INCIDENCE OF TUBERCULOSIS DISEASE AND ASSOCIATED FACTORS IN CHILDREN LIVING WITH HIV ON ANTIRETROVIRAL TREATMENT AND ISONIAZID PREVENTATIVE THERAPY IN DAR ES SALAAM TANZANIA: A RETROSPECTIVE COHORT STUDY

Edward Faustine Ngalya, MD

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INCIDENCE OF TUBERCULOSIS DISEASE AND ASSOCIATED FACTORS IN CHILDREN LIVING WITH HIV ON ANTI-RETRO VIRAL TREATMENT AND ISONIAZID PREVENTATIVE THERAPY IN DAR ES SALAAM TANZANIA: A RETROSPECTIVE COHORT STUDY.

By

Edward Faustine Ngalya

A Dissertation Submitted in (Partial) Fulfilment for the Requirement of Degree Master of Medicine (Paediatrics and Child Health) of

Muhimbili University of Health and Allied Sciences

October, 2024

CERTIFICATION

The undersigned certifies that they have read and, at this moment, recommend for examination by The Muhimbili University of Health and Allied Sciences, a dissertation entitled: **"*Incidence of Tuberculosis Disease and Associated Factors in Children Living with HIV on Anti Retroviral Treatment and Isoniazid Preventative Therapy in Dar es Salaam Tanzania*: A Retrospective** Cohort Study," in (partial) fulfillment of the requirement for the degree in Master of Medicine (Paediatrics and Child Health) of Muhimbili University of Health and Allied Sciences.

_____

Prof Karim Manji
(Supervisor)

Date: _____

_____

Dr. Evance Godfrey
(Co-Supervisor)

Date:_ _____

_____

Dr. Namala Mkopi
(Co-Supervisor)

Date:_ _____

DECLARATION AND COPYRIGHT

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DEDICATION

I dedicate this work to my beautiful children, Leroy, and Aurora Ngalya.

ABSTRACT

Introduction: Tuberculosis (TB) and Human Immunodeficiency Virus (HIV) continue to be major causes of morbidity and mortality among children due to their synergistic effects. Although significant strides have been made in reducing morbidity and mortalities due to HIV through strategies such as the '95-95-95' targets for HIV diagnosis, antiretroviral therapy (ART) initiation, and viral suppression among Children Living with HIV (CLHIV), TB remains a prevalent cause of morbidity and deaths. Isoniazid Preventive Therapy (IPT) is a critical intervention recommended by the World Health Organization (WHO) for high-risk groups, including CLHIV, to treat latent TB and prevent active TB disease. Despite its established efficacy in adults, evidence supporting IPT's effectiveness in reducing TB disease and mortality in children remains scarce.

Objective: This study was set to assess the impact of IPT on the incidence of TB disease and mortality among CLHIV aged 1-15 years who are on ART and attending high-volume Care and Treatment Clinics (CTCs) in Dar es Salaam, Tanzania.

Methodology: A retrospective open cohort study was conducted using data from the National AIDS Control Program (NACP)—Centre of Treatment and Care (CTC) database. The study included children aged 1-15 who were newly diagnosed with HIV and enrolled in care between January 1, 2019, and December 31, 2022. The cohort consisted of 480 eligible newly diagnosed CLHIV on ART. Participants were followed up for IPT use of which 268 received IPT and 212 did not receive IPT and assessed for the development of TB disease and mortality outcomes.

Results: Among the 480 participants, the median follow-up time was 6979.1 for IPT users and 1752.4 person-months for non-users. Most participants were aged 5-15 years (57.9%), with most attending Ilala Municipal Council clinics (46.3%) and Mbagala Rangi Tatu Health Centre (17.3%). A significant portion of the participants had advanced HIV (WHO clinical stages 3 and 4) (63.4%) and were underweight (26.3%). During the follow-up period, 13 CLHIV developed TB which 3 were diagnosed microbiologically, 3 clinically, 3 by chest x-ray 2 by combination of chest x-ray and microbiological evidence, most cases occurring within the first six months.

The incidence rate of TB showed higher trends among non-IPT users (228.3 cases per 100,000 CLHIV) compared to IPT users (129.0 cases per 100,000 CLHIV) however these were not statistically significant.

IPT usage significantly protected against mortality (cHR = 0.01, 95% CI: 0.001 – 0.08, P-value <0.001). Most deaths occurred within the first six months of follow-up (79.6%), with an incidence rate of 1649.6 per 100,000 CLHIV. The overall mortality rate was 639.3 per 100,000 CLHIV over 7664.6 person-months.

Conclusion and Recommendation: IPT used concurrently with ART significantly reduces the incidence of TB and mortality among CLHIV on ART. The incidence rate of TB was over 40% lower among IPT users, and mortality was reduced by more than 99% in the IPT group. These findings are in alignment with WHO recommendations and IPT use should be implemented consistently alongside other TB prevention strategies for all eligible CLHIV to reduce TB disease rates and improve survival outcomes effectively.

MUHTASARI

Utangulizi: Kifua kikuu (TB) na Virusi Vya Ukimwi (VVU) vimeendelea kuwa sababu kubwa za magonjwa na vifo miongoni mwa watoto kutokana na athari zao za pamoja. Ingawa mafanikio makubwa yamefanyika katika kupunguza magonjwa na vifo vinavyosababishwa na VVU kupitia mipango kama malengo ya '95-95-95' ya utambuzi wa VVU, kuanzishwa kwa matibabu ya kupambana na virusi (ART), na kudhibiti virusi miongoni mwa Watoto Wanaoishi na VVU (WWVVU), TB imebaki kuwa sababu kuu ya ugonjwa na vifo. Shirika la Afya Duniani (WHO) linapendekeza Tiba ya Kinga ya Isoniazid (IPT) kama hatua muhimu kwa makundi yaliyo katika hatari kubwa ikiwa ni pamoja na WWVVU kutibu maambukizi ya TB iliyofubaa na kuzuia ugonjwa wa TB hai. Mapendekezo ya sasa yalitolewa kutokana na ushahidi kwa watu wazima ambapo imeonekana kuwa na ufanisi, hata hivyo kuna ushahidi mdogo juu ya ufanisi wake wa dawa hizo katika kupunguza ugonjwa wa TB na vifo katika watoto.

Lengo: Utafiti huu ulilenga kutathmini athari za IPT kwenye kutokea kwa ugonjwa wa TB na vifo miongoni mwa WWVVU wenye umri wa miaka 1-15 walio katika matibabu ya ART na wanaohudhuria Kliniki za Matibabu na Huduma za za waathilika was VVU (CTC) zinazohudumia wateja wengi jijini Dar es Salaam, Tanzania.

Mbinu: Utafiti wa kikundi cha wazi kwa kutizama muda wa nyuma ulifanyika kwa kutumia taarifa kutoka kwenye Programu ya Taifa ya Kudhibiti UKIMWI (NACP)—katika vituo vya Matibabu na Huduma (CTC). Utafiti ulijumuisha watoto wenye umri wa miaka 1-15 waliogunduliwa upya na HIV na kuandikishwa kwenye utaratibu was matibabu kati ya Januari 1, 2019 na Desemba 31, 2022. Kikundi kilijumuisha watoto 480 waliogunduliwa upya na HIV na kuanza ART. Washiriki walifuatiliwa kuona kama walipata dawa za IPT ambapo 268 walipata IPT na 212 hawakupata IPT, kutathminiwa kama walipata ugonjwa wa TB na matokeo ya vifo.

Matokeo: Miongoni mwa washiriki 480, muda wa wastani wa ufuatiliaji ulikuwa miezi kati ya mtu 6979.1 kwa watumiaji wa IPT na miezi kati ya mtu 1752.4 kwa wasiotumia IPT. Washiriki wengi walikuwa na umri wa miaka 5-15 (57.9%) huku wengi wakihudhuria kliniki za Halmashauri ya Manispaa ya Ilala (46.3%) na Kituo cha Afya cha Mbagala Rangi Tatu (17.3%). Sehemu kubwa ya washiriki walikuwa na VVU ya hali ya juu (WHO

hatua ya 3 na 4) (63.4%) na walikuwa na uzito mdogo (26.3%). Wakati wa kipindi cha ufuatiliaji, watoto 13 wenye VVU walipata ugonjwa wa TB ambapo kesi nyingi zilijitokeza ndani ya miezi sita ya kwanza. Kiwango cha matukio ya ugonjwa wa TB kilikuwa juu zaidi kwa wasiotumia IPT (kesi 228.3 kwa kila watoto 100,000) ikilinganishwa na watumiaji wa IPT (kesi 129.0 kwa kila watoto 100,000). Matumizi ya IPT yalikuwa na ulinzi mkubwa dhidi ya vifo (cHR = 0.01 95% CI: 0.001 – 0.08, P-thamani <0.001). Vifo vingi vilitokea ndani ya miezi sita ya kwanza ya ufuatiliaji (79.6%) na kiwango cha matukio ya vifo kilikuwa 1649.6 kwa kila watoto 100,000. Kiwango cha jumla cha vifo kilikuwa 639.3 kwa kila watoto 100,000 zaidi ya miezi ya mtu 7664.6 cha ufuatiliaji.

Hitimisho na Mapendekezo: Matumizi ya IPT pamoja na ART yanapunguza sana matukio ya ugonjwa wa TB na vifo miongoni mwa WWVVU. Kiwango cha matukio ya TB kilikuwa chini kwa zaidi ya 40% miongoni mwa watumiaji wa IPT na vifo vilipungua kwa zaidi ya 99% katika kundi la IPT. Matokeo haya yanaendana na mapendekezo ya WHO na matumizi ya IPT yanapaswa kutekelezwa kwa uthabiti pamoja na mikakati mingine ya kuzuia TB kwa watoto wote wanaostahili ili kupunguza viwango vya ugonjwa wa TB na kuboresha matokeo ya maisha.

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LIST OF ABBREVIATIONS

ART – Anti-Retroviral Therapy

BAZ - BMI for Age Z-Score

CD4 - Clusters of Differentiation 4

CLHIV – Children Living with HIV

CTC - Care and Treatment Clinic or Centre

EPTB – Extra-Pulmonary Tuberculosis

HIV - Human Immunodeficiency Virus

INSTI - INtegrase Strand Transfer Inhibitors

IPT – Isoniazid Preventive Therapy/Treatment

IQR - InterQuartile Range

IRR – Incidence Risk Ratio

MC - Municipal Council

MNH – Muhimbili National Hospital

MoHCDGEC - Ministry of Health, Community Development, Gender, Elderly, and Children

NACP - National AIDS Control Program

NNRTI - Non-Nucleotide Reverse Transcriptase Inhibitors

PI - Protease Inhibitor

PLHIV – People Living with HIV

PTB – Pulmonary Tuberculosis

RAS - Regional Administrative Secretary

RR – Risk Ratio

TB – Tuberculosis

TPT - Tuberculosis Preventive Treatment

UNAIDS - United Nations Program on HIV/AIDS

VL – Viral Load

WAZ - Weight for Age Z-Score

WHO – World Health Organization

WHZ - Weight for Height Z-Score

DEFINITION OF KEY TERMS

IPT—Isoniazid Prevention Therapy/Treatment involves using Isoniazid monotherapy for high-risk groups to treat latent TB and prevent TB disease. These groups include CLHIV, who are not currently with TB disease.

95-95-95 – These are ambitious global targets established by the United Nations to eradicate the HIV/AIDS epidemic by 2030: 95% of individuals living with HIV should be aware of their HIV status, 95% of those who know their status should be receiving antiretroviral therapy (ART), and 95% of individuals on ART should achieve viral suppression.

High-Volume CTCs—Care and Treatment Clinics in Dar es Salaam, Tanzania, provide comprehensive care to over 1,500 PLHIV patients.

1.0 INTRODUCTION

1.1 Background

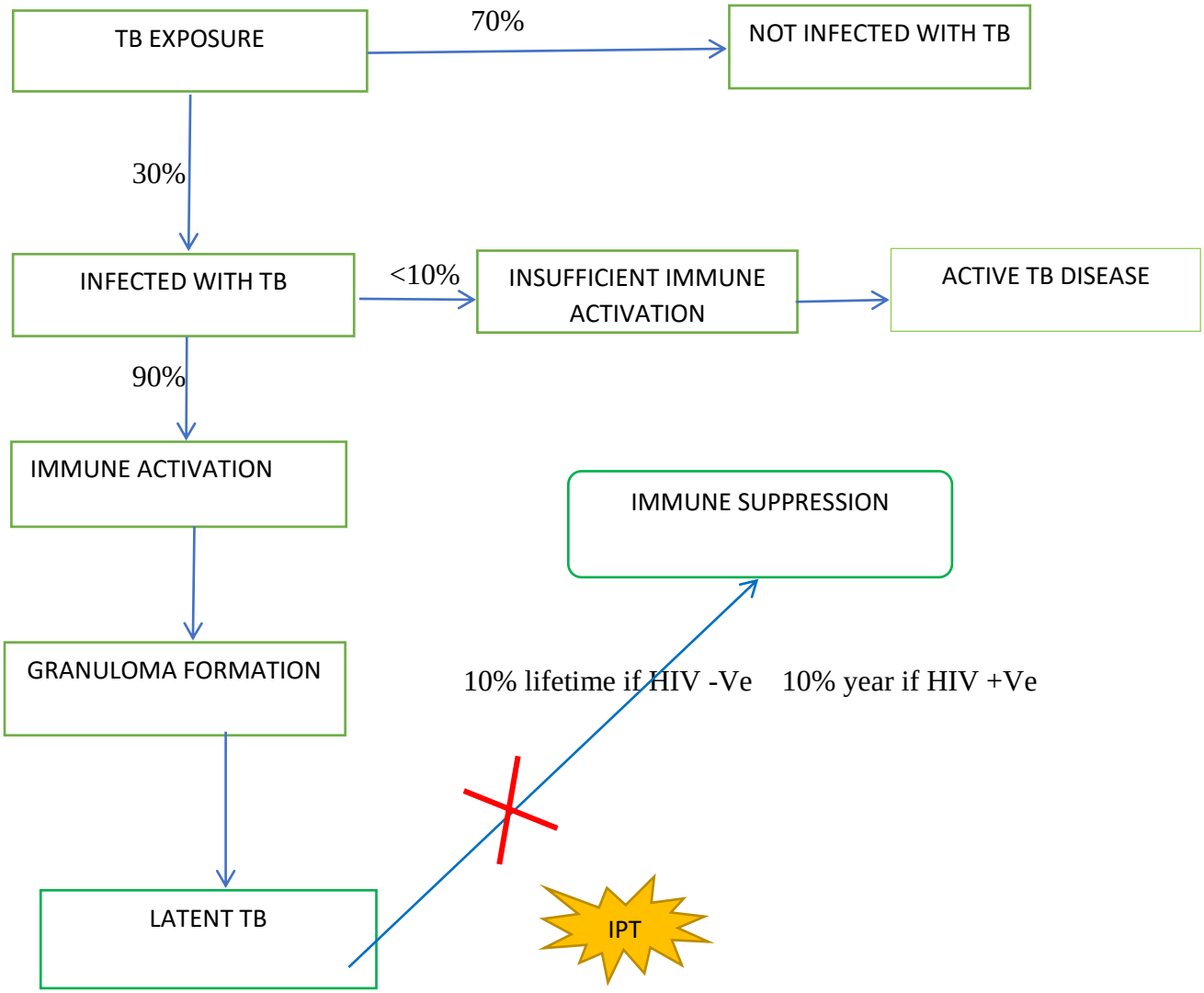
Tuberculosis (TB), caused by Mycobacterium tuberculosis (MTB), and Human Immunodeficiency Virus (HIV) have a profound and interdependent relationship, where each infection influences the progression of the other (1). Since the onset of the HIV epidemic in the 1980s, TB cases have surged worldwide, particularly in sub-Saharan African countries, which have been disproportionately affected due to the high burden of HIV in the region (2). TB is the leading opportunistic infection and a primary cause of mortality among People Living with HIV (PLHIV) (3,4). PLHIV are up to 30 times more likely to develop TB compared to individuals without HIV, making HIV the most significant risk factor for developing TB disease (1). Children under the age of 5 are among the high-risk groups for developing TB, with Children Living with HIV (CLHIV) facing an even greater risk(5).

MTB is primarily spread through aerosol droplets from an individual with active TB. The micro-organism then gains access to the alveoli in the lungs, where it is surrounded by macrophages and attracts other inflammatory cells to form a granuloma, leading to TB infection. Transmission is highly effective, as fewer than ten bacilli are sufficient to cause an infection. Fortunately, most individuals exposed to TB do not develop an infection (70%), and among those who do become infected (30%), the majority do not progress to TB disease. About 90% of those who develop a TB infection will have it contained within a granuloma, resulting in a latent infection (6). Granuloma formation restricts the bacterium's ability to replicate and spread. Individuals with latent TB infection do not exhibit symptoms or transmit the disease. However, approximately 10% of those infected with TB may progress to active TB disease.

Moreover, individuals with latent TB infection, if left untreated, have a 10% lifetime risk of reactivation and progressing to active TB disease (7). PLHIV who have latent TB infection face a 10% higher annual risk of reactivation from latent TB to active TB disease (7). In CLHIV, this risk is even higher due to low immunity(5). Treating latent TB with IPT in populations at heightened risk of reactivation and potential progression to TB

disease has proven to be the most effective strategy for reducing TB disease incidence globally (8).

Figure 1: Pulmonary TB natural course



Most people who get exposed to TB infection (70%) do not get infected, and those who get infected (30%), Only 10% of Tb infection results into TB disease from a primary infection but most(90%) undergo immune activation, form granuloma and end up with latent TB. People with Latent TB infection may remain so through out their life but carry a lifetime 10% risk of reactivation into TB disease. PLHIV carry a higher risk of 10% risk of reactivation into TB disease per year. CLHIV have even a higher risk than adults due to lower immunity.

As part of efforts to decrease morbidity and mortality from TB, the World Health Organization (WHO) recommends including 6months use of IPT in the comprehensive care package for all people living with HIV. Isoniazid prevents tuberculosis (TB) by inhibiting the synthesis of mycolic acids, essential components of the Mycobacterium tuberculosis cell wall, which weakens and kills the bacteria. It is particularly effective in eliminating actively replicating bacteria and is used to prevent latent TB infection from progressing to active disease, especially in high-risk individuals. Its ability to target and destroy TB bacteria makes it a crucial part of TB prevention and treatment. IPT is considered effective for preventing TB disease in this population (9,10). In 2011, the Tanzanian Ministry of Health (MOH) adopted and scaled up the use of IPT for people living with HIV (PLHIV), including children above the age of 1 year (11). Despite clear evidence found in adult patients, there is limited evidence supporting the benefit of IPT among CLHIV (12–14). This study will investigate the characteristics of children living with HIV (CLHIV) attending high-volume Centres of Treatment and Care (CTCs) in Dar es Salaam, Tanzania. It will assess the risk of developing TB disease among those who received IPT and compare it with CLHIV who did not receive IPT as part of their comprehensive HIV care.

1.2 Problem Statement

Research conducted globally on adult PLHIV has shown a decline in the incidence of TB disease and mortality when using IPT. However, there remains insufficient data on whether IPT has a similar effect among children living with HIV (CLIHIV), despite WHO's recommendations for its use.

CLHIV face the highest risk of developing TB disease and mortality from it. The current recommendation for IPT is primarily grounded in its observed effects in adult PLHIV (4,7,10,15–17). Pill burden is one of the significant challenges that affect the adherence to CLHIV on Antiretroviral therapy (ART), often leading to ART drug resistance and treatment failure(18,19)**.** For this reason, additional drugs given to CLHIV should have significant, evidence-based added advantage to this group (19–21).

1.3 Rationale

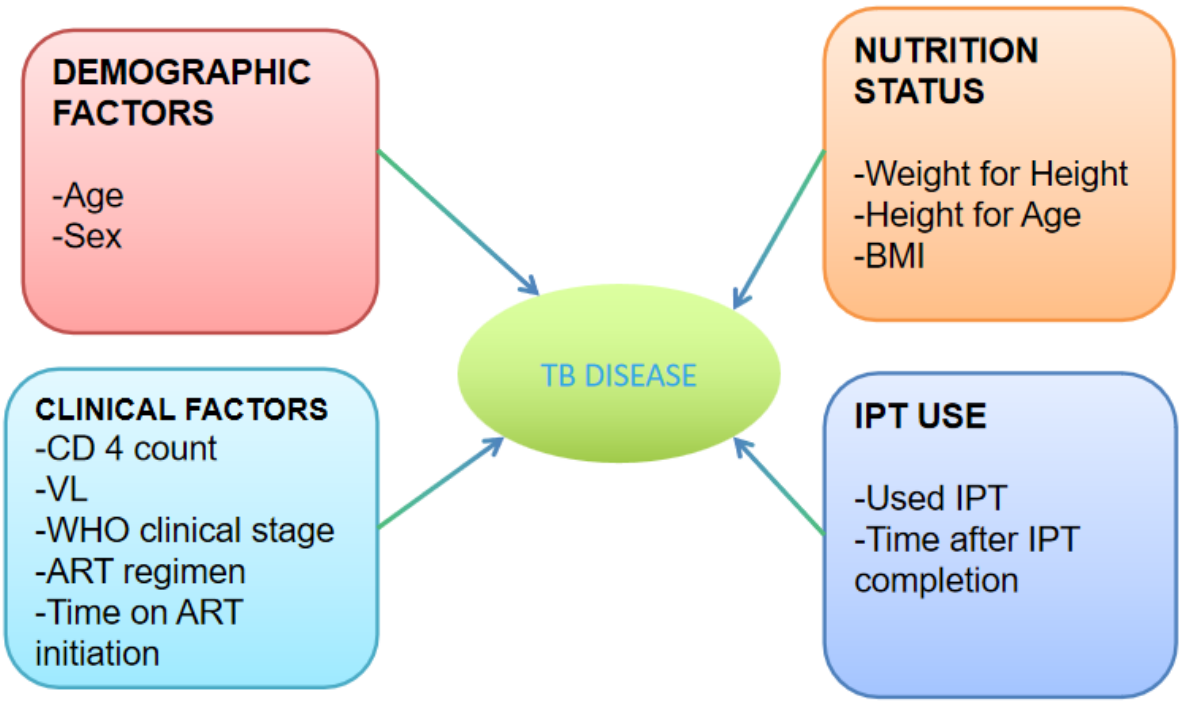
There is an urgent need for evidence supporting the use of IPT among children living with HIV (CLHIV). This study aimed to determine the difference in TB disease incidence between IPT users and non-users among CLHIV. Additionally, it sought to investigate whether IPT use in CLHIV yields significant reductions in TB disease incidence and mortality similar to those observed in adults. The findings aim to provide evidence-based recommendations and guidance on IPT use among CLHIV patients in Tanzania.

The evidence generated from this study aims to bolster interventions aimed at enhancing coverage and uptake of IPT among children living with HIV (CLHIV). By providing evidence-based recommendations to healthcare workers, parents, and caregivers of CLHIV, it seeks to support efforts to improve overall compliance with IPT. Additionally, the study aims to explore the relationship between IPT use and factors such as age, sex, CD4 count, viral load (VL), HIV WHO clinical stage, ART regimen, duration of ART, and duration of IPT.

These findings are expected to complement the efforts of the World Health Organization (WHO) and Ministry of Health (MOH) in achieving global targets, including reducing TB incidence by 80%, decreasing TB mortality by 90%, and alleviating TB-related household costs by 2030 (20).

1.4 Conceptual Framework

Figure 2: Conceptual framework of TB disease.



The conceptual framework illustrated in Figure 2 presents the relationship between various factors and the outcome of tuberculosis (TB) disease. At the core of the framework is the outcome, which is TB disease. Several factors potentially influence this outcome, grouped into four broad categories:

Demographic Factors: This category includes variables related to the patient's age and sex. These demographic characteristics are important determinants that may influence the susceptibility to TB disease.

Nutritional Status: Nutritional indicators, such as weight for height, height for age, and BMI, are included in this category. Adequate nutritional status plays a significant role in immune function, and malnutrition could increase vulnerability to TB disease.

Isoniazid Use: The framework considers the use of IPT as a preventive measure for TB. It captures whether IPT has been used or not, and if used, the time elapsed after IPT completion. This factor is critical in understanding the protective effects of IPT in relation to TB disease.

Clinical Factors: Several clinical elements are highlighted in this category, including viral load, CD4 count, WHO clinical stage, antiretroviral therapy (ART) regimen, and the duration on ART. These factors are essential in assessing the immune status and overall health condition of individuals, particularly those living with HIV, and how these influence the risk of developing TB disease.

This framework suggests that TB disease is influenced by a combination of demographic, nutritional, therapeutic, and clinical factors, each of which interacts in complex ways to either increase or decrease the likelihood of the disease occurring. The interactions among these factors can be crucial in understanding and addressing TB in populations at risk.

1.5 Research Hypothesis

Children living with HIV (CLHIV) who complete Isoniazid Preventive Therapy (IPT) are less likely to develop active tuberculosis (TB) compared to those who do not complete IPT.

1.6 Research questions

1. Does the use of IPT in CLHIV who are on ART have an additional reduction of the risk of development of TB disease?
2. Do demographic and clinical features of CLHIV on ART and their use of IPT have an association with the development of TB disease?
3. Does the use of IPT have an effect on the mortality of CLHIV?

1.7 Research objectives

1.7.1 Broad objective

To assess the effect of IPT on the incidence of TB disease and mortality of CLHIV on ART attending high volume CTC clinics in Dar es Salaam, Tanzania.

1.7.2 Specific Objective

1. To assess the effect of IPT on the reduction of the incidence of TB disease and CLHIV on ART.
2. To assess the association of demographic and clinical characteristics of CLHIV on ART with TB disease.
3. To assess the effect of IPT on the mortality of CLHIV on ART.

2.0 LITERATURE REVIEW

2.1 Epidemiology

In 2021, WHO estimated that 10.6 million people got TB disease, which included 1.2 million children. This marked an increase of 0.4 million cases compared to 2020. TB claimed the lives of approximately 1.6 million people in 2021, with 187,000 of those fatalities occurring among HIV-positive individuals. This contrasts with 1.5 million cases and 1.4 million deaths reported in 2020 and 2019, respectively (20). Tanzania ranks among the top ten countries worldwide contributing to 50% of people living with HIV (PLHIV). Additionally, it is among the 30 countries with the highest burden of tuberculosis (TB), accounting for over 87% of the global TB burden. Approximately 11% of TB cases globally are reported among children (20–22). Furthermore, the HIV burden is particularly severe in sub-Saharan Africa, which account over 66% of people living with HIV (25.6 million individuals) in 2021 (21,22). According to the Tanzania Ministry of Health, Community Development, Gender, Elderly and Children (MoHCDGEC), children accounted for 10% of all reported TB cases (23)

In 2021, Tanzania reported an estimated TB incidence of 132,000 cases, which represented a 32% decrease from the 2011 figures. Among these cases, 24,000 were among individuals living with HIV, and 22,000 affected children under 15 years of age (20). Despite the widespread use of ART among children living with HIV (CLHIV) and the fact that TB is preventable and treatable, it remains the leading cause of morbidity and mortality globally among PLHIV (24).

2.2 Latent Tb treatment

The WHO estimates that approximately a quarter of the global population has latent TB infection, which carries a risk of progressing (reactivating) to active TB disease (20). Latent TB infection is asymptomatic and not infectious, but treatment is essential to reduce the risk of progressing to active TB disease, especially in individuals with a higher risk of progression. In 1998, the WHO, in partnership with the Joint United Nations Programme on HIV/AIDS (UNAIDS), endorsed IPT as a critical intervention to combat TB among PLHIV. This intervention is now a fundamental component of the 3I's strategy for TB

prevention, which includes Intensified case finding and Infection control measures for TB (12).

IPT was recommended for individuals with latent TB infection who are at high risk of progressing to active TB disease. This recommendation aimed to reduce TB disease incidence and contribute to achieving the global target of reducing TB cases by 20% by 2020 (25). However, only about 50% of this global target was achieved by 2020, partly due to the disruptions caused by the COVID-19 pandemic (26). WHO recommends IPT for all children under the age of 5 years who have been exposed to TB, as well as for all children living with HIV (CLHIV), among other age groups (15). Initially, IPT was recommended to be administered once every two years for PLHIV. However, the current recommendation is to provide IPT once daily for six months, and it can be repeated if the child is exposed to an active TB case (11,27). The Tanzanian Ministry of Health adopted the WHO recommendation, which is included in the National Guidelines for the management of HIV. This recommendation applies to eligible children living with HIV above the age of 1 year, after ruling out TB disease (28). Before initiating IPT, children are screened for possible TB disease to prevent the initiation of monotherapy in patients already infected with TB. This precaution is crucial to mitigate the risk of developing drug resistance and to ensure timely treatment for those who require it (29). Treating latent TB with Isoniazid is not only an effective strategy for preventing TB disease but also a cost-effective approach to managing TB infection.

2.3 Use of IPT on incidence of TB disease

Studies conducted in adults, including a retrospective cohort study in Ethiopia, have shown the beneficial effect of IPT on reducing the incidence of TB. Among the 5407 patients analyzed, initiating IPT either before or during ART initiation led to a reduction in TB incidence by approximately 80% among people living with HIV (30). Another retrospective cohort study conducted in Dar es Salaam, Tanzania, involving 68,378 adult people living with HIV (PLHIV), demonstrated a significant decrease in TB disease incidence among those who used IPT while on ART. The incidence was found to be 48% lower compared to PLHIV who did not receive IPT(13)

There have been limited studies exploring whether similar effects are observed among children living with HIV, especially in sub-Saharan Africa. A prospective cohort study conducted in South Africa involving 263 children with HIV showed lower mortality rates among those taking IPT compared to those on placebo (8% vs. 16%), with a hazard ratio of 0.46 (95% CI). Additionally, the incidence of TB was lower among children using IPT compared to those on placebo (5 cases, 3.8% versus placebo) (13 cases 9.9%)(32).

However, a review paper on IPT involving 737 children living with HIV (CLHIV) below the age of 13 years, encompassing three randomized controlled trials conducted in South Africa and Botswana, concluded that IPT provided neither benefit nor harm in terms of mortality and the incidence of active TB (RR 1.45,95% CI 0.78 to 2.73 and RR 0.76,95% CI 0.50 to 1.14 respectively) (19,20,32,33).

A retrospective cohort study conducted in Kenya examined 606 HIV-infected children receiving routine HIV care at three HIV clinics, focusing on those initiated on IPT. The results indicated that 15 children (3%) on ART developed active TB while on IPT, with an overall mortality rate of 0.3% in the entire study cohort (35).

2.4 HIV-associated factors to the incidence of TB

TB disease remains a major contributor to illness and death globally, particularly affecting PLHIV. Numerous risk factors influence the development of TB disease in this population, such as age, sex, CD4 count, viral load (VL), WHO clinical stage, ART regimen, duration of ART, and time since completion of IPT.

Several studies have explored the relationship between age and TB disease among PLHIV. Research conducted in South Africa and Nigeria has highlighted that older age is linked to a higher risk of TB disease, particularly among females(36,37).

Sex is another identified risk factor for TB disease among people living with HIV. Research conducted in Thailand has indicated that males have a higher likelihood of developing TB disease compared to females(38). In contrast, a study conducted in Ethiopia reported that females were at a higher risk of developing TB disease compared to males among people living with HIV (39).

Research conducted in Zimbabwe and Ethiopia has extensively studied CD4 count and viral load (VL) as risk factors for TB disease among people living with HIV. Individuals with CD4 counts below 200 cells/mm³ are found to have an increased risk of developing TB disease. Similarly, individuals with high viral loads are more susceptible to developing TB disease (39,40).

The WHO clinical stage of HIV is recognized as a significant risk factor for TB disease among people living with HIV. Research conducted in Uganda revealed that individuals in advanced WHO HIV stages (III/IV) had a higher likelihood of developing TB disease compared to those in early stages (I/II) (41).

ART regimen, duration on ART, and duration after IPT are indeed significant factors influencing TB disease risk among people living with HIV. Research in Ethiopia has highlighted that individuals on a Tenofovir-based ART regimen have a reduced risk of developing TB disease compared to those on a Zidovudine-based regimen. Additionally, individuals who have been on ART for more than two years show a lower risk of TB disease compared to those on ART for less than two years (40,42).

2.5 Use of IPT on mortality of CLHIV

ART has indeed played a crucial role in reducing mortality rates among people living with HIV (PLHIV), including children. Nevertheless, despite the widespread availability of ART, mortality rates among PLHIV remain disproportionately high in resource-limited settings (43). Interventions like IPT have been implemented to further reduce the incidence of TB in people living with HIV (PLHIV) and potentially lower mortality rates. A review paper analyzing 13 studies highlighted reduced mortality among PLHIV who received IPT. The reported reduction in mortality ranged from 26% to 80%. Specifically, a study by Samandari et al. found a 33% decrease in mortality among PLHIV patients using IPT (44). Furthermore, the study conducted by Golub et al. reported a significant 80% reduction in mortality among people living with HIV (PLHIV) who used IPT (16). The review concluded that IPT is linked to a reduction in mortality among HIV-positive individuals who are also using ART. It was noted that the duration of IPT could influence the extent of this mortality reduction. However, the optimal duration of IPT remains uncertain,

highlighting the need for further research to determine the most effective duration for reducing mortality among PLHIV, particularly in CLHIV.

Understanding the interplay of these factors with TB disease is critical for enhancing TB prevention and management in CLHIV, and for developing targeted strategies. Currently, there is a significant lack of research on how these factors affect IPT usage in the pediatric population. Therefore, there is a pressing need to address this knowledge gap and conduct more studies focused on IPT use in children living with HIV.

3.0 METHODOLOGY

3.1 Study Design

A retrospective open cohort study was conducted using data from the Tanzania NACP-CTC database of preselected high-volume CTC clinics in the Dar es Salaam region, Tanzania.

3.2 Study Period

This study utilized data from all patients (children and adolescents) who were newly diagnosed as HIV-positive and enrolled in care, starting ART between January 1, 2019, and December 31, 2022.

3.3 Study Area

The study was conducted in the Dar es Salaam region, the largest city in Tanzania, located on the eastern coast along the Indian Ocean. Dar es Salaam is the principal port and central economic hub of Tanzania, with an estimated population of approximately 5,383,728 residents, according to the 2022 National Population and Housing Census. The study involved nine CTCs from three districts in Dar es Salaam: Ilala, Kinondoni, and Temeke, each with around 1.2 million residents. The CTCs were selected based on the number of clients they serve, specifically those with 1,500 or more PLHIV clients.

From the Ilala district, the selected CTCs were:

- Muhimbili National Hospital (MNH)
- Amana Regional Referral Hospital
- Mnazi Mmoja Hospital
- Buguruni Health Centre

From Temeke district, the selected CTCs were:

- Mbagala Rangi Tatu Hospital
- Temeke Regional Referral Hospital
- Upendano Dispensary

From the Kinondoni district, the selected CTCs were:

- Mwananyamala Regional Referral Hospital
- Magomeni Health Centre

Muhimbili National Hospital (MNH) serves as a teaching hospital affiliated with Muhimbili University of Health and Allied Sciences (MUHAS). Its CTC clinic, located in the main outpatient department building, provides care for 3,747 people living with HIV (PLHIV), including children, and operates on weekdays.

Additionally, Mnazi Mmoja Hospital's CTC serves 7,494 PLHIV, including children, also situated at the outpatient clinic of Mnazi Mmoja Hospital. Amana Regional Referral Hospital's CTC, located within the outpatient department, caters to 6,590 PLHIV, including children.

In the Ilala district, Buguruni Health Centre houses another CTC. In Kinondoni, the study includes Mwananyamala Regional Hospital's CTC serving 6,874 PLHIV, including children, and Magomeni Health Centre's CTC accommodating 5,054 PLHIV, including children, both located within their respective outpatient clinic buildings.

Further in Kinondoni, Temeke Regional Referral Hospital's CTC serves 6,638 PLHIV, including children, also within its outpatient clinic building. Nearby, Upendano Dispensary's CTC serves over 75,000 PLHIV, including children.

Moreover, Mbagala Rangi Tatu Hospital's CTC in Temeke serves 7,031 PLHIV, including children. All HIV CTC clinics are overseen by the Tanzania Ministry of Health, Community Development, Gender, Elderly and Children (MoHCDGEC) and utilize the same NACP database for all clients.

3.4 Study Population

The study analyzed data of all CLHIV aged 1-15 years who were diagnosed with HIV and enrolled in care from January 1, 2019, to December 31, 2022, in the preselected CTC clinics in Dar es Salaam, Tanzania.

3.5 Data source and study variables

This study utilized electronic data from the National AIDS Control Program (NACP) database, routinely collected at CTC clinical settings of all nine preselected CTC clinics in Dar es Salaam. A data review was conducted for all newly diagnosed HIV-positive patients on ART, aged 1-15 years, who were enrolled into care from January 1, 2019, through December 31, 2022. Data from all patients enrolled during the study period were extracted, and variables relevant to this study were compiled into a separate dataset for analysis.

The main focus of the study was the use of IPT during the study period. Therefore, patients' data were followed to track IPT usage. The primary outcome was the development of TB disease, and participants who had TB at ART initiation or within four weeks of ART initiation were excluded. Eligible participants were monitored for TB diagnosis and death throughout the study period. TB cases were cross-referenced with TB registers from the respective clinics.

Additional variables analyzed included age, sex, weight, height, ART regimen, duration on ART, WHO HIV clinical stage, CD4 cell count at ART initiation, and viral load at TB diagnosis or the most recent measurement before the end of the follow-up period. Z-scores for weight-for-height/length (WFHZ) and height-for-age (HFAZ) for children under five years and BMI for those over five years were calculated. Z-scores between the 3rd and 97th percentile were considered normal; below the 3rd percentile was defined as underweight, and above the 97th percentile was considered overweight. For TB-diagnosed patients, details on the diagnosis mode and type of TB disease were collected and analyzed. The status at the end of the follow-up time was recorded as alive, dead, or lost to follow-up (LTFU).

3.6 Data Analysis

Data extracted were cleaned and entered into IBM SPSS Version 27. Median and interquartile ranges were used for numerical variables, while proportions and frequencies summarized categorical variables. Kaplan-Meier analysis was used to analyse the rate of TB development, and the log-rank test was used to compare rates among groups. Univariate and multivariate Cox regression analyses were conducted to assess associated factors. P-values less than 0.05 were considered statistically significant.

3.7 Sample Size

The sample size included all children meeting the inclusion criteria in the preselected CTCs in Dar es Salaam.

3.7 Inclusion and Exclusion Criteria

3.7.1 Inclusion Criteria

CLHIV aged 1-15 years enrolled in HIV care and on ART from January 1, 2019, to December 31, 2022.

3.7.2 Exclusion Criteria

CLHIV aged 1-15 years enrolled in HIV care and on ART who were diagnosed with TB disease before, during, or within 28 days of ART initiation.

3.8 Ethical Issues

Ethical clearance for this study was obtained from the Research Ethics and Publications Review Committee of Muhimbili University of Health and Allied Sciences (MUHAS). Permission to conduct the study was also sought from the Director of Research, Training, and Consultancy at Muhimbili National Hospital (MNH) and the Medical Officers in charge of all participating health facilities. The study was deemed to pose no known risks to participants. All data were handled confidentially and were inaccessible to unauthorized personnel.

3.9 Limitations and Mitigations

As a retrospective study, some critical parameters, such as participant adherence, still needed to be fully explored, even though they may have significantly influenced the outcomes. Additionally, there were some missing data in the database, and viral loads were not taken at the beginning of participant follow-up, preventing analysis of their association with outcomes. Additionally, some important variables influencing outcomes, such as adherence to ART or socioeconomic factors, might not be thoroughly captured in a database, potentially limiting the study's ability to explore all associated factors of IPT outcomes

3.10 Data Dissemination

The results of this study will be presented to the Department of Paediatrics and Child Health, with the final report available at the MUHAS library. The findings will also be submitted to and made available at MNH, Mnazi Mmoja Hospital, Amana Regional Hospital, Mwananyamala Regional Hospital, Temeke Regional Hospital, Mbagala Rangi Tatu Hospital, Magomeni Health Centre, Buguruni Health Centre, and Upendano Dispensary. Additionally, the findings will be presented at scientific conferences and are expected to be published in a peer-reviewed medical journal.

4.0 RESULTS

The data of 523 newly diagnosed children living with HIV (CLHIV) enrolled into care and initiated on ART were assessed for eligibility. Forty participants were excluded due to having TB disease before, during, or within 28 days of enrolment. Additionally, three participants were excluded after later testing negative for HIV. The 480 participants, aged 1 to 15 years, who were followed up for IPT use and analysed for TB disease and mortality outcomes as summarised in Figure 3

Of note, most of the participants (59%) were active at the end of follow-up time, 22% were transferred out of CTCs of this study, 10% died, 7% were LTFU, and a few (2%) had missed appointments (Figure 4).

Figure 3: Flowchart of patient enrolment

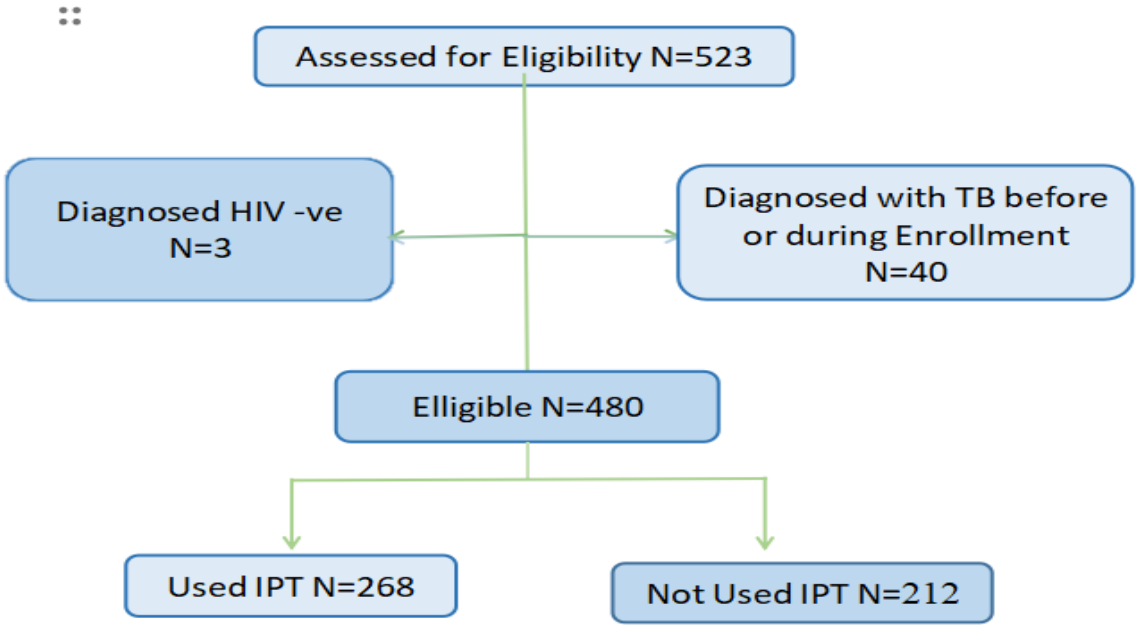
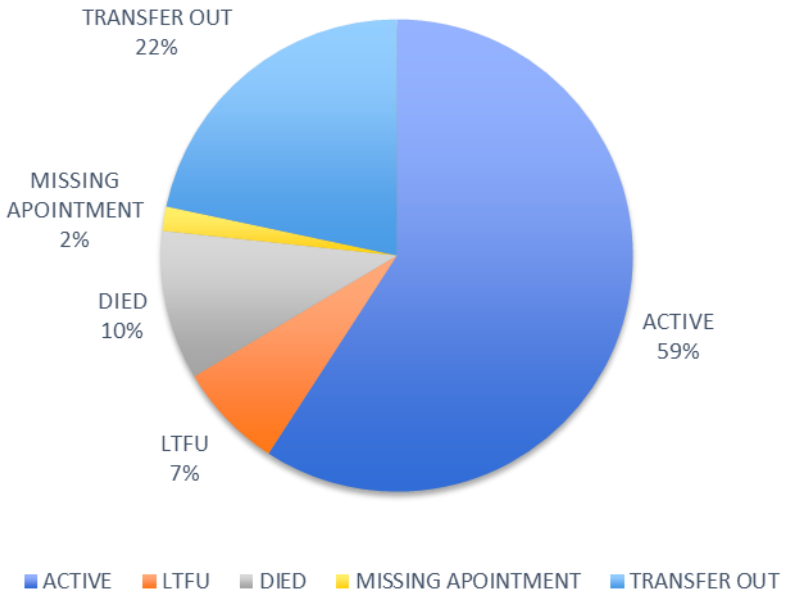


Figure 4: Pie chart summarising participant status at the end of the follow-up



4.1 Socio-demographics of newly diagnosed HIV-positive children on ART

Of the 480 study participants, 57.9% were aged 5 to 15, mainly from Ilala MC 46.3% and 17.3% attending Mbagala Rangi Tatu Health Centre CTC. The nutritional assessment showed that 50.4% were within the normal range, and 26.3% were underweight. Most participants (56%) achieved viral suppression <1000 copies/ml, though 40% had missing VL results. The majority (63.4%) had HIV WHO stages 3 and 4, with 60.0% having a CD4 count >350 cells/mm³. Many were on INSTI-based ART (71.4%), and 55.6% received Isoniazid preventive therapy during follow-up, as detailed in Table 1.

Table 1: Demographics and clinical characteristics of study participants

Variable	Number (n)	Percentage (%)
Age group (years)		
< 5	202	42.1
5 – 15	278	57.9
Median age in years (IQR)	**6 (2,12)**	
Sex		
Male	241	50.2
Female	239	49.8
Residence (Council)		
Ilala MC	222	46.3
Kinondoni MC	114	23.7
Temeke MC	144	30.0
Health facilities		
Amana was referred to a regional hospital	57	11.9
Buguruni health centre	39	8.1
Magomeni health centre	37	7.7
Mbagala Rangi tatu health centre	83	17.3
Mnazi Mmoja Health Centre	57	11.9
Muhimbili National hospital	69	14.4
Mwananyamala Regional Referral Hospital	77	16.0
Temeke Regional Referral Hospital	32	6.7
Upendano dispensary	29	6.0
Nutrition status (n = 478)		
Underweight	126	26.5
Normal	242	50.8
Overweight and obese	108	22.7
CD4 Count		
≤ 350 cells/mm³	192	40.0
>350 cells/mm³	288	60.0
WHO clinical stages		
Stage 1	73	15.2
Stage 2	102	21.3
Stage 3	234	48.8
Stage 4	70	14.6
missing	1	0.1
ART combination		
NNRTIs based combination	23	4.8
PIs based combination	113	23.5
INSTIs based combination	344	71.7
IPT use		
Yes	268	55.8
No	212	44.2
HIV VL category (n = 303)		
≤ 50 copies/ml	208	43.3
51- 1000 copies/ml	61	12.7
>1000 copies/ml	34	7.1
Missing	177	36.9

4.2 TB disease incidence rate among CLHIV

Most TB cases occurred within the first six months of follow-up, with an incidence rate of 347 per 100,000 CLHIV in non-IPT users compared to 264 per 100,000 CLHIV in IPT users without statistical significance. Overall, over 48 months, non-IPT users had a higher trends of TB incidence rate of 228 per 100,000 CLHIV compared to 128 per 100,000 CLHIV in IPT users Table 2.

Further analysis of TB incidence rates (Table 3) shows that for the first six months, it was 31% higher among non-IPT users (95% CI 0.19-7.73) compared to IPT users with no statistical significance (P-Value 0.72). Over the entire 48 months of follow-up, the risk was 99% higher among non-IPT users (95% CI 0.45–7.13); however, this also was not statistically significant (P-value 0.3).

Table 2: Incidence rate of TB among CLHIV

Time of follow-up	Total N	Person time (months)	TB n (%)	Incidence rate /100000 CLHIV	95% CI
0 – 6 months follow up					
IPT user	267	1517.7	4 (1.5%)	263.6	98.9 – 702.2
Non-IPT user	209	863.7	3 (1.43%)	347.4	112.2 – 1077.0
6 – 12 months follow up					
IPT user	236	1344.7	3 (1.27%)	223.1	72.0 – 691.7
Non-IPT user	102	444.9	1 (0.98%)	224.8	31.7 – 1595.6
>12 months					
IPT user	210	2193.1	2 (0.95%)	91.2	22.8 – 364.6
Non-IPT user	51	307.17	0 (0%)	0	
Overall, 48 months of follow-up					
IPT user	267	6979.1	9 (3.37%)	129.0	67.1 – 247.8
Non-IPT user	209	1752.4	4 (1.91%)	228.3	85.7 – 608.2

Table 3: TB disease incidence rates comparison among CLHIV on ART.

Time of follow-up/ Exposure – IPT use	cIR	95% CI	p-value
0 – 6 months follow up			
Non-IPT user	1.32	0.19 – 7.79	0.72
IPT user	Ref		
6 – 12 months follow up			
Non-IPT user	1.01	0.02 – 12.55	0.94
IPT user	Ref		
Overall, 48 months follow up.			
Non-IPT user	1.77	0.40 – 6.34	0.36
IPT user	Ref		

Key: cIR: crude Incidence Rate, Ref: Reference Category

4.3 Factors associated with TB disease incidence rate in CLHIV.

Throughout the follow-up, TB disease rates were consistently higher in children under five years compared to those aged 5-15 years. Male participants had higher TB rates than female participants. Among the three municipal councils, TB rates were highest in Temeke MC, followed by Kinondoni MC, and lowest in Ilala, particularly noticeable after the first year. Underweight participants (<3rd percentile) had higher TB rates, while those who were overweight (>97th percentile) had the lowest rates (Figure 5 a). Participants with advanced HIV disease had higher TB disease rates compared to those in earlier stages. Initially, TB disease rates were similar for participants with CD4 counts below and above 350 cells/mm³ but later increased for those below 350. Higher TB rates were observed in non-IPT users within the first 12 months, but rates later became higher in IPT users. Additionally, participants on INSTI-based ART regimens had higher TB disease rates compared to those on PI and NNRTI-based regimens (Figure b).

Figure 5a: Rates of occurrence of TB among CLHIV

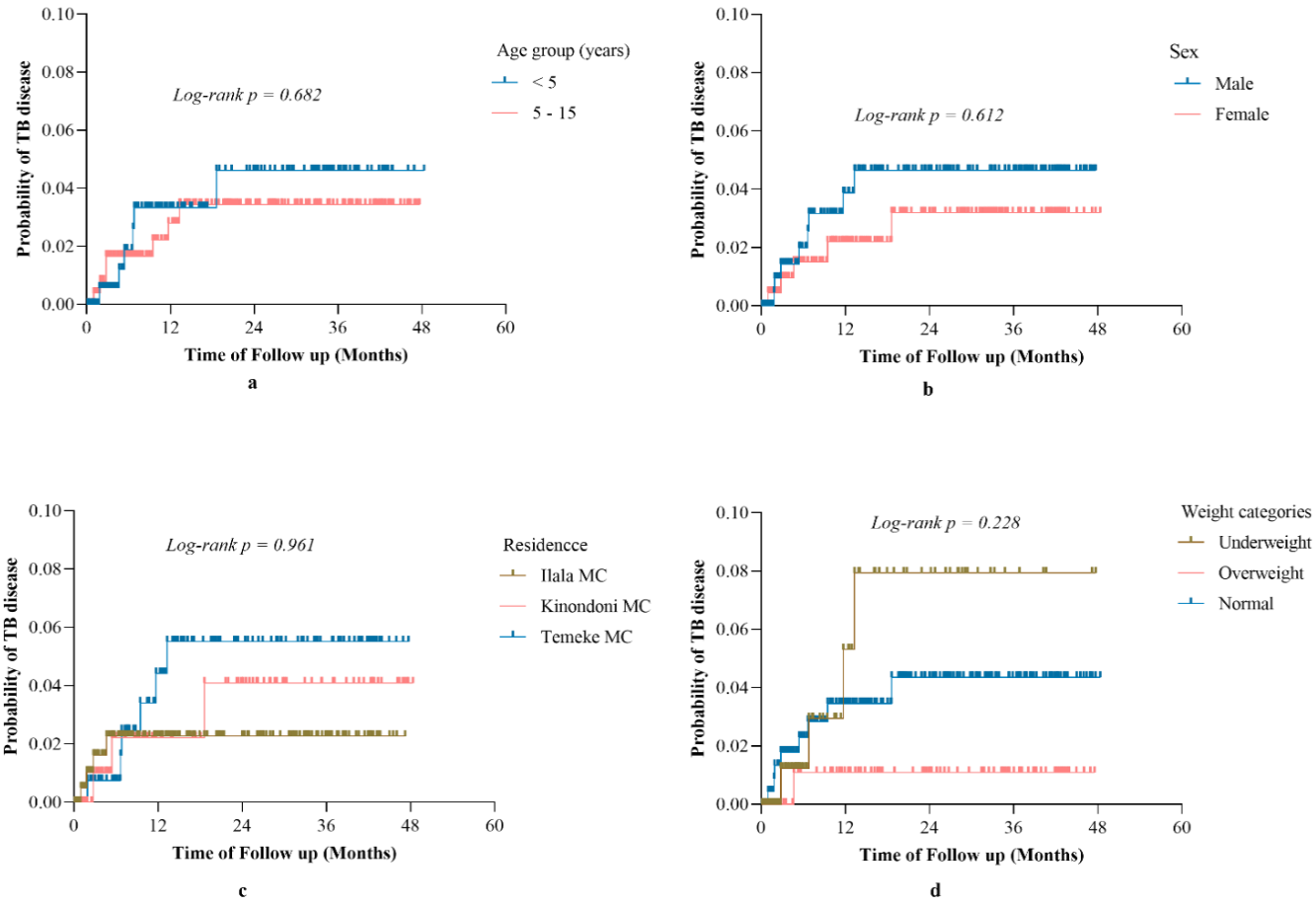
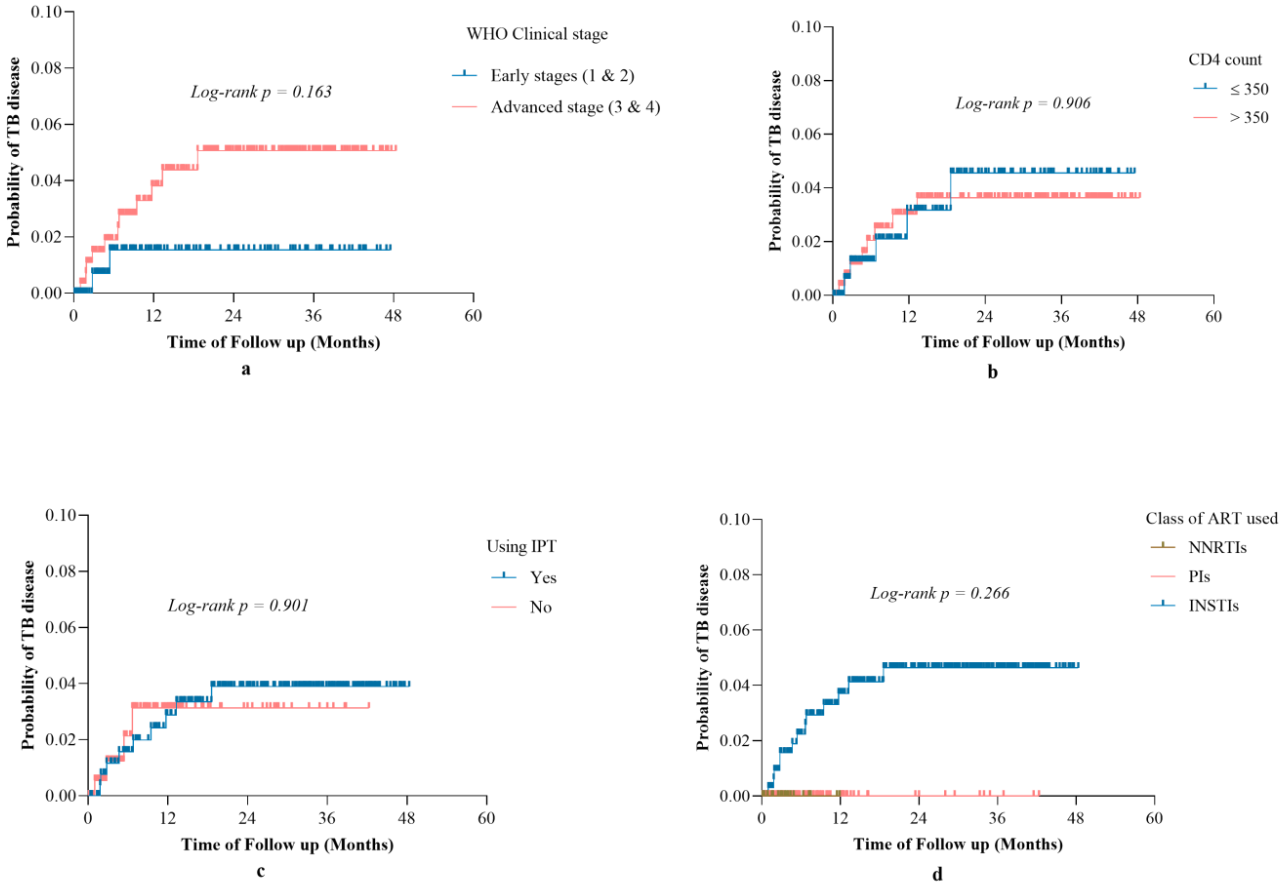


Figure 6b: Rates of occurrence of TB among CLHIV



4.4 Predictors for Tuberculosis Incidence Rate in CLHIV.

In the multivariate survival analysis using Cox regression, the analysis had no statistical significance found a higher rate of TB disease among children under five years 1.74 times (p = 0.348, 95% CI 0.55 – 5.45), males 1.58 times (p = 0.441, 95% CI 0.49 – 5.06), IPT users were 1% protected from developing TB disease compared to non-IPT users (p = 0.994, 95% CI 0.28 – 3.49). Advanced WHO clinical stage participants were 3.3 times more likely to develop TB (p = 0.125, 95% CI 0.72 – 15.21) compared to those in earlier stages. Attending CTC in Temeke MC and Kinondoni MC by 2.21 times (p = 0.231, 95% CI 0.60 – 8.13) and 1.58 times (p = 0.554, 95% CI 0.35 – 7.23) higher rates, respectively. Underweight participants had a 1.13 times higher likelihood of developing TB (p = 0.855, 95% CI 0.31 – 4.11) compared to those with normal weight, while overweight participants were 80% less likely to develop TB (p = 0.133, 95% CI 0.02 – 1.64). Participants with CD4 counts ≤ 350 cells/mm³ were 7% less likely to develop TB than those with higher counts (p = 0.895, 95% CI 0.29 – 2.92) (Table 4).

Table 4: Univariable and Multivariable analysis of the factors associated with the TB infection

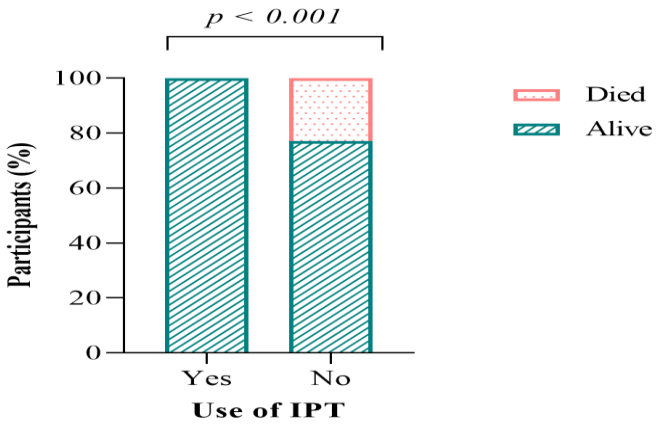
		Univariable analysis			Multivariable analysis		
Variable	**Category**	**cHR**	**95% CI**	**p-value**	**aHR**	**95% CI**	**p-value**
Age (years)	< 5	1.26	0.42 – 3.75	0.68	1.74	0.55 – 5.45	0.35
	5 – 15	Ref					
Sex	Male	1.55	0.51 – 4.73	0.44	1.57	0.49 – 5.03	0.45
	Female	Ref					
Residence	Temeke MC	1.86	0.52 – 6.58	0.34	2.19	0.60 – 8.07	0.24
	Kinondoni MC	1.30	0.29 – 5.83	0.73	1.57	0.35 – 7.19	0.56
	Ilala MC	Ref					
Nutrition	Underweight	1.48	0.44 – 4.89	0.53	1.14	0.31 – 4.14	0.85
	Overweight	0.25	0.03 – 2.01	0.19	0.20	0.02 – 1.64	0.13
	Normal	Ref					
CD4 count	≤ 350 cells/mm³	1.08	0.35 – 3.29	0.90	0.93	0.30 – 2.94	0.91
	>350 cells/mm³	Ref					
WHO stage	Stages 3 & 4	2.80	0.62 – 12.62	0.18	3.31	0.72 – 15.26	0.12
	Stages 1 & 2	Ref					
Use of IPT	Yes	0.91	0.277 – 3.07	0.89	0.99	0.28 – 3.47	0.99
	No	Ref					

Key: cHR: Crude Hazard Ratio, aHR: Adjusted Hazard Ratio, Ref: Reference Category

4.5 Mortality rate among CLHIV.

All mortality in this study occurred among non-IPT users over the entire follow-up period (see Figure 6). The overall follow-up time was 7664.6 person-months. The incidence rate of mortality was inversely proportional to follow-up time; mortality was highest within the first six months of follow-up, accounting for 79.6% of all deaths, with an incidence rate of 1649.6 per 100,000 CLHIV, for follow-up periods of 6 to 12 months and 12 to 24 months, it was 339.2 and 117.34, respectively. The overall mortality rate was 639.3 per 100,000 CLHIV (see Table 5).

Figure 7: Proportion of mortality among IPT users and non-IPT users.



IPT use	Alive	Died
Yes(n=267)	100%	0%
No (=209)	77.1%	22.9%

Table 5: Mortality rate

Time of follow-up	Total N	Person time (months)	Death n (%)	Incidence rate /100000 CLHIV	95% CI
0 – 6 months follow up	335	2364.2	39 (11.6%)	1649.61	1205.26 - 2257.78
6 – 12 months follow-up	257	1768.9	6 (2.3%)	339.19	152.39 – 755.00
12 – 24 months follow up	138	2255.57	4 (2.8%)	177.34	66.56 – 472.50
Overall, 48 months of follow-up	479	7664.6	49 (10.2%)	639.30	483.18 – 845.88

4.6 Predictors of mortality rate in CLHIV.

The multivariable Cox regression analysis revealed several significant associations with mortality among CLHIV. The use of IPT demonstrated remarkable protection against mortality (>99.9%) with a significant P-value (P < 0.001, 95% CI 0.001–0.08). Underweight children exhibited a five-fold increased likelihood of mortality compared to those with normal weight percentiles (P < 0.001, 95% CI 2.32–10.90), while overweight children demonstrated an 80% reduced likelihood of death (P = 0.040, 95% CI 1.05–7.58). Participants with a CD4 count of 350 cells/mm³ or lower were 2.56 times more likely to die than those with higher counts (P = 0.002, 95% CI 1.40–4.70). Although not statistically significant, those in WHO clinical stages 3 and 4 showed a 2.27 times increased likelihood of mortality compared to stages 1 and 2 (P = 0.020, 95% CI 0.72–15.21). Children on NNRTI had a substantially higher risk of death (13.14 times) than those on other ART regimens (P < 0.001, 95% CI 4.57–37.80). Other factors, such as age (<5 years) and gender (male), showed no statistically significant associations with mortality Table 6.

Table 6: Univariable and Multivariable analysis of the factors associated with mortality.

		Univariable analysis			Multivariable analysis		
Variable	**Category**	**cHR**	**95% CI**	**p-value**	**aHR**	**95% CI**	**p-value**
Age (years)	< 5	1.36	0.78 – 2.38	0.280	0.92	0.50 – 1.70	0.796
	5 – 15	Ref					
Sex	Male	1.09	0.62 – 1.91	0.771	0.79	0.44 – 1.42	0.423
	Female	Ref					
Residence	Temeke MC	0.69	0.35 – 1.39	0.300	1.00	0.49 – 2.06	1.000
	Kinondoni MC	0.99	0.50 – 1.95	0.978	1.12	0.54 – 2.30	0.764
	Ilala MC	Ref					
Nutrition	Underweight	8.96	4.26 – 18.82	< 0.001	5.03	2.32 – 10.90	< 0.001
	Overweight	1.86	0.72 – 4.82	0.203	2.82	1.05 – 7.58	0.040
	Normal	Ref					
CD4 count	≤ 350 cells/mm³	2.84	1.59 – 5.08	< 0.001	2.56	1.40 – 4.70	0.002
	>350 cells/mm³	Ref					
WHO stage	Advanced stages (3 & 4)	1.87	0.96 – 3.66	0.067	2.27	1.14 – 4.52	0.020
	Early stages (1 & 2)	Ref					
Use of IPT	Yes	0.01	0.001 – 0.08	< 0.001			
	No	Ref					
ART	NNRTIs	17.94	6.80 – 47.33	< 0.001	13.14	4.57 – 37.80	< 0.001
	PIs	11.92	5.98 – 23.76	< 0.001	10.51	4.74 – 23.31	< 0.001
	INSTIs	Ref					

Key: cHR: Crude Hazard Ratio, aHR: Adjusted Hazard Ratio, Ref: Reference Category

5.0 DISCUSSION

This study aimed to investigate the incidence of TB disease and associated factors among CLHIV on ART and IPT in Dar es Salaam, Tanzania. The findings provide insights into the protective effects of IPT on mortality and its non-significant impact on TB incidence, as well as highlight the demographic and clinical factors influencing these outcomes.

5.1 Demographic and Clinical Characteristics

The majority of study participants were aged 5–15 years, with many presenting in advanced stages of HIV (WHO stages 3 and 4), reflecting late HIV diagnosis and delayed initiation of ART. This is consistent with findings from other sub-Saharan African studies, where late presentation remains a major challenge (10,45,46). This highlights that there might be similar challenges in early HIV diagnosis in children and the critical importance of identifying and addressing gaps to ensure HIV early diagnosis in children to improve outcomes(47). Late HIV diagnosis delays ART initiation thus children with lower immunity have increased risk of developing TB disease(1,48). Most participants were from the Ilala Municipal Council, which could suggest potential differences in healthcare access or HIV awareness across different districts in Dar es Salaam and the importance of making appropriate consideration during resource allocations. INSTIs-based ART regimen was the most prescribed in CLHIV followed by PIs-based combinations, with a smaller percentage of NNRTIs-based regimens, highlighting the evolving landscape of ART prescription practices from PI-based regime used for many years to INSTIs-based regimen as the first line ART in Tanzania (49). Nutritional assessment revealed a notable proportion of children being underweight, indicating there are potential challenges in nutrition and overall health status among the pediatric population. There is a significant proportion of children suffering from malnutrition in Tanzania, with disproportionately higher in CLHIV which has implications for outcome of their management(50). Similar findings were reported in several other studies highlighting the need to allocate more resources to mitigate or curb malnutrition in this venerable population(51).

5.2 Tuberculosis disease incidence and use of IPT.

The study found a lower incidence of TB among IPT users compared to non-users, but this reduction was not statistically significant. This suggests that while IPT is associated with a downward trend in TB development, other factors, including adherence and duration of follow-up, may play a role in determining its effectiveness in preventing TB. Despite the lack of statistical significance, these results align with global recommendations advocating for IPT use in high-risk groups like CLHIV to prevent TB, supporting its role as a crucial intervention in pediatric HIV care (8). Similar findings were observed in CLHIV in sub-Saharan Africa in settings like ours (35,45).]. The study also identified a higher occurrence of TB disease among children aged < 5 years compared to those aged 5–15 years, emphasizing the vulnerability of younger children to TB co-infection. Similar findings were observed in other studies, highlighting the need to identify shortfalls and emphasize preventive measures of TB disease in this age group (35). Male participants had a higher trends of development of TB disease compared to females, suggesting potential gender-specific factors contributing to TB susceptibility. This was also reflected in another similar study of CLHIV and TB disease; it is yet to be explored to understand what makes CLHIV in a much more vulnerable position of getting TB disease (5,31,35,52). TB occurrence varied across municipal councils, with higher rates observed in Temeke MC, highlighting potential geographical differences in TB burden and healthcare access and the need to redirect more resources to Temeke MC CTCs. Underweight children had a higher likelihood of developing TB, underscoring the association between malnutrition and increased vulnerability to infectious diseases such as TB; hence, all children with malnutrition should be screened for TB and HIV and vice versa. This association between TB disease and malnutrition has been reported multiple times in literature and other studies(51,53). The use of IPT was associated with a reduced risk of TB disease during the first 12 months of follow-up, indicating the effectiveness of IPT in TB prevention among HIV-positive children, which is in keeping with the current recommendation of the use of IPT to treat latent TB to prevent TB disease.

5.3 Mortality Rates

One of the most significant findings in this study is the protective effect of IPT on mortality. CLHIV who used IPT had a drastically lower risk of death, underscoring IPT's importance as a life-saving intervention. Mortality was notably highest within the first six months of follow-up, particularly among those not receiving IPT, suggesting that early intervention with IPT can be critical in improving survival outcomes. These findings are consistent with other studies in sub-Saharan Africa that have shown the profound impact of IPT in reducing mortality among HIV-infected populations (45). The study reported a high mortality rate, particularly within the first six months of follow-up, emphasizing the importance of early diagnosis and prompt initiation of ART.

Underweight status, advanced WHO clinical stages, and lower CD4 counts were identified as significant risk factors for mortality, highlighting the importance of addressing nutritional needs and timely initiation of HIV treatment(51). Children on NNRTIs-based ART regimens had a significantly higher risk of mortality compared to other regimens, suggesting the need for further investigation into the effectiveness and safety of different ART combinations as well as initiation of ART regimens that have proven to be effective with early viral suppression hence early immunological recovery and prevention of clinical deterioration.

Particular recommendations are made on the use of IPT, which has been shown to lower the risk of mortality from CLHIV further. The findings underscore the need for targeted interventions to improve early HIV diagnosis, access to ART, and TB prevention strategies among HIV-positive children, particularly those at higher risk due to younger age, Malnutrition, and advanced disease stages.

5.4 Differences in IPT Uptake

A critical aspect of this study is the observed difference in IPT uptake, where some children received IPT and others did not. Several factors likely contributed to this disparity:

5.4.1 Screening and Clinical Practices: Not all children are routinely screened for latent TB infection or for eligibility to receive IPT, which may result in some children missing out on this crucial preventive therapy. Variations in clinical practices between health facilities, healthcare worker knowledge, and adherence to TB prevention guidelines may also contribute to differences in IPT uptake.

5.4.2 Resource Availability: Access to healthcare services and medications, including IPT, may differ across regions and facilities. The findings showed higher TB incidence in certain districts, such as Temeke, which could indicate that these areas also face challenges in implementing TB preventive measures consistently, including the provision of IPT. Limited resources, healthcare worker shortages, and inconsistent supply of IPT medications could lead to gaps in IPT administration.

5.4.3 Parental and Caregiver Knowledge and Adherence: The understanding and awareness of IPT's benefits among caregivers and parents play a significant role in whether a child completes or even begins IPT. Poor health literacy, stigma, or fear of additional medication may reduce caregiver adherence to recommended treatments like IPT. Educational interventions are needed to ensure caregivers understand the importance of IPT as part of comprehensive HIV care.

5.4.4 Eligibility Criteria: Not all CLHIV may meet the criteria for IPT, especially if they are suspected of having active TB, have experienced side effects from the medication, or have drug-drug interactions with their ART regimen. Additionally, some children might not have been eligible if they were not adequately screened for TB exposure, latent TB, or if there were gaps in follow-up care.

5.4.5 Health System Barriers: Systemic issues within healthcare delivery could also explain the difference in IPT uptake. For instance, delays in diagnosing TB or latent TB, failure to initiate timely treatment, or inconsistencies in recording and monitoring IPT adherence can result in some children missing the opportunity to benefit from the therapy. Additionally, policy-level challenges in scaling up IPT within certain healthcare settings may limit its use.

6.0 STRENGTH AND LIMITATIONS

6.1 Strength of the study

The study's dual focus is HIV/TB, especially in regions with high HIV prevalence, like sub-Saharan Africa. The methodology of a retrospective cohort study using a large dataset from the NACP—CTC database ensures robust data collection and analysis. This approach enhances the reliability of the findings by utilizing real-world data from high-volume clinics, thereby reflecting actual clinical scenarios and outcomes.

Moreover, the study provides valuable insights into the effectiveness of IPT in reducing TB incidence and mortality among CLHIV. It supports the implementation of IPT as a crucial intervention in HIV care programs.

Furthermore, the study's comprehensive analysis of the cohort's socio-demographic and clinical characteristics adds depth to the findings. By identifying predictors of higher TB risk, such as age, gender, and advanced HIV WHO clinical stages, the research offers actionable insights for targeted interventions and policy-making.

Overall, the thesis contributes significantly to the existing literature on TB and HIV co-infection and provides a solid evidence base for the continued use of IPT in the pediatric population.

6.2 Limitations of the study

Several limitations were noted in this study. Firstly, as a retrospective study, it relied on previously recorded data with some incomplete or missing vital information, such as 40 percent of the missing VL. Critical parameters such as adherence to ART and IPT were not fully explored, potentially impacting the accuracy of the findings. Secondly, critical data like viral loads were not consistently recorded at the beginning of participant follow-up, limiting the analysis of their association with TB development. Thirdly, the study's generalizability might be limited as it was conducted in specific high-volume CTC clinics in Dar es Salaam, which may not represent other regions or settings with different healthcare infrastructures and patient populations. Lastly, other potential confounding variables, such as nutritional status, socio-economic factors, and environmental exposures, were not accounted for in the study, which could influence the outcomes.

7.0 CONCLUSION AND RECOMMENDATIONS

7.1 Conclusion

This study assessed the incidence of tuberculosis (TB) disease and associated factors among CLHIV on ART in high-volume CTCs in Dar es Salaam, Tanzania. The findings demonstrate that the use of IPT was highly protective against mortality, significantly reducing the risk of death among CLHIV. However, while IPT users showed a lower TB incidence compared to non-users, this reduction was not statistically significant.

The study identified younger age (<5 years), male gender, advanced HIV clinical stages (WHO stages 3 and 4), and malnutrition (underweight status) as key risk factors associated with increased TB incidence and mortality. Children with lower CD4 counts were also found to be at higher risk of poor outcomes. Additionally, the study revealed that children on NNRTI-based ART regimens had higher mortality rates compared to those on INSTI and PI-based regimens.

In conclusion, while IPT plays a crucial role in reducing mortality among CLHIV, its effect on TB incidence requires further investigation. The findings underscore the importance of comprehensive care approaches, including early HIV diagnosis, timely ART initiation, IPT adherence, and nutritional support, to improve outcomes in this vulnerable population.

7.2 Recommendations

7.2.1 Scale-up of Isoniazid Preventive Therapy (IPT) Usage: The findings confirm that IPT is protective against the development of tuberculosis (TB) and significantly reduces mortality among children living with HIV (CLHIV). However, while the reduction in TB incidence was not statistically significant, the protective effect of IPT on mortality is remarkable. Therefore, there is a need to increase the coverage and adherence of IPT among CLHIV to maximize its benefits in TB prevention and reduction in mortality.

7.2.2 Comprehensive TB Screening and Preventive Measures: Regular TB screening at HIV diagnosis and during follow-up visits should be emphasized. Special attention should be given to high-risk subgroups, including younger children (<5 years), males, and those with advanced HIV stages or malnutrition. These groups showed higher vulnerability to TB and worse outcomes, which underscores the need for targeted interventions in this population.

7.2.3 Enhance Nutritional Support for CLHIV: Malnutrition, especially underweight status, was a significant risk factor for TB and mortality in CLHIV. Therefore, integrating comprehensive nutritional support with ART and IPT in HIV care programs is critical. All children with malnutrition should be routinely screened for TB and HIV and provided with necessary nutritional interventions.

7.2.4 Optimizing ART Regimens: The higher mortality among children on non-nucleoside reverse transcriptase inhibitors (NNRTIs) compared to other ART regimens highlights the need to investigate and potentially revise ART regimens in children with advanced disease or lower CD4 counts. Ensuring early viral suppression through optimal ART regimens could help prevent clinical deterioration and improve long-term outcomes.

7.2.5 Policy and Implementation Frameworks: To ensure sustained benefits of IPT and ART, the implementation of these interventions should be regularly monitored and evaluated in clinical settings. Health workers should receive training on the importance of IPT adherence and ART optimization, especially in vulnerable subgroups.

7.2.6 Further Research: Prospective studies are needed to further investigate the long-term impact of IPT, particularly on TB incidence, and to explore gender-specific differences in outcomes. Expanding research to other regions can help identify regional risk factors and tailor interventions accordingly.

These recommendations aim to strengthen the management and outcomes of CLHIV on ART by focusing on the use of IPT, nutritional support, and optimized ART regimens to improve TB prevention and reduce mortality.

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APPENDICES

Appendix 1: Ethical Clearances

UNITED REPUBLIC OF TANZANIA

MINISTRY OF EDUCATION, SCIENCE AND TECHNOLOGY

MUHIMBILI UNIVERSITY OF HEALTH AND ALLIED SCIENCES

OFFICE OF THE DIRECTOR – RESEARCH, PUBLICATIONS AND INNOVATION

Ref. No.DA.282/298/01.C/1810 Date: 20/07/2023

MUHAS-REC-07-2023-1810
EDWARD FAUSTINE NGALYA,
MUHAS.

RE: APPROVAL FOR ETHICAL CLEARANCE FOR A STUDY TITLED: INCIDENT OF TUBERCULOSIS DISEASE AND ASSOCIATED FACTORS IN CHILDREN LIVING WITH HIV ON ANTI-RETROVIRAL TREATMENT AND ISONIAZID PREVENTATIVE THERAPY (IPT) IN DAR ES SALAAM TANZANIA: A RETROSPECTIVE COHORT STUDY.

Reference is made to the above heading.

I am pleased to inform you that the Chairperson has on behalf of the University Senate, approved ethical clearance of the above-mentioned study, on recommendations of the Senate Research and Publications Committee meeting accordance with MUHAS research policy and Tanzania regulations governing human and animal subjects research.

APPROVAL DATE: 20/07/2023
EXPIRATION DATE OF APPROVAL: 20/07/2024

STUDY DESCRIPTION:
Purpose:
The purpose of this retrospective study is to determine the incident of Tuberculosis disease and associated factors in children living with HIV on Anti-retroviral treatment and Isoniazid Preventative Therapy (IPT) in Dar es Salaam Tanzania.

The approved protocol and procedures for this study is attached and stamped with this letter, and can be found in the link provided:
https://irb.muhas.ac.tz/storage/Certificates/Certificate%20-%2014825.pdf and in the MUHAS archives.

The PI is required to:

1. Submit bi-annual progress reports and final report upon completion of the study.
2. Report to the IRB any unanticipated problem involving risks to subjects or others including adverse events where applicable.
3. Apply for renewal of approval of ethical clearance one (1) month prior its expiration if the study is not completed at the end of this ethical approval. You may not continue with any research activity beyond the expiration date without the approval of the IRB. Failure to receive approval for continuation before the expiration date will result in automatic termination of the approval for this study on the expiration date.
4. Obtain IRB amendment (s) approval for any changes to any aspect of this study before they can be implemented.
5. Data security is ultimately the responsibility of the investigator.
6. Apply for and obtain data transfer agreement (DTA) from NIMR if data will be transferred to a foreign country.
7. Apply for and obtain material transfer agreement (MTA) from NIMR, if research materials (samples) will be shipped to a foreign country.
8. Any researcher, who contravenes or fail to comply with these conditions, shall be guilty of an offence and shall be liable on conviction to a fine as per NIMR Act No. 23 of 1979, PART III section 10 (2)
9. The PI is required to ensure that the findings of the study are disseminated to relevant stake holders.
10. PI is required to be versed with necessary laws and regulatory policies that govern research in Tanzania. Some guidance is available on our website https://d[illegible].tz/.

DIRECTOR Research, Publications & Innovations

Dr. N[illegible]Masoud.

Chairperson, MUHAS Research and Ethics Committee

Appendix 2: Introduction Letter at Upendo Dispensary

UNITED REPUBLIC OF TANZANIA
MINISTRY OF EDUCATION, SCIENCE AND TECHNOLOGY
MUHIMBILI UNIVERSITY OF HEALTH AND ALLIED SCIENCES
OFFICE OF THE DIRECTOR – POSTGRADUATE STUDIES

In reply quote:
Ref. No. HD/MUH/T.64/2021 14th July, 2023

The Medical Officer In charge,
Upendo Dispensary,
P.O. Box 78369,
DAR ES SALAAM.

Re: INTRODUCTION LETTER

The bearer of this letter is Edward Faustine (HD/MUH/T.64/2021), a student at Muhimbili University of Health and Allied Sciences (MUHAS) MMed. Paediatrics/Child Health.

As part of his studies he intends to do a study titled: **"Incident of Tuberculosis Disease and Assoiciated Factors in Children Living HIV on Anti-Retroviral Treatment and Isoniazid Preventative Therapy (IPT) in Dar es Salaam Tanzania: A Retrospective Cohort Study."** The research has been approved by the Chairman of University Senate.

Kindly provide him the necessary assistance to facilitate the conduct of his research.

We thank you for your cooperation.

Ms. Victoria Mwanilwa
For: DIRECTOR, POSTGRADUATE STUDIES

c.c Edward Faustine

9 United Nations Road; Upanga West; P.O. Box 65001, Dar Es Salaam: Tel. G/Line: +255-22-2150302/6; Ext. 1015; Direct Line:+255-22-2151378;Telefax:+255-22-2150465;E-mail:dpgs@muhas.ac.tz;Web:https://www.muhas.ac.tz

Appendix 3: Introduction Letter at Mwananyamala Regional Hospital

UNITED REPUBLIC OF TANZANIA
MINISTRY OF EDUCATION, SCIENCE AND TECHNOLOGY
MUHIMBILI UNIVERSITY OF HEALTH AND ALLIED SCIENCES
OFFICE OF THE DIRECTOR – POSTGRADUATE STUDIES

In reply quote:
Ref. No. HD/MUH/T.64/2021 14th July, 2023

The Executive Director,
Mwananyamala Regional Referral Hospital,
P.O. Box 61665,
DAR ES SALAAM.

Re: INTRODUCTION LETTER

The bearer of this letter is Edward Faustine (HD/MUH/T.64/2021), a student at Muhimbili University of Health and Allied Sciences (MUHAS) MMed. Paediatrics/Child Health.

As part of his studies he intends to do a study titled: **"Incident of Tuberculosis Disease and Assoiciated Factors in Children Living HIV on Anti-Retroviral Treatment and Isoniazid Preventative Therapy (IPT) in Dar es Salaam Tanzania: A Retrospective Cohort Study."** The research has been approved by the Chairman of University Senate.

Kindly provide him the necessary assistance to facilitate the conduct of his research.

We thank you for your cooperation.

Ms. Victoria Mwanilwa
For: DIRECTOR, POSTGRADUATE STUDIES

c.c Edward Faustine

9 United Nations Road; Upanga West; P.O. Box 65001, Dar Es Salaam: Tel. G/Line: +255-22-2150302/6; Ext. 1015; Direct Line:+255-22-2151378;Telefax:+255-22-2150465;E-mail:dpgs@muhas.ac.tz;Web:https://www.muhas.ac.tz

Appendix 4: Introduction Letter at Amana Regional Hospital

UNITED REPUBLIC OF TANZANIA
MINISTRY OF EDUCATION, SCIENCE AND TECHNOLOGY
MUHIMBILI UNIVERSITY OF HEALTH AND ALLIED SCIENCES
OFFICE OF THE DIRECTOR – POSTGRADUATE STUDIES

In reply quote;
Ref. No. HD/MUH/T.64/2021 14th July, 2023

The Executive Director,
Amana Regional Referral Hospital,
P.O. Box 25411,
DAR ES SALAAM.

Re: INTRODUCTION LETTER

The bearer of this letter is Edward Faustine (HD/MUH/T.64/2021), a student at Muhimbili University of Health and Allied Sciences (MUHAS) MMed. Paediatrics/Child Health.

As part of his studies he intends to do a study titled: **"Incident of Tuberculosis Disease and Assoiciated Factors in Children Living HIV on Anti-Retroviral Treatment and Isoniazid Preventative Therapy (IPT) in Dar es Salaam Tanzania: A Retrospective Cohort Study."** The research has been approved by the Chairman of University Senate.

Kindly provide him the necessary assistance to facilitate the conduct of his research.

We thank you for your cooperation.

Ms. Victoria Mwanilwa
For: DIRECTOR, POSTGRADUATE STUDIES

c.c Edward Faustine

Appendix 5: Introduction Letter at Temeke Regional Hospital

UNITED REPUBLIC OF TANZANIA
MINISTRY OF EDUCATION, SCIENCE AND TECHNOLOGY
MUHIMBILI UNIVERSITY OF HEALTH AND ALLIED SCIENCES
OFFICE OF THE DIRECTOR – POSTGRADUATE STUDIES

In reply quote:
Ref. No. HD/MUH/T.64/2021 14th July, 2023

The Executive Director,
Temeke Regional Referral Hospital,
P.O. Box 45232,
DAR ES SALAAM.

Re: INTRODUCTION LETTER

The bearer of this letter is Edward Faustine (HD/MUH/T.64/2021), a student at Muhimbili University of Health and Allied Sciences (MUHAS) MMed. Paediatrics/Child Health.

As part of his studies he intends to do a study titled: **"Incident of Tuberculosis Disease and Assoiciated Factors in Children Living HIV on Anti-Retroviral Treatment and Isoniazid Preventative Therapy (IPT) in Dar es Salaam Tanzania: A Retrospective Cohort Study."** The research has been approved by the Chairman of University Senate.

Kindly provide him the necessary assistance to facilitate the conduct of his research.

We thank you for your cooperation.

Ms. Victoria Mwanilwa
For: DIRECTOR, POSTGRADUATE STUDIES

c.c Edward Faustine

9 United Nations Road; Upanga West; P.O. Box 65001, Dar Es Salaam: Tel. G/Line: +255-22-2150302/6; Ext. 1015; Direct Line: +255-22-2151378;Telefax:+255-22-2150465,E-mail:dpgs@muhas.ac.tz;Web https://www.muhas.ac.tz

Appendix 6: Permission Letter At MNH

THE UNITED REPUBLIC OF TANZANIA

MINISTRY OF HEALTH

MUHIMBILI NATIONAL HOSPITAL

In reply please quote;

Ref. No.: MNH/CRTCU/Perm/2023/481 Date: 28th August, 2023

Head of Department,

New OPD

Muhimbili National Hospital

RE: PERMISSION TO COLLECT DATA AT MNH.

Name of Student	**Edward Justine**
Title	**"Incident of Tuberculosis Disease and Associated Factors in Children Living HIV on Anti-Retroviral Treatment and Isoniazid Preventive Therapy (IPT in Dar es Salaam Tanzania: a Retrospective Cohort Study".**
Institution	Muhimbili University of Health and Allied Sciences
Supervisors	Prof. Karim Manji (MUHAS)
Co - Supervisor	Dr. Namala Mkopi (MNH)
Period	28th August, 2023 to 30th February, 2024

Approval has been granted to the above mentioned student to collect data at MNH. **A final study report should be lodged with Clinical Research, Training and Consultancy Unit.** Dissemination of study findings to MNH stakeholders shall be overseen by **Dr. Namala Mkopi** (MNH) Co – supervisor.

Kindly ensure that the student abide to the ethical principles and other conditions of the research approval.

Sincerely,

TEACHING, RESEARCH & CONSULTANCY UNIT P.O. Box 65000 DAR-ES-SALAAM MUHIMBILI NATIONAL HOSPITAL

Dr. Jessie Mbwambo

Head of Clinical Research, Training and Consultancy Unit

c.c DMS

c.c Dr. Namala Mkopi

c.c **Edward Justine**