of maternal oral zidovudine to decrease vertical transmission of HIV-1 in breastfed African children

DITRAME ANRS 049 Study Group*

In a randomised, double-blind comparison of a maternal short regimen of oral zidovudine with placebo in West Africa the 15-month efficacy of zidovudine in preventing mother-to-child transmission of HIV-1 infection was estimated at 30% (95% CI 2 to 52).

Two randomised trials have shown that mother-to-child transmission of HIV-1 can be effectively decreased in breastfed African children with a short maternal regimen of oral zidovudine. Because transmission of HIV-1 via breastfeeding can occur as long as exposure persists, there is concern that the benefit of the intervention may not be sustained in the long term. We report the results of the DITRAME ANRS 049A trial conducted in Abidjan, Côte d'Ivoire, and Bobo-Dioulasso, Burkina Faso, which assessed after 15 months of follow-up of breastfed children the efficacy of a peripartum zidovudine regimen.

The methods of this phase II/III randomised double-blind placebo-controlled trial have been described previously. The oral regimen zidovudine or matching placebo was: daily treatment of 500 mg or 600 mg starting at 36–38 weeks of gestation, a single oral loading dose of 500 mg or 600 mg at the beginning of labour, a 7-day postpartum treatment of 500 mg or 600 mg per day, and no treatment of the neonate. Clinical follow-up of and blood collection from the child were conducted within 1 week of birth, then at day 45, day 90, and every 3 months until 15 months. Feeding practices were reported at each visit.

The sample collected at day 180, or an earlier one when that was not available, was systematically processed by PCR.

If that sample was positive, PCR was then applied to all the preceding available samples. DNA PCR was systematically used in Abidjan. In Bobo-Dioulasso, samples were analysed during phase II by DNA PCR and quantitative plasma RNA PCR (Amplicor HIV monitor, version 1.5, Roche Diagnostics Systems Inc, Branchburg, NJ, USA) and then by RNA PCR only. The diagnosis of HIV-1 infection in children was defined on the basis of one positive PCR. Serum samples collected at 9–15 months of age were screened for HIV-1 and HIV-2 antibodies by ELISA (Genelavia Mix, Diagnostics Pasteur, France, or Murex ICE 1-0-2, Murex Biotech Ltd, UK). Confirmation on the same sample was obtained with a synthetic peptide ELISA (Peptilav 1–2, Diagnostics Pasteur). A positive antibody test at 15 months was also a diagnostic criterion of HIV-1 infection in the child. Absence of infection was defined as a negative diagnosis 60 days or more after complete cessation of breastfeeding. A negative diagnosis on the last available sample while the child was still being breastfed or had been weaned for less than 60 days was defined as provisional absence of infection. Children who had no sample available for PCR and could not be followed up beyond 6 months of age were classified as of unknown HIV-1 status.

Enrolment ended in February, 1998.' The primary analysis of long-term efficacy was by intention-to-treat for liveborn children. Date of diagnosis of infection was the date of the first positive PCR test for children diagnosed before day 45 or the midpoint between the last negative and the first positive tests for those diagnosed after day 45. Endpoint date was 60 days after weaning for definitely uninfected children and the date of the last available negative test for children classified as provisionally uninfected. The probability of diagnosis by HIV-1 infection at a given age and the probability of breastfeeding were estimated by the Kaplan-Meier survival technique, and comparisons were made by the log-rank test. Efficacy was defined as 1 minus the ratio of the estimated transmission risks in the two treatment groups.

Between September, 1995, and February, 1998, 431 women were enrolled; 401 livebirths were included in this analysis after random selection of one livebirth in six pairs of twins. The trial profile is similar to that in our previous report, with updated data. There were 201 liveborn infants in the placebo group and 200 in the zidovudine group, with 236 in Abidjan and 165 in Bobo-Dioulasso. The median duration of the antepartum treatment was 21 days; intrapartum treatment was reported in 81% of deliveries and median length of postpartum maternal treatment was 7 days, without difference between the groups. Caesarean section was done in 2.5% of women.

Nine children in the zidovudine group and four in the placebo group were bottle fed from birth (p=0.16). The probability of being breastfed at 6 months, calculated for the remaining 388 children, was 90.7% in the zidovudine group and 93.8% in the placebo group; that at 15 months was 45.6% and 40.1%, respectively, without difference between the treatment groups (p=0.56). Among the 401 livebirths, seven children in the zidovudine group and three in the placebo group were definitely uninfected at birth (p=0.16). The probability of being breastfed at 6 months, calculated for the remaining 388 children, was 90.7% in the zidovudine group and 93.8% in the placebo group; that at 15 months was 45.6% and 40.1%, respectively, without difference between the treatment groups (p=0.56). Among the 401 livebirths, seven children in the zidovudine group and three in the placebo group were definitely uninfected at birth (p=0.16).
samples—an overall 2.5% loss to follow-up for the efficacy placebo group (p=0.22) were of unknown HIV-1 infection status because of early neonatal death and lack of blood samples—on average 2.5% loss to follow-up for the efficacy analysis. At age 15 months, 37 children in the zidovudine group and 57 in the placebo group were infected (table). Infection was diagnosed at a median age of 18 days (inter-quartile range 8–45) for the 70 children diagnosed before day 45 and at an estimated median age of 136 days (87–231) for the 24 children diagnosed as infected after day 45. Among the 297 uninfected children, 74 of 156 in the zidovudine group, and 61 of 141 in the placebo group (table) were definitely uninfected (p=0.56), diagnosed at a median age of 292 days (247–351). The probability of being infected (table) after 3, 6, and 15 months was significantly lower in the zidovudine group than in the placebo group (overall log-rank test p=0.022). The efficacy of zidovudine was thus estimated at 30% in reducing mother-to-child transmission of HIV-1 (95% CI 2–52) after 15 months of follow-up under predominant exposure to breastfeeding.

Our findings will require confirmation in other trials, particularly the nevirapine trial. To investigate postnatal transmission further, we will combine our results with those of a similar zidovudine trial done in Abidjan. The 1998 recommendation of use of short-course zidovudine is therefore reinforced in the context of African populations with high rates of breastfeeding.

In women receiving antiretroviral drugs in the peripartum period, infant feeding options should clearly be discussed as early as possible to guarantee maximum efficacy. Interventions influencing the conditions of breastfeeding and risk factors for postnatal transmission should also be considered. While such research is contemplated, implementation of antiretroviral drug regimens and active introduction of alternative means of infant feeding are urgently needed in Africa.


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Postcoital injuries treated at the Addis Ababa Fistula Hospital, 1991–97
Mulu Muleta, Gordon Williams

91 young Ethiopian women who had developed total faecal incontinence from injuries sustained from sexual intercourse within marriage or rape were successfully treated at this hospital.

In traditional societies such as those in Ethiopia, marriages are usually arranged by parents or elders, who decide at what age and whom the girl will marry. Decisions are usually based on financial interests, with the girl’s opinion rarely considered. Girls are given in marriage at an early age because of pressure to conform to tradition and to ensure that the girl is a virgin on marriage. Parents also wish to see their children married and settled before they themselves become old or die. Age differences between husbands and wives are frequent, with men usually aged between 18 and 20 years on marriage, by contrast with girls who may be married from the age of 6 years.

Girls who marry at an early age know little about their reproductive system and could be injured by being forced to become sexually active before reaching physical maturity. In addition, it is not unusual for a man who cannot afford a wife to kidnap a young woman, rape her repeatedly, and, if she is not injured, to then marry her. This forced abduction and rape is condoned by the potential husband’s family, and because of the ensuing shame, the girl and her family have little choice but to accept the offer of marriage.

We describe 91 girls and women who presented with total faecal incontinence following sexual abuse to the Addis Ababa Fistula Hospital between 1991 and 1997. 78 had been sexually abused under the cover of marriage; nine were kidnapped with the intention of marriage, raped, and then discarded by their would-be husbands; and four were kidnapped and raped. 24 presented within 12 months of injury; the remainder took up to 60 months to seek medical attention. Table 1 shows patients’ age and the circumstances of injury. Table 2 shows injury and outcome of surgical treatment.

In Ethiopian society a wife is totally dependent on her husband and his parents. If a girl who is too young to assume traditional domestic duties develops a vesicovaginal fistula, rectovaginal fistula, or 3rd degree tear after postcoital injury or birth trauma, she is usually perceived to have no further value as a wife. Of the 78 married women in this study who were injured, 59 were divorced and 19 were abandoned. Their total faecal incontinence means that these girls and young women are regarded as outcasts by society.

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<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Circumstances of injury</th>
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<tbody>
<tr>
<td></td>
<td>Marriage</td>
</tr>
<tr>
<td>6–10</td>
<td>12</td>
</tr>
<tr>
<td>11–15</td>
<td>51</td>
</tr>
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</tr>
<tr>
<td>21</td>
<td>4</td>
</tr>
<tr>
<td>Total</td>
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*Divorced 59.

Table 1: Patients’ age and circumstances of injury

<table>
<thead>
<tr>
<th>Injury (n)</th>
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<tbody>
<tr>
<td>RVVF</td>
<td>Cured at first operation</td>
</tr>
<tr>
<td>RVF</td>
<td>Cured at second operation</td>
</tr>
<tr>
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<td>45</td>
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<td>45</td>
<td>42</td>
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<td>3rd degree tear</td>
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RVF: rectovaginal fistula; VVF: vesicovaginal fistula.

Table 2: Injuries sustained and outcome of surgery

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