Outcomes of HIV-Exposed Children in Western Kenya: Efficacy of Prevention of Mother to Child Transmission in a Resource-Constrained Setting

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Objectives: To compare rates of mother to child transmission of HIV and infant survival in women–infant dyads receiving different interventions in a prevention of Mother to Child Transmission (pMTCT) program in western Kenya.

Design: Retrospective cohort study using prospectively collected data stored in an electronic medical record system.

Setting: Eighteen HIV clinics in western Kenya.

Population: HIV-exposed infants enrolled between February 2002 and July 2007, at any of the United States Agency for International Development–Academic Model Providing Access To Healthcare partnership clinics.

Main outcome measures: Combined endpoint (CE) of infant HIV status and mortality at 3 and 18 months.

Analysis: Descriptive statistics, χ^2 Fisher exact test, and multivariable modeling.

Results: Between February 2002 and July 2007, 2477 HIV-exposed children were registered for care by the United States Agency for International Development–Academic Model Providing Access To Healthcare partnership pMTCT program before 3 months of age. Median age at enrollment was 6.1 weeks; 50.4% infants were male. By 3 months, 31 of 2477 infants (1.3%) were dead and 183 (7.4%) were lost to follow-up. One thousand (40%) underwent HIV DNA Polymerase Chain Reaction virologic test at a median age of 8.3 weeks: 5% were HIV infected, 89% uninfected, and 6% were indeterminate. Of the 968 infants with specific test results or mortality data at 3 months, the CE of HIV infection or death was reached in 84 of 968 (8.7%) infants. The 3-month CE was significantly impacted (A) by maternal prophylaxis [51 of 752 (6.8%) combination antiretroviral therapy (cART); 8 of 69 (11.6%) single-dose nevirapine (sdNVP); and 25 of 147 (17%) no prophylaxis ($P < 0.001$)] and (B) by feeding method for the 889 of 968 (91.8%) mother–infant pairs for which feeding choice was documented [5 of 29 (17.2%) exclusive breastfeeding; 13 of 110 (11.8%) mixed feeding; and 54 of 750 (7.2%) formula feeding ($P = 0.041$)]. Of the 1201 infants ≥18 months of age: 41 (3.4%) were deceased and 329 (27.4%) were lost to follow-up. Of 621 of 831 (74.7%) infants tested, 65 (10.5%) were infected resulting in a CE of 103 of 659 (15.6%). CE differed significantly by maternal prophylaxis [52 of 441 (11.8%) for cART; 13 of 96 (13.5%) for sdNVP; and 38 of 122 (31.2%) no therapy group ($P < 0.001$)] but not by feeding method for the 638 of 659 (96.8%) children with documented feeding choice [7 of 35 (20%) exclusive breastfeeding, 14 of 63 (22.2%) mixed, and 74 of 540 (13.7%) formula ($P = 0.131$)]. On multivariate analysis, sdNVP (odds ratio: 0.4; 95% confidence interval: 0.2 to 0.8) and cART (odds ratio: 0.3; 95% confidence interval: 0.2 to 0.6) were associated with fewer CE. At 18 months, feeding method was not significantly associated with the CE.

Conclusions: Though ascertainment bias is likely, results strongly suggest a benefit of antiretroviral prophylaxis in reducing infant death and HIV infection, but do not show a benefit at 18-months from the use of formula. There was a high rate of loss to follow up, and adherence to the HIV infant testing protocol was less than 50% indicating the need to address barriers related to infant HIV testing, and to improve outreach and follow-up services.

Key Words: ARV prophylaxis, children, infant feeding, child survival, HIV, Western Kenya, pMTCT

(*J Acquir Immune Defic Syndr* 2010;54:42–50)

Received for publication August 5, 2009; accepted December 18, 2009.

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This study and its findings is original work and has not been presented or published elsewhere.

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INTRODUCTION

Most of the 1.8 million children currently living with HIV in sub-Saharan Africa contracted the infection from their mothers either during gestation, delivery, or through breastfeeding.[1] In the absence of interventions to prevent the passage of HIV from mother to child, transmission rates are approximately 26% in the developed world and as high as

48% in the developing world.[2,3] In resource-rich settings, the use of prepartum and peripartum antiretroviral therapy, cesarean section, and avoidance of breastfeeding have reduced the risk of HIV transmission to less than 2%.[4,5] In sub-Saharan Africa, resource constraints have limited antiretroviral-based prevention of mother to child transmission (pMTCT) strategies to single-dose Nevirapine (sdNVP) and short course antiretrovirals.[6–8] Routine use of cesarean section has not been advocated due to inadequate facilities, a paucity of trained personnel, and the potential for increased maternal morbidity. The use of infant formula as a suitable replacement feed is made challenging in this setting. Due to inadequate access to safe water, the prohibitive cost of formula and the increased rates of diarrheal illness associated with formula, many pMTCT programs in sub-Saharan Africa advocate exclusive breastfeeding for 6 months.[9–12] In addition, the Joint United Nations Program on HIV/AIDS, the World Health Organization and the United Nations Children's Fund recommend consideration of breast milk replacement feeding (infant formula) as a pMTCT strategy in resource-constrained settings only when it is deemed to be affordable, feasible, acceptable, sustainable, and safe.[13,14] Given these constraints, data are limited on the use of maternal triple-drug combination antiretroviral therapy (cART) and infant replacement feeding as pMTCT strategies in sub-Saharan Africa.

Three randomized clinical trials from sub-Saharan Africa using cART initiated during the second or third trimester in combination with infant postexposure prophylaxis have achieved peripartum transmission rates similar to those seen in resource-rich settings.[15–18] In the Allaitement Maternal sous Tritherapie Antiretroviral study, transmission rates at 6 weeks were documented at 1.4%, whereas in the Kisumu Breastfeeding Study (KiBS), they were 2.4%.[15,16] Four-week transmission rates were 1.2% in the Drug Resource Enhancement against AIDS and Malnutrition study conducted in Mozambique.[17] With regard to formula feeding, an early study conducted in Nairobi showed similar mortality rates between breast-fed and formula-fed HIV exposed infants at 2 years.[19] The more recent Mashi study, which compared the combined endpoints (CEs) of mortality and HIV transmission between breast-fed infants treated for 6 months with Zidovudine and formula fed infants treated for one month with Zidovudine, clearly represent the infant feeding dilemma. The formula-fed infants had higher mortality and lower transmission rates, whereas the breast-fed infants had low mortality rates, but higher rates of transmission resulting in no significant difference in the CE outcomes between the groups.[20] Based on the clinical trials presented above, one may conclude that late gestation cART is effective as a pMTCT strategy, whereas the use of infant formula as a safe replacement feed is not. However, the reproducibility of these results within public sector pMTCT programs in sub-Saharan Africa is as yet unknown.

The United States Agency for International Development (USAID)—Academic Model Providing Access to Healthcare (AMPATH) Partnership is a collaboration between Moi University, Moi Teaching and Referral Hospital (MTRH), partner institutions from the United States (lead by Indiana University), and USAID and was originally established to provide HIV care within public sector clinics in western Kenya.[21] The partnership currently provides HIV prevention and treatment services at 18 clinics in western Kenya, all but 1 of which is Ministry of Health (MOH) affiliated. All USAID-AMPATH HIV clinics are linked with the pMTCT program housed within the same facility and provide comprehensive services including cART to HIV-infected pregnant women. Infant feeding education and support is also a key component of the AMPATH pMTCT program, which during the period of this study included the provision of powdered infant formula milk as breast milk replacement to mothers who elected to utilize replacement feeding as a pMTCT strategy. The purpose of this study is to determine outcomes of infants born to HIV-infected mothers cared for within this integrated multidimensional pMTCT program and to evaluate outcomes of the infants based on the various treatment strategies and feeding approaches adopted.

METHODS

Study Design

The study was approved by the Institutional Research and Ethics Committee of the Moi University School of Medicine and Moi Teaching and Referral Hospital and the Institutional Review Board of the Indiana University School of Medicine. This was a retrospective cohort study using prospectively collected deidentified data stored in the computerized medical records system of pediatric and adult patients enrolled in the USAID-AMPATH clinics.[22]

Study Population and Setting

Records of HIV-exposed infants enrolled into the USAID-AMPATH Partnership between February 2002 and July 2007, were reviewed for inclusion into this study. Records were eligible for inclusion if the infant was enrolled before 3 months of age, was at least 6 months of age by October 31, 2007, and had both infant and maternal peripartum prophylaxis data available. These criteria were utilized to increase the probability that the infant had been exposed to the USAID-AMPATH pMTCT program and to ensure that the observation period was adequate to, at a minimum, achieve the 3-month endpoints. USAID-AMPATH electronic medical records from the mothers of these infants were also available and were linked with infant records in order to confirm maternal prophylaxis data.

During the study period, the USAID-AMPATH clinic system operated 18 clinics in western Kenya with the largest urban clinic located at the Moi Teaching and Referral Hospital in Eldoret. The other 17 clinics were located in 1 mission hospital, 2 subdistrict hospitals, 9 district hospitals, and 5 rural health centers located between 26 km and 150 km from Eldoret (Fig. 1). Antenatal clinics were conducted daily at all sites; adult, pediatric, or combined HIV clinics were conducted 2–5 days per week at all sites.[23,24]

Clinical Procedures

Locally developed USAID-AMPATH pMTCT protocols based on World Health Organization guidelines[25] evolved over the duration of the study period in response to changing

FIGURE 1. Geographical distribution of USAID-AMPATH clinics.

international guidelines and newly available information. Throughout the course of the program, women who were eligible for HIV treatment based on their own clinical and immunologic status received cART. The different regimen used between February 2002 and July 2007 are summarized in Table 1. For women receiving cART solely for pMTCT, antiretrovirals were discontinued 1–2 weeks after delivery, whereas women initiating treatment for their own health continued them indefinitely.

During the study period, all HIV-infected pregnant women were counseled on safe infant feeding options and, at the time, the USAID-AMPATH program strongly advocated for formula feeding and provided free powdered infant formula milk for 6 months. Women choosing to breast feed were strongly encouraged to exclusively breast feed and to wean their infants abruptly at 3–4 months of age, a practice that was recommended for HIV-infected breastfeeding women in resource-limited settings during the study period.[9,10,26]

TABLE 1. History of Treatment and Prophylaxis Regimens for HIV-Infected Pregnant Women

Date	Protocol
February 2002 to July 2003	Treatment*: nevirapine, lamivude, and zidovudine or stavudine
	Prophylaxis†: sdNVP during labor; sdNVP to infant
July 2003 to March 2006	Prophylaxis: (all CD4 counts) nevirapine, lamivude and zidovudine or stavudine
March 2006 to July 2007	Prophylaxis: (<250 CD4) nevirapine, lamivude, and zidovudine or stavudine
	Prophylaxis: (>250 CD4) nelfinavir, lamivude, and zidovudine or stavudine
July 2007 to present	Prophylaxis: (<250 CD4) nevirapine, lamivudine and zidovudine or stavudine
	Prophylaxis: (>250 CD4) lopinavir/ritonavir, lamivude, and zidovudine or stavudine

*Treatment = Women meeting World Health Organization criteria for treatment by the 2003 guidelines.

†Prophylaxis = Women not meeting World Health Organization criteria for treatment by the 2003 guidelines who are receiving ARVs only for pMTCT.

Women enrolled in the pMTCT program were asked to enroll their infants at a USAID-AMPATH clinic within 6 weeks of delivery to (1) evaluate infant feeding practices; (2) assess maternal and infant health; (3) evaluate infant HIV status; and (4) initiate cotrimoxazole prophylaxis. Once enrolled in the USAID-AMPATH clinic, these infants were seen monthly until 6 months of age and then every 3 months until 18 months of age. Per protocol, HIV-exposed infants received prophylactic cotrimoxazole from 6 weeks of age until documented to be HIV negative and no longer breastfeeding, whereas HIV-infected children continued to receive prophylaxis indefinitely. During the study period, infants received growth monitoring and treatment for intercurrent illnesses through the USAID-AMPATH clinics but were referred to the Maternal Child Health Clinic at their local health facility for immunizations.

Per protocol, infant HIV infection status was evaluated throughout the study period using an HIV DNA Polymerase Chain Reaction (PCR) (Amplicor, Roche, Basel, Switzerland). A DNA PCR was considered to be at the 3-month time point if it was obtained anytime between 6 and 12 weeks after birth. If the initial PCR was positive, repeat testing was performed during the infant's next clinic visit. Infants for whom the initial PCR was positive and the subsequent PCR was negative were tested a third time. Infants were classified as HIV positive at their 3-month time point (1) if they had 2 sequential positive PCRs; or (2) if 2 of 3 PCRs were positive; or (3) if 1 PCR was positive at 3-month time point and the 18-month HIV test was also positive. Initial negative PCR tests were not repeated unless there was a change in the child's clinical status before 18 months of age. At 18 months, all HIV-exposed infants had parallel HIV rapid tests using Bioline and Determine or a long enzyme-linked immunosorbent assay (ELISA) performed. An antibody test done anytime between 15 and 20 months of age was considered to be representative of the 18-month time point. Due to difficulties procuring HIV DNA test kits from January to August 2005, HIV DNA PCR testing was limited during this period. The results of CE of death or HIV infection at 3 months were carried forward to18 months. In addition, we assigned the 3-month results at the 18-month period if we had missing information on the CE at the later evaluation.

Data Collection and Management

Clinicians completed standard initial and return encounter forms at all USAID-AMPATH clinic visits for both the mothers and their infants (http://amrs.iu-kenya.org/download/forms). The initial maternal encounter form included standard demographic, birth and maternal prophylaxis history, dietary intake, social, physical, and laboratory data, and medications taken (antiretroviral drugs and opportunistic infection prophylaxis). The infant initial encounter form also included information about maternal peripartum antiretrovirals and details about the baby's delivery. At each subsequent clinical encounter with the mother–infant dyads, follow-up data were collected on intercurrent symptoms, medication adherence,

new diagnoses, laboratory data, and modifications in medication regimens. Dedicated data entry clerks entered this information into the USAID-AMPATH electronic medical record system.[22] Data were abstracted into SAS where infant and maternal data were linked using the mothers' USAID-AMPATH identification number. Data on peripartum antiretroviral prophylaxis were confirmed by maternal and infant clinical records. If the information differed, data from the mother's chart were used in the final data analyses, as these were considered to be the most accurate with regard to maternal prophylaxis.

Statistical Methods

The outcomes of interest for this study were the CE of death or HIV infection documented by 3 and 18 months of age among HIV-exposed children. The groups of interest were divided into maternal antiretroviral status: none, sdNVP, cART, and infant feeding modality used: breastfeeding, mixed feeding, and formula feeding.

Descriptive statistics such as mean, standard deviation, median, and range were used for the continuous variables, whereas frequency listings were used for categorical variables. The χ^2 test was used to assess any association between categorical variables. If any of the cell counts were below 10 then the Fishers exact test was used. Multivariate logistic regression was used to assess the association between a binary outcome and a number of explanatory variables simultaneously in the model. These variables included type of antiretroviral therapy (ART) (triple therapy, sdNVP, or no prenatal ART), feeding method information at 6 months (formula feeding, breastfeeding and mixed feeding), and type of clinic site (referral hospital, district hospital, or rural health center). Given the fact that the AMPATH pMTCT protocol at the time included triple therapy and encouraged formula feeding, we included interactions between feeding method and type of ART in the model as a higher proportion of mothers who were formula feeding their children were also receiving triple therapy, whereas a higher proportion of breastfeeding and mixed feeding mothers were receiving sdNVP or no prenatal ART. We also included mother's CD4 count at delivery, 3, 12, and 18 months post to a multivariate logistic regression model of HIV-positive status at 18 months and CD4 count at delivery and 3 months to a multivariate logistic regression model of HIV-positive status at 3 months. This was done in a subset of mother–baby pairs where it was possible to link the mother with her baby and where maternal CD4 data were available. We intended this as a sensitivity analysis to support the main thrust of our conclusions which were based on the entire database.

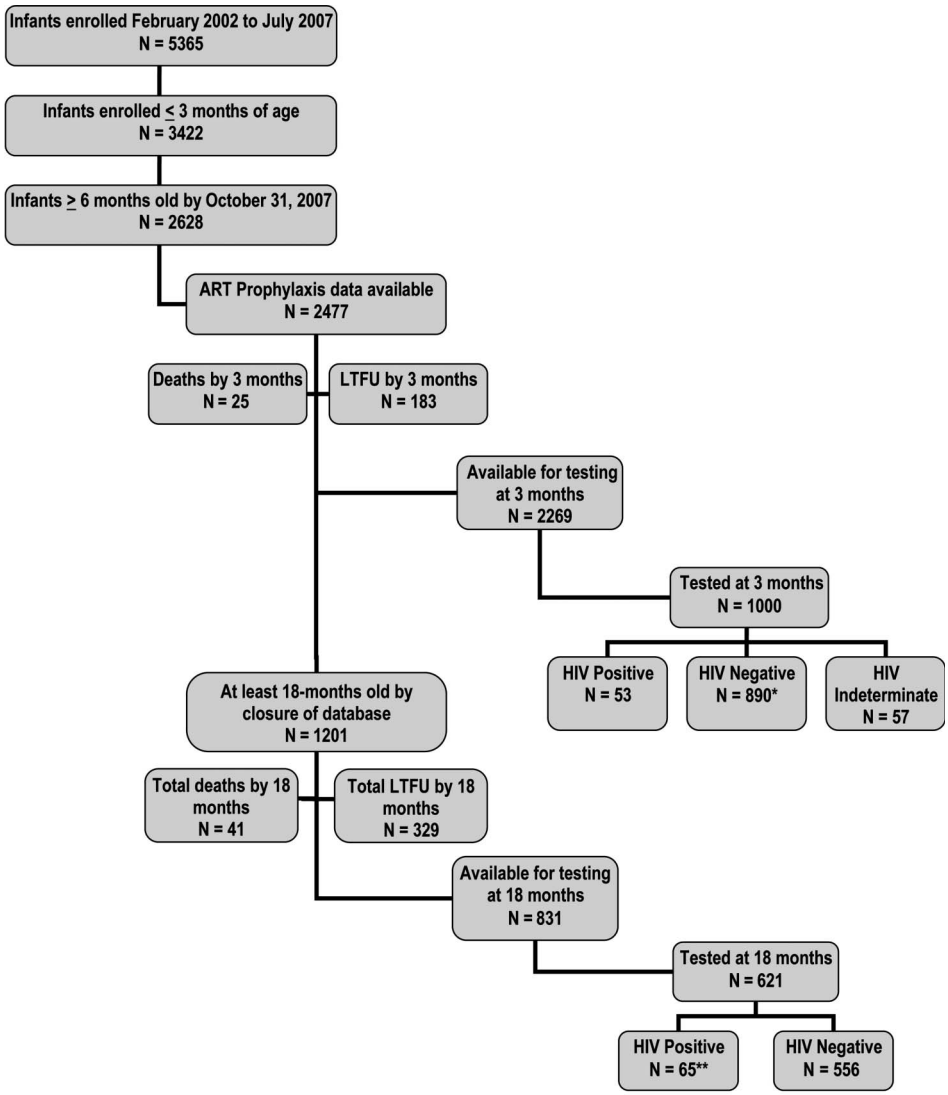
For this study, loss to follow-up was defined as a period of more than 3 months without a visit for children receiving cART or a period of more than 6 months without a visit for those not receiving cART. Rates of lost to follow-up (LTFU) were calculated by the method of Kaplan and Meier. Children who were LTFU were considered as having been lost at the time of their last visit, whereas those who remained in follow-up until the end of the study were censored at that time point. We explored the possibility of bias from the nonavailability of HIV or vital status due to loss to follow-up and missing data. We imputed the missing tests according to various scenarios assuming different rates of transmission in the group of children with missing test data. These scenarios included rates of HIV transmission and death equal to those in the observed data plus a number of scenarios where rates of HIV transmission and death among children with missing data were multiples of the observed rates by a factor in a spectrum from 0.5 to 2.0, that is, from half of the observed rates to double those observed in the available data. This analysis was done in both the 3-month and the 18-month time point.

RESULTS

Of 5365 children enrolled between February 2002 and July 2007, 3422 were less than 3 months of age and 2477 of these had peripartum prophylaxis data and were at least 6 months old by October 31, 2007, (Fig. 2). The median age at enrollment for these infants was 6.1 weeks and 50.4% were male. The majority of infants were born by spontaneous vertex vaginal delivery (56.2%). Nine hundred eighty-six (39.8%) infants were enrolled at the HIV clinic located in the Moi Teaching and Referral Hospital with 865 (34.9%) of them enrolled at district or subdistrict hospital sites and 626 (25.3%) in rural health centers (Table 2). Among the 2477 infants enrolled in the USAID-AMPATH program, 1783 (72%) were born to mothers who received cART and 1861 (75.1%) received formula (Table 2).

By 3 months of age, 31 of 2477 (1.3%) infants were deceased and 183 (7.4%) were LTFU. LTFU rates per feeding group were 8.0% for formula-fed infants, 23.5% in exclusively breast-fed infants, and 12.8% in mixed-fed infants. One thousand HIV-exposed babies 1000 of 2477 (40%) underwent HIV DNA PCR testing at a median of 8.3 weeks of age. At the 3-month time point, 53 of 1000 (5.3%) were found to be HIV infected, 890 of 1000 (89%) uninfected, and 57 of 1000 (5.7%) indeterminate (Fig. 2). Table 3 shows transmission by ART and feeding groups for those infants with definitive HIV test results (n = 943). LTFU and incomplete testing led to a missing CE in 32.5%, 50.5%, and 67.8% cases in formula-fed, mixed-fed, and breast-fed infants, respectively.

Among the infants not tested at 3 months, there were 25 who died by 3 months of age. There were also 6 deaths among the 890 infants who tested negative for HIV for a total of 31 deaths by 3 months. Of the 968 infants with specific test results or mortality data at 3 months, the CE was reached in 84 (8.7%) infants. The 3-month CE was significantly impacted by maternal prophylaxis with 51 of 752 (6.8%) infants born to mothers who had received cART, 8 of 69 (11.6%) sdNVP and 25 of 147 (17.0%) no antiretrovirals meeting criteria for the CE ($P < 0.001$). In the 889 of 968 (91.8%) infants with feeding data, attainment of the 3-month CE also differed by feeding method with 5 of 29 (17.2%) meeting the CE in the exclusive breastfeeding group, 13 of 110 (11.8%) in the mixed feeding group and 54 of 750 (7.2%) in the formula feeding group ($P = 0.041$) (Table 4). In a multivariate logistic regression analysis at 3 months, cART was found to reduce probability of CE by 60%, whereas formula feeding was not found to significantly impact CE rates once the effect of cART was considered in the statistical model (Table 5).



* There were 6 deaths among the 890 HIV-negative infants. Thus, there were 31 total deaths observed by three months.
** There were 3 deaths among the 65 HIV-positive infants at 18 months.

FIGURE 2. Patient schema.

Because of the large number of children with missing endpoints, we performed a sensitivity analysis where we imputed the missing data under a number of scenarios. This analysis showed that if the children with missing data had similar rates of CE to those children with available data, then feeding method was a significant predictor of the 3-month CE with formula showing a protective effect.

Of the 1201 infants who had attained the age of 18 months by the close of the study period, 41 (3.4%) were deceased and 329 (27.4%) were LTFU (Fig. 2). LTFU rates per feeding group by 18 months were 28.8% in the formula feeding group, 43.9% in the exclusively breast-fed group, and 39.0% in mixed-fed infants. Of the 621 of 831 (74.7%) children tested at the 18-month time point, 65 (10.5%) were infected (3 of whom were also deceased), resulting in an 18-month CE of 103/659 (15.6%) (Table 3). "LTFU and incomplete testing led to a missing CE in" 43.3%, 55.9%, and 51.4% for formula, mixed, and breast-fed infants, respectively. The CE differed significantly by maternal prophylaxis with 52 of 441 (11.8%) of mothers having received cART, 13 of 96 (13.5%) sdNVP, and 38 of 122 (31.1%) no antiretrovirals ($P < 0.001$) (Table 4). In the 638 of 659 (96.8%) children with documented infant feeding method, attainment of CE did not differ according to feeding method, with 7 of 35 (20%) meeting the CE in the exclusive breastfeeding group, 14 of 63 (22.2%) in the mixed feeding group, and 74 of 540 (13.7%) in the formula feeding group ($P = 0.131$) (Table 4). In a multivariate analysis at 18 months, sdNVP reduced attainment of the CE by 60% and cART by 70% compared with the no-prophylaxis group (Table 5). A sensitivity analysis similar to that described above for the 3-month CE was preformed for the 18-month outcomes and showed that only when the

TABLE 2. Infant Characteristics

Characteristic	N = 2477 Median (Range)
Age at enrollment (wks)	6.12 (0.14–13.0)
Gender, n (%)	
Male	1248 (50.4)
Female	1229 (49.6)
Clinic Type	
Referral hospital	986 (39.8)
District/ subdistrict hospital	865 (34.9)
Rural health center	626 (25.3)
Mode of delivery	
Spontaneous vaginal delivery	1391 (56.2)
C-section	102 (4.1)
Breech	5 (0.2)
Other	15 (0.6)
Unknown	964 (38.9)
ART Prophylaxis	
Nothing	508 (20.5)
Single-dose nevirapine (mother/baby)	186 (7.5)
Combination ART (mother)	1783 (72.0)
Infant feeding	
Breast fed	119 (4.8)
Replacement feeding (formula)	1861 (75.1)
Mixed	332 (13.4)
Unknown	165 (6.7)

proportion of missing endpoints were considered to be twice that observed in infants with available data did feeding type become statistically significant.

We performed 2 multivariate logistic regression models of HIV transmission at 3 and 18 months, which included the maternal CD4 data. Both models showed an overall downward trend of transmission rates with increasing CD4 count at delivery and 3 months. A less discernible association of HIV transmission rates at 18 months was observed with respect to CD4 count at 12 and 18 months. Adjusted for maternal CD4 count at delivery and at 3 months (infant HIV-positive status at 3 months) and maternal CD4 count at delivery, 3, 12, and 18 months (infant HIV-positive status at 18 months), the results with respect to feeding method and prenatal ART prophylaxis were the same as in the overall analysis.

DISCUSSION

Three major findings arise from this observational cohort study. First, a significant reduction in infant HIV infection and death was documented at both the 3-month and 18-month time points for infants whose mothers received antiretroviral prophylaxis, with prenatal cART conferring a greater benefit than sdNVP. Second, based on the multivariate analysis, no benefit in formula feeding was found at the 18-month time point in this population. Finally, we identified several potential challenges for pMTCT programs scaling up in resource-limited settings including high infant losses to follow-up and incomplete clinician adherence to clinical guidelines. We discuss these 3 key findings and then highlight the changes adopted by the program in response to some of the challenges of implementing a pMTCT program in this setting.

There was strong evidence supporting a significant benefit arising from using cART during pregnancy in this public sector clinic setting. However, the 3.5% transmission rate at 3 months documented in the cART prophylaxis group is higher than previously reported rates from Europe and clinical trials in sub-Saharan Africa.[4,5,15–17] We believe that the majority of the discrepancy between our early HIV transmission rates and those seen in Allaitement Maternal sous Tritherapie Antiretroviral, KiBS, and Drug Resource Enhancement against AIDS and Malnutrition are related to follow-up and testing biases associated with our high LTFU rates and our clinicians' incomplete adherence to testing protocols. We hypothesize that mothers are more likely to adhere to visits, and clinicians are more likely to perform HIV testing on children who seem ill rather than those who seem healthy, thus increasing the likelihood of PCR testing among HIV-infected infants. Failure to provide antiretroviral prophylaxis to neonates born to women who received more than 4 weeks of cART may also have contributed to higher transmission rates. However, this would be inconsistent with Pediatric AIDS Clinical Trials Group 316 which found no benefit from either maternal or infant sdNVP in the face of previous cART therapy.[27] Though not assessed in this study, it is possible that adherence in HIV-infected pregnant women attending public sector HIV clinics may be lower than for women who are targeted for and are motivated enough to enroll in a clinical trial. Taken together, these last 2 issues may

TABLE 3. HIV Transmission at 3 and 18 Months By pMTCT Intervention

pMTCT Intervention	3 Months, N	3 Months, HIV (%)	3 Months, *P* Value	18 Months, N	18 Months, HIV (%)	18 Months, *P* Value
Antiretroviral prophylaxis						
No prophylaxis	141	19 (13.5)	<0.0001	111	27 (24.3)	<0.0001
sdNVP	69	8 (11.6)		94	11 (11.7)	
cART	733	26 (3.6)		416	27 (6.5)	
Total	943	53 (5.6)	—	621	65 (10.5)	—
Feeding option in early infancy						
Exclusive breastfeeding	28	4 (14.3)	0.013	33	5 (15.2)	0.083
Mixed feeding	107	10 (9.4)		59	10 (17.0)	
Formula feeding	733	33 (4.5)		511	45 (8.8)	
Total	868	47 (5.4)	—	603	60 (10.0)	—

TABLE 4. CE of HIV Transmission and Death at 3 and 18-Months By pMTCT Intervention

pMTCT Intervention	3 Months, N	3 Months, CE (%)	3 Months, *P* Value	18 Months, N	18 Months, CE (%)	18 Months, *P* Value
Antiretroviral prophylaxis						
No prophylaxis	147	25 (17.0)	<0.001	122	38 (31.1)	<0.001
sdNVP	69	8 (11.6)		96	13 (13.5)	
cART	752	51 (6.8)		441	52 (11.8)	
Total	968	84 (8.7)	—	659	103 (15.6)	—
Feeding option in early infancy						
Exclusive breastfeeding	29	5 (17.2)	0.041	35	7 (20.0)	0.131
Mixed feeding	110	13 (11.8)		63	14 (22.0)	
Formula feeding	750	54 (7.2)		540	74 (13.7)	
Total	889	72 (8.1)	—	638	95 (14.9)	—

indicate the need to reassess the use of postpartum infant Nevirapine prophylaxis in populations where optimal adherence to cART is not consistently achieved. Furthermore, although adherence to the chosen infant feeding method was not measured in this study, we are cognizant of the fact that despite the mothers' selected method of feeding, mixed feeding was not always reported and may be an undocumented contributing factor to the transmission rates. Similarly, adherence to the ARV's was not explicitly measured and no specific adherence support protocol outside the routine clinic follow-up was in place during the period of this evaluation.

Despite the more intensive antenatal prophylaxis received by most of USAID-AMPATH cohort, the CEs (death and HIV transmission) at 3 months (7.2%) and 18 months (13.7%) found in the formula-fed infants are strikingly similar to those seen in the Mashi Study. In that study, CEs at the 1-month and 18-month time points were 8.9% and 13.9%, respectively.[20] As with the Mashi Study, we found no added benefit to formula feeding when compared with exclusive breastfeeding as a postpartum HIV prevention strategy. When we imputed missing endpoints occasioned by LTFU and missing HIV testing results, formula feeding was significantly associated with a decrease in CE at 3 months but did not seem to be significantly associated with the CE at 18 months. Thus, a possibly significant effect of feeding method on early HIV transmission cannot be discounted by our data, but there is no support of an impact of feeding method on late infection.

Our program, like other pMTCT programs in sub-Saharan Africa, has documented very high loss to follow-up rates.[28–30] Based on our experience, the following factors account for the majority of the loss to follow-up: competing health priorities, parental fear of receiving positive test results, transportation issues, family/employment obligations, and unreported deaths.[31] With regard to competing health priorities, immunization services are currently not available in the HIV clinic; thus for a healthy looking child, mothers may decide that attendance at the immunization clinic takes priority over the HIV clinic. In the Eldoret USAID-AMPATH clinic site where mother–child visits are not combined, pediatric patient visits are conducted in a separate module operated by the Division of Paediatrics. In this scenario, mothers may choose their own health care needs above those of their child, particularly if the children are asymptomatic.

Among those children retained in the cohort, the infant HIV testing rates at or before 3 months were disappointingly low. Similarly, only half of the children retained in care at 18 months of age had a 15–18 months ELISA documented. An informal analysis of the reasons for failure to test within our program revealed 4 key issues (1) HIV DNA PCR reagent shortages in the country, (2) maternal fear of infant phlebotomy, (3) clinicians forgetting to order tests, and (4) undocumented 18-month HIV ELISAs due to testing in the Voluntary Counseling and Testing Site rather than the HIV Clinic.

TABLE 5. Multivariate Analysis of CE at 3 and 18 Months By pMTCT Intervention

pMTCT Intervention	3 Months, OR	3 Months, 95% CI	18 Months, OR	18 Months, 95% CI
Antiretroviral prophylaxis				
No prophylaxis	Referent	Referent	Referent	Referent
sdNVP	0.7	0.3 to 1.9	0.4	0.2 to 0.8
cART	0.4	0.2 to 0.8	0.3	0.2 to 0.6
Feeding option in early infancy				
Exclusive breastfeeding	Referent	Referent	Referent	Referent
Mixed feeding	0.7	0.2 to 2.1	1.3	0.5 to 3.7
Formula feeding	0.5	0.2 to 1.4	1.0	0.4 to 2.5

CI, confidence interval; OR, odds ratio.

The greatest strength of this study is that it is conducted in the real world setting of MOH facilities in western Kenya. As a result, the findings of our study are more likely to reflect actual outcomes of cART interventions for pMTCT within public sector facilities in East Africa than do results from randomized clinical trials, even those conducted within sub-Saharan Africa. Another major strength of this investigation is the fact that data gathered from USAID-AMPATH facilities are representative of every level of the MOH health care system, from the rural health centers to the referral hospital. As a result, these findings are potentially applicable to a variety of health care settings within sub-Saharan Africa. These data must be interpreted in the context of the study design that has high LTFU rates and relatively low HIV testing rates in our exposed infant cohort. In addition, adherence to medications was not studied. As such, the results of this intervention cannot be confirmed without further studies.

Program Response to Challenges in Implementation

Based on the results of this analysis, and the preliminary results from the KiBS study, our program changed its policy on infant feeding in January 2008.[16] The USAID-AMPATH program currently advocates exclusive breastfeeding and cART with a goal of weaning between 6 and 8 months at which time women with pre-cART initiation CD4 counts >350 cells per cubic millimeter discontinue antiretroviral therapy. We are also assessing the outcomes of a small cohort who received a safe water and infant formula intervention under close monitoring by Community-Owned Resource Persons or community health workers.[32]

Due to the high loss to follow-up of mother–baby pairs, we implemented aggressive methods to identify and locate those not returning for appointments by sending our outreach team to trace them early.[31] We have also introduced more aggressive adherence counseling for mothers using cART during pregnancy and breastfeeding.

To address the issue of conflicting priorities by mothers and caregivers of children within our program, we have introduced the practice of HIV DNA PCR testing in the immunization clinic at MTRH and are linking the pediatric immunization data with the USAID-AMPATH ambulatory Medical Records System at 3 of our rural health centers. We hope to expand this to all of the program sites. Joint mother–child clinic visits are being conducted at the 17 other clinics, and discussions are underway as to how best to conduct joint clinic visits within the MTRH clinic in Eldoret. We are also in the process of assessing the logistics of providing infant immunization within the HIV clinic similar to what is described by Rollin et al.[33]

With regard to the issue of reagent shortages, the increasing number of programs conducting HIV DNA PCR testing in Kenya has provided an impetus for suppliers to consistently maintain stocks of reagents. In addition, the development of a laboratory consortium in western Kenya has allowed for the sharing of reagents between laboratories when stocks are low. Consequently, we have not encountered a reagent stock-out in nearly 2 years. To address maternal fears related to infant phlebotomy, USAID-AMPATH introduced the use of a heel prick dry blood spot technique in June 2008, a procedure which is much less invasive than phlebotomy. The program has also intervened in a number of ways to address the issue of clinician forgetfulness: at each site, we have identified a clinician to be responsible for pMTCT and have introduced pMTCT logs which track data (including HIV DNA PCR testing) on all pMTCT patients and their infants. These logs are reviewed quarterly and feedback is given to the clinician responsible for pMTCT at each site. We are also in the process of programming our electronic medical records system to produce a monthly report of all infants eligible for DNA PCR and to produce pediatric patient summary sheets which will include clinician reminders to perform HIV testing at the specified intervals. To address 18-month testing rates, we are considering introducing clinician or nurse based rapid HIV-testing into all clinics where HIV-exposed children are seen.

CONCLUSIONS AND RECOMMENDATIONS

We found that cART prophylaxis utilized within a large pMTCT program is both feasible and efficacious for reducing infant death and HIV transmission but that replacement feeding using formula does not seem to provide benefit at 18 months in this setting. Loss to follow-up rates for infants in this cohort were high and likely reflect the experience in other public pMTCT programs and clinical cohorts throughout sub-Saharan Africa.

It is therefore imperative that pMTCT programmatic priorities include identification of the reasons for LTFU and development of innovative ways to ensure follow-up and determination of outcomes among HIV-exposed infants. Provider adherence to infant HIV testing protocols was poor, indicating an urgent need to develop interventions that will ensure providers adhere to such protocols.

ACKNOWLEDGMENTS

This research was supported in part by a grant to the USAID-AMPATH Partnership from the United States Agency for International Development as part of the President's Emergency Plan for AIDS Relief (PEPFAR) and the East Africa International epidemiologic Databases to Evaluate AIDS (IeDEA) NIH grant number U01 AI069911. The authors give special thanks to the families and to the health care providers of USAID-AMPATH, including the consultant physicians and pediatricians, medical officers, nurses, clinical officers, nutritionists, pharmacy staff, outreach workers, social workers, and Community-Owned Resource Persons all who work tirelessly to ensure an HIV-free generation of children in western Kenya. We also would like to thank the data management team, including the data entry clerks for their tireless efforts at keeping our data usable. Finally, we would like to thank all the members of the pMTCT Working Group for continuously being ready to change care protocols depending on the available evidence.

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