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ABSTRACT

Background: Renal toxicity is a common side-effect during tenofovir (TDF)-use in human immunodeficiency virus (HIV)-infected, but not necessarily hepatitis B virus (HBV)-infected, patients. Nevertheless, little is known regarding TDF-use on renal impairment during HIV-HBV co-infection. We aimed to evaluate the progression and determinants of renal impairment in co-infected patients undergoing TDF.

Methods: 175 co-infected patients initiating TDF-containing antiretroviral therapy (ART) were prospectively followed. Estimated glomerular filtration rates (eGFR) were calculated at baseline and every 6-12 months. Determinants of eGRF change from baseline (ΔeGFR) were evaluated using mixed-effect linear regression and progression towards renal impairment using proportional-hazards regression.

Results: At baseline, average eGFR was 96.7 min/mL per 1.73m² (95%CI=93.8-99.6). During a median 58.3 months (IQR=33.7-92.1) of treatment, eGFR decreased a monthly average of -0.14 min/mL per 1.73m² (95%CI=-0.16,-0.12). Significantly faster ΔeGFR was associated with baseline eGFR>90 (*P*=0.002), male-gender (*P*=0.04), previous AIDS-defining illness at baseline (*P*=0.03), baseline liver cirrhosis (*P*=0.03), and concomitant protease inhibitor use (*P*=0.005). Between respective baseline and end of follow-up visits, the proportion of patients with renal impairment increased: normal function, 65.7% to 53.1%; mild impairment, 32.6% to 40.0%; moderate impairment, 1.7% to 6.9%. Higher age (*P*=0.01) and previous AIDS-defining illness (*P*=0.02) at baseline were independent risk-factors for developing impairment, while undetectable HBV-DNA on-treatment was protective (*P*=0.006). Five (2.9%) patients permanently discontinued TDF after a renal event.

Conclusions: Severe HIV- and HBV-related morbidity negatively affects renal function in co-infected patients undergoing long-term TDF. Although most patients only developed mild/moderate impairment, close renal monitoring is warranted for this particular population.

INTRODUCTION

In patients infected with the human immunodeficiency virus (HIV), roughly ten per cent worldwide are chronically infected with hepatitis B virus (HBV).[1] Active HBV replication is associated with increased liver fibrosis, hepatocellular carcinoma, and liver-related mortality [2,3]; and thus its control is highly recommended for HIV-HBV co-infected patients. Antiretroviral therapy (ART) containing tenofovir (TDF) is the preferred treatment strategy in co-infected patients due to its long-term effectiveness in suppressing both HIV and HBV replication without evidence of developing TDF-resistant HBV variants.[4]

Unfortunately, one of the more concerning side-effects of TDF-containing ART is impaired renal function. In studies of predominately HIV mono-infected patients, TDF is associated with faster declines in estimated glomerular filtration rate (eGFR) compared to other antiretroviral agents.[5] HIV-related factors, such as higher HIV-RNA viral loads and severe HIV-associated immunosuppression [6], and treatment combinations with other nephrotoxic agents and certain ritonavir-boosted protease inhibitors (PI) also contribute to increased risk of renal impairment.[7] In contrast, TDF treatment has not borne out as a major risk-factor for larger decreases in eGFR among HBV mono-infected populations when compared to other anti-HBV agents.[8]

For HIV-HBV co-infected patients, increased risk of renal impairment is apparent even before ART is initiated [9] and may be related to HIV and/or HBV disease, raising concerns for nephrotoxicity associated with TDF-containing ART. Only a handful of studies have examined the progression of renal function in co-infected patients undergoing TDF [10–12], with limited patient numbers, retrospective design, and/or without a comprehensive evaluation of the determinants associated with impairment. All have shown decreases in eGFR during therapy, yet it remains uncertain how HBV-related parameters, namely HBV replication or liver fibrosis,

would affect this decline. By increasing the numbers of patients and treatment duration compared to previous studies, we aimed at providing a more thorough characterization of the evolution of eGFR and rates of renal impairment, along with its determinants, in a large, prospective cohort of HIV-HBV co-infected individuals undergoing extensive treatment with TDF-containing ART.

METHODS

Study design

Patients from the French HIV-HBV Cohort were included in the present study, as described previously.[13] Briefly, 308 patients were recruited from seven centers located in Paris and Lyon, France during May 2002-May 2003. Inclusion criteria were HIV-positive serology confirmed by western blot and hepatitis B surface antigen (HBsAg) positive serology for at least six months. Patients were prospectively followed every 6 to 12 months until 2010-2011. All patients provided written informed consent to participate and the protocol was approved by the appropriate ethics committee, in accordance with the Helsinki Declaration.

Patients in this sub-study were included provided that they initiated TDF-containing ART during follow-up. Patients were not included if they had any one of the following: positive hepatitis C virus (HCV)-RNA by a sensitive PCR-based assay, positive hepatitis D virus (HDV) serology, did not have ≥2 consecutive study visits while undergoing TDF, discontinued TDF six months after initiation, and did not have available creatinine levels at baseline and for at least one follow-up visit.

HBV-related parameters

Plasma HBV-DNA viral load (VL) was quantified at baseline and every 6-12 months using a commercial PCR-based assay. Due to varying detection thresholds, undetectable HBV-DNA was defined at the highest detection threshold (HBV-VL <60 IU/mL). Qualitative HBsAg and hepatitis B "e" antigen (HBeAg) were detected at baseline and every yearly visit using a commercial enzyme immunoassay.

Alanine aminotransferase (ALT) levels were quantified using standard methods for every study visit. Liver fibrosis was assessed at each yearly interval by one or two non-invasive methods: Fibroscan® (Echosens, Paris, France), conducted by a trained clinical research associate, and Fibrotest®, calculated from a standard battery of biochemical levels.[14] METAVIR equivalents of these measures were used to grade liver fibrosis [15,16], with the highest level used in case of discordance.

HIV-related virological and immunological parameters

Plasma HIV-1 RNA VLs were measured using either a branched-DNA or real-time PCR technique at each study visit. CD4+ T cell counts were quantified using standard measurements at each study visit, while nadir CD4+ cell count was obtained from patient records prior to inclusion.

Assessing renal function

Creatinine levels were measured using the kinetic-based method for enzymatic quantification and were available at inclusion and every study visit. Estimated glomerular filtration rate (eGFR)

was calculated using the CKD-EPI equation.[17] Following guidelines from the Kidney Disease Improving Global Outcomes group [18], mild, moderate and severe renal impairment were defined by an eGFR of 60-89, 30-59, 15-29 mL/min per 1.73m^2, respectively, and kidney failure was defined by an eGFR <15 mL/min per 1.73m^2.

Assessing cardiovascular disease and diabetes

Patients were considered to have cardiovascular disease (CVD) if they were treated with an agent indicated for CVD (cardiac therapy, antihypertensives, diuretics, peripheral vasodilators, beta-blockers, calcium channel blockers, ACE inhibitors, angiotensin antagonists, or lipid modifying agents) or were diagnosed by their treating physician with any hypertensive, ischaemic or other forms of heart disease. Patients were considered diabetic if they were treated with insulin, insulin-analogues, or a blood glucose lowering agent or were diagnosed by their treating physician with diabetes.

Statistical Analysis

Baseline was defined as the study visit at which TDF was commenced. Follow-up began at baseline and continued until loss to follow-up, final visit of the cohort study, treatment discontinuation, or death; whichever occurred first. All statistical analyses were performed with STATA (v12.1; College Station, TX, USA) and significance was defined by a *P*-value <0.05.

The effects of various HIV- and HBV-related determinants were studied using stratum-specific estimates of monthly change in eGFR from baseline (ΔeGFR). In univariable analysis, each risk-factor, treatment duration, and the interaction between the two were placed in a mixed-effect linear regression model. For time-constant covariables at baseline [previous AIDS-defining

illness, CD4+ cell count, nadir CD4+ cell count, ART duration, HBeAg-status, ALT levels, liver cirrhosis, and prior adefovir (ADV)-exposure], a random-intercept was incorporated into the model. For time-varying covariables during follow-up (detectable HIV-RNA or HBV-DNA and concomitant PI-use), a random-coefficient and -intercept with unstructured variance-covariance structure was used to model random effects. The ΔeGFR at each level of risk-factor was directly obtained from this model, while differences in ΔeGFR across strata were tested from the parameter estimate of the interaction term. A multivariable model was then constructed by placing *a priori* age, gender, born in Sub-Saharan Africa, and baseline eGFR (as they are known to be strongly associated with eGFR), as well as all other covariables whose interaction term produced a *P*-value <0.1 in univariable analysis.

We also chose to study risk factors for regression or progression of renal function, since kidney damage is considered reversible in some instances.[19] In univariable analysis, determinants of time to impaired renal function (among patients with eGFR>90 min/mL/1.73m² at baseline) or time to normal renal function (among patients with eGFR≤90 min/mL/1.73m² at baseline) were evaluated using Cox proportional hazards models. For both end-points, a multivariable model was constructed by placing age, gender, and born in Sub-Saharan Africa *a priori*, then adding covariables with a *P*<0.1 in univariable analysis and removing variables above this *P*-value threshold in forward-stepwise fashion.

RESULTS

Description of the study population

Patient disposition is described in Figure 1. Of the 308 patients enrolled, 71 never received TDF-containing ART during participation in the cohort and 62 did not meet inclusion criteria. In the cohort study, TDF was not given to patients mainly because of less-active HBV infection and not due to concern over renal safety (as shown in *Description of patients with and without tenofovir use in the French HIV-HBV cohort study* of Additional File 1). In total, 175 patients were included in analysis.

At baseline (Table 1), almost two-thirds of patients were HBeAg-positive and HBV-DNA was detectable in 79.9% with a median HBV-DNA VL at 5.02 $\log_{10}$ IU/mL (IQR=2.94-6.88). Patients were nearly all ART-experienced, 58.1% of whom had undetectable HIV-RNA. TDF was administered in combination with other nucleotide/nucleoside reverse transcriptase inhibitors (NRTI, *n*=26), non-nucleotide/nucleoside reverse transcriptase inhibitors (NNRTI, *n*=52), PIs (*n*=66), integrase inhibitors (*n*=1), or both an NNRTI plus a PI (*n*=30). Of the PIs used in combination with ART, the most frequent was ritonavir-boosted (/r) lopinavir (*n*=56), followed by atazanavir (/r or non-r/, *n*=14), nelfinavir (*n*=14), saquinavir/r (*n*=11), amprenavir/r (*n*=6), fosamprenavir/r (*n*=6), indinavir/r (*n*=5), darunavir/r (*n*=3) and tipranavir/r (*n*=1). Of the 96 patients undergoing PIs, 85 (88.5%) had a ritonavir-boosted regimen. Eighteen patients (10.4%) had previous exposure to ADV prior to TDF-initiation.

Renal function at initiation of TDF-containing ART

A total of 115 (65.7%) patients had normal baseline renal function, while 57 (32.6%) and 3 (1.7%) patients had mild and moderate renal impairment, respectively. No patient had a previous kidney-related condition. Table 1 presents baseline characteristics of the study population, stratified on normal (>90 mL/min per 1.73m²) or impaired (≤90 mL/min per 1.73m²) renal function. Patients with renal impairment were significantly older, more likely to have CVD,

previous exposure to zalcitabine and ADV, concomitant PI-use, and less likely to have detectable HBV-DNA.

Follow-up and changes in estimated glomerular filtration rate

Patients were followed for a median 58.3 months (IQR=33.7-92.1), amounting to 9931.4 person·months of follow-up. During this period, the percentage of patients with undetectable HBV-DNA increased dramatically (from 20.1% at baseline to 83.4% by the end of follow-up, $P<0.001$). Meanwhile, improvements in both CD4+ cell counts (median 402/mm^3 at baseline to 506/mm^3 at end of follow-up, $P<0.001$) and increases in the proportion of patients with undetectable HIV-RNA (from 58.1% to 86.3% at end of follow-up, $P<0.001$) were observed.

During follow-up, average monthly decrease of eGFR was -0.14 min/mL per 1.73m^2 (95%CI=-0.16, -0.12). As shown in Figure 2A, average decreases in eGFR were stronger among patients with baseline eGFR >90 (monthly ΔeGFR=-0.16 min/mL per 1.73m^2) compared to those with baseline eGFR ≤90 (monthly ΔeGFR=-0.10 min/mL per 1.73m^2, *P* for interaction=0.002).

Table 2 reports stratum-specific estimates of ΔeGFR on a number of HIV- and HBV-related determinants. In multivariable analysis, significantly greater declines in eGFR were observed in patients who had a previous AIDS-defining illness at baseline, had >5 years of previous ART, were undergoing a PI-containing ART regimen during follow-up, and had liver cirrhosis at baseline.

Evolution of renal impairment during TDF-containing ART

As shown in Figure 2B, the proportion of patients with renal impairment increased significantly during follow-up (*P* for trend<0.001). Of note, no patient developed severe renal impairment or kidney failure.

In patients with normal renal function at baseline, 78/115 (67.8%) had normal function, 35/115 (30.4%) had mild impairment, and 2/115 (1.7%) had moderate impairment at the end of follow-up. Of those ending follow-up with normal function, 27/78 (34.6%) transiently developed mild renal impairment during treatment. Mild and moderate renal impairment occurred after a median 14.7 (IQR=7.0-34.8) and 78.6 (range=27.8-90.1) months after TDF-initiation (IR=20.3 and 0.7/100 person·years), respectively. In multivariable analysis (Table 3), significant risk-factors from normal to impaired renal function were increased age and previous AIDS-defining illness at baseline. Undetectable HBV-DNA VL during treatment was also a significant protective factor against renal impairment.

In patients with renal impairment, 15/60 (25.0%) had normal function, 35/60 (58.3%) had mild impairment, and 10/60 (16.7%) had moderate impairment at the end of follow-up. Of those ending follow-up with renal impairment, 11/45 (24.4%) temporarily regained normal renal function during treatment. Median time to normal renal function was 16.3 (IQR=8.9-23.4) months after TDF-initiation (IR=13.1/100 person·years). In multivariable analysis (Table 3), increased age, female gender, presenting with CVD, and undetectable HBV-DNA during follow-up were found to significantly prevent improvement to normal renal function.

Treatment discontinuation and renal safety

Overall, 17 patients discontinued TDF-treatment after a median 26.8 months (IQR=11.0-35.5) of follow-up. Reasons for treatment discontinuation were as follows: nephrotoxicity (*n*=6), switched

treatment due to HIV-resistance (*n*=2), poor adherence (*n*=2), hyperlactatemia (*n*=1), lipid abnormality (*n*=1), pregnancy (*n*=1), nevirapine-associated Lyell's syndrome (*n*=1), possible drug-drug interaction with another antiretroviral agent (*n*=1), patient's decision (*n*=1), and treatment simplification (*n*=1). Ten patients (58.8%) were able to reinitiate TDF a median 9.0 months (IQR=4.2-29.6) after discontinuation, one of whom had suspected renal toxicity.

At baseline, no significant differences in median baseline eGFR were observed between patients continuing versus discontinuing TDF-treatment (95.4 versus 98.0 min/mL per 1.73m², respectively, *P*=0.9), yet baseline eGFR was much lower among patients discontinuing due to nephrotoxicity (82.0 min/mL per 1.73m², *P*=0.08). Patients who discontinued TDF had a much steeper monthly mean ΔeGFR compared to the overall study population (-0.30 min/mL per 1.73m²; 95%CI=-0.41, -0.18). When patients discontinued TDF, a modest increase in eGFR per month was observed (0.08 min/mL per 1.73m²; 95%CI=-0.04, 0.20), yet this increase was not significant (*P*=0.2).

Renal-related events and overall mortality

Thirteen renal events occurred after a median 47.1 months (IQR=31.5-62.1) of follow-up, giving an IR at 1.6/100 person·years. Events were identified as follows: acute renal failure (*n*=6), Fanconi syndrome (*n*=1), unspecified nephritic syndrome (*n*=1), acute tubule-interstitial nephritis (*n*=1), end-stage kidney disease (*n*=1), kidney cyst (*n*=1), other kidney disorder (*n*=2). No patients developed hepatorenal syndrome while undergoing TDF-containing ART. Three patients died during follow-up, none had any underlying kidney-related disease.

DISCUSSION

In this large prospective cohort, we provide some of the most extensive data to date on renal function and kidney-related outcomes in TDF-treated patients co-infected with HIV and HBV. After TDF-initiation, modest and steady changes of -1.72 min/mL per 1.73m^2 were observed each year. These values fell strongly in line with other cohorts of TDF-treated individuals who were predominately HIV mono-infected (approximate yearly rates of eGFR decline ranging from -8.0 to -0.7 min/mL per 1.73m²) [12,20–24], HBV mono-infected (-2.9 to 0.6 min/mL per 1.73m²) [8,12,21], or even non-HIV/HBV infected undergoing pre-exposure prophylaxis (-2.3 to 0.1 min/mL per 1.73m²).[25,26] At the end of follow-up, renal impairment was present in almost half of included patients and eGFR under 60 min/mL per 1.73m², levels highly associated with CVD and overall morbidity [18], was found in 6% of the study population.

It should be stressed that our study population, compared to others, comprised almost exclusively ART-experienced patients. ART clearly influenced baseline renal impairment, specifically with prior exposure to zalcitabine and PIs, while longer duration of ART at baseline was strongly linked to faster declines of eGFR. Heightened concern for kidney damage would likely extend to co-infected patients with long-term ART, especially as they initiate treatment with TDF. In addition, because of previous ART-exposure, almost all patients had undetectable HIV-RNA viral loads at TDF-initiation or early-on during treatment and most improvements in CD4+ cell counts had already occurred prior to TDF-initiation.[13] Any effect of decreasing HIV-RNA viral load or immunoreconstitution on renal function [19,24,27] would have probably been masked.

Nevertheless, we did observe two main HIV-related determinants affecting kidney function in this study population. First, PI-containing ART was associated with much larger decreases in eGFR, as previously reported in HIV mono-infected patients.[23] Although the mechanism for kidney

damage induced by combination PI and TDF is uncertain, previous research has pointed towards the inhibition of TDF excretion in the kidney with specific PIs, in particular ones boosted with ritonavir.[28] TDF accumulates in the epithelial tubular cells as a result, where TDF-associated mitochondrial toxicity induces tubular necrosis and further reduces kidney function. Second, previous AIDS-defining illness was significantly associated with both faster eGFR declines and incident impaired renal function. Since nadir CD4+ cell count did not emerge as an independent determinant of renal impairment, it could be hypothesized that insult to kidney function in these patients was likely due to a combination of severe immunosuppression and opportunistic infections.[29]

With regards to HBV-related factors, HBV mono-infected patients with high levels of HBV-DNA replication have been shown to exhibit improvement in eGFR.[8] We similarly observed in HIV-HBV co-infection that controlled HBV-DNA replication was a protective factor against developing renal impairment, but only in patients with normal baseline renal function. For co-infected patients with renal impairment at TDF-initiation, having undetectable HBV-DNA in fact prevented improvement in renal function, which was a rather unexpected result. Patients with mild/moderate renal impairment were more likely to have undetectable HBV-DNA at baseline and perhaps those with detectable HBV-DNA during follow-up were more likely not to be adhering to TDF.[4] Patients continuing treatment with mild or moderate renal impairment could have had more consistent exposure to TDF and any expected benefit from HBV-DNA suppression would be overshadowed by their predisposed risk of decreased eGFR.[30]

Liver cirrhosis is also known to act on splanchnic arteriolar vasodilatation, resulting in systemic vascular resistance, central hypovoleamia, and activation of vasoconstrictor systems; all of which restrict renal blood flow and decrease glomerular filtration.[31] Cirrhotic HBV mono-infected patients, without previous anti-HBV therapy, have substantial decreases in liver fibrosis

during TDF-treatment[32,33] and hence liver fibrosis regression would likely translate into improvements in vasodilatation regulation, increased eGFR, and low risk of renal impairment [8,34] In contrast, cirrhotic patients in our cohort, largely pre-treated with lamivudine, had significantly faster declines of eGFR during TDF-containing ART, although they were not more likely to progress towards mild or moderate renal impairment. The discrepancy from HBV mono-infected patients could be explained in part by the slow or almost absent regression of liver fibrosis in TDF-treated co-infected patients.[35]

It remains uncertain how the effects of each infection, working individually or synergistically, influence renal function in HIV-HBV co-infection. Unfortunately, we did not have a similar cohort of HIV or HBV mono-infected patients to which our study population could have served as a comparator, yet some inference can be obtained from previous studies. In general, co-infected patients are not necessarily more likely to exhibit CKD or end-stage renal disease than HIV mono-infected patients while undergoing long-term ART.[5,30] With regards to exclusively TDF-treated populations, previous comparisons within the same catchment area have shown somewhat divergent results, while some describing much stronger declines in eGFR in HIV mono-infected patients [21] and others giving similar declines between co- versus mono-infected individuals.[12] In all of these studies, the distribution of HBV-associated liver disease, HIV-associated immunosuppression, and/or previous treatment experience were rather different across infection groups. Our findings shed light on the specific components of co-infection that need to be considered for these comparisons, namely the extent of HBV-suppression and liver cirrhosis coupled with previous AIDS-defining illnesses and ART duration.

Kidney-related events occurred at rate of 1.6/100 person·years. This rate was much higher compared to previous observations in either HIV or HBV mono-infected cohorts [30,36], assuming that information on these events were collected in a similar manner. The direct

implication of TDF-exposure is difficult to determine, with the exception of Fanconi syndrome, given the non-specific characterization of these events. Interestingly, only 10% of the overall study population discontinued TDF with one-third of the reasons attributed to kidney-related problems. This proportion is much higher among HIV-infected individuals from the UK-CHIC study, where roughly 25% of patients ended TDF-containing ART with two-thirds of discontinuations likely due to declines in eGFR.[37] It is surprising to observe such a difference given the similar levels and correlates of renal impairment between studies. However, co-infected patients do not have many options for potent antivirals with anti-HBV activity, steering physicians away from discontinuing TDF for concern over HBV reactivation. The novel pro-drug of tenofovir, tenofovir alafenamide (TAF), with anti-HBV and anti-HIV activity, has recently shown more favorable renal outcomes in HIV-HBV co-infected patients after switching from another ART regimen [38], and could provide an alternative treatment option in the future.

Other common adverse events in TDF-treated individuals include large decreases in bone mineral density (BMD) and bone fractures.[39] Indeed, previous data have shown a marginally increased risk of hip fractures in treated HIV-HBV co-infected patients compared to either mono-infection group, with an 8-year cumulative incidence of 2.5%.[40] It is worth noting that none of the patients in our cohort discontinued TDF due to osteoporosis, osteopenia, or bone fracture. Without any data on BMD, the underlying reasons for these observed discrepancies are difficult to explain and should be further investigated.

Certain limitations of our study need to be addressed. First, the CKD-EPI equation provides an estimation of glomerular filtration rates and notwithstanding its ability to reduce measurement error compared its predecessor (the “Modified Diet in Renal Disease” equation), GFR could still be underestimated specifically for those with mild renal impairment.[17] We also did not analyze other parameters of tubular dysfunction to complement results on eGFR. Second, black race,

an important risk-factor for chronic kidney disease, was not recorded in our study and country of origin was used instead. Some additional measurement error in eGFR could have resulted. Third, drop out during the study could be considered high in comparison to other large cohort studies; however, most patients ended follow-up due to the completion of the French HIV-HBV cohort. We did compare baseline characteristics between patients completing versus lost to follow-up, demonstrating no differences that would indicate a specific clinical reason for terminating study participation (data not shown). Nevertheless, residual bias as a result of differential loss to follow-up cannot be fully ruled out. Finally, regression to the mean could partly explain the greater decline in eGFRs observed in those with higher baseline levels, and the small numbers of patients in the analysis on improved renal function could have affected the power to establish certain risk-factors, while the resulting multivariable model could have been overfit (i.e. change in variance estimations when including gender as a risk-factor).

In conclusion, decreases in eGFR are frequently observed among HIV-HBV co-infected patients undergoing TDF-containing ART, especially with longer periods of previous antiretroviral exposure, while declines in renal function are strongly linked to the consequences of severe HIV and/or HBV disease. Despite the large proportion of patients ending follow-up with only mild or, to a much lesser extent, moderate renal impairment, these levels indicate increased risk for kidney disease progression. Patients exhibiting the HBV-specific risk-factors identified herein have no recommendation for increased monitoring in current CKD surveillance guidelines [7], and hence their inclusion should be paramount for future versions. Other therapeutic options with dual HIV/HBV activity and less nephrotoxic effects, such as TAF, should be considered for those at risk of worsening kidney function.

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TABLES

Table 1. Description of the study population at baseline

	Total (*n*=175)	Baseline creatinine clearance >90 mL/min/1.73m² (*n*=115)	Baseline creatinine clearance ≤90 mL/min/1.73m² (*n*=60)	*P*[†]
Demographics				
Sex ratio, males/females (% males)	149/26 (85.1)	97/18 (84.4)	52/8 (86.7)	0.7
Age, years*	41 (36-48)	40 (34-44)	44 (41-52)	0.0001
BMI, kg/m²* [N=168]	22.3 (20.9-24.5)	22.3 (20.9-24.2)	22.5 (20.7-24.7)	0.8
Born in Sub-Saharan Africa**	43 (24.6)	31 (27.0)	12 (20.0)	0.4
Cardiovascular disease**	27 (15.4)	12 (10.4)	15 (25.0)	0.01
Diabetes**	4 (2.3)	2 (1.7)	2 (3.3)	0.6
Intravenous drug-user**	4 (2.3)	2 (1.7)	2 (3.3)	0.6
HIV-related characteristics				
Years of known HIV infection*	10.9 (6.0-14.7)	10.6 (5.5-13.7)	12.6 (7.8-15.0)	0.11
Previous AIDS-defining illness**	49 (28.0)	28 (24.4)	21 (35.0)	0.14
CD4+, /mm^3** [N=174]				0.6
≥500	64 (36.8)	39 (34.2)	25 (41.7)	
≥350 and <500	47 (27.0)	33 (29.0)	14 (23.3)	
<350	63 (36.2)	42 (36.8)	21 (35.0)	
Nadir CD4+ <200/mm^3** [N=159]	72 (45.3)	46 (43.4)	26 (49.1)	0.5
Undetectable HIV-RNA** [N=174]	101 (58.1)	67 (58.3)	34 (57.6)	0.9
HIV-RNA, $\log_{10}$ copies/mL*[††]	4.02 (2.86-4.59)	4.08 (3.25-4.66)	3.43 (2.54-4.38)	0.2
ART-naïve**	2 (1.1)	1 (0.9)	1 (1.7)	0.9
Duration of ART, years*[‡]	6.9 (4.1-9.2)	6.5 (3.7-8.8)	7.4 (5.2-9.2)	0.09
Prior antiretroviral treatment**[‡]				
Zalcitabine	46 (26.6)	20 (17.5)	26 (44.1)	<0.001
Stavudine	108 (62.4)	66 (57.9)	42 (71.2)	0.09
Didanosine	103 (59.5)	71 (62.3)	32 (54.2)	0.3
Indinavir	78 (45.1)	46 (40.4)	32 (54.2)	0.08
Concomitant PI-use**	96 (54.9)	56 (48.7)	40 (66.7)	0.02
Atazanavir	14 (8.0)	9 (7.8)	5 (8.3)	0.9
Ritonavir-boosted PI	85 (48.6)	53 (46.1)	32 (53.3)	0.4
HBV-related characteristics				
Undetectable HBV-DNA**	35 (20.1)	18 (15.7)	17 (28.8)	0.04
HBV-DNA, $\log_{10}$ IU/mL*[††]	5.02 (2.94-6.88)	5.28 (2.95-7.24)	4.59 (2.94-6.58)	0.2
HBeAg-positive**	107 (61.1)	71 (61.7)	36 (60.0)	0.9
Previous LAM-exposure**[‡]	153 (88.4)	98 (86.0)	55 (93.2)	0.2
Cumulative LAM, months*[‡‡]	57.3 (33.1-79.1)	55.5 (31.8-75.9)	65.4 (36.7-81.5)	0.3
Previous ADV-exposure**[‡]	18 (10.4)	8 (7.0)	10 (17.0)	0.04
Cumulative ADV, months*[‡‡]	17.4 (10.4-30.3)	16.5 (10.4-27.5)	21.2 (10.4-33.3)	0.9
Concomitant LAM/FTC-treatment**	125 (71.4)	81 (70.4)	44 (73.3)	0.7
F4 fibrosis**	35 (20.0)	21 (18.3)	14 (23.3)	0.4
LAM-resistance [N=107]	71 (66.4)	46 (63.9)	25 (71.4)	0.4
ADV-resistance [N=25]	1 (4.0)	0 (0)	1 (11.1)	0.4
ALT, IU/mL* [N=172]	44 (28-74)	45 (29-83)	37 (27-68)	0.19
AST, IU/mL* [N=172]	37 (26-60)	38 (25-59)	34 (26-60)	0.9

[*] Median (IQR). [**] Number (%). [†] Significance between treatment groups determined using Kruskal-Wallis test for continuous variables and Pearson χ^2 test or Fisher's exact test for categorical variables.

[††] Only among patients with detectable HIV or HBV viral loads. [‡] Among ART-experienced patients.
[‡‡] Only among patients with previous LAM or ADV exposure.

Table 2. Determinants of change in estimated glomerular filtration rate (eGFR) from baseline

		Univariable		Multivariable**	
	*n**	Δ mL/min/1.73m² per month (95% CI)	*P* for intx	Δ mL/min/1.73m² per month (95% CI)	*P* for intx
Baseline factors					
Previous AIDS-defining illness			0.02		0.03
No	126	-0.13 (-0.15, -0.10)		-0.13 (-0.15, -0.11)	
Yes	49	-0.18 (-0.21, -0.14)		-0.18 (-0.21, -0.14)	
CD4+ cell count			0.11		
≥500/mm^3	64	-0.16 (-0.19, -0.13)			
≥350 and <500/mm^3	47	-0.14 (-0.19, -0.10)			
<350/mm^3	63	-0.12 (-0.15, -0.10)			
Nadir CD4+ cell count			0.2		
≥350/mm^3	34	-0.13 (-0.17, -0.09)			
≥200 and <350/mm^3	53	-0.13 (-0.17, -0.09)			
<200/mm^3	72	-0.16 (-0.19, -0.13)			
ART duration			0.06		0.06
≤5 years	55	-0.05 (-0.16, 0.07)		-0.03 (-0.15, 0.08)	
>5 years	120	-0.15 (-0.17, -0.13)		-0.14 (-0.17, -0.12)	
HBeAg-status			0.5		
Negative	68	-0.15 (-0.19, -0.12)			
Positive	107	-0.14 (-0.16, -0.11)			
Baseline ALT			0.3		
<1× ULN	62	-0.13 (-0.16, -0.09)			
1-2× ULN	64	-0.16 (-0.19, -0.13)			
>2× ULN	46	-0.15 (-0.19, -0.12)			
Liver fibrosis levels			0.02		0.03
F0-F1-F2-F3	140	-0.13 (-0.15, -0.11)		-0.13 (-0.15, -0.11)	
F4	35	-0.18 (-0.22, -0.14)		-0.18 (-0.22, -0.14)	
Prior adefovir-exposure			0.10		
≤1 year	164	-0.15 (-0.16, -0.13)			
>1 year	11	-0.08 (-0.16, -0.01)			
Factors during follow-up†					
HIV-RNA viral load			0.5		
≥50 copies/mL	73	-0.12 (-0.18, -0.07)			
<50 copies/mL	101	-0.14 (-0.17, -0.12)			
PI-containing ART			0.001		0.005
No	79	-0.09 (-0.12, -0.06)		-0.11 (-0.14, -0.07)	
Yes	96	-0.16 (-0.18, -0.13)		-0.16 (-0.19, -0.14)	
HBV-DNA viral load			0.4		
≥2000 IU/mL	91	-0.09 (-0.17, -0.01)			
≥60 IU/mL and 2000 IU/mL	49	-0.16 (-0.23, -0.08)			
<60 IU/mL	35	-0.15 (-0.17, -0.12)			

*Numbers of patients for each stratum. If a variable was treated as time-varying, the distribution at baseline was given.

**Model adjusted for age, gender, born in Sub-Saharan Africa, baseline eGFR, AIDS-defining illness, duration of ART (>5 years), concomitant protease inhibitor use, and liver cirrhosis.

[†]Using random-coefficient and intercept with unstructured variance-covariance structure of the random effects.

Table 3. Determinants from normal renal function to renal impairment and *vice versa*

	Normal → Impaired (*N*=115)				Impaired → Normal (*N*=60)			
	Univariable		Multivariable**		Univariable		Multivariable**	
	HR (95%CI)	*P*	HR (95%CI)	*P*	HR (95%CI)	*P*	HR (95%CI)	*P*
Age at baseline (per year)	1.04 (1.00-1.08)	0.03	1.05 (1.01-1.09)	0.01	0.91 (0.87-0.96)	<0.001	0.92 (0.87-0.97)	0.002
Female gender	0.98 (0.48-1.99)	0.9	1.64 (0.56-4.83)	0.4	0.24 (0.03-1.71)	0.15	0.18 (0.04-0.79)	0.02
Born in Sub-Saharan Africa	0.85 (0.46-1.58)	0.6	0.98 (0.38-2.52)	0.9	0.60 (0.21-1.72)	0.3	0.63 (0.19-2.10)	0.5
Cardiovascular disease at baseline	1.40 (0.86-2.29)	0.18			0.25 (0.09-0.72)	0.01	0.32 (0.14-0.77)	0.01
Diabetes at baseline	3.26 (1.55-6.86)	0.002			--			
Previous AIDS-defining illness	1.79 (1.11-2.87)	0.02	1.75 (1.10-2.80)	0.02	1.63 (0.74-3.60)	0.2		
CD4+ ≥500/mm^3 at baseline	1.05 (0.62-1.78)	0.9			0.71 (0.33-1.56)	0.4		
CD4+ ≥500/mm^3 during follow-up*	0.81 (0.64-1.01)	0.07			1.16 (0.69-1.95)	0.6		
Nadir CD4+ ≥200/mm^3 at baseline	0.84 (0.52-1.37)	0.5			1.09 (0.48-2.48)	0.8		
HIV-RNA <50 copies/mL during follow-up	0.69 (0.37-1.28)	0.2			0.63 (0.27-1.42)	0.3		
ART duration (>5 years) at baseline	1.03 (0.51-2.10)	0.9			0.58 (0.19-1.77)	0.3		
PI-containing ART during follow-up*	1.02 (0.81-1.28)	0.9			0.93 (0.60-1.46)	0.8		
HBV-DNA at baseline								
<60 IU/mL	1.00				1.00			
60-1999 IU/mL	0.98 (0.42-2.29)	0.9			0.52 (0.16-1.75)	0.3		
≥2000 IU/mL	1.39 (0.62-3.08)	0.4			1.92 (0.83-4.46)	0.13		
HBV-DNA <60 IU/mL during follow-up	0.55 (0.31-0.98)	0.04	0.43 (0.24-0.79)	0.006	0.23 (0.10-0.53)	0.001	0.20 (0.08-0.49)	<0.001
HBeAg-positive status at baseline	1.20 (0.70-2.06)	0.5			2.25 (0.94-5.39)	0.07		
ALT >2× ULN at baseline	1.24 (0.75-2.07)	0.4			2.16 (0.86-5.39)	0.10		
F4 liver fibrosis at baseline	1.53 (0.93-2.51)	0.09			0.35 (0.10-1.17)	0.09		
ADV exposure >1 year at baseline	1.47 (0.69-3.12)	0.3			0.51 (0.16-1.64)	0.3		

*Modelled as a time-varying covariable. – Parameter estimate could not be obtained.

**For the normal to impaired model, the following variables were removed from the model because their corresponding *P*-values were no longer below the pre-specified threshold: diabetes (*P*=0.221), CD4+ ≥500/mm^3 during follow-up (*P*=0.195), and F4 liver fibrosis at baseline (*P*=0.924, respectively). For the impaired to normal model, HBeAg-positive status and F4 liver fibrosis at baseline were removed from the model because their corresponding *P*-values were no longer below the pre-specified threshold (*P*=0.770 and *P*=0.601, respectively).

FIGURE LEGENDS

Figure 1. Flow chart of the study population

Figure 2. Evolution of estimated glomerular filtration rate (eGFR) and level of renal impairment during treatment with tenofovir

Changes of eGFR during tenofovir (TDF) containing antiretroviral treatment are depicted in (**A**). Analysis is stratified on patients with normal (eGFR>90 mL/min per 1.73m²) or impaired (≤90 mL/min per 1.73m²) renal function at baseline. Individual levels of eGFR are represented in dots, while average eGFR levels during treatment are represented as fitted lines. In **(B)**, percentage of patients with normal, mild (60-89 mL/min per 1.73m²), and moderate (30-59 mL/min per 1.73m²) renal impairment are given at every yearly interval of TDF. Numbers of patients continuing follow-up at each time-point are provided at the bottom of the graph.

Figure 1.

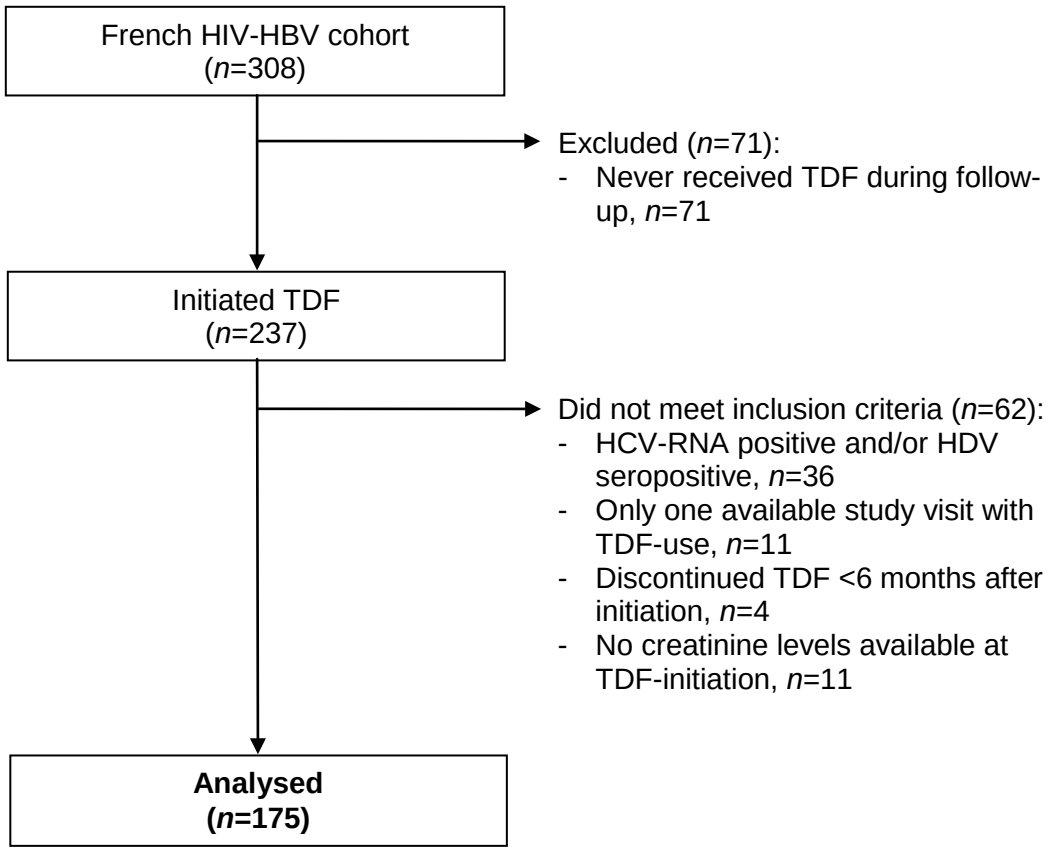
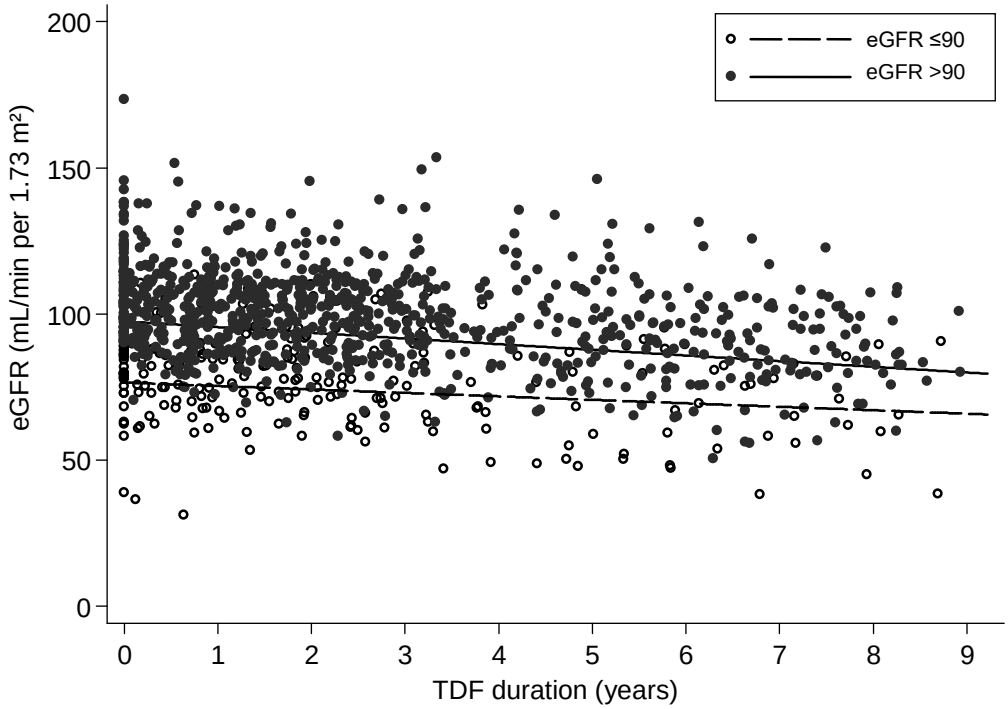
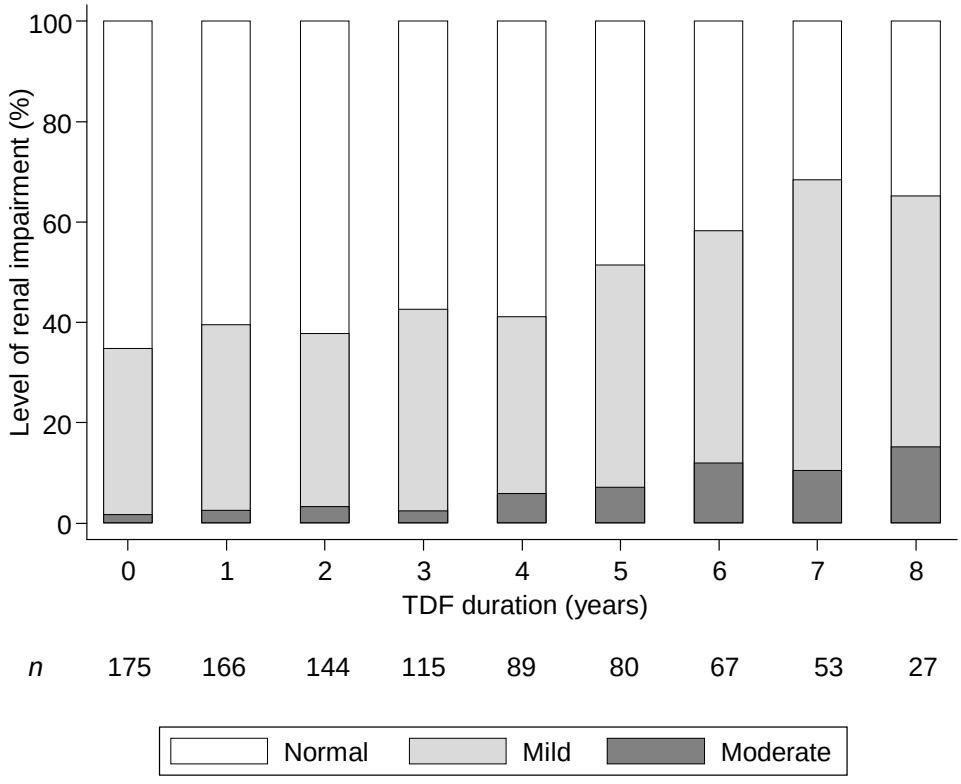

French HIV-HBV cohort
(*n*=308)
Excluded (*n*=71):
- Never received TDF during follow-up, *n*=71
Initiated TDF
(*n*=237)
Did not meet inclusion criteria (*n*=62):
- HCV-RNA positive and/or HDV seropositive, *n*=36
- Only one available study visit with TDF-use, *n*=11
- Discontinued TDF <6 months after initiation, *n*=4
- No creatinine levels available at TDF-initiation, *n*=11
Analysed
(*n*=175)

Figure 2.

A


eGFR ≤90
eGFR >90
eGFR (mL/min per 1.73 m²)
200
150
100
50
0
0 1 2 3 4 5 6 7 8 9
TDF duration (years)

B


Level of renal impairment (%)
100
80
60
40
20
0
0 1 2 3 4 5 6 7 8
TDF duration (years)
n 175 166 144 115 89 80 67 53 27
Normal
Mild
Moderate

Supplemental Table 1. Description of patients with and without tenofovir use in the French HIV-HBV cohort study

	Total (*n*=308)	Ever received therapy with TDF: No (*n*=71)	Ever received therapy with TDF: Yes (*n*=237)	*P*[†]
Demographics at inclusion				
Sex ratio, males/females (% males)	259/49 (84.1)	56/15 (78.9)	203/34 (14.4)	0.17
Age, years*	40 (35-45)	39 (32-43)	40 (35-45)	0.03
BMI, kg/m²* [N=291]	22.5 (21.0-24.2)	23.2 (21.1-25.8)	22.3 (20.9-23.9)	0.02
Born in Sub-Saharan Africa**	86 (27.9)	28 (39.4)	58 (24.5)	0.01
Cardiovascular disease**	35 (11.4)	9 (12.7)	26 (11.0)	0.7
Diabetes**	6 (2.0)	2 (2.8)	4 (1.7)	0.6
Intravenous drug-user**	23 (7.5)	6 (8.5)	17 (7.2)	0.7
HIV-related characteristics at inclusion				
Years of known HIV infection*	9.9 (3.6-14.0)	6.3 (2.1-12.6)	10.4 (4.9-14.3)	0.004
AIDS-defining illness**	79 (25.7)	12 (16.9)	67 (28.3)	0.05
CD4+, /mm^3** [N=307]				0.5
≥500	101 (32.9)	23 (32.4)	78 (33.1)	
≥350 and <500	84 (27.4)	23 (32.4)	61 (25.9)	
<350	122 (39.7)	25 (35.2)	97 (41.1)	
Nadir CD4+ <200/mm^3** [N=271]	147 (54.2)	35 (58.3)	112 (53.1)	0.5
Undetectable HIV-RNA** [N=307]	162 (52.8)	41 (57.8)	121 (51.3)	0.3
HIV-RNA, $\log_{10}$ copies/mL*[††]	3.90 (2.59-4.44)	4.00 (3.26-4.50)	3.74 (2.46-4.43)	0.2
ART-naïve**	30 (9.7)	13 (18.3)	17 (7.2)	0.005
Duration of ART, years*[‡]	5.6 (2.7-7.4)	3.7 (1.4-5.9)	6.0 (3.1-7.6)	<0.001
Prior antiretroviral treatment**[‡]				
Zalcitabine	67 (24.1)	9 (15.5)	58 (26.4)	0.09
Stavudine	170 (61.2)	28 (48.3)	142 (64.6)	0.02
Didanosine	159 (57.2)	30 (51.7)	129 (58.6)	0.3
Indinavir	121 (43.5)	17 (29.3)	104 (47.3)	0.01
Concomitant PI-use**	116 (37.7)	16 (22.5)	100 (42.2)	0.003
Atazanavir	1 (0.3)	0	1 (0.4)	0.9
Ritonavir-boosted PI	75 (24.4)	7 (9.9)	68 (28.7)	0.001
HBV-related characteristics at inclusion				
Undetectable HBV-DNA**	70 (22.8)	21 (29.6)	49 (20.8)	0.12
HBV-DNA, $\log_{10}$ IU/mL*[††]	4.26 (2.55-6.58)	2.88 (2.28-5.45)	4.40 (2.71-6.58)	0.005
HBV-DNA >2000 IU/mL**	136 (44.3)	21 (29.6)	115 (48.7)	0.004
HBeAg-positive**	160 (52.0)	24 (33.8)	136 (57.4)	<0.001
Previous LAM-exposure**[‡]	260 (93.5)	52 (89.7)	208 (94.6)	0.18
Cumulative LAM, months*[‡‡]	50 (24-70)	41 (15-63)	51 (27-70)	0.06
Previous ADV-exposure**[‡]	18 (6.5)	4 (6.9)	14 (6.4)	0.9
Cumulative ADV, months*[‡‡]	9 (5-10)	7 (4-15)	9 (5-10)	0.8
Concomitant LAM/FTC-treatment**	216 (70.1)	47 (66.2)	169 (71.3)	0.4
F4 fibrosis**	54 (17.7)	6 (8.5)	48 (20.4)	0.02
ALT, IU/mL* [N=301]	41 (25-74)	33 (24-47)	44 (27-88)	0.002
AST, IU/mL* [N=301]	37 (27-58)	34 (28-41)	39 (27-62)	0.07

Supplemental Table 1 (con't). Description of patients with and without tenofovir use in the French HIV-HBV cohort study

	Total (*n*=308)	Ever received therapy with TDF		*P*[†]
		No (*n*=71)	Yes (*n*=237)	
Renal function at inclusion				
Creatinine, µmol/L*	84 (74-95)	85 (72-93)	84 (74-95)	0.7
eGFR, mL/min/1.73m²*	98.7 (87.3-110.7)	103.1 (87.8-116.7)	97.8 (86.6-109.6)	0.10
eGFR**				0.3
≥90 mL/min/1.73m²	216 (70.8)	51 (72.9)	165 (70.2)	
60-89 mL/min/1.73m²	83 (27.2)	17 (24.3)	66 (28.1)	
30-59 mL/min/1.73m²	5 (1.6)	1 (1.4)	4 (1.7)	
<30 mL/min/1.73m²	1 (0.3)	1 (1.4)	0 (0)	
Baseline renal-related event**[¶]	3 (1.0)	1 (1.4)	2 (0.8)	0.5
Renal function during follow-up				
Median follow-up time, years*	7.2 (3.0-8.0)	3.1 (2.4-6.3)	7.6 (3.3-8.1)	<0.001
Last eGFR measurement [N=300]				0.03
≥90 mL/min/1.73m²	165 (55.0)	44 (66.7)	121 (51.7)	
60-89 mL/min/1.73m²	112 (37.3)	18 (27.3)	94 (40.2)	
30-59 mL/min/1.73m²	22 (7.3)	3 (4.6)	19 (8.1)	
<30 mL/min/1.73m²	1 (0.3)	1 (1.5)	0 (0)	
Renal-related event**[¶] [N=292]	22 (7.5)	3 (4.8)	19 (8.3)	0.9

[*] Median (IQR). [**] Number (%). [†] Significance between treatment groups determined using Kruskal-Wallis test for continuous variables and Pearson χ^2 test or Fisher's exact test for categorical variables.
[††] Only among patients with detectable HIV or HBV viral loads. [‡] Among ART-experienced patients.
[‡‡] Only among patients with previous LAM or ADV exposure. [¶] Defined as having any one of the following events: renal syndrome, acute or chronic tubule-interstitial nephritis, acute renal failure, end-stage kidney disease, Fanconi syndrome, kidney cyst, unspecified nephritic syndrome, or other kidney disorder.