Hepatotoxicity of nevirapine in virologically suppressed patients according to gender and CD4 cell counts*

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Objectives
A warning advising a higher risk of hepatotoxicity in antiretroviral-naive patients starting a nevirapine-containing combination antiretroviral therapy (NcART) has been issued by health authorities. It is unclear whether this higher risk also applies to stable virologically suppressed patients starting NcART.

Methods
We performed a meta-analysis of published randomized studies including virologically suppressed patients who switched to NcART with a follow-up ≥ 3 months. CD4 cell cell counts were classified as high (HCD4) (400 cells/μL for males and 250 cells/μL for females) or low (LCD4). The main endpoint was hepatotoxicity within the first 3 months.

Results
Four studies with a pooled total of 410 patients were included. The risk of hepatotoxicity within the first 3 months was 2% and 4% in the LCD4 and HCD4 groups, respectively, with a combined odds ratio of 1.46 [95% confidence interval (CI) 0.43–4.98; P = 0.54]. The risk of hepatotoxicity at any point during the study was similar in both groups, with a combined hazard ratio of 0.8 (95% CI 0.3–2.5; P = 0.80).

Conclusions
In our study, virologically suppressed patients switching to nevirapine did not have a significantly higher risk of hepatotoxicity or rash when stratified by gender and CD4 cell count, although small differences may have gone undetected because of the sample size limitation.

Keywords: CD4 count, gender, hepatotoxicity, meta-analysis, nevirapine

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Introduction
In January and March 2005, respectively, the US Food and Drug Administration [1] and European Medicines Agency (EMEA) [2] issued warnings in the nevirapine (NVP) package insert recommending against the initiation of NVP in adult women with CD4 lymphocyte counts above 250 cells/μL or in adult men with a count above 400 cells/μL, because of a higher risk of hepatotoxicity. The data were derived mainly from a retrospective analysis of the Boehringer Ingelheim databases, including almost exclusively antiretroviral (ARV)-naïve patients [3] who initiated an NVP-containing antiretroviral regimen (NcART), and further confirmed in a sub-analysis of the 2NN study [4]. When these gender and CD4 criteria were applied to the 2NN study, excluding a participating centre in Bangkok (which constituted most of the symptomatic hepatitis diagnoses), the risk of symptomatic hepatic events was around 4%; risk levels were almost identical in the efavirenz (EFV) and in the NVP qd and bid arms, respectively [5]. Because of its low price, favourable metabolic profile and proven safety for pregnant women and newborns, NVP...
has been used widely in both developed and developing countries [6]. NVP has also been used widely in the simplification of protease inhibitor (PI)-containing therapy [7], and the risk of major toxicities in this setting seems to be lower than in naïve patients [8].

We aimed to further confirm whether or not the increased risk of hepatotoxicity also applies to ARV-experienced patients as opposed to naïve patients, when women or men switch to NcART and their CD4 cell count is above 250 and 400 cells/µL, respectively. For that reason, we designed a meta-analysis of published randomized studies assessing the risk of NVP-associated hepatotoxicity, rash and death when stable and virologically suppressed patients were switched to NcART stratifying by gender and CD4 lymphocyte count.

Patients and methods

Patients

We included studies with virologically suppressed (defined as plasma HIV-1 viral load <50–200/mL for at least the previous 3 months) HIV-1-infected adults who were switched to an NcART regimen in the context of randomized published clinical trials before March 2005 identified through the PubMed database. Patients received 200 mg/day NVP for the first 2 weeks and then 400 mg/day NVP thereafter. For a study to be included in the analysis, we required the availability of the complete trial database consisting of comprehensive laboratory and adverse event data, and a sample size of at least 50 patients with a potential exposure to NVP of at least 3 months to ensure the availability and quality of the data. The following clinical trials were considered: NEFA [9], a randomized, multi-centre study to analyse the safety of the substitution of HIV-1 virologically suppressed patients treated with PI to NVP, EFV or abacavir (ABC); PREVHNE II [10], the GESIDA (Grupo de Estudio del SIDA) 26/02 study, a double-blind, placebo-controlled trial conducted to assess the impact of ceterizine to prevent NVP-associated rash; QDLluita [11], a randomized, multi-centre study to evaluate an ARV treatment simplification with NVP in protease inhibitor-experienced patients with HIV-associated lipodystrophy; and the Study 1100.138, an international randomized study sponsored by Boehringer Ingelheim [12] to analyse the effects of a short course of prednisone on the incidence of rash associated with NVP in HIV-1 patients. Demographic and clinical information including co-infection by hepatitis C or hepatitis B virus, baseline and follow-up alanine transaminase (ALT) or aspartate aminotransferase (AST), together with adverse events, were analysed at recruitment and during the study follow-up. Although patients should have been followed for at least 3 months, the actual minimal follow-up was 36 months in NEFA, 3 months in PREVHNE, 12 months in QDLluita and 24 months in Study 1100.138.

Statistical methods

For the purposes of this study, patients were classified into two groups according to the last CD4 cell count before study entry: high CD4 (HCD4) (if CD4 ≥400 cells/µL in males or ≥250 cells/µL in females) and low CD4 (LCD4) (if CD4 <400 cells/µL in males or <250 cells/µL in females).

The major endpoint was death or hepatotoxicity (defined as elevation of ALT or AST ≥200 UI/mL if normal at baseline or ≥threefold increase if abnormal at baseline [13]) within the first 3 months. Secondary endpoints were the development of hepatotoxicity at any time point or the development of hepatotoxicity or rash or symptomatic hepatitis or death within the first 3 months or at any time point during the study.

Baseline characteristics of the patients were described using median and interquartile range (IQR) or absolute frequency and percentage, in the case of quantitative and qualitative variables respectively, and were compared between the two groups (LCD4 and HCD4) by means of the Mann–Whitney U-test and Fisher's exact test, respectively. We estimated the risks for NVP discontinuation in the HCD4 group compared with the LCD4 group because of death or hepatotoxicity, or because of death, hepatotoxicity or rash during the first 3 months and at the end of the whole follow-up using random-effects meta-analyses. Random-effects meta-analyses estimate summary measure by weighting each individual study result by a factor of within- and between-study variance. The combined OR estimate was based on the DerSimonian–Laird method [14].

Homogeneity of study results was assessed using the Q statistic and the Galbraith plot [15]. Publication bias was assessed via Begg's test and funnel plot [16]. The influence of individual studies on the pooled OR was evaluated omitting one study at a time. A cumulative analysis was performed according to publication year and month. A meta-regression was performed in order to identify covariates associated to the outcome. This model was based on two additive components of variance, one representing the variance within studies and the other the variance between studies. Quantitative covariates were analysed as median study values and qualitative ones as the proportion of patients in each study with that characteristic.

The Kaplan–Meier method was used to estimate time to outcomes and the Log-rank test was used to compare the survivor functions between groups. The person–year incidence rates of outcomes within the first 3 months of
follow-up were compared with those of the latter period using Poisson regression models. All tests were two-tailed with a confidence level of 95%.

### Results

Four randomized controlled trials with a pooled total of 410 patients were analysed by the meta-analysis [155 (38%) from the NEFA study, 101 (25%) from GESIDA, 84 (20%) from QDLuita and 70 (17%) from Study 1100.138]. One hundred and thirty-three (32.4%) patients were categorized as LCD4 and 277 (67.5%) were categorized as HCD4. Baseline characteristics of the patients are summarized in Table 1. No statistical differences were observed between LCD4 and HCD4 groups in age, sex, CD4 nadir cell count, previous AIDS-defining events, risk group or hepatitis C or B co-infection, except for baseline abnormal ALT/AST serum levels that were more frequent in the LCD4 group (McNemar test, $P = 0.014$).

Within the first 3 months of NcART, three patients (2%) in the LCD4 group and 12 patients (4%) in the HCD4 group developed hepatotoxicity. Seventeen patients (13%) in the LCD4 group and 12 patients (4%) in the HCD4 group developed hepatotoxicity. Nineteen patients (14%) in the LCD4 group and 21 patients (8%) in the HCD4 group developed a rash. No patients in the LCD4 group and two (1%) patients in the HCD4 group developed symptomatic hepatitis. No patient died.

The combined OR estimate for hepatotoxicity or death during the first 3 months between groups was 1.46 [95% confidence interval (CI) 0.43–4.98; $P = 0.54$]. No statistical differences were observed between groups or studies (heterogeneity test, $P = 0.371$) (Fig. 1a). None of the studies had greater influence on the overall OR than the others, and studies included in the meta-analysis were not a biased sample of the study population (Begg’s test $P$-value = 1.00 and funnel plot, data not shown).

Using a meta-regression model, none of the following variables showed a statistically significant association with an increased risk of hepatotoxicity or death at 3 months: baseline CD4/gender, hepatitis C co-infection or age. Baseline ALT/AST levels showed a trend [crude coefficient $0.13$ (95% CI $-0.02$ to 0.27, $P = 0.084$)].

The combined OR for hepatotoxicity, rash or death within the first 3 months between groups was 1.17 (95% CI 0.56–2.42; $P = 0.680$) (Fig. 1b). The results of influence analysis and publication bias for studies were also not significantly different, similarly to those obtained for hepatotoxicity and death. In addition, similar results were obtained with the meta-regression model. Only baseline ALT/AST serum levels showed a trend for an association [crude coefficient $0.09$ (95% CI $-0.02$ to 0.19, $P = 0.095$)], with an increased risk of hepatotoxicity, rash or death at 3 months.

By the end of the whole follow-up period, 10 patients (8%) in the LCD4 group and 21 patients (8%) in the HCD4 group developed hepatotoxicity. Nineteen patients (14%) in the LCD4 group and 29 patients (10%) in the HCD4 group developed a rash. No patients in the LCD4 group and two patients (1%) in the HCD4 group developed symptomatic hepatitis.

One patient in each group died (0.7% in LCD4, 0.4% in HCD4); one death was attributed to lactic acidosis and the other one to a traffic accident. The risk of hepatotoxicity or death at any moment during the study was similar in both groups, with a combined HR of 0.77 (95% CI 0.30–1.99; $P = 0.646$).

The risk of hepatotoxicity or rash or death among groups disclosed similar results [combined HR of 0.99 (95% CI 0.61–1.60, $P = 0.964$)].

Moreover, comparing the survivor functions within groups, the person–year incidence rate of outcomes within the first 3 months [0.7 for LCD4 (95% CI 0.4–1.1) and 0.6 for HCD4 (95% CI 0.5–0.9)] was higher than later in the follow-up [0.06 for LCD4 (95% CI 0.03–0.1) and 0.03 for HCD4 (95% CI 0.02–0.06)] ($P = 0.001$, respectively).

Comparison between the survivor functions of the groups over the total period showed no differences: the proportion of patients with hepatotoxicity or who died was 16.38% (95% CI 8.72–29.59) and 10.23% (95% CI 6.62–15.63) in

### Table 1 Baseline characteristics of the patients

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<th>LCD4 (women</th>
<th>HCD4 (women</th>
<th>$P$-value</th>
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<tbody>
<tr>
<td>Total number (n = 410)</td>
<td>133</td>
<td>277</td>
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<tr>
<td>Median age, years (range)</td>
<td>39 (35–45)</td>
<td>38 (34–43)</td>
<td>0.09$^*$</td>
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<td>Male gender, n (%)</td>
<td>101 (76)</td>
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<td>CD4 T-cell count nadir (n = 211), median cells/μL (range)</td>
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<td>Prior AIDS-defining event (n = 155), n (%)</td>
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<td>A</td>
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<td>C</td>
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<tr>
<td>HCV co-infection (n = 336), n (%)</td>
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<td>HBV co-infection (n = 334), n (%)</td>
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<td>Abnormal baseline ALT/AST (n = 409)</td>
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$^*$McNemar test.

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$^*$Wilcoxon’s rank sum test.

LCD4, group of patients with low CD4 cell count at baseline (women with $<250$ cells/μL and men with $<400$ cells/μL); HCD4, group of patients with high CD4 cell count at baseline (women with $>250$ cells/μL and men with $>400$ cells/μL); ALT, alanine transaminase; AST, aspartate aminotransferase; CDC, Centers for Disease Control disease stage; HBV, hepatitis B virus; HCV, hepatitis C virus.

the LCD4 and HCD4 groups, respectively (Fig. 2a); the proportion of patients with hepatotoxicity, rash or who died was 27.08% (95% CI 18.53–38.52) and 19.61% (95% CI 14.89–25.59) in the LCD4 and HCD4 groups, respectively (Fig. 2b).

Discussion

Our results suggest that being a male with \( /C21 \) 400 cells/\( \mu L \) or a female with \( /C21 \) 250 cells/\( \mu L \) when starting NcART as simplification or maintenance therapy in virologically suppressed patients is not associated with an increased risk of hepatotoxicity or rash or death. However, with the sample size of this meta-analysis, differences in toxicity between both study arms of around 6% (OR upper limit 4.98) might exist without being detected; therefore, results should be interpreted with caution.

As expected, the risk of discontinuing NVP because of toxicities between both groups is higher within the first 3 months of therapy [7,17].

Recently, Mocroft et al. published the results of the EuroSIDA cohort [8] assessing the risk of discontinuation NVP caused by toxicity in HIV-infected patients; they identified 1484 patients that started NcART. Patients were classified in four groups according to being naïve or experienced and gender/CD4 cell count (high or low). In accordance with our results, they found that unlike the naïve patients, the ARV-experienced ones starting NcART, irrespective of having high or low CD4, had a similar risk of discontinuation caused by toxicities or patient/physician choice. Moreover, by the end of follow-up, although the outcomes were different, we also obtained similar rates of toxicity (27.08% in LCD4 and 19.61% in HCD4 in our study compared to 27.3% and 27.1%, respectively, in the EuroSIDA study).

In another study, German researchers reported the incidence of liver toxicity in a retrospective study, which included 507 treatment-naïve and -experienced patients who started NVP therapy. Similarly to our results, gender and CD4 cell count were not significantly associated with increased risk of liver toxicity [18].

More recently, data from the ATHENA cohort [19] have also suggested that the incidence of hypersensitivity reaction associated with NcART in patients with prior treatment experience is lower than in treatment-naïve patients, especially when HIV RNA load is undetectable at the start of NVP.
It should be noted that the mentioned studies are not randomized trials and their results should be interpreted with caution, although their data come from large databases with good-quality data. Our study, analysing data exclusively from randomized trials, controlled the quality and reliability of the data collected, limiting for potential confounding factors.

However, it could be argued that cases of severe life-threatening hepatotoxicity – in accordance with the Viramune™ (nevirapine) package insert – are particularly more frequent in the first 18 weeks of therapy, and that we have analysed data at month 3 or at the overall follow-up. We established this time point with the aim of including the highest number of randomized studies in the meta-analysis; however, as mentioned earlier, the minimal follow-up of three of the four studies included was 24 months.

On the other hand, our findings are supported by other cohorts in whom the follow-up of the studies was also analysed at 3 and 12 months (the EuroSIDA cohort), at 21 months (the German study) and at 18 weeks (the ATHENA cohort).

The mechanism of NVP-associated hypersensitivity is unclear. The association between NVP and higher CD4 T-cell counts suggests the involvement of CD4-dependent, major histocompatibility complex (MHC) class II-restricted immune responses directed against NVP and/or its metabolites. An association has been reported between hepatic/systemic NVP reactions and the human leucocyte antigen (HLA) class II allele HLA-DRB1*0101 among patients with a higher CD4 T-cell percentage [20]. However, this association seems not to be as strong as the HLA-B*5701-ABC hypersensitivity link [21].

NVP has proved to be highly effective in the simplification of highly active ARV therapy in patients with a sustained virological response [7] and has been used widely [6] – especially in resource-limited settings – because of its low cost and its confirmed role in reducing vertical transmission [22].

In summary, our results suggest that virologically suppressed patients switching to NVP as a part of a simplification regimen do not show a higher risk of hepatotoxicity or rash dependant on gender or CD4 cell counts. Therefore, the current warning against NVP use in patients with higher CD4 T-cells may not be applied in this clinical scenario.

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