Intrapartum and neonatal single-dose nevirapine compared with zidovudine for prevention of mother-to-child transmission of HIV-1 in Kampala, Uganda: 18-month follow-up of the HIVNET 012 randomised trial

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Summary

Background In 1999, we reported safety and efficacy data for short-course nevirapine from a Ugandan perinatal HIV-1 prevention trial when 496 babies were followed up to age 14–16 weeks. Safety and efficacy data are now presented for all babies followed up to 18 months of age.

Methods From November, 1997, to April, 1999, HIV-1 infected pregnant women in Kampala, Uganda, were randomly assigned nevirapine (200 mg at labour onset and 2 mg/kg for babies within 72 h of birth; regimen A) or zidovudine (600 mg orally at labour onset and 300 mg every 3 h until delivery, and 4 mg/kg orally twice daily for babies for 7 days, regimen B). Infant HIV-1 testing was done at birth, age 6–8 and 14–16 weeks, and age 12 months by HIV-1 RNA PCR, and by HIV-1 antibody at 18 months. HIV-1 transmission and HIV-1-free survival were assessed using Kaplan-Meier analysis. We recorded adverse experiences through 6–8 weeks postpartum for mothers, and 18 months for babies. Efficacy analyses were by intention to treat.

Findings We enrolled 645 mothers to the study: 313 were assigned regimen A, 313 regimen B, and 19 placebo. Eight mothers were lost to follow-up before delivery. 99% of babies were breastfed (median duration 9 months). Estimated risks of HIV-1 transmission in the zidovudine and nevirapine groups were 10·3% and 8·1% at birth (p=0·35); 20·0% and 11·8% by age 6–8 weeks (p=0·0063); 22·1% and 13·5% by age 14–16 weeks (p=0·0064); and 25·8% and 15·7% by age 18 months (p=0·0023). Nevirapine was associated with a 41% (95% CI 16–59) reduction in relative risk of transmission through to age 18 months. Both regimens were well-tolerated with few serious side-effects.

Interpretation Intrapartum/neonatal nevirapine significantly lowered HIV-1 transmission risk in a breastfeeding population in Uganda compared with a short intrapartum/neonatal zidovudine regimen. The absolute 8·2% reduction in transmission at 6–8 weeks was sustained at age 18 months (10·1% [95% CI 3·5–16·6]). This simple, inexpensive, well-tolerated regimen has the potential to significantly decrease HIV-1 perinatal transmission in less-developed countries.

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Introduction

In 2002, an estimated 800 000 children became infected with HIV-1 through mother-to-child transmission,[1] with more than 90% residing in resource-poor countries. In more-developed countries, mother-to-child transmission has been dramatically lowered through use of the Paediatric AIDS Clinical Trials Group (PACTG) 076 zidovudine regimen, given to the mother during pregnancy and labour and to the infant for 6 weeks after birth.[2] However, this regimen is too complex and expensive for use in resource-poor countries.

The knowledge that most mother-to-child transmission occurs late in pregnancy or during labour and delivery[3,4] led to shorter zidovudine regimens being given to women a few weeks before and during labour as prophylaxis. This strategy was shown to decrease mother-to-child HIV-1 transmission by 37–38% in breastfeeding populations and by 50% in non-breastfeeding populations.[5–7] However, these regimens, while simpler and less expensive, still remain problematic for implementation in some resource-poor countries, and transmission of HIV-1 postnatally via breast milk remains a problem.[8–10]

Because antiretroviral prophylaxis of the neonate during HIV-1 exposure at birth is thought to be an important mechanism for prophylaxis efficacy,[11] provision of antiretroviral therapy to the woman at onset of labour and for a short period postnatally to the infant was thought to be sufficient to decrease vertical transmission during the intrapartum and early breastfeeding period. This might offer a less complex and more affordable prophylaxis regimen for HIV-1 infected pregnant women in less-developed countries. The HIVNET 012 study team reported in 1999[12] that a single-dose intrapartum and neonatal nevirapine regimen significantly decreased the risk of transmission of HIV-1 from mother to child by 47% compared with a short intrapartum/neonatal zidovudine

regimen when 87% of babies in the trial had reached age 14–16 weeks. We report on the safety and efficacy of the nevirapine regimen in all study mothers through 6 weeks postpartum and all babies through to 18 months of age.

Methods

Participants and procedure

The HIVNET 012 study protocol was approved by institutional review boards (IRBs) in Uganda and the USA, and informed consent was obtained from all study participants before study enrolment. The study was originally designed to be a 1500 patient randomised placebo-controlled study assessing two intrapartum and neonatal postpartum regimens, one zidovudine and the other nevirapine. However, after demonstration of the efficacy of a short antepartum/intrapartum zidovudine regimen in Thailand[7] and after enrolment of only 49 women into HIVNET 012, randomisation into the placebo group was stopped. The trial was modified, with approval from Ugandan and US institutional review boards, to include only the two open-label antiretroviral groups. The planned sample size for the modified trial was 556 mother-baby pairs, to allow sufficient power to determine if the nevirapine group transmission rate was equivalent or lower than that in the zidovudine group. Detailed description of the study design, methods, and initial trial results for infants aged 14–16 weeks are provided elsewhere.[12]

After we had acquired verbal informed consent for undertaking screening tests, written informed consent was obtained from eligible HIV-1-infected pregnant women who were then randomised at more than 36 weeks' gestation to receive either intrapartum/neonatal nevirapine or zidovudine. The nevirapine regimen included a single 200 mg nevirapine tablet taken by the mother at the onset of labour and a single 2 mg/kg oral dose of nevirapine suspension given to the neonate at 72 h after birth or at discharge from the hospital, whichever occurred first. The zidovudine regimen included two 300 mg tablets of zidovudine at onset of labour followed by one 300 mg tablet every 3 h during labour; the neonates received 4 mg/kg zidovudine syrup twice daily for 7 days after birth.

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 birth. We assessed adherence to study drugs by interview and by counting of doses of remaining study drugs. Women had a medical history and physical examination before entry to the study (between 32 weeks' gestation and enrolment), on enrolment, delivery, discharge from the hospital, and 7 days and 6 weeks after delivery. Serum chemistries were done before entry and at 7 days and 6 weeks after delivery. After normal measurements had been noted in the first 100 enrolled women, we discontinued 6-week tests. A complete blood count and CD4-cell count were done before entry and on delivery. We carried out quantitative plasma HIV-1 RNA measurements (Roche HIV-1 Amplicor Monitor, Indianapolis, USA) before entry, at delivery, and at 7 days and 6 weeks after delivery.

Babies had a medical history and physical examination at birth, age 7 days, and at 6, 10, 14, 26, 39, 52, 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, at 14 weeks, and at 12 and 18 months. Qualitative HIV-1 RNA PCR assays were done at age 1–3 days, 6 weeks, 14 weeks, and 12 months on edetic-acid anticoagulated plasma separated from whole blood and frozen at –70°C within 24 h of collection. If HIV-1 RNA was detected, a second sample was obtained as soon as possible or at the next scheduled visit, for confirmation by HIV-1 RNA PCR or HIV-1 culture. If a baby was HIV-1 infected, we also quantified HIV-1 RNA levels on subsequent samples. We did HIV-1 antibody testing at age 18 months by enzyme immunoassay (EIA), and if reactive, confirmed by HIV-1 western blot.

Adverse events were recorded from mothers and babies through 6–8 weeks postpartum, and serious adverse events recorded for babies through to 18 months. A serious adverse event was defined as any clinical experience that was fatal, or life-threatening, permanently disabling, required inpatient admission, a congenital anomaly, cancer, or overdose, or was otherwise judged serious by the onsite clinician. Laboratory abnormalities detected on study-specific toxicity monitoring described above were assigned a toxicity grade based on toxicity tables for neonates, children, and adults developed by the Division of AIDS, US National Institute of Allergy and Infectious Diseases.

All HIV-1 test results and infant HIV-1-infection status were verified by the laboratory supervisor and the protocol chair who were unaware of the infants' treatment group. In addition, all available clinical, serological, and virological data were reviewed by the protocol chair, co-chairs, biostatisticians, and data manager to confirm infant HIV-1 infection status.

Infants were defined as HIV-1-infected based on a positive HIV-1 RNA PCR assay confirmed by either an HIV-1 RNA PCR assay or HIV-1 culture on a second blood sample. In the case of an infant death where there was only one positive RNA assay on the sample preceding death, the infant was considered to be infected.

Statistical analysis

Interim analyses of the data for the modified trial were done when 250 and 500 mother-baby pairs had completed 6 weeks' assessment. These analyses were reviewed by a National Institutes of Health data and safety monitoring board, which included a representative from Uganda. Efficacy monitoring boundaries were provided by O'Brien-Fleming guidelines.[13] The primary efficacy endpoints were the rates of HIV-1 infection and HIV-1-free survival at 6–8 weeks, 14–16 weeks, and 18 months, estimated with the Kaplan-Meier method. For each of these timepoints, a two-sided p value was found for the Z statistic, representing the difference between the Kaplan-Meier estimates at that timepoint (with standard errors obtained with Greenwood's formula). For the Kaplan-Meier method, the time to the first positive HIV-1 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 assay. For these two analyses, all other babies were censored with follow-up time set to the last negative test.

We used Cox's regression to obtain relative risks and CIs 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, prolonged rupture of membrane, method of delivery, birthweight, and sex of the neonate. The predictiveness of each of these covariates was also assessed.

Kaplan-Meier and Cox regression analyses were based on intention-to-treat populations. In the case of twins or triplets, only the firstborn babies were included. The three stillborns were included in the analyses. The safety and toxicity analyses included all mothers who received study drug and all babies (including second and third-borns) who received study drug or whose mothers were dosed.

Role of the funding source

Mary Glenn Fowler, Lynne Mofenson, and Paolo Miotti, associated with the sponsors of the study, the United States National Institutes of Health, assisted in the design, analysis, and interpretation of data, and helped to write the report. Boehringer-Ingelheim donated nevirapine oral suspension for the babies. M Gigliotti (Boehringer-Ingelheim) and D Bray (GlaxoWellcome) contributed to the design, analysis, and interpretation of the study with regard to drug dosing and packaging issues, but were not involved in the writing of the report or the decision to submit the paper for publication. Roche Molecular Systems had no role in study design, data analysis, interpretation, writing of the report, or the decision to submit the paper for publication.

Results

Enrolment began Nov 3, 1997, and ended on April 30, 1999. The last infant was born on June 19, 1999, and the last infant visit was done on Jan 22, 2001. 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).

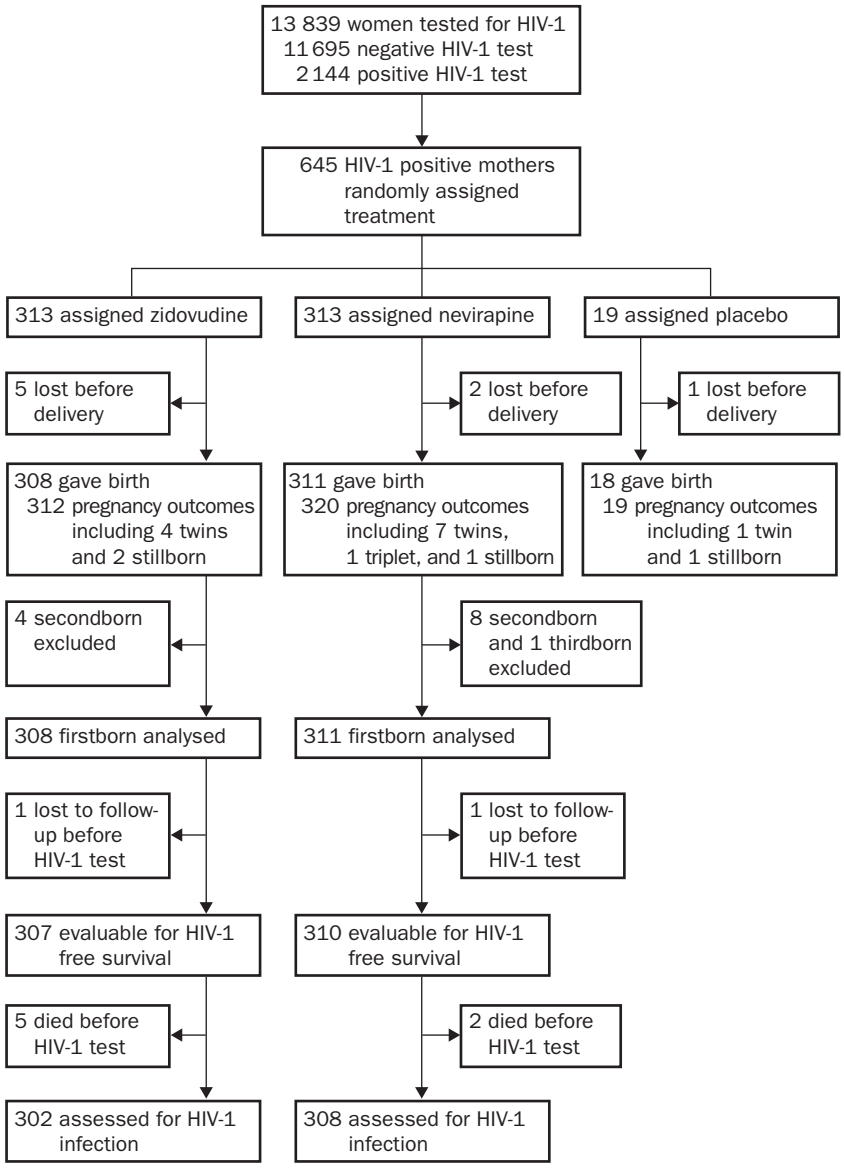


Figure 1: **Trial profile**

Characteristics of women who gave birth in the two treatment groups did not differ significantly at enrolment (table 1). Nine of 75 caesarean sections were listed as elective. 37 (6·0%) mothers delivered at home, at another clinic or hospital, or on the way to the study hospital.

Characteristics of the first-born babies, other than birthweight, were similar at birth in the two treatment groups (table 1). Overall, 99% of babies were breastfed. At 6 months, 80% were still being breastfed, whereas at 18 months the rate dropped to 12%. The rates of breastfeeding were similar between treatment groups with a median breastfeeding duration of 9·5 months (95% CI 8·8–10·3) in the zidovudine group and 8·8 months (7·9–9·7) in the nevirapine group.

The treatment groups did not differ in the proportion of mothers who received study drugs (302/308 [98·1%] of the zidovudine group and 306/311 [98·4%] of the nevirapine group). The median number of zidovudine doses received during labour (including the first 600 mg dose) was two (IQR 1–3). In the nevirapine group, all women given treatment during labour received a single 200 mg dose as per protocol. The study drug was withheld for five mothers (four in the nevirapine group and one in the zidovudine group) because they were in the second stage of labour (four) or receiving valium at the time of labour (one).

After exclusion of the nine babies who died or who were lost to follow-up before HIV-1 testing, 14 neonates did not start treatment (six in the zidovudine group and eight in the nevirapine group). For all but two of these 14 neonates (both zidovudine) their mothers received the study drug. For neonates in the zidovudine group who received any part of the study-drug regimen, treatment was started within the protocol-specified 24 h for 282 (95·9%) of them. The median number of zidovudine doses received by neonates was 14 (IQR 14–15) which was the number specified in the protocol. Of neonates who received any zidovudine, only two received fewer than seven doses and only nine 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 285 (96·3%). Since earlier nevirapine dosing was permitted at discharge from hospital, the median time to receipt of the dose was 28 h (IQR 20–37).

	Zidovudine	Total analysed	Nevirapine	Total analysed	p
Women who gave birth					
Total	308		311		
Age (median [IQR]) (years)	25 (22–28)	306	24 (21–27)	311	0·12*
CD4 count (cells/μL) at pre-entry (median [IQR])	426 (244–634)	307	459 (289–636)	309	0·26*
⩽200†	57 (18·6%)		43 (13·9%)		
201–500†	129 (42·0%)		129 (41·9%)		
>500†	121 (39·4%)		137 (44·3%)		
HIV-1 RNA (copies/mL, median [IQR] at pre-entry)	27 800 (8700–74 552)	299	25 247 (6427–85 972)	304	0·73*
Duration of labour (h, median [IQR])	8·2 (5·3–13·1)	296	9·3 (6·2–13·5)	288	0·069*
Caesarean section†‡	41 (13·9%)	295	34 (11·5%)	296	0·38§
Prolonged rupture of membrane (>4 h)†	38 (12·8%)	296	47 (16·0%)	294	0·28§
Firstborn infants					
Total	308		311		
Birthweight		299		305	
Birthweight (g, median [IQR])	3200 (2900–3500)		3100 (2800–3400)		0·0016*
<2500†	14 (4·7%)		21 (6·9%)		0·25§
Females	156 (51·0%)	306	154 (49·7%)	310	0·75§
Multiple births	4 (1·3%)	308	8 (2·6%)	311	0·25
Apgar ⩾9					
At 1 min	258 (88·4%)	292	268 (91·5%)	293	0·21
At 5 min	284 (97·6%)	291	285 (97·6%)	292	1·00
Breastfeeding rates (95% CI)¶		303		307	
At birth	98·7 (97·4–100)		99·3 (98–5–100)		0·400
At 6–8 weeks	95·6 (93·2–97·9)		96·7 (94·7–98·7)		0·485
At 12 months	36·1 (30·3–41·9)		31·3 (25·9–36·9)		0·243
At 18 months	14·6 (10·1–19·2)		10·0 (6·1–13·9)		0·134

All data are n (%) unless indicated· *Wilcoxon rank sum test. †Percentage based on non-missing data. ‡Reported only if delivery occurred at Mulago hospltal. §χ^2 test. ¶Kaplan-Meier cumulative rates and 95% CIs.

Table 1: **Characteristics of women and firstborn infants by treatment group**

Primary efficacy analysis

Two neonates who were 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). At 6–8 weeks, 15 (2·4%) of the 619 of firstborn babies were lost to follow-up without having reached the endpoint HIV-1 infection or death. At 18 months 5·0% (zidovudine: 19 [6·2%]; nevirapine: 12 [3·9%)]) were lost to follow-up. Babies with incomplete information are censored at the time of their last assessment.

Of the 124 babies with an initial positive plasma HIV-1 RNA test or reactive EIA by 18 months, 117 were confirmed to be positive with a subsequent sample. Five of the 124 babies died before a second blood sample could be obtained for testing and were defined as infected. Two babies had repeated subsequent negative samples by HIV-1 RNA PCR analysis and EIA and were defined as uninfected.

At ages 6–8 weeks, 14–16 weeks, 12 months, and 18 months, significantly more babies were HIV-1 infected in the zidovudine group than in the nevirapine group (table 2, figure 2). Compared with the zidovudine regimen, the nevirapine regimen lowered the risk of HIV-1 infection through 6–8 weeks of age by 42% (95% CI 13–62). After age 6–8 weeks the two groups were expected to have similar numbers of additional infections since no drug was present during this later breastfeeding period. From 8 weeks to 18 months of age we detected 16 additional HIV-1-positive babies in the zidovudine group and 11 in the nevirapine group. Nevirapine was estimated to decrease the hazard rate of HIV-1 infection through age 18 months by 41% (95% CI 16–59) in comparison with zidovudine (a total of 75 infections in the zidovudine group versus 47 in the nevirapine group). The 8·2% absolute reduction in infection rate at age 6–8 weeks (in the nevirapine compared with zidovudine group) was sustained at age 18 months, where the absolute reduction was 10·1% (95% CI 3·5–16·6).

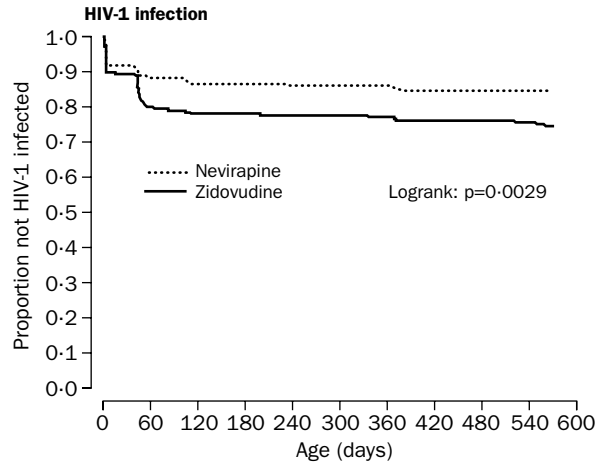
For the babies from the 13 multiple births (four zidovudine, eight nevirapine, one placebo), the HIV-1 infection status for siblings was concordant in all but three sets of twins. In these three sets (one each in the nevirapine, zidovudine, and placebo groups), the first-born was HIV-1 positive and the secondborn was HIV-1 negative.

Of the 619 firstborn babies, 41 in the zidovudine group died by age 18 months, 24 of whom were HIV-1 infected; 32 babies in the nevirapine group died by age 18 months,

	Zidovudine		Nevirapine		
	Number endpoint reached	Probability of endpoint (%) (95% CI)*	Number endpoint reached	Probability of endpoint (%) (95% CI)*	p†
HIV-1 infection					
Day 1–3	31	10·3 (6·9–13·8)	25	8·1 (5·1–11·2)	0·35
Week 6–8	59	20·0 (15·4–24·5)	36	11·8 (8·2–15·5)	0·0063
Week 14–16	65	22·1 (17·3–26·8)	41	13·5 (9·7–17·4)	0·0064
Month 12	70	23·9 (19·0–28·8)	46	15·3 (11·2–19·4)	0·0083
Month 18	75	25·8 (20·7–30·8)	47	15·7 (11·5–19·8)	0·0023
HIV-1 infection or death					
Day 1–3	37	12·1 (8·5–15·8)	27	8·7 (5·6–11·9)	0·17
Week 6–8	66	21·8 (17·1–26·5)	39	12·7 (9·0–16·4)	0·0027
Week 14–16	74	24·5 (19·6–29·3)	45	14·7 (10·7–18·7)	0·0023
Month 12	86	28·6 (23·5–33·7)	59	19·4 (14·9–23·8)	0·0076
Month 18	92	30·7 (25·5–36·0)	63	20·7 (16·2–25·3)	0·0048

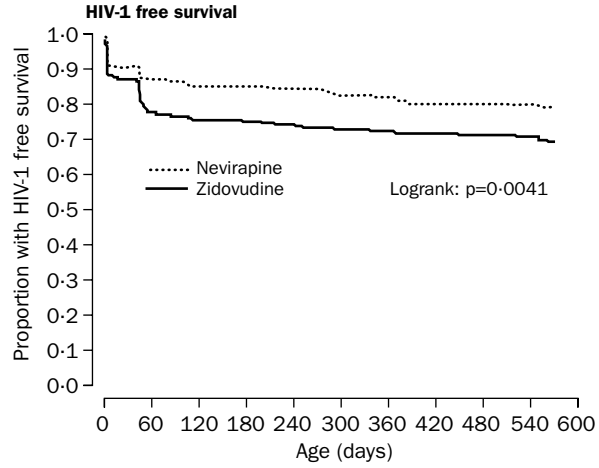
*Cumulative rates at day 3, 56, 112, 365, and 561 calculated by Kaplan-Meier method. †Two-sided p value for *Z* statistic of the difference in probabilities.

Table 2: **HIV-1 transmission and HIV-1 free survival at birth and at ages 6–8 weeks, 14–16 weeks, 12 months, and 18 months**



Numbers at risk

Nevirapine	308	262	249	248	247	247	246	238	237	232
Zidovudine	302	233	218	216	213	212	210	202	202	199



Numbers at risk

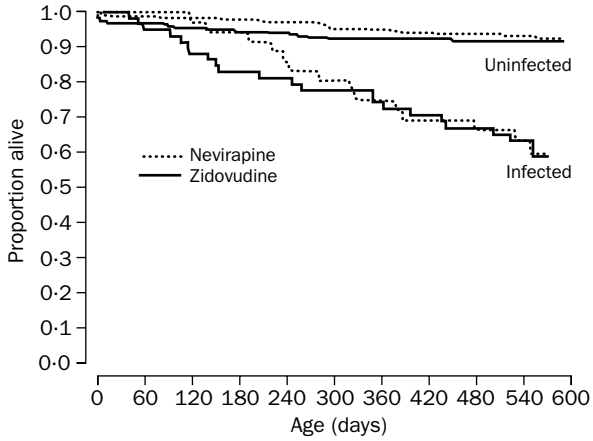
Nevirapine	310	263	256	256	253	248	247	240	239	233
Zidovudine	307	234	223	220	217	212	210	203	202	199

Figure 2: **Kaplan-Meier estimates of proportion of babies free from HIV-1 infection and with HIV-1 free survival through 18 months**

16 of whom were HIV-1 infected. 66 babies in the zidovudine group and 39 in the nevirapine group were HIV-1 infected or had died by 6–8 weeks of age. At age 18 months, 92 babies in the zidovudine group and 63 in the nevirapine group were HIV-1 infected or had died (table 2, figure 2). Compared with the zidovudine regimen, the nevirapine regimen reduced the risk of HIV-1 infection or death through age 18 months by 37% (95% CI 13–54).

When stratified by HIV-1 infection status at age 6–8 weeks, the Kaplan-Meier estimates for survival through age 18 months were similar in the two treatment groups. The estimated 18-month survival for babies who were HIV-1 uninfected at age 6–8 weeks was 92·2% for zidovudine and 92·5% for nevirapine recipients (figure 3). For babies diagnosed with HIV-1 infection by age 6–8 weeks, 59·3% survived in the zidovudine group and 59·9% in the nevirapine group.

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 619 firstborn babies (table 3). Results are presented only for HIV-1 infection, since the results of analyses for HIV-1-free survival were similar. Caesarean delivery, duration of labour, prolonged



Numbers at risk

Zidovudine infected	59	56	52	49	47	45	42	39	37	35
Nevirapine infected	36	36	35	34	31	29	27	25	24	23
Zidovudine uninfected	249	236	231	228	225	218	218	213	212	209
Nevirapine uninfected	275	264	261	260	258	252	251	249	247	241

Figure 3: **Kaplan-Meier estimates of babies' survival stratified by HIV-1 infection status at 6–8 weeks**

rupture of membrane, birthweight, and sex were not significantly associated with HIV-1 transmission. In the univariate models, baseline maternal CD4-cell count and plasma HIV-1 RNA were significantly associated with risk. There was a 1·29-fold increase (95% CI 1·18–1·40) in the risk of HIV-1 infection for every 100 cell decrement in CD4-cell count and a 2·24-fold increase (95% CI 1·73–2·89) for every 1 $\log_{10}$ increment in HIV-1 RNA copy number.

In analyses of possible confounders of the estimate of treatment effect, joint adjustment for both CD4-cell count and $\log_{10}$ RNA made no difference to the estimate; among other covariates, only birthweight was a possible confounder. A slight excess of babies in the nevirapine group with birthweight lower than 2800 g led to a slight increase (not significant) in the estimated treatment difference between nevirapine and zidovudine, when adjustment was made for birthweight.

In the multivariate analysis, including all variables in table 3, maternal baseline viral load and CD4-cell count and the treatment effect remained highly significant. When adjustment was done for breastfeeding status as a time-varying covariate in the Cox regression model, the estimate of the treatment effect remained unchanged. We also analysed recruitment period as a covariate in the

	Hazard ratio (95% CI)	p*
Univariate Cox regression models		
Treatment (nevirapine *vs* zidovudine)	0·59 (0·41–0·84)†	0·0039
Maternal HIV-1 RNA ($\log_{10}$) at pre-entry‡	2·24 (1·73–2·89)	<0·0001
Maternal CD4 at pre-entry§	1·29 (1·18–1·40)	<0·0001
Birthweight¶	1·16 (0·94–1·42)	0·16
Gender (female *vs* male)	1·09 (0·77–1·56)	0·63
Duration of labour (h)	1·00 (0·98–1·03)	0·92
Prolonged rupture of membrane (>4 h) (yes *vs* no)	1·11 (0·67–1·83)	0·69
Caesarean section (yes *vs* no)	0·79 (0·43–1·43)	0·43
Multivariate Cox regression		
Treatment (nevirapine *vs* zidovudine)	0·57 (0·40–0·83)	0·0033
Maternal HIV-1 RNA ($\log_{10}$) at pre-entry‡	1·81 (1·36–2·40)	<0·0001
Maternal CD4 at pre-entry§	1·19 (1·09–1·31)	<0·0001

*Computed from a Wald statistic. †Corresponding to a relative efficacy of 0·41 (95% CI 0·16–0·59). ‡For a unit increase of log, HIV-1 RNA copies/mL. §For a decrease of 100 cells/μL. ¶For a decrease of 500 g.

Table 3: **Prognostic factors for HIV-1 infection**

	Zidovudine (%)	Nevirapine (%)	p
Mothers			
Total	302 (100)	306 (100)	
First 8 weeks			
All adverse events*	259 (85·8)	263 (85·9)	0·948
Rash	20 (6·6)	21 (6·9)	0·906
Hepatic related†	5 (1·7)	2 (0·7)	0·247
Serious adverse events*	11 (3·6)	15 (4·9)	0·443
Deaths	3 (1·0)	0 (0·0)	0·081
Infants			
Total	309 (100)	320 (100)	
First 8 weeks			
All adverse events*	288 (93·2)	260 (81·3)	<0·0001
Infection	84 (27·2)	83 (25·9)	0·723
Rash	81 (26·2)	59 (18·4)	0·019
Conjunctivitis	54 (17·5)	61 (19·1)	0·607
Hepatic related†	67 (21·7)	30 (9·4)	<0·0001
Skin infection	54 (17·5)	31 (9·7)	0·004
Oral thrush	37 (12·0)	38 (11·9)	0·969
Serious adverse events*	35 (11·3)	29 (9·1)	0·348
Deaths	10 (3·2)	4 (1·3)	0·091
18 months			
Serious adverse events*	97 (31·4)	109 (34·1)	0·476
Deaths	42 (13·6)	34 (10·6)	0·253

Data are n (%) unless indicated. *Had at least one event. †Includes hepatomegaly, jaundice, or both.

Table 4: **Number of mothers and infants with adverse events**

efficacy analysis and the Kaplan-Meier estimates are similar; 18-month infection rates in babies born in the first half of the trial were 16% (nevirapine group) and 24% (zidovudine group) versus 15% and 28%, respectively, for babies born in the second half of the trial. When examining the treatment effect within CD4-cell quartiles (<278, 278–447, 448–643, >643 cells/μL), the relative risk for transmission in the zidovudine group compared with the nevirapine group was 1·7, 2·4, 1·1, and 1·7, respectively.

The maternal toxicity analysis includes the 608 mothers who received study drug—302 in the zidovudine group and 306 in the nevirapine group. These women were followed up through 6–8 weeks after delivery. Follow-up information through week 6 was available for 294/302 (97·4%) women receiving zidovudine and 300/306 (98·0%) receiving nevirapine.

Maternal serious adverse experiences with onset up to 56 days after delivery were balanced between the two treatment groups. 11/302 (3·6%) of women receiving zidovudine and 15/306 (4·9%) women receiving nevirapine had serious adverse experiences (table 4). Of the three maternal deaths occurring within 6–8 weeks after delivery, all three occurred in women receiving zidovudine. All maternal deaths were due to complications of HIV-1 infection and were not judged to be related to administration of study drug. The symptoms associated with the three maternal deaths were 1 month of dementia (CD4 cell count 63 cells/μL); broncho-pneumonia (CD4 cell count 28 cells/μL); and bronchopneumonia (CD4 cell count 224 cells/μL). Only two serious maternal adverse events were judged possibly related to study drug: one woman had hypertension in the zidovudine group and one woman had pre-eclampsia in the nevirapine group.

All maternal adverse events (serious and non-serious) were also balanced between the two groups, with at least one adverse event reported in 259 (85·8%) women receiving zidovudine and 263 (85·9%) receiving nevirapine. Non-HIV/non-malarial infection was the most frequent cause of maternal adverse experiences in both groups (22·2% in the zidovudine group *vs* 25·8% in the nevirapine group), followed by malaria (13·9% *vs* 15·7%), lymphadenopathy (12·6% *vs* 14·4%), anaemia (10·9% *vs* 13·7%), and hypertension (11·9% *vs* 7·5%).

Ten cases of maculopapular rash were reported, five in each treatment group; none of the rashes were serious and there were no cases of Stevens-Johnson syndrome. Adverse hepatic conditions were unusual, and included hepatomegaly (1·0% in zidovudine *vs* 0·7% in nevirapine recipients) and jaundice (0·7% *vs* 0%). The only hepatic serious adverse event reported was a case of hepatitis in a mother in the zidovudine group more than 56 days after delivery. Serious grade 3 or 4 laboratory toxicity was unusual, with no significant differences between treatment groups in serious laboratory toxicity for total bilirubin, haemoglobin, platelets, and white-blood-cell count, and no reports of grade 3 or 4 abnormalities in liver enzymes, absolute neutrophil count, or creatinine in either group.

The baby toxicity analysis includes the 629 babies who received the study drug, or whose mother received study drug, with 309 in the zidovudine group and 320 in the nevirapine group. Non-serious adverse events in the babies were reported through age 6–8 weeks and serious adverse experiences were reported through age 18 months. 293/309 (95%) babies in the zidovudine group and 309/320 (97%) in the nevirapine group were followed through age 6–8 weeks; 9/309 and 4/320 babies, respectively, had died before this visit. At the 18-month visit, 247/309 (80%) and 273/320 (85%) babies in the zidovudine and the nevirapine groups were still being followed up, and 42/309 (14%) and 34/320 (11%), respectively, had died before this visit.

Reported serious adverse events among babies with onset during the first 56 days after birth were balanced between the treatment groups: 35/309 (11·3%) in babies receiving zidovudine and 29/320 (9·1%) in those receiving nevirapine. The most frequently reported serious adverse event within 56 days of birth was sepsis followed by pneumonia, asphyxia, dyspnoea, fever, and meningitis. Of the 64 babies with at least one serious adverse experience reported within 56 days, seven (2·3%) in the zidovudine group and two (0·6%) in the nevirapine group were judged to be possibly related to the study drug. Each one of these possibly related serious adverse events were different conditions. In the seven babies in the zidovudine group, serious 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, presumed pneumonia 4 days after birth, sepsis and vomiting soon after delivery which resolved with antibiotics within 24 h, haemorrhagic disease of the newborn baby which resolved with vitamin K and antibiotics within 3 days, and an intrauterine death during labour. 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.

Reports of one or more serious adverse events through 18 months of follow-up were also balanced between the groups: 97/309 (31·4%) among babies receiving zidovudine and 109/320 (34·1%) in those receiving nevirapine. Anaemia was reported as a serious adverse event more often in the nevirapine group (9·4% *vs* 5·5%), however, all reports of serious anaemia occurred after 56 days of life and most are associated with the diagnosis of malaria. The only serious hepatic adverse events reported were one case of jaundice in each group, both occurring at or after age 1 year, and one hyperbilirubinaemia at day 5 in the zidovudine group.

There were 76 deaths among 629 (12·1%) babies in follow-up through 18 months (42/309 [13·6%] in the zidovudine group and 34/320 [10·6%] in the nevirapine group). The most frequent cause of death was pneumonia, followed by gastroenteritis/diarrhoea/dehydration, anaemia, and malaria.

All adverse events (serious and non-serious) that occurred in the first 6–8 weeks were significantly more frequent in babies randomly assigned to zidovudine, with 288/309 (93·2%) babies in the zidovudine group having at least one adverse event compared with 260/320 (81·3%) in the nevirapine group ($p<0·0001$; table 4). Certain conditions were substantially more frequent among the babies in the zidovudine group, including jaundice (18·4% *vs* 5·6%), skin infections (17·5% *vs* 9·7%), and pustular rash (4·5% *vs* 0·6%). The only condition with a difference in rates between groups larger than 3% and more frequent in the nevirapine group was dermal exfoliation (4·9% *vs* 8·4%), all of which were graded mild or moderate. In most cases this was described as "normal peeling skin of the newborn"; however, in four cases (three in the nevirapine group, one in the zidovudine group) the diagnosis was exfoliative dermatitis. No cases of Stevens-Johnson syndrome were reported. Within the first 56 days of life there were 21 cases of maculopapular rash, none of which was serious (12 cases in the zidovudine group and nine in the nevirapine group). Rashes in general were more commonly reported for the zidovudine group (26·2% in the zidovudine group and 18·4% in the nevirapine group). There were no significant differences between treatment groups in serious grade 3 or 4 laboratory toxicity for babies that we studied, and no reports of grade 3 or 4 abnormalities in liver enzymes (alanine aminotransferase) were reported in either group.

Discussion

In our initial report of the results of HIVNET 012, a single dose of nevirapine given to the mother intrapartum and to the baby postnatally lowered the risk of perinatal transmission by 47% compared with an intrapartum and 1 week postnatal regimen of zidovudine.[12] The current report is an 18-month follow-up and indicates persistent efficacy of the single-dose nevirapine regimen in breastfeeding babies. The nevirapine regimen achieved an absolute reduction of 8·2% in HIV-1 transmission at age 6–8 weeks that was sustained at 18 months with an absolute reduction of 10·1%. Nevirapine was also associated with significantly longer HIV-1-free survival at age 18 months. When stratified by babies' infection status at age 6–8 weeks, survival rates through age 18 months were similar between groups. This strongly suggests that the anticipated survival benefits, derived through nevirapine's reduction in risk of HIV-1 infection at 6–8 weeks, were fully achieved. In settings where breastfeeding is common, postnatal HIV-1 transmission may be high and the relative benefit may be less. Conversely, in settings where the duration of breastfeeding is shorter, the relative benefit of nevirapine may be greater, particularly if nevirapine, in addition to providing baby prophylaxis, also has a substantial effect on very early breastmilk transmission through lowering maternal viral load in breastmilk during the first few weeks of life.

The most frequently reported adverse events related to nevirapine are rash, fever, nausea, headache, and abnormal liver function tests. Life-threatening cases of Stevens-Johnson syndrome have occurred in nine (0·3%) of 2861 adult and paediatric patients on a daily nevirapine treatment regimen,[14] as well as several fatal or life-threatening cases of fulminant hepatitis in HIV-1 infected patients and uninfected patients taking antiretroviral prophylaxis for 4 weeks of treatment[15,16] or for occupational exposure to HIV-1.[17] However, these toxicities have been associated with repeated daily dosing, higher doses of nevirapine than in this study, and concomitant use of other antiretrovirals. By contrast, the nevirapine regimen used in our study and used similarly in more than 1300 mother-infant pairs in four other studies, has not been associated with increased clinical or laboratory toxicities, including rash and hepatotoxicity.[18–21]

The zidovudine and nevirapine regimens seemed to have similar low rates of serious adverse experiences in both mothers and babies, as well as similar rates of non-serious adverse events in mothers. However, non-serious adverse events among babies were significantly more frequent in the zidovudine group. Of the nine adverse experiences occurring in babies within 56 days of birth judged possibly related to study drug, seven (2·3%) were in the zidovudine group compared with only two (0·6%) in the nevirapine group. Non-serious rash and jaundice in babies were reported more frequently in the zidovudine than nevirapine group.

Although the zidovudine and nevirapine regimens used in this trial appeared to be safe over an 18-month period, we are unsure as to whether there are any longer-term toxicities for the zidovudine or nevirapine treated mothers and babies. However, such long-term toxicities seem unlikely for these regimens. The relative effect of these regimens on long-term survival and on transmission associated with extended breastfeeding for longer than 18 months is also unknown. Long-term follow-up of all HIVNET 012 babies through 5 years of age has been approved by the USA and Ugandan local regulatory bodies.

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 administration of treatment to babies, whereas many doses of the zidovudine regimen 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, be lower when given to women who arrive at the hospital in labour.

Our study design had similarities to one of the four groups in the PETRA intervention trial,[22] in which women received zidovudine and lamivudine as: an antepartum, intrapartum, and postpartum regimen; an intrapartum and postpartum regimen; or an intrapartum only regimen compared with placebo. The 42% relative efficacy of the HIVNET 012 nevirapine regimen compared with intrapartum/neonate zidovudine regimen at age 6–8 weeks is similar to the 37% relative efficacy of the intrapartum and postpartum PETRA group at 6 weeks compared with a placebo group. Unlike the PETRA study 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 36·7% among the 19 babies concurrently assigned placebo and 22·1% among those born to mothers concurrently assigned zidovudine suggests that short-course zidovudine may have had some benefit. Other observational data also suggest that intrapartum and infant zidovudine may decrease the risk of transmission.[23] If true, the decrease in risk with nevirapine compared with placebo would be even greater than that for nevirapine versus zidovudine.

Results of the SAINT trial showed the HIV-1 perinatal transmission rates at age 8 weeks to be similar in infants born to a group of mothers randomly assigned the

single dose intrapartum/neonatal nevirapine regimen with one extra dose to the mother compared with infants born to a group of women assigned the intrapartum and postpartum zidovudine and lamivudine PETRA regimen.[21] However, in the PETRA trial, HIV-free survival did not significantly differ between the intrapartum/postpartum and placebo groups at age 18 months,[22] whereas in HIVNET 012, the nevirapine group still had a significant 37% reduction in the risk of HIV-1 infection or death through age 18 months compared with the zidovudine regimen.

We cannot assess whether the HIVNET 012 nevirapine regimen would be as effective as the three-part PACTG 076 zidovudine regimen in breastfeeding settings,[2] which is currently the standard for prevention of transmission in more-developed countries for HIV-1-infected women who are counselled not to breastfeed. In many more-developed countries, HIV-1-infected pregnant women receive zidovudine with additional antiretroviral drugs for treatment of their HIV-1 infection.[24] Very low transmission rates (<2%) have been reported in non-breastfeeding women receiving highly active antiretroviral therapy during pregnancy.[25] We did not assess whether the addition of single-dose nevirapine to the PACTG 076 zidovudine regimen or potent combination therapy would further decrease HIV-1 transmission. However, results of a clinical trial, PACTG 316, done in non-breastfeeding women in the USA, Europe, and South America in which women received the PACTG 076 zidovudine regimen, potent combination therapy, or both, and were randomised to receive the HIVNET 012 nevirapine regimen or placebo, found that HIV-1 perinatal transmission rates were similar between the two groups (1·4% in the nevirapine group *vs* 1·6% in the control group).[20] A population of HIV-1 infected women in more-developed countries more similar to the women in the HIVNET 012 study are those first diagnosed with HIV-1 infection close to or during labour or who have not received antepartum antiretroviral therapy. In this situation, the HIVNET 012 nevirapine regimen is an effective alternative prophylactic regimen.[24] Further, to add the PACTG 076 neonatal component of a 6-week course of zidovudine to the nevirapine regimen could further reduce transmission. Conversely, we do not know whether the same efficacy seen in our trial could be achieved by dropping the neonatal or maternal dose of nevirapine which could further simplify the regimen.

Despite the success of nevirapine in decreasing HIV-1 transmission rates by about 41% during the course of 18 months, continuing HIV-1 transmission through breastmilk still occurred during the study. In babies between age 6–8 weeks and 18 months, there was an absolute increase of 3·9% in HIV-1 infections in babies in the nevirapine group (1·7% between 6–8 weeks and 14–16 weeks [0·8% per month], and 2·2% between 14–16 weeks and 18 months [0·2% per month]), resulting in an overall transmission rate of 15·7% at 18 months. A study in Malawi[10] found the incidence of infection through breastfeeding was highest during the early months of breastfeeding, with an incidence per month of 0·7% during age 1–5 months, 0·6% during age 6–11 months, and 0·3% during age 12–17 months. Similarly, 75% of all breastmilk transmission occurred during the first 6 months of breastfeeding in a randomised clinical trial of breast versus formula-feeding in Kenya.[26] The continuing risk of HIV-1 infection in breastfed babies suggests that there is a need to consider longer postnatal antiretroviral courses, early weaning, or both, to further decrease HIV-1 transmission in populations where no safe and sustainable alternative to breast milk is available.[8–10] Also a report suggesting that exclusive breastfeeding may be associated with a lower HIV-1 transmission rate than mixed feeding[27] requires further research. However, our study did not collect detailed information as to whether mothers exclusively breastfed or not, only if they breastfed and when they stopped.

One concern with the use of even a single dose of nevirapine is the possible emergence of HIV-1 resistance to nevirapine. We examined the emergence and fading of nevirapine-resistant HIV-1 in the mothers and infants in the HIVNET 006 and 012 studies.[28,29] We detected nevirapine-resistant HIV-1 6–8 weeks after delivery in 19% of mothers and 46% of infants, but not after 12–24 months after delivery.[29] We found no association between post-partum selection of nevirapine-resistant HIV-1 in women and the risk of transmission, nor did we find evidence of transmission of nevirapine-resistant HIV-1 to the infants. Our inability to detect nevirapine-resistant HIV-1 12–24 months after delivery suggests that this single regimen would remain effective for interruption of intrapartum transmission in subsequent pregnancies since most of the HIV-1 population would be sensitive at the time of administration during labour and delivery.

Theoretically, emergence of resistance with this regimen could affect the efficacy of future antiretroviral treatment options. However, it is not known whether transient resistance due to brief nevirapine exposure will be associated with treatment failure using nevirapine and additional drugs in the future. In any case, treatment options are currently very limited in less-developed countries; if treatment options are expanded in the future, women with nevirapine-resistant HIV-1 could be offered alternative antiretroviral treatment options. The potential for selection of nevirapine-resistant HIV-1 must be balanced against the documented efficacy, simplicity, and cost-effectiveness of the HIVNET 012 nevirapine regimen.[12,30]

Single-dose nevirapine given to the mother and the baby is cost effective[30] and is one of the few strategies that is deliverable and sustainable in resource-poor settings. Our data now indicate significant, persistent efficacy, and lack of toxicity of this regimen in breastfeeding infants followed to age 18 months, and the HIVNET 012 regimen is now one of the recommended regimens for less-developed countries.[31] However, despite the availability of a simple, effective, and inexpensive regimen, programmes to implement this regimen in resource-poor countries, where more than 90% of infected children are born, have been slow to get started. Obstacles include the limitations in the maternal-child health-care infrastructure and inadequate antenatal HIV counselling and testing facilities that exist in many resource-poor countries. However, implementation of this single-dose maternal/baby nevirapine regimen could prevent several hundred thousand babies or more from becoming HIV-1 infected and dying each year. The cost-effectiveness of this simple regimen has become even greater with the announcement by the manufacturer of nevirapine (Boehringer-Ingelheim) to provide the HIVNET 012 nevirapine regimen free of charge to all HIV-1 infected pregnant women in less-developed countries which agree to use nevirapine for this purpose. Efforts to simplify the uptake and implementation of this nevirapine regimen and increase the cost-effectiveness have already been reported.[32–34] Innovative strategies and a global collaborative effort are needed to ensure that this effective intervention is made available to the millions of HIV-1-infected pregnant women and babies in resource-poor countries.

Since the dataset was closed in March, 2001, subsequent extensive review of the data undertaken under the direction of the National Institute of Allergy and Infectious Diseases revealed the following updates. There was one additional death at 6 weeks of age of an infant in the zidovudine arm who had been lost to follow-up, but later found to have died (cause of death and HIV-1 infection status unknown). Nine new serious adverse events associated with eight infants during the first 6–8 weeks of age were discovered on review that had not been originally captured; none was judged related to study drug. Eight of the nine serious adverse events arose in the zidovudine arm: left hand extra digit, kwashiorkor, two cases of septic arthritis, hyperreflexia, hypotonia, seizures, and malaria. One additional serious adverse event (pneumonia) arose in the nevirapine arm. 11 infant adverse events (four in the zidovudine arm and seven in the nevirapine arm) were upgraded to serious adverse events on review: one case of pneumonia and ten congenital anomalies relating to extra digits on hands or feet (7), one case of Down's syndrome, one case of albinism, and one atrial septal defect case. Two serious adverse events associated with infants assigned to zidovudine were reclassified after review (convulsions instead of meningitis, and cor pulmonale instead of pneumonia). These revised figures increased the number of infants with at least one serious adverse event occurring within 6–8 weeks of age from 35 to 38 in the zidovudine arm and 29 to 35 in the nevirapine arm for a rate of 12·3% versus 10·9%, respectively.

Two new serious adverse events associated with two mothers assigned to the nevirapine arm were discovered on review that had not been originally captured (one case of thrombocytopenia and one case of puerperal sepsis). One case of thrombocytopenia at delivery in a mother assigned to zidovudine was upgraded to a serious adverse event on review. These maternal serious adverse events were not thought to be related to receipt of either study drug. None of these findings changed the interpretation regarding efficacy and safety of the original dataset.

Contributors

B Jackson, F Mmiro, L Guay, and P Musoke designed and implemented the study, interpreted the data, monitored adverse events, and wrote the paper. M G Fowler, P Miotti, and L Mofenson monitored adverse events and contributed to the design and interpretation of the study data and writing of the paper. T Fleming did the statistical analysis and helped to design the study and write the paper. D Bagenda and L Emel contributed to the design and analysis of the study. M Deseyve and A Mwatha did the statistical analysis. M Allen assisted with protocol development and monitored the study process. M Gigliotti and D Bray contributed to the design, analysis, interpretation, and implementation of the study with respect to drug dosing and packaging issues. M Mirochnick contributed to the design, analysis, and writing of the paper. J Sherman, P Bakaki, and M Owor collected data, and C Nakabiito recruited the study participants. C Ducar supervised the laboratory testing and contributed to the writing of the paper. C Duefield supervised onsite data management for the study.

Conflict of interest statement

None of the authors has a major conflict of interest in this study other than potentially M Gigliotti of Boehringer-Ingelheim and D Bray of GlaxoWellcome. J B Jackson, L A Guay, P Musoke, M Owor, P Bakaki, M Mirochnick, and F Mmiro have received honorariums and/or travel expense reimbursement over the past 2 years for giving talks at scientific meetings partly or wholly sponsored by the maker of nevirapine. J B Jackson received a one time consultation fee from Glaxo-Wellcome for attending a 1-day planning meeting subsequent to the publicaton of the preliminary trial results of the study. T Fleming received a consulting fee for a limited consultation with Boehringer-Ingelheim for a product in an unrelated indication. The Fred Hutchinson Cancer Research Center (T Fleming, L Emel, M Deseyve), which did the statistical analysis for the study, was paid by Boehringer-Ingelheim to organise data tables and figure images to support a US Food and Drug Administration submission for nevirapine. The study site in Uganda has also received some funding from Boehringer-Ingelheim to do a nevirapine implementation workshop on prevention of mother-to-infant transmission.

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