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Sex differences in apolipoprotein A1 and nevirapine-induced toxicity

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Nevirapine (NVP) is associated with severe liver and skin toxicity through sulfotransferase (SULT) bioactivation of the phase I metabolite 12-hydroxy-NVP [1–3]. The female sex, a well-known risk factor for NVP-induced toxicity, is associated with higher SULT expression [4] and lower plasma levels of 12-hydroxy-NVP [3]. Interestingly, apolipoprotein A1 (ApoA1) increases SULT2B1 activity and ApoA1 synthesis is increased by NVP [5,6]. Herein, we explore the effect of ApoA1 levels on NVP metabolism and liver function. The study protocol was firstly approved by the hospitals' Ethics Committees. All included individuals were HIV-infected patients treated with NVP for at least one month. The plasma concentrations of NVP and its phase I metabolites were quantified by HPLC [7]. ApoA1 levels were assessed by an immunoturbidimetric assay. Forty-nine HIV-infected patients on NVP were included (53% men, 59% Caucasian). NVP plasma levels were correlated with HDL-cholesterol (Spearman $r = 0.2631$; $p = 0.0441$) and ApoA1 (Spearman $r = 0.3907$; $p = 0.0115$). Women had higher ApoA1 levels than men (Student's *t* Test; $p = 0.0051$). In both sexes, 12-hydroxy-NVP levels were negatively correlated with ApoA1 (male: Spearman $r = -0.3810$; $p = 0.0499$ female: Spearman $r = -0.5944$; $p = 0.0415$). In men, ApoA1 was positively correlated with aspartate aminotransferase (AST, Spearman $r = 0.5507$; $p = 0.0413$), while in women ApoA1 was associated (Spearman $r = 0.6408$; $p = 0.0056$) with alanine aminotransferase (ALT). These results show sex differences in NVP-induced ApoA1 synthesis. The higher ApoA1 levels in women might stabilize SULT2B1 [6]. This would explain the lower levels of 12-hydroxy-NVP [3] and the higher hepatotoxicity found in women, due to increased sulfonation of this metabolite. These data support a role for ApoA1 in the sex dimorphic mechanism leading to NVP-induced toxicity.

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