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Persistent HBV replication and serological response during up to 15 years of tenofovir-based antiretroviral therapy in HIV/HBV-coinfected patients: a multicentre prospective cohort study

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► **To cite this version:**

Lorenza N C Dezanet, Patrick Mialhes, Caroline Lascoux-Combe, Julie Chas, Sarah Maylin, et al.. Persistent HBV replication and serological response during up to 15 years of tenofovir-based antiretroviral therapy in HIV/HBV-coinfected patients: a multicentre prospective cohort study. *Journal of Antimicrobial Chemotherapy*, 2021, 10.1093/jac/dkab294 . hal-03366382

HAL Id: hal-03366382

<https://hal.sorbonne-universite.fr/hal-03366382>

Submitted on 5 Oct 2021

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1 **Persistent HBV replication and serological response during up to fifteen years of tenofovir-based**
2 **antiretroviral therapy in HIV-hepatitis B coinfecting patients: a multicenter prospective cohort study**

3

4 **Running title:** Fifteen years of tenofovir in HIV-HBV coinfection

5

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28

29 **Abstract**

30 **Objectives**

31 To determine the extent of hepatitis B virus (HBV) suppression and its association with hepatitis “e” antigen
32 (HBeAg) and hepatitis B surface antigen (HBsAg)-seroclearance in HIV-HBV-coinfected patients undergoing
33 long-term tenofovir (TDF)-based antiretroviral therapy (ART).

34 **Methods**

35 We prospectively followed 165 HIV-HBV-coinfected patients undergoing TDF-based ART. Serum HBV-DNA
36 viral loads, HBeAg and HBsAg were obtained at TDF-initiation and every 6-12 months. We calculated the
37 proportion achieving virological response (VR, <60 IU/mL) during follow-up. We also calculated rates of
38 HBeAg- and HBsAg-seroclearance, which were compared between those who achieved versus never
39 achieved VR during follow-up using an exact binomial test.

40 **Results**

41 During a median 8.1 years (IQR=4.0-13.2) of TDF-treatment, 152 (92.1%) patients were able to achieve VR
42 and 13 (7.9%) never achieved VR (median HBV-DNA at the end of follow-up=608 IU/mL, range=67-
43 52,400,000). The prevalence of individuals with detectable HBV-DNA (≥ 60 IU/mL) decreased during TDF-
44 treatment: 15.1% ($n=14/93$) at 5-years, 3.2% ($n=2/62$) at 10-years and, 3.2% ($n=1/31$) at 15-years. 44/96
45 HBeAg-positive patients (6.15/100 person-years) had HBeAg-seroclearance and 13/165 patients overall
46 (0.87/100 person-years) had HBsAg-seroclearance. No difference in HBeAg-seroclearance was observed
47 between those who achieved versus never achieved VR (7.4 versus 3.7/100 person-years, $p=0.33$), while
48 HBsAg-seroclearance was only observed in those with VR (1.0 versus 0/100 person-years, $p=0.49$;
49 respectively). Individuals with VR also had a higher frequency of undetectable HIV-RNA during treatment
50 ($p<0.001$).

51 **Conclusions**

52 During long-term TDF-based ART for HIV-HBV coinfection, persistent HBV viremia is apparent, but becomes
53 less frequent over time. HBsAg-seroclearance only occurred in those with full HBV and relatively high HIV
54 suppression.

55 **Introduction**

56 In the past decade, liver-related mortality has continued to persist as one of the major causes of non-AIDS
57 related deaths in HIV-positive patients.^{1,2} Coinfection with hepatitis B virus (HBV) has been implicated as a
58 major reason for this finding.³ HBV infection by itself is associated with an increased risk of liver fibrosis
59 progression, cirrhosis and hepatocellular carcinoma (HCC) , which can be mitigated with effective HBV-DNA
60 suppression.⁴ Given that tenofovir (TDF) has dual activity against HIV and HBV, long-term administration of
61 TDF-containing antiretroviral therapy (ART) has been recommended for all HIV-HBV coinfecting patients.^{5,6}

62

63 Although TDF has a high genetic barrier to HBV resistance,⁷ at least 3 years of treatment may be required to
64 achieve virological response,⁸⁻¹⁰ while 10-20% of HIV-HBV coinfecting patients exhibit persistence of HBV
65 replication during longer periods of TDF.^{8,11-13} Nevertheless, almost all studies to date evaluating HBV
66 replication during TDF have followed patients for at most 5-10 years and consequently, it is uncertain what
67 proportion of patients achieve suppression of HBV-DNA viral load with longer TDF-use.^{8,14}

68

69 There are other therapeutic goals for improved prognosis, such as hepatitis B “e” antigen (HBeAg)-
70 seroclearance (for those with HBeAg-positive serology) and importantly, hepatitis B surface antigen
71 (HBsAg)-seroclearance. For TDF-treated HIV-HBV coinfecting patients, almost half of those who are HBeAg-
72 positive exhibit HBeAg-seroclearance and few overall attain HBsAg-seroclearance.^{8,15,16} Since HBeAg-
73 seroclearance and HBsAg-seroclearance seem to only occur among HIV-HBV coinfecting individuals
74 undergoing TDF with sustained HBV virological response,⁸ there is concern regarding the consequences of
75 persistent HBV replication on serological outcomes. Most of our understanding on HBV seroclearance rates
76 also stems from studies of HIV-HBV coinfecting and HBV-monoinfecting patients with limited duration of TDF
77 treatment.^{8,14}

78

79 In this study, we aimed to evaluate the extent of HBV suppression and determinants of various forms of HBV
80 persistence in patients coinfecting with HIV-HBV undergoing up to 15 years of continuous TDF-based ART.

81 We further intended to examine the relationship between HBV persistence and HBeAg- and HBsAg-
82 seroclearance.

83

84 **Patients and Methods**

85 ***Study population***

86 Patients were selected from the French HIV-HBV Cohort Study.¹⁷ Briefly, this longitudinal cohort study
87 included 308 HIV-positive patients with chronic HBV infection from four centers located in Paris and Lyon,
88 France. Patients were included if they had HIV-positive serological results confirmed by western blot and
89 HBsAg-positive serological results for >6 months. Participants were recruited in 2002-2003 and followed up
90 prospectively every 6-12 months until 2017-2018. The cohort design and procedures are described
91 elsewhere.^{17,18}

92

93 For this analysis, we included patients undergoing TDF-containing ART for ≥ 24 consecutive months. This
94 timeframe was chosen since studies in HBV mono-infection and HIV-HBV coinfection have demonstrated that
95 >90% achieve virological response within 24 months of nucleos(t)ide analogue (NA) therapy.¹⁹ We did not
96 include patients with concomitant interferon/pegylated interferon (peg-IFN) or detectable hepatitis C virus
97 (HCV) or hepatitis D virus (HDV) RNA.

98

99 ***Ethics***

100 All patients provided written informed consent to participate in the study and the protocol was approved by
101 the appropriate ethics committee (Paris, France) in accordance with the Helsinki Declaration.¹⁷

102

103 ***Data collection***

104 Demographic information was collected at study inclusion. HIV-related variables included HIV-RNA viral load
105 (HIV-VL) and CD4⁺ cell count, and were collected before TDF-initiation and at each follow-up visit. HBV-
106 related variables included HBV-DNA VL, alanine aminotransferase (ALT) levels, aspartate aminotransferase

107 (AST) levels, qualitative HBeAg, anti-HBe antibodies, HBsAg, and anti-HBs antibodies, and were collected
108 before TDF-initiation and at each follow-up visit. Cumulative exposure to viral replication was calculated
109 using time-averaged copy-years over follow-up time (copy-years_{TAVG}), as detailed elsewhere.¹⁸ At TDF-
110 initiation, L-nucleoside-associated HBV mutations at positions rt173, rt180, and rt204 of the *pol* gene and at
111 nucleotide 1896 of the *precore* gene were determined using DNA chip technology (bioMérieux, Marcy
112 l'Etoile, France).²⁰ Liver fibrosis was assessed at each yearly interval by the FibroTest[®] calculated from a
113 standard battery of biochemical markers.²¹ METAVIR equivalents of this measure, as established in the HIV-
114 HBV coinfecting population, were used to grade liver fibrosis (F2=0.48-0.58, F3=0.59-0.73, F4 \geq 0.74).²²

115

116 ***HBV replication profiles***

117 HBV replication profiles were based on HBV-viral load (VL) at the end of the follow-up, as defined
118 previously.⁸ First, patients were classified on whether or not they had undetectable HBV-VL at the last
119 follow-up visit (HBV-DNA <60 IU/mL). Second, those with undetectable HBV-VL were divided into two
120 subgroups: sustained virological response (sustained-VR; achieving and/or constantly maintaining HBV-DNA
121 <60 IU/mL thereafter) or transient persistent viremia (PV; attaining <60 IU/mL, intermittently \geq 60 IU/mL
122 thereafter and returning to undetectable levels at the last visit). Patients with detectable HBV-VL at the last
123 visit were divided into two subgroups: low-level persistent viremia (LL-PV; 60-2,000 IU/mL) or high-level
124 persistent viremia (HL-PV; >2,000 IU/mL). Sensitivity analysis was conducted in which transient-PV was
125 defined as having two or more visits with detectable HBV-DNA after VR and those with only one visit with
126 detectable HBV-DNA after VR were excluded.

127

128 ***Statistical analysis***

129 Baseline was defined as the study visit at or directly before TDF-initiation. Follow-up began at TDF-initiation
130 and continued until the last study visit, TDF-discontinuation, initiating peg-IFN, detection of HCV or HDV
131 RNA, or death, whichever occurred first.

132

133 We used several sets of endpoints to evaluate HBV-DNA suppression. First, the percentage with
134 undetectable HBV-DNA was calculated at the end of each yearly interval of follow-up. Second, the
135 cumulative proportion achieving VR (HBV-DNA <60 IU/mL) was calculated during continuous time. Third, in
136 the subset of patients who had achieved VR, we identified visits at which HBV-DNA VL was detectable
137 (≥ 60 /mL) after achieving VR [i.e. viral persistence]. Risk-factor analysis for viral persistence was performed
138 on this subset of patients using follow-up that began at the first undetectable HBV-DNA VL and continued
139 until right-censoring. Univariable odds ratios (OR) comparing the odds across levels of determinants over
140 time and their 95% confidence intervals (95%CI) were calculated from a logistic regression model, which
141 included a random-intercept to account for between-patient variation at baseline. A multivariable model
142 was constructed by adding all covariables with a p value <0.20 in univariable analysis and removing
143 nonsignificant variables in backward-stepwise fashion. Finally, we constructed HBV replication profiles as
144 defined above. Comparisons between HBV replication profiles were performed for all clinical parameters at
145 baseline and during follow-up using the Kruskal-Wallis test for continuous variables and Pearson's χ^2 test or
146 Fisher's exact test for categorical variables. Scatterplots and locally weighted scatterplot smoothing plots
147 were used to illustrate the evolution of HBV-DNA replication according to HBV replication profiles.

148
149 We then used HBeAg-seroclearance (for HBeAg-positive patients) and HBsAg-seroclearance as endpoints.
150 We estimated the cumulative proportion achieving these events, while only considering the first
151 seroclearance event and not taking into account transitioning back to antigen-positive status. We estimated
152 time to seroclearance using Kaplan-Meier curves and the incidence of seroclearance rates, which were
153 compared between those who achieved versus never achieved VR using a two-sided Exact binomial test with
154 mid-p assumption.

155
156 All statistical analyses were performed using STATA software (v15.1; College Station, Texas, USA) and
157 significance was determined using a p value < 0.05.

158

159 **Results**

160 ***Description of the study population***

161 Of the 308 patients included in the cohort, 143 were not included in analysis for the following reasons: did
162 not initiate TDF ($n=51$), used TDF for less than 24 months ($n=42$), used concomitant PEG-IFN or IFN ($n=20$),
163 ever had anti-HCV and/or anti-HDV antibody positive serology ($n=23$), or had insufficient information at
164 baseline ($n=7$). Thus, 165 individuals were included in the present analysis (Supplementary Figure 1).

165

166 Of these 165 patients, most were male (83.6%) with a median age of 41.7 years (IQR=36.4-48.3) at TDF-
167 initiation (Table 1). Almost all patients had previously initiated ART (99.4%), with a median 7.0 years of ART
168 exposure (IQR=4.4-9.2), and thus median CD4+ count was 410/mm³ (IQR=288-596) and 97 (58.8%) had
169 undetectable HIV-RNA. At baseline, 96 (58.2%) patients were HBeAg-positive and HBV-DNA was detectable
170 in 75.2% of participants. Of the 147 patients (89.1%) with previous lamivudine (LAM) exposure, median LAM
171 duration was 5.1 years (IQR=2.8-6.8) at TDF initiation and, among those with available information, 20/100
172 (20.0%) had baseline LAM resistance mutations. HBV genotype was determined in 105 patients, and most
173 harbored genotype A (67.6%), followed by G (15.2%), E (8.6%) and D (8.6%). Among patients with available
174 data on Fibrotest scores at TDF initiation ($n=147$), 36 (24.5%) had F3-F4 fibrosis.

175

176 ***HBV-DNA suppression during TDF-containing ART***

177 Patients were followed for a median 8.1 years (IQR=4.0-13.2), with a maximum follow-up of 15.7 years.

178 Three patients switched from tenofovir disoproxil fumarate to tenofovir alafenamide (TAF) based ART during
179 follow-up, while follow-up during TAF was still included in analysis (median TAF duration: 0.5 years,
180 range=0.2-5.6). The percentage of patients with undetectable HBV-DNA increased substantially in the first 6
181 years of TDF treatment, while, thereafter, ranging between 94.0-97.8% and never reaching 100% (Figure 1a).

182

183 163 (98.8%) patients were able to achieve virological response after a median 0.90 years (IQR=0.39-1.74) of
184 follow-up and of them, 30 (18.2%) had at least one visit with detectable HBV-DNA after achieving virological

185 response. The number of visits with detectable HBV-DNA for these patients were distributed as follows: 1,
186 $n=17$; 2, $n=7$; 3, $n=2$; 4, $n=2$; 10, $n=1$; and, 18, $n=1$. Risk factors for viral persistence over time are given in
187 Table 2. In multivariable analysis, positive HBeAg status at baseline ($p=0.04$), lower nadir CD4+ cell counts
188 ($p=0.002$) and undetectable HIV-VL ($p<0.001$) were significantly associated with viral persistence.

189

190 We then characterized HBV replication profiles based on HBV-VLs at the end of follow-up. Of the 152
191 (92.1%) patients with undetectable HBV-VL, 133 (87.5%) had remained undetectable (sustained-VR) and 19
192 (12.5%) had become detectable (median peak HBV-VL=2.54 \log_{10} IU/mL, range=1.79-8.04) after having
193 achieved undetectable HBV-VL (transient-PV). Among those with transient-PV, 10 had more than one visit
194 with detectable HBV-DNA, with the time from first to last detectable HBV DNA measurement lasting a
195 median 1.0 year (range=0.12-7.0). Of the 13 (7.9%) patients with detectable HBV-VL at the end of the follow-
196 up, 9 had LL-PV (median HBV-VL=272 IU/mL, range=67-1,341) and 4 had HL-PV (range HBV-VL=3.91-7.72
197 \log_{10} IU/mL). Of these patients, 11 had achieved HBV-VL <60 at least once during follow-up (LL-PV, $n=8$; HL-
198 PV, $n=3$). The proportion of patients with undetectable HBV-VLs are summarized between groups in Figure
199 1b, while changes in HBV-VLs are given for patients with sustained-VR in Figure 1c, transient-PV in Figure 1d
200 and LL-/HL-PV in Figure 1e.

201

202 At baseline, patients with transient-PV profile, as compared to sustained-VR, were significantly more likely to
203 be HBeAg-positive ($p=0.04$), to have detectable HIV-VL ($p=0.04$), lower nadir CD4+ cell count ($p=0.002$),
204 higher BMI ($p=0.01$), and shorter cumulative LAM treatment prior to TDF-initiation ($p=0.03$) (Table 3).
205 Patients with LL-/HL-PV profiles had significantly higher baseline ALT ($p=0.007$) and AST levels ($p=0.03$),
206 when compared to those with either sustained-VR or transient-PV. During follow-up, patients with
207 sustained-VR profile, compared to transient-PV, were significantly more likely to achieve virological response
208 at 24 months of therapy ($p=0.03$), showed higher frequency of suppressed HIV-VL ($p<0.001$) and lower
209 frequency of liver fibrosis progression from mild or moderate fibrosis (F0-F1-F2) to more advanced fibrosis
210 (F3-F4; $p=0.01$) (Table 4). In sensitivity analysis requiring two or more visits with detectable HBV-DNA to

211 define transient-PV, similar differences between groups were observed (Supplementary Tables S1 and S2 for
212 baseline and follow-up characteristics, respectively). Individuals with LL-/HL-PV profiles, when compared to
213 all other profiles, were significantly more likely to have shorter duration of follow-up ($p<0.001$), higher 12-
214 month ($p<0.001$) and 24-month change ($p<0.001$) in HBV-VL, higher maximum decrease ($p<0.001$) and
215 increase ($p<0.001$) of ALT levels from baseline, and higher ALT levels at the last follow-up visit ($p<0.001$).
216 Moreover, individuals with LL-/HL-PV profiles, compared to sustained-VR, had a lower frequency of
217 undetectable HIV-VL for all visits during follow-up (Table 4).

218

219 ***HBeAg- and HBsAg-seroclearance and its relation to viral persistence during TDF-containing ART***

220 Of the 96 HBeAg-positive patients at study inclusion, 44 lost HBeAg (cumulative incidence: 45.8%;
221 95%CI=35.6%-56.3%) after a median 4.9 years (IQR=3.0-9.0) of follow-up (incidence rate=6.1/100 person-
222 years). Of them, 2 reverted back to HBeAg-positive serology and 4 changed serostatus multiple times until
223 ending follow-up with HBeAg-negative serology. Of the 42 patients ending follow-up with HBeAg-negative
224 serology, acquisition of anti-HBe antibodies (anti-HBeAb) was achieved in 14 (33.3%) patients either at the
225 same visit as HBeAg-seroclearance ($n=10$) or from 1.7-11.4 years after HBeAg-seroclearance ($n=4$). Of these
226 patients, 6 (42.9%) lost anti-HBeAb by the end of follow-up.

227

228 No difference was observed in HBeAg-seroclearance between those who were able to achieve VR during
229 follow-up versus those who never achieved VR (7.4 versus 3.7/100 person-years respectively, $p=0.33$, Figure
230 2a). Of those who had HBeAg-seroclearance, 34 belonged to the sustained-VR, 8 transient-PV profile, and 2
231 LL-PV groups.

232

233 A total of 13 patients lost HBsAg (cumulative incidence: 7.9%; 95%CI=4.3%-13.1%) after a median 7.5 years
234 (IQR=3.8-11.2) of follow-up (incidence rate=0.9/100 person-years). Of these patients, two reverted back to
235 HBsAg-positive serology and one changed serostatus multiple times until ending follow-up with HBsAg-
236 positive serology. Of the 10 patients ending follow-up with HBsAg-negative serology, acquisition of anti-

237 HBsAb was achieved in six (60.0%) either at the same visit as HBsAg-seroclearance (n=3) or from 0.9-6.7
238 years after HBsAg-seroclearance (n=3). Additionally, 6 patients who lost HBsAg were HBeAg-positive at
239 baseline. For these patients, median time from HBeAg-seroclearance to HBsAg-seroclearance was 4.8 years
240 (range=0.5-13.5).

241

242 HBsAg-seroclearance was only observed in those who achieved VR, yet this rate was not significantly
243 different from those who were never able to achieve VR (1.0 versus 0/100 person-years, respectively,
244 $p=0.49$, Figure 2b). Of those who had HBsAg-seroclearance, 11 belonged to the sustained-VR and 2
245 transient-PV profile groups.

246

247 ***Severe liver-related morbidity and mortality and its relation to viral persistence during TDF-containing ART***

248 At TDF initiation, 4 patients had already experienced a severe liver-related event [portal hypertension n=1;
249 HCC, n=2; haemorrhagic necrosis of liver, n=1]. Of them, 2 had sustained VR, 1 had transient PV and 1 had
250 HL-PV. During TDF treatment, 3 patients developed portal hypertension (all with sustained VR profiles), 1
251 hepatorenal syndrome (HL-PV profile), 3 HCC (2 with sustained VR and 1 with LL-PV profiles), and 2
252 haemorrhagic necrosis of liver (1 with sustained VR and 1 with transient PV). Two deaths were the result of
253 HCC (1 with sustained VR and 1 with LL-PV profile) and one from decompensated liver with HCC and
254 complications due to septic shock (sustained-VR profile). All three patients who developed HCC during
255 follow-up had METAVIR F3-F4 fibrosis at TDF initiation, as measured by the FibroTest®. Ultrasound revealed
256 the presence of hepatic nodules for all three patients, along with steatosis (n=2) and portal vein thrombosis
257 (n=1).

258

259 **Discussion**

260 Using longitudinal data from one of the longest studies to date on TDF-use in HIV-HBV coinfecting individuals,
261 we observed that viral persistence continues to occur throughout TDF-treatment, with 18.2% of patients
262 exhibiting detectable HBV-DNA after having achieved virological response. Nevertheless, the probability of

263 having detectable HBV-DNA decreased as the duration of TDF increased and $\leq 6\%$ of patients consistently
264 had detectable HBV-DNA every year after 6 years of TDF. These data support the durability of HBV
265 suppression associated with TDF-use and suggest that viral persistence does not mitigate long-term viral
266 suppression.

267

268 The extent of persistent viremia in individuals with chronic HBV infection varies considerably across studies.
269 When defining persistence based on HBV-DNA levels at a maximum 24 months of follow-up, we found that
270 only 8% of patients presented with LL-/HL-PV. If minimum follow-up is extended to 60 months, where most
271 HIV-HBV coinfecting individuals appeared to have achieved HBV virological suppression, only 4% of patients
272 had LL-PV and no patient had HL-PV. The proportion of patients with HBV persistence in our study is
273 considerably lower when compared to other prospective studies in HIV-HBV coinfecting, reporting 14% to
274 54%.^{8,9,12} However, these studies used inability to achieve virological response at 12-months as the basis for
275 persistent viremia, which, given our data and others,⁹ is too short a timeframe to define persistence. When
276 defining persistence based on any detection of HBV-VL after achieving VR, we found that 20% of individuals
277 had at one point persistent viremia. In the GS-US-174-0102 and GS-US-174-0103 registration studies in HBV
278 mono-infected patients, this type of persistence occurred very rarely (0.9%).²³

279

280 We observed that median CD4⁺ cell count at last follow-up visit and the frequency of undetectable HIV-VL
281 over time were significantly higher in patients with sustained-VR compared to other profiles, while patients
282 who had higher CD4⁺ counts for longer periods of time were able to more frequently suppress HBV-DNA
283 replication after achieving initial virological response. Indeed, immunosuppression as an underlying factor
284 for viral persistence has been evoked in other studies.^{12,15} Previous research has suggested that HIV-HBV
285 coinfecting patients have lower levels of HBV-specific CD4⁺ T-cell responses,^{24,25} intrahepatic T cells, Kupfer
286 cells and NK cells,²⁶ as well as reduced intrahepatic inflammatory activity when compared to HIV-positive
287 patients without HBV infection. Taken together, these data highlight the importance of immunoregulation to

288 control HBV replication and could explain why persistence occurs more frequently in HIV-HBV coinfectd
289 versus HBV mono-infected patients.

290

291 Detectable HIV-RNA viremia was also more often observed during treatment for individuals with transient-
292 PV, LL- and HL-PV profiles and was strongly associated with HBV viral persistence after achieving virological
293 response. Similar findings have been observed by others.^{9,12} In general, detectable HIV-RNA, as determined
294 by most commercial assays, is either due to developing HIV resistant variants or inadequate adherence to
295 ART.²⁷ Given that no consistent mutation pattern for TDF resistance has yet to be observed,⁴ detectable
296 HBV-DNA would likely be the result of poor adherence.²⁸ Much of the concordance of simultaneously
297 detectable HIV-RNA and HBV-DNA would then likely be the result of insufficient adherence. We did not
298 collect data on HIV resistance and our data on HBV sequences are limited to the first 8 years of follow-up,
299 hence we are unable to confirm this speculation. TDF plasma concentrations were indeed lower or even
300 undetectable for individuals with profiles of LL/HL-PV in our previous study,⁸ while others have found lower
301 concentrations of intracellular drug levels of tenofovir-diphosphate, a measure of long-term adherence, for
302 HIV-HBV coinfectd individuals with HBV persistent viremia during TDF-treatment.²⁹ Nevertheless,
303 considering that HIV-RNA was undetectable for 71% of visits when HBV-VL was detectable (after initial HBV
304 virological response), adherence alone cannot fully explain HBV persistent viremia.

305

306 For individuals with persistent viremia, it is clear that the vast majority are able to eventually suppress HBV-
307 DNA. It remains debatable to what extent persistent viremia leads to major long-term serological
308 consequences. We observed that individuals with LL- and HL-PV profiles were never able to achieve HBsAg-
309 seroclearance. The reasons for this finding are not entirely clear. Large rebounds in HBV-DNA replication
310 have been shown to be associated with HBsAg-seroclearance, but is usually accompanied with ALT flares and
311 occurs mostly in HBV treatment cessation studies or during the course of natural infection;^{30,31} increases in
312 ALT levels were rarely observed during HBV viral persistence in our study population of TDF-treated
313 individuals. It could be that ability to achieve sustained VR is a proxy for tighter control of HBV viral activity

314 in general; however, further evidence would be needed to confirm this finding. Nevertheless, it should be
315 noted that only 7.9% of the entire study population were able to exhibit HBsAg-seroclearance, even after up
316 to 15 years of follow-up. The lack of function cure would appear to be more a general problem in treated
317 coinfecting patients.

318

319 The clinical consequences of persistent HBV viremia are also fairly unknown. From several studies during the
320 natural history of chronic HBV infection, consistently high levels of HBV-DNA (i.e. $\geq 10,000$ copies/mL) during
321 later phases of HBV infection are mostly associated with developing HCC and cirrhosis.³² Expectedly, our
322 data showed a low incidence of clinical liver-related outcomes, with no strong evidence that PV *per se* is
323 associated with higher rates of liver-related morbidity and mortality.

324

325 This study has several strengths, including possibly the longest follow-up to date in either HIV-HBV
326 coinfecting^{8,9,13,18} and HBV-monoinfecting patients^{14,33} with consistently measured virological and serological
327 markers of HBV. However, certain limitations need to be addressed. First, the time-dependent definitions of
328 HBV replications profiles might be inadequate for under 3 years of follow-up. Therefore, we decided to also
329 use persistent viremia after initial VR as a complementary definition of persistence. Second, we did not
330 measure plasma TDF concentrations to assess adherence, so we cannot determine if those patients with
331 viral persistence were adherent to ART or whether a decrease in frequency of persistence was due to
332 improved adherence over time. Third, our data represent a population that is highly ART-experienced and
333 more immunosuppressed compared to contemporary patient populations, but still actively seen in
334 outpatient settings. Finally, since genotypic data were not collected at later years of TDF use in our cohort,
335 we are unable to determine whether viral persistence is related to certain mutational patterns.³⁴ From our
336 last analysis, there were only 9 additional patients exhibiting an HBV-VL >1000 IU/mL, which would be ideal
337 for sequencing, and the small numbers would unlikely reveal any other mutation patterns explaining viral
338 persistence during TDF use.

339

340 In conclusion, we demonstrate that TDF is able to suppress HBV-DNA to undetectable levels in the majority
341 of ART-experienced HIV-HBV coinfecting patients undergoing up to 15 years of TDF-containing ART.
342 Nevertheless, a low proportion of patients do exhibit HBV viral persistence. A small proportion of patients
343 achieved HBV functional cure, which was exclusively observed in those with sustained HBV-VLs. This low
344 percentage of serological responders is quite similar to HBV mono-infected patients undergoing prolonged
345 TDF treatment¹⁴ and highlights the need to identify novel HBV treatment strategies against HBV. Still,
346 evaluating the relationship between HBV persistent viremia and more severe clinical outcomes is warranted
347 in larger, longitudinal cohort studies.

348

349 **Acknowledgements**

350 The authors are grateful to the patients and the clinical teams for their commitment to the French HIV-HBV
351 Cohort. This study was sponsored by the Institut de Médecine et d'Epidémiologie Appliquée (IMEA). L.N.C.D.
352 was awarded a post-doctoral fellowship from the France REcherche Nord&sud Sida-hiv Hépatites (ANRS).

353

354 **Role of each author.** L.N.C.D. was responsible for the statistical analysis, interpretation of the data, and
355 drafting the manuscript. S.M., A.G. and C.D. were responsible for interpretation of the data and drafting the
356 manuscript. H.R., P.M., C. L-C., and J.C. acquired data for the cohort, assisted in interpreting data, and gave
357 critical revisions of the manuscript. K.L. helped design, conceptualize, and obtain funding for the French HIV-
358 HBV cohort study, coordinated data collection, and drafted parts of the manuscript. A.B. coordinated data
359 analysis, gave important comments on data interpretation, drafted the manuscript, and provided critical
360 revisions of the manuscript. All authors approved the final version.

361

362 **Funding**

363 This study was supported by SIDACTION (AO 19) and the ANRS. Gilead Sciences, Inc. provided an
364 unrestricted grant for the French HIV-HBV cohort and was not involved in any part of the design, data
365 collection, analysis and manuscript writing.

366

367 **Transparency declarations**

368 None to declare.

369

370 **Supplementary Data**

371 Figure S1 is available as Supplementary data.

372

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455 chronic hepatitis B patients. *J Hepatology* 2019; **70**: 1093–102.

456

Table 1. Baseline characteristics among HIV/hepatitis B virus cohort participants (N=165).

Characteristic	N (%) or median (IQR)
Demographics	
Gender, male/female (% male)	138/25 (83.6)
Age, years*	41.7 (36.4-48.3)
BMI \geq 25 Kg/m ² , N=149*	27 (18.1)
Born in high HBV endemic zone [†]	45 (27.3)
HIV characteristics	
Ever having an AIDS-defining illness [†]	41 (24.9)
Known HIV infection duration, years*	11.1 (7.10-15.0)
Detectable HIV-RNA [†]	68 (41.2)
HIV-RNA [‡] , log ₁₀ copies/mL*	4.1 (2.9-4.6)
CD4 ⁺ cell count, per mm ³ , N=164*	410 (288-596)
CD4 ⁺ nadir cell count, per mm ³ , N=152*	224 (104-319)
Duration of prior ART, years, N=164*	7.0 (4.4-9.2)
Viral hepatitis B characteristics	
Known HBV infection duration, years, N=164*	8.3 (4.2-12.1)

Prior LAM exposure [†]	147 (89.1)
Cumulative prior LAM treatment, years, N=147*	5.1 (2.8-6.8)
LAM-resistant mutations, N=100 [†]	20 (20.0)
Detectable HBV-DNA [†]	124 (75.2)
HBV-DNA [‡] , log ₁₀ IU/mL*	5.2 (3.2-7.2)
HBeAg-positive [†]	96 (58.2)
ALT, IU/L, N=161*	40 (26-68)
AST, IU/L, N=161*	34 (25-56)
F3-F4 fibrosis [#] , N=147 [†]	36 (24.5)
<i>Precore</i> mutations, N=101 [†]	22 (21.8)
HBV genotype, N=105 [†]	
A	71 (67.6)
D	9 (8.6)
E	9 (8.6)
G	16 (15.2)

*Median (IQR).

[†] Number (%).

[#] Estimated using the FibroTest[®].

Abbreviations: AIDS, acquired immune deficiency syndrome; ALT, alanine aminotransferase; ART, antiretroviral therapy; AST, aspartate aminotransferase; BMI, body mass index; HBV, hepatitis B virus; HIV, human immunodeficiency virus; HBeAg, hepatitis B “e” antigen; LAM, lamivudine.

Table 2. Determinants of viral persistence (≥ 60 IU/mL) after having achieved virological response ($N=163$).

	Univariable			Multivariable ^b	
	<i>N</i> ^a	OR (95% CI)	<i>p</i> value	aOR (95% CI)	<i>p</i> value
Age at baseline, years	163	0.97 (0.91-1.04)	0.4		
Male gender	163	3.05 (0.54-17.35)	0.21		
High HBV-endemic zone	163	0.42 (0.11-1.58)	0.20		
BMI					
At baseline	147	1.06 (0.86-1.30)	0.6		
≥ 25 Kg/m ² at baseline	147	3.04 (0.79-11.76)	0.11		
During follow-up*	160	0.94 (0.90-0.99)	0.02		
Ever having an AIDS-defining illness	163	2.56 (0.73-8.92)	0.14		
Nadir CD4 ⁺ cell count (v/mm ³)	150	0.84 (0.75-0.93)	0.001	0.86 (0.78-0.95)	0.002
CD4 ⁺ cell count (v/mm ³)					
At baseline	162	0.88 (0.80-0.97)	0.01		
During follow-up*	163	0.99 (0.98-1.01)	0.30		
Undetectable HIV-RNA (≤ 50 copies/mL)	163	0.25 (0.12-0.55)	0.001	0.23 (0.10-0.51)	<0.001
HIV-RNA, log ₁₀ copies/mL [‡]	70	1.08 (0.58-2.00)	0.8		
HIV infection duration at baseline, years	163	0.98 (0.88-1.10)	0.7		

Duration of prior ART at baseline, years	163	0.95 (0.81-1.11)	0.5		
HBV infection duration at baseline, years	162	0.95 (0.86-1.06)	0.4		
Baseline HBV-DNA, log ₁₀ IU/mL [‡]	122	1.05 (0.77-1.42)	0.8		
HBeAg-positive					
At baseline	163	4.28 (1.24-14.71)	0.02	3.41 (1.08-10.78)	0.04
During follow-up*	163	0.97 (0.82-1.15)	0.7		
Previous LAM treatment	163	1.85 (0.27-12.69)	0.5		
Baseline LAM-resistant mutations	98	0.61 (0.08-4.53)	0.6		
Baseline <i>precore</i> mutations	99	1.53 (0.33-7.16)	0.6		
ALT >35 IU/mL					
At baseline	159	0.27 (0.08-0.93)	0.04		
During follow-up*	163	0.88 (0.76-1.03)	0.11		
AST >35 IU/mL					
At baseline	159	0.38 (0.12-1.20)	0.10		
During follow-up*	163	0.87 (0.74-1.02)	0.08		
Baseline F3-F4 fibrosis [#]	145	0.72 (0.19-2.73)	0.6		

*Time-dependent variables.

‡ Among patients with detectable HIV-RNA or HBV-DNA viral loads.

Estimated using the Fibrotest®.

^a Total number of patients in analysis.

^b BMI during follow-up was not considered in multivariable analysis because BMI <25 , ≥ 25 Kg/m² at baseline was preferred. All ORs are adjusted for the variables listed in the column.

Abbreviations: AIDS, acquired immune deficiency syndrome; ALT, alanine aminotransferase; aOR, adjusted OR; ART, antiretroviral therapy; AST, aspartate aminotransferase; BMI, body mass index; HBV, hepatitis B virus; HIV, human immunodeficiency virus; HBeAg, hepatitis B “e” antigen; LAM, lamivudine.

Table 3. Baseline characteristics of hepatitis B virus replication profiles.

Characteristics	Sustained VR (N=133)	Transient PV (N=19)	LL-/HL-PV (N=13)	<i>p</i> value <0.05 [§]
Demographics				
Gender, male/female (% male)	109/24 (82.0)	16/3 (84.2)	13/0 (100)	NS
Age, years*	42.3 (37.2-49.2)	39.7 (33.8-43.9)	39.8 (34.7-44.9)	NS
BMI, Kg/m ² , N=149*	22.3 (20.7-24.1)	23.7 (22.5-26.0)	22.2 (20.9-23.9)	1
Born in high HBV endemic zone [†]	38 (28.6)	5 (26.3)	2 (15.4)	NS
HIV characteristics				
Ever having an AIDS-defining illness [†]	30 (22.6)	8 (42.1)	3 (23.1)	NS
Known HIV infection duration, years*	11.3 (6.3-15.0)	10.1 (7.1-13.1)	10.2 (7.6-12.2)	NS
Detectable HIV-RNA [†]	51 (38.3)	12 (63.2)	5 (38.5)	1
HIV-RNA [‡] , log ₁₀ copies/mL*	3.7 (2.7-4.4)	4.4 (3.9-4.7)	4.3 (4.1-4.6)	NS
CD4 ⁺ cell count, per mm ³ , N=164*	440 (334-601)	262 (115-379)	500 (212-754)	1,3
CD4 ⁺ nadir cell count, per mm ³ , N=152*	238 (130-333)	121 (34-179)	96 (56-286)	1
Duration of prior ART, years, N=164*	7.0 (4.4-9.2)	7.6 (4.1-8.5)	6.4 (4.8-8.3)	NS

Viral hepatitis B characteristics

Known HBV infection duration, years, <i>N</i> =164*	8.3 (4.3-12.3)	9.3 (3.7-10.8)	6.1 (2.8-13.1)	NS
Prior LAM exposure [†]	118 (88.7)	16 (84.2)	13 (100)	NS
Cumulative prior LAM treatment, years, <i>N</i> =142*	5.5 (3.2-7.2)	3.8 (2.3-5.5)	4.9 (2.7-6.1)	1
Detectable HBV-DNA [†]	95 (71.4)	17 (89.5)	10 (76.9)	NS
HBV-DNA [‡] , log ₁₀ IU/mL*	5.2 (3.2-7.4)	4.6 (2.9-6.6)	6.6 (4.6-6.9)	NS
HBeAg-positive [†]	71 (53.4)	15 (79.0)	10 (76.9)	1
ALT, IU/L, <i>N</i> =161*	39 (26-68)	40 (23-64)	72 (54-145)	2,3
AST, IU/L, <i>N</i> =161*	33 (25-50)	28 (24-56)	66 (41-80)	2,3
F3-F4 fibrosis [#] , <i>N</i> =147 [†]	31 (26.5)	2 (10.5)	5 (38.5)	NS
LAM-resistant mutations, <i>N</i> =100 [†]	16 (20.3)	1 (9.1)	3 (30.0)	NS
<i>Precore</i> mutations, <i>N</i> =101 [†]	16 (20.5)	4 (30.8)	2 (20.0)	NS
HBV genotype, <i>N</i> =105 [†]				NS
A	54 (67.5)	9 (69.2)	8 (66.7)	
D	6 (7.5)	2 (15.4)	1 (8.3)	
E	6 (7.5)	2 (15.4)	1 (8.3)	
G	14 (17.5)	0 (0)	2 (16.7)	

*Median (IQR).

† Number (%).

§ Significance was determined using Kruskal-Wallis test for continuous variables and Pearson χ^2 test or Fisher exact test for categorical variables. Significant differences ($p < 0.05$) between profile groups were indicated as follows: 1, sustained virological VR and transient PV; 2, sustained VR and LL-/HL-PV; 3, transient PV and LL-/HL-PV.

¥ Among patients with detectable HIV-RNA or HBV-DNA viral loads.

Estimated using the Fibrotest®.

Abbreviations: AIDS, acquired immune deficiency syndrome; ALT, alanine aminotransferase; ART, antiretroviral therapy; AST, aspartate aminotransferase; BMI, body mass index; cART, combined ART; HBV, hepatitis B virus; HBeAg, hepatitis B “e” antigen; HIV, human immunodeficiency virus; HL, high level; LAM, lamivudine; LL, low level; NS, no significant differences between groups; PV, persistent viremia; VR, virological response.

Table 4. Clinical and serological characteristics of hepatitis B virus replication profiles during follow-up.

Characteristics	Sustained VR (N=133)	Transient PV (N=19)	LL-/HL-PV (N=13)	<i>p</i> value <0.05 [§]
Total follow-up, years*	8.1 (3.9-12.6)	13.7 (8.1-14.6)	4.1 (2.8-7.1)	1,2,3
HBV-DNA [‡]				
12-month change, log ₁₀ IU/mL*	-2.57 (-4.82, -0.85)	-2.80 (-4.70, -0.92)	-4.28 (-4.80, -2.80)	2,3
24-month change, log ₁₀ IU/mL*	-2.83 (-5.17, -1.10)	-1.58 (-4.80, -0.92)	-4.80 (-5.10, -2.80)	1,2,3
VR at 12 months [†]	86 (64.7)	10 (52.6)	7 (53.9)	NS
VR at 24 months [†]	110 (82.7)	11 (57.9)	9 (69.3)	1
VR at 36 months [†]	124 (93.2)	17 (89.5)	11 (84.6)	NS
HIV-RNA				
undetectable HIV VL in the last study visit [†]	123 (92.5)	19 (100.0)	10 (76.9)	NS
% undetectable HIV VLs during follow-up*	91.3 (80.0-100.0)	85.7 (52.9-91.3)	75.0 (58.3-88.2)	1,2
≥70% undetectable HIV VLs during follow-up [†]	111 (83.5)	11 (57.9)	8 (61.5)	1

Serological response

HBeAg loss ^{†‡}	34 (25.6)	8 (42.1)	2 (15.4)	NS
HBeAg seroconversion ^{†‡}	13 (9.8)	1 (5.3)	1 (7.7)	NS
HBsAg loss [†]	11 (8.7)	2 (10.5)	0 (0)	NS

ALT

Maximum decrease from baseline, IU/mL*	-12 (-39, -3)	-9 (-28, -2)	-84 (-92, -26)	1,2,3
Maximum increase from baseline, IU/mL*	9 (2-18)	12 (7-20)	51 (0-116)	1,2,3
Last follow-up visit, IU/mL	28 (21-36)	30 (18-39)	49 (32-78)	2,3

CD4⁺ cell count

Last follow-up visit, IU/mL	540 (408-779)	460 (331-708)	408 (289-660)	1,2
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Liver fibrosis[#]

F3-F4 at last follow-up visit [†] , N=161	37 (26.7)	7 (36.8)	5 (38.5)	NS
Progression from F0-F1-F2 to F3-F4 ^{&†} , N=147	12 (10.4)	6 (31.6)	0 (0.0)	1

*Median (IQR).

[†]Number (%).

[‡]Among patients with detectable HBV-DNA at baseline.

[#]Among HBeAg-positive patients.

Estimated using the Fibrotest®.

& From baseline to last follow-up visit, only in individuals with baseline F0-F1-F2 fibrosis.

§ Significance was determined using Kruskal-Wallis test for continuous variables and Pearson χ^2 test or Fisher exact test for categorical variables. Significant differences ($p < 0.05$) between profile groups were indicated as follows: 1, sustained virological VR and transient PV; 2, sustained VR and LL-/HL-PV; 3, transient PV and LL-/HL-PV.

Abbreviations: ALT, alanine aminotransferase; HBeAg, hepatitis B “e” antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HIV, human immunodeficiency virus; HL, high level; LL, low level; PV, persistent viremia; VL, viral load; VR, virological response.

Figure legends

Figure 1.

Viral suppression during tenofovir (TDF)-treatment in (a) all patients and (b) different profiles of HBV replication; and HBV-DNA viral loads during TDF-treatment in patients with (c) sustained virological response (VR), (d) transient persistent viremia (PV), and (e) low-level/high-level persistent viremia (LL-/HL-PV). Individual levels are expressed as gray lines.

Figure 2.

Cumulative probability of (a) hepatitis B 'e' antigen (HBeAg) and (b) hepatitis B surface antigen (HBsAg) seroclearance, according to different profiles of HBV replication.

Figure 1.

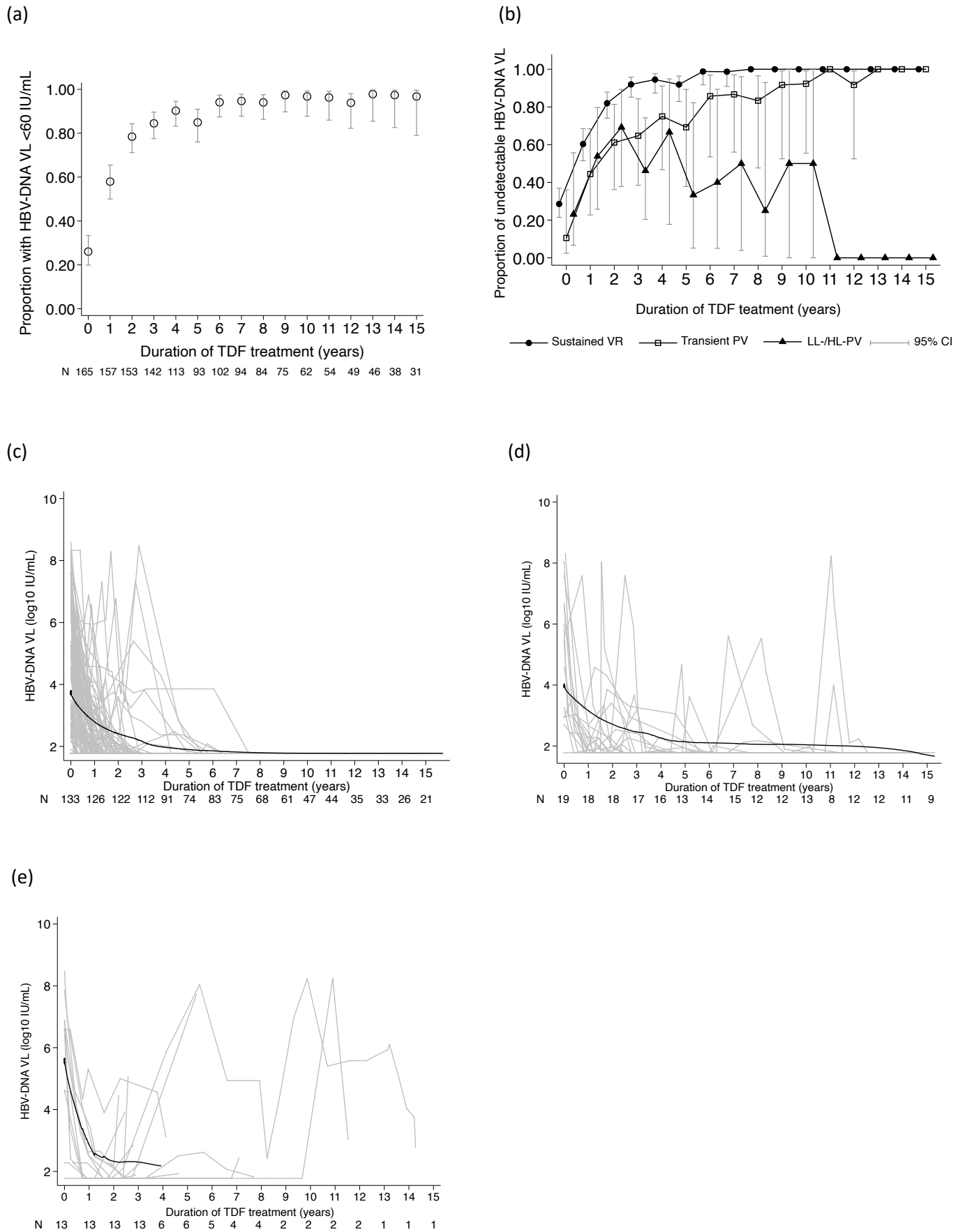
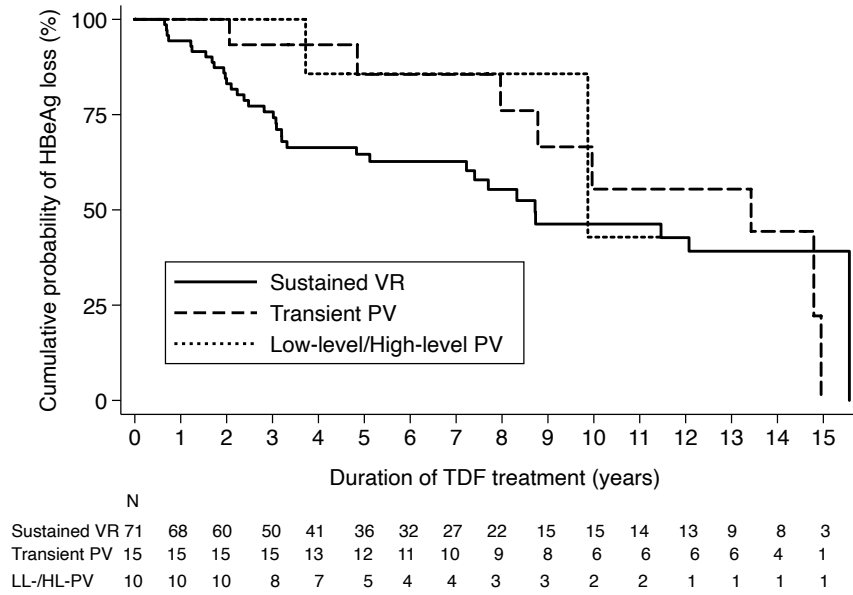


Figure 2.

(a)



(b)

