Early Infant Feeding Patterns and HIV-free Survival

Findings from the Kesho-Bora Trial (Burkina Faso, Kenya, South Africa)

Amandine Cournil, PhD, Philippe Van de Perre, PhD,† Cécile Cames, PhD,**
*Isabelle de Vincenzi, PhD,‡ Jennifer S. Read, MD,§ Stanley Luchters, MD,¶‖ Nicolas Meda, PhD,***
*Kevi Naidu, MD,†† Marie-Louise Newell, PhD,‡‡ and Kirsten Bork, PhD,**
for the Kesho Bora Study Group§§

Objective: To investigate the association between feeding patterns and HIV-free survival in children born to HIV-infected mothers and to clarify whether antiretroviral (ARV) prophylaxis modifies the association.

Methods: From June 2005 to August 2008, HIV-infected pregnant women were counseled regarding infant feeding options, and randomly assigned to triple-ARV prophylaxis (triple ARV) until breastfeeding cessation (BFC) before age 6 months or antenatal zidovudine with single-dose nevirapine (short-course ARV). Eighteen-month HIV-free survival of infants HIV-negative at 2 weeks of age was assessed by feeding patterns (replacement feeding from birth, BFC <3 months, BFC ≥3 months).

Results: Of the 753 infants alive and HIV-negative at 2 weeks, 28 acquired infection and 47 died by 18 months. Overall HIV-free survival at 18 months was 0.91 [95% confidence interval (CI): 0.88–0.93]. In the short-course ARV arm, HIV-free survival (0.88; CI: 0.84–0.91) did not differ by feeding patterns. In the triple ARV arm, overall HIV-free survival was 0.93 (CI: 0.90–0.95) and BFC <3 months was associated with lower HIV-free survival than BFC ≥3 months (adjusted hazard ratio: 0.36; CI: 0.15–0.83) and replacement feeding (adjusted hazard ratio: 0.20; CI: 0.04–0.94). In the triple ARV arm, 4 of 9 transmissions occurred after reported BFC (and 5 of 19 in the short-course arm), indicating that some women continued breastfeeding after interruption of ARV prophylaxis.

Conclusions: In resource-constrained settings, early weaning has previously been associated with higher infant mortality. We show that, even with maternal triple-ARV prophylaxis during breastfeeding, early weaning remains associated with lower HIV-free survival, driven in particular by increased mortality.

Key Words: infant, HIV-free survival, prevention of mother-to-child transmission, breastfeeding, antiretroviral therapy, Africa

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Identifying the optimal feeding strategy for infants of HIV-infected women in low- and middle-income countries remains crucial in the context of prevention of mother-to-child transmission of HIV. Although complete avoidance of breastfeeding prevents HIV transmission through breast milk, early weaning or replacement feeding from birth substantially increases infant morbidity and mortality in resource-constrained settings,[1–7] especially among HIV-infected children.[1,5] Continued breastfeeding in the absence of antiretroviral (ARV) prophylaxis during breastfeeding is associated with an increased risk of mother-to-child transmission.[8] When both death and HIV infection are combined in an HIV-free survival outcome, some studies have reported increased HIV-free survival among infants replacement-fed from birth compared to children breastfed for up to 6 months,[9,10] while others found risks of death or transmission in breastfed children to be similar to that in replacement-fed ones.[11–14]

Between 2005 and 2008, the Kesho Bora randomized controlled trial (RCT) enrolled HIV-infected pregnant women who were counseled to choose between exclusive breastfeeding for up to 6 months or replacement feeding from birth, as per World Health Organization (WHO) guidelines for HIV-infected women at the time.[15] They were randomly assigned to receive either triple ARV prophylaxis until cessation of breastfeeding (triple ARV arm) or zidovudine until delivery with single-dose nevirapine at the onset of labor (short-course ARV arm). This trial showed that maternal triple ARV prophylaxis during pregnancy and breastfeeding was safe and reduced the risk of overall mother-to-child transmission by 43% at 12 months.[16] A secondary analysis on this cohort indicated that in both arms, weaned and never breastfed children were at higher risk of mortality compared with children who were still breastfed.[1] Excess mortality was particularly marked when breastfeeding was stopped before 3 months of age.

The findings of the Kesho Bora RCT contributed to the updated 2009 WHO guidelines recommending extension of the breastfeeding period from 6 to 12 months and provision of ARVs during pregnancy and breastfeeding.[17] These guidelines were further updated in 2013, recommending universal maternal ARV therapy (ART) for life, or at least during pregnancy and breastfeeding.[18]

In this further analysis, we aimed to focus on HIV-free survival to take into account both mortality and transmission outcomes. We investigated the association between early feeding practices and HIV-free survival, and examined whether the presence or absence of ARV prophylaxis during breastfeeding modified this association.

From the *UMI 233, Institut de Recherche pour le Développement, Université Montpellier 1, Montpellier, France; †Department of Bacteriology-Virology, Institut National de la Santé et de la Recherche Médicale (INSERM) U1058; Université Montpellier and CHRU Montpellier, Montpellier, France; ‡Department of Reproductive Health and Research, World Health Organization, Geneva, Switzerland; §National Institutes of Health, Bethesda, Maryland; ¶International Centre for Reproductive Health (ICRH), Mombasa, Kenya; ‖International Centre for Reproductive Health, Ghent University, Ghent, Belgium; **Centre Muraz, Bobo-Dioulasso, Burkina Faso; ††University of KwaZulu-Natal, Durban, South Africa; ‡‡Africa Centre for Health and Population Studies, University of KwaZulu-Natal, Somkhele, South Africa; and §§The Kesho Bora Study Group members are listed in the Appendix.

Stanley Luchters, MD, is currently at the Centre for International Health, Burnet Institute, Melbourne, Victoria, Australia.

Marie-Louise Newell, PhD, is currently at the Faculty of Medicine, University of Southampton, Southampton, United Kingdom.

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Address for correspondence: Amandine Cournil, PhD, Institut de recherche pour le development, IRD/UM1, UMI233, BP 64501, 34394 Montpellier Cedex 5, France. E-mail: amandine.cournil@ird.fr.

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METHODS

Kesho Bora RCT and Study Population

The design of the Kesho Bora RCT has been described in detail previously.[16,19] Briefly, women were enrolled from June 2005 to August 2008 in 5 study sites (Bobo-Dioulasso, Burkina Faso; Mombasa, Kenya; Nairobi, Kenya; Durban, South Africa; and Somkhele, South Africa). Enrollment criteria for the RCT were: gestational age less than 34 weeks, WHO clinical stage 1, 2 or 3, and CD4 count of 200–500 cells/mm^3. Women were randomized to initiate an ARV intervention from 36 weeks gestation of either triple ARV prophylaxis (combination of zidovudine, lamiduvine, and lopinavir/ritonavir) until cessation of breastfeeding (triple ARV arm) or zidovudine until delivery with single-dose nevirapine at the onset of labor without postpartum prophylaxis (short-course ARV arm). Women enrolled in the RCT and their first live born infants were included in the present analysis if the child was still alive and HIV-uninfected at 2 weeks of age.

Follow-up Procedures

All mothers were counseled on infant feeding as per 2004 WHO guidelines.[15] Women who opted for replacement feeding from birth received free formula for up to 6 months. Demonstrations of formula preparations were performed. Those who opted for breastfeeding were supported and counseled to exclusively breastfeed and wean rapidly over a 2-week period, with complete cessation before the infant reached 6 months of age.[20] The importance of exclusive breastfeeding was emphasized, and optimal breastfeeding techniques were explained. Women in the triple ARV group received prophylaxis until cessation of breastfeeding for a maximum of 7 months. Those who ceased breastfeeding before 6 months were advised to stop taking ARVs at the subsequent follow-up visit (up to 1 month later), once complete cessation of breastfeeding was achieved.

Mother–infant pairs were seen at birth, every 2 weeks until 8 weeks after delivery, monthly until 12 months and then every 3 months until 18 months to assess clinical, nutritional and biological characteristics (a total of 17 follow-up visits).

Infant feeding patterns were assessed by interviewers who were not involved in infant feeding counseling (except the Bobo-Dioulasso study site) at each visit using an adaptation of the WHO infant feeding assessment tool.[21] At each visit, mothers were asked if their child had been given breast milk, replacement feeding or both. From the 2-week to the 6-month visit, an additional questionnaire was used for breastfeeding women to record foods or fluids ever given since the last scheduled visit.

All infants were prescribed cotrimoxazole prophylaxis from 6 weeks to 12 months of age. Such prophylaxis was discontinued earlier if all exposure to HIV had ceased and the infant was HIV-uninfected. When needed, ART was supplied to mothers and children, as was treatment for opportunistic infections and other intercurrent diseases.

The HIV infection status of infants was assessed at 6 weeks of age by a quantitative HIV RNA real-time PCR assay (Generic HIV-1 Charge Virale, Biocentric, Bandol, France). Infants who were HIV-uninfected at 6 weeks of age were tested again at 12 months of age or a stored blood sample from their last visit was tested if the infant died or was lost to follow-up before then. If an infant was HIV-infected, earlier stored blood samples were tested to identify the time of infection (defined as the midpoint between the last negative and first positive PCR assay result).[19] The 2-week blood sample was used to assess infant's HIV infection status at 2 weeks.

Definitions for This Analysis

Children who were exclusively replacement fed from birth (i.e., never reported breastfeeding at any visit) were assigned to the replacement feeding group. Children who were ever breastfed, irrespective of the duration of breastfeeding, were assigned to the breastfeeding group. Within this group, we distinguished those who ceased breastfeeding before 3 months and those who were still breastfed at 3 months of age. The time of breastfeeding cessation was defined as the last visit at which any breastfeeding (ie, any breastfeeding since the previous visit, irrespective of the duration) was reported by the mother without any other form of confirmation. In case of inconsistencies in breastfeeding reports, infants were assigned to the breastfeeding group until the last report of breastfeeding, even if the mothers had previously reported to have ceased breastfeeding and then resumed breastfeeding afterwards.

Statistical Analysis

The event of interest in survival analyses was death or HIV infection, and hazard ratios were calculated for HIV-free survival. Infants who never had a positive HIV test and who did not die during follow-up were censored at the age of their last negative test result. Cumulative HIV-free survival probabilities in the first 18 months of life were assessed by Kaplan–Meier analysis. The log-rank test was used for comparison. Cox proportional hazards models were used to determine the relationship between feeding practices and HIV-free survival. An interaction term combining feeding practices and ARV prophylaxis type was included in the models to determine whether receiving triple ARV prophylaxis would modify the association between feeding practices and HIV-free survival. Adjustment for confounding factors was performed using an infant feeding propensity score, intended to balance the covariates in the feeding groups as an alternative method to conventional multivariable analysis for confounding bias.[22,23] The propensity scores were calculated using multinomial logistic regression with feeding practices as the outcome. Maternal and infant baseline characteristics listed in Table 1 were included in the propensity score model. Multiple imputations were performed to address missing data for 3 variables (maternal viral load, CD4 count at delivery and infant birth weight).

In HIV-free survival analyses, death and infection were treated as identical events. In additional analyses, competing risks Cox models were used to estimate hazard ratios for the risk of death and infection separately.[24] Sensitivity analyses were implemented after exclusion of children who died or were lost to follow-up before 3 months and also using time-dependent variables for feeding patterns (breastfed, weaned or replacement fed from birth at each point of time) to avoid the 3-month cutoff.

The ethical and regulatory committees in Burkina Faso, Kenya, and South Africa, and at the WHO and the U.S. Centers for Disease Control and Prevention gave ethical clearance for the study. All women provided written consent. The RCT was registered with Current Controlled Trials, ISRCTN71468401.

RESULTS

Size and Characteristics of the Study Population

A total of 824 HIV-infected women were enrolled in the Kesho Bora RCT, of whom 805 delivered live born infants. Nine infants died before 2 weeks and 6 were lost to follow-up before that age. An additional 37 were diagnosed as HIV-infected at 2 weeks. Thus, the study population for this analysis comprised 753 infants (Fig. 1).

The proportion of breastfeeding mothers and the duration of breastfeeding differed markedly by study site (Table 1). Mothers who implemented replacement feeding at birth were more likely to have a higher education level, to be unmarried, and to have access to a protected source of water. They were also more likely to have a CD4 count less than 350 cells/mm^3 at delivery and to have had a caesarean delivery. Among ever-breastfeeding mothers, the median

TABLE 1. Maternal and Infant Characteristics According to Feeding Patterns at 3 Months

	Total	Replacement Feeding (N = 166)	BF Cessation <3 mo (N = 161)	BF Cessation ≥3 mo (N = 426)
	n (%)	n (%)	n (%)	n (%)
Study site				
Bobo Dioulasso, Burkina Faso	227 (30)	15 (9)	34 (21)	178 (42)
Nairobi, Kenya	41 (5)	10 (6)	11 (7)	20 (5)
Mombasa, Kenya	218 (29)	47 (28)	68 (42)	103 (24)
Durban, South Africa	178 (24)	76 (46)	28 (17)	74 (17)
Somkhele, South Africa	89 (12)	18 (11)	20 (12)	51 (12)
Period of enrollment				
2005–2006	288 (38)	54 (32)	65 (40)	169 (40)
2007–2008	465 (62)	112 (68)	96 (60)	257 (60)
Maternal age (years)				
<25	238 (32)	51 (31)	56 (35)	131 (31)
25–34	443 (59)	99 (60)	90 (56)	254 (60)
≥35	72 (10)	16 (9)	15 (9)	41 (9)
Education level				
None	111 (15)	6 (4)	16 (10)	89 (21)
Primary	255 (34)	40 (24)	62 (38)	153 (36)
Secondary	387 (51)	120 (72)	83 (52)	184 (43)
Marital status				
Married	404 (54)	66 (40)	92 (57)	246 (58)
Not married	349 (46)	100 (60)	69 (43)	180 (42)
Socioeconomic score				
Low	255 (34)	48 (29)	48 (30)	159 (37)
Medium	245 (32)	55 (33)	56 (35)	134 (32)
High	253 (34)	63 (38)	57 (35)	133 (31)
Protected source of water				
No	353 (47)	59 (36)	69 (43)	225 (53)
Yes	400 (53)	107 (64)	92 (57)	201 (47)
WHO clinical stage at delivery				
1	529 (70)	122 (74)	111 (69)	296 (70)
2 or 3	224 (30)	44 (26)	50 (31)	130 (30)
CD4 count at delivery (cells/mm^{3}l)*				
<350	172 (24)	53 (33)	39 (25)	80 (21)
≥350	532 (76)	107 (67)	117 (75)	308 (79)
Viral load at delivery (copies/mL)*				
≥300	362 (52)	80 (50)	84 (56)	198 (52)
<300	331 (48)	79 (50)	67 (44)	185 (48)
Mode of delivery				
Vaginal	664 (88)	132 (79)	146 (91)	386 (91)
Cesarean	89 (12)	34 (21)	15 (9)	40 (9)
Infant characteristics				
Gender				
Male	368 (49)	86 (52)	90 (56)	192 (45)
Female	385 (51)	80 (48)	71 (44)	234 (55)
Birth weight (g)*				
<2500	64 (9)	12 (7)	8 (5)	44 (11)
≥2500	652 (91)	152 (93)	144 (95)	356 (89)

*Forty-nine, 60 and 37 mothers had missing data for CD4 cell count, viral load and birth weight of their child, respectively.
BF indicates breastfeeding; WHO, World Health Organization.

duration of breastfeeding was 1.7 months (interquartile range: 0.9–2.0) in those who ceased <3 months and 5.3 months (IQR: 2.9–6.0) in those who ceased ≥3 months of age. Only 14 breastfeeding women reported mastitis problems, 5 and 9 (ie, 3.1% and 2.1%) among those who ceased breastfeeding <3 and ≥3 months, respectively. In the triple ARV arm, 43% of the 376 mothers reported at least 1 missed dose of ARVs during postpartum prophylaxis.

Forty-seven (6.2%) of the 753 children died between 2 weeks and 18 months of age; for 39 of them, the last PCR test was negative. Twenty-eight children became HIV-infected, of whom 8 died during follow-up (Table 2).

The estimated overall HIV-free survival at 18 months was 0.91 [95% confidence interval (CI): 0.88–0.93]. HIV-free survival was higher in the triple ARV prophylaxis arm (0.93; CI: 0.90–0.95) than in the short-course arm (0.88; CI: 0.84–0.91) (*P* value for log-rank test = 0.01).

Infant Feeding and HIV-free Survival

The multivariable Cox proportional hazard model including an interaction term combining type of prophylaxis and infant feeding pattern indicated that the relationship between infant feeding and HIV-free survival differed according to the type of prophylaxis (*P* value for interaction term = 0.04); thus, analyses were conducted separately for each type of prophylaxis. While in the short-course arm there was no significant association between HIV-free survival and feeding pattern, HIV-free survival was decreased in children who stopped breastfeeding <3 months compared with those who stopped ≥3 months of age in the triple ARV prophylaxis arm (Table 3). Moreover, when early weaned infants were compared to those replacement-fed from birth, the former had lower HIV-free survival (adjusted hazard ratio: 0.20; CI: 0.04–0.94). Sensitivity analyses were conducted excluding 15 children who died or were lost to follow-up before 3 months and led to similar results (Table 3).

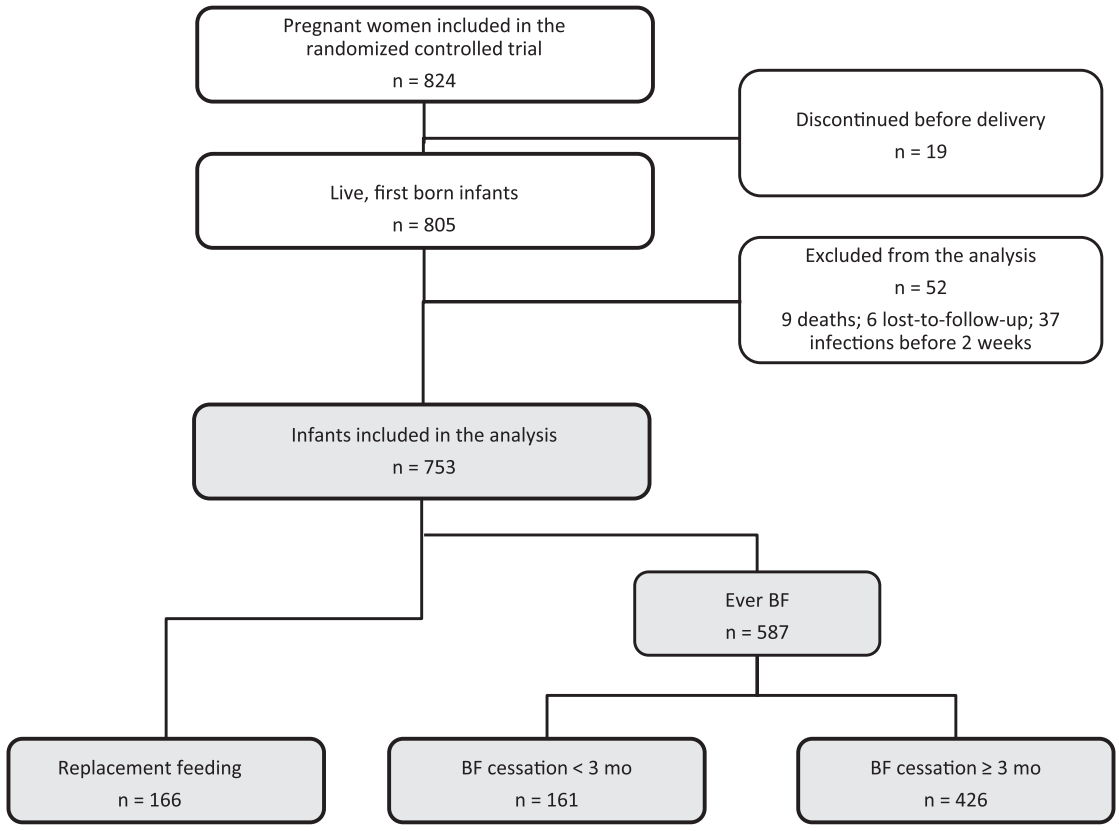

FIGURE 1. Flow diagram for population selection. BF, breastfeeding.

Additional analyses were conducted in which infant feeding was entered in the model as a time-dependent variable (still breastfeeding, reported to have stopped breastfeeding or never breastfed). In the triple ARV arm, HIV-free survival was lower in children for whom mothers reported to have ceased breastfeeding compared with still breastfed children (hazard ratio: 0.22; CI: 0.06–0.76). The HIV-free survival did not differ significantly between children still breastfed and those never breastfed [hazard ratio (still breastfed vs. never breastfed): 0.81; CI: 0.13–5.00].

Infant Feeding and Risk of Death or Infection (Competing Risks)

To further explore whether lower HIV-free survival among children who ceased breastfeeding in the triple ARV arm was mainly due to mortality or to transmission, the risks of death and of transmission were assessed separately using competing risks models. The risk of death was higher in children who stopped breastfeeding <3 months than in those who stopped ≥3 months (adjusted hazard ratio: 3.94; CI: 1.27–12.27). Risk of transmission did not significantly differ between the 2 feeding groups [adjusted hazard ratio (<3 vs. ≥3 months): 1.67; CI: 0.42–6.67].

Unreported Breastfeeding Continuation and Postnatal Transmission

Among the 28 HIV-infected children, 9 children who tested HIV-negative after reported breastfeeding cessation subsequently became HIV-infected, with 6 of these at the Bobo-Dioulasso study site. Thus, in the triple ARV arm, 4 of 9 HIV transmissions occurred during unreported breastfeeding continuation while the mother was no longer receiving ARVs (Table 2). In the

TABLE 2. Infant Deaths and HIV Infections by ARV Prophylaxis Arm and Feeding Patterns

	Triple ARV Arm (Including Postpartum Prophylaxis)			Short-Course ARV Arm (Without Postpartum Prophylaxis)			Total
		BF Cessation			BF Cessation		
Infant events, n (%)	RPF N = 85	<3 months N = 82	≥3 months N =209	RPF N = 81	<3 months N = 79	≥3 months N = 217	N = 753
Death	2 (2.4)	9 (11.0)	6 (2.9)	9 (11.1)	7 (8.9)	14 (6.5)	47 (6.2)
HIV infection	0 (0.0)	3+1 (4.9)*	2+3 (2.4)*	0 (0.0)	2 (2.5)	12+5 (7.8)†	28 (3.7)
Death or infection	2 (2.4)	11 (13.4)	11 (5.3)	9 (11.1)	7 (8.9)	27 (12.4)	67 (8.9)

*Transmissions which occurred after interruption of ARV prophylaxis.
†Transmissions which occurred after reported breastfeeding cessation.
BF indicates breastfeeding; RPF, replacement feeding since birth.

TABLE 3. Cox Proportional Hazards Analyses for HIV-free Survival Between 2 Weeks and 18 Months

	N = 753			N = 738*		
Feeding Patterns	n/N	HR	95% CI	n/N	HR	95% CI
Triple ARV arm (including postpartum prophylaxis)						
BF cessation >3 mo	198/209	1		198/209	1	
BF cessation <3 mo	71/82	0.36	0.15–0.83	68/78	0.40	0.17–0.98
RPF from birth	83/85	1.79	0.38–8.33	83/85	1.85	0.40–8.33
Short-course ARV arm (without postpartum prophylaxis)						
BF cessation >3 mo	190/217	1		190/217	1	
BF cessation <3 mo	72/79	1.22	0.52–2.94	68/74	1.85	0.69–5.00
RPF from birth	72/81	0.91	0.41–2.00	72/81	1.72	0.64–4.54

Models included propensity score for adjustment.
*Children who died or were lost to follow-up before 3 months were excluded from analyses.
BF indicates breastfeeding; HR, hazard ratio; n, number of survivors; N, number of infants at risk; RPF, replacement feeding.

short-course arm, 5 of 19 transmissions occurred after breastfeeding cessation report.

DISCUSSION

We assessed HIV-free survival associated with different feeding patterns in the presence or absence of maternal postpartum triple ARV prophylaxis to prevent transmission through breastfeeding. We show that the relationship between infant feeding pattern and HIV-free survival differed by type of prophylaxis: while in the short-course ARV arm (without postpartum prophylaxis), HIV-free survival did not differ by feeding pattern, in the triple ARV arm (with postpartum ARV prophylaxis for up to 6 months), cessation of breastfeeding <3 months of age resulted in the lowest HIV-free survival at 18 months, mainly driven by increased mortality. Our results thus suggest that while ART cover during breastfeeding in early life reduces transmission, early weaning remains associated with higher risk of mortality.[1,2,4,7,25] Our findings thus strengthen 2013 WHO guidelines which recommend initiation of triple ARV prophylaxis early in pregnancy to continue through the breastfeeding period (option B) or to provide lifelong triple ARV treatment for all HIV-infected pregnant or breastfeeding women (option B+).[18]

The Zambia Exclusive Breastfeeding study evaluated whether exclusive breastfeeding up to 4 months (without any ARV prophylaxis) followed by abrupt weaning would reduce postnatal transmission and mortality within the first 2 years of life.[5] In agreement with our observations in the short-course arm, the results indicated that early weaning did not improve the rate of infant HIV-free survival. Moreover, the benefit of early weaning in terms of reduced HIV transmission was unexpectedly low. In the present analysis, there was no difference in the rate of transmission between the 2 breastfeeding patterns (weaning <3 or ≥3 months of age) in the triple ARV arm where the overall transmission rate was lower.

Our results could be explained by the weaning period being a time of increased risk of transmission[26] or, as suggested previously, by much of postnatal transmission occurring soon after birth, probably because viral load in milk is higher in the early postnatal period.[27–30] Further, it has recently been suggested that cell-associated virus, which is less likely to be affected by ARV exposure than cell-free virus, plays an important role in early breast milk transmission in the presence of ARVs.[31,32] Indeed, activated CD4 T-cells producing HIV have been identified in the breast milk of HIV-infected women, including among women on ARVs.[33] Our results are consistent with observations suggesting that weaning in the early rather than later postnatal period does not substantially reduce the risk of transmission but increases risk of mortality, and support the WHO recommendations for continued breastfeeding up to at least 1 year of age while using ARV prophylaxis.[34]

In a previous analysis of Kesho Bora data, we showed that children of mothers who chose replacement feeding from birth were at higher risk of death than breastfed children, especially among children infected at birth.[1] Here, analyses were conducted in children uninfected at 2 weeks, and we find that HIV-free survival was similar for replacement-fed children and children breastfed ≥3 months. Women who chose to replacement feed from birth were further advanced in their HIV infection, which would have increased their transmission risk, but were also more educated and more likely to have access to safe water sources, which would have decreased mortality risk for their infants. These differences were taken into account in the analysis, but other unmeasured factors associated with survival might also differ across feeding groups.

Some children from mothers who reported to have ceased breastfeeding nevertheless acquired infection subsequently. Unreported breastfeeding continuation has been recognized in other studies and linked with concerns of societal criticism and worries about impact on infant health.[35–37] Of concern here would be the possibility that the transmission risk after interruption of preventive treatment may be increased due to a viral rebound in breast milk[38–40] and the infant might be at greater risk of receiving drug-resistant viruses.[41] Unreported breastfeeding observations suggest that option B+ with lifelong ARV treatment provided to the mother could be preferred to option B recommending ARV prophylaxis to be given only during the breastfeeding period.

Our analysis has some limitations. We cannot exclude reverse causality to partly explain the association between feeding patterns and HIV-free survival, although when we previously investigated this we found a low extent of time-dependent confounding.[1] This analysis addressed secondary objectives, for which the Kesho Bora RCT was not necessarily statistically powered. The number of events was limited and hindered further exploration of feeding practices in more detail. Finally, misclassification of feeding pattern among a nonnegligible proportion of infected and uninfected children could have occurred, but its importance is difficult to assess.

In conclusion, in the absence of maternal ARVs during breastfeeding in the first 6 months of life, HIV-free survival did not differ by feeding patterns. With 6-month maternal combination ARV during breastfeeding, overall infant HIV-free survival was

increased, but early weaning was associated with a significantly lower HIV-free survival than longer breastfeeding or replacement feeding among infants uninfected at 2 weeks of age. These observations support the 2013 WHO recommendations[18] that women should breastfeed for at least 1 year and continue taking triple ARVs throughout the breastfeeding period.

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APPENDIX: 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 coordinators), Paulin Somda, Hervé Hien, Patrice Elysée Ouedraogo, Dramane Kania, Armande Sanou, Ida Ayassou Kossiwavi, Bintou Sanogo, Moussa Ouedraogo, Issa Siribie (Investigators), Diane Valéa (Laboratory Coordinator), Sayouba Ouedraogo, Roseline Somé (Data Managers), François Rouet (Inter-Site Laboratory Coordination).

(2) Durban, South Africa (University of KwaZulu Natal): Nigel Rollins (Principal Investigator), Lynne McFetridge, Kevi Naidu (Study Coordinators).

(3) Mombasa, Kenya (International Centre for Reproductive Health): Stanley Luchters, Marcel Reyners (Principal Investigators), Eunice Irungu (Study Coordinator), Christine Katingima, Mary Mwaura, Gina Ouattara (Investigators), Kishor Mandaliya, Sammy Wambua (Laboratory Coordinators), Mary Thiongo (Data Manager).

(4) Nairobi, Kenya (Network for AIDS Researchers in East and Southern Africa): Ruth Nduati (Principal Investigator), Judith Kose (Study Coordinator), Ephantus Njagi (Laboratory Coordinator), Peter Mwaura (Data Manager).

(5) Somkhele, South Africa (Africa Centre for Health and Population Studies, University of KwaZulu Natal): Marie-Louise Newell (Principal Investigator), Stephen Mepham (Study Coordinator), Johannes Viljoen (Laboratory Coordinator), Ruth Bland (Investigator), Londiwe Mthethwa (Data Manager).

Supporting Institutions

(1) Agence Nationale de Recherches sur le SIDA et les hépatites virales, France: Brigitte Bazin, Claire Rekacewicz (Sponsor Representatives).

(2) Centers for Disease Control and Prevention, USA: Allan Taylor (Sponsor Representative and Co-Investigator), Nicole Flowers, Michael Thigpen, Mary Glenn Fowler, Denise Jamieson (Co-Investigators).

(3) *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, National Institutes of Health, USA: Lynne M. Mofenson (Sponsor Representative), Jennifer S. Read (Co-Investigator).

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

(5) International Centre for Reproductive Health (ICRH), Ghent University, Ghent, Belgium: Patricia Claeys, Marleen Temmerman, Stanley Luchters (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, Vincent Foulongne, Michel Segondy (Laboratory Coordination).

Study Coordination

World Health Organization, Geneva, Switzerland: Isabelle de Vincenzi (Study Coordinator), Philippe Gaillard (Site Coordinator), Tim Farley (Project Manager), Ndema Habib (Study Statistician) and Sihem Landoulsi (Study Analyst).

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