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Risk for Immune-Mediated Liver Reactions by Nevirapine Revisited

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Abstract

Implementation of combination antiretroviral therapies has transformed the prognosis of HIV infection during the past decade. Because of its low-pill burden, convenient administration once or twice daily without food restrictions and, in the case of nevirapine, favorable metabolic profile and proven safety in pregnant women and newborns, nonnucleoside reverse transcriptase inhibitors have been shown to be often superior to protease inhibitors as third agents in combination with a backbone of two nucleoside reverse transcriptase inhibitors. Therefore, two nucleoside reverse transcriptase inhibitors plus one nonnucleoside reverse transcriptase inhibitor are currently the most popular used first-line therapies. Hepatotoxicity during the first weeks of therapy with nevirapine, particularly when initiated in women with CD4 counts > 250 cells/mm^3, has prompted changes in guidelines and led to a modification in the product label. Recent data, however, suggest that virologically suppressed patients under any other antiretroviral drug combination may safely switch to nevirapine as a part of a simplification strategy, regardless of their current CD4 count. This subset of patients does not show an increased risk of hepatotoxicity or rash with elevated CD4 counts, as has been reported in drug-naive HIV persons. This information is important and may expand the number of candidates who could benefit from nevirapine use, since a substantial proportion of HIV patients show metabolic abnormalities (dyslipidemia, insulin resistance, liver steatosis) and are at increased cardiovascular risk. Fortunately, many of these conditions may ameliorate or improve using nevirapine. **(AIDS Rev. 2008;10:110-5)**

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Key words

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Introduction

All antiretroviral drugs are potentially hepatotoxic, and liver enzyme elevations are commonly seen in patients under prolonged highly active antiretroviral therapy (HAART)[1]. Several mechanisms of hepatotoxicity have been described, including metabolic host-mediated injury, hypersensitivity reactions, mitochondrial toxicity, and immune reconstitution phenomena (Table 1). More recently, two novel pathways for liver hepatotoxicity have been suggested. Insulin resistance in the context of the HAART-associated metabolic syndrome may lead to nonalcoholic steatohepatitis and ultimately to liver fibrosis[2]. On the other hand, some nucleoside analogs, particularly didanosine, might be involved in a cascade of liver events, starting with portal sinusoidal injury and thrombosis, leading to hypoperfusion of some parenchymal hepatic areas and nodular regenerative hyperplasia[3-5].

After initiating HAART, the reported incidence of severe liver toxicity ranges from 2-18%[6-16]. Besides

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Table 1. Mechanisms of drug-related liver injury in HIV-infected patients[1]

Metabolic host mediated (intrinsic & idiosyncratic)
– PI and NNRTI
– Occurrence can vary by agent
– Dose-dependence for intrinsic damage

Hypersensitivity
– Nevirapine > abacavir > fosamprenavir
– Occurs early, usually within 8 weeks
– Often associated with rash
– HLA-linked

Mitochondrial toxicity
– NRTI (ddI > d4T > AZT > ABC = TDF = 3TC/FTC)
– Tends to occur after prolonged exposure

Immune reconstitution
– Chronic hepatitis B (unclear for HCV)
– Occurs within the first month following initiation of HAART
– More common in patients with very low CD4 counts who experience robust immune recovery

PI: protease inhibitor; NNRTI: nonnucleoside reverse transcriptase inhibitor; NRTI: nucleoside reverse transcriptase inhibitor; HLA: human leukocyte antigen; ddI: didanosine; d4T: stavudine; AZT: azidothymidine; ABC: abacavir; TDF: tenofovir; 3TC: lamivudine; FTC: emtricitabine.

prolonged and continuous antiretroviral drug exposure, other comorbidities that predispose to liver damage are common among HIV-infected individuals, such as chronic hepatitis B or C, alcohol or illicit drug abuse, dyslipidemia, glucose metabolism abnormalities, and advanced immune suppression, all of which contribute in producing rapid, progressive, hepatic fibrosis[1,17-20]. When indicated, HAART should not be deferred for any concern about the risks of hepatotoxicity as the benefits of immune recovery generally overcome the risks for liver events[1]. However, prevention and management of antiretroviral-related hepatotoxicity have emerged as major issues for HIV-infected patients receiving HAART, since drug-associated hepatotoxicity can lead to liver-related morbidity and mortality[21], as well as to discontinuation of HIV treatment.

Skin reactions and hepatic toxicity within the first weeks of treatment are the Achilles' heel for nevirapine (NVP), an otherwise well-tolerated and effective antiretroviral agent, which has been shown to be particularly useful for alleviating metabolic disturbances, facilitating adherence, or effectively preventing mother-to-child HIV transmission. Worries about the prescription of NVP became particularly burdensome following reports of cases of liver failure in immunocompetent HIV-negative individuals exposed to NVP as postexposure prophylaxis, or in HIV-asymptomatic carriers with well-preserved immunity in whom NVP was part of the first-line regimen. The recognition that allergic phenomena involving either the skin or the liver may be more common in patients with elevated CD4 counts than in subjects with advanced immunodeficiency was the basis for the warning by health authorities regarding the use of NVP in men with > 400 CD4 T-cells/µl and women with > 250 cells/µl.

Benefits of nevirapine

Many characteristics make NVP convenient as part of first-line therapy of HIV infection. The Atlantic trial compared the combination of NVP, indinavir, or lamivudine, with a backbone of stavudine plus didanosine in antiretroviral-naive patients[22]. In terms of viral suppression, tolerability, and favorable metabolic profile, the NVP arm was superior to the other two arms. Similar results were obtained in the Combine study[23], in which NVP was compared to nelfinavir, both in association with zidovudine plus lamivudine. Again, the NVP arm was superior to the nelfinavir arm, in part due to greater nonadherence in patients assigned to receive nelfinavir. A more favorable metabolic profile was achieved with NVP compared to nelfinavir. Interestingly, in the two trials previously mentioned, NVP outperformed the comparative protease inhibitor, even in patients with higher baseline viral load.

A direct comparison of NVP with efavirenz was assessed in the SENC trial[24]. At 12 months, viral suppression and immunologic benefit were similar

in both arms, but neuropsychological adverse events were reported more frequently in the efavirenz arm. Since no major central nervous system events are seen in patients treated with NVP, in the context of neuropsychiatric abnormalities or drug dependence, NVP tends to be more convenient than efavirenz. Both nonnucleosides were also compared in the 2NN trial[25]. The proportion of antiretroviral-naive HIV patients who achieved undetectable viremia at week 48 was similar using either NVP or efavirenz, irrespective of baseline plasma viral load and whether NVP was administered once or twice daily. Interestingly, the metabolic subanalysis of this trial revealed that the glucose and lipid profile was more favorable with NVP than with efavirenz.

The trials mentioned above found similar efficacy in terms of viral suppression when NVP was compared to efavirenz or protease inhibitors. Therefore, antiretroviral-naive patients who will initiate HAART may consider regimens based on NVP. Due to its unique favorable metabolic profile, NVP may be preferred to the other options when prevention and/or treatment of lipid disorders and insulin resistance are advisable in patients with significant cardiovascular risk.

Since most protease inhibitor-based regimens are complex in terms of large pill burden, drug interactions and metabolic adverse events, several studies have investigated the outcome of simplification strategies with a switch to NVP-based regimens, once viral suppression has been obtained under a protease inhibitor-based regimen. As will be discussed later, this strategy has recently been evaluated in a meta-analysis of four trials[26-29]. All uniformly concluded that NVP outperformed protease inhibitor-based regimens in terms of metabolic profile, without increasing the risk of virologic failure[30].

One additional advantage of NVP is regarding its proven safety during pregnancy. Administration of NVP at pre-partum and to the newborn is more effective than using AZT alone in the prevention of vertical HIV transmission[31,32]. In a trial, the combination of NVP with AZT during the last two trimesters of pregnancy diminished the transmission of HIV-1 to 1.1%[33]. Since triple therapies are more effective and specific NVP-associated resistance mutations (e.g. Y181C or K103N) can be selected with mono or dual therapies, these strategies should be limited only to developing countries where full HAART is not yet available[34]. In developed regions, however, the lack of teratogenicity of NVP makes the drug particularly attractive for child-bearing women wanting to become pregnant. Finally, the relatively low price of the drug facilitates its wide access for almost all patients in need of antiretroviral therapy.

Risk of hepatotoxicity using nevirapine

The overall incidence of symptomatic events involving the liver in patients taking NVP is around 5%[35,36]. Hypersensitivity reactions, usually manifested as exanthema often accompanied by systemic symptoms (fever, malaise, etc.), may occur along with liver involvement. Cases of early-onset severe liver toxicity in HIV-seronegative individuals starting NVP as post-exposure prophylaxis suggest that this host-mediated pathway could be immune dependent[37]. In the FTC-302 trial, a higher incidence of hepatotoxicity was recorded in patients assigned to the NVP arm compared to the efavirenz arm[38]. Liver enzyme elevations predominated in black women, often in association with rash and fever, again consistent with a drug hypersensitivity reaction. Further analysis revealed that these events appeared to be linked to NVP use in women with CD4 counts > 250 cells/µl, emphasizing the importance of host immunity and neoantigen recognition in the pathogenesis of NVP-associated hypersensitivity reactions[39]. Other risk factors for NVP-associated hepatotoxicity included low body mass index[40] and host genetics. Persons with an HLA-DRB1*0101 background had an increased propensity for developing NVP-associated hypersensitivity reactions[41-43]. Of note, these episodes of liver enzyme elevations within a few weeks of initiation of NVP therapy were not more frequent in patients with underlying chronic hepatitis B or C.

In patients with a prolonged exposure to NVP, a subset with underlying chronic viral hepatitis may present with flares in liver enzymes, which could reflect intermittent episodes of cytolysis during the spontaneous course of chronic hepatitis B/C or delayed liver toxicity of NVP. This distinct pattern of drug injury due to NVP use may be recognized beyond 16 weeks of therapy, and is more consistent with a direct or idiosyncratic liver injury[44-46]. This late-onset hepatotoxicity of NVP has also been reported to occur in patients treated with efavirenz and could be considered as a class toxicity. The recognition of this alternative form of hepatotoxicity using nonnucleoside analogs is particularly important when

treating populations with a high prevalence of chronic hepatitis C (e.g. intravenous drug users) or chronic hepatitis B (e.g. patients from South East Asia). In other patient populations, this late-onset hepatotoxicity of NVP is rarely seen (~ 3%)[47]. Moreover, specific genetic polymorphisms of metabolizing enzymes and drug transporters seem to be involved in the pathogenesis of late-onset NVP-associated hepatotoxicity[35,48].

It should be highlighted that hepatotoxicity with either NVP or efavirenz does not appear to increase the risk of developing liver injury following exposure to the alternative nonnucleoside analog[49,50]. Altogether, these data suggest that in order to prevent NVP immune-mediated liver toxicity, the drug should be given only to women with CD4 counts < 250 cells/µl and to men with < 400 cells/µl. Close monitoring of liver enzymes is recommended during the first weeks of therapy, but only every 3-4 months in patients tolerating the drug well.

Safety of nevirapine in patients already on successful antiretroviral therapy

The advice to use NVP only in subjects with low CD4 counts in order to minimize the risk of hepatotoxicity was demonstrated in drug-naive subjects. However, several studies have recently shown that the risk of NVP-associated liver enzyme elevations could be lower in patients with complete suppression of HIV replication under HAART. In a recent meta-analysis[30], in which data from four large simplification trials using NVP were revisited (NEFA[26], GESIDA 26/02[27], QDLluita[28] and Study 1100.138[29]), there was a uniformly low risk of hepatotoxicity using NVP along with a lack of correlation with CD4 counts. All patients in those studies were under effective HAART and had undetectable plasma HIV RNA when starting NVP. The drug was always prescribed as currently recommended: 200 mg/day during the first two weeks and 400 mg/day thereafter; exposure for at least three months was assessed in all patients. Using as main endpoint the development of liver enzyme elevations grade 3-4 (ALT or AST > 200 IU/l if normal at baseline, or > 3-fold increase if abnormal at baseline), no differences in hepatotoxicity were seen when comparing with low or high CD4 counts.

It should be noted that a total of 410 patients were included in the pooled meta-analysis; 133 patients were categorized as with low CD4 counts (women < 250 cells/µl and men < 400 cells/µl) and 277 as with high CD4 counts. No significant differences were observed between the two groups at baseline in terms of age, sex, CD4 count nadir, or HCV coinfection rates. Within the first three months after switching to NVP, three patients (2%) in the low CD4 count group and 12 patients (4%) in the high CD4 count group developed hepatotoxicity. No patients in the former group and only two (1%) in the latter group developed symptomatic hepatitis; no deaths were registered.

Using a meta-regression model, none of the following variables showed a significant statistical association with an increased risk of hepatotoxicity or death using NVP in simplification strategies: baseline CD4 count, gender, HCV coinfection, or age. Only baseline ALT/AST levels showed a trend towards greater liver toxicity using NVP (OR: 0.13; 95% CI: -0.02 to 0.27; p = 0.08). By the end of the follow-up period, the risk of hepatotoxicity or death using NVP was similar in both groups, with a combined OR of 0.77 (95% CI: 0.61-1.60; p = 0.64) (Fig. 1).

These results clearly demonstrate that virologically suppressed HIV patients switching to NVP as a part of a simplification regimen do not show a higher risk of hepatotoxicity or rash depending on gender and/or CD4 cell counts. Thus, the current warning against NVP use in patients with high CD4 counts may not be applicable to patients already under HAART having complete viral suppression. In fact, fatal cases of liver toxicity using NVP have been reported among HIV-seronegative individuals or HIV-infected subjects naive for antiretroviral therapy. All these findings together may suggest that the risk for severe NVP reactions could be dependent on the cellular immunity and/or its abnormalities as result of uncontrolled HIV replication.

Conclusion

Nevirapine is being used widely in both developed and developing countries. Because of its favorable metabolic profile, antiviral potency, and proven safety for pregnant women and newborns, it is a good alternative to protease inhibitors. Efavirenz cannot be used in pregnant women. The current warning against NVP use in HIV patients with elevated CD4 counts may be only applicable to antiretroviral-naive individuals. In this population, elevated CD4 counts (> 400 cells/mm^3 in men and > 250 cells/mm^3 in women), baseline ALT/AST elevations, and HCV

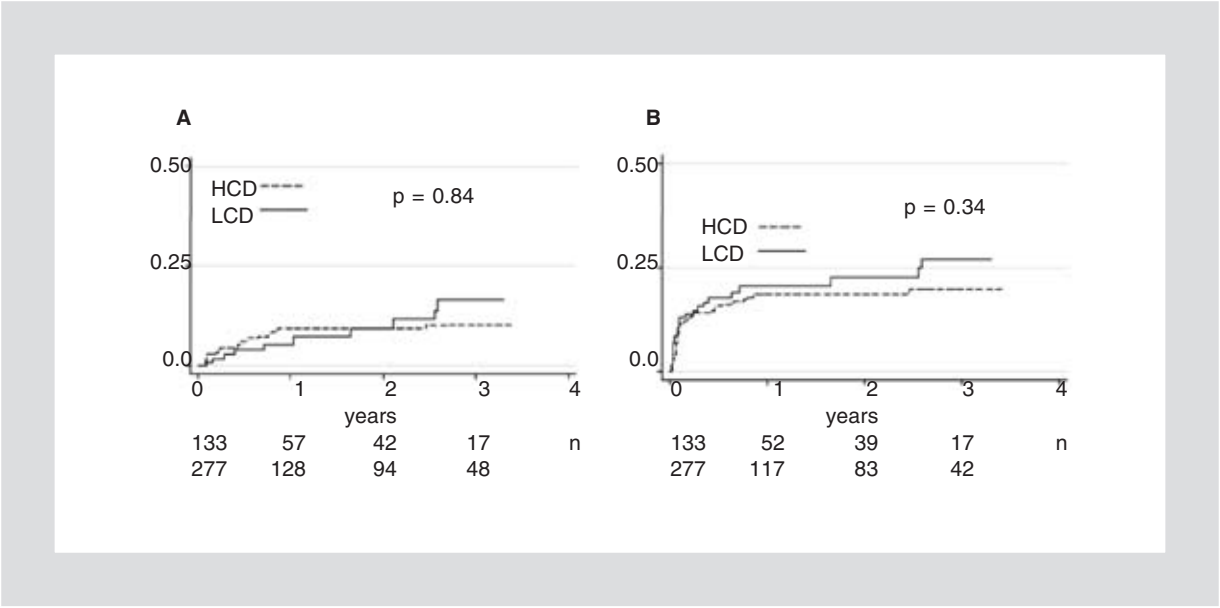

Figure 1. *Time to hepatotoxicity or death **(A)** and time to hepatotoxicity or rash or death **(B)** in 410 HIV patients included in a meta-analysis[30]. HCD: high CD4 defined counts (> 400 cells/µl in men and >250 cells/µl in women); LCD: low CD4 defined counts.*

coinfection are the most reliable predictors of NVP-associated hepatotoxicity. However, in HIV patients already on antiretroviral therapy and having complete viral suppression, the prescription of NVP is often made in the context of simplification strategies. In this setting, no increased risk of liver toxicity has been found in women with > 250 or males with > 400 $CD4^+$ T-cells/µl.

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