Extended antenatal antiretroviral use correlates with improved infant outcomes throughout the first year of life

Maria C. Marazzi, Giuseppe Liotta, Karin Nielsen-Saines, Jere Haswell, Nurja A. Magid, Ersilia Buonomo, Paola Scarcella, Anna M. Doro Altan, Sandro Mancinelli and Leonardo Palombi

Objectives: To evaluate the effect of extended antenatal triple antiretroviral therapy (ART) on infant outcomes.

Design: Retrospective cohort study using pooled data from health clinics in Malawi and Mozambique from July 2005 to December 2009.

Methods: Computerized records of 3273 HIV-infected pregnant women accessing Drug Resource Enhancement Against AIDS and Malnutrition centers were reviewed. ART regimens consisted of nevirapine-based HAART as of 14–25 weeks gestation until 6 months postpartum. Infant infection was determined at 1, 6 and 12 months of age by branched DNA.

Results: A total of 3071 pregnancies resulted in 3148 live births. Lost to follow-up, infant deaths and HIV-1 infection rates at 1 and 12 months were 1.3 and 11.5, 0.8 and 6.7 and 0.8 and 2.0, respectively. Infant HIV-1-free survival at 12 months was 92.5%. Mother-to-child transmission and/or infant deaths correlated with length of maternal antenatal ART by multivariate analysis at 1, 6 and 12 months: 14% in women with more than 30 days of triple antenatal ART and 6.9% in mothers receiving at least 90 days of antenatal ART, $P = 0.001$. Fifty percent of 54 episodes of transmission occurred in women with higher CD4 cell counts (>350 cells/μl). Infant mortality was 67/1000, lower than background rates (78–100/1000). Growth failure (weight-for-age Z score <−2) was present in 8% of infants around birth, 6% at 6 months, 23% at 12 months (lower than country-specific rates).

Conclusion: Extended antenatal ART is protective against adverse infant outcomes up to 12 months of age even in children born to mothers with higher CD4 cell counts.

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Keywords: antenatal triple antiretroviral therapy, HIV, infant outcomes, maternal HAART, prevention of mother-to-child-transmission

Introduction

The use of triple antiretroviral therapy (ART) for prevention of HIV-1 mother-to-child transmission (PMTCT) during pregnancy has proven to be extremely effective [1,2]. Currently, HIV-1 MTCT rates fall below 1% in the Western world, including mid-developed countries [3,4]. In sub-Saharan Africa, the use of triple ART for PMTCT purposes, although promising, has been primarily restricted to research settings. Owing to challenges in implementation, cost and feasibility, often viewed as insurmountable by policy makers, the

Division of Infectious Diseases, David Geffen UCLA School of Medicine, Los Angeles, California, USA.
Correspondence to Dr Karin Nielsen-Saines, MD, MPH, Division of Infectious Diseases, David Geffen UCLA School of Medicine, MDCC 22-442 10833 LeConte Ave, Los Angeles, CA 90095, USA.
Tel: +1 310 206 6640; fax: +1 310 825 9175; e-mail: knielsen@mednet.ucla.edu
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generalized use of triple ART in pregnancy has remained vastly restricted and often perceived as controversial despite its long established track record of efficacy and safety in developed countries.

We previously reported HIV-1 transmission rates of 5.3% at 6 months of age in 958 Mozambican infants born to women who received triple ART during pregnancy and infant formula with water filters in the postpartum period [5]. In a subsequent study of 879 similarly managed infants from Mozambique, Malawi and Tanzania, we reported HIV-1 transmission rates of 2.7% at 6 months of age [6]. In a small prospective study of 341 infants enrolled in Mozambique, whose mothers received triple ART antenatally and postpartum while breastfeeding, we reported HIV-1 transmission rates of 1.2% at 1 month, 1.9% at 6 months and 2.8% at 12 months of age, with an HIV-1 free infant survival rate of 93% at 12 months [7]. In order to evaluate the overall impact of maternal ART in our population, we conducted a detailed analysis in our largest cohort of mother-infant pairs evaluated to date. Parameters included: infant outcomes: HIV-1-free survival to 12 months of age and growth parameters; maternal outcomes: mortality, antiretroviral toxicities and development of antiretroviral resistance; pregnancy outcomes: miscarriage, stillbirth and prematurity rates. Infant outcomes are reported.

Materials and methods

Data was pooled from all Drug Resource Enhancement Against AIDS and Malnutrition (DREAM) centers in Mozambique and Malawi for a retrospective cohort study. All files available for mother-infant pairs followed in PMTCT programs from July 2005 to December 2009 were reviewed.

Study population

HIV-1-infected women followed at DREAM or DREAM-Project Malawi centers for prenatal care and their live-born infants. Inclusion criteria: antenatal care at a DREAM/DREAM-Project Malawi center; availability of pregnancy outcome data: miscarriage, stillbirth or delivery of a live-born infant; intent to follow-up in program; maternal informed consent to participate in program; intent to breast-feed. Patient selection for the retrospective cohort was based on fulfillment of entry criteria. Patients were referred to the program from surrounding institutions or self-referred. Data was analyzed in a blinded fashion with removal of patient identifiers. The study was approved by institutional review boards and regulatory institutions in Italy, Mozambique and Malawi.

Data collection

Maternal demographics, obstetrical and medical history (antiretroviral history and duration), gestational age, BMI, mortality data and HIV-1 laboratory parameters (virus load by HIV-1 RNA PCR and T-cell subsets) and general laboratory parameters (hemoglobin and transaminases) were collected. Infant data included medical history, birth weight/ weight in the first week of life, periodic measures of weight and height, HIV-1 infection status as measured by HIV-1 bDNA assays at 1, 6, and 12 months of age, hospitalizations and mortality data. All participating centers had electronic records with computerized access to medical, nutritional, and laboratory data.

Drug Resource Enhancement Against AIDS and Malnutrition antiretroviral treatment guidelines

Triple ART is provided at DREAM centers to HIV-infected patients according to WHO guidelines as part of a comprehensive care package, which also provides nutritional supplementation to those with low BMI, AIDS-defining conditions, and pregnancy/lactation [6]. Antiretroviral treatment was initiated at 14 weeks of gestation for women who required it for their own health (CD4 cell count of less than 350 cells/μl) or at 25 weeks of gestational age if prescribed for PMTCT purposes. Triple ART were maintained until 6 months postpartum if women chose to breastfeed and indefinitely if patients fulfilled treatment criteria. At 4–5 months postdelivery, women on ART for PMTCT were counseled to wean their infants over the next 2 months, a process supervised by nutritionists. ART were stopped once weaning was completed. An outreach program run by community activists provided support.

Statistical analysis

SPSS v. Win 16.0 (SPSS Inc., Chicago, Illinois, USA) was used for data analysis. Data was censored at the time of death, or at the last visit for patients were lost to follow-up, or at 31 December 2009. Ninety-five percent confidence intervals for incidence of transmission were calculated and Pearson r^2 test was used for the assessment of potential differences in HIV-1 transmission events according to length of maternal predelivery ART. To assess the impact of ART on transmission, data was dichotomized according to baseline CD4 cell counts and viral load in order to generate odds ratio (OR) for each strata and a cumulative Mantel–Haenszel OR for all strata. Binary logistic regression forward stepwise models were performed for the two main outcomes: pediatric HIV infections and infant mortality. For evaluation of HIV-free survival, a multivariate Cox proportional survival analysis by predelivery length of ART was performed.

Results

Records available for 3273 mothers followed at DREAM centers in Malawi and Mozambique from July 2005 to December 2009 were reviewed. As this was an evaluation of patients attending a public health program and not an

interventional clinical trial, women presented to medical care at different time points and not at strict intervals for treatment initiation. Some women were late presenters and sought medical care at delivery or shortly after delivery, not receiving extended prenatal triple ART.

HIV-1 mother-to-child transmission and infant HIV-free survival

As outlined in Fig. 1, of 3273 pregnancies, 3071 came to term with 3148 live births. Maternal death occurred in 1.2% with 21% occurring in the immediate postpartum period. By 1 month of age, 1.3% of infants were lost to follow-up, 0.8% died and 0.8% became HIV-infected. By 6 months, an additional 1.6% of infants were lost to follow-up, an additional 2.6% died and an additional 0.9% were HIV-infected. By 12 months, an additional 9.3% were lost to follow-up and 3.5% additional infants died with an additional 0.3% HIV-infections. Thus by 12 months, cumulative rates included: HIV-infection 2.0%, infant mortality 6.7%, and loss to follow-up 11.5%. HIV-1 free-survival was 92.5%.

HIV-1 transmission rates at 1 month of age (0.8%) varied considerably according to the use and length of maternal ART prior to delivery. Among women who received at least one dose of triple ART before delivery [median viral load logarithmic value (VL log) 3.55] the HIV-1 MTCT rate was 0.9%. However, among women who did not initiate triple ART until the time of delivery or following delivery the MTCT rate was 5.1% (VL log 4.51), ($P < 0.001$). As seen in Fig. 2, HIV transmission rates correlated with the length of maternal ART exposure prior to delivery. When infant death and/or HIV transmissions were combined in the analysis, women with HAART exposure for at least 90 days prior to delivery showed an incidence of 1.2% as opposed to 3.7% in women with 30 days or less of triple ART during pregnancy ($P = 0.013$). When the same comparison was performed in infants followed between 1 and 6 months of age, mothers who received triple ART for greater than 90 days predelivery had an HIV-1 transmission rate of 0.4%. This rate was 1.8% in mothers who received less than 30 days of triple ART predelivery ($P = 0.005$). Findings were similar when HIV transmissions and/or deaths were combined in the analysis. Transmission and/or death rates at 12 months were high and twice higher in women with more than 30 days of triple ART exposure predelivery (14%) as opposed to women who received 90 days of treatment predelivery (6.9%). In both scenarios, findings were statistically significant ($P = 0.001$).

HIV MTCT rates were low at all time points. The highest HIV transmission rate was at 1 month of age in infants born to women with less than 30 days of ART exposure (1.9%). Nevertheless, HIV infection and or infant mortality combined were always higher in infants born

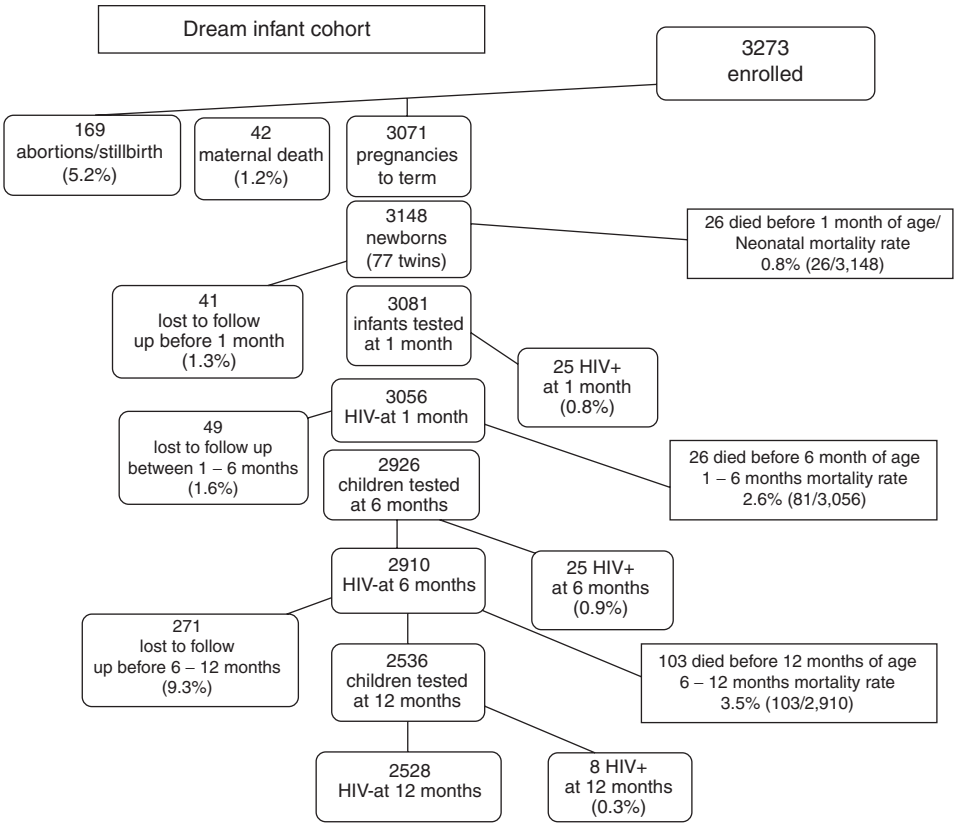

Fig. 1. Drug Resource Enhancement Against AIDS and Malnutrition Mother-Infant Cohort.

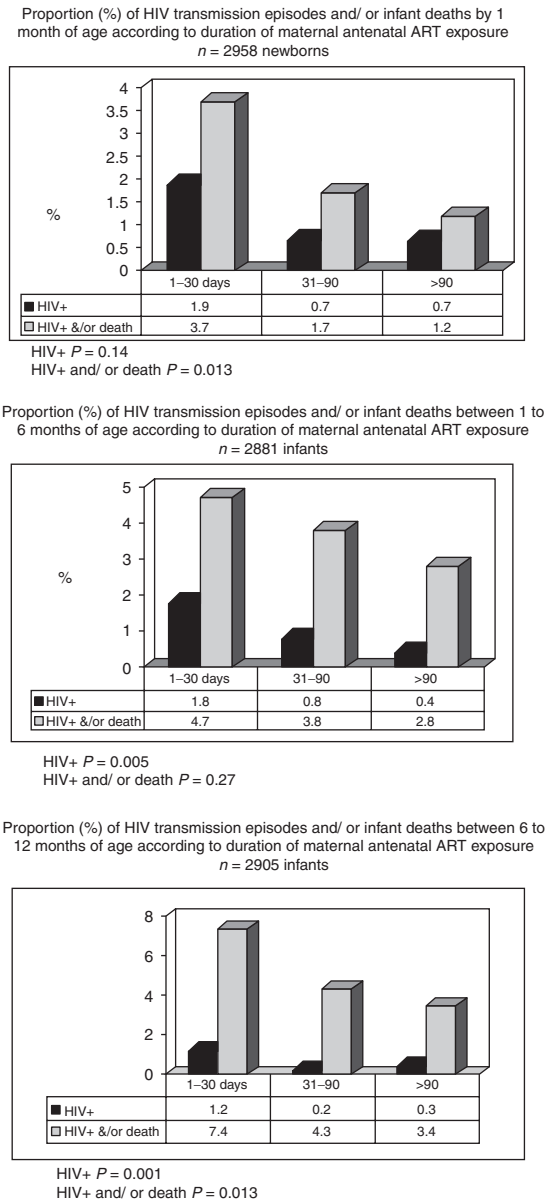

Fig. 2. Proportion of HIV-1 mother-to-child transmission episodes and/or infant deaths according to duration of maternal antenatal triple antiretroviral therapy exposure throughout the first year of life.

to women with less than 30 days of antenatal ART (3.7, 4.7 and 7.4% respectively), a finding that was statistically significant at the 1 and 12 month time points. Infant mortality was highest by 12 months, including infants of mothers with longer antenatal ART exposure (Fig. 2). This is likely reflective of weaning at 6 months of age in a large segment of infants with concurrent interruption of maternal ART. Because only a very small proportion of infants acquired HIV between 6 to 12 months of age ($n = 8$), HIV-infection is an unlikely cause of mortality.

Table 1 stratifies episodes of HIV-1 transmission by maternal CD4 cell count and duration of HAART exposure. Mothers with baseline CD4 cell counts of at least 350 cells/μl comprised 48% of HIV transmissions and/ or infant deaths at 1 month (24/50). Women with CD4 cell counts greater than 350 cells/μl initiated ART at a mean gestational age of 17.2 weeks whereas women with lower CD4 cell counts started treatment at a mean gestational age of 23.0 weeks, $P < 0.001$. Time in care during pregnancy was not very different between groups (mean 114 for women with higher vs. 121 for women with lower CD4 cells).

Regardless of maternal CD4 levels, HIV MTCT rates and/ or infant deaths by 1 month of age were less in women who received longer courses of prenatal ART. The reduction in transmission events and/or deaths by 1 month of age was 58% when maternal ART exposure prior to delivery was greater than 30 days. Among infants followed in the second semester of life, rates of HIV infection and/or death were high in both CD4 cell groups, and especially high in children born to women with lower CD4 cell counts who received a shorter course of triple ART antenatally (9.5%). The higher infant death rate in the second semester of life was likely owing to weaning practices as this period had an overall high mortality rate (3.5%). Of the 253 episodes of HIV-1 transmission and/or infant death at all time points reported in the table, 128 events (50.6%) occurred in mothers with CD4 cell counts of at least 350 CD4 cells/μl. Of the 54 episodes of HIV transmission, 50% (27 cases) occurred in women in the higher CD4 cell count strata. Longer periods of triple antenatal ART exposure (>30 days) were protective against HIV transmission and infant deaths in women with lower CD4 counts only throughout the entire first year of life. This finding was statistically significant. Antenatal triple ART exposure impacted infant outcome as late as the second semester of life, particularly in women with lower CD4 cell counts.

Results of a binary logistic regression analysis are demonstrated in Table 2. Absence of maternal ART prior to delivery was statistically associated with HIV transmission and/ or infant death at all time points with a relative risk of 1.6 at 1 month of age, 1.3 between 1 to 6 months of age and 1.5 between 6 and 12 months of age. An association between infant outcomes and baseline maternal CD4 cell count and maternal BMI were not found at any time point, likely because women made use of triple ART postpartum. Maternal viral load was associated with adverse infant outcomes (RR = 1.4) at the 1–6 month age time point. Maternal hemoglobin values were statistically associated with infant HIV infection status at 6–12 months of age with a relative risk of 9.0, but not at any other time point and not associated with HIV-infection status and/or death. This is likely a spurious finding as the number of HIV infections in the second semester was low ($n = 8$; 0.3%).

Table 1. HIV transmission and/ or death according to maternal predelivery length of HAART and baseline CD4 cell counts.

	Predelivery length of HAART	HIV-MTCT and or infant death	%	Odds ratio	Mantel–Haenszel odds ratio
One-month evaluation $N=2927$ infants					
Baseline CD4 cell count					
<350 cells/μl	<30 days	7/162	4.3	0.36*	
	>30 days	19/1195	1.6	0.15–0.88	0.42* 0.22–0.81
	Total	26/1357	1.9		
>350 cells/μl	<30 days	5/185	2.7	0.50	
	>30 days	19/1385	1.4	0.18–1.35	
	Total	24/1579	1.5		
Six month evaluation $N=2848$ infants					
Baseline CD4 cell count					
<350 cells/μl	<30 days	12/151	7.9	0.39*	
	>30 days	38/1172	3.2	0.20–0.76	
	Total	50/1323	3.8		0.64
>350 cells/μl	<30 days	4/172	2.3	1.81	0.37–1.10
	>30 days	43/1353	3.2	0.24–2.83	
	Total	47/1525	3.1		
12 month evaluation $N=2670$ infants					
Baseline CD4 cell count					
<350 cells/μl	<30 days	12/126	9.5	0.39*	
	>30 days	40/1020	3.9	0.20–0.76	0.46* 0.28–0.74
	Total	52/1146	4.5		
>350 cells/μl	<30 days	10/153	6.5	0.54	
	>30 days	44/1212	3.6	0.26–1.09	
	Total	54/1365	4.0		

MTCT, mother-to-child transmission.
*Denotes statistical significance.

The Kaplan–Meier curve in Fig. 3 demonstrates infant survival according to maternal ART exposure adjusted for maternal parameters including baseline CD4 cell counts, viral load, hemoglobin and BMI. Cumulative infant HIV-1 free survival at 12 months was 91% if mothers received less than 30 days of triple ART predelivery and greater than 93.5% if women received antiretrovirals for more than 30 days predelivery, $P<0.001$. As late as 18 months of age, cumulative HIV-free survival was higher in infants of mothers who received longer duration

Table 2. Multivariate analysis of infant outcomes at 1 month of age, between 1 and 6 months of age and between 6 and 12 months of age according to duration of maternal antenatal antiretroviral therapy exposure and baseline parameters.

	HIV+		HIV+ and/or death	
Baseline parameters	RR	CI 95%	RR	CI 95%
CD4 cell count (cell/μl)				
1 month of age	0.82	0.55–1.26	0.93	0.70–1.24
>1 to 6 mos. of age	0.93	0.60–1.46	1.01	0.82–1.24
>6 to 12 mos. of age	1.48	0.77–2.81	0.96	0.79–1.13
Viral Load (Log c/ml)				
1 month of age	1.29	0.65–2.57	1.35	0.84–2.17
>1 to 6 mos. of age	2.01	0.99–4.10	**1.44***	**1.03–2.01**
>6 to 12 mos. of age	3.21	1.27–8.13	1.20	0.87–1.66
BMI				
1 month of age	1.85	0.37–11.12	2.08	0.48–9.01
>1 to 6 mos. of age	1.43	0.54–4.12	1.74	0.34–6.51
>6 to 12 mos. of age	2.31	0.53–13.76	1.68	0.78–4.95
Hemoglobin (gm/100 cc)				
1 month of age	1.03	0.54–1.94	1.23	0.78–1.93
>1 to 6 mos. of age	1.44	0.70–2.96	0.89	0.66–1.20
>6 to 12 mos. of age	9.00	1.20–18.32	1.27	0.94–1.72
Days of antenatal ART				
1 month of age	1.20	0.65–2.21	**1.59***	**1.06–2.38**
>1 to 6 mos. of age	2.14	1.16–3.95	**1.34***	**1.04–1.80**
>6 to 12 mos. of age	2.07	0.89–4.83	**1.51***	**1.15–1.99**

All parameters were continuous variables. CD4s were categorized as 0 = <200, 1 = 200–350, 2 = 351–500, 3 = >500; Viral load: 0 = <10 000, 1 = 10 001–100 000, 2 = >100 000; BMI: 0 = <18.5, 1 = >18.5; HB: 0 = 8.0, 10 = 8.01–10.0, 2 = >10.0. Days of antenatal ART: 0 = no HAART, 10 = 1–30 days, 20 = 31–90 days, 30 = >90 days. RR, relative risk; CI, confidence interval.
*Denotes statistical significance.

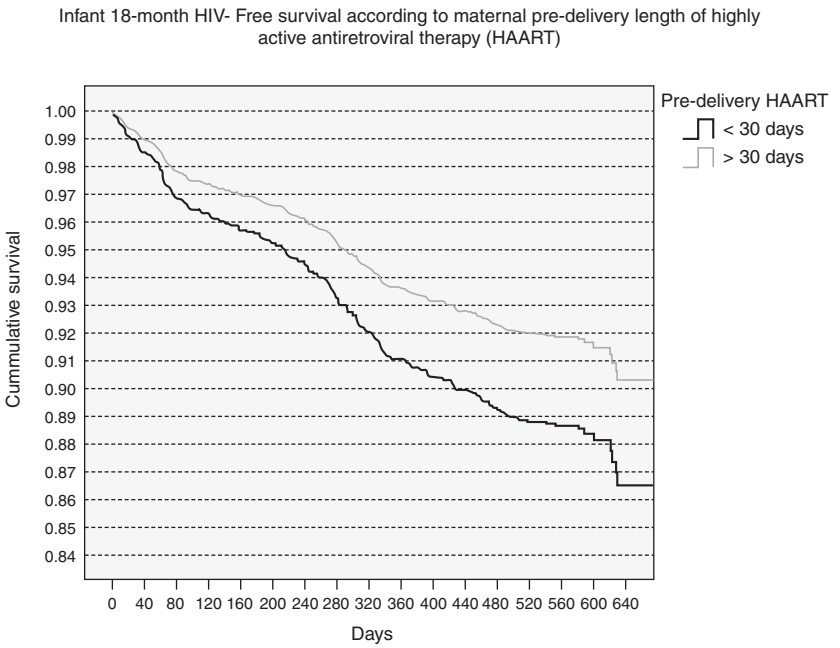

Fig. 3. Kaplan–Meier infant survival analysis according to duration of maternal antenatal triple antiretroviral therapy exposure (less or equal to 30 days/greater than 30 days).

of triple antenatal ART (92 vs. 89%). Because women received triple ART postpartum, HIV-free survival rates remained remarkably high even in mothers who received minimal to no antenatal ART. The overall infant mortality rate was 67/1000, significantly lower than infant mortality rates in the general population of Mozambique (100/1000) and Malawi (78/1000) [8].

Infant health parameters

Serious adverse events such as anemia (HB < 8.0 g/dl) or hepatic toxicity (five times the upper normal limit for liver function tests) were quite rare in the infant cohort. Rates of 3.9% anemia ($n = 122/3148$) and 0.3% hepatic toxicity ($n = 9/3148$) were observed in the first year of life. Growth parameters were slightly superior to that of the general population of infants born in Mozambique and Malawi. Moderate to severe growth failure as defined by weight-for-age Z scores (WAZ) of less than -2 were seen in 8.1% of 477 infants measured at 1 week of age and in 6% of 2002 infants measured at 6 months of age. At 12 months, the impact of weaning was visible, with 22.7% of 2518 infants having WAZ more than -2. The proportion of low-birth weight (<2.5 kg) in our cohort (11.5%) was also not inferior to countrywide statistics in the 496 infants for whom birth weights were available. Details on infant growth parameters for this cohort of patients, particularly following the weaning process are reported separately [9]. Provision of triple ART to breastfeeding mothers followed by careful weaning practices and nutritional supplementation favorably impacted growth outcomes and infant survival. Contrary to most mortality reports from developing countries, there was an inversion of mortality trends with a neonatal mortality rate of 0.3%, a 1–6 month of life mortality of 2.6% and a second semester mortality rate of 3.5%. Mortality rates remained significantly lower than that of countrywide statistics.

Maternal adverse reactions

Liver toxicities grades 3 or 4 likely associated with triple ART exposure were reported in 70 mothers (2.1%). They occurred in 1.6% of women with less than 350 cells/μl vs. 2.6% of women with 350 cells/μl or less ($P = 0.076$). Pregnant women receiving zidovudine-based triple ART had a higher incidence of anemia (9.8 vs. 6.0%; $P = 0.003$). The incidence of Steven–Johnson Syndrome and grade 3–4 skin rashes in the maternal cohort was 1.2 and 2.4%, respectively. The total number of patients who faced severe adverse reactions including hepatic toxicity, skin rash or Steven–Johnson Syndrome totalled 171 (5.2%). These patients were switched to alternate first line ART without additional complications. Details on maternal and pregnancy outcomes are reported separately [10].

Discussion

HIV-infected women with higher CD4 cell counts are generally not thought to be at risk for HIV MTCT in resource limited settings The WHO recently released a document containing guidelines for HIV PMTCT practices [11] where triple ART are recommended to all pregnant women with CD4 cell counts less than 350 cells/μl or if patients fall within WHO clinical

categories 3 or 4. Data from our cohort of 3273 pregnancies and 3148 infants followed from birth to 12 months of age demonstrates that triple ART both antenatally and postpartum is highly beneficial in HIV PMTCT and in reduction of infant deaths also for mothers with higher CD4 cell counts. The overall cumulative HIV transmission rate of 2.0% in this patient population by 12 months of age as well as the high infant HIV-free survival of 92.5% in the first year of life substantiate this observation. These findings occurred in the absence of elective C-sections or provision of infant formula. Although transmission events were overall low, women with CD4 cell counts greater than 350 cells/μl accounted for approximately 50% of the transmission events. Nearly half of infant deaths and/or transmission events occurred in mothers with higher CD4 cell counts. Women with higher CD4 cell counts initiated treatment later (mean 23 vs. 17 weeks), although the mean time in care during pregnancy was not remarkably different (mean of 7 days difference). This finding underscores the need for earlier initiation of antiretroviral treatment for all HIV-infected pregnant women. Other studies have documented high transmission rates in women with lower CD4 cell counts eligible for triple ART, but not in patients with higher CD4 cells [12].

Shorter duration of antenatal triple ART therapy was the only clinical parameter associated with a statistically significant risk of HIV-infection and/or death throughout the first year of life by binary logistic regression. It was the strongest predictor of a favorable outcome. Owing to the use of maternal triple ART, other clinical health indicators such as maternal BMI, anemia or CD4 cell count and even baseline virus load were not found to be associated with infant outcomes in most circumstances. This finding was also evident in the survival analysis, which demonstrated a significant impact on infant survival by duration of maternal antenatal ART exposure. Although infants of mothers with less antenatal ART exposure also survived, their survival rate was lower, and a catch-up phenomenon was not observed over time, regardless of the postnatal introduction of triple ART to all women. The beneficial effects of extended antenatal ART, although more pronounced in mothers with lower CD4 cell counts, were also visible in women with higher CD4 cells.

Infant HIV-free survival of 92.5% in a breastfeeding population in sub-Saharan Africa is outstanding in the context that this was not a controlled clinical trial, but an observational study of patients enrolled in a public health program. The use of triple ART as well as nutritional supplementation provided a significant incentive for patient retention as the overall loss to follow-up rate over 12 months was 11.5%. One likely explanation for a greater loss to follow-up of mother-infant pairs in the second semester was the interruption of triple ART postpartum for women with higher CD4 cell counts. The inversion of infant mortality parameters with a higher percentage of infant deaths occurring in the second semester (albeit lower than background mortality rates) as opposed to the neonatal period or first semester of life is likely also associated with maternal ART interruption. The weaning and introduction of other foods from 6 months of age onwards which accompanied maternal ART interruption in approximately half of the patients was likely an important contributor to both infant death and loss to follow-up.

Infant health parameters, particularly in the first month of life were much improved as compared with country background rates. Birth weights are not generally available in the first week of life in such settings as most infants are delivered at home. Nevertheless, nearly 500 infants had measurements with low-birth weight present in about 11%. Moderate-to-severe malnutrition was present in 6% of infants at 6 months and increased to 23% by 12 months. Severe malnutrition is estimated to affect 30% of children from the general population by 1 year of age [13]. The impact of weaning, necessary owing to suspension of maternal ART, translated into worsened growth parameters by 12 months.

Other studies have demonstrated that HIV-exposed uninfected infants are at increased risk of dying because of maternal HIV infection [14,15]. In these studies, however, the risk was associated with advanced maternal disease. In our study, women with higher CD4 cell counts were also at risk for adverse infant outcomes. Our data supports the premise that improved maternal health in the antenatal period correlates with improved infant outcomes in the first year of life. Improved maternal health in our setting was achieved though the provision of extended antenatal and postnatal triple ART and was sustained by nutritional supplementation. This led to very low-HIV MTCT rates and decreased infant mortality. The importance of extended antenatal ART therapy was such that infants whose mothers had longer exposure to ART in pregnancy had the highest HIV-free survival rate. Even though therapy was started for all women by the postnatal period, infants who had shorter ART antenatal exposure did not achieve comparable HIV-free survival rates. In the second semester of life, when half of the women stopped triple ART and breastfeeding was discontinued, although HIV transmissions were lower, infant mortality and loss to follow-up increased.

Although there is still skepticism about the feasibility of implementing triple ART to pregnant HIV-infected women in sub-Saharan Africa, our public health program and other similar programs [16,17] have proven this approach is feasible. It also curtails adverse infant outcomes. Postnatal maternal triple ART is a cornerstone in achieving high infant HIV-free survival rates, whereas its discontinuation coincides with a rise in adverse outcomes. The finding that antenatal ART therapy is

associated with beneficial infant outcomes as late as 12 months of age should encourage public health policies to promote universal use of triple ART to all HIV-infected women during pregnancy. As discontinuation of triple ART in the postpartum period coincides with an increased loss to follow-up and increased infant mortality, provision of ART throughout the extended breastfeeding period should be considered.

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