Lamivudine-Zidovudine Combination for Prevention of Maternal-Infant Transmission of HIV-1

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THE EFFICACY OF ANTIRETROVIral drugs to prevent maternal-infant transmission of human immunodeficiency virus 1 (HIV-1) was first demonstrated in 1994.[1] As soon as these data were made public, zidovudine monotherapy prophylaxis became the standard of care; a similar two-thirds decline in transmission rates was reported in observational cohort studies.[2,3] More recently, antiretroviral combinations have

Context Zidovudine reduces maternal-infant transmission of human immunodeficiency virus 1 (HIV-1) infection by two thirds. Combination antiretroviral therapies are potentially more effective prevention.

Objectives To assess the safety of perinatal lamivudine-zidovudine therapy, especially in children, and its effects on viral load, acquisition of drug resistance, and maternal-infant transmission of HIV-1 in a nonbreastfeeding population.

Design and Setting The Agence Nationale de Recherches sur le SIDA (ANRS) 075 Study, an open-label, nonrandomized intervention trial conducted in the context of an ongoing observational cohort study in 48 sites in France.

Patients A total of 445 HIV-1–infected pregnant women were enrolled as the study cohort from February 1997 to September 1998; controls consisted of 899 pregnant women who had received zidovudine monotherapy in May 1994 to February 1997 as standard care.

Intervention The study cohort received lamivudine in addition to the standard Pediatric AIDS Clinical Trial Group 076 Study zidovudine prophylaxis regimen. Lamivudine was initiated in women at 32 weeks' gestation through delivery at 150 mg twice per day orally; children received lamivudine, 2 mg/kg twice per day for 6 weeks.

Main Outcome Measures HIV-1 infection status and tolerance of therapy in children through age 18 months; maternal plasma HIV-1 RNA levels through 6 weeks after delivery.

Results The transmission rate in the study group was 1.6% (7/437; 95% confidence interval [CI], 0.7%-3.3%). In a multivariable analysis, transmission in the study group was 5-fold lower than in controls. In the study group, maternal plasma HIV-1 RNA level was less than 500 copies/mL at delivery in 74%; the median decrease was 1.24 (range, −1.63 to 3.40) $\log_{10}$ copies/mL. The M184V lamivudine resistance mutation was detected at 6 weeks after delivery in specimens from 52 of 132 women. The most frequent serious adverse events in children were neutropenia and anemia, requiring blood transfusion in 9 children and premature treatment discontinuation in 19. Two uninfected children died at age 1 year from neurologic complications related to mitochondrial dysfunction.

Conclusions Lamivudine-zidovudine may be effective in preventing maternal-infant HIV transmission. However, severe adverse effects and emergence of resistance to lamivudine occurred. Thus, the role of this combination therapy in this setting is as yet unclear, and further research involving a variety of strategies is needed to definitively ascertain its utility for preventing maternal-infant HIV transmission.
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been used in pregnancy for maternal health.[4,5] Combination therapies also have been considered increasingly as a means to further decrease risk of maternal-infant transmission. The combination most frequently used for this purpose since 1995 is lamivudine-zidovudine because it was shown to lower viral load and improve outcome in HIV-infected patients.[6] In a phase 1/phase 2 trial,[7] the pharmacokinetics of lamivudine were not modified by pregnancy, and placental blood concentrations were within the therapeutic range, suggesting passive placental transfer. We recently reported that lamivudine accumulates at 5-fold higher concentrations in amniotic fluid.[8] There are now preliminary observational studies of lamivudine-zidovudine in pregnancy,[9,10] as well as a large clinical trial that showed a decrease in maternal-infant transmission of up to 50% compared with placebo in a breastfeeding population in Africa.[11]

Despite the relative lack of published data regarding use of various combination therapies in pregnancy, clinical practice has evolved rapidly. In the latest updated US guidelines,[4] dual combination nucleoside analog therapy without addition of a protease inhibitor or a nonnucleoside reverse transcriptase inhibitor is no longer recommended because of the potential for inadequate viral suppression and rapid development of resistance, except as an option for women presenting in labor without prior therapy.

We performed this study to assess the impact of lamivudine-zidovudine as an alternative to zidovudine prophylaxis. The objectives were to evaluate the safety of the combination, in particular in infants, and its effects on viral load, acquisition of drug resistance, and maternal-infant transmission of HIV-1. At the time the study began in 1997, we judged that a classic randomized clinical trial was not feasible because many clinicians appeared to be convinced that the combination would necessarily be more effective than zidovudine monotherapy,[12] as evidenced by sharp increases in the frequency of lamivudine-zidovudine prescription for pregnant women in France

and the United States.[13] Nonetheless, we believed that women should be informed regarding the lack of data with which to weigh the benefits and risks of this option. The study was designed as an open-label, nonrandomized intervention study, performed in the context of an ongoing observational cohort study, allowing for comparison with a historical control group that had received zidovudine as standard prophylaxis. Lamivudine administration was begun in the third trimester to minimize the risk of selecting virus with drug resistance mutations and of toxic effects in the infants, and to attain the maximum possible antiretroviral efficacy at the end of pregnancy and during delivery, when the risk of transmission is greatest.[14]

METHODS
Study Setting and Design
The French Perinatal Study is an ongoing observational cohort study of HIV-infected women and their children, established in 1986. As previously described,[15] enrollment is offered with informed consent in 85 centers throughout France to all women who are confirmed to be HIV-seropositive during their pregnancy, up to the time of delivery but not beyond. Women were enrolled at delivery until 1997, and at any time during pregnancy or at delivery from 1997 onward. Clinical and biological (ie, involving hematologic or clinical chemistry testing) follow-up of children is performed at protocol visits through age 18 months, as previously reported.[15]

Until April 1994, standard care was to recommend antiretroviral therapy only in the case of advanced maternal immune deficiency. Following the announcement of the Pediatric AIDS Clinical Trial Group 076 Study (ACTG 076) results, national recommendations were issued, establishing zidovudine monotherapy as the standard of care for prevention of maternal-infant transmission. From May 1994 until February 1997, 1179 HIV-infected women were enrolled in the French Perinatal Study, of whom 59 were infected with HIV-2 and 1121 with HIV-1. Of the HIV-1–

infected women, 899 (80%) received zidovudine monotherapy, 128 (12%) received no antiretroviral drugs, 10 (1%) had unknown treatment status, and 84 (7%) received other antiretroviral drugs, mostly as therapy for their own health. The cohort study itself did not establish any criteria for choice of therapy, which was left to clinicians and patients in the context of standard recommendations.[5] The recommendations include discouraging HIV-infected women from breastfeeding, and very few women in the 2 cohorts breastfed their infants (**TABLE 1**).

The lamivudine-zidovudine intervention occurred in 48 of the 85 centers participating in the French Perinatal Study, starting February 1, 1997. All HIV-1–infected women who enrolled in the French Perinatal Study were eligible except those with a history of intolerance to lamivudine, those receiving any antiretroviral drug other than zidovudine beyond 12 weeks of pregnancy, and those having biological contraindications (ie, hematologic or serum biochemistry abnormalities, defined in the protocol as hemoglobin concentration <8 g/dL, neutrophil count $<1000 \times 10^6$/L, platelet count <50 000/μL, lipase level >1.5 times the upper limit of normal [ULN], transaminase level >2.5 times the ULN, and serum creatinine level >1.47 mg/dL [130 μmol/L]). The protocol did not set any virological or immunologic criteria for enrollment. The trial was approved by the appropriate regulatory agencies (the Comité Consultatif Pour le Traitement de l'Information en Matière de Recherche Dans le Domaine de la Santé and the Commission Nationale Informatique et Liberté, Paris, France) and institutional review board (Comité Consultatif de Protection des Personnes Dans la Recherche Biomédicale, Hôpital Cochin, Paris, France). Written informed consent was obtained from all participants.

Zidovudine was administered according to standard ACTG 076–based recommendations.[4,5] Enrollment in the study occurred at 32 weeks, with the beginning of administration of lamivudine. Lamivudine, 150 mg twice per day

orally, was given to women until delivery and then to children (2 mg/kg twice per day) for 6 weeks. Mode of delivery was not specified in the protocol. After delivery, decisions to stop, maintain, or change therapy were left to the clinicians and patients.

A planned a priori analysis was conducted in which results were compared, when appropriate, between the intervention group and a historical control group composed of 899 consecutive mother-infant pairs enrolled in the French Perinatal Study who had received zidovudine monotherapy during the period when it was the standard of care, from May 1994 until February 1997 (when the present intervention was initiated). As planned per protocol specifications, we did not include in the control group the small number of patients who received zidovudine monotherapy during the period when lamivudine-zidovudine was offered, nor did we include in the study group the large number of women treated with lamivudine-zidovudine who were not formally enrolled in the trial.

Follow-up of Women and Children

In addition to the usual follow-up of the French Perinatal Study,[3] women were followed up every 2 weeks from enrollment through delivery with clinical examination, hematologic and biochemical assays, and fetal nonstress test. Ultrasonographic imaging of the fetus and umbilical velocimetry (cord doppler) were performed monthly. Samples of plasma and peripheral blood mononuclear cells were obtained at enrollment, at delivery, and at the 6-week postpartum visit and subsequently frozen and stored. In children, samples were obtained for blood cell counts and transaminase, serum creatinine, and pancreatic lipase levels at birth, at ages 2, 4, and 6 weeks, and at ages 3 and 18 months, in addition to the standard clinical and biological follow-up through age 18 months.[3]

Toxic effects were graded according to the Agence Nationale de Recherches sur le SIDA (ANRS) system[16]; for bio-

Table 1. Maternal Demographics and Clinical Characteristics*

Characteristics	Lamivudine-Zidovudine Study Cohort (n = 445)	Zidovudine Control Cohort† (n = 899)	P Value
Age, median (range), y	30 (18-43)	29 (17-47)	.06
History of intravenous drug use, %	11	15	.04
Birth in sub-Saharan Africa, %	50	43	.02
CD4 cell count at enrollment, median (range), $\times 10^6$/L‡	426 (23-1440)	436 (0-3502)	.10
Viral load at enrollment, human immunodeficiency virus RNA log copies/mL‡	3.6 (<1.3-5.6)	3.6 (<2.3-5.8)	.33
Elective cesarean delivery, %	22	16	.005
Membrane rupture >4 h, %§	40	40	.90
Antiretroviral-experienced, %	25	14	.001
Breastfeeding, %	0.5	0.3	.67
Start of zidovudine, median (range), wk since last menstrual period	23 (<0-38)	23 (<0-41)	.42

*Missing values for variables ranged from 0 to 59, except for HIV RNA, which was reported for 109 women in the control cohort. For this cohort, viral load testing was largely not available until May 1996, and increasingly available thereafter; testing was done in all centers by the end of its enrollment period. Of a total of 199 women enrolled in the control cohort from May 1996 until February 1997, approximately one half (n=103) had HIV RNA test data recorded at delivery.
†Enrollment occurred between May 1994 and February 1997.
‡Enrollment occurred at start of lamivudine therapy in the ANRS 075 study and at delivery in the zidovudine control cohort.
§Elective cesarean deliveries were excluded.

logical adverse events in infants younger than 3 months, we used the age-adjusted ACTG classification system.[17] We limited the analysis to significant adverse events, defined as death, life-threatening conditions, major birth defects, disability, hospitalization, and moderate or severe hematologic or serum biochemical abnormalities, excluding mild-grade adverse events. The protocol did not require confirmation of all abnormal laboratory values with a second test unless deemed useful by a clinician. These were reported by fax to the coordinating center within 24 hours and transmitted to the trial sponsor (ANRS) and the national drug agency (Agence Française de Sécurité Sanitaire des Produits de Santé, Saint Denis, France). In such instances, according to the protocol, lamivudine was immediately stopped and discontinuation of zidovudine was decided on by the clinician. To avoid reporting bias, the database was checked for serious adverse events that had not been faxed by an investigator. Adverse events were reviewed by a safety board composed of pharmacologists and clinicians (obstetricians, infectious disease specialists, and pediatricians). The adverse

events were assessed and validated, and when required, clinicians were contacted for additional data and follow-up. Birth defects were classified according to European Registration of Congenital Anomalies Working Group definitions.[18] All safety data were further reviewed every 6 months by the data and safety monitoring board.

Virological Methods

Plasma HIV-1 RNA viral load was quantified using commercial tests, either reverse transcriptase polymerase chain reaction (RT-PCR; HIV Amplicor Monitor 1.5, Hoffmann LaRoche, Basel, Switzerland), with a cutoff value of 200 copies/mL, or branched DNA (bDNA; Quantiplex, Chiron Corp, Emeryville, Calif), with a cutoff value of 500 copies/mL, in laboratories within the ANRS quality control program.[19] To obtain comparable results with both techniques, bDNA values were adjusted by adding 0.35 $\log_{10}$ copies/mL to the values.[19] For the first 200 women enrolled, we retested all samples having less than 500 copies/mL of HIV-1 RNA in a single reference laboratory (Hôpital Necker, Paris) using the "ultrasensitive" procedure of the Amplicor tech-

nique (Hoffmann LaRoche, Basel), with a detection limit of 20 copies/mL.

Maternal plasma samples obtained at the 6-week postpartum visit from the first 200 women enrolled in the study were tested for resistance in the RT gene. Samples with less than 200 copies/mL of HIV-1 RNA were not tested because the methods do not usually allow for PCR amplification of HIV genes at very low viral levels. All selected samples ($\geq$200 HIV-1 RNA copies/mL) were tested with the line probe assay (LIPA) HIV-1 RT test (Murex-Innogenetics, Chatillon, France). The HIV RNA extraction, complementary DNA synthesis, and PCR with biotinylated primers were performed as described elsewhere.[20] Analyses of the wild-type RT gene or, if present, mutations at codons 41, 69, 70, 74, 184, and 215 were performed for each sample. Because of polymorphisms of the nucleotide sequence near the codons associated with resistance, LIPA provided incomplete results or no signal in some cases. These samples were tested by sequencing of the PCR products. Because we frequently found incomplete LIPA results for African viral strains, we decided to perform sequencing systematically for all samples from women born in sub-Saharan Africa. The PCR products were purified with the Qiaquick PCR purification kit (Quiagen Ltd, Courtaboeuf, France) and sequenced with the ABI Prism dye terminator cycle sequencing kit on a 373A automated sequencer. The sequences were aligned with sequence navigator software (Applied Biosystems, Warrington, England).

Assessment of HIV Infection in Children

The HIV DNA PCR was performed on peripheral blood mononuclear cells from samples taken at birth and at ages 1, 3, and 6 months. Primers located in at least 2 different genomic regions were used in all cases and a low positive control at 5 copies/mL of HIV DNA was included in each assay. Children were diagnosed as having HIV infection when 2 separate samples provided positive results and were considered uninfected when 2 samples provided negative results, 1 of which was obtained after 6 weeks of treatment. All HIV-infected children were followed up for at least 2 years and had seropositive status after age 18 months. Testing for antiretroviral resistance mutations in children was performed by sequencing the PCR products on the first seropositive sample.

Statistical Analysis

We chose a sample size of 460 mother-infant pairs to allow for detection of a difference in transmission rate from 6% in the historical control group (as estimated when the protocol was written) to 3% in the intervention group, with 80% power and an α level of .05. Proportions were compared by the χ^2 or Fisher exact tests (used when expected values were <5). When necessary, Geigy scientific tables were used to determine 95% confidence intervals (CIs). Quantitative variables were expressed as medians with ranges and compared using the nonparametric Wilcoxon test. When necessary, paired comparisons were made. We performed 2 logistic regression analyses, 1 to estimate the effects of each factor associated with the likelihood of acquiring virus with mutation and the other to estimate the independent effects of factors associated with maternal-infant HIV-1 transmission. In the latter analysis, we defined advanced maternal disease as being characterized by a CD4 cell count of less than 200×10^6/L or a percentage of less than 15% or a plasma HIV-1 RNA level of more than 3 $\log_{10}$ copies/mL. We entered into each model all variables found to be significantly associated with the outcome studied (P<.05) in univariate analyses. Analysis was performed with SAS 6.12 (SAS Institute Inc, Cary, NC).

RESULTS

A total of 445 women were enrolled in the study from February 1997 to September 1998. The study group constituted 53% of the 837 HIV-1–infected pregnant women enrolled in the French Perinatal Study in the same centers during the same period. Reasons for nonenrollment included late booking (29%), ongoing first-trimester therapy with antiretroviral drugs other than zidovudine (29%), biological contraindications (ie, involving hematologic or blood chemistry alterations; 4%), preterm delivery (<32 weeks' gestation; 3%), clinician's decision not to enroll patient (27%), and patient refusal of enrollment (8%). Therapies of the 392 women who were not enrolled in the intervention study were classified as follows: lamivudine-zidovudine (40%), other antiretroviral combinations (33%), no antiretroviral drug (7%), and unknown (3%); only 65 women (17%) received zidovudine monotherapy.

In the study group, median age (Table 1) was 30 years, 11% had a history of intravenous drug use, and 50% were born in sub-Saharan Africa. At enrollment, before receipt of lamivudine, the median plasma HIV-1 RNA level was 3.56 $\log_{10}$ copies/mL (range, <1.30-5.57 $\log_{10}$ copies/mL), and the median CD4 cell count was 426×10^6/L (range, 23-1440×10^6/L). Only 17 women (4%) had received lamivudine prior to the index pregnancy, and 111 women (25%) had received prior antiretroviral therapy, 41 for prophylaxis in a previous pregnancy and 70 for therapy. In women who received therapy at the beginning of the pregnancy, all antiretroviral drugs except zidovudine were stopped before 12 weeks' gestation. The route of delivery was vaginal in 63%, emergent cesarean in 15%, and elective cesarean (before labor and with membranes intact) in 22%. Only 2 women (0.5%) breastfed.

Zidovudine was started at a median of 23 weeks' gestation, administered for a median of 15 weeks (range, 1-38 weeks) during the pregnancy, and administered intravenously during delivery in 95% of women. Lamivudine was started at a median of 32 weeks' gestation, and the median duration of therapy from enrollment to delivery was 7 weeks (range, 0.1-15 weeks). Lamivudine and zidovudine were started simultaneously at 32 weeks' gestation in

28% of the women. At 6 weeks after delivery, 133 women (30%) were still receiving lamivudine-zidovudine, 1 woman's treatment status was unknown, 20 (5%) were receiving another antiretroviral combination, and 291 (65%) were not receiving therapy.

The 899 women in the zidovudine control group did not differ significantly from the study group in terms of CD4 cell counts or HIV-1 RNA levels at enrollment (Table 1). Among women in the study group, enrollment was at 32 weeks' gestation, but in the control group, enrollment was at delivery. Although the baseline points differed, the appropriateness of the comparison was justified because all women in the control group and three fourths of those in the study group were receiving zidovudine monotherapy at the time of sampling. Compared with the study group, the control group had a lower proportion of women born in Africa, a higher proportion with history of intravenous drug use, and a lower rate of elective cesarean delivery (16% vs 22%; P=.005). The gestational age at which zidovudine was started did not differ between the 2 groups.

Maternal-Infant HIV Transmission

A total of 452 children were born to the 445 women. After excluding 7 second twins, data on HIV infection status were available for 437 children, excluding 1 child whose mother had a history of HIV seropositivity but was later found to be HIV-negative, 1 child whose mother was infected with HIV-2, 1 stillborn child, and 5 who were lost to follow-up (all of whom had negative HIV test results by PCR at birth and at age 1 month). Seven (1.6%; 95% CI, 0.7%-3.3%) of the 437 children (TABLE 2) were diagnosed as having HIV infection. Three women who transmitted HIV had plasma HIV-1 RNA levels of less than 500 copies/mL at delivery. One had an elective cesarean delivery at 38 weeks (case 4), and the others had uneventful vaginal term deliveries. None of these women breastfed. The transmission rate was 1.10% (1/91) following elective cesarean delivery vs 1.75% (6/343) following other types of delivery. The difference was not statistically significant (P=.99 by the Fisher exact test). There was no difference in maternal plasma HIV-1 RNA levels between women who had an elective cesarean delivery or vaginal delivery (median, 2.4 $\log_{10}$ copies/mL for both groups; P=.91). The median duration of receipt of zidovudine during pregnancy did not differ significantly between infected and uninfected children (15 weeks [range, 5-36 weeks] vs 16 weeks [range, 1-40 weeks], respectively; P=.73), nor did the duration of receipt of lamivudine (5 weeks [range, 1-9 weeks] vs 7 weeks [range, 0.1-16 weeks], respectively; P=.14).

Among children born to the 899 women in the control group, infection status was available for 858, including only the first child for twin pairs and excluding 5 who were stillborn and 36 who were lost to follow-up. The maternal-infant transmission rate was 6.8% (58/858; 95% CI, 5.1%-8.7%), which was significantly higher than in the study group (P<.001). In the multivariable analysis, adjusting for mode of delivery, history of antiretroviral therapy, and ma-

Table 2. Maternal and Neonatal Characteristics of Cases of HIV-1 Transmission Despite Lamivudine-Zidovudine Therapy*

Characteristics	Cases						
	1	2	3	4	5	6	7
Maternal							
Prior antiretroviral therapy	Zidovudine	None	None	Zidovudine-didanosine	None	None	Lamivudine-zidovudine-indinavir
Prenatal zidovudine, d	102	71	37	255	37	143	151
Prenatal lamivudine, d	44	65	37	50	6	31	16
Prophylatic postnatal lamivudine-zidovudine, d	45	45	20	15	45	45	45
CD4 cell count at delivery, × 10⁶/L	459	297	396	528	331	629	110
Viral load at enrollment, HIV-1 RNA copies/mL	1097	278895	12005	3678	11937	60800	55000
Viral load at delivery, HIV-1 RNA copies/mL	150	572	229	276	21975	5482	9200
Mutations†	ND	M184V	M184V, M41	M184V, K70R	K70R	WT	M184V, K70R, T215Y/F
Neonatal							
Gestational age, wk	39	41	37	38	37	37	39
Birth weight, g	3500	3280	2530	2790	3120	3100	3700
Delivery mode	V	V	V	C	V	V	V
First HIV-1–positive test result	Birth	3 mo	Birth	3 mo	1 mo	3 mo	1 mo‡
Mutations†§	ND	ND	M184V, M41	WT	WT	WT	M184V, K70R

*HIV-1 indicates human immunodeficiency virus 1; V, vaginal; C, elective cesarean; and ND, not determined.
†Maternal samples were tested at 6 weeks postpartum. The M184V variant indicates resistance to lamivudine; M41, K7OR, and T215Y/F indicate resistance to zidovudine; and WT, wild type.
‡No sample was available at birth for this child.
§Mutations were assessed using the first seropositive sample.

Table 3. Multivariable Analysis of Risk Factors for Maternal-Infant HIV-1 Transmission*

Variables	Adjusted Odds Ratio (95% Confidence Interval)	P Value
Study group		
Lamivudine-zidovudine	0.22 (0.10-0.50)	<.001
Zidovudine (control)	Referent	
Mode of delivery		
Elective cesarean	0.30 (0.09-0.99)	.048
Other	Referent	
Advanced maternal HIV-1 disease†		
Yes	2.30 (1.25-4.22)	.007
No	Referent	
Prior antiretroviral use		
Yes	2.22 (1.15-4.28)	.02
No	Referent	

*Data were derived from multivariable regression analysis; each of the 4 analyses controlled for the other variables. HIV-1 indicates human immunodeficiency virus 1.
†Advanced disease defined as enrollment CD4 cell count $<200 \times 10^6$/L or $<15\%$ or HIV-1 RNA level $>3 \log_{10}$ copies/mL.

ternal HIV disease progression (defined as a CD4 cell count $<200 \times 10^6$/L or $<15\%$ or plasma HIV-1 RNA level $>3 \log_{10}$ copies/mL), the frequency of maternal-infant HIV-1 transmission in the study group was 5-fold lower than in the control group (TABLE 3).

Maternal Viral Load With Lamivudine-Zidovudine

Between enrollment and delivery, the median plasma HIV-1 RNA level decreased from $3.56 \log_{10}$ copies/mL (range, <1.30-$5.57 \log_{10}$ copies/mL) to $2.40 \log_{10}$ copies/mL (range, <1.30-$5.35 \log_{10}$ copies/mL; $P=.01$). The median decrease in paired samples (n=365) was $1.24 \log_{10}$ copies/mL (range, -1.63 to $3.40 \log_{10}$ copies/mL). The proportion with plasma HIV-1 RNA levels of less than 500 copies/mL increased from 23% at enrollment to 74% at delivery. Among samples retested using ultrasensitive RT-PCR, the proportion having less than 20 copies/mL increased from 3% (5/198) at enrollment to 20% (37/184) at delivery. At 6 weeks after delivery, the median viral load was $3.49 \log_{10}$ copies/mL (range, <1.30-$5.83 \log_{10}$ copies/mL). In the subgroup of the first 200 women for whom the ultrasensitive testing was made available (n=184 with samples available), the median HIV-1 RNA at 6 weeks after delivery was $3.50 \log_{10}$ copies/mL (range, <1.30-$5.83 \log_{10}$ copies/mL) vs $2.98 \log_{10}$ copies/mL (range, <1.30-$5.40 \log_{10}$ copies/

mL) in women subsequently enrolled (n=211; $P=.001$), indicating that there may have been some differences over time in the management of antiretroviral therapy after delivery; however, the viral load at enrollment did not differ between the 2 subgroups ($3.59 \log_{10}$ copies/mL [range, <1.30-5.57 copies/mL] vs $3.45 \log_{10}$ copies/mL [range, <1.30-$5.57 \log_{10}$ copies/mL]; $P=.11$).

Tolerance

Adverse Events in the Lamivudine-Zidovudine Group. One hundred twenty-four adverse events were reported in 99 women. Most of these events were related to documented pregnancy-related or postpartum complications. Two women discontinued study drugs because of elevation of transaminase levels to more than 5 times the ULN. Hemoglobin levels of less than 8 g/dL occurred in 29 women, half of whom had a known cause of anemia not related to study drugs. There were no cases of lactic acidosis. Thirty-eight adverse events were reported related to fetal well-being in 37 pregnancies, including 1 case of in utero death; the others were characterized by abnormal ultrasonographic findings or nonstress test results. In the case of the stillbirth, which occurred in a term infant with normal birth weight following an uneventful pregnancy, autopsy findings were negative, but because of maceration, no biochemical analyses could be performed.

For children in the study group, the mean (SD) duration of follow-up was 16 (4) months. Follow-up data were available after age 6 months for 96% of children and after age 12 months for 89%. The entire 6-week regimen of lamivudine-zidovudine was administered in 379 children. One was stillborn (as mentioned), 1 was withdrawn from the study by the mother at birth, 2 received no postnatal therapy, 4 received only zidovudine, and 65 discontinued lamivudine prematurely because of lack of compliance in 25 cases and adverse effects in 40 cases (9% of all children). Adverse effects leading to treatment discontinuation included hematologic disorders (30 cases), biochemical abnormalities (9 cases), and vomiting (1 case). Among the 65 children in whom treatment was prematurely discontinued, both lamivudine and zidovudine were stopped in 57, and in 8, lamivudine was stopped but zidovudine was continued.

A total of 397 adverse events, 180 biological (ie, involving hematologic or blood chemistry alterations) and 217 clinical in nature, were reported among 238 of the 452 children in the lamivudine-zidovudine cohort. Altogether, 151 hematologic adverse events, defined as moderate to severe according to the age-adjusted ACTG classification,[17] occurred during exposure to study drugs. These mostly consisted of neutropenia (81 cases) or anemia (68 cases), leading to blood transfusion because of clinical symptoms in 9 infants (5 had mild symptoms [pallor or tachycardia] and 4 had severe symptoms [cardiac insufficiency or dyspnea]) and to premature treatment discontinuation for 19 children. Of the children with hematologic toxic effects during receipt of lamivudine-zidovudine, none had persistent serious anemia at the last follow-up, and only 1 had persistent moderate neutropenia at age 6 months. Liver abnormalities without proven cause were recorded in 6 children (1 case of severe jaundice and 5 of alanine aminotransferase elevations >2.5 times the ULN); only 1 was persistent (3 times the ULN) at age 18 months. Six chil-

dren had asymptomatic elevations of serum lipase levels to more than 2.5 times the ULN. One of these children had a persistent lipase elevation (3 times the ULN) after age 1 year and was diagnosed with mitochondrial dysfunction, as previously reported.[21]

Of the 217 clinical adverse events reported among children, most were due to a known cause unrelated to study drugs (ie, perinatal complications, [53 cases, principally intrapartum asphyxia, withdrawal syndromes, and maternal-fetal bacterial infections], hospitalization for infectious disease [117 cases], or various other reasons [15 cases]). Sixteen children (4%) had major birth defects, including 4 cardiac malformation cases, 4 cases of polydactyly, 3 talipes cases, and 1 case each of congenital diaphragmatic hernia, hydronephrosis, imperforate anus, genu recurvatum with a suburethral cyst, and hypospadia. One child each had Down syndrome, Ito nevus, and sickle cell anemia. The prevalence of major birth defects was of the order expected in children not exposed to antiretroviral drugs, which ranges from 2% to 5%[22] in most registries and was 2.7% among liveborn children in Paris[23] during a 10-year period.

Neurologic signs/symptoms were reported in 12 children who did not have HIV infection and had no other known infectious or genetic disease. Six had febrile seizures without other symptoms. Two children with neurologic complications were diagnosed as having mitochondrial dysfunction and died at age 1 year, as previously discussed.[21] No other children died during follow-up. Two children had hydrocephalus, 1 of whom had severe neurodevelopmental delay; 1 had severe behavioral problems and cognitive delay; and 1 had Guillain-Barré syndrome. These 12 children all also were reported as having adverse events involving hematologic or blood chemistry alterations during the first 6 weeks. Another 2 children had unexplained failure to thrive. Follow-up of these children is ongoing. The prevalence of mitochondrial cytopathies in the general population has recently been estimated

Table 4. Neonatal and Selected Follow-up Characteristics of Children*

Characteristics	Lamivudine-Zidovudine Study Cohort (n = 452)	Zidovudine Control Cohort† (n = 910)	P Value
Stillbirths, %	0.2	0.5	.67
Birth weight, median (range), g	3110 (1470-4930)	3100 (700-4770)	.83
Length, median (range), cm	49 (41-55)	49 (35-57)	.73
Head circumference, median (range), cm	34 (27-39)	34 (22-40)	.15
Small for gestational age, %‡	17	17	.93
Gestational age, median (range), wk	39 (32-42)	39 (26-44)	.44
Premature (<37 wk), %	6	9	.08
Withdrawal syndrome, %	2	3	.60
Major birth defects, %	4	2	.26
Hemoglobin level, mean (SD), g/dL			
At birth	15.0 (2.2)	15.5 (2.5)	.004
At 1 mo	9.8 (1.4)	10.3 (1.6)	<.001
Neutrophil count, mean (SD), $\times 10^6$/L			
At birth	4392 (2473)	5813 (3850)	<.001
At 1 mo	2089 (1290)	2200 (1283)	.19
Human immunodeficiency virus 1 transmission, % (95% confidence interval)	1.6 (0.7-3.3)§	6.8 (5.1-8.7)	<.001

*There were 7 twin pairs in the study group and 11 twin pairs in the control group. For neonatal characteristics, the number of missing values for variables ranged from 8 to 47. For hematologic characteristics, missing values ranged from 55 to 95.
†Enrollment occurred between May 1994 and February 1997.
‡Small for gestational age was defined as <10th percentile.
§HIV infection status was determined for 437 children in the study group and 858 children in the control group.

as being about 60 in 100 000 in a large 7-year study in Finland.[24]

Comparison With the Control Group for Tolerance Outcomes. Rate of pregnancy complications did not differ between the 2 cohorts (M.-J. M., unpublished data). Birth characteristics of the children in the study group did not differ significantly from those of the control group with the exceptions noted below (**TABLE 4**). The proportion of infants requiring blood transfusion did not differ significantly between the groups (3% vs 2%, respectively). Frequency of moderate-to-severe anemia did not differ significantly between groups at birth (hemoglobin level <12 g/dL, 9% vs 7%, respectively; P=.21) or at age 1 month (hemoglobin level <8 g/dL, 4% vs 6%, respectively; P=.19). Similarly, frequency of moderate-to-severe neutropenia did not differ significantly at birth (neutrophil count <1250 $\times 10^6$/L on day 4, 2% vs 1%, respectively; P=.62) or at age 1 month (neutrophil count <900 $\times 10^6$/L, 6% vs 6%, respectively; P=.88). However, the mean (SD) hemoglobin level was significantly lower in the study group than

in the control group at birth (15.0 [2.2] g/dL vs 15.5 [2.5] g/dL; P=.004) and at age 1 month (9.8 [1.4] g/dL vs 10.3 [1.6] g/dL; P<.001). The mean (SD) neutrophil count was significantly lower in the study group than in the control group at birth, but not at age 1 month (Table 4).

Acquisition of Drug Resistance Genotypes

Genotyping was planned for the first 200 women enrolled in the study group. Samples obtained 6 weeks after delivery were selected for 137 women, of which 5 could not be tested because amplification was unsuccessful. Samples were not available for 36 and were not tested for 27 because the HIV-1 RNA level was less than 200 copies/mL. Of the 132 plasma samples amplified, zidovudine-resistant T215Y/F mutant quasispecies were detected in 9 (7%), M41L mutations in 9 (7%), and K70R mutations in 14 (11%). Lamivudine-resistant M184V mutations were detected in 52 (39%); these were predominant in 30 and associated with wild-type virus in 22 samples. If it is as-

Figure. Acquisition of the M184V Mutation in Women at 6 Weeks After Delivery by Plasma HIV-1 RNA Level at Enrollment and Duration of Lamivudine Treatment
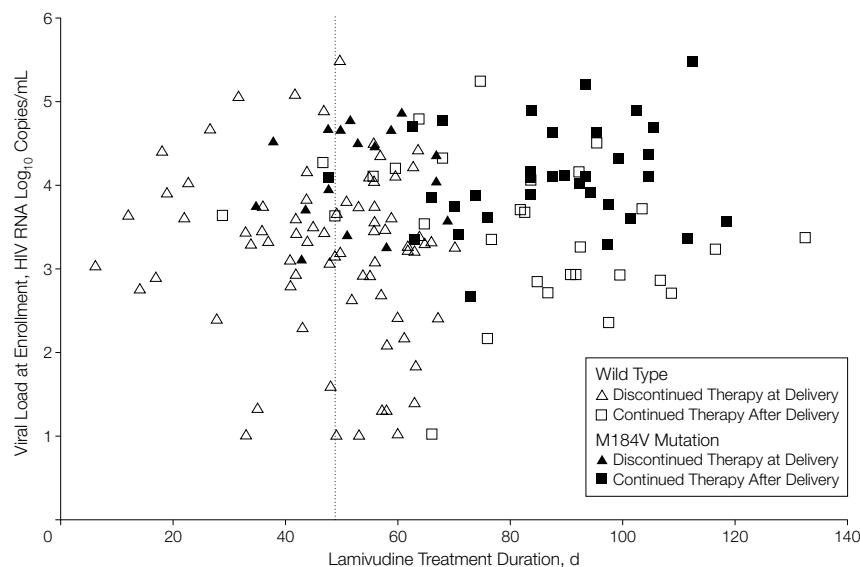
HIV-1 indicates human immunodeficiency virus 1. The vertical dotted line represents the median duration of lamivudine therapy from enrollment through delivery (49 days).

sumed that women with HIV-1 RNA levels of less than 200 copies/mL did not have the M184V variant, the proportion having lamivudine resistance would be 33% (52/159). Among women with M184V variants, 46 were also tested before initiation of lamivudine; 43 samples were amplifiable and only 1 (2%) already had an M184V variant. Compared with women who did not have the mutation (as defined above; n=107), the median CD4 cell count at enrollment in those with the mutation (n=52) was lower (292 vs 473×10^6/L, respectively; $P<.001$) and the HIV-1 RNA level was higher (4.1 vs 3.4 $\log_{10}$ copies/mL, respectively; $P<.001$). The median duration of receipt of lamivudine was longer for those who had the mutation, which was identified in 50% (37/74) of women who received lamivudine for more than 2 months, 20% (14/70) of those receiving it for 1 to 2 months, and none of the 12 women receiving it for less than 1 month ($P=.001$). The duration of therapy was not recorded in 3 women, including 1 with the mutation. The proportion who were antiretroviral-experienced prior to

the pregnancy was higher among women with the mutation than in those with wild-type virus (40.4% vs 13.2%, respectively; $P<.01$); however, few women (n=17) had ever received lamivudine previously. The proportion of African women did not differ significantly between those with M184V and those with wild-type virus (42% vs 51%; $P=.31$). In a multivariable model, the likelihood of having the M184V variant was not significantly associated with use of antiretroviral drugs prior to pregnancy (odds ratio [OR], 1.78; 95% CI, 0.67-4.74; $P=.25$) and was significantly associated with CD4 cell count (OR, 0.70 for each increment of 100×10^6/L CD4 cells; 95% CI, 0.53-0.93; $P=.01$), HIV-1 RNA level at enrollment (OR, 2.67 for each increment of 1 $\log_{10}$ copies/mL; 95% CI, 1.40-5.11; $P=.003$), and duration of receipt of lamivudine (OR, 3.10 for each increment of 30 days; 95% CI, 1.73-5.58; $P<.001$). The distribution of lamivudine resistance according to HIV-1 RNA level and duration of receipt of lamivudine is represented in the **FIGURE**. There was a trend toward a higher

transmission rate when the M184V mutation was present than when it was absent, but it did not reach statistical significance (7.7% vs 1.9%, respectively; $P=.09$). The overall transmission rate was higher in this subset of women who had samples tested for the M184V mutation than in the overall population.

COMMENT

The frequency of maternal-infant transmission observed with use of lamivudine-zidovudine was 1.6%, which, to our knowledge, is the lowest rate reported to date in a large prospective study. In comparison, the frequency of transmission rate with zidovudine monotherapy in the French Perinatal Study during the period when it was the standard of care was 6.8%. The comparison must be interpreted with caution because ours was not a randomized trial. Nonetheless, well-conducted observational studies have been shown to provide valid information.[25,26] In perinatal HIV cohort studies, zidovudine was associated with a two-thirds decrease in frequency of maternal-infant transmission compared with no therapy,[2,3] which is similar to that observed in the randomized, placebo-controlled ACTG 076 trial.[1] Elective cesarean delivery was associated with a similar decrease in transmission vs other types of delivery in large observational studies[27,28] and in a randomized trial.[29] There were obvious differences to be considered between our lamivudine-zidovudine and zidovudine-only groups, and it is possible that we may not have accounted for all of the temporal changes in management between the 2 groups. However, most of the characteristics in which differences occurred are not related to the risk of maternal-infant transmission, such as history of intravenous drug use or geographic origin.[15] Two of the major determinants of transmission risk, maternal CD4 cell count and plasma HIV-1 RNA level at enrollment,[30,31] did not differ between the 2 groups. However, in the lamivudine-zidovudine group, a higher proportion of women had elective cesarean delivery, which is known to be protective. Nonetheless, in a multivariable analysis accounting for

mode of delivery as well as maternal disease stage and prior antiretroviral experience, the adjusted OR of transmission was 5-fold lower in the lamivudine-zidovudine group than in the zidovudine group. Due to the small number of infected children, we were unable to assess the effect of elective cesarean delivery vs vaginal delivery. The apparent benefit of lamivudine-zidovudine may be related, at least in part, to its ability to decrease maternal plasma HIV-1 RNA levels by more than 1 $\log_{10}$ copies/mL compared with zidovudine alone.[32] On the other hand, our findings also show that transmission can occur even at low HIV-1 RNA levels.

The potential risks of drug toxicity are of particular concern for the majority of children who do not have HIV infection. A large body of data now exists involving children exposed to perinatal zidovudine monotherapy, most of which, having several years of follow-up, is reassuring,[33] although there have been case reports of lactic acidosis[34] and mitochondrial dysfunction.[21] The hematologic toxicity of zidovudine was demonstrated in the ACTG 076 trial, in which the incidence of anemia was significantly higher in infants exposed to zidovudine than placebo.[1] Protocol definitions (ACTG)[17] for anemia were a hemoglobin level of less than or equal to 14 g/dL at birth (age 1-7 days) and less than or equal to 10.5 g/dL at age 1 month. These values correspond to 2 SDs lower than normal reference values for term neonates (ie, 2.5% of a healthy population). In the analysis, we considered only moderate-to-severe anemia (grade 3 or 4, defined as a hemoglobin level <12 g/dL at birth and <8 g/dL at age 1 month). By definition, the expected frequency in a healthy population of term neonates would be less than 0.1%. However, because this is a population with various risk factors for anemia, the incidence may best be compared with that actually observed in the French Perinatal Study prior to use of zidovudine (before 1994). In 1230 children born to HIV-infected women during 1987-1994 and not exposed to antiretrovi-

ral therapy, the frequency of moderate-to-severe anemia was 3% at birth and 1% at age 1 month (M.-J. M., unpublished data). The difference between this cohort and the 2 treatment cohorts is statistically significant (P = .04). Concentrations in the zidovudine group were in the same range as in the ACTG 076 trial, in which the median hemoglobin concentration in the zidovudine group was 16.0 g/dL (range, 10.3-25.4 g/dL) at birth and 10.0 g/dL (range, 6.7-16.9 g/dL) at age 6 weeks.[1,35]

No data exist on the perinatal safety of lamivudine alone, as it is used in combination with other antiretroviral agents, and, until now, only preliminary data on the lamivudine-zidovudine combination were available. A study of 33 children exposed to lamivudine-zidovudine in utero reported anemia and mild elevations of liver enzyme levels in more than half of the children.[10] There have also been case reports of metabolic acidosis in pregnant women[36] and in infants.[9] In the present study, the occurrence of anemia and neutropenia was frequent and severe in a few cases, but these conditions usually resolved after discontinuation of antiretroviral drugs. Hemoglobin level and neutrophil count at birth were lower in children exposed to lamivudine-zidovudine than in the historical control group exposed to zidovudine alone, but the frequency of moderate-to-severe anemia or neutropenia did not differ significantly between the groups. Comparing tolerance outcomes between groups in a nonrandomized study is a difficult challenge. Our study has the strength of combining the methods of both a large clinical tolerance study with systematic review of adverse events and an ongoing observational cohort study. Mitochondrial dysfunction was diagnosed in 2 children who had fatal neurologic disorders and in a third child with a persistently elevated lipase level. The possible relation between these cases and exposure to the study drugs remains controversial, as previously discussed elsewhere.[21,37] It must be stressed that most of these events could not be identified at birth and were detected only through

an organized, systematic clinical and biological follow-up of children.

Another potential drawback to use of the lamivudine-zidovudine combination is the selection of virus with the lamivudine-resistant M184V mutation, which was estimated to occur in one third of the women in our study. Before the study began, it was known that this mutation is frequently selected in up to 80% to 90% of patients with more advanced HIV infection treated with lamivudine-zidovudine,[6] and this was recently reported in a study of 5 women treated during pregnancy.[38] Presence of the M184V variant may compromise the future efficacy of lamivudine. This issue should be taken into account, although the implication for the patients' future long-term therapy is a topic [39] that was not addressed by our study. In our study, selection of virus with the M184V variant occurred more frequently in women with high plasma HIV-1 RNA levels, low CD4 cell counts, or both, who, according to current guidelines,[4,5] would be offered highly active antiretroviral therapy to maintain their own health. The proportion of lamivudine-resistant virus also increased with the duration of treatment. Thus, lamivudine-zidovudine for prevention of vertical transmission should be started late in pregnancy and stopped promptly after delivery. Recently, the issue of selecting antiretroviral resistance has also been raised regarding use of chemo-prophylaxis with single-dose nevirapine.[40] In a study of 96 women receiving zidovudine monotherapy in the ACTG 076 trial, there was no acquisition of high-level resistance,[41] and only 7% of the women receiving lamivudine-zidovudine in our study had zidovudine-resistant mutations at 6 weeks after delivery. In addition to being a cause for concern regarding mothers' future therapy, development of drug resistance carries the risk of transmitting drug-resistant virus to children[42,43]; in our study, 2 children were infected with lamivudine-resistant variants.

The implications of our findings for prevention of maternal-infant HIV trans-

mission are not clear. Adding lamivudine to standard zidovudine prophylaxis in the third trimester may be a means to further reduce risk of infection. However, the precise relationship between incremental benefit and incremental risk remain to be determined, and compared with those of alternative prevention strategies. The combination of zidovudine and elective cesarean delivery, which is associated with a risk of transmission of about 1% to 2%,[27-29] is widely used in clinical practice and is the first-line recommendation in Europe.[5,44] For women who require antiretroviral treatment to maintain their own health, more aggressive therapies are now recommended in Europe and North America.[4,5] Although these combinations often include zidovudine and lamivudine, as well as a protease inhibitor or nonnucleoside reverse transcriptase inhibitor, the issues are different from those raised when antiretroviral drugs are used solely to prevent transmission. The increasing use of combination antiretroviral therapies as prophylaxis or as maternal therapy underscores the need for further clinical, animal, and laboratory studies to determine safety in the perinatal period.

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