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High prevalence of low-level viremia among infants initiated on antiretroviral drugs following mother-to-child transmission of HIV

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Abstract

Background With the current elimination of mother to child transmission (EMTCT) of HIV, the number of HIV-positive newborns has greatly reduced. Some countries have successfully eliminated HIV infections among newborn babies.

Methods This study was nested within the DRIBS (Drug Resistance testing among Infants at Baseline Study), which enrolled 100 infants at the time of treatment initiation between 2017 and 2023. Infants were followed for two years. Viral load (VL) was measured every six months and after completion of the three sessions of intensified adherence counseling (IAC). IAC and HIV drug resistance testing were performed for VL greater than 1000 copies/ml.

Results The median age at diagnosis was 79 (IQR, 57.75;140.75) days, with 4% of patients diagnosed within 6 weeks after delivery. The median age at the initiation of therapy was 110.5 (IQR, 87.0–162.0) days. The median baseline %CD4 was 26 (IQR, 18.75;32), with 9% of the babies being severely immunosuppressed (%CD4 < 15%). The median baseline log viral load was 4.44 (IQR, 3.19–5.58). At six months, 30% and 60% of the patients had a VL < 50 and < 1000 copies/ml, respectively. At 12 months, 36% and 69% of patients had a VL < 50 and < 1000 copies/ml, respectively. At 24 months, 63% and 83% had VL < 50 and < 1000 copies/ml, respectively. Post-IAC VL revealed that 35% of the children had low-level viremia (LLV) compared to mothers 11.5%. Kaplan-Meyer survival estimates showed that while it took 72 weeks for 50% of the mothers and infants to attain a VL less than 1000 copies/ml, it took 96 weeks for the infants to attain a VL < 50 copies/ml.

Conclusion A Viral load < 1000 copies/ml is achieved much more slowly in pediatric patients, implying that it might take longer for babies to achieve the third 95 (95% virally suppressed) of the UNAIDS targets. Furthermore, the greater prevalence of LLV in pediatric patients than in mothers has important implications for the response to therapy.

Keywords Mother-to-child transmission of HIV-1, Antiretroviral therapy, Viral load, Viral suppression, Low-level viremia, Intensified adherence counseling

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Introduction

To end the AIDS epidemic as a public health threat by 2030, special emphasis has been put on pregnant and breastfeeding women, children, adolescents and young women [1, 2]. In the pediatric arena, over the years, we have moved from prevention of mother-to-child transmission of human immunodeficiency virus (HIV) [3–9] to elimination of mother-to-child transmission (EMTCT) of HIV and the results are undeniable [10–14]. Globally, there is significant progress toward EMTCT, with the number of new child infections resulting from vertical transmission dramatically reducing from over 400,000 in 2000 to 130,000 in 2022 [15, 16]. Currently, the rate of mother-to-child transmission ranges from 2% in Botswana to 28% in the Democratic Republic of the Congo [15]. The variation reflects broader gaps in improving HIV treatment coverage among pregnant women, early diagnosis during pregnancy and starting treatment early, supporting women to continue on treatment and achieve viral suppression during pregnancy, breastfeeding and throughout their lives, and reducing HIV incidence among pregnant and breastfeeding women. Although great achievements have been attained in elimination of mother to child transmission of HIV, there are still challenges with HIV positive babies: only 63% of the babies have been diagnosed, 57% of these are on ART, and only 47% have attained viral suppression [15].

In 2015, the UNAIDS started the Start Free Stay Free and AIDS Free initiative [17]. Starting free ensures that babies do not acquire HIV during pregnancy, birth or breastfeeding to reduce the number of new annual pediatric infections to less than 40 000 2018 and 20 000 by 2020 and to attain and sustain 95% of pregnant women living with HIV with lifelong HIV treatment by 2018 [17]. The stay-free component is geared at preventing adolescent girls and young women from acquiring HIV as they grow up, while the AIDS-free component provides HIV diagnosis, treatment, care and support to children and adolescents living with HIV. Despite these initiatives and drives, the pace toward reaching the UNAIDS global goals of ending AIDS by 2030 has slowed, with 130,000 new HIV infections in 2022, which is six times greater than the 20,000 new infections set target for 2020 [15]. This clearly indicates that more interventions and research are still needed to address key gaps. In order to address these gaps, this study enrolled newly diagnosed HIV positive babies.

Methods

Study population

Between August 2017and October 2023, following a positive DNA PCR for early infant diagnosis (EID) test, we enrolled and followed 100 HIV positive babies together with their HIV positive mothers test into the DRIBS study at the Joint Clinical Research Center in Kampala, Uganda. Briefly, the Drug Resistance for Infants at Baseline Study (DRIBS) was a five-year longitudinal study under the EMTCT program with the major aim of assessing the impact of low-frequency HIV drug-resistant polymorphisms on the response to therapy in HIV seropositive infants born to HIV-positive mothers in Uganda. After obtaining informed consent from the mothers, babies with the following criteria were enrolled: babies aged six weeks to 12 months, ART naïve or have been on ART for less than 2 months and not involved in any other study. Babies who were enrolled into the study while on ART were those with a high index of suspicion of being HIV positive at the testing health facilities such that they were initiated on ART even before HIV DNA PCR results were available; therefore, in the study, some of the babies were enrolled while already receiving some treatment. Those who were not already receiving treatment were initiated on a LPV/ritonavir-containing regimen according to the National Treatment Guidelines at the time of enrollment in the study. Mothers who consented for their children were also enrolled.

For this sub-study, we focused on the rates of viral suppression and prevalence of LLV in the mother-infant pairs right from the time of enrollment into the study because various studies have shown that viral suppression rates in pediatrics are much lower than in adults. On the other hand, the prevalence of LLV and effect of intensified adherence counseling on viral suppression among pediatrics is not well documented. Since the mothers were already on ART for varying durations, the viral load at enrollment into the study was considered baseline; some mothers were virally suppressed. Informed consent was provided prior to study enrollment. Ethical approval and approval from the National Council of Science and Technology were obtained (JC3617 and HS 2383, respectively).

Patient recruitment and follow-up

Babies who met the study inclusion criteria (0–12 months, Anti retroviral therapy (ART) naïve or been on ART for less than 2 months, not involved in another study) were enrolled in the study after providing informed consent from the mothers. Infant variables such as age, sex, weight, mid-upper arm circumference (MUAC), and head circumference, age at diagnosis, age at initiation of ART, baseline CD4 cell count, baseline viral load, and Nevirapine exposure were collected at study enrollment and at every follow-up visit. In addition, the mothers' demographic information such as age, level of education, area of residence was also obtained. Mother-infant pairs were followed-up for two years and were reviewed at the following study visits after enrollment:

weeks 8 and 12 and every twelve weeks thereafter until week 96. The following interventions were performed: ART initiation at the time of enrollment into the study, then during the course of follow-up: self-reported adherence, viral load monitoring, intensified adherence counseling, and HIV drug resistance testing were performed as per the National Treatment Guidelines. At each visit, babies were assessed by a pediatrician. Self-reported adherence at each visit was recorded and this was rated as good (> 95%) or bad (< 95%). The primary end-point for the study was viral suppression; while the secondary end point was adherence.

Laboratory tests

At the time of enrollment into the study, a baseline CD4 cell count was measured. Viral load assays for mother-infant pairs were performed at the time of enrollment into the study and every six months. When a viral load greater than 1000 copies/ml was obtained for either the mother, baby or both, mothers underwent three sessions of intensified adherence counseling (a session each month for three months) followed by a repeat viral load, this is in accordance with the National treatment guidelines. If after the three sessions of intensified adherence counselling (IAC) the viral load was still greater than 1000 copies/ml, the patients underwent an HIV drug resistance test.

Table 1 Patient demographics

Variable	Median	IQR
Age in days		
Age at diagnosis	79	(57.75;140.75)
Age at initiation of ART	110.5	(87; 162)
Weight in kg	6.1	(3.9;9.5)
CD4 count (%)	26	(18.75; 32)
Baseline log viral load	4.44	(3.19;5.58)
Mother's age (years)	26	(19;35)
Variable	**Frequency(n)**	**Percent(%)**
Sex of the child		
Male	40	40
Female	60	60
Mother's education level		
No formal/primary education	60	60
Secondary/tertiary education	40	40
Mother's residence		
Urban	55	55
Rural	45	45
Nutrition assessment		
Red (Severe malnutrition)	3	3
Yellow (Moderate malnutrition)	9	9
Green (No malnutrition)	78	78
Child birth order		
1	30	30
2 to 4	61	61
≥ 5	9	9
Chronic conditions in mother		
Yes	84	84
No	16	16
Nevirapine exposure		
Yes	64	64
No	36	36

In-depth interviews

For the mothers whose children had viral loads > 1000 copies underwent IAC, in addition, a subset of 17 mothers underwent in-depth interviews in order to clearly map out the factors leading to delay in diagnosis, initiation of ART, and viral non-suppression. Interviews were recorded and transcribed.

Data analysis

Infant variables of interest including: age, sex, age at diagnosis, weight, head circumference, mid upper arm circumference, ART regimen, viral load, and CD4 cell count were extracted from the database. For the mother the following were extracted: age, occupation, area of residence, parity, regimen, and viral load. Coded data with patient identification numbers were used. The primary endpoint for this study was viral suppression. Viral response through 96 weeks was defined by two methods: (1) clinical endpoints (virologic success and failure); (2) time to viral suppression, i.e., any viral load (VL: copies/mL) < 1000 and < 50, using the Kaplan Meyer time-to-event methods. Participants with confirmed baseline VL < 1000 copies/mL were excluded from the time-to-suppression analyses.

Results

Participants and baseline characteristics

Between August 2017 and October 2023, 100 infants (60% female) were enrolled and followed up for two years in the DRIBS study. 12% of the infants had moderate to severe malnutrition at the time of enrollment and 64% had a history of Nevirapine exposure. There were 3 (3%) deaths in the study, one AIDS related and two accident related. The median age at diagnosis was 79 (IQR, 57.75;140.75) days, with only 4% of patients diagnosed within 6 weeks after delivery, the majority (67%) were diagnosed between 6 and 12 weeks (Table 1; Fig. 1). The median age at the initiation of ART was 110.5 (IQR, 87.0–162.0) days (Table 1; Fig. 1). It is important to note that some of the babies were initiated on ART prior to HIV diagnosis; these were babies who, at the time of birth, had a very high index of suspicion of being HIV positive. The median baseline %CD4 was 26 (IQR, 18.75;32), with 9% of the babies being severely immunosuppressed (CD4 < 15%) and 36% exhibiting moderate immunosuppression (CD4 15–25%) (Table 1). The median baseline log viral load was 4.44 (IQR, 3.19–5.58). At the time of

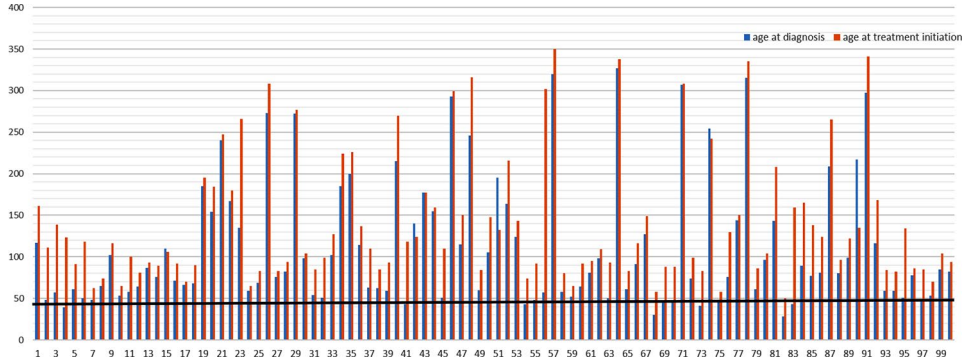

Fig. 1 Diagnosis and treatment initiation. DNA PCR was performed for early infant diagnosis at the earliest time the baby was presented to a health facility (blue). A positive HIV DNA test was then followed by initiation of ART according to the national treatment guidelines (red)

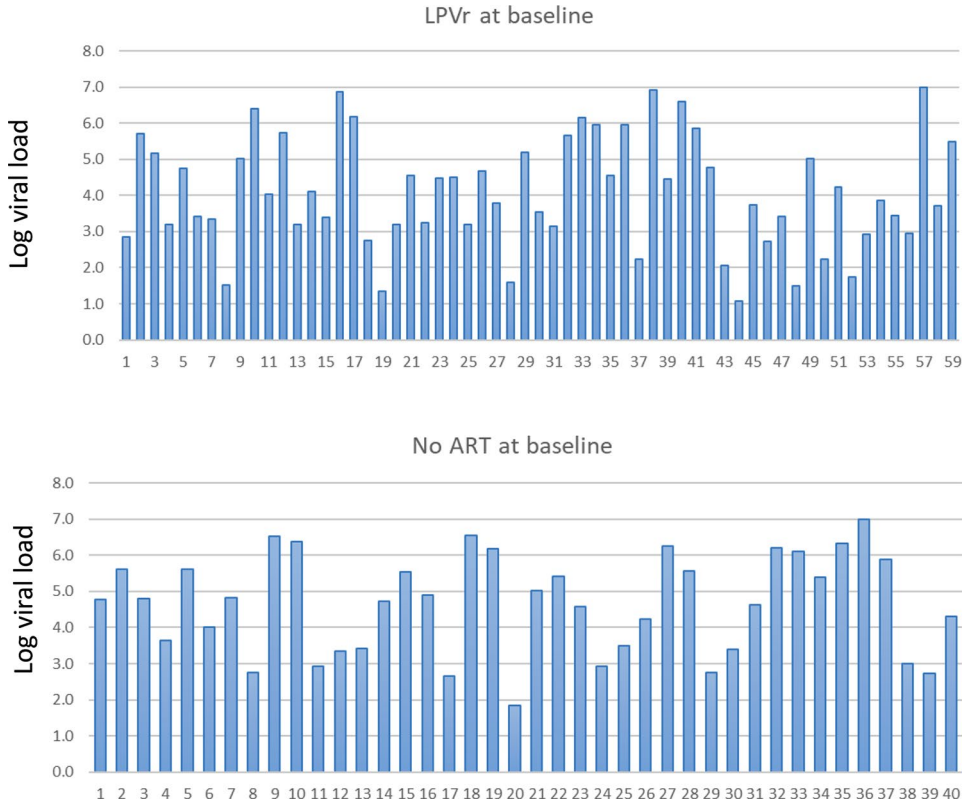

Fig. 2 Baseline viral load. A comparison of the viral load between babies treated with LPV (Figure 3a) and treatment-naïve babies (Figure 3b) is presented as log values

enrollment into the study, 10% of the babies had viral loads less than 1000 copies/ml (50–999 copies/ml). Baseline viral loads did not differ among those who were enrolled while on ART and the naïve ones (Fig. 2). Median age of the mothers was 26 (IQR,19;35) years with 40% of mothers having attained at least secondary level education.

Viral suppression over time

Although 10% of the babies had a viral load of less than 1000 copies/ml at the time of enrollment into the study, at six months, only 30% and 60% of babies had viral loads < 50 and < 1000 copies/ml, respectively. At 12 months, 36% and 69% of the babies had viral loads < 50 and < 1000 copies/ml, respectively. At month 18, 42% and 66% had viral loads < 50 and < 1000 copies/ml, respectively (Fig. 3), and at month 24, 63% and 83% had viral loads < 50 and < 1000 copies/ml, respectively. When compared to mothers, six months into the study, 62% and 73% of the mothers had viral loads < 50 and < 1000 copies/ml, respectively. Twenty-four months into the study, 71% and

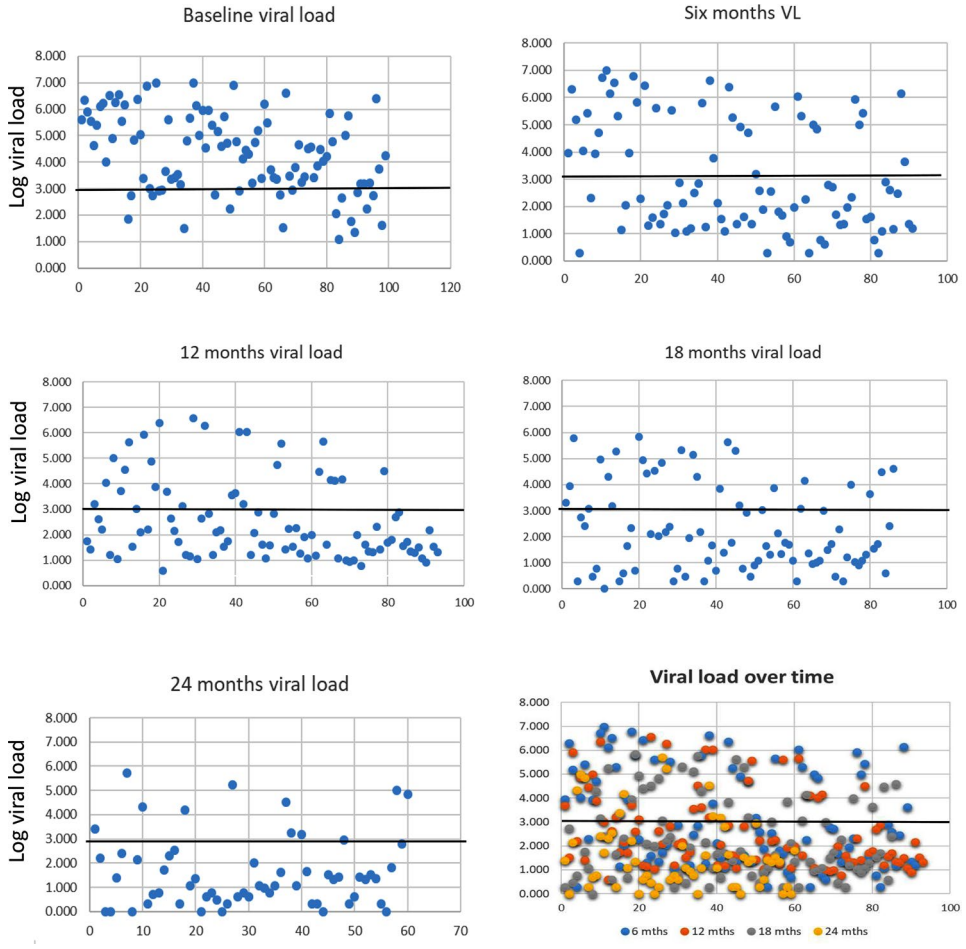

Fig. 3 Child viral load over time. Viral loads were measured every six months for the duration of the study to assess the response to therapy

82% of the mothers had viral loads < 50 and < 1000 copies/ml, respectively (Fig. 4).

Prevalence of low-level viremia

Next, we analyzed the data for the proportions of babies with LLV (50–999 copies/ml). At months 6, 12, 18 and 24 the proportions of LLV were 30%, 33%, 24% and 20%, respectively (Fig. 3). On the other hand, at six months, 11% of the mothers had LLV and at the end of the study (Fig. 4).

Time to viral suppression analysis

Kaplan–Meyer (K-M) survival estimates revealed that it took 72 weeks for 50% of the mothers and 50% of the infants to attain a viral load less than 1000 copies/ml (Fig. 5a). Furthermore, while it took 96 weeks for 50% of the children to attain a viral load < 50 copies/ml, it took 72 weeks for 50% of the mothers to attain the same viral load. (Fig. 5b).

Since some individuals did not reach viral suppression during the observation period (shown in the viral load trajectories of mother-baby pairs which we have added to supplemental information (supplementary Fig. S1), we were unable to do a correlation plot which requires numeric values of time to suppression for all mother-infant pairs.

Instead, we analyzed mother suppression status in discrete time to event analysis of viral suppression in babies in complementary log-log regression (*cloglog)* models, repeated for suppression below 1000 copies per ml and suppression below 50 copies per ml. In each case, we observe a strong association between mother suppression status and baby suppression status ($p < 0.001$, Table 2). Viral load trends in the mother-infant pairs were closely correlated (Supplementary Fig. S1).

Effect of regimen on viral suppression

During the course of the study, Dolutegravir (DTG) was approved for use in pediatric patients. Children on the study were transitioned from a LPV/ritonavir (LPV/r) to a DTG containing regimen. When we compared viral suppression by regimen, we found that a DTG-based regimen attained significantly better viral suppression when

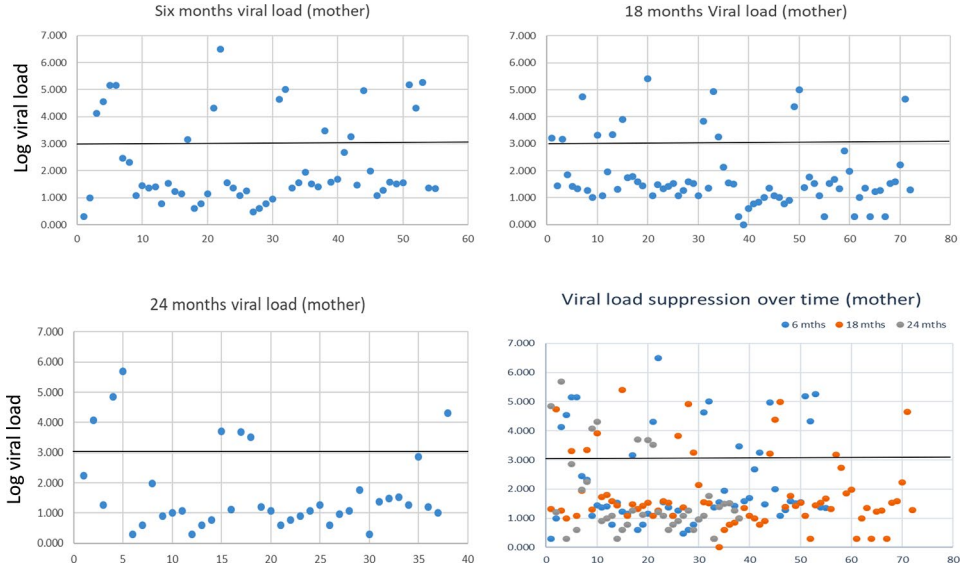

Fig. 4 Maternal viral load over time. Mothers' viral loads were measured every 6 months during the study so that a mother–infant comparison could be made at each time point

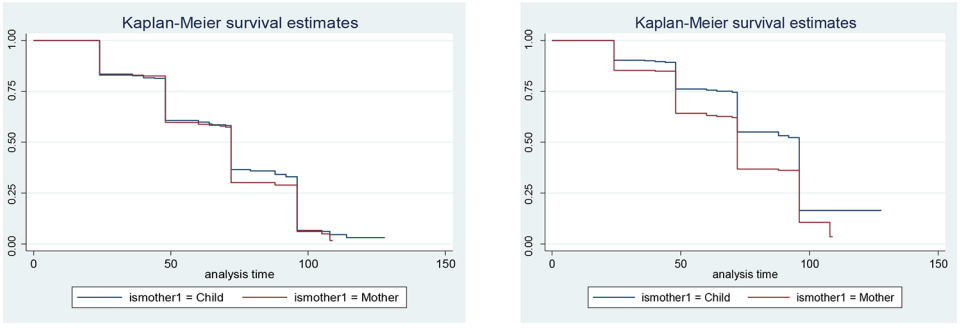

Fig. 5 Time to viral suppression. K–M analysis for time to attain < 1000 copies/ml for both the mothers and the children was performed (6a). Time to attain < 50 copies/ml for both mothers and children (6b)

Table 2 Time to viral suppression analysis

Time to viral suppression 1000copies/ml, in babies	Hazard ratio	Std Err	P>z	95%αlwr	95%αupr
Week 24 vs week 0	0.528	0.122	0.006	0.336	0.832
Week 48 vs week 0	0.503	0.152	0.023	0.279	0.909
Week 72 vs week 0	0.122	0.088	0.003	0.030	0.500
Week 96 vs week 0	0.889	0.409	0.798	0.360	2.192
Mothers suppressed below 1000cps vs mother not sup	2.513	0.688	0.001	1.469	4.298

Time to viral suppression 1000copies/ml, in babies	Hazard ratio	Std Err	P>z	95%αlwr	95%αupr
Week 24 vs week 0	0,116	0.040	0.000	0.056	0.230
Week 48 vs week 0	0.503	0.152	0.000	0.109	0.358
Week 72 vs week 0	0.122	0.088	0.000	0.126	0.443
Week 96 vs week 0	0.889	0.409	0.026	0.231	0.910
Mothers suppressed below 1000cps vs mother not sup	2.513	0.688	0.000	1.665	4.022

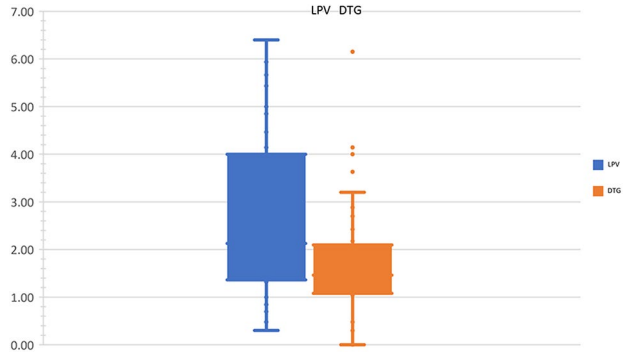

Fig. 6 Viral suppression by regimen. Comparison of viral suppression between the LPV-containing regimen and the dolutegravir-containing regimen. Analysis was performed on patients who transitioned from LPV to dolutegravir

compared to a LPV/ritonavir-based regimen (Fig. 6) ($p = < 0.00005$).

Effect of intensified adherence counseling on viral suppression

Post-intensified adherence counseling (IAC) viral load revealed that of the 58% of the babies who achieved viral loads < 1000 copies/ml, and only 23% had < 50 copies/ml. Notably, there was a high proportion of patients with LLV (35%) following IAC (Fig. 7a). On the other hand, 42% of the mothers had < 50 copies/ml with only 11.5% LLV (Fig. 7b).

Effect of socioeconomic factors on treatment outcome

In-depth interviews from a subset of mothers revealed that most of the mothers on the study had various socioeconomic issues. Some of the mothers were from discordant relationships, others had stigma issues and could not disclose their sero-status and that of the baby to family members, some did not have permanent places of residence and had to move from place to place to live with family members and friends; while others were involved in high risk sexual behavior.

Discussion

To attain an AIDS-free generation of children who acquire HIV from their mothers, early diagnosis within the first six weeks of delivery is paramount; this is followed by enrollment in care and initiation of treatment in a timely manner before immunosuppression kicks in. Studies have shown that early diagnosis followed by early initiation on ART is associated with a significant reduction HIV-related morbidity and mortality as well as a reduction in the size of the seeded HIV reservoir [18]. Finally, complete viral suppression is mandatory, and this calls for total adherence to the prescribed regimen. For any ART program to be successful there has to be complete viral suppression. In this cohort, there was a significant delay in diagnosis, and only 4% of the babies were diagnosed within 6 weeks of delivery. The major likely cause of this delay is that the majority of mothers give birth in neighborhood clinics where mandatory national guidelines for EMTCT are not followed hence these babies are not initiated on ART in a timely manner. In these clinics, the mothers do not disclose their HIV status. Mothers reported to larger health facilities much later when referred. In addition, in-depth interviews revealed that most of these mothers were either from discordant relationships, involved in high-risk sexual behavior, did not have a stable income so they moved from place to place, and some had stigma issues hence infant diagnosis and initiation on ART was delayed. Although there was a delay in diagnosis, hence initiation of ART, mortality in this cohort over a two-year follow-up was 3%, one child died of pneumonia while two were accident related deaths. At study enrollment, 9% of the babies we followed were severely immunosuppressed, 12% of the babies had moderate malnutrition, most of these, diagnosis was much later, hence a delay in treatment initiation. After initiation of ART and nutritional rehabilitation, these babies progressed normally. A study by Alabel showed that the mortality rate was 3.2 per 100 child

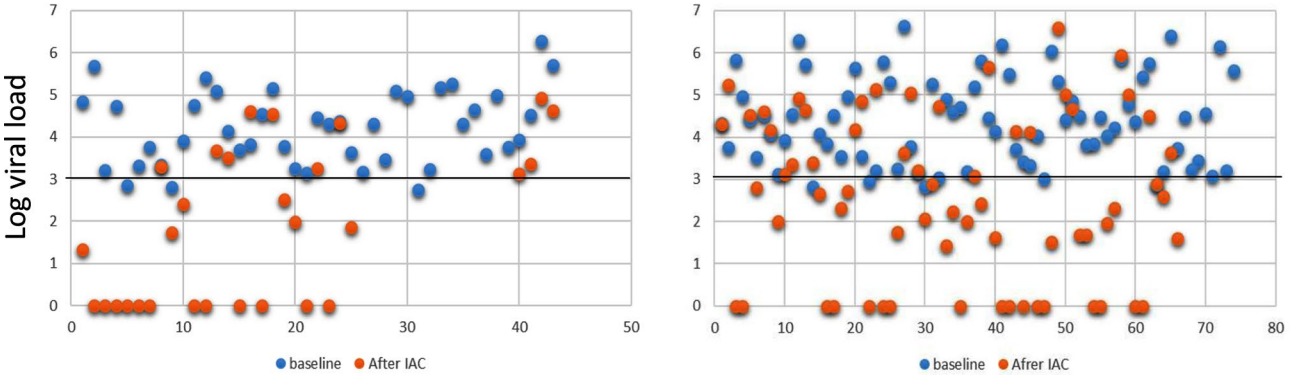

Fig. 7 Viral loads before and after intensified adherence counseling. Viral load was done before IAC then a repeat viral load was done after completion of the three recommended sessions of IAC

months and deaths were associated with opportunistic infections, anemia and severe immuno-suppression [19].

Although some babies were enrolled in the study after ART initiation, the viral loads did not significantly differ between the naïve group and the treatment group because they were enrolled within two months of treatment initiation.

Viral nonsuppression over time in pediatric patients is a major challenge that has been widely documented [20–27]. 60% of the babies had decreased to less than 1000 copies/ml by six months and 66% by twelve months in the study. Moyo et al. reported that the rate of viral suppression at six months was 54%. Nabukeera et al. reported a much lower rate of 23% after six months of treatment, which was associated with the WHO clinical stage as well as with ART-induced side effects [21]. Ashburn et al. showed that viral suppression and undetectable viral load at 6 months were 78.4% and 73.9%, respectively, improving to 90.2% and 87.3%, respectively, at 12 months [28]. They showed that the use of a family-based health care system improved adherence and retention in care when compared to having pediatric and adult clinics separated. Notably, with the family-centered care model, Eswatini is the only African country that is close to attaining 95-95-95 among children. It will be interesting to implement a family-centered HIV clinical model in different countries and determine whether this approach would improve adherence and ultimately improve viral suppression as we strive to reach 95-95-95 among pediatric patients. A study that examined the levels of diagnosis, initiation of ART and viral suppression in seven African countries showed that among all children living with HIV, 39.0% had not been previously diagnosed with HIV [29]. Among previously diagnosed children living with HIV, 48.3% experienced viral suppression within 6 months. This study clearly indicates that within many low- to middle-income countries, a number of children remain undiagnosed, a number of children are not receiving treatment, and among those accessing treatment, viral suppression is still a major challenge [29]. With such challenges, an AIDS-free initiative by UNAIDS among HIV-positive children still has a long way to go. In this study, by 96 weeks, 83% of the babies had attained a viral load < 1000 copies/ml, and 63% of the babies had viral loads < 50 copies/ml. Teasdale et al. showed that rates of complete viral suppression were much lower in children younger than 12 months than in older children [30]. This is because adherence of the baby is purely dependent on the caregiver, in this case, the mother, who is also on ART. In this study we show that poor viral suppression in the babies was also reflected in the mothers. It took much longer for the children to attain viral loads less than 50 copies/ml. The poor viral suppression within the mother-infant pairs still ties in with the socio-economic factors that affect these mothers and these as already mentioned include: non-disclosure associated with stigma, being in a discordant relationship, lack of permanent place to live. All these result in poor adherence hence a delay in attaining of complete viral suppression. With the global roll out of dolutegravir (DTG), babies in the study were transitioned from a LPV regimen to a DTG regimen. When the response to therapy was compared between the two regimens, we found that there was significantly better viral suppression with DTG ($p < 0.00005$) This could be attributed to DTG having better pill acceptance than LPV. The transition from LPV to DTG was associated with a steep increase in viral suppression (73% at month 18 vs. 83% at month 24). The ODYSSEY trial that followed children aged 1 to 14 years demonstrated that DTG was superior to LPV, as evidenced by the lower viral nonsuppression rate of 31% compared to 48% in the LPV arm over a period of 96 weeks [31]. Turkova et al. showed that viral suppression in children on a DTG-based regimen (87%) was better than that of the standard of care LPV-based regimen (79%) [32, 33]. The poor viral suppression seen with LPV has been attributed to the drug formulation, which presented a palatable challenge to the babies, this was improved with the transition to DTG.

Among the babies whose viremia was controlled to below 1000 copies/ml, a large proportion had viral loads between 50 and 999 copies/ml, indicating high levels of LLV among the children. LLV has been associated with HIV drug resistance.

For the third 95 to be attained, adherence is key. Approximately 80% of the mothers self-reported good adherence (> 95%). However, drug levels for the mother-infant pairs was not assessed. Intensified adherence counseling recommended by the World Health Organization (WHO) has been a major area of contention. In most of the adult studies, viral suppression after IAC was greater than 70% [34–37]; however, viral suppression post IAC in pediatric studies was lower [20, 22, 38]. In this study, we found that viral non-suppression in the child closely corresponded to that in the mother. Although IAC was performed, in-depth interviews revealed that there were a number of social-economic factors associated with poor adherence and viral non-suppression in the mother–infant pairs. In-depth interviews revealed that the challenges with these mothers ranged from not being in stable relationships, having a discordant partner, unemployment, a lack of permanent place to stay, and nondisclosure to family members, among others. These factors precluded them from receiving regular refills, and even when the medicines were available, they could not take them regularly or give the children medicine because of stigma. Child's birth order, mother's level of education and area of residence did not affect response to therapy.

In summary, in order to improve early diagnosis, early initiation on ART, and ensuring that babies take the prescribed medicines in a timely manner in order to improve viral suppression rate and also shorten time to viral suppression, there need to advocate for the family-based health care system discussed above (Ashburn at al). This model greatly improved adherence and retention in care when compared to having pediatric and adult clinics separated. Using this system, Eswatini is close to attaining 95-95-95. Implementing such a system will greatly improve age at diagnosis and treatment initiation since the mother and child visit the same clinic during the post-natal period, adherence, and viral suppression.

Conclusion

A Viral load < 1000 copies/ml is achieved much more slowly in pediatric patients and this is associated with a high prevalence of LLV especially in children on a LPV-based regimen compared to a DTG-based regimen. This implies that it might take longer for babies to achieve the third 95 of the UNAIDS targets. Furthermore, the greater prevalence of LLV in pediatric patients than in mothers has important implications for the response to therapy.

Study limitations

Although viral load data was available for mother infant pairs during the time on the study, most of the mothers' drug regimens were not captured for comparison with the child's regimen. However, from the available data, most of these mothers had been diagnosed less than a year prior to enrollment into the study. They were initiated on the recommended regimen at the time. Those who enrolled before DTG roll out were on either an Efavirenz containing regimen or LPV-containing regimen. Then, with the roll-out of DTG, they were on a DTG containing regimen.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12981-025-00701-3.

Supplementary Material 1: **Supplementary Fig. 1** Mother child viral suppression trends. Is mother = 1; is child = 0. Viral load for mother –infant pairs were measured every six months

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Author contributions
IN designed the research study. DR, RB, CM, PA and FM performed the research. CO analyzed the data, IN wrote the paper and CK reviewed the paper.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethical approval and consent to participate
Ethical approval and approval from the National Council of Science and Technology were obtained (JC3617 and HS 2383, respectively).

Consent for publication
This was obtained under the consent to participate in the study.

Competing interests
The authors declare no competing interests.

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