MAKERERE UNIVERSITY

INCIDENCE AND FACTORS ASSOCIATED WITH TUBERCULOSIS DISEASE AMONG PEOPLE LIVING WITH HIV WHO COMPLETED TUBERCULOSIS PREVENTIVE TREATMENT: A RETROSPECTIVE COMPARATIVE COHORT STUDY AT BAYLOR-UGANDA HIV CLINIC

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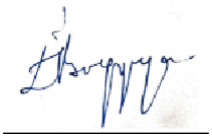
Signature:  Date: __21st Nov 2025____

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DECLARATION

I Pauline Mary Amuge, hereby declare that this dissertation entitled 'Incidence and factors associated with tuberculosis disease among people living with HIV who completed tuberculosis preventive treatment: a retrospective cohort study at Baylor-Uganda clinic' is my original work prepared and submitted in fulfilment of the requirements of the Master of Public Health and has not been submitted for any qualification at any other institution.

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DEDICATION

I thank my God Almighty, who gave me this opportunity to undertake this masters program, and enabled me to complete it as required. All glory belongs to God, my helper, source of wisdom and strength.

I dedicate this dissertation to my dear mother, Dr Mukwaya Josephine who encouraged me to continue studying after my masters of medicine in paediatrics. I also dedicate this work to my elder siblings, Dr Sande Isaac Ojangor, Engineer Josephine Apio Ahimbisibwe and Dr Emma Ewocu, who are role models in pursuing progress in life at all fronts.

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ACRONYMS

3TC	Lamivudine
ABC	Abacavir
ART	Anti-retroviral therapy
ATV/r	Atazanavir
BMI	Body mass index
COVID-19	Corona Virus Disease of 2019
DTG	Dolutegravir
DSDM	Differentiated Service Delivery Models
HIV	Human Immune-deficiency Virus
3HP	3months course of Isoniazid and Rifapentine
3RH	3months course of Isoniazid and Rifampicin
INH	Isoniazid (isonicotinylhydrazide)
IPT	Isoniazid Preventive Therapy
LTBI	Latent Tuberculosis Infection
LPV/r	Lopinavir boosted with ritonavir
MOH	Ministry of Health
NDA	National Drug Authority
NTLP	National Tuberculosis and Leprosy control Program
P-BC	Bacteriologically Confirmed Pulmonary Tuberculosis
P-CD	Clinically Diagnosed Pulmonary Tuberculosis
PLHIV	People Living with HIV
PTB	Pulmonary Tuberculosis
TB	Tuberculosis
TPT	Tuberculosis Preventive Treatment
WHO	World Health Organization

OPERATIONAL DEFINITIONS

Active TB disease: A person with symptoms and signs suggestive of tuberculosis and found to have the disease (through investigations or clinically).

Adolescent: A person of age 10-19 years at the time of assessment.

Adult: A person whose age is 18years and above.

Bacteriologically confirmed pulmonary TB case (P-BC): TB diagnosed in a biological specimen by smear microscopy, culture or a WHO-approved molecular test such as Xpert MTB/RIF

A Child: A person who is less than 18years of age.

Close TB contact: A person who is in the household or out of the household but shared an enclosed space, such as a social gathering place, workplace, or facility, for extended periods during the day with the index case (initially identified case) during the three months before the commencement of the current treatment episode.

Discontinuation of TPT: This is when a person stops taking the TB preventive treatment (TPT) for one month or more, due to severe side effects, active TB disease or new contraindications to isoniazid.

Household TB contact: A person who shares the same enclosed living space for one or more nights or for frequent or extended periods during the day with the index case (initially identified case) during the three months before the commencement of the current TB treatment episode.

Interruption of TPT: This is when a person stops taking TPT for 1 month or less.

Index TB case/patient: The initially identified case of new or recurrent TB in a person of any age in a specific household or other comparable setting in which others may have been exposed.

Infant: A child who is less than 12months of age.

TPT eligibility: A person who meets the criteria to be offered TB preventive treatment, which include; HIV positive person above age of 12months without TB disease, HIV positive person who has completed a full course of TB treatment, HIV positive child aged ≤12months and HIV positive individuals aged above 12months who are close contacts of a TB patient.

Isoniazid preventive therapy: The administration of a medicine called Isoniazid to individuals with a latent infection of Mycobacterium tuberculosis in order to prevent progression to active TB disease.

Latent TB Infection (LTBI): A state of persistent immune response to stimulation by *M. tuberculosis* with no evidence of clinically manifest TB disease. Also referred to as TB infection.

Loss to follow-up: A person who interrupts IPT for more than 1 month and does not return within 6months from start of the IPT.

People living with HIV: Children, Adolescents and Adults infected with the HIV virus in their body.

Presumptive TB patient: A person with symptoms or signs suggestive of the TB disease such as cough, fever, weight loss, and excessive night sweats.

TB contact tracing/investigation: Systematic screening of all house-hold contacts and close contacts of TB patients for active TB disease.

TB Preventive treatment (TPT): Treatment offered to individuals who are considered at risk of TB disease in order to reduce the risk. It is also referred to as TB preventive therapy, or treatment of latent TB infection (LTBI).

ABSTRACT

Introduction

The life-time risk of tuberculosis disease (TB) is higher among people living with HIV (PLHIV) compared to the general population. This study aimed to determine the incidence and factors associated with TB disease among PLHIV after completion of at least one course of TB preventive treatment (TPT).

Methods

This was a retrospective comparative cohort study among PLHIV of all ages, who initiated and completed TPT, in comparison with PLHIV who did not receive TPT at Baylor-Uganda HIV clinic for the period Jan 2016 to Dec 2021. The incidence of TB disease was reported as the number of new TB cases per 1000person years of follow-up. A multivariable Poisson regression model was used to assess for significant factors associated with TB disease after completion of TPT, adjusting for potential confounders.

Results

Of the 9505 PLHIV in care, 6014 (79.2%) initiated and completed TPT, and 1907 (20.0%) did not initiate TPT. Majority of PLHIV were female (61%). The TB incidence among PLHIV who completed TPT reduced over the study period, from 4.34 in 2016 to 1.71 TB cases per 1000person years in 2020, and increased slightly in 2021. Among PLHIV who completed TPT, unsuppressed viral load (≥1000 copies/mL) significantly increased TB risk (aIRR: 6.19; 95% CI: 2.80–13.69, p<0.001). The overall median survival time to TB disease after completing TPT PLHIV was 2.5 years (IQR: 2.3–2.8 years).

Conclusion and Recommendations

The TB incidence is low among PLHIV who complete TPT compared to PLHIV who do not receive TPT. After completing TPT, HIV viral non-suppression increases risk of TB disease by six times. Therefore, TB screening and treatment adherence support should continue after

completing TPT. The risk of TB disease after receiving TPT increases after 2.5 years. This calls for research on the need of repeat TPT doses in high-risk groups.

1.0 INTRODUCTION AND BACKGROUND

1.1 INTRODUCTION

Tuberculosis (TB) is spread through air, with estimates that a quarter of the world's population is infected with TB(1). Globally, the World Health Organisation (WHO) reported that TB remains the leading cause of death from a single infectious agent especially among people living with HIV (PLHIV) (2). In 2023, 10.8 million people were reported to have TB disease, with 25% of these reported in the Africa region (3).

HIV-associated TB is still prevalent even with high uptake of TB preventive treatment (TPT) because, HIV infection predisposes PLHIV to reactivation of latent TB infection (4), and progression to active TB disease (5, 6). Globally, HIV-associated TB accounted for 8% of the estimated incident TB cases in 2018, with 90% of these cases occurring in developing countries (7). Almost 80% of the TB-HIV co-infection burden is in Sub-Saharan Africa (8), with 11% being children 0–14 years). In 2020, 214,000 PLHIV died with TB disease, amidst the increasing uptake of TPT (9).

In 2008, the WHO launched the 3Is' policy, using three key strategies, to reduce TB burden(10). These included intensified case finding, isoniazid preventive therapy (IPT), and infection control at personal, and administrative levels. Out of the three strategies, IPT, now referred to as TB preventive treatment (TPT), and infection control remain the most promising strategies to reduce TB burden, especially after anti-retroviral therapy (ART) initiation (11).

The risk of mortality due to HIV-TB co-infection is double that due to HIV infection alone(12). This implies that HIV-associated TB increases the morbidity and mortality of PLHIV, even when on ART(13). Additionally, there are still some PLHIV who present with TB disease as part of advanced HIV disease due to late presentation for ART initiation, poor ART adherence, or HIV resistance to ART (14). Factors associated with TB disease among PLHIV include; advanced HIV disease stage 3 or 4 (15), low CD4 count <100cells/ul and high viral load at

ART initiation, low body weight <50kg, male sex, and prior TB disease events (14, 16), and non-use of ART (17). This underscores the need for regular TB screening and use of TPT among PLHIV on ART(18).

The WHO End TB strategy was launched in 2015 to prevent, control and end the TB epidemic by 2035 (19). The END TB global strategy milestone is to reduce the TB incidence rate by 90% compared to the 2015 rate, which translates to less than 55 TB cases per 100,000 population by 2025, and less than 10 TB cases per 100,000 population in 2035(20). Evaluation of progress towards achieving the UN high level meeting targets shows that 4 million people received TPT out of the targeted 6million people. However, even with the increasing uptake of TPT, there are still cases of TB disease among PLHIV, especially in high TB-HIV burden countries like Uganda (8).

1.2 BACKGROUND

Uganda is one of the top 30 high TB and TB-HIV burden countries and among the countries that contribute to 80% of the global TB cases that are not diagnosed or reported (9). In Uganda, the TB case notification rate was 150 cases per100,000 population, with 62,328 incident TB cases in 2019/2020, majority of them being male (63.7%) (21). In Kampala region alone, the TB case notification rate was 94.8% in 2019, declining to 77.3% in 2020 (21). Uganda registered a 75% uptake of TPT among PLHIV in 2020, which has progressively increased with recent TPT campaigns (22). However, the TB-HIV co-infection still oscillates around 30-39% in Uganda (21).

Among the key strategies recommended by the Uganda National TB and Leprosy Program (NTLP) and AIDS Control Program (ACP) to reduce the TB burden among PLHIV is administration of the TB preventive treatment (TPT). Preventing TB would also presumably eliminate the challenges related to diagnosis of TB among PLHIV. In 2019, Uganda launched and implemented the 100-day TPT initiation campaign in order to increase uptake among eligible PLHIV and children under five years with TB exposure(22).

Several factors contribute to low uptake of TPT among PLHIV. Individual barriers to TPT initiation include struggle with HIV chronic care and adherence, pill burden (ART plus TPT), stigma (TPT perceived as TB treatment), fear of side effects , misunderstanding about the importance or duration of TPT(23), and denial or non-disclosure of HIV positive status (24). Lack of social support and long distances to the health facilities have also contributed to socio-economic barriers (25). Health system barriers include frequent appointments, under reporting (no adolescent age bands), health workers' fear of developing drug resistant TB (26), interrupted drug supply (27), lack of health worker experience and knowledge (28), and clarity on the benefits of TPT, lack of parent and adolescent involvement (24). However, even after completion of TPT, some PLHIV progress from TB infection to TB disease. Factors associated with TB disease after completion of TPT among PLHIV are yet to be well-documented.

Understanding of the factors associated with TB disease even after completion of TB preventive treatment may offer clinicians and policy makers guidance on high-risk individuals to prioritise for TPT as the TB incidence reduces. This study therefore seeks to compare the incidence of TB disease among PLHIV who complete TPT with TB incidence among PLHIV who did not use TPT, and describe characteristics of PLHIV who develop TB after TPT completion, to re-direct focus among the most at-risk individuals.

The Baylor-Uganda center of excellence (COE) clinic is a family-centered tertiary HIV treatment center providing free comprehensive HIV and TB screening, testing, prevention and treatment services to more than 8000 children, adolescents and adults within central Uganda, majorly from Kampala and Wakiso districts. Baylor-Uganda COE clinic has been offering TPT services since 2015, according to the national guidelines. Participant eligible for TPT include PLHIV with no TB symptoms, those with TB symptoms who have been clinically assessed and confirmed not to have active TB disease, and those living in close contact with TB patients.

2.0 LITERATURE REVIEW

2.1 The burden of TB disease

TB is a preventable and curable disease, which still causes more than a million deaths worldwide(9). More than 2billion people worldwide are estimated to have latent TB infection(29). However, the overlap of latent tuberculosis infection (LTBI) and HIV infection has resulted in marked increases in TB incidence in countries with dual epidemics and TB, becoming the leading cause of death in HIV-infected people in Africa (30).

2.2 Epidemiology of TB infection and factors associated with progression to TB disease

After inhalation of the Mycobacterium tuberculosis bacteria, 5-10% of people exposed individuals go on to develop TB infection. Factors associated with TB infection include; severe TB disease in the index TB patient, prolonged periods of exposure to infectious index TB patients, poor ventilation, and limited exposure to ultra violet light during TB exposure(29). Active TB disease develops in 5-15% of those who develop TB infection, while the rest stay with latent TB infection (LTBI) (29, 31).

Populations at risk of TB infection and progression of TB infection to disease include both PLHIV, and household contacts of bacteriologically confirmed pulmonary (P-BC) TB cases (32). Pooled risk ratios from various studies reveal that all household contacts, children below age of five years, PLHIV, silicosis patients, people with malnutrition and end-stage renal disease, prisoners, poverty, the elderly, health workers, the homeless, and patients with diabetes, are substantially at higher risk for progression from LTBI to active TB disease (29, 31, 33, 34). Even though antiretroviral therapy (ART) reduces risk of incident TB among PLHIV, HIV positive patients receiving ART are still very susceptible to TB disease, because those with latent TB infection and untreated TB disease serve as infectious sources (31).

2.3 Benefits of TB preventive treatment

There is a wealth of evidence on the benefits of TPT as an approach to TB prevention among the high-risk groups such as PLHIV, and close TB contacts. TPT reduces TB incidence in close TB contacts especially in the first 2years after completion of TPT (35). Among PLHIV, TPT reduces the incidence of TB by up to 60% (36-38). Antiretroviral therapy (ART) reduces the risk further by 37% (39, 40). The combination of ART and isoniazid preventive therapy reduced incident TB or deaths by 60% in a retrospective cohort of PLHIV, compared to those on ART only in India (4).

In Uganda, the MOH implemented the first TPT program in 2014 using Isoniazid preventive therapy (IPT), and further strengthened its roll out in 2019 with an enhanced catch up phase to ensure that 90% of PLHIV eligible for TPT receive isoniazid (INH) preventive therapy (IPT) for six months (22). Currently, the MOH recommends several shorter TPT regimens in addition to IPT, such as isoniazid and rifapentine for 3months (3HP) or 1month (1HP), and isoniazid and rifampicin for 3months (3RH) (41).

2.4 Side effects of TB preventive treatment regimens

Even though known to be beneficial in high-risk groups, side effects have been reported among people using the recommended TPT regimens. Majority of the documented side effects due to IPT are low grade and transient, with up to 22% of children reporting side effects in a Kenyan study(42). Common side effects of IPT include; gastrointestinal symptoms, hepatotoxicity, skin rash, headache, sleep disturbance, perceived cognitive impairment, peripheral neuropathy and psychosis (43). Among those using a month of rifapentine and isoniazid (1HP) and for 3months (3HP)(44), only 6% and 4.9% experienced side-effects respectively which included; fever, peripheral neuropathy, elevated liver enzymes, nausea and vomiting(45). However, the occurrence of similar side-effects seems not to differ from those on ART alone compared to

those on ART and TPT (46). Therefore, TPT is considered safe and beneficial to high-risk groups, with majorly low-grade side-effects.

2.5 Prevalence and Incidence of TB among PLHIV who have received TB preventive treatment.

Among the high-risk groups, TPT offers up to 90% efficacy, however, some people still develop TB disease after successful completion of TPT (47). In Uganda, Andrew Kazibwe *et al* reported a TB disease cumulative incidence of 0.83%, and TB incidence of 18.9 per 100,000 person months of follow-up among PLHIV who initiated isoniazid preventive therapy (IPT) (48). However, this included individuals who initiated TPT and had interruptions, without comparison with those who never initiated TPT. There was also no age disaggregation to show prevalence in the high-risk groups such as children <5years and adolescents. In the Netherlands, the incidence of TB disease among close TB contacts who completed TPT was 187 per 100,000person years compared to 355 per 100,000person years among those not receiving TPT(35). The TB incidence in all persons who initiated, interrupted or completed TPT, is highest within the first year of LTBI diagnosis(35). However, there is still limited documentation of TB incidence among PLHIV who initiate and complete TPT in the era of increased access to anti-retroviral therapy (ART) and TPT regimens. In a cross-sectional study by Mebratu et al, found a higher TB prevalence of 48.5% among PLHIV who initiated IPT, compared to 8% among PLHIV who did not receive TPT. Such evidence from comparative cohorts in large HIV treatment centers is limited among PLHIV in Uganda.

2.6 Factors associated with TB disease among PLHIV

People living with HIV have a higher risk of TB infection after exposure to the mycobacterium tuberculosis, however, even among the PLHIV, there are correlates of progression from TB infection to TB disease which include low baseline CD4 count <200cells/ul, high HIV viral

load, increase in bio-markers such as β2 micro-globulin, neopterin, and tumour necrosis factor-α (TNF-α) (5).

Narasimhan et al summarises the risk factors for TB disease related to the index TB patient to include; exposure to untreated individuals with sputum smear positive pulmonary TB, exposure to a pulmonary TB patient with higher grade bacilli load in sputum, and close proximity or contact with a untreated TB patient (34).

Individual-related factors that are associated with TB disease within the general population include; HIV infection, malnutrition, age below 5years, diabetes mellitus, tobacco smoking, homelessness, overcrowding, alcohol and drug abuse(34). Among children and adolescent living with HIV (CALHIV), Mandalakas et al, reveals that age below 5years, severe immune suppression, advanced HIV disease, and delayed ART initiation more than 8weeks, were significantly associated with TB disease and unfavourable TB treatment outcomes among CALHIV of ages 0-19years in seven Sub-Saharan African HIV treatment centers (49).

Additionally, health system factors are also associated with risk of TB disease such as delayed TB diagnosis which increases exposure to infectious bacilli(34).

Gatechompol reported low CD4 count, BMI <18kg/m^2 and substance abuse as significantly associated with TB disease among PLHIV on long-term ART (18). However, this study did not assess the association between IPT uptake and TB disease due to the limited number of PLHIV on IPT within the retrospective cohort (49).

Among PLHIV who have completed TB preventive treatment, factors associated with TB disease include; HIV WHO disease stage III, and discontinuing TPT among PLHIV who initiate TPT in Uganda (48). Mebratu *et al* reported poor ART adherence, and non-use of cotrimoxazole prophylaxis as factors associated with TB disease among PLHIV(50), in a cross-sectional study, with a high prevalence of TB disease among users of IPT compared to those who did not use IPT (50). However, this data did not emphasise the prevalence in the various

age categories especially children and adolescents, and did not capture patient or care taker perceptions about benefits of TPT.

Conclusively, there are various factors that are associated with TB disease within the general population and PLHIV, which range from individual to health system factors. However, there is very limited evidence in Uganda, about the TB incidence after TPT completion among CALHIV, in comparison to those with no history of TPT use. This call for use of available data or research to close this knowledge gap.

3.0 STATEMENT OF THE PROBLEM AND JUSTIFICATION

3.0 STATEMENT OF THE PROBLEM

In Uganda, almost 40% of new TB cases are among PLHIV, with TB being the leading cause of mortality among PLHIV (51). There is adequate evidence that TPT reduces risk of TB disease by 60-90% (4). The MOH in Uganda has scaled-up TPT to at least 75% out of the targeted 90% PLHIV(21). However, there are still cases of incident TB disease among PLHIV who initiated TPT, with limited evidence on the burden and characteristics of PLHIV who develop TB after TPT completion. More so, information on factors associated with progression to TB disease is limited. In a retrospective cohort study conducted in eleven HIV treatment centers across Uganda and reported in 2022, TASO reported a TB incidence of 18.9 cases per 100,000person months among PLHIV who had initiated TPT, however, this is not representative of the entire country. In 2019, the NTLP reported a 39% prevalence of TB-HIV co-infection (21), however, there is no national data on TB incidence after TPT completion.

Incident TB disease after TPT may be due to TPT interruption, advanced HIV disease, exposure to TB infection, and severe immune suppression. HIV-TB co-infection leads to high TB-related mortality among PLHIV (12).Besides the high TB-related deaths among PLHIV, 53.1% of households with TB patients face catastrophic expenditures during TB treatment (52). This underscores the need to use available TPT options to reduce TB burden which perpetuates catastrophic household expenditures.

Prioritisation for repeat TPT doses among populations at risk of TB disease requires evidence on factors associated with TB disease among PLHIV who have completed TPT. Such data guides efforts towards ending the TB epidemic and facilitates targeted care and efficient use of the limited health-related resources. Otherwise, soon there will be saturation of TPT uptake among PLHIV, with limited guidance on individuals eligible for repeat TPT doses, as well as risk of resources wastage due to expiry of TPT commodities. This study therefore aimed to

determine the incidence and factors associated with TB disease among PLHIV after completion of TPT at Baylor-Uganda COE clinic, a high-volume HIV treatment site.

3.1 JUSTIFICATION

The End TB strategy focuses on three major indicators, one of which is to reduce TB incidence rate by 90% by 2035 to 10 cases per 100,000 population per year compared to 2015(20). Achieving the End TB strategy targets is grounded on three pillars, one of which is bold policies (19). This is well-aligned with sustainable development goal 3, target 3, aiming to end the epidemic of AIDS, and TB (53).

The overall goal of the Uganda National TB and Leprosy Strategic Plan 2020/21-2024/25 is to reduce the incidence of TB by 10% from 200/100,000 in 2019/20 to 180/100,000 (54), in line with the End TB strategy targets. However, there is still a high prevalence of HIV-related deaths with HIV-TB coinfection prevalence of 30%. There is need for transformation in the implementation of strategies to reduce TB incidence, such as leaving no one behind (55). This study was part of efforts to identify TB high-risk populations as focus of TB burden reduction strategies, in the era of increasing access to TB prevention services and ART among PLHIV (54).

The high uptake of TPT among PLHIV now raises questions of incidence of TB disease among PLHIV who complete at least one course of TPT. More to this, there is limited evidence about the characteristics of individuals who develop TB after completion of TPT, and possibly whether they may require repeat doses of TPT. Evidence on the TB incidence, characteristics of PLHIV who develop TB after TPT completion, and the time to TB disease after TPT completion is very critical to inform logistical planning, and guide policy on how to control TB among PLHIV in the era of high TPT and ART uptake.

3.2 CONCEPTUAL FRAMEWORK

Factors associated with TB disease after completion of TPT among PLHIV

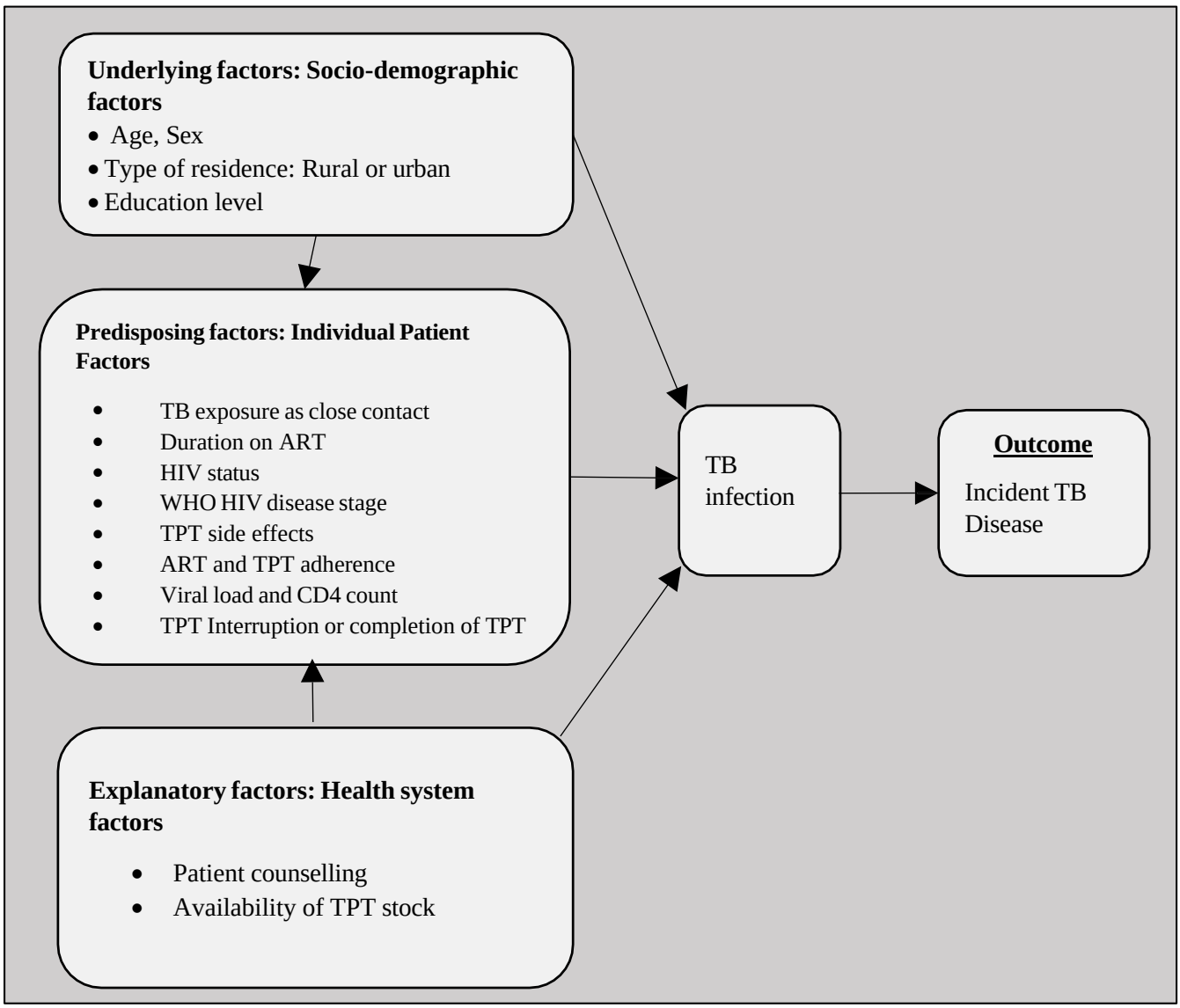

Figure 1. *A conceptual framework showing the relationship between TB disease and the different factors that can influence the progression of TB infection to TB disease. Adapted from Maciel et al (56)*

Conceptual framework narrative:

TB infection precedes TB disease. Factors that predispose to progression from TB infection to TB disease include; HIV infection, close contact with TB patients, age below five years, severe malnutrition, diabetes, and other forms of immune suppression. Factors that may be associated with development of TB disease after initiation and completion of TPT include, socio-

demographic factors such as age and sex, individual factors such as exposure to TB disease from a TB patient (56), and health systems structures such as interruption of TPT stock availability. For example, an individual's HIV status, increases risk to developing TB disease due to the reduction in the number and functionality of the T-lymphocytes (CD4 counts) which are also important in response to TB infection. Health systems factors such as stock availability and patient counselling may determine the patient's adherence to both ART and TPT. Interruptions in the supply of TPT implies that some PLHIV do not receive it, which contributes to their risk of developing TB disease. Longer duration on ART, HIV virological suppression, and completion of TPT have been significantly associated with reduced risk of TB disease among PLHIV(18). Conversely, advanced HIV disease, exposure to patients with TB disease, and poor adherence to ART may increase risk of TB disease even after completion of TPT(50). Congestion within households or congregate places such as prisons, schools, also increases risk of TB disease (5, 34), due to the high exposure to TB bacilli amidst the poor ventilation. TB disease has been found to be more prevalent among males, most probably due to extensive periods of exposure during working hours out of their households. Children below five years of age are also more at risk of TB disease due to the low functionality of their immune system(5, 34), as well as exposure to source cases within the households.

3.3 HYPOTHESES

Objective 1.

H_0: There is no difference between the TB incidence among the PLHIV who initiated and completed TPT, compared to the TB incidence among PLHIV who did not receive TPT.

H_A: The TB incidence among the PLHIV who initiated and completed TPT is lower, compared to the TB incidence among PLHIV who did not receive TPT.

Objective 2.

H_0: The factors associated with developing TB disease among PLHIV who initiated and completed TPT are similar to those among PLHIV who did not receive TPT.

H_A: The factors associated with developing TB disease among PLHIV who initiated and completed TPT, differ from those among PLHIV who did not receive TPT.

Objective 3

H_0: The time to TB disease among PLHIV who initiated and completed TPT does not differ by the different predictor variables.

H_A: The time to TB disease among PLHIV who initiated and completed TPT differs by the different predictor variables.

3.4 RESEARCH QUESTIONS

This study aimed to answer the following research questions;

1. What is the incidence of TB disease among PLHIV who completed TPT compared to those who did not receive TPT within the period 2016-2021?
2. What are the factors associated with TB disease among PLHIV who completed TPT compared to those who did not receive TPT within the period 2016-2021?
3. What is the median time to TB disease among PLHIV who initiated and completed TPT within the period 2016-2021?

4.0 STUDY OBJECTIVES

4.1 Aim

The aim of this study was to determine the TB incidence, factors associated with TB disease, and time to TB disease after initiating and completing TB preventive treatment, among PLHIV at Baylor-Uganda HIV clinic in Uganda.

4.2 Main Objective

To determine the incidence and factors associated with TB disease among PLHIV at Baylor-Uganda clinic who completed at least one course of TPT compared to those who did not receive TPT over a 6year period (2016 to 2021).

4.3 Specific Objectives

1. To estimate the incidence of TB disease among PLHIV who received and completed TPT, compared to PLHIV who did not receive TPT over a 6year period at Baylor-Uganda clinic.
2. To describe the factors associated with TB disease among PLHIV who received and completed TPT, compared to those who did not receive TPT over a 6year period at Baylor-Uganda clinic.
3. To determine the median time to TB disease after initiating TPT among PLHIV who received and completed TPT over a 6year period at Baylor-Uganda clinic.

5.0 METHODS

5.1 Study Site

The study was be conducted at an urban HIV treatment clinic in Kampala, the Baylor College of Medicine Children's Foundation-Uganda (Baylor-Uganda) center of excellence (COE) HIV clinic, located in Mulago national referral hospital. The Baylor-Uganda COE clinic is a family-centered tertiary HIV treatment center providing free comprehensive HIV and TB screening, testing, prevention and treatment services to more than 8000 children, adolescents and adults within central Uganda, majorly from Kampala and Wakiso districts. The clinic opens five days a week, with both counselling, psychosocial, general and specialized medical services, nutrition assessment and rehabilitation, medicines dispensing, laboratory, and social support services. Patients go through a standard patient flow based on whether they are stable or unstable. Patients can receive services at the health facility or within the community, based on national HIV treatment and prevention guidelines. During the five-year period of interest, only isoniazid preventive therapy was available and dispensed to patients. Currently, the clinic pharmacy has both isoniazid (6H) and isoniazid rifapentine (3HP) TPT regimens, used as recommended by the ministry of health.

At Baylor-Uganda clinic, PLHIV are screened for TB disease using a TB symptom screening tool at every clinic visit. Individuals with TB symptoms undergo a clinical evaluation, and TB diagnostic tests are done such as MTB/RIF GeneXpert, urine LAM for those with CD4 count <200cells/ul, and chest X-ray. Clients diagnosed with TB disease are started on TB treatment. Individuals without TB symptoms or found not to have TB disease after clinical evaluation, are offered TB preventive treatment according to the national guidelines. This includes PLHIV with no evidence of TB disease, PLHIV who are close contacts of TB patients, and PLHIV who have recently completed a full course of TB treatment. The ministry of health supplied isoniazid to be taken daily for six (6) months as TPT. This is dispensed with pyridoxine, to prevent peripheral neuropathy, a common side-effect of isoniazid. Individuals who develop

mild or moderate side effects, are usually advised to continue with the TPT as the side-effects are managed. Individuals who develop severe side effects may have the TPT withdrawn to first manage the side-effects.

Individuals who initiated TPT had monthly follow-up visits at the clinic to identify and manage side-effects, screen for TB symptoms, and assess adherence to the TPT and ART, if on ART. TB diagnostic tests are done for those with TB symptoms while on TPT. Those diagnosed with TB disease before completion of their full TPT course have their TPT stopped, and TB treatment started.

5.2 Study Population

This study enrolled people living with HIV (PLHIV) of all ages at Baylor-Uganda HIV clinic, who initiated and completed TPT, and those who did not receive TPT, within the 6year study period 1st January 2016 to 31st December 2021.

Selection Criteria

Inclusion Criteria

- *Exposed group:* HIV-infected individuals who completed TB preventive therapy within the period Jan 2016 to Dec 2021. Clients who did not complete TPT due to known reasons such as death, transfer-out, loss to follow-up (LTFU) were included.
- *Unexposed group:* HIV infected individuals who did not receive TB preventive therapy within the period Jan 2016 to Dec 2021.

Exclusion criteria

- Clients with incomplete records of TPT initiation and TPT completion during the study period.
- Clients who initiated TPT within the study period but did not complete for various unknown reasons were excluded from the analysis.

- Clients with diagnosis of TB disease at the start of the study period.

5.3 Study Design

A retrospective cohort study was conducted among PLHIV of all ages, who received TPT and those who did not receive TPT during the period Jan 2016 to Dec 2021, at Baylor-Uganda HIV clinic. Those who did not receive TPT during the study period were the non-exposed group for comparison in this analysis.

Justification for the retrospective cohort study design: A cohort study design is appropriate for estimating incidence of a disease (primary outcome of the study), disease risk (secondary outcome of this study), and relative risk. Due to the need for longer period of time to reach the primary outcome (TB disease) after the exposure (TPT completion vs No TPT), available data was obtained to conduct retrospective cohort study, where data is available at the same time on; the exposure status, the primary outcome of interest (TB disease), and the period/time of observation. The retrospective cohort study design is also affordable and time-saving, given the limited resources to conduct this study as a prospective study.

5.4 Sample size Estimation

Objective 1: To estimate the TB incidence among PLHIV who completed TPT compared with those who did not use TPT *(Objective 1);* the sample size calculation formula for estimating the incidence (or probability) of an event of two independent cohorts was used. The formula is given as follows (Kasiulevičius et al., 2006);

$$n = \frac{[Z_{\alpha}\sqrt{(1+\frac{1}{m})\bar{p}(1-\bar{p})} + Z_{\beta}\sqrt{\frac{p_0(1-p_0)}{m} + p_1(1-p_1)}]^2}{(p_0-p_1)^2}$$

This formula gives the minimum number of subjects **(n)** required to detect a true incidence rate with power **(1- β)** and two-sided type I error probability α, **m** is the number of control subjects (non-TPT patients) per experimental subject (TPT patients) required to detect a true relative risk

or experimental event rate with 80% power, $\boldsymbol{Z_\alpha}$ and $\boldsymbol{Z_\beta}$ are the standard normal critical values, $\boldsymbol{p_0}$ is the incidence (probability) of an event (TB infection) in controls, $\boldsymbol{p_1}$ is the incidence (probability) of an event (TB infection) in experimental subjects, and $\bar{p}$ is the mean probability of an event given by $\bar{p} = \frac{p_1 + mp_0}{m+1}$.

Assuming power of 80% (Z_β=0.84), 5% type I error (Z_α= 1.96); a ratio of control to experimental subjects of 1:3 based on a study in Uganda which estimated 75% uptake of TPT, hence m=1/3; an incidence of TB among the TPT patients of 0.83% (as estimated in Uganda by Kazibwe et al 2022); and at least 80% lower TB incidence among TPT patients compared to non-TPT patients (among the high-risk groups, and TPT offers up to 90% efficacy according Padmapriyadarsini et al., 2020).

The estimated minimum sample size of 583 patients (non-TPT 193, TPT 390) was required.

Objective 2: To determine factors associated with TB disease over a 6year period, the sample size estimation formula below was used.

$$n = \frac{[Z_\alpha \sqrt{(1 + \frac{1}{m})\bar{p}(1-\bar{p})} + Z_\beta \sqrt{p_0(1-p_0) + p_1(1-p_1)}]^2}{(p_0 - p_1)^2}$$

The p_0 was the incidence of TB in unexposed group, and p_1 was the incidence of TB in the exposed group. Among the factors documented to be associated with TB diseases among HIV patients treated with TPT was WHO staging (Kazibwe et al 2022). The study estimated TB incidence at 48.5 per 100,000person months (or 0.0485 per 1000 person months) among PLHIV with WHO stage III disease, compared to 17.3 per 100,000 person months (or 0.0173 per 100 person months) among PLHIV with WHO stage II disease (adjusted HR=3.66 (95%CI=1.08, 12.42)). This study was powered to detect a similar effect of WHO staging. Substituting for p_0=0.0173, p_1=0.0485, m=1, 80% power and 5% type I error, a minimal sample size of 512 was required to estimate factors associated with TB incidence.

Objective 3: To determine the median time to TB disease after completion of TPT among PLHIV who received TPT compared to those who did not receive TPT over a 6year period at Baylor-Uganda clinic *(Objective 3);* the median was first log-transformed to use the following formula.

$$n = 2\frac{(Z_\alpha + Z_\beta)^2\sigma^2}{(\mu_0 - \mu_1)^2}$$

Where n was the sample size, μ_0 was the log-transformed population survival median time, μ_1 was the log-transformed anticipated median time, σ was the standard deviation of the log-transformed survival time, and Z_α and Z_β are as described above. Again, based on estimates from the study by Kazibwe et al (2022), the median time to TB diagnosis after completing TPT treatment course was 18.5 months (interquartile range of 22.3), which was equivalent to 2.92 after performing log-transformation. The σ was approximated using log-transformed interquartile range which was equivalent to 3.1. Based on the above assumptions (μ_0=2.92 and σ=3.1), a minimal sample size of 443 was adequate to estimate a median survival time that is at least 20% of the hypothesized population value (μ_0=2.92), that is, $\mu_1$of at least 2.34.

Out of the three estimations, the highest sample size out of the three, 583, was considered as the minimum sample size to achieve the three study objectives.

In order to minimize the selection bias, all eligible participants in the available data were included in the analysis, exceeding the estimated minimum sample size of 583.

Using the observed TB incidence proportions among PLHIV who did not receive TPT and those who received TPT, (1907 and 6014) respectively. The achieved power was estimated at 100% at alpha=0.05, using the Pearson chi-square test.

5.5 Selection of study participants

A census was done, which included all PLHIV who completed TPT and those who did not receive TPT during the study period. The required data was abstracted from the electronic

medical records (EMR). The number of eligible clients exceeded the minimum sample size (193 non-TPT, 390 TPT) determined for objective 1, which was the biggest sample size out of the three objectives. Therefore, all available data was used for this study. Using all the eligible clients in the population eliminates the risk of sampling bias, which may be introduced by an unrepresentative sample, selected by traditional sampling methods.

5.6 Study Variables and measurement

5.6.1 The dependent variable

The dependent variable was a diagnosis of TB disease within the study period, which was reported as binary (TB disease vs No TB), for the PLHIV who completed TPT and those that did not receive TPT. The TB diagnosis considered was either clinically or bacteriologically confirmed, based on the patients' medical records. Therefore, the event of interest was TB disease. To estimate the incidence, the time to TB diagnosis was measured from date of starting TPT treatment among TPT clients and from date of the first visit recorded within the study period for all non-TPT clients. The diagnosis of TB disease was considered as either clinically diagnosed or bacteriologically confirmed TB disease, with or without initiation of TB treatment within the study period. All incidences of TB reported over the study period were recorded.

Exposure variable

The primary exposure was completion of TPT among PLHIV who received TPT.

Censorship

In the survival analysis, the event of interest was a diagnosis of TB disease after initiating TPT. The period of risk started on the date of TPT initiation and ended on the date of TB diagnosis, or the last visit date if TB was not diagnosed, date of death, last date of visit for the lost to follow-up and transferred out, whichever came first for each patient.

The patients who developed TB were censored on the date of TB diagnosis. Those who had died were censored at the date of death. Clients who were considered as lost-to-follow up,

transferred out, or missed appointment were censored at the date they were last observed in care. All active clients not diagnosed with TB were censored by December 31st, 2021 if they were not lost-to-follow-up dead or transferred-out. Loss to follow-up was defined as interruption of TPT for more than 1 month without return within 6months from start of the TPT. Cumulative incidence function was used to estimate the probability of TB disease after initiation of TPT.

5.6.2 Independent variables

The independent variables included; socio-demographic characteristics such as age and sex, antiretroviral treatment (ART) regimen, duration on ART, history of TB disease prior to TPT initiation, history of TB contact during or after TPT completion, concurrent medication, ART and TPT adherence, WHO HIV clinical stage, presence of side-effects due to isoniazid, baseline CD4 count, HIV viral load at start of TPT or within past 1year.

5.7 Data Collection

5.7.1 Data Collection Procedures

Data on the dependent and independent variables was abstracted from the electronic medical records (EMR) at Baylor-Uganda HIV clinic, using a data abstraction tool in excel with pre-specified variables. A list of those who received TPT within the study period was generated from the EMR. The control group who did not initiate TPT was selected within the same study period. Matching was not done to preserve more variables for the bi-variate and multi-variable analysis. All PLHIV who initiated TPT from 1st January 2016 to 31st Dec 2018 (3year-period), had follow-up data collected until 31st Dec 2021. This allowed a minimum follow-up period of 3years for each participant, which was slightly longer than the 18.5months median time to TB disease after TPT as reported in another Uganda study (48). The follow-up period was measured from start of TPT. Individuals recorded as TB retreatment cases were distinguished from those reported as new TB cases. The data was extracted as an excel sheet, cleaned and exported to STATA for analysis. The electronic medical records system at Baylor-Uganda is

used to collect individualised data about HIV treatment follow-up, TB screening, prevention and treatment data for all clients receiving HIV care at the clinic. Data collected was password protected, only accessible with permission. Data collected included, clinical assessments at every clinic visit, HIV-related conditions and other medical conditions, laboratory tests and results, counselling needs and services provided, drug prescriptions and dispensed drugs, conducted community/home visits, and medical history from first date of enrolment into the clinic. The data was downloaded for analysis on official request for performance review, check of quality health delivery indicators, and publication.

5.7.2 Quality Control

The data abstraction tool was tested for internal validity using some test patient records and revised based on data output from the EMR. The data collection tool was pre-tested on afew records and finalized before use. The research assistants were trained on the protocol and final data collection tool before conducting the data collection. All collected data was reviewed weekly for logical completion. Data cleaning was conducted in STATA version 16.0 before data analysis.

5.8 Data Management and Data Analysis

Data was abstracted from the electronic medical records at the Baylor-Uganda HIV clinic. All data was de-identified for analysis to maintain patient confidentiality. The abstracted data was stored as a password-protected excel sheet and backed-up on the Baylor-Uganda server for easy retrieval in the event of data loss on the working computer. The data was checked for completeness. Effort was made to obtain the missing data from the available electronic medical records. Patients with missing data on the inclusion criteria and outcome of interest were not included in the final dataset for analysis. Complete case analysis was considered where there was missing data. Only the trained research assistant had access to the data using passwords.

The data was exported to STATA version 16.0 for data cleaning and recoding of some variables before statistical analysis.

5.8.1 Measurement of study Outcome

The primary outcome, which is the incidence of TB disease, was reported as number of new TB cases per 1000person years of follow-up. This was calculated as the number of clients diagnosed with TB disease over the study period divided by person time of follow-up in years.

5.8.2 Data Analysis

Data was exported to STATA version 16.0 (Statacorp, College Station, TX) for cleaning and analysis. The data was checked for errors, and completeness, before analysis. Some variables were recoded for analysis.

Continuous variables were reported as means with standard deviations (for normally distributed data) or median with inter-quantile range (Q1, Q3) for skewed data.

The Shapiro-Wilk test was done to check whether the data is normally distributed. Categorical variables were summarised as frequencies and percentages, while continuous variables were summarised as either mean with standard deviation if normally distributed, or as median with interquartile range if they were not normally distributed. The age categorization was done to match the age categories used by the ministry of health in HIV reporting tools, with an interest to have 10year interval within each age group. Categorical variables were reported as frequencies and percentages. Incidence of TB disease was reported as the number of TB cases per 1000person years of follow-up.

Objective 1

The incidence of TB was estimated as the number of TB cases reported over the study period divided by total person time in years expressed as per 1000person years. The TB incidence was

presented as overall and by TPT group (received TPT vs did not receive TPT; completed TPT vs did not complete TPT) with 95% confidence intervals (CI). A Poisson regression model fitted to the number of TB events per client (usually one event) with person time set as an off-set variable was used to estimate the incidence rate and the 95%CI per group (received and completed TPT vs did not receive TPT). This was achieved by fitting an intercept model for each group. To compare TB incidence rates between those who completed TPT and those who did not complete TPT; a group indicator variable was entered into the Poisson regression model (again with person time as off-set variable) and incidence rate ratio (IRR) with 95%CI obtained to quantify the association. To adjust for potential confounders like age, sex, ART duration, WHO staging, and ART regimen among other factors, a multivariable Poisson regression model was considered. To assess if TB incidence varied across the years of follow-up, the analysis was stratified by cohort year of observation. Results from both unadjusted and adjusted analyses have been presented. Adjusted associations with p-value<0.05 were considered statistically significant.

Objective 2

To assess factors associated with TB disease among PLHIV, predictor variables were entered into the Poisson regression model and risk ratio (RR) with 95%CI obtained to quantify the association. Baseline variables included in the model included; age, regimen back born, ART line, WHO stage, and viral load. To adjust for potential confounders like age, sex, ART duration, WHO staging, and ART regimen among other factors, a multivariable Poisson regression model was considered.

All variables at bivariable analysis with p-values <0.2 and those known from literature to be associated with TB disease, were considered for multivariable analysis. Adjustment for baseline characteristics such as age, sex, and ART regimen were done to try and eliminate the imbalance between the two groups due to purposive selection. Calendar time was included in

the regression model, and trends analysis was done to assess whether the TB disease differs in the 3 years of follow-up.

A backward model building procedure was used and non-significant variables were dropped one at a time starting with the most non-significant, until only significant variables remained in the model. Confounding was tested for by bringing back the variables in the order they were dropped starting with the last to be dropped from the model. A variable was considered a confounder if the difference between the crude and adjusted risk ratios was >10%. Results from both unadjusted and adjusted analyses was presented. Associations with p-value<0.05 were considered statistically significant.

The model was checked for multicollinearity using variance inflation factor (VIF) whereby factors with VIF>10 were considered to cause multicollinearity problem. If multicollinearity existed, centering was considered for continuous variables, while categorical variables with minimal or no scientific and/or statistical significance were dropped out of the model. The model was also checked for influential outliers using Cooks distance (D). Observations with D>4/n (where n was the number of data points) were considered as outliers. The Deviance goodness of fit test was used to assess whether the Poisson regression model was fit for the data. A p-value >0.05 showed that the proposed regression model was a good fit for the study data.

Objective 3

To determine the median time to incident TB disease among both groups, time-to-event analysis was used and the median times between the two groups estimated. Participants with a diagnosis of TB disease were censored on the date the TB diagnosis was made by the clinician as recorded in the EMR. Participants who died in both groups before end of the follow-up period, were censored on the date of death, and those who were alive but did not develop TB disease during the follow-up period were censored on the last date of follow-up period.

Participants who were lost-to-follow-up were censored on the date of the last clinic visit. After data review, the beginning of the time at risk could not be clearly defined for the PLHIV who did not receive TPT, compared to the PLHIV who received TPT. Therefore, survival analysis was based on those who initiated and completed TPT. The TPT initiation date was considered as the start of the risk period for the PLHIV who initiated (and completed) TPT. The median survival time was considered as the time when 50% of the population at risk, had the event (TB disease). The Kaplan Meier (KM) curves were run and showed that the percent of PLHIV who completed TPT and developed TB disease were less than 50% (0.8% developed TB). So, the median survival time was not estimated using KM curves. Therefore, descriptive estimates for median and interquartile range were obtained, and the log-rank test was used to compare survivor functions. The analysis was repeated stratified by confounders ascertained in objective 2. Factors with log-rank test p-value<0.1 were included in a Cox Proportional hazards model to determine factors associated with time to TB disease after initiation of TPT. A global test was used to test the assumptions for the Cox proportional hazards model. A p-value of 0.062 provided some evidence that the hazards model assumptions were not violated. Any p-values <0.05 were considered significant.

5.9 Ethical Considerations

Ethical approval was obtained from the Makerere University School of Public health and Higher degrees research and ethics committee (MakSPH HDREC), with a waiver to obtain written informed consent because no human subjects were involved in collection of secondary data for this study. Administrative clearance was obtained from Baylor Uganda before start of the data collection. The data did not include patient identifying information such as names, address, or phone numbers to maintain patient confidentiality. The database was password protected, only accessible to the principal investigator and trained research assistants.

5.9.1 Dissemination of results

The study results will be disseminated to the Makerere University School of Public Health, the study site team, national TB and Leprosy Program and AIDS Control Program through continuous medical education sessions, journal club. The results will also be disseminated a wider audience through filing the dissertation in the college of health sciences library, abstract presentations, and publication in a peer-reviewed journal.

6.0 STUDY RESULTS

Baseline Characteristics of the PLHIV during the study period

Among the 9,505 PLHIV who received HIV care at Baylor-Uganda during the study period, 79.9% (7598/9505) initiated TPT, of whom 6014 (79.2%) completed their full TPT course. A total of 1907 (20%) patients in care, did not initiate TPT. The majority of PLHIV in the study period were female (61%), with comparable proportions of males in both groups. More females received and completed TPT (60.1%, 3617/6014) compared to males (39.9%, 2,397 /6014). The median age among those who did not initiate TPT was higher (24 years, IQR 10-32), than those who completed TPT (22years, IQR 16-31). Majority of those who completed TPT were adolescents aged 10-19years (35%, 2102/6014), and young adults aged 20-29years (31.2%, 1875/6014). Among those who did not initiate TPT, the majority were young adults aged 20-29years (27%, 514/1907), and children aged <10years (23.8%, 453/1907). The PLHIV who completed TPT had been on ART for a longer period (3.7years, IQR 0.9–7.2), compared to those who did not receive TPT (0.3 years, IQR 0.3-3.7). Underweight participants accounted for a substantial proportion of the study population (47.9%), with a higher prevalence among those who completed TPT (49.5%) compared to those who did not (43.2%). Individuals who had been on ART for 5-9 years were more common among those who completed TPT, compared to those who did not receive TPT (30.1% vs. 10.9%).

A quarter of those who completed TPT had advanced HIV disease (WHO stage 3 or stage 4) (34% and 14.2% respectively), while the majority of those who did not receive TPT had WHO stage 1 disease (30.9%, 590/1907). All the baseline characteristics of the study population are summarized in ***table 1.***

Among the PLHIV who received and completed TPT; 100% received isoniazid (INH) monotherapy for 6months (6H). Majority (98.6%) received one course of TPT, and only 1.4%

received two or more TPT doses. More than half had been on ART for more than 5years, and 75% were considered as virally suppressed (VL <1000copies/ml).

Table 1. Baseline characteristics of the study participants

Table 1. Baseline characteristics of the study participants			
	Did Not initiate TPT N=1,907	**Initiated and completed TPT** N=6,014	**Total** N=7,921
Sex	n (%)	n (%)	n (%)
Male	693 (36.3)	2,397 (39.9)	3,090 (39.0)
Female	1,214 (63.7)	3,617 (60.1)	4,831 (61.0)
Age (years)			
<10	453 (23.8)	369 (6.1)	822 (10.4)
10-19	338 (17.7)	2,102 (35.0)	2,440 (30.8)
20-29	514 (27.0)	1,875 (31.2)	2,389 (30.2)
30-39	379 (19.9)	982 (16.3)	1,361 (17.2)
40-49	172 (9.0)	474 (7.9)	646 (8.2)
50+	51 (2.7)	212 (3.5)	263 (3.3)
Median (IQR)	24 (10, 32)	22 (16, 31)	22 (15, 31)
BMI (kg/m^2)			
Normal	680 (35.7)	2,233 (37.1)	2,913 (36.8)
Underweight	824 (43.2)	2,974 (49.5)	3,798 (47.9)
Overweight	242 (12.7%)	791 (13.2%)	1,033 (13.0%)
Missing	161 (8.4)	16 (0.3)	177 (2.2)
Median (IQR)			19.5 (16.6, 22.7)
MUAC (cm)			
<12	173 (9.1)	99 (1.6)	272 (3.4)
>=12	1,552 (81.4)	5,908 (98.2)	7,460 (94.2)
Missing	182 (9.5)	7 (0.1)	189 (2.4)
Median (IQR)	23.1 (15.7, 26.8)	22.3 (17.5, 26.2)	22.5 (17.3, 26.4)
Duration on ART (years)			
<5	1,198 (62.8)	3,585 (59.6)	4,783 (60.4)
5-9	207 (10.9)	1,810 (30.1)	2,017 (25.5)
10+	82 (4.3)	615 (10.2)	697 (8.8)
Missing	420 (22.0)	4 (0.1)	424 (5.4)
Median (IQR)	0.3 (0, 3.7)	3.7 (0.9, 7.2)	3 (0.2, 6.6)
ART backbone			
AZT/3TC	323 (16.9)	2,496 (41.5)	2,819 (35.6)
ABC/3TC	685 (35.9)	1,587 (26.4)	2,272 (28.7)
TDF/3TC	892 (46.8)	1,913 (31.8)	2,805 (35.4)
Other	3 (0.2)	18 (0.3)	21 (0.3)
Missing	4 (0.2)	0 (0.0)	4 (0.1)
ART anchor drug class			
INSTI(DTG-based)	297 (15.6)	405 (6.7)	702 (8.9)
NNRTIs (EFV-based)	741 (38.9)	3,012 (50.1)	3,753 (47.4)
NNRTIs (NVP-based)	172 (9.0)	1,157 (19.2)	1,329 (16.8)
PI-based (ATV/r)	142 (7.4)	394 (6.6)	536 (6.8)
PI-based (LPV/r)	537 (28.2)	1,020 (17.0)	1,557 (19.7)
Tripple NRTIs (ABC/3TC/AZT)	12 (0.6)	19 (0.3)	31 (0.4)
Missing	6 (0.3)	7 (0.1)	13 (0.2)
ART line			
First (1st)	1,224 (64.2)	4,592 (76.4)	5,816 (73.4)
Second (2nd)	678 (35.6)	1,412 (23.5)	2,090 (26.4)
Third (3rd)	1 (0.1)	10 (0.2)	11 (0.1)
Missing	4 (0.2)	0 (0.0)	4 (0.1)

WHO HIV stage			
I	590 (30.9)	1,364 (22.7)	1,954 (24.7)
II	268 (14.1)	1,731 (28.8)	1,999 (25.2)
III	264 (13.8)	2,042 (34.0)	2,306 (29.1)
IV	377 (19.8)	854 (14.2)	1,231 (15.5)
Deferred	106 (5.6)	19 (0.3)	125 (1.6)
Missing	302 (15.8)	4 (0.1)	306 (3.9)
Viral load			
0-<50	423 (22.2)	4,037 (67.1)	4,460 (56.3)
50-<500	125 (6.6)	796 (13.2)	921 (11.6)
500-<1000	23 (1.2)	121 (2.0)	144 (1.8)
>=1000	304 (15.9)	997 (16.6)	1,301 (16.4)
Missing	1,032 (54.1)	63 (1.0)	1,095 (13.8)
CD4 count			
Median (IQR)	541 (265, 926)	596 (308, 1018)	581.5 (297, 993.5)

Incidence of TB disease among PLHIV

The TB incidence varied across the six-year period, with some significant differences observed between PLHIV who completed TPT compared to those who did not receive TPT. The overall TB incidence among PLHIV included in the study, increased from 3.24 TB patients per 1000-person years in 2016, to 56.67 TB patients per 1000-person years in the year 2021. Among PLHIV who completed TPT, TB incidence reduced from 4.34 (95% CI: 1.40-13.46) per 1000-person years in 2016, to 1.71 (95% CI: 0.24-12.15) per 1000-person years in 2021 (*see table 2*). Among the PLHIV who did not receive TPT, the TB incidence increased from 3.21 (95% CI: 2.65-3.90) per 1000-person years in 2016, to 84.95 (95% CI: 61.27-117.76) per 1000-person years in 2021 **(*see table 2*).** At bi-variate analysis, the unadjusted incidence rate ratio (IRR) reduced from 1.35 (95% CI: 0.43-4.26) in 2016, to 0.09 (95% CI: 0.02-0.38). After adjusting for baseline characteristics, the incidence rate ratio (IRR) comparing the PLHIV who completed TPT to those who did not receive TPT; significantly reduced from 2.08 (95% CI: 0.65-6.69, p=0.22) in 2016, to 0.10 (95% CI: 0.01-0.73, p=0.023) in 2021. The trends in TB incidence and IRR comparing the two groups from 2016 to 2021 are shown in ***table 2.***

Table 2. Comparison of annual TB Incidence among PLHIV who did not initiate TPT and those who completed TPT, for the period 2016 to 2021

	Participants N (%)	**Person time (1000pers on years)**	**Crude Incidence Rate per 1000 Person Years (95% CI)**	**Crude incidence rate ratio (IRR) (95% CI)**	**Adjusted IRR (95% CI)**	**p-value**
Cohort Year 2016						
Overall	**5980**	32758	3.24 (2.68-3.91)			
No TPT	5837 (97.6)	32067	3.21 (2.65-3.90)	1	1	
TPT	143 (2.4)	691	4.34 (1.40-13.46)	1.35 (0.43-4.26)	2.08 (0.65-6.69)	0.22
Cohort Year 2017						
Overall	6374	28928	4.53 (3.82-5.37)			
No TPT	6203 (97.3)	28242	4.39 (3.68-5.24)	1	1	
TPT	171 (2.7)	686	10.21 (4.87-21.41)	2.33 (1.09-4.98)	2.54 (1.14-5.66)	**0.022**
Cohort Year 2018						
Overall	6613	23426	6.06 (5.14-7.15)			
No TPT	5928 (89.6)	21341	6.28 (5.30-7.44)	1	1	
TPT	685 (10.4)	2086	3.84 (1.92-7.67)	0.61 (0.30-1.25)	0.90 (0.44-1.86)	0.785
Cohort Year 2019						
Overall	5535	13093	7.33 (6.00-8.96)			
No TPT	1290 (23.3)	2527	32.45 (26.13-40.29)	1	1	
TPT	4245 (76.7)	10566	1.33 (0.78-2.24)	0.04 (0.02-0.07)	0.08 (0.05-0.15)	<**0.001**
Cohort Year 2020						
Overall	1067	1698	25.92 (19.29-34.82)			
No TPT	652 (61.1)	1113	38.62 (28.64-52.07)	1	1	
TPT	415 (38.9)	584	1.71 (0.24-12.15)	0.04 (0.01-0.32)	0.10 (0.01-0.73)	**0.023**
Cohort Year 2021						
Overall	852	635	56.67 (40.87-78.56)			
No TPT	497 (58.3)	424	84.95 (61.27-117.76)	1	1	
TPT	355 (41.7)	212	7.83 (1.96-31.32)	0.09 (0.02-0.38)		

In 2018, the overall TB incidence further increased to 6.06 TB cases per 1,000 person-years, but the group-specific trend reversed, with TB incidence being lower among those who completed TPT (3.84 per 1,000 person-years), compared to those who did not receive TPT (6.28 per 1,000 person-years). However, the difference was not statistically significant (adjusted IRR = 0.90 (95% CI 0.44-1.86, p = 0.785).

By 2019, the TB incidence among the PLHIV who did not receive TPT significantly increased to 32.45 per 1,000 person-years, compared to only 1.33 per 1,000 person-years among PLHIV who completed TPT, with a significant adjusted IRR of 0.08 (95% CI 0.05-0.15, $p < 0.001$)

In 2020, the overall TB incidence surged to 25.92 per 1,000 person-years, with TB incidence among non-TPT individuals reaching 38.62 per 1,000 person-years, compared to 1.71 per 1,000 person-years among TPT recipients. The adjusted IRR was 0.10 (95% CI 0.01-0.73, $p = 0.023$).

By 2021, the non-TPT group experienced a much higher TB incidence (84.95 per 1,000 person-years), while no (00) TB cases were recorded among those who completed TPT, with an adjusted IRR of 0.09 (95% CI 0.02-0.38, $p = 0.001$).

Objective 2: Factors associated with TB disease among PLHIV who received TPT

Among the 6014 PLHIV who received and completed TPT, 33 (0.5%) PLHIV developed TB disease, compared to 162 (8.5%) out of the 1907 PLHIV who did not receive TPT (***See table 3).***

Table 3: Factors associated with TB disease among PLHIV who received and completed TPT compared to those who did not receive TPT over a 6year period at Baylor-Uganda clinic

	Did not Initiate TPT					Initiated and Completed TPT				
Variable	**None TB n(%)**	**TB Case n(%)**	**c RR (95% CI)**	**a RR (95% CI)**	**p-value**	**None TB n(%)**	**TB Case n(%)**	**c RR (95% CI)**	**a RR (95% CI)**	**P value**
Sex										
Female	1138 (93.7)	76 (6.3)				3599 (99.5)	18 (0.5)			
Male	607 (87.6)	86 (12.4)	1.98 (1.48, 2.66)	1.30 (0.90, 1.86)	0.156	2382 (99.4)	15 (0.6)	1.26 (0.64, 2.49)	0.97 (0.48, 1.99)	0.94
Age Group										
<10 years	377 (83.2)	76 (16.8)				367 (99.5)	2 (0.5)			
10 to 19 years	310 (91.7)	28 (8.3)	0.49 (0.33, 0.74)	0.80 (0.45, 1.41)	0.431	2091 (99.5)	11 (0.5)	0.97 (0.22, 4.34)	1.57 (0.22, 11.02)	0.652
20-29 years	485 (94.4)	29 (5.6)	0.34 (0.22, 0.51)	1.66 (0.68, 4.03)	0.264	1862 (99.3)	13 (0.7)	1.28 (0.29, 5.65)	2.60 (0.34, 19.73)	0.357
30-39 years	364 (96.0)	15 (4.0)	0.24 (0.14, 0.40)	1.75 (0.61, 4.99)	0.294	979 (99.7)	3 (0.3)	0.56 (0.10, 3.36)	1.38 (0.11, 16.85)	0.802
40-49 years	164 (95.4)	8 (4.6)	0.28 (0.14, 0.56)	1.86 (0.63, 5.52)	0.264	471 (99.4)	3 (0.6)	1.17 (0.20, 6.95)	3.90 (0.36, 41.75)	0.261
50+ years	45 (88.2)	6 (11.8)	0.70 (0.32, 1.53)	2.85 (0.72, 11.26)	0.136	211 (99.5)	1 (0.5)	0.87 (0.08, 9.54)	2.92 (0.21, 41.30)	0.428
BMI Category										
Normal	652 (95.9)	28 (4.1)				2220 (99.4)	13 (0.6)			
Underweight	706 (85.7)	118 (14.3)	3.48 (2.33, 5.19)	1.84 (1.08, 3.13)	**0.025**	2957 (99.4)	17 (0.6)	0.98 (0.48, 2.02)	1.25 (0.44, 3.60)	0.678
Overweight	237 (97.9)	5 (2.1)	0.50 (0.20, 1.29)	0.46 (0.15, 1.37)	0.163	788 (99.6)	3 (0.4)	0.65 (0.19, 2.28)	0.87 (0.25, 3.00)	0.829
MUAC Category										
<12	125 (72.3)	48 (27.8)				98 (99.0)	1 (1.0)			
≥12	1452 (93.6)	100 (6.4)	0.23 (0.17, 0.32)	0.44 (0.26, 0.73)	**0.002**	5876 (99.5)	32 (0.5)	0.54 (0.07, 3.89)	0.57 (0.07, 4.87)	0.604
ART Duration (years)										
<5	1121 (93.6)	77 (6.4)				3563 (99.4)	22 (0.6)			
5–9 years	196 (94.7)	11 (5.3)	0.83 (0.45, 1.53)	0.57 (0.26, 1.23)	0.15	1803 (99.6)	7 (0.4)	0.63 (0.27, 1.47)	0.67 (0.25, 1.83)	0.437
10+ years	79 (96.3)	3 (3.7)	0.57 (0.18, 1.77)	0.35 (0.10, 1.19)	0.092	611 (99.3)	4 (0.7)	1.06 (0.37, 3.07)	0.93 (0.22, 3.85)	0.914
Regimen Backbone										
AZT/3TC	309 (95.67)	14 (4.33)				2,491 (99.8)	5 (0.2)			
ABC/3TC	576 (84.09)	109 (15.91)	3.67 (2.14, 6.30)	1.30 (0.68, 2.49)	0.428	1,569 (98.9)	18 (1.1)	5.66 (2.11, 15.22)	5.29 (1.40, 20.05)	**0.014**
TDF/3TC	853 (95.63)	39 (4.37)	1.01 (0.56, 1.83)	0.67 (0.28, 1.57)	0.353	1,903 (99.4)	10 (0.5)	2.61 (0.89, 7.62)	1.55 (0.30, 7.89)	0.599
Other	3 (100.00)	0 (0.00)	NE	NE	<0.001	18 (100.00)	0 (0.0)	NE	NE	<0.001
Regimen Anchor Base										

INSTI (DTG-based)	277 (93.3)	20 (6.7)				400 (98.8)	5 (1.2)			
NNRTIs (EFV-based)	694 (93.7)	47 (6.3)	0.94 (0.57, 1.56)	1.04 (0.58, 1.85)	0.905	2,998 (99.5)	14 (0.5)	0.38 (0.14, 1.04)	0.20 (0.05, 0.74)	**0.016**
NNRTIs (NVP-based)	166 (96.5)	6 (3.5)	0.52 (0.21, 1.27)	0.79 (0.31, 2.03)	0.618	1,154 (99.7)	3 (0.3)	0.21 (0.05, 0.88)	0.14 (0.02, 0.97)	**0.047**
PI-based (ATV/r)	134 (94.4)	8 (5.6)	0.84 (0.38, 1.85)	1.31 (0.51, 3.37)	0.574	387 (98.2)	7 (1.8)	1.44 (0.46, 4.50)	0.43 (0.11, 1.67)	0.222
PI-based (LPV/r)	463 (86.2)	74 (13.8)	2.05 (1.27, 3.29)	0.68 (0.35, 1.35)	0.273	1,016 (99.6)	4 (0.4)	0.32 (0.09, 1.18)	0.08 (0.02, 0.44)	**0.004**
Triple NRTIs (ABC/3TC)	5 (41.7)	7 (58.3)	8.66 (4.57, 16.41)	1.74 (0.64, 4.73)	0.279	19 (100.00)	0 (0.00)	NE	NE	**<0.001**
WHO Stage										
I	575 (97.5)	15 (2.5)				1,360 (99.7)	4 (0.3)			
II	253 (94.4)	15 (5.6)	2.20 (1.09, 4.44)	1.66 (0.77, 3.54)	0.193	1,719 (99.3)	12 (0.7)	2.36 (0.76, 7.31)	2.66 (0.71, 9.96)	0.146
III	232 (87.9)	32 (12.1)	4.77 (2.63, 8.65)	2.76 (1.40, 5.45)	**0.004**	2,031 (99.5)	11 (0.5)	1.84 (0.59, 5.76)	2.19 (0.60, 8.02)	0.235
IV	305 (80.9)	72 (19.1)	7.51 (4.37, 12.91)	2.24 (1.13, 4.46)	**0.022**	848 (99.3)	6 (0.7)	2.40 (0.68, 8.47)	2.16 (0.44, 10.59)	0.344
Deferred	93 (87.7)	13 (12.3)	4.82 (2.36, 9.85)	1.74 (0.67, 4.50)	0.254	19 (100.0)	0 (0.0)	NE	NE	<0.001
Viral Load										
0-<50	414 (97.9)	9 (2.1)				4,026 (99.7)	11 (0.3)			
50-<500	115 (92.0)	10 (8.0)	3.76 (1.56, 9.05)	2.30 (0.85, 6.22)	0.101	791 (99.4)	5 (0.6)	2.31 (0.80, 6.62)	1.81 (0.65, 5.08)	0.257
500-<1000	21 (91.3)	2 (8.7)	4.09 (0.94, 17.85)	2.72 (0.68, 10.87)	0.156	121 (100.0)	0 (0.0)	NE	NE	**<0.001**
≥1000	268 (88.2)	36 (11.8)	5.57 (2.72, 11.38)	2.64 (1.27, 5.47)	**0.009**	980 (98.3)	17 (1.7)	6.26 (2.94, 13.32)	6.19 (2.80, 13.69)	**<0.001**
CD4 Count										
<200	229 (81.8)	51 (18.2)				916 (99.1)	8 (0.9)			
200–<350	202 (92.2)	17 (7.8)	0.43 (0.25, 0.71)	0.58 (0.34, 0.96)	**0.036**	729 (99.2)	6 (0.8)	0.94 (0.33, 2.71)	1.32 (0.43, 4.06)	0.633
350–<500	174 (94.1)	11 (5.9)	0.33 (0.17, 0.61)	0.49 (0.27, 0.90)	**0.021**	755 (99.5)	4 (0.5)	0.61 (0.18, 2.01)	0.85 (0.24, 2.99)	0.801
500+	768 (95.3)	38 (4.7)	0.26 (0.17, 0.39)	0.34 (0.23, 0.50)	**<0.001**	3333 (99.6)	15 (0.4)	0.52 (0.22, 1.22)	0.87 (0.30, 2.47)	0.787

NE: Not estimable due to the absence of participants in the TB case group

Age of 20years and above, and being male seemed to increase the risk of TB disease among PLHIV regardless of TPT status, although this was not statistically significant. Among the PLHIV who did not receive TPT, being underweight was significantly associated with TB disease (aIRR: 1.84; 95% CI 1.08- 3.13; p = 0.025). In contrast, BMI was not a significant predictor of TB disease among PLHIV who completed TPT. Among the PLHIV who did not receive TPT, MUAC ≥12 cm was significantly associated with lower risk of TB disease (aIRR=0.44; 95% CI: 0.26–0.73; p = 0.002). On the other hand, in the TPT group, MUAC had no significant association with TB disease (aIRR: 1.10; 95% CI: 0.38–3.22).

Duration on ART was not significantly associated with TB disease in either group. A slightly increased risk for TB was observed in both groups among PLHIV on ART for less than one year (aIRR=1.39 for non-TPT group; aIRR=1.66 for TPT completed group), and 1–3 years (aIRR: 1.23 non-TPT group; aIRR=1.28 for TPT completed group), although these findings were not statistically significant. Among the PLHIV who did not receive TPT, being on ART for 10 years or more seemed to reduce the risk of TB disease (aIRR: 0.45, 95% CI 0.10-1.19; p=0.092), although this was not statistically significant.

In the group that completed TPT, individuals on ABC/3TC as the ART backbone had a significantly higher TB risk (aIRR=5.29; 95% CI: 1.40–20.05, p= 0.014), more than five times higher compared to those on AZT/3TC. Among those who did not receive TPT, the ART backbone was not associated with TB disease.

In the group that completed TPT, the PLHIV on EFV-based regimens had a significantly lower TB risk (aIRR: 0.20; 95% CI: 0.05–0.74, P = 0.016) compared to those on DTG. Similar protective associations were observed for NVP (aIRR: 0.14; 95% CI: 0.02–0.97, P = 0.047) and LPV/r-based ART regimens (aIRR: 0.08; 95% CI: 0.02–0.44, P = 0.004). On the contrary, no anchor drug was significantly associated with TB risk in the PLHIV who did not receive TPT.

Among the PLHIV who did not receive TPT, individuals at WHO stage III (aIRR=2.76; 95% CI: 1.40–5.45, p=0.004) and stage IV (aIRR=2.24; 95% CI: 1.13–4.46, p=0.022) had significantly higher TB risk compared to those at stage I and II of HIV disease. However, in the group that completed TPT, WHO stage III and IV were not associated with risk of TB disease.

Viral load suppression emerged as a significant risk factor for TB in both groups. PLHIV with unsuppressed viral load (≥1000 copies/mL) had significantly higher TB risk, particularly among those who completed TPT (aIRR: 6.19; 95% CI: 2.80–13.69, p<0.001), and to a lesser extent in the non-TPT group (aIRR: 2.64; 95% CI: 1.27–5.47, p <0.001).

Having a CD4 count ≥200cells/µl was significantly associated with lower risk of TB disease among the PLHIV who did not receive TPT (CD4 200-<350cells/ul; aIRR=0.75, p=0.036; CD4 350–<500cells/ul; aIRR=0.63, p=0.021; CD4 >500cells/ul; aIRR=0.34, p<0.001). In contrast, among those who completed TPT, CD4 count was not significantly associated with TB disease.

Objective 3: Time to TB disease after completing TPT

The overall median survival time to TB disease after completing TPT PLHIV was 2.5 years (IQR: 2.3–2.8 years). The Kaplan-Meier curve survival below ***(figure 1a)*** illustrates the cumulative probability of PLHIV developing TB disease over a six-year period, after initiating TPT. The six-year survival rate of PLHIV who initiated TPT in this study was 99.3%.

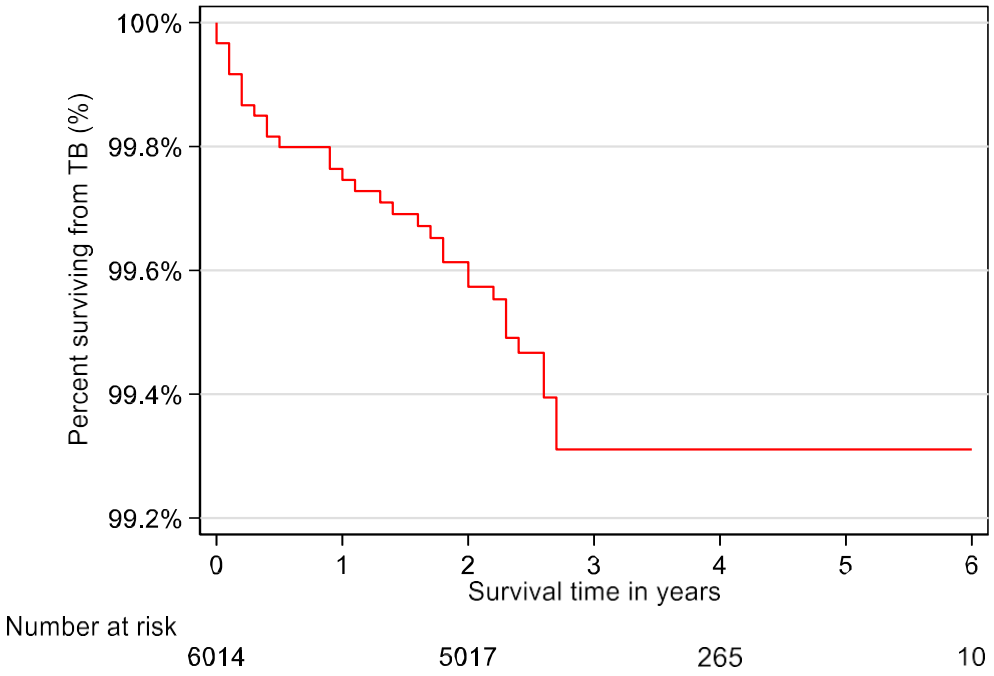

Figure 1(a) Survival curve showing the probability of PLHIV developing TB disease after initiating TPT

The cox proportional hazards model in ***table 4 below,*** revealed that there was no difference in the survival function between males and females, with both males and females exhibiting the same median survival time of 2.5 years.

Although males had a higher hazard ratio (HR = 1.23, 95% CI: 0.58–2.58, p = 0.590), the log-rank test revealed a significant difference in TB-free survival over time between the sexes (p = 0.023), suggesting a time-dependent divergence in risk (***see table 4).***

Age was a strong determinant of survival after completing TPT. Despite a relatively uniform median survival time across age categories (ranging from 2.4 to 2.6 years), individuals aged 40–49 years showed a significantly increased risk of TB disease (HR = 12.56, 95% CI: 1.30–

121.15, p = 0.029), which was supported by a statistically significant log-rank p-value (<0.001). Other adult age groups (20–29 years and 50+ years) also demonstrated elevated TB risk (HR = 5.69 and HR = 8.86, respectively), though not significant.

Table 4. Factors associated with the difference in survival time to TB disease after initiating and completing TPT among PLHIV

Variable	Median Time (Years)	IQR (p25-p75)years	HR (95% CI)	p-value	Log-rank p-value
Sex					**0.023**
Female	2.5	2.3 - 2.8	1	1	
Male	2.5	2.3 - 2.8	1.23 (0.58 - 2.58)	0.59	
Age Group (years)					**<0.001**
<10	2.4	1.4 - 2.8	1	1	
10-19	2.6	2.4 - 2.9	2.61 (0.49 - 13.86)	0.259	
20-29	2.5	2.3 - 2.8	5.69 (0.83 - 39.02)	0.077	
30-39	2.4	2.2 - 2.7	3.91 (0.41 - 37.34)	0.236	
40-49	2.4	2.1 - 2.7	12.56 (1.30 - 121.15)	0.029	
50+	2.5	2.2 - 2.8	8.86 (0.55 - 143.71)	0.125	
BMI Category					**<0.001**
Normal	2.5	2.3 - 2.8	1	1	
Underweight	2.6	2.3 - 2.9	1.07 (0.37 - 3.08)	0.907	
Overweight	2.4	2.0 - 2.7	0.37 (0.05 - 2.95)	0.351	
Duration on ART (years)					**<0.001**
<5	2.5	1.9 - 2.9	Reference		
05-09	2.5	2.3 - 2.8	0.30 (0.11 - 0.81)	0.018	
10+	2.5	2.3 - 2.8	0.39 (0.14 - 1.09)	0.072	
Backbone Regimen					**<0.001**
AZT/3TC	2.6	2.4 - 2.9	1	1	
ABC/3TC	2.5	2.3 - 2.8	2.24 (0.73 - 6.82)	0.157	
TDF/3TC	2.4	2.3 - 2.8	0.27 (0.06 - 1.15)	0.077	
TDF/FTC	2.5	2.3 - 2.8	0.89 (0.20 - 4.04)	0.879	
Other	2.5	2.3 - 2.8	NA	NA	
Anchor Regimen					**<0.001**
INSTI (DTG-based)	2.4	1.5 - 2.7	1	1	
NNRTIs (EFV-based)	2.6	2.4 - 2.9	0.86 (0.28 - 2.61)	0.784	
NNRTIs (NVP-based)	2.7	2.4 - 3.1	0.47 (0.05 - 4.91)	0.529	
PI-based (ATV/r)	2.4	2.3 - 2.7	1.21 (0.24 - 5.94)	0.818	
PI-based (LPV/r)	2.5	2.3 - 2.8	0.46 (0.11 - 1.88)	0.283	
WHO Stage					**<0.001**
I	2.4	1.7 - 2.8	1	1	
II	2.5	2.3 - 2.8	2.73 (0.84 - 8.84)	0.095	
III	2.5	2.3 - 2.8	1.64 (0.47 - 5.76)	0.437	
IV	2.5	2.3 - 2.8	1.73 (0.44 - 6.88)	0.436	
TPT Courses					0.668
1	2.5	2.3 - 2.8	1	1	
2+	2.3	1.9 - 2.8	38.45 (17.61 - 83.97)	<0.001	

Across the BMI categories, survival time did not vary significantly, with underweight individuals showing a slightly longer median survival time (2.6 years, IQR: 2.3–2.9), and overweight or obese individuals showing slightly shorter durations (2.4 years), though these differences were not statistically significant (HR = 1.07, p = 0.907). The log-rank p < 0.001 indicated that there is a significant difference TB-free survival over time between the different BMI categories.

Duration on ART was a significant determinant of TB risk. Those on ART for 5–9 years had a significantly lower hazard risk of developing TB (HR = 0.30, 95% CI: 0.11–0.81, p = 0.018). A similar protective, though not statistically significant effect was observed among individuals on ART for over 10 years (HR = 0.39, p = 0.072). The significant log-rank test (p < 0.001) shows a protective effect of longer ART exposure.

Regarding ART regimen, the median survival times were similar across groups (2.4–2.6 years). The log-rank test for backbone regimen differences was statistically significant (p < 0.001), suggesting variation in survival curves across regimens. The anchor regimen also showed variability in survival time, with INSTI-based regimens associated with the shortest median time (2.4 years) and NVP-based regimens with the longest (2.7 years). However, none of these differences were statistically significant (all p > 0.28), despite the log-rank test suggesting overall variation (p < 0.001).

WHO clinical stage at the time of TPT initiation was not significantly associated with TB risk. The median survival times were similar across WHO stages (2.4–2.5 years), but the log-rank p-value was significant (p < 0.001), indicating significant differences in survival experience across all WHO stages.

On the other hand, the number of TPT courses received emerged as a strong predictor. Individuals who received two or more courses had a significantly shorter median survival time (2.3 years, IQR: 1.9–2.8) and an extremely elevated risk of TB (HR = 38.45, 95% CI: 17.61–83.97, p < 0.001). However, this strong association from the Cox regression model was not supported by the log-rank test, which showed no statistically significant difference in survival curves between those who received one versus multiple TPT courses (p = 0.668).

7.0 DISCUSSION

In this study, the overall TB incidence among PLHIV increased from 3.24 TB patients per 1000-person years in 2016 to 56.67 TB patients per 1000-person years in 2021. The overall TB incidence in this study was very high compared to the TB incidence (0.189 per 1000-person years) that was reported among PLHIV in a Ugandan study by Kazibwe et al (48). This study showed increasing TB incidence among PLHIV who did not receive TPT (from 3.2 in 2016 to 84.95 TB cases per 1000person years in 2021), while the TB incidence among those who completed TPT reduced over the study period (from 4.34 in 2016 to 1.71 TB cases per 1000person years in 2020), with an increase in 2021. This trend is similar to what was reported in a similar comparison of PLHIV who received TPT and those who did not receive TPT in Ethiopia (57); although the TB incidence in our study was higher than the TB incidence reported among PLHIV in the Ethiopian retrospective cohort among those who initiated TPT (2.1 per 1000person years), but lower compared to the 71.8 per 1000person years for those who did not receive TPT in Ethiopia (57).The progressive reduction in TB incidence among PLHIV who completed TPT, emphasizes the evidence that TPT reduces the risk of TB among PLHIV.

In the earlier period 2016 to 2017, the incidence of TB was higher in the PLHIV who received TPT compared to those who did not initiate TPT. In this period, the TPT supply was very limited and often interrupted, which may have affected effectiveness of the TPT among those who received it. Additionally, TPT was prioritised for PLHIV who were close contacts of TB patients, who are most likely to progress from TB infection to TB disease. However, this trend was reversed in the period 2018 to 2021 where the TB incidence among PLHIV who initiated TPT declined and was lower compared to those who did not initiate TPT. This may be due to the augmented effect of optimal adherence to TPT and ART, and consistent access to TPT, which improves the effectiveness of TPT thus reducing risk of TB disease. There was also expansion of the eligibility criteria to include all PLHIV in care, from one year of age if they were confirmed not to have TB disease.

This study revealed that the incidence of TB disease significantly reduced by up to 96% among the PLHIV who completed TPT in 2019 to 2020, compared to those who did not receive TPT. The risk reduction observed among those who completed TPT was higher than the 55% risk reduction reported by Gavin Churchyard in South Africa among male HIV-infected miners who received TPT (57). The higher risk reduction for TB disease among PLHIV who received TPT may be due to the additional benefit of ART, which was reported to have reduced risk of TB disease among PLHIV in Ethiopia by 93.7% (57). This further emphasizes the need for ART adherence among PLHIV, even when they are taking TPT.

Although children below age 5years, living with HIV are at high risk of TB infection and progressing to TB disease, this study showed that older PLHIV aged 40 years and above are more than eight times at risk of TB disease. This is contrary to a study in India where age was not associated with Tb disease among PLHIV (58). Over the six year period, completing TPT significantly reduced the risk of TB disease by up to 96%, which aligns with evidence from the Indian study where PLHIV who did not receive TPT had higher odds of developing TB disease (58). Symptomatic HIV disease (HIV stage III to IV WHO disease) were significantly associated with TB disease, as in the Uganda study by Kazibwe, where PLHIV with WHO HIV stage III were four times at higher risk of developing TB disease compared with those of WHO stage II, although it was only among adult PLHIV who received TPT. The WHO stage III and IV are advanced HIV disease, and indicators of a defective immune system, increasing the risk of TB disease. Similar to the Thailand study by Gompol (61), PLHIV who did not receive TPT and had HIV viral non-suppression (viral load ≥10000copies/ml) were more than two times at increased the risk of TB disease. As reported by Samandari et al (62), higher CD4 count >500cells/ul, was strongly protective from TB disease among PLHIV who did not receive TPT. The higher CD4 count is an indicator of a strong immune system, that may surmount an effective immune response against TB infection, reducing progression to TB disease. The paradoxical finding was that PLHIV who completed TPT were six times more at risk of TB

disease. Having low BMI (<18.5-<25kg/m^2) increased the risk of TB disease by 84% among PLHIV who did not receive TPT. Good ART adherence improves immune recovery, achieves viral suppression which are associated with increase in BMI, and reduced TB risk (59, 60). This highlights the need for proper nutrition among PLHIV to reduce risk of TB disease. In a study among PLHIV in Ethiopia (50), BMI was not associated with TB disease, but the odds of developing TB were almost five times among PLHIV who did not receive cotrimoxazole prophylaxis (50). Due the change in the HIV treatment guidelines during the study period in Uganda, which limited cotrimoxazole prophylaxis to specific high-risk groups (newly enrolled in HIV care, pregnant and breastfeeding mothers, children <15years of age, on ART <1year, cotrimoxazole prophylaxis was not included in the multi-variable regression model. Although not found in other studies, PLHIV who received ABC/3TC as ART backbone were five times more at risk of developing TB disease. This may be due to the adherence to guidelines were ART changes or simplification were recommended for PLHIV diagnosed with TB.

The estimated median time to developing TB disease after completing TPT in this study was 2.5years, which was longer than the 18months (1.5years) reported by Kazibwe et al in a cohort of adult PLHIV in Uganda (48), 19months in an Ethiopian cohort on PLHIV (57), and 2.5months in a Kenyan cohort of PLHIV (59). The longer time to TB after receiving TPT may be due to the additional benefit of ART, and compliance to TB treatment guidelines that recommended repeat TPT for PLHIV who completed TB treatment. The short time to TB disease after TPT in the other PLHIV cohorts may be due to breakthrough TB (60), or missed TB diagnosis before initiating TPT. Breakthrough TB was less likely in our study most likely due to the routine TB screening at each clinic visit. Similar to the adult PLHIV in TASO HIV treatment centres, advanced HIV WHO clinical stage was significantly associated with higher risk of developing TB within the median time (48). None of these studies mentions recommended time after which to repeat a course of TPT among PLHIV, especially those identified as being at higher risk of developing TB even after receiving TPT.

7.1 Strengths

This study enrolled participants of all ages, compared to most studies which enrolled adults. Using the census approach, where all eligible participants were included in the study, eliminates the risk of sampling bias, which may be introduced by an unrepresentative sample, selected by traditional sampling methods.

This provided an opportunity to assess risk of TB disease among children and adolescents and adults living with HIV who received or did not receive TPT. The number of PLHIV enrolled in this study was high (7598), compared to other studies which mostly included between 1500 to 4000 PLHIV. The cohort study design was appropriate to study an outcome that requires a long follow-up period, and enabled the evaluation of risk within the limited time, compared to cross-sectional studies. This study compared TB incidence among PLHIV who received TPT with those who did not receive TPT, to clearly evaluate the benefit of TPT in reducing risk of TB disease among PLHIV.

7.2 Limitations

Although the cohort study design was appropriate to determine the primary outcome, the retrospective approach is prone to missing data and the non-random selection of study participants was a source of selection bias. The study site was a center of excellence (COE) for HIV care, which may also contribute to the limited external validity of the results, because the quality of HIV-TB care provided at a COE, may be different from that provided at other public and private health facilities.

This was a retrospective cohort study, with risk of missing data from available records. Missing data was handled by exclusion from analysis based on the extent and impact on the primary analysis. This study used routinely collected secondary data, which is prone to missingness of key variables. However, only patients with complete data for key variables were included in the analysis. The study period also included periods when there was limited supply of TPT drugs, periods on adequate supply. There were multiple TPT uptake campaigns run by the

ministry of health which increased TPT uptake, also affecting the number at risk of TB disease over the study period. This affected variation in the number of PLHIV who received TPT in the different years over the study period, contributing to the variation in number at risk of TB disease. The analysis was done to consider the numbers at risk of TB disease as those who had not received TPT in each year, instead of considering total number of PLHIV who did not receive TPT over the entire study period.

8.0 CONCLUSION

The TB incidence among PLHIV who received and completed TPT was lower compared to the TB incidence among PLHIV who did not receive TPT. This emphasizes the benefit of TPT in reducing risk of TB disease among PLHIV.

Even after completing TPT, viral non-suppression increases the risk of TB disease by six times. Among PLHIV who do not receive TPT, the risk of TB disease significantly increases with being underweight, having advanced HIV disease, unsuppressed viral load, and low CD4 count. On the other hand, having normal BMI, HIV viral suppression, and high CD4 count >200cells/ul, reduces the risk of TB among PLHIV, especially those that complete TPT.

These findings indicate that the median time to progression from completion of (TPT) to active TB disease among people living with HIV (PLHIV) was 2.5 years, suggesting that half of the number of PLHIV who initiated and completed TPT, developed TB within the first two and a half years after initiating TPT. This underscores the need for regular TB screening even after receiving TPT. There is also need for more longer-term targeted interventions to mitigate TB risk among PLHIV even after receiving TPT, especially among the high-risk groups such as those with non-suppressed HIV viral loads and low CD4 counts.

9.0 RECOMMENDATIONS

Health workers are to continue providing ART and TPT adherence support to PLHIV, so that they achieve and maintain viral suppression, and immunological recovery, which reduce their risk of TB disease. All PLHIV with advanced HIV disease, low CD4 count and un-suppressed viral load should be screened by health workers for TB disease, and offered TPT if found not to have TB disease. Health workers should continue providing nutritional support, ART adherence support and routine TB screening to PLHIV who have not yet received TPT, so as to reduce the risk of TB disease. The policy makers should review more evidence for consideration of repeat doses of TPT especially for PLHIV with viral load >1000copies/ml, CD4 count <500cells/ul, and advanced HIV disease (WHO stage III and IV). Implementation research or prospective studies are necessary, to determine the need and timing for repeat TPT doses is required.

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APPENDICES

Appendix I. Data Abstraction Tool

No.	Data item	Response. Circle or fill-in space	Comments/Instructions
1.	Patient ID	PIDC_____ AIDC	
2.	Age	_____months years	Age in years (if ≥1year) Age in months (if <1year)
3.	Sex	1. Male 2. Female	
4.	Pregnant during course of TPT	1. Yes 2. No 3. N/A	If female above
5.	On ART	1. Yes 2. No	On date of TPT start
6.	Duration on ART (if yes above)	_____years	On date of TPT start
7.	ART regimen	_____	On date of TPT start
8.	ART line	1. 1st 2. 2nd 3. 3rd	On date of TPT start
9.	WHO stage	1. I 2. II 3. III 4. IV	On date of TPT start
10.	History of TB disease before TPT initiation	1. Yes 2. No	
11.	History of TB symptoms before TPT initiation	1. Yes 2. No	
12.	History of close TB contact before TPT initiation	1. Yes 2. No	
13.	ART adherence on date of TPT initiation	1. Good (>95%) 2. Fair (85-94%) 3. Poor <85%)	
14.	Did the client start TPT?	1. Yes 2. No	If Yes, go to 15
15.	Date of TPT initiation	_____	DD/MMM/YYYY
16.	Reported side effects	1. Drug-induced hepatitis 2. Diarrhoea 3. Vomiting 4. Peripheral neuropathy 5. Jaundice 6. Psychosis 7. Other .....(specify)	
17.	History of TB symptoms during course of TPT	1. Yes 2. No	
18.	TPT outcome	1. Completed 2. Stopped 3. Died 4. Lost to follow-up 5. Unknown	
19.	Date of TPT completion	_____	DD/MMM/YYYY
20.	History of TB symptoms after completion of TPT	1. Yes 2. No	
21.	History of close TB contact after completion of TPT	1. Yes 2. No	
22.	Concurrent illnesses during course of TPT	1. _____ 2.	

		3. _____ 4.	
23.	Other concomitant medications taken during course of TPT	1. Yes 2. No	
24.	List concomitant medications taken during course of TPT	1. _____ 2. _____ 3. _____ 4.	
25.	Most recent Viral load from date of TPT initiation	1. _____copies/ml 2. Missing	
26.	Viral load suppression status	1. Suppressed (VL <1000copies/ml) 2. Non-suppressed (VL≥1000copies/ml)	
27.	Baseline CD4 count	1. _____cells/ul 2. Missing	On date of TPT initiation
28.	Most recent CD4 count	1. _____cells/ul 2. Missing	Preferably within 12months before TPT initiation
29.	ART delivery model	1. Community-based 2. Facility-based 3. Unknown	On date of TPT initiation
30.	Had interruptions during course of TPT	1. Yes 2. No	
31.	Reasons for TPT interruptions	1. Side effects 2. Missed doses (non-adherence) 3. Change in ART regimen 4. Clinical evaluation for presumptive TB status (had TB symptoms) 5. Other .....(specify)	If Yes above

Appendix 2. Approval Letter from School of Public Health Research Ethics Committee

MAKERERE UNIVERSITY
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COLLEGE OF HEALTH SCIENCES
SCHOOL OF PUBLIC HEALTH
Research and Ethics Committee

11th May, 2023

Ms. Pauline Mary Amuge
Master student, (2019/HD07/23670U)
School of Public Health, Makerere University

Re: Approval of a research Proposal titled: "Incidence and factors associated with tuberculosis disease among people living with HIV who completed tuberculosis preventive treatment: a retrospective comparative cohort study at Baylor Uganda Clinic"

This is to inform you that the Makerere School of Public Health Research and Ethics Committee (MakSPH-REC) has approved your study documents for the above referenced research study.

Please note that your study protocol number with MakSPH-REC is **186.** Please be sure to reference this number in any correspondence with MakSPH-REC. Note that your study was first approved by the MakSPH-REC on **11th/05/2023**, and therefore approval expires at every annual anniversary of this approval date. The current approval is therefore valid until: **11th/05/2024.**

Continued approval is conditional upon your compliance with the following requirements:

1) No other consent form(s), questionnaire and/or advertisement documents should be used. The consent form(s) must be signed by each subject prior to initiation of any protocol procedures. In addition, each subject must be given a copy of the signed consent form.

MAKERERE UNIVERSITY
SCHOOL OF PUBLIC HEALTH
APPROVED
VALID UNTIL
★ 11 MAY 2024 ★
RESEARCH & ETHICS COMMITTEE
P. O. BOX 7072, KAMPALA

2) All protocol amendments and changes to other approved documents must be submitted to MakSPH-REC and not be implemented until approved by MakSPH-REC except where necessary to eliminate apparent immediate hazards to the study subjects.

3) Significant changes to the study site and significant deviations from the research protocol and all unanticipated problems that may involve risks or affect the safety or welfare of subjects or others, or that may affect the integrity of the research must be promptly reported to MakSPH-REC.

4) For Masters Students in the School of Public Health, you are required to submit 2 copies of your proposal plus a letter of intention to submit a dissertation giving a period of 3 months to the School of Graduate Studies before you commence data collection

Please complete and submit reports to MakSPH-REC as follows:

a) Renewal of the study approval – complete and return the continuing Review Report – Renewal Request (Form 404A) at least 60 days prior to the expiration of the approval period. The study cannot continue until re-approved by MakSPH-REC.
b) Completion, termination, or if not renewing the project – send a final report within 90 days upon completion of the study.

Yours sincerely,

MAKERERE UNIVERSITY
SCHOOL OF PUBLIC HEALTH
APPROVED
VALID UNTIL
★ 11 MAY 2024 ★
RESEARCH & ETHICS COMMITTEE
P.O. BOX 7072, KAMPALA

Dr. Joseph Kagaayi

Chairperson: MakSPH- Research and Ethics Committee