



A Case Control Study to Assess Factors Associated with HIV Mother to Child Transmission in Kenya

Mazaher Hassan Jaffer^{1ID*}, Leonard Kingwara^{2ID}

¹Associate Professor of Clinical Medicine, Mount Kenya University, Nairobi, Kenya

²Head of Genomics, National Public Health Laboratory, Nairobi, Kenya

Corresponding Author: **Mazaher Hassan Jaffer** ^{ORCID iD}

Address: Associate professor, Department of clinical medicine, Mount Kenya University, P.O. Box 31117-00600, Nairobi, Kenya; Tel: +254 731344403; Email: mjaffer@mylife.mku.ac.ke

Received date: 10 July 2023; **Accepted date:** 28 July 2023; **Published date:** 04 August 2023

Citation: Jaffer MH, Kingwara L. A Case Control Study to Assess Factors Associated with HIV Mother to Child Transmission in Kenya. J Health Care and Research. 2023 Aug 04;4(2):71-80.

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Abstract

Background: With the proposal that people with undetectable serum viral loads of HIV cannot transmit, there is a large gap, either due to viral discordance or transcytosis, that would be explaining the persistent 4 to 7 percent vertical transmission of HIV to infants by Kenyan mothers.

Therefore, we looked for factors that predispose mothers with HIV to transmit the disease to their children so that policy can be generated for their screening to be conducted if they fit the specified criteria that identifies them as a high-risk group.

Methods: Through access to the National Database providing HIV treatment services country wide, we looked for the presence of the available factors from MTCT cases and assessed their association with increased risk of vertical transmission. The factors assessed were mother's blood plasma viral load (BPVL), geographic location of the mother and child (associated with specific higher and lower socioeconomic status), gender of the baby being born, time age after birth with confirmation of Mother to Child Transmission (MTCT), method of feeding chosen by mothers, age of the mothers, and the regimen of Highly Active Anti Retro Viral treatment (HAART) that the mother and child had been given.

Results: Mixed breast feeding posed a much higher risk, mothers of a younger age posed a higher risk, residents of some areas were at higher risks, of note the town of Lamu in Kenya. The at birth stat administration of Niverapin with Zidovudin (NVP+AZT) to the baby was very effective against the transmission, in comparison to any of the other interventions, and having an UD BPVL led to a six-fold reduction the risk of MTCT.

Conclusion: There are factors that are associated with a higher risk of vertical transmission from pregnant and lactating UD BPVL mothers which warrant implementation of more stringent policy in their case to achieve Elimination of MTCT(EMTCT) in Kenya. Other factors that were not in the available records and the ones found to have an impact need to be investigated with more accuracy through a prospective study.

Keywords

HIV, Highly Active Antiretroviral Treatment, Mother-to-Child Transmission, HIV Exposed Infant, Prevention of mother-to-child transmission, Viral Discordance

Abbreviations

HAART: Highly Active Antiretroviral Treatment; MTCT: Mother-to-Child Transmission; EMTCT: Elimination of MTCT; HEI: HIV Exposed Infant; PMTCT: Prevention of Mother-to-Child Transmission

Introduction

Literature Review:

Mother to Child Transmission (MTCT) contributes to 90% of cases in children with HIV. Globally the MTCT rate over the last decade has been reduced from 45% to around 2%- translating to about 160,000 newborn children being HIV positive in the year 2018 [1]. Kenya is one of the top 20 countries contributing to children dying from HIV globally and still struggles to reduce the transmission to levels consistently below 4% [2].

The proposal that Undetectable BPVL is tantamount to Untransmissible disease is one that clearly doesn't fit all populations and circumstances [3,4]. Especially in relation to vertical transmission, there are factors leading to significant risk of transmission despite achieving UD BPVL. These include immunological failure, some concomitant infections and some poorly understood socioeconomic and educational factors [5-9]. The mechanism of such transmission requires either viral discordance, which is a recognized phenomenon [8-12] or through the cell associated transmission of the HIV pro-viral DNA within CD4/CD8 cells with transcytosis of the pro-viral DNA to the CD4+ and CCR5+ cells found in large numbers over foetal and infant gut epithelia [13,14].

Unlike with the introduction of the Option B+ in Kenya where all mothers were given free treatment with PMTCT ARTs for their children [15,16], options of exclusive replacement feeding are not sustainable due to Kenya's limited resources for all breast-feeding mothers with HIV are not plausible, therefore we needed to identify the risk factors that increase MTCT after attaining UD BPVL using the current HAART regimens in mothers and PMTCT regimens in their infants. Most mothers would not be able to pay for their own appropriate exclusive replacement feeding methods for their children as the population in industrial countries are doing to achieve their elimination of MTCT [17]. If a subset of this population can be identified as higher risk, policies can be made to

prevent the transmission in only these mothers using these measures in a more sustainable way. It was also not very clear regarding the proportion of MTCT occurring through the process of giving birth itself in comparison to the transmission by breastfeeding in Kenya.

MTCT would be defined by a PCR result showing that the HIV Exposed Infant (HEI) is positive for HIV consistently until they stop exclusive breastfeeding at 6 months of age. This is reverified by a repeated blood DNA-PCR at 12 months of age in the children. Currently HAART regimens for mothers and PMTCT regimens for children in the EID program are provided without any cost to the patient at a national scale [18].

Aside from achieving EMTCT being part of the WHO's Millennium Development Goals for Kenya, the shadow value of these children's lives being even more than the estimated economic loss of up to 300 USD per person per year from reduced productivity alone. The loss translates to a cumulative value of 76 billion US\$ per year with an assumption of the current MTCT rate. Thus, it is paramount for further measures to be taken to ensure the complete elimination of MTCT (EMTCT) in Kenya [19].

It is therefore important to identify these risk factors in order to make the elimination of MTCT possible in the Kenyan setting through policies that will focus on the high-risk populations identified with our limited available resources.

Hypothesis

Null Hypothesis:

There is no significant difference in the MTCT rate at various time-points derived from retrospective case-control approach and mathematical modelling considering multiple variable factors.

Alternate Hypothesis:

There is a significant difference in the MTCT rate at various time-points derived from retrospective case-

control approach and mathematical modelling considering multiple variable factors.

Objectives

Broad Objective:

The study aims to measure the impact of breastfeeding method, maternal ART regimen, socioeconomic status (linked to geographical location), gender of the baby, maternal age at delivery, and PMTCT regimen as postulated factors that influence the rate of MTCT amongst the Kenyan HIV infected mothers.

Specific Objectives:

1. To determine postnatal MTCT (in up to 12 months after delivery) rates and trends in Kenya during the years 2016-2021
2. To calculate the proportion of transmission by spontaneous vaginal delivery versus breast milk in the confirmed EID cases over the same period
3. To identify the health centres and geographic areas (linked to the socioeconomic situation of the population in the area) where there is a higher prevalence of MTCT while simultaneously having UD BPVL in mothers
4. To establish the factors (Regimen of PMTCT used, methods of feeding followed, age of mother, gender of child, regimen of HAART mother was on during delivery) associated with higher risk of MTCT
5. To assess the effect that the COVID-19 pandemic and the introduction of Dolutegravir in the national HAART regimen in 2018 have had on the MTCT rates within Kenya.

Materials and Methods

We chose a case-control study design because MTCT is a rare condition. Our cases were defined by the HIV exposed infants (HEI) who turned into MTCT cases, and controls were the HEI who did not turn into MTCT cases. The records for the National Health Database were accessed only with regard to the patients who were receiving antiretroviral therapy for HIV under the government of Kenya, focusing on the women of child-bearing age, and the data with regards to Early Infant Diagnosis (EID) where infants underwent PCR testing from birth and 3 monthly intervals till 1 year of

life as per the national recommendations. Six million records were found from the raw extracted data of the People Living with HIV (PLWHIV) in the country over the period 2016 to 2021, and six hundred thousand infant's records for the EID were found. These had to be adjusted for duplication and using available 3-point demographics, we were able to combine data into individual number of patients that amounted to 51295 UD BPVL mothers and 314,815 mothers with unsuppressed BPVL.

Study Population:

The population was all the babies and their mothers amongst the PLWHIV who were captured in the EID data from any national health centre or clinic over the 1st of January 2016 until 31st December 2021.

Inclusion criteria:

1. Mother must be confirmed HIV positive.
2. Child should have tested for HIV status through PCR in a facility with a confirmed outcome at least once.

Exclusion criteria:

1. Mother's or child's status not confirmed
2. Patients with incomplete / lost data
3. Mothers who were not receiving drugs/tests from the National HAART dissemination system under NASCOP (not part of the registry).

Statistical Analysis:

We used data from Kenya National Master Health Facility List (MFL) to map the geographical location of all facilities providing PMTCT in Kenya.

Using Python v3.11 software, we overlaid the MFL with the Kenyan administrative units of October 2019 shape files and Google folium (CartoDB positron) maps.

We used the initial 6 points zoom for unsuppressed viral loads above 5% to depict the heatmaps of viral suppression in Kenya. For every year, we used color codes to show the magnitude of unsuppressed viral load in the counties as rings. The bigger the ring, the bigger the proportion of vertical transmission found.

We analyzed the clean EID data using the Statistical Analysis Software (SASv9.0). Viral loads of the mother were categorized into suppressed or unsuppressed with a cut-off point of 1,000 copies. Age of the mother and of the age of the child when they seroconverted were categorized into age groups. We used frequency percentages to describe the categorical variables and the means and medians to describe the numerical variables depending on whether the numerical variables were continuous or discrete. Where possible, we calculated the 95% confidence intervals (95%CI).

We used the chi-square to test for associations between the categorical variables. We finally used binary logistic regression models to the determinants of MTCT. We were investigating whether: age at seroconversion, breastfeeding method, sex, mother's age, year, child's HIV prophylaxis regimen, and the PMTCT intervention were associated with an increased MTCT outcome. The odds ratio was used as a measure of the association with alpha-level of significance set at 5%. Any p-value of 5% or above were considered an association [20-22]. We presented the results in tables and a Kenyan map.

The COVID-19 pandemic hit Kenya from January 2020 and its impact on MTCT was looked into through the trends found in the data before and after this date. Kenya introduced TLD as the first line for HAART in all PLWHIV including pregnant mothers in 2017 and the impact of this on MTCT was also assessed.

Sample Size Calculation and Methodology, and Ethical approvals

There was no need to calculate a sample size because all the available data from the population in question for the period in question was retrieved for analysis from the national database [23].

Ethical approval was obtained from the Mount Kenya University Research and Ethics Committee in Thika, and the license to conduct the study from the National Commission for Science Technology and Innovation (NACOSTI) was obtained.

Results

The crude 6,000,000 records over the period between 2016 and 2021 found in the database were filtered for the mothers living with HIV and the

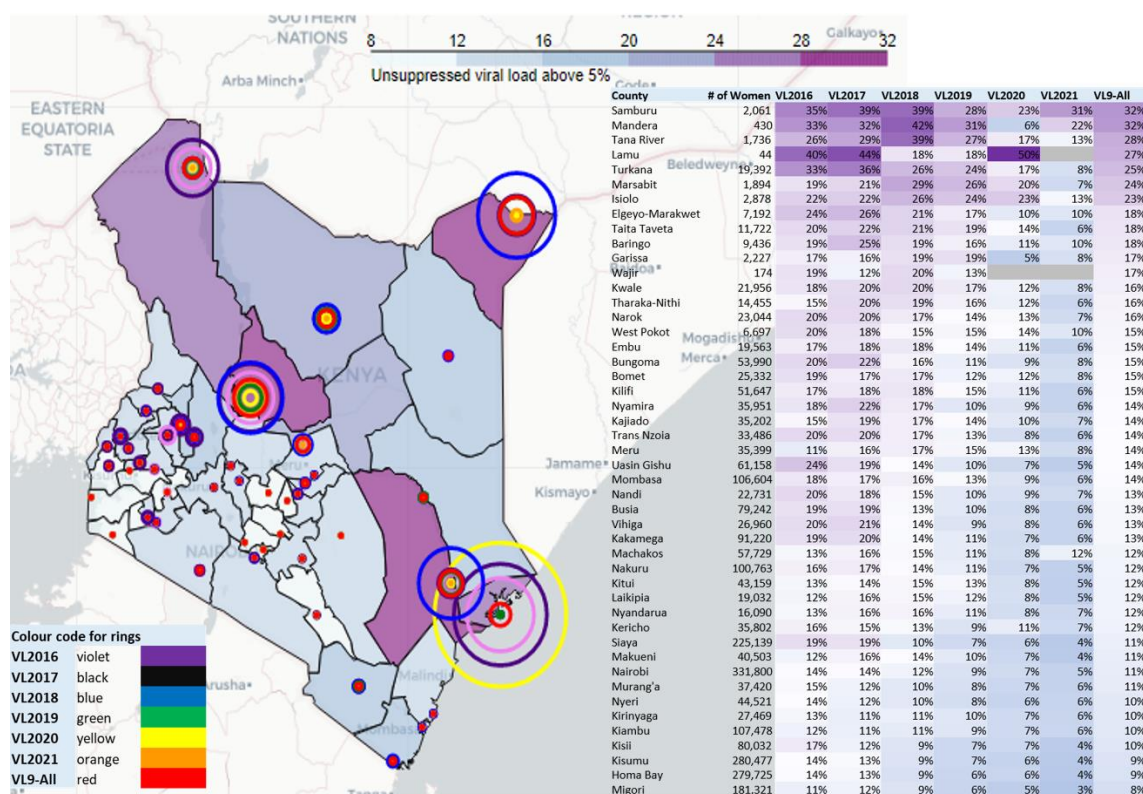


Fig-1: Geographic Distribution of the Collected Data

600,000 searched findings were adjusted using their demographics for double entries and entries that belonged to the same patients. This led to a total of around 350,000 patients out of which 300,000 had Undetected BPVL (UD BPVL) and around 50,000 had unsuppressed BPVL. Factors found amongst these in the data were categorized appropriately and chi-squared calculations with subsequent bivariate regression analysis was made for each factor in comparison to a standard in the group so that comparative risk for MTCT could be measured using

odds ratios.

We grouped results by geographic location as a measure of social-economic status and possible environmental factors effecting the MTCT in the population. The areas with unsuppressed viral loads were proportionately made a darker hue of purple, and the prevalence of MTCT in any area was demarcated by a circle with a diameter proportional to the prevalence. The color of the circle represented a specific year as per the color key (Fig-1).

Table-1: Proportion and odds of MTCT among Children whose Mothers had Undetectable Levels of HIV Virus

Characteristics	Category	N (51,295)	Within 0.9%	Between%	Crude OR	p-value	95% CI(OR)
ChildAge1	a. Birth	34,816	0.40%	68%	1		
	b. 3 months	3,566	1.80%	7%	4.67	0	(3.47, 6.28)
	c. 6 months	7,926	1.60%	15%	4.03	0	(3.16, 5.14)
	d. 12 month	4,987	2.30%	10%	5.83	0	(4.54, 7.48)
Feed	BF	5,384	1.80%	10%	1		
	EB	40,632	0.60%	79%	0.3	0	(0.24, 0.39)
	ER	558	1.60%	1%	0.88	0.704	(0.44, 1.74)
	MB	2,501	2.10%	5%	1.16	0.4	(0.83, 1.62)
	NB	2,130	2.30%	4%	1.26	0.195	(0.89, 1.78)
	No	90	1.10%	0%	0.6	0.613	(0.08, 4.35)
Baby's gender	Female	25,827	0.90%	50%	1		
	Male	25,468	0.90%	50%	0.98	0.852	(0.81, 1.18)
Mother's age	a. 16-19yrs	1,386	2.60%	3%	1		
	b. 20-29yrs	19,530	1.00%	38%	0.36	0	(0.25, 0.52)
	c. 30-39yrs	21,599	0.60%	42%	0.24	0	(0.16, 0.34)
	d. 40-45yrs	2,463	0.60%	5%	0.21	0	(0.12, 0.40)
	(blank)	6,317	1.10%	12%	-	-	-
Year	EID2016	1	100.00%	0%			
	EID2017	4	50.00%	0%			
	EID2018	7,017	0.80%	14%	1		
	EID2019	18,269	1.10%	36%	1.39	0.033	(1.03, 1.88)
	EID2020	15,538	0.80%	30%	1	0.977	(0.72, 1.37)
	EID2021	10,466	0.70%	20%	0.87	0.437	(0.61, 1.24)
Child Prophylaxis	AZT+NVP	44,628	0.70%	87%	1		
	NVP Only	52	9.60%	0%	15.64	0	(6.18, 39.56)
	No Regimen	2,493	3.20%	5%	4.93	0	(3.84, 6.32)
	Other Regimen	4,122	1.30%	8%	1.91	0	(1.43, 2.56)
Mother's ARV regime	a. TLE	32,914	0.90%	64%	1		
	b. TLD	12,891	0.70%	25%	0.72	0.007	(0.56, 0.91)
	c. Other Intervention	40	10.00%	0%	11.88	0	(4.20, 33.58)
	d. Other Regimen	4,673	0.60%	9%	0.6	0.012	(0.40, 0.89)
	f. No Intervention	81	14.80%	0%	18.59	0	(9.97, 34.68)
	g. No Data/Missing	696	1.10%	1%	1.24	0.546	(0.61, 2.52)

TLD- Tenofovir/Lamivudin/Dolutegravir; TLE- Tenofovir/Lamivudin/Effavirenz; AZT - Zidovudin NVP - Niverapin; EB- Exclusive Breastfeeding; MB- Mixed Feeding; BF- Breast Feeding (Unspecified); ER- Exclusive replacement Feeding; NB-Unsure breastfeeding technique; No- Not recorded at all

Table-2: Proportion and odds of MTCT among Children whose Mothers had Unsuppressed Levels of HIV Virus

Characteristic	Category	N (314,815)	Within 4.1%	Between%	Crude OR	p-value	95%CI(OR)
Child Age	a. Birth	1,87,425	2.20%	60%	1		
	b. 3 months	28,614	7.30%	9%	3.49	0	(3.30, 3.68)
	c. 6 months	59,940	5.80%	19%	2.75	0	(2.62, 2.88)
	d. 12 month	38,836	8.10%	12%	3.88	0	(3.70, 4.07)
Child Prophylaxis	AZT+NVP	1,50,980	2.60%	48%	1		
	No Regimen	34,201	11.80%	11%	4.95	0	(4.73, 5.18)
	NVP Only	90,004	3.80%	29%	1.47	0	(1.40, 1.54)
	Other Regimen	39,630	3.70%	13%	1.43	0	(1.34, 1.52)
Feeding method	BF	32,363	6.70%	10%	1		
	EB	2,30,752	2.80%	73%	0.4	0	(0.38, 0.42)
	ER	6,083	5.90%	2%	0.86	0.013	(0.77, 0.97)
	MB	22,111	10.50%	7%	1.62	0	(1.53, 1.73)
	NB	17,315	6.80%	6%	1.02	0.626	(0.95, 1.10)
	No	5,437	6.80%	2%	1.02	0.798	(0.91, 1.14)
	(blank)	754	4.00%	0%			
Baby's Gender	Female	1,58,584	4.20%	50%	1		
	Male	1,56,231	4.00%	50%	0.95	0.004	(0.92, 0.98)
Mother Age	a. 16-19yrs	4,551	6.50%	1%	1		
	b. 20-29yrs	46,987	4.00%	15%	0.59	0	(0.52, 0.67)
	c. 30-39yrs	41,961	2.60%	13%	0.38	0	(0.33, 0.43)
	d. 40-45yrs	4,289	2.40%	1%	0.35	0	(0.28, 0.44)
	(blank)	2,17,027	4.40%	69%			
Mother ART regimen	a. TLE Regimen	1,20,978	3.40%	38%	1		
	b. TLD Regimen	29,994	3.00%	10%	0.88	0.001	(0.82, 0.95)
	c. Other Intervention	94,582	4.00%	30%	1.19	0	(1.14, 1.25)
	d. Other Regimen	35,974	3.00%	11%	0.89	0.001	(0.83, 0.95)
	e. Baby Only	1,576	5.10%	1%	1.51	0	(1.21, 1.90)
	f. No Intervention	7,689	21.60%	2%	7.78	0	(7.31, 8.29)
	g. No Data/Missing	24,022	4.90%	8%	1.45	0	(1.36, 1.55)
Year	EID2016	53,187	5.80%	17%	1		
	EID2017	68,816	3.90%	22%	0.66	0	(0.63, 0.70)
	EID2018	74,782	3.50%	24%	0.59	0	(0.56, 0.62)
	EID2019	45,865	4.60%	15%	0.79	0	(0.74, 0.83)
	EID2020	43,137	3.40%	14%	0.57	0	(0.54, 0.61)
	EID2021	29,028	2.70%	9%	0.46	0	(0.42, 0.49)

TLD- Tenofovir/Lamivudine/Dolutegravir; TLE- Tenofovir/Lamivudine/Efavirenz; AZT - Zidovudine NVP - Niverapin; EB- Exclusive Breastfeeding; MB- Mixed Feeding; BF- Breast Feeding (Unspecified); ER- Exclusive replacement Feeding; NB-Unsure breastfeeding technique; No- Not recorded at all

Both the viral load and the progressive MTCT rate reduction were hampered in the years 2020 and slightly within the year 2019, likely due to the COVID-19 pandemic effecting the Kenyan health system. This was most pronounced over the town of Lamu in the coastal area of Kenya. Also the coastal and semi-arid areas of Kenya had significant MTCT than the cooler areas with higher average socioeconomic status in their population. MTCT in patients with UD BPVL was evident.

The data collected was categorized as in the tables below and found to have most transmission occurring through breast feeding because age of positivity played a significant increase of risk of transmission after birth (Table-1 and Table-2). In the table, the odds ratio of more than 1 would be attributed to a proportionate increase in risk of transmission, and vice-versa.

Each result was compared to the first variable in its column for effect and significance. Tables were drawn for those mothers with UD BPVL and those with Unsuppressed BPVL.

Discussion

The study was aimed at understanding the effect of selected available factors on the increase in risk of MTCT in mothers with HIV despite achieving UD BPVL. Statistical significance was calculated using chi-squared with a bivariate regression analysis on the categorical data.

The geographic data confirm that some cases of undetectable viral loads have incidences of vertical transmission as has been found in previous studies [5,7,17]. MTCT is six times more prevalent in areas with unsuppressed viral load, but the unsuppressed viral load areas are also concerning significant. This explains the exponential drop in MTCT with the progressive increase in prevalence of UD BPVL levels in PLWHIV in Kenya since 2017 [18].

Overall the number of MTCT have reduced relatively over the last 5 years even though there is still transmission ongoing after all the interventions in place. The year 2020 bore an unusual surge in MTCT around the coastal area of Lamu, which may be

attributed to the effect of COVID-19 on the country's health service delivery. Similar health effects have been found across the globe due to frustrations of health systems during the COVID-19 pandemic that caused up to 90% of countries reporting gaps in their essential health service deliveries and delaying the Global Millennium Development Goals targeted for 2030 [24,25].

The areas which were more developed and had a cooler climate seemed to have less risk of transmission, and viral loads with fewer incidences of unsuppressed BPVL. This shows that a more active lifestyle, higher socio-economic status and educational level positively contributes towards adherence to medication for HIV as shown in previous studies [26] leading to better outcomes and reduced transmission.

The risk of transmission from breastfeeding whether at 3 months, 6 months or one year was all much more significant with odds ratios of about 3 in comparison to the transmission from delivery of the babies. This also fits with the findings of breastfeeding method being the most pertinent intervention in successful prevention of MTCT found in previous studies [17].

From the modes of breast feeding, mixed feeding was clearly giving the highest risk of transmission versus exclusive breast feeding would give the lowest risk, though this was not significantly different from exclusive replacement feeding. A possibility of no breast feeding still leading to episodic transmission because of noncompliance due to lack of affordability and those with exclusive replacement feeds had a lower risk but not as much as the exclusive feeding option. It shows the non-compliance due to financial constraints prevents replacement feeding in the whole Kenyan population. This conforms to the Coovadia *H et al* study's findings.

Gender of baby had no difference in risk of transmission risk, the younger the age of the mother, the higher the risk of MTCT, and there was a progressive reduction in transmission over the years since the introduction of the Dolutegravir based regimen nationally since 2019, and the increased transmission in 2019 may be attributed to the health

delivery derangements brought about by the COVID-19 pandemic [27].

Younger mothers have a higher risk of MTCT, as has been found in previous studies. This is possibly due to inexperience in breastfeeding leading to higher incidences of mastitis and cracked nipples [28].

The PMTCT intervention delivering both Zidovudin and Niverapin at birth was very effective against any other intervention, especially noting the single Niverapin therapy – this re-enforces the synergistic effect of the combined therapy. The HAART therapies introduced have all been effective in transmission reduction with significant P valued at 95% CI in comparison to Tenofovir/Lamivudin/Effavirenz – proving that the advancement of the regimen nationally to Tenofovir/Lamivudin/Dolutegravir was a required and necessary intervention [27].

The relative effect of the factors in the unsuppressed are all similar to those with undetectable viral loads, however the number of MTCT cases by being unsuppressed increased six fold re-emphasizing the maintenance of the efforts in maintaining UD BPVL within our population of PLWHIV.

All the above findings conform to previous studies as discussed previously in regard to these risk and reinforce the need for the prospective study to incorporate more factors and to confirm the identification of the high risk groups for MTCT.

Limitations

The data collected in this study was subjected to loss of follow-up and recall bias. About 5% of the data was incomplete and therefore was eliminated from the sample. This initial phase estimated impact to be developed which is to serve as a guide toward a second phase – a prospective study with more reliability and accuracy that will enable appropriate use of resources for choice of factors to be focused on and populations to be proposed as higher risk, due to the rareness of the condition of viral discordance and MTCT in UD BPVL patients being assessed. The factors available to assess impact of from the retrospective data was limited available data collected, but

again this limitation will be covered by the prospective second phase where all factors in question postulated to play a part in risk increment will be incorporated.

Conclusion

The current interventions are optimally placed as per the national guidelines and are leading to a significant reduction in MTCT within the country. However, there seem to be other factors that increase the risk of transmission especially through breastfeeding, which once identified will enable us to focus on the higher risk groups for the little remaining MTCT to obtain complete elimination (EMTCT) as a nation.

Acknowledgements

I would like to appreciate the great assistance from the team who granted access to the raw data – Mr. Tim Ngugi, the statistician Mr. Lazarus Odeny and my supervisors Leonard Kingwara and Dr. Souzana Achilleos for their guidance.

I also thank the ERC of Mount Kenya University for their input in the study and the members of the NACOSTI who granted permissions required for the study.

Conflict of Interest

The authors have read and approved the final version of the manuscript. The authors have no conflicts of interest to declare.

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