Virologic and Clinical Outcomes in HIV/HBV Coinfected Patients on Tenofovir-Containing HAART

See "Long-term therapy with tenofovir is effective for patients co-infected with HIV and HBV," by de Vries-Sluijs TE, Reijnders JS, Hansen BE, et al, on page 000.

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Although human immunodeficiency virus (HIV) specialists and hepatologists have struggled to manage hepatitis C virus (HCV) infection in their HIV patients, the approach to HIV/hepatitis B virus (HBV) coinfection has been comparatively easier.[1] HIV patients with chronic hepatitis B respond well to antiretroviral regimens that contain molecules active against HBV replication. However, little long-term data on virologic, serologic, and clinical outcomes has been available until the study by de Vries-Sluijs et al[2] published in this issue of GASTROENTEROLOGY. What makes this study stand out from other studies is 2-fold:

1. The authors looked at highly active antiretroviral therapy regimens all of which contained tenofovir disoproxil fumarate (TDF), a molecule of proven efficacy against HBV and which induces little or no resistance.
2. They evaluated HIV/HBV co-infection only, excluding all patients with HCV or hepatitis delta (HDV) coinfection. This separation is relevant because coinfection with HDV or HCV has been associated with lower HBV replication and worse outcomes.[3]

The authors gathered data from 6 Dutch centers specializing in the care of patients living with HIV/AIDS. They followed all patients with chronic hepatitis B surface antigen (HBsAg) positivity (≥6 months), who had been treated with TDF alone or in combination with lamivudine or emtricitabine. All 102 patients were followed at ≥6-month intervals for the first 2 years, then yearly. The average follow-up was 4.5 years. Interestingly, a liver ultrasound was not routinely ordered, but only when clinical circumstances suggested development of cirrhosis (low platelets, low albumin, or splenomegaly) or hepatocellular cancer (HCC). Under those conditions, as the authors acknowledge, the presence of cirrhosis and HCC may have been underestimated. The primary end point was the attainment of a serum HBV DNA level <20 IU/ mL by a sensitive in-house polymerase chain reaction–based assay.

Of the 102 patients, 20 (20%) had undetectable serum HBV DNA before starting TDF, and 18 of those patients had been treated with lamivudine, on average, for 38 months. Two patients had never received anti-HBV medications.

In all 20 patients, TDF was used in the antiretroviral regimen and 19 of the 20 patients had undetectable HBV DNA at the end of follow-up. One patient had a virologic breakthrough without genotypic resistance, and developed HCC.

Eighty-two patients had measurable HBV DNA before TDF; 15 were hepatitis e antigen (HBeAg) negative with an average HBV viremia of 7 logs IU/mL. All 15 (100%) had unmeasurable HBV DNA after 4 years of TDF (Table 1). Thirteen percent also lost HBsAg. As expected, the 67 patients with detectable HBeAg (estimated baseline viremia >8 logs IU/mL) lost HBV DNA more slowly (Table 1), and HBsAg became undetectable in 12%. An important finding was that the viral decay curves (Figure 2 in de Vries-Sluijs et al) illustrating HBV DNA suppression in the 33 patients with lamivudine-resistance mutations at baseline versus the 49 without, were superposable.

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During the study period, 4 patients (<1%/year) developed detectable HBV DNA, fulfilling criteria for virologic breakthrough (>1 log increase in HBV DNA over nadir); none of them had lamivudine resistance at baseline. Two had HCC and only 1 demonstrated multiple polymerase mutations associated with drug resistance, including A181V. The other two had a concomitant HIV RNA rebound and were suspected of poor adherence. An additional 7 patients continued to have detectable HBV DNA without a breakthrough: 4 of those had baseline lamivudine resistance and 3 did not. Whether poor adherence was also at play in the last 3 patients is not known. Four of these 7 patients received an additional 1 mg of entecavir daily and all 4 (100%) responded with undetectable HBV DNA. One of 4 became HBeAg negative at the end of follow-up.

Another significant finding from this study was that 3 patients developed HCC and all had cirrhosis at baseline. Liver-related mortality (4 patients) was confined to the 14 patients who had a diagnosis of cirrhosis. Of the remaining 88, 3 patients died, unrelated to HBV. Renal complications were in the expected range; 2 patients developed creatinine elevations up to 2.2 mg/dL, with stabilization (but no improvement) after discontinuing TDF.

Other studies targeting HIV/HBV coinfection have been published; unfortunately, most were retrospective and included significant numbers of patients with HCV

Table 1. Virologic Outcomes in HIV/HBV Coinfected Patients With Detectable HBV DNA Before TDF Therapy

	67 HBeAg Positive (%)	15 HBeAg Negative (%)
HBV DNA < 20 IU/L at 1 yr	31	47
HBV DNA < 20 IU/L at 2 yr	70	85
HBV DNA < 20 IU/L at 5 yr	92	100 (4 yr)
HBsAg undetectable	12	13

and/or HDV. A summary of these articles[4–8] indicates that in the setting of HIV, HBV replication can be controlled with dual-activity antivirals (Table 2). In addition, HIV patients lose HBeAg and, surprisingly, HBsAg at significant rates each year. It is also true that HBsAg seroreversion occurs as well, 0.8 cases/100 person-years in patients with HIV and isolated hepatitis B core antibody in Taiwan.[6] The loss of HBsAg reported in this study[2] confirms recently published French survey data.[8] In fact, HBsAg loss is essentially the same in HIV patients,[2,4,6] as what is expected in immunocompetent patients treated with TDF for 1–2 years.[8]

The Dutch study,[2] in addition, provides useful information on the timing of HBV DNA suppression (Table 1) and the occurrence of breakthrough episodes. The latter were rare (<1% per year) and were associated with polymerase mutations in only 1 of 4 patients. In a similar TDF-treated cohort, breakthroughs were noted in 6% per year but there were no resistance data.[9]

This article adds key knowledge on clinical end points in HIV/HBV coinfected patients, mainly HCC diagnosis and liver-related mortality. It may be argued that the incidence of HCC was underestimated due to the lack of systematic imaging surveillance. However, the HCC incidence seems to be similar to that previously documented in HIV/HBV coinfection.[4] In France, the mortality from HCC in the setting of HIV sees to have reached a plateau from 2000 to 2005.[1] Possible explanations include a decrease in new HCC cases perhaps associated with better HBV control, or from use of locoregional therapies or liver transplantation. In the present study, the incidence of HCC was estimated to be 0.65%/year, almost identical to that (0.7%/year) estimated by a recently published literature review of HBV monoinfected individuals treated with oral antivirals.[10] Incidentally, the latter paper also confirms a much lower HCC incidence in non cirrhotics (0.15%/year) versus cirrhotics (3.2%/year).[10]

This study advances our current knowledge of hepatitis B in a number of ways. In the highly active antiretroviral therapy era, HBV outcomes in HIV seems to be very close to those in non-HIV patients[2,8,10]; thus, this author thinks that these findings can also be applied to monoinfected patients.

First, monotherapy with a potent antiviral such as TDF is appropriate in the majority of cases. Break-

Table 2. Comparison of HBV Outcomes in Association With HAART in HIV/HBV Coinfected patients

	Nunez et al[4]	Miailhes et al[5]	Sheng et al[6]	Matthews et al[7]	Piroth et al[8]	De Vries et al[2]
n	79	92	119	122	180	102
Study type	Retro	Pro	Pro	Retro	Retro	Pro
Baseline median CD4	210–360	303	125	438	401 (mean)	~300
Patient antiretroviral status	Any patient	Naive	Naive	Any patient	Any patient	Any patient
Medications	96% HAART 57% TDF ± Lamivudine	89% HAART, 93% Lamivudine	97% Lamivudine	84% HAART 50% TDF + Lamivudine or FTC	TDF + Lamivudine or FTC	TDF + Lamivudine or FTC
HCV and/or HDV	41% HCV	13%	9% HCV	No HCV	>12%	None
HBV genotype	57% A	71% A	—	80% A	55% A	64% A
Median follow-up (yrs)	4	5	5.2	~2	3.5	4.5
HBV DNA below quantification at end of follow-up	70% (<200 copies/mL)	—	—	30% (<100 IU/mL) TDF 77% (<100 IU/mL) TDF + lamivudine/FTC	87% (<2000 IU/mL)	92–100% (<20 IU/mL)
HBeAg neg	—	—	—	—	4.3%/y	10%/y
HBe SC	7%/y	3.4%/y	—	—	0.9%/y	—
HBsAg neg	3.3%/y	1.1%/y	2.6%/y	—	~1.7%/y	2.7%/y
HBs SC	—	—	1%/y	—	~1.7%/y	—
HCC	0.38%/y	—	—	—	—	0.65%/y
Mortality	1.5%/y	0.8%/y	4.5%/y	—	—	1.5%/y
Liver mortality	0.8%/y	0.4%/y	1.3%/y	—	—	0.9%/y

HDV, hepatitis delta; Pro, prospective; Retro, retrospective; — not available; SC, seroconversion; HCC, hepatocellular carcinoma; TDF, tenofovir disoproxil fumarate.

through instances were rare. In case of suboptimal response, one can probably wait until 2 years of therapy (at least in the absence of cirrhosis) before adding a new agent. Addition of another agent (in this case entecavir at 1 mg/d) is expected to achieve HBV DNA suppression in most cases. In HIV/HBV coinfected patients, the frequent usage of Truvada makes the peace between proponents of sequential monotherapy[2] and those who suggest that combination therapy may be needed from the beginning.[7]

Second, TDF is confirmed to be equally effective in lamivudine naïve patients, as in those who are lamivudine experienced or have proven lamivudine resistance.[2,9]

Last, this study shows that most, if not all the HCC and liver decompensation events occurred in patients with cirrhosis. At our center, the majority of patients with HBV (and particularly those with HIV), undergo surveillance for HCC with alpha-fetoprotein levels and liver ultrasonography every 6 months. This is due to the large prevalence of Asian patients in this practice, where HCC is diagnosed in patients without cirrhosis with regularity. I wonder whether in adult-acquired HBV, including our HIV/HBV coinfected population, we could actually relax the surveillance in noncirrhotics and rely on ultrasonography and alpha-fetoprotein yearly, to be more cost effective.

At this point, unanswered questions that require further investigation include whether the above interpretations and recommendations also apply to non-A HBV genotypes and to populations outside of Europe.[6] All published studies are mostly comprised of men and one wonders whether these conclusions apply equally to both genders. Also, archived mutations could potentially surface later in the follow-up of these patients, altering the natural history beyond 5 years of follow-up. The optimal frequency of HBV DNA measurements (and/or HBsAg quantification) and mutation analysis in clinical practice remains to be determined. Finally, because lactic acidosis was not mentioned in this article, this rare metabolic complication should perhaps be sought in future cohort studies.

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Reprint requests AQ:3
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Conflicts of interest AQ:4
Speaker's bureau or consultant for: Boehringer-Ingelheim, Pfizer, Bristol-Myers-Squibb, Merck-Schering, Genentech-Roche. Research: Boehringer-Ingelheim, EISAI, Roche.

0016-5085/$36.00
doi:10.1053/j.gastro.2010.10.039