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Increased Risk of Hepatotoxicity in HIV-infected Pregnant Women Receiving Antiretroviral Therapy Independent of Nevirapine Exposure

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Abstract

Objective—To estimate whether the association between nevirapine (NVP) and hepatotoxicity differs according to pregnancy status in HIV-infected women.

Methods—This analysis included HIV-infected pregnant women on ART from two multicenter, prospective cohorts: The Women and Infants Transmission Study (WITS) and the International Maternal Pediatric Adolescent AIDS Clinical Trials (IMPAACT) protocol P1025 and HIV-infected non-pregnant women from one multicenter, prospective cohort: The Women's Interagency HIV Study (WIHS). Using multivariate Cox proportional hazards regression, the interaction between NVP and pregnancy status in terms of hepatotoxicity was investigated. NVP use was dichotomized as use or no use and was further categorized according to ART exposure history. We investigated two outcomes: any liver enzyme elevation (LEE) (grade 1-4) and severe LEE (grade 3-4).

Results—Data on 2050 HIV-infected women taking ART were included, 1229 (60.0%) pregnant and 821 (40.0%) non-pregnant. Among the pregnant women, 174 (14.2%) developed any LEE and 15 (1.2%) developed severe LEE as compared to 75 (9.1%) and 5 (0.6%) respectively of the non-pregnant women. In multivariate adjusted models, NVP was not significantly associated with risk of LEE regardless of pregnancy status; however, pregnancy was associated with an increased risk of any LEE (RR 4.7, CI 3.4 – 6.5) and severe LEE (RR 3.8, CI 1.3 – 11.1). The association of pregnancy and LEE was seen regardless of prior ART and NVP exposure history.

Conclusions—No significant association between NVP and LEE was observed regardless of pregnancy status, but pregnancy was significantly associated with increased hepatotoxicity in HIV-infected women.

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Keywords

AIDS; antiretroviral therapy; hepatotoxicity; HIV; nevirapine; pregnancy; women

INTRODUCTION

Administration of combination antiretroviral therapy (ART) is recommended during pregnancy in HIV-infected women to reduce viral load, prevent vertical transmission and improve maternal health. While some studies have found few maternal toxicities associated with ART use [1,2], others have raised concerns of increased hepatotoxicity among pregnant women exposed to nevirapine (NVP), particularly in NVP naïve women with CD4+ cell counts > 250 cells/μL [3-5]. The goal of this study was to estimate whether the association between NVP and hepatotoxicity differs according to pregnancy status in HIV-infected women.

METHODS

Study Population

The index group included HIV-infected pregnant women on ART from two multicenter, prospective cohorts in the United States: The Women and Infants Transmission Study (WITS) and the International Maternal Pediatric Adolescent AIDS Clinical Trials (IMPAACT) protocol P1025. Details of these study populations have previously been published [6,7]. This analysis was limited to women enrolled since 2002 when aspartate aminotransferase (AST) and alanine aminotransferase (ALT) data were collected prospectively in both study cohorts. The reference group was comprised of HIV-infected, non-pregnant women on ART from one ongoing multicenter, prospective United States cohort: the Women's Interagency HIV Study (WIHS). Details of cohort recruitment, retention and characteristics are reported in detail elsewhere [8,9]. Inclusion in this study was limited to data obtained from July 2002 to June 2006 to match the temporality of the WITS and P1025 studies.

Women were included in the analysis whether they were ART naïve or had previous treatment with any ART regimen. NVP exposure was dichotomized as use or no use and further categorized according to ART exposure history: ART naïve, prior ART exposure, NVP naïve and prior NVP exposure. Women in WIHS who became pregnant, were > 45 years old after July 2002 or who did not receive ART were excluded from the analysis. Pregnant women who received only intrapartum or postpartum ART were not included. Women who did not have aminotransferase data were also excluded.

Data Collection

Data were collected on the pregnant women from their estimated date of conception through their postpartum visit. Both the WITS and P1025 protocols obtained aminotransferase data at the initiation of ART, each trimester, at delivery and at the postpartum visit, which occurred at 8 and 6 weeks postpartum in WITS and P1025, respectively. Data were collected on the non-pregnant women enrolled in WIHS every six months for approximately 12 months, or three visits total. The beginning of the observation period was selected to match the calendar times of the estimated date of conception of the pregnant women. This was done by randomly selecting the initiation of observation of women enrolled in WIHS so that the cumulative distribution of these initiation times corresponded to the cumulative distribution of the estimated date of conception of the pregnant women.

Outcomes

ALT and AST levels were classified based on changes relative to the upper limit of normal (ULN) according to the Division of AIDS toxicity guidelines for adults [10]. We investigated two hepatotoxicity outcomes: any liver enzyme elevation (LEE) (grade 1-4) and severe LEE (grade 3-4). Women with elevated pretreatment aminotransferase levels were graded based on changes relative to their baseline [11].

Statistical Analysis

Differences in baseline characteristics of the study population were compared according to pregnancy status. Continuous variables were analyzed using F tests. Categorical variables were analyzed using the Pearson chi-square test.

Cox proportional hazards models were used to estimate the association between NVP use and LEE while controlling for potential confounders including pregnancy status. Data were organized in the counting process style of input to model NVP exposure and other covariates as time-dependent variables [12]. Race, ART exposure prior to follow-up, and risk group for HIV transmission were the only covariates not modeled as time-dependent variables. Univariate analysis was first performed to identify covariates significant at $P=0.10$ to be included in multivariate analysis. These covariates were then evaluated in a multivariate Cox regression model stratified by year of delivery to identify possible effect modification. The SAS PHREG procedure (SAS version 8.2; SAS Institute Inc. Cary, NC) was used to perform these analyses.

RESULTS

A total of 2050 HIV-infected women taking ART were included, composed of 1229 (60.0%) pregnant and 821 (40.0%) non-pregnant women. The baseline demographic and clinical characteristics are shown in Table 1. The pregnant women were significantly younger, had higher CD4+ counts, lower HIV RNA levels, shorter duration of HIV infection, less chronic hepatitis and were more likely to be ART and NVP naive. Similar rates of NVP exposure were observed between the pregnant and non-pregnant women at 17.7% and 20.6% ($p=0.11$), respectively.

Pregnant women were significantly more likely to develop any LEE (14.2%) than non-pregnant women (9.1%) ($p = 0.0001$). Although pregnant women also had a higher rate of severe LEE (1.2%) than non-pregnant women (0.6%), this was not statistically significant ($p = 0.167$). Among the 387 women exposed to NVP, 41 (10.6%) developed any LEE and 3 (0.8%) developed severe LEE as compared to 208 (12.5%) and 17 (1.0%) respectively of the 1663 taking non-NVP regimens.

In univariate models, LEE was significantly associated with pregnancy status, chronic hepatitis, thrombocytopenia ($<150K$), HIV RNA level and baseline liver enzyme elevation, but not NVP use. In multivariate adjusted models, pregnancy was significantly associated with any LEE (RR 4.70, CI 3.39, 6.53) (Table 2, model 1) and severe LEE (RR 3.8, CI 1.3, 11.1) while NVP use was not significantly associated with any LEE (RR 1.17, CI 0.80 – 1.70) or severe LEE (RR 1.78, CI 0.40 – 7.82) regardless of pregnancy status (Table 2, model 2). Although NVP exposure history and CD4+ count were not significant variables in univariate analysis, due to unique concerns in the literature about their possible influence on hepatotoxicity in both pregnant and non-pregnant women, these variables were also introduced into multivariate models. NVP use continued to demonstrate no association with LEE regardless of prior NVP exposure history or CD4+ count (Table 2, models 3 and 4) while pregnancy continued to be a risk factor for developing any LEE.

Three secondary analyses were performed to address possible study design limitations. First, the frequency of data collection was reduced in the pregnant cohorts to mimic the non-pregnant six-month visit schedule of WIHS. This was performed by randomly selecting one AST and ALT measurement from the first two trimesters, one from the third trimester or delivery visit and the measurement from the postpartum visit. Both univariate and multivariate analyses using this limited data set again demonstrated that pregnancy was associated with a significantly increased risk of developing any and severe LEE with little alteration of the risk ratios displayed in Table 2. Second, a standard fixed effect Cox regression analysis (i.e. pregnant versus non-pregnant) was performed instead of the time-dependent counting process formulation. Stratifying this standard Cox model by enrollment age again demonstrated that pregnancy was associated with a significantly increased risk of any LEE. Finally, given that the comparison group (i.e., non-pregnant women enrolled in WIHS) were generally older and more likely infected through injection drug use, a multivariate analysis limited to women without a history of injection drug use was performed. This sensitivity analysis also found a significant increased risk of hepatotoxicity during pregnancy with very similar risk ratios to those reported in Table 2.

DISCUSSION

One of the primary drawbacks of most studies evaluating the relationship of hepatotoxicity and ART during pregnancy is the lack of an HIV-infected, non-pregnant comparison group [3,4]. Without this comparison group, one cannot determine if an increase in LEE with NVP use observed during pregnancy is associated with NVP, the pregnancy, or an interaction between these exposures. Our analysis suggests that a strong association between NVP and LEE was unlikely regardless of pregnancy status (adjusted RR 1.17, CI 0.80 – 1.70) and that pregnancy was a risk factor for LEE.

The only other study that examined the relationship between ART and hepatotoxicity in pregnant versus non-pregnant women compared outcomes of 186 pregnant and 186 non-pregnant women on nelfinavir- or nevirapine-containing regimens from 1997 through 2003 [13]. This study reported that grade 2 or higher LEE occurred more frequently in pregnant women taking NVP (19.0%) than in non-pregnant women taking NVP (4.2%) (OR 5.3, CI 1.6-17.6); however, this association was not seen in those taking nelfinavir (OR 0.9, CI 0.2-3.4). In contrast to these results, our findings did not demonstrate an increase risk of LEE with NVP use regardless of pregnancy status with a much narrower confidence interval.

We also found pregnancy to be an independent risk factor in developing LEE, regardless of concurrent NVP use or prior ART and NVP exposure history. While prior studies have suggested that the risk of developing significant maternal toxicity from antiretroviral use in pregnancy to be relatively small [2], pregnancy may provide a unique environment that predisposes women to drug-induced hepatotoxicity. Studies have demonstrated that women in general predominate among patients with drug-induced liver injury [14]. A number of purported risk factors for developing hepatotoxicity are overrepresented in the pregnant population including CD4+ count > 250 cells/ μ L and ART naiveté, although these factors were not significantly associated with LEE in our analysis. Physiologic changes in pregnancy result in alterations in hepatic metabolism, primarily via induction of certain cytochrome P-450 enzymes, possibly resulting in increased susceptibility to drug-induced hepatotoxicity [15-17]. Although the specific mechanism by which pregnancy may have increased the risk of LEE in our study is unclear, pregnancy has been shown to be an independent risk factor for developing hepatotoxicity in other diseases. Pregnant women with hepatitis E infection develop fulminant hepatic failure more frequently with associated mortality rates over 20% as compared to less than 0.1% in the non-pregnant population [18,19]. Alterations in the Th1-Th2 balance

towards Th2 predominance and impaired cellular immunity due to estrogen and progesterone have been hypothesized as possible explanations for this finding [20].

Our study has limitations that should be considered. The frequency of liver enzyme assessment in the pregnant women was significantly greater than the non-pregnant women leading to possible assessment bias. We attempted to address this concern by reducing the sampling frequency in the pregnant women to match the non-pregnant women. Another limitation of this study is that we were unable to distinguish drug-induced hepatotoxicity from hepatotoxicity due to other causes. It is reasonable to assume a portion of patients in our study population had LEE independent of ART exposure. Approximately 3% of pregnant women have LEE due to conditions unique to pregnancy [21]. It is possible that our inability to identify these causes of LEE in pregnancy may account for the association of LEE and pregnancy seen in our study. Despite these limitations, our analysis included a significantly larger population of women than the only other study that evaluated the association of NVP and LEE by pregnancy status [13]. These limitations also do not significantly affect our finding that NVP use was not associated with LEE in both pregnant and non-pregnant women, even when stratifying by ART exposure history and CD4+ count.

Another limitation of this study is that all three cohort studies were conducted in the United States raising questions about generalisability of the findings, particularly to resource-limited settings. While this study cannot account for possible differences in these populations, it is interesting to note that the studies that initially suggested a possible increased risk of hepatotoxicity with NVP use in pregnant and non-pregnant populations were also performed in the United States and other developed countries [3,4,22,23]. This concern has resulted in a reduction of use of NVP during pregnancy. Data from our study should be considered in assessing the recommendations for use of NVP in pregnancy. As noted in an FDA public health advisory for NVP [24], there remain multiple reasons why NVP remains an important part of ART regimens worldwide: triple antiretroviral regimens containing protease inhibitors or non-nucleoside reverse transcriptase inhibitors, such as NVP, are standard of care for HIV treatment; many options are needed for HIV-infected patients since resistance to specific drugs or entire classes can develop; alternatives to NVP are limited by other toxicities, potential drug interactions, and by the risk of drug-related birth defects if given in the first trimester of pregnancy; NVP is chemically stable in environmental conditions where other antiretrovirals are not; symptomatic liver toxicity has not been reported in HIV-infected children; and NVP is available in a liquid formulation while many other antiretrovirals are not. Finally, it is important to emphasize that the hepatotoxicity noted in patients taking continuous NVP has not been seen when NVP is used as a single, intrapartum dose [25,26].

While we support close monitoring of pregnant women for clinical or laboratory evidence of hepatotoxicity with any ART regimen, our results challenge the notion that NVP is uniquely associated with hepatotoxicity during pregnancy.

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TABLE 1

Description of population characteristics by pregnancy status

	Pregnant (N=1229)		Non-pregnant (N=821)		P value
	n	% (mean)	n	% (mean)	
NVP					
≤ 250	218	17.73	169	20.58	0.106
50	22	1.79	22	2.69	
> 250	160	12.92	136	16.73	
Race					
Caucasian	109	8.86	99	12.05	<0.001
African American	678	55.16	416	50.66	
Hispanic/Latino	415	33.76	167	20.34	
Other	27	2.19	139	16.93	
Age at Start of Follow up		(27.99)		(35.96)	<0.001
CD4+ Count Category					
≤ 250	224	19.21	148	18.59	0.731
> 250	942	80.78	648	81.40	
Platelet Count					
< 150,000 mm ³	77	6.4	62	7.70	0.260
≥ 150,000 mm ³	1126	93.59	743	92.29	
Log10 RNA		(1.97)		(2.74)	<0.001
ART Naivete	585	47.59	13	1.58	<0.001
NVP Naivete	1077	87.63	501	61.02	<0.001
Chronic Hepatitis*	107	8.70	259	31.54	<0.001
HIV Risk Group					
IV Drug Use	62	5.04	97	11.81	<0.001
Sexual	1088	88.52	532	64.79	<0.001
Transfusion	19	1.54	29	3.53	0.003
Duration of HIV Infection at start of follow-up (in years)		(4.16)		(15.43)	<0.001
Baseline Liver Enzyme Elevation	9	0.73	72	8.76	<0.001

* Chronic hepatitis was defined as the presence of either hepatitis C antibody or hepatitis B surface antigen

Table 2

Multivariate adjusted analysis for any Liver Enzyme Elevation (grade 1-4)

	Relative Risk	95% Confidence Intervals	P value
Model 1:			
Pregnant	4.70	(3.39, 6.53)	<0.01
Non-Pregnant	Ref.		
Model 2 **: :			
Pregnant	4.66	(3.35, 6.47)	<0.01
Non-Pregnant	Ref.		
NVP-	1.17	(0.80, 1.70)	0.42
NVP+	Ref.		
Model 3 :			
Pregnant	4.72	(3.36, 6.65)	<0.0001
Non-Pregnant	Ref.		
NVP +, NVP exposed	1.03	(0.50, 2.10)	0.9418
NVP -, NVP naïve	1.17	(0.67, 2.05)	0.5784
NVP -, NVP exposed	1.26	(0.65, 2.42)	0.4969
NVP +, NVP naïve	Ref.		
Model 4 :			
Pregnant	4.84	(3.33, 7.04)	<0.0001
Non-Pregnant	Ref.		
NVP -, CD4+ > 250	1.19	(0.78, 1.80)	0.4260
NVP +, CD4+ > 250	Ref.		

* Models were adjusted for chronic viral hepatitis, Log10 RNA, platelets count, immunostage, injection drug use and transfusion related risk factors and baseline elevated LEE.

** The interaction term between pregnancy status and NVP exposure was included in the multivariate analysis and was not significant