Long term Hepatitis B surface antigen decay in HIV-1/HBV coinfected adults initiating a tenofovir containing regimen

Short Title: Hepatitis B surface antigen decay on tenofovir


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Abbreviations: HBs antigen (HBsAg); tenofovir disoproxil fumarate (TDF); lamivudine (3TC), emtricitabine (FTC); antiretroviral therapy (ART)
Summary

HBsAg decay was explored in HIV-1/HBV coinfected patients initiating antiretroviral (ARV) therapy containing tenofovir disoproxil fumarate (TDF). The mean HBsAg decay was 0.38 Log10 IU/ml/year (95% CI: 0.71-0.05) in 18 patients with sustained plasma HIV-1 RNA suppression and 0.15 Log10 IU/ml/year (0.21-0.09) in 12 patients experiencing HIV-1 virologic failure due to suboptimal adherence to ARV (p=0.17). We estimated that six patients will attain HBsAg value below 10 IU/ml after ten years of treatment.

Hepatitis B viral suppression maintained by treatment with lamivudine (3TC), emtricitabine (FTC) and tenofovir disoproxil fumarate (TDF) reduce progression of disease to liver failure and the development of hepatocellular carcinoma in HIV-1 infected patients. In some patients, therapy induces a complete loss of HBsAg, indicating control of chronic HBV infection. HBsAg clearance was reported in 3% of HBeAg positive patients uninfected by HIV-1 after one year of treatment with 3TC, in 8% after 3 years of treatment with TDF and in 5% of HBeAg negative patients after 5 years of treatment with adefovir. We conducted a longitudinal analysis of HBsAg concentration in HIV-1/HBV coinfected patients to explore the long-term evolution of HBsAg concentration after initiation of antiretroviral therapy (ART) containing TDF. The impact of an imperfect adherence to ART on HBsAg decay was also explored.

Thirty HIV-1/HBV coinfected subjects followed in the Montpellier University Teaching Hospital were tested for HBsAg concentration after providing written informed consent. Patients had a chronic hepatitis B infection defined as a detectable serum HBsAg for more than 6 months. TDF was initiated as a part of an ARV therapy regimen containing 3TC or FTC and a non nucleoside reverse transcriptase inhibitor.
(11/30) or protease inhibitors (19/30). A mean (SD) of 8 (+/- 4) samples were quantified for HBSAg concentration per individual during a mean (SD) follow up under ART of 6.5 years (+/- 3).

To address the potential impact of suboptimal adherence to ART on HBsAg clearance, we included in the group with suboptimal compliance to therapy, 12 subjects that experienced HIV-1 RNA rebound exceeding 3 months during the follow-up and identified regular missed doses during interviews. Subjects who had detectable HIV-1 plasma RNA loads 9 months after initiation of ART were also included in this group. The other 18 individuals were categorized as being optimally treated. At the time of therapeutic initiation the mean age was 40 years (+/- 9); CD4 T cell count was 387/mm3 (+/- 100), median (IQR) HIV-1 RNA was 4.48 (3.69-5.21) Log10 copies/ml, HBV DNA 5.62 (4.90-7.16) Log10 IU/ml, 14/30 (47%) of the subjects were positive for HBeAg, 14/30 (47%) had elevated ALT (>40 U/L), and one patient had hepatitis C virus co-infection. None of the individuals included had hepatitis delta virus (HDV) coinfection (ETI-AB-DELTAK-2 assay, DiaSorin, Turin, Italy), malignancies or end-stage liver insufficiency. HBsAg concentrations were analyzed using the ETI-MAK-4 assay (DiaSorin, Turin, Italy) on a Triturus automate (Grifols, Barcelona, Spain) as previously described. Rates of HBsAg decay were estimated with the use of a longitudinal mixed-effects model (nlme package, R software, Version 2.14, Free Software Foundation, Inc. Boston MA). Comparisons of estimates between groups were made using a test of interaction. Evolution of population level of CD4 T cell count; HBV load and HIV-1 load in optimal and suboptimal treated groups were computed using cubic spline regression adjusting for subject effect (rm. boot function, Hmisc package). The P values presented are two-
sided, and a P value of less than 0.05 was considered to indicate statistical significance.

Pretreatment levels of HBsAg and HBV DNA were moderately correlated (r=0.65, p=0.007), data not shown). HBV DNA and HIV-1 RNA decline, and CD4 T cells recovery were faster in patients with sustained plasma HIV-1 RNA suppression by comparison with subjects that experienced HIV-1 RNA rebound (Fig. 1 a-b).

Overall, under ART the HBsAg concentration declined slowly in the both groups. We observed a mean decay of 0.38 Log10 IU/ml per year (95% CI: 0.71 to 0.05) in the optimally treated group, and 0.15 Log10 IU/ml per year (95% CI: 0.21 to 0.09) in the suboptimally treated group (p = 0.17). Visual inspection showed that the log-linear decay model fitted well with the data at individual level (Fig. 1 c-d). Important interindividual differences in the decrease of HBsAg were observed in the two groups, with the HBsAg Log10 decay per year ranging from 2.68 to 0.03 in the optimally treated group, versus 0.29 to 0.03 in the suboptimally treated group. We failed to observe a significant influence of CD4 T cells at baseline or CD4 T cell recovery on HBsAg decay (data not shown). In the optimally treated group, HBsAg clearance was seen in two patients with emergence of anti-HBs antibodies in one of them, and one patient reached HBsAg concentration below 10 IU/ml after two years of ARV. HBsAg clearance and emergence of anti-HBs antibodies (>10 IU/ml) was observed in one patient in the group experiencing HIV-1 virologic failure. Based on our observation we estimated that five patients from the optimally treated group but only one from the suboptimally treated group will attain value below 10 IU/ml after ten years of treatment. We calculated that four patients in the optimally treated group and one patient in the suboptimally treated group would never reach this value on therapy.
since more than 50 years of the current anti-HBV treatment would be required to reach HBsAg value below 10 IU/ml. Our findings indicate that in HIV-1/HBV coinfected individuals, HBsAg concentration decrease after therapeutic initiation of TDF/FTC or 3TC containing ARV regimes. Limitations of this study were small number and heterogeneity of patients tested. Hence, we were not able to compare HBsAg decline in patients grouped according to HBeAg status, the phases of persistent HBV-infection, or HBV genotypes. Previous studies have reported low variations of HBsAg concentration in HIV-1 uninfected subjects untreated by anti-HBV drugs. The reduction of HBsAg concentration may result from both a direct effect of the drugs on HBV polymerase, and the immune reconstitution that follows initiation of ART. We observed a faster rate of HBsAg decay than in a recent study by Thibault and co-workers exploring HBsAg evolution in a group of coinfected patients with undetectable HIV-1 RNA and HBV DNA in a TDF containing regimen, but comparable rates to the decay observed in HBV mono-infected patients and a recently reported study by Maylin and co-workers investigating HIV-1/HBV coinfected patients. The effect of adherence to treatment on the rate of HBsAg decline was less visible than that seen for HIV-1 RNA or HBV DNA decline or CD4 T cell recovery. While some HIV-1/HBV coinfected patients with good adherence to ART did not undergo a significant decline in HBsAg level, others likely have a good chance to reach HBsAg concentrations below 10 IU/ml during lifelong treatment for HIV-1 infection. These patients may have a lower risk of HBV reactivation since detection of HBsAg has been proposed as a marker of sustained HBV response after peg-interferon based regimens. The necessity of maintaining inclusion of TDF in ART regimes in these patients should be further evaluated.
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References:


Legend:

Figure 1. Longitudinal analysis of serum HBsAg concentration in HIV-1/HBV coinfected patients initiating tenofovir containing regimen.

Evolution of HIV-1 plasma RNA, HBV plasma DNA and CD4 T cell count in 18 patients with sustained plasma HIV-1 RNA suppression (a) and 12 patients experiencing HIV-1 virologic failure (b). Evolution of HBsAg serum concentration in patients with sustained plasma HIV-1 RNA suppression (c), and patients experiencing HIV-1 virologic failure (d). Color lines represent individual evolution of serum HBsAg concentration over a time. Black lines show slope of decline given by mixed effect linear models in the two groups.