Effect of viral replication and liver fibrosis on all-cause mortality in HIV/HBV coinfected individuals: a retrospective analysis of a 15-year longitudinal cohort

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Running title: Viral loads and mortality in HIV/HBV

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Key-points: Both current and cumulative HBV-DNA levels over time increased the risk of all-cause mortality in HIV-HBV co-infected individuals. Fibrosis was a major determinant of mortality; however, the leading causes of death were mostly extra-hepatic and non-AIDS related.

Abstract

Background

In individuals co-infected with HIV and hepatitis B virus (HBV), widespread tenofovir (TDF)-containing antiretroviral therapy (ART) has led to substantial decreases in HBV-DNA and HIV-RNA detection. However, the link between viral replication, liver fibrosis, and mortality remains unclear.

Methods

300 HIV-HBV co-infected individuals undergoing ART were prospectively followed. Virological and clinical data were obtained at baseline and every 6-12 months. We quantified the association between HBV-DNA, HIV-RNA, and liver fibrosis with risk of all-cause mortality using a joint longitudinal-survival model. Viral detection, viral loads, and time-averaged cumulative viral loads of HIV and HBV were modeled as three separate exposures.

Results

During a median 10.5 years (IQR=4.0-14.6), the proportion undergoing TDF-containing ART (baseline=18.7%, end of follow-up=79.1%) and with undetectable HBV-DNA (baseline=36.7%, end of follow-up=94.8%) substantially increased. HIV-RNA was mostly undetectable during follow-up (76.6%). 42 participants died (incidence rate=1.30/100person-years, 95%CI=0.96-1.76). The leading causes of death were non-AIDS/non-liver-related malignancies (28.6%), followed by liver-related (16.7%), AIDS-related (16.7%), and other (16.7%). All-cause mortality was associated with HBV-DNA viral load (adjusted-HR per $\log_{10}$IU/mL=1.41, 95%CI=1.04-1.93, *p*=0.03) or time-averaged cumulative HBV-DNA (adjusted-HR per $\log_{10}$IU-years=1.37, 95%CI=1.03-1.83, *p*=0.03), but not undetectable HBV-DNA (adjusted-HR=0.30, 95%CI=0.08-1.09, *p*=0.08). Advanced liver fibrosis at baseline was also associated with increased mortality rates (adjusted-HR=2.35, 95%CI=1.16-4.76, p=0.02). No significant association between HIV-RNA replication and mortality was observed.

Conclusions

Concurrent and historical HBV replication and liver fibrosis are important drivers of all-cause mortality in largely TDF-treated HIV-HBV co-infected individuals, despite one-fifth of deaths being

liver-related. HBV-DNA and liver fibrosis remain important prognostic indicators for this patient population.

Key-words: hepatitis B virus, HIV, mortality, tenofovir, joint models

Introduction

Roughly 8% of individuals living with human immunodeficiency virus (HIV) are chronically co-infected with hepatitis B virus (HBV) [1]. Without effective treatment, HIV-HBV co-infected individuals are at increased risk of liver-related and all-cause mortality when compared to HIV-positive individuals without HBV infection [2].

Treating co-infected individuals primarily involves controlling both HIV and HBV replication. Higher levels of serum HIV-RNA have been associated with increased risk of AIDS-related morbidity and mortality in HIV-positive individuals [3]. With effective antiretroviral therapy (ART), HIV replication is suppressed and the risk of HIV-related morbidity and mortality greatly decreases [4,5]. Likewise, higher levels of circulating HBV-DNA have been linked to fibrosis, hepatocellular carcinoma (HCC), and liver-related and overall death in HBV mono-infected individuals [6–8]. Currently available nucleoside/nucleotide analogues (NA) can suppress HBV-DNA replication, which coincides with liver fibrosis regression [9] and reduced risk of HCC [10]. Conveniently, some antiretroviral agents, such as tenofovir (TDF) and tenofovir alafenamide (TAF), possess potent anti-HIV and anti-HBV activity [11,12], and are thus ideal therapeutic options for HIV-HBV co-infected individuals [13]. It could be hypothesized that reductions in HIV and HBV replication would give way to lower incidence of both HIV- and HBV-related causes of morbidity and mortality.

Nevertheless, epidemiological studies in co-infected populations are not entirely clear on the relationship between active replication of these viruses and mortality. Recent research has demonstrated clear reductions in AIDS-related, liver-related and overall mortality in the years coinciding with widespread TDF-use [9,14]. However, incidence of HCC in TDF-treated co-infected individuals above the age of 45 remains high enough to warrant increased HCC screening [15]. Furthermore, large studies from Tanzania and Côte d'Ivoire have shown that HIV-HBV co-infected individuals, particularly when their HBV-DNA levels are high, are still at increased risk of overall

mortality despite TDF-containing ART [16,17]. The principal causes of death in these studies seem related to HIV-related illness or invasive bacterial infections. The common limitation shared across the studies conducted thus far is the lack of consistently collected data on both HIV- and HBV-replication.

The aim of the present study was then to describe detailed causes of mortality in a cohort of HIV-HBV co-infected individuals followed for up to 15 years with highly effective anti-HIV and anti-HBV treatment. We further develop our analysis by exploring the effect of HBV-DNA and HIV-RNA replication over time and liver fibrosis on all-cause mortality in this study population.

Methods

Study population

We analyzed HIV-HBV co-infected participants of the French HIV-HBV Cohort Study. Briefly, this was a closed, longitudinal cohort study including 308 HIV-positive patients with chronic HBV infection from four centers located in Paris and Lyon, France. Individuals were included if they had an HIV-positive serological result confirmed by western blot and HBsAg-positive serological results for >6 months. Participants were recruited in 2002-2003 and followed every 6-12 months until 2017-2018. The cohort design and procedures are described elsewhere [18]. For this analysis, we included participants who had at least two consecutive visits and available information on vital status.

All individuals provided written informed consent to participate in the study and the protocol was approved by a Hospital Ethics Committee (Paris, France) in accordance with the Helsinki Declaration.

Data collection

Demographic information was collected at study inclusion. Medical history on antiretroviral and anti-HBV treatments, alcohol consumption and the presence of comorbidities, including diabetes,

cardiovascular disease (CVD), renal and other liver diseases, were collected at study entry and at each follow-up visit.

Laboratory data were collected at study entry and at each follow-up visit. Commercial polymerase chain reaction (PCR)-based assays were used to quantify HBV-DNA viral load (VL; COBAS AmpliPrep/COBAS TaqMan; detection limit=12 or 38 IU/mL; COBAS Amplicor; detection limit=60 IU/mL; Roche Diagnostic Systems, Meylan, France). We defined undetectable HBV-DNA at the highest threshold (<60 IU/mL). HIV-RNA VL was measured using a commercial PCR-based assay and $CD4^+$ cell count using standard methods. Antibodies to hepatitis C virus (HCV) and hepatitis D virus (HDV) were measured with an ELISA-based assay and if positive, serum HCV-RNA and/or HDV-RNA was quantified by either commercial PCR-based assay (for HCV-RNA) or in-house assay (for HDV-RNA).

Liver fibrosis was assessed at study entry and each yearly interval using the FibroTest® [19]. METAVIR equivalents for HIV-HBV coinfected individuals were used to grade liver fibrosis (F2=0.48-0.58, F3=0.59-0.73, F4≥0.74) [20].

Mortality outcome assessment

Deaths observed during follow-up, along with the underlying cause of death and date of death, were reported by the treating physician. To obtain vital status for individuals lost to follow-up (LTFU), a trusted third party (Inserm U1018) was requested to link data from the French HIV-HBV cohort to a national identification registry (*Répertoire national d'identification des personnes physiques*). For individuals reported as deceased, the cause of death was then obtained by a separate trusted third party (*Centre d'épidémiologie sur les causes médicales de décès*, CépiDc), linking data from the French HIV-HBV cohort to a national registry of death certificates and death notifications. Both registries are managed by the *Institut National de la Statistique et des Etudes Economiques*. Causes

of death were classified by ICD-10 codes. We recategorized causes of death as liver-related, AIDS-related, non-AIDS and non-liver-related malignancies, CVD-related, other, or unknown [5].

Statistical analysis

Baseline was defined as the date of study entry. Follow-up began at baseline and continued until the date of death or the last study visit.

We assessed treatment efficacy with undetectable HBV-DNA (<60 IU/mL) and HIV-RNA (<50 copies/mL) VLs. The extent of replication was assessed with HBV-DNA (log_{10} IU/mL) and HIV-RNA (log_{10} copies/mL) levels. Finally, the historical extent of replication was assessed with time-averaged, cumulative copy-years over follow-up time (log_{10} copy-years$_{TAVG}$), as detailed elsewhere [21].

To analyze the contribution of HIV and HBV replication on mortality during follow-up, we simultaneously modeled (i) HBV replication, (ii) HIV replication, and (iii) all-cause mortality. We carried out a generalized, multivariate, joint longitudinal-survival model approach by which the link between these outcomes could be taken into account. First, we ran two submodels (on HBV-DNA and HIV-RNA) for three separate sets of replication outcomes (detectable VL, log-transformed VL, and log_{10} copy-years$_{TAVG}$). The probability of having a detectable VL was assumed to be Bernoulli-distributed and modeled using logistic regression, while mean log-transformed VL and mean log_{10} copy-years$_{TAVG}$ were assumed to be continuous Poisson-distributed and modeled using Poisson regression. We adjusted, in the model regressing HBV-DNA, for HBeAg serostatus at baseline and cumulative tenofovir use (as a cubic-spline function using 4 knots) and, in the model regressing HIV-RNA, for squared $CD4^+$ cell count and HIV treatment era (2002-2007, ≥2008). Second, the hazards of death were assumed to have an exponential survival function and were estimated using a parametric survival model. We included the two submodels of HBV-DNA and HIV-RNA to estimate the hazards ratio (HR) and 95% confidence intervals (CI) of increasing expected probability of

detectable VL, expected mean log-transformed VL, or expected mean log_{10} copy-$years_{TAVG}$ on all-cause mortality. The survival model also included age, previous history of an AIDS-defining illness and level of fibrosis at study entry (F0-F1-F2 and F3-F4) as covariates, selected from the analysis described in the Supplementary Materials. We included a random-intercept across all models to account for between-patient variance at baseline, while the random-intercepts were constrained at 1 for the two submodels. Parameters from the three models were jointly estimated via maximum likelihood using the 'merlin' program in STATA [22].

All statistical analyses were performed using STATA (v15.1; College Station, Texas, USA). Significance was defined as a *p* value <0.05.

Results

Description of the study population

Of the 308 cohort participants, 8 were excluded (only one visit, *n*=7; no information on vital status, *n*=1). The 300 included participants were mostly male (84.0%), with a median age of 40 years (IQR=35-45) at study entry. Participants had a median CD4+ count of 400/mm^3 (IQR=268-557) and 160 (53.5%) had undetectable HIV-RNA. Participants were mostly HBeAg-positive (52.0%) and 63.3% (*n*=190/300) had detectable HBV-DNA. Of the 281 individuals (94.9%) with previous lamivudine (LAM) exposure, median LAM duration was 3.5 years (IQR=1.4-5.5) at study entry and 90 (32.0%) harbored LAM-resistant mutations.

Participants were followed for a median 10.5 years (IQR=4.0-14.6), totaling 2934.5 person-years. 111 (37.0%) were LTFU, including 41 with known vital status and 70 with unknown vital status. Individuals LTFU had a significantly higher median HBV-DNA (for those with detectable levels), ALT and AST levels at inclusion (supplementary table 2). The proportion of participants undergoing ART was high at study inclusion (90.0%) and increased to 100% from the first year until the end of follow-

up. Consequently, improvements in $CD4^+$ cell counts (*p* for trend <0.001) were observed over time (Figure 1A). In addition, the proportion of individuals undergoing TDF-based ART increased from 18.7% at baseline to 40.1% at the first year and 79.1% at the end of follow-up (Figure 1B, *p* for trend <0.001).

Description of all-cause mortality

42 deaths (cumulative incidence=14.0%; 95%CI=10.3%-18.4%) occurred after a median 6.2 years (IQR=3.4-7.9) of follow-up (incidence=1.43/100 person-years) 7 of these deaths were obtained through linkage.

The most common causes of death were non-AIDS/non-liver related malignancies (*n*=12 [28.6%]; 0.41/100 person-years), liver-related (*n*=7 [16.7%]; 0.24/100 person-years), AIDS-related (*n*=7 [16.7%]; 0.24/100 person-years) and CVD-related (*n*=6 [14.3%]; 0.20/100 person-years) (Table 1). HCC and hepatic failure accounted for most liver-related deaths (*n*=4 and 1, respectively). 7 individuals (16.7%; 0.24/100 person-years) died from others causes of death, while for three (7.0%), the cause of death was unknown.

At study entry, individuals who died, compared to those alive, were older (*p*<0.001), more likely to come from zones of low/moderate HBV-prevalence (*p*<0.004), have acquired HIV infection by injecting drug use (IDU) (*p*<0.02), have other liver diseases or hepatic decompensation (*p*=0.001), have an AIDS-defining event (*p*<0.001), have longer duration since first positive HIV test (*p*=0.01), lower nadir CD4+ cell counts (*p*=0.03), longer duration of ART (*p*=0.05), higher levels of AST (*p*=0.01), HBeAg-positive status (*p*=0.02), and F3-F4 fibrosis (*p*<0.001) (Table 2).

During follow-up, individuals who died, when compared to those alive, were more often diagnosed with HDV coinfection (p=0.01), had shorter duration of cumulative tenofovir use (p<0.001), lower CD4+ cell counts (p=0.001), and detectable HBV-DNA at last follow-up visit (p=0.03) (Table 2).

HBV and HIV viral replication and all-cause mortality

The average individual proportion of detectable HBV-DNA VL during follow-up was higher in deceased versus alive individuals (52.6%, 95%CI=25.0-77.8 versus 25.0%, 95%CI=6.7-58.8; respectively, p<0.003). When HBV-DNA was detectable, median levels were at 5646 IU/mL (IQR=446-3,802,281). Deceased individuals were exposed to a higher level of time-averaged copy-years of HBV-DNA ($\log_{10}$copy-years$_{TAVG}$) than those remaining alive (Figure 2) (overall p-value <0.001). Conversely, the average individual proportion of detectable HIV-RNA VL during follow-up was no different between alive and deceased individuals (15.4%, 95%CI=4.0-48.1 versus 10.0%, 95%CI=0.0-60.0, respectively, p=0.6). When HIV-RNA was detectable, median levels were at 232 copies/mL (IQR=3,159-22,972). Time-averaged copy-years of HIV-RNA was similarly low in both groups during follow-up (p=0.6, supplementary Figure S1).

When jointly modeling HBV and HIV replication on all-cause mortality, we found no significant associations with undetectable HBV-DNA on mortality rates (p=0.08, Table 3). However, we did observe a higher rate of all-cause mortality with higher expected mean log-transformed HBV-DNA VL (p=0.03) and cumulative time-averaged copy-years of HBV-DNA (p=0.03) after adjustment for age, AIDS-defining illness and F3-F4 fibrosis level at study entry (Table 3). F3-F4 fibrosis level at study entry was the only covariate consistently and significantly associated with overall mortality. No significant association was found between any of the HIV-RNA outcomes and all-cause mortality (Table 3).

Discussion

In this long-term, prospective study of treated HIV-HBV co-infected individuals, the most common cause of death observed in our study was non-AIDS/non-liver-related malignancies, representing approximately one-third of deaths. Coupled with the high proportion of deaths due to CVD, the spectrum of mortality causes in HIV-HBV co-infection would appear to mirror that of aging HIV-positive individuals in general [23]. Nevertheless, liver-related and AIDS-related causes together represented one-third of deaths, which occurred even during periods when use of TDF-containing ART and suppression of HIV-RNA and HBV-DNA were common at the population level.

Interestingly, the concurrent and historical extent of HBV viremia over time, but not HIV, seemed to play a major role in all-cause mortality. This effect was not observed when modeling undetectable HBV-DNA over time. Other studies in HIV-HBV co-infected individuals have shown an association between higher HBV-DNA at treatment initiation and all-cause mortality [17,24]. The curious part of this previous finding was that it was observed in the presence of almost exclusively TDF-treated individuals, with assumedly extensive HBV DNA suppression. Given the findings in our study, perhaps the historical exposure of high HBV DNA explained the increased risk in mortality in these studies despite effective anti-HIV and anti-HBV treatment.

Conversely, HIV-RNA had no effect on all-cause mortality in our study. This result was somewhat surprising considering the well-described effects of HIV replication on AIDS and non-AIDS-related death [25]. Although a high proportion of individuals had detectable HIV-RNA levels at inclusion, most were able to achieve HIV-RNA suppression early in the cohort study. Under these conditions, AIDS-related mortality is generally associated with the time spent at lower CD4+ cell counts [26,27], while most individuals in our cohort attained levels of CD4+ associated with reduced risk of both AIDS-related and overall mortality. The low overall proportion of AIDS-related deaths is also in accordance with findings from European cohorts of HIV-positive individuals [28]. When comparing HIV and HBV replication, there were comparable degrees of HIV-RNA suppression for individuals

who remained alive and died during follow-up, while HBV-DNA was more frequently detectable in deceased than alive individuals. These differences were similarly observed in historical exposure and perhaps drove HBV-DNA, rather than HIV-RNA, to contribute more towards overall mortality in our study.

The question is then what aspects of HBV-DNA replication are driving overall mortality. Naturally, immunological responses against prolonged HBV infection are responsible for liver-related disease [29], which partly explains the association between advanced liver fibrosis and all-cause mortality. Although liver fibrosis is mostly known to affect liver-related mortality (i.e. death due to HCC or end-stage liver disease), we observed few liver-related deaths. These results are rather surprising. Most individuals were undergoing TDF-containing ART and hence this study population represents those with well-controlled HBV-DNA replication. The risk of HCC would be reduced at these HBV-DNA levels [10]. Nevertheless, individuals with liver cirrhosis do have a high risk of death due to invasive bacterial pathogens [30] and many of the other causes of death in our cohort were related to bacteremia. Although effective anti-HBV treatment is expected to decrease fibrosis in HBV mono-infected individuals [31], fibrosis levels are mostly unchanged or can progress during TDF-based ART in co-infected individuals [32]. Continued risk of death due to this comorbidity should be elucidated in larger cohorts.

One intriguing finding was that certain extra-hepatic malignant tumors caused several deaths in this study population. In fact, 40% of the 20 individuals who died from cancer developed an extra-hepatic tumor (i.e. anal cancer, cholangiocarcinoma, pancreatic adenocarcinoma, and non-Hodgkin lymphoma [NHL]). Previous research has found that HBsAg-positive individuals with high-risk human papillomavirus had an increased risk of high-grade anal squamous intraepithelial lesions compared to those who were HBsAg-negative [33]. Furthermore, HBsAg-positive individuals exhibiting high levels of HBV activity (i.e. HBeAg-positivity and detectable HBV-DNA) have a significantly higher risk

311 of pancreatic carcinoma compared to HBsAg-negative individuals [34]. Finally, although NHL is
312 normally related to immunocompromised individuals and is classified as an AIDS-defining illness,
313 growing evidence suggests that ART-treated individuals with chronic HBV infection are at increased
314 risk for NHL [35]. How HBV activity participates in the tumorigenesis of extra-hepatic tumors is not
315 clearly understood.
316
317 Similar to others [36], HDV-co-infected individuals had a higher all-cause mortality rate.
318 Unfortunately, due to its close association with fibrosis, we decided not to include HDV-co-infection
319 in multivariable analysis. Of the 22 individuals in our cohort with HIV-HBV-HDV infection, 7 died.
320 Despite the fact that 6 of these deceased individuals had advanced liver fibrosis and at least one
321 liver-related complication, only one died from liver-related diseases. In contrast to others [36], only
322 one HCV-positive individual (without HDV) died in our cohort, which could be a reflection of the low
323 overall proportion of IDU (7.7%) and the increasingly effective direct acting antivirals available by the
324 end of follow-up [37]. Given the very few individuals with tri-/quad-infection who remained in
325 follow-up, generalizability of our data to this population would be limited.
326
327 Our study has certain limitations. First, the study population involves HIV-positive individuals with
328 extensive ART-experience and larger degrees of immunosuppression compared to contemporary
329 patient populations, but still actively seen in outpatient settings. Second, HBsAg-seroclearance has
330 been shown to reduce all-cause mortality in HBV mono-infected individuals [38], yet we had an
331 insufficient number of events to validate this in our cohort. Third, there was a rather high rate of
332 LTFU. Individuals who were LTFU had higher HBV DNA, ALT/AST, but not fibrosis levels at cohort
333 inclusion, suggesting a higher risk of more HBV activity. It is difficult to assess the direction of this
334 differential LTFU bias without knowing whether they were virally suppressed after being LTFU.
335 Fourth, we had limited to no data on HBV-DNA and HIV-RNA replication prior to inclusion, alcohol
336 use, smoking, treatment adherence, and metabolic diseases, all of which could not be considered in

analysis. We also used a non-invasive measure to assess liver fibrosis, which involves some error [20]; however, the FibroTest® does accurately predict liver fibrosis evolution [39] and overall survival [40] in individuals with chronic HBV infection. Finally, we did not have enough power to determine which causes of death were more associated with HBV-DNA replication.

In conclusion, our findings provide strong evidence that HIV-HBV co-infected individuals who have been exposed to higher levels of HBV-DNA over time are at elevated risk for all-cause mortality. The lack of association with HIV-RNA replication could be due to the more extensive viral suppression overall compared to HBV-DNA. Accompanied by the strong association between advanced liver fibrosis and overall mortality, monitoring liver fibrosis and HBV-DNA VL should be an essential component to help assess the prognosis of co-infected individuals. The noticeably common deaths due to extra-hepatic malignancies should be further studied and perhaps increased screening is called for in the HIV-HBV co-infected patient population.

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Potential conflicts of interest

None to declare.

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

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Table 1. Causes of death observed in the French HIV-HBV cohort, 2002-2018.

Cause of death	All periods (*N*=42)	2002-2007 (*N*=10)	2008-2018 (*N*=32)
Liver-related disease	7 (16.7%)	2	5
Hepatocellular carcinoma	4	1	3
Cholangiocarcinoma	1	0	1
Liver failure	2	1	1
AIDS-related disease	7 (16.7%)	2	5
Kaposi sarcoma	1	1	0
Burkitt lymphoma	1	0	1
Other non-Hodgkin's lymphoma	1	0	1
Progressive multifocal leukoencephalopathy	1	1	0
HIV-associated neurocognitive disorder	1	0	1
Opportunistic infections	2	0	2
Non-AIDS and non-liver-related malignancy	12 (28.6%)	0	12
Anal cancer	5	0	5
Colorectal cancer	1	0	1

Pancreatic cancer	1	0	1
Prostate cancer	1	0	1
Lung cancer	1	0	1
Chronic lymphocytic leukaemia	1	0	1
Cancer of unknown primary origin	2	0	2
Cardiovascular disease	6 (14.3%)	2	4
Stroke	4	1	3
Sudden cardiac arrest	2	1	1
Others	7 (16.7%)	3	4
Septic Shock	5*	2	3
Pneumonia	1	1	0
Empyema	1	0	1
Crohn's disease	1	1	0
Quadriplegia	1	0	1
Subdural hematoma	1	0	1
Suicide	1	1	0
Unknown	3 (7.0%)	1	2

*4 patients died from multiple causes: hepatocellular carcinoma and sepsis (*N*=1, considered as a liver-related death), non-Hodgkin's lymphoma and sepsis (*N*=1, considered as an AIDS-related death), prostate cancer and sepsis (*N*=1, considered as a non-AIDS and non-liver malignancy death), and empyema and sepsis (*N*=1, considered as a death related to other diseases).

Table 2. Characteristics of study population (at cohort inclusion or during follow-up)

Characteristics	Vital status		
	Alive (n=258)	Died (n=42)	$p^{\S}$
Demographics			
Gender, male/female (% male)	213/45 (83)	39/3 (93)	0.09
Age at baseline, years*	39.5 (34.5-43.7)	43.5 (38.0-53.2)	<0.001
From zone of high HBV-prevalence[†]	81 (31.4)	4 (9.5)	0.004
Mode of HIV transmission[†]			
Heterosexual	95 (36.8)	10 (23.8)	0.10
MSM	143 (55.4)	25 (59.5)	0.6
IDU	16 (6.2)	7 (16.7)	0.02
Other/Unknown	4 (1.6)	0 (0)	0.9
Clinical characteristics at study entry			
BMI, Kg/m^2 [*N* = 284]*	22.6 (21.0-24.3)	21.9 (20.6-23.5)	0.11
Alcohol consumption, glasses/day [*N* = 288]*	1 (0 – 2.7)	1 (0 – 2)	0.4
Comorbidities[†]			
Cardiovascular disease	28 (10.9)	6 (14.3)	0.5

Diabetes	5 (1.9)	0 (0)	0.4
Renal disease	6 (2.3)	0 (0)	0.3
Other liver diseases[¥]	5 (1.9)	5 (11.9)	0.001
HIV infection variables at study entry			
Time since first HIV-positive test, years [*N* = 299]*	9.4 (3.2-13.2)	13.1 (7.1-15.6)	0.01
AIDS-defining illness[†]	57 (22.1)	21 (50.0)	<0.001
HIV-RNA > 50 copies/mL[†]	125 (48.5)	14 (34.2)	0.09
HIV-RNA, $\log_{10}$ copies/mL [*N* = 139]*	3.9 (2.2.6-4.4)	3.8 (2.6-4.1)	0.7
$CD4^+$ cell count, cells/µL*	405 (277-577)	370 (249-474)	0.25
Nadir $CD4^+$ cell count, cells/µL [*N* = 268]*	223 (108-329)	128 (65-304)	0.03
Initiated ART[†]	230 (89.2)	40 (95.2)	0.22
Duration of ART, years [*N* = 270]*	5.5 (2.6-7.3)	6.7 (3.7-8.8)	0.05
Viral hepatitis at study entry			
Time since first HBsAg-positive test, years [*N* = 297]*	6.1 (2.2-10.6)	6.7 (2.3-13.5)	0.19
HBV-genotype [*N* = 165][†]			
A	84 (61.3)	17 (60.7)	0.9
D	12 (8.8)	4 (14.3)	0.4

E	18 (13.1)	1 (3.6)	0.15
G	21 (15.3)	6 (21.4)	0.4
HBeAg-positive[†]	127 (49.2)	29 (69.1)	0.02
HBV-DNA > 60 IU/mL [*N* = 299][†]	163 (63.2)	27 (65.9)	0.7
HBV-DNA, $\log_{10}$ IU/mL [*N* = 190]*	5.1 (3.0-6.9)	5.0 (2.8-7.1)	0.6
ALT level, IU/mL [*N* = 294]*	40 (24-72)	42 (31-67)	0.4
AST level, IU/mL [*N* = 294]*	36 (26-52)	51 (31-82)	0.01
Metavir F3-F4 fibrosis[†]			
Estimated using *Fibrotest*® [*N* = 298]	62 (24.1)	24 (58.5)	<0.001
Determined by liver biopsy [*N* = 138][#]	33 (28.7)	10 (41.7)	0.22
Metavir F4 fibrosis[†]			
Estimated using *Fibrotest*® [*N* = 298]	31 (12.1)	18 (43.9)	<0.001
Determined by liver biopsy [*N* = 138][#]	9 (7.9)	8 (33.3)	0.001
Cumulative lamivudine use at study entry, years*	2.95 (0.83-5.45)	4.22 (2.10-5.54)	0.09
Variables assessed during follow-up			
Follow-up time, years*	14.2 (4.8-14.7)	6.2 (3.4-7.9)	<0.001
Cumulative tenofovir use, years*	7.0 (2.1-12.6)	3.1 (1.5-5.4)	<0.001

Cumulative lamivudine use, years*	7.32 (3.31-9.92)	7.46 (0.08-9.71)	0.5
Cumulative HBV-DNA (log_{10}copy-$years_{TAVG}$) at last follow-up visit*	2.01 (1.81-2.58)	2.43 (1.92-3.24)	0.01
HBV-DNA <60 IU/mL at last follow-up visit[†]	220 (85.3)	30 (71.4)	0.03
Cumulative HIV-RNA (log_{10}copy-$years_{TAVG}$) at last follow-up visit*	1.79 (1.71-2.30)	1.75 (1.70-2.27)	0.6
HIV-RNA <50 copies/mL at last follow-up visit[†]	221 (85.7)	34 (80.1)	0.4
$CD4^+$ cell count at last follow-up visit, cells/µL*	524 (369-696)	423 (201-531)	0.001
Ever HCV coinfected[†ϕ]	23 (8.9)	3 (7.1)	0.7
Ever HDV coinfected[†ϕ]	15 (5.8)	7 (16.7)	0.01
HBeAg loss[‡]	72 (56.7)	13 (44.8)	0.25
HBsAg loss	27 (10.5)	3 (7.4)	0.8

*Median (IQR).

[†] Number (%).

[§] Significance determined using Kruskal-Wallis test for continuous variables and Pearson χ^2 test or Fisher exact test for categorical variables.

[¥]Other liver diseases or hepatic decompensation: acute, subacute or unspecified hepatic failure; hemorrhagic necrosis of liver; fatty liver disease; portal hypertension; and hepatocellular carcinoma.

[#] In a subgroup of 138 individuals, liver biopsies were performed within 12 months before or at study entry, based on concomitant guidelines from the European Association for the Study of the Liver. Histological fibrosis and activity were scored with the METAVIR classification.

[ϕ] Established by a positive ELISA-based assay for HCV or HDV, and confirmed by a positive PCR-based assay for HCV-RNA or HDV-RNA, respectively.

[‡]In 156 HBeAg-positive individuals.

Abbreviations: ALT, alanine aminotransferase; ART, antiretroviral therapy; AST, aspartate aminotransferase; BMI, body mass index; HBeAg, hepatitis B "e" antigen; HBV, hepatitis B virus; HIV, human immunodeficiency virus; IDU, injection drug use; MSM, men who have sex with men; TAVG; time-averaged.

Table 3. Association of HBV-DNA and HIV-RNA replication with all-cause mortality (joint models) [a]

Parameter	Model: treatment efficacy [b]		Model: extent of replication [c]		Model: historical extent of replication [d]	
	Risk estimate [e] (95% CI)	*p*	Risk estimate [e] (95% CI)	*p*	Risk estimate [e] (95% CI)	*p*
HBV replication	OR		RR		RR	
HBeAg at baseline	0.04 (0.03-0.05)	<0.001	1.88 (1.79-1.97)	<0.001	2.02 (1.93-2.11)	<0.001
HIV replication	OR		RR		RR	
CD4+ cell count ($\sqrt{}$/mm^3) [§]	1.10 (1.08-1.12)	<0.001	0.987 (0.984-0.991)	<0.001	0.988 (0.985-0.992)	<0.001
HIV treatment era from 2002 to 2007 [Φ]	0.14 (0.11-0.17)	<0.001	1.22 (1.17-1.27)	<0.001	1.16 (1.11-1.20)	<0.001
Time to all-cause mortality	HR		HR		HR	
Age[§]	1.06 (1.02-1.10)	0.001	1.06 (1.02-1.10)	0.004	1.05 (1.01-1.09)	0.007
AIDS-defining illness at baseline	1.97 (1.00-3.87)	0.05	1.83 (0.94-3.54)	0.07	1.92 (1.00-3.71)	0.05
F3-F4 fibrosis at baseline[#]	2.33 (1.16-4.70)	0.02	2.35 (1.16-4.76)	0.02	2.37 (1.17-4.81)	0.02
HBV replication[¥]	0.30 (0.08-1.09)	0.08	1.41 (1.04-1.93)	0.03	1.37 (1.03-1.83)	0.03

HIV replication[¥]	0.42 (0.02-10.53)	0.6	2.43 (0.45-13.05)	0.30	2.80 (0.49-15.85)	0.25

[a] Analysis included 298 individuals, 41 of whom were deceased. Two individuals were not considered in this analysis due to missing data for level of fibrosis at baseline; one of them died during study follow-up.

[b] HBV replication was measured as longitudinal HBV-DNA VL detectability (<60 IU/mL versus ≥60 IU/mL); whereas HIV replication as longitudinal HIV-RNA detectability (<50 copies/mL versus ≥50 copies/mL).

[c] HBV replication was measured as longitudinal HBV-DNA (per $\log_{10}$ IU/mL); whereas HIV replication as longitudinal HIV-RNA (per $\log_{10}$ copies/mL).

[d] HBV replication was measured as time-averaged cumulative HBV-DNA (per $\log_{10}$copy-years$_{TAVG}$); whereas HIV replication as cumulative HIV-RNA (per $\log_{10}$copy-years$_{TAVG}$).

[e] Risk estimates are additionally adjusted for the cumulative duration of tenofovir according to a spline function restricted by 4 knots (0.021, 3, 8 and 11.978 years).

[§] Time-updated covariate.

[ϕ] Variable included percentage of visits during two HIV treatment eras, 2002-2007 and ≥2008.

[#] Estimated using the Fibrotest®.

[¥] Expected value as estimated from the respective submodels (HBV replication and HIV replication) as outcomes.

Abbreviations: AIDS, acquired immunodeficiency syndrome; HBV, hepatitis B virus; HIV, human immunodeficiency virus; TAVG, time-averaged.

Figure legends

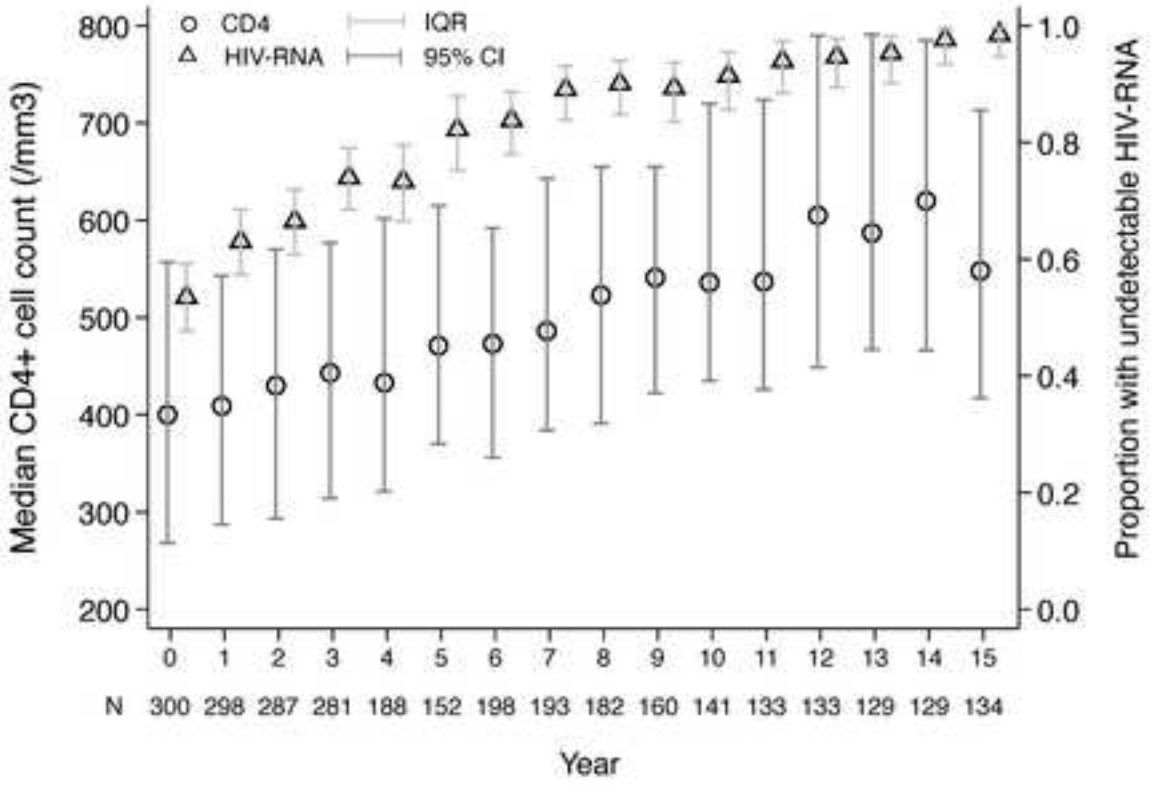
Figure 1. Evolution of HIV, hepatitis B virus (HBV), and antiviral treatment against hepatitis B virus over time.

The number of individuals continuing follow-up, as divided in yearly intervals, are provided at the bottom of each figure. In (A), undetectable HIV-RNA and median (IQR) CD4+ T-cell counts are displayed for each year. In (B), the proportion of individuals with undetectable HBV-DNA viral loads and the proportion undergoing antiviral therapy containing tenofovir are given for each year. Abbreviations: CI, confidence interval; HBV, hepatitis B virus; HIV, human immunodeficiency virus; IQR, interquartile range; TDF, tenofovir.

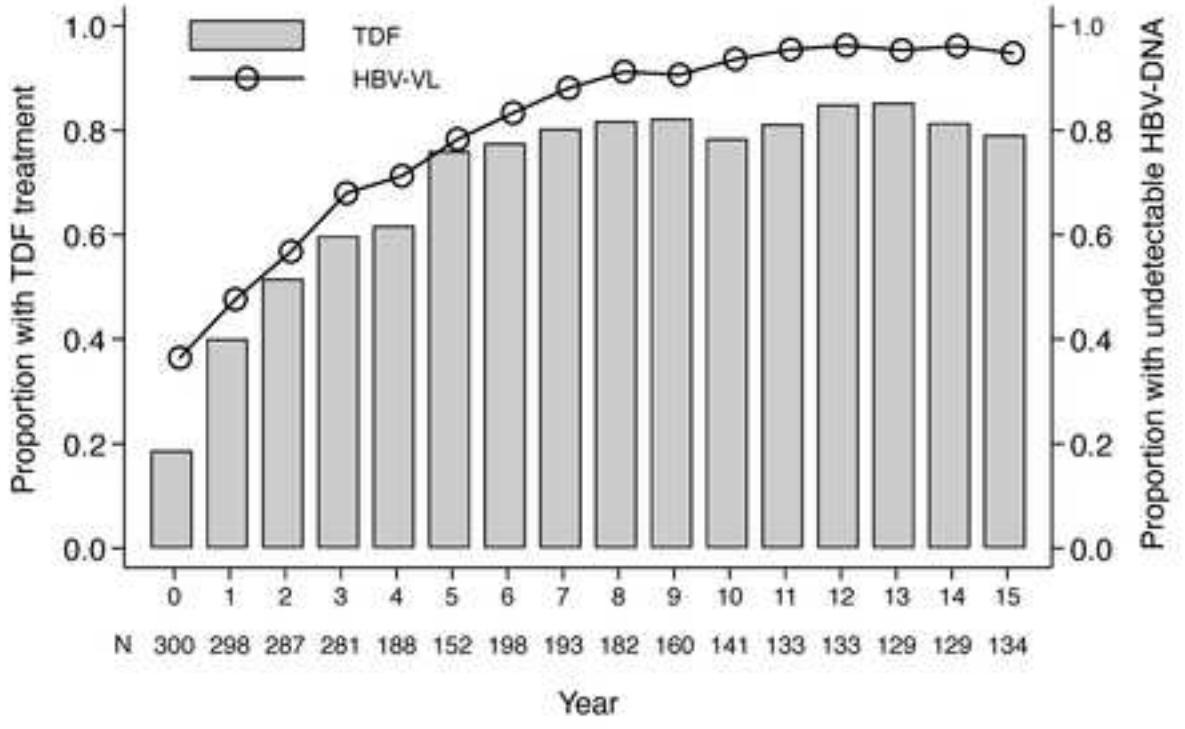
Figure 2. Evolution of the cumulative extent of viral replication over time

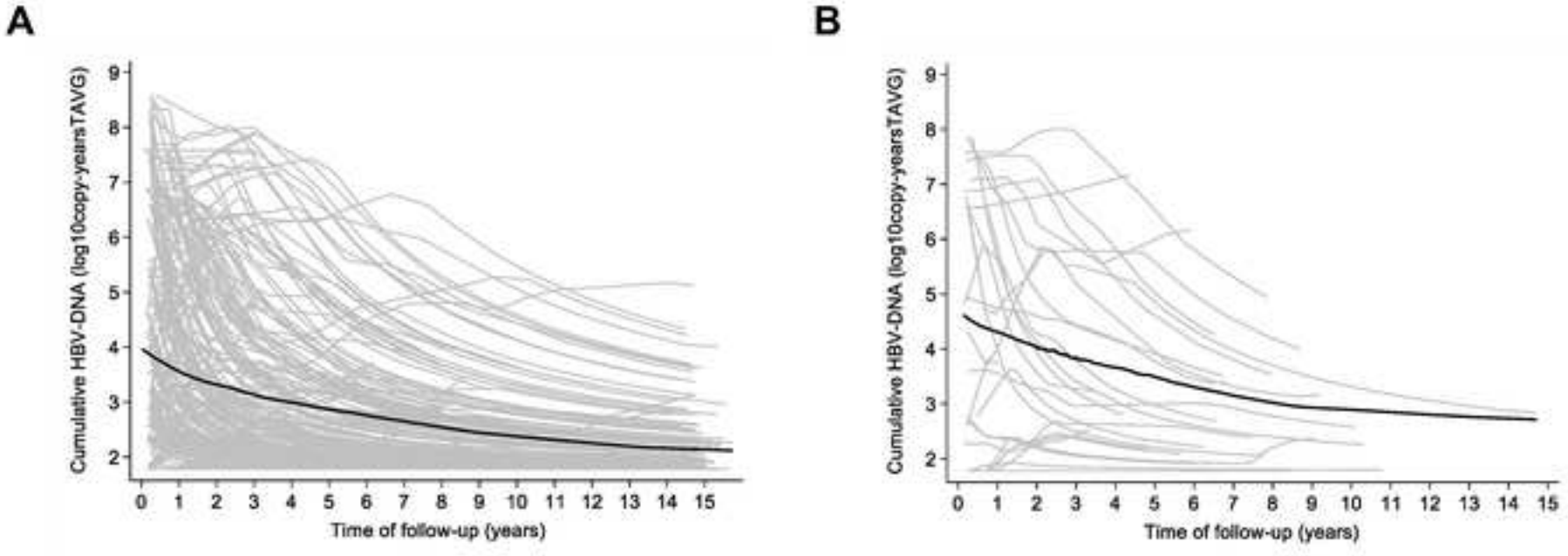
Evolution of cumulative HBV-DNA (log_{10} copy-$years_{TAVG}$) over time in (A) alive and (B) deceased individuals. Means are expressed as bold lines from a LOWESS curve and individual levels are expressed as gray lines. Abbreviation: TAVG, time-averaged.

A


CD4
HIV-RNA
IQR
95% CI
Median CD4+ cell count (/mm3)
Proportion with undetectable HIV-RNA
800
700
600
500
400
300
200
1.0
0.8
0.6
0.4
0.2
0.0
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15
N 300 298 287 281 188 152 198 193 182 160 141 133 133 129 129 134
Year

B


TDF
HBV-VL
Proportion with TDF treatment
Proportion with undetectable HBV-DNA
1.0
0.8
0.6
0.4
0.2
0.0
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15
N 300 298 287 281 188 152 198 193 182 160 141 133 133 129 129 134
Year


A
Cumulative HBV-DNA (log10copy-yearsTAVG)
9
8
7
6
5
4
3
2
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15
Time of follow-up (years)
B
Cumulative HBV-DNA (log10copy-yearsTAVG)
9
8
7
6
5
4
3
2
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15
Time of follow-up (years)

Supplementary materials to: Lorenza N. C. Dezanet, Raisha Kassime, Patrick Miailhes, et al. Effect of viral replication and liver fibrosis on all-cause mortality in HIV/HBV coinfected individuals: a retrospective analysis of a 15-year longitudinal cohort.

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Supplementary Table S1. Determinants for all-cause mortality.

Characteristics	Univariable		Multivariable[a]	
	HR (CI 95%)	*p*	HR (CI 95%)	*p*
Demographics				
Gender, male/female (% male)	2.62 (0.81-8.47)	0.11		
Age at baseline, years	1.07 (1.04-1.11)	<0.001	1.05 (1.01-1.09)	0.01
From zone of high HBV-prevalence	0.25 (0.09-0.71)	0.009		
Clinical characteristics at study entry				
BMI, Kg/m^2	0.92 (0.82-1.03)	0.15		
Alcohol consumption, glasses/day	1.03 (0.89-1.21)	0.7		
HIV infection variables at study entry				
Time since first HIV-positive test, years	1.08 (1.02-1.14)	0.01		
AIDS-defining illness	2.99 (1.63-5.47)	<0.001	2.35 (1.25-4.41)	0.008
CD4$^+$ cell count, per 100 cells/µL	0.92 (0.81-1.05)	0.23		
Nadir CD4$^+$ cell count, per 100 cells/µL	0.80 (0.64-1.00)	0.05		
Initiated ART	1.08 (0.99-1.17)	0.08		
Duration of ART, years	1.03 (0.98-1.09)	0.25		
Viral hepatitis				
Time since first HBsAg-positive test, years	1.03 (0.98-1.09)	0.22		
HBeAg-positive	2.07 (1.08-3.99)	0.03		
ALT level, IU/mL	1.00 (0.99-1.00)	0.8		
AST level, IU/mL	1.008 (1.002-1.01)	0.01		
Metavir F3-F4 fibrosis[†]				
Estimated using *Fibrotest*®	3.48 (1.87-6.48)	<0.001	2.12 (1.06-4.21)	0.03
Determined by liver biopsy [#]	1.70 (1.18-2.45)	0.005		
Ever HCV coinfected	0.28 (0.04-2.01)	0.20		
Ever HDV coinfected	3.13 (1.39-7.04)	0.006		
Variables assessed during the follow-up study				
Cumulative tenofovir use, years	0.98 (0.91-1.06)	0.6		
Time-updated CD4$^+$ cell count, cells/µL	0.997 (0.996-0.999)	0.003		
CD4$^+$ cell count at last follow-up visit, cells/µL	0.996 (0.995-0.998)	<0.001		
Time-updated F3-F4 fibrosis level	4.48 (1.43-14.08)	0.01		

[a] In multivariable modeling, BMI had too many missing data and was not considered further; AST levels, HDV coinfection, F3-F4 fibrosis (estimated using FibroTest) and time-updated F3-F4 fibrosis levels were collinear and we preferred F3-F4 fibrosis (estimated using FibroTest) at inclusion; CD4$^+$ cell count at the last follow-up visit, initiation of ART and nadir CD4$^+$ cell count were collinear and we preferred nadir CD4$^+$ cell count; HBeAg status and time-updated CD4$^+$ cell count were included in the submodels of the joint models analysis and were not considered further. The following variables were removed as their association was no longer significant in the multivariable model: male gender (p=0.63), from zone of high prevalence (p=0.17), and nadir CD4$^+$ cell count (p=0.42). The final multivariable model was adjusted by all covariates listed in the column.

[#] In a subgroup of 138 patients, liver biopsies were performed within 12 months before or at study entry, based on concomitant guidelines from the European Association for the Study of the Liver. Histological fibrosis and activity were scored with the METAVIR classification.

Abbreviations: ALT, alanine aminotransferase; ART, antiretroviral therapy; AST, aspartate aminotransferase; BMI, body mass index; HBeAg, hepatitis B "e" antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HIV, human immunodeficiency virus; IDU, injection drug use; MSM, men who have sex with men; ULN, upper limit of normal.

Supplementary Table S2. Characteristics of the study population at cohort inclusion, stratified by lost to follow-up.

Characteristics	Patients		*p*[§]
	Completed follow-up (n=147)	Lost to follow-up (n=118)[¶]	
Demographics			
Gender, male/female (% male)	119/28 (81.0)	99/19 (84.7)	0.53
Age at baseline, years*	40.0 (34.6-44.1)	38.1 (34.1-42.0)	0.10
From zone of high HBV-prevalence[†]	47 (32.0)	35 (29.7)	0.69
Mode of HIV transmission[†]			0.42
Heterosexual	57 (38.8)	42 (35.6)	
MSM	80 (54.4)	64 (54.2)	
IDU	7 (4.8)	11 (9.3)	
Other/Unknown	3 (2.0)	1 (0.9)	
Clinical characteristics at study entry			
BMI, Kg/m^2 [*N* = 251]*	22.4 (21.0-24.3)	22.7 (21.0-24.6)	0.58
Alcohol consumption, glasses/day [*N* = 254]*	1 (0-2)	1 (0-2.9)	0.67
Comorbidities[†]			
Cardiovascular disease	17 (11.6)	11 (9.3)	0.55
Diabetes	3 (3.0)	2 (1.7)	1.00
Renal disease	3 (2.0)	3 (2.5)	1.00
Other liver diseases[¥]	4 (2.7)	2 (1.7)	0.58
HIV infection variables at study entry			
Time since first HIV-positive test, years [*N* = 264]*	9.4 (3.8-13.1)	9.5 (2.8-14.5)	0.93
AIDS-defining illness[†]	30 (20.4)	29 (24.6)	0.42
HIV-RNA > 50 copies/mL[†]	64 (43.5)	63 (53.4)	0.14
HIV-RNA, $\log_{10}$ copies/mL [*N* = 127]*	3.9 (4.5-4.4)	3.9 (2.8-4.5)	0.74
CD4$^+$ cell count, cells/µL*	403 (283-557)	406 (249-586)	0.87
Nadir CD4$^+$ cell count, cells/µL [*N* = 235]*	212 (107-309)	236 (110-372)	0.20
Initiated ART[†]	135 (91.8)	102 (86.4)	0.17
Duration of ART, years [*N* = 230]*	5.9 (2.4-7.4)	4.8 (2.7-6.8)	0.33
Viral hepatitis at study entry			
HBV-genotype [*N* = 142][†]			
A	51 (68.0)	36 (53.7)	0.09
D	7 (9.3)	5 (7.5)	0.77
E	8 (10.7)	11 (16.4)	0.32
G	9 (12.0)	13 (19.4)	0.22
HBeAg-positive[†]	73 (49.7)	60 (50.9)	0.85
HBV-DNA > 60 IU/mL[†]	95 (64.6)	74 (62.7)	0.75
HBV-DNA, $\log_{10}$ IU/mL [*N* = 169]*	4.3 (2.9-6.6)	5.3 (3.6-6.9)	0.04
ALT level, IU/mL [*N* = 260]*	38 (22-64)	43 (28-88)	0.02
AST level, IU/mL [*N* = 260]*	33 (25-52)	38 (29-59)	0.03
Metavir F3-F4 fibrosis[†]			
Estimated using *Fibrotest*® [*N* = 264]	38 (26.0)	27 (22.9)	0.56
Determined by liver biopsy [*N* = 119][#]	22 (31.0)	13 (27.1)	0.65
Metavir F4 fibrosis[†]			
Estimated using *Fibrotest*® [*N* = 264]	21 (14.4)	13 (11.0)	0.42
Determined by liver biopsy [*N* = 119][#]	6 (8.5)	5 (10.4)	0.72
Ever HCV coinfected[†ϕ]	13 (8.8)	8 (6.8)	0.54
Ever HDV coinfected[†ϕ]	7 (4.8)	9 (7.6)	0.33
Cumulative lamivudine use at study entry, years*	2.8 (0.9-5.5)	3.1 (0.4-5.3)	0.74

*Median (IQR).

[†] Number (%).

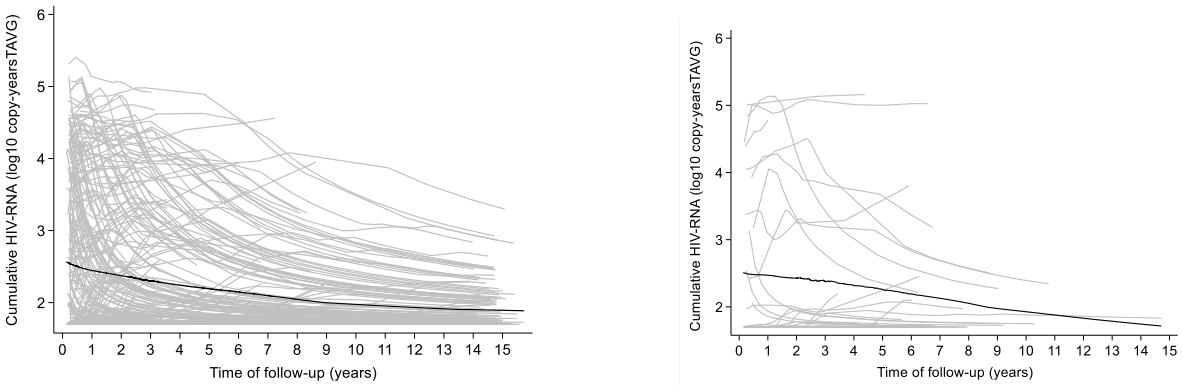
[¶]Does not include the 35 deceased individuals whose deaths were observed during follow-up.

[§] Significance determined using Kruskal-Wallis' test for continuous variables and Pearson's χ^2 test or Fisher's exact test for categorical variables.

[¥]Other liver diseases or hepatic decompensation: acute, subacute or unspecified hepatic failure; haemorrhagic necrosis of liver; fatty liver disease; portal hypertension; and hepatocellular carcinoma.

[#] In a subgroup of 138 patients, liver biopsies were performed within 12 months before or at study entry, based on concomitant guidelines from the European Association for the Study of the Liver. Histological fibrosis and activity were scored with the METAVIR classification.
[ϕ] Established by a positive ELISA-based assay for HCV or HDV, and confirmed by a positive PCR-based assay for HCV-RNA or HDV-RNA, respectively.
Abbreviations: ALT, alanine aminotransferase; ART, antiretroviral therapy; AST, aspartate aminotransferase; BMI, body mass index; HBeAg, hepatitis B "e" antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HIV, human immunodeficiency virus; IDU, injection drug use; MSM, men who have sex with men; TAVG; time-averaged.

Supplementary Figure S1. Evolution of cumulative HIV-RNA (log_{10} copy-years$_{TAVG}$) over time according to mortality outcome



Evolution of HIV-RNA log_{10} copy-years$_{TAVG}$ is given for alive patients in the left panel and for deceased patients in the right panel. Means are expressed as bold lines from a LOWESS curve and individual levels are expressed as gray lines. Abbreviation: TAVG, time-averaged.