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LIFELONG ANTIRETROVIRAL TREATMENT FOR THE PREVENTION OF MOTHER-TO-CHILD TRANSMISSION OF HIV IN ROUTINE HEALTHCARE IN TANZANIA, WHAT WORKS?

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Karolinska Institutet

Stockholm 2022

Published by Karolinska Institutet.
Printed by Universitetsservice US-AB, 2022

ISBN 978-91-8016-448-1

Lifelong antiretroviral treatment for the prevention of mother-to-child transmission of HIV in routine healthcare in Tanzania, what works?
THESIS FOR DOCTORAL DEGREE (Ph.D.)

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The thesis will be defended in public at Karolinska Institutet, Stockholm, 24th February 2022, 9:30AM

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Kwa wazazi wangu, kwani wao walipanda mbegu ya kuitafuta elimu kwangu

To my parents for they planted in me, a seed of the pursuit of knowledge

Kwa familia yangu, kwani wao waliipalilia mbegu hii mpaka kufikia tunda hili

To my family, for they nurtured this seed to this fruition

Kwa mwanangu Malaika na wadogo zake, kwani kwao nami na mama yao tunaipanda mbegu hii

To my daughter Malaika and her siblings, for to them I and their mother also plant this seed

POPULAR SCIENCE SUMMARY OF THE THESIS

Despite availability of effective antiretroviral medicines that prevent HIV transmission, more than 10 out of 100 children born to women with HIV, in low- and middle-income countries (LMIC) such as Tanzania, still acquire HIV infection from their mothers. Although women with HIV can pass HIV to their children during pregnancy, childbirth or breastfeeding; lifelong HIV treatment is known to be highly effective at ensuring that almost no child born to a woman with HIV acquires the infection. Lifelong HIV treatment, free of charge for all pregnant women with HIV, has been part of standard of care in LMIC for almost a decade now, hence it is important to understand why HIV transmission to children remains high in these settings. Motivated by this dilemma, we conducted research to find out how well current programs to prevent HIV infection from mothers to their children work, in Dar es Salaam, Tanzania, when and why it does not work well, and how to improve outcomes.

We identified and followed close to 16,000 pregnant women with HIV who were receiving HIV treatment to prevent HIV transmission to their children in routine healthcare settings of Dar es Salaam from 2014 to 2021. At the end of follow-up, we estimated the effectiveness of this treatment by whether the women had suppressed HIV replication and by the final HIV status of their children. We also assessed whether community leaders can contribute to improve male partner involvement in services for prevention of HIV transmission to the children as well as whether experienced peer mothers also living with HIV can help other women with HIV to ensure that their children are not infected during pregnancy and breastfeeding.

Our results, show that HIV treatment works very well in suppressing HIV replication for a large majority (90 out of every 100) of the women with HIV who received treatment in routine healthcare settings. Furthermore, the longer the women stayed in care, the more likely they were to be virally suppressed. We also found that very few (2 out of every 100) children born to these women acquired HIV infection. These findings implied that overall, lifelong HIV treatment for pregnant women and mothers living with HIV works very well in ensuring that they stay well and healthy, and that their children remain free from HIV. We however, observed poorer outcomes among young women below 20 years of age, women who start HIV treatment late in pregnancy and women with advanced HIV disease. On the contrary, women who start HIV treatment before pregnancy, receive care in health facilities with a high number of patients or at facilities with high couple attendance and HIV testing at antenatal care, have better outcomes. Furthermore, we learned that community leaders can contribute to improve male partner participation in services to prevent HIV transmission and that experienced peer mothers with HIV can play a role to ensure that pregnant women, especially those newly diagnosed with HIV, adhere to treatment and do not drop-out from care.

In conclusion we call upon focused efforts to help pregnant women with HIV who remain at risk of poor outcomes (adolescents, late care seekers, women with advanced HIV), and to intensify engagement of community leaders and peer mothers to further reduce HIV infections in children in LMIC.

ABSTRACT

Background: The UNAIDS estimate of the risk of mother-to-child transmission of HIV (MTCT) in Tanzania remains unacceptably high at 11%, despite 84% coverage of lifelong anti-retroviral treatment (ART) for the prevention of MTCT (PMTCT). ART is known to reduce MTCT to <2%, however its outcomes in routine healthcare have not been readily evaluated. This PhD thesis aimed to contribute knowledge on the outcomes of use of lifelong ART for PMTCT in routine healthcare in Dar es Salaam, Tanzania, and opportunities for improvement.

Methods: Two prospective cohort studies were conducted to evaluate maternal and infant outcomes of lifelong ART for PMTCT. The studies involved 15,586 (study I) and 13,790 (study II) pregnant women who enrolled in routine PMTCT care between 2014 to 2017 and were followed up until 2021. Study outcomes were viral suppression [<400 viral copies/ mL] (study I) and MTCT [infant testing HIV positive by polymerase chain reaction or antibody test at ≥18 months old] (study II), and their determinants. Study III was a 1-year implementation study that evaluated the effect of engaging community leaders to improve male involvement in antenatal care (ANC) and couple HIV testing in six intervention facilities compared to 203 control facilities. Study IV was a cluster randomized implementation study involving 23 intervention and 24 control facilities to evaluate the effect of peer mother services in improving retention in care, viral suppression and MTCT among women on lifelong ART for PMTCT.

Results: In study I, we observed 88.2% (95% CI: 87.8% to 88.7%) viral suppression among women on lifelong ART for PMTCT in routine care. Viral suppression improved on longer duration in care from 85.1% at 0-11 months to 90.6% at 36+ months since PMTCT enrolment. The risk of virologic failure was 76% higher in women aged <20 versus 30–39 years old; 28% higher in women starting PMTCT care in third versus first trimester; and 33% higher in women with advanced versus early stage HIV. Conversely, virologic failure was 19% lower among women at ANC clinics with high versus low couple HIV testing coverage. In study II we found a low MTCT risk of 1.8% (95% CI: 1.5% to 2.1%) by 18 months post-partum. The odds of MTCT were 2-3 times higher in women who started PMTCT care late in second/ third versus first trimester and twice as high in women with advanced versus early stage HIV. The odds of MTCT were 69% lower among women who started ART before pregnancy. In study III, the community-leaders intervention improved couple HIV testing from 11.9% to 36.0% (p <0.0001) at the intervention facilities compared to no change at the control facilities. In study IV, the peer-mother intervention, compared to control, resulted in significantly higher one-year ART retention (78.0% versus 73.6%) and higher viral suppression among ART naïve women at baseline (90.8% versus 88.1%). However, no significant difference was observed on MTCT.

Conclusion: The findings of this thesis reaffirm the effectiveness of lifelong ART in achieving and sustaining high (>90%) maternal viral suppression and low (<2%) risk of MTCT in routine healthcare. The findings indicate that adolescent mothers, late care seekers and women with advanced HIV remain vulnerable to poor outcomes. The findings also highlight need for and opportunities to strengthen male involvement and peer mother engagement to further improve outcomes of lifelong ART for PMTCT in routine healthcare.

LIST OF SCIENTIFIC PAPERS

I. **Lyatuu GW**, Mwashemele SZ, Urrio R, Naburi H, Kashmir N, Machumi L, Kibao A, Sellah Z, Ulenga N, OrsiniN, Biberfeld G, Kilewo C, Ekström AM. Long-term virological outcomes in women who started option B+ care during pregnancy for prevention of mother-to-child transmission of HIV in Dar es Salaam, Tanzania: a cohort study. *The Lancet HIV*. 2021;8(5):e256-e265.

II. **Lyatuu GW**, Urrio R, Naburi H, Lyaruu P, Simba B, Siril H, Philipo E, Machumi L, Kibao A, Kajoka D, Nyamhagatta M, Sando D, Biberfeld G, Orsini N, Kilewo C, Ekström AM. Final mother-to-child HIV transmission outcomes of women on lifelong antiretroviral treatment in routine healthcare settings in Dar es Salaam, Tanzania: a cohort study. *[submitted]*

III. **Lyatuu GW**, Naburi H, Urrio R, Mwashemele SZ, Mdingi S, Panga R, Koda H, ChendeY, Tsere M, Mhalu A, Siril H, Lema IA, Aris E, Muya AN, Galanti MR, Biberfeld G, Kilewo C, Ekstrom AM. Engaging community leaders to improve male partner participation in the prevention of mother-to-child transmission of HIV in Dar es Salaam, Tanzania. *PLoS One.* 2018;13(12):e0207986.

IV. **Lyatuu GW**, Naburi H, Mwashemele SZ, Lyaruu P, Urrio R, Simba B, Philipo E, Kibao A, Kajoka D, Sando D, Orsini N, Biberfeld G, Kilewo C, Ekström AM. The role of peer-mothers in improving prevention of mother-to-child HIV transmission outcomes among women on lifelong anti-retroviral treatment in routine healthcare in Tanzania. *[submitted]*

CONTENTS

LIST OF ABBREVIATIONS

AIDS	Acquired immunodeficiency syndrome
ANC	Antenatal care
ART	Anti-retroviral treatment
ARV	Anti-retroviral
CD	Cluster of differentiation
CHW	Community health worker
CI	Confidence interval
COVID	Corona virus disease
CTC	Care and treatment clinic
DHIS	District health information system
DNA	Deoxyribonucleic acid
EID	Early infant diagnosis
GDP	Gross domestic product
GEE	Generalized estimating equations
GPH	Global Public Health
HCP	Health care provider
HEI	HIV exposed infant
HIV	Human immunodeficiency virus
ID	Identification
IQR	Interquartile range
KI	Karolinska Institutet
LMIC	Low- and middle-income countries
LTFU	Loss to follow-up
MDH	Management and Development for Health
mL	Millilitre
µL	Microlitre
MTCT	Mother-to-child transmission of HIV
MUHAS	Muhimbili University of Health and Allied Sciences
NNRTI	Non-nucleoside reverse transcriptase inhibitor
PCR	Polymerase chain reaction
PEPFAR	United States President’s emergency plan for AIDS relief
PhD	Doctor of Philosophy
PI	Protease inhibitor
PMTCT	Prevention of mother-to-child transmission of HIV
RCH	Reproductive and child health
RCT	Randomized clinical trial
Sida	Swedish international development agency
SSA	Sub-Saharan Africa
UNAIDS	The joint United Nations program on HIV and AIDS
WHO	World Health Organization

1 INTRODUCTION

1.1 THE STATE OF THE HIV PANDEMIC IN THE WORLD

Four decades have passed since the acquired immunodeficiency syndrome (AIDS), the disease characterised by progressive depletion of CD4 T cells and opportunistic infections following infection by the human immunodeficiency virus (HIV), was first reported in the early 1980s [1-3]. By the end of 2020, there were an estimated 37.7 million people living with HIV globally [4]. In that year, the world had made remarkable progress on tackling the HIV and AIDS pandemic including 50% reduction in new HIV infections and 64% reduction in HIV related deaths from their peaks in late 1999 and 2006, respectively [4,5]. This progress was largely contributed by improvements in the diagnosis and access to lifelong treatment for people living with HIV using anti-retroviral (ARV) drugs, which is known to greatly reduce HIV morbidity, mortality and transmission [5-7]. By the end of 2020, 84% of the people living with HIV were diagnosed, 87% of those diagnosed were on lifelong anti-retroviral treatment (ART) and 90% of those on treatment had suppressed viral replication [6]. Nevertheless, in 2020, HIV and AIDS remained a major global health concern with 10.2 million people living with HIV not on ART, 1.5 million new HIV infections and 680,000 HIV related deaths [4,6]. Of concern, the 2020 data indicated that progress towards ending the AIDS epidemic is slowing down, hampered by slow progress in prevention of new HIV infections, inequalities in access to effective HIV prevention, treatment, and support, as well as HIV related stigma and discrimination [6]. Although it is home to only 15% of the global population, in 2020 sub-Saharan Africa (SSA) carried a disproportionate burden of 67% of all people living with HIV, 58% of new HIV infections and 68% of AIDS deaths [4,8]. Furthermore in 2020, SSA women, especially young women, continued to be at a greater risk of acquiring HIV infection, and children were being left behind on progress towards ending the AIDS epidemic [4,6].

1.2 THE HIV EPIDEMIC IN WOMEN

Half of the new HIV infections in the world in 2020 occurred in women, including 610,000 HIV infections among women of reproductive age (15 to 49 years) [4]. In SSA, women accounted for about two-thirds of the persons aged 15 to 49 years acquiring new HIV infections, with adolescent girls and young women (15 to 24 years) having more than three times higher risk of HIV infection than their male counterparts [4]. New HIV infections in women of reproductive age predisposes to the risk of vertical mother-to-child transmission of HIV (MTCT) during pregnancy, childbirth and breastfeeding as well as threatening the health and wellbeing of mothers, who are critical to the survival, health and wellbeing of their children [9-12]. Women acquiring new HIV infections particularly during pregnancy or breastfeeding have a markedly increased risk of MTCT by up to three times [13-15]. Adolescent girls and young women are particularly vulnerable as they carry higher risks of acquiring HIV themselves, have poor treatment uptake, adherence and outcomes, and have a higher risk of vertical HIV transmission to their infants [16,17]. Up to 85% of the 260,000 adolescent girls and young women who acquired HIV infection in 2020, resided in SSA [4].

1.3 THE HIV EPIDEMIC IN CHILDREN

In 2020 there were 150,000 new HIV infections in children below 15 years old globally, of which 130,000 (87%) occurred in SSA [4,16]. Although the 2020 estimates indicated a 53% decline in HIV infections in children since 2010, this progress was far short of the 2020 target of fewer than 20,000 children acquiring HIV (Figure 1) [16]. Furthermore, these were staggering numbers at a time when HIV infections in children can be largely prevented through the use of lifelong ART for all pregnant and breastfeeding women with HIV [18,19]. HIV infections in children are predominantly driven by vertical MTCT, which can occur during pregnancy, childbirth or breastfeeding [10]. Without any prevention intervention the MTCT risk among pregnant and breastfeeding women with HIV can be as high as 45% [9,10]. However, the use of lifelong ART can reduce MTCT risk to less than 5% in breastfeeding populations and less than 2% in non-breastfeeding populations [20-27]. Nevertheless, in 2020, the MTCT risk globally remained high at 12%, despite 85% coverage of lifelong ART among pregnant women living with HIV, highlighting persistent gaps in Prevention of MTCT (PMTCT) efforts [16].

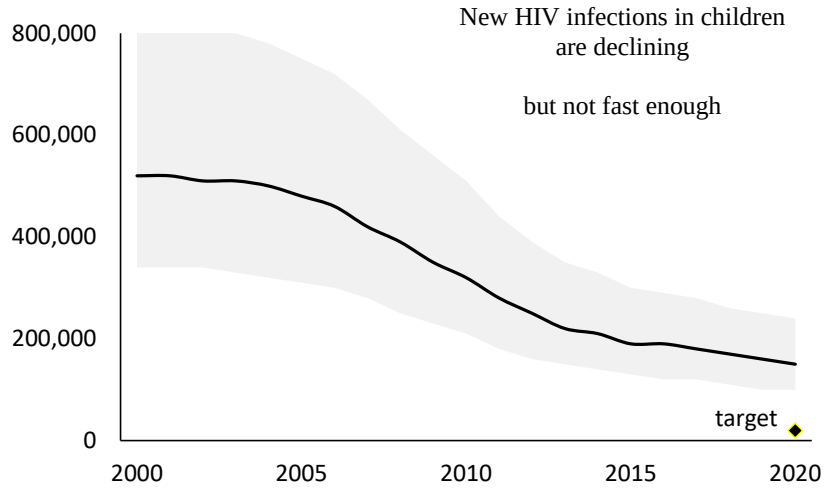

Figure 1. Global trend in new HIV infections in children across years
Source: UNAIDS HIV estimates, 2021 [https://aidsinfo.unaids.org/]

In 2020, twenty-one countries in SSA carried 80% of the global burden of children living with HIV and 83% of all pregnant women living with HIV [16]. These countries were designated by the UNAIDS as focus countries in efforts to end the AIDS epidemic in children [16]. The 21 focus countries accounted for 73% of the new HIV infections in children in 2020 [16]. Teasing out the unique peculiarities of these countries that hinder successful PMTCT and implementing targeted evidence-based solutions tailored to specific situations of these countries, is critical in efforts to end the AIDS epidemic in children.

1.4 PREVENTING MOTHER TO CHILD TRANSMISSION OF HIV

Approaches to prevent vertical HIV transmission during pregnancy and breastfeeding have evolved considerably over the past four decades of the HIV epidemic [19,28-33]. Use of ARV drugs for PMTCT started in mid/late 1990s and early 2000s, by then as single or dual drug regimens, following evidence from a series of randomized clinical trials (RCTs) [34-39]. By the 2000s triple ARV regimens for PMTCT were widely in use in high income countries, where they contributed to reducing the risk of MTCT to less than 2%, however access to these regimens in low- and middle-income countries (LMIC) was limited [30,40]. The 2010 WHO guidelines on the use of ART for treating pregnant women and PMTCT marked an important milestone in expanding access to triple ARVs for PMTCT in LMIC [32]. The guidelines recommended use of prophylaxis Options A or B for PMTCT in pregnant women with early-stage HIV disease (CD4 count >350cells/μL and clinical stage I or II) and lifelong ART to women with CD4 count ≤350cells/μL or clinical stage III or IV [32]. The main distinction between the two prophylaxis options was maternal use of either single-drug ARV from 14 weeks of pregnancy to one week after delivery (Option A) or triple ARVs from 14 weeks of pregnancy to one week after the end of breastfeeding (Option B) [32]. In 2012, the WHO issued an update to their 2010 guidelines recommending lifelong ART to all pregnant and breastfeeding women with HIV regardless of clinical or immunologic status, which became known as Option B+ [18]. The update was motivated by growing evidence in support of the use of triple ARVs for HIV prevention and treatment in pregnant and breastfeeding women with HIV in LMIC [7,20-27]. Moreover, Option B+ was also motivated by the decision of Malawi, one of the 21 focus countries in SSA, to offer lifelong ART to all pregnant women with HIV ahead of the WHO guidance [41,42]. The Option B+ provided a great momentum towards expanding access to lifelong ART containing triple ARVs for women living with HIV in LMIC as it allowed for a simplified public health approach that was easier to scale-up, monitor and achieve. Before long, in 2015, universal ART for all persons living with HIV was recommended as the mainstay approach to HIV treatment worldwide [43]. Despite the prospects that improved access to lifelong ART offered on ending MTCT there remained concerns as to whether asymptomatic women with HIV, diagnosed and starting ART due to pregnancy, will be motivated to adhere to lifelong ART long term [44-46]. Questions remained as to whether the success of triple ARVs in HIV prevention and treatment that were seen in highly controlled clinical trials settings can be achieved and sustained long term in less than ideal real-life settings. These questions were the motivation behind this PhD thesis, to evaluate the outcomes of use of lifelong ART for PMTCT in routine healthcare settings of Dar es Salaam, Tanzania.

1.5 ABOUT TANZANIA

Tanzania is one of the 21 focus countries in SSA that carry the highest global burden of HIV in children [16]. In 2020, the country had a projected population of 57.6 million people, of which the majority were predominantly young, with the median age of the population at 18 years old [47]. The country had a high annual population growth rate of 3.1%, driven by the high total fertility rate of 5 children per woman, and a life expectancy at birth of 66.1 years [47].

In 2020, the Gross Domestic Product (GDP) of Tanzania stood at USD 1,076 [8]. Tanzania had a good economic growth over the previous 20 years, with an average annual GDP growth of above 6%, which in 2020 contributed to reaching a lower middle-income status[8,48]. Nevertheless, a large proportion remains poor with close to a half of the population estimated to be living below the international poverty line of USD 1.9 per day [8,48]. Furthermore, like most of the world, the country's economy was impacted by the global response to the Corona virus disease (COVID) pandemic leading to a slowing down of GDP growth to 2% [8,48].

Tanzania has been successful in improving child survival, more than a 50% reduction in mortality rates per 1000 livebirths was realized among infants (99 to 43 deaths) and under-fives (147 to 67 deaths) from 1999 to 2015/16 [49]. However with regard to maternal mortality, there has been much less progress, with no significant changes in the past decade, stagnating at a high level of 556 maternal deaths per 100,000 livebirths in 2015/16 [49]. In 2015/16, 98% of Tanzanian women received antenatal care (ANC) from a skilled health care provider (HCP) during pregnancy and 63% delivered in health facilities, although only 24% started ANC in the first trimester of pregnancy and 49% made fewer than four visits before delivery [49].

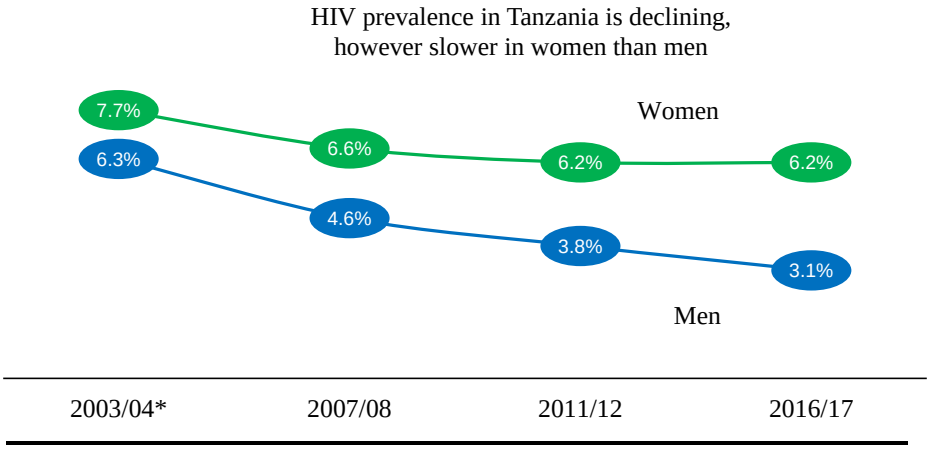

Figure 2. HIV prevalence in Tanzania by sex, across survey years
*Tanzania Mainland only. **Source:** Tanzania National Bureau of Statistics [https://www.nbs.go.tz/index.php/en/]

1.6 THE HIV EPIDEMIC AND RESPONSE IN TANZANIA

The adult (15 to 49 years old) HIV prevalence in Tanzania has been declining from a peak of 7.0% in 2003/04 to 4.7% in 2016/17, however the decline has been slower among women compared to men (Figure 2) [50,51]. In 2020 the country had an estimated 1.7 million people living with HIV, of which 59% were women aged 15 years and older [52]. Over 1.4 million (82%) people living with HIV were on lifelong ART [52]. In 2020, Tanzania had an estimated 68,000 new HIV infections, equivalent to an annual HIV incidence of 1.26 per 1000 persons, and 32,000 HIV related deaths[52].

Tanzania adopted and began nationwide roll-out of the use of lifelong ART for all pregnant women in PMTCT care (Option B+) in 2013, and later adopted lifelong ART for all people living with HIV in 2017 [53,54]. The country has had a notable progress in efforts to end the HIV epidemic in children including a 50% reduction in new HIV infections in children (from 20,000 to 10,000) from the year 2010 to 2020 [52]. Nevertheless, this progress was short of the UNAIDS fast-track targets of 75% reduction in new HIV infections by 2020 [55]. Furthermore, in 2020, the estimated MTCT risk in Tanzania was un-acceptably high at 11%, with 84% ART coverage among pregnant women with HIV [52]. This raises questions on how well lifelong ART for PMTCT works in Tanzania? What are the barriers or facilitators of success and how can the situation be improved? This PhD thesis was set out to answer these questions by investigating maternal virologic and infant MTCT outcomes of women on lifelong ART for PMTCT in routine healthcare in Tanzania, and, by evaluating interventions aimed to improve these outcomes.

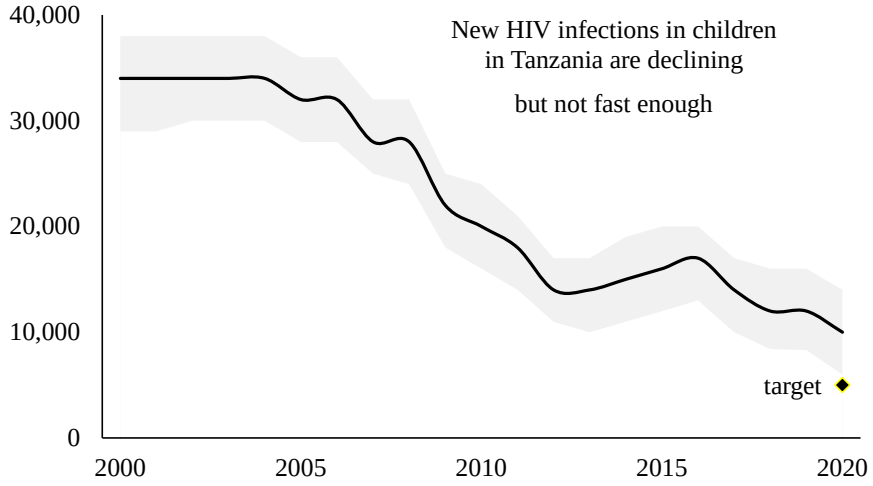

Figure 3. New HIV infections in children across years in Tanzania
Source: UNAIDS HIV estimates, 2021 [https://aidsinfo.unaids.org/]

2 LITERATURE REVIEW

2.1 GAPS IN PMTCT CARE IN THE ERA OF LIFELONG ART FOR PMTCT

Ever since the roll-out of lifelong ART for all in PMTCT care began, i.e. WHO's Option B+, there have been concerns on long-term effectiveness and outcomes, particularly in LMIC settings [44-46,56,57]. These concerns were driven by a lack of adequate clinical evidence on how to assure long-term ART adherence, retention in care and maternal and child outcomes, particularly beyond the pregnancy and breastfeeding period, and, in low-resource routine care settings [44,46,58]. Furthermore, the goal of universal access and uptake of HIV testing among all pregnant women attending ANC, meant that women in PMTCT settings were diagnosed with HIV and started lifelong ART at very early, often asymptomatic stages of their HIV infection It was, therefore, important to understand whether such women will keep their motivation to adhere to ART and be retained in care after delivery and breastfeeding, when PMTCT is no longer an issue [57-62]. Furthermore, there were concerns with regard to the feasibility of ensuring sustained access to lifelong ART for all in PMTCT care in resource constrained healthcare settings of LMIC [44-46]. This highlighted the need to expand the literature on the outcomes of lifelong ART for PMTCT in routine (i.e. non-research) healthcare settings to enable broader generalisation of the results.

The past decade has seen notable gains towards elimination of MTCT following the roll-out of lifelong ART for all in PMTCT care in LMIC. However the progress has slowed down in the past five years [16]. The 2021 UNAIDS' final report on the 2020 targets for ending the AIDS epidemic in children and adolescents – i.e. the Start Free, Stay Free, AIDS Free report – identified three major gaps that hinder successful PMTCT [16]:

- lack of or delayed access to ART before or during early pregnancy
- interrupted ART and/or disengagement from ART and PMTCT care
- incident HIV infections during pregnancy or breastfeeding

An analysis of country data by the UNAIDS indicated that the magnitude of these gaps in PMTCT varied considerably across SSA countries. Whereas in western and central Africa a major driver of MTCT (in up to 40%) was lack of access to ART, in eastern Africa up to 39% of MTCT was attributable to treatment interruption during pregnancy or breastfeeding and another 21% to incident maternal HIV infection during breastfeeding [63,64]. In southern Africa, 25% of MTCT was attributable to treatment interruption, 23% to lack of ART access and 21% to maternal HIV infection during breastfeeding [63,64].

Several underlying challenges contribute to the gaps in PMTCT: delays in HIV diagnosis before and/ or during pregnancy; delays in starting ANC during pregnancy; low male partner involvement in ANC and PMTCT care; inadequate primary HIV prevention in women at high risk of acquiring HIV during pregnancy and breastfeeding; as well as inadequate psychosocial and adherence support to women in PMTCT care [15,16,65-69]. Other challenges include: underequipped and overwhelmed healthcare systems, HIV related stigma and discrimination,

inadequate community engagement as well as poverty-related barriers hindering access to care [16,68,69]. This PhD thesis focuses on outcomes and gaps in the retention in PMTCT and ART care and adherence to ART, on viral suppression and on MTCT in routine healthcare settings in Tanzania. The following chapters provide an updated literature review of clinical studies across SSA on these focus areas.

2.2 FOCUS AREAS IN THIS PHD THESIS

2.2.1 Retention in PMTCT and ART care

Malawi was among the first countries to provide some evidence on outcomes following the implementation of lifelong ART for all women in PMTCT in routine care settings. In 2014, a study of 21,939 Malawian women who started ART under Option B+ revealed loss to follow-up (LTFU) rates of up to 17% in the first six months, with LTFU defined as not returning to the HIV clinic for more than 60 days since the last appointment [70]. Later on, in 2016 a subsequent publication from the same study team and setting reported LTFU rates of 22%, 27% and 28% at 12, 24 and 36 months, respectively, after starting ART among women who initiated lifelong ART during pregnancy or breastfeeding [71]. In this Malawian study; starting lifelong ART for PMTCT during pregnancy or breastfeeding, starting ART on the same day of HIV diagnosis, younger age and poor adherence were all associated with higher odds of LTFU [70,71]. On facility-level attributes, lower volume (numbers of) PMTCT clients to a certain clinic and the presence of additional adherence support services, i.e. peer counselling, were found to offer protection against LTFU [70]. Similar findings were reported from a study of 346 Ethiopian women starting lifelong ART for PMTCT, with LTFU rates of 12%, 16% and 23% at six, 12 and 24 months, respectively, after starting ART [72]. On the other hand, LTFU rates as high as 54% among 518 women, after 24 months of follow-up since starting ART and 40% among 2,160 women with a median ART follow-up of 20 months have been reported in Uganda [73,74]. In northern Tanzania, a study of 650 women who enrolled on lifelong ART for PMTCT during the early stages of the national roll-out in 2014, found that up to 59% were LTFU by 2 years post-partum [75]. However, these high LTFU rates may have been exaggerated by failure to adequately account for patient self-transfer, which was found in 36% of women previously categorized as LTFU in the study of 518 Ugandan women above, as well as for 30% of the women in another similar study in Malawi [73,76]. Across these studies, LTFU was associated with younger age, lack of formal education, non-disclosure of HIV status to partner, new HIV diagnosis in index pregnancy, and starting ART on the day of HIV diagnosis [72-76]. A meta-analysis of 35 studies in Africa by Knettel et al revealed consistent findings indicating a pooled retention rate of 73% at six months, and 76% at 12 months, after starting ART among women enrolling in PMTCT Option B+ [77]. This meta-analysis also identified younger age, starting ART on the day of HIV diagnosis, starting ART in pregnancy or late pregnancy, HIV-related stigma and inadequate social support as risk factors for poor retention in PMTCT and ART care [77].

2.2.2 Adherence to ART

Until recent years, the literature on virologic outcomes of patients on routine ART care in LMIC – the most objective standard measure of ART adherence - was not readily available [78]. Common measures of ART adherence that have been used previously, including patients' self-reports, pharmacy refill records and pill counts, are subjective and prone to bias [79]. Nevertheless, several studies on adherence to PMTCT regimens have been published using these more subjective adherence measures. A systematic review by Nachenga et al (2012) summarizes 51 such studies conducted prior to the era of lifelong ART for PMTCT, including 32 in Africa [58]. This review revealed that up to 76% of pregnant women were adherent to ARVs for PMTCT during pregnancy whereas only 53% were adherent postpartum [58]. However, the review had broad inclusion criteria, including defining optimum adherence as taking at least 80% of prescribed ARVs as well as use of older less efficacious PMTCT regimens such as single dose nevirapine and zidovudine [58]. Studies conducted in the era of lifelong ART for all women in PMTCT revealed varying proportions of women adherent to ART, from 33% in Nigeria, 39% in Zimbabwe, 43% in Tanzania, 51% in Uganda, 70% in Malawi, and 81% to 88% in Ethiopia [80-87]. However, across these studies, both adherence measures and threshold for optimum adherence varied widely. From these studies, optimum adherence to ART was associated with disclosure of HIV status, prior PMTCT exposure, presence of male partner and/or social support, more ANC visits, desire to prevent MTCT and higher education level [61,80,82,85,86,88]. On the other hand, poor adherence was associated with younger age, late ANC booking, new HIV diagnosis, ART side effects, feeling healthy, long distance/ duration/ cost of travel to access ART care, food deprivation and HIV related stigma [61,66,81,84,85].

Qualitative studies have also contributed to expand our understanding about factors influencing both adherence and retention in PMTCT care. They have provided key insights on barriers, perspectives and recommendations to improve uptake and outcomes of lifelong ART for PMTCT from the women in PMTCT care, their partners, HCPs and the community at large. In Malawi, a qualitative study involving 78 PMTCT clients (65 active and 13 previous defaulters), 19 HCPs and 32 community leaders identified fear of HIV status disclosure to partner, stigma and poor interaction with HCPs as barriers to optimum lifelong ART for PMTCT care [89]. These barriers, made women in PMTCT care take drastic measures to avoid them, which impaired their adherence, including skipping clinic visits for fear of being seen at the clinic or opting to go to another clinic more distant from their communities [89]. On the other hand, factors such as improved health outcomes of PMTCT clients over time and the desire to remain healthy and take care of one's children, were highlighted as facilitators of optimum uptake and outcomes of lifelong ART for PMTCT [89]. Another qualitative study of 57 Ugandan pregnant and breastfeeding women on ART care for at least six months found that a desire to have an HIV negative baby was a major motivator for women to start, adhere and remain on lifelong ART [90]. Other facilitators to optimum adherence included support from male partners, peers and support groups [90]. This Ugandan study highlighted fear of HIV-status disclosure to partner, stigma, inadequate counselling and ART initiation on the same day of HIV diagnosis, and ART side effects as major barriers to ART initiation and adherence [90]. In Malawi, a qualitative study

on the experiences of 39 pregnant and breastfeeding women on lifelong ART for PMTCT (14 active and 25 defaulters) revealed that major barriers to adherence and retention were lack of emotional and financial support from partners, inadequate counselling at ART initiation and lack of treatment supporter [88]. Moreover, women who were highly mobile due to personal socioeconomic reasons struggled to access/ continue with lifelong ART care in new settings [88]. Facilitators of adherence, retention and/or re-engagement to care after defaulting included good counselling from HCPs at ART initiation and follow-up, women's desire to be healthy, economic empowerment interventions, peer/ mentor mother counselling, social networks and meaningful male-partner engagement [88]. Recurring themes from these qualitative studies indicate that women's intrinsic motivation to remain healthy and have an HIV negative baby; comprehensive and client-centred ART counselling; support from partners, peer mothers and social networks; as well as a supportive stigma-free community, are powerful influencers of optimum uptake, adherence, retention and outcomes of lifelong ART for PMTCT [88-92].

2.2.3 Viral suppression

Evidence of undetectable/ low virus levels in the blood, i.e. viral suppression, is considered as an objective measure of optimum bioavailability of ARV drugs in blood and hence adherence to ART [93]. Conversely virologic failure - defined by the WHO as viral load count of 1000 or more copies per ml of blood, signifies suboptimal adherence or lack of treatment efficacy [19,94]. Roll-out of routine viral load monitoring of all patients on ART across most high HIV-burden countries, in recent years, has made it possible to objectively evaluate virologic outcomes of the use of lifelong ART for PMTCT in routine standard care settings [78,95]. In response to this, although still scarce, there has been a growing body of research on virologic outcomes of lifelong ART for PMTCT in routine care [96-99]. Nevertheless, most studies published thus far have been relatively small and with short follow-up periods of one to two years.

Viral suppression rates as high as 94%, using the <1000 copies/ml threshold, have been reported in a study of 165 Kenyan women enrolled on lifelong ART for PMTCT of whom, 82 were tested for viral load [96]. Of the 82 women, 22 were newly HIV diagnosed whereas 60 were known HIV positive prior to index pregnancy [96]. The median durations on ART at the time of viral load test were 6 months for the newly diagnosed women and 29 months for the known HIV positive women [96]. A viral suppression (<1000 copies/ml) rate of 85% was reported by a Rwandan study that investigated baseline virologic outcomes of 608 women enrolling on lifelong ART for PMTCT of whom 76% were already on ART with a median ART duration of 13.5 months - and 603 received a viral load test at enrolment [97]. Up to 52% of these women had an undetectable viral load, which in this Rwandan study the <20 copies/ml threshold was used [97]. In this Rwandan study, undetectable viral load was associated with higher gravidity, higher (secondary-level) education, disclosure of HIV status to partner, longer duration on ART and absence of ART side effects [97]. In Malawi, a cluster randomized trial of 1,269 women to evaluate ART uptake and retention strategies in PMTCT care settings that offer lifelong ART for PMTCT revealed a viral suppression of 84% among 833 women on median ART duration of nine months who were retained and tested for viral load at six months follow-up [98].

In this Malawian study, no statistically significant associations were observed between viral suppression and age, WHO clinical stage as well as among pregnant versus breastfeeding women [98]. A viral suppression of 81%, among 200 women on ART for a median of four years, was recorded in a Ugandan study [99]. This Ugandan study had among the longest reported median follow-up period since ART initiation at the time of viral load testing, however, up to 32% of the women enrolled were not available for viral load testing at study endpoint [99]. The study observed disclosure of HIV status to primary partner had close to five times higher odds of viral suppression[99].

2.2.4 Mother-to-child transmission of HIV

The ultimate goal of the PMTCT program is to prevent vertical HIV transmission from the mother to the infant during pregnancy, childbirth or breastfeeding and keep infants and mothers alive and healthy. To ascertain this goal, infants of women with HIV are normally followed up for up to two years of age, and tested for HIV several times to ascertain/ rule out MTCT during pregnancy, delivery or breastfeeding. In the first 18 months of life, virologic assays are used for early infant diagnosis (EID), the commonest being HIV deoxyribonucleic acid (DNA)-polymerase chain reaction (PCR) testing of infants dried blood spots. The WHO recommends that the first EID for HIV Exposed Infants (HEI) be done at four to six weeks of age and thereafter, upon a positive serological test, repeated when the baby is nine months and then three months after complete cessation of breastfeeding to obtain a final MTCT outcome [93].

Over the years, as PMTCT interventions have been evolving towards more robust longer regimens and expanding to reach more women, varying MTCT rates have been reported across studies, settings and PMTCT interventions. As highlighted earlier, the current Option B+ recommendation was motivated by studies that had shown that the use of triple ARVs during pregnancy and breastfeeding reduced MTCT risk to less than 5%. These studies included a prospective cohort of 1,150 mother-infant pairs who started maternal ART during pregnancy, regardless of WHO stage and CD4 count, from 2004 to 2006 across Mozambique, Tanzania and Malawi [22]. That study observed low MTCT rates of 0.8% (at one month of age) and 2.7% (at six months of age) among formula-fed infants, as well as 1.2% (at one month of age) and 2.2% (at six months of age) among breastfed infants [22]. Later on, from 2005 to 2008, a multi-centre RCT of 824 women who had CD4 counts of 200-500 cells/ml - across Burkina Faso, Kenya and South Africa - provided further evidence in support of longer duration triple ARV use for PMTCT [23]. The study revealed that infants of women with HIV who used triple ARVs during pregnancy and breastfeeding had almost half the risk of MTCT, at 12 months of age, of 5.4% compared to 9.6% among infants of women who used zidovudine and a single dose of nevirapine, which was the PMTCT recommendation at the time (i.e. not the triple ARV drugs/ ART regimen that is recommended today) [23]. Similarly, at six weeks of age, the MTCT rate was 3.3% in the triple ARVs group versus 5% in the zidovudine and single dose nevirapine group [23]. Low MTCT rates were observed in several other studies of women that had used triple ARVs during pregnancy and breastfeeding for PMTCT including 1.1% at six months among 709 HEI in Botswana, 1.3% at nine months among 532 HEI in Rwanda, 2.5% at six weeks and

6.7% at 18 months among 487 HEI in Kenya as well as 4.1% at six weeks and 6% at 18 months among 441 HEI in Tanzania [21,24-26].

Since the roll-out of Option B+, few studies have evaluated MTCT outcomes of women on lifelong ART for PMTCT in routine healthcare settings, particularly with longer follow-ups including the end of breastfeeding. A Malawian study of 11,285 HEI, enrolled at a median age of 1.7 months, is perhaps the largest to be published, that reported EID outcomes in HEI of women who used Option B+ [100]. In this study an MTCT rate of 0.7% by 8 weeks and 2.6% by 30 months post-partum was reported, however by 30 months, up to 58% of the HEI were LTFU [100]. To account for the unobserved EID outcomes due to LTFU, the authors performed inverse probability weighting which estimated an MTCT rate of 5.3% for the entire cohort [100]. Another nationally representative Malawian study of 2,505 mother-infant pairs found an MTCT rate of 3.7% among HEI aged 4-12 weeks of age whose mothers enrolled on lifelong ART for PMTCT, whereby 91% of the mothers used ART during pregnancy [101]. Several other emerging publications from smaller studies have observed similarly promising but varying results. In Zambia, MTCT rate of 3% was reported by 12 months post-partum among 827 mother-infant pairs enrolled on lifelong ART for PMTCT. In this study, among the 827 enrolled mother-infant pairs, up to 2.8% infants had died and 4.3% were lost to follow-up [102].

A study of 665 women in Swaziland who enrolled in PMTCT care at the time of the roll-out of lifelong ART for PMTCT observed only 7 (2.2%) HIV infections by six weeks, among 320 HEI tested [103]. However, up to 25% of the women in this study did not start ART and a half of the infants received EID [103]. In Rwanda, MTCT rates of 0.5% by six weeks and 2.2% by 24 months were observed among 608 women enrolled on Option B+, of whom 600 were followed until delivery and 597 HEI were live-born [104]. In this study 97% of the HEI were retained and tested for EID by six weeks and 76% by 24 months of age [104].

In Ethiopia, MTCT rates as low as 0.7% at a median of seven weeks post-partum was reported among 494 women enrolled in a prospective PMTCT cohort study who started/ were already using ART in index pregnancy [105]. In this study EID results were available in 87% of the women, with up to 66% of the HEI tested by eight weeks of age [105]. In Malawi, only 1 (0.5%) out of 204 HEI whose mothers started lifelong ART for PMTCT was found to be HIV positive by six weeks. However, likewise, in this study only 42% of the women enrolled had infants EID records [106]. In Lesotho, 1 (1.3%) out of 77 infants tested by six weeks of age was found to be infected in a cohort study that enrolled 107 pregnant women with HIV [107].

In Tanzania, a study that investigated the MTCT cascade among cohorts of women/ infants at different stages of PMTCT care, in the era of lifelong ART for PMTCT, observed an MTCT rate of 2.2% among 135 HEI who were tested for HIV at a median age of six weeks [108]. However, this study enrolled HEI post-partum and had up to 12% of the mothers and 25% of the HEI who did not receive correct ART intervention [108].

Fewer studies have reported factors associated with the risk of MTCT in the era of lifelong ART for PMTCT. The Malawian study of 2,505 mother-infant pairs found a higher risk of

MTCT in women with unknown HIV status/ not on ART during pregnancy compared to those on ART prior to pregnancy [101]. The Zambian study of 827 mother-infant pairs found that more maternal years of education, higher parity and institutional delivery were protective against the risk of MTCT or death [102]. In an unmatched case control study of 44 mothers living with HIV whose infants were HIV infected and 176 HIV-free controls by 24 months of age in Ethiopia, under the lifelong ART for PMTCT settings, non-participation in mother-to-mother support programs and low partner involvement were associated with up to five and seven times higher risk of MTCT, respectively [109]. Other MTCT risk factors identified included: poor adherence to ART, positive syphilis test, maternal malnutrition, unintended pregnancy and mixed feeding before six months of age [109]. Another unmatched case control study of 94 mothers of infected babies and 94 un-infected controls found a higher MTCT risk among women residing in rural areas, who delay enrolment to PMTCT, and whose infants miss ARV prophylaxis after birth [110].

2.2.5 Improving the use and outcomes of lifelong ART for PMTCT

Emerging research on interventions to improve the use and outcomes of lifelong ART for PMTCT in routine healthcare presents mixed findings [111-118]. In 2016, Ambia et al published a systematic review of 34 studies, 33 in Africa, that investigated interventions to improve PMTCT service delivery and retention. A majority of these studies were conducted prior to the era of lifelong ART for all women in PMTCT care and included 13 observational, 11 quasi-experimental and 10 randomized/ cluster randomized studies [112]. This review found that mobile phone-based reminders improved uptake of first EID by six weeks of age and male partner involvement reduced the MTCT risk, however psychological interventions did not have statistically significant effect [112]. A similar finding was observed in another systematic review of 10 studies (nine in SSA) which evaluated interventions to improve post-partum retention in PMTCT care by Geldsetzer et al [119]. Of note, both reviews highlighted low quality of included studies and heterogeneity as notable limitations [112,119].

A few available studies that evaluated the role of peer mothers living with HIV on improving PMTCT outcomes in the era of lifelong ART for PMTCT, have also reported mixed findings indicating a small or no significant effect associated with the intervention [116-118]. This includes two studies in Malawi and Nigeria that reported better ART retention in women receiving a peer mother intervention, whereas another Malawian study indicated a higher risk of attrition in a facility-based mentor mother intervention compared to community-based expert clients and community health workers (CHWs) [116-118]. Similarly, the two Malawian studies had mixed findings on virologic outcomes whereby in one study peer mothers contributed to significantly higher viral suppression whereas the other study reported no significant differences [117].

In a cluster randomized trial of 3,150 Tanzanian women on lifelong ART for PMTCT an enhanced paper-based appointment tracking and community outreach intervention resulted in a modest reduction in the rate of missing appointment from 37% to 34% compared to an increase from 39% to 45% in control sites receiving standard of care [120]. In Mozambique, a step wedge cluster randomized study of 761 pregnant women revealed that workflow

modification and active patient tracking improved 30-days retention to 71% compared to 52% in control sites. However, at 90 days follow-up retention rate was very low across both intervention (41%) and control (38%) sites [121].

In Kenya, randomized clinical trials evaluating the effect of text messaging on ART and PMTCT outcomes reported no significant differences in retention, viral suppression and MTCT comparing intervention to control facilities [115,122].

2.3 KNOWLEDGE GAPS ADDRESSED BY THIS PHD THESIS

The above literature review highlights that whereas lifelong ART for PMTCT has been successfully rolled out and contributed to accelerating progress towards ending HIV infections in children; uptake, adherence and outcomes vary widely across countries, settings and sub-groups. Furthermore, even in settings with a high uptake of lifelong ART for PMTCT, retention in care, treatment adherence and EID uptake remain notable barriers. In Tanzania, the existing research literature was particularly scarce on both maternal and infant outcomes of lifelong ART for PMTCT, as well as on effective strategies to address emerging challenges, namely long-term retention in PMTCT care, adherence to ART and MTCT at the end of breastfeeding. Thus, the main motivation behind this PhD thesis was to evaluate maternal and infant outcomes of the use of lifelong ART for PMTCT in routine healthcare settings of Tanzania, factors that influence these outcomes and what can be done to improve the outcomes. The thesis contributes to fill knowledge gaps on long-term maternal virologic and infant final MTCT outcomes of lifelong ART for PMTCT in routine healthcare settings of Tanzania, determinants of these outcomes, and effective interventions to improve them.

This PhD thesis, therefore, answers three main questions: How effective is the use of lifelong ART for PMTCT in achieving sustained viral suppression in women and preventing MTCT; what influences the effectiveness of lifelong ART for PMTCT; and how can PMTCT outcomes be improved in routine healthcare settings?

3 RESEARCH AIMS

3.1 AIM

To increase the knowledge on outcomes of lifelong ART for the prevention of mother-to-child transmission of HIV (PMTCT) in routine healthcare settings in Dar es Salaam, Tanzania, and, to identify opportunities for improvement.

3.2 SPECIFIC OBJECTIVES

1. To determine viral suppression rates and the risk of virologic failure among women living with HIV who use lifelong ART for PMTCT in routine healthcare settings [paper 1]

2. To determine the risk of mother-to-child transmission of HIV (MTCT) in infants of women using lifelong ART for PMTCT in routine healthcare settings [paper 2]

3. To evaluate two interventions, male partner involvement [paper 3] and peer mother engagement [paper 4], both aimed to improve outcomes of lifelong ART for PMTCT in routine healthcare settings

3.3 THEORETICAL FRAMEWORK

This PhD study draws upon the Dahlgren-Whitehead socio-ecological model of health to describe factors that influence outcomes of lifelong ART for PMTCT (Figure 4) [123].

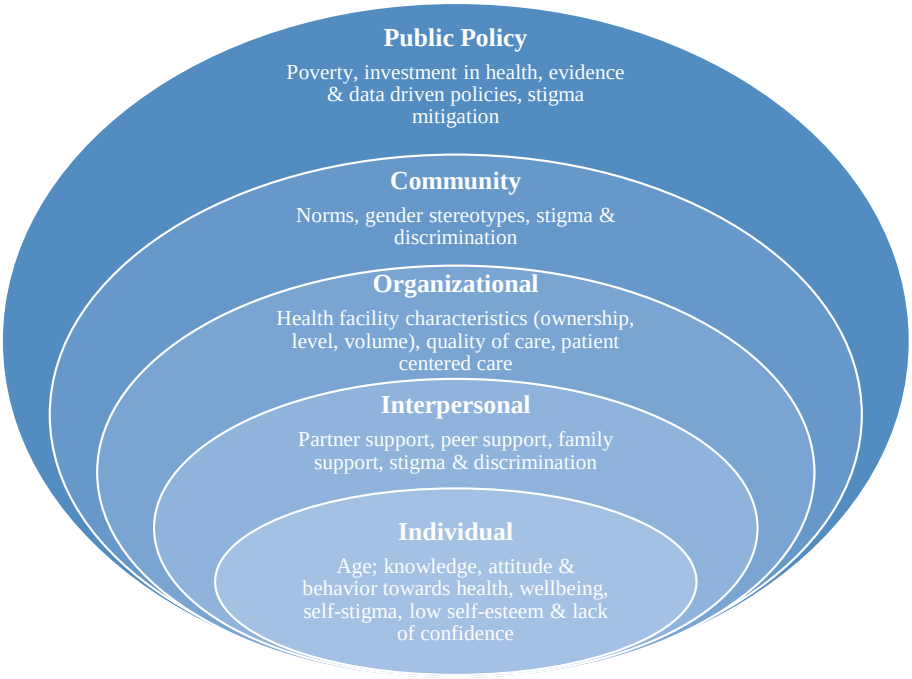

Figure 4. Socio-ecological model of health
Source: Dahlgren-Whitehead socio-ecological model of health (https://core.ac.uk/download/pdf/6472456.pdf)

These factors that influence uptake, adherence and outcomes of the use of lifelong ART for PMTCT, that have been explored in this thesis, are displayed across layers of influence from individual to public policy/ structural level. The model facilitates mapping of the relationship of the pregnant woman with HIV with her social environment and how this may influence her awareness and motivation to take sustained positive action towards improved uptake, adherence and desired ART and PMTCT outcomes. At an individual level, age is known to be an important non-modifiable determinant of attitude and behaviour towards health and PMTCT. Other modifiable determinants include knowledge, attitude and behaviour towards health (ANC, sexual and reproductive health, HIV prevention, ART and PMTCT care) as well as HIV related self-stigma and the associated low self-esteem and lack of confidence to make and sustain healthy choices and behaviours. At an interpersonal level support from partner, peers and family has been described, in the literature, to play an important role in terms of influencing uptake, adherence and outcomes of ART and PMTCT care. At the organizational level, the quality of the interactions and care that a woman living with HIV experiences from a health facility, can influence her uptake and outcomes of ART and PMTCT services. Quality of care and interactions between HCP and patients, are in turn influenced by facility characteristics such as ownership, level and volume, skills and competence of HCPs to offer patient centred care and support as well as HIV-related stigma and discrimination at facility level. At the community level, societal culture and norms shape many aspects of health attitudes, behaviour and social interactions. This includes gender stereotypes with regard to timing of ANC, male partner participation in ANC and PMTCT as well as stigma and discrimination towards people living with HIV. The policy and structural level shapes many aspects of social interactions, health, ART and PMTCT care across levels below it. This includes issues such as resources allocated to health care services, investment in health system strengthening, adaptive health care policies that are data driven and responsive to the evolving evidence and needs of people served as well as robust initiatives to mitigate HIV related stigma and discrimination.

In this PhD thesis, the influence of socio-ecological determinants of health described above, whose data were available in routine care records, on the outcomes of the use of lifelong ART for PMTCT in routine healthcare was examined (studies I and II). In studies III and IV, the effect of modifying some of these determinants to enhance the ART and PMTCT outcomes was also examined.

4 MATERIALS AND METHODS

4.1 STUDY DESIGN

This PhD thesis was designed to answer three key questions: (1) how well does *lifelong ART for PMTCT* work in routine health care settings; (2) what influences the success of the use of lifelong ART for PMTCT and (3) how can the outcomes of the use of lifelong ART for PMTCT be improved. Table 1 provides a summary of the methods for the four studies/ papers included in this thesis. The first two studies employed a prospective cohort study design to answer the first two questions on outcomes of pregnant women on lifelong ART for PMTCT and the determinants of these outcomes. Study I focused on the maternal virologic outcome whereas study II focused on mother-infant vertical HIV transmission outcome. The last two studies employed implementation research study designs to answer the third question on interventions to improve PMTCT outcomes among women on lifelong ART for PMTCT in routine healthcare. Study III was a non-randomized implementation evaluation study which evaluated an intervention that entailed engagement of community leaders to improve male partner participation in ANC and PMTCT services. This intervention was being scaled up in six purposively selected intervention sites whereas 203 other facilities served as control. Study IV was a cluster randomized implementation study, involving 23 intervention and 24 control clusters, that evaluated the role of peer mothers with HIV in improving PMTCT outcomes among pregnant women on lifelong ART for PMTCT.

Table 1: Summary of Methods for the four studies/ papers included in this thesis

Study/ Paper	Research Question	Study design	Main Exposures	Main Outcome	Data source
I	How well does *lifelong ART for PMTCT* work in routine healthcare? What influences its success?	Prospective cohort	Patient socio-demographic and clinical characteristics, and health facility attributes	Maternal viral suppression	National, routine care electronic databases of patients with HIV on lifelong ART and pregnant women receiving ANC in Tanzania
II				MTCT	
III	How can the outcomes of the use of *lifelong ART for PMTCT* be improved?	Implementation research	Community leaders promoting male partner participation in ANC and PMTCT	Couple HIV testing at antenatal care	
IV			Peer mother adherence and psychosocial support	ART retention, Maternal viral suppression and MTCT	

Abbreviations: ANC = Antenatal care, ART = Anti-retroviral treatment, HIV = Human Immunodeficiency Virus; MTCT = Mother-to-child transmission of HIV; PMTCT = Prevention of MTCT,

4.2 STUDY SETTING

All the four studies included in this thesis were conducted in routine healthcare settings of Dar es Salaam (Figure 5), the largest city and commercial capital of Tanzania, home to 9% of the country's total population of 58 million people[47]. Dar es Salaam is among the fastest growing cities in Africa, with rapid population growth and high in and out migration of people seeking better socioeconomic opportunities and/or healthcare[124,125]. In the 2016/17 Tanzania HIV Impact Survey, 4.3% of adults aged 15 to 49 years in Dar es Salaam were estimated to be living with HIV, with women having three times higher HIV prevalence of 6.3% compared to 2.0% among men [50]. Just as for Tanzania as a whole (Figure 2), the prevalence of HIV in Dar es Salaam has been on a declining trend, from 9.3% in 2007 to 4.3% in 2017, however at a slower pace among women from 10.4% to 6.3%, respectively [50,126].

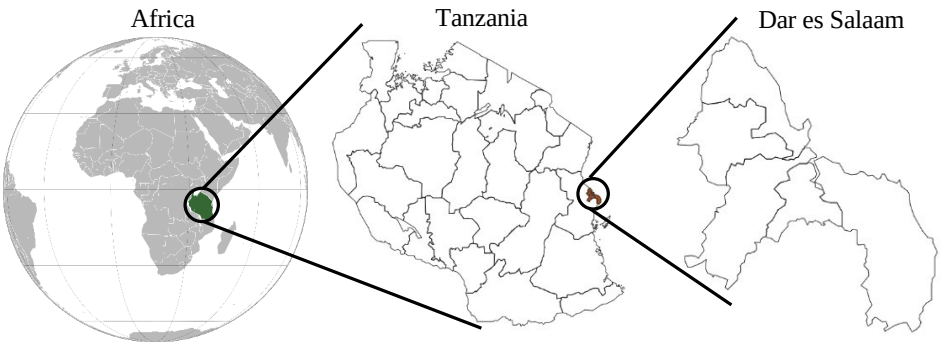

Figure 5. Geographical location of the study setting, Dar es Salaam Tanzania
Source: Wikipedia (https://en.wikipedia.org/wiki/File:Blank_Map-Africa.svg) for the map of Africa and the Tanzania District Health Information System (https://dhis.moh.go.tz/dhis-web-commons/security/login.action) for maps of Tanzania and Dar es Salaam.

In Tanzania, the government is the primary custodian of both ANC and HIV prevention, care and treatment services - including PMTCT - which are provided free of charge across public and private health facilities. HIV prevention, care and treatment services are supported, by up to 90%, through funding from United States President's Emergency Plan for AIDS Relief (PEPFAR) and the Global Fund [127]. At the regional and district level, HIV prevention, care and treatment services are managed by the local government authority in collaboration with PEPFAR/ Global Fund funded non-governmental organizations referred to as implementing partners [127]. In Dar es Salaam, Management and Development for Health (MDH) is the designated implementing partner supporting the management of HIV prevention care and treatment services and data. As part of routine care, all persons diagnosed with HIV in Tanzania are each issued a national unique HIV care and treatment clinic (CTC) identification (ID) number known as the CTC-ID, enrolled in CTCs and offered lifelong ART on the day of HIV diagnosis. The CTC-ID is used to register, record and manage ART care of all HIV patients using health facility charts (CTC2 cards) and the national electronic CTC2 database for ART care services, as well as to identify and link patients transferring care across facilities. Patients on ART care, are monitored through monthly/ quarterly/ semi-annual clinic visits and their

clinical progress, including laboratory monitoring, is recorded and managed via the CTC2 database. By the end of 2020, Dar es Salaam had a total of 176,593 persons living with HIV active on ART care [128].

In Tanzania, PMTCT care is integrated with ANC services and provided under one roof at ANC/ reproductive and child health (RCH) clinics as standard of care. All pregnant women registering for ANC are tested for HIV at their first ANC visit. Pregnant women are encouraged to attend ANC clinic together with their partners, from the first ANC visit, and are counselled on and offered couple HIV testing at ANC. Information on ANC attendance and HIV testing is captured via paper-based ANC registers and reported monthly via facility aggregate monthly summary reports which are entered in the web-based electronic district health information system (DHIS2) as part of routine care. Pregnant women who test positive for HIV at antenatal screening are issued CTC-IDs, registered in CTC2 database and enrolled in PMTCT/ ART care and follow-up at ANC. Pregnant women newly diagnosed with HIV are offered lifelong ART on the day of HIV diagnosis and those already on ART are enrolled in PMTCT care and continued on ART/ PMTCT follow up at ANC. In 2020, a total of 175,931 pregnant women registered for ANC across 356 ANC health facilities in Dar es Salaam [128]. Four percent of these women were HIV positive, with about a third of them newly diagnosed with HIV during the index pregnancy [128].

Prior to 2019, non-nucleoside reverse transcriptase inhibitor (NNRTI) containing regimens were the default adult ART regimen in Tanzania, including for pregnant and breastfeeding women. In 2019, Tanzania switched to an integrase inhibitor as first line ART regimen backbone using Dolutegravir and began stepwise transition of all patients on NNRTI- to dolutegravir- based regimens over two years. Protease inhibitors (PIs) remained as backbone regimens for second-line ART. Both ANC and PMTCT follow-up for pregnant women on ART care is done through integrated monthly visits for: clinical and laboratory monitoring; refills of ARV drugs and ANC supplements; as well as counselling on ANC, birth preparedness, ART adherence, infant feeding, EID and other ANC/ PMTCT services. As part of routine ART care, women with HIV who do not show up at their scheduled ART/ PMTCT follow-up visit are traced (after three days) via phone call and if unsuccessful, a home visit by a CHW is performed. Upon at least three unsuccessful tracking efforts over 90 days, these women are declared as lost to follow-up. In Tanzania, viral load monitoring is part of routine care for all patients on ART. Pregnant women already on ART before the index pregnancy are tested for viral load at first ANC visit whereas those newly HIV diagnosed during ANC receive their first viral load test three months after starting ART. Thereafter viral load monitoring is performed six-monthly until the end of breastfeeding for all women on PMTCT care, thereafter once annually. Women whose viral load results are high (1000 or more copies/mL) at any of the periods tested are enrolled on enhanced adherence counselling and follow-up over three months, thereafter re-tested for viral load and if non-responsive they are switched to a second line ART.

At birth, infants born to women with HIV, i.e. HIV exposed Infants (HEI) are given daily nevirapine prophylaxis for six weeks, with addition of zidovudine for high risk HEI (born to mothers on ART for less than four weeks or with high viral load). At six weeks, HEI are registered in PMTCT/ EID follow-up and issued unique HEI IDs, linked to their mother's CTC ID, that is used to record and manage their care and follow-up including EID tests. At six weeks HEI are also started on daily co-trimoxazole prophylaxis, and receive their first HIV test for EID using PCR. Mother-infant pairs in PMTCT care are followed, through monthly PMTCT clinic visits, for up to two years post-partum, or earlier upon a confirmed positive infant HIV test, at which point the HIV-diagnosed infant and mother are transitioned to routine ART care, and HIV negative infants are discharged.

4.3 STUDY POPULATION

The study population for this thesis comprised of pregnant women starting ANC (study III) and pregnant women with HIV (new, previously diagnosed and transfers), and later their infants, enrolling in PMTCT care (study I, II and IV) across up to 232 MDH supported health facilities in Dar es Salaam. These facilities accounted for about 90% of all the ANC, PMTCT and ART care in Dar es Salaam and were chosen because they had access to electronic routine healthcare data needed for the studies. In study I, participants included all pregnant women with HIV who enrolled in PMTCT care across 213 facilities from 1st October 2014 to 30th September 2016. Study II included all mother-infant pairs who enrolled in PMTCT care during pregnancy across 226 facilities from 1st January 2015 to 31st December 2017. In study III participants were new pregnant women who registered for ANC and tested for HIV across 209 facilities from 1st January 2015 to 31st March 2016. In study IV, participants included pregnant women with HIV who enrolled in PMTCT care from 1st January 2018 to 31st December 2019 and their infants. For both study II and IV, only the first-born infants were included from among mothers who gave birth to twins or triplets.

4.4 STUDY PROCEDURES AND DATA COLLECTION

As described in Table 1, the first two studies in this thesis evaluated the outcomes of the routine lifelong ART care for PMTCT (described above under study setting), whereas study III and IV evaluated the effect interventions aimed at improving these outcomes.

In study III, the core intervention entailed engagement of local community leaders of catchment areas surrounding the six intervention facilities to lead efforts in promoting male partner participation in ANC and PMTCT services. As part of the intervention these community leaders (at least one per facility) were identified, oriented and engaged to promote male partner participation in ANC and PMTCT services during their routine community activities, working in partnership with the HCPs. A key element of the intervention was for community leaders to buy-in to the agenda of promoting male partner participation in ANC and PMTCT services and deliver it to the community as their own. Additionally, the core message delivered by the community leaders was reframed to focus on the role and benefits of male partner participation in RCH services as whole with the aim of mitigating the barriers of the pre-conceived notions

of ANC clinics as women-only spaces as well as the stigma associated with HIV services. The 203 control facilities implemented standard of care (described above under study setting) with general HCP-driven efforts to promote male partner participation at ANC and PMTCT such as health education and priority service to couples.

In study IV, the core intervention entailed engagement of peer mothers living with HIV, who are experienced on ART and PMTCT care, to provide peer adherence and psychosocial support to other women living with HIV who are enrolling in PMTCT care. As part of the intervention 92 peer mothers were identified, trained and engaged to provide peer mother services in the 23 intervention facilities. A key element of peer mother services was for the peer mother to provide individualized health education, adherence and psychosocial support to new PMTCT clients through sharing her lived experience with HIV, lifelong ART and PMTCT care and techniques to overcome barriers that hinder successful ART and PMTCT outcomes. The 24 control facilities implemented standard of care (described above under study setting) with PMTCT health education and adherence support provided primarily by HCPs.

Upon enrolment in ANC and/ or PMTCT care, follow-up of women, infants and facilities included in all four studies was done through the routine ANC and/ or PMTCT/ EID clinic visits. In study I, II and IV, study participants were followed up prospectively from enrolment until study outcome ascertainment and their baseline/ follow-up data documented in the routine care CTC2 and HEI patient charts and entered in the electronic CTC2 database. The follow-up period for the three studies was from PMTCT enrolment to 8 March 2019 for study I, to 31st March 2021 for study II and to 31st July 2021 for study IV. In study III, study facilities were followed up - from 1st January 2015 to 31st March 2016 - and progress/ outcomes ascertained via monthly aggregate cross-sectional facility ANC reports available in the web-based DHIS2 database.

Data for studies I, II and IV were extracted from the electronic CTC2 database. This data included: the woman's date of birth, date of HIV diagnosis and date enrolled in PMTCT care; due date, WHO clinical stage, CD4 count, ART status, date started ART and ART regimen at PMTCT enrolment; as well as date of delivery and pregnancy outcome. Other data extracted included the woman's follow-up status (alive, died, transferred) as well as all available viral load tests with the corresponding date of viral load sample collection and numeric results. Infants data included date of birth, sex, date enrolled in EID, dates of all available EID tests, test type (antibody/ PCR) and results, as well as infant status (alive/ died/ transferred). Study data also comprised of attributes of study facilities including: level (dispensary/ health centre/ hospital), ownership (public/ private), total number of PMTCT clients per year as well as coverage of couple HIV testing at ANC. Several composite variables of clinical significance were also created from the extracted raw data. These included: gestational age in weeks, advanced HIV disease (WHO clinical stage III or IV or CD4 cell count <200 cells/μL) and facility annual volume of PMTCT clients (low/ medium/ high). For study III, data were extracted from the DHIS2 database and comprised of aggregate number of women who registered for ANC by age category (<20/ ≥20 years old) and gestational age (<12/ ≥12 weeks),

number tested for HIV (with/ without partner), and their HIV status (positive at entry/ tested positive/ tested negative).

4.5 DATA ANALYSIS

Continuous variables were described by medians and interquartile range (IQR), thereafter categorized based on clinical relevance, and categorical variables were summarized by proportions. Comparisons between groups were performed using a chi-square test (crude) and regression modelling (crude and adjusted) and analysis of trend performed using median values of categorized continuous variables, with a p value threshold of 0.05 for statistical significance. The statistical methods used in light of the data are presented below according to each study.

4.5.1 Statistical analysis for study I

The primary binary outcome for study I was maternal viral suppression defined as less than 400 viral copies per mL on repeated measures of viral load over time since PMTCT enrolment, after at least six months of ART use. Determinants of virological failure (≥400 viral copies/mL) were also examined from among the collected baseline socio-demographic and clinical characteristics of the women. Since we relied on data collected as part of routine clinical care, 30%-35% of the information was missing in some predictors or outcome variables. Women with no information about the primary outcome could not be included in the analyses. Missing data in predictor variables was handled by statistical approaches described below. Statistical inference on the outcome probability was conducted using a Poisson model estimated with generalized estimating equation (GEE) with robust error variance. Trends in proportion of women virally suppressed over time were investigated using all women with any available viral load data. This analysis was repeated in two sub-group analyses including only women with multiple viral load tests over at least three years and women with at least one viral load test per year over at least four years, to rule out the possible effect of selection bias due to incomplete follow-up of some women. The Poisson GEE was also used in a complete case multivariable regression to examine predictors of the risk of virologic failure using the baseline characteristics and duration of follow-up as potential risk factors. A parsimonious final multivariable model was constructed by starting with 16 possible predictors and then progressively reduce the number of predictors in case of no strong indication, as measured by a Wald-type test at 5% confidence level, against the hypothesis of no association with the outcome probability. Sensitivity analyses were performed to examine the effect of missing data using chained equations to impute missing data in predictor variables and the inverse probability weighting in the Poisson GEE model [129,130].

4.5.2 Statistical analysis for study II

In study II, the primary study outcome was the final MTCT status defined as infant antibody or PCR test at 18 or more months of age or a positive PCR test before 18 months old. Determinants of MTCT were also examined from among the collected baseline socio-demographic and clinical characteristics of mothers and infants. About 19% to 36% missing data was observed on predictor and outcome variables, therefore mother-infant pairs missing

data on the primary outcome could not be included in the analysis whereas missing data in predictor variables was handled using multiple imputation. A comparison of the baseline characteristics of mother-infant pairs included in the analysis versus those excluded due to missing outcome data was also performed to evaluate any systematic bias/differences. Multivariable complete case logistic regression with robust error variance and accounting for clustering at facilities, was performed to examine predictors of MTCT from among baseline maternal and infant characteristics as potential risk factors. The choice of variables included in the regression model was informed by existing published research and clinical reasoning. Sub-group analyses of the risk of MTCT within each category of the baseline characteristics of mother-infant pairs was also performed using bivariable logistic regression with robust error variance and controlling for clustering. This analysis aimed to describe the range of MTCT risk among different high and low risk sub-groups and estimate the extremes of MTCT risk in our data to provide some insight on the possible impact of missing outcome data on our MTCT estimate.

4.5.3 Statistical analysis for study III

In study III we focused on monthly aggregated data at facility-level, with health facilities serving as the unit of analysis. The primary outcome was the proportion of women who tested for HIV together with their partners at first ANC visit, i.e. couple HIV testing coverage, as a proxy measure of male-partner participation in ANC and PMTCT care. The change in the couple HIV testing coverage from baseline to one-year follow-up was compared between the six intervention facilities and 203 control facilities. The quarterly trend in couple HIV testing coverage from baseline to one-year follow-up in each of the six intervention facilities was also examined. A sensitivity analysis was performed to assess stability of the findings using a multivariable linear regression of the couple HIV testing coverage at one-year follow-up between the 6 intervention and 203 control facilities, adjusting for the baseline couple HIV testing coverage as well as facility ownership, level and volume of new ANC clients. This sensitivity analysis was repeated limiting to the six intervention facilities and 24 control facilities frequency matched (1:4) to the intervention sites by facility ownership, district, level and volume of new ANC clients.

4.5.4 Statistical analysis for study IV

In study IV three outcomes were evaluated i.e. a primary outcome of time to ART attrition and the corresponding one-year retention on ART and PMTCT care, and two secondary outcomes of viral suppression and MTCT by 12 or more months post-partum.

The statistical model was specified according to the type of outcome. These outcomes were defined as:

- *ART attrition:* discontinuing ART for any reason including death, stopping ART for more than 90 consecutive days, or loss to follow-up (no show for more than 90 consecutive days since last scheduled appointment among non-transfers).

- *One-year retention on ART and PMTCT care:* alive and picked ARVs within 90 days of the scheduled appointment during the first 12 months of PMTCT care, excluding transfers.
- *Viral suppression:* less than 400 viral copies per mL on repeated measures of viral load tests over time since enrolment in PMTCT care, after at least three months of ART use.
- *MTCT by 12 or more months post-partum:* infant PCR test by 12 or more months of age or antibody test by 18 months old

For the primary time-to-event outcome, the initial analysis of the time to ART attrition (based on a single failure per subject) and the one-year retention in ART and PMTCT care (unadjusted) were performed using the non-parametric Kaplan Meier method. Women who had no follow-up, i.e. made only one visit or experienced a failure event at first PMTCT visit, were assigned a 0.1-day of follow-up in order to retain them in the survival analyses, and women with documented transfer from the study facilities were right censored at their last visit date. All participants were censored on the 31st July 2021 (end of follow-up). Kaplan Meier survival curves of ART retention across months since enrolment in PMTCT care, were plotted and the unadjusted comparisons between peer-mother and control facilities performed using the log rank test. Sub-group analyses of the one-year retention on ART and PMTCT care by the women's baseline characteristics (unadjusted) were also performed comparing peer-mother versus control facilities using the log rank test. For the adjusted analysis a multivariable Cox proportional hazard regression of the hazard of ART attrition with shared frailties was done, controlling for clustering and baseline imbalances after randomization.

For the viral suppression binary outcome, a Poisson GEE with robust error variance was used to analyse and compare viral suppression on repeated measures of viral load tests over time since enrolment in PMTCT care, among women in peer-mother versus control facilities. Sub-group analysis of viral suppression by the women's baseline characteristics in the peer-mother versus control facilities was also performed using the predicted probabilities of viral suppression from bivariable Poisson GEE regression models. Thereafter a multivariable Poisson GEE regression of the risk of virologic failure (400 or more viral copies per mL) controlling for baseline imbalances after randomization, was estimated.

For the MTCT binary outcome, a logistic regression was estimated to compare the risk of MTCT by 12 or more months among mother-infant pairs in peer-mother versus control facilities. A random effect and a cluster variable were added to take into account the clustered nature of the data.

4.6 ETHICAL CONSIDERATIONS

All studies in this PhD thesis were embedded in routine healthcare practices with the aim of evaluating and improving outcomes of women with HIV receiving lifelong ART for PMTCT, their infants and families. The studies used de-identified data from electronic routine healthcare databases to analyse and ascertain study outcomes. Therefore, participants involved in these studies were not exposed to any excess risk beyond that which is associated to receiving routine healthcare. Waiver of informed consent was obtained from the ethical review boards on the

basis of minimal risks associated with the studies and the use of anonymized data from routine healthcare records. To assure privacy and confidentiality of study participants the de-identified study data, extracted from the routine healthcare records, was stored in password protected computers with access restricted to persons directly involved in the study. Ethical permit for the studies were obtained from the ethical review boards of Muhimbili University of Health and Allied Sciences (MUHAS), ref. 2017-06-28/AEC/Vol.XII/83, and the Tanzania National Institute for Medical Research, ref. NIMR/HQ/R.8a/Vol.IX/2594.

4.7 THE PHD STUDENT'S ROLE IN INCLUDED STUDIES

As PhD student, I played a leading role in all key aspects of the four studies included in this thesis. I led the literature review and formulation of research questions for all the four studies drawing from my work and experience overseeing MDH's PMTCT program at that time and in collaboration with the regional health management team, supporting the roll-out of the lifelong ART for PMTCT in Dar es Salaam. Through this work I gained insights on the clinical realities of PMTCT care and outcomes of women living with HIV and their infants, existing gaps in knowledge, care practices and outcomes and areas that needed improvement.

I designed the prospective cohort studies I and II that followed large cohorts of women with HIV and their infants who were enrolling in PMTCT care in Dar es Salaam to ascertain outcomes of the use of lifelong ART for PMTCT in routine healthcare and the factors influencing these outcomes. For studies III and IV, I led MDH's efforts to scale-up the initiatives to improve PMTCT outcomes in routine healthcare and later designed the two implementation studies to evaluate the effect of these initiatives on PMTCT outcomes. I led the writing of the study protocol that included all four studies as well as the submission for ethical clearance, with feedback from my supervisors and other co-investigators.

I worked with the MDH data analysts to extract the data for all four studies from the electronic routine healthcare database. Thereafter, I led the data organization, management, analyses, interpretation, visualization, reporting, manuscript writing and submission for publication for all four papers, working with the supervisors and co-authors at MUHAS and Karolinska Institutet (KI), MDH, Dar es Salaam region and the Ministry of Health in Tanzania.

5 RESULTS

This section provides a summary of the results of each study in this PhD thesis, organized under a subheading corresponding to each study. Collectively these results contribute knowledge to answer the three key questions of the thesis i.e. what are the outcomes of the use of lifelong ART for PMTCT in routine healthcare settings, what influences these outcomes and how can the outcomes be improved.

5.1 STUDY I: MATERNAL VIRAL SUPPRESSION IN PMTCT CARE

Study I included 10,161 women with HIV who enrolled in PMTCT care between 1st October 2014 to 30th September 2016 in routine healthcare settings of Dar es Salaam, after excluding 5,425 (34.8%) women who did not have viral load data (the primary outcome). These women were followed up for a maximum of 53 months with a median (IQR) follow-up of 37 (31 to 45) months. The median age (IQR) of these women was 31 (27 to 35) years, with 2.6% of the women below 20 years of age. Among 7,318 women with gestational age data, a majority started PMTCT care late in the second (64.1%) or third (17.0%) pregnancy trimester. At the start of PMTCT care, 48.2% of the women were already on ART and 33.4% of 10,131 women with data on disease stage had advanced HIV disease.

Overall 88.2% (95% CI: 87.8% to 88.7%) of the women studied were virally suppressed over the four and a half years of follow up. The proportion of women with viral suppression increased with time on ART care since PMTCT enrolment (Figure 6). The proportions ranged from 85.1% at viral load testing done in the first 11 months to 90.6% for tests done at 36 or more months after PMTCT enrolment ($p_{\text{-trend}}$ <0.0001). This observed trend of an increasing proportion of women who were virally suppressed on longer duration in care remained consistent upon restricting the analysis to women who had longer (at least three) years of follow-up and viral load data across the years.

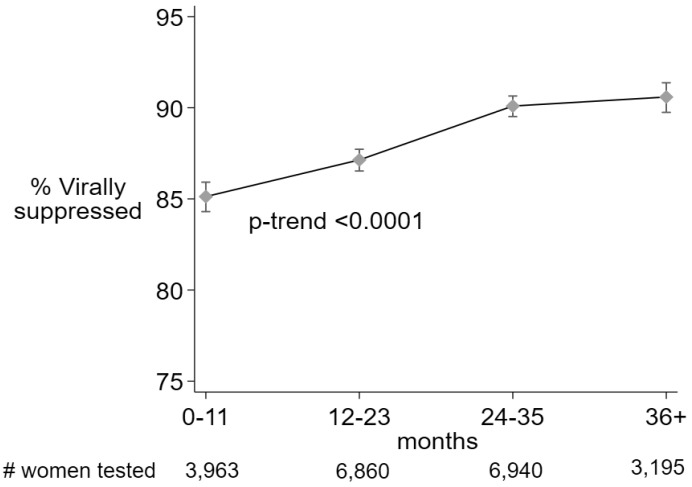

Figure 6. Viral suppression trend across months since PMTCT enrolment among 10,161 women studied

In the sensitivity analysis we did in order to estimate viral suppression rates in the entire cohort of 15,586 women enrolled in PMTCT care (including women excluded due to lack of viral load data) using inverse probability weights in a Poisson regression analysis, the overall weighted viral suppression remained unchanged at 88.1% (95% CI: 87.5% to 88.6%).

In the complete-case analysis (N =7,306) using multivariable Poisson GEE regression (Table 2), the risk of virologic failure decreased with increasing duration on ART since PMTCT

enrolment [adjusted risk ratio (95% CI) = 0.87 (0.80 to 0.95) at 12-23 months; 0.65 (0.59 to 0.72) at 24-35 months, and 0.63 (0.55 to 0.71) at 36+ months versus 0-11 months since PMTCT enrolment]. Conversely, the risk of virologic failure increased with younger age, higher gestational age, advanced HIV disease, and use of nevirapine versus efavirenz -based ART regimens at PMTCT enrollment, as well as on delayed ART initiation after enrolment in PMTCT care (Table 2). Furthermore, on health facility attributes,

Table 2: Risk factors for virologic failure (400 viral copies per mL) among women studied

Patient characteristics	adjusted risk ratio[†]
Months on care at viral load test	$p_{\text{-trend}} < 0.0001$
0 - 11	1 [referent]
12 - 23	0.87 (0.80, 0.95)
24 - 35	0.65 (0.59, 0.72)
36+	0.63 (0.55, 0.71)
Age at enrolment in PMTCT care	$p_{\text{-trend}} < 0.0001$
<20 years	1.76 (1.40, 2.23)
20-29 years	1.14 (1.02, 1.26)
30-39 years	1 [referent]
40+ years	0.84 (0.66, 1.08)
Gestational age, weeks (trimester)	$p_{\text{-trend}} < 0.0012$
<13 (first)	1 [referent]
13 to 27 (second)	1.02 (0.90, 1.17)
28+ (third)	1.28 (1.10, 1.50)
Advanced HIV disease[*]	p < 0.0001
no	1 [referent]
yes	1.33 (1.16, 1.51)
When ART was started	p < 0.064
before PMTCT enrolment	1.03 (0.91, 1.18)
at PMTCT enrolment	1 [referent]
31+ days after enrolment	2.55 (1.16, 5.62)
ART regimen at PMTCT start	p < 0.0039
efavirenz based (first line)	1 [referent]
nevirapine based	1.53 (1.18, 2.00)
protease Inhibitor based/ other	0.77 (0.43, 1.39)
Health facility attributes	
Level	p < 0.015
dispensary	1.19 (1.06, 1.35)
health centre	1.10 (0.94, 1.27)
hospital	1 [referent]
Ownership	p < 0.012
public	1 [referent]
private	1.16 (1.03, 1.31)
Couple HIV testing coverage at ANC	p < 0.044
≤50%	1 [referent]
51%+	0.81 (0.65, 0.99)

[†]Complete-case (N =7,306) multivariable Poisson Generalized Estimating Equation with robust error variance, adjusted for all variables in the table. Data in parenthesis are 95% CI, *WHO Stage III/IV/ CD4 count <200 cells/μL

women receiving care in dispensaries (versus hospitals) as well as those in private (versus public) facilities had a higher risk of virologic failure, whereas women in facilities with high coverage of couple HIV testing at ANC had lower risks of virologic failure (Table 2). Upon re-running the multivariable Poisson GEE regression after multiple imputation of missing data on predictor variables, thereby using all 10,161 women studied, no substantial change in the relative risks of virologic failure was observed.

5.2 STUDY II: MOTHER-TO-CHILD TRANSMISSION OF HIV

Table 3: Mother-to-child HIV transmission risks of the 8,886 mother-infant pairs studied, by baseline characteristics

Patient characteristics	n/N	% MTCT[†]
Maternal age, years		
<20	8/ 219	3.7 (1.8, 7.1)
20-29	72/ 3644	2.0 (1.6, 2.5)
30-39	71/ 4556	1.6 (1.2, 2.0)
40+	8/ 467	1.7 (0.9, 3.4)
Gestational age, weeks (trimester)		
<13 (first)	13/ 1377	0.9 (0.5, 1.6)
13-27 (second)	89/ 4728	1.9 (1.5, 2.3)
28+ (third)	35/ 1137	3.1 (2.2, 4.3)
Advanced HIV disease[*]		
no	111/ 6146	1.8 (1.5, 2.2)
yes	48/ 2740	1.8 (1.3, 2.3)
ART status		
already on ART	41/ 4188	1.0 (0.7, 1.3)
started ART in/after pregnancy	118/ 4698	2.5 (2.1, 3.0)
ART regimen backbone		
NNRTI (first line)	156/ 8789	1.8 (1.5, 2.1)
PI (second line)	3/ 97	3.1 (1.0, 9.2)
Infant sex		
male	63/ 4324	1.5 (1.1, 1.9)
female	96/ 4562	2.1 (1.7, 2.6)
Health facility attributes		
PMTCT clients' volume		
≤10 per year (low)	13/ 367	3.5 (2.1, 6.0)
11-100 per year (medium)	97/ 4233	2.3 (1.9, 2.8)
101-515 per year (high)	49/ 4286	1.1 (0.9, 1.5)
Couple HIV testing coverage ANC		
<50%	141/ 8205	1.7 (1.5, 2.0)
50%+	18/ 681	2.6 (1.7, 4.2)

[†]Data in parenthesis are 95% CI, *WHO Stage III/IV/ CD4 count <200 cells/μL

Study II included 8,886 mother-infant pairs who enrolled in routine PMTCT care during pregnancy between 1st January 2015 to 31st December 2017, after excluding 4,904 (35.6%) mother-infant pairs who lacked data on the final MTCT outcome (the primary outcome). These women were followed up for a median (IQR) of 49 (40 to 59) months. At PMTCT enrolment, the women had a median (IQR) age of 30 (25 to 34) years and 2.5% were adolescents aged less than 20 years. Also, 30.8% of the women had advanced HIV disease, 47.1% were already on lifelong ART, and majority of the 7,242 women with data on gestational age were in second (65.3%) or third (15.7%) trimester of pregnancy. Fifty-one percent of the infants studied were

female. About half (48.2%) of the mother-infant pairs received PMTCT care in high volume health facilities and 7.7% attended facilities with high couple HIV testing coverage at ANC.

In the final MTCT outcome by 18 months, 8,727 (98.2%) infants were discharged HIV free and 159 infants were diagnosed with HIV, yielding an MTCT risk of 1.8% (95% CI: 1.5% to 2.1%). The majority (61.6%) of the HIV infected infants were diagnosed with HIV by the age of two months. On the sub-group analysis by baseline characteristics (Table 3), MTCT risks were highest among adolescent women (3.7%), women at low volume facilities (3.5%) as well as women in third trimester of pregnancy (3.1%) or on PI-based ART (3.1%) at enrolment to PMTCT care.

In the complete case (N =7,242) multivariable random effects logistic regression, the odds of MTCT were higher among women who: enrolled in PMTCT care late in pregnancy, had advanced HIV disease, used PI-based regimen (versus NNRTI), and among female infants. Conversely, women already on ART prior to pregnancy and those receiving care in high volume PMTCT clinics had lower odds of MTCT. In this analysis, the odds of MTCT were:

- Two to three times higher among women in the second or third, versus the first, trimester
- Twice as high among women with advanced HIV disease versus early stage disease
- Four times higher among women on PI- versus NNRTI-based ART
- 51% higher among female infants
- 69% lower among women who started ART before versus at/ after pregnancy
- 62% lower among women in PMTCT clinics with high versus low patient volumes

Although the sub-group analyses (Table 3) indicated that adolescent mothers had the highest (3.7%) risk of MTCT, in the multivariable regression analysis, the odds of MTCT were higher but non-statistically significant, among adolescent mothers compared to women aged 30 to 39 years (adjusted odds ratio =1.43 (95% CI: 0.56 to 3.65). Upon re-running the multivariable random effects logistic regression after multiple imputation of missing data on gestational age, thereby using all 8,886 women studied, no substantial change was observed in the odds ratios of MTCT.

5.3 STUDY III: COMMUNITY LEADERS AND MALE INVOLVEMENT IN PMTCT

In study III, a total of 4,429 women at the six intervention facilities and 31,234 women at 203 control facilities were registered for ANC and tested for HIV at study baseline in January to March 2015. Among these women, 11.9% at the intervention facilities and 17.7% at the control facilities tested for HIV together with their partners i.e. couple HIV testing. At one-year follow-up, in January to March 2016, couple HIV testing coverage increased to 36.0% ($p < 0.0001$) at the six intervention facilities whereas it remained unchanged at 18.3% ($p = 0.07$) in the 203 control facilities (Figure 7). In the two sensitivity analyses using multivariable linear regression to control for baseline differences between intervention and control facilities, the intervention facilities tended to have higher but non-statistically significant couple HIV testing coverage compared to both the 203 control facilities ($p = 0.06$) as well as the 24 matched controls ($p = 0.06$).

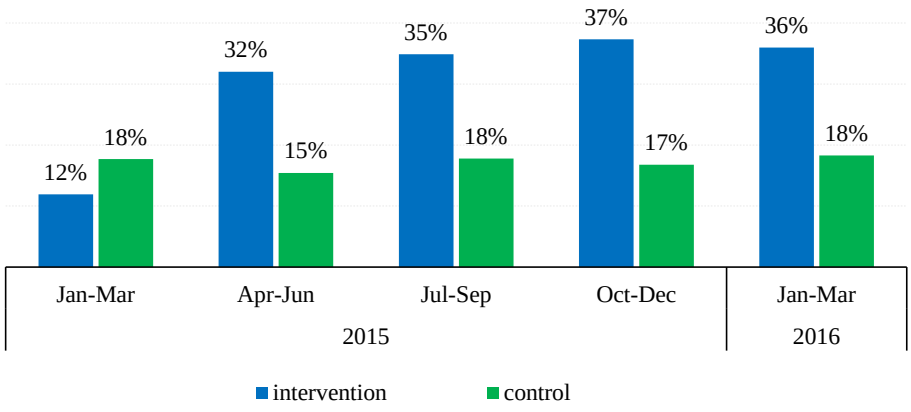

Figure 7. Quarterly trend in couple HIV testing coverage at the six intervention facilities versus 203 control facilities

5.4 STUDY IV: PEER MOTHERS AND PMTCT OUTCOMES

Study IV included 1957 women in 23 peer-mother facilities and 1384 women in 24 control facilities who enrolled in routine PMTCT care during pregnancy from 1st January 2018 to 31st December 2019 and were followed up for a median (IQR) of 23 (10 to 31) months. Women in the two cluster randomized facility groups were similar in their age distribution and infant sex, however the peer mother group had slightly fewer women in third trimester (14.5% versus 18.9%) and women with advanced HIV (22.3% versus 27.2%) but more ART naïve women (54.9% versus 47.3%). Below is a summary of the three outcomes evaluated in this study:

5.4.1 Attrition over 3.5 years and retention in the first year of follow-up

The peer mother intervention resulted in lower ART attrition rate (95% CI) per 1000 person-months in peer mother versus control facilities [(14.3 (13.1 to 15.5) versus 17.6 (16.0 to 19.3)] and higher one-year retention (95% CI) in PMTCT and ART care [78.0% (76.0% to 79.8%) versus 73.6% (71.1% to 76.0%)], in unadjusted analyses (Figure 8A). ART attrition was largely explained by loss to follow-up which accounted for 95% of the attrition in peer mothers and 96% in control facilities. The effect of the peer mother intervention on reducing ART attrition per 1000 person-months in peer-mother versus control facilities was more pronounced among ART naïve women (22.4 versus 32.0, p=0.0005) than ART experienced women (7.5 versus 9.9, p =0.011), Figure 8B. Similarly, peer mothers had a greater impact on the one-year retention among ART naïve women resulting in a nine-percentage points higher retention in peer mother versus control facilities, compared to the three-percentage points among ART experienced women.

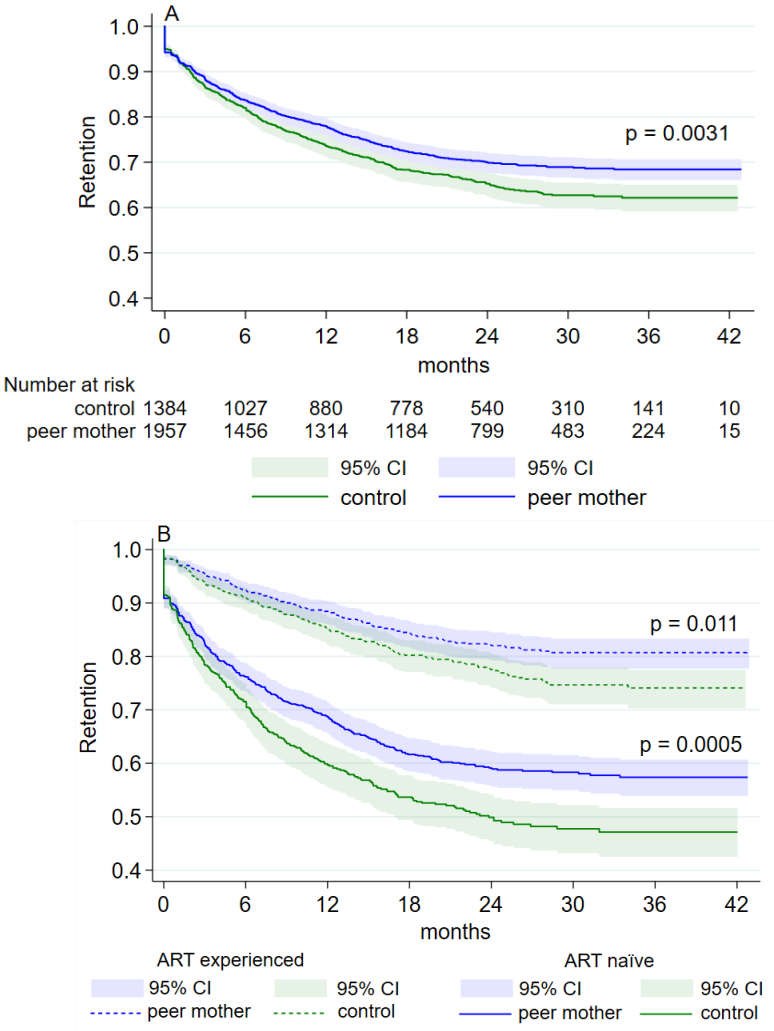

Figure 8. Kaplan Meier survival analysis of ART retention among 1957 women in peer mother facilities versus 1384 women in control facilities, (A) overall and (B) stratified by ART status at baseline (B)

In the sub-group analysis, aside from baseline ART status, significantly higher one-year retention in peer mother versus control facilities was also found among sub-groups of:

- women with early stage HIV disease (75.5% versus 68.7%, p =0.0009),
- women aged 30 to 39 years (84.1% versus 78.7%, p =0.014) and
- women on NNRTI regimen (77.5% versus 72.9%, 0.011).

On multivariable Cox regression, controlling for clustering as well as baseline maternal age, gestational age, advanced HIV disease status, ART status, ART regimen, facility PMTCT volume and facility couple HIV testing coverage, the hazards of ART attrition was lower but

non-significant in peer mother versus control facilities (adjusted hazard ratio = 0.85; 95% CI 0.67 to 1.08).

5.4.2 Viral suppression

The virologic outcome analysis included 1,564 (79.9%) women in peer mother and 1,073 (77.5%) women in control facilities who had viral load data. High proportions of women in both the peer mother (92.0%) and the control (91.1%) facilities were virally suppressed, with no significant differences between the two groups (p =0.18). The longer the women stayed on PMTCT care the higher was the likelihood of viral suppression in both peer mother and control facilities, with significant trends in both (Figure 9A).

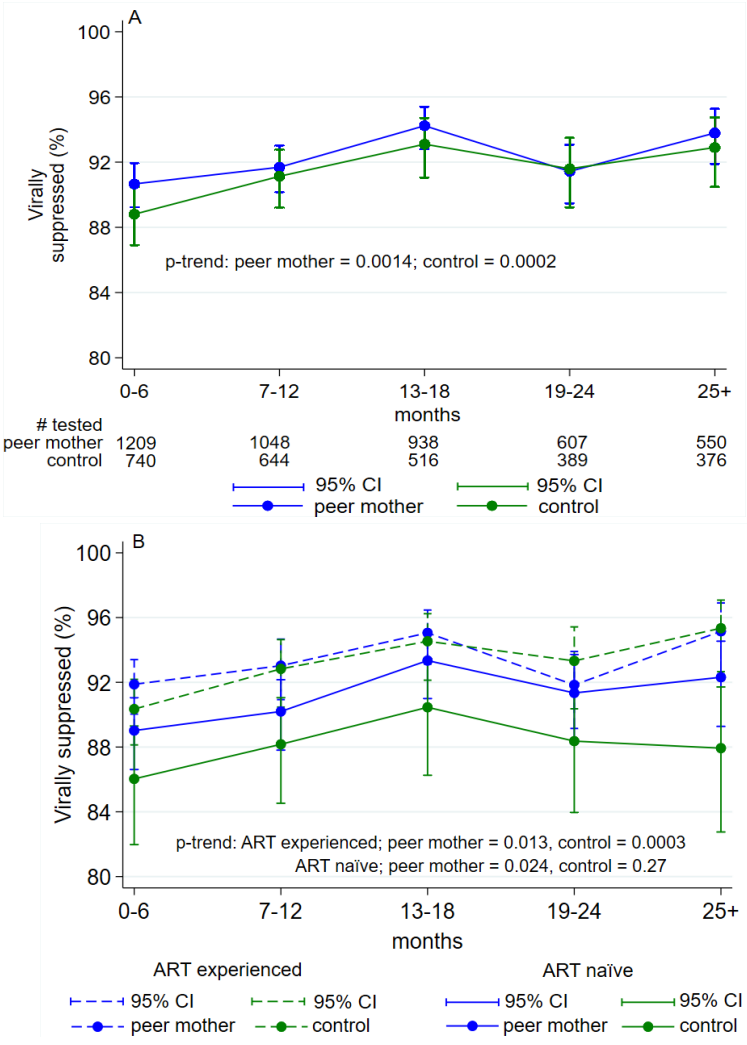

Figure 9. Viral suppression over time in PMTCT care among 1,564 women in peer mother facilities versus 1,073 women in control facilities, (A) overall and (B) stratified by ART status at baseline

Derived from Poisson generalized estimating equations with robust error variance.

In the sub-group analysis by baseline characteristics, viral suppression among women in peer mother versus control facilities was similar across all subgroups except among women who were ART naïve at baseline. In these women, who newly initiated ART during index pregnancy, those in peer mother facilities had significantly higher viral suppression than control facilities (90.8% versus 88.1%, p =0.032). Also, among ART naïve women, viral suppression improved significantly over time in PMTCT care in peer mother facilities (p = 0.024) but not in control facilities (p = 0.27), Figure 9B. On multivariable Poisson GEE regression, with robust error variance, the adjusted risk ratio of virologic failure in peer mother versus control facilities was 0.96 (95% CI: 0.78 to 1.19).

As seen in Figure 9, there was a drop in the proportion of women who were virally suppressed in both the peer mother and the control facilities from timepoint 13-18 months to 19-24 months, thereafter a recovery at timepoint of 25+ months. These timepoints (from 13-18 months to 19-24 months) correspond to the period during and shortly after the first wave of COVID global pandemic which was first reported in Tanzania in March 2020. During this period, peer mother services were temporarily suspended for about six months from April to October 2020 before resuming in November 2020.

5.4.3 Mother-to-child transmission of HIV

The MTCT analysis included 1,022 mother-infant pairs in peer mother facilities and 725 mother-infant pairs in control facilities who had a documented infant HIV test by 12 or more months post-partum. There were 20 confirmed HIV infections in peer mother facilities [MTCT = 2.2%, 95% CI: 1.4% to 3.4%)] and 9 HIV infections in control facilities [MTCT = 1.5%, 95% CI: 0.7% to 2.8%), with no significant differences between the two groups (p = 0.31). Most infant HIV diagnoses in both peer mother (16 out of 20) and control (6 out of 9) facilities were made by two months post-partum. Similarly, on multivariable random effects logistic regression no significant differences in MTCT by 12 or more months postpartum were found among mother-infant pairs in peer mother versus control facilities [adjusted odds ratio = 1.87 (95% CI: 0.69 to 5.08), p = 0.22].

6 DISCUSSION

This thesis was set out to answer three key questions i.e. how well does lifelong ART for PMTCT work in routine healthcare, what influences the success of lifelong ART for PMTCT and how can the PMTCT outcomes be improved. In this section the findings of the thesis are discussed in the context of these three questions:

6.1 HOW WELL DOES LIFELONG ART FOR PMTCT WORK IN ROUTINE HEALTHCARE?

The first two studies included in this thesis evaluated the maternal virologic and infant MTCT outcomes of women who used lifelong ART as part of routine PMTCT care. In the first study, high viral suppression (88%) was observed among 10,161 women who used lifelong ART for PMTCT, and were followed for up to 4.5 years, using a more stringent criteria (< 400 viral copies per mL) than the WHO recommended criteria (< 1000 viral copies per mL). In particular, the results provided a reassuring evidence that viral suppression was sustained and improved on longer duration in care from 85% at viral load tests performed between 0 to 11 months to 91% at 36 or more months since enrolment in PMTCT care. This finding refutes earlier concerns that had suggested that women who enrol in ART during pregnancy for PMTCT may have reduced motivation to adhere to ART during and beyond breastfeeding [44-46,56-58,78]. Other studies across Africa that evaluated virologic outcomes of women on PMTCT care during the era of lifelong ART for all women in PMTCT also reported similar findings [96-99]. Sustaining viral suppression during and beyond PMTCT is the overarching goal of lifelong ART and the mechanism through which it prevents vertical HIV transmission to the infant as well as assures survival and wellbeing of both mothers and infants. It also helps reduce women's risk of HIV transmission to uninfected sexual partners.

In study II, low risk of MTCT (1.8%) was observed among 8,886 mother-infant pairs who used lifelong ART in routine PMTCT care, in line with MTCT risks reported by the earlier RCTs across SSA in the 2000s, that evaluated this outcome and motivated the release of the WHO Option B+ recommendation. This finding corroborates the high viral suppression observed in study I and reaffirms the importance of lifelong ART in PMTCT to end the AIDS epidemic in children. Low MTCT risks have also been reported by other studies that evaluated the MTCT outcomes in the post 2010 era of lifelong ART for all women in PMTCT [108,131-134].

Collectively, studies I and II provide reassuring evidence that eliminating MTCT and keeping mothers living with HIV and their infants alive and healthy, is achievable also in resource-constrained settings through lifelong ART for PMTCT.

6.2 WHAT HINDERS OR INFLUENCE THE OUTCOMES OF LIFELONG ART FOR PMTCT IN ROUTINE HEALTHCARE?

Studies I and II also evaluated factors that hinder or influence maternal virologic and infant MTCT outcomes of lifelong ART for PMTCT. Across both of these studies, adolescent mothers were found to have up to 76% higher risk of virologic failure compared to women in their thirties, and they also had the highest risk of MTCT (3.7%) in sub-group analyses. In the

current literature, adolescents with HIV have a higher risk of sub-optimal treatment outcomes than other age groups [135-137]. This suggests that the current set up of HIV and PMTCT care is not adequately tailored to address the needs of this age group and needs reconsideration.

In studies I and II, it was also observed that women starting PMTCT care late in their second or third pregnancy trimester, and those with advanced HIV disease at PMTCT enrollment, have increased vulnerability to both virologic failure as well as MTCT. Starting PMTCT and ART late in pregnancy, implies that these women were untreated for their HIV in the early stages of their pregnancy, something we know can increase the risk of MTCT up to 10%[9]. Some of these women may also have acquired their HIV infection/ seroconverted during pregnancy, also known to markedly increase the risk of MTCT [13-15]. Advanced HIV disease is also known to predispose to poor immunological, virological and clinical response to ART, thereby predisposing to MTCT [138-142]. Starting PMTCT care late, and, having an advanced HIV disease may also be a proxy for overall health behavior, implying a higher risk of sub-optimal adherence to ART and concurrent primarily social risk factors that predispose them to an increased risk of virologic failure and MTCT [77,81,143]. The observation, in study II, that women on second line (PI-based) ART had a higher risk of MTCT, is likely an indicator of persisting sub-optimal adherence, drug resistance, riskier health behaviors or attitudes towards treatment [144,145]. Overall, the information derived from our studies on determinants of virologic and MTCT outcomes among women in PMTCT on lifelong ART, provides useful insights on areas and sub-populations that require increased attention to further improve the success of PMTCT.

Across studies I and II, four factors were observed to be protective against the risk of either virologic failure or MTCT i.e. being on ART prior to pregnancy, longer duration in PMTCT care, receiving care in facilities that had high coverage of couple HIV testing at ANC and receiving care in facilities that had high volume of PMTCT clients. Whereas being on ART before pregnancy did not seem to influence the risk of virologic failure (study I), it was observed to reduce the risk of MTCT by up to 69% (study II). This implies that the increased risk of MTCT in women who start ART after knowing about their pregnancy lies in the early pregnancy period before HIV diagnosis and ART initiation. Indeed, in study II, a majority (62%) of HIV exposed infants that were found to have been infected, were diagnosed by two months of age, suggesting that early HIV transmission in-utero or intrapartum was the leading driver of MTCT.

The beneficial effect of high couple HIV testing on reducing virologic failure, observed in study I, reaffirms the importance of male partner engagement in improving PMTCT outcomes. Although we measured couple HIV testing as a facility-level attribute, it is plausible that it reflected the attitude of the underlying community served by the facility with regard to male involvement in ANC and PMTCT. High male partner involvement in ANC and PMTCT care indicates more partner engagement and support for pregnant women living with HIV, which in-turn contributes to improved adherence to ART [77,146].

The finding that women in high volume facilities have a lower risk of MTCT is interesting and may reflect better access to monitoring, supervision, capacity building and experience of

PMTCT care for HCPs in high-volume facilities, resulting in higher competence and quality of care [147]. This finding underscores the need to optimize monitoring, supportive supervision and capacity building at low PMTCT volume facilities to ensure optimum quality and PMTCT outcomes.

6.3 HOW CAN OUTCOMES OF LIFELONG ART FOR PMTCT IN ROUTINE HEALTHCARE BE IMPROVED?

Studies III and IV evaluated the effect of two interventions, i.e. engagement of community leaders to improve male partner participation in ANC and PMTCT care (study III), and engagement of peer-mothers to improve ART and PMTCT outcomes in routine healthcare (study IV). In study III, one year of community leader engagement, led to a tripling of the proportion of couples attending ANC and receiving HIV testing together at first ANC, compared to no change in the control facilities. The novelty of this intervention, unlike previous approaches that have targeted ANC clinics, pregnant women and/or male partners directly [148-152], is its focus on changing community norms and attitudes towards the role of men by engaging community leaders as influencers and agents for change. This approach recognizes that it may be more strategic to focus direct efforts in community settings where attitudes, gender norms, dialogue and decisions are formed that affect male partner participation in ANC and PMTCT care [153-155]. Effective male partner participation, has both direct and indirect benefits for PMTCT outcomes. The direct benefits include the opportunity to ascertain the HIV status of both the pregnant woman and her partner in one sitting, thereby simplifying the process of disclosure of HIV status and appropriate counseling on HIV prevention to both partners depending on their HIV results [156-158]. This, in-turn, facilitates access to timely lifelong ART and/or pre-exposure prophylaxis (PrEP) to the HIV-negative partner, as well as preventing incident HIV infection during pregnancy and/ or breastfeeding, which markedly increases the risk of MTCT [13-15]. In-directly, effective male partner participation in ANC and PMTCT provides much needed partner support right from the beginning of PMTCT care, and enables a woman with HIV to take up and adhere to ART, hence promoting both her own health, and preventing HIV transmission[159].

The peer-mother intervention, in study IV, resulted in a significantly lower ART attrition rate per 1000 person months (14 versus 18), higher one-year retention in care (78% versus 74%) among all women studied, and a significantly higher viral suppression among women who were ART naïve at baseline (91% versus 88%). Across all outcomes the effect of the peer-mother intervention was more pronounced among women who were newly HIV diagnosed and ART naïve at baseline, a group that is known to be more vulnerable to sub-optimal PMTCT outcomes [77,160-162]. In spite of the modest effect sizes, this study provided valuable insights on the beneficial role of peer mothers, particularly in understaffed resource constrained settings, as well as opportunities to optimize and target the peer-mother intervention towards the major gap in PMTCT care, i.e. the high attrition from ART and PMTCT care. Similar beneficial outcomes of peer-mothers on ART retention and viral suppression have been reported in studies from Malawi and Nigeria that evaluated the role of peer-mothers in the era of lifelong ART for

PMTCT [117,163]. On our study IV the peer mother intervention, however, did not result in any significant impact on MTCT by 12 months postpartum or later, similar to the Malawian study [117].

6.4 METHODOLOGICAL CONSIDERATIONS

All the four studies included in this thesis, relied on routine care data to evaluate study outcomes. The choice of routine care data aimed to enhance generalizability of study findings to real life settings and minimize bias related to study procedures. Nevertheless, reliance on routine care data, could also have introduced several biases as discussed below.

6.4.1 Missing data and incomplete follow-up of study participants

Missing data on predictor variables affected 28% (study I), 19% (study II) and 14% (study IV) of the women studied. Missing data, a common challenge in studies that rely on data collected in routine healthcare [164,165], was largely attributable to incomplete documentation and cost-related unavailability of tests and/or tools in some facilities. Overall, the direction and magnitude of our findings obtained by the application of multiple imputation methods, provided no strong indication in favour of unobserved factors systematically biasing the interpretation of the data underlying the different outcomes. Studies I, II and IV were also affected by missing data on the outcome variable, which necessitated an exclusion of 30%-40% of the women/mother-infant pairs enrolled in PMTCT care, from some outcome analyses. Missing outcome data was caused by incomplete follow-up of study participants largely due to women's transfer outside of study facilities and loss to follow-up. This type of missingness may have introduced a selection bias i.e. exclusion of women/ infants with poorer outcomes and inclusion of women/ infants with more favourable outcomes, particularly in studies I and II, thereby predisposing to overestimation of the favourable study outcomes. Of note, study IV was less vulnerable to this type of bias because of the proportion of missing data on the outcome variable was similar in the intervention and the control facilities. To examine the impact of missing data on the study outcomes, multiple imputations of missing data on predictor variables, using chained equations, were performed, while inverse probability weighting was used for missing data on the outcome variables [129,130]. These sensitivity analyses did not result in any appreciable differences in the interpretation of the study outcomes. Study III was not affected by missing data due to the use of aggregated facility-level data, summarizing the characteristics of study participants on a monthly basis.

6.4.2 Unmeasured confounding

Unmeasured confounders not collected as part of routine care data, such as HIV-related stigma and quality of care, is another potential source of bias in the studies in this thesis. Such bias may affect the interpretation of risk factors associated with study outcomes in the cohort studies (I and II), or the effect of the intervention versus control on the outcome in the non-randomized study III. The cluster-randomized study IV was less susceptible to unmeasured confounding, however since the randomization was performed at cluster level, residual confounding may have persisted at an individual patient level.

To minimize the impact of this type of bias in studies I and II, a broad range of available individual and facility level variables were used in the multivariable regression model building, and composite variables (such as facility volume), with some association to the unmeasured confounders, were included in the final regression model. In study III, a sensitivity analysis was performed using multivariable regression that adjusted for baseline differences in couple HIV testing between intervention and control facilities, as well as an analysis with matched controls [166]. In study IV, a cluster randomized study design was used to achieve an uneven distribution of potential confounders between intervention and control clusters. Nevertheless, it is plausible to presume that some residual confounding remained as it is not feasible to address all unmeasured confounding.

7 CONCLUSIONS

In light of all evidence gathered in this thesis, the following conclusions are drawn:

1. Lifelong ART for all women in PMTCT care has greatly improved outcomes of pregnant women with HIV and their infants in routine healthcare settings in Tanzania, reaching ≥90% maternal viral suppression and <2% mother-to-child transmission of HIV.

2. Younger maternal age, starting PMTCT late in pregnancy (due to either late start of ANC or incident HIV infection later in pregnancy), advanced HIV disease, as well as the discontinuation of ART or PMTCT care, remain major barriers and risk factors of poor PMTCT outcomes.

3. Engaging community leaders and peer-mothers can contribute towards reducing current barriers to optimal ART and PMTCT outcomes, if their roles are clearly defined, optimized and strengthened particularly in the areas of:
    a. Male partner engagement in ANC, HIV testing, primary HIV prevention during pregnancy and breastfeeding as well as in ART and PMTCT care
    b. Mitigating barriers to retention in ART and PMTCT care, particulary among pregnant women newly diagnosed with HIV and starting ART
    c. Improving adherence to treatment and viral suppression among pregnant women with HIV who start on ART in PMTCT settings.

8 POINTS OF PERSPECTIVE

The findings of this thesis reaffirm that for women with HIV who remain in care, lifelong ART works remarkably well to ensure the long-term wellbeing of mothers, and keeps their infants free from HIV even in resource constrained routine healthcare settings such as in Tanzania. However, certain sub-populations remain vulnerable to poor PMTCT outcomes and require urgent attention, including: adolescent mothers, women starting PMTCT late in pregnancy (either due to delayed start of ANC or incident infections during pregnancy), as well as women diagnosed with HIV in advanced stages of the disease. Furthermore, the high incomplete follow-up/ attrition rate and the poor uptake of EID, needs urgent actions. Therefore, the following recommendation and implications are proposed for clinical practice and future research:

8.1 IMPLICATIONS FOR CLINICAL PRACTICE

- ANC, ART and PMTCT care of adolescent women living with HIV needs to be reorganized to adequately address their needs. This includes providing client centered and age appropriate differentiated care, enhancing adolescent and youth friendly services at ANC and PMTCT clinics, as well as strengthening age disaggregate routine monitoring of outcomes among women in ANC/ PMTCT care.
- Emphasizing a holistic and comprehensive approach to PMTCT care with increased investments towards early uptake of ANC, couple ANC attendance and effective engagement of male partners in ANC and PMTCT care.
- Strengthening primary HIV prevention among women with higher risk of MTCT during pregnancy and breastfeeding, such as women with high risk sexual behavior, with HIV positive partners and unknown partner HIV status.
- Enhance risk stratification among infants born to women with HIV including incorporating advanced HIV disease and second line ART use among the criteria used to identify infants at high risk of HIV.
- Optimize, focus and strengthen ongoing initiatives to improve PMTCT outcomes in routine care, such as peer mother interventions, to address current major drivers of attrition from care.

8.2 IMPLICATIONS FOR FUTURE RESEARCH

Building on the findings of this thesis, the following areas will benefit from further research:

- Implementation research to identify and/ or evaluate interventions that are effective at improving outcomes of lifelong ART for PMTCT among adolescent mothers
- Implementation research to optimize and evaluate interventions aimed at mitigating attrition from care among women enrolling in PMTCT care, and, their infants
- Clinical research to investigate ARV drug resistance and treatment outcomes of infants born to women on ART care, who acquire HIV through MTCT

9 ACKNOWLEDGEMENTS

I would like to begin by giving thanks to the Lord, God, almighty for his many blessings, his gifts of life, health and wellbeing, and the wisdom of his word which has been the light onto my path throughout this journey and my life.

The past five years of my PhD training were greatly enriched by the support, encouragement and guidance of many individuals including supervisors, mentors, colleagues, friends and family who inspired, advised, encouraged and supported me at every step. Although I mention only a few herein, I am eternally grateful to each and every one of you for your valuable contribution in this journey of my PhD training.

I am deeply grateful to my main supervisor Prof. Anna Mia Ekström, from KI's department of Global Public Health (GPH), for your excellent guidance, inspiration and support throughout my PhD training. I have learned, enjoyed and been greatly inspired by your amazing gifts of intellect, hard work, communication, multitasking and accomplishments. Your critical eye and spot-on detailed and constructive feedback to my work, your guidance and constant push to aim higher have really shaped my training and career.

To my PhD co-supervisors: Professor Emerita Gunnel Biberfeld of KI, I am honoured to have had you as a co-supervisor, your extensive knowledge, experience, intellect, wisdom, hard work, attention to detail and constant push for timely and quality deliverables have greatly enriched my PhD training. Professor Charles Kilewo of MUHAS, thank you for your wisdom guidance and support, I appreciate the many meetings and discussions we had at your office and the feedback and guidance on my PhD studies and writings that you provided. Docent Nicola Orsini of KI, thank you for your support, coaching and guidance to navigate the complex field of statistics and apply it to my PhD studies.

To my mentor Dr. Helga Naburi, I thank you for always being there to brainstorm on, review and provide feedback on my PhD work, and talk through various struggles during my training. Thank you for being such a great friend and mentor throughout my career and PhD training.

I am grateful to the Swedish international development agency (Sida) whose generous support funded my PhD training, as well as the staff at the international science office of Uppsala University, Sweden for your valuable administrative support throughout my PhD training.

I am grateful to Professor Said Aboud, the coordinator of the HIV sub-program of the Sida grant at MUHAS, Dr. Bruno Sunguya the Director of Research and Publication at MUHAS, and the entire MUHAS leadership across departments who were instrumental in facilitating my PhD training, travels and other administrative needs. I am particularly thankful to my fellow PhD students and graduates under the Sida training grant at MUHAS including Dr. Roseline Urrio, Dr. Diana Faini, Dr. Frank Msafiri, Dr. Fadhlun Alwy Al-beity, Masunga Iseselo, Dr. Mtebe Majigo and others for your friendship, interactions and the many dialogues we had about our PhD studies. I am also thankful to fellow students, colleagues and friends at KI's GPH department including Katrine de Ángeles, Karin Båge, Veronika Tirado, Carla Sturm,

Vijaylakshmi Prabhu and others who I have had the pleasure of knowing, interacting with, sharing an office, discussing PhD studies and enjoyed your support on many various issues.

I am deeply grateful to my employer MDH, for making it possible for me to pursue and complete my PhD training. My sincere appreciation to past and current MDH leadership including the late Dr. Guerino Chalamilla, Mr. Emilian Busara and Dr. David Sando for their vision of an MDH that is grounded on data, evidence and outcome driven ideals, and that encourages her staff continually pursue and expand their knowledge and skills. Special thanks to Mr. Busara, the former CEO and my line supervisor at MDH during four of the five years of my PhD training. It is a great honour to have had the opportunity to work under such an amazing and accomplished professional, leader, mentor and friend that you are. You have had an invaluable impact on my career and PhD training through your wisdom, leadership, dialogues, guidance, support and encouragement for which I am eternally grateful. To my friends and colleagues at MDH; Dr. Shally Mwashemele, Dr. Martha Tsere, Dr. Eric Aris, Dr. Beatrice Christian, Dr. Talumba Samatta, David Msengi, Damasco Peter, Stella Nghambi, Dr. Lameck Machumi, Dr. Nzovu Ulenga, Dr. Aisa Muya, Dr. Peter Lyaruu, Nassir Kashmir, Emmanuel Philipo, Dr. Brenda Simba and many others, I am grateful for your support throughout this journey. You shouldered my responsibilities many times when I had to be away for studies and some of you worked with me to design, implement, monitor, analyse discuss and publish my PhD studies, for which I am eternally grateful.

My sincere appreciation to the Dar es Salaam regional and municipal medical offices of health and the regional and council health management teams including Dr. Ayoub Kibao, Ms. Ziada Sellah, Ms. Rehema Panga and others who managed the ANC, PMTCT and ART care in Dar es Salaam and worked with me to integrate and undertake my PhD studies. Special thanks to the HCPs, PMTCT mentors (Sylvana Joseph, Joyce Temba, Wiliam Martin, Rahim Mwakitalu and others), peer mothers, women, men and children who provided or received PMTCT care in Dar es Salaam and participated in my PhD studies, this PhD thesis is the story of your work and lives and I am very grateful to have had the opportunity to document it.

I thank Dr. Deborah Kajoka, the national PMTCT coordinator and her entire team at the PMTCT unit of the Tanzania Ministry of Health, for the support, collaboration and inputs I received in the design, implementation and reporting of my PhD studies.

I conclude by expressing my heartfelt appreciation to my beloved wife Elizabeth and daughter Malaika for your love, encouragement and support at every step of the way, that gave me the strength, joy and warmth of a loving family throughout my journey. To my mother Mary and late father Willey, my brothers Herigod, Imanuel, Ivan and Isaac, and my sister Hilda and late sister Hellen, your spouses and children; you have been there with me throughout my journey; your love, encouragement and support kept me sharp and energized. I thank my friends Dr. Curthbert Goodluck, Dr. Haika Mariki, Dr. Happiness Koda, Frank Kileo and many others for your friendship, encouragement and support. My sincere appreciation to Ms. Hellen and Mr. Lyamchai who provided me a warm and comfortable home away from home every time I was in Stockholm for my PhD studies for which I am deeply grateful.

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