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COLLEGE OF HEALTH SCIENCES

Early Experiences With Isoniazid Preventive Therapy Roll-out In An ART programme: A Pharmacist's Perspective

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Submitted as the dissertation component in partial fulfilment for the degree of Masters in Pharmacy (Pharmacy Practice) in the School of Health Sciences, University of KwaZulu-Natal

28 NOV 2016

SUPERVISOR DECLARATION

As the candidate's supervisor I, XXXX, agree to the submission of this thesis.

Signed:  .....

Date: 28 NOV 2016

DECLARATION

I, Bhavna Maharaj, declare as follows:

1. That the work described in this dissertation has not been submitted to UKZN or any other tertiary institution for purposes of obtaining an academic qualification, whether by myself or any other party.

2. That my contribution to the project was as follows:

   2.1 Literature Review

   I started in 2013 with the literature review by using PubMed and Google Scholar as the primary source for collection of articles. Relevant articles were summarised and included as tables, figures or part of the narrative in this dissertation.

   2.2 Data Collection, clean-up and Analysis

   To ensure that the data presented in the manuscript and dissertation was valid and reliable a clean-up of all participants' files was conducted. During this process information was updated and verified with Data Management. I conducted review of clinic records, pharmacy prescriptions and other pharmacy records, including computerised dispensing records, conducted statistical calculations on MS Excel and created some of the figures used in the manuscript on Graph Pad Prism 5. The statistician verified all my calculations, figures, conducted all demographic tests, adherence assessments and multivariate analysis in SAS version 3.2.

   2.3 Write up of Manuscript

   I took overall responsibility for writing the manuscript before submitting a final draft to all co-authors for review and comments. All the co-authors reviewed and approved the final version of this manuscript which was submitted to the journal. The manuscript was submitted to Turnitin to verify for originality.

   2.4 Submission of Manuscript to Journal

   The manuscript was submitted for publication to International Journal of Tuberculosis and lung disease (IJTLD) on the 16 October 2016. Reviewer comments were received on 21 November 2016. These comments were addressed by the candidate and the revised manuscript was re-submitted on 26 November 2016. The article was accepted for publication on 6 January 2017 and is included in Chapter 3.

2.5 Write up of Dissertation

I took overall responsibility for writing the dissertation before submitting a final draft to my supervisor, XXXX, for review and final approval. The dissertation was submitted to Turnitin before final submission to the postgraduate office.

3. That the contributions of others to the project were as follows:
   XXXX – Supervisor and co-author of the manuscript
   Nonhlanhla Yende-Zuma – Statistician and co-Author of the manuscript
   Anushka Naidoo – Co- author of the manuscript
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Date: 28 NOV 2016

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ACRONYMS

aHR	Adjusted hazards ratio
AIDS	Acquired immune deficiency syndrome
aIRR	Adjusted incidence rate ratio
ALT	Alanine transaminase
aRR	Adjusted relative risk
ART	Antiretroviral therapy
ARV	Antiretroviral
ASP	Adherence support programme
AST	Aspartate transaminase
CCMDD	Centralised chronic medicines dispensing and distribution
CD4	T-lymphocyte bearing CD4 receptor
CDC	Centers for Disease Control and Prevention
CI	Confidence interval
CIPRA	Comprehensive International Program of Research on AIDS grant
CP	Continuation phase
CPT	Co-trimoxazole preventive therapy
DOH	Department of Health
DOT	Directly observed therapy
DR	Drug resistant
E	Ethambutol
GI	Gastrointestinal
H	Isoniazid
Hb	Haemoglobin
HCW	Healthcare worker

HIV	Human immunodeficiency virus
HR	Hazards ratio
ICF	Intensified case finding
IGRA	Interferon gamma release assay
INH	Isoniazid
IP	Intensive phase
IPT	Isoniazid preventive therapy
IR	Incidence rate
IRR	Incidence rate ratio
IUAT	International union against tuberculosis
KZN	KwaZulu-Natal
LTBI	Latent tuberculosis infection
LTFU	Lost to follow-up
MeSH	Medical subject headings
MDR-TB	Multi drug resistant tuberculosis
NIAID	National Institute of Allergy and infectious Disease
NICD	National Institute for Communicable Diseases
NIH	National Institutes of Health
NIMART	Nurse-initiated management of antiretroviral therapy
OI	Opportunistic infection
OR	Odds ratio
P	Placebo
100 P-Y	100 person years
PEPFAR	President’s Emergency Plan for AIDS Relief
PLHIV	People living with HIV
POC	Point-of-care

PPD	Purified protein derivate
PT	Preventive therapy
PY	Person years
R	Rifampicin
RPT	Rifapentine
sPT	Secondary Preventive Therapy
SA	South Africa
SMS	Short messaging service
SPSS	Statistical package for social sciences
SSA	sub-Saharan Africa
SDG	Sustainable development goal
TB	Tuberculosis
TST	Tuberculin skin test
UNDP	United Nations Development Programme
WHO	World Health Organization
XDR-TB	Extensively drug-resistant tuberculosis
Z	Pyrazinamide

ABSTRACT

Background: Tuberculosis (TB) remains the leading cause of mortality amongst people infected with Human Immunodeficiency Virus (HIV). Additionally, TB recurrence after successful treatment completion occurs more frequently amongst HIV positive people. Isoniazid provided as part of isoniazid preventive therapy (IPT) has been the gold standard of TB preventive therapy provision for the last few decades. IPT has been recommended by the World Health Organisation (WHO) and implemented by national health programmes in countries across the world. Despite global efforts and campaigns to promote IPT, uptake still remains a challenge and, progress in the operational scale- up of IPT is slow. Both international and in-country guidelines have advanced to recommending the use of IPT in HIV infected patients who have previously been treated for TB because these patients remain at risk for recurrent TB especially in TB endemic settings. However, there still remains a paucity in data on the successful programmatic use of IPT secondary to previous cured TB among HIV infected patients and is the focus of the current analysis from a pharmacists' perspective.

Methods**:** A retrospective secondary analysis was conducted from October 2009 to October 2013, amongst HIV infected patients, previously treated for TB, accessing HIV care at the urban CAPRISA clinical research clinic in Durban, South Africa. The aim of the study was to evaluate the implementation of Isoniazid Preventive Therapy (IPT) within the parent study titled "TB recurrence upon treatment with HAART" (TRuTH). Data was collected on IPT uptake, course completion, drug toxicity, treatment interruption, and the occurrence of incident TB either during treatment or post IPT completion. The multidisciplinary team approach in providing IPT to at risk HIV infected patients, including the specific role of the pharmacist, was also assessed.

Results**:** There were 402 patients enrolled in the parent study. Of these 344 (85.6%) were eligible to receive IPT and of whom 212 (61.6%) initiated IPT. Among those that commenced IPT, 184 (86.8%) completed the six-month course, 24 (11.3%) permanently discontinued IPT and of these, 3.8% discontinued due to side effects. More women (n=130; 61.3%) were initiated on IPT (p=0.001) than men. Overall median adherence to IPT was 97.6% (IQR: 94.2 - 99.4). There were 22 cases of incident TB in this cohort: 13 occurred prior to IPT and nine after IPT (incidence rate ratio 0.67; 95% CI 0.29-1.58; p=0.362).

CONCLUSIONS: Overall, we demonstrated a successful IPT roll-out in a high TB endemic setting with good uptake of IPT, minimal course interruptions or side effects reported. IPT is a safe and tolerable TB prevention intervention within ART programmes and importantly amongst patients on

ART with previous TB treatment experience. The pharmacist played an important role in continuum of care in IPT provision within an ART programme. This role included ensuring stable supply chain management, supporting clinic staff in monitoring safe IPT use and provided data on IPT course completion rates.

STRUCTURE OF THE DISSERTATION

The structure of this Master's thesis is based on guidelines provided by the College of Health Sciences, University of KwaZulu-Natal titled: Guidelines for Presentation of Masters and PHD Dissertations/Theses by Research, August 2015 version. The reference list for references cited in chapters 1, 2 and 4 are provided in this thesis after Chapter 4. The chapters are divided as follows:

Chapter 1, introduces the current scale of the HIV and TB co-infection epidemic, importance of isoniazid preventive therapy (IPT), challenges with IPT implementation, the global and local impact of TB and HIV epidemics, IPT provision and uptake data, the need for HIV and TB service integration and barriers associated with this. A review of the IPT literature covers data from systematic reviews and randomised control trials, IPT uptake, IPT implementation, adherence to IPT, IPT related adverse effects and INH resistance. The hypothesis, aims and objectives are presented thereafter. Chapter 1 ends with a conceptual framework of factors associated with IPT use.

The methodology used in the study is outlined in **Chapter 2**. This study is a secondary analysis of IPT programme roll out data amongst clinical trial participants. The study design, location and study population is described here. The steps involved in the implementation and the provision of IPT are discussed and illustrated. Finally, data collection methods, data analysis and the variables used for analysis are presented.

Chapter 3 contains the published manuscript titled: **"Implementing Isoniazid Preventive Therapy in a tuberculosis treatment-experienced cohort on ART"**. It was originally submitted to the International Journal of Tuberculosis and Lung disease on 16 Oct 16 and revision 1 of the manuscript was re-submitted on 26 November 2016. The article was accepted for publication on 6 January 2017. All communication with the journal can be found in appendix C. Chapter 3 also describes the findings of the Master's candidate's secondary analysis of IPT implementation and treatment outcomes, a summary of the candidate's and other co-authors contribution to the manuscript as well as references cited within the manuscript.

Chapter 4 provides an overall discussion of the major findings from the study and how the aims and objectives of the study were met. The discussion also compares and contrasts the relevance of the findings with currently published evidence, in addition to presenting the role of the pharmacist in IPT implementation and provision. Study limitations are highlighted and recommendations for clinical practice and future research are also put forward. The concluding statements summarise the findings and how they support integration of current practices in the field of HIV and TB services.

The appendices contain ethics committee approval for the study, communication with the journal editors, the capabilities of the computerised dispensing system used at pharmacy to integrate IPT and

ART dispensing, data collection documents and tools, as well as other supporting documents relevant to the study.

CHAPTER ONE: INTRODUCTION

1. CHAPTER ONE: INTRODUCTION

1.1 Background: Scale of the problem

Human immunodeficiency virus (HIV) is the one of the strongest risk factors for developing Tuberculosis (TB) in those with latent tuberculosis infection (LTBI), which occurs when an individual is infected with *mycobacterium tuberculosis* but does not have active TB disease (1, 2). The risk of developing TB in the 37 million people living with HIV globally is between 16 -27 times higher than the risk in the rest of the world's population (1). In terms of the burden of disease, 10% of all incident TB cases were among people living with HIV and, of these 74% are from African countries (1, 3). The proportion of TB cases who are co-infected with HIV may exceed 50% in parts of southern Africa. The latest World Health Organisation (WHO) report indicates that TB remains the leading cause of mortality amongst people infected with HIV (1). Of the 1.7 million deaths due to TB, approximately 0.4 million deaths occurred amongst HIV infected people in 2016 (1, 4).

Moreover, the rates of TB recurrence after treatment completion have also been shown to be higher in HIV positive people compared to HIV negative people (5-7). Among HIV negative individuals there is a 5 – 10% lifetime risk of LTBI progressing to active disease within the first five years of TB exposure (2). For people living with HIV their annual risk for TB acquisition is between 5-10% and progression from LTBI to active TB is most likely to occur 12-18 months after infection (2, 8). In a country like South Africa (SA), defined by WHO for the period 2016–2020 as one of 14 countries that carry a triple threat of a high TB burden, a high dual TB/HIV burden and a high MDR TB burden (1) targeted TB and HIV prevention strategies are therefore critical public health interventions to reduce the morbidity and mortality associated with TB infection.

TB preventive therapy is defined as the provision of one or more anti-TB drugs for LTBI in HIV positive individuals in order to prevent progression to active disease (9, 10). LTBI can be diagnosed using a tuberculin skin test (TST) or interferon-gamma release assay (IGRA) (9). Interventions include the provision of antiretroviral therapy (ART), co-trimoxazole therapy (CPT) provision and the roll-out of the Three I's for HIV/TB management: intensified case-finding of TB (ICF), isoniazid preventive therapy (IPT) and infection control for TB (11, 12). ICF and initiation of anti-TB treatment decreases the infectiousness of TB cases and reduces the risk of subsequent disease transmission and associated morbidity and mortality (12). Routine screening for active TB provides the opportunity to offer prophylaxis, such as IPT, to those who do not have signs and symptoms of TB. As part of IPT, treatment of TST positive HIV-infected patients with isoniazid (INH), reduces their lifetime risk of active TB to 4% or less (8).

INH was first discovered in 1912 and introduced for TB treatment in 1952 as one of the first drugs to treat TB effectively (13). INH remains one of the most potent TB drugs after more than 60 years of use and is relatively cheap to use for both treatment and prevention (13, 14). Although INH-resistant TB remains a challenge, high dose INH is still being used effectively to treat multi-drug resistant (MDR) TB cases (15). IPT has been the gold standard of TB preventive therapy for decades due to its known tolerance, potency and cost effectiveness and has established its place as a standard drug for TB prevention in resource-limited settings (12). More recently, the United States Food and Drug Administration (FDA) has approved the use of other drug regimens such as rifapentine (RPT) in combination with INH as TB preventive therapy, while other drug regimens testing different combinations, different dosing strategies and shorter courses are currently being investigated in clinical trials of both HIV infected and uninfected people (9).

Implementation of TB preventive therapy is improving globally, however not all people eligible for IPT are able to access prevention according to the 2017 Global TB report (1). Based on data from 60 countries, a total of 940 269 people who were newly enrolled in HIV care were started on TB preventive treatment in 2016. South Africa accounted for the largest share of the total (41%), followed by Mozambique, Zimbabwe and Malawi. Furthermore, of the 751 620 people newly initiated on HIV care in SA in 2016 approximately 385 932 are on IPT placing IPT coverage at 51% (1, 16). Promotion of IPT by healthcare workers (HCWs) and uptake of IPT by patients has been impeded by several factors. These include the lack of a standardised approach to exclude active TB disease, the fear of promoting INH resistance, additional pill burden, potential for additive side effects and the need for monthly clinic visits to assess for TB symptoms (17-19). Concerns regarding the optimal duration of treatment and the durability of the protective effect after IPT is stopped may be included as barriers to IPT scale-up (20).

1.2 Context for the study: The importance of IPT implementation

The integration of HIV and TB prevention care and treatment services to reduce morbidity and mortality caused by TB disease in people living with HIV is recommended to promote both convenient uptake of treatments by patients and to reduce complexity in providing treatment by HCWs (21). Best practices and models that have been used to integrate delivery of TB and HIV medication can be used to deliver IPT (22, 23). In Figure 1, a fully integrated service is proposed whereby a combined package of HIV and TB care is offered by healthcare personnel who are cross trained to provide screening, treatment and preventative therapy in a standardised approach to TB and HIV service delivery.

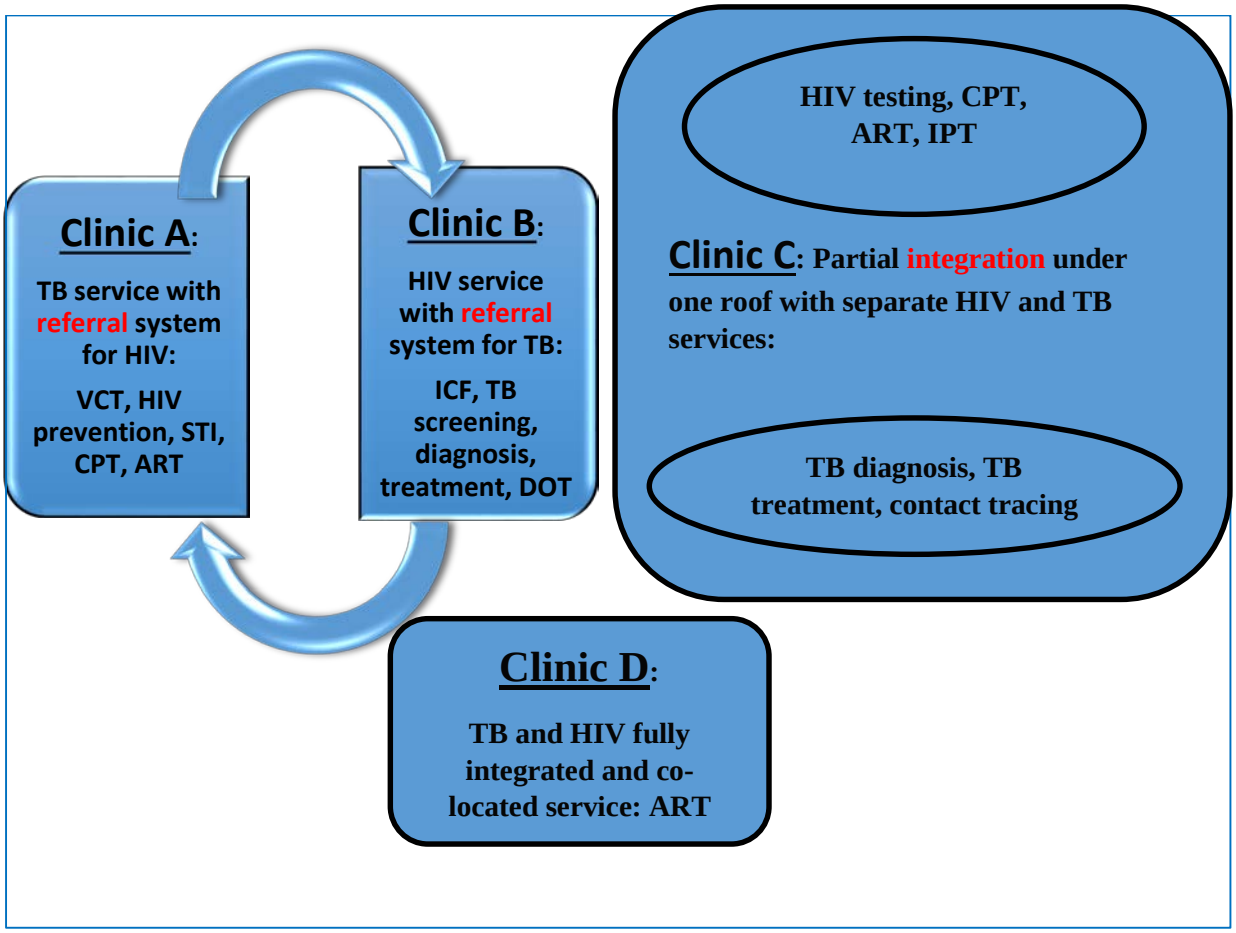

Figure 1: Integrated TB and HIV service delivery adapted from various models (22, 23)

As an important public health intervention for preventing the progression of LTBI to active TB disease among people living with HIV (24-26) IPT provision has been included in the WHO Stop TB and the new End TB strategy (27). Key WHO recommendations for TB strategies (Figure 2) have evolved as follows (27):

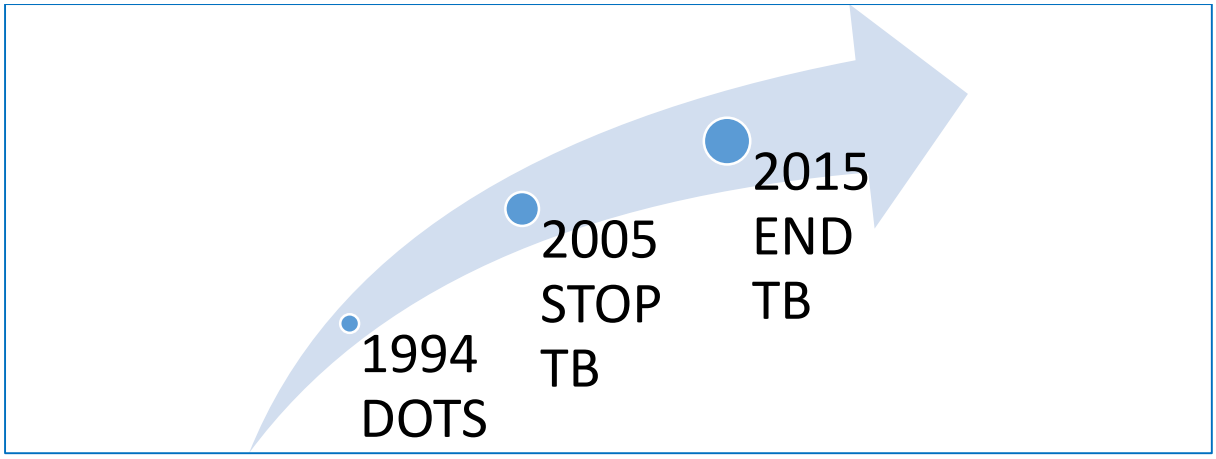

Figure 2: Progression of WHO global TB strategies (27)

- The Directly Observed Therapy (DOTS) strategy focused on government commitment, passive case finding, standardized treatment for all confirmed sputum smear positive TB, adequate drug supply of all essential anti-TB drugs, as well as establishment of a monitoring and evaluation system
- STOP TB strategy propagated the pursuit of high-quality DOTS; address the challenges of co-infection (TB/HIV) as well as MDR-TB; health system strengthening; engagement of all healthcare providers, people with TB and communities, create, promote and enhance research opportunities
- Going forward, the END TB strategy (Table 1) takes the following approach: Integrated, patient-centred care and prevention, bold policies and supportive systems, intensified research and innovation (27)

Table 1: End TB strategy 2015:WHO package of interventions for country level adaptation (27)

END TB PILLARS AND PRINCIPLES		
PILLAR 1	PILLAR 2	PILLAR 3
Integrated, patient-centred TB care and prevention	Bold policies and supportive systems	Intensified research and innovation
PRINCIPLES		
Government stewardship and accountability, with monitoring and evaluation		
Strong coalition with civil society organizations and communities		
Protection and promotion of human rights, ethics and equity		
Adaptation of the strategy and targets at country level, with global collaboration		

The WHO has created the End TB strategy by launching country specific responses to halt the spread of TB and realise the vision of " a world free of TB" (27). The End TB strategy aims to achieve one of the targets of the United Nations Development programme (UNDP) Sustainable Development Goals (SDG), specifically SDG 3, which endeavours to see the end of the TB epidemic by 2030 (28). In the last 12 years, under these directives, TB-related mortality has declined by 36% amongst HIV infected individuals and interventions to prevent, diagnose and treat TB have saved an estimated 37 million people between 2000 to 2013 (28).

The End TB package is based on 3 pillars and 4 principles (Table 1). One of the main components of the first pillar is preventive therapy. Based on country income, availability of resources and classification of TB burden, the WHO has put forward different recommendations for LTBI management (Table 2) which incorporates guidance on provision of IPT or other preventive regimens for LTBI.

Table 2: Current WHO recommendations for LTBI (27)

Recommendations for the management of LTBI	
COUNTRY GROUP	Resource-limited and other middle-income countries with an estimated TB incidence rate of > 100 per 100 000 population High-income and upper middle-income countries with an estimated TB incidence rate of < 100 per 100 000 population
AT RISK POPULATIONS	HIV infected Children under 5 years of age who are household contacts of someone with TB Strongly recommended for the following risk groups: • HIV infected people • Adults and children who are household or close contacts of pulmonary TB cases • Clinical indications - patients with silicosis; patients initiating anti-Tumour Necrosis Factor treatment; patients on dialysis; transplant patients
TESTING ALGORITHM	Investigate to exclude active TB. A LTBI test is not required prior to LTBI treatment, but is encouraged for those that are HIV infected. IGRA should not replace TST. A positive test, either a TST or IGRA test is required to diagnose LTBI.
TB PREVENTION OPTIONS	6 months daily INH 6 months daily INH 9 months daily INH 3 months weekly rifapentine plus INH 3 to 4 months daily INH plus rifampicin 3 to 4 months daily rifampicin

Key: IGRA= interferon gamma release assay; TST= tuberculin skin test

The impact of IPT on improving TB-related mortality and morbidity in HIV infected patients has been investigated (29-31). Although ART lowers the risk of TB due to restoration of immunity, preventive therapy with INH further reduces the incidence of TB compared to ART alone (32). The TEMPRANO study demonstrated six months of IPT combined with early ART resulted in a 44% reduction in risk of severe HIV related illness and reduced all-cause mortality by 35% (31). IPT was shown to decrease mortality amongst TST positive individuals with CD4+ T-cell counts >200 cell/mm^3 in Tanzania (30)

whilst in a study amongst South Africans on ART initiating IPT reported 49% reduction in mortality that remained significant even for those that had a past history of TB (29). Other trials have shown that overall maximum benefits from TB preventive therapy are achieved in HIV-infected persons with a positive TST (30, 33) and that TST positive patients were shown to benefit the most by completing a 36 month IPT course, resulting in a 74% decreased active TB risk and 68% decrease in mortality when compared to 6 months of IPT (34). However, benefit has also been shown among HIV-infected persons in general, regardless of their tuberculin test result (35). The Thibela study, which was conducted among mineworkers in whom HIV prevalence was not established, demonstrated a 58% reduction in TB infection during a 9 month course of IPT (36, 37). However, the protective effect diminished rapidly after IPT course completion. The authors suggest that this could possibly be due to reactivation of inadequately treated LTBI or reinfection caused by high rates of ongoing transmission in this group. (37).

After the earlier policy in 1998, the WHO released updated IPT guidelines in 2011 (Figure 3) and recommended the use of 36 months IPT for the HIV infected and TST positive individuals in high TB-prevalence and transmission settings, based on the results of unpublished studies (12). In 2015, the evidence was re-assessed and the conditional recommendation retained (38). This was significant for adults, adolescent, pregnant women and children living with HIV and those who have successfully completed TB treatment, on ART in settings with high TB and HIV prevalence and transmission.

The first South African (SA) guidelines for IPT were released in 2004 (39), revised in 2010 (10) and again in 2013 as part of the national ART guidelines (40) and subsequently as part of the 2015 national consolidated guidelines (41) (Figure 3). In 2004, the guidance excluded patients with any previous TB episode within the last 2 years, those who had started ART were not offered IPT as there was no evidence of benefit and IPT was not offered to TST negative patients (39). IPT could only be offered once and the protective effect was expected to last 18 months (39). With the evidence-based updates to the guidelines and in keeping with WHO recommendations (Table 3) HIV infected people on ART in SA are to be offered 12 months of IPT if they are TST negative and at least 36 months if they are TST positive (40, 41). TB preventive therapy is now seen as an intervention that should be part of the package of care for the HIV infected people and should be rolled out at all public health services. TB preventive therapy should only be offered under the following conditions: patients are screened for active TB disease before initiation of IPT; providers must follow up and monitor patients to encourage adherence, address side-effects and exclude active TB disease (41).

The criteria for non-eligibility to IPT has also been defined in the current South African guidelines (41):

- confirmed or presumptive active TB

- active liver disease (acute or chronic)
- peripheral neuropathy
- history of adverse reaction to INH
- HIV positive but TST negative in pre-ART care
- excessive alcohol use: more than 28 units per week for men and 21 units per week for women
- previous multidrug-resistant (MDR) or Extensively drug-resistant (XDR) TB
- currently ill and/or are in unstable condition

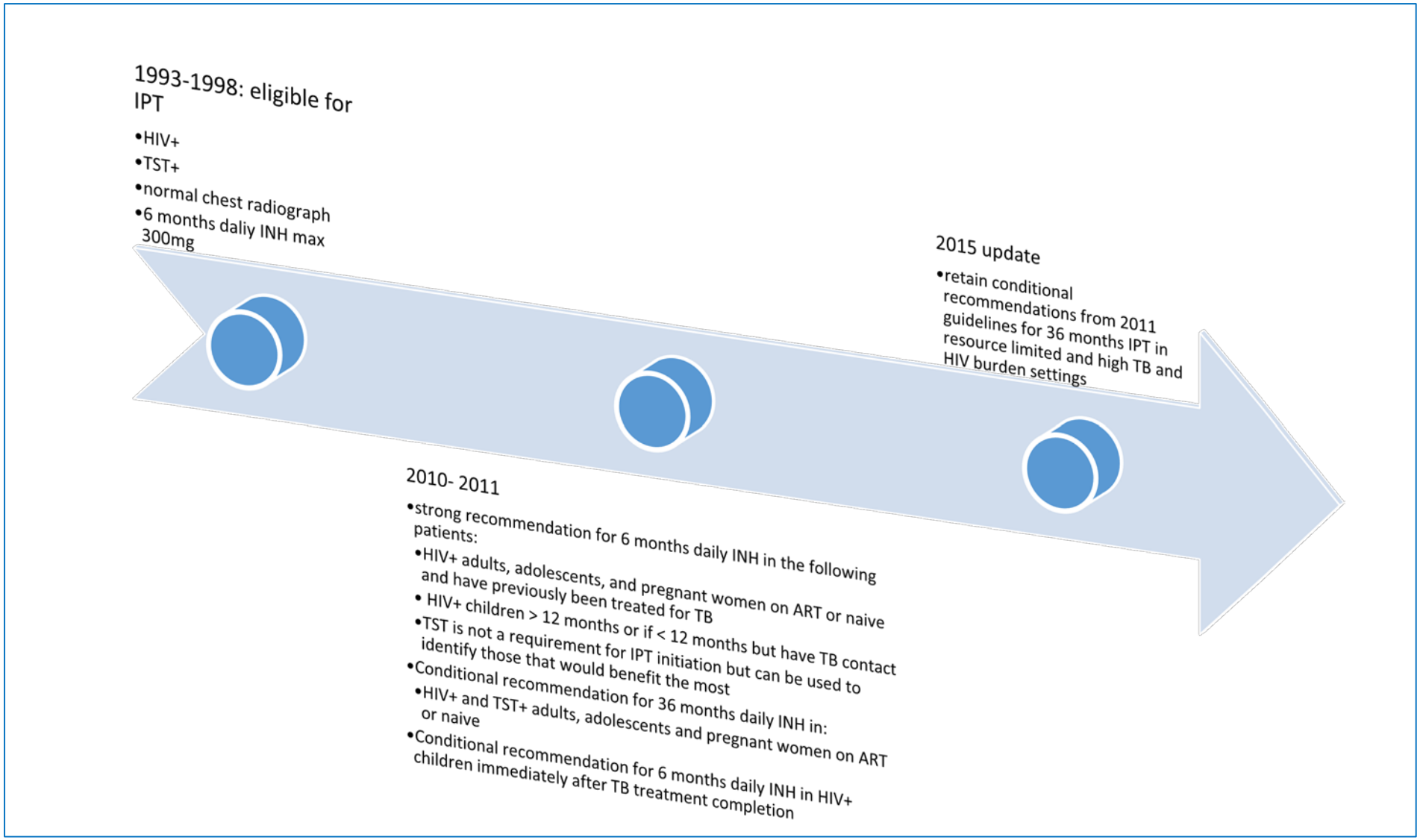

Figure 3: Timeline of WHO IPT guideline evolution [1993-2015] (12, 38, 42)

Table 3: Current SA IPT eligibility criteria (41)

POPULATION	DURATION OF IPT	COMMENT
Pregnant/breastfeeding HIV positive women	TST positive: 36 months TST negative: 12 months TST not available: 12 months	Lifelong ART preferred. Start IPT at any time during pregnancy/breastfeeding, first then add IPT after 1 month. If pregnant while on IPT, continue IPT. If TST negative, re-assess TST status 1 year after completing IPT.
Children <5years old with recent exposure to TB contact regardless of HIV status	6 months	Recent refers to <12 months. If re-exposed to a TB case after completion of 6 months IPT, repeat another course of IPT irrespective of interval between treatment and re-exposure. If child is exposed to new infectious source while on IPT, continue IPT for as long as source remains infectious.
All HIV-positive children up to 15years old with recent exposure to TB case		
Pre-ART patients regardless of CD4 (Adolescent/Adult)	TST positive: 36 months; TST negative: No IPT; TST not available: 6 months; If later TST becomes negative: stop IPT. If later TST becomes positive: extend to 36 months.	Only TST positive get IPT regardless of CD4. If TST negative, re-assess TST status annually in Pre-ART. IPT can be started anytime. If patient becomes eligible for ART while on IPT, initiate ART and continue IPT. If eligible for both ART and IPT, start with ART, followed by IPT when stable on ART.
Patients on ART (Adolescent/adult)	TST positive: 36 months; TST negative: 12 months; TST not available: 12 months. If later TST becomes positive: extend IPT to 36 months.	All eligible for IPT regardless of CD4 count. If TST negative, re-assess TST status and IPT eligibility 1 year after completing IPT.
Former TB adult patients (Excluding MDR/XDR and children)	TST positive: 36 months; TST negative: 12 months TST not available: 12 months; If later TST becomes positive: extend IPT to 36 months.	There must be documented proof of bacteriological cure. If there is no proof of cure, do not give IPT, re-assess for IPT eligibility after 3 months. Can be started immediately after completing TB treatment.

1.3 Literature Review

An extensive literature search on IPT, was conducted from 1980 to the current year 2016, using the following databases: PubMed, Google scholar and WorldCat. Key words and search strings included the following medical subject headings (MeSH): "isoniazid"[MeSH Terms] OR "isoniazid"[All Fields]) AND ("prevention and control"[Subheading] OR ("prevention"[All Fields] AND "control"[All Fields]) OR "prevention and control"[All Fields] OR ("preventive"[All Fields] AND "therapy"[All Fields]) OR "preventive therapy"[All Fields]) AND IPT[All Fields] AND TB[All Fields] AND ("prevention and control"[Subheading] OR ("prevention"[All Fields] AND "control"[All Fields]) OR "prevention and control"[All Fields] OR ("preventive"[All Fields] AND "therapy"[All Fields]) OR "preventive therapy"[All Fields]) AND TB[All Fields] AND ("prevention and control"[Subheading] OR ("prevention"[All Fields] AND "control"[All Fields]) OR "prevention and control"[All Fields] OR "prevention"[All Fields]). Research has focused on IPT use amongst special populations: HIV infected people, prisoners, mine workers, paediatrics and pregnant women. While mine workers are an at-risk population significant within the South African context and setting, the other special populations listed above were excluded from this literature review.

Systematic reviews

A Cochrane Review conducted in 2004 (43) included 8130 participants in 11 trials that demonstrated efficacy of IPT in HIV+ adults with an overall 32% reduction in TB. In 2010, another systematic review aimed at updating the previous review was conducted and also confirmed the above findings (44) after looking at 12 trials with 8578 participants. It was noted that the trials reviewed did not determine if HIV infected patients in high TB burden areas should get repeated courses or lifelong IPT, nor did they provide data on adherence, INH The first South African (SA) guidelines for IPT were released in 2004 (39), revised in 2010 (10) and again in 2013 as part of the national ART guidelines (40) and subsequently as part of the 2015 national consolidated guidelines (41) (Figure 3). In 2004, the guidance excluded patients with any previous TB episode within the last 2 years, those who had started ART were not offered IPT as there was no evidence of benefit and IPT was not offered to TST negative patients (39). IPT could only be offered once and the protective effect was expected to last 18 months (39). With the evidence-based updates to the guidelines and in keeping with WHO recommendations (Table 3) HIV infected people on ART in SA are to be offered 12 months of IPT if they are TST negative and at least 36 months if they are TST positive (40, 41). TB preventive therapy is now seen as an intervention that should be part of the package of care for the HIV infected people and should be rolled out at all public health services. TB preventive therapy should only be offered under the following conditions: patients are screened for active TB disease before initiation of IPT; providers must follow up and monitor patients to encourage adherence, address side-effects and exclude active TB disease (41) or cost effectiveness, effect of HIV disease staging at baseline and optimal duration of therapy.

This review also highlighted the need for clinical trial evaluations of the effectiveness of combined ART and TB preventive therapy.

In 2011 a systematic review on the integration of HIV and TB services amongst sub-Saharan African (SSA) countries (45) described the extent to which integration has occurred at various facility levels and what the overall impact was. This review looked at 56 articles (total number of participants not reported) and those findings specific to IPT and ART provision are highlighted here. Of the 81-93% of HIV positive people screened for IPT, 13- 95% were eventually initiated on IPT. Adherence to IPT was in the range of 75-92% and 6 month IPT completion rates were reported be between 47 – 88%. Some studies reported high IPT lost-to-follow-up rates. The prevalence of HIV was 9 - 85% and uptake of ART was ≤ 41%. This review confirmed the results of the Cochrane review that IPT did decrease the risk of all-cause mortality. IPT was found to be cost effective in comparison to secondary TB cases prevented. The review also reported that IPT reduced TB incidence risk by 62% in TST positive HIV infected individuals (relative risk: 0.38, 95% CI: 0.25 – 0.57) over those that received ART only or no treatment at all.

More recently a systematic review conducted by Ayele *et al.* in 2015, analysed IPT outcomes in comparison to placebo or no treatment in 7619 HIV positive populations from ten randomised control trials (46). Their main findings indicated that overall TB risk was reduced by 35% [RR = 0.65, 95%CI (0.51, 0.84)]. Similar to other reviews, those participants with a positive Tuberculin Skin Test (TST) achieved the most benefit [RR = 0.48; 95% CI (0.29 -0.82)]. A reduced risk of HIV disease progression was seen in all participants [RR = 0.69; 95% CI (0.48 - 0.99)]. IPT did not impact on all-cause mortality; however, 12 months IPT duration reduced risk [RR = 0.65; 95% CI (0.47- 0.90)]. IPT-related drug toxicity risk was not significant [RR = 1.20; 95% CI (1.20, 1.71)].

Specifically relevant to secondary preventive therapy (sPT) in patients previously treated for TB, a systematic review was conducted by Bruins and van Leth (47) that reviewed 4 articles and 1204 participants. They reported a beneficial effect of sPT in reducing TB incidence ranging from 55.0% to 82.1% (RR: 0.18–0.45). Their findings highlighted the following: the optimum duration of preventive therapy remains unknown, the ideal drug regimen/s that should be used is still under debate. sPT use varied from 6 months till 2 years and some drug regimens used included Rifampicin together with INH. The authors also suggested further studies be conducted to assess the impact of combined ART use with sPT as well as drug resistance.

Randomised Clinical Trials

Four major clinical trials to determine the efficacy of IPT have been completed:

BOTUSA Study (34, 48): This study was conducted in Botswana among a total of 1995 black adult miners ≥ 18 years. Only 2% were on ART at enrolment. Forty-five percent started ART at a median of 4 months after enrolment. The cohort comprised of 71% females; the CD4 median was 307 cell/mm^3 (176-457 cell/mm^3), mean CD4 was 220 cell/mm^3 and median age was 32. Patients were randomised to receive 6 months or 36 months IPT. Tuberculin skin tests (TST) were conducted at screening. Incident TB was the primary endpoint, with death being the secondary endpoint. It was found that the IPT protective effect, after a 6-month course, was lost after approximately 200 days. INH resistance was reported as 18% and similar to the known background resistance. Mortality was 1.3% per year. Mortality rates were the same between study groups, but for participants with a positive tuberculin skin test mortality was 3 times lower in the long term IPT group. It was found that a 36-month course resulted in a 43% reduction in incident TB and 74% amongst those who had a positive TST. The use of ART was found to be additive to the protective effect of IPT and did not escalate rates of INH induced hepatitis amongst the cohort. Severe side effects were similar in both arms: 1.4% in the 6-month group and 1.6% in the 36-month group. Study limitations included the following: only 61% of the TB cases in the study were culture positive; ART use was not controlled in the study but rather it was observed; findings may not be generalizable as screening procedures included more laboratory tests and chest radiographs not normally required as part of standard of care at the time.

Thibela Study (36, 37, 49): In the intervention arm of the Thibela Study, active TB screening was used to identify eligible patients and in turn offer them IPT. There was a massive scale-up of IPT provided as a 9 month course among miners in South Africa where 23585 patients started INH from July 06 – 31 Mar 09. In this study, there was a 58% reduction in TB incidence during treatment. However, the protective effect did not last long after treatment was stopped. The authors did report what the duration of the protective effect of IPT was in this study. The eventual overall outcome was that there was no difference between the intervention and control arms in terms of TB prevalence (2.35 % vs 2.14%) or incidence (3.02 vs 2.95 cases per 100 person years). Twenty-six adverse events were recorded: 60 hypersensitivity; 49 peripheral neuropathy; 14 hepatitis; 3 convulsions; 4 serious adverse events (SAEs): 3 hepatitis; 1 definitely related; 1 convulsion; possibly related. There were 33 deaths: 31 not related; 1 possibly related; 1 relationship to INH not coded. There was no evidence of increased INH resistance. The investigators highlighted that for community wide intervention to succeed and TB transmission to be interrupted, there would have to be faster IPT implementation, greater uptake and retention within a programme, in conjunction with ART provision as well as rapid TB case detection and treatment initiation. One of the limitations reported in the study included being unable to determine HIV prevalence among the study patients.

ThRio study (32): was conducted in Brazil to look at TB incidence among 11 026 HIV-infected patients in 29 public clinics in Rio de Janeiro, between September 2003 to September 2005. The cohort was from 16 – 84 years of age, 38.1% were females and more than 50% had CD4 > 200 cells/mm^3, with 73% on ART and 9.9 % on IPT at baseline. Results obtained as follows: 67 TB incident cases [IRR 2.28/100 person years; 95% CI 2.06 – 2.52]; without IPT or HAART, IR 4.01; HAART alone, IR 1.90 (95% CI 1.66 – 2.17); IPT alone, IR 1.27 (95% CI 0.41–2.95); HAART after IPT, IR 0.80 (95% CI 0.38–1.47). It was found that compared to treatment-naive patients, patients receiving HAART after IPT had a 76% reduced TB risk. Limitations reported by the study included: missing data due to the retrospective nature of study; no standardised method of clinical monitoring; reasons for eligibility or non-eligibility for TST; ART and IPT usage was known for some patients but not in others. Also that low IPT uptake could have impacted on TB incidence estimates.

TEMPRANO study (31): was designed to assess 4 different treatment approaches: immediate ART, 6 months of IPT, a combination of immediate ART plus 6 months IPT or deferred ART (until WHO defined criteria were met for initiation). Approximately 2056 adults ≥18 years were randomised to either early or deferred groups for ART and IPT, with > 75% females, median age 35, with CD4 =459 cells/mm^3 (deferred) and 466 cells/mm^3 (early). ART use was 71% in the deferred and 68% in the early group. Early ART effect seen at month 12 was 84% where viral loads were undetectable and at month 24 83% were undetectable. Overall, CD4+ T-cell count remained above 500 cells/mm^3 for 51% of the time. The cumulative probability of death or severe HIV-related illness in the early group was 5.7% and deferred group was 8.8%. The outcome of early ART and IPT initiation was 44% reduction of severe HIV-related illness and 35 % decrease in all-cause mortality (Table 4) when compared to the deferred group. Previous recommendations for early ART initiation were based on observational data; the landmark TEMPRANO study confirmed these findings. However, one of the limitations reported by the authors was that it could not be determined if ART should be started at higher CD4 levels or initiated in all HIV infected participants irrespective of the CD4 count. In a follow up study on the post-trial phase of TEMPRANO (50), the protective effect of IPT on mortality was demonstrated even in people with high CD4 counts on ART, with a 37% reduction in mortality that appeared to be sustainable for up to 6 years.

IPT effect on mortality

Studies conducted in the pre-ART era did not conclusively demonstrate that IPT reduced TB related deaths. In contrast to these pre-ART studies, findings from studies conducted in patients on ART and IPT did demonstrate an effect in decreasing mortality. An earlier study conducted in Haiti in 2000 (Table 4) amongst a mixed cohort HIV negative and positive people on IPT showed no effect on TB related mortality nor was there any protective effect seen among the HIV negative within the cohort(51).

Another 2001 Zambian study in HIV infected people not on ART used different preventive therapy regimens and found none of the regimens had any effect on mortality (52). Patients in Tanzania (30) had a 60% decrease in mortality if they completed IPT successfully. In a study done by Charalambous et al. those South Africans on ART that received IPT experienced significant mortality reduction of 48% if they had a past history of TB and 56% if no prior TB history, when compared to no IPT (7). A 2015 study in Ethiopia (53) demonstrated that the combined effect of ART and IPT reduced mortality by 60%. The major clinical trials like BOTUSA and TEMPRANO also reported statistically significant reductions in mortality in patients on ART and IPT (Table 4).

IPT protective effect duration

There have been inconsistent results reported on the duration of the protective effect offered by IPT amongst users (36, 46, 54-56) which limits implementation of IPT and minimises the potential benefits of IPT especially in high TB/HIV burden areas that are in most dire need of it. While in some high burden settings TB risk among IPT users escalated as soon as treatment was stopped, those that completed longer IPT courses had better long term outcomes (34, 36, 57). A subsequent study on the protective effect post IPT completion in the same cohort in Haiti discussed above revealed that the longer the duration of the IPT course the greater the length of time to TB incidence (Table 4), thereby prolonging the protection offered by IPT (58). The BOTUSA study demonstrated that the IPT protective effect lasted 200 days after 6 months IPT was completed (34). Post-trial data showed that TB cases occurred most frequently within the first year after IPT irrespective of whether the patient received 6 or 36 months IPT (57). A Zambian study demonstrated a protective effect for 2.5 years of follow up, but with steady decline in the effect occurring after the first 1.5 years (52). In Thailand, IPT benefit was significant for the first 6 months after completion before declining; with no difference in TB incidence between those that took IPT and those that didn't, at 4 years post IPT (59). In Uganda, the benefit of 6 months IPT was lost within one year and 3 months PT with INH plus rifampicin or pyrazinamide lasted for up to 3 years (60). The Thibela study also demonstrated loss in protective effect as soon as IPT was stopped (37).

IPT modelling

Mills et al. looked into modelling the effects of community-wide IPT implementation on TB incidence as well as to determine what differences may occur at population and individual level within high burden settings as a result (61). Their model found that TB was almost eliminated in some areas but in others, IPT was ineffective due to continuous re-infection. According to their findings, with the scale up of IPT the protective effect could vary depending on the force of TB transmission in that community. Importantly, while INH resistance may not be impacted at individual level, community wide IPT may increase population level resistance. Sumner et al. used mathematical modelling to investigate whether

IPT was able to 'cure' LTBI in patients on ART and thereby able to bestow increased duration of protection after course completion (62). They calculated the annual risk of infection to be 4.0% (2.6–5.8) and they estimated 35.4% (2.4-76.4) or one third of LTBI had been cured. Their model suggested that 12 months IPT may provide additional long-term benefit in patients on ART in low burden settings only and re-infection in high burden settings would limit the protective effect of IPT. Overall, it must be noted that the very assumptions made in order to construct various statistical models serve as limitations as they influence the final results or predictions obtained from these models. Models may suggest a trend or direct effect that may be over-, under- or incorrectly interpreted. So while modelling may help guide future research endeavours, it cannot confirm nor negate any clinical outcomes with complete accuracy.

Some models from studies conducted in settings like Brazil showed that combined IPT and ART delivery could result in reduction of TB incidence and mortality (55, 63, 64). Researchers in Brazil developed a transmission model using IPT implementation data among patient on ART in the THRio study. The model demonstrated IPT coverage at 20% of 2500 eligible patients every year and after 5 years, IPT had reduced general population TB incidence by 3.0% and in HIV infected by 15.6%; with TB mortality reduced by 4.0% and 14.3% respectively. A group of South African researchers took to modelling data from the Thibela TB study and discovered that very little of the LTBI was cured by IPT provision to gold miners in the study (65). Using the model to demonstrate an optimized IPT rollout only showed 10% increase in impact. The use of additional interventions such as reducing treatment delays, increased ART coverage, improved diagnostics, and continuous IPT with ART use in the model contributed to 30% reduction in TB incidence individually and 75% in combination, after 10 years. In 2015, Reid et al. (66) looked at the same model above in conjunction with another South African based modelling strategy (67) and further emphasized the necessity of a multi-pronged approach of treatment and prevention to end the TB epidemic in SA (66).

Effect on TB incidence

Table 4 includes the TB incidence reported by various clinical trial and observational studies. The benefits of combined ART and IPT are clearly evident with the lowest TB incidence levels occurring in patients on ART and IPT (31, 32, 53, 54, 57, 68). Also, IPT seems to be more effective in those with no history of previous TB or at least 1 past TB episode compared to > 1 episode of TB in the past (29, 69).

IPT secondary to previous TB

Only a few studies have been conducted in which the entire cohort had previous TB infection and were thus exposed to TB treatment; these studies occurred in the pre-ART area: Haller et al. in 1999,

Fitzgerald et al. in 2000 and Churchyard et al. in 2003. Haller et al. found that secondary IPT somewhat reduced mortality but noted a significant decrease in TB incidence as well as adverse events when compared to no IPT (70). In 2000, Fitzgerald et al. reported 72% reduction in TB incidence among HIV infected but no effect in HIV uninfected individuals (51). Churchyard et al. reported that IPT effect was strongest amongst those who had had 1 previous episode of TB specifically with 89% reduction compared to those that had more than one TB episode and that the recurrent TB incident rate increased with decreasing CD4+ T-cell counts (69).

Table 4: IPT implementation outcomes

Study	n	Age/ Race	Previous TB history	ART use	TST status	IPT regimen	IPT outcome		
							TB incidence/P100PY, IR, IRR, HR, aHR, RR, aRR	Mortality or Survival	Important observations
Europe, 1982 IUAT trial (71)	27830	20-64; European	Positive with **fibrotic lesions** excluded	No	No	3H300, 6H300 12H300 or *P*	*P:* no reduction, 3H:21% (RR), 6H 65% (RR1.4), 12H 75% (RR1.0)	1124 (4%) deaths over 5 years; 3 cases due to INH induced hepatitis where INH wasn't stopped at first signs of symptoms. 3 TB deaths all in *P* arm (0.42 /100PY)	Protective effect increased with IPT duration but efficacy of each regimen in comparison to placebo changed gradually during 5 year follow up. The greatest increase in number of TB cases prevented was during 12 to 24 weeks IPT. 6H **defers** rather than prevents TB.
Kenya, 1997 Hawken (72)	684	≥ 18, Black African	No- excluded	No	Positive & negative	6INH300 vs *P*	IR: IPT = 4.29/100PY [95% CI: 2.7–6.33] *P* =3.86/100PY [95% CI: 2.45–5.79] aRR = overall 0.92 (95% CI: 0.49–1.71); TST+ 0.60 (95% CI: 0.23–1.60) TST-1.23 (95% CI: 0.55–2.76) [p=0.26]	aRR for mortality overall: 1.18 (95% CI, 0.79-1.75) TST (+): 0.33 (95% CI, 0.09-1.23) TST (-): 1.39 (95% CI, 0.90-2.12).	70.2% completed treatment phase. INH resistance n=2 (11.8%)

Study	n	Age/ Race	Previous TB history	ART use	TST status	IPT regimen	IPT outcome		
							TB incidence/P100PY, IR, IRR, HR, aHR, RR, aRR	Mortality or Survival	Important observations
Uganda, 1997 Whalen (73)	2736	≥ 18, Black African	No- excluded	No- excluded	Positive and negative	TST (+) randomised to 6H300, 3H600/300, 3RZ600/2000, 6P TST (-) randomised to 6H300 or 6P Monthly visit for 6 months, then 3 monthly	RR compared to placebo: H=0.33 (0.14-0.77); HR= 0.40 (0.18 to 0.86); RZ= 0.51 (0.24-1.08)	overall mortality rate was > in PPD (-) than in the PPD (+) (P=0.001) but no difference in survival observed between the two groups Year 1 PPD (+) = 0.78 PPD (-) = 0.90 (P=0.001 by the log-rank test). TB cases: 20% mortality rate	6H300 reduced TB by 67% with minimal side effects compared to other regimens. Duration of protective effect was not established.
Zambia, 1998 Mwinga (74)	1053	≥ 15, Black African	Not reported	No	Positive and negative	3RZ600/3500 twice weekly VS 6H900 twice weekly VS placebo (3P twice weekly or 6P twice weekly)	IR p100PY/crude RR: H Arm- 2.74/0.56 vs P; RZ Arm- 3.16/0.65 vs P; P Arm- 4.94/0.6 for RZ or H vs P	185 deaths, mortality increased with follow up time but no change in effect; higher mortality associated with non-compliance, TST negative and Hb	96 cases (59 TB & 37 probable) TB rate increased and protective effect decreased with time= after 18 months i.e. 1 year post completion (p=0.25) Most effective in those with Lymphocyte count $2X10^9$ /l or higher, TST+ and Hb ≥ 10mg/dl
Africa, 1999 Haller (70)	263	≥ 18, Black African	Yes	No	Not known	6H300+ SP	↓ TB incidence (log rank test: p = 0. 0234),	Decrease in mortality (log rank test: p = 0.1736)	reduction of adverse events and sick days [22 (IPT) VS 77 (control)] prevention of wasting (p = 0.008) and anaemia (p = 0. 045)

Study	n	Age/ Race	Previous TB history	ART use	TST status	IPT regimen	IPT outcome		
							TB incidence/P100PY, IR, IRR, HR, aHR, RR, aRR	Mortality or Survival	Important observations
Haiti, 2001 Fitzgerald (51)	288	≥ 18, ?race	Yes	No	Negative	IPT=12H300 vs 12P, no DOT	*P* Arm IR 7.8 (4.1-13.3) IPT Arm 1.4 (0.0-3.4) 1 TB case during IPT	IPT did not affect mortality	TB regimen: 2RHZ daily regimen, weekly clinic visits, no DOT CP=4RH 2 X weekly regimen, DOT IPT had no effect on HIV negative 82% reduction TB recurrence occurred in those with HIV symptoms
Zambia, 2001 Quigley (52)	1053	≥15, Black African	No- excluded	No	Positive and negative	6H900 bi weekly, 3RZ600/300 bi weekly, 3*P* and 6*P*	IR: H: 3.0 /100PY, RZ: 3.7/100PY, P: 4.3/100PY	Higher mortality in RZ than placebo (confounding effect). Median survival time from TB diagnosis=33 months. PT did not slow HIV progression or affect mortality.	PT effect strongest on TST+ in the 1st 1.5 years TB protection for both H and RZ lasted 2.5 years compared to placebo RR: 0.54 (95% CI: 0.31-0.95; p= 0.033) No difference in TB incidence in H and RZ arms
South Africa, 2003 Churchyard (69)	559	≥ 18, Black African	Yes; previous MOTTS, unknown treatment failures and outcomes excluded	No	Not done / not reported	Indefinite H300	Overall 55% TB reduction aIRR: IPT- 0.45 (95% CI: 0.26–0.79); Control=1 IR: IPT: 8.6/100PY; Control: 19.1/100PY	Mortality rate ratio: 0.70 (95% CI: 0.39–1.24) p=0.22	IPT effect was strongest amongst the men who had 1 episode of MTB specifically: 89% reduction (IRR 0.11; 95% CI: 0.04–0.27). If >1 TB episode: IRR= 2.47 (0.30–20.5) Recurrent TBIR increased with decreasing CD4: (CD4 cell count ≥500 cells/mm^3: 6.9/100PY; 200–499 cells/mm^3: 8.6/100 PY; ≤ 200 cells/mm^3: 18.8/100PY; P trend=0.008)

Study	n	Age/ Race	Previous TB history	ART use	TST status	IPT regimen	IPT outcome		
							TB incidence/P100PY, IR, IRR, HR, aHR, RR, aRR	Mortality or Survival	Important observations
South Africa, 2005 Grant (36)	1655	≥ 18, Black African	Yes	No	Not done	6H300 or 12H00 if co-infected with silicosis	Prior to clinic enrolment TB incidence= 11.9 p100PY. After clinic TB incidence= 9p100PY; IRR=0.78(p=0.1) aIRR=0.68(p=0.03) (so TB incidence still remained high)	95 deaths (15%)-causes not reported	TB incidence ↓by 38% overall and by 46% if had no TB history. TB risk associated with increasing age, TB history, baseline WHO stage 3 and 4, silicosis grade probable or higher Short follow up time may account for higher protective effect than would be seen with longer follow up
Brazil, 2007 Golub (32)	11026	≥ 18, mixed race	Yes	Yes	Positive + negative	6H300	IR overall: 2.28/100PY (2.03-2.52) No ART or IPT: 4.01/100PY ART: 1.90/1000PY (1.66-2.17) IPT: 1.27/100PY (0.41-2.395) ART + IPT: 0.8/100py (0.38-1.47) 76% TB risk reduction (P<0.001) with IPT + ART use	Not assessed	Past history of TB ↑risk of TB during follow up for patients with higher CD4 ↑age ↓TB risk especially with lower CD4

Study	n	Age/ Race	Previous TB history	ART use	TST status	IPT regimen	IPT outcome		
							TB incidence/P100PY, IR, IRR, HR, aHR, RR, aRR	Mortality or Survival	Important observations
Tanzania, 2008 Munseri Ex-Dar Dar Study patients (75)	1975	≥ 18, Black African	Not known/not reported	No	Positive	6H300	Not provided	6 deaths (8%) none related to IPT	91% IPT uptake, 87% completed. Of the 13% Non- completion cohort: 4% Dr initiated, 7% patient and 1% death (not due to INH). Completers had a family member / friend with TB (65% vs.12%, 95% CI: 0.185–0.875, P < 0.03), think IPT was important (100% vs. 87%, 95% CI: 0.063–0.197, P < 0.001), found counselling helpful (91% vs. 63%, 95% CI: 0.0574–0.5086, P < 0.007), had family approval for their decision to take IPT (97% vs. 50%, 95% CI: 0.1411–0.6389, P < 0.001), clinic was close to their residence (72% vs. 43%, 95% CI: 0.01–0.672, P < 0.04). Reasons reported for IPT completion: fear of TB 44%, understanding of the importance of IPT 32%, fear of TB and HIV complications 22% and other 2%. Reasons for non-completion: fear of INH side effects 14%, travel distance to the clinic 14%) and spouse's advice 14%. Females were more likely to stop then males. Counselling and social support had impact on completion.

Study	n	Age/ Race	Previous TB history	ART use	TST status	IPT regimen	IPT outcome		
							TB incidence/P100PY, IR, IRR, HR, aHR, RR, aRR	Mortality or Survival	Important observations
South Africa, 2009 Golub (68)	2778	≥ 18, Black African	No – excluded	Yes	Yes	6H - dose not reported	No IPT and no ART: IR: 7.1/100PY; 95% CI: 6.2-8.2 IPT then ART: 85%↓ (IR=1.1/100py; IRR=0.15; 95% CI: 0.004-0.85) ART only VS No IPT and no ART: 35% ↓ IR: 4.6/100PY; IRR=0.65; 95% CI: 0.46-0.91 IPT only VS treatment naïve: 27 %↓ IR=5.2/100PY; IRR=0.73; 95% CI: 0.44-1.13 ART VS treatment naïve: 64% aHR=0.36; 95% CI 0.25-0.51) IPT VS treatment naïve: aHR=0.87; 95% CI: 0.55-1.36 IPT +ART VS treatment naïve: 89% aHR=0.11; 95% CI: 0.02-0.78	Not provided	Overall uptake = 13%; Urban cohort = 17%; Rural cohort =1%. Men more likely to get TB (IRR 1.46; 95% CI: 1.09-1.94) 30 – 49 years ↑TB risk than < 30 years
Botswana, 2010 Mosimaneotsile BOTUSA Study (48)	1995	≥18, Black African	Yes	Yes	Positive and negative	6H300	8 TB cases (0.4%) Lower TB rate attributed to concomitant ART	20 deaths (1%)	6H open label phase of BOTUSA Study Initially weight dependant dosing: 300mg: 30-49 kg 400mg: ≥ 50kg; then changed in Jan 2006 – 300mg all
South Africa, 2010 Charalambous (29)	3270	≥ 18, Black African	Yes 7.2% overall, 2.5% in IPT arm	Yes	Not reported	6H300	IPT: 3.71/100PY no IPT: 11.08/100PY. HR IPT arm: 0.34 (95% CI: 0.24 – 0.49).	Overall mortality 8.9/100PY; IPT associated with decreased mortality (aHR: 0.50, 95% CI: 0.32 – 0.80)	Those with a past history of TB aHR 0.52 (95%CI 0.32 – 0.82); those with no TB aHR 0.44 (95% CI: 0.22 – 0.89)

Study	n	Age/ Race	Previous TB history	ART use	TST status	IPT regimen	IPT outcome		
							TB incidence/P100PY, IR, IRR, HR, aHR, RR, aRR	Mortality or Survival	Important observations
Tanzania 2011 Kabali (30)	586	≥ 18, Black African	No	Yes Baseline & during follow up	Positive	6H300 IPT completers VS non-completers	No difference on TB incidence between IPT completers and non-completers HR=0.6 (95% CI: 0.3-1.3; log-rank P=0.92)	IPT completers had longer survival p<0.001, 60% ↓ in mortality, HR=0.4 (95% CI: 0.2-0.8)	Non-significant protective effect of IPT aHR=0.6 (0.3-1.3) 4.5 % non-completion rate
Botswana, 2011 Samandari BOTUSA Study (34)	1995	≥ 18, Black African	Yes	Yes 2% Baseline & 45% during follow up	Positive & negative	6H+30*P* vs 36H 300mg <50kg; 400mg ≥50kg	(HR 0.57; 95% CI: 0.33-0.99; p=0.047) 36H=↓TB incidence by 43% (In TST+: 74%) IPT arm: ART+IPT=50% TB reduction TST + 36H VS 6H HR: 0.26 (95% CI: 0.08-0.80, P=0.02) during trial; 0.33 (95% CI: 0.16-0.68; P=0.003) trial and post-trial; 0.40 (95% CI: 0.15-1.08; P= 0.07) post trial	TST+ had 3 times lower rates of TB and mortality. Mortality: TST + 36H VS 6H HR: 0.32 (95% CI: 0.11-0.90, P=0.0031) during trial; 0.41 (95% CI: 0.18-0.91; P=0.028) trial and post-trial; 0.62 (95% CI: 0.17-2.32; P= 0.48) post trial If CD4> 200 cells/mm^3: HR 0.26 (0.09-0.71) p<0.05 post-trial if 360 days ART VS no ART: HR 0.36 (0.17-0.75)	TST- had no significant IPT benefit but had ART benefit CD4>200 had more IPT benefit then CD4<200 IPT effect lasted 200 days post IPT completion

Study	n	Age/ Race	Previous TB history	ART use	TST status	IPT regimen	IPT outcome		
							TB incidence/P100PY, IR, IRR, HR, aHR, RR, aRR	Mortality or Survival	Important observations
South Africa 2011, Martinson (76)	1148	≥ 18, Black African	Not reported	No	positive	3RPT900/ H900, 3R600/ H900, 36H300, 6h300	TB IR: RPT/H- 3.1/100PY, RH-2.9/100PY, 36H- 2.7/100PY, 6H- 3.6/100PY(P>0.05 for all comparisons)	66 deaths overall incidence: 1.6 /100PY. no significant differences between the 3 cohorts and the control group (P>0.05 by log-rank test) 36H300 had lowest mortality and TB rate from all the groups	no additional benefit of 36H300 reported but this group had more discontinuations. Also post hoc analyses showed 36H300 effectiveness was lost when treatment ended but duration of protection not reported.
Botswana, 2011 Gust BOTUSA Study (77)	1995	≥ 18, Black African	*Yes-Not reported	Yes	Not done/ not reported	6H+30P vs 36H 300mg <50kg; 400mg ≥50kg	not assessed	Not assessed	Men had higher risk of non-adherence and LTFU (aOR: 2.24, 95% CI: 1.24-4.04) and (aOR: 3.08; 95% CI: 1.50-6.33) respectively. Self-reported reasons for non-adherence and LTFU: work commitment (18.9%; 19.3%), side effects (15.8%; 6%), thought they had completed study [but had not] (17.5%; 13.3%), relocated (7.9%; 18.1%),

Study	n	Age/ Race	Previous TB history	ART use	TST status	IPT regimen	IPT outcome		
							TB incidence/P100PY, IR, IRR, HR, aHR, RR, aRR	Mortality or Survival	Important observations
Ethiopia ,2014 Yirdaw (54)	5407	≥ 18, Black African	Not reported	Yes	Not done	6H300 for adults	TB IR: No intervention: 9.1, IPT only: 2.4, IPT before ART: 2.2, ART only: 6.9, IPT & ART simultaneously: 2.5, IPT after ART: 1.5 TBIR overall: IPT=0.7 P100PY & No IPT=6.1 P100PY [IRR:0.11(0.08-0.15)] Combined effect IPT plus ART compared to ART only = TB incidence↓ by 57% [IRR:0.43; 0.18-0.86]	Reported as patients lost to follow-up or dead IPT before ART=9% ART only=39% IPT and ART simultaneously=17%, IPT after ART= 9% overall among ART patients = 24%	IPT effect persisted even though IPT completion wasn't documented. First six months on ART was highest TB risk =8.00 P100PY, then pre – ART= 3.9 P100PY; risk then↓ as time on ART↑. Modelling shows that tripling the IPT initiation within a 2-year period would ↓ TB by 27% 39% uptake of IPT=2131, completion only documented in 24% of those who started
South Africa, 2014 Rangaka (78)	1329	≥ 18, Black African	Yes	yes	TST & IGRA positive & negative	12H vs 12*P* Dose: 200mg < 50kg 300mg ≥ 50kg	TB IR: IPT-2.3/100PY, (95% CI: 1.6–3.1), Placebo-3.6/100PY, 95% CI: 2.8–4.7); HR 0.63,(95% CI 0.41–0.94)→ 37% TB reduction with ART + IPT	overall rate all-cause mortality= 1/100PY 12H= 0.9/100PY 12*P*= 1.2/100PY HR 0.72 (95% CI: 0.34–1.34, log-rank p=0.32) 37 deaths: TB=8 (2 INH and 6 placebo) non-TB=13 unrelated to the study drug (6 INH and 7 placebo) unknown reasons =16	Effect was greatest in 1st year and then decreased over time. Insufficient statistical power to show formal interaction by time since randomization. No difference between IPT and Placebo arms for adverse effects, no additive toxicity due to concurrent IPT and ART. Contrary to other studies, both IGRA and TST negative patients benefited from IPT (aHR for patients with (-) tests 0·43 [0.21–0.86] and 0.43 [0.20–0.96]; for (+) tests 0.86 [0.37–2.00] and 0.55 [0.26–1.24]. Authors supported this finding -cited these may be false negative results in high TB burden areas especially in lower CD4 counts.

Study	n	Age/ Race	Previous TB history	ART use	TST status	IPT regimen	IPT outcome		
							TB incidence/P100PY, IR, IRR, HR, aHR, RR, aRR	Mortality or Survival	Important observations
Botswana, 2015 Post-trial BOTUSA study, Samandari (57)	1678	≥ 18, Black African	Yes	Yes 2% Baseline & 72% by Jun 11	Positive & negative	6H+30*P* vs 36H 300mg <50kg; 400mg ≥50kg	Post-trial period TB IR 36H (n=851): 0.93 6H (n=827): 1.13 TST +: 1.3/100PY	Mortality during trial = 1.4%; post trial-106 deaths: 0.6(6H) & 0.4% (36H); in TST+ 36H: deaths ↓63% after IPT (HR 0.37, p=0.088) and during & after trial ↓59% (HR 0.41, p=0.028) For death post-trial - If CD4> 200 cells/mm^3: HR 0.26(0.09-0.71) =74% and if 360 days ART VS no ART, HR 0.36 (0.17-0.75)=64%	98 incident TB cases- 83% DS, 6H: 4 cases DR & 36H: 1 DR; I MDR case in each arm
Tanzania 2015 Shayo (79)	1303	≥ 10, Black African	TB within last 2 years excluded	Yes	Not done / not reported	6H300 for adults	Not provided	1 death- cause not reported	1255 completed, 28 did not. Levels of acceptability, adherence and IPT completion were found to be all high.
Ethiopia 2015 Ayele (53)	1922	≥ 15, Black African	No	Yes	TST Not done	6H300	ART+IPT vs ART: aHR:0.40; (95 % CI: 0.18- 0.87) On ART, no IPT: aHR: 1; No ART, no IPT: aHR: 1.36 (0.97, 1.91) No ART, + IPT: aHR- 1.86 (0.68, 5.10)	258 cases reported as either developed TB or deceased (13.4 %)	IPT uptake 374 (19.4 %) The IPT-specific benefit in patients not on ART not assessed due to high rates of ART initiation.

Study	n	Age/ Race	Previous TB history	ART use	TST status	IPT regimen	IPT outcome		
							TB incidence/P100PY, IR, IRR, HR, aHR, RR, aRR	Mortality or Survival	Important observations
Ivory Coast, 2015 Temprano Study (31)	2056	≥ 18, Black African	Yes	Yes- early & deferred	TST not done. IGRA positive and negative	6H300- no IPT, early IPT, IPT deferred or none (ART+IPT)	IPT vs no IPT: aHR-0.43 (0.19-0.99) for those with positive IGRA. For negative IGRA: aHR-0.58 (0.21-1.61)	Cumulative probability of death or severe HIV-related illness: Early group=5.7%, Deferred group=8.8% → Early ART+IPT ↓severe HIV-related illness in by 44% and all-cause mortality by 35% Risk of death 35% decrease compared to deferred group.	Early ART effect: @M12-84%VL undetectable & @M24- 83%VL undetectable. Overall, CD4 remained>500 cells/mm^3 for 51% of the time. Cumulative probability of grade 3 and 4 illness/event: Early group=6.2% Deferred group=6.9%
Ethiopia, 2015 Assebe (80)	588	≥18, Black African	No- excluded	No	Not done	6H300 vs no IPT	IR: IPT arm- 2.2/100PY (1.29-3.82); no IPT= 5.06/100PY (3.65-7.02); overall TB incidence =3.78/100PY. aHR 2.02 (95% CI,1.04 -3.92) TB free survival in IPT group at 36m=93% and no IPT group=87% No IPT group had 2X higher risk for TB than IPT group	Not provided	Predictors of high TB risk: WHO stage 3 or 4 CD4<350 cells/mm^3 and 350-499 cells/mm^3 OI in the past

Study	n	Age/ Race	Previous TB history	ART use	TST status	IPT regimen	IPT outcome		
							TB incidence/P100PY, IR, IRR, HR, aHR, RR, aRR	Mortality or Survival	Important observations
Democratic Republic of the Congo, 2015 Yotobieng (81)	1532 adults	≥ 15, Black African	Yes	Yes	not reported	6H300	Not provided	Not provided	Findings for children not included here 73.7% uptake of IPT- of these 88.2% completed course; patients on ART at IPT initiation were more likely to complete IPT than those who were not (89.2 vs. 83.3%; aOR1.54 (95%CI1.02-2.32).
Swaziland, 2017 Mueller (82)	288	≥ 16, Black African	Yes, n=24 within last 6 months	Yes	217 TST (+), 47 converted to (+) at next TST 6 months later	36H300	5 (1.7%) initiated TB treatment 0.7/100 person-years (95% CI 0.3–1.7/100PY). 2 DS PTB , 1 TB spine, 2 INH mono-resistance	N= 5 (1.7 %)	Toxicity reported in year 1= 5.6% (15/286), year 2= 2.0% (5/253), year 3= 0.9% (1/234) 286 (99.3%) started IPT: 253 (87.8%), 234 (81.3%), and 228 (79.2%) were still on IPT after 48, 96, and 144 weeks. 40 patients did not complete IPT: n=21 defaulted (17/21 defaulted ART too) n=16 toxicity, n= 2 stopped IPT after 6 months in error instead of 36 months. N=9 patients (3.1%) transferred out while on IPT. Age, high CD4 at IPT entry, no adverse event and clinic were associated with better retention (p< 0.001).
Ivory Coast, 2017 Badje (50)	2056	≥ 18, Black African	Yes	Yes- early & deferred	TST not done. IGRA positive and negative	6H300- no IPT, early IPT, IPT deferred or none (ART+IPT)	Reported previously	37% reduction in mortality; absolute reduction of −2. 79% in the probability of mortality 6 years after enrolment	First RCT to demonstrate that IPT ↓mortality in adults on ART with high CD4 cell counts Max benefit achieved if ART and IPT combined not given separately

Key: H=isoniazid, R=rifampicin, Z=pyrazinamide, E= ethambutol, P=placebo, PY=person years; P100PY= per 100 person years, OI=opportunistic infection; HR=hazards ratio; aHR=adjusted hazards ratio; CI= confidence interval, IP=intensive phase, CP= continuation phase, DOT= directly observed therapy, IR= incidence rate, IRR= incidence rate ratio; HR= hazards ratio, PT=preventive therapy; GI=gastrointestinal; LTFU= lost to follow-up; Hb=haemoglobin, 6H300= 6 months of isoniazid at 300mg where 6 is duration in months H is the drug (isoniazid) and 300 is the dose in mg.

Resistance to INH

Continued surveillance for isoniazid resistance is essential. Balcells et al.(14) carried out a systematic review of 13 studies spanning a time period from 1951-2006 on resistance data collected from approximately 35000 patients on INH or placebo. Three of the 13 studies included HIV infected people from Africa (Zambia, Uganda and Kenya). The review highlighted the lack of INH resistance data. The relative risk was found to be 1.45 (95% CI; 0.85-2.47); similar in both HIV positive and negative patients and therefore indicative of no increase in INH resistance. Since the absolute risk of INH resistance could not be ruled out, it was put forward that active TB had to be excluded prior to IPT initiation and monitoring for INH resistance needed to continue.

In 2010, Van Halsema et al. studied TB outcomes in miners following exposure to IPT in the Thibela study (35). They reported the following INH resistance levels: 12.1% in first time TB cases and 7.7% among retreatment cases; the control group used in this study, consisting of TB cases identified in the Thibela study control cluster cohort, had 6.0% and 18.7% respectively in the first time and retreatment TB cases. The prevalence of isoniazid resistance among those exposed to IPT was similar to results obtained in a survey in the 1990's of 7.3% in first time TB cases and 14.3% in retreatment cases. The conclusion was that INH resistance after IPT was found to be similar to that of the background resistance and so fear of INH resistance should not hamper efforts to scale up IPT.

The South African Tuberculosis Drug-Resistance Survey 2012-14 (83) reported an increase in both Rifampicin [from 3.4% (95% CI: 2.8%-3.9%) to 4.6% (95% CI: 3.5%-5.7%)] and INH [currently 9.3%; 95% CI: 7.9%-10.7%] resistance from the previous survey in 2002. INH mono-resistance was up to 4.9% (95% CI: 4.1%-5.8%) from 2.7% (95% CI: 2.2%-3.2%). Fear of INH resistance remains a hindrance to fast tracking IPT implementation as prescribers still perceive IPT to perpetuate INH mono-resistance. The report also pushes for risk benefit analysis of IPT to investigate its contribution to the increase in INH mono-resistance. It should be noted that resistance levels reported in this survey are after 10-year time period and IPT uptake in SA has increased only in the last few years. Other factors should also be considered when investigating the contributing factors to INH resistance. However, a risk benefit assessment of IPT in the SA context is highly warranted to further inform relevant stakeholders and policy makers.

Adherence to IPT

Table 5 summarise studies in SSA that reported data on IPT adherence, either by pill count, patient recall, course completion, pharmacy refill or clinic visit attendance. In 2007 reports on poor adherence to IPT at proTEST study sites in Zambia and South Africa cited socio-economic reasons such as poverty, non-disclosure as well as adverse effects (24). Around this time ART was being introduced

through the state sector and the benefit of ART use with IPT was not known. However subsequent studies conducted in Botswana (48) in 2010 and in Ethiopia (84) in 2014 both found ART to improve and enhance adherence to IPT. In addition the study in Ethiopia identified other predictors of both adherence and non-adherence where being adherent was supported by receiving information on IPT and factors that contributed to non-adherence included forgetfulness and to a lesser extent illness, side effects, stigma and being away from home (84).

When the recommended 6 month INH course for IPT was studied in comparison to other regimens, researchers who conducted the study in 2011 reported that adherence was higher in the regimens that were of shorter duration viz. 3 months of rifapentine (RPT) and INH (76). The BOTUSA study showed a statistically significant association between IPT and concurrent ART use (48). Other recent studies of combined IPT and ART use in 2015 also showed high adherence for the duration of follow up at levels greater than 90% (31, 85). The studies included in Table 5 are representative of populations from high TB and HIV burden countries in SSA with some ART coverage in the more recent years and thereby able to reflect IPT adherence outcomes in the context of ART use.

Makanjuola et al. conducted a qualitative systematic review on factors associated with IPT adherence (86). Five themes were highlighted as findings: personal beliefs, issues related to HIV and ART, socio-economic issues, family and other psychosocial issues, and healthcare provider relationship. The fear of experiencing stigma related to being HIV positive prevented some patients from coming forward and taking up IPT. The qualitative data analysed in this review highlighted that there is overlapping interaction between multiple factors that impact on adherence. The authors recommended that these findings be taken into consideration by the various decision makers in order to engage patients better and thus ensure successful implementation of IPT programmes.

Table 5: Summary of reviewed articles on IPT adherence

Study	Age Race Sample size (n)	Previous TB	ART use	IPT regimen	Adherence
IUAT trial, 1982 (71)	20-64 years European n=27803	Positive with fibrotic lesions	No	3H300, 6H300, 12H300 or *P*	Overall not reported, majority were 'compliant' Above 80% was considered adherent
Kenya, 1997 Hawken (72)	≥ 18 years Black African n=684	No-excluded	None	6H300 vs *P*	Missed 1 week= 42%; 1-4 weeks= 27%, >5weeks= 31%
Uganda, 1997 Whalen (73)	≥ 18 years Black African n=2736	No-excluded	No-excluded	6H300, 3RH600/300, 3RZ600/2000, 6P Monthly visit X 6, then 3 monthly	Attendance at scheduled visits, , Patient self- report, urine test for INH metabolites - 75% had positive results, spot check at home = 80% positive
Zambia, 1998 Mwinga (74)	≥ 15 years Black African n=1053	Not reported	No	3RZ600/3500 twice weekly VS 6H900 twice weekly VS placebo (3P twice weekly or 6P twice weekly)	Drug calendars issued to patients Pill collection and patient report, considered compliant if collected all their tablets and adherence ≥ 80%, overall compliance in study was 74% - of which 92% were defined probably compliant and 8% possibly compliant
Botswana, 2010 Mosimaneotsile BOTUSA Study (48)	≥18 years Black African n=1995	Yes	Yes	6H: 300mg: 30-49 kg 400mg: ≥ 50kg; then changed in Jan 2006 – 300mg all	Adherence measured by attendance to clinic visits= 86% Pill counts done at M1, 3 & 6: 100% all 3 months =27%; >90% all 3 months =77%; >80% all 3 months = 91%; <80% any month= 9%; ART enhanced IPT adherence
South Africa, 2011 Martinson (76)	≥ 18 years Black African n=1148	Not reported	No	3RPT900/ H900, 3R600/ H900, 36H300, 6H300	Adherent if ≥ 90% RPT/H= 95.7%; RH= 94.8; 6H= 83.8%; 36H= 60.3%
Botswana, 2011 BOTUSA Study (77)	≥ 18 years Black African n=1995	*Yes-Not reported	Yes	6H+30P vs 36H 300mg <50kg; 400mg ≥50kg	Overall adherence to clinic visits over 3 year follow up: 6H: 78%; 36H:77%
Botswana, 2011 Samandari BOTUSA Study (34)	≥ 18 years Black African n=1995	Yes*	Yes; 2% Baseline & 45% during follow up	6H+30*P* vs 36H 300mg <50kg; 400mg ≥50kg	78% of patients attended ≥ 80% of pharmacy refill visits

Study	Age Race Sample size (n)	Previous TB	ART use	IPT regimen	Adherence
Ethiopia 2014, (84)	≥ 18 years Black African n=5407	Not reported	Yes	N/A	Survey: Adherence defined >80% of the prescribed INH in the past 7 days prior to survey. Self-reported adherence= 89.5%. Factors associated with adherence: People on ART, had IPT ≥ 5months, had info on why they took IPT, remembered taking a dose within last 1-11 hours prior to survey. Factors associated with non-adherence: Forgetting =45.2%, Drug out of stock =11%, Side effects =16.4%, too ill to take meds =16.4%, away from home=5.5%, Stigma=5.5%.
Tanzania, 2015 Shayo (79)	≥ 10 years Black African n=1303	TB within last 2 years excluded	Yes	6H300 for adults	Data on adults ≥ 18 years old only reported in this table Adherence defined as ≥ 90% Overall mean with SD 98.9% (±2.9), 18–29 years (98.3), 30–49 years (98.8) ≥ 50 years (98.5 %) [p = 0.011]
Ivory Coast,2015 Temprano Study (31)	≥ 18 years Black African n=2056	Yes	Yes- early & deferred	6H300- no IPT, early IPT, IPT deferred or none (ART+IPT)	Reported as completion rate: 94% completed IPT early group and 93% completed IPT deferred group. N=22/927=2.3% discontinued IPT for personal non-medical reasons, 13 discontinued due to pregnancy.
Swaziland, 2017 Mueller (82)	288	≥ 16, Black African	Yes, n=24 within last 6 months	36H300	Adherence assessed by pill count, urine test and interview Urine sample 1 – 30 hours after INH dose Positive result for INH was 80.1% (95%CI 76.9–82.9%). Negative result: only 11/141 patients reported no INH dose in the past 24 hours. Proportion of positive urine tests and pill count indicated decreasing adherence over time (test for trend P= 0.04 and 0.12) Reports of missed doses seemed to improve over time. The main reason given for missed drug intake: forgot, not having the drug with them, lack of food, feeling unwell, running out before next appointment date.

Key: H=Isoniazid, RPT=Rifapentine, P=placebo, SD=standard deviation, 6H300= 6 months of isoniazid at 300mg where 6 is duration in months H is the drug (isoniazid) and 300 is the dose in mg.

IPT adverse effects

Data has been collected on the adverse effects associated with use of INH for IPT from as early as 1982 and up to 2016 in Table 6. The International Union Against Tuberculosis (IUAT) were the first to report that IPT associated hepatitis most frequently occurred with the first three months of IPT start (71). This finding was also demonstrated years later in the BOTUSA study in Botswana (48). Interestingly, the position of the IUAT researchers was that IPT use resulted in more TB cases prevented per case of hepatitis caused. While earlier IPT recommendations warned against INH-induced hepatitis for those > 35 years of age, these concerns were laid to rest by Tedla et al. in 2010 and Gray et al. in 2016, that showed no significant interaction between hepatitis and age > 35 years while on IPT (87, 88).

Martinson et al. compared three preventive therapy regimens in 2011 and showed that the longer duration regimen of 36 months of INH resulted in more adverse effects than shorter courses of either INH alone for 6 months or ultra-short courses of INH in combination with other drugs (76). Currently published literature demonstrates overall safety and tolerability of INH when used as preventive therapy; however, the majority of the studies in Table 6 were among HIV infected people not on ART. Only one study by Tedla et al. showed (using data from the BOTUSA study) that any association between INH-hepatitis and concurrent use of ART with IPT was not statistically significant.

Table 6: Adverse effects associated with IPT

Study	Age Race Sample size (n)	Previous TB	ART use	IPT regimen	Toxicity
IUAT trial 1982 (71)	20-64 years White European n=27830	Positive with **fibrotic lesions**	No	3H300, 6H300, 12H300 or *P*	5 years of follow up Hepatitis [IPT: 0.5%, *P*: 0.1%] Most common within first three months of IPT. 6H300 prevented more TB cases (9.3/1000 persons TB cases prevented vs placebo in year 5) per case of hepatitis (3.6/1000 persons hepatitis cases incurred in excess over placebo in year 5) caused. Benefit-to-risk ratio was 2.6 at year 5 for 6H300
Kenya 1997 Hawken(72)	≥ 18 years Black African n= 684	No-excluded	None	6INH300 vs *P*	n=18(IPT), 12(*P*): AST/ALT>2ULN PN=8(IPT) Treatment stopped due to toxicity n=11(IPT), 5(*P*)
Uganda 1997 Whalen (73)	≥ 18 years Black African n=2736	No-excluded	No-excluded	6H300, 3RH600/300, RZ600/2000, 6P monthly visit X 6, then 3 monthly	304 AE, 43 discontinued treatment, AE frequency was greatest in the RZ arm Most common AE: Rash/pruritus=25, NV=8. Less common: arthralgia, paraesthesia 7 cases, clinical hepatitis – similar rate in HIV(-) and similar age group
Zambia 1998 Mwinga (74)	≥ 15 years Black African n=1053	Not reported	No	3RZ600/3500 twice weekly VS 6H900 twice weekly VS placebo (3P twice weekly or 6P twice weekly)	3% adverse drug reactions: Raised liver enzymes n=4 Rash n=7 GI symptoms=11 Other n=7
South Africa 2003 Churchyard (69)	≥ 18 years Black African n=559	Yes	No	Indefinite H300	Rash: 2 (re-started) + 3 (stopped), abdominal pain: n=1 nausea: n=1 no hepatitis or PN
South Africa 2005 Grant (36)	≥ 18 years Black African n=24221	Yes	No	6H300 or 12H00 if co-infected with silicosis	N=9 stopped IPT due to rash n= 7, rash + mild hepatitis n=1, mild PN n=1, and 2 of the 9 restarted; 13 others cases had PN and 9 had rash but all completed IPT
Tanzania 2008 Ex-Dar Dar Study patients Munseri (75)	≥ 18 years Black African n=1932	NK/NR	No	6H300	INH toxicity n= 3: PN n= 1, hepatitis n =2 INH intolerance: nausea = 4 psychiatric illness = 1

Study	Age Race Sample size (n)	Previous TB	ART use	IPT regimen	Toxicity
Botswana, 2010 BOTUSA Study (48)	≥18 years Black African n=1995	Yes	Yes	6H open label phase of BOTUSA Study, Initially weight dependant dosing: 300mg: 30-49 kg, 400mg: ≥ 50kg; then changed in Jan 2006 to 300mg all	28 severe AEs (1.4%) Hepatitis n=19 (including 1 death) Rash n=5 Seizure n=2 (1 suicide attempt by INH overdose) Other n=2
Botswana, 2010 BOTUSA Study (87)	18-70 years Black African n=1995	Yes	Yes	6H+30P vs 36H 300mg <50kg; 400mg ≥50kg	AST/ALT levels: 6H grade 1= 354(87%), grade 2 = 34(8.4%), grade 3= 15(3.7%). INH induced hepatitis= 1.1% with 1 death hepatic encephalopathy. In bivariate analysis CD4 < 200 cells/mm^3 associated with INH induced hepatitis (RR: 2.80; 95%CI, 1.14–6.84); multivariate showed it was ART not CD4. Age > 35 was non-significant with INH-hepatitis (RR, 1.56; 95% CI, 0.64–3.82). 1.6-fold higher risk for INH-hepatitis for those on ART+ IPT (not significant). 34% reported alcohol use and 5.6 % traditional medicine- authors feel this was underreported.
South Africa, 2010 Grant (49)	≥18 years Black African, n=22421	NK/NR	No	9H300	132 AEs (0.54%), 1 resulted in death (overall IPT risk 0.004%) Rash n=61 (0.25%) –median 20 days after started IP, graded mild or moderate, PN n=50(0.21%)-median 34 days after IPT start, graded mild or moderate Hepatoxicity n= 17(0.07%), all grades; median 117(2-263) days after IPT start Convulsions n=4 (0.02%), 1 death, reported alcohol use
Botswana, 2011 Samandari BOTUSA Study (34)	≥ 18 years Black African n=1995	Yes	Yes	6H+30*P* vs 36H 300mg <50kg; 400mg ≥50kg	Toxicity reported to be similar in both arms First six months: Control arm n= 10, 1.4 % (hepatitis=10, rash=2 and seizures=2); IPT arm n=16, 1.6% (hepatitis=10, rash=1, seizure=1, tinnitus=1, headache=1) After 6 months: Control Arm n=7, 1%; IPT arm n=11, 1.3% (p=0.36) Overall: INH induced hepatitis n= 29 for 3100 PY of INH use
South Africa, 2011 Martinson (76)	≥ 18 years Black African n=1148	NK/NR	No	3RPT900/ H900, 3R600/ H900, 36H300, 6H300	AST/ALT grade 2&3: RPT/H: 1.5%, RH: 2.4%, 36H300: 28.0%, 6H 5.5% (P<0.001 for 36H vs 6H)
South Africa, 2014 Rangaka (78)	≥ 18 years Black African n=1329	Yes	Yes	12H vs 12*P;* Dose: 200mg < 50kg and 300mg ≥ 50kg	ALT ≥ grade 3 (n=34); of which 29 stopped IPT - risk ratio 1·9 (95%CI 0·90–4·09) PN≥ grade 2 (n=3) Rash ≥ grade 2 (n=2)
Tanzania, 2015 Shayo (79)	≥ 10 years Black African n=1303	No-excluded	Yes	6H300 for adults	6/1303 stopped IPT due to side effects

Study	Age Race Sample size (n)	Previous TB	ART use	IPT regimen	Toxicity
Ivory Coast, 2015 Temprano Study (31)	≥ 18 years Black African n=2056	Yes	Yes	6H300- no IPT, early IPT, IPT deferred or none (ART+IPT)	UK cause of death (n=1) Elevated AST n=6 Psychiatric side effects n=4 Pruritus n=2
Australia, 2016 Gray (88)	≥ 18years Not reported n=94	NK/NR	Not reported	9H300 vs 4R	74% completion rate on H (IPT) and 86% on RIF 33% IPT and 23% on RIF experienced some LFT abnormality AST ≥ 5ULN =3% There was no association found with age but there was an association between baseline liver abnormality and developing drug-induced hepatitis during PT. Significant predictors of liver dysfunction during PT were risk factors for liver disease (p= 0.03) or abnormal pre-therapy LFT (p < 0.001). 3% stopped IPT due to INH-induced hepatitis overall 17% (3% grade 3/4 and 14% grade1/2) Males were twice as likely to have abnormal LFTs (p=0.02) No association between degree of LFT abnormality or age ≥ 35 with resolution of LFT abnormality (p=0.2).
Swaziland, 2017 Mueller (82)	288	≥ 16, Black African	Yes, n=24 within last 6 months	36H300	Hepatotoxicity n=3 (1.0%), 2 were severe (1 ALT 5–10 ULN, 1 jaundice) and 1 mild. No liver tests to confirm the diagnosis. Rash n=2, itching n=1, peripheral neuropathy n=2, nonspecific weight loss n=3, psychotic decompensation n=1, vertigo and nystagmus n=1. 16/22 patients had IPT stopped: 1 was found dead at home 2 months after IPT stopped, and 1 pregnancy resulted in stillbirth. Side-effects reported during adherence assessment interview at the 2 clinics decreased from 19.0% (16/79) and 50.0% (25/52) at 6 months, to less than 1% after 30 months.

H=Isoniazid, RPT=Rifapentine, R=Rifampicin, P=placebo, PY=person years, liver function test= LFT, AST= aspartate aminotransferase, ALT= alanine transaminase, ULN= upper limit of normal, NK/NR=not known or not reported, GI= gastrointestinal, PN=Peripheral neuropathy, UK=unknown, AE=adverse events, CI=confidence interval, 6H300= 6 months of isoniazid at 300mg where 6 is duration in months H is the drug (isoniazid) and 300 is the dose in mg.

IPT policy and implementation

While global support for IPT implementation increased during the period 2002 to 2009 (Table 7), the need remains for improved operational systems, continuous monitoring and evaluation of IPT implementation outcomes and the subsequent impact on both patients and staff on the ground level. The reporting mechanisms in place should efficiently disseminate these findings to facilitate reviews and evidence-based updates of existing IPT policy. The following barriers to IPT implementation were identified by Getahun et al. (19):

- Government- lack of leadership, TB care being ignored by HIV services, absence of or weak national policies, minimal collaboration between TB and HIV services, fear of INH resistance
- Service delivery related to TB diagnostics, TST administration, poor client adherence
- Supply related-lab supplies; poor TB and HIV supply management, TST supply, INH supply
- Healthcare worker (HCW) related – lack of training and supervision, poor perception of IPT, fear of INH toxicity and resistance, poor communication and inter-referral
- Health information system related – lack of adequate standardized indicators, monitoring and evaluation
- Health system financing related – allocation of funds and competing priorities for resources

Recommendations to improve IPT uptake by the authors (19) included: integrated operational approach between national TB and HIV programmes, simple TB symptom- based screening algorithms, patient monitoring and education to reduce the risk of INH toxicity and increase adherence, ensure effective INH access and supply system, set up monitoring and evaluation systems that are in line with internationally recognised systems and indicators, engaging and empowering affected communities in screening, prevention and education activities.

A survey was conducted amongst HCW at public hospitals to assess barriers to IPT implementation with regards to: leadership and governance, service delivery, supplies and products, health workforce, heath information system, and health system financing (89). About 22% physicians, 38% TB clinic nurses 39% HIV clinic nurses responded. Main barriers identified were: unclear national policy: 60%; fear of INH resistance: 52%; fear of poor adherence by nurses: 30%. Clinicians were more reluctant to implement IPT due to fear of increasing INH resistance (81%) whereas nurses were reluctant implementers due to the perceived higher workload. Hospitals implementing IPT programmes were motivated by (1) knowledge that IPT can prevent TB (63%), (2) the following of national guideline (34%), (3) concern for TB prevention even after the expansion of access to ART (32%). The authors felt that new evidence-based information may improve HCW's understanding of IPT, and subsequently enhance IPT programmatic implementation.

Chehab et al conducted a cross sectional study amongst NDOH clinics in SA (90, 91). They found that there was a lack of TB/HIV committees as well as trained staff or adequate access to guidelines; there was fear of INH resistance amongst HCW, and IPT counselling did not cover all essential topics. Amongst PEPFAR-assisted sites in South Africa, patients initiated on IPT increased from 1% in 2010 to 10 % in 2011(92). The availability of staff training, clinic registers, assurance of INH drug supplies and routine quarterly evaluation by the NDOH TB program contributed positively to this increase in IPT initiation. However, IPT adherence as well as IPT outcomes was not assessed. Lester et al (93) reported barriers to IPT implementation in SA, similar to those discussed previously. A survey conducted amongst clinic staff and patients in Gauteng highlighted the similar trends of lack of knowledge and experience amongst HCW; prescribers were unaware of IPT benefits and unclear about guidelines; they also believed that TB screening tools were inaccurate in HIV patients and there was thus a need to refer patients to separate clinics to conduct TB screenings (93).

Table 7: Summary of IPT implementation and policy articles

Study	Sample size	IPT policy and implementation
Global survey 2007 Date(94)	69 countries	59% 41 countries responded 51% had IPT national policy 28% implemented nationwide – of which a median of 3% were ART clinics and 50% TB clinics that provided IPT. Challenges & concerns included: Inadequate intensified TB case-finding, unable to exclude active TB, performing tuberculin skin tests, INH monoresistance, uncertain about effectiveness
2007 Churchyard (24)	N/A	Burden of LTBI greatest in Asia, West Pacific region, Africa and Mediterranean. Re-infection is a major problem in African settings. Benefit on mortality only seen in TST+ HIV infected people. IPT was found to reduce TB incidence, is safe and tolerable. Research required for new drugs and new diagnostics.
South Africa 2009 Mayosi (95)	N/A	SA has highest IPT 372994 patients in 2011, however 80% with HIV still require it strengthen research & development; training funding from DOH; research and evidence –based planning driven PHC re-engineering
Ati-Khaled 2009 (96)	N/A	Major barriers to IPT scale up: who takes responsibility of it, how to identify LTBI, how to rule out active TB, appropriate length and duration of treatment effect. Suggestions made by authors include: HIV services take responsibility of IPT provision; set up operational programmes to observe how best to implement routine IPT, develop algorithms for IPT eligibility, structured pre-ART programmes; patient-ready packs of INH, ongoing TB screening as well as monitoring and evaluation of IPT.
South Africa 2010 Lester (97)	22+20	10 HIV clinics- 22 staff and 20 patients had a survey on their knowledge and experience on IPT and related barriers. Findings: staff lack of knowledge due to low use of IPT in routine practice, unaware of efficacy, afraid of missing active TB and promoting resistance to INH, operational blocks included access to TB testing equipment, facilities and timely receipt of results. Patients surveyed never heard of IPT and when asked about pill burden and other socio-economic barriers responded that these could be overcome.
Durovni 2010 THRio study component (98)	1670	29 PHC HIV clinics; staff IPT training intervention on IPT; findings post training: 85% completed IPT; 1.2% had adverse reactions and stopped therapy; IPT completion was higher if patients were on ART compared to no ART. (87% vs 79%). Time to TST done and starting IPT were improving but still long. Combination of advocacy, service integration and training was successful in this setting.
Eldred 2010 (26)	N/A	Evidence to support implementation from Consortium to Respond Effectively to the AIDS-TB Epidemic (CREATE) projects: a) Thibela TB an implementation trial of community wise IPT among gold miners- enabled more ICF for active TB then existing health care services; b) THRio study – combined ART and IPT more effective; c) ZAMSTAR study- Zambia and South African sites for IPT pilots, ICF, social mobilisation, access to better diagnostics
Getahun 2010 (19)	N/A	Analysis of WHO databases on HIV/TB collaborations. 19-fold increase in global implementation from 2002-2009. Barriers included: no supportive government policy in place, poor service delivery, stock availability, HCW lack of training and knowledge, poor resources unable to establish monitoring system, lack of utilization of funds to scale up IPT. Solutions suggested: set up national policies and programmes, algorithm for TB screening and IPT eligibility, patient education and monitoring, effective access and supply of drugs and suitable dosage forms, design standardised indicators as part of monitoring and evaluation systems, community engagement.
South Africa 2011 Chehab (99)	2512	46% uptake TB/HIV service integration ongoing
South Africa 2012 Chehab (90)	2512	855 facilities with Integrated TB/HIV offered IPT vs 59% not integrated 29% felt no guidance or commitment from authorities 21% INH resistance concerns 64% had latest guidelines 78% had at least 1staff trained

Study	Sample size	IPT policy and implementation
South Africa 2012 Bristow (92)	N/A	IPT implementation in South Africa from January 2010-March 2011 in PEPFAR-assisted sites. 14-fold increase in patients started on IPT -went from 1% to 10.5%, just after new SA guidelines for IPT released. Authors reported that creation and dissemination of policy helped increase stakeholder implementation of IPT.
2012 Coebelens (100)	N/A	Systematic review on implementation of 5 WHO TB activities, one being IPT. The authors found major gaps in available evidence for scale-up the 5 TB interventions. Lacking at country level suggested that national implementation of these interventions would be precluded. They called for operational research in programmatic settings to provide more data on best use of new/existing TB interventions.
2015 Briggs (101)	N/A	Review of literature 1995- 2013 and included data on mortality, morbidity, cost effectiveness and retention in care of provision of IPT in low- or middle-income countries. This review did not consider other optimal drug regimens, duration of IPT efficacy, IPT adherence, side effects or INH resistance. The authors identified research gaps: duration of IPT protective effect varies according to burden setting, no clear definition of the optimal duration of course (short, lifelong, or repeated), possible INH resistance in programme, other shorter course preventive therapy drug regimens comparable in safety and efficacy and also in which settings these regimens are appropriate for scale up.
Thailand 2013 Moolphate (89)	198	HCW from 95 public hospitals responded to questionnaires. Lack of knowledge and concern about INH resistance were key barriers to implementation at hospitals where IPT was not implemented; having knowledge of the effectiveness of IPT as well as knowing and following national IPT policy were motivators at hospital with IPT implemented. Authors emphasised dissemination of and access to national policies and provision of updated information would promote IPT implementation.
South Africa 2014 Wood (102)	N/A	6 SA studies including 4 RCTs – only some showed IPT benefit that was significant. IPT combined with ART lowered TB incidence. Thibela Tb found 7% more TB in IPT arm at screening than standard of care. Rangaka et al. diagnosed more TB cases at baseline than the cases prevented by IPT.
2015 Akolo (103)	N/A	Counteracted the myths around IPT as flows: TB screening is effective in ruling out active TB, chest x-ray not compulsory for initiation, IPT does not promote INH resistance, IPT has combined effect with ART in reducing TB, adherence to IPT is good, IPT is safe, tolerable, cost-effective, recommended for use in children, TST not a requirement for initiation.

Key: RCT=randomised control trials, HCW=healthcare worker, SA= South Africa, PHC= primary health care, ICF= intensive case finding, WHO=World Health Organisation

1.4 Description and significance of the core research problem: Challenges of rolling out IPT in South Africa

Several studies published since 2010 have demonstrated the safety and effectiveness of integrating IPT and ART in patient care thereby improving both HIV and TB outcomes. (29, 32, 48, 59, 68, 104). However, implementation and IPT uptake has been relatively slow (12, 105). The reasons for the slow roll out of IPT could be related to the many HCW-related and patient-related barriers to IPT implementation.

Barriers to IPT implementation reported by HCW include potential long duration of treatment (90, 92, 93, 106-108), fear of INH stock outs (109) and fear of INH resistance developing (110). The lack of HCW experience (93, 109) as well as availability of IPT guidelines and training (90, 109) have also been previously observed. HCW also remain unconvinced of the effectiveness of IPT (93, 111) and subsequently lacked in reinforcing adherence among patients started on IPT (109). Non integration of HIV/TB services and having to refer patients out to other TB facilities for care was also reported as a contributing barrier for IPT implementation (93).

Qualitative data on IPT use have identified a few patient related barriers to IPT uptake and implementation. These include stigmatization (86) linked to HIV as well as non-disclosure of HIV status (86, 109). Other barriers related to IPT use are that patients may not know much about IPT nor fully understand the benefits of taking IPT (86, 93, 109, 112).

Despite the barriers mentioned the use of IPT has now gained momentum in recent years (92). To improve uptake and as part of the testing algorithm for HIV post-test counselling outlined by the SA national HIV testing services in its policy (113), clients are offered IPT as part of a comprehensive package of care, in keeping with in country and global recommendations. There has also been recommendations to update policy guidance as more evidence emerges on best practices to inform IPT provision (107). As of 01 September 2016, SA DOH has adopted the Test and Treat campaign for immediate ART initiation for a positive HIV diagnosis irrespective of CD4+ T-cell count. It is important to factor in what impact this would have on ART and IPT delivery. By the end of 2015, over 3.4 million of the 7 million HIV infected people in SA had access to ART (114). Using these estimates translates to approximately 3.6 million patients already eligible for immediate ART initiation, over and above the new HIV infections diagnosed. Once active TB is ruled out, then millions of people potentially become eligible for concurrent IPT initiation with ART or IPT provision following ART initiation. Consequently, this may result in further operational challenges for ART and IPT delivery increasing the burden on the public healthcare system.

Furthermore, with the updates to the South African guidelines since 2013 and 2015, patients can now receive IPT up to a maximum of 36 months' duration. This means that IPT programmes need to be maintained and monitored for a longer period of time so that the effectiveness of IPT as an intervention for TB prevention can be constantly evaluated. In the context the of scaling up treatment for TB/HIV integration lack of infrastructure and trained, experienced staff are reported barriers to effective progress in service delivery efficiency (115). Similar challenges will apply to large scale IPT provision (12). The establishment of a multi-disciplinary team approach to IPT provision within an integrated healthcare system is a very promising strategy. Various health care professionals including nurses, counsellors, pharmacists, clinicians as well as others, may contribute operationally to the landscape of combined HIV treatment and TB prevention services. For example, the pharmacist could play a significant role in staff training, patient education, counselling, assist with identifying symptomatic patients with presumptive TB, as well as be able to contribute to monitoring adherence to ART, IPT and clinical outcomes of IPT use. This task shifting or sharing of responsibilities to support IPT provision could lead to enhanced IPT uptake and improved quality of care. Innovative prospective steps need to be taken to ensure improved efficiency for long term sustainability of large scale ARV, TB treatment and TB preventive therapy provision in South Africa.

1.5 Problem statement

South Africa has dual epidemics of HIV and TB. Rapid re-infection and relapse rates of TB extenuate the circumstances and hinder any progress made towards TB prevention. HIV/TB service integration is the gateway to successful implementation of TB preventative based interventions such as IPT. However, the majority of data published on IPT was obtained from research conducted in the pre-ART era or in ART populations with no past history of TB, previous TB exposure being grounds for exclusion from IPT. There is a resultant paucity of data on IPT outcomes and effect on TB incidence in ART and TB treatment experienced populations.

1.6 Study hypothesis

The roll out of IPT within an ART programme, in a high TB burden area with limited resources, amongst TB treatment experienced patients will decrease TB incidence.

1.6.1 Study Aims

- To retrospectively report uptake and clinical outcomes of an IPT programme in a resource – limited urban clinic located in a high TB burden setting amongst HIV infected patients receiving ART.
- Describe the role of the pharmacist and pharmacy services in TB prevention through IPT

implementation and monitoring adherence to IPT.

1.6.2 Primary Objectives

- To assess the design and implementation of IPT roll-out within an ART programme
- To report on the outcomes of the IPT roll-out including:
  - IPT uptake, contribution of background TB to IPT ineligibility
  - Gender differences in IPT uptake
  - Assess IPT implementation among patients with a past history of TB treatment
  - Assess adherence to IPT
  - Assess adverse effects related to IPT
  - Describe the pharmacist's role in a multi-disciplinary approach to IPT implementation and roll-out

1.6.3 Secondary Objectives

- To report on areas of implementation that require strengthening or modification to enhance the quality and effectiveness of the IPT roll-out
- To identify any trends in IPT interruption, IPT completion as well as reasons for IPT refusal
- To determine TB incidence in patients, post IPT

1.7 Conceptual framework

The following key factors that impact IPT and the relationship among them has been depicted in Figure 4: population, community, clinic, healthcare system, as well as patient and medication factors.

Population Factors:

In areas endemic to HIV and TB, the high TB transmission and re-infection rates is exacerbated by high HIV incidence and prevalence (116). TB prevention strategies such as IPT are necessary to curb growing TB incidence (38). Recurrent TB is a concern in these settings especially in a population where there may be a history of multiple episodes of previous TB. These population factors impact the duration and durability of IPT to achieve a protective effect in a region of high` TB/HIV burden.

Community Factors:

The stigma associated with HIV still runs strong within communities. The resultant non-disclosure of HIV status has a negative impact on the uptake of IPT (117) as this service may inadvertently expose patients to discrimination amongst family, colleagues and peers, since TB related factors are associated with HIV within the community. TB related stigma itself has potentially huge negative consequences with late presentation of ill patients to clinics thus resulting in delayed TB diagnosis and initiation of treatment, propagation of TB transmission to household members or within the

community and possible treatment interruptions. People fear that having TB will lead to them being perceived in the community as being unhealthy, weak and not 'strong' (86, 118).

Clinic Factors:

The clinic environment can either promote or reduce patients' acceptability of IPT. The already understaffed clinic and subsequent overworked staff results in long queues, overcrowding, and sometimes poor rapport between patients and staff. A lack of facilities as well as limited staff access to IPT training, standard operating procedures (SOP), policies and guidelines negatively impacts staff's ability to adequate screen, educate and implement IPT use amongst patients (90). Patients in turn do not fully understand the importance of IPT for TB prevention and this may affect their adherence. However, some clinic environments with well trained staff, adequate privacy and well developed TB screening and IPT guidelines, counselling and policies in place promote an improved patient experience that would enhance their education, awareness and subsequent compliance to IPT course completion (119). It is also important to note that many clinics do not have a multi-disciplinary healthcare team available. This approach would provide much needed support to mainly nurse –run clinics and potentially result in more effective service delivery and clinical care of patients; where some of the burden of providing and monitoring IPT could be shifted from the clinic nurse to other skilled healthcare workers.

Healthcare Infrastructure:

Healthcare systems and infrastructure are linked to clinic capabilities to adequate roll out IPT and other TB prevention activities. This is dependent on having national policies and programmes in place, promoting integration of TB/HIV service provision (99). It is important to have systems in place for monitoring, evaluating IPT implementation as well as consistently reporting to the relevant stakeholders to ensure targets are met and programmatic challenges can be addressed(92).

Medication:

There are some medication related factors to take into consideration as well. Patients on ART and receiving treatment for other opportunistic infections or co-morbidities may experience an additional pill burden with IPT, and should be monitored and adequately counselled on side effects, dietary precautions if required, as well as other drug-drug interactions. In contrast, it should also be considered that being on lifelong ART would promote adherence to IPT (48).

Patient Factors:

The socio-economic status of patient's impacts on uptake, compliance, awareness and understanding of IPT as well. Travelling long distances to the clinic, migrating out of town for job opportunities, non-disclosure at work are some of the challenges that patients may face (75, 118). In addition, personal beliefs can hamper their commitment to IPT in terms of fear of side effects, fear of TB/HIV

complications, and concern about family/spouse support (75, 117). A patient who is well counselled and understands the importance of IPT would be more adherent due to his/her belief in protective effects of IPT (120)

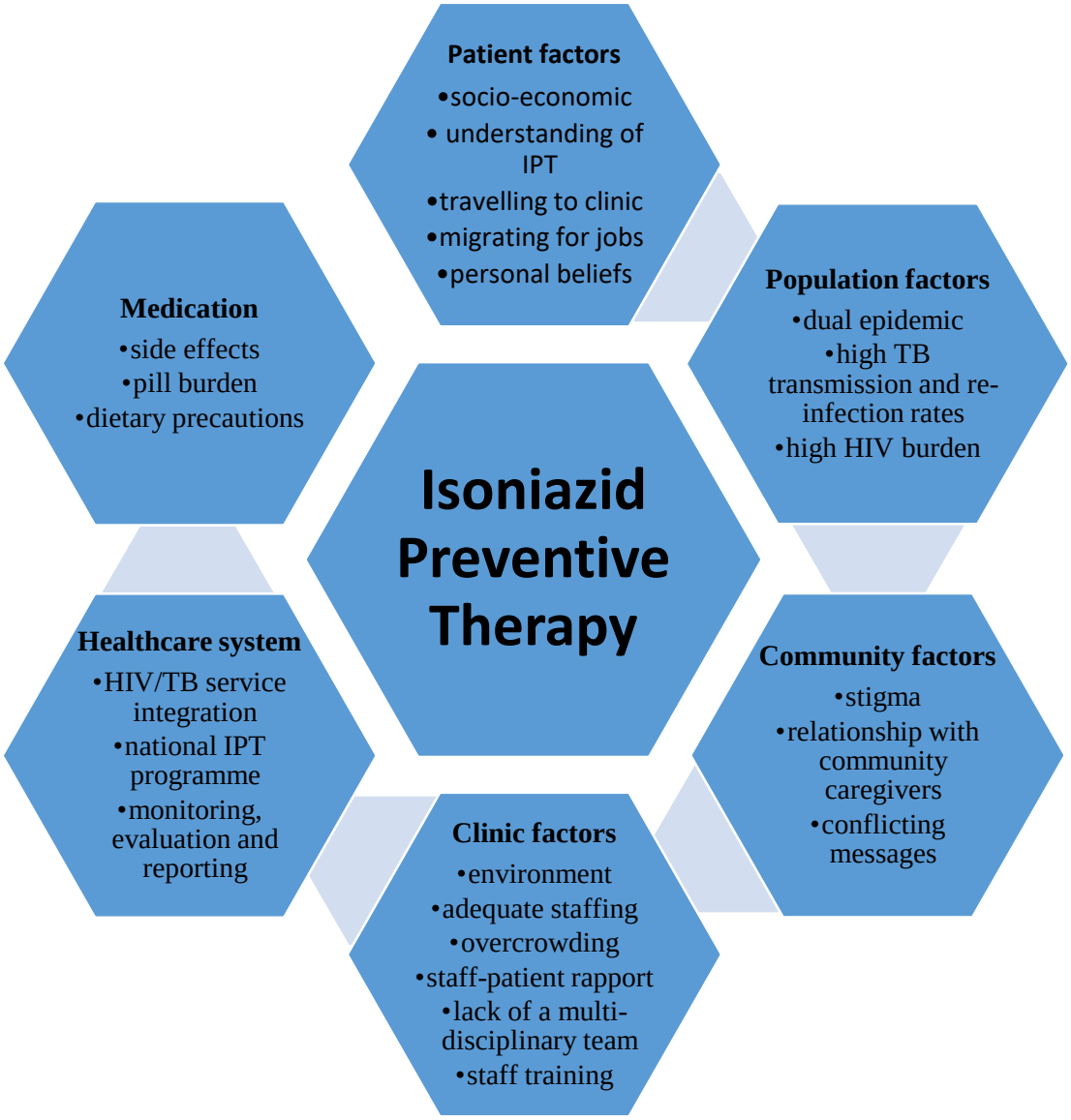

Figure 4: Conceptual Framework: Factors influencing IPT

CHAPTER TWO: METHODS

2. CHAPTER TWO: METHODS

2.1 Study design and period

This study assessing IPT implementation was designed as a secondary analysis of prospectively collected clinical and demographic data. Data was extracted from clinic files, Case Report Forms (CRFs) and computerized pharmacy dispensing records from the parent study, CAPRISA 005 TB Recurrence upon Treatment with HAART (TRuTH), conducted during the period October 2009 to October 2013. The TRuTH study was a prospective cohort study assessing TB recurrence among patients initiated on ART. From 2011 onwards IPT was offered to adult patients ≥ 18 years accessing HIV care, in accordance with national treatment guidelines.

The independent variable for this study was exposure to IPT. The dependent variable was the incidence of TB in patients receiving IPT. The control variable was exposure to ART. The present study analysed data generated over the same time period during which the TRuTH study was being conducted.

2.2 Study location

The Centre for the AIDS Programme of Research in South Africa (CAPRISA) eThekwini Clinical Research Site is an urban clinical research clinic, located at Durban's Warwick Triangle, KwaZulu-Natal which is one of the main bus and train hubs in and out of the city, making it easily accessible to people travelling from townships and rural areas. The site is located adjacent to the Prince Cyril Zulu Communicable Disease Centre offering facilities for TB/HIV care and serves the Durban functional region.

2.2.1 Provision of IPT

Programme implementation

All patients at the time of TRuTH study enrolment had experienced one or more previous episodes of TB and were stable on ART. Clinic visits were scheduled for provision of follow up care and ART supply every 3 months.

A clinic assessment was conducted prior to implementation of IPT in order to design the programme as well as identify relevant resources. This was followed by attendance of staff, including pharmacists, at IPT training workshop conducted by the South African Department of Health in 2010. The IPT rollout was designed in accordance with then current South African guidelines and implemented in October 2010. Patients were screened for TB (Figure 5) and those with no signs and symptoms of active TB and found to be eligible, were enrolled, if agreeable, onto a six month IPT course. Clinic staff queries and refresher training was overseen and conducted by pharmacy staff in conjunction with the project director.

INH was prescribed using weight-dependant dosing criteria and verified at the pharmacy as described in the instructional memo issued in 2010 by the NDOH on implementation of IPT guidelines (Appendix E). The dose of INH was prescribed and dispensed as 300mg for those ≥ 60 kg, 250mg for 50-59.9 kg, and 200mg for those weighing 40-49.9 kg. A prescription for INH (Appendix F) was written up the clinician at IPT initiation and thereafter completed monthly by either a clinician or nurse to document 'Yes' or 'No' responses to questions on the prescription related to potential TB symptoms. The pharmacy staff verified that this was completed in full every month for each patient to confirm continued eligibility to continue safely receiving IPT. Any weight changes were reviewed and a new INH dose was prescribed at a higher or lower dose according to the new weight-dependant dosing range. The pharmacy staff documented manual pill counts, calculated adherence and dispensed IPT, ART and other required supplementation or acute or chronic concomitant medication as prescribed.

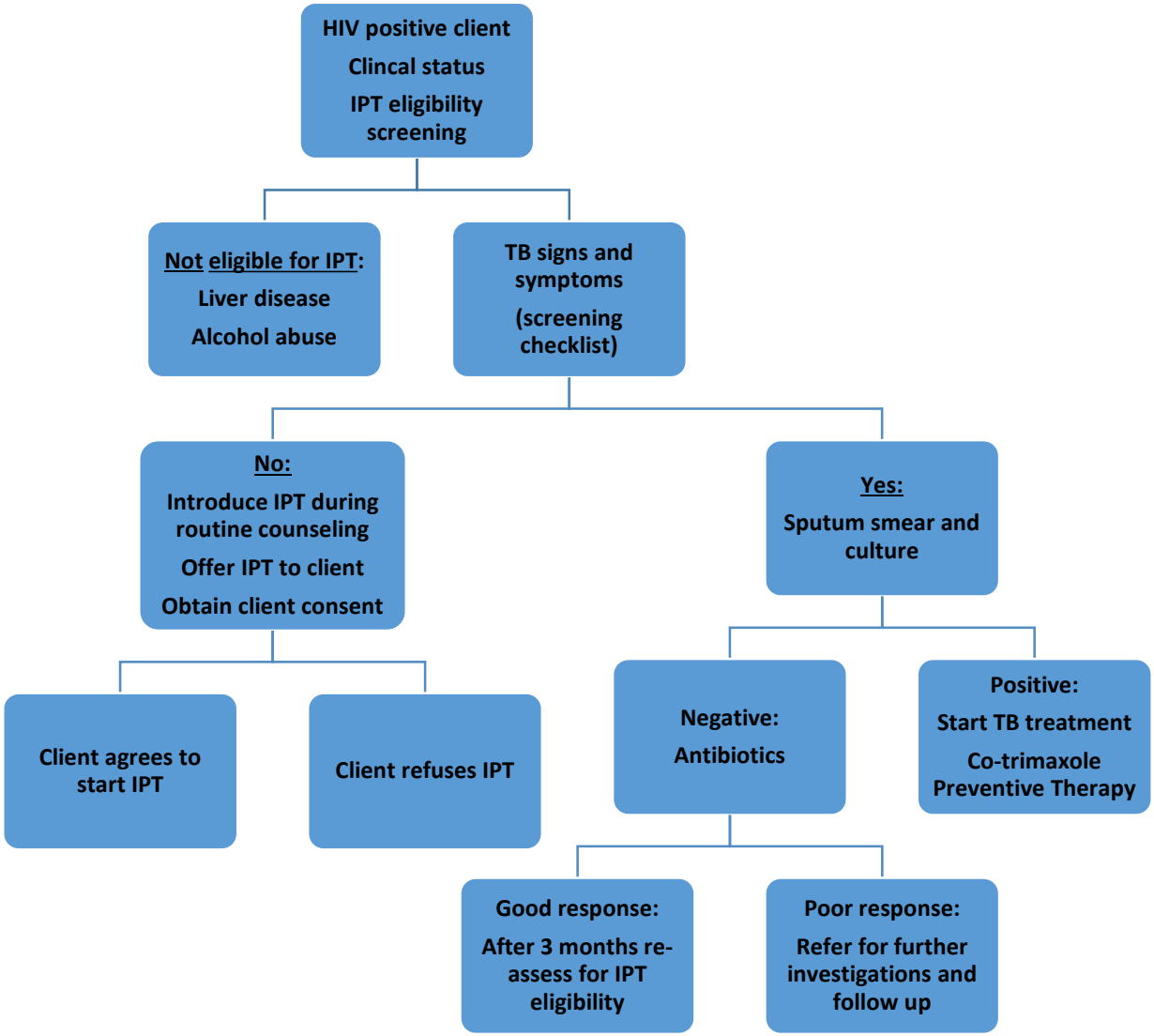

Figure 5: Screening algorithm for TB preventive therapy adapted from SA IPT guidelines, 2010 (10)

IPT clinic visits
INH was dispensed monthly to enrolled participants.

Each monthly visit comprised the following step and procedures (Figure 6):

- Vitals assessment– patient's general health status was assessed and TB screening was conducted by the staff nurse.

- Consultation – The professional nurse verified the patients continued eligibility for IPT or enrolment onto IPT by reviewing TB symptoms. The screening checklist on IPT side effect profile was assessed and counselling needs identified, if applicable. Complicated cases, TB suspects and potential enrolments were referred to the clinician for further work up.

- CAPRISA adherence support programme (ASP) – this programme was counsellor driven and aided by a multi-disciplinary inter-referral system between nurse, clinician and pharmacist. The pharmacist assisted with drawing up and reviewing counselling material and resources used on an ongoing basis, related to INH side effect management, adherence issues and motivational messaging and ensured that all relevant clinic staff were trained.

- Pharmacist role – the pharmacist reviewed the TB symptom screening checklist and confirmed eligibility for IPT on a monthly basis. In addition, the pharmacist monitored the patient weight and related INH dosing, conducted INH pill counts, identified patients with adherence issues that required intensified counselling, dispensed and counselled on appropriate INH use and storage. Patient questions, queries or concerns were communicated by clinic staff to the pharmacist and dealt with during face-to-face patient counselling in addition to ASP as pharmacy was the last point of call during the clinic visit.

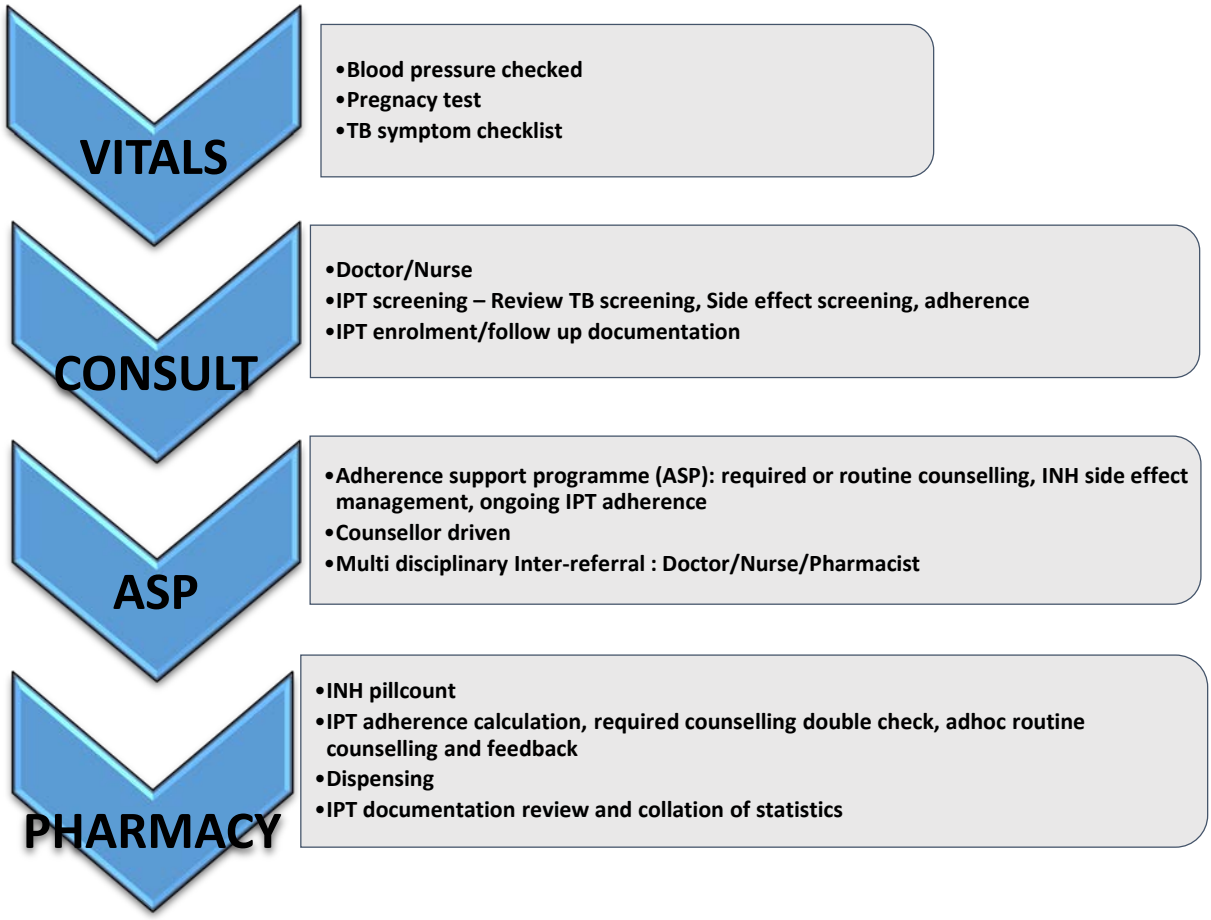

Figure 6: IPT clinic process flow

2.2.2 Patient clinical management

TB screening was conducted at every follow up visit (Figure 7). If a patient was symptomatic, investigations for active TB were initiated. If active TB was diagnosed, INH was stopped and the patient was referred to the adjacent TB facility located next to CAPRISA to initiate TB treatment immediately. If patient was asymptomatic, they were screened for INH side effects. Pyridoxine was prescribed for peripheral neuropathy, the development of a rash was treated symptomatically if it was not severe, or referred for further care if severe. Patients were screened for hepatitis and liver function was monitored whilst on IPT. The pharmacy staff calculated monthly adherence to INH and advised the clinical team when the 6-month course was completed9o.

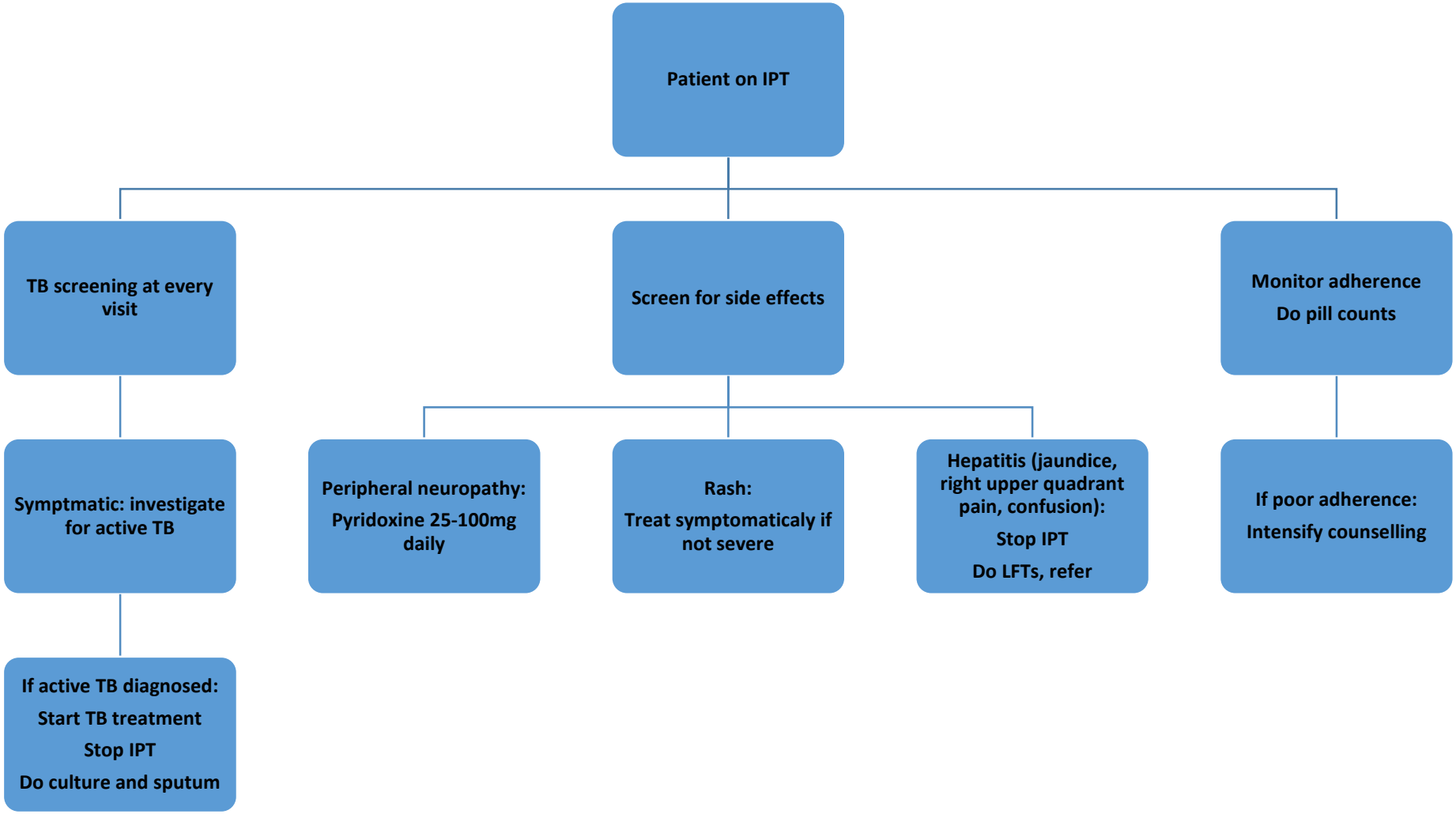

Figure 7: Algorithm for patient management during IPT follow up visits (121)

2.2.3 Monitoring and evaluation

Pharmacy compiled IPT dispensing statistics as well as data related to IPT interruptions including the duration of the IPT interruption. The pharmacist also verified IPT course completion and double checked the duration required by patients to complete IPT course or re-start IPT after course interruptions in accordance with guidelines in effect at the time. On a monthly basis, IPT dispensing statistics were circulated to the rest of the clinic team as well as relevant reporting authorities using the template provided by SA DOH.

2.3 Study population, sample size and sampling strategy

The masters' candidate conducted a retrospective analysis of all records of the 402 patients with a previous history of TB enrolled in the TRuTH who had been receiving ART at the CAPRISA clinic for several years at the time of IPT programme implementation.

2.4. Inclusion and exclusion criteria

This study included adult HIV infected patients ≥ 18 years old on ART. Those with no signs or symptoms of active TB documented and who met the criteria outlined in the South African IPT guidelines applicable at the time were deemed eligible to receive IPT while accessing care within the TRuTH Study.

Those excluded from IPT initiation were those who were being investigated for active TB, clinically assessed to be at risk for adverse effects or those who declined IPT.

2.5 Data collection

Participant data was collected in the TRuTH study on case report forms (CRF) for routine data-faxing into the secure CAPRISA participant database and included demographics (related to age, gender, education, employment, marital status), clinical TB symptom screening, past history of TB, household TB contacts, haemoglobin (Hb), Alanine transaminase (ALT), aspartate aminotransferase (AST), fasting cholesterol, liver function, glucose and triglycerides, temperature, blood pressure, pregnancy testing, contraceptive or family planning use, CD4+ T-cell count and viral load. Data collected at IPT initiation and follow up visits from 2011 onwards included the following variables: age at IPT start, weight at IPT start and during treatment, body mass index (BMI), date of IPT completion, date of IPT interruption, reasons for refusal of IPT uptake. All these descriptive variables in addition to monthly INH pill counts, IPT and ART adherence assessment, any changes to ART regimen were also recorded.

TB related procedures for those patients on TB treatment or under investigation for TB include data collected on diagnosis (PTB, MDR, XDR or extra pulmonary) Chest X-ray reports, sputum, smear microscopy, drug susceptibility testing (if applicable), ultrasound reports (if extra pulmonary TB), culture conversion, concomitant medication, TB treatment and phase (if applicable) start and end dates, treatment outcomes (in terms of success, failure, MDR or XDR TB diagnosis) and importantly contact tracing (if applicable) for immediate referral to local clinics.

Patients with no TB symptoms and deemed eligible for IPT underwent screening and initiation visits that included ASP counselling, the importance of IPT, reasons for starting IPT, how to use INH, the importance of maintaining adherence to avoid development of INH resistance, discussion of possible side-effects, avoiding contra-indicated substances and drugs, as part of the IPT package counselling.

A participant locator sheet was maintained by study staff that contained detailed information on the patients address and contact details at home and if applicable was reviewed and updated at each visit for being able to maintain contact with patients and physically tracking patients to bring them into the clinic to attended visits if necessary. The pharmacy assessed patient comprehension of the IPT counselling at the time of dispensing and in addition provided more motivational adherence counselling and advice on coping with pill burden. A counselling checklist and IPT counselling script was used by clinic and pharmacy staff to facilitate these counselling sessions. The candidate performed IPT related duties and processes as part of the pharmacy team that worked on the parent study.

The following IPT related CRFs and/or source documents were completed at IPT initiation, at monthly follow-up visits and ad-hoc as required at interim clinic visits or reporting periods:

- Plate #077 IPT Initiation/Follow up CRF (Appendix G) – If IPT started or not, reason for not starting, any change in IPT status, date and reason for change, any missed doses and reasons for it, side effects experienced and grading of severity, end date of IPT therapy
- Plate #078 IPT pill count CRF (Appendix H) - Visit date; IPT treatment; Drug Type; Drugs returned, lost or reported as remaining at home; and any reasons for missing doses
- Plate #76 Laboratory Results (Appendix I): AST, ALT
- Plate #64 TB screening and risk assessment (Appendix J)
- KZN DOH IPT monthly statistics reporting form (Appendix K)

The computer package known as iDART refers to the intelligent Dispensing of ART was a very useful tool in maintaining accuracy and accountability of drugs and electronic patient dispensing records in the pharmacy. The system was modified by the pharmacist to include INH in the existing

drug formulary of ART drugs to enable computerised dispensing of IPT, adherence calculation, data collection and IPT reporting. Capabilities available on iDART are detailed in Appendix L.

In addition, the pharmacy staff provided adherence support counselling as needed or referred cases identified back to clinic staff for targeted counselling. Tools to enhance adherence such as once or twice daily pillboxes, HART© blister packs and cell phone alarm reminders were recommended to patients who needed them. Patients were also trained and educated using Drug identification charts created by pharmacy staff to distinguish between the different ARVs drugs and INH they were taking for IPT, common and/or trade names, colour and shape of tablets and what the original drug packaging looked like. Pharmacy staff in conjunction with the multidisciplinary clinic team were committed to making concerted efforts to enable patients to be aware, responsible and continuously involved in the decision making process on their ART and IPT outcomes, adherence and overall good health and quality of life.

2.6 Data analysis

All TRuTH Study CRFs were Quality Controlled and data faxed into the CAPRISA database after validation for completeness and accuracy. The study statistician downloaded raw data collected from CRF completion per participant in the TRuTH study and provided an MS Excel spreadsheet to the candidate to perform data clean up and extraction for the secondary analysis. Any missing or conflicting data, trends or errors identified were verified by physical review of hardcopies of source documents and charts notes in the participants' clinic file and in turn sent back to the study statistician for review and re-faxing into the database.

The candidate selected the following variables (Table 8) related to IPT and patient characteristics that were analysed at different time points during the Truth Study:

- Baseline demographics at TRuTH enrolment: age, BMI, Hb, viral load, gender, race, marital status and employment.
- At, during and after IPT initiation: ALT, AST, ART regimen, CD4, viral load, Hb

Table 8: IPT and patient related variables for analysis

Variable	Variable Type	Descriptive measures
Age	Quantitative (Continuous)	Frequency
Gender	Quantitative / Categorical (Nominal)	Frequency
Marital status	Quantitative / Categorical (Nominal)	Frequency
Employment	Quantitative / Categorical (Nominal)	Frequency
Weight	Quantitative	Mean with Standard Deviation or Median with Interquartile Range
BMI	Quantitative	Median with Interquartile Range
CD4	Quantitative	Median with Interquartile Range
Viral load	Quantitative	Frequency
Hb	Quantitative	Mean with Standard Deviation
ALT	Quantitative	Median with Interquartile Range
AST	Quantitative	Median with Interquartile Range
IPT completion date	Quantitative	Numeric
IPT Interruption date	Quantitative	Numeric
Reasons for interruption	Qualitative	Frequency
Years on ART before IPT	Quantitative	Numeric
Adherence	Quantitative	Median with Interquartile Range

The candidate worked in conjunction with the statistician to perform the following statistical analysis:

- Continuous data were summarised using means with standard deviation or medians with interquartile range.
- Categorical data were summarised using percentages.

Wilcoxon signed rank sum test was used to compare selected laboratory measurements before and after IPT initiation. The statistician calculated the TB incidence rates and follow-up duration before and after IPT initiation from TRuTH study enrolment to either date of TB diagnosis or one day before date of IPT initiation and from IPT initiation to either date of TB diagnosis or study termination date respectively. The mean monthly adherence to IPT was assessed by the statistician using monthly pill count data by comparing the number of tablets returned at the current visit with the number of tablets dispensed at the last clinic visit compared to the number of tablets that should have been ingested between visits. The median adherence for each participant was calculated using the individual means.

The formula for the mean monthly adherence quantified as a percentage included:

$$\frac{\text{Number of tablets dispensed at the last clinic visit} - [\text{Number of tablets not ingested}]^{\#}}{\text{Number of tablets dispensed at the last clinic visit}} \times 100$$

Where no of tablets not ingested = [number of tablets returned + number of tablets reported at home + number of tablets lost]

Univariate and multivariate log-binomial regression models were used to identify predictors of IPT completion. To account for multiple measurements for each participant, generalised estimating equations (GEE) for a multivariate repeated measure logistic regression model was used to identify predictors associated with high IPT adherence (≥80%) over time. Previous studies have used 80-90% adherence threshold to describe optimal adherence to IPT (71, 85, 122). Statistical analysis was performed using SAS Version 9.4 (SAS Institute, Cary, North Carolina). All statistical tests were conducted at a 5% level of significance. The candidate used GraphPad Prism version 5.01 to create graphs depicting adherence and liver function test results.

2.7 Ethical considerations and confidentiality

As this is a retrospective review, no direct patient interaction occurred and thus informed consent was not required for this secondary analysis. However, informed consent was obtained in the parent study CAP005 TRuTH for the use of the clinical and demographic data. Expedited ethics approval and postgraduate approval for the secondary analysis was sought from the UKZN Biomedical research ethics committee. Ethics approvals for the parent CAPRISA 005 TRuTH Study where IPT was rolled out was obtained from UKZN Biomedical research ethics committee [BREC reference numbers: BE373/14 (secondary analysis), BF051/09 (parent study- CAP 005 TRuTH)]. Data extraction was conducted in such a manner that patient confidentiality was maintained at all times. Each patient was allocated unique participant identification number (PID) that was used documented on all case report forms; no patient names were linked with the PID and patient anonymity was maintained.

CHAPTER THREE: MANUSCRIPT

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3.1 Manuscript Implementing Isoniazid Preventive Therapy in a TB-treatment experienced cohort on ART

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Implementing isoniazid preventive therapy in a tuberculosis treatment-experienced cohort on ART

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SUMMARY

SETTING: Urban clinical research site in Durban, South Africa.

OBJECTIVE: To describe outcomes associated with the implementation of isoniazid preventive therapy (IPT) in a cohort of tuberculosis (TB) treatment-experienced human immunodeficiency virus (HIV) infected patients on antiretroviral therapy (ART).

DESIGN: We conducted a secondary analysis of data collected between October 2009 and October 2013 from patients enrolled in a prospective cohort study conducted in Durban, South Africa.

RESULTS: Of the 402 patients enrolled in the parent study, 344 (85.6%) were eligible for IPT, 212 of whom (61.6%) initiated IPT. Of those who initiated IPT, 184 (86.8%) completed the 6-month course, while 24 (11.3%) permanently discontinued IPT, 3.8% of whom due to side effects. More women than men initiated IPT ($n = 130$, 61.3% vs. $n = 82$, 38.7%, $P = 0.001$). Overall median adherence to IPT was 97.6% (interquartile range 94.2–99.4). There were 22 cases of incident TB in this cohort: 13 occurred before IPT and 9 after (incidence rate ratio 0.67, 95%CI 0.29–1.58, $P = 0.362$).

CONCLUSIONS: IPT implementation among ART and TB treatment-experienced patients was well tolerated, with good completion rates and fewer TB cases diagnosed after IPT.

KEY WORDS: human immunodeficiency virus; IPT; prophylaxis; latent tuberculous infection

TUBERCULOSIS (TB) was the cause of 1.8 million deaths globally in 2015, of which 0.4 million were among human immunodeficiency virus (HIV) co-infected individuals.[1] Over 35% of HIV-related deaths are attributed to TB co-infection, making TB the leading killer among people living with HIV (PLHIV).[2] Isoniazid (INH) preventive therapy (IPT), a public health intervention for the prevention of TB, is recommended by the World Health Organization (WHO)[3] and has been adopted by the South African National Department of Health for use in health care workers and PLHIV.[4] Despite the need for IPT, however, global uptake remains low.[5–9] In 2015, only nine of the 30 high TB-HIV burden countries reported providing IPT.[1] IPT coverage is currently reported at 38% in South Africa, similar to global trends.[1]

The impact of IPT on mortality and morbidity in HIV-infected patients has been investigated.[10–12] The TEMPRANO (Trial of Early Antiretrovirals and Isoniazid Preventive Therapy in Africa) study demonstrated that 6 months of IPT combined with early antiretroviral therapy (ART) resulted in a 44% reduction in the risk of severe HIV-related illness, and reduced all-cause mortality by 35%.[12] IPT was shown to reduce mortality among tuberculin skin test (TST) positive individuals with CD4+ T-cell counts >200 cells/mm^3 in Tanzania,[11] while a study conducted in South Africans on ART initiating IPT reported a 49% reduction in mortality that remained significant even for those with a past history of TB.[10] However, TST-positive patients were shown to benefit the most by completing a 36-month course of IPT, resulting in a 74% reduced risk of active TB and a 68% reduction in mortality compared to 6 months of IPT.[13]

Data on IPT outcomes in ART-experienced patients previously exposed to anti-tuberculosis treatment are limited. The purpose of the present study was to report on clinical, programme-related outcomes and challenges experienced with IPT implementation in an ART and TB treatment-experienced population and its effect on TB incidence in a high TB-HIV burden setting.

METHODS

Study setting and design

The study was based in Durban, KwaZulu-Natal, South Africa, where an estimated 70% of TB patients are HIV-co-infected.[14] Conducted between 2009 and

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2013, the Centre for the AIDS Programme of Research in South Africa's CAPRISA 005 TB Recurrence upon Treatment with HAART (TRuTH) study was a prospective cohort study assessing TB recurrence among patients initiated on ART. From 2011 onwards, IPT was offered to adult patients aged ⩾18 years accessing HIV care in an urban clinical research centre in accordance with national treatment guidelines.[15] We present a secondary analysis of prospectively collected clinical and demographic data extracted from patient files and computerised pharmacy dispensing records for the period from October 2009 to October 2013.

Antiretroviral therapy and tuberculosis treatment procedures

At IPT initiation, all patients were receiving ART according to current national treatment guidelines.[16] Adherence to ART was assessed using pill count data from returned unused medications. Patients diagnosed with active TB received a TB retreatment regimen aligned with the local standard of care. Patients who agreed to monthly IPT collection, with no signs and symptoms of active TB and no clinical contraindications to INH, were deemed eligible and offered a 6-month course of IPT. Patients were ineligible for IPT if they had a previous history of alcohol abuse, viremia or renal and/or hepatobiliary abnormalities. Routine TST was not required to screen for IPT eligibility.

Isoniazid preventive therapy procedures and patient management

INH was prescribed as follows: 300 mg for those weighing ⩾ 60 kg, 250 mg for those weighing 50–59.9 kg and 200 mg for those weighing 40–49.9 kg. A research nurse managed the patients on a monthly basis while they were on IPT, screened for TB symptoms and referred complicated cases and patients with presumptive TB to a clinician for assessment. If active TB was suspected, INH was stopped and the patient was referred immediately for investigation. Incident TB was diagnosed microbiologically using induced sputum smear microscopy and culture. Patients were screened for INH-related side effects, and those who showed symptoms of liver toxicity, or in whom the clinician suspected liver toxicity, underwent liver function monitoring. INH-related toxicity was graded using the Division of AIDS toxicity table for grading the severity of adverse events (Version 1.0 December 2004). Pyridoxine was co-administered for peripheral neuropathy prophylaxis.

The IPT adherence support programme (ASP) was counsellor-driven and aided by a multidisciplinary inter-referral system between nurse, clinician and pharmacist to improve IPT course completion rates. The pharmacist confirmed eligibility for IPT every month before dispensing INH, conducted pill counts, dispensed INH and counselled on its appropriate use and storage. Data generated from the computerised dispensing system were used to provide feedback to the clinical team on the duration of INH treatment, missed visits, course completion and interruptions.

Statistical analyses

Continuous data were summarised using means with standard deviation or medians with interquartile range (IQR). Categorical data were summarised using percentages. Wilcoxon signed rank-sum test was used to compare selected laboratory measurements before and after IPT initiation.

TB incidence rates and duration of follow-up before and after IPT initiation were calculated from TRuTH study enrolment to either date of TB diagnosis or one day before the date of IPT initiation, and from IPT initiation to either the date of TB diagnosis or the study termination date, respectively. Mean monthly adherence to IPT was assessed across all visits by comparing the number of tablets returned at the current visit with the number of tablets dispensed at the last clinic visit compared to the number of tablets that should have been ingested between visits. Overall median adherence was then calculated using the monthly mean adherence at each visit.

Univariate and multivariate log-binomial regression models were used to identify predictors of IPT completion. To account for multiple measurements for each participant, generalised estimating equations (GEE) for a multivariate, repeated-measure logistic regression model were used to identify predictors associated with high IPT adherence (⩾80%) over time. Previous studies have used a 80–90% adherence threshold to describe optimal adherence to IPT.[17–19]

Statistical analysis was performed using SAS, version 9.4 (Statistical Analysis System, Cary, NC, USA). All statistical tests were conducted at 5% level of significance.

Ethics

Ethics approval was obtained for the analysis from the University of KwaZulu-Natal (UKZN) Biomedical Research and Ethics Committee, Durban, South Africa (reference numbers: BE373/14 [secondary analysis], BF051/09 [TRuTH Study]).

RESULTS

Demographic and clinical data

Of the 212 patients initiating IPT, 38.7% were male, there was a median body mass index (BMI) of 26.5 kg/m^2 (IQR 23.3–30.3), and 26.3% had had more than one previous TB episode. Significantly more females than males initiated IPT ($n = 130$, 61.3% vs. $n = 82$, 38.7%, $P = 0.001$) (Table 1); however, other

Table 1 Characteristics of patients on IPT compared to those not on IPT

Variable	Initiated on IPT ($n = 212$) n (%)	Not initiated on IPT ($n = 190$) n (%)	P value
Baseline demographics			
Age, years, median [IQR]	37 [31.5–44]	37 [32–42]	0.811
Ethnicity			
Mixed race	1 (0.5)	2 (1.1)	0.605
Black	211 (99.5)	188 (98.9)	
Sex			
Male	82 (38.7)	104 (54.7)	0.001
Female	130 (61.3)	86 (45.3)	
Clinical characteristics			
CD4 count, cells/mm^3, median [IQR]*	470 [343–662]	426.5 [309–601]	0.069
Viral load*			
Detectable	31 (14.6)	42 (22.1)	0.069
Undetectable	181 (85.4)	148 (77.9)	
ALT, IU/l, median [IQR]†	19.5 [15–27]	20 [16–31]	0.153
AST, IU/l, median [IQR]†	27 [23–33]	28 [23–36]	0.441
Haemoglobin, g/dl, mean ± SD‡	13.4 ± 1.6	13.7 ± 1.6	0.037
Previous episode of tuberculosis			
1	139 (65.6)	140 (73.7)	0.084
>1	73 (34.4)	50 (26.3)	

* 23 with missing data.
† 6 with missing data.
‡ 21 with missing data.
IPT – isoniazid preventive therapy; IQR – interquartile range; IU – international unit; ALT – alanine aminotransferase; AST – aspartate aminotransferase; SD – standard deviation.

baseline characteristics were not statistically significantly different among IPT initiates and non-initiates. Approximately 77.4% of patients initiating IPT were on a tenofovir-containing first-line ART regimen and had received a median of 4.1 years of ART, 91% of whom were virologically suppressed, with a median CD4+ T-cell count of 571 cells/mm^3 (IQR 421–737).

Uptake of isoniazid preventive therapy

Among 402 patients assessed for IPT initiation (Figure 1), 344 (85.6%) were deemed eligible; 58 (14.4%) were not considered for IPT: 34 (8.4%) were ineligible and 24 (6%) exited the study before being offered IPT (lost to follow-up, deceased, withdrew from study participation or relocated). Reasons for IPT ineligibility were as follows: previous or current drug-resistant (DR) TB ($n = 7$, 1.7%), current active or presumptive drug-susceptible TB ($n = 9$, 2.2%), other clinical contraindications ($n = 10$, 2.5%), and a combination of the reasons mentioned above ($n = 8$, 2%). Among eligible patients, 212 (61.6%) initiated IPT, while 132 (38.4%) refused IPT: 119/344 (34.6%) due to inability to adhere to monthly visits, 9 (2.6%) did not provide any specific reasons, 2 (0.6%) refused due to added pill burden, and 2 (0.6%) for fear of additive toxicity. IPT completion rates were 86.8% and median adherence to IPT assessed by pill count was 97.6% (95% confidence interval [CI] 94.2–99.4) (Figure 2). There were no statistically significant predictors of IPT course completion (Table 2).

Isoniazid preventive therapy outcomes

Among IPT initiates, 167 (78.8%) completed the

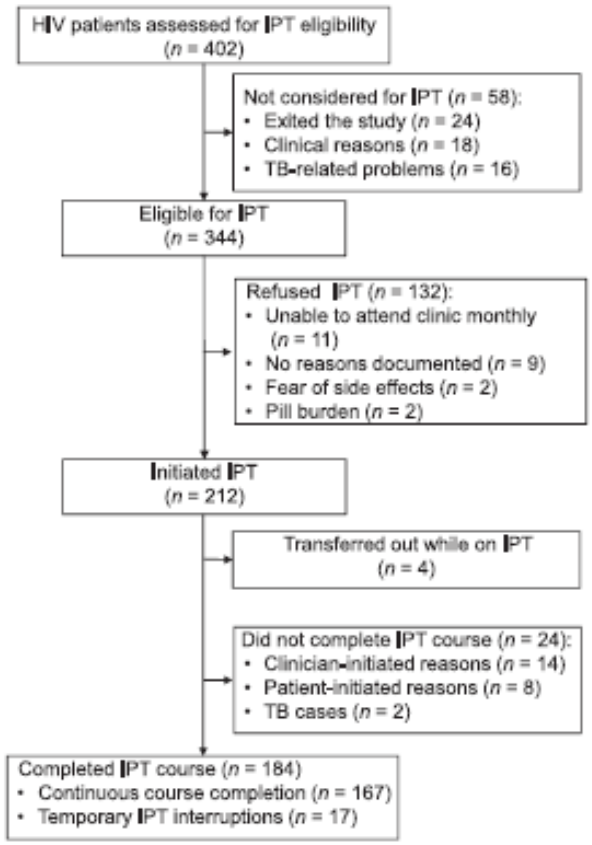

Figure 1 IPT uptake and course outcomes. HIV = human immunodeficiency virus; IPT = isoniazid preventive therapy; TB = tuberculosis.

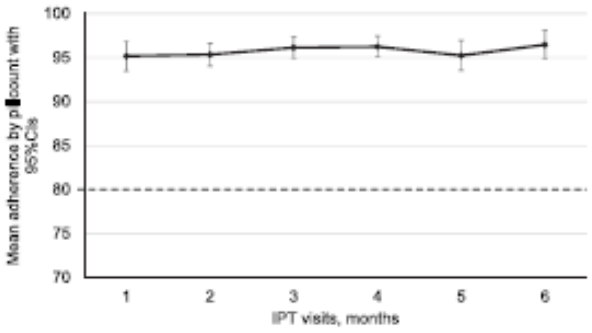

Figure 2 Adherence to IPT by monthly pill count. CI = confidence interval; IPT = isoniazid preventive therapy.

course of IPT (Figure 1) with no interruption. Overall median treatment duration was 174 days (IQR 167.0–180.3). IPT was interrupted in 45 patients: 24 (11.3%) permanently discontinued IPT, 17 (8%) temporarily interrupted treatment (16 due to suspected TB and 1 for an intercurrent illness), for a median duration of 64 days (range 52–92), and 4 (1.9%) transferred out before IPT completion. Reasons for permanent discontinuation included INH toxicity ($n = 8$), grade 2/3 skin rash and abnormal liver function tests [$n = 2$]), TB suspected ($n = 7$), patient requested withdrawal ($n = 3$), TB confirmed ($n = 2$), did not attend visits ($n = 2$), alcohol abuse ($n = 1$), and history of DR-TB that had been previously missed ($n = 1$).

Approximately 2.8% (6/212) of the study participants experienced moderate to severe liver function test abormality; however, only two needed to discontinue IPT. Participants' median aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels measured during IPT use were significantly higher (27 international units [IU]/l ALT, 32 IU/l AST) than levels measured before IPT (23 IU/l ALT, 29 IU/l AST; $P < 0.001$) (Figure 3). Median AST and ALT levels dropped after IPT to a median of 23 IU/l and 29 IU/l, respectively, compared to during IPT ($P < 0.001$) (Figure 3). There was no statistically significant difference of IPT effect on median AST ($P = 0.081$) and ALT ($P = 0.51$) levels before and after IPT.

Impact of isoniazid preventive therapy on tuberculosis incidence

There were 22 cases of incident TB in this cohort: 13 occurred before and 9 after IPT (incidence rate ratio 0.67, 95%CI 0.29–1.58, $P = 0.362$; Table 3). Of the 9 cases of TB that occurred in those who underwent IPT, 2 cases of drug-susceptible TB were diagnosed 5 months into IPT, while 6 patients developed TB after completing the IPT course and 1 patient who had not completed IPT later developed TB. Incident TB was diagnosed a median of 279 days (IQR 141–336) after completing the 6-month course of IPT.

DISCUSSION AND CONCLUSION

Our study showed high IPT uptake, adherence and completion rates, with minimal interruption for IPT-related adverse events among chronic stable HIV-infected patients on ART who had all been treated for TB previously. Presumptive TB impacted IPT initiation and interruption rates. Among ineligible patients, suspected TB, confirmed TB and/or DR-TB accounted for 27.6% of patients not being considered for IPT, while the majority of IPT interruptions (57.8%) were due to suspected TB. However, only two of the 26 patients who interrupted treatment were diagnosed with TB. Given the high TB burden in the study setting, the index of suspicion for incident TB by health care workers was understandably high, resulting in frequent IPT treatment interruptions for TB investigation.

Before 2010, patients previously exposed to anti-tuberculosis treatment were considered ineligible for IPT. Because of the small numbers and reduced

Table 2 Predictors of IPT adherence and IPT completion

	IPT adherence				IPT completion			
	Univariate		Multivariate		Univariate		Multivariate	
Variable	OR (95%CI)	*P* value	aOR (95%CI)	*P* value	RR (95%CI)	*P* value	aRR (95%CI)	*P* value
Age (per 5-year increase)	0.94 (0.81–1.1)	0.441	0.98 (0.83–1.17)	0.843	0.99 (0.97–1.02)	0.637	1.01 (0.77–1.32)	0.944
Sex (reference: male)								
Female	1.65 (0.99–2.72)	0.050	1.47 (0.73–2.97)	0.286	1.05 (0.94–1.18)	0.384	1.64 (0.63–4.24)	0.309
CD4+ cell count (per 50 cells/mm^3 increase)*	1.06 (1.01–1.12)	0.043	1.03 (0.97–1.1)	0.273	0.99 (0.98–1.01)	0.411	0.97 (0.88–1.06)	0.442
Years on ART*	1.09 (0.83–1.44)	0.536	1.01 (0.75–1.36)	0.952	0.97 (0.91–1.02)	0.256	0.81 (0.52–1.28)	0.372
Haemoglobin (per g/dl increase)*	0.92 (0.79–1.07)	0.286	0.99 (0.84–1.17)	0.956	0.79 (0.59–1.05)	0.104	No estimate	
Previous episodes of TB (reference: >1)								
1	1.09 (0.65–1.83)	0.744	1.03 (0.60–1.76)	0.912	0.89 (0.38–2.08)	0.784	1.10 (0.45–2.71)	0.828

* Before IPT initiation.
IPT = isoniazid preventive therapy; OR = odds ratio; CI = confidence interval; aOR = adjusted OR; RR = risk ratio; aRR = adjusted RR; ART = antiretroviral therapy; TB = tuberculosis.

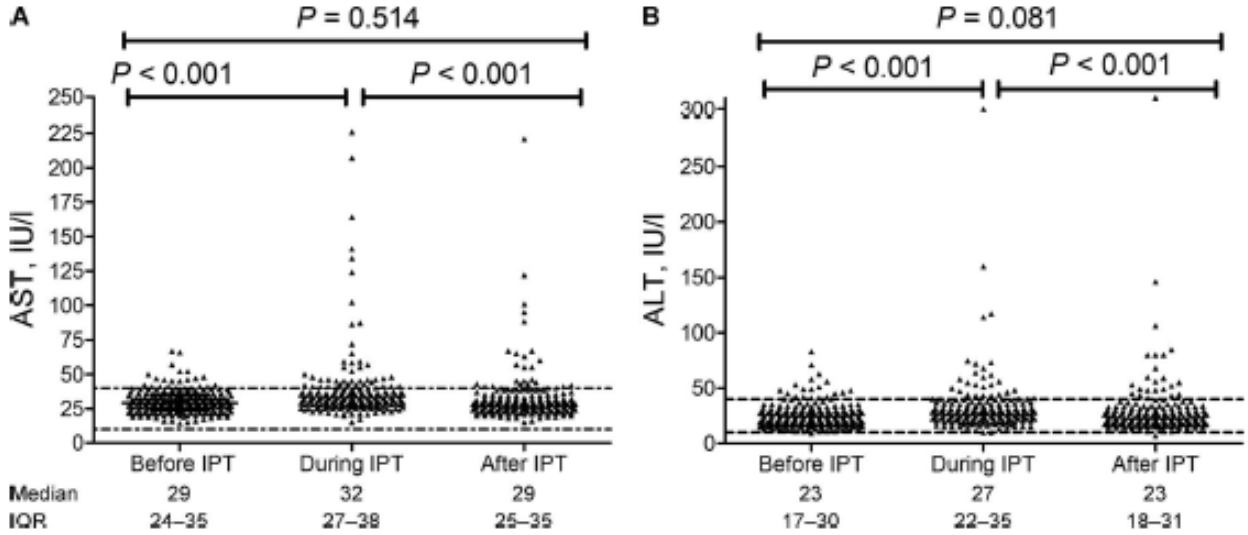

Figure 3 Liver function indicators in IPT users taken within 3 months before IPT initiation: **A)** AST; **B)** ALT. AST = aspartate aminotransferase; IU = international unit; IPT = isoniazid preventive therapy; ALT = alanine aminotransferase; IQR = interquartile range.

follow-up, we found a non-significant reduction in TB incidence of 33% after 6 months of IPT among patients with previous TB on ART. IPT is effective in this important group of individuals at high risk of both recurrent and DR-TB; however, a reduction by a third in incidence is not acceptable, given the high background TB transmission rates and the synergistic effect of ART in this population. Studies involving South African gold miners reported that 6 months of IPT significantly reduced TB incidence by 55% in one study and 38% in the other,[20,21] albeit in the absence of ART. Concomitantly administered IPT and ART in the THRio (TB/HIV in Rio) study showed a 76% reduction in TB incidence after adjusting for age, past TB and immune status.[22] Patients in our study had moderate immune dysfunction, as IPT was started at a median CD4$^+$ T-cell count of 571 cells/mm^3. Data from sub-Saharan Africa suggest that concurrent ART and IPT,[12,23,24] or ART initiation soon after IPT completion,[25] results in higher reductions in TB incidence than treatment with either IPT or ART alone. The TEMPRANO study, conducted in patients with a CD4$^+$ T-cell count > 500 cells/mm^3, also found a 57% reduction in TB incidence among early ART and IPT initiates compared to those who did not undergo IPT.[12] The gender disparity observed in this study, where more females initiated IPT than males, is congruent with previous reports.[12,13,25,26]

Our findings suggest that 6 months of IPT is safe and well tolerated in patients with previous TB disease, although a statistically significant protective effect was not shown in this cohort. Current WHO guidance, also supported by other research,[13,26,27] recommends that IPT be provided for up to 36 months in high TB burden settings.[3] It should be noted that the TEMPRANO trial reported that 6 months of IPT initiated with immediate ART significantly reduced the risk of severe HIV-related disease (44%) and all-cause mortality (35%).[12] Overall, we were able to successfully integrate IPT visits with existing clinic ART visits, resulting in high IPT completion rates, further underscoring the efficiency of IPT/ART programme integration, and reported benefits beyond the reduction in TB incidence.[22,25]

A meta-analysis reported highly variable IPT uptake in sub-Saharan Africa, ranging from 13% to 95%.[28] In our study, the requirements for monthly IPT follow-up visits was the most common reason for IPT refusal (34.6%), likely due to high unemployment and the costs associated with frequent clinic attendance. Strategies aimed at improving IPT uptake need to optimise IPT access, reduce clinic attendance, find innovative and convenient ways to enhance adherence to IPT and ART and monitor for TB disease.

The effect of IPT on liver toxicity and return to normal liver function post IPT cessation were similar to findings among patients taking 9 months of INH.[29] The prevalence of grade 2 and 3 liver toxicity events was similar to the 6-month, open-label phase of the BOTUSA (Botswana-USA Partnership) study.[30]

Adherence to IPT has been described previously using IPT completion rates, medication adherence

Table 3 TB incidence before and after IPT

	Before IPT initiation (n = 212)	After IPT initiation (n = 212)
TB cases, n	13	9
Person-years	328.1	337.3
TB incidence rate (95%CI)	4.0 (2.1–6.8)	2.7 (1.2–5.1)
IRR (95%CI)	0.67 (0.29–1.58); P = 0.362	

TB – tuberculosis; IPT – isoniazid preventive therapy; CI – confidence interval; IRR – incidence rate ratio.

(pill count) or prescription refills. Our IPT completion and adherence rates were similar to reports from other African studies, with findings ranging from 78% to 98.9%.[12,13,17,19,31–33] We attributed high IPT adherence to the well-resourced clinical research setting, structured adherence support programme and the need to attend the clinic for ART. There is strong evidence supporting the combination of ART use with IPT to significantly improve IPT adherence.[13,17,19,31] While some studies reported predictors of IPT completion and adherence such as ART use and/or knowledge on IPT,[17,34] we did not measure all these variables in our study. However, although this was not statistically significant, females tended to have greater adherence. Others have reported that men demonstrate increased odds for loss to follow-up and non-adherence to IPT than women.[35]

There were several study limitations. The small sample size undermined our ability to show a statistically significant impact of IPT in patients with previous TB. Furthermore, our model of IPT implementation may not be generalizable to the public sector health care setting, given the resources directed to regularly timed TB symptom screening and laboratory and radiological investigations aimed at evaluating incident TB in the parent study. This may have led to overly high rates of suspected TB and subsequent non-eligibility for IPT or IPT interruption.

IPT is an effective TB prevention intervention within ART programmes. The 6-month IPT roll-out in a TB-endemic setting was successful, with good uptake of IPT, minimal course interruptions or side effects reported, and the majority of the cohort of ART patients with a history of anti-tuberculosis treatment completed the IPT course. More efficient point-of-care diagnostics for TB may play a role in reducing IPT course interruptions and re-entry into the IPT programme. TB continues to undermine the success of ART programmes in sub-Saharan Africa, and our findings add to the body of evidence guiding operational IPT implementation.

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Conflicts of interest: none declared.

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3.2 Discussion of the paper

South Africa has the largest ART programme in the world and is also home to the largest cohort of patients ever initiated on IPT since the WHO recommended intervention for TB prevention was adopted, in country, in 2010. There is a paucity of IPT related data within TB/HIV integrated programmes in dual high burden settings. The paper submitted addresses IPT outcomes in an ART and TB treatment experienced urban population in keeping with the objectives outlined in this thesis with the intention to contribute to bridging the existing knowledge gap. We hypothesized that 6 months of IPT would decrease TB incidence in a high HIV/TB burden setting amongst a treatment experienced cohort.

The baseline social characteristics of patients enrolled into the TRuTH Study were presented using descriptive statistics. Other baseline patients' characteristics related to IPT were collected, at least within 3 months closer to the time point at which IPT initiation occurred. Data on various IPT implementation outcomes were reported. Wilcoxon signed rank sum test was used to compare selected laboratory measurements before and after IPT initiation. Univariate and multivariate log-binomial regression models were used to identify predictors of IPT completion. To account for multiple measurements for each participant, generalised estimating equations (GEE) for a multivariate repeated measure logistic regression model was used to identify predictors associated with high IPT adherence (≥80%) over time. The variables modelled included age, gender, Hb, CD4, number of TB episodes in the past and years on ART. Statistical analysis was performed using SAS Version 3.2 (SAS Institute, Cary, North Carolina).

Eligibility for IPT was high in this setting but uptake of IPT was moderate (61.6%). Trends for not accepting IPT were identified; more males refused IPT (54.7%; $p<0.001$) and the most commonly attributed reason for refusal was the inability to attend monthly clinic visits (34.6%) that were required for IPT. IPT exposure resulted in a non-significant decrease of 33% in the TB incidence rate amongst IPT users. There were 13 TB events before and 9 events after IPT exposure. Completion rate (86.8%) and adherence to IPT (97.6%) remained high amongst patients. Women and those with a higher CD4+ T-cell count tended to show better IPT adherence. Age, gender, CD4, Hb, previous TB episodes and years on ART were not identified as predictors IPT adherence or completion in the univariate or multivariate analysis. An investigation of LFT levels before, during and after IPT use showed no significant toxicity was sustained with 6 months IPT (AST: $p=0.514$; ALT: $p=0.081$). IPT was well tolerated overall and the occurrence of adverse events due to INH was minimal (3.8%).

Six month IPT roll-out in a TB/HIV endemic setting was successful. Overall, we demonstrated that IPT is a safe and tolerable TB prevention intervention within ART programmes and importantly amongst patients on ART with TB treatment experience.

3.3 Master's student contribution

Student Name: Bhavna Maharaj

Student number: 9705220

Title of the article: **Isoniazid Preventive Therapy implementation within an ART programme in a TB-treatment experienced cohort**

Authors: **B Maharaj**, XXXX, N Yende-Zuma, A Naidoo, K Naidoo

Journal: International Journal of Tuberculosis and Lung Disease

Master student's contribution:

1. CAPRISA 005 TB recurrence upon Treatment with HAART (TRuTH) Study-

I served as a pharmacist on the study within the pharmacy team, including amongst others Anushka Naidoo (Senior Pharmacist) and XXXX (Head of Pharmacy), who dispensed IPT and ART to all the patients enrolled. My duties and contribution included the following:

- Dispensed directly to patients using computerised dispensing system
- Involved in design and implementation of IPT Adherence Support Programme (ASP) material for ART/IPT counsellors at the clinic. This included initial training of counsellors for IPT ASP as well as ongoing staff refresher training and training of new staff. We conducted second check or verification of IPT ASP administered to patients by counsellors, regularly provided feedback on IPT ASP process by telephone, at meetings or face-to-face.
- Counselled patients with IPT adherence or compliance issues
- Referred patients with poor adherence to IPT at follow up visits for ASP, if needed
- Conducted physical pill counts and completed pill count plates at each monthly visit
- Ensured accurate completion of TB symptom Checklist on patients INH script by clinical staff at each monthly visit
- Verified weight based INH dosing reference ranges were adhered to and dose adjustments made if required, at each follow up visit
- Provided weekly/monthly feedback on IPT statistics to the clinic team and DOH
- Ordering and procurement of INH stock, stock management of INH stock to ensure site needs were met and adequate levels maintained at all times.

2. Formulation of Hypothesis

Working in conjunction with my supervisor, XXXX, we formulated the study hypothesis, concept sheet and research proposal for this post graduate study which was submitted to UKZN Biomedical Research Ethics Committee and Postgraduate Office for expedited review to obtain ethical clearance and full approval to conduct the study.

3. Study Design

Kogieleum Naidoo was the site project director and principal investigator in the TRuTH Study. She was involved in initial site IPT training and guided the TB incidence analysis. Santhana Gengiah served as TRuTH Study co-ordinator and assisted with integrated ART/IPT clinic flow design. The retrospective analysis of TRuTH Study data and pharmacy IPT data was designed and conducted by myself under supervision of Tanuja N. Gengiah, Head of Pharmacy.

4. Data Analysis

I reviewed pharmacy IPT prescriptions, pharmacy computerised dispensing records and source documents and CRFs in patient clinic files together with an MS Excel download of the study electronic database provided by the statistician, Nonhlanhla Yende-Zuma. I identified errors and incomplete data entries as well as resolved queries generated by the statistician on the relevant CRFs. The update CRFs were re-faxed into the electronic database after quality control and validation with CAPRISA data management department. I conducted some initial analyses on the pharmacy computerised dispensing system, iDART, as well as data extraction from clinical chart notes and CRFs using MS Excel and created some of the tables and figures used in the manuscript on Graph Pad Prism 5. The statistician, Nonhlanhla Yende-Zuma, created and reviewed tables and figures during all variable tests, adherence assessments and multivariate analysis in SAS version 3.2 and confirmed all analyses.

5. Write up

I took overall responsibility for writing up and preparing the draft manuscript before submitting to all co-authors for review and input. All the co-authors feedback and comments were considered and incorporated into the revised manuscript and then sent for internal review to the CAPRISA Scientific Review committee (SRC). Recommendations for improvement and approval to submit were received from the SRC before the final version of the manuscript was submitted to the journal. Turnitin was used to verify originality and authenticity of the manuscript before final submission.

I declare the above to be a true reflection of my contributions to this journal article.

Signature  Date: 28 NOV 2016

CHAPTER FOUR:
OVERALL DISCUSSION

4. CHAPTER FOUR: OVERALL DISCUSSION

4.1 Discussion of major findings

TB remains the leading cause of death amongst HIV positive people around the world (123). The 2016 WHO TB Global Report highlighted very disheartening statistics with only 9 of the 30 countries with the highest dual burden of TB and HIV reporting provision of TB preventive therapy (123). While IPT has been proven to be an effective strategy in many settings for TB prophylaxis, it is still an under-utilised intervention; irrespective of the clear evidence that it saves lives and offers a line of defence in the face of the overwhelming and rapidly increasing rates of TB transmission and re-infection amongst HIV infected people.

Prior to 2010, people with a past history of TB were excluded from receiving IPT since IPT was intended to be a primary preventive measure prior to a first episode of TB and there was not enough evidence to support its use in former TB patients. Moreover, ART provision and TB treatment services were segregated and still remain so globally, including regions in SSA. Previous reports have highlighted provider related barriers to IPT implementation. These include lack of knowledge of IPT, lack of access to policies, guidelines or adequate training which would translate to missed opportunities for other preventive measures including TB screening, IPT and ICF.

We were able to demonstrate that IPT could be successfully introduced into HIV care and taken up by a unique cohort of patients on ART where every single patient had TB previously and was exposed to TB treatment. IPT was safe and well tolerated among our patients. Importantly, once patients started IPT they maintained high levels of adherence and the majority completed the IPT course successfully. Our findings add to the existing evidence of the benefit of integrated IPT with ART in this specific high risk group of patients where previously published data on IPT outcomes has been very limited.

The aims for our study was to assess both the operational and clinical outcomes of IPT programme implementation in a high burden TB/HIV co-infection setting in a unique cohort of patients on ART and also previously exposed to TB disease and treatment. Each objective of this study was met as follows:

4.1.1 Primary Objective 1: To assess the design and implementation of IPT roll-out within an ART programme

A strategy entailing combining chronic clinic visits for ART collection with IPT collection at the same visit represents the ideal approach to aid successful uptake of IPT. In our study we were able to demonstrate effective integration of TB prevention services with HIV care. IPT provision was feasible in our HIV clinic, located in dual high disease burden setting, and found to be acceptable as demonstrated by the high uptake of IPT by patients on ART. The flow of the procedures required during IPT enrolment and follow up visits were integrated into existing ART clinic visits. The high

IPT adherence and 6-month course completion rates were attributed to patients being accustomed to taking ART and being encouraged by the staff to adopt the same adherence strategies with IPT as they did with ART. The current research showed that the majority of patients that were poor adopters of IPT due to the monthly clinic visits required for IPT collection. These patients remained at risk for incident TB or if they were previously exposed to TB, but now stable on ART, at higher risk for recurrent TB. Integrating IPT implementation into existing ART programmes provides an opportunity to increase retention rates, improve IPT uptake and enhance adherence to the IPT regimen

In support of concomitantly administered IPT and ART, the THRio study demonstrated a 76% reduction in TB incidence after adjusting for age, past TB and immune status (32). Researchers that assessed the 6 month open label phase of IPT in the BOTUSA study linked the lower incident TB rate observed with concomitant use of ART amongst the patients enrolled in the study (48). Data from SSA has demonstrated that concurrent ART and IPT (31, 53, 54) or initiating ART soon after completing IPT (68) results in higher reductions in TB incidence compared to treating with either IPT or ART alone. It is important to remember that even though not statistically significant in our study, TB incidence was reduced among those patients that took IPT. When comparisons were made of TB incidence or the number of TB cases reported before and after IPT exposure, TB incidence of those that did not take up IPT remained the same in the study (Table 9).

More recent findings from Tanzania also reported high acceptability of IPT integration among patients on ART and corresponding high rates of IPT adherence and course completion (85). A study conducted in the Democratic Republic of Congo in 2014 reported rates of IPT uptake at 73% and 88.2% completion; notably patients on ART at IPT initiation were more likely to complete IPT than those who were not [89.2 vs. 83.3%; aOR1.54 (95%CI,1.02- 2.32)] (81). The TEMPRANO study, conducted in patients with a CD4+ T-cell count > 500 cell/mm3 also demonstrated 57% decrease in TB incidence among early ART and IPT initiates compared to those who didn't use IPT (31). The effect of early ART initiation was seen at month 12 with 84% of the cohort had achieved undetectable viral loads & 83% remained undetectable at month 24. Overall, CD4+T-cell count remained>500 cells/mm^3 for 51% of the time. The cumulative probability of death or severe HIV-related illness was 5.7% in the early arm and 8.8% in the deferred arm. Thus the main finding from TEMPRANO highlighted that early ART integrated with IPT lowered severe HIV-related illness by 44% and all-cause mortality by 35%. The risk of death also decreased by 35% compared to the deferred group.

Looking at the benefits derived from IPT implementation in the studies described above, we can see that our study re-affirmed that the implementation of IPT can reduce incident TB among patients on ART previously treated for TB, although this was not statistically significant. Adopting IPT as part of a TB prevention package with ART enhanced the level of clinical care provided and improved outcomes in patients at high risk for recurrent TB.

Over and above the beneficial impact that IPT implementation had on patient health, the clinical skills of the healthcare providers at our clinic were improved. Having the capacity to provide clinical care for both HIV and IPT resulted in a more comprehensive healthcare service to the HIV infected patient. In addition, service integration provided an opportunity to conduct intensified case finding of TB and provide IPT services for TB prevention within an already strong, established HIV setting with many support structures in place to act as an adjunct to the implementation of TB prevention efforts. The roll out of IPT began efficiently with minimal logistic or operational issues experienced since it was built upon an existing HIV services in our facility. There was little to no need for extensive resources to be laid out so minimum effort but maximum output of IPT programme implementation benefit was achieved.

The provision of ART, TB and IPT services as part of an integrated package is integral to the success of TB prevention campaigns. The ultimate goal of national health programmes in SA and other high burden countries around the world should be to aspire to attain zero TB transmission and re-infection rates, with IPT and other TB preventive measures as part of the arsenal. Much work is still needed to "stop TB in our lifetime" (Stop TB partnership World TB Day 2012/2013 slogan: Stop TB in my lifetime).

4.1.2 Primary Objective 2: To report on the outcomes of the IPT roll-out

The current study was able to explore TB incidence and other clinical outcomes of IPT as well as areas of IPT implementation that require strengthening and modification. This objective was achieved as follows:

Our study showed good IPT uptake, high adherence and completion rates with minimal course interruption for IPT related adverse events. These findings suggest that 6 months of IPT was safe, effective and well tolerated amongst stable HIV infected patients on ART who had all been treated for TB previously.

IPT uptake

We found the overall IPT uptake in our study (61.6%) to be good but lower than expected in this context. Previous reports of low uptake and course completion were due to poor knowledge of IPT and poor patient understanding of the concept of TB prevention (93), whilst others reported being motivated by fear of TB and its related complication or being knowledgeable of the potential benefit of IPT that contributed to high IPT completion rates (75). Similarly, our patients were kept informed through education, awareness campaigns and information sharing sessions via group education sessions. Routine individual adherence support was provided by all categories of staff (counsellors,

pharmacy staff, nurses and clinicians) on aspects including, but not limited to, IPT importance, management of side effects and how to cope with co-infection.

Taking into consideration the support given knowledge and experience our patients have gained by being on ART for years and having managed either one or more courses of TB treatment, we had anticipated a much higher percentage than the 61.6% of the cohort accepting the benefits of TB prevention. With this history in mind, the candidate looked further into patients' reasons for refusal of IPT. Socioeconomic related factors, most-likely may have contributed to the lower than the 75-80% uptake expected. In our study the requirements for monthly IPT follow up visits was the commonest reason for IPT refusal (34.6%), probably due to high unemployment rates and the associated costs of frequent clinic attendance. This reasoning provides a partial explanation, as we also noted that more males (54%) refused IPT, which was a significant finding observed in this study and discussed further below.

Various studies have reported on themes related to stigma and poor socio-economic status, amongst others, which have had a detrimental effect on IPT use (86, 118, 120). Norms of society dictate that men are usually the breadwinners in the household (124). It can be safely inferred that the added burden of loss of earnings with having to miss days at work every month in order to attend clinic, or being afraid to request time off from work as a result of non-disclosure contributed to IPT refusal. Stigma associated with HIV and TB still exists in communities. A meta-analyses shows highly variable IPT uptake in SSA ranging from 13-95%(45). Even more concerning were the high rates of loss-to-follow-up reported with associated poor IPT course completion and outcomes (118, 125). In comparison, the majority of patients in our study that started IPT eventually completed the course, contributing to the high completion rate observed (86.8%). Strategies aimed at improving IPT uptake and retention need to optimise IPT access, reduce clinic attendance, find innovative and convenient ways to enhance adherence to IPT and ART and symptom monitoring for new TB infection.

Contribution of background TB to IPT ineligibility

It was observed amongst ineligible patients in our study that presumptive TB, confirmed TB and/or drug resistant (DR) TB accounted for almost a third of patients not being considered for IPT. Once patients initiated IPT, continuity of the course was monitored and reasons for any IPT interruptions was documented. One of the main reasons cited for IPT interruptions was presumptive TB. However, only two of the 26 interruptions were eventually diagnosed with TB. Given the high TB burden in the study setting, the index of suspicion for incident TB by HCWs was understandably raised, resulting in frequent IPT treatment interruptions for TB investigation. A study that conducted an operational assessment of IPT in Uganda reported that of those non-eligible for IPT, 79% were due to active or presumptive TB (125). Findings from Botswana looking at reasons for non-eligibility for IPT highlighted that 66% of those found in-eligible at the first phase of IPT screening had illness, though

not necessarily indicative of TB, and the subsequent second phase of IPT screening identified 35% not eligible due to chest radiograph indicative of active or presumptive TB (48). More efficient point of care diagnostics for TB such as GeneXpert may play a role in reducing IPT course interruptions, and re-entry into the IPT programme.

Gender disparity in IPT uptake

Gender differences in IPT uptake are evident with more females taking up the TB prevention intervention than males consistent with other studies: a study in South Africa (19) in 2009 reported 80% of IPT users were female while researchers in Ethiopia observed uptake of IPT of 61.4 – 69.6% in women (13, 24). Another study observed that more men were reported as non-adherent and lost-to-follow-up (aOR: 2.24, 95%CI, 1.24-4.04) and (aOR: 3.08; 95%CI, 1.50-6.33) respectively. A study in South Africa reported men were more likely to get TB (IRR 1.46; CI 1.09-1.94). It can be inferred from these findings that targeting males for enhanced supportive TB preventive counselling would be a valuable intervention to consider in improving IPT uptake in men.

Effect of IPT on TB incidence

For those patients in the TRuTH study that did not initiate IPT, the TB incidence rate remained more or less the same for the duration of the study. Due to the small numbers and reduced follow-up, we noted a decrease in TB incidence after 6-months of IPT exposure that was not statistically significant, among patients with previous TB on ART. We demonstrated that IPT works in this important group of individuals at high risk of both recurrent and drug resistant TB; however, a one third reduction in incidence is not acceptable considering the high background TB transmission rates and the synergistic effect of ART in this population.

Additional data on TB incidence data, one of the main objectives of the parent TRuTH study will appear in the publication of the outcomes of the parent study. For the purposes of this thesis, there were limited permissions granted with regards the extent to which TB incidence data could be reported in the IPT manuscript prior to the TRuTH study manuscript being published. Hence we looked at TB incidence only among those that took IPT. For the purposes of the thesis only, permission was granted from the parent study PI to discuss TB incidence among the entire cohort including those that were not exposed to IPT. These findings are presented in table 9, specifically for thesis purposes only and not for inclusion in the IPT manuscript.

Table 9: TB incidence in the TRuTH study

Variable	All patients: No IPT phase	Never started IPT	Initiated on IPT	
			Before IPT	After IPT
No. of TB cases	38	25	13	9
Person-years	906.1	578.6	328.1	337.3
TB incidence	4.2	4.3	4.0	2.7
95% CI	3.0 - 5.8	2.8-6.4	2.1-6.8	1.2 - 5.1

While TB incidence remain unchanged in those patients not exposed to IPT, there was a statistically non-significant decrease in TB incidence among those patient ever initiated on IPT compared to those who did not.

Implementing IPT among patients with a past history of TB and TB treatment exposure

Prior to 2010, patients previously exposed to TB treatment were considered ineligible for IPT. However, subsequent studies amongst mine workers in South Africa in the absence of ART provision have demonstrated an increased risk of recurrent TB for patients who have experienced previous episodes of TB (36, 69) and that IPT was effective, (RR 0.19; 95% CI: 0.04-0.42) and (IRR 0.62; 95% CI: 0.43-0.89) respectively. In settings with routine ART provision such as Brazil, the TB risk still remained (RR=1.37; 95% CI 1.04-1.80) (32). The similar risks would apply in our cohort where all 100 % had previously been treated for TB. The non-significant reduction in TB could also be interpreted as an indication that in this type of high risk cohort other interventions need to be put in place in conjunction with IPT implementation to enhance the protective effect. More research should be done on longer duration of IPT, combination preventive therapy with additional drugs or other re-purposed interventions specifically for those patients receiving preventive therapy secondary to TB treatment.

IPT associated resistance to INH

Two cases of TB were diagnosed while the affected patients were on their fifth month of IPT. Both cases stopped IPT and went on to be successfully treated for drug-susceptible TB. As discussed previously, fear of INH resistance has been reported as a major barrier to IPT implementation in the past yet existing evidence has shown that IPT has not significantly raised INH resistance (34, 35). It is important to continue track the impact of IPT on INH resistance. More research is needed on this particular aspect.

Duration of IPT

Current WHO guidance, supported by other research,(34, 76, 126) recommend that IPT be provided for up to 36 months in a high TB burden setting (38). Several studies have shown that IPT was more effective if the duration of IPT went beyond six months. In South Africa, a study conducted in Soweto using 12 months IPT either simultaneously or after ART reported TB incidence of 2.3 per 100 p-y compared to 3.6 per 100 p-y using placebo (126) .The BOTUSA Study reported a 43% TB reduction with 36 months of IPT compared to six months IPT provision in Botswana; the strongest impact occurring amongst TST positive individuals who demonstrated 74% TB reduction. Another South African study demonstrated that continuous IPT for 6 years resulted in 58% reduction in TB risk and death compared to 6 months IPT (76). Interestingly, the TEMPRANO trial demonstrated that 6 months of IPT initiated with immediate ART reduced the risk of severe HIV-related disease (44%) and all-cause mortality (35%) significantly (31). It stands to reason that the co-treatment with ART contributes to the benefits seen and should be considered along with the duration of IPT exposure. The above pinpoints a few reasons for the non-significant IPT effect seen in our cohort: small number of patients, shortened follow up time and insufficient duration of IPT. More research needs to be done to determine if patients with a past history of TB on ART would benefit more from extended IPT regimens rather than 6 months IPT.

Adherence to IPT

Adherence to IPT has been described previously using IPT completion rates, medication adherence (pill count) or prescription refills. Our IPT completion and adherence rates were similar to reports from other African studies with findings ranging from 78- 98.9 %.(31, 34, 48, 75, 81, 84, 85). The BOTUSA study measured adherence at Month 1, 3 and 6 where 91% of the cohort maintained > 80% adherence indicated by refill rate; notably 78% maintained > 80% adherence over 36 months of IPT use (34, 48). The TEMPRANO study showed 6-month completion rates of 94% in early IPT use and 93% amongst deferred IPT users. In our study we were able to report adherence by pill count as well as IPT course completion rate. We noted an IPT course completion rate of 86.8% similar to reports from other African studies: 87% in Tanzania (75) and 88.2 % in Kinshasa (81) respectively. Our finding of 97.6% adherence measured by pill counts was higher than the 89.5% self-reported adherence in Ethiopia (122) but slightly lower than a Tanzanian study that reported 98.9% (85) . High adherence in the current study may be attributed to the well-resourced clinical research setting, the structured adherence support programme, the patient being on ART and needing to come in to collect treatment. In addition, at the IPT screening visit patients who felt that they could not adhere to treatment or were deemed by the HCW as potentially non-adherent would have been excluded from the IPT programme after mutual agreement between the patient and HCW.

There is strong evidence for combining ART use with IPT to significantly improve adherence to IPT (34, 48, 85, 122). While some studies reported predictors of IPT completion and adherence such as ART use and/or knowledge on IPT (86, 122), other studies predicted non-completion in patients who

considered themselves to be at low risk for TB or did not recognise the benefits of IPT (127). We did not measure all these variables in our study. However, we noted a trend towards females being more adherent by pill count, although this finding was not statistically significant. A study conducted in 2011 similarly reported that men had increased odds of lost-to-follow up and non-adherence to IPT than women (117).Some of the more recent studies have raised the threshold of IPT adherence to 90% (previously 80%) (76, 85). Since concurrent use of ART and IPT is associated with enhanced adherence to IPT, we support raising the benchmark measurement of IPT adherence to 90%. This level would also not have any effect on our reported adherence to IPT in this study, as the average and median scores per participant as well as the overall median where all far above 90%.

Adverse effects related to IPT

The effect of IPT on liver toxicity and the return to normal liver function post IPT cessation was similar to findings amongst patients taking nine months of INH where the majority of the hepatic dysfunction cases resolved after IPT completion and the remaining IPT users noted an improvement to less than 3 times the upper limit of normal (88). There was a significant association between baseline liver function abnormality prior to IPT initiation and abnormal liver enzymes during IPT. The same study (88) also noted that liver enzyme abnormalities peaked at a median of three months after IPT initiation, also seen in the BOTUSA study that reported a prevalence of 1.1% hepatoxicity amongst the 26% of the cohort that received six months of IPT and ART (87).

There was also a similar prevalence of grade 2 and 3 liver toxicity events compared to the 6 month open label phase of the BOTUSA study (87). IPT interruptions due to toxicity in our study was minimal, side effects were reported in 3.8% of the cohort that were within the range of previous reports, usually ranging from 0.5% - 4% (31, 48, 126, 128). There were similarities identified between the side effects experienced by the patients in our cohort and other findings from SSA in terms of nature, severity and frequency the symptom. The most common side effect reported in our study that resulted in IPT being stopped was rash and is in keeping with reports from other studies (48, 69, 128). Some studies reported more cases of hepatitis and grade 2 or 3 LFT abnormalities, especially if the duration of IPT was longer than 6 months (126). Other studies reported pruritus, psychiatric symptoms, and other side effects that were not observed/reported in our patients (31).

Overall, we were able to successfully integrate IPT visits with existing clinic ART visits resulting in a high IPT completion rates, further underscoring the efficiencies of IPT/ART programme integration, and reported benefit beyond reduction in TB incidence (32, 68). It is imperative that we disseminate such findings to hasten IPT rollout in other countries that have yet to adopt this intervention. Foremost should be the outcome of IPT of any duration used in conjunction with TB prevention strategies among HIV infected people on ART and at risk of recurrent TB risks within high transmission burden settings.

4.1.3 Primary Objective 3: To describe the pharmacist's role in a multi-disciplinary approach to IPT implementation and roll-out

Community screening

Community/ retail pharmacists are relatively accessible HCWs (129) and are often the first point of contact for sick people (130, 131) and so are well placed to be able to identify and refer symptomatic patients with presumptive TB for further investigation, as well as household contacts of TB cases for IPT screening. Therefore, pharmacists and trained pharmacy staff could potentially play a dual role in assisting with detection of TB symptoms as well as promoting TB prevention through referrals of those who may benefit (131-133).

Monitoring IPT and TB symptom screening

Pharmacists would be an efficient and strategic cadre of HCW to monitor patients receiving IPT on an ongoing basis and continue to identify those displaying symptoms suggestive of presumptive TB or INH toxicity. In that way further investigations of side effects, diagnostic tests, intensified case finding and/or TB treatment initiation can be fast tracked. The standard dispensing roles would also apply to the operational aspects of the pharmacist activities within an IPT programme viz. procurement of INH, performing pill counts and adherence assessment. The pharmacist, in a combined role with other HCW, would ensure optimum use of INH for IPT by verifying that the correct dose was prescribed in accordance with the correct weight range and offer a shared role to decongest health care service with other members of the clinical team. In our study, the pharmacy staff reviewed whether weight and dose verification had been conducted by the nurses and clinicians and assessed the TB symptom screen outcomes as part of routine procedures during the clinic visits for each patient.

Data collection and reporting including tracking and retention efforts

As part of the multidisciplinary team the pharmacist and pharmacy staff contributed to tracking and retention of patients. The pharmacist played an advisory role by using auto generated computerised dispensing reports describing IPT initiations, missed IPT visit reports, IPT interruptions and IPT course completions. This data collection and reporting role also extended to reporting IPT programme statistic to the SA DOH.

Role in multidisciplinary team: dispensing, training, education, IPT outcome monitoring and evaluation

As part of ongoing capacity building the pharmacy team was also tasked with training of new staff (pharmacy staff, counsellors, nurses) as well as provide refresher training at regular intervals on IPT provision. Together with other members of the team, patient counselling and education (134) became a shared role and responsibility in addition to helping patients cope with HIV/TB co-infection in the TRuTH study. Some researchers have also cited pharmacists as being able to aid patients in

overcoming barriers to medication adherence by providing tools such as medication diaries, pillboxes or helping patients to set up alarm reminders as prompts to take medication timeously and correctly (135).

Supply chain management

The pharmacy staff ensured that INH was timeously procured and accessible for all patients on IPT for the duration of their course. We were able to procure sufficient stock through the private sector. This is not always the case in the public sector with limited resources and so INH drug shortages or stock outs is a real operational challenge faced by many HCW and subsequently patients. Some studies have described how stock outs negatively impacted on IPT implementation and provision of INH (19). In Ethiopia 11 % of patients were reported to be non-adherent to IPT due to drug stock outs (84). Within SA, INH stock outs have also recently been cited as a major hindrance to IPT where 86% of patients who did not complete IPT were as a result of INH being out of stock (136). While not all clinics or health facilities have a pharmacist on site, ensuring adequate and unbroken supplies of drugs required for IPT is a critical role under the scope of practice of a pharmacist that should not be neglected.

Overall, the pharmacist was able to contribute to staff and patient education and training through development of learning materials, tools and counselling guides. Power point slide presentations were created for clinic staff re-fresher training on IPT provision and INH side effects in addition to counselling tools and quick checklists for staff to use during patient education sessions. The operational experience gained from IPT implementation in the TRuTH study has helped to prepare for TB prevention interventions in other projects. For another TB study currently running at site, the Improving Retreatment Success (IMPRESS) study, patients on IPT are scheduled for clinic follow-up visits every 2 months and telephonic monitoring on alternate months using a telephone counselling guide developed by the pharmacist (Appendix M); in addition, IPT related data is captured on revised IPT CRFs, the development of which the pharmacist contributed to significantly as part of the multidisciplinary clinical team.

There has been very little data published on the role of the pharmacist in the provision of TB care in the form of treatment or prevention (137-141). Findings from a clinic for HCWs with LTBI and on IPT run by a pharmacist in the United States in the early to mid-1990's, demonstrated how the pharmacist was able to provide face-face or telephonic follow-up to dispense INH monthly, assess the overall status of HCWs as well as monitor and manage adverse effects (141). IPT outcomes showed a high completion rate (93%) amongst those HCWs ever initiated on IPT, with no incident TB cases reported (141). More recently researchers have identified the pharmacists' role in TB related care (133) in the following areas: surveillance, detection, treatment, collaboration and engagement with the

private sector as well as professional regulation. This can be also easily applied as TB prevention strategies for the family and household contacts of those patients identified with TB. TB treatment and prevention go hand in hand and should not be handled in isolation from each other.

4.2 Study limitations

There were several study limitations. The small sample size, in this secondary analysis undermined our ability to show a statistically significant impact of IPT in preventing new cases of TB in patients who have had TB previously. The CAP 005 TRUTH study and this IPT sub-analyses were not powered to detect any significant differences in TB incidence among those initiated on IPT and those not initiated on IPT. A post-hoc assessment confirmed that the current study sample size of (n=212) participants was insufficiently powered (22%) to detect a significant difference in TB incidence before and after exposure to IPT.

Additionally, our model of well-resourced IPT implementation may not be generalizable to other settings given the resources directed to regularly timed TB symptom screening, routine laboratory investigations and chest radiographs aimed at evaluating incident TB as well as the multi-disciplinary healthcare team utilised in the parent study. This may have led to over -reporting of suspected TB and subsequent non-eligibility for IPT or IPT interruptions. Increased personnel and infrastructural resources enabled rapid confirmation or exclusion of incident TB and efficient identification of patients eligible for IPT. Well-resourced clinical trial settings create a strict monitoring environment that encouraged focused and targeted attention on patient adherence to treatment, study visits retention and clinical outcomes. This may have contributed to higher IPT adherence and completion rates reported in the study. We also did not measure qualitative factors that may have had an impact on IPT uptake such as patients' perception of TB risk, disclosure of HIV status, understanding the importance of IPT for TB prevention, level of education or economic status at the time of IPT eligibility assessment.

4.3 Recommendations for clinical practice

The following recommendations regarding operational considerations, clinical outcomes and the role of the pharmacist in IPT programmes are put forward:

- Scale up efforts for HIV/TB/IPT service integration, previously reported in 2012 to be at 59% (99). There is a need to re-frame integration expectations to emphasize that the principle of one clinical consultation to cover all chronic requirements should be adopted, not the current system in place at some facilities at the moment where patients are seen "under one roof" but still have separate consults and follow multiple queues resulting in a prolonged clinic visits and treatment of disease in isolation.

- Test and treat campaigns that have been launched by the SA DOH in September 2016 recommends immediate ART initiation in all HIV infected patients. Opportunities to promote IPT uptake should also be incorporated as part of the package of benefits with early ART and IPT initiation.
- Adopt separate strategies for IPT management based on duration of ART (treatment naïve or experienced at time of IPT initiation) and tailor IPT adherence counselling support accordingly. Treatment naive patients may need more frequent contact for monitoring both IPT and ART use compared to experienced patients stable on ART.
- Restructuring of current DOH recommendation for implementing long term IPT -for TST positive patients on ART provision of a 36 month IPT course includes monthly follow up for first 6 months followed by quarterly visits (142). Based on our experience derived from IPT roll-out, this schedule may hinder IPT uptake due to frequent clinic visits required. We would suggest a visit 1 month after IPT initiation for safety evaluations and then move to quarterly visits with telephonic based follow up in between to maintain contact, conduct TB symptom screening and promote retention in care
- Surveillance for incident TB by conducting TB symptom screening routinely in between physical clinic consultations
- Standardised dosing of INH as 300mg daily and not weight based in order to align with current WHO guidelines (38). This would simplify the dispensing process, facilitate ease of use for patient, decrease pill burden, and avoid dosing errors. It would also be a step closer to merging IPT and ART provision within the newly launched Centralised Chronic Medicines Dispensing and Distribution (CCMDD) system, implemented in April 2016 in 11 districts around SA.
- Provide IPT carrier cards similar to those used for TB treatment monitoring so that patients on extended IPT (12 and 36 months) can be monitored for IPT course duration, IPT history and treatment interruptions.
- Prioritise those with a past history of TB and males for targeted counselling on IPT benefits in order to promote uptake
- Revise pharmacy undergraduate curriculum to incorporate public health and pharmacoepidemiology courses, including IPT and TB prevention concepts of public health, into their curriculum and equip pharmacists as public health professionals (143)
- Revise the role of the pharmacist within existing TB care and control policies between WHO and the International Pharmaceutical Federation, (FIP) to include IPT as a key component within the TB care continuum (144).
- Review and revise models used for nurse-initiated management of ART (NIMART) training to incorporate IPT principles and patient management.

- DOH and other related researchers (e.g. NICD) to make data more widely circulated, accessible and available on INH resistance patterns to keep service providers informed and assess the ongoing impact of IPT on INH resistance, if any. This can be achieved by commissioning the SA TB Drug Resistance Survey Report (83) to be conducted more frequently and disseminate the findings on a larger scale. One of the recommendations in the survey is that further research, such as risk benefit assessments be conducted, in order to determine if IPT is driving INH resistance and assess the continued effectiveness of IPT as INH resistance increases.
- Promote the use of point-of-care (POC) diagnostics to rule out TB and thereby hasten the process of initiation onto IPT, reduce course interruptions once initiated, and ensure re-entry onto IPT and course completion. With the use of GeneXpert® for POC diagnosis of TB, the risk for false positives is a concern. Some researchers have identified the potential risk of GeneXpert false positivity in re-treatment TB cases to be 1 in 7 (145). GeneXpert may still play a valuable role in the IPT setting as opposed to none, until other point-of-care diagnostics with higher specificity for re-treatment TB become available. Another POC diagnostic developed by Yoon et al. has potential to be used to confirm IPT eligibility via C-reactive protein testing (146).
- Innovative use of available technology over and above point-of-care diagnostics, such as mobile based technology, has the potential to play a crucial role in enhancing the delivery of IPT care to patients. Some possibilities include use of short messaging service (SMS): sending out motivational text messages about the benefits of taking and completing IPT, tracking and retention related messages for clinic appointment reminders, prompts to those who defaulted visit and general broadcast messages about TB prevention
- Stock visibility system (SVS) - mobile technology based stock management system, with automated alerts and SMS notifications for drugs low in stock. This can be used to prevent any course interruptions or non-adherence to IPT due to INH stock out.
- Promote the use of computerised dispensing systems for improved accuracy and monitoring of drug dispensing processes such as by improving access and availability of Rx solutions system being rolled out in the public sector.

4.4 Recommendations for future research

Recommendations for future research include:

- Determine the impact of extended IPT duration in TB treatment experienced cohorts
- Identify, assess and report on factors that may predict IPT refusal and aim targeted interventions at these predictors e.g. male gender and targeted counselling for promotion of IPT uptake

- Design and implement innovative ways of using mobile technology to improve IPT uptake, enhance long term IPT adherence and continuous ongoing screening for TB and adverse effects with long term INH use during IPT
    - SATIETY (Self-Assessment Tool for IPT Extended therapY) is a mobile application I designed as a self-assessment tool for TB screening (Appendix N). This was conceptualised for a grant funding opportunity where it was proposed for use as a mobile technology based programme to enable patients on IPT to conduct self-assessed TB symptom screening in between clinic follow ups. The initial grant application was not successful but I plan to pursue this endeavour (see Appendix O for NIH R21 grant application review committee feedback). Some baseline data has been collected on cellphone infiltration and capabilities amongst TB and TB/HIV co-infected patients in the CAPRISA 011 IMPRESS study which would help facilitate further development in this project.
    - A poster presented at the TB 2016 pre-conference during AIDS 2016 on TB screening and referral using technology in India private sector (131) showed the potential of a public-private partnership linking into the national Indian government digital TB monitoring system known as Nikshay to scale up TB treatment; similarly there is potential for IPT as TB prevention to be referred into this system and monitored. More research targeted at IPT could be an investigation into the feasibility of tracking IPT initiates electronically on national TB prevention programmes.
    - ENhance Initiation and Retention in Isoniazid Preventive Therapy (IPT) Care for HIV Study (ENRICH Study) is a cluster randomised trial in progress at 10 HIV clinics in Ethiopia with behavioural combination interventions (including real time adherence monitoring in the form of IVR on mobile phones) vs standard of care. This type of intervention shows promise and should be investigated further in the South African context, with SA having the largest HIV and IPT programmes in the world.
- Conduct IPT modelling research similar to the examples listed below to describe clinical outcomes further in former TB patients who received IPT. Such models could shed more light on the optimal way to approach TB prevention in this high risk population and whether long term protective benefits will be sustainable.
    - Tom Sumner et al. – post treatment effect of IPT on TB incidence: ART makes IPT effect more durable in low burden settings, but not in high burden settings where the protection is limited due to high transmission and re-infection rates (62)
    - Houben et al. demonstrate the ability of IPT to cure latent TB (147)
- Investigate other TB preventive drug regimens. Some selected studies/drug regimens that are underway and being tested in the field:

- CORTIS-01: weekly RPT/INH for 3 months in HIV negative people
- ACTG 5279: daily RPT/INH for 1 month in HIV positive people

Special emphasis should be placed on patients with prior TB and TB treatment exposure especially in high TB burden and dual HIV/TB burden settings to be included in above suggested studies; a history of prior TB should not be selected as criteria for exclusion from studies

- Preventive therapy for MDR TB contacts. To date, there is no recommendation or policy in place in SA or globally for preventing TB amongst household contact of MDR/XDR TB patients. What are effective treatment regimens for household contacts of patients being treated for MDR- TB? Studies underway or proposed:
  - Levofloxacin 6 months [TST+ adults, Vietnam, V-QUIN study]; [any HIV and TST status children <5 years old, South Africa, TB-CHAMP study]
  - Delaminid 6 months [HIV positive and any age, ACTG IMPAACT networks, PHOENIx study]- Preventive therapy for MDR TB in children, adolescents and adult household contacts (pregnant women)

  Too little to none has been accomplished in this field. More studies, more investigational drugs re-purposed for TB prevention as well as other interventions need to be more broadly investigated.
- Promote awareness within the pharmacy fraternity and send out a call for more research on the role of the pharmacist in TB prevention

4.5 Concluding statements

In conclusion, the statements below summarise the findings and support the use of IPT in HIV infected patients on ART with TB treatment experience:

- IPT is an effective TB prevention intervention within ART programmes.
- Six month IPT course can be successfully rolled out in a TB endemic setting with good uptake of IPT, where minimal course interruptions or side effects were reported and majority of the cohort completed the IPT course.
- Importantly, IPT was safe and well tolerated amongst patients on ART with TB treatment experience.

Current evidence still strongly maintains that IPT does not increase resistance to INH; the longer the duration of IPT the better the protection; independent ART or IPT use in HIV infected people does offer protection against TB. However, integrated ART and IPT provision is most effective in reducing the risk of mortality. TB continues to undermine the success of ART programmes in SSA, and our findings add to the body of evidence guiding operational IPT implementation.

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APPENDICES

APPENDICES

A. Supervisor / Student Memorandum of Understanding

Supervisor-Student Memorandum of Understanding
Prepared by Prof MJ Chimbari

This memorandum states the responsibilities of the supervisor(s) and postgraduate student and requires both parties to accept the responsibilities by signing.

Details of Student, Supervisors, and Project

Student Name: **Bhavna Maharaj**

Student Number: **9705220**

School: **School of Health Sciences**

Degree: **Master of Pharmacy (Pharmacy Practice)**

Supervisor(s): **Tanuja Gengiah**

Research Topic: **Early experiences with Isoniazid Preventive Therapy roll-out in an ART programme: A Pharmacist's perspective**

Date: **05 June 15**

Responsibilities of the Postgraduate Student
While there are many responsibilities carried by a student in pursuing postgraduate studies the following are the minimum expected.

1. Student should identify a research topic acceptable to the supervisor in order to register
2. Student must show commitment to the degree programme and undertake to produce a full proposal within 3 month of registering
3. Student must produce written work that is their best effortt for comments by the supervisor
4. Student should meet at least once per month (in person or through skype) with the supervisor and have the courage to request for such meetings. In all such meetings the student should provide a brief report of their work and take minutes of the discussions and retain such records until the degree has been awarded
5. Students must keep a laboratory manual where all experimental procedures and data are recorded. This laboratory manual remains the property of the university
6. Student must demonstrate the highest level of scientific honesty at all *stages (proposal writing, seeking ethical approval, collecting data, analyzing data and writing thesis or manuscripts)* of the degree programme.
7. Students must familiarize themselves with the university's policy on Plagiarism
8. Students should follow the advice provided by the supervisor and if they choose not to they should discuss the matter with the supervisor immediately
9. Student must always inform the supervisor of their whereabouts
10. Student should keep up to date with literature in their field of study and share any new literature they come across with the supervisor

11. Student must agree to complete studies within the time specified in the CHS handbook for the specific degree programme
12. Student should allow the supervisor to publish their work if they do not do so or show interest one year after graduating on the understanding that the student will be co-author

Responsibilities of the Supervisor

1. Supervisor must support student at all stages of the degree programme *(settling down, proposal writing, ethical applications, data collection, data analysis and write up of thesis or manuscripts)*
2. Supervisor must be sensitive to the overall well-being of the student
3. Supervisor must have good knowledge of the research area of the student
4. Supervisor must be available to the student and should have regular meetings (face to face or by skype) with the student. If the supervisor must be away for an extended period they should identify a co-supervisor to assist the student during that period
5. Supervisor must read work submitted by student for comments and give feedback within 3 weeks depending on the nature of the work submitted
6. Supervisor must be constructively critical to the student's work
7. Supervisor must have sufficient interest in the work of the student
8. In instances of co-supervision the supervisors must avoid confusing the student by giving conflicting opinions/comments. If there are differences in opinion those should be discussed among the supervisors and the student given the agreed opinion.
9. Supervisor should, where funds permit, facilitate arrangements for masters and doctoral students to present a paper or a poster at an international conference as part of training
10. Supervisor must provide an annual progress report on the research and progression of the student to the discipline
11. Supervisor must protect the work of the student by not pre-maturely publishing it or assigning another student to similar work
12. Student must always be the first author of their work and any co-authorship with other people not on the supervision team should be clarified at an early stage of the project

Conflict Resolution

Should there be a conflict or disagreement between supervisor and student which cannot be resolved by the parties involved, then either party can approach the Academic Leader Research or Dean and Head of School (or the College Dean of Research if the Dean and Head of School is one of the conflicting parties) about the conflict. The Dean and Head of School (or College Dean of Research) will then either arbitrate or choose a senior academic of the School not involved in the conflict to arbitrate. The arbitrator's decision is final and cannot be appealed.

Signatures:

Student 

Supervisor(s) 

Academic Leader Research or D&HoS.....

B. BREC Approval Letter

UNIVERSITY OF
KWAZULU-NATAL
INYUVESI
YAKWAZULU-NATALI
RESEARCH OFFICE
Biomedical Research Ethics Administration
Westville Campus, Govan Mbeki Building
Private Bag X 54001
Durban
4000
KwaZulu-Natal, SOUTH AFRICA
Tel: 27 31 2604769 - Fax: 27 31 2604609
Email: BREC@ukzn.ac.za
Website http://research.ukzn.ac.za/Research-Ethics/Biomedical-Research-Ethics.aspx

03 November 2015

Mrs Bhavna Maharaj
2nd Floor, DDMRI
719 Umbilo Road
Durban
4041
maharajb1@ukzn.ac.za

Dear Mrs Maharaj

PROTOCOL: Early experiences with Isoniazid Preventive Therapy roll-out in an ART programme: a Pharmacist's perspective: Degree Purposes (Masters). BREC REF: BE373/14

RECERTIFICATION APPLICATION APPROVAL NOTICE

Approved: 04 December 2015
Expiration of Ethical Approval: 03 December 2016

I wish to advise you that your application for Recertification received 02 November 2015 for the above protocol has been noted and approved by a sub-committee of the Biomedical Research Ethics Committee (BREC) for another approval period. The start and end dates of this period are indicated above.
If any modifications or adverse events occur in the project before your next scheduled review, you must submit them to BREC for review. Except in emergency situations, no change to the protocol may be implemented until you have received written BREC approval for the change.

This approval will be **ratified** by a full Committee at its next meeting taking place on **08 December 2015**

Yours sincerely

Mrs A Marimuthu
Senior Administrator: Biomedical Research Ethics

C. Communication with Journal

Bhavna Maharaj

From:	The International Journal of Tuberculosis and Lung Disease <onbehalfof+ijtld+theunion.org@manuscriptcentral.com>
Sent:	16 October 2016 11:36 AM
To:	Bhavna Maharaj; Bhavna Maharaj; Tanuja Gengiah; Nonhlanhla Yende; Santhana Gengiah; Anushka Naidoo; kogieleum.naidoo@caprisa.org
Subject:	Manuscript submitted IJTLD-10-16-0775

Dear Authors

Your manuscript entitled

"Implementing Isoniazid Preventive Therapy in a TB-treatment experienced cohort on ART"

has been successfully uploaded to The International Journal of Tuberculosis and Lung Disease. It will now be checked by the Editorial Office and released to the editor for assignment of reviewers.

Your manuscript number is: IJTLD-10-16-0775. Any correspondence concerning the article should include this number in the subject line, and should be sent to ijtld@theunion.org.

This message has also been sent to your corresponding author, who is responsible for all communications regarding the paper.

Please note that if the article is accepted, all of the co-authors will be contacted to log onto the site to submit an electronic copyright form.

Thank you for your interest in The International Journal of Tuberculosis and Lung Disease.

Sincerely,

The Editorial Office
IJTLD

Bhavna Maharaj

From:	The International Journal of Tuberculosis and Lung Disease <onbehalfof+drtomboyles+gmail.com@manuscriptcentral.com>
Sent:	22 November 2016 11:17 AM
To:	Bhavna Maharaj; Bhavna Maharaj
Cc:	drtomboyles@gmail.com; kathy.deriemer@gmail.com
Subject:	IJTLD - Decision on Manuscript ID IJTLD-10-16-0775

22-Nov-2016

Dear Dr. Maharaj

Ref: Manuscript ID IJTLD-10-16-0775

According to the rules of The International Journal of Tuberculosis and Lung Disease, your article entitled

"Implementing Isoniazid Preventive Therapy in a TB-treatment experienced cohort on ART" (Original Article)

has been submitted to careful peer review.

Although they found merit in your study, the reviewers have raised a number of serious concerns that preclude its acceptance in its present form.

However, because of the interest of the subject, we would be prepared to re-examine the paper for inclusion in the journal if the modifications proposed are taken into account.

Please include these changes in your article, replying to all of the comments made, before a final decision is made concerning the paper's acceptance or refusal.

The revised version may be reevaluated by the original reviewers.

To revise your manuscript, please log on to ScholarOne Manuscripts (https://mc.manuscriptcentral.com/ijtld), and enter the Author Center. Click on "Manuscripts with Decisions", find the article, then click on "Create a revision".

You will find the reviewers' comments at the bottom of the decision letter. Please respond point by point to the reviewers' comments in the space provided at the bottom of the screen.

You will be unable to make revisions directly in the originally submitted ScholarOne Manuscripts version of your manuscript. Instead, you should revise your manuscript using a word processor and then resubmit the revised version, ensuring that it is marked R1 (or, in the case of re-revision, R2, R3, etc). Please use red font instead of black to indicate the revised portions of your manuscript (do not use the track changes function). You will also need to resubmit any figures.

PLEASE NOTE: Journal requirements in terms of article length must be respected in the revised version (see Instructions to Authors on the ManuscriptCentral site). Please include the final word count for summary and text, and the number of references, tables and figures on the title page of your revised article. Articles that are too long will be returned to the corresponding author.

To upload the revised version, click on "File upload" , where you can resubmit your manuscript in the same fashion as the original version (please ensure that you have deleted the original version, it may mask the revision). Instructions are provided on the screen, and you can also contact the Editorial Office for assistance (ijtld@theunion.org). Manuscript and author information can also be edited as necessary.

Your manuscript will be kept on file for 3 months as of today. If we do not hear from you within 3 months, we will presume you have withdrawn the manuscript from consideration for publication in the IJTLD.

I suggest that you remove the section regarding reduction of incidence of TB as you have not made a convincing argument for this. Instead, re-submit as a short communication highlighting the operational outcomes of IPT roll-out.

Sincerely,

Dr. Tom Boyles
Associate Editor

Editor's Comments to Author/s:

Reviewers' Comments to Author/s:
Reviewer: 1

Comments to the Author
The effect of secondary preventive therapy as a treatment strategy in high incidence settings has not been thoroughly investigated. The authors attempt to do this in a secondary analysis to a clinical trial. The methods used, particularly for comparing impact on TB incidence are either not clearly explained or done incorrectly, making the interpretation of these findings difficult to follow. IPT adherence was remarkably high, while uptake was moderate. I believe these findings could be significantly reduced to highlight the excellent implementation/operational aspects of integrating secondary IPT, however, the impact on TB incidence should be more appropriately analyzed/reported, or removed from the analysis.

Major issues:
1. Abstract states that IPT "demonstrated a protective effect against TB acquisition". How did it do that? The IRR was 0.67 with a p-value of 0.362.
2. It appears, though it is not clear, that TB incidence rate was calculated in the same group of patients before and after IPT initiation. Table 3 has 212 people in the before and after columns. How is this possible? If there were 13 cases of TB before IPT initiation, why would they continue to be followed after IPT initiation?
3. Line 183 states "we found a non-significant decrease in TB incidence of 33% after 6-months of IPT among patients with previous TB on ART." Was your comparison those who received 6 months of IPT vs those who did not? If so, this is not clear.

Minor issues:
1. Line 59 - either South Africa should be Botswana, or wrong study is cited.
2. Do guidelines cited in 15 (line 75) recommend secondary IPT?
3. How do you calculate median adherence for "each patient"? (Line 114)

Reviewer: 2

Comments to the Author
A well written clear paper that is worth publishing after minor adaptations:
The authors should more clearly explain the process of offering IPT, were all offered? In the discussion reference is made to before and after initiation suggested the study did not start with offering IPT..
Minor edits:

Row 91, 95 indicate what defines suggestive Row 94 remove extra . (point) Row 129 indicate the number of patient initiating IPT Row 144-145: did those that refused IPT differed significantly from those accepting (or those not eligible)?
Row 152 is the median duration reported overall or for those interrupting IPT?
Row 171 how much time after completing the 6 months IPT did these patients developed TB?
Row 176-177 please use the term presumptive instead of suspected TB Row 199 – authors indicate it is effective while earlier they state that the impact in not enough with just 33% reduction, this seems contradictory, also the authors make a statement on IPT 6 months versus 36 months while they did not measure it in their study and it was indicated the follow up time was minimal therefore a statement based on the study results on this seems not valid, they can hypothesize but this should then be clearly indicated..
Row 237-238: GeneXpert can help but there is also the risk to detect 'old TB' with this tool and therefore for identifying TB in this group it might not be as promising as suggested.

Bhavna Maharaj

From: The International Journal of Tuberculosis and Lung Disease <onbehalfof+ijtld+theunion.org@manuscriptcentral.com>
Sent: 26 November 2016 11:43 PM
To: Bhavna Maharaj; Bhavna Maharaj
Subject: IJTLD- Manuscript IJTLD-10-16-0775.R1

Dear Mrs. Maharaj

Your revised manuscript entitled

"Implementing Isoniazid Preventive Therapy in a TB-treatment experienced cohort on ART"

has been successfully resubmitted to the IJTLD, and the Associate Editor has been advised.

You will receive a final decision on your article shortly.

With kind regards

The Editorial Office

CAPRISA
CENTRE FOR THE AIDS PROGRAMME OF RESEARCH IN SOUTH AFRICA

UNAIDS
CAPRISA is the UNAIDS Collaborating Centre for HIV Research and Policy

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26 November 2016

Dear Dr. Boyles,

Re: Decision on manuscript ID IJTLD-10-16-0775

Thank you for the review of the above manuscript. We found the review constructive and take this opportunity to address queries/concerns raised by the reviewers. We have considered the suggestion to submit a short communication describing the operational outcomes of secondary IPT implementation and found this to be a suitable alternative should the manuscript not be accepted. However, we would like to provide further clarity on the current analysis and request that the revised manuscript be reconsidered.

Below we have listed the reviewers' comments and our responses follow **in bold:**

Reviewer 1

Abstract states that IPT "demonstrated a protective effect against TB acquisition". How did it do that? The IRR was 0.67 with a p-value of 0.362.

Author response: We agree that protection was not statistically significant and have revised the conclusion of the abstract to more accurately reflect the finding. The conclusion now reads as follows: "IPT implementation amongst ART and TB treatment experienced patients was well tolerated with good completion rates and fewer TB cases diagnosed after IPT exposure."

2. It appears, though it is not clear, that TB incidence rate was calculated in the same group of patients before and after IPT initiation. Table 3 has 212 people in the before and after columns. How is this possible? If there were 13 cases of TB before IPT initiation, why would they continue to be followed after IPT initiation?

Author response: The primary aim of the parent study was to monitor and diagnose TB recurrence in the entire cohort over the study period. TB diagnosis in the parent study was not an exclusionary criteria for IPT provision (when it became available) provided the TB episode was completely cured. IPT was not available at the initiation of the parent study. Those diagnosed with TB prior to the IPT programme being rolled out were treated for TB and when the IPT programme

was rolled out all patients were assessed for eligibility to receive IPT. This enabled us to assess TB incidence in the time periods prior to and after IPT exposure. In accordance, TB incidence was assessed in the same group of 212 IPT patients for the period from parent study initiation to the day before IPT start and was then compared to the TB incidence in the period after IPT completion up to exit from the parent study. For those who did not develop TB, time at risk is calculated from IPT initiation date to parent study termination date. For those who developed TB, time at risk is calculated from IPT initiation date to date of TB diagnosis. This explanation is detailed in lines 109-111.

3. Line 183 states "we found a non-significant decrease in TB incidence of 33% after 6-months of IPT among patients with previous TB on ART." Was your comparison those who received 6 months of IPT vs those who did not? If so, this is not clear.

Author response: A comparison was made in the same 212 patients who served as their own control for the periods prior to and after IPT exposure.

Minor issues:

1. Line 59 - either South Africa should be Botswana, or wrong study is cited.

Author response: Line 57 through to line 61 was not referenced correctly-this was an oversight. The sentence has been updated to include the correct citations and reads as follows: "IPT was shown to decrease mortality amongst tuberculin skin test (TST) positive individuals with CD4+ T-cell counts >200 cell/mm^3 in Tanzania [11] whilst in a study amongst South Africans on ART initiating IPT reported 49% reduction in mortality that remained significant even for those that had a past history of TB [10]."

2. Do guidelines cited in 15 (line 75) recommend secondary IPT?

Author response: Yes. Page 5, reference 15, refers to the Guidelines for Tuberculosis Preventive Therapy among HIV infected individuals in South Africa, May 2010 and this guideline recommends secondary IPT in former TB patients.

3. How do you calculate median adherence for "each patient"? (Line 114)

Author response: The manuscript has been updated to clarify the calculation and reads as follows: "The mean adherence to IPT for each participant across all visits was assessed by comparing the number of tablets returned at the current visit with the number of tablets dispensed at the last clinic visit compared to the number of tablets that should have been ingested between visits. The overall median adherence was then calculated using the monthly mean adherence at each visit.

Reviewer: 2

Minor edits:

1. Row 91, 95 indicate what defines suggestive

Author response: The word 'suggestive' was meant to indicate 'symptomatic of'. "Suggestive' has been deleted and replaced to reflect the clinical process. The sentence now reads as follows: "Patients were screened for INH related side effects and those who showed symptoms of liver toxicity or where the clinician suspected liver toxicity underwent liver function monitoring."

2. Row 94 remove extra. (point)
Author response: The extra period has been deleted.

3. Row 129 indicate the number of patient initiating IPT

Author response: The number of patients initiating IPT (n=212) has been included in row 129. The amended sentence reads as follows: "Among the 212 patients initiating IPT, 38.7% were male, had a median BMI of 26.5 (23.3 - 30.3), and 26.3% had more than one previous TB episode."

4. Row 144-145: did those that refused IPT differed significantly from those accepting (or those not eligible)?
Author response: Those that refused or were ineligible for IPT were included for comparison with acceptors within the group that did not start IPT and the differences are reported in row 130-132 as follows: "Apart from significantly more females (n=130; 61.3%) than males initiating IPT (p=0.001) (Table 1), baseline characteristics were not statistically significantly different among IPT initiates and non-initiates."

5. Row 152 is the median duration reported overall or for those interrupting IPT?
Author response: This is the median duration reported overall and the sentence has been amended to clarify this: Overall median duration of treatment was 174 days (IQR: 167.0 - 180.3).

6. Row 171 how much time after completing the 6 months IPT did these patients developed TB?

Author response: It is estimated that there was a median of 279 (IQR: 141-336) days between the completion of the 6 month IPT course to the date of new TB diagnosis. This information has been added to line 173-174.

7. Row 176-177 please use the term presumptive instead of suspected TB

Author response: The word 'suspect' has been replaced with 'presumptive' to read as follows: "Presumptive TB impacted IPT initiation and interruption rates."

8. Row 199 – authors indicate it is effective while earlier they state that the impact in not enough with just 33% reduction, this seems contradictory…

Author response: Agreed. From the findings the protective effect was not statistically significant. Line 202 has been amended to read as follows: "Our findings suggest that six months of IPT is safe and well tolerated in patients with prior TB disease, while a protective effect in this cohort was not shown".

9…… also the authors make a statement on IPT 6 months versus 36 months while they did not measure it in their study and it was indicated the follow up time was minimal therefore a statement based on the study results on this seems not valid, they can hypothesize but this should then be clearly indicated.

Author response: Agreed. The text on lines 203-204 is meant to explain what current recommendations are and not stated in association with the current study. The standalone statement reads as follows: Current WHO guidance, supported by other research,[13, 26, 27] recommends that IPT be provided for up to 36 months in a high TB burden setting.[3*]

10. Row 237-238: GeneXpert can help but there is also the risk to detect 'old TB' with this tool and therefore for identifying TB in this group it might not be as promising as suggested.

Author response: We acknowledge the reviewer's comment and recognise this important caveat. The risk for false positives is a concern. For primary TB the positive predictive value of the new generation test is approximately 99.5%. In TB re-treatment cases the risk of GeneXpert false positivity is estimated to be 1 in 7 (Theron G, Venter R, et al. Clin Infect Dis. 2016;62 (8):995-1001). GeneXpert or the newer generation Xpert Ultra may still play a valuable, albeit limited, role in the IPT setting until other point-of-care diagnostics with higher specificity for patients with previous TB become available.

The manuscript has been revised to remove rather than explain further the reference to GeneXpert, as follows, lines 241-242: "Point of care TB diagnostics with higher specificity for patients with previous TB infection may play a role in reducing IPT course interruptions, and re-entry into the IPT programme."

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Bhavna Maharaj

From: The International Journal of Tuberculosis and Lung Disease <onbehalfof+drtomboyles+gmail.com@manuscriptcentral.com>
Sent: Friday, 06 January 2017 12:41 PM
To: Bhavna Maharaj; Bhavna Maharaj
Cc: drtomboyles@gmail.com; ijtld@theunion.org; kathy.deriemer@gmail.com
Subject: IJTLD - Decision on Manuscript ID IJTLD-10-16-0775.R1

06-Jan-2017

Dear Mrs. Bhavna Maharaj

Thank you for sending us the revised version of your article entitled

"Implementing Isoniazid Preventive Therapy in a TB-treatment experienced cohort on ART" (Original Article)

and your reply to the reviewers' comments.

I am pleased to inform you that your manuscript has been accepted for publication in one of the forthcoming issues of the IJTLD, subject to the usual editorial revisions.

Your article will be checked before being prepared for publication, and you will be contacted by the Editorial Office if there are any elements missing.

If you have any queries, please contact the Editorial Office at ijtld@theunion.org. Remember to include the IJTLD number of your accepted manuscript in the subject line of your e-mail.

With kind regards,

Sincerely,

Dr. Tom Boyles
Associate Editor
IJTLD

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D. TRuTH study informed consent forms

PID :

STUDY INFORMED CONSENT FORM

TITLE OF PROGRAMME: CAPRISA AIDS TREATMENT PROGRAMME (ENGLISH)

TITLE OF STUDY:

Is TB Recurrence in Treated TB-HIV Co-infected?

Patients Relapse or Re-infection?

Principal Investigator (s): Dr Kogieleum Naidoo, MBChB
Prof. Salim S Abdool Karim, MBChB, PhD

INTRODUCTION

You are being asked to take part in this research study because you are eligible for the CAPRISA AIDS Treatment Programme (CAT). The doctor in charge of this study at this site (CAPRISA) is Dr Kogieleum Naidoo, MBChB. Before you decide if you want to be a part of this study, we want you to know about the study.

This consent form gives you information about this study, which will be done at Prince Cyril Zulu Communicable Disease Centre (PCZCDC). Ask questions and discuss any concerns you may have with the research staff. If you agree to take part in this study, you will be asked to sign this consent form. You will be given a copy of this consent form to keep.

Please note that:

- Your participation in this study is entirely voluntary. You may decide not to participate in the study, but you are still eligible for anti-retroviral therapy. You may decide to obtain your HIV care through your own medical care provider.
- You may stop taking part in the study at any time and this will not affect the care you receive through the CAT Programme.
- You will be informed of any new information that may arise, which could affect your decision to remain apart of the study.

WHY IS THIS STUDY BEING DONE?

The purpose of this study is to learn why some HIV –infected patients on Highly Active Antiretroviral Therapy (HAART) acquire Tuberculosis (TB), even after being cured of the TB previously. Very little is known about why HIV patients on HAART can acquire several episodes of TB and the main purpose of this study is to monitor patients whom we know have had TB in the past for new episodes of TB.

WHAT IS THE DURATION OF THE STUDY?

The study will be conducted over 3 years (36 months).

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?

About 550 people will take part in this study.

WHAT DO I HAVE TO DO IF I PARTICIPATE IN THIS STUDY?

If you join this study, you will need to come into the clinic for examinations, interviews, and laboratory tests frequently. You will be required to come to the clinic monthly for the first three months after enrollment and then once every 3 months for approximately three years there after. If you miss appointments, the persons you named will be contacted or field workers will be sent to your home. Please inform a study staff member , should you wish not to be visited at home.

Any time that results of exams and laboratory tests such as viral load (which measures how much HIV virus is in your blood), CD4+ T cell counts (immune cells that help fight infection such as HIV), sputum, chest x-rays and safety tests are known, they will be given to you. There may be times that you must come for additional visits if these exams or tests show abnormal results. Some of the blood drawn and sputum taken throughout the study can be stored. You will be asked for your permission to store the blood and sputum for future research and asked to sign a separate consent form if you agree to do this. You may still participate in the study if you do not agree to have blood stored.

Screening and Study Visits

You will be asked questions about your medical history and any medicines that you have taken. You will be asked how to be contacted in case you miss a visit or there are ever problems with your lab results. You will be given a physical exam and have about 60 mL (about 4 tablespoons) of blood drawn for routine tests, CD4 + cell counts, and viral load assessments. You will have a blood draw and chest x-ray at entry into the study and then every 6 months thereafter. You will be told your test results throughout the study. Some of your blood will be stored for future HIV-related testing including a test for HIV resistance (to see if the HIV is able to respond to the ART). Sputum samples will also be taken from you once every 3 months to test for the presence of TB. Your blood and sputum samples will be identified by a number and not your name. If you are a woman and able to become pregnant, you will be asked to provide some urine for a routine pregnancy test. If you are admitted to hospital, you will be asked questions about the reasons for your stay there.

USE OF STORED SAMPLES

The stored samples may be used for future research, to confirm test results, or to do additional testing. Your samples will not be sold or used in products that make money for the researchers. You will be asked to sign a separate form asking for your consent to have your samples stored. Should you decide not to have your samples stored; this will not affect your ability to take part in the study.

WHY YOU MAY BE WITHDRAWN FROM THE STUDY WITHOUT YOUR CONSENT?

You may be removed from the study without your consent for the following reasons:

- The study is stopped or cancelled.
- The study staff feels that staying in the study may be harmful to you.
- You are not able or willing to attend study visits or to complete the study procedures.

WHAT OTHER CHOICES DO I HAVE BESIDES THIS STUDY?

Instead of being in this study you have the choice of:

- Participation in the CAT programme.
- Treatment with ART through the South African national rollout programme .
- No treatment

Antiretroviral medications, laboratory tests to monitor the effectiveness of these medications, and quality medical care for HIV/AIDS may or may not be available to you outside the study. The clinic staff will discuss with you other treatment choices in your area and the risks and the benefits of all the choices.

WHAT ABOUT CONFIDENTIALITY?

Your medical records, personal information, and the results of your HIV tests and other medical and laboratory evaluations will be kept strictly confidential within the extent of South African law. Only your doctor and/or nurse will know the results of your tests. Your records will be identified by a study code. Any publication of this study will not use your name or identify you personally.

Every effort will be made to protect your confidentiality but we cannot guarantee absolute confidentiality. Your personal information may be disclosed if required by law. Your records may also be reviewed by regulatory authorities, namely the Biomedical Research Ethics Committee, Centres for Disease Control (CDC), Medicines Control Council and study staff.

WHAT ARE THE RISKS AND DISCOMFORTS ASSOCIATED WITH THE STUDY?

Taking blood may cause some discomfort, bleeding, or bruising where the needle enters the body, lightheadedness, and in rare cases, fainting or infection. Many people do not understand the facts about infection with the AIDS virus. Being HIV positive can be a very stressful experience. You may be treated badly by friends and family if you are HIV positive and your HIV status becomes known to others. If you have a Chest X-ray and you are pregnant , then there is a risk to your unborn baby.

WHAT HAPPENS IF I BECOME PREGNANT?

If you think you may be pregnant at any time during the study, tell your study staff right away. The study staff will talk to you about your choices and refer you to a provider of prenatal care if you do not have one. You may still continue to be part of the study, however, you will not have the chest x-rays done during the duration of your pregnancy due to the risk this poses to your unborn baby. All female patients who participate in this study will be offered a pregnancy test at every study visit.

WHAT ARE THE BENEFITS ASSOCIATED WITH THE STUDY?

If you participate in this study, there may be a direct benefit to you, but no guarantee can be made. Your health will be followed more closely than usual while you are on the study, which may help you to feel better.

WILL I RECEIVE ANY PAYMENT?

Participants will be reimbursed R50 on enrollment in the study and for every scheduled study visit thereafter.

WHAT ARE THE COSTS TO ME?
The HIV treatment will be provided free of charge while you are on study. If you require HIV treatment that does not include these drugs, you will receive this care from a local authority and/or provincial health facility. Provincial hospitals may ask you to pay a fee, depending on your income.

If you acquire TB, then TB treatment is provided free of charge to you by the Tuberculosis Control Study at the CDC.

WHAT HAPPENS IF I AM INJURED?
It is very unlikely that you will become injured as a result of involvement in this study. However, in the case of a research related injury, you will be referred to the King Edward hospital for treatment. The cost of this treatment will be borne by the research team. There is, however, no compensation provided for research related injuries. You do not give up any legal rights by signing this consent form.

For questions about this study or a research-related injury, contact any of the following persons:

Clinic Manager at Prince Cyril Zulu Communicable Disease Clinic:
Dr. Nesri Padayatchi
CAPRISA Deputy Director
Tel: (031) 260-4574

Principal Investigator :
Dr. Kogieleum Naidoo
Tel: (031) 260-4687/1922

For questions about your rights as a research participant, you may contact:
BREC Administrator or Chair – for reporting of complaints/problems-
Biomedical Research Ethics Committee
Private Bag X54001
Durban
4000
Telephone: +27 (0) 31 260 4769
Fax : +27 (0) 31 260 4609
E-mail: ramnaraind@ukzn.ac.za

STUDY INFORMED CONSENT SIGNATURES PAGE

I have read this form, or had it read to me, and voluntarily agree to take part in the study. The purpose of the study, the procedures, and the risks and benefits has been explained to my satisfaction. My signature, thumbprint or mark indicates that I consent to take part in the study, have received a copy of this consent form, and that I understand what is required from me and the consequences of taking part in the study.

_____	_____
Participant's Name (print)	Participant's Signature and Date
_____	_____
Witness Name (print)	Witness Signature and Date
_____	_____
Translator's Name	Translator's Signature and Date

Withdrawal of Consent

I hereby withdraw my consent to participate in this study. I am aware that I may withdraw my consent at any time without prejudice to further care.

_____ Date:_____
Participant Name and Signature

_____ Date:_____
Witness Name and Signature

_____ Date:_____
Translator's Name and Signature

ADDENDUM INFORMED CONSENT FOR PARTICIPATION IN RESEARCH ACTIVITIES

TITLE OF PROGRAMME: CAPRISA AIDS TREATMENT PROGRAMME

TITLE OF STUDY:

Is TB Recurrence in Treated TB-HIV Co-infected?

Patients Relapse or Re-infection?

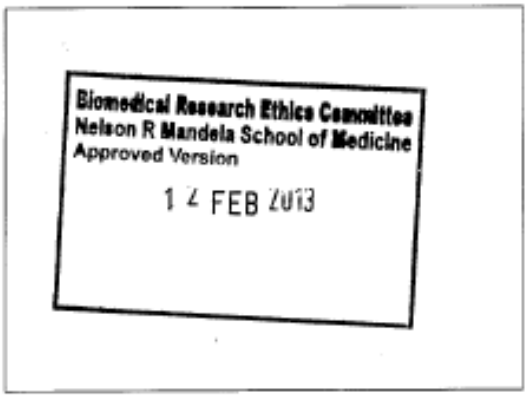
Principal Investigator : Dr Kogieleum Naidoo, MBChB

Dear Patient

You are currently taking part in the above-named research study. The purpose of this document is to provide you with more information about the study, which will be discussed with you by a study staff member.

Since the time you signed the original consent form for this study, new information related to the study has become available. The study researchers have taken a decision to increase the length of the study. In the original informed consent it was stated that the study will run for 36 months. However, the study will now be extended for an additional 12 months. The reason for this extended study duration is so that we may observe patients over a longer time to better understand why some HIV infected patients acquire TB even after being cured of TB previously. We have found that 36 months may not have been adequate to answer this question.

Your continued participation in this research is voluntary and refusal to take part will involve no penalty to you or loss of any benefits to which you are otherwise entitled. You may withdraw from the research study now or at any time without penalty or loss of benefits to which you are otherwise entitled. You will be informed of any significant new findings developed during the course of participation in this research that may have a bearing on your willingness to continue in the study. The investigator may withdraw you from this research if circumstances arise which makes this necessary.



WHAT WILL I HAVE TO DO?
Should you agree to participate in the 12 month extended follow up you will be asked to sign this form.

STUDY VISITS:
The schedule of study visits will remain the same as explained in the original consent form. A study nurse will review the procedures in the study with you from the original consent form. If you would like, the information in the original consent form may be reviewed with you.

WILL I RECEIVE ANY PAYMENT?
Participants will be reimbursed R50 for every scheduled study visit.

WHAT IF I HAVE QUESTIONS OR PROBLEMS?
For questions about this study or a research-related injury, contact:
Principal Investigator
Dr Kogieleum Naidoo
Tel: (031) 260 4687

Investigator
Dr Nesri Padayatchi
Tel: (031) 260 4574

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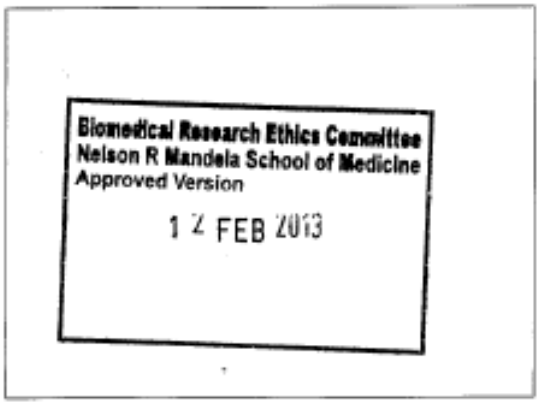

E. KZN DOH 2010 IPT memorandum

HEALTH
KwaZulu-Natal

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Ref.: IPT -2
Ref. No.: 17/P; 17/2
Index No.:09/2010/117
Circular No.:G44/2010
nirupa.misra@kznhealth.gov.za
22 September 2010

To: **District Managers**
Hospital Managers
Institutional Pharmacy Managers
District Pharmacy Managers

Re.: Implementation of the New Isoniazid Preventive Therapy (IPT) Guidelines

Background

The guidelines for Tuberculosis Preventive Therapy among HIV infected individuals in South Africa were published in May 2010 by NDOH. TB Preventive therapy is the administration of one or more anti-tuberculosis drugs to individuals with latent infection with M. Tuberculosis in order to prevent progression to active TB disease.

ISONIAZID PREVENTIVE THERAPY (IPT): Isoniazid is given to individuals with latent infection with Mycobacterium tuberculosis in order to prevent progression to active disease.

Eligibility Criteria for IPT:

- **All HIV positive people** with no signs and symptoms of TB are potentially eligible for TB preventive therapy. Prior to initiation of IPT, patients should be screened for signs and symptoms of active TB disease
  - Particular attention to: miners, prisoners, TB contacts, Health Care Workers and Children
  - Pregnant mothers without symptoms of TB
  - ➢ PMTCT is a realistic entry point for integrated HIV/TB care and prevention
  - ➢ IPT can be started at anytime during pregnancy and should be completed if a woman falls pregnant while taking IPT.
  - **IPT and ART**: IPT should be continued even when the patient is initiated on ART. Patients already on ART are also eligible for IPT.
  - **Former TB patients**- HIV positive patients who successfully completed TB treatment may be offered IPT after having been done sputum for DST to exclude resistance to INH.

If there is any suspicion that the patient has active TB they should not be started on IPT!

Exclusion Criteria for IPT

- HIV negative patient
- Patient with active liver disease or active alcohol abuse
- Potential hepatotoxicity of the drug used for preventive therapy. If potential hepato-toxicity is suspected, then a doctor should assess the risks
- Patient with symptoms of TB

Prior to initiation of TB preventive therapy, patients should be screened for signs and symptoms of active TB disease:

- Cough > 24 hours
- Fever > 2 weeks
- Unintentional weight loss or anorexia
- Drenching/soaking night sweats
- Sputum production, pleuritic chest pain, haemoptysis or dyspnea
- Swelling of lymph nodes

All patients with 1 or more sign or symptom must be further investigated for active TB disease as per National TB guidelines. They are not eligible for TB preventive therapy until active TB disease have been excluded on the basis of sputum smear microscopy and mycobacterial culture.

Implementation Strategy (as per revised HAST implementation plan)

- **A phased in approach is recommended**.
- IPT should be started at all hospitals, CHCs and **selected PHC clinics** especially those with increased TB case load, good bacteriological coverage and treatment outcomes.
- As additional PHC Clinics are identified to start IPT the TB/ HAST co-ordinators must inform Pharmaceutical Systems Development and the HAST unit.
- This is critical for drug supply management.

Pharmaceutical Services IPT implementation strategy

Availability of and Access to INH 100MG and 300mg

- Isoniazid 100mg and 300mg tablets are on the revised requisition for TB supplies order form (August 2010).
- All Hospitals and CHCs can start implementing IPT provided that they comply with the requirements of a well performing site.
- In order to facilitate the down-referral of patients who have been initiated on IPT at a hospital level all PHC clinics can access the INH 100mg and 300MG tablets.
- Only those PHC Clinics that are on the list submitted by the District HAST/ TB Co-ordinators should be initiating patients on IPT.
- All other PHC Clinics will be able to access INH 300mg for continuation of IPT in patients down-referred from the hospitals and CHCs.
- Quantification for the tablets has been done using the HAST IPT targets (see attached).
- It is critical that PSD is informed of new sites that will be initiating IPT in order to ensure a sustainable supply of drug.
- Additional PHC clinics who wish to implement IPT must inform the TB and HAST Co-ordinators and the District Pharmacy Managers so that drug supply can be managed.

Ordering of INH

- Quantification of drugs has been done using the HAST Business plans and targets for IPT.
- Each district has been given a monthly target to reach for IPT.

- Each District should develop a plan for reaching this target which will include targets per facility.
- These district/ facility targets must be sent to Pharmaceutical Services to enable appropriate allocation of drugs.
- The depot will monitor orders for INH according to the targets set.
- It is critical that communication regarding the targets be sent to all doctors and nurses that are implementing IPT so that if these targets are exceeded the additional drugs required can be planned for.
- Exceeding the Provincial target of 10 000 new patients per month will result in a shortage of INH.
- Statistics on the number of patients initiated on IPT must be submitted monthly to the HAST unit and PSD in order to manage drug supply.

Recommended Regimen

The standard regimen for TB preventive therapy is:

Adults: Isoniazid (INH) 5mg/kg/day (maximum 300mg per day)

Children: Isoniazid (INH) 10mg/kg/day (maximum 300mg per day)

ADULT DOSE CALCULATION GUIDE: 5mg / kg /day

BODY WEIGHT	INH DOSAGE (300 mg tablet)	INH DOSAGE (100mg tablet)
30 – 39.9 Kg	150 mg (½ tab)	
40 – 49.9 Kg		200 mg (2 tab)
50 -59 Kg		250 mg (2 ½ tab)
60 kg upwards	300 mg (1 tab)	
Maximum dose: 300 mg per day		

CHILDREN DOSE CALCULATION GUIDE: 10mg / kg / day

BODY WEIGHT	INH DOSAGE (100 mg tab)
2 - 3.4 Kg	25 mg (1/4 tab)
3.5 - 6.9 Kg	50 mg (1/2 tab)
7 - 9.9 Kg	100 mg (1 tab)
10 - 14.9 Kg	125 mg (1 ¼ tab)
15 - 19.9 Kg	150 mg (1 ½ tab)
20 - 24.9 Kg	200 mg (2 tab)

Vitamin B6 (Pyridoxine) 25 mg per day should be given concomitantly with Isoniazid to prevent the occurrence of peripheral neuropathy.

Recommended duration

6 months of continuous treatment (can be completed over 9 months).

TB preventive therapy should be given once only. The protective effect of TB preventive therapy is expected to last for 18 months.

Monitoring and Evaluation

- All facilities implementing IPT must ensure that the indicators indentified by HAST as per SOP is collected monthly.
- The DHIS currently captures the no. of HIV positive patients commenced on IPT. This needs to be strengthened.
- In the interim facilities are requested to extract the relevant data from the Pre-Art registers and submit to Pharmaceutical Systems Development by the 7th of each month.
- A data collection sheet has been developed in order to facilitate collection of the data to manage the programme.
- It is recommended that this information be collected on a monthly basis and submitted to Pharmaceutical Systems Development. Although Pharmacists may not have direct access to this info it is recommended that the Pharmacist facilitate the submission of this data as failure to monitor the programme may increase drug resistance.
- **Data must be submitted on:**
  - **Number of people who are started on IPT**
  - **Number of people who complete 6 months of IPT**
  - **Number of people who develop active TB when taking IPT**
- The above mentioned data should be recorded in the Pre-ART / Wellness Register.

Initiation of IPT

- Information about TB, including preventive therapy, should be made available to all people living with HIV and AIDS.
- The importance of adherence must be stressed.
- During post-test counselling following diagnosis of HIV, the patient should be informed about benefits of TB preventive therapy, and should be invited to return to the clinic for this service.
- It is **not** recommended that TB preventive therapy be initiated immediately after informing a patient of his/her HIV status.
- The known HIV-infected patient must be screened for signs and symptoms of active TB disease.
- This screening is essential to exclude active TB disease that would require a full treatment regimen.
- **Since TST is no longer recommended, IPT can be started at the first visit if the patient is asymptomatic, well informed and willing to start IPT.**
- If the patient is not ready to start IPT then an appointment for a second visit should be given to assess readiness to start treatment.
- Record the weight of the patient.
- Please ensure that the number of patients initiated on IPT is in line with the targets set and any deviations are reported to the District Pharmacy Manager.

IPT Prescription forms

- It is critical that the patient be screened on every visit for active TB.
- Failure to monitor patients for development of active TB, adherence and treatment interruption may place patients at risk of developing drug resistance.
- In order to assist with the monitoring of IPT a pre-printed prescription form has been developed. This includes the screening tool and allows 6 monthly repeat prescriptions to be dispensed. The pre-printed prescription form can be used as a tool to monitor adherence and ensure that TB is excluded at every visit.
- This is a recommendation and facilities may adopt the use of the pre-printed prescription form. Alternatively exiting models of prescribing and dispensing can be used.
- It is critical to ensure adherence to therapy and exclude active TB at every visit.

Follow-up visits:

- Record the weight of the patient
- On-going counselling sessions, about HIV, symptoms of active TB, adherence, side effects of isionazid (e.g.nausea and vomiting, jaundice, dark urine, right upper quadrant abdominal pain, convulsions, severe rash, psychosis and peripheral neuropathy)
- Importance of immediately stopping Isoniazid and seeking care if the patient develops side effects of Isoniazid.
- **Patients starting TB preventive therapy should be given a one-month supply at a time.**
- They are expected to complete the 6 months of therapy
- Patients should be screened for TB and side effects at **every follow-up visit** and referred for further investigation
- Patients who are symptomatic must be investigated according to TB guidelines
- If TB is confirmed, they should start TB treatment and receive Co-trimoxazole prophylaxis
- Eligibility for ART must be assessed
- If TB is not confirmed and they are not on ART, they can be reassessed after three months for IPT.

Monthly Monitoring Visits: Patient on IPT

- Patients are requested to collect their supplies on a monthly
- Provide on-going counselling, identification of side-effects and early detection of active TB
- Monitor adherence to preventive therapy
- Do pill counts
- If the patient develops symptoms of active TB, the patient should be investigated for active TB disease.
- A full TB treatment regimen should be started if active TB is confirmed
- Vitamin B6 (Pyridoxine) 25 mg per day should be given concomitantly with Isoniazid to prevent the occurrence of peripheral neuropathy.
- If cases of mild peripheral neuropathy occur, Vitamin B6 (pyridoxine) 25mg daily should be prescribed until the symptoms disappear.
- If the peripheral neuropathy is severe or worsens, then Isoniazid should be discontinued immediately
- If the patient develops signs and symptoms suggestive of Hepatitis, Isoniazid should be stopped immediately, and the patient should be referred immediately to a medical officer

- If the patient interrupts therapy, the health care provider should inquire about the reasons for interruption, and should counsel the patient on the importance of adherence.
- Isoniazid may be restarted after the health care provider has verified that the patient has no symptoms suggestive of active TB disease, and that obstacles to adherence have been addressed.
- **The health care provider should make sure that the 6 months of therapy is taken within a 9 month period.**
- If the patient interrupts TB preventive therapy for a second time, the health care provider should consider stopping the therapy

Please ensure compliance to the guidelines for implementation of IPT especially submission of statistics, monitoring of side effects and adherence

Thank you

Yours Faithfully

N Misra, B. Pharm. M. Med. Sc

Mrs. N. Misra
Pharmaceutical Policy Specialist: EDP

F. KZN DOH IPT prescription

September 2010 – version2
Complete in duplicate: 1 copy to stay in patients file, 1 copy to hand to patient.

HEALTH
KwaZulu-Natal

ISONIAZID PRESCRIPTION FORM FOR INH PREVENTIVE THERAPY

Patient name:_____ **Date :**____/___/____

GENDER: (TICK)		**MALE:** □				**FEMALE:** □						
AGE:	**Weight(kg)**											
PATIENT RECORD OR FOLDER NUMBER												
PATIENT CONTACT NUMBER												
NAME OF FACILITY:												

Month	**1**		**2**		**3**		**4**		**5**		**6**	
DIAGNOSIS (please tick yes(y) /no(n) on every visit)	**y**	**n**	**y**	**n**	**y**	**n**	**y**	**n**	**y**	**n**	**y**	**n**
1. Has the client been coughing for 24hrs or longer?												
2. Has the client recently coughed blood in the sputum?												
3. Has the client experienced loss of appetite?												
4. Has the client experienced loss of weight?												
5. Has the client been sweating unusually at night?												
6. Has the client had recurrent fever/chills lasting more than 3 days?												
7. Has the client experienced chest pains, fast breathing and/or difficulty in breathing?												
8. Does the client have swellings in the neck, armpits or elsewhere?												

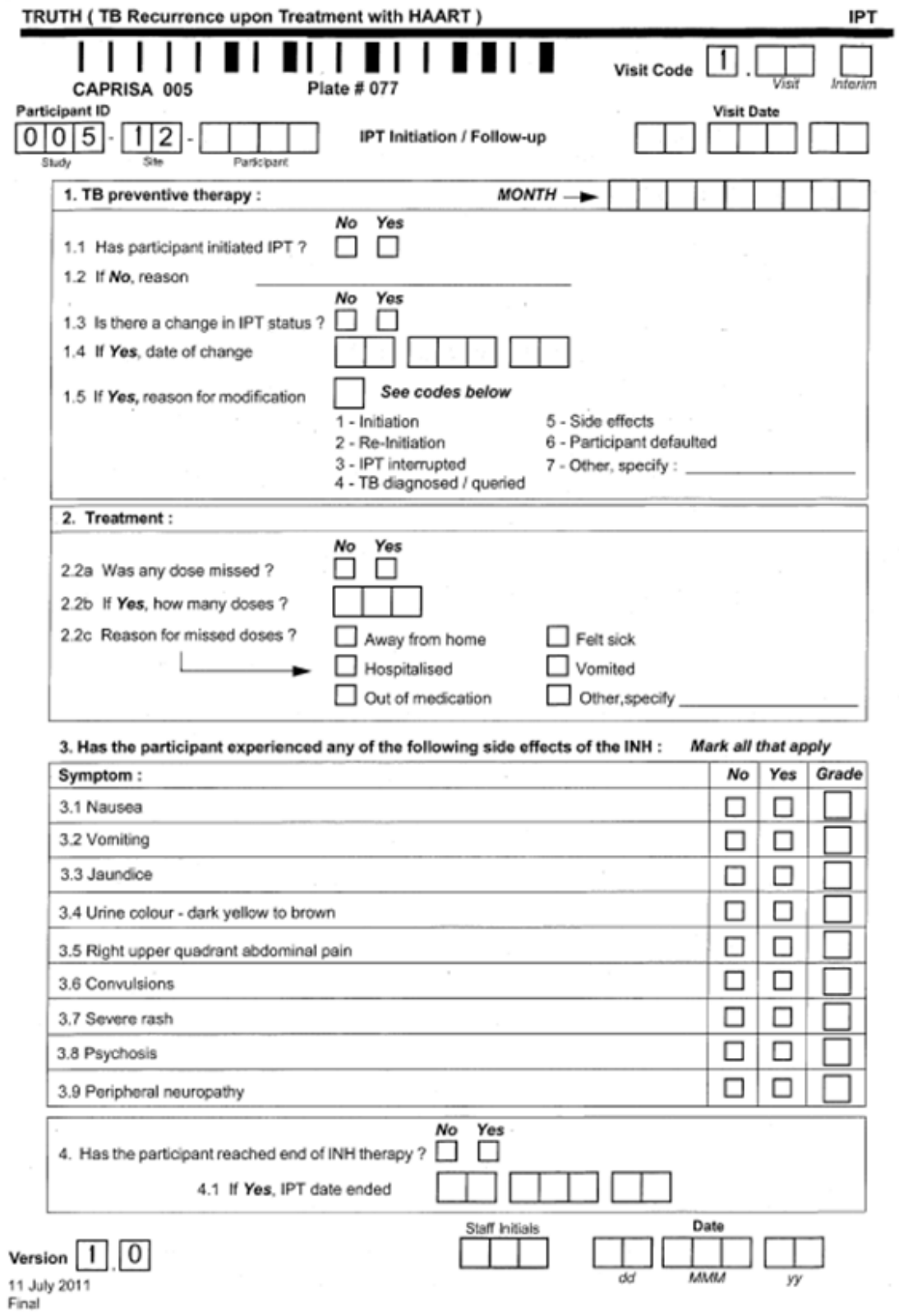
If **"yes"** to one or more of the questions, **suspect TB.** Clinically evaluate the patient using the NTB Guidelines, enter patient details in the suspect register, continue with further investigations including sputum for microscopy.
If **"No"** to all questions, inform the patient of the benefits of IPT and assess the patient eligibility. Start IPT if indicated. Repeat the screening at every contact with the patient. Record the info on the wellness/pre-ART register.

DIAGNOSIS (PLEASE TICK ONE)	**New y □ n □**	**Interrupted tx y □ n □**	**Interrupted tx. y □ n □**
Dosage form (please tick)	**INH TABLETS (100MG) □**	**INH TABLETS (300MG) □**	**PYRIDOXINE 25MG □**
Total dosage prescribed:			
Directions:			
Duration			

Initiating facility (name)		**Patient to be down-referred: yes □ no □**	**Down-refer to: (name)**
Name of prescriber:		**Signature of prescriber**	
Name of Dispenser:		**Signature of Dispenser:**	

Date of issue						
Batch number						
Signature of Dispenser						
Signature of patient						

G. Plate #077 TRuTH IPT CRF



TRUTH (TB Recurrence upon Treatment with HAART) **IPT**

CAPRISA 005 Plate # 077

Visit Code 1 . ___ (Visit) ___ (Interim)

Participant ID: 005 - 12 - ____ (Study - Site - Participant)

IPT Initiation / Follow-up

Visit Date: ___ ___ ___

1. TB preventive therapy : *MONTH* →

	No	Yes
1.1 Has participant initiated IPT ?	☐	☐

1.2 If **No**, reason _____

	No	Yes
1.3 Is there a change in IPT status ?	☐	☐

1.4 If **Yes**, date of change ___ ___ ___

1.5 If **Yes,** reason for modification ☐ *See codes below*

1 - Initiation
2 - Re-Initiation
3 - IPT interrupted
4 - TB diagnosed / queried
5 - Side effects
6 - Participant defaulted
7 - Other, specify : _____

2. Treatment :

	No	Yes
2.2a Was any dose missed ?	☐	☐

2.2b If **Yes**, how many doses ? ☐☐☐

2.2c Reason for missed doses ?

- ☐ Away from home
- ☐ Felt sick
- ☐ Hospitalised
- ☐ Vomited
- ☐ Out of medication
- ☐ Other,specify _____

3. Has the participant experienced any of the following side effects of the INH : *Mark all that apply*

Symptom :	No	Yes	Grade
3.1 Nausea	☐	☐	☐
3.2 Vomiting	☐	☐	☐
3.3 Jaundice	☐	☐	☐
3.4 Urine colour - dark yellow to brown	☐	☐	☐
3.5 Right upper quadrant abdominal pain	☐	☐	☐
3.6 Convulsions	☐	☐	☐
3.7 Severe rash	☐	☐	☐
3.8 Psychosis	☐	☐	☐
3.9 Peripheral neuropathy	☐	☐	☐

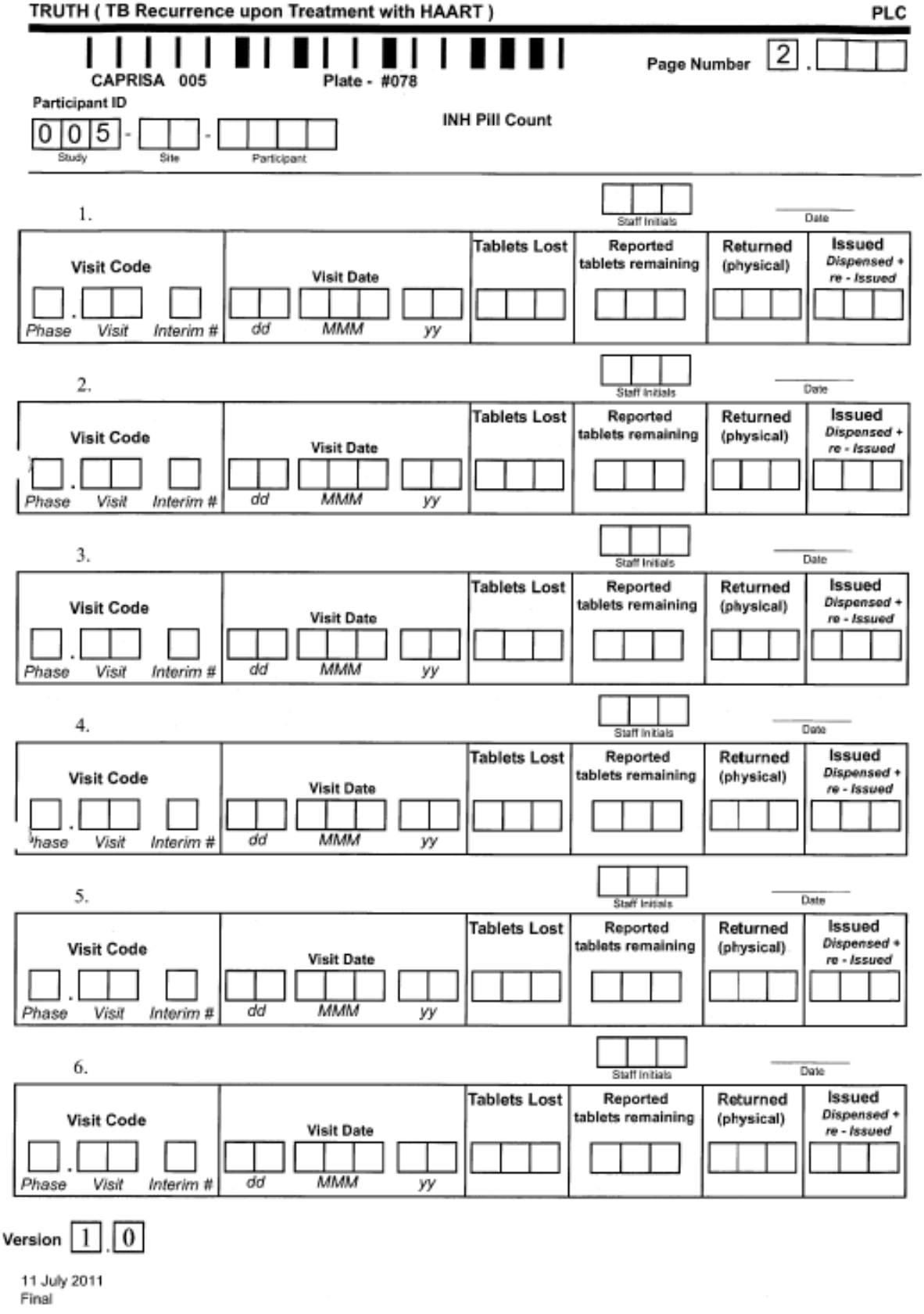
	No	Yes
4. Has the participant reached end of INH therapy ?	☐	☐

4.1 If **Yes**, IPT date ended ___ ___ ___

Staff Initials ___ Date ___ ___ ___ (dd / MMM / yy)

Version 1.0
11 July 2011
Final

H. Plate #078 TRuTH IPT pill count



TRUTH (TB Recurrence upon Treatment with HAART) PLC

CAPRISA 005 Plate - #078 Page Number 2 . ___

Participant ID

0 0 5 - ___ - ___ (Study - Site - Participant)

INH Pill Count

1. Staff Initials ___ Date ___

Visit Code (Phase . Visit, Interim #)	Visit Date (dd MMM yy)	Tablets Lost	Reported tablets remaining	Returned (physical)	Issued (Dispensed + re - Issued)

2. Staff Initials ___ Date ___

Visit Code (Phase . Visit, Interim #)	Visit Date (dd MMM yy)	Tablets Lost	Reported tablets remaining	Returned (physical)	Issued (Dispensed + re - Issued)

3. Staff Initials ___ Date ___

Visit Code (Phase . Visit, Interim #)	Visit Date (dd MMM yy)	Tablets Lost	Reported tablets remaining	Returned (physical)	Issued (Dispensed + re - Issued)

4. Staff Initials ___ Date ___

Visit Code (Phase . Visit, Interim #)	Visit Date (dd MMM yy)	Tablets Lost	Reported tablets remaining	Returned (physical)	Issued (Dispensed + re - Issued)

5. Staff Initials ___ Date ___

Visit Code (Phase . Visit, Interim #)	Visit Date (dd MMM yy)	Tablets Lost	Reported tablets remaining	Returned (physical)	Issued (Dispensed + re - Issued)

6. Staff Initials ___ Date ___

Visit Code (Phase . Visit, Interim #)	Visit Date (dd MMM yy)	Tablets Lost	Reported tablets remaining	Returned (physical)	Issued (Dispensed + re - Issued)

Version 1 . 0

11 July 2011
Final

I. Plate #060 TRuTH LFT CRF

TRUTH (TB Recurrence upon Treatment with HAART) LUEL

CAPRISA 005 Plate 060 Visit Code 1 . Visit Interim

Participant ID 0 0 5 - 1 2 - Study Site Participant

U&E - LFT

Specimen Date dd MMM yy

1. Sodium ..... mmol/l
2. Potassium ..... mmol/l
3. Chloride ..... mmol/l
4. Urea ..... mmol/l
5. Bicarbonate ..... mmol/l
6. Creatinine ..... µmol/l
7. Total protein ..... g/l
8. Albumin ..... g/l
9. Bilirubin (total) ..... µmol/l
10. Alkaline phosphatase ..... IU/L
11. g-Glutamyl transferase ..... IU/L
12. ALT (GPT) ..... IU/L
13. AST (GOT) ..... IU/L
14. Lactate dehydrogenase ..... IU/L
15. Glucose random ..... mmol/l

Version 1 . 0

07 September 2009
Final

Staff Initials

Date dd MMM yy

J. TRuTH TB screening checklist

TRUTH (TB Recurrence upon Treatment with HAART) TBSRA

CAPRISA 005 Plate - #076

Visit Code 1 . Visit Interim

Participant ID 0 0 5 - 1 2 - Study Site Participant

TB Symptom Checklist and Risk Assessment

Visit Date dd MMM yy

1. TB Symptom Checklist : **If more than ONE symptom, please complete questions 3 and 4.**

	No	Yes	Duration → Days	Months	Grade
1.1 Unexplained persistent cough for more than 2 weeks	☐	☐	☐☐☐	☐	☐
1.2 Coughed up blood	☐	☐	☐☐☐	☐	☐
1.3 Loss of appetite	☐	☐	☐☐☐	☐	☐
1.4 Unexplained weight loss	☐	☐	☐☐☐	☐	☐
1.5 Drenching night sweats	☐	☐	☐☐☐	☐	☐
1.6 Fevers	☐	☐	☐☐☐	☐	☐
1.7 Chills	☐	☐	☐☐☐	☐	☐
1.8 Fatigue	☐	☐	☐☐☐	☐	☐
1.9 Nausea	☐	☐	☐☐☐	☐	☐
1.10 Vomiting	☐	☐	☐☐☐	☐	☐
1.11 Abdominal pain	☐	☐	☐☐☐	☐	☐
1.12 Chest pain	☐	☐	☐☐☐	☐	☐
1.13 Difficulty in breathing	☐	☐	☐☐☐	☐	☐

2. TB Risk Assessment : Sign : _____

	No	Yes
2.1 Are you in close contact with someone who has TB ?	☐	☐
2.2 Have you had contact with someone who has multidrug resistant TB (MDR TB) ?	☐	☐
2.3 Have you had contact with someone who has XDR TB ?	☐	☐
2.4 Do you live in a hostel or informal settlement ?	☐	☐
2.5 Have you been imprisoned in the past year ?	☐	☐
2.6 Have you been hospitalized in the past year?	☐	☐

3. Referred participant for further TB investigation ? No ☐ Yes ☐

4. Participant referred for : ☐ Sputum smear ☐ Culture ☐ Chest X-ray

☐ Other, specify : _____

Staff Initials ☐☐☐ Date dd ☐☐ MMM ☐☐☐ yy ☐☐

Sign : _____ Date : _____

Version 1 . 0

07 September 2009
Final

K. KZN DOH IPT monthly statistics reporting form

HEALTH
KwaZulu-Natal

ISONIAZID PREVENTIVE THERAPY - MONTHLY STATISTICS

Every Facility must report independently

Please complete the blank sections and email to: pharmacy.ho@kznhealth.gov.za

Fax to: 033 846 7280
Phone: 033 8467267/9

INSTITUTION	
NAME OF PERSON COMPLETING THE FORM	
REPORTING PERIOD	

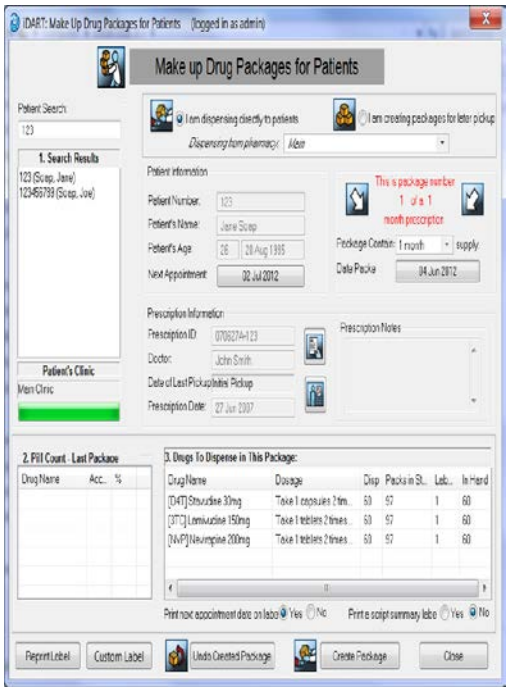
Indicator	Adults	Children
No. of patients on IPT at the start of the reporting period		
No. of new patients started on IPT during the reporting period		
No. of people completing 6 months of IPT during the reporting period		
No. of patients who developed active TB when taking INH during the reporting period		
No. of patients who interrupted INH during the reporting period.		
Total number of patients on IPT at the end of the reporting period		

PRESCRIPTIONS FOR IPT				
Number of prescriptions dispensed in this reporting period	New Adult patient	Repeat Adult patient	New child	Repeat child

Please ensure that statistics are submitted by the 7th of each month

L. iDART capabilities

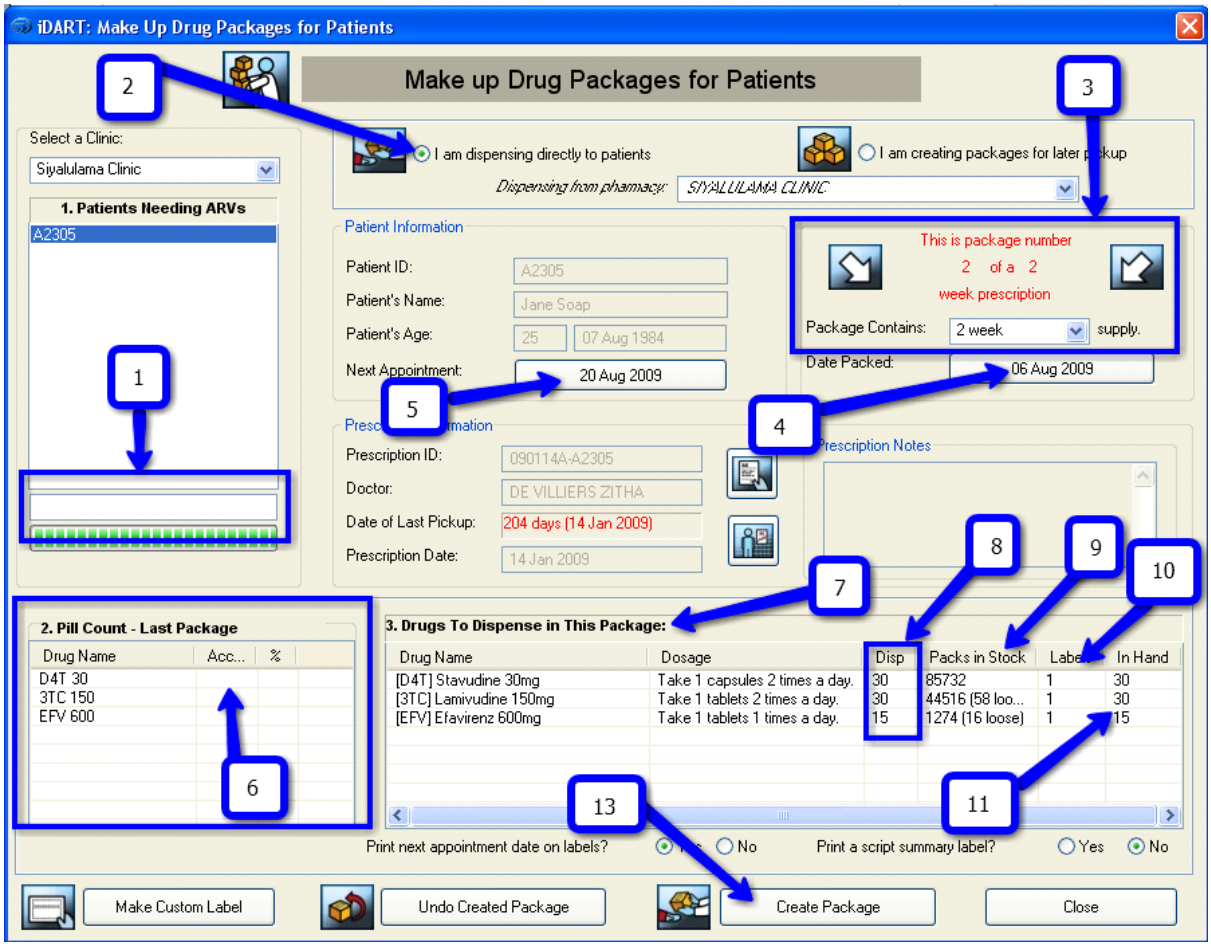
The computerised dispensing system iDART include: general admin [add new users, drugs, stock locations, load doctors details and option to update details in these categories]; patient admin [add new patients, create new or update prescription, generate patient specific reports such as adherence history]; dispensing [add stock, dispense stock, do stock takes and generate reports] and reports.



iDART sample screens (148)

The main functions of the iDART system that were utilized for IPT and ART provision:

- A Pharmacy stock location for ARVs and INH from where stock was selected for dispensing and stock balances could be reviewed.
- An IPT Clinic was created to record all participants initiated onto IPT and facilitated dispensing of INH to participants by recording details of dispensing process such as pills returned from previous visit, quantity and batch number of drug dispensed at current visit.
- Product labels: labels generated displayed the amount of study drug that was re supplied and/or re-issued, the next appointment date, the participant number, participant initials, etc.
- Reports generated to assist with patient tracking and retention, IPT course outcomes in terms of start and end dates, patient adherence reports, electronic pill counts, missed visits, patients expected on a day, monthly drug usage, daily dispensing totals, packages leaving pharmacy for the day, monthly issues and receipts, stock take, clinic indicators report, PEPFAR reports, etc. This system had the advantage of also assisting the pharmacy staff in picking up any discrepancies as well as identifying errors that could be rectified quickly within a short space of time. Dispensing time was shortened and errors minimised as this system served as a double check of the IPT and ART dispensing process.



Dispensing on iDART (148)

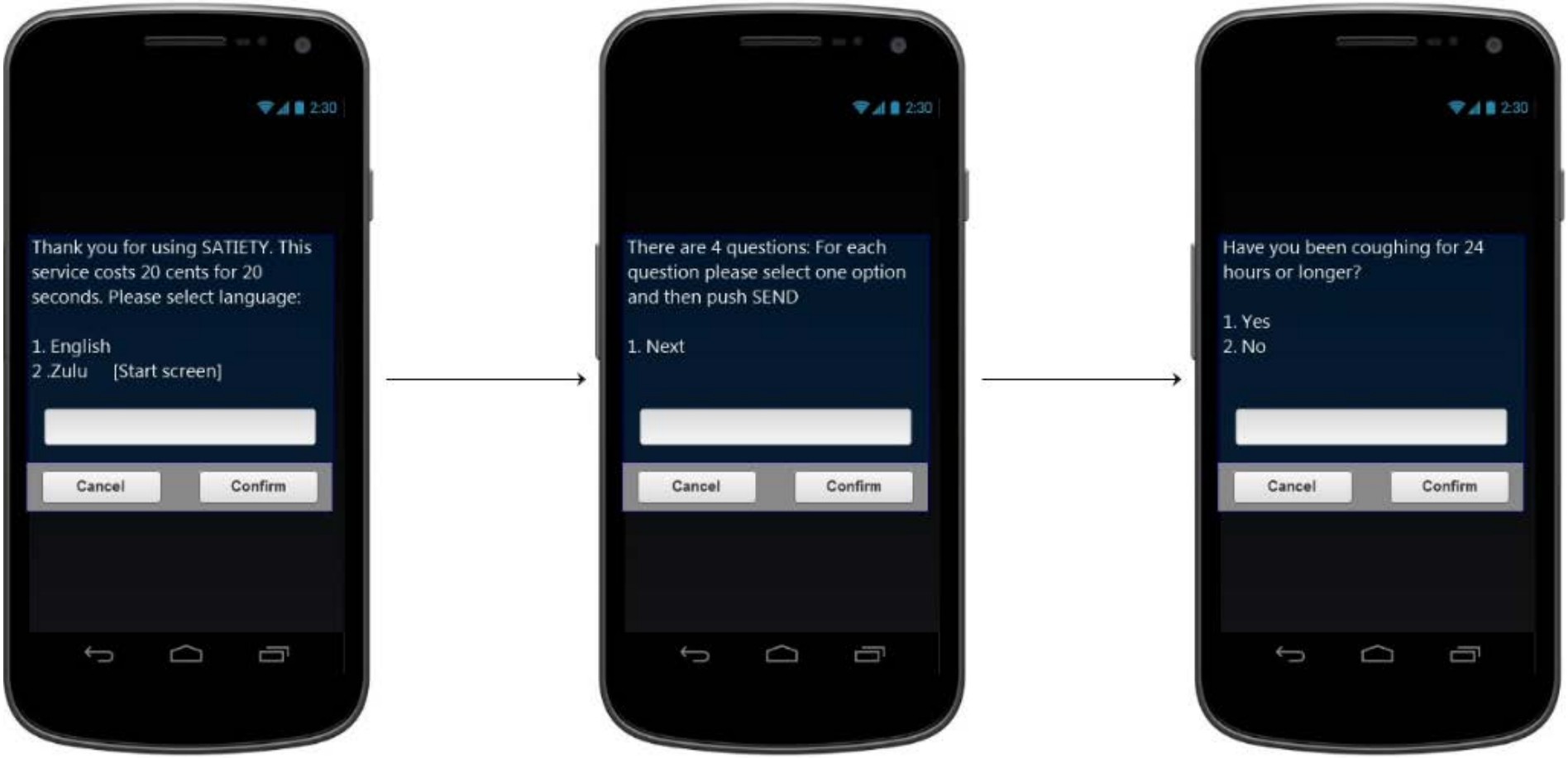
1. Dispensing directly to patients is selected
2. The prescription issue number and the no of months' supply to dispense.
3. Date Packed – this is the date that the dispensing took place.
4. Next Appointment. This is based on the Date Packed as well as the months' supply or can be adjusted manually.
5. The pill count feature may be used to check the adherence then enter the amount of pills returned from the previous package dispensed. Green > 94%; Yellow 90%-94%; Red < 90%
6. Drugs to Dispense in This Package table- each row represents a prescribed drug. It shows the Drug Name and the Dosage (based on the prescription you've already captured).
7. The Dispense column tells you how many units of the drug will be dispensed. To change the quantity, click in the row and the Batch Information Screen loads. On this screen, you can change the quantities, the batch from which the medication was given as well as the amount of labels to print.
8. A column to inform the user how much stock is left of the drug (Packs in Stock). You cannot change this value here; it is shown more for reference purposes so that you can see when you're running low on each drug item.

9. If the amount of pills dispensed is more than the amount in the bottle, then a 2nd label is printed to stick onto the second bottle. That column tells you how many labels will be printed (Labels). You can change this if you want by clicking in this column.
10. The In Hand column tells the user how much medication the patient will have in their hands when they leave the pharmacy. If you used the pill count feature, this will be the amount they came back with, plus the amount you have dispensed.
11. Note that if your patients keep their left over pills from the previous visit, then the value in the In Hand column should automatically be the combined amount. If you have to change it every time, then you must speak to an iDART technician to change your settings.
12. Click the Create Package button to dispense the package. You'll be prompted to print the labels.

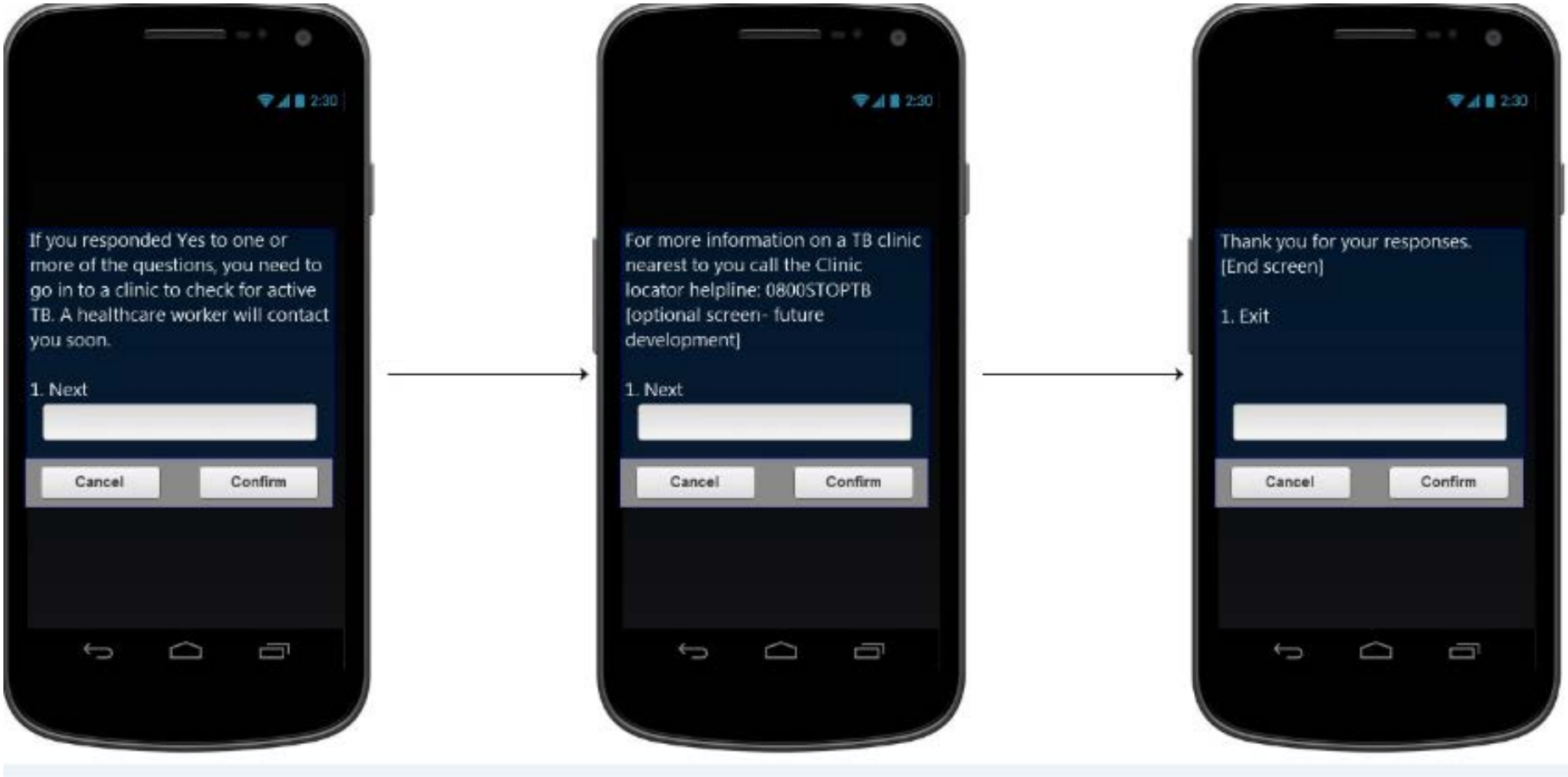
M. IPT telephonic checklist (IMPRESS Study checklist)

TB PREVENTIVE THERAPY TELEPHONIC CHECKLIST			
PATEINT DETAILS Name: DOB: PID : Contact No: (Confirm contact number and update locator if changed) **Date contact made:**			
INH SIDE EFFECTS	**YES**	**NO**	**N/A**
Nausea			
Vomiting			
Jaundice			
Urine colour - dark yellow to brown			
chest pain (right upper quadrant abdominal pain)			
convulsions			
rash			
psychosis			
peripheral neuropathy			
TB SYMPTOM SCREENING	**YES**	**NO**	**N/A**
Do you have any of the following:			
drenching night sweats or sweating unusually at night			
loss of weight			
coughing for XX (2 weeks or more)			
coughed blood			
fever or chills lasting 3 or more days			
chest pains or difficulty breathing			
swelling in the neck and/or armpits			
TB RISK	**YES**	**NO**	**N/A**
Any TB contact since the last visit/staff contact?			
Action required (If yes to any of the questions above):	**YES**	**NO**	**N/A**
refer for clinical review of responses			
book clinic consult for further investigation			
Comments:			
Staff sign:	Date:		

N. SATIETY: patient self –assessment tool for TB




2:30
Have you had recurrent fever/chills lasting more than 3 days?
1. Yes
2. No
Cancel
Confirm
2:30
Have you been sweating unusually at night?
1. Yes
2. No
Cancel
Confirm
2:30
Have you experienced any loss of weight?
1. Yes
2. No
Cancel
Confirm


If you responded Yes to one or more of the questions, you need to go in to a clinic to check for active TB. A healthcare worker will contact you soon.
1. Next
Cancel
Confirm
For more information on a TB clinic nearest to you call the Clinic locator helpline: 0800STOPTB [optional screen- future development]
1. Next
Cancel
Confirm
Thank you for your responses. [End screen]
1. Exit
Cancel
Confirm

O. Extract from National Institutes of Health R21 grant application review committee feedback for SATIETY USSD project: outcome – not funded

SUMMARY STATEMENT
(Privileged Communication)

PROGRAM CONTACT:
Robin Huebner
240-627-3216
rhuebner@niaid.nih.gov

Release Date: 08/14/2014

Application Number: 1 R21 AI116072-01

Principal Investigators (Listed Alphabetically):
HOWARD, ANDREA ALLOCCO MD
MAHARAJ, BHAVNA (Contact)

Applicant Organization: CENTRE/AIDS PROGRAMME/RES/SOUTH AFRICA

Review Group: ZRG1 IDM-C (52)
Center for Scientific Review Special Emphasis Panel
RFA Panel: US-South Africa Collaborative Biomedical Research

Meeting Date: 07/29/2014
Council: OCT 2014
Requested Start: 11/01/2014

RFA/PA: AI14-010
PCC: A27E

Dual IC(s): TW

Project Title: Mobile technology to enhance uptake and adherence to Isoniazid Preventive Therapy
SRG Action: Impact Score: 41
Next Steps: Visit http://grants.nih.gov/grants/next_steps.htm
Human Subjects: 30-Human subjects involved - Certified, no SRG concerns
Animal Subjects: 10-No live vertebrate animals involved for competing appl.
Gender: 1A-Both genders, scientifically acceptable
Minority: 5A-Only foreign subjects, scientifically acceptable
Children: 1A-Both Children and Adults, scientifically acceptable
Clinical Research - not NIH-defined Phase III Trial

Project Year	Direct Costs Requested	Estimated Total Cost
1	162,143	188,226
2	112,858	131,012
TOTAL	275,001	319,238

ADMINISTRATIVE BUDGET NOTE: The budget shown is the requested budget and has not been adjusted to reflect any recommendations made by reviewers. If an award is planned, the costs will be calculated by Institute grants management staff based on the recommendations outlined below in the COMMITTEE BUDGET RECOMMENDATIONS section.

1R21AI116072-01 MAHARAJ, BHAVNA

RESUME AND SUMMARY OF DISCUSSION: In this R21 application, the investigators propose to implement and evaluate a mobile technology platform as a means to increase adherence and retention of isoniazid preventive therapy (IPT) in people living with HIV (PLHIV). If successful, the proposed studies may lead to improvements in implementation and adherence to IPT which may potentially reduce the burden of tuberculosis (TB). The leadership plan between the South African and US investigators is appropriate and the collaboration appears mutually beneficial. Strengths of the application include the strong research team with complementary expertise, the straightforward pre- and post-intervention study design, the availability and widespread usage of the technology, and the importance of the health issue for South Africa. Several weaknesses are identified that include the lack of validation of patient responses, the inclusion of only people that have cell phones, the lack of plans to provide phones to those that do not have one, the lack of plans for tuberculin skin testing and cost effectiveness analysis and the lack of details for the analysis of the data. Additionally, there is some concern that besides monthly clinic visits, other barriers to successful implementation and adherence of IPT are not taken into account in the study design. Collectively, these weaknesses diminish the overall enthusiasm for the proposed studies.

DESCRIPTION (provided by applicant): Tuberculosis (TB) remains the leading cause of death amongst people living with HIV (PLHIV). Provision of isoniazid (INH) to Tuberculin Skin Test (TST)-reactive PLHIV reduces their lifetime risk of tuberculosis to 4% or less. The South African Department of Health introduced the roll-out of isoniazid preventative therapy (IPT) in May 2010. This intervention aims to reduce TB co-infection in immune-compromised PLHIV, in keeping with World Health Organisation (WHO) recommendations. South Africa (SA) is a resource-limited country with dual epidemics of TB and HIV, where healthcare facilities are short staffed and overburdened. There is an urgent need for implementation of interventions that enhance general health system capabilities to roll out IPT programmes, strengthen day-to-day system functioning and retain patients in care while improving patient treatment outcomes. IPT implementation has proved challenging due to the intensity of patient follow-up required. On a monthly basis, patients need to be screened for TB symptoms to ensure early incident TB case finding and treatment initiation, counselled on IPT use and assessed for side effects, in addition to receiving care for HIV including ART. The monthly check is a major reason for refusal. In order to increase uptake and retention in IPT programmes a simpler approach to implementing and monitoring IPT is needed. Widespread availability of mobile technology in resource-limited settings has prompted interest in using this tool to enhance medication adherence and retention in care. Cellular networks are well-developed in SA and according to the Groupe Speciale Mobile Association (GSMA) Africa Mobile Observatory conducted in 2011 there were an estimated 117.6 cell phones per 100 inhabitants in SA. The extensive use of mobile technology in both urban and rural communities suggests that it would be an appropriate resource to enhance service delivery of IPT. We therefore propose to use mobile technology to enhance IPT uptake, adherence and completion. In this pilot study, a mobile technology program will be developed and implemented and its impact on IPT refusal rates and retention will be assessed. We hypothesize that using a mobile phone-based TB symptom screening tool at monthly intervals and clinic-based follow-up every three months will improve uptake and completion rates of IPT. This hypothesis will be addressed by the following aims: (1) develop and implement a mobile technology program to support monthly screening and follow-up of patients receiving IPT for more than 6 months and (2) assess impact of intervention on IPT uptake, adherence and retention/ completion rates. This innovative pilot project proposes to safely monitor for active TB in HIV infected individuals in order to increase IPT coverage with benefits expected at a public health level. The use of a mobile technology program to conduct TB symptom screening aims to shift current practice and improve scientific knowledge by assessing new approaches with the potential to resolve the current programmatic challenges of IPT implementation.

PUBLIC HEALTH RELEVANCE: Isoniazid preventive therapy (IPT) is a key public health intervention for the prevention of Tuberculosis (TB) among people infected with HIV/AIDS, yet TB remains the leading cause of death amongst this population. The uptake of IPT in the face of various programmatic challenges is too low; hence the urgent need for implementation of interventions that enhance general health system capabilities to roll out IPT programmes, strengthen day-to-day system functioning and retain patients in care while improving patient treatment outcomes. The proposed study will pilot a mobile technology program to enhance the uptake of IPT and assess its impact on IPT refusal and retention rates.

CRITIQUE 1:

Significance: 3
Investigator(s): 3
Innovation: 4
Approach: 5
Environment: 3

Overall Impact: The research could lead to refinement of an intervention to improve the scale-up and adoption of the WHO recommended practice of TB preventive therapy for people living with HIV (PLHIV) for whom TB has been ruled out. The intervention may prove to improve patient adoption, adherence, and completion of IPT and also make it easier for healthcare workers to manage and oversee the provision of IPT. The benefits for patients and healthcare workers could ultimately result in decreased TB morbidity and mortality among PLHIV as a result of the innovative use of a widely adopted technology (mobile phones). The narrow scope of the study is both a strength and weakness because it is focused with clear objectives but success is based on the assumption that the targeted barrier to IPT adoption, adherence, and completion is the number of clinic encounters required for patients and/or the amount of work for healthcare workers to initiate and monitor IPT among PLHIV. The results of what is essentially an efficacy study (because of the level of excellence at the study site) could lead to data to support the more widespread implementation and evaluation of a relatively low cost intervention for active case finding and preventing TB among PLHIV.

1. Significance:

Strengths

- Issue of poor initiation, adherence, and completion of TB preventive therapy (IPT) is critical to reducing TB related morbidity and mortality among people living with HIV (PLHIV)
- Addressing the scale-up of IPT in South Africa which has among the highest rates in the world of TB, HIV, and co-occurrence of TB/HIV
- Innovative approach to support the scale-up of IPT in a high burden setting to address the leading cause of death among PLHIV
- If successful, the intervention could reduce the burden of IPT management for both healthcare workers and patients.
- The intervention is also a strategy for active case finding and perhaps earlier diagnosis and treatment of TB among PLHIV.

Weaknesses

- Much of the success of the intervention is based on the assumption that monthly clinic visits are the primary barrier to improved uptake of IPT (the authors identify other possible barriers such as missing work, lack of transportation, clinicians' concern about providing monotherapy for people for whom a diagnosis of TB is missed, etc.).

PUBLIC HEALTH RELEVANCE: Isoniazid preventive therapy (IPT) is a key public health intervention for the prevention of Tuberculosis (TB) among people infected with HIV/AIDS, yet TB remains the leading cause of death amongst this population. The uptake of IPT in the face of various programmatic challenges is too low; hence the urgent need for implementation of interventions that enhance general health system capabilities to roll out IPT programmes, strengthen day-to-day system functioning and retain patients in care while improving patient treatment outcomes. The proposed study will pilot a mobile technology program to enhance the uptake of IPT and assess its impact on IPT refusal and retention rates.

CRITIQUE 1:

Significance: 3
Investigator(s): 3
Innovation: 4
Approach: 5
Environment: 3

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2. Investigator(s):

Strengths

- The research team has extensive experience with both clinical practice and research addressing TB/HIV.
- Notable that the majority of the research team resides and works in South Africa

Weaknesses

- Research team could be strengthened by the inclusion of a behavioral scientist to better investigate and describe barriers to IPT initiation, adherence, and completion.

3. Innovation:

Strengths

- Utilizing an existing resource (mobile phones) that are readily available and used by a majority of the population
- The USSD technology planned for implementing the intervention (screening and reminders) has already been adopted by many people for purchasing airtime and mobile banking
- Reduces the number of visits required by patients and workload for healthcare workers
- Team has already developed plans to address potential problems with use of the technology (e.g., loss of battery power during information exchange).
- Possibility of also incorporating "TB Clinic Locator" feature – but unclear the extent to which this is planned

Weaknesses

- No way to validate or further explore responses to the mobile screening questions.
- Innovation only addresses one possible barrier to IPT implementation (e.g., number of required clinic visits).

4. Approach:

Strengths

- Innovative use of a relatively accessible technology to reduce the number of clinic visits required to receive IPT and to facilitate remote screening for TB among PLHIV on IPT
- Pre and post intervention design to measure impact
- Evaluating acceptance, adherence, and completion of up to 12 months of IPT
- Automated nature of the intervention (including notification of healthcare workers of patients with symptoms of TB disease) and real time or timely availability of data

Weaknesses

- The eligible study population is limited to PLHIV with mobile phones. The researchers point out in the background that lack or resources can be a barrier to IPT initiation and adherence. People that lack mobile phones are perhaps the most impacted by resource limitations and could perhaps most benefit from this intervention.
- Intervention only targets one barrier to screening and IPT (i.e., decreases number of trips to the clinic) and does not address issues regarding transportation, lack of sufficient nutrition to

tolerate meds, distance required to travel to clinic, stigma associated with visiting a clinic near where a patient lives, etc.

- There is a lot to learn about the piloting of the use of mobile phones and USSD technology to promote initiation, adherence, and adherence to IPT but how generalizable are the findings since the study is limited to one of the premier HIV care and treatment centers in the world

5. Environment:

Strengths

- Ideal environment to implement a study on the efficacy of using mobile phones to promote IPT implementation because of the burden of disease, mobile phone accessibility, and clinical/research resources and expertise
- History successfully conducting large scale high impact studies at the study site

Weaknesses

- None noted.

Protections for Human Subjects:

Acceptable Risks and/or Adequate Protections

- Measures in place to ensure patient consent to participate and data confidentiality

Inclusion of Women, Minorities and Children

- Sex/Gender: Distribution justified scientifically
- Race/Ethnicity: Distribution justified scientifically
- Inclusion/Exclusion of Children under 21: Including ages < 21 justified scientifically

Vertebrate Animals:

Not Applicable (No Vertebrate Animals)

Biohazards:

Not Applicable (No Biohazards)

Budget and Period of Support:

Recommend as Requested

Additional Comments to Applicant (Optional):

- Proposal mentions providing participant reimbursements (page 40). Is that to cover the cost of the airtime vouchers (page 58)?
- Strongly encourage the research team to modify the proposal to include the provision of phones for patients that don't have them so they can be included in the study. Otherwise, you are excluding the group that could perhaps most benefit from your intervention.

- Consider including a behavioral scientist and focus group discussions with patients that have poor adherence to the intervention so that you can better understand reasons why the intervention was not adopted by some groups or issues such as whether patients purposefully responded that they did not have symptoms when in fact they did to avoid having to make additional trips to the clinic for follow-up investigations for possible TB disease.
- I assume the analysis will take into consideration CD4 count and ART status when examining the number of people developing TB after starting IPT.

CRITIQUE 2:

Significance: 4
Investigator(s): 4
Innovation: 3
Approach: 4
Environment: 6

Overall Impact: The main goal is to develop a Mobile technology program for cell phones, and to provide the devices to persons eligible for IPT. The project aims to assess the use of this technology on the uptake and retention of IPT. The conceptual framework of the project is that mobile phone symptom screening for TB at monthly intervals and clinic based follow up every three months will improve uptake and completion rates of IPT. It is addressing an important question, as uptake of IPT is low, and patients experience several barriers to keep on IPT. Many of these are associated with the monthly follow up visits to clinics. The project plan is quite feasible to lead to the desired outcomes within two years. The likelihood of the project exerting a sustained powerful influence on the research fields of IPT and mobile technology is high. There is limited evidence on the optimal content and user acceptability of mobile health and the findings of this project will be valuable to inform future use. The project team is well put together with complementary expertise, and cell phone usage is very high under the target populations. Mobile technology is recognized as an emerging technology with huge potential to deliver cheap, patient centered and health care directly to the person. There is limited evidence on large scale implementation of this technology, or its use by TB control programs. Despite these limitations, this pilot phase project has the potential to lead to high and sustained impact on the field of chronic care delivery. The feasibility of successful completion of the project is medium; however challenges encountered in this project should be similar for others' when developing the technology. The project team is strong, the environment very good, and the approach appropriate to lead to the desired outcomes. It is not well described how the project team will ensure that the cellphones are indeed only used by the study participants. Additionally, there may be data loss due to some participants being unfamiliar with mobile health care delivery. Several research areas will be influenced by the project including TB/HIV prevention and treatment, health systems, mobile health, clinical practice.

1. Significance:

Strengths

- Use of mobile technology to deliver services to the cell phones of patients
- Study sites exceptionally well suited for the project
- Adherence to IPT, an important problem, will be addressed. A major challenge in the roll out of IPT is low adherence and there are several reasons for this. Some of the reasons will be explored in this project and there will be an attempt to determine if mobile health can overcome these.