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Nevirapine and Zidovudine at Birth to Reduce Perinatal Transmission of HIV in an African Setting

A Randomized Controlled Trial

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ABSTRACT

Context Antenatal counseling and human immunodeficiency virus (HIV) testing are not universal in Africa; thus, women often present in labor with unknown HIV status without receiving the HIVNET 012 nevirapine (NVP) regimen (a single oral dose of NVP to the mother at the start of labor and to the infant within 72 hours of birth).

Objective To determine risk of mother-to-child transmission of HIV when either standard use of NVP alone or in combination with zidovudine (ZDV) was administered to infants of women tested at delivery.

Design, Setting, and Participants A randomized, open-label, phase 3 trial conducted between April 1, 2000, and March 15, 2003, at 6 clinics in Blantyre, Malawi, Africa. The trial included all infants born to 894 women who were HIV positive, received NVP intrapartum, and were previously antiretroviral treatment-naïve. Infants were randomly assigned to NVP (n = 448) and NVP plus ZDV (n = 446). Infants were enrolled at birth, observed at 6 to 8 weeks, and followed up through 3 to 18 months. The HIV status of 90% of all infants was established at 6 to 8 weeks.

Intervention Mothers received a 200-mg single oral dose of NVP intrapartum and infants received either 2-mg/kg oral dose of NVP or NVP (same dose) plus 4 mg/kg of ZDV twice per day for a week.

Main Outcome Measures HIV infection of infant at birth and 6 to 8 weeks, and adverse events.

Results The mother-to-child transmission of HIV at birth was 8.1% (36/445) in infants administered NVP only and 10.1% (45/444) in those administered NVP plus ZDV ($P = .30$). A life table estimate of transmission at 6 to 8 weeks was 14.1% (95% confidence interval [CI], 10.7%-17.4%) in infants who received NVP and 16.3% (95% CI, 12.7%-19.8%) in those who received NVP plus ZDV ($P = .36$). For infants not infected at birth and retested at 6 to 8 weeks, transmission was 6.5% (23/353) in those who received NVP only and 6.9% (25/363) in those who received NVP plus ZDV ($P = .88$). Almost all infants (99%-100%) were breastfed at 1 week and 6 to 8 weeks. Grades 3 and 4 adverse events were comparable; 4.9% (22/448) and 5.4% (24/446) in infants receiving NVP only and NVP plus ZDV, respectively ($P = .76$).

Conclusions The frequency of mother-to-child HIV transmission at 6 to 8 weeks in our 2 study groups was comparable with that observed for other perinatal HIV intervention studies among breastfeeding women in Africa. The safety of the regimen containing neonatal ZDV was similar to that of a standard NVP regimen.

INTRODUCTION

Mother-to-child transmission of human immunodeficiency virus (HIV) in sub-Saharan Africa can be decreased with use of nevirapine (NVP) and zidovudine (ZDV).¹⁻³ Phase 1 and 3 studies have evaluated the pharmacokinetics, safety, and efficacy of NVP among women and infants who received various ZDV regimens.⁴⁻⁶ Information on the efficacy of adding neonatal ZDV to a standard regimen of NVP (the HIVNET 012 regimen of an intrapartum single 200-mg oral dose plus a single infant oral dose of 2 mg/kg¹) is limited. This information is needed because most women in sub-Saharan Africa do not receive antenatal antiretroviral treatment of ZDV or other regimens and present in labor with HIV status unknown. We hypothesized that in situations in which the mother is tested for HIV at the time of presentation for delivery, giving 2 short drug regimens to the infant at birth would be more effective in increasing viral suppression and thus reducing mother-to-child transmission of HIV than a single regimen.⁷ Additionally, a dual regimen could limit development of antiviral resistance to NVP because this has been reported to occur rapidly and frequently in more than 40% of infants who received a single NVP dose.⁸⁻⁹ With extensive evidence that substantial transmission occurs very late during gestation,¹⁰ it is difficult to assume that the impact of postexposure prophylaxis with ZDV, especially when combined with NVP (which has a long-acting effect),^{4, 11-12} will be limited only to uninfected infants at birth.

We recently reported that postexposure prophylaxis with NVP plus ZDV only to the infant, without the mother receiving intrapartum NVP, significantly reduced mother-to-child transmission of HIV by approximately 36% in Malawi, Africa.¹³ In the current study, our goal was to assess mother-to-child transmission when both mother and infant had received a standard NVP regimen compared with mother-to-child transmission when both mother and infant had received the same standard NVP regimen with the addition of the infant receiving ZDV for a week.

METHODS

Study Design and Population

A randomized, open-label, phase 3 clinical trial was conducted at 6 clinics in the city of Blantyre and its suburbs in Malawi, southeast Africa. Women included in this study are termed *early presenters* because they arrived early to the labor ward and thus time from admission to delivery (expected to deliver 4 or more hours after arrival based on the initial clinical examination) was adequate to consent, HIV counsel (pretest and posttest), and administer NVP (200-mg single dose orally) to those women found infected with HIV prior to delivery. A total of 288 (34.3%) of 840 women, with data on time of admission and delivery, delivered in less than 4 hours from time of admission to the labor ward and distribution by study group was similar (145 [34.5%] of 420 in the NVP plus ZDV group and 143 [34.1%] of 420 in the NVP-only group). The 4-hour period was chosen based on practical and logistical reasons. Time of dosing with NVP prior to delivery is important in that it is generally agreed that women should receive intrapartum NVP at least 2 hours before delivery for the concentration to be high enough in infant cord blood to be protective.¹⁴ Women were eligible for enrollment if they provided written informed consent, were HIV positive, and the infant was not anemic (hemoglobin <10 g/dL), preterm, or had other disorders requiring admission to the neonatal intensive care unit. Study staff interacting with the women were female study nurses.

Randomization and Treatment

Infants were randomized to receive either NVP alone (2-mg/kg single oral dose) or NVP (same dose) plus ZDV (4 mg/kg orally twice per day [vs 2 mg/kg 4 times per day, to simplify dosing and encourage compliance] for 7 days). Each clinic was assigned a separate list of computer-generated random allocation numbers (involving permuted blocks of 10 with a ratio of 1:1 allocation). For allocation concealment, the

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randomization instructions were given to study nurses in sequentially numbered, opaque, sealed envelopes, which were only opened when a woman had consented to enroll and the infant was determined to be eligible for enrollment in the study. Used envelopes with the assignment instruction enclosed were sent to a central office and were regularly audited by the study coordinator.

Based on the random allocation instruction, the infant was administered the study treatments promptly after delivery, when having the ability to swallow fluids. The mothers and infants were typically discharged within 6 to 48 hours after delivery. A study nurse directly administered NVP to the infant (according to weight) with the use of a fine calibrated tuberculin syringe, and also gave the first dose of ZDV to the infant while still in the hospital, and any subsequent doses if the infant stayed for an extended period. For infants randomized to receive ZDV, the mother was given the remaining ZDV syrup in plastic bottles containing sufficient amounts for a total of 1 week and directed to give the remaining doses to the infant at home every day at morning and evening. To assess adherence, mothers were interviewed after 1 week, regarding a dosing information form (completed by a study nurse) involving the ascertainment of the exact number of doses administered to the infant. Empty bottles were collected but this source of information was less complete.

Enrollment, Study Procedures, and Follow-up

Routine medical care for mothers and their children and referral, when necessary, were provided in the study clinics. All mothers were given multivitamin tablets in the postnatal period. All infants received *Pneumocystis jiroveci* pneumonia trimethoprim-sulfamethoxazole prophylaxis up to age of 6 months as recommended in Malawi. Data on demographics, pregnancy, and intrapartum and delivery histories were obtained at the time of birth. Follow-up visits were scheduled at 1 week and 6 to 8 weeks, and 3, 6, 9, 12, 15, and 18 months. Unscheduled interim visits were allowed and documented. Data on adverse events were collected by using a clinical history form at every visit, including unscheduled visits.

Laboratory Testing

For assessment of maternal HIV status, venous blood samples were tested by using a rapid HIV test (Determine HIV-1/2, Abbott Laboratories, Tokyo, Japan). The results were available in approximately 20 to 30 minutes. All HIV-positive samples were confirmed by using an enzyme-linked immunosorbent assay (ELISA) HIV test (Wellcozyme, Murex Biotech Limited, Dartford Kent, England); these results were available before discharge from the hospital or at the first postnatal follow-up visit. No Western blot testing was performed as World Health Organization guidelines¹⁵ recommend 2 tests (rapid and ELISA) in settings where HIV prevalence is high. After enrollment and before discharge from the hospital, maternal venous blood specimens were obtained for syphilis testing and baseline measurement of HIV viral load and a complete blood cell count. Those women who were reactive for syphilis were provided appropriate treatment at no cost. Assessment of maternal viral load took place in the United States (University of North Carolina, Chapel Hill) by using an HIV RNA assay (Roche Amplicor Monitor, Indianapolis, Ind). Complete blood cell count measurements were performed locally by using an analyzer (Coulter ACT Diff Hematology Analyzer, Coulter Corp, Miami, Fla).

Infant heelprick blood specimens were collected on filter paper cards as described previously.¹⁶ These dried blood spots were used in HIV-1 RNA assays at birth and visits using nucleic acid sequence-based amplification assay technology (NucliSens HIV-1 RNA QL assay, BioMerieux, Durham, NC). The testing occurred in the United States (University of North Carolina, Chapel Hill) by laboratory staff unaware of study treatment assignment. All 6- to 8-week samples were tested first and for those found positive, dried blood spot samples from birth were tested. If the dried blood spot specimen from birth was negative, the 3-month visit specimen was tested to confirm the 6- to 8-week visit HIV RNA result. An infant was identified as HIV infected at 6 to 8 weeks if 2 separate specimens tested positive (samples from either 6-8 weeks and birth or 6-8 weeks and 3 months). All HIV RNA positive tests were repeated on the same sample for confirmation (all were confirmed positive [either on the same sample or a separate sample]; included were samples from infants lost to follow-up between 6 and 8 weeks and 3 months [13 did not return for the 3-month visit]). In some instances, testing was performed on later visit samples to further confirm the infant's HIV status. Seven infants were tested at a later visit, specifically the 6-month visit. Of these, 2 were tested at 6 months to confirm an HIV RNA-positive test at the 6- to 8-week visit, and

tested positive at 6 months. The other 5 were HIV negative at birth, missed the 6- to 8-week and 3-month visits, but returned for the 6-month visit and were found to still be HIV RNA negative. Birth dried blood spots were also tested for infants who died or were lost to follow-up between birth and the 6- to 8-week visit; these infants were considered infected if they were HIV positive at birth. Counseling regarding the HIV status of their infants was provided to mothers as soon as test results were available.

The safety of the intervention was monitored via venous blood samples obtained from all infants at birth and 6 weeks for complete blood cell count measurement using the analyzer. Alanine aminotransferase was measured on specimens collected at birth and 6 weeks in infants at the start of the trial¹⁷ (ASCA AGII Chemistry System, Landmark Scientific Inc, Greensboro, NC). Of the NVP plus ZDV and NVP-only groups of infants, 37 and 43, respectively, were tested for alanine aminotransferase at baseline, and 80 and 84, respectively, were tested at 6 weeks.¹⁷ The number tested at birth is smaller than at 6 weeks because of difficulties in obtaining unhemolyzed heelprick samples. Infants from another study¹³ involving NVP were also tested.¹⁷ At time of testing, data from the HIVNET 012 study¹ in Uganda indicated no major safety concerns with use of the single-dose NVP regimen but no such toxicity data were available from Malawi; therefore, a limited assessment was performed. More infants would have been tested had the data been suggestive of toxicity.

Assessment of Adverse Events

A clinical history form was used to record adverse events, including level of severity (mild, moderate, severe, or life-threatening) and relatedness to the intervention. Adverse event interpretation was based on the National Institutes of Health Division of AIDS Toxicity Table.¹⁸ Regardless of relatedness, infant deaths were separately reported. Two independent pediatricians (members of the data and safety monitoring board of this study) assessed on a regular basis all reported infant deaths to ascertain the most likely causes. Laboratory monitoring of adverse events was based on complete blood cell count on all infants and alanine aminotransferase measurements on a sample of these infants. Adverse event summaries were presented to the data and safety monitoring board at the time of interim analyses.

Statistical Analyses

Data were double entered for cross-verification, managed on site, and rechecked at the Johns Hopkins University. An as-randomized analysis, subject to available data, was followed. Comparisons of treatment groups were performed for binary characteristics using proportions and exact tests; continuous characteristics were compared using means and *t* tests. The *P* values were all 2-sided. We calculated the proportion of infants infected at birth and the proportion of those infected at 6 to 8 weeks among those infants not infected at birth and retested at 6 to 8 weeks. The primary outcome was overall HIV infection at 6 to 8 weeks calculated by the life table approach¹⁹ as $\{1 - [(1 - \text{proportion of infants infected at birth}) \times (1 - \text{proportion of those infants not infected at birth who became infected at 6 to 8 weeks})]\}$. The Greenwood approach to estimation of variance of the survival function²⁰⁻²¹ was used to calculate confidence intervals for the survival estimate, and make statistical comparisons of survival estimates.

Logistic regression was used to adjust the comparisons of HIV infection at 6 to 8 weeks for maternal HIV viral load and other factors possibly related to HIV infection. Treatment groups were compared regarding secondary censored binary outcomes such as mortality using Kaplan-Meier curves. Maternal viral load was \log_{10} transformed for a more symmetrical distribution having no outliers. Maternal viral load was also evaluated as a categorical variable by dividing it into approximate tertiles (<10 000 copies/mL, 10 000-99 999 copies/mL, and $\geq 100\ 000$ copies/mL). In the final analysis, a cutoff of less than 100 000 copies/mL vs at least 100 000 copies/mL was used because transmission frequency was similar in lower viral load categories. A sample size of 890 infants (445 per group) was originally planned to have more than 80% power (even with 10% dropout) to detect a reduction of 6- to 8-week mother-to-child transmission (in infants tested at 6 to 8 weeks) from 14% in the group without ZDV to 7% in the group with ZDV using an O'Brien-Fleming α spending function with $\alpha = .05$ and 2 interim analyses. SAS statistical software version 8.2 (SAS Institute Inc, Cary, NC) was used for all statistical analyses. $P \leq .05$ was considered statistically significant.

Approvals and Monitoring

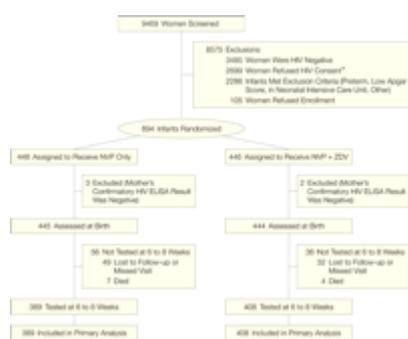
This study was approved by institutional review boards in Malawi (the University of Malawi College of Medicine Research and Ethics Committee) and in the United States (the Johns Hopkins Bloomberg School of Public Health Committee on Human Research). All women gave written informed consent for HIV testing and enrollment. This study underwent monitoring by a 5-member data and safety monitoring board with expertise in clinical trials, clinical practice in Malawi, and statistics. Two independent scientists (an internist and an internist/pharmacologist) from the University of Malawi with expertise in clinical practice and clinical trials performed a 10-day monitoring of all study sites, including the clinics, laboratory, and data entry site, as well as review of the study conduct and procedures in the first 6 months of the study.

RESULTS

Overall, from April 1, 2000, to March 15, 2003, 9469 early presenting women were screened and 8575 women were excluded, of whom about 41% were HIV negative, 31% declined to speak with the counselor regarding counseling about HIV and the study, and 28% did not fulfill inclusion criteria (Figure 1). Thus, 894 women were enrolled and their infants randomized; 446 were randomized to NVP plus ZDV and 448 were randomized to NVP alone. Because the initial HIV test was a rapid test, 5 women were excluded after the ELISA test was found negative (2 in the NVP plus ZDV group and 3 in the NVP-only group). The excluded women were counseled again and followed up with their infants throughout the study. The baseline characteristics by study group were comparable (Table 1), with the exception of mode of delivery; more cesarean deliveries (mostly nonelective) were performed in women with infants in the NVP-only group (for the NVP plus ZDV group, 1 [0.24%] of 423 deliveries were elective and for the NVP-only group, 1 [0.24%] of 421 deliveries were elective). There were no significant differences between the 2 groups in viral load and almost all infants were still breastfed by 1 week and 6 to 8 weeks (Table 1).

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Figure. Study Flow of Participating Women and Infants

HIV indicates human immunodeficiency virus; NVP, nevirapine; ZDV, zidovudine; ELISA, enzyme-linked immunosorbent assay. *These women declined to speak with the counselor regarding counseling about HIV and the study.

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Table 1. Comparison of Baseline Characteristics*

From maternal dosing with NVP to delivery, the median length of time was 4.2 hours (interquartile range [IQR], 2.3-8.5) in mothers of infants who received NVP and 3.9 hours (IQR, 2.5-8.0) in mothers of infants who received NVP plus ZDV (Wilcoxon rank test, $P = .54$). There were no statistically significant differences between the 2 study groups when maternal NVP dosing time was dichotomized to less than 2 hours and 2 hours or more (Table 1). Median times from birth to administration of NVP to the infant were 9.5 hours (IQR, 4.9-16.0) and 9.3 hours (IQR, 4.7-15.4), respectively (Wilcoxon rank test, $P = .47$), for the groups that received NVP only and received NVP plus ZDV. Based on the maternal histories taken, more than 90% of the infants randomized to ZDV received the complete ZDV regimen (14 doses).

Transmission was comparable at birth (ie, before the infants were differentially treated, with some

receiving NVP only and others receiving NVP plus ZDV); 36 (8.1%) of 445 infants who received NVP alone were HIV positive at birth vs 45 (10.1%) of 444 infants who received NVP plus ZDV ($P = .30$; [Table 2](#)). In infants who were HIV negative at birth and retested at 6 to 8 weeks, the frequency of infection between birth and 6 to 8 weeks was nearly identical for the 2 treatment groups; 6.5% in those infants who received NVP alone and 6.9% in those who received NVP plus ZDV ($P = .88$).

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Table 2. Proportion of Infants With HIV Infection by Randomization Status*

[Table 2](#) shows that the life table estimates of mother-to-child transmission at 6 to 8 weeks were 14.1% (95% confidence interval [CI], 10.7%-17.4%) in those infants who received a standard NVP regimen vs 16.3% (95% CI, 12.7%-19.8%) for infants who received NVP plus ZDV, which corresponds to a risk ratio of 1.15 (95% CI, 0.84-1.60). Controlling for important risk factors known to influence mother-to-child transmission (viral load at delivery, rupture of membranes ≥ 4 hours, and mode of delivery) did not change the lack of association between treatment and overall HIV infection at 6 to 8 weeks (adjusted odds ratio for NVP plus ZDV vs NVP alone, 1.19; 95% CI, 0.79-1.79; [Table 3](#)). Maternal NVP dosing time of less than 2 hours was not significantly associated with mother-to-child transmission in the univariate analysis (odds ratio, 1.01; 95% CI, 0.65-1.86) and was thus not included in the adjusted model.

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Table 3. Factors Associated With HIV Infection in Infants at 6 to 8 Weeks

Maternal viral load, however, was strongly associated with transmission (adjusted odds ratio, 2.66; 95% CI, 1.95-3.63). There was also a clear trend of increase in mother-to-child transmission with increase in maternal viral level in each of the treatment groups. In infants who received NVP only, the life table estimate of 6 to 8 week transmission was 11.7% when maternal viral load was less than 100 000 copies/mL and 21.5% when maternal viral load was 100 000 copies/mL or more ($P = .03$). In infants who received NVP plus ZDV, transmission was 12.9% when maternal viral load was less than 100 000 copies/mL and 25.9% when maternal viral load was 100 000 copies/mL or more ($P = .01$).

A limited number of infants who did not test positive at birth ($n = 36$ in the NVP plus ZDV group and $n = 56$ in the NVP-only group) were not tested at 6 to 8 weeks because they died, missed the 6- to 8-week visit, or were lost to follow-up ([Figure 1](#)). In each study group, a similar number of infants (4 and 7, respectively) died by 6 to 8 weeks. Maternal viral load levels, an important determinant of mother-to-child transmission, did not significantly differ by treatment group in those infants who did not return for the 6- to 8-week visit. For example, the median maternal viral load level for 35 infants who received NVP plus ZDV and did not return for the 6- to 8-week visit was 33 838 copies/mL and for 53 infants who received NVP only and did not return for the 6- to 8-week visit, the median maternal viral load level was 24 460 copies/mL (Wilcoxon rank test, $P = .98$); the differences in data from the data given in [Figure 1](#) (36 and 56, respectively) are due to missing data for viral load.

Safety analyses for infants enrolled in this study showed that numbers of grade 3 or 4 adverse events (severe or life-threatening) were similar between treatment groups (22 [4.9%] in 448 infants in the NVP-only group and 24 [5.4%] in 446 infants in the NVP plus ZDV group; $P = .76$). Less than 3% of adverse events were determined to be probably or possibly related to the intervention in the entire study (6 cases of rash, 7 cases of various skin manifestations other than rash, 3 cases of sepsis, and 8 cases of miscellaneous conditions [fever, cough, diarrhea, and oral lesions]). Severe adverse events were considered to be mainly due to infections; of the 46 grade 3 or 4 adverse events, 25 cases (54%) were coded as pneumonia, diarrhea, or malnutrition possibly related to infections. Changes in laboratory parameters of alanine aminotransferase and hemoglobin, packed cell volume, and other hematological indices were largely consistent with grade 1 (mild) toxicity.¹⁷ For example, based on the National

Institutes of Health Division of AIDS Toxicity [Table 1](#) classifications of safety for children younger than 3 months,¹⁸ of 670 infants with hemoglobin results available at 6 to 8 weeks in the study herein, 78% had normal results, and the hematological changes were mild in 12%, moderate in 7%, and severe (hemoglobin <7 g/dL) in 3%. Severe hematological changes were observed in 15 (4.39%) of 342 of the NVP plus ZDV group and 7 (2.13%) of 329 of the NVP-only group (Fisher exact test, $P = .13$).

Based on Kaplan-Meier analyses, survival probabilities were comparable for infants who only received NVP to those for infants receiving NVP plus ZDV at 12 months (89% if NVP was administered vs 90% if NVP plus ZDV was administered) and 18 months (85% vs 87%, respectively). Survival analyses were based on 227 children in the NVP plus ZDV group and 240 in the NVP-only group for the 12-month Kaplan-Meier curves, and 166 and 172 for the respective groups for 18-month analyses. There was no statistically significant difference at 12 or 18 months (log rank $P = .50$ and $P = .51$, respectively). Attenuation in follow-up is due to deaths and other causes of attrition (loss to follow-up, lack of interest in the study, and moving out of study area). For 78 infants who died by 18 months, the main reported causes of death were pneumonia, malaria, gastroenteritis, malnutrition, septicemia, tuberculosis, and meningitis, accounting for more than 85% of reported causes of death.

COMMENT

A standard NVP regimen (single intrapartum dose to the mother and single oral dose to the infant) achieved an overall (per life table estimate) 6- to 8-week mother-to-child transmission of 14.1% (95% CI, 10.7%-17.4%). This is comparable with that observed in the HIVNET 012 study²² in Uganda (11.8%; 95% CI, 8.2%-15.5%), and the SAINT trial²³ in South Africa, which included a maternal postnatal NVP dose in addition to the standard mother/infant dosing (12.3% [95% CI, 9.7%-15.0%] overall rate at 8 weeks). Transmission at 6 to 8 weeks excluding infections at birth in our study was similar for infants who received NVP only (6.5%) and those who received NVP plus ZDV (6.9%). The small difference in overall transmission of 14.1% and 16.3% may be due to residual difference in transmission at birth (8.1% in infants receiving only NVP and 10.1% in those receiving NVP plus ZDV). Transmission between birth and 6 to 8 weeks in infants who received a standard NVP regimen in our study (6.5%; 95% CI, 4.2%-9.6%) was also similar to that of the SAINT study (5.7%; 95% CI, 3.7%-7.8%).

Compared with the risk of mother-to-child transmission when a standard NVP regimen was used, addition of a short neonatal ZDV course to the NVP regimen did not lead to increased reduction in mother-to-child transmission as we originally anticipated. However, safety results were comparable between the 2 study groups that included and did not include ZDV in the prophylaxis regimen for infants. At the time this study was designed, few antiretroviral options were available in sub-Saharan Africa and a dual prophylactic regimen was justifiable based on potential benefits and risks. Today more information is available. For example, the PETRA study²⁴ provided safety and efficacy data on lamivudine in combination with ZDV, and the SAINT study²³ compared a combination of these drugs with NVP. The addition of lamivudine to short intrapartum and neonatal regimens to increase efficacy and limit development of resistance to NVP should be considered.²⁵ Similar to our findings of a lack of an effect, an international study (PACTG 316 study) in nonbreastfeeding women receiving antenatal antiretroviral treatment showed no additional benefit when intrapartum and newborn NVP were administered.²⁶ However, the risk of perinatal transmission was extremely low in the PACTG 316 study, in which a substantial proportion of women received highly active combinations of antiretroviral treatments antenatally, and 34% of women had elective cesarean delivery.

We do not know the exact biological or pharmacological explanations for why addition of a short neonatal ZDV regimen to a standard NVP regimen did not lead to further reduction in mother-to-child transmission. The safety of NVP in the presence of ZDV has been shown in prior studies in which ZDV was used as the standard of care in the United States, or when ZDV was started late during pregnancy and continued postpartum.^{5-6,26-27} No significant drug interactions have been reported when NVP is used as short prophylaxis. The combination of NVP and ZDV previously reduced mother-to-child transmission when the mother did not receive intrapartum NVP¹³ (ie, when the infant was not initially primed through an

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intrapartum maternal dose) but did not achieve the same degree of protection in the study herein when the mother was dosed.

We speculate that in infants born to women who had intrapartum NVP, the effect of NVP is substantially powerful and cellular inhibition is maximal to the extent that addition of short course neonatal ZDV would have no effect. On the other hand, in infants not exposed at all to NVP through the maternal route, both ZDV and NVP may initiate simultaneous inhibition of HIV; possibly ZDV starting earlier because of its faster absorption of approximately 1 hour after dosing²⁸ and this inhibition being complemented by NVP, which has a long-acting effect.^{4, 11-12} We do not have data to support these arguments, but there have been studies that showed reduction in mother-to-child transmission with addition of NVP intrapartum^{6, 27} in which the mothers were using ZDV during pregnancy for at least 4 weeks or more. Thus, possibly either higher levels of ZDV in cord blood were achieved by the time NVP was administered intrapartum, or reductions in maternal viral load were already achieved. The additional reduction in mother-to-child transmission when intrapartum NVP is administered to women who were taking antenatal ZDV for a long period may be due to a combination of several factors.

A limitation common to our studies (and other perinatal trials conducted more recently) is lack of a control group in which both women and infants did not receive treatment. However, perhaps the historical rate of 28% mother-to-child transmission that has been observed in Malawi²⁹⁻³⁰ might reflect what the mother-to-child transmission would have been in this population if no treatment had been administered. Potential bias may arise from use of an open-label design. We opted not to conceal the treatments to simplify the regimens and because NVP was provided to all infants directly by a research nurse while in the hospital. Additionally, the ZDV regimen was administered for 1 week and with the exception of the first dose, all doses were administered at home by the mother, and adherence reports might not have been accurate. However, the level of reported adherence was high (approximately 90%). Similar open-label designs were also used in other HIV perinatal trials conducted in Africa, including the HIVNET 012 in Uganda¹ and SAINT in South Africa.²³ Also, in this study setting, in which resources are limited, diagnoses may be presumptive and based on clinical judgment; thus, misclassifications are possible.

Our studies in Malawi suggest several possible options for prevention of HIV transmission in breastfed infants and in the context of the resource constraints of sub-Saharan Africa. First, voluntary counseling and testing should be available early during pregnancy (or even before pregnancy), allowing HIV-infected women and their infants to receive standard NVP prophylaxis (eg, a woman could self-administer NVP when labor contractions commence). Our current study and other studies in Africa^{1, 23} indicate that this regimen appears to be safe and effective. Second, women who present at the labor ward with unknown HIV status should be tested and offered a standard NVP regimen (for both mother and infant), if time is adequate to counsel, test for HIV, and give intrapartum NVP (if indicated). Third, women arriving too late to the labor ward to be counseled, tested for HIV, and treated intrapartum, should be tested postnatally, and if positive, their infants should be given postexposure prophylaxis. We published a study¹³ showing that a regimen of NVP plus ZDV administered to the infant with the mother receiving no intrapartum NVP reduced mother-to-child transmission in Malawi. Other regimens to prevent mother-to-child transmission could be equally appropriate, based on prevailing circumstances and resources, or more effective, and should also be given consideration,³¹ taking into account issues of possible resistance involving antiretroviral drugs, such as NVP.⁸⁻⁹

In our study, the regimen that included ZDV in addition to a standard NVP regimen appeared to be equivalent to the standard NVP regimen. It could have more value if addition of ZDV limits the appearance of resistance to NVP by reducing HIV replication while NVP concentration decreases. We do not have this information yet, but testing for resistance is in progress. The costs of a standard dose of NVP for mother and infant previously,¹ or as in the study herein, or postexposure prophylaxis of the infant alone with NVP plus ZDV¹³ is approximately equivalent (US \$4-5); addition of a 7-day course of ZDV (for the infant) to a standard NVP regimen (for both mother and infant) approximately doubles the cost. These drugs, however, are becoming more and more accessible through governmental and nongovernmental organizations at no cost. Additional research should focus on evaluation of antiretroviral extended regimens to prevent transmission of HIV via breastmilk and on treatment of the women.

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