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Dually Active HIV/HBV Antiretrovirals as Protection Against Incident Hepatitis B Infections: Potential for Prophylaxis

Mohaned Shilaih,[1,2] Alex Marzel,[1,2] Alexandra U. Scherrer,[1,2] Dominique L. Braun,[1,2] Helen Kovari,[1] Mathieu Rougemont,[3] Katharine Darling,[4] Manuel Battegay,[5] Matthias Hoffmann,[6] Enos Bernasconi,[7] Cedric Hirzel,[8] Huldrych F. Günthard,[1,2] and Roger D. Kouyos[1,2]; The Swiss HIV Cohort Study[a]

[1]Division of Infectious Diseases and Hospital Epidemiology, University Hospital Zurich, [2]Institute of Medical Virology, University of Zurich, [3]Infectious Diseases Department, Genève University Hospital, [4]Infectious Diseases Department, Lausanne University Hospital, [5]Division of Infectious Diseases and Hospital Epidemiology, University Hospital Basel, [6]Infectious Diseases Department, St Gallen Kantonal Hospital, [7]Division of Infectious Diseases, Regional Hospital Lugano, and [8]Department of Infectious Diseases, Inselspital, Bern University Hospital, University of Bern, Switzerland

Background. Hepatitis B virus (HBV) has a detrimental effect on human immunodeficiency virus (HIV) natural course, and HBV vaccination is less effective in the HIV infected. We examine the protective effect of dually active antiretroviral therapy (DAART) for HIV/HBV (tenofovir, lamivudine, and emtricitabine) in a large cohort encompassing heterosexuals, men who have sex with men, and intravenous drug users who are HIV infected yet susceptible to HBV, with comprehensive follow-up data about risky behavior and immunological profiles.

Methods. We defined an incident HBV infection as the presence of any of HBV serological markers (hepatitis B surface antigen, anti–hepatitis B core antibodies, or HBV DNA) after a negative baseline test result for anti–hepatitis B core antibodies. Patients with positive anti-hepatitis B surface antigen serology were excluded. Cox proportional hazards models were used, with an incident case of HBV infection as the outcome variable.

Results. We analyzed 1716 eligible patients from the Swiss HIV Cohort Study with 177 incident HBV cases. DAART was negatively associated with incident HBV infection (hazard ratio [HR], 0.4; 95% confidence interval [CI], .2–.6). This protective association was robust to adjustment (HR, 0.3; 95% CI, .2–.5) for condomless sex, square-root–transformed CD4 cell count, drug use, and patient demographics. Condomless sex (HR, 1.9; 95% CI, 1.4–2.6), being a man who has sex with men (2.7; 1.7–4.2), and being an intravenous drug user (3.8; 2.4–6.1) were all associated with a higher hazard of contracting HBV.

Conclusions. Our study suggests that DAART, independently of CD4 cell count and risky behavior, has a potentially strong public health impact, including pre-exposure prophylaxis of HBV coinfection in the HIV infected.

Keywords. HBV prevention; HIV coinfection; tenofovir; lamivudine; emtricitabine.

The prevention of hepatitis B virus (HBV) transmission in individuals infected with human immunodeficiency virus (HIV) is important because both viruses share common transmission modes and have detrimental effects on each other's natural course of infection [1–3]. HBV is a worldwide leading cause of chronic hepatitis, responsible for roughly half of deaths due to hepatocellular carcinoma and a third of those related to liver cirrhosis [4]. It is estimated that, globally, HBV affects 10% of all HIV-1–infected individuals [5, 6]. In addition, HBV and hepatitis C virus together are responsible for approximately 15% of deaths in HIV-infected patients in the Swiss HIV Cohort Study (SHCS) [7].

Vaccination against HBV remains the mainstay of preventing HBV acquisition both in HIV-infected and uninfected individuals. However, owing to the effect of HIV on the immune system, mounting and maintaining a protective immune response against HBV is sometimes unattainable, with success rates between 18% and 71% [8–10].

Given the unfavorable course of HIV/HBV coinfections, it is of great public health value to prevent HBV acquisition in HIV-infected individuals. Earlier studies focused on the protective effect of dually acting HIV-1 antiretroviral drugs (tenofovir [TDF], lamivudine [3TC], and emtricitabine [FTC]) [11–14] against HBV, mainly in men who have sex with men (MSM). Considering that heterosexual transmission remains the main driver of HIV propagation in sub-Saharan Africa and many parts of Asia [15], intravenous drug use is responsible for 30% of HIV cases outside sub-Saharan Africa [16], and the highest HBV burden lies in sub-Saharan Africa and Southeast Asia [17], it is of great importance to evaluate the protective effect of dually active antiretroviral therapy (DAART) in all 3 of these major transmission groups.

Consequently, in the current study, we examined the effect of DAART-containing regimens (TDF, 3TC, and FTC) in

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[a]Members of the Swiss HIV Cohort Study are listed in the Acknowledgments.
Correspondence: R. D. Kouyos, University Hospital Zurich, Division of Infectious Diseases and Hospital Epidemiology, Rämistrasse 100, CH-8091 Zurich, Switzerland (roger.kouyos@usz.ch).

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protecting against incident HBV infections in heterosexuals (HET), MSM, and intravenous drug users (IDU). Our study has among the largest number of HBV-susceptible HIV-positive individuals and incident cases examined so far in the context of the protective effects of antiretroviral therapy (ART), and it is unique in its generalizability, because it considers the 3 main transmission groups. Using the SHCS's comprehensive longitudinal data on patients' sexual behavior, drug use, and immunological and ART status, we aim to quantify the effects of DAART and disentangle the effects of the aforementioned factors from DAART's direct effect, which would provide a more concrete estimate of the degree of protection DAART confers against incident HBV infections. A strong protective effect would call for early treatment initiation and, especially, for favoring regimens containing DAART in settings where rates of vaccination or vaccination success are low and HBV is common. We hypothesize that DAART has a protective effect against HBV but that the magnitude of the association could be modified, masked, or confounded by behavioral, demographic, and immunological factors.

METHODS

Patients

The SHCS is an ongoing, prospective, national observational cohort study with biannual follow-up visits, and it started in 1988. Written informed consent was obtained from all patients. CD4 and CD8 cell counts and HIV-1 viral load are collected continuously (in general every 3 months). In addition, detailed treatment/ART history is recorded for each patient. Age, transmission group, and ethnicity are also recorded, along with condom usage. In particular, at each of the biannual follow-up visits, individuals were asked, concerning in the preceding 6 months (1) whether they had occasional partners, (2) whether they had sex with an occasional partner, and (3) how often they used condoms. The SHCS has an excellent coverage, including >70% of patients receiving ART in Switzerland [7].

The study population included all HIV-1–infected individuals taking part in the SHCS from 1992 to 2014 who were tested more than once for one or more of the following HBV markers: hepatitis B surface antigen, anti–hepatitis B core antibodies (anti-HBc), or HBV DNA. Next, patients positive for any of the aforementioned HBV markers at baseline were excluded from the analysis (borderline test results were considered positive). Successful vaccination is highly protective against HBV infection. Accordingly, patients with positive anti-hepatitis B surface antigen (anti-HBs) serology at baseline were excluded. For patients in whom positive anti-HBs results occurred during follow-up, only the time at risk before the first positive anti-HBs result was included. An incident case patient was then defined as a person in whom any of the 3 HBV markers of interest turned positive after a negative anti-HBc result at least at baseline.

An isolated positive anti-HBc serology has been linked to several factors, including the assay method, the viral strain, and the immunological status of the patient [18], and its clinical and physiological significance remains unclear. Hence, we performed a sensitivity analysis excluding patients with an isolated positive anti-HBc serological results to assess the robustness of the associations. In all analyses, only patients with an observation time >6 months were examined.

Statistical Methods

We used both univariable and multivariable Cox proportional hazards models to address our hypothesis. The outcome variable in the analysis was an incident case of HBV infection, and the main explanatory variable was the proportion of observation time with the patient receiving ART, calculated by dividing the number of months a patient received ART by the number of months he or she was observed (later further subdivided into individual DAART and ART regimens). In a sensitivity analysis, we also determined the proportion of observation time during ART when a patient's viral load was suppressed (ie, <400 copies/mL) or nonsuppressed. Given the longitudinal nature of the data and the fact that the outcome variable (HBV infection) cannot be observed exactly (unlike death, for example), as a sensitivity analysis, we used a parametric interval-censored model with time-varying covariates [19] (see Supplementary Material for methods, R code, and simulated data).

The covariates tested were the CD4 and CD8 cell counts closest to infection or censoring time, because both are implicated in the natural course of both HBV and HIV [20, 21]. Both counts were square-root transformed, which provides more normally distributed values and variance stabilization. Having had unprotected sex (occasional or with stable partner), as reported by the patient (during follow-up before censoring or the event) was taken as a proxy for risky behavior. We also considered baseline CD4 and CD8 cell counts, age at enrollment, history of drug use, ethnicity, and an interaction term of sex with transmission group (ie, male-HET, female-HET, male-MSM, male-IDU, or female-IDU), as well as the nadir CD4 cell count, calculated as the lowest count observed during the observation time for an individual patient.

RESULTS

Starting with all SHCS patients registered (December 2014; N = 18 663), we kept only those who had a negative baseline HBV serological result, had ≥1 test after baseline, and who belonged to one of the major transmission groups (MSM, HET, or IDU) (n = 1716), Figure 1. The risk group distribution was 936 HET (54%), 220 IDU (13%), and 612 MSM (33%). A total of 4532 individuals were excluded owing to the unavailability of their HBV tests; these patients were mostly recruited early in the cohort (median year, 1990; interquartile range [IQR], 1988–1992), and 95% died or were lost to follow-up by 1996.

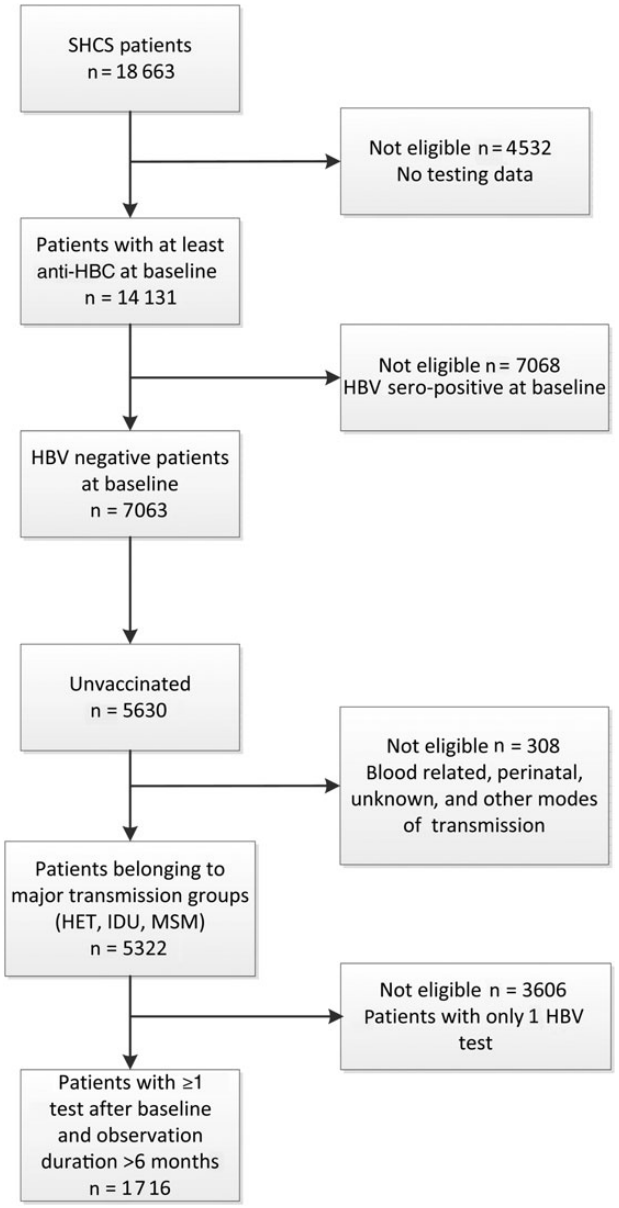

Figure 1. Patient selection flowchart. Abbreviations: Anti-HBC, anti–hepatitis B core antibodies; HBV, hepatitis B virus; HET, heterosexuals; IDU, intravenous drug users; MSM, men who have sex with men; SHCS, Swiss HIV Cohort Study.

Table 1. Baseline Characteristics of the 1716 Patients Eligible for the Study Based on Their HBV Status

Characteristic	Patients, No. (%)[a]	
	Incident HBV Infection (n = 177)	No Incident HBV Infection (n = 1539)
Sex		
Male	141 (80)	971 (63)
Female	36 (20)	568 (37)
Transmission group		
HET	49 (28)	887 (58)
IDU	42 (24)	178 (12)
MSM	86 (48)	474 (31)
CD4 cell count, median (IQR), cells/mL	429 (265–636)	432 (271–625)
Age at registration, median (IQR), y	33 (27–38)	33 (28–40)
HIV-1 RNA, median (IQR), $\log_{10}$ copies/mL	3.5 (2.1–4.7)	3.4 (2.0–4.4)
Ethnicity		
White	151 (85)	1246 (81)
Black	10 (6)	170 (11)
Hispano-American	6 (3)	52 (3)
Asian	6 (3)	30 (2)
Other/unknown	4 (3)	41 (3)
Proportion of observation time on treatment, median (IQR), %		
DAART	35 (0–80)	60 (15–94)
Non-DAART	0 (0–30)	0 (0–14)
Year of enrollment, median (IQR)	1996 (1992–2001)	1998 (1994–2003)
Tests performed, median (IQR), No.	2 (2–2)	2 (2–3)
Observation time, median (IQR), mo	59 (32–99)	66 (34–111)
History of drug use	2 (1)	16 (1)
Year of ART initiation, median (IQR)	1997 (1996–2002)	1998 (1996–2004)
Year of infection, median (IQR)	2006 (2002–2010)	. . .

Abbreviations: ART, antiretroviral therapy; DAART, dually active ART; HBV, hepatitis B virus; HET, heterosexuals; HIV, human immunodeficiency virus; IDU, intravenous drug users; IQR, interquartile range; MSM, men who have sex with men.

[a] Data represent No. (%) unless otherwise specified.

The total number of incident HBV cases was 177, of which 86 (49%) occurred in MSM. Patient observation time started from the date of the first negative test results and ended the last time the patient was tested or when an event occurred. Most patients had only 2 tests (n = 1129; 66%; IQR 2–3 tests), and the median (IQR) time between tests was 29 (12–58) months (Table 1). The total observation time was 10 682 person-years. The overall incidence rate per 1000 person-years was 16 (95% confidence interval [CI], 14–19). The transmission group incidence rates were as follows, per 1000 person-years: HET, 9 (95% CI, 6–11); IDU, 28 (21–38); and MSM, 25 (21–31).

Both univariable and multivariable analysis showed a strong reduction in the risk of acquiring HBV for patients receiving DAART. In univariable analysis, DAART had a protective effect against HBV acquisition, with a hazard ratio (HR) of 0.4 (95% CI, .2–.6), whereas other ART regimens had none (HR, 1.63; 95% CI, .94–2.81) (Figure 2 and Table 2). Furthermore, the exclusion of patients with isolated positive anti-HBc serology did not affect the associations (HR, 0.4; 95% CI, .2–.8). The proportion of time a patient was receiving DAART with an HIV RNA viral load <400 copies/mL showed similar protective effect (HR, 0.4; 95% CI, .2–.6), while receiving DAART without suppression offered no significant protection (0.6; .2–1.7). Other non-DAART antiretrovirals showed no protective effect even with suppression (HR, 1.4; 95% CI, .70–2.7); moreover, being on non-DAART regimens and not being suppressed was associated with higher HBV incidence (3.4; 1.2–10.0), but this association was not significant in the multivariable model (2.0; .5–7.5). The log-likelihood ratio (LLR) test showed no significant

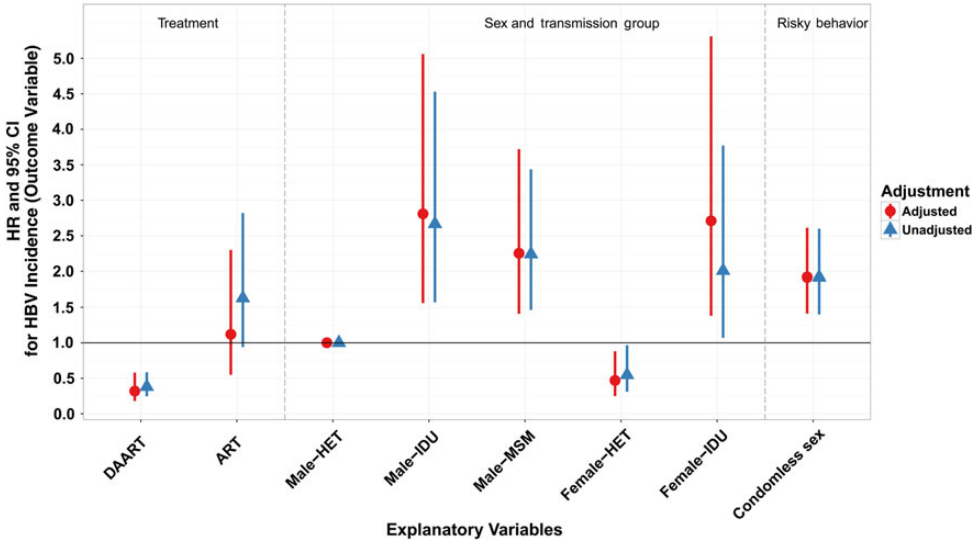

Figure 2. Hazard ratios (HRs) of the different factors influencing hepatitis B virus (HBV) incidence. Adjusted model covariates are shown in Table 2. Results for antiretroviral therapy (ART; human immunodeficiency virus only) and dually active ART (DAART) represent proportion of observation time. Abbreviations: CI, confidence interval; HET, heterosexuals; IDU, intravenous drug users; MSM, men who have sex with men.

difference between the unadjusted model with DAART only and the model with DAART conditional on suppression ($P = .29$); however, the difference was borderline significant when the adjusted models were compared ($P = .055$).

The univariable analysis also demonstrated a higher burden of incident cases in MSM and IDU than in HET (Table 2). Compared with the male-HET group, the female-HET group had lower odds of acquiring HBV (HR, 0.5; 95% CI, .3–1.0).

Self-reported risky sexual behavior was associated with higher risk of acquiring HBV. A history of condomless sex was associated with higher HBV acquisition risk (HR, 1.9; 95% CI, 1.4–2.6), whereas having used intravenous drugs at any point during the observation time was not (HR, 1.0; 95% CI, .2–3.8).

We examined the square-root–transformed ($\sqrt{}$) CD4 cell count closest to the HBV coinfection date as a proxy for the immune-mediated effect of ART on HBV, and a protective association was observed, but it was not statistically significant (HR, 0.98; 95% CI, .96–1.002). Neither the baseline $\sqrt{}$CD4 cell count nor $\sqrt{}$CD8 cell count had an influence on the risk of HBV acquisition. Using non–square-root–transformed CD4 and CD8 cell counts did not alter the associations.

One notable observation was the stronger protective effect of DAART in patients with CD4 cell count nadir $\geq 200 \times 10^6$/mL (635 patients; 38%). In those patients, the HR for DAART's protective effect was 0.2 (95% CI, .1–.5) in the univariable and 0.1 (CI, .1–.4) in the multivariable model. DAART also had a protective effect in patients with a CD4 cell count nadir $<200 \times 10^6$/mL (1062 patients; 62%), but this was significant only in the univariable model (univariable HR, 0.5 [95% CI, .3–.8]; multivariable HR, 0.5 [.2–1.1]). The difference in DAART's effect between patients with CD4 cell count nadirs $\geq$200 versus $\leq$200 10^6/mL was not statistically significant in a multivariable Cox model with an interaction term between the proportion of time receiving DAART and the nadir CD4 cell count.

The adjusted analysis displayed the same direction of association in terms of the protective effect of DAART (HR, 0.3; 95% CI, .2–.6; Table 2). $\sqrt{}$CD4 was not significant in the multivariable model (HR, 1.0; 95% CI, .98–1.03), but condomless sex remained significant (1.9; 1.4–2.6). The protective association of DAART was not affected by adjusting for these variables. The protective association of DAART was also robust to model choice, as evident in a sensitivity analysis using an interval-censored parametric survival model with an exponential hazard function and fixed and time-varying covariates (univariable HR, 0.5 [95% CI, .3–.6]; adjusted HR, 0.5 [.4–.7]).

In univariable analysis, the hazard of HBV acquisition for patients receiving 2-agent DAART (TDF plus 3TC or TDF plus FTC) was half that of patients receiving single-agent DAART (TDF or 3TC alone; FTC was not prescribed alone) (unadjusted HR for 2-agent DAART, 0.2 [95% CI, .1–.6]; unadjusted HR for single-agent DAART, 0.4 [.3–.7]). The protective effect of dual therapy was further strengthened after adjustment (adjusted HR for 2-agent DAART, 0.1 [95% CI, .0–.3]; adjusted HR for single-agent DAART, 0.4 [.2–.6]). We tested the statistical significance of the reduction of risk for 2- versus single-agent DAART regimens using the likelihood-ratio test, and obtained P values of .17 and .01 for the univariable and adjusted models, respectively.

Table 2. Univariable and Multivariable Cox Proportional Hazards Models for the Factors Associated With HBV Incidence

Covariate	HR (95% CI)	
	Univariable Analysis	Multivariable Analysis of Complete Cases Only (n = 1697)
Proportion of observation time on treatment		
DAART	0.38 (.25–.58)	0.32 (.18–.58)
ART	1.63 (.94–2.81)	1.12 (.55–2.30)
Sex interaction with transmission group		
Male-HET	1 (Reference)	1 (Reference)
Male-IDU	2.67 (1.57–4.53)	2.81 (1.56–5.06)
Male-MSM	2.24 (1.46–3.44)	2.33 (1.46–3.72)
Female-HET	0.55 (.31–.97)	0.47 (.25–.88)
Female-IDU	2.01 (1.07–3.77)	2.71 (1.38–5.31)
Ethnicity		
White	1 (Reference)	1 (Reference)
Black	0.62 (.33–1.18)	1.52 (.71–3.26)
Hispano-American	1.03 (.46–2.34)	1.53 (.66–3.53)
Asian	1.77 (.78–4.01)	2.37 (.96–5.85)
Other/unknown	1.38 (.51–3.74)	1.18 (.42–3.31)
Age at cohort enrolment	1.00 (.98–1.02)	1.01 (.99–1.03)
History of condomless sex[a]	1.92 (1.41–2.61)	1.89 (1.36–2.63)
Registration year	1.04 (1.01–1.07)	1.06 (1.03–1.10)
$\sqrt{}$CD4 cell count at test time	0.98 (.96–1.00)	1.00 (.98–1.03)
$\sqrt{}$CD8 cell count at test time[b]	1.01 (.99–1.03)	1.00 (.98–1.03)
$\sqrt{}$Baseline CD4 cell count	1.00 (.92–1.01)	0.98 (.95–1.00)
History of IDU[c]	0.92 (.23–3.73)	. . .

Abbreviations: $\sqrt{}$, square-root–transformed; ART, antiretroviral therapy; CI, confidence interval; DAART, dually active ART; HBV, hepatitis B virus; HET, heterosexuals; HR, hazard ratio; IDU, intravenous drug users; MSM, men who have sex with men.

[a] Values missing in 17 patients.

[b] Values missing in 3 patients.

[c] Excluded for possible collinearity with IDU transmission group.

Table 3. Univariable and Multivariable Cox Proportional Hazards Models for the Factors Associated With HBV Incidence

Covariate	HR (95% CI)	
	Univariable Analysis	Multivariable Analysis in Complete Cases Only (n = 1697)
Proportion of observation time on treatment		
TDF	0.56 (.12–2.56)	0.23 (.04–1.14)
3TC	0.42 (.28–.68)	0.41 (.22–.75)
TDF + 3TC	0.02 (.00–.34)	0.03 (.00–.43)
TDF + FTC	0.42 (.14–1.22)	0.16 (.05–.55)
Other ART regimens	1.02 (.57–1.80)	1.17 (.57–2.40)
Sex interaction with transmission group		
Male-HET	1 (Reference)	1 (Reference)
Male-IDU	2.67 (1.57–4.53)	2.83 (1.57–5.09)
Male-MSM	2.24 (1.46–3.44)	2.33 (1.46–3.71)
Female-HET	0.55 (.31–.97)	0.47 (.25–.88)
Female-IDU	2.01 (1.07–3.77)	2.69 (1.37–5.26)
Ethnicity		
White	1 (Reference)	1 (Reference)
Black	0.62 (.33–1.18)	1.50 (.70–3.22)
Hispano-American	1.03 (.46–2.34)	1.55 (.67–3.60)
Asian	1.77 (.78–4.01)	2.35 (.95–5.81)
Other/unknown	1.38 (.51–3.74)	1.18 (.42–3.29)
Age at cohort enrollment	1.00 (.98–1.02)	1.01 (.99–1.03)
History of condomless sex[a]	1.92 (1.41–2.61)	1.96 (1.41–2.73)
Registration year	1.04 (1.01–1.07)	1.08 (1.04–1.11)
$\sqrt{}$CD4 cell count at test time	0.98 (.96–1.00)	1.00 (.97–1.03)
$\sqrt{}$CD8 cell count at test time[b]	1.01 (.99–1.03)	1.00 (.98–1.02)
$\sqrt{}$Baseline CD4 cell count	1.00 (.92–1.01)	0.98 (.96–1.00)

Abbreviations: $\sqrt{}$, square-root–transformed; 3TC, lamivudine; ART, antiretroviral therapy; CI, confidence article; FTC, emtricitabine; HBV, hepatitis B virus; HET, heterosexuals; HR, hazard ratio; IDU, intravenous drug users; MSM, men who have sex with men; TDF, tenofovir.

[a] Values missing in 17 patients.

[b] Values missing in 3 patients.

After demonstrating an overall strong protective effect of DAART against HBV coinfections, we went further to disentangle the effects of the different DAART regimens (Table 3). DAART regimens containing TDF in combination with 3TC or FTC displayed the strongest protective effect against HBV (adjusted HR, 0.03 [95% CI, .0–.4] and 0.2 [.1–.5], respectively). Furthermore, DAART regimens containing 3TC as the only dually active substance were comparable to regimens with TDF as the only dually active substance (Table 3). TDF-only regimens had wide CIs because of the short observation time for patients receiving TDF monotherapy. In the unadjusted model there was no significant difference in the LLR test comparing all DAART combined versus individual DAART regimens ($P = .1$), but the difference was statistically significant in the adjusted model ($P = .01$).

DISCUSSION

In this study we analyzed a large cohort of HIV-1–infected individuals at risk of acquiring HBV, to evaluate the protective effect of DAART in the 3 major HIV transmission groups (HET, IDU, and MSM). We confirm earlier reports about the protective effect of DAART, and we report a strong protective effect of all DAART [11–14] in said risk groups. We also show that risky sexual behavior plays a key role in the acquisition of HBV infection because it independently increases the risk even in patients receiving DAART; however, it does not seem to be a confounder of DAART's protective effect. Finally, we found that the immune status close to infection time, as measured by CD4 cell count, was not a main actor influencing the risk of HBV acquisition for patients receiving DAART. However, DAART had a higher protective effect in patients with a better long-term immunological status (represented by nadir CD4 cell count $\geq 200 \times 10^6$/mL).

Our findings confirm the importance of viral suppression (and the implicit adherence) in reaching the protective effect of DAART [11]. We observed that the protective effect of

DAART was absent in the phases in which individuals were not virologically suppressed. This further underlines a direct effect of DAART, because treatment failure is associated with poor adherence [22, 23] and generally with low plasma levels of antiretrovirals. For non-DAART regimens, we found an increase in the hazard of an HBV infection in nonsuppressed individuals, but this association was not robust to adjustment (multivariable HR, 2.0; 95% CI, .5–7.5). On a speculative note, this could reflect the fact that lower adherence is associated with more risky behavior [24, 25] and hence a higher HBV incidence.

The lack of a statistically significant difference in the LLR between the models with or without suppression could indicate a power issue, given the short periods patients are usually not suppressed (and receiving ART or DAART). This is further supported by the fact that the likelihood ratio test result was borderline significant ($P = .055$) when the adjusted models were compared. Fortunately, 96% of patients receiving ART in the SHCS are suppressed, so this problem is less concerning in our setting [26]. The Joint United Nations Programme on HIV/AIDS gap report [16] showed that 76% of patients receiving ART achieved viral suppression, yet the bigger problem remains: 47% of the HIV infected are unaware of their positive status.

Our findings also suggest that 2-agent DAART regimens (ie, TDF plus FTC or 3TC) are superior to single-agent DAART regimens in protecting against incident HBV. This finding may be relevant for optimizing ART regimens in settings where HBV incidence is high and vaccination coverage or response is low. One caveat is that the majority of observation time with one drug was with 3TC, with the observation time for TDF alone being much shorter (no patient was prescribed FTC alone). Thus, it is plausible that the observed enhancement of protection is due to TDF. The likelihood ratio test showed that this difference was present only in the adjusted model, implying that other factors (eg, immunological status and risk behavior) could have confounded the association in the unadjusted model.

Previous findings [12, 14] suggest a superior protection for TDF compared with 3TC-containing regimens. We did not observe a clear superiority of TDF over 3TC regimens in our data, as shown by the likelihood ratio test and the overlapping CIs of the respective regimens. However, this could be due to the different ways treatment was accounted for in the different studies. Gatanaga et al [14] pooled TDF-plus-FTC regimens along with other TDF regimens and did not encode the treatment as proportion of observation time, whereas Heuft et al [12] adopted treatment averaging with categorization (detailed in the next paragraph).

As with all observational studies, ours has limitations. The longitudinal and periodic nature of the data collection gives rise to uncertainty as to the precise date of HBV infection (Supplementary Figure S1). Interval-censored models with time-varying covariates account for this varying exposure (ie, treatment changes). However, these models are scarcely described or used in the literature [19]. Heuft et al [12] shared the same concerns about the interval-censored nature of the data, but they circumvented this problem by coding for the different treatments as proportion of observation time with the respective treatments, with <20% equivalent to no treatment and higher percentages equivalent to receiving a certain treatment. This method of handling treatment indeed avoids some issues related to treatment changes and interruptions but remains problematic because patients who have received DAART for 21% of their observation time would are considered equal to for example those who received DAART since their diagnosis (ie 100% of their observation time) (as discussed in [12]).

To further assess the issue of unknown HBV infection times, we considered a parametric survival model with fixed and time-varying covariates. This model showed a similar protective effect of ART, though the magnitude was slightly smaller than with the Cox proportional hazards model. The estimates of both models are in line with earlier reports [11–14].

Data on HBV incidence in Switzerland remain scarce, but it is plausible that it is on the decline, because vaccination against HBV was ramped up and better harm reduction interventions were used for IDU, particularly needle exchange programs [27]. To account for this potential confounding, we performed a sensitivity analysis correcting for calendar time, and the protective effect of DAART remained robust (unadjusted HR, 0.4 [95% CI, .2–.6]; adjusted HR, 0.3 [.2–.5]).

Black ethnicity remains underrepresented in studies addressing the protective effect of ART against. Both our study and that of Heuft et al [12] take place in a majority-white population, and those of Gatanaga et al [14] and Sheng et al [13] both comprised an Asian majority. The consistency of the findings in previously conducted studies and ours, however, suggests that the findings are independent of ethnicity. Moreover, given the evidence and plausibility of a direct drug-mediated effect, it is also unlikely that this protection depends on ethnicity.

In our analysis, 70 patients were considered positive based only on an isolated anti-HBc serological result. Their exclusion did not alter the protective DAART association (data not shown), suggesting that this serological profile is probably caused by HIV coinfection [18, 28] and not by false-positive laboratory results, as some studies suggested [18]. Isolated anti-HBc serology in HIV-infected individuals are usually caused by a recently resolved infection with low or undetected anti-HBs.

One interesting population that we were unable to examine is patients who were vaccinated but did not mount an immune response. Such an analysis was not possible using the SHCS data set, because the SHCS does not collect patients' vaccination records.

One modeling study concluded [29] that even with 100% vaccination uptake by all susceptible patients, a large fraction

of patients would remain at risk of HBV acquisition, owing to the lower vaccination response in HIV-infected patients. Hence, our retrospective observational study suggests that DAART—after additional confirmation in a randomized-controlled setting—might be worth serious consideration as an additional means of fighting HBV infections in HIV-infected individuals, in general and especially in settings where HBV vaccination uptake is low. Moreover, our study adds to the growing body of evidence that early ART initiation [30], regardless of CD4 cell counts, has a strong beneficial public health impact, including preexposure prophylaxis of HBV coinfections.

Supplementary Data

Supplementary materials are available at http://jid.oxfordjournals.org. Consisting of data provided by the author to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the author, so questions or comments should be addressed to the author.

Notes

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SHCS members: V. Aubert, M. B., E. B., J. Böni, D. L. B., H. C. Bucher, C. Burton-Jeangros, A. Calmy, M. Cavassini, G. Dollenmaier, M. Egger, L. Elzi, J. Fehr, J. Fellay, H. Furrer (chairman of the Clinical and Laboratory Committee), C. A. Fux, M. Gorgievski, H. F. G. (president of the SHCS), D. Haerry (deputy of the Positive Council), B. Hasse, H. H. Hirsch, M. H., I. Hösli, C. Kahlert, L. Kaiser, O. Keiser, T. Klimkait, R. D. K., H. K., B. Ledergerber, G. Martinetti, B. Martinez de Tejada, K. Metzner, N. Müller, D. Nadal, D. Nicca, G. Pantaleo, A. Rauch (chairman of the Scientific Board), S. Regenass, M. Rickenbach (head of the Data Center), C. Rudin (chairman of the Mother & Child Substudy), F. Schöni-Affolter, P. Schmid, J. Schüpbach, R. Speck, P. Tarr, A. Trkola, P. Vernazza, R. Weber, and S. Yerly.

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