Protective effect of hepatitis B virus-active antiretroviral therapy against primary hepatitis B virus infection

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Objective: Current guidelines advise to vaccinate every hepatitis B virus (HBV)-susceptible HIV patient against HBV until sufficient antibody titers have been reached. However, in this era of combination antiretroviral therapy (cART), acute HBV infection rarely occurs in patients who lack this immune protection. We analyzed whether HBV-active cART (lamivudine, emtricitabine, tenofovir) might work as a preexposure prophylaxis (PrEP) to explain this effect.

Methods: From our HIV cohort at the Onze Lieve Vrouwe Gasthuis hospital ($N = 2942$), patients were selected retrospectively for negative HBV serology (HBsAg, anti-HBs and anti-HBc-negative) at cohort entry. Men who have sex with men (MSM) with a second HBV serology available were included for analysis. The incidence of anti-HBc conversion was determined and correlated with the use of HBV-active drugs. Kaplan–Meier curves and log-rank tests were used to compare HBV-free survival for MSM.

Results: In total, 33 HBV infections occurred in 381 eligible MSM over a median follow-up of 2470 days (interquartile range 1146–3871.5). The incident rate per 100 patient-years of follow-up was 1.10 overall, but differed strongly dependent on the use of HBV-active drugs: 2.85/100 patient-years of follow-up in the absence of HBV-active drugs, 1.36 when only lamivudine was used, and 0.14 in the presence of tenofovir. Furthermore, HBV-free survival rate was significantly higher when HBV-active cART was used, in particular when this HBV-active cART contained tenofovir (log-rank $P < 0.001$).

Conclusion: Our findings demonstrate that HBV-active cART protects against the occurrence of de-novo HBV infection, most strongly when tenofovir is used.

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Keywords: antiretroviral therapy, hepatitis B virus, HIV, incidence, lamivudine, preexposure prophylaxis, tenofovir

Introduction

HIV-infected patients are frequently exposed to hepatitis B virus (HBV) due to their shared routes of transmission, namely, sexual intercourse or blood contact [1]. Up to 9% of HIV patients are coinfected with chronic HBV [2,3] and studies have shown that patients infected with HBV experience more complications if they are coinfected with HIV [4,5]. Because since 1996 combination antiretroviral therapy (cART) reduced the AIDS-related mortality impressively, liver disease caused by previously acquired coinfection with hepatitis B emerged as a

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relatively important cause of death in HIV-infected individuals [6–8].

As there is an effective vaccine available, all HIV patients, and especially men who have sex with men (MSM), are advised to get vaccinated against HBV. However, many immune-deficient patients do not respond effectively to this vaccination: 30–75% of HIV patients who receive standard-dose HBV vaccination fail to develop immunity to HBV. Current policy is to revaccinate patients until sufficient titers (anti-HBs >10 IU/ml) are reached, but even after revaccination, only 50.7% of nonresponders developed protective titers. Furthermore, despite the recommendation, many patients do not receive any vaccination. Altogether, risk for acquiring an HBV infection remains an important issue for HIV patients.

At the present time, however, acute HBV infection infrequently occurs in HIV-infected patients who lack immune protection. We considered that this might be explained by the fact that some antiretroviral drugs are effective against both HBV and HIV [lamivudine (3TC), emtricitabine (FTC), and tenofovir (TDF)].

We analyzed whether these HBV-active antiretroviral drugs might work as a preexposure prophylaxis and protect against primary HBV infection.

Methods

Participants

The Onze Lieve Vrouwe Gasthuis (OLVG) is a general, public hospital in the inner city of Amsterdam, providing medical care to the largest cohort of HIV-infected individuals in the Netherlands. Data from this cohort, followed between 1983 and September 2012 ($n = 2942$), were used. First, all patients susceptible to HBV infection were identified by analyzing the first HBV serology at entry into the cohort (negative result for anti-HBc and HBsAg, and an anti-HBs titer <10 IU/l). Second, patients with a follow-up HBV serology test already determined were selected or HBV serology was performed on the latest frozen sample available. Occurrence of primary HBV infection was defined as anti-HBc seroconversion. Anti-HBs seroconversion only (positive anti-HBs titer >10 IU/l) was ascribed to successful vaccination. Patients without a second HBV serology were excluded from the analysis. Furthermore, to identify the exact period of HBV infection in those patients with anti-HBc seroconversion, we tried to perform HBV serology on stocked blood samples, wherever available, and we screened the individual charts for periods of clinical hepatitis (alananine aminotransferase increase above two times the upper limit of normal) in relation to medication use. Finally, we documented the course of the occurred HBV infections (HBsAg and HBeAg conversion and response to therapies).

Analyses

Data were collected for the whole cohort, but, as HBV conversion occurred particularly in MSM, we decided to concentrate our analyses on patients from this risk group only. Therapy regimens changed frequently and often treatments were only used for a short period of time. To ensure that short treatment periods could not have a too substantial influence on the results, we defined a period receiving HBV-active cART less than 20% of the observation time as a period not receiving therapy. Three treatment groups were delineated: receiving HBV-active cART less than 20% of the observation time ('no treatment'), receiving more than 20% HBV-active cART, but 'no tenofovir' (i.e. less than 20% of the observation time on tenofovir), and receiving HBV-active cART, including 'more than 20% tenofovir'. The observation period of a patient started at the date of entry into the database and stopped at the date of the first positive test (converters) or the last negative anti-HBc test (nonconverters).

Statistics

Patient characteristics were described as median (interquartile range = 25–75%) or frequencies (%). Continuous variables were compared using the Kruskal–Wallis test. Categorical variables were compared using the χ^2 test.

Incident rates were calculated per 100 patient-years of follow-up (PYFU) for all patients eligible for analysis: MSM and non-MSM. We calculated incident rate for MSM patients separated by medication use as well. The incidence rate ratio (IRR) was calculated to compare incidence rates between all groups (MSM versus non-MSM; no-HBV-active cART versus HBV-active cART, no TDF; no-HBV-active cART versus HBV-active cART with TDF). Cumulative event rates according to three treatment groups were estimated with the Kaplan–Meier method and compared with the log-rank test. Patients were censored at the date of last known follow-up. To adjust for the nonrandomized allocation into the different medication groups, the relation of timing to HBV conversion was investigated using Cox proportional hazards regression.

A covariate was allowed in the model when in univariate analyses, its P value was <0.10. Data were analyzed in SPSS version 18 (SPSS Inc., Chicago, Illinois, USA); P value <0.05 was considered statistically significant.

Results

Out of the 2942 (MSM = 2280) patients in the OLVG HIV cohort, 871 (MSM = 590) were found to be HBV susceptible at entry and 736 (MSM = 518) had a second HBV serology test available. Of these patients, 171 of the

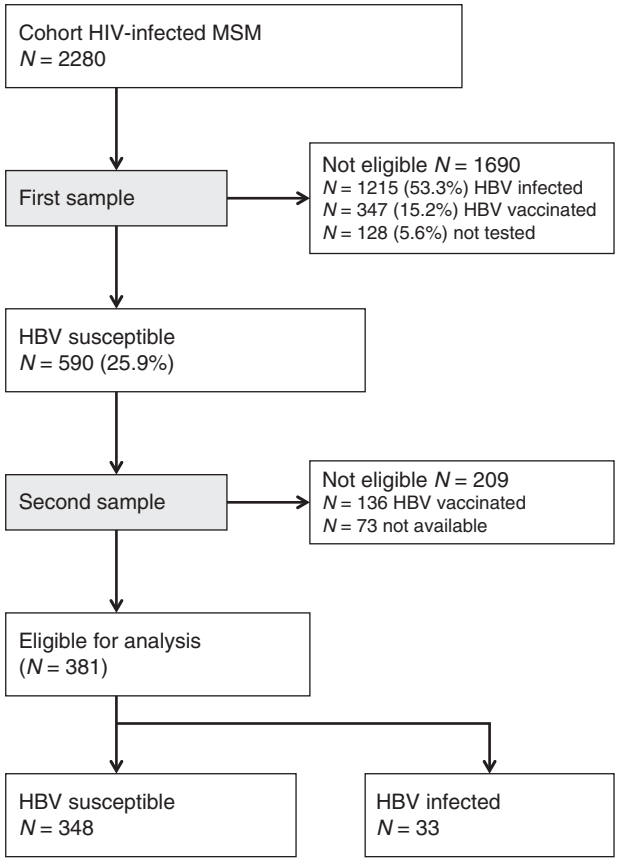


Fig. 1. Flowchart of selected MSM patients.

736 patients (23.2%) had been successfully vaccinated [MSM 136/518 (26.2%)]. Of the remaining 564 (MSM = 381) HBV-susceptible patients, 35 of 564 (6.2%) converted to an anti-HBc-positive state [MSM 33/381 (8.7%)] and 529 of 564 (93.8%) remained negative for all HBV serology tests [MSM 348/381 (91,3%); see Fig. 1 (MSM only)].

Within the HBV-susceptible MSM ($n = 381$), three groups were differentiated by the exposure to HBV-active medication. The groups did not differ significantly in median age at entry ($P = 0.101$), but differed significantly in duration of follow-up time ($P < 0.001$), median year of observation ($P < 0.001$), as well as (by matter of definition) in the use of HBV cART and the use of tenofovir. Use of tenofovir was combined with either 3TC or FTC in most cases (patient characteristics; Table 1).

Incidence rate for HBV was 0.79 per 100 PYFU for the whole group, but was higher in MSM versus non-MSM (respectively, 1.10 versus 0.14 per 100 PYFU; IRR 8.03; 95% confidence interval, CI 1.93–33.46). In MSM, the lowest incidence rate was found in persons using HBV-active cART containing tenofovir (0.14 per 100 PYFU; IRR 0.05; 95% CI 0.01–0.21), compared with persons without HBV-active cART (incident rate 2.85). The group with HBV-active cART, but no tenofovir, also had a lower incidence rate, 1.36 (IRR 0.48; 95% CI 0.23–0.98; Table 2).

The HBV-free survival for MSM, split for the three groups, is shown in the Kaplan–Meier curve (Fig. 2). The hazard for HBV conversion was significantly higher for patients receiving non-HBV-active cART compared with patients receiving HBV-active cART without tenofovir (log-rank $P = 0.001$), while the significantly smallest chance of HBV infection was observed in patients receiving HBV-active cART with tenofovir (log-rank $P < 0.001$). In fact, after an observation of 6000 days (16.4 years), 40% of patients without active-HBV cART had seroconverted compared with only 2% of patients receiving HBV-active cART with tenofovir.

Comparing patients not receiving HBV-active cART to the two other medication groups in a Cox-regression analysis, confirmed the results of the three-risk group analysis. This showed that, compared with patients not receiving HBV-active cART, patients receiving HBV-active cART without tenofovir had a reduced hazard rate of HBV infection (hazard ratio = 0.43, 95% CI 0.21–0.89). The HBV hazard was even lower in patients receiving HBV-active cART with tenofovir (hazard ratio = 0.07, 95% CI 0.02–0.25). Age and year of observation were not significant independent predictors in Cox-regression analysis for HBV infection (age: hazard ratio = 0.98, 95% CI 0.94–1.02, P value = 0.336; year of observation: hazard ratio = 0.96, 95% CI 0.88–1.06, P value = 0.432).

Thirty-three cases of HBV conversion were observed in MSM. Fifteen of these 33 patients used no HBV-active medication during the observation period at all, two hardly any, whereas only two patients used a substantial proportion of the observed time tenofovir (65 and 72% of time). Three patients used HBV-active medication throughout most of the observation period (>80%), but without tenofovir (in fact only 3TC) and the remaining 11 patients had a more mixed pattern of coverage; only eight patients used tenofovir for a short time (2–14% of time).

After searching the individual 33 MSM files for episodes of clinical hepatitis, these could only be identified in seven patients. During four of these episodes, no HBV-active medication was used; in the other three episodes, 3TC was used as an HBV-active drug in the cART regimen. Only in one situation (a man on cART containing 3TC for 5.5 years), this hepatitis was diagnosed as such by the clinician. In his HBV DNA, sampled during conversion, no 3TC-resistant mutations (YMDD) were found.

From all 33 HBV infections in MSM, six of the seven men with clinical hepatitis remained both HBsAg-positive and HBeAg-positive during the rest of the follow-up. All

Table 1. Patient characteristics of selected groups (MSM).

	<20% HBV-active cART N = 106	>20% HBV-active cART, no TDF N = 82	>20% HBV-active cART with TDF N = 193	P value
Age at entry (years)[a]	32.5 (28–38)	31.5 (26.75–40)	35 (29–42)	101[b]
Observation time (days)[a]	1632 (716–3386)	3511 (2375–5214)	2242 (1075–3786)	<0.001[b]
Year of observation				<0.001[c]
Median between 1983 and 1993	2 (1.9)	1 (1.2)	–	
Median between 1993 and 2003	29 (27.4)	44 (53.7)	16 (8.3)	
Median between 2003 and 2013	75 (70.8)	37 (45.1)	177 (91.7)	
Days of medication use				
No HBV-active cART[a]	1632.5 (716–3283)	866.5 (106–2379)	374 (58–1172)	<0.001[b]
Lamivudine mono[a]	0 (0–0)	2568.5 (1500–2970)	0 (0–568)	<0.001[b]
Tenofovir mono[a]	0 (0–0)	0 (0–0)	0 (0–0)	<0.001[b]
Lamivudine/tenofovir[a]	0 (0–0)	0 (0–0)	0 (0–0)	<0.001[b]
Emtricitabine/tenofovir[a]	0 (0–0)	0 (0–26.5)	970 (497–1603)	<0.001[b]
Absolute medication users				
Lamivudine mono				
No lamivudine mono	94 (88.7)	0	127 (65.8)	
<20% lamivudine mono	12 (11.3)	2 (2.4)	19 (9.8)	
>20% lamivudine mono	0	80 (97.6)	47 (24.4)	
Tenofovir mono				
No tenofovir mono	106 (100.0)	73 (89)	158 (81.9)	
<20% tenofovir mono	0	9 (11)	20 (10.4)	
>20% tenofovir mono	0	0	15 (7.8)	
Lamivudine/tenofovir				
No lamivudine/tenofovir	104 (98.1)	77 (93.9)	156 (80.8)	
<20% lamivudine/tenofovir	2 (1.9)	5 (6.1)	14 (7.3)	
>20% lamivudine/tenofovir	0	0	23 (11.9)	
Emtricitabine/tenofovir				
No emtricitabine/tenofovir	95 (89.6)	62 (75.6)	17 (8.8)	
<20% emtricitabine/tenofovir	11 (10.4)	20 (24.4)	13 (6.7)	
>20% emtricitabine/tenofovir	0	0	163 (84.5)	

Values in parentheses are percentages, unless indicated otherwise. cART, combination antiretroviral therapy; HBV, hepatitis B virus; TDF, tenofovir.
[a]Values are median (interquartile range).
[b]Kruskal–Wallis test.
[c]Chi square test.

other patients had full seroconversion to both anti-HBs and anti-HBe. The six not fully converted patients received tenofovir-containing medication after the study period and reached fully suppressed HBV-DNA levels (data not shown).

Discussion

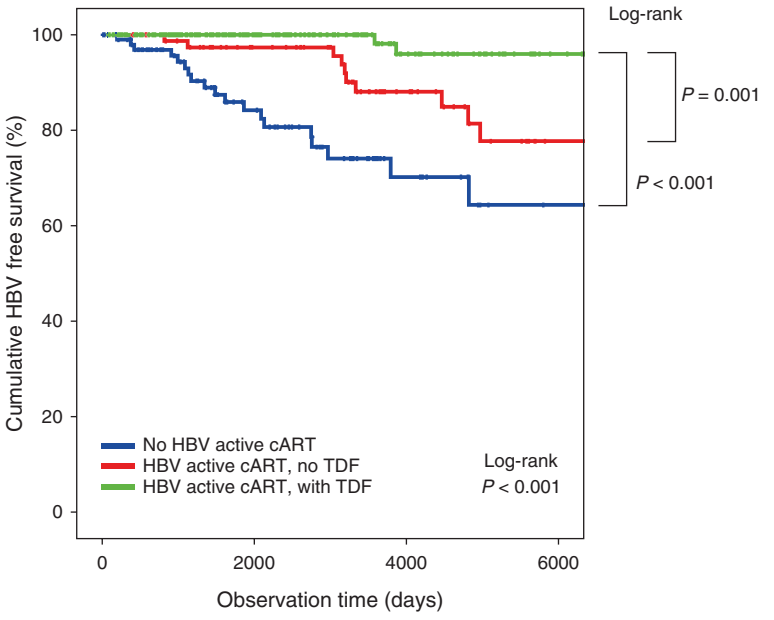
Over an observation period of 4445 patient-years in 564 HBV-susceptible patients, HBV seroconversion was an infrequent event. We only observed 35 cases, leading to a calculated incidence of 0.79 cases per 100 PYFU for the whole group and 1.10 cases per 100 PYFU in MSM. Most cases were asymptomatic and six of the 33 (18%) MSM did not clear HBsAg or HBeAg.

The literature about HBV incidence among HBV-susceptible HIV-infected MSM is scarce; most studies only report the prevalence of HBsAg. In a study from the United Kingdom, Price *et al.* [9] reported an incidence of 0.7 new HBV seroconversions per 100 PYFU among

Table 2. Hepatitis B virus incidence per 100 years of observation.

	Cases, N (%)	Patient-years	Incidence rate/100 PYFU	Incidence rate ratio	95% CI
Whole group (n = 564)	35 (6.2%)	4444.85	0.79		
No MSM	2 (0.4%)	1454.82	0.14	Referent	
MSM	33 (5.9%)	2990.03	1.10	8.028	(1.926–33.457)
MSM (n = 381)					
<20% HBV-active cART	19 (5%)	666.78	2.85	Referent	
>20% HBV-active cART, no TDF	12 (3.1%)	885.28	1.36	0.476	(0.231–0.980)
>20% HBV-active cART, TDF	2 (0.5%)	1437.97	0.14	0.049	(0.011–0.210)

CI, confidence interval; HBV, hepatitis B virus; TDF, tenofovir.



Numbers in observation

No HBV active cART	106	49	18	7
HBV active cART, no TDF	81	63	32	14
HBV active cART, with TDF	194	53	42	14

Fig. 2. Kaplan–Meier curves for hepatitis B virus-free survival in relation to treatment groups. Blue line, hepatitis B virus (HBV)-active combination antiretroviral therapy (cART) less than 20% of the observation time ('no treatment'); green line, HBV-active cART, including tenofovir (>20% of the observation time); red line, more than 20% of HBV-active cART, but 'no tenofovir' (less than 20% of the observation time on tenofovir).

HIV-infected patients between 1996 and 2009, with a higher risk among MSM and persons using intravenous drugs. In this cohort, 16.5% of patients remained HBsAg-positive. In an earlier study by Kellerman *et al.* [3], an incidence of IgM anti-HBsAg seroconversion of 0.71 per 100 PYFU among HIV-infected MSM was found between 1998 and 2001, before the introduction of tenofovir. These authors described a protective effect of cART in general, but were unable to find an extra protective effect of 3TC-containing cART compared to other cART. Gatanaga *et al.* [10] recently described an incidence of 6.73 HBV infection per 100 PYFU in a cohort of 354 HBV-susceptible MSM from Japan, when no ART was used and an incidence of 0.67 HBV infection per 100 PYFU in the period when 3TC or tenofovir was used. Although the prophylactic effect of these HBV active drugs was highly significant ($P < 0.001$), the authors did not describe extra protection in case of tenofovir usage.

In our study, we were able to not only demonstrate the protective effect of HBV-active cART on the incidence of new HBV infection, but furthermore to show a superior protective effect on HBV seroconversion in the group using tenofovir for at least 20% of observation time. In fact, HBV infection occurred in only two patients who had a substantial exposure to tenofovir during the observation period. In one of them, (mild) clinical hepatitis was observed before the start of tenofovir, but unfortunately no samples could be recovered to demonstrate HBV conversion at that time. In the other patient, we have no formal proof, whether the patient became HBV-infected before or during treatment with tenofovir. In the group with HBV-active cART, but no tenofovir (in fact only 3TC-containing cART), the protective effect against an HBV seroconversion was also observed, but to a lesser extent than when patients used tenofovir. In this arm, seven patients with a substantial use of 3TC during their observation period experienced HBV seroconversion. In three of them, clinical hepatitis was observed during the period with 3TC treatment and in one patient, HBV infection with a 3TC-sensitive HBV strain was demonstrated. Altogether, these observations not only demonstrate that HBV-active cART indeed protects against HBV infection as a preexposure prophylaxis, but also that 3TC alone seems less protective than tenofovir-containing cART, with some HBV infection taking place in this arm. As almost all patients who were treated with tenofovir used either 3TC or FTC at the same moment (Table 1), we cannot exclude that the extra protective effect was probably related to the combination of the drugs and not to tenofovir alone. In treatment of chronic HBV settings, however, additional use of either 3TC or FTC showed no

extra therapeutic effect above tenofovir treatment [11–13].

From 1988 onwards, the incidence of hepatitis B in the Netherlands remained grossly unchanged, so the difference between the groups regarding the median year of observation is unlikely to act as a confounding factor [14].

Our analysis has limitations typical of a retrospective analysis. First, patients often switched and/or interrupted their medication. In the approach we used, there is no difference in a patient using drugs 100% or 21% of the follow-up. A more extensive mathematical model might solve this problem. Second, the exact moment of seroconversion remains uncertain in several cases. We tried to solve this by searching stocked samples, but we did not succeed in all cases. Finally, we are not informed about the risk behavior the cohort participants had during the observation. For this reason, we decided to focus on MSM only. We tried to collect data about syphilis exposure as a proxy for risk behavior, but data were too incomplete for appropriate analysis.

Current guidelines advise to vaccinate all HIV-infected patients, who are susceptible for HBV, especially risk groups such as MSM, professional sex workers, and intravenous drug users. Although this advice is not followed in all patients, successful protection is only reported in 30–75% of vaccinated individuals [15–17], possibly related to the impaired immunity of the HIV-infected individuals. Intensified revaccination protocols result in better responses [18], but still a substantial proportion of individuals are reported to remain susceptible for HBV infection. In our own cohort, this proportion was 564 of 736 (76.6%) for the whole group and 381 of 590 (64.6%) for MSM. Although HBV vaccination will always be the preferred advice for HIV-infected persons at risk for HBV, one might reconsider the current guidelines to revaccinate every patient not getting sufficient titers after the first cycles of HBV vaccination. In these unresponsive patients, inclusion of tenofovir (and to a lesser extent 3TC) as part of their cART regimen seems to be protective enough against primary HBV infection.

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M.H. was responsible for data and file searches for master project and wrote the first version of the article. S.H. was a research analyst and was responsible for data searching, analyses, and article revision. G.v.d.B. was responsible for medical content and developing the final research question and was master student project supervisor and revised the article. T.S.v.d.H. started the first data and file searches for master project and revised the article. A.v.D. was responsible for laboratory analysis and searching of stored samples and for article revision. L.D. was responsible for statistical methods and article revision. R.R. was responsible for cohort database and analysis, and article revision. K.B. was responsible for overall supervision of medical content, research question, and data analyses, and wrote the final version of the article.

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Conflicts of interest

M.H., S.H., T.S.v.d.H., A.v.D., L.D., and R.R. have no conflicts of interest to declare. G.v.d.B. has been consultant in advisory boards for Abbott, Janssen, and MSD. K.B. has been consultant in advisory boards for Viiv, Gilead, Abbott, BMS, MSD, and Janssen.

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