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"The continuum of care from HIV exposure to early diagnosis, early treatment and sustained viral suppression in infants, in southern Mozambique"

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SUMMARY

Following the Global plan for the elimination of pediatric HIV and the Start Free Stay Free AIDS Free framework, remarkable progress in the prevention of mother-to-child transmission (PMTCT), in treatment access and in reduction of pediatric AIDS related deaths, has been reported. However in 2018, new 160.000 pediatric infection occurred globally, only 52% of infants accessed early diagnosis and only half of the 1.7 million children living with HIV received antiretroviral treatment (ART). Recent data from the Population HIV Impact Assessment in 10 African countries reported 37% viral suppression (VS) among children 0-14 years. In the current global effort to attain elimination of new paediatric HIV infection, ensure early universal access to ART and achieve sustained VS among children, a better understanding of complexities in the PMTCT continuum of care till final infants' diagnosis, linkage to ART care for infected ones and VS pattern, is key for a tailored and effective response in this population.

In Mozambique, HIV prevalence among women of child bearing age is 15.4% and despite over 95% HIV testing and ART coverage among pregnant women accessing antenatal care, vertical transmission rate is 10%, unacceptably high, 16.000 new pediatric infections occurred in 2018 and VS among children is 46%. Data are scarce on the existing gaps in the PMTCT pathway and evidence on viral response to ART among infected infants who start early treatment is lacking.

The main objective of this project is to improve current knowledge on underlying gaps in the infants' continuum of care from HIV exposure to early diagnosis, early treatment and viral suppression in southern Mozambique, where HIV prevalence is 22.8%.

First, a cross sectional analytical study using data from the national 2015 HIV Survey was conducted to investigate factors associated to the condition of 'unknown HIV exposure status' and 'HIV exposure' in children under 2 years of age. The study found a high proportion of children with unknown HIV serostatus, 32%, and associated factors were living in the northern and central region of the country, in rural areas, mother with no education and male as head of the household.

Second, a retrospective cohort study analyzed the magnitude of HIV Exposed Infants lost to follow-up (LTFU) before definitive diagnosis and related factors, in southern Mozambique. A high rate, 16%, of LTFU was found; underlying factors were age older than 2 months at entry into post-natal care, non-exclusive breastfeeding and poor cotrimoxazole adherence. We also found that less than half of HIV infected infants were diagnosed early, before 2 months of age.

Third, a cohort study described viral response up to 18 months follow-up in infants who started ART at one month of age. Viral suppression (<1000 copies/ml) was achieved by 60% of infants, 47%

sustained VS thorugout the follow-up period; cumulative probability of VS among all infants was 43% at 6 months, 56% at 12 months, 73% at 18 months. The main constraint to achieve VS was adherence to treatment.

Finally, a qualitative analysis evaluated whether the standard adherence and psychosocial package (APSS) of care applied to infants' caregivers, identified correlates of viral response in infants starting ART at one month of life. Evidence showed that the routine APSS approach did not clearly and timely identified infants who had poor viral response.

Overall, this research project increased our understanding of some key gaps in the PMTCT and pediatric HIV program in Mozambique such as suboptimal access and high drop out of mom-baby pair from the program and some of associated factors. Another important finding was the poor viral response to ART among infants starting early treatment and the need of a tailored psychosocial support package to better address adherence's challenges among caregivers. Findings are important to inform the HIV and PMTCT program for designing differentiated model of care addressing mothers and their infant's specific needs.

Additional research is needed to study the magnitude of lost to follow-up of HEI in other provinces of the country and underlying socio-economic determinants especially gender dynamics within the family and the male role in contributing to the elimination of pediatric HIV. Moreover, further studies are crucial to evaluate the continuum of APSS care during infancy and childhood to obtain a more robust evidence factors affecting caregivers' adherence and how they can effectively be addressed.

RIASSUNTO

A seguito del Piano Globale per l'eliminazione dell'HIV pediatrico e del Start Free Stay Free AIDS Free framework, sono stati fatti notevoli progressi nella prevenzione della trasmissione verticale dell'HIV (PMTCT), nell'accesso al trattamento antiretrovirale (ART) e nella riduzione dei decessi dovuti all'AIDS pediatrico. Tuttavia nel 2018, 160.000 nuove infezioni pediatriche si sono verificate a livello globale, il 52% dei bambini ha avuto accesso ad un test per la diagnosi precoce e solo la metà dei 1,7 milioni di bambini infetti ha ricevuto il trattamento. Dati recenti della valutazione dell'impatto dell'HIV nella popolazione hanno riportato una soppressione virale (SV) del 37% tra i bambini. Nell'attuale sforzo globale per ottenere l'eliminazione di nuove infezioni pediatriche, garantire l'accesso universale precoce all'ART e ottenere una SV sostenuta tra i bambini, é necessaria una migliore comprensione del continuum di cure del PMTCT fino alla diagnosi finale, all'accesso ai servizi di cura e il pattern della risposta virologica nei bambini, per disegnare una risposta su misura ed efficace.

In Mozambico, la prevalenza dell'HIV tra le donne in età fertile è del 15,4% e nonostante piú del 95% delle donne in gravidanza che accedono alle cure prenatali abbiano fatto il test dell'HIV e ricevuto il tratamento antiretrovirale, il tasso di trasmissione verticale è del 10%, si sono verificate 16.000 nuove infezioni pediatriche nel 2018; la soppressione virale tra i bambini è del 46%. Ci sono pochi dati sulle lacune del programma PMTCT e sulla risposta virale all'ART nei bambini che iniziano il trattamento ad 1 mese di vita. L'obiettivo principale di questo progetto è migliorare le attuali conoscenze sulle lacune nel continuum di assistenza alle mamme e ai bambini esposti all'HIV fino alla diagnose, al tratamento precoce e alla soppressione virale nel Mozambico meridionale, dove la prevalenza dell'HIV è del 22,8%.

In primo luogo, è stato condotto uno studio analitico trasversale utilizzando i dati dell'indagine nazionale sull'HIV 2015 per studiare i fattori associati allo stato di esposizione all'HIV in bambini di età inferiore ai 2 anni. Lo studio ha rilevato il 32% di bambini con stato di esposizione all'HIV sconosciuto; i fattori associati erano: residenza nella regione settentrionale e centrale del Mozambico, nelle zone rurali, madre senza istruzione e avere come capofamiglia l'uomo.

In secondo luogo, uno studio di coorte retrospettivo ha analizzato la proporzione dei bambini esposti all'HIV che non hanno completato il follow-up (LTFU) fino alla diagnosi definitiva e i fattori correlati. È stato trovato un tasso del 16% di LTFU. I fattori associati erano l'età inferiore ai 2 mesi all'entrata nel servizio postnatale, l'allattamento al seno non exclusivo, la scarsa aderenza alla profilaxia con cotrimoxazolo.

In terzo luogo, uno studio di coorte ha descritto la risposta virale durante 18 mesi di follow-up dei bambini che hanno iniziato il trattamento a 1 mese di età. La soppressione virale (SV) (<1000 copie/ml) è stata raggiunta dal 60% dei bambini, il 47% ha mantenuto la SV; la probabilità cumulativa di SV era del 43% a 6 mesi, 56% a 12 mesi, 73% a 18 mesi; il principale ostacolo per ottenere la SV era l'adesione all' ART.

Infine, un'analisi qualitativa ha valutato se il pacchetto standard di supporto psicosociale (APSS) usato com i genitori dei bambini in trattamento, identifica i fattori correlati com il tipo di risposta virale. I risultati hanno dimostrato che l'approccio di routine APSS non ha identificato in modo chiaro e tempestivo i bambini con scarsa risposta virale.

Nel complesso, questo progetto di ricerca ha migliorato la comprensione delle principali lacune del programma PMTCT in Mozambico come l'accesso non ottimale e l'abbandono elevato della coppia mamma-bambino dal programma e i fattori associati; ha prodotto dati sulla risposta virale dei bambini che iniziano il tratamento ad 1 mese di vita e la necessità di un pacchetto di APSS su misura per i genitori di questi bambini.

I risultati sono importanti per informare il programma dell'HIV e PMTCT nazionale al fine della progettazione di un modello di assistenza differenziata per le madri e le esigenze specifiche dei loro bambini.

Sono necessarie ulteriori ricerche per studiare l'entità della perdita dei bambini esposti all'HIV dal follow-up e i determinanti socio-economici sottostanti, in particolare le dinamiche di genere all'interno della famiglia e il ruolo maschile nell'eliminazione dell'HIV pediatrico. Inoltre, ulteriori studi sono cruciali per valutare il continuum delle cure APSS durante l'infanzia per ottenere evidenze più solide sui fattori che influenzano l'aderenza dei genitori e come questi possono essere affrontati in modo efficace.

ABBREVIATIONS

AIDS	Acquired Immune Deficiency Syndrome
AJUDA	Addressing Joint Underperformance through Direct Assistance
ANC	Antenatal Care
ART	Antiretroviral Treatment
ARV	Antiretroviral Treatment
BCG	Bacille Calmette-Guérin
BF	Breast Feeding
CCR	Child at Risk Consultation
CCS	Healthy Child Clinic
CHER	Children with HIV Early Antiretroviral Therapy trial
CNCS	National AIDS Council
CTX	Cotrimoxazole
DBS	Dried Blood Spot
DNA	Deoxyribonucleic Acid
DSD	Differentiated Service Delivery
DTP	Diphtheria-Tetanus-Pertussis (vaccine)
EBF	Exclusive Breastfeeding
EID	Early Infant Diagnosis
EFV	Efavirenz
FP	Family Planning
HEI	HIV Exposed Infant
HF	Health Facility
HIV	Human Immunodeficiency Virus
HUI	HIV Unexposed uninfected infant
HUI	HIV Unexposed Unifected infant
INH	Isoniazid
LTFU	Lost to follow-up
LPV/r	Lopinavir/ritonavir
MCH	Mother and Child Health
MOH	Ministry of Health
NAT	Nucleic Acid Testing

NRTI	Nucleoside Reverse Transcirptase Inhibitor
NNRTI	Non-nucleoside Reverse Transcirptase Inhibitor
NVP	Nevirapine
PEES	Health Sector Strategic plan
PEN	National Strategic Plan for Response to HIV and AIDS
PEPFAR	President's Emergency Plan for AIDS Relief
PES	Economic and Social Plan
PI	Protease Inhibitor
PCR	Polimerase Chain Reaction
PICT	Provided Initiated Counseling and Testing
PLHIV	People living with HIV
PMTCT	Prevention of Mother-to-child Transmission
PNC	Postnatal Care
POC	Point-of-care
STI	Sexually Transmitted Infection
TDF	Tenofovir
VL	Viral load
VLS	Viral Load suppression
VT	Vertical Transmission
WHO	World Health Organization
ZDV	Zidovudine
UNAIDS	Joint United Nations Program on HIV/AIDS

CHAPTER 1 INTRODUCTION

1. INTRODUCTION

1.1 Elimination of Mother-to-child transmission of HIV

In 2011 UNAIDS elaborated the Global Plan for the Elimination of new HIV infections among children by 2015 and for keeping their mothers alive. The plan prioritized 22 countries[1] where 90% of pregnant women living with HIV resided (1). Two global targets were set: 1) to reduce the number of new pediatric HIV infections by 90% and 2) to reduce the number of HIV-related maternal deaths by 50%, emphasizing the importance of comprehensive care as an essential element to reach these targets. In 2016, building on achievements and lessons learned from the Global plan experience, a new framework, the 'Start Free, Stay Free, AIDS Free', was launched, setting new targets: 1) to eliminate new pediatric HIV infections by reducing the number of children newly infected to fewer than 40 000 annually by 2018 and fewer than 20 000 by 2020; 2) to reach 95% of pregnant women living with HIV and sustain them on lifelong HIV treatment by 2018 (2).

Since the beginning of the epidemic, great progress in drugs development has been made and evidence has been generated on the best antiretrovirals (ARV) combination to prevent vertical transmission of HIV and preserve mother's health. WHO guidelines have been evolving as more data became available: from the use of zidovudine (ZDV) administered during pregnancy and the first 6 weeks post-partum (Pediatric AIDS Clinical Trials Group-PACTG076) (3), to lifelong antiretroviral treatment (ART) for all HIV positive pregnant women ("Option B+") in 2013, with one pill a day of fixed-drug combination of tenofovir, lamivudine and efavirenz (4) and the recent dolutegravir based regimen, as the preferred ART for pregnant women (5).

Recommendations on HIV exposed infant prophylaxis have also been updated according to the best evidence: from single dose nevirapine (NVP) to the newborn, after the HIVNET012 trial in Uganda(6) to the recent enhanced prophylaxis of 12 weeks NVP plus 6 weeks ZDV for infants at high risk of acquiring infection (7).

Treatment for life and integration of opt-out HIV testing approach and ART care into mother and child health (MCH) service in several high burden countries, resulted in significant gains for prevention of mother-to-child transmission (PMTCT) programs (8). Globally HIV testing coverage of pregnant women increased from 44% in 2013 to 92% in 2018 and 82% of HIV infected pregnant women received ART compared to 49% in 2014 (9). The vertical transmission rate decreased from

[1] The Global Plan prioritized 22 countries: 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.

18% in 2010 to 9% and new pediatric infections have halved from 280.000 to 160.000. According to countries reports, transmission dynamics seem to have shifted towards an increased transmission during the postnatal period (10,11).

Unsolved challenges prevent reaching all women living with HIV and their infants undermining the elimination of pediatric HIV and achievements of set targets by 2020.

The first missing opportunity is poor HIV screening and re-testing of previously negative pregnant and breastfeeding women. Available data show high number of HIV incident cases in women during pregnancy and post-partum in Sub-Saharan African countries such as Uganda, Kenya, Zimbabwe and South Africa, Tanzania, Rwanda, Botswana and Mozambique ranging from 4.28/100 women-years up to 16.8/100 women-years (12–20). All these studies highlight the need to keep track of women who seroconvert in the pre-natal and post-natal period and have the higher risk to transmit the virus (21,22).

Although guidelines on HIV testing have been disseminated (23), implementation is not consistent among countries. A recent review on timing of maternal retesting, found that in high prevalence countries such as Kenya, South Africa, Tanzania, Uganda, Zambia, Zimbabwe, regular retesting was part of the norms; on the contrary, in others countries with high rate of vertical transmission, they were not consolidated (24). In some context, access to ANC and first HIV testing is also critical, being related to socio-economic correlates such as education, poverty and cultural factors. Literacy was associated with underuse of ANC service in Nigeria (25), Kenya (26) and Ghana (27), while in South Africa, Malawi, Tanzania, Uganda and Kenya a correlation was described between knowledge on health service and HIV and access and retention into PMTCT care (28,29).

Once the woman in engaged in care, suboptimal adherence to treatment and poor retention are frequent, leading to low level of viral suppression and high rate of vertical transmission. It is estimated that 20% of pregnant women who start ART during pregnancy are lost to follow up before giving birth (10). A review of studies on adherence reported 76% adherence to ART during pregnancy and 53% in the post-partum period to ART in Kenya, South Africa and Zambia (30). A pooled analysis evaluating lost to follow-up (LTFU) in 6 African Countries, found 49% LTFU between ANC and delivery, 34% LTFU between delivery and 3 months post-partum and 46% after Early Infant Diagnosis (EID) test (31). Data confirming retention challenges after the roll out of Option B-plus, described 6 months retention rate of 73% and the first 6 months after ART initiation the period with higher risk of defaulting care (32).

In 2013 WHO recommended viral load test (VL) to monitor treatment response (7), but since then, roll out has been slow and suboptimal test access has been reported (33). Among pregnant and breastfeeding women in Sub Saharan countries, VL coverage varied from 11% to 91%, with majority of countries below 50% and VL suppression (VLS) ranged from 30% to 98% at the time of delivery. Sustaining undetectable viremia was also found to be a challenge: in the same review only half of women who reached VLS, sustained suppression through 12 months post-partum (34). In South Africa 70% of women starting ART during pregnancy reached VLS at 12 months but 22% of them had at least one episode of viremia above 1000c/ml, which was more frequent in the post-partum period, in women who started ART in the 3rd trimester and with history of defaulting (35). Higher risk of rebound during pregnancy and post-partum among women already on ART before pregnancy, was confirmed by another South African study (36). Suboptimal VLS is a risk to develop drug resistance and to transmit a resistant virus (37). In Malawi, where VLS after 6 months of treatment was 84%, women with detectable viremia presented 35% of NNRTI resistance (38).

In pregnant and breastfeeding women, achieving and maintaining VLS is the ultimate goal, so monitoring VL frequently, throughout the breastfeeding period with provision of rapid intervention in case of detectable virus must be a priority for HIV programs (39). Attention should shift to the long-term results for achievements of desired health outcomes for HIV infected women and their infants.

A virologic test is the gold standard for HIV diagnosis in HIV exposed infants (HEI) under 18 months; it was recommended from 4-6 weeks of age (40) and now from birth (41) although a strategic introduction considering feasibility and capacity to manage a newborn on ART, is needed before expansion to primary health level.

The first technology available in low-middle income countries for EID, was around 2005 in few countries and gradually expanded in the following years. It uses dried blood spot (DBS) samples collected at health facilities and sent to referral laboratories for processing. The result turnaround time may take from 30-90 days and may contribute to late ART initiation of HIV infected infants and eventually to lost to follow up (42). In the last four years the Nucleic Acid Testing (NAT) simplified technology, at point-of-care (POC) operated by nurses at MCH service, using capillary blood from finger or heel-prick tests, providing same day test result, was expanded in some African countries, resulting in earlier and higher rates of ART initiation among HIV-infected infants (43). Despite the

expansion of conventional DBS and POC technologies, coverage of EID in the first 2 months of life, although improved from 31% in 2010 to 52% in 2018, remains appallingly low (10).

Along with the scale up of the POC technology, interventions to improve early access to post-natal care at site level and in the community need to be strengthened and we have already evidence of successful strategies such as mentor mothers (44). An early HIV test result is the key to early initiation of lifesaving treatment of an infected infant.

1.2 HIV infection in infants, early treatment and viral response

Globally 1.7 million children are living with HIV, half of them are receiving treatment and 160.000 new pediatric infections occurred in 2018. Majority of infected children are in Africa, where timely diagnosis and initiation of treatment cover only half of those in need, and where reported AIDS related deaths are still high, approximately 100.000 (9).

It is known that infected children experience rapid disease progression in the first 24 months of life and, if untreated, mortality is above 50% (45–47). In perinatally infected infants, starting ART as early as possible is crucial to reduce infants' disease progression and mortality which are higher in the first months of life (48–51). After the release of CHER trial results, showing 76% decrease in infant mortality and 75% decrease in progression to AIDS if treatment is start within 12 weeks of age (48), WHO recommended universal ART for children under 2 years (52). Following further evidence, criteria of the best timing to start ART changed and now treatment is recommended for all HIV-infected children, as soon as HIV is diagnosed, irrespective of clinical and immunological status (41).

Recommended antiretroviral (ARV) regimen also changed over time, from the initial regimen composed of 2NRTI + 1NNRTI drugs (AZT/ABC/d4T+3TC+NVP/EFV), d4T was stopped and in 2013 NVP was replaced with the Protease Inhibitor, lopinavir (LPVr) in younger children and from 2018, two Integrase Inhibitors, dolutegravir or raltegravir, are the recommended ARV to use in the first line treatment (5,53).

Progress in development of effective, tolerable formulations, easy to administer and to store, has been slower compared to development of drug for adults (54,55) and consists a challenge for HIV programs and especially caregivers.

Early identification of infected infants and ART initiation in the first months of life, has numerous benefits: starting treatment within the first 3-4 months of life has shown to have a better immunologic and virologic response (56–58); faster growth recovery, has been described in infants

starting before 6 months of age (59), improvement of neuromotor development was higher if treatment started before 12weeks of age (60). However, reaching and maintaining undetectable viremia in children has been shown to be problematic.

Sub-optimal viral response among children 0-14 years, in low and middle-income countries compared to those in high-income countries has been described (61). In a recent South African cohort of children 0-12 years, on PI-based ART regimen, cumulative incidence of VLS (<1000 copies/mL) at 6, 12 and 24 months was 57.6%, 78.7% and 84.0% respectively (62). Among children VL response varies according to age. In infants < 12 months of age, VLS rate was found to be lower compared to older children: at 12 months only 46.6% achieved VLS <50 copies/mL compared to 76.9% of children 6-12 years. The same study also found that infants had had twofold increased risk of VL rebound after reaching suppression (62).

A review of studies describing viral response in infants starting ART with age <12 months, found great variability in VLS, from 19% to 81%, showing no clear association between median age at ART initiation and viral suppression rates (63).

In case the virus has not developed resistance to ARVs, the major contributor to poor viral response in the pediatric population, is suboptimal adherence (64–67). Adherence to treatment is even more difficult in infants, who totally rely on caregiver's support and behavior for taking the medications (67). Younger age is also a risk factor for attrition from routine care (68) and consequent ART interruption.

Maintaining viral suppression will also prevent development of resistant virus and preserve pediatric regimens (69–71), a big constraint in Sub Saharan Africa where available drugs for younger patients are limited (72).

It is undeniable that to achieve long term benefits, prevent HIV-related complication and allow infants to grow into adolescence and live healthy lives, viral suppression must be reached early and maintained lifelong. HIV programs need to identify and address all the barriers and design urgent interventions to support health staff and caregivers for the best management of a child living with HIV.

1.3 The continuum of care of mother-baby pair from PMTCT to early ART initiation

Differently from the 'conventional' continuum of care described for adult HIV patients (73), the PMTCT continuum of care involves the mother and the infant and multiple transitions across different services at the health facility. Pregnant women have to move from the ART clinic to the

MCH clinic for pregnancy follow up, then within the MCH services from ANC, to Maternity, to Post-Partum care and then again back to the Adult HIV clinic. Health services need to be organized and staff prepared to receive the mother at any timepoint in the cascade, provide the due care and fill previous gaps if mother comes late or becomes lost during follow-up (74).

To achieve elimination of pediatric HIV, ensure the continuum of care in the PMTCT cascade is key. Each of the steps must be achieved, gaps identified and quickly filled in a short time period of few months during which the mother must start ART, be adherent, reach VLS and maintain undetectable viremia to reduce the chance to transmit the virus. Various models exist to offer all care components of the PMTCT pathway.

The first step of the cascade is to ensure that all women of child bearing age know their HIV status. Counselling and testing policies have evolved and HIV testing is available at Health facilities as a voluntary or provider-initiated approach at all services (23). Community based testing has been implemented to reach people who cannot access health facilities, through mobile clinic, home-testing, testing at school, in the work place and at other venue according to country policy.

If the HIV test is negative, retesting is recommended after 3 months, although guidelines may differ among countries. In case of a positive result, women enter the HIV care and treatment pathway and are offered lifelong ART for their own health and to prevent transmission to their baby. Once started ART attentive monitoring of VL is crucial.

At delivery the HIV exposed new born receives ARV prophylaxis and, in some countries, an HIV virologic test. More commonly the HIV test is offered at 4-6 weeks of age when mom-baby pair access post-natal care. Result is available in 1-2 months or on the same day if POC simplified technology is in place (75). After HEI enrolment in post-natal care (PNC), ARV prophylaxis is continued, cotrimoxazole prophylaxis is started, clinical monitoring is provided until 18 months or 2 months after weaning when the final HIV test is repeated (40). In the meanwhile, the mother receives ART, clinical and virologic monitoring at PNC with her infant.

In case the infant has a final negative HIV test he/she is referred to the Healthy Child clinic. In case the test is positive he/she is referred to the ART clinic to start treatment and continue follow up with the mother (Fig. 1).

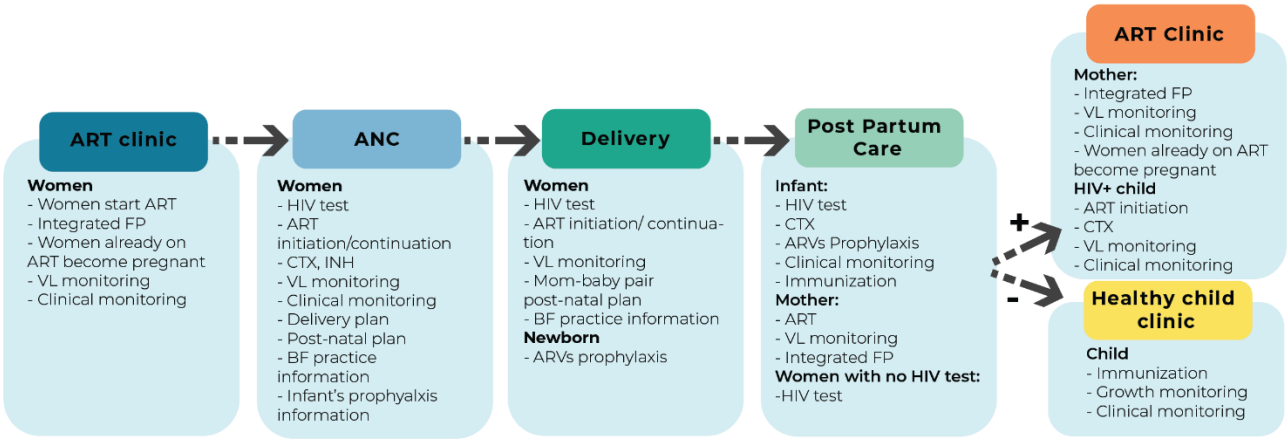


Fig1. PMTCT continuum of care and linkage to ART care

1.3.1 Gaps in the continuum of care

Gaps in the continuum of care in the PMTCT pathway till early treatment initiation for HIV infected infants and sustained viral suppression are summarized below (Fig.2):

I. Women during pregnancy and breastfeeding are not aware of their HIV status and are not on ART (10,28)

II. Pregnant and breastfeeding women seronegative at the first HIV test do not repeat the test to rule out incident HIV infection (12,15,18,22,76)

III. Pregnant and breastfeeding women living with HIV do not start treatment or start late or are not adherent to ART throughout pregnancy or breastfeeding (10,30,31)

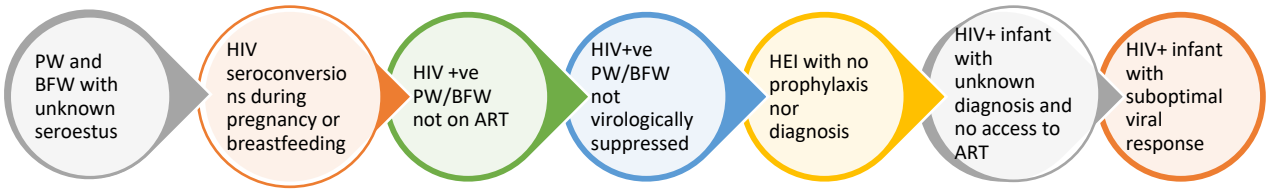
IV. Pregnant and breastfeeding women living with HIV do not receive viral load test monitoring, or present a suboptimal viral response, or has viremia peak after viral suppression (34–36)

V. HIV exposed infants access post-natal care late or not at all and miss early HIV diagnosis as well as prophylaxis with NVP and CTX (31,77)

VI. HIV exposed infants do not complete post-natal care till definitive diagnosis (31)

VII. HIV infected infants are not identified and do not access ART care or are identified late and start ART late in infancy (77,78)

VIII. HIV infected infants who start early treatment have suboptimal viral suppression and are at risk of viral rebound (62,63)



(PW=pregnant women; BFW=breastfeeding women; HEI= HIV exposed infants)

Fig.2. Gaps identified in the PMTCT continuum of care

The persistence of all these bottlenecks affects not only the effectiveness of the PMTCT program, but also undermines the success of the pediatric HIV program. For long term benefits, both for mothers and infants, programs need to focus on closing those gaps.

Therefore, it is critical to develop a more robust evidence of underlying complexities of mom-baby pair follow up. The knowledge can be used by programs to adapt existing strategies and develop innovative interventions towards elimination of vertical transmission and towards sustained viral suppression of children living with HIV, for an healthy future into adolescence and adulthood.

1.4 The HIV epidemic in Mozambique

1.4.1 Context

Mozambique is a country in the Southern Africa region, with a total area of 799,380 km^2 and a coastline of 2470 Km. It is divided into three regions (North, Centre and South) and a total of 11 provinces (Fig.3). It has a population of approximately 27.9 million people, 52% are women and 46.6% have less than 15 years of age. Sixty percent of the population lives in rural areas, 36% has access to safe water and 46% to adequate sanitation, 39% of adults are illiterate (79,80). The country was ranked 180 out of 187 countries by the Human Development Index rank in 2015. The World Bank estimated that 60% of Mozambicans in 2014 lived on less than $1.25 per day. Poverty is more prevalent in rural areas and varies widely between and within provinces (81).

Fig 3. Map of Mozambique (Green=Northern region, Yellow=Central region, Red=Southern region)

Life expectancy at birth is estimated at 53.7 years. Disease that contribute to the country burden of disease are malaria (which counts for one third of deaths), diarrhea, HIV/AIDS, respiratory infections, tuberculosis and vaccines preventable diseases. Key health indicators have improved over time but vary significantly by province: maternal mortality rate is 452/100.000 live births, infant mortality rate 64/1.000 live births, under-5 mortality rate is 90/1.000 live birth, institutional delivery increased to 70%; chronic malnutrition in children under the age of 5 years is at 43% (79,82).

1.4.2 The health system and policy

Health services are provided mainly by the public sector, being the private sector divided into non-profit aid, with national and international Non-Governmental Organization collaborating with the public sector, and the lucrative practice limited in urban areas. The national health service (NHS) is structured into four levels of service delivery: the primary level provides basic health care at health centers and in the community; the secondary level comprises District, General and Rural Hospitals; the tertiary level provide care at Provincial Hospitals and the quaternary level at Central and Specialized Hospitals where differentiated care is provided by specialized professionals. Some of the major challenges the NHS is facing are insufficient infrastructures and critical shortage of qualified human resources. There is a total of 7.8 doctors, 26.8 nurses, and 100.2 health care workers per 100,000 people unevenly distributed across provinces. The health policy framework for national planning is articulated in several documents, one of those is the Health Sector Strategic Plan (PEES) 2014-2019, which delineates the objectives of the health sector considering regional and global initiatives such as the Development Goals (83).

1.4.3 The national response to the HIV epidemic

In Mozambique, the HIV epidemic is generalized with an estimated national HIV prevalence of 13.2%, with variation among provinces, ranging from 5.2% in Tete to 24.4% in Gaza Province. The prevalence is higher among women compared to men, 15.1% versus 10.2% (84). An estimated 2.2 million people are living with HIV (PLHIV), 140.000 are children under 15 years (9,85). The government is responsible for HIV/AIDS-related service delivery, along with the development, implementation and oversight of policies, guidelines and interventions, through the National STD-HIV/AIDS program and the National AIDS Council (CNCS). Development of such strategies is guided by the Economic and Social plan 2018 (PES), the National Strategic Plan for Response to HIV and AIDS (PEN IV 2016-2020) and the 2016-2020 HIV Policy Statement which aims to reach the 90-90-90 targets and move towards HIV elimination by 2030 (83).

The STD-HIV/AIDS program has the mandate to coordinate interventions and monitor activities which provide care and treatment for PLWH through synergic implementation of its components: 1) counseling and testing; 2) control of sexual transmitted diseases; 3) prevention of mother-to-child transmission; 4) clinical care and treatment for pediatric, adolescents and adult patients; 6) adherence and psychosocial support and positive prevention management; 7) TB/HIV and other

opportunistic infections; 8) quality improvement; 9) monitoring and evaluation; and 10) key populations.

The response to the HIV epidemic started in 2003, when care was initially provided at few Central hospitals by specialized medical doctors. It expanded gradually and in 2007 the decentralization process resulted in expansion of HIV care at primary health care facilities and in task shifting from medical doctors to medical assistant and nurses. The number of health facilities offering ART increased from 12 in 2003, to 255 in 2011 and to 1,455 in 2018, 89% of HF of the Country (85) (Fig 4).

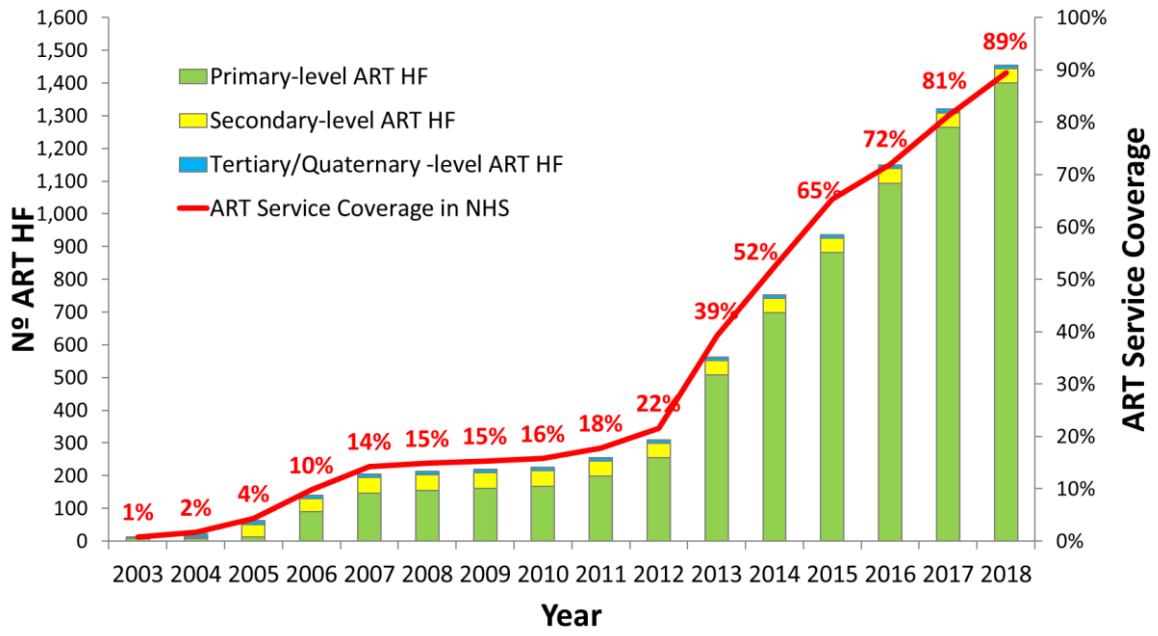


Fig 4 Scale up of HIV care to primary care level 2003-2018- Mozambique (From MOH Report 2018)

National guidelines for management of PLWH followed WHO updates and new strategies for prevention, treatment and retention have been introduced responding to context specific challenges and evolving HIV epidemic. Program's history reflects key interventions which expanded ART access to an increased number of patients: universal treatment access for children under 2 years of age in 2009, for under-5 in 2014, for all pregnant women in 2014, and finally in 2017 the uptake of the test and treat strategy. Since 2013, the number of people on ART has increased dramatically from 400.000 to 1.212.562 in 2018, following the launch of the National HIV and AIDS Response – Strategic Acceleration Plan for Mozambique 2013-2017, the adoption of the Accelerating Children HIV/AIDS Treatment initiative in 2014 and the introduction of Test and Start strategy in 2016.

Despite great achievements in expansion and inclusion of people on ART, the number of new infections and AIDS related deaths are stagnant. The number of new infections is estimated at 150.000 and AIDS related deaths at 564.000 (9).

Mozambique is one of the 35 priority countries for the Fast Track initiative launched in 2014 by UNAIDS and the government agreed to accelerate the HIV response to control the epidemic by 2020 and eliminate HIV by 2030 (81). However, the country is challenged by a low national retention rate with an overall 12-month retention rate of 68% among PLHIV newly initiating ART, 67% among pregnant woman, 70% among children under 15 years old. Consequently, viral load suppression rate is 32% among all patients on ART. Considering the 90-90-90 targets, 73% of PLWH know their HIV status, 55% are on treatment and 32% achieved viral suppression in 2018 (85) (Fig 5).

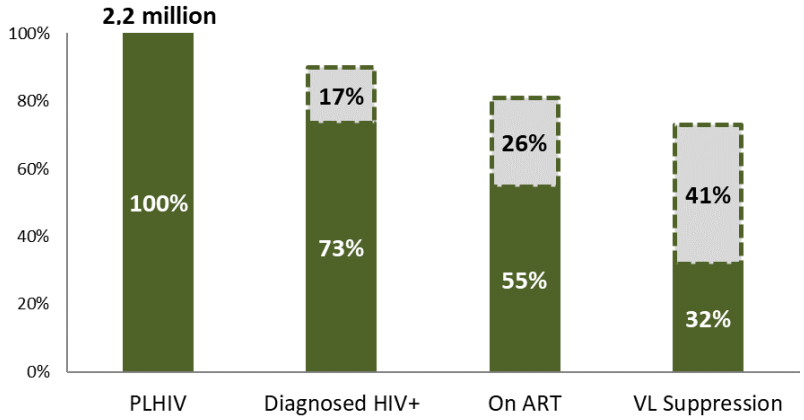


Fig 5. 90-960-90 national achievement by 2018 -Mozambique (MOH report 2018)

At the beginning of 2019, to respond to the above challenges, the MOH, CNCS and PEPFAR implementing partners developed the AJUDA approach (Addressing Joint Underperformance through Direct Assistance) (81). It aims to identify PLWH not yet engaged into care through innovative HIV testing modalities and to retain patients on treatment, including pregnant, breastfeeding women, children and adolescents, pursuing viral suppression by strengthening retention, adherence and psychosocial support interventions based on MOH retention pillars and investing in community based best practices.

1.4.4 Prevention of Mother to Child Transmission of HIV

Mozambique started implementing treatment for the prevention of Mother to child transmission (PMTCT) in 2003 at 8 HF. In the following years, the PMTCT program was officially launched and integrated into the MCH services offering the 'one stop model', where women receive counselling and testing, ARVs, prophylaxis, lab tests and monitoring of pregnancy in the same room. By the end

of 2018, ART for preventing MTC is offered at 98% of country HF. Thanks to Option B plus, rolled out in 2014, the number of women attending ANC who received ART for life increased from 72% in 2011 to 93% in 2018. National data on retention of pregnant women showed a 67% retention rate at 12 months and viral suppression of 76% (81,85).

HEI care is offered at Child at Risk Consultation at MCH where mom-baby pair is linked at 4 weeks post-delivery and followed till 2 months after weaning. Virologic HIV test for EID is recommended from 4 weeks of age, it was introduced in 2006, initially at 4 HF, using PCR DBS technique, and samples were sent and processed at the laboratory of the National Institute of Health in Maputo. Since then, access to EID expanded to all HF offering PMTCT care and capacity was built at 6 more laboratories across the country. EID access improved from 35% in 2013 to 66% in 2018 (Fig.6).

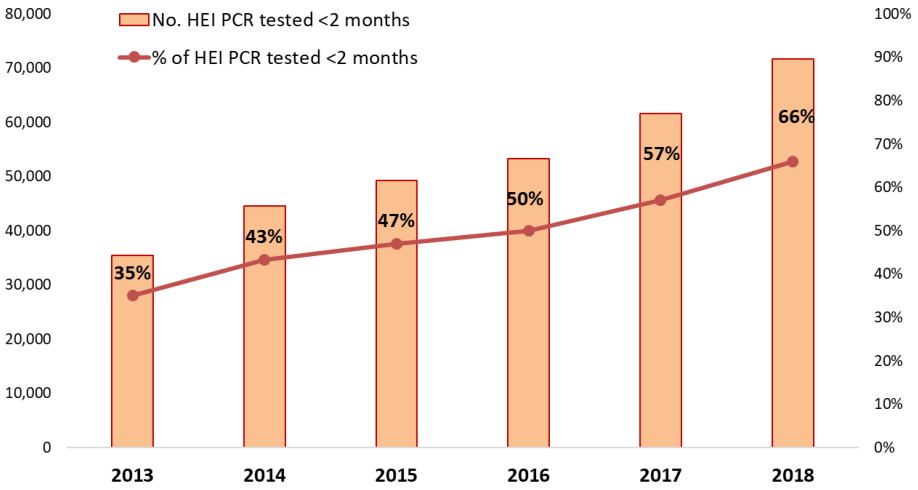


Fig 6. Coverage of EID 2013-2018 Mozambique (From MOH report 2018)

In 2016 simplified NAT-POC technology for EID was introduced firstly in Maputo province and expanded to all main district health facilities in the provinces by the end of 2018 covering 28% of the EID capacity, while other HF still rely on DBS (85). Birth testing is not yet included in the national guidelines. Vertical transmission rate has been projected at 18%, considering 12 months breastfeeding duration; in the last MOH report it is reported at 10%. However only 78% of expected HEI accessed post-natal care at any age. The high rate of vertical transmission is partially due to inadequate retention in care among pregnant and breastfeeding women and suboptimal viral response. In addition, a high proportion of resistance to NRTI and NNRTI has been recently found in the adult population already on ART (data presented at IAS 2019). To this respect the HIV program is moving to DTG based regimen for all adolescents and adults patients as recommended by WHO (5).

1.4.5 Paediatric HIV care and treatment

In Mozambique, children acquire HIV mainly through vertical transmission. By the end of 2018 140.000 children 0-14yrs are living with HIV and 86.920 are on treatment (85). The number of new infections and deaths has been reducing, especially in the youngest from 16.000 in 2010 to 8.700 in 2018 (9).

Care and treatment for children living with HIV started at Maputo Central Hospital in 2003 and followed the national decentralization process in 2007. Medical doctor first and medical assistants later were trained to treat children in the peripheral HF of the country with improved results in terms of access to treatment and 12 months retention (86).

Guidelines for pediatric HIV treatment followed WHO recommendations, starting universal ART below 2 years of age in 2009, then covering children less than 5 years in 2014 and all children in 2017 with the test and treat strategy. However, despite universal access and the launch of the Accelerating Children HIV/AIDS Treatment initiative in 2014, ART coverage is still low. By the end of 2018 only 62% of children living with HIV were receiving treatment, although with different performance across provinces: in the southern region coverage is 92.5%, in the central region is 38.8% and in the northern region is 38.1%% (85).

Prompt ART initiation is limited by inadequate identification of infected children mainly due to a) poor linkage of mom-baby pair to post-natal care after delivery, b) long turnaround time from test to diagnosis at HF without NAT POC technology and c) slow uptake of the MOH provider-initiated counseling and testing algorithm in the pediatric wards and under-5 clinics, where the positivity yield is high (87).

Recommended first line ART regimen for children less than 4 years is LPVr based if exposure to PMTCT occurred or NVP-based if not. However, majority of children are on NVP due to cold chain storage constraints of the available liquid formulation. In mid-2019, granules and pellets became available and the HIV program is moving to transitioning all children on NVP to LPVr or DTG by 2020.

Twelve months retention rate among the pediatric population, although increased from 65% in 2010 to 70% in 2018, is still below the set target (85). It varies cross age bands being lower among infants less than 1 year of age (88).

Viral suppression among 0-14 year was 46% in 2018 (81). The low rate of viral suppression is partially due to adherence issues but also to the current use of NVS-based first line regimen in a context were NNRTI transmitted resistance has been documented to be around 55% (37).

The HIV program response to improve pediatric HIV outcomes is: a) to introduce DTG for kids over 20 kg by the end of 2019 and transition younger children to LPVr based regimen in 2020; b) to strengthen clinical mentoring and monitoring for PICT guidelines uptake; c) to intensify retention activities such as implementation of differentiated service delivery (DSD) models including family approach and mentor mother strategies (81).

CHAPTER 2 OBJECTIVES

2. OBJECTIVES

2.1 Justification

Despite all the progress in the prevention of mother to child transmission occurred in the past twenty years, elimination of pediatric HIV has not yet been achieved in most countries where the HIV epidemic is generalized and majority of children acquire the infection from the mother. Globally vertical transmission rate was 9%, the number of new pediatric infection in 2018 was 160.000 globally and only half of children with HIV are on ART (10).

Indeed, there are still underlying issues that hamper women to access antenatal care, to get tested and re-tested (15,22), to receive antiretroviral treatment, have optimal adherence and achieve sustained undetectable viremia (30,34). At the same time, there are factors preventing infants to access post- natal care and complete follow up till definitive diagnosis (31). Finally, for infants who unfortunately are perinatally infected, early access to early treatment and achievement of sustained viral suppression are the major constraints (62).

The persisting gaps are the evidence of complexities in the PMTCT continuum of care which programs have tried to understand and solve in the past 15 years.

Infants living with HIV have different characteristics and needs compared to older children and require a tailored approach for AIDS free survival and healthy development.

Identifying bottlenecks in the mom-baby pair continuum of care and addressing barriers to the effective uptake of services, optimal adherence and retention deserve now more attention especially in Africa where majority of HIV exposed infants lives and most pediatric HIV infection occur.

In Mozambique, HIV prevalence among women of child bearing age is 15.4% (84) and despite over 95% HIV testing and ART coverage among pregnant women accessing antenatal care, vertical transmission rate is 10%, unacceptably high, 16.000 new pediatric infections occurred in 2018 and viral suppression among children is 46% (81,85). Here, evidence is scarce on the existing gaps in the PMTCT pathway and data on viral response to ART among infected infants who start early treatment is lacking. In particular, there are no data on underlying factors associated to the status of 'unknown HIV exposure' in children less than 2 years of age; there are no data on completeness of follow up of HIV exposed infants till definitive diagnosis and related factors; there are no data on sustained viral response in infants starting ART at one month of age with a LPVr based regimen; there are no data exploring the APSS package of care offered to caregivers of infants on ART.

2.2 Objectives

Main objective

The main objective of this project is to improve current knowledge on underlying gaps in the infants' continuum of care from HIV exposure to early diagnosis, early treatment and viral suppression in Mozambique.

Specific objectives

1. To evaluate factors associated to 'unknown HIV exposure status' and to 'HIV exposure status' in children less than 2 years of age in Mozambique.
2. To describe completeness of follow up among HIV-exposed infants receiving routine care and to identify factors associated to lost to follow up after the first HIV negative test.
3. To describe virologic response in HIV perinatally infected infants who start a PI-based antiretroviral treatment in the first month of life.
4. To evaluate weather the adherence and psychosocial package offered to caregivers of infants starting ART in the first month of age allows health staff to identify infants at risk of poor adherence.

Findings will inform the HIV program on existing gaps and will contribute identifying key aspects to consider when designing differentiated model of care tailored to mothers and their infant's needs and help in strengthening interventions for elimination of pediatric HIV.

CHAPTER 3 METHODOLOGY

3.METHODOLOGY

3.1 Study population and setting

The majority of studies for this project were undertaken in Maputo Province, located in the southern region of Mozambique, while one study considered the whole Country (Fig 3).

Maputo province extends over an area of 26 058 km², has a population of approximately 2.000.000 inhabitants, 52% are women, 38% are children <15 years; 19% of people are illiterate. Seventy one percent of people lives in an urban area. The province is divided administratively in eight districts (Matola, Boane, Marracuene, Manhiça, Matutuine, Namaacha, Moamba and Magude) and Matola, the province capital, accounts for 1 million people being the most populated district of the province (89).

Maputo province has a total of 102 health facilities (HF), majority are primary health care centres, three are Rural hospitals, one is a Provincial Hospital and one a National Referral TB Hospital. According to the National Institute of Statistics report 2017, the number of inhabitants per health facility is 18.045/health unit, ANC coverage is 61%, institutional delivery is 48%, BCG vaccination coverage 71%, DPT 3 coverage 72% and infant mortality rate is 58/1000 live birth.

HIV prevalence in the adult population (15-49 years) is 22.9% compared to 13.2% of the country and the second highest after Gaza province (24.4%) (84). Ninety five of the 102 HF offer HIV care are offering Option B plus integrated into ANC. By the end of 2018 a total of 135.000 patients were receiving antiretroviral treatment of which approximately 11.300 children of 0-14 years. Population ART coverage among all ages is 40.2%, 39.5% in adults, 68% among pregnant women and 51.6% among children. Retention rate at 12m among all patients is 74% (85). There are many daily labor commuters from Maputo province, especially from Matola district, who travel to Maputo city to work and some people may access care at HF, public or private, at Maputo city.

At the end of 2018, 100% of pregnant women accessing antenatal care in Maputo province received an HIV test result, 100% received ART (57% being already on ART at their first ANC visit); 33% of women's partner were present and all were tested for HIV. Among pregnant women on ART, 12month retention rate was 70%, viral suppression was 85% (PEPFAR programmatic data 2018). Early infant diagnosis is provided by conventional DBS technique at most health facilities, while 13 HF have the NAT-POC simplified technology with same day test result. Vertical transmission rate calculated using programmatic data was overall of 3% and at health facilities using POC technology was of 5%. However, only 53% of expected HIV exposed infants accessed post-natal care and received a virologic test before 2 months of age compared to 66% of the country (85).

In Maputo Province at the end of 2018, a total of 11.299 children were on ART, and 1706 new children started treatment in the same year; 12 months retention rate among the pediatric population was 75% among 0-14 years old, 62% among infants <1 year; viral suppression was 52% among 0-14 years old, 46% among infants < 1 year of age; in this age group coverage of viral load test is suboptimal (PEPFAR programmatic data 2018).

3.2 Methodology of studies

The research project consists of four studies developed applying different research methodologies. The detailed methodology of each study is described in each paper in the following chapters.

The studies included:

1. A cross sectional analytical study using data from the National 2015 HIV, malaria and immunization survey, with the aim to investigate underlying factors associated to unknown HIV exposure status and to HIV exposure status in children under 2 years of age in Mozambique.
2. A retrospective cohort study using prospectively collected data stored in files of HIV exposed infants enrolled at Child at Risk Consultation at MCH clinic of four primary health centers in Maputo province, with the aim to analyze completeness of HIV exposed infant's follow-up till definitive diagnosis and factors associated to lost to follow-up.
3. A descriptive cohort study of HIV perinatally infected infants recruited at two health facilities in Maputo province, who started ART within 2 months of life and followed for 2 years with the aim to describe their viral response to treatment.
4. A qualitative analysis based on review of infants' files, caregiver's questionnaires and first adherence and psychosocial support (APSS) session, with the aim to analyze whether the standard APSS package of care applied to infants' caregivers in Mozambique can efficiently identify factors influencing caregiver adherence behavior and to determine whether they correlate with infant's viral response.

BIBLIOGRAFY OF CHAPTERS 1 – 2 – 3

1. UNAIDS. Countdown to zero: global plan towards the elimination of new HIV infections among children by 2015 and keeping their mothers alive, 2011-2015. Geneva: UNAIDS; 2011.

2. UNAIDS, UNICEF, WHO, PEPFAR. Start Free. Stay Free. AIDS Free. [Internet]. 2016 [cited 2019 Sep 25]. Available from: https://free.unaids.org/

3. Connor EM, Sperling RS, Gelber R, Kiselev P, Scott G, O'Sullivan MJ, et al. Reduction of Maternal-Infant Transmission of Human Immunodeficiency Virus Type 1 with Zidovudine Treatment. New England Journal of Medicine. 1994 Nov 3;331(18):1173–80.

4. WHO. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach. Geneva: World Health Organization; 2013.

5. WHO. Update of recommendations on first- and second-line antiretroviral regimens. [Internet]. Geneva, Switzerland; 2019 [cited 2019 Sep 26]. Available from: http://www.who.int/hiv/pub/arv/en/

6. Guay LA, Musoke P, Fleming T, Bagenda D, Allen M, Nakabiito C, et al. Intrapartum and neonatal single-dose nevirapine compared with zidovudine for prevention of mother-to-child transmission of HIV-1 in Kampala, Uganda: HIVNET 012 randomised trial. The Lancet. 1999 Sep 4;354(9181):795–802.

7. WHO. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach. [Internet]. 2016 [cited 2019 Sep 6]. Available from: http://apps.who.int/iris/bitstream/10665/208825/1/9789241549684_eng.pdf

8. Hensen B, Baggaley R, Wong VJ, Grabbe KL, Shaffer N, Lo Y-RJ, et al. Universal voluntary HIV testing in antenatal care settings: a review of the contribution of provider-initiated testing & counselling. Tropical Medicine & International Health. 2012;17(1):59–70.

9. UNAIDS. UNAIDS data 2019 [Internet]. 2019 [cited 2019 Jul 23]. Available from: https://www.unaids.org/en/resources/documents/2019/2019-UNAIDS-data

10. UNAIDS. Start Free Stay Free AIDS Free - 2019 report [Internet]. 2019 [cited 2019 Sep 17]. Available from: https://www.unaids.org/en/resources/documents/2019/20190722_UNAIDS_SFSFAF_2019

11. WHO. WHO | HIV diagnosis and ARV use in HIV-exposed infants: a programmatic update [Internet]. WHO. 2018 [cited 2019 Sep 1]. Available from: http://www.who.int/hiv/pub/paediatric/diagnosis-arv-infants/en/

12. Rogers AJ, Akama E, Weke E, Blackburn J, Owino G, Bukusi EA, et al. Implementation of repeat HIV testing during pregnancy in southwestern Kenya: progress and missed opportunities. J Int AIDS Soc [Internet]. 2017 Dec 13 [cited 2019 Jul 3];20(4). Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5810348/

13. Kinuthia J, Drake AL, Matemo D, Richardson BA, Zeh C, Osborn L, et al. HIV acquisition during pregnancy and postpartum is associated with genital infections and partnership characteristics. AIDS. 2015 Sep 24;29(15):2025–33.

14. Kinuthia J, Kiarie JN, Farquhar C, Richardson B, Nduati R, Mbori-Ngacha D, et al. Cofactors for HIV-1 incidence during pregnancy and postpartum period. Curr HIV Res. 2010 Oct;8(7):510–4.

15. Moodley D, Esterhuizen TM, Pather T, Chetty V, Ngaleka L. High HIV incidence during pregnancy: compelling reason for repeat HIV testing: AIDS. 2009 Jun;23(10):1255–9.

16. Munjoma MW, Mhlanga FG, Mapingure MP, Kurewa EN, Mashavave GV, Chirenje MZ, et al. The incidence of HIV among women recruited during late pregnancy and followed up for six years after childbirth in Zimbabwe. BMC Public Health. 2010 Nov 3;10:668.

17. Thomson KA, Hughes J, Baeten JM, John-Stewart G, Celum C, Cohen CR, et al. Increased Risk of HIV Acquisition Among Women Throughout Pregnancy and During the Postpartum Period: A Prospective Per-Coital-Act Analysis Among Women With HIV-Infected Partners. J Infect Dis. 2018 Jun 5;218(1):16–25.

18. Kalk E, Slogrove A, Speert DP, Bettinger JA, Cotton MF, Esser M. HIV sero-conversion during late pregnancy – when to retest. Southern African Journal of HIV Medicine. 2013 Jan 1;14(2):90-92–92.

19. De Schacht C, Hoffman HJ, Mabunda N, Lucas C, Alons CL, Madonela A, et al. High rates of HIV seroconversion in pregnant women and low reported levels of HIV testing among male partners in Southern Mozambique: results from a mixed methods study. PLoS ONE. 2014;9(12):e115014.

20. Gray RH, Li X, Kigozi G, Serwadda D, Brahmbhatt H, Wabwire-Mangen F, et al. Increased risk of incident HIV during pregnancy in Rakai, Uganda: a prospective study. The Lancet. 2005 Oct 1;366(9492):1182–8.

21. Newell M-L, Peckham C. Vertical transmission of HIV infection. Acta Paediatrica. 1994;83(s400):43–5.

22. Drake AL, Wagner A, Richardson B, John-Stewart G. Incident HIV during Pregnancy and Postpartum and Risk of Mother-to-Child HIV Transmission: A Systematic Review and Meta-Analysis. PLOS Medicine. 2014 Feb 25;11(2):e1001608.

23. WHO. WHO | Consolidated guidelines on HIV testing services [Internet]. Geneva, Switzerland; 2015 [cited 2019 Jul 3]. Available from: http://www.who.int/hiv/pub/guidelines/hiv-testing-services/en/

24. Drake AL, Thomson KA, Quinn C, Newman Owiredu M, Nuwagira IB, Chitembo L, et al. Retest and treat: a review of national HIV retesting guidelines to inform elimination of mother-to-child HIV transmission (EMTCT) efforts. J Intern AIDS Soc. 2019 Apr;22(4):e25271.

25. Adewuyi EO, Auta A, Khanal V, Bamidele OD, Akuoko CP, Adefemi K, et al. Prevalence and factors associated with underutilization of antenatal care services in Nigeria: A comparative study of rural and urban residences based on the 2013 Nigeria demographic and health survey. Oh J, editor. PLoS ONE. 2018 May 21;13(5):e0197324.

26. Ng'anjo Phiri S, Kiserud T, Kvåle G, Byskov J, Evjen-Olsen B, Michelo C, et al. Factors associated with health facility childbirth in districts of Kenya, Tanzania and Zambia: a population based survey. BMC Pregnancy Childbirth. 2014 Jul 4;14:219.

27. Nketiah-Amponsah E, Codjoe EA, Ampaw S. HIV/AIDS Awareness and Knowledge Among Ghanaian Women of Reproductive Age: What Are the Correlates? Journal of Asian and African Studies. 2019 Mar;54(2):267–81.

28. Hodgson I, Plummer ML, Konopka SN, Colvin CJ, Jonas E, Albertini J, et al. A Systematic Review of Individual and Contextual Factors Affecting ART Initiation, Adherence, and Retention for HIV-Infected Pregnant and Postpartum Women. PLOS ONE. 2014 Nov 5;9(11):e111421.

29. Donahue MC, Dube Q, Dow A, Umar E, Van Rie A. “They Have Already Thrown Away Their Chicken”: barriers affecting participation by HIV-infected women in care and treatment programs for their infants in Blantyre, Malawi. AIDS Care. 2012 Oct;24(10):1233–9.

30. Nachega JB, Uthman OA, Anderson J, Peltzer K, Wampold S, Cotton MF, et al. Adherence to Antiretroviral Therapy During and After Pregnancy in Low-, Middle and High Income Countries: A Systematic Review and Meta-Analysis. AIDS. 2012 Oct 23;26(16):2039–52.

31. Sibanda EL, Weller IVD, Hakim JG, Cowan FM. The magnitude of loss to follow-up of HIV-exposed infants along the prevention of mother-to-child HIV transmission continuum of care: a systematic review and meta-analysis. AIDS. 2013 Nov 13;27(17):2787–97.

32. Knettel BA, Cichowitz C, Ngocho JS, Knippler ET, Chumba LN, Mmbaga BT, et al. Retention in HIV Care During Pregnancy and the Postpartum Period in the Option B+ Era: Systematic Review and Meta-Analysis of Studies in Africa. J Acquir Immune Defic Syndr. 2018 Apr 15;77(5):427–38.

33. Peter T, Zeh C, Katz Z, Elbireer A, Alemayehu B, Vojnov L, et al. Scaling up HIV viral load – lessons from the large-scale implementation of HIV early infant diagnosis and CD4 testing. J Int AIDS Soc [Internet]. 2017 Nov 12 [cited 2019 Sep 25];20(Suppl Suppl 7). Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5978645/

34. Abuogi LL, Humphrey JM, Mpody C, Yotebieng M, Murnane PM, Clouse K, et al. Achieving UNAIDS 90-90-90 targets for pregnant and postpartum women in sub-Saharan Africa: progress, gaps and research needs. J Virus Erad. 4(Suppl 2):33–9.

35. Myer L, Dunning L, Lesosky M, Hsiao N-Y, Phillips T, Petro G, et al. Frequency of Viremic Episodes in HIV-Infected Women Initiating Antiretroviral Therapy During Pregnancy: A Cohort Study. Clin Infect Dis. 2017 Feb 15;64(4):422–7.

36. Chetty T, Newell M-L, Thorne C, Coutsoudis A. Viraemia before, during and after pregnancy in HIV-infected women on antiretroviral therapy in rural KwaZulu-Natal, South Africa, 2010–2015. Tropical Medicine & International Health. 2018;23(1):79–91.

37. Jordan MR, Penazzato M, Cournil A, Vubil A, Jani I, Hunt G, et al. Human Immunodeficiency Virus (HIV) Drug Resistance in African Infants and Young Children Newly Diagnosed With HIV: A Multicountry Analysis. Clin Infect Dis. 2017 Nov 29;65(12):2018–25.

38. Hosseinipour M, Nelson JA, Trapence C, Rutstein SE, Kasende F, Kayoyo V, et al. Viral suppression and HIV drug resistance at 6 months among women in Malawi’s Option B+ program: Results from the PURE Malawi Study. J Acquir Immune Defic Syndr. 2017 Jun 1;75(Suppl 2):S149–55.

39. Myer L, Essajee S, Broyles LN, Watts DH, Lesosky M, El-Sadr WM, et al. Pregnant and breastfeeding women: A priority population for HIV viral load monitoring. PLOS Medicine. 2017 Aug 15;14(8):e1002375.

40. WHO. WHO recommendations on the diagnosis of HIV infection in infants and children. [Internet]. 2010 [cited 2019 Sep 18]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK138551/

41. WHO. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach. [Internet]. 2016 [cited 2019 Jul 30]. Available from: http://apps.who.int/iris/bitstream/10665/208825/1/9789241549684_eng.pdf

42. Jani IV, Meggi B, Mabunda N, Vubil A, Sitoe NE, Tobaiwa O, et al. Accurate Early Infant HIV Diagnosis in Primary Health Clinics Using a Point-of-Care Nucleic Acid Test. JAIDS Journal of Acquired Immune Deficiency Syndromes. 2014 Sep 1;67(1):e1.

43. Bianchi F, Cohn J, Sacks E, Bailey R, Lemaire J-F, Machekano R, et al. Evaluation of a routine point-of-care intervention for early infant diagnosis of HIV: an observational study in eight African countries. The Lancet HIV. 2019 Jun 1;6(6):e373–81.

44. Teasdale CA, Besser MJ. Enhancing PMTCT programmes through psychosocial support and empowerment of women: The mothers2mothers model of care. Southern African Journal of HIV Medicine. 2008 Jan 1;9(1):60-64–64.

45. Newell M-L, Coovadia H, Cortina-Borja M, Rollins N, Gaillard P, Dabis F. Mortality of infected and uninfected infants born to HIV-infected mothers in Africa: a pooled analysis. The Lancet. 2004 Oct;364(9441):1236–43.

46. Marinda E, Humphrey JH, Iliff PJ, Mutasa K, Nathoo KJ, Piwoz EG, et al. Child Mortality According to Maternal and Infant HIV Status in Zimbabwe: The Pediatric Infectious Disease Journal. 2007 Jun;26(6):519–26.

47. Marston M, Becquet R, Zaba B, Moulton LH, Gray G, Coovadia H, et al. Net survival of perinatally and postnatally HIV-infected children: a pooled analysis of individual data from sub-Saharan Africa. Int J Epidemiol. 2011 Apr 1;40(2):385–96.

48. Violari A, Cotton MF, Gibb DM, Babiker AG, Steyn J, Madhi SA, et al. Early Antiretroviral Therapy and Mortality among HIV-Infected Infants. N Engl J Med. 2008 Nov 20;359(21):2233–44.

49. Collins IJ, Jourdain G, Hansudewechakul R, Kanjanavanit S, Hongsiriwon S, Ngampiyasakul C, et al. Long-Term Survival of HIV-Infected Children Receiving Antiretroviral Therapy in Thailand: A 5-Year Observational Cohort Study. Clin Infect Dis. 2010 Dec 15;51(12):1449–57.

50. Goetghebuer T, Haelterman E, Le Chenadec J, Dollfus C, Gibb D, Judd A, et al. Effect of early antiretroviral therapy on the risk of AIDS/death in HIV-infected infants. AIDS. 2009 Mar 13;23(5):597.

51. Innes S, Lazarus E, Otwombe K, Liberty A, Germanus R, Van Rensburg AJ, et al. Early severe HIV disease precedes early antiretroviral therapy in infants: Are we too late? Journal of the International AIDS Society. 2014 Jan;17(1):18914.

52. WHO. Antiretroviral therapy for HIV infection in infants and children ; towards universal access: recommendations for a public health approach. Geneva: World Health Organization; 2010.

53. WHO. Updated recommendations on first-line and second-line antiretroviral regimens and post-exposure prophylaxis and recommendations on early infant diagnosis of HIV: interim guidelines. Supplement to the 2016 consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection. [Internet]. Geneva, Switzerland; 2018 [cited 2019 Sep 26]. Available from: http://www.who.int/hiv/pub/arv/arv-2016/en/

54. Penazzato M, Townsend CL, Rakhmanina N, Cheng Y, Archary M, Cressey TR, et al. Prioritising the most needed paediatric antiretroviral formulations: the PADO4 list. The Lancet HIV. 2019 Sep 1;6(9):e623–31.

55. Dahourou DL, Leroy V. Challenges and perspectives of compliance with pediatric antiretroviral therapy in Sub-Saharan Africa. Médecine et Maladies Infectieuses. 2017 Dec;47(8):511–8.

56. Chiappini E, Galli L, Tovo P-A, Gabiano C, Gattinara GC, Guarino A, et al. Virologic, immunologic, and clinical benefits from early combined antiretroviral therapy in infants with perinatal HIV-1 infection. :9.

57. Goetghebuer T, Haelterman E, Le Chenadec J, Dollfus C, Gibb D, Judd A, et al. Effect of early antiretroviral therapy on the risk of AIDS/death in HIV-infected infants: AIDS. 2009 Mar;23(5):597–604.

58. Prendergast A, Mphatswe W, Tudor-Williams G, Rakgotho M, Pillay V, Thobakgale C, et al. Early virological suppression with three-class antiretroviral therapy in HIV-infected African infants. AIDS. 2008 Jul 11;22(11):1333.

59. Shiau S, Arpadi S, Strehlau R, Martens L, Patel F, Coovadia A, et al. Initiation of Antiretroviral Therapy Before 6 Months of Age is Associated with Faster Growth Recovery in South African Children Perinatally Infected with Human Immunodeficiency Virus. The Journal of Pediatrics. 2013 Jun 1;162(6):1138-1145.e2.

60. Doaré KL, Bland R, Newell M-L. Neurodevelopment in Children Born to HIV-Infected Mothers by Infection and Treatment Status. Pediatrics. 2012 Nov 1;130(5):e1326–44.

61. Boerma RS, Boender TS, Bussink AP, Calis JCJ, Bertagnolio S, Rinke de Wit TF, et al. Suboptimal Viral Suppression Rates Among HIV-Infected Children in Low- and Middle-Income Countries: A Meta-analysis. Clin Infect Dis. 2016 Dec 15;63(12):1645–54.

62. Teasdale CA, Sogaula N, Yuengling KA, Wang C, Mutiti A, Arpadi S, et al. HIV viral suppression and longevity among a cohort of children initiating antiretroviral therapy in Eastern Cape, South Africa. J Intern AIDS Soc. 2018 Aug;21(8):e25168.

63. Shiau S, Abrams EJ, Arpadi SM, Kuhn L. Early antiretroviral therapy in HIV-infected infants: can it lead to HIV remission? The Lancet HIV. 2018 May;5(5):e250–8.

64. Teasdale CA, Abrams EJ, Coovadia A, Strehlau R, Martens L, Kuhn L. Adherence and Viral Suppression among Infants and Young Children Initiating Protease Inhibitor-Based Antiretroviral Therapy. Pediatr Infect Dis J. 2013 May;32(5):489–94.

65. Haberer JE, Cook A, Walker AS, Ngambi M, Ferrier A, Mulenga V, et al. Excellent Adherence to Antiretrovirals in HIV+ Zambian Children Is Compromised by Disrupted Routine, HIV Nondisclosure, and Paradoxical Income Effects. PLOS ONE. 2011 Apr 21;6(4):e18505.

66. Haberer JE, Kiwanuka J, Nansera D, Ragland K, Mellins C, Bangsberg DR. Multiple Measures Reveal Antiretroviral Adherence Successes and Challenges in HIV-Infected Ugandan Children. PLOS ONE. 2012 May 9;7(5):e36737.

67. Vreeman RC, Wiehe SE, Pearce EC, Nyandiko WM. A Systematic Review of Pediatric Adherence to Antiretroviral Therapy in Low- and Middle-Income Countries. The Pediatric Infectious Disease Journal. 2008 Aug;27(8):686.

68. Sengayi M, Dwane N, Marinda E, Sipambo N, Fairlie L, Moultrie H. Predictors of loss to follow-up among children in the first and second years of antiretroviral treatment in Johannesburg, South Africa. Global Health Action. 2013 Jan 1;6(s1):19248.

69. Szubert AJ, Prendergast AJ, Spyer MJ, Musiime V, Musoke P, Bwakura-Dangarembizi M, et al. Virological response and resistance among HIV-infected children receiving long-term antiretroviral

therapy without virological monitoring in Uganda and Zimbabwe: Observational analyses within the randomised ARROW trial. PLoS Med. 2017 Nov;14(11):e1002432.

70. Delaugerre C, Teglas J-P, Treluyer J-M, Vaz P, Jullien V, Veber F, et al. Predictive Factors of Virologic Success in HIV-1???Infected Children Treated With Lopinavir/Ritonavir: JAIDS Journal of Acquired Immune Deficiency Syndromes. 2004 Oct;37(2):1269–75.

71. Barth RE, Tempelman HA, Smelt E, Wensing AMJ, Hoepelman AI, Geelen SP. Long-term Outcome of Children Receiving Antiretroviral Treatment in Rural South Africa: Substantial Virologic Failure on First-line Treatment. The Pediatric Infectious Disease Journal. 2011 Jan;30(1):52.

72. Penazzato M, Gnanashanmugam D, Rojo P, Lallemant M, Lewis LL, Rocchi F, et al. Optimizing Research to Speed Up Availability of Pediatric Antiretroviral Drugs and Formulations. Clin Infect Dis. 2017 Jun 1;64(11):1597–603.

73. McNairy ML, El-Sadr WM. The HIV care continuum: no partial credit given. AIDS. 2012 Sep 10;26(14):1735.

74. McNairy ML, Teasdale CA, El-Sadr WM, Mave V, Abrams EJ. Mother and Child Both Matter: Re-conceptualizing the PMTCT Care Continuum. Curr Opin HIV AIDS. 2015 Nov;10(6):403–10.

75. Bianchi F, Cohn J, Sacks E, Bailey R, Lemaire J-F, Machekano R, et al. Evaluation of a routine point-of-care intervention for early infant diagnosis of HIV: an observational study in eight African countries. The Lancet HIV. 2019 Jun;6(6):e373–81.

76. De Schacht C, Mabunda N, Ferreira OC, Ismael N, Calú N, Santos I, et al. High HIV incidence in the postpartum period sustains vertical transmission in settings with generalized epidemics: a cohort study in Southern Mozambique. J Int AIDS Soc. 2014;17:18808.

77. Penazzato M, Lule F, Essajee S. Paediatric HIV: the unfinished business. The Lancet HIV. 2017 Oct;4(10):e425–7.

78. Ananworanich J, Abrams EJ. Time to prioritise the UNAIDS 90-90-90 targets for infants. The Lancet HIV. 2016 Jun;3(6):e241–3.

79. INE Instituto Nacional Estatistica. CENSO 2017. IV Recenseamento Geral da População e Habitação [IV Population and Households Census 2017] [Internet]. 2017 [cited 2019 Sep 5]. Available from: http://www.ine.gov.mz/operacoes-estatisticas/censos/censo-2007/censo-2017

80. IDS 2011.pdf — Instituto Nacional de Estatistica [Internet]. [cited 2019 Sep 26]. Available from: http://www.ine.gov.mz/operacoes-estatisticas/inqueritos/inquerito-demografico-e-de-saude/ids-2011.pdf/view

81. PEPFAR. Mozambique Country Operational Plan 2019 Strategic Direction Summary [Internet]. 2019 [cited 2019 Sep 23]. Available from: https://www.state.gov/pepfar/

82. UNICEF. Situação das Crianças em Moçambique 2014 [Condition of Children in Mozambique 2014] [Internet]. 2014 [cited 2019 Sep 27]. Available from: https://www.unicef.org/mozambique/relatorios/situa%C3%A7%C3%A3o-das-crian%C3%A7as-em-mo%C3%A7ambique-2014

83. MISAU. Plano Estratégico do Sector da Saúde PESS 2014-2019 [Health Secotr Strategic Plan 2014-2019] [Internet]. Maputo; 2013 [cited 2019 Sep 27]. Available from: http://www.misau.gov.mz/index.php/planos-estrategicos

84. MISAU, INE, ICF. Inquérito de Indicadores de Imunização, Malária e HIV/SIDA em Moçambique [Immunization, Malaria and HIV/AIDS Survey in Mozambique] (IMASIDA) 2015 [Internet]. 2018 Feb [cited 2019 Jul 2]. Available from: https://dhsprogram.com/publications/publication-ais12-ais-final-reports.cfm

85. MISAU. Relatório Anual das Actividades Relacionadas ao HIV/SIDA [Annual Report of HIV/AIDS activities] - 2018. 2019 p. 100.

86. Fayorsey RN, Saito S, Carter RJ, Gusmao E, Frederix K, Koech-Keter E, et al. Decentralization of Pediatric HIV Care and Treatment in Five Sub-Saharan African Countries. J Acquir Immune Defic Syndr. 2013 Apr 15;62(5):e124–30.

87. Nhabomba C, Chicumbe S, Muquingue H, Jahit S, Lara J, Couto A, et al. Clinical and Operational Factors Associated with Low Pediatric Inpatient HIV Testing Coverage from Mozambique. Public Health Action. 2019 In press;

88. McNairy ML, Lamb MR, Carter RJ, Fayorsey R, Tene G, Mutabazi V, et al. Retention of HIV-infected children on antiretroviral treatment in HIV care and treatment programs in Kenya, Mozambique, Rwanda and Tanzania. J Acquir Immune Defic Syndr. 2013 Mar 1;62(3):e70–81.

89. INE National Institute of Statistics. Anuário Estatistico, Província de Maputo 2017 [Annual Statistics, Maputo Province 2017] [Internet]. 2017 [cited 2019 Sep 26]. Available from: http://www.ine.gov.mz/@@search?SearchableText=matola

CHAPTER 4:

High proportion of unknown HIV exposure among children aged less than 2 years: an analytical study using Mozambique 2015 National HIV Survey

High proportion of unknown HIV exposure among children aged less than 2 years: an analytical study using Mozambique 2015 National HIV Survey.

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Abstract

Background: Knowing infant's HIV exposure status is mandatory to ensure timely access to appropriate care and definitive diagnosis. HIV prevalence among Mozambican women aged 15-49yrs is 15% and despite achieving in 2015 95% HIV testing coverage and 91% treatment coverage at Antenatal Care and delivery, vertical transmission rate is still high (9%). The study investigated underlying factors associated to unknown HIV exposure status and to HIV exposure in children aged < 2 years in Mozambique.

Methods: Cross sectional analytical study using data from the 2015 HIV, malaria and immunization national Survey in Mozambique. A total of 2141 women (15-49 years) with child <24 months were interviewed. Dependent variables were: 'child's known HIV exposure status' and 'child exposed to HIV'; explanatory variables were social, demographic, economic and reproductive characteristics of women. Binary and logistic regression estimated OR and 95% CI of the association between dependent and independent variables at significant a level of p <.05. Analysis was weighted and adjusted for complex sample.

Results: Infant's HIV exposure status was unknown in 32% of interviewed women (95% CI 28.5-35.7%) and 4.5% (CI 95% 3.6-5.5%) had an HIV exposed infant. Factors associated with both 'infant unknown HIV exposure status' and 'infant exposed to HIV' where place of residence; breastfeeding duration, access to Mother and Child Health Services. Education, number of children and age of the youngest were associated with unknown HIV exposure status; gender of household head was associated with HIV exposed status.

Conclusion: To reduce the number of children with unknown HIV exposure status, it is imperative ensuring continuum of care throughout the PMTCT pathway without forgetting women who did not access care. Synergism of multisectoral actors' is crucial to tackle access to education, poverty, remote location and other social factors limiting women to seek appropriate care.

Keywords: Prevention of Mother to Child Transmission-PMTCT, HIV exposed infants, Mozambique

Introduction

In 2011 the WHO/UNAIDS Global plan to eliminate pediatric HIV by 2015 was launched covering all low- and middle-income countries but focusing on 23 priority countries with the highest burden of HIV [1]. The plan focused on HIV prevention, treatment and care interventions, to reach all pregnant women living with HIV and their children along the continuum of care, prior and through pregnancy and throughout breastfeeding. At the end of 2014, following the adoption of lifelong antiretroviral treatment (ART) to all pregnant women living with HIV (Option B+), despite an increase in ART coverage in pregnancy to 78% and a decline of new pediatric infections by 48% globally, approximately 170.000 newly HIV infected children were born in priority countries [2]. Still approximately 1.2 million women of reproductive age (15-49 years) were living with HIV and the number of those who newly acquired the virus was still high with an estimated 540.000 new infections in high HIV burden countries, with over 1 million HIV exposed infants worldwide each year [2].

Mozambique is one of the priority countries included in the global plan. The average country HIV prevalence in the adult population (15-49 years) is 13.2%, ranging from 5.2% in Tete (Central region) to 24.4% in Gaza Province in the Southern region [3]. It is estimated that 2.1 million people are living with HIV, 59% of them know their HIV status and 54% are on antiretroviral treatment [4]. Since the launch of Option B+ in 2013, progress has been remarkable and encouraging results have been achieved. By the end of 2015, 95% of women at Antenatal Care clinic (ANC) were tested for HIV and 91% received highly effective treatment, vertical transmission rate decreased to 9% and new pediatric infections declined by nearly 70% since 2009 [2,5]. However, identification of all HIV exposed infants and vertically infected children was not happening as early as desired; only 43% of infants had access to a virologic test within the first 2 months of age [2,5].

Along the prevention of Mother to Child Transmission (PMTCT) cascade there are ongoing challenges which prevent reaching all women living with HIV and their HIV exposed infants. Similar to other HIV priority countries in the African region [6], in Mozambique HIV testing and retesting is offered, as per WHO recommendations [7], at ANC and other Mother and Child Health (MCH) services (Maternity ward, Post-partum care, Family planning clinic). However, there are no systematic data collection about HIV re-testing along the pregnancy-breastfeeding period for those women who first tested HIV negative and need to repeat the test. A study in Mozambique of 2011 showed an HIV incidence rate as high as 4.92 per 100 women-years up to 18 months after a negative

test at delivery [8] and other studies of neighboring countries, reported high numbers of women infected after the first negative test [9–12].

In order to eliminate vertical transmission, it is imperative that all women of childbearing age, pregnant and breastfeeding, have continuum access to HIV test, know their HIV status and consequently are aware of their infant's HIV exposure and access adequate care. Indeed, knowing infant's HIV exposure is the pre-requisite for success of the Early Infant Diagnosis program and early ART initiation in case of an infected infant and eventually HIV cure interventions.

Knowing factors associated to the condition of unknown HIV exposure status in infants and of being HIV exposed is key to identify gaps in the provision of health services to mom-baby pair and to guide development of focused interventions to achieve elimination of vertical transmission and contribute to the end of the AIDS epidemic by 2030.

To our knowledge there are no population-based studies describing those factors in Mozambique or in other countries. Thereby the aim of the study is to evaluate characteristics associated to unknown HIV exposure status and to HIV exposure status in infants and children less than 2 years of age in Mozambique using data collected through the National HIV Survey of 2015 (3).

Methods

Study design

This is a cross sectional analytical study that uses data from the 2015 National survey whose primary aim was to estimate HIV prevalence in the adult population, malaria prevalence and immunization coverage in children under-5 years of age in Mozambique [3]. Besides the standard household module, the survey included childbearing age women module focusing on malaria, immunization, maternal and child health and HIV. The questionnaires were designed following standard questionnaires from the Demographic and Health Surveys (DHS), which were customized for incorporating the purpose of capturing HIV indicators, including women ever been tested for HIV, HIV testing at the ANC, at delivery, and during the post-natal period, the HIV test result at each of the previous contacts with the health services, and testing for HIV offered to the child. Standard questions were also asked regarding the mother and child health, including health seeking behavior, medicines taken, nutrition and immunization practices. Consenting women were HIV tested on the day of the survey following the national HIV testing algorithm [13]. The survey was conducted between June and September 2015 and used a systematic, multi-stage, stratified (urban and rural) and proportionate to size sampling, as described elsewhere [3]. The overall sample of the survey

was designed for HIV prevalence estimates with 95% confidence interval and an error margin of 5% and 80% power, as well as for rural and urban areas and provincial level representativeness. A total of 7368 household were identified and 7749 women were interviewed. The National HIV survey in 2015 included a total of 6.946 women of child bearing age (15-49 years) who were interviewed for the women and child health module [3].

For the purpose of our analysis, we restricted the database to women (15-49 years) who had at least one child with age of 24 months or younger on the day of the interview, corresponding to 2141 women. Weights were computed by the Demographic and Health Survey Program - DHS [14] and provided as variable in the accessed database, allowing to adjust our analysis for unequal selection probabilities. DHS is a USAID funded program which, in collaboration with National Bureau of Statistics, routinely collects nationally-representative household data on demographic, social and health indicators. It is implemented worldwide and mainly in low- and middle-income countries.

Dependent variables

The analysis considered two dependent variables – known child HIV exposure status, coded '1' if 'infant is known to have been HIV exposed OR known to not have been HIV exposed' and '0' if HIV exposure could not be ruled out – 'infant's unknown HIV exposure'; and child exposed to HIV, coded '1' if 'exposed to HIV', coded '0' if 'not exposed to HIV' and '8' if 'unknown exposure to HIV'. The variable 'child exposed to HIV' was computed by the DHS program and provided in the accessed data base.

Independent variables

Studies evaluating determinants of the use and access to HIV prevention and care constituted the basis for defining key independent variables [15–19]. Besides demographics, education, employment, religion, area and region of residence, socioeconomics and amenities of the households, independent variables included variables of health services seeking behavior and utilization. Health utilization was composed by use of antenatal care, institutional delivery and use of pos-natal consultation; wealth index was provided as computed by the DHS [14] – which used a factor analysis for household amenities such as television, radio, refrigerator, bicycle, motorcycle, computer, water supply, sanitation and cooking fuel [14]. Through transformations, we computed nominal independent variables: time to health facilities results in a corresponding independent variable (distance to nearest health facility less vs more than 30 minutes); exposure to media was

based on household having and using radio or television; immunization status of the child considered age adjusted vaccination for diphtheria, tetanus, pertussis and hepatitis B and measles; answers to questionnaire on who decides on household matters, finances, health and social events allowed to compute for the binary variable on mother's participation on household decisions. Participating in decision was coded '1' if she decided alone or with other members and '0' if she reported no participation at all in decisions around family, health and economic matters of the household.

Statistical Methods

The analysis was weighted and adjusted for the complex sampling using the statistical package for social sciences (SPSS) version 24. First, descriptive statistics results are expressed as absolute and relative frequencies with respective 95% confidence interval (CI) of percentages. Second, separate analyses were carried out on correlates of 'known status of child HIV exposure' and 'child exposed to HIV' against explanatory variables by bivariate association expressed by *p,* Odds Ratio (OR) and 95% CI. Third, binary logistic regression was used to estimate adjusted OR and 95% CI of being a child with known HIV exposure status and of being an HIV exposed child, both against sociodemographic, health behavior and health services utilization covariates collected by the survey.

Ethical considerations

The 2015 HIV, malaria and immunization survey - IMASIDA 2015- was approved by the Ministry of Health, the National Bioethics Committee (IRB00002657, reference 262/CNBS/2014). The participation was voluntary. The database is anonymized and publicly available through an application process to the *Instituto Nacional de Saúde de Moçambique* or DHS program platforms. Authorization for the use of database for this study has been issued by the DHS program (https://dhsprogram.com/Data/terms-of-use.cfm).

Results

Among 2141 interviewed women, a total of 1769 (85%, CI 95% 83.0-86.8%) were breastfeeding at the moment of the interview and 66 (3%, CI 95% 2.3-4.0%) were pregnant.

The social and demographic characteristics of our sample are described in Table 1. Sixty-eight percent of women were less than 30 years of age, 37.2% (CI 95% 33.4-41.2%) were from the

Northern region, 42% (CI 95% 38-46.1%) from the Central and 20.8% (CI 95% 18.3-23.4%) from the Southern region. Majority of them 74% (CI 95% 70.8-77.2%) were living in a rural area; 68% (CI 95% 63.8-72%) did not have access to piped water and 91% (CI 95% 89.1-92.4%) did not have access to improved sanitation; 75.7% (CI 95% 73-78.3%) did not have radio or television at home; only 1.7% (CI 95% 1.2-2.4%) used improved fuel for cooking. Families with at least 4 members were 83.6% (CI 95% 81.5-85.4%), the head of the house was male in 65% (CI 95% 62.1-67.7%) and 9.5% (CI 95% 8-11.3%) of women referred to participate in the decision-making process regarding family matters such as health or money management among others. Fifty five percent of women (CI 95% 51.5-58.7%) referred having primary education, while 28% (CI 95% 27.4-31.7%) referred no education; 44% (CI 95% 40.1-47.9%) referred having a job and 45.7% (CI 95% 42.2-49.2%) referred to have a mean of transportation; 29.4% (CI 95% 25.7-33.5%) were of Catholic religion, 19.6% (CI 95% 16.3-23.3%) of Islamic religion and 28.3% (CI 95% 25.3-31.6%) of others Christian religions such as protestant and evangelic. Approximately 67% had more than one child (30% more than 5). When asked about their last pregnancy, 93% referred to have attended antenatal care and 60.3% (CI 95% 56.3-64.1%) completed four or more ANC visits, 70% (CI 95% 65.8-73.9%) gave birth in a health facility and 76% (CI 95% 72.6-79.1%) had postnatal consultation within the second month of life of her child. When asked about infant vaccination, 74.6% infants (CI 95% 71.1-77.8%) completed the immunization schedule adjusted to infant's age. Seventy three percent (CI 95% 69.6-76.4%) of women had HIV test at ANC or maternity and 8.3% (CI 95% 6.3-10.9%) didn't know if they did or not the test; 68% (CI 95% 64.4-71.6%) referred a negative result, 4.9% (CI 95% 4-6%) a positive one; 21.4% (CI 95% 18.2-24.9%) said they had never been tested before and 5% (CI 95% 3.6-6.8%) said they did not receive the result. Among 1579 women tested on the day of the interview 7.2% (95% CI 5.9-8.7%) resulted HIV positive. The proportion of women whose infant's HIV exposure status was unknown at the time of the interview was 32% (95% CI 28.5-35.7%); among infant's with known HIV exposure status, 4.5% (CI 95% 3.6-5.5%) were HIV exposed.

Table 1. Characteristics of interviewed women- Mozambique 2015 (N= 2141)

		Total	Estimate	95% Confidence Interval	
				Lower	Upper
Mother's age (years)	15-19	406	18.8%	16.7%	21.1%
	20-24	607	28.3%	26.1%	30.6%
	25-29	448	20.9%	19.0%	23.0%
	30-34	313	14.6%	12.8%	16.6%
	35+	367	17.4%	15.5%	19.4%
	Total	2141	100.0%	100.0%	100.0%
Family members	≤ 3 people	325	16.4%	14.6%	18.5%
	≥ 4 people	1816	83.6%	81.5%	85.4%
	Total	2141	100.0%	100.0%	100.0%
Highest educational level	No education	531	28.0%	24.7%	31.7%
	Primary	1135	55.1%	51.5%	58.7%
	Secondary	475	16.9%	14.6%	19.3%
	Total	2141	100.0%	100.0%	100.0%
Sex of household head	Male	1348	65.0%	62.1%	67.7%
	Female	793	35.0%	32.3%	37.9%
	Total	2141	100.0%	100.0%	100.0%
Participation in family decision	No	1920	90.5%	88.7%	92.0%
	Yes	221	9.5%	8.0%	11.3%
	Total	2141	100.0%	100.0%	100.0%
Mother job	No job	1188	56.0%	52.1%	59.9%
	With job	953	44.0%	40.1%	47.9%
	Total	2141	100.0%	100.0%	100.0%
Religion	Catholic	502	29.4%	25.7%	33.5%
	Islamic	381	19.6%	16.3%	23.3%
	Other Christian	724	28.3%	25.3%	31.6%
	Other	531	22.6%	19.5%	26.1%
	Total	2138	100.0%	100.0%	100.0%
Mean of transportation	No	1190	54.3%	50.8%	57.8%
	Yes	951	45.7%	42.2%	49.2%
	Total	2141	100.0%	100.0%	100.0%
Source of water at home	no piped water	1325	68.0%	63.8%	72.0%
	with piped water	816	32.0%	28.0%	36.2%
	Total	2141	100.0%	100.0%	100.0%
Toilet	not improved	1863	90.9%	89.1%	92.4%
	improved	278	9.1%	7.6%	10.9%
	Total	2141	100.0%	100.0%	100.0%
Media utilization	No	1476	75.7%	73.0%	78.3%

	Yes	665	24.3%	21.7%	27.0%
	Total	2141	100.0%	100.0%	100.0%
Cooking fuel	Improved Cooking Fuel	62	1.7%	1.2%	2.4%
	Coal or Wood	2053	97.2%	96.3%	97.8%
	Not applicable	26	1.1%	.7%	1.7%
	Total	2141	100.0%	100.0%	100.0%
Travel in the past 12 months	No	1638	79.4%	77.3%	81.3%
	Yes	503	20.6%	18.7%	22.7%
	Total	2141	100.0%	100.0%	100.0%
Place of residence	Urban	775	25.9%	22.8%	29.2%
	Rural	1366	74.1%	70.8%	77.2%
	Total	2141	100.0%	100.0%	100.0%
Region of residence	North	628	37.2%	33.4%	41.2%
	Center	892	42.0%	38.0%	46.1%
	South	621	20.8%	18.3%	23.4%
	Total	2141	100.0%	100.0%	100.0%
Number of live children	1	526	23.2%	21.0%	25.6%
	2	397	18.5%	16.8%	20.4%
	3	338	15.8%	13.9%	18.0%
	4	261	12.6%	11.1%	14.3%
	5+	619	29.9%	27.7%	32.1%
	Total	2141	100.0%	100.0%	100.0%
Sex of child	Male	1051	50.0%	47.3%	52.6%
	Female	1090	50.0%	47.4%	52.7%
	Total	2141	100.0%	100.0%	100.0%
Current age of child (years)	0	1033	47.5%	45.3%	49.7%
	1	1014	48.2%	46.1%	50.3%
	2	94	4.3%	3.4%	5.4%
	Total	2141	100.0%	100.0%	100.0%
Currently breastfeeding	No	406	16.8%	14.8%	19.0%
	Yes	1735	83.2%	81.0%	85.2%
	Total	2141	100.0%	100.0%	100.0%
Currently pregnant	No or unsure	2075	97.0%	96.0%	97.7%
	Yes	66	3.0%	2.3%	4.0%
	Total	2141	100.0%	100.0%	100.0%
Breastfeeding duration	6 months	62	2.6%	1.9%	3.4%
	12 months	125	5.6%	4.6%	6.8%
	18 months	148	6.0%	5.0%	7.3%
	Still breastfeeding	1769	85.0%	83.0%	86.8%
	Never breastfed	24	.8%	.5%	1.4%

	Total	2128	100.0%	100.0%	100.0%
Time to reach Health Facility	Up to 30 minutes	793	36.1%	31.9%	40.6%
	> 30 minutes	1209	63.9%	59.4%	68.1%
	Total	2002	100.0%	100.0%	100.0%
ANC consultation (nr)	0	134	7.1%	5.2%	9.5%
	1 to 3	652	32.6%	29.5%	36.0%
	4+	1355	60.3%	56.3%	64.1%
	Total	2141	100.0%	100.0%	100.0%
Institutional Delivery	No	550	30.0%	26.1%	34.2%
	Yes	1591	70.0%	65.8%	73.9%
	Total	2141	100.0%	100.0%	100.0%
Baby postnatal visit within 2 months	No	421	20.7%	18.0%	23.8%
	Yes	1648	76.0%	72.6%	79.1%
	Don't know	66	3.3%	2.3%	4.6%
	Total	2135	100.0%	100.0%	100.0%
Utilization Health Service	No	1176	58.8%	54.9%	62.5%
	Yes	965	41.2%	37.5%	45.1%
	Total	2141	100.0%	100.0%	100.0%
Child Immunization up to date	No	468	25.4%	22.2%	28.9%
	Yes	1673	74.6%	71.1%	77.8%
	Total	2141	100.0%	100.0%	100.0%
HIV test at ANC or Delivery	Not done	346	18.6%	16.3%	21.1%
	Done	1650	73.1%	69.6%	76.4%
	Unknown	145	8.3%	6.3%	10.9%
	Total	2141	100.0%	100.0%	100.0%
Self-reported HIV Status	Positive	142	4.9%	4.0%	6.0%
	Negative	1520	68.1%	64.4%	71.6%
	Indeterminate	9	.3%	.2%	.7%
	Refused to answer	7	.2%	.1%	.5%
	Did not receive result	81	5.0%	3.6%	6.8%
	Never tested	382	21.4%	18.2%	24.9%
	Total	2141	100.0%	100.0%	100.0%
Result of HIV test	Negative	1423	92.2%	90.6%	93.5%
	Positive	142	7.2%	5.9%	8.7%
	Undetermined	7	.3%	.1%	.7%
	Missing result	7	.3%	.2%	.8%
	Total*	1579	100.0%	100.0%	100.0%
Child exposed to HIV	Not exposed	1435	63.6%	60.0%	67.0%
	Exposed	129	4.5%	3.6%	5.5%
	Unknown	577	32.0%	28.5%	35.7%
	Total	2141	100.0%	100.0%	100.0%

Child HIV Exposure Status	Unknown	577	32.0%	28.5%	35.7%
	Known	1564	68.0%	64.3%	71.5%
	Total	2141	100.0%	100.0%	100.0%

* n=1579/2141 women eligible for testing on the day of the survey as per the survey protocol

Firstly, we analyzed factors associated with infant's 'unknown HIV status exposure'. In the bivariate analysis (Table 2), factors positively associated to infant 'unknown HIV exposure status' were: household head being a male (OR 1.31 95% CI 1.032-1.68), no education and primary education versus secondary education of the mother (OR 7.98 95% CI 4.67-13.64 and OR 4.47 95% CI 2.81-7.12 respectively), living in the Northern region of the Country (OR 8.84 95% CI 5.38-13.13) or in the Center (OR 6.95 95% CI 4.57-10.58) with respect to the South, age of the youngest child between 1 and 2 years (OR 2.04 95% CI 1.13-3.81), duration of breastfeeding of 12 months (OR 5.33 95% CI 1.31-21.63), being breastfeeding (OR 4.67 95% CI 1.23-17.7), being in the poorer categories of wealth index (OR 11.23 95% CI 6.3-19.9), not having had an ANC visit (OR 15.5 95% CI 8.06-29.8), not having used any health service during and after pregnancy -ANC, institutional delivery, post-partum consultation (OR 2.64 95% CI 1.85-3.76), not being updated with infant's vaccination schedule (OR 2.16 95% CI 1.59-2.93). Factors negatively associated to infant 'unknown HIV exposure status' were: age of the woman between 30 and 34 year (OR 0.56 95% CI 0.37-0.84), living in a urban area (OR 0.20 95% CI 0.14-0.29), having four children (OR 0.59 95% CI 0.39-0.90), living less than 30 minutes from the HF (OR 0.64 95% CI 0.46-0.90) and being of other Christian religion (OR 0.66 95% CI 0.47-0.94).

Table 2. Factors associated with child unknown HIV exposure status - Mozambique 2015

Child unknown HIV exposure status		**Bivariate analysis**				**Multivariate analysis**			
		p value	**OR**	**95% CI**		***P value***	**Adjusted OR**	**95% CI**	
				Lower	**Upper**			**Lower**	**Upper**
Sex of household head	Male vs. Female	.027	1.317	1.032	1.680	.104	1.285	.950	1.738
Family members (nr)*	≤3 vs. 4+ people	.235	1.211	.882	1.663	-	-	-	-
Participation in family decision*	No vs. Yes	.052	1.547	.996	2.403	-	-	-	-
Mother's job*	No vs. Yes	.674	.934	.679	1.285	-	-	-	-
Mother's age (years)	15-19 vs. 35+	.155	.773	.543	1.102	.318	.731	.394	1.354
	20-24 vs. 35+	.097	.744	.524	1.056	.827	.944	.563	1.582
	25-29 vs. 35+	.076	.724	.507	1.035	.552	.873	.558	1.368
	30-34 vs. 35+	.005	.560	.372	.841	.212	.736	.454	1.192

Highest educational level	No education vs. Secondary	.000	7.986	4.674	13.643	.004	2.726	1.386	5.361
	Primary vs. Secondary	.000	4.475	2.812	7.120	.031	1.826	1.057	3.153
Religion	Catholic vs. Other	.274	1.212	.858	1.713	.518	.851	.521	1.389
	Islamic vs. Other	.162	1.361	.883	2.096	.822	1.077	.564	2.056
	Other Christian vs. Other	.022	.667	.471	.944	.243	.807	.562	1.158
Wealth index	Poorest vs. Richest	.000	11.195	6.380	19.643	.391	1.464	.611	3.505
	Poorer vs. Richest	.000	11.234	6.313	19.993	.117	1.985	.842	4.678
	Middle vs. Richest	.000	8.556	4.703	15.564	.168	1.787	.781	4.087
	Richer vs. Richest	.018	2.178	1.146	4.138	.876	1.059	.511	2.198
Place of residence	Urban vs. Rural	.000	.205	.144	.292	.004	.419	.233	.753
Region of residence	North vs. South	.000	8.408	5.381	13.138	.000	4.411	2.181	8.919
	Center vs. South	.000	6.959	4.573	10.588	.000	3.015	1.861	4.886
Number of live children	1 vs. 5+	.587	.916	.668	1.257	.044	1.810	1.016	3.225
	2 vs. 5+	.016	.641	.447	.921	.907	.968	.559	1.676
	3 vs. 5+	.437	.838	.535	1.311	.302	1.254	.815	1.928
	4 vs. 5+	.016	.599	.395	.909	.047	.606	.370	.993
Current age of child (yr)	0 vs. 2	.040	1.859	1.029	3.358	.086	1.926	.911	4.075
	1 vs. 2	.017	2.084	1.139	3.811	.039	2.107	1.039	4.276
Breastfeeding duration	≤ 6 months vs. Never	.090	3.633	.817	16.157	.067	3.633	.911	14.488
	≤ 12 months vs. Never	.019	5.333	1.315	21.630	.016	4.486	1.321	15.234
	≤ 18 months vs. Never	.147	2.873	.688	12.001	.239	2.286	.576	9.074
	Still breastfeeding vs. Never	.024	4.671	1.231	17.718	.160	2.296	.718	7.341
Time to reach Health Facility	Up to 30 minutes vs. ≥ 30 minutes	.011	.648	.465	.904	.365	1.172	.831	1.653
ANC consultation (nr)[#]	1-3 vs. 4+	.000	2.165	1.606	2.918	-	-	-	-
Baby postnatal visit within 2 months*	No vs. Don't know	.814	1.080	.568	2.053	-	-	-	-
	Yes vs. Don't know	.254	.701	.381	1.293	-	-	-	-
Utilization Health Service	No vs. Yes	.000	2.640	1.852	3.763	.000	1.905	1.422	2.552
Child Immunization up to date	No vs. Yes	.000	2.162	1.595	2.930	.161	1.246	.916	1.695
Travel in the last 12 months	No vs. Yes	.053	1.369	.995	1.884	-	-	-	-

*Variable not analyzed in the Multivariate analysis because its association was not significative in the bivariate.

[#] Variable not analyzed in the Multivariate analysis because it is part of the variable "Utilization Health Service".

In the multivariate analysis, factors which persisted associated with infant 'unknown HIV status exposure' were living in the North region (AOR 4.41 95% CI 2.18-8.91), living in the Center (AOR 3.01 95% CI 1.86-4.88), living in the urban area (AOR 0.41 95% CI 0.23-0.75), mother with no education (AOR 2.72 95% CI 1.38-5.36) or with primary education (AOR 1.82 95% CI 1.05-3.15) with respect to secondary education, having 4 children (AOR 0.60 95% CI 0.37-0.99), current age of the last child between 1 and 2 years (AOR 2.10 95% CI 1.03-4.27), duration of breastfeeding of 12 months (AOR 4.48 95% CI 1.32-15.23), not having utilized the Health services -ANC, institutional delivery or post-partum consultation- (AOR 1.9 95% CI 1.42-2.55).

We also looked at factors associated with the condition of child 'being HIV exposed', and results are described in Table 3. In the bivariate analysis, factors negatively associated with being a HIV exposed infant are: household head being a male (OR 0.47 95% CI 0.31-0.70), mother age between 15 and 19 years (OR 0.27 95% CI 0.12-0.64) and between 20 and 24 years (OR 0.33 95% CI 0.16-0.68), living in the central region of the country (OR 0.30 95% CI 0.18-0.50) and in the northern (OR 0.13 95% CI 0.05-0.31) compared to the southern; being of the Islamic religion (OR 0.35 95% CI 0.12-0.98), being in the poorer wealth category (OR 0.13 95% CI 0.04-0.40), not having travelled in the past 12 months (OR 0.39 95% CI 0.26-0.60), having one child (OR 0.39 95% CI 0.21-0.71), mother still breastfeeding (OR 0.20 95% CI 0.06-0.58), having had between 1 and 3 ANC consultation (OR 0.41 95% CI 0.23-0.73), not having accessed Health services along the PMTCT continuum of care (OR 0.43 95% CI 0.26-0.71). The only factor positively associated with being an HIV exposed child is mother not currently breastfeeding (OR 2.19 95% CI 1.41-3.38).

Table 3. Factors associated with the condition 'HIV exposed child'- Mozambique 2015

Child HIV exposed		**Bivariate analysis**				**Multivariate analysis**			
		p value	**OR**	**95% CI**		***P value***	**Adjusted OR**	**95% CI**	
				Lower	**Upper**			**Lower**	**Upper**
Sex of household head	Male vs. Female	.000	.472	.315	.707	.000	.418	.261	.667
Family members (nr)*	≤3 people vs. 4+	.727	.899	.495	1.634	-	-	-	-
Mother's age (years)	15-19 vs. 35+	.003	.277	.120	.642	.208	.393	.091	1.687
	20-24 vs. 35+	.003	.334	.163	.684	.055	.416	.170	1.018
	25-29 vs. 35+	.259	.666	.328	1.352	.412	.720	.327	1.584
	30-34 vs. 35+	.848	1.063	.567	1.995	.655	1.169	.587	2.327
Number of live children	1 vs. 5+	.002	.393	.216	.715	.316	.553	.173	1.764
	2 vs. 5+	.069	.532	.270	1.050	.368	.677	.289	1.585

	3 vs. 5+	.697	1.120	.633	1.982	.612	1.205	.584	2.484
	4 vs. 5+	.757	1.099	.601	2.011	.247	1.492	.756	2.943
Highest educational level*	No education vs. Secondary	.055	.518	.265	1.015	-	-	-	-
	Primary vs. Secondary	.869	1.045	.621	1.759	-	-	-	-
Source of water at home**	No piped water vs. Piped water	.000	.413	.259	.658	-	-	-	-
Toilet type**	not improved vs. Improved	.313	.718	.377	1.368	-	-	-	-
Media utilization**	No vs. Yes	.147	.726	.471	1.119	-	-	-	-
Cooking fuel**	Improved vs. Not applicable	.549	.570	.090	3.599	-	-	-	-
	Coal or Wood vs. Not applicable	.660	.710	.153	3.289	-	-	-	-
Participation in family decision*	No vs. Yes	.970	1.013	.527	1.945	-	-	-	-
Mother job*	No job vs. Yes job	.992	.998	.640	1.555	-	-	-	-
Wealth index	Poorest vs. Richest	.001	.163	.055	.481	.161	.357	.084	1.512
	Poorer vs. Richest	.000	.134	.044	.406	.056	.296	.085	1.032
	Middle vs. Richest	.533	.820	.438	1.534	.116	1.870	.856	4.083
	Richer vs. Richest	.273	.754	.454	1.252	.814	.932	.516	1.682
Place of residence	Urban vs. Rural	.049	1.553	1.002	2.405	.750	.910	.509	1.628
Region of residence	North vs. South	.000	.135	.058	.314	.028	.264	.080	.867
	Center vs. South	.000	.304	.184	.503	.006	.430	.235	.787
Religion	Catholic vs. 4 Other	.640	.849	.425	1.693	.280	1.513	.712	3.214
	Islamic vs. 4 Other	.046	.351	.126	.980	.654	.748	.209	2.679
	Other Christian vs. Other	.071	1.619	.959	2.735	.163	1.515	.845	2.715
Current child age (yr)*	0 vs. 2	.562	1.320	.516	3.377	-	-	-	-
	1 vs. 2	.964	.978	.370	2.586	-	-	-	-
Breastfeeding duration	≤ 6 months vs. Never	.191	2.352	.651	8.492	.105	3.459	.771	15.515
	≤ 12 months vs. Never	.195	.453	.136	1.504	.630	.698	.161	3.027
	≤ 18 months vs. Never	.004	.081	.015	.436	.009	.070	.010	.512
	Still breastfeeding vs. Never	.004	.200	.068	.587	.101	.342	.095	1.234
Time to reach Health Facility	Up to 30 minutes vs. ≥ 30 minutes	.029	1.652	1.052	2.595	.544	1.160	.718	1.875
Utilization Health Service	No vs. Yes	.001	.436	.265	.718	.007	.520	.323	.836

Child Immunization up to date*	No vs. Yes	.188	.648	.340	1.237	-	-	-	-
Currently breastfeeding*	No vs. Yes	.000	2.190	1.415	3.389	-	-	-	-
Currently pregnant*	No or unsure vs. Yes	.632	1.343	.400	4.516	-	-	-	-
ANC consultation (nr)#	1-3 vs. 4+	.003	.414	.234	.735	-	-	-	-
Institutional Delivery*	No vs. Yes	.064	.575	.319	1.033	-	-	-	-
Baby postnatal check within 2 months*	No vs. Don't know	.623	1.639	.227	11.836	-	-	-	-
	Yes vs. Don't know	.455	2.051	.309	13.600	-	-	-	-
Travelled in the last 12m	No vs. Yes	.000	.398	.264	.601	.282	.769	.475	1.244

*Variable not analyzed in the Multivariate analysis because it was not significative in the bivariate

**In the multivariate analysis the variable was combined in the wealth index variable

In the multivariate analysis the variable is part of variable Utilization Health Service.

In the multivariate analysis, factors which persisted significantly associated with infant 'being HIV exposed' were: household head being a male (AOR 0.41 95% CI 0.26-0.66), living in the Northern region of Mozambique (AOR 0.26 95% CI 0.08-0.86) and in the Centre (OR 0.43 95%CI 0.23-0.78), duration of breastfeeding of 18 months (AOR 0.070 95% CI 0.01-0.51), not having used the ANC, maternity or post-natal consultation (AOR 0.52 95% CI 0.32-0.83).

Discussion

To our knowledge, this is the first study describing factors associated to the condition of unknown HIV exposure status among infants and factors associated to the condition of infant's being HIV exposed. We found that 21% of interviewed women, majority of them breastfeeding or pregnant, reported never being tested for HIV and 5% said they did not receive the test result done in the past. However, according to the primary study outcome, 32% of infants had an unknown HIV exposure status. Considering that more than 80% of interviewed women were breastfeeding, having one third of infants with unknown HIV exposure in the first two years of age is worrisome.

One previous study in Mozambique using data from the 2009 National Survey on Prevalence, Behavioral Risks and Information about HIV and AIDS reported that almost 57% of interviewed women were unaware of their HIV status [20]. A more recent study in a high HIV prevalence district of southern Mozambique showed that around 39% of people with a past positive HIV test, repeated

the test [21]. These two studies, done in the same context of our analysis, suggest that there is a large proportion of people who do not know their HIV status.

Studies in the region, report the proportion of women with unknown HIV status, tested at delivery and their infants at vaccination visit, which ranged between 5% in Tanzania [22] to 58% in Kenya [9]. However, to our knowledge there is no population-based report of the proportion of infants with unknown HIV exposure status up to 24 months of age and our study showed robust evidence.

From our population-based study, it is evident that women who need to be tested and re-tested are being missed: 12% did not attend any ANC visit, 30% delivered outside a health facility and 24% did not have a post-natal visit within the second month of life of their baby. In the same national survey, 52% of HIV infected women between 15-49 years knows their HIV status, that's higher in the south of the country [3]. Results highlight that there are still missing opportunities along the path to prevent mother-to-child transmission both in the pre-natal and post-natal period, the first one being poor HIV screening and re-testing of previously HIV negative women.

In Mozambique it is part of MCH routine care to offer a pregnant woman the HIV test at the first consultation as well as check at delivery and in the post-partum if she needs to repeat the test, in case the first result was negative and older than 3 months, as recommended by WHO [7,13]. As a result, at the end of 2015 HIV test coverage at ANC and Maternity was of 95% [5] which is in contrast with our findings of 32% of women unaware of her child HIV exposure status. This is alarming considering the high number of HIV incident cases in women during pregnancy or breastfeeding reported in Mozambique and also in neighboring Sub-Saharan Africa ranging from 4.4/100 women-years up to 16.8/100 person-years [9–12,23–25]. In Southern Mozambique an incidence rate of 4.28/100 women-years was described [26].

Despite a first negative HIV test, pregnancy and postpartum are periods of persistent risk of HIV acquisition and higher risk of vertical transmission as compared to women with chronic infection [27] and retesting every 3 months to rule out seroconversion and manage acute infection is recommended [6,7]. In South Mozambique, a longer follow-up was done until 18 months after delivery, which is the usual duration of breastfeeding and sero-conversion rate was about 3.20/100 women-years occurring mainly (39%) between 16-18 months after delivery [8]. Although retesting guidelines are already in place, uptake is not optimal. A recent paper reviewed and characterized guidelines of Africa Countries on timing and frequency of maternal retesting and found that in high prevalence countries such as Kenya, South Africa, Tanzania, Uganda, Zambia, Zimbabwe, regular retesting was part of the norms but in others countries with high rate of mother to child

transmission, they were not consolidated [6]. Strengthening HIV screening practice in the post-partum setting and during infancy must be the focus of interventions among health staff and lay counsellors at the health facilities as well as in the community; messages targeting women need to be boosted and spread in the community. Our results indicate that in 2015 much was to be done to screen and test for HIV all women throughout the PMTCT pathway till the end of breastfeeding.

We found, and it is indeed expected, that women who referred not having used health services during the antenatal period, or who did not have an institutional delivery nor a post-natal consultation for their infant, have more chance of not knowing their infant's HIV exposure, and this is because of missed the opportunity to be tested. Another evidence of missing opportunities after the baby is born, is the interesting finding that women with last child aged between 1 and 2 years of age had more chance of unknowing their infant's HIV exposure and that the longer the breastfeeding practice the higher the odds of not knowing the HIV status [28]. Despite lot of attention being paid to the mom-baby pair until delivery it is likely that, along the mother and child continuum of care, after the baby is born, systematic follow-up and offer of HIV testing and prevention practices during prolonged breastfeeding is somehow neglected.

The vaccination appointment is certainly another opportunity to screen mothers and infants for HIV. A study in Tanzania showed that integration of HIV testing in the immunization clinic can increase identification of HIV-infected mothers and exposed infants [22]. National figures show a DPTHbHBV coverage at 4 months of 82% and a measles coverage of 83% [3], however, in our sample 25% of children vaccination schedule was not up to date, and in the unadjusted analysis, not having completed the vaccination schedule was associated with 2-fold increased chance to have an unknown HIV status exposure. Our results cover the entire vaccination period adjusted for children age at time of interview, which is different from the study of Goodson et al, which limited analysis to the first vaccination visit at 2 months after birth.

Thinking about MCH services integration, it is also important to consider that synergism of existing services can benefit both programs outcomes as there is some evidence that HIV-exposed infants have lower up-take of childhood vaccination in Sub Saharan Africa [29]. Nevertheless, implications of using the immunization platform to improve HIV screening need to be carefully designed considering mothers' and health staff acceptance [30].

Interestingly, other factors, in the multivariate analysis, associated with infant 'unknown HIV status exposure' were the region and area of residence with lower HIV prevalence, mother education and the number of children. A woman living in the northern and central region had 3-4 times more

chance to have an infant with unknown HIV status with respect to a woman living in the south. The northern region of Mozambique which include the provinces of Cabo Delgado, Nampula, Niassa, is poorer, less developed and majority of people live in rural area, a condition that, in our results, is also associated with double chance to have an infant with unknown HIV status. Poverty and underdevelopment, may be related to the condition of not knowing the infant HIV serostatus, because they imply factors limiting access to health facility, such as big distances from home, bad road conditions, limited transport availability or lack of money itself. Similar factors which limit the use of health facilities during the antenatal period are well reported in other studies of Sub-Saharan African countries. In Uganda poorer and less educated women were more likely to deliver at home [31], in Kenya low socio-economic status was associated with lower knowledge of ANC care services and lower institutional delivery [32], in Nigeria poverty and living in rural setting were described associated with underuse of ANC consultation [16]. However, these studies do not specifically analyzed correlates of infant's HIV exposure status.

Access to education is another factor directly related to poverty and to living in a rural area: in general women have less chance to go to school, and it has been reported that 35% of women without education live in the rural area versus 17% living in the urban area [3]. It is also described that the chance to go to school increase with the increase of wealth index within the family [19] and in our sample, which is representative of Mozambican women, majority of women are poor and do not have access to basic life conditions such piped water (32%), improved sanitation (9.1%), improved cooking fuel (1.7%). In our finding, women with no education have 3 times more chance to not know her infant's HIV status. Literacy certainly facilitates awareness of available services for ANC and post-natal care period and empower a woman to seek care for herself and her children as described in Nigeria [16], Kenya [32] and Ghana [19] where no education or primary education is a factor associated with underuse of ANC.

Poverty limits access to media and lack of information can contribute to poor knowledge about HIV prevention and care. Many studies describe the correlation between knowledge about health service and HIV, access and retention into PMTCT care in neighboring countries such as South Africa, Malawi, Tanzania, Uganda and Kenya [33,34]. In Mozambique, only 30% of girls and 51% of boys aged 15-24 years, referred comprehensive knowledge about HIV prevention practices [35] and information is certainly the starting point for reducing new HIV infections among child-bearing age women. Despite the initiative of the Ministry of Health and the Institute of Social Communication to produce and disseminate television spots and radio programs in local languages to disseminate

HIV prevention and early testing messages to communities, few people are being reached. In fact, in our sample 76% of interviewed women reported no access to TV or radio at home; which is consistent with the overall results for Cabo Delgado and Nampula where more than 80% of women reported not having access to any form of media [3]. In Nigeria no access to media was a factor associated with underuse of ANC among women [16]. It is true that in Mozambique one strategy is to run videos with health messages in the waiting area of health facilities, but while we are targeting people attending the clinic, on the other hand, we are not reaching people who do not access health facilities and live in rural areas. Communication campaigns with itinerant theatres have been used by Institute of Social Communication but the coverage is limited.

Our secondary outcome indicates that 4.5% of children were HIV exposed. Given that the HIV prevalence among child-bearing age women is 15.4% [3], this result is lower than expected and in part, it may be due to the fact that 32% of children of our samples had an unknown HIV exposure status. We found that factors negatively associated with infant 'being HIV exposed' were living in the North and Central region of Mozambique, where HIV prevalence is lower, the household head being a male, duration of breastfeeding of 18 months, not having used the ANC, Maternity or Post-natal consultation.

In Mozambique, breastfeeding practice for women living with HIV, follows WHO recommendations up to 12 months of age [36]. A mother who is breastfeeding for longer than twelve months is more likely to be HIV negative and her infant being HIV unexposed because in our context, mothers who do not breastfeed are usually those who are sick or have any other health contraindication, although no empirical reports have been published.

Not attending a post-natal consultation within 2 months of life of the infant (AOR 0.49 95% CI 0.25-0.93) is associated with lower chances to have an HIV exposed infant which is an unexpected result. It may be due to the fact that intense HIV counselling for postnatal consultation is targeting mainly HIV infected mothers and focus to retain and link into post-natal care HIV exposed newborns. Counselling for post-natal consultation might be neglected for those women with HIV negative test at delivery. This hypothesis is supported by studies from Zambia and Tanzania, where women who received an HIV test were more likely to give birth at health facility [32] suggesting potential positive effects of intensive counselling to this group on continuous utilization of health services.

Having a male as head of the family showed lower chance of being an HIV exposed infant and we also found a positive association with the 'unknown infant's HIV serostatus'. The reason is not clear however we think that it is related with cultural behavior and gender dynamics [37]. Families in

Mozambique are headed predominantly by males who decide on all family matters; in our samples only 9.5% of women were participating in the household decision process. In the case a woman is HIV infected, it is common that partner rejects the wife and leave the family [38–40]. Male role and contribution to the PMTCT success shall be a matter of further studies, however HIV and gender dynamics studies support our suggestion [33]. In Mozambique and elsewhere, it has been described that fear of stigma, discrimination and of losing their home are barriers for women to get tested and to access care [26,41,42]. De Schacht et al. found that 20% of women did not know if the husband was HIV tested as a prove that HIV infection is a topic not routinely discussed at home [26]. On the other hand, men were interviewed in Lesotho and North Mozambique and reported fear of testing for HIV, lack of education and information about HIV/AIDS [41,43]. Decisions regarding pregnancy and infant care taken by someone else other than the mother, such as elder female family member or grandmothers has been shown to affect HIV care adherence and retention among women in Kenya and Malawi [33,44,45] and limited involvement in family decision has been found in our study as well which may have led to less use of health service. Other studies described how masculinity affects willingness to engage in HIV prevention strategies, such as HIV testing and disclosure [46,47]. Engaging men constructively in gender equality and sexual health interventions is indeed crucial to address family health needs, reduce HIV, and in our case, achieve pediatric HIV elimination [48].

The analysis has few limitations. The survey was primarily powered to study the HIV prevalence in adult population and not for the purpose of our analysis. The logistic regression did not control for clustering of children at mother's level, however possible clustering is deemed negligible as the number of women with more than 1 children aged 24 months or less was only 3.2% (n=68). Additionally, as we restricted the sample to women with at least one live child of less than 2 year of age, the sample size was reduced and may be seen as possible selection bias. However, the sample is still large and the restriction allowed to gain control on the much crucial recall bias as well as to focus the study on the PMTCT targeted population for the complete follow up period of 24 months. Non-disclosure of serostatus during the survey may have underestimated the number of exposed children in favor of overestimation of unknown HIV exposure status. Even if that is the case, results are still valid since the outcomes balance each other in terms of bias direction, as well share similar, consistent and programmatically relevant associated factors. DHS questionnaire in the National survey did not explore stigma and discrimination as possible factors of not accessing HIV testing and we could not evaluate this potential cause of unknown HIV serostatus.

Conclusions

Knowing the mother's HIV status is the first step to halt vertical transmission. Despite the existence of national retesting guidelines throughout pregnancy and breastfeeding period, implementation and uptake are clearly not optimal and there are still many women and infants with unknown HIV serostatus. Our study points at persistent missing opportunities to prevent vertical HIV transmission in Mozambique as shown by having one third of infant's with unknown HIV exposure status while their mothers accessed health care services and more alarming, majority of them were still breastfeeding.

Programmatic data on HIV testing coverage at mother and child health clinic do not reflect findings from this population survey. This highlights that, if we want to achieve elimination of pediatric HIV, more need to be done to offer a continuum of care to women who utilize the health services without forgetting to reach those who do not access health care at all. By covering all steps of the PMTCT pathway, the risk of having an infected child can be reduced to less than 2%.

Strengthening the practice of HIV retesting among eligible women until the end of breastfeeding period, to detect incident cases of HIV, must be the focus of interventions among health providers and lay counsellors both in the health facilities and in the community. Adaptation of HIV testing delivery modality, expanding community HIV testing and care program through consolidating and scaling up mobile health clinic strategy for example, will allow to move from a Health facility centered to a patient centered approach taking health closer to where women live. Furthermore, community mobilization and engagement of people living with HIV to participate and contribute in delivering key messages and support care, such as Mentor Mother strategy or patients advocates, will allow to retain women and engage those who escaped the Health service. Moreover, resources need to be re-directed for effective communication strategy which is a critical component of the global effort in HIV prevention and education of rural communities and women who do not have access to conventional media.

Access to education and place of residence are factors strongly associated with women awareness of their HIV status and affect health seeking behavior for themselves and their children for which improvements depend on policies beyond the health sector. Multisectoral actors must work in synergy to tackle social factors which limit women to use the health services, and must direct more investment to empower women socially and economically. Drive actions beyond partner testing towards women empowerment is key to minimize negative effects of gender dynamics on HIV infection prevention and management within the family.

Finally, resources directed to the HIV program and related interventions to eliminate the HIV epidemic should not only focus on special populations such as pregnant women but also result in a stronger MCH services all over the country, including provinces and districts with lower HIV prevalence, which are poorer, remote and where women with no or lower education live. In the era of sustainable development goals, all the efforts done so far will remain elusive unless the social demographic and reproductive health factors, which are still preventing childbearing age women to know their HIV status, are improved.

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References

1. UNAIDS. Countdown to zero: global plan towards the elimination of new HIV infections among children by 2015 and keeping their mothers alive, 2011-2015. Geneva: UNAIDS; 2011.

2. UNAIDS. 2015 Progress report on the Global Plan-towards the elimination of new HIV infections among children and keeping their mothers alive. UNAIDS; 2015.

3. MISAU, INE, ICF. Inquérito de Indicadores de Imunização, Malária e HIV/SIDA em Moçambique [Immunization, Malaria and HIV/AIDS Survey in Mozambique] (IMASIDA) 2015 [Internet]. 2018 Feb. Available: https://dhsprogram.com/publications/publication-ais12-ais-final-reports.cfm

4. USAID. Country factsheets- Mozambique 2017 - HIV and AIDS Estimates [Internet]. 2017 [cited 3 Jul 2019]. Available: https://www.unaids.org/en/regionscountries/countries/mozambique

5. MISAU. Relatório Anual das Actividades Relacionadas ao HIV/SIDA [Annual Report of HIV/AIDS activities] - 2015. 2016.

6. Drake AL, Thomson KA, Quinn C, Newman Owiredu M, Nuwagira IB, Chitembo L, et al. Retest and treat: a review of national HIV retesting guidelines to inform elimination of mother-to-child HIV transmission (EMTCT) efforts. J Int AIDS Soc. 2019;22: e25271. doi:10.1002/jia2.25271

7. WHO | Consolidated guidelines on HIV testing services. In: WHO [Internet]. [cited 3 Jul 2019]. Available: http://www.who.int/hiv/pub/guidelines/hiv-testing-services/en/

8. De Schacht C, Mabunda N, Ferreira OC, Ismael N, Calú N, Santos I, et al. High HIV incidence in the postpartum period sustains vertical transmission in settings with generalized epidemics: a cohort study in Southern Mozambique. J Int AIDS Soc. 2014;17: 18808. doi:10.7448/IAS.17.1.18808

9. Rogers AJ, Akama E, Weke E, Blackburn J, Owino G, Bukusi EA, et al. Implementation of repeat HIV testing during pregnancy in southwestern Kenya: progress and missed opportunities. J Int AIDS Soc. 2017;20. doi:10.1002/jia2.25036

10. Moodley D, Esterhuizen TM, Pather T, Chetty V, Ngaleka L. High HIV incidence during pregnancy: compelling reason for repeat HIV testing: AIDS. 2009;23: 1255–1259. doi:10.1097/QAD.0b013e32832a5934

11. Kinuthia J, Drake AL, Matemo D, Richardson BA, Zeh C, Osborn L, et al. HIV acquisition during pregnancy and postpartum is associated with genital infections and partnership characteristics. AIDS Lond Engl. 2015;29: 2025–2033. doi:10.1097/QAD.0000000000000793

12. Munjoma MW, Mhlanga FG, Mapingure MP, Kurewa EN, Mashavave GV, Chirenje MZ, et al. The incidence of HIV among women recruited during late pregnancy and followed up for six years after childbirth in Zimbabwe. BMC Public Health. 2010;10: 668. doi:10.1186/1471-2458-10-668

13. MISAU. Directriz Nacional para a implementação do aconselhamento e testagem em saude [National guidelines for implementation of counseling and testing for health] [Internet]. MAPUTO; 2015. Available: http://www.misau.gov.mz/index.php/directrizes-nacionais

14. Croft TN, Marshall AMJ, Allen CK. Guide to DHS Statistics [Internet]. Rockville, Maryland, USA: DHS Program - ICF; 2018. Available: https://dhsprogram.com/publications/publication-dhsg1-dhs-questionnaires-and-manuals.cfm

15. Sia D, Onadja Y, Hajizadeh M, Heymann SJ, Brewer TF, Nandi A. What explains gender inequalities in HIV/AIDS prevalence in sub-Saharan Africa? Evidence from the demographic and health surveys. BMC Public Health. 2016;16. doi:10.1186/s12889-016-3783-5

16. Adewuyi EO, Auta A, Khanal V, Bamidele OD, Akuoko CP, Adefemi K, et al. Prevalence and factors associated with underutilization of antenatal care services in Nigeria: A comparative study of rural and urban residences based on the 2013 Nigeria demographic and health survey. Oh J, editor. PLOS ONE. 2018;13: e0197324. doi:10.1371/journal.pone.0197324

17. Hladik W, Benech I, Bateganya M, Hakim AJ. The utility of population-based surveys to describe the continuum of HIV services for key and general populations. Int J STD AIDS. 2016;27: 5–12. doi:10.1177/0956462415581728

18. Hutchinson PL, Mahlalela X. Utilization of voluntary counseling and testing services in the Eastern Cape, South Africa. AIDS Care. 2006;18: 446–455. doi:10.1080/09540120500213511

19. Nketiah-Amponsah E, Codjoe EA, Ampaw S. HIV/AIDS Awareness and Knowledge Among Ghanaian Women of Reproductive Age: What Are the Correlates? J Asian Afr Stud. 2019;54: 267–281. doi:10.1177/0021909618810037

20. Dokubo EK, Shiraishi RW, Young PW, Neal JJ, Aberle-Grasse J, Honwana N, et al. Awareness of HIV Status, Prevention Knowledge and Condom Use among People Living with HIV in Mozambique. PLoS ONE. 2014;9. doi:10.1371/journal.pone.0106760

21. Fuente-Soro L, Lopez-Varela E, Augusto O, Sacoor C, Nhacolo A, Honwana N, et al. Monitoring progress towards the first UNAIDS target: understanding the impact of people living with HIV who re-test during HIV-testing campaigns in rural Mozambique. J Int AIDS Soc. 2018;21. doi:10.1002/jia2.25095

22. Goodson JL, Finkbeiner T, Davis NL, Lyimo D, Rwebembera A, Swartzendruber AL, et al. Evaluation of Using Routine Infant Immunization Visits to Identify and Follow-Up HIV-Exposed Infants and Their Mothers in Tanzania: JAIDS J Acquir Immune Defic Syndr. 2013;63: e9–e15. doi:10.1097/QAI.0b013e31828a3e3f

23. Kinuthia J, Kiarie JN, Farquhar C, Richardson B, Nduati R, Mbori-Ngacha D, et al. Cofactors for HIV-1 incidence during pregnancy and postpartum period. Curr HIV Res. 2010;8: 510–514.

24. Thomson KA, Hughes J, Baeten JM, John-Stewart G, Celum C, Cohen CR, et al. Increased Risk of HIV Acquisition Among Women Throughout Pregnancy and During the Postpartum Period: A Prospective Per-Coital-Act Analysis Among Women With HIV-Infected Partners. J Infect Dis. 2018;218: 16–25. doi:10.1093/infdis/jiy113

25. Kalk E, Slogrove A, Speert DP, Bettinger JA, Cotton MF, Esser M. HIV sero-conversion during late pregnancy – when to retest. South Afr J HIV Med. 2013;14: 90-92–92.

26. De Schacht C, Hoffman HJ, Mabunda N, Lucas C, Alons CL, Madonela A, et al. High rates of HIV seroconversion in pregnant women and low reported levels of HIV testing among male partners in Southern Mozambique: results from a mixed methods study. PloS One. 2014;9: e115014. doi:10.1371/journal.pone.0115014

27. Drake AL, Wagner A, Richardson B, John-Stewart G. Incident HIV during Pregnancy and Postpartum and Risk of Mother-to-Child HIV Transmission: A Systematic Review and Meta-Analysis. PLOS Med. 2014;11: e1001608. doi:10.1371/journal.pmed.1001608

28. Slogrove AL, Esser MM, Cotton MF, Speert DP, Kollmann TR, Singer J, et al. A Prospective Cohort Study of Common Childhood Infections in South African HIV-exposed Uninfected and HIV-unexposed Infants. Pediatr Infect Dis J. 2017;36: e38–e44. doi:10.1097/INF.0000000000001391

29. Adetokunboh OO, Uthman OA, Wiysonge CS. Non-uptake of childhood vaccination among the children of HIV-infected mothers in sub-Saharan Africa: A multilevel analysis. Hum Vaccines Immunother. 2018;14: 2405–2413. doi:10.1080/21645515.2018.1502524

30. Chamla D, Luo C, Adjorlolo-Johnson G, Vandelaer J, Young M, Costales MO, et al. Integration of HIV infant testing into immunization programmes: a systematic review. Paediatr Int Child Health. 2015;35: 298–304. doi:10.1080/20469047.2015.1109233

31. Tann CJ, Kizza M, Morison L, Mabey D, Muwanga M, Grosskurth H, et al. Use of antenatal services and delivery care in Entebbe, Uganda: a community survey. BMC Pregnancy Childbirth. 2007;7: 23. doi:10.1186/1471-2393-7-23

32. Ng'anjo Phiri S, Kiserud T, Kvåle G, Byskov J, Evjen-Olsen B, Michelo C, et al. Factors associated with health facility childbirth in districts of Kenya, Tanzania and Zambia: a population based survey. BMC Pregnancy Childbirth. 2014;14: 219. doi:10.1186/1471-2393-14-219

33. Hodgson I, Plummer ML, Konopka SN, Colvin CJ, Jonas E, Albertini J, et al. A Systematic Review of Individual and Contextual Factors Affecting ART Initiation, Adherence, and Retention for HIV-Infected Pregnant and Postpartum Women. PLOS ONE. 2014;9: e111421. doi:10.1371/journal.pone.0111421

34. Donahue MC, Dube Q, Dow A, Umar E, Van Rie A. "They Have Already Thrown Away Their Chicken": barriers affecting participation by HIV-infected women in care and treatment programs for their infants in Blantyre, Malawi. AIDS Care. 2012;24: 1233–1239. doi:10.1080/09540121.2012.656570

35. UNAIDS. Start Free Stay Free AIDS Free — 2017 progress report. UNAIDS; 2017 p. 84.

36. WHO, UNICEF. Guideline: updates on HIV and infant feeding. The duration of breastfeeding, and support from health services to improve feeding practices among mothers living with HIV [Internet]. Geneva, Switzerland; 2016. Available: http://www.ncbi.nlm.nih.gov/books/NBK379872/

37. Bandali S. Norms and practices within marriage which shape gender roles, HIV/AIDS risk and risk reduction strategies in Cabo Delgado, Mozambique. AIDS Care. 2011;23: 1171–1176. doi:10.1080/09540121.2011.554529

38. Duff P, Kipp W, Wild TC, Rubaale T, Okech-Ojony J. Barriers to accessing highly active antiretroviral therapy by HIV-positive women attending an antenatal clinic in a regional hospital in western Uganda. J Int AIDS Soc. 2010;13: 37. doi:10.1186/1758-2652-13-37

39. Mepham S, Zondi Z, Mbuyazi A, Mkhwanazi N, Newell ML. Challenges in PMTCT antiretroviral adherence in northern KwaZulu-Natal, South Africa. AIDS Care. 2011;23: 741–747. doi:10.1080/09540121.2010.516341

40. Bwirire LD, Fitzgerald M, Zachariah R, Chikafa V, Massaquoi M, Moens M, et al. Reasons for loss to follow-up among mothers registered in a prevention-of-mother-to-child transmission program in rural Malawi. Trans R Soc Trop Med Hyg. 2008;102: 1195–1200. doi:10.1016/j.trstmh.2008.04.002

41. Bandali S. HIV Risk Assessment and Risk Reduction Strategies in the Context of Prevailing Gender Norms in Rural Areas of Cabo Delgado, Mozambique. J Int Assoc Provid AIDS Care JIAPAC. 2013;12: 50–54. doi:10.1177/1545109712453937

42. Turan JM, Miller S, Bukusi EA, Sande J, Cohen CR. HIV/AIDS and maternity care in Kenya: how fears of stigma and discrimination affect uptake and provision of labor and delivery services. AIDS Care. 2008;20: 938–945. doi:10.1080/09540120701767224

43. DiCarlo AL, Mantell JE, Remien RH, Zerbe A, Morris D, Pitt B, et al. 'Men usually say that HIV testing is for women': gender dynamics and perceptions of HIV testing in Lesotho. Cult Health Sex. 2014;16: 867–882. doi:10.1080/13691058.2014.913812

44. O'Gorman DA, Nyirenda LJ, Theobald SJ. Prevention of mother-to-child transmission of HIV infection: Views and perceptions about swallowing nevirapine in rural Lilongwe, Malawi. BMC Public Health. 2010;10: 354. doi:10.1186/1471-2458-10-354

45. Ujiji OA, Ekström AM, Ilako F, Indalo D, Wamalwa D, Rubenson B. Reasoning and deciding PMTCT-adherence during pregnancy among women living with HIV in Kenya. Cult Health Sex. 2011;13: 829–840. doi:10.1080/13691058.2011.583682

46. Dageid W, Govender K, Gordon SF. Masculinity and HIV disclosure among heterosexual South African men: implications for HIV/AIDS intervention. Cult Health Sex. 2012;14: 925–940. doi:10.1080/13691058.2012.710337

47. Katz DA, Kiarie JN, John-Stewart GC, Richardson BA, John FN, Farquhar C. Male perspectives on incorporating men into antenatal HIV counseling and testing. PloS One. 2009;4: e7602. doi:10.1371/journal.pone.0007602

48. Aluisio A, Richardson BA, Bosire R, John-Stewart G, Mbori-Ngacha D, Farquhar C. Male Antenatal Attendance and HIV Testing Are Associated with Decreased Infant HIV Infection and Increased HIV Free Survival. J Acquir Immune Defic Syndr 1999. 2011;56: 76–82. doi:10.1097/QAI.0b013e3181fdb4c4

CHAPTER 5:

Correlates of missed diagnosis and lost-to-follow up among HIV exposed infants throughout the breastfeeding period in southern Mozambique.

Correlates of missed diagnosis and lost-to-follow up among HIV exposed infants throughout the breastfeeding period in southern Mozambique.

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Abstract

Background: Elimination of vertical transmission requires strong linkages across all the steps of the Prevention of Mother to Child transmission (PMTCT) pathway until follow up of all HIV exposed infants (HEI) is completed and HIV infection is ruled out. However early linkage, early identification of positive infants and completeness of follow up are not happening as desired. Factors associated to HEI lost to follow-up (LTFU) is a knowledge gap. This study aims to analyze HEI follow-up completeness and factors associated to LTFU in a routine care setting where HIV prevalence is 22,9% and vertical transmission rate is estimated at 18%. Findings will assist HIV program in designing differentiated model of care tailored to mothers and their infant's needs.

Methods: Retrospective cohort study using prospectively collected data stored in files of HEI enrolled from June 2017 to June 2018 at Mother and Child Health clinic of Primary Health Centers in Maputo province, Southern Mozambique and followed up till June 2019. Primary outcomes were the proportion of infants with follow up completed and with definitive diagnosis; secondary outcomes were the number of clinical events during follow-up. Kaplan Meier analysis was used to calculate the cumulative probability of LTFU; Cox Regression analysis was used to calculate the Hazard Ratio (HR) and Adjusted HR with 95% CI of LTFU of enrolled infants and of clinical events towards explanatory variables: health facility, place of delivery, type of delivery, mother on antiretroviral treatment, infant's gender, age at entry, nevirapine prophylaxis, feeding practice, cotrimoxazole prophylaxis, malnutrition at entry, clinical event.

Results: A total of 1413 infants were enrolled (49% males) at a median age of 32 days (IQR 31-41); median follow-up time 12 months (IQR 8.2-14.2); 1129 (80%) infants completed follow up and had a definitive diagnosis, 57 (4%) infants were HIV positive, 225 (16%) were LTFU, 8 died (0.6%), 51 (3.6%) were transferred out before definitive diagnosis. In the multivariate analysis factors associated with LTFU were: age at entry > 2 months (AHR 1.62 CI 95% 1.11-2.36), non-exclusive breastfeeding (AHR 1.48 CI 95% 1.03-2.14), clinical event during follow up (AHR 0.50 CI 95% 0.33-0.77), incomplete cotrimoxazole prophylaxis (AHR 3.31 CI 95% 1.51-7.22). Factors associated with clinical events were: malnutrition at entry (AHR 10.06 CI 95% 5.92-17.09), non-exclusive breastfeeding (HR 1.98 CI 95% 1.34-2.93), no NVP prophylaxis (AHR 1.67 CI 95% 1.18-2.36), incomplete cotrimoxazole prophylaxis (AHR 2.62 CI 95% 1.10-6.22),

Conclusion: The study found high rate of HEI LTFU before HIV definitive diagnosis and late identification of HIV infected infants. These two major gaps jeopardize the achievement of elimination of pediatric HIV and the success of the pediatric HIV program. Intensification of

successful interventions already in place such as mentor mothers in the community and the provider-initiated counselling and testing approach at all pediatric entry points at HF, must be ensured. A standardized tool at site level, to track mom-baby pair along the continuum of care, can assist in finding infants who drop out of the path, in identifying the infected ones and monitor the mother's transition from MCH to HIV clinic at the end of the cascade. Innovative and differentiated interventions appropriate to mother and infants as well as culturally sensitive, must aim at ensuring completeness and quality of follow up.

Keywords: PMTCT, HIV exposed infants, Lost to follow up, Early Infant Diagnosis

Introduction

Elimination of vertical transmission requires strong linkages between all the steps of the Prevention of Mother to Child transmission (PMTCT) pathway until follow-up of all HIV exposed infants (HEI) is completed and HIV infection is ruled out. HEI have been recognized as a vulnerable group which deserves full attention till follow up is concluded. In fact, a growing body of evidence highlighted increased HEI morbidity and mortality compared to HIV unexposed uninfected infant (1–5) and other possible long-term health needs, still not well defined, as potential consequence of exposure to HIV and antiretroviral drugs (ARV) during pregnancy and breastfeeding (6).

Since the beginning of the HIV epidemic response, in resource limited countries, HIV programs moved from a vertical HEI care to an integrated approach into maternal and child health (MCH) services at primary level as a way to reach all patients in need (7). Guidelines have been developed and disseminated for HEI best care (8–10).

In Mozambique as well, to improve retention throughout antenatal care (ANC), delivery and post-natal care (PNC), HEI and mother care is integrated at MCH clinic in a consultation where mom-baby pair is attended the same day. However, early linkage, early identification of positive infants and completeness of follow up are not happening as desired (11–13).

In the focus countries, only 52% of HEI accessed early infant diagnosis (EID) before 6 weeks of age in 2018 (14) and pooled estimates showed that lost to follow-up (LTFU) after the first HIV test can reach up to 45.5% before definitive diagnosis (11).

In Mozambique, HIV prevalence in the adult population (15-49 years) is 13.2% (15) and approximately 109.000 women were pregnant and living with HIV in 2018 (16). Despite ART coverage above 95% among pregnant women at ANC (16,17) and the decrease in pediatric HIV infection since the adoption in 2013 of lifelong antiretroviral treatment to all pregnant and breastfeeding women living with HIV (Option B+), important gaps remain along the prevention of PMTCT cascade. Ongoing challenges which prevent all women living with HIV and their HEI to receive proper care have been reported and need to be addressed. Seroconversion of women during 18 months post-partum period is 4.92 per 100 women-years (18); access to EID within 2 months of life is 66% of expected infants (17) and vertical transmission up to 24 months of breastfeeding, is estimated at 18%, varying largely among provinces (16).

Completeness of HEI follow up and factors associated to LTFU are a knowledge gap. Understanding correlates of HEI LTFU to design better health systems and community response is fundamental to prevent drop-outs of infants from care and to reach those who never accessed care (19). In fact,

many studies have described lost to follow-up in pregnant women (20), while fewer analyzed completeness of HEI follow up after the first negative virologic test result till the end of the period at risk of vertical transmission (11).

In Mozambique there are no data on long term HEI follow up. This study aims to analyze completeness of follow-up of HEI enrolled in routine care and factors associated to LTFU in a setting where estimated vertical transmission rate is 18% (16). Findings will inform the HIV program and contribute to design differentiated model of care tailored to mothers and their infant's needs.

Methods

This is a retrospective cohort study of HIV exposed infants enrolled at Child at Risk Consultation (CCR) at MCH clinic of four primary health centers (PHC) in Maputo province in the districts of Boane, Matola and Marracuene, which have been deliberately deidentified. The enrollment period was from 1st of June 2017 to 30th of June 2018 and follow up till June 2019. Health facilities were purposely chosen among PHC with high volume of patients at MCH and CCR clinic (average of 30 patients/1 or 2 MCH nurse/day) and equipped with point-of-care (POC) technology for HIV nucleic acid testing for EID, which provides same day test result.

The health care package offered to HIV exposed infants at CCR included: HIV virologic test at the first encounter and then at specific time points during follow-up according to the national EID algorithm at 9 months and 2 months after weaning or at any time in case of symptoms suggestive of HIV; cotrimoxazole prophylaxis from the 4th week of age, continuation of NVP prophylaxis till 6 weeks of age, assessment of anthropometric parameters such as weight, height, head circumference, clinical evaluation and symptoms management using the Integrated Management of Childhood Illnesses (IMCI) package of care, monitoring of immunization schedule, vitamins supplementation and deworming (21). HEI follow up starts at 4 weeks of age and end when HIV definitive diagnosis is established. According to the definitive confirmatory HIV test result, infant is linked to ART care at any age in case of positive virologic test or in case of positive HIV rapid test after 18 months of age; infants with HIV negative diagnosis are referred to the Healthy Child Clinic (CCS). In case the first virologic test is negative, infant continues monthly follow up at CCR till 18 months or 2 months after weaning when a rapid test is done.

Data collection and analysis

Data were collected by retrospective review of patients' files, prospectively filled by the nurse at each monthly visit during follow-up. Collected variables were: health facility, place of delivery, type of delivery, mother on antiretroviral treatment at entry, date at entry, gender, birth date, nevirapine prophylaxis at entry, feeding practice at entry, cotrimoxazole at all visits, nutritional classification at entry, HIV tests performed, type of test (virologic and rapid test), clinical events during follow up and treatment received, referral to another service, transfer to another health facility.

Primary outcomes of our analysis were: the proportion of HEI with follow up completed and the proportion of HEI with definitive diagnosis. Infant with completed follow up is an infant who has being transferred to ART clinic, or to Child Health Clinic, or died or has been transferred to another health facility. Infant LTFU is an infant without a definitive positive or negative diagnosis reported in the file. Definitive diagnosis is defined as HIV positive or HIV negative. HIV positive diagnosis is defined as two positive virologic test results at any age, or a positive HIV rapid test after 18 months of age. HIV negative diagnosis is defined as a negative HIV rapid test performed after 2 months of weaning at age > 9 months. Indeterminate HIV diagnosis is defined as an indeterminate HIV rapid test result (22).

Secondary outcomes were the number of clinical events during follow up recorded by the nurse as fever, cough, diarrhea, skin problems and others, according to the IMCI and classified in our database as Respiratory infection, Gastrointestinal disease, Fever of Unknown Origin, Skin problems and Malnutrition.

Descriptive analyses were used to summarize the baseline characteristics of the HEI at enrolment and during follow up period and mothers' characteristics at enrollment. Kaplan Meier analysis was used to calculate the cumulative probability of LTFU during the studied period. Cox Regression analysis was used to calculate the Hazard Ratio (HR) and Adjusted HR with 95% CI of LTFU of enrolled infants and of clinical events using the following explanatory variables. Explanatory variables: health facility, place of delivery, type of delivery, mother on antiretroviral treatment at entry, gender, age at entry, nevirapine prophylaxis at entry, feeding practice at entry, cotrimoxazole prophylaxis adherence, malnutrition at entry, clinical events during follow up.

Ethical considerations

Data for this study are deidentified and collected from primary data collected in patients' record, as part of the routine national health information system. The system was created by the MOH and

granted access for patients follow up and monitoring and evaluation purpose, as it is the current study. The current study is also part of an amendment to a study approved by the National Bioethics Committee and MOH (reference IRB00002657 83/CNBS/2017).

Results

Characteristics of infants at first CCR visit are described in Table 1. A total of 1413 infants were enrolled at the selected HF, 687 (49%) were male, median age at enrolment was 32 days (IQR 31-41). At entry median weight was 4250gr (IQR 3800-4800), 98.5% had a weight for height z score ≥-1SD, 1199 (85%) were exclusively breastfeeding. A total of 1348 (95%) mothers delivered at HF, 10% had cesarean section, median birth weight was 3050gr (IQR 2800-3400). A total of 1159 (82%) infants were on NVP prophylaxis at entry, 1398 (99%) mothers were on ART at the time of first visit at CCR and 98% of infants received cotrimoxazole prophylaxis during follow up.

A total of 57 infants were diagnosed HIV positive: 53 (3.8%) at entry, 4 during follow up, after the initial negative virologic test done at 1 month of age. Twenty-five (44%) of HIV positive infants had HIV diagnosis with age less than 2 months; 32 (56%) were diagnosed HIV positive at age ≥ 2 months. A total of 274 (20%) infants had an indeterminate rapid test result at 9 months which was not followed by a virologic PCR test on the same day, 218 of them received a rapid test three months later, 3 of them had an HIV positive diagnosis and 56 did not repeat any other HIV test.

The median follow-up time was 12 months (IQR 8.2-14.2), median age at last visit was 13 months (IQR 11-16). A total of 1129 (80%) infants completed follow up and had a definitive diagnosis, 8 died (0.6%), 51 (3.6%) were transferred to another health facility or province before definitive diagnosis, 225 (16%) were LTFU (Fig 1).

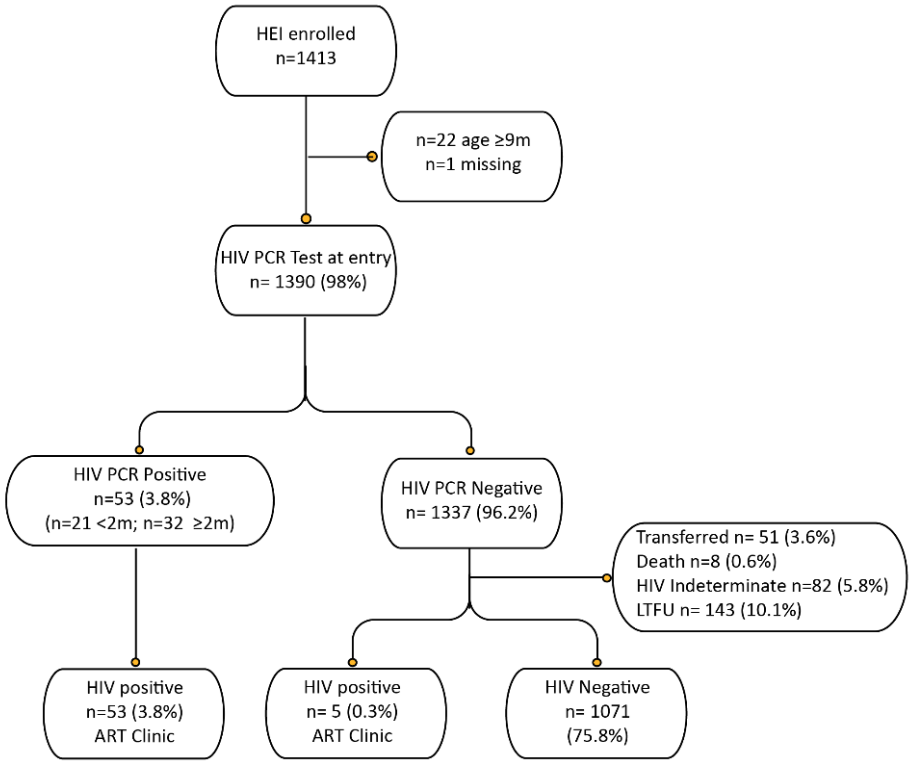

Fig.1 HEI follow up cascade

Among infants who were transferred 71% were transferred within the first three months after enrolment and 96% within the first 6 months. Among infants LTFU, 46% left within the first three months after enrolment, 65% within the first 6 months. The cumulative probability of LTFU at 3, 6 and 9 months was 8%, 11%, 13.5% respectively (Fig. 2).

In the bivariate analysis factors associated with LTFU were (Table 2): age at entry > 2 months (HR 1.77 CI 95% 1.27-2.45), non-exclusive breastfeeding (HR 1.75 CI 95% 1.26-2.45), incomplete cotrimoxazole prophylaxis (HR 3.51 CI 95% 1.65-7.46) and clinical event during follow-up (HR 0.53 CI 95% 0.36-0.79). In the multivariate analysis (Table 2), the same factors persisted associated with lost to follow up: age at entry > 2 months (AHR 1.62 CI 95% 1.11-2.36), non-exclusive breastfeeding (AHR 1.48 CI 95% 1.03-2.14), incomplete cotrimoxazole prophylaxis (AHR 3.31 CI 95% 1.51-7.22) and clinical event during follow up (AHR 0.50 CI 95% 0.33-0.77).

A total of 282 clinical events were described during follow up: 32% respiratory tract infections, 30% gastrointestinal disease, 7% fever of unknown origin, 3% skin problems. The incidence rate was of 29events/person/year. A total of 7 infants were referred to a clinician or admitted during follow up.

In the bivariate analysis, factors associated with clinical events were (Table 3): health facility 3 (HR 0.26 CI 95% 0.19-0.35), health facility 4 (HR 0.34 CI 95% 0.23-0.51), age at entry >2m (HR 1.88 CI 95% 1.33-2.64), malnutrition at entry (HR 7.68 CI 95% 4.60-12.82), mother not on ART (HR 6.66 CI 95% 2.95-15.02), non-exclusive breastfeeding (HR 1.67 CI 95% 1.17-2.38), no NVP prophylaxis (HR 1.71 CI 95% 1.26-2.30), incomplete cotrimoxazole prophylaxis (HR 6.00 CI 95% 2.82-12.77).
In the multivariate analysis (Tab.3), factors associated to clinical events were: Health facility 3 (AHR 0.22 CI 95% 0.16-0.30), Health facility 4 (AHR 0.35 CI 95% 0.23-0.52), malnutrition at entry (AHR 10.06 CI 95% 5.92-17.09), no exclusive breastfeeding (HR 1.98 CI 95% 1.34-2.93), no NVP prophylaxis (AHR 1.67 CI 95% 1.18-2.36), incomplete cotrimoxazole prophylaxis (AHR 2.62 CI 95% 1.10-6.22).
The cumulative probability of clinical event at 3, 6, 9 and 12 months was 1.6%, 2.5%, 6% and 19% respectively (Fig. 3).

Discussion

Our analysis showed that a high proportion of infants did not complete follow up (16%) and did not have a definitive HIV diagnosis. This is a new evidence for the HIV program in Mozambique and highlights an important gap in the continuum of PMTCT cascade. In our cohort, almost half of LTFU infants left within the first 3 months after enrolment, at a median age of 4 months. Another study in Kenya reported 43% of drop-out within two months of enrollment (23). This very young age has the highest risk of morbidity and mortality (24) and infants continue to be at risk of HIV transmission during breastfeeding, especially if the mother stopped treatment (25,26). Knowing the time mother-infant pair is more likely to drop out of care is important to tailor effective interventions and direct resources to cover that specific timeframe. Our findings call for intensified counselling and retention activities in the first quarter after delivery.
Efforts devoted to strengthen HEI linkage to post-natal care for EID in the first 2 months after delivery, showed excellent results for neighboring countries such as South Africa and Eswatini who linked 80% and 78% infants respectively while many other countries are still below 50% (27). In Mozambique, in the past eight years, EID access improved from 36% in 2010 to 66% in 2018 (16). A meta-analysis of 11 Sub-Saharan African countries including Mozambique reported a pooled estimate of 34% LTFU HEI within 3 months from delivery (11). Nevertheless, studies describing the completeness of follow up, after the first negative HIV test, throughout breastfeeding up to 12-18 months, are limited: the same review reported 45.5% LTFU overall after HIV testing (11). Two of the very first studies in South Africa reported 50% to 85% LTFU at 12 months (28,29), data from Uganda

described 12m LTFU of 50% (30), in Kenya 18m LTFU was 66% and 20% in two different studies (23,31), in Nigeria it was 21% (32). All the above studies reported outcomes of programs in the pre-Option B+ era and in most contexts where HIV care to mom-baby pair was not provided at the MCH clinic, knowing that these two factors are likely to negatively affect retention.

Integration of PMTCT interventions and HIV care of infected breastfeeding women into MCH care is recommended by WHO (9) as an approach to improve mom-baby pair retention along the PMTCT pathway, but evidence produced so far is not strong. A review of studies on different interventions to reduce post-partum LTFU showed weak evidence of effectiveness of integrated ANC and ART care for retention of pregnant women enrolled in PMTC programs (33–36). This suggests that health services integration alone, although proved critical in Mozambique to increase testing and treatment coverage among pregnant and breastfeeding women (16), is not enough to fill the post-partum linkage gap till completeness of infant's care. Other factors affecting retention into care, described more than ten years ago but still valid, are related to the psycho-social and economic context and continue to affect PMTCT continuum of care (37–39). Therefore, synergism of health and community-based interventions is key to complement successes obtained with re-organization of health system services and differentiated care. Recent published studies on diverse intervention addressing PMTCT retention into care, showed improved infants' retention (up to 9-12m) using text messaging to mother along the post-natal period (40,41), improved women long-term retention and stigma reduction with male involvement in PMTCT care and counselling group sessions (42–44). Mentor mothers is another successful intervention resulted in higher retention rate at 12m after delivery compared to 'standard peer' support (45,46), as well facility and community-based peer support resulted in increased retention rate at 24 months compared to no peer interventions (47). Only one study on the efficacy of mother support groups, showed no difference in HEI retention at 12m (48).

We included in the group of LTFU infants, those with final indeterminate HIV diagnosis. In fact, 5% of HEI remained without a definitive diagnosis while a large proportion did not receive proper virologic test at 9 months. This finding highlights some challenges among MCH nurses in applying the EID algorithm correctly at all steps of the diagnosis cascade. Supportive mentorship of nurses and simplification of diagnosis guidelines may be needed to minimize delays in finding HIV infected infants and complete definitive diagnosis as suggested by WHO (22).

In our cohort factors significantly associated with higher risk of LTFU were age older than 2 months at entry, non-exclusive breastfeeding, poor cotrimoxazole adherence during follow up. Late age at

enrolment suggests that mothers may not had access to ANC and missed counselling sessions about prompt PNC for HEI. However, our data showed that almost all mothers were on ART at the time of enrolment suggesting they had previous contact with health staff but eventually were unable to link early. Other unknown underlying socio-economic factors may have affected 'full' retention but our study did not capture socio-economic determinants as analyzed data were those routinely collected in infant's file. These factors are indeed important to understand if early linkage and completeness of follow-up are affected by the same determinants affecting ANC phase, as plausible (38,49).

Exclusive breastfeeding during the first 6 months of life is the norm in Mozambique and women are counselled from the first ANC. Finding that mothers who are not exclusively breastfeeding are those who are at higher risk of LTFU may indicate that they did not access ANC and/or not received proper feeding counselling. Another study showed that early weaning is associated with high risk of LTFU (30). Evidence is clear about the protective effect of exclusive breastfeeding on mortality (50) and those who left the program may have presented a severe clinical event and have not be able to seek care on time.

Poor adherence to cotrimoxazole prophylaxis suggests poor adherence to care in general (51). Special attention by MCH nurses, counselors and mentor mothers to identify those factors and intensify support to mothers at risk of LTFU should be considered from the first visit.

Similar to another study in Uganda (30), presenting a clinical event during follow up was protective for LTFU. It reflects the habit mothers have to seek care when there is a health problem. Those mothers may have received a more intense counselling which contributed to maintain them into care till the end of infant's follow up period. Differently from our cohort where moderate malnutrition at entry was not related to LTFU, another author described severe malnutrition a risk factor for LTFU (31). Similarly, a more intense counselling and nurse's ability to identify risk factors for LTFU may have played a role in keeping mothers of malnourished infants in care. It is important to remind that several predictors of LTFU among HEI correlates also with HIV vertical transmission (52), highlighting once again how crucial is keeping HEI in care especially those presenting risk factors.

We found that 4% of enrolled infants were transferred to another health facility before definitive diagnosis, the majority within the first three visits. Although our data are limited in describing detailed reasons for transfer, this is a frequent situation in Mozambique. It is in fact part of the culture for pregnant women to spend the last month of pregnancy and first months after delivery at the mother's or relatives house (53). In these cases, while the first baby consultation is done at

the health facility close to the mother's house, follow up will not be completed there. Travelling with limited stock of ARVs for the period spent far from the health facility of origin, possible lack of disclosure to mother or other household members of the 'host' house, may jeopardize optimal retention not only for infants but also among mothers, including adherence to ART.

In Mozambique, as well as other African countries, this is the momentum for HIV programs to design and implement differentiated service delivery (DSD) appropriate to their context (54). Our study reports data which programs must consider when designing differentiated models of care and acknowledge the cultural element of women travelling close to delivery date. In this perspective, it is important to think about a DSD for pregnant and breastfeeding women and their exposed infants and help them stay adherent to ART. Data of transferred patients also add an important information to account for when analyzing coverage results of HEI definitive diagnosis and retention for pregnant and breastfeeding women into PMTCT programs.

Among infants who completed follow up, vertical transmission rate up to the end of breastfeeding was 4%, which is similar with data reported for HF using POC technology in Maputo province, 5% (16) and with another study done in Manhiça district, in the same province, which found an HIV prevalence among HIV Exposed children < 4 years of 5% (55). The vertical transmission rate we found is lower than the one of 18% estimated by Spectrum, which assumed breastfeeding till 24 months of age (16). In our sample the median follow-up time was 12 months and by that time, majority of infants had stopped breastfeeding. However, considering the non-negligible proportion of infants who did not complete follow up, this VT rate cannot be considered definitive.

Despite the low transmission rate, it is worrisome that less than half of infected infants were diagnosed before 2 months of age, the recommended age to start ART and prevent the highest morbidity and mortality in this group (24). We are missing early identification of infected infants, mainly because of late PNC enrolment and poor active case findings at services with high HIV prevalence such as pediatric ward and nutrition clinic (56). In Zambezia, central Mozambique, enhanced referral from maternity to PNC showed to increase linkage to EID by three times (57). The new recommendation of extensive prophylaxis for all HEI till 12 weeks of age the HIV program recently introduced (58), will not benefit HEI who are presenting at CCR after 2 months of age. So, effort to minimize LTFU from delivery to PNC must be redoubled.

In Zambia and Malawi, provider-initiated counselling and testing (PICT) at under-5 clinic and pediatric ward proved to increase identification of HIV positive infants whose mothers did not link to post-partum care, (59–61). In Mozambique despite the PICT approach having been launched

many years ago (62), uptake by health staff is poor: in a study of 11 pediatric wards, only 46% of children eligible for testing and a median age of 23 months, received an HIV test (63).

Clinical events were frequent, 19% of our infants presented at least one clinical event: majority were respiratory and gastrointestinal symptoms, minority presented mild malnutrition, very few infants were referred to a clinician. Malnutrition at entry, non-exclusive breastfeeding, and poor cotrimoxazole adherence were factors significantly associated to a higher risk of clinical event. As already reported in the literature cotrimoxazole and breastfeeding are factors protecting infants from increased morbidity (5,10,50).

Studies in the pre-ART era described increased mortality and morbidity in the first two years of life of HEI compared to HIV unexposed uninfected Infants (HUI) (5,64–67) while in the post-ART era results were inconsistent, some showing no difference while others, including one from Mozambique, showing increased risk (68). Causes of reported morbidity were lower respiratory tract infection, skin infection and oral thrush, diarrheal diseases (1,69,70), impaired growth, and other common causes of childhood morbidity (1). In South Africa, Slogrove et al, found that in the first 6 months of life hospitalization and infectious causes of hospitalization were similar among HEI and UH, but that severe infections were more frequent among HEI (71). In our cohort we lost the majority of infants within 3 months after enrolment, at approximately at 4 months of age, when increased morbidity among HEI was reported compared to HUI (1).

In our cohort we did not have maternal information such as viral load or CD4 count which correlate with increased infant morbidity and mortality (64,72,73), they are not routinely included in the child file, and this is a limitation of the study. Another limitation, due to the type of study, was the impossibility to collect data on mother's socio-economic factors.

Data are from health facilities of Maputo province; hence results cannot be generalized to the entire country. Provinces in Mozambique have different contexts and are at different stages of HIV program implementation, however results call for a need to study completeness of PMTCT cascade till definitive HEI diagnosis also in other provinces, where transmission rate is higher, to possibly identify specific characteristics and develop responses tailored to each context. However, we believe that findings, presumably shared among the HEI population and their mothers, may be applied to other provinces as well. A strength of this study is that it is conducted in the 'real world' setting of primary care facilities in a very busy MCH clinic and results are more likely to reflect real outcomes of service delivered to HEI.

Conclusions

The study found high rate of HEI LTFU before HIV definitive diagnosis and late identification of HIV infected infants. These two major gaps jeopardize the achievement of elimination of pediatric HIV and the success of the pediatric HIV program. There is still much to do to address clinical and structural factors affecting long-term adherence of mothers and their infants and promote early access to post-natal care to earlier diagnose HIV infected infants. Intensification of successful interventions already in place such as mentor mothers in the community and the PICT approach at all pediatric entry points at HF, must be ensured. Innovative and differentiated interventions appropriate to mother and infants as well as culturally sensitive, must aim at ensuring completeness and quality of follow up.

A standardized and easy tool at site level, to track mom-baby pair along the continuum of care, can assist in finding infants who drop out of the path, in identifying the infected ones and monitor the transition of the mother from MCH to HIV clinic at the end of the cascade. The monitoring tool, would also be an opportunity for establishing a national monitoring of HIV exposed uninfected infants, followed at under-5 clinic, to study long-term outcomes and understand if specific interventions are necessary in this population.

Acknowledgments

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Tables and Figures

Table 1. Characteristics of HIV Exposed infants and their mothers enrolled at High Risk Consultation (CCR)

		N	Percent	95% Confidence Interval	
Health Facility	HF 1	217	15.4	13.5	17.2
	HF 2	594	42.0	39.5	44.6
	HF 3	290	20.5	18.4	22.6
	HF 4	312	22.1	19.9	24.2
	Total	1413	100.0		
Gender	Female	721	51.2	48.4	53.6
	Male	687	48.8	46.0	51.2
	Missing	5			
	Total	1413	100.0		
Institutional Delivery	No	48	3.4	2.5	4.3
	Yes	1348	96.6	94.3	96.5
	Missing	17			
	Total	1413	100.0		
C-Section	No	1253	89.8	87.0	90.3
	Yes	143	10.2	8.5	11.7
	Missing	17			
	Total	1413	100.0		
Mother on ART	No	15	1.1	0.5	1.6
	Yes	1398	98.9	98.4	99.5
	Total	1413	100.0		
On NVP at entry	No	254	18.0	16.0	20.0
	Yes	1159	82.0	80.0	84.0
	Total	1413	100.0		
CTX adherence	No	20	1.4	0.8	2.0
	Yes	1387	98.6	97.5	98.9
	Missing	6			
	Total	1413	100.0		
Feeding practice at entry	Formula	62	4.4	3.3	5.5
	EBF	1199	85.0	83.0	86.7
	Mix	97	6.9	5.5	8.2
	Compl Feed	53	3.8	2.8	4.7
	Missing	2			
	Total	1413	100.0		
Nutritional status at entry (WHZ-score)	≥-1 SD	1392	98.8	97.9	99.1
	≥-2 <-1 SD	6	.4	0.1	0.8
	≥-3 <-2 SD	9	.6	0.2	1.1
	<-3 SD	2	.1	0.0	0.3
	Missing	4			
	Total	1413	100.0		
First clinical event during follow up	No	1146	81.2	79.1	83.1
	Yes	266	18.8	16.8	20.9

	Missing	1			
	Total	1413	100.0		
Type Clinical Event	Respiratory	85	32.0	4.8	7.3
	GI	79	29.7	4.4	6.8
	Fever	20	7.5	0.8	2.0
	Skin Problem	9	3.4	0.2	1.1
	Tb exposure	13	4.9	0.4	1.4
	Malnutrition	60	22.6	3.2	5.3
	Total	266	100.0	16.8	20.9
	No clinical event	1147			
	Total	1413	100.0		
Virologic test result at entry	Neg	1337	96.2	93.4	95.8
	Pos	53	3.8	2.8	4.7
	Not applicable	22		0.9	2.2
	Missing	1			
	Total	1413	100.0		
Any Positive Virologic test	No	1356	96.0	94.9	97.0
	Yes	57	4.0	3.0	5.1
	Total	1413	100.0		
Indeterminate HIV test with no virologic test done	No	1139	80.6	78.5	82.7
	Yes	274	19.4	17.3	21.5
	Total	1413	100.0		
Outcome of follow up	LTFU	143	10.1	8.5	11.7
	Death	8	.6	0.2	1.0
	Transferred	51	3.6	2.6	4.6
	CCS	1071	75.8	73.6	78.0
	TARV	58	4.1	3.1	5.1
	No Definitive Diagnosis	82	5.8	4.6	7.0
	Total	1413	100.0		

Table 2. Factors related to Lost to Follow up - Bivariate and multivariate analysis

	Bivariate					Multivariate				
	Wald Test	p value	HR	95% CI		Wald Test	p value	AHR	95% CI	
				Lower	Upper				Lower	Upper
HF 1	5.34	.149				5.74	.125			
HF 2	1.97	.161	1.36	.88	2.10	1.24	.265	1.30	.82	2.05
HF 3	1.48	.223	1.25	.87	1.79	0.40	.529	1.13	.77	1.65
HF 4	0.35	.557	0.87	.56	1.37	1.28	.258	0.76	.47	1.22
No Institutional delivery*	0.31	.577	1.21	.62	2.36	-	-	-	-	-
C section*	0.07	.790	1.06	.69	1.63	-	-	-	-	-
Male*	0.01	.905	0.98	.76	1.28	-	-	-	-	-
Birth Weight*	0.03	.861	0.98	.73	1.29	-	-	-	-	-
Mother Not on ART*	0.36	.549	1.53	.38	6.17	-	-	-	-	-
no NVP	1.48	.224	1.23	.88	1.73	.41	.524	0.88	.59	1.31
Age > 2 mo at entry	11.43	.001	1.77	1.27	2.45	6.17	.013	1.62	1.11	2.36
no EBF	10.87	.001	1.75	1.26	2.45	4.38	.036	1.48	1.03	2.14
CTX incomplete	10.61	.001	3.51	1.65	7.46	8.99	.003	3.31	1.51	7.22
WHZ-score <-1SD at entry*	0.00	.947	1.05	.26	4.22	-	-	-	-	-
Clinical Event yes	9.49	.002	0.53	.36	0.79	10.27	.001	.50	.33	.77

*Variable not analyzed in the Multivariate analysis because its association was not significative in the bivariate.

Table 3 Factors associated with clinical event. Bivariate and Multivariate analysis

	Bivariate					Multivariate				
	Wald	p value	HR	95% CI		Wald	p value	AHR	95% CI	
				Lower	Upper				Lower	Upper
HF 1	102.36	.000				114.16	.000			
HF 2	0.01	.915	1.02	.73	1.42	0.02	.883	1.03	.72	1.46
HF 3	78.14	.000	0.26	.19	0.35	91.02	.000	0.22	.16	0.30
HF 4	27.27	.000	0.34	.23	0.51	25.57	.000	0.35	.23	0.52
No Institutional Delivery*	0.31	.578	1.18	.66	2.11	-	-	-	-	-
C-section*	0.00	.955	0.99	.64	1.52	-	-	-	-	-
Male*	1.51	.219	0.86	.67	1.09	-	-	-	-	-
Birth Weight*	0.01	.913	1.01	.78	1.32	-	-	-	-	-
Mother Not on ART	20.85	.000	6.66	2.95	15.02	2.67	.102	2.21	0.85	5.73
No NVP	12.21	.000	1.71	1.26	2.30	8.27	.004	1.67	1.18	2.36
Age >2mo at entry	12.95	.000	1.88	1.33	2.64	0.07	.786	1.06	0.70	1.60
No EBF	8.07	.004	1.67	1.17	2.38	11.85	.001	1.98	1.34	2.93
CTX incomplete	21.57	.000	6.00	2.82	12.77	4.77	.029	2.62	1.10	6.22
WHZ-score <-1SD at entry*	60.61	.000	7.68	4.60	12.82	72.98	.000	10.06	5.92	17.09

*Variable not analyzed in the Multivariate analysis because its association was not significative in the bivariate.

Fig.2 Cumulative probability of lost to follow-up of HEI

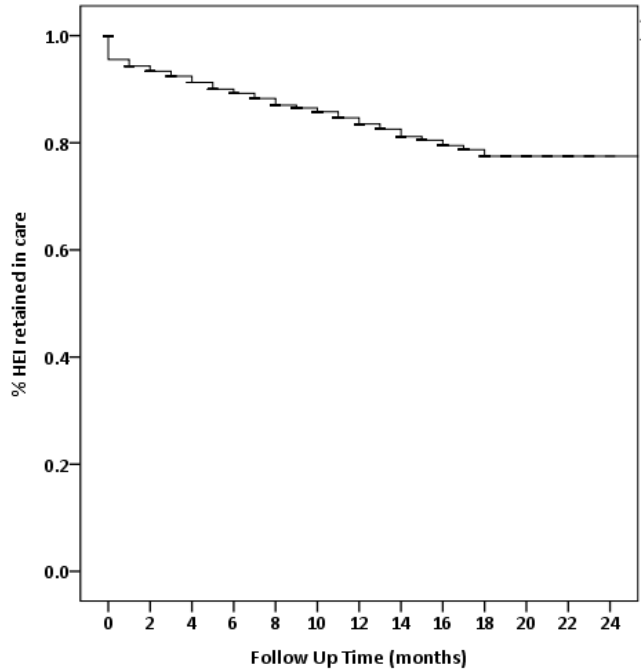
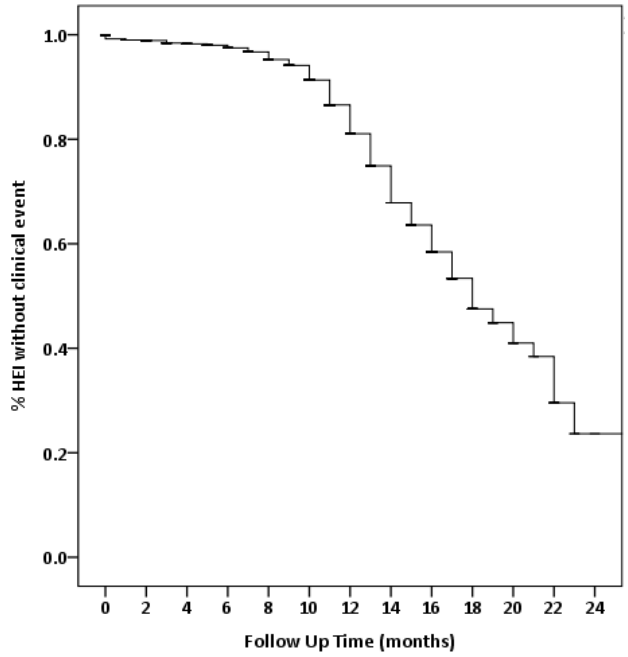


Fig.3 Cumulative probability of clinical event during follow-up



References

1. Slogrove AL, Goetghebuer T, Cotton MF, Singer J, Bettinger JA. Pattern of Infectious Morbidity in HIV-Exposed Uninfected Infants and Children. Front Immunol [Internet]. 2016 [cited 2019 Jul 31];7. Available from: https://www.frontiersin.org/articles/10.3389/fimmu.2016.00164/full

2. Koyanagi A, Humphrey JH, Ntozini R, Nathoo K, Moulton LH, Iliff P, et al. Morbidity Among Human Immunodeficiency Virus-exposed But Uninfected, Human Immunodeficiency Virus-infected, and Human Immunodeficiency Virus-unexposed Infants in Zimbabwe Before Availability of Highly Active Antiretroviral Therapy: Pediatr Infect Dis J. 2011 Jan;30(1):45–51.

3. Locks LM, Manji KP, Kupka R, Liu E, Kisenge R, McDonald CM, et al. High Burden of Morbidity and Mortality but Not Growth Failure in Infants Exposed to but Uninfected with Human Immunodeficiency Virus in Tanzania. J Pediatr. 2017 Jan 1;180:191-199.e2.

4. Slogrove A, Reikie B, Naidoo S, De Beer C, Ho K, Cotton M, et al. HIV-Exposed Uninfected Infants are at Increased Risk for Severe Infections in the First Year of Life. J Trop Pediatr. 2012 Dec 1;58(6):505–8.

5. Roux SM le, Abrams EJ, Nguyen K, Myer L. Clinical outcomes of HIV-exposed, HIV-uninfected children in sub-Saharan Africa. Trop Med Int Health. 2016;21(7):829–45.

6. Shapiro RL, Lockman S. Mortality among HIV-Exposed Infants: The First and Final Frontier. Clin Infect Dis. 2010 Feb 1;50(3):445–7.

7. Abrams EJ, Simonds RJ, Modi S, Rivadeneira E, Vaz P, Kankasa C, et al. PEPFAR scale-up of pediatric HIV services: innovations, achievements, and challenges. J Acquir Immune Defic Syndr 1999. 2012 Aug 15;60 Suppl 3:S105-112.

8. Mofenson LM, Brady MT, Danner SP, Dominguez KL, Hazra R, Handelsman E, et al. Guidelines for the Prevention and Treatment of Opportunistic Infections Among HIV-Exposed and HIV-Infected Children: Recommendations from CDC, the National Institutes of Health, the HIV Medicine Association of the Infectious Diseases Society of America, the Pediatric Infectious Diseases Society, and the American Academy of Pediatrics. MMWR Recomm Rep Morb Mortal Wkly Rep Recomm Rep Cent Dis Control. 2009 Sep 4;58(RR-11):1.

9. WHO. PMTCT strategic vision 2010–2015 : preventing mother-to-child transmission of HIV to reach the UNGASS and Millennium Development Goals. [Internet]. Geneva, Switzerland; 2010 [cited 2019 Aug 14]. Available from: https://www.who.int/hiv/pub/mtct/strategic_vision/en/

10. Zachariah R, Harries AD, Luo C, Bachman G, Graham SM. Scaling-up co-trimoxazole prophylaxis in HIV-exposed and HIV-infected children in high HIV-prevalence countries. Lancet Infect Dis. 2007 Oct 1;7(10):686–93.

11. Sibanda EL, Weller IVD, Hakim JG, Cowan FM. The magnitude of loss to follow-up of HIV-exposed infants along the prevention of mother-to-child HIV transmission continuum of care: a systematic review and meta-analysis. AIDS Lond Engl. 2013 Nov 13;27(17):2787–97.

12. Phelps BR, Ahmed S, Amzel A, Diallo MO, Jacobs T, Kellerman SE, et al. Linkage, initiation and retention of children in the antiretroviral therapy cascade: an overview. AIDS Lond Engl. 2013 Nov;27(0 2):S207–13.

13. Woldesenbet SA, Jackson D, Goga AE, Crowley S, Doherty T, Mogashoa MM, et al. Missed Opportunities for Early Infant HIV Diagnosis: Results of A National Study in South Africa. J Acquir Immune Defic Syndr 1999. 2015 Mar 1;68(3):e26–32.

14. UNAIDS. Start Free Stay Free AIDS Free - 2019 report [Internet]. 2019 [cited 2019 Sep 17]. Available from: https://www.unaids.org/en/resources/documents/2019/20190722_UNAIDS_SFSFAF_2019

15. MISAU, INE, ICF. Inquérito de Indicadores de Imunização, Malária e HIV/SIDA em Moçambique [Immunization, Malaria and HIV/AIDS Survey in Mozambique] (IMASIDA) 2015 [Internet]. 2018 Feb [cited 2019 Jul 2]. Available from: https://dhsprogram.com/publications/publication-ais12-ais-final-reports.cfm

16. MISAU. Relatório Anual das Actividades Relacionadas ao HIV/SIDA [Annual Report of HIV/AIDS activities] - 2018. 2019 p. 100.

17. UNAIDS. UNAIDS data 2019 [Internet]. 2019 [cited 2019 Jul 23]. Available from: https://www.unaids.org/en/resources/documents/2019/2019-UNAIDS-data

18. De Schacht C, Mabunda N, Ferreira OC, Ismael N, Calú N, Santos I, et al. High HIV incidence in the postpartum period sustains vertical transmission in settings with generalized epidemics: a cohort study in Southern Mozambique. J Int AIDS Soc. 2014;17:18808.

19. Modi S, Callahan T, Rodrigues J, Kajoka MD, Dale HM, Langa JO, et al. Overcoming Health System Challenges for Women and Children Living With HIV Through the Global Plan. J Acquir Immune Defic Syndr 1999. 2017 May 1;75(Suppl 1):S76–85.

20. Knettel BA, Cichowitz C, Ngocho JS, Knippler ET, Chumba LN, Mmbaga BT, et al. Retention in HIV Care During Pregnancy and the Postpartum Period in the Option B+ Era: Systematic Review and Meta-Analysis of Studies in Africa. J Acquir Immune Defic Syndr 1999. 2018 Apr 15;77(5):427–38.

21. WHO. WHO | Integrated Management of Childhood Illness (IMCI) [Internet]. Geneva, Switzerland; 2014 [cited 2019 Sep 22]. Available from: http://www.who.int/maternal_child_adolescent/topics/child/imci/en/

22. WHO. WHO | HIV diagnosis and ARV use in HIV-exposed infants: a programmatic update [Internet]. WHO. 2018 [cited 2019 Sep 1]. Available from: http://www.who.int/hiv/pub/paediatric/diagnosis-arv-infants/en/

23. Hassan AS, Sakwa EM, Nabwera HM, Taegtmeyer MM, Kimutai RM, Sanders EJ, et al. Dynamics and Constraints of Early Infant Diagnosis of HIV Infection in Rural Kenya. AIDS Behav. 2012 Jan 1;16(1):5–12.

24. Violari A, Cotton MF, Gibb DM, Babiker AG, Steyn J, Madhi SA, et al. Early Antiretroviral Therapy and Mortality among HIV-Infected Infants. N Engl J Med. 2008 Nov 20;359(21):2233–44.

25. Bispo S, Chikhungu L, Rollins N, Siegfried N, Newell M-L. Postnatal HIV transmission in breastfed infants of HIV-infected women on ART: a systematic review and meta-analysis. J Int AIDS Soc. 2017;20(1):21251.

26. Read DJS. Late Postnatal Transmission of HIV-1 in Breast-Fed Children: An Individual Patient Data Meta-Analysis. J Infect Dis. 2004 Jun 15;189(12):2154–66.

27. UNAIDS. Start Free Stay Free AIDS Free — 2017 progress report. UNAIDS; 2017 p. 84.

28. Sherman GG, Jones SA, Coovadia AH, Urban MF, Bolton KD. PMTCT from research to reality - results from a routine service. S Afr Med J. 2004 Jan 1;94(4):289-292–292.

29. Doherty TM, McCoy D, Donohue S. Health system constraints to optimal coverage of the prevention of mother-to-child HIV transmission programme in South Africa: lessons from the implementation of the national pilot programme. Afr Health Sci. 2005 Jan 1;5(3):213-218–218.

30. Ahoua L, Ayikoru H, Gnauck K, Odaru G, Odar E, Ondoa–Onama C, et al. Evaluation of a 5-year Programme to Prevent Mother-to-child Transmission of HIV Infection in Northern Uganda. J Trop Pediatr. 2010 Feb 1;56(1):43–52.

31. Braitstein P, Katshcke A, Shen C, Sang E, Nyandiko W, Ochieng VO, et al. Retention of HIV-infected and HIV-exposed children in a comprehensive HIV clinical care programme in Western Kenya. Trop Med Int Health. 2010;15(7):833–41.

32. Oladokun RE, Awolude O, Brown BJ, Adesina O, Oladokun A, Roberts A, et al. Service uptake and performance of the prevention of mother-to-child transmission (PMTCT) programme in Ibadan, Nigeria. 2010 [cited 2019 Aug 16]; Available from: http://ir.library.ui.edu.ng/handle/123456789/2475

33. Geldsetzer P, Yapa HMN, Vaikath M, Ogbuoji O, Fox MP, Essajee SM, et al. A systematic review of interventions to improve postpartum retention of women in PMTCT and ART care. J Int AIDS Soc. 2016;19(1):20679.

34. Turan JM, Onono M, Steinfeld RL, Shade SB, Owuor K, Washington S, et al. Effects of antenatal care and HIV treatment integration on elements of the PMTCT cascade: Results from the SHAIP cluster-randomized controlled trial in Kenya. J Acquir Immune Defic Syndr 1999. 2015 Aug 15;69(5):e172–81.

35. Mwapasa V, Pro G, Chinkhumba J, Mukaka M, Kobayashi E, Stuart A, et al. Mother–Infant Pair Clinic and SMS Messaging as Innovative Strategies for Improving Access to and Retention in eMTCT Care and Option B+ in Malawi: A Cluster Randomized Control Trial (The PRIME Study). J Acquir Immune Defic Syndr. 2014;67:5.

36. Ong JO, Kose J, Audo M, Matu L, Savosnick P, Guay L. Provision of Services and Care for HIV-Exposed Infants: A Comparison of Maternal and Child Health Clinic and HIV Comprehensive Care Clinic Models. J Acquir Immune Defic Syndr. 2012;61(1):7.

37. Turan JM, Miller S, Bukusi EA, Sande J, Cohen CR. HIV/AIDS and maternity care in Kenya: how fears of stigma and discrimination affect uptake and provision of labor and delivery services. AIDS Care. 2008 Sep;20(8):938–45.

38. Jones SA, Sherman GG, Varga CA. Exploring socio-economic conditions and poor follow-up rates of HIV-exposed infants in Johannesburg, South Africa. AIDS Care. 2005 May;17(4):466–70.

39. Bwirire LD, Fitzgerald M, Zachariah R, Chikafa V, Massaquoi M, Moens M, et al. Reasons for loss to follow-up among mothers registered in a prevention-of-mother-to-child transmission program in rural Malawi. Trans R Soc Trop Med Hyg. 2008 Dec 1;102(12):1195–200.

40. Finocchario-Kessler S, Gautney BJ, Khamadi S, Okoth V, Goggin K, Spinler JK, et al. If you text them, they will come: using the HIV infant tracking system to improve early infant diagnosis quality and retention in Kenya. AIDS Lond Engl. 2014 Jul;28(0 3):S313–21.

41. Mwapasa V, Joseph J, Tchereni T, Jousset A, Gunda A. Impact of Mother–Infant Pair Clinics and Short-Text Messaging Service (SMS) Reminders on Retention of HIV-Infected Women and HIV-Exposed Infants in eMTCT Care in Malawi: A Cluster Randomized Trial. J Acquir Immune Defic Syndr. 2017;75:9.

42. Peltzer K, Babayigit S, Rodriguez VJ, Jean J, Sifunda S, Jones DL. Effect of a multicomponent behavioural PMTCT cluster randomised controlled trial on HIV stigma reduction among perinatal HIV

positive women in Mpumalanga province, South Africa. SAHARA-J J Soc Asp HIVAIDS. 2018 Jan 1;15(1):80–8.

43. Shargie MB, Eek F, Abaychew A. Prophylactic treatment uptake and compliance with recommended follow up among HIV exposed infants: a retrospective study in Addis Ababa, Ethiopia. BMC Res Notes. 2011 Dec 27;4(1):563.

44. Kim MH, Ahmed S, Buck WC, Preidis GA, Hosseinipour MC, Bhalakia A, et al. The Tingathe programme: a pilot intervention using community health workers to create a continuum of care in the prevention of mother to child transmission of HIV (PMTCT) cascade of services in Malawi. J Int AIDS Soc. 2012;15(S2):17389.

45. Sam-Agudu NA, Ramadhani HO, Isah C, Anaba U, Erekaha S, Fan-Osuala C, et al. The Impact of Structured Mentor Mother Programs on 6-Month Postpartum Retention and Viral Suppression among HIV-Positive Women in Rural Nigeria: A Prospective Paired Cohort Study. J Acquir Immune Defic Syndr. 2017;75:9.

46. Teasdale CA, Besser MJ. Enhancing PMTCT programmes through psychosocial support and empowerment of women: The mothers2mothers model of care. South Afr J HIV Med. 2008 Jan 1;9(1):60-64–64.

47. Phiri S, Tweya H, van Lettow M, Rosenberg NE, Trapence C, Kapito-Tembo A, et al. Impact of Facility- and Community-Based Peer Support Models on Maternal Uptake and Retention in Malawi's Option B+ HIV Prevention of Mother-to-Child Transmission Program: A 3-Arm Cluster Randomized Controlled Trial (PURE Malawi). J Acquir Immune Defic Syndr. 2017;75:9.

48. Foster G, Orne-Gliemann J, Font H, Kangwende A, Rusakaniko S, Shumba B, et al. Impact of Facility-Based Mother Support Groups on Retention in Care and PMTCT Outcomes in Rural Zimbabwe: The EPAZ Cluster-Randomized Controlled Trial. J Acquir Immune Defic Syndr. 2017;75:9.

49. Ioannidis JP, Taha TE, Kumwenda N, Broadhead R, Mtimavalye L, Miotti P, et al. Predictors and impact of losses to follow-up in an HIV-1 perinatal transmission cohort in Malawi. Int J Epidemiol. 1999 Aug 1;28(4):769–75.

50. Kuhn L, Sinkala M, Semrau K, Kankasa C, Kasonde P, Mwiya M, et al. Elevations in Mortality Associated with Weaning Persist into the Second Year of Life among Uninfected Children Born to HIV-Infected Mothers. Clin Infect Dis. 2010 Feb 1;50(3):437–44.

51. Kohler PK, Chung MH, McGrath CJ, Benki-Nugent SF, Thiga JW, John-Stewart GC. Implementation of free cotrimoxazole prophylaxis improves clinic retention among antiretroviral therapy-ineligible clients in Kenya: AIDS. 2011 Aug;25(13):1657–61.

52. Ioannidis JPA, Tatsioni A, Abrams EJ, Bulterys M, Coombs RW, Goedert JJ, et al. Maternal viral load and rate of disease progression among vertically HIV-1-infected children: an international meta-analysis. :10.

53. McNairy ML, Teasdale CA, El-Sadr WM, Mave V, Abrams EJ. Mother and Child Both Matter: Re-conceptualizing the PMTCT Care Continuum. Curr Opin HIV AIDS. 2015 Nov;10(6):403–10.

54. WHO. WHO | What's new in service delivery [Internet]. 2015 [cited 2019 Jul 26]. Available from: http://www.who.int/hiv/pub/arv/arv2015-service-delivery-factsheet/en/

55. Fuente-Soro L. Community HIV Prevalence and Factors associated with mortality in HEI children aged<4 years. IAS 2019; 2019 Jul; Mexico City.

56. Cohn J, Whitehouse K, Tuttle J, Lueck K, Tran T. Paediatric HIV testing beyond the context of prevention of mother-to-child transmission: a systematic review and meta-analysis. Lancet HIV. 2016 Oct 1;3(10):e473–81.

57. Ciampa PJ, Tique J, Jumá N, Sidat M, Moon TD, Rothman RL, et al. Addressing poor retention of infants exposed to HIV: a quality improvement study in rural Mozambique. J Acquir Immune Defic Syndr 1999. 2012 Jun 1;60(2):e46–52.

58. WHO. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach. [Internet]. 2016 [cited 2019 Sep 6]. Available from: http://apps.who.int/iris/bitstream/10665/208825/1/9789241549684_eng.pdf

59. Mutanga JN, Raymond J, Towle MS, Mutembo S, Fubisha RC, Lule F, et al. Institutionalizing Provider-Initiated HIV Testing and Counselling for Children: An Observational Case Study from Zambia. PLOS ONE. 2012 Apr 20;7(4):e29656.

60. Weigel R, Kamthunzi P, Mwansambo C, Phiri S, Kazembe PN. Effect of provider-initiated testing and counselling and integration of ART services on access to HIV diagnosis and treatment for children in Lilongwe, Malawi: a pre- post comparison. BMC Pediatr. 2009 Dec 18;9(1):80.

61. Kranzer K, Meghji J, Bandason T, Dauya E, Mungofa S, Busza J, et al. Barriers to Provider-Initiated Testing and Counselling for Children in a High HIV Prevalence Setting: A Mixed Methods Study. PLOS Med. 2014 May 27;11(5):e1001649.

62. MISAU. Directriz Nacional para a implementação do aconselhamento e testagem em saude [National guidelines for implementation of counseling and testing for health] [Internet]. MAPUTO; 2015 [cited 2019 Aug 20]. Available from: http://www.misau.gov.mz/index.php/directrizes-nacionais

63. Nhabomba C, Chicumbe S, Muquingue H, Jahit S, Lara J, Couto A, et al. Clinical and Operational Factors Associated with Low Pediatric Inpatient HIV Testing Coverage from Mozambique. Public Health Action. 2019 In press;

64. Marinda E, Humphrey JH, Iliff PJ, Mutasa K, Nathoo KJ, Piwoz EG, et al. Child Mortality According to Maternal and Infant HIV Status in Zimbabwe: Pediatr Infect Dis J. 2007 Jun;26(6):519–26.

65. Brahmbhatt H, Kigozi G, Wabwire-Mangen F, Serwadda D, Lutalo T, Nalugoda F, et al. Mortality in HIV-Infected and Uninfected Children of HIV-Infected and Uninfected Mothers in Rural Uganda: JAIDS J Acquir Immune Defic Syndr. 2006 Apr;41(4):504–8.

66. Sutcliffe CG, van Dijk JH, Bolton C, Persaud D, Moss WJ. Effectiveness of antiretroviral therapy among HIV-infected children in sub-Saharan Africa. Lancet Infect Dis. 2008 Aug 1;8(8):477–89.

67. Newell M-L, Coovadia H, Cortina-Borja M, Rollins N, Gaillard P, Dabis F. Mortality of infected and uninfected infants born to HIV-infected mothers in Africa: a pooled analysis. The Lancet. 2004 Oct;364(9441):1236–43.

68. Evans C, Jones CE, Prendergast AJ. HIV-exposed, uninfected infants: new global challenges in the era of paediatric HIV elimination. Lancet Infect Dis. 2016 Jun;16(6):e92–107.

69. Koyanagi A, Humphrey JH, Ntozini R, Nathoo K, Moulton LH, Iliff P, et al. Morbidity Among Human Immunodeficiency Virus-exposed But Uninfected, Human Immunodeficiency Virus-infected, and Human Immunodeficiency Virus-unexposed Infants in Zimbabwe Before Availability of Highly Active Antiretroviral Therapy. Pediatr Infect Dis J. 2011 Jan;30(1):45.

70. Mussi-Pinhata MM, Freimanis L, Yamamoto AY, Korelitz J, Pinto JA, Cruz MLS, et al. Infectious Disease Morbidity Among Young HIV-1–Exposed But Uninfected Infants in Latin American and Caribbean Countries: The National Institute of Child Health and Human Development International Site Development Initiative Perinatal Study. Pediatrics. 2007 Mar 1;119(3):e694–704.

71. Slogrove AL, Esser MM, Cotton MF, Speert DP, Kollmann TR, Singer J, et al. A Prospective Cohort Study of Common Childhood Infections in South African HIV-exposed Uninfected and HIV-unexposed Infants. Pediatr Infect Dis J. 2017 Feb;36(2):e38–44.

72. Landes M, Lettow M van, Chan AK, Mayuni I, Schouten EJ, Bedell RA. Mortality and Health Outcomes of HIV-Exposed and Unexposed Children in a PMTCT Cohort in Malawi. PLOS ONE. 2012 Oct 17;7(10):e47337.

73. Kuhn L, Kasonde P, Sinkala M, Kankasa C, Semrau K, Scott N, et al. Does Severity of HIV Disease in HIV-Infected Mothers Affect Mortality and Morbidity among Their Uninfected Infants? Clin Infect Dis. 2005 Dec 1;41(11):1654–61.

CHAPTER 6

Viral response among HIV perinatally infected infants who started antiretroviral treatment in the first month of life: description of a cohort in southern Mozambique

Viral response among HIV perinatally infected infants who started antiretroviral treatment in the first month of life: description of a cohort in southern Mozambique

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Abstract

Background: Starting early antiretroviral treatment is crucial to reduce infants' morbidity and mortality. Viral suppression must be reached and maintained to achieve long term benefit and allow infants to grow into adolescence. The study aims to describe the viral response of a cohort of infants who started ART in the first month of life in southern Mozambique.

Methods: Descriptive cohort study of HIV perinatally infected infants who started antiretroviral treatment in the first month of life and were followed for two years. Viral suppression (VS), sustained VS and rebound were described using Kaplan–Meier estimator. Descriptive analyses were used to summarize infants' and mothers' characteristics according to virologic response. Trends of anthropometric measures z-scores based on WHO reference population were calculated.

Results: Eighteen infants (60%) out of 30 reached VS <1000c/ml, 9 (50%) had a rebound; fourteen (47%) sustained viral suppression during follow up. Cumulative probability of viral suppression among all infants was 56% at 12 months on ART and 73% at 18 months. Among infants adherent to ART, the median time to suppress the virus was 3 months; 89% reached undetectable viral load at 12 months. Anthropometric measurements during follow up, especially WAZ score, showed better performance among infants who presented viral load suppression compared to those with no viral load suppression.

Conclusion: Low rate of viral suppression and high rate of viral rebound are frequent among infants and need urgent response by the HIV program. Clinical benefits gained with early diagnosis and early treatment initiation must be maintained throughout child ART care by enabling caregivers to build a strong adherence behavior. Adapt the psychosocial approach model currently in place, offer a targeted care in a tailored environment at MCH clinic, till viral suppression is achieved, are approaches to consider. At the same time, build skills and abilities of nurses and clinicians to early recognize clinical signs of poor adherence by using easy tools already in place such as growth monitoring and combining it with viral test result, is of paramount importance and need to be accurately examined.

Keywords: viral load suppression, rebound, paediatric HIV, growth, early antiretroviral therapy

Introduction

Remarkable results were achieved in reducing new infection among infants after the Global plan for elimination of pediatric HIV and the start the Start Free Stay Free AIDS Free framework (1,2). However, still 160.000 new pediatric infections and 100.000 deaths occurred in 2018 (3). Majority of infected children are in Sub Saharan Africa and acquire HIV through vertical transmission (3) and for them the final goal is to reach viral suppression (4). With the increased expansion of early infant diagnosis technologies, identification and treatment initiation of infants within the first two months of life is possible and has increased over time in priority countries (5–9). Starting antiretroviral treatment (ART) as early as possible is crucial to reduce infants' morbidity and mortality (10–13) and guidelines have been adopted worldwide since dissemination of CHER trial's results (14). Starting treatment in the first 3 months of life has shown also to have a better immunologic and virologic response (15,16).

However, viral suppression must be sustained to achieve long term benefits and allow infants to grow into adolescence as well as to prevent HIV-related complication (12,15). Maintaining undetectable viremia, will also prevent ART resistance development (17–19), which may be a big constraint in Africa where available drugs for younger patients are limited and first line regime must be preserved as much as possible (20,21).

Sub-optimal long term viral response among children in low and middle-income countries compared to children in high-income countries has been described in a meta-analysis (22).

Viral response has been described in older cohorts (18,19,23–27). Infants starting ART with age <2 months showed a great variability in reaching viral suppression from 19% to 81% (28), and generally have worse response compared to older children (23). Infants have also increased risk of VL rebound after reaching suppression (23).

Adherence correlates with viral suppression in children and infants (29–31) and suboptimal adherence was shown to be a major contributor to poor ART response in the pediatric population (32). Adherence is also related to retention into care, evidence shows that keeping children into HIV care program is another constraint, being younger age one of the risk factors for attrition (33).

Little is known about challenges to achieve sustained viral control and risk of rebound in infants starting ART in the first month of life. In children, especially in infants, adherence to ART and consequently good virologic response are related to caregivers adherence behavior (32).

Mozambique has a high HIV burden (34), 140.000 children were living with HIV, approximately 60% were on ART, HIV vertical transmission was 10% and 66% of HIV exposed infants had access to

diagnosis within 2 months of life in 2018 (35). Nucleic Acid Testing simplified point of care technologies for HIV diagnosis, provide same day test result and reduced delay in treatment initiation (5,6). Therefore, benefits gained with early diagnosis and early ART must be maintained throughout ART care by ensuring adherence to attain sustained viral suppression.

However, retention into ART care remains a challenge: 12 months retention rate in the 0-14 years old was 70% (35) and viral suppression was 46% (36). Moreover, programmatic unpublished data suggest that differences do occur in retention and virologic response among pediatric age group and this is certainly an area where reliable evidence is needed to tailor interventions. The Ministry of Health (MOH) in Mozambique recommends viral load as the preferred test to monitor ART response in all patients (37,38). However, there are no data in Mozambique describing viral response in infants who started ART in the first months of life, nor data on sustained viral suppression in this age group.

This study aims to describe the viral response among a cohort of infants who started ART at one month of age. Findings will contribute to build knowledge and critical evidence to inform guidelines review on improved follow up ART care for infants.

Methods

This is a descriptive cohort study of HIV perinatally infected infants diagnosed and recruited within the second month of life in two Health Centers of Matola district (Machava 2, Matola 1), in Maputo province, southern Mozambique. The cohort is part of a primary study called 'Immunity and HIV persistence in perinatal HIV infection', funded by the National Institute of Health NIH (AI127347), and developed in collaboration with *Instituto Nacional de Saúde (INS)*, Mozambique, and *Fundação Ariel Glaser contra o SIDA Pediatrico*, Miami University and *Ospedale Bambino Gesú*, Rome, Italy. The primary objective of the longitudinal study is to assess latent and active reservoirs in peripheral blood in the context of a developing immune system, early ART initiation and response to childhood vaccinations in HIV perinatally infected infants starting ART at age ≤2 months and to compare their vaccine responses with those of exposed uninfected infants.

The study started in 2017 and infants follow up was 2 years. Clinical follow up, according to MOH guidelines, consisted of monthly clinical and psychosocial support visits provided by a multidisciplinary team composed of a Pediatrician, a nurse and a psychologist. Adherence to treatment was self-reported by the caregiver. Samples were collected before starting ART and then at the following intervals: 1, 2, 4, 5, 8, 9,11, 17, 17 and 1 week, 18 and 23 months after ART initiation.

Whole blood was drawn in EDTA tubes and sent to the Molecular Virology and Immunology laboratory of the INS. HIV -1 Plasma viral load (VL) was quantified using COBAS® AmpliPrep/COBAS® TaqMan® HIV-1 Test, version 2.0 (Roche Diagnostics, Germany) with a limit detection of 20 copies/ml. Reminiscent blood was prepared and stored for PBMC and immunological tests. In case of plasma HIV RNA viral load > 1000c/ml, intensive psychosocial support sessions were offered and the test repeated as per MOH guidelines.

Statistical Analysis

For the purpose of this study were included infants with at least 4 viral load (VL) measurements. The primary outcome was viral load suppression (VLS) defined as HIV RNA plasma < 1000copies/ml after ART initiation, which is the WHO and national HIV program definition of viral suppression (38). Secondary outcomes were: 1) sustained VLS defined as two or more consecutive measurements of plasma HIV RNA <1000 copies/ml and 2) viral rebound defined as a measure of viral load >1000 copies/ml after reaching VLS. According to viral response, infants were grouped in infants with VLS, infants with no VLS, infants with sustained VLS and infants without sustained VLS. The prevalence of primary and secondary outcomes was calculated. Descriptive analyses were used to summarize the baseline characteristics of infected infants (N=30) according to the virologic response. The non-parametric Wilcoxon and Mann-Whitney tests were used when appropriate to assess the differences among the different groups of infants: those with VLS, with no VLS, with sustained VLS and with no sustained VLS. Kaplan–Meier estimator was used to calculate the cumulative probability of viral load suppression among all infants who started ART, among those who were adherent to treatment and according to the pre-ART viral load; cumulative probability of time to rebound was also calculated; log-rank test was used to compare results among the two groups (39). We used ANTRHO package to calculate anthropometric measures z-scores based on WHO reference population (40). Time course of weight for age z-score, weight for height z-score and head circumference z-score, during follow up has been represented according to viral response to treatment.

Ethical considerations

The study was approved by the National Bioethics Committee (IRB00002657, reference 102/CNBS/2016), the Ministry of Health, the University of Miami and Ospedale Bambino Gesú

Institutional Review Board. Caregivers consented the participation in the study and signed an informed consent.

Results

The cohort included 38 HIV perinatally infected infants: thirty infants (19 female) had a pre-ART VL and at least 3 VL measurements after ART initiation, in the first six months after ART initiation. Eight children were excluded: 3 had one visit and then left the study, 3 had 3 VL measurement and 2 did not have the pre-ART viral load.

The median follow-up time was 17.5 months (4.6-25). Infants' characteristics at baseline are described in Table 1. Median age at diagnosis and ART initiation was 34 days (IQR 18), median weight was 3.8 Kg (IQR 1.1], weight for height Z-score was >=-1SD in 83% of them, 22 (73%) were exclusively breastfeeding, 27 (90%) were asymptomatic (WHO stage I); the median CD4 % was 30% (IQR 12.6), CD4 absolute count was 1,993 (IQR 946); median pre-ART VL was 1.988.708 copies/ml (IQR 4.661.355) with mean Log_{10} 6.06 (SD 0.82); 13 (43%) infants had a VL <1.000.000 copies/ml while 7 (23%) had a VL >6.000.000 copies/ml. A total of 24 (80%) infants received NVP prophylaxis. Eighteen infants out of 30 (60%) reached VLS of plasma HIV RNA <1000 copies/ml after a median time of 2.93 months (min 0.92, max 16.41) on ART, 16 (53%) of them reached HIV RNA <500 copies/ml; nine infants out of 18 (50%) had a rebound and 5 re-suppressed; 14 (46.6%) of those who reached VLS, maintained viral suppression according to study definition.

Among all infants of the cohort, the cumulative probability of VLS was 43% at 6 months of ART, 56% at 12 months and 73% at 18 months (Fig. 1). Among children who were adherent to ART and reached VLS, the probability of VLS was 72% at 6 months and 89% at 12 months of ART (Fig. 2). We also compared the probability to VLS according to pre-ART viral load using the cut off of Log_{10} >6. Infants with lower pre-ART VL had a more rapid VLS compared to those with higher pre-art VL, however not statistically significant (Long-rank test p= 0.261): more than 55% of infants with lower VL were suppressed at 2 months compared to 11% of those with higher VL (Fig. 3). The median duration of viral suppression among those infants who reached VLS was 3.32 months (min 1.05, max 9.93) and the cumulative probability of rebound at 6 months was of 50% (Fig 4). The probability of re-suppression among infants who had a rebound was of 22% within 2 months, and 33% at 3 months (Fig. 5).

We compared baseline clinical characteristics of the children with no-VLS with those with VLS and we did not find significant differences among the two groups (Table 2). Mothers characteristics

among the two groups were also compared (Table 2). Except for one mother of an infant who reached VLS who started ART after delivery, all the others were already on ART at the time of delivery; mothers of infants with no VLS were on ART for a shorter time with respect to mothers of infants with VLS, median of 168 [304] days vs 211 [565] respectively; 4/10 mothers of infants with no-VLS, had undetectable viremia during follow up, compared to 10/14 mothers of infants with VLS; 11/12 vs 13/15 mothers referred to have disclosed her HIV status within the family in the no-VLS vs VLS group. No statistical significance was reported for any variable among the two groups.

Clinical events classified as WHO stage 3 or 4 occurred in infants who did not reached or maintained viral suppression: one child developed toxoplasmosis and died, one pulmonary tuberculosis, one had encephalopathy and died and two had severe malnutrition; another infant died after leaving the study at 8 months without reaching VLS. No adverse events were reported during follow up.

Trend of weight for age z score (WAZ), height for age z score (HAZ) and head circumference for age z score (HCZ) during follow up, were different: all parameters scored higher in children who had sustained VLS compared to those without sustained VLS (Fig 6,7,8).

Discussion

Our analysis is the first one describing viral response in a cohort of infants who started antiretroviral treatment at one month of age in Mozambique and had repeated measurements of plasma VL during the first two year of follow up. Despite being in a study context and children receiving care from a multidisciplinary specialized team, viral suppression was achieved by 60% of infants and only 30% sustained viral control till the end of follow up. If we consider all infants who started treatment, the probability to reach viral suppression was 56% at 12 months and 73% at 18 months. On the other hand, in infants who were adherent to medication, the probability to VLS was 72% at 6 months and 89% at 12 months of ART. In Mozambique, national prevalence of viral suppression among 0-14years old children was 46% in 2018 (36). Suboptimal viral suppression is partially due to the large proportion of children on Nevirapine based regimen to which high primary resistance has been documented in perinatally infected infants (41). However, infants in our cohort were on LPV/r and the low suppression rate is worrisome.

Sub-optimal viral response among children in low and middle-income countries compared to children in high-income countries has been described in a meta-analysis (22). In South Africa, a cohort of children of 0-12 years old, on PI based regimen, presented a cumulative incidence of viral suppression (<1000c/ml) at 6, 12 and 24 months of 57.6%, 78.7% and 84.0% respectively. Infants, in

the same cohort, had a lower viral suppression (<50c/ml) rate compared to older children, 46.6% VS 76.9% at 12 months (23). In the EPPICC cohort which included, infants starting ART within 12m of age, 62% achieved viral suppression at 12m. Moreover they found that VLS was less likely to occur in infants younger than 3 months of age compared to those aged 6-12m (42). A review of studies describing infants who started ART in the first 6 months of life, found great variability in the initial VLS, from 31% to 72% at 6 months (43–45) and from 50% (46) to 72% or 80% at 12m, these last two studies included only infants who were adherent to treatment (15,47). Older cohorts showed higher success of virologic suppression from 72% to 93% after 24 months of treatment (44,48,49).

In our subgroup of adherent infants, response to treatment was rapid, irrespectively of baseline viral load: despite a high pre-ART VL (≥6Log), which has been described elsewhere in this age group (15,44,50), the median time to viral suppression was approximately 3 months, lower (44,51) or similar to other studies findings (47,52). Interestingly, although our sample size was small, time to VLS among infants with higher pre-ART VL did not differ compared to infants with lower pre-ART VL, contrasting past report (42,53). This finding suggests that if the medication is taken and the virus is not resistant, viral decay is rapid even in younger infants (28,54).

In line with the literature, we found that, once achieved undetectable viremia, sustaining viral suppression was a challenge. Half of infants who reached VLS, had a rebound within 3 months after the first VLS measure, even though majority of them suppressed again in the following 3 months after the peak of viremia. Two studies found that the risk of rebound in infants was up to two times higher compared to children (23,44). On the contrary, a study which compared sustained VLS among infants starting ART before 6 months of age with those starting between 6-24m, found that early ART is protective to viral rebound (43). Other studies in older children described 38% viral rebound within one year after reaching undetectable plasma viral load (48), others described lower rate and probability of rebound with respect to our cohort (55), but higher in children with opportunistic infection such as tuberculosis and in younger age (53,56).

In our cohort, where it was possible to measure viral load at very frequent points in time, especially in the first 12 months on ART, we observed different and unpredictable pattern of viral response among all infants, those with and without VLS. The big variability in individual viral response's trajectories, supports the fact that adherence played a major role in determining viral response. In our study, ART adherence was measured by caregiver self-report and all caregivers of infants with no-VLS or whit viral rebound reported poor adherence. They disclosed several dynamic and complex

issues in daily routine which affected compliance, which is the main reason of virologic failure also reported elsewhere (48).

Another element we analyzed to better understand adherence, was the caregiver viral response. Mothers viral response during follow up was found to be similar to infant's viral response: majority of mothers of infants whit no VLS also had high viral load measurements during follow up. It is likely that if the mother does not take the medication, she will not give it to her baby. A correlation between child and caregiver's viral response was described in Kenya, where children, whose caregiver was not virally suppressed, were at higher risk of non-viral suppression (57). Even if the study included older children it highlights the importance to also focus on mother adherence during pregnancy and post-partum. Mothers of infants with no-VLS, were on ART for a shorter time compared to mothers of infants with VLS. However, majority of mothers started ART long before delivery and this suggests that despite several opportunities to receive psychosocial support and counselling sessions, they had along the PMTCT care cascade, a different approach is needed for them to mold a strong adherence behavior for themselves and their baby. Understanding the reasons why the mother does not take the medication herself, will be of help in perceiving weather she will give it to her baby. All mothers of infants with no-VLS did not miss any visit but we saw that being adherent to clinical visits does not guarantee drugs are regularly administered. Many studies, although focused on older children, have described barriers to ART adherence in Sub-Saharan African countries and showed that stigma, discrimination and lack of family support are the main barriers reported by caregivers (58–60). In our cohort however, majority of mothers disclosed their status within the family and reported to receive family support, apparently not enough to ensure full adherence.

All these findings suggest that psychosocial support for mothers of infants living with HIV, has to be rethought to enable health staff foreseeing and addressing potential adherence problems starting from the ANC period till post-partum care. All these factors need to be further studied and addressed as suboptimal adherence among family members could result in suboptimal care for the child.

In Mozambique, efforts done to strengthen linkage between PMTCT and HIV care for perinatally infected infants are showing increased early ART initiation in the youngest. However, continuum of care for mom-infected-baby pair need to be improved to ensure full adherence of both. Transition of mom-infected-baby pair to adult HIV clinic, where the context may not be favorable for a mother who is learning how to deal with an infected baby, has to be re-taught (7). We think that the

approach to continue follow up for a short period after ART initiation at MCH clinic with familiar staff already aware of existing problems, will probably better prepare the patients for transition, while monitoring adherence.

In our cohort, a difference in trends of anthropometric measurements was evident, particularly the weight-for-age Z score: infants with sustained VLS presented a better WAZ-score compared to those with no sustained VLS and was more noticeable from the age of 8-9 months. Correlation between AIDS progression and malnutrition and the beneficial effect of ART in growth recovering has been well described in literature(61–65). Head circumference-for-age Z score performed better in infants with sustained VLS and studies are many on the effect of the virus in delaying infants neurological development (66–68). Our data highlights, once more, how fast the virus acts in young infants and how easy is to suspect treatment non-adherence by simply looking at anthropometrics indicators.

In Mozambique, viral load is now the preferred test to monitor response to ART, it is recommended 6 months after ART initiation and then every year if VLS is achieved (38). Roll out started in 2017 but uptake is slow: programmatic data show that not all eligible infants receive a VL test and test results turnaround time may take some time. Moreover, correct interpretation of VL test result in younger infants is another challenge for non-specialized clinicians, especially when the result is above the suppression threshold and the mother is referring good adherence to medication. Not knowing how to interpret the result leads to under-use of this important test. A careful monitoring of growth parameters during routine visits, weight in particular, is an easy and invaluable tool that can and must be used, especially in resource limited settings, where viral load is not yet widely available. Combining VL test result with weights trend may be of support in clinical practice.

The study has several limitations. Firstly, the sample is small and is not possible to generalize conclusions. However, it highlights important observational and clinically grounded findings which need further investigation, such as correlates of adherence and viral suppression beyond health package and quality of care offered. The recruitment occurred during two years, so not all patients have the same follow up length: however, patient's data have been censored for the analysis. The results are generated in a study context which may be different from the 'real life' context and overestimate results such as viral response and retention. However, descriptive results presented are of value as indicate that if "ideal care conditions" did not guarantee optimal VLS for all infants, in the "real-life health services scenario" where psychosocial support is provided by lay counsellors and care by non-specialized staff, results may be even worse.

We defined sustained VLS as two consecutive results of VL below 1000c/ml and in our cohort the time interval between two measurements could range from 1 to 6 months, so children who maintained viral suppression according to our definition could have maintained it for a variable period of ≥ 3 months. We could not perform resistance test among infants who did not respond to treatment, to ascertain whether lack of response was caused by virus resistance, however, all mothers of infants with no-VLS referred poor adherence to medications, majority of them had also high viral load and pattern of viral load response suggested that medication was not administered at all or consistently.

Conclusions

Low rate of viral suppression and high rate of viral rebound are frequent among infants and need urgent response by the HIV program. Clinical benefits gained with early diagnosis and early treatment initiation must be maintained throughout child ART care by enabling caregivers to build a strong adherence behavior. It is therefore urgent to adapt the clinical and psychosocial approach model currently in place in order to prompt identify potential non-adherent caregivers and offer them proper support. Offer a targeted care in a tailored environment, strengthening the continuum of care of mom-infected-baby pair and continue their follow up after ART initiation at MCH clinic, till viral suppression is achieved, is an approach to consider. At the same time, build skills and abilities of nurses and clinicians to early recognize clinical signs of poor adherence by using easy tools already in place such as growth monitoring and combining it with viral test result, is of paramount importance and need to be stressed with the same effort reserved to viral load test monitoring.

Finally, it is key to bear in mind that restricting interventions at health facility level, may not fully solve other social barriers and dynamics acting at community and family level which need to be investigated and properly addressed by involving multi-sectoral actors.

Acknowledgments

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Tables and Figures

Table 1: Characteristics of infants at enrollment

Characteristics at enrollment	HIV perinatally infected infants N=30 (%)
Sex	
Male	11 (36.67)
Female	19 (63.33)
Age at HIV diagnosis (days)	
Median [IQR]	34 [18]
Age at ART initiation (days)	
Median [IQR]	34 [18]
Time from dx to ART (days)	
Mean [Min, Max]	0.87 [0,14]
Post-natal prophylaxis	
No	2 (6.66)
Yes	24 (80)
Missing	4 (13.33)
Weight (Kg)	
Median [IQR]	3.8 [1.1]
Weight for Height z -score (WHZ)	
≥ -1SD	25 (83.33)
≥ 2SD e <-1SD	5 (16.67)
Feeding practice at enrollment	
Exclusive Breast Feeding	22 (73.33)
Mixed Feeding	5 (16.67)
Formula Feeding	3 (10)
WHO stage	
I	27 (90)
II	2 (6.67)
III	0
IV	1 (3.33)
CD4 count (cell/mm3)	
Median [IQR]	1,993 [946]
CD4 Percentage (%)	
Median [IQR]	30 [12.6]
Hgb (g/dl)	
Median [IQR]	10.3 [2.5]
Missing	3 (10)
pre ART Viral Load RNA	
Median (copies/ml) [IQR]	1,988,708 [4,661,355]
Mean $\log_{10}$ (sd)	6.06 (0.82)
Viral load (copies/ml) among cohort - n (%)	

<100.000	2 (6.67)
[100.000-500.000)	7 (23.33)
[500.000-1.000.000)	4 (13.33)
[1.000.000-6.000.000)	10 (33.33)
>= 6.000.000	7 (23.33)

Table 2: Characteristics of infants who reached viral load suppression (VLS) and who did not reach viral suppression (No VLS)

Characteristics of infants	Virologically suppressed (VLS) N=18	Non virologically suppressed (No VLS) N=12	P-value
Sex, n (%)			
Male	6 (33.33)	5 (41.67)	
Female	12 (66.67)	7 (58.33)	0.7116[1]
Age at ART initiation (days)			
Median [IQR]	34.5 [20]	33 [7.5]	0.5224[2]
Post-natal prophylaxis, n (%)			
No	2 (11.1)	0	
Yes	13 (72.22)	11 (91.67)	0.4923[1]
Missing	3 (16.67)	1 (8.33)	
WHZ score at baseline, n (%)			
>=-1SD	13 (72.22)	12 (100)	0.0657[1]
>=2SD e <-1SD	5 (27.78)	0	
WHO stage at baseline, n (%)			
I	17 (94.44)	10 (83.33)	
II	1 (5.56)	1 (8.33)	0.4975[1]
III	0	0	
IV	0	1 (8.33)	
CD4 at baseline Median [IQR]			
cd4mm	2,081 [1,137]	1,905 [575]	0.4187[2]
cd4%,	32 [12.1]	26 [10]	0.0650[2]
Hgb (g/dl) at baseline			
Median [IQR]	9.6 [2.7]	10.6 [2.51]	0.2307[2]
Missing	3 (16.67)	0 (0)	
Infant pre-ART VL			
Median [IQR]	1,348,664 [4,684,542]	2,014,386 [6,637,924]	0.6900[2]
Mean $\log_{10}$ (sd)	5.99 (0.94)	6.17 (0.62)	0.9204[2]
Mother VL during follow up, n (%)			
Detectable	4 (22.22)	6 (50)	0.1221[1]
Undetectable	11 (61.11)	4 (33.33)	
Missing	3 (16.67)	2 (16.67)	
Mother ART interruption before delivery, n (%)			
No	6 (33.33)	5 (41.67)	
Yes	8 (44.44)	7 (58.33)	1.0000[1]
Missing	4 (22.22)	0	
Mother time on ART at delivery (days)			
Median [IQR]	261.5 [562.5]	168 [304]	0.6889[2]

Mother time on ART at delivery, n (%)			
<3months	3 (16.67)	0	0.1522[1]
3m-9m	6 (33.33)	8 (66.66)	
>9m	8 (44.44)	3 (25)	
Missing	1 (5.56)	1(8.33)	
Mother self-disclosure within family			
Yes	13 (72.22)	11 (91.67)	1.0000[1]
No	2 (11.11)	1 (8.33)	
Missing	3 (16.67)	0	

[1] Fisher's Exact Test [2] Mann-Whitney Test

Fig 1: Cumulative probability of viral suppression among all infants who started ART

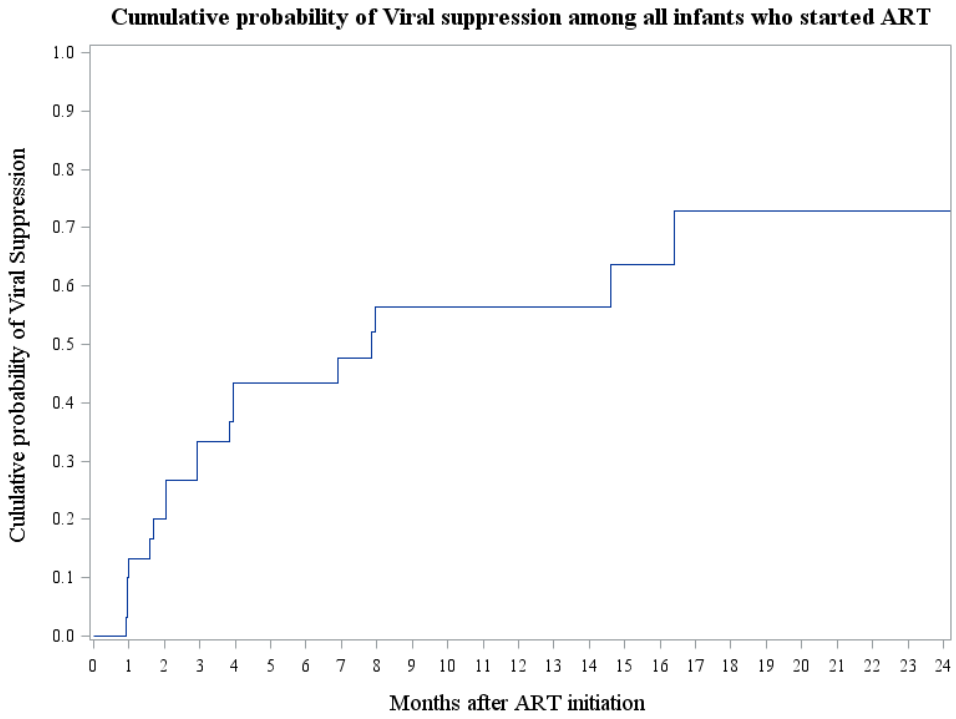


Fig. 2: Cumulative probability of viral suppression among infants who were adherent to treatment

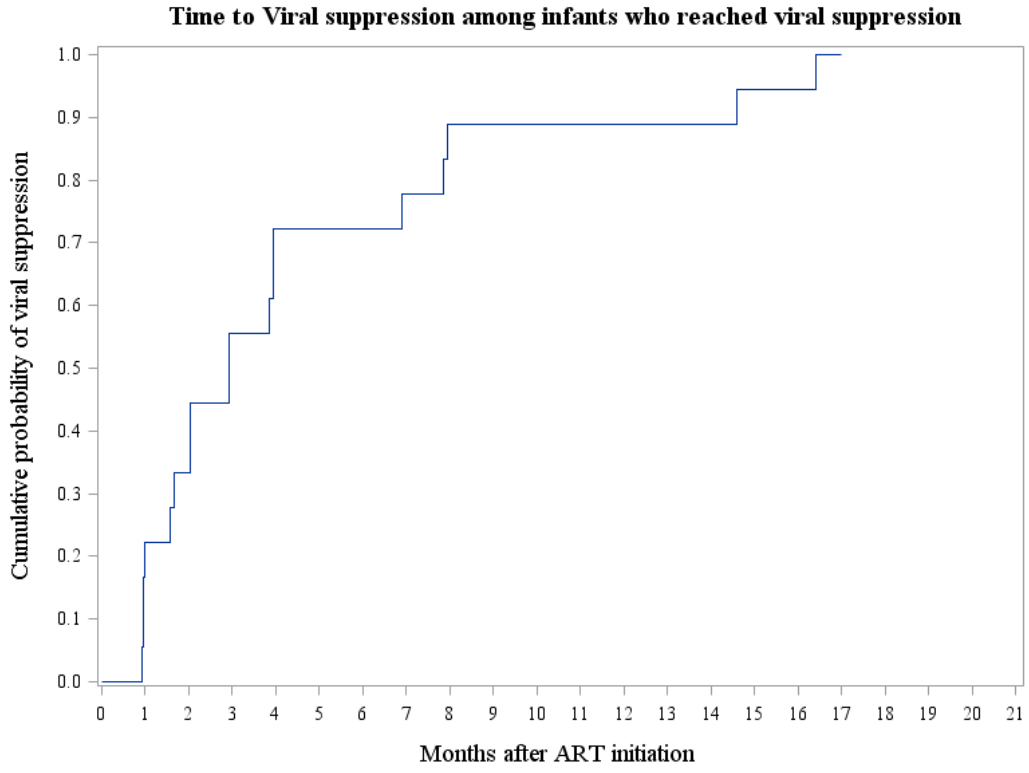


Fig. 3: Cumulative probability of suppression according to pre-ART viral load

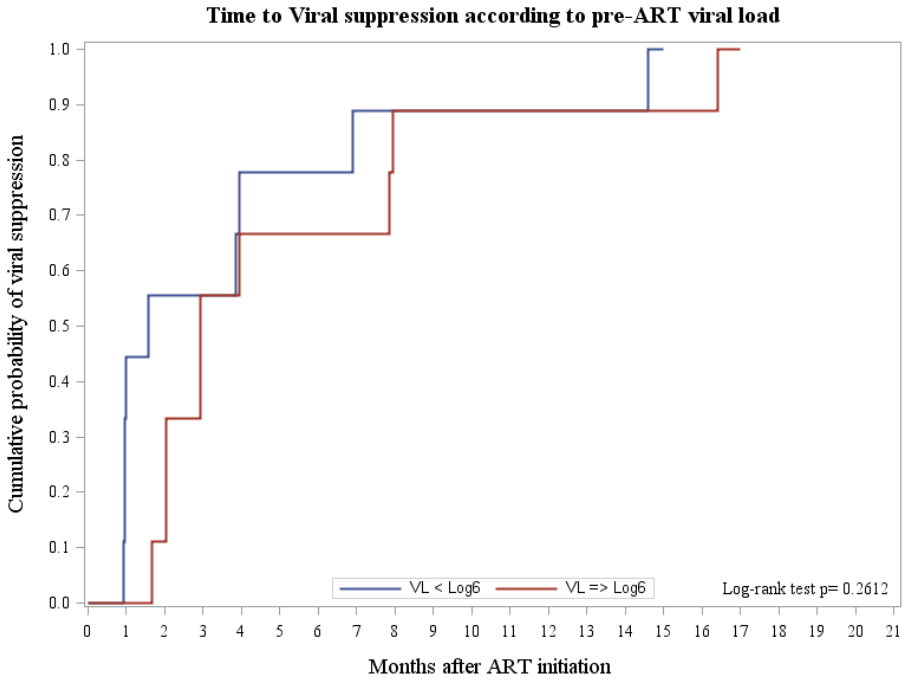


Fig. 4: Cumulative probability to viral rebound among infants who reached viral suppression

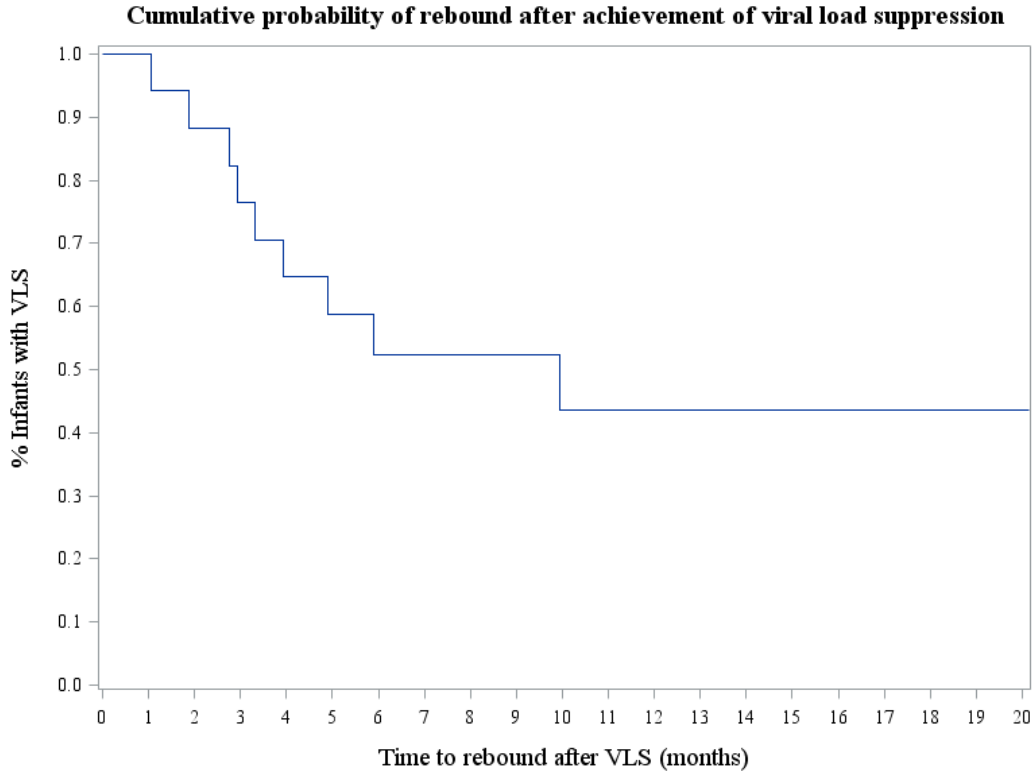


Fig.5: Cumulative probability of re-suppression among infants who had a rebound

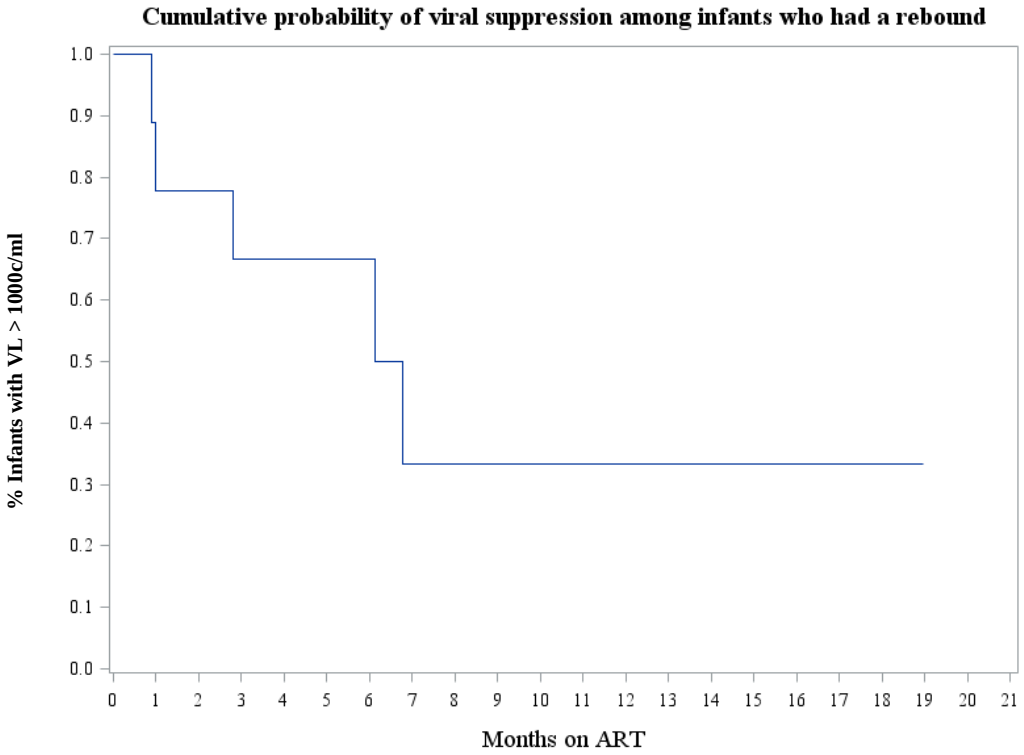


Fig. 6: Trend of Weight-for-Age z-score among infants with Sustained VLS (S) and with No-Sustained VLS (NS)

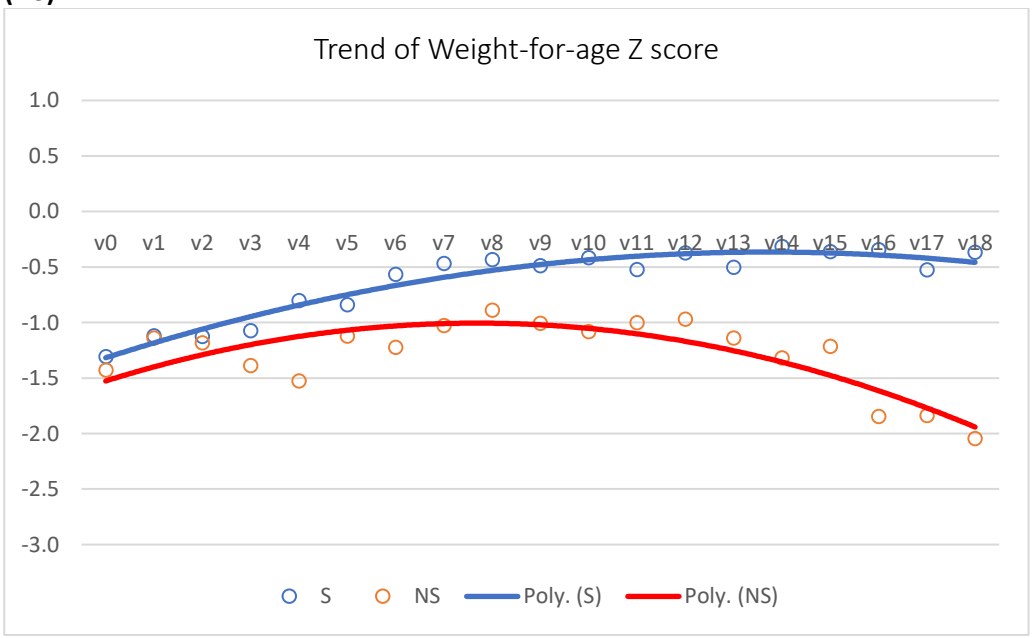


Fig. 7: Trend of Height-for-Age z-score among infants with Sustained VLS (S) and with No-Sustained VLS (NS)

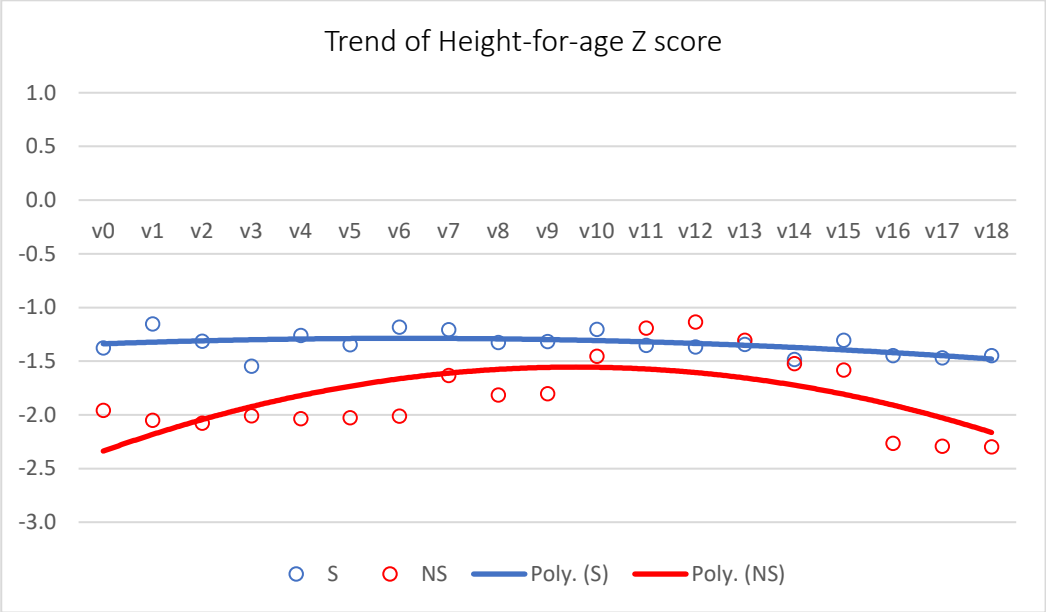
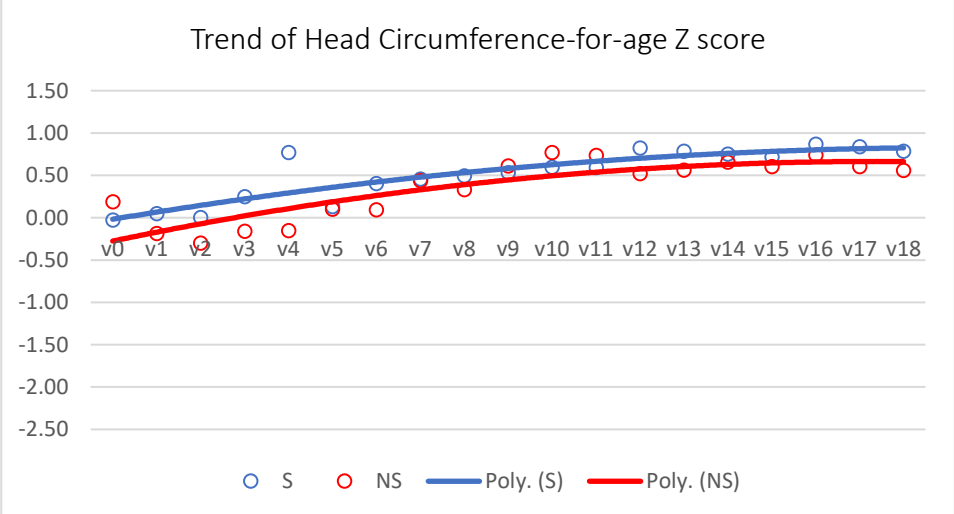


Fig. 8: Trend of Head Circumference-for-age z-score among infants with Sustained VLS (S) and with No-Sustained VLS (NS)



References

1. UNAIDS. Countdown to zero: global plan towards the elimination of new HIV infections among children by 2015 and keeping their mothers alive, 2011-2015. Geneva: UNAIDS; 2011.

2. UNAIDS. Start Free Stay Free AIDS Free - 2019 report [Internet]. 2019 [cited 2019 Sep 17]. Available from: https://www.unaids.org/en/resources/documents/2019/20190722_UNAIDS_SFSFAF_2019

3. UNAIDS. UNAIDS data 2019 [Internet]. 2019 [cited 2019 Jul 23]. Available from: https://www.unaids.org/en/resources/documents/2019/2019-UNAIDS-data

4. UNAIDS. 90-90-90: An ambitious treatment target to help end the AIDS epidemic [Internet]. Geneva, Switzerland; 2014 [cited 2019 Jul 24] p. 40. Available from: https://www.unaids.org/en/resources/documents/2017/90-90-90

5. Bianchi F, Cohn J, Sacks E, Bailey R, Lemaire J-F, Machekano R, et al. Evaluation of a routine point-of-care intervention for early infant diagnosis of HIV: an observational study in eight African countries. Lancet HIV. 2019 Jun 1;6(6):e373–81.

6. Jani IV, Meggi B, Loquiha O, Tobaiwa O, Mudenyanga C, Zitha A, et al. Effect of point-of-care early infant diagnosis on antiretroviral therapy initiation and retention of patients. AIDS. 2018 Jul 17;32(11):1453.

7. Hsiao N-Y, Stinson K, Myer L. Linkage of HIV-Infected Infants from Diagnosis to Antiretroviral Therapy Services across the Western Cape, South Africa. PLOS ONE. 2013 Feb 6;8(2):e55308.

8. Penazzato M, Revill P, Prendergast AJ, Collins IJ, Walker S, Elyanu PJ, et al. Early infant diagnosis of HIV infection in low-income and middle-income countries: does one size fit all? Lancet Infect Dis. 2014 Jul 1;14(7):650–5.

9. Essajee S, Vojnov L, Penazzato M, Jani I, Siberry GK, Fiscus SA, et al. Reducing mortality in HIV-infected infants and achieving the 90–90–90 target through innovative diagnosis approaches. J Int AIDS Soc. 2015;18(7S6):20299.

10. Violari A, Cotton MF, Gibb DM, Babiker AG, Steyn J, Madhi SA, et al. Early Antiretroviral Therapy and Mortality among HIV-Infected Infants. N Engl J Med. 2008 Nov 20;359(21):2233–44.

11. Collins IJ, Jourdain G, Hansudewechakul R, Kanjanavanit S, Hongsiriwon S, Ngampiyasakul C, et al. Long-Term Survival of HIV-Infected Children Receiving Antiretroviral Therapy in Thailand: A 5-Year Observational Cohort Study. Clin Infect Dis. 2010 Dec 15;51(12):1449–57.

12. Goetghebuer T, Haelterman E, Le Chenadec J, Dollfus C, Gibb D, Judd A, et al. Effect of early antiretroviral therapy on the risk of AIDS/death in HIV-infected infants. AIDS. 2009 Mar 13;23(5):597.

13. Innes S, Lazarus E, Otwombe K, Liberty A, Germanus R, Van Rensburg AJ, et al. Early severe HIV disease precedes early antiretroviral therapy in infants: Are we too late? J Int AIDS Soc. 2014 Jan;17(1):18914.

14. WHO. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach. [Internet]. 2016 [cited 2019 Jul 7]. Available from: http://apps.who.int/iris/bitstream/10665/208825/1/9789241549684_eng.pdf

15. Chiappini E, Galli L, Tovo P-A, Gabiano C, Gattinara GC, Guarino A, et al. Virologic, immunologic, and clinical benefits from early combined antiretroviral therapy in infants with perinatal HIV-1 infection. :9.

16. Goetghebuer T, Haelterman E, Le Chenadec J, Dollfus C, Gibb D, Judd A, et al. Effect of early antiretroviral therapy on the risk of AIDS/death in HIV-infected infants: AIDS. 2009 Mar;23(5):597–604.

17. Szubert AJ, Prendergast AJ, Spyer MJ, Musiime V, Musoke P, Bwakura-Dangarembizi M, et al. Virological response and resistance among HIV-infected children receiving long-term antiretroviral therapy without virological monitoring in Uganda and Zimbabwe: Observational analyses within the randomised ARROW trial. PLoS Med. 2017 Nov;14(11):e1002432.

18. Delaugerre C, Teglas J-P, Treluyer J-M, Vaz P, Jullien V, Veber F, et al. Predictive Factors of Virologic Success in HIV-1???Infected Children Treated With Lopinavir/Ritonavir: JAIDS J Acquir Immune Defic Syndr. 2004 Oct;37(2):1269–75.

19. Barth RE, Tempelman HA, Smelt E, Wensing AMJ, Hoepelman AI, Geelen SP. Long-term Outcome of Children Receiving Antiretroviral Treatment in Rural South Africa: Substantial Virologic Failure on First-line Treatment. Pediatr Infect Dis J. 2011 Jan;30(1):52.

20. PENPACT-1 (PENTA 9/PACTG 390) Study Team, Babiker A, Castro nee Green H, Compagnucci A, Fiscus S, Giaquinto C, et al. First-line antiretroviral therapy with a protease inhibitor versus non-nucleoside reverse transcriptase inhibitor and switch at higher versus low viral load in HIV-infected children: an open-label, randomised phase 2/3 trial. Lancet Infect Dis. 2011 Apr;11(4):273–83.

21. Penazzato M, Gnanashanmugam D, Rojo P, Lallemant M, Lewis LL, Rocchi F, et al. Optimizing Research to Speed Up Availability of Pediatric Antiretroviral Drugs and Formulations. Clin Infect Dis. 2017 Jun 1;64(11):1597–603.

22. Boerma RS, Boender TS, Bussink AP, Calis JCJ, Bertagnolio S, Rinke de Wit TF, et al. Suboptimal Viral Suppression Rates Among HIV-Infected Children in Low- and Middle-Income Countries: A Meta-analysis. Clin Infect Dis. 2016 Dec 15;63(12):1645–54.

23. Teasdale CA, Sogaula N, Yuengling KA, Wang C, Mutiti A, Arpadi S, et al. HIV viral suppression and longevity among a cohort of children initiating antiretroviral therapy in Eastern Cape, South Africa. J Int AIDS Soc. 2018 Aug;21(8):e25168.

24. Chouraya C, Ashburn K, Khumalo P, Mpango L, Mthethwa N, Machekano R, et al. Association of Antiretroviral Drug Regimen With Viral Suppression in HIV-positive Children on Antiretroviral Therapy in Eswatini. Pediatr Infect Dis J. 2019 Aug;38(8):835.

25. Jaspan HB, Berrisford AE, Boulle AM. Two-Year Outcomes of Children on Non-Nucleoside Reverse Transcriptase Inhibitor and Protease Inhibitor Regimens in a South African Pediatric Antiretroviral Program. Pediatr Infect Dis J. 2008 Nov;27(11):993.

26. Fassinou P, Elenga N, Rouet F, Laguide R, Kouakoussui KA, Timite M, et al. Highly active antiretroviral therapies among HIV-1- infected children in Abidjan, Coˆ te d'Ivoire. :9.

27. Estripeaut D, Mosser J, Doherty M, Acosta W, Shah H, Castaño E, et al. Mortality and Long-Term Virologic Outcomes in Children and Infants Treated with Lopinavir/Ritonavir. Pediatr Infect Dis J. 2013 Dec;32(12):e466–72.

28. Shiau S, Abrams EJ, Arpadi SM, Kuhn L. Early antiretroviral therapy in HIV-infected infants: can it lead to HIV remission? Lancet HIV. 2018 May;5(5):e250–8.

29. Teasdale CA, Abrams EJ, Coovadia A, Strehlau R, Martens L, Kuhn L. Adherence and Viral Suppression among Infants and Young Children Initiating Protease Inhibitor-Based Antiretroviral Therapy. Pediatr Infect Dis J. 2013 May;32(5):489–94.

30. Haberer JE, Cook A, Walker AS, Ngambi M, Ferrier A, Mulenga V, et al. Excellent Adherence to Antiretrovirals in HIV+ Zambian Children Is Compromised by Disrupted Routine, HIV Nondisclosure, and Paradoxical Income Effects. PLOS ONE. 2011 Apr 21;6(4):e18505.

31. Haberer JE, Kiwanuka J, Nansera D, Ragland K, Mellins C, Bangsberg DR. Multiple Measures Reveal Antiretroviral Adherence Successes and Challenges in HIV-Infected Ugandan Children. PLOS ONE. 2012 May 9;7(5):e36737.

32. Vreeman RC, Wiehe SE, Pearce EC, Nyandiko WM. A Systematic Review of Pediatric Adherence to Antiretroviral Therapy in Low- and Middle-Income Countries. Pediatr Infect Dis J. 2008 Aug;27(8):686.

33. Sengayi M, Dwane N, Marinda E, Sipambo N, Fairlie L, Moultrie H. Predictors of loss to follow-up among children in the first and second years of antiretroviral treatment in Johannesburg, South Africa. Glob Health Action. 2013 Jan 1;6(s1):19248.

34. MISAU, INE, ICF. Inquérito de Indicadores de Imunização, Malária e HIV/SIDA em Moçambique [Immunization, Malaria and HIV/AIDS Survey in Mozambique] (IMASIDA) 2015 [Internet]. 2018 Feb [cited 2019 Jul 2]. Available from: https://dhsprogram.com/publications/publication-ais12-ais-final-reports.cfm

35. MISAU. Relatório Anual das Actividades Relacionadas ao HIV/SIDA [Annual Report of HIV/AIDS activities] - 2018. 2019 p. 100.

36. PEPFAR. Mozambique Country Operational Plan 2019 Strategic Direction Summary [Internet]. 2019 [cited 2019 Sep 23]. Available from: https://www.state.gov/pepfar/

37. WHO. WHO | What's new in treatment monitoring: viral load and CD4 testing [Internet]. [cited 2019 Jul 18]. Available from: http://www.who.int/hiv/pub/arv/treatment-monitoring-info-2017/en/

38. MISAU. Directriz, Implementação da carga viral de HIV em Moçambique. [Guidelines for HIV viral load implementation in Mozambique] [Internet]. 2015 [cited 2019 Jul 21]. Available from: http://www.misau.gov.mz/index.php/directrizes-nacionais

39. Kaplan EL, Meier P. Nonparametric Estimation from Incomplete Observations. J Am Stat Assoc. 1958 Jun;53(282):457–81.

40. WHO Anthro Survey Analyser and other tools [Internet]. WHO. [cited 2019 Sep 28]. Available from: http://www.who.int/childgrowth/software/en/

41. Ismael N, Bila D, Mabunda N, Penazzato M, Vubil A. Primary drug resistance among children infected with HIV-1 in Mozambique: Impact of maternal and neonatal prophylaxis. Virus Evol. 2018;4(Suppl.1).

42. Judd A. Early antiretroviral therapy in HIV-1-infected infants, 1996-2008: treatment response and duration of first-line regimens. AIDS Lond Engl. 2011 Nov 28;25(18):2279–87.

43. Shiau S, Strehlau R, Technau K-G, Patel F, Arpadi SM, Coovadia A, et al. Early age at start of antiretroviral therapy associated with better virologic control after initial suppression in HIV-infected infants. AIDS Lond Engl. 2017 Jan 28;31(3):355–64.

44. Asbjornsdottir KH KH, HUGHES JP, WAMALWA D, LANGAT A, SLYKER JA, OKINYI HM, et al. Differences in virologic and immunologic response to antiretroviral therapy among HIV-1 infected infants and children. AIDS Lond Engl. 2016 Nov 28;30(18):2835–43.

45. Tukei VJ, Murungi M, Asiimwe AR, Migisha D, Maganda A, Bakeera-Kitaka S, et al. Virologic, immunologic and clinical response of infants to antiretroviral therapy in Kampala, Uganda. BMC Pediatr. 2013 Mar 27;13(1):42.

46. Luzuriaga K, McManus M, Mofenson L, Britto P, Graham B, Sullivan JL. A Trial of Three Antiretroviral Regimens in HIV-1–Infected Children. N Engl J Med. 2004 Jun 10;350(24):2471–80.

47. Prendergast A, Mphatswe W, Tudor-Williams G, Rakgotho M, Pillay V, Thobakgale C, et al. Early virological suppression with three-class antiretroviral therapy in HIV-infected African infants. AIDS. 2008 Jul 11;22(11):1333.

48. Barth RE, Tempelman HA, Smelt E, Wensing AMJ, Hoepelman AI, Geelen SP. Long-term Outcome of Children Receiving Antiretroviral Treatment in Rural South Africa: Substantial Virologic Failure on First-line Treatment. Pediatr Infect Dis J. 2011 Jan;30(1):52–6.

49. Jaspan HB, Berrisford AE, Boulle AM. Two-Year Outcomes of Children on Non-Nucleoside Reverse Transcriptase Inhibitor and Protease Inhibitor Regimens in a South African Pediatric Antiretroviral Program: Pediatr Infect Dis J. 2008 Nov;27(11):993–8.

50. Van der Linden D, Hainaut M, Goetghebuer T, Haelterman E, Schmitz V, Maes P, et al. Effectiveness of a early initiation of protease inhibitor-sparing antiretroviral regimen in human immunodeficiency virus-1 vertically infected infants. Retrovirology. 2008 Apr 9;5(1):P24.

51. Tagarro A, Chan M, Zangari P, Ferns B, Foster C, De Rossi A, et al. Early and Highly Suppressive Antiretroviral Therapy Are Main Factors Associated With Low Viral Reservoir in European Perinatally HIV-Infected Children. JAIDS J Acquir Immune Defic Syndr. 2018 Oct 1;79(2):269.

52. Chadwick EG, Pinto J, Yogev R, Alvero CG, Hughes MD, Palumbo P, et al. Early Initiation of Lopinavir/Ritonavir in Infants Less Than 6 Weeks of Age: Pharmacokinetics and 24 Week Safety and Efficacy. Pediatr Infect Dis J. 2009 Mar;28(3):215–9.

53. Reitz C, Coovadia A, Ko S, Meyers T, Strehlau R, Sherman G, et al. Initial Response to Protease-Inhibitor-Based Antiretroviral Therapy among Children Less than 2 Years of Age in South Africa: Effect of Cotreatment for Tuberculosis. J Infect Dis. 2010 Apr 15;201(8):1121–31.

54. Chan MK, Goodall R, Judd A, Klein N, Chiappini E, Klimkait T, et al. Predictors of faster virological suppression in early treated infants with perinatal HIV from Europe and Thailand. AIDS [Internet]. 2019 Feb 1 [cited 2019 Aug 7]; Available from: http://doi.org/10.1097/QAD.0000000000002172

55. Tagarro A, Chan M, Zangari P, Ferns B, Foster C, De Rossi A, et al. Early and Highly Suppressive Antiretroviral Therapy Are Main Factors Associated With Low Viral Reservoir in European Perinatally HIV-Infected Children: JAIDS J Acquir Immune Defic Syndr. 2018 Oct;79(2):269–76.

56. MEYERS T, YOTEIENG M, KUHN L, MOULTRIE H. Antiretroviral Therapy Responses among Children Attending a Large Public Clinic in Soweto, South Africa. Pediatr Infect Dis J. 2011 Nov;30(11):974–9.

57. Humphrey JM, Genberg BL, Keter A, Musick B, Apondi E, Gardner A, et al. Viral suppression among children and their caregivers living with HIV in western Kenya. J Int AIDS Soc. 2019 Apr;22(4):e25272.

58. Wilson D, Keiluhu AK, Kogrum S, Reid T, Seriratana N, Ford N, et al. HIV-1 viral load monitoring: an opportunity to reinforce treatment adherence in a resource-limited setting in Thailand. Trans R Soc Trop Med Hyg. 2009 Jun;103(6):601–6.

59. Simoni JM, Montgomery A, Martin E, New M, Demas PA, Rana S. Adherence to antiretroviral therapy for pediatric HIV infection: a qualitative systematic review with recommendations for research and clinical management. Pediatrics. 2007 Jun;119(6):e1371-1383.

60. Haberer J, Mellins C. Pediatric Adherence to HIV Antiretroviral Therapy. Curr HIV/AIDS Rep. 2009 Nov;6(4):194–200.

61. Achan J, Kakuru A, Ikilezi G, Mwangwa F, Plenty A, Charlebois E, et al. Growth Recovery Among HIV-infected Children Randomized to Lopinavir/Ritonavir or NNRTI-based Antiretroviral Therapy. Pediatr Infect Dis J. 2016 Dec;35(12):1329.

62. Verweel G, van Rossum AMC, Hartwig NG, Wolfs TFW, Scherpbier HJ, de Groot R. Treatment With Highly Active Antiretroviral Therapy in Human Immunodeficiency Virus Type 1-Infected Children Is Associated With a Sustained Effect on Growth. PEDIATRICS. 2002 Feb 1;109(2):e25–e25.

63. Muenchhoff M, Healy M, Singh R, Roider J, Groll A, Kindra C, et al. Malnutrition in HIV-Infected Children Is an Indicator of Severe Disease with an Impaired Response to Antiretroviral Therapy. AIDS Res Hum Retroviruses. 2018;34(1):46–55.

64. Aurpibul L, Puthanakit T, Taecharoenkul S, Sirisanthana T, Sirisanthana V. Reversal of Growth Failure in HIV-Infected Thai Children Treated with Non-Nucleoside Reverse Transcriptase Inhibitor–Based Antiretroviral Therapy. AIDS Patient Care STDs. 2009 Nov 12;23(12):1067–71.

65. Shiau S, Arpadi S, Strehlau R, Martens L, Patel F, Coovadia A, et al. Initiation of Antiretroviral Therapy Before 6 Months of Age is Associated with Faster Growth Recovery in South African Children Perinatally Infected with Human Immunodeficiency Virus. J Pediatr. 2013 Jun 1;162(6):1138-1145.e2.

66. Gómez LA, Crowell CS, Njuguna I, Cranmer LM, Wamalwa D, Chebet D, et al. Improved Neurodevelopment After Initiation of Antiretroviral Therapy in Human Immunodeficiency Virus–infected Children. Pediatr Infect Dis J. 2018 Sep;37(9):916.

67. Whitehead N, Potterton J, Coovadia A. The neurodevelopment of HIV-infected infants on HAART compared to HIV-exposed but uninfected infants. AIDS Care. 2014 Apr 3;26(4):497–504.

68. McHenry MS, McAteer CI, Oyungu E, McDonald BC, Bosma CB, Mpofu PB, et al. Neurodevelopment in Young Children Born to HIV-Infected Mothers: A Meta-analysis. Pediatrics. 2018 Feb 1;141(2):e20172888.

CHAPTER 7

Optimizing adherence and psychosocial support model of care for caregivers of HIV infected infants: descriptive case series from southern Mozambique

Optimizing adherence and psychosocial support model of care for caregivers of HIV infected infants: descriptive case series from southern Mozambique

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Abstract

Background. Administration of antiretroviral treatment (ART) as recommended is critically important for HIV-infected infants for them to achieve and sustain viral suppression and is dependent upon the caregiver. During the first few months after diagnosis and treatment initiation, caregivers are in need of support from health workers and lay staff to address potential barriers to optimal adherence. Limited evidence exists about best practices of psychosocial support tailored to infants' caregivers. The aim of the study is to analyze whether the standard adherence and psychosocial support (APSS) package of care applied to infants' caregivers in Mozambique can efficiently identify factors influencing caregiver adherence behavior and determine whether they correlate with viral response of infants starting ART at one month of life.

Method. This is a case series analysis based on review of infants' files for results of viral load measurements, caregiver's questionnaires and first APSS sessions. Qualitative content analyses of themes related to adherence behavior of caregivers were performed and compared with infants' viral response during follow up.

Results. Thirty-one infants started treatment at one month of age. Reports of first APPS visit of 31 caregivers and 26 questionnaires were analyzed. Nine of 31 infants had good virologic response while the remaining 22 were poor virus controllers. With the exception of problems in administrating the drugs identified among majority of mothers of infants with poor viral response, the APSS package of care did not clearly and timely differentiate elements peculiar to infants who had a poor viral response.

Conclusions. To build a strong adherence behavior among infants' caregivers, the APSS model has to move from a managed care to a patient-centered model focusing on social, economic and inter-personal matters affecting caregivers and taking into consideration family, community, society and health facility context. Mobilization of family members and ART Directly Observed Therapy at home through "mentor mothers" are suggested strategies to invest on and reduce the burden on health system. Additional research is needed to evaluate the continuum of APSS care during infancy and childhood and determine the family's perspective on infant HIV treatment and long terms goals for a healthy life.

Key words: adherence, HIV infected infants, psychosocial support, caregivers, viral suppression

Introduction

In 2006 WHO recognized and proposed decentralized service delivery and standardized simplified care and treatment protocols as the best approach to reach a larger number of patients living with HIV in developing countries (1). Evaluation of effectiveness of this approach showed that integration of HIV care at primary care level and task shifting among staff increased program efficiency offering high-quality and cost-effective care to more patients than a centralized model (2–6). Since then, based on experience and lessons learned from program implementation, service delivery recommendations have evolved (7–10). For pediatric HIV care, the evidence after decentralization to primary care showed increased numbers of children on antiretroviral treatment (ART) with lower rates of attrition and mortality (11,12).

In Mozambique, decentralization of patient care from secondary and tertiary hospitals to primary health care facilities and task shifting among health staff started in 2007 (13). All these innovations resulted in expansion of ART care from less than 100 health facilities in 2005 to 1455 in 2018 as well as task shifting of HIV patients management from specialized doctors to medical assistants and nurses at all levels of care (13–15). Management of pediatric HIV patients from pediatricians to medical doctors and subsequently to medical assistants was a success (11,16) allowing access to life-saving treatment to more than 86.000 children at the end of 2018 (14,17).

To respond to the increasing patients' psychosocial needs, adherence and psychosocial support (APSS) care followed the same approach of clinical care and APSS care shifted from psychologist to lay counsellors, peer educators, home based-care volunteers and recently to patients themselves, for example expert patients and mentor mothers (12,13,18). However, to maintain optimal standard of care in a decentralized model and not compromise patient outcomes, continuous support to less specialized health staff, especially lay counsellors, needs to be part of the system innovation (12,19,20). Consolidation of new knowledge and abilities in order to provide quality care and at the same time conditions for a functional referral service for complex cases, especially children, has to be created and sustained (19,21,22).

In Mozambique, APSS package has been evolving since the beginning of the HIV program, aiming at patient's support from HIV pre-test and post-test counselling, through ART adherence and retention during follow up (13,23). APSS actors are clinicians, psychologists, lay counsellors, peer educators and patients living with HIV interacting with patients at different stages of the continuum of care. They use a package of APSS and 'positive prevention' to assist patients in optimal HIV management in 'day-to-day life' and for assessment of adherence risk factors and healthy living habits (23,24).

Lately, APSS performance quality indicators have been developed and are part of the national quality improvement strategy for the HIV program (23).

The ultimate goal and main challenges are to reach and sustain viral suppression in patients on ART, a task that can be achieved, in the absence of viral resistance, if patients are adherent to treatment. This goal is indeed more critical in infants as morbidity and mortality are higher in the first months of life (25). Many studies described the best way to measure adherence among caregivers (26–29) and barriers to adherence in older children (30–34), adolescents and health staff. However, limited evidence exists about ART adherence barriers among caregivers of infants, and more importantly, on best practices of psychosocial support tailored for them other than family centered approach (35).

With viral load (VL) monitoring, adherence to ART can be measured by looking at the test result. However, the first VL result is available 6 or more months after ART initiation and cannot substitute the invaluable APSS assessment. The first few months after diagnosis and treatment initiation constitute a critical phase in which caregiver needs support from health and lay staff to address potential barriers to adherence with proper solutions for the benefit of the infant. In Mozambique there is no specific APSS package tailored to caregivers of infants as most emphasis is given to older children and adolescents disclosure (23). If we consider that ART must be started as early as possible after infection is diagnosed and is for a lifetime, we need to understand the nature of adherence behavior among caregivers, anticipate potential threats to optimal compliance and be prepared to find solutions to help caregivers with their infants. To our knowledge no studies have evaluated the quality of APSS sessions offered to caregivers of HIV infected infants.

The aim of the study is to analyze whether the standard APSS package of care applied to infants' caregivers can efficiently identify factors influencing caregiver adherence behavior and determine if those factors correspond to viral response trajectories of infants starting ART at one month of life. Our question is whether a different psychosocial support package is needed for caregivers of HIV perinatally infected infants to build an adherence behavior that will give our youngest patients an opportunity to achieve and maintain viral suppression.

Methods

Study setting and population

This study was conducted at Maputo Provincial Hospital, in Matola district, Maputo Province, southern Mozambique. Matola is a district with a population of 1.616.000 people, 48% being

women between 15-49years (36) and an HIV prevalence of 22.9% (37); has a limited area with urban characteristics, in that the vast majority is composed of peripheral neighbourhoods, far from the hospital.

Patients included in the study were caregivers and HIV perinatally infected infants who started antiretroviral treatment at one month of age and were followed for two years. All caregivers had an adherence and psychosocial support session (APSS) at recruitment with the nurse at Mother and Child Health Clinic (MCH) and, 15 days later, at the first visit with the psychologist at Matola Provincial Hospital, followed by monthly APSS sessions.

The study started in 2017 and is part of a primary cohort study called 'Immunity and HIV persistence in perinatal HIV infection', funded by the National Institute of Health NIH (AI127347), developed in collaboration with *Instituto Nacional de Saúde*, Mozambique, and *Fundação Ariel Glaser contra o SIDA Pediatrico*, University of Miami USA and *Ospedale Bambino Gesú*, Rome, Italy.

Study design and data collection

This is a case series analysis based on review of infants' file where results of viral load measurements were reported as well as caregiver's entry questionnaire (Annex 1: questionnaire) and first psychosocial support session with the psychologist. Collection and analysis of the first APSS visit notes and answers to the questionnaire was performed using qualitative content analysis to identify themes related to adherence behavior among caregiver and compared with infant's viral response trends.

Entry study questionnaire was applied to infant's caregiver to identify conditions possibly related to adherence risk as well as to determine potential elements to support caregiver. Information that was collected and analyzed included the following: mother's discontinuation of ART in the past, mother's education, number of people living in the same household, infant's ARV administration, assistance if any in administering the ARV drugs, difficulties encountered in child's ingestion of ARV, times caregiver forgot giving ARV, attendance of traditional healer, child serostatus disclosure within family or friends.

In addition, APSS session was based on the proposed themes of the standard Ministry of Health (MOH) APSS package of care applied to HIV infected patients. Themes and related questions are described as follows. *HIV related questions*: basic knowledge of HIV including prevention and disease progression, acceptance of HIV status, belief in ART efficacy, fear of adverse events and management, pill burden. *Adherence to ART*: regularity in taking medication (time and dose),

adherence needs, plan of adherence. *Health related questions:* feeling sick, depression, anxiety, alcohol or drug abuse, sexual behavior and condoms use, sexual transmitted disease, family planning, safe pregnancy. *Family, psychosocial and economic related questions:* violence, support, disclosure to partner and family, food availability, transport issues, stigma and discrimination. *Community related questions*: traditional medicine, cultural factors, stigma and discrimination, need for community support, participation in support groups. *Questions focusing on children care*: person in charge of administering the medication, disclosure, time and dosing of ART.

Psychosocial support framework

We designed an analytical framework which describes factors affecting caregiver's adherence and care seeking behavior, taking into account elements that in our context are part of day-to-day caregiver's life and standard adherence risk elements defined in the MOH APSS package of care (Fig. 1). In fact, caregiver's adherence behavior is determined by several psychosocial and economic factors acting in four different dimensions: the caregivers experience, which are the personal self, the household, the community and the health facility dimensions (32). Response to all those factors build an adherence behavior which is dynamic according to continuous interactions among external and internal factors. All the elements in the four dimensions of the framework may play positive and negative, expected and unexpected effects on caregiver's adherence behavior.

Fig.1 Analytical framework of factors affecting caregiver's adherence behavior (developed by the author inspired by https://www.freepikcompany.com)

Dimensions of the framework

The personal-self dimension includes the following key elements: education, self-esteem, confidence, fear of disclosure, knowledge about HIV prevention and care, resilience, habits such as diet, substance abuse, culture, traditions, religion among others (38–41).

The household dimension includes the following key elements: number and type of people living in the same house such as partner, other children or adolescents, mother, mother in law, sisters, brothers, aunts. They determine daily tasks and housekeeping workload but may also serve as a dependable support system. Family members' knowledge and attitude towards HIV/AIDS affects self-disclosure, fear of stigma and discrimination, fear of domestic violence. Other key elements are norms and practices within marriage, participation in family decisions, income and job that may

affect economic independence and travel to the HF (39,42). In our context, as in many other African countries, decisions regarding health and family matters are taken by the partner or by the mother-in-law, thereby greatly limiting a woman's ability to openly discuss health matters and disclose HIV status (43–45). We believe that elements of self-dimension such as culture and literacy combined with household and family dimension have major impact on determining caregiver's adherence behavior.

The community dimension includes the following key elements: the neighborhood, neighbors, friends, church, traditions, work environment, support groups. They all affect disclosure, health and help seeking behavior and are at the same time a potential source of stigma, discrimination and support.

The health facility dimension includes the following key elements directly related to health staff and structural elements. Among health staff, competence and knowledge of HIV management and APSS package for caregivers and infants, confidentiality, attitude towards the patient such as empathy or judgement (46–48); education of patients with relation to this disease, team work between clinicians and lay counselors or psychologists are key components for building adherence behavior. Structural elements can include the waiting time before the visit, room privacy, availability of staff such as lay counsellors or psychologists, availability of drugs, implementation of adherence strategy such as family approach, mentor mothers or peer educators and health facility-based support groups.

Data analysis

Data have been qualitatively analyzed with reference to the framework elements and to the APSS package of care recommended by the MOH. We examined whether the APSS standard of care had been applied to caregivers and identified potential psychosocial factors influencing caregiver's adherence behavior. Comparison between APSS baseline findings and infants' viral load response was done to see if factors identified in the first visit corresponded with poor or good viral response and thus adherence.

For the purpose of this analysis, virologic response was defined as good or poor. Good virologic response is when virologic suppression (plasma HIV-RNA <1000copies/ml) was achieved and maintained in all the subsequent measurements. Poor virologic response is when infants never achieve viral suppression, or when, after achieving viral suppression have one or more measurement above HIV-RNA plasma of 1000 copies/ml during follow up measurements. The

threshold of 1000 copies/ml was chosen according to WHO and MOH national guidelines which define viral suppression as a value of viral load below 1000 copies/ml (49).

Ethical considerations

The study was approved by the Ministry of Health, the National Bioethics Committee (IRB00002657, reference 102/CNBS/2016), the University of Miami IRB and Ospedale Bambino Gesú IRB. Caregivers agreed to participation in the study and signed an informed consent.

Results

Characteristics of participants. Sociodemographic characteristics of mother's and children are described in Table 1. A total of 31 infants (61% female) were followed for a median follow up time of 18 months; 1 infant was transferred to another province and later died, 2 children died during follow up and 3 became orphans. The median age of mothers was 28 years (IQR 11), majority (93%) were literate, more than half (55%) were living with the partner, almost all (90%) disclosed their serostatus within the family. The majority (77%) did not have a permanent job, less than half of partners (43%) were infected with HIV, while 6 mothers did not know their partner's serostatus. Twelve mothers lived in nuclear family (baby with mother and/or father), while 9 mother-baby pair lived in a household with more than one adult.

Virologic response among infants. Nine infants had good virologic response and 22 had poor virologic response. Among infants with poor response: 12 never achieved viral suppression, 10 reached viral suppression but had a rebound within 6 months after suppression. Of those who rebounded, 6 again achieved viral suppression (Fig 2, 3).

Adherence and psychosocial support visits report. A total of 31 first APSS visits reports and 26 entry questionnaires to caregivers were available and analyzed; 3 mothers died and were not interviewed. All caregivers attended scheduled appointments: 50% of children returned on the scheduled day in both groups, mean delay was around 3 days in both groups, with a maximum of 30 days for few cases in both groups.

Main psycho-social elements reported in files and compared among the two groups of infants with good and poor virologic response

Distance from Hospital

Majority of children of our cohort, lived in the most peripheral neighbourhood of Matola district, however children with good and poor virologic response did not differ in terms of distance from home to the Hospital, majority were living not so close to the hospital, and 40% from areas relatively close to Matola city center and the hospital. It is of note that, in the context of the study, participants were reimbursed for transportation costs.

Disclosure of HIV infant serostatus and family support

Majority of mothers (23), 16 in the group of poor viral response, reported that they disclosed child status to family members or friends. Nevertheless, few records in both groups detailed whether any discussion happened about difficulties faced by the caregiver after having disclosed the situation. Irrespective of infant's viral response, few records explicitly indicate lack of family support (6/31) and very few reported any discussion on discrimination issues at home or within the community.

> *'The husband's family where mother and baby live is not aware of the infant's and couple serostatus.' (Poor VR)*
>
> *'The mother indicates she needs to disclose her serostatus to her partner; while the mother-in-law, with whom she lives, knows she has anemia' (Good VR)*
>
> *'The father lives in South Africa, he is not aware of the child serostatus and he is seronegative' (Poor VR)*
>
> *'According to the mother, the father is HIV positive and on ART since 2012, she found the hospital card, but he didn't disclose to the wife. However, he is supporting economically and also in giving drugs to the child' (Good VR)*

Administration of antiretroviral drugs to infant

Majority (17) of mothers, 12 of the group of infants with poor virologic response, reported they shared responsibility with other family member to administer ART to the infant. However, with the exception of two twin sisters, mother was the only caregiver present at the first APSS and subsequent visits for both groups of infants. Fourteen caregivers reported problems with administration of drugs: 10 (32%) referred vomits, 9 being in the group of poor response; 4 of them reported also delay with respect of chosen time of administration; 1 mother of an infant with poor response reported giving the wrong dose; 3 mothers referred they forgot giving the medication, 2 of them being in the poor response group. Nine mothers referred no problems at all, 8 being of

infants with poor response. Occurrence of adverse events due to new medication were poorly reported in infant's files (only in 2).

'The child lives with parents, mother HIV infected and father not HIV infected. Father helps with the medication, check the time using mobile phone. Mother refers some delays, 10-15 minutes, in the evening dose'. (Poor VR)

'The aunty refers diffficulties in giving the correct dose at the scheduled time. Diagnosis: poor adherence' (Poor VR)

'Mother refer no delay nor skipping medication, just vomits sometimes. She has disclosed her and infant's serostatus to the father, who is HIV negative but always help' (Poor VR)

'Mother does not count on partner's support in giving the medication to the baby' (Poor VR)

'Father is helping in giving the medication in the morning but in the afternoon he is at work' (Poor VR)

'The mother refers the baby is taking all medication without spitting' (Good VR)

Assessment of adherence and adherence plan

The psychologist documented adherence and a plan to strengthen counselling and adherence for 16 infants, 10 of them with poor viral response, which corresponds to less than half of children who lately had poor virologic control (10/22). While 6 of 9 (67%) infants who had subsequent good viral response had an adherence plan in the file. No mention of adherence plan was found in 50% of children of the cohort.

'The mother did not bring the medication with her to check how many pills remained' (Poor VR)

'I counselled the mother to ask the father to support giving medication' (Poor VR)

'The mother refers good adherence to treatment even if sometimes she gives the medication with delay' (Poor VR)

'Diagnosis of child at risk of adherence' (Poor VR)

'The mother said that she will arrange someone to stay with the baby when she will return to work' (Good VR)

Traditional healer's frequentation

The habit to visit traditional healer was frequently reported: 42% (13/31) of caregivers reported their infant took traditional medication and it was more frequently reported in infants who had

good response (5/9) compared to those with poor response (8/22). In five infants there was no report about traditional medicine.

> *'The mother refers she is giving the 'moon remedy' because the mother-in-law, is insisting and checking on her. The mother-in-law is not aware of mother and infant's serostatus' (Poor VR)*

Mother's history of ART and virologic control

Regarding mother's history of ART we found that mothers of infants with poor response were on ART for a shorter time compared to mothers of infants with good virologic control. More mothers in the group of infants with poor viral control, 13 versus 4, reported to have interrupted ART before delivery and more mothers of this group, 10 versus 1, had also poor virologic response during follow up (Tab. 2). All this information though was not reported in the psychologist note, but gathered from the questionnaire and mother's file.

Mother mental status and stigma

With the exception of one mother of an infant with poor viral response who was diagnosed with depression, no information exploring mother's anxiety or depression, situations of stigmatization, gender-based violence, substance abuse, social issues in the family, nor linkage to support groups was reported in infant's file, suggesting possible difficulty in exploring these conditions.

HIV basic knowledge

No report in infants file was found about discussion of HIV basic knowledge questions suggested in the MOH APSS checklist.

Discussion

Viral response depends on regular adherence to medication and if the virus does not develop resistance, undetectable viremia can be sustained as long as the medication is taken (50). The striking evidence from our study is that few infants had a good viral response and that viral response pattern varied a lot among all infants. In fact, in our cohort, we had infants who reached and sustained viral suppression during the entire follow up period, infants who never reached viral suppression, infants who reached viral suppression, had a rebound and never controlled the virus again and finally infants who had a rebound and later controlled the virus (Fig 2-3). This shows how

variable and unpredictable the viral response is among infants, in a short follow up period and in a crucial moment of infant's life for healthy development. Frequent rebound after viral suppression has been described in a South African cohort of infants (51) and reflects changes in caregiver's adherence behavior. Dynamic psychosocial factors, especially within family and community, affected and changed adherence pattern even among those caregivers who initially were compliant and whose infants sustained viral suppression for a certain period.

To our best knowledge, there are no studies describing adherence behavior among caregivers of infants nor evidence of best APSS approach for this population, while most studies evaluated barriers among children and adolescents (30,31,52–54). In the first APSS session it was possible to identify some infants at risk of poor adherence. In fact, mothers of majority of infants with poor viral response referred difficulties in administering the medications from the beginning, such as infant refusal, vomiting, delay in dose administration or giving the incorrect dose. In another study, the same factors have been found associated to higher risk of poor adherence (55). All these reports are the first alarm and must be considered major adherence risk factors when approaching infants. Showing the mother how to prepare the drug and give it to the baby during the APSS session, should be part of the standard of care for infants. Learning from the experience of TB program (56), a Directly Observed Therapy (DOT) strategy for administering ART, already evaluated and proved to increase adherence (57), could be suggested for programs that are implementing mentors mothers. ART DOT at health facility followed by ART DOT at home for one or two weeks under the supervision of a trained mentor mother should be considered for all newly infected infants or in case caregiver is reporting any difficulties in administering the medication. Mentor mothers living with HIV are trained to support other pregnant and breastfeeding mothers living with HIV and assist them in finding resources within the family and community to cope with the new condition (18). The strategy has been shown to be effective in improving adherence in the PMTCT cascade (18) and in Mozambique it has been rolled out since 2018. Moreover, scale up community ART distribution through mobile clinic, recommended by WHO (8) and ongoing in Mozambique, may be paired with the cost-less component of mentor mothers and benefit infants' caregiver.

Except among very few orphaned or abandoned infants, mother was the primary caregiver for almost all children. Even if majority of them reported that they had someone at home to help administering the medication, counselling was not directly given to other family members, which could have helped in better management of infant at home (58–60). Disclosure to family and partner was high in mothers of both groups, but fathers rarely appeared for the APSS session with the

spouse. Encouraging partner's engagement in infant's care requires a different and stronger program response. Male engagement strategy was launched in 2018 in Mozambique (61), however, national data show 57% testing among partners of pregnant women at ANC, 33% in Maputo Province (14).

Multiple caregivers, often ignoring baby's status, job related issues are factors revealed by mothers who were not adherent to ART, and were also reported by other authors more commonly adversely influenced adherence (62). It has been shown that the risk of being non adherent was three times higher when the mother was the only one to know the serostatus of the infant (34). In our study, despite majority of mothers referred to having disclosed the infant's serostatus within the family, it appears that disclosure alone had limited contribution to good adherence and achievement of good viral response. Lessons learned from the family centered approach in the PMTCT setting and HIV clinic (63–67) can be applied to adapt the APSS model tailored to families and caregivers of infants. Two key elements, not mentioned in the APSS report, where the duration of ART among mothers and their viral load test results. Looking at the infant's and mother's files we found that majority of our mothers started ART before or during pregnancy (Tab. 2) having being supposedly exposed to several counselling sessions along the continuum of care at MCH or at ART clinics. We also found that almost all mothers with poor viral response had infants with poor viral response. This shows once again that it is crucial to evaluate infant's adherence and viral response in light of mother's viral load test result (68,69).

Another element poorly explored in the APSS session of our cohort, but very important for the infant's care, was the mother's mental health status. Perinatal depression is a frequent condition with a reported prevalence of 18% in Sub Sharan Africa (70–72), affecting also pregnant and breastfeeding women living with HIV and found associated with poor ART adherence (70,73). A study in Brazil found that components such as mental health, cognitive status and quality of life were important predictors of adherence among caregivers although of older children than ours (27). Additional evidence have been published about the negative psychosocial impact on mothers of early HIV diagnosis in her infant and how proper counseling and support group participation was key to cope with the new condition (74). Assessment and management of mental health, in particular depression is a WHO recommendation; an easy tool to screen mother's mental health should be developed and included in the mother's APSS package (9).

Although messages emphasizing the importance of ART for infant's health were reiterated at every encounter, disclosure of barriers to adherence was a lengthy process, obtained during the course of

several visits, which reflects mothers' difficulties in openly sharing with health staff all challenges faced in her daily life and in giving the medication regularly (46). In our cohort, adherence was self-reported and documented in files of almost all the patients by the psychologist. However, this method to measure adherence is known to be inaccurate and to bear no correlation with viral response rate (27,75–77). Reconciliation of medicines or monitoring pharmacy visits has shown to be a better indicator of adherence (26,75). However, in our context, adherence to a scheduled visit, including drug pick-ups, were not related to adherence and need to be interpreted with caution as retention into care does not necessarily reflect adherence to treatment. Our results highlight the need to go beyond this approach towards promoting and building a 'safe and confidential' environment to enable patients to honestly share personal life details and struggles with health providers (46).

Viral load (VL) measurement is the test of choice to monitor response to ART and, indirectly, adherence (9). In Mozambique is available since 2016 (49) but uptake has been slow. Moreover, VL may be difficult to interpret, especially by medical assistants and MCH nurses, limiting this important tool to be properly used for the benefit of patients. By looking at viral response trajectories we have presented (Fig.2-3), clinicians, psychologists and counsellors can identify cases at risk of poor adherence and promptly tailor a specific approach based on viral response pattern, thereby relying also on a biomarker indicator for identifying difficult cases. In our guidelines, in case VL is above 1000 copies/ml, APSS sessions remain scheduled once a month for three months before repeating the test, while other experiences in South Africa described intensified APSS visits once a week for 4 weeks (78). In infants time is limited to influence AIDS free survival, mortality and morbidity are higher than in any other age (25). It is thus necessary and justified to respond quickly and differently from the adult patients. Improved adherence will also reduce potential development of drug resistance with preservation of first line ARVs for younger patients which are limited (79).

The goal of APSS care must be to enable caregiver to manage an infected HIV infant and to openly ask for support when needed. The process needs to be continuous and attentive to dynamic of family and community. In a PHC setting, standardizing package of care such as the Integrated Management of Childhood Illnesses (80), has shown to be effective for non-specialized staff in managing common childhood clinical conditions, but we believe that for management of HIV infection and psychosocial support of infants and children a different approach is needed. Current MOH guidelines for infants who start ART recommend a monthly psychosocial support visit during the first six months and then every 3 months for the first year on ART. In most health facilities, a

trained lay counsellor, leads the APSS session using a standardized checklist of potential barriers to compliance to identify patients at risk of poor adherence and to convey standardized messages. Such abilities are difficult to apply in the pediatric population and infants in particular and, other than asking who is giving the drugs and, in case of older children, if disclosure of HIV status has been done, there is no specific checklist to apply to caregivers of infants.

Our analysis suggests that APSS sessions following a standardized care pattern were lacking focus on many relevant social, economic and personal matters that may affect caregivers' therapy, adherence and eventually infant's viral response. Only few cases recorded thoughtful discussions beyond HIV disclosure and medication adherence. Such particular issues would be missed if the APSS models rely mostly on a managed care approach (60,64). With exception of problem identification when administrating medicines, the APSS model as it has been implemented in our cohort, did not help the psychologist to clearly and timely differentiate infants who had a poor viral response. The complexity of the situation mothers face in resource-poor context urges for re-thinking and adapting the APSS approach and design a different checklist for infants and younger children. Clinicians, psychologists and lay counsellors must be mentored to develop the skills to investigate and identify changes and exploring situations beyond the APSS check list, putting the patient-caregiver in the center of the counselling session.

Finally, the model of APSS at the facility level needs to be complemented with social support incentives at the community level (60,64), although confidentiality issues, cultural norms and similar barriers may challenge such an approach (59).

The study has a few limitations. Being a qualitative study of case series, it does not allow us to generalize our findings, although we believe that it gives key elements to reflect around a very critical component of care influencing outcomes of infants and children on ART. Another limitation of the study, knowing that adherence factors change over time, is that our data analyzed the first APSS session, when it was possible to identify factors present at the time of the first visit only. However, we think that the first evaluation is crucial and needs to be as accurate and as complete as possible in order to promptly identify potential risk factors and act on them quickly. Moreover, reports from caregivers may present social desirability bias; depending on the relationship with the interviewer, parents tend to respond in a favorable and expected way so as not to be judged, leading to over-report of good adherence and under reporting problematic situations or undesirable behaviors.

Further studies are crucial to evaluate the continuum of APSS care during the entire follow up and to obtain a more robust evidence of how factors related to adherence are changing over time and how they can effectively be addressed.

Conclusions

Achieving and sustaining viral suppression is the ultimate goal in infants and children living with HIV and depends mainly on adherence to ART, a challenge caregivers face every day. The APSS model has to move from a managed care- to a patient-centered model, focusing on interplaying social, economic and personal matters affecting caregivers in different contexts such as family, community, society and health facility. Thus clinicians, psychologists, lay counselors, mentor mothers and patients living with HIV, have to work in synergy in order to tailor support to mothers and their infants using an integrated and comprehensive APSS package specific for them. Mobilization of family members and ART DOT at home through mentor mothers, where available, should be one of the strategies to consider to improve engagement in HIV care and reduce the burden on health system.

Additional research is also needed to determine caregivers and family's perspective on long term goals for infant HIV treatment success. Additional studies are advisable to evaluate the continuum of APSS care during infancy and childhood to assist in developing a better approach for this age groups.

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Tables and Figures

Table 1: Mothers characteristics at enrolment

Mother's characteristics	HIV infected infants N =31
Mother's Age (yrs)	
Median	28 [11]
Mother alive	
Yes	28 (90.3)
No	3 (9.7)
Marital status	
Single	13 (42)
Married/living together	17 (54.8)
Missing	1 (3.2)
Disclosure of serostatus to family	
Yes	28 (90.3)
No	2 (6.5)
Missing	1 (3.2)
Permanent job	
Yes	4 (13)
No	24 (77.4)
Missing	3 (9.6)
Fixed income	
Yes	17 (54.9)
No	11 (35.4)
Missing	3 (9.7)
Education	
No education	2 (6.45)
Primary	9 (29.03)
Secondary	17 (54.83)
Missing	3 (9.67)
Partner HIV positive	
Yes	12 (38.7)
No	10 (32.2)
Don't know	6 (19.3)
Missing	3 (9.6)

Tab.2 Mothers antiretroviral treatment (ART) and viral load (VL) response profile per infants' viral response

Mothers ART history and VL response	Good viral response n=9 (%)	Poor viral response n=22 (%)
Time on ART before delivery		
<3months	1 (11%)	3 (14%)
3m-9m	4 (44%)	12 (55%)
>9m	4 (44%)	5 (23%)
Missing	0	1
Self-report ART interruption		
Yes	4 (44%)	13 (59%)
No	4 (44%)	9 (41%)
Missing	1 (11%)	0
VL during follow-up		
Undetectable	5 (56%)	10 (45%)
Detectable	1 (11%)	10 (45%)
Missing (mother Died or Left Baby)	3 (33%)	2 (9%)

Good viral response= infants who reached viral load suppression and never had viral rebound
Poor viral response= infants who never reached viral load suppression or reached viral load suppression and had a rebound.

Fig.2: Individual trajectories of viral load of infants who reached viral suppression during 18 months follow-up

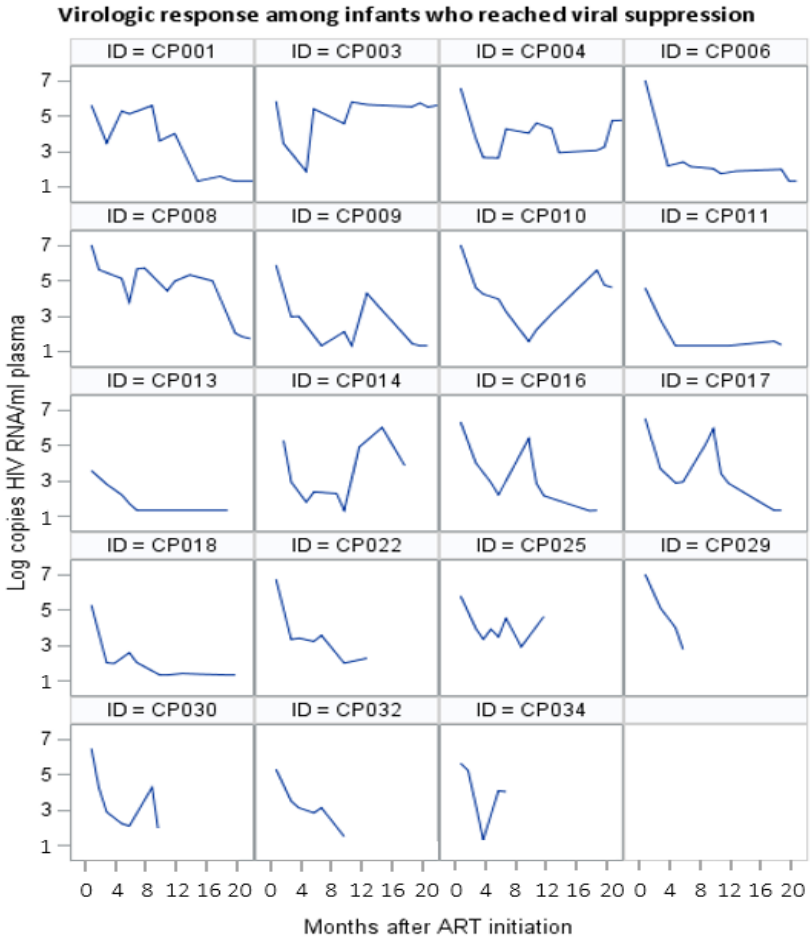
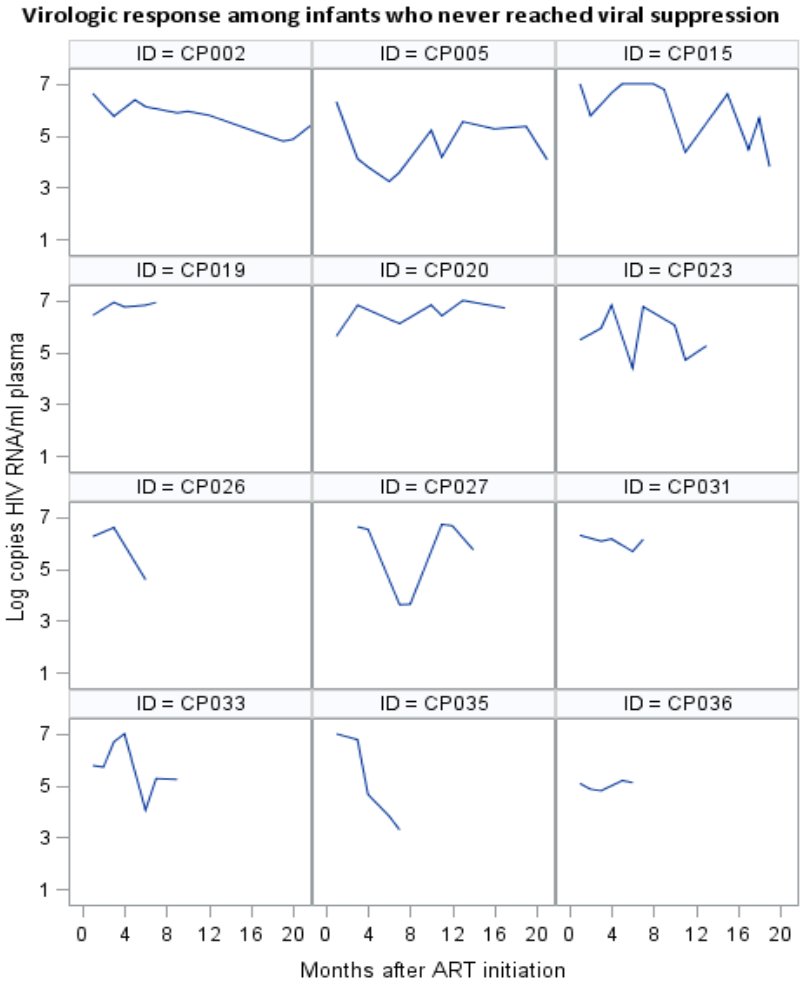


Fig. 3: Individual trajectories of viral load of infants who never reached viral suppression during 18 months follow-up



References

1. Gilks CF, Crowley S, Ekpini R, Gove S, Perriens J, Souteyrand Y, et al. The WHO public-health approach to antiretroviral treatment against HIV in resource-limited settings. The Lancet. 2006 Aug 5;368(9534):505–10.

2. Callaghan M, Ford N, Schneider H. A systematic review of task- shifting for HIV treatment and care in Africa. Hum Resour Health. 2010 Mar 31;8(1):8.

3. Suthar AB, Rutherford GW, Horvath T, Doherty MC, Negussie EK. Improving antiretroviral therapy scale-up and effectiveness through service integration and decentralization. AIDS. 2014 Mar;28:S175.

4. Ferradini L, Jeannin A, Pinoges L, Izopet J, Odhiambo D, Mankhambo L, et al. Scaling up of highly active antiretroviral therapy in a rural district of Malawi: an effectiveness assessment. The Lancet. 2006 Apr 22;367(9519):1335–42.

5. Bemelmans M, Akker TVD, Ford N, Philips M, Zachariah R, Harries A, et al. Providing universal access to antiretroviral therapy in Thyolo, Malawi through task shifting and decentralization of HIV/AIDS care. Trop Med Int Health. 2010;15(12):1413–20.

6. Penazzato M, Davies M-A, Apollo T, Negussie E, Ford N. Task Shifting for the Delivery of Pediatric Antiretroviral Treatment: A Systematic Review. J Acquir Immune Defic Syndr. 2014;65(4):9.

7. WHO. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach. Geneva: World Health Organization; 2013.

8. WHO. What's new in service delivery [Internet]. 2015 [cited 2019 Jul 26]. Available from: http://www.who.int/hiv/pub/arv/arv2015-service-delivery-factsheet/en/

9. WHO. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach. [Internet]. 2016 [cited 2019 Jul 7]. Available from: http://apps.who.int/iris/bitstream/10665/208825/1/9789241549684_eng.pdf

10. Grimsrud A, Bygrave H, Doherty M, Ehrenkranz P, Ellman T, Ferris R, et al. Reimagining HIV service delivery: the role of differentiated care from prevention to suppression. J Int AIDS Soc. 2016;19(1):21484.

11. Fayorsey RN, Saito S, Carter RJ, Gusmao E, Frederix K, Koech-Keter E, et al. Decentralization of Pediatric HIV Care and Treatment in Five Sub-Saharan African Countries. J Acquir Immune Defic Syndr 1999. 2013 Apr 15;62(5):e124–30.

12. Chan AK, Mateyu G, Jahn A, Schouten E, Arora P, Mlotha W, et al. Outcome assessment of decentralization of antiretroviral therapy provision in a rural district of Malawi using an integrated primary care model. Trop Med Int Health. 2010;15(s1):90–7.

13. MISAU. Plano de Aceleração da resposta ao HIV SIDA em Moçambique 2013-2015. [Acceleration plan for HIV/AIDS response in Mozambique 2013-2015] [Internet]. 2013 [cited 2019 Aug 5]. Available from: http://www.misau.gov.mz/index.php/planos-estrategicos-do-hiv

14. MISAU. Relatório Anual das Actividades Relacionadas ao HIV/SIDA [Annual Report of HIV/AIDS activities] - 2018. 2019 p. 100.

15. Lambdin BH, Micek MA, Sherr K, Gimbel S, Karagianis M, Lara J, et al. Integration of HIV Care and Treatment in Primary Health Care Centers and Patient Retention in Central Mozambique: A Retrospective Cohort Study. J Acquir Immune Defic Syndr 1999. 2013 Apr 15;62(5):e146–52.

16. Pfeiffer J, Montoya P, Baptista AJ, Karagianis M, Pugas M de M, Micek M, et al. Integration of HIV/AIDS services into African primary health care: lessons learned for health system strengthening in Mozambique - a case study. J Int AIDS Soc. 2010 Jan 20;13(1):3.

17. UNAIDS. UNAIDS data 2019 [Internet]. 2019 [cited 2019 Jul 23]. Available from: https://www.unaids.org/en/resources/documents/2019/2019-UNAIDS-data

18. Teasdale CA, Besser MJ. Enhancing PMTCT programmes through psychosocial support and empowerment of women: The mothers2mothers model of care. South Afr J HIV Med. 2008 Jan 1;9(1):60-64–64.

19. WHO. WHO recommendations for clinical mentoring to support scale-up of HIV care, antiretroviral therapy and prevention in resource-constrained settings [Internet]. World Health Organization; 2006 [cited 2019 Jul 26]. Available from: https://apps.who.int/iris/handle/10665/43555

20. Mutevedzi PC, Lessells RJ, Heller T, Bärnighausen T, Cooke GS, Newell M-L. Scale-up of a decentralized HIV treatment programme in rural KwaZulu-Natal, South Africa: does rapid expansion affect patient outcomes? Bull World Health Organ. 2010 Aug;88:593–600.

21. Stringer JS, Chisembele-Taylor A, Chibwesha CJ, Chi HF, Ayles H, Manda H, et al. Protocol-driven primary care and community linkages to improve population health in rural Zambia: the Better Health Outcomes through Mentoring and Assessment (BHOMA) project. BMC Health Serv Res. 2013 May 31;13(2):S7.

22. Workneh G, Scherzer L, Kirk B, Draper HR, Anabwani G, Wanless RS, et al. Evaluation of the effectiveness of an outreach clinical mentoring programme in support of paediatric HIV care scale-up in Botswana. AIDS Care. 2013 Jan 1;25(1):11–9.

23. MISAU. Directriz Nacional de Apoio Psicossocial e Prevenção Positiva [National Guidelines on Psychosocial Support and Positive Prevention] [Internet]. 2015 [cited 2019 Jul 26]. Available from: http://www.misau.gov.mz/index.php/guioes-de-cuidados-e-tratamento

24. MISAU. Guião de Actividades de Apoio Psicossocial e Prevenção Positiva [Manual for Psychosocial Support and Positive Prevention Activities] [Internet]. 2015 [cited 2019 Jul 26]. Available from: http://www.misau.gov.mz/index.php/guioes-de-cuidados-e-tratamento

25. Violari A, Cotton MF, Gibb DM, Babiker AG, Steyn J, Madhi SA, et al. Early Antiretroviral Therapy and Mortality among HIV-Infected Infants. N Engl J Med. 2008 Nov 20;359(21):2233–44.

26. Bagenda A, Barlow-Mosha L, Bagenda D, Sakwa R, Fowler MG, Musoke PM. Adherence to tablet and liquid formulations of antiretroviral medication for paediatric HIV treatment at an urban clinic in Uganda. Ann Trop Paediatr. 2011 Aug 1;31(3):235–45.

27. Cruz MLS, Cardoso CAA, Darmont MQ, Souza E, Andrade SD, D'Al Fabbro MM, et al. Viral suppression and adherence among HIV-infected children and adolescents on antiretroviral therapy: results of a multicenter study. J Pediatr (Rio J). 2014 Nov;90(6):563–71.

28. Davies M-A, Boulle A, Fakir T, Nuttall J, Eley B. Adherence to antiretroviral therapy in young children in Cape Town, South Africa, measured by medication return and caregiver self-report: a prospective cohort study. BMC Pediatr. 2008 Sep 4;8(1):34.

29. Duarte HA, Harris DR, Tassiopoulos K, Leister E, Negrini SFB de M, Ferreira FF, et al. Relationship between viral load and behavioral measures of adherence to antiretroviral therapy in children living with human immunodeficiency virus in Latin America. Braz J Infect Dis. 2015 May 1;19(3):263–71.

30. Campbell C, Skovdal M, Mupambireyi Z, Madanhire C, Nyamukapa C, Gregson S. Building adherence-competent communities: Factors promoting children's adherence to anti-retroviral HIV/AIDS treatment in rural Zimbabwe. Health Place. 2012 Mar 1;18(2):123–31.

31. Fetzer BC, Mupenda B, Lusiama J, Kitetele F, Golin C, Behets F. Barriers to and Facilitators of Adherence to Pediatric Antiretroviral Therapy in a Sub-Saharan Setting: Insights from a Qualitative Study. AIDS Patient Care STDs. 2011 Aug 8;25(10):611–21.

32. Naar-King S, Arfken C, Frey M, Harris M, Secord E, Ellis D. Psychosocial factors and treatment adherence in paediatric HIV/AIDS. AIDS Care. 2006 Aug 1;18(6):621–8.

33. Mavhu W, Berwick J, Chirawu P, Makamba M, Copas A, Dirawo J, et al. Enhancing Psychosocial Support for HIV Positive Adolescents in Harare, Zimbabwe. PLOS ONE. 2013 Jul 23;8(7):e70254.

34. Nabukeera-Barungi N, Kalyesubula I, Kekitiinwa A, Byakika-Tusiime J, Musoke P. Adherence to antiretroviral therapy in children attending Mulago Hospital, Kampala. Ann Trop Paediatr. 2007 Jun 1;27(2):123–31.

35. Leeper SC, Montague BT, Friedman JF, Flanigan TP. Lessons learned from family-centred models of treatment for children living with HIV: current approaches and future directions. J Int AIDS Soc. 2010 Jun 23;13(2):S3.

36. INE Instituto Nacional Estatistica. CENSO 2017. IV Recenseamento Geral da População e Habitação [IV Population and Households Census 2017] [Internet]. 2017 [cited 2019 Sep 5]. Available from: http://www.ine.gov.mz/operacoes-estatisticas/censos/censo-2007/censo-2017

37. MISAU, INE, ICF. Inquérito de Indicadores de Imunização, Malária e HIV/SIDA em Moçambique [Immunization, Malaria and HIV/AIDS Survey in Mozambique] (IMASIDA) 2015 [Internet]. 2018 Feb [cited 2019 Jul 2]. Available from: https://dhsprogram.com/publications/publication-ais12-ais-final-reports.cfm

38. Akinde Y, Groves AK, Nkwihoreze H, Aaron E, Alleyne G, Wright C, et al. Assessing the Acceptability of a Peer Mentor Mother Intervention to Improve Retention in Care of Postpartum Women Living with HIV. Health Equity. 2019;3(1):336–42.

39. Bwirire LD, Fitzgerald M, Zachariah R, Chikafa V, Massaquoi M, Moens M, et al. Reasons for loss to follow-up among mothers registered in a prevention-of-mother-to-child transmission program in rural Malawi. Trans R Soc Trop Med Hyg. 2008 Dec 1;102(12):1195–200.

40. Ioannidis JP, Taha TE, Kumwenda N, Broadhead R, Mtimavalye L, Miotti P, et al. Predictors and impact of losses to follow-up in an HIV-1 perinatal transmission cohort in Malawi. Int J Epidemiol. 1999 Aug 1;28(4):769–75.

41. Shubber Z, Mills EJ, Nachega JB, Vreeman R, Freitas M, Bock P, et al. Patient-Reported Barriers to Adherence to Antiretroviral Therapy: A Systematic Review and Meta-Analysis. PLOS Med. 2016 Nov 29;13(11):e1002183.

42. Bandali S. Norms and practices within marriage which shape gender roles, HIV/AIDS risk and risk reduction strategies in Cabo Delgado, Mozambique. AIDS Care. 2011 Sep;23(9):1171–6.

43. Hodgson I, Plummer ML, Konopka SN, Colvin CJ, Jonas E, Albertini J, et al. A Systematic Review of Individual and Contextual Factors Affecting ART Initiation, Adherence, and Retention for HIV-Infected Pregnant and Postpartum Women. PLOS ONE. 2014 Nov 5;9(11):e111421.

44. O'Gorman DA, Nyirenda LJ, Theobald SJ. Prevention of mother-to-child transmission of HIV infection: Views and perceptions about swallowing nevirapine in rural Lilongwe, Malawi. BMC Public Health. 2010 Jun 21;10(1):354.

45. Ujiji OA, Ekström AM, Ilako F, Indalo D, Wamalwa D, Rubenson B. Reasoning and deciding PMTCT-adherence during pregnancy among women living with HIV in Kenya. Cult Health Sex. 2011 Aug 1;13(7):829–40.

46. Duff P, Kipp W, Wild TC, Rubaale T, Okech-Ojony J. Barriers to accessing highly active antiretroviral therapy by HIV-positive women attending an antenatal clinic in a regional hospital in western Uganda. J Int AIDS Soc. 2010 Sep 23;13(1):37.

47. Turan JM, Miller S, Bukusi EA, Sande J, Cohen CR. HIV/AIDS and maternity care in Kenya: how fears of stigma and discrimination affect uptake and provision of labor and delivery services. AIDS Care. 2008 Sep;20(8):938–45.

48. Varga C, Brookes H. Factors Influencing Teen Mothers' Enrollment and Participation in Prevention of Mother-to-Child HIV Transmission Services in Limpopo Province, South Africa. Qual Health Res. 2008 Jun;18(6):786–802.

49. MISAU. Directriz, Implementação da carga viral de HIV em Moçambique. [Guidelines for HIV viral load implementation in Mozambique] [Internet]. 2015 [cited 2019 Jul 21]. Available from: http://www.misau.gov.mz/index.php/directrizes-nacionais

50. Prendergast A, Mphatswe W, Tudor-Williams G, Rakgotho M, Pillay V, Thobakgale C, et al. Early virological suppression with three-class antiretroviral therapy in HIV-infected African infants. AIDS. 2008 Jul 11;22(11):1333.

51. Teasdale CA, Sogaula N, Yuengling KA, Wang C, Mutiti A, Arpadi S, et al. HIV viral suppression and longevity among a cohort of children initiating antiretroviral therapy in Eastern Cape, South Africa. J Int AIDS Soc. 2018 Aug;21(8):e25168.

52. Gibb DM, Goodall RL, Giacomet V, Mcgee L, Compagnucci A, Lyall H, et al. Adherence to prescribed antiretroviral therapy in human immunodeficiency virus-infected children in the PENTA 5 trial. Pediatr Infect Dis J. 2003 Jan;22(1):56.

53. Haberer JE, Cook A, Walker AS, Ngambi M, Ferrier A, Mulenga V, et al. Excellent Adherence to Antiretrovirals in HIV+ Zambian Children Is Compromised by Disrupted Routine, HIV Nondisclosure, and Paradoxical Income Effects. PLOS ONE. 2011 Apr 21;6(4):e18505.

54. Haberer J, Mellins C. Pediatric Adherence to HIV Antiretroviral Therapy. Curr HIV/AIDS Rep. 2009 Nov;6(4):194–200.

55. Santarem Ernesto A, Muller Banzato Pinto de Lemos R, Huehara MI, Moreno Morcillo A, dos Santos Vilela MM, Nolasco da Silva MT. Usefulness of pharmacy dispensing records in the evaluation of adherence to antiretroviral therapy in Brazilian children and adolescents. Braz J Infect Dis. 2012 Jul 1;16(4):315–20.

56. WHO. Compendium of WHO guidelines and associated standards: ensuring optimum delivery of the cascade of care for patients with tuberculosis [Internet]. Geneva, Switzerland; 2017 [cited 2019 Sep 3]. Available from: http://apps.who.int/iris/bitstream/10665/259180/1/9789241512572-eng.pdf

57. Gigliotti F, Murante BL, Weinberg GA. Short Course Directly Observed Therapy to monitor compliance with Antiretroviral Therapy in Human Immunodeficiency Virus-Infected Children. Pediatr Infect Dis J. 2001 Jul;20(7):716.

58. Van Winghem J, Telfer B, Reid T, Ouko J, Mutunga A, Jama Z, et al. Implementation of a comprehensive program including psycho-social and treatment literacy activities to improve adherence to HIV care and treatment for a pediatric population in Kenya. BMC Pediatr. 2008 Nov 21;8(1):52.

59. Amzel A, Toska E, Lovich R, Widyono M, Patel T, Foti C, et al. Promoting a Combination Approach to Paediatric HIV Psychosocial Support. AIDS Lond Engl. 2013 Nov;27(0 2):S147–57.

60. Richter L. An introduction to family-centred services for children affected by HIV and AIDS. J Int AIDS Soc. 2010 Jun 23;13(2):S1.

61. MISAU. Directrizes para engajamento do homen nos cuidados de saúde [Guidelines for male engagement in health care] [Internet]. 2018 [cited 2019 Sep 3]. Available from: http://www.misau.gov.mz/index.php/directrizes-nacionais

62. Seth A, Gupta R, Chandra J, Maheshwari A, Kumar P, Aneja S. Adherence to antiretroviral therapy and its determinants in children with HIV infection – Experience from Paediatric Centre of Excellence in HIV Care in North India. AIDS Care. 2014 Jul 3;26(7):865–71.

63. Betancourt TS, Abrams EJ, McBain R, Fawzi MCS. Family-centred approaches to the prevention of mother to child transmission of HIV. J Int AIDS Soc. 2010 Jun 23;13(2):S2.

64. Rochat TJ, Bland R, Coovadia H, Stein A, Newell M-L. Towards a family-centered approach to HIV treatment and care for HIV-exposed children, their mothers and their families in poorly resourced settings. Future Virol. 2011 Jun 1;6(6):687–96.

65. Abrams EJ, Myer L, Rosenfield A, El-Sadr WM. Prevention of mother-to-child transmission services as a gateway to family-based human immunodeficiency virus care and treatment in resource-limited settings: rationale and international experiences. Am J Obstet Gynecol. 2007 Sep 1;197(3, Supplement):S101–6.

66. Myer L, Abrams EJ, Zhang Y, Duong J, El-Sadr WM, Carter RJ. Family Matters: Co-enrollment of Family Members Into Care Is Associated With Improved Outcomes for HIV-Infected Women Initiating Antiretroviral Therapy. J Acquir Immune Defic Syndr 1999. 2014 Dec 1;67(Suppl 4):S243–9.

67. Luyirika E, Towle MS, Achan J, Muhangi J, Senyimba C, Lule F, et al. Scaling Up Paediatric HIV Care with an Integrated, Family-Centred Approach: An Observational Case Study from Uganda. PLOS ONE. 2013 Aug 6;8(8):e69548.

68. Humphrey JM, Genberg BL, Keter A, Musick B, Apondi E, Gardner A, et al. Viral suppression among children and their caregivers living with HIV in western Kenya. J Int AIDS Soc. 2019 Apr;22(4):e25272.

69. Wrubel J, Tedlie Moskowitz J, Anne Richards T, Prakke H, Acree M, Folkman S. Pediatric adherence: Perspectives of mothers of children with HIV. Soc Sci Med. 2005 Dec;61(11):2423–33.

70. Stringer EM, Meltzer-Brody S, Kasaro M, Stuebe AM, Wiegand S, Paul R, et al. Depression, pregnancy, and HIV: the case to strengthen mental health services for pregnant and post-partum women in sub-Saharan Africa. Lancet Psychiatry. 2014 Jul;1(2):159–62.

71. Sawyer A, Ayers S, Smith H. Pre- and postnatal psychological wellbeing in Africa: A systematic review. J Affect Disord. 2010 Jun;123(1–3):17–29.

72. Myer L, Smit J, Roux LL, Parker S, Stein DJ, Seedat S. Common Mental Disorders among HIV-Infected Individuals in South Africa: Prevalence, Predictors, and Validation of Brief Psychiatric Rating Scales. AIDS Patient Care STDs. 2008 Feb 1;22(2):147–58.

73. Bennetts A, Shaffer N, Manopaiboon C, Pattrawan Chaiyakul, Siriwasin W, Mock P, et al. Determinants of depression and HIV-related worry among HIV-positive women who have recently given birth, Bangkok, Thailand. Soc Sci Med. 1999 Sep;49(6):737–49.

74. Varga C, Sherman G, Maphosa J, Jones S. Psychosocial Consequences of Early Diagnosis of HIV Status in Vertically Exposed Infants in Johannesburg, South Africa. Health Care Women Int. 2005 May 1;26(5):387–97.

75. Teasdale CA, Abrams EJ, Coovadia A, Strehlau R, Martens L, Kuhn L. Adherence and Viral Suppression among Infants and Young Children Initiating Protease Inhibitor-Based Antiretroviral Therapy. Pediatr Infect Dis J. 2013 May;32(5):489–94.

76. Müller AD, Bode S, Myer L, Roux P, von Steinbüchel N. Electronic Measurement of Adherence to Pediatric Antiretroviral Therapy in South Africa: Pediatr Infect Dis J. 2008 Mar;27(3):257–62.

77. Bagenda A, Barlow-Mosha L, Bagenda D, Sakwa R, Fowler MG, Musoke PM. Adherence to tablet and liquid formulations of antiretroviral medication for paediatric HIV treatment at an urban clinic in Uganda. Ann Trop Paediatr. 2011 Aug;31(3):235–45.

78. Calmy A, Ford N, Hirschel B, Reynolds SJ, Lynen L, Goemaere E, et al. HIV Viral Load Monitoring in Resource-Limited Regions: Optional or Necessary? Clin Infect Dis. 2007 Jan 1;44(1):128–34.

79. WHO. The 2018 Optimal Formulary and Limited-Use List for paediatric ARVs [Internet]. 2018 [cited 2019 Sep 4]. Available from: https://www.who.int/hiv/pub/paediatric/optimal-paediatric-arv-formulary/en/

80. WHO. Integrated Management of Childhood Illness (IMCI) [Internet]. Geneva, Switzerland; 2014 [cited 2019 Sep 22]. Available from: http://www.who.int/maternal_child_adolescent/topics/child/imci/en/

CHAPTER 8: CONCLUSIONS

8. CONCLUSIONS

The main objective of this project was to advance our knowledge on underlying gaps in the infants' continuum of care from HIV exposure (Chapter 4) to early diagnosis (Chapter 5), early treatment and viral suppression (Chapter 6-7) in Mozambique. This is an area of particular interest in the current global effort to achieve elimination of paediatric HIV and sustained viral suppression of children on treatment.

Evidence from the studies shows that, despite progress of PMTCT and HIV programs after the introduction of Option B+, universal access to ART for children, expansion of EID including point of care simplified technology, gaps still exist throughout the PMTCT continuum of care and beyond, into early treatment initiation and achievement of viral suppression in perinatally HIV infected infants. Results can be applied at national level to design differentiated model of care tailored to mothers and their infant's with special attention to long term care of HIV infected children on ART. Results are summarized, limitation and strengths are described, recommendations and implications for future research are discussed below.

8.1 Results summary

Results are summarized below according to specific objectives of the research project.

Objective 1- To evaluate factors associated to 'unknown HIV exposure status' and to 'HIV exposure status' in children less than 2 years of age in Mozambique.

1) We found a high proportion (32%) of children under 24 months of age with unknown HIV serostatus in Mozambique. Underlying factors associated with this condition were residence in the northern and central region of Mozambique, in rural areas, mother with no education and household having a male as head of the family.

2) We found that factors negatively associated with the condition of being an 'HIV exposed' infant were region of residence, northern and central region of Mozambique, head of household being a male, breastfeeding duration of 18 months, mother not having accessed ante-natal care, maternity or post-natal consultation.

Objective 2- To describe completeness of follow up among HIV-exposed infants receiving routine care and to identify factors associated to lost to follow up after the first HIV negative test.

1) At selected health facilities in Maputo province, we found a high rate (16%) of lost to follow-up among HIV Exposed Infants before HIV definitive diagnosis. Underlying factors were age older than 2 months at enrolment into post-natal care, non-exclusive breastfeeding at entry and poor cotrimoxazole adherence during follow up; the presence of clinical events showed to be protective against lost to follow-up.

2) Challenges have been documented in following the national Early Infant Diagnosis testing algorithm: a relevant proportion (20%) of infants whose rapid test at 9 months was indeterminate and required a confirmatory virologic test the same day, was not offered the test, and received a rapid test three months later; nevertheless 5.8% of HEI remained without a definitive diagnosis.

3) We found a vertical transmission rate, up to the end of breastfeeding period, of 4%. It is lower compared to the 17.6% estimated for Maputo province, but in line with 5% HIV prevalence found in HIV Exposed children < 4 years in Manhiça district (a district in Maputo Province).

4) We found that less than half of infected infants were diagnosed before 2 months of age, highlighting the need to intensify efforts on early post-partum linkage interventions.

5) We found that 19% of HEI presented a clinical event during follow up: majority were respiratory and gastrointestinal symptoms, minority presented mild malnutrition, very few infants presented severe illnesses. Malnutrition at entry, non-exclusive breastfeeding and poor cotrimoxazole adherence were factors associated to a higher risk of clinical event.

Objective 3- To describe virologic response in HIV perinatally infected infants who start a PI-based antiretroviral treatment in the first month of life.

1) Our analysis is the first describing viral response in a cohort of infants who started antiretroviral treatment with LPV/r-based regimen at one month of age in Mozambique and had repeated measurement of plasma viral load during a median follow up time of 17 months. We found low

rate of viral suppression and high rate of viral rebound, mainly due to poor caregiver adherence. Among adherent infants, viral suppression was reached in a median time of 3 months. Viral rebound was frequent and occurred after a median time of three months from the first viral load suppression measurement.

2) We did not find significative difference in the time to reach viral suppression according to pre-ART viral load using the cut off of Log10 6.

3) We found, and re-confirmed, that growth development is affected in children who did not achieve viral load suppression. Monitoring trends, in particular WAZ-score, can assists clinicians to suspect poor adherence before viral load result is available.

4) We found that mother's viral response during follow up was similar to infant's viral response. Majority of mothers of infants with high viral load, also had detectable viremia during follow up, although statistical significance was not found due to the small sample size. This finding suggests that if the mother is not adherent for her-self there is a possibility she won't be for her baby.

Objective 4 - To evaluate weather the adherence and psychosocial package offered to caregivers of perinatally infected infants starting ART in the first months of age allows health staff to identify infants at risk of poor adherence.

1) We found that the standard APSS package of care did not clearly and timely differentiate elements peculiar to infants who had a poor viral response. We described very different and unpredictable viral load response trajectories among all infants. We had infants who reached and sustained VLS during the entire follow up period, infants who never reached VLS, infants who reached VLS, had a rebound and did not suppressed the virus again and finally infants who had a rebound and later re-suppressed. This supports the fact that adherence was the major challenge to achieve and maintain VLS and that it is a dynamic and complex issue determined by several factors which need further studies.

2) We found that majority of women disclosed their HIV status to partner and family. However, disclosure alone did not appear to support mothers to being adherent.

8.2 Limitations and strengths

The analyses presented in this dissertation have several limitations.

1) The first research study using the National survey data was based on a survey primarily powered to study the HIV prevalence in adult population and not for the purpose of our analysis. However, the sample was still large and the applied restrictions allowed to control on the crucial recall bias as well as to focus on the PMTCT target population and the entire 24 months post-partum period. Non-self-disclosure of serostatus during the survey may have underestimated the number of exposed children in favor of overestimation of unknown HIV exposure status. Even if that is the case, results are still valid as outcomes balance each other in terms of bias direction, as well share similar, consistent and programmatically relevant associated factors. The study presents its own strength: is the first study describing factors associated with the condition of unknown HIV exposure status among infants and factors associated to the condition of infant's being HIV exposed using national survey data in large sample of women with children up to 24 months of age, the recommended follow up period in the PMTCT pathway.

2) The research study investigating lost to-follow -up among HIV exposed infants and related factors was a retrospective analysis of secondary data collected in a routine setting which may have led to some incompleteness of information. For the same reason, maternal information such as viral load or CD4 count and mother's socio-economic factors which could have enriched our analysis, are missing. Another limitation is that results come from selected health facilities of Maputo province and cannot be generalized to other provinces as they have different context and are at different stages of HIV program implementation. However, we believe that key findings, are shared among HEI and their mothers and should be considered to improve PMTCT program implementation in other provinces as well. The strength of this study is that it reported for the first time in Mozambique the magnitude of lost to follow-up among HEI and correlated factors. Reliability of results is strengthened by the 'real life' context of the study considering primary care facilities with high patient's workload at MCH clinic.

3) The study on viral response is the first one in Mozambique describing viral response in a cohort of infants who started antiretroviral treatment with LPVr based regimen at one month of age. Its limitation is the small sample size and different duration of follow up time for each child,

although children were censored in the analysis. For such a reason, conclusions on sustained viral suppression rate are not generalizable to the entire country. The sample size also limited the analysis of clinical and maternal factor possibly associated with outcomes.

Despite the small number of infants, the repeated measurement of plasma viral load in the 24 months after ART initiation, gave a more complete description of frequent viral load variations and rebounds in infants, including those who initially responded very well suggesting the need to apply a different monitoring algorithm from the one in use. Moreover, it highlights important observational clinically grounded findings which need further investigation such as major correlates of adherence and sustained viral suppression in the first year of life.

Another limitation was that we could not perform resistance test among infants who did not respond to treatment, to ascertain whether lack of response was due to ARV resistance. However, all mothers of infants who did not suppress the virus referred poor adherence to medications, majority of them had also high viral load and child's pattern of viral load response suggested that medication was not administered at all or not consistently.

4) The qualitative study on the APSS package of care, may bring social desirability bias and does not allow to generalize our findings. However, we believe it gives key elements to reflect around a very critical component of care influencing outcomes of infants and children on ART. Another limitation of the study, knowing that adherence factors change over time, is that our data analyzed the first APSS session, when it was possible to identify only factors present at the time of the first visit and not those emerging later. However, we think that the first evaluation is crucial and needs to be as accurate and as complete as possible in order to promptly identify potential risk factors and act on them quickly.

8.3 Implications and future directions

The findings from this research project have several important implications for clinical practice, for policy makers, program manager and future studies.

To ensure that each step of the PMTCT pathway till early engagement of HIV infected infants in care for sustained viral suppression is achieved, efforts need to converge in those specific gaps unique to pregnant and breastfeeding women, their infant and families.

Recommendations for health care providers

1) It is necessary to provide intense support to mom-baby pair in the first 3-6 months after enrolment at PNC to prevent LTFU. MCH nurse should identify HIE infants at risk and mentor mothers should intensify support at home.

2) In Mozambique many difficulties have been reported in using and interpreting viral load test results, especially in infants. It is important for clinicians to consider the following a) infants on PI-based regimen usually respond to treatment within the first 3-6 months if they are adherent to the medication, b) in this specific population, once achieved viral load suppression, the possibility of a rebound in the following months is high and continuous APSS support must be offered at the same time with strict growth and virologic monitoring.

3) The APSS package of care need to be comprehensive and must include evaluation of infant's adherence and viral response in light of mother's viral load results and adherence behavior.

4) It is essential to assess mother's mental health status and refer the mother for specialized support.

5) Adherence to a scheduled visit, including drug pick-ups, does not always reflect medication adherence and need to be interpreted with caution.

6) It necessary to go beyond measuring adherence by asking the number of remaining pills. Indeed, it is crucial to promote and build a safe and confidential environment among health providers and caregivers for them to honestly share their struggle in managing their infant.

Recommendations for program managers

1) The PMTCT program should focus on women who have no access to ANC and on those who are lost in the cascade. A standardized and easy tool to track mother-baby pair at site level will assist to find infants who drop out of the path. This would also be an opportunity for establishing a national monitoring of HIV Exposed Uninfected infants referred to under-5 clinic and obtain data to study their long-term need, understand if specific interventions are necessary in this population. The monitoring system will also inform whether transition of women from MCH services to ART clinics, after their infant definitive diagnosis has been established, happened.

2) Knowing the mother's HIV status is the first step to halt vertical transmission and eliminate pediatric HIV. Implementation of national guidelines on testing pregnant and breastfeeding women and uptake among health care providers need to be strengthened. More investment should be direct in other HIV testing modalities targeting women of child-bearing age, such as community HIV testing at home, at school, in the work place, through mobile health clinic or school health corners. Furthermore, community mobilization and engagement of people living with HIV to contribute in delivering key messages and support care, such as mentor mothers, will allow to retain women and engage those who did not access the health system.

3) The HIV program should direct special attention to caregivers of HIV infected infants, who have specific needs and require specific strategies different from those designed for adults patients. In the infant population, time is limited to influence AIDS free survival, it is thus necessary and justified to respond quickly and differently. Clinical benefits gained with early diagnosis and early treatment initiation must be maintained throughout child ART care by ensuring caregivers the best support for adherence to reach and sustain viral suppression in their infants.

4) HIV perinatally infected infants are identified late or not at all. It is urgent to put in place intense mentoring to strengthen HIV screening among infants and children at pediatric wards and outpatients' clinics as well as strengthen mentor mothers effort to retain HIV women throughout the breastfeeding period.

5) A simplified diagnosis algorithm for HEI should be developed, especially for management of indeterminate test results.

6) Mozambique is moving towards the use of LPVr in the first line for all children under 20 kg, and while other ARVs in the pipeline will be available, it is advisable to have a different approach for viral monitoring and adapt the viral load algorithm for this age group. A more frequent monitoring will help in preserving PI drugs, prevent the emergence of viral drugs resistance and most of all, identify infants who really need intensified support for adherence.

7) The APSS package of care did not clearly and timely differentiate elements peculiar to infants who had a poor viral response. It is urgent to develop an APSS package tailored to caregivers of

younger children, to enable them building an adherence behavior which will benefit their children and family in the long term.

8) To assist counsellor in assess mother's mental health and eventually refer those in need of specialized support, it is advisable to develop an easy tool to screen mother's mental health and include it in the APSS package.

9) To support caregivers in the management of ARV medication for their infant, the implementation of ART directly observed therapy at home using trained mentor mothers should be considered as a part of the ongoing Mentor Mother strategy.

Recommendations for policy makers

1) There are still women who do not access health care when they are pregnant or have a child and reasons are not only related to the health sphere. Restricting interventions at health facility level, may not fully solve other social factors and dynamics acting at community and family level which need to be properly addressed. Multisectoral actors must work in synergy to tackle social factors which limit women to use the health services, and must direct more investment to empower them socially and economically.

2) Resources need to be re-directed for an effective and comprehensive communication strategy as a critical component of the global effort in HIV prevention and education, with the goal to reach rural communities and women who do not have access to conventional media.

3) Resources directed to the HIV program to eliminate HIV should not only focus on special populations such as HIV positive pregnant women but also result in a stronger MCH services all over the country, including provinces and districts with lower HIV prevalence, which are poorer, remote and where women have less access to health care.

Recommendations for future research studies

1) Additional research is needed to study the magnitude of lost to follow-up of HEI in the other provinces and underlying socio-economic determinants especially gender dynamics within the family and the male role in the elimination of pediatric HIV.

2) To better understand how to support caregivers and families to live with an HIV positive infant and build a consistent adherence behavior, further studies are crucial to evaluate the continuum of APSS care during infancy and childhood to obtain a more robust evidence of how factors related to adherence are changing over time and how they can effectively be addressed.

3) Sustained viral suppression is the requisite to grow healthy into adolescence and adulthood. Full engagement of families is needed and for this, a deeper understanding of family's perspective about infant's disease, HIV treatment and long terms goals for the child is crucial.

4) HIV birth testing, as an approach to identify earlier infected infants, is not yet part of Mozambique guidelines and HIV program is cautious in moving towards this approach. It is thus necessary to study which model of care is more appropriate to follow up HIV infected neonates who start ART in settings where there are no specialists.

CHAPTER 9: PUBLICATIONS

9. PUBLICATIONS

9.1 Articles in peer-review journals

1. Maria Grazia Lain, Sergio Chicumbe, Aleny Couto, Esmeralda Karajeanes, Carlo Giaquinto, Paula Vaz. *High proportion of unknown HIV exposure among children aged less than 2 years: an analytical study using Mozambique 2015 National HIV Survey.*
    - Submitted to PLOS-ONE (PONE-D-19-23928)

2. Stefano Rinaldi, Suresh Pallikkuth, Mark Cameron, Lesley R. de Armas, Nicola Cotugno, Rajendra Pahwa, Brian Richardson, Shelly R. Saini, Maria G. Lain, Sion Williams, Paolo Palma, and Savita Pahwa. *Impact of early ART initiation on HIV-specific CD4+ and CD8+ T cell functionality in perinatally infected children.*
    - Submitted to Journal of Immunology (ID 19-00856-FLR)

9.2 Abstracts and poster to International Conferences

1. S.Dominquez, P.Rojo Conejo, M.G.Lain, A.Liberty, S.Barnabas, E.Lopez Varela, K.N.Otwombe, S.Danaviah, E.Nastuoli, M.Serna Pascual, V.Gianuzzi, C.Giaquinto, L.Khun, A.Tagarro, for the EPIICAL Consortium. *Mothers Adherence helps identifying more infants in need of extended prophylaxis.* Abstract n 2575- Submitted to CROI 2020.

2. M.G.Lain, P.Vaz, N.Ismael , A.Cantarutti , G.Porcu , P.Palma , N.Cotugno, D.Bila, S.Rinaldi, S.Pallikkuth, R.Pahwa, E.Taibo, E.Karajeanes, C.Giaquinto, S.Pahwa. *Viral response in HIV infected infants starting ART at 1 month in southern Mozambique*. Abstract n 2969- Submitted to CROI 2020.

3. S.Rinaldi, N.Cotugno, E.Morrochi, S.Pallikkuth, R.Pahwa, M.G.Lain, M.Cameron, P.Palma, *Effect of early treatment initiation on HIV-specific T cells immune response in children with perinatal HIV infection.* Miami Winter Symposium-Evolving Concepts in HIV & Emerging Viral Infections. January 2019 Miami -USA. Poster P2.28

4. E.Karajeanes, D.Bila, O.Augusto, M.G.Lain, B.Muianga, C.Muluana, N.Macuacua, V.Chavane, P.Vaz. *Uptake and retention in care of pregnant women starting Option B+ in Maputo.* CROI 2017 February 2017, Seattle-USA. Abstract n 766

5. E.Karajeanes, O.Augusto, Maria G.Lain, S.José, J.Pita, N.Calú, S.Agostinho, V.Chavane, J.Sacarlal, P.Vaz. *Factor associated to attrition from the ART program in Mozambique* – Poster - IAS Conference 2016 Durban

9.3 Papers under review for journal submission

1. Correlates of missed diagnosis and lost-to-follow up among HIV exposed infants throughout the breastfeeding period in southern Mozambique.

2. Viral response among HIV perinatally infected infants who started antiretroviral treatment in the first month of life: description of a cohort in southern Mozambique

3. Optimizing adherence and psychosocial support model of care for caregivers of HIV infected infants: descriptive case series from southern Mozambique