

ORIGINAL ARTICLE

Intrapartum Exposure to Nevirapine and Subsequent Maternal Responses to Nevirapine-Based Antiretroviral Therapy

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ABSTRACT

BACKGROUND

A single intrapartum dose of nevirapine for the prevention of mother-to-child transmission of human immunodeficiency virus (HIV) leads to the selection of resistance mutations. Whether there are clinically significant consequences in mothers who are subsequently treated with a nevirapine-containing regimen is unknown.

METHODS

We randomly assigned 1844 women in Thailand who received zidovudine during the third trimester of pregnancy to receive intrapartum nevirapine or placebo. In the postpartum period, 269 of the women with a CD4 count below 250 cells per cubic millimeter began a nevirapine-containing antiretroviral regimen. Plasma samples were obtained 10 days post partum and analyzed for resistance mutations. Plasma HIV type 1 (HIV-1) RNA was measured before the initiation of therapy and three and six months thereafter.

RESULTS

After six months of therapy, the HIV-1 RNA level was less than 50 copies per milliliter in 49 percent of the women who had received intrapartum nevirapine, as compared with 68 percent of the women who had not received intrapartum nevirapine ($P=0.03$). Resistance mutations to nonnucleoside reverse-transcriptase inhibitors were detectable in blood samples obtained 10 days post partum from 32 percent of the women who had received intrapartum nevirapine; the most frequent mutations were K103N, G190A, and Y181C. Among the women who had received intrapartum nevirapine, viral suppression was achieved at six months in 38 percent of those with resistance mutations and 52 percent of those without resistance mutations ($P=0.08$). An HIV-1 RNA level at or above the median of $4.53 \log_{10}$ copies per milliliter before therapy and intrapartum exposure to nevirapine were independently associated with virologic failure. After six months of therapy, there was no significant difference between groups in the CD4 count ($P=0.65$).

CONCLUSIONS

Women who received intrapartum nevirapine were less likely to have virologic suppression after six months of postpartum treatment with a nevirapine-containing regimen. Our data suggest the need for strategies to maximize the benefits of both antiretroviral prophylaxis against mother-to-child transmission of HIV and antiretroviral therapy for mothers.

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IN THE DECLARATION OF COMMITMENT endorsed during its June 2001 Special Session on HIV/AIDS, the United Nations General Assembly linked the prevention of mother-to-child transmission of the human immunodeficiency virus (HIV) with antiretroviral treatment for women. Most of these prevention programs consist of prophylactic zidovudine, nevirapine, or both. However, resistance mutations to both these drugs have been reported.¹⁻¹¹ In many studies, resistance mutations to nonnucleoside reverse-transcriptase inhibitors (NNRTI) were found in 15 to 40 percent of women who received a single intrapartum dose of nevirapine.^{4-6,9-11} Since NNRTI-based combinations of antiretroviral agents are recommended as first-line regimens for adults, especially in resource-poor settings,¹² it is of major clinical and public health importance to determine whether intrapartum exposure to a single dose of nevirapine could compromise the efficacy of future nevirapine-containing regimens. Therefore, we determined the rate of virologic suppression six months after the initiation of nevirapine-based triple therapy among immunocompromised women who had received intrapartum nevirapine and among those who had not received intrapartum nevirapine.¹³

METHODS

PATIENTS

The follow-up data analyzed in this report are for women who received a nevirapine-containing regimen post partum after participating in the Perinatal HIV Prevention Trial 2 (PHPT-2), a multicenter, double-blind, randomized, placebo-controlled trial assessing the safety and efficacy of adding nevirapine to zidovudine for the prevention of mother-to-child transmission of HIV. The results of this trial are reported elsewhere in this issue of the *Journal*.¹³ All 37 sites involved in the study were public hospitals; two thirds were located in urban areas, and 1 was a university hospital. In addition to receiving zidovudine starting at 28 weeks of pregnancy or as soon as possible thereafter and throughout labor, the women were randomly assigned to receive a single dose of nevirapine at the onset of labor, with their newborns given a single dose 48 to 72 hours after birth; a single dose of nevirapine at the onset of labor, with their newborns given placebo 48 to 72 hours after birth; or placebo at the onset of labor, with their newborns given placebo 48 to 72 hours after birth.

The treating physicians, virologist, and laboratory technicians were unaware of the women's intrapartum nevirapine status.

After the first interim analysis showed a significantly lower rate of mother-to-child transmission in the group of women and infants who received nevirapine than in the group of women and infants who were given placebo, the latter group was discontinued on May 2, 2002, and all women received intrapartum nevirapine.

In the PHPT-2, consenting, HIV-infected pregnant women underwent baseline evaluations, including measurement of the viral load and CD4 cell count during the second trimester of pregnancy. Women with CD4 counts of less than 250 cells per cubic millimeter were given *Pneumocystis carinii* prophylaxis and referred to the department of internal medicine of the hospital in which they were being monitored. Ten days, six weeks, and four months after delivery, the women underwent a physical examination, had blood drawn for hematologic and virologic substudies, and were referred to the hospital internist for further follow-up. Highly active antiretroviral therapy (HAART) was offered to women whose CD4 counts were below 250 cells per cubic millimeter at any time post partum. Pretreatment evaluations included a clinical evaluation, a complete blood count and differential count, and measurement of hemoglobin, CD4 cells, viral load, alanine aminotransferase, and creatinine. After the initiation of antiretroviral therapy, a medical history was obtained and a clinical examination performed every month; a complete blood count was obtained and levels of alanine aminotransferase and viral load were assessed at three and six months, and CD4 cell counts were determined at six months.

The choice of first-line antiretroviral regimen was based on a clinical and biologic assessment. The Thai Ministry of Public Health provided antiretroviral drugs, and care was provided according to national recommendations.¹⁴ Until June 2002, the least expensive antiretroviral combination available in Thailand was a regimen based on ritonavir and indinavir at a price of \$120 per month. In June 2002, the Government Pharmaceutical Organization launched the "GPOvir" one-pill formulation combining 200 mg of nevirapine, 150 mg of lamivudine, and 30 mg of stavudine (or 40 mg for patients weighing over 60 kg) at a price of \$30 per month, which substantially expanded access to treatment.

SEQUENCING

HIV type 1 (HIV-1) genotyping was performed retrospectively on plasma samples obtained 10 days post partum from a subgroup of 256 women with the use of the ViroSeq HIV-1 Genotyping system version 2.0 (Applied Biosystems), which allows codons 1 through 335 of the reverse-transcriptase gene to be sequenced. We attempted to sequence all samples that contained more than 400 copies of HIV-1 RNA per milliliter. Sequencing products were analyzed on a genetic analyzer (model 3100, ABI PRISM). Sequences were assembled and analyzed with the use of version 2.5 of the ViroSeq HIV-1 Genotyping system for the mutations associated with resistance to NNRTI and nucleoside reverse-transcriptase inhibitors (NRTI), according to the October 2003 resistance-mutation tables of the International AIDS Society–U.S.A.¹⁵ Sequences of HIV protease reverse transcriptase were aligned with the use of Clustal X software.^{16,17} Phylogenetic trees were constructed by means of a neighbor-joining method (100 bootstrap replicates) to genotype the virus and confirm the absence of contamination.¹⁸

MEASUREMENT OF PLASMA HIV-1 RNA

Plasma HIV-1 RNA levels were assessed according to the standard protocol (limit of detection, 400 copies per milliliter) or the ultrasensitive protocol (limit of detection, 50 copies per milliliter) of the Cobas Amplicor HIV-1 Monitor kit (version 1.5, Roche Molecular Systems).

STATISTICAL ANALYSIS

The approach to the statistical analysis of the clinical effect of intrapartum exposure to nevirapine on the subsequent response to treatment of the women who participated in the PHPT-2 was not described in detail in the original protocol because at that time the availability of antiretroviral therapy was not assured. However, after a recommendation by the data and safety monitoring board and the increasing availability of antiretroviral therapy in Thailand, a formal analysis plan was drafted before any data were examined. The main objective was to assess, in the subgroup of women who initiated HAART after delivery, whether the rate of virologic success in those exposed to intrapartum nevirapine differed from that in the women who were not exposed to intrapartum nevirapine. The second objective was to study, among women who had received intrapartum nevirapine, the association between virologic

failure and the presence of resistance mutations detectable at 10 days post partum by means of bulk sequencing.

The proportions were compared with the use of Fisher's test, and distributions with the use of the Kruskal–Wallis test. To verify that intrapartum nevirapine had no effect on the time between the initial exposure to nevirapine and the initiation of HAART, we performed a Cox regression analysis in which data on women who did not begin HAART were censored. We compared the rates of virologic suppression (defined as less than 50 copies of HIV-1 RNA per milliliter) after three and six months (± 1.5 months) of therapy among women who had received intrapartum nevirapine and women who had not received intrapartum nevirapine. In addition, we examined the association of virologic suppression and the presence of detectable HIV reverse-transcriptase resistance mutations to NNRTIs among the women who had received intrapartum nevirapine.

Using a stepwise backward approach to variable selection, we fitted a multivariate logistic-regression model to study baseline variables found to be significantly associated with virologic failure ($P < 0.3$) in the univariate analysis. We then studied the effect of NNRTI and NRTI resistance mutations after adjustment for the variables that had remained independently associated with virologic failure, by introducing them as variables in the fitted model. Adjusted odds ratios and 95 percent confidence intervals were estimated from the final model. Analyses included all patients with blood samples available at the time of assessment. All reported *P* values are two-sided. No correction was made for multiple comparisons.

RESULTS

POSTPARTUM INITIATION OF HAART AND STUDY POPULATION

Among the 1844 women enrolled in the PHPT-2, 316 began to receive HAART before August 1, 2003. The time to the initiation of HAART was significantly associated with intrapartum exposure to nevirapine (relative risk for women exposed to intrapartum nevirapine as compared with women without intrapartum exposure, 1.4; 95 percent confidence interval, 1.1 to 1.8; $P = 0.008$), but this effect was no longer significant after adjustment for the period of the PHPT-2, before or after May 2, 2002, when the placebo group was discontinued and all women re-

ceived nevirapine (relative risk, 1.0; 95 percent confidence interval, 0.8 to 1.3; $P=0.95$). When only women who delivered before May 2, 2002, were included in the analysis, intrapartum exposure to nevirapine had no significant effect on the time to the initiation of HAART (relative risk, 1.0; 95 percent confidence interval, 0.7 to 1.3; $P=0.85$).

We present the results for the 269 women who received a nevirapine-containing regimen (backbone NRTI treatment, lamivudine plus stavudine in all but 1 woman, who received lamivudine plus zidovudine). Other women received either a protease inhibitor (44 women) or efavirenz (3 women) (Fig. 1). As a result of the early termination of the placebo group after the first interim analysis, 221 women received a single intrapartum dose of nevirapine and 48 did not. At the time of enrollment in the PHPT-2, nine women had reportedly received a short course of zidovudine during a previous pregnancy, and one had received triple therapy.

BASELINE CHARACTERISTICS

The baseline characteristics of the 221 women who had received intrapartum nevirapine were similar to those of the 48 women who had not received intrapartum nevirapine, except for the median time to the initiation of HAART (6.1 months vs. 14.9 months, $P<0.001$) (Table 1). When the analysis was confined to the 137 women who had given birth before May 2, 2002, there were no significant differences between the groups (Table 1).

VIROLOGIC EVALUATIONS

A total of 209 of the 221 women who had received intrapartum nevirapine (95 percent) and 47 of the 48 women who had not received intrapartum nevirapine (98 percent) underwent HIV-1 genotyping of blood samples obtained 10 days post partum (Fig. 1). Plasma samples were available for the measurement of viral load in 87 percent and 92 percent of the women, respectively, three months after the initiation of HAART and in 85 percent of both groups at six months.

Phylogenetic analysis of protease reverse-transcriptase genes indicated that 247 of the 256 isolates (96 percent) clustered within the circulating recombinant form CRF01_AE, 7 within subtype B, 1 within subtype C, and 1 within CRF07_BC. No NNRTI resistance mutations were found among the women who had not received intrapartum nevirapine, whereas 66 of the 209 women tested who had received intrapartum nevirapine had at least one

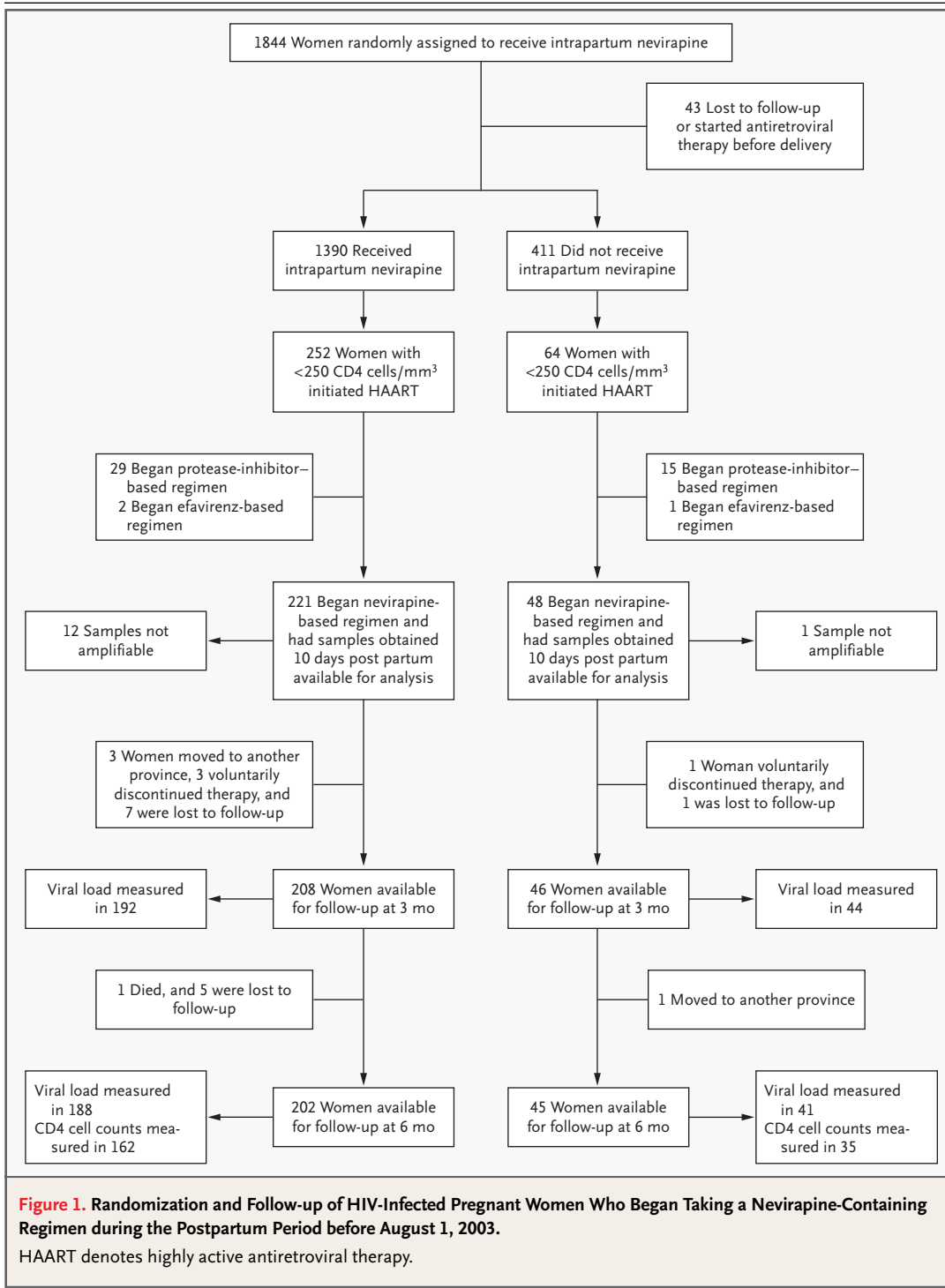
NNRTI resistance mutation (32 percent; 95 percent confidence interval, 25 to 38), 8 (4 percent) had two mutations, and 2 (1 percent) had three mutations (Table 2). The most common resistance mutation was K103N, occurring in 21 percent. Owing to a false or prolonged labor, 9 women received a second dose of intrapartum nevirapine and 1 received a third dose; none of these 10 had NNRTI resistance mutations at 10 days (one sample was not amplifiable). The rate of detection of NNRTI resistance mutations was 20 percent among women with a viral load that was below the median during pregnancy (4.53 log copies of HIV-1 RNA [on a base 10 scale] per milliliter) and 42 percent among those with a viral load at or above the median ($P=0.001$). In addition, 5 percent of all women had a viral population with at least one NRTI resistance mutation (Table 2).

VIROLOGIC RESPONSE TO NEVIRAPINE-BASED THERAPY

Three months after the initiation of HAART, the HIV-1 RNA level was below 50 copies per milliliter in 34 percent of the women (80 of 236), and there were no significant differences according to intrapartum exposure to nevirapine ($P=0.55$). Six months after the initiation of HAART, the HIV-1 RNA level was below 50 copies per milliliter in 49 percent of the women who had received intrapartum nevirapine (92 of 188), as compared with 68 percent of the women who had not received intrapartum nevirapine (28 of 41, $P=0.03$). In an analysis restricted to women who delivered before May 2, 2002, virologic suppression was seen at six months in 51 percent of the women who had received intrapartum nevirapine (43 of 84) and 68 percent of those who had not received it (27 of 40). Although consistent with the overall results, this difference was not significant ($P=0.12$). Among the women who had received intrapartum nevirapine, 38 percent of those with NNRTI resistance mutations had virologic suppression after six months of treatment (23 of 61), as compared with 52 percent of the women without detectable NNRTI resistance mutations (62 of 119, $P=0.08$) (Fig. 2).

RISK FACTORS FOR VIROLOGIC FAILURE

The univariate analysis (Table 3) showed that virologic failure six months after the initiation of HAART was associated with a viral load at or above the median at the beginning of therapy ($P<0.001$), a CD4 count below the median of 174 cells per cubic millimeter at the initiation of therapy ($P=0.004$), in-



trapartum exposure to nevirapine ($P=0.03$), the detection of NNRTI resistance mutations ($P=0.02$), and the detection of NRTI resistance mutations ($P=0.06$). Among the women who had received intrapartum nevirapine, the rate of virologic failure did

not differ significantly between those who initiated HAART within six months after delivery and those who began treatment more than six months after delivery ($P=0.25$).

In the multivariate logistic-regression analysis,

Table 1. Baseline Characteristics of Women Who Began Receiving HAART in the Postpartum Period.

Characteristic	All Women			Women Who Delivered by May 2, 2002		
	Intrapartum Nevirapine (N=221)	No Intrapartum Nevirapine (N=48)	P Value	Intrapartum Nevirapine (N=92)	No Intrapartum Nevirapine (N=45)	P Value
Age at delivery — yr			0.18			0.25
Median	27.3	28.4		27.5	28.8	
Interquartile range	24.0–32.0	25.3–31.5		24.0–31.8	25.9–31.5	
During second trimester of pregnancy						
Absolute CD4 count — no./mm ³			0.11			0.92
Median	184	193		189	196	
Interquartile range	138–229	150–272		157–262	154–274	
Plasma HIV-1 RNA — log ₁₀ copies/ml			0.64			0.71
Median	4.47	4.68		4.46	4.68	
Interquartile range	3.87–4.96	3.83–4.97		3.86–4.97	3.84–4.95	
Hepatitis B surface antigen — no. (%)	11 (5)	1 (2)	0.70	2 (2)	1 (2)	1
Hepatitis C antibodies — no. (%)	7 (3)	5 (10)	0.04	3 (3)	3 (7)	0.39
At initiation of antiretroviral therapy*						
Weight — kg			0.42			0.97
Median	50	48		48	48	
Interquartile range	46–56	46–56		45–54	46–54	
Hemoglobin level — g/dl			0.85			0.73
Median	11.2	11.3		11.3	11.3	
Interquartile range	10.0–11.9	10.0–11.9		10.2–12.1	10.1–11.9	
White-cell count — no./mm ³			0.59			0.92
Median	5120	5300		5295	5360	
Interquartile range	4135–6450	4365–6490		4185–6485	4400–6480	
Neutrophils — no./mm ³			0.34			0.35
Median	3370	2825		3015	2547	
Interquartile range	2281–4608	2136–4416		2074–4057	2084–3550	
Platelets — no./mm ³			0.37			0.05
Median	251,000	266,000		237,500	271,000	
Interquartile range	213,000–307,000	238,500–305,000		208,000–287,000	240,000–314,000	
Creatinine — mg/dl†			0.91			0.81
Median	0.6	0.6		0.6	0.6	
Interquartile range	0.5–0.7	0.5–0.7		0.5–0.7	0.5–0.7	
Alanine aminotransferase — IU/liter			0.98			0.84
Median	20	19		21	19	
Interquartile range	13–31	14–30		13–30	14–30	
Absolute CD4 count — no./mm ³			0.88			0.33
Median	174	182		149	171	
Interquartile range	87–219	88–230		70–211	77–227	
Plasma HIV-1 RNA — log ₁₀ copies/ml			0.65			0.77
Median	4.60	4.77		4.73	4.81	
Interquartile range	4.00–5.08	4.18–5.16		4.11–5.14	4.19–5.23	
Interval between delivery and initiation of treatment — mo			<0.001			0.60
Median	6.1	14.9		15.8	15.8	
Interquartile range	2.7–14.0	8.6–19.5		11.6–19.5	12.8–19.6	

* Laboratory examinations were performed when antiretroviral treatment was initiated. If a sample was missing, the most recent result available during pregnancy was used as the baseline value, excluding samples drawn from the onset of labor to 10 days after delivery for the measurement of the viral load.

† To convert values for creatinine to micromoles per liter, multiply by 88.4.

a viral load at or above the median at the beginning of HAART, as compared with one that was below the median (odds ratio, 3.0; 95 percent confidence interval, 1.7 to 5.2; $P < 0.001$), and exposure to nevirapine during labor, as compared with no exposure (odds ratio, 2.6; 95 percent confidence interval, 1.2 to 5.5; $P = 0.01$), were independently associated with virologic failure at six months. There was no significant interaction between viral load and exposure to intrapartum nevirapine. When the analysis was restricted to women who delivered before May 2, 2002, the odds ratios for viral load and intrapartum exposure to nevirapine were 2.1 and 2.1, respectively (95 percent confidence intervals, 1.0 to 4.4 and 0.9 to 4.7, respectively; $P = 0.05$ and $P = 0.07$, respectively). In the multivariate model that included all women who had received intrapartum nevirapine, detectable NNRTI and NRTI resistance mutations were not associated with virologic failure ($P = 0.28$ and $P = 0.31$, respectively), after adjustment for viral load at the initiation of treatment.

CD4 CELL COUNTS AND CLINICAL EVALUATIONS

After the first six months of HAART, the CD4 count had increased by a median of 120 cells per cubic millimeter in the group as a whole, and no significant difference was found between the women who had received intrapartum nevirapine and those who had not ($P = 0.65$). The median weight gain after six months was 0.5 kg in the former group and 0.95 kg in the latter group ($P = 0.32$).

No serious adverse effects related to the liver (liver failure or an increase to grade 4 in alanine aminotransferase levels) were observed during the first six months of therapy. However, 24 serious adverse events were reported among 16 women during this period — 11 women who had received intrapartum nevirapine (5 percent), including rashes in 5, and 5 women who had not received intrapartum nevirapine (10 percent). There were two deaths, both among women who had received intrapartum nevirapine — one woman stopped therapy after three days, switched one month later to an efavirenz-based regimen that she took for two days, and died three months later from an unknown cause; the second woman received a diagnosis of abdominal tuberculosis five months after starting therapy and died two months later. Nevirapine was replaced with ritonavir-boosted indinavir in 1 woman and with efavirenz in 26 women (17 of whom had received intrapartum nevirapine and 9 of whom had

Table 2. Characteristics of HIV-1 Resistance Mutations to NNRTIs and NRTIs among Women Who Began Taking Antiretroviral Therapy in the Postpartum Period, According to Whether They Received Intrapartum Nevirapine.*

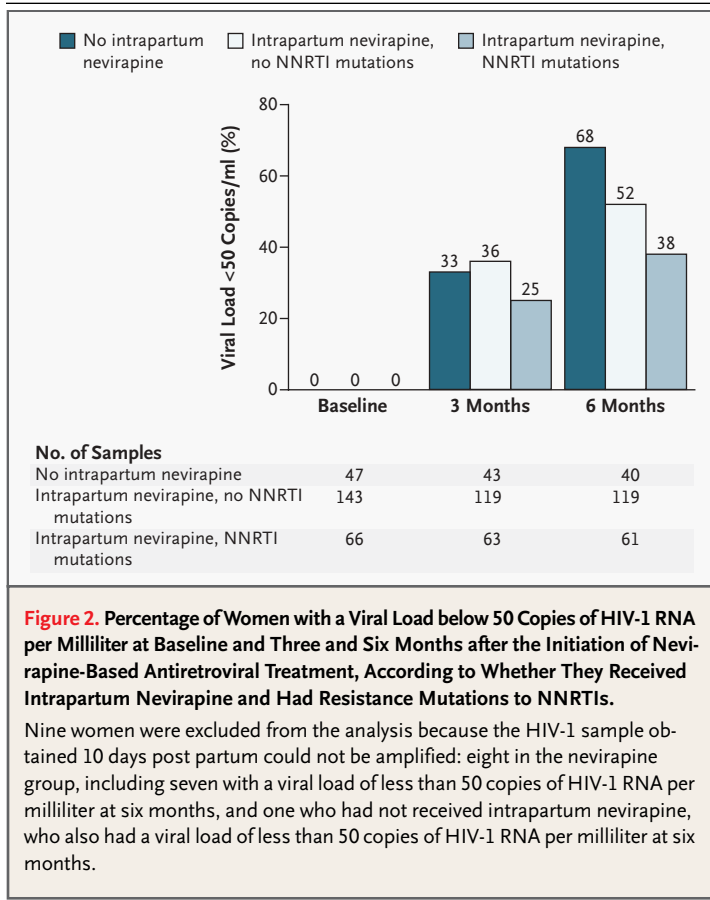
Variable	Women Who Received Intrapartum Nevirapine (N=209)	Women Who Did Not Receive Intrapartum Nevirapine (N=47)	All Women Analyzed (N=256)
	<i>no. of patients (%)</i>		
NNRTI resistance mutations			
At least one mutation	66 (32)	0	66 (26)
Only one mutation	56 (27)	0	56 (22)
Two mutations	8 (4)	0	8 (3)
Three mutations	2 (1)	0	2 (1)
K103N	44 (21)	0	44 (17)
V106A	3 (1)	0	3 (1)
V108I	1 (<1)	0	1 (<1)
Y181C	8 (4)	0	8 (3)
Y188C	1 (<1)	0	1 (<1)
G190A	20 (10)	0	20 (8)
P225H	1 (<1)	0	1 (<1)
L101I, V106M, Y181I, Y188LH, G190S, M230L, or P236L	0	0	0
NRTI resistance mutations			
At least one mutation	10 (5)	2 (4)	12 (5)
Only one mutation	8 (4)	2 (4)	10 (4)
Two mutations	2 (1)	0	2 (1)
D67N	2 (1)	0	2 (1)
K70R	9 (4)	2 (4)	11 (4)
K219Q	1 (<1)	0	1 (<1)
M41L, E44D, A62V, K65R, T69D, L74V, V75I, F77L, Y115F, F116Y, V118I, Q151M, M184V, L210W, T215YF, or K219E	0	0	0

* The resistance-mutation tables of the International AIDS Society—U.S.A. were used.¹⁵ In both groups, plasma samples were obtained a median of 12 days after delivery (interquartile range, 10 to 14).

not) owing to rash, tuberculosis, or elevated liver-enzyme levels.

DISCUSSION

We found that, among HIV-infected women who began taking a nevirapine-based regimen after delivery, intrapartum exposure to nevirapine was associated with a significant decrease in the rate of vi-



rologic suppression at six months. A large viral load at the initiation of therapy was independently associated with a decreased rate of viral suppression. Clinical and immunologic outcomes after six months of therapy did not differ significantly between the women who had received intrapartum nevirapine and those who had not received it.

Of all the baseline characteristics of the women who began taking a nevirapine-containing regimen after delivery, only the duration between delivery and the initiation of HAART differed between those who had received intrapartum nevirapine and those who had not received it. This difference resulted from two unrelated events that occurred during the same period: the discontinuation of the placebo group of the clinical trial and the subsequent availability of the nevirapine-containing one-pill combination produced by the Government Pharmaceutical Organization. As a consequence, the average interval between delivery and the initiation of HAART was longer among women who had not received intrapartum nevirapine than among those who had.

However, the Cox survival analysis that included all women in the PHPT-2 who delivered before the first interim analysis showed that exposure to intrapartum nevirapine itself was not associated with the time to the initiation of therapy, be it protease-inhibitor or NNRTI based.

It is possible that some women who began HAART shortly after delivery were at a late stage of the disease or, conversely, that some women who started therapy later had become more immunocompromised than those who began therapy soon after delivery. Both situations probably occurred, as evidenced by the fact that key baseline characteristics during pregnancy or at the initiation of therapy, such as clinical status, viral load, and CD4 cell count, were similar between women who had received intrapartum nevirapine and those who had not received it. In addition, the risk of virologic failure was not associated with the duration of the interval between delivery and the initiation of HAART, and restricting the analysis to women who delivered before the discontinuation of the placebo group did not significantly change the proportions of women with virologic suppression in the two groups.

Our results suggesting that intrapartum exposure to nevirapine, even in the absence of detectable resistance mutations, may compromise a woman's subsequent response to NNRTI therapy are consistent with reports by others^{19,20} showing that low-frequency mutations that are not detected by means of standard, population-based sequencing methods²¹⁻²³ affect the success of therapy. It is important to note that a substantial proportion of the women with nevirapine resistance mutations still had a response to the nevirapine-based regimen.

The frequency of nevirapine resistance mutations has been reported to decrease with the time after exposure to nevirapine.^{5,8,11} Whether this factor is associated with an improved response to a subsequent nevirapine-based regimen is uncertain. Our data are inconclusive in this regard, and longer follow-up is required to address the question.

Further research is needed to answer the critical questions raised by this and other studies. For example, what would the outcome of treatment be among the less immunocompromised women who did not start therapy shortly after delivery? Will the rate of treatment success increase as the interval between intrapartum exposure to nevirapine and the initiation of HAART increases? Would regimens based on protease inhibitors result in a higher rate of virologic suppression in this setting?

Table 3. Risk Factors for Virologic Failure Three and Six Months after the Initiation of Antiretroviral Treatment among Women Who Began Taking a Nevirapine-Based Regimen in the Postpartum Period.*

Variable	Women with Virologic Failure at 3 Mo	P Value†	Women with Virologic Failure at 6 Mo	P Value†
	<i>no./total no. (%)</i>		<i>no./total no. (%)</i>	
Median CD4 count of 186/mm ³ during second trimester of pregnancy		0.22		0.09
Below median	84/120 (70)		63/118 (53)	
At or above median	72/116 (62)		46/111 (41)	
Median CD4 count of 174/mm ³ at initiation of therapy		0.02		0.004
Below median	88/120 (73)		65/113 (58)	
At or above median	68/116 (59)		44/116 (38)	
Median HIV-1 RNA level of 4.53 log ₁₀ copies/ml during second trimester of pregnancy		<0.001		0.29
Below median	62/114 (54)		49/112 (44)	
At or above median	94/122 (77)		60/117 (51)	
Median HIV-1 RNA level of 4.61 log ₁₀ copies/ml at initiation of therapy		<0.001		<0.001
Below median	64/117 (55)		38/110 (35)	
At or above median	92/119 (77)		71/119 (60)	
Median of 70 days of zidovudine prophylaxis during pregnancy		1.0		0.90
Below median	76/115 (66)		51/109 (47)	
At or above median	80/121 (66)		58/120 (48)	
Intrapartum nevirapine		1.0		0.03
Yes	127/192 (66)		96/188 (51)	
No	29/44 (66)		13/41 (32)	
Multiple intrapartum doses of nevirapine		0.32		0.50
Yes	5/10 (50)		3/9 (33)	
No	149/224 (67)		106/220 (48)	
NNRTI resistance mutations		0.20		0.02
Yes	47/63 (75)		38/61 (62)	
No	105/162 (65)		70/159 (44)	
NRTI resistance mutations		0.17		0.06
Yes	9/10 (90)		8/10 (80)	
No	143/215 (67)		100/210 (48)	
Switched to another combination before viral load assessed		0.66		0.68
Yes	18/25 (72)		11/26 (42)	
No	138/211 (65)		98/203 (48)	
Reported missing >1 dose per week at any visit during first 3 mo of therapy		0.45		0.12
Yes	112/165 (68)		81/158 (51)	
No	44/71 (62)		28/71 (39)	
Initiation of antiretroviral therapy		0.21		0.18
≤6 mo after delivery	73/103 (71)		51/96 (53)	
>6 mo after delivery	83/133 (62)		58/133 (44)	

* Virologic failure was defined by an HIV-1 RNA level of at least 50 copies per milliliter.

† Fisher's exact test was used to calculate the P values.

The problem of the emergence of resistance mutations after a single dose of nevirapine was identified several years ago. Our study, although observational in nature, reports findings that are internally consistent and fit our current understanding of how resistance mutations are selected for under drug

pressure, how mutations may later disappear from the circulating HIV while persisting in the viral reservoir, and how they reappear if drug pressure is re-applied. Our findings do not provide definitive answers to the many questions that surround the issue of prevention of mother-to-child transmission of

HIV and maternal treatment of the infection. However, they do provide a point of departure from which further advances can proceed. They should also incite people in the field to design appropriate clinical research studies that focus on optimizing the treatment of women during pregnancy and post partum.

The results of the PHPT-2,¹³ reported elsewhere in this issue of the *Journal*, demonstrate that rates of maternal–fetal transmission of HIV can be markedly reduced in resource-constrained settings. Although this companion report of the effect of intrapartum exposure to nevirapine on subsequent maternal treatment should be interpreted as sounding a note of caution, we believe that the regimen of zidovudine during the last trimester of pregnancy and intrapartum nevirapine should be offered wherever feasible.²⁴ In the rapidly evolving field of HIV medicine and international public health, the choice is no longer restricted to the welfare of the child or that of the mother. There are now many more options to consider. Strategies are already available that maximize both the prevention of mother-to-child transmission of HIV and antiretroviral treatment options for mothers. In countries where antiretroviral combinations for the treatment of immunocompromised women are increasingly available and the issue of nevirapine resistance therefore arises, numerous strategies are being investigated, including the use of triple therapy during pregnancy when feasible and desirable,^{25–28} initiating therapy with a protease-inhibitor–based regimen, or providing additional antiretroviral agents immediately after intrapartum nevirapine to suppress viral replication during the period in which plasma nevirapine levels remain detectable.²⁹

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APPENDIX

The following hospitals, coinvestigators, and study coordinators participated in the Perinatal HIV Prevention Trials in Thailand and in the postpartum follow-up (the numbers of women at each hospital are given in parentheses): Rayong (44): W. Dumrongkitchaiporn, C. Pinyowittayakool, C. Tantiywarong; Nakorping: V. Gomuthbutra, S. Sahintapongs, C. Sirinirundr, and Health Promotion Region 10 Chiang Mai (44): A. Limtrakul; Prapokklao (36): N. Chuachamsai, P. Yuthavisuthi, D. Sinthuvanich; Chonburi (24): N. Chotivanich, P. Kittikoon, C. Tantiywarong; Phayao Provincial (22): W. Leongjiranothai, S. Sangsawang, S. Techakulviroj, S. Attawibool; Nakhonpathom (21): O. Kam-sao, V. Chalermopolprapa, P. Hirunchote; Hat Yai (20): A. Nilmanat, S. Lamlerkitikul, K. Veerapradist; Chacheongsao (19): P. Wittayapraparat, A. Kanjanasing, R. Kaewsonthi, C. Jirawison, V. Latdthivongsakorn; Bhumibol Adulyadej (19): S. Prommas, K. Kengsakul, P. Praeteeprat, Y. Vonglertvit; Mae Sai (17): C. Jongpipan, S. Kunkongkapan, T. Meephan, K. Kongsing; Samutsakorn (17): A. Chutananta, T. Sukhumanant, C. Pinsuwan; Chiangrai Prachanukroh (17): J. Achalapong, R. Srismith, S. Yanpaisan; Chiang Kham (15): Y. Buranawanit-chakorn, C. Putiyanun, C. Kulkolakan; Phan (14): S. Jungpichanvanich, T. Changchit, S. Suwan; Ratchaburi (13): W. Panitsuk, T. Chonladarat, N. Pinyotrakool, M. Jittwatanakorn, P. Bunjongjit; Pranangkla (12): S. Pipatnakulchai, S. Hongyok; Lamphun (11): N. Wirayutwat-thana, W. Matanasaravoot, K. Pagdi, R. Somsamai, C. Wannalit, S. Yanpaisan; Somdej Prapinkla (11): P. Wongsarajana, S. Suphanich, P. Kanchanakitsakul, N. Kamolpakorn, P. Sunalai; Samutprakarn (11): N. Eiamsirikit, P. Sabsanong, C.M. Hongsawinitkul; Mae Chan (10): S. Buranabanjasatean, S. Piyaworawong; Banglamung (10): J. Ithisuknanth, K. Boonrod, J. Ithisuknanth, P. Jitwattanapongs; Kalasin (9): P.

Thaingamsilp, B. Suwannachat, S. Nitpanich; Buddhachinaraj (8): S. Tunsupasawasdikul, W. Wannapira, P. Thanomrat, W. Boonyawatana; Mahasarakam (8): C. Churaree, S. Nakhpongse, S. Tonmat, W. Worngsatthanaphong; Somdej Pranangchao Sirikit (7): V. Attakornwatana, W. Pornkitprasarn, W. Rutirawat; Khon Kaen (7): J. Ratanakosol, M. Onchan, V. Jarupoonphol; Nong Khai (7): N. Yuthakasaemsan, N.P. Ruttana-Aroongorn, T. Wichatrong; Health Promotion Region 6 Khon Kaen (6): N. Winiyakul, W. Sinchai; Chiang Khong Royal Crown Prince (5): S. Monchit; Klaeng (5): B. Chetanachan, S. Techapalokul, S. Sungpapan; Phaholpolphayuhasena (5): P. Jirawattanapant, Y. Sri-varasat, T. Buddhaboriwan; Prajaksilapakom Army (5): P. Nakchun, D. Langkafa, S. Pratchayakul, Bamrasnaradura (4) S. Tunsupasawaskul; Nopparat Rajathanee (4): J. Wongchinsri, S. Surawongsin, T. Chanpoo, N. Thamanavat, P. Hotrarapavanond; Banchang (3) N. Sangwannakul; Phayamengrai (3): S. Kamsrisuk; Srinagarind (3): P. Chetchotisakd, C. Sakondhavat, W. Laupattarakasem, S. Kraitrakul; Kranuan Crown Prince (3): R. Thongdej, T. Chaibabut, P. Kovit, S. Benchakhanta, A. Rattanaparinya; Roi-et (3): B. Jeerasuwannakul, W. Athakorn, W. Supanchaimat.

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