Articles

Intrapartum and neonatal single-dose nevirapine compared with zidovudine for prevention of mother-to-child transmission of HIV-1 in Kampala, Uganda: HIVNET 012 randomised trial

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Summary

Background The AIDS Clinical Trials Group protocol 076 zidovudine prophylaxis regimen for HIV-1-infected pregnant women and their babies has been associated with a significant decrease in vertical HIV-1 transmission in non-breastfeeding women in developed countries. We compared the safety and efficacy of short-course nevirapine or zidovudine during labour and the first week of life.

Methods From November, 1997, to April, 1999, we enrolled 626 HIV-1-infected pregnant women at Mulago Hospital in Kampala, Uganda. We randomly assigned mothers nevirapine 200 mg orally at onset of labour and 2 mg/kg to babies within 72 h of birth, or zidovudine 600 mg orally to the mother at onset of labour and 300 mg every 3 h until delivery, and 4 mg/kg orally twice daily to babies for 7 days after birth. We tested babies for HIV-1 infection at birth, 6–8 weeks, and 14–16 weeks by HIV-1 RNA PCR. We assessed HIV-1 transmission and HIV-1-free survival with Kaplan-Meier analysis.

Findings Nearly all babies (98·8%) were breastfed, and 95·6% were still breastfeeding at age 14–16 weeks. The estimated risks of HIV-1 transmission in the zidovudine and nevirapine groups were: 10·4% and 8·2% at birth (p=0·354); 21·3% and 11·9% by age 6–8 weeks (p=0·0027); and 25·1% and 13·1% by age 14–16 weeks (p=0·0006). The efficacy of nevirapine compared with zidovudine was 47% (95% CI 20–64) up to age 14–16 weeks. The two regimens were well tolerated and adverse events were similar in the two groups.

Interpretation Nevirapine lowered the risk of HIV-1 transmission during the first 14–16 weeks of life by nearly 50% in a breastfeeding population. This simple and inexpensive regimen could decrease mother-to-child HIV-1 transmission in less-developed countries.

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Introduction

HIV-1 transmission from an infected mother to her baby is estimated to be 21–43% in less-developed countries,[1] with more than half of transmission probably occurring late in pregnancy or during labour and delivery.[2,3] Results of Pediatric AIDS Clinical Trials Group protocol 076 (ACTG 076) showed that an intensive regimen of zidovudine started at 14–34 weeks' gestation, given intravenously during labour and delivery, and orally to babies for the first 6 weeks of life lowered the rate of HIV-1 vertical transmission by two-thirds.[4] Shorter zidovudine regimens given to women a few weeks before and during labour have also decreased mother-to-child HIV-1 transmission by 37–38% in breastfeeding populations, and by 50% in non-breastfeeding populations.[5–7] One of the potential mechanisms for the efficacy of the ACTG 076 zidovudine regimen in decreasing HIV-1 transmission is antiretroviral prophylaxis of the neonate during the time of HIV-1 exposure at birth.[8] If this hypothesis is correct, the provision of antiretroviral therapy at the onset of labour could be sufficient to decrease vertical transmission during the peripartum period and would offer a less complex and more affordable prophylaxis regimen for HIV-1-infected pregnant women in less-developed countries.

In addition, nearly all HIV-1-infected mothers in Uganda breastfeed for at least the first few weeks after birth, which continues the risk of infection.[9–11] The use of an antiretroviral drug that could provide prophylaxis to babies during weeks 1–2 of life could lower the risk of early transmission of HIV-1 through breastmilk.

Nevirapine is a non-nucleoside reverse-transcriptase inhibitor that has potent antiviral activity (inhibitory concentration [IC_{50}] 0·01 μg/mL), is rapidly absorbed when given orally, and passes quickly through the placenta. The drug has a long half-life in pregnant women and babies (median 61–66 h in pregnant women after a single 200 mg dose during labour, and 45–54 h in babies), which makes it an excellent candidate for use as a single-dose intervention during labour.[12,13] Therefore, we assessed the safety and efficacy of short-course nevirapine compared with zidovudine given to women during labour and to neonates during the first week of life.

Methods

Patients

After receiving pretest counselling, women attending general antenatal clinics at Mulago Hospital in Kampala, Uganda, who consented were screened for HIV-1 infection by EIA for HIV-1 antibody. If a woman tested positive, she received post-test counselling about her infection status and was informed about the opportunity to enroll in HIVNET 012 or other concurrent protocols. Women were eligible for the study if: they were aged at least 18 years; at more than 32 weeks' gestation, confirmed by menstrual history or ultrasonography; were positive on EIA and western blot for HIV-1 antibody; and lived within 15 km of Mulago Hospital. Exclusion criteria were: current antiretroviral or HIV-1 immunotherapy; uncontrolled hypertension; haemoglobin concentration lower than 75 g/L; blood creatinine concentration higher than 1·5 mg/dL; blood alanine aminotransferase concentration more than three times the upper limit of normal; chronic alcohol or illicit drug use; and receipt of benzodiazepines, anticoagulant therapy, or magnesium sulphate within 2 weeks of enrolment or would need them during labour or at delivery. All women who participated in our trial gave written informed consent.

Trial design

HIVNET 012 was originally designed to be a randomised, placebo-controlled, double-blind, phase III trial of 1500 mother-baby pairs to investigate the safety and efficacy of oral zidovudine and oral nevirapine for the prevention of vertical transmission of HIV-1 from pregnant women to neonates in Uganda. Enrolment started in November, 1997. However, after the results were announced of a trial of a short antepartum and intrapartum zidovudine regimen in Thailand in February, 1998,[7] we dropped the placebo group after only 49 women had enrolled and had given birth (19 women had been randomly assigned placebo, and 15 each to the zidovudine and nevirapine groups).

After approval was received from the institutional review boards in Uganda and the USA, we modified the study to include only the two open-label antiretroviral groups. We did an interim study to provide data on the safety and rates of HIV-1 transmission for the two regimens and to guide a decision about which of these two short-course regimens should be included in a future phase III trial to compare the chosen regimen against a standard antiretroviral regimen, to be selected based on the anticipated results of other continuing perinatal trials. Because of nevirapine's long half-life, potent antiviral activity, safety profile, and favourable cost, we planned that the nevirapine group would be included in the phase III trial if transmission rates were equivalent to or lower than those seen with the short-course intrapartum and postpartum zidovudine regimen. The primary efficacy endpoints of this interim study were HIV-1 infection of neonates and HIV-1-free survival rates at ages 6–8 weeks, 14–16 weeks, and 18 months. We assessed maternal safety in the 6-week postpartum period, and safety analyses in babies continued until age 18 months.

Randomisation and methods

The statistical centre generated an allocation schedule with individuals as the unit of randomisation, from a computer random-number generator, to select random permutated blocks of 12. We concealed treatment assignment by prepackaging study drugs in sequentially numbered individual drug kits according to the allocation schedule. On enrolment, each woman received a unique study identification number and was assigned the next sequentially numbered drug kit containing a sufficient supply for her and her baby to complete the prescribed regimen. Initially, the pharmacist at Johns Hopkins Hospital Pharmacy, and later the study pharmacist in Kampala, dispensed the drugs into the prepared kits. The study drugs were stored at room temperature between 15°C and 30°C. All study staff other than the pharmacist (who had no direct contact with participants) were masked to treatment status until after randomisation. After randomisation, on-site study staff and investigators became aware of the treatment and infection status of the mother-baby pairs. Mothers also knew to what study group they had been assigned after randomisation and were told the infection status of their babies during the study.

We randomly assigned women at more than 36 weeks' gestation nevirapine or zidovudine. The nevirapine regimen included oral administration of a single 200 mg tablet given to the mother at the onset of labour, and a single oral dose of nevirapine suspension of 2 mg/kg for the neonate, administered by study staff with a calibrated oral syringe at 72 h after birth or at discharge from hospital, whichever occurred first. The zidovudine regimen included administration of two 300 mg tablets at onset of labour, followed by one 300 mg tablet every 3 h during labour and, for neonates, administration with a calibrated oral syringe of zidovudine syrup, 4 mg/kg twice daily for 7 days after birth. The neonates' zidovudine dose was given by the study staff and mothers together in the hospital and by mothers at home. The first dose of each drug for mothers was given to women to take home with them at about 36 weeks' gestation; we asked them to take the study drug at onset of labour pains and to come to the hospital to deliver their babies. On admission to the hospital, women were examined and asked about the time at which labour started and when they took the study drug. If assigned zidovudine, midwives administered 300 mg tablets every 3 h from the time of the first dose until delivery. If the woman had vomited within 0·5 h of taking the study drug, a second dose was given. If false labour occurred after taking the study drug, women were discharged and given an additional dose to take when labour began. Women in the nevirapine group were instructed to start treatment again if labour began 48 h or more after their last dose; women in the zidovudine group were instructed to start treatment again if labour began 6 h or more after their last dose. If the woman did not receive the study drug or less than 1 h had elapsed between taking the study drug and delivery, neonates were given the study drug immediately after delivery. Neonates who were born at home or at an outside hospital were given the study drug as soon as they arrived at the clinic if they presented within the first 7 days of life. We assessed adherence to study drugs by interview and counting of doses of remaining drugs.

We excluded from study-drug administration women who: presented in second-stage labour without previous self-administration of study drug; had an intrapartum seizure; were unable to take oral drugs; or had severe infection, shock, or other potentially serious or life-threatening disorders. We gave the neonates of these women the assigned study drug immediately after delivery. We excluded neonates from study-drug administration if they had an immediate life-threatening disorder; received anticoagulant therapy, benzodiazepines, or magnesium sulphate; or had severe anaemia or hyperbilirubinaemia that required transfusion or volume replacement.

We took complete medical histories and did physical examinations of all women before entry to the study (between 32 weeks' gestation and enrolment), on enrolment, at delivery, at discharge from hospital, and at 7 days and 6 weeks after delivery. Serum chemistries were done before entry and at 7 days and 6 weeks after delivery. After normal chemistries were seen in the first 100 enrolled women, we discontinued 6-week tests. Complete blood counts and CD4-cell counts were done before entry and on delivery. Quantitative plasma HIV-1 RNA measurements were done before entry, at delivery, and at 7 days and 6 weeks after delivery.

We took histories and carried out physical examinations of babies at birth, age 7 days, and age 6 weeks, 10 weeks, 14 weeks, 26 weeks, 39 weeks, 52 weeks, and 78 weeks. Serum chemistries and complete blood counts were done at 24 h, 7 days, and 6 weeks after birth. CD4-cell counts were done at birth, and at ages 14 weeks, 12 months, and 18 months for all babies. We did qualitative HIV-1 RNA PCR assays on edetic-acid anticoagulated plasma separated from whole blood and frozen at −70°C within 24 h of collection. Testing was done typically within 1 week of collection. Blood samples were collected at 24 h, 6 weeks, and 14 weeks after birth for all babies. If HIV-1 RNA was found, we took second samples as soon as possible or at the next scheduled visit, for confirmation by quantitative HIV-1 RNA PCR or HIV-1 culture. If a baby was HIV-1 infected, we also measured quantitatively HIV-1 RNA load at 12 months and 18 months. We tested all babies for HIV-1 antibody at

18 months by EIA and, if reactive, confirmed the result by HIV-1 western blot.

Criteria for grading of toxic effects were based on toxicity tables for neonates, children, and adults developed by the Division of AIDS, National Institute of Allergy and Infectious Disease.

All laboratory testing, including CD4-cell counts, viral cultures, and qualitative and quantitative HIV-1 RNA PCR assays, was done in real time at the Makerere University-Johns Hopkins University-Case Western Reserve University Collaborative Laboratory at the Uganda Cancer Institute, Kampala. This laboratory conformed to the US Clinical Laboratory Improvement Act of 1988 regulations for these assays.

We screened plasma from mothers for HIV-1 antibody with a licensed assay (HIV type 1 Vironostika, Organon-Teknika, Durham, NC, USA). If the test was reactive, a second HIV-1 antibody test was done on the same sample with the Murex 1+2 assay (Murex Diagnostics SA, Chatillon, France). For women with blood samples that were reactive on both tests, we took a second sample and did an HIV-1 western blot analysis (Cambridge Biotech, Rockville, MD, USA) for confirmation of HIV-1 infection.

From November, 1997, to February, 1998, CD4-cell counts were done with an EPIC Profile II flow cytometer (Coulter Corporation, Miami, FL, USA) for CD4-cell percentages, and a Coulter T 540 haematology analyser (Coulter Corporation) for absolute lymphocyte counts. After February, 1998, we measured CD4-cell counts with a fluorescence-activated cell-sorting instrument (Becton-Dickinson, San Jose, CA, USA). Quantitative and qualitative plasma HIV-1 RNA measurements were assessed with the Roche AMPLICOR MONITOR assay (Roche Diagnostics, Indianapolis, IN, USA) with the 1.0 version kit, with additional primers if tested before November, 1998, and with the 1.5 version primers if tested after that date.[14] The qualitative HIV-1 RNA assay is similar to the quantitative HIV RNA kit for primers, use of an internal standard, control of amplification variables, and detection methods with the same 0·2 optical density cut-off, except that the detection is based on the optical density equivalent to that of the first well of the five-fold dilution series used in the quantitative assay. If a baby had only one positive HIV-1 RNA result, then the optical density had to be more than 1·0 to be taken as a positive result. HIV-1 cell cultures were done on babies' peripheral blood mononuclear cells with the ACTG virus isolation procedure.[15]

All HIV-1 test results and the HIV-1 infection status of babies were verified by the laboratory supervisor and the protocol chairperson, who were unaware of the babies' treatment status. In addition, all available clinical, serological, and virological data were reviewed by the protocol chairperson, cochairpersons, biostatisticians, and the data manager to confirm HIV-1 infection status for babies. HIV-1 infection was defined as a positive qualitative HIV-1 RNA assay confirmed by quantitative HIV-1 RNA assay or HIV-1 culture on a second blood sample. If babies died after only one positive RNA assay on the sample, we classified the baby as being infected.

Statistical analysis

The target sample size for the interim protocol was 556 women to yield 500 fully assessable pairs of mothers and neonates. This sample size was chosen to provide at least 80% probability of correctly choosing nevirapine as the experimental regimen for the phase III trial if the true HIV-1 transmission rate on nevirapine was the same or less than that on zidovudine, and at least 80% probability of correctly choosing zidovudine as the experimental regimen if the true HIV-1 transmission rate in that group was at least 8% lower than that in the nevirapine group. With inclusion of the 19 women who were randomly assigned placebo, 575 women were to be randomised. We decided, however, to extend enrolment by 1 month (until April 30, 1999) after the planned number of women had been enrolled to accommodate a large number of women who had already been screened and had received study counselling by the time of that decision.

The study was monitored after 250 and 500 fully assessable mother-baby pairs had completed 6-week assessment. Monitoring was done by a National Institutes of Health data and safety monitoring board, which included a representative from Uganda. Efficacy boundaries were provided by O'Brien-Fleming guidelines.

The primary efficacy endpoints were the rates of HIV-1 infection and HIV-1-free survival at 6–8 weeks and 14–16 weeks. We used the Kaplan-Meier method to calculate rates of infection and survival. The two-sided p value at any time point was found with a Z statistic, calculated from the difference between the Kaplan-Meier estimates at that time (with SE). For the Kaplan-Meier method, the time to the first positive HIV-1 RNA assay was used as the time to endpoint for babies defined as HIV-1-infected. For HIV-1 free survival, we used the time to death or the first positive HIV-1 RNA assay. For these two analyses, all other babies were censored with follow-up time set to the latest negative RNA PCR assay.

Unless indicated otherwise, analyses of efficacy results and demographic characteristics are based on all mothers in the zidovudine and nevirapine groups and first-born babies for whom follow-up information could be obtained. Analyses were on data collected until June 30, 1999. Analyses of adverse events or toxic effects were based on the first 556 pairs of mothers and babies assigned zidovudine (n=279) and nevirapine (n=277).

We used Cox's regression to estimate relative risks with CI and p values for the two primary clinical-efficacy endpoints (HIV-1 infection and HIV-1-free survival), and to provide adjustments for potential prognostic factors such as maternal baseline CD4-cell and plasma HIV-1-RNA concentration, duration of labour, method of delivery, birthweight, and sex of the neonate. The predictiveness of each of these covariates was also assessed.

Results

Enrolment began November, 1997, and ended on April 30, 1999, and the last neonate was born on June 19, 1999; 645 women were enrolled, of whom 626 were randomly assigned zidovudine or nevirapine, with 313 in each group; 19 mothers were randomly assigned placebo (figure 1). 1499 mothers with positive HIV-1 tests were excluded because they did not return for HIV-1 test results, did not want to give blood samples, were enrolled in other trials, delivered before they could be enrolled, or had an indeterminate or negative western blot.

Characteristics of women who gave birth in the two treatment groups did not differ significantly at enrolment (table 1). Nine caesarean sections were listed as elective. 37 (6·0%) mothers delivered outside the study hospital at home, at another clinic or hospital, or on the way to the hospital.

Characteristics of first-born babies were similar at birth in the two treatment groups. The median 1 min and 5 min Apgar scores were 10. For singletons, the differences in birthweight between treatment groups remained significant (p=0·0019). No neonate weighed less than 1500 g at birth; 0·8% weighed between 1500 g and 2000 g; and 5·0% weighed between 2000 g and 2500 g. 50% of neonates were female. Overall, 98·8% of babies were breastfed; 98·0% were still breastfeeding at 6–8 weeks, and 95·6% at 14–16 weeks. The two groups did not differ in the proportion of babies breastfed overall or over time.

The treatment groups did not differ in the proportion of mothers who received study drugs (96·2% of the zidovudine group and 96·8% of nevirapine group). The median number of zidovudine doses received during labour (including the first 600 mg dose) was two (IQR 1–4). Only one mother in the nevirapine group received two doses of treatment. Study drug was withheld for five mothers (four in the nevirapine group and one in the zidovudine group) because of being in the second stage of labour (four) or receiving valium at the time of labour (one).

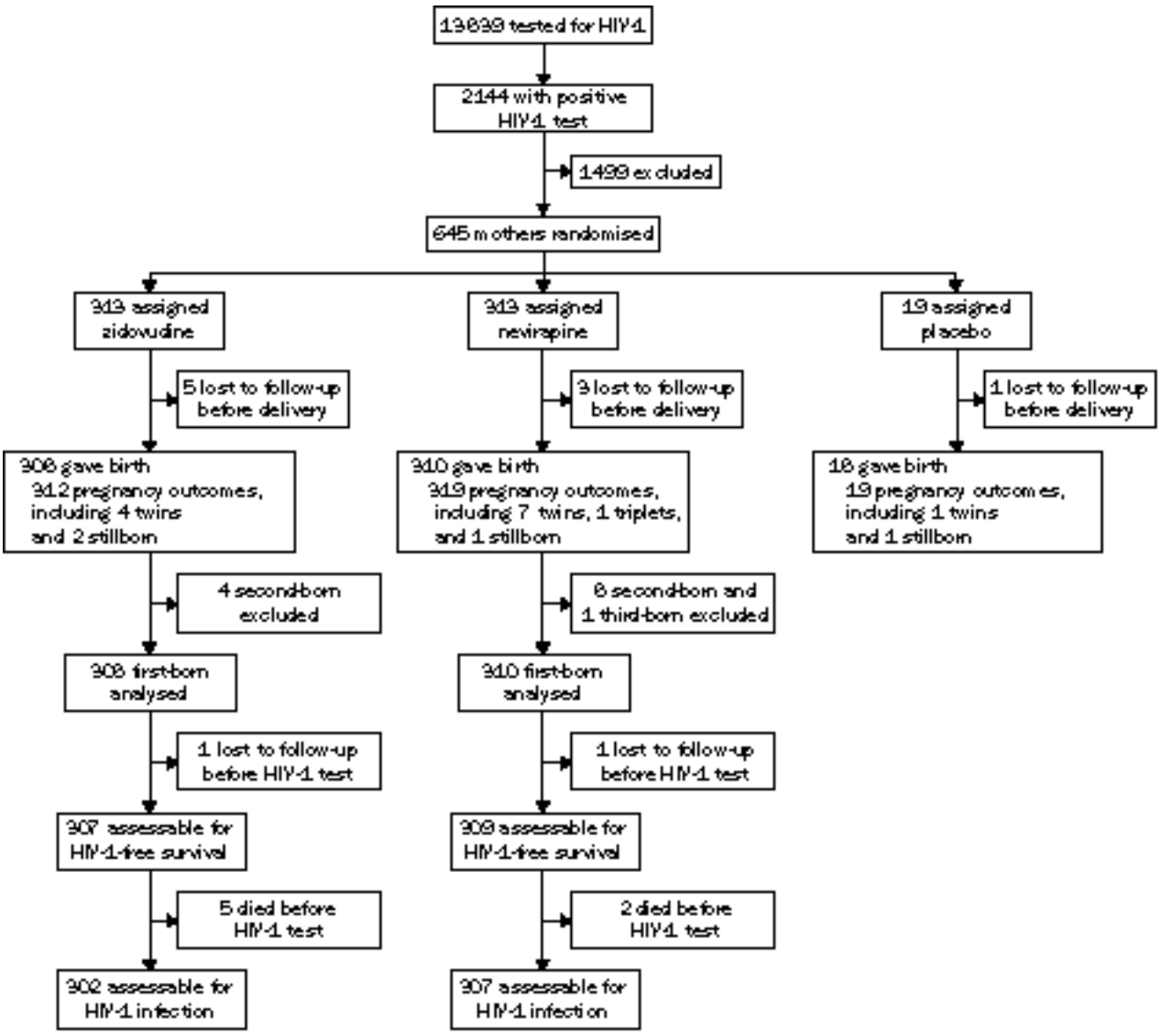

Figure 1: **Trial profile**

After exclusion of the nine babies who died or who were lost to follow-up before HIV-1 testing, 13 neonates did not start treatment (six in the zidovudine group and seven in the nevirapine group). For neonates in the zidovudine group who received any of the study-drug regimen, treatment was started within the protocol-specified 24 h for 96·5%. The median number of zidovudine doses received by neonates 14 (14–15), which was the number specified in the protocol. Of neonates who received any zidovudine, only two (0·7%) received fewer than seven doses and only nine (3·1%) received fewer than ten doses. For neonates in the nevirapine group who received the single dose, the dose was administered within the protocol-specified 72 h in 93·5%. Since earlier nevirapine dosing was permitted at discharge from hospital, the median time to receipt of the dose was 24–30 h.

Primary efficacy analysis

The two neonates lost to follow-up before receiving study drug were excluded from the analyses of HIV-1-free survival and time to HIV-1 infection; seven babies who died before HIV-1 testing were also excluded from the time to HIV-1-infection analysis (figure 1).

We measured directly HIV-1-free survival at age 14–16 weeks in 496 of the 616 assessable babies. Of the other 120 babies (57 in the zidovudine group and 63 in the nevirapine group), 82 had not yet reached age 14–16 weeks (18 had not yet reached age 6–8 weeks), 13 were lost to follow-up, and 25 who had reached age 14–16 weeks missed the 14–16 week visit, had a missing HIV-1 RNA PCR result at the time of analysis, or both. Babies with incomplete information were censored at the time of their last assessment.

Of the 103 babies with an initial positive plasma HIV-1 RNA assay at 14–16 weeks, 98 were confirmed to be positive with a subsequent sample. Four of these babies who died before a second blood sample could be obtained for testing were taken to be infected, and one who had repeated subsequent negative samples on HIV-1 RNA PCR analysis was taken to be not infected.

At ages 6–8 weeks and 14–16 weeks, significantly more babies in the zidovudine group than in the nevirapine group were HIV-1 infected (table 2, figure 2). Compared with the zidovudine regimen, the nevirapine regimen lowered the risk of HIV-1 infection up to age 14–16 weeks by 47% (95% CI 20–64). By age 14–16 weeks, 65 babies in the zidovudine group and 37 in the nevirapine group were

	Zidovudine		Nevirapine		p
	n	Value	n	Value	
Women who gave birth					
Total	308		310		
Median (IQR) age (years)	303	25 (22–28)	306	24 (21–27)	0·089*
CD4-cell count (cells/μL) before entry	307		308		
Median (IQR)		426 (244–638)		461 (291–637)	0·26*
≤200†		57 (18·6%)		42 (13·6%)	
201–500†		128 (41·7%)		129 (41·9%)	
>500†		122 (39·7%)		137 (44·5%)	
Median (IQR) HIV-1 RNA (copies/mL) before entry	299	27 902 (9216–74 552)	303	25 198 (6338–85 711)	0·59*
Median (IQR) duration of labour (h)	291	8·0 (5·3–12·8)	287	9·3 (6·1–13·5)	0·042*
Caesarean section†‡	295	41 (13·9%)	296	34 (11·5%)	0·38§
Prolonged rupture of membrane (>4 h)†	287	36 (12·5%)	290	47 (16·2%)	0·21§
Median (IQR) time from first dose to delivery (h)	293	5·8 (3·0–14·2)	294	6·9 (3·0–13·2)	0·99*
First-born neonates					
Total	308		310		
Birthweight (g)	297		304		
Median (IQR)		3200 (2900–3500)		3100 (2800–3400)	0·0010*
<2500		14 (4·7%)		21 (6·9%)	0·25§
Breastfed					
At birth†	288	280 (97·2%)	299	293 (98·0%)	0·54§
At 6-week visit†	261	254 (97·3%)	277	273 (98·6%)	0·31§
At 14-week visit†	217	208 (95·9%)	234	223 (95·3%)	0·78§

*Wilcoxon's rank sum test. †Percentages based on non-missing data. ‡Reported only if delivery occurred at Mulago hospital. §χ^2 test.

Table 1: **Characteristics of women and first-born neonates at enrolment**

HIV-1 infected (table 2, figure 2). Compared with the zidovudine regimen, the nevirapine regimen lowered the risk of HIV-1 infection or death up to age 14–16 weeks by 48% (24–65).

If all babies from multiple births were included, HIV-1-infection outcomes were concordant in all cases other than in three sets of twins. In these three sets (one in each of the nevirapine, zidovudine, and placebo groups), the first-born was positive and the second-born was negative.

Rates of HIV-1 infection were assessed in the 49 pairs of mothers and babies enrolled before discontinuation of the placebo group. At 14–16 weeks, six babies in the placebo group (Kaplan-Meier estimated infection rate 36·7% [95% CI 13·2–60·1), three in the zidovudine group (20·0% [0–40·2]), and one in the nevirapine group (7·1 [0–20·6]) were HIV-1 infected. For HIV-1-free survival, seven babies in the placebo group (40·2%[17·0–63·3]), four in the zidovudine group (26·7% [4·3–49·0]), and two in the nevirapine group (13·3% [0–30·5]) were HIV-1 infected or had died by age 14–16 weeks. The higher Kaplan-Meier estimates for the placebo group reflect the loss of one mother in that group to follow-up before delivery, loss of one baby to follow-up, who was censored at day 2, and a baby being stillborn.

Prognostic factor analysis of outcome

To assess the prognostic influence of various factors on HIV-1 infection and HIV-1-free survival, Cox's regression models were applied to the cohort of 618 first-born babies (table 3). Results are presented only for HIV-1 infection, since the results of analyses for HIV-1-free survival were similar. Weak associations with HIV-1 infection were found for caesarean delivery, duration of labour, birthweight, and sex. In the univariate models, baseline maternal CD4-cell count and plasma HIV-1 RNA were significantly associated with risk. There was a 1·26-fold increase (1·15–1·38) in the risk of HIV-1 infection for every 100-cell decrease in CD4-cell count, and a 2·07-fold increase (1·57–2·72) for every $\log_{10}$ increment in HIV-1 RNA copy number.

In analyses of possible confounders of the estimate of treatment effect, joint adjustment for CD4-cell count and $\log_{10}$ RNA made no difference to the estimate; nevirapine was estimated to decrease the hazard rate of HIV-1 infection or death by 48% (23–65) and the hazard rate of HIV-1 infection alone by 47% (20–64) compared with zidovudine. Among other covariates, only birthweight was a possible confounder. A slight excess of babies in the nevirapine group with birthweights lower than 2800 g led to a slight increase in the estimated treatment difference between nevirapine and zidovudine when adjustment was made for birthweight.

In the multivariate analysis, which included all the variables listed in table 3, the estimate of the treatment effect was unchanged. Although the point estimates for the relative risks for maternal viral load and maternal CD4-cell count differed from the univariate analysis estimates, these variables were independently predictive and remained highly significant.

Adverse events and toxic effects

The rates of maternal serious adverse events were similar in the two groups (4·4% in the zidovudine group, 4·7% in the

	Zidovudine		Nevirapine		p
	Number who reached endpoint	Probability of endpoint (95% CI)*	Number who reached endpoint	Probability of endpoint (95% CI)*	
HIV-1 infection					
Day 1–3	31	10·4% (7·0–13·9)	25	8·2% (5·1–11·3)	0·35
Week 6–8	59	21·3% (16·4–26·2)	35	11·9% (8·2–15·7)	0·0027
Week 14–16	65	25·1% (19·5–30·8)	37	13·1% (9·1–17·1)	0·00063
HIV-1 infection or death					
Day 1–3	37	12·2% (8·5–15·9)	27	8·8 (5·6–12·0)	0·17
Week 6–8	66	23·1% (18·2–28·1)	38	12·8% (9·0–16·7)	0·0012
Week 14–16	74	27·6% (22·0–33·3)	41	14·4% (10·2–18·5)	0·00021

*Cumulative rates at days 3, 56, and 112 calculated by Kaplan-Meier method.

Table 2: **HIV-1 transmission and HIV-1-free survival at ages 1–3 days, 6–8 weeks, and 14–16 weeks**

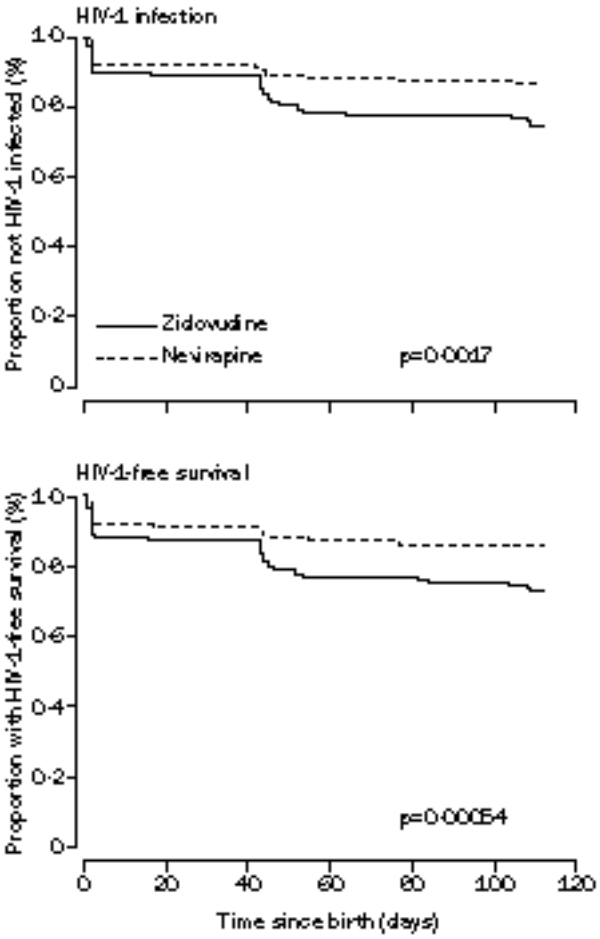

Figure 2: **Kaplan-Meier estimates of proportion babies free from infection and with HIV-1-free survival at 16 weeks**

nevirapine group). One mother in the zidovudine group died 2 weeks after delivery and had bronchopneumonia. One serious event, anaemia, was possibly associated with zidovudine, but excessive blood loss at delivery may have accounted for the anaemia. The occurrence of clinical or laboratory abnormalities in mothers was similar in the two groups (82·2% in the zidovudine group and 80·7% in the nevirapine group had at least one such event). The most frequent adverse clinical event was bacterial or viral infection, occurring in 18·2% of women receiving zidovudine and 20·4% of those receiving nevirapine, followed by parasitic infection in 12·4% and 15·0%, respectively, followed by anaemia in 10·5% and 13·1%, respectively. Nine mothers (four in the zidovudine group, five in the nevirapine group) had maculopapular rash, but no case was serious.

In babies, adverse events were uniformly recorded up to age 6 weeks, whereas only serious adverse events continued to be recorded at each visit up to age 18 months. The rate of serious adverse events in the two groups was similar up to the 18-month visit (19·8% in the zidovudine group, 20·5% in the nevirapine group), with the median age at last visit being 183 days (IQR 102–276). 38 (6·8%) babies died (22 [7·9%] in the zidovudine group, 16 (5·7%) in the nevirapine group). The most frequent cause of death was pneumonia, followed by gastroenteritis, diarrhoea, dehydration, and sepsis. The most frequent causes of serious adverse events within 56 days of birth were sepsis, pneumonia, fever, congenital anomaly, asphyxia, and dyspnoea. Of the 59 serious adverse events reported in the first 56 days of life, those that occurred in four (1·4%) babies in the zidovudine group and in two (0·7%) babies in the nevirapine group were judged to be possibly, but unlikely to be, related to study drug. In the four babies in the zidovudine group, adverse events were sudden-infant-death syndrome 24 h after delivery, transient tachypnoea at birth requiring oxygen, birth asphyxia with death due to fetal distress after caesarean section, and presumed pneumonia 4 days after birth. In the two babies in the nevirapine group, adverse events were transient respiratory distress at birth with meconium staining requiring oxygen, and a non-macerated stillbirth to a mother who received nevirapine 3·5 h before delivery.

18 babies had maculopapular rash, no case of which was serious (nine in the zidovudine group, nine in the nevirapine group). Within the first 56 days of life, 22 babies had grade 3 anaemia (nine in the zidovudine group, 13 in the nevirapine group), with haemoglobin values ranging from 85–118 g/L. No case was judged to be serious or clinically important. The frequency and severity of laboratory-detected toxic effects, including neutropenia, thrombocytopenia, and abnormalities in creatinine or bilirubin, were similar in the two groups.

	Hazard ratio (95% CI)	p*
Treatment (nevaripine vs zidovudine)	0·53 (0·36–0·80)†	0·0022
Maternal HIV-1 RNA (log_{10}) before entry‡	2·07 (1·57–2·72)	<0·0001
Maternal CD4-cell count before entry§	1·26 (1·15–1·38)	<0·0001
Birthweight‖	1·16 (0·93–1·45)	0·18
Sex (female *vs* male)	1·16 (0·79–1·72)	0·45
Duration of labour (h)	0·99 (0·96–1·02)	0·44
Caesarean section (yes *vs* no)	0·84 (0·44–1·61)	0·59

*Calculated for Wald statistic. †Corresponding to relative efficacy 0·47 (95% CI 0·20–0·64). ‡Per unit increase of log_{10} HIV-1 RNA copies/mL. §Per decrease of 100 cells/μL. ‖Per decrease of 500 g.

Table 3: **Prognostic factors for HIV-1-infection in univariate Cox's regression models**

Discussion

The drug regimens used in this trial were specifically designed to provide antiretroviral prophylaxis to the neonate during labour, delivery, and in the first week of life to lower the risk of HIV-1 transmission. Single-dose oral nevirapine administered at the onset of labour to HIV-1 infected women and to babies within 72 h of birth, significantly lowered the risk of HIV-1 perinatal transmission and was associated with significantly longer HIV-1-free survival than treatment with short-course zidovudine administered over a similar time period. The two regimens were well tolerated, with similar rates of serious and non-serious adverse events in mothers and babies. No adverse event was definitely or probably related to the study drugs.

Limitations of our study were that investigators and mothers were not masked to treatment status or outcome after randomisation. The nevirapine regimen involved directly observed and administered treatment to babies, whereas with the zidovudine regimen, many doses were given to babies unobserved. Mothers were identified before labour and given the study drug to take at home. The efficacy of the nevirapine regimen may, therefore, have been lowered when given to women who arrived at the hospital in labour.

We were unable to estimate directly the efficacy of the nevirapine regimen compared with placebo. However, the estimated risk at age 14–16 weeks of HIV-1 infection of 37% among babies born to mothers assigned placebo and 20% among those born to mothers concurrently assigned zidovudine suggests that short-course zidovudine may have

had some benefit. If true, the decrease in risk with nevirapine compared with placebo would be even greater than that seen when compared with zidovudine.

The 25·1% HIV-1 transmission rate at age 14–16 weeks seen in the zidovudine group in our study seems similar to the 26·1% transmission rate in the placebo group and higher than the 16·5% rate in a short-course antepartum and intrapartum zidovudine regimen at age 3 months in a study done in a breastfeeding Côte d'Ivoire population.[5] However, the maternal median CD4-cell count of that population was about 100 CD4 cells/uL higher than in our study and, more importantly, our zidovudine regimen was not started until labour, compared with at 36 weeks' gestation in the Côte d'Ivoire study.

Our study design had similarities to one of the four groups in the PETRA intervention trial,[16] in which women received antepartum, intrapartum, and postpartum, intrapartum and postpartum, or intrapartum zidovudine and lamivudine compared with placebo. The 47% relative efficacy of the nevirapine regimen in our study at age 14–16 weeks was similar to the 37% relative effiacy of the intrapartum and postpartum PETRA group at 6 weeks and the 50% relative efficacy of the antepartum, intrapartum, and postpartum PETRA group. The results are not directly comparable because of differences in study populations between the two studies. Although further studies will be needed to find out whether the regimens are equivalent, the nevirapine regimen used in our study was simpler and less expensive than any of the regimens in the PETRA intervention trial.

Most vertical HIV-1 transmission occurs during active labour because of maternal blood transfusions to neonates and direct exposure to the virus during passage through the birth canal. Therefore, maternal viral load must be substantially decreased by the time of labour or the baby must have systemic concentrations of active drug present at the time of HIV-1 exposure to successfully lower risk of transmission. Nevirapine has several characteristics that distinguish it from zidovudine, which may explain why its use as an intrapartum and postpartum regimen is superior in lowering transmission risk. Unlike zidovudine, nevirapine can decrease plasma HIV-1 RNA concentration by at least 1·3 log after a single dose,[13] is active immediately against intracellular and extracellular virus,[17] and does not have to be taken up by the cell and metabolised to its active form. Therefore, nevirapine could be more effective than zidovudine when given close to the time of exposure, and may have had a more striking effect in decreasing viral load in colostrum and early breastmilk samples. Nevirapine also has a long half-life compared with zidovudine and needs to be administered to babies only once to maintain a plasma drug concentration more than ten times the IC_{50} for 7 days. Furthermore, the variability of drug concentrations during the first week of life would be expected to be much less than that seen with zidovudine, which has a short half-life and requires multiple dosing to maintain virucidal concentrations. Therefore, maintenance of an effective prophylactic drug concentration during the first week of life, when additional HIV-1 exposure may occur through breastmilk, may be important in explaining the relative efficacy of nevirapine compared with zidovudine in a breastfeeding population.

We did not address whether the nevirapine regimen used would be as effective as the Thai zidovudine regimen (starting zidovudine at 36 weeks' gestation until delivery), which is currently recommended for less-developed countries.[18] The 47% relative efficacy of nevirapine compared with zidovudine in babies aged 14–16 weeks in our trial was similar or perhaps better than the 37–38% relative efficacy of zidovudine compared with placebo at 3 months in a breastfeeding population[5,6] and the 50% relative efficacy in a non-breastfeeding population.[7] However, such comparisons are difficult to interpret because of differences in baseline characteristics of the women, modes of delivery, and breastfeeding patterns. The addition of this simple nevirapine regimen to an effective short-course zidovudine regimen could improve efficacy, but this strategy would need to be tested before any recommendations could be made.

Likewise, we did not investigate whether the nevirapine regimen used would be as effective as the ACTG 076 zidovudine regimen in a non-breastfeeding population. The women enrolled in ACTG 076 and in HIVNET 012 differed substantially. For example, nearly all mothers in HIVNET 012 breastfed, compared with none in the zidovudine group of ACTG 076. In our study, women had a median baseline CD4-cell count that was more than 100 cells/μL lower and a median plasma viral load that was five times higher than those in women in ACTG 076. The rate of cesarean deliveries was also much lower in our study (12·7 *vs* 27·0%). Therefore, we cannot judge the efficacy of the nevirapine regimen used in our study compared with the full three-part zidovudine regimen that is currently standard for prevention of transmission in more-developed countries. The data from our trial do not change recommendations in the USA,[19] Europe, and other more-developed countries for prenatal HIV-1 counselling and testing coupled with use of the three-part zidovudine regimen for prevention of transmission.

Many women in developed countries receive potent antiretroviral therapy with zidovudine combined with additional antiretroviral drugs during pregnancy for treatment of HIV-1 infection. We did not assess whether the addition of single-dose nevirapine to the three-part zidovudine ACTG 076 regimen or potent combination therapy would further decrease HIV-1 transmission. However, a continuing study (National Institutes of Health sponsored Pediatric AIDS Clinical Trials Groups protocol 316) in the USA, Europe, and South America is investigating this question.

The nevirapine regimen could have some use in more-developed countries in HIV-1-infected women who are first diagnosed with HIV-1 infection close to or during labour or who have received no antiretroviral therapy during pregnancy. The nevaripine regimen we used offers an alternative prophylactic regimen for such women.

Although the zidovudine and nevirapine regimens we used seemed safe, long-term follow-up of the babies remains a high priority to find out about possible long-term toxic effects. In addition, despite the success of nevirapine in decreasing HIV-1 transmission by about 50% in the short term, the impact of the two study regimens on long-term survival and on later transmission associated with breastfeeding needs further investigation. A study in Malawi found a cumulative risk of HIV-1 infection associated with breastfeeding of 7·0% at age 11 months and 10·3% at age 23 months.[11] The continuing risk of HIV-1 infection in breastfed babies suggests the need to consider longer courses of antiretroviral treatment, early weaning, or both, to further decrease HIV-1 transmission.[9–11]

Despite the simplicity, the efficacy, and the low cost (around US$4.00 wholesale cost) of this nevirapine regimen, obstacles to implementation still remain. Centres

that offer voluntary counselling and HIV-1 testing are not available to many pregnant women in developing countries. During screening for our trial, many women refused to be counselled or tested or did not return for their test results. Presumably, the availability of an affordable and effective intervention will be an incentive for more women to agree to counselling and testing, but access to testing and antenatal care is likely to be difficult in many places with poor resources. A combination of counselling and rapid testing for HIV-1 antibody for pregnant women at or near the time of labour, with immediate provision of nevirapine could increase the number of women treated. However, until appropriate counselling and testing infrastructures can be put in place, one option that should be taken into account is to provide all pregnant women in high HIV-1 seroprevalence areas with nevirapine before or at onset of labour if the drug proves to be safe in long-term follow-up. This strategy is similar to the recommendation to provide universal iron supplementation to pregnant women in the USA and Uganda.[20] This approach would be cost-effective and would bring the number of women receiving an effective intervention to a maximum. compared with giving the drug only to pregnant women who are identified as HIV-1 infected.[21]

Single-dose nevirapine given to the mother and the baby is likely to be one of the few deliverable and sustainable strategies for prevention of perinatal HIV-1 transmission in resource-poor settings. The challenge is to rapidly translate our findings into public-health policy to bring an effective HIV-1 intervention within the reach of millions of HIV-1 infected pregnant women in less-developed countries.

Contributors

J B Jackson and F Mmiro were the protocol chairpersons and L Guay and P Musoke were the protocol cochairpersons, who were responsible for the design, conduct, and interpretation of the study, including monitoring of adverse events and writing the paper. M G Fowler was a National Institutes of Health medical officer and monitored adverse events and contributed to the design and interpretation of the study, and writing of the paper. L Mofenson contributed to the design and interpretation of the study and the wiriting of the paper. T Fleming was the protocol statistician and was instrumental in study design, statistical analysis, and writing of the paper. D Bagenda and L Emel were the data managers and contributed to study design and analysis. M Deseyve did the calculations for the statistical analysis. M Allen was the protocol specialist and study monitor. P Miotti was a National Institutes for Health medical officer for the study, contributed to analyses and interpretation, and the writing of the paper. K Dransfield and D Bray contributed to the design, analysis, interpretation, and execution of the study for drug dosing and packaging. M Mirochnick was the protocol pharmacologist and contributed to study design and analysis, and writing of the paper. J Sherman and P Bakaki were the on-site paediatricians responsible for the follow-up of the babies, and C Nakabiito was the on-site obstetrician primarily responsible for the recruitment and daily care of the mothers. C Ducar was the on-site laboratory administrator who supervised most of the laboratory testing.

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