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A Study of Nevirapine Toxicity in HIV Infected Pregnant Women at the University Teaching Hospital in Lusaka, Zambia

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ABSTRACT

Objective: The general objective of the study was to determine incidence of nevirapine toxicity in pregnant HIV infected women commenced on nevirapine-based regimen in the current pregnancy with CD4 counts up to 350 cells/mm^3 at the University Teaching Hospital, Lusaka, Zambia.

Design: Longitudinal observational study with 2 arms

Group 1 (low CD4 count arm): HIV infected pregnant women with CD4 counts less than 250 cells/mm^3 commenced on nevirapine based regimen in pregnancy.

Group 2 (higher CD4 count arm): HIV infected pregnant women with CD4 counts between 250 and 350 cells/mm^3 commenced on nevirapine based regimen in pregnancy.

Main outcome: Nevirapine toxicity (eithercutaneous and/or Hepatotoxicity)

Measures:

Rash- at least grade 2 rash with or without mucous membrane involvement.

Hepatic toxicity – at least grade 2 rise in aspartate aminotransferaseor alanine amino transferase

The grading of toxicity was as per WHO toxicity estimates (2006 WHO ART guidelines)

Results: The incidence of nevirapine toxicity (at least grade 2 rash with or without mucous membrane involvement and/or at least grade 2 rise in Aspartate AminoTransferase) was found to be 0% in women with CD4 counts below 250cells/mm^3; it was 13.5% (p=0.005) in women with CD4 counts between 250 to 350cell/mm^3.

Conclusions: Though the study was powered to detect a15% difference, the results of the study show that women with CD4 counts of 250 to 350cells/mm^3 are at substantial risk of nevirapine toxicity when commenced on nevirapine based HAART regimen in pregnancy.

INTRODUCTION

The use of Highly Active Antiretroviral Therapy (HAART) to prevent mother-to-child HIV transmission (PMTCT) has demonstrated to be effective[1,2]. This has been shown to be true also in developing countries even in the face of breastfeeding [3,4].

Data on safety ofnevirapine in pregnancy has given rise to concern. Risk of toxicity has been shown to increase with CD4 counts greater than 250cells/mm^{3}especially during pregnancy[5,6,7].

The US Food and Drug Administration (FDA) as well as the World Health Organization advises use of nevirapine based regimen in women with CD4 counts greater than 250 with caution[8,9].

Nevirapine has been widely used in pregnancy both as single-dose therapy during labour and as part of short-term and long-term highly active antiretroviral therapy. It is an effective and well tolerated non-nucleoside reverse transcriptase inhibitor (NNRTI) that is widely available to prevent HIV infection in resource-poor populations[10,11].

In developing countries, choice of highly active antiretroviral drugs in pregnancy for therapy or for PMTCT remains a challenge. Efavirenz is a non nucleoside reverse transcriptase inhibitor that has been associated with neural tube defects when used in the first trimester. Niverapine based regimens have well documented cutaneous and hepatic toxicities when used in women with high CD4 counts. Nevirapine based regimen is inexpensive compared to both efavirenz and protease inhibitor based regimens [12]. Protease inhibitor (PI) based regimens form the back-bone of second line therapy and are therefore not recommended as first line regimen.

The Zambian MOH 2007 ART protocol guidelines (as well as WHO 2006 ART guidelines in resource poor settings) recommend initiating HAART for all HIV-1 infected pregnant women with CD4 counts less than 350cells/mm^3. Nevirapine based regimen is the first line therapy for pregnant women with CD4 counts less than 250cells/mm^3. For women with CD4 counts between 250 and 350cells/mm^3, either nevirapine with frequent checks on liver function tests or efavirenz commenced after the 1st trimester is recommended [9,13].

The study determined the incidence of nevirapine toxicity in HIV-1 infected women commenced on nevirapine based regimen (zidovudine/lamivudine/nevirapine or stavudine/lamivudine/nevirapine) in the current pregnancy with CD4 counts up to 350 cells/mm^3 at the University Teaching Hospital, Lusaka, Zambia. It compared the incidence of nevirapine toxicity (cutaneous and hepatic toxicity) in women with CD4 counts below 250cells/mm^3 to that of women with CD4 counts between 250 to 350cells/mm^3.The studyalso documented the prevalence of hepatitis B co-infection in the study population as this is an important confounder.

METHODS

Study design: Longitudinal observational study with 2 arms

Group 1 (low CD4 count arm): HIV infected pregnant women with CD4 counts less than 250 cells/mm^3 commenced on nevirapine based regimen in pregnancy.

Group 2 (higher CD4 count arm): HIV infected pregnant women with CD4 counts between 250 and 350 cells/mm^3 commenced on nevirapine based regimen in pregnancy.

Study duration: The study took about 11 months from inception

- Training study assistants-1 week
- Baseline data collection -8 months
- Additional follow up time- 2 months
- Data analysis -1 month

Target population: All pregnant HIV infected women presenting to the University Teaching Hospital.

Study population: HIV infected pregnant women with CD4 counts of up to 350cells/mm^3 commenced on nevirapine based antiretroviral therapy in current pregnancy.

Selection of subjects

Inclusion criteria:

- Pregnant women with documented HIV-positive status with CD4 counts less than or equal to 350 cells/mm^3 commenced on nevirapine based regimen in current pregnancy
- More than 18 years and able to give informed consent
- Willingness to attend antenatal and postnatal care at UTH

Exclusion criteria

- Patients who were less than 18 years old or unable to give informed consent
- Patients who had been on cumulative 7 days or more of HAART

Study site: The study was undertaken at the University Teaching Hospital (UTH) Department of Obstetrics and Gynaecology in the Adult Infectious Disease Center (AIDC).***Description of the study site:*** UTH is the largest as well as highest referral hospital in Zambia. Although primarily a referral center, UTH also provides care to self-referred patients. It therefore has a wide spectrum of patients in terms of social-economic status and educational background.

Antenatal patients are seen in the UTH antenatal care clinic. After passing through the clerk's desk, patients receive different counseling sessions (conducted by midwives) before they are seen by the doctors. After the counseling sessions, opt out HIV testing is offered as part of the routine antenatal package.

Women who tested positive as well as those who already had a documented HIV positive status were routinely examined to asses clinical stage of the disease and bloods taken for CD4 counts and other baseline investigations (FBC, LFTs, Creatinine, RPR, hepatitis B).The patients were then referred to the UTH ART-antenatal care clinic at the Adult Infectious Disease Centre (AIDC).

The study followed up women with CD4 counts less than or equal to 350cells/mm^{3}who were commenced on nevirapine-based antiretroviral therapy for about 12 to 14 weeks in order to evaluate their risk of nevirapine toxicity.

***Sampling*:** Convenience sampling was used to enroll 146 patients into the study. All HIV-infected pregnant women with CD4 counts less than or equal to 350 cells/mm^3 commenced on nevirapine based antiretroviral therapy seen during the study period where enrolled if they consented and they fulfilled the eligibility criteria.

Women with CD4 counts less than 250 cells/mm^3 commenced on nevirapine based regimen were allocated to group 1 arm and women with CD4 counts between 250 and 350 cells/mm^3 commenced on nevirapine based regimen in this pregnancy, to the group 2 arm.

Sample size calculation

1. Alternative hypothesis(one sided): The incidence of nevirapine toxicity in HIV infected pregnant women who start HAART with CD4 counts between 250 and 350cells/mm^3 is higher than that of women who start with CD4 counts < 250cells/mm^3.
2. P1 = from the literature, the incidenceof nevirapine toxicity in HIV infected pregnant women who start HAART with CD4 counts less than 250cells/mm^3 is about1%.
3. P2 = from the literature, the incidenceof nevirapine toxicity in HIV-1 infected pregnant women who start HAART with CD4 counts greater than 250cells/mm^{3}is about 16%.
4. Alpha (one sided) = 0.05.
5. At 80% power; Beta = 1 – 0.80 = 0.20.

To detect a 15% difference in the incidence of nevirapine toxicity in the two arms, the required sample size was 71 participants in each arm i.e. a total of 142 participants. This was adjusted to 146 patients at 10% loss to follow up per year.

RESULTS

Variable	Mean	Standard deviation	meadian	minimum	maximum
Age (n=148)	30.8	5.1	31	18	43
Gravidity	3.1	1.7	3	1	9
Parity	1.8	1.5	2	0	8
# of Children alive	1.7	1.2	2	0	6
Gestation at enrollment	28.9	7.1	29.5	9	41
Initial CD4 count	223.4	82.2	240.5	39	350

Variable		**Proportion**
Education	*1^0*	*16(11%)*
	2^0	*83 (56%)*
	3^0	*45 (32%)*
	No formal edu	*2 (1%)*
Occupation	*Housewife*	*60 (41%)*
	Formal	*51 (34%)*
	Self	*33 (22%)*
	Other	*4 (3%)*
Household income(ZK)	*>1M*	*46 (31%)*
	500 000-1M	*52 (36%)*
	<500 000	*49((33%)*
Marital Status	*married*	*132 (89%)*
	Never married	*10 (7%)*
	Divorced	*4 (3%)*
	Widow	*2 (!%)*
Referral to the PMTCT/ANC clinic	*Local clinic*	*83 (56%)*
	Self	*54 (37%)*
	Other	*11 (7%)*
WHO clinical stage of disease	*Stage 1*	*125 (87%)*
	Stage 2	*11 (8%)*
	Stage 3	*6 (4%)*
	Stage 4	*2 (1%)*
HAART regimen	*AZT/3TC/NVP*	*121 (82%)*
	D4T/3TC/NVP	*27 (18%)*
Cotrimoxazole (malaria prophylaxis)	*On cotrimoxazole*	*136 (82%)*
	Not on cotrimoxazole	12 (8%)
Hepatitis B co infection	Negative	142 (85%)
	Positive	8 (6%)
	Not done	13 (9%)
1. Proportion with grade 2 or more elevation in AST/ALT i.e hepatic toxicity	CD4 count < 250 (n=77)	0
	CD4 count250-350 (n=74)	6 (8%)
2. Proportion with grade 2 or more Nevirapine rash	CD4 count < 250 (n=75)	0
	CD4 count250-350 (n=78)	6 (7%)
Incidence of Nevirapine toxicity	(either 1 and/or 2)	13.55 *p*=0.005

DISCUSSIONS

The aim of the study was to evaluatethe incidence of nevirapine toxicity in pregnant HIV-infected women commenced on nevirapine based regimen in the current pregnancy with CD4 counts less than or equal to 350 cells/mm^3 at the University Teaching Hospital, Lusaka, Zambia. It also aimed to compare the incidence of nevirapine toxicity in women with CD4 counts less than 250 cells/mm^3 to that of women with CD4 counts of 250 to 350 cells/mm^3 as well as to evaluate the prevalence of hepatitis B co-infection in the study population.

The incidence of hepatic toxicity was 8%.That of cutaneous toxicity was about 7%. The combined incidence was 13.5%. The prevalence of hepatitis B co infection was 6%.

The findings in this study may be used in accessing the safety of nevirapine-based regimen in HIV positive pregnant women. As Ministry of Health rolls out the PMTCT program, more pregnant women are likely to commence HAART. More women with CD4 counts less than 350cells/mm^3 will be exposed to nevirapine based

highly active antiretroviral therapy regimen as this is the recommended first line regimen.

Social demographic data: The age distribution of women in the study ranged from 18 to 43 years with an average of 30.8 years.Fifty six percent (56%) had only up to secondary school education while 1% had no formal education. Thirty four (34%) of women were in formal employment and 22% where self employed. The low educational levels and the low employment levels contribute to the low income levels with about 33% of women coming from households with less than five hundred thousand kwacha total income per month.

Eighty nine percent (89%) of the women were married. This figure represents women whose partners are either already infected or are at very high risk of being infected. The huge number of married women reflects the need for PMTCT programs to rigorously incorporate other aspects of ART care such as partner notification. While antenatal care is an opportunity for client entry into other services such as primary health care, family planning, screening for cervical cancer etc, it is also an opportunity for entry of these women`s husbands and children into ART care and ART-related services such as counseling and social support.

Fifty six percent (56%) of women were seen at the AIDC clinic by reason of being referred to the University Teaching Hospital for complicated care while 37% where fee paying patients in search of better care.

The mean gravidity was 3.1 with a maximum of 9 pregnancies while the mean parity was 1.8 with a maximum of 8. The average number of children was 1.5. The progressive decrease from gravidity, parity to the number of children alive may be explained by the relatively higher incidence of pregnancy loses (miscarriages and still births) and pediatric deaths associated with the HIV infection.

The average gestation at enrollment was about 29 weeks, with 4 women enrolling at 41 weeks. Being referred may be a contributing factor to late enrollment as 56% of the women were referred from local clinics for complicated care. However, pregnant women and their partners need to be sensitized regarding the benefits of starting ART sooner in order to maximize outcome for both the mother and the baby.

Seventy seven (52%) women had CD4 counts less than 250 cells/mm^3 while seventy one (48%) women had CD4 counts between 250 and 350 cells/mm^3 at enrollment. There was poor correlation between the WHO clinical stage and the CD4 count in the 2 cohorts as 87% of women enrolled had WHO clinical stage 1 disease. Eighty two percent (82%) of women were commenced on AZT/3TC/NVP. The 27 patients (18%) commenced on D4T/3TC/NVP had hemoglobin less than 10g/dl when starting HAART. Ninety two percent (92%) of patients took cotrimoxazole prophylaxis as per the 2007 Ministry of Health, Zambia ART guidelines. Four (4) of the 6 patients who did not take cotrimoxazol had reported prior allergy to the drug.

Prevalence of Hepatitis B co-infection: 8 (6%) of 142 patients had hepatitis B co-infection. These were clinically stable patients with normal baseline aspartate alanine transferase before commencing HAART. 2 of the 8 patients with hepatitis B co-infection had deranged liver function tests grade 1 and grade 2 respectively after commencing nevirapine based HAART regimen.

Incidence of hepatic toxicity (deranged aspartate aminotransferase levels): 2 (3%) of 77 patients with CD4 count less than 250cells/mm^3 had deranged aspartate aminotransferase. Both patients had grade 1 elevation of the enzyme.

9 (12%) of 74 patients with CD4 counts between 250 to 350cells/mm^3 had altered aspartate aminotransferase. 3 of the nine patients had grade 1 elevation in ALT while 6 (8%) patients had grade 2 or more elevations in ALT.

Incidence of nevirapine rash. No patient with CD4 count less than 250cells/mm3 developed rash after being commenced on nevirapine based HAART regimen.

7 (9%) of the 71 patients with CD4 counts of 250 to 350 had generalized maculopapular rash after being commenced on Nevirapine based regimen. 1 Patient had grade 1 rash. She was managed conservatively and continued on the same regimen. The other 6 (7%) had either grade 2 or 3 rash. None of the patients developed grade 4 rash and none were admitted. Nevirapine was promptly discontinued if rash is grade 2 or more. Steroids and antihistamines were given and all patients recovered well.

Incidence of Nevirapine toxicity (combined hepatic and cutaneous toxicity). The incidence of nevirapine toxicity (defined as either 1and/or 2):

1. Rash- at least grade 2 rash with or without mucous membrane involvement.
2. Hepatic toxicity – at least grade 2 rise in Aspartate AminoTransferaseor Alanine Amino Transferase

Nevirapine toxicity in the CD4 count arm less than 250 was 0%.

In the CD4 count arm 250 to 350 cells/mm^3; 6 of 74 patients had grade 2 or more elevation in ALT and 6 of 71 patients had grade 2 or more maculopapular rash. 2 of these patients had both elevation in ALT and rash. Therefore the incidence of nevirapine toxicity is 13.5% *(p*= 0.005) in this study population.

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