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# Analysis of Severe Hepatic Events Associated with Nevirapine-Containing Regimens

## CD4+ T-Cell Count and Gender in Hepatitis C Seropositive and Seronegative Patients

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## Abstract

**Background:** Nevirapine-containing regimens have been associated with a risk of significant elevations of liver transaminase levels. Higher risk in antiretroviral-naive populations has been related to gender and CD4+ T-cell count (women with CD4+ T-cell counts of ≥250/mm$^3$ or men with CD4+ T-cell counts of ≥400/mm$^3$, i.e. group at risk). However, recent studies do not confirm this association in HIV populations comprising patients who are antiretroviral-experienced. Moreover, the predictive value of gender and CD4+ T-cell count on the risk of raised transaminase levels has been poorly investigated in populations of patients co-infected with hepatitis C virus (HCV).

**Methods:** Analysis of HIV-positive patients receiving nevirapine-containing regimens for the first time was conducted. Grade ≥III hepatotoxicity (i.e. ≥5 × upper limit of normal in alanine aminotranferase or aspartate aminotransferase levels) was the primary endpoint. Univariate and multivariable Cox proportional hazard regression models were separately conducted among HCV-antibody (Ab)-positive and HCV-Ab-negative patients.

**Results:** Amongst 905 patients, 49% were HCV-Ab-positive and 79% were antiretroviral-experienced. Grade ≥III liver transaminase elevations developed in 7.1% of patients, accounting for an incidence of 2.47 (95% CI 1.97, 3.09) per 100 patient-years of follow-up. HCV-Ab reactivity was associated with a 3-fold increase in risk of developing relevant liver transaminase elevations (95% CI 1.75, 5.3; $p < 0.001$), whereas gender and CD4+ T-cell count did not impact significantly. When analysis was performed in HCV-Ab-negative patients, the outcome was independently correlated with the group at risk (hazard ratio [HR] 3.66; 95% CI 1.20, 11.14; $p = 0.022$). By contrast, in HCV-Ab-positive patients, the group at risk was not significantly associated with the outcome.

**Conclusions:** Most of the excess rates of relevant raised transaminase levels in patients prescribed nevirapine-containing regimens could be attributed to HCV co-infection. Gender and CD4+ T-cell count appeared to have a statistically significant impact on the risk of relevant transaminase level elevations in HCV-negative, but not in HCV-positive patients, probably due to a diluting effect of HCV. Incidence of hepatic events after nevirapine-containing regimens did not appear to be a major concern in our cohort of patients who were mainly antiretroviral-experienced and negative for HCV-Ab. Preferably, nevirapine should be avoided in HCV co-infected patients and in males with CD4+ T-cell counts of ≥400/mm$^3$ or females with CD4+ T-cell counts of ≥250/mm$^3$.

## Background

Raised liver transaminase levels are commonly observed with all antiretroviral regimens, especially in patients chronically co-infected by hepatitis viruses. Nevirapine is a first-choice drug in developing countries and is also frequently used in developed countries, especially in Europe. However, nevirapine has been associated with a high potential for increasing transaminase levels.[1-4] In the international, randomised, multicentre 2NN (2 non-nucleosides) study, antiretroviral-naive patients receiving nevirapine were found to have a higher rate of relevant raised transaminase levels (i.e. hepatotoxicity) than patients receiving efavirenz and this difference reached statistical significance for symptomatic hepatotoxicity.[5] In a *post hoc* analysis, the risk of hepatotoxicity was associated with gender and CD4+ T-cell count, the risk being higher in female patients with CD4+ T-cell counts of ≥250/mm$^3$ and in male patients with CD4+ T-cell counts of ≥400/mm$^3$.[6] Subsequent analyses of this trial revealed an excess of hepatotoxicity with nevirapine in Thai patients; however, the excess in symptomatic and asymptomatic hepatotoxicity disappeared in non-Thai women with CD4+ T-cell counts of <250/mm$^3$ or non-Thai men with CD4+ T-cell counts of <400/mm$^3$.[7]

The aim of this study was to assess the risk of nevirapine-associated hepatotoxicity in patients who were either experienced or naive to antiretroviral drugs in a clinical setting, where the prevalence of hepatitis C virus (HCV) co-infection was substantial. Moreover, we investigated the impact of gender and CD4+ T-cell count on the risk of hepatotoxicity after controlling for possible confounders, including HCV co-infection. In other words, we explored whether risk assessment may provide different results in HCV-positive patients compared with those not infected by HCV, with particular focus on the possible association of CD4+ T-cell count relative to gender.

## Materials and Methods

### Patients

The study consisted of a retrospective analysis of prospectively collected data from a cohort of HIV-infected patients attending the Institute of Infectious and Tropical Diseases of the University of Brescia, a major referral centre for HIV-care in Italy. The cohort included all sequential patients formerly naive to nevirapine who had started any highly active antiretroviral therapy (HAART), including nevirapine, since June 1996 and had maintained it for at least 1 month. Follow-up was censored in case of occurrence of the outcome, nevirapine discontinuation, loss to follow-up or at month 36, whichever came first. The database was 'frozen' for the analysis in October 2005. Patients were stratified into HCV-positive or HCV-negative groups by the results of HCV antibody (Ab) test at inclusion. A descriptive analysis of patients was performed to better characterise the hepatotoxicity events.

### Endpoint

Any increase of ≥5 × upper limit of normal (ULN) in alanine aminotranferase (ALT) or aspartate aminotransferase (AST) [i.e. grade III hepatotoxicity as defined by the AIDS Clinical Trial Group classification][8] during the course of the follow-up was considered to be the primary endpoint. Normal ranges of liver transaminase levels were 0–50 IU/L in male and 0–35 IU/L in female patients. The endpoint was not adjusted for baseline elevations of ALT/AST to increase the sensitivity of capture of hepatotoxicity events.

### Statistical Analysis

Separate Cox proportional hazard regression models were conducted in HCV-Ab-positive and in HCV-Ab-negative patients. This stratification was applied to avoid the possible effect of HCV coinfection (the major risk factor of hepatotoxicity) in diluting the associations with other variables whose impact on the risk of hepatotoxicity was less strong.

The following factors assessed at baseline were tested by proportional hazard regression models for their possible associations with occurrence of the study endpoint in both groups (HCV-Ab-positive and -Ab-negative): gender, age, intravenous drug use as a risk factor for HIV acquisition, antiretroviral-treatment history, hepatitis B surface antigen (HBsAg) serostatus, CD4+ T-cell count at nadir (i.e. the lowest CD4+ value ever recorded), baseline CD4+ T-cell count (i.e. at starting nevirapine-containing regimen), baseline ALT level, baseline AST level, group at risk by gender and CD4+ T-cell count (i.e. female patients with CD4+ T-cell counts of ≥250/mm$^3$ or male patients with CD4+ T-cell counts of ≥400/mm$^3$), and AST-to-platelet ratio index (APRI score)[9] as a surrogate of stage of liver disease.

Among treatment-experienced patients, the possible impact of CD4+ T-cell count on the risk of hepatotoxicity could be masked by consideration of this variable at baseline (just before starting nevirapine), while the risk could be better indicated by the nadir CD4+ T-cell count, reflecting the actual derangement of immune function that may predispose to hepatotoxicity. To address this, nadir CD4+ T-cell count was used in a sensitivity analysis conducted in antiretroviral-experienced patients, replacing CD4+ T-cell count assessed at baseline.

The variables found to be significant ($p \leq 0.2$) at univariate analysis and group at risk by gender and CD4+ T-cell count as previously defined were entered into multivariable models. Statistica 7.0 (StatSoft, Tulsa, Oklahoma, USA, 2001) and Stata 8.0 (Stata Corporation, College Station, Texas, USA, 2003) were used to perform the analyses. A p-value of $< 0.05$ indicated conventional statistical significance.

## Results

### Population Characteristics

A total of 1155 patients started nevirapine-containing regimens in the study period. Among these patients, 250 (21.6%) were excluded from the analysis because they did not complete 1 month follow-up on nevirapine. Among them, 83 of 250 (33.2%) patients were still on nevirapine or were lost to follow-up at the time of 'freezing' of the database, while reasons for premature nevirapine discontinuation in the remaining 167 patients were as follows: skin rash in 96 of 167 (57.5%) patients (only 1 case of grade ≥III AST/ALT elevation was recorded), grade ≥III liver transaminase elevations in 2 of 167 (1.2%) patients; gamma glutamyl tranferase (γ-GT) elevation in 2 of 167 (1.2%) patients and intolerance or lack of compliance in 67 of 167 (40%) patients. Patients who were excluded from the study did not differ significantly from the others for any factor, including group at risk (either overall or by reason of premature follow-up discontinuation).

Characteristics of the 905 patients who were further studied are illustrated in table I. The majority of patients were Italian (87%), male (66%) and antiretroviral therapy-experienced (79%), and 46% of them had acquired HIV through intravenous drug use. A total of 436 (48%) were positive for HCV-Ab and 470 (52%) had a CD4+ T-cell count higher than the threshold considered at risk for hepatotoxicity (229 women with CD4+ counts of ≥250/mm$^3$ and

**Table I.** Patient characteristics of the 905 study patients starting nevirapine-containing regimens

| Characteristics | HCV-Ab-negative patients (n = 469) | HCV-Ab-positive patients (n = 436) | Total (n = 905) | p-Value |
|---|---|---|---|---|
| **Qualitative (%)** | | | | |
| Female gender | 43 | 24 | 34 | <0.001 |
| Group at risk[a] | 49 | 35 | 52 | <0.001 |
| Risk factor (IVDU) | 6 | 88 | 46 | <0.001 |
| Nationality (Italian) | 77 | 98 | 87 | <0.001 |
| Positive HBsAg | 6 | 6 | 6 | NS |
| Naive to ARV drugs | 25 | 13 | 21 | <0.001 |
| EFV-experienced | 17 | 16 | 16 | NS |
| PI-naive | 44 | 61 | 52 | 0.03 |
| APRI score | | | | |
| >0.71 | 0.2 | 13 | 7 | |
| >0.81 | 0.2 | 10 | 5 | <0.0001 |
| **Quantitative [median (IQR) for all variables or mean (SD) for age]** | | | | |
| Age (years) | 43 (10) | 42 (5) | 43 (8) | NS |
| Nadir CD4+ T-cell count in cells/mm$^3$ | 206 (95–305) | 166 (69–267) | 182 (82–290) | <0.001 |
| CD4+ T-cell count at baseline in cells/mm$^3$[b] | 329 (219–489) | 299 (192–442) | 317 (204–464) | 0.007 |
| ALT at baseline in IU/L[b] | 26 (17–38) | 50 (33–81) | 35 (22–57) | <0.001 |
| AST at baseline in IU/L[b] | 26 (20–33) | 43 (30–62) | 32 (23–48) | <0.001 |
| Number of experienced treatment lines | 2 (0–4) | 3 (1–5) | 3 (2–5) | <0.001 |

a Group at risk: female patients with CD4+ T-cell count ≥250/mm$^3$ or male patients with CD4+ T-cell count ≥400/mm$^3$.

b Baseline is defined as the value soon before introduction of nevirapine.

**ALT** = alanine aminotransferase; **APRI** = AST-to-platelet ratio index; **ARV** = antiretroviral; **AST** = aspartate aminotransferase; **EFV** = efavirenz; **HBsAg** = hepatitis B surface antigen; **HCV-Ab** = hepatitis C virus antibody; **IQR** = interquartile range; **IVDU** = intravenous drug use (as a risk factor for HIV acquisition); **NS** = not significant; **PI** = protease inhibitor; **SD** = standard deviation.

241 men with CD4+ counts of ≥400/mm$^3$). Overall, 21 cases of skin rashes leading to nevirapine interruption were recorded and were not associated with severe hepatotoxicity as far as AST/ALT levels determined within 1 month around the time of rash were considered, except from one case due to unavailability of AST/ALT measurement. Forty-six female patients were pregnant; none of them developed severe hepatotoxicity during nevirapine treatment. Only two of these patients stopped nevirapine because of rash and neither had any evidence of concomitant hepatotoxicity.

## Incidence of Hepatotoxicity

Grade ≥III AST/ALT elevations developed in 64 of 905 (7.1%) patients, accounting for an incidence of 2.47 (95% CI 1.97, 3.09) per 100 person-years of follow-up. Patients who were HCV-Ab-negative had an incidence of 1.23 (95% CI 0.79, 1.90) per 100 person-years. In contrast, patients who were seropositive for HCV-Ab had an incidence of 3.85 (95% CI 2.97, 5.01); thus, accounting for a 3-fold increase in the risk of hepatotoxicity with respect to HCV-Ab-negative patients (hazard ratio [HR] 3.04; 95% CI 1.75, 5.30; p = 0.001) [figure 1].

Other concomitant risk factors for raised liver transaminase levels in patients experiencing hepatotoxicity were alcohol abuse, reported in 14 of 64 (22%) patients (13 HCV-Ab-positive and 1 HCV-Ab-negative) and HBsAg positivity in 10 of 64 (16%) patients (7 were positive for HCV-Ab and 1 patient had stopped a lamivudine- and tenofovir-based regimen, explaining the occurrence of the outcome).

Regarding concomitant antiretroviral drugs, dideoxynucleoside compounds, which are know to induce liver damage, were used as follows: 11 of 64 (17.2%) patients were taking didanosine, 15 of 64 (23.4%) patients were taking stavudine and 8 of 64

(12.5%) patients were taking didanosine plus stavudine. Besides antiretroviral drugs, no other hepatotoxic drugs were prescribed at the time of hepatotoxicity.

Interestingly, 32 of 64 (50%) patients had γ-GT levels above the ULN normality before presenting hepatotoxicity, and γ-GT increase paralleled AST/ALT increase in patients who had hepatotoxicity. Moreover, among 54 patients with available determinations of alkaline phosphatase (ALP) levels concomitant with hepatotoxicity, 18 of 54 (33.3%) had a biochemical pattern indicative of 'cytolitic' damage (ALT : ULN/ALP : ULN ≥5), 12 of 54 (22.2%) had a 'cholestatic' liver damage (ALT : ULN/ALP : ULN ≤2) and 24 of 54 (44.4%) had a 'mixed' pattern of liver damage (ALT : ULN/ALP : ULN = 2–5), following an accepted definition.[10]

## Predictors of Hepatotoxicity

### *Hepatitis C Virus Antibody (HCV-Ab)-Positive Patients*

The results of the analysis of potential risk factors associated with hepatotoxicity in HCV-Ab-positive patients are shown in table II. On univariate analysis, the presence of HBsAg and elevated baseline AST and ALT levels were associated with an increased risk of developing hepatotoxicity; therefore, they were input in the multivariable model. On this model, baseline ALT and AST levels were the only independent predictors of relevant hepatotoxicity. Importantly, no significant impact was apparently exerted by the group at risk by gender/CD4+ T-cell count.

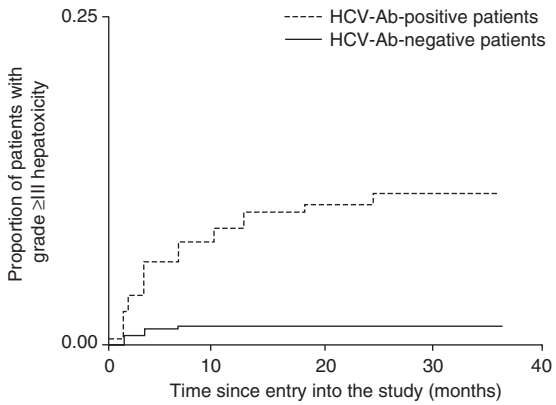


**Fig. 1.** Incidence of grade ≥III hepatotoxicity in hepatitis C virus antibody (HCV-Ab)-positive and HCV-Ab-negative patients.

### *HCV-Ab-Negative Patients*

As shown in table III, when univariate analysis was performed in HCV-Ab-negative patients, the outcome was not correlated with being a female with a baseline CD4+ T-cell count of ≥250 cell/mm$^3$ or a male with a count of ≥400/mm$^3$ to a statistically significant level. However, on multivariable analysis, the group at risk emerged as a significant predictor of hepatotoxicity, independently from positive HBsAg, intravenous drug use as a risk factor for HIV acquisition and elevated baseline ALT and AST levels.

Figure 2 shows a gradient in the risk of hepatotoxicity in HCV-Ab-negative patients according to the group at risk. Female patients with CD4+ T-cell counts of ≥250/mm$^3$ showed a higher risk compared with men who had CD4+ T-cell counts of <400/mm$^3$ (log-rank p = 0.031).

Multivariable analysis conducted in antiretroviral-experienced patients confirmed the association of hepatotoxicity with CD4+ T-cell count and gender. However, prediction was not statistically significant when nadir CD4+ T-cell count was used to define the group at risk (HR 2.97; 95% CI 0.84, 10.55; p = 0.092).

## Discussion

The main aim of this study was to verify whether CD4+ T-cell count and gender are associated with risk of hepatotoxicity for patients receiving nevirapine-containing regimens. An increased risk of hepatotoxicity in women[11] and in antiretroviral-naive patients with high CD4+ T-cell counts have been demonstrated.[6] In contrast, several studies have suggested that this is not the case in mixed cohorts of antiretroviral-naive and -experienced patients,[12-14] and even in a cohort of HIV-1 infected pregnant women.[15] The studies presented so far offer important insights; however, they are limited by the small numbers of patients. Moreover, HCV

**Table II.** Factors associated with hepatotoxicity in hepatitis C virus antibody-positive patients

| Factors | Unadjusted HR (95% CI) | p-Value | Adjusted HR (95% CI) | p-Value |
|---|---|---|---|---|
| Group at risk[a] | 0.94 (0.52, 1.70) | 0.841 | 1.11 (0.61, 2.04) | 0.731 |
| Positive HBsAg | 2.30 (0.97, 5.41) | 0.057 | 1.93 (0.81, 4.61) | 0.137 |
| ALT at baseline[b] (per 50 IU/L increase) | 2.69 (1.64, 4.38) | <0.0001 | 1.64 (1.00, 2.11) | <0.0001 |
| AST at baseline[b] (per 50 IU/L increase) | 2.69 (1.64, 4.38) | 0.005 | Not tested[c] | |

a Group at risk: female patients with CD4+ T-cell counts of ≥250/mm3 or male patients with CD4+ T-cell counts of ≥400/mm3.

b Baseline is defined as the value soon before introduction of nevirapine.

c Not tested due to co-linearity (in a separate model including AST instead of ALT, HR 1.64; 95% CI 1.13, 2.10; p = 0.007; in this model, HR associated with group at risk remained not statistically significant).

**ALT** = alanine aminotransferase; **AST** = aspartate aminotransferase; **HBsAg** = hepatitis B surface antigen; **HR** = hazard ratio.

co-infection is one of the main factors explaining raised liver transaminase levels in patients undergoing HAART; therefore, it could dilute the associations with other variables that do not have as much of an impact on the risk of hepatotoxicity. This possible bias may occur easily when the number of patients is small.

Specifically, the possible 'background' effect of HCV co-infection may have confounded the association between high CD4+ T-cell counts relative to gender in the studies conducted so far. A further analysis was conducted in a larger cohort of patients, concluding that those who are antiretroviral-experienced, with high CD4+ T-cell counts, had a reduced risk of nevirapine discontinuation compared with patients whose CD4+ T-cell count was low.[16] However, investigators studied the risk of discontinuation of nevirapine due to any toxicity or patient choice; thus, the possible influence of CD4+ T-cell count and gender on the risk of hepatotoxicity cannot be deduced.

In the present analysis, we stratified patients into positive or negative groups at HCV-Ab test and then conducted separate analyses in these two groups. Such methodology was useful to rule out the possible confounding effect of HCV co-infection. No apparent influence of CD4+ T-cell count relative to gender was found in HCV-Ab-positive patients. However, in HCV-Ab-negative patients, the risk was associated with gender and high CD4+ T-cell counts and was independent from other confounding factors. Interestingly, a high CD4+ T-cell count also acted as a risk factor among experienced patients, suggesting that this parameter should also be taken into account when simplification or salvage therapy is prescribed.

**Table III.** Factors associated with hepatotoxicity in hepatitis C virus antibody-negative patients

| Factors | Unadjusted HR (95% CI) | p-Value | Adjusted HR (95% CI) | p-Value |
|---|---|---|---|---|
| Group at risk[a] | 2.36 (0.83, 6.70) | 0.106 | 3.66 (1.20, 11.14) | 0.022 |
| Positive HBsAg | 5.08 (1.66, 15.60) | 0.004 | 4.43 (1.25, 15.66) | 0.021 |
| IVDU | 4.64 (1.51, 14.23) | 0.007 | 5.74 (1.79, 18.46) | 0.003 |
| ALT at baseline[b] (per 50 IU/L increase) | 2.69 (1.64, 4.38) | 0.004 | 2.69 (1.64, 4.38) | 0.025 |
| AST at baseline[b] (per 50 IU/L increase) | 2.69 (1.64, 4.38) | <0.0001 | Not tested[c] | |

a Group at risk: female patients with CD4+ T-cell count ≥250/mm3 or male patients with CD4+ T-cell count ≥400/mm3.

b Baseline is defined as the value soon before introduction of nevirapine.

c Not tested due to co-linearity (in a separate model including AST instead of ALT, HR 2.69; 95% CI 1.64, 6.45; p = 0.001; in this model, HR associated with group at risk remained statistically significant, HR 4.36; 95% CI 1.33, 14.35; p = 0.015).

**ALT** = alanine aminotransferase; **AST** = aspartate aminotransferase; **HBsAg** = hepatitis B surface antigen; **HR** = hazard ratio; **IVDU** = intravenous drug use (as a risk factor for HIV acquisition).

The association of hepatotoxicity with high AST/ALT levels at baseline is not unexpected.[17,18] It occurred both in HCV-Ab-positive and in HCV-Ab-negative patients, indicating that a careful evaluation of these parameters is important. Intravenous drug use was associated with hepatotoxicity in HCV-Ab-negative patients. The interpretation of this association is not straightforward. It is possible that some patients with intravenous drug use as a risk factor for HIV acquisition were co-infected by HCV notwithstanding HCV-Ab negativity.[19] An alternative hypothesis could be that intravenous drug use is correlated with previous or concurrent causes of liver inflammation, not detected in this study, such as alcohol abuse or use of recreational drugs. Importantly, the risk of hepatotoxicity was correlated with HBsAg serum-reactivity, indicating that a careful management of active HBV co-infection is necessary. The availability of antiretroviral drugs with a concomitant activity against HIV and HBV could improve the control of chronic HBV hepatitis.

Two-thirds of hepatotoxicities were classified as 'cholestatic' or 'mixed', and half of all cases of hepatotoxicity were preceded by abnormal γ-GT values. This finding can not be generalised to all cases of nevirapine hepatotoxicity. Early-onset hepatotoxicities (i.e. occurring during the first month) were excluded from the analysis since nevirapine was stopped for different reasons (mainly rash) and liver function test values were not available in most of these cases. Early-onset hepatotoxicity could be mostly characterised by a 'cytolitic' rather than 'cholestatic' or 'mixed', pattern, whether or not this is associated with an 'idiosyncrasic' reaction to nevirapine. CD4+ T-cell recovery was independently associated with severe hepatotoxicity, suggesting that hepatic injury may be caused by immune-mediated mechanisms in some patients, especially in HCV-co-infected patients, in whom a reactivation of HCV replication may occur during the initial period of treatment.[1,20] Taken together, these observations suggest that two different patterns of hepatotoxicity may occur with nevirapine-containing regimens: late-onset hepatotoxicity characterised either by a 'cholestatic' or 'mixed' pattern. Further pathogenetic and clinical studies are necessary to clarify this issue.

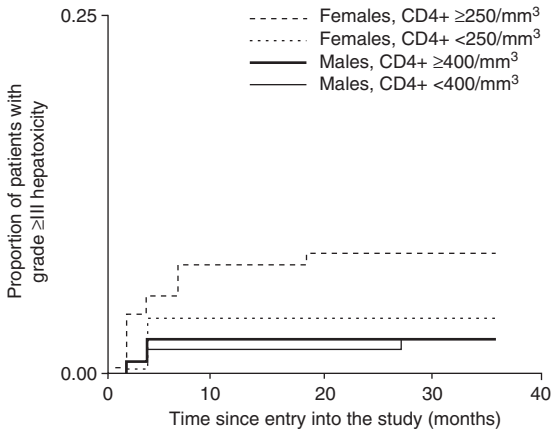


**Fig. 2.** Incidence of grade ≥III hepatotoxicity in hepatitis C virus antibody (HCV-Ab)-negative patients.

The incidence of hepatotoxicity in our population was 2.47 (95% CI 1.97, 3.09) per 100 patient-years of follow-up: 3.85 (95% CI 2.97, 5.01) and 1.23 (95% CI 0.79, 1.90) in HCV-Ab-positive and HCV-Ab-negative patients, respectively. This estimation is comparable with what has been found in different studies and for different drugs.[21,22] Our study was not controlled; thus, we cannot infer how the incidence of nevirapine-associated hepatotoxicity compare with that of different regimens. This was not our objective. Although nevirapine appeared to be well tolerated as far as hepatotoxicity is concerned, consistently with other observations,[23] other studies have found an increased risk of hepatotoxicity after nevirapine compared with different drugs.[1,4] Our previous analysis, conducted in a larger cohort of patients, concluded that an increased risk of hepatotoxicity after regimens containing non-nucleoside reverse transcriptase inhibitors is only present in experienced patients, without any significant difference between nevirapine and efavirenz.[18] However, two studies have found an increased risk of hepatotoxicity associated with nevirapine compared with efavirenz.[1,4] Altogether, these observations support the suggestion that careful monitoring is needed when nevirapine-containing regimens are

prescribed, even in patients who are taking this drug over the long-term.

Our study has important limitations that need to be recognised. Complete information about medication adherence, use of alcohol, liver biopsy results and nevirapine plasma drug concentrations were not available in this observational study. This further information would have helped to determine the actual aetiology of raised liver transaminase levels. For instance, high nevirapine plasma concentrations were correlated with occurrence of hepatotoxicity in a study conducted by De Requeña and colleagues.[24] The possible influence of the associated drugs, previous drug exposure and previous hepatotoxicity events were ignored, and patients were retained in the analysis as long as nevirapine was taken. Moreover, both the retrospective and the observational nature of the study could lead to confounding by indication bias. Lastly, although exclusion of patients stopping nevirapine early in the course of treatment allowed us to evaluate specifically the cases of liver transaminase elevations, some cases of raised transaminase levels could have been missed, simply because these were not determined before stopping the drug. Thus, the actual incidence of nevirapine-associated hepatotoxicity could have been underestimated. The same limitations may affect results of most of the studies performed so far.

## Conclusions

In conclusion, we have estimated factors associated with the risk of hepatotoxicity in a cohort of patients at their first experience of nevirapine, most of whom were antiretroviral-experienced. Gender and CD4+ T-cell counts had a significant independent impact on the risk of hepatotoxicity in HCV-Ab-negative patients, while this impact did not appear to be significant in HCV-positive patients. Although patients receiving nevirapine merit careful monitoring for liver toxicity, particularly during the first months of therapy, the incidence of hepatotoxicity after the first month was low in our cohort, especially in those negative for HCV-Ab and with CD4+ T-cell counts of $<250/mm^3$ (if women) or $<400/mm^3$ (if men).

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