MAJOR ARTICLE

A Multicenter Randomized Controlled Trial of Nevirapine Versus a Combination of Zidovudine and Lamivudine to Reduce Intrapartum and Early Postpartum Mother-to-Child Transmission of Human Immunodeficiency Virus Type 1

Dhayendre Moodley,[1] Jagidesa Moodley,[1] Hoosen Coovadia,[1] Glenda Gray,[2] James McIntyre,[2] Justus Hofmyer,[3] Cheryl Nikodem,[3] David Hall,[5] Maria Gigliotti,[5] Patrick Robinson,[5] Lynette Boshoff,[4] and John L. Sullivan,[6] for the South African Intrapartum Nevirapine Trial (SAINT) Investigators

[1]Department of Obstetrics and Gynaecology, Paediatrics and Child Health, Nelson R. Mandela School of Medicine, University of Natal, KwaZulu Natal, and [2]Perinatal HIV-1 Research Unit, Chris Hani Baragwanath Hospital, and [3]Coronation Hospital, Gauteng, and [4]Boehringer-Ingelheim, Randburg, South Africa; [5]Boehringer-Ingelheim Pharmaceutical, Ridgefield, Connecticut; [6]University of Massachusetts Medical School, Worcester

To determine the efficacy and safety of 2 inexpensive and easily deliverable antiretroviral (ARV) regimens for the prevention of mother-to-child transmission (MTCT) of human immunodeficiency virus (HIV) type 1 during labor and delivery, HIV-infected pregnant women were screened at 11 maternity health institutions in South Africa and were enrolled in an open-label short course ARV regimen of either nevirapine (Nvp) or multiple-dose zidovudine and lamivudine (Zdv/3TC). The overall estimated HIV-1 infection rates in 1307 infants by 8 weeks were 12.3% (95% confidence interval [CI], 9.7–15.0) for Nvp and 9.3% (95% CI, 7.0–11.6) for Zdv/3TC ($P = .11$). Excluding infections detected within 72 h (intrauterine), new HIV-1 infections were detected in 5.7% (95% CI, 3.7–7.8) and 3.6% (95% CI, 2.0–5.3) of infants in the Nvp and Zdv/3TC groups, respectively, in the 8 weeks after birth. There were no drug-related maternal or pediatric serious adverse events. Common complications were obstetrical for mothers (Nvp group, 24.3%; Zdv/3TC group, 26.3%) and respiratory for infants (Nvp group, 16.1%; Zdv/3TC group, 17.0%). This study further confirms the efficacy and safety of short-course ARV regimens in reducing MTCT rates in developing countries.

In 1994, a long and complex regimen of zidovudine (Zdv) was reported to reduce mother-to-child transmission (MTCT) of human immunodeficiency virus (HIV) type 1 by 67% [1] in a non–breast-feeding population. This stimulated a search for practical and effective short-course antiretroviral (ARV) regimens for the prevention of MTCT of HIV-1 in developing countries [2–7].

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Reprints or correspondence: Dr. D. Moodley, Dept. of Obstetrics and Gynaecology, Nelson R. Mandela School of Medicine, University of Natal, Private Bag 7, Congella 4013, South Africa (moodleyj@nu.ac.za).

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Before enrollment, study procedures were discussed with the women in their respective native languages, and a written informed consent was signed by the participants who voluntarily consented. The study was approved by the Ethics Committees of the affiliated academic institutions of the study sites and the South African Medicines Control Council.

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Most MTCT occurs during labor and delivery (intrapartum) and after delivery (postpartum) through breast-feeding [8–11]. Short-course ARV regimens during the last 4 weeks of pregnancy have resulted in MTCT rates being reduced by half in non–breast-feeding populations [3, 7]. However, similar multiple-dose ARV regimens studied in breast-feeding populations report lower efficacy rates due to breast-feeding transmission [5, 6]. The Perinatal Transmission (PETRA) study compared different courses of Zdv and lamivudine (3TC) in breast- and formula-fed populations in Africa [6]; a significant reduction in MTCT in the intrapartum/postpartum Zdv/3TC group of the PETRA study was observed at 3 months, but efficacy was lost by 18 months, which was attributed to breast-feeding transmission.

In contrast, the HIVNET 012 model, in which a single dose of nevirapine (Nvp) administered to the mother during labor and to the infant 24 h later, has demonstrated sustained efficacy for 12 months in breast-fed infants [4, 12]. The aim of our study was to compare an Nvp course similar to that used in HIVNET 012, to the intrapartum/7-day postpartum Zdv/3TC PETRA regimen (PETRA B). In an attempt to provide added protection against early breast-feeding transmission, we included in the Nvp group an additional maternal dose between 24 and 72 h after delivery. These simpler regimens may become the treatment of choice for many resource-poor settings, where an integration of antenatal HIV-1 counseling and testing programs into existing antenatal care services presents as the primary hurdle in pilot programs. Both regimens are also practical options for >10% of African women who first register at an antenatal clinic after 36 weeks of gestation or who present to maternity health care settings for the first time in early labor, thus precluding commencement of ARV regimens at 36 weeks [11, 13].

SUBJECTS AND METHODS

Subjects. Eleven public hospitals in South Africa participated in this study between May 1999 and February 2000. Pregnant women aged >16 years who were confirmed to be HIV-1 antibody positive (ELISA Abbott HIV-1/2 III), ARV naive for >12 months, and at >38 weeks gestation (or >35 weeks and in labor) were enrolled prenatally or in latent labor. Elective cesarean section has been shown to independently reduce the risk of intrapartum transmission of HIV-1 [14]. Therefore, women who had a planned cesarean section (elective cesarean section) or who presented with life-threatening complications were excluded from the study.

Study end points. Our objective was to compare and confirm the efficacy and safety of 2 short-course ARV regimens for the prevention of intrapartum and early postpartum HIV-1 MTCT. The primary end points for this study were intrapartum and early postpartum HIV-1 transmission and drug safety. Perinatal HIV-1 infections were documented by the detection of HIV-1 nucleic acids in peripheral blood samples obtained from infants between birth and 8 weeks. Secondary end points addressed the timing of transmission up to 8 weeks (intrauterine, intrapartum, or early postpartum up to 4 weeks during breast-feeding and early postpartum during breast-feeding between 4 and 8 weeks) and HIV-1–free survival rates up to 8 weeks of age [15]. The relationship between HIV-1 infection and putative risk factors for transmission was examined.

Trial design. This study was a multicentered, randomized, open-label controlled trial. Laboratory investigations for the mother and infant were scheduled within 12 h of treatment and at birth, week 4, and weeks 6–8, which included CD4 cell counts and virological assessments to confirm infant HIV-1 infection status and to determine risk factors for transmission. Positive HIV-1 results at the last visit (6–8 weeks) were verified by an additional test at 8–12 weeks. Adverse events for mothers and infants were recorded between the time of enrollment and 12 weeks postpartum. These events were either clinical diagnoses or laboratory abnormalities, or both. Laboratory monitoring included a complete blood-cell count and measurement of hemoglobin, leukocytes, lymphocytes, thrombocytes, creatinine, and liver enzyme levels for both mother and infant at birth, as well as a complete blood-cell count and measurement of hemoglobin, leukocyte, lymphocyte, and thrombocyte levels at 4 weeks for the mother and infant. Grade 3 adverse events were reported within 24 h as serious adverse events to the data management center at Boehringer Ingelheim (Ridgefield, CT and Randburg, South Africa). Interim reports of such adverse events also were communicated to the South African Medicines Control Council (Pretoria, South Africa) and the institutional regulatory boards. There was active monitoring of deaths until 8 weeks and passively until 12 weeks. All deaths that occurred during 8–12 weeks postpartum were analyzed.

Determination of infant HIV-1 infection status. All laboratory testing was done at a central laboratory in South Africa (Barc Pathology, Johannesburg) certified both by regional and international quality assurance programs. Blood samples were transported from all study sites to the laboratory within 72 h of collection. Whole-blood samples for HIV-1 RNA and DNA polymerase chain reaction (PCR) analysis (infants) and HIV-1 RNA PCR analysis (mothers) were collected and centrifuged within 6 h of collection, to separate cells from plasma. Plasma specimens then were stored at 2°C–8°C and shipped in cool boxes to the central lab for testing. Specimens were tested within 48 h of receipt by the virology laboratory or were held at −20°C until tested. After completion of testing, aliquots of plasma specimens were stored at −70°C. Results were available to all investigators within a week of testing. Several reports comparing the sensitivity of both DNA and RNA PCR analyses

at birth have suggested that HIV-1 RNA assays may be more sensitive for diagnosis of infant HIV-1 infection than DNA PCR in the presence of ARV therapy [16, 17]. For this reason, both DNA and RNA PCR tests (Roche HIV-1 Diagnostic Systems) were performed on infant samples at birth, but only DNA PCR tests were performed at all subsequent visits. During the initial stage of the study, the Food and Drug Administration–licensed version 1.0 of the Amplicor DNA and RNA PCR assays were used. After the introduction of the Amplicor version 1.5 with reportedly increased sensitivities (99.1% vs. 97%) for most viral subtypes, all subsequent samples were tested using this version [18]. In addition, all previous samples that tested negative before confirmation of a positive sample, were retested with the new version. When results were discordant both at birth and between visits, specimens were reassayed using both the version 1.0 and version 1.5 assays to ensure maximum sensitivity to circulating HIV-1 strains. An independent virology committee, blinded to treatment, reviewed the results. The committee set up criteria such that, if any assay was positive and a later sample was positive, then the earlier positive result was considered to be evidence for infection at the earlier time point.

Definition of infant HIV-1 infection. Infection was defined as any blood sample testing positive by any assay (DNA/RNA; Amplicor DNA 1.0/Amplicor DNA1.5) and confirmed by a positive result on a later blood sample. The earliest blood sample that tested positive was used for the timing of infection. Infants who tested positive for HIV-1 within 72 h of birth were considered to be infected during the intrauterine period [16]. Infants who tested negative after DNA and RNA PCR tests within 72 h of birth and subsequently tested positive at 4 weeks were considered to be infected during the intrapartum or early postpartum/breast-feeding period. Studies on mucosal infection in the infant monkey model suggest that intrapartum infection does not result in detectable plasma viral RNA within 72 h but is only detectable in the bloodstream only after 5–7 days [19]. Furthermore, because of potential transmission during the early (first 4 weeks) breast-feeding period, it was not possible to differentiate between intrapartum and early postpartum infections. Infants who tested negative within 72 h of birth, negative at 4 weeks, and subsequently positive at 6–8 weeks, were considered as being infected only during the early postpartum/breast-feeding period. Infants with 1 positive PCR test, followed by loss to follow-up, had a second aliquot of the positive specimen tested for confirmation. The independent virology committee, blinded to treatment assignment, reviewed all infants with ≥ 1 positive test result. The virology review committee determined the infection status and onset date on the basis of the standard algorithm noted above. Results judged to be indeterminate were excluded from analyses.

Sample size. Sample size was based on an anticipated infection rate for untreated infants of 7% intrauterine and 18% intrapartum/early postpartum [8]. The intrapartum/postpartum treatment was expected to be at least 50% effective, reducing the intrapartum/early postpartum infection rate to 9%. The trial had 80% power to demonstrate the difference between treatments that were 50% and 75% effective. Thus, the trial was planned to have 80% power for comparing treatments with intrapartum/early postpartum infection rates of 9% and 4.5%. It was not designed to demonstrate equivalence with a predefined bound on clinically meaningful differences. The target was a total of 974 evaluable infants, with "evaluable" defined as "not infected intrauterine" and "not lost to follow-up" after discharge from the hospital. The target enrollment was determined on the basis of preliminary information about the rate of loss to follow-up.

Randomization, treatment, and evaluation. Women were randomized to treatment when presenting in early or latent labor by use of computer generated scratch-card sheets. The randomization code was unknown to investigator and mother, until the mother was prepared to begin treatment. The random assignment code was generated in blocks of 4, with a 2:2 ratio for Nvp and Zdv/3TC. The Nvp regimen was 200 mg of Nvp administered orally in labor plus an additional dose 48 h later if still in labor, followed by 200 mg 24–48 h postpartum. Infants were given 6 mg of Nvp oral suspension (10 mg/mL) 24–48 h after delivery. Infants born within 2 h of the maternal labor dose received an additional 6-mg dose within 6 h after delivery.

The Zdv/3TC regimen was a loading dose of 600 mg of Zdv and 150 mg of 3TC administered orally, followed by 300 mg of Zdv every 3 h and 150 mg of 3TC every 12 h until delivery. Mothers continued on a twice-daily dose of Zdv (300 mg) and 3TC (150 mg) for 1 week after delivery. Infants who weighed >2 kg commenced therapy for at least 12 h after birth and continued for 1 week with twice-daily doses of Zdv syrup (12 mg) and 3TC oral solution (6 mg). Infants who weighed <2 kg received Zdv (4 mg/kg) and 3TC (2 mg/kg). Infants born within 2 h of the first maternal dose started their treatment within 6 h after delivery.

Treatment compliance. All study drugs, with the exception of the 1-week postpartum regimen of Zdv/3TC, were administered by research nurses in the various hospitals and were recorded in treatment logs. Compliance with the 1-week postpartum Zdv/3TC regimen was assessed by interview with patients and by estimated measurement of remaining volumes of drugs that were returned.

Trial monitoring and preliminary analysis. A preliminary analysis of efficacy and safety was reviewed by an independent Data and Safety Monitoring Board (DSMB). Interruption of the trial would have been guided by safety of the drugs. No serious adverse events related to either drug were reported during the trial, and the study was completed without an inter-

ruption. The DSMB also evaluated the validity and reliability of the assumptions documenting intrauterine infections.

Infant feeding advice. Women were advised on the risks and benefits of different infant feeding practices. Of particular importance, women who chose to breast-feed were advised to exclusively breast-feed and also were informed of the dangers of mixed feeding [20, 21, 22]. Interviews with the women on infant feeding methods were conducted at each clinic visit. The feeding questions were asked in terms of whether the infant was receiving breast milk, formula, or a mixture of breast milk and formula. Women who chose to breast-feed were further questioned with regard to the inclusion of other liquids or solids given to the infant during the breast-feeding period. Infant formula was offered for free or at a low cost, depending on site-specific policies.

Statistical analysis. The primary analysis examined infant infections that were documented >72 h after birth and before 8 weeks of age (intrapartum/early postpartum infections). Infants with documented infections before 72 h (38 in the Zdv/3TC group and 45 in the Nvp group) or those lost to follow-up before the 4-week visit (143 in the Zdv/3TC group and 149 in the Nvp group) were excluded from the primary analysis. In the estimation of treatment-specific infection rates, Kaplan-Meier analysis was applied to adjust for loss to follow-up between the 4- and 6–8-weeks visits by the alignment of per visit time windows. Logistic regression models were used to analyze infection risk factors for each time interval: intrauterine (first 72 h of birth), intrapartum or early postpartum (day 3 to week 4), and early postpartum (weeks 4–8). Analysis strategy included univariate models for each factor, bivariate models for each factor with treatment (Zdv/3TC vs. Nvp), and multivariate models including all factors. Factors that were found to have no effect on transmission were eliminated after evaluation of univariate and bivariate models. Putative risk factors included breast-feeding, maternal CD4 cell count, and maternal HIV-1 RNA level at baseline within 12 h of treatment and delivery, emergency cesarean section, timing of intrapartum maternal dosing, prolonged rupture of membrane, and duration of labor. Cox regression techniques also were applied to adjust for the putative risk factors identified above, but differences in risk between time intervals made by visit analyses were more insightful. Although proportionality was observed for treatment through time, breast-feeding and other risk factors did not meet proportionality assumptions.

Other analyses included infant mortality, HIV-1 infection–free survival, and all HIV-1 infections documented through 8 weeks, using the same methods as for the primary analysis. For infant mortality and HIV-1 infection–free survival, Cox regression models were the basis of risk ratios, with infants censored at their last follow-up visit. Analyses used all available data pertaining to the question addressed, without imputing missing values, and implicitly assuming noninformative censoring. Statistical analyses were performed using SAS version 6.12 (SAS Institute), and all tests and confidence intervals (CIs) were considered to be significant at $P \leq .05$ (2-sided).

RESULTS

Between May 1999 and February 2000, 1331 infants (including 14 pairs of twins) were born to 1317 women who were receiving treatment in the study. Of these infants, 663 were born to mothers randomized to receive Nvp, 666 were born to mothers randomized to receive Zdv/3TC, and 2 were stillbirths born to women randomized to receive Zdv/3TC. Follow-up of infants up to 8 weeks was completed by June 2000. In the primary analysis of efficacy, a pair of twins was regarded as a single infant unit and infected if either infant was infected. The flow of participants through the trial is described in figure 1.

Maternal characteristics. As shown in table 1, women in both treatment groups were comparable, with the exception of

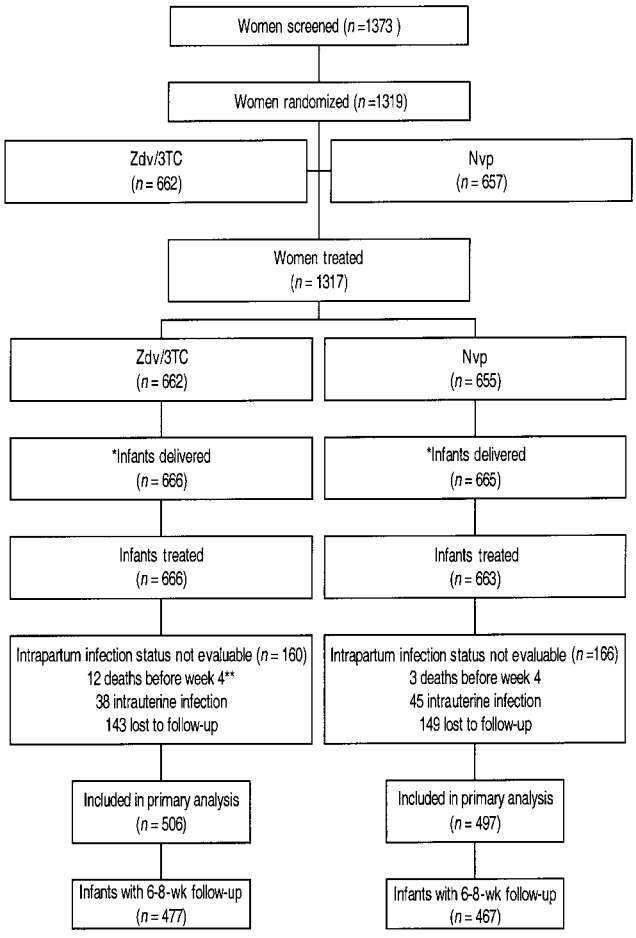


Figure 1. Flow diagram of patient participation in trial. Nvp, nevirapine; Zdv, zidovudine; 3TC, lamivudine. *, Categories not mutually exclusive; **, Fourteen pairs of twins (6 Zdv/3TC and 8 Nvp).

Table 1. Maternal and infant characteristics.

Characteristic	Nvp	Zdv/3TC	Total	P^a
Women who received study drug, no.	655	662	1317	
Age at entry, median years	25	25		
Gestational age at delivery, median weeks	38.1	38.0		
CD4 cell count at delivery, cells/mm^3				.995
Median	404.5	384.5		
Mean (±SD)	436 (246)	436 (253)		
<200	103 (15.9)	85 (13.1)		
200–399	212 (32.8)	256 (39.5)		
>400	331 (51.2)	307 (47.4)		
Mode of delivery				
Cesarean section	182 (27.8)	208 (31.4)	390 (29.6)	
Vaginal	467 (71.3)	453 (68.4)	920 (69.9)	
Not recorded	6 (0.9)	1 (0.2)	7 (0.5)	
Maternal HIV-1 RNA level at delivery, $\log_{10}$ copies/mL				
Geometric mean	10,351	7674		.009
<500	81 (12.7)	88 (13.8)		
500–1000	37 (5.8)	39 (6.1)		
1001–5000	113 (17.8)	136 (21.4)		
5001–10,000	62 (9.8)	81 (12.7)		
10,001–50,000	186 (29.3)	172 (27.0)		
>50,000	157 (24.7)	120 (18.9)		
No. of infants	663	666		
No. of singletons	647	654		
No. of twins	16 (8 pairs)	12 (6 pairs)		
Birth weight, g				
<2000	7 (1.1)	5 (0.8)		
>2000	653 (98.5)	659 (98.9)		
No record	3 (0.5)	2 (0.3)		
Median time from initial treatment to delivery, h	4.4	4.4	4.4	
Breast-fed				
Ever	306 (46.2)	317 (47.7)	623 (46.9)	
Reported at delivery	298 (45.0)	307 (46.2)	605 (45.6)	
Reported at 4 weeks	224 (33.8)	222 (33.4)	446 (33.6)	
Reported at 8 weeks	207 (31.2)	218 (32.8)	425 (32.0)	

NOTE. Data are no. (%) of subjects, unless otherwise indicated. HIV-1, human immunodeficiency virus type 1; Nvp, nevirapine; Zdv/3TC, zidovudine and lamivudine.

[a] Two-tailed *t* tests of differences in means, CD4 cell count (cells/mm^3), and HIV RNA level ($\log_{10}$ copies/mL).

maternal virus load at delivery, which was significantly higher in the women in the Nvp group than those in the Zdv/3TC group (geometric mean, 10,351 and 7674 copies/mL, respectively; $P = .01$). At screening, 15.9% and 13.1% in the Nvp and Zdv/3TC groups, respectively, had CD4 cell counts <200 cells/mm^3. Both treatment groups had mean CD4 cell counts of 436 cells/mm^3. Women in the Nvp and Zdv/3TC groups had similar labor and delivery characteristics; the median duration of labor was 10.3 and 10.5 h, respectively, and the rate of emergency cesarean section deliveries was 27.8% and 31.4%, respectively. The frequency of emergency cesarean section delivery varied from 0% (0/7) to 53% (9/17) across hospital centres. The 3 largest centres had rates of 43% (149/343), 31% (108/350), and 15% (42/282). These variations in frequency may not affect the applicability of the results to other African populations, since emergency cesarean section delivery is not known to be protective [14]; thus, the efficacy of the regimens may be the same. None of the women had an elective cesarean section, and, because of logistical constraints, increased morbidity, and cultural aspects of vaginal delivery, an analysis of the protective effect of this procedure in this population may not be feasible. In the Nvp and Zdv/3TC groups, 27.9% and 26.6% of women gave birth within 2 h of

Table 2. Rates of infant human immunodeficiency virus type 1 (HIV-1) infections by 4 weeks and from 4 to 8 weeks in mother-infant pairs given either nevirapine (Nvp) or zidovudine and lamivudine (Zdv/3TC).

	Nvp		Zdv/3TC		
Timing of transmission	Observed for time interval[a]	Kaplan-Meier infection rate/ 100 infants	Observed for time interval[a]	Kaplan-Meier infection rate/ 100 infants	Difference/ 100 infants
Intrauterine	45		38		
Positive PCR result at birth		7.0 (5.0–9.0)		5.9 (4.1–7.7)	1.1 (−1.6–3.8)
Intrapartum	18		11		
Positive PCR result 4 weeks after birth		10.4 (7.9–12.8)		7.9 (5.8–10.1)	2.4 (−0.8–5.7)
Early postpartum	10		7		
Positive PCR result 4–8 weeks after birth		12.3 (9.7–15.0)		9.3 (7.0–11.6)	3.0 (−0.5–6.6)
Intrapartum, early postpartum	28		18		2.1
Positive PCR result 8 weeks after birth		5.7 (3.7–7.8)		3.6 (2.0–5.3)	

NOTE. Data are percentage (95% CI), unless otherwise indicated. CI, confidence interval; PCR, polymerase chain reaction.

[a] Data are no. of observed infections are new HIV-1 infections defined as positive by HIV-1 DNA/RNA PCR analysis at birth and/or positive DNA PCR result at subsequent visits

commencing study drugs. No doses were received before delivery for 3.8% and 3.2% of women in the Nvp and Zdv/3TC groups. The median number of doses before delivery in the Nvp and Zdv/3TC groups were 1 and 2, respectively, with 265 (40%) receiving only 1 dose in the Zdv/3TC group.

Infant feeding patterns. Infant feeding patterns in both treatment groups were similar. After delivery, 278 (41.9%) and 282 (42.3%) infants in the Nvp and Zdv/3TC groups, respectively, were breast-fed. Less than 4% were reported to be fed by both breast-milk and formula. The remaining 55.7% and 54.8% of infants in the Nvp and Zdv/3TC groups, respectively, were only given formula. Breast-fed infants had a crude mortality rate of 3.5% (21/601), and formula-fed infants had a rate of 2.3% (16/691).

Primary end points. A total of 1307 infants (includes twins as pairs, as described above) were included in efficacy analysis. Intrauterine infections were observed in 38 (5.9%) Zdv/3TC-treated infants and 45 (7.0%) Nvp-treated infants. Excluding intrauterine HIV-1 infections, 3.6% (95% CI, 2.0–5.3) and 5.7% (95% CI, 3.7–7.8) of the infants were estimated to be infected between birth and at 6–8 weeks of age in the Zdv/3TC and Nvp groups, respectively (table 2). These infections are considered to be the events that treatment was intended to prevent. There was no significant difference in the incidence of intrapartum and early postpartum transmission ($P = .11$, log-rank test) between treatment groups.

There was no significant difference in the frequency of maternal adverse events, serious adverse events, or deaths between the treatment groups. The most common maternal adverse events through 28 days after delivery were related to obstetrical procedures (24.3% in Nvp group; 26.3% in Zdv/3TC group; $P = .40$; table 3). There were no adverse hematological or hepatic adverse events reported for either treatment group.

Common adverse events reported through 28 days of life were similar in both treatment groups, of which most were respiratory system disorders (table 3). The rates of serious adverse events (clinical or laboratory abnormalities) were similar in the 2 treatment groups: 9.0% (Nvp) and 10.4% (Zdv/3TC). The most frequent serious adverse events were respiratory system disorders (Nvp, 4.1%; Zdv/3TC, 4.2%; including asphyxia, respiratory distress syndrome, aspiration, and dyspnea) and infections (Nvp, 2.6%; Zdv/3TC, 3.2%). There were 15 infant deaths (1.2% of all infants and 38% of documented deaths) within 4 weeks of age. Infant mortality was 3.1% for those who were delivered vaginally and 2.8% for those who were delivered via cesarean section. HIV-1 infection was the primary factor associated with infant mortality. Infants whose mothers had higher CD4 cell counts at baseline had decreased risk of death independent of HIV-1 infection (table 4).

Secondary end points. Estimated infection rates (Kaplan-Meier) through 8 weeks were 12.3% (95% CI, 9.7–15.0) in the Nvp group and 9.3% (95% CI, 7.0–11.6) in the Zdv/3TC group ($P = .11$; table 2). HIV-1–free survival rates for the Nvp and Zdv/3TC groups at 8 weeks were estimated to be 85.9% (95% CI, 82.9–88.9) and 87.5% (95% CI, 84.7–90.3), respectively (figure 2). The estimated difference in HIV-1–free survival rates was 1.6% (95% CI, 2.5–5.7). Infant mortality was strongly associated with HIV-1 infection (table 4), with multivariate Cox model risk ratio 65.9 (95% CI, 8.3–526.5; $P < .001$). Maternal CD4 cell count was an independent risk factor, with risk increasing as CD4 cell count decreased.

Additional analyses. The HIV-1 infection rates were significantly higher for breast-fed infants than for formula-fed infants ($P < .05$). There was a 2-fold increased odds (univariate OR, 2.12; 95% CI, 1.00–4.49) of HIV-1 infection with breast-feeding during the first 4 weeks and an ~7-fold increase (uni-

Table 3. Adverse events of clinical importance occurring in trial participants.

Events	Zdv/3TC	Nvp	Total
Maternal	662	655	1317
Deaths[a]	4 (0.6)	5 (0.8)	9 (0.7)
Obstetrical procedures	174 (26.3)	159 (24.3)	333 (25.3)
Rash	5 (0.8)	4 (0.6)	9 (0.7)
Cesarean section	208 (31.4)	182 (27.8)	390 (29.6)
Prolonged labor	129	119	248
Fetal compromise	63	50	113
Other indications	16	13	29
Infant	666	663	1329
Respiratory disorders	113 (17.0)	107 (16.1)	220 (16.6)
Infections	60 (9.0)	51 (7.7)	111 (8.4)
Serious events[b]	21 (3.2)	17 (2.6)	38 (2.9)
Hepatic adverse events	22 (3.3)	18 (2.7)	40 (3.0)
Neonatal jaundice	20 (3.0)	13 (2.0)	33 (2.5)
Hepatosplenomegaly	2 (0.3)	3 (0.5)	5 (0.4)
Hepatomegaly	0 (0)	1 (0.2)	1 (0.1)
Increased SGPT	0 (0)	1 (0.2)	1 (0.1)
Rash[c]	17 (2.6)	10 (1.5)	27 (2.0)
Deaths[d]	19 (2.9)	19 (2.9)	38 (2.9)
Neonatal death	8	4	12
Diarrhea/gastroenteritis	4	6	10
Pneumonia	1	4	5
Birth aphyxia	3	1	4
Other[e]	3	4	7

NOTE. Data are no. or no./total no. (%) of trial participants. Adverse events occurred from labor to 28 days postpartum, except for deaths, which are represented from labor through 8–12 weeks postpartum). SGPT, serum glutamic pyruvic transaminase.

[a] Causes of maternal death in the 2 groups were as follows: Nvp group, unknown causes (2), meningitis (1), sudden death (1), and dyspnea (1); Zdv/3TC group, sepsis (2), pulmonary tuberculosis (1), and cerebral vascular accident (1).

[b] Serious adverse events of infection are a subset of all adverse events of infection.

[c] Skin rashes that occurred in 2 participants in the Nvp group and 2 in the Zdv/3TC group were determined by the investigators to be treatment related.

[d] In addition, there were 2 stillbirths reported in this study (Zdv/3TC group). Of the 38 reported deaths, 18 occurred among infants who were positive for human immunodeficiency virus type 1 (HIV-1) (4 in the Zdv/3TC group and 14 in the Nvp group).

[e] "Other" includes septicemia (1 in the Zdv/3TC group and 2 in the Nvp group), fever (1 in the Zdv/3TC group and 1 in the Nvp group), congenital heart disease (1 in the Nvp group), and intracranial hemorrhage (1 in the Zdv/3TC group).

variate OR, 7.23; 95% CI, 2.06–25.34) between weeks 4 and 8 (table 5).

Risk factors differed for intrauterine, intrapartum/early postpartum (0–4 weeks), and early postpartum (4–8 weeks) infections (table 6). The only significant factor for intrauterine infection was baseline maternal HIV-1 RNA levels >50,000 copies/mL, leading to an ~3-fold increase in risk (multivariate OR, 2.9; 95% CI, 1.8–4.8).

For intrapartum/early postpartum infection, which was documented by 4 weeks, risk factors included maternal HIV-1 RNA, first maternal dose <2 h before delivery, and emergency cesarean section. Although maternal dose <2 h before delivery increased the risk of infection by 3-fold (multivariate OR, 3.1; 95% CI, 1.4–7.1), an emergency cesarean section increased the risk of infection by 2.5-fold (multivariate OR, 2.5; 95% CI, 1.1–5.6). In the Nvp group, infants delivered <2 h after maternal dosing had a 6.3% HIV-1 infection rate (8/128), compared with 3.2% (12/372) for those delivered >2 h after maternal dosing. Similarly, in the Zdv/3TC group, infection rates were 3.8% (5/132) and 1.9% (7/379), respectively. Breast-feeding (multivariate OR, 2.2; 95% CI, 0.9–4.7; $P = .06$) and prolonged rupture of membranes (multivariate OR, 2.8, 95% CI; 0.9–7.9; $P = .06$) also increased the risk of infection.

For infection documented between 4 and 8 weeks, breast-feeding was a significant factor for infection (multivariate OR, 7.9; 95% CI, 2.2–28.3), as was maternal CD4 cell count. Each 100-cell increase in maternal CD4 cell count was associated with a decrease in the risk of infection by 40% (multivariate OR, 0.6; 95% CI, 0.4–0.9).

Analyses also were performed by restricting attention to formula-fed infants. Kaplan-Meier estimates of infections rates were 5.6% and 7.1% for intrauterine infection and 6.9% and 10.6% for all infections through 8 weeks for the Zdv/3TC and Nvp groups, respectively.

DISCUSSION

In this study, an ultrashort course of Nvp and a short course of Zdv/3TC, both administered during to subjects during labor, were shown to be safe and effective in reducing the risk of intrapartum and/or early postpartum transmission of HIV-1 from mother to child. Importantly, the SAINT results have confirmed the results of HIV-1NET 012 in Uganda [4] by extending the findings across populations, regions and clades (clades A and D in Uganda and clade C in South Africa).

The World Health Organization has recommended that countries move beyond pilot programs to reduce MTCT on a wider scale [22]. The choice of effective ARV regimens rests on assessment of the advantages and shortcomings of each ARV regimen and the appropriateness for a particular population and country. This study is the first direct comparison of 2 practical regimens of proven efficacy [4, 6]. The simplicity of the regimens, which are the least demanding for antenatal clinic services, are of special interest to African countries, where up to 10% of pregnant women have no access to antenatal services and which carry the heaviest global burden of HIV-1 infection [13]. The current cost in South Africa of the Nvp regimen is approximately $3 US and that of Zdv/3TC regimen is $41 US.

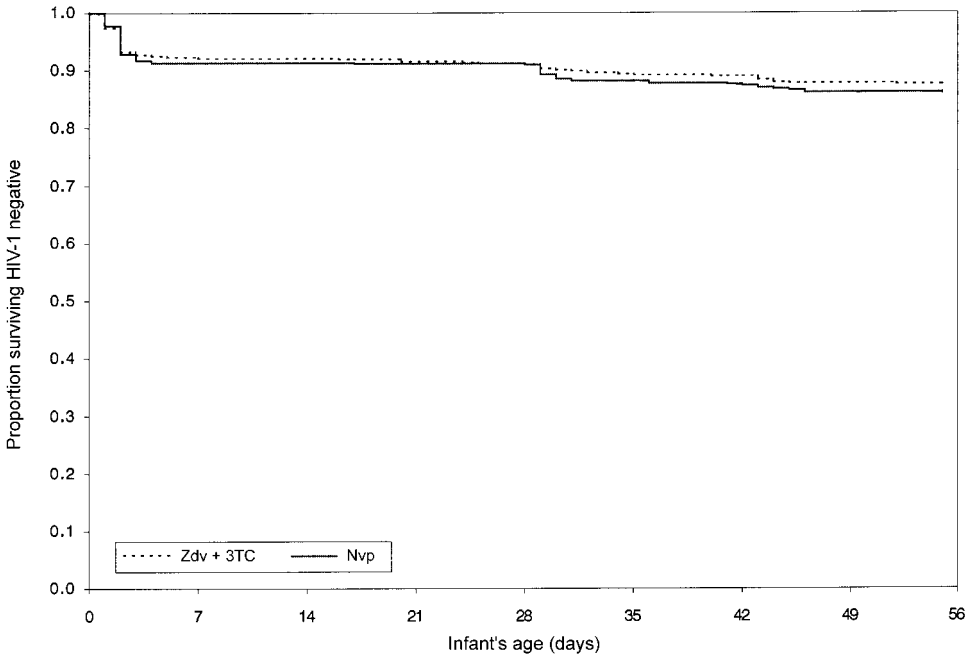
The Zdv/3TC regimen was identical to that in the PETRA

Table 4. Univariate and multivariate Cox regression analysis of risk factors for perinatal deaths documented within 8 weeks (all 1 *df*).

Risk factor	Model with treatment and 1 factor			Multivariate, all factors in model		
	χ^2	RR (95% CI)	*P*	χ^2	RR (95% CI)	*P*
Nvp vs. Zdv/3TC	1.15	0.66 (0.31–1.41)	.284	0.45	1.47 (0.47–4.57)	.505
Cesarean section	0.17	0.84 (0.36–1.97)	.685	0.97	0.46 (0.10–2.17)	.324
Maternal CD4 cell count/100 cells	9.23	0.70 (0.56–0.88)	.002	5.48	0.62 (0.42–0.93)	.019
Maternal HIV-1 RNA level >50,000 copies/mL	2.17	1.84 (0.82–4.14)	.141	0.51	1.53 (0.47–4.89)	.475
Infant HIV-1 positive	19.81	103.11 (13.39–792.93)	<.001	15.61	65.93 (8.26–526.53)	<.001
Prolonged rupture	0.03	1.13 (0.27–4.76)	.872	0.08	1.25 (0.27–5.86)	.780
Breast-feeding	1.53	1.63 (0.7–.52)	.217	0.12	0.83 (0.2–.51)	.735
Maternal dose <2 h before birth	1.56	0.61 (0.2–.33)	.212	0.74	0.61 (0.2–.88)	.388

NOTE. Models include treatment and single risk factor. CI, confidence interval; HIV-1, human immunodeficiency virus type 1; Nvp, nevirapine; RR, risk ratio; Zdv, zidovudine; 3TC, lamivudine.

B group, whereas the Nvp regimen was similar to the Nvp regimen in the HIV-1NET 012 [4, 6]. In addition to the HIV-1NET 012 Nvp regimen, the SAINT regimen included a second dose of Nvp given to the mother between 24 and 48 h after delivery. The 8-week HIV-1 infection and death rate in the Zdv/3TC group of 9.3% was similar to the 11.6% of PETRA at 6 weeks, and the 12.3% for Nvp was comparable to the 12.8% of HIV-1NET 012 at 6–8 weeks. These consistent results confirm that both regimens are robust and attractive choices for developing countries. In the setting where Nvp cannot be



		Day 3	Day 28	Day 42	Day 56
Nvp	Followed	496	462	380	44
	Events	45	64	68	75
Zdv/3TC	Followed	511	485	395	50
	Events	41	56	61	68

Figure 2. Kaplan-Meier estimates of human immunodeficiency virus (HIV) type 1–free survival through 8 weeks. Nvp, nevirapine; Zdv, zidovudine; 3TC, lamivudine.

Table 5. Rates of infant human immunodeficiency virus type 1 infection by 4 weeks and between 4 and 8 weeks, according to feeding practice, in mother-infant pairs given either nevirapine (Nvp) or zidovudine and lamivudine (Zdv/3TC).

Timing of transmission	Nvp		Zdv/3TC		OR for breast-feeding (95% CI)
	Bottle feeding	Breast-feeding	Bottle feeding	Breast-feeding	
Intrauterine	25/351 (7.1)	20/292 (6.9)	19/340 (5.6)	19/306 (6.2)	1.03 (0.66–1.61)
Intrapartum, 0–4 weeks	9/298 (3.0)	9/196 (4.6)	3/290 (1.0)	8/213 (3.8)	2.12 (1.00–4.49)
Early postpartum, 4–8 weeks	2/283 (0.7)	8/179 (4.5)	1/274 (0.4)	6/199 (3.0)	7.23 (2.06–25.34)

NOTE. Data are no./total no. (%) of infection. CI, confidence interval; OR, odds ratio.

given in the antenatal clinic or outpatient setting, the intrapartum Nvp regimen should be administered at the onset of labor in the labor ward.

The recent report of the PETRA trial found that the >50% reduction in MTCT observed with a 2-drug short-term prophylactic ARV regimen in infants at 6 weeks of age was not sustained when measured as HIV-1–free survival at 18 months of age in a predominantly breast-feeding population [6]. These results are in contrast with the results of a maternal short-course Zdv regimen to prevent MTCT in a breast-feeding population in West Africa, where sustained efficacy was demonstrated at 24 months [23]. The West African study also made the important observation that efficacy was observed only among women with CD4 cell counts $\geq$500 cells/mm^3 [23]. Although attempts were made to measure both CD4 cell counts and virus loads before treatment, in several cases circumstances did not allow for this, and blood samples could only be obtained after delivery. Other limitations of the study were the lack of long-term follow-up of infants, to examine for potential sustained efficacy of both drug regimens among breast-fed infants, and the paucity of information regarding breast-feeding practices.

Estimated intrauterine transmission rates approached the 7.3% rate calculated from recent studies [24]. Although this study was designed to reduce the risk of intrapartum/early postpartum transmission, intrauterine transmission rates reported here for both the Nvp and Zdv/3TC groups confirm the need for cheaper and simpler ARVs for use during pregnancy [25], particularly in poor countries.

The intrauterine infection rate can be used to calculate an expected infection rate for untreated formula-fed infants. Approximately one-third of infections are detectable within 72 h of birth [26], which is our definition of intrauterine infections. On this basis, expected infection rates would be 3 times that of intrauterine rates: 21.4% for Nvp and 16.8% for Zdv/3TC. Efficacy is estimated by comparing these rates with the observed rates. Estimated efficacy in preventing intrapartum and early postpartum infections was 75.8% and 88.2%, respectively. Overall efficacy in preventing infection is estimated as 50.6% for Nvp and 58.8% for Zdv/3TC. The numbers needed to treat, that is, the number of mother and infant pairs treated to prevent 1 infant infection, are estimated as 9.3 for Nvp and 10.1 for Zdv/3TC. Both lower and higher infection rates have been observed in untreated populations; thus, potential inaccuracies of estimates must be considered.

The maternal dose <2 h before delivery increased the odds of intrapartum infection 3-fold. This important finding confirms the explanations provided by the Ugandan study (HIVNET 012), that the efficacy of Nvp was probably lowered since some women only received their first dose when admitted during advanced labor [4]. To avoid late dosing, we, therefore, recommend that women who are tested during the antenatal period, be given Nvp during the antenatal period and be advised

Table 6. Multivariate logistic regression analysis of risk factors for perinatal human immunodeficiency virus type 1 (HIV-1) transmission through intrauterine, intrapartum, and early postpartum routes.

Variable	Intrauterine			Intrapartum through 4 weeks			Intrapartum through 4–8 weeks		
	Univariate	Multivariate		Univariate	Multivariate		Univariate	Multivariate	
	OR (95%CI)	OR (95%CI)	*P*	OR (95%CI)	OR (95%CI)	*P*	OR (95%CI)	OR (95%CI)	*P*
Nvp vs. Zdv/3TC	1.2 (0.8–1.9)	1.1 (0.7–1.8)	.572	1.7 (0.8–3.6)	1.47 (0.67–3.25)	.340	1.5 (0.6–3.9)	1.4 (0.5–3.8)	.521
Emergency cesarean section	1.0 (0.6–1.6)	1.11 (0.66–1.87)	.689	2.1 (1.0–4.4)	2.44 (1.07–5.60)	.034	1.4 (0.5–3.9)	1.1 (0.4–3.4)	.818
Maternal CD4 cell count/100 cells	0.9 (0.8–1.0)	0.92 (0.83–1.03)	.162	0.9 (0.7–1.1)	0.93 (0.77–1.12)	.443	0.6 (0.5–0.8)	0.6 (0.4–0.9)	.004
Maternal HIV-1 RNA level >50,000 copies	3.5 (2.2–5.5)	2.96 (1.82–4.81)	.0001	3.0 (1.4–6.4)	2.55 (1.12–5.81)	.026	2.8 (1.0–7.4)	1.5 (0.5–4.4)	.418
Prolonged membrane rupture	1.3 (0.6–2.9)	1.33 (0.59–2.98)	.488	3.1 (1.1–8.3)	2.75 (0.96–7.86)	.060	3.3 (0.9–11.7)	3.5 (0.9–13.4)	.073
Breast-feeding	1.0 (0.7–1.6)	1.03 (0.66–1.60)	.911	2.1 (1.0–4.5)	2.15 (0.98–4.73)	.056	7.1 (2.0–25.0)	7.9 (2.2–28.3)	.002
Maternal dose <2 h before birth	1.6 (1.0–2.5)	1.6 (1.0–2.6)	.058	2.1 (1.0–4.5)	3.10 (1.36–7.08)	.007	1.3 (0.4–3.6)	1.57 (0.51–4.87)	.438

NOTE. CI, confidence interval; Nvp, nevirapine; OR, odds ratio; Zdv, zidovudine; 3TC, lamivudine.

to take the tablet at the first sign of labor. The protocol-specified dosage to the infant within 6 h of birth was not able to compensate for the delay or the absence of the maternal dose. Our findings further suggest that, in circumstances in which Nvp cannot be dispensed at the antenatal clinic, the intrapartum Nvp regimen may still be more efficacious in reducing intrapartum/early postpartum transmission, even when administered at the labor ward at least 2 h before delivery.

In contrast to the recent findings of the PETRA study, in which both elective and emergency cesarean sections were protective [6], emergency cesarean sections in our study was associated with increased risk of intrapartum infection. Emergency cesarean sections are usually performed on women with prolonged labor, which is associated with prolonged rupture of membranes, numerous vaginal examinations, and delivery of the fetal head, deep in the pelvis. All these features are associated with extensive fetomaternal mixing of blood, amniotic fluid, and vaginal secretions, which, therefore, incur a higher risk for intrapartum infection. The authors of the PETRA study postulate that the emergency cesarean sections in their study were associated with a shorter duration of labor and therefore did not pose a higher risk for intrapartum transmission [6]. The high rate of emergency cesarean sections in both studies is probably due to a high cephalo-pelvic disproportion that is a common obstetric complication in the black African population in the province of KwaZulu Natal. The small gynecoid pelvis does not lend itself to assisted vaginal deliveries. The overall cesarean section rates in the nonstudy population during the same time period in KwaZulu Natal was 30%. Furthermore, most of the study sites were obstetric centers to which most high risk obstetric cases are referred for antenatal care and delivery.

This trial, which incorporated both formula- and breast-fed infants, shows that breast-feeding is the most significant risk factor for the outcomes measured and significant for transmission from day 3 to 4 weeks, as well as from 4 to 8 weeks. The difference in MTCT rates (by 8 weeks) between formula-fed and breast-fed infants in this study was 5.6%, which is similar to 6.3% (6 weeks) in Nairobi, but >3.6% (6–8 weeks) in the Uganda HIV-1NET 012 trial and 3.9% in the Durban, South African, feeding study [4, 21, 27]. Although, the SAINT included an additional Nvp dose to the mother, its similar efficacy to the single-dose HIVNET 012 regimen leads us to recommend the latter regimen.

This study confirms that both regimens appear to be similarly effective and to provide similar safety profiles. Although the development of transient viral resistance to Nvp has been reported in the HIV-1NET 012 [28], selection for viral resistance is being currently investigated for Nvp, Zdv, and 3TC in the SAINT study, and data will be available in a subsequent report. The competitiveness of Zdv/3TC in developing countries is contingent on price and practical issues. Adherence to this regimen cannot always be ensured because of multiple doses after discharge from the hospital. Both regimens also are suitable for HIV-1–infected women who delay antenatal services and therefore are ineligible for other ARV regimens that include antepartum therapy.

SAINT STUDY MEMBERS

The following centers and investigators participated in the SAINT study (the number of women enrolled at each hospital and investigators are provided in parentheses): King Edward VIII ($n = 363$) and Prince Mshiyeni Memorial Hospitals ($n = 352$), KwaZulu Natal (D.M., J.M., and H.M.C.); Coronation Hospital, Gauteng ($n = 291$) (J.H. and C.N.); Chris Hani-Baragwanath Hospital, Gauteng ($n = 149$) (G.G., J.M, and S. Lala); Karl Bremmer, Western Cape ($n = 59$) (P. Duminy and M. Winters); Empangeni Hospital, KwaZulu Natal ($n = 48$) (S. Raymond and N. Kapongo); Kalafong Hospital, Gauteng ($n = 44$) (B. Jeffrey and M. Kruger); Pretoria Academic Hospital, Gauteng ($n = 26$) (P. de Witt and P. MacDonald); University of Free State Hospital, Free State ($n = 17$) (H. Cronje and R. H. Bam); University of Cape Town Hospital, Western Cape ($n = 10$) (E. Coetzee); and Medunsa Hospital ($n = 18$) (O. Towobola).

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