6-month efficacy, tolerance, and acceptability of a short regimen of oral zidovudine to reduce vertical transmission of HIV in breastfed children in Côte d’Ivoire and Burkina Faso: a double-blind placebo-controlled multicentre trial

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Summary

Background Zidovudine reduces the rate of vertical transmission of HIV in non-breastfed populations. We assessed the acceptability, tolerance, and 6-month efficacy of a short regimen of oral zidovudine in African populations practising breastfeeding.

Methods A randomised double-blind placebo-controlled trial was carried out in public clinics of Abidjan, Côte d’Ivoire, and Bobo-Dioulasso, Burkina Faso. Eligible participants were women aged 13 years or older, who had confirmed HIV-1 infection and pregnancy of 36–38 weeks duration, and who gave written informed consent. Exclusion criteria were severe anaemia, neutropenia, abnormal liver function, and sickle-cell disease. Women were randomly assigned zidovudine (n=214; 300 mg twice daily until labour, 600 mg at beginning of labour, and 83% post partum) or matching placebo (n=217). The primary outcome was the diagnosis of HIV-1 infection in the infant on the basis of sequential DNA PCR tests at days 1–8, 45, 90, and 180. We compared the probability of infection at a given age in the two groups. Analyses were by intention to treat.

Findings Women were enrolled between September, 1995, and February, 1998, when enrolment to the placebo group was stopped. Analysis was based on 421 women and 400 limborn infants. Baseline demographic, clinical, and laboratory characteristics were similar in the two groups. The Kaplan-Meier probability of HIV infection in the infant at 6 months was 18.0% in the zidovudine group (n=192) and 27.5% in the placebo group (n=197; relative efficacy 0.63 (95% CI 0.45-0.86); p=0.027). Adjustment for centre, period of recruitment, mode of delivery, maternal CD4-cell count, duration of labour, prolonged rupture of membranes, and duration of breastfeeding did not change the treatment effect. The proportions of women taking more than 80% of the planned maximum dose were 75% before delivery, 81% during labour, and 83% post partum, without statistical difference between the groups. No major adverse biological or clinical event was reported in excess among women and children of the zidovudine group.

Interpretation A short course of oral zidovudine given during the peripartum period is well accepted and well tolerated, and provides a 38% reduction in early vertical transmission of HIV-1 infection despite breastfeeding.

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See Commentary page 766

Introduction

Mother-to-child or vertical transmission of HIV leads to 1500 new paediatric HIV infections each day in Africa. Most observational studies estimate the risk of HIV vertical transmission to be 20–35% in developing countries in the absence of intervention. Prenatal transmission through breastfeeding is thought to account for most of the excess risk observed in Africa compared with more developed countries.

The efficacy of zidovudine in reducing HIV vertical transmission by two-thirds was shown by the multicentre AIDS Clinical Trials Group (ACTG) 076/Agence Nationale de Recherches sur le SIDA (ANRS) 024 clinical trial in the USA and France. This result, obtained in the absence of breastfeeding, has led to public-health recommendations and to increasing use of zidovudine monotherapy in pregnant women. As a consequence, vertical transmission rates now do not exceed 5% in this context. The results of that trial are not directly applicable in developing-country settings, for the following reasons: the unknown efficacy of zidovudine monotherapy in pregnant women if breastfeeding cannot be discontinued; logistic difficulties, including the need for early prenatal visits; intravenous infusion during labour; and cost. Simpler and more affordable regimens of...
zidovudine started to be evaluated in 1995 in several developing countries. The release in February, 1998, of the initial results of the zidovudine trial in Bangkok, Thailand, by the US Centers for Disease Control and Prevention was a first step in this respect. The reduction by half of the vertical transmission rate in the absence of breastfeeding had two immediate consequences: a worldwide policy of zidovudine prophylaxis was adopted and the placebo groups were discontinued in all of the trials under way in Africa under various sponsorships. We report the initial results of the DITRAME ANRS 049a trial carried out in Abidjan, Côte d'Ivoire, and Bobo-Dioulasso, Burkina Faso, to evaluate a short course of oral zidovudine among breastfeeding West African women.

Methods

Study population

The trial was carried out in two large cities with good access to and coverage of antenatal care services. In Abidjan, the economic capital of Côte d'Ivoire (3 million inhabitants), the Yopougon district is the most densely populated, with 500 000 inhabitants, a university hospital, and a network of public clinics offering prenatal, obstetric, and paediatric care. Bobo-Dioulasso has 400 000 inhabitants and is the second largest city in Burkina Faso. It has a public hospital and neighbourhood prenatal clinics. 1995 HIV seroprevalence estimates in pregnant women are available through unlinked serosurveys and range from 7.5% in Bobo-Dioulasso to 14.2% in Abidjan. Vertical transmission rates were estimated at 24.7% for HIV-1 and 1.2% for HIV-2 in a cohort study in Abidjan in 1991. The choice of the study protocol was partly based on the results of a feasibility survey carried out in this population in 1995. The study was a randomised double-blind placebo-controlled clinical trial. It started as a phase II tolerance trial and was extended as a phase III efficacy study, including the phase II observations with extended follow-up. The study protocol was approved by the Ethical Committee of the National AIDS Control Programme in Côte d'Ivoire, the National AIDS Control Committee in Burkina Faso, and in France by the Ethical Committee of the Bordeaux University Hospital, and the Institutional Review Board of the ANRS.

All pregnant women attending the selected prenatal clinics were systematically offered pretest counselling and HIV testing if they were at least 18 years old; presented before 32 weeks of gestation according to the best possible method of estimation, ultrasound examination, history of last menstrual period, or uterine height at clinical examination; lived within the city limits; and planned to give birth in one of the study clinics. A blood sample was obtained for the detection of HIV infection from each woman who signed an informed consent form. All serum samples were screened for HIV-1 and HIV-2 antibodies by a commercial ELISA (Genelavia Mix, Diagnostics Pasteur, Paris, France or Murex ICE 1-O-2, Murex Biotech Ltd, Dartford, UK). Confirmation and discrimination were obtained by use of a commercial synthetic peptide ELISA (Peptivat 1-2, Diagnostics Pasteur). Results were given to women who returned for post-test counselling, generally within 2 weeks. A second sample was then obtained from each woman who reacted to the first HIV test to verify her HIV status with a rapid discriminant test (Multipot, Diagnostics Pasteur).

Women who tested positive for HIV-1 or whose serological reaction was dually reactive for HIV-1 and HIV-2 were systematically asked to enter the trial. After informed consent had been given, blood was collected for haemoglobin electrophoresis, complete blood counts, and measurement of liver function. Reasons for exclusion were sickle-cell markers SS, SC, or SC haemoglobin, haemoglobinemia below 7 g/dL, absolute neutrophil count below 0.75 x 10^9/L, and alanine and aspartate aminotransferases above 2.5 times the standard value for the laboratory. Women who met all the inclusion criteria and accepted the study principles were scheduled for enrolment between 36 and 38 weeks of gestation.

Study methods

The oral regimen of zidovudine or matching placebo was prepartum treatment twice daily, a single oral loading dose at the beginning of labour, and a 7-day course of postpartum treatment twice daily. Zidovudine formulation was in 250 mg tablets for phase II, replaced by 300 mg tablets for phase III because the 250 mg formulation was no longer available from the manufacturer. Thus, the prepartum and postpartum treatment regimens were either 500 mg or 600 mg once. The intrapartum treatment package was given to each woman at inclusion. Intrapartum treatment was self-initiated by the woman as soon as labour started, either at home or in the delivery room. No treatment was given to the newborn infant.

Sequentially numbered sealed packages were prepared by an independent central pharmacy according to the randomisation list drawn by the independent statistician with SAS Version 6.11. Block randomisation (in blocks of ten) was used with stratification by centre, to assign eligible women to one of the study regimens. The study drugs were stored in prepackaged envelopes containing 1 week of treatment with written instructions.

Demographic and clinical information, and CD4-lymphocyte count were obtained at entry to the study. Women were given a weekly prepartum appointment for interview, clinical follow-up, and drug distribution, to allow documentation of compliance and tolerance. Women were asked to come to the study clinic to give birth and be admitted to hospital for at least 24 h. Delivery characteristics were recorded. Postpartum treatment was initiated, with an appointment 1 week later at the end of the treatment period, then at days 45, 90, and 180. If delivery occurred anywhere other than the study clinic, postpartum treatment and follow-up were initiated as soon as possible. Clinical follow-up of the child followed the same schedule as for the mother. Feeding practices were reported at each visit.

Intrapartum, breast milk, and long-term follow-up of the women and children included complete blood count at days 8 and 45 postpartum, and assessment of liver function at the same dates during phase II. Children's blood samples were also obtained for diagnosis of HIV infection. Maternal plasma and breast milk samples were routinely collected and tested for HIV RNA in the first consecutive 164 mothers. Results of this subsample will be published elsewhere.

Medical and psychosocial support was also available from study teams between scheduled visits. All prescribed medications, hospital stays, and transportation were offered free of charge during the study period. Long-term follow-up, scheduled for 2 years, is still under way.

Capillary blood was collected in microtainer tubes containing edetic acid from neonates between days 1 and 8. Peripheral blood (1-2 mL) was taken at days 45, 90, and 180. Peripheral-blood mononuclear cells were separated by gradient centrifugation. A nested PCR assay was done with three pairs of HIV-1-specific oligonucleotide primers (Eurogentec, Herstal, Belgium) according to previously described techniques. The amplified sequences were located in gag (GAG881-882/SDK38-39) and pol (H1POL42/54/54-44 and POL001-004/082-003) regions of the HIV-1 genome. All tests were done in duplicate, with positive and negative controls, and distilled water as an internal control. Validation of nested PCR amplification used calibrated DNA from 8E5 cells as positive controls with a detection level of five copies of proviral DNA per 10^6 cells. In samples negative by the two pol primer pairs, DNA quality was verified by PCR with HLA-DQA primers. PCR was classified as positive when a positive signal was obtained for at least two of the three primer pairs. All
negative PCR on the last available sample or by a negative serological result with the techniques reported for maternal infection. Absence of infection was defined by a plasma RNA PCR test (Amplicor Monitor, version 1.5, Roche Diagnostics Systems, Branchburg, NJ, USA), which gave concordant results. Samples collected at day 180, or earlier when not available, were systematically processed for PCR, which was then applied to all the preceding samples for a given child if the first sample tested gave a positive result. In Bobo-Dioulasso, samples were also subsequently analysed by commercial quantitative tests and applied to samples collected every 3 months from analysis.

According to international standards, the diagnosis of HIV-1 infection in the child was defined on the basis of one positive PCR. The first positive test in the series allowed estimation of the timing of infection. Absence of infection was defined by a negative PCR on the last available sample or by a negative serological result with the techniques reported for maternal infection and applied to samples collected every 3 months between 9 and 18 months of age. Children who had no sample available for PCR and could not be followed up beyond 6 months of age were classified as having unknown HIV status.

Maternal severe anaemia was defined by haemoglobin concentration below 7 g/dL at days 8 or 45 post partum and neutropenia by a neutrophil count below $0.5 \times 10^9/L$. Infant anaemia was defined by haemoglobinemia below 10 g/dL at days 1-8 or below 8 g/dL at day 45, and neutropenia by a neutrophil count below $0.5 \times 10^9/L$ at one of these two measures. All maternal (<42 days post partum) and infant deaths were taken into account.

Estimation of compliance with treatment was based on weekly interviews and pill count. Good compliance was defined by a treatment including above 80% of the number of pills that should have been taken based on its duration. Because zidovudine increases the mean corpuscular volume even after short periods of treatment, we used this variable measured at each maternal haematological investigation to assess compliance indirectly.

Statistical analysis

The sample size (n=780) was calculated to detect a 40% reduction in the vertical transmission rate at 6 months of age from a baseline rate of 25%, with a type I error of 5% (two-sided test), power of 90%, and 20% loss to follow-up. We chose the intention-to-treat approach for analysis, keeping all available records. One interim analysis was planned with 500 observations. Because enrolment was stopped in February, 1998, the study was terminated after review of the randomised observations by the independent data and safety monitoring board.

Group comparisons used Student's $t$ test or the non-parametric Mann-Whitney test for quantitative variables and $\chi^2$ test or Fisher's exact test for qualitative variables when appropriate. The probabilities of infection at a given age, continued breastfeeding at a given age, and infant death were estimated by the Kaplan-Meier survival technique, and comparisons used the log-rank test. Cox multivariate proportional hazards model was used to study zidovudine relative efficacy. Point estimates of summary statistics are reported with their 95% CI. To guarantee statistical independence of observations, we randomly selected only one infant from each multiple pregnancy.

Results

Study population

Details of the HIV screening programme and the difficulties encountered with acceptability of HIV screening and uptake in the trial have been reported elsewhere and are summarised in figure 1. Between September, 1995, and February, 1998, 431 women were enrolled in the trial, 164 during the phase II inclusion period (September, 1995, to October, 1996) and 267 during phase III (February, 1997, to February, 1998). Ten women were excluded from analysis because their serological diagnosis of HIV infection could not be confirmed in time. This report is based on 421 maternal records, 248 from the Abidjan centre and 173 from the Bobo-Dioulasso centre (figure 1, table 1). Among the 421 pregnant women, 406 livebirths and eight stillbirths were recorded. There were seven pairs of twins, one with a stillbirth (zidovudine group), and six with two livebirths each (figure 1, table 1). In each case one liveborn twin was included in the analysis.

Five women were dually reactive to HIV-1 and HIV-2. The zidovudine and placebo groups showed similar distributions and values for all baseline maternal variables (table 1). 76% of pregnant women were aged below 30 years, and 24-5% were primiparous. The median number of pregnancies was three, and
The median duration of postpartum maternal treatment was 7 days in both groups (table 2). 11 women in the zidovudine group and 16 in the placebo group did not receive any postpartum treatment. 11 children in the zidovudine group and four in the placebo group were bottlefed from birth (p=0.07). The probability of continued breastfeeding at 3 months was 85.9% in the zidovudine group and 89.8% in the placebo group; the probability had fallen to 74.0% and 78.4%, respectively, at 6 months (p=0.27).

### Adherence to treatment
Cumulative treatment was calculated and compared with the maximum number of pills to be taken according to duration (table 2). 78.1% of the zidovudine group and 75.4% of the placebo group (p=0.52) took more than 80% of the planned prepartum treatment, and 86% of women took at least 50% of cumulative treatment overall. Intrapartum treatment was either not given or given properly, with an overall use in 81.3% of women. 85.0% of the zidovudine group and 81.3% of the placebo group (p=0.35) took more than 80% of planned postpartum treatment. Maternal mean corpuscular volume (table 2) increased by 4.0 \( \mu \text{L} \) over the treatment period in the zidovudine group and decreased by 0.15 \( \mu \text{L} \) in the placebo group (p=0.0001 for the comparison of changes between groups).

### Tolerance
There was no interruption of treatment other than in women lost to follow-up. Two women in the placebo group and one in the zidovudine group died in the first

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**Table 1: Baseline and follow-up characteristics of participants**

<table>
<thead>
<tr>
<th>Baseline characteristics</th>
<th>Zidovudine</th>
<th>Placebo</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnant women assessed*</td>
<td>Total 209 212</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (range) gestation at enrolment</td>
<td>202 (14-176) 197 (92-306)</td>
<td>0.097</td>
<td></td>
</tr>
<tr>
<td>Median (range) haemoglobin (g/dL)§</td>
<td>9.6 (7.0-14.2) 9.5 (7.1-12.3)</td>
<td>0.237</td>
<td></td>
</tr>
<tr>
<td>Median (range) CD4-cell count (/\mu L)§</td>
<td>569 (21-1140) 530 (14-1870)</td>
<td>0.724</td>
<td></td>
</tr>
<tr>
<td>&lt;100 CD4 cells/\mu L</td>
<td>17 (8-38%) 17 (8-2%)</td>
<td>0.904</td>
<td></td>
</tr>
<tr>
<td>AIDS clinical stage§</td>
<td>1 (0-0%) 1 (0-0%)</td>
<td>1.000</td>
<td></td>
</tr>
</tbody>
</table>

*Comparison of proportion of neonatal deaths by treatment group among all infant deaths. Severe anaemia was defined for women as haemoglobin <7 g/dL, and for infants <50 g/dL on days 1-8 or <6 g/dL on day 45. Severe anaemia was defined as counts of <0.5 x 10^9/L for all participants.

**Table 3: Biological tolerance to treatment and vital status of women and children post partum**

The median duration of postpartum maternal treatment was 7 days in both groups (table 2). 11 women in the zidovudine group and 16 in the placebo group did not receive any postpartum treatment. 11 children in the zidovudine group and four in the placebo group were bottlefed from birth (p=0.07). The probability of continued breastfeeding at 3 months was 85.9% in the zidovudine group and 89.8% in the placebo group; the probability had fallen to 74.0% and 78.4%, respectively, at 6 months (p=0.27).

### Adherence to treatment
Cumulative treatment was calculated and compared with the maximum number of pills to be taken according to duration (table 2). 78.1% of the zidovudine group and 75.4% of the placebo group (p=0.52) took more than 80% of the planned prepartum treatment, and 86% of women took at least 50% of cumulative treatment overall. Intrapartum treatment was either not given or given properly, with an overall use in 81.3% of women. 85.0% of the zidovudine group and 81.3% of the placebo group (p=0.35) took more than 80% of planned postpartum treatment. Maternal mean corpuscular volume (table 2) increased by 4.0 \( \mu \text{L} \) over the treatment period in the zidovudine group and decreased by 0.15 \( \mu \text{L} \) in the placebo group (p=0.0001 for the comparison of changes between groups).

### Tolerance
There was no interruption of treatment other than in women lost to follow-up. Two women in the placebo group and one in the zidovudine group died in the first
placebo group (p=0.47; table 3). One woman in each weeks and treatment group during the first 6 months of life
par". Two women in the zidovudine group and seven in the placebo group, with 26 in the placebo'group, with

died with HN-related symptoms after 6 weeks post

months of life was significantly highFin the children of

transient anaemia was diagnosed post partum in 5.6%

and again was corrected by day 45.

Efficacy
Efficacy analysis is based on follow-up of 400 liveborn children. Eight children in the zidovudine group and three in the placebo group were of unknown HIV infection status and were excluded from the analysis. Eight children in the zidovudine group and three in the placebo group were of unknown HIV infection status and were excluded from the analysis.

Table 5: Probability of HIV-1 infection in children during the first 6 months of life

<table>
<thead>
<tr>
<th>Timepoint</th>
<th>Children at risk</th>
<th>Cumulative number infected</th>
<th>Probability (%) of infection (95% CI)</th>
<th>Relative efficacy* (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Zidovudine</td>
<td>Placebo</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 45</td>
<td>133</td>
<td>113</td>
<td>0.05 (0.96-0.76)</td>
<td>0.80 (0.69-0.91)</td>
</tr>
<tr>
<td>Day 90</td>
<td>145</td>
<td>131</td>
<td>0.05 (0.96-0.76)</td>
<td>0.80 (0.69-0.91)</td>
</tr>
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</table>

*1-hazard ratio (univariate analysis). Eight children in the zidovudine group and three in the placebo group were of unknown HIV infection status and were excluded from the analysis.

Figure 2: Probability of HIV-1 infection in infants according to treatment group during the first 6 months of life
Kaplan-Meier analysis of zidovudine (n=192) versus placebo (n=197).

6 weeks post partum. Two women, one in each group, died with HIV-related symptoms after 6 weeks post partum. Two women in the zidovudine group and seven in the placebo group reported severe signs and symptoms during the treatment period, including fever, diarrhoea, nausea, or muscular pain. Severe but transient anaemia was diagnosed post partum in 5.6% of women in the zidovudine group and 4.0% in the placebo group (p=0.47; table 3). One woman in each group developed severe but transient neutropenia.

The two groups showed little, if any, difference in anthropometry of neonates or adverse perinatal outcomes (table 4). 17 infant deaths were reported in the zidovudine group and 26 in the placebo group of neonates or adverse perinatal outcomes (table 4). 17 infant deaths were reported in the zidovudine group and 26 in the placebo group.

The probability of death was 4.0% at 4 weeks and 8.8% at 6 months in the zidovudine group, versus 2.0% and 13.6%, respectively, in the placebo group (p=0.16). Ten (5.2%) neonates in the zidovudine group and 12 (6.2%) in the placebo group developed severe anaemia, but this abnormality was corrected by day 45. Severe neutropenia was less common (table 3), and again was corrected by day 45.

Discussion
We report the efficacy of a short regimen of oral zidovudine in reducing vertical transmission of HIV-1 in a breastfed population, with about 40% reduction in the rate of transmission estimated at 6 months of age. The demonstrated efficacy of this zidovudine regimen was obtained with only a short course of treatment in a population with generally mild HIV-1-related immunodeficiency. Treatment was well accepted and well tolerated.

Several factors strengthen these conclusions. The two randomised groups were similar in terms of all relevant characteristics at baseline. Losses to follow-up did not exceed 6% (women and children combined) and data were generally available for more than 95% of the records. The estimate of the vertical transmission rate in the placebo group is compatible with those reported elsewhere, including for Côte d'Ivoire. Finally, our findings are consistent with other trial results showing higher efficacy in non-breastfed populations and a similar study in another breastfed population in Côte d'Ivoire. The reduction in transmission rate is close to the assumption made for the sample-size calculation.

Probabilities of infection over time in the placebo group were consistent with previous estimates in Rwanda and the Democratic Republic of Congo (former Zaïre). Maximum efficacy of zidovudine was estimated at 38% (95% CI 5-60) in reducing vertical transmission of HIV-1.

In Cox multivariate analysis that took account of the variables listed in table 6, zidovudine reduced vertical transmission by 42% (5-65; p=0.028). Prolonged rupture of membranes multiplied the risk of transmission by almost 2, independently of the treatment effect, and low maternal CD4-cell count also increased the transmission rate independently of treatment effect. Duration of breastfeeding did not influence the treatment effect.

### Table 6: Determinants of overall HIV-1 vertical transmission according to treatment group

| Hazard ratio (95% CI) p |
|------------------------|------------------|
| Zidovudine vs placebo   | 0.58 (0.35-0.96)*| 0.028 |
| Prolonged rupture of membranes (>4 h) | 1.93 (1.15-3.22) | 0.015 |
| Maternal CD4-cell count at inclusion† | 2.05 (1.09-3.92) | 0.0004 |
| Duration of labour‡ | 0.95 (0.96-1.02) | 0.045 |
| Duration of breastfeeding§ | 1.07 (0.84-1.36) | 0.618 |
| Abdomen vs Bobo-Dioulasso | 1.20 (0.69-1.94) | 0.634 |
| Phase II vs phase III | 0.90 (0.67-1.23) | 0.878 |
| Caesarean section | 1.40 (0.82-2.42) | 0.224 |

*Corresponding to a relative efficacy of 0.42 (95% CI 0.05-0.64). **For an increase of 100/µL, $For an increase of 1 h. 1 For an increase of 1 month of the duration of breastfeeding. Zidovudine group: 25 infected/140. Placebo group: 43 infected/140.

The two groups showed little, if any, difference in the children of Zidovudine group mothers than in the children of zidovudine-group mothers (log-rank test p=0.027; table 5, figure 2). The efficacy of zidovudine was thus estimated at 38% (95% CI 5-60) in reducing vertical transmission of HIV-1.
obtained before day 8. Curves of acquisition of infection in the two groups were very similar after 1 week. Increased postnatal transmission was not observed in the zidovudine group by 6 months of age. This rebound effect was theoretically possible with an increase in viral load when maternal zidovudine treatment stopped. Reduction in transmission obtained with this peripartum intervention was thus compatible with reports in non-breastfed populations.24 Identification of the zidovudine group by less than 40% of our cases. Our data do not allow us to make conclusions about the respective contribution of each component of the treatment. The similarity of our findings with those of the other Côte d'Ivoire trial22 does not allow us to draw conclusions on the efficacy of a single dose versus repeated doses of oral zidovudine during labour and 1 week of postpartum maternal treatment. Efficacy was influenced by maternal CD4-cell count independently of treatment effect, as in other trials,25,26 but the frequency of severe immunodeficiency was low, as is generally the case in developing countries.22 We cannot yet report on the long-term efficacy of the intervention because breastfeeding continues in this cohort.26 Owing to the threat of late postnatal transmission,27 long-term efficacy may best be assessed from combination of several trial reports, as has been done for observational studies.28

No serious adverse pregnancy outcome was reported in excess at birth or during follow-up in the zidovudine group. Haematological toxic effects were uncommon, and abnormal findings were always transient. This profile is compatible with a report of the ACTG 076/ANRS 024 trial, which looked at long-term safety of zidovudine.29 The fact that severe anaemia was rare, despite the low haemoglobin concentrations at enrolment, shows that zidovudine monotherapy can be offered to most African pregnant women, many of whom present with mild anaemia,30 as long as iron and folate supplementation is systematically given, as it was in our trial.

Adherence to the overall intervention was good. Compliance to prepartum treatment was not optimum, but haematological indices showed that at least some zidovudine had actually been taken. The main limiting factor for intrapartum treatment was that 40% of the women did not reach the study clinic to give birth. Information to patients should therefore emphasise the importance of taking the oral loading dose of zidovudine as soon as labour starts. Treatment was not repeated during labour, but this procedure may be complex and will not be suitable for women who will give birth in uncontrolled conditions.31 Efforts to identify simpler antiretroviral regimens are needed. Such investigations will be difficult to design because the results of this trial and others set a new standard of care for developing countries,32 against which new treatments should be compared.

The public-health implications of our findings can be discussed in the light of the latest WHO guidelines.33 A 3-week regimen of zidovudine monotherapy at the end of pregnancy and during labour can be recommended on the basis of its proven efficacy, but infant-feeding options should be discussed with each woman to guarantee maximum efficacy. Programmes to lower the rate of vertical transmission of HIV require not simply drug delivery but also comprehensive and upgraded antenatal, obstetric, and postnatal care, including maternal HIV screening and alternatives to breastfeeding.34 The cost of antiretroviral treatment is therefore not only the cost of the drug.35 This trial and others24,36 are a first step towards a global strategy for maternal and child health programmes in countries with high HIV seroprevalence.

Contributors
F Dabis, P Maeliati, and N Meda cowrote the protocol and coordinated the study. G Wolffa-Elewa was an obstetrician primary coinvestigator. B You, C Mombocho, O Maniagit, and A Sivonew were responsible for molecular biology. V Leroy contributed to design and was in charge of statistical analysis. M Carteux contributed to design and organisation of antenatal HIV screening procedures. P Combe and A Omner supervised laboratory activities. R Ramon and O Ky-ko were trial monitors. R Salamon provided methodological expertise to trial design and project direction. C Rouzioux assisted in the implementation of molecular biology and organised quality control. P Van de Perre contributed to the design and conduct of the research, and provided direction to all virological aspects of the project. L Mandebrot cowrote the protocol and was an obstetrician primary coinvestigator. F Dabis wrote the paper.

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