Persistence of Nevirapine Exposure During the Postpartum Period After Intrapartum Single-Dose Nevirapine in Addition to Zidovudine Prophylaxis for the Prevention of Mother-to-Child Transmission of HIV-1

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Objective: To determine nevirapine (NVP) plasma levels during the postpartum period after a single intrapartum NVP dose for the prevention of mother-to-child transmission.

Methods: Plasma samples at delivery and during days 8 to 45 postpartum were obtained from HIV-infected Thai women who received an intrapartum NVP dose in the Perinatal HIV Prevention Clinical Trial-2 (PHPT-2) for the prevention of perinatal HIV transmission. These data were combined with NVP concentration data from 2 phase 1 studies of NVP for a population analysis.

Results: The median NVP level fell to 68 ng/mL (range: <50–228, n = 43) 8 to 14 days after dosing and to 51 ng/mL (range: <50–166, n = 25) between 15 and 21 days. During the second and third weeks postpartum, NVP levels were below the limit of quantitation in 23% and 44% of samples, respectively. Between 21 and 45 days, no sample had a quantifiable NVP concentration. A simulation derived from the population analysis predicts that NVP concentration falls to less than 10 ng/mL in 5% of women by 11 days, in 50% of women by 17.5 days, and in 95% of women by 28 days.

Conclusions: Significant NVP concentrations remained for up to 20 days in these Thai women. To ensure that coverage is maintained until NVP concentrations fall to nonsuppressive levels, 1 month of additional antiretroviral treatment after delivery should be considered to prevent the emergence of resistant viruses.

Key Words: nevirapine, prevention mother-to-child HIV transmission, pharmacokinetics

Although suboptimal when compared with the treatment of maternal HIV-1 infection with highly active antiretroviral therapy (HAART),[1] several lower intensity antiretroviral regimens using zidovudine (ZDV) alone or in combination with lamivudine (3TC) or nevirapine (NVP) alone have been shown to significantly reduce mother-to-child HIV transmission.[2–4] Recently, in Thailand, the Perinatal HIV Prevention Clinical Trial (PHPT-2) study demonstrated that combining a single NVP dose administered to women at the onset of labor and to their infants at 48 to 72 hours after birth with ZDV prophylaxis starting at 28 weeks of gestation reduced transmission similar to rates observed with HAART during pregnancy.[5]

Enthusiasm for the use of NVP for prevention of mother-to-child HIV transmission has been tempered by the observation that exposure of pregnant women to a single intrapartum NVP dose is frequently associated with the selection of high-level nonnucleoside reverse transcriptase inhibitor (NNRTI)–resistant viruses during the postpartum period. NNRTI resistance results from a single mutation, such as the K103N mutation, in the reverse transcriptase gene. Early in the development of NVP, it was observed that NVP monotherapy can select such resistant viruses after as little as 1 week of exposure.[6] In the HIV Network for Prevention Trial (HIVNET) 012, where a single intrapartum NVP dose was used without ZDV, NNRTI-resistant virus was detected in 19% of 111 women tested 6 to 8 weeks after delivery.[7] In the Pediatric AIDS Clinical Trials Group (PACTG) 316 study, where women received various combination antiretroviral regimens during pregnancy plus single intrapartum NVP doses, NNRTI-resistant virus was detected in 15% of 95 women at 6 weeks postpartum.[8] In all these studies, the K103N mutation was the most common mutation detected.

NVP is highly lipophilic and readily absorbed (>90%) after oral administration in adults, remains essentially non-ionized at physiologic pH, readily crosses the placenta, and has a reported half-life of 45 hours (single dose) and 25 to 30 hours (multiple doses).[9,10] Phase 1 studies of the safety and pharmacokinetics of NVP in Ugandan and American women demonstrated that 200-mg doses administered to HIV-infected women during labor were rapidly absorbed and achieved NVP concentrations more than 10 times the concentration required to inhibit by 50% (IC_{50}) value in the newborn at delivery.[11,12] When the infant received an additional 2-mg/kg dose at 48 to 72 hours of life, infant NVP concentration was maintained at greater than the target of 100 ng/mL through the age of 7 days.[11,12] The mothers in both studies demonstrated prolonged elimination of NVP, with a reported median elimination half-life ($T_{1/2}$) of 61.3 hours (range: 27–90 hours) in the Ugandan women. Sampling in both studies stopped 7 days after dosing, and NVP concentrations in the final samples ranged from 40 to 596 ng/mL.

To date, no data on NVP plasma concentrations beyond 1 week postpartum are available in HIV-infected pregnant women receiving single-dose NVP during labor. The objective of this study was to determine the length of time during which NVP was present in the plasma of women after a single NVP dose at the onset of labor for the prevention of mother-to-child HIV transmission to help define the period when there is a risk of developing NVP resistance postpartum and when specific interventions such as a short course of additional antiretroviral treatment could prevent this risk.

METHODS

Study Population

The study database consisted of plasma NVP concentrations collected from Thai women. All study women were infected with HIV and received a single dose of NVP during labor. Eighty-one of the Thai women were participants in the PHPT-2, a multicenter, randomized, 3-arm, double-blind, controlled study assessing the efficacy in preventing mother-to-child HIV transmission of single-dose NVP given at the onset of labor and to the infant 48 to 72 hours after birth in addition to ZDV starting at 28 weeks of gestation or as soon as possible thereafter. Plasma samples were also obtained from 26 Thai women who were participants in a pilot pharmacokinetics (PK) substudy performed before initiation of PHPT-2 and from 3 Thai women who received open-label single-dose nevirapine because they had not completed the required 2 weeks of ZDV prophylaxis before enrollment in the PHPT-2.

In the PHPT-2, blood draws were scheduled for mothers immediately after delivery as well as 10 days, 6 weeks, and 4 months postpartum for pharmacokinetic and virologic studies. Patient samples were selected based on the timing of their postpartum sample and time of NVP intake. Women who received a placebo or more than 1 dose of NVP (ie, for false labor or a prolonged labor) were excluded. No concomitant treatments with drugs that affect NVP pharmacokinetics were used in these women. Plasma samples for NVP assay were obtained from at least 2 time points: at delivery and between 8

and 45 days after dosing. In women participating in the pilot NVP substudy before PHPT-2, samples were also available 1 day after delivery. A total of 241 samples were assayed from 110 Thai women. All patients provided written informed consent, and the PHPT-2 study was approved by the Ethics Committee of the Harvard School of Public Health; Ministry of Public Health, Thailand; and Faculty of Associated Medical Sciences (AMS), Chiang Mai University, Thailand. The data from these Thai women were then nested in a population analysis as described below with the data from previously published phase 1 pharmacokinetic protocols of single intrapartum dosing in Ugandan and American women.[11,12]

Sample Preparation and Nevirapine Assay

Blood samples were centrifuged, and the plasma was aliquoted and frozen within 1 hour of collection at −20°C. NVP plasma drug concentrations were measured at the Faculty of Associated Medical Sciences (AMS), Chiang Mai University, by a validated high-performance liquid chromatography (HPLC) assay described previously.[13] The lower limit of assay quantitation (LLQ) was 50 ng/mL. This method was validated in the laboratory in Chiang Mai using the AIDS Clinical Trials Group (ACTG) method validation guidelines with inter- and intra-assay variability of a coefficient of variation (CV) <15% at the LLQ and CV <20% at 3 levels of the calibration curve. The laboratory participates in the international external quality control (QC) programs of the ACTG,[14] Pharmacology Quality Control (Precision Testing) program, and ASQUALAB, France.[15] Patient plasma samples and all calibration and control samples were heat-inactivated in a water bath at 56°C for 30 minutes before assay. Sample preparation and NVP assay methodology for the samples from the Ugandan and American women have been previously described.[11,12]

Population Pharmacokinetic Analysis

NVP plasma concentration data from the Thai women were combined with those from the previously published phase 1 studies. Because no samples collected beyond 21 days after dosing had quantifiable NVP concentrations, only samples collected before 21 days after dosing were included in the population database. Population pharmacokinetic analysis of the combined database was performed using the population mixed-effect modeling program NONMEM (version 5.1) with an MS Powerstation Fortran Compiler (Microsoft Corp, Redmond, WA).[16] Model development was performed in 3 steps: (1) development of an initial pharmacokinetic model, (2) evaluation of patient characteristics as potential covariates of pharmacokinetic parameters, and (3) optimization of the final model.[17] The effects of individual covariates on model fit were evaluated independently. All significant covariates were then added to the model and removed 1 at a time in order of decreasing improvement in the objective function. Only covariates showing a significant contribution were conserved in this intermediate model. After all significant patient characteristics had been evaluated in this way, each included covariate was re-evaluated, and only those parameters that continued to improve the fit of the model significantly were retained. After the final structural model was accepted, different error models were evaluated. The final structural and

error model was then re-evaluated with first-order conditional estimation. The resulting pharmacokinetic parameters were used in a Monte Carlo simulation of 1000 subjects to generate NVP concentration-time plots from intrapartum dosing through 30 days after dosing.

RESULTS

Patient Characteristics

Table 1 shows the baseline characteristics of the Thai women, which were similar to those observed in the entire PHPT-2 population. No concomitant treatments with drugs that affect NVP pharmacokinetics were used by these patients. At delivery, median weight was 63 kg (range: 40–106 kg) for the 110 Thai women compared with 61.5 kg (range: 48–72 kg) for the 20 Ugandan women and 69 kg (range: 48–138 kg) for the 10 American women included in the population analysis.

Nevirapine Pharmacokinetics at Delivery

NVP plasma levels were measured immediately after delivery in 110 Thai women. All women had detectable NVP levels at delivery, and Figure 1 shows the individual NVP plasma concentrations measured. The median time between NVP intake and blood draw at delivery was 7.9 hours (range: 0.2–47 hours), and the median NVP plasma level at delivery was 1695 ng/mL (range: 161–3737 ng/mL).

Postpartum Nevirapine Pharmacokinetics

For each of the 110 Thai patients, single NVP plasma levels were also measured during the postpartum period, and the time between NVP intake and their first postpartum visit and blood draw varied from 8 to 45 days. Figure 1 shows the individual NVP plasma concentrations measured for each patient during this postpartum period. NVP was detectable in plasma up to 21 days postpartum.

Patient NVP postpartum plasma level results were separated based on the time between NVP intake and blood draw postpartum. Forty-three samples were available between 1 and 2 weeks postpartum (range: 8–14 days), and the median NVP level was 68 ng/mL (range: ≤50–228 ng/mL). Between 2 and 3 weeks postpartum (range: 15–21 days), 25 samples were available, and the median NVP concentration was 51 ng/mL (range: ≤50–166 ng/mL). During the second and third weeks postpartum, 23% and 44% of the samples, respectively, had median NVP levels <50 ng/mL. Forty-five patients had plasma samples between 21 and 45 days after NVP intake assayed, and all were undetectable (Fig. 2).

TABLE 1. Summary of the 110 Thai Patients' Baseline Characteristics

	Median	Range
Age (y)	27	(16–39)
Weight*	63	(40–106)
CD4 count (cells/mm^2)	409	(47–1007)
HIV-1 RNA (log$_{10}$ copies/mL)	3.89	(<2.6–5.57)

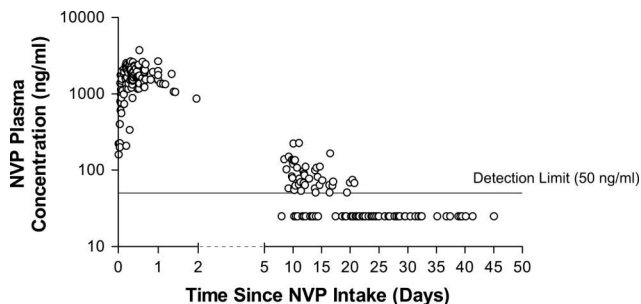*Weight taken at the last visit before delivery.

FIGURE 1. Nevirapine (NVP) plasma levels in women after a single 200-mg dose taken at the onset of labor for the prevention of mother-to-child HIV transmission. In 110 Thai patients, NVP plasma levels were assayed immediately after delivery and during the postpartum period. Samples below the assay limit of detection of 50 ng/mL were plotted at 25 ng/mL.

Population Pharmacokinetics

The combined data set included a total of 560 concentrations from 140 women, of whom 110 were Thai, 20 were Ugandan, and 10 were American. A single-compartment model with first-order absorption was used. The model fit improved with inclusion of a lag time for absorption. Scaling the apparent volume of distribution for weight significantly improved model fit and was retained in the final model. Inclusion of covariates providing separate parameters for an elimination rate constant or apparent volume of distribution for each study population failed to improve the model. Population average pharmacokinetic parameters from the final model are presented in Table 2. A plot of the predicted NVP concentrations from our model versus the observed concentrations is presented in Figure 3. The derived elimination half-life was 55.0 hours. Simulated NVP concentration-time curves from a 1000-patient simulation using these parameters are presented in Figure 4a. Using this simulation, a graph showing the percentage of women with NVP levels greater than the assay lower limit of quantitation (50 ng/mL) and greater than
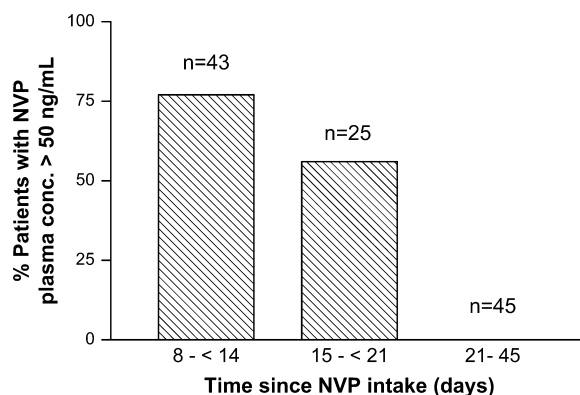

FIGURE 2. Percentage of patients with detectable (>50 ng/mL) nevirapine (NVP) plasma levels between 8 and ≤14 days, 15 and ≤21 days, and 21 and 45 days after NVP intake in women after a single 200-mg dose taken at the onset of labor for the prevention of mother-to-child HIV transmission. N indicates number of samples assayed.

TABLE 2. Typical Parameter Values From the Population Analysis

Elimination rate constant = 0.0126/h
Vd = 1.75 L/kg
Absorption rate constant = 0.79/min
Absorption lag time = 0.194 hours
Interpatient and residual error
Elimination rate constant = 27.9%
Vd = 27.0%
Absorption rate constant = 111.8%
Proportional residual error = 21.0%
Additive residual error = 37.5 ng/mL

Vd, volume of distribution.

the approximate IC_{50} for wild-type HIV (10 ng/mL) was generated for up to 28 days postpartum (see Fig. 4b).

DISCUSSION

The objective of the current study was to describe MVP elimination after intrapartum single doses to help identify the length of time postpartum during which NVP plasma concentrations remain high enough to select for resistant viruses. NVP plasma concentrations were determined in samples obtained immediately after delivery and between days 8 and 45 after delivery from Thai women who received single intrapartum NVP doses. Plasma NVP concentrations less than the assay lower limit of quantitation were observed as early as 8 days after dosing, whereas the latest sample with a detectable NVP concentration was collected on day 20 after dosing. Previous data describing the duration of NVP in plasma after a single intrapartum dose are limited. The original phase 1 studies after single doses administered during labor in Ugandan and American women stopped sampling approximately 1 week after delivery; at that time, NVP plasma concentrations were greater than 100 ng/mL in nearly all women.[11,12] In a recent study of 44 HIV-negative, healthy, nonpregnant women who received a single 200-mg NVP dose,
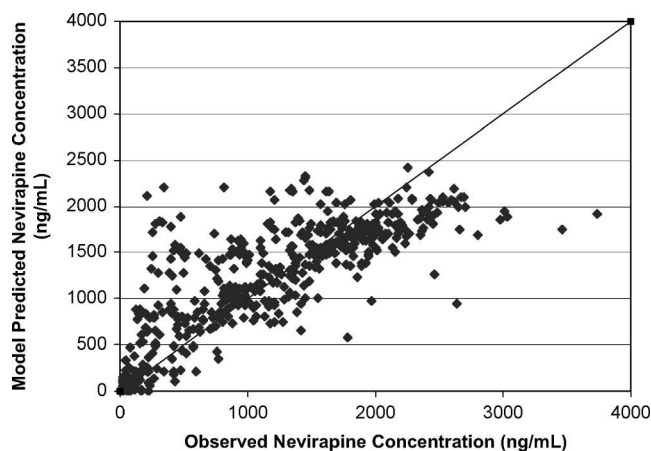

FIGURE 3. Model predicted versus observed nevirapine concentrations from a Bayesian post hoc analysis of the final model.
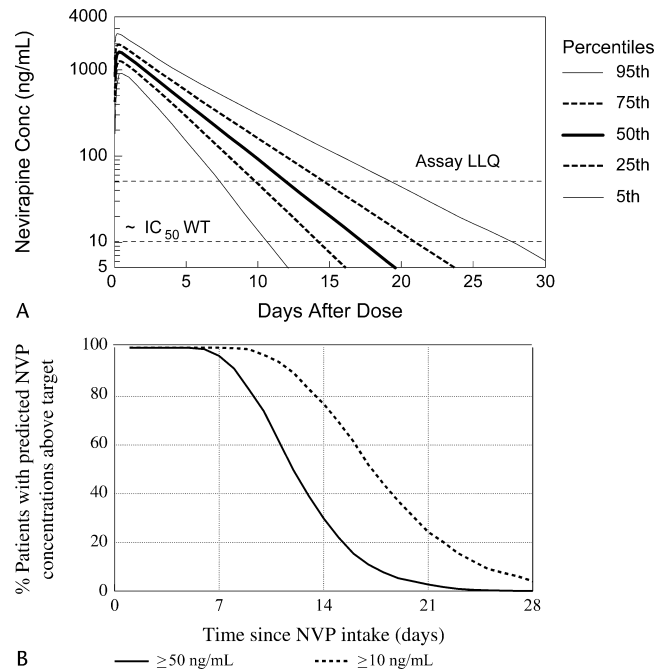

FIGURE 4. A, Plot of simulated nevirapine (NVP) concentration time curves, with fifth, 25th, 50th, 75th, and 95th percentiles. Lower limit of quantitation (LLQ, 50 ng/mL) and approximate concentration required to inhibit by 50% (IC_{50}) for wild-type (WT) HIV (10 ng/mL) are indicated by dashed lines. B, Percentage of patients with NVP levels above the target thresholds. Solid line indicates assay lower limit of quantitation (50 ng/mL), and dashed line indicates approximate IC_{50} for WT type HIV (10 ng/mL).

NVP remained detectable in 7 women at greater than the lower limit of assay quantitation of 150 ng/mL on the last day of sampling 22 days after dosing.[18]

The lower limit of quantitation of the assay used to analyze the samples from the Thai women was 50 ng/mL, greater than the ~10 ng/mL NVP IC_{50} of wild-type HIV. To extrapolate to concentrations less than 50 ng/mL, we combined the Thai data with the phase 1 data from Ugandan and American women and used population analysis techniques to generate simulated NVP concentration-time curves down to 5 ng/mL. This simulation predicts that NVP concentration falls to less than 10 ng/mL in 5% of women before 11 days after dosing, in 50% of women by approximately 17.5 days after dosing, and in 95% of women by 28 days after dosing, which was consistent with the raw data from the Thai women postpartum.

NVP concentrations after intrapartum dosing demonstrate considerable variability. When the data from the Ugandan and American phase 1 studies were pooled, elimination half-life averaged 72.5 hours, with a standard deviation of 36.2 hours.[19] The reason for the high interpatient variability in postpartum elimination of plasma NVP is probably multifactorial. Difference in NVP absorption rates during labor may account for some of the variability observed. Also, genetic differences could contribute to pharmacokinetic variability. NVP is metabolized by the hepatic oxidative cytochrome P450 (CYP) enzyme system, primarily the CYP3A family and, to

a lesser degree, CYP2B6; however, currently defined molecular variations in the CYP3A4 gene do not seem to contribute substantially to interindividual variability in the disposition of CYP3A4 substrate drugs.[20]

ZDV prophylaxis was given before and during labor in addition to the single intrapartum dose, but it is known that these 2 drugs have no drug-drug interactions. The American women weighed more than the Thai and Ugandan women, but once volume of distribution was scaled for weight in the population analysis, there were no significant differences in pharmacokinetic parameters among the 3 populations.

In many developing countries, a NVP-based combination regimen is often the first-line antiretroviral regimen. These regimens are often administered as fixed-dose combination pills combining NVP with 2 nucleoside reverse transcriptase inhibitors. Many women exposed to single-dose NVP during labor are later prescribed a NVP or NNRTI-based combination when they need antiretroviral treatment for their own health. Although the clinical significance of postpartum NVP resistance on future NNRTI treatments is not fully known, data from this cohort suggest that combination regimens including NVP are less successful in terms of virologic suppression in women who recently were exposed to intrapartum single doses, indicating that NVP resistance likely contributes to these treatment failures.[5] Strategies are needed to try to prevent the selection of NVP resistance after a single intrapartum dose for prevention of mother-to-child transmission of HIV (PMTCT). One proposed strategy was to use supplemental postpartum antiretroviral therapy to suppress viral replication until NVP concentrations are no longer sufficient to select for resistant HIV. Recently, preliminary data from the Treatment Options Preservation Study (TOPS) in South Africa were reported, showing a statistically significant reduction in detectable NNRTI resistance mutations in women 6 weeks after intrapartum NVP when administered 4 to 7 days of ZDV plus 3TC (50% [n = 18] versus 9% [n = 43] in women who did not receive this additional treatment).[21] Also, a report on a small group of HIV-infected adults receiving chronic combination antiretroviral regimens including NVP suggests that continuation of the other antiretrovirals for 1 week after cessation of NVP may prevent the development of NVP resistance.[22] Chronic nevirapine therapy results in more rapid drug elimination through autoinduction, however, resulting in a shorter duration greater than the IC_{50} than in pregnant women receiving only single intrapartum NVP doses. In addition, viral replication was fully suppressed in nearly all these patients before NVP was stopped, making them much less likely to select for NNRTI resistance as NVP concentrations declined. The optimal duration of supplemental postpartum antiretroviral therapy that needs to be provided is unclear. The major aim of the current analysis was to determine how long NVP persists postpartum at plasma concentrations likely to select for HIV resistance. Although the minimum concentration needed to select for the development of NVP-resistant HIV is not known, concentrations around the IC_{50} are likely to be sufficient. These data suggest that studies investigating the potential benefit of a short course of antiretroviral therapy after a single intrapartum NVP dose to suppress replication should continue to provide supplemental antiretrovirals for 4 weeks after delivery.

This analysis has several limitations. The simulation is not based on any direct observations of concentrations less than 50 ng/mL. NVP elimination appears linear down to the 50-ng/mL level. Our model assumes that elimination continues to be linear below this concentration and not affected by a late deep tissue distributive phase. The population pharmacokinetic model also did not include an autoinduction component, which may begin to occur even after a single dose. The population database incorporated data from 3 studies, each using different sampling designs, ethnic populations and drug assays. Nevertheless, all the assays were validated, the concentrations around delivery were equivalent among the 3 studies, and the population analysis showed no significant variation in elimination rate constant or volume of distribution among the studies, suggesting that the data from the 3 studies are suitable for combination in 1 data set for modeling.

In conclusion, these data demonstrate that plasma NVP concentrations around the IC_{50} may persist in some women for as long as 4 weeks after administration of single intrapartum NVP doses. With the growing use of combination antiretroviral regimens including NVP as first-line treatments for HIV-infected women around the world, prevention of postpartum NVP resistance may be important in ensuring the future well-being of mothers receiving single-dose intrapartum therapy. The preliminary data from the TOPS study suggest that 4 or 7 days of postpartum antiretroviral treatment reduces the selection of NNRTI-resistant virus. These data need to be confirmed, and based on the results of our study, the efficacy of longer postpartum treatments covering the entire NVP tail needs to be determined.

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