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Serious toxicity associated with continuous nevirapine-based HAART in pregnancy

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Objective This study was designed to determine the safety of nevirapine (NVP)-based highly active antiretroviral therapy (HAART) in a cohort of HIV-positive pregnant women.

Design This was a prospective cohort study of HIV-positive pregnant women.

Population and setting All HIV-positive women treated with HAART during pregnancy from January 1997 to February 2004 at the British Columbia (BC) Women's Hospital in Vancouver, BC, Canada.

Methods Demographic and clinical data were collected to compare antiretroviral drug toxicities in women treated antenatally with NVP-based or non-NVP-based HAART. Multivariate analyses were then used to investigate determinants of toxicity.

Results From 1997 to 2004, 103 HIV-positive pregnant women received HAART. Equivalent numbers of women were initially treated with NVP-based (54%) and non-NVP-based (46%) HAART. The groups did not differ by clinical or demographic parameters and duration of HAART exposure was similar between groups. Toxicities necessitating treatment discontinuation were observed in 6 of 56 NVP-exposed women (2 cases each of grade 2, 3, and 4 toxicity) compared with 1 of 47 in the non-NVP-exposed women. First time use of NVP approached significance as a predictor for toxicity, with a toxicity rate of 12.5% (6/48) observed among those taking NVP for the first time (adjusted OR 2.68, 95% CI 0.49–14.6).

Conclusion Continuous NVP use in pregnancy resulted in a relatively higher rate of toxicity, and all cases of NVP toxicity occurred in women exposed to NVP for the first time during pregnancy.

Keywords Continuous nevirapine, HAART, pregnancy, toxicity.

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Introduction

Treatment of HIV-positive pregnant women with potent highly active antiretroviral therapy (HAART) is now standard of care in the developed world.[1,2] With HAART, vertical transmission rates of less than 2% are achievable.[3] Although these results are notable, maternal toxicities associated with use of specific HAART regimens during pregnancy remain a serious concern.

Before 2004, the HAART combinations most commonly used to achieve viral suppression during pregnancy at our institution included zidovudine or stavudine, lamivudine, and nelfinavir or nevirapine (NVP). In 2004, concerns were raised following a report of a maternal death from liver failure in an AIDS Clinical Trials Group (ACTG) randomised trial comparing efficacy of continuous-use NVP versus nelfinavir during pregnancy.[4] The same study also found an association between NVP toxicity and a high CD4 (>250) count at treatment initiation.[4] This prompted a multiple site review of pregnancy outcomes where NVP therapy was used antenatally as part of a HAART regimen. Our site contributed pregnancy outcome data to this international canvass, which culminated in an advisory issued by the Food and Drug Administration (FDA) cautioning against continuous NVP use in pregnancy in women with a CD4 > 250.[5]

A relationship between toxicity and continuous NVP use in pregnancy has since been confirmed by a number of smaller scale studies that also identified high baseline CD4 counts and

Black ethnicity as potential maternal risk factors for toxicity.[6–8] However, it is critical to continue to gather such data regarding NVP toxicity as these small studies tend to be underpowered, and extrapolation of study results may be limited to populations with similar ethnic and demographic characteristics. In addition, fewer options may be available for therapy in some cases, for example, NVP continues to be commonly used in the developing world. For these reasons, here we present data from our provincial cohort study designed to determine the safety of HAART use in pregnant women.

Methods

Setting and study participants

This is a population-based review of all HAART-treated HIV-infected pregnant women in British Columbia (BC), Canada from January 1997 to February 2004. The Oak Tree Clinic, located at Children's and Women's Health Centre of British Columbia is BC's only tertiary referral centre for HIV-positive women and children and participates in the care of all HIV-positive pregnant women in the province. BC has a population of approximately 4.35 million people, and the most recent epidemiological estimates suggest that 12 300 people are currently living with HIV.[9,10] Antiretroviral medications are provided free of cost to all HIV-positive individuals in the province through the British Columbia Centre for Excellence in HIV/AIDS Drug Treatment Program.

This study was approved by both the BC Women's Hospital and Health Centre Research Review Committee (W02-0009) and the University of British Columbia Clinical Research Ethics Board (H01-70499).

Clinical management

Prior to the FDA warning in February 2004 against the use of continuous NVP in pregnancy, one of the two HAART regimens were used in antiretroviral therapy (ART)-naïve women referred antenatally to the Oak Tree Clinic: a NVP-based triple therapy regimen or a non-NVP-based triple therapy regimen. The nucleoside backbone therapy used in all women included zidovudine or stavudine, and lamivudine. During this time period, there was clinical equipoise regarding the best regimen for pregnancy, so women were placed on one of the two regimens.

Women who presented to the clinic already on therapy were continued on their initial treatment regimen if their viral load was suppressed, the regimen was compatible with pregnancy, and the drugs were tolerated. During the course of pregnancy, a change in HAART was made if the woman experienced serious adverse effects, toxicity, or if there was evidence of virological breakthrough. For the purpose of this analysis, women were identified by the first regimen that they were prescribed in pregnancy. If they later switched treatment regimens, they were still analysed as belonging to the initial treatment group, that is 'intention-to-treat' analysis was performed. During this time period, there were a small number of women taking alternate regimens for salvage treatment; these pregnancies were excluded from the present analysis. Of note, there were no toxicities documented in this small group on salvage therapy.

Data collection

All data were collected prospectively and entered into an Access database as part of a continuing observational provincial perinatal outcomes study. Demographic data including pre-treatment hepatitis C virus (HCV) serology, injection drug use (IDU), and smoking status were collected on all women. Laboratory evaluation including CD4 cell count, HIV viral load, complete blood count, liver transaminases, urea, creatinine, lactate, and bilirubin were collected at baseline (HAART initiation) and at every month thereafter until delivery for all women. Further investigation was undertaken if clinical signs or symptoms of toxicity developed.

Data on all toxicities associated with HAART use were also collected. Toxicities were graded according to the National Institute of Allergy and Infectious Disease Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events. This is a descriptive scale used in all clinical trials developed and/or sponsored by the ACTG to standardise reporting of adverse events ranging from grade 1 – mild, grade 2 – moderate, grade 3 – severe to grade 4 – potentially life threatening.[11] The ACTG grading scheme for ART-associated hepatotoxicity is defined using the patient's baseline serum aminotransferase concentrations. In women with normal pre-treatment transaminases, a five-fold or ten-fold increase is graded as moderate or severe, while in women with elevated pre-treatment liver enzymes, a 3.5-fold or 5-fold increase is considered indicative of moderate or severe hepatotoxicity, respectively.[12]

Statistical analysis

Statistical analysis was carried out using SPSS (v. 11). Bivariate analyses were conducted to identify differences in personal, clinical and treatment characteristics between subjects who experienced toxicities and those who did not. Multivariate analyses were conducted to identify possible determinants of the occurrence of these toxicities. Variables significant at the 0.1 level in bivariate investigations were selected for inclusion in multivariate modelling. In addition, NVP inclusion in the treatment regimen, as a hypothesised *a priori* variable of interest, was forced into each model building run.

Results

Ninety-one women had 103 HAART-treated pregnancies in this 7-year provincial data set. No toxicities occurred in the 12

Table 1. Demographic, clinical, and treatment characteristics at baseline (pre-treatment) of HIV-positive pregnancies among women exposed (n = 42) and not exposed (n = 50) to NVP during pregnancy

Characteristic	No NVP (n= 47)	NVP exposed* (n = 56)	All women (n = 103)
Number of valid responses	42	50	92
Ethnicity			
Caucasian	17 (40)	22 (44)	39 (42)
Aboriginal	8 (19)	14 (28)	24 (26)
Black	11 (26)	9 (18)	20 (21)
Hispanic	0	1 (2)	1 (1)
Other/unknown	6 (14)	2 (4)	8 (9)
Median age (IQR)	28 (8)	28 (7.5)	28 (8)
Currently smoking	22 (52)	33 (66)	55 (60)
IDU (present use)	6	17	24
Median CD4 (IQR)	350 (230)	380 (285)	370 (260)
CD4 > 250 c/mm	36 (80.0)	45 (80.4)	81 (80.2)
Median pVL (IQR)	11 950 (83 525)	11 900 (25 075)	11 900 (31 820)
Coinfected with HCV	22 (47)	32 (57)	54 (52)
Weeks of any treatment exposure in pregnancy (IQR)	20 (8)	17 (13.5)	18 (12)

IQR, interquartile range; pVL, plasma viral load.
Values are expressed as n (frequency, %) unless other stated.
*Any NVP exposure ≥ 7 days during pregnancy. Of these, 48 were NVP naïve at start and 8 had prior NVP exposure.

subsequent pregnancies studied in this cohort. Demographic data of the two treatment groups are presented in Table 1. The majority of women were of Caucasian (44%) ethnicity, followed by Aboriginal (26%) and, then Black (20%). Of note, Aboriginal and Black women were over-represented in this cohort in comparison with provincial population rates (provincial percentages are 4 and 3.9%, respectively).[9] Equivalent numbers of women were exposed to NVP-based (n = 56) and non-NVP-based (n = 47) HAART, even when stratified by ethnicity. Treatment groups did not differ in age, initial CD4, median viral load, or weeks of HAART exposure, but there were more current smokers, injection drug users and HCV antibody positive women in the NVP-treated group, most likely reflecting consensus that this population would better adhere to the lower pill burden of an NVP-based regimen.

Of the 103 pregnancies studied, 7 women experienced toxicity severe enough to require discontinuation of therapy. Six of these seven women were in the NVP-exposed group. These included two cases of grade 2 toxicity (rash/fever syndromes), two cases of grade 3 toxicity (hyperbilirubinaemia/liver toxicity), and two cases of grade 4 toxicity (one rash and one hepatotoxicity). Of note, all six of these women had never been exposed to NVP in the past, giving a toxicity rate among first time users of 12.5% (6/48). The time in days to onset of toxicity in the six NVP-treated women ranged from 7 to 49 days.

Table 2. Clinical course and description of NVP-based HAART associated toxicities (n = 6)

ID	Prior ART	Pre- HAART CD4	Pregnancy HAART regimen	Days to toxicity	GA at initiation	HCV antibody positive	Pre-HAART transaminases	Toxicity grade
1	Naive	220	Combivir, NVP	17	23 + 6	No	Normal	Grade 2
2	Naive	230	Combivir, NVP	27	20 + 0	No	Normal	Grade 3
3	Naive	290	Combivir, NVP	30	18 + 0	No	Normal	Grade 3
4	Naive	490	Combivir, NVP	24	23 + 5	Yes	AST 77, ALT 124, GGT 66	Grade 4
5	Naive	560	Combivir, NVP	49	27 + 0	Yes	AST 63, ALT 75, GGT 63	Grade 4
6	D4T, 3TC, indinavir	380	D4T, DDI, NVP	7	30 + 2	Yes	AST 200, ALT 368, GGT 46	Grade 2

GA, gestational age; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transferase; D4T, stavudine; 3TC, lamivudine; DDI, didanosine.

As noted in Table 2, two of the NVP-treated women who developed toxicity had CD4 counts below 250 at the time of treatment initiation. Of the women who experienced a significant toxicity, 4/6 (66%) were Aboriginal. None of the women who experienced toxicity were Black. Three of the six women with toxicity were HCV antibody positive and had elevated transaminases at the initiation of NVP treatment.

A comparison of the demographic, clinical and treatment characteristics at baseline of all treated women by presence or absence of a serious adverse event is shown in Table 3. There was no difference with respect to presence or absence of adverse events and median age ($P = 0.8$), median CD4 at treatment initiation ($P = 0.63$), CD4 > 250 c/mm^3 at treatment initiation ($P = 0.62$), median plasma viral load at treatment initiation ($P = 0.53$), hepatitis C virus (HCV) antibody status ($P = 1.0$), current smoking ($P = 0.34$) or IDU ($P = 1.0$).

The single case of toxicity in the non-NVP-treated group involved the development of renal calculi (non-ACTG category toxicity) while being treated with indinavir-based HAART. This was severe enough to require hospitalisation and medication discontinuation.

Analysis for possible determinants of severe adverse drug events was performed using first pregnancy by first regimen (OR = 2.68, 95% CI 0.49–14.6) and all pregnancies by first regimen (OR = 2.61, 95% CI 0.48–14.1). We confirmed that the above analyses were not biased by including those who had treatment switches within the studied pregnancy by obtaining similar results with an analysis of all pregnancies by all regimens (OR = 2.65, 95% CI 0.49–14.26). Adjusted odds ratios were not significant (due to wide confidence intervals), but a trend towards NVP use and adverse events was suggested.

Discussion

The challenge of HIV care in pregnancy is to provide the lowest risk of vertical transmission with the least toxicity to mother and child. With several documented reports of significant maternal toxicity associated with NVP use in pregnancy,[6–8] we were obliged to investigate such adverse effect profiles in our population. Of note, the data presented in this study contributed to the international multicentre FDA review.[5]

We identified significant toxicity (grades 2–4) in 12.5% of women treated with a continuous NVP containing regimen who started this therapy for the first time in pregnancy. None of the observed toxicities led to a maternal death; it is highly likely that severe consequences were avoided due to intensive clinical monitoring and rapid drug discontinuation at the first sign of adverse reaction. Even so, two of the women developed Stevens–Johnson Syndrome. One case was characterised by significant mucocutaneous involvement that required prolonged hospitalisation and intravenous antibiotic therapy for the resulting bacterial superinfection.

Given the small number in this cohort, first time use failed to be significant as a predictor for toxicity by multivariate analysis, but a trend is suggested as only one (1/47, 2%) case of toxicity was noted in the non-NVP-based treatment group. This consisted of renal calculi in a woman treated with indinavir and was significant enough to require hospitalisation and discontinuation of medication.

Table 3. Comparison of demographic, clinical, and treatment characteristics at baseline of HAART-treated HIV-positive pregnancies among women experiencing either no/mild adverse events or serious adverse events associated with HAART ($n = 103$)

Characteristic	No event ($n = 96$)	Adverse event ($n = 7$)	*P* value
Ethnicity			
Caucasian	44 (45.8)	1 (14.3)	
Aboriginal	22 (22.9)	5 (71.0)	0.10 (Fisher's exact test)
Black	20 (21.0)	0	
South-East Asian	7 (7.3)	1 (14.3)	
Median age (IQR)	28 (8)	28 (8)	0.80 (Wilcoxon rank-sum test)
Median CD4 (IQR)	375 (270)	350 (310)	0.63 (Wilcoxon rank-sum test)
CD4 > 250 c/mm	76 (80.9)	5 (71.4)	0.62 (Fisher's exact test)
Median pVL (IQR)	11 800 (33 180)	16 300 (21 551)	0.53 (Wilcoxon rank-sum test)
Coinfected with HCV	50 (52.1)	4 (57.1)	1.0 (Fisher's exact test)
HAART therapy			
PI only	46 (47.9)	1 (14.3)	0.12 (Fisher's exact test)
NVP exposure*	50 (52.1)	6 (85.7)	
Naïve at baseline	42 (84.0)	6 (100)	0.58 (Fisher's exact test)
Prior NVP exposure	8 (16.0)	0	

IQR, interquartile range; pVL, plasma viral load.
Values are expressed as *n* (%) unless other stated.
*Any NVP exposure ≥ 7 days during pregnancy. Of these, 48 were NVP naïve at start and 8 had prior NVP exposure.

Previously, Hitti *et al.*[4] reported that Black ethnicity is a risk factor for toxicity with NVP use in pregnancy. The number of Black women in our study was small and may explain why we did not detect such a relationship. However, our results do suggest a relationship between Aboriginal ethnicity and toxicity to NVP, but again, due to our small sample size, we lacked sufficient power to demonstrate this unequivocally. Hitti *et al.*[4] also reported an association between high CD4 counts at treatment initiation and NVP toxicity: in their study, all five adverse events attributed to NVP occurred among women with CD4 counts > 250 c/μl, including one documented maternal death. In contrast, we did not find evidence of a positive association between CD4 count and risk of toxicity in our cohort, which is in agreement with other recent studies.[6,13]

Unlike previous studies,[4,6] our cohort contained a larger proportion of women coinfected with HCV that had elevated transaminases prior to HAART initiation. Coinfection with HCV has been previously associated with NVP toxicity in both nonpregnant adults and pregnant women.[14,15] In this study, the relationship between HCV antibody positivity and serious adverse events was not significant, although three of six women who developed toxicity to NVP did have elevated transaminases at treatment initiation.

The onset of NVP toxicity in our cohort varied from 7 to 49 days following initiation of HAART. In all women, toxicity symptoms and findings resolved completely on discontinuation of NVP and the nucleoside backbone was not changed on treatment re-initiation with a different base. This suggests that the toxicities seen were not due to the nucleoside backbone component of HAART.

It is important to note that despite toxicities necessitating therapy termination and switching, there were no documented cases of vertical HIV transmission in this study.

At this time we cannot extrapolate our results to comment on single use NVP as it is used in the developing world or in high risk, undiagnosed obstetric cases in the developed world. However, toxicity under these circumstances has not been reported in the literature to date.

Conclusion

Our results confirm that the toxicity associated with continuous NVP use in pregnancy is significant and potentially life-threatening, particularly when it is used for the first time. However, unlike previous studies, we did not find an association between CD4 count and risk for NVP-based toxicity. This study emphasises the need for continued surveillance and dissemination of novel maternal and fetal toxicities associated with ART, particularly among divergent ethnic populations. Identification of the factors that place individuals at high risk for ART toxicity is critical, and priority should be given to compiling meta-analyses of data from a number of centres that provide care for HIV in pregnancy. Prevention of mother-to-child HIV transmission is a major international healthcare issue, and only through enhanced knowledge will improved care and health outcomes be possible for HIV-positive women and their unborn children.

Contribution to authorship

J.E.v.S. was a fellow in Infectious Diseases at the time of the research project and is now a staff Obstetrician and Gynaecologist with Infectious Disease expertise. She contributed to the overall chart reviews and was the primary author for manuscript completion.

A.A. is an expert in Paediatric HIV infection and part of the clinical team that evaluates the HIV-exposed children and has contributed significantly to editing of the manuscript.

D.K. was the clinical pharmacist working on the multidisciplinary team at the Oak Tree Clinic, was involved with discussing the various HAART regimens used in the study cohort, and was responsible for the medication counselling for the women outlining the importance of adherence and adverse drug monitoring.

E.M. is the research nurse for our HIV clinic and was extensively involved in data management.

J.C.F. is a Paediatric Infectious Diseases expert and co-Director of the Women and Family HIV Centre (Oak Tree Clinic). He was involved in editing of the manuscript.

D.R.B. is an Adult Infectious Diseases expert and co-Director of the Women and Family HIV Centre. He reviewed the records of all women with major toxicities and was involved in editing several versions of the manuscript.

S.G. has been a research assistant with the Oak Tree Clinic during medical school training and had played an active part in chart reviews, data abstraction, data entry and data analysis.

D.M.M. is an Obstetrician/Gynaecologist with Infectious Diseases fellowship training who is the lead for the Perinatal HIV program at the Oak Tree Clinic and has been the lead on this research study and supervisor for J.E.v.S. during her fellowship.

Details of ethics approval

This study was approved by both the BC Women's Hospital and Health Centre Research Review Committee (CW02-0009; approved 20 February 2003 and renewed annually) and the University of British Columbia Clinical Research Ethics Board (H01-70499; approved 6 December 2001 and renewed annually).

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