Risks of Infections among HIV Exposed Infants during the First 18 Months of Life in Western Kenya

Winnie A. Majanga*, Daniel Onguru, Lorine K. Kangwana and George Ayodo

- Department of Biomedical Sciences, School of Health Sciences, Jaramogi Oginga Odinga University of Science and Technology, Bondo, Kenya.

***Corresponding Author:** Winnie Awuor Majanga, Department of Biomedical Sciences, School of Health Sciences, Jaramogi Oginga Odinga University of Science and Technology, Bondo, Kenya. Email: winniemajanga@gmail.com

Summary

BACKGROUND

Infants exposed to HIV are more vulnerable to infections compared to those not HIV exposed. The occurrence and risks of infections among these infants are less understood. High maternal viral load can result in advanced disease, low maternal survival rates and puts the infant at higher risk of having early T- cell abnormality [24].

AIM

This study aimed at characterizing the infections among HIV Exposed Infants (HEI) and establishing the risk factors associated with infections for interventions that will improve their health outcomes.

METHODOLOGY

A cohort study was conducted using records of HEI enrolled at the PMTCT program in Kisumu County Referral Hospital (KCRH) in western Kenya, between January 2015 and December 2017. Using a simple random sampling technique, 260 records were obtained and a structured checklist resembling HEI follow-up cards was developed for quality assurance in data abstraction. Targeting those who had completed the 18 months follow-up, died or confirmed HIV positive during the process. Excluded were transfers, loss to follow-up and infants who had incomplete records. Data entry was done using Microsoft Excel then exported to SPSS version 20 for data analysis.

RESULTS

A total of 46 infants reported different infections with an incidence rate of 17.3 new cases per 100 persons. Respiratory tract infections were the leading cause of infections contributing to 34.6% (18) of the infections. Other infections were malaria 17.4% (9), gastroenteritis 8 15.4% (8), oral thrush 11.5% (6), measles 9.6% (5), UTIs 5.8% (3). The risks to infections were high maternal viral load (OR 8.20 CI 3.32-20.25, p≤ 0.001), incomplete Co-trimoxazole prophylaxis (OR 2.23 CI 0.91- 5.50, p≤0.050) and mixed feeding (OR 2.59 CI 1.05 -6.36, p≤0.040). High burden of gastroenteritis peaking at around the 7 th month of the 18 month was recorded.

CONCLUSION

High maternal viral load, incomplete Co-trimoxazole prophylaxis dosage and mixed feeding are a risk to infections among HEI. These findings provide critical information for health promotion and improvement of PMTCT interventions. Lifespan approach in understanding and protecting these infants from risks and infections, pneumonia in particular is crucial.

RECOMENDATIONS

Home delivery and breastfeeding for only 1 year compared to the recommended breastfeeding duration of 2 years should be discouraged. Future studies be conducted in multiple sites involving HIV infant comparator to enrich the findings.

Keywords: HIV Exposed Infants, Infections, 18 Months

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Introduction

Since the beginning of the epidemic, some 14.8 million HIV exposed infants were born to HIV positive mothers and remained uninfected [1]. The expansion of Prevention of Mother-to-Child Transmission of HIV/ AIDs (PMTCT) has resulted not only in a marked reduction of HIV transmission but also increased the number of HEIs significantly [2]. While PMTCT programs which includes comprehensive care of HEI (early infant diagnosis, immunization, monitoring growth and development, nutritional assessment and prevention as well as treatment of opportunistic diseases)
[3] had made great achievements in improving the health outcomes of those infants, the rate of infections had remained high even among infants enrolled into the program [4].

HEI are more susceptible to severe lower respiratory tract during the first year of their life
[5]. Other infections common to HEI are diarrheal diseases including gastroenteritis, viral infections *(cytomegalovirus*) and bacterial sepsis [4]. Skin rash, fever and oral thrush have been reported too [6].

Though causes of morbidity among HEI were also common to HIV unexposed infants, infections were more severe in HEI and were characterized by frequent hospitalizations and mortality [7]. HEI were more susceptible to infections compared to HIV unexposed infants [4, 8-10]. Their vulnerability could be due to common childhood risk factors such as prematurity or low birth weight, suboptimal breastfeeding and poverty [11].

However, it may also be due to in *utero* exposure of the fetus to maternal HIV during pregnancy and postnatal exposure of the infant during breastfeeding coupled with exposure to co-infections which cause deregulation in the maternal immune system altering the infants' *immune milieu* [4].

Infant immune system resulting from deregulation of the mother's immune system by HIV and other comorbidities, lowered trans-placental transfer of antibodies from the mother, high burden on the household caused by HIV, maternal mortality and suboptimal breastfeeding resulting from avoidance of breastfeeding in order reduce perinatal HIV transmission [4, 8, 9, 12].

However, the occurrence and risk factors to those infections as those infants grew were poorly understood and a lifespan approach in understanding and protecting them is required. The current study seeks to characterize infections reported by HEI enrolled in PMTCT program in Western Kenya and further determine the risk factors associated with infections to inform interventions that will improve their health outcomes.

MATERIALS AND METHODS

Study Site

The study was conducted at Kisumu County Referral Hospital (KCRH). KCRH is located in Kisumu city, the western part of Kenya. KCRH has a PMTCT unit and a comprehensive care centre managed by a collaboration between FACES (Family Aids Care & Education Services) and the Ministry of Health, Kenya. The HIV prevalence among adults in Kisumu was 16.3% and the MTCT rate of 8.7% [13].

Study Design

A retrospective cohort study was employed. The study involved 260 HIV exposed infants on the PMTCT program between January 2015 and December 2017. The exposure variables were high maternal viral load, place of delivery, incomplete co-trimoxazole prophylaxis, mixed feeding, incomplete immunization, breastfeeding for less than one year and low infant birth weight. The outcome variable was any infection recorded during the 18 months of follow-up.

Study Participants

The target population for this study was HEI who completed the 18 months follow-up, died or confirmed HIV positive during the follow-up. Exclusion criteria included transfers, loss to follow-up and infants who had incomplete records. The simple random sampling method was employed.

Data Collection and Quality Control

A structured checklist was developed resembling HEI follow-up cards. Data were collected by reviewing both the HEI register and HEI follow-up cards. All completed checklists were rechecked for completeness, clarity and consistency.

Follow-up and Measurement

According to the PMTCT guideline in Kenya, all infants born to HIV positive mothers should be enrolled on PMTCT care by the sixth week of their life or during the first contact with a health facility thereafter. The infant should be given ARV prophylaxis for the first 6 weeks or 12 weeks of their life while the mother continues on HAART, Highly Active Antiretroviral Therapy for life. The mother-infant pair is then followed monthly for 18 months.

Comprehensive care of these infants includes:

(a). Growth and development monitoring,
(b). Immunization.
(c). Prevention as well as treatment of opportunistic infections.
(d). Nutritional counselling.
(e). Support and early infant diagnosis.

Care of HEI should follow these guidelines: Early diagnosis of HIV in those infants was done using DNA-PCR. A positive antibody test at 18 months also confirms infection in these children. Infants who become positive were initiated on lifelong HAART immediately. In addition, those infants were given co-trimoxazole prophylaxis monthly until the cessation of breastfeeding for HEI who were discharged negative and for the rest of the life of HEI who were infected [3].

Reliability and Validity of Data Collection Instrument

The data collection tool was validated by two experts i.e study supervisors and necessary adjustment were done appropriately. In addition, the checklist was made to resemble the HEI card, a document that has been tested by the Ministry of Health and is being used for follow-up of HEI in Kenya. All variables in the HEI card were captured ensuring content validity.

Data Analysis

Entry of data was done using Microsoft Excel after which data exploration and cleaning to check the coding errors, inconsistencies, missing information and outliers were done and corrections made appropriately.

Data were then exported to SPSS version 20 for data analysis. Descriptive analysis of baseline mother-infant characteristics and proportion of infections was conducted. Binary logistic regression was run to assess the associations between independent variables and the dependent variable (infections) to find the odds of infections at 95% CI.

All variables that were significant on bivariate regression ($p \leq 0.05$) were included in the final multivariate model adjusting for age of infants at enrolment to obtain adjusted odds ratios for infections.

Ethical Considerations

The ethical clearance to conduct this study was obtained from Jaramogi Oginga Odinga Teaching and Referral Hospital Review Board. The study was commenced after receiving a research license from NACOSTI, National Commission for Science, Technology and Innovation and a letter of approval from the Kisumu County Department of Health and Sanitation.

RESULTS

Characteristics of Infant-Mother Pairs

Out of the 260 HEI records sampled, 248 records were retrieved and included in the analysis. The mean age at enrollment of the infants was 6.87 ±0.367 weeks (SD 5.774) while the mean weight at birth was 3.17±0.48 kg (SD 0.72). The proportion of females was slightly higher compared to that of male infants (50.4% vs. 49.6%). Only four infants did not receive ARV prophylaxis. All mothers were alive at enrollment and were the primary caregivers to these infants. The average age mother of those infants was 28.27±0.325 years (SD 5.980). No HEI reported any signs of tuberculosis infection. *Table 1* shows the characteristics of mother infants' pair at enrolment.

Table 1: *Characteristics of Infant-Mother Pairs Enrolled for The Follow-Up n=248*

Baseline Characteristics	**n (%)**
Age at enrollment	
≤ 6 weeks	227(91.5)
7-12 weeks	16(6.5)
Greater than 12 weeks	5(2.0)
Infant Gender	
Male	123(49.6)
Female	125(50.4)
Birth Weight	
≥ 2.5 kg	178 (78.1)
<2.5 kg	50 (21.9)
Mothers' age	
16-24 year	52(21.1)
25-30 years	127(51.4)
Above 31 years	68(27.5)
Viral Load	
High viral load	31(13.8)
Low viral load	194(86.2)
Maternal ART	
Yes	243(98.0)
No	5(2.0)

The incident rate of infections among the children during the 18 months of follow-up was 17.3 new cases per 100 population. Respiratory tract infections contributed to 18 (34.62%) of the infections with pneumonia accounting for 7 (41.17%). Respiratory tract infections were more prevalent during the first year of infant life. Malaria was the second leading cause of infectious morbidity 9 (17.4). Other causes of infections among these infants were; gastroenteritis 8(15.38%), oral thrush 6 (11.53%), measles 5(9.62%), urinary tract infections, UTIs 3 (5.77%). 90.38% of the infections occurred during the first year of the infants' life. Figure 1 illustrates the types of infections reported among HIV exposed infants.

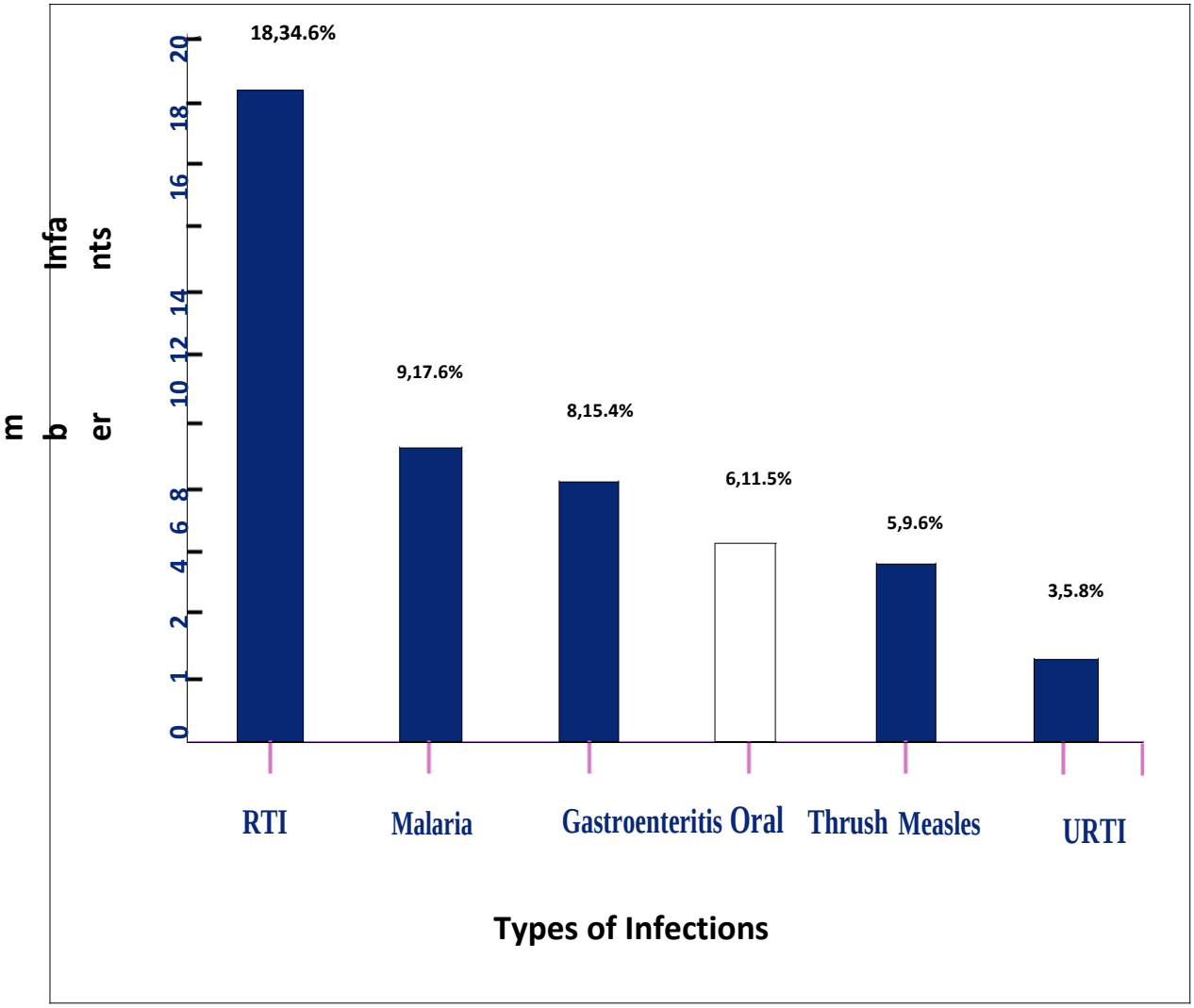

Figure 1: *Types of Infections among HIV Exposed Infants*

Cases of *gastroenteritis* and diarrheal disease were less frequent before the 5th month (18.2%). The frequency increased after the 6th month with the introduction of weaning. The median age of reporting gastroenteritis was the 7th month. The prevalence of gastroenteritis was higher in the mixed-fed infants compared to their exclusively breastfed peers.

Majority of the infants who reported different infections did not complete the immunizations as scheduled by the Kenya Expanded Program on Immunization (KEPI), 60.87%. Moreover, the number of children vaccinated increased with the integration of PMTCT service into Maternal Health Care, MCH. On the other hand, only 63.04% completed the Co-trimoxazole prophylaxis schedule.

Risk Factors to Infections among HIV Exposed Infants

HEI who were mixed-fed were most likely to get infections [OR 2.55 (95% CI 1.17-5.57); p≤0.020] compared to HEI who were breastfed exclusively for 6 months or those who had exclusive replacement feeding. An incomplete Co-trimoxazole prophylaxis session was also 1.9 times associated with the likelihood of reporting infection among these infants [OR 1.94 (95% CI 0.95-3.99) p≤0.060].

Moreover, Infants whose mothers had a high viral load were about 7 times more likely to report infections [OR 7.21(95% CI 3.18-16.37); p≤0.001]. Low infant birth weight and incomplete routine immunization

(according to KEPI) also increased the odds of reporting infections [OR 1.97 (95% CI 0.92-4.17); p≤0.080] and [OR 1.50 (95% CI 0.78- 2.91); p≤0.260] respectively. Likewise, home delivery and being breastfed for only 1 year compared to the recommended breastfeeding duration of 2 years also increased the likelihood of getting infections (OR 1.87(95% CI 0.77- 4.54); p≤0.160 and [OR 1.67(95% 0.72-3.80); p≤0.230 respectively). *Table 2* shows the risk factors for infections among HIV exposed infants.

Table 2: *Risk to Infections among HIV Exposed Infants*

Risk Factors	**Infection (n (%)))**		**OR (95% CI)**	**P-Value**
	No	Yes		
Birth weight				
Normal	151(66.2%)	27(11.8%)	1.97(0.92-4.17)	-
Low	37(16.2%)	13(5.7%)		≤0.080
Immunization				
Complete	104(41.9%)	18(7.3%)	1.50(0.78-2.91)	
Incomplete	100(40.3%)	26(10.5%)		≤0.260
Feeding Practice 0-6 months				
EBF/ERF	177(71.7%)	32(13.0%)	2.55(1.17-5.57)	-
Mixed Fed	26(10.5%)	12(4.9%)		≤0.020
Maternal Viral Load				
Low	169(75.1%)	25(11.1%)	7.21(3.18-16.37)	-
High	15(6.7%)	16(7.1%)		≤0.001
Mode of delivery				
C-S	34(13.9%)	8(3.3%)	0.89(0.38-2.08)	-
Virginal	168(68.6%)	35(14.3%)		≤0.780
Place of delivery				
Facility	180(73.5%)	35(14.3%)	1.87(0.77-4.54)	-
Home	22(9.0%)	8(3.3%)		≤0.160
Breastfeeding to 1 year				
BF	172(71.1%)	31(12.8%)	1.67(0.72-3.80)	-
NBF	30(12.4%)	9(3.7%)		≤0.230
Co-trimoxazole prophylaxis				
Complete	161(64.9%)	29(11.7%)	1.94(0.95-3.99)	
Incomplete	43(17.3%)	15(6.0%)		≤0.060

Upon adjusting for the age of infants at enrollment, only mixed feeding, high maternal viral load and incomplete co-trimoxazole were significantly associated with infections among HIV exposed infants. *Table 3* show the risk factors associated with infections among HIV exposed infants.

Table 3: *Risk Factors Associated with Infections among HIV Exposed Infants*

Risk factors	Infection (n %)		OR (95% CI)	P value	AOR (95% CI)	P value
	Yes	No				
Feeding Practice 0-6 months						
EBF / ERF	177(71.7%)	32(13.0%)	-	-	-	-
Mixed Fed	26(10.5%)	12(4.9%)	2.55(1.17-5.57)	≤0.020	2.59(1.05-6.36)	≤0.040
Maternal Viral Load						
Low	169 (75.1%)	25(11.1%)	-		-	-
High	15(6.7%)	16(7.1%)	7.21(3.18-16.37)	≤0.001	8.20(3.32-20.25)	≤0.001
Cotrimoxazole Prophylaxis						
Complete	161(64.9%)	29(11.7%)	-	-	-	-
Incomplete	43(17.3%)	15(6.0%)	1.94(0.95-3.99)	≤0.060	2.23(0.91-5.50)	≤0.050

Discussion

For clinical management of infections among HEI, it is important to understand the rate and risk of infections. In this study, the rate of infections among infants was 17.3%, a result comparable to 16.8% obtained in a previous study of a large retrospective review of the medical history of HEI [14].

On evaluating the specific infections, common infections such as RTIs, malaria, gastroenteritis, oral thrush, measles, and UTIs were reported among HEI in this study. Our findings are consistent with other results that reported RTIs as the leading cause of infections among these infants with pneumonia in particular [10].

This study also reported a high burden of gastroenteritis peaking at around the 7th month of the 18month. A study in India also reported gastroenteritis as the major cause of hospitalization among HEI. However, the peak was at 9th month [15]. The same peak time for gastroenteritis infections suggests a possible cause of infection and essentially explains the need to understand the risk of infections among HEI.

A high number of *gastroenteritis* infections in this population could also be attributed to abrupt weaning and poor water quality. Moreover, our study shows malaria as the second leading cause of infection among those infants. This contradicts the finding from a Ugandan study that was carried out in a high malaria transmission area but reported a low prevalence of malaria infections. These findings should be interpreted with a lot of caution given the enhanced prevention and control of malaria in the area of study. Likewise the protective effect of co-trimoxazole on malaria infections [4, 16].

Co-trimoxazole prophylaxis protects HEI from morbidities and mortalities due to malaria and pneumonia [3]. Infants who completed Cotrimoxazole in this study were twice less likely to report infections compared to those who had incomplete Co-trimoxazole.

A study conducted by Davis *et al*. assessing the impact of Cotrimoxazole Prophylaxis on Malaria among HEI established that complete Co-trimoxazole prophylaxis dosages conferred over 70% protection against malaria among these infants [17]. Furthermore, Co-trimoxazole prophylaxis was found to decrease the rate of all-cause morbidity in a study done in Malawi [18].

Mixed feeding was also significantly associated with infections in this study, a result similar to that reported by [4]. In addition, a study conducted in Myanmar established an association between mixed feeding and poor health outcomes among HEI [19]. Exclusive breastfeeding in the context of infant ARV prophylaxis and mother HAART confers protection against common childhood illnesses [3, 20-22].

The advanced maternal disease has been linked to increased susceptibility of HEI to severe infections [23]. In addition, the survival and health of the mothers was vital in reducing poor health outcomes among these infants [6]. High maternal viral load can result in advanced disease, low maternal survival rates and puts the infant at higher risk of having early T- cell abnormality [24].

This is important to point out that there are still gaps in the current PMTCT interventions. Current interventions are solely geared towards the elimination of mother-to- child transmission of HIV. However, the incorporation of interventions that reduce the risk of infections among HEI will greatly improve the PMTCT outcomes.

Study Limitation

The study was retrospective and therefore some key variables that could be important in an understanding outcome such as maternal level of education and parity could not be explored. Besides, this study was conducted on a single site and we recommend that future studies on the subject be conducted in multiple sites to enrich our findings. Finally, this study did lack An Hiv Unexposed Infant Comparator.

Conclusions

This study shows that high viral maternal load, incompletion of co-trimoxazole prophylaxis dosage and mixed feeding a risks to infections among HEI. Re-enforcing models that improve maternal adherence to ART or using an alternative regimen to reduce mothers' viral load during the time of exposure coupled with health promotion to improve uptake of exclusive

breastfeeding and Co-trimoxazole prophylaxis is urgently needed to improve PMTCT interventions.

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Conflict of Interest

The authors of this study declare that there is no conflict of interest regarding the publication of this article.

Authors Contribution

All authors of these studies made substantial contributions towards the designing of the study, data instrument validation, data collection, cleaning and analysis, interpretation of the results and manuscript preparation. The authors read the manuscript before submission.

Authors Contact Information

Lorine K. Kangwana, Email- lauryn.kemunto@yahoo.com
George Ayodo, Email- gayodo@gmail.com
Daniel Onguru, Email- danonguru@yahoo.com
Winnie A. Majanga, Email- winniemajanga@gmail.com

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Availability of Data

Data that has been used to support the findings of this study are included in the article. Raw data can be obtained from the corresponding author upon request.

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