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## Case report

# Abacavir-induced liver toxicity



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### ABSTRACT

Abacavir-induced liver toxicity is a rare event almost exclusively occurring in HLA B\*5701-positive patients. Herein, we report one case of abnormal liver function tests occurring in a young HLA B\*5701-negative woman on a stable nevirapine-based regimen with no history of liver problems or alcohol abuse after switching to abacavir from tenofovir. We also investigated the reasons for abacavir discontinuation in a cohort of patients treated with abacavir-lamivudine-nevirapine.

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## Introduction

Drug-induced hepatotoxicity represents an important side effect of highly active antiretroviral therapy (HAART), complicates the management of HIV-infected patients and, although infrequently, may have serious consequences.<sup>1</sup> Possible pathogenic mechanisms involved in hepatotoxicity are multiple, including direct drug toxicity, immune reconstitution in the presence of hepatitis C (HCV) and/or hepatitis B (HBV) co-infections, hypersensitivity reactions with liver involvement, and mitochondrial toxicity.<sup>1</sup>

Abacavir (ABC)-induced liver toxicity is a rare event almost exclusively occurring in HLA B\*5701-positive patients,<sup>2</sup> with a handful of cases reported in non carriers of the HLA allele risk.<sup>3,4</sup> All cases happened in patients on a stable nevirapine (NVP)-based regimen after switching to ABC from another nucleoside analog. Herein, we report one case of abnormal

liver function tests occurring in a young HLA B\*5701-negative woman on a stable NVP-based regimen with no history of liver problems or alcohol abuse after switching to ABC. In order to assess the incidence of ABC liver toxicity in the HIV population treated with ABC, lamivudine, and NVP, which is a poorly investigated but currently used combination in clinical practice, mainly in countries with economic constraints, we investigated the reasons for ABC discontinuation in patients on NVP-based regimens from our clinical database.

## Case report

A 33-year-old woman was switched from tenofovir/emtricitabine/NVP to ABC/lamivudine/NVP after seven years on initial treatment to avoid tenofovir related long-term toxicity. Our choice was based on the low body weight of the patient – which is risk factor for the development of long-term

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tenofovir complications<sup>5</sup> – and the observed mild increase in serum creatinine concentrations. She tested negative for HLA B\*5701 and hepatitis viruses. Her transaminases levels had always been normal along her antiretroviral treatment but eight weeks after switching to ABC aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels progressively increased to 222 and 518 UI/mL, respectively. The patient has always been asymptomatic. Serology for hepatitis A (HAV IgM), hepatitis B (HBsAg, HbAbIgM), and hepatitis C (HCVAb) were negative, as were hepatitis C viral load (HCV RNA undetectable). Autoantibody screening tests were negative. The patient did not take concomitant medications after switching to ABC and was not given acetaminophen, a drug known to induce liver toxicity eventually exacerbated by ABC.<sup>6</sup> Given the previous long term tolerability to NVP, ABC was discontinued and the patient was switched back to tenofovir with subsequent normalization of AST and ALT within six weeks.

In order to properly address the incidence of ABC liver toxicity in patients on stable treatment with NVP, we retrospectively searched our clinical database and identified 1004 male and female HIV-infected patients referring to our Department between 2000 and 2013 who began receiving ABC as part of their first or subsequent antiretroviral treatment regimen. Eighty-three HIV-infected patients (51 males, 32 females), with a median age of 46 years (range 30–72), received a stable NVP-containing regimen before starting ABC. The main reasons for switching to ABC were (a) lipodystrophy and lipid abnormalities in patients treated with zidovudine (27 patients); (b) to avoid tenofovir related toxicity (38 patients); stavudine and didanosine replacement (10 patients). Overall, 26 out of the 83 (24%) patients subsequently discontinued ABC treatment due to the following reasons: virologic failure ( $n=11$ ), rash ( $n=5$ ), in three cases before the availability of genetic testing for HLA B\*5701, gastrointestinal side effects ( $n=2$ ), pregnancy ( $n=2$ ), patient request ( $n=2$ ), one patient discontinued due to change in treatment strategy, one patient due to high cardiovascular risk, and hepatotoxicity ( $n=2$ , both cases tested negative for HLA B\*5701). Of the two suspensions due to hepatotoxicity, one patient had no viral hepatitis co-infection and presented clinical and demographic characteristics similar to those described in previous reports,<sup>3,4</sup> while the other was coinfecting with HCV and had not had previous raise in liver enzymes. Interestingly, 82% (9 out of the 11 pts) of the virologic failures were observed in patients with a long history of HIV treatment including antiretroviral regimens that are no longer recommended.

## Discussion

ABC-induced liver injury in the context of a negative HLA B\*5701 test is an uncommon event. As a matter of fact, extensive evidence is now available showing that HLA-B\*5701 screening is an effective way to prevent hypersensitivity to ABC in susceptible subjects.<sup>7,8</sup> To the best of our knowledge only three cases of hepatotoxicity occurring in HLA B\*5701-negative patients with no viral hepatitis co-infection or history of alcohol abuse have been reported; all cases were on a stable NVP-based regimen after switching to ABC from

another nucleoside analog.<sup>3,4</sup> Here, we confirm these findings by documenting that in our cohort ABC-related hepatotoxicity was an uncommon, but clinically relevant event. A pharmacokinetic drug-to-drug interaction between ABC and NVP is unlikely because ABC is not metabolized by cytochromal enzymes.<sup>9</sup> We have also excluded a potential contribution of acetaminophen on the observed ABC/NVP-related liver toxicity<sup>6</sup> because this drug was used, if any, in very few patients from our cohorts and for short time periods. Accordingly, potential pharmacodynamic mechanisms explaining ABC/NVP liver toxicity can be eventually advocated. Indeed, evidence is available showing that both drugs separately can favor the bioactivation of reactive molecules capable of forming protein products ultimately leading to liver toxicity.<sup>10-12</sup> On the other hand, it should be considered that very limited and scanty data are available not only on the safety but also on the efficacy ABC/lamivudine/NVP combination,<sup>13,14</sup> despite the fact that this regimen has now become a very attractive option for the very low cost, limited metabolic impact, and low pill burden. We, therefore, extended previous findings by assessing the frequency of ABC-related hepatotoxicity in HIV-infected patients on NVP based-regimens and by describing the efficacy of this regimen in a real life scenario. Indeed, a higher incidence of virologic failure was found in our cohort of patients compared with the only available study to date which has formally investigated ABC/lamivudine/NVP as a simplification strategy for HIV patients with undetectable viral load.<sup>13</sup> The possibility that the increased pill burden (as in the case of switching from zidovudine + lamivudine coformulation to ABC/lamivudine as single components) might have contributed, at least in part, to the virologic failures observed in patients cannot be definitively ruled out. It should be considered, however, that large part of our failures were driven by events occurring in patients with long term history of antiretroviral therapy which included mono or dual regimens no longer recommended. As a result, it can be reasonably speculated that some of the virologic failures apparently observed with ABC may have been significantly influenced by previous antiretroviral regimens.

In conclusion, clinicians should remain alert for signs of hepatitis in patients treated with ABC, while, at the same time, consider the efficacy of ABC/lamivudine/NVP combination as a simplification option only in patients not previously treated with suboptimal antiretroviral regimens.

## Conflicts of interest

CG has received educational grants from Merck Sharp & Dome, Janssen-Cilag, Bristol Myers Squibb, Gilead and Abbvie. AR has received educational grants from Merck Sharp & Dome, Janssen-Cilag, Bristol Myers Squibb, Gilead, ViiV and Novartis.

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