Scholars Journal of Applied Medical Sciences (SJAMS) **ISSN 2320-6691 (Online)**
Sch. J. App. Med. Sci., 2015; 3(1F):396-407 **ISSN 2347-954X (Print)**

(An International Publisher for Academic and Scientific Resources)
www.saspublishers.com DOI: 10.36347/sjams.2015.v03i01.079

Research Article

The Early Infant Diagnosis (EID) Programme in Kenya: A Case-control Evaluation of PCR testing, ART Initiation and Adherence among HIV Exposed Children in Nairobi County

Christopher L. Imbaya[1], Zipporah Ng'ang'a[1], Yeri Kombe[2]
[1]College of Health Sciences Jomo Kenyatta University of Agriculture & Technology Nairobi, Kenya
[2]Centre for Public Health Research Kenya Medical Research Institute Nairobi, Kenya

***Corresponding author**
Christopher L. Imbaya
Email: chrisimbaya@yahoo.com

Abstract: Over half of 2 million children below 2 years who live with Human Immunodeficiency Virus (HIV) die by the second birthday if they are not diagnosed and treated. Early Infant Diagnosis (EID) of HIV permits timely initiation of Antiretroviral Therapy (ART) which reduces paediatric morbidity and mortality. The Kenyan government launched the EID programme in 2006 through which over 300,000 children have undergone Polymerase Chain Reaction (PCR) testing. Seven years after the launch and in view of the rapid up-scaling of ART usage we purposed to evaluate the success of the programme as seen by the age of PCR testing among HIV exposed children, the children's adherence rate to ART and the maternal-child factors influencing pediatric ART adherence in Nairobi County. Using standardized questionnaires we established that 53% of HIV exposed children received a PCR test within 6 months of age, 29% of them between 6 and 18 months of life while 18% were tested after the age of 18 months. About half (52%) of the mothers faced situations that made it difficult to give ART to their children. Poor maternal ART adherence, caretaker forgetfulness and facing difficult situations negatively impacted on children's ART adherence. Significantly higher (p=0.023) adherence was seen among PCR- children on prophylactic ART compared to PCR+ children on Highly Active Antiretroviral Therapy (HAART). We recommend health workers community networking and engagement, heightened public education on EID coupled with the use of maternal adherence reminder techniques to promote early PCR testing and enhance ART uptake and adherence.
Keywords: HIV/AIDS, EID, PCR, ART, Adherence.

INTRODUCTION

It is estimated that more than 190,000 children aged between 0 to 14 years are living with HIV or Acquired Immune Deficiency Syndrome (AIDS) in Kenya out of whom 10,000 died due to AIDS related illness in 2013 [1]. Nairobi County, the capital city of Kenya accounts for over 13,000 (7%) of these cases ranking it 4th among the top 5 out of the 48 Kenyan counties in terms of the highest number of HIV+ children [1]. Early Infant Diagnosis (EID) refers to making HIV diagnosis in infants and young children before 18 months of age which gives an opportunity for early identification of HIV exposed and infected infants thereby linking them to early care plus treatment for the infected as well as prevention for the exposed [2]. In a bid to curb HIV/AIDS related childhood morbidity and mortality the Kenyan Ministry of Health (MOH) introduced the EID programme in the country in 2006 which is intended to test all HIV exposed children followed by provision of treatment for those who are infected and follow-up preventive support for the uninfected. The National EID testing and treatment algorithms have been standardized with the World Health Organization (WHO) guidelines which recommend that all HIV exposed infants should be tested using PCR tests from 6 weeks of age or the first contact thereafter following which ART should be initiated in all PCR+ infants regardless of their clinical or immunological status [2]. The algorithm further recommends HIV antibody testing among infants whose initial PCR test is negative at 9 and 18months or at 2months after cessation of breastfeeding whichever comes earlier. Since the inception of the EID programme up to date more than 3,000 EID testing sites are active in Kenya with Nairobi County having the largest number of 192 testing centers [3]. The EID sites in Nairobi provide Counseling and Testing (CT) services following which Dried Blood Spots (DBS) are drawn from HIV exposed infants and relayed to the testing laboratories that are located at the Kenya Medical Research Institute (KEMRI) in Nairobi. As a result of the EID programme activities in Kenya more than 300,000 infants have been tested for HIV using PCR between 2006 and 2014 [3].

The global epidemiological estimates indicate that only 8% of infants receive virological testing during the first 2 months of life contrary to the WHO recommended age of 6 weeks for testing PCR among HIV exposed children [4] with majority of them being referred to Comprehensive Care Centers (CCC) for testing much later in life while being treated for acute and chronic diseases. Furthermore as the number of EID testing sites continues to rise globally and in Kenya particularly more children are expected to be initiated on Antiretroviral (ARV) drugs upon testing PCR+. Diagnosing HIV among children and initiating ARV treatment form the first major steps in the EID process which should be followed by the utilization and adherence to the ARV's by the patients in order for the process to be successful. With concerted global efforts being directed towards scaling up the access to ART the role of ensuring that adherence to the ARV's takes place is increasingly becoming important thereby necessitating treatment programs to implement mechanisms that will encourage and monitor the patients' adherence to their ARV medications [5].We purposed to evaluate the success of the EID programme in Nairobi County first by assessing the age at which the study participants were tested for PCR, then by determining the level of ARV adherence among the children that were on ARV's and finally by evaluating the maternal-child factors that reduce ARV adherence among the children in the study group. For the first time we also made a case-control comparison of the impact that various well known difficult situations have on pediatric ARV adherence among PCR+ children (cases) that were receiving Highly Active Antiretroviral Therapy (HAART) and PCR- children (Controls) who were taking prophylactic regimens of Prevention of Mother to Child Transmission (PMTCT) ARV 's. Lastly we made a comparison between the ARV adherence among the cases and the controls.

MATERIALS AND METHODS

Scientific and Ethical approval of the study protocol was obtained from the Kenya Medical Research Institute (KEMRI) Scientific and Ethical Review Unit (SERU), Jomo Kenyatta University of Agriculture and Technology (JKUAT) and the Nairobi County Medical Officer of Health. Participants whose results we are presenting were drawn from a larger case control study in which we were evaluating maternal ARV adherence among mothers to PCR+ children and mothers to PCR- children. The settings of the study were various public health facilities that were randomly selected from health institutions that offer EID, CCC and PMTCT services within Nairobi County. The cases and the controls were identified using their PCR results in the health records at the study sites. To be included in the study the children had to be 5 years of age and below with cases having a positive PCR test result and the controls PCR- results. The adults who were accompanying the children were mainly their mothers who were introduced to the study and informed of its objectives before their consent to participate in it with their children was obtained. Children's ARV adherence information was thereafter elicited through the administration of the Paediatric AIDS Clinical Trial Group (PACTG) questionnaire in face to face interviews by trained research assistants. Women who were unwilling to participate in the study or those whose children were above 5 years of age or not on ARV's were excluded from the study. Maternal ARV adherence was also evaluated using the Adults AIDS Clinical Trial Group (AACTG) questionnaire.

The first part of the study questionnaire focused on obtaining the maternal-child socio-demographic characteristics that ranged from mother's age, mother's marital status (single, married, separated, divorced, widowed), mother's highest level of education (none at all, primary school, secondary school, college, university),average monthly domestic expenditure for the family, the medical care that they had received in the previous four months as assessed by the number of days the mother stayed in bed unwell (1-2,3-5, 6-10, 11-16 and >16), number of days the mother cut down her normal activities due to illness (1, 2, 3, 4, >5), number of days the mother was admitted in a hospital ward (1, 2, 3, 4, >5), the number of days she visited the hospital emergency room (1, 2, 3, 4, >5), rating of own health status as perceived by mother herself (Excellent, very good, good, fair, poor) and rating of their own maternal health on a scale of 1 to 100 where 1 was the worst health possible and 100 the best health possible. The questionnaire further tested the maternal working situations which were described as (not working not looking for work, not working looking for work, working part time and working fulltime), their ARV utilization information starting with whether the mother was taking ARV's (yes, no), number of ARV doses the mother missed (the previous day, 2 days ago, 3 days ago and 4 days ago), how maternal ARV schedule was followed over the previous 4 days (never, some of the time, about half of the time, most of the time, always), whether mothers were given any special instructions to follow when taking the ARV's (yes, no), if yes how they followed the instructions during the previous 4 days (never, some of the time, about half of the time, most of the time, always) and the last time the mother missed any of their medications (within past week, 1-2 weeks ago, 2-4 weeks ago, 1-3 months ago, >3 months ago, never missed medications).

The second part of the questionnaire focused on evaluating information on the child's characteristics namely age of the child, sex of the child, birth ranking of the child, method of delivery (vaginal, caesarian section), birth weight, feeding method (exclusive breastfeeding, exclusive formula feeding, mixed breastfeeding, other-specify), PCR status, age when PCR was conducted on the child, type of ARV regimen, the number of ARV doses that the child had missed to take (in the previous 3 days,2 days and one day), the

last time the child missed to take a dose of their ARV medications (never, in the previous 2weeeks, one month, more than a month ago and can't remember). Lastly the questionnaire evaluated whether there were any situations that made it difficult for the child to be given ARV's. This was achieved through administration of a 20 item menu that listed possible situations that could have made it difficult for the mother to give the child their ARV's with ranking on how frequently the caretakers encountered such situations i.e. 0-never encountered the difficult situation, 1- encountered it 1 to 2 times per month, 2- encountered it1 to 2 times per week, 3- encountered it more than 3 times per week). The situations that were evaluated included the following: Running out of medicine, medicine tasting bad, forgetting to take the medicine, worrying about the medicine's side effects, change in mother's daily routine, mother too busy with the baby/child, the baby/child refusing to take the medicine or spitting it out, many people looking after the child where mother is not always available, not wanting to be noticed giving the medicine by other people, baby/child was ill, thinking that the child no longer needed the medicine, being told by someone not to give the medicine, mother/caretaker being ill, thinking that the medicine might be harmful to the baby, baby/child staying at different location from where medicine was, maternal/care giver depression, child/baby being well, too much medicine to be given, mother being away from home, being busy with other things, and any other reasons (specify).

For security and confidentiality purposes the questionnaires were locked in safe drawers after the collection of the data. The information was then coded and keyed into an MS Access database using a double entry system before being transported into the IBM statistical package for social sciences (SPSS) version 20 for cleaning and analysis. The necessary precautions were taken to ensure data security by using passwords to access it, backing up on external media and use of antivirus software. Exploratory techniques were employed to uncover the structure of the data before proceeding to univariate analysis with which we determined the descriptive statistics that were used to summarize categorical variables and measures of central tendency for continuous variables. To assess children's ARV non-adherence we measured the missed number of doses as a percentage of the total prescribed doses over the 3 day recall period as well as doses that were skipped by the patients within two weeks, one month and more than a month prior to the interview. Adherence was deemed to have occurred where no missed ARV doses were reported or at least 90% of the prescribed medication doses were taken during the period in question while below this threshold the children were deemed to be non-adherent. Similar rationale was used in determining maternal ARV adherence over the previous 4 days as per the AACTG criteria. Some continuous variables like age of the children/mothers and the domestic monthly expenditure were categorized for the analysis. Missing continuous data were treated as missing in the analysis models while for the categorical variables we added a missing category. Association between ARV adherence and non-adherence among cases and controls was tested using Pearson's Chi-square test or fisher exact test. Univariate logistic regression models were constructed to generate measures of strength of association with the outcome of interest (adherence or non-adherence at different levels) and crude odds ratios and their respective 95% confidence intervals reported. The threshold for statistical significance was set at $\alpha = 0.05$ and a two-sided p value at 95% confidence intervals (CI) reported for corresponding analysis. Different multivariable regression models were then constructed for the children's ARV adherence at different recall periods versus various maternal-child socio-demographic characteristics and the situations that made it difficult to administer the ARV's. Finally Adjusted Odds Ratios (AOR) with their respective 95% CI were used to estimate the strength of association between the retained independent variables and children's ARV adherence.

Using the case control sample size computation method below (where n= desired sample size of cases, r=ratio of controls to cases, σ^2 is the standard deviation, $Z\beta$ is the power of the study (typically 0.84 for 80%), $Z\alpha/2$ is the level of statistical significance (1.96) and the difference in means is the effect size) a sample of 52 PCR+ and 52 PCR- children was sufficient to detect children's ARV adherence at a mean difference of 5.5 with 80% power and 95% level of statistical significance assuming a standard deviation of 10.

$$n = \left(\frac{r+1}{r}\right)\frac{\sigma^2(Z_\beta + Z_{\alpha/2})^2}{(\text{difference})^2}$$

$$n = (2)\frac{10^2(7.84)}{(5.5)^2} = (2)1.8^2(7.84) = 52$$

However the recruitment of the cases and controls had to be continued up to 72 and 73 respectively in order to achieve the maternal sample size that met the threshold necessary for correlating with the children's ARV adherence in order to test two null hypotheses i.e. There is no difference in children's adherence to PMTCT and HAART ARV regimens and, There is no difference in the difficult situations that are experienced by mothers to PCR+ and mothers to PCR- children when administering HAART and prophylactic ARV regimens to the children.

RESULTS AND DISCUSSION

Between April 2013 and September 2014 a total of 145 children were recruited into this study out of whom 72 had positive PCR results (cases) and 73 were PCR- controls. Out of these participants 87 children (60%) were taking ARV's and being eligible

for evaluation in the study they consisted of 68 cases (78%) who were receiving HAART and 19 controls (22%) that were taking prophylactic ARV's for PMTCT purposes. The other 58 children (40%) who were not taking ARV's were ineligible for evaluation in the study. They consisted of four (6.8%) PCR+ and 54 (93.2%) PCR- children all of who were not on any form of ARV treatment (figure 1). The study participants were recruited from 7 different sites as shown in figure 2. A summary of the maternal-child socio-demographic characteristics of the children that were evaluated for ARV adherence is shown in table 1 below. Most (65.6%) of the children were taking Nevirapine (NVP) based regimens while others were on Abacavir (ABC) and Efervirenz (EFV) based regimens (Table 2). Majority of the children (94%) had been delivered through the spontaneous vaginal method with 54% of them being fed through the mixed breastfeeding method. About half (53%) of the children received their first PCR test within 6 months after birth, more than a quarter (29%) received the test between 6 and 18 months while the rest (18%) received their PCR when they were above 18 months. Most of the mothers (61%) had low formal education (primary school and below) while the average family monthly income fell below 210 United States Dollars (USD) or otherwise 20,000 Kenya shillings for 73% of the participants (Table 1).

Out of the 87 children that were receiving ART we collected adherence data to ARV's (3 days recall) for 84/87 (97%) of them. Overall mothers to 76 (91%) children reported 100% ARV adherence by their children with 1 (1.2%) reporting 92% adherence and 7 (8.3%) reporting adherence below 90% within 3 days of recall. On sub-analysis for the same recall time frame all the 17 children whose mothers responded from the control group reported 100% adherence to their ARV medications while among the cases 59/67 (88%) of them reported 100% ARV adherence, one of the cases (1.5%) reported 92% ARV adherence and 7 cases (10.5%) had ARVs adherence below 90%. Two children from the control group and one child from the cases group did not provide their 3 days recall adherence data respectively (Figure 1).

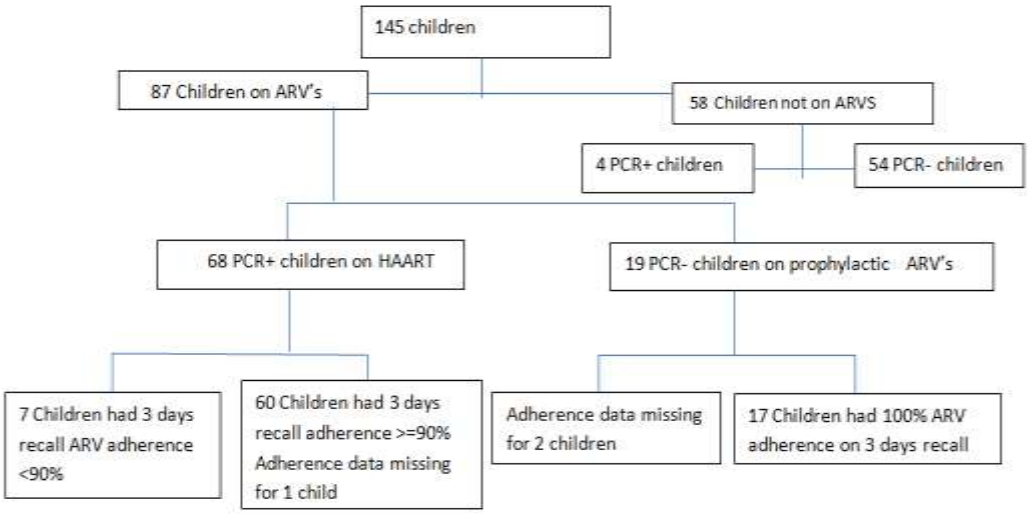

Fig. 1: Flowchart showing distribution of study participants

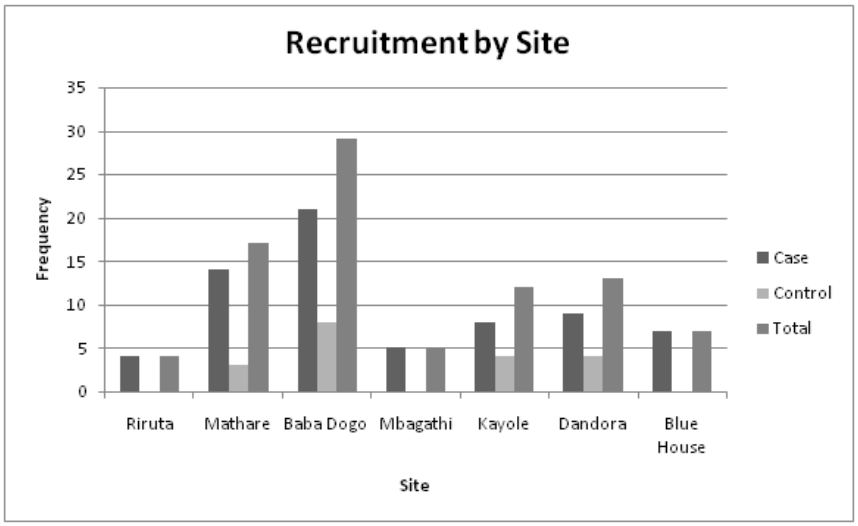

Fig. 2: Distribution of the study participants by site

Table 1: A summary of the Maternal-child socio-demographic characteristics of the study participants

Variable*	Case (68)	Control (19)	Overall (87)
Recruitment site			
Riruta	4 (5.9)	0	4 (4.4)
Mathare	14 (21)	3 (16)	17 (20)
Baba Dogo	21 (31)	8 (42)	29 (33)
Mbagathi	5 (7.4)	0	5 (5.5)
Kayole	8 (11.8)	4 (21)	12 (14)
Dandora	9 (13)	4 (21)	13 (15)
Blue House	7 (10)	0	7 (8.1)
Mother's age in years			
<25years	18 (26)	8 (42)	26 (30)
25-30years	30 (44)	3 (16)	33 (38)
30-35years	14 (21)	5 (26)	19 (22)
35years and above	6 (8.8)	3 (16)	9 (10)
Mother's marital status			
Single	11 (16)	3 (16)	14 (16)
Married	46 (68)	14 (74)	60 (69)
Separated	3 (4.4)	1 (5.3)	4 (4.6)
Divorced	5 (7.4)	0	5 (5.8)
Widowed	3 (4.4)	1 (5.3)	4 (4.6)
Mother's highest level of education			
Primary and below	40 (59)	13 (68)	53 (61)
Secondary School	23 (34)	4 (21)	27 (31)
College and above	5 (7.4)	2 (10.5)	7 (8)
Family's average monthly income in USD			
<105	11 (17)	8 (47)	19 (24)
105=<160	12 (19)	3 (18)	15 (19)
160=<210	20 (32)	4 (24)	24 (30)
210=<265	8 (13)	2 (12)	10 (13)
265 and above	12 (19)	0	12 (14)
Baby feeding methods			
Exclusive breastfeeding	22 (36)	10 (56)	32 (41)
Exclusive bottle/formula feeding	4 (6.6)	0	4 (5)
Mixed breastfeeding	35 (57)	8 (44)	43 (54)
Birth method			
spontaneous vaginal delivery	62 (93)	19 (100)	81 (94.2)
caesarean section	5 (7.5)	0	5 (5.8)
Birth order			
First born	25 (37)	5 (26)	30 (35)
Second born	19 (28)	9 (47)	28 (32)
Third born and above	24 (35)	5 (26)	29 (33)
HIV tested used			
Antibody	65 (96)	19 (100)	84 (97)
ELISA	3 (4.4)	0	3 (3.0)
CD4 Cell count (Cells/mm)†			
<350	32 (59)	9 (60)	41 (59)
350 and above	22 (41)	6 (40)	28 (41)
Gestation age when starting ARVs			
Before conception	4 (6.9)	1 (5.9)	5 (7)
During pregnancy	26 (45)	11 (65)	37 (49)
After delivery	28 (48)	5 (29)	33 (44)
Baby's age in months			
0-12 months	22 (32)	16 (84)	38 (44)
13-24 months	11 (16)	0	11 (13)
24-36 months	9 (13)	1 (5.3)	10 (12)
36-48 months	15 (22)	1 (5.3)	16 (18)
Above 48 months	11 (16)	1 (5.3)	12 (13)
Baby's gender			
Male	34 (51)	12 (63)	46 (53)
Female	34 (49)	7 (37)	41 (47)
Baby's Birth weight (kgs)	3.2 (2.7-3.5)	3.2 (2.8-3.6)	3.2 (2.8-3.5)
Age in months at which PCR test			
6weeks to 5 months	29 (43)	17 (89)	46 (53)
6 to 11 months	14 (21)	0	14 (16)
12 to 18 months	11 (16)	0	11 (13)
Above 18 months	14 (21)	2 (10.5)	16 (18)

Table 2: Participant's ARV medication regimens

ARV Regimens	Cases	Controls	Overall
NVP/3TC/ABC	25 (37)	0	25 (29)
NVP	1 (1.5)	17 (90)	18 (21)
NVP/3TC/AZT	14 (21)	0	14 (15.5)
KLT/ABC/3TC	11 (16)	0	11 (12.5)
ABC/3TC/LPV/RTV	10 (15)	0	10 (12)
Others	7 (10)	2 (11)	9 (10)
Totals	68	19	87

Others: EFV/ABC/3TC-3, ABC/NVP-2, NVP/AZT/ABC-1, NVP/3TC/TDF-1, AZT/3TC/RTV/LPV-1, ABC/RTV/ LPV-1

When asked to report the last time their children had missed ARV medications 87 mothers responded where 55(63%) of all them reported that their children had never missed any dose of their ARV's, 10 (12%) had missed doses within the previous two weeks, 4 (4.5%) had missed ARV doses within the last month, 13 (15%) had missed ARV's more than a month before while 5 (5.0%) couldn't remember the last time they missed a dose of their ARV's (Table 3).

Table 3: The last time the child missed their ARVs medications

Last time child missed any of medications	Case	Control	Overall
Never skip medications	39 (57)	16 (83)	55(63.4)
Previous 2 weeks	10 (15)	0	10 (11.5)
The last one month	4 (5.9)	0	4 (4.5)
Over a month ago	13 (19)	0	13 (14.9)
Don't remember	2 (2.9)	3 (17)	5 (5.7)
Totals	68	19	87

Overall there was no difference in the ARV adherence between the cases and the controls (chi = 2.13, p= 0.145) within the 3days recall period. However at the one month recall time frame the entire 19 children from the control group had not missed any ARV doses while 14/68 (21%) of the cases reported having missed varying doses of ARVs giving a Fisher's exact value of 0.0034 and P = 0.023.

Table 4: Situations that made it difficult for mothers to give children ARV medications daily

	How often the listed situation made it difficult to give ARVs medication		
Problem identified (N=45)	**1-2 times per month**	**1-2times per week**	**>=3 times per week**
I ran out of medicine	5 (11)	0	0
The medicine tastes bad	2 (4.4)	2 (4.4)	2 (4.4)
I just forgot	6 (13.3)	0	0
I was worried about the side effects	1 (2.2)	0	0
There was a change in daily routine	5 (11)	0	0
Too busy with the baby/child	4 (8.9)	2 (4.4)	0
Child refused to take medicine or spat it out	1 (2.2)	4 (8.9)	0
There are a lot of people looking after the baby	1 (2.2)	0	0
My child was ill	0	1 (2.2)	0
The child was not staying in the house where the medicine was kept	3 (6.7)	0	0
My baby/child was well	1 (2.2)	1 (2.2)	
I was away from home	4 (8.9)	0	0
I was busy with other things	0	0	1 (2.2)

Mothers to 45 (52%) of the 87 children that were taking ARV's reported that they experienced various situations that made it difficult for them to give their children every dose of their ARV medications. Thirty nine of these children (87%) were cases while the other 6 (13%) were controls. However the

difference in the occurrence of the reported difficult situations among cases and controls was not statistically significant (chi-square = 3.29, p=0.07). In summary five caregivers to cases reported that they ran out of drugs while 5/6 (83%) of the caregivers who reported that the medicine tasted bad were mothers to cases. All the six caregivers who reported forgetting to give their children ARV medications were mothers to cases as well as the one caregiver who was worried of side effects of ARV's. Among the caregivers that reported a change in their daily routine which made it difficult to give ARV medications 4/5 (80%) of them were mothers to cases while all the 6 caregivers who reported being too busy with the baby/children were all mothers to cases. Three out of 5 women (60%) who reported that the child refused to take the medicine were mothers to cases while one case caregiver reported there were many people looking after the baby which made it difficult to administer every dose of the ARV medication. Another mother to a case reported the baby/child was ill while 3 mothers to cases reported that their children were not staying in the house where the medicine was kept which made it difficult to administer the medication. Two mothers to cases reported their children were well, 4 mothers to cases were away from home while one case caregiver was busy with other things all of which made it difficult to administer the ARV medication (Table 4).

The detectable child related factors that were associated with non-adherence to ARVs by the children consisted of all the difficulties that mothers encountered while giving ARVs to the children (OR 4.10; 95% CI 1.05-15.93, P-value 0.04) and caregivers forgetting to give ARVs (OR 6.36; 95% CI 1.14-35.61, P-value=0.04). Caregiver specific factors that were associated with children defaulting to take their ARVs within the one month recall time frame included poor maternal ARV adherence (OR 23.33; 95% CI 4.90-111.02, P<0.0001 and 27.2; 5.42-136.59, p<0.0001 at one week and one month periods respectively). Children whose mothers reported encountering situations that made it difficult to administer ARV's were 4 times (OR 4.10) more likely to default taking their ARVs compared to children whose mothers reported that they never encountered any problems when giving their children ARV's . Children whose mothers skipped taking their maternal ARVs had up to 23 to 27 higher chances of failing to take their paediatric ARV doses (OR 23.33-27.2).Other child related factors which we tested such as method of delivery, gender, method of feeding, age and birth weight did not influence their ARV adherence significantly. Neither did maternal factors such as maternal age, family income, level of education, working status and marital status affect the children's ARV adherence.

Table 5: Influence of various maternal –child factors on children's adherence to ART

Maternal-Child factors	Crude OR	p-value	Adjusted OR	p-value
Gender				
Male	1	Reference	1	Reference
Female	0.98 (0.30-3.21)	0.98	1.85 (0.23-14.99)	0.57
Child age in months				
0-12 months	1	Reference	1	Reference
13-24 months	3.19 (0.59-17.16)	0.177	3.77 (0.23-60.98)	0.35
25-36 months	3.64 (0.66-20.01)	0.14	1.57 (0.09-25.54)	0.75
37-48 months	1.96 (0.39-9.99)	0.42	0.86 (0.07-11.05)	0.91
Above 48 months	0.77 (0.08-7.66)	0.83	0.45 (0.01-21.30)	0.69
Age in months when PCR was done				
<18 months	1	Reference		
18 months and above	0.76 (0.15-3.80)	0.73		
Birth weight	1.04 (0.87-1.24)	0.7		
Any problems encountered giving ARVs to child	4.10 (1.05-15.93)	0.04	8.51 (0.64-114.05)	0.11
Ran out of medicine	3.89 (0.59-25.77)	0.16		
Forgot to give medicine	6.36 (1.14-35.61)	0.04	6.41 (0.94-43.76)	0.06
Too busy with the child	1.05 (0.11-9.70)	0.97		
Child refused to take medicine	1.33 (0.14-12.84)	0.81		
Away from home	1.79 (0.17-18.62)	0.62		
Child vomits the drug	2.3 (0.58-9.11)	0.24		
Maternal ARV adherence				
Maternal one week ARV adherence				
Never skipped a dose of ARV	1	Reference	1	Reference
Skipped at least a dose in one week	23.33 (4.90-111.02)	<0.0001	9.79 (0.44-216.92)	0.15
Caregivers one month ARV adherence				

Never skipped a dose of ARV	1	Reference	1	Reference
Skipped at least a dose in previous month	27.2 (5.42-136.59)	<0.0001	9.80 (0.31-314.11)	0.2
Caregiver stayed in hospital ward at least a night	2.57 (0.58-11.47)	0.22		
Birth method				
Spontaneous vaginal delivery	1	Reference		
Caesarean section	1.31 (0.14-12.66)	0.82		
Family's monthly income (Kshs)				
15000 and below	1	Reference		
Above 15000	1.07 (0.29-3.93)	0.92		
Mother's highest level of education				
Primary and below	1	Reference		
Secondary	2.3 (0.71-7.42)	0.16		
College and above	3.54 (0.75-7.42)	0.75		
Birth order				
First	1	Reference		
Second	0.60 (0.13-2.78)	0.51		
Third	1.30 (0.35-4.86)	0.69		
Mother working status				
Working full time	1	Reference		
Working part time	0.97 (0.22-4.16)	0.96		
Not working	0.64 (0.15-2.71)	0.55		
Breastfeeding method				
Exclusive breastfeeding	1	Reference		
Exclusive bottle/formula feeding	5.0 (0.34-72.77)	0.24		
Mixed breastfeeding	2.92 (0.56-15.10)	0.2		
Caregiver age in years				
<25 years	1	Reference		
25 to 30 years	0.58 (0.14-2.42)	0.45		
31 to 35 years	0.79 (0.16-3.79)	0.77		
Above 35 years	1.20 (0.19-7.63)	0.85		
Mother's marital status				
Single	1	Reference		
Married	0.65 (0.15-2.79)	0.56		
Separated/Divorced/Widowed	0.67 (0.09-4.80)	0.69		

DISCUSSION

It is estimated that globally more than 2 million children aged below 2 years are living with HIV/AIDS and nearly 80% of them reside in Sub-Saharan Africa [5]. Owing to high morbidity and mortality rates among undiagnosed HIV+ children it has been advocated that intervention measures should focus on early identification of HIV infected children who should be rapidly initiated on ART [2, 5]. Without access to Cotrimoxazole, ART and supportive care it is reported that one third of HIV+ children die by one year of age and half of them by the second year [6, 7]. The identification of the infected children forms the first component of the EID process and it involves conducting PCR tests on HIV exposed children to establish their serostatus which should be followed by regular antibody tests when the first PCR is negative, a process that should run up to 18 months of life [2]. This study established that just over half (53%) of the HIV exposed children had undertaken their first PCR within the first 6 months of life with 29% of them taking the test between 6 and 18 months while a significant proportion (18%) took their PCR test well beyond the 18 months time frame usually when they were brought to health clinics for illness treatment rather than for HIV follow-up purposes (Table 1). These findings show a higher PCR testing rate when compared to the global statistics where only 8% of infants that are born to women with HIV infection are reported to receive virological testing during the first two months of life [4]. However there are still significant gaps that need to be filled as far as PCR testing is concerned especially given that Nairobi County is not only the capital city of Kenya but it also commands the highest number of EID sites which enjoy heavy presence of both government and non-governmental health infrastructure support that is not necessarily available in the other rural and remote counties in the country. Elsewhere in Sub-Saharan Africa 80% of children in Malawi were referred to ART clinics as a result of provider initiated testing and counseling in acute and chronic care facilities [8]. The above findings from Nairobi County and the Malawi report concur with the global trend where many children have been reported to be entering HIV care and

treatment programmes after being identified in acute and chronic care facilities rather than as a result of follow-up in PMTCT and CCC services [9]. Constraints to accessing EID services have previously been identified and reported to include low knowledge and understanding of the services by service providers and caregivers, lack of EID test kits and delay of providing the results as well as costs of accessing the EID services which range from transport costs to the hospitals, long waiting periods leading to loss in productivity and costs of meals that are taken by the caretaker and accompanying persons while waiting to be served [10, 11]. Although this study did not evaluate the causes that led to the delays we observed in the PCR testing among the HIV exposed children the findings point at weaknesses in the delivery of EID services within Nairobi County. The rapid uptake and retention of children in EID programmes can be improved by developing and using innovative mechanisms to improve transport times and logistics which pose barriers to reaching families that need EID services in a timely manner [9]. This involves strengthening health systems capacities such as establishing networks that effectively link diagnosis with care [9] and also improving community health workers programmes for increased dissemination of EID information to the public [11,12]. The findings of this study clearly expose a gap in the delivery of health services that calls for scaling up of programmes that provide EID services to HIV exposed children in Nairobi County.

The success of the EID programme is connected to the timely initiation of ART among children that are diagnosed to be PCR+ which is further linked to optimum adherence to the ARV drugs. ARV adherence implies that patients should take their medicines in the prescribed quantities and at intervals that they have been instructed along with observation of any accompanying special instructions. Successful HIV treatment requires ARV adherence that is near perfect [12, 13] whereas sub-optimal adherence to ART has been associated with disease progression, increased morbidity due to opportunistic infections leading to a rise in hospitalizations, higher viral drug resistance , decline in CD4 counts and ultimately treatment failure[14, 15, 16] which in turn causes high mortality rates. From this study we established that PCR+ children formed 6.8% of the participants that were not on ARV's. There were no visible reasons or explanations as to why these children were not receiving ARV treatment despite the stipulation by the national treatment guidelines that all children who are PCR+ should be initiated on ART as soon as the diagnosis has been arrived at [2]. Among those children that were taking ARV's a large proportion (37%) of the caretakers reported that their children missed taking their ARV's during various recall time frames as shown in Table 3 above, a figure that is similar to what has been reported in Nigeria and other parts of the world where almost 40% of caretakers reported non-adherence among children on HAART [16, 17]. A systematic review of pediatric ARV adherence studies in middle and low income countries found that estimates of ART adherence levels ranged from 49% to 100% with 76 articles reporting adherence greater than 75% [18]. Achieving optimum ARV adherence still remains a major challenge in many countries [19] yet in order sustain viral load suppression HIV infected children need high levels of adherence with a minimum of 90% of the prescribed medications being taken [20].In this study 7/68 (10.25%) of the children on HAART reported ARV adherence that was below 90% at the 3 days recall period. This figure doubled to 20.5 % at the one month recall period where 14 PCR+ children reported having missed various ARV doses within the previous month (Table 3). Furthermore the children who were PCR+ and receiving HAART exhibited significantly higher levels of non adherence compared to PCR- children that were receiving prophylactic ARV regimens ($p=0.023$) thus leading to rejection of the null hypothesis that there was no difference in ARV adherence between these two groups. Children whose mothers defaulted on their maternal ARV doses showed a 20 fold increase in non-adherence compared to children whose mothers were adherent to their maternal ARV regimens. These findings suggest that women whose children are PCR- and those who are adherent to their own maternal ART have higher motivation to ensure that their children don't miss ARV treatment whether it is for prophylaxis or HAART purposes. The findings reveal that children whose mothers default on ARV are at a higher risk of ARV non adherence and therefore treatment failure. Since maternal ARV non-adherence impacted negatively on children's ARV adherence an opportunity exists to improve children's ARV adherence by addressing the underlying causes that contribute to maternal non adherence. A systematic review and meta-analysis on ART adherence during pregnancy and the postnatal period in low, middle and high income countries reported that only 73.5% of pregnant women achieve optimal ART adherence and that reaching adequate adherence levels was a challenge during pregnancy and especially in the postnatal period [19]. Previous studies in populations of women and children similar to the current study have reported that underlying factors such as poverty, low levels of education, ignorance and stigma reduce maternal ARV adherence [11, 20, 21] even though these factors showed no direct negative impact on the children's ARV adherence in this study. The mothers that we interviewed had rather low formal education majority of them (61%) not having gone beyond primary school while most of them (73%) earned monthly income of less than 210 USD per family (Table 1). Such low levels of maternal education and poverty have been associated with poor maternal ARV adherence [20]. Our findings from this urban low socio-economic population sample highlight important ARV adherence gaps that need to be addressed if the MOH is to realize

the reduction of HIV related morbidity and mortality among children. Maternal-child ARV treatment should be integrated as far as possible into services where their adherence counseling, drug refills and intermittent laboratory testing will be harmonized [10]. The introduction of structural interventions aimed at alleviation of poverty, food-shortages and the hardships of women's lives including educational opportunities, small scale business or job training support and involvement of fathers and partners in child care at the community level are likely to raise the maternal ARV adherence [5, 21] which will in turn impact positively on their children's ARV adherence. Psychosocial issues that demotivate women from adhering to ARV's should also be established and addressed through repeated adherence counseling support [21]. As the Kenyan pediatric ART programmes are scaled up it is expected that challenges for achieving and maintaining ART adherence such as constrained health resources and a high burden of co-morbid diseases that face similar developing nations will continue to be encountered [22, 23]. Measuring and monitoring pediatric ARV adherence is made more complex due to the fact that there is no gold standard measuring tool whereas several monitoring approaches have different strengths and weaknesses (23). Various correlates of adherence which have been reported are grouped as those relating to the medication, the patient, and the caregiver/family [24]. Some of these factors which are well documented reasons for non-adherence to ART such as forgetting to swallow the medicines, running out of drug supplies, feeling of wellness, changes in the daily routine and stigma related issues like not wanting to be seen giving the children medicines were frequently reported among the participants in this study. More than half (52%) of the mothers reported that they encountered various situations that made it difficult for them to give every dose of ARV to their children. The mothers and children in the case and control arms of this study faced similar difficulties in the administration of the ARV's to their children and there was no statistical difference between the two arms as far as the influence that the difficulties they faced had on the children's ARV adherence was concerned (p= 0.07) even though the difficult situations were reported more frequently by mothers to PCR+ children than the mothers whose children were PCR-. This observation therefore leads us to accept the null hypothesis that women who administer ARV's to their children face similar difficulties regardless of whether they are giving prophylactic PMTCT or chronic HAART ARV regimens. To address these issues we recommend the implementation of direct observation treatment strategies, home visits, reminder telephone calls, use of reminder alarms and mobile phone short message service (SMS) reminders which have been reported to complement and improve ARV adherence and monitoring elsewhere [25, 26] yet we did not see them being practiced at the sites in this study.

CONCLUSION

The EID programme in the facilities where we conducted this study within Nairobi County in Kenya faces challenges similar to those that have been reported in other developing nations namely late entry of children into the programmes through delays in PCR testing, delayed initiation of ART among children who test PCR+ and poor adherence to the medications once ART has been initiated. The PCR+ children in this study were less adherent to their ARV medication and therefore more prone to treatment failure with increased risk of morbidity and mortality. Children's non-adherence to ARV's was worsened by poor maternal ARV adherence. Furthermore mothers to both PCR+ and PCR- children faced similar difficulties in administering ARV medications to their children. Based on these findings we recommend the implementation of enhanced health worker driven community engagement programmes that will raise EID awareness and promote early PCR testing among HIV exposed children. We further recommend the addition and routine use of adherence reminder techniques such as SMS alerts and provision of patients with simple alarm devices to the current EID programme strategies. Structural programmes that will address well known factors that demotivate and reduce maternal ARV adherence through poverty alleviation, raising women's levels of education and providing psychosocial counseling support should also be included as part and parcel of the EID programmes. While implementing adherence enhancing techniques the EID programs should also incorporate routine adherence monitoring using various complementary methods. Future surveillance studies on EID uptake and ARV utilization should be extended to remote and rural communities in the country. Further studies need also to be conducted to establish the underlying factors that contribute to the observed lower ARV adherence among PCR+ children as compared to the children that were taking prophylactic ARV's.

ACKNOWLEDGEMENT

We acknowledge with gratitude the approval of this study protocol by JKUAT and the SERU at KEMRI. Further appreciation goes to the Nairobi County Medical officer of health, the Nairobi district medical officers and various health centers in charges and their staff who facilitated and allowed the collection of the study data to take place in their premises of jurisdiction. We thank Moses Ngari for statistical input, the mothers and children who accepted to be interviewed in this study and all those that we are unable to mention individually who assisted us with ideas, data collection and data entry among others. Overall we thank God almighty for making this study to be a reality.

DECLARATION: The authors hereby declare no competing interests in the designing, funding, and conduction of this study.

REFERENCES

1. Ministry of Health; Kenya HIV estimates. 2014. Available from www.nacc.or.ke
2. Kenya National AIDS Control Programme; Guidelines for prevention of mother to child transmission of HIV/AIDS in Kenya. 4th edition, Kenya Government Printers, Nairobi, 2012: 44-48.
3. Kenya National AIDS Control Programme; Early infant diagnosis system. Available from www.nascorp.org/eid
4. World Health Organisation; Towards universal access: scaling up priority HIV/AIDS interventions in the health sector progress report. 2008. Available from http;//www.who.int/hiv/pub/2008progressrport/en/
5. UNAIDS; Global report 2013, From access to adherence: Challenges of antiretroviral treatment. Available from http://who.int/medicinedocs/en/d/js13400el
6. Marston M, Beckeut R, Zaba B, Moulton LH, Gray G, Coovadia H et al.; Net survival of perinatally and postnatally infected children: a pooled analysis of individual data from sub-saharan Africa. International Journal of Epidemiology, 2011; 40(2): 385-396.
7. Newell ML, Coovadia H, Cortina-Borja M, Rollins N, Gaillard P, Dabis F; Mortality of infected and uninfected infants born to HIV-infected mothers in Africa: a pooled analysis. Lancet, 2004; 364(9441): 1236-1243.
8. Ministry of Health, Lighthouse Trust; Center for Disease Control and prevention Malawi. Report of a country-wide survey of HIV/AIDS services in Malawi for the year 2006. Available from http://r4d.dfid.gov.uk/PDF/Outputs/HIV_AIDS/malawi-rep.pdf
9. UNICEF; Scaling up early infant diagnosis and linkages to care and treatment. Available from www.unicef.org/.../Early_Infant_Diagnosis_Briefing_Note_Feb_2009.p
10. Hassan A, Sakwa EM, Nabwera HM, Taegtmeyer MM, Kimutai RM, Sanders EJ et al.; Dynamics and constraints of early infant diagnosis of HIV infection in rural Kenya. AIDS Behav., 2012; 16(1): 5-12.
11. Imbaya CL, Odhiambo-Otieno GW, Okello-Agina BM; Socio-demographic characteristics, Antenatal Clinic attendance and PMTCT knowledge of postnatal HIV+ women at an urban public health facility in Nairobi, Kenya. East and Central Africa Medical Journal, 2014; 1(1): 33-40.
12. Pathfinder International; Strengthening Community and Health Systems for Quality PMTCT: Applications in Kenya, Nigeria, South Africa, and Ethiopia. 2013. Available from http://www.pathfinder.org/../pdfs/Pathfinder-Integrated-Systems-Strengthening-Framework_4Jan13.pdf
13. Paterson DL, Swindells S, Mohr J, Brester M, Vergis EN, Squier C ; Adherence to protease inhibitor therapy and outcomes in patients with HIV infection. Ann Intern Med., 2000; 133(1): 21-30.
14. Panel on antiretroviral therapy and medical management of HIV-infected children. Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection. Available from http://aidsinfo.nih.gov/ContentFiles/PediatricGuidelines.pdf
15. Bangsberg DR, Perry S, Charlebois ED, Clark RA, Roberston M, Zolopa AR; Non-adherence to highly active antiretroviral therapy predicts progression to AIDS. AIDS, 2001; 15(9): 1181-1183.
16. Ugwu R, Eneh A; Factors influencing adherence to paediatric antiretroviral therapy in portharcout, South-South Nigeria. Pan Af Med J., 2013; 16: 30.
17. Reddington C, Cohen J, Baldillo A, Toye M, Smith D, Kneut C et al.; Adherence to medication regimens among children with human immunodeficiency virus infection. Pediatr Infect Dis J., 2000; 19(12):1148-1153.
18. Vreeman RC, Wiehe SE, Sarah E, Pearce EC, Nyandiko E, Winstone M; A systematic review of pediatric adherence to antiretroviral therapy in low- and middle-income countries. Pediatr Infect Dis J., 2008; 27(8): 686-691.
19. Nachega JB, Uthman OA, Anderson J, Peltzer K, Wampold S, Cotton MF et al.; Adherence to antiretroviral therapy during and after pregnancy in Low-income, middle-income and high-income countries: A systematic review and Meta-analysis. AIDS, 2012; 26(16): 2039-2052
20. UNAIDS 2013 Global report; From access to adherence: Challenges of antiretroviral treatment. Available from http://who.int/medicinedocs/en/d/js13400el
21. Ngarina M, Popenoe R, Kilewo C, Biberfeld G, Ekstro N AM; Reasons for poor adherence to antiretroviral therapy postnatally in HIV-1 infected women treated for their own health experiences from the Mitra Plus study in Tanzania. BMC Public Health, 2013, 13: 450.
22. WHO; Scale up of HIV-related prevention, diagnosis, care and treatment for infants and children. World Health Organization, Geneva, 2008. Available from http://www.who.int/hiv/pub/paediatric/framework_2008/en/index.html.
23. Haberer J, Mellins C; Pediatric adherence to HIV antiretroviral therapy. Current HIV/AIDS Reports, 2009; 6(4): 194–200.
24. Simoni JM, Montgomery A, Martin E, New M, Penelope A, Demas P et al.; Adherence to antiretroviral therapy for pediatric HIV infection: A qualitative systematic review with recommendations for research and clinical management. Pediatrics, 2007; 119(6): e1371-ee1383.
25. Lester R, Ritro P, Mills EJ, Kariri A, Karanja S, Chung MH; Effects of a mobile phone SMS on

ARV treatment in Kenya. Lancet, 2010; 376(9755): 1838 -1845.

26. Burns DN, Mofenson LM; Paediatric HIV-1 infection. Lancet, 1999; 354(S2):1–6.
27. Wiznia A, Stanley K, Krogstad P, Johnson G, Lee S, McNamara J; Combination nucleoside analog reverse transcriptase inhibitor(s) plus nevirapine, nelfinavir, or ritonavir in stable antiretroviral therapy-experienced HIV-infected children: week 24 results of a randomized controlled trial-PACTG 377, Pediatric AIDS Clinical Trials Group 377 Study Team. AIDS Res Hum Retroviruses, 2000; 16(12) :1113–1121.