INCIDENCE AND FACTORS ASSOCIATED WITH MOTHER TO CHILD TRANSMISSION OF HIV AMONG EXPOSED INFANTS ON HIV PROPHYLAXIS IN TANZANIA FROM 2017 TO 2021

Faraja David Ng'ida, MD

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Department of Epidemiology and Biostatistics

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By

Faraja David Ng'ida

A Dissertation Submitted in (Partial) Fulfilment of the Requirements for the Degree of Master of Science (Applied Epidemiology) of

Muhimbili University of Health and Allied Sciences
October, 2024

CERTIFICATION

The undersigned certify that they have read and hereby recommend for acceptance by Muhimbili University of Health and Allied Sciences a dissertation entitled: **''Incidence and factors associated with mother to child transmission of HIV among exposed infants on HIV prophylaxis in Tanzania from 2017 to 2021'', in** (partial) fulfilment of the requirements for the degree of Master of Science in Applied Epidemiology of Muhimbili University of Health and Allied Sciences.

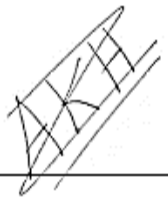
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Dr. Mucho Mizinduko

(Supervisor)

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Date



Dr. Ally K. Hussein

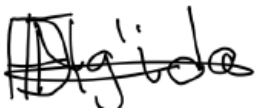
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I, **Faraja David Ng'ida**, declare that this **dissertation** is my original work and that it has not been presented and will not be presented to any other University for a similar or any other degree award.



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DEDICATION

I would like to dedicate this work to my family. They instilled in me a desire to learn and made sacrifices so I would achieve this important milestone.

ABSTRACT

Background: Roughly 160,000 children were newly infected with HIV in 2021 worldwide. Overall, 4% of people living with HIV (PLHIV) in 2021 were children aged 0 to <15 years. About 85% are from sub-Saharan Africa. In Tanzania, MTCT (Mother to Child Transmission) is 3.6% at six weeks and can triple by the end of breastfeeding if proper interventions are not taken. UNAIDS (Joint United Nations Program on HIV/AIDS) 2023 report states the overall transmission rate to be 6.9% including those who are breastfeeding. The provision of HIV triple therapy to HIV exposed infants is among the latest prevention opportunities. Despite these interventions, there is still a substantial rate of vertical transmission at 6.9% versus the country's target which is <4% necessitating the need to assess the contributing factors especially after this latest intervention.

Objective: The study mainly aims at determining the incidence rate of mother to child transmission and factors associated with transmission among HIV exposed infants receiving HIV prophylaxis in Tanzania.

Methods: A retrospective cohort study involving mother-child pairs from all 26 regions of Tanzania's mainland was conducted using existing routine data (secondary data) from the HIV care and treatment electronic (CTC3) database. All HIV-exposed infants aged ≤ 18 months registered in health facilities offering PMTCT services in the country from January 2017 to December 2021 were enrolled in the study. Infants were followed up for 18 months from birth; between June 2018 to June 2023. Data was summarized appropriately: Age was summarized by median and interquartile range after testing for normality. Categorical variables were summarized using frequencies and percentages. The incidence rate of MTCT is estimated. Factors associated with HIV transmission were established using a bivariable and multivariable Cox proportional hazard model. All analysis were considered statistically significant at 0.05 significance level.

Results: A total of 16,917 mothers-infant pairs were analyzed, of which 8,578 (50.71%) were female infants. The overall incidence rate was 1.69 (95% CI, 1.63 – 1.75) per 1,000 person-years with variation across various groups (Antiretroviral drugs (ARV) adherence status and WHO clinical stage of the mothers, HIV prophylaxis provision at birth and feeding mode for the first six months of life for infants). Factors such as increase in age of the mother decreased the risk of vertical transmission. Infants born to mothers with poor ARV adherence aHR 2.52 (95% CI, 1.60-3.97), those who were mixed fed during the first six of months of life aHR 6.16(95% CI, 4.69-8.10) and those who were kept on Nevirapine therapy only aHR 3.89 (2.99-4.68) had elevated risk for mother to child transmission of HIV and the associations were statistically significant.

Conclusion: Overall incidence rate of Mother to Child Transmission of HIV was found to be low after initiation of triple therapy prophylaxis for high-risk HIV exposed infants. However, the rate varies across various groups from mother factors to infant's factors. Mother's age, ARV adherence of the mother, feeding mode of the infant and type of prophylaxis given to the infant were identified as factors associated with mother to child transmission of HIV.

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ABBREVIATIONS

3TC	Lamivudine
AIDS	Acquired Immunodeficiency Syndrome
ART	Antiretroviral Therapy
ARV	Antiretroviral drugs
AZT	Zidovudine
CDC	Centers for Disease Control and Prevention
EID	Early Infant Diagnosis
HEIs	HIV Exposed Infants
HAART	Highly Active Antiretroviral Therapy
HIV	Human Immunodeficiency Virus
MOH	Ministry of Health
MTCT	Mother to Child Transmission
MUHAS	Muhimbili University of Health and Allied Sciences
NASHCoP	National AIDS, STIs and Hepatitis Control Program
NVP	Nevirapine
PEPFAR	U.S. President's Emergency Plan for AIDS Relief
PLHIV	People Living With HIV
PMTCT	Prevention of Mother to Child Transmission
SVD	Spontaneous Vaginal Delivery
TFELTP	Tanzania Field Epidemiology and Laboratory Training Program
UNAIDS	Joint United Nations Program on HIV/AIDS
UNICEF	United Nations Children's Fund
WHO	World Health Organization

DEFINITIONS OF TERMS

TERM	DEFINITION
Antiretroviral Drugs (ARV)	Medicines used to treat HIV **(WHO).**
Antiretroviral Therapy (ART)	The use of a combination of three ARV drugs for treating HIV infection. It involves lifelong treatment **(WHO).**
Exclusive breastfeeding	When a child is fed on breast milk alone without any other foods or liquids (including infant formula or water), with the exceptions of medications, oral rehydration solution, vitamin, and mineral supplements **(CDC).**
High risk exposed Infant	An infant whose mother was first identified as HIV-infected at delivery or in the postpartum, infected during pregnancy or breastfeeding, started ART late in pregnancy, or did not achieve viral suppression by the time of delivery (1).
HIV exposed infant	An infant born to an HIV positive mother until when he/she is reliably determined to be HIV uninfected (1).
HIV free survival	A child born to a mother living with HIV who remains both HIV uninfected and alive over a defined follow-up period. It is commonly reported at 18 months (1).
Infant	A baby from birth to around 1 year of age **(UNICEF).**
Low risk exposed infant	An Infant born to a mother with known HIV status, who received antiretroviral drugs for at least ten consecutive weeks during pregnancy with viral suppression (HIV RNA level <50 copies/ml within four weeks prior to delivery) and with no concerns related to maternal antiretroviral medication adherence or acute HIV infection during pregnancy (1).

Mixed feeding	when an infant is fed on formula milk or cow's milk or any other liquids and/or food together with breastmilk during the first six months of life **(CDC).**
Mother to child Transmission (MTCT) or Vertical transmission	Transmission of HIV that occurs from an HIV positive mother to her infant. This may occur prenatally, perinatally, or postnatally through breastfeeding **(WHO).**
Prevention of Mother to Child Transmission (PMTCT)	Prevention of transmission of HIV from a mother to her child prenatally, perinatally, or postnatally through breastfeeding **(WHO).**
Triple therapy HIV prophylaxis	Zidovudine (AZT) + Lamivudine (3TC) (Combivir) + Nevirapine Syrup **(WHO).**

CHAPTER ONE

1.0 INTRODUCTION

1.1 Background

Globally, approximately 1.7 million children were living with Human Immunodeficiency Virus (HIV) in 2021 accounting for 4% of all people living with HIV (PLHIV)(3). Among them, roughly 160,000 were new HIV infections (3). Around 740 and 274 children were infected with HIV and died from AIDS related causes respectively daily in 2022 globally which is in accordance with UNICEF report of 2022.

Without Antiretroviral therapy (ART), about 50%-60% of HIV-infected children die by the age of two years (4,5) and 80% by the age of 5 years globally (5). However, with the proper use of ARTs, majority of them are expected to survive into adulthood (4). Adequate management of HIV-infected pregnant women and prevention of vertical transmission have prevented many of these children from being infected with HIV as vertical transmission (Mother to Child Transmission) can occur prenatally, postnatally or perinatally through breastfeeding (6).

About 85% of MTCT occurred in sub-Saharan Africa (3). Vertical transmission prenatally, perinatally or postnatally through breastfeeding is the major root of pediatric HIV infection in this region contributing to greater than 90% of HIV infections in children (7). Prevention of mother-to-child transmission (PMTCT) of HIV is still a challenge in most resource-limited settings, particularly in Africa (8).

Eastern and Southern Africa are the largest affected regions globally, accounting for more than half of all new HIV infections in all age groups (9), with the rate of MTCT after breastfeeding approximated to be 8.6% (9).

According to UNICEF Tanzania report data of 2019, MTCT rate in the country is at 3.6% when a baby is six weeks old, however, without monitoring and treatment, it can double by the end of breastfeeding (10). UNAIDS report of 2023 shows that the final MTCT rate in Tanzania,

including during breastfeeding, was 6.9% in the year 2022, however the overall incidence rate of HIV is 0.54 per 1000 population across all age groups (11).

PMTCT is critical to reduce infant infections. Both single-dose nevirapine and triple therapy have been used for PMTCT for low-risk infants and high-risk infants respectively. The later was introduced by WHO in 2016 and adopted by the Tanzanian government in 2017 and it is in practice up to date (12).

In a resource limited country where MTCT rate is still high, assessing the risk factors for vertical transmission is of paramount importance in efforts to reduce child morbidity and mortality through strengthening PMTCT programs. Therefore, this study aims at determining incidence rate of mother to child transmission and factors associated (both maternal and infant) with transmission among HIV exposed infants receiving HIV prophylaxis in Tanzania.

1.2 Problem Statement

In Eastern and Southern Africa, the MTCT rate is at 8.6% (3). In Tanzania , MTCT rate is at 3.6% when an infant is six weeks old, however, it can double by the end of breastfeeding if no monitoring and treatment (10). In 2022, vertical transmission rate at 18 months, in Tanzania, was 6.9% (11).

Different strategies for PMTCT have been conducted by the Ministry of Health (MOH) and other stakeholders. The most recent intervention is the adoption of triple therapy prophylaxis for high-risk exposed infants, which was introduced by WHO in 2016 and adopted in the country in 2017 and has been in practice to date (6). Since the introduction of triple therapy, vertical transmission rate is reported to decrease from 16.2% in 2015 to 6.9% in 2022 (11).

Despite these interventions there is still a substantial rate of vertical transmissions at 6.9% versus the country's target which is <4% by 2025 (2) hence necessitating the need to assess the contributing factors especially with this latest intervention. About 50%-60% of HIV-infected children die by the age of two years (4,5) and 80% by the age of 5 years globally if interventions are not taken timely and adequately (5).

Therefore, this study aims at determining the incidence rate of MTCT of HIV and associated factors among HIV exposed infants on prophylaxis for HIV in Tanzania since the introduction of triple therapy prophylaxis in 2017.

1.3 Conceptual Framework

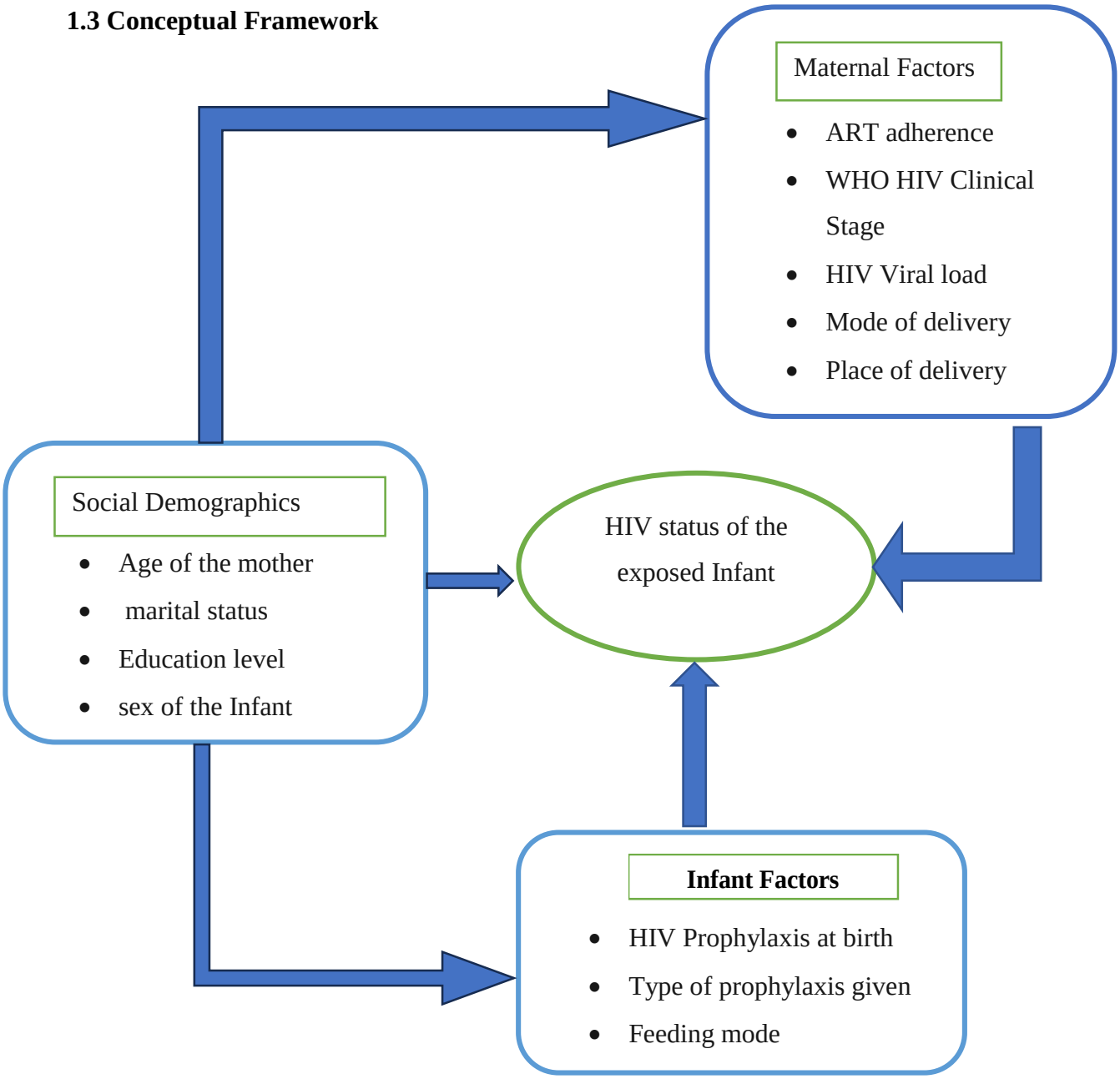


Figure 1: Conceptual framework of Mother to Child Transmission of HIV (13)

The relationship between dependent and independent variables is shown in the figure above. The independent variables in this study were divided into mother and Infant factors. Demographic characteristics included age and marital status of the mother and sex of the infant. Mother factors assessed were WHO clinical stage and ART adherence. Infant factors were if the

infant was given HIV Prophylaxis or not at birth, type of HIV prophylaxis given (Nevirapine only or triple therapy) and feeding mode for the first six months of life (whether exclusively breastfed or mixed fed) were assessed. The outcome variable is the HIV status of the infant which was considered at eighteen (18) months of age.

1.4 Study Rationale

MTCT of HIV is still of public health concern despite efforts taken to combat it. Among the efforts taken, triple therapy prophylaxis for high-risk exposed infants is shown to reduce the burden. The Tanzanian government started implementing this intervention in 2017 and it is in practice to date. However, we still see several mother to child transmission of HIV occurring at higher rate than expected (6.9% vs <4% by 2025) (2). Thus, it is pertinent to determine possible reasons for such rate of transmissions in the country. Findings from this study will shed light on possible factors linked to higher rate of transmission and the magnitude of the problem in the country. Thus, the MOH through the PMTCT Section and other stakeholders will make use of this study findings to strengthen the PMTCT program.

1.5 Study Questions

1.5.1 Broad study question

What is the incidence rate of MTCT of HIV and the associated factors among HIV exposed infants on prophylaxis for HIV in Tanzania from January 2017 to December 2021?

1.5.2 Specific study questions

1. What is the incidence rate of MTCT of HIV among HIV exposed infants on prophylaxis in Tanzania from January 2017 to December 2021?
2. What are the maternal factors associated with MTCT of HIV among HIV exposed infants on prophylaxis in Tanzania from January 2017 to December 2021?
3. What are the infant factors associated with MTCT of HIV among HIV exposed infants on prophylaxis in Tanzania from January 2017 to December 2021?

1.6 Study Objectives

1.6.1 Broad objective

To determine the incidence rate of MTCT of HIV and associated factors among HIV exposed infants on prophylaxis for HIV in Tanzania from January 2017 to December 2021

1.6.2 Specific Objectives

1. To determine the incidence rate of MTCT of HIV among HIV exposed infants on prophylaxis for HIV in Tanzania from January 2017 to December 2021.
2. To determine maternal factors associated with the rate of MTCT of HIV among HIV exposed infants on triple therapy prophylaxis for HIV in Tanzania from January 2017 to December 2021.
3. To determine infant factors associated with the rate of MTCT of HIV among HIV exposed infants on prophylaxis for HIV in Tanzania from January 2017 to December 2021.

CHAPTER TWO

2.0 LITERATURE REVIEW

2.1 Incidence rate of MTCT of HIV in the era of Triple therapy HIV Prophylaxis among HIV exposed infants

MTCT rate remains low in developed countries in comparison to developing countries including Tanzania. Studies conducted in China shows MTCT rate to be 2.3%-6.6% (14,15). The incidence rate is shown to decrease from 26.1% to 1.5% in some areas of China after introduction of effective PMTCT services (16). In India the incidence is 5 per 1000 persons months by 24 months of age, with the prevalence of 7.8% in 2010 (17). In Brazil the rate is 9.9% in 2007-2009 (18). Another study in Brazil shows the incidence rate of vertical transmission to be 2.7% in 2007-2009 when all HIV positive pregnant women were given Zidovudine monotherapy , 1% in 2010-2015 when triple therapy was given to those with high viral load (>1000 copies) and low CD4 (<200) and zidovudine monotherapy to the stable patients and 0% in 2016-2018 when triple therapy is given to all infected mothers (19). According to European Collaborative Study, after the initiation of Highly Active Antiretroviral therapy (HAART), the rate dropped to 2.87% from 5.06% (20) with the risk being lower among those who started ARTs before pregnancy in comparison to those who started during pregnancy (20).

In Africa, MTCT rate is still high ranging from 6.5%-33% at 18 months of age (7,21–23). Initiation of ARVs among pregnant women reduces the rate by 24% among low and middle income countries (24). HAART initiation reduced the rate from 9.6% to 2.8% in South Africa (25). In Malawi the vertical transmission rate after introducing option B+ in 2011 is 3.7% at 12 weeks of age (26). In Namibia the incidence rate of MTCT is 1.74% at 4-12weeks of age (27) however it is 0.76% when mother received ART and infant received ARV prophylaxis, 2.67% when only mother received ART, 9.62% if only infant received ARV prophylaxis, and 22.32% when neither mother nor infant received ARVs in Namibia (27). In Lesotho, South Africa the vertical transmission rate at six weeks is reported to be 1.3% (28).

In Dar es Salaam Tanzania, in 2021, 3.1% of infants born to HIV mothers were HIV positive by 18 months of age (7). Another study conducted in Tanzania (Lake zone) reports the incidence of MTCT to be 6.1% (16). Similar study reveals the vertical transmission to be higher among pregnant women on single dose Zidovudine compared to those on triple therapy (16). The incidence rate is 9.6% at the first DNA test in Kilimanjaro region (29).

Hence this study aimed at determining the incidence rate of MTCT of HIV and associated factors among exposed infants on HIV prophylaxis in all the regions of the Tanzania mainland after introduction of triple therapy prophylaxis in 2017 since the previous studies focused on individual regions which are mostly urban leaving out the full picture from the rural areas.

2.2 Maternal factors associated with incidence rate of MTCT of HIV in the era of triple therapy HIV prophylaxis among HIV exposed infants.

2.2.1 ART adherence Status

Mothers with poor adherence to ARTs are three to fourteen times more likely to transfer HIV infection to their babies in comparison to mothers with good adherence to treatment (24,30,31). Moreover in Malawi, mothers who started ART after delivery and those with poor adherence are 17 and 9 times more likely, respectively, for vertical transmission than those initiated on ART before pregnancy with good adherence (26). Mothers not on ART during pregnancy are 19 times more likely for vertical transmission (26). In Dar es Salaam Tanzania, ART adherence of the mother is also shown to affect infants status by 1.05 more risk for those with poor adherence in comparison to those with good adherence (7).

Hence this study aimed at determining the impact of ART adherence of the mother to MTCT rate in all the regions of Tanzania mainland after the introduction of triple therapy prophylaxis since the previous studies in the country focused on individual regions.

2.2.2 WHO HIV Clinical Stage

Advanced maternal WHO stage of HIV is shown to be a risk factor for MTCT in Europe (20). Mothers who are HIV WHO clinical stage 3 and 4 are 1.96 more prone to vertical transmission than their counterparts in stage 1 and 2 (32). In Dar es Salaam, Tanzania babies born to mothers who are in stage 3-4 have MTCT rate of 9.4% while those born to WHO stage 1 and 2 mothers have a transmission rate of only 2.7% (7), hence this study will assess the relationship between WHO clinical stage and incidence of MTCT in all the regions of mainland Tanzania unlike the previous studies which focused on individual regions.

2.3 Infant Factors associated with incidence rate of MTCT of HIV in the era of triple therapy HIV prophylaxis among HIV exposed infants.

Transmission rate is shown to be higher among female infants in comparison to their male counterparts (4.43 higher odds) (32,33). However in Tanzania the rate is almost similar between males and females (3.1% versus 3.2%) (7).

2.3.1 Mode of Feeding

Various studies in Africa show mixed feeding to be more associated with MTCT of HIV ranging from 29-42 times higher odds compared to those who were exclusively breastfed for six months (24,26,30–32,34). In East Africa, Infants who were mixed fed has 6.22 times odds of acquiring HIV infection from their mothers in comparison to those who were exclusively breastfed (35). These are similar to Dar es Salaam City, where mixed fed infants has a higher rate of transmission (19%) unlike those infants who were exclusively breastfed (2.6%) (7).

There is limited information on the relationship between mode of feeding and rate of MTCT in Tanzania especially from rural areas impairing focused interventions in those areas. Therefore, this study will determine this relationship across Tanzania mainland.

2.3.2 Type of Prophylaxis given

Provision of Nevirapine single therapy to exposed infants is shown to be a risk factor for MTCT in Europe (20).

Studies conducted in various African countries show single therapy (Nevirapine only) HIV prophylaxis to be more associated with MTCT of HIV ranging from 15-24 times higher odds compared to provision of triple therapy prophylaxis (24,26,30–32,34).

In East Africa, Infants who were kept on Single dose prophylaxis had 4.32 times higher odds of acquiring HIV infection from their mothers in comparison to those who were kept on triple therapy (35). These are similar to Dar es Salaam City, where infants on single dose therapy have a higher rate of transmission (12%) unlike those infants who were kept on triple therapy (3.2%) (7).

There is limited information on the relationship between the type of HIV prophylaxis given to an exposed infant and rate of MTCT in Tanzania especially from rural areas. Therefore, this study will determine this relationship across Tanzania mainland.

2.3.3 Infant ARV prophylaxis at birth

In Brazil, not receiving ART prophylaxis at birth is associated with vertical transmission 3 times higher than receiving prophylaxis at birth (19,34). Similar results are shown in various African countries where Infants who were not given ARVs for prophylaxis at birth have two to five times higher chances of acquiring vertical transmission in comparison to those who received prophylaxis (19,30,36).

Tanzania is similar to other countries, where Vertical transmission rate is higher among infants who were not given prophylaxis at birth in comparison to those who were given, according to a study conducted in lake zone (16).

This study therefore will shed light on the relationship between infant ARV prophylaxis given at birth or not and rate of MTCT in other parts of the country by involving all the regions of mainland.

CHAPTER THREE

3.0 METHODOLOGY

3.1 Study Design

A retrospective cohort study was conducted using existing routine data (secondary data) from the HIV care and treatment electronic (CTC3) database (PMTCT and EID national data), from January 2017 to December 2021, as triple therapy prophylaxis was initiated in the country in 2017. Infants were followed up for 18 months from birth which was between June 2018 to June 2023.

3.2 Study Population

The study population involved all HIV-exposed infants aged ≤ 18 months and received HIV prophylaxis registered in all health facilities providing PMTCT services in all 26 regions of Tanzania mainland from January 2017 to December 2021.

3.2.1 Inclusion Criteria

HIV-exposed Infants born between January 2017 to December 2021 and received HIV prophylaxis.

3.2.2 Exclusion Criteria

1. HIV-exposed Infants with missing outcome of interest in the database.
2. HIV-exposed Infants with inconsistent potential dates (entry date to the study and date of outcome occurrence).

3.2.3 Sample Size

The power of the study was calculated instead of sample size since the data is already available. The formula for calculation of power for cohort studies portrayed underneath was used to calculate power of the study (37).

$$Power = \Phi\left(\frac{\sqrt{(n_1 * \Delta^2)} - z_{1-\alpha/2}\sqrt{(1+1/\kappa) * p * q}}{\sqrt{(p_1 * q_1) + (p_2 * q_2 / \kappa)}} \right)$$

The symbols for the formula are:

Δ = difference of risk of outcome between exposed group and unexposed group

κ = ratio of sample size: unexposed group / exposed group

p1= risk of outcome among the exposed group.

p2= risk of outcome among the unexposed group.

p = (p1*n1+p2*n2) / (n1+n2)

q= 1-p

n1= available sample size amid the exposed group

n2= available sample size amid the un-exposed group

The below stated presumptions will be used:

Approximately 16,917 HIV positive mothers in the database from 2017 to 2021

We took Feeding mode (EBF/MF) as a variable for comparison.

Infants who were exclusively breastfed in the first six months of life were used as Un-Exposed group where there are 12,428.

Those who were mixed fed in the first six months of life were the exposed group where there are 4,489.

Calculating K, we obtained 0.36.

n1=4,489, n2=12,428

So, in this study the outcome of interest was HIV status of the infant at 18 months, Risk in Exposed group is 3.73% and risk in the Un-exposed group is 0.96%

Power was computed using openEpi software version 3.01 which is available at https://www.openepi.com/Power/PowerCohort.htm

Power of the study is 99.9%

3.2.4 Dataset description and Data abstraction procedure

This study used secondary data of the country gleaned from the HIV care and treatment electronic (CTC3) database. This dataset comes from the Ministry of Health (MOH) which supports the PMTCT initiative.

In RCHs, all pregnant women who attend ANC clinics are counselled and tested for HIV, and their results are documented in ANC registers. When determined to be HIV positive, they are registered in PMTCT care registers. Infants born to mothers who are HIV-positive are tracked until 18 months of age in EID (Early Infant Diagnosis) registrations after delivery. During this monthly follow up at PMTCT clinic, mothers are counseled on HIV prevention measures for their infants who are free from HIV infection. The infants who contract the HIV infection during PMTCT follow-up are transferred to pediatrics care and treatment at CTC. Since all mother-child pairs are registered in the database, these data represent true incidence of PMTCT and associated factors in the country. Nevertheless, there is a possibility of a small proportion of missed cases not attending the health facilities throughout the follow-up period. Pre-testing tools were used to collect data to determine whether the information meets the needs of the research.

A Stata data file (DTA) dataset was obtained from the national HIV database main server hosted by University Computing Centre at the University of Dar es salaam. This was imported into Stata Version 15.1 software for data cleaning, coding of variables and creation of logical commands as per objectives of analysis through preparation of do-files. These do-files were tested for analysis, if give outputs of study objectives using the same dataset provided. After successful executions, then the final do-file was sent to the main server for execution and the final outputs of the analysis were recorded and served for report writing.

3.3 Study Area

This study was conducted in Tanzania mainland involving all the 26 regions.

The United Republic of Tanzania is a country in East Africa. It is formed by a union between Tanzania mainland (Tanganyika) and Zanzibar Island. It is bordered to the North by Uganda,

Northeast by Kenya, to the East by the Indian Ocean, to the South by Mozambique and Malawi, to the Southwest by Zambia, and to the West by Rwanda, Burundi, and the Democratic Republic of the Congo (38). According to the 2022 national census, Tanzania was stated to have a population of nearly 62 million (38).

HIV prevalence in the mainland Tanzania is 4.5% among adults aged 15 years and older (0.8% to 13% among females, and 0.3% to 8.4% among males) (39). According to Tanzania HIV Impact Survey (THIS) report of 2022-2023, this is equivalent to 1.4 million PLHIV aged 15 years and older in the country (39).

This study involved 6,829 facilities providing PMTCT services in all the 26 regions of Tanzania mainland. It used secondary data of the country gleaned from the HIV care and treatment electronic (CTC3) database.

3.4 Study Variables

3.4.1 Dependent variable

The dependent variable in this study is HIV status of an HIV exposed infant. The final status was considered at 18 months of age. The outcome was defined as HIV positive or censored (negative, died or lost to follow-up).

3.4.2 Independent variables

Independent (exposure) variables included:

- Maternal Factors
    - Age of the mother (<25, 25-35, >35 years)
    - Marital Status of the mother (Married/Cohabiting, Single, widowed)
    - ARV adherence (good or poor).
    - WHO HIV Clinical stage (stage 1, 2, 3 and 4).
- Infant Factors
    - HIV prophylaxis at birth (YES/NO)

- Type of prophylaxis given (Nevirapine only or triple therapy)
- Feeding mode (exclusive breastfeeding or mixed feeding)

3.5 Data Management and Analysis

The age of the mother was summarized by using medians with its corresponding interquartile ranges, after testing for normality which was found to be skewed. Categorical variables were summarized using frequencies and percentages.

We calculated the overall and covariate specific incidence rate per 1000 person-years (Person-years) among HIV-exposed Infants born between January 2017 to December 2021.

The incidence rate of MTCT between infants who were exclusively breastfed for the first six months of life and those who were mixed fed, which is our main exposure, was displayed through Kaplan Meir curves and a log rank test was used to test statistical significance differences between the survival curves.

Missing data were handled through deleting of records with missing outcome of interest or inconsistent potential dates.

Factors associated with incidence rate of MTCT were established through bivariable and multivariable cox proportional hazard model, considering the assumption that the risks change over time. Verification of Proportional hazards model was achieved through Proportion Hazard test (PH test) where all the variables met the proportional hazards assumptions after running a PH test and the global p-value was greater than 0.05.

In the bivariable analysis, parameters that are statistically significant at a p-value of ≤ 0.25 and those with clinical plausibility were entered in the multivariable model. The adjusted hazard ratio and its 95% confidence interval are presented. All analyses were considered statistically significant at p value < 0.05.

3.6 Ethical Considerations

This study used secondary data from routine service provision. To protect participant identity, unique identification numbers were used during data extraction to ensure confidentiality and anonymity. Ethical clearance to conduct the study was obtained from Muhimbili University of Health and Allied Sciences institution review board. Further permission to use the data was obtained from the ministry of health through the National AIDS, STIs and Hepatitis Control Program (NASHCoP).

CHAPTER FOUR

4.0 RESULTS

4.1 Baseline demographic and clinical characteristics of mother-child pairs enrolled for care to PMTCT in Tanzania from January 2017 to December 2021

A total of 18,886 clients records were found in the National AIDS control program database during the study period January 2017 to December 2021. Of these, 1,969 (10.5%) were excluded from the analysis due to missing important records such as missing outcome of interest, potential dates such as date of entry into the study and date of outcome occurrence. A total of 16,917 records were enrolled in the study. **(Figure 2)**

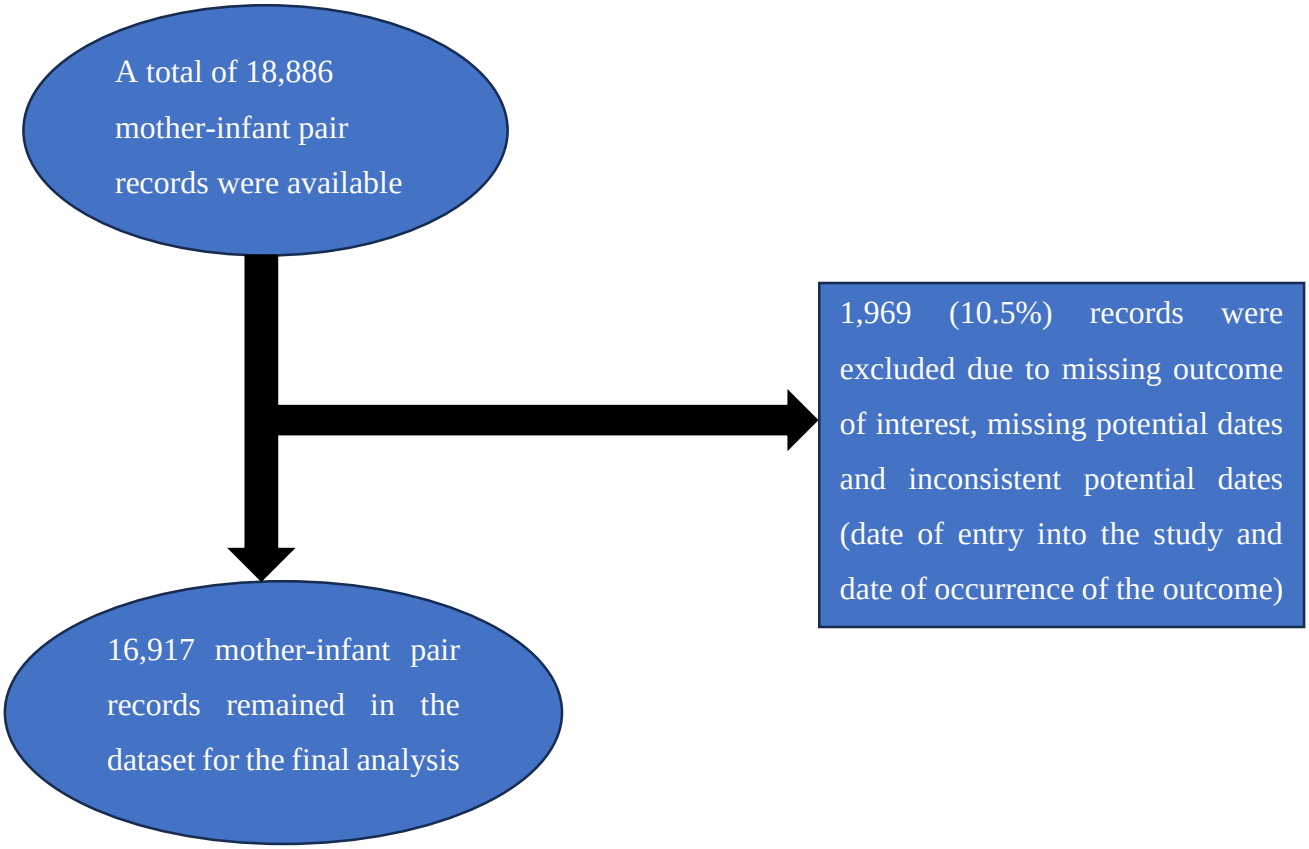


Figure 2: Flowchart for the selection procedure of study participants for final analysis

Baseline demographics and clinical characteristics of the study participants are presented in **Table 1** below. More than half of the mothers (54.38%) were between the age of 25-35 years with the median age of 32(27-37), married/cohabiting (58.12%), had good ARV adherence (66.86%) and were in WHO clinical stage 1 (53.75%). Majority of the infants were females (50.71%), received HIV prophylaxis at birth (77.77%), received Nevirapine only prophylaxis (97.28%) and were exclusively breastfed (73.46%). Other demographic and clinical characteristics are presented in (**Table 1**) respectively.

Table 1: Baseline demographic and clinical characteristics of mother-child pairs enrolled for care to PMTCT in Tanzania from January 2017 to December 2021 (N=16,917)

Variables	Frequency (n)	Percentage (%)
Maternal Factors		
Age of the mother (in years)		
<25	2,906	17.18
25-35	9,200	54.39
>35	4,810	28.43
Median 32(IQ 27,37)		
Marital Status of the mother (n= 14,304)		
Married/cohabiting	9,833	68.74
Widowed	334	2.34
Single	4,137	28.92
ARV adherence (n=11,645)		
Good	11,310	97.12
Poor	335	2.88
WHO HIV Clinical stage (n=15,969)		
Stage 1	9,093	56.94
Stage 2	2,585	16.19
Stage 3	3,651	22.86
Stage 4	640	4.01
Infant Factors		
Sex		
Female	8,578	50.71
Male	8,339	49.29
HIV Prophylaxis at birth		
Yes	13,156	77.77
No	3,761	22.23
Type of prophylaxis given		
AZT+3TC+NVP	460	2.72
Nevirapine only	16,457	97.28
Feeding mode		
EBF	12,428	73.46
Mixed feeding	4,489	26.54

4.2 Incidence rate of MTCT of HIV in the era of Triple therapy HIV Prophylaxis among HIV exposed infants

A total of 16,917 infants were observed for varying periods of time ranging from one day to 18 months. The overall incidence rate among the infants who were followed up was reported to be 1.69 per 1000-person months [95% Confidence Interval [CI], 1.63 – 1.75].

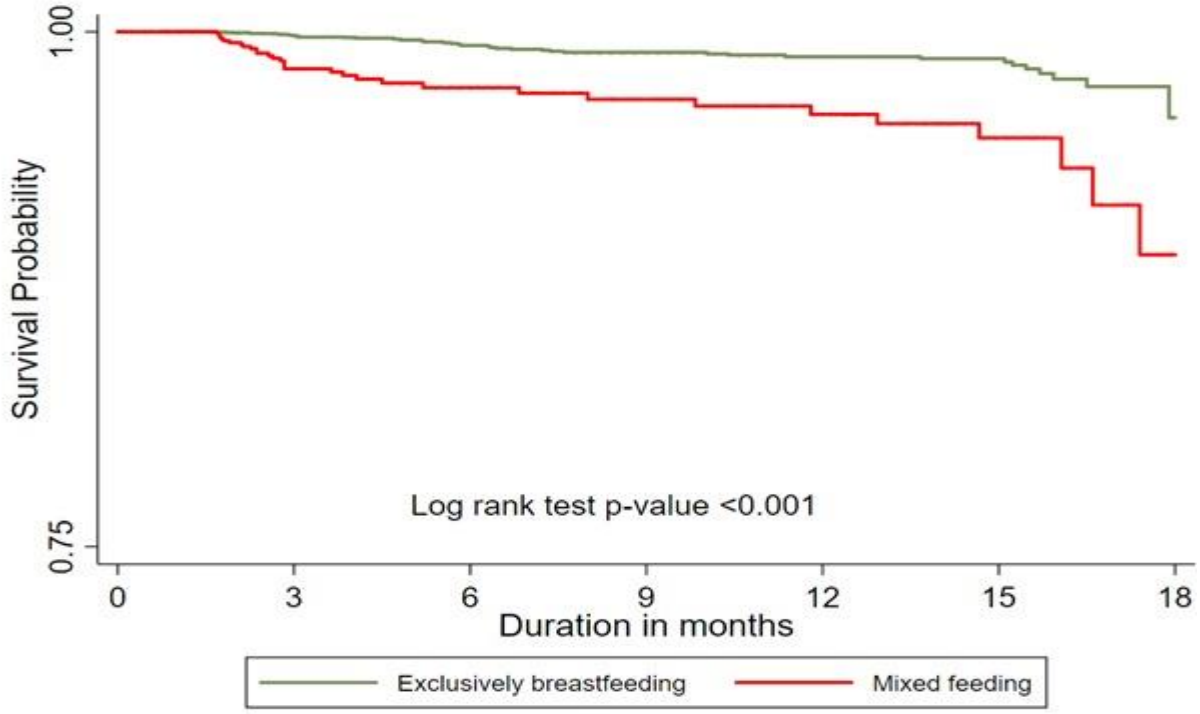
The study found that infants born to younger mothers, with poor ARV adherence and in early WHO Clinical stages (1 and 2) and those infants who did not receive HIV prophylaxis at birth, those who were kept on Nevirapine therapy only and those who were mixed fed during the first six months of life to have higher incidence rates of mother to child transmission compared to their counterparts.

Table 2 below provides detailed information on incidence rates across different variables.

Table 2: Incidence rate of MTCT of HIV by demographic and clinical characteristics among infants enrolled to PMTCT program from January 2017 to December 2021.

Variables	Person months	HIV positive	Incidence rate per 1000 person-months (95% CI)
Crude incidence rate	**1,673,146**	**2,829**	**1.69 (1.63-1.75)**
Maternal Factors			
Age of the mother (in years)			
<25	253,097	679	2.68 (2.49– 2.89)
25-35	937,855	1,525	1.63 (1.55- 1.71)
>35	482,141	625	1.30 (1.20– 1.40)
Marital Status of the mother			
Married/cohabiting	1,025,774	1,759	1.71 (1.64 – 1.80)
Widowed	34,648	45	1.30 (0.97- 1.74)
Single	370,726	660	1.78 (1.65 – 1.92)
ARV adherence			
Good	829,749	1,011	1.22 (1.14-1.30)
Poor	18,800	65	3.46 (2.71-4.41)
WHO HIV Clinical stage			
Stage 1	490,993	745	1.52 (1.41- 1.63)
Stage 2	161,328	232	1.43 (1.26 -1.64)
Stage 3	273,047	303	1.11 (0.99- 1.24)
Stage 4	47,019	57	1.21 (0.94-1.57)
Infant Factors			
HIV Prophylaxis at birth			
Yes	603,891	824	1.36 (1.27-1.46)
No	1,069,254	2005	1.88 (1.79 -1.96)
Type of prophylaxis given			
AZT+3TC+NVP	7,230	4	0.12
Nevirapine only	1,033,645	681	6.82 (4.18-11.12)
Feeding mode			
EBF	316,516	303	0.96 (0.86-1.07)
Mixed feeding	195,167	727	3.73 (3.46- 4.01)

Infants who were mixed fed for the first six months of life had higher probabilities of mother to child transmission of HIV (worse survival prognosis) compared to those who were exclusively breastfed. (**Figure 2**).



EBF: Exclusive Breastfeeding, MF: Mixed feeding

Figure 3: Kaplan-Meier survival curves showing survival probabilities among HIV exposed infants on HIV prophylaxis in Tanzania from 2017 to 2021 based on their feeding mode in the first six months of life

4.3 Factors associated with mother to child transmission of HIV among exposed infants on prophylaxis.

As shown in **Table 3**, with bivariable analysis; age of the mother, ARV adherence of the mother, WHO clinical stage of the mother, whether the infant was given HIV prophylaxis at birth or not, type of prophylaxis given to the infant and feeding mode of the infant were factors with a p value of less than 0.25 hence were considered as potential predictors of mother to child transmission of HIV and were included in multivariable cox proportional hazards model. Using

adjusted cox regression analysis; increase in age of the mother decreased the risk of vertical transmission and infants born to mothers with poor ARV adherence aHR 2.52 (95% CI, 1.60-3.97), those who were kept on Nevirapine therapy only aHR 3.89 (2.99-4.68) and those who were mixed fed during the first six of months of life aHR 6.16[95% CI, 4.69-8.10] had elevated risk for mother to child transmission of HIV and the associations are statistically significant.

Table 3: Multivariable cox regression on factors associated with mother to child transmission of HIV among exposed infants on prophylaxis from 2017 to 2021

Covariates	Bivariable analysis		Multivariable analysis	
	Crude hazard ratio (95% CI)	P-value	Adjusted hazard ratio (95% CI)	P-value
Maternal Factors				
Age of the mother (in years)				
<25	Reference		Reference	
25-35	0.61(0.55-0.66)	<0.01	0.71 (0.54-0.95)	0.02
>35	0.48 (0.43-0.54)	<0.01	0.641 (0.46-0.89)	0.01
Marital Status of the mother				
Married/ Cohabiting	Reference		Reference	
Widowed	0.75 (0.56-1.01)	0.06		
Single	1.05 (0.96-1.14)	0.32		
ARV adherence				
Good	Reference		Reference	
Poor	2.75 (2.14–3.54)	<0.01	2.52(1.60-3.97)	<0.01
WHO Clinical Stage				
Stage 1	Reference		Reference	
Stage 2	0.94 (0.81–1.09)	0.41	0.64 (0.45-0.90)	0.01
Stage 3	0.73(0.64-0.83)	<0.01	0.88(0.68-1.13)	0.32
Stage 4	0.79(0.60-1.03)	0.09	0.70(0.39-1.23)	0.21
Infant Factors				
HIV Prophylaxis at birth				
Yes	Reference		Reference	
No	1.38 (1.27-1.50)	<0.01	1.03(0.80-1.32)	0.81
Type of prophylaxis given				
AZT+3TC+NVP	Reference		Reference	
Nevirapine only	4.32 (3.52-5.04)	<0.01	3.89 (2.99-4.68)	<0.01
Feeding mode				
EBF	Reference		Reference	
Mixed feeding	5.3 (4.63-6.17)	<0.01	6.16(4.69-8.10)	<0.01

CHAPTER FIVE

5.0 DISCUSSION

We assessed the incidence rate and factors associated with mother to child transmission of HIV among exposed infants on HIV prophylaxis in Tanzania. The study revealed that incidence rate varied across various groups, being lower among infants born to mothers with good ARV adherence and infants who were kept on triple therapy and those who were exclusively breastfed for the first six months of life.

10.5% of data were deleted due to missingness which could have led to potential information bias in our study.

5.1 Incidence rate of MTCT of HIV in the era of Triple therapy HIV Prophylaxis among HIV exposed infants

In the current study it was observed that introduction of triple therapy prophylaxis for high risk HIV exposed infants had a positive effect on outcome of exposed infants where overall incidence rate was lower which is in line with the country's target of <4% by 2025 (2). This is expected because the use of more than one drug has synergistic effect on the outcome in comparison to a single drug, hence the use of triple therapy, especially for the high-risk HIV exposed, has a greater positive impact on MTCT unlike the use of a single therapy prophylaxis drug.

Additionally, improvement of services provided in PMTCT services throughout the country such as maternal retesting of HIV for the mothers who were HIV negative in the first trimester could also be contributing factors (40).

Despite the lower incidence rate observed, it was still high across various groups. The higher incidence rate of MTCT among mothers with poor ARV adherence is possibly due to; with poor ARV adherence, there is reduced chances of decreasing viral load hence increasing the chances for transmission from the mother to their children.

The higher incidence rate among infants who did not receive prophylaxis at birth is possibly due to the delay in initiating the prophylaxis on the infants decreases the effectiveness of the prophylaxis unlike if it was initiated timely, hence increasing the chances of developing the disease.

Infants who were mixed fed during the first six months of life had higher incidence of acquiring HIV infection from their mothers and this is mainly due to immature gut of the infants in this stage of life hence more prone to bruises hence penetration of the virus from the mother's milk to the infant's blood via the circulatory system. These findings are in line with various other studies conducted both inside and outside Africa (7,13,15,19–20,22,28,30–32,34,39–42).

Moreover, the current study found that incidence rate decreases with the increase in maternal age which could be attributed to maturity of the mother as age increases hence increasing adherence to management and other preventive measures to reduce risk of vertical transmission. This finding is in contrast with a study conducted in Brazil, where incidence did not vary significantly with mother's age, which is possibly due to differences in culture and other socio-economic factors with our setting (19).

It is further observed in this study that infants born to mothers who are in early WHO stages (stage 1 and 2) have higher incidence of acquiring HIV from their mothers in comparison to those in late stages (stage 3 and 4), this could be attributed by the attitude of members in our setting of not adhering to management as well as preventive measures properly when not feeling sick unlike when the disease is advanced. This finding is different from studies conducted in Uganda and Kenya which showed the rate of transmission to be higher among infants born to mothers which is possibly due to the differences of attitude among community members in these settings (6,44).

5.2 Maternal factors associated with incidence rate of MTCT of HIV in the era of triple therapy HIV prophylaxis among HIV exposed infants.

The results of this study revealed that infants born to mothers with poor ARV adherence to be more likely to acquire vertical infections from their mothers unlike those born to mothers with good ARV adherence. It is well established that good ARV adherence is critical in boosting immunity by increasing CD 4 count and decreasing viral load which in turn reduces the risk of person-to-person transmission eventually decreasing the risk of MTCT. This result is in line with other studies conducted in Canada, China, Mozambique, Ethiopia, Uganda and Kenya (6,30,36,41–44).

Moreover, age of the mother is shown to be associated with the rate of MTCT, advanced maternal age (>25 years of age) is found to be protective of MTCT. And this is possibly due to the mature nature of the mothers in this age hence more prone to adhere to management and other preventive measures. This finding is in contrast with a study conducted in Brazil, where risk did not vary significantly with mother's age, which is possibly due to differences in culture and other socio-economic factors with our setting (19).

5.3 Infant Factors associated with incidence rate of MTCT of HIV in the era of triple therapy HIV prophylaxis among HIV exposed infants.

This study showed mixed feeding in the first six months of life of the infant to be a risk for Mother to Child Transmission. As it is well established through literatures that the gut of an infant in this stage of life is immature and vulnerable to bruises from other feeds apart from the mother's milk, so by introducing other feeds together with mother's milk in this stage increases the chances of passage of viruses from the mother's milk to the infant's circulatory system hence vertical transmission from the mother to the infant. This is in line with other studies conducted in Brazil, China, Malawi, Mozambique, Kenya, Uganda and Tanzania (7,21–23,33,41,45).

5.4 Study Limitations and Mitigations

1) Since the data is secondary, the information gathered was not complete for some variables, this was mitigated through dropping records with missing potential data such as outcome of interest.
2) Inconsistent potential dates (Entry date to the study and date of outcome occurrence). This was mitigated through cleaning of the data and involving only participants with consistent potential dates.

CHAPTER SIX

6.0 CONCLUSION AND RECOMMENDATIONS

6.1 Conclusion

Our study highlighted a lower overall incidence rate of HIV among infants born to HIV mothers in Tanzania mainland after initiation of triple therapy prophylaxis for high-risk HIV exposed infants from 2017 to 2021. However, the rate varies across groups; infants born to mothers with good ARV adherence versus those with poor ARV adherence, as well as across the four WHO stages, and for infants who received HIV prophylaxis at birth versus those who did not, those who received Nevirapine only therapy versus those who received triple therapy prophylaxis, and those who were exclusively breastfed for the first six months versus those who were mixed fed. Understanding the differences in incidence rates across the groups is essential in formulating targeted health interventions and approaches of care over time. The findings of our study give a general overview of the program performance through various interventions that have been carried out for the past 5 years aiming to improve the clinical outcomes of the HIV exposed infants in Tanzania. Mother's age, ARV adherence of the mother, type of prophylaxis given to the infant and feeding mode of the infant were identified as significant factors associated with mother to child transmission of HIV.

6.2 Recommendations

To accelerate further reduction of mother to child transmission of HIV in Tanzania, it is recommended to have a tailored intervention, by the ministry of health through the PMTCT program and other stakeholders, to the groups with higher incidence rates; infants born to young aged mothers (<25 years of age), mothers in early stages of WHO (stage 1 and 2) and those with poor ARV adherence, also for those infants who did not receive prophylaxis at birth, were kept on Nevirapine only therapy and those who were mixed fed during the first six months of life.

It is vital, for healthcare providers, to provide more education on young mothers on PMTCT measures and how to adhere to them to minimize the rate of them transmitting infections to their infants.

Furthermore, emphasis for mothers in early stages of WHO (Stage 1 and 2) to adhere to preventive measures to avoid vertical transmission to their infants. Healthcare providers should educate these women on the effect of neglecting their health and preventive measures, especially when not feeling sick; both to themselves and their infants as well.

Not only that, but also, emphasis on good adherence of ARV, including enhanced adherence counselling sessions for mothers with poor adherence should be conducted by healthcare providers among pregnant women living with HIV to reduce the rate of MTCT.

Moreover, is more emphasis on EBF for the first six months of life by the healthcare providers to the mothers which will be of great importance in reducing mother to child transmission of HIV.

The ministry of health through the PMTCT program and other stakeholders should work on provision of triple therapy prophylaxis for all HIV-exposed infants and not only the high-risk ones, as triple therapy prophylaxis is shown to be more effective than Nevirapine only therapy in PMTCT.

Healthcare providers should adhere to timely initiation of prophylaxis (at birth) for all HIV exposed infants. In addition to that, they should also educate affected mothers during their ante-natal visits on adhering to this and consequences of their infants not receiving prophylaxis at birth or within 72 hours of life.

In addition to that, further studies (prospective cohort studies using primary data) are required to account for the limitations of using secondary data such as missing data and some key variables such as Education level of the mother, Mode and place of delivery and HIV viral load of the mother, which are also considered to be important factors for MTCT according to literature. On top of that, a prospective study will ensure adherence of classification of infants as high-risk or low-risk by the healthcare providers.

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APPENDICES

Appendix I: Data abstraction tool

MATERNAL FACTORS															
S/N	Age	Marital Status	Region	Council	Facilty	CTC number	Patient ID	Clinic Visit date	ARV adherence	WHO Clinical Stage	Results date for HIV Viral Load				
INFANT FACTORS															
S/N	Sex	Age	Region	Council	Facility	Exposed Infant's ID	Mother Patient ID	Date of Birth	Clinic Visit date	HIV prophylaxis given at birth	Feeding mode	HIV test results at each visit	Date the HIV results were obtained	Medications given at each visit	Infant Status at 18 months of age

Appendix II: Ethical Clearance Letter

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/2017 Date: 07/02/2024

MUHAS-REC-02-2024-2017
FARAJA DAVID NG'IDA
SCHOOL OF PUBLIC HEALTH AND SOCIAL SCIENCES
MUHAS

RE: APPROVAL FOR ETHICAL CLEARANCE FOR A STUDY TITLED: INCIDENCE AND FACTORS ASSOCIATED WITH MOTHER TO CHILD TRANSMISSION OF HIV AMONG HIGH-RISK EXPOSED INFANTS ON TRIPLE THERAPY PROPHYLAXIS FOR HIV IN TANZANIA FROM 2017 TO 2021

Reference is made to the above heading,

I am pleased to inform you that the Chairman 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: 07/02/2024
EXPIRATION DATE OF APPROVAL: 07/02/2025

STUDY DESCRIPTION:
Purpose:

The purpose of the retrospective cohort study is to determine the incidence rate of mother to child transmission and factors associated with transmission among HIV exposed infants receiving HIV triple therapy prophylaxis in 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-%2014554.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. Apply for and obtain permission to publish the results from National Institute for Medical Research. The application should be before submitting to a publisher and not concurrently through the email publications@nimr.or.tz.
9. 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)
10. The PI is required to ensure that the findings of the study are disseminated to relevant stake holders.
11. 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://drp.muhas.ac.tz/.

Dr. Nahya Salim Masoud,
Chairperson, MUHAS Research and Ethics Committee

Muhimbili University of Health and Allied Sciences
DIRECTOR
Research & Publications
Box 65001

Appendix III: NASHCoP approval letter

THE UNITED REPUBLIC OF TANZANIA
MINISTRY OF HEALTH

Telegrams: "**AFYA**", **DODOMA**
Telephone: +255 026 2323267
Email Address: **ps@afya.go.tz**
(All letters should be addressed to
The Permanent Secretary
In reply please quote:

Government City - Mtumba,
Afya Road,
P.O. Box 743,
40478 DODOMA.

Ref. No. PA.104/262/01/336

6th June, 2024

Faraja Ng'ida,
P.O. Box 65091,
DAR ES SALAAM.

REF: REQUEST FOR AN APPROVAL TO USE DATA FOR RESEARCH PURPOSES

Please refer to the heading above.

2. The Ministry of Health acknowledges receipt of your letter dated 21st February 2024 with a title of request of an approval to use data for research purpose.

3. The Ministry of Health would like to inform you that, your request has been approved to use secondary data from National AIDS, STIs and Hepatitis Control program – NASHCoP.

4. Thank you for your collaboration.

Dr. Samwel L. Nhiga
For: PERMANENT SECRETARY

Copy: Permanent Secretary,
Ministry of Health,
40478 DODOMA. (To see in the file)