UNIVERSITAT DE BARCELONA

Characterization of the prevention and care cascade in children living with HIV in the Manhiça district, Mozambique

Sheila Fernández Luis

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Doctoral thesis report submitted by **Sheila Fernández Luis** to obtain a doctoral degree by the University of Barcelona

Co-Supervised by:

Dr. Denise Naniche Instituto de Salud Global de Barcelona (ISGlobal)

Dr. Elisa López Varela Instituto de Salud Global de Barcelona (ISGlobal) and Centro de Investigação em Saúde de Manhiça (CISM)

Tutor:

Jaume Ordi ISGlobal, Hospital Clínic, Universidad de Barcelona

Doctoral programme in Medicine and Translational Research Faculty of Medicine and Health Sciences, University of Barcelona

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September 2022

Dr. Denise Naniche

and

Dr. Elisa López Varela

CERTIFIED

that the thesis entitled

Characterization of the prevention and care cascade in children living with HIV in the Manhiça district, Mozambique,

submitted by Sheila Fernández Luis, has been developed under their supervision and that is presented following recommendations from the University of Barcelona for the submission of a Doctoral Thesis by a compendium of publications, and to opt to the mention of International Doctoral Research Component.

They also certify that this work has followed the codes of ethics and good practice and are not aware of any plagiarism.

Dr. Denise Naniche

Dr. Elisa López Varela

Acknowledged by doctoral candidate

A todas as crianças que vivem com HIV no distrito da Manhiça

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Glossary

AIDS: acquired immune deficiency syndrome
ART: antiretroviral therapy
AZT: zidovudine
CI: confidence Interval
CLHIV: children living with HIV
COVID-19: coronavirus disease 2019
DTG: dolutegravir
ePTS: electronic patient tracking system
HDSS: health and demographic surveillance system
HIV: human immunodeficiency virus
HRQoL: health-related quality of life
IQR: interquartile range
ISGlobal: Barcelona Institute for Global Health
LTFU: loss to follow-up
MDH: Manhiça District Hospital
CISM: Manhiça Health Research Centre
NNRTI: non-nucleoside reverse transcriptase inhibitors
NRTI: nucleoside/tide reverse transcriptase inhibitors
NVP: nevirapine
PCR: polymerase chain reaction
PI: protease inhibitor
PLHIV: people living with HIV
POC: point-of-care
PrEP: pre-exposure prophylaxis
PVT: prevention of vertical transmission
RIC: re-engagement in care
UNAIDS: Joint United Nations Programme on HIV/AIDS
VL: viral load
VT: vertical HIV transmission
WHO: World Health Organization

List of the articles that comprise the thesis

Thesis in the form of a collection of published articles

This thesis comprises 1 main objective, 5 specific objectives, and 6 articles

1. Laura Fuente-Soro, **Sheila Fernández-Luis**, Elisa López-Varela, Orvalho Augusto, Tacilta Nhampossa, Ariel Nhacolo, Edson Bernardo, Blanca Burgueño, Bernadette Ngeno, Aleny Couto, Helga Guambe, Kwalila Tibana, Marilena Urso, Denise Naniche.

   Community-based progress indicators for prevention of mother-to-child transmission and mortality rates in HIV-exposed children in rural Mozambique.

   BMC Public Health. 2021 March 17;21 (1):1–12. Doi: 10.1186/s12889-021-10568-4.

   2021 Impact factor: 1.16 (JCR)

   Q1 (Public Health, Environmental and Occupational Health)

2. **Sheila Fernández-Luis,** Laura Fuente-Soro, Tacilta Nhampossa, Elisa López-Varela, Orvalho Augusto, Ariel Nhacolo, Olalla Vazquez, Helga Guambe, Kwalila Tibana, Bernadette Ngeno, Adelino Jose Chingore Juga, Jessica Greenberg Cowan, Marilena Urso, Denise Naniche.

   Prompt HIV diagnosis and antiretroviral treatment in postpartum women is crucial for prevention of mother to child transmission during breastfeeding: Survey results in a high HIV prevalence community in southern Mozambique after the implementation of Option B+.

   PLoS ONE. 2022 August 2;17 (8): e0269835. Doi: 10.1371/journal.pone.0269835.

   2021 Impact factor: 0.85 (JCR)

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3. **Sheila Fernández-Luis***, Maria Grazia Lain*, Miquel Serna-Pascual, Sara Domínguez-Rodríguez, Louise Kuhn, Afaaf Liberty, Shaun Barnabas, Elisa Lopez-Varela, Kennedy Otwombe, Siva Danaviah, Eleni Nastouli, Paolo Palma, Nicola Cotugno,Moira Spyer, Viviana Giannuzzi, Carlo Giaquinto, Avy Violari, Mark F Cotton, Tacilta Nhampossa, Nigel Klein, Nastassja Ramsagar6, Anita Janse Van Rensburg, Osse Behuhuma, Paula Vaz, Almoustapha Issiaka Maiga, Andrea Oletto, Denise Naniche, Paolo Rossi, Pablo Rojo4**,Alfredo Tagarro** on behalf of the EPIICAL Consortium.

   Optimizing the World Health Organization algorithm for HIV vertical transmission risk assessment by adding maternal self-reported antiretroviral therapy adherence.

   BMC Public Health. 2022 July 08;22 (1):1–9. Doi: 10.1186/s12889-022-13543-9.

   2021 Impact factor: 1.16 (JCR)

   Q1 (Public Health, Environmental and Occupational Health)

4. **Sheila Fernández-Luis**, Tacilta Nhampossa, Laura Fuente-Soro, Orvalho Joaquim Augusto, Aina Casellas, Edson Bernardo, Maria Ruperez, Raquel Gonzalez, Sonia Maculuve, Anna Saura, Clara Menendez, Denise Naniche*, Elisa Lopez-Varela*.

   Pediatric HIV Care Cascade in Southern Mozambique: missed opportunities for early ART and re-engagement in care.

   Pediatr Infect Dis J.2020 May 1;39 (5):429-434. doi:10.1097/INF.0000000000002612.

   2020 Impact factor: 1.03 (JCR)

   Q1 (Pediatrics, Perinatology and Child Health)

5. Tacilta Nhampossa, **Sheila Fernández-Luis**, Laura Fuente-Soro, Edson Bernardo, Arsenio Nhacolo, Orvalho Augusto, Ariel Nhacolo, Charfudin Sacoor, Anna Saura-Lázaro, Elisa Lopez-Varela, Denise Naniche.

   The impact of the caregiver mobility on child HIV care in the Manhiça District, Southern Mozambique: A clinical based study.

   PLoS One. 2021 December 16;16 (12):e0261356.Doi:10.1371/journal.pone.0261356.

   2021 Impact factor: 0.85 (JCR)

   Q1 (Multidisciplinary)

6. **Sheila Fernández-Luis***, Anna Saura-Lázaro*, Tacilta Nhampossa, Edson Bernardo, Laura Granés, Laura Fuente-Soro, Orvalho Augusto, Elisa Lopez-Varela, Denise Naniche.

   Health Related Quality of Life in children living with HIV in Manhiça, Mozambique.

   Manuscript under preparation.

SUMMARY / RESUMEN

Thesis summary in English

Characterization of the prevention and care cascade in children living with HIV in the Manhiça district, Mozambique

Introduction

Children acquire human immunodeficiency virus (HIV) infection mainly due to vertical transmission (VT) from their mothers, during pregnancy, delivery or breastfeeding (1). Without immediate access to antiretroviral treatment (ART), half of all children living with HIV die of acquired immunodeficiency syndrome (AIDS) related causes before the age of two (2). Although the number of newly infected children between 2010 to 2020 was reduced by 54% (3), there are still 1.7 [interquartile range (IQR):1.2 – 2.2] million children less than 15 years of age living with HIV worldwide and 150 000 [IQR:100 000–240 000] new infections per year (3), most of them in sub-Saharan Africa.

The sequential steps of medical attention that people living with HIV experience from diagnosis to linkage to HIV medical care, receipt of ART, retention in care, to achieving sustained viral suppression, is known as the HIV care cascade (4,5). Viral suppression has been classically considered the ultimate goal because it is associated with good clinical outcomes (6). However, health related quality of life (HRQoL) goes beyond viral suppression and considers social, emotional and physical well-being, which are particularly important for children, who will endure HIV and related struggles for their entire lives (7,8).

Global strategies in the fight against HIV/AIDS between 2015 and 2020 were focused on the 90-90-90 targets, which contemplated that by 2020, 90% of people living with HIV would know their HIV status, 90% of people who knew their HIV status would access ART, and 90% of people on ART would have suppressed viral load (9). In addition, a particular strategy for children, the super-accelerated "Start Free, Stay Free, AIDS Free", was established in 2016 among the 21 African countries with the highest burden of pediatric HIV worldwide (10). The strategy included the goals of reducing the annual number of new pediatric infections to fewer than 20,000 and providing ART to 1.4 million children (aged 0-14) living with HIV in the 21 focus countries by 2020 (10). By that year, the global 90-90-90 values among children lagged behind those for adults (59-54-40 vs 82-74-67) and the total number of children receiving ART among the focus countries remained 34% below the target of 1.4 million on ART (11). In addition, the results in 2020 were uneven across countries indicating that to achieve the new global goals of "Ending inequalities and getting

on track to end AIDS by 2030", specific gaps in pediatric prevention and care need to be identified and addressed at the local level.

Mozambique is one of the countries with a high burden of pediatric HIV, with 130 000 [IQR:100 000 – 170 000] children living with HIV and a VT rate of 13% (6% during pregnancy and delivery and 8% during breastfeeding) in 2020 (3,11), which placed it among the 3 countries in the world with the highest proportion of children acquiring HIV, in the same year (11).

In 2013, Mozambique adopted the Option B+, which recommended lifelong ART to HIV-positive pregnant and breastfeeding women, regardless of their CD4 count and postnatal prophylaxis with 6 weeks Nevirapine (NVP) for their HIV-exposed children infants (12–15). Programmatic data showed that in 2018, poor adherence to ART was identified as a major obstacle to decreasing VT (16). Viral load (VL) monitoring is also a big challenge in the country, and only 11% of all eligible pregnant women (those with at least 3 months on ART) had a VL requested in 2018. From them, only 6% received a VL result 3 to 6 months after ART initiation treatment (16).

Regarding the pediatric HIV care cascade, despite the progressive expansion of ART in the country since the adoption of test and treat strategy in 2016, treatment coverage (the second 90 target) among children living with HIV was still low, 64% in 2020 (3). For the third 90 target, it lagged even further behind with only 36% of those children on treatment achieving viral suppression, suggesting challenges for retention in HIV care (3).

Hypothesis

We hypothesize that, in the Manhiça district, major gaps in the pediatric HIV prevention and care cascade reside, respectively, in the prevention of VT during the postpartum period and in the retention in care of children after ART initiation.

Objective

The main objective of the research presented in this thesis is to identify the weakest steps in the pediatric HIV prevention and care cascade in the Manhiça district; a rural area of southern Mozambique with high HIV prevalence.

Methods and Results

The research presented in this thesis was conducted in the district of Manhiça, a semi-rural area located at 80km of the capital in Southern-Mozambique, which harbors high rates of labor migration to South Africa, and an estimated community prevalence of HIV among adults of 33.6% (95% CI 32.5 to 34.6) in 2015 (17,18).

This thesis is structured in 6 articles:

1. In the first article, we estimated VT among HIV-exposed children less than 4 years of age in the community. A cross-sectional household survey was conducted in the Manhiça district between October 2017 and April 2018, including live births in the previous 4 years, which were randomly selected within the Manhiça Health Demographic Surveillance System (METRO study). HIV status was ascertained through clinical documentation or/and HIV appropriate testing at survey, and in case of death, through verbal autopsy. We found a VT rate below 5% among HIV-exposed children under 4 years of age at the end of the breastfeeding period, which is within the WHO target for breastfeeding population, but a case rate of new pediatric HIV infections of 1654 per 100,000 live births. We also found a sevenfold tenfold higher risk of death among children living with HIV compared to HIV-exposed uninfected children.

2. The second article was a sub-analysis nested in the METRO study. We compared self-reported breastfeeding duration among HIV-exposed and HIV-unexposed children and found a significantly shorter duration among HIV-exposed children [Median 13.0 (95%CI:12.0–14.0) months] compared to HIV-unexposed [20.0 (95%CI:19.0–20.0) months], $p<0.001$. We also estimated postpartum VT, defined as children with an initial HIV positive result beyond 6 weeks of life who initiated breastfeeding if 1) they had a first negative PCR result during the first 6 weeks of life or 2) whose mother had an estimated date of infection after the child's birth. We found that 27.5% of HIV infections in children occurred during pregnancy and delivery, 49.0% during postpartum had an unknown time of infection for 23.5%. Newly acquired infections of mothers and delayed initiation of ART after delivery were risk factors for postpartum VT.

3. In the third article, we used data from a prospective cohort of infants with perinatal HIV infection and their mothers who were enrolled from May-2018 to May-2020 in Mozambique, South Africa, and Mali. We retrospectively compared the performance of the World Health Organization (WHO) algorithm for HIV vertical transmission risk assessment with a modified algorithm, which included

mothers' adherence as an additional factor when the maternal VL was unavailable. We found that a VL result within 4 weeks before delivery was unavailable in almost 90% of the mothers and that the inclusion of maternal-reported adherence to ART when VL results were not available, resulted in a nearly 50% increase in the identification of infants at high risk of VT.

4. In the fourth article, we estimated the pediatric HIV Care Cascade among a prospective cohort of children <15 years, that was followed from enrollment in HIV care (January 2013 to December 2015) at the MDH until December 2016. Loss to follow-up (LTFU) was defined as not attending the HIV hospital visits for ≥90 days, following last visit attended. Among the 438 children included, 78% of eligible children started ART and 63% of them were retained in care at 12 months after ART initiation. Children less than 1 year of age had higher risk of LTFU, which happened in a median time of 6 months after ART initiation. Once LTFU, only a quarter of those children return to the health unit during the 36 months of follow-up since ART initiation.

5. In the fifth article, we evaluated the impact of mobility on child HIV care, through a clinic-based cross-sectional survey conducted at the Manhiça District Hospital between December-2017 and February-2018. We enrolled children living with HIV accompanied by a caregiver who self-reported having moved outside of Manhiça District within 12 months prior to survey, and non-migrant caregiver, matched by the child age and sex. None of the migrant caregivers traveling with their HIV-positive children picked up ART at a destination clinic. They transported ART to their destination through a family member, which led to avoidance of mobility having a significant impact on the child's retention on ART.

6. Finally, in the sixth article, we estimated health related quality of life (HRQoL) among children living with HIV in care at the Manhiça District Hospital using the PedsQL™ 4.0 questionnaire. From May 2021 to February 2022, a cross sectional study was conducted, including children living with HIV aged 2 to 10 years, who were on ART for 12-36 months at their routine HIV scheduled visit. We also included a control group of age-matched children attending either the triage with minor acute ailments or the healthy child consultation, and having a negative HIV result in the previous 30 days. We found a good parent-reported HRQoL among children living with HIV, with a total PedsQL™ scale score above 90 points out of 100 for all age groups. Children living with HIV between 2 and 4 years of age had a poorer HRQoL score in the social domain compared to children without HIV infection.

Conclusions and recommendations

- As long as HIV prevalence in women of childbearing age remains above 10% in the district, the rate of new HIV infections per 100,000 live births will fall below WHO targets. Therefore, there is a need to focus on reducing the rate of VT and HIV incidence in women of reproductive age. Our results suggest that increasing early diagnosis and treatment of mothers who become infected after delivery would reduce postpartum VT. Moreover, in a context as Manhiça, where viral load monitoring is challenging, self-reported maternal adherence to ART is an effective alternative to increase the identification of children at high risk of postpartum VT. Our results also suggest that the benefits of extending the duration of breastfeeding up to two years, as in HIV-unexposed children, according to WHO recomendation, may outweigh the risk of VT.

- By 2015, progress in the pediatric HIV care cascade in Manhiça lagged far behind the UNAIDS 90-90-90 targets and retention in care was the main hurdle throughout the cascade, particularly among infants less than 1 year of age. Our results also found that families put in place informal social support to mitigate the lack of structural services in the administration of adapted ART to children living with HIV who migrated with their parents. In addition, we found that mortality in children under 4 years of age living with HIV in the community was disproportionately high compared to HIV-exposed uninfected children. Finally, this research was the first description of HRQoL in children living with HIV in Mozambique. It showed an overall good parent-reported HRQoL among children 2-10 years old in ART, but a poorer HRQoL score in the social domain in the preeschoolar children living with HIV compared to those without HIV infection. However, further studies are needed to delve deeper into the HRQoL issues of children living with HIV compared to the general pediatric population, and to eventually design strategies to support and enhance HRQoL.

Resumen en castellano

Caracterización de la cascada de prevención y cuidados en niños que viven con VIH en el distrito de Manhiça, Mozambique

Introducción

Los niños adquieren la infección por el virus de la inmunodeficiencia humana (VIH) principalmente por transmisión vertical (TV) de sus madres durante el embarazo, el parto o la lactancia (1). Sin acceso inmediato al tratamiento antirretroviral (TAR), la mitad de los niños que viven con el VIH fallecen por causas relacionadas con el síndrome de inmunodeficiencia adquirida (SIDA) en los primeros dos años de vida (2). Aunque el número de nuevas infecciones pediátricas se redujo en un 54% entre 2010 y 2020 (3), datos de 2020 muestran que todavía hay 1.7 [rango intercuartílico (IQR):1.2 – 2.2] millones de niños menores de 15 años viviendo VIH en todo el mundo y 150.000 [IQR:100 000-240 000] nuevas infecciones al año (3), que en su mayoría ocurren en África subsahariana.

Las etapas secuenciales en la atención médica de las personas que viven con el VIH, que comienzan con el diagnóstico y continúan con la vinculación a los cuidados del VIH, el acceso al TAR, la retención en los cuidados, hasta lograr la supresión viral sostenida, se conoce como la cascada de cuidados (4,5). La supresión viral se ha considerado clásicamente el objetivo final de la cascada de cuidados porque se asocia con buenos resultados clínicos (6). Sin embargo, la calidad de vida relacionada con la salud (CVRS) va más allá de la supresión viral y tiene en cuenta el bienestar social, emocional y físico, que son especialmente importantes para los niños, porque conviven con el VIH durante toda su vida (7,8).

Las estrategias mundiales en la lucha contra el VIH/SIDA entre 2015 y 2020 se centraron en los objetivos 90-90-90, que contemplaban que en 2020 el 90% de las personas viviendo con VIH conocieran su estado serológico, el 90% de las personas que conocían su estado serológico accedieran al TAR y el 90% de las personas en TAR tuvieran la carga viral suprimida (9). Además, en 2016 se estableció la estrategia "Start Free, Stay Free, AIDS Free", centrada en los 21 países africanos con la mayor carga de VIH pediátrico del mundo (10). Esta estrategia incluía entre sus objetivos, la reducción de las nuevas infecciones pediátricas anuales a menos de 20 000 y la administración de TAR a 1.4 millones de niños menores de 15 años para 2020 en los 21 países (10). Sin embargo, en 2020, los valores globales de 90-90-90 conseguidos en la población pediátrica fueron inferiores a la de los adultos (59-54-40 frente a 82-74-67) y el total de niños

con TAR entre los países objetivo seguía estando un 34% por debajo del objetivo de 1,4 millones (11). Además, los resultados en 2020 fueron ampliamente desiguales entre los países. Esto sugiere que para alcanzar los nuevos objetivos mundiales de "Acabar con las desigualdades y ponerse en marcha para poner fin al sida en 2030", es necesario identificar y abordar a nivel local las deficiencias específicas en materia de prevención y atención pediátrica relacionada con el VIH.

Mozambique es uno de los países con mayor carga de VIH pediátrico, con 130 000 [IQR: 100 000 – 170 000] niños viviendo con VIH y una tasa de TV del 13% (6% durante el embarazo y el parto, y 8% durante la lactancia) en 2020 (3,11). En ese mismo año Mozambique se situó entre los 3 países del mundo con mayor proporción de nuevas infecciones pediátricas (11).

En 2013, Mozambique adoptó la Opción B+, que recomendaba TAR de por vida a las mujeres embarazadas y lactantes viviendo con VIH, independientemente de su recuento de CD4, junto con profilaxis postnatal con Nevirapina (NVP) durante 6 semanas para sus hijos expuestos al VIH (12–15). Datos nacionales programáticos de 2018, identificaron la mala adherencia al TAR como uno de los principales obstáculos para la disminución de la VT (16). No obstante, la monitorización de la carga viral (CV) supone también un gran desafío en el país. En 2018 solo el 11% de todas las mujeres embarazadas elegibles (aquellas que llevaban al menos 3 meses en TAR) tenían una solicitud de CV y tan solo el 6% recibió un resultado de CV en los 3 a 6 meses después del inicio del TAR (16).

En cuanto a la cascada de cuidados de VIH pediátrico, a pesar de la progresiva expansión del TAR en el país desde la adopción de la estrategia de testar e iniciar en 2016, la cobertura del tratamiento entre los niños viviendo con VIH (el segundo objetivo de los 90) seguía siendo baja en 2020, del 64% (3). Para el tercer objetivo de los 90, el déficit es aún mayor, ya que solo el 36% de los niños en tratamiento lograron la supresión viral, lo que sugiere problemas de retención en el cuidado del VIH (3).

Hipótesis

Nuestra hipótesis es que en el distrito de Manhiça, las principales lagunas en la cascada de prevención y de cuidados de VIH residen en la prevención de la TV postparto y en la retención en los cuidados después del inicio del TAR.

Objetivo

El objetivo principal de la investigación presentada en esta tesis es identificar las principales debilidades en la cascada de prevención y de cuidados de VIH en la población infantil del distrito de Manhiça; una zona rural del sur de Mozambique con alta prevalencia de VIH.

Métodos y resultados

La investigación presentada en esta tesis se llevó a cabo en el distrito de Manhiça, una zona semirrural situada a 80 km de la capital en el sur de Mozambique, que alberga altas tasas de migración laboral a Sudáfrica, y una prevalencia comunitaria estimada de VIH en adultos del 33.6% (IC 95%: 32.5 a 34.6) en 2015 (17,18).

Esta tesis se estructura en 6 artículos:

1. En el primer artículo, se estimó la TV en la comunidad entre los niños menores de 4 años expuestos al VIH. Se realizó una encuesta transversal de hogares en el distrito de Manhiça entre octubre de 2017 y abril de 2018, en la que se incluyó una selección aleatoria de 5 000 nacidos vivos en los 4 años anteriores, que fueron seleccionados a través del Sistema de Vigilancia Demográfica de Salud de Manhiça (estudio METRO). El seroestado de VIH se determinó a través de la documentación clínica o/y las pruebas apropiadas del VIH durante la encuesta, y en caso de muerte, a través de autopsia verbal. Encontramos una tasa de TV inferior al 5% entre los niños menores de 4 años expuestos al VIH al final del periodo de lactancia, cuyo valor se encuentra dentro del objetivo de la OMS para la población lactante. Sin embargo, la tasa de casos de nuevas infecciones pediátricas por VIH fue de 1 654 por cada 100 000 nacidos vivos, que supera ampliamente el objetivo de 50 por cada 100 000. También se encontró que el riesgo de muerte entre los niños viviendo con VIH era siete veces superior en comparación con los niños expuestos al VIH y no infectados.

2. El segundo artículo se trata de un subanálisis anidado en el estudio METRO. En él, se comparó la duración de la lactancia materna entre los niños expuestos y los no expuestos al VIH. La duración de la lactancia materna fue significativamente más corta entre los niños expuestos al VIH [mediana de 13.0 (IC del 95%: 12.0-14.0) meses] en comparación con los no expuestos al VIH [20.0 (IC del 95%: 19.0-20.0) meses], p<0.001. Se estimó también la TV posparto, definida como aquella en los niños que iniciaron la lactancia materna y tuvieron un resultado positivo al VIH posterior a las 6

primeras semanas de vida, en el caso de que: 1) tuviesen un primer resultado negativo de PCR durante las primeras 6 semanas de vida o 2) la fecha estimada de infección materna fuese posterior a la fecha de nacimiento del niño. Se encontró que el 27.5% de las infecciones por VIH en niños se habían producido durante el embarazo y el parto, el 49.0% durante el postparto y en el 23.5% se desconocía el periodo de transmisión. Las nuevas infecciones maternas y el retraso en el inicio del TAR después del parto en las madres fueron factores de riesgo para la TV posparto.

3. En el tercer artículo, utilizamos datos de una cohorte prospectiva de niños viviendo con VIH y sus madres, que habían iniciado los cuidados desde mayo de 2018 hasta mayo de 2020 en Mozambique, Sudáfrica y Malí. Comparamos retrospectivamente el rendimiento del algoritmo de la Organización Mundial de la Salud (OMS) en la evaluación del riesgo de TV de VIH, con un algoritmo modificado, que incluía la adherencia de las madres como un factor adicional cuando la CV materna no estaba disponible. Descubrimos que aproximadamente el 90% de las madres no tenían un resultado de carga viral reciente disponible en el parto (en el periodo comprendido en las 4 semanas anteriores al parto). Además, la inclusión de la adherencia materna al TAR en el algoritmo cuando los resultados de la CV no estaban disponibles, permitió incrementar la identificación de los niños con alto riesgo de TV en aproximadamente un 50% .

4. En el cuarto artículo, estimamos la cascada de cuidados pediátricos del VIH en una cohorte prospectiva de niños <15 años, que fue seguida desde la vinculación en los cuidados del VIH (enero de 2013 a diciembre de 2015) en el MDH hasta diciembre de 2016. El abandono del tratamiento se definió como la ausencia de visitas a la consulta clínica de seguimiento de VIH durante ≥90 días, después de la última visita asistida. Entre los 438 niños incluidos, el 78% de los niños elegibles iniciaron el TAR y el 63% de ellos se mantuvieron en los cuidados en los 12 meses después del inicio del TAR. Los niños menores de 1 año tuvieron un mayor riesgo de abandono del tratamiento, que se produjo en una mediana de 6 meses tras el inicio del TAR. Solo una cuarta parte de los niños con abandono regresaron a la unidad sanitaria durante los 36 meses de seguimiento en el estudio desde el inicio de TAR.

5. En el quinto artículo, evaluamos el impacto de la movilidad en la retención de los cuidados del VIH infantil, a través de una encuesta transversal en el Hospital del Distrito de Manhiça, realizada entre diciembre-2017 y febrero-2018. Se incluyeron niños viviendo con VIH acompañados por un cuidador que autodeclaró haberse mudado fuera del Distrito de Manhiça en los 12 meses anteriores a la encuesta, o por un cuidador no migrante, emparejado por la edad y el sexo del niño/a. Ninguno de los cuidadores migrantes que viajaban con sus hijos que vivían con VIH declaró haber recogido

medicación en una clínica en el lugar de destino. No obstante, el envío de medicación desde el distrito de Manhiça al lugar de destino a través de un familiar les permitió contrarrestar el impacto de la movilidad en la retención del niño.

6. Por último, en el sexto artículo, estimamos la calidad de vida relacionada con la salud (CVRS) a través del cuestionario PedsQL™ 4.0, entre los niños viviendo con VIH que estaban en seguimiento clínico en el Hospital de Distrito de Manhiça. Entre mayo de 2021 y febrero de 2022 se realizó un estudio transversal durante las consultas programadas de VIH, en el que se incluyeron niños viviendo con VIH de entre 2 y 10 años de edad y que llevaban 12-36 meses en TAR. También se incluyó a un grupo de control de niños de la misma edad que tenían un resultado negativo de VIH en los 30 días anteriores y que acudieron o bien al triaje de las consultas externas con dolencias agudas leves, o bien a la consulta del niño sano. Encontramos una buena CVRS informada por los cuidadores entre los niños viviendo con VIH, con una puntuación total en la escala PedsQL™ superior a 90 puntos sobre 100, para todos los grupos de edad. Sin embargo, los niños viviendo con VIH de 2-4 años tuvieron una puntuación más baja que los niños sin infección por VIH.

Conclusiones y recomendaciones

- Mientras la prevalencia del VIH en las mujeres en edad fértil se mantenga por encima del 10% en el distrito, la tasa de nuevas infecciones por VIH por cada 100 000 recién nacidos vivos no podrá descender hasta los objetivos de la OMS. Por lo tanto, es necesario priorizar la reducción de la TV y de la incidencia del VIH en las mujeres en edad reproductiva. Nuestros resultados sugieren que el aumento del diagnóstico y el tratamiento precoz de las madres con nuevas infecciones por VIH posteriores al parto permitiría reducir la TV posparto. Por otro lado, en contextos como el de Manhiça en el que la monitorización de la carga viral materna es un reto, la adherencia materna autodeclarada resulta una alternativa eficaz para aumentar la identificación de los niños con alto riesgo de TV posparto. Además, en paralelo a los esfuerzos para garantizar una adecuada prevención de la TV postparto, la ampliación de la duración de la lactancia materna hasta los dos años, similar a la de los niños no expuestos al VIH, tal y como recomienda la OMS, podría tener beneficios que superasen el riesgo de TV.

- En 2015, los avances en la cascada de cuidados pediátrica de VIH en Manhiça estaban lejos de los objetivos 90-90-90 de ONUSIDA y la retención en la atención suponía el principal obstáculo a lo largo de la cascada, especialmente entre los lactantes menores de un año. Nuestros resultados mostraron

también que las familias que migraban del distrito pusieron en marcha un apoyo social informal para mitigar la falta de servicios estructurales para la administración del TAR pediátrico durante los periodos migratorios. Además, descubrimos que la mortalidad de los niños menores de 4 años que vivían con el VIH en la comunidad era desproporcionadamente alta en comparación con los niños sin infección por VIH. Por último, la investigación en esta tesis incluye la primera descripción de la CVRS en los niños que viven con el VIH en Mozambique. Los cuidadores de los niños de 2 a 10 años de edad en TAR declararon una buena CVRS. Sin embargo, los niños preescolares viviendo con VIH obtuvieron una puntuación significativamente menor en el ámbito social, en comparación con los niños sin infección por VIH. Sin embargo, se necesitan más estudios para entender los problemas de calidad de vida en los niños que viven con el VIH en comparación con la población pediátrica en general, y eventualmente diseñar estrategias para apoyar y mejorar la CVRS.

INTRODUCTION

Introduction

Current status of the HIV epidemic in children: global metrics and inequalities

Pediatric HIV infections occur mostly through vertical transmission (VT) from their mothers during pregnancy, delivery or breastfeeding. Without preventive interventions, the risk of VT during pregnancy, delivery or the breastfeeding ranges from 30 to 40% (1). However, specific preventive interventions including ART for the mother and postnatal prophylaxis for the child, can reduce VT to less than 5%, in the context of high HIV burden settings (1). Once they have acquired human immunodeficiency virus (HIV) infection, children are especially vulnerable to it. Without immediate access to antiretroviral treatment (ART), half of all children living with HIV die of acquired immunodeficiency syndrome (AIDS) related causes before the age of two(2).

Major progress has been made in the fight against the HIV epidemic in children over the past decade, including a 54% reduction in the number of newly infected children between 2010 to 2020 (3). However, there are still 1.7 [interquartile range (IQR): 1.2 – 2.2] million children less than 15 years of age living with HIV worldwide, and 150 000 [IQR: 100 000–240 000] new infections per year, according to 2020 data (3). Critical barriers to scaling up pediatric HIV diagnosis, treatment and care remain. By 2020, 46% (800 000/1.7 million) of children living with HIV were not on lifesaving ART, and AIDS-related deaths among children in 2020 totaled 99 000 [IQR:68 000-160 000] globally (3).

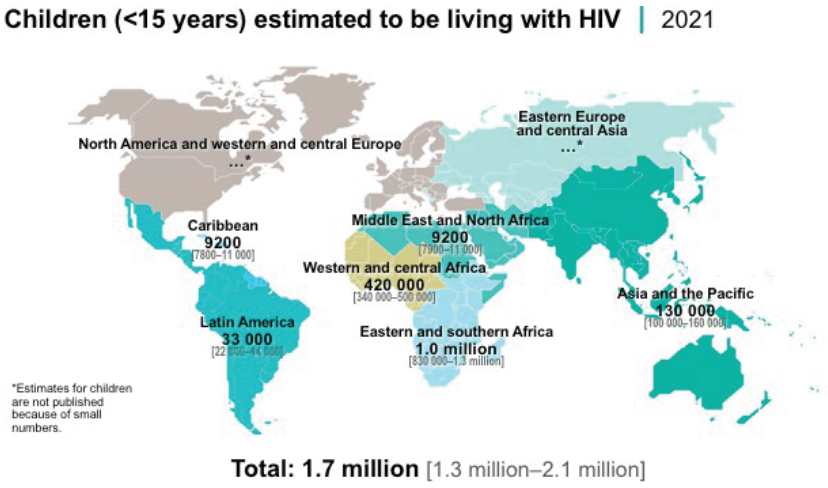


Figure 1. Children less than 15 years old living with HIV globally in 2021.

Extracted from: UNAIDS DATA 2021 (3).

Perhaps most concerning are the wide pediatric HIV inequalities between countries. More than 80% of children living with HIV are concentrated in 21 countries in sub-Saharan Africa: Angola, Botswana, Burundi, Cameroon, Chad, Côte d'Ivoire, Democratic Republic of the Congo, Eswatini, Ethiopia, Ghana, Kenya, Lesotho, Malawi, Mozambique, Namibia, Nigeria, South Africa, Uganda, United Republic of Tanzania, Zambia and Zimbabwe(10). These 21 countries account for 83% of the global number of pregnant women living with HIV. In 2011, global strategies began intensifying to end the HIV epidemic among children living in these countries (10,19).

Pediatric HIV Continuum of Care: definition, applications and limitations of the HIV Care Cascade.

The HIV care cascade, first described by Gardner et al(20), consists of the sequential steps of medical attention that people living with HIV (PLHIV) experience from diagnosis to achieving sustained viral suppression(4). It includes diagnosis of HIV infection, linkage to HIV medical care, initiation of ART, retention in care, and achievement and maintenance of viral suppression (5) (Figure 2).

Figure 2. HIV Care Continuum (cross sectional linear model).
Extracted from: HIV.gov (21)

The HIV care cascade is used as a cross-sectional linear model to assess care outcomes not only at an individual, but also at a facility or population-level. Analyzing the proportion of people with HIV at each successive step of care allows policy makers to visualize a specific population at a particular timepoint,

and to design targeted strategies with the ultimate goal of achieving and sustaining viral suppression in all PLHIV over their lifetime. It is also use as a public health tool to compare the performance of HIV care programmes in different populations and to evaluate progress towards the global goals.

However, the classic conceptualization of the HIV care cascade as a cross-sectional linear model has several limitations. First, is the inability to consider the time it takes for an individual to progress from one step to the next. Therefore, it detracts, for example, from the importance of early diagnosis and treatment, which are crucial in the clinical outcomes of children(22). Second, the linear cascade does not reflect the transition forward and backward between the stages over time, due for example, to viral rebound or ART interruptions (23,24). Third, including in the denominator, only individuals at the time of assessment whilst excluding deaths leads to overestimating the coverage at different stages of the cascade, and de-emphasizes the relevance of mortality as an outcome (23–25). As alternative, longitudinal care cascades have been proposed in the literature to account for bidirectional relationships between steps along the continuum of care and incorporate changes over time (24,26) (Figure 3). The longitudinal dynamic cascade model, although more difficult to obtain than the linear model, facilitates the identification of areas for improvement in a particular setting.

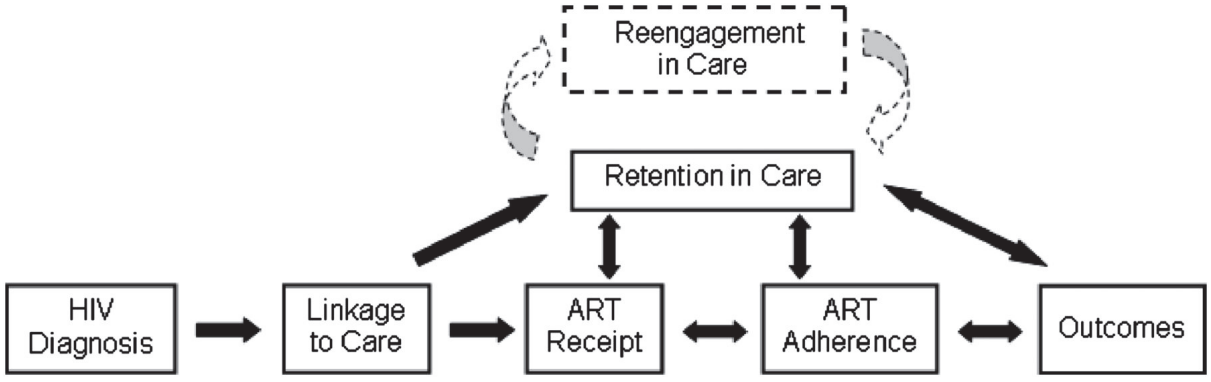


Figure 3. Longitudinal and dynamic HIV care cascade.

Extracted from: The State of Engagement in HIV Care in the United States: From Cascade to Continuum to Control (26).

Finally, viral suppression has been classically considered the ultimate goal in the cascade, as it predicts that people living with HIV live long healthy lives(6). However, in recent years, a more holistic view of health has guided the proposal of a cascade which includes additional steps in in the continuum of care,

including health-related quality of life (HRQoL) (27). The well-being of PLHIV may be affected by serious non-communicable diseases, stress, or HIV-related stigma and discrimination, even after viral suppression has been achieved (27,28). Addressing and mitigating these challenges, which go beyond viral suppression, is particularly important for children, who will endure HIV and related struggles for their entire lives, both directly and indirectly through parental infection (29).

Pediatric HIV epidemic control: strategy, goals and achievements

a) Fast-Track Strategy 2016–2021: 90-90-90 Targets

In agreeing to the Sustainable Development Goals, in particular Goal 3 on good health and well-being, all United Nations Member States adopted an ambitious target of ending the AIDS epidemic by 2030(30). In order to control the epidemic, in 2014, the Joint United Nations Programme for HIV/AIDS (UNAIDS) launched the 90-90-90 targets. These ambitious targets established that by 2020, among all people living with HIV, 90% of them would know their HIV status, 90% of those who knew their HIV status would access ART, and 90% of those on ART would have a suppressed viral load (VL). This would result in 73% of all people living with HIV achieving viral suppression (9) (Figure 4).

Figure 4. The treatment targets proposed in 2014 by UNAIDS to strive towards ending the HIV epidemic.
Extracted from: 90-90-90 An ambitious treatment target to help end the AIDS epidemic (9).

In order to monitor the HIV epidemic and measure the progress towards global targets, UNAIDS and the World Health Organization (WHO) support national programmes to make annual estimates of key HIV indicators through the Spectrum projection package, which uses modelling based on different data sources including national programmes(31,32). By the end of 2020, a total of 8 countries worldwide reported the fully achievement of the 90-90-90 targets, and 11 countries achieved viral suppression equivalent to 73% among all PLHIV (3) (Figure 5).

	90–90–90 value (all)	90–90–90 value (children aged 0–14 years)	90–90–90 value (women aged 15+ years)	90–90–90 value (men aged 15+ years)	Viral suppression level (all)
Eswatini	>98–>98–95	>98–>98–91	>98–>98–95	94–>98–94	97
Switzerland[a]	93–>98–96				88
Rwanda	93–>98–96	54–>98–89	96–>98–96	93–>98–96	89
Qatar[a]	93–>98–96		>98–>98–81	90–97–>98	86
Botswana	91–95–>98	62–>98–94	94.5–>98–>98	88–87–97	85
Slovenia	90–97–96				85
Uganda	91–>98–90	63–>98–78	96–>98–92	88–97–89	85
Malawi	91–94–94	73–>98–73	94–94.9–95	90–92–94	85
Zimbabwe	93–>98–89	72–>98–72	96–>98–91	92–>98–88	82
Kenya	96–89–94	84–>98–86	>98–92–94	91–83–94	81
Namibia	89.9–98–91	81–92–80	92–>98–93	86–94–89	80
Cambodia	84–>98–97	60–>98–88	82–>98–98	86–>98–97	81
Lesotho	94–87–97	83–>98–92	94.6–92–97	93–79–97	80
Burundi	89–>98–89.7	31–>98–70	>98–>98–91	85–96–89	79
Uruguay					79
Norway					79
Thailand	94–84–97	>98–76–87	92–86–97	96–81–97	77
Zambia	86–95–93	58–>98–84	89–94–94	84–95–93	76
Croatia	84–88–>98		80–92–>98	84–87–>98	73

Reached the 90–90–90 targets
Reached only the 73% viral load suppression target
Not reached the 90–90–90 target
Data not available

Figure 5. Countries reaching the HIV treatment cascade targets, 2020.

Extracted from: UNAIDS 2021 data (3).

By 2020, 90-90-90 values in children lagged behind those for adults, even in countries with better performance (Figure 5). Globally, treatment coverage among children was 54% versus 74% among adults, and only 40% of children were virally suppressed in 2020, compared to 67% of adults (Figure 6) (3). The same trend can be observed in the Eastern and Southern African region, who achieved remarkable gains in the 90-90-90 targets, reaching 90-78-72 in adults by 2020, but only 65-57-43 among children (3).

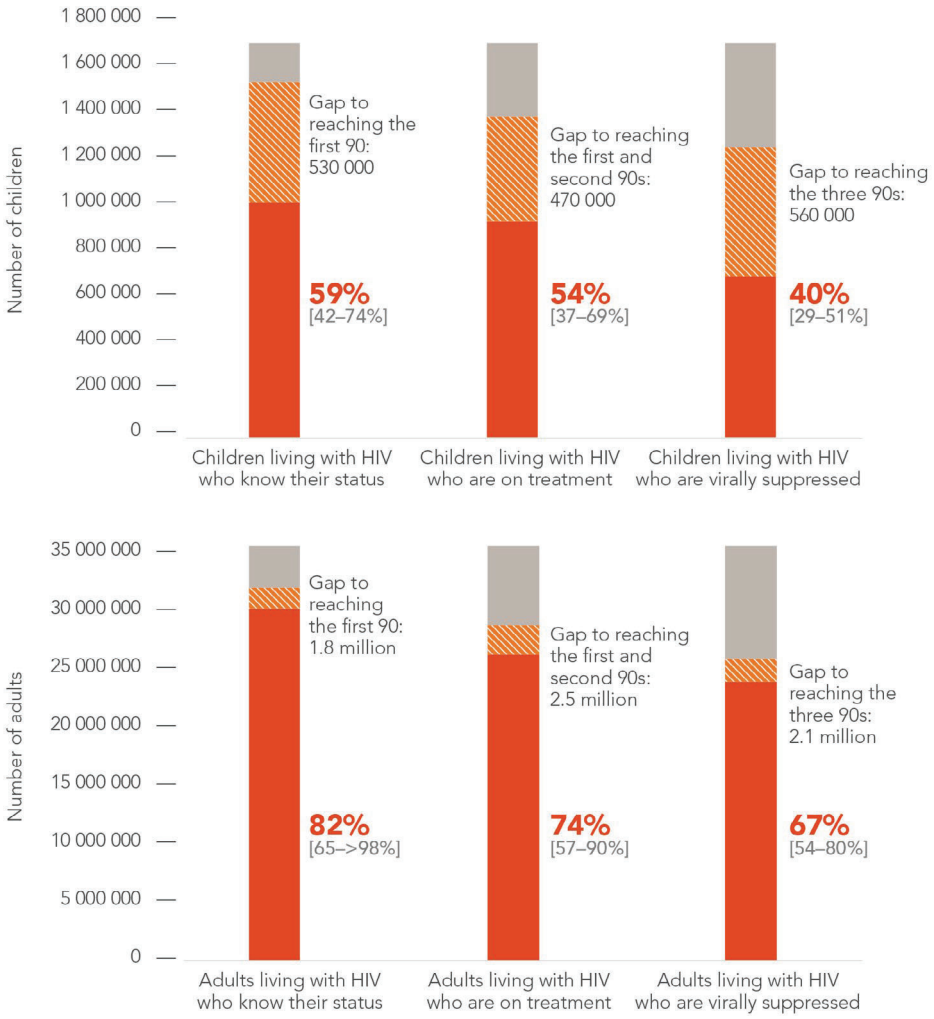


Figure 6. HIV care cascade, children (aged 0-14 years) compared to adults (aged 15 years and older), global 2020.

Extracted from: UNAIDS 2021 data (3).

b) Start Free, Stay Free, AIDS Free strategy

A particular strategy for children, the super-accelerated "Start Free, Stay Free, AIDS Free" framework, was launched in 2015 by the global community (10). It aimed to end AIDS as a public health threat among children, adolescents and young women by 2020(10). Although the targets were global, the framework was focused in the 21 countries with the highest burden of HIV in children and mothers, listed above. The "Start Free, Stay Free, AIDS Free strategy" goals included 1) reducing the number of newly infected children annually to fewer than 20 000 by 2020, 2) reaching 95% of pregnant women living with HIV on lifelong treatment and 3) provide ART to 1.4 million children (aged 0-14) living with HIV, by 2020 (10).

None of these ambitious targets established in the "Start Free, Stay Free, AIDS Free strategy" were fully achieved by 2020, and the results varied significantly among the focus countries. The rate of VT by 2020 ranged from 2% in Botswana to 28% in the Democratic Republic of the Congo(11) (Figure 7). The final report of "Start Free, Stay Free, AIDS Free strategy" identified the absence of maternal ART, loss to follow-up (LTFU) of women during pregnancy or breastfeeding, and new HIV infections in women during pregnancy and breastfeeding as major gaps in preventing VT (11).

By 2020, a total of 920 000 children were receiving treatment, a gap of 34% with respect to the target of 1.4 million on ART. Again, global ART coverage remained considerably lower in children compared than adults (11) (Figure 8). One of the major gaps for reaching the target absolute number of children on treatment, according to the "Start Free, Stay Free, AIDS Free Final report", was the failure of early HIV diagnosis. Furthermore, coverage of early infant diagnostics in 2020 also varied substantially among focus countries, from 2% in Angola to 99% in Namibia and Bostwana (11).

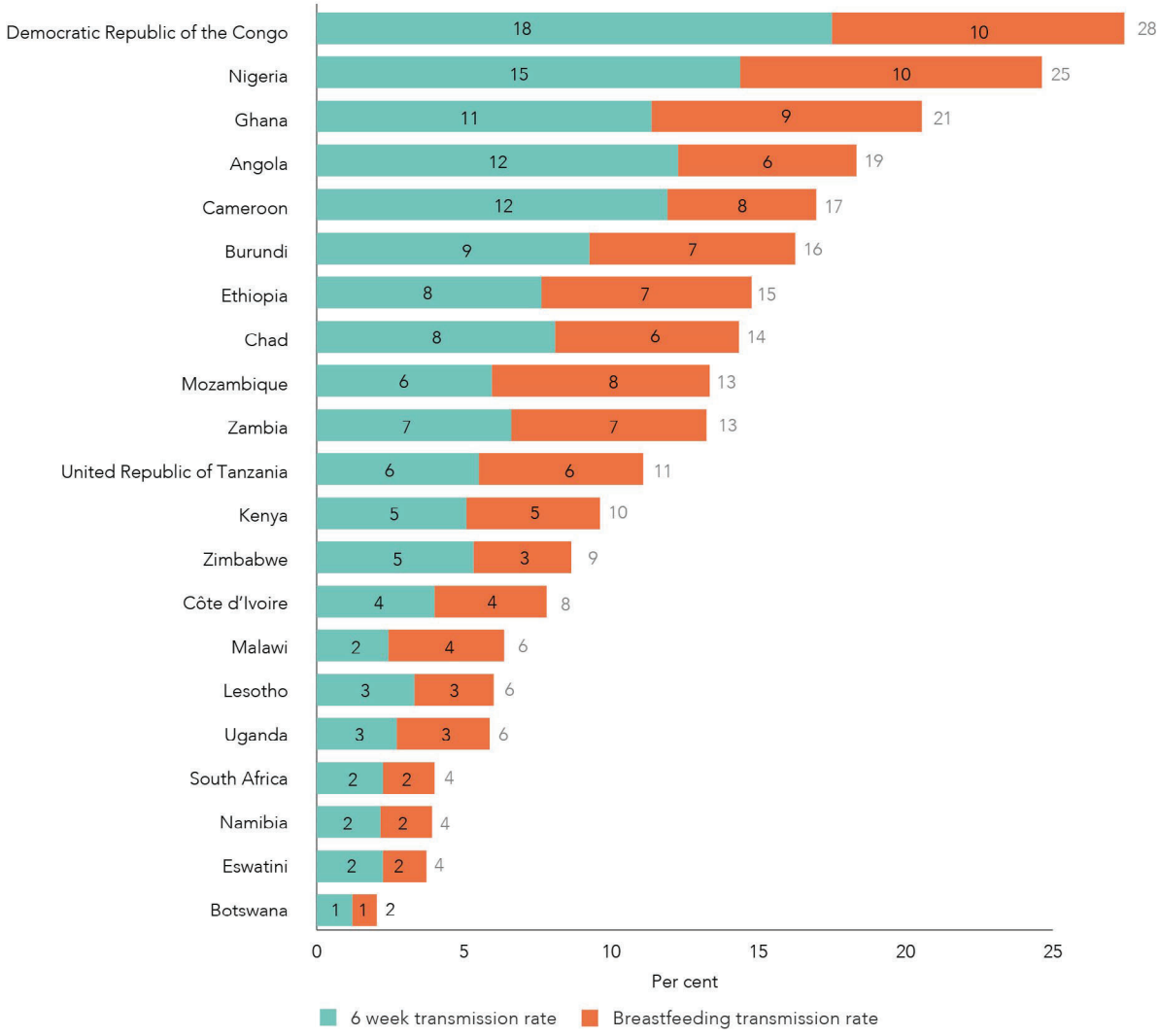


Figure 7. Mother-to-child transmission of HIV, by timing of transmission, focus countries, 2020.

Extracted from: Start Free, Stay Free, AIDS Free Final report on 2020 targets (11).

The numbers in the blue bars represent the six-week transmission rate, the numbers in the orange bar represent the breastfeeding transmission rate and the number at the end of the bar is the final transmission rate.

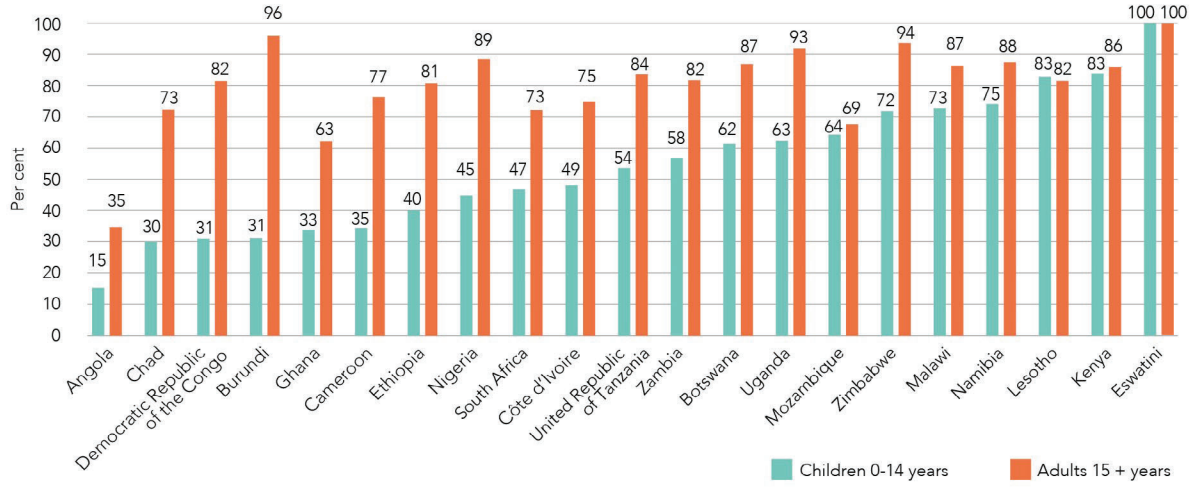


Figure 8. Percentage of people living with HIV receiving treatment among children and adults, focus countries, 2020

Extracted from: Start Free, Stay Free, AIDS Free Final report on 2020 targets (11).

c) Current 2021-2025 global AIDS strategy: 95-95-95 targets and beyond

Following the evaluation of the 90-90-90 targets at the end of 2020, the international community established the 2021-2025 global AIDS strategy, taking as a framework the commitment "Ending inequalities and getting on track to end AIDS by 2030", adopted at the United Nations General Assembly in 2021 (34). Global AIDS strategy for 2021-2025 priorities were defined as: equitable and equal access to HIV services, removing barriers to achieving HIV outcomes, and resourcing and sustaining effective and integrated HIV responses (Figure 9). The new goals for 2025 include: eliminating VT (which imply achieving a VT rate less than 5% in breastfeeding populations and a rate of new pediatric infection less than 50/100 000 live births (35), ending pediatric AIDS (which requires access to quality HIV treatment to avoid AIDS definition conditions), as well as achieving the 95–95–95 targets for HIV testing and treatment (95% of all PLHIV with a diagnosis, 95% of those diagnosed on ART, and 95% of those treated virally suppressed) (34). Although the new strategy does not include a fourth "95" target, regarding HRQoL, as proposed in literature (36,37), it puts more focus on stigma and universal health coverage (34). It establishes the 10-10-10 goals, that consist in less than 10% of countries having punitive legal and policy environments, less than 10% of people living with HIV and key populations experiencing stigma and discrimination, and less than 10% of women, girls, people living with HIV and key populations experiencing gender inequality and gender based violence (34).

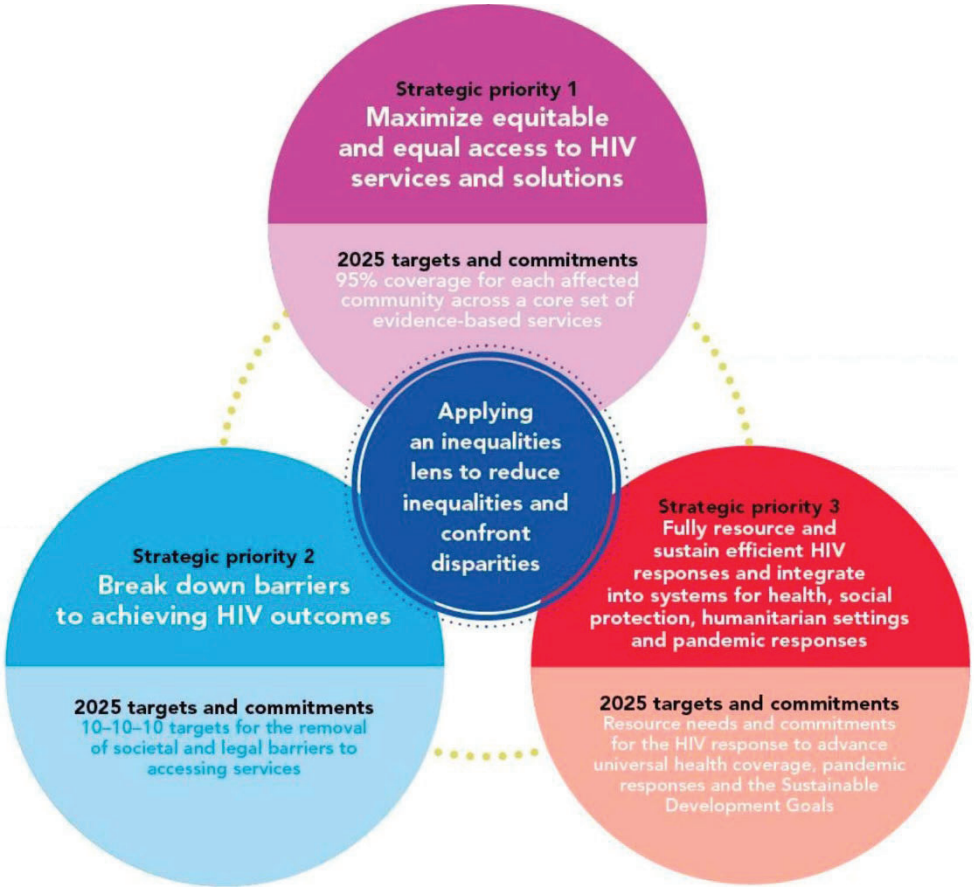


Figure 9. Global AIDS strategy 2021-2026 strategic priorities.

Extracted from: END INEQUALITIES.END AIDS. GLOBAL AIDS STRATEGY 2021-2026 (38).

In addition, following the Start Free Stay Free AIDS Free Partnership, a new Global Alliance for Ending AIDS in Children by 2030 (39) was announced on August 2nd, 2022 at the International AIDS Conference in Montreal. It will focus on prevention, detection, treatment and care for pregnant and lactating adolescent girls and women, as well as early testing and optimized high quality treatment and care for children exposed to and living with HIV (39,40).

Pediatric HIV epidemic in Mozambique: HIV prevention and care strategies

Mozambique is one of the twenty-one countries with the highest burden of pediatric HIV, with 130 000 [IQR: 100 000 – 170 000] children living with HIV in 2020 (3). Despite major efforts to control the pediatric HIV pandemic (16), Mozambique still has a disproportionately high VT rate estimated nationally at 13% (6% during the first 6 weeks of life and 8% during breastfeeding) in 2020 (3,11) which placed it among the 3 countries in the world with the highest proportion of children acquiring HIV, together with Nigeria and South Africa (11).

a) Prevention of vertical transmission in Mozambique

Specific strategies to control VT in Mozambique started with the establishment of the national program for the prevention of VT in 2002, which was implemented nationally in 2004 and integrated into the maternal and infant health services by 2006 (12). The country has adapted its national HIV treatment policies for pregnant and breastfeeding women according to the successive WHO recommendations on prevention of VT (Table 1). In 2002, the country adopted the use of single dose of Nevirapine (NVP) intrapartum, and in 2006, the use of Zidovudine (AZT) prophylaxis starting at 28 weeks of pregnancy (20). In 2010, mothers with CD4 count > 350 cells/mm3, who did not meet criteria for starting ART at the moment, were offered Option A, which included maternal AZT starting from 14 weeks of gestation and continued during pregnancy, and infant daily NVP during breastfeeding (41,42). In 2013, Mozambique adopted Option B+, which recommended lifelong ART to all HIV-positive pregnant and breastfeeding women, regardless of their CD4 count and postnatal prophylaxis with 6 weeks NVP for their HIV-exposed children infants (12–15) (Table 1). Option B+ preceded the global recommendation for 'test and treat' for all PLHIV which was implemented in 2016 in Mozambique(43). In September 2019, postnatal prophylaxis was reinforced, consisting in ZDV and NVP for the first 6 weeks of life, followed by NVP for 6 weeks to all infants, as all HIV-exposed infants were considered at high-risk for VT (44).

Year	Activity	Evolution of Therapeutic Options
2002	Prevention of VT begins to be implemented in 8 health facilities	Single Dose Nevirapine
2006	Integration of prevention of VT into maternal and child health services	AZT - 28 weeks
2010	Adoption of Treatment Option A	AZT - 14 weeks
2013	Option B + implementation started (June)	742 US Option B + (59.4% US PTV)/505 US Option A

Table 1. Evolution of recommendations for the prevention of vertical transmission in Mozambique

Adapted from: Relatório Final Diagnóstico Situacional da Implementação da Opção B+ em Moçambique. (12)

Estimations from Spectrum showed that VT decreased significantly, from 33% in 2010 to 13% in 2020, according to UNAIDS data(3). However, the overall national rate of VT has not fallen below 10%(16). Some of the main challenges in the national scale up of VT prevention strategies reported in the literature were the difficulties in decentralizing care to more rural areas and in expanding the coverage of laboratory analysis, such as access to maternal CD4 results which, until option B+, determined eligibility for ART among mothers (45,46) (Figure 10).

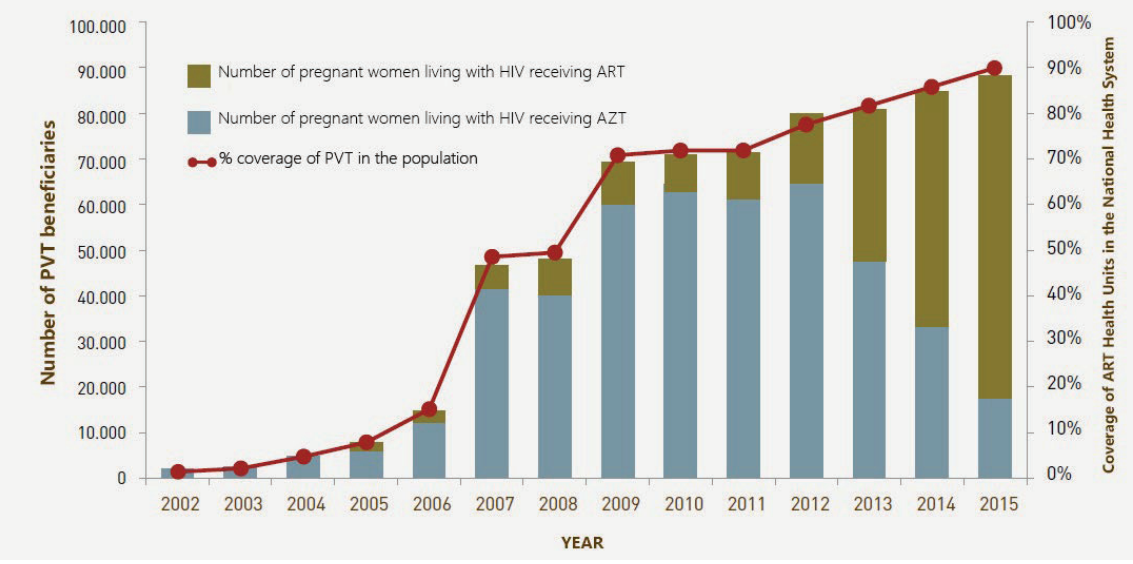


Figure 10. Expansion of the prevention of vertical transmission program in Mozambique.

PVT: prevention of vertical transmission. ART: antiretroviral treatment

Extracted from: Plano de Aceleração da Resposta ao HIV e SIDA Moçambique 2013-2015.

Since 2015, coverage of ART among pregnant women has improved. Programmatic data shows that in 2018, 98% of women in prenatal consultation knew their HIV status and 93% received ART (16). It also identified poor adherence to ART as a major obstacle to decreasing VT (16). Faulty adherence, results in low levels of viral suppression among pregnant and breastfeeding women thus allowing VT (16). However, VL monitoring is also a big challenge in the country, even among pregnant and breastfeeding women, who are considered a priority group in the expansion of VL testing. VL monitoring requires transportation and processing infrastructure, supply chain management, financial and human resources(47). All pregnant women should have a first VL performed 3 months after ART to assess achievement of VL suppression(48). Data from the National Program Quality of the National HIV Program in May 2018 showed that, only 11% of all eligible pregnant women (at least 3 months on ART) had a VL request, and only 6% received a VL result 3 to 6 months after initiation of ART (16) (Figure 11).

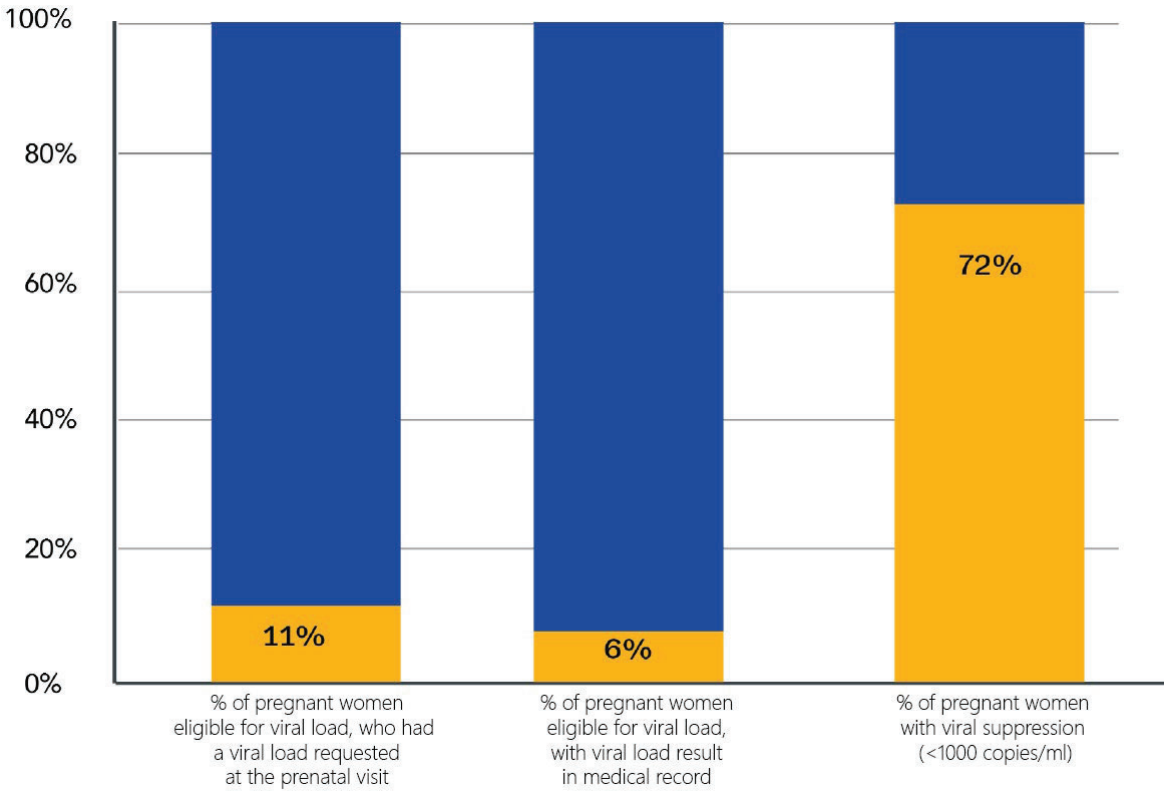


Figure 11. HIV viral load coverage in prenatal visits 2018.

Extracted from: Plano Nacional de Tripla Eliminação da Transmissão vertical do HIV, Sífilis e Hepatite B em Moçambique 2020-2024 (16).

Currently, a "National Plan for Triple Elimination of Vertical Transmission of HIV, Syphilis and Hepatitis B" has been launched for the period 2020-2024(16). Its ultimate goal related to HIV is putting Mozambique on the path to elimination of VT (16) for which it will be necessary to: 1). decrease VT to less than 5% and 2). decrease new pediatric infections to fewer than 750 cases per 100 000 live births (35).

b) Pediatric HIV care in Mozambique

Definitive diagnosis in infants requires a molecular virologic test, which in Mozambique was only available in centralized reference laboratories until recently, hindering the access and delivery of results (49). For this reason, although 73% of HIV-exposed children born from mothers attending prenatal consultations were tested with PCR in the first two months of age, more than a third of them did not have a definitive diagnosis at 18 months, according to 2018 data(16). In 2017 and 2018, point-of-care (POC) testing for early infant diagnosis, which produces a result in approximately 1 hour (49,50) was scaled up in the country (51). A cluster-randomized trial conducted in Mozambique during the scaling up of POC, showed that the median time from sample collection to diagnosis decreased from 125 days to 0, and the time between sample collection to ART initiation from 152 to 0 days, for the POC arm and the referred laboratory arm, respectively. (52). Data from UNAIDS 2020 showed that more than 80% of children living with HIV in Mozambique received an early diagnosis, defined as a diagnosis within the first two months of life(3).

Early diagnosis must be accompanied by early treatment, as it dramatically affects the clinical outcomes and child's wellbeing(53). The national criteria for initiating ART have evolved over time according to international pediatric ART guidelines and evidence. Historically, eligibility for ART was based on clinical (WHO stage) and immunologic (CD4 cutoffs) criteria(54,55). In 2008, national guidelines recommended ART initiation for all children living with HIV younger than 1 year, regardless of CD4 or WHO clinical stage(54,55). In 2010, this was expanded to children younger than 2 years (56,57) and in 2013 to those under 5(58,59). On the other hand, ART initiation for children 5 years or older, aligned with adult guidelines, continued to be based on clinical and immunologic criteria until 2016, when the test and treat strategy was adopted(43). During the imple¬mentation of the studies presented in this thesis, universal ART was recommended for children less than 5 years. For children 5 years or older criteria to initiate ART evolved from 350 cells/mm3 to 500 cells/mm3 in May 2015 (14,60), and to universal treatment in April 2017, when Test and Treat was fully implemented in the Manhiça district (12) (Figure 12). First and second line ART included two Nucleoside/tide Reverse Transcriptase Inhibitors (NRTI) and one Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTI) or protease inhibitor (PI)(14,61). Integrase inhibitors regime were progressively introduced for children since 2019 (44).

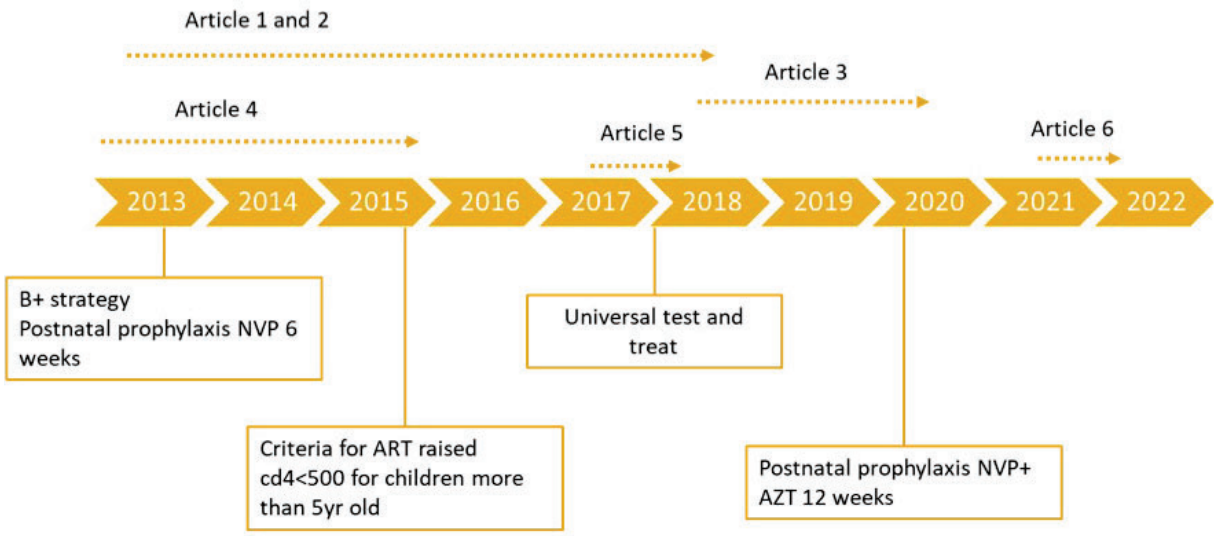
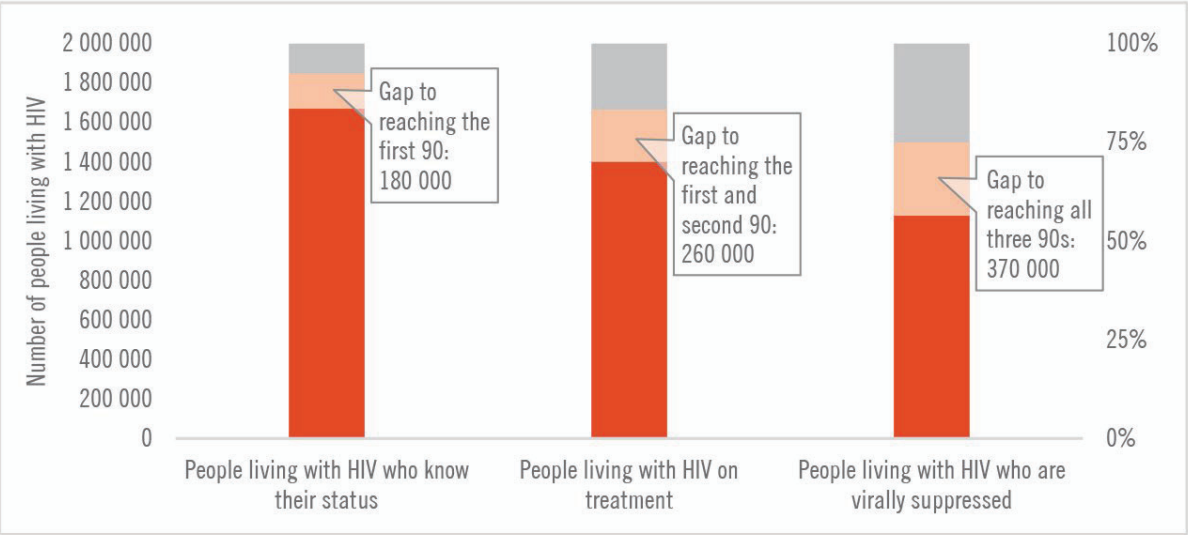


Figure 12. Timeline of this thesis research and the HIV prevention and treatment policies for children in Mozambique.

(Original)

Despite the progressive expansion of ART in the country, ART coverage among eligible children has remained low. The number of sites providing pediatric ART increased from 3 in 2003 to 223 in 2010 (56). However, in December 2010, 17 395 children were on antiretroviral treatment, constituting 34% of eligible children in the country(56). In addition, maintaining high quality of HIV care during rapid scaling of ART can be challenging. A study including a nationally representative sample of PLWHIV initiating ART in Mozambique in 2014, found lower retention among those patients who had initiated ART at small peripheral health units compared with those in the main health units(62). Currently, treatment coverage among children living with HIV is still low, 64% in 2020 (3). Nevertheless, the gap is even wider for viral suppression, which was only attained by 36% of those children on treatment, highlighting that obstacles on retention in care and on adherence to ART remain (3) (Figure 13).



All ages	81% [66–101%]	68% [55–85%] 1 402 900	55% [45–68%]
Children (0–14)	64% [51–87%]	64% [51–87%] 83 082	36% [28–48%]
Women (15+)	88% [71–108%]	73% [59–89%] 884 187	60% [49–74%]
Men (15+)	73% [59–91%]	62% [50–77%] 435 631	50% [40–62%]

Figure 13. HIV testing and treatment cascade in 2020 in Mozambique.

Extracted from: UNAIDS data 2021 (3).

Among the measures implemented in the country to improve pediatric HIV retention are the differentiated care models, including multimontlhy ART dispense, which was expanded in 2019 for clinically stable children older than 2 years (42,43).

The Manhiça District

The research presented in this thesis was conducted in the district of Manhiça, a semi-rural area located at 80km of the capital in Southern-Mozambique (Figure 14). The Manhiça Health Research Centre (CISM) has run a continuous health and demographic surveillance system (HDSS) for vital events since 1996(63), which since 2014, covers the entire district (17). In 2020, Manhiça constitutes an area of 2380 km2, with 201 845 inhabitants living in 46 441 households(17). The district's population pyramid is expansive, with large percentages of the population in the younger age groups, and skewed towards more women due to higher mortality for men as well as high rates of male labor migration to South Africa, particularly to the mines (17,64).

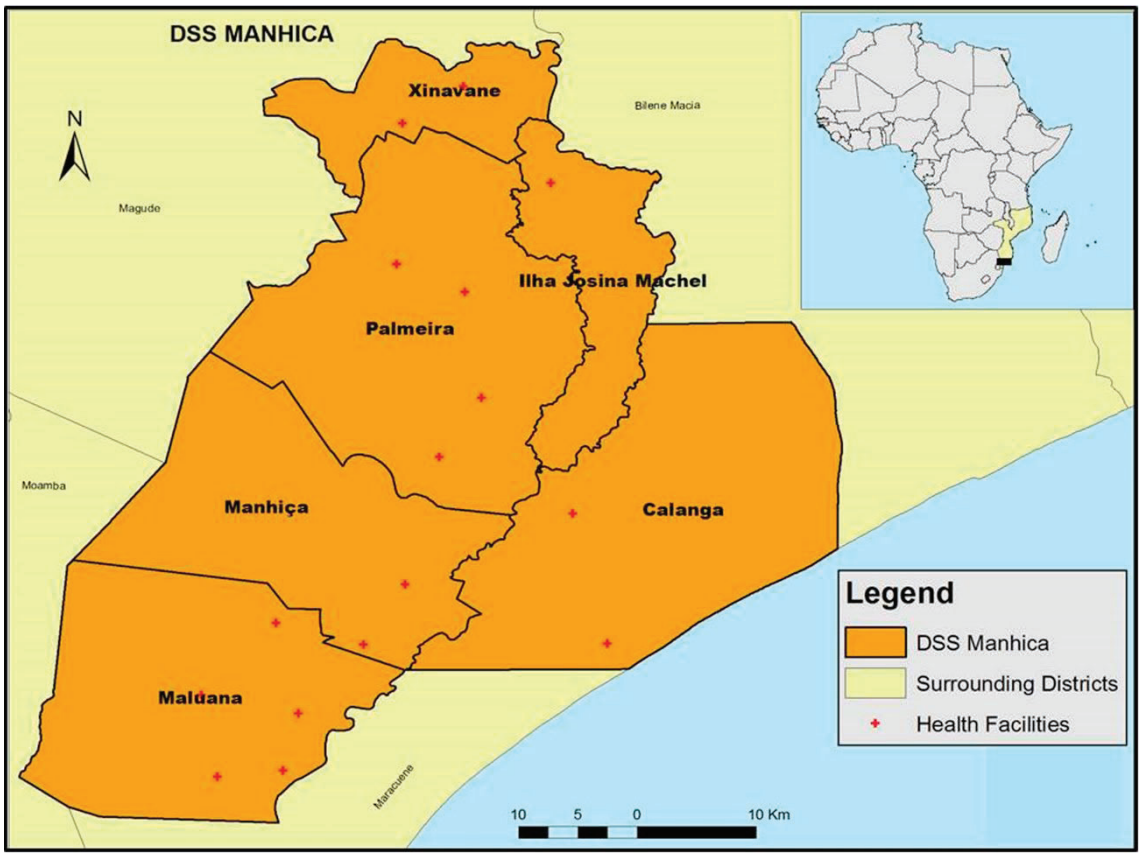


Figure 14. Location of the Manhiça health and demographic surveillance system study area.

Extracted from: Community knowledge and practices regarding antibiotic use in rural Mozambique: where is the starting point for prevention of antibiotic resistance? (65)

Mortality in children <5 years in the district has decreased dramatically, from 132 under-5 deaths per 1000 live births in 1998 to 76.4 in 2013 and 46.6 in 2019 (Figure 15) (17). Between 1997 and 2006, malaria and pneumonia were the leading causes of death among children (<15 years) in the district, accounting for 30% of deaths in this population (66). Therefore, the reduction in mortality is likely related to, among other factors, the introduction of the 10-valent pneumococcal conjugate vaccine in 2013(67), and the decline in malaria admissions and deaths in children in the district since 2002 (68) .

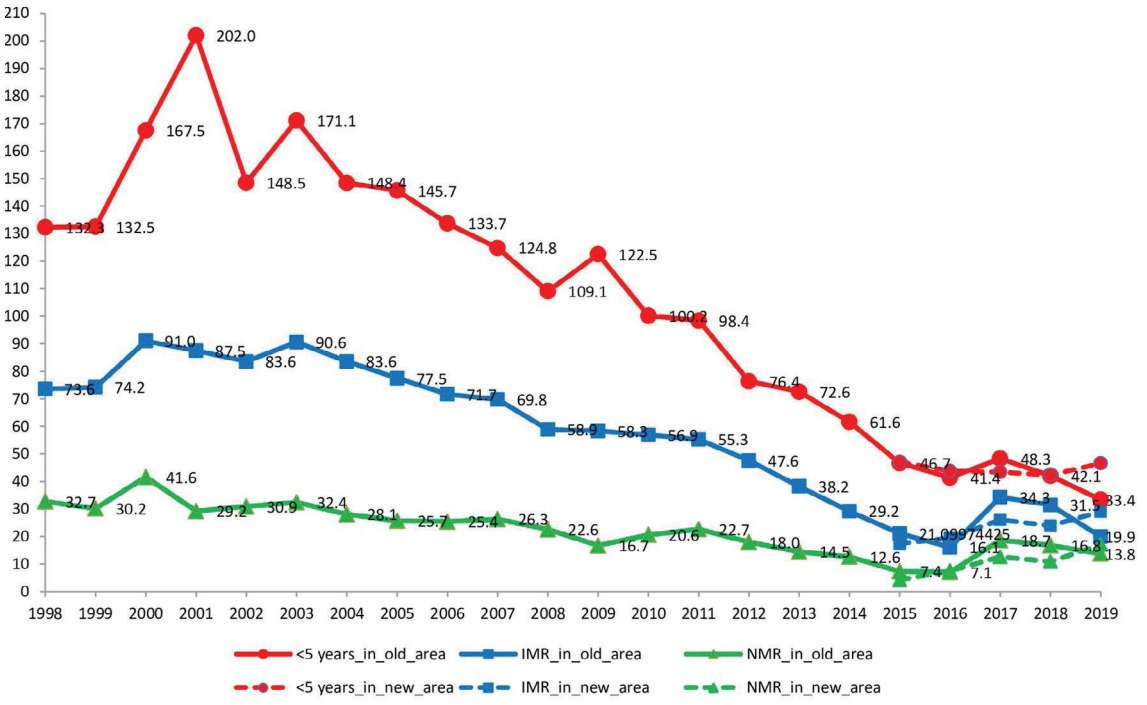


Figure 15. Mortality rates in neonates, infants and children <5 years old, Manhiça 1998–2019.

Extracted from: Cohort Profile Update: Manhiça Health and Demographic Surveillance System (HDSS) of the Manhiça Health Research Centre (CISM) (17).

The Manhiça District is served by fifteen health centers(17), including one rural hospital and the Manhiça District Hospital (MDH), the referral district hospital. HIV care is offered free of charge In all health facilities and routine patient-level HIV clinical data are prospectively trans¬cribed from paper-based patient charts into an electronic Patient Tracking System (ePTS), a database co-managed by the Ministry of Health and other stakeholders which was launched in 2012(69,70).

The estimated community prevalence of HIV among adults was 33.6% [95% Confidence Interval (CI): 32.5 to 34.6)] in 2015(18). Previous to the research included in this thesis, there were no estimates of pediatric prevalence in the Manhiça district. However, a prospective, observational cohort study conducted between August 2008 and June 2009, estimated a VT rate of 9% (95% CI: 3.7 to 14.7) in the first month of life among children born to mothers living with HIV and delivering a singleton live born at the Manhiça District Hospital (71).

The steps of the HIV care cascade were estimated for adults through a prospective cohort of adults newly diagnosed with HIV between 2014 and 2015 at the District (72). The overall linkage to care, as defined by having a CD4 count, was 43.7%, and 83.7% of eligible adults living with HIV initiated ART within the following 3 months, with a median time from diagnosis to ART initiation of 46 days [(IQR): 31–78]. Of those who initiated ART, the 12-month retention was 75.6% (95% CI: 70.2 to 80.5)(72). However, the pediatric HIV care cascade in the district and the impact of social realities on HIV care, such as migration, had not been evaluated before the research presented in this thesis.

COVID-19 pandemic: impact on HIV services

Since 2020, the COVID-19 pandemic has impacted HIV policies and continuity of HIV care worldwide. People living with HIV have been largely affected by the disruption of health services due to restrictive measures related to the COVID-19 pandemic (73). HIV prevention, testing and ART initiation of new patients, including testing and treatment services for the prevention of VT, were the most severely impacted, according to UNAIDS data (74). In contrast, countries implemented innovations in service delivery policy which ensured uninterrupted treatment among people already on ART(74).

Mozambique, in particular, declared a state of emergency in March 2020. This led to adaptations in the HIV program with the aim of maintaining uninterrupted HIV services, while reducing the frequency of visits and waiting time at health centers (75). Community-based HIV testing services and supportive and outreach home visits were suspended from April 2020 to Mid-September 2020(75). However, eligibility criteria for differentiated models were relaxed and access to mobile brigades in the community was expanded (76).

All research in this thesis was performed before the COVID-19 pandemic, with the exception of the evaluation of HRQoL among children living with HIV and HIV-negative children, which was performed post/during COVID-19 pandemic. This may have affected our results as COVID-19 has proven to have a negative impact on the HRQoL of children and adolescents (77).

Justification of the thesis

The objectives and results presented in this thesis are aligned with current international research priorities to “End inequalities and get on track to end AIDS by 2030”(34). A people-centered approach, that monitors progress and identifies gaps in the continuum of care among vulnerable subpopulations in the most affected geographic areas is essential to address inequities and reach the global goals.

Children at risk, affected or living with HIV, are clearly a vulnerable population whose care is lagging behind that of adults. The quality and achievements of the pediatric HIV prevention and care cascade differ greatly within and between countries. Mozambique is one of the countries with the highest number of new pediatric infections annually compared to others sub-Saharan African countries (11) and within the country, Southern Mozambique in general, and the Manhiça district in particular, has a disproportionately high HIV burden compared to the north of the country(78). The pediatric population of Manhiça, on which the research of this thesis is focused, is therefore a priority vulnerable group.

One of the priorities of the 2021-2026 global AIDS strategy is to maximize equitable and equal access to HIV services and solutions. Within this strategic priority there are 3 focus areas, including “Ending pediatric AIDS and eliminating vertical transmission” and “95-95-95 for HIV testing and treatment by 2025”(34), to which specific objectives 1-4 of the thesis are respectively aligned. The specific objective 5 of this thesis goes one step further and focuses on outcomes related to overall health and well-being, which is contemplated in the international key commitments of “Universal Health Coverage and Inclusion”(34). In addition, the results of this thesis presented in 6 manuscripts provide data to better understand pediatric epidemic and performance along the continuum of HIV care at subnational level. Therefore, our results are guiding more focused investments and services toward eliminating vertical transmission and improving the well-being of children living with HIV in the Manhiça District and in the country.

HYPOTHESIS

Hypothesis

To achieve the global target of eliminating new HIV infections among children and reach the 95/95/95/95 goals in the pediatric population by 2030, specific obstacles to quality of care must be identified and addressed through targeted interventions. We hypothesize that in the Manhiça district, major gaps reside in the prevention of VT during the postpartum period and in the retention in care of children after ART initiation. Identifying the steps of the prevention and care cascade amenable to quality improvement is key to improve service delivery.

OBJECTIVES

Objectives

The main objective of the research presented in this thesis is to identify the weakest steps in the pediatric HIV prevention and care cascade in the Manhiça district; a rural area of southern Mozambique with high HIV prevalence. This thesis will characterize the pediatric HIV prevention and care cascade and health related outcomes in children, from birth through to 15 years of age in the Manhiça district. Our results will inform public health interventions to address the specific obstacles and improve the delivery of comprehensive HIV prevention and care services for the wellbeing of children born to women living with HIV, at local level and in similar contexts.

The specific objectives of the study are:

1. To evaluate the risks and factors associated with vertical transmission in HIV- exposed children born to women during the 4 years after the rollout of the option B+.
    1.1. To estimate VT at the end of the breastfeeding period in children under 4 years of age. (Article 1).
    1.2. To identify sociodemographic and HIV-care factors associated with postpartum VT. (Article 2).
    1.3. To assess whether duration of breastfeeding is associated with higher postpartum VT. (Article 2).
2. To explore the optimization of the WHO algorithm for identification of infants with high risk of VT by including self-reported adherence to ART among mothers living with HIV. (Article 3).
3. To characterize the pediatric HIV care cascade in the Manhiça district and analyze factors associated with loss to follow up in the pre-test and treat era.
    3.1. To calculate rates of ART initiation, retention, LTFU and re-engagement in care (RIC) during a 3-year period after ART initiation among children living with HIV in the Manhiça district. (Article 4).
    3.2. To identify clinical and sociodemographic factors associated with LTFU and RIC. (Article 4).
4. To evaluate the impact of caregiver's mobility on the pediatric continuum of care. (Article 5).
5. To measure health related outcomes among children living with HIV in the Manhiça district.
    5.1. To estimate the mortality in children under 4 years of age born to HIV-positive mothers in the district of Manhiça after the adoption of the Option B+. (Article 1).
    5.2. To determine the health-related quality of life scores at 12-24 months after ART initiation among children in care at Manhiça District Hospital. (Article 6).

MATERIALS, METHODS AND RESULTS

Article 1

Community-based progress indicators for prevention of mother-to-child transmission and mortality rates in HIV-exposed children in rural Mozambique

Laura Fuente-Soro, **Sheila Fernández-Luis**, Elisa López-Varela, Orvalho Augusto, Tacilta Nhampossa, Ariel Nhacolo, Edson Bernardo, Blanca Burgueño, Bernadette Ngeno, Aleny Couto, Helga Guambe, Kwalila Tibana, Marilena Urso, Denise Naniche.

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Q1 (Public Health, Environmental and Occupational Health)

Specific objectives 1 and 5 and subobjectives 1.1 and 5.1

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BMC Public Health

RESEARCH ARTICLE Open Access

Community-based progress indicators for prevention of mother-to-child transmission and mortality rates in HIV-exposed children in rural Mozambique

Laura Fuente-Soro[1,2,3*], Sheila Fernández-Luis[1,2], Elisa López-Varela[1,2], Orvalho Augusto[1], Tacilta Nhampossa[1,4], Ariel Nhacolo[1], Edson Bernardo[5,6], Blanca Burgueño[2], Bernadette Ngeno[7], Aleny Couto[8], Helga Guambe[8], Kwalila Tibana[8], Marilena Urso[9] and Denise Naniche[1,2]

Abstract

Background: Eliminating mother-to-child HIV-transmission (EMTCT) implies a case rate target of new pediatric HIV-infections< 50/100,000 live-births and a transmission rate < 5%. We assessed these indicators at community-level in Mozambique, where MTCT is the second highest globally..

Methods: A cross-sectional household survey was conducted within the Manhiça Health Demographic Surveillance System in Mozambique (October 2017–April 2018). Live births in the previous 4 years were randomly selected, and mother/child HIV-status was ascertained through documentation or age-appropriate testing. Estimates on prevalence and transmission were adjusted by multiple imputation chained equation (MICE) for participants with missing HIV-status. Retrospective cumulative mortality rate and risk factors were estimate by Fine-Gray model.

Results: Among 5000 selected mother-child pairs, 3486 consented participate. Community HIV-prevalence estimate in mothers after MICE adjustment was 37.6% (95%CI:35.8–39.4%). Estimates doubled in adolescents aged < 19 years (from 8.0 to 19.1%) and increased 1.5-times in mothers aged < 25 years. Overall adjusted vertical HIV-transmission at the time of the study were 4.4% (95% CI:3.1–5.7%) in HIV-exposed children (HEC). Pediatric case rate-infection was estimated at 1654/100,000 live-births. Testing coverage in HEC was close to 96.0%; however, only 69.1% of them were tested early(< 2 months of age). Cumulative child mortality rate was 41.6/1000 live-births. HIV-positive status and later birth order were significantly associated with death. Neonatal complications, HIV and pneumonia were main pediatric causes of death.

Conclusions: In Mozambique, SPECTRUM modeling estimated 15% MTCT, higher than our district-level community-based estimates of MTCT among HIV-exposed children. Community-based subnational assessments of progress towards EMTCT are needed to complement clinic-based and modeling estimates.

Keywords: HIV, MTCT, Mozambique, Africa, Mother-to-child transmission, HIV-prevalence

* Correspondence: laura.delafuente@isglobal.org
[1]Centro de Investigação em Saúde de Manhiça, Maputo, Mozambique
[2]Barcelona Institute for Global Health, Barcelona, Spain
Full list of author information is available at the end of the article

Introduction

Elimination of mother-to-child HIV transmission (EMTCT) is a critical milestone in ending the HIV epidemic globally by 2030. The World Health Organization (WHO) defines EMTCT as a rate of < 50 new pediatric HIV infections per 100,000 live births and a transmission rate < 5% in breastfeeding infants, maintained for at least 1 year [1]. In 2012, with the aim of reducing mother-to-child HIV transmission (MTCT), the WHO recommended Option B+, an approach that ensured universal lifelong treatment for pregnant women (regardless of CD4 count) and daily nevirapine or zidovudine for their children during the first 4–6 weeks of life regardless of whether or not they were breastfeeding [2]. Currently, prevention and surveillance of MTCT (PMTCT) for HIV-exposed children (HEC) includes early infant diagnosis conducted between 4 and 6 weeks of life and clinical follow-up until 18 months of life or until the end of breastfeeding. Although the global number of annual new infections in children (aged 0–14 years) has decreased from 230,000 to 160,000 and the associated HIV-associated child mortality from 170,000 to 100,000 deaths (2012–2018), the absolute numbers of annual cases remain elevated, especially in sub-Saharan Africa [3]. In 2017, UNAIDS estimated that in Mozambique, 18,000 (95% confidence interval [CI]: 10,000–27,000) children aged 0–14 years were newly infected with HIV [3].

In resource-limited countries, retention in PMTCT services is sub-optimal. Nearly 40% of HIV-exposed uninfected children are lost to follow-up before the age of 18 months [4, 5], and less than 43% of HEC undergo recommended early testing (before 2 months of age) [6]. These children are at higher risk of infection and death [4, 7, 8], and, without treatment, half of HIV-positive children may die before 2 years of age [8]. Identification of HEC as well as early diagnosis and initiation of ART are crucial to reducing HIV-related mortality rates in children [8].

In 2018, Mozambique accounted for 10% of global MTCT worldwide [9], and national estimates from SPECTRUM and from a population-based survey showed MTCT of 15 and 12.6%, respectively [10, 11]. SPECTRUM is a mathematical model recommended by WHO to measure PMTCT program success [12]; however, estimates depend on the quality of clinical and population data and assumptions used by the algorithm. Contrasting these models with data from community-based measurements within mother-child pairs is key to understanding the final MTCT rates (i.e. after cessation of breastfeeding) and the impact of PMTCT programs in context [13].

We measured the EMTCT impact indicators among HIV-exposed children in the Manhiça district in Southern Mozambique born after country implementation of Option B+. Our results complement clinic-based and model-based predictions to provide more accurate progress indicators.

Methods

Study area and population

This cross-sectional household survey was conducted in the Manhiça District in southern Mozambique. In this semi-rural district of the Maputo province, the Centro de Investigação em Saúde de Manhiça (CISM)'s continuous HDSS documents vital events, including pregnancies, births, deaths, and migrations, since 1996 [14]. At the time of the study, the HDSS covered a total population of 186,000 individuals, 14% of whom were children aged < 5-years. In the District, community HIV-prevalence among women was estimated at 43.1% (95% CI: 37.6–48.5%) and 29.4% (95% CI: 26.7–32.0%) [15] for pregnant women attending antenatal consultations. This study included all six district administrative posts: Manhiça, 3 Fevereiro, Ilha Josina, Calanga, Maluana, and Xinavane.

The Manhiça District has 15 health centers, one rural hospital, and one referral district hospital where HIV care is offered free of charge and where Option B+ is recommended. After birth, HEC initiate 6 weeks of nevirapine, regardless of whether they were exclusively breastfed, and were tested by polymerase chain reaction (PCR; between 4 weeks and 9 months of age) and by rapid diagnostic test and confirmatory PCR (after 9 months of age). A final HIV test was performed at 18 months or 2 months after the end of breastfeeding following age-appropriate testing. Exclusive breastfeeding was recommended during the first 6 months and complementary breastfeeding during the first year [16].

National age-appropriate HIV-testing algorithm

The national algorithm for adults and children (aged > 18 months) uses two rapid antibody tests (Determine and Unigold) in series. Documented known HIV-positive individuals are not re-tested, but those who do not know their status or self-report being HIV-negative are tested according to the algorithm. Dried blood spot samples of children aged < 18 months are laboratory tested via HIV cDNA PCR, which detects proviral DNA. Non-reactive specimens are considered HIV-negative. Reactive specimens receive a second confirmatory HIV DNA PCR. A child with positive PCR and positive confirmatory PCR results is considered HIV-positive. In the case of discordant results, a second dried blood spot sample is collected, and a third PCR test is conducted. HIV testing is accompanied by pre-test and post-test counseling, and anyone who tests positive is referred for HIV care and treatment [17].

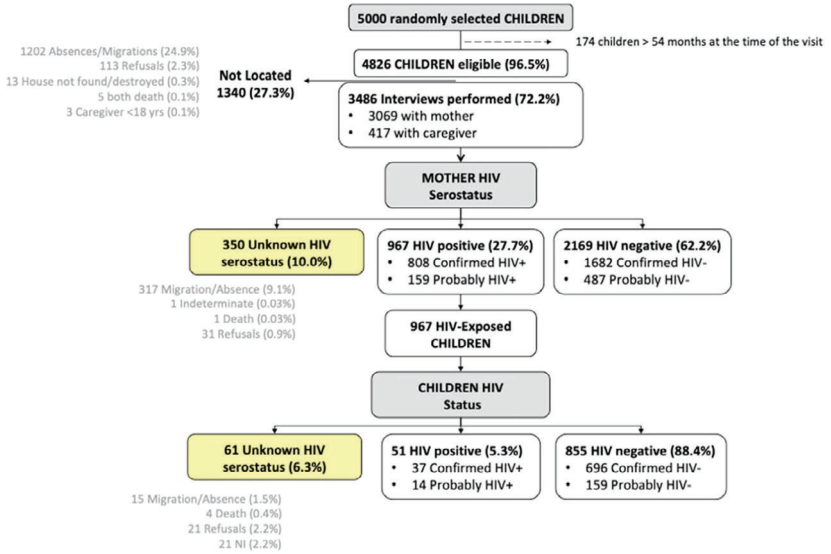

Fig. 1 Study profile of 5000 mother-child pairs randomly selected for the study of mother-to-child transmission of HIV. Percentages are calculated over the previous parent box. Definitions: Probably HIV+ included participants (i) who reported a previous HIV-positive result and without a confirmatory test result (ii) those with indeterminate confirmatory tests result or (iii) those who had died whose verbal autopsy suggested an HIV-positive status. Abbreviation: NI, no information

Study procedures and definitions

We used simple random selection to identify 5000 children born alive within the 4 years before study implementation (September 1, 2013–October 31, 2017) from a list of mothers aged > 14 years and residing in the HDSS area. A household visit was conducted between October 2017 and April 2018, and consenting mothers/caregivers completed a study-specific questionnaire. For each participant, three household visit attempts were made before defining the status as absent. If the mother was not available (due to absence, migration, or death), the child's main caregiver provided informed consent and completed the survey. Following the National population-based survey methodology [10], for all participants (mothers and children aged > 18 months) found HIV-positive during the study visit (through documentation or new diagnosis during the household visit), a laboratory confirmation was conducted through Geenius HIV-1/2 confirmatory assay. Mother and child HIV-status was determined through documentation, age-appropriate testing, laboratory confirmation, or verbal autopsy. For those children whose mother was not available and the main caregiver provided consent, age-appropriate testing was also offered. All methods were carried out in accordance with relevant guidelines and regulations.

Probable HIV-positive included mothers or children who reported a previous HIV-positive result and without a confirmatory test result after the household visit, those whose confirmatory tests had indeterminate results, or mothers or children who had died with retrospective verbal autopsy suggesting a HIV-positive status. Confirmed HIV-positive included mothers or children with documentation of a previous HIV-positive result or those with a HIV-positive result and a positive confirmatory test after the household visit. Children out of the MTCT services included known HEC who never tested for HIV before the study visit.

Data collection and management

The study-specific questionnaires included information on the pregnancy, history of previous HIV-testing for both mother and child, and sociodemographic information. Data from the home visits were directly collected in tablets using Open Data Kit software 1.4 [18] and were uploaded into a database in Research Electronic Data Capture (REDCap) at the end of the day [19]. Verbal autopsy interviews, adapted from the 2012 and 2016 WHO verbal autopsy sample questionnaire, were routinely conducted by CISM-trained laypersons as part of the HDSS, and results were analyzed using InterVA-M software, following the InterVA-4 model. Moreover, in all district health centers, since the day of HIV diagnosis, routine patient-level HIV clinical data are prospectively entered into an electronic patient tracking system, a Microsoft access database co-managed by the Ministry of Health and other stakeholders, where each participant had a unique numeric identifier that allows follow-up

Table 1 Baseline characteristics of HIV-exposed children ($n = 967$) by children's serostatus in Manhiça District, Mozambique

		UNKNOWN STATUS ($N = 61$)		HIV POSITIVE ($N = 51$)		HIV NEGATIVE ($N = 855$)	
Characteristics		**N**		**N**	**%**	**N**	
Median age at delivery in years (mother) (IQR)		30.7 (23.2–34.0)		25.9 (21.7–33.0)		28.7 (23.6–33.4)	
Mother age at delivery (years)	**< 19**	5	8.2%	8	15.7%	92	10.8%
	20–24	15	24.6%	11	21.6%	171	20.0%
	25–34	31	50.8%	27	52.9%	463	54.2%
	> 35	10	16.4%	5	9.8%	129	15.1%
Mother alive	**Yes**	59	96.7%	50	98.0%	847	99.1%
	No	2	3.3%	1	2.0%	8	0.9%
Educational level	**No education**	7	11.5%	8	15.7%	174	20.4%
	Basic	42	68.9%	36	70.6%	596	69.7%
	Medium/High	12	19.7%	7	13.7%	72	8.4%
	NI	0	0.0%	0	0.0%	13	1.5%
Marital status	**Single**	6	9.8%	3	5.9%	112	13.1%
	Married	48	78.7%	41	80.4%	604	70.6%
	Divorced/Widowed	7	11.5%	7	13.7%	139	16.3%
Income	**Domestic**	3	4.9%	1	2.0%	6	0.7%
	No fixed salary/agriculture	35	57.4%	24	47.1%	438	51.2%
	Fixed Salary	23	37.7%	26	51.0%	409	47.8%
	NI	0	0.0%	0	0.0%	2	0.2%
Type of administrative post (habitants)	**Big cities (> 15,000)**	20	32.8%	21	41.2%	353	41.3%
	Medium posts (5000)	34	55.7%	26	51.0%	401	46.9%
	Small posts (< 5000)	7	11.5%	4	7.8%	101	11.8%
ANC visits[a]	**No**	1	1.6%	3	5.9%	14	1.6%
	Yes	60	98.4%	48	94.1%	841	98.4%
Mother newly HIV diagnosed	**No**	57	93.4%	48	94.1%	801	93.7%
	Yes	4	6.6%	3	5.9%	54	6.3%
Parity at the time of the child's birth	**1**	10	16.4%	9	17.6%	117	13.7%
	2	13	21.3%	14	27.5%	157	18.4%
	3 or more	38	62.3%	28	54.9%	581	68.0%
Other children who died after born alive (including stillbirths)	**No**	48	78.7%	33	64.7%	596	69.7%
	Yes	13	21.3%	18	35.3%	255	29.8%
	NI	0	0.0%	0	0.0%	4	0.5%
Preterm birth	**Yes**	4	6.6%	3	5.9%	72	8.4%
	No	31	50.8%	24	47.1%	459	53.7%
	NI	26	42.6%	24	47.1%	324	37.9%
Place of birth	**Peripheric Health Unit**	44	72.1%	34	66.7%	527	61.6%
	Manhiça District Hospital	12	19.7%	14	27.5%	270	31.6%
	Home/On the way	4	6.6%	1	2.0%	37	4.3%
	NI	1	1.6%	2	3.9%	21	2.5%
Age at visit (months)	**< 6**	2	3.3%	0	0.0%	25	2.9%
	6–12	8	13.1%	10	19.6%	111	13.0%
	12–18	10	16.4%	6	11.8%	131	15.3%

Table 1 Baseline characteristics of HIV-exposed children ($n = 967$) by children's serostatus in Manhiça District, Mozambique *(Continued)*

		UNKNOWN STATUS ($N = 61$)		HIV POSITIVE ($N = 51$)		HIV NEGATIVE ($N = 855$)	
Characteristics		**N**		**N**	**%**	**N**	
	18–24	13	21.3%	8	15.7%	147	17.2%
	> 24	28	45.9%	27	52.9%	441	51.6%
Median age at visit in months (IQR)		22.8 (16.1–34.4)		25.3 (13.8–37.3)		24.6 (15.7–36.5)	
Sex	**Male**	23	37.7%	22	43.1%	434	50.8%
	Female	38	62.3%	29	56.9%	421	49.2%
Child breastfeed	**Yes**	57	93.4%	51	100.0%	831	97.2%
	No	4	6.6%	0	0.0%	24	2.8%
Median time of brestfeeding (IQR)		10.2 (6.0–15.0)		12.1 (9.1–18)		12.0 (7.0–16.0)	
Order of birth	**<= 3**	31	50.8%	30	58.8%	477	55.8%
	> 3	30	49.2%	21	41.2%	378	44.2%
Child born in Mozambique	**No**	1	1.6%	2	3.9%	21	2.5%
	Yes	60	98.4%	49	96.1%	834	97.5%
HIV prophylaxis (syrup)*	**Yes**	49	80.3%	29	56.9%	708	82.8%
	No	2	3.3%	7	13.7%	23	2.7%
	NI	10	16.4%	15	29.4%	124	14.5%
Updated age-appropriated vaccines	**Yes**	16	26.2%	18	35.3%	308	36.0%
	No	21	34.4%	16	31.4%	294	34.4%
	NI	24	39.3%	17	33.3%	253	29.6%
Child with OPD visits*	**No**	29	47.5%	12	23.5%	383	44.8%
	Yes	32	52.5%	39	76.5%	472	55.2%
Median number of OPD visits (IQR)*		1 (0–3)		2 (1–5)		1 (0–4)	
Number of OPD visits*	**None**	29	47.5%	12	23.5%	383	44.8%
	1–2	15	24.6%	16	31.4%	184	21.5%
	3–5	12	19.7%	11	21.6%	142	16.6%
	≥ 6	5	8.2%	12	23.5%	146	17.1%
Child with INPD visits*	**No**	57	93.4%	38	74.5%	804	94.0%
	Yes	4	6.6%	13	25.5%	51	6.0%
Median number of INPD visits (IQR)*		0.1 (0–0)		0.3 (0–1)		0.1 (0–0)	
Number of INPD visits*	**None**	57	93.4%	38	74.5%	804	94.0%
	1	4	6.6%	10	19.6%	42	4.9%
	2	0	0.0%	3	5.9%	9	1.1%

Abbreviations: *IQR* interquartile range, *ANC* antenatal consultations, *FU* follow-up, *OPD* out-patient department, *INPD* in-patient department, *NI* no information available. [a]ANC Visits: participants were asked if they performed at least one antenatal consultation during their pregnancy
* $p < 0.05$, ttest or Fisher's exact test, as appropiate

through the continuum of care. After data collection and extraction, the three databases were merged to construct the final study dataset for analysis.

Statistical analysis

We conducted descriptive analysis stratified by child HIV-serostatus, assessing proportions by Pearson and Fisher exact chi-square tests. HIV-prevalence and transmission were calculated through two different methods: naïve, which excluded mothers and children with unknown HIV-status from the denominator, and adjusted for missing HIV-status by multiple imputation chained equation (MICE). Following MICE procedures and assuming data were missing at random, 30 cycles of imputation were generated from the missing survey data, including age, education, marital status, religion, and

Table 2 Community HIV-prevalence in mothers and vertical transmission among HIV-exposed children for interviewed mother/caregiver-child pairs ($n = 3486$)

AGE GROUP	HIV PREVALENCE & TRANSMISSION				
	Naive[a]	95% CI	MICE[b]	95% CI	Fold-change in prevalence
MOTHER (years)	30.8%	29.2–32.5	37.6%	35.8–39.4	1.2
< 19	8.0%	5.9–10.9	19.1%	15.7–22.6	2.4
20–24	21.3%	18.7–24.1	31.8%	28.7–34.9	1.5
25–34	40.4%	37.7–43.1	44.8%	42.0–47.5	1.1
> 35	43.3%	39.0–47.6	47.4%	43.2–51.6	1.1
Child TOTAL	5.6%	4.3–7.3	4.4%	3.1–5.7	0.8
< 24 months	5.5%	3.7–8.1	4.9%	2.9–6.9	0.9
≥ 24 months	5.8%	4.0–8.3	4.0%	2.4–5.5	0.7

[a]For naive calculations, in both cases (mother and children), individuals with unknown serostatus were excluded. Thus, the denominators for naive community HIV prevalence were $n = 3136$ for mothers and $n = 906$ for children. [b]Mothers and children with unknown serostatus were treated as missing values, and estimates of prevalence and transmission were adjusted by multiple imputation (MICE). In children, the selected age to stratified the cohort was 24 months to compare our results with national data [10]. Fold-change in prevalence between naïve and adjusted values was calculated following the definition in the Methods section.
Abbreviations: *CI* confidence interval, *MICE* multiple imputation chained equation

neighborhood. The 30 prevalence estimates were combined according to Rubin rules [20]. Fold-change in prevalence between naïve and adjusted values were calculated by dividing the adjusted by the naïve estimate. Case rate of new pediatric HIV infections was calculated as the number of children exposed to HIV per 100,000 live births multiplied by the MTCT. Logistic regression was performed to assess factors associated with children with unknown HIV status and with a late infant HIV diagnosis. Variables with $p < 0.2$ on univariate analysis were included in multivariable analysis. Fine and Gray model was applied to estimate retrospectively the cumulative mortality rate and identify risk factors among participants over the 54 months preceding the study visit. Cumulative incidence estimation in the presence of competing risks was calculated following Coviello et al. [21]. Hazard ratios of the sub-distribution (sHR) and the corresponding 95% CIs were used as a measure of association. Statistical analyses were performed using Stata 15 [22].

Results

Study profile and baseline characteristics

Among the mother-child pairs randomly selected from the HDSS (Fig. 1), 4826 children were aged < 54 months at time of visit. Of those, 3486 (72.2%) mother/caregiver-child pairs (MCCP) participated. In most of the interviews, the respondent was the biological mother of the selected child, while 12.0% of mothers were not available (Fig. 1), and the child's caregiver completed the interview.

We identified 967 mothers and 51 children as probable or confirmed HIV-positive. An additional 350 (10.0%) mothers and 61 (6.3%) HEC had an unknown serostatus. Migration and absence during the study period were the main reasons for the mothers' unknown serostatus.

Baseline characteristics of HEC did not differ by child's serostatus for most variables (Table 1); however, a significantly ($p < 0.001$) lower proportion of HIV-positive children (56.9%) had received nevirapine prophylaxis compared to HIV-negative children (82.8%) or children with unknown status (80.3%). From birth until the survey, HIV-positive children (76.5%) had more outpatient hospital visits than did HIV-negative children (55.2%) or those with unknown serostatus (52.5%; $p = 0.01$) as well as more hospital admissions (25.2, 6.0, and 6.6%, respectively; $p < 0.001$). The median duration of breastfeeding in HEC was 12 months (interquartile range [IQR], 7.1–16.0) and significantly lower than median duration among HIV-unexposed children (for further information on breastfeeding among this cohort see Fernández-Luis et al. [23]).

Maternal HIV-prevalence and EMTCT impact indicators

The estimated unadjusted community HIV-prevalence among women with a live birth in the previous 4 years was 30.8% (95% CI: 29.2–32.5%; Table 2). However, after adjustment for mothers with unknown HIV serostatus, the estimate of HIV-prevalence increased significantly to 37.6% (95% CI: 35.8–39.4%). Specifically, adjusted HIV-prevalence doubled in mothers aged < 19 years (from 8.0 to 19.1%) and increased 1.5 times- in mothers aged < 25 years (from 21.3 to 31.8%; Table 2) as compared to unadjusted prevalence.

HIV transmission in HEC, adjusted for unknown maternal and child serostatus was 4.4% (95% CI: 3.1–5.7%) among children < 48 months and 4.9% (95% CI: 2.9–6.9%) among those aged < 24 months (Table 2). The cumulative rate of new pediatric HIV infections occurring

Table 3 Analysis of factors associated with never being HIV-tested before the study recruitment for HEC

		OR	95% CI	*p* value	aOR	95% CI	*p* value
Median age at delivery in years (mother)		**0.94**	**0.87–1.02**	**0.141***	0.92	0.83–1.01	0.094
Mother age at delivery (years)	**< 19**	ref	–	–			
	20–24	1.03	0.19–5.47	0.975			
	25–34	0.61	0.13–2.92	0.539			
	> 35	0.25	0.02–2.82	0.262			
Educational level	**None**	ref	–	–			
	Some	0.55	0.19–1.60	0.275			
Marital status	**Single**	**ref**	**–**	**–**	ref	**–**	**–**
	Married	**0.43**	**0.13–1.39**	**0.158***	0.43	0.11–1.75	0.241
	Divorced/Widowed	**0.62**	**0.13–2.87**	**0.544**	0.23	0.03–1.87	0.171
Income	**No fixed salary**	ref	–	–			
	Fixed Salary	0.79	0.30–2.10	0.634			
Type of administrative post (habitants)	**Big cities (> 15,000)**	ref	–	–			
	Medium posts (5000)	1.22	0.48–3.89	0.721			
	Small posts (< 5000)	2.03	0.74–9.89	0.324			
Parity	**1**	ref	–	–			
	2	2.85	0.33–24.9	0.344			
	3 or more	1.72	0.22–13.56	0.606			
Preterm birth (< 37 weeks)	**No**	**ref**	**–**	**–**	ref	**–**	**–**
	Yes	**5.72**	**1.58–20.73**	**0.008***	3.83	0.79–18.04	0.093
Place of birth	**Peripheric Health Unit**	**ref**	**–**	**–**	ref	–	–
	Manhiça District Hospital	**0.32**	**0.70–1.45**	**0.138***	0.23	0.04–1.23	0.086
	Home/On the way	**3.13**	**0.65–15.19**	**0.156***	2.64	0.40–17.29	0.312
Sex	**Male**	ref	–	–			
	Female	1.16	0.44–3.05	0.760			
Child breastfeed	**Yes**	**ref**	**–**	**–**	ref	–	–
	No	**4.62**	**0.98–21.67**	**0.052***	4.73	0.65–34.57	0.126
Order of baby	**<=3**	ref	–	–			
	> 3	0.61	0.22–1.67	0.333			
Child born in Mozambique	**No**	**ref**	**–**	**–**	ref	–	–
	Yes	**0.10**	**0.02–0.51**	**0.006***	0.16	0.02–1.48	0.107
HIV prophylaxis (syrup)	**Yes**	**ref**	**–**	**–**	**ref**	**–**	**–**
	No	**29.90**	**6.84–130.71**	**< 0.001***	**36.45**	**5.09–260.82**	**< 0.001***

This analysis was performed among HIV-exposed children, excluding those who died before 2 months of age, in Manhiça District, Mozambique ($n = 694$). Owing to adjustments for missing data with multiple imputation, no absolute numbers were included in the table, only proportions. *Abbreviations*: *CI* confidence interval, *OR* odds ratio, *aOR* adjusted odds ratio. * Variable with p < 0.2 on univariate analysis included in multivariable analysis

between birth was estimated at 1654 new infections per 100,000 live births.

Early infant testing and associated factors

Of the 967 mothers living with HIV (MLHIV) (see Figure S1), 708 (73.2%) received the diagnosis before the delivery of the child and 169 (17.5%) after delivery; for 90 (9.3%) of the MLHIV, the date of diagnosis was unknown. Although 95.6% (677/708) of the HEC had been tested for HIV at some point before our survey, only 69.1% (489/708 [95% CI: 65.5–72.5%]) had been tested in the first 2 months of life.

Risk factors for not having an HIV test were assessed among HEC of mothers infected before delivery (Table 3). Calculations excluded children who died in the first 2 months of life and for whom there was not enough time for initial testing. Multivariate logistic regression analysis showed that those children who did not receive HIV prophylaxis during their first 6 weeks of life were 36.45 (95% CI: 5.09–260.82) times more likely

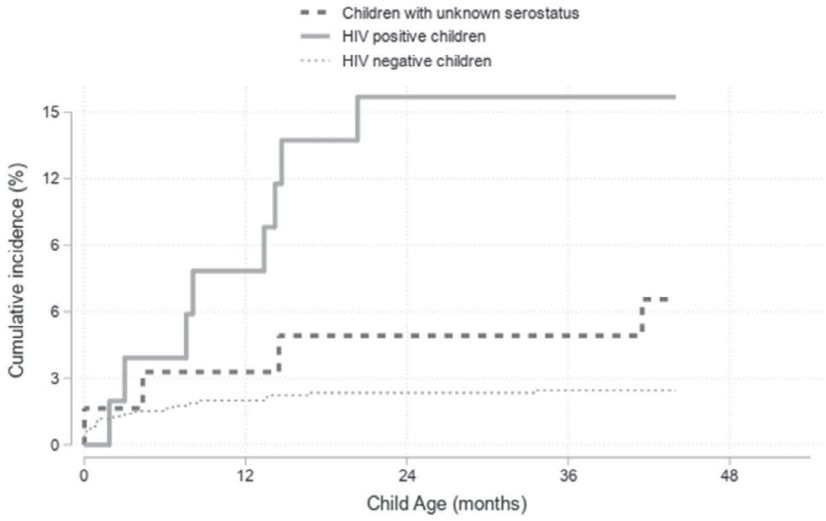

Fig. 2 Cumulative incidence of mortality, in the presence of competing risk, among HEC and stratified by children serostatus. Competing risk included migration outside of the health and demographic surveillance system

to be out of the MTCT services than those who did. Variables highly associated with a child never testing such as educational level and not attending antenatal consultations [ANC]) were not included in the multivariable model due to collinearity. All HEC whose mothers had medium/high education had been previously tested. All HEC whose mothers self-reported not attending ANC had not previously been tested (See Figure S2 for further information regarding the PMTCT retention in care among found mothers).

Child mortality

The cumulative incidence of death in the overall cohort was 41.6/1000 live births in the 54 months before the survey. Figure 2 shows the cumulative incidence of mortality among HEC, by serostatus and with the competing risk of migration. Among HEC and after adjusting by sex and birth order (Fig. 2), risk factors associated with death included HIV-positivity (asHR, 7.2 [95% CI: 3.3–15.9]; $p < 0.001$) and birth order > 3 (asHR, 3.1 [95% CI: 1.5–6.5]; $p = 0.003$). Moreover, close to the margin of significance ($p = 0.055$), children with unknown serostatus were 2.8 times (95% CI: 1.0–8.0) more likely to die than HIV-negative children.

Of the 149 children who died, 33 had been exposed to HIV. Cause of death was determined by verbal autopsy for 55.0% of the deceased children (see Table S1). Neonatal complications (30.5%; e.g., neonatal pneumonia, congenital malformations, sepsis, prematurity, and birth asphyxia), HIV-related causes (24.4%), and acute respiratory infections including pneumonia (17.1%) were the leading causes of death, followed by malaria (8.5%), non-communicable diseases (7.3%; mainly malnutrition), and diarrhea (6.1%). Median age of children who died of HIV-related causes was 14.0 months (IQR, 7.8–16.3); for those with unknown cause of death, median age was 7.7 months (IQR, 1.7–15.9); overall, median age at death was 6.8 months (IQR, 0.9–14.2).

Discussion

Our findings show that in the district of Manhiça, approximately one third of women who had had a child in the previous 4 years were living with HIV. Although the mother-to-child transmission was below 5%, the case rate of new pediatric HIV infections was 1654 per 100,000 live births, which exceeds the WHO target rate of 50 new HIV infections per 100,000 required to eliminate MTCT. The proportion of HEC our cohort that have been tested for HIV at some point before the study visit (thus before the age of 54 months) was close to 96%, however, early infant testing only occurred in 69.1% of these children. The main factors associated with not testing were lack of ANC for the mother and lack of infant HIV-prophylaxis in the first weeks of life. The cumulative overall child mortality rate in our cohort was 41.6 per 1000 live births; with HIV-infection and later birth order significantly associated with death. Neonatal complications, HIV, and pneumonia were the main causes of death in our pediatric cohort.

Our results show that the high HIV-prevalence in women who had a baby in the last 4 years, especially in women aged > 25 years, impedes reaching the EMTCT impact target of < 50 new HIV infections per 100,000 live births even with an MTCT rate < 5%. Although great

improvements in MTCT rates have been achieved, the case rate of new infections continues to exceed the WHO target and is similar to previous estimates [24]. As Goga et al. stated, in settings where HIV-prevalence in women is ≥10%, the case rate objective < 50 is not achievable [25]. With increasing access to lifelong ART, the HIV-prevalence in women of childbearing age may remain high for the next decade, even if we succeed in dramatically decreasing the rate of new infections in these women. Our findings thus support the global need of new monitoring targets adapted to high HIV-prevalence settings. Indeed, after adjusting for missing data, our estimates of prevalence in young women doubled, strongly suggesting that clinical and population-based estimates of prevalence may be underestimated in this population. Young women may be disproportionately left behind by the health system when monitoring the progress toward the global elimination of the HIV epidemic. HIV-testing for women of reproductive age is mainly performed during pregnancy via ANC services; however, several studies, especially in sub-Saharan Africa, have demonstrated that many young women do not access ANC services [26, 27]. Additionally, previous results at the national level show that close to 65% of pregnant women are lost to follow-up before completing the four recommended ANC visits [10], commonly due to migration, as described by our group and studies in other neighboring regions, such as KwaZulu Natal, where close to 50% of young women reported high rates of mobility [13, 28]. Migration and lack of access to ANC makes this vulnerable group less likely to be aware of their HIV-positive status and thus at higher risk of transmitting HIV to their children.

Our community-based MTCT estimates of 4.4% contrast with the national vertical transmission estimated at 15% by SPECTRUM and 12.6% in the national population-based survey conducted in 2015 [10, 11]. Both methods estimated MTCT at the national, whereas we have estimated at the district level. In addition, the accuracy of the SPECTRUM estimates depends on the availability and quality of the data used, however, in most resource-limited countries, clinical follow-up at health facilities is recorded on paper, and electronic monitoring tracking systems only include patients after their HIV-positive diagnosis, and no information regarding patients' relatives is registered. One of the main limitations of this model is that in the absence of quality data, the estimates generated through the model nay not represent the true situation of the epidemic in the country. After maternal HIV-diagnosis, follow-up of HEC is the second most crucial challenge to monitoring MTCT. Our findings highlight the importance of collecting community-based data and conducting analysis at subnational-level that allows to track mother-child pairs, link their clinical data and obtain more accurate and updated estimates at regional level that could be used to adjust national ones. The INDEPTH network of HDSS has shown the contribution of community-based demographic surveillance to improving estimates of malaria, fertility rates and death rates among others. Mozambique has three demographic HDSS which could be leveraged to help adjust program implementation indicators that might otherwise be overestimated [12, 13, 29].

Lack of ANC uptake in mothers and subsequent lack of PMTCT services among HEC were found to be the main factors associated with late HIV-testing (2 months after birth). In our cohort, coverage of HIV testing among HEC was high (96%), compared to national estimates where only half of HEC were tested after 2 years of age [10]; however timely diagnosis occurred in less than 70% of them. Early infant diagnosis and early treatment has been widely associated with decreased child mortality [10]. The lack of sustained ART for HIV-positive children, due to low testing and/or ART coverage, was shown across nine sites in South Africa to be largely responsible for rates of mortality. We found that children living with HIV are seven times more likely to die than HIV-negative children, and our findings support others that HIV continues to be the second leading cause of death among children aged < 5 years. Effective interventions that identify HEC and increase HIV testing, including mHealth, and healthcare strategies to improve the quality of care at facilities could help improve outcomes for HEC in high-HIV burden settings [30–33].

Community interventions that promote health education among adolescent mothers both during the prenatal and postnatal period have substantially decreased infant mortality rates and increased ANC uptake [34]. Strategies such as phone reminders, personal counseling, or home-visits may help re-engage women lost from ANC and maternal and child health care and ensure that those women who initially tested HIV-negative during pregnancy or breastfeeding [35] receive repeat testing [36, 37]. These strategies in parallel with linking mother and child clinical information would optimize the impact of PMTCT programs decreasing the number of new pediatric HIV infections and facilitating the timely diagnosis of HIV and treatment initiation among HEC. Furthermore, trans-border strategies could help facilitate clinical follow-up of young populations and ensure their health coverage to help control the HIV epidemic [38–40].

Strengths of our study include the HDSS platform, which not only records information on migration and deaths but also links the information of mother-child pairs and facilitates accurate HIV-prevalence estimates and MTCT rates among HEC at community level. Our

study had several limitations. First, even though we used different sources to determine the HIV status of all participants, 10% of the mothers and 6.3% children still did not know their serostatus. To account for these missing values, we applied multiple imputation assuming that HIV status was missing at random. However, there is evidence that these values may not be missing random; thus, we cannot exclude selection bias [41–43]. Second, our analysis is limited by the small sample size of the HIV-positive pediatric cohort and encourages caution as to the magnitude of associations of risk factors and not receiving timely testing.

Conclusions

In areas with high prevalence of HIV, even with an MTCT rate < 5%, the EMTCT impact target of < 50 new HIV infections per 100,000 live births may not be achievable. Indicators to galvanize PMTCT programs should be designed specifically for a spectrum of HIV-prevalence values > 10% in women of childbearing age. There is a need for novel models that also estimate the maximum incidence of new HIV infections in young women who will be bearing children in the next decade in order to truly reach the EMTCT targets. Ensuring that all pregnant women attend ANC services, especially adolescents and young mothers, could help reduce HIV incidence and increase ART coverage. Ensuring that all HIV-positive women know their status and that their children receive the necessary preventive care in a timely manner could help prevent HIV transmission and decrease mortality in CLHIV. Finally, quality community-level data are needed to adjust prevalence data in women of childbearing age as well as to adjust estimates on prevention of mother-to-child HIV transmission.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12889-021-10568-4.

Additional file 1: Figure S1. HIV testing history among seropositive women in our cohort and their children who participated in a study of mother-to-child transmission of HIV in Manhiça District, Mozambique. **Table S1**. Leading causes of death among deceased children (n = 82) in a study of mother-to-child transmission of HIV in Manhiça District, Mozambique. Children with unknown cause of death due to absence of verbal autopsy were excluded from the denominator. **Figure S2**. HIV testing history and PMTCT retention among women found at home who participated in a study of mother-to-child transmission of HIV in Manhiça District, Mozambique.

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Authors' contributions
DN, ELV, MU and LFS originated the concept for the study. LFS, SFL, OA, TN, EB, AN and BB developed and implemented study procedures. LFS, OA, ELV, SFL and DN analyzed the data. BN, AC, HG and KT aligned the protocol to national programme priorities. LFS wrote the initial draft of the manuscript and all authors contributed to revisions. All authors reviewed and approved the report.

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Availability of data and materials
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
This study was approved by the Mozambican National Bioethics Committee, the Institutional Review Boards at the Hospital Clinic of Barcelona (Spain) and the Manhiça Health Research Centre. It was also reviewed in accordance with the Centers for Disease Control and Prevention (CDC) human research protection procedures. The purpose of the study was explained to all participants, and written informed consent was obtained from mother/caregiver. For mothers aged 14–16 years, informed consent was provided by the legal representative of the young mother, after the mother assented.

Consent for publication
Not applicable.

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

Author details
[1]Centro de Investigação em Saúde de Manhiça, Maputo, Mozambique. [2]Barcelona Institute for Global Health, Barcelona, Spain. [3]ISGlobal, Barcelona Institute for Global Health, Rossello, 132, 08036 Barcelona, Spain. [4]Instituto Nacional de Saúde, Maputo, Mozambique. [5]Manhiça District Health Services, Maputo, Mozambique. [6]Vanderbilt Institute for Global Health, Nashville, Tennessee, USA. [7]Division of Global HIV and Tuberculosis, U.S. Centers for Disease Control and Prevention, Atlanta, USA. [8]Ministério da Saúde de Moçambique, Maputo, Mozambique. [9]Division of Global HIV and Tuberculosis, U.S. Centers for Disease Control and Prevention, Maputo, Mozambique.

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Publisher's Note

Article 2

Prompt HIV diagnosis and antiretroviral treatment in postpartum women is crucial for prevention of mother to child transmission during breastfeeding: Survey results in a high HIV prevalence community in southern Mozambique after the implementation of Option B+

Sheila Fernández-Luis, Laura Fuente-Soro, Tacilta Nhampossa, Elisa López-Varela, Orvalho Augusto, Ariel Nhacolo, Olalla Vazquez, Helga Guambe, Kwalila Tibana, Bernadette Ngeno, Adelino Jose Chingore Juga, Jessica Greenberg Cowan, Marilena Urso, Denise Naniche.

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Q1 (Multidisciplinary)

Specific objective 1 and subobjective 1.2 and 1.3

1. To evaluate the risks and factors associated with vertical transmission in HIV- exposed children born to women during the 4 years after the rollout of the option B+.

    1.2. To identify sociodemographic and HIV-care factors associated with postpartum VT.
    1.3. To assess whether duration of breastfeeding is associated with higher postpartum VT.

PLOS ONE

RESEARCH ARTICLE

Prompt HIV diagnosis and antiretroviral treatment in postpartum women is crucial for prevention of mother to child transmission during breastfeeding: Survey results in a high HIV prevalence community in southern Mozambique after the implementation of Option B+

Sheila Fernández-Luis[1,2]*, Laura Fuente-Soro[1,2], Tacilta Nhampossa[1,3], Elisa Lopez-Varela[1,2], Orvalho Augusto[1], Ariel Nhacolo[1], Olalla Vazquez[4], Anna Saura-Lázaro[1,2], Helga Guambe[5], Kwalila Tibana[5], Bernadette Ngeno[6], Adelino José Chingore Juga[7], Jessica Greenberg Cowan[7], Marilena Urso[7], Denise Naniche[1,2]

1 Centro de Investigação em Saúde de Manhiça (CISM), Maputo, Mozambique, **2** ISGlobal, Hospital Clínic, Universitat de Barcelona, Barcelona, Spain, **3** Instituto Nacional de Saúde (INS), Maputo, Mozambique, **4** Hospital Clínico Universitario de Santiago de Compostela, Santiago, Spain, **5** Ministério da Saúde de Moçambique (MISAU), Maputo, Mozambique, **6** U.S Centers for Disease Control and Prevention (CDC), Atlanta, Georgia, United States of America, **7** U.S Centers for Disease Control and Prevention (CDC), Maputo, Mozambique

* sheila.fernandez@isglobal.org

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Abstract

Objective

World Health Organization recommends promoting breastfeeding without restricting its duration among HIV-positive women on lifelong antiretroviral treatment (ART). There is little data on breastfeeding duration and mother to child transmission (MTCT) beyond 24 months. We compared the duration of breastfeeding in HIV-exposed and HIV-unexposed children and we identified factors associated with postpartum-MTCT in a semi-rural population of Mozambique.

Methods

This cross-sectional assessment was conducted from October-2017 to April-2018. Mothers who had given birth within the previous 48-months in the Manhiça district were randomly selected to be surveyed and to receive an HIV-test along with their children. Postpartum MTCT was defined as children with an initial HIV positive result beyond 6 weeks of life who initiated breastfeeding if they had a first negative PCR result during the first 6 weeks of life or whose mother had an estimated date of infection after the child's birth. Cumulative incidence accounting for right-censoring was used to compare breastfeeding duration in HIV-exposed

Data Availability Statement: Data cannot be shared publicly because of ethical restrictions. Data contain potentially sensitive information and national ethics committee (CNBS) does not authorize data sharing without a protocol request specifying the objectives and the researchers who will have access to the data. Data are available under request (contact via llorenc.quinto@isglobal.org) for researchers who meet the criteria for access to confidential data. We are sharing a copy, in both the original language and English of the questionnaire of the study as Supporting Information.

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and unexposed children. Fine-Gray regression was used to assess factors associated with postpartum-MTCT.

Results

Among the 5000 mother-child pairs selected, 69.7% (3486/5000) were located and enrolled. Among those, 27.7% (967/3486) children were HIV-exposed, 62.2% (2169/3486) were HIV-unexposed and for 10.0% (350/3486) HIV-exposure was unknown. Median duration of breastfeeding was 13.0 (95%CI:12.0–14.0) and 20.0 (95%CI:19.0–20.0) months among HIV-exposed and HIV-unexposed children, respectively (p<0.001). Of the 967 HIV-exposed children, 5.3% (51/967) were HIV-positive at the time of the survey. We estimated that 27.5% (14/51) of the MTCT occurred during pregnancy and delivery, 49.0% (2551) postpartum-MTCT and the period of MTCT remained unknown for 23.5% (12/51) of children. In multivariable analysis, mothers' ART initiation after the date of childbirth was associated (aSHR:9.39 [95%CI:1.75–50.31], p = 0.001), however breastfeeding duration was not associated with postpartum-MTCT (aSHR:0.99 [95%CI:0.96–1.03], p = 0.707).

Conclusion

The risk for postpartum MTCT was nearly tenfold higher in women newly diagnosed and/or initiating ART postpartum. This highlights the importance of sustained HIV screening and prompt ART initiation in postpartum women in Sub-Saharan African countries. Under conditions where HIV-exposed infants born to mothers on ART receive adequate PMTCT, extending breastfeeding duration may be recommended.

Introduction

Globally in 2019 there were 1.7 million children living with HIV [1]. Children predominantly acquire HIV infection through mother-to-child transmission (MTCT), either during pregnancy, delivery, or breastfeeding. Without preventive interventions, the risk of MTCT is 30–40%, and breastfeeding is responsible for one-third to one-half of these transmissions [2]. However, specific preventive interventions such as antiretroviral treatment (ART) to the mother and antiretroviral prophylaxis to the child can reduce MTCT to less than 5%, even in high HIV burden settings [3, 4].

In order to eliminate MTCT, the Joint United Nations Programme on HIV/AIDS (UNAIDS) and United States President's Emergency Plan for AIDS Relief (PEPFAR) launched the Start Free Stay Free AIDS Free strategy in 2016 [5]. It focuses on the 23 countries with the highest burden of pregnant women and children living with HIV. In 2018, these 23 countries had a rate of MTCT during pregnancy and delivery, (calculated as first 6-week MTCT-rate), of 6.3% [95%CI: 4.9–9.1%] and a rate of MTCT at the end of breastfeeding of 11.8% [95%CI: 9.8–15.2%] [5]. The number of new infections was unevenly distributed; of 130 000 children who acquired HIV in 2018, half came from just six countries (Kenya, Mozambique, Nigeria, South Africa, Uganda and the United Republic of Tanzania) [5].

Breastfeeding contributes substantially to the health, development and survival of young children, particularly in settings with high mortality from diarrhea, pneumonia and malnutrition among children under five years of age [6]. Among HIV-exposed children, breastfeeding has been shown to increase the HIV-free survival at 9 and 18 months of life compared with

formula-feeding [7, 8]. Breastfeeding practices of women living with HIV are influenced by the social circumstances in which mothers make decisions, the fear of transmission, and also the attitudes, knowledge, and updating of health care workers about current guidelines [9–11].

World Health Organization (WHO) adapted its guidelines over time, aiming to balance the benefits of breastfeeding with the risks of HIV transmission. In 2007, WHO recommended exclusive breastfeeding for six months unless replacement feeding was feasible, sustainable and safe for the HIV-positive mothers and their infants [12]. In 2010, the recommendation was extended to 12 months, while antiretrovirals were provided either to the mother or the infant throughout breastfeeding to reduce the risk of postnatal HIV transmission [13]. By 2016, the B + strategy was brought to scale globally, ensuring that the HIV-positive pregnant and breastfeeding women were offered lifelong ART regardless of their CD4 count. At the same time, enhanced post-natal prophylaxis with daily zidovudine (ZDV) and nevirapine (NVP) for a total of 12 weeks was recommended among HIV-exposed children at high risk of acquiring HIV who were breastfeeding [14]. With the expansion of durable ART access for lactating women, WHO again updated its recommendations, advising that HIV+ women should continue to breastfeed for at least 12 months, but ideally for up to 24 months or longer while remaining fully ART adherent [15]. However, this revised guidance promoting extended breastfeeding was based on low to moderate quality evidence [15].

Mozambique adopted the B+ strategy in 2013 [16] and the "test and treat" strategy, in which ART is initiated for all people living with HIV as soon as possible after diagnosis, in 2016 [17]. Nevertheless, in 2018, although more than 95% of HIV-positive pregnant women in Mozambique received ART, the rate of MTCT at the end of breastfeeding was 15.0% [95% CI: 11.8–19.0%]:7% during the first 6-weeks postpartum and 8% during breastfeeding [5], accounting for 10% of global MTCT infections among the Start Free Stay Free AIDS Free priority countries [5]. In 2011, the median duration of total breastfeeding in the general population of Mozambique was 20.8 months [18]. However, there are no updated data on total duration of breastfeeding disaggregated by mother's HIV-serostatus or on the impact of breastfeeding duration on mother-to-child transmission in Mozambique. Although there are no data about ART adherence and viral load during breastfeeding period at national level, a controlled clinical trial performed in central Mozambique between 2014–2015 among pregnant and breastfeeding women in B+ showed that without intervention, 52.3%, 46.1% and 38.3% of them returned for 30-day, 60-day and 90-day ART refills, respectively [19]. In the other hand, PEPFAR data showed viral load coverage in pregnant women was approximately 60% and viral suppression 80% at national level in 2020 [20]. Until September 2019, postnatal prophylaxis consisted of 6 weeks NVP to all infants [21, 22] and thereafter enhanced postnatal prophylaxis has been recommended to all HIV exposed infants in Mozambique [23].

We compared the duration of breastfeeding in HIV-exposed and HIV-unexposed children and we identified sociodemographic and HIV-care factors associated with postpartum MTCT, through a cross-sectional household survey in a semi-rural population of southern Mozambique with a high HIV community prevalence [24].

Methods

Study setting

The study was conducted within the Health and Demographic Surveillance System (HDSS) run by the Manhiça Research Health Center since 1996, which is located in Maputo Province, southern Mozambique [25]. The HDSS platform currently extends over the entire district of Manhiça, which has an area of 2,380 square kilometers and covers 46,441 households and 201,383 inhabitants, each one with a unique identification number. Every household is visited

twice a year to collect data on vital events such as births, deaths, pregnancies and migrations [25]. Verbal autopsies are used to attribute a cause of death to all recorded death events, including those that occurred in the community, in accordance with WHO Verbal Autopsies Instrument Form 2016 [26].

The Manhiça District is served by fifteen health centers, one rural hospital and one referral district hospital. All public health facilities offer free access to HIV care and treatment. Routine patient-level HIV clinical data is recorded by providers in a paper-based system and prospectively entered into an electronic patient tracking system.

At the time of the study, the B+ strategy was already implemented in all the health facilities which provided free ART to HIV-positive pregnant or breastfeeding mothers and 6 week Nevirapine prophylaxis for HIV-exposed children, regardless of both the feeding method and whether the mother's diagnosis and ART initiation occurred during pregnancy or breastfeeding period [21, 27]. The ART regimen that most pregnant and lactating women received during the time period of this study was Tenofovir Disoproxil Fumarate/Lamivudine/Efavirenz (TDF+3TC+EFV) [21, 27].

Study design and study population

Between October 2017 and April 2018, 5000 of the total children born alive in the previous 48 months within the HDSS were randomly selected to participate in this cross-sectional household survey. After informed consent was obtained, the survey was conducted with mothers, or in case of a mother's absence, migration or death, with the child's primary caregiver. Study HIV counselors administered a specific questionnaire designed to capture sociodemographic characteristics, HIV testing history and ART, antenatal care and duration of breastfeeding.

For each individual mother and child, HIV-status was ascertained through documentation of previous testing, conducting age-appropriate testing with laboratory confirmation or verbal autopsy. Mothers who do not know their status or self-report being HIV-negative were tested at survey, as well as the HIV-exposed children. For children under 18 months of age, HIV diagnosis was determined with molecular testing through HIV DNA Polymerase Chain Reaction (PCR). Children 18 months or older and mothers were tested following the National HIV testing algorithm [21] which included two serial rapid diagnostic tests, Determine [28] and Unigold [29]. Documented known HIV-positive individuals were not re-tested, however for study purposes, all HIV positive participants (including those who were diagnosed prior to or during the study visit) underwent confirmatory testing through Geenius HIV-1/2 Confirmatory Assay [30]. Clinical documentation was also used to obtain information about gestational age and infant antiretroviral prophylaxis. Verbal autopsy from HDSS database was used to ascertain HIV status in children and mothers who had died before the survey. Hospitalizations and outpatients' visits were also obtained through the HDSS database. Information about maternal viral load and CD4 was extracted from the routinely collected data in the electronic patient tracking system, a Microsoft access database [31] co-managed by the Ministry of Health and other stakeholders, where each participant living with HIV had a unique numeric identifier that allows follow-up through the continuum of care [32].

Definitions

HIV exposure was defined as follows: i) a child whose mother had a documented HIV-infection before birth or at the end of breastfeeding (confirmed exposure) and ii) a child born to a self-reported HIV-positive mother for whom the time of the mother's infection could not be determined (probable exposure). Children born from HIV negative mothers were considered

HIV-unexposed. If the mother was deceased and her HIV-status could not be confirmed, the child´s exposure was considered unknown and were excluded from the analysis.

Date of HIV infection in the mother was estimated as follows:

1. In case of documentation of a previous HIV-negative test, date of infection was assumed to be equal to the midpoint between the last negative HIV test and the day of the survey for mothers of children who are less than 23 months of age. If the interval between the test and the survey was less than 24 months, the midpoint between last negative HIV test and first positive test was used. If the interval was greater than 24 months, the date of seroconversion was not estimated due to the larger uncertainty in the estimation.
2. In case of documentation of a previous HIV-positive test, this was assumed to be the date of infection.
3. In case of no previous documentation and a first positive test on the day of the survey, time of infection was defined as the midpoint between serosurvey and date of most recent delivery.

MTCT was assumed to occur during pregnancy and delivery if the child had a positive PCR result during the first 6 weeks of life [15, 33, 34]. Postpartum MTCT was defined for children with an initial HIV positive result beyond 6 weeks of life who initiated breastfeeding if 1) they had a first negative PCR during the first 6 weeks of life, or 2) did not have a prior negative PCR but whose mother had an estimated date of infection after the child's birth. For children born to mothers with date of infection prior to child's birth but without a DNA PCR by 6 weeks of age, the date of MTCT was considered unknown.

Breastfeeding included any type of breastfeeding (exclusive, mixed and any breastfeeding after the introduction of complementary feeding) since birth. The mother or caregiver self-reported the total duration of any breastfeeding in months at the time of survey.

Statistical analysis

Medians and interquartile ranges (IQR) were calculated to describe continuous variables and categorical variables were summarized using frequencies and its 95% confidence intervals. Comparisons between groups were made using Pearson chi-square or Fisher exact test and Kruskal Wallis tests, as applicable. In addition, we performed two analyses:

First, we estimated breastfeeding duration in HIV-exposed and HIV-unexposed children with cumulative incidence of breastfeeding cessation, accounting for right censoring. Children who had not initiated breastfeeding were excluded from this analysis. HIV-exposure was evaluated as a factor associated with breastfeeding duration through Fine-Gray regression, using mortality as competing risk and adjusted for age and sex in a multivariable model.

Second, among HIV-exposed children who had been breastfed at any time, we performed a Fine-Gray regression analysis to assess factors associated with postpartum MTCT, adjusting for age and sex and considering mortality a competing risk factor. Infants with MTCT during pregnancy and delivery and children in which it was not possible to establish whether MTCT was during pregnancy and delivery or postpartum were excluded from this analysis. A multivariable model was built including the variables with a p-value lower than 0.20 in the bivariate analysis and with less than 20% missing values. Time-varying covariates were handled by episode splitting. Variables age of the child, sex of the child, mother ART initiation and breastfeeding duration were forced-in covariates due to their clinical relevance. The variable 'mother ART initiation' was treated as a binary variable: ART initiation before delivery yes/no, and had more than 20% missing values. The missing data was addressed through multiple imputation

using a logistic regression imputation method including our outcome variable and the other predictor variables. A total of 20 imputations were performed.

Data was analyzed using Stata statistical software version 16 (Stata Corp., College Station, Texas, USA) [35].

We conducted a sensitivity analysis considering the time of infection of the mother as random date selected from a uniform distribution, a point at the quarter of the interval between the two dates considered at definition and a point at the three-quarters of the interval between the two dates specified above in definitions section.

We conduct another two sensitivity analysis considering the 61 children HIV-exposed with unknown HIV serostatus as HIV-positive and the 12 children HIV-positive with no information on time of HIV acquisition as postpartum MTCT, respectively.

Ethics statement

This study was approved by the Mozambican National Bioethics Committee and the Barcelona Hospital Clinic Institutional Review Board. It was also reviewed in accordance with CDC human research protection procedures and was determined to be research, but CDC investigators did not interact with human subjects or have access to identifiable data or specimens for research purposes. Written informed consent was obtained from the mothers/caregivers of all children for the mothers/caregiver and children participation. In case of mothers between 14–16 years old, informed consent was provided by the legal representative of the young mother, after the mother's consent.

Results

Among the 5000 mother/caregiver-child pairs randomly selected for participation, 4826 children were eligible (96.5%) and 174 children were older than 54 months at the time of the visit, and excluded of the study. A total of 1340 mother/child pairs were not located and 3486 were enrolled. Among those, 27.7% (967/3486) children were considered to be HIV-exposed (probable or confirmed), 62.2% (2169/3486) were HIV-unexposed and for 10.0% (350/3486) HIV-exposure was unknown (Fig 1). Taking into account the estimated date of infection of the mother according to assumptions in methods, 77.7% (751/967) were considered exposed to HIV during pregnancy and delivery, 13.2% (128/967) were exposed only in the postpartum period and 9.1% (88/967) were unknown. Among the children exposed only in the postpartum period, 47.6% (61/128) were characterized as HIV-exposed based on maternal HIV testing performed during the study visit and 14% (18/128) were still breastfeeding when their mothers started on ART.

Baseline characteristics differed between HIV-positive and HIV-negative mothers, and their respective children, with the exception of place of birth, child's gender, gestational age and age of the child at the time of study visit (Table 1).

HIV positive mothers were significantly more absent from the household at the time of survey with the caregiver responding, as compared to HIV-negative mothers (8.8% vs 0.0%, $p<0.001$). HIV-positive mothers were significantly older, with a median age of 28.7 years (IQR: 23.4–33.4) compared with HIV-negative mothers whose median age at survey was 22.6 years (IQR: 18.8–29.3), $p<0.001$. Almost all the mothers had attended at least one antenatal visit, but the proportion was higher among the HIV-positive mothers (98.1% vs 93.0%, $p<0.001$).

Only 34.1% (330/967) of HIV-positive mothers had at least one viral load result at the time of survey. However, 75.8% (250/330) of the mothers with viral load results were virally suppressed.

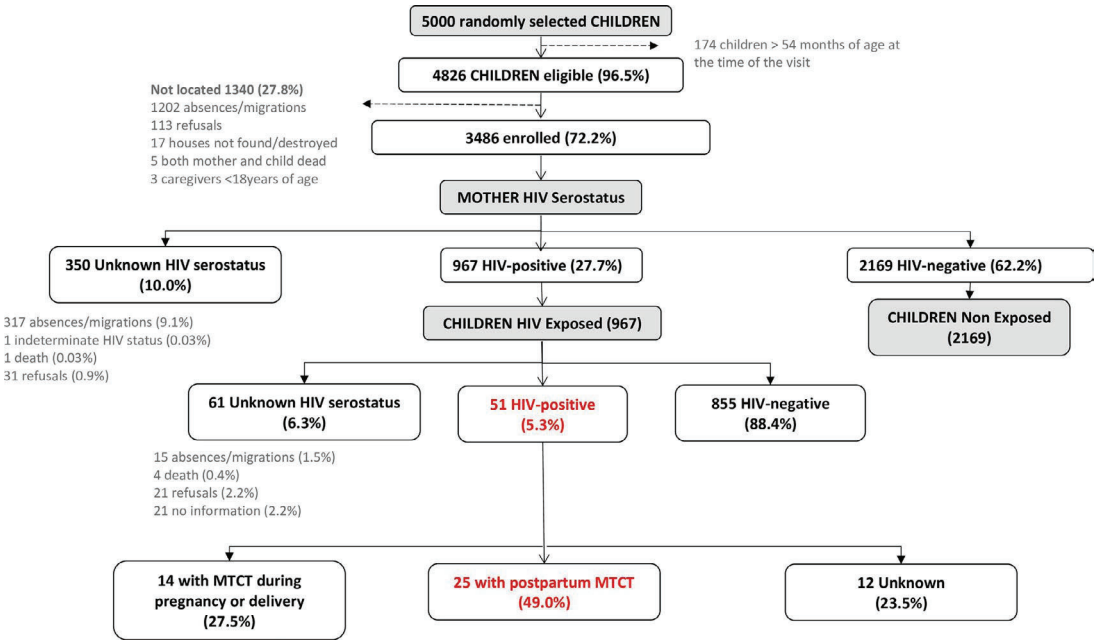

Fig 1. Study profile among the 5000 mother-child pairs randomly selected for the study. Percentages are calculated over the previous parent box. MTCT = maternal to child transmission. MTCT during pregnancy and delivery was defined as having a positive PCR result during the first 6 weeks of life. Postpartum MTCT was defined for children with an HIV positive result beyond 6 weeks of life who initiated breastfeeding if 1) they had a first negative PCR during the first 6 weeks of life, or 2) did not have a prior negative PCR but whose mother had an estimated date of infection after the child's birth.

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Breastfeeding duration among HIV-exposed and HIV-unexposed children

In our cohort, the proportion of children who had never breastfed was significantly higher among HIV-exposed children (2.9%, 28/967), than among HIV-unexposed children (0.5%, 11/2169), p<0.001 (Table 1).

The median duration of breastfeeding was 13.0 (95%CI: 12.0–14.0) and 20.0 months (95% CI: 19.0–20.0) among HIV-exposed and HIV-unexposed children respectively, and the risk of discontinuing breastfeeding was almost two-fold higher among HIV-exposed children [adjusted Sub-Hazard Ratio (aSHR) 1.85 (95%CI: 1.67–2.05), p<0.001] (Fig 2). The cumulative incidence of HIV-exposed children breastfeeding dropped at 6 months as compared to unexposed children. At 12 months, only 56.4% (95%CI: 53.2%-59.5%) of HIV-exposed infants were breastfeeding as compared to 77.3% (75.4%-79.0%) of unexposed infants. The gap in breastfeeding between HIV exposed and unexposed children continued through to 18 months of age.

Postpartum MTCT and associated factors

Of the 967 HIV-exposed children, 5.3% (51/967) were HIV-positive, 88.4% (855/967) were HIV-negative and 6.2% (61/967) with unknown serostatus at the time of the survey. Among the HIV-positive, according to the definitions in methods, we estimated that 49.0% (25/51) of the MTCT occurred postpartum, 27.5% (14/51) during pregnancy and delivery and for 23.5% (12/51) of children the period of infection remained unknown.

Table 1. Characteristics of HIV-exposed and HIV-unexposed children at the time of the survey (n = 3136). The 350 children for whom HIV exposure could not be ascertained are not included.

		HIV-UNEXPOSED (N = 2169)		HIV-EXPOSED (N = 967)		TOTAL (N = 3136)		
		N	%	N	%	N	%	p value
MOTHER								
Age of the mother at delivery in years (IQR)*		22.6 (18.8–29.3)		28.7 (23.4–33.4)		24.8 (19.7–31.2)		**<0.001**
Mother located during the household survey**	**Yes**	2164	99.8%	871	90.1%	3035	96.8%	**<0.001**
	Absent or migrated	0	0.0%	85	8.8%	85	2.7%	
	Died	5	0.2%	11	1.1%	16	0.5%	
Education level**	**Illiteracy**	295	13.6%	189	19.5%	484	15.4%	**<0.001**
	Primary	1555	71.7%	674	69.7%	2229	71.1%	
	Seconday or higher	317	14.6%	91	9.4%	408	13.0%	
	Unknown	2	0.1%	13	1.3%	15	0.5%	
Marital status***	**Single**	265	12.2%	121	12.5%	386	12.3%	**<0.001**
	Married	1737	80.1%	693	71.7%	2430	77.5%	
	Divorced/Widowed	167	7.7%	153	15.8%	320	10.2%	
Main source of Income**	**Domestic**	66	3.0%	10	1.0%	76	2.4%	**<0.001**
	No fix salary/agriculture	974	44.9%	497	51.4%	1471	46.9%	
	Fix Salary	1129	52.1%	458	47.4%	1587	50.6%	
	Unknown	0	0.0%	2	0.2%	2	0.1%	
Parity**	**Primipara**	723	33.3%	136	14.1%	859	27.4%	**<0.001**
	Secundipara	458	21.1%	184	19.0%	642	20.5%	
	Multipara	987	45.5%	647	66.9%	1634	52.1%	
	Unknown	1	0.0%	0	0.0%	1	0.0%	
Antenatal clinic visit**	**No**	152	7.0%	18	1.9%	170	5.4%	**<0.001**
	Yes	2017	93.0%	949	98.1%	2966	94.6%	
CHILD								
Child found	**Yes**	2107	97.1%	920	95.1%	3027	96.5%	**0.018**
	Absent or migrated	23	1.1%	15	1.6%	38	1.2%	
	Died	39	1.8%	32	3.3%	71	2.3%	
Age at survey in months (IQR)		23.5 (14.5–35.3)		24.6 (15.7–36.4)		23.9 (14.9–35.7)		0.053
Gender	**Female**	1126	51.9%	479	49.5%	1605	51.2%	0.218
	Male	1043	48.1%	488	50.5%	1531	48.8%	
Born in Mozambique	**No**	38	1.8%	24	2.5%	62	2.0%	0.175
	Yes	2131	98.2%	943	97.5%	3074	98.0%	
Gestational Age	**<37 weeks**	153	7.1%	79	8.2%	232	7.4%	0.088
	≥ 37 weeks	1243	57.3%	514	53.2%	1757	56.0%	
	Unknown	773	35.6%	374	38.7%	1147	36.6%	
Birth order of baby	**1–3**	1524	70.3%	538	55.6%	2062	65.8%	**<0.001**
	>3	644	29.7%	429	44.4%	1073	34.2%	
	Unknown	1	0.0%	0	0.0%	1	0.0%	
Breastfeeding at any time	**No**	11	0.5%	28	2,9%	39	1.2%	**<0.001**
	Yes	2158	99.5%	939	97,1%	3097	98.8%	

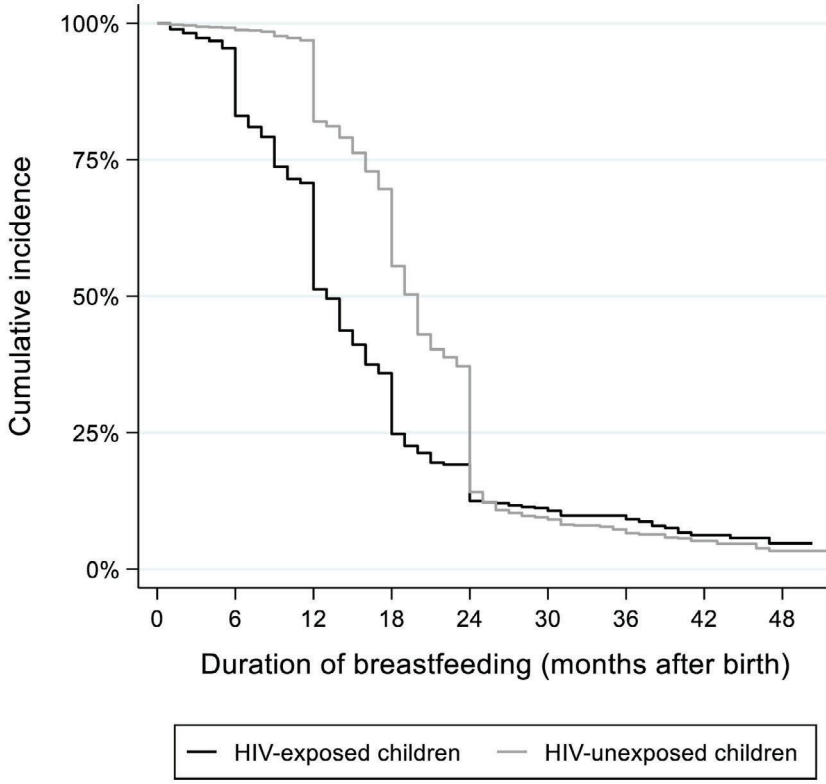
IQR: Interquartile Range.

*Kruskal Wallis test.

**Fisher exact test.

***Pearson chi-square

https://doi.org/10.1371/journal.pone.0269835.t001



		Duration of breastfeeding (months after birth)								
		0	6	12	18	24	30	36	42	48
Number of Children at risk	**HIV_unexposed**	2158	2035	1672	929	353	66	40	22	6
	HIV-exposed	939	861	539	220	95	43	27	14	4
	TOTAL	3097	2896	2211	1149	448	109	67	36	10

Fig 2. Breastfeeding duration among HIV-exposed and HIV-unexposed breastfed children. Cumulative incidence was expressed as the proportion of children breastfeeding in a given time period after birth accounting for right censoring and adjusted by sex and age of the child. Children who had not initiated breastfeeding were excluded from this analysis. N = 3097.

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Among the 61 children with unknown HIV serostatus, 62.3% (38/61) were female, 4 never breastfed and among the 57 who initiated breastfeeding, the median duration of breastfeeding was 12 (95%CI: 10.4–15.1) months. From 12 of children with unknown period of MTCT, 41.7% (5/12) were female, and all had initiated breastfeeding with the median duration being 15.0 months, (95%CI: 5.6–24.0).

The estimation of the period of MTCT among the 51 HIV-positive children remained the same regardless of the method of estimating the infection time of the mother (as random date selected from a uniform distribution, as a point at the quarter of the interval between the two dates considered at definition and as a point at the three-quarters of the interval between the two dates specified above in definitions section).

Table 2 shows the sociodemographic and clinical characteristics among children with postpartum MTCT compared to HIV-exposed uninfected children, after the exclusion of children with unknown HIV-status, children with MTCT during pregnancy or delivery, children with HIV infection without attribution to pregnancy, delivery or breastfeeding and children who never initiated breastfeeding.

Mothers with postpartum MTCT were mostly diagnosed (60.0%) and initiated ART (52.0%) after the child was born, compared with the 12.3% and 11.4% of diagnosis and ART initiation after the birth among the mothers of HIV exposed uninfected children, $p<0.001$. Furthermore, only 52.0% (13/25) of children with postpartum MTCT had received antiretroviral prophylaxis at any time after birth compared to 82.8% (688/831) of HIV-exposed uninfected children, $p<0.001$.

A total of 80.0% (20/25) of children with postpartum-MTCT had attended at least one unscheduled outpatient visits before the survey and a total of 28.0% (7/25) had been hospitalized, compared with the 55.0% (457/831) and 5.8% (48/831) of the HIV exposed uninfected children $p = 0.021$ and $p = 0.001$, respectively.

Table 3 shows bivariable and multivariable analysis of factors associated with postpartum MTCT after adjusting for child's sex and age at survey. Children with unknown HIV-status, children with MTCT during pregnancy or delivery and children who never initiated breastfeeding were excluded from this analysis.

Our results show that the duration of breastfeeding was not associated with postpartum MTCT (aSHR: 0.99 [95%CI: 0.96–1.03], $p = 0.707$). By contrast, children born from mothers who initiated ART at any time after delivery were more likely to acquire HIV postpartum (aSHR: 9.39 [95%CI: 1.75–50.31], $p = 0.009$).

The estimations obtained in postpartum MTCT related factors were not impacted when we performed sensitivity analysis including the children with unknown HIV status (61 children) or the children with unknown period of HIV infection (12 children): breastfeeding was not associated with postpartum MTCT (aSHR: 0.99 [95%CI: 0.96–1.02] $p = 0.547$ and aSHR: 0.99 [95%CI: 0.96–1.03] $p = 0.660$, respectively) and children born from mothers who initiated ART at any time after delivery were more likely to acquire HIV postpartum (aSHR: 8.77 [95% CI: 1.61–47.77] $p = 0.012$ and aSHR: 8.67 [95%CI: 1.64–45.87] $p = 0.011$, respectively).

Discussion

In this study, HIV-exposed children breastfed for significantly less time and had a nearly two-fold higher risk of discontinuation of breastfeeding over 48 months compared with non-exposed children. Evidence of association between breastfeeding duration and postpartum MTCT was not observed. In contrast, mother ART initiation after the date of child birth was associated with a nearly ten-fold higher risk of postpartum MTCT (aSHR: 9.39 [95%CI: 1.75–50.31], $p = 0.009$).

Table 2. Mother and child clinical and sociodemographic characteristics of HIV-exposed uninfected children and HIV-exposed children who acquired HIV through postpartum MTCT. N = 856. Children who never breastfed, children with HIV unknown status, children who acquired HIV through MTCT during pregnancy and delivery and HIV positive children with no information on time of HIV acquisition were excluded from this analysis.

		HIV-exposed uninfected children (N = 831)		HIV exposed children with postpartum MTCT (N = 25)		TOTAL (N = 856)		
Characteristics		**N**	**%**	**N**	**%**	**N**	**%**	**p value**
MOTHER								
Age of the mother at delivery in years. Median (IQR)*		28.7 (23.4–33.4)		26.5 (22.4–33.0)		28.7 (23.4–33.3)		0.577
Mother located during the household survey**	**yes**	748	90.0%	23	92.0%	771	90.1%	1.000
	absent or migrated	75	9.0%	2	8.0%	77	9.0%	
	died	8	1.0%	0	0.0%	8	0.9%	
Education level**	**Illiteracy**	171	20.6%	3	12.0%	174	20.3%	0.403
	Primary	579	69.7%	18	72.0%	597	69.7%	
	Seconday or higher	68	8.2%	4	16.0%	72	8.4%	
	Unknown	13	1.6%	0	0.0%	13	1.5%	
Marital status**	**Single**	112	13.5%	1	4.0%	113	13.2%	0.321
	Married	586	70.5%	21	84.0%	607	70.9%	
	Divorced/Widowed	133	16.0%	3	12.0%	136	15.9%	
Main source of Income**	**Domestic**	6	0.7%	0	0.0%	6	0.7%	0.456
	No fix salary/agriculture	428	51.5%	16	64.0%	444	51.9%	
	Fix Salary	395	47.5%	9	36.0%	404	47.3%	
	Unknown	2	0.2%	0	0.0%	2	0.2%	
Parity**	**Primipara**	116	14.0%	4	16.0%	120	14.0%	0.906
	Secundipara	152	18.3%	4	16.0%	156	18.2%	
	Multipara	563	67.7%	17	68.0%	580	67.8%	
Antenatal clinic visit**	**No**	14	1.7%	1	4.0%	15	1.8%	0.361
	Yes	817	98.3%	24	96.0%	841	98.2%	
Mother HIV diagnosis**	**Before the date of childbirth**	653	78.6%	9	36.0%	662	77.3%	**<0.001**
	After the date of childbirth	102	12.3%	15	60.0%	117	13.7%	
	Unknown	76	9.1%	1	4.0%	77	9.0%	
Mother ART initiation***	**Before the date of childbirth**	513	61.7%	6	24.0%	519	60.6%	**<0.001**
	After the date of childbirth	95	11.4%	13	52.0%	108	12.6%	
	Unknown	223	26.8%	6	24.0%	229	26.8%	
Mother CD4 at childbirth**	**<200 cel/mm3**	42	5.1%	4	16.0%	46	5.4%	0.083
	200–500 cel/mm3	175	21.1%	5	20.0%	180	21.0%	
	>500 cel/mm3	327	39.4%	6	24.0%	333	38.9%	
	Unknown	287	34.5%	10	40.0%	297	34.7%	
Mother viral load at childbirth**	**<1000copies/ml**	247	29.7%	7	28.0%	254	29.7%	0.352
	≥1000copies/ml	45	5.4%	3	12.0%	48	5.6%	
	Unknown	539	64.9%	15	60.0%	554	64.7%	
CHILD								
Child located during the household survey**	**yes**	813	97.8%	20	80.0%	833	97.3%	**<0.001**
	absent or migrated	2	0.2%	0	0.0%	2	0.2%	
	died	16	1.9%	5	20.0%	21	2.5%	
Age at survey in months. Median (IQR)		24.6 (15.6–35.6)		30.0 (20.9–34.2)		24.6 (15.7–36.5)		0.369
Gender***	**Female**	420	50.5%	9	36.0%	429	50.1%	0.152
	Male	411	49.5%	16	64.0%	427	49.9%	

(*Continued*)

Table 2. (Continued)

		HIV-exposed uninfected children (N = 831)		HIV exposed children with postpartum MTCT (N = 25)		TOTAL (N = 856)		
Characteristics		**N**	**%**	**N**	**%**	**N**	**%**	**p value**
Born in Mozambique**	**No**	19	2.3%	1	4.0%	20	2.3%	0.451
	Yes	812	97.7%	24	96.0%	836	97.7%	
Gestational Age**	**<37 weeks**	67	8.1%	2	8.0%	69	8.1%	0.345
	≥ 37 weeks	451	54.3%	10	40.0%	461	53.9%	
	Unknown	313	37.7%	13	52.0%	326	38.1%	
Birth order of baby ***	**1–3**	463	55.7%	13	52.0%	476	55.6%	0.713
	>3	368	44.3%	12	48.0%	380	44.4%	
Number of Outpatient visits before survey***	**0**	374	45.0%	5	20.0%	379	44.3%	**0.021**
	1	92	11.1%	6	24.0%	98	11.5%	
	≥2	365	43.9%	14	56.0%	379	44.3%	
Number of Hospitalizations before survey**	**0**	783	94.2%	18	72.0%	801	93.6%	**0.001**
	1	39	4.7%	5	20.0%	44	5.1%	
	≥2	9	1.1%	2	8.0%	11	1.3%	
Duration of breastfeeding in months. Median (IQR)		12.0 (8.0–17.0)		12.2 (12.0–18.0)		12.0 (8.0–17.0)		0.310
Received Antiretroviral prophylaxis**	**Yes**	688	82.8%	13	52.0%	132	15.4%	**<0.001**
	No	20	2.4%	3	12.0%	701	81.9%	
	Unknown	123	14.8%	9	36.0%	23	2.7%	

IQR: Interquartile Range.

*Kruskal Wallis test.

**Fisher exact test.

***Pearson chi-square

Sociodemographic data (Age, Eductional level, Marital status, Income, Parity), antenatal clinic visits and breastfeeding information were self-reported.

HIV data were obtained through medical documentation (Mother HIV diagnosis, Mother ART initiation) or HIV database (Mother cd4 at child birth, Mother viral load at child birth). Hospitalizations and outpatients' visits were obtained through HDSS database.

Gestational Age and Infant Antiretroviral prophylaxis were obtained through medical documentation.

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Our results demonstrate that children born from mothers who initiated ART after childbirth had a higher risk of acquiring HIV during the breastfeeding period, as previously indicated by other studies [36]. At the time of the study, the B+ strategy was already implemented and lifelong ART was recommended to HIV-positive pregnant or breastfeeding mothers [21], [27]. However, success of the B+ strategy in reaching all pregnant and breastfeeding women is highly dependent on a sustained frequency of HIV testing not only during pregnancy but during the post-partum period. The reasons for not initiating ART could be multiple: mothers may not have initiated lack of awareness of HIV status, death, not willing or because of service delivery shortfalls or stockouts. A study conducted in southern Mozambique between 2008 to 2011 before B+ implementation, found an HIV incidence in women of 3.2/100 women-years (95%CI: 2.30–4.46) in breastfeeding women during the postpartum period. In absence of treatment, this was reflected by a postpartum-MTCT rate of 21% at 18-months of age among their children [37]. In Mozambique, at the time of the study, re-testing in all pregnant women every three months during pregnancy was recommended, however, delivery and the postpartum period were not targeted time points for re-testing [38, 39]. Our results suggest that establishing specific retesting times during the postpartum period in areas of high HIV incidence could

Table 3. Mother and child clinical and sociodemographic risk factors associated with postpartum MTCT among HIV-exposed children. N = 856. Fine-Gray subdistribution hazard regression with death as a competing risk was conducted. The same exclusion factors as those described in Table 2 were applied. The multivariable model was built of including the variables with a p-value lower than 0.20 in the bivariate analysis and with less than 20% missing values. Variables age of child, mother ART initiation and breastfeeding duration were forced-in covariates due to their clinical relevance. Multiple imputation was performed in mother ART initiation. Mother HIV diagnosis was excluded because of collinearity.

Factors		Univariable Model*			Multivariable Model**		
		SHR	(95% Conf. Interval)	p-value	aSHR	(95% Conf. Interval)	p-value
Mother							
Age of the mother at delivery (in years)		0.99	0.93–1.05	0.627			
Education level (N = 843)	**No education**	1		0.284			
	Basic	1.76	0.52–5.96				
	Medium/High	3.31	0.74–14.82				
Marital status	**Single**	1		0.333			
	Married	3.95	0.53–29.39				
	Divorced/Widowed	2.52	0.26–24.24				
Parity	**Primipara**	1		0.931			
	Secundipara	0.77	0.19–3.07				
	Multipara	0.87	0.29–2.60				
Antenatal clinic visit	**No**	1		0.398			
	Yes	0.44	0.06–3.01				
Mother HIV diagnosis[1] (N = 779)	**before the date of childbirth**	1		**0.008**			
	after the date of childbirth	4.20	1.46–12.06				
Mother ART initiation[1]	**before the date of childbirth**	1		**<0.001**			
	after the date of childbirth	9.18	3.87–21.80		9.39	1.75–50.31	**0.009**
Mother cd4 at childbirth (N = 559)	**<200 cel/mm3**	1					
	200–500 cel/mm3	0.32	0.09–1.16	**0.042**			
	>500 cel/mm3	0.20	0.06–0.71				
Mother viral load at childbirth (N = 302)	**<1000copies/ml**	1					
	≥1000copies/ml	2.30	0.60–8.82	0.226			
Children							
Age at survey in months		1.01	0.99–1.04	0.348	1.01	0.97–1.06	0.577
Gender	**Male**	1		0.160	1		
	Female	1.80	0.79–4.06		1.99	0.67–5.96	0.218
Gestational Age (N = 530)	**<37 weeks**	1		0.699			
	≥ 37 weeks	0.74	0.16–3.40				
Birth order of baby	**1–3**	1		0.722			
	>3	1.15	0.53–2.52				
Born in Mozambique	**No**	1		0.575			
	Yes	0.56	0.07–4.24				
Median time of breastfeeding		1.01	0.98–1.05	0.557	0.99	0.96–1.03	0.707
Received Antiretroviral prophylaxis (N = 724)	**Yes**	1			1		
	No	7.25	2.13–24.73	**0.002**	3.01	0.55–16.54	0.205

*N = 856 unless otherwise specified

** N = 818

SHR: subhazard ratio.

aSHR:adjusted subhazard ratio.

1 Time-varying covariates. Time-varying covariates were handled by episode splitting

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reinforce the prevention of MTCT in LMIC, particularly in areas of high HIV prevalence where the risk of contracting HIV during the breastfeeding period is high. This would facilitate initiation of ART in breastfeeding mothers and antiretroviral prophylaxis in their HIV exposed infants. In addition to retesting, pre-exposure prophylaxis (PrEP) among women who remain at risk for HIV acquisition in the postpartum period may be an effective approach to reduce MTCT. In 2018 Mozambique began with the pilot implementation of PrEP in sero-discordant couples in Zambezia province and will expand PrEP nationally in 2022 to additional target groups, including pregnant and breastfeeding women at risk and key populations [40].

The vast majority (>97%) of the mothers in our study initiated breastfeeding. This is in agreement with data from Demographic and Health Surveys (2000–2013) for 57 countries which showed a consistently high percentage of children who had ever breastfed across all regions (weighted mean 98.2%, range of countries 87.8–99.8%) [41]. In terms of duration of breastfeeding, in a study conducted in 2019 in an urban population of South Africa, similar to our results, the duration of breastfeeding was also significantly lower among HIV-positive mothers as compared to HIV-negative mothers [3.9 months vs 9.0 months, respectively, $p<0.001$] [42]. The striking difference in the duration of breastfeeding between women in our study and those studies by Roux et al are likely due to shorter breastfeeding duration in urban compared to rural populations, compounded by social and contextual barriers, as previously described [43, 44]. Advice of health workers, influence of relatives, stigma, conflicting opinions about the risk for MTCT and poor dissemination of policies have been described as main reasons affecting breastfeeding among HIV-positive women in the past [45–47]. However, little is known about the barriers for prolonged breastfeeding after the implementation of the 2016 WHO feeding guidelines.

The higher risk of discontinuing breastfeeding in HIV-exposed children could have important health implications for this population. A clinical trial conducted in Uganda demonstrated higher rates of serious gastroenteritis among HIV-exposed uninfected infants with early breastfeeding cessation (8.0/1000 child-months) when compared to later breastfeeding cessation (3.1/1000 child-months; $p<0.001$) [48]. In addition, early cessation of breastfeeding is associated with a lower probability of HIV-free survival compared with longer breastfed infants who had lower overall mortality [44].

Our results suggest that in the context of B+ (lifelong ART to the mother and antiretroviral prophylaxis to the children), duration of breastfeeding is not associated with an increased risk of postpartum MTCT. Bispo et al (2017) in their systematic review found a pooled estimated rate of overall HIV transmission by age six months of 3.5% and a pooled postnatal transmission rate by six months of 1.1% in women who were on ART from early-mid pregnancy and breastfed for 6 months [4]. To our knowledge, no such study has been published after the expansion of B+ prevention MTCT programs. Thus, our results fill the gap in knowledge on the risk of MTCT associated with breastfeeding beyond 6 months of age in the context of B + strategy that recommends lifelong antiretroviral treatment for all pregnant and breastfeeding women living with HIV.

Effective strategies to increase the duration of safe breastfeeding in HIV-exposed children could allow them to reap the benefits of breastfeeding through the second year of life such as decreased morbidity and mortality in comparison to HIV exposed infants who are weaned earlier [49, 50]. Highlighted strategies proposed by the literature to promote breastfeeding among HIV-exposed children include increased coverage of extended nevirapine prophylaxis to the infants, active support and breastfeeding counseling [51]. Other strategies such as widespread access to viral load testing could mitigate the fear of HIV transmission, reported by mothers and health workers as a barrier to breastfeeding [52]. In the absence of viral load testing, expansion of antiretroviral prophylaxis among HIV-exposed children until the end of breastfeeding i one strategy supported by literature [44].

This study has several limitations. First, 27% of the randomly selected mother/child pairs were not located and we do not have information about their HIV status. Second, breastfeeding duration was self-reported (in months) by mothers/caregivers for both HIV-exposed and HIV non-exposed children patients at the time of the survey. As we have analyzed children born up to 48 months prior to data collection, potential memory bias could affect the estimations of breastfeeding duration. Third, due to missing data, it was not possible to establish the HIV status of 6.2% (61/967) of HIV exposed children and it was not possible to establish the period of MTCT (during pregnancy and delivery or during breastfeeding) of 23.5% (12/51) of HIV infected children. We conducted a sensitivity analysis considering the 61 children with unknown HIV serostatus as HIV-positive and the 12 HIV-infected children with unknown period of MTCT as postpartum MTCT. It did not impact the estimates of postpartum-MTCT and associated factors, even if the 12 with had a median duration of breastfeeding of 15 months (95%CI: 5.6–24.0) Further studies with larger sample size and breastfeeding periods of 24 months or longer are needed. Fourth, the exact date of mothers' seroconversion was unknown and was established according to the assumptions described in the methods section. A sensitivity analysis considering the time of infection as random date selected from a uniform distribution, a point at the quarter of the interval between the two dates and a point at the three-quarters of the interval between the two dates was robust and did not impact the classification of time of HIV acquisition among HIV-positive children. Fifth, service delivery shortfalls or stockouts of ART were not assessed during the study, which may have affected the ART initiation of among HIV-positive mothers and ARV prophylaxis among HIV-exposed infants. Finally, in Mozambique viral load became routinely available after 2016, and viral load coverage has slowly climbed over time. As a result, more than 60% of HIV infected mothers included in the study did not have any viral load results prior to the survey, thus no adjustments by viral suppression were possible in the multivariable model.

Conclusion

The risk for postpartum MTCT was nearly tenfold higher in women who were newly diagnosed or initiated ART during the postpartum period as compared to those who initiated ART prior to childbirth. HIV-exposed children breastfed for significantly less time compared with non-exposed children. Breastfeeding duration was not observed to be associated with an increased risk of MTCT in the postpartum period in women on ART. These results emphasize the importance of repeat HIV testing in the postpartum period, and support PrEP in breastfeeding women at high risk for HIV infection. Moreover, further public health messaging to encourage prolonged breastfeeding among HIV-exposed infants born to mothers adherent to ART in Sub-Saharan African countries could bring long term health benefits for children.

Supporting information

S1 Appendix. Study questionnaires in English.
(ZIP)

S2 Appendix. Study questionnaires in Portuguese.
(ZIP)

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Author Contributions

Conceptualization: Elisa Lopez-Varela, Marilena Urso, Denise Naniche.

Data curation: Ariel Nhacolo.

Formal analysis: Sheila Fernández-Luis, Orvalho Augusto, Olalla Vazquez, Anna Saura-Lázaro, Denise Naniche.

Funding acquisition: Elisa Lopez-Varela, Marilena Urso.

Investigation: Tacilta Nhampossa, Olalla Vazquez.

Methodology: Laura Fuente-Soro, Tacilta Nhampossa, Denise Naniche.

Supervision: Laura Fuente-Soro, Tacilta Nhampossa.

Writing – original draft: Sheila Fernández-Luis.

Writing – review & editing: Elisa Lopez-Varela, Orvalho Augusto, Helga Guambe, Kwalila Tibana, Bernadette Ngeno, Adelino José Chingore Juga, Jessica Greenberg Cowan, Marilena Urso, Denise Naniche.

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Article 3

Optimizing the World Health Organization algorithm for HIV vertical transmission risk assessment by adding maternal self-reported antiretroviral therapy adherence

Sheila Fernández-Luis*, Maria Grazia Lain*, Miquel Serna-Pascual, Sara Domínguez-Rodríguez, Louise Kuhn, Afaaf Liberty, Shaun Barnabas, Elisa Lopez-Varela, Kennedy Otwombe, Siva Danaviah, Eleni Nastouli, Paolo Palma, Nicola Cotugno,Moira Spyer, Viviana Giannuzzi, Carlo Giaquinto, Avy Violari, Mark F Cotton, Tacilta Nhampossa, Nigel Klein, Nastassja Ramsagar6, Anita Janse Van Rensburg, Osse Behuhuma, Paula Vaz, Almoustapha Issiaka Maiga, Andrea Oletto, Denise Naniche, Paolo Rossi, Pablo Rojo4**,Alfredo Tagarro** on behalf of the EPIICAL Consortium.

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Specific objective 2

2. To explore the optimization of the WHO algorithm for identification of infants with high risk of VT by including self-reported adherence to ART among mothers living with HIV.

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Optimizing the World Health Organization algorithm for HIV vertical transmission risk assessment by adding maternal self-reported antiretroviral therapy adherence

Sheila Fernández-Luis[1,2*†], Maria Grazia Lain[3*†], Miquel Serna-Pascual[4], Sara Domínguez-Rodríguez[4], Louise Kuhn[5], Afaaf Liberty[6], Shaun Barnabas[7], Elisa Lopez-Varela[1,2], Kennedy Otwombe[6,8], Siva Danaviah[9], Eleni Nastouli[10], Paolo Palma[11,12], Nicola Cotugno[11,12], Moira Spyer[10], Viviana Giannuzzi[13], Carlo Giaquinto[14], Avy Violari[6], Mark F. Cotton[7], Tacilta Nhampossa[1,15], Nigel Klein[9,10], Nastassja Ramsagar[6], Anita Janse van Rensburg[7], Osee Behuhuma[9], Paula Vaz[3], Almoustapha Issiaka Maiga[16], Andrea Oletto[17], Denise Naniche[1,2], Paolo Rossi[18], Pablo Rojo[4†], Alfredo Tagarro[4,19,20†] and EPIICAL Consortium

Abstract

Background: The World Health Organization (WHO) risk assessment algorithm for vertical transmission of HIV (VT) assumes the availability of maternal viral load (VL) result at delivery and early viral control 4 weeks after initiating antiretroviral treatment (ART). However, in many low-and-middle-income countries, VL is often unavailable and mothers' ART adherence may be suboptimal. We evaluate the inclusion of the mothers' self-reported adherence into the established WHO-algorithm to identify infants eligible for enhanced post-natal prophylaxis when mothers' VL result is not available at delivery.

Methods: We used data from infants with perinatal HIV infection and their mothers enrolled from May-2018 to May-2020 in Mozambique, South Africa, and Mali. We retrospectively compared the performance of the WHO-algorithm with a modified algorithm which included mothers' adherence as an additional factor. Infants were considered at high risk if born from mothers without a VL result in the 4 weeks before delivery and with adherence <90%.

Results: At delivery, 143/184(78%) women with HIV knew their status and were on ART. Only 17(12%) obtained a VL result within 4 weeks before delivery, and 13/17(76%) of them had VL ≥1000 copies/ml. From 126 women on ART without a recent VL result, 99(79%) had been on ART for over 4 weeks. 45/99(45%) women reported suboptimal (< 90%) adherence. A total of 81/184(44%) infants were classified as high risk of VT as per the WHO-algorithm. The modified algorithm including self-adherence disclosure identified 126/184(68%) high risk infants.

†Sheila Fernández-Luis, Maria Grazia Lain, Pablo Rojo and Alfredo Tagarro contributed equally to this work.

*Correspondence: sheila.fernandez@isglobal.org; sheila.fernandez@manhica.net; mlain@arielglaser.org.mz

[1] Centro de Investigação em Saúde de Manhiça (CISM), Bairro Cambeve, Rua 12, Distrito da Manhiça, CP 1929 Maputo, Mozambique
[3] Fundação Ariel Glaser Contra o SIDA Pediátrico, Maputo, Mozambique
Full list of author information is available at the end of the article

Conclusions: In the absence of a VL result, mothers' self-reported adherence at delivery increases the number of identified infants eligible to receive enhanced post-natal prophylaxis.

Keywords: Vertical transmission, Mother-to-child transmission, HIV-exposed infants, Paediatric HIV, Prevention of mother-to-child transmission, Enhanced post-natal prophylaxis

Background

Vertical transmission (VT) of HIV remains an unacceptable 12% in many Global Plan priority countries, where 90% of the world's pregnant women are living with HIV [1]. Since implementation of Option B+ strategy, [2] antiretroviral therapy (ART) coverage among pregnant women in eastern and southern Africa increased from 84 to 92% [3]. However, the goal of eliminating new paediatric infections by 2030 [4] will likely be compromised by multiple challenges in the VT-prevention cascade, including access to adequate postnatal prophylaxis among HIV-exposed infants [1, 5–11].

VT prevention guidelines have evolved recently. Extended nevirapine (NVP) postnatal prophylaxis and dual or triple antiretroviral (ARV) prophylaxis have shown to halve VT among HIV-exposed infants compared with short courses of AZT or NVP alone [12–17]. The latest World Health Organization (WHO) guidelines recommend enhanced post-natal prophylaxis with daily zidovudine (ZDV) and NVP for the first 6 weeks of life for HIV-exposed infants at high-risk of HIV acquisition, followed by an additional 6 weeks if high-risk and breastfeeding. HIV-exposed infants at low-risk of VT should receive 4–6 weeks of prophylaxis with daily NVP (or twice-daily AZT) [18].

High-risk infants have mothers diagnosed with HIV at delivery and are either: 1.) not on ART 2.) started treatment within 4 weeks before delivery, or 3.) had a plasma viral load (VL) > 1000 copies/mL in the 4 weeks before delivering [18]. WHO designed an algorithm to assess HIV-exposed infants risk for HIV acquisition at delivery and to identify high-risk infants eligible for enhanced post-natal prophylaxis [19]. The implementation of the WHO algorithm is challenging due to the paucity of required information for risk stratification [20]. The 'high-risk criteria' assume VL result availability, adequate maternal adherence, and early and sustained viral suppression after 4 weeks of ART [18]. However, VL testing coverage and monitoring, especially during pregnancy, is challenging in low-and-middle-income countries (LMIC). Many countries have scaled VL testing via point of care or dried blood spot testing. However, in routine operating conditions, many patients who are tested either don't receive results or they are extremely delayed [1, 21, 22]. Women with poor adherence or interrupted ART during pregnancy or breastfeeding have viral rebound and increased risk of VT [23–26]. In fact, peripartum viral suppression varies from 30 to 98% in different sub-Saharan African settings, and despite an estimated 92% ART coverage among pregnant women, nearly 30% of new pediatric infections in East and Southern Africa in 2018 were related to ART interruptions during pregnancy or breastfeeding [3, 10].

We retrospectively characterized post-natal prophylaxis coverage among infants living with HIV in sub-Saharan Africa and assessed whether the inclusion of readily accessible information such as mothers' self-reported ART adherence into the WHO algorithm improved the identification of infants with perinatal HIV infection when maternal VL resulted unavailable.

Methods

Study population

This analysis was nested under a broader prospective cohort study (A prospective, observational, cohort, multicentre study of Early Anti-Retroviral Treatment in HIV- infected Infants: EARTH) within the EPIICAL project (Early treated Perinatally HIV-Infected individuals: Improving Children's Actual Life Project). The EARTH study aimed to monitor clinical, virological and immunological features of HIV-positive, HIV early treated children during the first 4 years of age, in order to identify participants with excellent viral and immunological control. The EARTH study included 1) perinatally infected infants who initiated ART ≤90 days after diagnosis and 2) breastfed infants diagnosed with HIV ≤90 days of age and starting ART ≤90 days after diagnosis.

Standard of care for PMTCT

Lifelong ART to all pregnant women living with HIV was offered at all sites. In Mozambique, HIV-exposed infants prophylaxis consisted of 6 weeks NVP to all infants until September 2019, [19, 27] and thereafter ZDV and NVP for the first 6 weeks of life, followed by NVP for 6 weeks to all infants, as all HIV-exposed infants were considered at high-risk for VT [28]. In South Africa and Mali, enhanced post-natal prophylaxis was implemented for high-risk HIV-exposed infants throughout enrollment [19].

Data collection and analysis

The target sample size for the EARTH study was 300 children. For this analysis, we included mother-infant pairs recruited in the EARTH study from May 1st, 2018 to May 1st 2020 ($N = 184$) in 2 Mozambican sites, 3 South African sites and 1 site in Mali. Infants receiving an HIV diagnosis at the clinic were selected to participate along with their mothers. After obtaining informed consent, study personnel administered a study-specific questionnaire to the mother in a private room at the hospital, ensuring confidentiality. This questionnaire took 30 minutes on average and included information about sociodemographic characteristics, pregnancy and delivery, HIV diagnosis and care of the mother and a specific question on the number of doses missed by the mother during the month prior to the infant's enrollment in the study. Suboptimal adherence was considered if >10% of the ART doses were missed in the last month.

We retrospectively classified infants at high or low VT risk according to the WHO algorithm. We then modified the algorithm to include the maternal self-assessment of adherence to ART. For all women on ART for over 4 weeks and without a VL test result 4 weeks upon delivery, suboptimal and optimal adherence were defined as <90% and ≥90% self-reported ART adherence during pregnancy, respectively. Infants of mothers with suboptimal adherence were considered high risk.

CompareGroups R package [29] was used to compare sociodemographic and clinical baseline information of mothers and their infants classified as HIV-exposed infants at high risk of VT according to the two algorithms, as described previously. The variables included were infant's age and sex, maternal WHO stage, employment, marital status, education, and maternal health conditions or severe life events that arose at any later postnatal point during the study (change in employment, break-up, new partner, loss of home or moving/relocation, death in the family). We also included infant's post-natal prophylaxis regimens: standard (≤6 weeks with ZDV or NVP) or extended (≥ 6 weeks with NVP or ZDV or with NVP plus ZDV).

The normality of continuous variables was tested using the Shapiro-Wilk test. The Mann-Whitney Wilcoxon test was used to compare non-normally distributed continuous variables. For categorical variables, absolute and relative frequencies were calculated, and Chi-squared tests or exact Fisher tests (frequencies< 5) were performed.

Results

A total of 184 infants living with HIV ($n = 96$ male) and their mothers were studied, 112 (61%) from South Africa, 64 (35%) from Mozambique and 8 (4%) from Mali (Fig. 1). A total of 143 (78%) women were known HIV-positive and on ART at delivery. However, 29 women (16%) had their HIV diagnosis at delivery and were not on ART and 12 (7%) were known to be HIV-positive prior to delivery but were not on ART. Among them, only 17/143 (12%) had a VL result within 4 weeks before delivery, 13/17 (76%) of them had VL ≥1000 copies/ml. Therefore, most known HIV-positive women on ART (126/143, 88%) did not have a VL result. Of them, 99/126 (79%) had been on ART for over 4 weeks and 27/126 (21%) under 4 weeks. A total of 45/99 (45%) mothers reported suboptimal adherence to ART.

Using the WHO algorithm, 81/184 (44%) of infants with HIV were defined as high risk of VT with VL

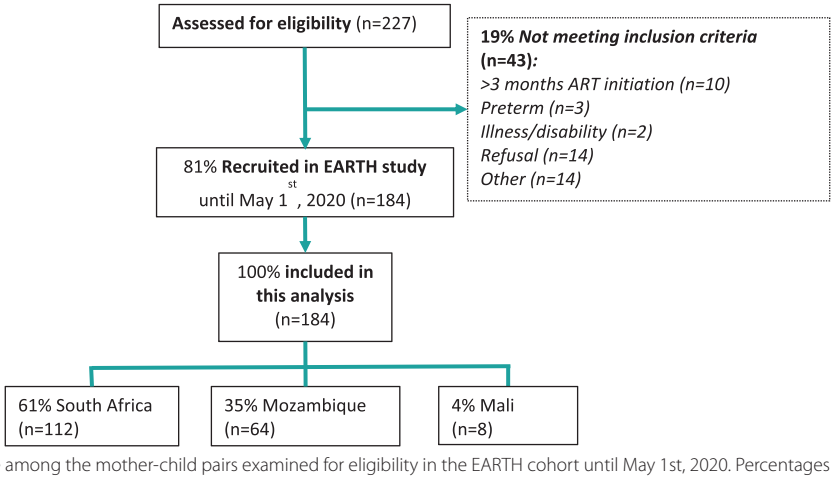

Fig. 1 Study profile among the mother-child pairs examined for eligibility in the EARTH cohort until May 1st, 2020. Percentages are calculated over the previous parent box. ART = antiretroviral treatment

available data. Following the inclusion of the self-reported adherence risk factor applied to 99 mothers on ART greater than 4 weeks without VL test result, an additional 45 high-risk infants were identified. In total, the modified algorithm classified 126/184 (68%) infants as high risk of MTCT – assuming that infants born to mothers with suboptimal adherence are high risk (Fig. 2). The modified algorithm, identified higher number of high risk children than the WHO algorithm ($p = 0.0001$).

Among the 81 at high risk of MTCT according to WHO algorithm, 40% (32/81) received enhanced post-natal prophylaxis, 30% (24/81) standard post-natal prophylaxis, 22% (18/81) did not received any post-natal prophylaxis and 9% (7/81) did not have information about the post-natal prophylaxis.

In table 1, we compared clinical and sociodemographic characteristics that could have acted as confounding factors in the risk of VT, between participants classified as

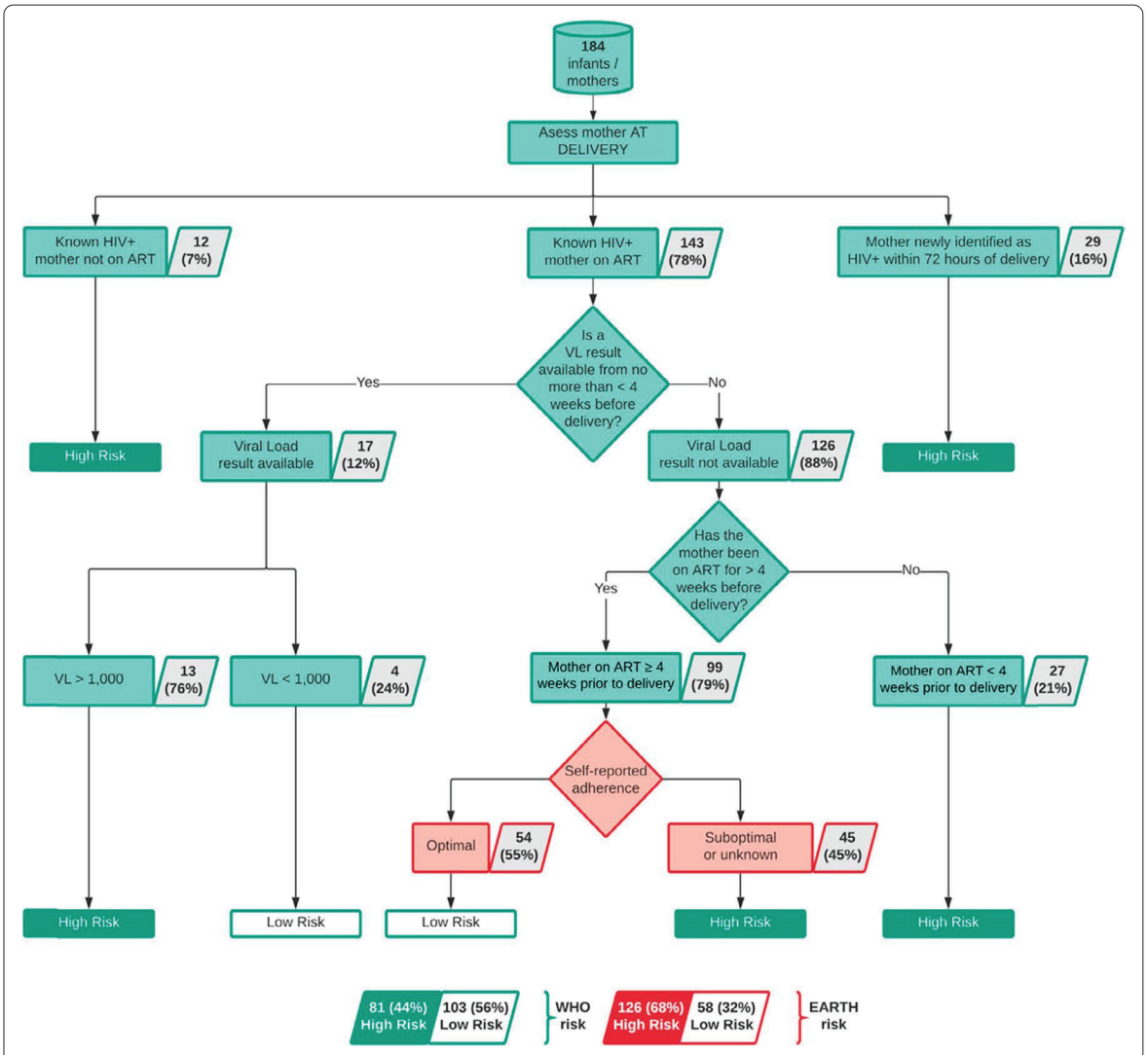

Fig. 2 Classification of infants into high or low risk of HIV vertical transmission according to the WHO algorithm and WHO modified algorithm. The additional question was added at the last step for mothers on ART ≥4 weeks before delivery with no VL test result (in red). The WHO algorithm is described in green as well as the final classification of high-risk infants. The additional risk factor included in the modified WHO algorithm is depicted in red as well as the final classification of high-risk infants. Percentages were calculated using as denominator the number of mothers from the preceding classification step. ART = Antiretroviral treatment; VL = Viral Load

Table 1 Baseline characteristics of study participants classified as High-Risk by the WHO algorithm and the additional participants classified as high risk when maternal adherence was incorporated into the algorithm

Variable	Total	WHO Algorithm High-Risk	Additional High-Risk with the inclusion of maternal adherence	*p*-value
	***n* = 126**	***n* = 81**	***n* = 45**	
Age of Children at Enrollment (months)	*n = 126*	*n = 81*	*n = 45*	
	1.57 [0.98;2.91]	1.64 [0.98;3.48]	1.38 [0.98;2.62]	0.277
Missing values	0 (0%)	0 (0%)	0 (0%)	
Sex of Children at Birth:	*n = 125*	*n = 80*	*n = 45*	
Female	55 (44.0%)	33 (41.2%)	22 (48.9%)	0.523
Male	70 (56.0%)	47 (58.8%)	23 (51.1%)	
Missing values	1 (0.8%)	1 (1.2%)	0 (0%)	
Mother WHO HIV Status:	*n = 123*	*n = 78*	*n = 45*	
Clinical stage 1/2	115 (93.5%)	72 (92.3%)	43 (95.6%)	1.000
Clinical stage 3	7 (5.69%)	5 (6.4%)	2 (4.4%)	
Clinical stage 4	1 (0.81%)	1 (1.28%)	0 (0.00%)	
Missing values	3 (2.4%)	3 (3.7%)	0 (0%)	
Mother Severe Life Events / Health Issues:	*n = 115*	*n = 74*	*n = 41*	
No	62 (53.9%)	41 (55.4%)	21 (51.2%)	0.813
Yes	53 (46.1%)	33 (44.6%)	20 (48.8%)	
Missing values	11 (8.7%)	7 (8.6%)	4 (8.9%)	
Mother Social Adverse Events:	*n = 126*	*n = 81*	*n = 45*	
No	5 (3.97%)	3 (3.7%)	2 (4.4%)	1.000
Yes	121 (96.0%)	78 (96.3%)	43 (95.6%)	
Missing values	0 (0%)	0 (0%)	0 (0%)	
Mother Employment Status	*n = 123*	*n = 79*	*n = 44*	
Employed	14 (11.4%)	10 (12.7%)	4 (9.1%)	0.763
Unemployed	109 (88.6%)	69 (87.3%)	40 (90.9%)	
Missing values	3 (2.3%)	2 (2.5%)	1 (2.2%)	
Mother Marital Status	*n = 126*	*n = 81*	*n = 45*	
Single	76 (60.3%)	49 (60.5%)	27 (60.0%)	1.000
Married	47 (37.3%)	30 (37.0%)	17 (37.8%)	
In a relationship, not cohabiting	3 (2.38%)	2 (2.47%)	1 (2.22%)	
Missing values	0 (0%)	0 (0%)	0 (0%)	
Mother Education	*n = 126*	*n = 81*	*n = 45*	
No school	3 (2.38%)	2 (2.47%)	1 (2.22%)	0.850
Primary	44 (34.9%)	26 (32.1%)	18 (40.0%)	
Secondary	74 (58.7%)	49 (60.5%)	25 (55.6%)	
University	5 (3.97%)	4 (4.94%)	1 (2.22%)	
Missing values	0 (0%)	0 (0%)	0 (0%)	

Continuous variables summarized as: median [IQR], and categorical variables as: n (% of subjects within classification group, excluding missing values). The first row of each section shows the number of subjects without missing corresponding information, and last row number and percentage of missing values compared to the total number of subjects. Mother Severe Life Events: Any during the time of the study, including change in employment, separation or relationship break-up, new partner, loss of home or move, death in the family, other. Mother Health Issues: Any during the time of study. Mother Employment status, Marital status and Education asked at enrolment. Mother Social Adverse Events: Unemployed, single status or did not attend high school/university (asked at enrollment). Standard Post-natal prophylaxis: < 6 weeks with one of Zidovudine (AZT) or Nevirapine (NVP)

high-risk by the WHO algorithm and the additional participants classified as high risk when maternal adherence was incorporated into the algorithm. We did not find any differences in age, sex, maternal WHO status at delivery, maternal health, or social adverse events.

Discussion

In our study, nearly 90% of mothers of infants diagnosed with HIV did not have a VL result at delivery; a result on which the WHO algorithm relies. When applied in our cohort, the WHO algorithm identified 44% of the infected infants as high-risk for VT. When we added

mothers' self-reported ART adherence to the WHO algorithm, the proportion of high-risk infants increased to 68%, suggesting that suboptimal adherence is associated with high risk. This modification of the algorithm increased the number of infected infants being classified as high-risk and eligible for enhanced post-natal prophylaxis.

This study also showed that information is often missing when assessing VT risk assessment according to the WHO algorithm, which jeopardizes early prescription of enhanced post-natal prophylaxis [15]. Only 12% of mothers on ART had a VL result 4 weeks prior to delivery. Similarly, a cross-sectional study of programmatic data in Zimbabwe revealed that the risk of MTCT using the WHO algorithm could not be determined in 90% of HIV-exposed infants due to lack of data [20]. A more recent study of 2080 HIV-exposed infants from Zimbabwe showed that 80% of mothers did not have a VL result between 28 weeks gestation to delivery [30]. Therefore, other factors should be considered to establish the risk of VT. Our results suggest that self-reported maternal adherence to ART could be an additional clinical factor to be considered in order to improve the algorithm to assess the risk of VT in the absence of VL. We also evaluated other socio-clinical factors that could potentially affect the risk of MTCT, such as maternal WHO stage, level of education, employment status or adverse social events between the two algorithms. We didn't find any difference among the participants newly classified as high risk of VT according to maternal ART adherence and the participants classified by the WHO algorithm as high risk of VT. However, further studies evaluating additional socio-clinical variables could inform more targeted algorithms to improve prevention of VT.

ART duration over 4 weeks, as incorporated in the algorithm, does not justify the assumption of viral suppression or the low VT risk. Although many countries have recently changed from EFV-based maternal ART to Dolutegravir, which has been shown to have superior early virologic suppression [31], adherence remains a paramount. Poor maternal adherence or interrupted ART during pregnancy and breastfeeding may cause high VL and subsequent increased transmission risk [23–26]. As such, infants are misclassified as 'low-risk' and do not receive appropriate e-PNP. The use of point-of-care devices for VL may be used at delivery and provide results in under 90 minutes, however, these devices are not widely available in LMIC [32]. Modification of the existing WHO risk evaluation algorithm to include a maternal self-reported adherence may significantly benefit countries without a consolidated laboratory network capacity to ensure optimal VL monitoring. Investigating the mothers' self-reported ART adherence at delivery is an easy and low-cost intervention to guide nurses in identifying high-risk infants eligible for enhanced post-natal prophylaxis in the absence of VL result.

In our cohort, 45% of mothers on ART for over 4 weeks without a VL result reported sub-optimal adherence. The actual proportion might be higher, since self-reported adherence is a reliable method with low cost and good specificity [33] widely used in clinical practice, but tends to overestimate adherence behavior compared with other methods [9]. Low self-reported adherence during pregnancy and breastfeeding is associated with viremia and virological treatment failure [34, 35]. The high number of women who self-disclosed ART-adherence difficulties in our study suggests that in the absence of VL result, time on ART is not enough to evaluate VT risk. Effective interventions to support adherence during pregnancy must be considered.

Our findings showed that 30% of HIV-exposed infants at high-risk of HIV infection according to WHO algorithm had no access to enhanced post-natal prophylaxis, which can be partially due to the recent guideline implementation in Mozambique [28]. A study in Zimbabwe also showed low enhanced post-natal prophylaxis coverage rates among HIV-exposed infants [20]. We also found a high proportion (17%) of HIV-exposed infants who alarmingly did not receive any PNP at all. Further studies should evaluate enhanced post-natal prophylaxis compliance and algorithm feasibility in the clinical setting, including HIV-exposed children at high risk of VT who never become infected. Nevertheless, our results suggest that besides modifying the WHO algorithm and training health staff on its correct application, further efforts are needed to ensure access to timely maternal VL testing and infant enhanced post-natal prophylaxis.

Our results have implications for policy, practice and public health. This study provided a comprehensive evaluation of the WHO risk assessment algorithm for VT. On one hand, we identified that the coverage of enhanced postnatal prophylaxis among infants with high risk of VT transmission was not optimal. On the other hand, our results suggested that adding maternal adherence to ART could increase the coverage of enhanced postnatal prophylaxis in high-risk infants, thus reinforcing WHO recommendations in clinical practice. The application of this simple measure would be especially beneficial in settings with less structural capacity to obtain viral load results. It would allow the allocation of limited resources towards prevention measures for children at high risk and inform interventions to improve VT prevention.

This study has several limitations. First, we included only infants confirmed to have HIV infection, and retrospectively reviewed their VT risk classification. For this reason, we could not calculate the specificity of the two

algorithms. Second, the mothers' ART adherence was self-reported at recruitment and recall bias, as well as social desirability bias, may have led to over-reporting of good adherence. We defined 1 month prior to study enrollment as the time interval for observing the number of missed doses in order to improve the validity of past reporting. We based this on the fact that a shorter time frame allows the respondent to more easily recall an event rather than having to recall a behavior over a large period of time. However, further studies evaluating a standardized method and definition of self-reported adherence would be important to generalize our results on ART adherence and validate the inclusion of the self-reported adherence to ART in the algorithm in other contexts. Third, we didn't find difference in the confounders factors analyzed, however other potential confounding factors such as type of infant feeding, home delivery or maternal drug resistance have not been accounted for. Fourth, the relatively small sample size can compromise the generalizability of the results. Further studies with larger sample size are needed to validate this results in populations from different settings.

In conclusion, incorporation of maternal self-reported adherence in the WHO algorithm for VT risk assessment improves the identification of infants eligible for enhanced post-natal prophylaxis and should be considered in the algorithm. A study including HIV-exposed uninfected infants is needed to assess whether the modified WHO algorithm adequately identifies infants who do not need enhanced post-natal prophylaxis and remain HIV-free after breastfeeding.

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[1]Centro de Investigação em Saúde de Manhiça (CISM), Maputo, Mozambique.
[2]ISGlobal, Hospital Clínic, Universitat de Barcelona, Barcelona, Spain.
[3]Fundação Ariel Glaser Contra o SIDA Pediátrico, Maputo, Mozambique.
[4]Pediatrics Department, Pediatric Research and Clinical Trials Unit (UPIC), Fundación para la Investigación Biomédica del Hospital 12 de Octubre, Instituto de Investigación Sanitaria Hospital 12 de Octubre (IMAS12), Madrid, Spain.
[5]Gertrude H. Sergievsky Center, Vagelos College of Physicians and Surgeons, Columbia University Irving Medical Center, New York, NY, USA.
[6]Perinatal HIV Research Unit, Chris Hani Baragwanath Academic Hospital, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa.
[7]Family Center for Research with Ubuntu, Department of Paediatrics and Child Health, Faculty of Medicine and Health Sciences, Stellenbosch University, Cape Town, South Africa.
[8]School of Public Health, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa.
[9]Africa Health Research Institute (AHRI), KwaZulu-Natal, South Africa.
[10]Great Ormond Street Institute for Child Health (GOS ICH), University College London (UCL), London, UK.
[11]Research Unit in Clinical Immunology and Vaccinology, Bambino Gesu' Children's Hospital, 00165, Rome, Italy.
[12]Chair of Pediatrics, Department of Systems Medicine, University of Rome "Tor Vergata", Rome 00133, Italy.
[13]Fondazione per la Ricerca Farmacologica Gianni Benzi onlus.
[14]Department of Mother and Child Health, University of Padova, Padova, Italy.
[15]Instituto Nacional de Saúde (INS), Mozambique.
[16]Department of Medical Biology, Gabriel Toure University Hospital, Bamako, Mali.
[17]PENTA Foundation. Padova, Italy.
[18]Pediatrics Department, Hospital Universitario Infanta Sofía; Infanta Sofia University Hospital and Henares University Hospital Foundation for Biomedical Research and Innovation (FIIB HUIS HHEN), San Sebastián de los Reyes, Madrid, Spain.
[19]Pediatrics Research Group, Universidad Europea de Madrid, Madrid, Spain.
[20]Academic Department of Pediatrics, Children's Hospital Bambino Gesù, Rome, Italy.
[21]Department of Clinical Virology, University College London Hospitals (UCLH) NHS Foundation Trust, London, UK.
[22]Imperial College Healthcare NHS Trust (ICHT), United Kingdom.
[23]University of Miami Miller School of Medicine, USA.
[24]Johns Hopkins University, Baltimore, USA.
[25]University of Utrecht, The Netherlands.
[26]University of Massachusetts Medical School Worcester. USA.
[27]Centre de Recherche du Centre Hospitalier de l'Universitè de Montreal – University of Montreal. Canadá.
[28]The Children's Hospital Corporation d/b/a Boston Children's Hospital. USA.
[29]Umkhuseli Innovation and Research Management RF NPC. South Africa.
[30]The Brigham & Women's Hospital, Inc. USA.
[31]Research Triangle Institute dba RTI International. USA.

Authors' contributions

AT conceptualized and designed the study. SDR, AT, and MSP performed the data management. MSP performed the statistical analysis. MGL and SFL drafted and reviewed the manuscript. AT, PR and LK were involved in the preparation and review of the final manuscript. AL, SB, ELV, KO, SD, EN, PP, NC, MS, VG, CG, AV, MC, TN, NK, NR, AJR, OB, PV, AM, AO, DN, PR, other co-authors implemented the study, enrolled participants and participated in the management of the study and the collection of data. All co-authors participated and were involved in the critical review of the final manuscript. The author(s) read and approved the final manuscript.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
The study was approved by Mozambique National Bioethics Committee, 53/CNBS/2018; Stellenbosch University Bioethics Committee, 1832; University of Witwatersrand and AHRI Bioethics Committee, 171114, and Bamako Faculté de Médecine Bioethics Committee, 2019/53. Mothers signed an informed consent for their infants as well as their participation in the study. All methods were carried out in accordance with relevant guidelines and regulations. Data was managed according to the European General Data Protection Regulation 2016/679.

Consent for publication
Not applicable.

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

Author details
[1]Centro de Investigação em Saúde de Manhiça (CISM), Bairro Cambeve, Rua 12, Distrito da Manhiça, CP 1929 Maputo, Mozambique. [2]ISGlobal, Hospital Clínic, Universitat de Barcelona, Barcelona, Spain. [3]Fundação Ariel Glaser Contra o SIDA Pediátrico, Maputo, Mozambique. [4]Pediatrics Department, Pediatric Research and Clinical Trials Unit (UPIC), Fundación para la Investigación Biomédica del Hospital 12 de Octubre, Instituto de Investigación Sanitaria Hospital 12 de Octubre (IMAS12), Madrid, Spain. [5]Gertrude H. Sergievsky Center, Vagelos College of Physicians and Surgeons, Columbia University Irving Medical Center, New York, NY, USA. [6]Perinatal HIV Research Unit, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa. [7]Family Center for Research with Ubuntu, Department of Paediatrics and Child Health, Faculty of Medicine and Health Sciences, Stellenbosch University, Cape Town, South Africa. [8]School of Public Health, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa. [9]Africa Health Research Institute (AHRI), Durban, KwaZulu-Natal, South Africa. [10]Great Ormond Street Institute for Child Health (GOS ICH), University College London (UCL), London, UK. [11]Research Unit in Clinical Immunology and Vaccinology, Bambino Gesu' Children's Hospital, 00165 Rome, Italy. [12]Chair of Pediatrics, Department of Systems Medicine, University of Rome "Tor Vergata", 00133 Rome, Italy. [13]Fondazione per la Ricerca Farmacologica Gianni Benzi onlus, Valenzano, Italy. [14]Department of Mother and Child Health, University of Padova, Padova, Italy. [15]Instituto Nacional de Saúde (INS), Mozambique, Maputo, Mozambique. [16]Department of Medical Biology, Gabriel Toure University Hospita, Bamako, Mali. [17]Fondazione Penta ONLUS, Padova, Italy. [18]Academic Department of Pediatrics, Children's Hospital Bambino Gesù, Rome, Italy. [19]Pediatrics Department, Hospital Universitario Infanta Sofía; Infanta Sofia University Hospital and Henares University Hospital Foundation for Biomedical Research and Innovation (FIIB HUIS HHEN), San Sebastián de los Reyes, Madrid, Spain. [20]Pediatrics Research Group, Universidad Europea de Madrid, Madrid, Spain.

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Publisher's Note

Article 4

Pediatric HIV Care Cascade in Southern Mozambique: missed opportunities for early ART and re-engagement in care

Sheila Fernández-Luis, Tacilta Nhampossa, Laura Fuente-Soro, Orvalho Joaquim Augusto, Aina Casellas, Edson Bernardo, Maria Ruperez, Raquel Gonzalez, Sonia Maculuve, Anna Saura, Clara Menendez, Denise Naniche*, Elisa Lopez-Varela*.

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3. To characterize the pediatric HIV care cascade in the Manhiça district and analyze factors associated with loss to follow up in the pre-test and treat era.

    3.1. To calculate rates of ART initiation, retention, LTFU and re-engagement in care during a 3-year period after ART initiation among children living with HIV in the Manhiça district.

    3.2. To identify clinical and sociodemographic factors associated with LTFU and RIC.

Pediatric HIV Care Cascade in Southern Mozambique: Missed Opportunities for Early ART and Re-engagement in Care

Sheila Fernández-Luis, MD†, Tacilta Nhampossa, PhD*‡, Laura Fuente-Soro, PhD*†, Orvalho Augusto, MD*, Aina Casellas, MSc†, Edson Bernardo, PhD*‡, Maria Ruperez, PhD§, Raquel Gonzalez, PhD*†¶, Sonia Maculuve, MD*, Anna Saura-Lázaro, MD†, Clara Menendez, PhD*†¶, Denise Naniche, PhD*†¶, and Elisa Lopez-Varela, PhD*†*

Background: There are 170,000 children living with HIV in 2017 in Mozambique. Scaling-up HIV care requires effective retention along the cascade. We sought to evaluate the pediatric cascade in HIV care at the Manhiça District Hospital.

Methods: A prospective cohort of children <15 years was followed from enrollment in HIV care (January 2013 to December 2015) until December 2016. Loss to follow-up (LTFU) was defined as not attending the HIV hospital visits for ≥90 days following last visit attended.

Results: From the 438 children included {median age at enrollment in care of 3,6 [interquartile range (IQR): 1.1–8.6] years}, 335 (76%) were antiretroviral therapy (ART) eligible and among those, 263 (78%) started ART at enrollment in HIV care. A total of 362 children initiated ART during the study period and the incidence rate of LTFU at 12, 24, and 36 months post-ART initiation was 41 [95% confidence interval (CI): 34–50], 34 (95% CI: 29–41), and 31 (95% CI: 27–37) per 100 children-years, respectively. Median time to LTFU was 5.8 (IQR: 1.4–12.7) months. Children 5–9 years of age had a lower risk of LTFU compared with children <1 year [adjusted subhazard ratio 0.36 (95% CI: 0.20–0.61)]. Re-engagement in care (RIC) was observed in 25% of the LTFU children.

Conclusions: The high LTFU found in this study highlights the special attention that should be given to younger children during the first 6 months post-ART initiation to prevent LTFU. Once LTFU, only a quarter of those children return to the health unit. Elucidating factors associated with RIC could help to fine tune interventions which promote RIC.

Key Words: HIV children, HIV care cascade, HIV care continuum, retention in HIV care, lost to follow up, sub-Saharan Africa

(*Pediatr Infect Dis J* 2020;39:429–434)

There are 2.1 million Mozambicans living with HIV and 170,000 of them are children under 15 years of age.[1]

From the *Centro de Investigação em Saúde de Manhiça (CISM), Maputo, Mozambique; †ISGlobal, Hospital Clínic—Universitat de Barcelona, Barcelona, Spain; ‡Instituto Nacional de Saúde (INS), Mozambique, Maputo; §London School of Hygiene and Tropical Medicine London, United Kingdom; and ¶CIBER Epidemiología y Salud Pública (CIBERESP), Barcelona, Spain.

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Denise Naniche and Elisa Lopez-Varela have contributed equally to the work.

Conceived and designed the study: E.L.-V., D.N., S.F.-L., and L.F.-S. Implemented the study: L.F.-S., S.F.-L., T.N., S.M., M.R., R.G., and E.B.; supervised by E.L.-V., D.N., and C.M. Analyzed the data: A.C., E.L.-V., O.A., and A.S. Wrote the article: S.F.-L., T.N., L.F.-S., O.A., E.L.V., and D.N. All authors contributed to refinement of the study protocol and approved the final manuscript.

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Address for correspondence: Sheila Fernández-Luis, MD, Bairro Cambeve, Rua 12, Distrito da Manhiça, CP 1929, Maputo-Moçambique. E-mail: Sheila.fernandez@isglobal.

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The cascade in HIV care describes the sequential stages of medical attention that people living with HIV experience between diagnosis and achieving sustained viral suppression.[2] The WHO has adopted the UNAIDS 95-95-95 targets to reach 95% of people living with HIV diagnosed; 95% of diagnosed initiating antiretroviral therapy (ART); and 95% on ART with viral load suppression to end the AIDS epidemic by 2030.[3] The pediatric HIV care cascade has not been studied well and the available reports on the quality of pediatric HIV care have documented high rates of loss to follow-up (LTFU) and early mortality.[4–9] Additionally, little is reported about the dynamics of re-engagement in care (RIC) in children living with HIV who were LTFU.

This study aims to evaluate the HIV care cascade, factors associated with LTFU and the dynamics of RIC in a cohort of children enrolled at the Manhiça District Hospital (MDH), Mozambique.

METHODS

Study Setting

The study was conducted at the MDH, a public hospital located in a semi-rural area in southern Mozambique, with an estimated overall HIV community prevalence in adults of 39.9% [95% confidence interval (CI): 35.9%–43.8%] in 2012.[10] Since 1996, the Manhiça Health Research Centre has run a continuous health and demographic surveillance system (HDSS) for vital events including births, deaths, and migrations covering a total population of nearly 174,000 individuals.[11] At the time of the study, children under age 18 months were diagnosed with HIV infection through a DNA polymerase chain reaction assay in the reference laboratory. After age 18 months, serologic testing was used for HIV diagnosis. Clinical consultations were monthly but could be spaced to every 2 months or quarterly in children with good clinical and immune response. Children ≥5 years of age were eligible for ART if based on CD4+ T-lymphocyte (CD4) cell count below 350 cell/mm^3 or below 500 cell/mm^3, before and after May 2015, respectively, or WHO stage III–IV. Universal treatment was recommended for all HIV-infected children <5 years of age.[12] Pharmacy pickup of ART was monthly for all children. First-line treatment was zidovudine (AZT) + lamivudine (3TC) + nevirapine (NVP) for children ≥5 years of age and <35 kg and tenofovir disoproxil fumarate (TDF) + 3TC + efavirenz (EFV) for those ≥5 years of age and ≥35 kg. Children under 5 years who had previously received prophylaxis for prevention of mother-to-child transmission were given AZT + 3TC + lopinavir/ritonavir (LPVr) and those who had not received prophylaxis for prevention of mother-to-child transmission were given AZT + 3TC + NVP according to national guidelines.[12,13]

Study Design and Procedures

This is a descriptive study of a prospective cohort including all children <15 years newly enrolled in HIV care at the MDH between January 2013 and December 2015. Children transferred to

MDH from another health facility were excluded from this analysis. Patients were followed in the context of the study from their date of enrollment in HIV care until December 2016, for a maximum study period of 4 years.

Information about the frequency of clinical consultations, ART pharmacy pick-up and referrals was extracted from the routinely collected data in the electronic MDH HIV pediatric database. Mortality and sociodemographic data were extracted from HDSS database. Clinical information was collected in a specific questionnaire in electronic format in Open Data Kit software 1.4[14] during the clinical visits and uploaded into a database in Research Electronic Data Capture Software 5.7.3.[14]

Study Definitions

Care cascade indicators included proportion of children eligible for ART at enrollment in care, proportion of children initiating ART during the first 3 months after enrollment in care among those eligible, and proportion of children retained in HIV care at 12 months post-ART initiation.

Enrollment in care was defined as having a first clinical consultation in the HIV clinic.

LTFU was defined for children on ART as not having attended their clinical consultation appointment or pharmacy pickup for ≥90 days following last consultation/pharmacy visit attended among patients considered alive and not transferred to another unit which implies a delay of at least 60 days in ART pick-up. The date of the last attended visit was considered the date of LTFU.

Among patients considered LTFU, RIC was defined as the date that the patient returned to clinic or the pharmacy. Those participants who had RIC followed by a new LTFU episode during the study period were classified as "RIC and LTFU."

Immunosuppression was defined as severe suppression (<15%), moderate suppression (15 to <25%) and no evidence of suppression (≥25%).[15]

Socioeconomic status (SES) was represented by a wealth index generated by an asset-based, multiple-correspondence analysis to categorize the household SES into 5 wealth quintiles as previously described.[16] The 2 lowest quintiles were grouped as "low SES" and the remaining 3 quintiles as "higher SES."

Z-scores for nutritional status evaluation were calculated using the WHO Child Growth Standard 2006.[17] Stunting was defined as height-for-age z-score (HAZ) <−2 SD. Underweight was defined as weight-for-age z-score <−2SD for children <10 years. Wasting was defined as weight-for-height Z-score <−2SD for children <5 years and body mass index-for-age Z-score <−2SD for children 5–19 years.

Anemia was defined as Hb≤ 8g/dl.[12]

Health problems were self-reported by the parents/caregivers.

Statistical Considerations

Data were analyzed using Stata statistical software version 15 (Stata Corp., College Station, TX).[18]

Medians and interquartile ranges (IQR) were calculated to describe continuous variables and categorical variables were summarized using frequencies.

Cumulative incidence estimation was used to describe LTFU incidence post-ART initiation among children who started ART at enrollment or during follow-up, excluding those initiating ART during the last 90 days of the study or those who were transferred before ART initiation. Censored individuals were included in the denominator.

Competing-risks regression for death and migration according to the method of Fine and Gray[19] was used to assess which variables were related to the first episode of LTFU. A multivariable model was built performing a stepwise selection of the variables with significance lower than 0.20 in the bivariable analysis.

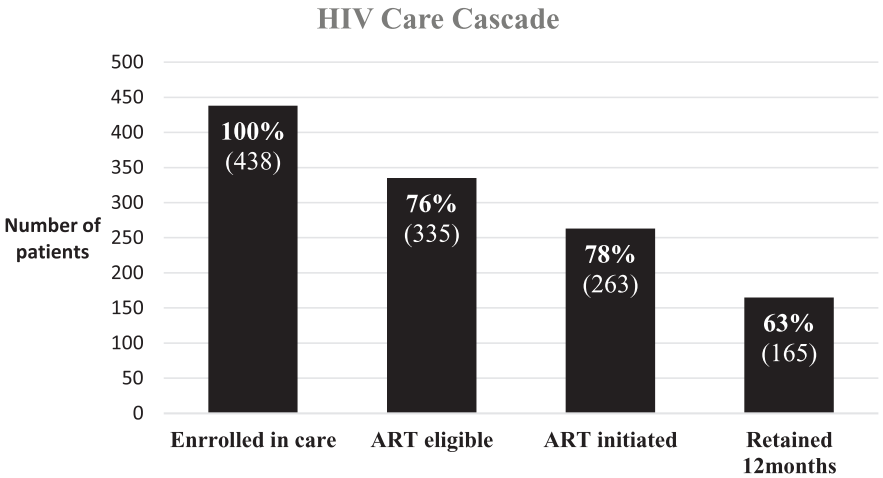

FIGURE 1. HIV care cascade from enrollment to 12-month retention conditioned on the previous step of the cascade. The percentage in each column was calculated using as denominator the number of children in the previous column. Enrolled in care: with a first clinical visit. ART eligible at enrollment in care according to national criteria explained in methods. ART initiated: those who initiated ART within 3 months of enrollment in care. Retained 12 months: retention 12 months after ART initiation with no episode of LTFU. ART indicates antiretroviral therapy; LTFU, lost to follow-up.

Ethics Statement

This study was approved by the Mozambican National Bioethics Committee and the Barcelona Hospital Clinic Institutional Review Board. Written informed consent was obtained from the parents/caregivers of all children.

RESULTS

Baseline Characteristics of the Cohort at Enrollment in HIV Care

Among 438 children enrolled in HIV care, the proportion of enrollment by year was 0.43, 0.31 and 0.25 in 2013, 2014, and 2015, respectively. Median age at enrollment was 3.6 (IQR: 1.1–8.6) years and 209 (48%) were female (baseline characteristics, Supplemental Digital Content 1, http://links.lww.com/INF/D786).

Advanced WHO stage (III–IV) was present in 39 (9%) children but 134 (31%) did not have a WHO staging at enrollment. However, when including anemia and wasting as advanced stage, the number of children considered to have advanced WHO at enrollment was 106 (24%). Severe immunosuppression was present in 86 (25%) of the 345 with a CD4 result and moderate immunosuppression in 128 (37%). Although data on immunosuppression and WHO stage was missing for 21% and 24% children, respectively, only 29 (7%) were missing both. Median values of weight-for-age z-score, weight-for-height Z-score, and body mass index-for-age Z-score were −1.18 (95% CI: −1.35 to −1.01), −0.34 (95% CI: −0.52 to −0.16), and −0.27 (95% CI: −0.41 to −0.14), respectively. A health problem during the month before enrollment in care was reported by 71 (16%) patients, 40 (56%) of them requiring hospitalization.

Seventy-seven (18%) of children were 10–15 years of age at enrollment in care. Among these, 39% and 23% presented with moderate and severe immunosuppression respectively. Only 1 (1%) reported PTV, while 44% reported not receiving PTV and 55% were unknown.

Twelve-month Pediatric HIV Care Cascade Post-ART Initiation

Of 335 (76%) enrolled children who were ART eligible, 263 (78%) started ART within 3 months of enrollment in care (Fig. 1), with a median time between enrollment and ART initiation of 17 (IQR: 6–35) days.

At 12 months post-ART initiation, 165 (63%) of the 263 children who initiated ART had been continuously retained in care (Fig. 1), while 51 (20%) presented at least 1 LTFU episode, 10 (4%) had died, and 35 (13%) had transferred to another facility.

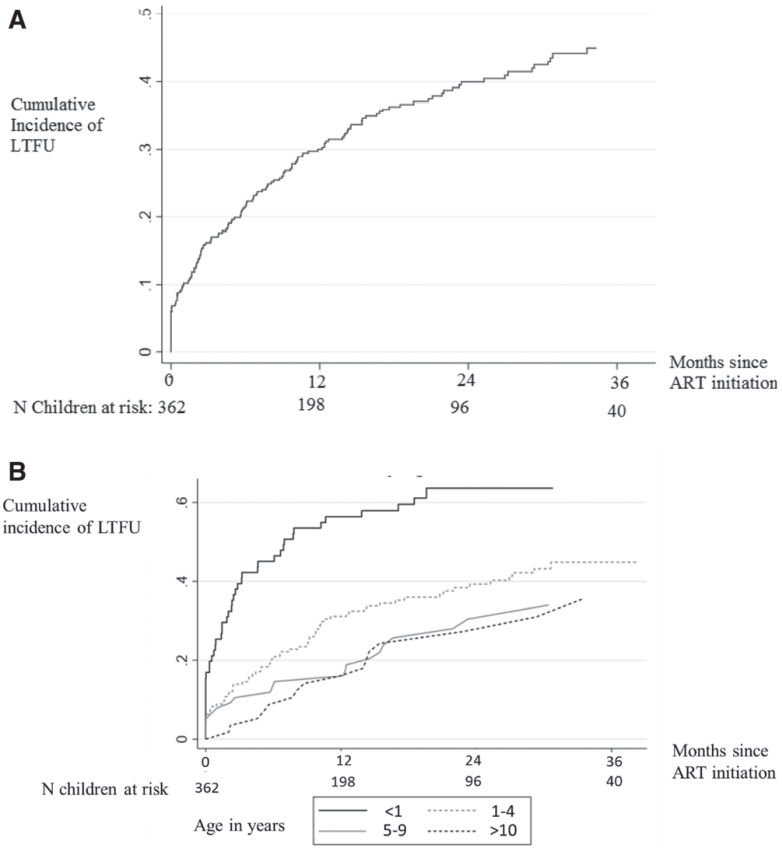

FIGURE 2. Cumulative incidence of LTFU after ART initiation among children who initiated ART at any time before the final 90 days of the study period (N = 362) for the overall population (A) and according to age group (B) Cumulative incidence is expressed as the proportion of LTFU in a given time period. ART indicates antiretroviral therapy; LTFU, lost to follow-up.

No differences in mortality at 12 months post-ART initiation were observed by age group ($P = 0.268$).

Among the 66 not eligible and the 37 with missing data for ART eligibility at enrollment, 58 (56%) became eligible during the 12-month follow-up period and all of them initiated ART.

Incidence of LTFU Over 36 Months Following ART Initiation

We then assessed LTFU in children who initiated ART at any time before the last 90 days of the study period. This population of 362 children included the 263 who initiated ART within 3 months of enrollment, 44 who initiated ART later and 55 children who become eligible and initiated ART in the above specified time period.

Figure 2 shows the cumulative incidence of LTFU from ART initiation until the end of the study period, among the 362 children who initiated ART. The median time of follow-up from ART initiation to the end of the study period (December 31, 2016) was 32.6 (IQR: 20.8–39.9) months.

At 12, 24, and 36 months post-ART initiation, of the 362 children having initiated ART, there were a total of 107 children [30% (95% CI: 25–35)], 136 children [38% (95% CI: 33–43)], and 146 children [40% (95% CI: 35–46)], respectively, with at least 1 LTFU episode. The LTFU incidence rate was 41 (95% CI: 34–50), 34 (95% CI: 29–41), and 31 (95% CI: 27–37) per 100 children years at month 12, 24, and 36, respectively.

Among the 146 children who fulfilled the definition for an LTFU episode the median time from ART initiation until the first LTFU episode was 5.8 (IQR: 1.4–12.7) months.

Factors Associated with First Episode of LTFU Post-ART Initiation

We then assessed factors associated with first episode of LTFU post-ART initiation including the 362 children who initiated ART at any time before the last 90 days of the study period.

Bivariable competing risks proportional sub-hazards regression identified younger age at ART initiation ($P < 0.0001$), unknown immunosuppression status ($P = 0.0007$), lower/unknown SES ($P = 0.0497$), and advanced WHO stage ($P = 0.0837$) as significantly associated with increased incidence of LTFU (Table 1).

In the multivariable model, younger age at ART initiation and unknown immunosuppression status were the independent factors associated with LTFU. Children 5–9 years of age had an adjusted sub-hazard ratio of 0.36 (95% CI: 0.20–0.61) for LTFU compared with children <1year of age $P < 0.0001$ (Table 1). Those with unknown immunosuppression status (no CD4 results) had an adjusted sub-hazard ratio of 2.50 (95% CI: 1.56–4.01) compared with those with no immunosuppression even after adjustment for WHO stage. Those with moderate or severe immunosuppression showed a trend for higher LTFU but did not reach significance. At 2 years post ART initiation, children 5–15 years of age at ART initiation had a 34 % risk of LTFU whereas children <1 year of age at ART initiation had close to a 62% risk of LTFU (Fig. 2B).

TABLE 1. Cox Regression of Factors Associated with First Episode of LTFU After ART Initiation with Competing-risks for Death and Migration

		Bivariable Model			Multivariable Model*		
Factors		SHR	95% Confidence Interval	*P*-value	SHR	95% Confidence Interval	*P*-value
Sex (n = 362)	Male	1		0.6511	1		0.8697
	Female	1.08	0.78–1.49		0.97	0.64–1.47	
Age at ART initiation (n = 362)	<1	1		<0.0001	1		<0.0001
	1–4	0.50	0.33–0.74		0.41	0.25–0.68	
	5–9	0.32	0.19–0.55		0.24	0.12–0.47	
	10–15	0.31	0.18–0.54		0.26	0.13–0.53	
Year of enrollment in care (n = 362)	2013	1		0.3053			
	2014	1.33	0.92–1.93				
	2015	1.12	0.73–1.71				
Time from enrollment in care to ART initiation		1	1	0.046			
Mother and father status (n = 362)	Both present	1		0.3164			
	One or both absent	0.80	0.51–1.24				
Socioeconomic index (SES) (n = 304)	Low SES	1		0.0839			
	Higher SES	0.72	0.50–1.04				
Immunosupression (n = 296)	No	1		0.4609			
	Moderate	1.33	0.84–2.11				
	Severe	1.22	0.76–1.96				
Anemia (n = 275)	No	1		0.0290			
	Yes	1.67	1.05–2.65				
WHO stage at enrollment in care (n = 243)	I–II	1		0.0431	1		0.0554
	III–IV	1.70	1.02–2.84		1.66	0.99–2.78	
Health problem during the month before enrollment in care 1 (n = 312)	Yes	1		0.4699			
	No	0.84	0.53–1.34				
Stunting (n = 343)	No	1		0.5108			
	Yes	0.89	0.64–1.25				
Wasting (n = 309)	No	1		0.0395			
	Yes	1.67	1.03–2.73				

Severe suppression was defined as CD4 percentage <15%, moderate suppression as CD4 percentage 15 to <25% and no evidence of suppression as CD4 percentage ≥25%. Stunting was defined as Height-for-age z-score (HAZ) <−2 SD. Underweight was defined as weight-for-age z-score (WAZ) <−2 SD for children <10 years. Wasting was defined as weight-for-height Z-score (WHZ) <−2 SD for children <5 years and body mass index (BMI)-for-Age Z-score (BAZ)<−2 SD for children 5–19 years. Anemia was defined as hemoglobin concentrations of ≤8 g/dL.

*Number of observations = 243.

SHR, Subhazal ratio.

Re-engagement in Care After a LTFU Episode

We then assessed the dynamics of RIC among the 146 children who had a LTFU episode during the study period. Longer median times between ART initiation and the end of the study period allowed demonstration of LTFU-RIC cycles after ascertainment of child status through HDSS and clinical records ($P = 0.0156$). The overall median follow up time for the 146 children with an LTFU episode was 32.4 (IQR: 23.6–40.8) months.

By the end of the study period, of the 146 children with initial LTFU episodes recorded, 94 (64%) had never come back to the health unit, 5 (3%) had died after becoming LTFU, 10 (7%) had migrated to another district, and 37 (25%) had reengaged. Median time to RIC was 4.6 (IQR: 3.2–6.2) months.

Of those 37 children who were LTFU and RIC, 22 (60%) continued RIC at the end of the study period and 15 (40%) presented another LTFU episode. Median age at ART initiation was 2.3 (IQR: 0.5–9.5) years for those who continued RIC and 2.5 (IQR: 0.7–11.0) years for those who RIC and presented another LTFU episode and median follow time was 35.7 (IQR: 30.4–40.8) months and 39.4 (IQR: 31.9–43.4) months, respectively.

Of the 64% of LTFU who never returned, the median age at ART initiation was 1.7 (IQR: 0.9–4.9) years and follow-up time was 30.6 (IQR: 20.5–38.7) months.

DISCUSSION

This analysis documents that younger age at ART initiation increases the risk for LTFU, mainly occurring in the first 6 months post-ART initiation. Not having a CD4 result was also associated with a high risk of LTFU. A follow-up time of over 3 years allowed us to estimate that one quarter of LTFU children reengaged in care in a median time of 4.6 months after LTFU.

A high rate of LTFU, particularly for younger children, has also been observed in pediatric cohorts from Kenya, Mozambique, Rwanda, and Tanzania in 2005–2011.[20] However, few studies have explored mothers' reasons for LTFU which may include lack of money for transportation and/or medication side effects.[21] Nearly half of the children had moderate to severe immunosuppression at enrollment in care. Similar levels in other pediatric cohorts from Mozambique in 2013[22] and other sub-Saharan African countries in 2004–2012[23] suggest little improvement over time. Another 20% were missing a CD4 result, which could indicate a lower quality of care and it was associated with a 2.3 higher risk of LTFU as compared with non-immunosuppressed children.

The decrease in numbers of children enrolled at the MDH between 2013 and 2014–2015 was likely related to Mozambique's decentralization of HIV care to lower level health facilities, since the MTCT rate remained relatively stable in Mozambique.[24]

The high proportion of children with immunosuppression along with the elevated median age at enrollment in care points toward a missed opportunity for more timely diagnosis both in infants with known perinatal HIV exposure and/or in infants whose mothers acquired HIV infection in pregnancy or during breast-feeding. The implementation of point-of-care infant HIV diagnosis in 2017 may improve early diagnosis in infants with known perinatal HIV exposure. However, HIV incidence in postpartum women in Mozambique in 2008–2011 was 3.20/100 women-years (95% CI: 2.3–4.5) with an associated MTCT rate of 21% (95% CI: 5–36).[25] Similar incidence (average 4%) in pregnant and breast-feeding women have also been observed in other sub-Saharan Africa countries.[26] Mozambican guidelines recommends HIV testing every 3 months for key populations, sero-discordant couples, blood donors, pregnant women, and her partners.[27] Reduction of time between tests as well as self-testing options for lactating mothers living in areas of high HIV incidence may be promising interventions to ensure that seroconversions during breast-feeding are diagnosed in a timely fashion.

This analysis revealed that 25% of those LTFU reengaged in care. However, this number is likely to be underestimated since we did not have sufficient follow-up time for all of the LTFU in the study. Additionally, further studies are needed to evaluate the impact that LTFU-RIC cycles have on immunosuppression, nutritional status and other clinical parameters. RIC has been described very little in the literature, especially in children. In a study of adults in Kenya, the cumulative incidence of reengaging in care, to either a new clinic or the original clinic was 14% (95%CI: 7%–23%) at 3 months and 60% (95% CI: 48%–69%) at 6 months after the most recent attended clinic appointment.[28]

Understanding a child's LTFU-RIC cycles is fundamental to having a more global view of retention, limiting LTFU and accelerating time to RIC in this vulnerable population. Assessing routinely collected data could contribute to identifying factors associated with RIC and designing specific interventions. However, paper-based charts, lack of unique identifiers and high rates of transfer and migration complicate the task. Considering the 5.8-month median time from ART initiation to the first LTFU episode in the PECA cohort, there is a window of opportunity for interventions during the first 6 months in all children initiating ART both to minimize LTFU and to promote timely RIC.

The Expanded Programme on Immunization programs in sub-Saharan African countries have a high vaccination coverage and extend to rural areas such as the Manhiça district.[29] A systematic review on integration of HIV testing during immunization clinic visits in SSA reported over 90% acceptability by mothers.[30] Such programs could also be used as a platform to send reminders to mothers and children HIV counseling and visits.

Our study has several limitations. First, enrollment in the study happened during the first consultation. The diagnosis of HIV was not made during the study and we cannot guarantee the identification of false-positives. However, we assume compliance with the Mozambican guidelines that all children under 18 months should be diagnosed and confirmed by virologic methods, which minimizes the possibility of bias. Second, the high proportion of missing data in CD4 and WHO stage could have resulted in underestimates of ART eligibility. Third, lack of systematic active tracing of LTFU children results in some children classified as LTFU who are actually silent. Incomplete identification of deaths, despite HDSS access, could also results in some deaths being classified as LTFU, further contributing to overestimates of. Fourth, the median of follow-up from ART initiation to the end of the study was 32 months. Censored data could have affected the estimation of LTFU at 36 months post-ART initiation and proportion of the RIC after LTFU.

CONCLUSIONS

The high LTFU found in this study highlights the special attention that should be given to younger children during the first 6 months after ART initiation to prevent LTFU. Once LTFU, only a quarter of those children return to the health unit, mostly within the first months after drop out. Elucidating factors associated with RIC could help to refine interventions which promote RIC.

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Article 5

The impact of the caregiver mobility on child HIV care in the Manhiça District, Southern Mozambique: A clinical based study

Tacilta Nhampossa, **Sheila Fernández-Luis**, Laura Fuente-Soro, Edson Bernardo, Arsenio Nhacolo, Orvalho Augusto, Ariel Nhacolo, Charfudin Sacoor, Anna Saura-Lázaro, Elisa Lopez-Varela, Denise Naniche.

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Specific objective 4

4. To evaluate the impact of caregiver's mobility on the pediatric continuum of care.

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RESEARCH ARTICLE

The impact of the caregiver mobility on child HIV care in the Manhiça District, Southern Mozambique: A clinical based study

Tacilta Nhampossa[1,2]*, Sheila Fernández-Luis[1,3], Laura Fuente-Soro[1,3], Edson Bernardo[1,4], Arsenio Nhacolo[1], Orvalho Augusto[1], Ariel Nhacolo[1], Charfudin Sacoor[1], Anna Saura-Lázaro[3], Elisa Lopez-Varela[1,3], Denise Naniche[1,3]

1 Centro de Investigação em Saúde de Manhiça (CISM), Maputo, Mozambique, **2** Instituto Nacional de Saúde, Ministério de Saúde (INS), Maputo, Mozambique, **3** Barcelona Institute for Global Health (ISGlobal), Hospital Clinic de Barcelona, Barcelona, Spain, **4** Serviço Distrital de Saúde, Mulher e Acção Social de Manhiça, Maputo, Mozambique

* tacilta.nhampossa@manhica.net

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Abstract

Introduction

Manhiça District, in Southern Mozambique harbors high HIV prevalence and a long history of migration. To optimize HIV care, we sought to assess how caregiver's mobility impacts children living with HIV (CLHIV)´s continuation in HIV care and to explore the strategies used by caregivers to maintain their CLHIV on antiretroviral treatment (ART).

Methods

A clinic-based cross-sectional survey conducted at the Manhiça District Hospital between December-2017 and February-2018. We enrolled CLHIV with a self-identified migrant caregiver (moved outside of Manhiça District ≤12 months prior to survey) and non-migrant caregiver, matched by the child age and sex. Survey data were linked to CLHIV clinical records from the HIV care and treatment program.

Results

Among the 975 CLHIV screened, 285 (29.2%) were excluded due to absence of an adult at the appointment. A total of 232 CLHIV-caregiver pairs were included. Of the 41 (35%) CLHIV migrating with their caregivers, 38 (92.6%) had access to ART at the destination because either the caregivers travelled with it 24 (63%) or it was sent by a family member 14 (36%). Among the 76 (65%) CLHIV who did not migrate with their caregivers, for the purpose of pharmacy visits, 39% were cared by their grandfather/grandmother, 28% by an aunt/uncle and 16% by an adult brother/sister. CLHIV of migrant caregivers had a non-statistically significant increase in the number of previous reported sickness episodes (OR = 1.38, 95%CI: 0.79–2.42; p = 0.257), ART interruptions (OR = 1.73; 95%CI: 0.82–3.63; p = 0.142) and lost-to-follow-up episodes (OR = 1.53; 95%CI: 0.80–2.94; p = 0.193).

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Competing interests: The authors have declared that no competing interests exist.

Conclusions

Nearly one third of the children attend their HIV care appointments unaccompanied by an adult. The caregiver mobility was not found to significantly affect child's retention on ART. Migrant caregivers adopted strategies such as the transportation of ART to the mobility destination to avoid impact of mobility on the child's HIV care. However this may have implications on ART stability and effectiveness that should be investigated in rural areas.

Introduction

The New York Declaration for Refugees and Migrants encourages countries to address the vulnerabilities to human immunodeficiency virus (HIV) and the specific health care needs experienced by migrant and mobile populations, as well as by refugees and crisis-affected populations, and to support their access to HIV prevention, treatment, care and support [1]. However, evidence suggests that the Southern African Development Community (SADC) countries remain poorly equipped to initiate and manage the political discussions within and between member states that are required to develop appropriate regional responses to migration, mobility, and HIV [2].

Mozambique is a SADC member with the southern region of the country harboring high rates of population movement within and between countries such as Eswatini and South Africa [3, 4]. Such high mobility has contributed to the spread of HIV via well-documented corridors of population movement [5–9]. The patterns and types of migration have changed considerably over the decades from the colonial era state-controlled "male-only" labor migration to mines and farms to a mix of clandestine work-seeking migrants or refugees fleeing from the civil war and environmental catastrophes in Mozambique [10]. Women represent an increasingly large segment of employment mobility corresponding to about 50% of migrants in some regions of the country and working in less specialized sectors of activity such as agriculture, fishing, informal trade or domestic work [11, 12].

The effect of migration and mobility on HIV care has been mostly described among adults. Studies have shown that the combination of high HIV prevalence and differing patterns of mobility has a negative impact on access to HIV and sexually transmitted infections prevention and care for migrants and their sexual partners, both at the origin and destination households [13–15]. Regarding children living with HIV (CLHIV), previous studies have demonstrated that the distance as well as the time spent outside of the origin household by caregiver may have a large impact on childhood immunizations [16]. Nevertheless, data describing the effects of caregiver's mobility on the continuation of their children's HIV care is unknown in Mozambique.

In Mozambique, as at the end of 2019 it was estimated 150,000 CLHIV, with 15,000 new infections among children younger than 15 years of age [17, 18]. The country was committed to achieve the UNAIDS 95-95-95 targets by 2020, but retention on antiretroviral treatment (ART) presents a particular challenge, with recent reports estimating a 70% retention at 12 months of ART initiation [19, 20]. Given the high mobility, it is very likely that a proportion of these children retained in care have migrant or mobility caregivers, but our understanding of the specific strategies used by migrants and mobility caregivers to retain their children in HIV care and ART is limited.

The main objectives of this study were to describe the pattern of mobility among caregivers of children enrolled in HIV care at the Manhiça District Hospital (MDH), to assess how

caregiver's mobility affects CLHIV continuation in HIV care, and to explore the strategies used by mobile caregivers to retain their CLHIV in HIV care and on antiretroviral treatment.

Materials and methods

Study setting

The study was conducted in Manhiça, a rural area located 80 kilometers north of the capital Maputo that has 21 health centers, one rural hospital and one referral district hospital, the Manhiça District Hospital (MDH). A Health and Demographic Surveillance System (HDSS) run by the *Centro de Investigação em Saúde de Manhiça* (CISM) has been in place in Manhiça since 1996, facilitating confirmation of vital status, migration and socio-economic status, among others [21]. The area is endemic for HIV and as at the end of 2017, 2237 children were registered with pediatric HIV services across the district, of which 30% were followed at HDM (Manhiça health authority's communication, 2017). HIV services are offered free of charge in all health facilities. Every newly HIV diagnosed patient is encouraged to enroll in care and patients can be tracked within sites using a unique numeric identifier which is used in charts, paper registers, and in Minister of Health (MoH) electronic HIV patient tracking systems (ePTS) [22]. At the time of the study, first and second line ART included two Nucleoside/tide Reverse Transcriptase Inhibitors (NRTI) and one Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTI) or protease inhibitor (PI) [23]. Clinical consultations for children were routinely scheduled monthly during the first-year post diagnosis and then extended to bimonthly, while ART pick-ups were scheduled monthly. Since 2015, several differentiated service delivery (DSD) models including the family-based care model, expedited clinical appointments, three-month drug distribution, and community ART support groups (CASG) have been applied to improve retention in ART.

Study design, participants and procedures

This cross-sectional survey took place in the MDH between December 2017 and February 2018, the period during which there is a two to three fold increase in hospital visits due to the return of migrants for the holiday period. CLHIV consecutively presenting for scheduled clinic visits at the MDH pediatric ART visit were screened for the following inclusion criteria: 1) child accompanied by an adult caregiver (aged >18 years), 2) residency in the Manhiça HDSS for at least three months, 3) enrolled in the MDH HIV clinic and 4) a history of ART initiation at least one year prior to the survey date. Caregivers of the CLHIV fulfilling the aforementioned criteria, were invited to participate in the study, and after signing informed consent they were asked about their history of mobility (HM) during the last year. For each enrolled child with a caregiver with HM, another child with a caregiver without HM was enrolled. The matched CLHIV was identified during the 7 days following the date of enrolment of the child with a primary caregiver with HM. Children were matched by gender and age, with a ± 6 months range for CLHIV aged 0–59 months old and ± 2 years for those aged 5–15 years old,. The caregiver was asked about mobility patterns, child health and adherence to HIV care and reported barriers to HIV care continuation after the mobility episode. The answers were recorded in an electronic questionnaire specifically designed for the study in REDCAP [24]. Finally, caregiver's data was matched to their children's clinical data and retrospectively evaluated.

Sample size calculation

Based on prior clinic visit volumes it was anticipated that MDH would see approximately 20 daily pediatric visits during December 2017 and February 2018 in the HIV care and treatment

program and that 30% of these visits would meet eligibility criteria as a participant with history of migration out of the district. Assuming an acceptance rate of 80%, we expected to recruit one hundred fifty children with a history of parental migration and one hundred fifty children without for a total of three hundred children/caregivers. As our estimated recruitment sample was fixed (based on convenience), the statistical power to detect a difference in LTFU was variable depending on actual LTFU rates in each group (i.e. for a LTFU of 20% in the non-mobile group, we would expect a 96% power to detect a difference if the LTFU was 40% in the migrant group, but only a 46% power to detect a difference if the LTFU was 30% in the migrant group).

Study definitions

For the purpose of the study, history of mobility (HM) was defined as home-absenteeism over 4 consecutive nights at least 3 times throughout the past year or definitive address change according to the answers given in the study questionnaire. Following The United Nations Recommendations on Statistics of International Migration, migration destination was classified in internal and external if mobility was within or outside the country, respectively; and in short-, medium- and long- term if the stay was less than 3 months at destination; between 3 and 11months or at least 12 months respectively [25]. Primary caregiver education was stratified in two groups: no formal education (no education or did not complete primary education) and some formal education (at least completed primary education).

We defined "*delayed ART pick-up*" if the patient had at least a 15 to 60 days delay in picking up their ART and lost to follow-up (LTFU) was defined as pharmacy default >60 days regardless of the fact that they all were back in care at the time of completing the survey according to the hospital records. ART interruption was self-reported by caregivers as some days missed ART administration when it was available.

Statistical methods

All analyses were conducted using Stata® software (version 15.0) (StataCorp LP, College Station, TX, USA). A descriptive analysis was performed with frequencies and percentages, stratifying by history of mobility. Differences in the distribution of socio-demographic variables between participants with and without HM were assessed by means of Chi-squared test for categorical variables, Chi-squared or Fisher's for categorical variables and Mann-Whitney U test for continuous variables, respectively. We then conducted conditional logistic regression analysis where the dependent variables included: reported illness, hospitalization and ART missed daily doses, ART pick-up delays and LTFU episodes occurring during the previous year. Odds ratios, as a measure of association with a 95% confidence interval (95% CI), were presented as crude (OR) values. The results with a p-value <0.05 were considered statistically significant.

Ethical considerations

The protocol and informed consent (obtained and signed by the parents or legal guardians of minors) were approved by the Institutional Committee for Bioethics in Health of CISM (CIBS-CISM/169/2017).

Results

Study population

A total of 975 CLHIV were screened for study inclusion criteria and among these, 35.1% (344/975) did not meet criteria and were not invited to participate (Fig 1). Nearly one third 29.1% (285/975) of the CLHIV screened were excluded because they came alone for their

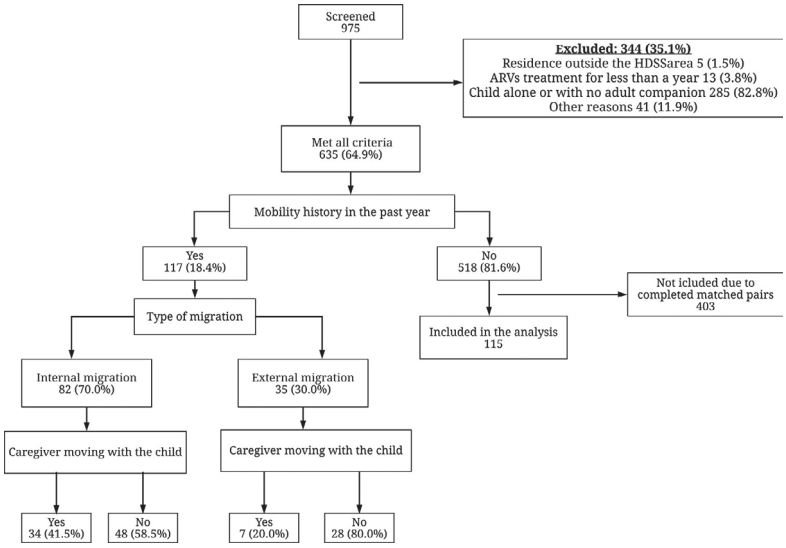

Fig 1. Study profile showing number of patients and reason for not recruiting (December 2017—February 2018).

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appointment or accompanied by a minor. Other exclusion criteria included not having been on ART for 12 months (3.8%, 13/344) and having the last known residence outside the HDSS area 1.5% (5/344) (Fig 1). Among the 635 eligible children, 117 were children whose caregivers had a HM. They were matched to 115 without HM. After matching was completed, the remaining 403 with no HM were not included in the study. Children not included in the analysis presented a similar distribution of sex and age categories as those included in the analysis ($p = 0.487$ and $p = 0.248$, respectively), but their ART retention patterns were not analyzed.

Baseline characteristics

The median age of the children was 7.8 years (IQR 4.9–10.5), 48% (111/232) were female, and most were under ART for more than two years (84%) (Table 1). Regarding caregivers, 39% didn't have any formal education and 38% had a fixed salary. Some differences were found according to the HM. For 82% of the children with HM, the mother was the main caregiver, as opposed to 66% of those without HM ($p = 0.017$). In addition, those caregivers with HM were more likely to have a fixed salary ($p<0.001$) and a cell phone ($p = 0.011$).

Caregiver's migration patterns

In 70% of the children with HM the migration occurred within Mozambique, and among those, Maputo City (55%) followed by Gaza Province (23%) were the most frequent destinations (Table 2). Nearly all of the 30% that migrated outside the country y went to South Africa. Most of the caregivers (90%) reported short-term -stays each trip as follows: less than a week (45%), less than 15 days (24%) and from 15 days to 3 months (21%); and 97% had between 2–5 mobility events during the preceding year. Between the mobility episodes, caregivers stated staying at home for: 1–3 months (68%), only on weekends (16%), more than 3 months (7%) and about one month (2%). The most frequent reason for mobility events were work/ business or looking for opportunities (41%) followed by visit or support to family/relatives (27%),

Table 1. Socio-demographic and clinical characteristics of children and their caregivers according to the caregiver' mobility history at the enrolment, number (percentages).

Characteristics	Caregiver mobility history		Total N = 232	P value[1]	P value[2]
	Yes N = 117	No N = 115			
	Child				
Age in years: median (IQR)	7.7 (4.9–10.4)	8.0 (10.7–4.7)	7.8 (4.9–10.5)		0.947*
Age group (in years)					
0–4	30 (26)	31 (27)	61 (27)		
5–9	103 (43)	53 (46)	103 (44)		
≥10	37 (31)	31 (27)	68 (29)	0.257	0.735*
Child sex					
Male	58 (50)	63 (55)	121 (52)		
Female	59 (50)	52 (45)	111 (48)	0.125	0.427*
Child's vaccination status					
Yes	91 (78)	83 (72)	174 (75)		
No	4 (3)	3 (3)	7 (3)		
Don t know	21 (18)	29 (25)	50 (22)	0.379	0.409
Time period on ARVs					
At least 1 year	21 (18)	16 (14)	37 (16)		
More than 2 years	96 (82)	98 (86)	194 (84)	0.273	0.417
School—daycare attendance					
Yes	75 (64)	80 (70)	155 (67)		
No	18 (15)	17 (15)	35 (15)		
No information	24 (21)	18 (15)	42 (18)	0.210	0.598
Child primary caregiver					
Mother	76 (65)	94 (81)	170 (73)		
Grandfather/grandmother	9 (8)	3 (3)	12 (5)		
Father	24 (20)	10 (9)	34 (15)		
Brother or sister	3 (3)	2 (2)	5 (2)		
Aunt or uncle	5 (4)	6 (5)	11 (5)	0.017	0.027
	Caregiver				
Formal education					
No formal education	47 (40)	44 (38)	91 (39)		
Some formal education	70 (60)	71 (62)	141 (61)	0.696	0.766
Fixed salary					
Yes	58 (50)	31 (27)	89 (38)		
No	59 (50)	84 (73)	143 (62)	<0.001	<0.001
Religion					
Other Christian	69 (59)	60 (53)	129 (56)		
Zione	27 (23)	30 (26)	27 (25)		
Protestants / Anglicans	18 (15)	21 (18)	18 (17)		
Islam	3 (3)	3 (3)	3 (2)	0.836	0.807
Number cellphone					
None	13 (11)	17 (15)	30 (13)		
Only one	94 (80)	97 (84)	191 (82)		
More than one	10 (9)	1 (1)	11 (5)	0.011	0.019

* Pairing variable; 1 Conditional logistic analysis; 2 Chi-squared or Fisher's for categorical variables and Mann-Whitney U test for continuous variables.

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Table 2. Migration patterns of HIV children's caregivers enrolled in care at Manhiça District Hospital.

Characteristics	N (%)
Destination of mobility	
Internal migration	82 (70)
External migration	35 (30)
Which province if internal migration N = 82	
Maputo City	45 (55)
Gaza	19 (23)
Maputo Province	7 (9)
Other provinces	11 (13)
Which country if external migration N = 35	
South Africa	34 (97)
Multiple countries (South Africa—Malawi—Eswatini)	1 (3)
Have a passport if external migration	
Yes	24 (69)
No	11 (31)
Number of mobility events (over the last 12 months)	
2–5 times	114 (97)
Once a week	3 (2)
Once a month	1 (1)
Length stay at destination	
Less than a week	53 (45)
Less than 15 days	28 (24)
From 15 days to 3 months	24 (21)
From 3 to 9 months	11 (9)
More than 9 months	1 (1)
Reason of the mobility	
Work or business or looking for opportunities	48 (41)
Visit or support for relatives	32 (27)
Following the partner	14 (12)
Religious ceremonies	10 (9)
Others (studies, alternative residency and undisclosed reasons)	13 (11)
Residence at the destination	
Family house	53 (45)
Own house	36 (31)
Rented house	22 (19)
Job house or church or institute	6 (5)
The child moved with the caretaker	
Yes	41 (35)
No	76 (65)

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following the partner (12%) and participating in religious ceremonies (9%). Compared to caregivers with external migration, those with internal migration were more likely to stay less than three months (short term length-stay) at destination ($p<0.001$) and to travel with their CLHIV ($p = 0.010$).

Strategies used by caregivers to retain their children in HIV care

Fig 2 presents the strategies used by caregivers to retain their children in HIV care. Of the 41 (35%) CLHIV moving or travelling with their caregivers, 3 (7%) interrupted ART during the

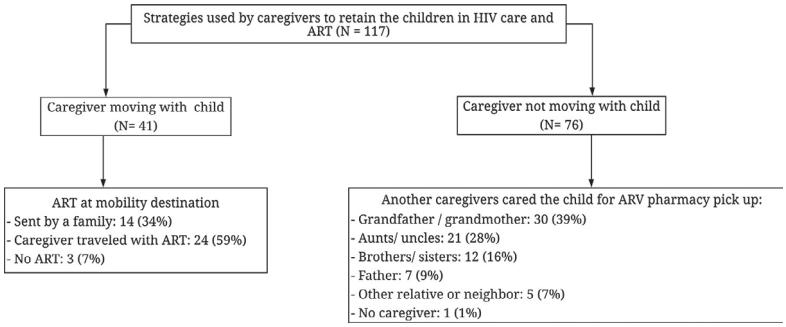

Fig 2. Strategies used by caregiver s to retain their children in HIV care and ART among those with mobility history.

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mobility event while 38 (93%) had access to ART at the destination because either the caregivers travelled with it 24 (63%) or it was sent by a family member 14 (37%). None of the caregivers reported accessing ARVs at a destination clinic. Among the 76 (65%) children who did not move or travel with their caregivers, for the purpose of pharmacy ART pick-up and HIV-care visits most were taken care of by their grandparents 30 (39%), aunts/uncles 21 (28%) or brothers/sisters 12 (16%).

Despite the previous described strategies which contributed to increase ART availability, 12 (16%) caregivers moving with their children and 8 (20%) of those not moving with their children reported missed ART daily administration (defined as ART interruption in this study) at some point. Nevertheless, in terms of ARTs interruptions, there were no statistically significant differences between children who travelled or moved with their caregivers compared to those not moving with their caregiver (p = 0.610). No differences regarding ART delay pick up (p = 0.9780), occurrence of LTFU episodes (p = 0.768) and nor reported sickness episodes (p = 0.353) were found either.

Among those children who did not move with their caregiver and ARTs interruptions were reported, children who were taken care of by their grandfather/grandmother had the highest (39%) proportion of ART interruptions, followed by aunts/uncles (28%) and brothers/sisters (16%) (p = 0.045).

The impact of the caregiver mobility on child´s HIV care

CLHIV of caregivers with HM had a non-statistically significant increase in the number of previous reported sickness episodes (45% vs 37%; OR = 1.38, 95%CI: 0.79–2.42; p = 0.257), ART interruptions (17% vs 10%; OR = 1.73; 95%CI: 0.82–3.63; p = 0.142) and LTFU episodes (34% vs 26%; OR = 1.53; 95%CI: 0.80–2.94; p = 0.193) compared to those children whose caregivers did not have HM (Table 3). In addition, none of the caregiver's migration patterns variables were either significantly associated with child continuation in HIV-care.

When returning from a mobility episode, most caregivers 102 (88%) referred no barriers to continuation in care. Among the 14 caregivers reporting barriers, they included mistreatment by health personnel 7 (50%), long waiting times 5 (36%) and not finding the correct visit room 2 (14%). When asking about alternative ART dosing schedules that could help facilitate ART access for their children, caregivers reported preferring a 3-month dosing schedule 82 (71%), followed by a 6-month dosing schedule 26 (22%) and 3 to 6-month dosing schedule 8 (7%).

Table 3. Impacts of caregiver´s mobility on child´s health and HIV care during the mobility events period.

Characteristics	Mobility history			OR	95%CI	P value[3]
	Yes N = 117	No N = 115	Total N = 232			
Reported sickness [1]						
No	64 (55)	72 (63)	136 (59)			
Yes	52 (45)	42 (37)	94 (41)	1.38	0.79–2.42	0.257
Hospitalization[1]						
No	106 (91)	105 (91)	211 (91)			
Yes	11 (9)	10 (9)	21 (9)	1.13	0.43–2.92	0.808
ART missed days doses [1]						
No	97 (83)	103 (90)	200 (86)			
Yes	20 (17)	12 (10)	32 (14)	1.73	0.82–3.63	0.142
ART pick-up delays[2]						
No	65 (60)	63 (59)	128 (60)			
Yes	43 (40)	44 (41)	87 (40)	0.81	0.48–1.37	0.422
LTFU[2]						
No	71 (66)	79 (74)	150 (70)			
Yes	37 (34)	28 (26)	65 (30)	1.53	0.80–2.94	0.193

[1]Reported by the caregiver

[2]According to hospital records

[3]Conditional logistic analysis (not adjusted).

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Discussion

Describing migration patterns and their association with HIV care constitute a priority in areas with large people living with HIV on ART such as the Manhiça District. These data are crucial to guide health care providers in implementing interventions aiming to improve HIV care and avoid interruptions in ART. To the best of our knowledge, this is the first report describing the impact of mobility on child HIV care in Mozambique.

This clinic-based study has reported high proportions of internal migration as well as short-term stays among caregivers of CLHIV during their HIV care. Maputo City, the capital of Mozambique, and South Africa, the highest-income country among those bordering Mozambique were the most frequent destinations. Indeed, mobility and migration occur mostly with the hope of improving quality of life [26, 27]. Most of the time, migrants come from places that are affected by various issues like poverty or high unemployment rate and they seek settings that may create opportunity for a better life. In fact, in this study, the main motivations for mobility were work or business or looking for opportunities. In addition, in this study, 66% of the caregivers with mobility history were the child's mother. Data from ongoing demographic surveillance in Manhiça indicate that over 50% of households are led by women and this may have contributed to the short-term pattern observed. The head woman of the household must undergo a double-shift exercise, that is, the woman who is the bread-winner of the family and the woman "caregiver of the home" (taking care of children, taking care of her husband, cooking, washing, among others home tasks) [28, 29]. Being the primary caregiver doesn't permit long term absences from the household and this was decisive for the short-term stay mobility pattern found in this district.

One of the main objectives of this study was to assess the impact of caregiver's mobility on their CLHIV continuation in HIV care. Published studies have shown the association between

mobility health care and retention on HIV treatment with, emphasis on external mobility [30–32]. However, our results show that none of the mobility pattern impacted on the child HIV care. Our results suggested that caregivers adopted strategies to avoid impact on the child's HIV care. Our study population was clinic-based and thus was more likely to recruit caregivers who may be more diligent in care-seeking behaviors and thus not be generalizable to the entire population. Future studies assessing the impact of caregiver's mobility on children's HIV health and care should be carried out in the community in order to increase generalizability and reduce this potential selection bias.

Another finding to highlight was that almost one third of the screened children presented to the HIV clinic alone or with an underage companion, and were thus not included in our study due to lack of a caregiver to give consent. The reasons for attending the clinic unaccompanied as well as the associations with mobility of caregivers need to be elucidated. Indeed children lacking adequate supervision have been linked to unintentional childhood injuries, to antisocial and risky behaviors, poorer school performance, sexual abuse, poor HIV care and other harmful consequences for children in low- and middle-income countries [33, 34]. Furthermore, this result suggest the need to engage caregivers in CLHIV HIV care. The family-based care model, a DSD model that is being implemented by the MoH in which adult and pediatric services are provided together in a single setting, could be instrumental, however challenging in mobile caregivers.

Among the strategies used by primary caregivers to retain CLHIV in HIV care and ART during the mobility event, was the substitution of the primary caregiver by another caregiver who took the CLHIV to the clinic and pharmacy visits. Children who were taken care of by their grandparents had the highest proportion of ART interruptions compared to those cared for by siblings and other non-relatives. This may be related to the fact that grandparents in general are less literate and more likely to get sick which can lead to errors in the dates or loss of visits respectively. Thus, it will be necessary to understand the reasons for interruptions in care among the different types of substitute caregivers.

Moreover, we found that 93% of the primary caregivers moving with the children took ARTs with them or asked a relative to send the ART to the mobility destination. Again, this finding demonstrates that this population of caregivers recognized the importance of retaining their children on ART. However, the conditions for transporting medicines from one place to another can impact the drug´s stability, which is fundamental to their effectiveness [35, 36] and should be investigated in Mozambican rural areas. Lopinavir/ritonavir oral solution which constituted the main formulation in younger children at the time of the study and requires 2˚C to 8˚C cold chain handling, may quickly be rendered ineffective simply due to inconsistent refrigeration [37]. This could be mitigated with the introduction of paediatric dolutegravir in the ART regimens in Mozambique [38]. In addition transporting medicines increase the risk of drug losing or running out and interrupting some daily doses.

At the national level, since 2013, the Mozambican government has made great efforts to ensure that, using the unique identification number and an electronic HIV patient tracking systems (ePTS), patients have access to ARV in any part of the country. However a downside to this policy is that mobile populations can only pick-up ART in a different health unit once during the mobility transit and the following pick-ups must take place at the original health unit. Internationally, migrants have experienced continued difficulties accessing ART as there are reports documenting that an insufficient attention has been paid in recent years to address the health needs of the increased numbers of migrants and refugees worldwide [2, 39, 40]. Understanding the HIV care needs for mobile populations provides an opportunity to adapt differentiated service delivery models to the specificities of dissimilar mobility patterns.

The strength of this study was the triangulation of survey data and children's HIV care history retrieved from the HIV routine clinical data at the MDH. However there are several limitations. Due to the high number of missing data in the ePTS database and lack of uniformity of the data recorders, it was not possible to assess the association between mobility and other clinical variables such as WHO clinical stage, CD4 count or viral load. Secondly, in the hospital setting where this study took place, we were not able to capture information from children without caregiver at the HIV visit. Finally, the data presented in this manuscript are three years old, nevertheless there hasn't been other data related to impact of mobility on child HIV care to date.

Conclusions

The caregiver mobility was not found to significantly affect child's retention on ART. To ensure CLHIV's retention in ART and avoid impact of mobility on the CLHIV's HIV care, caregivers adopted strategies such as the identification of another caregiver to take care of their CLHIV and the transportation of ART from origin households to the mobility destination. However, transporting medicines may have implications on stability, which is fundamental to maintain the effectiveness of medicines and must be investigated in rural areas. By other side, nearly one third of the CLHIV in Manhiça came to their HIV appointments without the companion of an adult reflecting the need of differentiated service delivery models which target these mobile populations with the purpose of engaging caregivers in CLHIV HIV care.

Supporting information

S1 File. Questionnaire for child with a caregiver with history of mobility (HM) in Portuguese.
(DOCX)

S2 File. Questionnaire for child with a caregiver without history of mobility (HM) in English.
(DOCX)

S3 File. Questionnaire for child with a caregiver with history of mobility (HM) in Portuguese.
(DOCX)

S4 File. Questionnaire for child with a caregiver without history of mobility (HM) in English.
(DOCX)

S1 Dataset.
(RAR)

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Author Contributions

Conceptualization: Laura Fuente-Soro, Ariel Nhacolo, Elisa Lopez-Varela, Denise Naniche.

Data curation: Tacilta Nhampossa, Sheila Fernández-Luis, Arsenio Nhacolo, Orvalho Augusto, Anna Saura-Lázaro, Denise Naniche.

Formal analysis: Arsenio Nhacolo, Orvalho Augusto, Anna Saura-Lázaro.

Methodology: Laura Fuente-Soro, Edson Bernardo, Ariel Nhacolo, Charfudin Sacoor, Elisa Lopez-Varela, Denise Naniche.

Project administration: Tacilta Nhampossa, Sheila Fernández-Luis.

Supervision: Tacilta Nhampossa, Sheila Fernández-Luis, Laura Fuente-Soro, Edson Bernardo, Elisa Lopez-Varela, Denise Naniche.

Writing – original draft: Tacilta Nhampossa.

Writing – review & editing: Tacilta Nhampossa, Sheila Fernández-Luis, Laura Fuente-Soro, Edson Bernardo, Arsenio Nhacolo, Orvalho Augusto, Ariel Nhacolo, Charfudin Sacoor, Anna Saura-Lázaro, Elisa Lopez-Varela, Denise Naniche.

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Article 6

Health Related Quality of Life in children living with HIV in Manhiça, Mozambique

Sheila Fernández-Luis*, Anna Saura-Lázaro*, Tacilta Nhampossa, Edson Bernardo, Laura Granés, Laura Fuente-Soro, Orvalho Augusto, Elisa Lopez-Varela, Denise Naniche.

Manuscript under preparation.

Specific objective 5 and subobjective 5.1

5. To measure health related outcomes among children living with HIV in the Manhiça district.

   5.1. To determine the health-related quality of life scores at 12-24 months after ART initiation among children in care at Manhiça District Hospital.

Health Related Quality of Life in children living with HIV in Manhiça, Mozambique

Sheila Fernández-Luis*[1,2,§], Anna Saura-Lázaro*[1,2], Tacilta Nhampossa[1,4], Edson Bernardo[1,5], Laura Granés[3], Laura Fuente-Soro[1,2], Orvalho Augusto[1,6,7], Elisa Lopez-Varela[1,2], Denise Naniche[1,2].

[1] Centro de Investigação em Saúde de Manhiça (CISM), Maputo, Mozambique.
[2] ISGlobal, Hospital Clínic, Universitat de Barcelona, Barcelona, Spain.
[3] Hospital Clínic, Barcelona, Spain.
[4] Instituto Nacional de Saúde (INS), Mozambique
[4] Manhiça District Health Services, Maputo Province, Mozambique
[6] Faculty of Medicine, University Eduardo Mondlane, Maputo, Mozambique
[7] Department of Global Health, University of Washington, Seattle, Washington, USA
*Contributed equally to this work
[§] Corresponding author: Sheila Fernández-Luis

Bairro Cambeve, Rua 12,
Distrito da Manhiça, CP 1929, Maputo-Moçambique
Phone: (+258) 21810002
Email: Sheila.fernandez@isglobal.org

E-mail addresses of authors:
SFL: sheila.fernandez@isglobal.org.
ASL: anna.saura@isglobal.org
TN: Tacilta.Nhampossa@manhica.net.
EB: edson.bernardo@manhica.net.
LG: GRANES@clinic.cat
LFS: laura.delafuente@isglobal.org.
OA: orvaquim@gmail.com.
ELV: elisa.lopez@isglobal.org.
DN: denise.naniche@isglobal.org.

Keywords: health related quality of life, children, HIV, sub-Saharan Africa, Mozambique

Abstract

Introduction: Children living with HIV (CLHIV), at different clinical stages face challenges which may affect their Health Related Quality of Live (HRQoL) (1,2). Research on the HRQoL and well-being among children is limited and the few studies conducted among CLHIV in low- and middle-income countries report contradictory results. This study assesses HRQoL among CLHIV and compares it to that of children without HIV infection in the Manhiça District, Southern Mozambique.

Methods: We conducted a cross-sectional study from May 2021 to February 2022 at the Manhiça District Hospital (MDH). CLHIV aged 2 to 10 years and who were on ART for 12-36 months were recruited at their routine HIV scheduled visit. Controls were age-matched children attending either the triage with minor acute ailments or the healthy child consultation, and having a negative HIV result in the previous 30 days. HRQoL was measured using the parent proxy version in Portuguese of the PedsQL™ 4.0 questionnaire, which includes four multidomain scales: physical, emotional, school, and social. Mann-Whitney U test was used to compare the HRQoL scored between CLHIV and the children without HIV infection and the ratio of IQR was estimated to compare data dispersion between both groups. Linear regression was used to explore associations between sociodemographic and clinical characteristics and the HRQoL Total score, among CLHIV.

Results: We found a good parent-reported HRQoL among children 2-10 years old, with a total PedsQL™ scale score above 90 points out of 100, for all age groups. We did not observe differences in median scores of HRQoL between CLHIV and controls, except for the social domain in the 2-4 age group [CLHIV: median100 (IQR:90.0 - 100) vs children without HIV infection: median 100 (IQR:100 - 100), p=0.024]. However, we found that 10% of the preschooler and preadolescent CLHIV reported total HRQoL scored below 80 points, but any of the children without HIV infection did it. HRQoL scores among CLHIV were poorer when reported by their parents compared to those reported by other non-parent relatives. No other factors were found to be associated with HRQoL among CLHIV.

Conclusions: CLHIV in care at MDH had an overall good HRQoL. CLHIV between 2 and 4 years of age had a poorer HRQoL score in the social domain compared to children without HIV infection. Future research is needed to elucidate determinants of lower scores in the social domain among preeschooler children living with HIV to compare HRQoL to the general pediatric population.

Introduction

There were 1.7 million children living with HIV (CLHIV) in 2020, two thirds of them in Eastern and Southern Africa (3). Mozambique has one of the highest burdens of pediatric HIV globally, with approximately 130,000 children living with HIV in 2020 (4).

Once infection is acquired, for an adequate clinical management, CLHIV must be diagnosed, linked to care, initiate antiretroviral treatment (ART) and eventually achieve HIV viral suppression (VS). These stages are collectively referred to as continuum of HIV care (5,6). Although VS, which dramatically impacts clinical prognosis (7,8), has historically been considered the ultimate goal in the continuum of HIV care, patient well-being and health-related quality of life (HRQoL) have gained momentum in the global HIV/AIDS strategy (9,10).

HRQoL is a multidimensional concept, which includes individual perceived social, emotional and physical functioning or well-being (11,12). It also has been directly associated with clinical outcomes among people living with HIV, such as hospitalization and mortality (13). The HRQoL of CLHIV, at different stages of the disease, can be affected by some distinctive vulnerabilities and the common challenges faced by them and their families, such as comorbidities, mental health conditions, family financial stress, stigma, regular hospital visits, and periods of school absence (1,2). Yet, there is limited research focused on HRQoL and well-being among children, particularly in sub-Saharan Africa, where near 80% of CLHIV live (3). The few studies conducted report contradicting results, with some showing lower HRQoL in CLHIV compared to children without HIV infection (14,15), while others finding no differences (16). To our knowledge, to date, there hasn´t been any study performed among children living with or without HIV in Mozambique.

This study aimed to evaluate the HRQoL among CLHIV on ART in the Manhiça District, Southern Mozambique, compared to children without HIV infection and to identify sociodemographic and clinical factors associated to HRQoL in CLHIV.

Methods

We conducted a cross-sectional study from May 2021 to February 2022 at the Manhiça District Hospital (MDH). The Manhiça District is a semi-rural area in southern Mozambique with an estimated community HIV prevalence among HIV-exposed children less than 4 years in 2018 of 4.4% [95% confidence interval (CI):3.1–5.7%] (17).

We included CLHIV aged 2 to 10 years, who: 1) were attending their scheduled routine visit in the MDH and 2) had initiated ART in the preceding 12 to 36 months, and 3) had resided in the Manhiça district for at least 3 months. Since there were no baseline data on HRQoL in CLHIV from Mozambique, in order to facilitate interpretation of results of HRQoL in CLHIV, we consecutively enrolled controls without HIV innfection who were matched by sex and age (with ± 6 months of difference for cases aged 12-59 months and ± 2 years for cases aged 5-10 years) and were: 1) evaluated with mild acute symptomatology at the triage unit of the outpatient clinic or attending routine well child scheduled visits and 2) if they had an HIV-negative result in the clinic at survey or with a documented negative HIV-result in the last 30 days. Children of both groups were excluded if they had not resided in Manhiça for at least 3 months.

Measurements

Sociodemographic, clinical and HIV-related characteristics

After informed consent was obtained, study HIV counsellors administered a specific electronic questionnaire in REDCap (Research Electronic Data Capture) (18), designed to capture sociodemographic characteristics, HRQoL data, clinical symptoms and, for CLHIV, adherence to ART HIV. Other HIV related variables were retrospectively collected through MDH HIV electronic patient tracking system (ePTS) (19). We defined baseline CD4 counts and World Health Organization (WHO) stage as those recorded at ART initiation within a 3-months window). The closest viral load (VL) to the survey (with a 12-month window) was also recorded. Mozambique discontinued the use of regular CD4 determinations for ART monitoring after March 2019 (20), and thus, this information was not included in the study.

Pediatric Quality of Life Inventory™ 4.0 (PedsQL™ 4.0)

HRQoL was measured using the parent proxy version of the PedsQL™ 4.0 questionnaire (21,22). The original English instrument was translated into Portuguese and into the local language of the district; Changana, using the forward and backward translation method (23). The generic PedsQL™ 4.0 is a validated questionnaire developed to measure HRQoL in healthy and chronically or acutely ill children, although this questionnaire had not been previously tested in Mozambique. It includes 23 items, divided in four domain scales: physical (8 items), emotional (5 items), school (5 items), and social (5 items), and three summary scores: physical health summary score, psychosocial health summary score, and total score (21). Age was categorized based on questionnaire guidelines. The questionnaire for the youngest

group (2-4 years) doesn't include the school domain. The various scale scores and summary scores were calculated as per the PedsQL 4.0 questionnaire guidelines (21). The total score ranges from 0 to 100, with higher scores indicating better quality of life for children. We defined HRQoL as good (total score 80-100%) and suboptimal (total score <80%), according to categorizations previously performed in the literature (16).

Pediatric AIDS clinical trials group adherence questionnaire (PACTG)

In CLHIV, we assessed adherence and reasons for non-adherence with a forward-backward Portuguese or Changana translation of the English version of PACTG (23). This questionnaire contains two modules, which measure parent proxy-reported adherence and assesses barriers, respectively. Module 1 identifies ART medications and asks the respondent about missed doses for each medication in the last 3 days. Module 2 asks the caregiver if any potential problems with adherence have occurred in the past 14 days. CLHIV were classified as adherent if their caregiver indicated no doses of any ART medication were missed during the 3 days before the report (24).

Statistical Analysis

No sample size calculation was defined for detect a difference between CLHIV and children without HIV infection, although we aimed to recruit 50 CLHIV and children without negative infection during the recruitment period.

Results were summarized as absolute numbers, proportions and medians with interquartile ranges (IQR). Sociodemographic and clinical characteristics were compared between groups using Chi-square and Fisher's exact tests. Internal consistency reliability of the PedsQL™ scales was determined with Cronbach's alphas (α); >0.70 was considered to be good, 0.40–0.70 medium, and <0.40 weak. Mann-Whitney U test was used to compare the HRQoL between children living with HIV and the children without infection, both the domain-specific and the summary scores. Domains with a Cronbach's α <0.70 were considered not comparable between groups (25). To increase internal reliability Cronbach's alpha coefficient was recalculated by removing an individual item from the questionnaire, when the obtained "alpha if item deleted" achieved a value ≥0.7 and the comparation group had alpha ≥0.7 (26). In addition, the ratio of IRQ between children without HIV and CLHIV was estimated to compare data dispersion between both groups and Bootstrap percentile-based 95% CI were estimated.

Univariable and multivariable linear regression analyses were used to explore associations between HRQoL, and sociodemographic and clinical characteristics, including the PACTG instrument reported ART adherence. Covariates with a p-value<0.2 in the univariable analysis were taken into the multivariable model.

A p-value <0.05 was taken as statistically significant. Stata Statistical Software, release 16 (StataCorp LP, College Station, TX, USA) was used for the analyses.

Ethical Considerations

This study was approved by the Mozambican National Bioethics Committee (455/CNBS/20). Written informed consent was obtained from the caregivers of all children for the mothers/caregiver and children participation.

Results

Study population characteristics

A total of 49 CLHIV and 33 children without HIV infection were included in the study. Overall, more than half were females (43/82, 53.4%) and were between 2 and 4 years of age (42/82, 51.2%) (**Table 1**). Most of the questionnaires were completed by the mother (62/82, 75.6%) followed by the father among controls (3/33, 9.1%) and among CLHIV by another family member (13/49, 26.5%), p=0.013. The presence of symptoms was more frequent among the children without HIV infection than CLHIV (84.4% vs 2.1% vs p<0.001), with cough and fever being the most common ones (40.7% and 3.7%, respectively). No other differences were found between the two groups of children.

Table 1. Characteristics of HIV-positive and children without HIV infection at the time of the survey

Characteristics		CLHIV N=49		Children without HIV N=33		TOTAL N=82		
		N	%	N	%	N	%	p value
Gender	Female	25	51.02%	18	54.55%	43	53.44%	0.754*
	Male	24	48.98%	15	45.45%	39	47.56%	
Age at survey	2-4 years	22	44.90%	20	60.61%	42	51.22%	
	5-7 years	16	32.65%	8	24.24%	24	29.27%	0.374*
	8-10 years	11	22.45%	5	15.15%	16	19.51%	
Education	Toddler	33	68.75%	25	78.13%	58	72.50%	0.358*
	Primary school	15	31.25%	7	21.88%	22	27.50%	
Interviewee	Mother	33	67.35%	29	87.88%	62	75.61%	
	Father	3	6.12%	3	9.09%	6	7.32%	**0.013****
	Another relative	13	26.53%	1	3.03%	14	17.07%	
Symptoms at study visit (n=81)	Yes	1	2.08%	27	84.38%	28	35.00	**<0.001****
	No	47	97.92%	5	15.63%	52	65.00	
Symptoms (N=96*)**	None	47	97.92%	5	15.63%	52	65.00%	
	Fever	0	0.00%	10	30.30%	10	12.20%	
	Cough	1	2.04%	17	51.52%	18	21.95%	**0.607****
	Headache	0	0.00%	4	12.12%	4	4.88%	
	Skin lesions	0	0.00%	3	9.09%	3	3.66%	
	Other	1	2.04%	8	24.24%	9	10.98%	

CLHIV: children living with HIV

*Pearson chi-square **Fisher exact test.

*** N is considered the number of participants who presented with the symptom

Table 2 describes the clinical characteristics of CLHIV. At the time of study enrolment, the median time on ART was 39.1 months (IQR: 30.9 - 48.2) at study visit, most had WHO stage I-II (65.3%) and a VL<1,000 copies/ml (63.3%). At the time of ART initiation, most had CD4 counts ≥ 500 (65.3%). A total of 63.3% (31/49) caregivers reported good child adherence to ART and only 8.2% (4/49) of the CLHIV were aware of their HIV status, disclosed to them by caregiver.

Table 2. Clinical characteristics of children living with HIV at survey

Clinical characteristics of children living with HIV. N=49			
Characteristics		**N (median)**	**% (IQR)**
Adherence	Good	31	63.27%
	Poor	8	16.33%
	No information	10	20.41%
Time between diagnosis and ART initiation (days). Median IQR. n=47		(0.0)	(IQR:0-7)
Time between ART initiation and survey (months). Median IQR n=48		(39.1)	(IQR: 30.92 - 48.17)
Child aware of their HIV status (disclosed by the caregiver)	Yes	4	8.16%
	No	42	85.71%
	No information	3	6.12%
WHO stage at ART initiation (+/- 3 months)	I-II	40	81.63%
	III-IV	5	10.20%
	No information	4	8.16%
WHO stage at survey (+/- 12 months)	I-II	32	65.31%
	III-IV	15	30.61%
	No information	2	4.08%
CD4count at ART initiation (+/- 3 months)	<200	3	6.12%
	200-500	3	6.12%
	≥500	32	65.31%
	No information	11	22.45%
VL at survey (+/-12 months)	<1000	31	63.27%
	≥1000	9	18.37%
	No information	9	18.37%
ART regime at survey	ABC-3TC + LPV/r	29	59.18%
	ABC-3TC + NVP	1	2.04%
	ABC-3TC + DTG	10	20.41%
	No information	9	16.37%

ART= antiretroviral treatment, VL=Viral load, WHO stage=WHO Disease Staging System for HIV Infection, ABC-3TC=Abacavir/Lamivudine, LPV/r=Lopinavir/Ritonavir, NVP=Nevirapine, DTG=Dolutegravir, IQR: interquartile range

Parent proxy-reported adherence through Pediatric AIDS clinical trials group adherence questionnaire (PACTG)

HIV-negative children were not included.

Aware: refers to the adult caregiver having disclosed the information to the child.

HRQoL scores

Overall, all age groups of CLHIV had good HRQol with a total score ranging from 91.3 (IRQ: 88.0-100) among the oldest children aged 8-10 years to 97.2 (IRQ: 90.5-100) among the youngest group (2-4 years) (**Table 3**).

Table 3. Health Related Quality of Life (HRQoL) comparison between CLHIV and children without HIV by age

PedsQL™ domains	Children without HIV Median (IQR)	CLHIV Median (IQR)	p-value*	Ratio IQR (95% CI)**
2-4 years (n=42)				
Physical	100 (93.75 - 100)	100 (93.75 - 100)		1.00 (0.00 to 1.00)
Emotional	90.00 (80.00 - 100)	100 (90.00 - 100)		2.00 (0.24 to 4.00)
Social	100 (100 - 100)	100 (90.00 - 100)	**0.024**	0
Psychosocial	93.75 (87.50 - 95.00)	95.00 (87.50 - 100)		0.60 (0.25 to 3.00)
Total score	94.44 (91.67 - 97.22)	97.22 (90.48 - 100)		0.58 (0.18 to 2.00)
5-7 years (n=24)				
Physical	100 (98.44 - 100)	100 (100 - 100)		0
Emotional	95.00 (85.00 - 100)	100 (81.25 - 100)	0.891	0.8 (0.00 to 3.20)
Social	90.00 (90.00 - 95.00)	97.50 (90.00 - 100)		0.50 (0.00 to 2.00)
School	72.5 (65.00 - 80.00)	97.50 (90.00 - 100)	0.074	1.50 (0.00 to 3.00)
Psychosocial	92.5 (86.67 - 97.50)	95.00 (90.00 - 100)	0.448	1.08 (0.00 to 3.33)
Total core	95.83 (90.40 - 97.92)	96.98 (93.48 - 100)	0.515	1.15 (0.19 to 3.69)
8-10 years (n=16)				
Physical	100 (93.75 - 100)	100 (85.71 - 100)		0.44 (0.00 to 1.00)
Emotional	90.00 (80.00 - 100.00)	90.00 (80.00 - 100)	0.859	1.00 (0.00 to 3.00)
Social	90.00 (90.00 - 100)	100 (90.00 - 100)		1.00 (0.00 to 1.00)
School	90.00 (90.00 -100)	87.50 (81.25 - 100)	0.678	0.53 (0.00 to 1.60)
Psychosocial	86.67 (86.67 - 100)	93.33 (86.67 - 100)	0.953	1.00- (0.00 to 2.50)
Total core	91.30 (89.13 - 97.83)	91.30 (88.04 - 100)	0.909	0.73 (0.00 to 4.00)

CLHIV: children living with HIV, IQR: interquartile range, CI: confidence interval

HRQoL was measured through parent proxy version of the PedsQL™ 4.0 questionnaire

*U-Mann Whitney was used to compare the HRQoL between CLHIV and children without HIV

**Ratio of the IQR between CLHIV and children without HIV. Bootstrap percentile-based 95% CI were estimated.

School Functioning was not calculated at preschooler age

Median comparation p value was not specified for not comparable groups (Cronbach's α <0.70)

Cronbach's α estimates showed heterogeneous reliability estimates according to domain and age group (Supplementary Table 1). Thus, domains not reaching a Cronbach's α estimate >0.70 (Physical, Emotional, Psychosocial and Total scale score among 2-4 years age group; and Physical and Social for 5-7 years and 8-10 years 2-4 years age group) could not be compared between CLHIV and children without HIV infection (**Supplementary Table 1**). In those comparable domains, both CLHIV and children without HIV infection showed similar PedsQL™ scores, except for the social domain in the 2-4 year age group [CLHIV: median100 (IQR:90.0 - 100) vs children without HIV infection: median 100 (IQR:100 - 100), p=0.024 **(Table 3).** No statistically significant data dispersion was observed between both groups as demonstrated by similar ratios of the IQR.

However, As shown in **Figure 1**, a total of 10.2% (4/49) CLHIV from the 2-4 year and 8-10-year age groups reported suboptimal HRQoL (total score bellow 80 points), whereas none of the 33 children without HIV infection did, p=0.070.

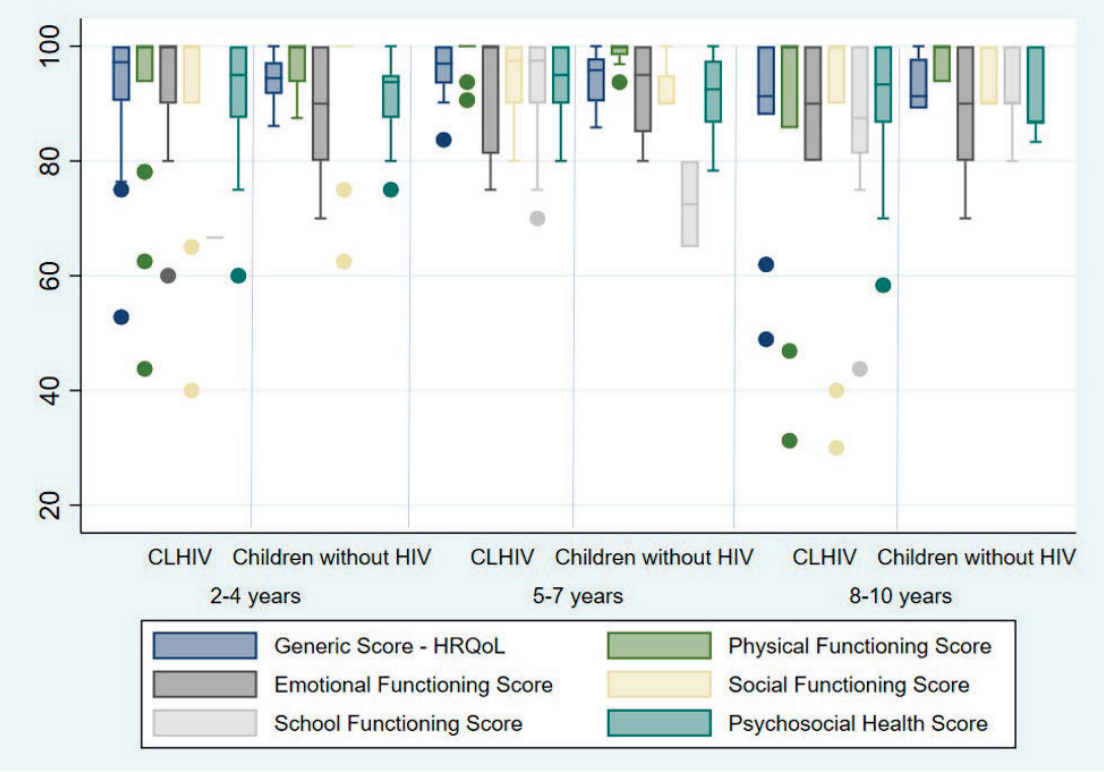

Figure 1: Comparison of HRQoL between CLHIV and children without HIV by age.

HRQoL vertical box plot by HIV serostatus and group of age.

HRQoL: health related quality of life. CLHIV: children living with HIV

Table 4 shows the analysis of sociodemographic and clinical factors associated with suboptimal HRQoL among the 49 CLHIV. The person interviewed was the only factor that was significantly associated with a suboptimal HRQoL. Family members other than the parents reported higher HRQoL as compared to the parents (β coefficient 4.7 (95% CI:1.5 to 10.4), p=0.018).

Table 4. Sociodemographic and clinical factors associated with HRQoL among CLHIV registered in the Manhiça district (n=48)

Factors	Univariable model			Multivariable model (n=38)		
	β coefficient	(95% CI)*	p-value	β coefficient	(95% CI)*	p-value
Gender						
Male	ref					
Female	3.25	(-3.20 to 10.16)	0.354			
Age						
2-4 years	ref					
5-7 years	3.46	(-1.62 to 9.46)	0.208			
8-10 years	-5.02	(-16.36 to 4.65)	0.349			
Interviewer						
Mother	ref			ref		
Father	-24.39	(-44.65 to - 0.96)	**0.041**	-15.44	(-43.27 to 13.31)	0.374
Another relative	5.11	(1.56 to 9.54)	**0.009**	4.71	(1.53 to 10.40)	**0.018**
ART adherence (n=39)						
Adherent	ref			ref		
Non-adherent	5.00	(-0.20 to 10.98)	0.070	1.55	(-2.53 to 5.86)	0.484
WHO stage at study visit (+ 12 months) (n=47)						
I-II	ref			ref		
III-IV	-7.86	(-16.99 to 0.51)	0,066	-6.20	(-14.59 to 0.86)	0.114
CD4 counts at ART initiation (+/- 3 months) (n=38)						
<250	ref					
250-500	1.33	(-3.26 to 6.06)	0.580			
>500	-5.28	(-10.83 to 0.59)	0.066			
VL at study visit (+/- 12 months) (n=40)						
<1,000 copies/ml	ref					
≥1,000 copies/ml	2.13	(-2.83 to 7.42)	0.442			
Time from ART initiation to study visit	-0.21	(-0.61 to 0.16)	0.273			

HRQoL: health-related quality of life, CLHIV: children living with HIV, CI: confidence interval

*Bootstrap percentile-based 95% CI.

Discussion

This cross-sectional study revealed good parent-reported HRQoL among 2 to 10 year-old children in HIV care at the Manhiça District Hospital (MDH), and found a PedsQL™ scale score above 90 points out of 100 within all age groups. No significant differences were found between CLHIV and children without HIV infection in any of the PedsQL™ domains compared, except for the social domain in the 2-4 age group [CLHIV: median100 (IQR:90.0 - 100) vs children without HIV infection: median 100 (IQR:100 - 100), p=0.024]. HRQoL among CLHIV was higher when reported by a family member other than a parent compared to that reported by parents (β coefficient 4.7 (95% CI:1.5 to 10.4), p=0.018).

The good overall HRQoL scores obtained among the participants living with HIV in our study could be attributed to them being on ART and having a good clinical (65.3% WHO stage I-II) and virologic (63.3% viral load< 1000copies/ml) status at the time of the survey, as well as good immunological status at ART initiation (65.3% cd4>500). In line with this hypothesis, data prior to the test-and-treat era showed lower quality of life among untreated children compared with those on ART (15,27,28), while other studie conducted in Nigeria after universal access to ART found, as we did, good HRQoL among CLHIV, with PedsQL™ total scores above 80 (29). The data encouragingly shows that good HRQoL is possible in children living with HIV who are retained on treatment.

Similar to our results, equivalent overall HRQoL between CLHIV on ART and children without HIV infection has been reported in children between 5 and 18 years of age in other sub-Saharan African contexts, as well as in Asia and Europe (16,30,31). However, we found significantly lower scores in the social domain in CLHIV compared to children without HIV infection among the 2-4-year-old age group. One of the few studies reporting HRQoL among children under 4 years conducted in Indonesia between 2012-2013 reported a global parent proxy social score above 80 (32). However, they did not disaggregate PedsQL™ subscales scores by age (32). To our knowledge, no previous studies evaluated HRQoL among children under 4 years old in sub-Saharan Africa. Even though assessing the social domain through a parent proxy in young children is challenging because it goes beyond observable characteristics (such as other children not wanting to be his/her friend) (33), our results suggest that HIV, which is a neurotropic virus (34), may affect social interactions with peers during the first years of life. Data published in 2022 among HIV-exposed children in South Africa showed that infants exposed to HIV presented affected social interaction measured through Neurobehavioral Assessment Scale compared with infants non-exposed to HIV (35). In addition, environmental factors such as more isolation may also play a role in the affected social interaction (36). Further research is needed to investigate the mechanisms by which HIV exposure and infection affects the children social sphere and how it is minimized in late childhood.

None of the sociodemographic or clinical factors evaluated showed an association with HRQoL at the time of the survey, except for the relationship of the caregiver to the child. Previous studies in Indonesia showed an association between higher caregiver coping and poor HRQoL among CLHIV (37). Therefore, a higher maternal coping gained through the struggles of keeping her CLHIV healthy, compared with a more distant relationship of other relatives, could lead to reporting lower HRQoL among their CLHIV. Although other factors such as WHO stage and viral load directly impacted the clinical outcomes of CLHIV, the perception of quality of life is complex and captures information beyond measurable biological parameters (14,38). In addition, parameters such as CD4 count and HIV-stigma, have been reported in the literature as factors associated with HRQoL among CLHIV (14,16,39–41), but could not be evaluated in this study. Specific HRQoL modules for HIV would facilitate the evaluation of stigma and other particularities related to HIV that can affect HRQoL of CLHIV.

Finally, our data showed that although overall HRQoL was good among CLHIV, there were 10% of CLHIV with a suboptimal total HRQoL score, less than 80 points, in the 2-4 and 8-10 years age groups. Future research is needed to elucidate the underlying potential reasons for suboptimal and/or poor HRQoL scores among CLHIV, particularly in pre-schooler and preadolescent age groups. These are key developmental age groups and specific interventions could potentially improve their HRQoL. A systematic review published in 2017 found that psychosocial support interventions, such as play groups, homework clubs and home-based care programmes improved the psychosocial well-being of CLHIV in low and middle income countries including Uganda, South Africa and Kenia, although most of the interventions were directed at children over seven years of age (42).

This study has several limitations. First, the small sample size limited our power to detect a significant difference between groups and identify factors associated with HRQoL scores among the CLHIV. Second, since no baseline data exists on HRQoL in CLHIV from Mozambique, children without HIV infection were invited to participate in the HRQoL assessment in order to facilitate interpretation of results of HRQoL in CLHIV. However, selection bias might have minimized differences in HRQoL scores between groups, because children without HIV infection were recruited at the hospital, and even minor acute ailments could have affected the perception of HRQoL at the time of survey. In addition, an internal consistency and reliability below the standard of 0.70 in several subscales among groups without HIV infection was found. Cronbach's alpha coefficient was therefore recalculated by removing an individual discordant item in the questionnaire (26), as explained in methods, and for those subscales that remained with low reliability, a descriptive analysis in the group of study without any comparisons between groups was performed. Further studies are needed to confirm the comparison between children living with and without HIV in Mozambique or similar resource limited settings with high HIV prevalence. Third, this research was conducted during/post-COVID-19 pandemic. This may have a negative impact on HRQoL in both groups of children (77). Finally, the caregiver

reported PedsQL™ instrument for all ages was used, which some authors consider may limit the accurate assessments of the children's HRQoL compared to a self-reported assessment leading to both overestimation and underestimation of the result (33). However, children under the age of five cannot reliably self-report (33,43), and parent proxy PEDSQL has shown to be reliable, and has been validated for ages 2–16 years (44).

Conclusions

This is a first description of HRQoL in a sample of CLHIV and children without HIV infection in Mozambique. CLHIV on ART at the Manhiça District Hospital had an overall good HRQoL. We found no differences between CLHIV and children without HIV infection, except for the social domain in the 2-4 year age group. HRQoL scores among CLHIV were poorer when reported by their parents compared to those reported by other non-parent relatives. Further studies are needed to understand the impact of HIV in HRQoL in comparison with the paediatric general population and its determinants, with the ultimate goal of improving children outcomes beyond clinical parameters.

Competing interests and Source of Funding

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Authors' contributions

DN, ELV and SFL conceptualized and designed the study. SFL, AN, LG and EB developed and implemented study procedures. AS, LG and SFL analyzed the data. SFL and AN wrote the initial draft of the manuscript and all authors contributed to revisions. All authors reviewed and approved the report.

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Supplementary Material

Supplementary table 1: Cronbach's α estimation by PedsQL™ domain and group of age

To increase internal reliability Cronbach's alpha coefficient was recalculated by removing an individual item in the questionnaire, when the obtained "alpha if item deleted" achieved a value ≥0.7 and the comparation group had alpha ≥0.7.

Supplementary Table 1. Cronbach's α estimation by PedsQL™ domain and group of age

PedsQL™ domains	2-4 years		5-7 years		8-10 years	
	CLHIV	Children without HIV	CLHIV	Children without HIV	CLHIV	Children without HIV
	N=22	N=20	N=16	N=8	N=11	N=5
Physical	0.79	0.37	0.30	^	0.93	0.40
Emotional	0.54	0.27	**0.65****	**0.70**	**0.66**	**0.75**
Social	**0.71**	**0.92***	0.31	^	0.86	^
School	NA	NA	**0.67**	**0.99**	**0.69*****	**0.69**
Psychosocial	0.71	0.50	**0.69**	**0.89**	**0.88**	**0.67**
Total score	0.81	0.44	**0.72**	**0.85**	**0.95**	**0.79**

^alpha not calculated because all items in analysis sample were constant

* alpha if item score_g2_3_op3 (Getting teased by other children) deleted.

** alpha if item score_g3_2_op4 (Trouble sleeping) deleted

*** alpha if item score_g4_4_op4 (Missing school because of not feeling well) deleted

In bold the groups considered comparable

DISCUSSION

Discussion

The research in this thesis contributes to the understanding of gaps in HIV prevention and care in children living in a semirural district in southern Mozambique from birth to adolescence. It identifies weaknesses along the different steps of the pediatric HIV prevention and care cascade and proposes targeted interventions. The results are notably relevant as they address the key obstacles slowing progress towards the elimination of VT and the global 95/95/95/95 goals in children. Moreover, the findings are guiding health policy towards optimization of pediatric HIV prevention and care strategies in Manhiça and similar settings with high burden of pediatric HIV infections.

Gaps in prevention of vertical transmission of HIV

Prevention of VT of HIV is the cornerstone of ensuring children's wellbeing in areas with a high HIV prevalence in women of reproductive age. The case rate for new pediatric HIV infections depends not only on VT, but also on maternal HIV prevalence (79). As previously stated by Goga et al., eliminating VT may be difficult to achieve among countries with more than 10% background prevalence of HIV among pregnant women(79). WHO developed in 2017 the "Path to Elimination Initiative", which adapts VT targets in order to more accurately monitor the progress of HIV prevention programmes, in high HIV prevalence settings (35). Countries with high burden of maternal HIV are classified as "gold", if they have a case rate of acquiring HIV less than 250 per 100 000 live births; "silver", less than 500; and "bronze", less than 750 (35). Our community-based estimates during the 4 years after the implementation of B+ strategy showed a VT near 5% among HIV-exposed children under 4 years of age at the end of the breastfeeding period, which is significantly lower than the national average of 13% in 2020(3), and approaching the WHO target of <5% for breastfeeding populations(80). However, the case rate of new pediatric HIV infections of 1654 per 100 000 live births, similarly to previous estimates (81), exceeds the target of 50 new HIV infections per 100 000 live births required to eliminate VT (80). Therefore, the high HIV-prevalence in women who gave birth in the last 4 years in Manhiça renders it almost impossible to achieve the WHO case rate target of new HIV infections, even with an VT rate < 5%. Thus, in addition to decreasing HIV incidence among women in reproductive age, attention must be given to obstacles in maternal and infant care, that hinder progress towards lowering the VT rate.

One obstacle revealed by our findings was the delay in diagnosis and treatment of maternal HIV infection during the postpartum period. Mothers who were diagnosed with HIV and initiated ART after delivery had a

ten-fold higher risk of postpartum VT, compared with those initiating ART before delivery. As the research was conducted after the B+ strategy was implemented(82), the reasons for not starting ART primarily included lack of awareness of HIV status and newly acquired infections during the postpartum, although denial, or stock shortages may also be involved. New maternal infections during breastfeeding together with delays in the diagnosis and ART initiation, are associated with VT due to the high VL present at the onset of HIV infection(83). Accordingly, 2008-2011 data from southern Mozambique showed an HIV incidence of 3.2 new infections/100 women-years (95%CI: 2.30–4.46) in breastfeeding women during the postpartum period and a postpartum VT rate of 21% among their children at 18-months of age (84). In Mozambique, at the time of the study, repeated HIV testing was recommended every three months during pregnancy, but there were no specific approaches for repeated testing after delivery (85,86). Our results led to establishing specific retesting times in national guidelines not only during pregnancy, but also during the breastfeeding period, in order to facilitate early diagnosis and ART initiation in mothers and antiretroviral prophylaxis in their infants exposed to HIV. In addition to retesting, our findings support pre-exposure prophylaxis (PrEP) among women at risk of HIV acquisition in the postpartum period (87). Estimations in the context of a PrEP model in a demographic setting developed for South Africa, which has an HIV prevalence of 19% in population 15-49 years(3), projected a reduction in the total of new infant infections of 13%-41% for the 2020-2030 period (88).

Antiretroviral prophylaxis among HIV-exposed children is critical to prevent VT(89). In 2016, the WHO designed an algorithm to identify infants exposed to HIV at high risk of VT eligible for enhanced post-natal prophylaxis with daily AZT and NVP for the first 12 weeks of life (90). The algorithm heavily relies on maternal VL information and the research in this thesis highlighted that, the paucity of maternal VL information in many low resource settings hinders the implementation of the WHO risk assessment algorithm for HIV VT. Our results found that nearly 90% of mothers of infants diagnosed with HIV did not have a VL result at delivery, jeopardizing the early prescription of enhanced post-natal prophylaxis. Similarly, a study conducted in Zimbabwe in 2018-2019 showed that only 10% of the 1970 women living with HIV included, had a VL result available in medical records during the third trimester of pregnancy (91). In the absence of VL result, the WHO risk algorithm doesn't take into account poor ART adherence and considers low risk of VT among all mothers on ART for at least 4 weeks before delivery. Although adult ART regimes in many African countries, including Mozambique, progressively transitioned to Dolutegravir since 2019 with superior early virologic suppression (44,92), adherence remains critical. Poor maternal adherence during pregnancy and breastfeeding may cause high VL and HIV resistance, increasing VT risk subsequently (93–96). When applied in our cohort, the WHO algorithm identified 44% of the infected infants as high-risk for VT. When we added mothers' self-reported ART adherence to the WHO algorithm among mothers without VL result and with > 4 weeks on ART prior to delivery, the proportion of high-risk infants increased to 68%, suggesting that

suboptimal adherence is associated with high risk. Assessment of self-reported maternal ART adherence at delivery is an easy, low-cost intervention. It would guide clinicians in identifying infants at high risk of VT and tailoring interventions to, such as the type and duration of postnatal prophylaxis, when VL results are not available.

Balancing the benefits of breastfeeding with the risks of HIV infection during breastfeeding and ensuring HIV-free survival has been a primary goal in prevention of VT (97). After the expansion of the B+ strategy, WHO guidelines aligned recommendations on the duration of breastfeeding for mothers living with HIV with those for mothers without HIV infection, recommending breastfeeding for at least 12 months, but ideally up to 24 months or longer, while maintaining full adherence to ART (98). However, data from the Manhiça district showed that children exposed to HIV breastfed for significantly less time compared with children non-exposed to HIV. In those children exposed to HIV who breastfed even up to a median of 13 months, we did not detect an increased risk of VT in the postpartum period among our cohort of mothers on ART, most of whom (66%) had no VL result prior to the survey. In those 34% of women with a VL result, 76% were virally suppressed. Our results suggest that under conditions where infants exposed to HIV born to virally suppressed mothers on ART receive adequate postnatal prophylaxis, extending the duration of breastfeeding up to two years, as in HIV-unexposed children, according to WHO recommendations, may have benefits (99–101) that outweigh the risk of VT. Similarly, a prospective study conducted after B+ implementation, between 2013 and 2016, in Tanzania found no VT among virally suppressed mothers on ART who breastfed for a median of 12 months(102). According to the evidence, we propose to combine measures for the prevention of VT whose effectiveness is well known, such as extended perinatal prophylaxis for infants until the end of breastfeeding among children with high risk of VT (103–105), with maternal ART adherence support and breastfeeding counseling (106), as well as widespread access to VL testing among mothers during breastfeeding (107), in order to promote safe extended breastfeeding among HIV-exposed children.

Pediatric HIV care cascade, measuring progress in the fight against the HIV epidemic in children.

For those children who have already acquired the infection and are living with HIV, early ART initiation and retention in care along the continuum of care is crucial to achieve and maintain viral suppression and wellbeing. The sequential steps in the continuum of care constitute the pediatric HIV care cascade, which in turn serves as a tool for monitoring the overall 95-95-95 goal.

Our characterization of the pediatric HIV care cascade preceded the implementation of test and treat strategy in Manhiça and the target date of 2020 for the 90-90-90 goal. We found that by the end of 2015, a total of 78% of ART eligible children-initiated ART, and that only 63% of children were retained in care at 12 months after ART initiation. LTFU occurred mainly among children less than 1 year old during the first six months after ART initiation. Similarly, studies in sub-Saharan Africa from 2005-2011 also found higher rates of LTFU among younger children(108). In addition, we found than a quarter of LTFU children re -engaged in care (RIC) in a median time of 4.6 months after LTFU. Our RIC rate in the first few months suggests that a portion of patients LTFU were aware of the importance of HIV care and returned at the earliest opportunity. Identifying strategies and entry points in health system to RIC patients into care is critical. Additionally, the LTFU-RIC cycles shown in our results highlighted the unreliability of existing registries, unsustainability of using specific study questionnaires and difficulties obtaining quality data amenable to be analyzed to estimate retention in HIV care from a broader perspective.

Mobility and migration for work or other activities poses a challenge to health care continuity in general, and HIV retention in care in particular. Southern Mozambique harbors a long history of migration, mainly to South Africa(109). Globally, higher risk for HIV acquisition has been shown among migrant adults (110,111), as well as increased rates of LTFU (112). However, little is known about the continuum of care of their children living with HIV. We thus explored how caregiver's mobility within or outside the country impacted retention in care among their children living with HIV. We found that caregivers migrating outside Manhiça district adopted strategies to ensure continuity of their children's treatment during the mobility episode, such as establishing alternative caregivers who accompanied the child to the HIV clinic during their absence, or transporting ART for children traveling to the destination with the parent. Our results identified a structural gap for children of migrant populations living with HIV, which was covered through informal social support from friends and family. However, children staying at home, may move from one alternative caregiver to another, making continuity of care difficult (113). On the other hand, none of the parents who brought their children to the destination reported accessing ART at a destination clinic. They transported pediatric antiretroviral drugs which increases the risk of drug loss and may affect their stability and efficacy, as in the case of Lopinavir/ritonavir oral solution, which was part of the first line treatment at the time of the study (114,115). Adapting differentiated service delivery models to the specificities of mobile populations, including expanded dispensing intervals of ART and trans-border mobile strategies for ART delivery, could help facilitate clinical follow-up of children and caregivers and ensure their retention in care, while reducing the burden of informal social support they are forced to seek.

Mortality and health-related quality of life; the neglected indicators in the HIV care cascade

Most cascade indicators, such as those included in the WHO global top 10 indicators for monitoring the HIV response, are defined in cross-sectional terms and they consider individuals who are HIV infected and alive at a specific time (24,116). However, death is the most important clinical outcome among children living with HIV and can occur along the entire HIV care continuum. In 2018, we found a cumulative incidence of death among HIV exposed children in the first 54 months of life of 44.9/1000 live births, and children living with HIV had a seven-fold increased risk of dying than children without HIV infection. Overall under-five mortality more than halved in Manhiça in the last 10 years, from 122.5/1000 live births in 2009 to 33.4/1000 live births 2019(17). However, our data showed significant disparities among children living with HIV and HIV-unexposed children. Major causes of mortality among children living with HIV in low- and middle-income countries are AIDS-defining illnesses, such as pneumonia, tuberculosis, diarrhea and severe malnutrition (117,118). In our community-based survey, we found that the main causes of death after the neonatal period were AIDS-defining illnesses, according to verbal autopsy data (119).To reduce under-five mortality among children living with HIV in Manhiça, in addition to facilitating early diagnosis and treatment of HIV, is necessary to better prevent and treat the specific causes of death among children living with HIV.

Finally, although increased importance is being given to HRQoL among PLHIV, there is little to no data among children living with HIV in sub-Saharan Africa. We found a good overall parent-reported HRQoL among children 2-10 years old on ART at the Manhiça District Hospital. At the same time, CLHIV between 2 and 4 years of age had a poorer HRQoL score in the social domain compared to children without HIV infection. In addition, we found that 10% of the preschooler and preadolescent CLHIV presented total HRQoL scored below 80 points, but any of the children without HIV infection did it. However, the HIV-positive group was skewed towards adherent children and the comparison group without HIV infection was small. This was a first descriptive study and further studies are needed to dissect quality of life issues in children living with HIV compared to the general pediatric population, and to eventually design strategies to support and enhance HRQoL.

Future recommendations and research priorities

This thesis provides a comprehensive evaluation of the pediatric HIV prevention and care cascade in Manhiça district, including Global AIDS strategy 95-95-95 targets, "Start Free, Stay Free, AIDS Free strategy" indicators and transversal clinical outcomes along all steps of the cascade, such as mortality and HRQoL. The results have implications for policy, clinical practice and public health, of which some have already informed Mozambican national recommendations.

Our results identified the following priority areas for adapting policies and future research in order to 1) reduce VT and 2) improve retention and clinical outcomes among children living HIV in our setting and other similar context:

1) Priority areas for policy and future research in prevention of vertical transmission:

- Prevention of HIV infection among women of reproductive age, particularly during breastfeeding, and ensuring expansion of PrEP in this population.
- Early diagnosis and treatment of mothers living with HIV during the postpartum, through regular testing and re-testing throughout the entire breastfeeding period.
- Use of alternatives to maternal VL, such as maternal self-reported adherence to ART, to guide recommendations on postnatal prevention of VT until adequate maternal VL monitoring coverage is achieved.
- Promotion of breastfeeding up to two years among children who are receiving appropriate postnatal prophylaxis and whose mothers are well controlled and fully adherent on ART.

2) Priority areas for policy and future research in pediatric HIV care:

- Facilitation of retention and re-engagement in care through integrated approaches.
- Expansion of differentiated care services and facilitating ART delivery in mobile and migrant pediatric populations in the district.
- Identification and prevention of specific causes of deaths among children living with HIV.
- Determination of factors associated with HRQoL among CLHIV and design of strategies to support these children in leading fulfilled lives.

The country has made significant progress in these directions. In 2018, Mozambique piloted a Pre-exposure prophylaxis (PrEP) program in sero-discordant couples in Zambezia province(120) and the country will expand PrEP nationally in 2022 to include pregnant and breastfeeding women (121). In addition, after our results showed the importance of early diagnosis and treatment among newly infected breastfeeding women, specific timelines for re-testing every three months during the first 9 months of breastfeeding were established (122).

On other hand, Mozambique is transitioning towards more integrated health services and differentiated care models for adults but also children. The provision of one-stop maternal and newborn health services (integration of the maternal and infant HIV care in the prenatal consultation, postpartum consultation and consultation of the child at risk, in the same clinical consultation and by the same health provider) has been implemented in Mozambique since 2010 and integrated family care (HIV care of the members of the family on the same day, in the same clinical consultation and by the same provider) is one of the main differentiated care approaches (122). Other differentiated models, which are being prioritized in the country, include multimonthly ART refills, which was expanded in 2019, reducing the eligibility critera of 12 months stably on ART to 3 months stably on ART (76). However, some specific groups in rural settings, such as the Manhiça district still lack a specific approach tailored to their needs. This is the case of emigrant populations in Manhiça and countrywide, which in 2019 represent up to 1 million of people of the country (109).

In addition, the country recently published the national Guideline for Management of the Patient with Advanced HIV Disease in 2022(123). These guidelines include recommendation for screening, prophylaxis and treatment for opportunistic infections for adults and children living with HIV, that could reduce mortality among children living with HIV.

Finally, a finding common to most of the studies included in our research was the inherent limitations of existing HIV-related indicators. Therefore, a last general recommendation would be related to the necessity of improving data quality. Strategies such as the establishment of a unique health identifier and the transition from paper charts to electronic systems(124), could facilitate the collection and management of national health system data and help report indicators more accurately and with subregional granularity.

CONCLUSIONS

Conclusions

1. As long as the HIV prevalence in women of child bearing age is over 10%, the case rate of new HIV infections per 100 000 live births in the Manhiça district cannot fall below WHO targets. The focus must thus be on reducing the VT rate, in parallel to efforts to reduce incidence of HIV in women of reproductive age.

2. Newly acquired infections of mothers and delayed initiation of ART after delivery were risk factors for postpartum VT. This underscores the importance of increasing the frequency of postpartum testing, and supports the use of PrEP in breastfeeding women at high risk for HIV infection.

3. Breastfeeding duration was not associated with an increased risk of VT in the postpartum period in women on ART, but HIV-exposed children in the Manhiça district breastfed for significantly less time compared with non-exposed children. Under adequate VT prevention conditions, extending the duration of breastfeeding up to two years, as in HIV-unexposed children, following the WHO recommendations, may have benefits that outweigh the risk of VT.

4. The paucity of maternal VL information for VT risk stratification hinders the implementation of the WHO risk assessment algorithm for VT of HIV. Including mothers' self-reported ART adherence when maternal VL results are unavailable, improves the identification of infants eligible for enhanced post-natal prophylaxis by nearly 50%.

5. In 2015, progress in ensuring that 90% of children diagnosed with HIV were on ART was far below target in Manhiça and continues to be low on a national level in 2020. Additionally, viral suppression estimates are likely to be even lower when considering poor retention in care and LTFU-RIC cicles. A subnational granular view and the incorporation of a time dynamic perspective of the second and third 90 targets is necessary to tailor appropriate support interventions.

6. Migrant caregivers living with HIV who are traveling with their children have developed solutions to minimize the impact of mobility on the child's HIV care through informal social support strategies. Health systems need to promote structural solutions such as adapting differentiated service delivery models and dispensing intervals to reduce barriers to care in this vulnerable population.

7. Children living with HIV had a seven-fold increased risk of dying compared to HIV-exposed children without HIV infection. Prophylaxis and monitoring tools are available to prevent a large proportion of these deaths. Implementation research is necessary to identify appropriate strategies to ensure delivery of prevention and prompt treatment to these children.

8. Although the HRQoL score of children living with HIV was considered good, poor minimum values were found among a subset of children living with HIV. Future studies are need to understand the determinants of HRQoL in specific pediatric populations living in settings of high HIV burden, and the impact of HIV on dimensions of HRQoL.

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There still are 1.7 million children under 15 years of age living with HIV worldwide and 150.000 new infections every year. There are particularly wide pediatric HIV inequalities between countries, and Mozambique is among the 3 countries in the world with the highest proportion of children acquiring HIV in 2020. “Ending inequalities and getting on track to end AIDS by 2030” is the new Global AIDS Strategy.

In line with the global strategy, the main objective of the research presented in this thesis is to identify the weakest steps in the pediatric HIV prevention and care cascade in the Manhiça district; a rural area of southern Mozambique with high HIV prevalence. Results will inform public health interventions to address the specific obstacles and improve the delivery of comprehensive HIV prevention and care services for the wellbeing of children born to women living with HIV, at a local level and in similar contexts.