Association of Nevirapine Levels with Rash or Hepatotoxicity Among HIV-Infected Thai Women

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Abstract: Background: We performed a nested case-control study of Thai women prescribed nevirapine-based antiretroviral therapy (ART) to determine if development of rash or hepatotoxicity during the first 24 weeks of treatment is associated with plasma nevirapine concentrations.

Method: From May 2005-January 2007, we enrolled 217 women initiating nevirapine-based ART in Thailand. Cases (n = 54) were women who during the first 24 weeks of treatment with nevirapine developed rash (any grade, n = 42) or hepatotoxicity (≥grade 2, n = 22, [10 had both]). Controls were the next enrolled woman who was confirmed not to meet the case definition during the first 24 weeks. Nevirapine concentrations after the two week lead-in dose of 200 mg once daily were compared between cases and controls by Wilcoxon rank-sum tests.

Results: We found no difference in Week 2 pre-dose nevirapine concentrations: cases median = 3,528 ng/mL (n = 24), controls median = 3,150 ng/mL (n = 30), p = 0.5. Cases had higher post-dose nevirapine concentrations (median = 6,150 ng/mL, n = 21) than controls (median = 4,746 ng/mL, n = 20, p = 0.02). When limited to cases who developed a rash at Week 2, we found no differences in the pre-dose (median = 3,270 ng/mL, n = 12, p = 0.9) or post-dose nevirapine concentration (median = 5,443 ng/mL, n = 9, p = 0.4) compared with controls.

Conclusions: We cannot conclude definitively that nevirapine concentrations at two weeks of therapy are associated with rash or hepatotoxicity. It is unlikely that therapeutic drug monitoring at that time will improve identification of patients at risk for rash or hepatotoxicity.

Keywords: Adverse effect, antiretroviral, hepatotoxicity, nevirapine, rash, Thailand.

INTRODUCTION

An estimated 7-15% of patients receiving nevirapine experience drug rash or toxicity, although higher rates have been reported in Thai populations [1,2]. One possible explanation is that Thai patients may have higher plasma concentrations of nevirapine than North American or European patients when treated with the same dosage. The TREAT Asia cohort has found that a significant proportion of drug discontinuations (23%) are attributed to nevirapine-induced rashes [2]. These drug discontinuations have programmatic implications for national treatment programs since nevirapine is part of the first-line regimen in many countries.

The original dosing regimen of nevirapine was developed in western countries in the 1990s and consists of a standard lead-in dose of 200 mg once daily for the first two weeks of therapy followed thereafter by 200 mg twice daily. This lower lead-in dose is given to minimize the risk of adverse reactions to nevirapine observed in pre-clinical trials [3,4]. After a two-week dosing period, auto-induction of hepatic P450 isoenzymes results in an approximate two-fold increase in nevirapine clearance [5].
The usual target trough (C_{min}) plasma concentration for nevirapine considered necessary for optimal virologic response is >3,000 ng/mL [6]. The association of nevirapine concentrations and toxicity is still under debate. One study in Amsterdam found a significant association between the development of rash and nevirapine concentrations greater than 5,300 ng/mL [7]. A study in Spain found an association between increased liver transaminases and nevirapine trough concentrations greater than 6,000 ng/mL [8]. A study in Italy, however, did not find an association between nevirapine concentrations and hepatotoxicity [9]. The multi-country “2NN Study” which included patients from Thailand, South Africa, South America, and other Western countries examined the pharmacokinetics of nevirapine and the relation to adverse events [10,11]. For patients receiving the standard dose of nevirapine 200 mg twice daily, the average C_{max} was 7,030 ng/mL and C_{min} was 4,950 ng/mL across the entire cohort. The investigators found that patients from Thailand had 22% lower clearance of nevirapine than patients from South America or Western countries. They reported no association between rash, or other adverse events, and nevirapine concentrations [10]. Another study conducted in Thailand found the mean nevirapine concentration in patients taking nevirapine-based ART drawn on average approximately 9 hours after a dose to be 8,720 ng/mL [12]; this value was higher than the C_{max} reported in the 2NN Study from multiple countries [10]. The average concentrations drawn between 0 – 9.9 hours was 9,900 ng/mL and between 10 – 14 hours after a dose (indicative of trough concentrations) was 7,960 ng/mL [10].

The NNRTI Response study was a multi-site observational study conducted in Thailand, Zambia, and Kenya [13]. This nested case-control sub-study from the Thailand portion of the study was undertaken to determine if plasma nevirapine concentrations were associated with the development of rash or hepatotoxicity during the first 24 weeks of nevirapine-based ART.

METHODS

Definition of Cases and Controls

A total of 217 HIV-infected women were enrolled in Bangkok, Thailand at two sites – Siriraj Hospital and Rajvithi Hospital [13]. At enrollment and at weeks 2, 4, 8, 16, and 24, participants had serum alanine transaminase (ALT) and aspartate transaminase (AST) measured and were evaluated clinically for signs and symptoms of hepatitis and rash. We graded adverse events including hepatotoxicity and rash according to the National Institutes of Health’s Division of AIDS guidelines as previously reported [14,15].

Cases in this analysis were women who during the first 24 weeks of treatment with nevirapine-based HAART developed 1) any grade of rash or 2) an increase of at least one grade from baseline in ALT or AST to at least grade 2. Only rash or increase in ALT or AST that the study team determined to be “possibly”, “probably”, or “definitely” related to nevirapine, considering character and timing of the reaction, was considered. Controls were selected as the next enrolled participant at the same study site who was confirmed not to have met the case definition during the first 24 weeks of treatment.

Clinical care was provided by physicians with expertise in HIV disease at each of the study hospitals. The study protocol did not direct individual treatment decisions and the clinicians used their discretion to continue nevirapine through a mild reaction, to interrupt nevirapine therapy and restart it, or to change therapy substituting either efavirenz or a protease inhibitor for nevirapine.

Specimens and Bioanalytical Methods

Blood specimens were collected in Becton Dickinson Vacutainer® tubes containing ethylenediaminetetraacetic acid as an anticoagulant and were stored at room temperature until transported on ice to the laboratory. Plasma was separated and frozen within six hours of blood collection. The time and date of specimen collection was recorded by study nurses. CD4 cell counts were measured as previously described [13]. We tested for hepatitis B surface antigen and for hepatitis C antibody with Murex Enzyme Immunoassays (Abbott Diagnostics, Dartford, UK). Stored plasma specimens collected at 2, 4, and 8 weeks of the study were assayed for nevirapine, stavudine, and lamivudine concentration.

Stavudine, lamivudine, and nevirapine concentrations in plasma specimens were determined using an LC-MS/MS method [High Performance Liquid Chromatography (HPLC, Acquity™ Ultra Performance LC, Waters Co., Ltd. USA), Mass Spectrometer (Quattro Premier XE, Micromass Technologies, UK) and Masslynx v 4.1 software (Micromass Technologies, UK)]. The method had been developed and validated by the Department of Pharmacology, Faculty of Medicine Siriraj Hospital, Mahidol University (Bangkok, Thailand) according to the US FDA Guidance for Industry: Bioanalytical Method Validation (2001). The validation demonstrated that the method was reliable and reproducible for the intended use with respect to selectivity, sensitivity, linearity, accuracy, precision, and stability of the drugs in plasma. The assay had a linearity range of 1-8,000, 1-12,500, and 1-25,000 ng/mL for stavudine, lamivudine, and nevirapine, respectively.

Assignment of Pre- and Post-Dose Nevirapine Concentrations

Participants took versions of locally produced medications as either a fixed-dose combination of stavudine (30 or 40 mg), lamivudine (150 mg), and nevirapine (200 mg) [GPO-vir, Government Pharmaceutical Organization (GPO), Bangkok, Thailand] or as individual formulations of stavudine (30 or 40 mg) and lamivudine (150 mg) (GPO, Bangkok, Thailand). To accommodate the need for a two-week lead-in phase of nevirapine 200 mg daily, women took GPO-vir once daily in the morning and stavudine and lamivudine as individual products in the evening. After two weeks, women took GPO-vir twice daily. Adherence support and counseling was provided by the clinical staff and study nurses who met with each participant at each study visit to record adherence to medications and to provide additional counseling. Upon enrolling in the study, participants were instructed to choose a time of day for ingestion of antiretroviral drugs that would best meet their needs.

Although the time when antiretroviral medications were generally given (e.g., 9 AM and 9 PM) was known, the precise time of the most recent dose of medications was not
recorded. We relied on the concentrations of stavudine and lamivudine (while not considering the corresponding nevirapine concentrations) to determine if a plasma specimen was classified as pre-dose or post-dose. Stavudine and lamivudine are both renally cleared with plasma half-lives of ~1 hour [16] and ~5-7 hours [17], respectively. There is substantial fluctuation in the plasma concentrations of stavudine and lamivudine over a 12-hour dosing interval. The typical peak and trough stavudine concentrations following twice daily doses of 30 or 40 mg are >600 ng/mL (range ~600 – 1,200) and <25 ng/mL (range, undetectable - <200) [18-21], respectively. The same values for lamivudine following twice daily doses of 150 mg are >1000 ng/mL (range ~500 – 2,000) and <200 (range, <50 – 500) [22-24], respectively. In contrast, there is relatively little fluctuation in plasma nevirapine concentrations over a 12-hour dosing. Nevirapine is metabolized by hepatic cytochrome P450 isoenzymes, primarily CYP3A4, and auto-induces its own metabolism so that the terminal half-life decreases from ~45 hours after the first dose to ~25-30 hours following multiple dosing [25].

Considering these pharmacokinetic data, we characterized pre-dose specimens as those that had concentrations of: 1) stavudine ≤200 ng/mL and lamivudine ≤500 ng/mL, or 2) stavudine ≤25 ng/mL and lamivudine <650 ng/mL. The latter was chosen to accommodate specimens with very low stavudine concentrations and relatively low lamivudine concentrations in order to include more data points in the pre-dose group. Post-dose specimens had concentrations of stavudine >200ng/mL and lamivudine >500 ng/mL. Specimens that did not meet either of these definitions were censored from the analyses.

Statistical Analysis

We calculated standard summary statistics of the enrollment characteristics including counts, proportions, medians, and quartile ranges. Nonparametric Wilcoxon rank-sum tests were used to compare the medians of selected baseline variables between cases and controls. Chi-square or Fisher’s exact tests were used to compare categorical covariates. For comparisons of nevirapine concentrations between two groups of participants, we used Wilcoxon rank-sum tests. Women had at most one nevirapine concentration determined for analysis (either pre-dose or post-dose) at each of week 2, 4, or 8. Our primary comparison was of the plasma nevirapine concentrations at week 2, where all but one woman had a specimen available. Adverse effects present at week 2 or week 4 that resulted in substitution of another drug for nevirapine confounded statistical comparisons at week 4 and week 8 (i.e., nevirapine had been discontinued before the week 4 and week 8 visit for these women), thus we did not make statistical comparisons using those data. We present the raw values for concentrations at weeks 4 and 8 for visual inspection. We also tested for differences in nevirapine concentrations according to participants’ use of fluconazole and serum hepatitis B surface antigen status. We plotted nevirapine concentrations versus body-mass index and calculated Pearson’s correlation coefficient to determine if there was a linear relationship. All of these statistical calculations were performed using SAS software, version 9.2 (SAS Institute, Inc., Cary, North Carolina).

Written informed consent to participate in this study was obtained from each participant according to the protocol approved by the Ethical Review Committee for Research in Human Subjects of Thailand Ministry of Public Health (Rajvithi Hospital) and the Institutional Review Boards of the Siriraj Hospital and of the CDC.

RESULTS

We identified 54 cases and selected 54 controls (Table 1), which included 34 cases and 34 controls from among 115 women enrolled at Rajvithi Hospital and 20 cases and 20 controls from among 102 women enrolled at Siriraj Hospital (p = 0.26 Chi-square test for proportion of cases by site). Among the 54 cases, 42 (78%) women had rash and 22 (41%) had hepatotoxicity; 10 (19%) women had both rash and hepatotoxicity. The rash was first noted at week 2 for 25 women, at week 4 for eight women, at week 8 for seven women, and at week 16 for two women. Hepatotoxicity was first noted at week 2 for eight women, at week 4 for 11 women, at week 8 for one woman, and at week 16 for two women. There were 270 samples assayed for lamivudine, stavudine, and nevirapine. We assayed samples from all 54 controls at weeks 2, 4, and 8 and from cases at week 2 for 53 women (one woman had no sample available), at week 4 for 35 women (19 had discontinued nevirapine), and at week 8 for 20 women (34 had discontinued nevirapine). Based on the stavudine and lamivudine concentrations, we classified 136 (50%) samples as pre-dose, 108 (40%) samples as post-dose, and 26 (10%) as samples unclassifiable or censored. Median pre-dose concentrations were: stavudine 8 ng/mL (interquartile range [IQR], below level of quantification – 22), lamivudine 191 ng/mL (IQR, 141 – 293), and nevirapine 4,377 ng/mL (IQR, 3,190 – 6,234). Median post-dose concentrations were: stavudine 643 ng/mL (IQR, 448 – 914), lamivudine 2,038 ng/mL (IQR, 1,458 – 2,878), and nevirapine 6,671 ng/mL (IQR, 5,059 – 8,934). The median post-dose nevirapine concentration was higher than the pre-dose nevirapine concentration at week 2 (p <0.001), week 4 (p <0.01), and week 8 (p = 0.02) indicating the assignment of pre-dose and post-dose based on the concentrations of stavudine and lamivudine was valid (Fig. 1).

Nevirapine Concentrations in Cases and Controls

We found no difference in pre-dose plasma nevirapine concentrations at week 2 comparing cases (3,528 ng/mL, n = 24) with controls (3,150, n = 30, p = 0.5) (Fig. 1). Post-dose nevirapine concentrations were higher for cases who developed rash at any time (median = 6,150 ng/mL, n = 21) versus controls (median = 4,746 ng/mL, n = 20, p = 0.02); however, when limited to cases who developed a rash at week 2, we observed no differences in either pre-dose or post-dose week 2 plasma nevirapine concentrations: median 3,270 ng/mL (n = 12, p = 0.9) and median 5,443 ng/mL (n = 9, p = 0.4), compared with the same controls, respectively. When limiting the analysis to only women who had hepatotoxicity, we found that they had similar pre-dose and post-dose plasma nevirapine concentrations at week 2 compared with controls. Women who developed both rash and hepatotoxicity likewise had similar pre-dose and post-dose nevirapine concentrations compared with controls at week 2.
Investigation of Other Co-Factors that Might be Associated with Nevirapine Concentrations

Fluconazole was prescribed for 32 patients at the time of the week 2 visit, for 26 patients at week 4, and for 23 patients at week 8. There were no differences in pre-dose or post-dose nevirapine concentrations among patients taking fluconazole compared with patients not taking fluconazole at weeks 2, 4, or 8. There were also no differences in pre-dose and post-dose nevirapine concentrations at weeks 2, 4, or 8 comparing women who were positive for hepatitis B surface antigen versus negative. There were too few women who were hepatitis C antibody positive to make meaningful comparisons. There was a marginally significant relationship between body-mass index and the post-dose plasma nevirapine concentration at week 2 (Pearson’s $r = -0.31$, $p = 0.051$), but not at week 4 ($r = 0.02$, $p = 0.90$) or week 8 ($r = 0.09$, $p = 0.64$), and no significant relationship between body-mass index and pre-dose nevirapine concentrations at week 2 ($r = -0.013$, $p = 0.92$), week 4 ($r = -0.06$, $p = 0.69$) or week 8 ($r = 0.20$, $p = 0.25$) (Fig. 2).

Strata of Nevirapine Concentrations

At week 2 while on nevirapine 200 mg once daily, pre-dose nevirapine concentrations ranged from <3,000 ng/mL for 39% of women to ≥9,000 ng/mL for 2% of women. Post-dose concentrations ranged from <3,000 ng/mL for 12% of women to ≥9,000 ng/mL for 15% of women (Table 2). At week 2, cases were not more likely than controls to have a pre-dose concentration ≥6,000 ng/mL ($p = 0.78$ by Fishers exact test; sensitivity = 0.13, specificity = 0.93, predictive value positive = 0.60, predictive value negative = 0.57) or a post-dose nevirapine concentration ≥9,000 ng/mL ($p = 0.18$, sensitivity = 0.24, specificity = 0.95, predictive value positive = 0.83, predictive value negative = 0.54). At weeks 4 and 8 (while on nevirapine 200 mg twice daily), there were fewer pre-dose or post-dose nevirapine concentrations <3,000 ng/mL. Nevirapine concentrations ≥9,000 ng/mL were found at week 4 for 13% of pre-dose and 46% of post-dose observations and at week 8 for 11% of pre-dose and 13% of post-dose concentrations.

Strata of Nevirapine Concentrations and Effect on Subsequent Virologic Response

At week 2, a pre-dose nevirapine concentration <3,000 ng/mL was found for 21 (39%) of 54 women and a post-dose nevirapine concentration <3,000 ng/mL was found for 5 (12%) of 41 women (Table 2). After week 2, an additional 5 women had a pre-dose ($n = 4$) or post-dose ($n = 1$) nevirapine concentration <3,000 ng/mL for a total of 31 women who ever had a measured nevirapine concentration below the usual targeted threshold considered optimal for

| Enroll Characteristic | Cases (n = 54) | Controls (n = 54) | p-Value |
|-----------------------|---------------|------------------|---------|
| Age (years)           | Median (range)| 31 (23-50)       | 31 (24-55) | 0.8 |
| Weight (kg)           | Median (range)| 50.5 (31.5-74)   | 50 (30-97) | 0.3 |
| Body Mass Index (kg/m²)| Median (range)| 21.0 (12.6-29.3) | 21.1 (13.3-37.9) | 0.4 |
| World Health Organization Stage | | | |
| Stage 1               | N             | 16               | 23       |
| Stage 2 - Mild        | N             | 19               | 15       |
| Stage 3 - Moderate    | N             | 8                | 8        |
| Stage 4 - Severe      | N             | 11               | 8        |
| HIV Viral Load (copies/ml) | Median (range)| 67,558 (2,059 - >750,000) | 91,427 (852 - >750,000) | 0.9 |
| CD4 count (cell/µL)   | Median (range)| 148 (0-330)     | 138 (0-390) | 0.7 |
| Hepatitis B Surface Antigen Positive | N          | 8                | 8        |
| Hepatitis C Antibody Positive | N          | 4                | 2        |
| Characteristic of Toxicity | | | |
| Rash Grade            |               | n/a              | 1       |
| 1 (mild)              |               | 16               |
| 2 (moderate)          |               | 18               |
| 3 (severe)            |               | 5                |
| 4 (life-threatening)  |               | 3                |
| Hepatotoxicity Grade  |               | n/a              | 11      |
| 2 (2.5 – 4.99 x ULN*) |               | 9                |
| 3 (5.0 – 9.99 x ULN)  |               | 9                |
| 4 (≥10 x ULN)         |               | 2                |

*ULN – upper limit of normal for ALT or AST result.
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maintaining virologic control. Viral load was available at week 24 for 98 women in this analysis who continued on NNRTI-based ART (10 women were changed to a protease inhibitor or dropped out of the study). Viral load was <400 copies/mL for 29 (100%) of 29 women who ever had a pre-dose or post-dose nevirapine concentration <3,000 ng/mL and for 64 (93%) of 69 women who never had a pre-dose or post-dose nevirapine concentration <3,000 ng/mL (p = 0.3).

Fig. (1). Nevirapine Concentrations at 2, 4, and 8 Weeks after Starting Treatment, Bangkok, Thailand, 2005-2007.

Box-whisker plots (center line = median, top and bottom of box = interquartile range, ends of vertical line = minimum and maximum values) of pre-dose and post-dose plasma nevirapine concentrations at 2, 4, and 8 weeks after starting treatment for women with hepatotoxicity or rash (cases) and women without hepatotoxicity or rash (controls) during the first 24 weeks of nevirapine-based antiretroviral therapy. Participants received nevirapine 200 mg once daily for the first 2 weeks, then 200 mg twice daily.

| Visit week | Pre-Dose | Post-Dose |
|------------|----------|-----------|
| Case       | Control  | p-Value   | Case       | Control  | p-Value   |
| 2 week     | n        | NVP       | n          | NVP      |           |
| 3,528      | 3,150    | 0.5       | 21         | 6,150    | 0.02      |
| 4 week     | 5,995    | 31        | 5,703      | -        | -         |
| 6,078      | 4,363    | -         | 8          | 6,286    | -         |
| 8 week     | 6,078    | 27        | 4,363      | -        | -         |

NVP = median nevirapine concentration (ng/mL)
p-value is by Wilcoxon test comparing nevirapine concentration for cases versus controls at week 2. We present the raw values of concentrations at weeks 4 and 8, without statistical comparisons, for visual inspection.
DISCUSSION

Among Thai women, rash or hepatotoxicity during the first 24 weeks of NNRTI-based ART was associated with higher post-dose, but not pre-dose, plasma nevirapine concentrations at week 2 while taking nevirapine once daily. There was a marginal association of lower body-mass index with higher post-dose nevirapine concentrations at week 2, although this finding must be interpreted cautiously since the body-mass index only explained approximately 9% of the variation seen in nevirapine concentrations at this time point.

A higher post-dose nevirapine concentration after 2 weeks of the recommended lead-in dose of 200 mg daily suggests that persons who will develop rash or hepatotoxicity may have elevated concentrations of nevirapine soon after starting nevirapine. However, an elevated post-dose concentration at week 2 alone does not appear to be sufficient to explain these reactions, since many
between cases and controls. Likewise, our comparisons for detecting relatively small differences in nevirapine concentrations were limited by small numbers for comparisons. We had to design our analysis to account for uncontrolled timing of ingestion that may have resulted in women with varying pre-dose or post-dose nevirapine concentrations, and for cases who changed from nevirapine to another drug after a reaction resulting in decreasing numbers of observations over time. This limitation reduced our sample size for comparisons and limited our ability to detect an association with rash or hepatotoxicity with smaller differences in pre-dose nevirapine concentrations.

We did not conduct similar drug concentration testing among the Kenyan and Zambian women enrolled in this study, therefore we have no data on those women using this study design. Lastly, we did not test for other possible chemical causes of hepatitis such as aflatoxin exposure.

In conclusion, we could not demonstrate definitively that nevirapine concentrations after a two week lead-in dose of 200 mg daily are associated with rash or hepatotoxicity among Thai women. Many patients who tolerated nevirapine well for 24 weeks had week 2 concentrations that were much higher than weeks 2, 4 and 8 after the dose had been escalated to 200 mg twice daily. It is reassuring that a nevirapine concentration <3,000 ng/mL measured at week 2 was not associated with virologic failure while on NNRTI-based ART at week 24.

Nevirapine-associated rash, hepatotoxicity, and rash-associated hepatotoxicity typically occur in the first few weeks to months of therapy; patients who tolerate nevirapine for the first few months will likely tolerate it indefinitely [2]. Some studies have supported an association between risk for hepatotoxicity and CD4 cell count ≥250 cells/µL in women [26,27] but others have not [14,28]. We have previously demonstrated from the parent study of this sub-study that among women taking nevirapine-based ART, severe hepatotoxicity and rash-associated hepatotoxicity were predicted by abnormal baseline ALT or AST results but not by a CD4 count ≥250 cells/µL [14]. Co-infection with viral hepatitis B or C has also been associated with hepatotoxicity from antiretroviral therapy in some [29,30] but not all studies [30,31].

We did not record the precise time of ingestion of the antiretroviral drug in relation to the time the blood sample was taken. We characterized the nevirapine concentrations as either pre-dose or post-dose based on the concentration of stavudine and lamivudine from the same sample. The rationale for doing so was strengthened by the fact that nevirapine, stavudine, and lamivudine were taken simultaneously in the same fixed-dose combination tablet and the three drugs have relatively different pharmacokinetic properties. Our sample size for any one comparison was smaller than if we had a priori designed the study to collect all pre-dose samples. This limited our ability to detect relatively small differences in nevirapine concentrations between cases and controls. Likewise, our comparisons for other co-factors associated with nevirapine concentrations (e.g., concomitant fluconazole use, hepatitis B surface antigenemia) were limited by small numbers for comparisons. We had to design our analysis to account for uncontrolled timing of ingestion that may have resulted in women with varying pre-dose or post-dose nevirapine concentrations, and for cases who changed from nevirapine to another drug after a reaction resulting in decreasing numbers of observations over time. This limitation reduced our sample size for comparisons and limited our ability to detect an association with rash or hepatotoxicity with smaller differences in pre-dose nevirapine concentrations.

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In conclusion, we could not demonstrate definitively that nevirapine concentrations after a two week lead-in dose of 200 mg daily are associated with rash or hepatotoxicity among Thai women. Many patients who tolerated nevirapine well for 24 weeks had week 2 concentrations that were much higher than some of those who developed rash or hepatotoxicity. It is unlikely that therapeutic drug monitoring after the first two weeks of therapy will substantively improve identification of patients at risk for these nevirapine-associated adverse events.

**ROLES OF AUTHORS**

Study Concept and Design: Drs. Ratanasuwan, Jariyasethpong, Anekthananon, Intalapaporn were the primary Thai investigators, Drs. Raengsakulrach, Peters, McNicholl, McConnell, and Weidle were the primary CDC Investigators responsible for design of the study.

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Statistical Analysis: Ms. Chantharowijong, Dr. Ratanasuwon, Dr. Peters, Dr. McConnell and Dr. Weidle led the statistical analysis and interpretation.

Writing: Drs. Ratanasuwon, Peters and Weidle wrote the main draft of the manuscript. All co-authors reviewed, critiqued, and provided written concurrence with the final draft of the manuscript.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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