AIDS Rev. 2013;15:139-45

Liver Toxicity in HIV-Infected Patients Receiving Novel Second-Generation Nonnucleoside Reverse Transcriptase Inhibitors Etravirine and Rilpivirine

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Abstract

There are few data on the hepatic safety profile of the novel second-generation nonnucleoside reverse transcriptase inhibitors etravirine and rilpivirine. Previous extensive studies including other drugs of the same class, nevirapine and efavirenz, have shown an incidence of liver toxicity of 3-20%, higher in the case of nevirapine. The pathogenic mechanisms involved are related to hypersensitivity, as described with nevirapine, impaired metabolism and therefore increased drug levels, and direct toxic effects with production of toxic metabolites. Hepatitis C coinfection seems to be the most important factor for toxicity, especially in the case of advanced liver fibrosis. Etravirine showed a similar rate of liver toxicity to placebo in regulatory studies, but this seems to be lower in the clinical setting, as has been observed in the Expanded Access Program and in cohort studies including HCV/HIV-coinfected patients with different degrees of fibrosis. Also, rilpivirine showed a low rate of liver toxicity, similar to the comparator efavirenz in development studies, even in coinfected patients. Both second-generation nonnucleoside reverse transcriptase inhibitors are rarely associated to hypersensitivity reactions, and drug metabolism is not severely altered in the case of HCV coinfection, at least in the absence of severe fibrosis. Also, both drugs are weak hepatic cell inducers. Therefore, clinical and pathogenic data suggest that both etravirine and rilpivirine are safe to be used in the clinical setting, including patients with liver abnormalities at baseline. **(AIDS Rev. 2013;15:139-45)**

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Key words

NNRTI. HCV. Hepatotoxicity. Liver. Adverse events.

Introduction

Highly active antiretroviral therapy (HAART) has dramatically improved the natural course of HIV infection. However, the long-term use of antiretroviral therapy has been associated with a broad range of adverse events involving kidney, bone, liver, and the central nervous system[1]. Specifically, liver toxicity is one of the most relevant adverse effects of antiretroviral therapy, owing to its frequency and significance. Clinically, it may present with clinical and pathological manifestations that may oscillate from asymptomatic liver enzyme elevations to fulminant liver failure[2,3].

The data available on the exact incidence of liver toxicity related to HAART are contradictory due to several factors[4]. Some episodes do not fulfill the criteria necessary for a temporal relationship and for the exclusion of other causes of increased liver enzymes such as alcohol. HAART always includes at least three drugs administered in combination, which makes it extremely difficult to identify the definitive causal agent. In addition, biopsy-based data on drug-induced liver injury are limited. Elevated liver enzyme levels have been used as a surrogate marker of liver toxicity in all HIV cohort studies and clinical trials, but the lack of a standardized definition has resulted in a wide variation, from less than 2 to 37% of cases[5,6]. Most clinical trials

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define severe liver toxicity (grade 3 or 4) as a greater than fivefold increase in levels of alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) above the upper limit of normal (ULN), following the criteria used by the AIDS Clinical Trials Group (ACTG)[7]. Since most patients could have increased transaminases at baseline, a modified version of the ACTG criteria defines toxicity as any increase in ALT or AST levels above 200 IU/ml if baseline values are normal, or more than 3.5-fold baseline levels if they are abnormal[7]. Using these criteria, most studies have found the incidence of elevated liver enzyme levels after six or more months of HAART to be approximately 2-18%[8-10]. However, a majority of cases of elevated liver enzyme values does not lead to serious liver injury, and the more common outcomes are benign and are associated with resolution of elevated liver enzyme values[11,12], regardless of whether the antiretroviral drug possibly responsible was modified or not, suggesting the possibility of underdiagnosed cases. This fact could explain the differences in the rate of toxicity between clinical trials and observational cohorts, since visits are more frequent in clinical trials, allowing the detection of more laboratory abnormalities.

Most cohort studies show that coinfection with hepatitis B virus (HBV), and specially with hepatitis C virus (HCV), is the most consistent risk factor for increases in liver enzyme levels[13,14], and it has been demonstrated that the presence of HCV increases by 2- to 10-fold the risk of developing transaminase increases during HAART[13-15]. The mechanism by which HCV may lead to a higher risk of elevated liver enzyme values is not fully elucidated. The evidence that HCV is associated with elevated liver enzyme values caused by immune restoration is not as convincing as that in hepatitis B. Several studies have reported decreases in HCV viral load because of immune restoration[16], or even HCV-specific immune responses, T-cell activation, and inflammation to be associated with hepatotoxicity[17]. However, because most antiretroviral drugs are metabolized by the liver, overexposure to antiretrovirals could be more common in HIV-infected persons with hepatic insufficiency[18]. Any compromise in liver function in patients with chronic viral hepatitis is mainly due to the loss of a substantial proportion of hepatocytes, which are replaced by fibrotic tissue. As a consequence, the ability of the liver to clear drugs from blood might be significantly compromised. In a study of 107 patients, we found a close relationship between the degree of liver fibrosis and the risk of developing elevated liver enzyme values. An incidence of 38% was noted in those who had advanced (F3 or F4) fibrosis, compared with 15% in those who had minimal (F1 or F2) fibrosis[19]. Thus, the severity of liver disease may play a role in increasing the risk of elevated liver enzyme values. In addition, the rate of hepatic events has been demonstrated to be lower (9.3%) in patients who achieved HCV clearance, compared with 37.5% in those without sustained virological response to interferon therapy[20]. In any case, patients coinfected with HIV/HCV who are at increased risk for elevated liver enzyme values also are more likely to discontinue HAART because of toxicity[21].

First-generation nonnucleoside reverse transcriptase inhibitors: efavirenz and nevirapine

In some series, the incidence of liver toxicity with NNRTI is not higher compared to other antiretrovirals. This is especially true in populations with a low prevalence of chronic HCV infection, but it seems to be higher compared with protease inhibitors (PI), and involves several aspects and mechanisms[22]. In different studies comparing both NNRTI, the frequency of toxicity in patients on efavirenz ranges from 1 to 8%, whereas in patients treated with nevirapine, it ranges from 4 to 18%[13,14]. As expected, hepatitis coinfection increases the risk of elevated liver enzyme values with either nevirapine or efavirenz, increasing to 19% of those taking nevirapine and up to 15% of those taking efavirenz, and concomitant use of NNRTI and PI also seems to increase the risk of elevated liver enzyme values[23-25].

However, there are differences in the rate of toxicity between nevirapine and efavirenz. For example, in the 2NN trial the subgroup of patients treated with efavirenz presented liver toxicity in 4.5% of cases, whereas the patients treated with nevirapine, once and twice per day, presented frequencies of 13.2 and 7.8%, respectively[26]. In the NEFA trial only 0.6% of patients who received efavirenz showed grade 3 or 4 toxicity compared with 4% of those treated with nevirapine[27]. In comparative cohort studies, efavirenz liver toxicity was observed in 8%, compared with 16% in the nevirapine group. Also, in 298 patients included in a Spanish hospital, 4% of patients receiving efavirenz and 12% of those receiving nevirapine developed severe hypertransaminasemia[13]. Taken together, the incidence of liver toxicity seems to be nearly threefold more frequent for nevirapine than for efavirenz. Thus, in a recent meta-analysis of 18 studies including 17,512 patients, those receiving nevirapine were more likely to experience any grade of hepatotoxicity (OR: 1.5; 95% CI: 1.3-1.8)

Table 1. Incidence of hepatic adverse events and rate of discontinuation because of liver toxicity in the DUET trials.

	HIV/HCV coinfection		HIV-monoinfected patients	
	Etravirine (n = 72)	Placebo (n = 68)	Etravirine (n = 494)	Placebo (n = 496)
Any hepatic AE n (%)	13 (18)	10 (15)	34 (7)	30 (6)
Grade 3-4 transaminases				
– ALT increase	10 (14)	61 (9)	15 (3)	10 (2)
– AST increase	8 (11)	5 (7)	15 (3)	10 (2)
– Discontinuation due to hepatic events	2 (3)	2 (3)	5 (1)	3 (<1)
– Rash (any grade)	15 (21)	6 (9)	103 (21)	60 (12)

Data modified from Clotet B, et al.[37].

or severe hepatotoxicity (OR: 3.3; 95% CI: 2.5-4.2) compared to patients on efavirenz, although there was a prevalence in the population of hepatitis C coinfection ranging from 3 to 40% and the risk in this subgroup was not analyzed separately[28]. Moreover, this wide study shows a pooled rate of drug discontinuation of 9% and 6% for nevirapine and efavirenz, respectively.

The mechanism of NNRTI toxicity is likely to be heterogeneous, varying with respect to the drug and characteristics of the patient population. As mentioned, some evidence supports the association with immune restoration, but this evidence is less convincing for the occurrence of immune-related flares related to chronic HCV infection than for HBV, and this is not a specific reason to explain the different rates of toxicity with NNRTI. An immune-mediated mechanism is responsible for the hypersensitivity reaction and liver abnormalities seen with nevirapine because it is associated with higher CD4 counts[29]. Thus, in the specific case of nevirapine, the incidence of hepatitis due to hypersensitivity can reach rates of almost 3%[30]. Hypersensitivity reactions to efavirenz, if any, are less frequent than those related to nevirapine[31].

However, the hepatotoxicity of nevirapine-containing regimens had a later onset with an increase in the cumulative incidence over time[32]. Therefore, there is a second mechanism through which nevirapine causes liver toxicity, more common than the hypersensitivity syndrome. The HIV-infected patients with underlying chronic hepatitis C and worse degree of fibrosis were more prone to have higher plasma levels of NNRTI than HCV/HIV-coinfected individuals with milder stages of liver fibrosis. The NNRTI are metabolized in the liver through the cytochrome pathways and may cause liver toxicity when there are polymorphisms in the enzymes, leading to significant heterogeneity in drug metabolism. Both efavirenz and nevirapine are metabolized through cytochrome P450, specifically by the isoenzyme CYP 2B6. The CYP 2B6 G/T polymorphism has been associated with higher plasma concentrations of efavirenz and nevirapine[33]. However, only higher plasma levels of efavirenz, but not of nevirapine, have been moderately associated with increased risk of liver toxicity[34]. In fact, a substudy of the 2NN trial showed a correlation between the incidence of elevated levels of liver enzymes and plasma concentrations of efavirenz during the first six weeks of treatment.

Finally, direct toxicity of the drug is possible. It is proposed that metabolic activation of nevirapine and subsequent binding of reactive metabolites to cellular proteins play a causative role in liver toxicity. Thus, the metabolite 12-hydroxynevirapine has been suggested as a mediator of nevirapine-induced hepatotoxicity and skin rash[35].

Novel nonnucleoside reverse transcriptase inhibitors

Etravirine

Most safety reports of etravirine are based on HIV-1-infected, treatment-experienced patients receiving 200 mg twice daily in combination with a background regimen in the DUET studies[36]. After a median exposure of 52.3 weeks, discontinuation due to side effects occurred in 5.2% of patients using etravirine. Data on liver toxicity were available for 566 etravirine- and 564 placebo-treated patients, of whom 72 (13%) and 68 (12%), respectively, were coinfected with HBV/HCV. Irrespective of coinfection status, the etravirine and placebo groups were comparable for the incidence of grade 3-4 adverse events (Table 1). Consistent with

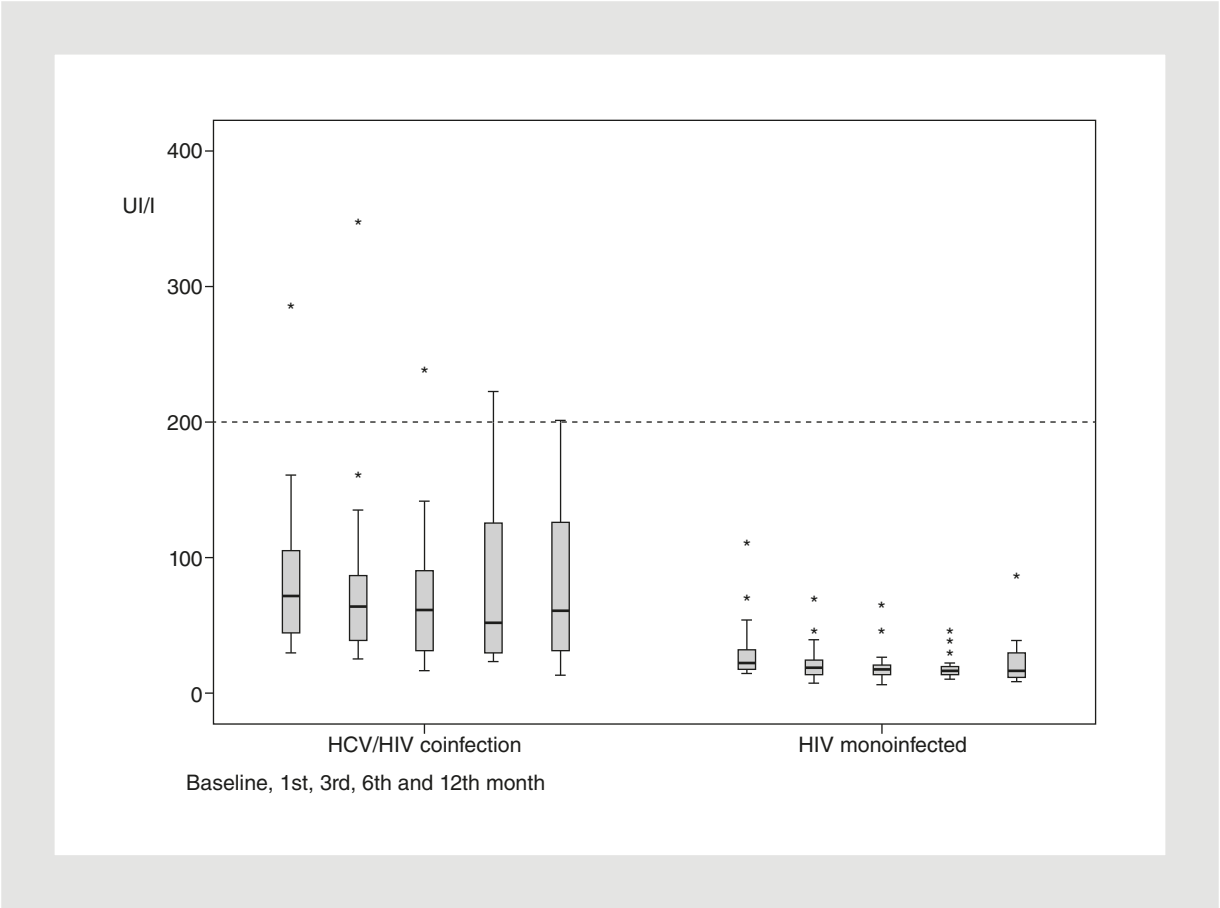
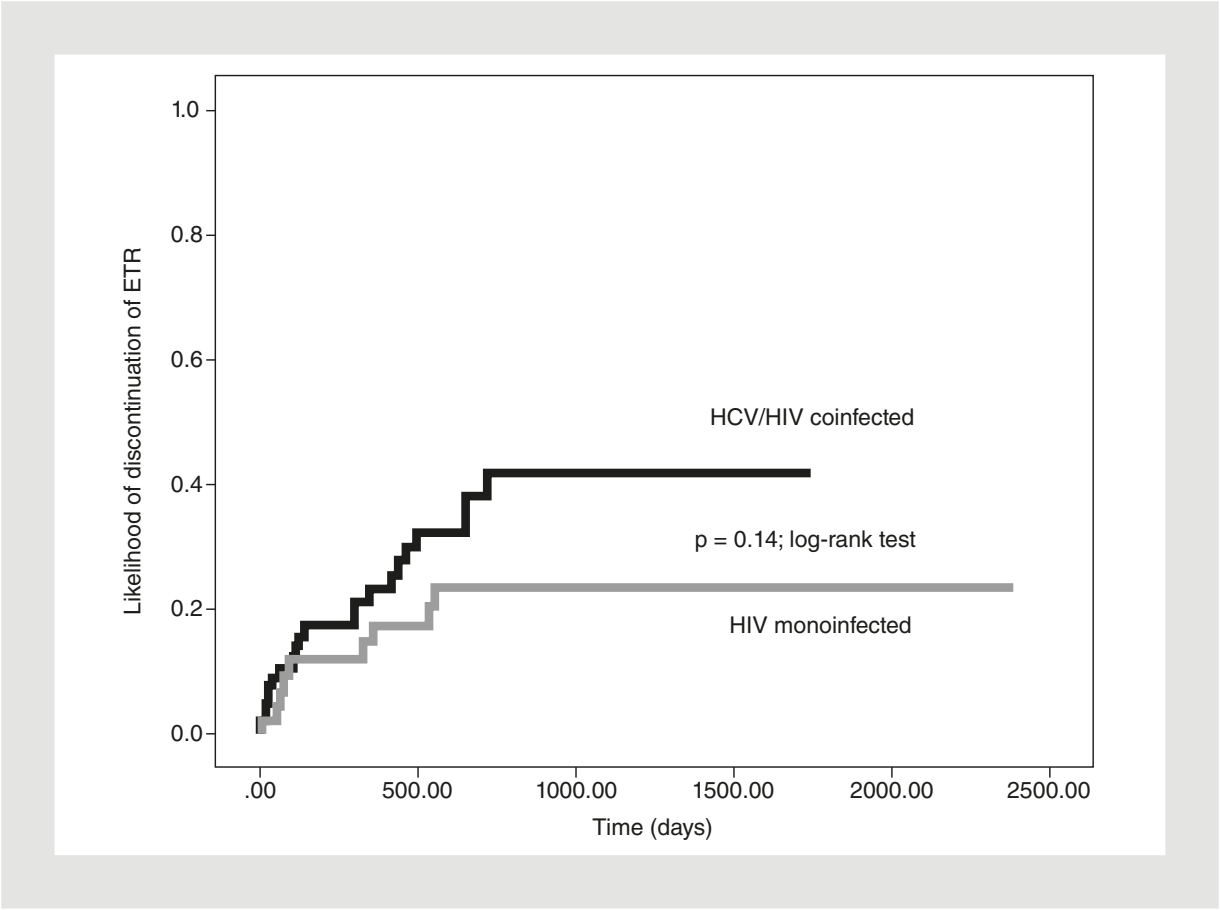


Figure 1. *Transaminase evolution after etravirine initiation, comparing patients with hepatitis C/HIV coinfection and HIV-monoinfected patients.*

the role of HCV as the main risk factor, coinfected patients had a higher incidence of hepatic events (18%) with etravirine versus placebo (15%), with grade 3-4 transaminase elevations in 11 vs. 7%, respectively. Also, discontinuation due to hepatic adverse events was low and comparable between the treatment groups, regardless of coinfection status[37]. However, patients in the DUET trials had been treated with up to a dozen HIV drugs, had suffered one or more AIDS-defining illnesses, and their HIV tended to be highly resistant to treatment. Moreover, the concomitant use of darunavir and other drugs in the background regimen could potentially have confounded the results.

In the 2,578 patients included in the Expanded Access Program of etravirine, with 15% of patients with hepatitis B or C coinfection, mean changes from baseline in ALT and AST levels were minimal[38]. Globally, only 40 (1.7%) and 41 (1.7%) patients experienced treatment-emergent grade 3-4 ALT and AST abnormalities, respectively. Overall, the incidence of grade 3-4 ALT and AST increase was slightly higher in patients with hepatitis B/C coinfection (3.7 and 3.8%, respectively) compared with patients without coinfection (1.4 and 1.5%, respectively). These data on liver toxicity were corroborated in the SENSE trial, with 79 naive patients receiving etravirine (10% HCV coinfected), with an incidence of transaminase elevation lower than 3%, similar to that observed with efavirenz[39].

Additional data on toxicity according to liver fibrosis were obtained in a cohort in our setting[40]. In an observational study of 120 patients, 70 of them coinfected with HCV, there were no cases of grade 3-4 liver toxicity, as defined by the modified ACTG criteria. Of note, liver fibrosis was seen in 44 patients through transient elastography at baseline, 39% of them with fibrosis 4 or cirrhosis. Again, there were no cases of liver toxicity in this subgroup of patients in a median follow-up of 352 days (15-1,255; 47.9 patient-years on therapy), confirming the low risk of hepatic events with this drug. Moreover, no patient discontinued etravirine because of liver toxicity. Transaminase changes for mono- and



Figures 2. *Rate of discontinuation of etravirine according to hepatitis C coinfection in a cohort of 120 patients with follow-up at our unit.*

coinfected patients are shown in figure 1, without significant differences with respect to baseline at any time point. There was only one case of toxicity grade 1 at the first month and another at 48 weeks and no cases of toxicity grade 2 among HIV-monoinfected patients. Moreover, one patient with HIV/HCV coinfection developed a toxicity grade 2 at the first month, and one additional coinfected patient starting with baseline ALT values > 200 IU/ml increased to 348 IU/ml, but no more patients met the criteria for toxicity grade 2. There were no significant differences in the rate of discontinuation according to HCV coinfection (Fig. 2).

The low incidence of hepatotoxicity with etravirine could be related to several factors. First, hypersensitivity seems to be exceptional, although cases of severe, potentially life-threatening, and fatal reports of Stevens-Johnson syndrome, toxic epidermal necrolysis and erythema multiforme have been described. Of note, only a total of 2.2% of HIV-1-infected patients in phase III trials receiving etravirine discontinued due to rash. Second, in a phase I study, no clinically relevant differences with regard to the pharmacokinetics of etravirine were observed between patients with mild or moderate hepatic impairment and HIV-negative subjects, and no dose adjustment was necessary[41]. Also, etravirine oral clearance seems not to be affected by hepatitis B coinfection[42]. However, in a case report of a patient with severe hepatic dysfunction (decompensated liver cirrhosis) who received standard doses of tenofovir, etravirine, and darunavir/ritonavir, etravirine levels were 3,257 ng/ml, approximately 60-times higher than the expected concentrations with standard etravirine dosing, suggesting the influence of advanced liver fibrosis on the metabolism of etravirine. Of note, the patient did not experience any clinical adverse event. Finally, etravirine is a weak inducer of CYP3A4 and an inhibitor of CYP2C9 and CYP2C19, and provokes lower hepatic cell induction than other NNRTI[43]. Therefore, the pathogenic mechanisms discussed before could be less important with this drug. Thus, these data confirm the low risk of hepatotoxicity in HIV-infected patients with hepatitis C coinfection receiving etravirine.

Table 2. Clinical efficacy and safety of rilpivirine at 48 weeks, according to HCV coinfection, in the ECHO and THRIVE studies

	HIV/HCV coinfection		HIV-monoinfected patients	
	Rilpivirine (n = 49)	Efavirenz (n = 63)	Rilpivirine (n = 621)	Efavirenz (n = 602)
% (95% CI) < 50 copies/ml	73.5 (60.7-86.3)	79.4 (69.1-89.6)	85 (82.2-87.8)	82.6 (79.5-85.6)
Δ CD4+ (cells/mm^3)	+137 (100-175)	+192 (147-238)	+197 (186-273)	+173 (161-185)
Any hepatic AE, n (%)	15 (27.8)	17 (25.8)	23 (3.6)	28 (4.5)
Grade 3-4 transaminases				
– ALT increase, n (%)	9 (16.7)	11 (16.7)	1 (0.2)	12 (2.0)
– AST increase, n (%)	7 (13.0)	5 (7.6)	7 (1.1)	14 (2.3)
– Discontinuation	2 (4.0)	6 (10)	1 (0.1)	3 (0.5)

AE: adverse event; ALT: alanine aminotransferase; AST: aspartate aminotransferase. *Data modified from Nelson, et al.*[45].

Rilpivirine

Rilpivirine has been licensed for use in naive patients with a viral load < 100,000 copies/ml. At the approved dose of 25 mg once daily, rilpivirine has shown an excellent safety and tolerability profile in clinical trials, with low rates of grade 2-4 adverse events and toxicity-related discontinuations[44]. The ECHO and THRIVE studies included 1,368 patients randomized to rilpivirine or efavirenz, 7% of them with hepatitis B or C coinfection. A significantly lower incidence of grade 2-4 ALT and AST elevations was observed in the rilpivirine group than in the efavirenz group (5.1 vs. 9.9%; p = 0.0009 and 4.8 vs. 9.0%; p = 0.003, respectively). The incidence of serious hepatic adverse events was low in both treatment arms and lower in patients receiving rilpivirine. No serious treatment-related hepatic adverse events leading to discontinuation were observed in the rilpivirine group, whereas two cases were reported in patients receiving efavirenz. Overall, at 48 weeks, the incidence of transaminase elevation grade 3 or 4 was 2% with rilpivirine, significantly lower than the 3.7% observed with efavirenz[45]. Most cases were observed in patients coinfected with HCV, as expected (Table 2), and similar to that observed with efavirenz. Less data exist on the risk of liver toxicity in coinfected patients in the clinical setting. Rilpivirine undergoes hepatic metabolism, but it provokes less induction than other NNRTI, so the impact of liver impairment should be limited. In a study comparing eight subjects with mild hepatic impairment (Child-Pugh score A) to eight matched controls, and eight subjects with moderate hepatic impairment (Child-Pugh score B) to eight matched controls, the multiple-dose exposure of rilpivirine was 47% higher in subjects with mild hepatic impairment and 5% higher in subjects with moderate hepatic impairment. Thus, no dose adjustment is required for rilpivirine in patients with mild or moderate hepatic impairment. In addition, the incidence of rash was significantly lower in the rilpivirine group than in efavirenz patients (3 vs. 14%; p < 0.0001), suggesting a low incidence of hypersensitivity reactions. However, since registration studies may not reflect real-world patient populations, hepatotoxicity should be evaluated in large patient cohorts to determine the incidence of significant elevations of enzyme levels in HIV-infected adults after the administration of this drug.

Conclusion

Novel second-generation NNRTI show promising data on liver toxicity, even in patients coinfected with hepatitis C. The rarity of hypersensitivity reactions, a lower induction of liver enzymes, and a low impact of liver fibrosis on the drug metabolism of these drugs, suggest an adequate safety in this subgroup of hard-to-treat patients. However, there are few comparative data in the same patient population, which could put into perspective the risk of liver toxicity. In addition, future studies should include fibrosis assessment in all coinfected patients. Meanwhile, the limited experience in the clinical setting, under different conditions, makes it necessary to continue the clinical observation. In this way, a high degree of suspicion that any liver disease may be related to drug exposure, a consistent time sequence, and a cautious exclusion of other causes of liver disease continue to be fundamental.

Disclosure statement

The author has no commercial or other association that may pose a conflict of interest.

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