ORIGINAL ARTICLE

Antiretroviral Regimens in Pregnancy and Breast-Feeding in Botswana

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ABSTRACT

BACKGROUND

The most effective highly active antiretroviral therapy (HAART) to prevent mother-to-child transmission of human immunodeficiency virus type 1 (HIV-1) in pregnancy and its efficacy during breast-feeding are unknown.

METHODS

We randomly assigned 560 HIV-1–infected pregnant women (CD4+ count, ≥200 cells per cubic millimeter) to receive coformulated abacavir, zidovudine, and lamivudine (the nucleoside reverse-transcriptase inhibitor [NRTI] group) or lopinavir–ritonavir plus zidovudine–lamivudine (the protease-inhibitor group) from 26 to 34 weeks' gestation through planned weaning by 6 months post partum. A total of 170 women with CD4+ counts of less than 200 cells per cubic millimeter received nevirapine plus zidovudine–lamivudine (the observational group). Infants received single-dose nevirapine and 4 weeks of zidovudine.

RESULTS

The rate of virologic suppression to less than 400 copies per milliliter was high and did not differ significantly among the three groups at delivery (96% in the NRTI group, 93% in the protease-inhibitor group, and 94% in the observational group) or throughout the breast-feeding period (92% in the NRTI group, 93% in the protease-inhibitor group, and 95% in the observational group). By 6 months of age, 8 of 709 live-born infants (1.1%) were infected (95% confidence interval [CI], 0.5 to 2.2): 6 were infected in utero (4 in the NRTI group, 1 in the protease-inhibitor group, and 1 in the observational group), and 2 were infected during the breast-feeding period (in the NRTI group). Treatment-limiting adverse events occurred in 2% of women in the NRTI group, 2% of women in the protease-inhibitor group, and 11% of women in the observational group.

CONCLUSIONS

All regimens of HAART from pregnancy through 6 months post partum resulted in high rates of virologic suppression, with an overall rate of mother-to-child transmission of 1.1%. (ClinicalTrials.gov number, NCT00270296.)

HIGHLY ACTIVE ANTIRETROVIRAL THERapy (HAART) used to prevent in utero and intrapartum mother-to-child transmission of human immunodeficiency virus type 1 (HIV-1) is among the most successful public health interventions of the HIV era.[1,2] However, the use of HAART in mothers to prevent mother-to-child transmission through breast-feeding in areas of the world where replacement feeding is neither safe nor feasible remains an unproven strategy.[1,3] We compared different HAART regimens used in pregnancy and during breast-feeding to determine whether the regimens differ with respect to virologic suppression during pregnancy and breast-feeding, pregnancy outcomes, and toxic effects in mothers and infants.

METHODS

TRIAL DESIGN

Between July 2006 and May 2008, we enrolled pregnant women with HIV-1 infection in the Mma Bana Study (meaning "mother of the baby" in Setswana) in southern Botswana. Women with CD4+ cell counts of 200 or more were randomly assigned (in permuted blocks stratified according to clinical site) to receive either 300 mg of abacavir, 300 mg of zidovudine, and 150 mg of lamivudine coformulated as Trizivir (GlaxoSmithKline) twice daily (the NRTI group) or 400 mg of lopinavir and 100 mg of ritonavir coformulated as Kaletra (Abbott) with 300 mg of zidovudine and 150 mg of lamivudine coformulated as Combivir (GlaxoSmithKline) twice daily (the protease-inhibitor group). Women with CD4+ cell counts of less than 200 cells per cubic millimeter or with an acquired immunodeficiency syndrome (AIDS)–defining illness received standard-of-care treatment for Botswana: 200 mg of nevirapine, 300 mg of zidovudine, and 150 mg of lamivudine twice daily (after a 2-week lead-in period of once-daily nevirapine at a dose of 200 mg) (the observational group). Women in the randomized groups began to receive HAART between 26 and 34 weeks' gestation and continued it through weaning or 6 months post partum (whichever occurred first), and women in the observational group began to receive HAART between 18 and 34 weeks' gestation and continued treatment indefinitely. We report results for the primary end points at 6 months post partum.

Infants received single-dose nevirapine (6 mg) at birth and received zidovudine (4 mg per kilo-gram of body weight twice daily) from birth through 4 weeks. Women were counseled to exclusively breast-feed and to complete weaning 3 days before the 6-month study visit. Infants were provided free formula and foods from the time of weaning (whenever it occurred) through 12 months.

Study drugs were provided by GlaxoSmithKline (Trizivir and Combivir) and Abbott Pharmaceuticals (Kaletra), but these companies had no other role in the design of the study, the accrual or analysis of the data, the preparation of the manuscript, or the decision to submit the manuscript for publication. The Botswana government provided nevirapine, Combivir, additional medications, and some laboratory testing. The Health Research Development Committee of Botswana and the Human Subjects Committee of the Harvard School of Public Health approved the study protocol and amendments. An independent data and safety monitoring board reviewed safety and efficacy data approximately every 6 months. The full study protocol including the statistical-analysis plan, is available with the full text of this article at NEJM.org. All authors vouch for the completeness and veracity of the reported data and analyses and attest that the study as reported conforms with the protocol.

STUDY POPULATION AND MONITORING

Pregnant women with HIV-1 infection were referred to study locations in Gaborone, Lobatse, Molepolole, and Mochudi. Eligibility criteria were a pregnancy of 26 to 34 weeks' gestation (for the randomized groups) or 18 to 34 weeks' gestation (for the observational group), HIV-1 infection confirmed by two blood samples that were positive on enzyme-linked immunosorbent assay (ELISA), an age of 18 years or older, a hemoglobin level of 8.0 g per deciliter or higher, an absolute neutrophil count of 1000 cells per cubic millimeter or more, and alanine aminotransferase and aspartate aminotransferase levels that were no more than 2.5 times the upper limit of the normal range. Women who preferred to feed their infants exclusively with formula from birth were excluded. Participants provided written informed consent that was approved by the ethical review boards.

Women were evaluated before the initiation of HAART and monthly through 6 months post partum. Gestational age was assessed according to the last menstrual period and by means of ultrasonographic findings. Adherence to the HAART

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regimen was assessed on the basis of self-report, as well as pill counts. Laboratory monitoring (complete blood count with a differential count and measurements of electrolytes, blood urea nitrogen, creatinine, alanine aminotransferase, aspartate aminotransferase, total bilirubin, lipase, amylase, and glucose) was performed at enrollment and 1 month later, at delivery, and at 3 and 6 months post partum. Alanine aminotransferase, aspartate aminotransferase, and total bilibubin levels were checked 2 weeks and 2 months after the initiation of nevirapine therapy. The plasma HIV-1 RNA level and CD4+ cell counts were determined at baseline, at delivery, and at 1 month (RNA only), 3 months, and 6 months post partum; additional RNA testing was performed if HAART was discontinued before 6 months post partum. HIV-1 RNA testing was monitored by the Virology Quality Assessment Program of the National Institute of Allergy and Infectious Diseases, Division of AIDS. HIV-1 RNA was quantified by the automated Cobas Amplicor and Ampli Prep HIV-1 Monitor Test (version 1.5, Roche Molecular Systems) with the use of standard testing at baseline (range of limit of detection, 400 to 750,000 copies per milliliter) and ultrasensitive testing for subsequent samples (range of limit of detection 50 to 100,000 copies per milliliter). Breast-milk supernatant (spun at 800×g for 15 minutes) from women with late breast-feeding transmission of HIV-1 was evaluated for HIV-1 RNA by automated ultrasensitive testing. Retrospective HLA-B*5701 testing was performed in 418 women with available samples.

Infant evaluations were scheduled at birth and monthly through 6 months. Prematurity was defined as a gestation of less than 37 weeks, and low birth weight as a weight of less than 2500 g. Peripheral blood was obtained at birth and 1 month, 3 months, and 6 months for a complete blood count with a differential count. Laboratory values (levels of electrolytes, blood urea nitrogen, creatinine, glucose, alanine aminotransferase, aspartate aminotransferase, and total bilirubin) were checked at birth, if clinically indicated, and routinely at 1 month, 3 months, and 6 months. HIV-1 testing by means of a qualitative polymerase-chain-reaction (PCR) DNA assay was performed (Amplicor HIV-1, Roche Diagnostic Systems) in samples obtained at birth, 1 month, and 6 months. Additional PCR testing was per-

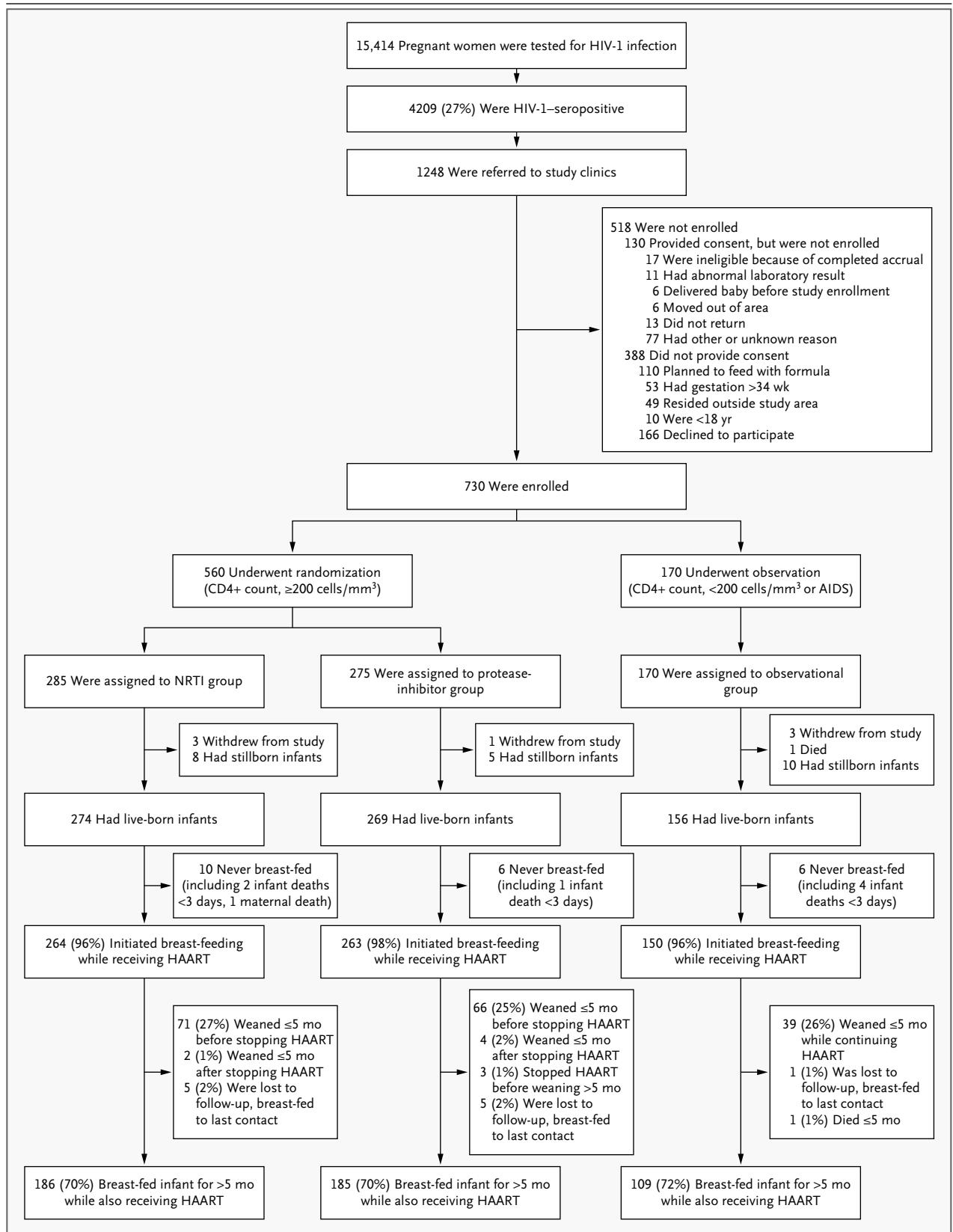**Figure 1 (facing page). Enrollment and Follow-up of Study Participants.**

Women assigned to the nucleoside reverse-transcriptase inhibitor (NRTI) group received coformulated abacavir, zidovudine, and lamivudine. Women assigned to the protease-inhibitor group received lopinavir–ritonavir plus zidovudine–lamivudine. Women assigned to the observational group received nevirapine plus zidovudine–lamivudine. In the observational group, one woman who delivered a live-born twin and a stillborn twin was included in the live-born category. HAART denotes highly active antiretroviral therapy, and HIV-1 human immunodeficiency virus type 1.

formed with stored samples obtained at 3 months, if the results at 6 months were positive, and, if possible, with samples obtained at the time of death for infants who died.

PRESPECIFIED STUDY OBJECTIVES AND DEFINITIONS

The primary study objective was to compare the NRTI and protease-inhibitor groups with respect to the percentages of women with a plasma HIV-1 RNA level of less than 400 copies per milliliter first at delivery and then throughout the breast-feeding period, as determined at 1 month, 3 months, and 6 months post partum or at all visits before weaning and at the time of discontinuation of HAART. The size of the randomized sample provided 80% power to detect an increase in the rate of virologic suppression during the breast-feeding period from 75% to 85% with the use of a two-sided type I error rate of 0.05, allowing for 4% loss to follow-up. An additional primary study objective was to determine the rate of mother-to-child transmission, with the 95% confidence interval, among all infants (including those in the observational group). The study was not powered to compare the rates of mother-to-child transmission between the randomized groups.

In utero transmission was defined as a confirmed positive HIV-1 PCR assay of DNA from a blood sample obtained from infants less than 4 days after birth. Both intrapartum transmission and early breast-feeding transmission were defined as a negative result at birth and a first confirmed positive test at 1 month. Late breast-feeding transmission was defined as a negative test at 1 month and a first confirmed positive test thereafter. Death from an AIDS-defining illness sufficed to confirm a single positive PCR result.

15,414 Pregnant women were tested for HIV-1 infection

↓

4209 (27%) Were HIV-1–seropositive

↓

1248 Were referred to study clinics

↓

518 Were not enrolled
  130 Provided consent, but were not enrolled
    17 Were ineligible because of completed accrual
    11 Had abnormal laboratory result
     6 Delivered baby before study enrollment
     6 Moved out of area
    13 Did not return
    77 Had other or unknown reason
  388 Did not provide consent
    110 Planned to feed with formula
    53 Had gestation >34 wk
    49 Resided outside study area
    10 Were <18 yr
   166 Declined to participate

↓

730 Were enrolled

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560 Underwent randomization
(CD4+ count, ≥200 cells/mm³)

170 Underwent observation
(CD4+ count, <200 cells/mm³ or AIDS)

285 Were assigned to NRTI group

275 Were assigned to protease-inhibitor group

170 Were assigned to observational group

3 Withdrew from study
8 Had stillborn infants

1 Withdrew from study
5 Had stillborn infants

3 Withdrew from study
1 Died
10 Had stillborn infants

274 Had live-born infants

269 Had live-born infants

156 Had live-born infants

10 Never breast-fed
(including 2 infant deaths <3 days, 1 maternal death)

6 Never breast-fed
(including 1 infant death <3 days)

6 Never breast-fed
(including 4 infant deaths <3 days)

264 (96%) Initiated breast-feeding while receiving HAART

263 (98%) Initiated breast-feeding while receiving HAART

150 (96%) Initiated breast-feeding while receiving HAART

71 (27%) Weaned ≤5 mo before stopping HAART
2 (1%) Weaned ≤5 mo after stopping HAART
5 (2%) Were lost to follow-up, breast-fed to last contact

66 (25%) Weaned ≤5 mo before stopping HAART
4 (2%) Weaned ≤5 mo after stopping HAART
3 (1%) Stopped HAART before weaning >5 mo
5 (2%) Were lost to follow-up, breast-fed to last contact

39 (26%) Weaned ≤5 mo while continuing HAART
1 (1%) Was lost to follow-up, breast-fed to last contact
1 (1%) Died ≤5 mo

186 (70%) Breast-fed infant for >5 mo while also receiving HAART

185 (70%) Breast-fed infant for >5 mo while also receiving HAART

109 (72%) Breast-fed infant for >5 mo while also receiving HAART

STATISTICAL ANALYSIS

The predefined primary analyses of virologic suppression were based on observed measurements, but sensitivity analyses in which missing measurements at delivery or during breast-feeding were classified as nonsuppression were similar to the results of the primary analyses. Exact 95% confidence intervals based on the binomial distribution were used to compare events and to evaluate mother-to-child transmission. Logistic regression, adjusted for randomized treatment assignments, was used to identify potential predictors of a lack of suppression at delivery.

RESULTS

STUDY ENROLLMENT

Of 15,414 pregnant women screened for HIV-1 infection by government-run antenatal clinics during the study period, 4209 (27%) had HIV-1 infec-

Table 1. Characteristics of the Patients.*

Characteristic	Observational Group	NRTI Group	Protease-Inhibitor Group
Mothers at enrollment			
Study site — no./total no. (%)			
City of Gaborone	58/170 (34)	99/285 (35)	98/275 (36)
Village of Molepolole	39/170 (23)	83/285 (29)	81/275 (29)
Village of Mochudi	42/170 (25)	50/285 (18)	44/275 (16)
Town of Lobatse	31/170 (18)	53/285 (19)	52/275 (19)
Median age at enrollment — yr	29	26	25
Education — no./total no. (%)			
None or primary	41/170 (24)	57/285 (20)	57/275 (21)
Secondary	126/170 (74)	211/285 (74)	208/275 (76)
University	3/170 (2)	17/285 (6)	10/275 (4)
Personal monthly income, in U.S. $ — no./total no. (%)			
None	75/170 (44)	146/285 (51)	146/275 (53)
<$100	42/170 (25)	66/285 (23)	62/275 (23)
$101–$200	31/170 (18)	34/285 (12)	38/275 (14)
>$200	22/170 (13)	38/285 (13)	29/275 (11)
Electricity in the home — no./total no. (%)	69/170 (41)	94/285 (33)	98/275 (36)
Gestational age at enrollment — wk			
Median	26.1	27.1	27.1
Interquartile range	22.6–28.4	26.4–29.9	26.4–29.9
Median hemoglobin level — g/dl	10.4	10.8	10.7
Positive hepatitis B status — no./total no. (%)	5/170 (3)	16/285 (6)	8/275 (3)
CD4+ count — cells/mm³			
Median	147	393	403
Interquartile range	115–183	305–514	297–514
HIV-1 RNA — copies/ml			
Median	51,700	13,300	9,100
Interquartile range	14,400–179,000	2340–50,900	2210–39,900
HIV-1 RNA level — no./total no. (%)			
≥100,000 copies/ml	63/170 (37)	44/285 (15)	36/275 (13)
<1000 copies/ml	10/170 (6)	42/285 (15)	47/275 (17)

Characteristic	Observational Group	NRTI Group	Protease-Inhibitor Group
Table 1. (Continued.)			
Live-born infants at birth			
Gestational age — wk†			
Median	39.4	39.3	39.0
Interquartile range	38.4–40.3	37.9–40.3	37.4–40.0
Premature (<37 wk of gestation) — no./total no. (%)	16/156 (10)	42/283 (15)	61/270 (23)
Very premature (<32 wk of gestation) — no./total no. (%)	2/156 (1)	4/283 (1)	8/270 (3)
Birth weight — kg			
Median	2.9	3.0	2.9
Interquartile range	2.6–3.2	2.7–3.3	2.6–3.2
Low birth weight (<2.5 kg) — no./total no. (%)	23/156 (15)	37/283 (13)	45/270 (17)
Very low birth weight (<1.5 kg) — no./total no. (%)	3/156 (2)	4/283 (1)	1/270 (<1)
Medication received			
Single-dose nevirapine — no./total no. (%)	155/156 (99)	280/283 (99)	268/270 (99)
Zidovudine — no. (%)	155/156 (99)	282/283 (100)	269/270 (100)
Congenital abnormality — no./total no. (%)‡	5/156 (3)	5/283 (2)	5/270 (2)
HIV-1 DNA PCR status known — no./total no. (%)	154/156 (99)	282/283 (100)	270/270 (100)

* HIV denotes human immunodeficiency virus, and PCR polymerase chain reaction.
† Gestational age was determined at first contact according to the date of the last reported menstrual period (LMP) and confirmed by means of ultrasonographic findings. If the ultrasonographic findings were inconsistent with the gestational age determined according to the LMP by 1 week or more in the first trimester, 2 weeks or more in the second trimester, or 3 weeks or more in the third trimester, gestational age was determined according to the results of the first ultrasonographic examination.
‡ Congenital abnormalities included polydactyly (in six infants), undescended testis (in seven infants), dextrocardia (in one infant), and hydrocephalus (in one infant); all were determined to be "not related" or "probably not related" to study drugs.

tion, 1248 were referred to a study site, and 730 were enrolled. Of the women who were enrolled in the study, 560 were randomly assigned to a treatment group (285 to the NRTI group and 275 to the protease-inhibitor group), and 170 were followed observationally (Fig. 1). Maternal baseline characteristics were balanced among the groups (Table 1). The median duration of HAART before delivery was 11 weeks in the randomized groups and 13 weeks in the observational group.

FOLLOW-UP AND ADHERENCE TO PROTOCOL

Before delivery, seven women left the study (three in the NRTI group, one in the protease-inhibitor group, and three in the observational group), and one died (in the observational group). After delivery, 26 women left the study before 6 months (12 in the NRTI group, 12 in the protease-inhibitor group, and 2 in the observational group), and 3 died (1 in the NRTI group and 2 in the obser-

vational group). Thus, 95% of the women were followed from enrollment to 6 months post partum or earlier death.

HIV-1 RNA was measured within 4 days after birth in 98% of women who delivered during the study period, with one subsequent measurement during breast-feeding in 99.7% of the women who breast-fed. Among live-born infants, 99.6% had a known HIV-1 infection status at birth (three died shortly after birth without having undergone testing). A final HIV-1 infection status was confirmed in 95% of infants at either 6 months or within 1 day after death. One infant died after a single positive PCR test at birth. The remaining 5% tested negative on at least one occasion before 6 months or before death from a non–AIDS-related illness. Three percent of infants were withdrawn from the study before 6 months for a reason other than death.

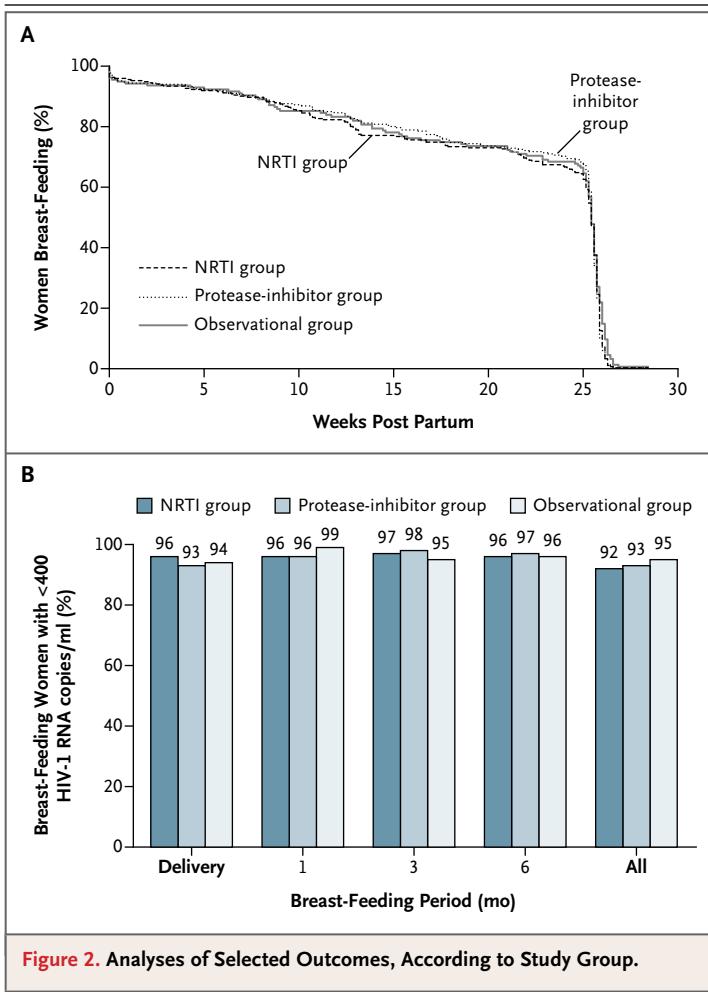Among women with live-born infants, 97%

Figure 2. Analyses of Selected Outcomes, According to Study Group.

vational group), including 6% who missed 3 days or more (6% in the NRTI group, 8% in the protease-inhibitor group, and 4% in the observational group).

BIRTH OUTCOMES

There were 709 live-born infants (283 in the NRTI group, 270 in the protease-inhibitor group, and 156 in the observational group) and 24 stillbirths: 8 in the NRTI group (3%), 5 in the protease-inhibitor group (2%), and 11 in the observational group (7%). The characteristics of the live-born infants at birth are shown in Table 1. Prematurity was more common in the protease-inhibitor group than in the NRTI group (accounting for 23% of infants vs. 15%; 95% confidence interval [CI] for percentage-point difference, <1 to 16). The proportion of infants with low birth weight did not differ significantly according to group (13% in the NRTI group, 17% in the protease-inhibitor group, and 15% in the observational group).

VIROLOGIC SUPPRESSION IN MOTHERS

Suppression of the plasma HIV-1 RNA level to less than 400 copies per milliliter did not differ significantly according to randomization group at delivery (96% in the NRTI group vs. 93% in the protease-inhibitor group; 95% CI for percentage-point difference, −2 to 10), or throughout breast-feeding (92% in the NRTI group vs. 93% in the protease-inhibitor group; 95% CI for percentage-point difference, −8 to 6) (Fig. 2B). The observation group had similarly high rates of suppression to less than 400 copies per milliliter (94% at birth and 95% throughout the breast-feeding period). The rate of suppression of HIV-1 RNA to less than 50 copies per milliliter differed significantly between the NRTI group and the protease-inhibitor group at delivery (81% and 69%, respectively; 95% CI for percentage-point difference, 4 to 20) but not during breast-feeding (83% and 77%, respectively; 95% CI for percentage-point difference, −3 to 14). The rate of suppression to less than 50 copies per milliliter in the observational group was 77% at delivery and 84% throughout the breast-feeding period.

RISK FACTORS FOR LACK OF VIROLOGIC SUPPRESSION AT DELIVERY

Risk factors for a lack of HIV-1 suppression to less than 400 copies per milliliter at delivery in the randomized groups included a higher baseline

breast-fed. Breast-feeding continued for at least 5 months in 71% of women (70% in the NRTI group, 73% in the protease-inhibitor group, and 71% in the observational group) (Fig. 2A). Almost all women who weaned their infants after 5 months (94%) did so the week before the 6-month visit, with less than 1% of women reporting breast-feeding thereafter. Among women who breast-fed, 93% reported that breast-feeding before weaning was exclusive (i.e., no other foods or liquids were given). Discontinuation of HAART before confirmed weaning occurred in 1% of women, with a maximum interval of 42 days between discontinuation of treatment and weaning.

By self-report, 21% of women missed 1 day or more of HAART during pregnancy or breast-feeding (22% in the NRTI group, 22% in the protease-inhibitor group, and 15% in the obser-

HIV-1 RNA level (P<0.001) and later gestational age at enrollment (P<0.001), but these associations did not differ significantly between the NRTI and protease-inhibitor groups. With baseline HIV-1 RNA levels of 1000 copies per milliliter or less, 1001 to 10,000 copies per milliliter, 10,001 to 100,000 copies per milliliter, and 100,000 or more copies per milliliter, the respective rates of virologic suppression were 100%, 99%, 95%, and 90% in the NRTI group, as compared with 96%, 95%, 91%, and 86% in the protease-inhibitor group. With initiation of HAART at 26 to 27 weeks of gestation, at 28 to 30 weeks of gestation, and at 31 to 34 weeks of gestation, the respective rates of virologic suppression were 99%, 95%, and 91% in the NRTI group, as compared with 96%, 96%, and 78% in the protease-inhibitor group.

HIV-1 TRANSMISSION TO INFANTS

The rates of mother-to-child transmission were low: 8 of the 709 live-born infants were infected by 6 months of age (1.1%; 95% CI, 0.5 to 2.2), including 6 infants infected in utero (4 in the NRTI group, 1 in the protease-inhibitor group, and 1 in the observational group) and 2 infants infected through late breast-feeding transmission (both in the NRTI group). These results include one unconfirmed in utero infection in the NRTI group, in an infant who died without a confirmed AIDS-defining cause after a positive PCR result at birth. The study was not powered to compare rates of mother-to-child transmission according to randomized group, and no significant between-group differences were detected: 6 of 283 live-born infants in the NRTI group (2.1%) were infected, as compared with 1 of 270 live-born infants in the protease-inhibitor group (0.4%) (percentage-point difference, 1.7; 95% CI, −2.0 to 7.1). The timing and characteristics of transmission are included in Table 2.

ADVERSE EVENTS

Rates of adverse events were similar in the randomized groups and were generally higher among women in the observational group (Table 3). Four women died by 6 months post partum. One or more grade 3 or 4 events occurred in 58 women (6% in the NRTI group, 6% in the protease-inhibitor group, and 15% in the observational group). Adverse events requiring modification of the HAART regimen occurred in 31 women (2% in the NRTI group, 2% in the protease-inhibitor group, and 11% in the observational group).

Table 2. Timing and Characteristics of Transmission of HIV-1 from Mothers to Infants.*

Mother–Infant Pair No.	Study Group	Mothers						Infants			
		Duration of HAART at First Positive DNA PCR (wk)	Baseline CD4+ Count (cells/mm³)	Baseline HIV-1 RNA (copies per milliliter)	Plasma HIV-1 RNA at Delivery	Plasma HIV-1 RNA at 1 and 3 Mo	Breast-Milk HIV-1 RNA at 1 and 3 Mo	HAART Adherence Issues†	Age at First Positive DNA PCR (day)	Gestational Age at Delivery (wk)	Status at 6 Mo
1	NRTI	7.0	237	80,300	<50	NA	NA	No	1	39	Alive
2‡	NRTI	3.4	317	>750,000	None§	NA	NA	Yes	1	30	Dead
3	NRTI	11.6	322	128,000	51	NA	NA	Yes	1	39	Alive
4	NRTI	10.9	524	204,000	<50	NA	NA	Yes	2	38	Alive
5	Protease-inhibitor	7.1	213	176,000	542	NA	NA	Yes	1	41	Alive
6	Observational	1.9	193	124,000	917	NA	NA	No	1	28	Alive
7	NRTI	17.0	331	171,000	257	<50, <50	<50, <50	No	94¶	32	Alive
8	NRTI	26.9	448	28,500	<50	<50, <50	<50, <50	Yes	91‖	40	Alive

* HAART denotes highly active antiretroviral therapy, HIV-1 human immunodeficiency virus type 1, NRTI nucleoside reverse-transcriptase inhibitor, and PCR polymerase chain reaction.
† Adherence issues included an incorrect pill count or self-report of nonadherence at any visit before the first positive DNA PCR result in the infant.
‡ There was unconfirmed transmission from this mother to the infant, who died on day 12, before confirmatory testing.
§ There was no measurement of HIV-1 RNA because the mother died at delivery.
¶ The last negative HIV-1 DNA PCR result was at 28 days.
‖ The last negative HIV-1 DNA PCR result was at 30 days.

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Table 3. Adverse Events at 6 Months.*

	Observational Group	NRTI Group	Protease-Inhibitor Group
	no./total no. (%)		
Mothers			
Death†	3/170 (2)	1/285 (<1)	0
≥1 grade 3 or 4 diagnosis‡	25/170 (15)	17/285 (6)	16/275 (6)
Any grade 3 or 4 laboratory event	48/170 (28)	42/285 (15)	32/275 (12)
Common grade 3 or 4 laboratory event			
Anemia	19/170 (11)	15/285 (5)	12/275 (4)
Neutropenia	19/170 (11)	18/285 (6)	5/275 (2)
Elevated level of alanine aminotransferase, aspartate aminotransferase, or total bilirubin	1/170 (1)	4/285 (1)	4/275 (1)
Elevated level of amylase or lipase	13/170 (8)	6/285 (2)	8/275 (3)
Treatment-modifying adverse event	18/170 (11)	7/285 (2)	6/275 (2)
Live-born infants			
Death§	7/156 (4)	7/283 (2)	7/270 (3)
≥1 grade 3 or 4 diagnosis¶	13/156 (8)	28/283 (10)	17/270 (6)
Any grade 3 or 4 laboratory event	64/156 (41)	116/283 (41)	125/270 (46)
Common grade 3 or 4 laboratory event			
Anemia	31/156 (20)	36/283 (13)	43/270 (16)
Neutropenia	34/156 (22)	43/283 (15)	49/270 (18)
Bilirubin	5/156 (3)	34/283 (12)	43/270 (16)

* Events were graded with the use of the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, National Institutes of Health, December 2004. NRTI denotes nucleoside reverse-transcriptase inhibitor.
† Maternal deaths (also included as grade 3 or 4 diagnoses) were caused by the following: NRTI group, postpartum hemorrhage; observational group, *Pneumocystis jiroveci* pneumonia, congestive heart failure from probable cardiomyopathy, and nevirapine hypersensitivity reaction (Stevens–Johnson syndrome) followed by sepsis.
‡ Grade 3 or 4 diagnoses included the following: NRTI group, preeclampsia or eclampsia (in 3 women), postpartum hemorrhage (in 2 women), confirmed or suspected pulmonary or extrapulmonary tuberculosis (in 1 woman), hepatitis (in 1 woman), rash (in 1 woman), cardiomyopathy (in 2 women), congestive heart failure (in 1 woman), pulmonary hypertension (in 1 woman), cellulitis (in 1 woman), hypertension (post partum) (in 1 woman), premature rupture of membranes (in 1 woman), prolapsed umbilical cord (in 1 woman), and psychosis (in 1 woman); protease-inhibitor group, preeclampsia or eclampsia (in 2 women), pregnancy-induced hypertension (in 1 woman), postpartum hemorrhage (in 2 women), confirmed or suspected pulmonary or extrapulmonary tuberculosis (in 2 women), hepatitis (in 1 woman), deep-vein thrombosis (in 2 women), fracture (in 1 woman), mastitis (in 1 woman), oligohydramnios (in 1 woman), pneumonia (in 1 woman), postoperative peritonitis (in 1 woman), premature rupture of membranes (in 1 woman), and syphilis (in 1 woman); observational group, preeclampsia or eclampsia (in 5 women), pregnancy-induced hypertension (in 1 woman), confirmed or suspected pulmonary or extrapulmonary tuberculosis (in 5 women), rash (in 3 women), cardiomyopathy or heart failure (in 2 women), abruptio placenta (in 2 women), acute renal failure (in 1 woman), appendicitis (in 1 woman), cerebral toxoplasmosis (in 1 woman), cholangitis (in 1 woman), chorioamnionitis (in 2 women), diabetes (in 1 woman), esophageal candidiasis (in 1 woman), gastritis (in 2 women), gestational diabetes (in 1 woman), nevirapine hypersensitivity reaction (in 1 woman), pancreatitis (in 1 woman), *P. jiroveci* pneumonia (in 1 woman), postcesarean wound infection (in 1 woman), and sepsis (in 2 women).
§ Infant deaths (also included as grade 3 or 4 diagnoses when known) were caused by the following: maternal NRTI group, neonatal sepsis (in 3 infants), gastroenteritis (in 2 infants), respiratory distress, pneumonia, or aspiration (in 1 infant), and meningitis (in 1 infant); maternal protease-inhibitor group, respiratory distress, pneumonia, or aspiration (in 2 infants), tuberculosis (in 1 infant), hydrocephalus (in 1 infant), gastroenteritis (in 1 infant), neonatal sepsis (in 1 infant), and unknown (in 1 infant); maternal observational group, respiratory distress, pneumonia, or aspiration (in 5 infants), gastroenteritis (in 1 infant), and neonatal sepsis (in 1 infant).
¶ Grade 3 or 4 diagnoses included the following: maternal NRTI group, sepsis (in 8 infants), gastroenteritis (in 11 infants), respiratory distress, pneumonia, or aspiration (in 7 infants), tuberculosis (in 1 infant), meningitis (in 4 infants), and eczema (in 2 infants); maternal protease-inhibitor group, neonatal sepsis (in 5 infants), gastroenteritis (in 2 infants), respiratory distress, pneumonia, or aspiration (in 5 infants), tuberculosis (in 2 infants), meningitis (in 1 infant), hydrocephalus (in 1 infant), and sepsis (after 28 days of life in 1 infant); maternal observational group, neonatal sepsis (in 3 infants), gastroenteritis (in 1 infant), respiratory distress, pneumonia, or aspiration (in 8 infants), and hypoxic encephalopathy (in 1 infant).

There were no confirmed hypersensitivity reactions to abacavir, and no woman tested positive retrospectively for HLA-B*5701. No ischemic cardiovascular events occurred.

Among live births, 2% of infants in the NRTI group, 3% in the protease-inhibitor group, and 4% in the observational group died by 6 months; 9 of 21 deaths (43%) occurred in the first week of life (2 in the NRTI group, 2 in the protease-inhibitor group, and 5 in the observational group), and 14 deaths occurred among premature infants (5 in the NRTI group, 6 in the protease-inhibitor group, and 3 in the observational group). Most adverse events in infants were reversible anemias or neutropenias (on the basis of norms developed for the United States) or elevated bilirubin levels.

DISCUSSION

In this randomized trial comparing different HAART regimens initiated in pregnancy, similarly high rates of virologic suppression were achieved at delivery and during breast-feeding among women receiving all HAART regimens. High virologic suppression was mirrored by low rates of mother-to-child transmission at delivery and throughout the breast-feeding period, with 1.1% overall mother-to-child transmission at 6 months.

Our virologic-suppression rates were similar or superior to those in cohorts of nonpregnant adults in Africa,[4-8] suggesting that neither pregnancy nor breast-feeding adversely affects achievable rates of virologic suppression. Although concern has been expressed regarding the lower levels of lopinavir in the third trimester of pregnancy,[9,10] these levels have not been associated with virologic failure.[11] Therefore, although this explanation for the lower percentage of women in the protease-inhibitor group with suppression to less than 50 copies per milliliter at delivery is possible, we believe it is unlikely, particularly among women who had not previously received protease inhibitors.[12]

The rate of virologic suppression in the abacavir–zidovudine–lamivudine group was high, in contrast to the findings in a previous study, which showed that this regimen was inferior to efavirenz-based HAART.[13] The high rate of suppression in our study was in accord with the results of studies comparing the abacavir–zidovudine–lamivudine with unboosted protease-inhibitor–based HAART.[14,15] Unlike some previous studies,[14,16] treatment with abacavir–zidovudine–lamivudine was as effective as other HAART regimens when the baseline HIV-1 RNA level was more than 100,000 copies per milliliter. Rates of suppression with nevirapine-based HAART in the observational group were also high, despite more advanced disease and more toxic effects requiring treatment modification among women in this group. We believe that good adherence in all treatment groups and initiation of HAART early in the third trimester in most women accounted for the excellent suppression rates at and after delivery. The initiation of HAART before 30 weeks' gestation improved virologic suppression at delivery and may have reduced the risk of in utero transmission.

The 1.1% rate of mother-to-child transmission compares favorably with that reported in previous studies in developed countries among non–breast-feeding women who received HAART.[17-19] Rates of mother-to-child transmission across all strata of CD4+ cells were lower than those in previous studies in Africa that did not use HAART, although previous studies provided shorter antepartum or postpartum prophylaxis.[20-24] Two transmissions occurred during breast-feeding, for a transmission rate of less than 1%; this rate is similar to or lower than those recently reported in smaller trials or observational studies in Africa.[25-30] Although more transmissions occurred in the NRTI group than in the protease-inhibitor group or the observational group, the absolute numbers were low, and the difference was not significant. The two breast-feeding transmissions in the NRTI group were not associated with detectable HIV-1 RNA in either maternal plasma or breast milk.

Conflicting data have been reported for associations between HAART and stillbirths,[31-33] prematurity,[31-40] and low birth weight.[31,33,36,37,39] Stillbirth rates in our study were consistent with those in other cohorts of HIV-1–infected women in Africa,[41-43] particularly among women with low CD4+ cell counts.[42,44] Our randomized study confirmed the previously observed associations between protease inhibitors and prematurity. Although birth weight was not significantly associated with treatment group, low birth weight

was twice as common as in our previous study, which involved women who did not receive HAART for prevention of mother-to-child transmission.[20] These data suggest that a modest increase in prematurity should be anticipated when protease inhibitors are used, and they support previous findings from data in Africa that low birth weight may complicate the use of HAART in pregnancy.[39]

The most important limitation of this study was that it was not powered to detect differences in rates of mother-to-child transmission according to study group. We believe that HIV-1 RNA suppression was an appropriate proxy end point for comparing HAART regimens, since viral suppression is the most important goal in using HAART for prevention of mother-to-child transmission in pregnancy.[1,2] The randomized aspect of our study was limited to women with CD4+ cell counts of 200 cells per cubic millimeter or more, and the median HIV-1 RNA level was lower than that in many treatment settings. Therefore, extrapolation of the results of our randomized comparisons to women with lower CD4+ cell counts may be limited. Finally, our study was not intended to answer some important policy questions regarding the prevention of mother-to-child transmission, including whether the use of HAART in women is superior to short-course zidovudine with prolonged nevirapine prophylaxis in infants during breast-feeding among women with higher CD4+ cell counts, and whether the use of HAART in women who breast-feed for more than 6 months remains protective.

In conclusion, the rates of HIV-1 RNA suppression to less than 400 copies per milliliter were similar at delivery and throughout breast-feeding in all study groups. A total of 1.1% of all infants were infected with HIV-1 at 6 months of age; this is a low rate of mother-to-child transmission for a breast-feeding cohort. These findings suggest that the use of HAART in women from early in the third trimester of pregnancy through 6 months of breast-feeding is an effective strategy for preventing mother-to-child transmission while allowing for the benefits of breast-feeding.

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