting IPT in the sparsely inhabited districts indicates the need for improving the monitoring of this programme. Clearly, the implementation of this health intervention in a high TB-burden setting of Lesotho needs further scale up.

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CHAPTER FIVE

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CHAPTER FIVE: THE EFFECT OF ISONIAZID PREVENTIVE THERAPY ON THE OCCURRENCE OF TUBERCULOSIS IN LESOTHO

ABSTRACT

Background: Little is known about the effectiveness of isoniazid preventive therapy (IPT) for the prevention of TB in people living with HIV (PLHIV) in high TB-burden settings. This study assessed the treatment effect of IPT and the risk conferred by patient characteristics, including time to IPT initiation relative to ART commencement on the occurrence of TB in the high TB-burden setting of Lesotho in southern Africa.

Methods: The study was based on Cox's proportional hazards regression analyses of 2 955 HIV-positive medical records randomly selected from eight health institutions in six districts of Lesotho. Factor selection into the model was based on univariate Kaplan-Meier survival functions, Wilcoxon's log-rank test, and Cox's regression analysis. Two patient cohorts, one enrolled into antiretroviral therapy (ART) before (2004-2010 cohort) and the other one after the launch of IPT (2011-2016 cohort), were included in the study.

Results: The overall TB incidence rate was 2.0 per 100 person-years in 12 208 person-years. Thirty-nine (15.9%, n = 246) patients developed TB after IPT. TB incidences per 100 person-years by timing of IPT were: (a) IPT before ART (1.7); (b) IPT after ART (1.8); (c) no IPT (2.6); (d) IPT within one year of ART commencement (1.3); and (e) IPT 3-5 years after ART initiation (2.3). IPT effectiveness rapidly deteriorated after four years in patients given IPT within one year of ART commencement. The most common side effects to IPT were skin rash (37.2%), peripheral neuropathy (25.4%) and liver toxicity (9.4%). Gender, baseline WHO clinical stage, district category and time to IPT relative to ART commencement emerged as significant predictors of TB occurrence. Increasing time to IPT by one six-month interval increased the risk of contracting TB by between 6% and 59%, depending on the cohort.

Conclusion: Delayed IPT after ART commencement significantly affects the effectiveness of this intervention. Patient characteristics associated with higher risk of contracting TB in this study are important for policy making. The need to consider booster doses of IPT cannot be overemphasised.

Keywords: Isoniazid preventive therapy; PLHIV; timing of IPT; tuberculosis

5.1 INTRODUCTION

5.1.1 Background

Tuberculosis (TB) is the most frequent life-threatening opportunistic disease in people living with human immunodeficiency virus (HIV) (WHO 2014). *Mycobacterium tuberculosis* poses a serious threat to HIV-positive people. The organism is known to reactivate and cause tuberculosis when the immune system is weakened by HIV virus (Gengenbacher & Kaufmann 2012). Of the 1.5 million people who died from the disease in 2013 alone, 360 000 were people living with HIV (WHO 2014). Lesotho is one of the countries that are worst affected by TB, having the second highest estimated TB incidence in the world (WHO 2014).

The effectiveness of the drug isoniazid, also known as isonicotinylhydrazine (INH), and recommended by the WHO in 2004 for the prevention of TB in people living with HIV (PLHIV), has been demonstrated to be effective in many TB high-burden settings, including but not limited to Ethiopia, Brazil, Botswana, Cambodia and South Africa (Dowdy, Golub, Saraceni, Moulton, Cavalcante, Cohn, Pacheco, Chaisson & Durovni 2014; Hanrahan, Martinson, Link-Barnes, Msandiwa, Chaisson & Golub 2015; Tedla, Nguyen, Sibanda, Nyirenda, Agizew, Girde, Rose & Samandari 2015; Van Griensven, Choun, Chim, Thai, Lorent & Lynen 2015; Ayele, Mourik & Bonten 2016). One key recommendation from these previous studies was that concurrent IPT and ART were more effective than the individual therapies (Rangaka, Wilkinson, Boulle, Glynn, Fielding, Van Cutsem, Wilkinson, Goliath, Mathee & Goemaere 2014).

The optimal timing of IPT relative to ART for optimal reduction of TB incidence in PLHIV has, however, remained unclear since the WHO 2010 policy guidelines on IPT were released (WHO 2011). Houben, Sumner, Grant and White (2014) note that more

evidence of optimal timing for IPT relative to ART is required in limited resource settings where IPT uptake is slow. More so, the effect of IPT when prescribed many years after ART commencement to individuals living in high TB-burden settings where chances of reinfection are high, also remains obscure.

Lesotho is a small independent country of about two million people, and is completely surrounded by the Republic of South Africa (GoL 2013). The United Nations (2009) notes that Lesotho is a poor country, with 40% of its population living below the official poverty line of US$1.25 per day. With a 23.5% adult HIV prevalence rate, Lesotho has the second highest prevalence rate of HIV worldwide (UNAIDS 2016). Furthermore, with an incidence rate of TB which is estimated at 852 per 100 000 population in the general population (WHO 2015), the country ranks third highest globally, after South Africa and Swaziland, with Swaziland topping the list (Ragonnet, Trauer, McBryde, Houben, Denholm, Handel & Sumner 2017). IPT was introduced to Lesotho in 2011, and delayed commencement of IPT relative to ART has continued since the programme was launched (GoL 2013).

Not much is known about the effectiveness of IPT and the risk factors for the occurrence of TB in the high TB-burden setting of Lesotho, given the slow initiation of IPT relative to ART commencement. The country's policy on IPT recommends that the drug be prescribed, subject to exclusion of TB symptoms, to all PLHIV - including children and adolescents (GoL 2013) - regardless of time of enrolment into HIV care. This study evaluated the associations between patient characteristics and the effectiveness of IPT while in HIV care. The main aim of the study was to establish the optimal timing of IPT initiation relative to ART commencement in the high TB-burden setting of Lesotho. In addition, this study also reports the common side effects of IPT in Lesotho.

5.2 METHODS

5.2.1 Study design

This longitudinal retrospective cohort study modelled the relative risk of developing TB conferred by patient characteristic in PLHIV in Lesotho, considering time to TB as the dependent variable, using Cox's proportional hazards regression function. The study is based on quasi-experimental quantitative analysis of ART records of PLHIV randomly sampled from the study population. The study assessed the effect of patient characteristics, including the duration of time between ART commencement and IPT uptake, on the occurrence of TB.

5.2.2 Study population

The target population for the study was HIV-positive people enrolled for HIV care between 2004 and 2016 in the eight district hospitals. The target population of PLHIV excluded patients with past TB, those on TB treatment at enrolment, and transfer-in patients with insufficient information. For purposes of analyzing the effect of the duration of ART on the occurrence of TB, patients were categorised into two groups, with the first group comprising patients enrolled on ART before IPT was launched in Lesotho in 2011 (2004-2010 cohort), and the second group consisting of the patients enrolled on ART from 2011 onwards (2011-2016 cohort). ART records of HIV-positive children, adolescents, adults, including geriatric patients and pregnant women, were selected using stratified systematic random sampling across eight health facilities to ensure proportional representation of all patient categories including gender, age and period of enrolment.

5.2.3 Sample size calculation

The minimum sample size was calculated following standard guidelines for studies estimating incidences of disease conditions with a preset relative precision (Lwanga &

Lemeshow 1991). The minimum number of patients' records, based on a minimum relative precision of 10% and a significance level of 5% (Lwanga & Lemeshow 1991) was 385 at each hospital, or 3 080 in the eight hospitals. However, more patient records were required to account for data attrition due to exclusion criteria and incomplete records. A sufficient buffer for this loss was estimated at 40%, implying that at least 4 620 patient files were required. In addition, the minimum sample size per hospital was proportionally adjusted for slight differences in the study populations at the hospitals, following rules for stratified systematic random sampling.

Data were collected from January 2016 to October 2016 from the paper-based registers for ART, IPT and TB. To improve the quality of data entry, a Microsoft Access database application tool was used to capture data from the files. Data were captured into the database tool in six-month discrete intervals.

5.2.4 Patient sampling and data collection

File selection was based on a sampling frame. The sampling frame was prepared from the ART attendance registers by drawing a list of all the patients enrolled into HIV care since 2004. The total number of files to be sampled per hospital was obtained by dividing the total number of patients enrolled in HIV care by the proportional target sample size for the hospital. For example, in a hospital with 2 000 patients enrolled and a target sample size of 350, one in six patients was systematically selected by sampling every 6^{th} patient from the patient register.

5.2.5 Final sample selection criteria

Overall, 4 122 patient files were collected. Of the 4 122 patients, 1 167 were excluded because they were transfer-in (118), past TB cases (337 were on TB treatment at enrolment or were diagnosed with TB within one month of enrolment (482), had less than six months of follow-up time, had died before the IPT programme was launched

(131), or had insufficient information (99) (see Figure 5.1). Therefore, the final sample size was 2 955.

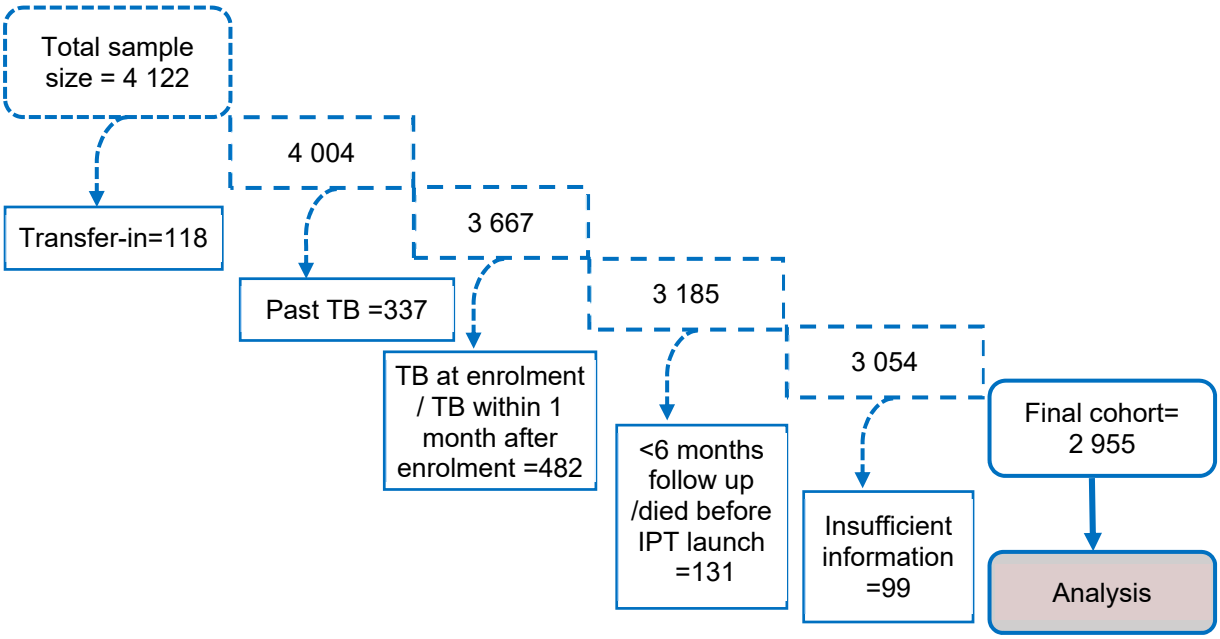

Figure 5.1 Exclusion criteria for the patients

Insufficient information referred to patient files with grossly missing data; past TB= having a diagnosis of TB before enrolment into HIV care; TB=tuberculosis.

5.2.6 Patient data and outcome measures

For purposes of evaluating the associations between patient characteristics and the occurrence of TB, duration of ART, time to TB (in years), demographic, baseline clinical data and ART, follow-up information were required. Thus, demographic information including gender, date of birth and marital status of the patients meeting the selection criteria were collected from the records. Their clinical data - including dates of HIV diagnosis; enrolment into HIV care; ART commencement and IPT initiation; baseline indicators including CD4 count, viral load, patient ART status, TB status, and WHO clinical stage; ART and IPT regimens; side effects to IPT and check-up information at each visit; adherence records; and laboratory monitoring data - were also extracted from the records. Time-variant variables, including age, were calculated according to the time at enrolment into HIV care. Poor adherence was defined as an overall score

below ≤75% of the doses prescribed, where 100% denoted perfect adherence. Patients late for their scheduled appointments by more than a month, and those who did not return for ART services, were classified as drop-outs.

Time to IPT relative to ART commencement was obtained by subtracting the date ART was first prescribed from the date IPT was first prescribed. Of note is the fact that a negative difference signified that IPT was given before ART, whilst a zero difference indicated that IPT and ART were prescribed simultaneously. Time to TB diagnosis was calculated by subtracting the date of enrolment into HIV care from the date the patient was diagnosed with TB. Patient treatment outcomes were assessed by median CD4 and viral load values. The duration of the period before ART commencement (in years), known as the Pre-ART period in this study, was calculated by subtracting the date of HIV diagnosis from the date of ART commencement.

5.2.7 Data preparation and verification

Data captured in the Microsoft Access (Microsoft, Richmond, USA) database were verified, and for further cleaning and analysis, data were exported to Stata version 13.1 (StataCorp, Texas, USA). Data were formatted for survival analysis as discrete-time data with interval date as the time variable, and the occurrence of TB event as the 'failure' outcome. For purposes of calculating Cox's proportional hazards ratios, entry time into the risk set was delayed by one month to correct for inconsistencies at first entry into the risk set. The date of enrolment into HIV care and the exit date marked the left and right censoring times, respectively.

5.2.8 Modelling patient characteristics associated with TB outcome

This analysis modelled the incidence of TB and identified patient characteristics associated with the occurrence of TB through the Cox's hazard regression function. The method was applied taking the hazard as a probability of a TB event in a specified

time for an individual with given characteristics. Breslow's correction for tied data was used to correct the assumption that survival times in the study were distinct (Kleinbaum & Klein 2005). Follow-up times were subdivided into six-month discrete intervals due to the inevitable observation gaps for the patients (Singer & Willett 2003).

To assess the patient characteristics associated with the occurrence of TB, descriptive statistics of the data were summarised by cross-tabulating the patient characteristics with the occurrence of TB outcome. Chi-square values indicated the magnitude of the significance of the differences. Patient characteristics were further analysed using cumulative probability distribution plots and univariate Kaplan-Meier curves to determine their suitability in the model. Further, Wilcoxon's log-rank test and Cox's regression analysis were used to determine equality across strata for categorical variables and continuous variables, respectively. Predictors with *p*-values <0.3 were included in the test model.

Nine predictors namely, gender, patient status, treatment failure, baseline CD4 count, time to IPT relative to ART, duration of pre-ART, baseline WHO clinical stage, geographic location, and duration on ART were selected into the test model and successively excluded using the stepwise method. The variable, period of enrolment, was selected *a priori* as a strata variable. Four variables, namely time to IPT relative to ART, gender, geographic location, and baseline WHO clinical stage remained in the model.

The model was tested for predictor interaction and resultantly, baseline WHO clinical stage was found to have a significant ($p<0.05$) interaction with time to IPT relative to ART. The model with and without the interaction variables was compared using the likelihood ratio (Lrtest), and the difference was found to be significant (Chi(3)=19.7 and $p=0.002$), implying that the bigger model with the interaction variables was superior to the one without. The analysis therefore proceeded with the interaction-inclusive model.

The model was checked for proportionality using the Schoenfeld and scaled Schoenfeld residuals (Phtest) test. One categorical variable, district category (p=0.045), significantly violated the proportionality assumption. To correct for this anomaly, stratified analysis with period of enrolment as the strata variable was adopted.

5.2.9 Ethical aspects and ethical clearance

Ethical approval was granted by the Institutional Review Board of the National University of Lesotho and the Ethics Committee of the Ministry of Health of Lesotho. Permission to collect data was also granted by the relevant hospital authorities. To protect patient privacy, computer-generated identification numbers were used instead of patient names. Patient data in the medical records were treated with confidentiality. Furthermore, all data are presented as overall anonymised summaries.

5.3 RESULTS

5.3.1 Associations between patient characteristics and the occurrence of TB

In total, 2 955 patients were included in the final analysis. The overall follow-up time ranged from 0.5 to 12 years [median=4.5; interquartile range (IQR): 2.5–6.5]. Table 5.1a –5.1d present the characteristics of the 2 955 patients considered in the final analysis, and their TB outcomes. Overall, 246 (8.3%) developed TB during follow up (Table 5.1a). More males developed TB compared to females (11.5% of the males versus 6.6% of the females; p<0.001). However, the rates of TB did not differ significantly (p=0.839) by age group and marital status (p=0.476).

The rates of TB significantly varied (p<0.001) by district. Maseru district (14.8%) had the highest TB rates, while Qacha's Nek (1.0%), a sparsely populated district, had the lowest rate (Table 5.1a). Overall, the densely populated districts, which constituted

64.7%, had significantly (p<0.001) higher rates of TB compared to the sparsely inhabited ones.

TB rates for the patients enrolled on ART before IPT was launched in Lesotho (2004-2011 period) (14.9%) were significantly higher (p<0.001) than those enrolled after 2011 (4.2%) (Table 5.1a). The most common entry point into HIV care was the outpatient department (77.7%) (Table 5.1b). Mother and child health (MCH) (9.1%), self-refer (7.9%), and the HIV testing and counselling centres within the hospital (4.0%) were the other notable entry points into HIV care. Rates of TB significantly (p= 0.012) varied by entry point into HIV care.

Tenofovir/lamivudine/efavirenz, with 58.6%, was the most common baseline ART regimen (Table 5.1b). At the time the study was terminated, 84.4% patients were still continuing ART; the remaining were drop-outs (9.0%), or they had died (4.1%) or being transferred out (2.6%) (Table 5.1b). The drop-outs category had the highest rate of TB (17.0%); the group continuing ART had the lowest rate (7.1%). Overall, the rates of TB significantly (p<0.000) varied by patient status at study exit time.

The majority (79.1%) of patients had a good rating of adherence to ART; those with poor adherence had insignificantly (t=2.8; p=0.061) higher rates of TB (10.2%) compared to those with good adherence (7.8%) (Table 5.1b).

Out of only 1.6% patients who had their ART baseline regimens changed due to treatment failure, 26.1% developed TB compared to those with no failure (8.0%) (Table 5.1b). Treatment failure was significantly (t=19.3; p<0.000) associated with the TB outcome.

Table 5.1a Associations between patient characteristics and the occurrence of TB in PLHIV in Lesotho

Patient characteristic	Total	Developed TB while in HIV care		
Sub-category		No	Yes	
	Column% (*n*)	Row% (Freq)	Row% (Freq)	Chi-square; *p*-value
Total	100 (2 955)	91.7 (2 709)	8.3 (246)	
Gender				
Female	65.7 (1 942)	93.4 (1 813)	6.6 (129)	21 (0.000)
Male	34.3 (1 013)	88.5 (896)	11.5 (117)	
Age				
0-9	1.8 (52)	88.5 (46)	11.5 (6)	2.3 (0.941)
9-18	1.3 (38)	92.1 (35)	7.9 (3)	
18-25	9.1 (269)	93.3 (251)	6.7 (18)	
25-35	34.8 (1 027)	91.5 (940)	8.5 (87)	
35-45	27.9 (824)	91.9 (757)	8.1 (67)	
45-55	16.1 (477)	91.4 (436)	8.6 (41)	
55-65	7.6 (224)	91.5 (205)	8.5 (19)	
65-84	1.5 (44)	88.6 (39)	11.4 (5)	
Marital status				
Married	59.3 (1 752)	91.4 (1 602)	8.6 (150)	5.5 (0.476)
Divorced	0.4 (11)	81.8 (9)	18.2 (2)	
Separated	6.5 (193)	93.3 (180)	6.7 (13)	
Widowed	15.5 (458)	93.4 (428)	6.6 (30)	
Cohabiting	0.2 (6)	83.3 (5)	16.7 (1)	
Single	14.9 (440)	90.9 (400)	9.1 (40)	
(-)	3.2 (95)	89.5 (85)	10.5 (10)	
District				
Berea	18.3 (540)	95.4 (515)	4.6 (25)	111 (0.000)
Maseru	38.7 (1 145)	85.2 (975)	14.8 (170)	
Mohale's Hoek	7.7 (228)	96.9 (221)	3.1 (7)	
Mokhotlong	11.4 (336)	95.2 (320)	4.8 (16)	
Qacha's Nek	10.2 (302)	99 (299)	1 (3)	
Thaba Tseka	13.7 (404)	93.8 (379)	6.2 (25)	
Geographic location				
Dense	64.7 (1 913)	89.4 (1711)	10.6 (202)	35.5 (0.000)
Sparse	35.3 (1 042)	95.8 (998)	4.2 (44)	
Period enrolled into HIV care				
2011-2016	59.1 (1 745)	96.2 (1 679)	3.8 (66)	115.2 (0.000)
2004-2010	40.9 (1 210)	85.1 (1 030)	14.9 (180)	

(-)=missing information; ART=antiretroviral therapy; IPT=isoniazid preventive therapy; *n*=number of patients; TB=tuberculosis; tnd=target not detected; WHO=World Health Organization.

Table 5.1b Associations between patient characteristics and the occurrence of TB in PLHIV in Lesotho (continued)

Patient characteristic	Total	Developed TB while in HIV care		
Sub-category		No	Yes	
	Column% (*n*)	Row% (Freq)	Row% (Freq)	Chi-square; *p*-value
Total	100 (2 955)	91.7 (2 709)	8.3 (246)	
Entry				
Adolescent clinic	0.4 (12)	100 (12)	0 (0)	15.8 (0.015)
HTC	4 (118)	91.5 (108)	8.5 (10)	
MCH	9.1 (268)	94 (252)	6 (16)	
OPD	77.7 (2 295)	91 (2 089)	9 (206)	
Self-refer	7.9 (232)	96.1 (223)	3.9 (9)	
Under-5 clinic	0.2 (6)	100 (6)	0 (0)	
Hospital ward	0.8 (24)	79.2 (19)	20.8 (5)	
Baseline regimen				
TDF+3TC+EFV	58.6 (1 732)	94.5 (1 636)	5.5 (96)	71.5 (0.000)
AZT+3TC+EFV	23.8 (704)	85.5 (602)	14.5 (102)	
AZT+3TC+NVP	5.9 (173)	97.1 (168)	2.9 (5)	
D4T+3TC+NVP	4.1 (120)	85 (102)	15 (18)	
D4T+3TC+EFV	2.8 (84)	86.9 (73)	13.1 (11)	
TDF+3TC+NVP	2.2 (65)	92.3 (60)	7.7 (5)	
ABC+3TC+NVP	1.1 (32)	84.4 (27)	15.6 (5)	
ABC+3TC+EFV	1 (29)	93.1 (27)	6.9 (2)	
ABC+3TC+kaletra	0.5 (16)	87.5 (14)	12.5 (2)	
Patient status				
Drop-outs	9 (265)	83 (220)	17 (45)	34.5 (0.000)
Dead	4.1 (121)	86.8 (105)	13.2 (16)	
Transfer out	2.6 (76)	90.8 (69)	9.2 (7)	
ART continuing	84.4 (2 493)	92.9 (2315)	7.1 (178)	
Adherence to ART				
Good	79.1 (2 336)	92.2 (2 153)	7.8 (183)	3.5 (0.061)
Poor	20.9 (619)	89.8 (556)	10.2 (63)	
Treatment failure				
No	98.4 (2 909)	92 (2 675)	8 (234)	19.3 (0.000)
Yes	1.6 (46)	73.9 (34)	26.1 (12)	
Duration of Pre-ART				
<1	72 (2 127)	91.5 (1 947)	8.5 (180)	6.1 (0.108)
01-Feb	9.1 (269)	89.2 (240)	10.8 (29)	
03-May	11.6 (344)	92.2 (317)	7.8 (27)	
>5	7.3 (215)	95.3 (205)	4.7 (10)	

ART=antiretroviral therapy; ABC=abacavir; AZT=zidovudine; 3TC=lamivudine; NVP=nevirapine; kaletra=lopinavir/ritonavir; EFV=efavirenz; TDF=tenofovir; BL=baseline; HBsAg=Hepatitis B surface antigen; HTC=HIV testing and counselling; IPT=isoniazid preventive therapy; MCH=mother and child health; OPD=outpatient department; *n*=number of patients; TB=tuberculosis

Table 5.1c Associations between patient characteristics and the occurrence of TB in PLHIV in Lesotho (continued)

Patient characteristic	Total	Developed TB while in HIV care		
Sub-category		No	Yes	
	Column% (*n*)	Row% (Freq)	Row% (Freq)	Chi-square; *p*-value
Total	100 (2 955)	91.7 (2 709)	8.3 (246)	
BL CD4 count				
1-100	21.6 (639)	87.8 (561)	12.2 (78)	19.7 (0.000)
101-350	58 (1714)	92.1 (1 579)	7.9 (135)	
351-500	12.1 (357)	95 (339)	5 (18)	
501-1512	8.3 (245)	93.9 (230)	6.1 (15)	
Median viral load				
Tnd	9.1 (268)	89.9 (241)	10.1 (27)	25.4 (0.000)
Low	1.3 (38)	89.5 (34)	10.5 (4)	
High	2.1 (61)	91.8 (56)	8.2 (5)	
Very high	2.8 (84)	77.4 (65)	22.6 (19)	
(-)	84.7 (2 504)	92.4 (2 313)	7.6 (191)	
BL WHO clinical stage				
I	35.5 (1 049)	96.9 (1 016)	3.1 (33)	145.7 (0.000)
II	41.3 (1219)	92.3 (1 125)	7.7 (94)	
III	17.5 (516)	79.1 (408)	20.9 (108)	
IV	5.8 (171)	93.6 (160)	6.4 (11)	
Oral thrush at BL				
No	89.4 (2 642)	92.3 (2 438)	7.7 (204)	11.9 (0.001)
Yes	10.6 (313)	86.6 (271)	13.4 (42)	
Hrpes zoster at BL				
No	93.6 (2 767)	91.9 (2 543)	8.1 (224)	3 (0.083)
Yes	6.4 (188)	88.3 (166)	11.7 (22)	
Cryptococcoccal meningitis at BL				
No	98.5 (2 910)	91.8 (2 671)	8.2 (239)	3.1 (0.077)
Yes	1.5 (45)	84.4 (38)	15.6 (7)	
HTN diagnosis				
No	96.3 (2 845)	91.7 (2 610)	8.3 (235)	0.4 (0.517)
Yes	3.7 (110)	90 (99)	10 (11)	
DM diagnosis				
No	99.5 (2 939)	91.7 (2 695)	8.3 (244)	0.4 (0.544)
Yes	0.5 (16)	87.5 (14)	12.5 (2)	
Abnormal LFTs				
No	66.9 (1 976)	93.4 (1 846)	6.6 (130)	23.8 (0.000)
Yes	33.1 (979)	88.2 (863)	11.8 (116)	

BL=baseline; HBsAg=Hepatitis B surface antigen; *n*=number of patients; TB=tuberculosis; CD4 counts are in cells/mm^3;

Table 5.1d Associations between patient characteristics and the occurrence of TB in PLHIV in Lesotho (continued)

Patient characteristic	Total	Developed TB while in HIV care		
Sub-category		No	Yes	
	Column% (*n*)	Row% (Freq)	Row% (Freq)	Chi-square; *p*-value
Total	100 (2 955)	91.7 (2 709)	8.3 (246)	
Abnormal serum creatinine (renal disease)				
No	70.2 (2 075)	93.6 (1 942)	6.4 (133)	33.5 (0.000)
Yes	29.8 (880)	87.2 (767)	12.8 (113)	
HBsAg positive				
No	99.5 (2 940)	91.6 (2 694)	8.4 (246)	1.4 (0.242)
Yes	0.5 (15)	100 (15)	0 (0)	
Anaemia at BL				
No	28.1 (831)	94.7 (787)	5.3 (44)	69.7 (0.000)
Yes	49.9 (1 474)	87.5 (1 290)	12.5 (184)	
(-)	22 (650)	97.2 (632)	2.8 (18)	
Number of IPT interventions received				
0	31 (917)	92 (844)	8 (73)	15.6 (0.001)
1	64.3 (1 900)	92.2 (1 751)	7.8 (149)	
2	4.5 (132)	82.6 (109)	17.4 (23)	
3	0.2 (6)	83.3 (5)	16.7 (1)	
Time to IPT from date of enrolment (years)				
<1	24.6 (727)	97 (705)	3 (22)	71.6 (0.000)
1-2	9.1 (268)	94.4 (253)	5.6 (15)	
3-5	21.8 (644)	89 (573)	11 (71)	
>5	12.9 (381)	83.2 (317)	16.8 (64)	
No IPT	31.6 (935)	92.1 (861)	7.9 (74)	
Number of TB sign events				
none	85.9 (2 539)	93.7 (2 379)	6.3 (160)	96.7 (0.000)
once	11.3 (334)	79.3 (265)	20.7 (69)	
>2	2.8 (82)	79.3 (65)	20.7 (17)	

(-)=missing information; ART=antiretroviral therapy; BL=baseline; HBsAg=Hepatitis B surface antigen; IPT=isoniazid preventive therapy; *n*=number of patients; TB=tuberculosis

Overall, the range of pre-ART period was 0-8 years (median=3 months; interquartile range (IQR): 0–1 year). The majority of the patients (72.0%) received ART within one year of testing positive for HIV, while the 11.6% had delayed ART commencement by 3-5 years (Table 5.1b). By proportion, 7.3% had delayed ART by more than 5 years. The rates of TB significantly (t=17.9; p<0.000) varied with the length of pre-ART time, with the highest rate (10.8%) of TB occurring in those exposed to ART within 1-2 years

of testing positive, and the lowest rate (7.8%) occurring in those who delayed ART by three to five years.

Overall, the baseline CD4 count ranged from 3 to 1512 cells/mm^3 (median=223; interquartile range (IQR): 115–330) (Table 5.1c). The most common (58.0%) range of baseline CD4 count was 100-350 cells/mm^3, followed by 1-100 cells/mm^3 with 21.6%. The 1-100 cells/mm^3 had the highest rate (12.2%) of TB. The overall median viral load ranged from below the detectable range (<50 copies/mm^3) to very high (>10,000 copies/mm^3) (Table 5.1c). Patients with a very high median viral load had the highest rate of TB, while those with the median viral load below the detectable range had the lowest rate (22.6%).

Baseline WHO clinical stage II (41.3%) was the most common baseline WHO stage. While baseline stage III had the highest rate of TB (20.9%), whilst the lowest rate was baseline stage I with only 3.1% developing TB while in HIV care (Table 5.1c). Oral thrush (10.6%), herpes zoster (6.4%) and cryptococcal meningitis (1.5%) were the most common opportunistic infections at baseline (Table 5.1c). By proportion, oral thrush at baseline (t=11.9; p=0.001); herpes zoster and cryptococcal meningitis were not significantly (p>0.050) associated with higher TB outcomes while in HIV care.

The majority (95.6%) of the patients had missing information about the diagnosis of chronic non-communicable diseases (NCDs), particularly hypertension and diabetes (Table 5.1c). Nearly half (49.9%) of the patients had anaemia at baseline (Table 5.1d). More than a third (33.1%) of patients were diagnosed with liver disease at least once during HIV care through liver function tests; a third (29.8%) were diagnosed with renal disease at some point during follow-up tests, while only 0.5% were diagnosed with hepatitis B viral infection (Table 5.1d). Of these conditions, having a diagnosis of anaemia, liver or renal disease was significantly (p<0.050) associated with the occurrence of TB. Hepatitis B viral infection was insignificantly (t=1.4; p=0.242)

associated with TB outcome. Defaulting IPT was insignificantly (t=2.5; *p*=0.282) associated with the development of TB.

Overall, time to IPT from date of enrolment ranged from four years before ART to eleven years after ART commencement (median=1.5; IQR: 0.5–3.6) (Table 5.1d). Almost a third (31.6%) of the patients had not received IPT at the exit time of the study; 24.6% received IPT within a year of enrolment. Patients who received IPT more than five years after enrolment had the higher rates of TB (16.8%); whilst only 3.0% patients who received IPT within a year of enrolment developed TB.

The occurrence of TB was insignificantly (t=96.7; *p*<0.001) associated with the number of times TB signs were detected in a patient during checkup visits (Table 5.1d). Only 6.3% of the patients who had no TB signs developed TB while in HIV care.

5.3.2 The effectiveness of TB screening criteria and IPT intervention outcomes

Out of the 246 patients who developed TB, 68 (27.6%) patients had TB signs that were ruled out in the previous visit (see Figure 5.2A). Of the 68 patients miss-diagnosed for TB, 17 (25.0%) were erroneously given IPT after TB had been ruled out incorrectly. Skin rash (37.2%) and peripheral neuropathy (25.4%) were the most common side effects associated with the use of IPT (Figure 5.2B & 5.2C). However, 9.4% had raised liver function tests results indicative of liver disease during the IPT course or within one month of completing the course.

Only 0.7% were stopped from taking IPT due to side effects (Figure 5.2D). In addition, only 6.6% defaulted IPT (Figure 5.2E). Out of the 246 patients who developed TB while in HIV care, 39 (15.9%) patients developed TB after receiving IPT, irrespective of the time the patient had developed TB (Figure 5.2F). Time from TB post exposure to IPT (Figure 5.3) ranged from 0 to 49 months (median=14; IQR: 6–30). Of the 39 patients

who developed TB after receiving IPT, 12.8% developed TB during the six-month course of IPT; whilst 25% developed TB one to six months after taking IPT.

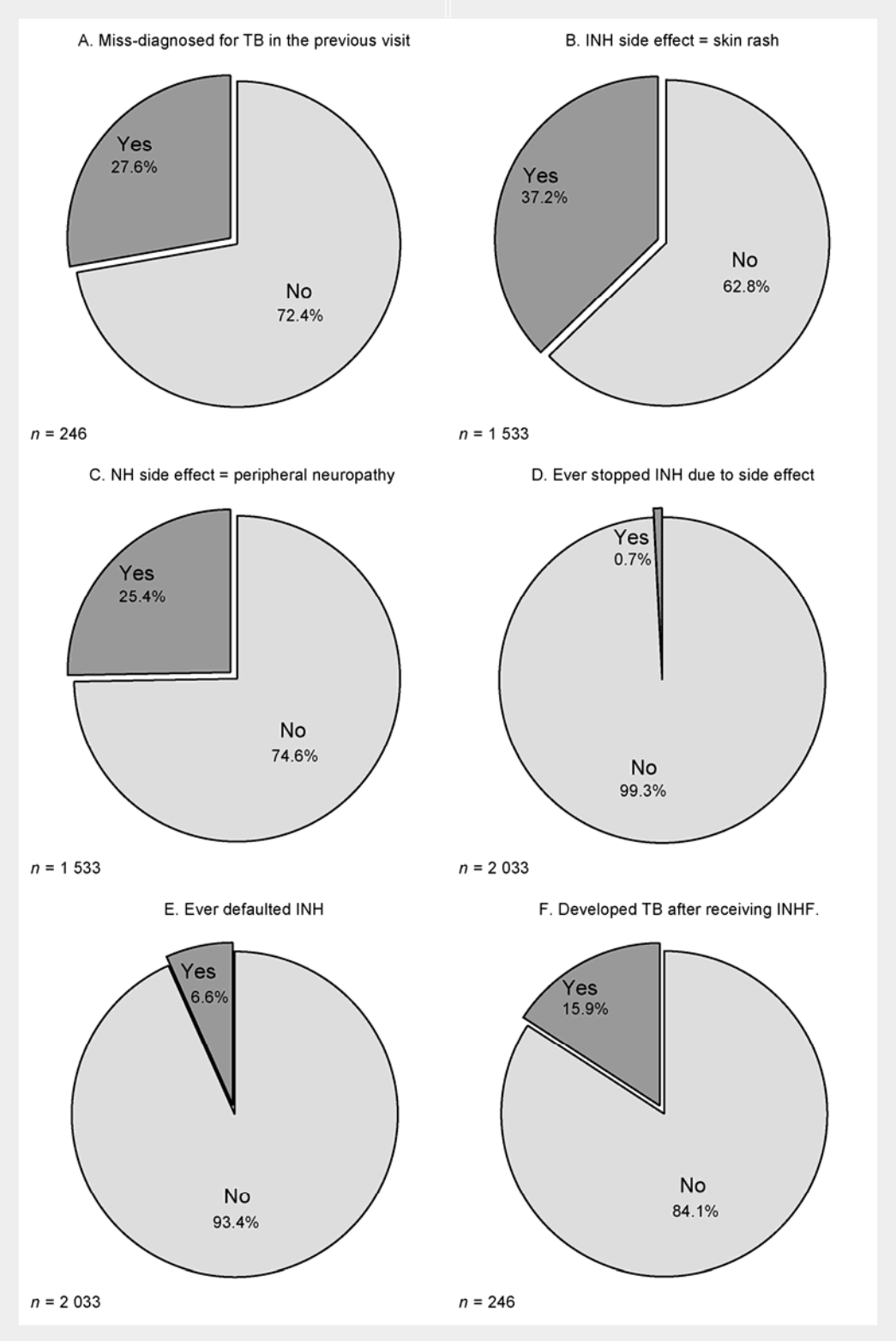

Figure 5.2 IPT treatment outcomes

Miss-diagnosed for TB in the previous visit=patient diagnosed of TB on the following visit after the previous visit erroneously ruled out TB based on the WHO TB screening tool; Developed TB after receiving IPT=patient developed TB during or after finishing the IPT course (irrespective of the time the TB developed); *n*=number of patients; INH=isonicotinylhydrazine (isoniazid); TB=tuberculosis.

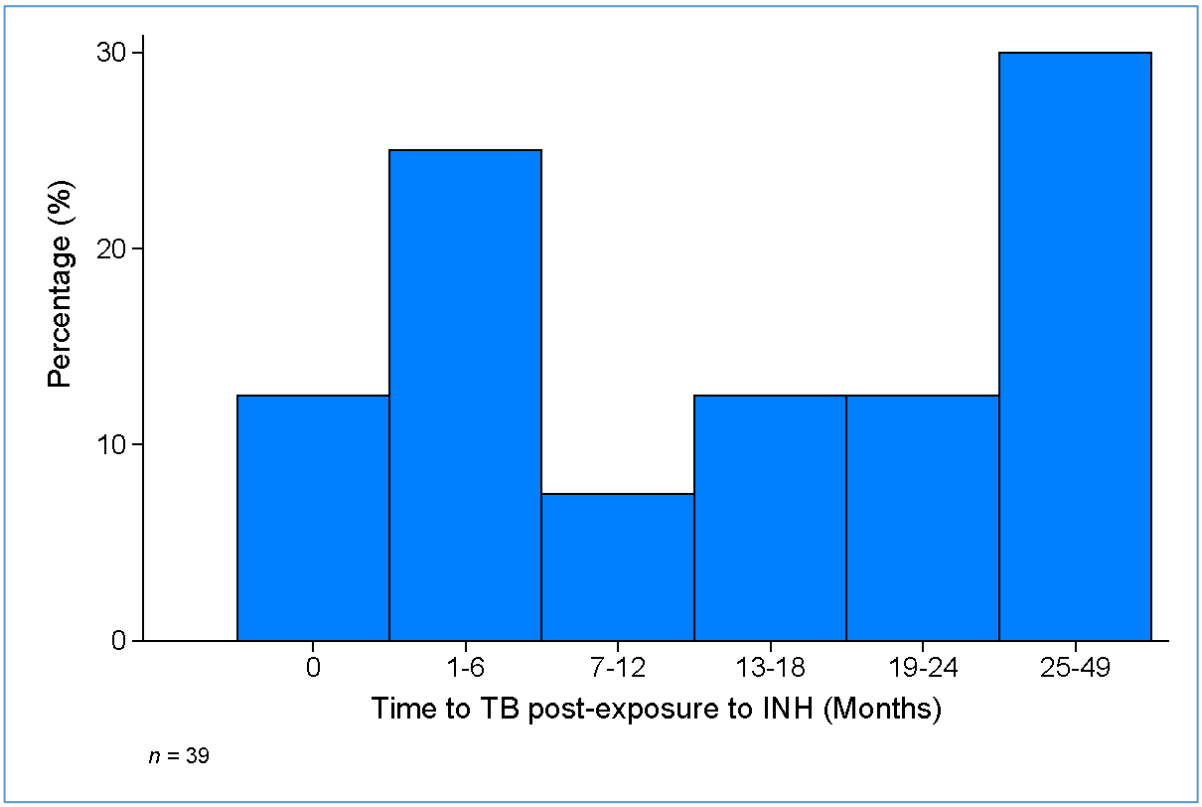

Figure 5.3 Time to TB during or after IPT

Developed TB at time zero means the patient developed TB during IPT; post exposure=after; INH=isonicotinylhydrazine (isoniazid); TB=tuberculosis; *n*=*n*umber of patients who developed TB after exposure to IPT.

5.3.3 The occurrence of TB by predictor variables

Table 5.2a – 5.2c present the occurrence of TB by predictor variables. The total number of incident TB cases was 246 (8.3%, *n* = 2 955) in 12,208 person-years (PY) of observation. Relapse TB cases occurred in 43 (17.5%) of the 246 patients who developed TB. Overall, the incidence rate was 2.0 per 100 PY of follow-up (Table 5.2a). Compared to the incidence rate of the patients who received IPT before ART (1.7 per 100 PY), patients who received IPT after starting ART had an incidence rate of 1.8 per 100 PY, while that of patients who received no IPT was 2.6 per 100 PY (Table 5.2b).

Table 5.2a Stratified model of the associations between predictors and the occurrence of TB in PLHIV in Lesotho

Predictor	Overall		Enrolment period 2004-2010					Enrolment period 2011-2016				
	% TB cases (*n*)	Incidence per 100 person-years	Total (*n*)	Incident TB Row% (n)	Person-years	TB incidence per 100 person-years	Chi-value (p-value)	Total (*n*)	Incident TB Row% (n)	Person-years	TB incidence per 100 person-years	Chi-value (*p*-value)
Total	8.3 (2 955)	2.0	1 210	14.9 (180)	7 985	2.3		1 745	3.8 (66)	4 223	1.6	
Age												
Children	11.5 (52)	2.4	31	19.4 (6)	189	3.2	2.3 (0.510)	21	0.0 (0)	61	0	1.4 (0.708)
Adolescent	5.5 (55)	2.2	12	16.7 (2)	61	3.3		43	2.3 (1)	74	1.3	
Adult	8.4 (2 703)	2.0	1 116	15.1 (168)	7 416	2.3		1 587	3.8 (60)	3 849	1.6	
Elderly	6.2 (145)	1.6	51	7.8 (4)	318	1.3		94	5.3 (5)	239	2.1	
Total	8.3 (2 955)	2.0	1 210	14.9 (180)	7 985	2.3		1745	3.8 (66)	4 223	1.6	
Gender												
Female	6.6 (1 942)	1.6	798	12.3 (98)	5 330	1.8	11.8 (0.001)	1 144	2.7 (31)	2 856	1.1	12.4 (0.000)
Male	11.5 (1 013)	2.9	412	19.9 (82)	2 656	3.1		601	5.8 (35)	1 367	2.6	
Total	8.3 (2 955)	2.0	1 210	14.9 (180)	7 985	2.3		1 745	3.8 (66)	4 223	1.6	
District population density												
Sparse	4.2 (1 042)	1.2	288	8.7 (25)	1 749	1.4	8.1 (0.005)	754	2.5 (19)	1 772	1.1	4.3 (0.039)
Dense	10.6 (1 913)	2.3	922	16.8 (155)	6 237	2.5		991	4.7 (47)	2 452	1.9	
Total	8.3 (2 955)	2.0	1 210	14.9 (180)	7 985	2.3		1 745	3.8 (66)	4 223	1.6	
Baseline CD4 count												
1-100	12.2 (639)	2.7	321	19.0 (61)	2 168	2.8	5.7 (0.160)	318	5.7 (18)	757	2.4	4.5 (0.290)
101-350	7.9 (1 714)	1.8	757	13.2 (100)	4 957	2.0		957	3.6 (34)	2 603	1.3	
351-500	5 (357)	1.8	81	12.3 (10)	531	1.9		276	2.9 (8)	477	1.7	
501-1572	6.1 (245)	2.1	51	17.6 (9)	329	2.7		194	3.1 (6)	387	1.5	
Total	8.3 (2 955)	2.0	1 210	14.8 (180)	7 985	2.3		1 745	3.8 (66)	4 223	1.6	

Incident TB cases are expressed as row percentages of row totals; ART=antiretroviral therapy; BL=baseline; IPT=isoniazid preventive therapy; TB=tuberculosis; WHO= World Health Organization; CD4 counts are in cells/mm^3; *n*=number of patients.

Table 5.2b Stratified model of the associations between predictors and the occurrence of TB in PLHIV in Lesotho (continued)

Predictor	Overall		Enrolment period 2004-2010					Enrolment period 2011-2016				
	% TB cases (*n*)	Incidence per 100 person-years	Total (*n*)	Incident TB Row% (n)	Person years	TB incidence per 100 person-years	Chi-value (p-value)	Total (*n*)	Incident TB Row% (n)	Person-years	TB incidence per 100 person-years	Chi-value (*p*-value)
Total	8.3 (2 955)	2.0	1 210	14.9 (180)	7 985	2.3		1 745	3.8 (66)	4 223	1.6	
Timing of IPT												
<ART	6 (83)	1.8	11	9.1 (1)	77	1.3	7 (0.219)	72	5.6 (4)	206	1.9	5 (0.415)
0-1>ART	3.6 (811)	1.3	47	12.8 (6)	299	2		764	3.0 (23)	1 861	1.2	
2-3>ART	8.6 (509)	1.7	262	10.7 (28)	1 608	1.7		247	6.5 (16)	961	1.7	
3-5>ART	15 (321)	2.3	287	15.3 (44)	1 956	2.3		34	11.8 (4)	156	2.6	
6-11>ART	16.1 (279)	2.0	278	16.2 (45)	2 239	2		1	0.0 (0)	6	0	
No IPT	7.9 (952)	2.6	325	17.2 (56)	1 806	3.1		627	3.0 (19)	1 034	1.8	
Total	8.3 (2 955)	2.0	1 210	14.9 (180)	7 985	2.3		1745	3.8 (66)	4 223	1.6	
BL WHO clinical stage												
I	3.1 (1 049)	1.0	246	7.3 (18)	1 578	1.1	46.7 (0.000)	803	1.9 (15)	1 813	0.8	40.1 (0.000)
II	7.7 (1 219)	1.6	609	11.7 (71)	4 061	1.8		610	3.8 (23)	1 664	1.4	
III	20.9 (516)	4.2	295	27.8 (82)	1 985	4.1		221	11.8 26)	577	4.5	
IV	6.4 (171)	2.1	60	15 (9)	362	2.5		111	1.8 (2)	169	1.2	
Total	8.3 (2 955)	2.0	1 210	14.9 (180)	7 985	2.3		1745	3.8 (66)	4 223	1.6	
Adherence to ART												
Good	7.8 (2 336)	2.1	843	15.5 (129)	5 502	2.3	0.6 (0.443)	1 493	3.6 (54)	3421	1.6	0.1 (0.737)
Poor	10.2 (619)	1.9	367	13.9 (51)	2 483	2.1		252	4.8 (12)	803	1.5	
Total	8.3 (2 955)	2.0	1 210	14.9 (180)	7 985	2.3		1 745	3.8 (66)	4 223	1.6	

Incident TB cases are expressed as row percentages of row totals; timing of IPT is in relation to ART commencement. ART=antiretroviral therapy; BL=baseline; IPT=isoniazid preventive therapy; TB=tuberculosis; WHO= World Health Organization; *n*=number of patients.

Table 5.2c Stratified model of the associations between predictors and the occurrence of TB in PLHIV in Lesotho (continued)

Predictor	Overall		Enrolment period 2004-2010					Enrolment period 2011-2016				
	% TB cases (*n*)	Incidence per 100 person-years	Total (*n*)	Incident TB Row% (n)	Person years	TB incidence per 100 person-years	Chi-value (p-value)	Total (*n*)	Incident TB Row% (n)	Person-years	TB incidence per 100 person-years	Chi-value (*p*-value)
Total	8.3 (2 955)	2.0	1 210	14.9 (180)	7 985	2.3		1 745	3.8 (66)	4 223	1.6	
Median viral load												
tnd	10.1 (268)	2.0	150	13.3 (20)	1 017	2	6.8 (0.080)	118	5.9 (7)	360	1.9	2.2 (0.537)
Low	10.5 (38)	2.1	22	9.1 (2)	149	1.3		16	12.5 (2)	42	4.7	
High	8.2 (61)	1.5	35	11.4 (4)	261	1.5		26	3.8 (1)	71	1.4	
Very high	22.6 (84)	3.6	54	29.6 (16)	443	3.6		30	10.0 (3)	82	3.7	
Total	12.2 (451)	2.2	261	16.1 (42)	1 870	2.3		190	6.8 (13)	556	2.3	
Duration on ART (years)												
0-2	2.2 (737)	2.7	59	11.9 (7)	83	8.4	6.6 (0.007)	678	1.3 (9)	514	1.8	2.0 (0.417)
3-4	6.7 (717)	2.2	63	28.6 (18)	306	5.9		654	4.6 (30)	1 830	1.1	
5-6	9.1 (701)	1.8	313	12.1 (38)	1 790	2.1		388	6.7 (26)	1 745	1.1	
>6	14.8 (800)	2.0	775	15.1 (117)	5 806	2.0		25	4.0 (1)	134	0.8	
Total	8.3 (2 955)	2.0	1 210	14.9 (180)	7 985	2.3		1 745	3.8 (66)	4 223	1.6	
Duration on pre-ART												
<1	8.5 (2 127)	2.0	892	14.1 (126)	5 786	2.1	2.7 (0.442)	1 235	4.4 (54)	3 049	1.8	4.1 (0.320)
1-2	10.8 (269)	2.4	121	20.7 (25)	816	3.0		148	2.7 (4)	377	1.1	
3-5	7.8 (344)	1.9	135	15.6 (21)	465	2.2		209	2.9 (6)	538	1.1	
>5	4.7 (215)	1.6	62	12.9 (8)	168	2.0		153	1.3 (2)	258	0.8	
Total	8.3 (2 955)	2.0	1 095	14.9 (180)	7 236	2.3		1 745	3.8 (66)	4 223	1.6	

Incident TB cases are expressed as row percentages of row totals; ART=antiretroviral therapy; TB=tuberculosis; viral load ranges in copies/mm^{3}are as follows; tnd (0-50); low (50-500); high (500-10 000); and very high (>10 000); *n*=number of patients.

The length of time to IPT relative to starting ART was an important variable. For example, compared to those who received IPT three to five years after starting ART, and who had a rate of 2.3 per 100 PY, those who received IPT within one year of starting ART had a rate of 1.3 per 100 PY. Incident rates of TB also varied from 1.2 to 2.6 by time to IPT from date of enrolment (Table 5.2b).

The category of patients who received timeous IPT intervention, particularly before ART and within one year of starting ART was higher in the group of patients who did not develop TB, compared to those who developed TB during follow up (Table 5.2b). Median viral load, duration on ART and duration on pre-ART were not significantly associated with TB outcome (Table 5.2c)

Figures 5.4 and 5.5 present the predictor effect of selected categorical predictor variables with significant (p<0.2) effect in Table 5.2a – 5.2c, based on the Kaplan-Meier survival plots of the cumulative occurrence of TB event over the follow-up time.

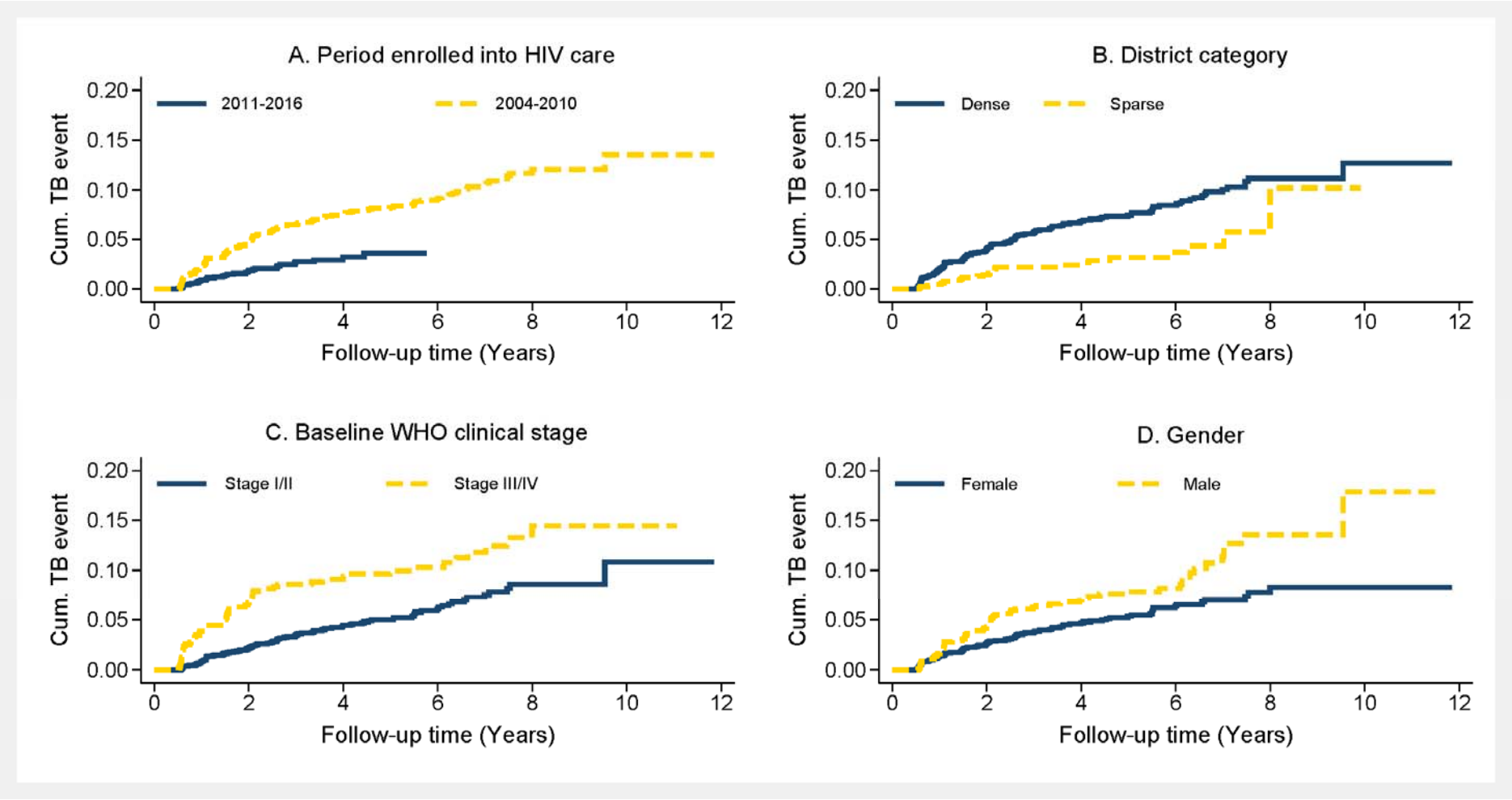

Figure 5.4 Cumulative occurrence of first TB event by predictor variable (A-D)

The predictors – period of enrolment, district category, baseline WHO clinical stage and gender had clear influence on the occurrence of TB. Note that the follow-up time for patients enrolled before 2011 was shorter than that of patients enrolled after 2011, which justified stratified analysis of the two cohorts; cum=cumulative.

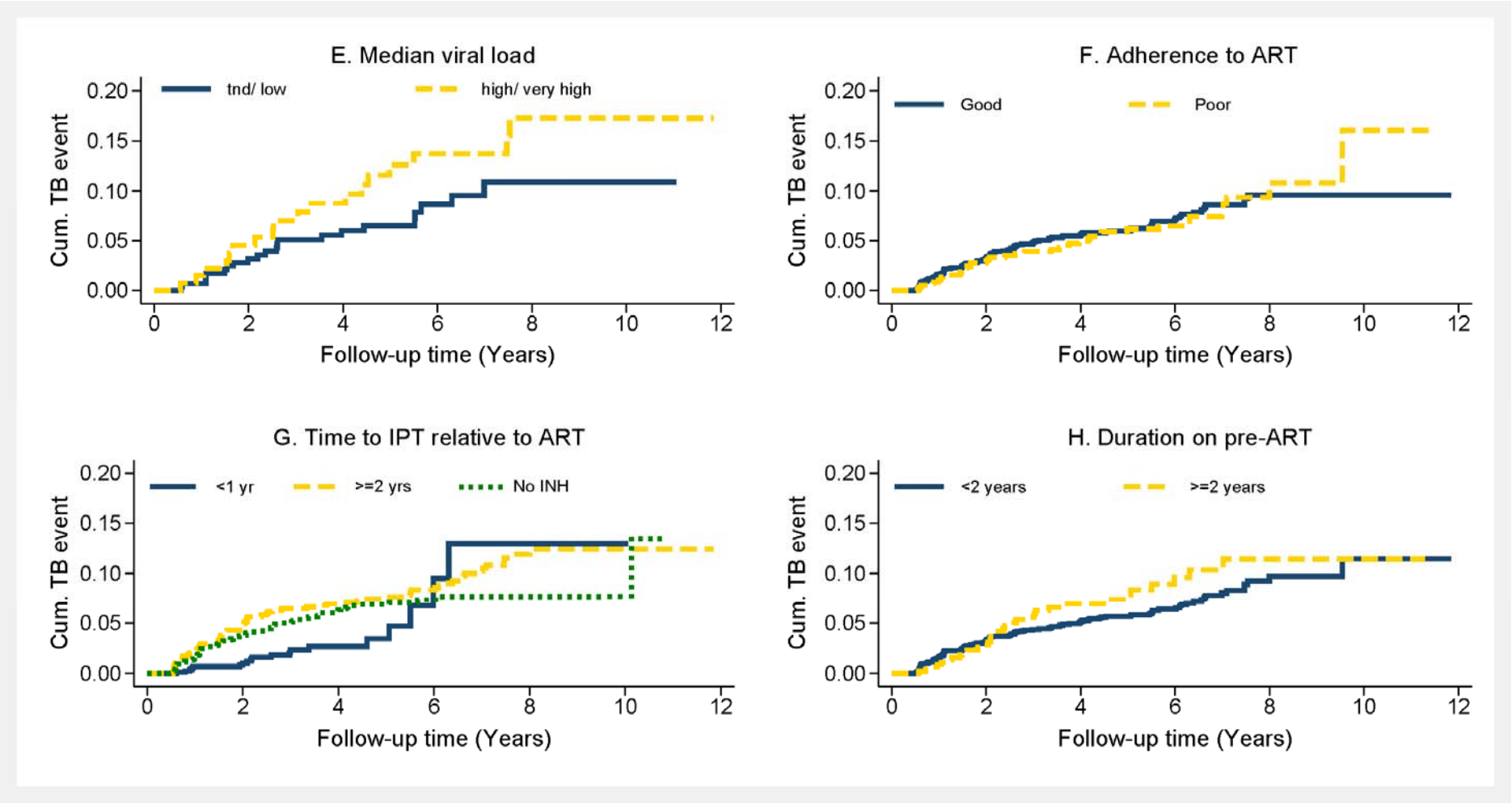

Figure 5.5 Cumulative occurrence of first TB event by predictor variable (E-H)

Median viral load (E), time to IPT relative to ART (G) and duration on pre-ART (H) were important predictors of TB outcome, while adherence to ART (F) was not a decisive factor. Note the beneficial effect of receiving IPT within one year of starting ART, and the loss of protection after four years (G); cum=cumulative; viral load ranges in copies/mm^3 are as follows; tnd (0-50); low (50-500); high (500-10 000); and very high (>10 000).

5.3.4 The effect of IPT on the occurrence of tuberculosis

Table 5.3a – 5.3c present Cox's proportional hazards model for the effect of isoniazid preventive therapy (IPT) on the occurrence of TB. Out of ten variables considered in the model, four predictors - time to IPT relative to ART, gender, district category and baseline WHO clinical stage - emerged as significant (p<0.050) predictors.

In the final model stratified by period of enrolment into HIV care (Table 5.3a), and considering the patients enrolled on ART before 2011 and prior to the launch of IPT in Lesotho, the following findings were noted: (1) patients in the densely populated districts had a higher relative risk (HR=1.42; 95% CI: 1.06-1.92) of developing TB compared to people living in the sparsely populated districts; (2) only baseline WHO clinical stages III and IV had a higher relative risk of developing TB compared to stage I [8.09; 95% CI (3.57-18.30) and 6.05; 95% CI (1.82-20.06), respectively]; (3) increasing time to IPT by one unit of time (equivalent to one-six month interval), and holding all other variables constant, increased the relative risk of developing TB by only 6% (HR=1.06; 95% CI: 0.88-1.25); and (4) males had a higher risk of developing TB compared to females (HR=1.64; 95% CI: 1.35-1.98).

Considering patients enrolled on ART after 2011, on the other hand (Table 5.3a), notable findings were: (1) similar to the 2004-2010 cohort with respect to geographic location, patients in the densely inhabited districts had a higher relative risk of developing TB (HR=1.11; 95% CI: 0.86-1.44); (2) similar to the 2004-2010 cohort, males had a higher relative risk of developing TB (HR=1.42; 95% CI: 1.14-1.77) compared to females; (3) slightly different to the 2004-2010 cohort, all higher baseline WHO clinical stages II-IV were associated with higher relative risks of developing TB compared to those in stage I. For example, patients in stage III had a relative risk 26 times (HR=26.01; 95% CI: 13.27-51.02) higher than those in stage I; (4) contrary to

findings with the 2004-2010 cohort, comparing two subjects in baseline WHO clinical stage I, and increasing the time to IPT relative to ART by one year, had an overall effect of increasing the occurrence of TB by 59% (HR=1.59; 95% CI: 1.01-2.50). However, comparing two subjects in baseline WHO clinical stage II, and considering the interaction terms, increasing time to IPT relative to ART by one unit (equivalent to one six-month interval) while holding all other variables constant, yielded an overall relative risk of 21% compared to stage I (Table 5.3b). Furthermore, increasing the time interval by a year raised the relative risk by 52%. Stage III had a 22% higher relative risk compared to stage I, while the relative risk of patients in stage IV was 24.2% compared to stage I (Table 5.3b). In a nutshell, increasing time to IPT relative to ART had a greater effect in the 2004-2010 cohort compared to the 2011-2016 cohort.

Table 5.3a Cox's proportional hazards model of the effect of IPT on the occurrence of TB in PLHIV in Lesotho

Predictor	Outcome		Unstratified model				Model stratified by period of enrolment	
			2004-2016				2004-2010	2011-2016
	Total (*n*)	TB incidence per 100 PY	Unadjusted HR (95% CI)	*p*-value	Adjusted HR (95% CI)	*p*-value	Adjusted HR (95% CI)	Adjusted HR (95% CI)
Enrolment period								
2011-2016	1 745	1.6	1 (base)		1 (base)			
2004-2010	1 210	2.3	2.37 (1.77-3.17)	36.5; 0.000	1.53 (0.98-2.41)	0.064		
Time to IPT/ART	2 955	2.0	1.18 (1.08-1.27)	15.5; 0.000	1.20 (1.07-1.36)	0.024	1.06 (0.88-1.25)	1.59 (1.01-2.50)
Baseline WHO stage								
I	1 049	0.9	1 (base)		1 (base)		1 (base)	1 (base)
II	1 219	1.6	1.95 (1.31-2.90)	0.007	2.62 (1.53-4.46)	0.000	1.82 (0.73-4.54)	3.61 (1.67-7.80)
III	516	4.2	5.17 (3.50-7.64)	0.000	17.12 (10.75-27.28)	0.000	8.09 (3.57-18.30)	26.01 (13.27-51.02)
IV	171	2.1	2.21 (1.12-4.38)	0.851	9.50 (4.98-18.13)	0.000	6.05 (1.82-20.06)	9.72 (3.75-25.21)
Gender								
Female	1 942	1.6	1 (base)		1 (base)		1 (base)	1 (base)
Male	1 013	2.9	1.84 (1.43-2.36)	0.004	1.54 (1.34-1.79)	0.000	1.64 (1.35-1.98)	1.42 (1.14-1.77)
District population density								
Sparse	1 042	1.2	1 (base)		1 (base)		1 (base)	1 (base)
Dense	1 913	2.3	2.06 (1.49-2.86)	0.000	1.25 (1.04-1.52)	0.021	1.42 (1.06-1.92)	1.11 (0.86-1.44)

*Predictor insignificant when controlled for gender, baseline WHO clinical stage, district category and time to IPT relative to ART; Hazard ratios for predictors remaining in the model after stepwise predictor selection process was calculated with period of enrolment as a strata variable; WHO=World Health Organization, time to IPT-ART =time to IPT relative to ART; ART= antiretroviral treatment; Patient status=patient status at study exit time; *n*=number of patients; PLHIV=people living with HIV.

Table 5.3b Cox's proportional hazards model of the effect of IPT on the occurrence of TB in PLHIV in Lesotho (continued)

Predictor	Outcome		Unstratified model				Model stratified by period of enrolment	
			2004-2016				2004-2010	2011-2016
	Total (*n*)	TB incidence per 100 PY	Unadjusted HR (95% CI)	*p*-value	Adjusted HR (95% CI)	*p*-value	Adjusted HR (95% CI)	Adjusted HR (95% CI)
BL. WHO stage # Time to IPT-ART								
I	1 049	0.9			1 (base)		1 (base)	1 (base)
II	1 219	1.6			0.87 (0.76-1.00)	0.058	0.93 (0.76-1.14)	0.62 (0.35-1.09)
III	516	4.2			0.77 (0.68-0.88)	0.000	0.88 (0.73-1.058)	0.63 (0.39-1.00)
IV	171	2.1			0.80 (0.67-0.94)	0.009	0.86 (0.66-1.11)	0.86 (0.46-1.59)
Age*								
Children	52	2.4	1 (base)		1 (base)			
Adolescents	55	2.2	0.70 (0.18-2.91)	0.349	1.04 (0.09-11.50)	0.976		
Adult	2 703	2.0	0.79 (0.35-1.77)	0.296	1.17 (0.29-4.74)	0.828		
Elderly	145	1.6	0.60 (0.21-1.69)	0.350	0.77 (0.15-4.00)	0.758		
Baseline CD4 count*								
1-100	639	2.7	1 (base)		1 (base)			
101-350	1 714	1.8	0.62 (0.47-0.83)	0.307	0.79 (0.56-1.11)	0.179		
351-500	357	1.8	0.55 (0.32-0.93)	0.997	1.05 (0.57-1.95)	0.875		
501-1572	245	2.1	0.63 (0.37-1.10)	0.951	1.14 (0.59-2.22)	0.169		
Patient status*								
Drop-outs	265	4.1	1 (base)		1 (base)			
Dead	121	5.5	1.23 (0.70-2.19)	0.799	1.34 (0.46-3.92)	0.594		
Transfer out	76	2.1	0.52 (0.23-1.15)	0.136	0.68 (0.26-1.79)	0.437		
Art cont.	2 493	1.7	0.42 (0.30-0.58)	0.000	0.52 (0.34-0.81)	0.004		

*Predictor insignificant when controlled for gender, baseline WHO clinical stage, district category and time to IPT relative to ART; Hazard ratios for predictors remaining in the model after stepwise predictor selection process were calculated with period of enrolment as a strata variable; time to IPT-ART =time to IPT relative to ART; ART= antiretroviral treatment; Patient status=patient status at study exit time; *n*=number of patients; PLHIV=people living with HIV.

Table 5.3c Cox's proportional hazards model of the effect of IPT on the occurrence of TB in PLHIV in Lesotho (continued)

Predictor	Outcome		Unstratified model				Model stratified by period of enrolment	
			2004-2016				2004-2010	2011-2016
	Total (*n*)	TB incidence per 100 PY	Unadjusted HR (95% CI)	*p*-value	Adjusted HR (95% CI)	*p*-value	Adjusted HR (95% CI)	Adjusted HR (95% CI)
Treatment failure*								
No	2 909	2.0	1 (base)		1 (base)			
Yes	46	3.4	2.24 (1.25-4.03)	0.000	1.54 (0.79-3.00)	0.209		
Duration on ART (years)*								
0-2	737	2.6	1 (base)		1 (base)			
3-4	717	2.2	1.28 (0.72-2.27)	0.823	2.71 (0.82-9.02)	0.103		
5-6	701	1.8	1.45 (0.83-2.53)	0.891	3.04 (0.92-10.03)	0.068		
>6	800	2.0	1.90 (1.11-3.27)	0.652	3.28 (0.963-11.16)	0.058		
Duration on pre-ART*								
<1	2 127	2.0	1 (base)		1 (base)			
1-2	269	2.4	1.22 (0.82-1.80)	0.011	1.34 (0.84-2.16)	0.223		
3-5	344	1.9	0.66 (0.36-1.21)	0.134	1.02 (0.47-2.21)	0.958		
>5	215	1.6	0.74 (0.31-1.81)	0.361	2.61 (0.93-7.39)	0.070		
Timing of IPT/ART*								
<ART	83	1.8	1 (base)		1 (base)			
0-1>ART	811	1.3	0.71 (0.27-1.82)	0.271	0.57 (0.22-1.48)	0.047		
2-3>ART	509	1.7	1.20 (0.48-3.04)	0.296	0.94 (0.37-2.37)	0.092		
3-5>ART	321	2.3	1.82 (0.72-4.57)	0.205	1.29 (0.51-3.28)	0.552		
6-11>ART	279	2.0	1.76 (0.69-4.44)	0.235	1.18 (0.46-3.02)	0.022		
No IPT	952	2.6	1.62 (0.66-4.03)	0.292	1.20 (0.48-2.98)	0.038		

*Predictor insignificant when controlled for gender, baseline WHO clinical stage, district category and time to IPT relative to ART; Hazard ratios for predictors remaining in the model after stepwise predictor selection process was calculated with period of enrolment as a strata variable; WHO=World Health Organization, time to IPT-ART =time to IPT relative to ART; ART= antiretroviral treatment; *n*=number of patients; PLHIV=people living with HIV.

5.4 DISCUSSION

The main purpose of this study was to model the effect of patient characteristics, including the timing of IPT in relation to ART, on the occurrence of TB. Four predictors in this study influenced the occurrence of TB when adjusted for the period of enrolment into HIV care. Patients with delayed IPT after starting ART; higher baseline WHO clinical stages; living in densely populated districts; and being male were all associated with higher risks of developing TB while in HIV care. With respect to the timing of IPT, the model revealed that increasing time to IPT relative to ART increased the risk of contracting TB. These findings point to the need for timely IPT intervention relative to ART; timely initiation of ART when patients still have better immunity; intensified TB interventions in the densely populated districts; and closer monitoring of males.

Studies that have modelled the effect of time to IPT relative to ART are scarce. Notably, one study by Yirdaw, Jerene, Gashu, Edginton, Kumar, Letamo, Feleke, Teklu, Zewdu and Weiss (2014), which had similar findings to this study, categorised the timing of IPT relative to ART as 'IPT-before-ART'; 'IPT-and-ART started simultaneously'; and 'IPT-after-ART'; but did not model the timing of IPT relative to ART as a continuous variable. In the study by Yirdaw *et al*. (2014), receiving IPT after starting ART had limited impact on TB incidence compared to 'IPT-before-ART' and simultaneous commencement of IPT and ART.

Giving IPT within six months of starting ART reduced the occurrence of TB by 59% in this study. Although this finding is comparable to previous studies, the main difference is that previous studies evaluated the effect of IPT as a categorical variable. For example, studies on the effect of combined IPT and ART reveal that concurrent IPT and ART reduces the risk of contracting TB by between 37% (HR = 0.63, 95 % CI 0.41-

0.94) and 60 % (HR = 0.40; 95 % CI 0.18 - 0.87), in comparison to ART without IPT (Rangaka *et al.* 2014; Ayele, Van Mourik & Bonten 2015a). However, the results of this study indicate that timing of IPT is critical to its effectiveness. Although, Golub, Cohn, Saraceni, Cavalcante, Pacheco, Moulton, Durovni and Chaisson (2015) note that the six-month IPT course reduces the risk of contracting TB for at least seven years, the findings of this study suggest that the effectiveness of IPT in Lesotho starts to decline after two years, and rapidly deteriorates after four years, which indicates the need for booster doses.

Many studies also report the impact of IPT as a categorical variable. Yirdaw *et al.* (2014) report that, in Ethiopia, starting IPT before ART, or simultaneously with ART, reduced the risk of contracting TB by 82% (HR=0.18, 95% CI=0.08–0.42) and 80% (HR=0.20, 95% CI=0.10–0.42) respectively. In Brazil, receiving both ART and IPT reduced the risk of contracting TB by 76% (HR=0.24; 95% CI=0.11–0.53) (Golub, Saraceni, Cavalcante, Pacheco, Moulton, King, Efron, Moore, Chaisson & Durovni 2007). Semu, Fenta, Medhin and Assefa (2017) report that the TB incidence rate in Ethiopia was significantly lower in the IPT-treated group (0.21 per 100 person-years), compared to the untreated 7.18/100 per 100 person-years.

Of note is the fact that IPT had higher benefits in the patients enrolled on ART after IPT was launched in this study. For patients enrolled on ART before IPT was launched, cutting the time to IPT relative to ART by six months reduced TB by only 6%; while in the patients enrolled on ART after IPT was launched, TB occurrence was reduced by 59%. Although this difference may be due to the high TB rates in the first few months of ART, this result suggests that IPT may have a limited impact on patients enrolled into ART for many years.

Higher baseline clinical stages increased the risk of contracting TB. Patients in stage III had a relative risk 26 times (HR=26.01; 95% CI: 13.27-51.02) higher than those in stage I. Late testing for HIV and poor linkage to HIV care have been cited as main contributors to higher WHO stages at ART enrolment (Van Rooyen, Barnabas, Baeten, Phakathi, Joseph, Krows, Hong, Murnane, Hughes & Celum 2013). The high proportion of patients in WHO baseline stage III (1%), and the occurrence of TB within a few months of enrolment into HIV care indicate the extent of the problem of late HIV testing. This finding may explain why OPD was the main (77.7%) entry point into HIV care. Most of the patients may have entered into HIV care due to some ailment related to HIV infection. In addition, higher WHO baseline stages may also explain why a considerable proportion of patients had herpes zoster (6.4%) and oral thrush (10.6%) at baseline.

Males had a higher risk of developing TB relative to females in the cohort enrolled on ART after IPT was launched (HR=1.42; 95% CI: 1.1-1.77), and in the cohort enrolled into HIV care before 2011 (1.64; 95% CI: 1.35-1.98), compared to females. This implies that males continue to have a higher risk of developing TB since 2004. In Ethiopia, Yirdaw *et al.* (2014) report similar findings with respect to males (HR=1.42; 95% CI: 1.13–1.79). The higher rates of TB in males emphasise the need for targeted interventions, including scaling up IPT uptake in this patient group.

A significant improvement in the relative risk of contracting TB occurrence in densely populated districts was found between the 2004-2010 (HR=1.42; 95% CI: 1.06-1.92) and the 2011-2016 cohorts (HR=1.11; 95% CI: 0.86-1.44). In one report based on data collected between 2013 and 2014, PEPFAR Lesotho (2016) highlights that densely populated districts in Lesotho had the highest overall TB notification rates compared to sparsely populated districts in the general population (81% versus 19%). Thus, the

results of this study may signify the need to intensify scale up of HIV/TB activities in the densely populated districts.

A considerable proportion (15.9%; *n*=246) of the patients who developed TB after receiving IPT had the TB occurrence during the IPT course (12.8%), while 13% developed TB one to six months after taking IPT. Underlying TB, or lack of adherence to IPT, explains this occurrence of TB during or soon after IPT (Mesfin, Deribew, Yami, Solomon, Van Geertruyden & Colebunders 2012; Ayele, Van Mourik, Debray & Bonten 2015b). However, these figures are relatively higher than those reported in literature. Griensven, Choun, Chim, Thai, Lorent and Lynen (2015) report that 3% developed TB while on IPT. The results of this study imply that, without the tuberculin skin test (TST) and efficient screening for underlying TB in high TB-burden countries, a considerable proportion of patients may receive IPT when it is contraindicated. Ayele *et al.* (2015b) note that the TST has benefits in countries with a high burden of TB. The fact that 27.6% patients who developed TB had TB signs that were ruled out in the previous visit, and that 25.0% of those ruled out of TB were erroneously given IPT, emphasises the need to improve TB screening.

Skin rash (37.2%), peripheral neuropathy (25.4%) and liver impairment (9.4%) were the most common side effects associated with the use of IPT. The proportion (9.4%) with impaired liver function tests in this study is lower than those reported in other studies. Griensven *et al.* (2015) report a higher proportion of 22%. The results of this study may have been affected by underreporting of liver toxicity possibly due to challenges with laboratory monitoring of liver function tests. Hayashi, Fontana, Chalasani, Stolz, Talwalkar, Navarro, Lee, Davern, Kleiner, Gu, Hoofnagle and Injury (2015) highlight that underreporting of liver toxicity is common in settings prescribing IPT, and that IPT is one of the leading causes of drug-induced liver injury. The fact that

only 0.7% were stopped from taking IPT due to side effects suggests that further research, particularly related to the side effects associated with discontinuation of IPT, are needed. The 15.9% occurrence of TB after taking IPT emphasises the need for further interventions to mitigate the occurrence of TB during HIV care.

A limitation of this study was the inability to assess the duration of HIV infection. This variable has remained elusive in studies evaluating the effectiveness of IPT, including the study by Ayele *et al.* (2015a). In addition, the effect of time to IPT relative to ART in this study was confounded by baseline WHO clinical stage - more especially in the patients enrolled on ART after IPT was launched. More studies that include stratified analysis are therefore needed for further assessment of the effect of time to IPT relative to ART.

The main strength of this study is that it presents data on IPT's effectiveness from a high TB-burden setting with a fairly high follow-up time. The modelling of IPT's effectiveness as a continuous variable is another important contribution to the current literature on this intervention. This study also demonstrates the usefulness of routine ART data in developing countries in the evaluation of the effectiveness of IPT.

5.5 CONCLUSION

This study investigated the effect of longer durations between commencing ART and IPT and other important predictors of TB occurrence in a setting characterised by slow implementation of the IPT intervention, mostly given as a once-off six-month course. Better outcomes of IPT with respect to its effectiveness in mitigating TB incidence in high TB-burden settings are realised when IPT is given in the early stages of ART commencement. Clearly, the IPT intervention is having a limited effect in high TB-burden settings such as Lesotho, with longer durations between ART and IPT

commencement being the biggest challenge. Besides the timing of IPT, population density and gender are important predictors of TB occurrence in Lesotho during and after IPT. More efforts are therefore needed to address these risk factors in the country.

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CHAPTER SIX

This chapter has been partially published as a journal article:

Mugomeri, E., Olivier D. & van den Heever-Kriek. Health system challenges affecting the implementation of isoniazid preventive therapy in people living with HIV in Lesotho. *HIV & AIDS Review*; 17 (4): 299-307.

CHAPTER SIX: HEALTH SYSTEM CHALLENGES AFFECTING THE IMPLEMENTATION OF ISONIAZID PREVENTIVE THERAPY IN PEOPLE LIVING WITH HIV IN LESOTHO

ABSTRACT

Background: The six-month course of isoniazid preventive therapy (IPT) has been demonstrated to be an effective intervention for mitigating the occurrence of tuberculosis (TB), particularly in high TB-burden settings. However, its implementation in sub-Saharan countries remains subdued. This study investigated the factors inhibiting IPT uptake in the high HIV/TB burden setting of Lesotho.

Methods: Data were obtained from 46 healthcare workers, key informants at the Ministry of Health of Lesotho, and representatives of partner organisations, who were purposively selected for their roles in IPT implementation. Data were coded to identify themes, and the emerging themes were benchmarked to previous typologies for evaluating the implementation of best practices in health interventions, namely effectiveness; reach; sustainability and adaptation. Each main theme was further linked to the World Health Organization's building blocks of national health systems.

Results: Seven health system challenges affecting the implementation of IPT were identified, namely poor decentralisation of HIV services; inefficient monitoring and evaluation systems; ineffective service delivery; interrupted supply chains; undertrained and inadequate health workforce; insufficient health system financing and inefficient health information systems.

Conclusion: These findings indicate that a wide spectrum of challenges has affected the implementation of IPT in Lesotho. This indicates that a wider reform of the national health system is imperative when implementing key health interventions that need complex execution strategies.

Keywords: Health system challenges; isoniazid preventive therapy; PLHIV; tuberculosis; uptake of health interventions

6.1 INTRODUCTION

6.1.1 Background

Tuberculosis (TB) is the most common opportunistic disease in people living with human immunodeficiency virus (HIV). Of the 1.5 million people who died from TB in 2013, nearly 25% were HIV-positive (WHO 2014). Yet, preventative interventions to curb the incidence of TB in this subgroup often fail to take off to scale (Yamey 2012). One such intervention is isoniazid preventive therapy (IPT), recommended by the WHO (2004) as a preventative therapy against TB in people living with HIV (PLHIV). A number of studies have reported the uptake of IPT in a number of countries, and concluded that this intervention had a slow scale up (Adams, Talbot, Odato, Blunt & Steingart 2014; Adjobimey, Masserey, Adjonou, Gbenagnon, Schwoebel, Anagonou & Zellweger 2016; Ayele, Mourik & Bonten 2016; Charles, Lindegren, Wester, Blevins, Sterling, Dung, Dusingize, Avit-Edi, Durier, Castelnuovo, Nakigozi, Cortes, Ballif, Fenner & International Epidemiology 2016). However, the factors underpinning its implementation are not well understood.

Examples of sluggish scale up of health interventions in developing countries are many, and many lessons can be drawn from these past challenges (Lengeler 2004). McCannon, Berwick and Massoud (2007) recount that many sound solutions exist, but their adoption is slow. Buekens, Keusch, Belizan and Bhutta (2004) observe that the main challenge lies in how new health interventions should be delivered. Yet, the task of evaluating the implementation of health interventions is often daunting due to the spectrum of challenges involved (Yamey 2012). Often such evaluations lead to discovering deficiencies in the healthcare systems under investigation (WHO 2007).

The WHO (2007) recommends increasing access to new health interventions without compromising the quality and safety of the interventions (WHO 2007). Health

interventions are therefore expected to balance between access, coverage, quality and safety through judging how well the six building blocks of health systems, namely – service delivery; health workforce; information; medical products; financing; and leadership have been painstakingly considered in the new intervention (WHO 2007). Furthermore, the evaluation of health interventions should include the qualitative and quantitative evidence of best practices in local settings namely, effectiveness, accessibility, feasibility, sustainability, and transferability – where transferability refers to the extent to which the practice can be applied to or adapted to various contexts (Spencer *et al.* 2013). In principle, the higher the quality of evidence, the better the practice for the new intervention.

Getahun, Granich, Sculier, Gunneberg, Blanc, Nunn and Raviglione (2010), in their investigations on the implementation of IPT in its early years of this intervention, note that ineffective leadership and governance, service delivery, supply chains, health workforce, health information system and inadequate health system financing were likely to affect IPT implementation, given the scale of the resources required for this intervention. Since then, no further information has emerged on factors affecting the implementation of IPT in most other countries that have implemented IPT - Lesotho included.

Lesotho is a small country of about two million people. The country is completely surrounded by the Republic of South Africa (GoL 2013). The country has a mountainous terrain with only about 10% arable land. Poverty is a problem in the country. The United Nations (2009) notes that Lesotho is a poor country, with 40% of its population living below the official poverty line of US$1.25 per day. Lesotho has the second highest estimated TB incidence in the world, and a high HIV coinfection rate of about 74% of the TB cases (WHO 2014).

IPT was introduced to Lesotho in 2011 (GoL 2013). Poor uptake of the drug has continued since the launch of the programme (GoL 2013). This paper analyses the contextual factors inhibiting the uptake of IPT in PLHIV in the high TB-burden setting of Lesotho. The aim of this study is to establish, within the context of the health system of Lesotho, the compelling barriers to IPT implementation that need to be addressed.

6.2 METHODS

6.2.1 Study design

This qualitative study explored the contextual constraints affecting IPT implementation in people living with HIV in Lesotho, based on interviews with healthcare workers, Ministry of Health (MoH) officials and representatives of HIV/TB programmes' implementing partners, purposively sampled for their roles in the provision of HIV/TB services.

6.2.2 Qualitative interviews

6.2.2.1 Interview guides

Interview guides used to conduct the interviews with both healthcare workers and implementing partners were designed by the researcher, based on the theoretical framework for developing and implementing best practices in health interventions (Spencer, Schooley, Anderson, Kochtitzky, DeGroff, Devlin & Mercer 2013) (see Figure 6.1). The interview guide had the following sections: (i) Effectiveness – the extent the practice achieves the desired outcomes; (ii) Reach – the extent IPT covers the intended target population; (iii) Sustainability – the extent to which the practice can be maintained and monitored; (iv) Adaptation – the extent to which the IPT intervention has been applied to and adapted to the local context.

The interview guide was translated by a language specialist from English to vernacular language (*Sesotho*), and was validated by pilot testing it with ten selected healthcare workers and two key informants with experience in the implementation of health interventions in Lesotho.

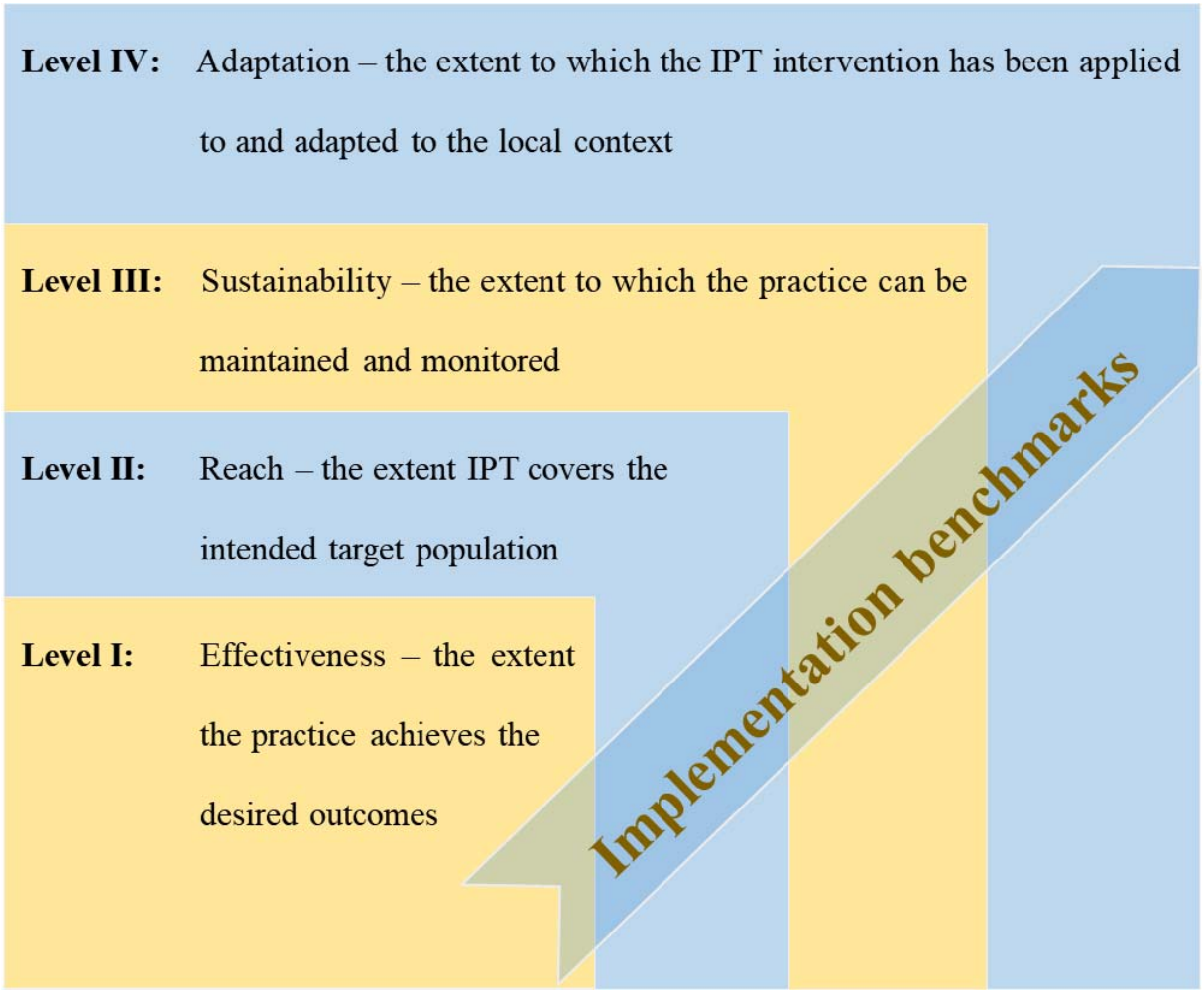

Figure 6.1 Benchmarks for evaluating the effectiveness of health interventions
This framework was developed based on the elements of the framework for developing and implementing best practices in health interventions by Spencer *et al.* (2013).

6.2.2.2 Data collection

To minimise bias, healthcare workers were interviewed first, and thereafter their responses were cross examined with responses from representatives of partner organisations and the Ministry of Health (MoH) officials. All healthcare workers working with IPT who were willing to participate in the study, including nurses; pharmacists;

laboratory technicians and counsellors were interviewed individually for about 30 minutes, until data saturation was reached. Responses were noted down manually during the interviews. Representatives of partner organisations were also interviewed individually, with each interview lasting for about an hour. Responses from all the interview responses were manually transcribed from vernacular (Sesotho) into English by a language specialist, using open coding before analysis.

6.2.3 Analysis of interview data

Data were coded to identify themes, and the emerging themes were benchmarked to previous typologies for evaluating the implementation of best practices in health interventions, according to the conceptual framework of Spencer *et al.* (2013) (see Figure 6.1). Each main theme was further linked to the World Health Organization's six building blocks of a health system, namely: (i) leadership and governance; (ii) service delivery; (iii) supplies and products; (iv) training and supervision; (v) health information system; and (vi) health system financing (WHO 2007), for purposes of benchmarking the effectiveness of the implementation of health interventions.

6.2.4 Ethical aspects

The study was approved by the Ministry of Health of Lesotho. The researcher observed standard ethical principles. Interview respondents were invited to participate in the study. They were informed that their participation was voluntary, that they could withdraw from the study at any moment if they so wish. All respondents were asked to sign a written consent form. Information on the background of the study was availed to them in English and vernacular (Sesotho) languages, where appropriate. To ensure interviewees' anonymity, information that would identify the interviewees was removed from this study.

6.3 RESULTS

6.3.1 Health system challenges constraining the implementation of isoniazid preventive therapy in people living with HIV in Lesotho

Table 6.1a—6.1c present the demographic information and the relevant working experience of the study participants. Overall, 42 healthcare workers employed by the Government of Lesotho comprising nurses (33), pharmacists (5), counselors (2) and laboratory personnel (2) were interviewed. In addition, four nurses employed by Elizabeth Glaser Pediatric AIDS Foundation (EGPAF), one EGPAF senior official, two Ministry of Health (MoH) officials and one US President's Emergency Plan for Aids Relief (PEPFAR) senior official were interviewed.

The following sections present the themes that emerged from the interviews categorised according to the benchmarks for evaluating the effectiveness of health interventions.

Table 6.1a Demographic information and the relevant working experience of the study participants

ID	District	Profession	Relevant experience	Qualification
HCW1	Thaba Tseka	Pharmacist	5-8 years dispensing ART/TB drugs	Honour's degree in pharmacy
HCW2	Thaba Tseka	Nurse	1-7 years ART/ANC	Diploma in general nursing and midwifery
HCW3	Thaba Tseka	Nurse	7 and 9 years ART	Diploma in general nursing and midwifery
HCW8	Thaba Tseka	Nurse	TB officer for 3 years	Diploma in general nursing
HCW9	Thaba Tseka	Laboratory personnel	5 to 7 years ART laboratory monitoring	Diploma in bio-medical technology; Certificate in microscopy.
HCW10	Qacha's Nek	Pharmacist	8 years dispensing ART/TB drugs	Diploma in pharmacy technician
HCW13	Qacha's Nek	Nurse assistant	6 years ART	Certificate in nurse assistance
HCW14	Qacha's Nek	Nurse	4 years ART	Diploma in general nursing
HCW15	Qacha's Nek	Nurse	10 years ART	Diploma in general nursing and midwifery
HCW16	Qacha's Nek	Nurse	8 years ART	Diploma in general nursing and midwifery
HCW17	Qacha's Nek	Counsellor	5-6 years adult ART patient counselling	Bachelor’s degree in pastoral care and counselling
HCW18	Mokhotlong	Pharmacist	6 years dispensing ART/TB drugs	Honour's degree in pharmacy
HCW20	Mokhotlong	Nurse assistant	34 years nursing experience	Certificate in nurse assistance
HCW21	Mokhotlong	Nurse	3 years ART	Diploma in general nursing and midwifery
HCW22	Mokhotlong	Nurse	1 year ART	Bachelor's degree in nursing
HCW23	Mokhotlong	Nurse	6 years adolescent ART	Diploma in general nursing and midwifery

HCW=healthcare worker; IPT=isoniazid preventive therapy; MOH=Ministry of Health;

Table 6.1b Demographic information and the relevant working experience of the study participants (continued)

ID	District	Profession	Relevant experience	Qualification
HCW24	Mokhotlong	Nurse	7 years TB clinic	Diploma in general nursing and midwifery
HCW25	Mohale's Hoek	Nurse	7 years TB clinic	Certificate in nurse assistance
HCW26	Mohale's Hoek	Nurse	2 years adolescent ART	Diploma in general nursing
HCW27	Mohale's Hoek	Pharmacist	[unspecified] years dispensing ART/TB drugs	Honours degree in pharmacy
HCW28	Mohale's Hoek	Nurse	4 years ART	Diploma in general nursing
HCW30	Mohale's Hoek	Counsellor	5 years adult ART patient counselling	Bachelor's degree in pastoral care and counselling
HCW31	Mohale's Hoek	Nurse	4 years ART/MCH	Diploma in general nursing
HCW32	Mohale's Hoek	Nurse	3 years adolescent ART	Diploma in general nursing
HCW33	Mohale's Hoek	Nurse assistant	4 years TB clinic	Certificate in nurse assistance
HCW34	Maseru	Nurse	2 years ART	Diploma in general nursing
HCW35	Maseru	Nurse	4 years ART	Diploma in general nursing and midwifery
HCW36	Maseru	Nurse	5 years ART	Bachelor's degree in nursing
HCW37	Maseru	Nurse assistant	5 years ART	Certificate in nurse assistance
HCW38	Maseru	Nurse	7 years ART/MCH	Diploma in general nursing
HCW39	Maseru	Pharmacy technician	5 years assisting dispensing ART/TB drugs	Diploma in pharmacy technician
HCW40	Maseru	Nurse assistant	1 year TB clinic	Certificate in nurse assistance

HCW=healthcare worker; IPT=isoniazid preventive therapy; MCH=Mother and child health; MOH=Ministry of Health;

Table 6.1c Demographic information and the relevant working experience of the study participants (continued)

ID	District	Profession	Relevant experience	Qualification
HCW41	Maseru	Nurse	2 years ART	Diploma in general nursing
HCW42	Maseru	Nurse	2 years ART	Diploma in general nursing
HCW43	Maseru	Nurse	10 years ART	Master's degree in nursing
HCW44	Maseru	Nurse	1 year adolescent ART	Bachelor's degree in nursing
HCW45	Maseru	Nurse	<1 year ART	Diploma in general nursing
HCW46	Maseru	Nurse	9 years ART/TB	Master's degree in nursing
HCW47	Maseru	Laboratory personnel	10 years ART laboratory monitoring	Diploma in pharmacy technician
HCW48	Berea	Nurse assistant	8 years ART/MCH	Certificate in nurse assistance
HCW49	Berea	Nurse assistant	11 years ART/MCH	Certificate in nurse assistance
EGPAF1	Berea	Nurse	3 years EGPAF HIV/TB Clinical Mentorship team	Diploma in general nursing and midwifery
EGPAF2	Berea	Nurse	5 years EGPAF HIV/TB Clinical Mentorship team	Bachelor's degree in nursing
EGPAF3	Maseru	Quality Improvement officer	5 years EGPAF Quality Improvement team	Bachelor's degree in nursing
EGPAF4	Thaba Tseka	Nurse (EGPAF)	2 years ART/MCH nurse	Diploma in general nursing
EGPAF5	Maseru	Medical doctor	5 years EGPAF senior management, Lesotho	Medical degree; Master’s degree in public health
PEPFAR	Maseru	PEPFAR	PEPFAR Lesotho	Medical degree; Master’s degree in public health
WHO	Maseru	Medical doctor	Senior management, WHO country office, Lesotho	Medical degree; Master’s degree in public health
MOH1	Maseru	Public health nurse	Representative at HIV/TB Directorate	Master’s degree in public health
MOH2	Maseru	Medical doctor	Representative at HIV/TB Directorate	Medical degree; Master’s degree in public health

EGPAF= Elizabeth Glaser Pediatric AIDS Foundation; HCW=healthcare worker; PEPFAR= US President’s Emergency Plan for Aids Relief; MOH=Ministry of Health; WHO=World Health Organization.

Level I: Effectiveness – the extent the practice achieves the desired outcomes

Most of the healthcare workers affirmed that IPT was largely effective in mitigating the occurrence of TB. Cases of TB had significantly gone down in patients who had taken IPT. However, they noted that the continued occurrence of TB after taking IPT was worrying. One healthcare worker mentioned that:

> *"Although the number of cases of TB among HIV patients are dwindling, TB cases continue to occur occasionally after IPT. Three patients exposed to IPT developed TB last month."* [EGPAF1]

The main barriers to the effective implementation of IPT included ineffective monitoring and evaluation particularly inadequate laboratory monitoring, ineffective health information systems, an inadequately managed patient referral system and poor knowledge, attitudes and practices (KAPs) of healthcare workers. For example, concerning monitoring and evaluation, some HCWs were not sure of IPT coverage in their respective centres citing that:

> *"The total IPT enrolment is not known because some ART patients are not recorded in the register when we run out of registers and because our monthly reports are not analysed longitudinally. The reports are send to the MOH for congregate analysis but we often do not get feedback."* [HCW17]

On cross-interviewing the representative of the MoH about the deficiency of cohort analysis of IPT indicators, the officials had this to say:

> *"Note that due to resource constraints, it is not feasible for MOH to frequently assess the effectiveness of the programmes they are implementing. The major goal of the MOH is to increase IPT uptake alongside ARVs and TB treatment."* [MoH1]

Despite the affirmation by healthcare workers that IPT was generally effective, the most cited concerns for IPT effectiveness included poor monitoring and evaluation resulting in late detection of side effects, and in some patients developing TB post exposure to IPT. For example, healthcare workers categorically stated that:

"Timely detection of side effects to ART and co-drugs such as cotrimoxazole is important. In this hospital, one patient reacted to concurrent cotrimoxazole and IPT two weeks after initiation of TDF/3TC/EFV." [EGPAF3]

Underreporting of monthly statistics, a point emphasised by representatives of the implementing partner organisations, was another main element affecting the efficiency of the health information system. One source commented as follows:

> *"Although the MoH has adopted 3 key indicators for monitoring IPT, the indicator system is paper-based. Inaccurate reporting and underreporting of data from health care centres is common."* [WHO]

The paper-based monitoring system in the country is also affecting the patient referral system. A representative for the organisation, PEPFAR, confided that:

> *"The paper-based patient referral system in the country needs more resources including stationery and patient registers. Confirmation of patients' arrival at the referred centres is often lacking. This confounds the national monthly statistics."* [PEPFAR]

Healthcare workers noted that more frequent visits of patients were required to improve monitoring. However, concerning the need to increase hospital visits to improve patient monitoring, one representative of implementing partners had a different opinion:

> *"Note that the frequency of check-up dates in under-resourced countries is guided by the need to balance between the amount of resources the patients have and the need for the hospital visits."* [PEPFAR]

Level II: Reach – the extent IPT covers the intended target population

According to the Ministry of Health officials, IPT uptake had a slow start and a suboptimal trend over the years since its inception. With respect to coverage, the main challenge was that densely inhabited districts had a lower coverage, compared to the sparsely populated districts. In their own words:

> *"Probably about two-thirds of patients on ART have received IPT in the sparsely populated districts since 2011 compared to 50% in the densely inhabited districts since 2011."* [MoH1]

According to representatives of MoH and partner organisations, the main barrier to IPT implementation was inadequate national planning. On this point, one of the representatives revealed that:

> *"One may attribute the success or failure of HIV/TB interventions to lack of foresight at the planning stage with regard to the amount and nature of resources required and poor capacity to solve problems that arise."* [PEPFAR]

Representatives of partner organisations noted that the Lesotho Government was doing all in its power, but that sufficient capacity was lacking. In their own words, they expressed that huge amounts of resources were required but were not available. Concerning these challenges, representatives for PEPFAR observed that:

> *"The government of Lesotho is doing reasonably well… however, the MOH has no sufficient capacity to implement HIV/TB programmes exclusively…"* [PEPFAR]

> *"Resource constraints are a major challenge. With a population of about 2 million, the country has an estimated 500, 000 HIV positive people. This number is too high and requires a massive amount of resources."* [PEPFAR]

With respect to barriers inhibiting IPT reaching the target population, fear of side effects was also reiterated by healthcare workers. One commented as follows:

> *"In one hospital, sporadic cases of severe side effects of liver toxicity while on IPT resulted in some ART nurses declining to prescribe IPT for months. IPT had been given to patients with compromised liver function without following the guidelines"* [HCW32]

Other barriers included social and economic factors such as lack of disclosure of HIV status, and lack of money for transport. Ineffective service delivery, particularly ineffective TB screening, was the main barrier to IPT uptake in many areas of the country:

> *"Those with presumptive signs of TB; patients declining to submit sputum for TB screening are delayed until TB is ruled out."* [HCW49]

One sticking point on IPT implementation in the country is the slow scale up of IPT uptake in patients enrolled on ART before IPT was launched in 2011. The representatives of the implementing partners mentioned that:

> *"There is a general perception that [patients long on ART] have a low risk of developing TB after taking ART for a long time. For this reason, IPT was prescribed mostly to new patients in the initial stages of the programme."* [PEPFAR]

On the same point of delayed IPT uptake in patients on ART for a long time, one PEPFAR representative revealed that "technical challenges in reviewing the manual patient files to identify patients long on ART" was the reasons for this problem.

One pertinent theme on the delayed IPT uptake was poor staff education. The representatives of partner organisations opinioned that staff education remained a challenge and was to blame, at least in part, for the poor uptake of IPT in the country. The representatives gave these insightful comments:

> *"HCWs, hesitant to initiate IPT concurrently with ARVs before ruling out side effects of the ARVs, take too long to rule out the side effects. Inadequate training is the main reason behind this. In practice, the hesitation leads to loss of patients through the cracks."* [EGPAF5]

Level III: Sustainability – the extent to which the practice can be maintained and monitored

Concerning the sustainability of the intervention, additional resources were required, including human resources, particularly data clerks, file managers, nurses and pharmacists – for the sparsely populated districts; physical infrastructure – laboratory upgrades in particular, and improved registers. A stricter monitoring and evaluation scheme entailing changes such as increasing the frequency of hospital visits by some patient groups, integrating the IPT and ART registers, was viewed as a way of improving IPT uptake and its outcomes. In addition, some healthcare workers

lamented the intermittent stock outs of the necessary supplies and products. In one hospital, a healthcare worker had this to say:

> *"We often run out of stock for vitamin B6, cotrimoxazole and dapsone … for adults. These drugs run out of stock more frequently than other drugs, sometimes for two months on end. Vitamin B6 is supplied in small quantities."* [HCW27]

MoH officials expressed that health system financing needed to be increased to improve the sustainability of the HIV/TB programmes, including IPT. Staff shortage was another problem. One MoH official remarked that:

> *"Staff shortages are a major challenge. Inadequate community health workers to oversee the implementation of the three I's programme which includes IPT is a challenge."* [MoH2]

Level IV: Adaptation – the extent to which the IPT intervention has been applied to and adapted to the local context.

Lack of engagement of healthcare workers responsible for implementing IPT was a challenge inhibiting IPT uptake. One important point was that some nurses were not familiar with IPT prescription requirements for children. One healthcare worker observed that:

> *"Nurses are not entirely familiar with IPT prescription and monitoring guidelines for children." [HCW49]*

To address this gap and improve adaptation of IPT practice for local need, health workers needed clearer guidelines on the ideal timing of IPT relative to ART commencement, and the duration after which IPT should be repeated for patients previously exposed to IPT. For the record, one healthcare workers had this to say concerning repeated IPT:

> *"Guidelines are not clear on the duration after which IPT should be repeated. Ideally, we repeat IPT every two years in some patients."* [HCW25]

Lack of clarity of guidelines was also echoed by other healthcare workers. Their concern was that there was too much room for discretional IPT prescription. This contributed to poor implementation of IPT. One healthcare remarked as follows concerning the excessive discretional IPT prescription without following the guidelines:

> *"In practice, we initiate ART before IPT to unmask side effects to ARVs. However, this practice is discretional for prescribers*." [EGPAF2]

6.4 DISCUSSION

A number of challenges in the health system of Lesotho are hampering effective implementation of the IPT programme. The spectrum of the challenges in the health system is wide and spans the 'six building blocks' of the national health system, as advocated by the WHO (2007). Poor decentralisation of HIV services, an inefficient monitoring and evaluation system, and ineffective service delivery were some of the main challenges at the core of the problem of IPT uptake in Lesotho. Furthermore, interrupted supply chains, health workforce factors, inadequate health system financing and inefficient health information systems were the other challenges identified. The study also found that the interrelatedness of these factors called for a multifactorial approach to addressing them.

In particular, poor decentralisation of HIV/TB services was found to be a barrier affecting the reach of IPT to some geographic locations in the country. HIV/TB services, including the IPT programme, remain disproportionately more concentrated in Maseru District, despite efforts to scale up HIV/TB services in other densely populated districts of the country. Another finding attributed to the unbalanced decentralisation of HIV/TB services is the gap in scaling up IPT in children, particularly in non-scale up districts. The majority of children exposed to TB have not been given IPT due to challenges hampering reaching out to children in their homes. This

emphasises the need to improve decentralisation of HIV/TB services to address this challenge. To illustrate the problem of decentralisation of HIV/TB services in the country, the majority of healthcare workers, and 75% of GeneXpert machines were still located in the densely populated districts in 2014 (PEPFAR Lesotho 2016). Notably, Tesfaye, Fiseha, Assefa, Klinkenberg, Balanco and Langley (2017) note that the investment cost for full implementation of GeneXpert machines remains far beyond the budgets of the national TB control programmes in developing countries, particularly those in sub-Saharan Africa, and they suggest that other cheaper alternatives may be needed.

Late onset of antenatal care (ANC) by pregnant women, a problem commonly observed in Lesotho (Mugomeri, Musa & Chatanga 2016), is another challenge affecting the implementation of IPT. Tiam, Machekano, Gounder, Maama-Maime, Ntene-Sealiete, Sahu, Isavwa, Oyebanji, Ahimbisibwe, Mokone, Barnes, Chaisson, Guay and Kassaye (2014) also reported that at least 32% of pregnant women attend ANC for the first time in the third trimester, and can therefore only start with IPT at a late stage. Further decentralisation of healthcare services is therefore needed to improve the uptake of IPT. However, the decentralisation of Lesotho's healthcare system faces many challenges, including shortages of healthcare workers (Bemelmans, Goux, Baert, Van Cutsem, Motsamai, Philips, Van Damme, Mwale, Biot & Van Den Akker 2015).

Ineffective TB screening and poor adherence to ART further delay IPT uptake due to the need to rule out TB before starting IPT. Ayele, Van Mourik and Bonten (2015) note that lack of access to latest technologies for excluding a pre-existing TB infection prior to treatment initiation is a challenge in developing countries. This problem in Lesotho is compounded by slow uptake of GeneXpert technology. PEPFAR Lesotho (2016)

note that Lesotho had a total of 28 GeneXpert machines that were not yet fully utilised due to shortages of healthcare workers. The problem of healthcare worker shortage affecting TB screening and resulting in slow uptake of IPT is a typical example of factor interplay in the health system of Lesotho. As the WHO (2007) notes, dynamic interrelationships of factors in the healthcare system need to be delineated in efforts to address challenges in health systems.

Poor monitoring and evaluation of HIV/TB services is a challenge affecting the effectiveness of IPT intervention in developing countries, Lesotho included. The need to rule out side effects to ART and ensure that patients are stable on ART before IPT is initiated, remains a challenge. Late detection of side effects is another symptom of poor monitoring systems and poor staff education. It is important to note that developing countries continue to find it difficult to meet minimum clinical and laboratory monitoring tests recommended by the WHO (WHO 2011). One solution for this problem is to intensify staff development programmes in the country, a solution also noted by Buchbinder and Shanks (2016).

One notable theme which emerged from healthcare workers was the need to improve patient monitoring schedules. However, to improve patient adherence to ART/IPT, evaluation studies on the merit of stricter patient monitoring schedules - particularly the effectiveness of the current frequency of check-up visits - are required. PEPFAR representatives in the study noted that there is need for a balance between the amount of resources available to the patients, and the need for hospital visits.

Healthcare worker factors, particularly poor KAPs, were a main barrier to effective IPT implementation. The need for intensive training of healthcare workers to remove the general perception that patients enrolled on ART before IPT was launched, have a lower risk of developing TB compared to patients enrolled on ART after IPT was

launched, cannot be over-emphasised. Ayele *et al.* (2015) and Noé, Ribeiro, Anselmo, Maixenchs, Sitole, Munguambe, Blanco, Souef and García-Basteiro (2017) emphasise the need for healthcare worker education in high TB-burden settings to improve healthcare workers' perceptions and knowledge of IPT practice guidelines.

The need to monitor adherence to ART before administering IPT is one critical factor hindering IPT implementation. Healthcare workers in this study delayed giving IPT to patients with poor adherence to ART until the patients were stable on ART. In addition, patients deemed too sick were also delayed. Apparently patients deemed too sick are at the greatest risk of developing TB (Collins, Juste, Koenig, Secours, Ocheretina, Bernard, Riviere, Calnan, Dunning & Hurtado Rúa 2015). Healthcare worker education is therefore required to address this problem.

Poor monitoring of the effectiveness of the IPT programme, mainly due to a weak monitoring system, needs attention in Lesotho. Timely detection of patients getting infected by TB after IPT is necessary to inform IPT policy for improvement (Churchyard, Mametja, Mvusi, Ndjeka, Hesseling, Reid, Babatunde & Pillay 2014). Without a systematic collection of data providing evidence of the effectiveness or failure of an intervention programme such as IPT, it is difficult to convince healthcare workers to change or improve in certain area of practice (Saito, Howard, Chege, Ellman, Ahoua, Elul & Rabkin 2015). The lack of longitudinal analysis of data supporting the effectiveness of IPT, and poor monitoring and evaluation may be a symptom of a sub-optimal monitoring and evaluation system in the country. Lack of skills in healthcare workers involved in data gathering and analysis may be the root cause, while other challenges, including poor implementation of electronic medical records (EMR) systems and over-reliance on paper-based monitoring systems, may be nested in the problem of skills shortage in the country. Suggestions for improving

monitoring systems include providing hands-on support for data collection and use at facility and national levels, utilising web-based databases for data entry, and efficient dissemination of results (Saito *et al.* 2015).

Health workforce factors are also a challenge to improving the adaptation of IPT practice to suit the local context. Healthcare workers do not seem to have a uniform approach to the implementation of IPT. Some nurses are not entirely familiar with IPT prescription and monitoring guidelines for children. The timing of IPT initiation relative to ART remains largely discretional in many hospitals, with some prescribers initiating IPT six months after starting the ART, and some only two weeks after ART. This points to a paucity in the clarity of IPT guidelines at the extent of adaptation of the guidelines to suit the local context. More training and supervision is therefore required.

A number of changes to the health system are needed to maintain and sustain the IPT programme. Additional health system financing is needed to acquire additional healthcare workers, data clerks, stationery - particularly integrated ART/IPT registers and combined ART/IPT dosage forms. In addition, improved supply chains and additional resources are also needed to sustain the programme. Furthermore, physical infrastructure – laboratory upgrades in particular - are required.

The incidence of TB in Lesotho is estimated at 852/100,000 in the general population, making the country a high TB-burden setting (WHO 2015). Although IPT is expected to have a high impact in Lesotho, the contextual underpinnings behind the slow uptake of IPT are an important research problem. The slow trend of IPT uptake is a loss of opportunity to leverage the existing HIV services for an intervention particularly ear-marked for high TB-burden countries such as Lesotho. Underestimation of potential public health impact has been identified as the main cause of the delayed implementation of this intervention in the Ivory Coast (Temprano ANRS 12136 Study

Group 2015). Healthcare worker education is therefore needed to improve IPT implementation in the country.

Out of the major barriers to the scaling up of health interventions in developing countries outlined by Yamey (2012) - the barriers re-echoed in this study - include: limited human resources; leadership challenges; poor health systems capacity; and lack of engagement of local implementers. Therefore, to address the problems hampering IPT uptake in Lesotho, there is need to examine these challenges in the health system reform programme of the country, as the barriers are better addressed through a comprehensive reform programme.

6.5 CONCLUSION

The spectrum of the challenges curtailing the implementation of IPT in Lesotho is evidently wide. As such, these challenges call for a systems approach to addressing them. Particular elements of the themes emanating from this study that have a direct effect on the implementation of IPT, and which resonate with global challenges inhibiting scale up of this particular intervention in developing countries, include ineffective TB screening, late detection of side effects due to weak monitoring systems and inadequate healthcare worker education. Clearly, these challenges indicate the need for a health systems approach to the implementation of IPT and other complex health interventions in developing countries.

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CHAPTER SEVEN

CHAPTER SEVEN: CONCLUDING REMARKS

7.1 BACKGROUND

The global syndemic of HIV and TB remains a public health threat, particularly in people living with HIV (PLHIV) in developing countries with high TB burdens. The World Health Organization (WHO) recommends the use of isoniazid preventive therapy (IPT) to reduce TB incidence in PLHIV, and continues to appeal for member countries to scale up the implementation of this intervention. The WHO remains concerned about the slow rates of IPT initiation and inadequate reporting of IPT outcomes in countries with poor IPT uptake. In addition, barriers to scaling up health interventions in developing countries remain obscure, despite the fact that understanding the contextual factors underpinning these barriers is pivotal for policy making.

This study set out to investigate the rate of initiation and retention on IPT, its effectiveness and the contextual constraints affecting its implementation in Lesotho, a small country in Southern Africa regarded as a high TB-burden setting, and having one of the highest incidences of HIV globally. IPT was introduced to Lesotho in 2011. Data on IPT from this setting is important to the global audience for answering at least three research questions: (1) Is the rate of initiation and retention on IPT in high TB-burden countries good enough to have a significant impact on TB incidence in these countries? (2) Is IPT effective in circumstances where IPT is given years after starting ART? (3) What health system factors are hampering the implementation of IPT in developing countries?

7.2 CONCLUDING REMARKS

While there are challenges in the implementation and effectiveness of IPT in Lesotho, the IPT intervention has considerably reduced the incidence of TB in PLHIV in the country. The various challenges discussed in this study may contribute to policy discourse on preventing the occurrence of TB in PLHIV in Lesotho.

Concerning the rate of initiation and retention on IPT, this study found a fairly high overall uptake, but with a slow rate of IPT initiation and low proportion of defaults (see Chapter Four). The problem of poor uptake of IPT was more pronounced in the patients enrolled before the intervention was launched. In addition, children and adolescents were more affected compared to adults. Furthermore, densely populated districts had poorer uptake of IPT compared to the sparsely populated districts, although the gap has been narrowing since 2011. The problem of poor uptake of IPT in these groups points to the need for reforming the health sector, particularly decentralising HIV/TB services and improving health service delivery.

The investigations on the effect of longer durations between commencing ART and IPT revealed that better outcomes of IPT are achieved when IPT is given in the early stages of ART commencement, with the best results obtained when IPT is prescribed within six months of starting ART (see Chapter Five). Of note, delaying IPT after starting ART renders IPT less effective to a level comparable to no IPT intervention at all. The investigations in this study revealed that the loss of effectiveness of IPT is another challenge in Lesotho which calls for booster doses of IPT to prevent the occurrence of TB after exposure to IPT. Concerning the predictors of TB occurrence, lower immunity at the time of enrolment into HIV care, geographic location and gender

emerged as significant risk factors for contracting TB in this study, implying that these factors need to be considered in the policies on TB prevention in the country.

With respect to the health systems challenges curtailing the implementation of IPT, (see Chapter Six), the study found that ineffective TB screening, late detection of side effects due to weak monitoring systems, and inadequate education of healthcare workers are the most critical barriers to IPT implementation of IPT. In addition, the range of the factors underpinning the implementation of IPT in Lesotho was wide, which calls for holistic reforms of the health system, particularly in the domains of decentralisation; monitoring and evaluation; service delivery; supply chain; health workforce; health system financing and health information system.

7.3 LIMITATIONS OF THE STUDY

The findings of this study are not without limitations, the most critical being that the effectiveness of the IPT intervention was evaluated in isolation, leaving out the impact of the other TB intervention programmes, such as the infection control (IC) and intensive case finding (ICF) sub-programmes of the Three I's programme (IC). It is hard to establish the effectiveness of health interventions due to the complexity of the factors involved. Therefore, despite the importance of the findings of this study, they need to be interpreted with these limitations in mind.

7.4 FURTHER RECOMMENDED RESEARCH

Findings from this study evoked further research questions which need to be answered in further research. These questions include, but are not limited to, the following:

- The occurrence of TB after IPT poses an important research question on the need to find the optimal duration after which IPT should be repeated in high TB-burden settings where reinfection is likely.
- Further research should also identify deficiencies in infection control programmes that are worsening reinfection rates in patients exposed to IPT in high TB-burden settings such as Lesotho.
- The contextual constraints affecting the implementation of IPT call for further research on the statuses of developing countries' national healthcare systems with respect to capacities for implementing health interventions. Such research may need to focus on debating the most critical elements of the national health systems that need to be reformed. Particular elements pertinent to improving the implementation of preventative health interventions such as IPT may include decentralisation and healthcare service delivery reforms.

APPENDICES

Appendix A1 Interview guide 1: Policies and guidelines for IPT intervention in Lesotho

INTERVIEW GUIDE

ISONIAZID PREVENTIVE THERAPY ON TUBERCULOSIS OCCURRENCE IN HIV-POSITIVE PATIENTS IN LESOTHO

1. Respondent number _____ 2. Date of interview _____

PART 1: POLICIES AND GUIDELINES FOR IPT INTERVENTION (Ministry of Health officials and support partners)

1. Respondent information

a. Profession	b. Gender	c. Job description

2. Policies & guidelines on IPT implementation in Lesotho

2A Leadership and governance-related	Response (Please explain your answer or give examples)
1. TB is still a health challenge in Lesotho despite interventions such as IPT. How would you rate the implementation and outcomes of IPT	
2B Service delivery-related	
1. Do you think standard TB screening algorithms for screening TB before IPT are adequate? What challenges are being encountered in the roll out of GeneXpert machines in screening TB?	
2C Supplies and products-related	
1. Are you aware of any challenges facing the availability of laboratory reagents and equipment used in the monitoring of TB/HIV and IPT? Examples include: Test kits for hepatitis B screening, liver function tests and GeneXpert.	

2. Is IPT adequately available in the right dosages (e.g.300 mg) in all settings? Are we likely to see a single tablet dosage form for Cotrimoxazole, IPT and Vitamin B6 in the near future?	
2D Training and supervision	
1. What plans are there to ensure supervision of TB/HIV and IPT implementers?	
2. What challenges does the TB/HIV and IPT patient referral system face?	
2E Health information system-related	
1. What are the main weaknesses in monitoring and evaluation of TB/HIV programmes, including IPT implementation?	
2. Is there a clear strategy for collecting and analysing the evidence of IPT effectiveness?	
3. Which key indicators are being used for monitoring and evaluation of IPT implementation, and how is the IPT programme performing?	
2F Health system financing-related	
1. Is there adequate funding for the IPT programme in the medium and long term?	

Appendix A2 Interview guide 2: Implementation of IPT intervention in Lesotho

INTERVIEW GUIDE

ISONIAZID PREVENTIVE THERAPY ON TUBERCULOSIS OCCURRENCE IN HIV-POSITIVE PATIENTS IN LESOTHO

1. Respondent number

2. Date of interview

PART 2: IMPLEMENTATION OF IPT INTERVENTION IN LESOTHO (For healthcare workers)

1. Demographic characteristics of the respondent

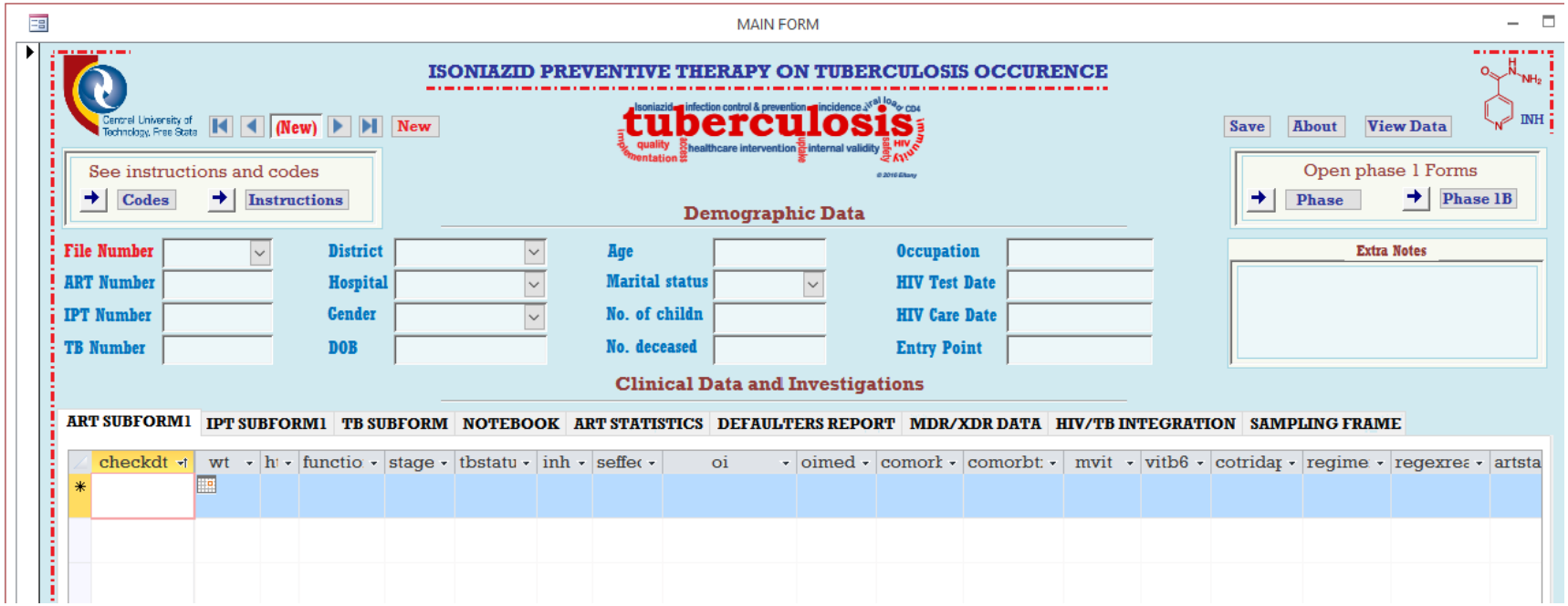
3. **District #**	4. **Health Facility**	5. **Profession**	6. **Highest Qualification**	7. **Gender**	8. **Age**	9. **Experience in years**

2. Implementers of IPT intervention in Lesotho

3A Reach: Extent that the IPT intervention covers the intended and critical target population	**Response (Please explain your answer or give examples)**
1. Which groups of people are getting IPT in this setting?	
2. How many of these groups have been given IPT? (Please give an estimate)	
3. Which patients do you sometimes delay to give IPT, and why?	
3B Effectiveness: Extent to which IPT has achieved the desired outcomes	
1. To what extent is IPT stopping the occurrence of TB in this setting?	
2. Which adverse reactions to IPT do you often encounter, and in which groups of patients?	

3C Barriers to implementing IPT intervention	
1. Which of the following factors do you consider as barriers to IPT uptake in this setting? *Side effects; Non-adherence; fear of toxicity of IPT; fear of drug resistance; and social factors*	
3D Sustainability: Extent to which the practice can be maintained and monitored	
1. What extra work does IPT add to existing ART procedures and processes?	
2. Have you ever run out of IPT, vitamin B6 or Cotrimoxazole in this setting?	
3. What additional resources are required to sustain IPT intervention over time?	
3E Adaptation: Extent to which IPT intervention has been adapted to the local context	
1. Describe how IPT is prescribed and monitored in this setting. Include in your answer how often the patients have to come for checkup while on IPT.	

Appendix A3 The user interface for the database tool used to extract data from the patient records



Note: The database tool had a module for automating the creation of the sampling frame. Also, for quality control purposes, data for the initiation of IPT were collected in duplicate from the ART and IPT registers.

Appendix B Clinical and laboratory data extraction form for phase 2 of the study

CLINICAL & LABORATORY DATA EXTRACTION FORM

1. Patient code | Secured |

3. District #	4. Health Facility	5. Gender	6. Age	7. DOB	8. Marital
e.g. Maseru	Any of the 5 hospitals	Male/ Female		DD/MMYY	

9. Confirmed HIV+	10. Enrolled in HIV care	11. Transfer-in	12. ART start	13. 1st regimen	14. 2nd-line regimen	15. 3rd line	16. Dead	17. Transfer-out
DD/MM/YY	DD/MM/YY	DD/MM/YY	DD/MM/YY	e.g. TDF/3TC/EFV	e.g. TDF/3TC/EFV		Y/N	Y/N

18. Stop/ Lost-ART DD/MM/YY	19. Reason	20. ART restart DD/MM/YY	21. Stop/ Lost IPT DD/MM/YY	22. Reason	23. IPT restart DD/MM/YY

24. Check-up Date	25. Follow-up date	26. Duration (m)	27. Wt (kg)	28. Ht (m)	29. Preg status	30. WHO stage	31. ARV drugs	32. Side effects	33. TB status	34. TB Meds	35. Side effects	36. IPT	37. Side effects	38. Opp. Infection	39. Cotrimoxazole	40. CD4 cell s/cm^3	41. VL (c/ml)	42. Hgb (g/dl)	43. HBsAg +/-	44. Diabetes +/-	45. Liver dis. +/-	46. HTN +/-

Wt=weight; Ht=height; Preg=pregnancy; Opp. Infection=opportunistic infection; VL=viral load; Hgb=haemoglobin; HTN=hypertension; HBsAg=hepatitis B surface antigen; Liver dis=diagnosis of liver disease based on clinical and laboratory liver function profile; HTN=hypertension; Kidney dis=kidney disease.

Appendix C1 Information sheet for study participants: English version

STUDY TITLE:

ISONIAZID PREVENTIVE THERAPY ON TUBERCULOSIS OCCURRENCE IN HIV-POSITIVE PATIENTS IN LESOTHO

Dear respondent

Introduction

Tuberculosis (TB) is an important opportunistic disease in people living with human immunodeficiency virus (HIV). TB is caused by a bacterium known as *Mycobacterium tuberculosis.* Lesotho is one of the countries that are worst affected by TB. The effectiveness of the drug isoniazid preventive therapy (IPT), which was recommended in 2004 by the World Health Organization for the prevention of TB, is of high importance to prevent TB infections among vulnerable groups such as HIV-positive people. However, the uptake and the effectiveness of IPT in Lesotho is not fully known. More importantly, there is little evidence to inform the process of formulating the best way of improving the uptake, retention and monitoring the effectiveness of IPT in HIV-positive people within the country.

We intent to determine the level of coverage, uptake and retention in treatment for IPT. We also intend to study the extent to which isoniazid preventive therapy (IPT) is effective in preventing TB infection in HIV-positive patients. The occurrence of adverse reactions and the associated risk factors will also be studied. The study will culminate in the determination of the best way of improving uptake, retention and monitoring of IPT intervention in Lesotho.

What the study involves

The study will be carried out in two phases. Phase 1 will seek to evaluate the extent of coverage, local adaptation of the guidelines and sustainability of IPT intervention among HIV-positive people in different settings in Lesotho. Participants will be sampled from among Ministry of Health officials, Government partners and health workers involved in

TB/HIV programmes. An interview guide designed by the researcher will be used to collect qualitative data. The researcher will identify patterns and themes which will emerge from the interviews. The themes will be analysed to identify factors affecting the coverage, contextual adaptation of the guidelines and sustainability of IPT intervention in Lesotho.

Phase 2 will be based on medical records of HIV-positive patients. The study will include patients from the current register of ART patients at the five health institutions. The main outcome variables include the proportion of patients on IPT, retention records, adherence to IPT, occurrence of active tuberculosis, and adverse drug reactions to IPT.

Notification of results of the study

The study report will be submitted to the relevant authorities in the Ministry of Health and all the hospitals participating in the study. The results are expected to improve IPT practice and HIV treatment outcomes in Lesotho. The findings of the study will be sent for review and possible publication in suitable journals.

Risks of being involved in the study

No adverse events are anticipated to the patients and the participants in the study. The researcher will not carry out any medical procedure or administer any drug to the patients. The study will make use of routine clinical and laboratory data. However, some participants, particularly in phase 1 of the study, may face risks, including consequences of information disclosure during the interviews. To safeguard patient information privacy, the researcher will observe standard ethical principles for conducting medical research, including voluntary participation, the right to decline answering certain questions, and the right to withdraw their participation at any time.

Benefits of participating in the study

No financial benefits will be awarded to the participants in the study. However, participants will gain important information from the study outcomes.

Participation in the study is voluntary

Participation in the study is entirely voluntary. The officials from the Ministry of Health and Government partner organisations, as well as hospital administrators included in the study reserve the right to deny the researcher access to the patients' records. In addition, the officials and the hospital administrators can terminate participation in the study at any time.

Confidentiality

Efforts will be made to keep personal information confidential. Personal information will only be disclosed if required by law. The Ethics Committee of the Ministry of Health of Lesotho reserves the right to demand inspection of the data records if the need arises. However, publication of the results will not directly lead to identification of the patients included and individuals participating in the study.

If you have questions about your rights as a research subject, you may contact the researcher at emugomeri@nul.ls or the Secretariat of the Ethics Committee of the Ministry of Health of Lesotho at telephone number (+266) 2222 6317.

Appendix C2 Information sheet for study participants: *Sesotho* version

SEHLOHO

PATLISISO EA LITLA-MORAO TSA TSEBELISO EA ISONIAZID (INH) THIBELONG EA TB BAKULING BA NANG LE HIV LESOTHO

Ho ba tla nka Karolo

***Selelekela**:*

*Lefuba (TB) ke lefu le ka sehlohong le nkang monyetla ho t'soara bakuli ba koatsi ea bosolla hlapi (HIV), mme TB e bakoa ke **Mycobacterium tuberculosis.** Lesotho le oela hara linaha tse nang le sekhahla se phahameng sa TB. Bohlokoa ba tsebeliso ea INH ho thibela lefu lena la TB bathong ba nang le HIV e khothalelitsoe ka selemo sa 2004 ke mokhatlo oa lefatse oa bophelo (WHO) lehoja, matla a t'sebeliso ena ea INH e keneng t'sebetsong ka 2011 Lesotho a sa tsejoe.*

Re ikemiselitse ho ithuta tsela eo INH e thibelang TB bakuling ba HIV. Re ikemiselitse hape ho fumana sekhahla sa t'sebeliso ea INH thibelong ea TB. Re tla ithuta hape le ka litla-morao tse amanang le t'sebeliso ea INH. Boithuto bona bo tla thusa ho fumana t'sebeliso e nepahetseng le tatello ea t'sebeliso ea INH thibelong ea TB lesotho.

***Sekenellang ka hara boithuto**:*

Boithuto bona bo tlaba mekhahlelo e mmeli. Mokhahlelong oa pele, re tla ithuta ka kanetso le t'sebeliso e it'sematletseng ea tataiso ea t'sebeliso ea INH litsing tse fapaneng hara batho ba nang le HIV Lesotho. Ba tla nka karolo ba tla khethoa hara basebetsi ba lekala la bophelo, mekhatlo enang le selekane le mmuso le basebeletsi ba tsa bophelo ba shebaneng le mananeo a HIV/TB. Mofuputsi o tla hlopha lipotso e le ho fuputsa lintla, moo a tla hloaea lintlha abe ali lotomanye tafolaneng khahlanong le lintlha tsa bona tse phethahetseng ho fumana tsetiso le liphephetso tse tobileng t'sebeliso e phethahetseng ea INH lesotho.

Mokhahlelo oa bobeli o tla manolla manane a lihlopha tsa bakoli ba nang le HIV. boithuto bona bo tla shebana le lihlopha tsa bakoli ba ngolisitsoeng hajoale ba sebelisang litlhare tsa HIV litsing tse hlano tse kenelletseng boithutong. Lintlha-kholo li kenyeletsa karolo ea

bakoli ba sebelisang INH, poloko ea manane, ho t'sepahalla INH, boteng ba TB le litla-morao tsa tsebeliso ea INH.

***Tsebiso ea sephetho sa boithuto**:*

Tlaleho ea sephetho e tla isoa ho ba ikarabellang lekaleng la bophelo le litsing tse nkileng karolo boithutong bona. Sephetho se reretsoe ho ntlafatsa tsebeliso ea INH thibelong ea TB le ho ntlafatsa bophelo ba bakuli ba sebelisang litlhare tsa HIV. Liphuputso tsohle li tla hlahlojoa mme li phatlalatsoe.

***Kotsi ea ho kenella boithutong**:*

Ha ho na litla-morao tse mpe tse lebeletsoeng ho bakuli ba nkang karolo boithutong bona. Mofuputsi a ke ke a fa motho ea nkang karolo setlhare sefeng kapa sefeng. Boithuto bo tla sebelisa litlaleho tsa ngaka. E le ho boloka lekunutu la bakuli, mofuputsi o tla latela melaoana ea bofuputsi e khothalelitsoeng ke Helsinki ka 2013.

***Melemo ea honka karolo**:*

Ha ho na chelete eo mokuli eo ho sebelisitsoeng litokomane tsa hae a tla e fumana.

***Ho nka karolo ke boithaopo**:*

Ho nka karolo ke boikhethelo ba motho ka mong. Bookameli ba litsi tseo boithuto bona bo tla etsoa ho tsona bo na le tokelo ea ho hana ka litokomane tsa bakuli kapa hona ho khina boithuto bona nako eohle.

***Poloko ea lekunutu**:*

Lintlha tsa mokuli li tla t'sireletsoa ka hohle-hohle, li tla tsebisoa ha fela molao o lumela. Komiti ea molao ho tsoa lekaleng la bophelo ena le tokelo ea ho hlahloba liphuputso ha ho hlokahala. Le ha ho le joalo, phatlalatso ea sephetho e ke ke ea supa ba nkileng karolo ka kotloloho.

Ha u na le lipotso kapa u hloka tlhakisetso mabapi le litokelo tsa hao ho nkeng karolo boithutong bona, u ka letsetsa lekhotlana la ketsa-molao la lekala la bophelo nomorong tse latelang (+266) 2222 6317. Moo o ka fumanang moetapele oa boithuto: E Mugomeri email e.mugomeri@nul.ls or emugomeri@yahoo.com.

Appendix D1 Consent form: English Version

CONSENT TO PARTICIPATE IN RESEARCH

You have been asked to participate in a research study.

You have been informed about the study by the principal researcher, Mr E. Mugomeri.

You can also contact E. Mugomeri at: e-mail address: e.mugomeri@nul.ls or emugomeri@yahoo.com or the Secretariat of the Ethics Committee of the Ministry of Health of Lesotho at +266 2222 6317 should you have questions pertaining to the research.

You may contact the Secretariat of the Ethics Committee of the Faculty of Health Sciences, University of the Free State (UFS) at telephone number (051) 4052812 if you have questions about your rights as a research subject.

Your participation in this research is voluntary, and you will not be penalised or lose benefits if you refuse to participate, or decide to terminate your participation in the study.

If you agree to participate, you will be given a signed copy of this document, as well as the participant information sheet, which is a written summary of the research.

The research study, including the above information, has been verbally described to me. I understand what my involvement in the study means, and I voluntarily agree to participate.

_____ _____

Signature of participant Date

_____ _____

Signature of witness Date

_____ _____

Signature of translator Date

Appendix D2 Consent form: *Sesotho* Version

Tumellano ea ho nka karolo boithutong

U kopiloe ho nka karolo boithutong bona.

U tsebisitsoe ka boithuto bona ke E. Mugomeri

U ka letsetsa lekhotlana la ketsa-molao la lekala la bophelo la Lesotho linomorong tsena: +266 2222 6317 nako eohle ha o na le lipotso mabapi le boithuto bona. Moo o ka fumanang moetapele oa boithuto: email e.mugomeri@nul.ls or emugomeri@yahoo.com

U ka letsetsa lekhotlana la ketsa-molao la lekalana la tsa mahlale a bophelo, University of Free State (UFS) linomorong tse latelang: (051) 4052812 ha eba o na le lipotso kapa o hloka tlhakisetso ka litokelo tsa hao boithutong bona.

Ho nka karolo ha hao boithutong bona ke ka boithaopo, ha o na ho nkeloa likhato kapa oa lahleheloa ke letho ha o ka khetha ho se kenelle boithutong bona kapa ha o ka khetha ho itokolla hara nako ea boithuto.

Ha u lumela ho kenella boithutong bona, o tla fumana tokomane ena e tekennoe le kakaretso ea boithuto bona ka bokhuts`oanyane.

Ke hlaloselitsoe lintlha tse kaholimo le kakaretso ea boithuto ka mantsoe mme ke utloisisa karolo ea ka boithutong bona, ka hona ke ithaopela ho nka karolo boithutong bona.

_____	_____
Motekeno oa moithopi	*Letsatsi*
_____	_____
Motekeno oa paki	*Letsatsi*
_____	_____
Motekeno oa toloko	*Letsatsi*

Appendix E Letter of approval for ethical clearance

LESOTHO

Ministry of Health
PO Box 514
Maseru 100

REF: Proposal ID58-2015

Date: 15 September 2015

Category of Review:
[x] Initial Review
[ ] Continuing Annual Review
[ ] Amendment/Modification
[ ] Reactivation
[ ] Serious Adverse Event
[ ] Other _____

To: **Eltony Mugomeri**
Department of Pharmacy, National University of Lesotho

Dear Eltony

RE: Isoniazid Preventive Therapy on TB Occurrence within HIV Positive Patients in Lesotho

This is to inform you that on 15 September 2015 the Ministry of Health Research and Ethics Committee reviewed and **APPROVED** the above named protocol and hereby authorizes you to conduct the study according to the activities and population specified in the protocol. Departure from the approved protocol will constitute a breach of this permission.

This approval includes review of the following attachments:
[x] Protocol version dated 14 September 2015
[x] English consent forms
[x] Sesotho consent forms
[x] Data collection forms
[x] Participant materials- Participants information sheet
[x] Other materials [CV of the PI]

This approval is **VALID** until **13 September 2016.**

Please note that an annual report and request for renewal, if applicable, must be submitted at least 6 weeks before the expiry date.

All serious adverse events associated with this study must be reported promptly to the MOH Research and Ethics Committee. Any modifications to the approved protocol or consent forms must be submitted to the committee prior to implementation of any changes.

We look forward to receiving your progress reports and a final report at the end of the study. If you have any questions, please contact the Research and Ethics Committee at *[insert contact number/email]*.

Sincerely,

Dr. Nyane Letsie
Director General Health Services (a.i)

DR. Jill Sanders
Co-Chairperson NH-REC