Morbidity and Mortality in Breastfed and Formula-Fed Infants of HIV-1–Infected Women

A Randomized Clinical Trial

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Context Breastfeeding among women infected with human immunodeficiency virus type 1 (HIV-1) is associated with substantial risk of HIV-1 transmission, but little is known about the morbidity risks associated with formula feeding in infants of HIV-1–infected women in resource-poor settings.

Objective To compare morbidity, nutritional status, mortality adjusted for HIV-1 status, and cause of death among formula-fed and breastfed infants of HIV-1–infected women.

Design Randomized clinical trial conducted between 1992 and 1998.

Setting Four antenatal clinics in Nairobi, Kenya.

Participants Of 401 live-born, singleton, or first-born twin infants of randomized HIV-1–seropositive mothers, 371 were included in the analysis of morbidity and mortality.

Interventions Mothers were randomly assigned either to use formula (n=186) or to breastfeed (n=185) their infants.

Main Outcome Measures Mortality rates, adjusted for HIV-1 infection status; morbidity; and nutritional status during the first 2 years of life.

Results Two-year estimated mortality rates among infants were similar in the formula-feeding and breastfeeding arms (20.0% vs 24.4%; hazard ratio [HR], 0.8; 95% confidence interval [CI], 0.5-1.3), even after adjusting for HIV-1 infection status (HR, 1.1; 95% CI, 0.7-1.7). Infection with HIV-1 was associated with a 9.0-fold increased mortality risk (95% CI, 5.3-15.3). The incidence of diarrhea during the 2 years of follow-up was similar in formula and breastfeeding arms (155 vs 149 per 100 person-years, respectively). The incidence of pneumonia was identical in the 2 groups (62 per 100 person-years), and there were no significant differences in incidence of other recorded illnesses. Infants in the breastfeeding arm tended to have better nutritional status, significantly so during the first 6 months of life.

Conclusions In this randomized clinical trial, infants assigned to be formula fed or breastfed had similar mortality rates and incidence of diarrhea and pneumonia during the first 2 years of life. However, HIV-1–free survival at 2 years was significantly higher in the formula arm. With appropriate education and access to clean water, formula feeding can be a safe alternative to breastfeeding for infants of HIV-1–infected mothers in a resource-poor setting.

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We conducted a randomized clinical trial of breastfeeding and formula feeding in Nairobi, Kenya, and previously reported that the estimated risk of breast milk transmission of human immunodeficiency virus type 1 (HIV-1) was 16%.[1] Forty-four percent of all HIV-1 infections among those in the breastfeeding arm were attributable to breastfeeding. This result, in conjunction with results from clinical trials of short-course antiretrovirals that have reported approximately 40% to 50% reductions in perinatal transmission rates, suggest that it may be possible to reduce substantially mother-to-child transmission of HIV-1 in the developing world with interventions of moderate cost.[2]

In resource-poor settings where the most prevalent causes of infant morbidity and mortality are infectious, there is the possibility that breast milk avoidance would be accompanied by an in-

For editorial comment see p 2462.

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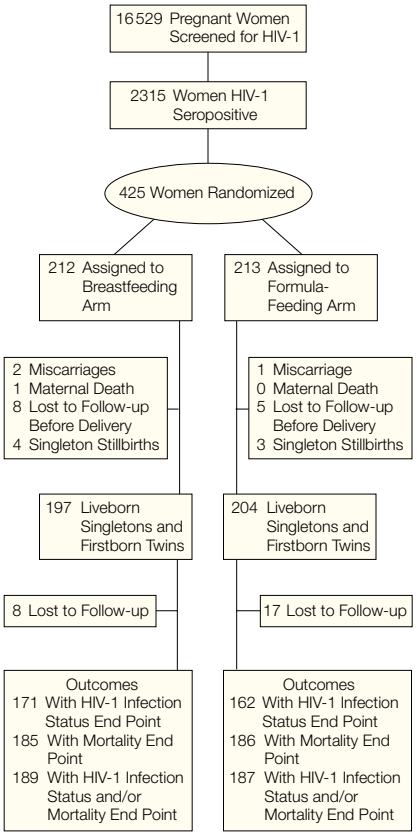
Figure 1. Trial Flow Diagram of Participants



HIV-1 indicates human immunodeficiency virus type 1.

crease in mortality that might offset any gains achieved by decreasing HIV-1 transmission. To enable the formulation of safe infant-feeding policies for HIV-1–infected women in resource-poor settings, it is important to have accurate estimates of the risks associated with the use of artificial feeds by infants of HIV-1–seropositive mothers in developing countries.

The risk of mortality associated with the use of artificial feeding has been reported in a number of observational studies from developing countries.[3,4] In a recent meta-analysis, the increased mortality risk due to infectious diseases among nonbreastfeeders was substantial, particularly among very young infants (odds ratio [OR], 5.8 for 0-2 months of age; OR, 4.1 for 2-3 months; OR, 2.6 for 4-5 months; and lower thereafter).[4] Observational studies have reported substantially increased diarrhea risk in artificially fed infants, with highest risk being noted in the first 2 to 3 months of life.[3,5] The protective role of breastfeeding with regards to other infectious diseases in developing countries has not been studied as extensively. However, there are some data that suggest that formula fed infants are at increased risk of pneumonia compared with breastfed infants.[3,6]

One of the major mechanisms of the protection conferred through breastfeeding is by the passive transfer of antibodies, immune-competent cells, and cytokines.[7] For mothers with HIV-1–related immunocompromise, it is unknown whether breastfeeding would confer the same magnitude of protection. No study to date has definitively evaluated the degree of protection that breast milk affords infants of HIV-1–infected mothers.

Our randomized clinical trial of breastfed and formula fed infants of HIV-1–seropositive women in Nairobi, Kenya, was conducted with the primary goal of determining the frequency of breast milk transmission of HIV-1. This unique trial also provided an opportunity to compare morbidity and mortality in children according to randomized feeding modality. We previously reported that 2-year mortality rates among children in the formula feeding and breastfeeding arms were similar.[1] In this companion article, we provide additional data regarding mortality as well as analyses of diarrhea, pneumonia, other childhood morbidities, and nutritional status.

METHODS

Study Population and Procedures

The methods of the randomized clinical trial were published in our original article,[1] including a detailed description of the study population, study procedures, feeding intervention, laboratory testing, criteria for infant HIV-1 infection status, ethical approval, and data and safety monitoring board deliberations. In brief, HIV-1–seropositive women were recruited from antenatal clinics in Nairobi and randomly assigned to breastfeed or to use formula to feed their infants. Mother/infant pairs were followed-up for 2 years after delivery.

At each visit, information was obtained about feeding status, current and interim morbidity, and history of hospitalization. A physical examination was conducted, including measurement of weight and recumbent length. Ill children received outpatient care from the study clinicians. In the event of diarrhea, mothers were advised to initiate the use of oral rehydration solutions before bringing the child to the research clinic. Children requiring hospital admission were managed by Kenyatta National Hospital staff and pertinent clinical information was abstracted from the hospital records. Verbal autopsies were conducted to assign a possible cause of death for all children who died outside of Kenyatta National Hospital.

Clinical Definitions

Current morbidity was determined by study clinicians using standard diagnostic criteria. Interim infant morbidities were based on maternal history. Diarrhea was defined as the passage of 3 or more loose or watery stools during a 24-hour period for at least 2 days. Chronic diarrhea was defined by diarrhea lasting for more than 1 month. Dehydration was defined as the presence of 1 or more of the following clinical signs and symptoms: abnormal thirst, dry oral mucosa, reduced skin turgor, sunken eyes, or decreased urine output. A diagnosis of pneumonia was made if a child had a cough with tachypnea. A presumptive clinical diagnosis of malaria was made in children with history of travel to a malaria-endemic area who presented with fever (axillary temperature >37.5°C) in the absence of any localizing site of infection. Weight for height was used to evaluate nutritional status. We calculated *Z* scores using Epinet (Centers for Disease Control and Prevention, Atlanta, Ga) and values below –2 SD were used to define malnutrition.[8]

Statistical Analysis

All data were analyzed using SPSS 10.0 for Windows (SPSS, Chicago, Ill) or S-Plus 2000 (MathSoft, Inc, Seattle, Wash).

Comparisons were made on an intent-to-treat basis. Pearson χ^2 test and Fisher exact test were used to compare categorical variables and the Mann-Whitney U test to compare continuous variables. Infant mortality in the 2 randomization groups was compared using Kaplan-Meier analysis. Cox regression was used to compare survival in the 2 groups adjusted for HIV-1 infection status as a time-dependent covariate. A child was considered to have an unknown HIV-1 infection status if the last HIV-1 test was more than 3 months before the last determination of vital status and if they had a negative test result at that time.

The incidence of infant illnesses in formula feeding and breastfeeding arms over the 2 years of follow-up and by quarter was compared using Andersen-Gill proportional hazards models, adjusting for number of clinic visits and with robust variance estimates.[9] For analyses stratified by infant HIV-1 infection status, we excluded the interval between the last negative HIV-1 test and the first positive HIV-1 test for infected children. For children who remained HIV-1 uninfected, we excluded any visits after the last negative HIV-1 test. Random effects models were used to compare anthropometric indices.[10]

RESULTS

Characteristics of the Study Population

A detailed description of the randomized clinical trial participants and primary end point results has been published.[1] Of 425 women enrolled in the study between 1992 and 1998, 213 were randomly assigned to the formula feeding arm and 212 to the breastfeeding arm (FIGURE 1). The women in each group had similar enrollment characteristics.[1]

Four hundred twenty infants were born to the 408 women who were in follow-up at the time of delivery. After excluding stillbirths and second born twins, there were 204 infants in the formula feeding arm and 197 in the breastfeeding arm. The infants in the 2 groups were comparable at birth with regards to anthropometric measurements, gestational age, sex, and morbidity[1] (data not shown). Follow-up information on infant morbidity and mortality during the first 2 years of life was available for 186 infants in the formula feeding and 185 in the breastfeeding arm, while HIV-1 infection status information was available for 162 infants in the formula feeding and 171 in the breastfeeding arms.[1]

A total of 4733 infant follow-up visits were made in the first 2 years of life, including 2579 in the formula feeding and 2154 in the breastfeeding arms. Infants in the breastfeeding arm attended significantly fewer scheduled visits to the clinic (median 9, range 1-19) than infants in the formula feeding arm (median 12, range 1-19, $P<.001$). Infants in the breastfeeding arm also tended to have fewer nonscheduled visits (median, 2 vs 3; $P=.06$). The median of the average intervisit interval for infants in the 2 arms was identical (36 days). The median durations of follow-up were 1.7 and 1.3 years in the formula feeding and breastfeeding arms, respectively, yielding total follow-up times of 257 and 228 person-years.

Compliance with randomized feeding modality was significantly higher in the breastfeeding arm than the formula feeding arm of the study (96% vs 70%, $P<.001$). The median duration of breastfeeding among infants randomized to breastfeed was 17 months, and the median age of introduction of supplemental feeds was 3.8 months.

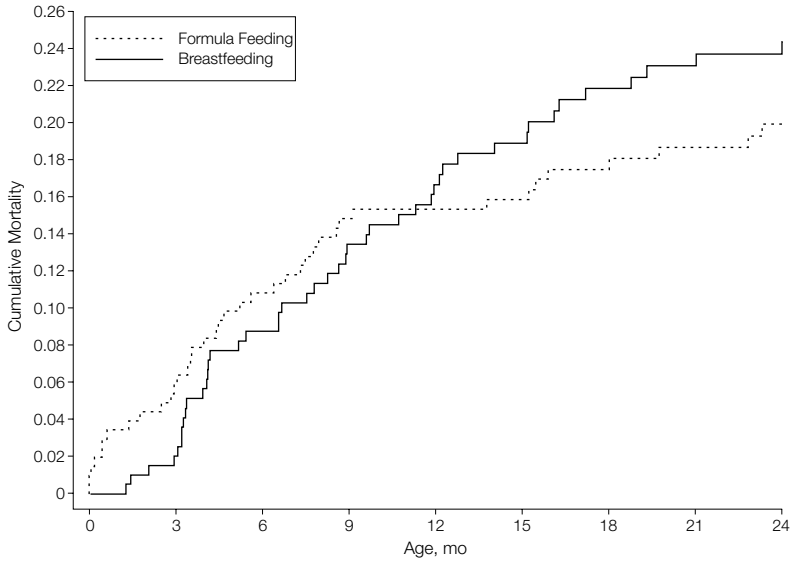
Ninety-two infants acquired HIV-1 infection during the study, 31 in the formula feeding arm and 61 in the breastfeeding arm. The cumulative proportion of HIV-1 infection at 2 years of follow-up was 21% in the formula feeding arm and 37% in the breastfeeding arm of the study ($P=.001$).[1]

Mortality

Of the 401 live-born infants in the study, 84 infants died during the course of follow-up, 39 in the formula feeding arm and 45 in the breastfeeding arm.

The cumulative mortality rates in the 2 groups are presented in FIGURE 2. Mortality rates in the formula feeding and breastfeeding arms did not significantly differ either at 12 months (15.4% vs 16.7%, $P=.71$) or at 2 years (20.0% vs 24.4%; hazard ratio [HR], 0.8; 95% confidence interval [CI], 0.5-1.3; $P=.30$).

Figure 2. Mortality of Children in the Formula Feeding and Breastfeeding Arms



Additional data regarding cumulative mortality are presented in reference 1.

There was a trend for increased mortality in the formula arm at 6 weeks (3.9% vs 1.0%, $P=.06$), but 38% of these deaths were due to complications of delivery and could not be attributable to formula exposure (TABLE 1). Among infants who remained HIV-1 uninfected throughout follow-up, the 2-year cumulative mortality rate was 10.0% in the formula feeding arm and 8.1% in the breastfeeding arm ($P=.59$). Among infants who became HIV-1 infected during the course of the study, the 2-year cumulative mortality rates were 40.2% in the formula arm and 46.0% in the breastfeeding arm ($P=.41$). We used Cox regression to examine the independent effects of randomization group and HIV-1 status on mortality, and there was no significant difference in mortality in the formula and breastfeeding arms (HR, 1.1; 95% CI, 0.7-1.7; $P=.77$). However, HIV-1 infection was associated with a 9.0-fold increased mortality risk (95% CI, 5.3-15.3; $P<.001$). Using Cox regression to analyze mortality risk in formula and breastfeeding arms after stratifying by ultimate HIV-1 –infection status, the hazard ratios did not significantly differ between HIV-1 uninfected (HR, 1.3; 95% CI, 0.6-3.0; $P=.49$) and HIV-1 infected (HR, 0.9; 95% CI, 0.5-1.8; $P=.82$) children.

Two-year mortality rates were much higher for children infected during the first 2 months of life than for children infected after 2 months of age (63.2% vs 8.8%, $P<.001$).

In a separate analysis we found that women who were randomly assigned to the breastfed group had an approximate 3-fold higher mortality rate over 2 years than women in the formula arm, and that maternal death was associated with increased risk of subsequent infant death.[11] We analyzed the infant mortality data controlling for maternal vital status. The relative effect of formula feeding compared with breastfeeding remained unchanged (HR, 0.8; 95% CI, 0.5-1.2).

One hundred thirty-eight infants died or became HIV-1 infected during the course of follow-up, including 58 in the formula arm and 80 in the breastfeeding arm. The percentage of infants who were dead or infected at 24 months was significantly lower in the formula arm (30% vs 42%, $P=.02$).[1] Formula feeding conferred a 28% protective effect from an adverse outcome (HIV-1 infection or death).

Precise information about causes of death was not available because of limited availability of diagnostic tests in health care facilities and reliance on verbal autopsies for children who died at home. For the 78 deaths for which potential contributing causes of death were known, information was obtained by review of hospital records for 41 (53%) and by verbal autopsy for 37 (47%). Pneumonia was the most common cause (53%). Other major contributing causes of death included diarrhea (39%), sepsis (10%), and failure to thrive (41%). Over the 2-year period, children in the 2 groups were comparable for causes of death, except for a higher frequency of sepsis in the formula group ($P=.02$) as well as a higher frequency of neonatal noninfectious deaths ($P=.04$, Table 1). In a stratified analysis, there were no significant differences in cause of death between the 2 groups for HIV-1–uninfected children. Among HIV-1–infected children, those in the formula arm were more likely to die from sepsis than those in the breastfed group (33% vs 0%, $P=.007$). During the first 6 months of life, pneumonia was a more common cause of death in the breastfeeding arm than in the formula arm ($P=.01$).

Diarrheal Morbidity

The incidence of diarrhea (defined by history of diarrhea since the last visit) during the 2 years of follow-up was almost identical in infants randomized to receive formula and to breastfeed (155 vs 149 per 100 person-years, respectively; HR, 0.9; 95% CI, 0.7-1.1) (TABLE 2). The incidence of diarrhea in-

Table 1. Potential Contributing Causes of Death by Randomization Arm*

	Deaths Between 0 and 6 mo			Deaths Between 6 and 24 mo			All Deaths		
Variables	Formula Feeding, No. (%) (n = 21)	Breastfeeding, No. (%) (n = 18)	*P* Value	Formula Feeding, No. (%) (n = 14)	Breastfeeding, No. (%) (n = 26)	*P* Value	Formula Feeding, No. (%) (n = 35)	Breastfeeding, No. (%) (n = 43)	*P* Value
Pneumonia	11 (52)	16 (94)	.01	5 (36)	9 (35)	.99	16 (46)	25 (58)	.27
Diarrhea	8 (38)	2 (12)	.14	8 (57)	12 (46)	.51	16 (46)	14 (33)	.24
Failure to thrive	7 (33)	5 (29)	.80	6 (43)	14 (54)	.51	13 (37)	19 (44)	.53
Sepsis	6 (29)	1 (6)	.10	1 (7)	0 (0)	.35	9 (20)	1 (2)	.02
Meningitis	2 (10)	2 (12)	.99	1 (7)	3 (12)	.99	3 (9)	5 (12)	.72
Malaria	1 (5)	0 (0)	.99	0 (0)	3 (12)	.54	1 (3)	3 (7)	.62
Measles	0 (0)	0 (0)	. . .	2 (14)	0 (0)	.12	2 (6)	0 (0)	.20
Tuberculosis	1 (5)	1 (6)	.99	0 (0)	1 (4)	.99	1 (3)	2 (5)	.99
Encephalopathy	0 (0)	0 (0)	. . .	0 (0)	2 (8)	.53	0 (0)	2 (5)	.50
Cerebral abscess	0 (0)	0 (0)	. . .	0 (0)	1 (4)	.99	0 (0)	1 (2)	.99
Neonatal noninfectious†	4 (19)	0 (0)	.11	0 (0)	0 (0)	. . .	4 (11)	0 (0)	.04
Road traffic accident	0 (0)	0 (0)	. . .	0 (0)	1 (4)	.99	0 (0)	1 (2)	.99

*More than one potential contributing cause of death was present for many children. Ellipsis indicates not applicable.
†Birth asphyxia (n = 2), cord improperly tied (n = 1), prematurity (n = 1).

Table 2. Incidence of Diarrhea by Randomization Arm

Symptoms	Incidence per 100 Person-Years (No. of Cases)		Hazards Ratio (95% Confidence Interval)*	*P* Value
	Formula Feeding	Breastfeeding		
All children, person-years	257	228		
Diarrhea (history of episodes since last visit)	155 (397)	149 (340)	0.9 (0.7-1.1)	.21
Oral rehydration solution use	77 (198)	70 (159)	1.0 (0.8-1.2)	.85
Chronic diarrhea	9 (23)	11 (24)	0.7 (0.4-1.5)	.37
>5 Stools/d	58 (150)	54 (123)	1.0 (0.7-1.4)	.99
Stools with blood	19 (50)	20 (46)	0.8 (0.5-1.5)	.45
Current diarrhea (at the time of a visit)	122 (313)	116 (264)	0.9 (0.7-1.2)	.51
Dehydration	16 (41)	13 (30)	1.2 (0.7-2.0)	.53
HIV-1–uninfected children, person-years	211	169		
Diarrhea (history of episodes since last visit)	150 (318)	140 (237)	0.9 (0.7-1.2)	.43
Oral rehydration solution use	74 (157)	68 (115)	0.9 (0.6-1.3)	.61
Chronic diarrhea	8 (16)	10 (17)	0.6 (0.3-1.4)	.39
>5 Stools/d	57 (121)	54 (91)	0.9 (0.6-1.4)	.79
Stools with blood	18 (38)	15 (26)	0.9 (0.4-2.2)	.92
Current diarrhea (at the time of a visit)	119 (251)	109 (185)	0.9 (0.6-1.2)	.41
Dehydration	12 (26)	11 (19)	0.9 (0.5-1.7)	.82
HIV-1–infected children, person-years	20	35		
Diarrhea (history of episodes since last visit)	241 (48)	247 (86)	1.1 (0.7-1.9)	.73
Oral rehydration solution use	146 (29)	106 (37)	1.4 (0.7-2.8)	.34
Chronic diarrhea	30 (6)	14 (5)	2.0 (0.5-8.6)	.29
>5 stools/day	96 (19)	78 (27)	1.4 (0.7-2.9)	.41
Stools with blood	30 (6)	46 (16)	0.7 (0.2-2.2)	.64
Current diarrhea (at the time of a visit)	191 (38)	190 (66)	1.1 (0.6-2.1)	.82
Dehydration	50 (10)	23 (8)	2.1 (0.5-8.6)	.34

*Hazards ratios are from Anderson-Gill proportional hazards model with robust variance estimate and controlling for number of visits.

creased with age and peaked at 9 to 12 months (FIGURE 3). When analyzed by 3-month quarter, there were no significant differences in diarrheal incidence between the 2 trial groups for any quarter.

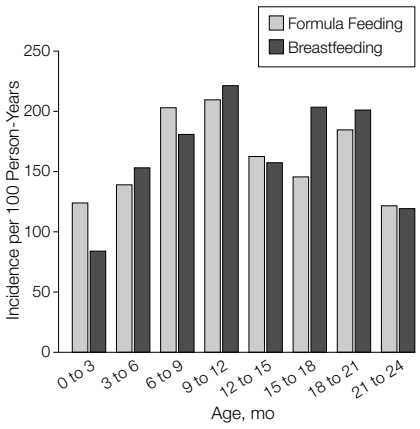
Among infants with diarrhea, the severity of diarrhea was similar in the 2 groups. Twelve percent of episodes of diarrhea were associated with bloody stools and 36% with more than 5 stools per day. Forty-five percent of episodes prompted the mother to administer oral rehydration solution and 8% of children with diarrhea at the time of a clinic visit presented with dehydration. Chronic diarrhea was reported by 10% of the study subjects. All of these characteristics were similar in the 2 groups (data not shown), as was the incidence of these measures of the severity of diarrhea over the 2-year period (Table 2). Investigating the severity of diarrhea by 3-month quarter, the incidence of dehydration (HR, 9.7; 95% CI, 1.3-74.0; $P=.03$) and current diarrhea (at the time of a visit) (HR, 2.1; 95% CI, 1.2-3.8; $P=.01$) were significantly higher in the formula group in the first 3 months of life while the incidence of diarrhea with more than 5 stools per day was significantly lower in the formula feeding group between ages 18 and 21 months (HR, 0.4; 95% CI, 0.2-0.8; $P=.01$).

After stratifying by HIV-1 infection status, there was no significant difference in incidence of diarrhea between formula and breastfeeding arms in either HIV-1 infected (241 vs 247 per 100 person-years) or uninfected infants (150 vs 140 per 100 person-years) (Table 2). This was true for the 2-year follow-up period as well as when analyzed by 3 month quarter. Likewise there were no significant differences for any of the measures of severity of diarrhea over the 2-year follow-up period.

Pneumonia

The incidence of pneumonia during the first 2 years of life in infants randomized to the formula and breastfeeding groups was identical (62 per 100 person-years; HR, 0.9; 95% CI, 0.7-1.3; $P=.74$) (TABLE 3). Pneumonia occurred with similar frequency in the 2 groups during every quarter of follow-up. There was no difference in pneumonia incidence over the 2-year period between the 2 groups after stratifying by HIV-1 infection status, ei-

Figure 3. Incidence of Diarrhea by Randomization Arm and Quarter



ther overall or for any quarter. Among HIV-1–infected children, the incidence of pneumonia was 188 per 100 person years among formula fed and 150 per 100 person-years among breastfed (HR, 1.2; 95% CI, 0.8-1.9; $P=.33$). Among HIV-1–uninfected children, the comparable figures were 50 vs 45 (HR, 0.9; 95% CI, 0.6-1.4; $P=.73$).

Other Morbidities

The overall incidence of various infant morbidities for the 2 randomization arms is presented in Table 3. There were no significant differences between the study arms for the incidence of any of the infant morbidities over the 2-year follow-up period although there was a trend for lower incidence of otitis media and higher incidence of conjunctivitis in the formula arm. We also compared morbidity incidence between the 2 groups during each quarter of follow-up. There were no significant differences between the 2 groups for any of the morbidities for any quarter of life.

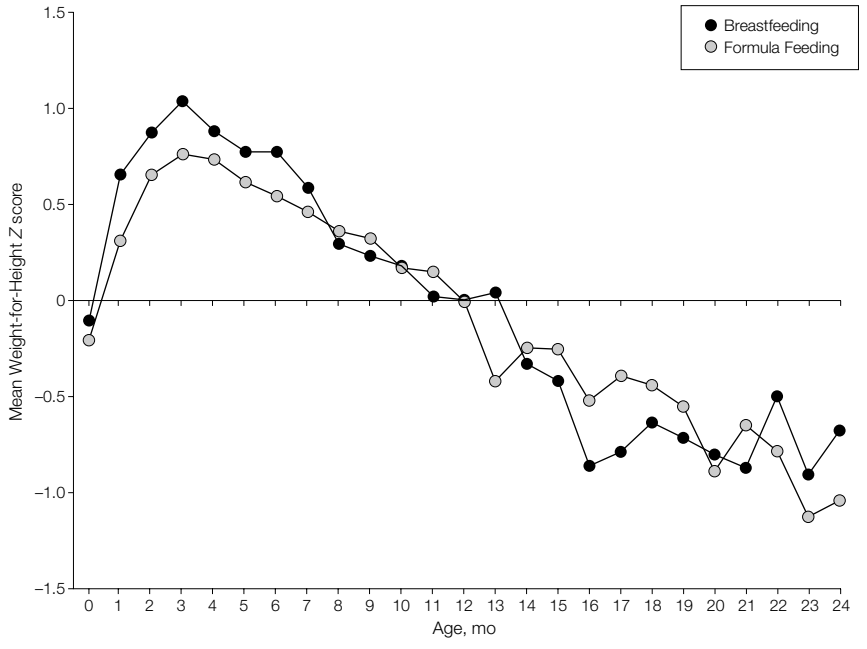
When stratifying by HIV-1 infection status, there was a higher incidence of sepsis in the formula arm compared with the breastfeeding arm among HIV-1–infected infants (HR, 13.7; 95% CI, 1.4-130.8; $P=.02$). No other significant differences were found between the 2 groups. Comparing morbidity incidence between the 2 groups during each quarter of follow-up, the only significant difference was an increased risk of reported hospitalization between 9 and 12 months in those infected with HIV-1 in the formula arm (HR, 8.7; 95% CI, 1.0-74.7, $P=.05$).

Table 3. Incidence of Other Morbidities by Randomization Arm

Variables	Incidence per 100 Person-Years (No. of Cases)		Hazards Ratio (95% Confidence Interval)*	*P* Value
	Formula Feeding (257 Person-Years)	Breastfeeding (228 Person-Years)		
Hospitalization since last visit	18 (47)	20 (46)	0.9 (0.6-1.5)	.71
Fever since last visit	265 (680)	255 (582)	0.9 (0.8-1.1)	.32
Vomiting since last visit	89 (228)	82 (188)	1.0 (0.8-1.3)	.84
Fever on examination	41 (104)	35 (81)	1.0 (0.7-1.5)	.83
Pneumonia	62 (159)	62 (142)	0.9 (0.7-1.3)	.74
Measles	4 (10)	3 (7)	1.1 (0.4-3.1)	.81
Malaria	81 (207)	71 (162)	1.0 (0.8-1.3)	.80
Thrush	43 (110)	45 (102)	0.9 (0.6-1.4)	.78
Otitis media	32 (83)	43 (98)	0.6 (0.4-1.0)	.06
Upper respiratory tract infection	343 (881)	322 (736)	1.0 (0.9-1.1)	.79
Conjunctivitis	30 (77)	22 (50)	1.4 (1.0-2.1)	.09
Sepsis	7 (18)	5 (12)	1.4 (0.6-3.0)	.54

*Hazards ratios are from Anderson-Gill proportional hazards model with robust variance estimate and controlling for number of visits.

Figure 4. Mean Weight-for-Height *Z* Scores by Randomization Arm and Age



Nutritional Status

The mean weight-for-height *Z* scores for infants by age and randomization group are shown in FIGURE 4. There was a trend for the breastfeeding arm to have better nutritional status overall ($P=.06$) and significantly better nutritional status in the first 6 months of life ($P=.003$). After adjusting for HIV-1 infection status, children in the breastfeeding arm had significantly better nutritional status than those in the formula arm over the 2-year period ($P=.04$), particularly during the first 6 months ($P=.002$). Malnutrition (weight-for-height *Z* scores that were less than −2 SDs) occurred at some time in 27 (15%) of 183 children in the formula fed and 17 (9%) of 181 children in the breastfeeding arm ($P=.12$). The proportion of children with malnutrition was relatively low in the first year of life, but increased with age (2% during the first year of life and 15% during the second year). The proportion of children with malnutrition did not differ significantly by randomization group overall or during any quarter of follow-up. Among HIV-1–infected children, 29% in the formula arm and 14% in the breastfeeding arm had malnutrition at some time during follow-up ($P=.12$). Among HIV-1–uninfected children, malnutri-

tion occurred in 11% of those in the formula arm and 7% in the breastfeeding arm ($P = .19$).

COMMENT

In this randomized clinical trial, we found no significant difference in 2-year mortality rates between infants randomly assigned to be formula fed or to be breastfed. Because HIV-1 infections occurred with higher frequency in the breastfeeding arm, we considered the possibility that excess formula-associated deaths might be masked by excess HIV-1–related deaths in the breastfeeding arm. However, even when we performed analyses that adjusted for or stratified by HIV-1 infection status, there was no significant difference in 2-year mortality rates between the 2 trial arms. The major causes of death in the study were infections, and there was no difference in cause-specific infection mortality between the 2 study arms except for an increased frequency of sepsis as a contributing cause of death in the formula arm. Thus, in this study population, formula feeding and breastfeeding were associated with similar mortality risks during the first 2 years of life.

At first glance, our results may seem paradoxical. Breastfeeding was associated with higher rates of HIV-1 transmission; HIV-1 infection in infants was associated with higher mortality; formula resulted in no increased mortality. One might have predicted that we would have seen significantly higher mortality risk in the breastfeeding arm. However, our trial terminated with only 2 years of follow-up, by which time many deaths had occurred among infants infected in utero, peripartum, or through early breastfeeding, but relatively few among infants with later acquisition of HIV-1 through breast milk. Of children infected after 2 months of age, only 9% had died by 2 years but most of the remaining children would be expected to die sometime during childhood. At study end, there were 19 HIV-1 infected children who were alive at their last visit in the formula arm and 35 in the breastfeeding arm. The 2 years of follow-up was sufficient to capture any potential adverse consequences of formula feeding but not all of the adverse consequences of breastfeeding with respect to HIV-1 related mortality. Because of this, HIV-1–free survival (the percentage of children who remained alive and HIV-1 uninfected) best captures the combined risks of feeding modality and HIV-1 infection. In this trial, HIV-1–free survival at 2 years was significantly higher in the formula arm.

The mortality risk among the children in this study was high, largely because of infant HIV-1 infection which was associated with a 9.0-fold increased risk of dying during the first 2 years of life. Among children who remained HIV-1 uninfected, the 12 month infant mortality rate (7.0%; 95% CI, 3.9%-10.0%) was not significantly different than the infant mortality rate of 4.1% reported for Nairobi or 7.4% reported for Kenya as a whole[12] although it is higher than what might have been predicted given the level of medical care available in the research context. This suggests that infants of HIV-1–infected mothers may have a somewhat elevated mortality risk, even if they themselves escape HIV-1 infection.

There have been concerns that the use of formula by women infected with HIV-1 in resource-poor settings would result in increases in diarrheal morbidity and mortality.[13,14] We found no significant difference in diarrheal incidence in the 2 study groups of the trial over the 2 year follow-up period. This was true for the group of infants as a whole and after stratifying by HIV-1 infection status. We did find an increased incidence of current diarrhea (at the time of a visit) and dehydration in the formula feeding arm during the first 3 months of life. This coincides with the period during which most breastfed infants were fed exclusively by breast milk (the median age of introduction of supplemental feeds was 3.8 months) and were thus at low risk of exposure to diarrheal pathogens from food sources. Our results are consistent with previously published observational studies in which breast milk has been most protective against diarrheal disease in the first 3 months of life,[3,4,5] a finding that underscores the necessity of careful follow-up of formula fed infants during early infancy.

In the cohort overall, we did not observe increased risk of any major childhood morbidities, including pneumonia, sepsis, malaria, or otitis media, associated with formula feeding. Among HIV-1–infected formula feeders, there was an increased risk of sepsis during the 2 years of follow-up and an increased risk of hospitalization toward the end of the first year of age. Although our study suggests that formula feeding by HIV-1–infected mothers does not increase the risk of most childhood morbidities, there may be some increased risk among HIV-1–infected infants.

Infants in the breastfeeding arm had better nutritional status than those in the formula feeding arm, particularly during the first 6 months of life, consistent with observational studies.[15] We observed a fairly high prevalence of malnutrition during the second year of life, consistent with patterns of malnutrition seen in sub-Saharan Africa, due in part to repeated infections and introduction of poor weaning diets. However, there was no difference in the prevalence of malnutrition in the 2 study groups. Thus, with adequate supplies of formula and nutrition counseling, the mothers in this trial were able to administer formula feeds without seriously compromising the nutritional status of their infants. However, the better growth in breastfed infants, particularly during the first 6 months, highlights the importance of nutritional counseling for mothers of formula feeding infants.

The major strength of our study was its randomized clinical trial design. Choice of infant feeding modality may be influenced by factors that affect infant health outcomes and not all observational studies have controlled for important confounding factors such as educational level, socioeconomic status, and low birth weight. Nor have most studies addressed the possibility of reverse causality, eg, that changes in infant feeding modality (and in particular a switch from breast milk to formula) may be influenced by childhood illnesses. Our randomized clinical trial de-

sign allows us to present data regarding morbidity and mortality associated with formula that are not potentially confounded.

There are several limitations of our trial that warrant discussion. First, compliance with feeding modality in the formula feeding arm was imperfect, and 30% of such infants had some exposure to breast milk. In our intent-to-treat analyses, this could potentially result in underestimates of risk associated with formula feeding. However, when we repeated our mortality analyses using true feeding modality rather than randomization group, we found similar results. Two-year mortality was 18.8% among true formula feeders and 22.0% among true breastfeeders ($P = .39$). Among HIV-1–uninfected children, the 2-year mortality was 8.7% among true formula feeders and 7.3% among true breastfeeders ($P = .74$). Second, we relied on maternal histories to capture childhood illnesses that occurred between clinic visits, so our estimates of morbidity may be underestimates. In addition, our study was not designed to determine causes of death and these data are imprecise because of limited availability of diagnostic testing and reliance on verbal autopsies. Finally, the number of visits to the clinic was lower for breastfeeding than formula feeding children. Although this would not affect our mortality rates, it could influence our estimates of the incidence of diarrheal disease and other morbidities. We corrected for this in our analyses by adjusting all relative risks for the various infant morbidities of interest by the number of clinic visits made.

Our estimates of morbidity and mortality risk are not generalizable to all women in developing countries. Our results represent the best-case scenario. All women participating in the trial had access to potable water, extensive health education regarding safe preparation of formula, a reliable supply of formula, and access to medical care for their infants. The magnitude of risks associated with formula feeding will vary in different settings depending on differences in these important variables. Because of these differences, we would advocate context-specific counseling for HIV-1–infected expectant mothers so that each woman can select the feeding method that maximizes benefits and minimizes risks given her individual situation, as is recommended by the World Health Organization.[16] In addition, our trial was conducted among HIV-1–infected mothers and the results may not be generalizable to uninfected women. It is possible that the breast milk of HIV-1–infected women lacks factors that confer protection from death, diarrheal disease, and pneumonia.

We previously reported that the use of formula could prevent 44% of HIV-1 infections in infants of HIV-1–seropositive mothers.[1] Our current results demonstrate that in a developing country setting, it is possible for this gain to be realized without increased morbidity or mortality during the first 2 years of life. In our trial, formula-fed infants clearly had a better outcome than breastfed infants because they were more likely to be alive and HIV-1 uninfected at the age of 2 years.[1] Formula feeding conferred a 28% protective effect from an adverse outcome (HIV-1 infection or death). In addition, mothers who used formula were more likely to be alive 2 years after delivery than mothers who breastfed.[11] Thus, formula provided advantages for both mother and child. Our current analyses show that the use of formula to prevent HIV-1 transmission can be a safe and viable option even in resource poor settings, if maternal education, clean water, a supply of formula, and access to health care are available.

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