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EFFECTIVENESS OF ISONIAZID PREVENTIVE THERAPY ON INCIDENCE OF TUBERCULOSIS IN ADULT PEOPLE LIVING WITH HIV IN SELECTED DISTRICTS OF RWANDA

BY

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DECLARATION

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ABSTRACT

Tuberculosis (TB) is a common complication and leading cause of death in people living with HIV infection. In Rwanda, TB is the main opportunistic infection and it is the leading cause of death in HIV infected patients (Rwanda Ministry of Health, 2005).

Whereas some literature have shown that the use of Isoniazid as a prophylaxis reduced the TB incidence in HIV/TB co-infected patients by 70–90 percent (Whalen et al., 1997; Gordin et al., 1997) others yielded conflicting results. For example a study from Brazil revealed that IPT mostly worked with ART whereby ART alone was independently associated with 59 per cent reduction in tuberculosis incidence, while the effect of IPT alone was no longer significant (Golub et al., 2007). Despite good evidence that Isoniazid Preventive Therapy (IPT) reduces the incidence of TB among people with HIV infection, implementation of IPT is low at the global perspective. Although, Rwanda is among few countries in the region implementing six months IPT strategy, but there is no published literature on its effectiveness in the country. This gap called for further studies to extend the knowledge on IPT, to support its implementation and to relate the known to country's context. Therefore the present study intended to establish whether IPT reduced the incidence of active TB in people living with HIV (PLHIV).

This was a retrospective cohort study design using medical records of PLHIV from six health facilities in three districts of Rwanda. The period of study extended between 1st August, 2011 and 31st January, 2014. Out of 2172 PLHIV, 1,086 were on IPT and 1,086 were not. Survival analysis and Poisson regression with SPSS version 20.0 were used to compare rates of TB and factors contributing to it in PLHIV on IPT to those not on IPT.

The overall TB incidence was 1.131 cases per 100 person-years (PY) [95 confidence interval (CI) 0.98-1.44]. The incidence rate of TB in patients on IPT was significantly lower than those who were not on IPT (0.56/100PY *vs* 2.04/100PY) and Incidence Rate Ratio (IRR) was 0.275 [95% CI 0.152-0.493]. Multivariate Cox proportional hazard model revealed 73 per cent reduction in TB risk among patients who received IPT. Among IPT completers, the risk of developing TB reduced up to 87.5 per cent (HR=0.125 P value<0.00). Being on ART, having CD4 cell count >350, HIV clinical stage 1 and 2 and high income, were factors contributing to lower incidence of TB among PLHIV on IPT.

By comparing the time of TB occurrence among PLHIV who took IPT with those who did not, the present study showed that the protective effect of IPT seemed to be gradually lost over time. It did not decline as rapidly as it has been reported in patients not on IPT. The use of Isoniazid in People Living with HIV was associated with low incidence of Tuberculosis.

Keywords: Isoniazid Preventive Therapy, Tuberculosis, People living with HIV, Rwanda

DEDICATION

To my late parents Ruhumuliza Evariste and Mukarubuga Félicitée, who unfortunately, did not live long to see me at this moment and whose effort and parental pieces of advice made me attain this level.

To my loving and ever-supportive Husband Nyirinkwaya Serge.

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ACRONYMS

ART…….Anti retro Viral Therapy

CD4…….Cluster of Differentiation Four

CDC……Centre for Disease Control and Prevention

CHUK…….Centre Hospitalier Universitaire de Kigali

CI…….Confidence Interval

CTXp……...Cotrimoxazole

DOTS……...Dosage Observed Treatment Strategy

DH……District Hospital

HC……Health Center

HR……....Hazard Ratio

HIV/AIDS……....Human Immunodeficiency Virus/ Acquired Immunodeficiency Syndrome

IBM SPSS……International Business Machines Statistical Package for Social Scientists

ICAD……Interagency Coalition on AIDS and Development

IDSA…… Infectious Disease Society of America

INH……...Isoniazid

IPT……....Isoniazid Preventive Therapy

IPT E……Isoniazid Preventive Therapy Exposed

IPT NE…… Isoniazid Preventive Therapy Non Exposed

IR……..Incidence Rate

IRR……...Incidence Rate Ratio

IUATCP……...International Union Against Tuberculosis Committee on Prophylaxis

KR…….....Kwacha Rebased

LCD……..Liquid Crystal Display

Ml……..Milliliter

MOH…….Ministry of Health

n…….Sample population

N……....Population

PLHIV……..Persons Living with Human Immunodeficiency Virus

PY…….....Person-Year

RBC……....Rwanda Biomedical Center

RWF……...Rwandan Franc

RNA……Ribonucleic Acid

SA……South Africa

SD……Standard Deviation

TB……...Tuberculosis

TST…….Tuberculin Skin test

µL……Cubic millimeter

UN……...United State

UNAIDS…….United Nation for Acquired Immune Deficiency Disease Syndrome

UNZA…….University of Zambia

UK……..United Kingdom

USA……United State of America

VL……..Viral Load

WHO……..World Health Organization

CHAPTER 1: INTRODUCTION

1.1. Background information

Tuberculosis, commonly known as TB, is a contagious and an often severe droplet disease caused by a bacterial microorganism, the tubercle bacillus or *Mycobacterium tuberculosis*. It typically affects the lungs, but it may also affect any other organ of the body (Konstantinos, 2010). Tuberculosis occurs in every part of the World. In 2011, 8.7 million people contracted TB amongst which 1.4 million died from it. Sub-Saharan Africa carried the greatest proportion of new cases per population with over 260 cases per 100 000 population (WHO, 2012a). Looking at the Rwandan context as the World Bank (2012) reported, the incidence rate of TB per 100,000 people in Rwanda was 86 in 2012.

Human Immunodeficiency Virus/ Acquired Immunodeficiency Syndrome (HIV/AIDS) is the strongest risk factor for developing tuberculosis. Persons co-infected with HIV/TB, are 21 to 34 times more likely to develop active TB disease than people without HIV (WHO, 2012a-13). Almost 25 per cent of deaths among people with HIV are due to TB. In 2011, there were 34 million people living with HIV (PLHIV) globally. At least one third of these had latent TB and 1.1 million contracted new TB infections (WHO, 2012a-13). In Sub-Saharan Africa, HIV is the fuel of TB infection and seven per cent of patients who developed new TB were from this region (WHO, 2011a-13). In Rwanda, TB is the main opportunistic infection and it is the leading cause of death in HIV infected patients (Rwanda Ministry of Health, 2005).

To halt the burden of TB, the Dosage Observed Treatment Strategy (DOTS) was developed and adopted by all United Nations country members. The DOTS strategy was largely developed in the pre-HIV era, and its implementation between 1995 and 2010 helped successfully to treat 46 million people with TB and save 6.8 million lives (WHO, 2011a). Although the DOTS strategy is essential for people with and without HIV, it is unlikely to reduce the incidence and prevalence of TB in countries where HIV is highly prevalent (De Cock & Chaisson, 1999).

In addition to DOTS, The WHO recommended Anti Retroviral Therapy (ART) in 2009 for all adults with Cluster of Differentiation Four (CD4) counts less than 350 cells per cubic millimeter of blood (μL) and for all TB patients irrespective of CD4 count (WHO, 2010b).

To this effect, ART alone has been found to reduce the risk of tuberculosis infection by 64 per cent (Golub et al., 2009).To improve on that, from 2010 the WHO further recommended a range of collaborative activities including three I's for HIV/TB management: (1) Intensified TB case-finding, (2) Isoniazid Preventive Therapy (IPT), and (3) TB Infection control (WHO, 2011b). Amongst these activities, IPT consists of using Isoniazid (INH), one of first-line anti-tuberculosis treatment, for a certain time (usually between 6 to 36 months) to prevent the occurrence of active TB. IPT had been known to reduce incidence of TB before the HIV era for more than 40 years, and as a preventive therapy in HIV/TB co-infected patients (WHO, 2011b). In the process to find out a better solution, IPT and ART came to be associated as an effective measure to fight against HIV/TB (Charalambous, 2010; Golub, 2007; Smart, 2009). Thereafter, the WHO recommended the use of ART and IPT combination to reduce the burden of TB among HIV infected patients (WHO, 2010a).

However, the global policy regarding IPT in patients with HIV infection has been ambivalent. The WHO and United Nation Programme for HIV/AIDS (UNAIDS) had recommended in 1998 that IPT must be offered to HIV-infected patients, but did not endorse it for public purpose (WHO, 1998). As a result, IPT has been rarely implemented and considerable reluctance to resort this intervention persisted (Golub et al., 2007). The policy of 1998 implied the use of chest radiography and Tuberculin Skin Test (TST) for TB screening. Yet many clinicians worried that in settings with limited diagnostic capacity, active TB disease cannot be conclusively ruled out in HIV-infected patients. To be specific with the case, patients with active TB would receive Isoniazid monotherapy, which could potentially result in INH drug resistance and an increased risk of a multiple-drug resistant TB (I-TECH, 2011).

In early 2010, new guidelines about IPT were adopted to review the IPT policy of 1998. Those guidelines recommended the use of a simplified screening algorithm that relies on four clinical symptoms (current cough, fever, weight loss and night sweat) to identify those eligible for either IPT or further diagnostic work-up for TB. Hence, the chest radiography and TST were no longer mandatory investigations before starting IPT (WHO, 2010).

Taking cognizance of this recommendation, the national TB/HIV joint programme in Rwanda, adopted these new guidelines on IPT implementation.

The Rwandan TB programme's guidelines recommend that INH should be given to patients at a daily dose of 5 mg/kg, and a maximum dose of 300 mg/day for a period of 6 months (RBC, 2012). The current programme is still being implemented as a pilot experience, although it is not the first time to attempt to the programme. Actually, the first attempt was launched in 2003 and was unexpectedly discontinued after one year. The new programme for adults (fifteen years and above) was launched from August 2011 in only two health centers Kimironko and Kivumu as well as in one district hospital - Kabgayi. The main goal of the current IPT programme is to strengthen the existing strategies to bring down the TB in PLHIV (RBC, 2012).

Since the start of the programme in 2011, an estimated number of four thousand adult PLHIV took Isoniazid (RBC, 2012). However, to the best of our knowledge, no research has been done to evaluate the effectiveness of the programme. It is in this premise that the researcher intended to evaluate the effectiveness of IPT programme on TB incidence in adult PLHIV.

1.2. Problem statement

HIV/AIDS and TB are a major public health threats for PLHIV (WHO, 2008 & WHO, 2012a). With reference to UNAIDS (2012) global report on AIDS epidemic, the worldwide number of people with TB with known HIV status was 2,469,370 and around 40 per cent are in sub-Saharan Africa. Concerning Rwanda, WHO estimates that the TB prevalence decreased from 521 per 100,000 populations in 1990 to 106 per 100,000 populations in 2010 and 86 per 100,000 in 2012, representing a decrease of more than 75 per cent. Despite efforts invested by the government of the Republic of Rwanda and the international community, TB is still one of the causes of morbidity and mortality in Rwanda and its severity is fuelled by HIV. For instance, from July 2011 to June 2012, 6352 TB cases were registered and 1742 of them were HIV positive. This implies that the prevalence of HIV among TB patients was estimated to reach around 28 per cent (RBC, 2012).

Isoniazid preventive therapy is cost effective, safe and feasible drug of choice to reduce the incidence of TB among PLHIV infected persons especially in resource limited settings (Granich et al., 2010). According to WHO (2008) IPT given to PLHIV reduces the risk of developing TB by 33–67 per cent for up to 48 months. Nevertheless, IPT has been rarely implemented particularly in countries with high TB burden.

In 2007 for example, only 0.1 per cent of people living with HIV worldwide were on IPT (Modi & Dave, 2012). The public health importance of IPT in Rwanda is not known, as such it is empirically not possible to ascertain the extent to which IPT prevent TB among PLHIV, hence the need to conduct this study.

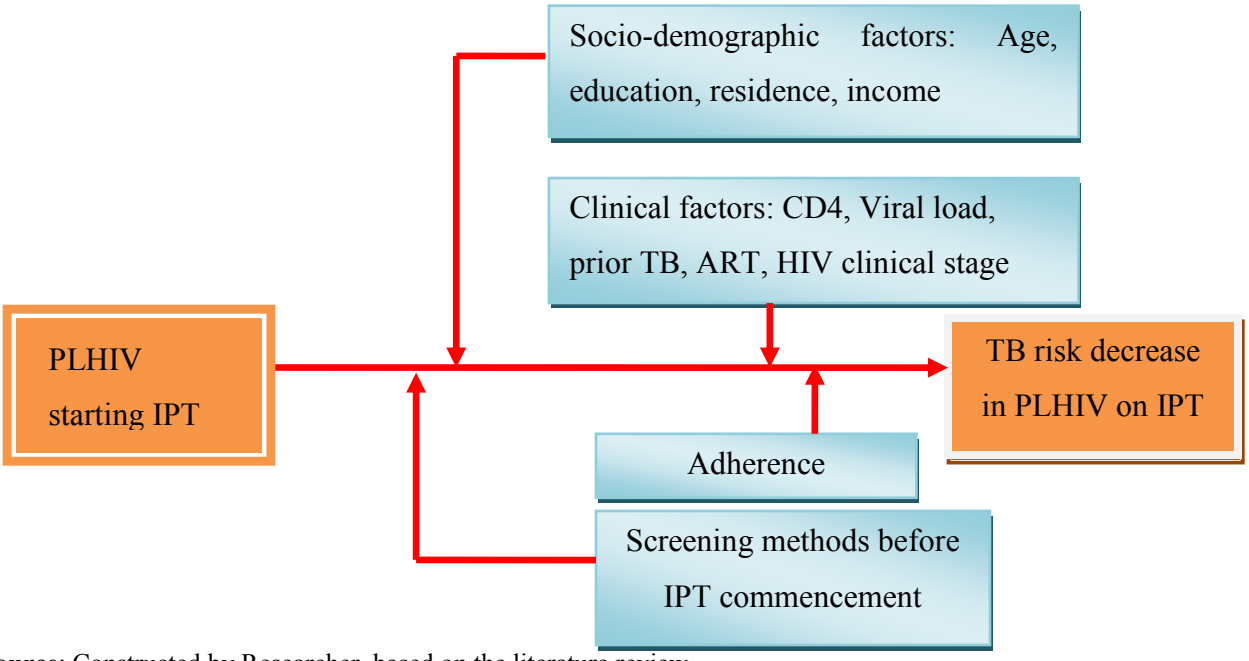
1.3. Study justification

The present study aimed at evaluating the effectiveness of IPT on TB incidence in PLHIV. Findings of this study will contribute towards knowledge of IPT effectiveness in PLHIV especially that it was an analytical study. Hopefully the results will further support the already instituted initiatives in Rwanda aimed at improving management of HIV patients. Specifically, the information from this study will guide national HIV and TB programmes to roll out the IPT programme in the whole country. In addition, the study will provide information on IPT programme challenges for health planners and managers and generate further researches.

1.4. Conceptual framework

After reviewing the literature, the conceptual framework was constructed as shown in the figure below.

Figure 1.1: Effect of IPT on TB in PLHIV and factors determining TB in PLHIV on IPT



Source: Constructed by Researcher, based on the literature review

The figure 1.1 displays the expected effect of IPT to PLHIV. This effect depends on some factors that may determine TB in PLHIV taking IPT. These factors include socio-demographic, clinical factors and other factors like adherence and screening methods before IPT commencement

Socio-demographic factors associated with Tuberculosis include age, gender, employment status, residence and income. Starting by age, more cases of TB in many developing countries occur among the age group of 15-54 years (the most productive age group) than in the developed countries where elderly people are more affected (Reid & Shah, 2009).

Concerning gender as another socio-demographic factor, more men are diagnosed and die from TB than women. However TB is a leading infectious cause of death among women and it affects women when they are economically and reproductively active (WHO, 2014). Different social and economic roles and activities may lead to differential exposure to tuberculosis bacilli. A number of studies suggest that responses to illness differ in women and men, and that barriers to early detection and treatment of TB vary (and are probably greater) for women than for men (WHO, 2014). In terms of poor nutrition and human immunodeficiency virus status, the risk of disease may be increased in women than men.

Other socio-demographic factors determining TB are employment status and residence. People who live or work in certain settings (health care workers, TB drug treatment centers, carpenters and other people who may be exposed to TB on the job) are at higher risk for TB disease because they are more likely to develop the disease once infected with certain medical conditions, especially HIV infection (Simon &Abdool Karim, 2006).

Income deprivation in developing countries is also associated with higher rates of HIV-TB and non-HIV-TB and over 95 per cent of cases and deaths are from this area (WHO, 2012). Residence in the port area at census tract level, household crowding contextual are also associated with HIV-related TB incidence (Cordoba-Dona et al., 2012).

As for clinical factors associated with Tuberculosis, they include the CD4 cell count, viral load, HIV clinical stage, previous TB, ART. Regarding CD4 cells, they are again called T-helper cells; a type of white blood cell that fights infection. These cells are made in bone-marrow, mature in the thymus gland. They move throughout the body, and help both to identify and destroy bacteria and viruses. The CD4 count help to tell how much strong the immune system is.

HIV can destroy entire families of CD4 cells, and in that case opportunistic infections like TB are likely to develop. CD4 counts are reported as the number of cells in a cubic millimeter of blood. A normal CD4 count is from 500 to 1,500 cells per cubic millimeter of blood. Note that the number of CD4 cell counts is associated with the level of viral load (Bendavid et al., 2008).

Moving to viral load factor, this term is used to describe the amount of HIV in the blood. The higher the viral load, the faster CD4 cell count will fall, predisposing to development of opportunistic infections like TB (Bendavid et al., 2008). A viral load of < 10,000 copies/ml would be considered low while >100,000 would be considered high (Bendavid et al., 2008). At viral copies below 40 or 50 copies/ml, the viral load becomes less sensitive, and the test is reported undetectable viral load.

Another clinical factor which would determine TB is the stage of HIV. WHO disease staging system for HIV infection and disease in adults and adolescents is an approach for use in resource limited settings. This system classifies individual into four stages I, II, III and IV. The stage III and IV are most commonly with advanced stage with association of opportunistic diseases such as TB (WHO, 2005). It is also worth mentioning that the importance of prior TB should not be undermined. It has been seen that for prior TB in a setting with a high risk of tuberculosis infection, HIV increases the risk of recurrent tuberculosis because of an increased risk of re-infection. That explains why it is important to measure the effect of prior TB in such study even in people on ART (Sonnenberg et al., 2001).

Antiretroviral therapy is another clinical factor that has substantial potential to prevent HIV-associated tuberculosis. Antiretroviral therapy is strongly associated with a reduction in the incidence of tuberculosis across all CD4 count strata. Earlier initiation of antiretroviral therapy and early diagnosis may be a key component of global and national strategies to control the HIV-associated tuberculosis syndemic (Amitabh et al., 2012)

The occurrence of TB in PLHIV taking IPT is not only determined by the above clinical factors but also the degree to which a patient is complying with drug. Adherence to IPT means to stick firmly to the 6 months of IPT regimen, taking it every day and exactly as prescribed.

Adherence to IPT increases the chance to act properly to prevent mycobacterium to multiply, prevent the resistance mostly to people with prior TB (Reid &Shah, 2009).

The last factor to consider is screening method which actually has led to global policies and the beginnings of implementation of HIV/TB joint activities including IPT. The main issue in debates remains about the best methods of screening for pulmonary tuberculosis among people living with HIV/AIDS in resource-limited settings. More widely available methods, such as symptom screening, sputum smear microscopy, chest radiography, and tuberculin skin testing have important shortcomings, especially in people living with HIV/AIDS. However, until simpler, cheaper, and more sensitive diagnostics for tuberculosis are available in peripheral healthcare settings, a strategy must be developed that uses current evidence to combine available screening tools (Reid & Shah, 2009).

1.5. Research question

What is the effectiveness of primary IPT on incidence of active TB in adult PLHIV in selected districts of Rwanda?

1.6. Objectives

1.6.1. General objective

To evaluate the effectiveness of primary IPT programme on incidence of active TB, in adult PLHIV in selected districts of Rwanda.

1.6.2. Specific objectives

1. To compare the incidence of active TB among adult PLHIV who took with those who did not take IPT.
2. To identify the socio-demographic and clinical factors contributing to active TB in PLHIV on IPT.
3. To compare the time of TB occurrence among PLHIV who took IPT with those who did not.

1.7. Research Hypothesis

The alternative hypothesis of the study was: The use of Isoniazid Preventive Therapy reduces the incidence rate of Tuberculosis in people living with HIV

1.8. Research Variables

The table 1.1 summarizes all variables of interest and their level of measurement.

Table 1.1: Research variables

Variable	Cut off point	Indicator
Dependent variable		
TB occurrence	Yes, NO	Positive spit, extra-pulmonary TB
Time to TB occurrence	Number of Months	
Independent variables		
IPT exposure	Yes, No	Took INH regardless months taken
IPT status	Yes, No	Completed 6 months
Socio demographic factors Age Sex Marital status Educational Income Residence	 Age at birth Female , Male Divorced, separated, cohabitation, Single, Married, None, Primary, secondary, Tertiary, other Low, medium, high Kamonyi,Muhanga,Gasabo,other	 Low (0-100,000 RWF), middle (100,001-200,000 RWF) and high (200,001 RWF and above).
Clinical factors ART initiation Baseline HIV clinical stage Baseline CD4 count Viral road Cotrimoxazole Previous TB	 Yes, No Year started ART Stage 1, Stage 2, Stage 3, Stage 4 Cells per cubic millimeter of blood (μL) Copies/ml Yes, No Yes, No	

Source: Researcher

The dependent variable in survival analysis is composed of two parts: one is the time to event and the other is the event itself (Indrayan et al., 2001). From there, two functions that are dependent on time, the survival and hazard functions are estimated. One part of the dependent variable in the present study was the occurrence of TB which was dichotomized in a binary variable (yes, no), and the second part was the time when TB occurred, which was a continuous variable estimated in number of months. The main exposure was IPT, also categorised as a binary variable. Furthermore, there were other factors that would determine the occurrence of TB as it was illustrated in the above table.

1.9. Definitions of key terms

Active Tuberculosis: TB that has been confirmed by clinical and positive sputum smear, chest x-ray result suggestive of TB and ganglion TB.

People Living with HIV (PLHIV): In the present study PLHIV refers to individuals whose HIV tests indicated that they are infected with HIV, regardless of the stage of HIV.

IPT exposed (IPT E): In the present study IPT E refers to PLHIV who took IPT regardless the duration within the study period from August 2010 to January 2014.

IPT non-exposed (IPT NE): In the present study IPT NE refers to PLHIV who did not take IPT before and during the study period.

IPT completers: In the present study Isonizaid Preventive Therapy completers refer to PLHIV who took IPT during the period of study and completed a six months session.

IPT incompleters: In the present study Isonizaid Preventive Therapy incompleters refer to people who took IPT during the period of study but did not complete a six months session.

Cohort study: This is a type of an analytical study in which a group having one or more similar exposure (such as IPT in this study) is closely monitored over time simultaneously with another group free from that exposure (IPT NE group in this study) (USA National Cancer Institute dictionary).

Retrospective cohort study: is a cohort that takes a look back at events that have already taken place.

Medical records of groups of individuals who are alike in many ways, but differ by certain characteristics (IPT in this study) are compared for a particular outcome (TB in this study) (USA National Cancer Institute dictionary). In the case of a retrospective cohort study, the investigator collects data from past records and does not follow patients up as is the case with a prospective study. However, the starting point of this study is the same as for all cohort studies (Mann, 2003). In Retrospective Cohort Study, all the events - exposure, latent period, and subsequent outcome have already occurred in the past. We merely collect the data now, and establish the risk of developing a disease if exposed to a particular risk factor (Mann, 2003).

Income status: In the present study, income is the amount of monthly income per individual grouped as low (0-100,000 RWF), middle (100,001-200,000 RWF) and high (200,001 RWF and above).

CHAPTER 2: LITERATURE REVIEW

2.1.Introduction

The literature review below examines selected empirical studies and publications related to IPT in PLHIV. Its sources are published articles and accredited books from computerized data and libraries. This important section contains four major points: the concept and history of IPT in PLHIV, IPT practices in global, regional and national context, a look at scientific results regarding IPT, and finally different concerns on IPT.

2.2.Overview of IPT in PLHIV

In 1998, the WHO defined Isoniazid Preventive Therapy (IPT) as the use of Isoniazid, which is one of anti-tuberculosis drugs given to individuals with latent infection with mycobacterium tuberculosis in order to prevent the progression to active disease. At that time, HIV was the most powerful known risk factor for progression from latent infection with mycobacterium tuberculosis to active disease. Therefore, considering the large increase in the incidence of tuberculosis in populations with a high prevalence of HIV infection, new measures had to be taken. In February 1998, the WHO and UNAIDS convened a meeting to review the data available and to make recommendations to governments that would serve to update the guidelines published in 1993. Then, The WHO and UNAIDS recommended to governments that IPT should be part of a package of care for PLHIV (WHO, 1998).

IPT delivery to PLVIH had to include a range of services or steps. These are (1) counselling on tuberculosis, (2) screening for active tuberculosis, (3) targeting of those most likely to benefit from IPT, (4) provision of preventive therapy to those without active tuberculosis, (5) monitoring for adherence and toxicity and (6) evaluation of outcome.

As regards screening for active tuberculosis, TST and chest x-ray were mandatory to rule out active TB before IPT commencement. But this seemed a barrier to the implementation of IPT policy in most of developing countries where the burden of TB in HIV was high and without sufficient resources (WHO, 1998).

Later on in 2010, the TB/HIV collaborative activities incorporating IPT were introduced to provide well established framework for countries in their response to HIV-related TB.

The recently updated collaborative TB/HIV activities policy recommends national programmes and other stakeholders to incorporate TB/HIV activities into routine HIV prevention package. The aim of collaborative TB/HIV activities was and still remains to reduce the dual burden of TB and HIV in people living with the disease or at risk of disease (WHO, 2011b).

The new WHO's IPT definition in collaborative TB/HIV refers to the use of Isoniazid (usually 300 mg per day) to stop the development of active TB a condition known as latent TB infection. At least self-administered six months of IPT are recommended for children and adults including pregnant women, people living with HIV, those receiving ART, and those who have successfully completed TB treatment. IPT for duration of 36 months is conditionally recommended in settings with a high transmission of TB among PLHIV. In contrast to the 1998's policy, the revised guidelines emphasize that a tuberculin skin test (TST) and chest X-ray are not a requirement for initiating IPT in PLHIV. However, in some settings where it is feasible, TST can help to identify those who would benefit most from IPT (WHO, 2011b).

2.3.Current global, regional and national programme practices

According to the global TB control (WHO, 2010a), in 2009 around 80,000 HIV positive people were provided with IPT, which accounts for less than 1 per cent of the estimated number of eligible people living with HIV. Afterward, in 2010, the global number of HIV positive individuals without active TB who enrolled on IPT was estimated at 180,000 which are seven times significant to the level achieved in 2005 and three-fold in 2008.

High burden countries contributed to more than ninety four per cent to this figure, of which eighty nine per cent (160,000) of individuals were from Africa. The WHO classified forty-one countries as high burden countries where 29 of which are from Africa continent (WHO, 2011a).

Before starting, many HIV and TB programmes in Africa had waited to learn from the experience of the IPT programme in Botswana. In 2001, it became the first and only country giving IPT to adults with HIV as a public health measure. But at the Stop TB Symposium, held in Cape Town in 2007, the Director of TB programme reported different challenges accoutered which made the report to sound like a mixed success at best. During that time, the programme screened over 71,000 HIV positive people, and 67,413 started IPT.

For those put on IPT however, only 37 per cent were either currently on treatment or were reported as completing the six-month course of IPT, while as many as 63 per cent were listed as non-completers. In 2007, Botswana was revising its national guideline to fit into this recommendation. But questions still remained about how best to scale up IPT from pilot projects at the national level (Nam, 2007).

South Africa was effective in IPT programme delivery and implementation whereby in 2009 alone, the country reported 23,583 HIV infected persons who had received prophylaxis for TB. Namibia and Botswana were ranked second and third (Getahun et al., 2010). The WHO (2011a) report indicated that South Africa took the lead in reaching 124,049 HIV infected individuals with IPT, which accounts 79.5 per cent of African coverage. Despite everything, Smart (2009) reported that in South Africa there was an ongoing debate on about how long IPT should be given, and what should be the best methods of screening patients eligible to IPT.

Coming to the regional level, the process is not yet taken too far. In 2011 in Nairobi-Kenya, there was a workshop to accelerate the implementation of the three I's principles for HIV and TB in East Africa. This was about the collaborative activities of the WHO for HIV/TB management: (1) Intensified TB case-finding, (2) Isoniazid Preventive Therapy (IPT), and (3) TB Infection control. It was realized that apart from Rwanda, other countries of East Africa were not yet commencing IPT implementation (Kenya Legal & Ethical Issues Network on HIV & AIDS, 2011).

Regarding the Rwandan situation, Rwanda national TB/HIV programme has started implementing IPT in adult since August 2011 as a pilot programme in three health facilities. Since the start of the programme, an estimated four thousand adult PLHIV took the Isoniazid (RBC, 2012).

However it is worth mentioning that no research has been done so far to document the efficacy of this programme.

2.4.Effectiveness of IPT and factors that would determine the incidence of TB in PLHIV based on scientific results

With reference to the WHO statement, IPT works, but the way it works depends upon different factors such as the risk of active TB, duration of treatment, adherence and other factors (Nam, 2007). According to a study published in 1982 by the International Union Against Tuberculosis Committee on Prophylaxis (IUATCP), the preventive effect of IPT became evident after the first 12 weeks on treatment with a 31 per cent reduction in incidence of active disease among 28,000 people. The effect increased to 69 per cent after 24 weeks of IPT, and to over 93 per cent at 52 weeks in adherent/completer patients. The analysis showed less difference between six and twelve months of IPT, and because of a risk-benefit analysis taking into account the risk of cumulative liver toxicity while taking IPT for long time, the study concluded that taking IPT for six months was better, and that was what the 1998 WHO policy recommended (Nam, 2007).

However countries like the United State of America (USA) reached different conclusions. Its public health officials reviewed the combined data on IPT and determined that the best risk benefit ratio for duration was nine months. After that, the CDC/ATS guidelines were changed and six to nine months is now the practice in USA. The USA is among countries with low burden of TB. So, it is right to reason that if the US analysis was on target, then six months is in a way low for a high burden setting (Nam, 2007).

The reality is that the optimum length of time for IPT has never really been established in people with HIV, who have a dramatically great risk of developing active disease in their lifetime. Nevertheless it can even be difficult to recognise latent TB infection in someone with HIV, because the tuberculin skin test (TST) for latent disease can be difficult to interpret.

Therefore, some PLHIV did not react on TST and some experts recommend using a lower cut-off (a reaction ≥ 5mm rather than ≥10mm) as a positive result. But the study by Cobelens et al (2007), has found that this makes the test much less specific for TB particularly in areas where BCG vaccination and exposure to cross-reactive non tuberculous mycobacteria are frequent (like in sub-Saharan Africa) and not that much more sensitive (Nam, 2007). So TST interpretation isn't perfect. Thus, where the risk of TB exposure is considered very high, programmes pursue current WHO policy where TST is not necessary to all eligible people with HIV (WHO, 1998).

Basing on the above point, clinical trials in PLHIV have reported somewhat variable success rates using IPT. According to a Cochrane meta-analysis of these studies published in 2004, IPT reduces the risk of developing active disease in PLHIV and a positive TST by about 64 per cent and the risk of mortality by 26 per cent (Woldehanna & Volmink, 2004). This analysis did not find IPT to be of benefit to people without positive TSTs even where the risk of exposure to TB is high. However, when the data from all participants (those with and without latent TB) were pooled, IPT still significantly reduced the risk of active TB by 33 per cent.

Another study looked at the introduction of IPT into a high exposed workplace HIV clinic at a mine in South Africa. The researchers enrolled 1655 HIV-positive men; 679 of those who had no signs of active tuberculosis started Isoniazid therapy. TSTs were not routinely performed because the majority of employees were assumed to have latent TB infection. After a median follow-up of 22 months, the clinic saw a 32 per cent overall drop in the number of active cases (for the entire population, both on and not on IPT). In a multivariate analysis, if men with a history of TB (who were not eligible for IPT in the programme) were excluded, IPT treatment led to a 46 per cent drop in the incidence of active TB. But "despite our intervention, the TB incidence rate in the post-clinic phase remained unacceptably high at 9 per 100 person-years", the authors wrote. They came up with a number of potential reasons for this, one being that adherence may have been less than that in clinical trial conditions, which may have resulted in a reduced effect (Garant et al., 2009)

Poor adherence is the primary reason of IPT failure. In a study in public health facilities, Addis Abbaba, Ethiopia poor adherence was one reason among others to stop IPT, concomitantly completing IPT reduced TB incidence by 96.3 per cent (IRR=0.037; $P< 0.001$) than NE patients and by 2.5 per cent (IRR=0.275; P=0.013) than in-completers. Lost to follow up, drug stock out were other determinant factors for IPT discontinuation. But the study did not show the effect of ART on those who completed from those who didn't. However patients who took IPT with ART has 0.42/100P-Y TB IR and 92.7 per cent (IRR =0.063; P=0.001) incidence and 93.7 per cent (HR=0.073; P<0.001) hazard reduction than ART alone (Mahlet et al., 2013).

A retrospective chart review published in Rio de Janeiro, Brazil, suggested that IPT works with ART.

The study was comparing TB rates in 11026 people with HIV who received care 1) without ART or IPT, 2) with ART alone, 3) with IPT alone, 4) with ART plus IPT at 29 public clinics in Rio de Janeiro, Brazil between September 2003 and September 2005 (Golub et al., 2007).

Out of the total cohort, 11,096 patients (~10%) started IPT and 834 (76.1%) completed six months. The majority of those who started IPT had had a positive TST. For the cohort overall, the incidence of active TB was 2.28 cases/100 person-years (PY) [95% CI 2.06–2.52] twenty times higher than for the general population (0.38–1.47). In a multivariate analysis, after adjusting for age, previous tuberculosis diagnosis, and CD4 cell counts at baseline, ART alone was independently associated with 59 per cent reduction in tuberculosis incidence, P<0.001), while the effect of IPT alone was no longer significant (adjusted relative hazard 0.57; *P*=0.34) contrary to Namibia (Mekonen, et al., 2012) and Kenya (Diero et al., 2007).

The ability to accurately gauge IPT's effect could have been limited by the small proportion of people taking IPT as well as the way doctors prescribe IPT in Brazil. However, the use of both IPT and ART together significantly reduced the incidence by 76 per cent (*P*<0.001). Similar benefits were observed in people with CD4 cell counts below and above 350 cells. As a retrospective chart review, the study was limited in some respects to know why some patients underwent TST and why some patients began IPT or ART whereas others did not (Golub et al., 2007).

The study from Brazil (Golub et al., 2007) also included those with a previous TB diagnosis (17% of the total patients) who were at a very high risk of recurrent or reactivated TB. The study by Churchyard et al. (2003) to show if Isoniazid preventive therapy should follow TB treatment in HIV/TB co-infection, provided consistent findings that IPT could also have significant benefit in this population. Comparing 338 HIV positive gold miners in one South African mine who received Isoniazid (INH) with 221 who did not (all had prior TB), the researcher found that there was a much lower rate (a reduction of 55%) of active TB in those who were treated with INH than among those who were not (Nam, 2007).

The benefit of a course of IPT does not necessarily last long. With reference to some findings, clinical studies report mixed results following six months of IPT.

A study in Zambia suggested that the protective effect could last up to three years (Quigley, 2001) and it went up to 30 months in Northern Namibia (Mekonen, et al., 2012). However, a study from Uganda found the effect only lasted one year (Johnson, 2001). So again, perhaps IPT needs to be given longer in people with HIV.

Concerning some factors contributing to IPT effect for PLHIV, the study by Durovni et al. (2013) found age and gender to change the incidence of TB. During the control period, 221 cases of tuberculosis were diagnosed (1.31 per 100 person-years) compared with 254 (1.10 per 100 person-years) in the intervention period (unadjusted hazard ratio [HR] 0.87; 95% CI 0.69-1.10). Rates of tuberculosis incidence or death were 3.64 and 3.04 per 100 person-years, respectively (0.76; 95% CI 0.66-0.87). When adjusted for age, sex, entry CD4 count, and use of antiretroviral therapy, the HR for tuberculosis was 0.73 (95% CI 0.54-0.99) and for tuberculosis or death was 0.69 (0.57-0.83).

In the same point of view, a retrospective cohort study by Mahlet et al. (2013) on incidence of active TB among PLHIV, who took IPT in public health facilities of Addis Ababa, IPT significantly, decreased TB incidence and hazard by 93.7. In this study low CD4 count cell ($\leq$ 200) was seen to be associated with high risk of TB but new factors like WHO stage of HIV/AIDS 3 and 4, male sex, employment and residence place extended the list of factors for TB incidence in PLHI.

The last consideration regarding scientific results is that Isoniazid, like any other drug, has side effects which may be seen early in the course of treatment or after mostly in people who are taking IPT with ART. Isoniazid can cause nausea, which can be reduced by taking it with food, unless it is severe and associated with other symptoms of hepatitis such us rash, fever, mild central nervous system effects and peripheral neuropathy, the risk of which may be attenuated somewhat by taking vitamin B6 (Nam, 2007).

During the 1970s, reports of fatal liver damage in some patients surfaced. In the IUATCP study, hepatitis occurred in 0.5 per cent of the people on Isoniazid versus 0.1 per cent of the people on placebo. Three cases resulted in death (0.14 per 1000 persons on the drug).

Each of these three had continued taking Isoniazid after liver problems had been recognised, and the study's authors concluded the risk of hepatitis and subsequent death might have been avoided by the knowledge available today (Nam, 2007). Twenty-five years later, the risks are much better characterised. With proper management, most serious events can be averted.

In a public health setting in Seattle, Washington, forgoing laboratory monitoring, reported only 11 cases of hepatitis in over seven years in a cohort of 11,141 people on Isoniazid and only one of the cases required hospitalisation (Nolan et al., 1999).

2.5.Different concerns on IPT

The utilization of IPT is still lower despite the availability of policies and recommendations on the significant evidence that IPT reduces incidence of TB in PLHIV than expected due to diverse arguments. Most of the countries are still reluctant to implement IPT. Moreover, lack of standard operating procedures, guidelines and screening algorithms; lack of health care provider capacity in providing the service; fear to resistance and shortage of preventive therapy supplies contributes to the low availability and poor uptake of IPT (Golub et al. 2007; Granich et al. 2010; Eldred et al. 2010; Mosimaneotsile et al. 2010 & Gao et al. 2010). Equally, important side effects, drug toxicity, poor adherence, INH resistance and duration of IPT protection are also concerned (WHO, 2008; Golub et al. 2007).

In the same point of view, a cluster randomized trial conducted by Garant et al. (2010) showed that the low performance of IPT programme has been primarily due to fear of adverse effects. Among 24,221 study participants, 61 (0.25%) developed mild-to-moderate degree of hyper-sensitivity, 50 (0.21%) peripheral neuropathy, 17 (0.07%) hepatotoxicity and 4 (0.05%) had convulsion.

It is also possible that IPT may lead to the selection of Isoniazid resistance in individuals undergoing treatment; even though no evidence of many trials seems to be noticed. As an example, in the Nairobi trial, the rate of resistance in the Isoniazid arm was not statistically different from the rate in HIV-positive individuals (Hawken et al., 1997). More generally, a systematic review of IPT trials which assessed the risk of acquired resistance as a result of IPT by Balcells et al. (2006), found no statistically significant relationship between Isoniazid resistance and completion of IPT.

2.6.Conclusion

In reviewing the literature on IPT, conflicting views and therefore different concerns were noticed. Some views argue whereas others contrast the effectiveness of IPT. In 2009, the WHO reported the situation of the countries on IPT implementation (Getahun, 2010). This report ascertains that IPT is low implemented; it also shows that some countries like Rwanda and Malawi had time to stop the programme and restart later. Other countries used IPT as clinical trials which were not followed by a policy on IPT. For instance, this is the case of Zambia (Quigley et al., 1998). Again, with reference to some previous studies (as mentioned above), researchers do not value in the same way concerns that regard different screening methods before starting IPT as well as demographic and clinical factors contributing to TB in PLHIV. Therefore, there is a need to extend the knowledge on IPT in order to support its implementation and relate the known to the country context.

CHAPTER 3: RESEARCH METHODOLOGY

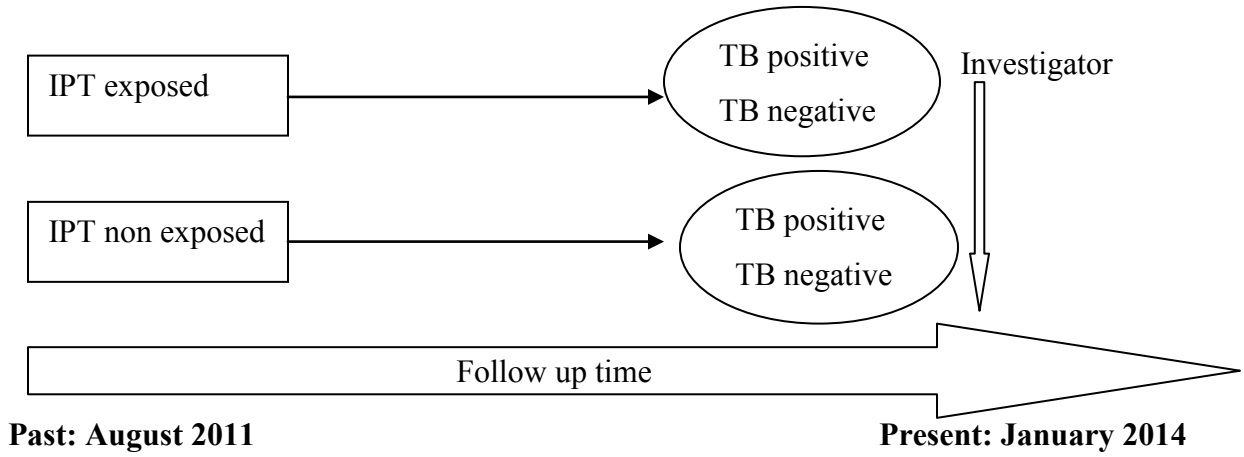
3.1. Introduction

This chapter describes the methods used in this study comprising the study design, study setting, study population, sample selection, data collection, data analysis and ethical consideration.

3.2. Study design

A research design is a plan, structure, and strategy of investigations for answering the research question. It is the overall plan or blue print the researchers select to carry out their study (Polit, and Beck, 2012).The present study is a retrospective cohort design in which secondary data were analysed. Using medical records, PLHIV who took IPT from August 2011 up to January 2014 were followed backward and compared with those who did not take IPT during the same period. The purpose was to determine the occurrence of TB during that specific time. The figure below summarizes the retrospective design used in this study.

Figure 3.1: The design summary of the study



Resource: Researcher (2013)

3.3. Study setting

Study setting is the physical location and a condition in which data collection takes place (Polit & Beck, 2012). As for this study, it was conducted in six public health facilities in three districts of Rwanda. Among these six health facilities, three are exclusively in a pilot programme providing IPT in the whole country and other three are not.

The three selected facilities which provide IPT are; Kabgayi District Hospital (DH), Kimironko and Kivumu health centers, while the others three health facilities which do not provide IPT are Rukoma DH, Kinyinya and Gitarama health centers. It was not possible to get the comparison group within the same institutions providing IPT because most of the PLHIV in those health centers took the prophylaxis before and this was against the objective of the study. Therefore, the nearest health facility was chosen on that basis as shown in the table below.

Table 3.1Study setting

IPT E sites	IPT NE sites	District/Province
Kabgayi District Hospital (DH)	Remera Rukoma DH	Kamonyi district/Southern province
Kivumu Health Center	Gitarama Helth Center	Muhanga district/Southern province
Kimironko Health Center	Kinyinya Helth Center	Gasabo district/Kigali city

3.4. Study Population

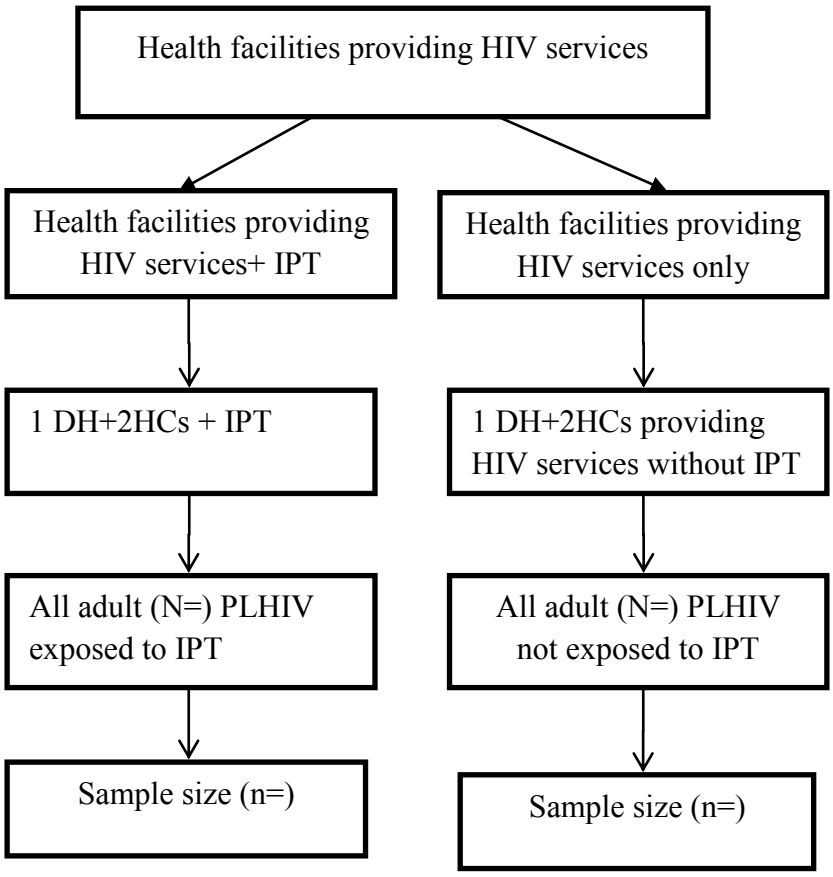
A population is the entire aggregation of cases in which a researcher is interested. The population may consist of events, places, objects, animals, or individuals (Burns & Grove 2005). In most researches, two populations are illustrated, the target population and the accessible population. The target population is the aggregate of cases about which the researcher would like to generalize. The accessible population is the aggregate of cases that conform to designated criteria and that are accessible for a study (Polit & Beck, 2012). In the present study, the target population comprised the adult category of PLHIV (15years old and above), and the accessible population comprised the adult category of PLHIV who visited the study settings between August 2011-January 2014.

3.5. Sample selection and sample technique

Sampling is the process of selecting cases to represent an entire population so that inferences about the population can be made (Polit & Beck, 2012). A sample is a subset of population elements, which are the most basic units about which data are collected (Joubert & Ehrlich, 2007; Polit & Beck, 2012). The sample for the present study was selected from health facilities described above.

To avoid selection bias, a systematic random sampling technique was used to select all patients' medical records who were active in the programme and those who were no longer active but were at least in care up to July 2012. The first medical record was randomly selected after which; every *k*th where *k* refers to the sample interval was selected.

Figure 3.2: Sample selection in this study



Source: Researcher (2013)

Selection criterion

Eligible participation in the present study included only files for TB screened PLHIV in adult category (15 years old and above), recruited from the period of August 2011-January 2014. PLHIV in the present study were either on ART or never for the whole period of the study. Those who were not in care at least for one year were excluded to allow a minimum time of follow up. We also excluded files of those who came in from other health facilities during the period of study because it was not easy to know their prior history or to get some clarifications on the records in their files when needed.

The table below, summarizes both inclusion and exclusion criteria of patients' files for this study.

Table 3.2 Selection criterion for participant

Exposure	**IPT E**	**IPT NE**
Inclusion	All 15 year and above PLHIV screened for TB	
	Took IPT August 2011-January 2014	Didn't take IPT between August 2011- January 2014
	ART initiated or never taken	ART initiated or never taken
Exclusion	Took IPT but were not on follow up for minimum of 1 year	PLHIV who were not in care for minimum of 1 year
	All patients under 15 years, All transferred- in patients	

3.5.1. Sample size

The equal allocation sample size formula by Elwood (1998) was used to determine the sample size because of its appropriateness for cohort studies.

$$n = \frac{(p1q1 + p2q2).(Z\alpha + Z\beta)^2}{(p1 - p2)^2}$$

n = size of each group; p1, p2; cumulative incidences, q1, q2= 1-p1, 1-p2

$Z\alpha$ = Z statistic = 1.96 if α =0.05 $Z\beta$= 1.28 for 90% power,

The cumulative incidences were derived from a four years cumulative incidence from the study by Mahlet et al. (2013) in Ethiopia ; 0.01 (1%) in IPT exposed group and 0.03(3%) in unexposed group.

The sample size calculation:

$$n = \frac{\big((0.01)(0.99) + (0.03)(0.97)\big).(1.96 + 1.28)^2}{(0.01 - 0.03)^2}$$

n = 1024 in each group; total sample size of 2048.

During the process of the pilot study it was realized that there was a file which had missing data after every four or five files. Even if the filing system followed some categories, there were some files which were misclassified. This influenced the decision to systematically add forty per cent of sample size (instead of the recommended ten per cent) to take care of incomplete patient records. As a consequence, the final sample size changed to 1086 PLHIV in each group, making a total sample of 2172.

3.6. Data Management

3.6.1. Data collection tool

A tool is any instrument used to collect information from the population of study (Polit & Beck, 2012). In the present study, data was collected using a pre-coded medical record abstraction sheet. The medical record abstraction sheet is an established list of questions and statements with tick boxes for gathering answers from patients' records (Shamoo & Resnik, 2003). For the present study, an abstraction sheet was developed containing closed statements with tick boxes for gathering answers from patients' records. The development of the abstraction sheet was based on the national ART and TB entry follow up forms as well as the national TB/HIV guideline and existing literature on TB/HIV. The TB/HIV collaborative activity and the ART unit reviewed the tool. The abstraction sheet included four sections. The first one (section A) was about the follow up time, which was the criteria to continue to the next session. This means that when an individual was not fulfilling the one year of follow up eligibility, the session might be discontinued. The second section (section B) included socio-demographic characteristics. The third one (Section C) was about clinical characteristics of participants. The last section (section D) included information on TB status.

3.6.2. Data collection methods and techniques

Data collection techniques are methods used to collect data to answer research question, and allow for systematic collection of information about the participants of study (Shamoo & Resnik, 2003). The data regarding this study was extracted using record review technique of secondary data source. A second review technique is where the researcher uses available or existing information (Shamoo & Resnik 2003).

The medical records, registration books and electronic information of IPT exposed patients were reviewed to extract data. The starting point to follow a participant was IPT commencement and the ending point included loss of follow up, transfer out, the date TB was diagnosis, the date ART was initiated during the follow up and when the study period ended. For the IPT non exposed group the same methods were applied. Six ART nurses were recruited and oriented on the objectives of the study as well as on the data collection process using data abstraction sheet. Data was collected between January 1st and 30th, 2014.

3.6.3. Validity and reliability of the tool

Validity

Validity is the degree to which an instrument measures what it intends to measure (Polit & Beck, 2012; Joubert & Ehrlich, 2007). Polit and Beck (2008) define face validity (quality validity) as the degree to which the measurement creates a sense to the interviewer or individuals who have understanding on the subject matter or those who are familiar with the language and culture. Whereas, content validity is described as the extent to which instrument has suitable contents for the subject being measured.

To ensure the validity of the present study, the quality of data was upheld throughout the research process starting from the development of appropriate data abstraction sheet up to the data entry and analysis process. Indeed an already existing ART and TB intake and follow-up format was used to develop the questionnaire which maintains the validity. In addition, all terms were defined and contextualized for the specific research and the instrument was developed to answer the study questions with reference to research objectives. An extensive literature review was also done to ascertain the content validity for data abstraction sheet. All formats were checked for completeness and uniformity to ensure both the content and face validity. Again, it is worth mentioning that pilot study, strict and rigorous supervision also maximized the validity in this study. Equally important, all variables as well as the confounding factors were considered in this study by capturing them on abstraction sheet during data collection. The IPT and no IPT group were matched (1:1) by considering all factors.

Reliability

The ability of an instrument is considered reliable when it measures the target attribute consistently and accurately and provide the same result again (Dyson & Brown, 2006). Reliability is the degree of consistency or dependability with which an instrument measures the attribute (Polit & Beck, 2012; Joubert &Ehrlich 2007). In the present study the same data collection tool and method were used on all the participants. Abstractions forms were piloted before its implementation. Regarding data collectors, they were ART nurses in each facility.

Pilot Study

According to Houser (2008) a pilot study is an intentionally smaller version of a study, with a limited sample size or group of measures. In this study it was conducted before the actual study to determine the overall feasibility of the methods and procedures planned. Adjustments were made to tool so that it suits the local participants; different mistakes, errors and inefficiencies prior to the use of the larger sample were corrected. Ten files in each group were chosen at random and formed the pilot study

3.7. Ethical and cultural considerations

Ethics can be defined as system of moral values that is concerned with the degree to which research procedures adhere to professional, legal and social obligations to participants (Polit & Beck, 2012). This study also considered both ethical and cultural issues as briefly discussed in the following points.

3.7.1. Ethical permission

Ethics can be defined as system of moral values that is concerned with the degree to which research procedures adhere to professional, legal and social obligations to participants (Polit & Beck, 2012). This study also considered both ethical and cultural issues as briefly discussed in the following points. Before starting to collect data, the Scientific Review approval was given by Rwanda National Health Research Committee (NHRC).

The ethical approval was also granted by the Institutional Review Board of University of Rwanda; College of Medicine and Health Sciences.

In additional, the Rwanda Biomedical Centre through Institute of HIV/AIDS disease and TB prevention control provided the authorization to the researcher to collect data. Then, necessary information was given to hospital Directors and health personnel‘s in the ART and TB services.

3.7.2. Informed consent

Since the present study was retrospective in nature, there was no direct contact with participants. Therefore, there was no need to develop an informed consent. After securing ethical clearance and scientific review, permission to use the data from the hospitals was obtained.

3.7.3. Protecting the right of the participants

Anonymity

In order to maintain anonymity, any information (patient name) that can potentially expose recognition of a particular study participant was excluded from the tool and analysis was done in aggregates. File numbers were used to protect the participants' identity, meaning that no data could be traced back to an individual. The same principles were also followed while presenting and disseminating results.

Confidentiality

The information was kept anonymous and confidential at all times and used only for the purpose of the current study. The data was kept in a secure place to which only the investigator has access. It will be kept for a period of five years after which it will be burnt. To maximise the confidentiality data collection was done by ART nurses working at HIV services because that is part of their daily responsibility to ensure confidentiality of the patients 'information. No third person had access to the data other than the study team. Note also that the computers used for data analysis were password protected.

Beneficence

Beneficence involves need to reduce harm and maximize benefits on the study participants (Polit & Beck 2008). The purpose of this study was to determine the effectiveness of IPT on TB incidence. On the part of the participants, the benefit was to gain the awareness on the effect of the prevention they are getting.

Non-maleficience

The present study did not involve a clinical experiment and no potential harm or risks were foreseen. There was no direct contact with the participants or any kind of procedures during the process of conducting the study. Therefore, the study had no emotional, social or physical harm to the participants.

3.7.4. Protecting the rights of the Institution

Permission to publish the results will be requested from Rwanda Ministry of Health and RBC.

3.7.5. Human Right

This study was retrospective based on record review and all information was collected in a confidential way and ART nurses were recruited for data collection. Thus, this guaranteed confidentiality. No third person had access for the data without permission from hospital or health bureau.

CHAPTER 4: DATA ANALYSIS AND PRESENTATION OF FINDINGS

4.1.Introduction

In this chapter, data processing and analysing are detailed and the results are presented. The findings have been presented in different forms such as tables, bar charts, pie charts and cross tabulations.

4.2.Data analysis

Data Analysis is the process of systematically applying statistical and/or logical techniques to describe and illustrate, condense and recap, and evaluate data (Shamoo & Resnik 2003). According to these authors various analytic procedures provide a way of drawing inferences. In the present study, all abstraction sheets were reviewed for completeness and then data was entered using International Business Machine Statistical Package for Social Scientists software *(*IBM SPSS) version 20.0. The Analysis was conducted in the following stages:

Descriptive statistics which is normally used to describe and summarise the main characteristics of a collection of data (Shamoo & Resnik 2003) were performed on all patients and groups characteristics where frequencies, mean, median, minimum and maximum values were computed depending on each type of variable. Cross tabulations were done on categorical variables to ensure the matching within the cohort at a P value of not ≤ 0.05. In addition, the overall Incidence rate (IR), Relative risk or Rate ratio (RR) with exact confidence intervals (95% CI) for rates were calculated based on Poisson distribution using Generalized Linear Model: First Generalized Linear model option then Generalized Estimating Equation to model differences in time.

Survival analysis was used to assess survival difference in IPT E and IPT NE as follows: The Cox Regression procedure which is useful for modeling the time to a specified event (TB in the present study) (Hui, 2013), based upon the value of a given covariate was used. With Cox regression one (IPT in the present study) or more covariates (CD4, ART and others, in the present study) are used to predict a status (TB in this study). Cox regression assesses relationship between survival time and covariates (Bian, 2013).

The central statistical output was the hazard ratio (HR); which estimated the probability of the event (TB) to occur at any time of follow-up. Both Uni-variance and multi-variance modeling were done to compute unadjusted and adjusted HR with relative 95% CI.

Kaplan-Meier intuitive graphical presentation commonly used to describe survivorship of study population/s or to compare two study populations (Bian, 2013), was used to show the survival difference among IPT and no IPT groups. To compare the significance of survival functions between IPT and non IPT group; log-rank test was used. The original cohort was 2748; the final analysis took 1086 PLHV in each group, with 2172 making a total number of the sample.

To avoid competing risks of mortality, through deaths from undiagnosed tuberculosis, dead participants were excluded from analysis. Other reasons of exclusion from the sample are also detailed in the table below.

Table 4.1: Details of the original cohort, showing the reasons whys some were excluded from the final analysis

	Isoniazid Preventive Therapy		
Reasons	Yes (n)	No	Total
Transfer out before 1 year of follow up	76	58	134
Deaths during the study	5	6	11
Missed before 1 year follow up	10	17	27
Transfer in after August 2011	35	54	89
Tuberculosis not screened	0	9	9
PLHIV who were in care less than 1 year	134	100	234
IPT starting and end date not known	32	0	20
Date of ART not Known	0	10	10
Randomly removed to have equal number in two groups	20	10	30
Analysis	1086	1086	2172
Total	1398	1350	2748

Source: study results

4.3.Data presentation

After processing and analyzing the data, it was presented in tables, graphs. Numerical descriptions and tests of significance were given to show the relationships among variables so as to make the data more meaningful.

4.4.Presentation of Findings

Section1: Demographic factors

Table 4.2 shows that the participants' age ranged from 16-77 years. Above one third (37.7%) of participants in both groups were aged between 36-45years; the Median (41) was closer to Mean 41.8 ± 10.7(SD). Majority of participants were female (60%).

There was no statistical difference between the two groups regarding gender (*P* value > 0.05). Nearly the majority (43.1 %) of both groups was living in marital union and there was no statistical difference between two groups regarding the marital status (*P* value > 0.05). Of the overall number of study participants, 52 per cent represented districts in the Southern province and there was no statistical difference between IPT E and IPT NE groups regarding residence. Concerning participants' education level, most of them (62.5%) in both groups had only attained primary education while 20.8 per cent did not even attend primary. Then, only 8.1 per cent and 2.4 per cent reached respectively secondary and tertiary education. The remaining percentage refers to other kind of education such as post primary training.

There were statistically significant differences between those on IPT and those who were not on IPT regarding education level (*P* value < 0.04) and marital status (*P* value <0.03).

Table 4.2: Demographic characteristics (n=2172)

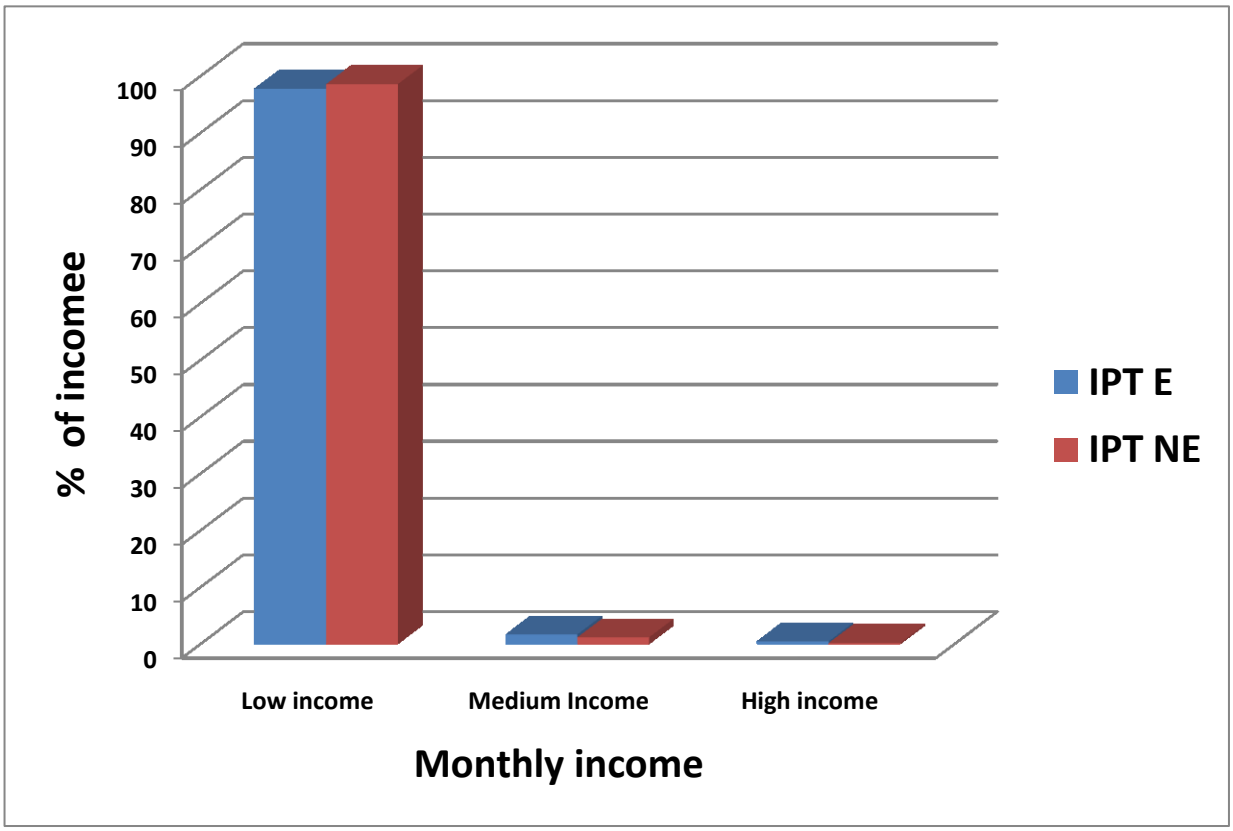
Demographic characteristics	Categories	Isoniazid Preventive Therapy		*P* value	Total
		Yes	No		
Age	**16-25**	75	64		139 (6.4%)
	26-35	232	237		469(21.6%)
	36-45	426	389		806(37.7%)
	46-5	235	253		488(22.5%)
	56 and above	118	152		270 (12%)
Gender	**Female**	657	429		1315 (60.5%)
	Male	658	428		857 (39.5%)
Residence	**Southern Province**	565	565		1130 (52%)
	Kigali City	521	521		1042(48%)
Marital status	**Single**	218	165		383 (17.6%)
	Married	453	484		937 (43.1%)
	Divorced	73	80		18 (14.2%)
	Cohabitation	123	91		214 (9%)
	Widow	219	266		485 (22.3%)
Education	**None**	211	240		451 (20.8%)
	Primary	664	694		1358 (62.5%)
	Secondary	101	74		175(8.1%)
	Tertiary	21	13		34 (2.4%)
	Others	89	65		154(7.1%)

Source: study results

B. Social factors

The only social factor analysed in the present study was the income status of participants at enrollment of study.

Figure4.1: Percentages of monthly income level in two groups of participants (n=2172)



Source: Results of the present study

Figure 4.1 shows that, of all participants, less than 1 per cent were in the high income category while a high percentage (98.2%) belonged to the low income category. Consequently there was no statistical difference between the two groups, regarding income (*P* value > 0.05).

Section 2: Baseline clinical characteristics

The clinical characteristics presented are characteristics of participants at enrollment of study. HIV clinical stage, CD4, ART, Cotrimoxazole and previous TB are some clinical factors analysed below.

Table 4.3: Baseline clinical characteristics of patients at enrollment of study (n=2172)

Baseline clinical factors		Isoniazid Preventive Therapy: Yes	Isoniazid Preventive Therapy: No	*P*-value	Total	
IPT		1086 (50%)	1086 (50%)	1	2172(100)	
Clinical stage	**1**	342	336	0.915	678 (31.4%)	
	2	526	524		1054 (48.5%)	
	3	201	205		406 (18.4%)	
	4	17	21		38(1.7%)	
Baseline CD4	**≥350**	709	699	0.686	1408 (64.8%)	Median
	<350	377	388		769 (35.2%)	=425
ART	**Yes**	981	979	0.942	1960 (90.2%)	
	No	105	107		212 (9.8 %)	
Cotrimoxazole	**Yes**	1086	1086	1	2172 (100%)	
	No	0	0		(0%)	
Previous TB	**Yes**	52	62	0.336	114 (5.2%)	
	No	1034	1024		2058 (94.8%)	

Source: Results of the present study

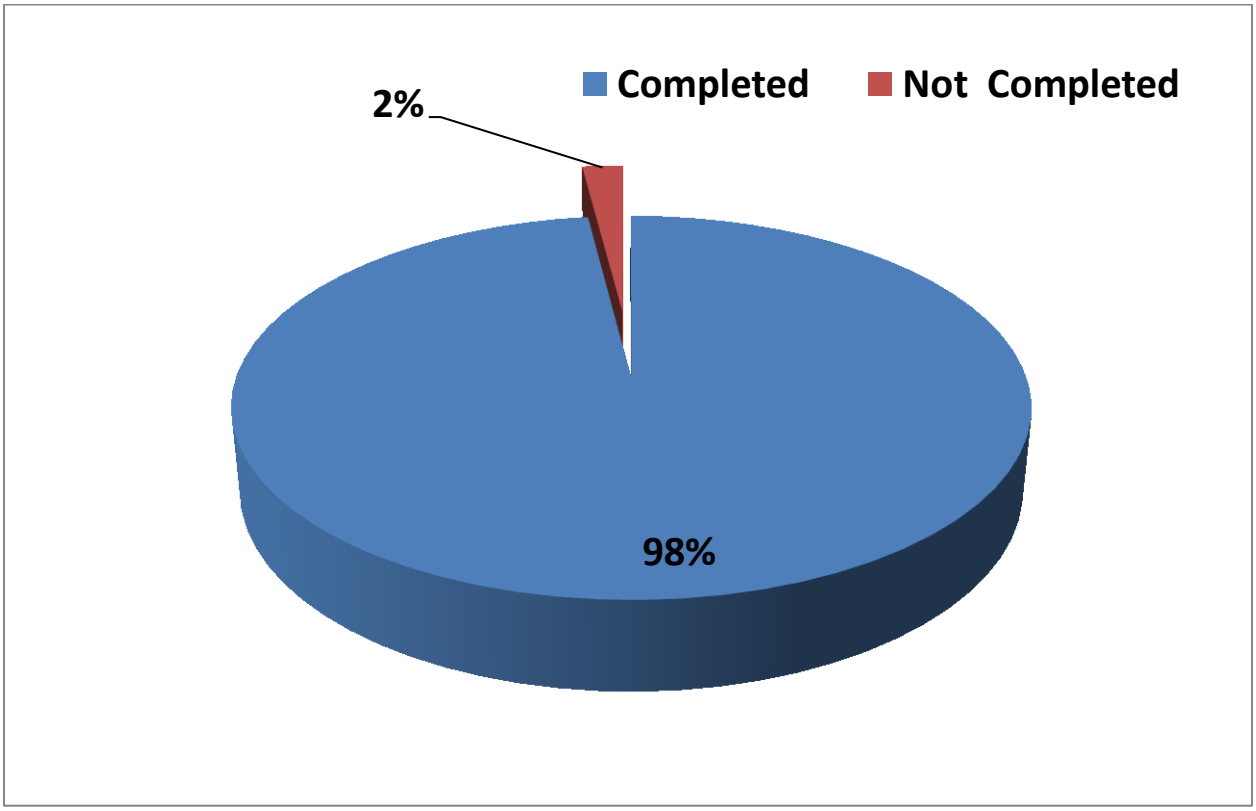
Table 4.3 shows that IPT E and IPT NE participants were matched in the same proportion (50%). Regarding WHO clinical stage, almost half of all the participants (48.5 %) were in

stage II, one third (31.4%) in stage I, less than one third (18.4%) were in stage III and only 1.7 per cent of participants were in clinical stage IV. Consecutively, there was no statistical difference between the two groups (*P* value =0.915). Concerning CD4 cell count, the median CD4 cell count was 425, more than a half (64.5 %) had CD4 cell count >= 350 and there was no statistical difference between the two groups (*P* value = 0.686). About 90.2 per cent of all participants were on ART and less than a tenth (9.8%) were not, and even in both groups ART was equally distributed (*P* value=0.942). All participants were on cotrimoxazole, and the lowest level (5.2%) had prior TB. There was no statistical difference between the two groups regarding prior TB as well.

Section3: Comparison of incidences of TB between participants on IPT and those without IPT

Before comparing the incidence between participants in the two groups, this section starts with IPT adherence analysis. It also presents the total tuberculosis cases and stratifies tuberculosis cases among IPT E group. The overall tuberculosis incidence rate and incidence rate ratio are then calculated. The section ends with uni-variables and Multi-variables Cox proportional hazards model for all PLHIV to control the effect of socio demographic and clinical factors on TB incidence.

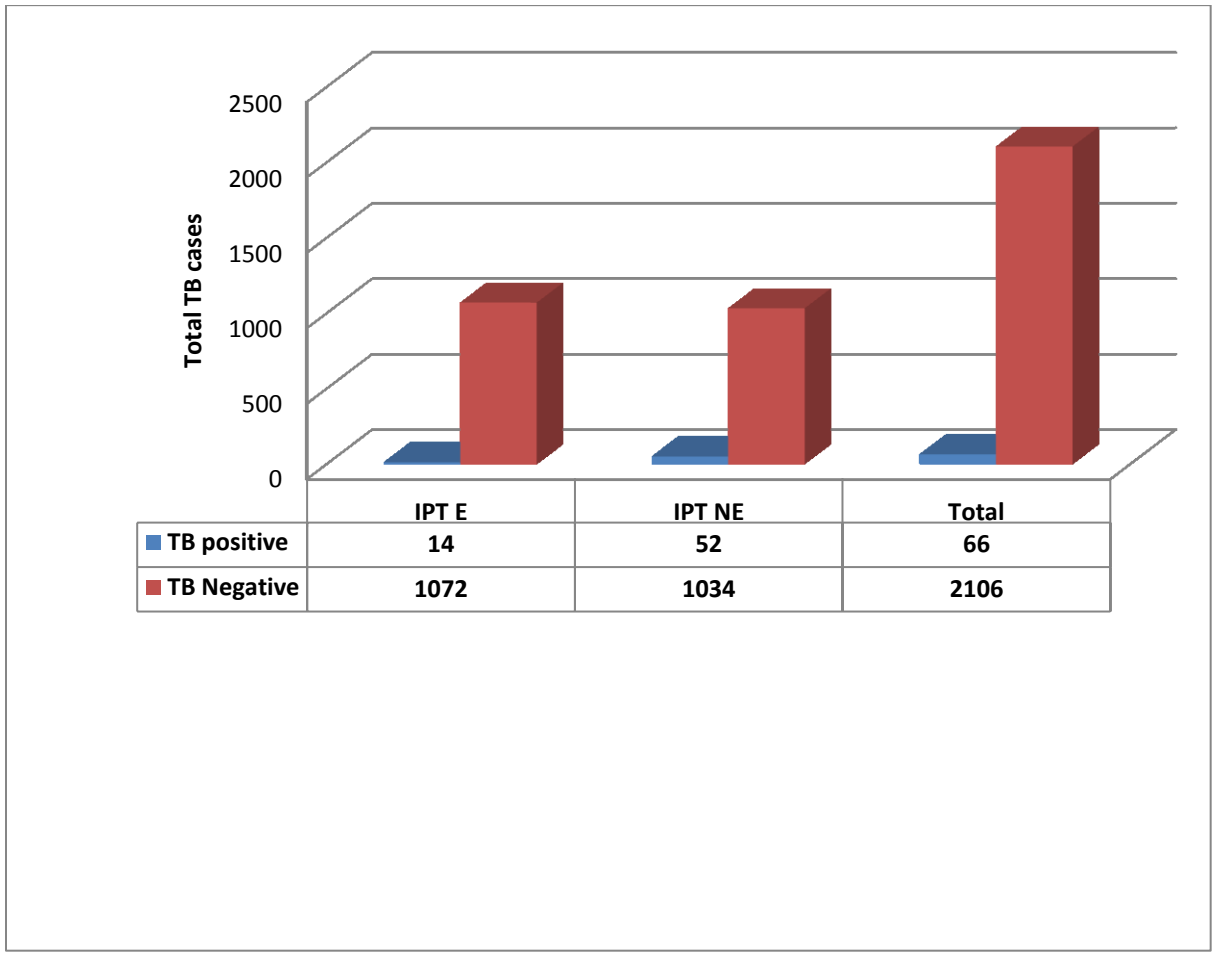
Figure 4.2: Adherence status in Isoniazid preventive Therapy group (n=2172)



Source: Results of the present study

Figure 4.2 shows that from the overall participants; only 2 per cent did not complete 6 months of IPT, while the highest percentage of participants (98%) completed 6 months of IPT.

Figure 4.3: Total Tuberculosis cases among those on IPT and those without IPT (n=2172)



Source: Results of the present study

Figure 4.3 illustrates that in both groups of IPT E and IPT NE, 66 TB cases occurred during a follow up of 30 months. The IPT exposed group only had 14 TB cases and in comparison with the IPT no exposed group, the number of TB cases increased almost four times (52 TB cases).

Table 4.4: Tuberculosis cases among IPT E group (n=14)

IPT Status	Positive tuberculosis	Per centage
Completers	9	64.3
Incompleters	5	35.7
Total	14	100

Source: Results of the present study

Table 4.4 stratifies tuberculosis cases among IPT E group into IPT completers and IPT incompleters. It shows that 35.7 per cent who developed TB did not complete six months of treatment. On the other hand, only 9 TB cases were found in those who completed six months of treatment.

Table 4.5: The overall tuberculosis Incidence Rate and Incidence Rate Ratio, calculated using Poisson regression (n=2172)

IPT	Status	Person-years	TB cases	IR (per 100PY) 95% CI	RR 95% CI	*P*-value
	Yes	2499.08	14	0.56(0.26-0.67)	0.273 (0.152-0.493)	<0.001
	No	2548.74	52	2.04 (1.61-2.72)		<0.001
	Total	5047.82	66	1.31 (0.98-1.44)		<0.001

Source: Results of the present study

Table 4.5 shows that the overall tuberculosis incidence was 1.31 cases per 100PY. Those who did not receive IPT had the incidence increased twofold at a rate of 2.05 PY (95% 1.61-2.72) while those who received IPT had a rate of 0.56 PY (95% CI 0.26-0.67). The incidence rate decreased at 72.7 in those who were on IPT (IRR= 0.273 95% CI = 0.152-0.493.

Section 4: Association between variables

This section discusses the association of IPT and TB and other factors that would determine TB in PLHIV

Table 4.6: Uni-variable and Multi-variable Cox proportional hazards model for all PLHIV with socio-demographic factors (n=2172)

Variables		Unadjusted HR (95%CI)	*P* value	Adjusted for all other variables HR (95%CI)	*P* value
Age	**16-25**	1		1	
	26-35	2.36 (0.794-7.024)	0.122	1.35 (0.37-4,99)	0.664
	36-45	1.75 (0.69-4.429)	0.231	1.02 (0.37-2.43)	0.956
	46-55	0.97 (0386-2.48)	0.963	1.16 (0.44-3.02)	0.758
	>56	1.72 (0.683-4.334)	0.250	1.59 (0.62-4.08)	0.334
Gender	**Male Female**	0.510 (0.314-0.82)	0.007	1.40 (0.82-2.39)	0.209
Education level	**None**	1		1	
	Primary	1.368 (0.51-3.64)	0.750	0.519 (0.15-1.72)	0.285
	secondary	0.806 (0.316-2.59)	0.806	0.543(0.178-1.65)	0.283
	college	0.696 (0.18-2.59)	0.187	0.513 (0.08-2.95)	0.455
	University	0.66 (0.174-0.2.3)	0.727	3.865 (0.25-59.74)	0.333
	Others(Post primary)	0.656 (1.22-2.10)	0.968	.000	0.980
Residence	**Muhanga**	1		1	
	Kamonyi	1.054 (0.30-3.67)	0.931	1.28 (0.31-5.34)	0.727
	Kigali	1.443 (0.44-4.66)	0.540	1.12 (0.29-4.31)	0.869
	Ruhango	0,789 (0.23-0.98)	0.983	1.95 (0.52-7.32)	0.320

Source: Results of this study

Table 4.6 shows that there was no risk of developing TB associated with age, gender, education and residence (*P* value > 0.05) in PLHIV taking IPT. Commenting a bit on income factor, it does not appear on the table above because 98.2 per cent of the whole population belonged in low income (figure 3.1.); hence its influence on TB is obvious.

Table 4.7: Uni-variable and Multi- variables Cox proportional hazars model for all HIV-infected patients with clinical factors (n=2172)

Variables		Unadjusted HR (95%CI[b])	*P* value	Adjusted for all other variables HR (95%CI)	*P* value
IPT	**Yes** **No**	0.261 (0.14-0.48)	<0.001	0.19 (0.102-0.52)	<0.001
ART	**Yes** **No**	0.088 (0.42-0.11)	<0.001	0.064 (0.034-0.106)	<0.001
CD4	**< 350** **>= 350**	3.93 (2.39-6.644)	<0.001	3.302 (1.84-5.90)	<0.001
Clinical stage	**1 and 2** **3 and 4**	7.659 (4.61-12.70)	<0.001	5.10 (2.88-9.28)	<0.001
Previous TB	**Yes** **No**	0.562 (013-2.29)	0. 423	0.364-1.232	0.092

Source: Results of the present study

Table 4.7 indicates both unadjusted and adjusted proportional hazards ratio analysis. The results of unadjusted model in those on INH indicated that the probability of developing TB was reduced by 74 per cent at any given time over 30 months (HR 0.261; *P* value < 0.001) while in adjusted model the probability of reducing TB increased at 81 per cent (HR =0.19; *P* value < 0.001). Compared with patients who were not on ART, patients who were on ART had a decreased risk of TB at 91.2 per cent (HR=0.088; *P* value <0.001), that probability increased in the adjusted model (HR=0.064; *P* value<0.001) at 93.4 per cent. CD4 count <350 both in unadjusted (HR= 3.93; *P* value=0.00) and adjusted model, were significantly associated with an increased risk of TB when compared with patients with >=350 CD4 count. Previous TB was not statistically significant (*P* value >0.005) both in unadjusted and adjusted model. In unadjusted model patients with a clinical stage 3 and 4, were significantly seven times more at risk to develop TB than people with clinical stage 1 and 2 (HR=7.659; *P* value <0.001), in the adjusted model the risk was five times more (HR=5.10;*P* value =0.001).

Table 4.8: Univariable and Multi-variable Cox proportional hazards model excluding Isoniazid incompleters (n=2150)

Variables		Unadjusted HR (95%CI)	*P* value	Adjusted HR (95%CI)	*P* value
IPT	**Yes**	0.175 (0.14-0.48)	<0.001	0.125(0.05-0.23)	<0.001
	No				
ART	**Yes**	0.088 (0.42-0.11)	<0.001	0.086(0.046-0.163)	<0.001
	No				
CD4	**< 350**	3.93 (2.39-6.644)	<0.001	3.202 (1.77-5.94)	<0.001
	>= 350				
Clinical stage	**2 and 3**	7.659 (4.61-12.70)	<0.001	5.6 (3.04-10.48	<0.001
	3 and 4				

Source: Results of this study

Table 4.8 gives the results of PLHIV who completed six months. After excluding non completers, the probability of developing TB reduced from 74 per cent to 83.5 per cent in unadjusted model (HR 0.175; *P* value<0.001) and to 87.5 per cent (HR =0.125; *P* value <0.001) in adjusted model. This implies a reduction of 13 percent associated with IPT completion. Compared to patients who were not on ART, patients who were on ART had a decreased risk of TB of 91.2 per cent (HR=0.088; *P*=0.00), but that probability increased in the adjusted model (RH=0.064; *P* value <0.001); 91.4 per cent. Lower CD4 count <350 (HR= 3.93; *P* value <0.001) both in unadjusted and adjusted model were significantly associated with an increased risk of TB when compared to patients with >=350 CD4 account. Again, In the unadjusted model, patients with a clinical stage of 3 and 4, were significantly at risk to develop TB seven times more than people with clinical stage 1 and 2 (HR=7.659; *P* value <0.001),while this risk was five times more (HR=5.10; *P* value <0.001) in the adjusted model.

Table 4.9: Restricted uni-variable and Multi-variables Cox proportional hazards model, after controlling other factors

Variables	Unadjusted HR 95%CI	P value	Adjusted HR 95%CI	*P* value
ART (n= 1960)				
IPT	0.393 (0.174-0.887)	0.025	0.283 (0.106-0.759)	0.012
CD4	3.703	0.001	3.034 (1.412-6.519)	0.004
Clinical stage	6.033 (2.88-12.63)	0.00	5.33 (2.42-11.72)	0.002
CD4 cell account <350 (n=765)				
IPT	0.137 (0.11-0.48)	<0.001	0.098 (0.038-0.249)	<0.001
clinical stage 3 and 4 (n=435)				
IPT	0.137 (0.11-0.48)	<0.001	0.098 (0.038-0.249)	<0.001

Source: Results of this study

Table 4.9 illustrates how IPT was effective in different categories of PLHIV (ART, low CD4 and advanced clinical stage). In the category of ART, IPT reduced the risk of TB (HR=0.393; *P* value=0.025) in unadjusted model and in adjusted model (HR=0.283; *P* value=0.012). In PLHIV with low CD4 count cell, IPT reduced the risk of TB at 99.02 per cent (HR= 0.098; *P* value =<0.001). The result was the same in PLHIV with advanced clinical stage (3 and 4) where IPT reduced the risk of TB at 86.8 per cent (HR= 0.132; *P* value<0.001) in the unadjusted model and 99 per cent (HR=0.086; P value =<0.001) in the adjusted model.

Section 4: Survival function among PLHIV who took IPT from those who did not

This section presents the time to TB occurrence among the two groups being compared.

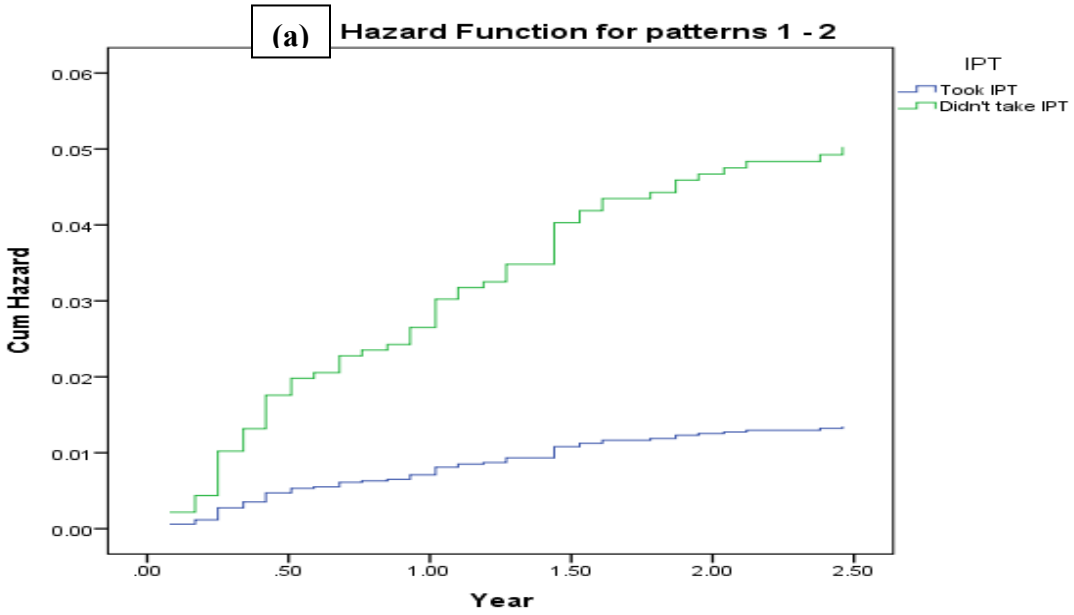
Table 4.10: Time to tuberculosis occurrence in months (n=2172)

IPT status	Intervals start time in months	Number of tuberculosis cases	Cumulative proportional surviving at end of interval	*P* value
IPT Exposed	0	0	1.00	
	5	3	1.00	
	10	4	0.99	
	15	2	0.99	
	20	2	0.99	
	25	3	0.98	<0.001
	30	0	0.989	
	Subtotal	**14**		
IPT NE	0	18	0.98	
	5	11	0.98	
	10	8	0.97	
	15	12	0.97	
	20	3	0.95	
	25	0	0.95	
	30	0	0.95	
	Subtotal	**52**		
Total	**66**			

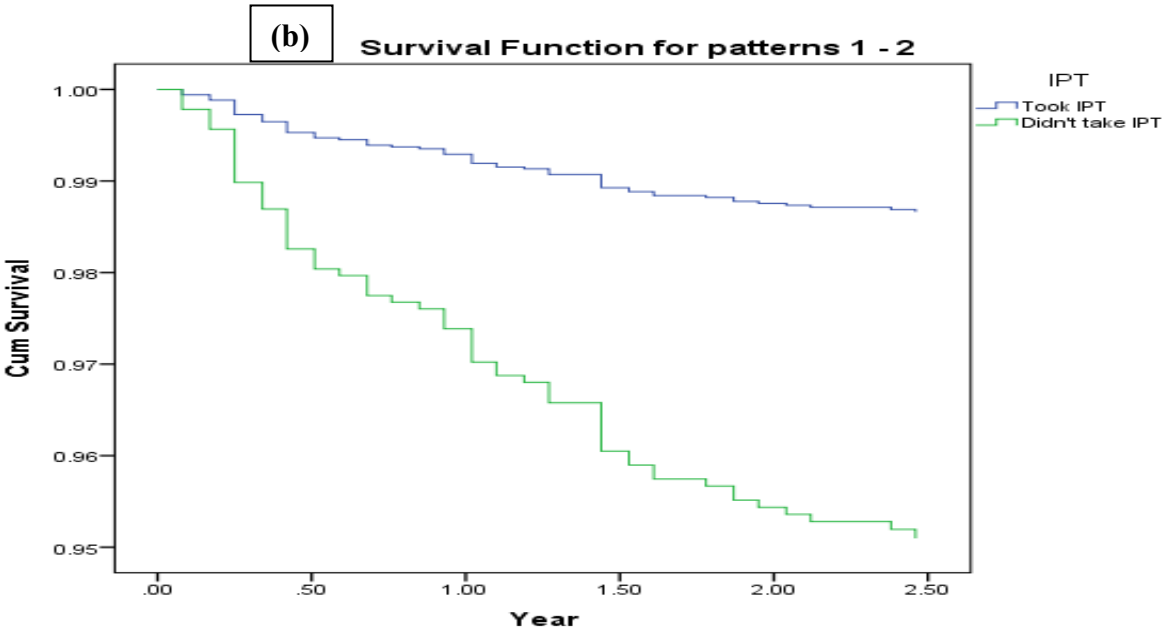
Source: Results of the present study

Table 4.10 presents time to TB occurrence and survival time between the two groups. In the first five months, no TB case found in IPT E group but almost a third of TB cases were found in IPT NE group. In ten months later less than five per cent TB cases (3 cases) occurred in IPT E while almost a half TB cases (29 cases =44%) occurred in the same period in the group of IPT NE. At the end of the study, 0.989 (98.9 %) PLHIV survived from TB, and 0.95 (95%) of those who were not on IPT survived. Therefore, PLHIV on IPT significantly survived more (almost 4%) than those who were not on IPT (P value <0.001).

Figure 4.4: A piloted hazard risk and survival function of TB among all IPT exposed and IPT NE, by Kaplan-Meier (n=2172)



Comparing figure 3.4.a with figure 3.4.b, there was 73.2 per cent decrease risk of TB in PLHIV on IPT (IR is 0.56 PY in IPT E and 2.04 in IPT NE PY) (figure 3.4 a). At the end of the study, 0.989 (98.9 %) PLHIV exposed on IPT survived from TB, while the study reveals the survival rate of 0.95 (95%) for those who were not on IPT. Therefore, PLHIV on IPT survived much more (almost 4%) than those who were not on IPT (figure 3.4 b).



CHAPTER 5: DISCUSSIONS

5.1. Introduction

Isoniazid Preventive Therapy is a key tuberculosis prevention strategy in high HIV-prevalent settings as recommended by World Health Organisation (WHO, 2012a). This section discusses the results of IPT effectiveness presented above in light of related literature and makes conclusions grounded in the data and supported by other research findings where possible. Findings are discussed with reference to the objectives of the study.

5.2. Characteristics of the sample

These were included so that they provide the researcher with a better understanding of how they may influence the effect of IPT in PLHIV. The characteristics of PLHIV were divided into socio-demographic characteristics and clinical characteristics. The study sample consisted of 2172 women and men 15 years old and above, among them 1086 took IPT and the remaining part did not. Participants' age ranged from 16-77 years, the Median (41) was closer to Mean 41.8 ± 10.7(SD) and the majority of participants were female (60%). Nearly the majority (43.1 %) of both groups was living in marital union. Of the overall number of study participants, 52 per cent represented districts in the Southern province. Concerning participants' education level, most of them (62.5%) in both groups had only attained primary education then, only 8.1 per cent and 2.4 per cent reached respectively secondary and tertiary education (table 4.2). Of all participants, less than 1 per cent was in the high income category while a high percentage (98.2%) belonged to the low income category (figure 4.1)

Regarding IPT distribution among participants, they were matched in the same proportion (50%). Coming to the WHO clinical stage, almost half of all the participants (48.5 %) were in stage II, one third (31.4%) in stage I, less than one third (18.4%) were in stage III and only 1.7 per cent of participants were in clinical stage IV. Concerning CD4 cell count, the median CD4 cell count was 425, more than a half (64.5 %) had CD4 cell count >= 350. About 90.2 per cent of all participants were on ART. All participants were on cotrimoxazole, and the lowest level (5.2%) had prior TB (table 4.3).

5.3. Comparison between the incidences of TB in PLHIV exposed to IPT with those who are not

This study shows a significant difference between the incidences of TB in PLHIV exposed to IPT with those who are not exposed it. It has revealed that TB incidence among those who received IPT is less (0.56 cases per 100P) than those who did not IPT (2.04 cases per 100 PY) (table4.5). This implies that IPT was associated with a substantial decrease of 73 per cent (IRR 0.275 CI 0.12-0.493) (table4.7). This association persisted after controlling all confounders and it interestingly increased from 81 per cent to 87.5 per cent in participants who completed six months (table4.8). In addition, it was found that IPT was significantly associated with tuberculosis reduction in the population with advanced HIV clinical stage, those with low CD4 cell counts (<350 cell per cubic millimeter of blood) and more interestingly IPT was found to be an additional tool for those who were taking concurrent antiretroviral therapy.

By comparing equal proportion groups, the results of this study were found consistent and confirmed the separate observations of previous studies on low risk of TB while taking IPT. Frigati et al. (2011) proved that HIV infected persons who did not enroll on INH had a greater tuberculosis incidence when compared to those who received it. Also, Padmapriyadarsini et al (2011) reported a 67 per cent overall reduction of TB when taking INH.

Similarly, Smart (2009) confirmed the lower risk of tuberculosis among people who received IPT and the same time taking concurrent antiretroviral therapy. In the Smart (2009)'s study, the rate of tuberculosis in the people who received placebo was significantly higher at 3.6 per 100 person years compared to the rate in the INH group which was 2.3 per 100 person years giving a hazard ratio of 0.63. In other words there was a 37 per cent reduction in the risk of tuberculosis in the patients who received INH versus patients who were only receiving ART.

The findings of the present study corroborate the ideas of Grant (2009) in United Kingdom, who suggested that tuberculosis preventive therapy should be considered in addition to ART. According to Grant (2009), Tuberculosis incidence falls gradually with increasing time after starting ART but it remains high, especially in individuals with low CD4 cell counts. For this effect, Grant (2009) agrees that IPT itself should be added to ART.

The findings are consistent with other results of Charalambous et al. (2010) who support the routine use of IPT, even in patients on ART. In the same point of view, a Cochrane meta-analysis of the studies published in 2004 revealed that IPT reduced the risk of developing active TB in people with HIV. IPT reduced about 64 per cent and by 33 per cent when the data from all participants were pooled (Woldehanna & Volmink, 2004).

As mentioned previously, in the analysis restricted to patients who completed 6 months of IPT, the incidence rate of TB decreased further compared to the whole participants. This finding is in agreement with Mahlet et al. (2013)'s findings study which showed that IPT completion reduces TB incidence and hazard by 96.3% by 95.8% respectively. This finding further supports the idea of Reid &Shah (2009) who agreed that adherence to IPT can increase the chance to act properly to prevent mycobacterium multiplication.

The findings of the present study particularly extended the effectiveness of IPT by decreasing TB at high percentage (>60%). However Golub et al. (2007) writing from Brazil, found that IPT works better only when associated with ART. IPT alone was associated with 64 per cent (HR=0.36; P value=0.02) in unadjusted model and 43 per cent in adjusted model (HR= 0.570) but the results were not statistically significant (P value=0.34). Again, in people with CD4 cell count less than 350, IPT alone was not effective (HR=0.88; P value=0.86). These results are different from the present study probably because of low adherence of IPT (76.1%) compared to the present study findings (98%). However, a better explanation of that situation lies in the differences in research design of both studies. The Brazil study was evaluating the effect of ART at the same time with IPT but, the objective of the present study was not targeting the combination effect of IPT and ART on TB. Rather, it considered ART as a covariate and further analysed the effect of IPT in people taking ART. Thus, the study revealed that IPT has an added value for PLHIV on ART. However further studies strictly designed to investigate the combined effect of ART and IPT are recommended.

In South Africa, IPT alone was found to be not effective. Compared to treatment-naïve patients, the effect of IPT alone was not statistically significant; after adjustment for CD4 cell count and other variables [adjusted hazard ratio (HR) = 0.87; 95% CI 0.55–1.36].

But ART alone was strongly associated with a decreased risk of incident tuberculosis (HR = 0.36; 95% CI 0.25–0.51) and furthermore, patients who received both IPT and ART showed a strong reduction in tuberculosis risk (HR = 0.11; 95% CI 0.02–0.78) (Golub et al., 2009).

The results of the above study are different to the present study probably due to a small number of people who were on IPT (550) compared to those with IPT NE (1660). In addition, the sample in Golub's study was composed of people mostly with advanced HIV (median CD4 in their study was very low; 155 CD4 cell counts) and the ART was started at a low level of CD4 (<200). As Golub et al.'s study was prospective; it would be recommendable for future researches in our settings to use the same design to be able to do a better comparison.

5.4. Socio demographic and clinical factors associated with TB in PLHIV on IPT

After evaluating the incidence of TB, the purpose of the present study was to further identify factors such as socio-demographic and clinical factors that would influence TB incidence in PLHIV taking IPT. The results showed that ART, CD4, HIV clinical stage and income are socio and clinical factors determining TB in PLHIV whereas prior TB, Age, sex, residence, education and marital status were not associated with TB.

Regarding ART, the present study revealed that ART reduced TB incidence by 92 per cent in unadjusted model and 94 per cent in adjusted model in the whole population. But this should be interpreted with caution because the study was not designed to evaluate both the combined effect of ART and IPT and the majority of the population in this (90.2%) was on ART. To be specific on this point, the analysis was further restricted to participants on ART. Those on ART-IPT continued to have lower incidence rates than those on ART alone. The present study also showed that TB risk increased when CD4 cell count decreased. In accordance with the present results, Grant (2009) has demonstrated that CD4 cell counts are independent risk factors for tuberculosis after ART start.

The association of TB with low CD4 cell count in PLHIV while taking INH was also confirmed by other studies namely Golub et al. (2007)'s study from Brazil; Golub et al. (2009) from South Africa and Mahelet et al. (2013)'s study from Ethiopia.

Concerning the clinical stage, in the present study people with HIV clinical stage 3 and 4 had more risk to develop TB than those with clinical stage 1 and 2. This accords with Golub et al. (2007); Mahlet et al. (2013) & WHO (2005) observations, which showed that HIV stage 3 and 4 are most commonly associated with TB.

Coming to income, it was obvious to see its association with TB. All 66 TB cases occurred in the population with low income and even 98.2 per cent of the whole sample belonged to the low income. This finding is in accordance with WHO statement (2014) which indicates that poor economic status and HIV status can increase the risk of developing TB. Similarly these results match those observed in a South African study (Grant et al., 2005) and in an Ethiopian study (Mahlet et al. 2013).

Contrasting findings from above studies, prior TB was not found to be a determinant of TB in this study neither in CD4 cell count > 350 nor in CD4 cell count <350. We suggest three possible explanations to that situation. One could probably be the social and financial status which might help the patients in the present study to maintain their life healthy, or not being exposed to TB. The second reason is that most of those patients with prior TB were on ART; and it is known to reduce the occurrence of TB in PLHIV (Golub et al. 2007). The third and last reason could be low rates of interruption in TB treatment in Rwanda (RBC, 2012).

As regards age, the results of the present study did not show any significant association of TB with age. To this effect, the findings do not support the previous studies by Mahlet et al. (2013), Golub et al. (2007) & Charalambous et al. (2010). The reason for this contrast is not clear but it may have something to do with the study design, population characteristics and the difference in the TB/HIV prevalence in the respective countries.

In the same connection, the present study did not find the association between TB and sex. The same, most previous studies did not analyse the importance of sex in determining TB. However a study by Mahlet et al. (2013) found that sex determines the occurrence of TB among patients on IPT. The author did not show which sex was more at risk than another and it is getting difficult to explain the reasons for those discrepancies.

5.5. The time to TB occurrence

Another objective addressed by the present study was to ascertain whether the time of TB occurrence was significantly different in participants who were on INH compared to participants who were not. The present study demonstrated that the protective effect of IPT did not seem to wear off very quickly. It seemed to be gradually lost over time and it did not decline as rapidly as it has been reported in patients not on IPT. For example, in the first five months no TB case occurred in IPT E group while almost a third (18 over 66) of all TB cases occurred among IPT NE group. In ten months later, less than five per cent TB cases (3 cases/66) occurred in IPT E but a half of TB cases (29 cases/66 =44%) occurred in IPT NE group (table 4.10). Therefore, PLHIV on IPT survived much more than those who were not on IPT. At the end of the study 98.9 per cent of PLHIV who were on IPT survived from TB but in participants who were not on IPT the survival time decreased by 4 percent (95%) (Figure 4.4). In this regard, these results match those observed in earlier studies by Golub et al. (2009) and Charalambous et al. (2010).

However, clinical studies reported mixed results following six months on the point of IPT protection (time to TB occurrence). One study in Zambia suggested that the protective effect could last up to three years (Quigley et al., 2001). In Northern Namibia it was 30 months (Mekonen, et al., 2012) and 3 to 4 years in Ethiopia (Mahlet et al., 2013) but a study from Uganda found that the effect only lasted one year (Johnson, 2001). Again, perhaps IPT needs to be given longer to people with HIV.

By considering the disparity regarding other findings, the results published by Houben et al. (2013) differ from above mentioned studies. The author says that IPT only protects patients during therapy but the protection provided by IPT against tuberculosis disease is quickly lost after cessation of therapy. According to Houben et al. (2013), it is not known whether this loss of protection is due to re-infection and rapid progression to disease, or lack of cure of IPT. However data from Houben et al. (2013)'s study must be interpreted with caution because the study was designed to participants with latent TB. Consequently, further researches on this topic needs to be undertaken before the protection of IPT is more clearly understood.

5.6. Implications to Nursing

This section is going to discuss the implication of the study to nursing. The implications are discussed under the following headings: nursing practice, nursing administration, nursing education and nursing research.

5.6.1. Nursing Practice

In Rwanda, Nurses play the crucial role in TB control in the whole population and in HIV population, for example nursing role in TB case detection, Directly Observed Therapy (DOTS) and monitoring drug regimens including Isoniazid Preventive Therapy. The results of this study therefore, will help nurses to know the outcome of their daily practices. Again, different recommendations given will help them to improve the patient care.

5.6.2. Nursing Administration

The results of this study should be given priority as Nurses should be regularly supervised as they administer Isoniazid to PLHIV. In-service training should be provided to qualified nurses on HIV/TB management to enable them identify and facilitate prompt interventions to improve PLHIV.

5.6.3. Nursing Education

There is need to strengthen the component HIV/TB management and Nurse Educators should ensure that nurses have updates in the new concepts, protocols and provided with adequate resources for teaching.

5.6.4. Nursing Research

Nurse researchers should be encouraged to conduct research on IPT so as to find ways of means of upgrading life among PLHIV.

5.7. Limitations of the study

It is important to be mindful of the limitations that might accompany the present study. First and foremost, it is acknowledged that this study used secondary data.

Because of that, there were missing data for some variables such as viral load making it harder to exclude all residual confounding.

To minimize this limitation however the data collection process was closely and strictly monitored and on top of this the analyses controlled for other well recognized potential confounding factors.

The other limitation to mention is that the present study was not able to determine the exact protective durability of IPT, as the period of follow up was short. However the protective effect of IPT did not seem to wear off very quickly. It seemed to be gradually lost over time and it did not decline as rapidly as has been reported in patients not on IPT.

5.8. Recommendations

Isoniazid preventive therapy is cost effective, safe and feasible drug of choice to reduce the incidence of TB among PLHIV infected persons. Based on the findings of the present study, the following recommendations have been made:

To Rwanda Ministry of Health

A number of randomized clinical trials have demonstrated that IPT can reduce tuberculosis incidence in HIV-infected patients, and this study showed that IPT reduces TB incidence. Hence it would be beneficial for the population if the programme is scaled-up in the whole country.

To the Rwanda National TB and HIV Programmes

It has been observed that in reporting TB cases, IPT does not appear on the reporting chart. The National TB and HIV programmes should put in place documentation strategies which would facilitate to trace back people who took IPT and developed TB at the same time.

To Health facilities implementing IPT programme and other HIV programmes in Rwanda

In health facilities used as study settings, it is not every visit that takes comprehensive assessment and consequently demographic and clinical factors are not updated. It is recommended that every clinical data should be recorded on patients chart for care continuation, research, monitoring and evaluation purposes.

To Researchers

The researcher would recommend further researches on IPT and preferably in the following areas:

- Prospective study with a long period of time should be conducted to make a comparison with the results of the present retrospective study.
- To get the whole picture of the IPT programme in Rwanda, the same study should be extended in children population.
- A particular study mainly designed for IPT and ART association might further explore the concurrent effect of both therapies on TB.
- The fear of developing Multi Drugs Resistance TB has been reported as one of reasons why different TB programmes in some countries become reluctant to implement the policy of IPT therefore a study in that area might clarify the situation.
- Clinical studies report mixed results on the point of IPT protection, further researches in this domain may not only determine the protective durability of IPT but also the duration of its administration.

5.9. Conclusions

The study was carried out to evaluate the effectiveness of IPT on TB incidence in PLHIV. In the present study, IPT was effective and in overall, it reduced the incidence of TB by 73 per cent to 81 per cent. In IPT completers, the risk of developing TB reduced up to 87.5 per cent. In PLHIV on ART, IPT reduced the risk of TB from 60.7 to 71.7 per cent. Furthermore, in CD4 cell count <350, IPT reduced the risk of TB by 82.6 per cent to 91.2. Finally in people with WHO clinical stage 3 and 4, IPT reduced the risk of TB by 86.8 per cent to 92.4 per cent

In addition, the demographic and clinical factors that determined the TB incidence are ART, CD4 cell count, WHO clinical stage, and income. The study further revealed that certain factors were not associated with TB. These factors were age, sex, marital status, residence, education and previous TB.

Finally, by comparing the time of TB occurrence among PLHIV who took IPT with those who did not, the present study also showed that the protective effect of IPT seemed to be gradually lost over time and it did not decline as rapidly as it has been reported in patients not on IPT.

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APPENDIX I: ABSTRACTION SHEET

THE UNIVERSITY OF ZAMBIA

SCHOOL OF MEDICINE

DEPARTMENT OF NURSING SCIENCES

TOPIC: EFFECTIVENESS OF ISONIAZID PREVENTIVE THERAPY ON ACTIVE TB INCIDENCE IN PEOPLE LIVING WITH HIV/AIDS

INSTRUCTIONS FOR THE COLLECTORS

Before putting a code read the instruction related to the item

Use a pencil to write " C" on each consulted medical records, for you to not repeat it again

Do not put the name of the patient on the abstraction sheet

Write the appropriate code to each question

All information collected should be kept in strict confidence

Use additional blank paper if the space provided is not enough

INTRODUCTION

No of abstraction sheet ☐

Place ☐

Kabgayi	1	Remera Rukoma	2
Kimironko	3	Kinyinya	4
Kivumu	5	Gitarama	6

Date of data collection _____/____/____

Name of the abstractor _____ Signature of the abstractor _____

Time started _____ Time ended _____

Name of the supervisor _____Signature of the supervisor_____

Records reviewed: Patient file ☐ Computer data base ☐ B register ☐

Others (specify) _____

File Number_____

FOLLOW UP INFORMATION

The purpose of this section is to know the PLHIV who are eligible for analysis

NO	Variable	Code	Remark
1	Time entered in clinic	Date _____/____/____	
2	Date confirmed HIV	Date _____/____/____	
3	Follow up	Start _____/____/____ Stop follow up _____/____/____	
4	Total time follow up	Years _____ Months _____ Days _____	
Note: if time followed is less than one year; document the reasons and close the session			
5	Reasons to close	Transfer out Death Missed	

SECTION A: Socio-demographic characteristics

No	Variable	Coding	Remark
6	Age	____/___/_____	
7	Sex	0. Female 1. Male	
8	Marital status	Single Married Divorced, Cohabitation Widow	
9	Educational status	None Primary Secondary Tertiary Others(Specify)_____	
10	Residence	Muhanga Kamonyi Kigali Other(Specify) _____	
11	Income	1. Low (0-100000 RWF), 2. Middle(100001-200000 RWF) 3. High (200001 RWF and above)	

Section B: Clinical Factors

12	Screened for TB	Yes No	
13	INH before August 2012, as mean of prevention	Yes No	
14	IPT form August 2011	1.Yes	

		2. No	
15	If (13)yes	Start date_____/____/____ Discontinue date_____/____/____	
16	If discontinue before 6 months; Reasons to stop INH	1. Side effects 2. INH stock out 3.Refusal 4. Other (specify) _____	
17	CD4 test	1.Yes 2.No	
18	If (16) yes, complete the available results in different intervals	At Baseline: Date_____/____/____ Results_____ <350 >350	
		At 6 months: Date_____/____/____ Results_____ <350 >350	
		At 12 months : Date_____/____/____ Results_____ <350 >350	
		At 18 months: Date_____/____/____ Results_____ <350 >350	
		At 24 months: Date_____/____/____ Results_____ <350 >350	
		At the time of TB Diagnosis: Date_____/____/____	

		Results_____ <350 >350	
19	Viral load	1. Yes 2. No	
21	If (18) yes, complete the available results in different intervals	At Baseline: Date_____/____/____ Results_____ <10000 >10000	
		At 6 months: Date_____/____/____ Results_____ <10000 >10000	
		At 12 months: Date_____/____/____ Results_____ <10000 >10000	
		At 18 months: Date_____/____/____ Results_____ <10000 >10000	
		At 24 months: Date_____/____/____ Results_____ <10000 >10000	
		At the time of TB Diagnosis: Date_____/____/____ Results_____ <10000 >10000	
22	HIV clinical stage	At Baseline: Date _____/____/____	

		Results_____ 1or 2 3 or 4	
		At 6 months Date: _____/____/____ Results_____ 1or 2 3 or 4	
		12 months: Date_____/____/____ Results_____ 1or 2 3 or 4	
		18 months: Date_____/____/____ Results_____ 1or 2 3 or 4	
		24 months: Date_____/____/____ Results_____ 1or 2 3 or 4	
		At the time of TB Diagnosis: Date_____/____/____ Results_____ 1or 2 3 or 4	
23	ART	Yes No	
24	If (21) yes	Start date_____/____/____ Discontinue date_____/____/____	
25	CPTs	Yes No	

26	If (23) yes	Start date_____/____/____ Discontinue date_____/____/____	

SECTION D: Tuberculosis information

27	Had TB before study	1.Yes 2.No	
28	If (26)	Start date____/_____/_____	
29	Had TB during study period	Yes No	
30	If (27) yes	Start date____/_____/_____	
31	If (27) yes Means of Diagnosis	Smear Chest x-ray Ganglionic TB	

APPENDIX II: BUGET

Item Description	Unit Cost (KR)	Multiplying Factor	Total Cost KR)
Stationery			
Reams of paper	25	25.00 x 5	125
Rubber	0.5	.50 x 6	3
Pencils	0.5	.50 x 6	3
Staples	20	20.00 x1 Box	20
Staplers	60	60.00 x 2	120
Calculators	95	95.00 x 2	190
Tipex	7.5	7.50 x 2	15
Note Books	2	2.00 x 6	12
Flip charts	50	50.00 x 2	100
Markers	5	5.00 x 4	20
Spirals	3	3.00 x 3	9
Flash disks	150	150.00 x 3	450
File folders	5	5.00 x 6	30
Subtotal			1,106
Secretarial Services			
Typing and setting and printing proposal	25	.250 x 25 pages x 3 drafts	187.5
Typing and setting and printing abstraction sheets	25	2.50 x 8pages	20
Photocopying abstraction sheets	0.25	.135 x 8 pages x 3000	3240
Typing and setting and printing draft reports	25	2.50 x 69 pages x 3 copies	375
Typing and setting and printing final report	25	2.50 x 69 pages x 4 copies	500
Binding final dissertation report	85	85.00 x 4 copies	340
Bag for stationery	25	25.00 x 6 bags	150
Subtotal			**4,812.5**
Training of (6) assistants			
Lunch allowance	50	50.00 x 6 x 2 days	600
Venue	600	600.00 x 2 days	1,200
Subtotal	1,080		1,800
Field expenses			
Lunch allowance	50	20.00 x 1x 60 days	1,200
Transport allowance	20	20.00 x 1x 60 days	1,200
Research assistants allowances	50	20,00x6x30days	3,600
Statistician	150	150.00 x 3 days	450
Subtotal			**6,450**
Grand Total			**14159.5**

Sources of Funding

The present study was partly sponsored by the Rwanda Education Board and the other part was funded by the researcher herself.

APPENDIX III: TABLE OF ACTIVITIES

Activity	Responsible Person/Time Frame	June 2013	July 2013	August 2013	September 2013	October2013	November 2013	December 2013	January 2013	February 2013	March	April	May	June	July
Presentation to the Department	Investigator														
Submission of proposal to Assistant Dean (PG) office	Investigator														
Presentation at GPPF	Investigator														
Submission of proposal to Institution Review board															
Submission to IRB															
Collecting data	Research Team														
Analyzing data	Investigator														
Writing of dissertation	Investigator and Secretary														
Presentation of Results	Investigator														
Submission of Final copy, Publication	Investigator														

APPENDIX IV: LETTER FOR PERMISSION TO CARRY OUT THE STUDY

The University of Zambia
School of Medicine
Department of Nursing Sciences
P. O. Box 50110
Ridgeway Campus
LUSAKA
15th September, 2013

The Medical Director of …….Hospital
UFS: Assistant Dean Postgraduate, School of Medicine, University of Zambia

Dear Sir / Madam,

RE: PERMISSION TO CONDUCT RESEARCH

I am a postgraduate student pursuing a master's degree programme Nursing Sciences (MSc.N) at the University of Zambia, School of Medicine, and Department of Nursing. As part of the programme requirements I have to undertake a dissertation. It is in this premise that I write to seek permission to undertake a research at **…….**

The title of the research is "**EFFECTIVENESS OF PRIMARY ISONIAZID PREVENTIVE THERAPY ON INCIDENCE OF TUBERCULOSIS IN ADULT PEOPLE LIVING WITH HUMAN IMMUNODEFICIENCY VIRUS IN SELECTED DISTRICTS OF RWANDA**". I intend to carry out the study from October, 2013 to January, 2014.

It is my hope that the findings will help to give the effect of Isoniazid so far before scaling up the programme.

Your favourable response to my request will highly be appreciated.

Yours faithfully,

Marie Claire UWAMAHORO Computer No: 521808902
Contacts: Email: clairuwa@yahoo.fr
Cell: +250788402547

APPENDIX V: ETHICAL CLEARANCE

University of Rwanda

College of Medicine and Health Sciences

P.O. Box: 3286 Kigali – Rwanda
Tel: (250) 25257188 ; (250) 788665979
Fax: (250) 571787
E-mail: info@khi.ac.rw

INSTITUTIONAL REVIEW BOARD

Kigali, on 10/12/2013

N° 36/UR-CMHS /IRB/13

MS MARIE CLAIRE UWAMAHORO
UR-Kigali Campus/ (Former KHI)
Kigali

RE: ETHICS CLEARANCE

Reference is made to your application for ethics clearance for the study entitled "***Evaluation of the Effectiveness of Primary Isoniazid Preventive Therapy Programme on Incidence of Active TB, in Adult People Living With HIV, Rwanda***"

You will be pleased to learn that the ethics clearance has been granted to your study by the UR-CMHS Institutional Review Board (IRB) on behalf of the National Ethics Committee (NEC) in accordance with the authority granted to the IRB by the National Ethics Committee letter of 13th May 2010 and in line with the "Rwanda Ministry of Health Guidelines for Researchers Intending to do Health Research in Rwanda" of February 2012.

You shall be required to submit the progress report and any other major changes made in the proposal during the implementation stage. Likewise, at the end of the study the Institutional Review Board shall also require to be given a final report of the study.

I wish you success in this important study.

Thank you.

Prof Kato J. NJUNWA
Chairperson
Institutional Review Board

Cc:
- Director Research Ethics Committee
- Director, Academic Quality Assurance, KHI
- Members of IRB

APPENDIX VI: PERMISSION FROM HIV/TB DIVISION

RWANDA BIOMEDICAL CENTER

A Healthy People, A Wealthy Nation

INSTITUTE OF HIV/AIDS DISEASES PREVENTION CONTROL
TB & OTHER RESPIRATORY COMMUNICABLE DISEASES DIVISION
Po.Box 2315 KIGALI

Kigali, 18/11/2013
Ref: N°213/RBC/TB&ORD/13

UWAMAHORO Marie Claire
University of Zambia
School of Medicine
Lecture at Kigali Health Insitute

Concern: Your request of authorization to conduct a research on TB

Dear Madam,

In response to your letter of November 14, 2013, addressed to RBC/TB&ORD Division requesting the permission to conduct a research entitled "Evaluation of Effectiveness of Primary Isoniazid Preventive Therapy on active TB incidence, in adult people living with HIV, Rwanda", as part of your Master's degree programme in Nursing Sciences at University of Zambia, The Tuberculosis & Other Respiratory Communicable Diseases Division is providing with you the permission. This authorization will be exercised within the limits of rules of Research Institutions in Rwanda. You have to make sure that all necessary permissions are obtained before collecting data.

The final report and copies of all published papers on this research will be provided to the Tuberculosis & Other Respiratory Communicable Diseases Division, for use and archive.

Sincerely,

HEAD OF TB & OTHER RESPIRATORY COMMUNICABLE DISEASES DIVISION
RWANDA BIOMEDICAL CENTER

Dr Michel GASANA
Head of TB & ORD Division/IHDPC/RBC

APPENDIX VII: SCIENTIFIC REVIEW APPROVAL

Republic of Rwanda

RWANDA BIOMEDICAL CENTER

A Healthy People. A Wealthy Nation

P.O. Box 84 KIGALI

National Health Research Committee
Ref: NHRC/2013/PROT/0124

To: **UWAMAHORO Marie Claire**
Principal Investigator

Scientific Review Approval Notice

Dear UWAMAHORO Marie Claire,

With reference to your request for approval of the Research Protocol entitled; **<< Evaluation of the effectiveness of primary Isoniazid preventive therapy on incidence of active TB, in adult people living with HIV, Rwanda >>**, We are pleased to inform you that, following a thorough review and critical analysis of your proposal (**Ref: NHRC/2013/PROT/0124 dated** 12/November/2013), your Research Protocol has been approved by National Health Research Committee.

However,

1) Changes amendments on approach and methodology must be submitted to the NHRC for review and approval to validate the changes.
2) A submission of quarterly progress report is mandatory
3) Submission to NHRC of final results before publication is mandatory
4) Failure to fulfill the above requirements will result in termination of study

Once again National Health Research Committee appreciates your interest in research and requests you to submit this proposal to the National Ethics Committee or IRB and then share a copy of the approval letter from them.

Your final approval reference number is **NHRC/2013/PROT/0124**

Yours Sincerely,

Dr. Parfait UWARIRAYE
Chairperson of NHRC

Signature:.....

Date:.....02/12/13

Dr. Jean de Dieu NGIRABEGA
Vice-Chairperson of NHRC

Signature:.....

Date:.....