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Extended Antiretroviral Prophylaxis to Reduce Breast-Milk HIV-1 Transmission

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ABSTRACT

BACKGROUND

Effective strategies are urgently needed to reduce mother-to-child transmission of human immunodeficiency virus type 1 (HIV-1) through breast-feeding in resource-limited settings.

METHODS

Women with HIV-1 infection who were breast-feeding infants were enrolled in a randomized, phase 3 trial in Blantyre, Malawi. At birth, the infants were randomly assigned to one of three regimens: single-dose nevirapine plus 1 week of zidovudine (control regimen) or the control regimen plus daily extended prophylaxis either with nevirapine (extended nevirapine) or with nevirapine plus zidovudine (extended dual prophylaxis) until the age of 14 weeks. Using Kaplan–Meier analyses, we assessed the risk of HIV-1 infection among infants who were HIV-1–negative on DNA polymerase-chain-reaction assay at birth.

RESULTS

Among 3016 infants in the study, the control group had consistently higher rates of HIV-1 infection from the age of 6 weeks through 18 months. At 9 months, the estimated rate of HIV-1 infection (the primary end point) was 10.6% in the control group, as compared with 5.2% in the extended-nevirapine group ($P < 0.001$) and 6.4% in the extended-dual-prophylaxis group ($P = 0.002$). There were no significant differences between the two extended-prophylaxis groups. The frequency of breast-feeding did not differ significantly among the study groups. Infants receiving extended dual prophylaxis had a significant increase in the number of adverse events (primarily neutropenia) that were deemed to be possibly related to a study drug.

CONCLUSIONS

Extended prophylaxis with nevirapine or with nevirapine and zidovudine for the first 14 weeks of life significantly reduced postnatal HIV-1 infection in 9-month-old infants. (ClinicalTrials.gov number, NCT00115648.)

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IN SUB-SAHARAN AFRICA, WHERE BREAST-feeding is critical for infant survival, postnatal transmission of human immunodeficiency virus type 1 (HIV-1) occurs in up to 16% of untreated infants when breast-feeding continues into the second year of life.¹ Although effective interventions have been identified to reduce in utero and intrapartum transmission of HIV-1 in resource-limited countries,² breast-feeding attenuates the efficacy of such methods.^{3,4} Thus, a major concern in developing countries is HIV-1 transmission through breast milk.⁵ To optimize the survival of infants who are born to mothers with HIV-1 infection, interventions that allow safe breast-feeding during the first 6 months of life or longer are needed.

The aim of our trial, called the Post-Exposure Prophylaxis of Infants (PEPI) trial, was to determine whether extended prophylaxis of infants with nevirapine or with nevirapine plus zidovudine until the age of 14 weeks (when the infant immunization schedule is completed in Malawi) would decrease the rate of HIV-1 infection, as compared with single-dose nevirapine combined with 1 week of zidovudine (control regimen). The control regimen, which was previously shown to be effective in a randomized trial in Malawi, is recommended in resource-limited settings, including Malawi.⁶⁻⁸

METHODS

STUDY POPULATION

Pregnant women who presented for either antenatal or delivery services at Queen Elizabeth Central Hospital or at one of five other health centers in Blantyre, Malawi, were offered HIV-1 counseling and testing. All women with HIV-1 infection, except those whose HIV-1 infection was not identified until after they gave birth (late presenters), received intrapartum single-dose nevirapine. Women could be enrolled in the trial if they had HIV-1 infection, were at least 18 years of age (although women <18 years of age could be enrolled if they consented and a guardian gave permission), were pregnant or had given birth within the previous 24 hours at one of the study clinics, were a resident of the study area, were willing to return for postnatal follow-up visits for up to 2 years, and intended to breast-feed. Infants with life-threatening conditions requiring immediate care were excluded. All eligible women provided written informed consent at enrollment.

The protocol and study consent forms were approved by institutional review boards at the University of Malawi, Johns Hopkins University, and the Centers for Disease Control and Prevention. Enrollment began on April 20, 2004. The current analysis includes data on women and their infants who were enrolled in the study through August 7, 2007. All authors vouch for the completeness and accuracy of the data presented.

STUDY DESIGN

In our randomized, controlled, open-label, phase 3 clinical trial, infants were randomly assigned at birth to receive one of three regimens: single-dose nevirapine combined with 1 week of daily zidovudine (control group) or the control regimen followed by extended daily prophylaxis with either oral nevirapine (extended-nevirapine group) or oral nevirapine plus zidovudine (extended-dual-prophylaxis group) until the age of 14 weeks. Women were counseled at each visit to breast-feed exclusively for 6 months and to consider weaning thereafter.

STUDY-DRUG REGIMENS

Beginning immediately after birth, all infants received a single oral dose of nevirapine (2 mg per kilogram of body weight) plus oral zidovudine (4 mg per kilogram), given twice daily for 1 week. Zidovudine was given for 1 week rather than 4 weeks for the following reasons: the 1-week regimen was shown to be more effective than single-dose nevirapine alone in a randomized trial in Malawi^{6,7} and is the recommended regimen for infants born to women who have not received antenatal antiretroviral prophylaxis in Malawi; no clinical trials have shown that a 4-week regimen is superior to a 1-week regimen when single-dose nevirapine is also given; and in a study in South Africa,⁹ a 6-week regimen of zidovudine provided no better protection than single-dose nevirapine alone.

Drugs for infants in the two extended-prophylaxis groups were dispensed to the mothers starting at the 1-week study visit and at subsequent visits until the infant completed the 14-week regimen. In the extended-prophylaxis groups, the oral dose of nevirapine was 2 mg per kilogram once daily during week 2, then 4 mg per kilogram once daily during weeks 3 through 14. The oral dose of zidovudine was 4 mg per kilogram twice daily during weeks 2 through 5, 4 mg per kilogram three times daily during weeks 6 through 8, and

6 mg per kilogram three times daily during weeks 9 through 14.

Prophylaxis regimens were discontinued for infants in the extended-prophylaxis groups who were found to have HIV-1 infection during the first 14 weeks of life. However, these infants were still followed for the duration of the study.

STUDY FOLLOW-UP AND PROCEDURES

Study visits were conducted at 1, 3, 6, 9, and 14 weeks and at 6, 9, 12, 15, 18, and 24 months of infant age. Infant blood samples were collected by heel-stick or venous puncture for HIV-1 testing and dried-blood spot storage at each visit except week 3. Specimens for a complete blood count and testing of alanine aminotransferase levels were collected at each visit through 6 months; plasma was collected at birth, at 6 and 14 weeks, and at 6, 12, and 18 or 24 months.

All women in the study and any of their infants who were found to have HIV-1 infection were referred for antiretroviral therapy at clinics at a study health center, although the availability of antiretroviral treatment in Malawi was limited, with increased availability only late in the study. Only small percentages of women (2.6% in the control group, 2.8% in the extended-nevirapine group, and 3.2% in the extended-dual-prophylaxis group) received antiretroviral therapy before 14 weeks post partum ($P=0.77$ for all comparisons). The maternal rates of antiretroviral therapy were slightly higher after the 14-week study period (11.8% in the control group, 12.2% in the extended-nevirapine group, and 11.4% in the extended-dual-prophylaxis group) ($P=0.87$ for all comparisons). All infants who were exposed to or infected with HIV-1 received prophylaxis with trimethoprim-sulfamethoxazole to prevent pneumocystis pneumonia. Further details regarding the monitoring and randomization of patients and the collection of data are available in the Supplementary Appendix, available with the full text of this article at www.nejm.org.

STUDY END POINTS

The primary study end point was the rate of HIV-1 infection by the age of 9 months among live-born infants who were negative for HIV-1 infection on DNA polymerase-chain-reaction (PCR) assay at birth (i.e., within the first 48 hours). Infants were evaluated for the presence of HIV-1 infection at 6, 9, and 14 weeks and at 6, 12, 18, and 24 months. Additional primary end points were

survival free of HIV-1 infection during follow-up and the safety of the experimental regimens.

The presence or absence of HIV-1 infection was determined by Roche Amplicor 1.5 DNA PCR (Roche Molecular Systems). Positive specimens were confirmed by testing a second specimen obtained as soon as possible after an initial positive test. Specimens with discrepant test results at the local laboratory were retested in a reference laboratory at the University of North Carolina, Chapel Hill. Final infection status was determined by three investigators who were unaware of infants' study-group assignments. For infants whose infection status was not resolved by retesting at the reference laboratory (e.g., because no sample was available for repeat testing), those with a positive test result that was followed by multiple negative tests (either on DNA PCR or on HIV-antibody enzyme immunoassays) were considered to be uninfected. All other infants whose HIV-1 status still could not be resolved (e.g., owing to termination from the study because of relocation or removal from the study by a parent) were excluded from the analysis, including 14 infants in the control group, 5 in the extended-nevirapine group, and 15 in the extended-dual-prophylaxis group.

Diagnosis of HIV-1 infection was based on a positive HIV-1 DNA PCR assay at any visit or a positive enzyme-linked immunosorbent assay (ELISA) and Western blot analysis at the age of 15 months or later. An infant with at least two positive HIV-1 test results on separate visits was classified as having confirmed HIV-1 infection, and an infant with only a single positive result (due to the death of the infant, loss to follow-up, or a pending confirmatory test) was classified as having presumptive HIV-1 infection. All identified adverse events were documented and graded with the use of a toxicity table adopted in April 1994 by the Division of AIDS at the National Institutes of Health.

STATISTICAL ANALYSIS

We present all data that were obtained through the cutoff date for the second interim analysis (August 7, 2007). Study groups were examined for similarity according to baseline covariates (continuous or categorical) with the use of the t-test, analysis of variance, Fisher's exact test, and the chi-square test.

In an intention-to-treat analysis, we compared each extended-prophylaxis group with the

control group. We used Kaplan–Meier analyses to estimate the time until the first positive HIV-1 test (either confirmed or presumptive, with data for infants without a positive HIV-1 test censored at the time of death), the time to death, and the time to either death or the first positive HIV-1 test (whichever came first), according to study group. Cox proportional-hazards models of the time until the first positive HIV-1 test, with adjustment for study group and other covariates that were considered to have biologic or epidemiological importance, were performed with SAS software, version 9.1 (SAS Institute).

The study was designed to enroll 3500 infants to include at least 3000 who were not infected with HIV-1 at birth on the basis of an assumed rate of infection of 8% and an assumed rate of postpartum transmission of 14% at 9 months in the control group. The data and safety monitoring board recommended that enrollment in the study be stopped at the second interim analysis (December 10, 2007), since the P value for the difference between the extended-nevirapine group and the control group exceeded a Bonferroni-adjusted O'Brien–Fleming rejection threshold (alpha level, 0.0063). At this time, 3016 infants who were not infected with HIV-1 at birth were enrolled in the study. A total of 2522 infants either with HIV-1 infection or without HIV-1 infection were enrolled for at least 9 months.

RESULTS

PATIENTS

A total of 46,186 women underwent screening for HIV-1 infection. Women with HIV-1 infection who met the inclusion criteria and signed an informed consent form were enrolled in the study. Of 3276 infants who were enrolled and underwent randomization at birth, 260 were excluded from the efficacy analysis: 226 because they were found to have HIV-1 infection and 34 because their HIV-1 status at birth was not known. These exclusions were distributed equally among the three study groups. Therefore, 3016 infants were included in the primary analysis (Fig. 1).

Baseline demographic and laboratory characteristics of the women and their infants were similar in the three study groups (Table 1). All infants received a single dose of nevirapine at birth, and of the 2427 infants who returned for the first-week visit, 99% received zidovudine. At

14 weeks, adherence (defined as the proportion of infants who received treatment among those who returned for the visit) was 97.3% (658 of 676 infants) in the extended-nevirapine group and 97.8% (673 of 688 infants) in the extended-dual-prophylaxis group ($P=0.60$).

FREQUENCY OF BREAST-FEEDING

The frequency of reported breast-feeding was high up to the age of 6 months, ranging from nearly all infants at 1 week to approximately 90% at 6 months in all three study groups. Between the ages of 6 and 9 months, there was a substantial reduction in the frequency of breast-feeding in all three groups, with rates at 9 months of 32.0% in the control group, 26.9% in the extended-nevirapine group, and 29.2% in the extended-dual-prophylaxis group ($P=0.16$ for all comparisons). By the age of 15 months, the rate of breast-feeding had declined to 19.4% in the control group, 14.4% in the extended-nevirapine group, and 18.1% in the extended-dual-prophylaxis group (Table 2).

HIV-1 INFECTION

Of the 3016 infants, 255 were found to have HIV-1 infection by August 7, 2007. Of these cases, 242 were confirmed and 13 were presumptive; the frequency of HIV infections that were classified as presumptive was similar in the three study groups ($P=0.22$ for all comparisons). Both confirmed and presumptive HIV-1 infections were included in the primary analysis, although limiting the analysis to only confirmed HIV-1 infections produced similar results (data not shown). The rates of HIV-1 positivity on DNA analysis at birth were 6.5% in the control group and 7.1% in both extended-prophylaxis groups ($P=0.85$ for all comparisons). Before the primary end point at 9 months, the numbers of infants who were lost to follow-up without a positive HIV-1 test were 136 in the control group, 131 in the extended-nevirapine group, and 109 in the extended-dual-prophylaxis group.

Among infants who were not infected at birth (i.e., excluding infants with positive DNA PCR tests for HIV), between the ages of 6 weeks and 18 months, the control group had consistently higher rates of HIV-1 infection, as compared with both extended-prophylaxis groups (Fig. 2A). Among 9-month-old infants, the rate of HIV-1 infection, as estimated from Kaplan–Meier curves

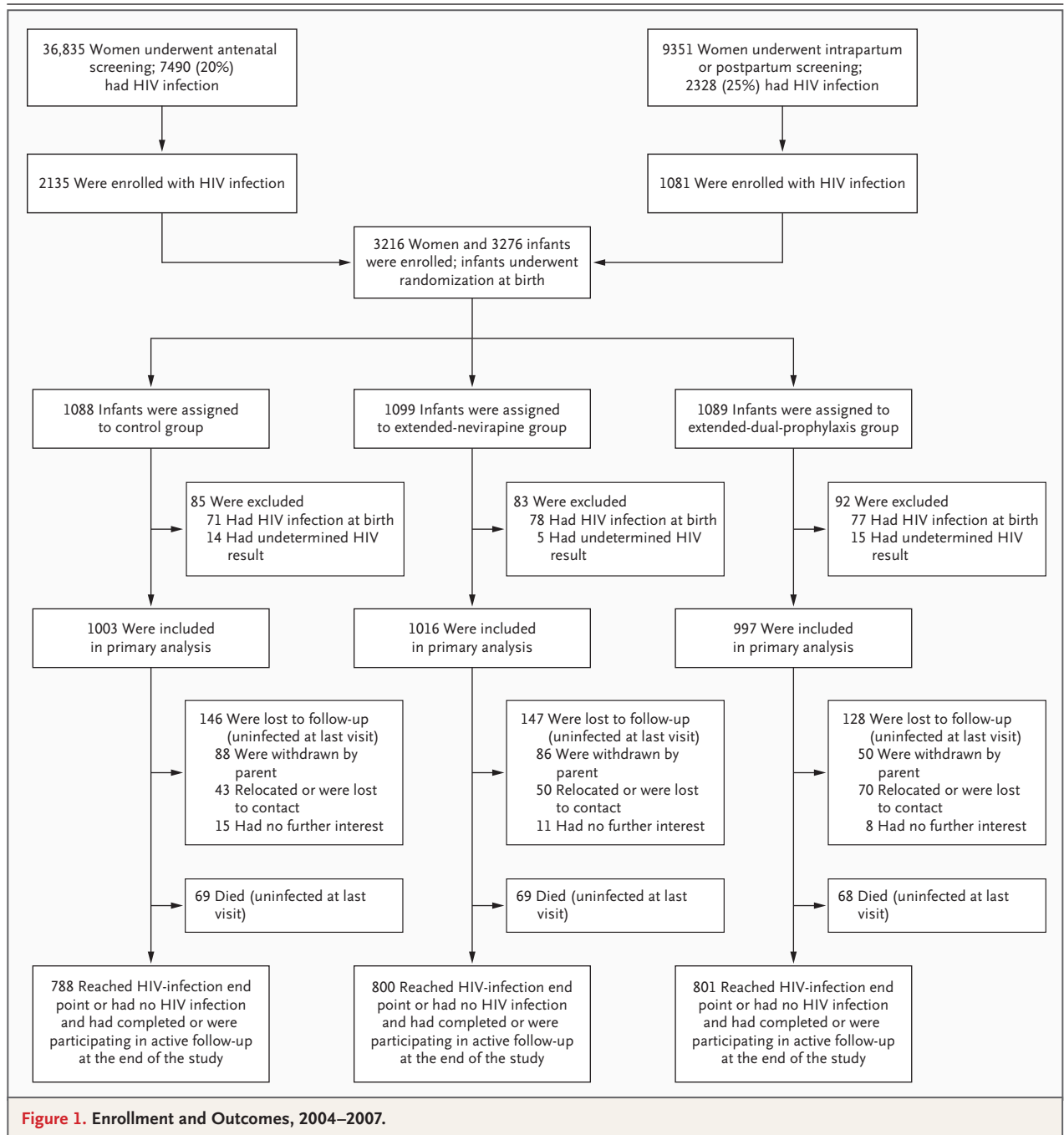


Figure 1. Enrollment and Outcomes, 2004–2007.

for which data were censored at the time of loss to follow-up, was 10.6% (95% confidence interval [CI], 8.7 to 12.8) in the control group, 5.2% (95% CI, 3.9 to 7.0) in the extended-nevirapine group ($P < 0.001$ for the comparison with the control group), and 6.4% (95% CI, 4.9 to 8.3) in the extended-dual-prophylaxis group ($P = 0.002$ for the comparison with the control group). The total

numbers of infants with positive results on HIV-1 DNA PCR at 9 months were 98 in the control group, 51 in the extended-nevirapine group, and 61 in the extended-dual-prophylaxis group. The estimated protective efficacy¹⁰ of the extended-nevirapine regimen was 67% (95% CI, 43 to 81) at 6 weeks, 67% (95% CI, 49 to 79) at 14 weeks, 60% (95% CI, 42 to 73) at 6 months, and 51% (95% CI,

Table 1. Baseline Characteristics of Mothers and Infants.*

Variable	Control Group	Extended-Nevirapine Group	Extended-Dual-Prophylaxis Group	P Value†
Mothers				
No. of patients	989	993	980	
Age — yr	26.1±4.9	26.1±4.6	26.5±4.8	0.16
Weight — kg	56.8±7.7	57.0±7.9	57.1±8.4	0.66
Education — no. (%)				0.65
≤Grade 8	636 (64.3)	646 (65.1)	618 (63.1)	
>Grade 8	353 (35.7)	347 (34.9)	362 (36.9)	
Have electricity at home — no. (%)	329 (33.3)	304 (30.6)	332 (33.9)	0.25
Hemoglobin — g/dl	11.5±1.8	11.6±1.9	11.5±1.8	0.67
White cells per mm ³ — thousands	11.5±5.4	11.4±4.7	11.4±4.8	0.89
Absolute neutrophil count per mm ³ — thousands	8.2±5.4	8.1±4.1	8.1±4.0	0.96
CD4 cells per mm ³				0.08
Median	401.0	379.0	400.5	
Interquartile range	263.0–587.0	245.0–570.5	280.0–581.0	
CD8 cells per mm ³				0.90
Median	884.0	882.5	901.0	
Interquartile range	634.0–1206.0	647.0–1191.0	632.0–1231.0	
Presentation status — no. (%)				0.66
Early (>4 hr before delivery)	677 (68.5)	675 (68.0)	684 (69.8)	
Late (≤4 hr before delivery)	312 (31.5)	318 (32.0)	296 (30.2)	
Time of ≥4 hr since rupture of membranes — no./total no. (%)	152/955 (15.9)	166/952 (17.4)	146/938 (15.6)	0.51
Mode of delivery — no. (%)				0.59
Spontaneous vertex	947 (95.8)	949 (95.6)	935 (95.4)	
Cesarean section	26 (2.6)	22 (2.2)	30 (3.1)	
Vacuum extraction, breech, or forceps	16 (1.6)	22 (2.2)	15 (1.5)	
Infants				
No. of patients	1003	1016	997	
Male sex — no. (%)	540 (53.8)	501 (49.3)	495 (49.6)	0.08
Birth weight — g	3034.6±451.5	3007.6±451.6	3011.6±453.8	0.35
Nevirapine (single dose) — no. (%)				0.66‡
Before arrival in labor ward	515 (51.3)	528 (52.0)	539 (54.1)	
On arrival in labor ward	175 (17.4)	162 (15.9)	157 (15.7)	
None	313 (31.2)	326 (32.1)	301 (30.2)	
Apgar score at 5 min§	9.9±0.6	9.9±0.4	9.9±0.5	0.70
Gestational age — wk	38.6±1.8	38.7±1.8	38.6±1.9	0.49
Admitted to special baby-care unit — no. (%)	20 (2.0)	34 (3.3)	35 (3.5)	0.08
Started breast-feeding before discharge — no. (%)	809 (80.7)	823 (81.0)	788 (79.0)	0.50

* Plus-minus values are means ±SE.

† P values were calculated with the use of Fisher's exact test for categorical data, analysis of variance for continuous data reporting mean values, and the Wilcoxon rank-sum test for continuous data reporting median values.

‡ P value was calculated with the use of a chi-square test.

§ Apgar scores range from 1 to 10, with higher scores indicating better function.

Table 2. Frequency of Breast-Feeding, According to Study Visit.*

Visit	Control Group			Extended-Nevirapine Group			Extended-Dual-Prophylaxis Group		
	EBF	MBF	NBF	EBF	MBF	NBF	EBF	MBF	NBF
	<i>percent</i>								
1 Wk	99.8	0.1	0.1	99.5	0.2	0.3	99.6	0.2	0.2
3 Wk	98.8	0.2	1.0	99.4	0.3	0.3	99.3	0.4	0.3
6 Mo	66.9	23.7	9.4	64.3	25.4	10.3	61.1	29.3	9.7
9 Mo	2.9	29.1	68.0	2.7	24.2	73.1	1.6	27.6	70.8
15 Mo	0.5	18.9	80.6	1.9	12.4	85.6	0.2	17.8	81.9

* EBF denotes exclusive breast-feeding, MBF mixed breast-feeding, and NBF no breast-feeding.

30 to 66) at 9 months. The estimated protective efficacy of the extended-dual-prophylaxis regimen was 69% (95% CI, 45 to 83) at 6 weeks, 66% (95% CI, 48 to 78) at 14 weeks, 49% (95% CI, 27 to 64) at 6 months, and 40% (95% CI, 16 to 57) at 9 months. There were no significant differences between the two extended-prophylaxis groups at any time point.

DEATH

Regardless of HIV-1-infection status, 285 infants died during the study: 106 in the control group, 89 in the extended-nevirapine group, and 90 in the extended-dual-prophylaxis group. Of these infants, those who had already died by the age of 9 months included 71 in the control group, 55 in the extended-nevirapine group, and 51 in the extended-dual-prophylaxis group. Although mortality in the control group exceeded that in the two extended-prophylaxis groups after the age of 6 months, the differences were not significant (Fig. 2B). At 9 months, mortality was 8.9% (95% CI, 7.1 to 11.1) in the control group, 6.8% (95% CI, 5.2 to 8.7) in the extended-nevirapine group, and 6.3% (95% CI, 4.8 to 8.2) in the extended-dual-prophylaxis group.

Table 3 shows the results of the Cox proportional-hazards analyses of risk factors for HIV-1 infection and for either HIV-1 infection or death. In the adjusted analysis, both extended-prophylaxis regimens were significantly associated with a reduced risk of HIV-1 infection; a decrease in the maternal CD4 cell count was associated with an increased risk of infection. Lower infant birth weight was also associated with an increased risk of either HIV-1 infection or death.

The primary causes of infant death were gastroenteritis (30% in the control group, 26% in the extended-nevirapine group, and 30% in the

extended-dual-prophylaxis group) and pneumonia (26%, 23%, and 21%, respectively). HIV-1-free survival was significantly better in both extended-prophylaxis groups through the age of 9 months and in the extended-nevirapine group through the age of 15 months (Fig. 2C).

SERIOUS ADVERSE EVENTS

Overall, 1283 serious adverse events were reported in 887 infants, with no significant differences among the three study groups for any adverse event ($P=0.34$ for all comparisons by Fisher's exact test) or for ordered treatment relatedness of adverse events ($P=0.14$ by the Jonckheere-Terpstra test¹¹) (Table 4). The most frequent serious adverse events in all three groups were respiratory (329 events), gastrointestinal (227 events), and hematologic (191 events), and the rates were similar in all three study groups (Table 2 in the Supplementary Appendix). Overall, most serious adverse events (87.3%) were not significantly associated with a study drug. However, there were significantly more infants with serious adverse events that were deemed to be possibly related to a study drug in the extended-dual-prophylaxis group than in either the extended-nevirapine group or the control group ($P=0.02$ for all comparisons). The most common serious adverse event in the extended-dual-prophylaxis group was neutropenia. The numbers of events that were deemed to be probably related to a study drug were low and did not differ among the study groups ($P=0.42$ for all comparisons).

DISCUSSION

We evaluated two different extended 14-week post-exposure regimens to reduce postnatal HIV-1 transmission in a large, randomized clinical tri-

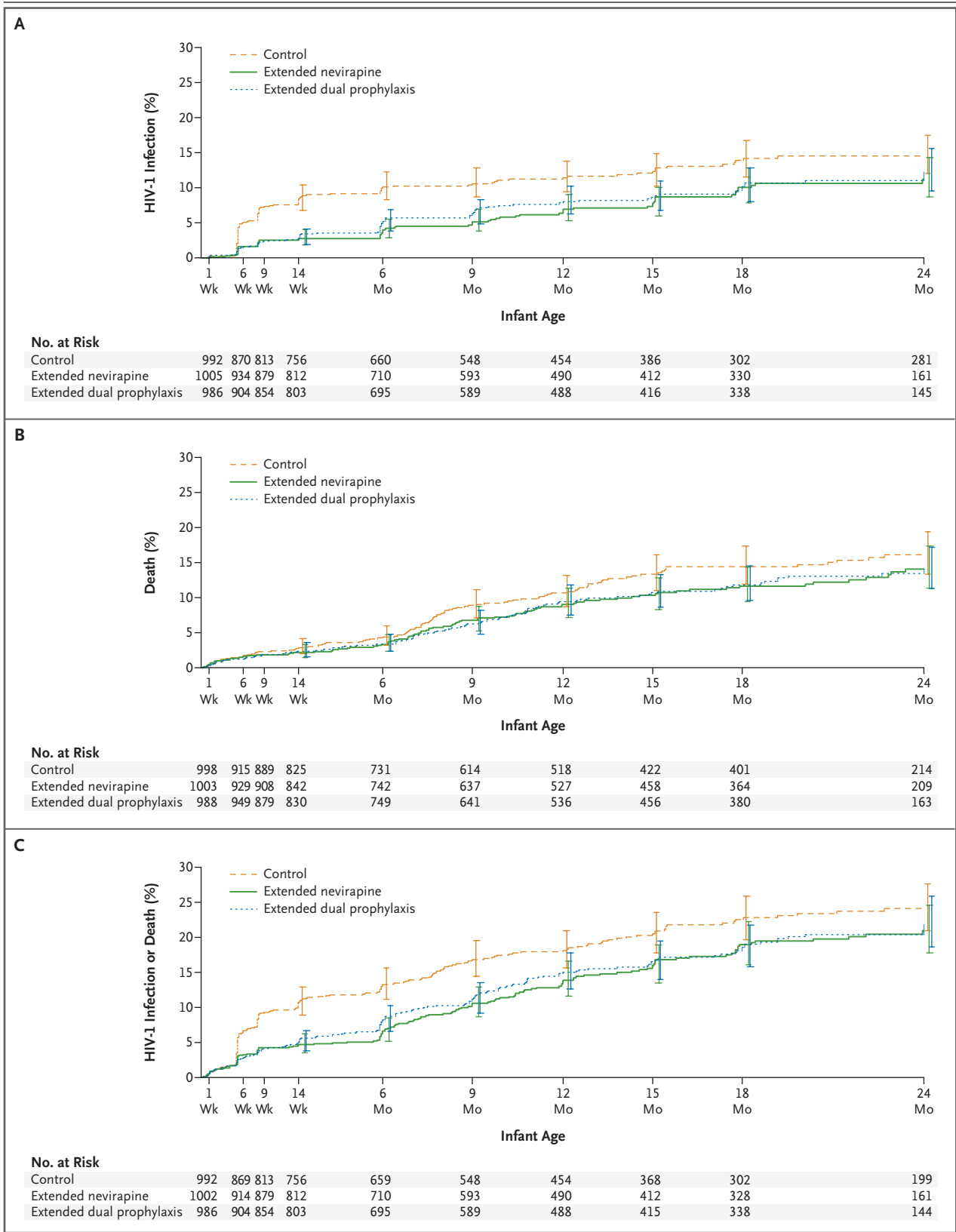


Figure 2 (facing page). Kaplan–Meier Estimates of the Rates of HIV-1 Infection, Death, and a Composite of HIV-1 Infection or Death among Infants during Their First 24 Months.

Among infants who were uninfected with HIV-1 at birth on the basis of DNA polymerase-chain-reaction assay, rates are shown for HIV-1 infection (Panel A), death (Panel B), and either HIV-1 infection or death (Panel C) during the first 24 months in the three study groups. The I bars represent 95% confidence intervals.

al. Our study demonstrated that both extended-prophylaxis regimens significantly reduced the risk of postnatal transmission at 14 weeks with a protective efficacy of more than 60%. The cumulative risk of postnatal infection between birth and 14 weeks was 8.4% in the control group, as compared with approximately 2.8% in the extended-prophylaxis groups. This net difference of approximately 5% between the extended-prophylaxis groups and the control group continued at 24 months.

Although there were no significant differences in overall mortality, the control group had consistently higher mortality after the age of 6 months than did either of the extended-prophylaxis groups, a difference that appeared to be largely due to a higher rate of HIV-1 infection in the

control group. There were significant increases in HIV-1-free survival for the infants in both extended-prophylaxis groups at the age of 9 months and for those in the extended-nevirapine group up to the age of 15 months.

The frequency of breast-feeding was high during the first 6 months (approximately 90%). Although most infants were weaned between the ages of 6 and 9 months, more than 20% were still breast-feeding at that time. After discontinuation of extended prophylaxis, the rate of postnatal HIV-1 infection occurring in infants between the ages of 14 weeks and 9 months was similar in the three study groups, with a rate of additional HIV-1 infections of 2.2% in the control group, 2.4% in the extended-nevirapine group, and 3.5% in the extended-dual-prophylaxis group.

The choice of providing daily prophylaxis up to 14 weeks was based on the recommended infant immunization schedule in Malawi, which is completed at 14 weeks. Most infants do not return to the clinic until the age of 9 months to receive measles immunization. Therefore, from a public health point of view, an approach to HIV-1 prophylaxis that is integrated into the typical infant immunization schedule would facilitate implementation in resource-constrained settings. There were no significant differences in

Table 3. Associated Risk Factors for HIV-1 Infection and for a Composite of HIV-1 Infection or Death.

Risk Factor	Unadjusted		Adjusted*	
	Hazard Ratio (95% CI)	P Value	Hazard Ratio (95% CI)	P Value
For HIV-1 infection				
Extended-nevirapine group vs. control group	0.59 (0.44–0.80)	<0.001	0.56 (0.41–0.76)	<0.001
Extended-dual-prophylaxis group vs. control group	0.66 (0.49–0.88)	0.005	0.65 (0.48–0.88)	0.006
Maternal CD4 count (per decrease of 100 units)	1.27 (1.19–1.36)	<0.001	1.27 (1.19–1.36)	<0.001
Maternal presentation (late vs. early)	1.26 (0.98–1.62)	0.08	1.23 (0.94–1.60)	0.13
Sex of infant (female vs. male)	0.90 (0.71–1.15)	0.41	0.95 (0.73–1.23)	0.67
Birth weight (per increase of 1 kg)	0.74 (0.57–0.96)	0.03	0.87 (0.66–1.15)	0.33
For HIV-1 infection or death				
Extended-nevirapine group vs. control group	0.72 (0.58–0.90)	0.004	0.69 (0.55–0.87)	0.001
Extended-dual-prophylaxis group vs. control group	0.76 (0.61–0.95)	0.02	0.72 (0.57–0.90)	0.004
Maternal CD4 count (per decrease of 100 units)	1.15 (1.10–1.20)	<0.001	1.14 (1.09–1.19)	<0.001
Maternal presentation (late vs. early)	1.16 (0.96–1.40)	0.14	1.07 (0.87–1.31)	0.52
Sex of infant (female vs. male)	1.00 (0.83–1.20)	0.97	0.97 (0.80–1.18)	0.80
Birth weight (per increase of 1 kg)	0.59 (0.49–0.72)	<0.001	0.63 (0.51–0.77)	<0.001

* Hazard ratios were adjusted for all variables listed.

Table 4. Serious Adverse Events.*

Relationship to a Study Drug	Control Group (N=1003)		Extended-Nevirapine Group (N=1016)		Extended-Dual-Prophylaxis Group (N=997)		Total (N=3016)		P Value†
	No. of Infants	No. of Events	No. of Infants	No. of Events	No. of Infants	No. of Events	No. of Infants	No. of Events	
Not related	257	367	275	383	255	370	787	1120	0.69
Possibly related	37	38	44	45	62	67	143	150	0.02
Probably related	2	2	6	6	5	5	13	13	0.42
Total	278	407	310	434	299	442	887	1283	0.34‡

* The numbers of infants with at least one serious adverse event are listed. Infants could have events in more than one category.

† P values are for the overall comparison among study groups for the number of infants with serious adverse events; values were calculated with the use of Fisher's exact test.

‡ P=0.14 by the Jonckheere–Terpstra test.¹¹

efficacy between the two extended-prophylaxis groups. However, serious adverse events (primarily neutropenia) that were possibly related to a study drug were more frequent in the extended-dual-prophylaxis group. Whether the two-drug regimen would reduce the risk of resistance to nevirapine among infants who become infected with HIV-1 despite extended prophylaxis is being investigated.

Another approach to the prevention of postnatal transmission of HIV-1 is the treatment of mothers with HIV-1 infection with highly active antiretroviral therapy (HAART). Although maternal HAART is clearly warranted in women who require therapy for their own health, the benefits and safety of HAART used solely for prevention of postnatal transmission in healthy women with HIV infection have not yet been demonstrated in clinical trials, although several observational studies suggest it may be effective.¹²⁻¹⁴ Data from two observational studies in Tanzania have suggested that infant antiretroviral prophylaxis (the MITRA study¹⁴) and maternal HAART prophylaxis (the MITRA-Plus study¹⁵) may result in similar postnatal transmission rates. Since HAART that is used solely for prophylaxis is stopped after the infant is weaned, the mother may receive 9 months or more of HAART (if therapy is started before birth), followed by an interruption. The effect of interruption of long-term HAART on maternal health is unknown. Some studies have demonstrated an increased risk of disease progression and death among HIV-1-infected adults with high CD4 counts who interrupted treatment, as compared with that associated with continuous therapy.¹⁶⁻¹⁸ Antiretroviral

treatment of the mother may also expose infants to potential toxic effects or drug resistance if the infant becomes infected because of a potential elevation in the plasma concentration of these drugs in the infant.¹⁹⁻²² Thus, further evaluation of maternal HAART that is used solely for prophylaxis is needed to determine efficacy and long-term safety for both mothers and infants.

On the basis of data from our trial, the 14-week extended nevirapine regimen appears to be safe, with the rate of adverse events similar to that in the control group. This infant-only antiretroviral prophylaxis is practical and effective in reducing HIV-1 transmission and in improving HIV-1-free survival in settings in which breast-feeding is common. The question of whether infants who are born to HIV-1-infected mothers should receive antiretroviral prophylaxis for the entire duration of breast-feeding needs to be assessed, including analysis of safety, added efficacy, and cost-effectiveness.

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