Eighteen-Month Follow-Up of HIV-1–Infected Mothers and Their Children Enrolled in the Kesho Bora Study Observational Cohorts

The Kesho Bora Study Group

Objective: To assess the effectiveness and safety of antiretrovirals (ARVs) used for treatment or prophylaxis in a breastfeeding population of HIV-1–infected women (Burkina-Faso, Kenya, South Africa).

Methods: HIV-1–infected pregnant women with <200 CD4 cells per cubic millimeter or with World Health Organization stage 4 disease (cohort A) and asymptomatic women with >500 CD4 cells per cubic millimeter (cohort B) were enrolled into 2 prospective cohorts. Women with 200–500 CD4 cells per cubic millimeter were enrolled in a parallel randomized trial. Women in cohort A initiated antiretroviral therapy. Women in cohort B received zidovudine from 34 to 36 weeks gestation until delivery, with single-dose nevirapine in labor (cohort B). All children received single-dose nevirapine.

Results: Of 248 women enrolled, 111 (cohort A) and 125 (cohort B) infants alive at 24 hours after birth were analyzed. Sixty-nine percent and 42% of women had undetectable viral load at delivery, respectively. Ten children in each cohort died. The 18-month cumulative incidences of HIV-1 infection were 7.5% (95% confidence interval: 3.8% to 14.5%) (cohort A) and 5.8% (2.8% to 11.8%) (cohort B). Sixty-one percent (cohort A) and 78% (cohort B) were breastfed for a median duration of 20 weeks. Four children in cohort A and only 1 in cohort B became HIV-1 infected after 6 weeks of age.

Conclusions: Antiretroviral therapy initiated a median of 7 weeks before delivery in women with advanced HIV-1 disease was associated with a significant residual risk of HIV-1 transmission due to insufficient decrease in viral load by the time of delivery. Among women with >500 CD4 cells per cubic millimeter, the risk of breast-milk transmission was very low despite lack of postnatal prophylaxis.

Key Words: antiretrovirals, breastfeeding, HIV, mother-to-child transmission of HIV, sub-Saharan Africa

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INTRODUCTION

Short-course antiretroviral (ARV) regimens for prevention of mother-to-child transmission (MTCT) of HIV-1 in resource-limited settings can reduce the risk of MTCT during pregnancy and delivery. However, the overall transmission rate remains at approximately 20%–30% without interventions to prevent transmission during prolonged breastfeeding.[1–2] This rate remains far higher than the 1%–2% transmission rate observed in resource-rich settings using a combination of interventions as follows: (1) potent ARV regimens during pregnancy that maximally suppress viral load (VL), (2) cesarean section before labor and ruptured membranes when indicated; (3) complete avoidance of breastfeeding and (4) infant ARV postexposure prophylaxis.[3–4]

Since 2004, World Health Organization (WHO) has recommended that HIV-1–infected pregnant women should be clinically and, where possible, immunologically evaluated such that women with advanced stages of HIV-1 infection receive long-term antiretroviral therapy (ART).[5] ART is not only beneficial for maternal health but is expected to reduce the risk of MTCT during pregnancy, delivery, and breastfeeding.[6–8] However, data regarding benefits and risks of ART for mothers and children in settings where breastfeeding is common are limited.

Because the risk of MTCT of HIV-1[9,10] and the risk of maternal AIDS or death[11,12] are strongly associated with the stage of maternal HIV-1 disease, the Kesho Bora Study ("A better future", Swahili) followed different ARV treatment and prophylaxis strategies according to antenatal maternal CD4 cell counts. Mothers with intermediate stage HIV-1 disease (CD4 counts 200–500 cells/mm^3) were enrolled in a randomized controlled trial comparing continued ARV use during breastfeeding with the standard WHO-recommended short-course prophylactic regimen. Final results will be available in 2010.[13] Women with CD4 counts outside this

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The Members of the Kesho Bora Study Group are listed in the Appendix I.

The findings and conclusions in this article are those of the authors and do not necessarily represent the views of their agencies or the funding organizations.

Correspondence to: Dr. Isabelle de Vincenzi, World Health Organization (RHR), 20, Avenue Appia, CH-1211 Geneva 27, Switzerland (e-mail: devincenzii@who.int).

range and their children in 3 of the 5 study sites were followed in 2 cohorts: (cohort A) women with antenatal CD4 counts below 200 cells per cubic millimeter or WHO Stage 4 clinical disease (advanced HIV-1 disease) received ART for their own health[11]; and (cohort B) asymptomatic women with antenatal CD4 counts above 500 cells per cubic millimeter (early stage HIV-1 disease) received WHO-recommended MTCT prophylaxis. We now report transmission rates, morbidity, and mortality data up to 18 months after delivery/birth for these women and their children.

METHODS

Study Population and Interventions

From January 2005 to September 2006, HIV-1–infected pregnant women at less than 32 weeks of pregnancy (gestational age assessed using uterine height and date of last menstrual period, and ultrasound when available) and seen in selected antenatal clinics associated with 3 study sites (Centre Muraz, Bobo-Dioulasso, Burkina-Faso; International Centre for Reproductive Health, Mombasa, Kenya; and Kenyatta National Hospital, Nairobi, Kenya) were offered enrollment into the Kesho Bora study. All participating women provided written informed consent before enrollment. Women with contraindications for rapid initiation of ARVs were excluded [known allergy to ARVs or benzodiazepines; treatment with drugs interacting with ARVs; or significant (grade >2[14]) anemia, neutropenia, liver, or renal failure]. The study protocol was approved by the relevant ethical committees in Burkina-Faso and in Kenya, and at WHO and the US Centers for Disease Control and Prevention.

Women with CD4 counts <200 cells per cubic millimeter or WHO Stage 4 clinical disease[11] were enrolled in cohort A. They were offered ART as per WHO guidelines,[11] consisting of oral zidovudine (ZDV) (300 mg twice per day), lamivudine (150 mg twice per day), and nevirapine (NVP) (200 mg per day for the first 2 weeks, and 200 mg twice per day thereafter). Treatment was initiated as soon as possible after 18 weeks of pregnancy. It was continued through delivery, postpartum, and as long as required, according to WHO or national guidelines.

Asymptomatic women with CD4 counts >500 cells per cubic millimeter were enrolled in cohort B. They were offered short-course MTCT prophylaxis consisting of ZDV (300 mg twice a day) alone initiated between the 34th and the 36th week of pregnancy until delivery, and a single dose of ZDV (600 mg) and NVP (200 mg) at the onset of labor.[5]

All children received a single dose of 0.6 mL oral NVP suspension (approximately 2 mg/kg) preferably within 72 hours of birth (but no later than 7 days after birth). They also received co-trimoxazole prophylaxis from age 6 weeks (stopped if HIV-1 uninfected and no longer exposed to breastfeeding).

All mothers were counselled on infant feeding according to WHO guidelines[15] adapted to the study context. Specifically, those choosing replacement feeding received free formula, and those choosing to breastfeed were supported and counselled to exclusively breastfeed and stop when the child reached 6 months of age.

Women were seen weekly from enrollment until delivery, and mother–infant pairs were seen at 2, 4, 6, and 8 weeks after delivery/birth, then monthly until 1 year after delivery/birth, and 3 monthly thereafter. Active tracing of women who missed a study visit was implemented to minimize losses to follow-up. At each scheduled visit, clinical events, adherence to ARV regimen, and nutritional status were recorded using standardized case report forms. Children's feeding patterns were assessed using the WHO Infant Feeding Assessment tool,[16] and blood samples were collected from mothers for toxicity monitoring and from children for toxicity monitoring and for diagnosis of HIV-1 infection.

A serious adverse event (SAE) was defined as any experience that was fatal or life threatening, required in-patient hospitalization or prolongation of an existing hospitalization, resulted in a persistent or significant disability or incapacity, was a congenital anomaly, or cancer (except AIDS-associated malignancies). The severity of clinical adverse experiences and laboratory abnormalities was graded using standard US National Institutes of Health, Division of AIDS (DAIDS) toxicity tables.[14] All grade ≥ 3 events and grade ≥ 2 skin rashes and hepatic symptoms were considered SAEs.

Children's HIV-1 infection status was assessed using a quantitative HIV-1 RNA real-time polymerase chain reaction (PCR) assay (Generic HIV Charge Virale, Biocentric, Bandol, France) in Burkina-Faso and Mombasa[17] and a qualitative HIV-1 DNA PCR assay in Nairobi (Amplicor HIV-1 DNA v1.5 assay, Roche Diagnostics, Branchburg, NJ). Children were systematically tested at age 6 weeks. Children with undetectable HIV-1 at age 6 weeks were systematically tested again at age 12 months (or last available sample was tested if the child died or was lost to follow-up before 12 months). If a child was found to be infected with HIV-1, earlier stored samples were tested to further determine the time of infection (defined as the mid-point between last negative and first positive PCR assay result). All children who reached age 18 months had their HIV-1 infection status confirmed through HIV-1 serology. HIV-1 infection was defined as a positive HIV-1 test confirmed on a second sample, either by PCR or, if the child was at least 18 months old, by serology. The transmission was considered to have occurred in utero if the PCR was positive at birth; peripartum (during labor, delivery or early breastfeeding) if the PCR was negative at birth and positive at 6 weeks; and late postnatal if the PCR was negative at 6 weeks and subsequently positive.

Statistical Analysis

Group comparisons were made using Student t test or Wilcoxon rank sum test for quantitative and χ^2 square or Fisher exact test for categorical variables. Eighteen-month HIV-1 transmission, mortality, and HIV-1–free survival rates were estimated using the Kaplan–Meier life-table method and the effect of potential cofactors of transmission (study site, infant feeding mode, mode of delivery, CD4 count, duration of ARV and self-reported adherence) with the Cox proportional hazards regression model. Only the first live-born infant from each multiple pregnancy was considered. Only infants alive

at least 24 hours after birth were included in the HIV-1 transmission and infant survival analyses. Children lost before reaching a study end point (HIV infection or death) were censored at the date of last negative HIV-1 test (HIV-1 transmission analysis) or date last seen alive (survival and HIV-1–free survival analyses).

RESULTS

Study Populations

The derivation of the study population is shown in Figure 1. Of 248 women enrolled (119 in cohort A and 129 in cohort B), 246 were followed until delivery. These women [94 (38%) in Bobo-Dioulasso, 54 (22%) in Mombasa, 98 (40%) in Nairobi] delivered 236 singleton or first-born infants who remained alive 24 hours after birth (111 in cohort A and 125 in cohort B).

Mothers

First, characteristics of the mothers were evaluated across sites (data not shown). There were few differences between women in Mombasa and Nairobi. Compared with women in Burkina-Faso, women in Kenya were more educated (97% versus 66% ever attended school, $P < 0.0001$), more likely single (13% versus 4%; $P = 0.02$) and to have disclosed their HIV-1 infection status to their regular partner (73% versus 44%; $P < 0.0001$). Age and the proportions employed and primigravida were similar in the 3 sites. In Bobo-Dioulasso, 4% were delivered by cesarean section compared with 19% in Mombasa and 28% in Nairobi ($P = 0.0004$).

Next, characteristics of the mothers were assessed across cohorts (Table 1). Women in cohort A were older ($P < 0.0001$), and fewer were primigravid ($P = 0.002$) compared with those in cohort B (Table 1). There were no statistically significant differences in education, occupation, marital status, disclosure of HIV-1 infection status, or mode of delivery between the 2 cohorts. Women in cohort A received ARVs for a longer duration before delivery (median of 7 versus 6 weeks, $P = 0.004$), but adherence to ARVs was similar. The median CD4 count increased in both cohorts after initiation of ARVs, with a greater increase in cohort A. In cohort A, 69% of the women had undetectable VL by the time of delivery. Those with detectable VL at delivery had higher levels at enrollment (5.14 compared with 4.77 $\log_{10}$ copies/mL, $P = 0.03$), had received less ARVs before delivery (median 40 compared with 50 days, $P = 0.02$), and showed a median decrease of 1.99 $\log_{10}$ copies per milliliter. By 18 months postpartum, VL was undetectable in 71% of cohort A. In cohort B, 42% had undetectable VL at the time of delivery. The remaining 58% had higher VL at enrollment (3.90 versus 3.32 $\log_{10}$ copies/mL, $P = 0.0005$), similar duration of ARV prophylaxis, and a small decrease in VL by the time of delivery (0.25 $\log_{10}$ copies/mL). Grade 3 or 4 anemia at delivery was more common among women in cohort A than cohort B ($P = 0.0037$), as was grade 3 or 4 neutropenia at 3 months postpartum ($P = 0.03$). No cases of grade 3 or 4 hepatic

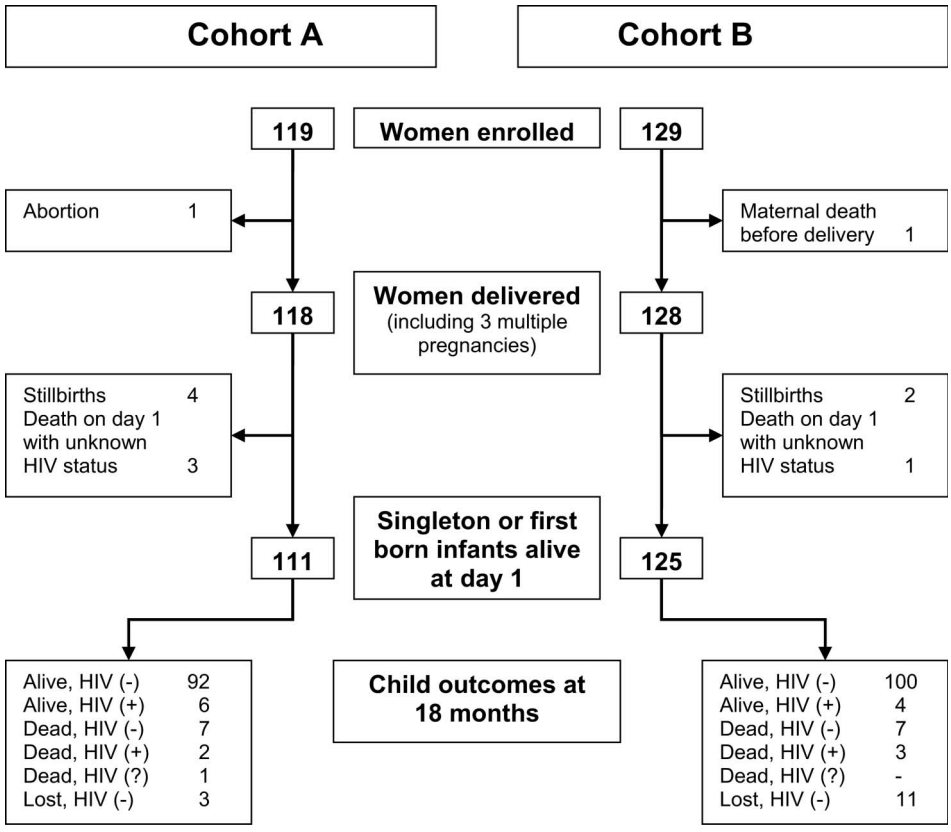

FIGURE1. Derivation of the study population.

TABLE 1. Characteristics and Follow-Up of Enrolled Women Followed Through Delivery to 18 Months Postpartum (n = 246)

	Cohort A (n = 118), n (%)	Cohort B (n = 128), n (%)	*P*
Study site			
Bobo Dioulasso	46 (39)	48 (38)	0.002
Mombasa	36 (31)	18 (14)	
Nairobi	36 (31)	62 (48)	
Age (mean, SD), yrs	28.7 (4.3)	26.4 (4.9)	<0.0001
Education at enrollment			
Never attended school	19 (16)	16 (12)	0.65
Primary school	57 (48)	61 (48)	
At least some secondary school education	42 (36)	51 (40)	
Occupation at enrollment			
Unemployed	80 (68)	91 (71)	0.62
Self-employed	29 (25)	31 (24)	
Salaried job	8 (7)	6 (5)	
Working, occupation type not specified	1 (1)	—	
Marital status at enrollment			
Married, monogamous	71 (60)	79 (62)	0.27
Married, polygamous	21 (18)	21 (16)	
Unmarried, regular partner	18 (15)	12 (9)	
Single	8 (7)	16 (13)	
Disclosure of HIV-1 infection status to partner			
Yes	64 (58)	72 (64)	0.35
No	46 (42)	40 (36)	
Not applicable (no regular partner)	8	16	
Primigravid	9 (8)	28 (22)	0.002
Mode of delivery, n (%)			
Vaginal	101 (86)	104 (81)	0.23
Cesarean section before labor and rupture of membranes	4 (3)	13 (10)	
Cesarean section after labor and/or rupture of membranes	12 (10)	11 (9)	
Cesarean section unknown timing	1 (1)	0	
Duration of receipt of ARVs before delivery			
>8 weeks	35 (30)	17 (13)	0.003
7–8 weeks	30 (25)	27 (21)	
5–6 weeks	32 (27)	44 (35)	
<5 weeks	21 (18)	40 (31)	
Adherence to ARVs, n (%)*			
No missed doses before delivery	91/116 (78)	101/127 (80)	0.84
Received the NVP dose at delivery	NA	115/119 (97)	
No missed doses during first 6 months postpartum	59/118 (50)	NA	
No more than 1 missed dose during first 6 months postpartum	85/118 (72)	NA	
CD4+ count (cells/mm^3) (median and interquartile range)*			
At enrollment†	134 (91–170)	622 (559–730)	<0.0001
At delivery†	184 (129–269)	736 (603–906)	
At 12 months postpartum†	304 (228–419)	678 (542–875)	
At 18 months postpartum†	323 (229–402)	657 (507–833)	
VL			
At enrollment (log_{10}copies/ml, median IQR), n (%) with undetectable VL (<300 copies/mL)	4.89 (4.35–5.25)	3.61 (2.97–4.21)	<0.001
At delivery*	78/113 (69)	50/118 (42)	
At 18 months postpartum*	77/108 (71)	17/111 (15)	
Laboratory serious adverse events (SAEs)*			
Grade 3 or 4 anemia (hemoglobin < 7 g/L)			
At delivery	13/116 (11)	2/114 (2)	0.0037
At 3 months postpartum	2/112 (2)	1/121 (1)	0 .61
At 12 months postpartum	1/109 (1)	NA	

TABLE 1. (*continued*) Characteristics and Follow-Up of Enrolled Women Followed Through Delivery to 18 Months Postpartum (n = 246)

	Cohort A (n = 118), n (%)	Cohort B (n = 128), n (%)	*P*
Grade 3 or 4 neutropenia (absolute neutrophil count $<750/mm^3$)			
At delivery	2/102 (2)	0/94 (0)	0.50
At 3 months postpartum	7/104 (7)	1/111 (1)	0.03
At 12 months postpartum	3/109 (3)	NA	—
Clinical SAEs			
Women (%) with at least 1 SAE	26 (22)	15 (12)	0.03
SAEs (number, rate per 100 women)	50 (42 per 100)	19 (15 per 100)	—
Infectious diseases	33	10	—
Obstetrical pathology	8	4	—
Other	9	5	—
Deaths (%)	5 (4)	0 (0)	0.02

*Reasons for missing data: home delivery, missed visit, missing sample, death, loss-to-follow-up, and withdrawal.
†Based on 118, 114, 111, and 107 valid values at enrollment, delivery, 12 and 18 months (cohort A), and 128, 114, 112, 111 (cohort B).
NA, not applicable.

enzyme elevations were noted. Clinical SAEs were more often reported in cohort A than cohort B ($P = 0.03$). Most (62%) were infections, and 17% were obstetrical problems (other than cesarean sections and preterm deliveries). Five women (4%) in cohort A died during follow-up—3 while receiving ART (causes of death: cerebral malaria, bacterial meningitis, tuberculosis) and 2 who decided to stop all ART and subsequently developed tuberculosis and cardiac failure. In cohort B, 1 woman died before delivery (Fig. 1) due to acute respiratory distress of unknown origin. No women in cohort B died after delivery. In cohort A, drug substitutions occurred in 17 of 118 women (14%) due to initiation of tuberculosis treatment (contraindication for concomitant use of NVP (n = 8), anemia (n = 5), neutropenia (n = 2), and rash (n = 2, both occurring within 4 weeks of treatment initiation).

Children

Evaluation of characteristics of the children across sites (data not shown) revealed that the rate of low birth weight was higher in Burkina-Faso (15%) than in the Kenyan sites (6%), $P = 0.03$. Thirty-five percent of children from Mombasa were born with severe anemia, 10 times the rates observed in Bobo Dioulasso (4%) or Nairobi (3%).

The children in the 2 cohorts were similar with respect to gender, receipt of neonatal NVP dose, preterm birth, and low birth weight (Table 2). However, the proportion of ever breastfed infants was higher in cohort B ($P = 0.004$), but the median duration of breastfeeding in ever breastfed children was similar.

Three children in cohort A and 11 in cohort B were lost to follow-up before age 18 months (18-month cumulative child follow-up rates 97% and 91%, respectively). All of these 14 children were HIV-1–uninfected when last seen alive.

The proportions of children in each cohort with laboratory SAEs (anemia, neutropenia) were similar. The rates of grade 3 or 4 anemia were high in both cohorts at birth but had resolved by 3 months of age. Only 1 infant born to a mother from cohort B had elevated transaminase at birth (not confirmed on a second sample collected a few days later). The proportions of children in each cohort with clinical SAEs were similar. Apart from preterm birth and low birth weight, a total of 149 clinical SAEs were experienced by 100 (42%) of the 237 children (incidence: 63 per 100 children), with a similar frequency in both cohorts. Sixty-four percent were infectious diseases (including 20 malaria episodes, 25 gastroenteritis cases, and 29 respiratory infections). Congenital abnormalities included inguinal hernias (n = 4), naevus (n = 1), minor abnormalities of the male genitals (n = 5), polydactyly (n = 2), tongue tie (n = 1), and ventricular septal defect (n = 1).

There were 10 deaths before 18 months in cohort A (Table 3 and Fig. 2B). Causes of death were AIDS (n = 2), presumed malaria (n = 3), dehydration (n = 1), and bacterial infections (n = 4; fever with diarrhoea and respiratory distress). Ten children in cohort B died: AIDS (n = 3), preterm birth (n = 1), intestinal intussusception (n = 1), bacterial infections (n = 4), and sudden, unexplained death (n = 1). The 18-month cumulative HIV-1 infection rate was 7.5% (3.8–14.5) in cohort A (Table 3 and Fig. 2A), similar among ever and never breastfed children (data not shown). Of the 8 infected children, 4 were positive by age 6 weeks [peripartum transmission rate 3.7% (1.4–9.5)] and the remaining 4 became positive later [late postnatal transmission rate 3.9% (1.2–9.3)]. In cohort B, the cumulative 18-month HIV-1 infection rate was 5.8% (2.8–11.8) (Table 3 and Fig. 2B). Six children were HIV-1 infected by age 6 weeks [peripartum transmission rate 4.9% (2.2–10.6)] and the other later [late postnatal transmission rate 0.9% (0.1–4.7)]. Overall, 5 of the 15 HIV-1–infected children died by age 18 months, all of whom were HIV-1 infected by 6 weeks. In a multivariate analysis, none of the following factors were significantly related to transmission risk in cohort A (ever breastfed $P = 0.95$; mode of delivery $P = 0.99$; maternal enrollment CD4 count $P = 0.39$; duration of ARV before delivery $P = 0.37$; missed doses before delivery $P = 0.07$) or cohort B (ever breastfed $P = 0.99$; mode of delivery $P = 0.27$; maternal enrolment CD4 count $P = 0.60$; duration of ARV before delivery $P = 0.69$; missed doses before delivery $P = 0.70$). The cumulative 18-month rate of HIV-1

TABLE 2. Characteristics and Follow-Up of Live-Born Children (n = 246)

	Cohort A, (n = 111), n (%)	Cohort B (n = 125), n (%)	*P*
Gender, n (%)			
Male	63 (57)	58 (46)	0.11
Female	48 (43)	67 (54)	
Neonatal dose of NVP received			
Yes	107 (97)	117 (97)	1.00
No	3 (3)	4 (3)	
Missing	1	4	
Low birth weight (<2500 g), n (%)			
Yes	13 (13)	8 (7)	0.14
No	88 (87)	108 (93)	
Missing	10	9	
Preterm birth (<37 weeks from last menstrual period)			
Yes	11 (10)	12 (10)	0.94
No	100 (90)	113 (90)	
Ever BF			
No	43 (39)	27 (22)	0.004
Yes	68 (61)	98 (78)	
Among ever BF:			
Duration of BF in weeks—median (IQR)	20.7 (12.0–26.1)	18.7 (11.6–25.1)	0.57
Exclusively BF up to last visit <3.5 months			
Yes	23/68 (34)	46/95 (48)	
No	45/68 (66)	49/95 (52)	
Missing	0	3	0.06
Laboratory SAEs*			
Grade 3 or 4 anemia, n (%)			
At birth (hemoglobin < 12g/L)	15/92 (16)	9/98 (9)	0.14
At 3 month (hemoglobin < 7 g/L)	2/92 (2)	0/106 (0)	0.21
Grade 3 or 4 neutropenia, n (%)			
At birth: $<1500/mm^3$ (data missing for 72)	8/81 (10)	6/83 (7)	0.54
At 3 months: $<400/mm^3$	1/86 (1)	1/97 (1)	0.99
Clinical SAEs (not including preterm birth or LBW)			
Children (%) with at least 1 SAE	50 (45)	50 (40)	0.43
SAEs (Number per 100 children)	72 (65 per 100)	77 (62 per 100)	
Infectious diseases (n)	50	46	
Malnutrition/wasting (n)	7	6	
Congenital abnormalities (n)	7	8	
Other SAE (n)	8	17	
Deaths	10	10	

*Reasons for missing data: home delivery, missed visit, missing sample, death, loss to follow-up, and withdrawal.
BF, breast fed.

infection or death was 14.4% (9.1–22.5) in cohort A and 11.6% (7.0–18.7) in cohort B ($P = 0.54$) (Table 3 and Fig. 2C). There were no deaths or new HIV-1 infections between ages 12 and 18 months.

DISCUSSION

Women with advanced HIV-1 disease initiating triple ARV therapy during pregnancy had an MTCT rate of 7.5% [95% confidence interval (CI): 3.8 to 14.5], half of the transmissions being late postnatal transmissions. Among women with early-stage disease (asymptomatic and CD4 counts >500 cells/mm^3), receipt of the WHO-recommended short-course regimen resulted in a risk of MTCT of HIV-1 below 6%, in a population where 78% of mothers breastfed, with a late postnatal transmission rate less than 1%.

Although much lower than rates observed when similar women received only short-course prophylaxis during pregnancy,[18] the transmission rate observed with ART was higher than expected with a fully suppressive ART regimen. However, it was similar to the 6.7% (95% CI: 3.2 to 13.9] transmission rate observed in the Kisumu Breastfeeding Study (KiBS) observational cohort study in Kenya, in a group of mothers with CD4 count <250 at entry who received the same

TABLE 3. Life-Table Cumulative Rates of HIV-1 Infection, Death, or Both

		Cohort A		Cohort B	
Endpoint	**Time**	**Events (cum)/at Risk**	**Rate (95% CI)**	**Events (cum)/at Risk**	**Rate (95% CI)**
HIV-1 infection	Birth	2/110	1.8 (0.5 to 7.1)	2/125	1.6 (0.4 to 6.3)
	6 weeks	4/104	3.7 (1.4 to 9.5)	6/115	4.9 (2.2 to 10.6)
	6 months	7/97	5.6 (2.5 to 12.0)	6/109	4.9 (2.2 to 10.6)
	12 months	8/94	7.5 (3.8 to 14.5)	7/101	5.8 (2.8 to 11.8)
	18 months	8/83	7.5 (3.8 to 14.5)	7/86	5.8 (2.8 to 11.8)
Log rank test (stratified on centre) $P = 0.55$					
Death	Birth	0/111	0.0	0/125	0.0
	6 weeks	4/107	3.6 (1.4 to 9.3)	1/121	0.8 (0.1 to 5.6)
	6 months	6/104	6.3 (3.1 to 12.8)	5/115	4.1 (1.7 to 9.6)
	12 months	10/100	9.0 (5.0 to 16.1)	10/106	8.3 (4.6 to 14.9)
	18 months	10/98	9.0 (5.0 to 16.1)	10/102	8.3 (4.6 to 14.9)
Log rank test (stratified on centre) $P = 0.80$					
HIV-1 infection or death	Birth	2/111	1.8 (0.5 to 7.0)	2/125	1.6 (0.4 to 16.2)
	6 weeks	7/104	6.3 (3.1 to 12.8)	7/115	5.7 (2.7 to 11.5)
	6 months	13/99	11.7 (7.0 to 19.3)	9/111	7.3 (3.9 to 13.6)
	12 months	16/94	14.4 (9.1 to 22.5)	14/103	11.6 (7.0 to 18.7)
	18 months	16/92	14.4 (9.1 to 22.5)	14/100	11.6 (7.0 to 18.7)
Log rank test (stratified on centre) $P = 0.54$					

NVP-based ART regimen from 34 weeks gestation until delivery.[19] A lower rate of transmission was achieved in the MTCT+ program in Cote d'Ivoire [3.3% (0.0% to 6.9%) at 12 months] using the same NVP-based ART regimen,[20] possibly because of an earlier initiation of ART at median 27 weeks of pregnancy, that is, 13 weeks before delivery. It seems difficult to achieve adequate viral suppression by delivery (the time of greatest transmission risk) with a median of 7–8 weeks of ART, as in KiBS and Kesho Bora. Early initiation of ARV is probably particularly important to reduce the risk of transmission among such women.

A relatively low rate of ARV-related toxicity was observed in women and children exposed to ART when compared with those exposed to short-course ARV prophylaxis: no serious hepatic toxicity, more frequent but rapidly reversible hematologic abnormalities, no excess of clinical SAEs, and no increase in the proportion of infants born preterm. Although the rate of low birth weight in cohort A was twice the rate in cohort B, the difference was not statistically significant, possibly due to the small sample size.

Immunocompromised women using ART were less likely to breastfeed their children than healthier women on short-course ARV prophylaxis (61% versus 78%), possibly because they felt too sick to breastfeed or because of greater concerns regarding HIV-1 transmission or ARV toxicity for their breastfed child. This was also observed in a South-African study.[21] Despite this higher breastfeeding rate and ART during breastfeeding, half (4 of 8) of the transmissions in cohort A compared with only 1 of 8 transmissions in cohort B clearly occurred during the postnatal period. The risk of late postnatal transmission was only 0.9% in cohort B, similar to the 1.4% risk of transmission between 6 weeks and 24 months among women with CD4 counts >500 cells per cubic millimeter enrolled in a West African study,[9] despite no use of ARVs during the postnatal period. This rate of MTCT during breastfeeding is also similar to rates observed when mothers received triple prophylaxis during breastfeeding (women not meeting eligibility criteria for long-term ART)—between 0.5% and 0.9% in Rwanda,[22] Mozambique,[23] Tanzania,[24] and Kenya.[19]

The overall 18-month rate of transmission in cohort B was 5.8% (95% CI: 2.8 to 11.8), lower—although not significantly—than the 9.1% (95% CI: 4.8 to 13.4) observed in West African women with CD4>500 cells per cubic millimeter receiving ZDV only.[9] Earlier initiation or a more intensive prophylactic regimen as now recommended[25] may help further reduce the risk of peripartum transmission.

Limitations of this study are similar to those of other observational cohorts. The purpose of this study was not to establish differences between the cohorts, and its design does not allow definitive comparisons between these groups. No factor was found associated with the risk of HIV-1 transmission in either cohort, but this may be due to small size of the 2 cohorts and their relative homogeneity having been established according to CD4 count strata. Because these 2 cohorts of women were part of a larger research project including a randomized controlled trial, the enrolled women benefited from an intensive follow-up and active tracing. The follow-up rates were high in both cohorts (97% and 91% at 18 months in cohorts A and B, respectively). Those women in cohort A had greater motivation to remain in the study because of continued access to ART.

In conclusion, in addition to preserving the health of the mother, ART during pregnancy and breastfeeding for pregnant women with low CD4 counts was associated with a risk of MTCT lower than reported with short-course prophylaxis, but transmissions still occurred. From a programatic perspective, strategies remain to be developed to ensure timely HIV-1

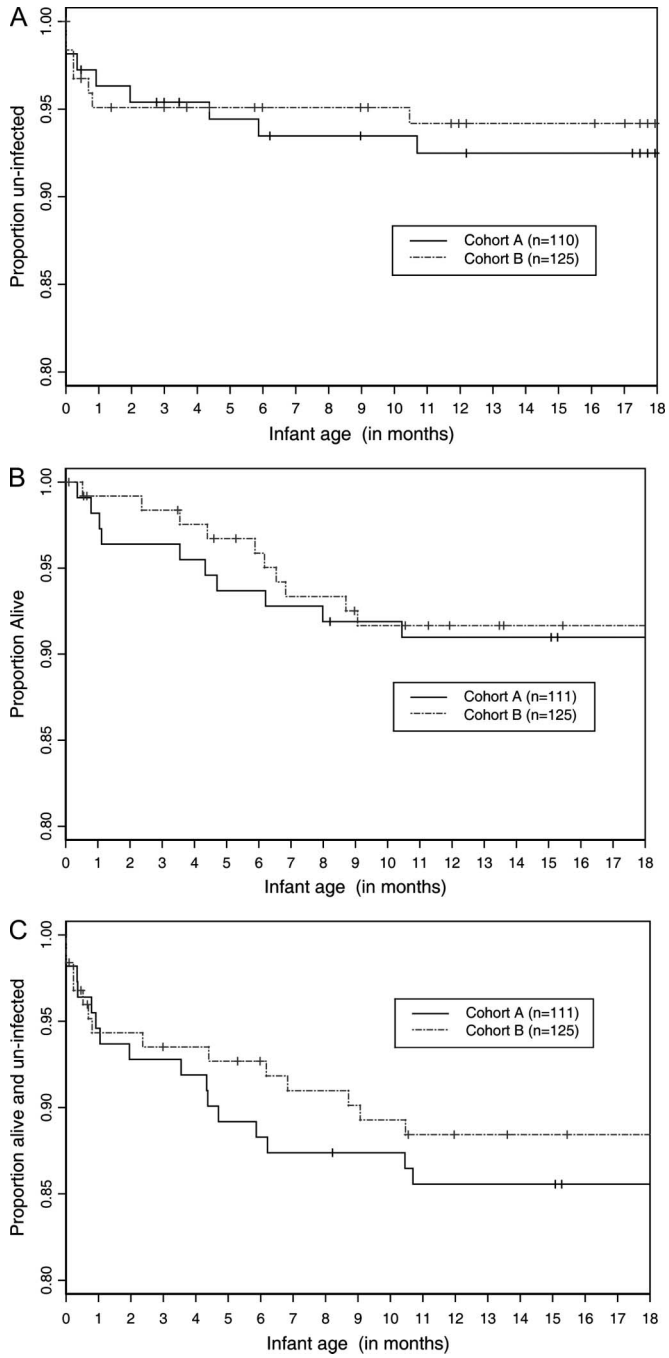

FIGURE 2. Life-table estimates of proportion of infants free of HIV-1 infection, alive or both. A, Infants free of HIV-1 infection; B, Infant survival; C, Infant HIV-1–free survival.

screening and staging (clinical and CD4 counts), rapid and/or priority access to ART when indicated such that treatment can be initiated well before delivery, and comprehensive but rapid counselling to ensure good adherence to treatment. On the other end of the HIV-1 spectrum, asymptomatic women with high CD4 counts—who represented over one third of HIV-1–infected pregnant women in the Kesho Bora study sites (data not shown) and elsewhere[26]—have a low risk of late postnatal transmission, and the benefits in terms of HIV-1 transmissions avoided may not outweigh the potential problems of continued maternal ARV prophylaxis during breastfeeding such as selection for drug resistance, supply, adherence, and cost issues. A group of experts convened by WHO in October 2009[25] did not discuss the specific needs of women with CD4 counts> 500 but recommended to provide the same ARV prophylaxis to all women with CD4 >350 cells per cubic millimeter. Based on randomized trials,[13,27,28] which also included women with CD4 lower than 350 cells per cubic millimeter, these experts concluded that an ARV prophylaxis during breastfeeding (ARV prophylaxis given either to the lactating mother or to the breastfed child) would be effective to reduce postnatal transmission. In view of the results presented here, the new recommendations may have a greater impact on MTCT rates by promoting early ART initiation for women with CD4 <350 cells per cubic millimeter and early initiation in pregnancy of ZDV-based or even triple ARV prophylaxis for women with CD4 >350 cells per cubic millimeter.

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APPENDIX I: THE KESHO BORA STUDY GROUP

Study Sites

1. Bobo-Dioulasso, Burkina-Faso (Centre Muraz): Nicolas Meda (principal investigator), Paulin Fao, Odette Ky-Zerbo, Clarisse Gouem (study co-ordinators), Paulin Somda, Hervé Hien, Patrice Elysée Ouedraogo, Dramane Kania, Armande Sanou, Ida Ayassou Kossiwavi, Bintou Sanogo, Moussa Ouedraogo, Issa Siribie (investigators), Diane Valéa (laboratory co-ordinator), Sayouba Ouedraogo and Roseline Somé (data manager), François Rouet (intersites laboratory co-ordination);

2. Mombasa, Kenya (International Centre for Reproductive Health): Stanley Luchters, Marcel Reyners (principal investigators), Eunice Irungu (study co-ordinator), Christine Katingima, Mary Mwaura, and Gina Ouattara (investigators), Kishor Mandaliya, Sammy Wambua (laboratory co-ordination), Mary Thiongo (data manager);

3. Nairobi, Kenya (NARESA): Ruth Nduati (principal investigator), Judith Kose (study co-ordinator), Ephantus Njagi (laboratory co-ordinator), Peter Mwaura (data manager).

Supporting Institutions

1. Agence Nationale de Recherches sur les SIDA et les hépatites virales, France: Brigitte Bazin and Claire Rekacewicz (sponsor representatives);

2. Centers for Disease Control and Prevention, USA: Allan Taylor, Nicole Flowers, Michael Thigpen, Mary Glenn Fowler, Denise Jamieson (sponsor representatives and co-investigators);

3. Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health, USA: Jennifer S. Read (sponsor representative and co-investigator);

4. Institut de Recherche pour le Développement, Montpellier, France: Kirsten Bork-Simondon, Cécile Cames and Amandine Cournil (Nutrition Coordination);

5. International Centre for Reproductive Health, Ghent, Belgium: Patricia Claeys, Marleen Temmerman (Sponsor Representatives);

6. Université Montpellier 1, EA 4205 "Transmission, Pathogenèse et Prévention de l'infection par le VIH"; and CHU Montpellier, Laboratoire de Bactériologie-Virologie, Montpellier, France: Philippe Van de Perre, Pierre Becquart (until December 2006), Vincent Foulongne, Michel Segondy (laboratory co-ordination).

Study Co-Ordination

World Health Organization, Geneva, Switzerland: Isabelle de Vincenzi (Study Coordinator), Philippe Gaillard (site co-ordinator), Tim Farley (project manager), Ndema Habib (study statistician), Sihem Landoulsi (study analyst).