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Nevirapine-Induced Hepatotoxicity: Incidence, Risk Factors, and Associated Mortality in a Primary Care ART Programme in South Africa

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ABSTRACT

Background Nevirapine (NVP) is used by more than 60% of patients on first line antiretroviral therapy (ART) in low-income countries. One of the primary concerns with NVP is associated severe hepatotoxicity (HT). International guidelines recommend frequent screening of alanine transferase (ALT) serum levels. This is often not feasible in resource limited settings. We describe the incidence, risk factors, and associated mortality of NVP-associated HT in a primary care antiretroviral therapy (ART) programme in Khayelitsha, South Africa.

Methods Prospective cohort study of all treatment-naïve adults initiating NVP-based ART in Khayelitsha from November 2002 to December 2006. We used Kaplan-Meier analyses to estimate time to HT and mortality, and Cox proportional hazards regression to model risk factors of HT and mortality. Logistic regression was used to determine factors associated with HT at baseline. HT was defined as ALT above 5 times the upper limit of normal.

Results 1831 adults were initiated on NVP-based ART during the study period. 382 (21.1%) were male. The median baseline CD4 count was 112 cells/ µl. South African guidelines were recommending ALT measurements at 0, 2, 4, 8, 12, and 24 weeks. Only 6.9% of patients had ALT measured according to protocol. A baseline CD4 count below 50 cells/µl was associated with baseline HT (OR 16.5, 95% CI: 1.8-151.3). 26 (1.4%) of 1831 patients developed HT. The incidence of early hepatotoxicity on protocol was 1.9% (18/911) compared to 0.9% (8/920) off protocol (p=0.045). Of those that were on protocol, 12 (1.3%) developed HT by 4 weeks, 4 (0.4%) between 4- 8 weeks, and 2 (0.2%) between 8-12 weeks. Of the 8 who inadvertently continued NVP, all resolved their HT. The median time to HT was 56 days (IQR 28-121). Three (0.16%) patients died. All had discontinued NVP and had been restarted on efavirenz.

Conclusion The overall incidence of HT in this cohort was lower than reported in clinical trials. HT at baseline and female gender were not found to be associated with HT contrary to previous studies. HT resolved despite continuing NVP in a subset of patients. ALT screening according to protocol was only accomplished in a small proportion of patients. This highlights the difficulties in implementing serial ALT monitoring in a high burden resource limited setting. In this context, ALT measurements are usually prompted by clinical symptoms. Further research into the sensitivity of symptoms is needed to determine whether clinical criteria alone should be recommended to monitor HT in resource poor settings.

Background

Nevirapine (NVP) is used by more than 60% of patients on first line antiretroviral therapy in low income countries. One of the primary concerns with NVP is associated severe hepatotoxicity (HT). International guidelines recommend frequent screening of alanine transferase (ALT) serum levels. This is often not feasible in resource limited settings.

Objectives

The objectives of this study were to describe the incidence, risk factors, and associated mortality of NVP-associated hepatotoxicity in a primary care antiretroviral therapy (ART) programme in Khayelitsha, South Africa.

Setting: Khayelitsha, South Africa

- Treatment naïve HIV + individuals over 16 years on NVP-based ART from November 2002 until the end of December 2006 were included.
- Women who had previously received NVP-based therapy via the prevention of mother to child transmission (PMTCT) program were included.
- Serum ALT was graded using criteria established by the AIDS Clinical Trial Group : grade 0: < 1.25x upper limit of normal (ULN); grade 1: 1.25-2.5x ULN; grade 2: 2.6-5.0x ULN, grade 3: 5.1-10x ULN; grade 4: > 10x ULN. Early hepatotoxicity was defined as an increase in ALT from grade 0-2 at baseline to grade 3 or 4 within 102 days of starting ART.
- Sequential ALT measurements – at baseline, 4, 8, and 12 weeks- were defined as "on protocol". Patients who had at least a baseline and a 4 week ALT were considered in the "ALT protocol" cohort for description of baseline characteristics.

Baseline Characteristics

Table 1: Patient characteristics at initiation of ART

Baseline Characteristics	Total Cohort
Total on NVP	1831
Males	387 (21)
Age on starting NVP based ART, years	32 (28-37)
Baseline CD4+ count, cell/µl	112 (57-164)
Baseline viral load, log_{10} copies	5.0 (4.5-5.5)
WHO clinical staging on starting ART	
Stage 1	161 (9)
Stage 2	198 (11)
Stage 3	930 (51)
Stage 4	542 (230)
Weight on starting ART, kg	60 (53-69)
Follow-up time on NVP-based ART, months	13 (6-22)
6 month mortality	77 (4.2)

Continous variables are given as medians (interquartile range). Ordinal and discrete variables are given as n(%). NVP, Nevirapine. ART, antiretroviral therapy. WHO, World Health Organization.
* Patients with at least a baseline and a 4 week ALT measurement

- From November 2002 to December 2006, 3728 individuals were initiated on ART in Khayelitsha.
- Of these,1831 (49%) were started on NVP-based ART.
- 911 (50%) patients were "on protocol" with at least a baseline and a 4 week ALT measurement.

Grade of Hepatotoxicity

Table 2: Grade of Alanine Aminotransferase on Nevirapine Based Antiretroviral Therapy

	Baseline	4 weeks	8 weeks	12 weeks	Total*
On Protocol	1444 (78.9)	911 (49.7)	368 (20.1)	127 (6.9)	**2850**
ALT Grade					
Grade 0	1314 (90.3)	779 (85.6)	321 (87.2)	105 (82.7)	2519 (88.4)
Grade 1	110 (7.6)	86 (9.4)	33 (9.0)	17 (13.4)	246 (8.6)
Grade 2	13 (0.9)	32 (3.5)	9 (2.4)	3 (2.4)	57 (2.0)
Grade 3	6 (0.4)	5 (0.6)	3 (0.8)	2 (1.6)	16 (0.6)
Grade 4	2 (0.1)	9 (0.1)	2 (0.5)	0 (0.0)	13 (0.5)

Ordinal and discrete variables are given as n(%). ALT, alanine aminotransferase. ALT grade 0: < 1.25x upper limit of normal (ULN); grade 1: 1.25-2.5x ULN; grade 2: 2.6-5.0x ULN, grade 3: 5.1-10x ULN; grade 4: > 10x ULN.
*Total visits while on protocol

Incidence of Hepatotoxicity

- The proportion of early hepatotoxicity on protocol was 1.9% (18/911) and 0.9% (8/920) off protocol (p=0.045).
- Of those that were on protocol, 12 (1.3%) developed HT by 4 weeks, 4 (0.4%) between 4- 8 weeks, and 2 (0.2%) between 8-12 weeks.
- Of the 26 patients with early HT, 8 (30.7%) inadvertently continued NVP-based ART. All had grade 3 HT which subsequently resolved without treatment modification.
- Of the 18 who stopped NVP, 17 (94.4%) were switched to efavirenz (EFV) based-ART. Of these, 2 (11.8%) developed further HT on EFV; 1 resolved spontaneously and one had to stop ART.
- Eleven (0.6%) additional patients developed late hepatotoxicity (after 12 weeks) between 121-891 days.

Risk Factors of Hepatotoxicity and Mortality

- There was no association between gender, age, baseline CD4 count less than 50 cells/µl, baseline viral load, concurrent TB infection, history of participation in PMTCT, or baseline weight <60 kilograms and hepatotoxicity (data not shown).
- Three patients with early hepatotoxicity died. All had grade 4 HT.
- CD4 less than 50 cells/µl was associated with mortality.

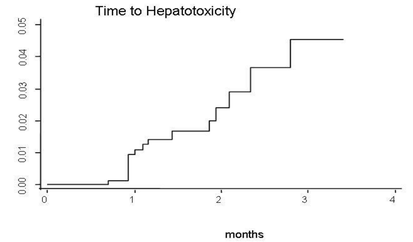
Table 3: Risk Factors of Mortality

	Univariate			Multivariate		
	HR	95% CI	p	HR	95% CI	p
Males	1.12	(0.64-1.97)	0.693	1.40	(0.78-2.53)	0.265
Age on starting NVP based ART, years	1.00	(0.98-1.04)	0.490	1.01	(0.99-1.04)	0.299
Baseline CD4 count<50 cell/µl	3.80	(2.42-5.93)	<0.001	3.88	(2.47-6.07)	<0.001
Concurrent TB infection	0.93	(0.54-1.62)	0.807			
PMTCT	0.81	(0.60-1.10)	0.184			
Hepatotoxicity	2.65	(0.83-8.44)	0.098	2.4	(0.77-7.74)	0.215
Grade 3 or 4 ALT at baseline	3.48	(0.48-25.06)	0.215			

NVP, Nevirapine. ART, antiretroviral therapy.WHO, World Health Organization. TB, tuberculosis. PMTCT, preventing
*Analysis restricted to the fist 6 months

Time to Hepatotoxicity

Figure 1: Time to Hepatotoxicity on Protocol



Number at risk	911	640	209	57	0
Number hepatotoxic	(7)	(6)	(3)	(0)	(0)

- Median time to HT was 32 (IQR 28-58) days

Discussion and conclusions

- The overall incidence of HT in this cohort was lower than reported in clinical trials.
- HT resolved despite continuing NVP in a subset of patients.
- Low CD4 count and gender were not found to be associated with HT contrary to previous studies.
- Most hepatotoxic events occurred during the first 8 weeks on ART.
- ALT screening according to protocol was only accomplished in a small proportion of patients. This highlights the difficulties in implementing serial ALT monitoring in a high burden resource-limited setting. In this context, ALT measurements are usually prompted by clinical symptoms.
- Serial ALT monitoring is likely to be even less feasible in settings with less resources than South Africa.