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ORIGINAL RESEARCH

Safety of nevirapine-containing antiretroviral triple therapy regimens to prevent vertical transmission in an African cohort of HIV-1-infected pregnant women

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Objective

To assess the incidence and consequences of adverse reactions among African HIV-positive pregnant women treated with fixed-dose combinations of a nevirapine-containing antiretroviral (ARV) triple therapy.

Methods

A retrospective analysis of the clinical files of 703 HIV-1-positive pregnant women treated with a nevirapine-containing regimen between May 2002 and July 2004 was conducted. Selection criteria for inclusion in the analysis were: (a) taking ARV for more than 14 days; (b) baseline values of transaminases below the threshold of 2.5 times the upper limit of normal (ULN). The women were on a nevirapine-containing regimen for a median of 127 days [interquartile range (IQR) 86–190 days], starting on average at the 27th week of gestation (standard deviation ± 9.5) and continuing up to a maximum of 6 months after delivery. All women were offered formula milk to feed the babies. Highly active antiretroviral therapy (HAART) was continued beyond 6 months only if the patient qualified on the first visit. The main outcome measures were incidence of hepatotoxicity, skin rashes and Stevens–Johnson syndrome. Multivariate analysis to assess the impact of several factors on the adverse reaction rate was performed.

Results

As of 1 August 2004, 554 pregnancies reached term, 96 women were still pregnant, and 53 women dropped out of the programme before giving birth. After 2 months of therapy the percentage of patients with a viral load less than 1000 HIV-1 RNA copies/mL increased to 78.6%; average CD4 cell counts increased from 490 cells/μL before therapy to 630 after therapy. The incidence of grade 3–4 adverse reactions (hepatotoxicity, skin rashes and Stevens–Johnson syndrome) was 6.5, 2.4 and 1.1%, respectively. Five women died during pregnancy (0.88%). Only one of the deaths could be associated with ARV treatment.

Conclusion

Nevirapine-containing regimens in pregnant woman, at all CD4 cell count levels, appear to be safe in African settings.

Keywords: hepatotoxicity, HIV mother-to-child transmission, nevirapine-containing regimen, public health, resource-limited settings

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Introduction

A number of studies have recently raised the issue of the toxicity of nevirapine (NVP) administered during pregnancy to HIV-1-positive women [1–7]. The findings of

these studies have not, however, been consistent. Some studies found an increased incidence of NVP-related adverse reactions, especially hepatotoxicity, in pregnant women with high CD4 cell counts. However, other studies did not confirm these observations. One of the reasons for these contradictory results may be the limited power of the analyses because of the small number of patients enrolled in each study.

Drug Resources Enhancement against AIDS and Malnutrition (DREAM) is a programme designed and run by the Community of Sant'Egidio [8–11] in Mozambique as well as in other sub-Saharan African countries.

A major focus of the programme is the prevention of mother-to-child transmission during pregnancy, delivery and breast-feeding. Mothers are kept on highly active antiretroviral therapy (HAART) if they qualify for this treatment at the time of diagnosis. Antiretrovirals (ARVs), nutritional supplements and laboratory tests are provided free of charge.

To assess the potential toxicity of, and damage caused by, NVP-containing regimens, a cohort of 703 pregnant women enrolled in DREAM were analysed retrospectively.

Patients and methods

Patients

The clinical files of all 999 pregnant women enrolled in the programme between 1 May 2002 and 31 July 2004 were reviewed. The baseline characteristics of the patients are presented in Table 1.

Of these patients, 28 had taken HAART for less than 14 days; 109 had not yet begun HAART because of the stage of their pregnancy; 84 refused to continue treatment after the first visit, and 53 stopped treatment before delivery [the overall refusal/lost-to-follow-up rate was 13.7% (137 patients out of 999)]; and 22 had liver enzyme measurements 2.5 times higher than the upper limit of normal (ULN) before starting HAART. Therefore, the total number of women included in this analysis was 703.

Methods

The CD4 cell count was determined using a Beckman-Coulter EPICS-XL MCL flow cytometer (Beckman-Coulter, Inc., Fullerton, CA, USA) equipped with an argon ion laser (488 nm). The lymphocyte subset count was determined in dual platform mode using the haematology analyser SYSMEX KX21 (Sysmex Co, Kobe, Japan). The antibodies used were CD45-FITC and CD4-PE, and CD8-Pcy5 if required (Beckman-Coulter, Inc.). Viral load tests were performed with System 340 (Bayer Diagnostic, Tarrytown, NY, USA) using branched-DNA technology (version 3.0, detection limit 50–500 000 HIV-1 RNA copies/mL).

Table 1 Baseline characteristics and toxicities for the pregnant women included in the study ($n = 703$)

Characteristic	Value
Age (years) [median (IQR)]	24.5 (21.5–28.6)
CD4 count (cells/μL) [median (IQR)]	492 (315–691)
Viral load (copies/mL) [median (IQR)]	11 300 (2625–31 150)
Haemoglobin (g/100 mL) [median (IQR)]	9.8 (8.7–10.6)
CD4 count (cells/μL) [*n* (%)]	
>250	574 (81.7)
≤ 250	129 (18.3)
Total	703 (100.0)
Viral load (copies/mL) [*n* (%)]	
$>55\,000$	115 (83.7)
$\leq 55\,000$	688 (16.3)
Total	703 (100.0)
WHO clinical stage classification [*n* (%)]	
1–2	658 (93.6)
3–4	45 (6.4)
Total	703 (100.0)
ARV regimen [*n* (%)]	
ZDV/3TC/NVP	629 (89.6)
d4T/3TC/NVP	74 (10.4)
Total	703 (100.0)
Baseline ALT/AST higher than ULN [*n* (%)]	
ALT	165 (23.5)
AST	141 (20.1)
ALT and/or AST higher than ULN	234 (33.3)
Baseline haemoglobin >8 g/100 mL [*n* (%)]	74 (10.4)
Malaria episodes [*n* (%)]	93 (13.2)
Active TB diagnosis [*n* (%)]	14 (2.0)

ALT, alanine aminotransferase, AST, aspartate aminotransferase; ARV, antiretroviral; ZDV, zidovudine; 3TC, lamivudine; NVP, nevirapine; d4T, stavudine; IQR, interquartile range; TB, tuberculosis; WHO, World Health Organization; ULN, upper limit of normal.

The protocol provided ARV administration to all the women irrespective of their CD4 cell count and viral load starting from the 25th week of pregnancy [8] or later, if the first ante-natal visit occurred later in the pregnancy. If, on their first visit, the patient's clinical condition was classified as stage 3–4 using the World Health Organization (WHO) Clinical Classification for Resource-Limited Countries [12], or if her CD4 cell count was <200 cells/μL or her viral load exceeded 55 000 copies/mL, ARV treatment was started in the 15th week.

Patients with a CD4 count <200 cells/μL were also given cotrimoxazole. For asymptomatic patients with a CD4 count >200 cells/μL and a viral load $<55\,000$ copies/mL, ARV treatment was continued for a maximum of 6 months after birth. The ARV drugs administered consisted of two generic fixed-dose combinations, both including NVP: (a) 629 patients (89.6%) were given zidovudine (ZDV) 300 mg twice daily, lamivudine (3TC) 150 mg twice daily and NVP 200 mg twice daily (once daily during the first 14 days of treatment); (b) 74 patients (10.4%) with haemoglobin levels <8 g/100 mL received stavudine (d4T) 30 or 40 mg twice daily instead of ZDV.

The protocol included monitoring the levels of haemoglobin and transaminases before starting ARVs, and then every 2 weeks for the first month and every 4 weeks thereafter. Adverse reactions were defined according to the Aids Clinical Trial Group (ACTG) Adult Adverse Experiences Grading Scale [13]. The mean number of transaminase measurements taken was 4.1 [median 4; interquartile range (IQR): 3–5; range 2–10]. The number of measurements was significantly higher in the subsample of patients with liver toxicity (4.7 vs 3.2 for the whole sample; $P<0.01$). If one of the transaminase measurements was greater than five times the normal value (grade 3–4 toxicity) and did not decrease on the next monthly visit, or if clinical symptoms suggested any liver toxicity, therapy was suspended. In the case of severe adverse reactions (grade 3–4) attributed to NVP, it was replaced by nelfinavir or indinavir.

Diagnosis of malaria was supported by laboratory evidence and tuberculosis diagnosis was made on the basis of sputum examination, chest X-ray and clinical examination. After delivery, formula milk was provided to the mothers, as well as a bottle and a filter for preparation of clean water. The entire package (including antiviral drugs and laboratory monitoring) was offered to the women free of charge.

Statistical analyses were performed using the SPSS statistical package (version 11.3; SPSS, Inc., Chicago, IL, USA). Generic statistical tests were performed as well as a Cox proportional hazard regression analysis. To assess the difference in the mean onset time of hepatic toxicity, an analysis of variance (ANOVA) univariate analysis was performed using the least significant difference (LSD) test and the Bonferroni test if equal variances were assumed, or the Games–Howell test if equal variances were not assumed. A linear regression was set up to assess the relation between hepatic toxicity onset time and pre-HAART CD4 cell count in these patients.

Results

ARVs and effectiveness

By the end of the study, 554 pregnancies reached term, while 149 (21.2%) women had not yet delivered. On average, therapy was started in the 27th week of pregnancy [standard deviation (SD) $\pm$ 4.8] and the median time of exposure to ARV before the end of the pregnancy (for the 554 women whose pregnancies reached term) was 81 days (IQR: 55–102 days). The median time of exposure before the end of ARV treatment or the end of the study period was 118 days (IQR: 75–164 days; $n = 703$).

After 60 days of treatment, median viral load sharply decreased from 4.05 log HIV-1 RNA copies/mL (IQR: 3.41–4.49 log copies/mL) to 1.7 log copies/mL (IQR: $<$1.60–2.51 log copies/mL). A viral load $<$3.0 log copies/mL was achieved in more than 75% of women. Similarly, CD4 cell counts increased from a median of 496 cells/μL (IQR: 308–697 cells/μL) before therapy to 630 cells/μL (IQR: 418–874 cells/μL) after 2 months of therapy, and to 694 cells/μL after 4 months of therapy (IQR: 494–918 cells/μL).

Considering triple therapy in relation to the prevention of mother-to-child HIV transmission, 331 babies, born before February 2004, were tested at 18 months (Rapid Test Determine, Abbott Laboratories, Chicago, IL, USA, plus Unigold, Trinity Biotech Plc, Bray, Ireland, for confirmation in the case of a positive test result). The infection rate was 3% [10 of 331; 95% confidence interval (CI): 1.1–4.9]. The mortality rate for these children was 4.9% (95% CI: 2.7–7.1).

The maternal post-partum drop-out rate was 7.8% (55 of 703 women). The maternal drop-out rate pre- and post-partum was 21.5%.

ARVs and safety

During the 27 months of observation, five deaths were registered during pregnancy (a maternal mortality rate of 0.8%), which is lower than the registered national average for all women in Mozambique (1%) [14]. Only one death was preceded by an increase in liver enzymes, which was detected after 21 days of treatment. This patient had a CD4 cell count of 322 cells/μL before treatment.

It is not always possible to obtain detailed information about the cause of death. Nevertheless, the available clinical and laboratory data seem sufficient to allow us to exclude use of ARV drugs as the cause of death. Neither a pathological increase in transaminases nor skin rashes were observed in the four remaining cases. At her initial visit, the first patient presented with severe anaemia (7.1 g/mL haemoglobin) and a respiratory pathology. ARV treatment with stavudine/lamivudine/NVP was begun along with antibiotic treatment and the oral administration of iron. After 2 weeks, she did not show clinical signs of toxicity or an alteration of laboratory test values. The patient died 4 days later of unknown causes. The second case involved a patient who died after 40 days of therapy without any specific pathology observed. Again a severe anaemic state (7.2 g/mL haemoglobin) was reported along with a high viral load of 5.6 log copies/mL. The third patient died after about 60 days of treatment; she was symptomatic on her first visit (oral and vaginal candidiasis) and had respiratory disturbances. This patient was also anaemic (7.1 g/mL haemoglobin), as was the fourth woman who died. This last

Table 2 Adverse reactions

Adverse reaction	Number (%) of patients	95% CI	Mean (days)	Univariate ANOVA	
				SD	*F*- and *P*-values
Hepatotoxicity					
Grade 2	40 (5.7)				
Grade 3	35 (5.0)				
Grade 4	11 (1.6)				
Total	86 (12.3)	9.8–14.8			
Grade 3–4 hepatotoxicity by CD4 count (cells/μL)					
≤250	12/129 (9.4)				
>250	34/574 (5.9)				
Onset time (days) for grade 2–4 hepatotoxicity by CD4 count					
≤250	23/129 (17.8)		217.1	± 191.9	$F = 11.107$
251–500	26/231 (11.2)		107.9	± 88.7	$P < 0.001$
>500	37/343 (10.8)		72.4	± 60.4	
Skin rash (grade 3–4)	17 (2.4)	1.3–3.5			
Stevens–Johnson syndrome	8 (1.1)	0.4–2.0			
Anaemia	100/629* (15.9)	13.2–18.6			

*Seventy-four patients had anaemia before starting highly active antiretroviral therapy (HAART).
ANOVA, analysis of variance; CI, confidence interval; SD, standard deviation.

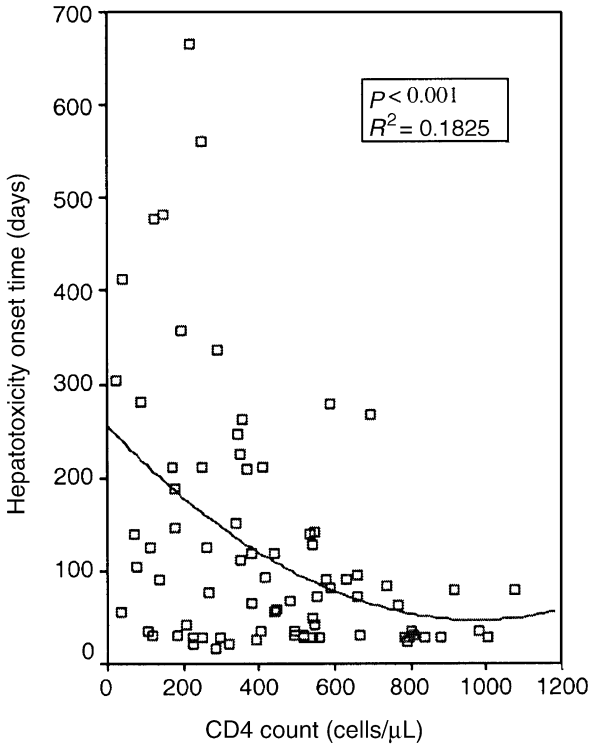

Fig. 1 Linear regression model for 2-4 grade hepatotoxicity and pre-HAART CD4 cell count (86 patients).

patient, who died after less than a month on HAART, showed no symptoms or signs of an adverse reaction involving the liver or skin.

Grade 3–4 hepatic adverse reactions occurred in 46 of the 703 patients; 6.6% of the cohort (Table 2). Liver enzyme values were checked until the end of 2004 for these cases. In these 46 patients, the increase in liver enzymes peaked during the first 2 months of therapy (median 74 days; IQR 29–143 days), and in 36 cases values returned to baseline despite continuation of ARV treatment. In 10 cases (1.4% of the overall sample) the women had skin rashes or Stevens–Johnson syndrome (SJS) and nausea or jaundice combined with liver toxicity, and NVP was discontinued. When the liver enzyme values returned to baseline or to below the 2.5 times ULN threshold (grade 2 toxicity), the patients re-started ARVs without prejudice after indinavir/nelfinavir has been substituted for NVP. Grade 3–4 hepatic toxicity incidence rates were 9.4% (12 out of 128 patients) for patients with pre-ARV CD4 cell counts <250 cells/μL and 5.9% (34 out of 573) for those with pre-ARV CD4 cell counts >250 cells/μL ($P = 0.15$) (Table 2). In addition, 40 cases of grade 2 liver toxicity were detected [7.0% and 5.4% ($P = 0.7$) in the groups with CD4 cell counts below and above 250 cells/μL, respectively]. None of the patients with grade 2 liver toxicity showed any clinical signs of toxicity so the ARVs were not discontinued.

The observation period for patients in the subsample with grade 3–4 liver toxicity was extended to the end of 2004. All but seven patients showed a return to normal values; six patients moved from grade 3 to grade 2 toxicity and one patient died, as reported above. The return to normal transaminase levels or at least to values below the threshold of 2.5 times ULN occurred in 32 days, on average,

Table 3 Risk of grade 3–4 hepatic toxicity by CD4 cell count, adjusted for malaria episodes, using Cox proportional hazard model

				95% CI per exp(B)	
	B	SE	Exp(B)	Lower	Upper
CD4 count (>250 vs ≤ 250 cells/μL)	−0.095	0.255	0.909	0.551	1.500
Malaria episodes	0.363	0.315	1.438	0.776	2.665

CI, confidence interval; SE, standard error; B, regression coefficient; Exp(B), hazard ratio.

for the patients who suspended therapy, and in 101 days for those who did not suspend therapy ($P = 0.004$).

A statistically significant association between higher CD4 cell count and shorter grade 2–4 hepatotoxicity onset time was observed (Fig. 1 and Table 2). The average number of days before grade 2–4 hepatic toxicity onset was 217 days (median 146 days; IQ 42–357 days) for patients with a pre-ARV CD4 cell count <250 cells/μL, 107 days (median 72 days; IQ 32–164 days) for patients with CD4 cell counts between 251 and 500 cells/μL, and 72 (median 63 days; IQ 28–91 days) for patients with counts >500 cells/μL ($P<0.001$). The Cox proportional hazards survival analyses, performed to assess the determinants of hepatic toxicity, showed no association between the onset of toxicity and high CD4 cell count levels, even after adjusting for malaria episodes. In fact, no significant difference was found between the two strata (Table 3).

During the entire period of observation, eight cases (1.1%) of SJS were recorded. None was lethal, but in each case ARVs were suspended for the time required for the patient to recover. Then treatment was resumed with a regimen without NVP being administered. In addition to the eight cases of SJS, 17 patients were observed to have skin rashes of grade 3 severity (2.4%). In these cases also, a regimen without NVP was substituted after a short suspension of ARVs.

The total number of patients who stopped NVP-containing regimens because of SJS, skin rashes or hepatic toxicity was 25 out of 703 patients (3.5%).

Before beginning treatment, 74 women had haemoglobin levels >8 g/100 mL, so they started HAART with stavudine; among the remaining 629 who started therapy with ZDV, 100 (15.9%) were placed on triomune because their haemoglobin level fell below 8 g/100 mL.

Discussion

When treating pregnant women, our goal should be to decrease the viral load as quickly and effectively as possible. It is clear from this and other studies that ARV triple therapy represents the gold standard for accomplishing this goal [15–18]. The limited drop-out rate for patients in this large programme run in a public health setting in a limited-resource environment provides reassurance that this goal is possible even in developing countries.

The incidence rate of toxicity of NVP-containing regimens was consistent with that reported in other studies [2,4,7,19], and toxicity was frequently self-limiting. While a grade 3–4 elevation of alanine aminotransferase (ALT)/aspartate aminotransferase (AST) level was detected in 6.6% of women using a NVP-containing regimen, most of these elevations resulted in no significant clinical hepatotoxicity. Most of the 3–4 grade toxicities (36 out of 46) resulted in transient elevations of transaminase levels, which had decreased again by the next check-up without ARV treatment being stopped or changed. It is likely that the majority of these elevations in liver enzymes were the result of the NVP in the regimen [1–7]. The incidence rate of hepatic toxicities was higher in the women undergoing long-term treatment [20].

It is interesting that our data did not confirm an association between hepatic toxicity and high CD4 cell count. However, we observed an earlier onset of hepatic toxicity in the group with CD4 cell counts >250 cells/μL. This observation is compatible with the hypothesis that hepatic toxicity is caused by an immune-mediated toxic effect on the liver, which is more rapid when the immune system itself is less compromised.

Five deaths occurred in this ARV-treated cohort of patients. Only one of these deaths could be associated with elevation of liver enzymes (incidence rate 0.18%; 95% CI: 0.00–0.54). With regard to the other four deaths, none of these patients had either elevated transaminases or skin rashes. The small percentage of deaths that could be related to liver toxicity is consistent with that reported in other studies [19].

Reliance on a retrospective analysis of clinical files resulted in some limitations. In each case, the discontinuation of NVP occurred in patients who experienced a skin rash or SJS at the same time.

The present study did not allow us to measure the impact of several other related factors, such as the prevalence of hepatitis B virus and hepatitis C virus infection. Such factors could have had important effects on liver toxicity associated with ARVs in our study [21].

The incidence of episodes of serious skin rashes and SJS was also low in this study (3.5%) and comparable to that observed by other authors [3].

The incidence of anaemia highlights one of the disadvantages of using zidovudine, although this drug is one of the most effective in preventing mother-to-child transmission.

The protocol did not include tests on the babies other than for diagnosing HIV infection using branched-DNA at 1, 6 and 12 months of age. This meant that we were not able to evaluate possible hepatic toxicity in the babies resulting from the therapy taken by their mothers. However, the low mortality rate (4.9%) among the infants compared with that of the overall paediatric population in Mozambique indicates that the presence of any toxicity had little impact.

The results obtained here, showing a high rate of prevention of mother-to-child transmission, suggest that the use of triple therapy is effective in greatly reducing the number of HIV-infected newborns. The use of formula milk to avoid transmission after delivery could be limited by social and economic difficulties. Triple therapy after delivery could therefore be an effective means of preventing HIV transmission after delivery in resource-limited settings.

In conclusion, the low frequency and mainly minor consequences of adverse reactions to a NVP-based regimen in poor women in this resource-limited environment suggest that such a regimen should be considered by policy makers and those involved in HIV programmes as the preferred treatment regimen for HIV-positive pregnant women.

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