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Prevention of mother-to-child transmission (PMTCT) of HIV in Mozambique: engagement in care and programmatic challenges for the B+ Strategy

Laurence Ahoua-Leray

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THÈSE PRÉSENTÉE
POUR OBTENIR LE GRADE DE

**DOCTEUR DE
L'UNIVERSITÉ DE BORDEAUX**

ÉCOLE DOCTORALE : Sociétés, Politique et Santé publique

SPÉCIALITÉ : Santé Publique

OPTION: Épidémiologie

Par Laurence AHOUA-LERAY

**Prévention de la transmission du VIH de la mère à l'enfant (PTME)
au Mozambique: engagement dans les soins
et défis programmatiques de la stratégie B+**

**Prevention of mother-to-child transmission (PMTCT) of HIV
in Mozambique: engagement in care and programmatic challenges
for the B+ Strategy**

Sous la direction de : François DABIS

Soutenue le 20 Septembre 2019

Membres du jury :

Mme LEROY Valériane, DR, Inserm U1027, Université de Toulouse, France - Présidente

Mme NEWELL Marie Louise, Professeur, Southampton University, United Kingdom - Rapportrice

Mr NAGOT Nicolas, Professeur, Inserm UMR 1058, Université de Montpellier, France - Rapporteur

Mr BECQUET Renaud, CR1, Inserm U1219, Université de Bordeaux, France - Examineur

Mme ELUL, Batya, Professeur, Columbia University, New-York, États Unis d'Amérique -Invitée

Titre : Prévention de la transmission du VIH de la mère à l'enfant au Mozambique: engagement dans les soins et défis programmatiques de la stratégie B+

En 2015, l'Organisation Mondiale de la Santé a mis en œuvre des nouvelles lignes directrices sur la prévention de la transmission de la mère à l'enfant (PTME) du VIH recommandant à toutes les femmes enceintes et allaitantes séropositives, d'initier la trithérapie antirétrovirale à titre de traitement à vie (option B+). Cependant, il existe de plus en plus d'inquiétudes quant à l'efficacité de cette stratégie pour réduire réellement la transmission verticale du VIH à la lumière des défis programmatiques de sa mise en œuvre ; on observe en particulier des niveaux sous-optimaux de suivi dans les soins chez le couple mère/enfant en Afrique sub-Saharienne. Notre thèse vise à évaluer, d'un point de vue de santé publique, l'engagement dans les soins du couple mère/enfant en prenant l'exemple du Mozambique, pays connu pour avoir l'une des prévalences du VIH les plus élevées au monde. Nous analysons, plus particulièrement trois aspects importants de l'engagement dans les soins : les résultats du programme PTME avec une attention toute particulière sur la rétention des femmes enceintes séropositives initiant la trithérapie antirétrovirale et la couverture du dépistage du VIH chez l'enfant exposé ; les interventions visant à améliorer ces résultats et les méthodes de mesures de rétention dans les soins et leurs impacts programmatiques.

Nous observons dans ce contexte mozambicain une couverture élevée du dépistage du VIH, une amélioration significative de la couverture du traitement antirétroviral au cours du temps et une meilleure acceptation du traitement chez les femmes enceintes séropositives. Cependant, la rétention dans les soins à la fin de la première année du traitement antirétroviral chez les femmes enceintes VIH+ et la couverture du dépistage du VIH chez les nourrissons exposés restent sous-optimales. Nous concluons que les interventions visant à améliorer l'engagement dans les soins du couple mère-enfant doivent être systématiquement encouragées. Enfin, nous soulignons la grande hétérogénéité des définitions des indicateurs utilisées dans les différents programmes de PTME.

Ce travail met en évidence les lacunes dans l'engagement du couple mère-enfant dans les soins pour la PTME et ses conséquences sur l'élimination virtuelle de la transmission vertical du VIH. Nous soulignons également l'importance d'une approche consensuelle pour mesurer les indicateurs clés afin de permettre des comparaisons à l'échelle nationale et internationale. Les efforts visant à suivre les femmes sous traitement tout au long de leur vie, en veillant à ce que leurs nourrissons exposés au VIH reçoivent les soins attendus jusqu'à ce que leur statut VIH définitif soit déterminé, constituent la pierre angulaire de l'obtention d'une génération sans Sida pédiatrique d'ici 2030.

Mots-clés : PTME, VIH, option B+, engagement dans les soins, rétention, Mozambique

Title: Prevention of mother-to-child transmission (PMTCT) of HIV in Mozambique: engagement in care and programmatic challenges for the B+ strategy

In 2015, the World Health Organization published new guidelines for the prevention of mother-to-child transmission (PMTCT) of HIV and recommended that all seropositive pregnant and breastfeeding women be provided with lifelong anti-retroviral therapy (ART) (option B+). However, there are rising concerns about the effectiveness of the strategy in truly reducing the number of vertical HIV transmissions; there are indeed programmatic challenges related to its implementation; in particular, the sub-optimal levels of engagement in care of mother/infant pairs observed mainly in sub-Saharan Africa. The aim of the present thesis was to discuss, from a public health perspective, the programmatic challenges of engagement in care under option B+ strategy, with the example of Mozambique, a country known to have one of the highest HIV prevalence figures in the world. More specifically, we focused on three important aspects of engagement in care: PMTCT outcomes with a special focus on maternal ART retention and HIV infant testing uptake; interventions aimed at improving these PMTCT outcomes and methods of measurements of retention in care with their potential programmatic impact. We observed a high uptake of HIV testing, significant improvement in ART coverage over time and a better acceptance of ART at initiation in HIV+ pregnant women. Retention in care by the end of the first year of ART in HIV+ pregnant women and HIV testing coverage in HEI remain sub-optimal. Therefore, interventions to improve the mother-infant pair's engagement in care should be systematically promoted. Finally, we underscore the considerable heterogeneity of definitions of outcomes used across various PMTCT programs.

This work has highlighted the gaps in optimal engagement care of the mother-infant pair and its consequences on achieving virtual elimination of MTCT of HIV. We also highlighted the importance of having a consensus approach to measure PMTCT programme outcomes to allow national and international comparisons. Efforts to retain women under lifelong ART, ensuring their HIV-exposed infants receive the expected PMTCT services at the right moments along the continuum until final HIV status is determined, is the cornerstone of achieving an AIDS-free generation by 2030.

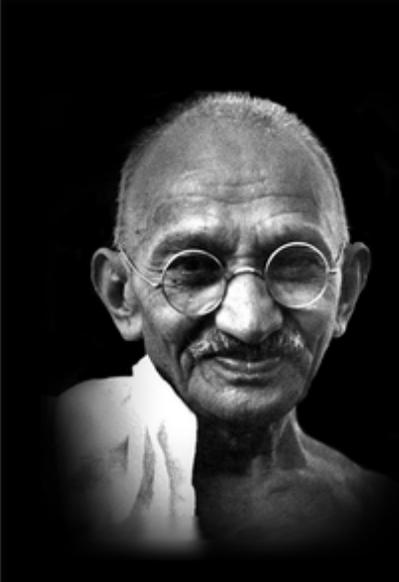
Key words: PMTCT, HIV, option B+, engagement in care, retention, Mozambique

INSERM U1219 – Bordeaux Population Health Centre

ISPED – Université de Bordeaux

146 rue Léo Saignat - CS61292, 33076 Bordeaux Cedex, France.

If I had to choose 2 inspiring lives....



Keep your thoughts positive,
because your thoughts become your words.
Keep your words positive,
because your words become your behaviors.
Keep your behaviors positive,
because your behaviors become your habits.
Keep your habits positive,
because your habits become your values.
Keep your values positive,
because your values become your destiny.

—Mahatma Gandhi

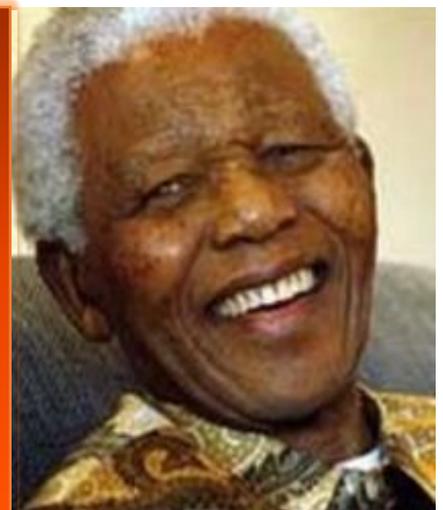


*'Let us remind ourselves that our
work is far from complete.*

*Where there is poverty and
sickness, including AIDS, where
human beings are being
oppressed, there is more work to
be done. Our work is for freedom
for all'*

Nelson Mandela

(1918-2013)



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List of acronyms and abbreviations

3TC	Lamivudine
AGYW	Adolescent girls and young women
AIDS	Acquired Immunodeficiency Syndrome
ANC	Ante-Natal Clinic
ART	Anti-Retroviral Treatment
ARV	Anti-Retroviral
AZT	Zidovudine
CDC	Centre for Disease Control and Prevention
CNCS	National AIDS Council
DBS	Dried Blood Spot
DHIS2	District Health Information System Software 2
DQA	Data Quality Assessment
DTG	Dolutegravir
EFV	Efavirenz
EID	Early Infant Diagnosis
eMTCT	Elimination of Mother to Child Transmission
ePLD	Electronic Patient-Level Data
FP	Family Planning
FSW	female sex workers
FTC	Emtricitabine
GDP	Gross Domestic Product
GF	Global Fund
HDI	Human Development Index
HEI	HIV-Exposed Infants
HIS	Health Information System
HIV	Human Immunodeficiency Virus
HRT	HIV Rapid Testing
HTC	HIV testing and counselling
ICAP	International Centre for AIDS Care and Treatment Program
IMASIDA	Indicator survey on immunization, malaria and HIV/AIDS in Mozambique (<i>Inquérito de Indicadores de Imunização, Malária e HIV/SIDA em Moçambique</i>)
INSPIRE	INtegrating and Scaling up PMTCT through Implementation REsearch
InSTI	Integrase Strand Transfer Inhibitor
LTFU	Lost to Follow-up
M&E	Monitoring and Evaluation

MCH	Mother and Child Health
MDGs	Millennium Development Goals
MIP	Mother-infant pair
MISAU	Ministry of Health of Mozambique (<i>Ministério de Saúde de Moçambique</i>)
MSM	Men who have sex with men
MTCT	Mother to Child Transmission
NFU	No Follow-Up
NNRTI	Non-Nucleoside Reverse Transcriptase Inhibitor
NTD	Neural Tube Defect
NVP	Nevirapine
OpenMRS	Open Medical Record System
PCR	Polymerase Chain Reaction
PEN IV 2015-2019	National Strategic Plan IV 2015-2019 (<i>Plano Estratégico Nacional IV</i>)
PEPFAR	United States Presidents' Emergency Plan for AIDS Relief
PFaCTS	Programme and Facilities Characteristics Tracking System
PLHIV	People Living with HIV
PMTCT	Prevention of Mother to Child Transmission
POC	Point-of-Care
SEA	Southern and Eastern Africa
SI	Strategic Information
T&T strategy	Test and Treat strategy
TDF	Tenofovir Disoproxil Fumarate
U=U	Undetectable = Untransmittable
UNAIDS	The Joint United Nations Programme on HIV/AIDS
VCT	Voluntary Counselling and Testing
VL	Viral Load
WHO	World Health Organization

Glossary

Antiretroviral Therapy	Standard antiretroviral therapy (ART) consists of the combination of antiretroviral (ARV) drugs to maximally suppress the HIV virus and stop the progression of HIV disease. ART also prevents onward transmission of HIV, reduces morbidity and mortality in people living with HIV.
Engagement in care	Patient engagement in his/her's own health, care and treatment. Specifically, engagement in HIV care refers to a patient who is actively engaged in and receiving regular HIV care, by a dynamic navigation through the complete spectrum of HIV care and treatment with the final goal of achieving and maintaining viral suppression.
HIV continuum of care	The HIV continuum of care defines the dynamic and bidirectional relationship that exist between steps or stages of HIV medical care that people living with HIV go through from initial diagnosis to achieving the goal of viral suppression.
HIV treatment cascade	The HIV treatment cascade depicts prevalence estimates for discrete steps along the HIV care continuum from HIV diagnosis through viral suppression. The cascade is outcome-oriented: it begins with quantitative estimates of prevalent HIV cases, successive bars illustrating the subsequent steps of HIV diagnosis, linkage to care, retention in care, antiretroviral therapy (ART) receipt, and plasma viral suppression.
HIV testing yield	The proportion of clients undergoing HIV testing who test positive
Option B and B+ strategies	Strategies used for the Prevention of Mother to child transmission of HIV. Option B recommends ART for all HIV-infected pregnant and lactating women beginning in the antenatal period and continuing throughout the duration of breastfeeding. At the end of breastfeeding those who do not yet require ART for their own health would discontinue ART and continue to monitor their CD4 count, eventually re-starting ART when the CD4 falls below 350 cells/mm ³ . <u>Option B+</u> recommends life-long ART for all pregnant and breastfeeding women living with HIV regardless of their CD4 count.
Prevention of Mother to Child Transmission (PMTCT) of HIV	Prevention of mother-to-child transmission (PMTCT) of HIV comprise a set of interventions to prevent the vertical transmission of HIV from the HIV-infected women to her HIV-exposed infant. Effective preventive interventions are provided during the periods of pregnancy, labour, delivery, and breastfeeding.
Unmet need for family planning	Percentage of women of reproductive age, either married or in a union, who have an unmet need for family planning. Women with unmet need are those who want to stop or delay childbearing but are not using any method of contraception.

Scientific valorisation

Scientific publications related to the thesis

Article submitted

PMTCT care cascade and factors associated with attrition in the first 4 years following Option B+ implementation in Mozambique. **L Ahoua**, T Tiendrebeogo, S Arikawa, V Journot, Lahuerta M, Abrams E, Aly Dario, Becquet R, F Dabis. Submitted to Tropical Medicine & International Health journal.

Measuring retention in care for HIV-positive pregnant women in Prevention of Mother to Child Transmission of HIV (PMTCT) option B+ programs. The Mozambique experience. **L Ahoua**, T Tiendrebeogo, S Arikawa, V Journot, Lahuerta M, Aly Dario, Becquet R, F Dabis. Submitted to BMC Public Health journal.

Article in preparation

Interventions to improve PMTCT outcomes under option B+ strategy: a systematic review. **L Ahoua**, S Arikawa, R Becquet, F Dabis.

Communication at international conferences

Retention of mother/baby pairs along the PMTCT cascade: a systematic review and meta-analysis of current evidence of Options B and B+ strategies. **Laurence Ahoua**, Shino Arikawa, Renaud Becquet, François Dabis. Poster presented at the International AIDS Society Conference (IAS), Paris, France 2017. POSTER #MOPEC0632.

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A combination strategy for enhancing linkage to and retention in HIV care among adults newly diagnosed with HIV in Mozambique: study protocol for a site-randomized implementation science study. Elul B, Lahuerta M, Abacassamo F, Lamb MR, **Ahoua L**, McNairy ML, Tomo M, Horowitz D, Sutton R, Mussa A, Gurr D, Jani I. BMC Infect Dis. 2014 Oct 15;14:549. doi: 10.1186/s12879-014-0549-5.

A combination intervention strategy to improve linkage to and retention in HIV care following diagnosis in Mozambique: A cluster-randomized study. Elul B, Lamb MR, Lahuerta M, Abacassamo F, **Ahoua L**, Kujawski SA, Tomo M, Jani I. PLoS Med. 2017 Nov 14;14(11):e1002433. doi: 10.1371/journal.pmed.1002433. eCollection 2017 Nov.

Feasibility and Acceptability of Health Communication Interventions Within a Combination Intervention Strategy for Improving Linkage and Retention in HIV Care in Mozambique. Sutton R, Lahuerta M, Abacassamo F, **Ahoua L**, Tomo M, Lamb MR, Elul B. J Acquir Immune Defic Syndr. 2017 Jan 1;74 Suppl 1:S29-S36.

Factors Associated with Use of Short-Term Pre-Exposure Prophylaxis for HIV Among Female Partners of Migrant Miners in Mozambique. Falcao J, Zerbe A, Lahuerta M, Baggaley R, **Ahoua L**, DiMattei P, Morales F, Ramiro I, El-Sadr WM. AIDS Patient Care STDS. 2017 Dec;31(12):528-534. doi: 10.1089/apc.2017.0179.

Willingness to use short-term oral pre-exposure prophylaxis (PrEP) by migrant miners and female partners of migrant miners in Mozambique. Joana Falcao, **Laurence Ahoua**, Allison Zerbe, Pietro di Mattei, Rachel Baggaley, Victor Chivurre, Prince Mulondo, Isaias Ramiro, Shona Dalal, Fernando Morales, Kevin O'Reilly & Wafaa El-Sadr (2017). *Culture, Health & Sexuality*, DOI: 10.1080/13691058.2017.1316424

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1 General introduction

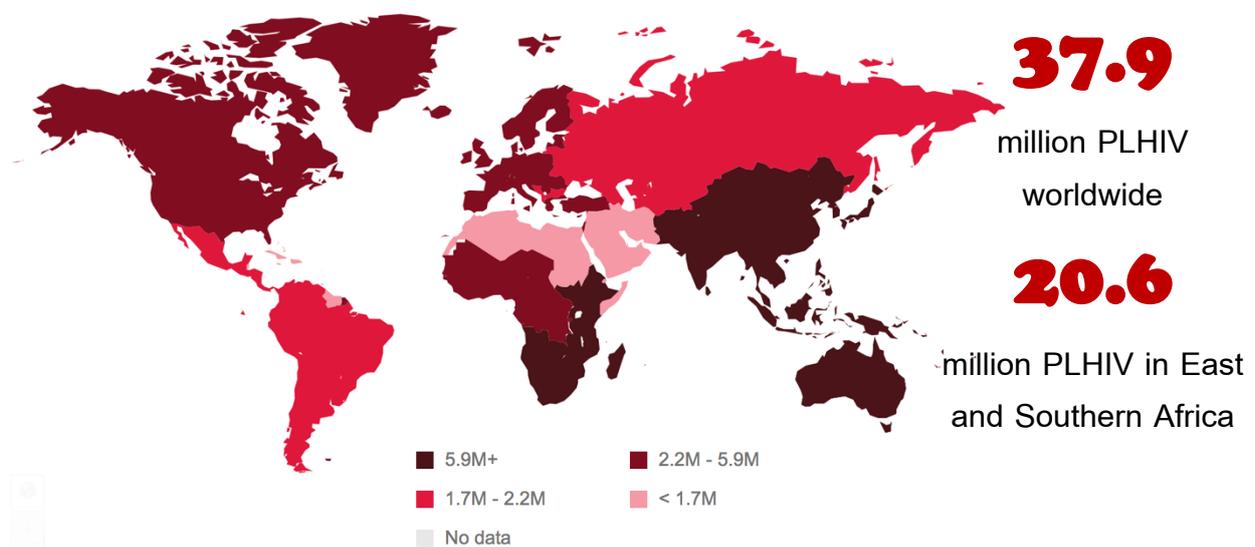
1.1 HIV/AIDS epidemic in East and Southern Africa

1.1.1 Epidemiology of the HIV epidemic

By the end of 2018, there were an estimated 37.9 million people living with HIV (PLHIV) worldwide. Of these, more than a half (20.6 million, 54%) were living in East and Southern Africa (Figure 1.1) [1]. This high-burden region also bears the highest numbers of new infections, with 47% of 1.7 million new infections estimated worldwide. Of the 20.6 million PLHIV in East and Southern Africa, 1.1 million were children less than 15 years of age. Most of these children were infected by their HIV-positive mothers during pregnancy, childbirth, or breastfeeding. By the end of 2018, a total of 310,000 people died from AIDS-related illnesses, bringing the total number who have died from AIDS-related illnesses since the start of the epidemic to 17.5 million in the region.

Remarkable efforts have been made over the past two decades in reducing HIV-associated morbidity, mortality, transmission, and stigma as well as in improving the quality of life of PLHIV. In East and Southern Africa, new HIV infections and deaths decreased by 28% and 44%, respectively, owing largely to the investments, commitments, and innovations used to respond to the HIV epidemic.

Figure 1.1: Number of people living with HIV/AIDS worldwide, all ages, 2018



Source: UNAIDS, AIDSinfo, 2018 [1]

1.1.2 The paradigm shifts in the approach to antiretroviral treatment scale-up

Since 2000, there has been a growing evidence that PLHIV who are virally suppressed cannot transmit the virus to their sexual partners [2]. Three major studies undertaken between 2007 and 2016 in more than 20 different countries confirmed the absence of sexual transmission of the virus from virally suppressed HIV-positive patients to their seronegative partner [3–5]. Early initiation of antiretroviral treatment (ART) and Pre-exposure prophylaxis (Prep) using ARV drugs for HIV prevention can achieve significant reduction in the number of HIV transmission and accelerate the response to the HIV epidemic. As treatment services are scaled-up, rather than focusing on a single time point, a more longitudinal assessment of engagement in care was needed to better measure the outcomes of ART programs. In this context, the priority was then shifted to monitor progress along the HIV continuum of care by measuring patients receiving services at each step of the HIV care cascade.

With the ultimate goal of HIV care and treatment programs being to end the HIV epidemic by 2030, three major approaches all coherent with this new vision, have been promoted by the international community: United Nations Program on HIV/AIDS (UNAIDS)' 90-90-90 targets, WHO's 'Test and Treat' strategy and the Prevention Access Campaign's 'U=U' campaign.

The 90-90-90 HIV care cascade

In 2014, ambitious targets were set by UNAIDS and its partners, known as the '90-90-90' treatment target. It aims that by 2020, 90% of all PLHIV should know their HIV status; of those tested HIV-positive, 90% will receive sustained ART; and of those receiving ART, 90% will have viral suppression (Figure 1.2). If these targets were met, at least 81% of all PLHIV would be on treatment, 73% of all PLHIV would be virally suppressed. New HIV infections and HIV-related deaths would be reduced to less than 500,000. Statistical modelling has suggested that achieving these targets by 2020 could lead to the end of the AIDS epidemic by 2030.

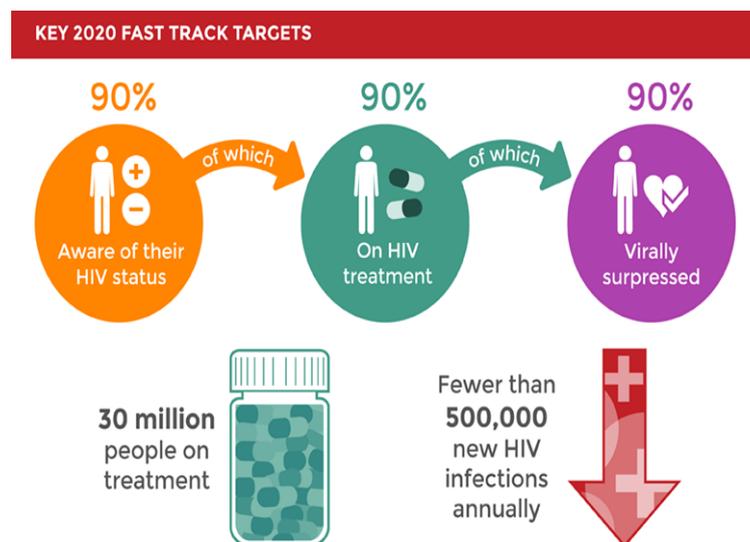
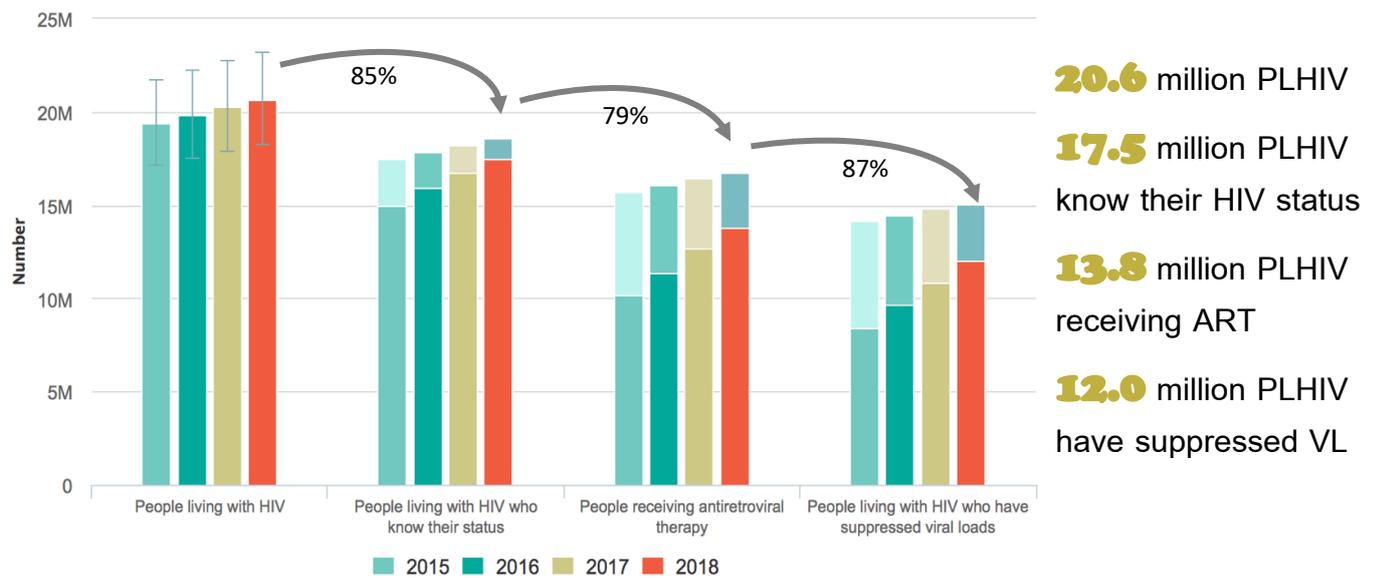


Figure 1.2 : Key Fast Track Targets
Source: UNAIDS 2014 [6]

However, the current status of the 90-90-90 cascade in East and Southern Africa falls short of the expected targets. At the end of 2018, 85% of the estimated 20.6 million PLHIV knew their status, 79% were on ART and 87% of PLHIV on ART had suppressed viral loads, making the achievement of the target at '85-79-87' (Figure 1.3). This is a significant improvement compared to previous years and compared to the global figures for the same year ('79-78-86')[1].

Figure 1.3: Progress towards 90-90-90 target, Eastern and Southern sub-Saharan Africa, 2015 to 2018.



Source: UNAIDS, AIDSinfo, 2018 [1]; note: the lighter colour in the bars correspond to the estimated number of missing to PLHIV to reach the 90-90-90 targets.

The 'Test and Treat' strategy and the new WHO 2018 ART guidelines

WHO recommended in 2016 the 'Test and Treat' (T&T) strategy, in which all children, adolescents, and adults, including all pregnant and breastfeeding women, living with HIV should be provided with lifelong ART regardless of CD4 cell count, as a way to decrease community viral load and to reduce the rate of new HIV infections[7]. The preferred first-line regimen was tenofovir disoproxil fumarate (TDF) + lamivudine (3TC) (or emtricitabine, FTC) + efavirenz (EFV).

Recent studies have demonstrated an increase in the levels of pre-treatment ARV drug resistance in low- and middle-income countries ranging from 3% to 30%, with higher rates of resistance observed for NNRTI-based regimens mainly due to sub-optimal viral suppression [8–11]. In response, WHO issued guidelines recommending that countries with pre-treatment resistance to EFV or nevirapine (NVP) at or above 10% should urgently consider revising their first-line regimens [12]; and in 2018, a dolutegravir (DTG)-based regimen was recommended as the preferred first-line regimen [13]. The drug has shown an improved safety profile compared with EFV in randomized studies [14–16] and also has a high barrier to development of drug resistance [17,18]. In addition, DTG has been found to be effective for pregnant women and was also found in breast milk, resulting in significant plasma concentration in infants and, thus, a potential important drug to reduce mother-to-child transmission (MTCT) of HIV [19]. However, an observational study in Botswana, the TSEPAMO Study, reported in 2012 a potential safety risk for developing neural tube defects among infants born to women who were taking DTG at conception [20,21].

Since then, several studies have provided additional safety data of DTG in pregnancy[22–26]. An observational cohort study in Botswana of 1,729 pregnant women showed similar rates of adverse birth outcomes (including stillbirth, neonatal death, preterm birth) in both women receiving dolutegravir-based ART and those receiving efavirenz-based ART in pregnancy[23]. A systematic review of 1,200 pregnant women treated with DTG reported similar percentages of adverse birth outcomes and congenital abnormalities compared to historical control studies

of HIV-positive women[24]. After an extended period of surveillance, new findings from the TSEPAMO study reported that prevalence of neural-tube defects associated with DTG exposure at conception declined from 0.94% to 0.30% of deliveries although still significantly higher than the 0.10% observed among women receiving non-dolutegravir ART [27] (ref). By mid-2019, based on these results, caution was still recommended by WHO when providing DTG-based ART regimens in adolescent girls and women of childbearing age. Consistent and reliable contraception method is recommend to be systematically provided for them to avoid potential neural tube defects among newborns [13].

The 'U=U' campaign

In 2016, the official 'Undetectable=Untransmittable' (U=U) campaign was launched by the Prevention Access Campaign, which has since then been endorsed by more than 60 countries worldwide. The 'U=U' campaign has been an important message of 2017 to fight the HIV epidemic and to promote the 'Test and Treat' strategy as its pillar for achievement of the UNAIDS's 90-90-90 target by 2020. The campaign has already been successful in influencing national HIV treatment policies, public opinions, and encouraging more and more people living with HIV to seek treatment [2].

However, implementing these new approaches has important implications for programme priority-setting, funding and service delivery, especially in high HIV burden countries. As more people are expected to start ART earlier, the burden on health facilities is expected to increase, which could lead to reduced quality of services and increased risk of patients' dropping out of care.

1.2 Prevention of Mother-to-Child Transmission (PMTCT) of HIV

1.2.1 What is PMTCT of HIV?

Mother-to-Child Transmission (MTCT) of HIV is one of the leading causes of HIV transmission in children. It can occur during pregnancy, delivery or breastfeeding (Figure 1.4). In the absence of any intervention, MTCT rates range from 25% to 40% among infants who were breastfed. Over a half of infants vertically infected with HIV would die before the age of 2 years [28,29]. Maternal viral load is a strong predictor of the risk of transmission regardless of timing of transmission. The rate can be reduced to less than 5% when women achieve viral suppression[30–33] through various interventions put in place during the periods of pregnancy, labour, delivery, and breastfeeding, including ARV treatment for the mother which will be discussed in further detail.

Figure 1.4: Timing of Mother-to-Child transmission and transmission risk estimates in the absence of ARVs for PMTCT



In resource-poor settings where formula feeding is not a viable option due to lack of access to clean water, women living with HIV are recommended to exclusively breastfeed (rather than mixed feeding), providing that they are on ART. The revised 2016 WHO guidelines recommend exclusive breastfeeding for the first six months of life, followed by continued breastfeeding with introduction of appropriate complementary foods thereafter [34].

WHO recommends an early infant diagnosis (EID) using HIV virologic testing for HIV-exposed infants (HEI) between 4 and 8 weeks of age. Another HIV test should be done at 18 months of age and/or when breastfeeding ends to provide the final infant diagnosis. Infant ARV prophylaxis varies according to mother's course of ARVs and the infant feeding method: once-daily nevirapine or twice-daily zidovudine from birth to 4 to 6 weeks of age. In addition, all infants who are found to be positive for HIV should be immediately initiated on treatment[7].

Besides improving mothers' survival, PMTCT protects HIV-exposed children from infection and decreases infant morbidity and mortality[35]. Thus, in a global effort to significantly contribute to achieving the Millennium Development Goals (MDGs) in reducing child mortality by two-thirds between 1990 and 2015 (MDG 4) and reducing maternal mortality rate by three-quarters between 1990 and 2015 (MDG 5), two major turning points in PMTCT care occurred since 2010: the call for a 'Global Plan Towards the Elimination of New HIV Infections Among Children by 2015 and Keeping Their Mothers Alive' in 2011 and the recommendation for providing ART for HIV-positive pregnant and breastfeeding women, also called the Option B+ strategy in 2012.

1.2.2 UNAIDS' call for a virtual elimination of MTCT (eMTCT) of HIV

In 2009, during the week of the World Health Assembly, UNAIDS called for a virtual elimination of MTCT of HIV by 2015. At the 2011 United Nations High Level Meeting on AIDS, world leaders presented the UNAIDS-crafted 'Global Plan Towards the Elimination of New HIV Infections Among Children by 2015 and Keeping Their Mothers Alive' [36].

It covered all low- and middle-income countries but focused on the 22 countries¹—including Mozambique—with the highest estimated numbers of pregnant women living with HIV and that were home to nearly 90% of pregnant women living with HIV in need of services.

Barriers still exist to attain the complete elimination of MTCT (e.g. late maternal HIV diagnosis, insufficient ART access or adherence, ARV-resistant virus strains, maternal/infant ARV toxicities). In addition, although intensive efforts are ongoing for the development of a vaccine, HIV-1 curative strategies are still in their infancy stage [37]. Therefore, the *virtual* elimination - and not the *complete* elimination - of MTCT of HIV has been recognised and accepted by UNAIDS and partners. For this reason, the 'Global Plan' called for a 90% reduction in the number of new HIV infections among children, a 50% reduction in the number of AIDS-related maternal deaths, a reduction of final MTCT rates to 5% or less among breastfeeding women, and to 2% or less among non-breastfeeding women by 2015.

To achieve these goals, four prongs were identified with specific targets for each of them (Figure 1.5). Prongs 1, 2 and 3 are necessary to reach the first target of reducing new child infections while only prong 3 will affect the second target to lower the transmission rate.

¹ Angola, Botswana, Burundi, Cameroon, Chad, Côte d'Ivoire, Democratic Republic of the Congo, Ethiopia, Ghana, India, Kenya, Lesotho, Malawi, Mozambique, Namibia, Nigeria, South Africa, Swaziland, Uganda, United Republic of Tanzania, Zambia and Zimbabwe.

Figure 1.5: Targets for each of the four prongs in the Global Plan Towards the elimination of new HIV infections among children by 2015 and keeping their mothers alive

Prong 1 target	Prong 2 target	Prong 3 target	Prong 4 target
<ul style="list-style-type: none"> Reduce HIV incidence among women and their partners by 50%. 	<ul style="list-style-type: none"> Reduce unmet need for family planning among women to zero (MDG goal). 	<ul style="list-style-type: none"> Reduce mother-to-child transmission rate to 5% or less among breastfeeding women, and 2% or less among non-breastfeeding women; 90% of mothers receive perinatal antiretroviral therapy or prophylaxis; 90% of breastfeeding infant-mother pairs receive antiretroviral therapy or prophylaxis. 	<ul style="list-style-type: none"> Provide life-long antiretroviral therapy to 90% of pregnant women in need of antiretroviral therapy for their own health. Provide life-long antiretroviral therapy to all children living with HIV

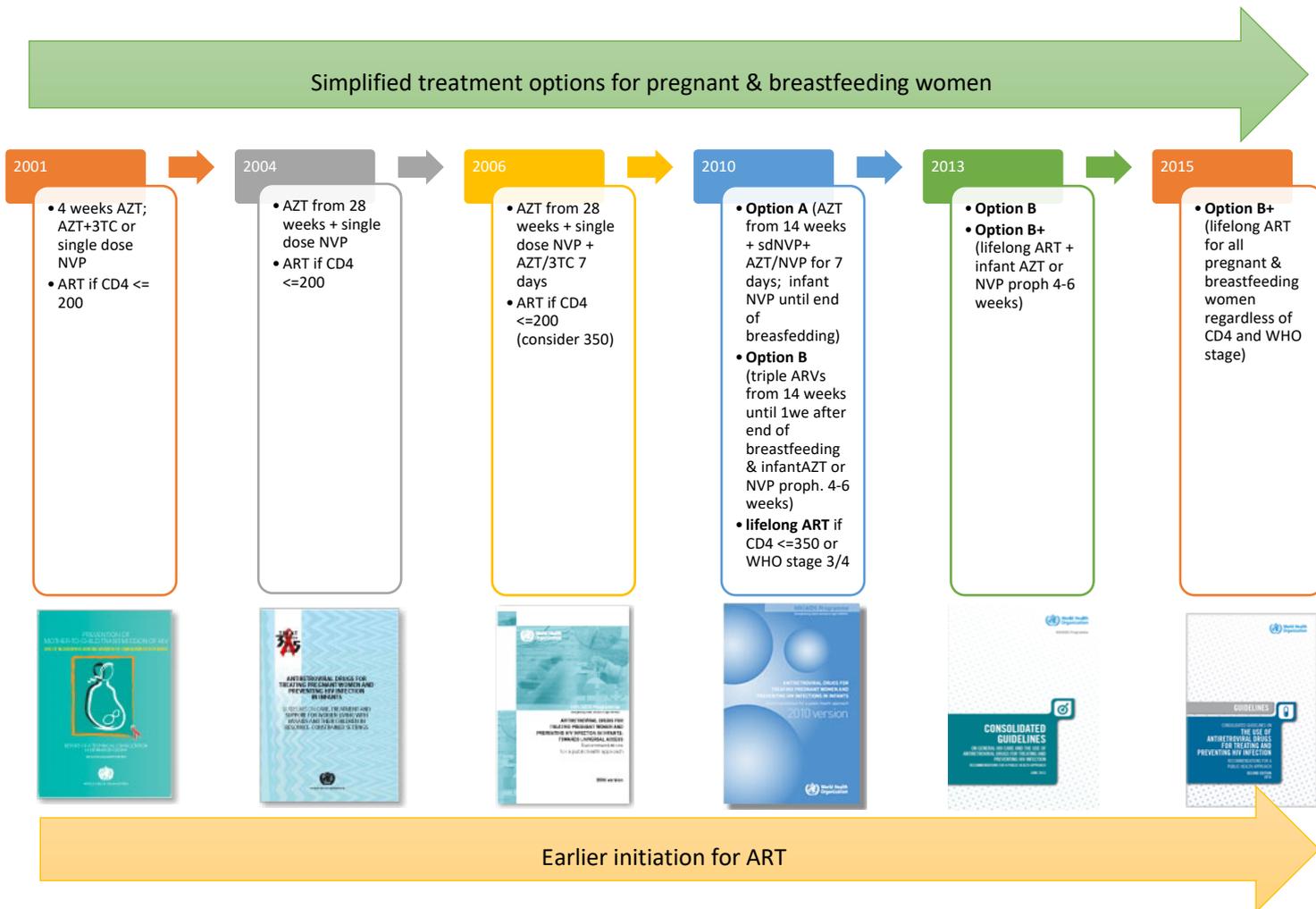
Source: Joint United Nations Programme on HIV/AIDS, UNAIDS 2011 [36]

Similar to UNAIDS' 90-90-90 target, the key principles of success of this plan was that the mother/infant pair is now seen as a unique entity that should be followed up for a longer continuum of care engagement with other essential health and non-health services provided.

1.2.3 Evolution of WHO treatment guidelines for PMTCT from 2005 to 2015

Since 2001, great progress has been made to provide pregnant and breastfeeding women with a more efficacious and simplified ARV regimen to prevent vertical transmission of HIV from the mother to her exposed infant while offering her improved treatment for her own health (Figure 1.6). In 2010, WHO guidelines recommended two options, Options A and B, for HIV-positive pregnant women with CD4 cell counts of 350 or less to start lifelong ART using a triple-combination regimen [38]. Under Option A, women receive antenatal and intrapartum ARV prophylaxis along with an ARV postpartum 'tail' regimen to reduce risk of drug resistance, while infants receive postpartum ARV prophylaxis throughout the duration of breastfeeding. Under Option B, all HIV-positive pregnant and lactating women are offered ART to continue throughout the duration of breastfeeding. At the end of breastfeeding, those women who do not yet require ART for their own health would discontinue treatment, and would continue to have their CD4 count monitored, eventually re-starting ART when the CD4 falls below 350 cells/mm³.

Figure 1.6: Evolution of WHO treatment guidelines for PMTCT from 2005 to 2015



Note: Option A and Option B were offered if CD4 count > 350 cells/mm. The recommended first-line ART for lifelong treatment was a once-daily regimen of EFV/TDF/3TC.

In 2013, WHO released a ‘programmatic update’ to its 2010 guidelines recommending countries to phase out Option A and replace it with either Option B or Option B+ to provide HIV-positive pregnant women with lifelong ART regardless of their CD4 count and WHO staging[39]. Options B and B+ provide the advantages of offering all HIV-positive pregnant women the same triple-combination regimen. An important benefit of Option B+ is that it can lower the risk of HIV transmission to male partners since being on ART will make women less infectious. Option B+ should also reduce the risk of MTCT of HIV in subsequent pregnancies.

From a programmatic standpoint, this makes drug procurement, distribution, and prescribing more straightforward. Furthermore, when considering PMTCT-related costs and child infections, Option B+ is the most cost-effective strategy compared with Option A and averts more child infections compared with Option B [40]. Thus, in 2015, WHO recommended that all pregnant women be provided with Option B+ [7].

For many countries, the simplicity of Option B+ was a ‘game changer’ in efforts to prevent MTCT of HIV, its main outcome being progress made in maternal ART coverage. By the end of 2017, all priority countries except Nigeria had a national Option B+ coverage above 80% (Figure 1.7).

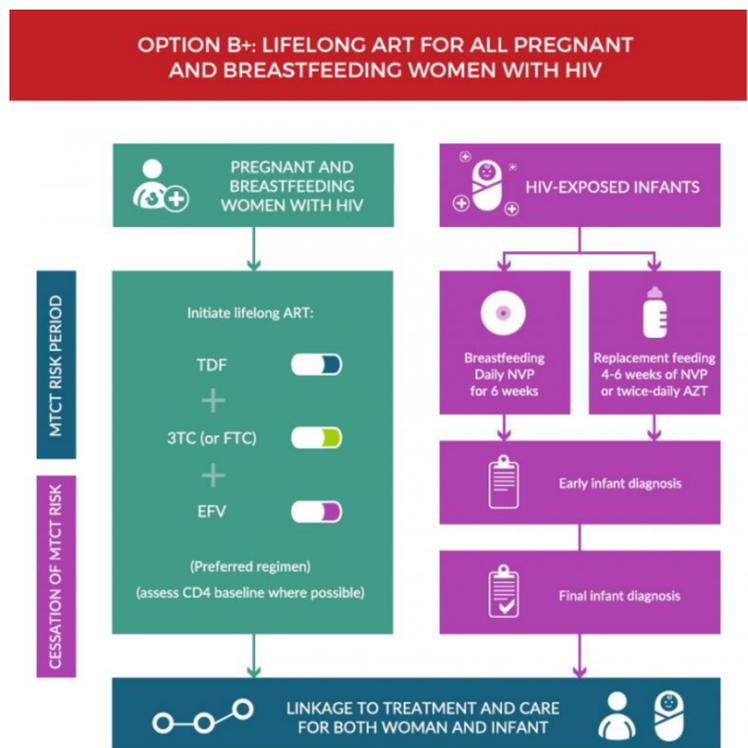
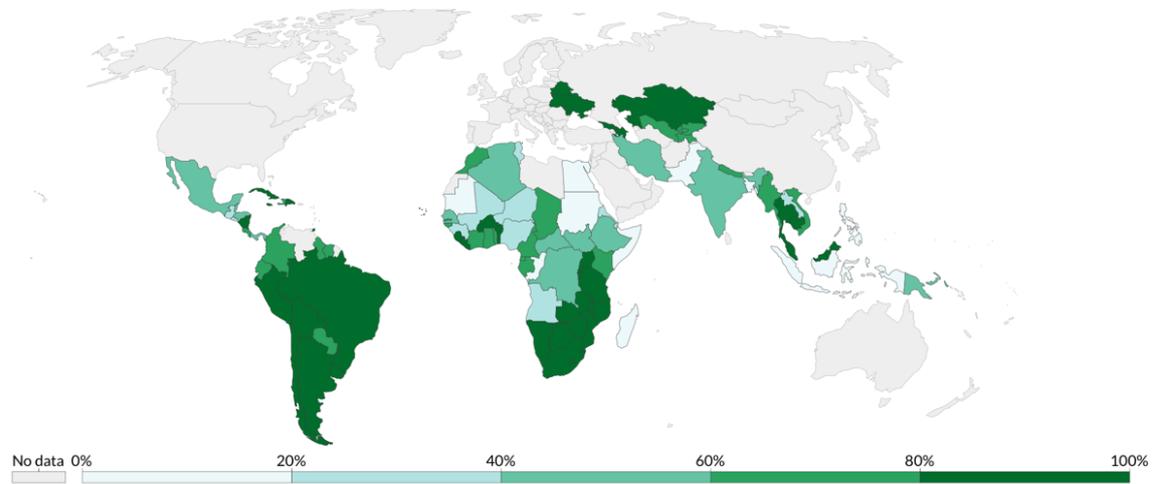


Figure 1.7: Share of pregnant women who receive antiretroviral therapy, by end of 2017.

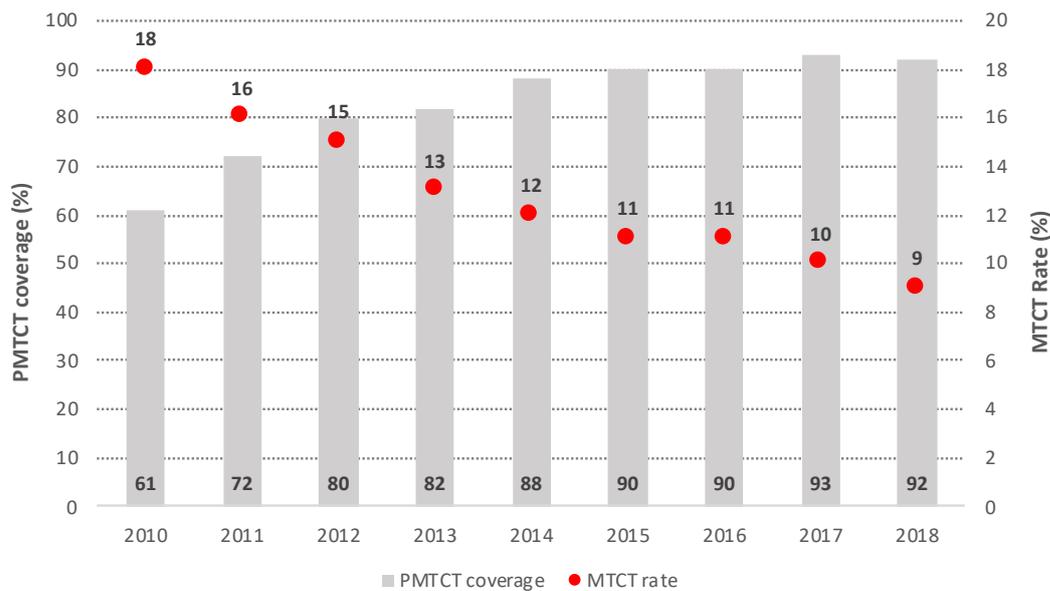
Percentage of pregnant women with HIV who receive antiretroviral therapy for PMTCT



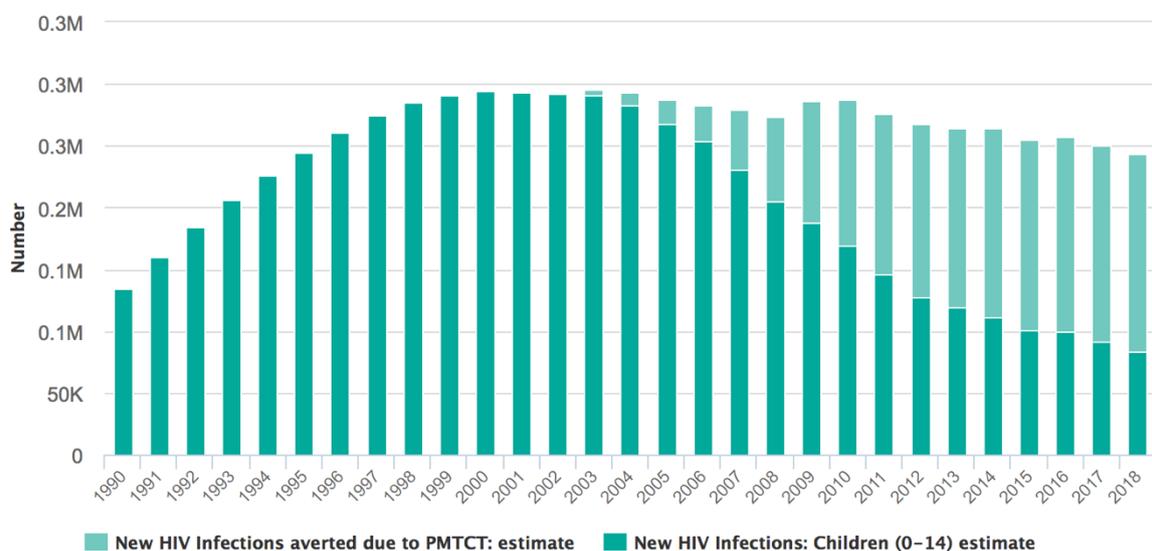
Source: Our World in Data, World Bank, UNAIDS estimates 2017 [41]

1.2.4 Current PMTCT situation and challenges

The introduction of highly efficacious ARV regimens and rapid expansion of comprehensive services over the past decade have contributed to remarkable results, especially in the Southern and Eastern Africa (SEA) region where PMTCT efforts have yielded the greatest achievements. There has been a significant increase in ARV coverage in HIV-infected pregnant women from 61% in 2010 to 92% in 2018 (figure 1.8) due to the expansion of PMTCT services. This has translated into similar increase the in number of pediatric infections averted from 110,000 to 160,000 children during that same period (figure 1.9). Since 2010, estimated rate of MTCT decreased by 50%, reaching 9.24% [IdC95%: 7.6 - 12.5%] (by 18 months post-partum) at the end of 2018 (figure 1.8). Still this rate represents an estimated 84,000 newly infected children in 2018 in the SEA region due to the significant numbers of pregnant women who acquire HIV infection during pregnancy or the postpartum period who are not diagnosed and offered antiretroviral medicines and due to the low coverage of early infant testing (estimated at 68% [95%CI: 56 - 91%] in 2018)[42].

Figure 1.8 : PMTCT coverage (%) and MTCT rate (%) in Eastern and Southern Africa, 2018

Source: UNAIDS, AIDSinfo, 2018 [1]

Figure 1.9: Estimated number of new HIV child infections vs. number of new infections averted due to PMTCT, Eastern and Southern Africa, 1990-2018

Source: UNAIDS, AIDSinfo, 2018 [1]

Programmatic challenges to Option B+ implementation are numerous in resource limited settings. Although a large proportion of HIV-infected pregnant women have access ART in ANC, retaining them in care and ensuring their adherence to treatment remain a challenge, especially during the postpartum period. While more than 75% of pregnant women were reported to adhere to ART during pregnancy, only 53% did so during the postpartum period due to inadequate follow-up and support provided to mothers during the breastfeeding period[43–46]. Therefore, approximately half of all new HIV infections among HEI now

occur during breastfeeding. Reasons behind non-adherence to PMTCT services can be various. Some pregnant women are reluctant to take ARV drugs while they feel healthy[47,48], or due to fear of disclosure or stigma[49–51]. Possible drug side effects can also lead to non-adherence and dropping out of care[48,52]. Some women gradually stop taking ARV drugs after giving birth due to other competing priorities, such as child care[53,54]. Perinatal depression is a common condition of pregnancy and the postpartum period but remain frequently undiagnosed in MCH services as it is not part of the standard of care in most sub-Saharan African countries[55]. Nevertheless, it has been reported that perinatal depression can occur in nearly 50% of women enrolled in MCH services and can lead poor PMTCT outcomes, including dropping out of care[56–58]. Some mothers after giving birth change residency and self-transfer to another health facility close to their family in-law and are considered lost to follow-up[50,59].

Virologic testing for HEI is not consistently available due to low geographical coverage and often accessible only in high volume centralized provincial or district hospital. When it is available, virologic testing is often time-consuming with challenges in transport of samples to centralized laboratories and potential delays in the return of results. In SEA region, only Malawi reach an EID coverage of > 95% in 2018. Other countries in the region have an average of 68% EID testing coverage [1].

The introduction of Option B+ and the interrelationship between ANC, post-natal care, ART, and child care services have highlighted important gaps in the PMTCT cascade monitoring [60]. While aggregated and cross-sectional data are used to construct the PMTCT cascade, women and children are not tracked across services, especially in population with high mobility and settings with weak health information systems[61].

1.2.5 Country validation criteria for eMTCT

Although the overall goal of reducing new HIV infections among children by 90% by 2015 was not met, remarkable achievements in terms of PMTCT services expansion, ART coverage and number of pediatric infections averted, have built the momentum and opened the pathway for efforts to be sustained by the international community in reaching virtual elimination of MTCT of HIV and make good on the commitment to deliver an AIDS-free generation. In May 2016, the dual elimination of MTCT of HIV and syphilis has been identified as a global public health priority². Therefore, a set of criteria for eMTCT country validation for the dual elimination of HIV and syphilis were defined [62]:

- Impact criteria for HIV: fewer than 50 cases per 100,000 live births, a transmission rate below 5% if mothers are breastfeeding and below 2% if they are not breastfeeding for at least 1 year;
- Process criteria at service delivery level: ≥ 95% of pregnant women to receive antenatal care (ANC); ≥ 95% of pregnant women to receive HIV and syphilis testing in pregnancy; ≥ 95% of pregnant women diagnosed with HIV or syphilis to receive treatment.

In addition, WHO requires that eMTCT of HIV and syphilis processes and indicators are achieved within a context of human rights, gender equality, and community engagement.

To date, five countries and several island states and territories have reached eMTCT of HIV³. For example, Thailand was the first Asian country to receive WHO validation of the eMTCT

² Impact targets must be met for at least 1 year prior to eMTCT validation assessment

³ Armenia, Belarus, the Caribbeans (Anguilla, Antigua and Barbuda, Bermuda, Cayman Islands, Montserrat and Saint Kitts and Nevis), Cuba, Thailand and Malaysia which was proclaimed by WHO in October 2018

of HIV-1 (see Case study box) [63]. With an adult prevalence of 1% and 440,000 PLHIV in 2017, Thailand is the only country thus far with a generalized epidemic to achieve eMTCT[62,64]. Compared to Mozambique, Thailand had a lower HIV prevalence rate among pregnant women, a higher ANC coverage and strong public health infrastructures. In addition, the country had a self-reliant national budget, a strong engagement of nongovernmental and civil society partners, and a robust prevention of MTCT monitoring program.

Case study: eMTCT in Thailand

1) HIV generalized epidemic since the early 1990s

Adult (15-49) HIV prevalence (2017) = 1%; 440,000 of PLHIV

ANC coverage (2015) = 98.3% (at least one ANC visit)

Introduction of option B+ in 2014 (with exclusive breastfeed for at least 6 months)

Estimated MTCT rate declined from 24.2% in 1994 to 1.9% in 2015

2) eMTCT validation in May 2016 (for HIV & Syphilis)

3) Programme and country attributes towards eMTCT:

A. Near universal healthcare access

i. 99.9% of Thai citizens have government supported insurance

ii. Additional 1.4 million non-Thai migrants have health insurance

B. All PMTCT services (ANC, screening and treatment for HIV and syphilis) financed through national budget with free access for migrants

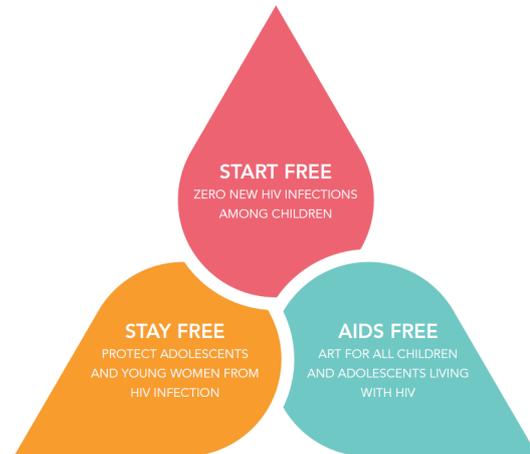
C. Routine antenatal screening for syphilis for more than 30 years

D. Routine antenatal screening for HIV for approximately 20 years

1.2.6 Start Free, Stay Free, AIDS Free

The ‘Global Plan’ was recognized as one of the greatest public health achievements of recent times. Building on its remarkable success, the international community called in 2016 for a ‘Start Free, Stay Free, AIDS Free’ Super-Fast-Track framework and accelerated implementation plan to reduce the number of new HIV infections among children as well as increase the number of children with HIV on treatment [65]. The framework establishes three blocks of programme activity that are closely interrelated:

- **START FREE:** by preventing new HIV infections among children during pregnancy, birth and throughout the breastfeeding period;
- **STAY FREE:** by preventing new HIV infections among adolescents and young women as they grow up;
- **AIDS FREE:** by providing HIV treatment, care and support to children and adolescents living with HIV.



Of particular interest for PMTCT of HIV is the first block ‘START FREE’ which recommends full programme scale to reach the following targets: 1) reduce the number of children (aged 0–14) newly infected annually to less than 40,000 by 2018 and 20,000 by 2020; 2) Reach and sustain 95% of pregnant women living with HIV with lifelong HIV treatment by 2018. The elimination of new HIV infections among children can be achieved only if these ambitious targets are reached. These targets are complementary to 90-90-90 targets but are to be achieved in a shorter time frame. To reach these targets, countries must ensure that at least 95% of pregnant women living with HIV receive Option B+ PMTCT services by 2018 and that these women are retained in care during the breastfeeding period.

1.3 HIV epidemic in Mozambique

1.3.1 Country profile

The Republic of Mozambique, one of the largest southern African countries (799,380 km² in size), has 2,300 kilometers along the Indian Ocean on its eastern coast. The country borders with Tanzania, Malawi, Zambia, Zimbabwe, South Africa, and Swaziland. Approximately 70% of the population of 28.9 million (2017 census) live and work in rural areas [66,67].

Nampula is one of the 11 provinces of Mozambique. Located in the Northern region, it had an estimated population of 6.1 million habitants in 2017, representing a 50% increase since 2007. Nampula is the most populous province of the country with 74.8 people/km² for a surface of 81,606 km² - almost 30 times higher than the national average of 2.55 people/km² [41]. Zambézia is a province located in the central region of Mozambique. It is the second largest province after Niassa (105,008 km²) and second most populous after Nampula (5,110,787 habitants and population density population of 48,7 people/km²). Zambézia's population increase was 31% since 2007. Both provinces have a majority of women: 52% in Nampula and 53% in Zambia [68].



Mozambique is considered a low-income country, and more than half of its people continue to live below the poverty line. With an annual population growth of 3%, and additional challenges in recent years including a regional drought in 2016, increasing debt, decreased external investment, and declines in exports, the economic growth of the country has slowed even further. The annual gross domestic product (GDP) growth decelerated to 3.7% in 2017, down from 6.7% in 2016 and well below the 7% GDP growth achieved on average between 2011 and 2015³⁶. In 2016, Mozambique was among the bottom eight countries in the UNDP's world Human Development Index (HDI) report, ranking 181 out of 188 [69].

Two-thirds of the population is 24 years of age or younger, mostly unemployed and dependent on the older third [67,71]. Life expectancy at birth has improved and is currently 58 years [66]. The adult literacy rate increased from 27.1% in 1980 to 58.8% in 2015 and is improving at an average annual rate of 22.15% [73]. Despite these improvements, Mozambicans, especially in the rural areas, are still affected by an epidemiological profile dominated by the three major communicable diseases, HIV, malaria and tuberculosis, and by persistent poor living conditions, such as high food insecurity, low levels of educations, poor access to safe water and poor sanitation.

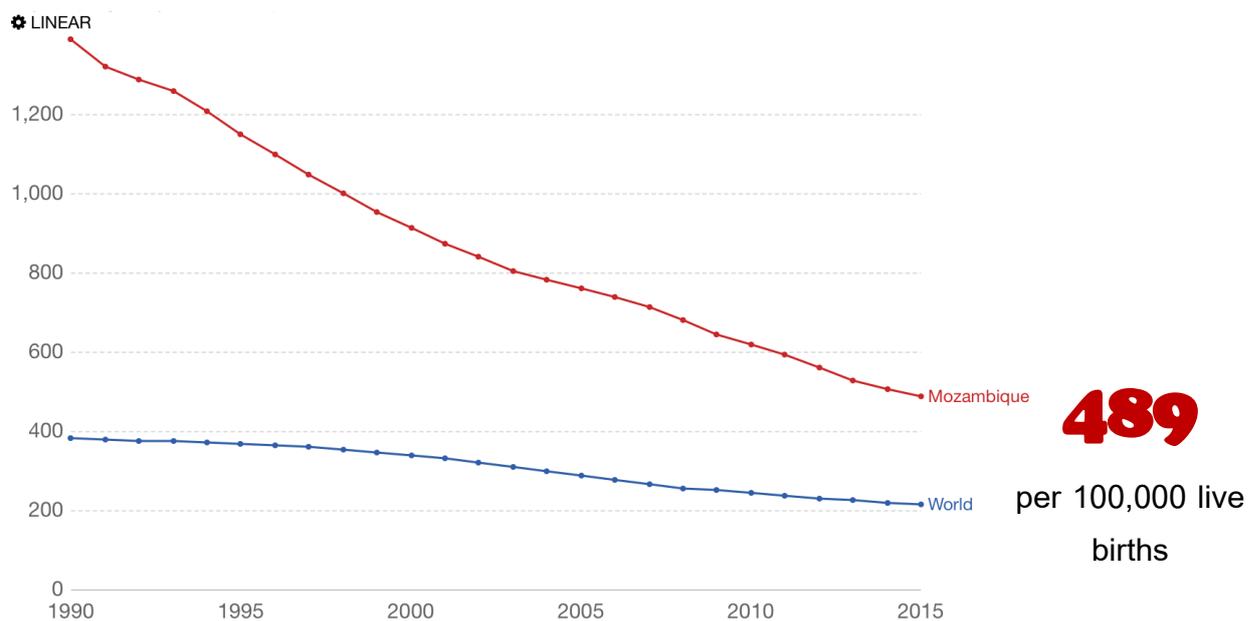
Women in Mozambique are highly vulnerable. Gender inequality in Mozambique remains a major challenge in the access to health services. The Gender Inequality Index synthesises gender-based inequalities in three dimensions—reproductive health, empowerment, and economic activity—on which Mozambique ranks 138 of 160 countries [69]. Since 2010, the government of Mozambique is committed to achieving the MDGs [74]. Despite the reduction between 1997 and 2003 [75,76], the maternal mortality ratio in more recent years has been stagnant and still unacceptably high (489/100,000 live births in 2015), compromising the achievement of the MDG target (Figure 1.10) [77]. Exposure to the risk of maternal death is still high due to several factors, among which is the overall fertility rate of 5.3 children per

woman, slightly lower than in 2011 (5.9). Teenage pregnancy also remains unacceptably high and increased from 38% in 2011 to 46% in 2015, with the risk of death among pregnant teenagers four times higher than for women above the age of 20. Other factors contributing to the high rates of maternal mortality are low utilization of family planning (FP) services, low antenatal care (ANC) coverage (at least four visits), and low institutional delivery. Although use of modern contraceptives increased from 14% in 2003 to 25% in 2015, it still remains low, and 23% of married women have unmet needs for family planning. Similarly, ANC coverage (at least four visits) was estimated at 55%, a slight increase from 2011 (53%), and seven of ten births (73%) were attended by skilled personnel [78,79]. Recent national MCH program data from 2018, report a decrease in the ANC coverage (at least 4 visits) of 49% and a slight improvement in institutional delivery coverage of 87%.

Child health indicators show remarkable and consistent progress in recent years. Mortality rates for children under 5 years of age decreased by more than 100% between 1997 and 2011 (Figure 1.11). However, the decrease in neonatal mortality is occurring at a slower pace, requiring special attention considering that approximately 81% of these deaths occur during the first week of life and 32% of them on the first day. In the last decade, there has been an improvement in the immunization level, with vaccination coverage increasing from 63% in children aged 12 to 23 months completely vaccinated in 2003 to 65% in 2015.

Figure 1.10: Maternal Mortality Ratio, Mozambique 1995-2015.

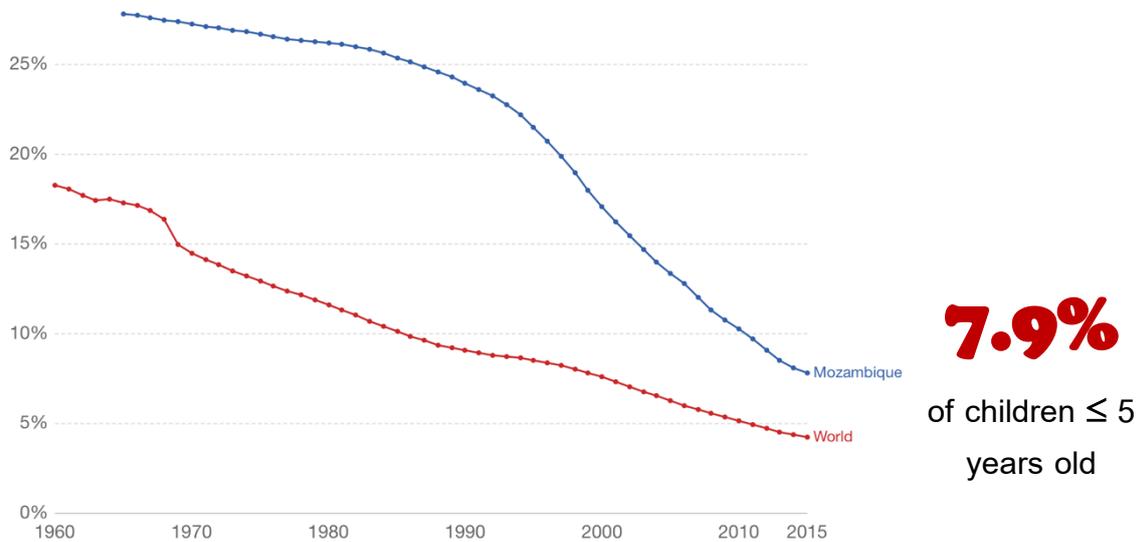
Maternal mortality ratio is the number of women who die from pregnancy-related causes while pregnant or within 42 days of pregnancy termination per 100,000 live births.



Source: Our world In Data, World Bank, data source from World Health Organization, 2015 [80]

Figure 1.11: Child Mortality Rate, Mozambique, 1960-2015.

The child mortality rate measures the share of children that die reaching the age of 5.



Source: Our world In Data, World Bank, data source from World Health Organization, 2015 [80]

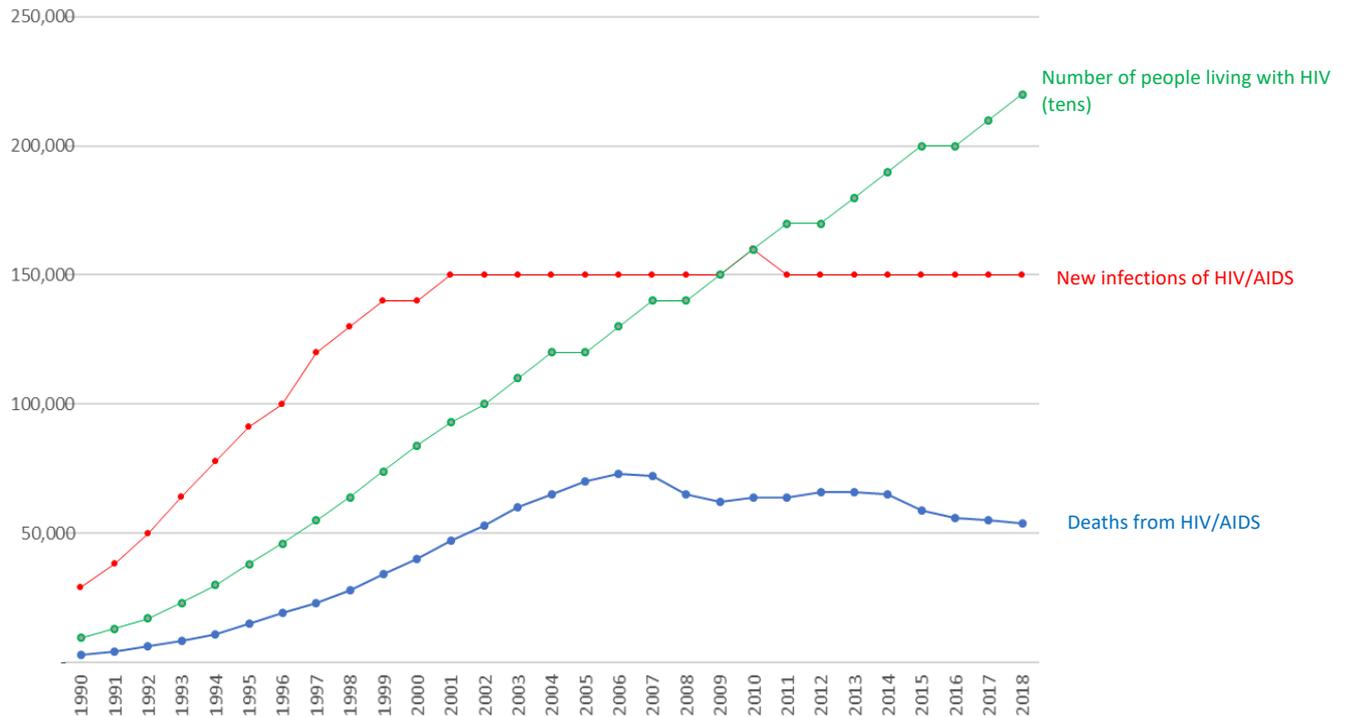
1.3.2 Epidemiological trends of HIV infection

Mozambique has a generalized HIV/AIDS epidemic (i.e. HIV prevalence exceeds 1% of the general adult population). In 2013, a mode of transmission study was conducted using data from INSIDA, DHS2011 and the different IBBS surveys from 2011-2012 [81]. Transmission of HIV occurred through stable heterosexual relationships (25.6%), people with multiple heterosexual sex partners (22.6%), regular partners of people with multiple heterosexual sexual partners (21.6%) and clients of female sex workers (FSW) (18.4%). Among the children, the principal mode of transmission was mother-to-child transmission of HIV. Until 2016, HIV/AIDS was the main cause of deaths in the country, as reported by the Global Burden of Disease[82].

Mozambique has one of the highest adult (ages 15-49) prevalence rate in the East and Southern African region: 12.6% estimated in 2018[1]. Because of the population growth and the significant expansion of ART coverage between 2010 and 2018, the absolute number of PLHIV has increased from 1.8 to 2.2 million amidst a drop-in incidence of 7% and a steady reduction in the number of deaths by 16% (Figures 1.12 and 1.13). Nevertheless, Mozambique was the third country of the East and Southern African region to have the highest incidence rate (5/1,000 population) behind Lesotho and Eswatini and the second country to have the highest AIDS-related deaths (54,000 deaths) behind South Africa [1].

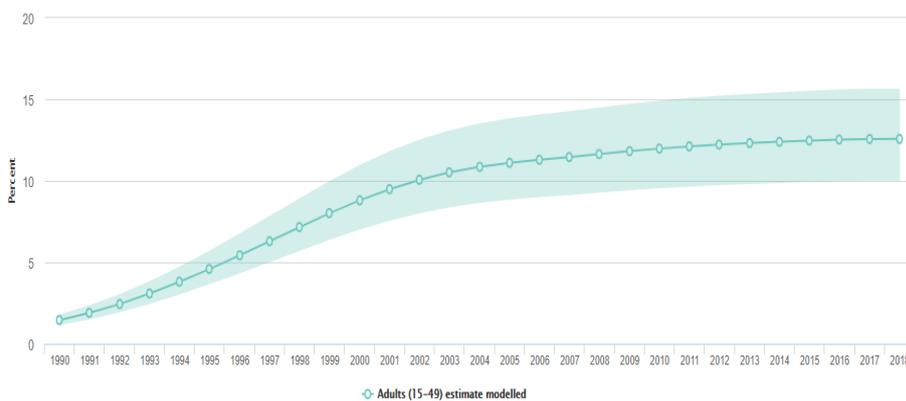
Figure 1.12: Prevalence, new cases, and deaths from HIV, Mozambique, 1990-2018.

Total number of deaths from HIV/AIDS (not including deaths from tuberculosis), new cases of HIV infection per year, and total number of people living with HIV. The total number of people living with HIV is measured in tens.



Source: UNAIDS, AIDSinfo, 2018 [1]

Figure 1.13: HIV Prevalence among adults (aged 15-49 years), Mozambique, 1990-2018.



2.2
million PLHIV

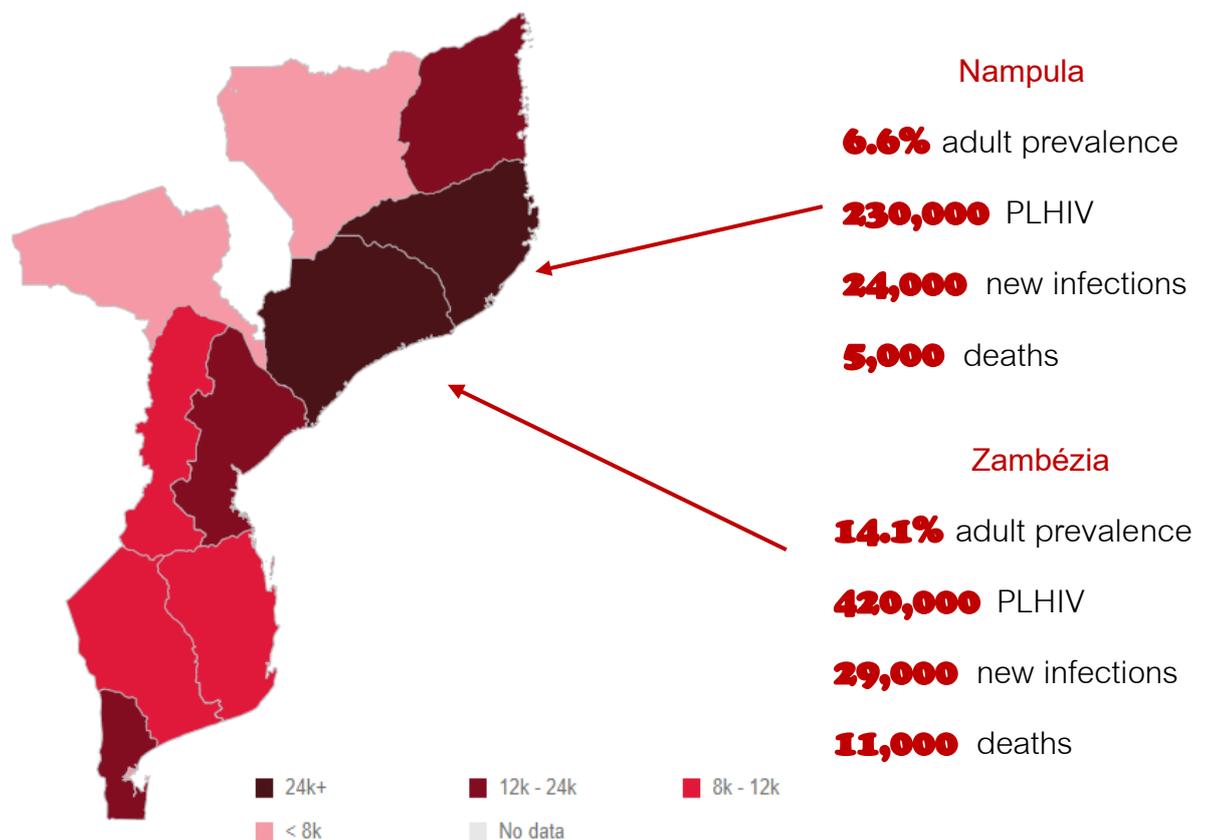
12.6%
adult (age 15-49)
HIV prevalence

Source: UNAIDS, AIDSinfo, 2018 [1]

The HIV prevalence varies significantly by geographic location, age, and gender. The country's southern region still registered the highest prevalence, particularly Gaza Province (23.9%), Maputo Province (22.2%), and Maputo City (16.9%) [1], which could partly be explained by circular migration of migrant labor between these provinces, South Africa, and Swaziland. The risk factors in the region include inequality, transactional sex, and casual partnerships [79]. The central region including Sofala (15.6%), Manica (13.3%), Zambézia (14.1%), and Tete (5.3%) remains the second most affected. This region is a major transport corridor with numerous hotspots. Zambézia accounts for 420,000 PLHIV, representing 19% of the country's PLHIV population, while the northern region's lower prevalence is partially explained by higher rates of circumcision due to local social-cultural norms and the presence of Voluntary Male Circumcision services offered by partners (Figure 1.14).

Of the total number of PLHIV, 140,000 (6.4%) are children aged 0 to 14 years. Women comprise 1.2 million (60%) of the 2 million adult PLHIV with a higher HIV prevalence rate (15%) than in men (9.9%). Prevalence peaks among women aged 35 to 39, while incidence is highest among the vulnerable group of adolescent girls and young women aged 10 to 24. For males, prevalence also peaks between ages 35 to 39, while incidence is highest between ages 20 to 29. This implies possible sexual networking among older males and young girls and subsequent spread within marriages and other concurrent relationships [79]. The age and sex variations in HIV prevalence underscore the need to integrate interventions targeted to adolescent girls, young women, and their male partners as well as for intensified efforts for increased male involvement, early treatment initiation using the "Test and Treat all" strategy and close follow-up and retention in care.

Figure 1.14: HIV Prevalence among adults (aged 15-49 years), by provinces, Mozambique, 2018.



Source: UNAIDS, AIDSinfo, 2018 [1]

1.3.3 National HIV response efforts

The HIV response in Mozambique is coordinated by the National Control Programme for STI-HIV/AIDS at the Ministry of Health of Mozambique - MOH (*Ministério de Saúde de Moçambique - MISAU*) and the National AIDS Council (CNCS) with support from key stakeholders and partners including UNAIDS, the United States Presidents' Emergency Plan for AIDS Relief (PEPFAR), the Global Fund (GF), additional bilateral and multilateral partners, and civil society. Approximately 95% of the HIV response is funded through external donors, and 5% through domestic funding resources.

Several national plans have guided the HIV response, the most recent of which are:

- The 'National Plan for Accelerating the Response to HIV/AIDS (2013-2017)' ⁴ based on the UNAIDS' call for accelerating the response for HIV/AIDS [83]. The Plan's goal was to achieve substantial reductions in HIV transmission, with targets including: 80% of eligible HIV-infected adults and children receiving treatment, 50% reduction in new infections, and reduction in MTCT of HIV to less than 5% by 2015. The evaluation of the plan's achievements was, however, mixed: 55% of HIV-infected patients were receiving ART by then end of 2018, stagnant annual number of new infections, and an estimated 18% of MTCT of HIV (Figure 1.15) [85].
- The 'National Strategic Plan for the HIV/AIDS response (PEN IV 2015-2019)' [86]. This HIV Strategic Plan provides a combined response for the provision of prevention, care, and treatment services and mitigation of the consequences of HIV tailored to the social context and conditions of the country. Its three main goals are to reduce the mortality due to HIV by 40% in 2019, reduce the number of new infections by 30% by 2019, Reduce the rate of HIV transmission from mother to child to <5 % by 2019. Outcomes to achieve these three goals were set out.
- The 'Political Declaration of HIV 2016-2020': specific national care and treatment targets were revised to align with UNAIDS 90-90-90 targets and to reach an AIDS free generation by 2030. The new targets included: reduce the number of new infections by 50% by 2020, reduce the mortality caused by HIV infection by 37% by 2020 and increase the ART coverage to 81% by 2020.

⁴ Originally developed for the years 2013-2015 and subsequently extended to the year 2017.

Figure 1.15: Target achievements of the 'National Plan for Accelerating the Response to HIV/AIDS (2013-2018), Mozambique.



Source: Spectrum 5.754 (2018); figure extracted from National HIV programme report, Ministry of Health, 2018 [85]. Note: with the implementation of 'Test and Treat' strategy, eligible patients are defined as all HIV-positive patients.

In addition, over the past 5 years, national treatment guidelines were revised to reflect the changes in international policy recommendations to scale-up availability of ART and viral load (VL) monitoring for PLHIV (Table 1.1). These include increasing the ART eligibility threshold from a CD4 cell count of less than 350 cells/ μ L to a CD4 cell count of less than 500 cells/ μ L, with universal access for specific populations, phased implementation of the 'Test and Treat' strategy, and routine VL implementation for all districts implementing the T&T strategy. The T&T strategy was piloted in 12 high-burden districts in late 2016. The expansion continued to reach all districts by December 2018, reaching the objective of nationwide coverage within the scheduled timeframe.

Table 1.1 : National Antiretroviral Therapy ART-eligibility Guidelines from 2013 to 2017, Mozambique Ministry of Health (MISAU).

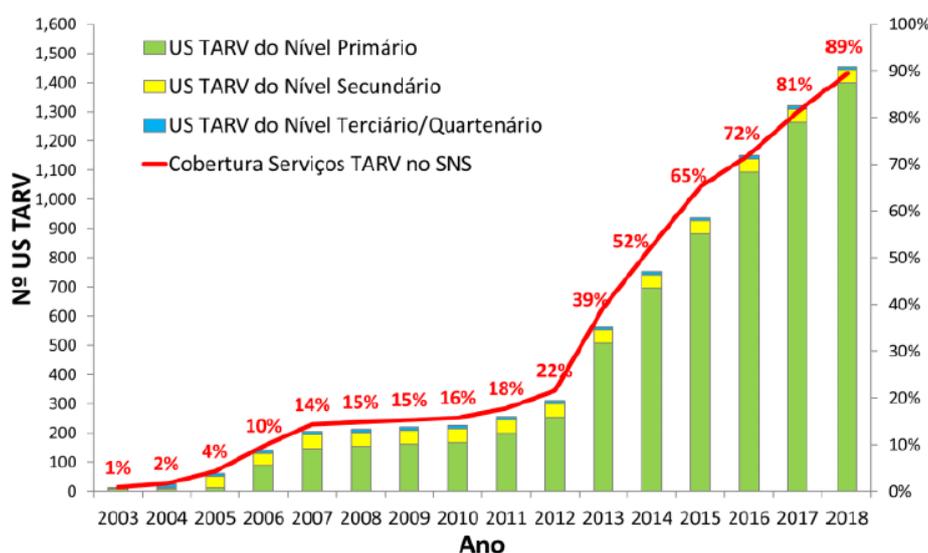
WHO stage	CD4 cell count not available	CD4 cell count available
2013 through 2016		
I/II	Do not initiate ART	Initiate ART if CD4 ≤ 350 cells/μL
III	Initiate ART	Initiate ART independent of CD4 count
IV	Initiate ART	Initiate ART independent of CD4 count
2016* through 2017		
I/II	Do not initiate ART	Initiate ART if CD4 ≤ 500 cells/μL
III	Initiate ART	Initiate ART independent of CD4 count
IV	Initiate ART	Initiate ART independent of CD4 count
2018		
All patients : 'Test and Treat strategy		

Source: National HIV/AIDS treatment guidelines, Ministry of Health (MISAU), 2018 [87]. Abbreviations: WHO, World Health Organization; ART, antiretroviral therapy.

*The 'Test and Treat' (T&T) strategy started to be implemented in a phased way in August 2016.

These efforts have led to a remarkable scale-up of HIV services in Mozambique over the past 7 years (Figure 1.16). In 2018, 89% of the 1,455 health facilities in the country offered ART, up from 72% in 2016. However, there remains a large gap in access to ART service, with only 56% of PLHIV in need of ART actually receiving it[1].

Figure 1.16: Trends in the number of health facilities providing ART services, Mozambique (2003-2018)



Data source: extracted from the National HIV/AIDS program, Ministry of Health, 2019 report [85]

1.3.4 The 90-90-90 cascade

In Mozambique, the testing and treatment cascade is based on a combination of the information provided by the Spectrum estimates (number of PLHIV), the 2015 Indicator survey on immunization, malaria and HIV/AIDS in Mozambique (IMASIDA) data (percentage who knows their status; percentage virally suppressed) and the routine monitoring of ART (number of HIV-positive patients on ART). Figure 1.17 shows this cascade for the period 2015-2018, including the gaps (in lighter color in the bars) remaining to reach the 90-90-90 targets: by end of 2018, 72% of the estimated 2.2 million PLHIV knew their HIV status; of those diagnosed with HIV, 77% were on ART. Viral load testing is not yet done routinely in all PLHIV in treatment. Availability of testing capacity is still limited, and priority is given to patients with treatment failure. Therefore, routine viral load testing coverage is insufficient for national level estimates of PLHIV who are virally suppressed. However, the 2015 IMASIDA survey, reported that only 59% of patients on ART were virally suppressed[79].

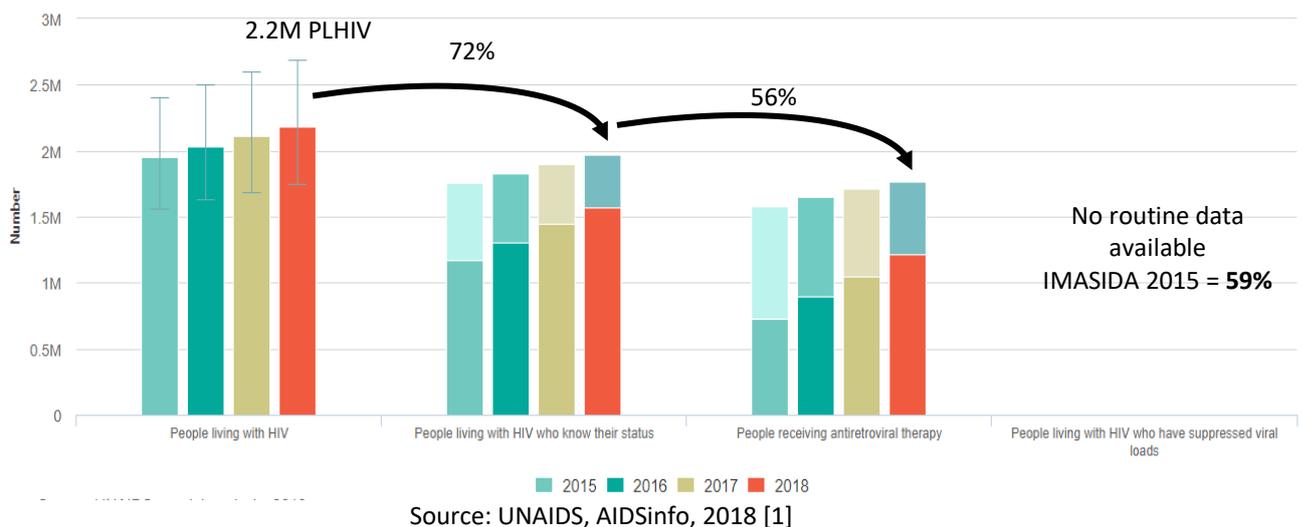
The major gap is in the first ‘90’ for HIV diagnosis. HIV testing and counselling (HTC) services are widely available in the country and are implemented in all levels of the healthcare system—primary, secondary and tertiary, and in clinical settings either via routine opt-out testing (e.g. in high risk paediatric clinics, inpatient wards, TB, ANC, Voluntary Male Medical Circumcision (VMMC) services, surgery, blood bank clinics, or emergency care unit) or via testing of symptomatic patients (e.g. in adult outpatient care, well-child care, urgent care and dentistry). Despite high HTC service coverage, HTC is still a weak component of the Mozambique HIV prevention strategy. Women are accessing HTC services more than men through essentially MCH services, although testing coverage is low for both groups. Based on IMASIDA data, 29% of women and 19% of men were tested in the last 12 months and had received their test results. Strong stigma and discrimination persist against people infected with HIV which has been reported as a barrier to HIV testing and counselling [88–90]. Expanding community testing through self-testing with facilitated referral to health services are known to increase uptake of HTC and linkage to care, especially in men and high-risk individuals[91]. However, community HTC is only being implemented at sub-national levels by organizations funded by PEPFAR, Global Fund, and the private sector. Some community HTC activities are specifically targeted to FSW, men who have sex with men (MSM), adolescent girls and young women (AGYW) and prisoners through focused projects. Index case testing strategy is also at sub-national scale whereby index cases are identified at the health facility, and with the consent of the index case, HTC services are offered to their sexual partners and children with age under 10 years (who have not been tested before). Self-testing has not yet been implemented in the country.

Of those HIV-infected, only an estimated 77% were actually receiving ART reflecting the great ART service expansion started in 2013 and the simplification of eligibility criteria. In addition, ART coverage is highest among adult women (64%) probably due to the systematic screening in MCH services and the introduction of Option B+ in 2013. The ART coverage among paediatric patients is low (60% of the estimated children 0-14 years living with HIV), most probably due to the low number of HIV-exposed children accessing HIV services and who are tested and initiated on ART (see section 1.3.5 ‘PMTCT overview’).

According to IMASIDA, only 59% of HIV-infected patients receiving ART are virally suppressed. The three major factors contributing to low VL testing coverage are the high LTFU rate within the first year of ART initiation, the absence of routine VL testing and the weak supply chain systems in the country. Indeed, from 2015 to 2018, the retention at 12-months post-ART initiation has been stagnant at 68% for adults and 70% for children. The absence of increase in retention rates is due to the over-saturation of high-volume sites offering ART: 75% of patients receiving ART are actually followed in only 20% of health facilities offering ART services in the country [85]. Consequently, a decrease in quality of care and insufficient

resources to correctly follow-up patients and missed appointments leads to high drop-outs rates. Most health facilities use targeted VL only for pregnant women, children under 5 years of age, and suspected treatment failures. In addition, lack of human resource capacity and weak systems for cold chain management, warehousing, and transportation contribute further to sub-optimal VL testing services. Implementation of routine VL is planned to be introduced progressively along with the ‘Test and Treat all’ strategy but will require significant health systems strengthening to respond to the increased demand.

Figure 1.17: HIV testing and treatment cascade, Mozambique, 2015- 2018



1.3.5 PMTCT overview

Key National Strategies

The PMTCT program in Mozambique first started in 2002 in 8 health facilities. In 2004, the program was then integrated in the ‘2004-2008 National Health Plan’ and in 2006, PMTCT services were offered in MCH consultations offering Option A to all pregnant women and their HEI (national guidelines 2010).

According to UNAIDS, Mozambique contributes to 8.2% of new pediatric infections globally in 2009, ranking third of the 22 countries that most contribute to the global burden of new HIV infections after Nigeria and South Africa. To accelerate the response, Mozambique endorsed in 2011 the ‘Global Initiative for the Elimination of Vertical Transmission 2012-2015’, constituting radical change in the prevention paradigm to eliminate MTCT of HIV in children while ensuring the mother/infant pair’s survival. It is in this context that the country reviewed its PMTCT targets to align with those of the ‘National Plan for Accelerating the Response to HIV/AIDS (2013-2017)’: reducing MTCT to less than 5% and increasing PMTCT coverage to 90% by 2015. To better respond to this challenge, the MOH developed the ‘National Plan of the Elimination of Vertical Transmission of HIV 2012-2015’, providing guidelines to more effective PMTCT interventions, including introduction of Option B+ strategy, task shifting of HIV care and treatment to Mother and Child Health (MCH) nurses, improving family planning and HIV service integration, enhancing community support and tracing [92].

Option B+ recommendations

Option B+ was rolled out nationally at the beginning of 2013. PMTCT services are offered free of charge via a ‘One-stop model’ and ‘Test and Treat’ approach in which ART consultation is performed by nurses trained in both MCH and PMTCT guidelines. In the ‘Test and Treat’ approach, a pregnant woman is counselled and tested for HIV at first ANC visit and if found HIV+, she would initiate ART during the consultation. Thus, HIV care and treatment services were integrated into MCH services. All HIV-positive women who become pregnant are referred from the ART clinic to MCH services to receive PMTCT.

First-line treatment was one daily fixed-dose combination of Tenofovir/Lamivudine/Efavirenz. Monthly clinical follow-up was done during the first six months of ART, then bi-monthly during breastfeeding until 12 months of treatment and bi-annually thereafter until end of breastfeeding. ART counselling and drug pickup was done monthly. Routine viral load (VL) monitoring was recommended at 3 and 12 months after ART initiation and annually thereon.

HEI received daily dose of Nevirapine from birth until 6 weeks postnatal and were followed monthly during the first year, then bi-monthly until final HIV serostatus was determined. Exclusive breastfeeding was recommended for at least the first 6 months post-partum. The first virologic test (DNA PCR HIV test) was recommended between 1 and 2 months post-partum and if result was negative and infant was still being breastfed, HIV test should be repeated 2 months after breastfeeding cessation. The mother-infant pair was followed in MCH services until the final HIV status of the exposed infant was determined [87].

After final testing of the HIV-exposed infant is completed in the MCH sector, HIV-positive mothers (and her child if tested positive) are transferred to ART clinics for follow-up. Health facilities are supported by community health workers who assist in counselling and community-based care for PMTCT, however no official community outreach guidelines are available.

Achievements

The PMTCT program in Mozambique succeeded in a steady scale up and improvement of services. PMTCT services are provided at primary and secondary health centres as well as tertiary referral hospitals. Health facilities providing ART also provide Option B+, whereas health facilities without ART services continue to provide Option A. By the end of 2018, PMTCT was rolled out to almost all health facilities (93%) in the country, and 93% of these 1,520 PMTCT facilities was applying Option B+ (corresponding to 97% of all facilities providing ART) [85].

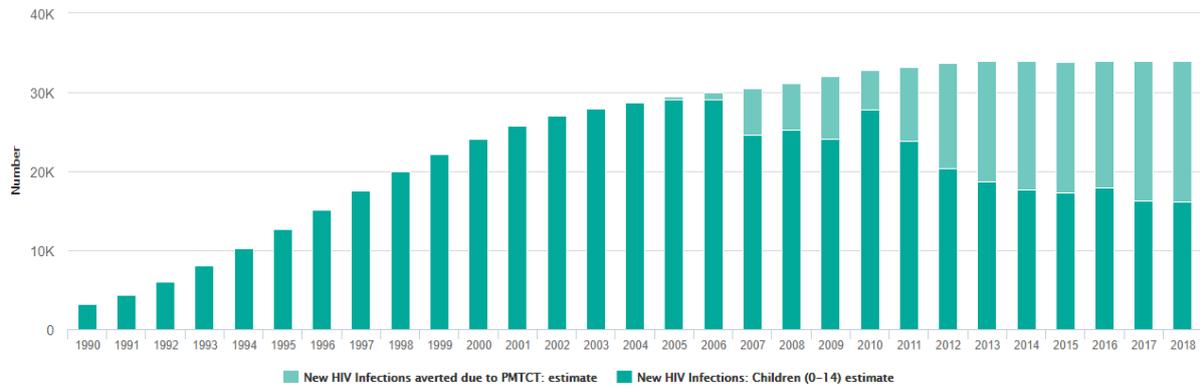
Since first implementation of PMTCT services in the country in 2002, population coverage has increased markedly with higher proportions of women knowing their HIV status and receiving ART since the introduction of Option B+. By the end of 2018, 98% of pregnant women enrolled in ANC knew their HIV status, 8% of these were HIV-positive and 94% of those tested HIV-positive were on ARVs of any kind for PMTCT, of whom 99% were receiving ART.

Due to the increase in PMTCT service coverage, its integration into MCH services and the introduction of Option B+, a total of 127,500 new child infections have been averted since 2010 and the annual number of new infections among children decreased from 28,000 in 2010 to 16,000 in 2018 (Figure 1.18). In addition, monitoring efforts have been made by the MOH in 2015, with the revision of the monitoring and evaluation tools to provide a paper-based registers allowing better capture the longitudinal follow-up of mothers enrolled in the programme.

Early infant diagnosis has expanded, reaching 92% of health facilities providing PMCT services by end of 2018. However, diagnosis coverage remains low. Program data from 2018 show that of the 91,776 HEI that reached at-risk child consultation before 8 weeks of age, 71,754 (78%) had a polymerase chain reaction (PCR) HIV test at less than 8 weeks of age [85]. If we consider

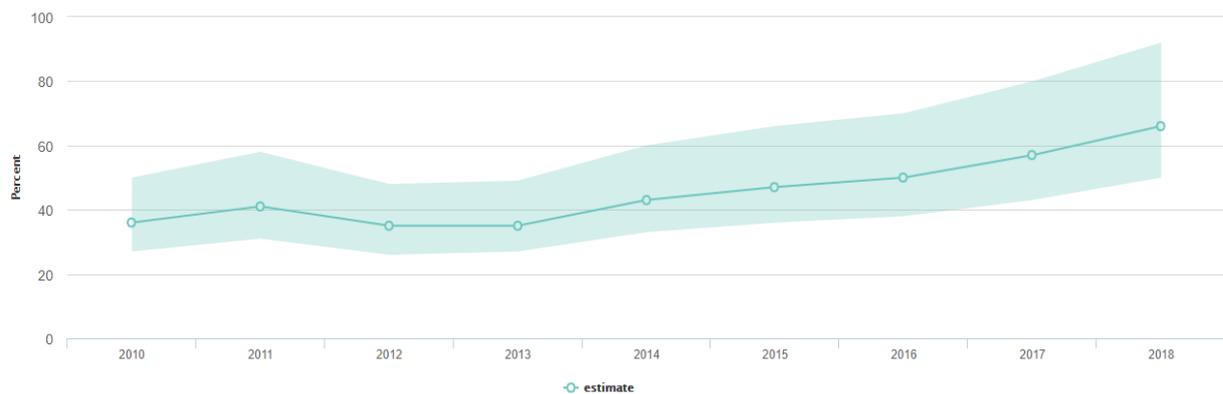
as a denominator the estimated number of HIV-positive pregnant women in the same period, only 66% of HEI received an EID test at less than 2 months of age (Figure 1.20).

Figure 1.18: Trends in number of new HIV child infections vs. number of new infections averted due to PMTCT, Mozambique 2002-2018.



Source: UNAIDS, AIDSinfo, 2018[1]

Figure 1.19: Trends in percentage of HIV-exposed infants tested in Early Infant Diagnosis (EID) care, Mozambique 2002-2018.

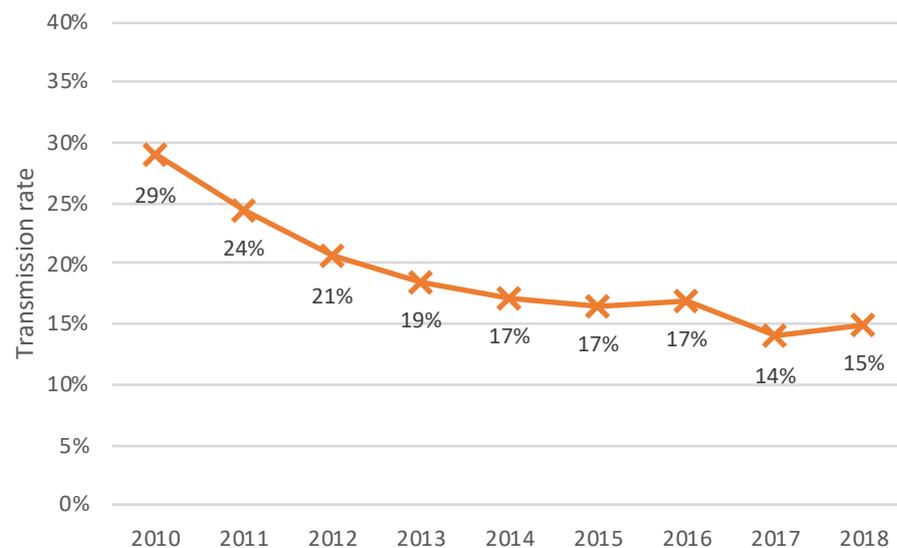


Source: UNAIDS, AIDSinfo, 2018[1].

The National Strategic Plan (*Plano Estratégico Nacional*) PEN IV 2015-2019 and the Political Declaration 2016-2020 called to reduce the MTCT rate of HIV to <5% by 2020. According to Spectrum estimates, the MTCT of HIV rate has significantly declined from 19% in 2013 to 17% in 2016, and further increased to 15% in 2018⁵ (Figure 1.21). Nevertheless, accelerated efforts are to be made if the <5% target is to be reached within a 3-year period.

⁵ Modelling estimates of MTCT of HIV includes the breastfeeding period.

Figure 1.20: Trends in Mother-to-Child Transmission of HIV, Spectrum modelling estimates, Mozambique 2000-2017



Source: UNAIDS, AIDSinfo, 2018 [1]

Challenges

Efforts to prevent MTCT of HIV have been slowed by several socio-cultural barriers and health system challenges in Mozambique. The persistent low levels of knowledge of HIV in Mozambique hampers the level of engagement in care of PMTCT clients. In 2015, the IMASIDA survey reported low levels of comprehensive knowledge of HIV among the 15-49 years old (31% among men and 30% among women)[79]. For women, the 2009 INSIDA and the 2011 DHS showed similar percentages, indicating no improvements made over the years[78,93]. Only 54% of women and 50% of men knew that HIV could be transmitted from mother-to-child through breastfeeding and that administration of antiretrovirals could reduce the risk of transmission. Male partner involvement in ANC has also been low, with only 48% of male partners reported to have been tested in ANC in 2017[94].

Due to the expansion of ART and PMTCT services across the country, public health facilities have faced a significant increase in patient volume, even more so since the progressive implementation of the 'Test and Treat all' strategy which started in late 2016[94]. The lack of human resources along with insufficient formative supervision may have led to decrease in quality of care. Consequently, treatment drop-out rates among pregnant and breastfeeding women were high: in 2018, the national HIV program reported a 12-month retention rate of 65%, much lower than the rate for adults (excluding pregnant women of 70%) [85].

The number of National laboratory sites have increased from 347 in 2015 to 406 in 2018 but with still a low coverage: 25% of all health facilities in the country. Most laboratories are located in a centralized area, at provincial or district level hospitals with long distance specimen transport. They often run with only one technician in weak infrastructures (i.e. small and inadequate layout), and cold chain problems are recurrent. In addition, the laboratory information system is, in 90% of the cases, paper-based which limits timely reporting of results back to the patient.

Currently in Mozambique, the national health information system continues to be paper-based using a cross sectional approach: compilation of data from the registers to produce monthly

reports are done manually at each MCH entry point; tracking of mother–infant pairs across different MCH services within the same health facility and across various health facilities is lacking. The cross-sectional approach of data compilation does not account for patient movement across the health sector. This occurs when the mother moves from ANC to maternity for delivery and then to post-partum care, leading to inaccurate or incomplete reporting of patient engagement in care throughout the pregnancy, delivery and breastfeeding period.

2 Importance of engagement in care for PMTCT programs

The WHO refers to patient's engagement in care as 'the process of building the capacity of patients, families, care givers, as well as health care providers, to facilitate and support the active involvement of patients in their own care, in order to enhance safety, quality and people-centeredness of health care service delivery' [95]. This definition applies to high, middle and low-income countries and to all types of diseases.

Specifically, engagement in HIV care refers to a patient who is actively engaged in and receiving regular HIV care, by a dynamic navigation through the complete HIV care continuum with the final goal of achieving and maintaining viral suppression[96]. Therefore, engagement in HIV care is vital to PLHIV and too often confused with 'retention in care' viewed as a patient present in care at a certain time point. We know that the proportion of patients diagnosed with HIV infection but not engaged in medical care is distributed heterogeneously across the care continuum: some may have been diagnosed but did not successfully linked to care, other may have linked and initiated ART but subsequently dropped out of care – either never returned after the first visit or after a certain period of time and, some may be reengaging in care elsewhere. Thus, engagement in HIV care is dynamic, allowing people to cycle in and out of HIV treatment over the course of their life with HIV.

For PMTCT programmes, engagement in care implies the client is seen as dual entity composed by the HIV-positive women and her HIV-exposed infant. Therefore, the potential benefits of ART encompass improving long-term maternal health and reducing MTCT risk, both linked to maternal viral suppression. Furthermore, to achieve eMTCT of HIV at least 95% of pregnant women should receive the required service delivery at each step of the PMTCT cascade. In this context, engagement in care for the women during the pre-natal phase and for the mother-infant pair during post-partum are of paramount importance to guarantee important milestones of PMTCT care such as rapid maternal viral control before delivery, EID testing at 6-8 weeks and final HIV infant testing at 12-18 months post-partum (Figure 2.1)[97,98]. Furthermore, compared to previous PMTCT regimens (Options A or B), lifelong ART provided to pregnant women under Option B+ has the additional public health benefit of guaranteeing viral suppression for subsequent pregnancies while keeping mothers alive[99]. Thus, disengagement from PMTCT care share the common consequence as for the general 'Test and Treat all' approach of poor viral control for the HIV-positive women but adds-in the failure of elimination of MTCT of HIV.

Factors that influence engagement in PMTCT care can be complex and multilevel, such as individual characteristics (e.g., age, sex, education, marital status), disease characteristics (e.g., clinical staging, immunological and virologic stages), pregnancy/birth characteristics (physiological changes of pregnancy and post-partum, HIV- and/or ART-related concerns, adverse pregnancy or birth related outcomes, post-partum depression), characteristics of the setting (e.g., type of provider, type of services available) and cultural norms. Therefore, improvement of just one of these factors would have little effect on the ultimate goal of viral suppression and eMTCT. This underscores how imperative it is to recognize engagement in PMTCT care as a comprehensive approach as it guarantees efficient and effective passage of mother-infant pairs through the care continuum[100].

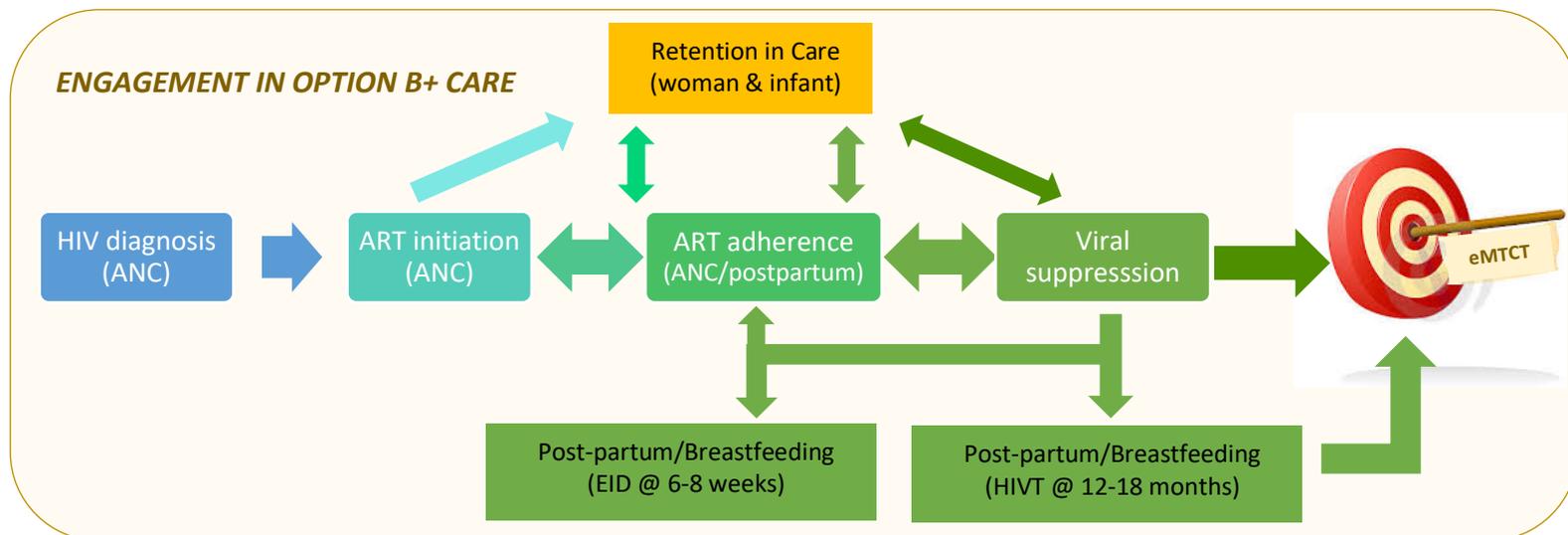
Originally, Option B+ was introduced in PMTCT programs to allow a simplification of treatment regimen across the entire adult population, a simplification of clinical and laboratory follow-up for pregnant and breastfeeding women while offering a cost-effective alternative to previous preventive ARV regimen. Thus, women initiated on ART under Option B+ would have better levels of engagement in care compared to those non-pregnant and non-breastfeeding and initiated on ART for their own health as the perceived benefit of Option B+ is both for their new-born and for their maternal health. As explained earlier, the timing of ART initiation along the PMTCT cascade of care is of paramount importance and can be influenced by various

system and individual factors. Women initiating lifelong ART during pregnancy would have better levels engagement in PMTCT care than women initiating late during the breastfeeding period as we can hypothesize that the latter group are less likely to be retained in regular care because they seek and access MCH services only in the post-partum period. We also discussed previously in chapter 1.2, that maternal viral load is a strong predictor of risk of vertical transmission. Thus, in the absence early ART initiation, these breastfeeding women are at higher risk of MTCT as risk of HIV transmission during pregnancy and delivery can reach up to 40% in the absence of ARVs for PMTCT [30–33].

In a resource limited setting such as Mozambique, intervention to improve women's engagement in long-term PMTCT care starting during pregnancy is of paramount important if the approach of Option B+ strategy is likely to succeed in reaching the global public health target of reducing MTCT rate to less than 5% [62].

Figure 2.1: Processes of engagement in care for HIV+ women for ART treatment and eMTCT success, in low- and middle-income countries.

This figure demonstrates the dynamic and multi-directional nature and relationship of various steps of the Option B+ PMTCT care cascade and how a woman and her HIV-exposed infant move along the care continuum. Source: Figure adapted from Mugavero et al. 'The State of Engagement in HIV Care in the United States: From Cascade to Continuum to Control'. Clinical Infectious Disease 2013 [96]. Abbreviations: ANC: antenatal care; ART, antiretroviral therapy; EID: early infant diagnosis; HIVT: HIV testing; eMTCT: elimination of mother to child transmission of HIV.



3 Justification and objectives of the PhD thesis

3.1 Justification of the thesis

With rapid expansion of Option B+ PMTCT services, the main challenge is to ensure effective follow-up of the mother/infant pair. Indeed, sub-optimal levels of engagement in care for the HIV-infected mother leads to ART non-adherence, the increase risk of unsuppressed viral load, and the need to switch to more expensive second- and third-line treatment regimens after first-line treatment failure. Without optimal viral suppression in the mother, the HEI is also at higher risk of HIV infection through vertical transmission. At a public health level, the risk is to undermine programme effectiveness, waste precious resources, and see the emergence of drug resistant strains of HIV. It is therefore crucial to engage the mother and her HEI as early as possible along the continuum in sustainable manner.

Based on the programmatic challenges faced under Option B+, especially the high rates of women drop-outs and low infant testing coverage in numerous resources limited settings, a review of recent evidence of types of interventions tested to improve maternal ART retention and infant testing would be useful for programme managers and policy makers to strengthen their PMTCT programmes and improve outcomes for mothers and their children.

When first implemented in Mozambique, the Option B+ strategy had the potential to improve ART access for pregnant women, mothers, and their children. In addition, having the same regimen for all women would simplify messages delivered to patients, providers, and communities about the necessity to adhere to ART for life once started. The strategy would also provide a more comprehensive approach, as ART and PMTCT services are integrated with one another.

Despite such promises, the estimated MTCT rate remains high (15% in 2018) in Mozambique and raises concerns about the effectiveness of the strategy in truly reducing vertical HIV transmission. Low retention in care has been identified in Mozambique as a threat to achieve the 90-90-90 targets and the virtual elimination of vertical transmission of HIV[84]. Identifying where progress has been made in the PMTCT cascade and where gaps still remain would help to provide insights on where to focus efforts to reach the 'last mile' for virtual elimination of MTCT by 2020.

For women and children enrolled in PMTCT programmes, attendance at the clinic at a certain time point is often considered as full retention over this period. However, regularity of attendance is an important parameter to take into consideration if we are to evaluate the quality of engagement in care. As for Mozambique, where routine health information systems fail to capture patient-based viral load testing results, regular attendance at scheduled visits is a good indicator of levels of engagement in care for women initiating ART under Option B+. Exploring different measures of retention considering the level of attendance of scheduled visits during follow-up could help better measure women's engagement along the continuum of PMTCT cascade of care.

3.2 Objectives of the thesis

3.2.1 General objective

The thesis aims to highlight, from a public health perspective, the programmatic challenges of engagement in care for the Option B+ strategy in sub-Saharan Africa, with the example of Mozambique, a country known to have one of the highest HIV prevalence in the world. To assess the level of engagement in care of the mother/infant pair, this work focused on three programmatic aspects of PMTCT Option B+ strategy: PMTCT outcomes with a special focus on maternal ART retention and HIV infant testing uptake; interventions aimed at improving these PMTCT outcomes and methods of measurements of retention in care with their potential programmatic impact.

3.2.2 Objectives of the thesis

Specific objectives of the thesis are to:

1. Quantify risk of attrition associated with reason for ART initiation (ART initiation under Option B+ versus ART initiation for own health) in a PMTCT program in Mozambique;
2. Describe interventions aimed at improving PMTCT outcomes in programs offering B+ strategy with a special focus on maternal ART retention and HIV infant testing uptake;
3. Evaluate the impact of various definitions of ‘retention in care’ on the programmatic interpretation of PMTCT Option B+ strategy.

A framework has been elaborated to provide an overall picture of the thesis work, to visualize how the three analyses proposed respond to the three objectives, how they relate to one another and how they fit into the overall problematic of engagement in care under PMTCT Option B+ strategy (Figure 3.1).

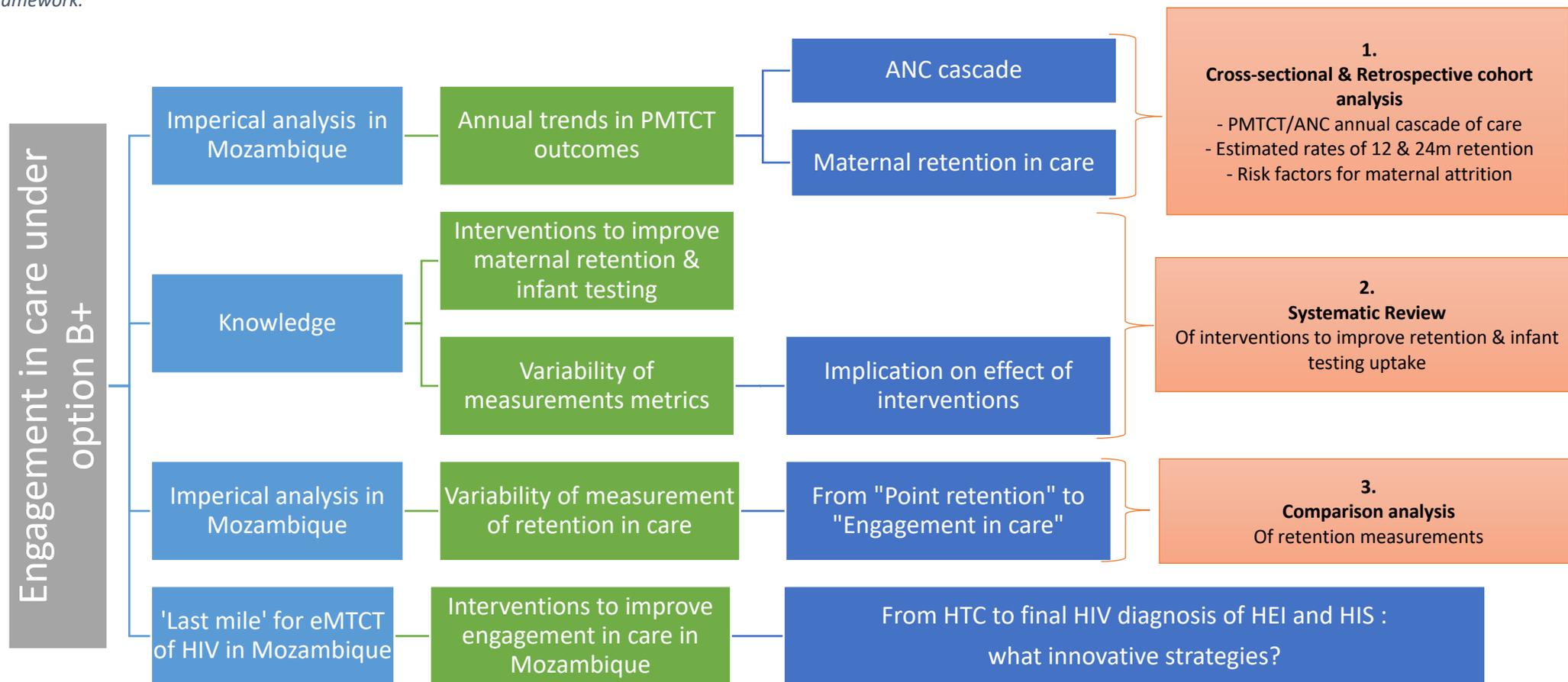
To respond to the **first objective**, an empirical analysis of routine data from the first 4 years of PMTCT Option B+ program implementation in Mozambique was conducted to analyse annual trends in PMTCT program outcomes. This study focused on the ANC cascade of pregnant women enrolled in PMTCT and women retention in care 12 months after ART initiation.

To respond to the **second objective**, a systematic review focused on interventions to improve ART retention and infant testing was conducted. This systematic review aims to synthesis types of interventions tested and discuss the heterogeneity of measurements metrics used to define both retention on ART and infant testing uptake and their impact on the effects of interventions.

To respond to the **third objective**, a comparative analysis using 6 different definitions of ‘retention in care’, was performed to highlight the variability of measurement metrics and discuss their impact on estimating level of engagement in care of HIV-positive women enrolled under Option B+ in Mozambique.

Based on the results of this thesis work, innovative strategies to improve engagement in care of the mother-infant pair (MIP) at each step of the PMTCT Option B+ care cascade are proposed considering the Mozambican context. The proposed strategies focus on providing solutions to the gaps identified in the care continuum with the goal of achieving the “last mile” for eMTCT of HIV in Mozambique.

Figure 3.1: Prevention of mother-to-child transmission (PMTCT) of HIV in Mozambique: engagement in care and programmatic challenges for the B+ Strategy: the thesis framework.



4 Institutional setting for the PhD

4.1 ICAP at Columbia University

Founded in 2004 at Columbia University's Mailman School of Public Health, ICAP is one of the world's largest implementation and technical assistance providers for HIV and related health programs and a global leader in research and public health. To date, ICAP has supported HIV prevention, care, treatment, and related services at more than 6,000 sites across 30 countries in Africa, the Caribbean, and Southeast and Central Asia, as well as in the United States.

ICAP's technical expertise and experience span over three broad health-related areas: 1) service delivery and service-delivery-strengthening activities, including PMTCT, HIV/AIDS care and treatment, Tuberculosis/HIV integration, integration of PMTCT and Maternal Child Health/Reproductive Health, laboratory strengthening, infrastructure development, workforce development, treatment adherence, and support for PLHIV and their families; 2) training, clinical service mentorship programs, and development of training materials, and use of distance education; and 3) monitoring, evaluation, and research.

With support from PEPFAR, ICAP's technical assistance and support has resulted in nearly 32 million individuals being tested for HIV—including over 8.6 million pregnant women tested in ANC; nearly 2.4 million people have received HIV care and 1.46 million have received ART at ICAP-supported health facilities.

4.2 ICAP in Mozambique

ICAP has supported the transformational scale-up of HIV prevention, care, and treatment services in Mozambique as a major technical support partner to the MOH since 2004.

ICAP supported some of the first ART clinics in the public sector in Mozambique and has played a key role in each stage of the HIV response, including the effort to decentralise and expand HIV care and treatment services. Since 2004, more than 300 health facilities in five provinces (Nampula, Zambézia, Inhambane, Maputo, and Gaza) have benefited from ICAP's comprehensive technical and operational support.

From 2012 to 2017, ICAP was the leading partner in Zambézia province, supporting 7 out of 17 districts, and was the main implementing partner in Nampula province, supporting all 21 districts. In addition, Zambézia was identified as one of the MOH's priority provinces due to its high HIV prevalence and population size.

In 2013, ICAP supported PMTCT sites in Nampula and Zambézia for the transition from Option A to Option B+ by providing in the first 18 months of programme implementation training for more than 280 MCH nurses on Option B+ and ART, extending in-service training to all sites shortly after transition, purchasing additional equipment (e.g. file cabinets) to support patient monitoring activities, and re-enforcing the monitoring and evaluation system to capture specific ART information for pregnant and breastfeeding women enrolled in Option B+ while improving the quality of the data.

Photo 1: A normal day at the Zimpeto Health Centre (patients waiting area for consultation & pharmacy drug pick-up), Maputo, Mozambique 2016 (photo credit: ICAP Mozambique).



Photo 2: Outpatient consultations, Mulaha Expansão Health centre, Nampula, Mozambique 2014 (photo credit: ICAP Mozambique).



4.3 My role at ICAP in Mozambique and related work for the PhD thesis

From August 2012 to August 2016, I was the Strategic Information and Monitoring and Evaluation (SI and M&E) Director for ICAP Mozambique. Based in Maputo capital city, I was responsible for managing a total of 40 staff at central and provincial levels (Zambézia and Nampula). The M&E team was composed of a reporting officer, M&E officers in charge of each clinical area, m-health officer and senior database managers at the central level, and teams of M&E officers and data entry officers at provincial levels. Research teams were composed of a research coordinator, field research supervisors, interviewers, and data entry officers.

The main objective of the SI and M&E unit is to provide relevant, up-to-date, and high-quality information from efficient routine health information systems and operational research studies. The evidence-based results produced are used to monitor and assess the progress of implemented activities to improve patient care.

Over the 4-year period, we have made great progress in implementing more efficient health information systems to produce reliable data for decision-making both in M&E and research (Table 4.1). In 2013, we implemented a new health information system, DHIS2 (District Health Information System Software 2), an open-source health management data platform that provides aggregated health facility data for routine reporting purposes [101]. This system enabled us to significantly improve the completeness and accuracy of the data ICAP reported on a quarterly basis to the MOH, Centre for Disease Control and Prevention (CDC) in Mozambique, and ICAP headquarters in New York. ICAP was one of the first organizations to develop an electronic patient-level data (ePLD) system in Mozambique. To re-enforce the quality of the routine data reported, in collaboration with the MOH and other implementing partners, we implemented routine data quality assessment runs on a quarterly basis. See paragraph below for more detailed description of the ICAP's health information system (HIS).

I initiated my PhD part-time in 2014, while working at ICAP Mozambique on a full-time basis. During that period, the programme faced many challenges in implementing Option B+ strategy, among which one was maintaining women engaged in care throughout the PMTCT cascade. Collecting routine information on pregnant HIV-positive women enrolled in PMTCT and initiating ART in more than 80 supported sites with patient-level data was a unique opportunity to understand the underlying programmatic challenges faced and to provide programme managers and clinicians practical recommendations to improve quality of care provided to the mother and her HIV-exposed infant.

Table 4.1 : Summary of key SI and M&E activities that have been implemented, 2012- 2016, ICAP, Mozambique.

Area	Activities performed (2012 – 2016)
M&E supervision	<p>Key M&E activities implemented:</p> <ul style="list-style-type: none"> - Migration from Excel individual district files to DHIS2 national Health Information System (1st PEPFAR funded partner in Mozambique) - Expansion from 5 to 8 central M&E officers - Hiring of 2 new provincial M&E managers - Expansion from 12 to 30+ M&E officers/data Officers - Creation of an annual M&E workplan (previously non-existent) - Creation of the SI Unit annual logic framework (previously non-existent) - Support of implementation of clinical specific strategies to improve pre-ART and ART retention: ACT initiative, SMS, i-DART - Patient level data analysis of patient enrolled on community support groups
CDC funded Strategic Information award (5-year project)	<p>Implementation of 2 new PEPFAR funded projects. L Ahoua was the project manager</p> <ol style="list-style-type: none"> 1) OpenMRS MCH module project 2) National HIV tools revision project
Research activities	<p>‘Engage 4 Health’ study. L Ahoua was the ICAP-Mozambique research director.</p> <p>Implementation science study using a two-arm cluster site-randomised design to determine the effectiveness of a combination intervention strategy (CIS) using (1) point-of-care (POC) CD4 count testing, (2) accelerated ART initiation for eligible individuals, and (3) SMS reminders for linkage to and retention in care—as compared to the standard of care (SOC) in 2 provinces Mozambique [102–104].</p> <p>‘Discrete Choice Experiment’ study. L Ahoua provided the technical support for field study implementation.</p> <p>Discrete choice experiment in Ethiopia and Mozambique to identify health system characteristics preferred by HIV-infected women to promote continuity of care [105].</p> <p>‘Prep phase I’ study. L Ahoua was the ICAP-Mozambique research supervisor</p> <p>A cross-sectional study to assess the willingness of migrant miners and female partners of miners to take short-term pre-exposure prophylaxis (PrEP) for prevention of HIV acquisition in Gaza Province, Mozambique [106].</p> <p>‘Prep phase II’ study. L Ahoua was the ICAP-Mozambique research supervisor</p> <p>A prospective cohort study to evaluate the feasibility, acceptability, and adherence with short-term PrEP among female sexual partners of migrant miners in Mozambique [107,108].</p>

M&E: Monitoring and Evaluation; DHIS: District Health Information System Software 2; HIS: Health Information System; ACT: Accelerating Children’s HIV/AIDS Treatment (ACT) Initiative; i-DART: Intelligent Dispensing of Antiretroviral Treatment; MCH: maternal and child health; PrEP: pre-exposure prophylaxis.

4.4 ICAP Mozambique Health Information system

4.4.1 District Health Information System (DHIS) version 2.21

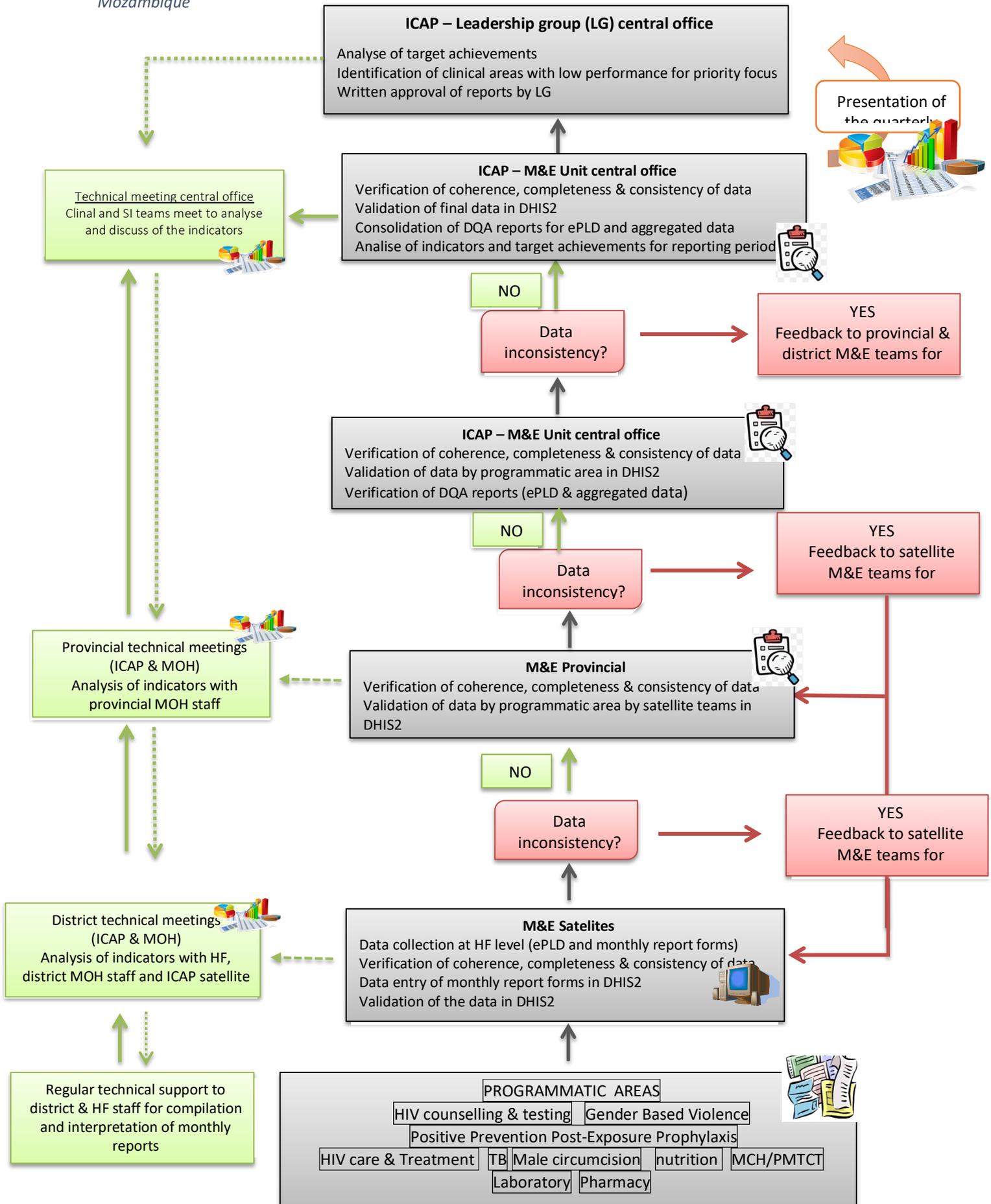
General overview

The DHIS2 is ICAP's principal internal Health Information System (HIS). The system was implemented in 2013. Figure 4.1 summarises the data and communication flow of the HIS in ICAP Mozambique from peripheral to central level, including the various data sources and process utilized for collecting, verifying, analyzing and reporting programme indicators. The MoH paper-based report forms are collected by the M&A Officer from the satellite team (i.e. ICAP district based staff overseeing of 1 or 2 districts) on a monthly basis and computerized by the data officer directly into the system for the following clinical programs: MCH/PMTCT, HIV counselling and testing, Gender Based Violence, nutrition, positive prevention, post-exposure prophylaxis, HIV/ART, tuberculosis, laboratory, pharmacy, voluntary male circumcision. DHIS2 data entry forms were regularly updated to reflect latest changes in the national guidelines and paper-based tools.

To ensure timeliness of data collection, ICAP's M&E staff performed data entry into DHIS2 directly on site at the HF or at the district health directorate (also called the M&E Satellite). Data verification for coherence, completeness and consistency is done at each level of the HIS with regular feedback to the lower levels for corrections. This is an ongoing process where clinical and M&E teams both from ICAP and the MOH are involved. Immediately after data entry, internal data quality checks (DHIS' run validations rules) have been embedded in the electronic forms to guaranty a minimum of data quality. ICAP's M&E staff works in close collaboration with the MOH district M&E officer to take immediate corrective actions for any errors on the monthly reports. Participation of the clinical team in reviewing the monthly statistics are organized with ICAP's and MOH's staff to ensure correct interpretation of clinical data during the on-site review process, to discuss/resolve any problems with the clinical staff and to know what are the M&E challenges encountered during data collection that can help interpret better the programs' performances.

One of the main challenges is the constant changes in indicators to be reported (definition, age and sex desegregations, etc....) and the absence of MOH tools for some programmatic areas (resulting in creation of parallel reporting systems) which made the data collection process tedious and time consuming. This is tackled by reviewing and updating all DHIS2 forms on a quarterly basis before each reporting period. Another challenge is the limited technical capacity of the health facility staff in correctly filling the paper-based registers and monthly reports. For this purpose, ICAP's clinical and M&E staff re-enforce on-site mentoring to improve correct completion of the registers and forms during site supervision visits. Focus is given to high volume sites and sites where data quality and completeness are the most problematic.

Figure 4.1: Data and communication flows for ICAP's Heal Information System (HIS), 2013-2017, Mozambique



ANC/PMTCT data

For the second work of the PhD, I extracted the ANC/PMTCT variables from DHIS2 (table 4.2). These variables are from the ANC clinic monthly reports forms which are based on longitudinal cohort-based follow-up registers (figures 4.2 and 4.3). Pregnant women who come for their first ANC visit are registered and given a unique identification number, sequential number based on the site code, date of registration and consecutive enrolment number. This unique identification number is captured in her health passport. The national MCH program recommendation is for a pregnant woman to remain in care in the ANC health facility where she first enrolled, to deliver at the maternity ward of that health facility or at the corresponding referral maternity closest by and then to come back to the original facility for post-partum care [87]. If a pregnant woman attends more than one facility in the area, her unique identification number from her health passport is used and she is enrolled as a follow-up pregnant woman (as opposed to a new enrollee). A woman receives a new ANC number for each new pregnancy. Therefore, subsequent pregnancies are not linked to one another.

If she is already on ART at enrolment, her unique HIV identification number is also registered. This number is also based on sequential number using the health facility code, HIV service code and a sequential enrolment number (see section ‘4.4.2 Electronic Patient Level data (ePLD)’ below for more details).

The MCH nurses provides integrated care for all pregnant women including diagnosis and treatment for nutrition support, syphilis and other sexual transmitted diseases, malaria prophylaxis, vaccination, tuberculosis prophylaxis or treatment continuation and PMTCT care. If a pregnant woman is newly tested HIV-positive in ANC, an individual patient file will be opened, a new HIV patient code will be attributed, and she will register at HIV care clinic although she will still be followed-up in ANC under the ‘one-stop model’ approach for Option B+, until final diagnosis of her HIV-exposed infant is obtained. The patient file is the same as for any HIV-positive patient enrolled in HIV care and treatment service (see section ‘4.4.2 Electronic Patient Level data (ePLD)’ below for more details). HIV-related laboratory results and pharmacy records are linked through the patient’s HIV patient code.

Table 4.2 : List of the variables and correspondent data elements used for the PhD work and their definition, ICAP Mozambique 2013-2017.

Name of variable	DHIS data element
Total number of pregnant women enrolled during the reporting period	CPP.CONDUTA.1- Total das 1as Consultas
Pregnant women with unknown status at ANC entry	SMI.CPN.FA.1- Número de MG HIV Desconhecidas a entrada
Pregnant women HIV+ at ANC entry	CPN_ Positivos a Entrada
Pregnant women HIV counselled and tested with test results positive	CPN_ Aconselhados e Testados_Primeiro Teste Positivo
Pregnant women HIV counselled and tested with test results negative	CPN_ Aconselhados e Testados_Primeiro Teste Negativo
Pregnant women HIV+ initiated sdNVP Only	SMI.CPN.FA.5- Número de Mulheres Grávidas que Inicia NVP dose única
Pregnant women HIV+ initiated biprophylaxis (AZT+NVP)	SMI.CPN.FA.7- Número de Mulheres Grávidas que Inicia biprofilaxia (AZT+NVP)
Pregnant women HIV+ initiated ART	SMI.CPN.FA.8- Número de Mulheres Grávidas Inicia o TARV
Pregnant women HIV+ already on ART @ 1st visit	SMI.CPN.FA.6- Número de Mulheres Grávidas Em TARV a entrada

Figure 4.3: ANC Health Facility monthly report form, Mozambique 2013-2017.



REPÚBLICA DE
MOÇAMBIQUE
MINISTÉRIO DA SAÚDE

PROVINCIA: _____

DISTRITO: _____

UNIDADE SANITÁRIA: _____

MOD - SIS - B01 - B

MÊS _____

RESUMO MENSAL DA UNIDADE SANITÁRIA – SMI - CONSULTA PRÉ-NATAL

Implementa a Opção B+?

SIM	NÃO
-----	-----

		Indicadores/Características	TOTAL	
1	1 ^{as} consultas	Total das 1as Consultas		
2		Idade	Mulheres grávidas com idade entre 10 a 14 anos	
3			Mulheres grávidas com idade entre 15 a 19 anos	
4			Mulheres grávidas com idade entre 20 a 24 anos	
5			Mulheres grávidas com idade ≥ a 25 anos	
6		Idade Gestacional	Mulheres grávidas com menos de ou igual 12 semanas na primeira consulta	
Para os indicadores a seguir colher as informações de todas as mulheres que tiveram a 1ª consulta 6 meses atrás				
7	Coorte 6 meses	Total de mulheres grávidas inscritas no período (Total da COORTE)		
8		Total de mulheres grávidas que fizeram a 4 ou mais consultas pre-natais		
9		Nutrição	Mulheres grávidas com Ganho < 1.5 Kg/mês a partir do 2º trimestre	
10			Mulheres grávidas que tiveram Desnutrição aguda grave (DAG)	
11			Mulheres grávidas que tiveram Desnutrição aguda moderada (DAM)	
12			Mulheres grávidas que iniciaram e/ou receberam suplementos nutricionais	
13			Total Gestantes com Desnutrição aguda curadas	
14			Total Gestantes com Desnutrição aguda que abandonaram	
15			Mulheres grávidas que receberam desparasitante	
16			Mulheres grávidas que receberam a 3ª dose (ou mais) Sal ferroso com Ac Fólico	
17		ITS	Mulheres grávidas com diagnóstico sintromico para ITS	
18			Mulheres grávidas com tratamento sintromico para ITS	
19			Mulheres grávidas testadas positivas para sífilis	
20			Mulheres grávidas testadas negativas para sífilis	
21			Mulheres grávidas que receberam 3ª dose de tratamento de sífilis	
22			Parceiros que receberam tratamento de sífilis	
23	HIV	Mulheres grávidas HIV positiva a entrada		
24		Mulheres grávidas testadas HIV negativas durante a CPN		
25		Mulheres grávidas testadas HIV positivas durante a CPN		
26		Parceiros testados negativos na CPN		
27		Parceiros testados positivos na CPN		
28		Mulheres grávidas que Iniciaram CTZ		

29			Mulheres grávidas em TARV a entrada	
30			Mulheres grávidas cuja profilaxia final foi Monoprofilaxia (NVP)	
31			Mulheres grávidas cuja profilaxia final foi Biprofilaxia (NVP+AZT)	
32			Mulheres grávidas que iniciaram TARV durante a gravidez	
33	Coorte 6 meses	Malária	Mulheres grávidas que receberam 2 doses de TIP	
34			Mulheres grávidas que receberam 4 ou mais doses de TIP	
35			Mulheres grávidas que receberam Rede Mosquiteira (REMTIL)	
36			Mulheres grávidas com diagnóstico laboratorial de malária	
37			Mulheres grávidas que receberam tratamento para malária	
38		Prevenção HPP	Mulheres grávidas que receberam Misoprostol	
39		VAT	Mulheres grávidas que receberam 1ª Dose VAT	
40			Mulheres grávidas que receberam 2ª-5ª dose VAT	
41		Tuberculose	Início de Profilaxia com INH	
42			Início de Tratamento para Tuberculose	

4.4.2 Electronic Patient Level data (ePLD)

From 2013 to 2017, the number of HFs providing HIV care and treatment services increased from 110 to 218 in both Namupla and Zambezia. To follow the expansion of HIV care services, ICAP expanded its ePLD system coverage from 35% (38/110) of HFs with HIV/ART services to 40% (87/218) during that same period. High volume sites with more than 500 PLHIV active on ART, adequate infrastructure and electricity power were the priority sites. This represented a coverage of 67% of PLHIV currently receiving ART by the end of 2017.

When a patient is found to be HIV-positive, he/she is referred to the HIV care and treatment service to register, receive a new HIV unique identification number and open a clinical file (Figures 4.4 and 4.5). The unique HIV identification number is a sequential code based on the health facility code, HIV service code and a sequential enrolment number. This unique identification number should only be given once in a lifetime. National guidelines recommend to systematically check if the patient has been previously enrolled in HIV care and treatment service using the HIV identification code before opening a new file, but this can only be verified within the same site as there is no health information system linking data from different health facilities. After the first clinical visit, the information from the patient file is entered retrospectively in the ePLD by data entry clerks using the unique identification number. Laboratory and pharmacy results are linked with the patient file through this number. From thereon, for each subsequent visit at the health facility, information on clinical visit, pharmacy drug pickup, counselling session and/or laboratory results are retrospectively updated in the ePLD. For each reporting period, ePLD data is extracted to produce specific HIV program indicators by the M&E staff.

When PMTCT Option B+ was implemented, the ePLD was modified to capture information on pregnant and breastfeeding women: gestational age at ART initiation and if the woman was initiating ART for PMTCT (status 'pregnant' or 'breastfeeding' at ART initiation). No other MCH specific variables were captured in the ePLD.

The first ePLD system used MS Access database then, in 2014, we progressively switched to an open source patient level data system, Open Medical Record System (OpenMRS) to align with other implementing partners in the country and with the MOH's new national guidance on M&E systems. In 2016, we developed in collaboration with other partners the specific MCH OpenMRS module for specific patient-level monitoring of the mother/infant pair enrolled under Option B+. The tool produced was to be piloted in 2017 in a three Option B+ sites with an expansion scheduled for late 2018/beginning of 2019. Unfortunately, the project was stopped due to cut of funds.

The two main challenges with the ePLD system are first the low expansion of the electronic system compared to that of HIV care and treatment service expansion (especially in Zambézia), due to various internal (logistics, infrastructure renovations, etc...) and external (security, lack of ownership of the MOH, etc...) constraints. Second, is the absence of linkage between various site level databases making it impossible to track the patients who silently transfer to another site or who re-engage in care after a certain time of absence at the same site or at another site. Duplicate patient records are however tracked on a quarterly basis at ICAP central level by the M&E team once all ePLDs are merged together using the following data elements: sex, age (or date of birth), outcome status (i.e. death, transferred-out, alive, stopped treatment), date of outcome status, date of enrolment, last date of visit. If a duplicate is found, data is reviewed on a case by case basis and if applicable, merged into one single patient follow-up file using the first HIV patient identification number.

Figure 4.4: MOH Patient file, admission form and follow-up form, Mozambique 2013-2017

Referido de - UATS, SMI, TB, enfermaria, outro serviço(especifique) _____				
ARVs tomados anteriormente				
(S/N)	ARV tomados anteriormente	Data		
	Nenhum			
	ARV no PTV (CPN/Post-Parto)?	__/__/__	Onde? _____	ARVs _____
	Fez ARV mas sem transferência	__/__/__	Onde? _____	ARVs _____
	Data	TARV - Coorte (Mês / Ano) _____/_____		
	__/__/__	Transferido em TARV de _____		
		ARVs _____		
1.ª Linha	__/__/__	Início do regime ARV inicial de 1.ª linha _____		
	No início do TARV	Peso _____ Gravidez _____	<input type="checkbox"/> Não <input type="checkbox"/> Sim	
		Estadio da OMS _____ CD4 (N.º / %)		
	Substituição dentro da 1.ª linha			
	__/__/__	Novo Regime _____ Porquê? _____		
	__/__/__	Novo Regime _____ Porquê? _____		
2.ª Linha	Mudança para a 2.ª linha (ou substituição dentro da 2.ª linha)			
	__/__/__	Novo Regime _____ Porquê? _____		
	__/__/__	Novo Regime _____ Porquê? _____		
Estado de Permanência				
Interrupção do tratamento ARV - Suspensão ou Abandono do tratamento				
Suspensão ou Abandono	<input type="checkbox"/> Suspensão <input type="checkbox"/> Abandono	<input type="checkbox"/> Suspensão <input type="checkbox"/> Abandono	<input type="checkbox"/> Suspensão <input type="checkbox"/> Abandono	<input type="checkbox"/> Suspensão <input type="checkbox"/> Abandono
Data				
Porquê				
Reinício- Data				
		Data		
Transferido para		__/__/__	Para onde _____	
Falecido		__/__/__		

4.5 Data Quality assessment (DQA)

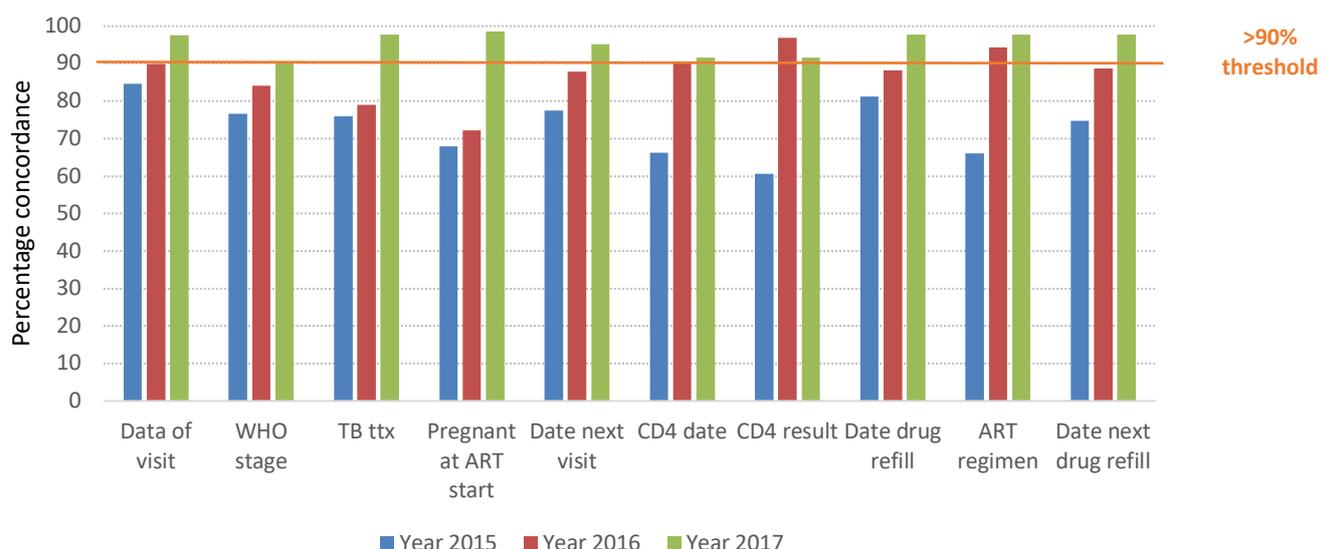
Data Quality Assessments (DQA) has been elaborated by the MOH in collaboration with the Implementation partners' Strategic Information (SI) working group in 2014. The pilot was tested in 2015 with an official phased national roll-out in 2015/2016.

The DQA is done in a nationally representative sample of 30 randomly selected health facilities, stratified by province and size of health facility. It verifies the quality of reported data by quantifying concordance between data recorded in the source documents and data reported in the electronic database. Specific standard operating procedure (SOP) and Excel spreadsheet have been created for this purpose. Data collection is done by ICAP's M&E provincial and district level staff in collaboration with their MOH counterparts.

Specifically, a cohort of 30 randomly selected HIV-positive patients initiating ART over a 3-month period, 12 to 15 months prior to the DQA assessment, is identified using the patient files, patient registers and pharmacy files. Then for those patients, information in the ePLD is compared to monthly reports. According to national guidelines, a concordance between both data sources >90% is considered as "good quality", between 90% and 80% as "medium quality" and <80% as "bad quality". After each exercise, data is analysed and a data quality improvement plan is elaborated at site level to be implemented and monitored during the next reporting period.

Figure 4.6 illustrates the DQA results for ePLD database comparing data in the database to the patient files. The sample included 30 sites randomly selected annually for the years 2015, 2016 and 2017. Because of enhanced M&E mentoring, regular on-site trainings and supervisions of M&E officers, the overall concordance increased from an average 73% in 2015 to 87% in 2016 to 96% in 2017.

Figure 4.6: DQA annual results for ePLD for random sample of HIV-positive patients currently receiving ART, ICAP supported sites, 2015-2017.



Nevertheless, the main challenge for DQAs is the ownership of the exercise by the MOH staff at provincial and district level. Support for the monitoring of the quality improvement plan at site level is re-enforced through regular site visits by the ICAP staff.

Photo 3: ICAP Strategic Information and M&E team members, Mozambique, 2016 (photo credit: ICAP Mozambique)



5 Results

The following chapter presents results of the PhD original research. It is articulated in three parts: (1) a cascade analysis and a retrospective cohort analysis to evaluate annual trends of outcomes in HIV-infected pregnant women initiating ART under Option B+ in the first 4 years PMTCT program implementation in Mozambique, (2) a systematic review of interventions to improve maternal ART retention and testing uptake of HEI under Option B+ strategy in low and middle income countries, and (3) a retrospective cohort analysis of HIV-infected pregnant women initiating ART using six different definitions of ‘retention in care’ to evaluate the operational impact of these definitions on PMTCT Option B+ programme outcomes.

5.1 PMTCT care cascade and risk of attrition in the first 4 years following Option B+ implementation in Mozambique

5.1.1 Introduction and methodology

In 2013, ICAP Mozambique was one of the first PEPFAR funded implementing partners to provide enhanced support to the MOH to roll-out Option B+ in Zambézia and Nampula provinces. ICAP provided technical assistance for task-shifting of ART from clinician to nurses while integrating HIV care and treatment within MCH services using a one-stop model of care. These activities allowed a rapid scale-up of Option B+ and ART coverage: the number of ART sites providing Option B+ increased from 81% (78/96) in 2013 to 98% (117/120) of health facilities in 2014 in Nampula and 91% (85/93) in 2013 to 96% of health facilities (137/143) in 2014 in Zambézia. As mentioned previously, ICAP Mozambique was one of the pioneers in collecting patient-level HIV/ART data using electronic patient tracking system and was the first organization in the country to implement DHIS2 as its health information system for monitoring all its service delivery related activities.

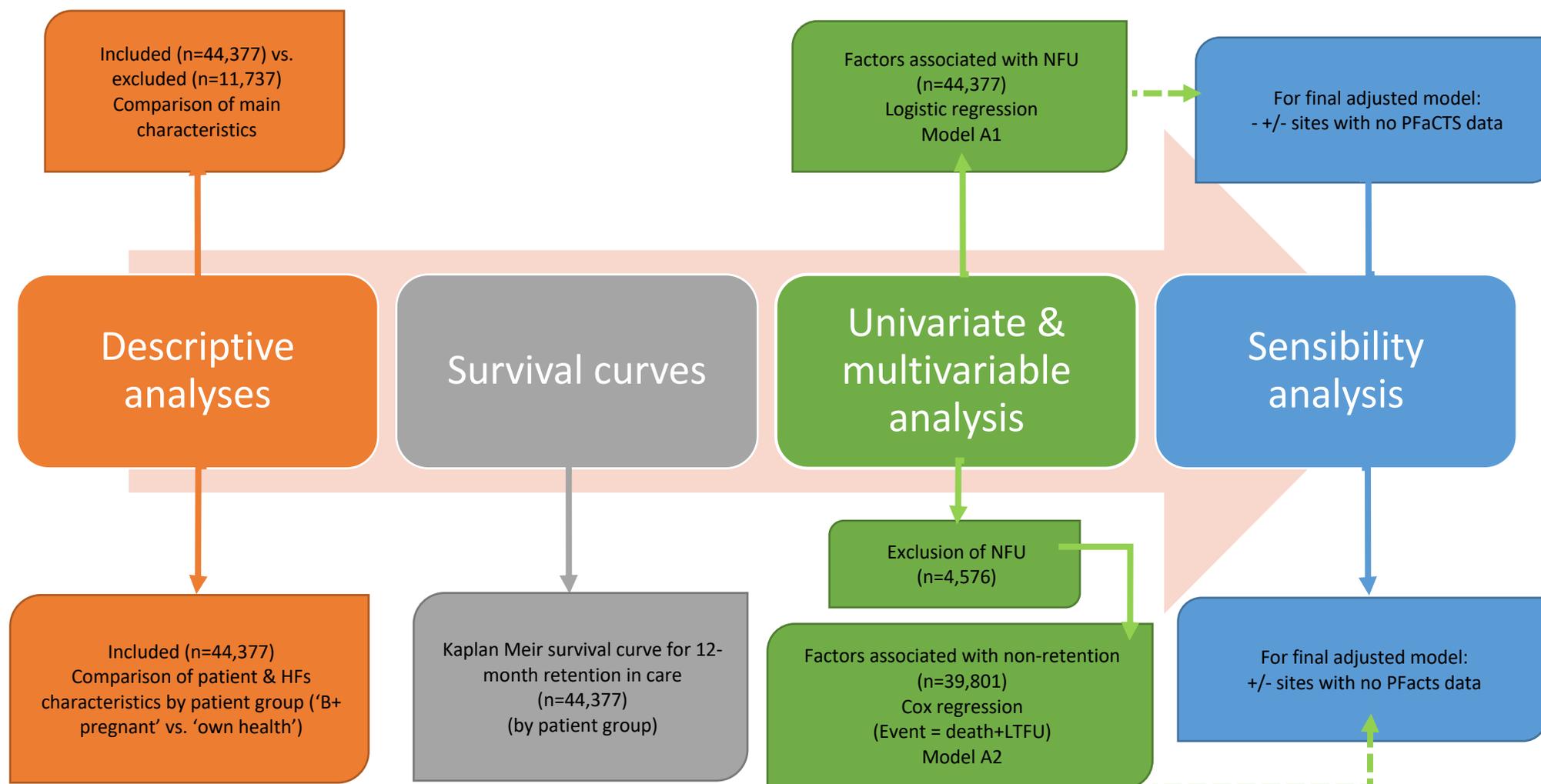
After 4 years of program implementation, we had the unique opportunity to analyze the program’s performance highlighting programmatic gaps and persistent challenges of retaining HIV-positive women in care in Zambézia and Nampula, two of the highest HIV burden provinces in the country. This study is a combination of two distinctive analyses: 1) the PMTCT ANC cascade of care using aggregated facility-level data from DHIS2, 2) factors associated with attrition in HIV-positive women initiating ART during the Option B+ era using patient-level data.

To describe the annual trends of the PMTCT Option B+ program, the ANC cascade was disaggregated by year of ART initiation from 2013 to 2017. For the retrospective cohort analysis using patient-level data, we hypothesised that not returning to care after the first visit was more likely to be related to patient’s reluctance to initiate ART whereas non-retention might be related to sub-optimal quality of care. Under this hypothesis, we characterized to types of attrition: 1) no follow-up (NFU) and 2) not retained in care.

Figure 5.1 summarizes the statistical analysis conducted for both types of attrition in the retrospective cohort analysis.

The manuscript was submitted to the TMIH journal on the in June 2019, accepted in September 2019 (with comments to be addressed).

Figure 5.1: Methodological details of the retrospective cohort analysis of HIV+ women initiating ART in HIV care and treatment health facilities, Nampula and Zambézia, Mozambique.



HF: Health facilities; NFU: no follow-up; LTFU: lost to follow-up; PFACTS: Programme and Facilities Characteristics Tracking System.

5.1.2 Manuscript

PMTCT care cascade and factors associated with attrition in the first four years following Option B+ implementation in Mozambique

Short title: PMTCT care attrition following Option B+ implementation

Authors: Laurence Ahoua^{1,2}, Thierry Tiendrebeogo¹, Shino Arikawa¹, Maria Lahuerta^{3,4}, Dario Aly², Valerie Journot⁵, Elaine J Abrams^{3,4,6}, Renaud Becquet¹, Francois Dabis¹

Affiliations:

¹INSERM U1219 - Bordeaux population health, Institute for Public Health, Epidemiology, and Development (ISPED), Bordeaux university, 33000 Bordeaux, France

² ICAP at Columbia University, Mailman School of Public Health, Rua Francisco Matange, 224/246, Caixa Postal n.º1747, Maputo, Mozambique

³ ICAP at Columbia University, Mailman School of Public Health, New York, New York, 10032, United States

⁴ Department of Epidemiology, Mailman School of Public Health, Columbia University, New York, New York, 10032, United States

⁵ Centre INSERM U897-Epidemiologie-Biostatistique, 33000 Bordeaux, France

⁶ Department of Pediatrics, Vagelos College of Physicians and Surgeons, Columbia University, New York New York, 10032, United States

Corresponding author:

Laurence Ahoua, MD, MPH

INSERM U1219 - Bordeaux population health, Institute for Public Health, Epidemiology, and Development (ISPED), Bordeaux university, 146 rue Léo Saignat 33076 Bordeaux Cedex, France

Email: laurence_ahoua@yahoo.fr

Abstract

Objective: To evaluate the effectiveness of the prevention of mother-to-child transmission (PMTCT) Option B+ programme in two provinces with high human immunodeficiency virus (HIV) burden in Mozambique over the first four years of programme implementation.

Methods: We assessed the PMTCT cascade in antenatal care (ANC) from July 2013 to December 2017 using facility-level data and performed a retrospective cohort analysis with patient-level data. We compared the 12-month antiretroviral therapy (ART) retention rates between women with HIV infection who initiated ART under Option B+ ('B+ pregnant') and those non-pregnant and non-breastfeeding who initiated ART for their own health ('own health').

Results: A total of 916,280 pregnant women enrolled in ANC. The proportion of women with a documented HIV status increased from 93% in 2013 to 96% in 2017. The proportion of those tested HIV-positive decreased from 8% to 6% while that of those HIV-positive on ART increased from 42% to 95%. Of the 44,377 HIV-positive women included in the retrospective cohort analysis, 35% were lost to care. 'B+ pregnant' women initiating ART in 2015 were less likely to have no follow-up (NFU) compared to 'own health' women starting ART during the same period (adjusted odds ratio: 0.77, 95% confidence interval [CI]: 0.64-0.94, P=0.01). There was no statistical difference between the two groups during the other years in which ART was initiated. Of those returning for care after their first visit (N=39,801), the 'B+ pregnant' women showed a higher risk of non-retention than the other group (adjusted hazard ratio: 1.14, 95% CI: 1.03-1.25) when ART was initiated in 2013. The risk decreased during the subsequent years, with no difference observed between the groups.

Conclusion: PMTCT Option B+ programme scale-up has yielded positive results, including the achievement of high HIV testing and ART initiation rates in ANC. Challenges still remain, however, in improving immediate engagement in care and long-term retention. Seeking alternative service delivery models to support existing health systems and prevent defaulters is required to achieve the UNAIDS 95-95-95 targets for PMTCT in Mozambique.

Keywords: PMTCT; Option B+; attrition; retention; cohort analysis; retrospective study

Conflict of interest and funding: The authors declare no conflicting interests. No source of funding was used for this study.

Introduction

Mozambique's HIV prevalence is one of the highest in the world, with 12.5% of the adult population (aged 15-49) living with HIV in 2017¹. In 2011, the country endorsed the 'Global Initiative for the Elimination of Mother-to-Child transmission' (eMTCT) policy, in which ambitious antiretroviral therapy (ART) coverage targets were set for HIV-positive pregnant women (100%) and for the Mother-to-Child Transmission (MTCT) rate of HIV (5%), to be achieved by 2020²⁻⁴. To achieve these targets, the country officially adopted the prevention of mother-to-child transmission (PMTCT) Option B+ strategy in 2013; as part of this, lifelong ART was initiated among pregnant and breastfeeding women found to be HIV-positive at their first visit to mother and child health (MCH) services, regardless of gestational age, CD4 cell count and/or clinical staging⁵.

This new strategy has led to the expansion of ART coverage, which is among the key successes of Option B+⁶. However, emerging studies from the early years of B+ implementation indicate poor retention rates among women who had initiated ART under the new strategy. In Central Mozambique, less than 45% of women were retained at 90 days following ART initiation^{7,8}. Another study also suggested that women with ART initiation under Option B+ were significantly likelier to be lost to follow-up in the first year or have no follow-up after their first visit than those who initiated ART for their own health⁹. These reports suggest poor levels of engagement in care among women under universal ART, raising concerns pertaining to the effectiveness of the strategy, not only in terms of maternal ART outcomes, but also the programme's success in achieving eMTCT HIV targets. Since the introduction of Option B+ in 2013 in Mozambique, few studies have evaluated the progress made in the implementation of the strategy; in particular, the remaining gaps in the continuum of PMTCT care have not been investigated.

We evaluated the PMTCT Option B+ strategy in two of the most highly populated provinces of Mozambique Nampula and Zambezia between 2013 and 2017. More specifically, we aimed to estimate the progress in the key indicators related to the PMTCT cascade in pregnant women enrolled in antenatal care (ANC) services under Option B+. We also aimed to assess whether women with ART initiation under Option B+ had an increased risk of attrition compared to those who initiated it for their own health.

Methods

PMTCT programme in Mozambique

In Zambezia and Nampula, the Option B+ programme was officially initiated in July 2013 with the 'one-stop-model' and 'test and treat' approach, wherein pregnant or lactating women with HIV had access to HIV care and treatment within MCH services. ART is provided by MCH nurses. Pregnant and breastfeeding women living with HIV are followed-up in MCH services until the final HIV status of the exposed infant is determined; once this status is confirmed, these women are referred for follow-up HIV care and treatment services. Women have monthly clinical visits during the first six months after ART initiation followed by bi-monthly visits until 12 months, and bi-annual visits thereafter until the end of breastfeeding. ART counselling and drug pickup are performed on a monthly basis. Routine viral load (VL) monitoring is recommended at 3 and 6 months after ART initiation and annually thereon. First-line treatment is a once-daily fixed-dose of the tenofovir/lamivudine/efavirenz combination. HIV-exposed infants receive a daily dose of nevirapine from birth until 6 weeks postnatally and are followed-up on a monthly basis during their first year, then bi-monthly until the final HIV serostatus is determined.

For non-pregnant and non-breastfeeding women, the ART initiation criteria changed overtime (Supplemental Digital 1). Between 2013 and 2016, adults with World Health Organisation (WHO) stage I/II disease and a CD4 count <350 cells/ μ L and those with WHO stage III/IV disease irrespective of CD4 count were deemed eligible for ART initiation. From 2016 to 2017, the CD4 threshold was changed to 500 cells/ μ L⁵. A phased implementation

of the ‘test & treat all’¹⁰ approach was initiated in late 2016 in 12 high-burden districts; this was then scaled up to reach 65 districts by December 2017.

Study design, data collection and statistical analyses

We included data from 86 Ministry of Health facilities providing HIV care and treatment in Nampula and Zambezia that were receiving technical support from ICAP at Columbia University through funding from the United States President’s Emergency Plan for AIDS Relief*.

PMTCT cascade in ANC

For this assessment, we used existing ANC aggregated data from facility reports and those captured through ICAP’s aggregate database using DHIS2¹¹. Simple statistics were calculated and expressed in number and proportions (%) for the following indicators: number of pregnant women enrolled in ANC; proportion of pregnant women with a documented HIV status at the first ANC visit; proportion of HIV-positive pregnant women at the first ANC visit; and proportion of HIV-positive pregnant women receiving ART. For this analysis, we included all pregnant women enrolled in ANC between the July 1, 2013 and December 31, 2017. The indicators have been disaggregated by year of ART initiation from 2013 to 2017 to highlight the potential evolution in programme implementation.

Risk of attrition analyses

For the assessment of attrition risk, we performed a retrospective cohort analysis using data from an electronic patient-level database (ePLD). We also used data from the Program and Facilities Characteristics Tracking System (PFaCTS) round 8 (May 2015). This is an ICAP facility-level survey conducted every two to three years to gather information on the characteristics of health facilities and their services at ICAP-supported sites^{12,13}. Data from the ePLD and PFaCTS were merged by a facility code to allow for the analyses of the potential effects of facility-specific characteristics on the risk of attrition in each patient.

Our main exposure variable was patient group, for which patients were categorised into two groups based on their pregnancy status and ART eligibility criteria: (1) ‘own health’, if women were neither pregnant nor breastfeeding and ART was initiated based on national eligibility criteria; (2) ‘B+ pregnant’, if women were pregnant at the time of ART initiation. The outcome event was attrition, which was divided into two types of losses: (1) No follow-up (NFU), corresponding to women who never returned to the health facility after the first visit in which ART was prescribed and (2) Non-retention, corresponding to women who dropped out from care after the second visit, due to death (documented date of death) or those lost to follow-up (LTFU, defined as not having been seen for a period of 30 days or longer prior to the 365th day since ART initiation). We hypothesised that while the NFU cases were likelier to be related to patients’ reluctance to initiate ART, non-retention may have been related to a sub-optimal quality of care.

We included women enrolled in HIV services who initiated ART any time between July 1, 2013 and December 31, 2016. We included data from follow-up until December 31, 2017. Women were excluded if their HIV status was not confirmed or they had missing information on pregnancy status and eligibility criteria for ART initiation

*US Centers for Disease Control and Prevention (CDC) under PEPFAR, through cooperative agreements: Building Mozambican Capacity to Implement Quality HIV/AIDS Prevention, Care and Treatment in the Republic of Mozambique under PEPFAR (CA#U2GPS002756); Technical Assistance to the Ministry of Health for HIV Services and Program Transition in the Republic of Mozambique under PEPFAR 9CA#1U2GGH000424); Supporting Sustainable Implementation of HIV and TB Services for Epidemic Control in The Republic of Mozambique (CA# NU2GGH001944).

since this information was used to classify patients into groups. We also excluded a small number of breastfeeding women who had been previously enrolled in HIV care but who initiated ART only after July 2013 (n=280) due to specific characteristics related to the timing of diagnosis and duration of follow-up in HIV care, which did not allow for comparability.

The patients' baseline characteristics were described as frequencies for categorical variables and median for continuous variables and were compared by patient group using Chi-square and Wilcoxon tests. For biological and immunological measurements, we used the most updated data within the range of 90 days prior to or 30 days after ART initiation. A patient retained in care was defined as being alive and present in care at 12 months following ART initiation or any time after. Women transferred to another facility were right-censored at the date of transfer. The Kaplan-Meier method was used to estimate the probability of retention in care at 12 months after ART initiation for each patient group, with differences in crude estimates assessed by a log-rank test.

To assess the risk of having an NFU status at 12 months after ART initiation, we used logistic regression models with the cluster effect on the facility. For the risk of non-retention at 12 months after ART initiation, we used Cox proportional hazard models with random effects accounting for the clustering of patients in the same health facility. For both models, we explored the association between the patient group ('B+ pregnant' vs. 'own health') and outcome (NFU or non-retention), adjusting for socio-demographic, clinical, immunological and facility-related characteristics. Covariates were first selected based on prior knowledge on associated predictors, which were tested in the univariate analysis. Multivariable models were then constructed. Final models were obtained using a backward elimination procedure. We systematically tested the interaction between the year of ART initiation and patient group in both models as we hypothesised that the Option B+ programme may have evolved in a certain manner over the four-year period and influenced the association between patient group and attrition. Adjusted odds ratios (aORs) and adjusted hazard ratios (aHRs) were reported with their 95% confidence intervals (CIs). We performed a sensitivity analysis to assess whether the exclusion of health facilities with missing information on facility-related characteristics had any effect on the results. All statistical analyses were performed with Stata version 14.0 (Stata Corp., College Station, TX, USA).

Ethical approval

This study was part of the 'Analysis of existing aggregate data included in routine reports generated by ICAP-supported HIV and other health programmes in Mozambique' study and the 'Identifying Optimal Models of HIV Care and Treatment' collaboration, which were approved by the Mozambican National Ethics Committee and the Columbia University Medical Center IRB. Additional technical and administrative approval was received from the US Centers for Disease Control and Prevention and the Office of the Global AIDS Coordinator, US Department of State. Informed consent to participate was not required as this study was solely based on secondary data analyses of de-identified routine service delivery data. Both as part of the 'Analysis of existing aggregate data' study and the 'Optimal Models' Collaboration, the Columbia University IRB Committee did not consider this study to be a human subject research, as there was no interaction with subjects and no intervention, and private, identifiable information was not collected.

Results

PMTCT cascade in antenatal care

A total of 916,280 women enrolled in ANC under Option B+ between July 2013 and December 2017. The proportion of women with a documented HIV status increased from 93% in 2013 to 96% in 2017 (Figure 1). The proportion of women who tested HIV-positive decreased from 8% to 6%. Among the HIV-positive women, the proportion of those who initiated ART at the first ANC visit increased from 32% to 60%. The proportion of women who had been on ART before ANC enrolment also increased from 10% to 35%. Overall, the proportion of HIV-positive pregnant women on ART at the first ANC visit increased from 42% to 95% between 2013 and 2017.

Attrition risk at 12 months following ART initiation

A total of 44,377 HIV-positive women were included in this retrospective cohort analysis. Of these, ART was initiated in 31,186 women while they were pregnant ('B+ pregnant') and ART was initiated in 13,191 women based on immunological or clinical criteria ('own health') (Figure 2).

Table 1 shows the baseline characteristics of the women included in the analyses. Overall, the median age at ART initiation was 26 years (interquartile range [IQR]: 21-32). More than 12% of the women had no education, 63% were unemployed and 56% were in a couple or married. The median gestational age at ART initiation for the 'B+ pregnant' women was 25 weeks (IQR: 19-29). The median follow-up time under ART was 13 months (IQR: 3-24). In 44% of the women, ART was initiated between 2013 and 2014, in 31% in 2015, and in 25% in 2016.

On comparing the two groups, the proportion of women who initiated ART at WHO clinical stage IV was higher in the 'own health' group (23% vs. 2% in the 'B+ pregnant' group). Among the women with available information (N=24,509), those in the 'own health' group had a lower median CD4 cell count than the 'B+ pregnant' group women: 240 (IQR: 128-348) vs. 386 (IQR: 234-572) cells/ μ L, respectively. In more than 90% and 36% of the women, ART was initiated on the same day of HIV diagnosis in the 'B+ pregnant' and 'own health' groups, respectively (Table 1).

Table 2 describes the distribution of patients according to the health facility characteristics. More than 70% of the women were enrolled in public primary health facilities (type I). Only 53% had access to VL sampling at the health facility in which they received routine HIV care. Individual and/or group ART counselling was widely accessible (83%); however, more targeted approaches including support groups and peer education were less commonly provided (65% and 69%, respectively). Of 44,377 patients, 1,678 (4%) were enrolled in HIV care at the 12 facilities which did not have any information on facility-related characteristics. The baseline characteristics of the women included in the analyses were comparable to those who were excluded (N=11,737) (Supplemental Digital 2).

Figure 3 describes the probability of retention by patient group and ART initiation year. The probability of retention at 12 months post ART initiation was significantly lower in the 'B+ pregnant' women than the 'own health' women, irrespective of year. From 2013 to 2016, the probability of retention increased from 64% (95% CI: 62-66) to 74% (95% CI: 73-75) for the 'B+ pregnant' women and from 71% (95% CI: 69-73) to 77% (95% CI: 73-75) for the 'own health' women.

Of the 44,377 women included in the analyses, 22% (n=9,905), 29% (n=12,795) and 35% (n=15,326) dropped out of care by 3, 6, and 12 months post ART initiation, respectively. Of those who dropped out of care at 12 months, 30% (4,576/15,326) did so immediately after their first visit, corresponding to the definition of NFU; 7% (1,011/15,326) died and 63% (9,739/15,326) were LTFU. On comparing the two groups of women, the proportion of those with an NFU status was significantly higher in the 'B+ pregnant' group than the 'own health' group: 11% (3,462/31,186) and 8% (1,114/13,191), respectively (P<0.0001). The proportion of women considered as non-

retained in care (death and LTFU) was also significantly higher in the ‘B+ pregnant’ group than the ‘own health’ group, at 26% (7,978/31,186) and 21% (2,772/13,191), respectively ($P < 0.0001$).

We found a significant interaction effect between ART initiation year and patient group. Therefore, we presented the results stratified by ART initiation year (2013, 2014, 2015 and 2016) for both models (Tables 3 and 4).

As Table 3 shows, the effect of patient group was different according to the year of ART initiation after adjustment for age at ART initiation, education level, employment, CD4 cell count at enrolment, same-day ART initiation, tuberculosis treatment at ART initiation, type of health facility and presence of a support group for HIV+ patients at the health facility. Women who initiated ART during pregnancy in 2013 were at a higher risk of having an NFU status than women who initiated for their own health, although no statistically significant difference was found. For the following years, women with ART initiation during pregnancy were less likely to have an NFU status than the ‘own health’ women with ART initiation during the same period; statistical significance was found only for those with ART initiation in 2015 (aOR: 0.77, 95% CI: 0.64-0.94, $P = 0.01$) (Table 3). Our results were comparable after the exclusion of patients from sites without data on facility-related characteristics.

Table 4 shows the risk of non-retention among women who completed at least one visit after ART initiation ($N = 39,801$). Similar to the results of the previous analysis, we found a significant interaction between patient group and ART initiation year. After adjustment for age, employment status, CD4 cell count at enrolment, same-day ART initiation as well as the availability of family planning services onsite, ‘B+ pregnant’ women showed a significantly higher risk of non-retention than women who initiated ART for their own health (aHR: 1.14, 95% CI: 1.03-1.25) when ART was initiated in 2013. The risk decreased during the subsequent years, with no statistically significant difference observed between the two groups. These findings did not change after the exclusion of patients from sites with no data on facility-related characteristics.

Discussion

This study assessed the effectiveness of the Option B+ strategy in two provinces in Mozambique over four years of the PMTCT programme implementation. We believe that our study makes a significant contribution to the literature by documenting in detail the progress made in implementation of the PMTCT Option B+ in a high HIV disease burden country in sub-Saharan Africa.

In terms of the ANC cascade, we reported an improved HIV testing uptake at the first ANC visit, a reduction in the HIV-positivity rate, and an increase in the rates of ART initiation. We also found that the proportion of women already on ART at the first ANC visit increased, accounting for over 30% of HIV-positive pregnant women enrolled by 2017. These results provide evidence of the positive evolution of the Option B+ roll-out in Mozambique, contributing to better access to and acceptability of essential treatments.

Over the four-year period, the overall retention rates at 12 months after ART initiation improved in both groups, at 74% and 77% of the women in the ‘B+ pregnant’ and ‘own health’ groups, respectively. Greater improvements were noted in the ‘B+ pregnant’ group, with retention rates that had increased from 64% in 2013 to 74% in 2017. Similar results were reported in a systematic review focusing on retention in HIV care under Option B+ in Africa, in which the pooled estimate was 76% at 12 months¹⁴. Despite the apparent progress, the overall attrition rate remains unacceptably high for both groups with one out of four women being lost to care within their first year of treatment; this highlights the importance of ensuring early and intensified quality ART adherence through counselling and peer support¹⁵.

Interestingly, time effects came into play in the determination of the risks of attrition in our study. In the early years of Option B+ implementation (2013-2014), we did not observe a higher risk of immediate drop-out in

pregnant women compared to women on ART for their own health, as observed elsewhere ^{7,8,16}. Conversely, in 2015, the risk of immediate drop-out was significantly lower among the 'B+ pregnant' women than 'own health' women. The fact that several national efforts were implemented by the Ministry of Health with the support of other partners in 2015 may explain those results ¹⁷. In 2015, improvements in the quality of care in PMTCT-related services were called for, and several tangible efforts were made, such as the provision of continuous training for MCH nurses in ART, increased frequency of supervision visits to health units, publication of the new PMTCT guideline handbook for healthcare workers and the establishment of a communication strategy for the elimination of the vertical transmission of HIV among girls and young women. Additionally, awareness on Option B+ was raised in the community and reinforced through Information Education and Communication material updates for Mother2Mother groups. As the expansion of ART and Option B+ services continued throughout 2016, the effects of such interventions may have 'spilled-over' to non-pregnant women, resulting in a similar low risk of immediate drop-outs as observed in 2016.

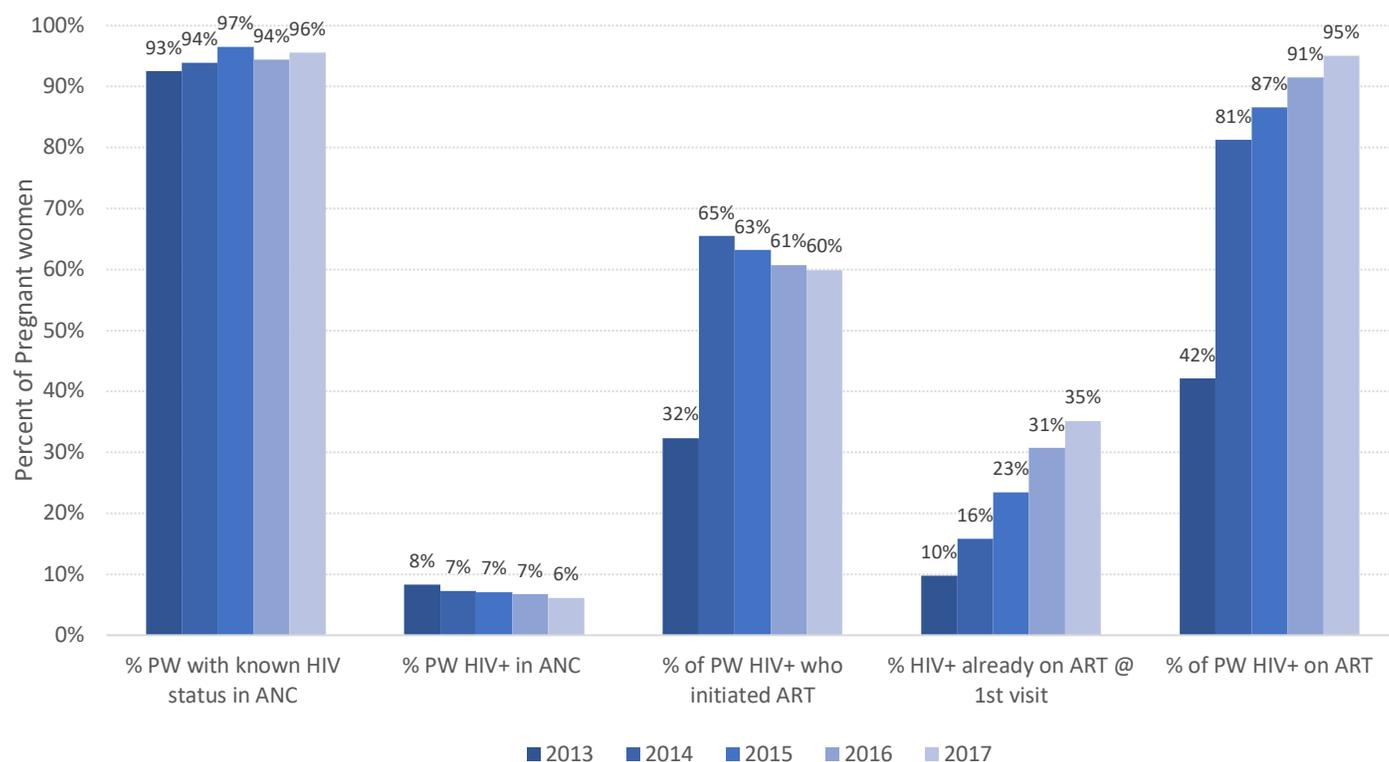
The risk of non-retention was 12% higher in the 'B+ pregnant women' than 'own health' women when ART was initiated in the first year of programme implementation. This risk decreased over the years and was similar in both groups by 2016. Haas et al. reported similar findings in a cohort of women enrolled in Malawi's Option B+ programme between 2011 and 2012 ¹⁸: women in Option B+ had a higher risk of being lost to follow-up in years 1 and 2 of ART than those who initiated ART for their own health. However, the retention rates did not change as the Option B+ programme matured. Our results suggest improvements achieved over time as the PMTCT Option B+ programme matured with better counselling including reinforced education messages about the benefits of ART during the first ANC visit and importance of adherence to long-term care during subsequent follow-ups. We observed that the initiation of ART on the same day as HIV diagnosis significantly increased both the risk of having an NFU status and non-retention, confirming that pregnant women may still experience considerable staff pressure to undergo immediate ART initiation without sufficient time to disclose to their partner or relative or reflect on their HIV sero-status and the implications of lifelong treatment ^{14,15,16,19}. A greater degree of acceptability of lifelong treatment under Option B+ can be achieved with male-partner knowledge and support as well as strengthened community sensitization ^{20,21}.

The strengths of our study lie in the number of sites included, which resulted in the inclusion of more than 40,000 eligible women in the analysis, increasing the statistical power and reliability of our results. In addition, coupling individual-level data with health facility-related characteristics provided a unique opportunity to identify actionable measures to improve the quality of care of PMTCT services. However, our study has several limitations that should be discussed. Firstly, the data did not allow us to verify if a woman with an LTFU status in a given health facility was actually being followed-up elsewhere. As the patients' data were fully anonymised, 'silent transfer' could not be detected in a systematic manner, which may have caused the misclassification of the status of self-transferred patients as 'LTFU'. It has been reported that accounting for self-transferred patients is likely to increase the estimates of patient retention ^{22,23}. Nevertheless, we assume that the rate of self-transfer is likely to be similar in both groups (nondifferential misclassification); thus, the association between the patient status and risk of attrition would not be affected significantly ²⁴. Secondly, we analysed routine data for which nearly 7% of women did not have information on ART eligibility criteria. While routine health information systems are critical for programme evaluations, efforts to overcome the barriers of missing or inconsistent data are essential to enable the effective use of such data sources for policymaking, programme actions, and research ^{25,26}.

In conclusion, we demonstrated that the PMTCT Option B+ strategy in Nampula and Zambezia yielded positive results as the programme matured over four years, including the achievement of high HIV testing uptake and ART initiation rates in ANC. Improving women's engagement in care remains a challenge. It is important to seek alternative service delivery models ^{27,28,29} to support the existing health system and prevent

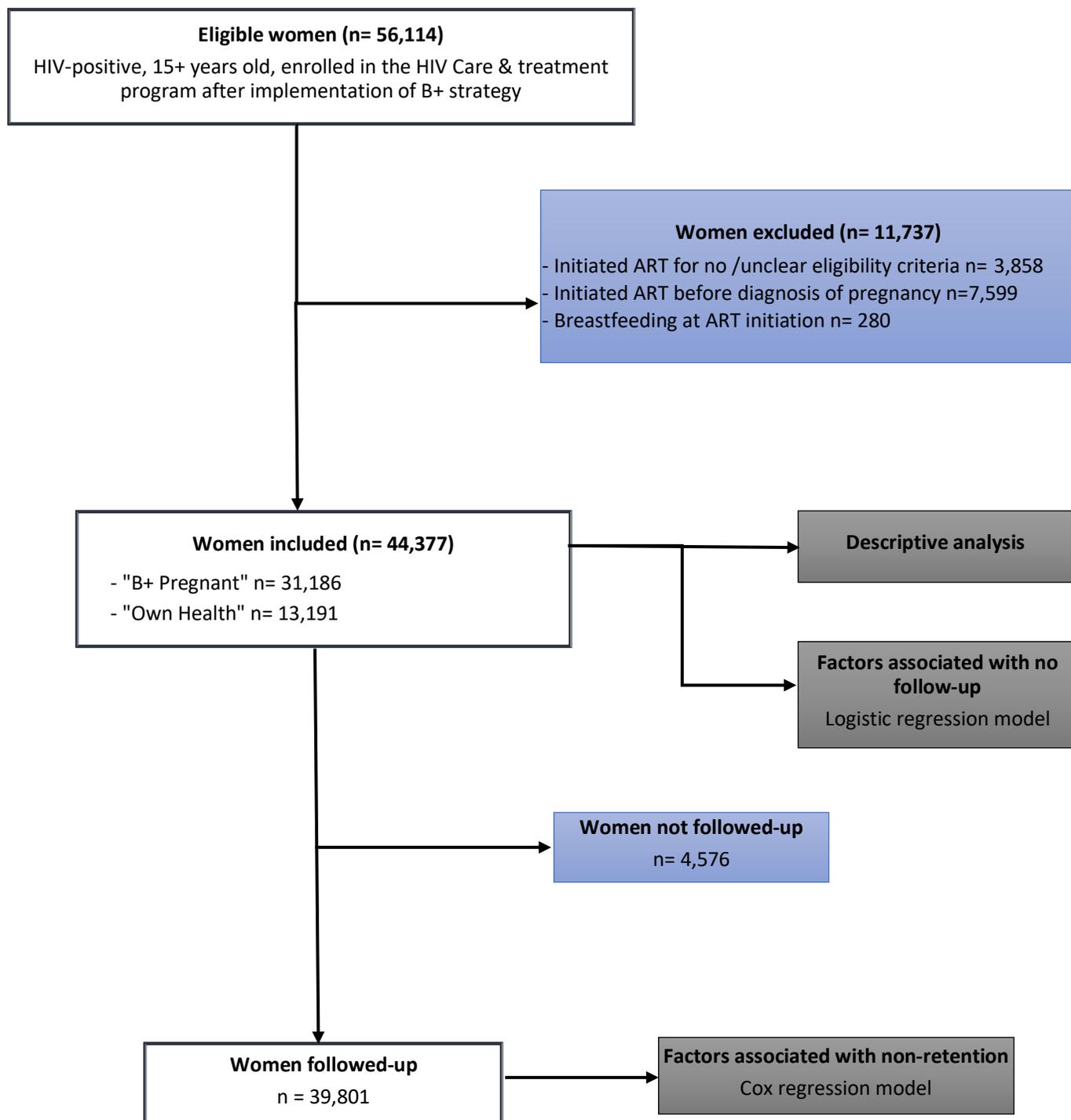
potential defaulters to achieve the UNAIDS' 95-95-95 targets for PMTCT and the virtual elimination of the MTCT of HIV.

Figure 1: Prevention of mother-to-child transmission of HIV (PMTCT) cascade of care, antenatal care sites, Nampula and Zambézia provinces, Mozambique 2013-2017 (n=86 sites, 916,280 women). Source: DHIS2



Source of data : DHIS2 aggregated facility reports; proportion of Pregnant women (PW) with known HIV status at 1st antenatal care (ANC) visit: numerator = # of pregnant women who received their test results (i.e. test results positive, negative and undetermined) plus those already known as HIV+, denominator = # PW enrolled in 1st ANC; Proportion of HIV+ PW in 1st ANC visit: numerator = # of PW HIV-positive, denominator = # with known HIV status; Proportion of HIV+ PW who initiated ART: numerator = # of PW HIV-positive who initiated ART at 1st ANC visit, denominator = # of PW HIV-positive; Proportion of HIV+ PW already on ART: numerator = # of PW HIV-positive already receiving ART at 1st ANC visit, denominator = # of PW HIV-positive; Proportion of PW HIV+ on ART: numerator = sum of # of PW HIV-positive who initiated ART and # of PW HIV-positive already receiving ART at 1st ANC visit, denominator = # of PW HIV-positive.

Figure 2: Inclusion cascade of HIV+ women in the retrospective cohort analysis using electronic patient-level data, Nampula and Zambézia provinces, Mozambique 2013-2017, (n=86 sites).



Source of data: electronic patient-level database (ePLD) merged with health facility characteristics data from the Program and Facilities Characteristics Tracking System (PFaCTS); Note: See definition of "B+ pregnant" and "own health" in Measurements section.

Table 1: Demographic, clinic-immunological and treatment characteristics of women included, Nampula and Zambézia provinces, Mozambique (n=86 sites, 44,377 women)

Patient characteristics	“B+ pregnant” (N=31,186)	“Own health” (N= 13,191)	Total (N=44,377)
Median age, years [IQR]	25 [21 - 30]	30 [24 - 39]	26 [21 - 32]
Age group (%)			
15-19 y	7,095 (23)	1,193 (9)	8,288 (19)
20-24 y	9,346 (30)	2,592 (20)	11,938 (27)
25-34 y	10,639 (34)	4,898 (37)	15,537 (35)
35+y	4,106 (13)	4,508 (34)	8,614 (19)
Education level (%)			
None	3,122 (10)	2,179 (17)	5,301 (12)
Primary & above	20,985 (67)	7,928 (60)	28,913 (65)
No information	7,079 (23)	3,084 (23)	10,163 (23)
Marital status (%)			
Couple/married	19,367 (62)	5,600 (42)	24,967 (56)
Single	5,559 (18)	4,496 (34)	10,055 (23)
Widowed	884 (3)	741 (6)	1,625 (4)
Other/no info	5,376 (17)	2,354 (18)	7,730 (17)
Employment status (%)			
Unemployed	21,280 (68)	6,555 (50)	27,835 (63)
Working/student	6,806 (22)	5,191 (40)	11,997 (27)
No information	3,100 (10)	1,445 (11)	4,545 (10)
Clinical stage (%)	n=30,027	n=12,828	n=42,855
Stage I/II	24,700 (82)	3,808 (30)	28,508 (67)
Stage III	4,724 (16)	6,095 (47)	10,819 (25)
Stage IV	603 (2)	2,925 (23)	3,528 (8)
CD4 testing, median [IQR]	n=15,076	n=9,433	n=24,509
CD4 cell count	386 [234 - 572]	240 [128 - 348]	319 [183 - 496]
CD4 cell count group (%)			
<200	2,992 (20)	3,822 (41)	6,814 (28)
200-349	3,667 (24)	3,295 (35)	6,962 (28)
350-499	3,462 (23)	1,262 (13)	4,724 (19)
>=500	4,955 (33)	1,054 (11)	6,009 (25)
Follow-up pre-ART (days), median [IQR]	0 [0 - 1]	6 [0 - 32]	0 [0 - 15]
Follow-up under ART (month), median [IQR]	13 [3 - 24]	14 [4 - 25]	13 [3 - 24]
Year of ART initiation (%)			

Patient characteristics	“B+ pregnant” (N=31,186)	“Own health” (N= 13,191)	Total (N=44,377)
2013	4,045 (13)	1,661 (13)	5,706 (13)
2014	9,929 (32)	3,746 (28)	13,675 (31)
2015	9,693 (31)	3,996 (30)	13,689 (31)
2016	7,519 (24)	3,788 (29)	11,307 (25)
ART regimen (%)			
TDF-3TC-EFV	24,105 (77)	10,673 (81)	34,778 (78)
AZT-3TC-NVP/EFV	2,111 (7)	1,588 (12)	3,699 (8)
D4T-3TC-NVP/EFV	124 (.4)	222 (2)	346 (1)
Other	4,751 (15)	599 (5)	5,350 (12)
Non specified	95 (.3)	109 (1)	204 (.5)
Same day ART initiation (%)	28,953 (93)	4,812 (36)	33,765 (76)
On TB treatment (%)	740 (2)	1,401 (11)	2,141 (5)

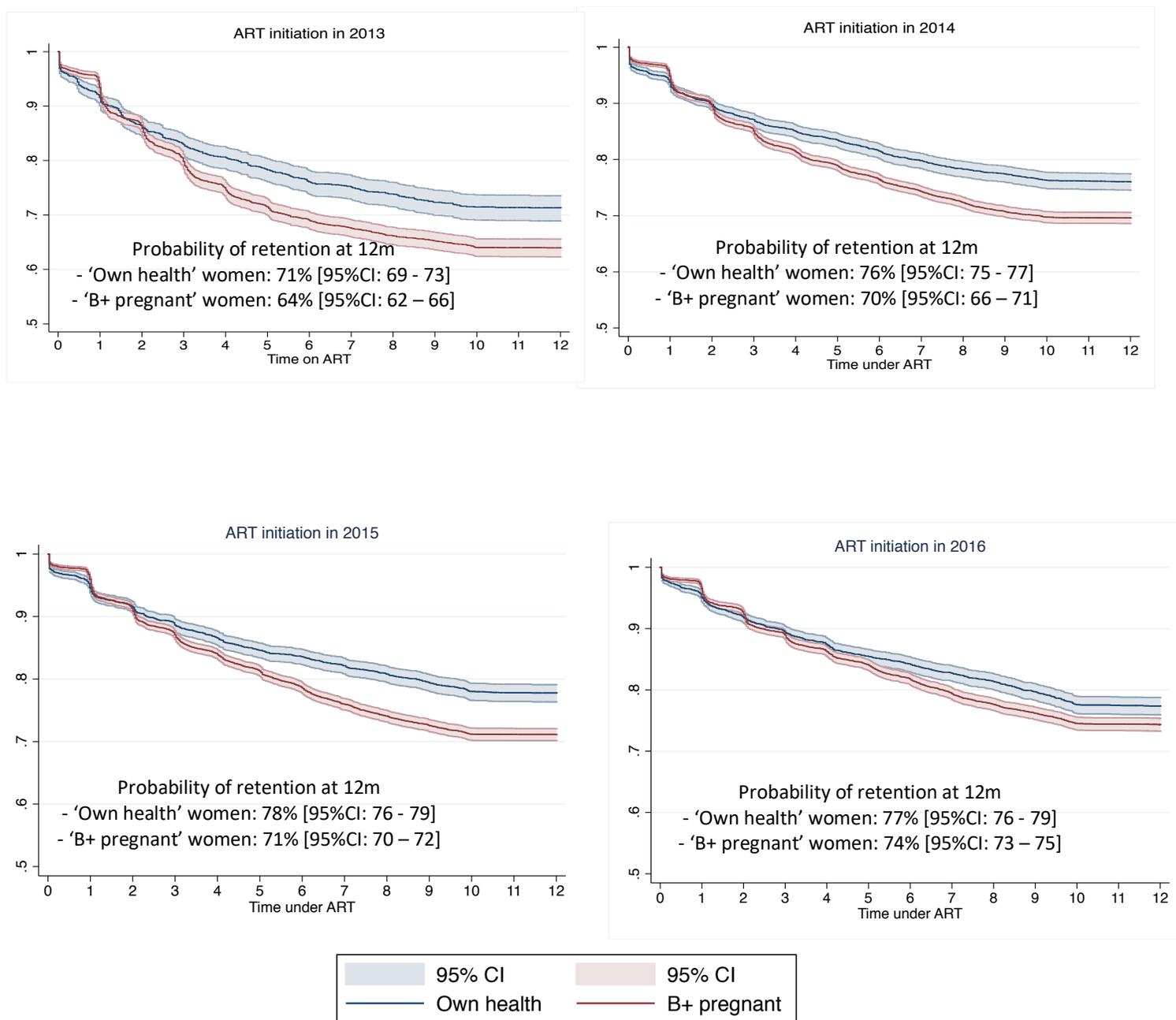
IQR: Interquartile range; ART: anti-retroviral treatment; TDF: Tenofovir; 3TC: Lamivudine; EFV: Efavirenz; AZT: Zidovudine; NVP: Nevirapine; D4T: Stavudine; TB: tuberculosis. Note: See definition of “B+ pregnant” and “own health” in Measurements section. P values of statistical tests are not presented, as all tests are highly significant, despite the Bonferroni correction (corrected $\alpha = 0.05/13 = 0.004$).

Table 2: Health facility characteristics, Nampula and Zambézia provinces, Mozambique (n=86 sites, 44,377 women)*

	“B+ pregnant” (N=31,186)	“Own health” (N= 13,191)	Total (N=44,377)
Health facility and services			
PMTCT option (%)			
New B+ site	186 (1)	65 (1)	251 (1)
Switched from option A to B+	29,342 (94)	12,589 (95)	41,931 (94)
No PMTCT services	288 (1)	229 (2)	517 (1)
No information	1,370 (4)	308 (2)	1,678 (4)
Type of Health Facility (%)			
Public I (HC clinic)	22,924 (74)	9,023 (68)	31,947 (72)
Public II (dist./prov. hosp.)	6,432 (21)	3,401 (26)	9,833 (22)
Public III (teaching/nation. ref. hosp.)	460 (1)	459 (4)	919 (2)
No information	1,370 (4)	308 (2)	1,678 (4)
Location (%)			
Urban-city	12,787 (41)	3,958 (30)	16,745 (38)
Semi-urban	4,923 (16)	1,866 (14)	6,789 (15)
Rural	12,106 (39)	7,059 (54)	19,165 (43)
No information	1,370 (4)	308 (2)	1,678 (4)
Laboratory services			
Location cd4 testing (%)			
Blood sample & test at HF	8,117 (26)	5,531 (42)	13,648 (31)
Blood sample at HF /test at other HF	19,190 (62)	6,774 (51)	25,964 (58)
Not available	2,509 (8)	578 (5)	3,087 (7)
No information	1,370 (4)	308 (2)	1,678 (4)
Location of viral load sampling [#] (%)			
Not available at HF and/or referred to another HF	12,695 (41)	6,430 (49)	19,125 (43)
Available onsite	17,092 (55)	6,453 (49)	23,545 (53)
Missing	1,399 (4)	308 (2)	1,707 (4)
Other service availability on site			
Type of ART counseling (%)			
None	3,913 (13)	2,024 (16)	5,937 (13)
One on one	3,282 (10)	1,869 (14)	5,151 (12)
Group	2,433 (8)	901 (7)	3,334 (7)
Both	20,188 (65)	8,089 (61)	28,277 (64)
Missing	1,370 (4)	308 (2)	1,678 (4)
ART counselling by outreach worker (%)			
No	25,475 (82)	10,403 (79)	35,878 (81)
Yes	4,341 (14)	2,480 (19)	6,821 (15)
Missing	1,370 (4)	308 (2)	1,678 (4)
<i>Support group services:</i>			
Support groups (%)	20,191 (65)	8,748 (66)	28,939 (65)
Peer educator program (%)	22,110 (71)	8,418 (64)	30,528 (69)
<i>Action after missed visits for ART patients:</i>			
Call/SMS (%)	23,551 (76)	9,840 (75)	33,391 (75)
Home visits (%)	27,370 (88)	11,649 (88)	39,019 (88)

HF: health facility; ART: anti-retroviral treatment. Note: See definition of “B+ pregnant” and “own health” in Measurements section. *P* values of statistical tests are not presented, as all tests are highly significant, despite the Bonferroni correction (corrected $\alpha = 0.05/12 = 0.004$). * 1,678 women with no information on health facility characteristics (12 Health facilities).

Figure 3: Twelve-month probability of retention in HIV+ women after ART initiation, by status and period of ART initiation, Mozambique 2013-2017 (n=86 sites, 44,377 women).



ART: anti-retroviral treatment; 95%CI: 95% confidence interval. Note: See definition of “B+ pregnant” and “own health” in Measurements section. Log-rank test for equality of survivor functions, by patient status (“B+ pregnant” vs. “own health”): for women initiating ART in 2013: $p < 0.00001$; for women initiating ART in 2014: $p < 0.00001$; for women initiating ART in 2015: $p < 0.00001$; for women initiating ART in 2016: $p = 0.002$

Table 3: Factors associated with no follow-up after start of art, Logistic regression models, Nampula and Zambézia provinces, Mozambique (n=86 sites, 44,377 women)

	Events n/N (%)	Univariate model			Multivariable model		
		OR	95% CI	P	Adjusted OR [†]	95% CI	P
Status of HIV+ women							
Year of ART initiation: 2013							
Own health	160/1,661 (10)	Ref.	-	0.0005	Ref.	-	0.37
B+ pregnant	531/4,045 (13)	1.56	1.21– 2.00		1.12	0.88 – 1.42	
Year of ART initiation: 2014							
Own health	345/3,746 (9)	Ref.	-	0.0002	Ref.	-	0.6
B+ pregnant	1,325/9,929 (13)	1.40	1.17– 1.67		0.96	0.81 – 1.12	
Year of ART initiation: 2015							
Own health	370/3,996 (9)	Ref.	-	0.12	Ref.	-	0.01
B+ pregnant	1,075/9,693 (11)	1.17	0.96 – 1.42		0.77	0.64 – 0.94	
Year of ART initiation: 2016							
Own health	239/3,788 (6)	Ref.	-	0.06	Ref.	-	0.3
B+ pregnant	531/7,519 (7)	1.27	1.00 – 1.62		0.88	0.70 – 1.10	
Socio-demographic maternal factors							
Age at ART initiation							
35+y	684/8,614 (8)	Ref.	-		Ref.	-	
25-34 y	1,553/15,537 (10)	1.29	1.13 - 1.46	0.0001	1.15	1.02 - 1.28	0.0023
20-24 y	1,330/11,938 (11)	1.45	1.19 - 1.77		1.29	1.10 - 1.51	
15-19 y	1,009/8,288 (12)	1.60	1.30 – 2.00		1.37	1.16 - 1.60	
Education level							
Primary and above	2,591 /28,913 (9)	Ref.	Ref.	<0.00001	Ref.	-	<0.00001
No school education	569/5,301 (11)	1.22	0.97 - 1.53		1.33	1.11 - 1.60	
No information	1,416/10,163 (14)	1.64	1.32 – 2.04		1.33	1.17 - 1.52	
Employment							
Working	929/11,997 (8)	Ref.	Ref.	<0.00001	Ref.	Ref.	0.0001
Unemployed	2,867/27,835 (10)	1.36	1.13 - 1.65		1.16	0.98 - 1.38	
No information	780/4,545 (17)	2.46	1.92 – 3.18		1.56	1.26 – 1.92	

	Events n/N (%)	Univariate model			Multivariable model		
		OR	95% CI	P	Adjusted OR [†]	95% CI	P
Clinic-immunological maternal factors							
CD4 cell count							
>=350	715/10,733 (7)	Ref.	-	<0.00001	Ref.	-	<0.00001
<350	922/13,776 (7)	1.00	0.87 - 1.15		1.07	0.93 - 1.23	
Missing	2,939/19,868 (15)	2.43	2.00 - 2.95		2.17	1.78 - 2.63	
Same day ART initiation							
No	737 /10,612 (7)	Ref.	-	<0.00001	Ref.	-	0.002
Yes	3,839/33,765 (11)	1.72	1.48 - 1.99		1.27	1.09 - 1.48	
TB treatment at ART initiation							
No	4,473/42,236 (11)	Ref.	-	<0.00001	Ref.	-	<0.00001
Yes	103/2,141 (5)	0.43	0.34 - 0.53		0.48	0.38 - 0.61	
Health facility factors							
Type of Health Facility							
Public I (HF clinic)	3,661/31,947 (11)	Ref.	-	<0.00001	Ref.	-	0.0007
Public II (dist./prov. hosp.)	738/9,833 (8)	0.62	0.49 - 0.79		0.75	0.61 - 0.92	
Public III (teaching/nation. ref. hosp.)	58/919 (6)	0.52	0.42 - 0.64		0.75	0.64 - 0.89	
No information	119/1,678 (7)	0.59	0.42 - 0.83		0.64	0.44 - 0.91	
Support groups for HIV+ patients							
No	2,518 /21,321 (12)	Ref.	-	0.002	Ref.	-	0.03
Yes	1,939 /21,378 (9)	0.74	0.59 - 0.93		0.81	0.67 - 0.98	

OR: Odds ratio; CI: confidence interval; TB: tuberculosis; ART: antiretroviral treatment; HF: health facility. Note: See definition of “B+ pregnant” and “own health” in Measurements section.

Table 4: Factors associated with non-retention 12 months after ART initiation, Cox regression models, Nampula and Zambézia provinces, Mozambique (n=86 sites, 39,801 women)

	Events (n/PM)	Univariate models			Multivariable model		
		Crude HR	95% CI	P	Adjusted HR [†]	95% CI	P
Status of HIV+ women							
Year of ART initiation: 2013							
Own health							
B+ pregnant	375/13,435	Ref.	-	<0.0001	Ref.	-	0.01
	1168/29,290	1.46	1.34– 1.60		1.14	1.03 – 1.25	
Year of ART initiation: 2014							
Own health							
B+ pregnant	702/32,126	Ref.	-	<0.0001	Ref.	-	0.21
	2,450/78,296	1.38	1.28– 1.48		1.06	1.97 – 1.15	
Year of ART initiation: 2015							
Own health							
B+ pregnant	707/34,800	Ref.	-	<0.0001	Ref.	-	0.78
	2,360/80,398	1.29	1.20 – 1.39		1.00	0.91 – 1.07	
Year of ART initiation: 2016							
Own health							
B+ pregnant	721/33703	Ref.	-	<0.0001	Ref.	-	0.40
	1,685/66,195	1.24	1.15 – 1.35		0.96	0.88 – 1.05	
Socio-demographic maternal factors							
Age at ART initiation							
35+y	1,546/76,064	Ref.	-		Ref.	-	
25-34 y	3,326/132,009	1.22	1.15 - 1.30	<0.00001	1.16	1.09 - 1.23	<0.00001
20-24 y	3,031/95,915	1.54	1.44 - 1.63		1.40	1.32 - 1.50	
15-19 y	2,265/64,254	1.69	1.58 - 1.80		1.50	1.40 - 1.60	
Employment							
Working	2,403/105,545	Ref.	-	<0.00001	Ref.	-	<0.00001
Unemployed	6,842/227,764	1.26	1.20 - 1.32		1.15	1.10 - 1.21	
No information	923/34,935	1.13	1.04 – 1.23		1.05	0.97 - 1.14	
Clinic-immunological maternal factors							
CD4 cell count							
≥ 350	2,464/95,336	Ref.	-	<0.00001	Ref.	-	<0.00001

	Events (n/PM)	Univariate models			Multivariable model		
		Crude HR	95% CI	<i>P</i>	Adjusted HR [†]	95% CI	<i>P</i>
< 350	2,790/121,574	0.88	0.84 - 0.93		0.98	0.93 - 1.04	
Missing	4,914/151,333	1.20	1.14 - 1.27		1.18	1.12 - 1.24	
Same day ART initiation							
No	2,020/93,946	Ref.	-	<0.00001	Ref.	-	<0.00001
Yes	8,148/274,298	1.37	1.31 - 1.45		1.20	1.22 - 1.27	
Health facility factors							
Family planning services (%)							
Available onsite	3,727/153,767	Ref.	-	0.007	Ref.	-	0.007
Not available at HF	6,441/214,477	1.30	1.08 - 1.57		1.29	1.07 - 1.55	

PM, Person-Months; CI, confidence interval; HR, Hazard ratio; ART: anti-retroviral treatment; HF: health facility.

†Ratios from multiple Cox regression allowing for clustering by health facility. See definition of “B+ pregnant” and “own health” in Measurements section.

Supplemental Digital 1: National Antiretroviral Therapy ART-eligibility Guidelines from 2013 to 2017, Mozambique Ministry of Health.

WHO stage	CD4 cell count not available	CD4 cell count available
2013 through 2016		
I/II	Do not initiate ART	Initiate ART if CD4 ≤ 350 cells/μL
III	Initiate ART	Initiate ART independent of CD4 count
IV	Initiate ART	Initiate ART independent of CD4 count
2016 through 2017 *		
I/II	Do not initiate ART	Initiate ART if CD4 ≤ 500 cells/μL
III	Initiate ART	Initiate ART independent of CD4 count
IV	Initiate ART	Initiate ART independent of CD4 count

Abbreviations: WHO, World Health Organization; ART, antiretroviral therapy.

*A phased implementation of the “Test & Treat all” approach started in late 2016 in 12 high-burden districts which scaled up to reach 65 districts by December 2017.

Supplemental Digital 2: Comparison of main characteristics of women included vs. excluded, Nampula and Zambézia provinces, Mozambique (n=86 sites, 56,114 women)

Patient characteristics	Excluded (N=11,737)	Included (N=44,377)	Total (N=56,114)
Median age at enrolment, years [IQR]	28 [23 - 36]	26 [21 - 32]	27 [22 - 33]
CD4 at enrolment (%)	N=5,316 367 [203-574]	N=23,405 328 [187-511]	N=28,721 335 [189-522]
WHO clinical stage (%)	N=6,828	N=42,855	N=49,683
Stage 1-2	4,839 (71)	28,508 (67)	33,347 (67)
Stage 3	1,769 (26)	10,819 (25)	12,588 (25)
Stage 4	220 (3)	3,528 (8)	3,748 (8)
ART treatment			
Follow-up under ART (m), median [IQR]	12 [5 - 25]	13 [3 - 24]	13 [3 - 24]
TB treatment at ART start (%)	497 (4)	2,141 (5)	2,638 (5)
Cohort outcome at 12m after ART start (%)			
Dead	160 (1)	1,011 (2)	1,171 (2)
Transfer out	255 (2)	1,722 (4)	1,977 (3)
No follow-up	367 (3)	4,576 (10)	4,943 (9)
Alive and retained in care with ART	7,875 (67)	23,290 (53)	31,165 (55)
Alive and retained in care with no ART	1,230 (11)	4,039 (9)	5,269 (9)
Lost to follow-up	1,850 (16)	9,739 (22)	11,589 (20)
PMTCT site (%)			
New option B+ site	113 (1)	251 (1)	364(1)
Old option A site	10,509 (90)	41,931 (94)	52,440 (94)
No PMTCT services	215 (2)	517 (1)	732 (1)
Missing information	900 (7)	1,678 (4)	2,578 (5)
Type of Health Facility (%)			
Public I (HF clinic)	9,643 (82)	31,947 (72)	41,590 (74)
Public II (dist./prov. hosp.)	1,130 (10)	9,833 (22)	10,963 (20)
Public III (teaching/nation. ref. hosp.)	64 (1)	919 (2)	983 (2)
No information	900 (7)	1,678 (4)	2,578 (4)
Location (%)			
Urban-city	6,025 (51)	16,745 (38)	34,065 (40)
Semi-urban	1,610 (14)	6,789 (15)	13,373 (15)
Rural	3,202 (27)	19,165 (43)	35,379 (40)
No information	900 (8)	1,678 (4)	4,688 (5)

Patient characteristics	Excluded (N=11,737)	Included (N=44,377)	Total (N=56,114)
Point of service providing ART (%)			
Only HIV clinic	79 (1)	2,336 (5)	2,415 (4)
HIV clinic & all MCH services	3,596 (31)	12,551 (28)	16,147 (29)
HIV clinic & not all MCH services	7,162 (61)	27,812 (63)	34,974 (62)
No information	900 (7)	1,678 (4)	2,578 (5)

IQR: Interquartile range; WHO: World Health Organization; TB: tuberculosis; MCH: mother and child health; CI: confidence interval; HR: Hazard ratio; †Ratios from multiple Cox regression. All *p* values of statistical tests are < 0.0001 except for the variable PMTCT site (*p*=0.015).

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5.1.3 Results of additional analyses

The post-partum period is known to be a high-risk period of drop-out. In the ePLD database, it was not possible to assess the exact date of delivery as the information was not reported in the electronic file. Nevertheless, in our cohort, 61% (19,150/31,186) of the ‘Option B+ pregnant’ women had information on gestational age. The median gestational age at ART initiation in these women was 25 weeks (IQR:19–29) which corresponds to 6 months of pregnancy. Therefore, assessing the 12-month ART retention would include up to 9 months of post-partum. The Kaplan-Meier survival curves show that retention rates dropped significantly within the first 3 months after ART initiation, suggesting that the most difficult period for retaining women in Mozambique is at the early stage of ART treatment. We also examined whether timing of ART initiation varied according to the gestational age and we did not find any specific trends.

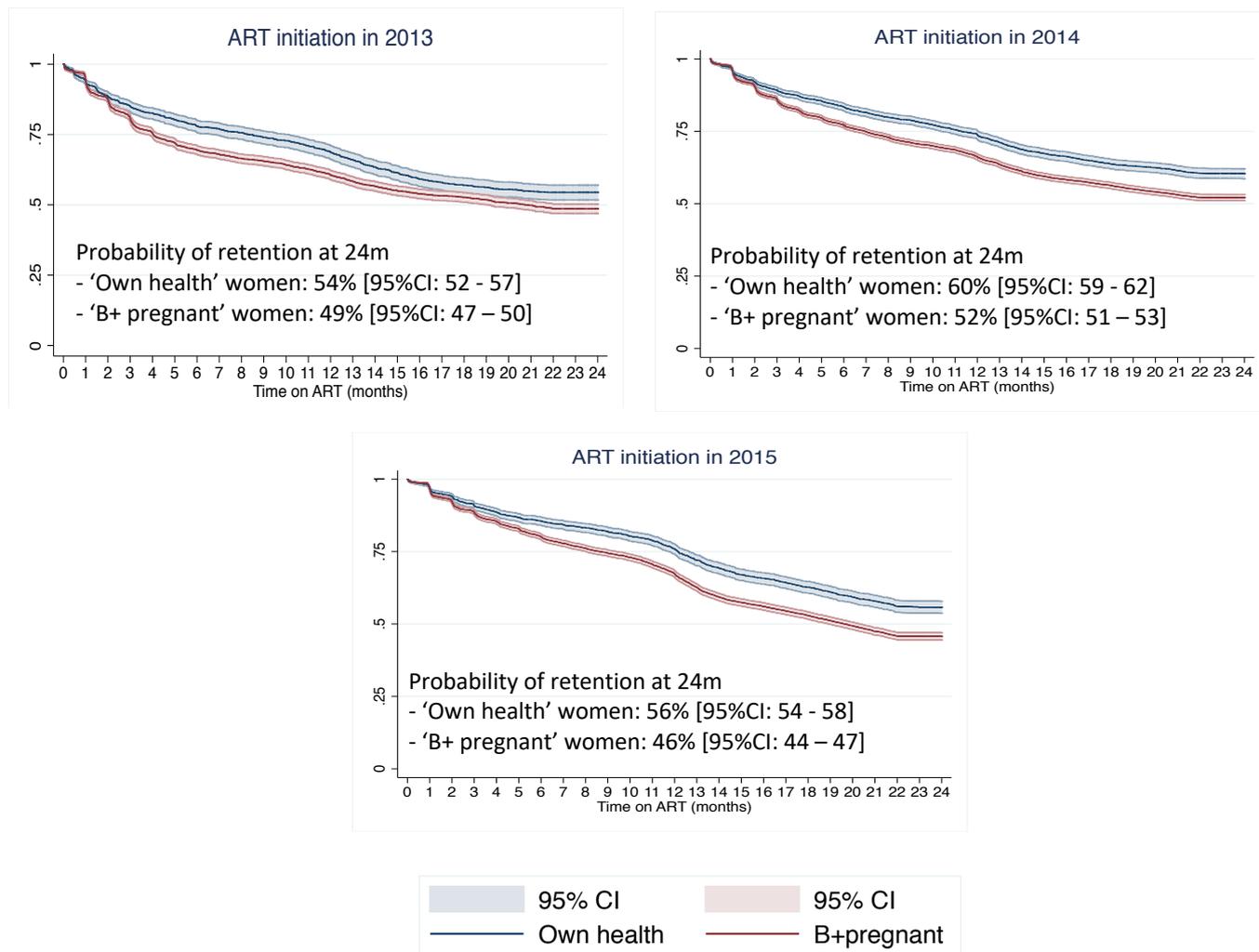
To provide insights on late post-partum retention outcome, we also evaluated the 24-month retention estimates. We included women who enrolled in HIV services in whom ART was initiated any time between July 1, 2013 and December 31, 2015, and with follow-up data until December 31, 2017 (i.e. at least 24 months of theoretical follow-up). Of 44,377 women included, 29,112 (66%) were analysed: 21,046/31,186 (67%) for ‘B+ pregnant’ and 8,066/13,191 (61%) for ‘own health’ women. The probability of being retained in care at 24 months significantly varied overtime for both groups of patients. For the ‘B+ pregnant’ women, the probability of retention at 24 months after ART initiation increased from 49% to 52% when ART was initiated in 2013 and 2014, respectively; then this probability decreased to 46% when ART was initiated in 2015. For women starting ART for their own health, similar trends in retention were observed over time with significantly higher results (Figure 5.2).

In the manuscript, we included HIV-positive women initiating ART during pregnancy to characterize Option B+ enrolment and to compare with non-pregnant women initiating ART for their own health. We excluded women who initiated ART during breastfeeding (n=280) and those already on ART before pregnancy (n= 7,599).

As the table 5.1 shows, women initiating ART while breastfeeding (‘B+ BFW’) had a median age at ART initiation of 25 years (IQR: 22 – 30), 38% were in WHO stage 3 or 4, and their median CD4 cell count was 303 cells/mm³ (IQR: 221-411). Only half of them initiated ART on the same day of HIV diagnosis. Among the ‘B+ BFW’ women who had information on the date of delivery (64%, 179/280), the median time of start of ART after birth was 46.5 days (IQR: 0-186). The probability of retention in care at 12 months after ART initiation was 80% with no significant difference by year of ART start (log-rank test, p=0.27) (Figure 5.3).

For HIV+ women who initiated ART before diagnosis of pregnancy, age at ART initiation was 29 years (IQR: 23 – 37). The median time between ART initiation and pregnancy detection was 2 months (IQR: 28 - 137) and median gestational age was 26 weeks (IQR: 19-31). Sixty-one percent were WHO stage 1 or 2 and median CD4 cell count was 320 cells/mm³ (IQR: 174-509). The majority of this group were enrolled in primary care health facility in an urban setting. The probability of being retained in care at 12 months post-ART initiation significantly improved over the years increasing from 68% when ART was initiated in 2013 to 84% when ART was initiated in 2016 (log rank test, p<0.00001) (Figure 5.3).

Figure 5.2: Estimated Kaplan Meir survivor curves for retention over time for HIV+ women up to 24 months after ART initiation, by status and period of ART initiation, Mozambique 2013-2017 (n=86 sites, 29,112 women).

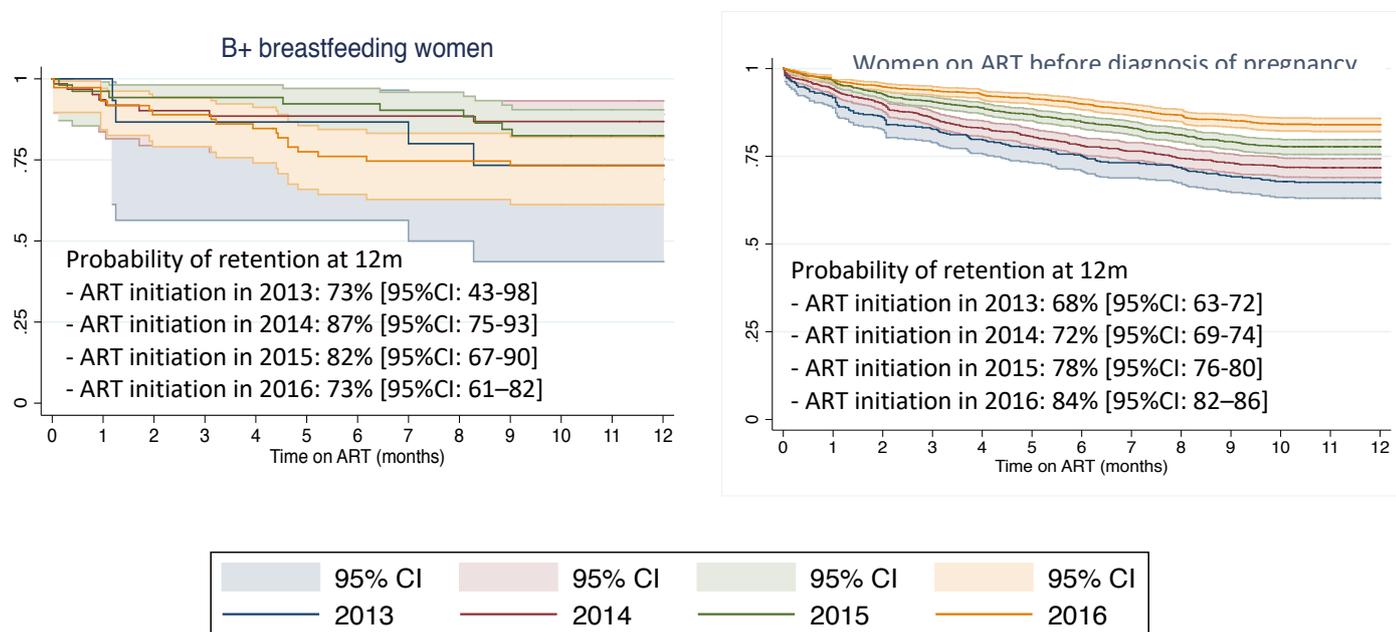


Note: Log-rank test for equality of survivor functions, by patient status ('B+ pregnant" vs. "own health"): for women initiating ART in 2013: $p < 0.00001$; for women initiating ART in 2014: $p < 0.00001$; for women initiating ART in 2015: $p < 0.00001$; for women initiating ART in 2016: $p < 0.00001$.

Table 5.1: Principal characteristics of B+ breastfeeding women ('B+ BFW', n=280) and of women already on ART before diagnosis of pregnancy (n=7,599), Nampula and Zambézia provinces, Mozambique (n=86 sites)

Patient characteristics	B+ BFW (N=280)	Already on ART before diagnosis of pregnancy (N=7,599)
Median age at ART initiation, years [IQR]	25 [22 - 30]	29 [23 - 37]
Marital status (%)		
Couple/married	187 (67)	3,513 (46)
Single/widowed	65 (23)	2,565 (34)
Other/no info	28 (10)	1,521 (20)
Education level (%)		
None	35 (13)	833 (11)
Primary & above	195 (69)	5,246 (69)
No information	50 (18)	1,520 (20)
Employment status (%)		
Unemployed	198 (71)	4,660 (61)
Working/student	65 (23)	2,242 (30)
No information	17 (6)	697 (9)
CD4 cell count (%)	N=201 303 [221-411]	N=3,623 320 [174-509]
WHO clinical stage (%)		
Stage 1-2	139 (50)	4,632 (61)
Stage 3	88 (31)	1,629 (22)
Stage 4	20 (7)	185 (2)
Missing	33 (12)	1,153 (15)
ART treatment		
Follow-up under ART (m), median [IQR]	12.7 [3.9 – 21.3]	9.9 [4.9 – 18.5]
Same day ART initiation	142 (51)	-
TB treatment @ ART start (%)	12 (4)	478 (6)
PMTCT site (%)		
New B+ site	1 (0)	56 (1)
Switched from Option A to B+	268 (96)	6,849 (90)
No PMTCT services	1 (0)	133 (2)
Missing information	10 (4)	561 (7)
Type of Health Facility (%)		
Public I (HC clinic)	206 (74)	6,392 (84)
Public II (dist./prov. hosp.)	51 (18)	615 (8)
Public III (teaching/nation. ref. hosp.)	13 (5)	31 (1)
No information	10 (4)	561 (7)
Location (%)		
Urban-city	100 (36)	4,584 (60)
Semi-urban	28 (10)	785 (10)
Rural	142 (50)	1,669 (22)
No information	10 (4)	561 (8)
Point of service providing ART (%)		
Only HIV clinic	23 (8)	7 (0)
HIV clinic & all MCH services	58 (21)	2,084 (27)
HIV clinic & not all MCH services	189 (68)	4,947 (65)
No information	10 (4)	561 (7)

Figure 5.3: Estimated Kaplan Meir survivor curves for retention over time for HIV+ women up to 12 months after ART initiation, by status and period of ART initiation, Mozambique 2013-2017 (n=86 sites, 280 B+ BFW and 7,599 women already on ART before diagnosis of pregnancy)



Note: Log-rank test for equality of survivor functions, by year of ART initiation (2013/2014 vs. 2015/2016): for 'B+ breastfeeding' women: $p=0.27$; for women already on ART before diagnosis of pregnancy: $p<0.00001$.

5.1.1 Discussion

The results of the manuscript combined with the additional analyses presented here provide a broader picture of the successes and challenges of Option B+ implementation in Mozambique. Over the course of 4 years, Option B+ PMTCT program showed performance improvement for pregnant women initiating ART in ANC, women initiating ART for their own health and those already on ART before diagnosis of pregnancy detection. Women already on ART before pregnancy detection showed similar patterns of retention than 'B+ pregnant' women although probabilities of retention in care was higher in this group than in the 'B+ pregnant' group. It is possible that a proportion of these women may have been misclassified as not being 'B+ pregnant' due to delayed detection of pregnancy. This calls for an earlier and more systematic screening of pregnancy and an improvement in reporting of test results in the HIS.

The 'B+ BFW' women have a particular behaviour pattern. We can hypothesise that when breastfeeding women are initiated on ART, the benefit of ART on preventing vertical transmission to their HEI outweighs their desire to drop out of care. The timing of ART initiation for many of them corresponded to the first or second vaccination visit of their child. This calls for a better integration of HIV care and MCH services (with post-partum care or immunization for example) with early detection HIV infection for women who have already given birth. In addition, rapid treatment initiation to obtain rapid viral suppression is of paramount importance to reduce the risk of vertical transmission to less than 5%.

As presented previously, the major drop-outs occur in the first 3 months of ART initiation for which the majority of our 'B+ pregnant' cohort corresponds to the last trimester of pregnancy.

The delicate period around delivery can be challenging. Major physiological changes, excess fatigue when performing daily household chores can contribute to disengagement from care. Pre- and post-partum depression remains often undiagnosed but has been increasingly reported as a major factor contributing to disengagement from care[58]. In addition, women often move to their parents or in laws' location to give birth and/or for nursing further increasing the risk of dropping out of care for both the mother and her new-born.

As the 'Test and Treat all' strategy expands, an increasing number of women is expected to be on ART when they become pregnant, as we have observed in our analysis. The steady improvement of retention in care over time observed in our cohorts is certainly a positive outcome, however healthcare providers will face challenge for ensuring viral suppression in these women throughout both pre-natal and post-natal care. Accelerated efforts are thus needed to improve immediate (i.e. first three months) and long-term retention seeking innovative ways of delivering a patient tailored care to women and their children if we are to reach eMTCT in Mozambique.

5.2 Interventions to improve PMTCT outcomes under option B+ strategy: a systematic review

5.2.1 Introduction

In the first work of the thesis, we evaluated the effectiveness of the PMTCT Option B+ programme in two high HIV burden provinces in Mozambique over the first four years of program implementation. The results showed achievement of high HIV testing and ART initiation rates in ANC with challenges remaining in improving immediate engagement in care and long-term retention in care.

The lack of PMTCT engagement in care of women has been reported specifically under the Option B+ strategy. The barriers are predominantly women-specific such as younger maternal age [49,59], same day ART initiation [54,109–112] or missing CD4 cell count at ART initiation; poor birth outcome (miscarriage or stillbirth) was also associated to increased risk of lost-to-follow [113] as well as lack of confidentiality [111], perceived or self-stigma [50–52]; finally, lack of disclosure to partner or family has been frequently reported as a reason for dropping out of care [53,59,113]. Other health system and programme implementation challenges have also been identified such as lack of client friendly services or health workers insufficiently training on Option B+ or long waiting time at the clinic [51,53,54,112,113]. Therefore, interventions aimed at individual and health system constraints should help improve women's engagement in PMTCT care. Such interventions are even more so needed, since 2016 with the scale-up of the "test and treat" strategy, to address the additional challenge of the significant increase in patient volume at health facility level. This increase has in turn further diminished the quality of services offered in the last few years and triggered the need to promote further decentralization of services to the community level [114–116].

While previous PMTCT Options A and B provided anti-retroviral medication for a limited time, the added challenge in Option B+ is to maintain HIV-positive women under lifelong ART. Thus, under Option B+, specific interventions to improve women's retention in care should cover not only short term but also have a long term post-partum effect to sustain engagement in care guaranteeing the expected benefits of viral load suppression, lower risk of HIV transmission to uninfected male partners and lower risk of MTCT of HIV in subsequent pregnancies. This systematic review focuses on specific interventions to improve PMTCT

outcomes under Option B+ with a special focus on women's retention in care and infant testing uptake.

5.2.2 Manuscript

Interventions to improve outcomes of preventing mother-to-child transmission of HIV under the Option B+ strategy: a systematic review

Laurence Ahoua, MD, MPH,¹ Shino Arikawa, MPH,¹ Renaud Becquet, PhD,¹ Francois Dabis, MD, PhD¹

¹University of Bordeaux, INSERM, Bordeaux Population Health Research Center, Team IDLIC, UMR 1219, Bordeaux, France

Corresponding author: Laurence Ahoua, MD, MPH

University of Bordeaux, INSERM, Bordeaux Population Health Research Center, Team IDLIC, UMR 1219, 146 rue Léo Saignat, 33076 Bordeaux cedex, France. Tel: +351 919 231 533. ORCID iD: 0000-0002-6565-502X

Email: laurence_ahoua@yahoo.fr

Email addresses of authors :

Shino Arikawa : shino.arikawa@u-bordeaux.fr

Renaud Becquet : renaud.becquet@u-bordeaux.fr

Francois Dabis : francois.dabis@u-bordeaux.fr

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ARTICLE SUMMARY SECTION

Abstract

Objective: To systematically review interventions aiming to improve maternal retention and infant testing uptake in the prevention of mother-to-child transmission (PMTCT) programmes under the Option B+ strategy.

Design: Systematic review

Methods: Electronic databases and grey literature were searched to identify studies published from January 2010 to December 2018. Study outcomes were maternal retention in care at 6, 12, and 24 months since antiretroviral therapy (ART) initiation and uptake of early infant diagnosis (EID) (age 4–8 weeks) and final infant testing (age 12–18 months). Outcomes were summarised according to intervention type.

Results: Fifteen studies were included. Four studies reported on maternal retention through peer support, deployment of community health workers (CHWs), and point-of-care CD4 testing, which yielded retention rates of 74–79%, 61–78%, and 70–74% at 6, 12, and 24 months since ART initiation, respectively. The rates were not significantly different from those reported in a standard-of-care context. Twelve studies reported on outcomes related to infant testing uptake through peer support, CHW outreach, SMS, healthcare provider-oriented strategies, or a combined package of interventions. The proportions of HIV-exposed infants tested were 49–94% and 68–95% for age 6–8 weeks and 12–18 months, respectively. A high infant testing uptake was observed under combined interventions (>94% at ages 2 and 18 months). High heterogeneity in study outcomes was observed, mostly due to important variability in definitions. Both maternal and infant outcomes were likely to be overestimated because the outcomes were measured without considering consistency in maternal engagement.

Conclusions: A combined package of interventions could effectively address different barriers to maternal engagement. Outcome definitions should be standardised to reduce inter-study heterogeneity and enable correct comparability of results for clear policy guidance. Indicators should be quality-based and process-oriented to allow precise understanding of maternal engagement to PMTCT care.

Keywords: Systematic review; PMTCT; Option B+; retention; HIV-exposed infant; Early Infant Diagnosis; infant testing.

Strengths and limitations of this study

- This is a systematic review of interventions aimed at improving maternal engagement to care under the Option B+ strategy, with a particular focus on maternal ART retention and infant testing uptake.
- Electronic databases such as MEDLINE, EMBASE, and Cochrane CENTRAL as well as grey literature were searched to identify relevant studies on outcomes of prevention of mother-to-child transmission under the Option B+ strategy.
- The results of the review provide valuable data on maternal engagement in the PMTCT of HIV and can help in defining outcomes for clear policy guidance.
- We identified studies in which insufficient information on the health system that delivered the interventions limited the generalisability of the results.

INTRODUCTION

In 2013, the World Health Organization (WHO) revised its guidelines to recommend Option B+ as a strategy to prevent mother-to-child transmission (PMTCT) of HIV.[1] By providing all HIV-infected pregnant women with lifelong triple antiretroviral therapy (ART) irrespective of CD4 cell count, this new strategy aimed to ensure effective PMTCT and achieve viral suppression in mothers while simplifying service delivery. However, emerging evidence suggests higher drop-outs of women under Option B+ than in the general population of adults initiating ART for their own health.[2–4] Poor retention of mothers in PMTCT programmes and low uptake of infant HIV testing can be considered as an indicator of suboptimal performance of PMTCT programmes under Option B+, which represents a threat to the target of the Joint United Nations Programme on HIV/AIDS (UNAIDS) of reducing the number of newly infected children to <20,000 by 2020.[5] Various interventions have been tested to improve mother-infant engagement in care. In this study, we aimed to systematically review these interventions with a particular focus on their effectiveness on maternal retention in care at 6, 12, or 24 months since ART initiation as well as uptake of early infant diagnosis (EID) (4–8 weeks of age) and final infant testing (12–18 months of age).

METHODS

Electronic databases (MEDLINE, EMBASE, and Cochrane CENTRAL trials) were searched to identify relevant papers using combinations of the following terms: PMTCT, HIV, Option B+, retention, lost (or loss) to follow-up, and early or final infant HIV diagnosis (Supplementary Table 1). Bibliographies of relevant articles were reviewed to identify additional studies. In addition, grey literature including those available in Google Scholar and abstracts from international conferences were searched. We included papers published between January 2010 and December 2018 in English, French, or Portuguese. When studies had comparative data on interventional and standard-of-care settings, only data related to the intervention group were extracted. If multiple publications were found to be related to the same data source, the publication with the most complete data was selected.

Study outcomes were maternal ART retention and infant testing uptake under Option B+. For maternal ART retention, we searched for papers that reported a proportion of HIV-positive women who remained in care at 6, 12, and 24 months after ART initiation. For infant testing uptake, outcomes were defined as the proportion of infants who received EID at 4–8 weeks and those tested at 12–18 months of age. Outcome definition and its methodologies were study-specific. When necessary, we contacted authors to obtain additional information.

We used a modified version of the Cochrane data extraction form to report the characteristics and outcomes of included studies.[6] A narrative synthesis of the results was generated according to the types of interventions.[7] We judged that the data were not suitable for meta-analysis due to variability in study contexts and methodologies used. To assess the quality of evidence, we used the Evidence for Policy and Practice Information and Co-ordinating Centre (EPPI) approach.[8,9] The approach had four criteria: trustworthiness, appropriateness, relevance, and overall weight. Each criterion was assessed using the Jadad scale, with a score between 0 and 5.[10,11] A score of 0 or 1 was considered as ‘low’, 2 as ‘medium,’ and 3–5 as ‘high’ quality.

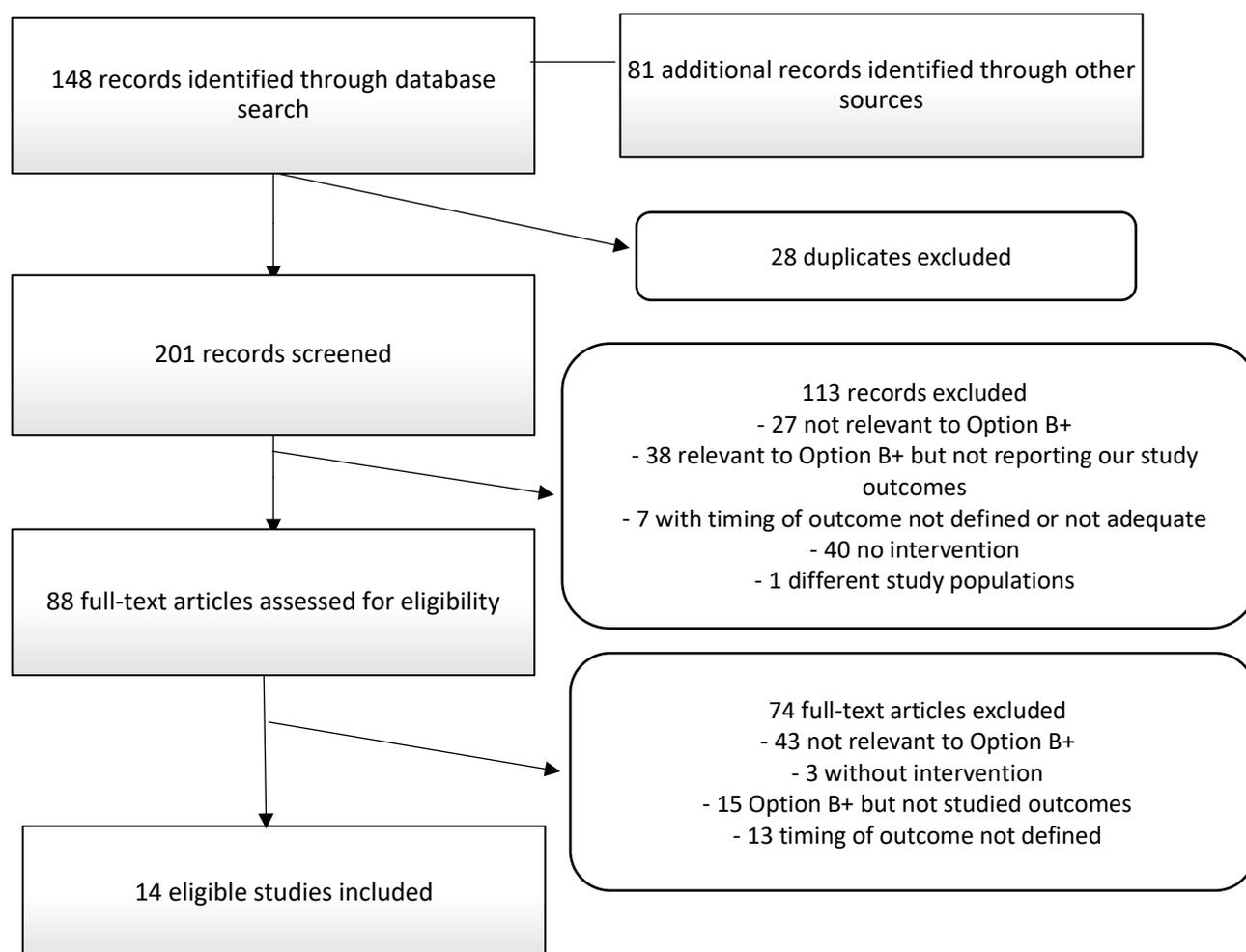
L.A. performed the literature searches and extracted the data. S.A. verified the selection process and checked the eligibility, inclusion, and exclusion criteria for 15% of a random sample of

included and excluded studies. Where discrepancies were found, a final decision was obtained by consensus.

RESULTS

Overview of the characteristics of included studies

We identified 229 eligible records (Figure 1). After removing duplicates, we screened the titles and abstracts of 201 records and retained 88 for full-text review. Of these, 74 were excluded for not being relevant to Option B+ (n=43), for not reporting our study outcomes (n=15), for lack of information on the timing of the outcome measure (n=13), and for being without interventions (n=3). Finally, a total of 14 articles were included in our review, and these articles represented 6311 HIV-positive pregnant or breastfeeding women and 1920 HIV-exposed infants (HEIs) who have been exposed to at least one type of intervention to improve PMTCT outcomes. All studies were conducted in sub-Saharan Africa except for one which was undertaken in India (Supplementary Table 2).[12] There were seven cluster-randomised controlled trials,[12–18] six cohort studies,[19–23] one pre/post-quasi-experimental study,[24] and one cross-sectional evaluation.[25] Additional information on the included studies is available in Supplementary Table 3.

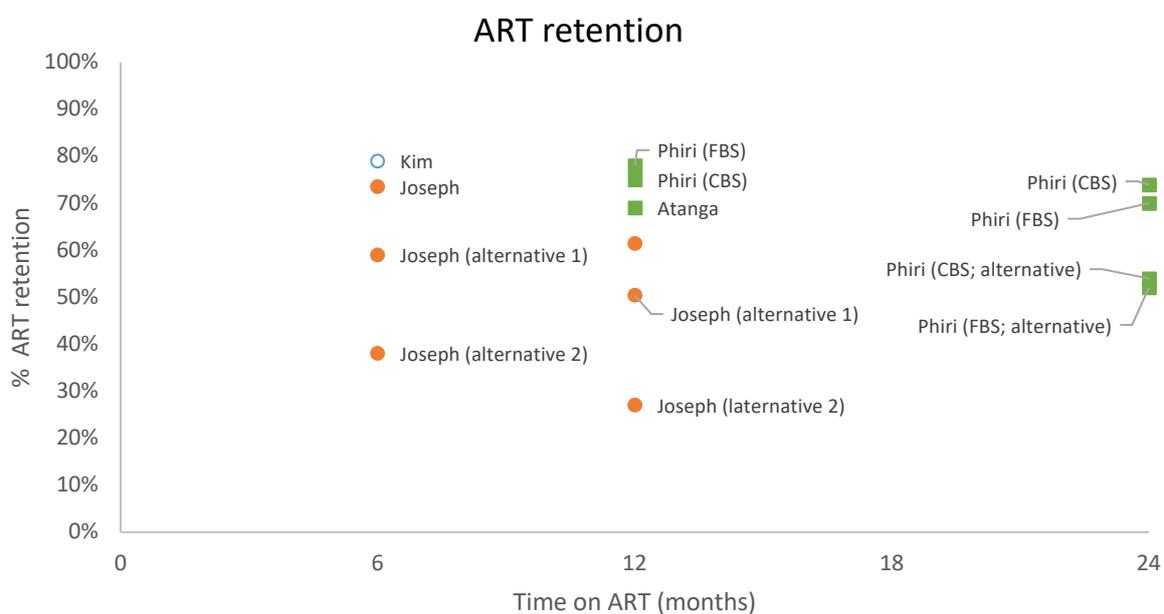
Figure 1 Flow chart of study selection and inclusion

Overview of the interventions undertaken

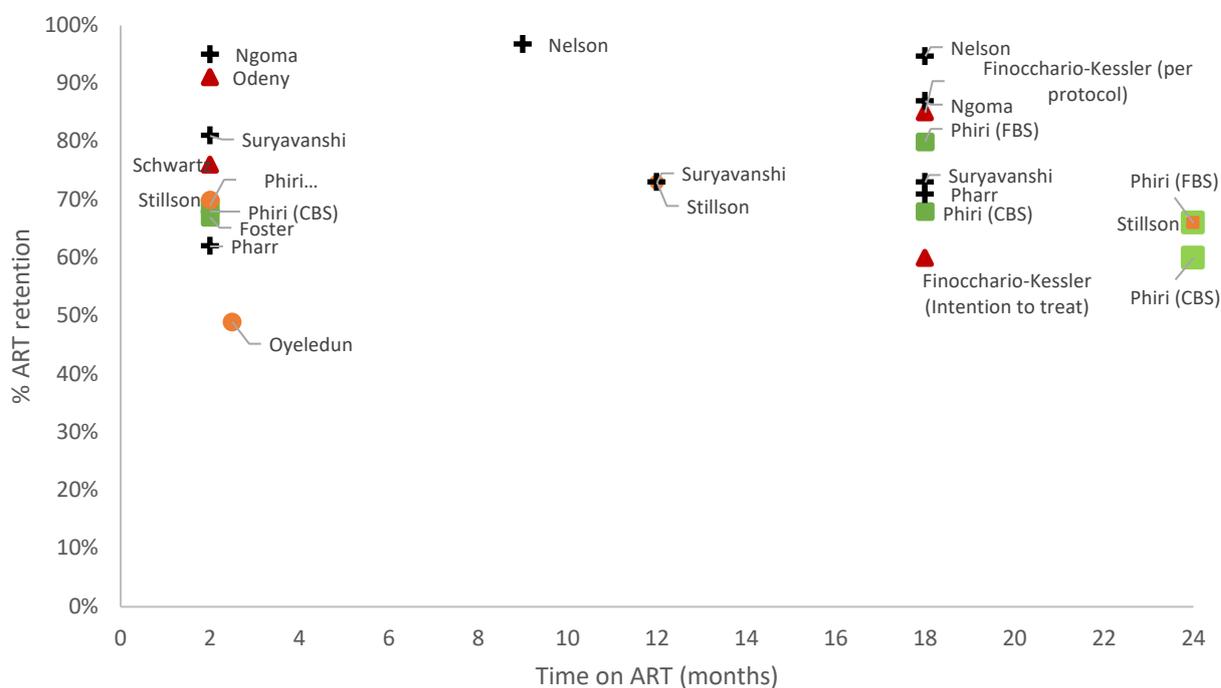
We identified various strategies that were used to improve maternal ART retention and infant testing outcomes within the context of Option B+ (Supplementary Table 2). There seemed to be two types of barriers that the strategies attempted to address. The first barrier included patient-level factors such as lack of awareness, HIV-related stigma and discrimination, and transport cost. The second barrier was related to the health system such as limited human resources and suboptimal quality of care. Community-level interventions through peer educators or community health workers (CHWs) seemed to be a frequent approach for addressing patient-level barriers.[13,14,19,24] These interventions supported women by improving treatment literacy, providing psychosocial support, and encouraging disclosure and adherence to treatment. In addition, to improve patient awareness and patient-healthcare provider communication, interventions called mHealth (mobile health) were largely deployed, which used telephone calls and/or SMS to remind mothers of their clinical appointments.[15,16,23] To strengthen the capacity of healthcare services, point-of-care (POC) CD4 testing was used to facilitate turnaround time for CD4 test results.[17] Moreover,

continuous quality improvement (CQI) was used to support utilisation of data to monitor progress and improve decision-making.[18] Similarly, mentorship programmes for PMTCT service providers offered guidance and support to improve the quality of services.[25] Certain studies used a combination of interventions. One such example was the postnatal clubs (PNCs), where several health services were integrated and made accessible simultaneously.[20] In another setting, SMS reminders were sent to mothers combined with economic incentives such as stipends for food and transport.[21] A church-driven educational programme provided opportunities for free laboratory screening.[22] Finally, a package of services known as COMBIND (COMmunity home Based INDia) included the deployment of community-based outreach workers (ORWs), enhanced patient-provider communication, and mHealth strategies to effectively address both patient- and health service-level factors simultaneously.[12] Figure 2 illustrates the study outcomes of retention in care and infant testing by type of interventions.

Figure 2 Outcome results by type of interventions for ART retention of HIV-positive women and infant testing for HIV-exposed infants (n=14 studies)



HIV-exposed infant testing



Outcome synthesis by type of interventions

Patient-oriented strategies

Peer support

Three studies reported maternal ART retention outcomes through peer support programmes. In Cameroon, community peer educators were employed to track women who had missed appointments, leading to 69% of women being retained at 12 months since ART initiation.[19] In Malawi, a study assessed how facility-based and community-based peer support influenced maternal retention and infant testing outcome. In both models, ‘mentor mothers’ provided one-on-one patient education and visit reminders and organised support groups at the health facility or in the community.[13] These mentor mothers were HIV-positive women who recently underwent PMTCT and were on ART. For maternal retention outcome at 12 months since ART initiation, the facility-based model yielded higher results than the community-based model: 78% vs. 75%, respectively. At 24 months, however, the results were better with the community-based model than the facility-based model: 74% vs. 70%, respectively. For infant testing uptake at 6–8 weeks post-partum, both approaches led to similar outcomes: 68% (community-based) and 69% (facility-based). At 12–18 months post-partum, the facility-based model showed a much better outcome than the community-based model: 80% vs. 68%, respectively. In Zimbabwe, the mentor mother programme was used both at the health facility and in the community which led to 67% of HEIs being tested at 6–8 weeks of age.[14]

Community health workers

One study reported results of interventions on CHWs. In Malawi, a CHW followed, on average, 35–50 HIV-positive women to ensure that women adhere to the entire PMTCT process, starting from HIV testing to the final confirmation of the serostatus of the infant. This intervention led to a 6-month maternal retention of 79%.[24]

mHealth

Two studies reported infant testing outcomes under the mHealth strategy. In South Africa, mothers received telephone calls and weekly SMSs as a support to remain in care from pre-delivery to 6–8 weeks post-partum.[23] This intervention led to a 76% increase in infant testing by 6–8 weeks of age. In the TextIT (Texting to Improve Testing) study in Kenya, women received a series of tailored messages for a specific time point during pregnancy or post-partum, in a language of their choice.[16] This highly personalised approach has led to extremely high results, reaching 91% of HEIs being tested by 6–8 weeks of age. Similarly, an HIV infant tracking system (HITSsystem) in Kenya tracked HEIs from enrolment to final HIV diagnosis, monitoring key interventions including EID and timely notifications of results by SMS to facilitate rapid ART initiation in case of positive testing.[15] This intervention yielded a high uptake, and 85% of HEIs were tested by 18 months of age.

Healthcare-oriented strategies

Four studies reported maternal and infant outcomes through strategies designed to improve the quality of healthcare. A study in Zimbabwe focused on the loss of patients between uptake of biological testing and delivery of test results and assessed the effects of POC CD4 testing on maternal retention in care at 6 and 12 months from ART initiation.[17] The retention was 74% and 61%, respectively. In Nigeria, a specific assessment was undertaken for CQI, which enabled an improved understanding of the drivers of low retention in care, leading to 49% of HEIs tested between 6 and 10 weeks of age.[18] In Malawi, PMTCT service providers participated in a national mentorship programme where a team of mentors provided hands-on training on data collection, testing procedures, documentation, and patient tracking.[25] This comprehensive training package has led to 70%, 73%, and 66% of HEIs being tested at 2, 12, and 24 months of age, respectively.

Combined interventions

Four studies reported the outcomes related to infant testing within the context of an intervention package. The PNCs in South Africa were formed by 2–10 mother-infant pairs who met monthly or quarterly until 18 months post-partum.[20] The women in the PNCs had access to integrated maternal, child, and HIV health services including mental health, nutrition advice, and early childhood development support.[26] The PNCs have yielded very positive results, and the proportion of HEIs tested reached 97% and 95% at 9 and 18 months of age, respectively.

In Zambia, the intervention package consisted of enhanced counselling for ART adherence, SMS reminders on clinic appointment, and provision of stipends for food and transport equivalent to US\$6 per visit.[21] Mothers were enrolled during pregnancy and followed until 18 months post-partum. This package of interventions led to the high uptake of infant testing: 95% and 87% by 6–8 weeks and 18 months of age, respectively.

In Nigeria, the Healthy Beginning Initiative (HBI) was used to improve infant testing. In this initiative, women received information on healthy habits delivered by lay health workers while participating in a baby shower at a local church.[22] In addition, these women were offered free laboratory screenings for HIV, hepatitis B, and sickle cell genotype. With this initiative, the uptake of infant testing reached 62% at 6–8 weeks and 71% at 18 months of age. Finally, the PMTCT programme in India used a combination of different interventions (COMBIND), including counselling by ORWs, provision of educational material for PMTCT as well as the use of an mHealth application for ART adherence, exclusive breastfeeding, postpartum care, and the need for EID.[12] The proportion of infants tested with EID at 6 weeks of age was 81%, and those tested with infant HIV testing at 12 and 18 months of age was 73%.

Assessment of quality of evidence

Based on the EPPI criteria, we assessed the quality of evidence of the 15 studies included in this review. Six studies were considered as having a high quality overall,[12–15,17,18] six were medium,[16,19,21–23] and three were low[20,24,25] (Supplementary Table 4). The high-quality studies provided sufficient information on key characteristics of the programme settings as well as methodologies, and the results seemed generalisable to other similar settings. Moreover, these studies used the recommended international definition of infant testing uptake. For the remaining studies, lower classifications were assigned due to insufficient information on study context, outcome definition, and study design.

DISCUSSION

We systematically reviewed interventions that aimed to improve maternal engagement to care in the context of Option B+, with a particular focus on postpartum retention and uptake of infant testing. Our results have shown that numerous attempts have been made in different settings yielding various outcomes. The Option B+ strategy presents an additional challenge since the women who are enrolled are required to remain in care under ART for life under the Option B+ strategy unlike in previous PMTCT options.

We identified four studies that reported the effects of interventions on maternal retention. Through peer approach, deployment of CHWs, and enhanced access to POC CD4 testing, the reported retention rates ranged 74–79% at 6 months, 61–78% at 12 months, and 70–74% at 24 months after ART initiation, respectively. The pooled estimates on retention under Option B+ in Africa, reported by Knettel et al. within a context of standard of care were 72.9% (95% CI: 66.4–78.9) at 6 months and 76.4% (95% CI: 69.0–83.1) at 12 months after ART initiation.[27] Thus, the rates found in our study were not significantly higher than those in a non-interventional setting, suggesting that interventions might not automatically guarantee improved retention outcomes. Studies have shown that loss to care is caused by different factors including non-disclosure of patient's HIV status,[14,17,28–32] stigma or fear of discrimination,[19,33,34] lack of involvement of partner and social support,[18,36,34] and lack of money for transport.[19,28,29] In addition, ART-related side effects[33] or perinatal depression[35,36] could explain why women drop out of care, especially in the post-partum period. Moreover, health system-related issues including long waiting hours,[30,37] long turnaround time for infant PCR (polymerase chain reaction) test result,[38] or inadequate opening hours of health services[28,29,37] can discourage women from remaining in care. Because of such complexity behind maternal disengagement, interventions need to be carefully designed and address a pathway to improvement. While our review did not find any studies

that investigated the effectiveness of the combined approach on maternal retention, it confirmed the potential benefits of such an approach on infant testing uptake. One study using a package of interventions had achieved extremely high infant testing outcomes, reaching >90% of HEIs being tested by 18 months of age.[20]

Our review found that infant testing outcome reported by the 11 studies varied significantly: 49–94% by 6–8 weeks of age and 68–95% by 12–18 months of age. Such variability might be attributed to the different nature of the intervention, small sample size,[23] or particular context in which the study was undertaken.[20,22,23] In addition, comparison of the study results was constrained by heterogeneity in outcome definitions (Supplementary Table 5). In most studies, retention in care was based on point retention defined as whether women came to the clinical appointment at a specific time point.[19] Other studies took into account the level of consistency in clinical attendance by considering the gap between two clinical appointments (e.g. for >60 days)[13] or the number of visits done on time.[17] We found that these differences in outcome definition directly influenced retention estimates. Phiri et al. reported that retention estimates fluctuated by 20% depending on the definitions used.[13] Moreover, Joseph et al. have highlighted considerable fluctuation in retention estimates depending on the threshold used in terms of timeliness of scheduled visits.[17] Currently, there is no consensus on the definition of retention in PMTCT programmes.[39–42] While retention can be simply defined as being present at a given appointment, such definition tends to overestimate retention rates by failing to take into account the process of care that is necessary to reach the ultimate goal of elimination of mother-to-child transmission of HIV. In addition, we note that only one study reported long-term maternal retention (i.e. 24 months after ART initiation). Option B+ has a particular challenge of retaining women on lifelong ART in a sustainable manner. As an increasing number of countries adapt this new strategy, the impact of different interventions on long-term retention merits further investigation.

Similarly, infant testing outcomes were measured very differently. Some studies used a total number of HIV-positive women enrolled as a denominator,[12,14,15,23] while others used the number of live births[16,18,21,22] of HEIs alive at a specific time point.[13,20] Postnatal deaths were excluded from the denominator in certain studies, while they were accounted for in others. In our review, only three used the number of infants born to HIV-infected women as a denominator, in accordance with the official recommendation by the WHO.[43] From the programme point of view, however, the proportion of infant testing uptake might not represent the true value of engagement to care. Additionally, process indicators in the continuum of care, such as timely enrolment of HEIs, initiation of co-trimoxazole prophylaxis, and rapid turnaround time of test results should be taken into account to define engagement. In this context, the definition used by Finocchiaro-Kessler et al. seems to provide an alternative approach as it incorporates the notion of receiving complete EID services by 18 months. Unsurprisingly, engagement was reduced when such a complex definition was used, and the reported rate reduced from 85% to 60%, suggesting overestimation of engagement to care when a simple definition of HEIs tested by 18 months of age was used.[15]

While we found potential benefits of the combined approach, it is worth noting that 9 out of 15 studies were rated as having a medium to low quality of evidence. Such a low rating was mainly due to insufficient information on the health system in which the interventions were delivered. Effectiveness of an intervention depends largely on the local context where its feasibility and acceptability are determined.[19,44] Thus, it was not possible for us to fully understand the underlying mechanism that ensures effectiveness in certain interventions, limiting our ability to generalise the study results to other settings.

CONCLUSIONS

Ensuring maternal engagement throughout the continuum of care is critical in achieving the goal of elimination of HIV/AIDS by 2030. Our review has suggested that a package of interventions could effectively address the different barriers to maternal engagement. Outcome definitions should be standardised to ensure correct comparability of results for clear policy guidance. Moreover, quality-based and process-oriented indicators should be used to allow a precise understanding of maternal engagement.

Legend for Figure 2

Study legends: ■ = peer and mentor support; ● = community health workers and lay workers;
 ▲ = mHealth; ● = provider-oriented strategies; + = combined interventions

Notes: Joseph (alternative 1) corresponds to the study definition requiring 75% of visits to be on time; Joseph (alternative 2) corresponds to the study definition requiring 100% of visits to be on time. Phiri (CBS) corresponds to community-based support intervention arm; Phiri (FBS) corresponds to the facility-based support intervention arm. Phiri (CBS; alternative) corresponds to the community-based support intervention arm using the trial definition of retention (i.e. alive and on ART without any gap in care >60 days after a scheduled visit among those who started ART); Phiri (FBS; alternative) corresponds to the facility-based support intervention arm using the trial definition. Finocchario-Kessler (intention to treat) corresponds to percentage of HEIs who received complete EID services until 18 months post-partum defined by the receipt of all indicated age-specific interventions until 18 months post-partum (for HIV-negative infants) or ART initiation (for HIV-positive infants); Finocchario-Kessler (per protocol) corresponds to the percentage of HEIs tested by 18 months of age. All other definitions presented in the graphs are those of the Ministry of Health national guidelines.

Author Contributions

L.A. initiated and led the study. L.A. and S.A. planned the analyses. L.A. performed the literature searches and extracted the data. S.A. verified the selection process and checked the eligibility, inclusion and exclusion criteria for 15% of a random sample of included and excluded studies. Where discrepancies were identified, a final decision was obtained by consensus. L.A. and S.A. worked independently to assess the quality of evidence and resolve disagreements. L.A. and S.A. wrote the first draft of the paper. All authors interpreted the data and input to subsequent drafts of the paper and approved the final version.

Competing interests

The authors declare no competing interests.

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Patient consent for publication

None required.

Disclaimer

None.

Data sharing statement

Analytical process and code index are provided in supplementary materials. No additional data are available. The datasets analysed during the current study are currently not publicly available but can be available from the corresponding author on request.

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2017;74(Suppl 1):S29–36.

SUPPLEMENTARY MATERIAL**Supplementary Table 1** Literature search strategy

Search set	Medline/PubMed	Other databases
1	(Infectious AND disease AND transmission AND vertical) OR (vertical infectious disease transmission) OR (vertical AND transmission) OR (vertical transmission)	(HIV-positive pregnant) OR (HIV-positive breastfeeding women)
2	INFECTIOUS DISEASE TRANSMISSION, VERTICAL	vertical infectious disease transmission
3	Sets 1-2 combined with ‘OR’	Sets 1-2 combined with ‘OR’
4	HIV OR human immunodeficiency virus	Prevention of Mother-To-Child Transmission or PMTCT
5	HIV	(mother-to-child-transmission) OR (MCH)
6	HIV INFECTIONS	Sets 3-5 combined with ‘OR’
7	INFECTIONS/THERAPY	HIV-exposed infant
8	Sets 4-7 combined with ‘OR’	(early infant diagnosis) OR (EID)
9	(Infant test) OR (infant testing) OR (early infant diagnosis) OR (HIV-exposed infant)	final infant HIV diagnosis
10	INFANT	Sets 7-9 combined with ‘OR’
11	DIAGNOSTIC TECHNIQUES AND PROCEDURES	(option B+) OR (option B-plus) OR (option B plus)
12	Sets 9-11 combined with ‘OR’	Retention
13	RETENTION IN CARE OR (retention)	intervention
14	(intervention) OR CLINICAL STUDY	Sets 3, 6, 11, 12 and 13 combined with ‘AND’
15	(option B+) OR (option B-plus) OR (option B plus)	Sets 6, 10, 11, 12 and 13 combined with ‘AND’
16	Sets 3, 8, 13, 14 and 15 combined with ‘AND’	
17	Sets 3, 8, 12, 14 and 15 combined with ‘AND’	

In addition, other electronic databases were searched: Embase, ScienceDirect, Web of Science, and Cochrane databases.

Supplementary Table 2 Summary of study characteristics of included studies (n=14 studies)

No.	Name of the article	Country (location and sites)	Study design	Year of Option B+ initiation <u>Study enrolment</u>	Sample size	Interventions to increase retention or reduce FU
Peer and mentor support						
1	Atanga 2017[49]	Cameroon; 5 sites (Kumba Health District, South West region)	A prospective cohort study	<u>2012</u> 2013 (Oct)-2014 (Dec)	268 HIV-positive pregnant and breastfeeding women	Team of peer educators (PE) trained to implement community follow-up of clients and especially tracking cases of women missing their clinic appointments and getting them back to care (telephone calls or home visits)
2	Phiri 2017[117] ^a	Malawi (3 of the 5 health zones: Central West, South East, and South West)	A 3-arm stratified cluster-randomised controlled trial	<u>2011</u> 2013 (Nov)-2014 (Nov)	1269 HIV-positive women (pregnant=1094, breastfeeding=175)	Intervention comparing facility-based and community-based models of peer support with SOC: - SOC : participants received routine HIV care according to Malawi MOH guidelines - Facility-based peer support : women received SOC and met with 'mentor mothers' (i.e. women living with HIV who recently underwent PMTCT and were on ART) who provided one-on-one support at each clinic visit, led weekly clinic-based support groups, and contacted women within 1 week of a missed appointment – model adapted from the mothers2mothers model of clinical service delivery - Community-based peer support : women received SOC and met with 'expert mothers' (i.e. women living with HIV who recently underwent PMTCT and were on ART) who conducted routine home visits to study participants to provide HIV education and clinic visit reminders; led monthly community-based support group meetings; were responsible for contacting women in the community within 1 week of a missed scheduled clinic visit.
3	Foster 2017[118] ^b	Zimbabwe – Eastern region (Mutare and Makoni Districts of Manicaland Province); 27 clinics	A cluster-randomised controlled trial	<u>2013</u> 2014 (July)-2015 (Oct)	348 HIV-positive PW (188 intervention arm, 160 SOC arm)	The mother support groups (MSGs) was established in 14 clinics randomly selected. The HIV-positive mothers conducted the MSGs and mentor other HIV-positive mothers at health facilities or in communities; meetings were planned to function twice / month; attendance was from enrolment to 6 months postpartum; MSG meeting reminders were sent to members, including an additional reminder to mothers who missed a meeting.
Community health workers and lay workers						
4	Kim 2015[119] ^c	Malawi (Area 25 and Kawale, 2 large urban health centres, Lilongwe)	A pre/post quasi-experimental study	<u>2011</u> 2011 (Oct)-2013 (Mar)	For the 6-month ART outcomes: 984 HIV-positive PW newly initiated on ART after PMTCT enrolment (225 pre-Option B+ and 759 post-Option B+)	Community health workers (CHWs) : 1 CHW assigned to each HIV-positive pregnant woman at PMTCT enrolment. Each CHW follows an average of 35-50 patients: longitudinal care support throughout the full PMTCT cascade. Other CHW responsibilities include facility-based health talks, nutritional assessments at clinic visits, and HIV testing and counselling. Standard VHW is no VHW accompaniment.
mHealth						

No.	Name of the article	Country (location and sites)	Study design	Year of Option B+ initiation Study enrolment	Sample size	Interventions to increase retention or reduce FU
5	Schwartz 2015[120]	South Africa; 1 site (Witkoppen Health and Welfare Centre, Johannesburg)	A prospective pilot intervention	2012 ^d 2013 (May-Jun)	50 HIV-positive PW pre-intervention and 50 HIV-positive PW post-intervention	Text messages and calls from a case manager (CM) who provided support and motivation for participants to remain in care (senior HIV lay counsellors with previous PMTCT counselling experience) Weekly pre-scripted text messages to the participants' cell phones, which continued until 6 weeks postpartum (or up to 8 weeks if the participant did not return for the 6-week clinic visit), plus 1 pre-delivery and 2 post-delivery telephone calls made by the CM ^e
6	Finocchiaro-Kessler 2018[121]	Kenya (6 public hospitals: 2 pre-urban and 4 urban)	A cluster-randomised trial	2012 ^f 2014 (Feb)-2015 (Dec)	690 MIPs (392 for HITSystem, 298 for SOC)	HIV Infant Tracking System (HITSystem) : a web-based intervention linking providers of early infant diagnosis, laboratory technicians, and mothers and infants to improve outcomes for HEIs; infants are tracked regularly throughout the EID cascade of services from enrolment until final HIV status if established (up until 18 months post-partum).
7	Odeny 2018[122]	Kenya, Nyanza region, western region, 5 health facilities (mix of rural and urban settings)	A parallel-cohort randomized controlled trial	2012 ^f 2012 (April – Oct)	187 HEIs in the intervention group, 181 HEI in the control group; 510 HEI in the ineligible for RCT group	TextIT (Texting to Improve Testing) : text intervention (a 2-way theory-based text messaging system); 14 text messages tailored for specific points during pregnancy and the postpartum period
Provider-oriented strategies						
8	Joseph 2017[113]	Zimbabwe (3 provinces, 32 sites)	A 2-arm cluster-randomised controlled trial	2013 2014 (Jan)-2015 (Jun)	1150 HIV-positive PW (n=547 in SOC, n=603 in POC Plus)	POC CD4 testing of HIV-positive PW before ART initiation + CD4 count-specific counselling, retraining on the use of POC CD4 and quality assurance of the POC CD4 instruments themselves Sites randomised to the 'POC Plus' arm were provided with POC CD4 devices. Healthcare workers were trained on their use and participated in a quality assurance programme throughout the trial period. In addition, they were trained to provide specific counselling using a predefined script that emphasised how ART will maintain high CD4 counts and how low CD4 counts need ART to improve immune system response
9	Oyeledun 2017[123] ^g	Nigeria, northern part (Benue and Kaduna states); 32 facilities (20 primary and 12 secondary health level)	A cluster-randomised controlled trial	2016 2014 (Jul) -2016 (Oct)	403 HEIs (194 HEIs in control group, 209 HEIs in the intervention group)	Continuous quality improvement (CQI) : a health system's intervention methodology that uses serial reviews of local facility data to understand the primary and secondary drivers for low retention in care among HIV-positive mothers. The breakthrough series (BTS) is a specific short-term CQI approach (6-15 months) that brings together teams from several health facilities ('collaboratives') to jointly review progress and share solutions in a focused topic area
10	Stillson 2018[124]	Malawi (expansion from 5 districts in the southern region to national scale – 400 HFs)	A national mentorship programme evaluation	2011 2016 (April)-2018	None specified	A national mentorship programme for PMTCT service providers: reviewing and strengthening patient flow, testing procedures, and documentation practices; use of a mentorship checklist and facility-specific data sheets to identify areas for improvement; deployment of mentors to HFs (teams of 3) The programme first focused on health facilities with a high volume of patient flow, then gradually scaled up to other sites. This resulted in nearly every site in the country receiving at least one mentorship visit, with most receiving at least 3 visits
Combined interventions						

No.	Name of the article	Country (location and sites)	Study design	Year of Option B+ initiation Study enrolment	Sample size	Interventions to increase retention or reduce FU
11	Nelson 2018[125]	South Africa (Khayelitsha, Town 2 clinic)	A retrospective cohort analysis	2015 2016 (Jul)- 2018 (Jun)	335 mothers (18 high-risk) and 340 infants	Differentiated model of care using postnatal clubs (PNCs) formed according to the infants' dates of birth into clubs of 2-15 MIPs and held at regular intervals until 18 months of age PNCs were adapted from the adult ART adherence club model to provide double integration of care (maternal health, child health, and HIV services) and components of the first 1000 days (mental health, nutrition advice, and early childhood development activities) for HIV-positive mothers (stable and high risk) and their HIV-exposed uninfected infants
12	Ngoma 2015[126]	Zambia (Chelstone Public Clinic, Lusaka)	A prospective observational cohort study	NS 2008 (Dec)-2009 (Dec)	HEIs: 231 live births	Women received adherence counselling, text message reminders for clinic visits and stipends for food and transport (30,000 kwacha, equivalent to US\$6 per visit).
13	Pharr 2016[127]	Nigeria; 40 churches, Enugu State	A nested cohort study of HEIs within the HBI trial (A 2-arm cluster randomized trial)	2016 ^h 2013 (Jan-Sept)	69 HEI (live births)	Healthy Beginning Initiative (HBI): congregation-based baby shower intervention delivered by lay health advisors at local churches (intervention) vs. a clinic-based approach (control) on HIV testing Intervention arm: provision of an educational programme that included healthy habits and information about important laboratory screenings during pregnancy. Additionally, participants were offered free integrated laboratory screenings during the baby shower, including tests for HIV, hepatitis B, and sickle cell genotype
14	Suryavanshi 2018[128]	India, four districts of Maharashtra (Pune, Thane, Sangli, Satara)	A cluster-randomised controlled trial	2014 2015 (Apr)-2017 (Mar)	1191 women: 640 women assigned to 60 ORWs (COMBIND arm), 551 women to 56 ORWs (SOC arm)	COMmunity home Based INDia (COMBIND) PMTCT intervention using 4 combined interventions: 1) Specialised ORW interactive motivational counselling training 2) Use of an mHealth open-source platform called eMOCHA to facilitate communication with ORWs and women using educational videos and smart form-based counselling scripts 3) Strategic feedback to ORWs 4) Targeted feedback to HIV-positive women

^aThe PMTCT Uptake and Retention (PURE) study.

^bInformation on PMTCT programme protocol and ART regimen was extracted from the MOH national guidelines (Ministry of Health and Child Care, Zimbabwe. Operational and Service Delivery Manual for the Prevention, Care, and Treatment of HIV in Zimbabwe. Harare, Zimbabwe: Ministry of Health and Child Care 2014. www.differentiatedcare.org (accessed 25 Mar 2017).

^cThe Tingathe programme.

^dOption B+ was not yet the standard of care in South Africa at the time of this study.

^eAdditional telephone calls were made to the participant if requested by free-of-charge 'Please call me' text messages.

^fIn settings with the capacity to initiate and monitor triple therapy in HIV infected pregnant women.

^aThe Lafiyan Jikin Mata or ‘Excellent Health for Mothers’ study. Information on PMTCT programme protocol and ART regimen was extracted from Oyeledun B, Oronsaye F, Oyelade T, et al. Increasing retention in care of HIV-positive women in PMTCT services through continuous quality improvement-breakthrough (CQI-BTS) series in primary and secondary health care facilities in Nigeria: a cluster randomized controlled trial. The Lafiyan Jikin Mata Study. *J Acquir Immune Defic Syndr* 2014;67(Suppl 2):S125–31.

^bOption B+ was implemented at study sites in 2013, but national policy approved in 2016.

ART: antiretroviral therapy; HEIs: HIV-exposed infants; HFs: health facilities; mHealth: mobile health; MIPs: mother-infant pairs; MOH: Ministry of Health; ORWs: community-based outreach workers; PMTCT: prevention of mother-to-child transmission; POC: point of care; PW: pregnant women; SOC: standard of care

Supplementary Table 3 Description of key programme characteristics of included studies

Name of the article	Aim or objectives (primary and secondary)	Study settings	Inclusion criteria for study participants	Exclusion criteria for study participants
Peer and mentor support				
Atanga 2017[49]	To assess linkage and retention in care along the Option B+ PMTCT cascade	MCH services on-site with >90% ANC population coverage; study sites were pilot sites for Option B+ using task-shifting (midwives and nurses prescribed ART). Peer educator providing community follow-up and tracking LTFU	HIV-positive PW and BFW: including treatment-naïve women and women who had initially started Option A and consented to be switched to Option B+. Age was not an exclusion criterion, but adolescents needed parental consent	Women coming from other districts
Phiri 2017[117]	To evaluate whether facility- and community-based peer support by women with similar experience would improve uptake and retention of mothers and infants in Option B+ programme compared with the national SOC at 2 years post-initiation of treatment	Sites were eligible if they provided Option B+ services, did not have other PMTCT interventions or research activities beyond the Malawi national standard of care and were expected to have at least 20 women eligible for Option B+ in a 6-month period (27 sites selected, 7 sites/zone, 3 zones) Baseline assessment of selected sites reported that defaulter tracing was rarely if ever, occurring in any of the facilities. Most facilities had few or no health surveillance assistants (HSAs) and lay health providers who were trained in PMTCT Authors reported that in intervention sites, in both facility- and community-based models, support groups were poorly attended	Women: 15 years or older, known previously or newly tested HIV-positive and ART-naïve HEIs: all infants born to women in the study were enrolled at birth or at maternal enrolment if breastfeeding	None specified
Foster 2017[118]	To evaluate whether MSGs newly established in clinics improved HIV-exposed infants' (HEIs) and their HIV positive mothers' retention rates in postnatal follow-up and other programme outcomes.	Selected clinics located within rural communal and commercial farming areas. Study sites were considered as early learning sites for Option B+. PMTCT retention in the ANC period was 100% at sampled sites; but at delivery, 43% of HIV-positive mothers were not recorded as having delivered at the clinic; only 53% of HEI underwent an early DNA PCR test for HIV; the number of HEI visiting clinics for postnatal review declined progressively with duration of follow-up	HIV-positive, 18 years or older, lived in the clinic catchment area, and were under 35 weeks of gestation	None specified
Community health workers and lay workers				
Kim 2015[119]	To compare service uptake and antenatal outcomes throughout the PMTCT cascade from the identification of HIV-infected PW at ANC to infant delivery pre- and post-Option B+ implementation	Two large urban centres in the capital city where the Tingathe programme operated. High ANC coverage (96% for at least 1 ANC visit); high volume of deliveries (15,000 deliveries/year) The Tingathe programme started 2 years before the national Option B+ implementation: HIV service programme that uses dedicated CHWs as CMs to support women to navigate the multiple steps in the PMTCT cascade	Only HIV-positive PW enrolled in the Tingathe ANC programme	Those known to have been transferred out or receiving ART outside health facilities (18 pre- and 51 post-patients) for the 6-month outcomes among the women newly initiating ART
mHealth				
Schwartz 2015[120]	To assess the acceptability, feasibility, and potential for scale-up of a mobile phone-based case management intervention piloted at a primary health centre implementing Option B+ in South Africa	WHWC, a high-volume non-governmental primary health clinic in the capital city which serves an urban township and surrounding areas. WHWC sees 680 PW a month, 33% of which are HIV-infected. Option B+ was piloted at the site approximately a year before a national roll-out	All HIV-positive PW \geq 36 weeks' gestation owning a cell phone, being able to read text messages in English and willing to receive text messages and calls from a CM. Moreover, both women already on ART at the time of pregnancy and women not yet ART-initiated at time of pregnancy were eligible for this study	None specified

Name of the article	Aim or objectives (primary and secondary)	Study settings	Inclusion criteria for study participants	Exclusion criteria for study participants
Finocchario-Kessler 2018[121]	To evaluate the efficacy of the HITSystem on key outcomes of EID	Government-funded sites; provision of a comprehensive package of PMTCT services including EID and ART services; at least one dedicated EID provider; and maintained medical files for HEIs Rate of mobile phone use in Kenya was estimated at 90% (2016)	HIV-positive mothers aged 18 years or older, with an HEI presenting for their first EID appointment through the MCH department, and who presented for EID care when their infant was younger than 24 weeks	Mothers enrolled in EID services who did not meet the eligibility criteria
Odeny 2018[122]	To determine whether interactive text messages improved rates of clinical attendance and early infant testing	A mix of rural and urban settings. Health facilities supported by Family AIDS Care and Education Services (FACES). These health facilities offer PMTCT services including testing for infant HIV infection, using a specific family model of HIV care and treatment[129]	Women 18 years of age or older, pregnant at ≥ 28 weeks' gestation (or had delivered on the day of enrolment), enrolled in the PMTCT programme, planning to remain in the study area, had access to a mobile phone and reported ability to read or have someone who read text messages on their behalf	Women who reported sharing phones were ineligible unless they had disclosed their HIV status to the person sharing the phone
Provider-oriented strategies				
Joseph 2017[113]	To evaluate the impact of POC CD4 testing with CD4 count-specific adherence counselling (POC Plus) vs. SOC on retention in care among HIV-positive PW initiating ART	Sites were excluded if[130]: <ul style="list-style-type: none"> • No women had been initiated on ART in 2012 • ART initiation rates were $\geq 80\%$ • Fewer than 24 women tested HIV-positive in ANC in 2012 • Previous or existing POC CD4 capacity • Routine data were internally inconsistent (poor quality) • Challenging geographical access 	HIV-positive, ART-naïve PW attending their ANC booking	Already having initiated ART or for false pregnancies
Oyeledun 2017[123]	To examine whether a BTS-CQI intervention can improve retention in care, defined as attendance at 6 months postpartum while not missing previously scheduled visits, among mothers living with HIV who have started lifelong ART	Eligible facilities: existing PMTCT services for >6 months, regularly identified >1 pregnant woman per month, provided onsite delivery and postpartum care, and had at least 2 trained community health extension workers	HIV-positive women whose gestational age was 34 weeks or less, who were ART-naïve and who agreed to start lifelong ART	None specified
Stillson 2018[124]	To increase testing uptake across routine milestones for HIV-exposed children through national mentorship	The mentorship consisted of a half-day in-service guided mentorship for PMTCT service providers The goal of the mentorship: to identify and address specific facility-level barriers to testing uptake and service provision, while strengthening documentation practices Sites were initially identified based on testing volume during the first 4 rounds of mentorship, after which sites with lower volumes and performance were prioritised over higher-performing sites. This resulted in nearly every site in Malawi receiving at least one mentorship visit, with most receiving at least 3 visits	Programme evaluation; no inclusion criteria	No exclusion criteria
Combined interventions				

Name of the article	Aim or objectives (primary and secondary)	Study settings	Inclusion criteria for study participants	Exclusion criteria for study participants
Nelson 2018[125]	To analyse and describe maternal and child data collected during PNC intervention The aims of the PNCs are the improvement of retention in care and the following health outcomes for the MIPs: HIV VL suppression, vaccination coverage, and infant HIV testing uptake	Postnatal PMTCT estimated at 4.3% at 18 months The study site was a peri-urban informal settlement, the ANC HIV prevalence estimated to be 33% (2015) Access to postnatal services, uptake of infant HIV testing and maternal retention in care postpartum were poor Integrated MCH services included one-stop shops, clinical visit at every session, pre-packed medicine, experienced nurse (ART, MCH) Integration of HIV and non-HIV care included VL, FP, and Pap smear for mothers, and HIV testing, growth monitoring, feeding support, and immunisations and IMCI for children A PNC included 2-15 MIPs	HIV-positive mothers and HEIs: - Women stable on ART - 'High-risk' women with high VL or other characteristics based on the South Africa risk of treatment failure programme [131]	- HEIs already tested as HIV-positive - Mothers with active tuberculosis - Mothers who refused to have their ART care in the same clinic as the baby
Ngoma 2015[126]	To assess the efficacy and safety of continued breastfeeding while the mother receives combined ART	The study site was an urban public clinic in the capital city Services provided: reproductive health services which include PMTCT, FP, voluntary male circumcision and voluntary counselling. User fees were removed in 2013[132]	Age 15 years and older, HIV-positive, confirmed pregnancy with the ability to initiate cART at 14-30 weeks' gestation, intention to do EBF for 6 months, ability to give informed consent and ability to attend follow-up visits	Previous cART, known major illness likely to influence pregnancy outcome or leading to increased risk for adverse events from cART or continuing therapy with medications, which are contraindicated for co-administration with ritonavir/lopinavir None specified
Pharr 2016[127]	To report the impact of the HBI on rates of antiretroviral prophylaxis, EID, HIV status and linkage to care among infants born to HIV-infected mothers	40 churches were defined as study sites with church attendance approaching 90% and an extensive network of faith-based institutions Each church had a health team (HT) comprising the priest, women's and men's group leaders, and 2 volunteer health advisors, 1 of whom is trained to perform venepuncture. Prevention, education, Treatment, Training and Research-Global Solutions (PeTR-GS) conducted training workshops for all study staff and church-based volunteer health advisors	PW attending study churches	None specified
Suryavanshi 2018[128]	To assess the impact of a novel mHealth and community health worker empowerment intervention on the uptake of the 4 key components of PMTCT: 1. ART at delivery 2. EBF for 6 months 3. NVP prophylaxis for infants up to 6-12 weeks 4. EID at 6 weeks and at 6, 12 and 18 months	Maharashtra is the second largest state in India (population of >123 million) and has one of the highest HIV prevalence in the country Community ORWs were trained to help navigate barriers to uptake of the PMTCT programme. ORWs were peer women and were identified in the community through local advertisement. They were former PMTCT clients. These ORWs were supervised by the PMTCT coordinators of that district level ICTCs identified HIV-positive women, who were then linked to ORWs. Each ICTC may have >1 ORW working in the project catchment area, depending on the HIV burden. Every public ANC clinic had an attached ICTC ORWs accompanied HIV-positive PW to the ART centre for registration, supported the women with monthly home visits during pregnancy and attended during labour and immediately afterwards, as well as up to 18 months post-delivery[133]	Mothers above 18 years of age and who provided consent for participation	None specified

ACT: Accelerating Children on Treatment initiative; ANC: antenatal care; ART: antiretroviral therapy; BFW: breastfeeding women; BTS-CQI: breakthrough series-continuous quality improvement; cART: combination antiretroviral therapy; CHWs: community health workers; CM: case manager; EBF: exclusive breastfeeding;

EID: early infant diagnosis; FP: family planning; HBI: Healthy Beginning Initiative; HEIs: HIV-exposed infants; HFs: health facilities; HITSystem: HIV Infant Tracking System; ICTC: integrated counselling and testing centre; IMCI: integrated management of childhood illnesses; LTFU: lost to follow-up; MCH: mother and child health; MIPs: mother-infant pairs; MSF: Médecins Sans Frontières; MSGs: mothers support groups; NVP: nevirapine; ORWs: community-based outreach workers; PMTCT: prevention of mother-to-child transmission; PNC: postnatal clubs; POC: point of care; PW: pregnant women; SOC: standard of care; VHWs: village health workers; VL: viral load; WHWC: Witkoppen Health and Welfare Centre.

Supplementary Table 4 Weighting of studies by quality, according to the 4 EPPI criteria [134]

Name of the article	A Trustworthiness	B Appropriateness	C Relevance	D Overall weight
Peer and mentor support				
Atanga 2017	Low	Medium	High	Medium
Phiri 2017	High	High	High	High
Foster 2017	High	High	High	High
Community health workers and lay workers				
Kim 2015	Low	Low	High	Low
mHealth				
Schwartz 2015	Low	Low	High	Medium
Finocchario-Kessler 2018	High	High	High	High
Odeny 2018	High	Medium	High	Medium
Provider-oriented strategies				
Joseph 2017	High	High	High	High
Oyeledun 2017	High	High	High	High
Stillson 2018	Low	Low	High	Low
Combined interventions				
Nelson 2018	Low	Low	High	Low
Ngoma 2015	Low	Medium	High	Medium
Pharr 2016	Medium	Medium	Medium	Medium
Suryavanshi 2018	High	High	High	High

A = The trustworthiness of the results judged by the quality of the study within the accepted norms for undertaking the particular type of research design used in the study (methodological quality). B = The appropriateness of the use of that study design for addressing the systematic review's research question (methodological relevance). C = The appropriateness of focus of the research for answering the review question (topic relevance). D = Judgement of the overall weight of evidence (WoE) based on the assessments made for each of the criteria A-C. Each of the 4 criteria was scored using the Jadad scale[135,136]: a score of 0 or 1 was considered as 'low' quality, a score of 2 was described as 'medium', and scores of 3-5 were considered 'high' quality.

Supplementary Table 5 Definition of outcomes of interest (n=14 studies)

Name of the article	Definition of outcome
Peer and mentor support	
Atanga 2017[49]	Retention in care: % women who had started on lifelong Option B+ ART and attended clinic visits at 12 months or who were transferred out but known to continue ART following tracing information
Phiri 2017[117] ^a	1) ART retention in care at 1 and 2 years from ART initiation: MOH definition: being alive and in care at 1 or 2 years regardless of earlier outcomes Trial definition: alive and on ART without any gap in care >60 days after a scheduled visit among those who started ART 2) % of HEIs tested at 6 weeks, 12 and 24 months: Numerator: number of HEIs alive and tested at 6 weeks, 12 and 24 months Denominator: number of HEIs alive at 6 weeks, 12 and 24 months (deaths excluded from denominators)
Foster 2017[118] ^b	EID performed at 6 weeks (±2 weeks): Numerator: number of HEIs tested at 6 weeks Denominator: number of women enrolled
Community health workers and lay workers	
Kim 2015[119] ^c	% alive on ART at 6 months after ART initiation: definition not specified. Note: women defined as lost to follow-up were those who did not return to care for >60 days and could not be traced
mHealth	
Schwartz 2015[120]	% of HEIs receiving PCR at 6 weeks (pre- and post-intervention period): Numerator: number of HEIs tested Denominator: total number of HIV-positive PW women enrolled
Finocchario-Kessler 2018[121]	% of HEIs with complete EID retention until 18 months postpartum: Numerator: number of HEIs who received complete EID services Denominator: number of MIPs enrolled (deaths and documented transfers were excluded from the denominator) Complete EID retention: receipt of all indicated age-specific interventions ^d until 18 months postpartum (for HIV-negative infants) or ART initiation (for HIV-positive infants)
Odeny 2018[122]	% of HEIs tested (median time from birth to HIV virologic testing was 7 weeks): Numerator: number of HEIs tested Denominator: number of HEI live births ^e (deaths, stillbirths, and documented transfers were excluded from the denominator)
Provider-oriented strategies	
Joseph 2017[113]	POC CD4 testing. Study definition (75% on-time): 1) % of HIV-positive PW retained on ART after 6 months (see the definition for 12 months) 2) % of HIV-positive PW retained on ART after 12 months: having had an ART refill visit a minimum of 335 days post-ART initiation and on-time attendance ^f for at least 75% of scheduled ART refill visits, up to and including the 12-month visit Study definition (100% on-time): strictest definition, requiring all visits to be on time MOH definition: only 1 visit after 6 or 12 months post-ART initiation

Name of the article	Definition of outcome
Oyeledun 2017[123] ^g	Quality improvement. % of HEIs born to enrolled mothers and tested by DBS/PCR between 6 and 10 weeks of age Denominator: live births with the exclusion of miscarriages, unknown delivery status, stillbirth, and neonatal death
Stillson 2018[124]	HF staff mentorship. % of HEIs tested at 2, 12 and 24 months Numerator: number of known HEIs with a test result recorded Denominator: total number of HEIs enrolled in the PMTCT programme from a given birth cohort (deaths and loss to follow-up are included in the denominator)
Combined interventions	
Nelson 2018[125]	Uptake of infant RHT at 9 and 18 months: Numerator: number of infants who underwent RHT at 9 and 18 months Denominator: number of HEIs attending visits at 9 and 18 months
Ngoma 2015[126]	% of HEIs who underwent PCR by 6-8 weeks, 12 months and 18 months: Numerator: number of infants tested Denominator: number of live births
Pharr 2016[127]	% of HEIs tested with EID at 6-8 weeks of age and with RHT after 18 months: Numerator: number of infants tested Denominator: number of live births
Suryavanshi 2018[128]	% of infants tested: EID at 6 weeks, infant HIV testing at 12 months and infant HIV testing at 18 months Numerator: number of live-born infants tested for HIV at 4-time points Denominator: number of HIV-positive women enrolled

^aThe PMTCT Uptake and Retention (PURE) study.

^bInformation on PMTCT programme protocol and ART regimen was extracted from the MOH national guidelines (Ministry of Health and Child Care, Zimbabwe. Operational and Service Delivery Manual for the Prevention, Care, and Treatment of HIV in Zimbabwe. Harare, Zimbabwe: Ministry of Health and Child Care 2014. www.differentiatedcare.org (accessed 25 Mar 2017).

^cThe Tingathe programme.

^dEligible services comprised initiation of co-trimoxazole for opportunistic infection prophylaxis, PCR testing and return of results to the hospital, notifying the mother of the PCR results, and initiation of ART (HIV-positive infants only). And retesting at 9 and 18 months (HIV-negative infants only)

^eCalculated using available data.

^fA visit was considered on time if the actual visit occurred before, on or up to 14 days after the next scheduled visit date. Any woman with a gap in care for >90 days was considered not retained. In addition, deaths and outward transfers were not considered retained.

^gThe Lafiyen Jikin Mata or 'Excellent Health for Mothers' study. Information on PMTCT programme protocol and ART regimen was extracted from Oyeledun B, Oronsaye F, Oyelade T, et al. Increasing retention in care of HIV-positive women in PMTCT services through continuous quality improvement-

breakthrough (CQI-BTS) series in primary and secondary health care facilities in Nigeria: a cluster randomized controlled trial. The Lafiyan Jikin Mata Study. *J Acquir Immune Defic Syndr* 2014;67(Suppl 2):S125–31.

DBS/PCR: dried blood spot polymerase chain reaction; EID: early infant diagnosis; HEIs: HIV-exposed infants; MIPs: mother-infant pairs; MOH: Ministry of Health; POC: point of care; PCR: polymerase chain reaction; RHT: rapid HIV antibody test.

5.2.3 Discussion

The results of this work suggest that PMTCT Option B+ programs need to incorporate a package of interventions to support retention in care and infant testing uptake addressing the various barriers to engagement in care of the mother-infant pair. This recommendation is based on the hypothesis of acting on different types of barriers and at different time points in the continuum of care will produce more favorable outcomes than acting on a single time point using one type of intervention [137,138]. Therefore, the package of interventions should not only aim at changing the behavior of patients and their communities but also change the organization of care providing a more integrated approach carrying health care services away from an already overcrowded facility-based system to a more mother/infant-centered approach at community level. In addition, interventions to improve retention in care are equally applicable to women initiating ART at PMTCT enrolment as to women already on ART while becoming pregnant. Even more so for the latter group as these women should be more stable patients who can receive a more differentiated model of care [12].

In our systematic review, only one eligible study reported on long term retention beyond 12 months of ART. Therefore, future research analyzing the impact of interventions to improve PMTCT outcomes should report on long term retention outcomes (i.e. >24 months after ART initiation) to account for the additional challenges of retaining women under lifelong ART after the end of the PMTCT period. We also found that all interventions which have been evaluated to date have limited impact on engagement in care for women enrolled under Option B+ suggesting that women prioritise their health care in ways that programmes do not yet understand. The results for this review can best be adapted to local context using informative research. Particularly, for the Mozambican context, further qualitative research is needed to address the particular local health system and socio-cultural challenges faced by women, such as migration, lack of tracking of women between clinics, for example. Results of such research can then help inform the specific intervention needed to improve their engagement in care.

Finally, in this systematic review we also highlighted the plethora of definitions used to characterize women retained in care and the absence of use of the international recommended definition of infant testing. Based on these findings, from a programmatic stand-point to measure engagement in PMTCT care we recommend incorporating the element of completeness of follow-up in the measurement metrics of retention and infant testing.

5.3 Measuring retention in care for HIV-positive pregnant women in Prevention of Mother to Child Transmission of HIV (PMTCT) option B+ programs. The Mozambique experience.

5.3.1 Introduction

The first work of the thesis consisted in estimating retention rates in two high HIV burden provinces in Mozambique over the course of 4 years of Option B+ programme implementation. We observed low retention rates in pregnant women enrolled in PMTCT care. The second work highlighted the great heterogeneity of definitions used in the literature when defining women retained in care under Option B+ programmes and its impact on result interpretation. This third work is a sensitivity analysis of our cohort analysis by estimating the effect of different definitions of retention in care. We discuss here the advantages and limitations of each definitions in the context of engagement in care for HIV+ pregnant women initiating ART under Option B+ in Mozambique.

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5.3.2 Manuscript

Measuring retention in care for HIV-positive pregnant women in Prevention of Mother-to-Child Transmission of HIV (PMTCT) option B+ programmes: the Mozambique experience

Laurence Ahoua^{1,2}, Thierry Tiendrebeogo¹, Shino Arikawa¹, Maria Laheurta^{3,4}, Dario Aly², Renaud Becquest¹, Francois Dabis¹

Authors' affiliations

¹ University of Bordeaux, INSERM, Bordeaux Population Health Research Center, Team IDLIC, UMR 1219, Université de Bordeaux, Case 11, 146 rue Léo Saignat, 33076 Bordeaux Cedex, France; Tél: +33 (0)5 57 57 13 93; Fax: +33 (0)5 56 24 00 81

² ICAP at Columbia University, Mailman School of Public Health, Rua Francisco Matange, 224/246, Caixa Postal n.º1747, Maputo, Mozambique. Tel: +258 21 315 170

³ ICAP at Columbia University, Mailman School of Public Health, Columbia University, 722 West 168th Street, New York, NY 10032, United States. Tel: +1 212-342-0505

⁴ Department of Epidemiology, Mailman School of Public Health, Columbia University, 722 West 168th Street, New York, NY 10032, United States. Tel: +1 212-305-9412

Corresponding author

Dr. Laurence Ahoua, University of Bordeaux, INSERM, Bordeaux Population Health Research Centre, Team IDLIC, UMR 1219, 146 rue Léo Saignat 33076 Bordeaux Cedex, France

Email: laurence_ahoua@yahoo.fr

Abstract

Background: Failure of retention of HIV-positive pregnant women on ART leads to increased mortality for the mother and her child. This study evaluated different retention measures intended to measure women's engagement along the continuum of care for prevention of mother-to-child transmission (PMTCT) option B+ services in Mozambique.

Methods: We compared 'point' retention (patient's presence in care at 12-months post-antiretroviral treatment (ART) initiation or any time thereafter) to the following definitions: alive and in care at 12 months post-ART initiation (Ministry of Health); attendance at a health facility up to 15 months post-ART initiation (World Health Organisation); alive and in treatment at 1, 2, 3, 6, 9, and 12 months post-ART initiation (Inter-Agency Task Team); and alive and in care at 12 months post-ART initiation with $\geq 75\%$ appointment or on-time adherence during follow-up ('appointment adherence' and 'on-time adherence' retentions). Kaplan-Meier survival curves were produced to assess variability in retention rates. We used 'on-time adherence' retention as a gold standard to estimate sensitivity, specificity, and proportion of misclassified patients.

Results: Considering the 'point' retention definition, 16,840 HIV-positive pregnant women enrolled in option B+ PMTCT services were identified as 'retained in care' 12 months post-ART initiation. Of these, 60.3% (95% CI 59.6–61.1), 84.8% (95% CI 84.2–85.3), and 16.4% (95% CI 15.8–17.0) were classified as 'retained in care' using MOH, WHO, and IATT definitions, respectively, and 1.2% (95% CI 1.0–1.4) were classified as 'retained in care' using the ' $\geq 75\%$ on-time adherence' definition. All definitions provided specificity rates of $\geq 98\%$. The sensitivity rates were 3.0% with 78% of patients misclassified according to the WHO definition and 4.3% with 54% of patients misclassified according to the MOH definition. The 'point' retention definition misclassified 97.6% of patients. Using IATT and 'appointment adherence' retention definitions, sensitivity rates (9.0% and 11.7%, respectively) were also low; however, the proportion of misclassified patients was smaller (15.9% and 18.3%, respectively).

Conclusion: More stringent definitions indicated lower retention rates for PMTCT programmes. Policy makers and programme managers should include attendance at follow-up visits when measuring retention in care to better guide planning, scaling up, and monitoring of interventions.

Keywords: PMTCT, option B+, retention, sensitivity, specificity

Background

Retention in prevention of mother-to-child transmission of HIV (PMTCT) care has both individual and public health consequences. At the mother-infant pair level, being in care contributes to higher maternal antiretroviral therapy (ART) adherence, better viral suppression, and ensures better post-natal care, including full ART prophylaxis and complete infant testing to HIV-exposed infants (HEI) (1,2). In contrast, failure to be retained in care can lead to delayed or inconsistent use of antiretroviral medications, higher rates of maternal viral load failure, and increased morbidity and mortality for the mother and her child (3–5). In addition, recent publications have reported an upward trend in acquired drug resistance to first-line ART across low- and middle-income countries, principally due to sub-optimal viral suppression (6–8). Therefore, non-achievement of viral suppression can lead to a higher risk of HIV transmission and secondary infections with acquired drug resistance strains and is, therefore, considered a public health threat (9).

When referring to retention in care, publications often consider ‘point’ retention, which is defined in relation to a patient’s presence in care at a certain time point. For women and children enrolled in PMTCT services, attendance at a clinic at a certain time point is often considered to be full retention over this time period. While such a simple definition is useful, it has been demonstrated for HIV-infected adults that between one- and two-thirds of patients are not in regular care (10). Therefore, regularity of attendance is an important parameter to consider if quality engagement in care is to be evaluated (11).

To address shortcomings in this simple definition, attempts to better measure retention in care in PMTCT services have been made (12,13). In 2014, a World Health Organisation (WHO) monitoring and evaluation working group published consolidated strategic information guidelines and proposed that retention in care of HIV-infected pregnant and breastfeeding women was equivalent to attendance at a health facility at 12-months post-initiation of ART, or at any time up to 3 months later (12). The 12-month time point was agreed to align with the adult ART monitoring

guidelines; however, it fails to address the ongoing risk period associated with continued breastfeeding beyond 12 months. In 2015, the Inter-Agency Task Team (IATT) on Children and HIV and AIDS defined maternal retention as ‘the proportion of HIV-positive pregnant and/or breastfeeding women on ART alive and in treatment at 1, 2, and 3 months post-ART initiation (early retention), and then at 6, 9, and 12 months post-ART initiation’, where retention was considered as a continuous engagement (13). Despite such efforts, there is no consensus on what constitutes ‘retention in care’, with no gold standard determined. In 2010, Mugavero et al. provided a synopsis of five commonly used definitions of retention in HIV care and treatment services, ranging from a simple count of the number of missed visits to a more complex medical visit performance measure that incorporated elements of appointment consistency and gaps in care (10). While that study provided important insights on methodological and conceptual strengths and limitations of each definition, no comparative analysis of these definitions has been undertaken. In this study, we aimed to evaluate different measures of retention that could reflect more accurately the nature of women’s engagement along the PMTCT care continuum. We hypothesised that ‘point’ retention’ might overestimate the level of engagement in care of women enrolled in PMTCT programmes, and that programme outcomes in a high HIV-burden country such as Mozambique would be better evaluated when the level of attendance of scheduled visits during follow-up was taken into account. More specifically, the objectives of this analysis were to: i) assess the variability of different measures of retention at 12 months post-ART initiation under PMTCT option B+ programmes using different definitions of retention in care; ii) compare the sensitivity and specificity of the different definitions in detecting women fully engaged in care at 12 months post-ART initiation; and iii) discuss the programmatic implications of each definition in the context of PMTCT option B+ programmes.

Methods

Setting

Data for the present analyses were extracted from electronic patient-level databases (ePLD) from 86 Ministry of Health (MOH) facilities providing PMTCT option B+ and HIV care and treatment services in Nampula and Zambézia provinces in Mozambique. The programmes were supported by ICAP at Columbia University through funding from the United States President's Emergency Plan for AIDS Relief (PEPFAR).

Officially adopted in 2013, the option B+ strategy in Mozambique uses a 'one-stop-model' and 'Test and Treat' approach where pregnant and breastfeeding women are counselled and tested in mother and child health (MCH) services and, if found HIV-positive, are started on lifelong ART that same day. HIV care and treatment are integrated within MCH services and ART provision is administered by nurses. For HIV-positive pregnant women, a second consultation occurs within the first week post-ART initiation, and a monthly clinical follow-up is conducted during the first 6 months of ART, followed by bi-monthly follow-ups during breastfeeding until 12 months of treatment and bi-annually thereafter until the end of breastfeeding. ART counselling and drug pickup are conducted on a monthly basis for the first year of treatment. Routine viral load (VL) monitoring is recommended at 3 and 12 months post-ART initiation and annually thereafter. HIV-positive women are followed in MCH services until the final HIV status of the exposed infant is determined (14). More detailed descriptions of the PMTCT programme settings and data sources are described elsewhere (*manuscript, L Ahoua, 2019*).

The Mozambique provinces targeted for the study officially implemented option B+ in July 2013. Of all HIV-positive women who were enrolled in PMTCT option B+ programmes and who were started on ART between July 1st, 2013 and December 31st, 2017, we selected those who were considered as 'retained in care' at 12 months post-ART initiation according to the 'point' retention definition (i.e.

patient alive and present in care at 12 months post-ART initiation, or any time thereafter) and with a follow-up time of at least 12 months under ART to allow complete assessment of engagement in care during the first year of treatment. These selected women constituted the basis of comparison for the subsequent analyses assessing variability in different definitions concerning retention measures.

Comparing definitions

The 'point' retention definition was compared against the following five definitions: MOH (15), WHO (12), IATT (13), 'appointment adherence' retention (10), and 'on-time adherence' retention (16) (Table 1). Similar to the 'point' retention definitions, the MOH and WHO retention definitions assess retention at a single time point. For women's attendance at a clinic, we considered different types of visits including medical consultations, pharmacy drug refills, counselling, or laboratory analysis. This approach allowed us to consider HIV care as a holistic strategy, given that HIV care is provided in an increasingly team-based environment with non-prescribing healthcare professionals taking on expanded roles in direct patient care. Table 1 summarises the definitions of retention according to different measures and shows how failure events were accounted for in statistical analyses.

Statistical analysis

Women's appointment adherence, as well as their on-time adherence to scheduled visits, were expressed as percentages, median, and interquartile range [IQR]. Women's retention status was classified into a binary outcome (retained vs. not retained in care) using a 75% threshold for clinical attendance. Each woman contributed to the analyses from the date of ART initiation to the first occurrence of a failure event, as described in Table 1. To allow sufficient time to analyse clinical attendance within the first year of treatment, we only included women who initiated ART up until December 31st, 2016 and for whom the theoretical follow-up time under ART was ≥ 12 months.

Kaplan-Meier survival curves were produced to estimate retention in care at 3, 6, 9, and 12 months post-ART initiation using each of the definitions described above. We assessed variability in the

different measures of retention between respective definitions used. We did not consider ‘appointment adherence’ retention for the survival analysis, as this definition does not contemplate a time event, but rather a total number of visits completed during the observation period.

We assessed sensitivity, specificity, and the proportion of misclassified women for each alternative definition of retention compared to the reference of an ‘ideal case scenario’ of full ‘on-time adherence’ retention, defined as a woman alive and in care 12 months post-ART initiation and $\geq 75\%$ of scheduled visits attended on time (± 15 days). Sensitivity and specificity values were calculated with 95% confidence intervals.

Results

A total of 31,186 HIV-positive women were enrolled in the PMTCT option B+ programme initiating ART during the study period. Of these, 18,739 were considered as being retained in care at 12 months post-ART initiation according to the ‘point’ retention definition. We excluded 1,899 women with a follow-up ART time of < 12 months. Finally, 16,840 women were included in this study.

Of 16,840 women included, only 2,764 (16%) and 407 (2%) were considered retained at 12 months post-ART initiation when considering regularity and timeliness of appointment attendance, respectively (Figure 1). The occurrence of irregular (IATT’s definition) and delayed (‘on-time’ definition) clinical attendance was documented as early as 2–3 months post-ART initiation. The median frequency of appointment adherence to scheduled visits for all women included was 66.7% (IQR 57.1%–80.0%) and the median frequency of on-time adherence was 40.0% (IQR 22.2% – 52.9%).

Figure 2 shows Kaplan-Meier survival curves for retention over time up to 12-months post-ART initiation using the different definitions. Among the 16,840 B+ pregnant women considered retained in care according to the ‘point’ retention definition, 84.8% (95% CI 84.2–85.3) were actually defined as retained in care when estimated using the WHO definition (i.e. attendance at a health facility up to

15 months post-ART initiation), 60.3% (95% CI 59.6–61.1) with the MOH definition (i.e. alive and in care at 12 months post-ART initiation), and 16.4% (95% CI 15.8–17.0) with the IATT definition (i.e. alive and on treatment at 1, 2, 3, 6, 9, and 12 months post-ART initiation), respectively. When using the ‘on-time adherence’ retention definition (i.e. alive and in care at 12 months post-ART initiation with at least 75% of on-time adherence during follow-up), only 1.2% (95% CI 1.0–1.4) were defined as retained in care.

We considered the gold standard category to be the 407 women alive and in care 12-months post-ART initiation with at least 75% on-time adherence. We calculated the sensitivity and specificity of other definitions to more accurately classify the women into a more suitable category of retention and determine the proportion of misclassified patients. While all definitions provided specificity rates of $\geq 98\%$, the sensitivity to detect a patient actually retained in care with $\geq 75\%$ of on-time adherence was $< 12\%$ (Table 2). The WHO and MOH retention definitions provided the lowest sensitivity figures and the highest proportion of women misclassified as retained in care as follows: 3.0% sensitivity (95% CI 2.7%–3.3%) with 78% of patients misclassified according to the WHO definition and 4.3% sensitivity (95% CI 3.9%–4.7%) with 54% of patients misclassified according to the MOH definition. In addition, the ‘point’ retention definition misclassified 97.6% of patients. Although sensitivity rates were also low when using the IATT and ‘appointment adherence’ retention definitions, the proportion of misclassified patients was relatively smaller (15.9% and 18.3%, respectively).

Discussion

We analysed six different definitions of ‘retention in care’ for HIV-positive pregnant women enrolled in PMTCT option B+ programmes ranging from the most lenient definition using a ‘point’ retention approach to the most stringent definition using an ‘on-time adherence’ retention approach. Of the six definitions, three definitions assess retention at a single time point (‘point’ retention, WHO, and MOH). The IATT, the ‘appointment’ and the ‘on-time adherence’ retentions approaches reflect a

more continuous engagement in care, where follow-up visits between initiation of ART and the endpoint date are considered.

As expected, we found that the more stringent the definition, the lower the probability for women to be defined as retained in care; and when levels of attendance to visits during follow-up were considered, estimates were even lower (85% and 60% when using the WHO and MOH definitions compared to 16% and 1% when using the IATT and 'on-time adherence' retention definitions). At the end of the first year, most women starting ART had not adhered to their scheduled visits, with median appointment adherence at 66% and median on-time adherence at 40% among the 16,840 women considered as retained in care using the 'point' retention definition. Of these, only 16% and 2% were actually defined as retained in care 12 months post-ART initiation, if we considered a threshold of $\geq 75\%$ for appointment and on-time attendance, respectively.

Initial visits in the first year of ART initiation are critical to ensure successful engagement in care, involving intensive counselling, peer support, conveying important preventive healthcare and risk reduction messages, and monitoring patterns of healthier behaviour for the women and their exposed children. This interaction between the health system and the HIV-infected women determines the likelihood of survival of the pair and the mother-to-child transmission of HIV. Adding the frequency and regularity of visits into the concept of retention increases the quality of the PMTCT programme evaluations, enabling a distinction to be made between women who attend for all or some care and treatment, and those who completely fail to adhere to scheduled visits and are therefore considered not to be engaged in care.

Table 3 provides a summary of the advantages, limitations, and programmatic implications of the six measures of retention concerning the PMTCT option B+ programmes (10,11). Based on our results, the three-single time point measures, namely, the 'point', WHO, and MOH definitions, were a classical programmatic approach to measure retention in care under ART. While relatively easy to

use, they do not capture important milestones in the PMTCT context; for example, at delivery, at 2-months post-partum for early infant diagnosis, or at the end of breastfeeding for the final HIV determination of the HIV-exposed infant. In addition, they do not consider visit consistency, which has been demonstrated to be significantly associated with ART adherence and viral suppression among HIV-positive adults (17,18). However, the three definitions that capture visit consistency along the continuum of care, namely, the IATT, ‘appointment’ and ‘on-time adherence’ definitions, were more complex to use as they included multiple clinic visits (repeated measures) occurring longitudinally over time. This could become extremely challenging in limited-resource settings where limited qualified human resources are available to document such information, data collection tools are not adapted to capture longitudinal follow-up, and there are numerous entry points where women are followed within the same health facility or between sites (11,19). To correctly capture patients’ follow-up, different data sources need to be combined or triangulated, for example, with counselling registers and with laboratory or pharmacy records. Electronic databases may help this process, but these are generally implemented in high volume and accessible sites and may not necessarily be representative of the entire country for national programmes. However, all three definitions enabled adding the concept of a continuum of care to point retention estimates.

When considering ‘on-time adherence’ retention as the gold standard, all other definitions provided very low sensitivity rates to accurately detect patients retained in care, with high rates of misclassified patients. The WHO and MOH retention definitions provided the lowest sensitivity rates, that is, 3% and 4%, respectively. For the ‘point’ retention, WHO, and MOH definitions, which did not consider continuous follow-up in their calculations, the proportion of misclassified patients ranged from 54% to 97%. The ‘appointment adherence’ definition provided the highest sensitivity rate (11.7%), with a fairly low proportion of misclassified patients (18.3%) compared to all other definitions analysed. We found that the median time to first failure of correct follow-up was short (≤ 3 months), if visit attendance during follow-up was considered, which demonstrated the need to implement early

preventive measures to avoid patients on the PMTCT programme disengaging from care. Such strategies should focus on already well-known barriers to regular attendance, such as a lack of disclosure, poor staff attitudes, competing personal priorities, medication side-effects, or transport difficulties (16).

While our definition of ‘on-time adherence’ retention represents the ideal situation in which an HIV-positive pregnant woman enrolls in a PMTCT programme and starts ART under option B+ should be considered as fully engaged in care to ensure an optimal viral response, it is perhaps too stringent for PMTCT programme evaluations. It is also time consuming to use on a routine basis and may not be compatible with current PMTCT service settings. Therefore, we recommend either using the IATT or the ‘appointment adherence’ retention definitions to better measure levels of engagement in care for mother-infant pairs.

Our analysis had several limitations. To accurately evaluate attendance at scheduled visits, it is desirable to distinguish visits cancelled in advance (either by the patient or the care provider) from ‘no show’ visits that are actually visits missed by the patient (10). Our data did not allow this distinction to be made as this information was not captured in the database. Therefore, our results may have underestimated the real values of women’s engagement in care when analysing ‘appointment’ and ‘on-time’ adherence retentions.

Some women, although defined as having a full attendance at scheduled visits, did not follow per se the recommended schedule of visits as per national guidelines. More frequent visits may indicate a more advanced HIV disease, problems in counselling that need to be addressed, or drug or laboratory reagent stock-outs (19). Less frequent clinical visits may reflect a stabilised disease stage or temporary silent transfers (i.e. women receiving ART services elsewhere for a short period of time). For this reason, we chose to use all scheduled visits, regardless of whether the visits fell into expected time intervals. We did not analyse treatment interruptions and gaps in care for similar reasons. Further

research is warranted to investigate the effect of a lack of observation of the recommended schedule of visits as per national guidelines on PMTCT programme outcomes.

Finally, we analysed data from health facilities with ePLD in two provinces in Mozambique. Although these two provinces are among the most populated in the country, with large volumes of patients seen at health facilities, our results may not be generalisable to other regions in Mozambique or to other resource-limited settings.

Conclusion

Balancing the need to reflect correct attendance and capture the regularity of visits without involving complex computer processing of the available routine data can be a daunting task. In addition, applying more stringent definitions is likely to result in lower reported rates of retention in care for PMTCT programmes. However, policy makers and programme managers should consider systematically taking into account attendance at follow-up visits to better guide decision-making concerning planning or scaling up interventions for mother-infant pairs. A consensus on a practicable definition is urgently needed, based on data availability, clinic scheduling practices, and local analytical capacities. Without overall agreed guidelines, findings from different programmes and interventions cannot be satisfactorily compared. Finally, a retention indicator is used in modelling estimates for vertical transmission of HIV. Without accurate and correct estimates, it is not possible to evaluate programme achievements effectively in respect of elimination of mother-to-child transmission of HIV. This consideration may become particularly important as recent programmatic data seem to indicate a stagnation in the achievements of PMTCT programmes worldwide, which suggests the need for revised global, national, and local strategies to end the HIV epidemic by 2030 (20).

List of abbreviations

PMTCT	Prevention of mother-to-child transmission of HIV
ART	Antiretroviral treatment
WHO	World Health Organisation
IATT	Inter-Agency Task Team
HEI	HIV-exposed infants
ePLD	Electronic patient-level database
PEPFAR	United States President's Emergency Plan for AIDS Relief
MCH	Mother and child health
VL	Viral load
MOH	Ministry of Health
IQR	Interquartile range

Declarations

Ethics approval and consent to participate: This study was part of the 'Identifying Optimal Models of HIV Care and Treatment' collaboration which was approved by the Mozambican National Ethics Committee and the Columbia University Medical Center IRB. Additional technical and administrative approval was received from the US Centers for Disease Control and Prevention and the Office of the Global AIDS Coordinator, US Department of State. Informed consent to participate was not required as this study was solely based on secondary data analyses of de-identified routine service delivery data. As part of the 'Optimal Models' Collaboration, the Columbia University IRB Committee did not consider this study to be a human subject research, as there was no interaction with subjects and no intervention, and private, identifiable information was not collected.

Consent for publication: All authors have provided consent for the publication of this manuscript.

Availability of data and material: No original data were used in the study; only secondary routinely collected de-identified service delivery data were used. The datasets analysed during the current study are currently not publicly available. An anonymised dataset can be available from the corresponding author on reasonable request.

Competing interests: The authors declare that they have no competing interests.

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Authors' contributions: LA, TT, SA, RB participated in the study design. LA carried out the data collection and LA, TT, SA participated in the data analysis. LA drafted the manuscript, TT, SA and DA participated in the revision of the drafted manuscript and all authors read and approved the final manuscript

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Table 1: Retention definitions and methods of calculation. B+ PMTCT programme, Mozambique, 2013-2017

Type of retention	Definition of a patient 'alive and retained in care' at 12 months post-ART initiation	Failure event
'Point' retention	Alive and had a visit at the health facility 12 months post-ART initiation or if was known to have had a visit at a health facility any time after	Death, LTFU, and transfer-out are counted if they occurred within the first 12 months post-ART initiation
WHO	Attendance at a health facility at 12 months post-ART initiation*, or at any time up to 3 months later	Death, LTFU, and transfer-out are counted if they occurred within the first 15 months post-ART initiation. Patients transferred out were right-censored at the date of transfer-out
MOH	Attendance at a health facility at 12 months post-ART initiation*	Death or LTFU are counted if either occurred within the first 12 months post-ART initiation Patients transferred out are excluded from the analysis
IATT	Attendance at a health facility and on treatment at 1, 2, 3, 6, 9, and 12 months post-ART initiation #	Death, LTFU, transfers-out and failure to attend either the 1-, 2-, 3-, 6-, 9-, or 12-month visit, whichever comes first Patients are right-censored at the date of the 1 st failure event.
'Appointment adherence' retention	Attendance at a health facility at 12-months post-ART initiation * and $\geq 75\%$ of appointment adherence to scheduled visits 'Appointment adherence' was estimated using the number of visits attended divided by the number of total scheduled visits during the 12-month observation period	Not applicable
'On-time adherence' retention	Attendance at a health facility at 12 months post-ART initiation * and $\geq 75\%$ of 'on-time attendance to scheduled visits A visit on time is defined as a visit that occurred within +/- 15 days of the date of the expected scheduled visit 'On-time adherence' is estimated using the number of visits attended on-time divided by the number of total scheduled visits. Unscheduled visits occurring before the date of appointment were not counted as missed visits	Death, LTFU, transfer-out, and failure to attend a visit on-time, whichever comes first. Patients were right-censored at the date of the 1 st failure event

ART, antiretroviral therapy; LTFU, lost to follow-up

*For these definitions, we considered a window period of +/- 15 days around the theoretical date of 12-month post-ART initiation.

We allowed a +/-15-day window period for each stage of ART follow-up. Note: We did not consider 'appointment adherence' retention for the survival analysis, as this definition does not contemplate a time event but rather the total number of visits completed during the observation period.

Table 2: Sensitivity and specificity of various definitions of retention in care among B+ HIV+ pregnant women defined as alive and retained in care according to the 'point' retention definition (n = 16,840).

Retained in care according to type of definition (n = 16,840)	Alive and retained in care with $\geq 75\%$ of visits in time (Gold standard)		Sensitivity 95% CI	Specificity 95% CI	% of misclassification
	Yes	No			
'Point' retention	407	16,433	-	-	97.6%
WHO	405	13,154	3.0% [2.7%–3.3%]	99.9% [99.8%–100%]	78.1%
MOH	407	9,093	4.3% [3.9%–4.7%]	100% [99.9%–100%]	54.0%
IATT	249	2,515	9.0% [8.0%–10.1%]	98.9% [98.7%–99.0%]	15.9%
'Appointment adherence' retention	407	3,076	11.7% [10.6%–12.8%]	100% [100%–100%]	18.3%

Note: The 'on-time adherence' definition of retention is considered as the gold standard (n = 407 women retained in care at 12-months post-ART initiation and with $\geq 75\%$ on-time adherence to scheduled visits). The percentage of misclassified patients is calculated using the sum of patients incorrectly classified according to each definition divided by the total number of patients included in the analysis.

Table 3: Advantages, limitations, and programmatic practicality of six measures of retention in care for PMTCT option B+ programmes.

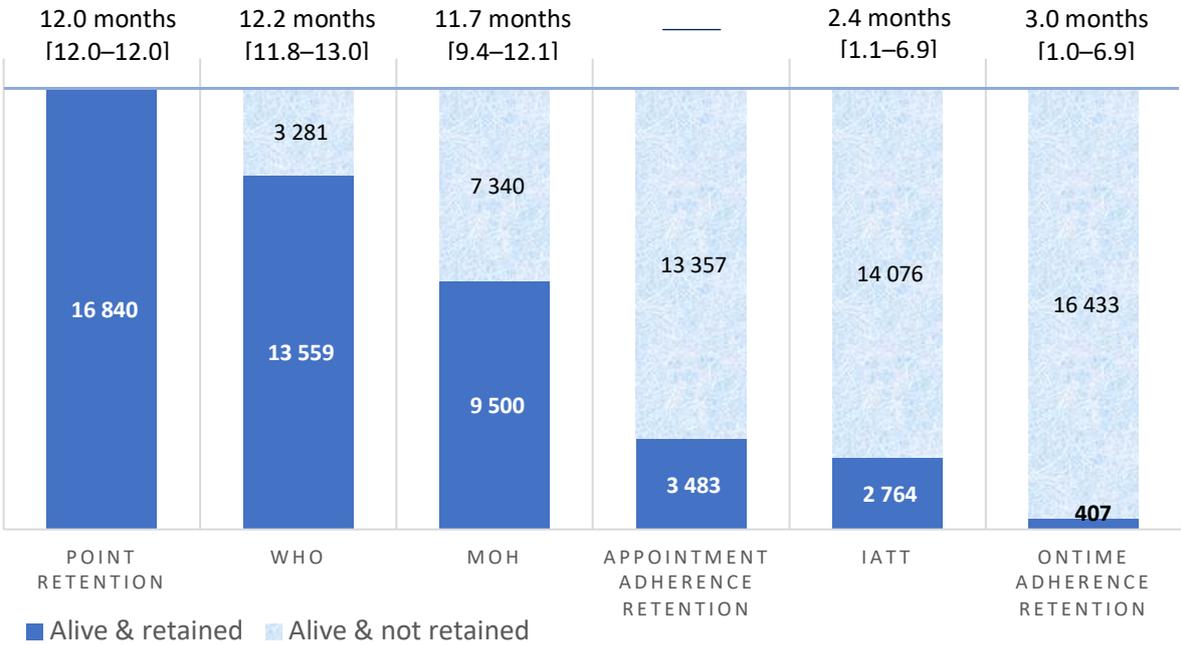
Retention definition	Advantages	Limitations	Programmatic practicality
'Point' retention	Easy to measure Assessed at a single time point Provide a transversal picture of retention	Does not consider visit consistency of the MIP Does not consider whether the women fully adhered to the 12-month visit schedule Not aligned with important PMTCT milestones (i.e. delivery, EID, or final HIV testing)	Programmatic definition of retention Achievable with simple health information systems (e.g. paper-based registers)
WHO	Easy to measure Assessed at a single time point Provide a transversal picture of retention More specific in detecting patients adhering to the 12-month visit (up to 15-months only)	Does not consider visit consistency of the MIP Not aligned with important PMTCT milestones (i.e. delivery, EID, or the end of breastfeeding)	As above
MOH	Easy to measure Assessed at a single time point Provides a transversal picture of retention Considers whether the women fully adhered to the 12-month visit schedule	As above	Programmatic definition of retention Achievable with simple health information systems (e.g. paper-based registers) Cohort based approach for calculation
IATT	Considers whether the women fully adhered to the 12-month visit schedule Captures visit consistency Can be adapted to align with the follow-up of the MIP	More complex to measure (ideally requires an ePLD or POC EMR) Not systematically aligned with national PMTCT follow-up guidelines but can be modified accordingly Probable need of data triangulation with other data sources (e.g. pharmacy, laboratory) and linkage with unique IDN	Relevant in capturing visit consistency of the MIP, can be aligned with important PMTCT milestones Ideal if integrated POC testing services for the MIP are available Better alternative than single time point estimations
'Appointment adherence' retention	Considers whether the women truly adhered to the 12-month visit schedule Capture visit consistency Measurable with paper-based longitudinal cohort based registers (total # of completed visits done/total scheduled visits)	Does not capture the regularity or timeliness of completed visits Not aligned with important PMTCT milestones for the MIP Highly dependent on data completeness of denominator (# of scheduled visits) Need of data triangulation with other data sources (e.g. pharmacy, laboratory) and linkage with unique IDN	Achievable with simple health information systems Better alternative than single time point estimations
'On-time adherence' retention	Considers whether the women fully adhered to the 12-month visit schedule Ideal to capture correct levels of engagement in care for PMTCT (regularity and timeliness) Aligned with important milestones of PMTCT follow-up for the MIP	More complex to measure (requires an ePLD or POC EMR) Highly dependent on data completeness of denominator (# of scheduled visits) Need of data triangulation with other data sources (e.g. pharmacy, laboratory) and linkage with unique IDN Time consuming activity not compatible with one-stop model PMTCT services in the absence of electronic databases	Adapted for research purposes Not compatible with routine monitoring of retention in care of MIPs

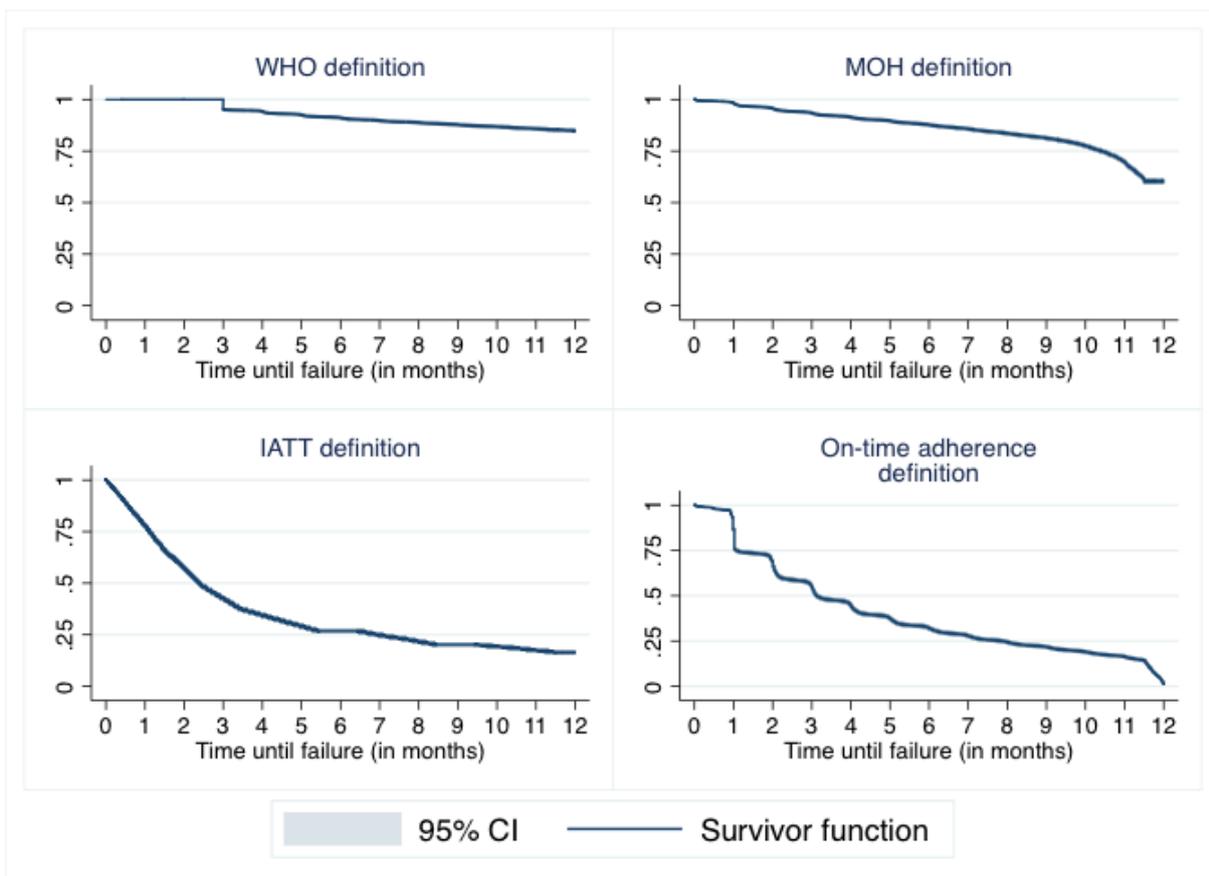
Note: EID, early infant diagnosis; EMR, electronic medical record; ePLD, electronic patient-level database; IDN, identification number; MIP, mother-infant pair; POC, point-of-care

Figure legends

Figure 1. *B+* pregnant women retained in care 12 months post-ART initiation: time to first failure event.

Figure 2. *Estimated Kaplan-Meier survival curves for retention over time, by retention definition.*





Time to failure event	0 months	3 months	6 months	9 months	12 months
WHO definition					
# at risk	16,840	16,838	15,359	14,793	11,448
# events	-	797	703	559	493
# events (cumulative)	-	797	1,500	2,059	2,552
Retention (95% CI)	-	95.3% (94.9-95.6)	91.1% (90.7-91.5)	87.8% (87.3-88.3)	84.8% (84.2-85.3)
MOH definition					
# at risk	15,750	14,743	13,834	12,829	6,099
# events	-	759	902	1,011	3,302
# events (cumulative)	-	759	1,661	2,672	5,974
Retention (95% CI)	-	93.4% (93.0-93.8)	87.7% (87.2-88.2)	81.3% (80.7-81.9)	60.3% (59.6-61.1)
IATT definition					
# at risk	16,840	7,163	4,514	3,402	1,855
# events	-	5,937	2,649	1,112	637
# events (cumulative)	-	5,937	8,586	9,698	10,335
Retention (95% CI)	-	42.5% (41.8-43.3)	26.8% (26.1-27.5)	20.2% (19.6-20.8)	16.4% (15.8-17.0)
On-time definition					
# at risk	15,232	8,508	4,907	3,265	154
# events	-	4,838	3,420	1,551	2,979
# events (cumulative)	-	4,838	8,258	9,809	12,788
Retention (95% CI)	-	54.8% (53.9-55.6)	32.2% (31.4-32.9)	21.8% (21.2-22.5)	1.2% (1.0-1.4)

Note: Kaplan-Meier survival curves for retention over time are presented by retention definition for B+ HIV-positive pregnant women up to 12 months post-ART initiation.

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5.3.3 Discussion

We demonstrated that measuring retention in care using ‘point retention definition’ does not reflect accurate level of engagement in care of women enrolled in PMTCT Option B+ program. Such definition of engagement fails to capture adherence to scheduled visits. It also highlights the health system’s inefficiency in incentivizing PMTCT clients to adhere to scheduled visits. Importance of attendance to scheduled visits and of adherence to treatment need to be emphasized at enrolment and throughout pre and post-natal care to achieve and ensure viral suppression. More flexible opening hours could also help patients living far away or women who have professional/economical/household commitments. This work has confirmed the findings of the literature review related to the heterogeneity of definitions used and the absence of international consensus.

This study only relates to HIV-positive women starting ART in pregnancy. However, with expansion of Option B+ and ‘Test and Treat’ strategy the number of women already on ART before pregnancy is expected to increase. These women are also likely to be more stable patients than those newly initiated on ART. Additional analysis in the first work showed good levels of retention in women already on ART before diagnosis of pregnancy (up to 84% for those who initiated ART in 2016). Nevertheless, the importance of regular attendance to scheduled visits also applies to these women as a key to maintain viral suppression.

Based on the results of the first part of the thesis, the median gestational age at ART start was 25 weeks and for those with available information on the date of delivery (19,150/31,186, 61.4% of ‘B+ pregnant women’ included), the median time between ART initiation and delivery was 3.6 months (IQR: 2.6 - 4.9). Therefore, a 12-month post-ART assessment of retention covers the time around delivery, known to be at increased risk of LTFU. Although not widely used in the literature, the IATT or the ‘appointment adherence’ retention definitions seems to be good alternatives to measure levels of engagement in care for mother-infant pairs. The added value of the IATT definition is that it assesses specific time points that can capture the period before and after delivery.

6 General discussion

6.1 Work synthesis

The aim of the PhD was to discuss, from a public health perspective, the programmatic challenges of engagement in care for PMTCT Option B+ strategy in sub-Saharan Africa, with the example of Mozambique. More specifically, we focused on three important programmatic aspects of engagement in care: retention in care of HIV-positive pregnant women initiating ART, HEI testing coverage and methods of measurements of retention in care with their potential operational impact. We also proposed some alternative definitions to better measure levels of engagement in care of the mother/infant pair enrolled under Option B+ programs.

The **first part of this work** provides an update of the PMTCT situation in Mozambique over the course of 4 years of program implementation from 2013 to 2017. It evaluated the Option B+ care cascade in ANC and investigated the risk of attrition from a large sample of more than 30,000 HIV-infected pregnant women on ART ('B+ pregnant'). We noted substantial improvement in outcomes in the care cascade: the proportion of women with documented HIV status increased from 93% in 2013 to 96% in 2017; the HIV testing yield (i.e. the proportion of clients undergoing HIV testing who test positive) decreased from 8% to 6% and the ART coverage increased from 42% to 95%. We also noticed a substantial increase in women already on ART enrolling in ANC of more than a 3-fold in 5 years, suggesting that ART coverage in Mozambique in pregnant women will reach saturation. As the PMTCT program matures, an increasing proportion of women will already be on ART when pregnancy will be diagnosed. When comparing 'B+ pregnant' women and 'own health' women, the retention at 12 months after ART initiation improved in both groups reaching 74% and 77%, respectively. Greater improvement was noted in the 'B+ pregnant' group, as retention increased from 64% in 2013 to 74% in 2016. Despite the seeming progress made, the overall attrition remained unacceptably high for both groups of women with 35% of women being lost to care within three months of treatment. In addition, year of ART initiation significantly impacted risks of attrition: this risk was 14% higher in 'B+ pregnant' women compared to 'own health' women when they initiated ART in the first year of program implementation. This difference in risk decreased over the years and reached similar levels in both groups by the end of the study period which suggest programmatic improvements achieved over time as the PMTCT Option B+ programme matured with better supervision and training of nurses on quality of care and counselling. And a greater degree of acceptability of lifelong treatment under Option B+ has been achieved; nevertheless we found that initiation of ART on the same day as HIV diagnosis significantly increased both the risk of having an NFU status and non-retention which indicates that women in Mozambique may still experience considerable staff pressure to undergo immediate ART initiation without sufficient time to disclose to their partner or relative or reflect on their HIV sero-status. Additional analyses showed that less than a half of women were retained in care 24-months after ART initiation. Women who initiated ART before the diagnosis of their pregnancy had similar patterns of improvement in retention rates than 'B+ pregnant' women. Finally, we also revealed high rates of retention (80% at 12-month post ART initiation) for 'B+ breastfeeding' women with no significant difference over the years. The retention rates in the latter group were even better than for the 'B+ pregnant' women and women who initiated ART pregnancy was formally detected. If women initiate ART before pregnancy the rate of MTCT can be similar to that observed in high-income countries [139]. The challenge will remain for the incident HIV infection during late pregnancy (for those accessing ANC late in their pregnancy), perinatal and breastfeeding period, as mother not being on ART during pregnancy and late ART initiation is strongly associated with MTCT [140].

Based on the gaps and challenges identified in this first part regarding persistent low retention rates of women enrolled in Option B+ in Mozambique, the next question would be to identify

what interventions could improve women's engagement in care? We have seen that although ART coverage in ANC reaches 95%, the estimated MTCT rate remains still unacceptably high at 15% in 2018. While efforts have been made to improve PMTCT services in the antenatal and maternity settings, the postpartum and infant components of the continuum of care of PMTCT programs have not been receiving equivalent attention and follow-up of HIV-exposed infants remains sub-optimal. Hence, the need also to identify what potential interventions could improve the post-partum component of engagement in option B+ PMTCT measured by the infant testing uptake.

The **second work** provides a critical overview of rates of maternal ART retention and HIV infant testing coverage when interventions to improve such outcomes are implemented. Fourteen studies were included, representing 6,311 HIV+ pregnant or breastfeeding women and 1,920 HIV-exposed infants receiving an intervention to improve PMTCT outcomes. All but one study reported data from PMTCT programs implemented in Sub-Saharan Africa. A wide variety of interventions were examined: three used peer and mentor support, one used community health workers or lay workers, three used mHealth interventions, three used provider-oriented strategies and four used a package of interventions. The interventions analysed in our review did not seem to show any improvement in retention in care for pregnant and/or breastfeeding women when compared to settings where no intervention were implemented. Indeed, when no intervention is implemented, retention at 12 months after ART initiation under Option B+ in sub-Saharan Africa is 76.4% (95% CI: 69.0–83.1) [141]. In our review, retentions estimates ranged from 61–78% at 12 months post-ART initiation. The highest results for infant testing uptake were obtained when a package of interventions was implemented. All these studies reported only on HIV infant testing outcomes and reported infant testing coverage above 70%. The major advantage of using of a combination of interventions is that it addresses simultaneously structural, biomedical, and behavioral barriers to MIP follow-up along the PMTCT continuum of care. Nevertheless, the remaining 30% of HEI who were not reached is substantial and demonstrates that follow-up of HIV-exposed infants during post-partum still remains a challenge in resource limited settings. These MIPs are probably those most vulnerable or hard to reach, experimenting frequent socio-economical barriers to access to care as previously mentioned, such as long distance, insufficient financial or social support, physiological and/or psychological changes related to the breastfeeding period. The review also enabled to point out serious heterogeneity in definitions used to estimate program outcomes. We also highlighted the importance of combining retention with level of clinical attendance during women follow-up to provide a better representativeness of engagement along the continuum of care in PMTCT programs. Likewise, the ideal definition for infant testing is the one used by Finocchiaro-Kessler et al which estimated the proportion of HEI receiving complete EID services by 2 week or 18 months' for HEI infant testing [121]. This definition allows to capture the important milestones an exposed-child should receive for correct PMTCT of HIV from enrolment after delivery to final HIV status determination, including initiation of co-trimoxazole prophylaxis and timely testing of HIV according to the national algorithm. In the Mozambican context, the results of this literature review point out 2 major findings. First, there is a need to explore the impact of a package of interventions to improve women retention in care specifically in the prenatal phase, focusing more on the most vulnerable and at risk women with low social-economical means and/or the most hard to reach. A package of intervention implemented at community level such as the PNCs or the combined package of adherence counselling, mHealth through text message reminders for clinic visits and stipends for food and transport could have the potential to improve women's engagement in early ANC care [125,126]. For the postpartum phase, however, none of the package of interventions reviewed offered integrated family planning services which was found to be associated with the risk of attrition in our cohort analysis. Thus, further research will be needed

to evaluate in the specific context of Mozambique, the impact of a package of intervention including integrated family planning services on improving post-partum engagement in care. Second, the retention in care estimates from the first work are probably overestimating the levels of true engagement of pregnant women initiating ART in our cohorts. Thus, if we consider levels of timeliness and completeness of attendance at scheduled visits during the first year under ART, how would such heterogeneity of measurements metrics impact of programmatic interpretation of study outcomes? Are there any alternative definition that can be used to better capture level of engagement in follow-up care of women initiating ART under Option B+? These are the questions we tentatively responded to in the third work of this thesis.

The **third work** has investigated the heterogeneity of definitions related to ‘retention in care’ for women enrolled under Option B+. It confirmed the findings of our systematic review highlighting the importance of combining appointment adherence with ART retention measurement to correctly evaluate levels of engagement in care, as using a ‘point retention’ definition most probably underestimates the true levels of engagement in care of women on ART. Six different definitions of ‘retention in care’ were analysed and compared to the ‘point retention’ definition used in the second part of the thesis. The definitions ranged from the most lenient definition using a ‘point’ retention approach, where women were considered retained in care if they had a visit at 12-months post-ART initiation or later, to the most stringent definition of ‘on-time adherence’ retention which considered only those with a reported visit at 12-months post-ART initiation with at least 75% of scheduled visits done on-time during follow-up. The more stringent the definition, the lower was the probability for women to be defined as retained in care: 85% and 60% when using the WHO and MOH definitions compared to 16% and 1% when using the IATT and ‘on-time adherence’ retention definitions. By the end of the first year, many women initiating ART did not adhere to their scheduled visits: median appointment adherence was 66% and median on-time adherence was 40%. Based on these results, we recommend either using the IATT or the ‘appointment adherence’ retention definitions as alternatives to better measure levels of engagement in care for mother-infant pairs. These definitions should better capture visit consistency along the continuum of care, embracing the delicate period around delivery and the post-partum phase. Furthermore, the IATT definition can be modified and aligned to important milestones in the pregnancy/post-partum phases to better capture regular ANC and childhood immunization visits. The recent 2016 WHO guidelines on ANC recommend a minimum of eight contacts to reduce perinatal mortality and improve women’s experience of care [142]. Thus, for example, an alternative of the IATT definition would be “attendance at a health facility and on ART treatment at 10, 20, 26, 30, 34, 36, 38 and 40 weeks of pregnancy, at delivery, and at 8 weeks, 3, 4, 9 and 18 months postpartum. Assuming that the woman either starts ART at first ANC visit or will already be on ART when she becomes pregnant (which the latter group is increasingly more frequent as observed on our first work).

KEY MESSAGES

- 1) Between 2013 and 2017, we observed improved uptake of HIV testing (93% to 96%), improved ART coverage (42% to 95%) in ANC in Mozambique
- 2) Improved 12 months retention in care for B+ pregnant women with an increase from 64% when ART was initiated in 2013 to 74% when ART was initiated in 2016 in Mozambique
- 3) Overall attrition was unacceptably high with one out of four women being lost to care within the first three months of treatment in Mozambique
- 4) A package of interventions has yielded better infant testing outcomes (>70% of HEI tested for HIV by 12-18 months post-partum) compared to a single-based intervention under option B+ programs
- 5) Importance of capturing attendance of scheduled visits during follow-up to better measure engagement in care along the PMTCT continuum. Proposed outcome definitions: 'Attendance at a health facility and on treatment at 1, 2, 3, 6, 9 and 12 months post-ART initiation' (IATT definition) or 'attendance at a health facility at 12-months post-ART initiation and \geq 75% of appointment adherence to scheduled visits' ('appointment adherence' definition) for maternal retention and 'proportion of HEI receiving complete EID services by 2 weeks or 18 months of age' for HEI infant testing.

6.2 Limitations and methodological challenges

It was unfortunately not possible to measure maternal viral suppression and the full PMTCT cascade including vertical transmission due to unavailability of patient level VL test results in the database and absence of link between the clinical and laboratory HIS. In addition, although Mozambique national guidelines recommended a VL monitoring for HIV-infected pregnant/breastfeeding women under Option B+ at 3 and 12 months after ART initiation and annually thereon, very few patients actually received testing and had their test results entered in the ePLD: of the 31,186 'B+ pregnant' women included, 23 (0.07%) had a result available in the database.

No information on pregnancy outcomes or exposed infant related data were collected in the ePLD. Therefore, the paucity of post-partum information did not allow us to analyse these variables that could have influenced the interpretation of our results. The patient status ('B+ pregnant' vs. 'own health') can change over time due to multiple pregnancies; thus, our primary exposure variable could be considered as a time-varying variable. However, we considered the 'patient status' as a fixed variable for the following reasons: for the 'B+ pregnant' group the median number of reported pregnancies per woman was one pregnancy ([IQR: 1-3]), 42% (19,013/ 44,998) had missing information on actual date of birth and no information on duration of breastfeeding was collected.

Although it was possible to distinguish between LTFU and death (if date of death was recorded in the patient file), we know that a significant proportion of deaths remain unreported in such limited resource settings where true outcomes of LTFU patients cannot be systematically ascertained [143]. For this reason, we chose to estimate factors associated with the combined event of LTFU *and* death (i.e. 'non-retention') after excluding patients transferred-out.

Due to the nature of the paper-based registers and the lack of data triangulation between health facilities, if a woman attends more than one HIV or ANC clinic without providing voluntarily her HIV identification number, she will be considered as a new patient initiating ART. This often happens when she fears stigma and discrimination. As a mitigation action after merging

all 86 sites ePLD together, we searched for duplicate patients using the following data elements: sex, age (or date of birth), outcome status, date of outcome status, date of enrolment, last date of visit. If a duplicate was found, data was reviewed on a case by case basis and if applicable, merged into one single patient follow-up using the first HIV identification number attributed. This exercise is also routinely done at central level before quarterly reporting. It is not possible to evaluate to what extent duplicate patients impact on study results. Nevertheless, we can assume that this proportion is similar in both patient groups.

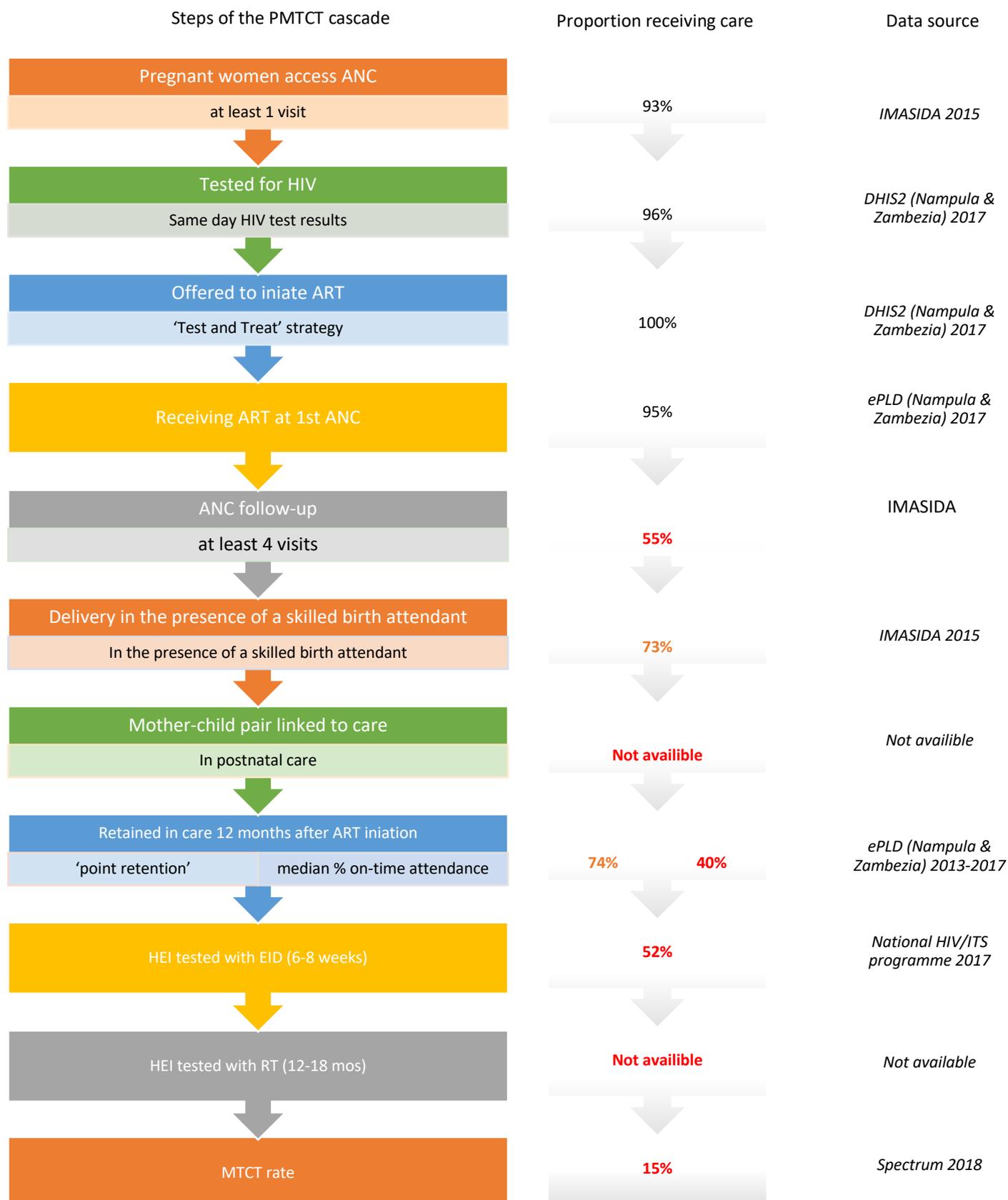
6.3 The PMTCT Option B+ care cascade: success and challenges

Based on results from this thesis and available population-based surveys done in Mozambique, we have re-created a detailed PMTCT Option B+ cascade of care (Figure 6.1). Considering each step of the cascade, 93% of pregnant women have enrolled in the first ANC visit with high HIV testing uptake and ART initiation $\geq 95\%$ for those tested HIV-positive.

However, numerous challenges remain. We observed that the first ANC visit is performed late in pregnancy, only at the beginning of the 3rd trimester and 14% of women dropped-out of care immediately after ART initiation, meaning they did not receive treatment. An estimated 55% of pregnant women complete their required four ANC visits and 73% of them delivery in the presence of a skilled birth attendant. There is a persistent low rate (74%) of retention in care 12 months after ART initiation and only 40% of scheduled visits during follow-up are done on-time. Finally, infant testing uptake remains low (52%) with an estimated MTCT rate of 15% in 2018.

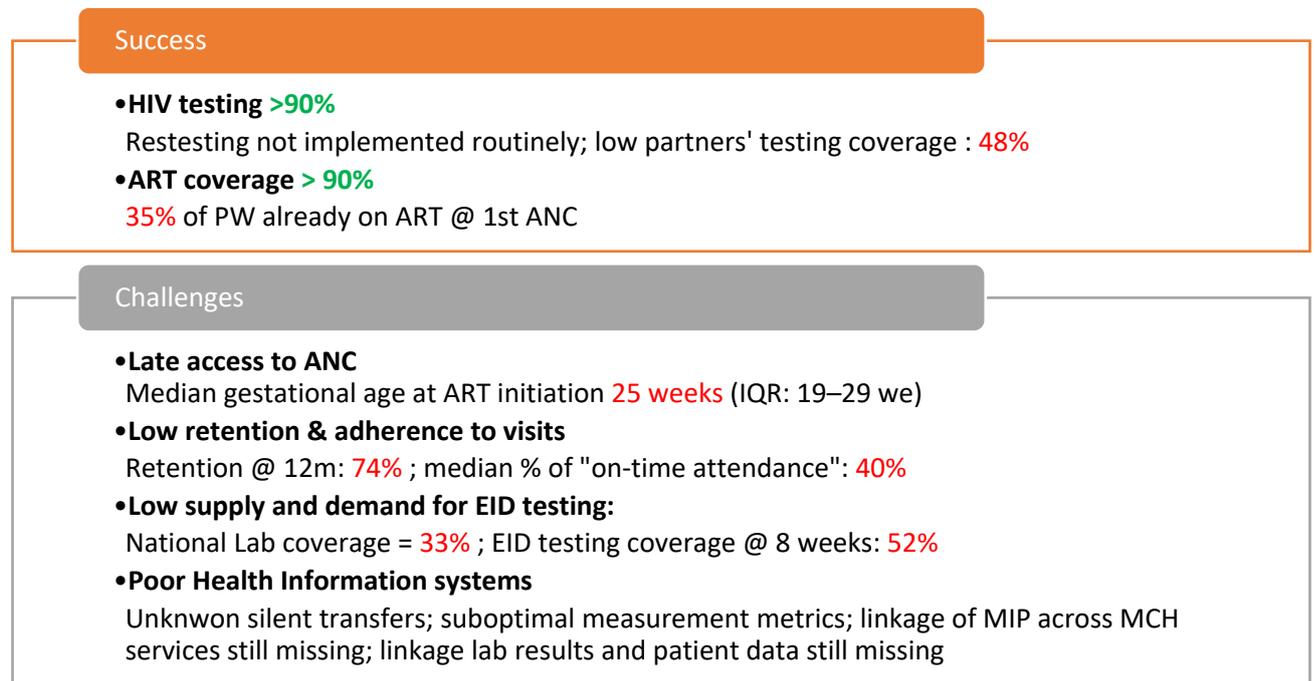
The main successes of the program owed to the strong political will of the Mozambican government since 2011 to accelerate the response for elimination of MTCT through the development of a series of national policies; an accelerated expansion of PMTCT services at the health facility providing PMTCT services in MCH through a “one-stop model” and “test and treat” strategy. The integration of ANC and HIV services coupled with the task-shifting from clinicians to nurses of ART initiation, although programmatically challenging in the first years of program implementation has resulted in high uptake of HIV testing, improvement in ART coverage and a better acceptance of ART initiation in HIV-positive pregnant women over time.

The challenges remain during follow-up of women and their HIV-exposed infants as shown in the cascade figure above. Lost-to follow-up occurs because of barriers such as low socio-economical means that can be exacerbated during the post-partum period (i.e. depression, house chores or silent migration). In addition, weak health systems such as low supply and demand for early infant testing and poor health information systems are also contributing factors of the low performance of PMTCT Option B+ in the country. The heterogeneity of measurement metrics, without international consensus, makes it even more difficult to estimate correctly levels of engagement in care for pregnant women enrolled under ART. Finally, the follow-up across various MCH services is still the important missing component of an efficient HMIS to track correctly the MIP across the continuum of care. Figure 6.2 summarizes the successes and challenges of PMTCT Option B+ in Mozambique.

Figure 6.1 : Summary of the PMTCT care cascade in Mozambique

Note: figures for proportion receiving care are those from most recent data available; percentages presented are estimated percentages from the row above; EID testing coverage is calculated using the number of HIV+ pregnant women recorded in ANC during the period.

Figure 6.2 : Summary of the success and challenges of the PMTCT Option B+ program in Mozambique



6.4 How far is Mozambique from virtual elimination of MTCT of HIV by 2030?

Mozambique is still a stretch away from virtual elimination of vertical transmission of HIV (Table 6.1). Great efforts have been made, as discussed previously, but the Achilles' Heel to achieving virtual eMTCT of HIV is the 'leakage' of women and infants during follow-up after ART is initiated in ANC with 3 major challenges directly linked to their engagement in care: 1) sub-optimal retention of women after ART initiation, 2) low infant testing coverage and 3) a weak health information system to measure correctly PMTCT outcomes.

Table 6.1 : Targets versus current situation in Mozambique in 2018: main indicators for validation of eMTCT of HIV

WHO country validation criteria	Target	Mozambique achievement
Number of cases of HIV per 100,000 live births	< 50 cases	NA
Transmission rate in breastfeeding population	< 5%	15%
Access to ANC for pregnant women	>95%	93%
Testing of HIV in pregnancy	>95%	96%
Treatment for pregnant women diagnosed with HIV	>95%	Receiving ART @ 1 st visit =95% Retained @ 12 m = 74%

Note: ANC: antenatal care, NA: not available.

Results for the indicator 'Treatment for pregnant women diagnosed with HIV' are the probability of retention as provided by the retrospective cohort analysis.

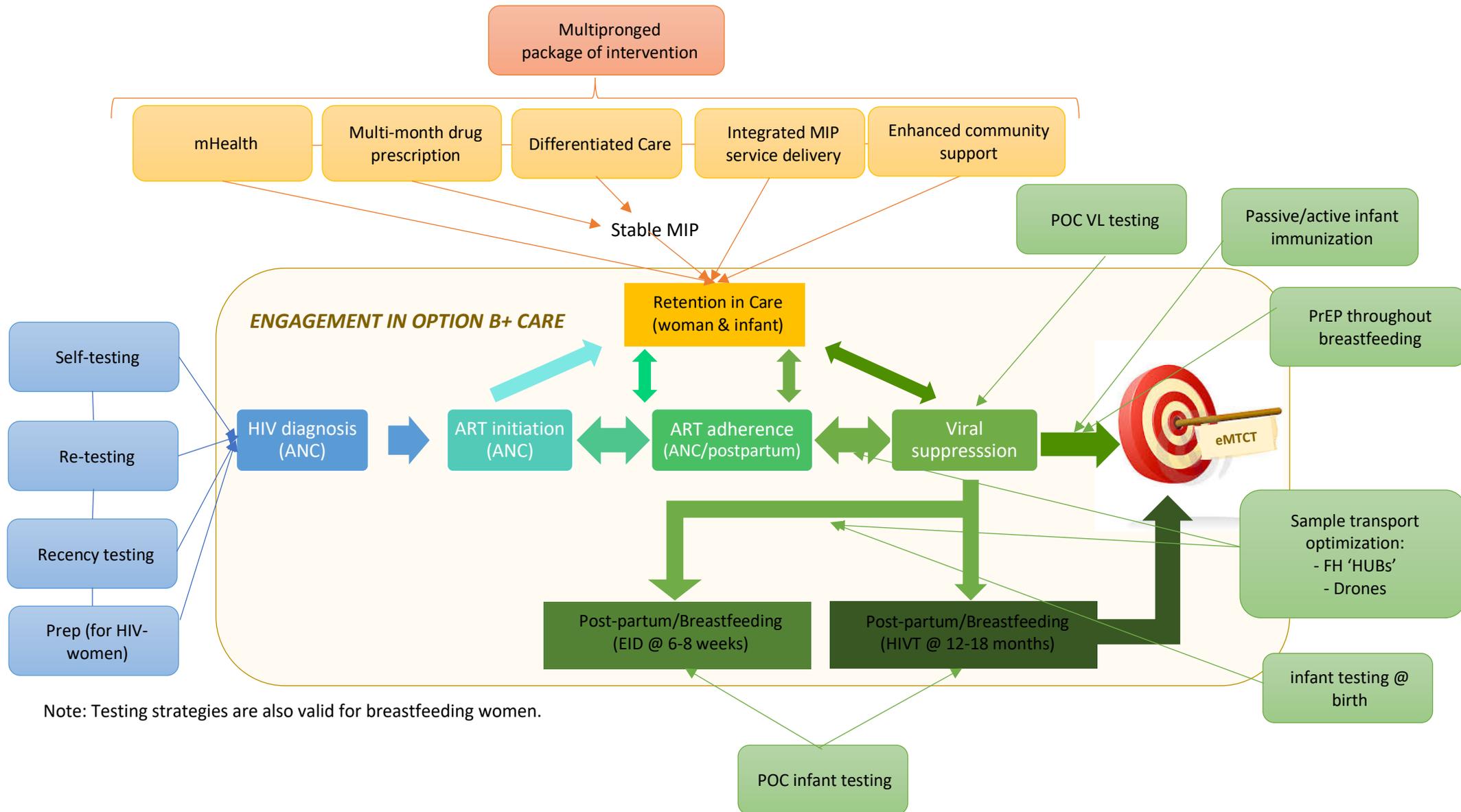
6.5 The 'last mile' to achieve eMTCT in Mozambique

As demonstrated through this work, engagement in care of the MIP is one of the major pillars to reach virtual eMTCT of HIV. There is no single risk factor that universally drives mother-infant pair's engagement in PMTCT care. Instead, the etiologies of disengagement are multi-causal and multi-levels.

Achieving the 'last mile' to reach eMTCT relies complementary strategies addressing simultaneously structural, biomedical, and behavioral barriers to the mother-infant pair care and treatment. These strategies combined would improve each step of the PMTCT cascade, *sine qua none* condition necessary to reduce the vertical transmission to less than 5%.

In the spirit of the 2016 'Start Free, Stay Free, AIDS Free' Super-Fast-Track framework, we address in this paragraph the feasibility of achieving virtual eMTCT in Mozambique by 2030 proposing innovative strategies which have demonstrated effectiveness in improving the continuum of care in similar settings (Figure 6.3).

Figure 6.3: Innovative strategies to reach the 'last mile' for eMTCT in Mozambique



HIV diagnosis

Significant numbers of women acquire HIV during pregnancy and while breastfeeding without being diagnosed. A meta-analysis of 19 studies showed that pregnancy and postpartum periods are times of persistent HIV risk, at rates similar to “high risk” cohorts[144]. MTCT risk was two to three times higher among women with incident versus chronic HIV infection in the postpartum period or in pregnancy and postpartum periods combined. In Mozambique, De Schacht et al. reported an estimated HIV incidence in postpartum women of 3.20/100 women-years (95% CI: 2.30–4.46), with the highest rate among the 18- to 19- year-olds (4.92 per 100 women-years; 95% CI: 2.65–9.15). In addition, of the new infections, 34% were identified during the first six months postpartum, 27% between 6 and 12 months and 39% between 12 and 18 months postpartum[145].

In Mozambique, the first ANC visit occurs during the 3rd trimester, only 55% of pregnant women complete four ANC visits. In this context, a great number of HIV-negative pregnant and breastfeeding women are not being retested and may be unaware of the need to take additional precautions to avoid acquiring HIV. This represents missed opportunities to improve HIV testing coverage and is of major concern in a country with such high HIV disease burden.

This highlights the increased risk of MTCT of HIV in pregnant women who are not engaged in care. The risk is particularly high for those newly infected due to the very high viremia associated with new HIV infection. The study from Mozambique reported a vertical transmission rate of 21% (95% CI: 5–36) among newly infected women[145]. Another study in Malawi presenting estimates of early MTCT of HIV in a nationally representative sample of HIV-exposed infants aged 4–12 weeks. The results showed higher risk of MTCT in women not on ART with an unknown HIV status during pregnancy compared to mothers on ART before pregnancy status was diagnosed (adjusted odds ratio 19.1, 95%CI:8.5–43.0)[140]. Furthermore, Mandelbrot L et al. showed that early access to PMTCT Option B+ services in ANC with rapid achievement of viral suppression reduces significantly the risk of vertical transmission: MTCT rate is 0.4% if ART is started in the first trimester, 0.9% if started in the 2nd trimester compared to 2.2% if started in the 3rd trimester. If the women is under ART at pre-conception, the MTCT rate drops to 0.2%[32]. Thus, in a country like Mozambique where fertility rate is high - 5.3 children per woman, ANC coverage (at least 4 visits) is low - 49% and immunization coverage of children aged 12 to 23 months completely vaccinated is sub-optimal at 65%, ART counselling for all HIV-positive women, and especially for those starting ART for their own health, should emphasize on the importance of engaging in regular PMTCT care and correctly adhering to ART throughout the pregnancy and breastfeeding period.

The introduction of HIV self-testing has increased the uptake of testing among men, female sex workers, young adolescents and first time testers in a variety of settings, including Malawi, Myanmar, the United Kingdom, and Zimbabwe[146–149]. Such intervention, especially in the community coupled with enhanced peer support and effective referral system through CHWs, could provide better access to HTC when access to health facility is impractical[150]. HIV retesting with the option of self-testing should be a standard part of the basic package of services for antenatal and postnatal care in places that have a high prevalence of HIV and long distance to health facilities is a barrier to access to care. To best adapt this strategy in the Mozambique context, further formative research is needed to understand how best to implement self-testing at the community level for it to be acceptable and successful.

Another HIV prevention strategy for women within sero-discordant couples is Pre-exposure prophylaxis (PrEP)[151]. Pregnancy is recognised as a period with increased HIV vulnerability. PrEP for pregnant and breastfeeding women taken daily reduces by 90% risk of transmission. Preventing HIV infection during pregnancy and breastfeeding has important implications for transmission to the child because women who seroconvert during pregnancy or breastfeeding are 18% and 27% likely to transmit the virus to their unborn child, respectively. Since 2016,

WHO recommends that women taking PrEP should continue taking PrEP at least during high-risk period of pregnancy and breastfeeding[12,152]. In a country where the prevalence of sero-discordant couples is 10%, PrEP could be an effective prevention strategy.

Effective eMTCT requires quick detection of HIV infection in women and immediate initiation of ART to obtain rapid viral suppression. As reported above, pregnancy and postpartum periods are ‘high risk’ periods for acquiring the virus and vertical transmission can reach more than 20%. A new emerging technology using Point-of-care recency tests (POC-RT), such as the Asante HIV-1 Rapid Recency Assay could be an innovative way for rapid detection of HIV incidence infection (< one year) in this group of ‘high risk’ women. The test combines HIV diagnosis and detection of recent HIV-1 infection in one testing device. It can be completed in 20 minutes, making it a fast way to test individuals. The introduction of recency testing in routine HIV testing services was experienced in five countries in Central America by The Center for Disease Control and Prevention (CDC)[153,154]. It was shown to increase HIV case finding and linkage to services through index partner testing resulting in rapid response interventions. If used in MCH services, especially in ANC for partner case finding, recency testing can be advantageous in identifying populations, defined by behavior and/or geography, where current transmission is occurring. This could be further effective in high HIV burden locations where HIV testing yield in HTC services remain low.

Retention in care of MIP

A pooled analysis of the INSPIRE studies showed that scaling-up targeted interventions to improve retention would avert almost 3,000 infant infections annually in the 3 countries where the studies took place (i.e. Malawi, Nigeria, and Zimbabwe)[155]. Therefore, even the modest improvement of retention can translate into large numbers of infant infections averted. In Mozambique, under Option B+, women are immediately initiated on ART after HIV test results, under the ‘one-stop’ and ‘test and treat’ model. This has enabled to improve ART initiation reaching >95% of HIV-positive pregnant women on ART at first ANC visit. Therefore, ART initiation under Option B+ strategy may no longer be an issue but rather maintaining these women on ART through pregnancy, delivery and end of breastfeeding (which can be as long as two years post-partum) remains the principal public health challenge.

Considering expansion of the ‘Test and Treat all’ policy, the substantial increase in the number of HIV-infected pregnant women already on ART and enrolled in ANC is observed; of these a proportion will be stable and virally suppressed. Additionally, the increased volume of PLHIV attending health services has put further strain on the already weak health system of the country: Mozambique has low levels of human resources for health with only 8 doctors and 27 nurses per 100,000 people. Consequences observed at health facility level has been long waiting hours, poor clinical attendance with suboptimal counselling. Factors all contributing to disengagement from care for the mother-infant pair.

In the second work of this thesis, no single based intervention seems to improve ART retention for pregnant and breastfeeding women. The four studies which combined a package of interventions seemed to yield better infant testing outcomes than single-based interventions. Of particular interest are three studies which yielded the highest infant testing uptake: one used a differentiated model of care to provide integrated health care in the post-partum period and two others included mHealth interventions either to facilitate communication or provide reminders for clinical visits. Unfortunately, none of these studies have reported on women retention.

Nevertheless, differentiated models of care is a promising solution especially for high volume sites[156]. The advantages are numerous: reduce burden on the health system and on the patient while ensuring a tailored client-centered service approach. In addition, less frequent visits can increase the likelihood of retention and can improve clinical outcomes[114,156,157]. The

model can vary from one setting to another, but in general patients receive multi-month drug prescriptions (i.e. 3 to 6 months) and enhanced community-based support by lay counsellors or peer educators. In the post-partum period, a package of combined services for both the mother and infant until the end of breastfeeding can also be delivered. WHO recommends that HIV-positive pregnant and breastfeeding women stable on ART for at least 12 months with evidence of viral suppression should be eligible to receive such services as they have a very low risk of HIV transmission[32]. Such models have been tested in women enrolled in PMTCT Option B+ programs in South Africa and show promising results[125,158].

This type of innovative service delivery models providing a MIP-tailored approach with integrate service delivery for both the mother and her newborn using a multipronged package of interventions to improve PMTCT outcomes can be adapted to the Mozambican context and can yield better levels of engagement in care. The objective being to improve retention in care while aligning to important women and child health care milestones, including rapid (or maintenance of) HIV VL suppression, regular attendance to ANC/post-partum visits, complete vaccination coverage, and infant HIV testing uptake. For example, a package of intervention similar to the PNCs model from South Africa can be adapted [125]. The difference is that the package should be started at enrolment into PMTCT during pre-natal care and would offer: integrated MCH services included one-stop shops, clinical visit at every session by an experienced nurse (ART, MCH), pre-packed medicine, VL testing, integrated family planning services, and Pap smear for mothers, and HIV testing, growth monitoring, feeding support, and immunizations and IMCI for children. Peer support groups would also be offered in this package and tailored to the pre-/post-partum stage in which the women is. However, in this new model of care from South Africa, multi-months ART dispensing is proposed coupled with community-based distribution of ART, adherence clubs and longer intervals between clinical visits[159]. But, no data yet is available to help define which criteria to use for defining a 'stable HEI'. Further research is thus warranted to better identify which infant can be safely enrolled and followed-up under such a strategy.

For better child service integration, MIP clinical visits should be aligned with standard post-natal care including immunization calendar, child nutritional assessments and timely infant testing. With an integrated service approach, infant testing can be offered to young children who present with illnesses using a specific screening tool for EID testing at EPI services, malnutrition services, in-patient ward or tuberculosis treatment sites[160,161]. However, a qualitative study in Tanzania that had explored the feasibility of integrating pediatric HIV prevention services with routine infant immunization visits revealed that perceived mandatory HIV testing, lack of confidentiality during testing and fear of stigma and discrimination were raised as a concern[162]. In a similar setting such as Mozambique, the success of such integrated services at health facility or community levels can be achieved only if confidentiality of patients is guaranteed.

A new challenge is posed by the introduction of DTG-based ART regimen recommended in 2016 by WHO, particularly in pregnant and breastfeeding women. At the time of the publication of the first recommendations, the biological mechanisms that underlied between this new regimen and adverse outcomes in pregnancy and birth were not completely understood. An important potential safety concern was reported suggesting that DTG may be associated with an increased risk of neural tube defects among infants born to women receiving the drug during the periconception period in the TSEPAMO study in Botswana [21,163]. Thus, a note of caution was published in December 2018 for using DTG in women and adolescent girls of childbearing potential [13]: "Adolescent girls and women of childbearing potential who do not currently want to become pregnant can receive DTG together with consistent and reliable contraception". In 2018, Mozambique has adopted the new WHO recommended DTG-based ART regimen and introduced it in a phased manner. Although, pregnant and breastfeeding women are not yet switched to the new regimen until further WHO guidance, an increased number of HIV-infected

women of childbearing age will already be on DTG-based regimen while becoming pregnant. Since then, a number of clinical trials, observational cohort studies, systematic reviews and drug safety monitoring data from Brazil, Botswana and northern countries have been published providing further insight into the association between DTG-based regimen and adverse birth outcomes. For example, data from the Antiretroviral Pregnancy Registry (APR) with most reports coming from North America and Europe, described central nervous system (CNS) defects and NTD in infants born to women receiving DTG as an integrase strand transfer inhibitor (InSTI). The authors reported a NTD prevalence of 0.40% (1 case in 248 births) for periconception DTG-based ART regimen [164]. Another clinical trial from Uganda and South Africa, the DOLPHIN-2 study, evaluated viral suppression at delivery in pregnant women initiating ART from 28 weeks gestation to DTG vs EFV plus 2 NRTIs [165]. The authors reported that DTG was well-tolerated and achieved more rapid virological suppression before delivery compared to EFV. Of 270 live births, congenital anomalies were reported in 17 infants (8 with DTG vs. 9 with EFV) up to 6 weeks of age; no NTDs were observed. Finally, additional data from the TSEPAMO study reported 5/1,683 NTDs among births to women receiving DTG at conception, bringing down the prevalence rate from 0.94% to 0.3% but still with a slight significant prevalence difference of 0.20% (95% CI: 0.01-0.59) compared to non-DTG based regimens [27]. Overall, NTD prevalence has decreased with increased exposure numbers, but it remains significantly higher than all other exposure groups. The NTD risk is thus not zero in the absence of drug but this risk is still relatively small. More recently, increased weight gain has been reported in patient receiving DTG-based regimens compared to those on NNRTI-based regimens [166,167]. For example, two major large efficacy trials of DTG conducted in Africa, the ADVANCE trial [168] and the New Antiretroviral and Monitoring Strategies in HIV-Infected Adults in Low-Income Countries (NAMSAL) ANRS 12313 trial [169] have demonstrated that DTG-based ART was noninferior to EFV-based treatment. However, in the ADVANCE trial, dolutegravir was unequivocally associated with excessive weight gain, particularly with TAF–emtricitabine. Patients treated with this regimen gained a mean of 6 kg with no leveling off at 48 weeks; 14% became newly obese. Similarly, in the NAMSAL trial, the incidence of obesity at 48 weeks was 12.3% in the DTG group, as compared with 5.4% in the EFV group. Based on these new findings, WHO now recommends DTG-based ART for all and this recommendation includes women of reproductive potential [170]. Knowing drug side effects, such as weight gain, and adverse birth outcomes are factors of LTFU in PMTCT programs, this will require a more active pharmacovigilance monitoring of adverse outcomes and assessment of safety of such drugs for the mothers and their exposed children [171].

Maternal viral load suppression

Recent evidence suggests that VL testing should be undertaken more frequently during pregnancy and breastfeeding, with the goal of achieving suppression before delivery and maintaining suppression during breastfeeding. Proposed interventions include VL testing four weeks prior to delivery to set the stage for postpartum interventions in the event of high maternal VL, including targeted birth testing and enhanced ARV birth prophylaxis [12,172]. With low laboratory coverage, particularly in rural primary health care settings, an alternative option would be the use of Point-of-Care (POC) VL testing to monitor viral suppression. HIV-positive women could be tested at the clinical visit and receive same-day results [173–176]. POC devices for virologic testing machines are likely to be too expensive to be placed at all primary care facilities. However, they would have the potential to greatly increase access to virologic testing by at least two approaches. Either they could be placed at intermediate level facilities (i.e. district “hubs”) so that patients could periodically be referred to those centers for

testing, or mobile labs could periodically be scheduled to visit primary health centers to offer such testing to eligible patients⁷.

Improving HIV-pre-exposure prophylaxis for infant

Using Nevirapine as a single-agent for PrEP in HIV-exposed uninfected infants has been demonstrated to significantly decrease HIV transmission through breastfeeding during the first 6 months of life [177]. In 2016, Nagot et al. demonstrated in 4 sub-Saharan Africa settings that the use of lopinavir–ritonavir and lamivudine as an extended PrEP strategy through breastfeeding in HEI up to 50 weeks was safe and led to very low rates of HIV-1 postnatal MTCT of 1.4% and 1.5%, respectively [178]. Based on these findings, there is a potential to further extend infant ARV prophylaxis throughout breastfeeding exposure to reduce risk of HIV transmission and make breastfeeding safe [179]. In the context of Mozambique where we have highlighted that a substantial proportion of pregnant and breastfeeding women access late MCH services, or for whom HIV infection is diagnosed postnatally, maternal ART alone in such cases would be sub-optimal to prevent breastfeeding transmission [180]. Thus, longer course of infant PrEP throughout the breastfeeding period in this case should be evaluated for safety and efficacy as this strategy could be a potential intervention to help reach virtual elimination of HIV in the country [181].

Infant HIV testing

Early infant diagnosis of HIV is one of the biggest challenges in PMTCT programs in Mozambique. On the demand side, programmatic data from 2018 shows only 91,776 HEI of the estimated 116,371 HIV+ pregnant women were enrolled in the at risk child clinic, and 71,754 (78%) of them had a sample collected for PCR analysis within 8 weeks of age which represent an estimated population based coverage of 62%[94]. On the supply side, EID has been gradually expanded and by the end of 2018 was available in 1,401 health facilities (92% of PMTCT facilities with Option B+). However, national coverage of laboratories processing EID remains low: 135 of 400 laboratories in the country process VL/EID testing by end of 2018. The long delay in returning test results often causes loss-to-follow-up of the MIP.

In addition to low EID supply and demand challenges, children who acquire HIV in utero have increased risk of rapid disease progression and higher mortality rates than children who acquire HIV through breastfeeding, highlighting the need to provide treatment as early as possible after diagnosis confirmation[182]. Diagnosis at birth has shown to improve infant outcomes. South Africa is among the countries now conducting testing at birth and once the infant reaches 10 weeks[183]. In a setting such as Mozambique where EID coverage is poor, at-birth testing could be a good option to reduce the HEI who are lost to care before 8 weeks of age.

Similar to VL testing for HIV-positive pregnant women, increase in access to point-of-care technologies for EID (POC EID) would make a massive difference; increasing both rapid diagnosis of infants living with HIV and improve timely pediatric treatment initiation in a cost-effective way. Jani et al. reported in 2017 testing outcomes of POC EID compared to the standard of care (SOC) using conventional laboratory testing in Mozambique[184]. In the SOC arm, the median turnaround time for conventional EID was 125 days whereas all results for infants tested by POC diagnostic were available at the health facility. Of the POC results, 99.5% were provided to the infant's caregiver, compared to 65% of the SOC test results. In a UNITAID

⁷ Since 2016 the MOH (MISAU) has been rolling out POC EID testing and training DPSs and health facilities workers to perform the test in Maputo Province, Gaza, and Sofala. Currently, approximately 5% of PMTCT health facilities are offering POC EID.

supported project, the routine use of POC EID in sub-Saharan African countries improved significantly the proportion of results with a turn-around time of less than 60 days compared to conventional testing methods (99.5% versus 11.8%). All results using POC EID were returned to the caregiver on the same day as the test was performed, compared to a median of 122 days with conventional methods; and 87% of HIV-positive children were initiated on ART within 60 days compared to 13% using conventional testing methods[185]. The strategy has the potential to identify and fast-track ART initiation in infants especially in pediatric in-patient ward, malnutrition or tuberculosis services where HIV testing yield in children are the highest. As mentioned above, the success of such intervention can only be achieved if confidentiality of settings are guaranteed to maintain patient privacy.

While waiting for larger scale use of POC EID, another approach to enhance transportation of EID samples for conventional laboratory diagnostic is to use health facility ‘HUBs’. Based on a geographical mapping of health facility networks using Geographical Information System (GIS) and of quality of road access, regional referral hospitals, district hospitals and other health facilities are identified as sample transport ‘HUBs’ to receive samples and results at the sub district level. The ‘HUB’ model has been tested in Uganda and significantly improved referral network drastically reducing transportation costs by 62% and reducing turn-around times by 46.9%[186]. This low-cost health system strengthening initiative could critically improve quality of laboratory and diagnostic services in Mozambique.

Finally, a recent innovative strategy to enhance healthcare delivery is the use of drones for sample transportation or delivery of medicine to health care workers or patients. Drones are pilotless aircrafts that were initially used exclusively by the military but are now also used for various scientific purposes including healthcare service delivery. Their technical capabilities and ease of use can benefit access to health services in remote rural areas with difficult road access which otherwise would be impossible to reach in a timely manner[187]. In the context of PMTCT health care services, drone-aided delivery and pickup of blood samples have the potential to reduce transportation and the turn-around time for early infant testing. In Malawi, a private company partnered with UNICEF to pilot the transport of EID samples from a remote clinic to a central laboratory in the capital Lilongwe. The test flight showed promising results leading to a larger scale project with a cost comparison with road transport[188].

Passive or active immunization

Finally, we have talked about *virtual* elimination of MTCT of HIV. Although efforts are crucial for Mozambique and other resources limited countries to attain UNAIDS’ ‘Global Plan’ targets, we should strive towards the *complete* elimination of MTCT of HIV, which will in turn accelerate towards the ultimate goal of an AIDS-free generation by 2030. Efforts to improve engagement in care of the mother/infant pair along the PMTCT continuum, addressing the gaps we have discussed, is the first step. Complete elimination through this mode of transmission will require additional measures[189,190]. Passive or active immunization of the mother and/or infant may enable to eradicate this form of transmission[191,192]. Few studies have analysed the combined strategies of ART with immunotherapy and showed promising results[193,194]. For example, the passive administration of broadly neutralizing antibodies (bNabs) to HIV-1-exposed infants has the potential to further (and fully?) protect from postnatal HIV-1 transmission[194]. Further research combining current preventive packages with vaccination or passive immunization is warranted to identify potentially efficacious interventions to help achieve the goal of a generation free of HIV by 2030.

Strengthen the Health Information System (HIS) for better data reporting

PMTCT Option B+, compared to ART in the general adult population and to previous PMTCT Options A and B, have the unique particularity of intersecting two cascades: one for the prevention of HIV infection in children and another for the life-long care and treatment of mothers[61]. The HIS in resource poor settings such as Mozambique has thus an additional challenge to improve collection of accurate data on the continuum of care across service delivery sites with strong linkages of the mother–infant pair, especially to measure important impact indicators such as HIV incidence in pregnant and lactating women who were initially HIV negative, viral suppression in HIV-positive women and MTCT of HIV.

In Mozambique, challenges persist to maintain a robust HIS system to track the mother-infant pair which also needs to mirror the more and more frequent changes in WHO and national PMTCT and HIV treatment guidelines. PMTCT interventions are provided through various service delivery points. Currently, the paper-based HIS at health facility limits the ability to analyse MIP outcomes using a longitudinal cohort approach. This can be easily done using an electronic patient-level database, as demonstrated in the second part of this thesis. However, patient-level retention in care is only monitored by partners who have ePLD allowing measuring this indicator with an estimated coverage of 80% of all PLHIV in treatment in the country. But even so, in the absence of means to track the MIP across various entry points of the health sector, which is currently the case, gaps in capturing the full follow-up picture will still remain. The use of an electronic medical record compiling longitudinal follow-up data coupled with a unique national health identifier code would facilitate tracking mother–baby pairs throughout the health care sector from pregnancy through delivery and breastfeeding (both at community and facility levels)[195–199]. This follow-up should be done until at least two years post-delivery to measure final MCH outcomes and eMTCT criteria.

As mentioned previously, the current lack of linkage between the laboratory HIS and clinical information does not allow to estimate maternal viral load suppression and MTCT rates. Transfer of automated laboratory data from the laboratory HIS into a database format that enables linkage to clinical and pharmacy data would enable for example to rapidly assess the viral load response to antiretroviral therapy, to investigate interference between laboratory tests and drugs, to study the risk of adverse drug reactions, and to take immediate action for treatment failure[200,201]. It would also enable to link infant testing results to the mother’s profile for MTCT transmission outcomes. Linkage should ideally be real-time using clinical, pharmacy and laboratory databases linked through the unique national health identifier code. This would require multiple software applications at different entry points across the health sector, all interoperating together. OpenMRS, the official national patient-level open-source platform since 2016 has the potential for interoperability with other open-source platforms such as OpenELIS (Laboratory Information System) and OpenLMIS (Logistics Management Information System)[202]. Developing such a framework for interoperability of health information systems could significantly improve PMTCT program monitoring.

Global efforts have been made to have a common and harmonised M&E framework for monitoring progress for PMTCT programs with more emphasis on monitoring the impact of ART on MTCT and measuring the retention of pregnant women initiating ART and of mother-infant pairs[203]. However, the lack of consensus and absence of alignment of definitions make comparison of PMTCT outcomes difficult across countries and settings[204–206]. National and international stakeholders and researchers need to commit to more standardised reporting methodologies to allow international comparisons of PMTCT indicators. Based on the results of this thesis and the importance of engagement in care of the MIP, we recommend using ‘attendance at a health facility and on treatment at 1, 2, 3, 6, 9 and 12 months post-ART initiation’ (IATT definition) (or its alternative definition as suggested in chapter ‘6.1 Work synthesis’) or ‘attendance at a health facility at 12-months post-ART initiation and $\geq 75\%$ of

appointment adherence to scheduled visits' ('appointment adherence' definition) to define maternal retention and 'proportion of HEI receiving complete EID services by 2 week or 18 months' for HEI infant testing.

Reduce unintended incidence pregnancy

In this work, we have focused on women already infected by HIV. However, family planning remains a core pillar of the four-pronged approach to comprehensive programming to prevent MTCT[207]. We have seen that in Mozambique, women are the most vulnerable population with nearly a quarter of new HIV infections occurring among young women aged 15–24 years[1]. In addition, women's experiences and decisions regarding pregnancy are more influenced by social and cultural norms than medical advice[208]. Therefore, unmet needs in family planning remain high. In the 2015 IMASIDA survey, 49.6% of married women aged 15-49 years reported having unmet need for modern methods of family planning and only 27% of them used any form of contraception[79]. Studies have found that pregnant adolescents and young women living with HIV were much less likely than their older peers to start ARV prophylaxis, and there is evidence that they also have poorer outcomes along the cascade of PMTCT services[209].

In addition, the results of our first work highlighted the need for better integrated family planning services as in the absence of such services, the risk of attrition was significantly higher. In July 2019, following the new ART guidance for use of DTG-based regimen for all HIV-positive patients including women of childbearing age, WHO released a specific tool for “HIV treatment and contraceptive services integration implementation” [210]. This tool provides guidance to ensure access to integrated, rights-based, client-centred, high-quality contraceptive care for women and adolescent girls living with HIV and receiving ART across the life-course in HIV treatment programmes.

Thus, efforts to reduce the risk of MTCT by reducing the number of reproductive-age women acquiring the virus is a major HIV prevention strategy, especially for adolescent young women. To reach an AIDS free generation in Mozambique, both incidence of infection in women of childbearing age and unmet family planning needs should be reduced. Providing appropriate counselling, support and contraceptives to women to meet their family planning goals and spacing of pregnancies will optimise their health outcomes and reduce the number of infants exposed to or infected with HIV.

7 Conclusion

This work has provided a comprehensive view of the level of engagement in care under the PMTCT Option B+ strategy from ANC enrolment of HIV-positive pregnant woman to final HIV testing of the exposed infant. Highlights of the gaps in optimal engagement care of the mother-infant pair and its consequences on achieving virtual elimination of MTCT of HIV have been discussed. To reach eMTCT, Mozambique's government need to focus efforts to reinforce engagement in care of MIPs during follow-up, especially in the first 3 months after ART initiation in pregnancy.

We highlighted the exponential benefit of a multipronged approach to provide a package of interventions to improve each step of the PMTCT cascade. Nevertheless, the cost-effectiveness and sustainability of such interventions should be considered by both the national HIV program and the international stakeholders for programmatic decision making and policy change.

We also emphasized the importance for the international community to have a consensus approach for PMTCT programme outcomes measurement to allow national and international comparisons. If adherence to schedule visits is not considered, measurement of retention and infant testing will fail to accurately estimate program success.

Engagement across the continuum of PMTCT care is dynamic and impacts individual and population-level outcomes. Efforts to retain women under lifelong ART, ensuring their HIV-exposed infants receive the expected PMTCT services at the right moments along the continuum until final HIV status is determined, is the cornerstone of achieving an AIDS-free generation by 2030 in Mozambique.

8 Place of the PhD work in my personal scientific career

This 4-year PhD work has enabled me to combine the application of rigorous epidemiological and biostatistical methods with the knowledge and built-up experience of my 16+ years of career working as a medical epidemiologist in resource-limited settings in sub-Saharan Africa. My professional interest is further confirmed in the use of quality data to produce evidence-based results to help identify programmatic challenges and propose practical solutions. Focusing on infectious disease epidemiology, reproductive health and mother and child health has been and will always be my personal motivation. Thus, I will continue working as a public health professional, committed to high quality international development projects to improve human health and the well-being of the most vulnerable populations in world.

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Titre : Prévention de la transmission du VIH de la mère à l'enfant au Mozambique: engagement dans les soins et défis programmatiques de la stratégie B+

Introduction

En 2015, l'Organisation Mondiale de la Santé a mis en œuvre des nouvelles lignes directrices sur la prévention de la transmission de la mère à l'enfant (PTME) du VIH. Appelée « Option B+ », cette stratégie recommande que toutes les femmes enceintes et allaitantes séropositives initient le traitement antirétroviral (TARV) et le continuent à vie. Cependant, à la lumière des défis programmatiques de sa mise en œuvre, de plus en plus d'inquiétudes se font jour quant à l'efficacité de cette stratégie pour réduire réellement la transmission verticale du VIH. On observe en particulier des niveaux sous-optimaux d'engagement et de suivi dans les soins chez le couple mère-enfant en Afrique sub-Saharienne.

L'engagement dans les soins du VIH fait référence à un patient pleinement impliqué dans un processus de soins réguliers dynamique tout au long du continuum de soins du VIH avec l'objectif final de parvenir à la suppression virale permanente (1). Par conséquent, l'engagement dans les soins, trop souvent confondu avec la « rétention dans les soins », est vital pour les personnes vivant avec le VIH (PVVIH).

Concernant en particulier les programmes de PTME, l'engagement dans les soins implique que la femme séropositive et son bébé soient considérés comme étant une seule et même entité ; les avantages potentiels du TARV peuvent être par conséquent améliorés en réduisant le risque d'infection VIH de la mère à l'enfant. En outre, pour atteindre l'élimination virtuelle de la transmission mère-enfant (eTME), au moins 95% des femmes enceintes devraient bénéficier des soins de PTME. Dans ce contexte, l'engagement précoce et continu dans les soins de la période prénatale pour la mère jusqu'à 18 mois après la naissance pour le couple mère-enfant est essentiel pour les différentes étapes de la PTME tels que le contrôle rapide de la charge virale de la mère avant l'accouchement, le test de dépistage précoce de l'enfant à l'âge de 6-8 semaines et le test définitif du VIH à 12-18 mois (2,3).

Ainsi, le désengagement des soins de PTME a le même effet néfaste sur la suppression de la charge virale, que celui pour le traitement universel des femmes séropositives, mais à cela, s'ajoute en plus le risque d'échec de l'élimination de la TME du VIH. Dans un pays aux ressources limitées tel que le Mozambique, des interventions visant à améliorer l'engagement dans les soins des femmes inscrites dans les programmes de PTME dès le stade précoce de la grossesse est d'une importance primordiale si l'on veut que la stratégie Option B+ puisse permettre d'atteindre l'objectif de santé publique consistant à réduire le taux de TME à moins de 5% (4).

Objectifs

La thèse vise à mettre en évidence, du point de vue santé publique, les défis programmatiques relatifs à l'engagement dans les soins de la stratégie Option B+ en Afrique subsaharienne en utilisant l'exemple du Mozambique, un pays connu pour avoir l'une des prévalences du VIH les plus élevées au monde. Pour évaluer le niveau d'engagement dans les soins du couple mère/enfant, ces travaux ont porté sur trois aspects programmatiques de la stratégie Option B+: les résultats du programme de PTME avec un accent particulier sur la rétention maternelle sous TARV et le recours au dépistage du VIH chez l'enfant exposé, les interventions visant à améliorer les résultats de ces programmes et les méthodes de mesure de la rétention dans les soins et leur éventuels impacts programmatiques.

Les objectifs spécifiques de la thèse sont les suivants:

1. Quantifier le risque d'attrition associé à la raison de l'initiation du TARV (initiation de l'Option B+ dans la cadre de la PTME versus initiation pour la propre santé de la femme séropositive) au Mozambique ;
2. Décrire les interventions visant à améliorer les résultats du programme PTME B+ avec un accent particulier sur la rétention sous TARV de la mère et le recours au test de dépistage du VIH chez l'enfant ;
3. Évaluer l'impact des diverses définitions de « rétention dans les soins » sur l'interprétation des résultats programmatiques de la stratégie Option B+.

Méthodes

Pour répondre au **premier objectif**, une analyse empirique des données de routine des quatre premières années (2013-2017) de mise en œuvre du programme PTME Option B+ au Mozambique a été réalisée pour analyser les tendances annuelles des résultats programmatiques. Cette étude s'est focalisée sur la cascade des soins prénatals des femmes enceintes séropositives et sur leur rétention dans les soins à 12 mois après le début du TARV.

Pour répondre au **deuxième objectif**, une revue systématique de la littérature axée sur les interventions visant à améliorer la rétention maternelle sous TARV et le dépistage du VIH pour les enfants exposés a été réalisée. Cette revue systématique vise à synthétiser les différents types d'interventions évaluées et à discuter de l'hétérogénéité des paramètres de mesure utilisés pour définir à la fois la rétention sous TARV et le recours aux tests de dépistage pour les enfants exposés ainsi que leur impact sur les résultats d'interventions.

Pour répondre au **troisième objectif**, une analyse comparative utilisant six définitions différentes de « rétention dans les soins » a été réalisée pour mettre en évidence la variabilité des paramètres de mesure et discuter de leur impact sur l'estimation du niveau d'engagement dans les soins des femmes séropositives sous l'Option B+ au Mozambique.

Résultats

Manuscrit 1: « Cascade de soins de PTME et facteurs liés à l'attrition dans les quatre premières années suivant la mise en œuvre de l'Option B+ au Mozambique »

Objectif: Évaluer l'efficacité du programme de PTME Option B+ dans deux provinces du Mozambique à charge de morbidité élevée du VIH durant les quatre premières années de mise en œuvre du programme.

Méthodes: Nous avons évalué la cascade de la PTME dans les soins prénatals de juillet 2013 à décembre 2017 en utilisant des données agrégées des centres de santé et effectué une analyse de cohorte rétrospective avec des données individuelles des patientes. Nous avons comparé les taux de rétention après 12 mois de TARV entre les femmes séropositives ayant débuté un traitement dans le cadre de l'Option B+ (« enceintes B+ ») et les femmes non enceintes et non allaitantes ayant initié un traitement pour leur propre santé (« propre santé »).

Résultats: Un total de 916 280 femmes enceintes ont été inscrites en consultation prénatale (CPN). La proportion de femmes ayant un statut VIH documenté est passée de 93% en 2013 à 96% en 2017. La proportion de séropositivité a diminué de 8% à 6%, tandis que celle des femmes séropositives sous TARV passait de 42% à 95%. Parmi les 44 377 femmes séropositives ayant initié le TARV et incluses dans l'analyse de cohorte rétrospective, 35% ont été perdues de vue. Les femmes « enceintes B+ » débutant le TARV en 2015 étaient plus susceptibles de faire l'objet d'un suivi comparé aux femmes ayant commencé un traitement antirétroviral pour leur « propre santé » au cours de la même année (rapport de cotes ajusté: 0,77, intervalle de confiance à 95% [IC95%]: 0,64 -0,94, p = 0,01). Il n'y avait pas de différence statistique significative entre les deux groupes au cours des autres années durant lesquelles le TARV avait été initié. Parmi les patientes qui ont initié le TARV en 2013 et qui sont revenues

pour une visite de suivi après leur première visite (N=39 801), les femmes « enceintes B+ » présentaient un risque plus élevé de non-rétention que l'autre groupe (ratio de risque ajusté: 1,14, IC95%: 1,03-1,25). Ce risque diminue au cours des années suivantes avec aucune différence observée entre les groupes.

Conclusion: L'expansion du programme PTME Option B+ a donné des résultats positifs, notamment l'atteinte de taux élevés de dépistage du VIH et d'initiation du TARV dans les soins prénatals. Cependant, il reste encore des difficultés pour l'amélioration de l'engagement immédiat dans les soins et la rétention à long terme. La recherche de modèles alternatifs de prestation de services afin d'alléger les systèmes de soins existants et prévenir les pertes de vue est essentielle si l'on veut atteindre les objectifs 95-95-95 de PTME de l'ONUSIDA au Mozambique.

Manuscrit 2: «Interventions visant à améliorer les résultats des programmes de prévention de la transmission du VIH de la mère à l'enfant dans le cadre de la stratégie Option B+: une revue systématique»

Objectif: Examiner systématiquement les interventions visant à améliorer la rétention maternelle et le recours au dépistage de l'enfant dans les programmes de PTME Option B+.

Méthodes: Les bases de données électroniques et la littérature grise ont été consultées pour identifier les études publiées entre janvier 2010 et décembre 2018. Les résultats évalués étaient la rétention maternelle à 6, 12 et 24 mois depuis le début du TARV, le recours au diagnostic précoce infantile chez le nourrisson (âgé de 4 à 8 semaines) et le recours au test VIH rapide chez l'enfant (âgé de 12 à 18 mois). Les résultats ont été résumés en fonction du type d'intervention.

Résultats: 14 études ont été incluses. Quatre études ont rapporté des résultats relatifs à la rétention maternelle par le biais du soutien par des pairs, du déploiement d'agents de santé communautaires et par l'utilisation de tests CD4 au point de prestation de service. Ces interventions ont donné des taux de rétention de 74–79%, 61–78% et 70–74% à 6, 12 et 24 mois après l'initiation du TARV, respectivement. Les taux n'étaient pas significativement différents de ceux rapportés dans un contexte de soins standard (sans intervention). Douze études ont rapporté les résultats liés à l'utilisation de tests de dépistage infantile par le biais du soutien des pairs, de la sensibilisation promulguée par les agents de santé communautaire, d'envoi de SMS, de stratégies pour améliorer les services de santé donnés par le personnel de santé ou par le biais d'un ensemble d'interventions combinées. Les proportions d'enfants exposés au VIH testés étaient respectivement de 49 - 94% à l'âge 6-8 semaines et de 68 - 95% à l'âge 12 -18 mois. Un taux élevé de recours aux tests de dépistage infantile a été observé lorsque les interventions étaient combinées (> 94% des enfants exposés). Une hétérogénéité élevée des résultats a été observée, principalement en raison de la variabilité importante des définitions utilisées. Les résultats rapportés étaient probablement surestimés car mesurés sans tenir compte du niveau d'engagement dans les soins de la mère tout au long de son suivi.

Conclusions: Un ensemble d'interventions combinées pourrait effectivement éliminer différents obstacles à l'engagement maternel. Les définitions doivent être normalisées afin de réduire l'hétérogénéité existante entre les études et de permettre une comparabilité correcte des résultats dans le but de formuler des orientations politiques et programmatiques claires. Les indicateurs doivent être basés sur la qualité et le processus de prestations de services afin de permettre une évaluation précise du niveau d'engagement de la mère et de son enfant tout au long du suivi dans les programmes PTME.

Manuscrit 3: «Mesurer la rétention dans les soins pour les femmes enceintes séropositives dans le cadre des programmes PTME Option B+: l'expérience du Mozambique»

Contexte: L'échec de la rétention dans les soins des femmes enceintes séropositives pour le VIH sous TARV entraîne une mortalité accrue pour la mère et son enfant. Cette étude a évalué différentes mesures de rétention destinées à mesurer l'engagement des femmes tout au long du continuum de soins pour la PTME Option B+ au Mozambique.

Méthodes: Nous avons comparé la rétention dite « à un temps t » (présence de la patiente dans les soins à 12 mois après le début du TARV ou à tout moment par la suite) avec les définitions suivantes: vivante et suivie à 12 mois après l'initiation du traitement (Ministère de la Santé); fréquentation d'un établissement de santé jusqu'à 15 mois après l'initiation du traitement (Organisation mondiale de la santé); vivante et suivie sous traitement à 1, 2, 3, 6, 9 et 12 mois après l'initiation du traitement (Inter-Agency Task Team- IATT); et vivante et suivie à 12 mois après l'initiation du traitement avec une observance de 75% ou plus des consultations au cours au suivi (avec ou sans respect de la ponctualité des rendez-vous). Des courbes de survie de Kaplan-Meier ont été produites pour évaluer la variabilité des taux de rétention. Nous avons utilisé la rétention avec observance de 75% ou plus des consultations avec respect de la ponctualité des rendez-vous comme référence pour estimer la sensibilité, la spécificité et la proportion de patientes mal classées.

Résultats: En tenant compte de la définition de la rétention dite « à un temps t », 16 840 femmes enceintes séropositives inscrites aux services PTME Option B+ ont été identifiées comme vivantes et suivies à 12 mois après l'initiation du traitement. Parmi celles-ci, 60,3% (IC95%: 59,6–61,1), 84,8% (IC95%: 84,2–85,3) et 16,4% (IC95%: 15,8–17,0) ont été classées comme «retenues dans les soins» en utilisant la définition du Ministère de la Santé, de l'OMS, et de l'IATT et 1,2% (IC95% : 1,0-1,4) ont été classées comme vivantes et suivies à 12 mois en utilisant la définition de rétention avec observance de 75% ou plus des consultations avec respect de la ponctualité des rendez-vous. Toutes les définitions donnaient des taux de spécificité $\geq 98\%$. Les taux de sensibilité étaient de 3% avec 78% de patientes classées incorrectement selon la définition de l'OMS et 4,3% avec 54% de patientes classées incorrectement selon la définition du Ministère de la Santé. Basé sur la définition de la rétention dite « à un temps t », 97,6% des patientes sont mal classifiées. En utilisant les définitions de rétention de l'IATT et celle avec observance de 75% ou plus des consultations, les taux de sensibilité étaient également faibles (9,0% et 11,7%, respectivement); Cependant, la proportion de patientes mal classées était moins importante (15,9% et 18,3%, respectivement).

Conclusion: L'utilisation de définitions plus strictes produisait des taux de rétention dans les programmes de PTME plus faibles. Les décideurs et les responsables de programme devraient inclure l'observance aux visites de suivi lors de la mesure de la rétention dans les soins afin de mieux orienter la planification, l'expansion et le suivi des interventions.

Discussion et conclusion générale

Ce travail a fourni une vue d'ensemble du niveau d'engagement dans les soins dans les programmes PTME Option B+, depuis l'inscription de femmes enceintes séropositives à la consultation prénatale jusqu'au test final de l'enfant exposé au VIH. La mise en évidence de lacunes dans la prise en charge du couple mère-enfant et des conséquences néfastes sur l'atteinte de l'objectif d'élimination virtuelle de la TME du VIH, ont été discutés. Pour atteindre l'élimination virtuelle de la TME du VIH, le gouvernement du Mozambique doit concentrer ses efforts sur le renforcement de l'engagement dans les soins des couples mères-enfants au cours du suivi, en particulier au cours des trois premiers mois suivant l'initiation du traitement antirétroviral durant la grossesse.

Nous avons mis en évidence l'avantage d'une approche pluridimensionnelle consistant à proposer un ensemble d'interventions visant à améliorer chaque étape de la cascade de la PTME. Néanmoins, la rentabilité et la pérennité de telles interventions devraient être prises en compte

à la fois par le programme national de lutte contre le VIH et par les parties prenantes internationales impliquées dans les formulations de décisions stratégiques et changement de politique de santé.

Nous avons également souligné l'importance pour la communauté internationale d'adopter une approche consensuelle pour mesurer les résultats des programmes de PTME afin de permettre des comparaisons nationales et internationales. Si l'observance des visites programmées au cours du suivi n'est pas prise en compte, la mesure des résultats ne permettra pas d'estimer avec précision le succès du programme.

L'engagement tout au long du continuum de soins pour la PTME est un phénomène dynamique et a un impact sur les résultats programmatiques à la fois au niveau de l'individu et de la population. Les efforts visant à retenir les femmes sous TARV tout au long de leur vie, en veillant à ce que leurs enfants exposés au VIH reçoivent les services de PTME attendus au bon moment et ce jusqu'à la détermination du statut final du VIH, constituent la pierre angulaire de la réalisation d'une génération sans SIDA d'ici 2030 au Mozambique.

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