Dually Active HIV/HBV Antiretrovirals Protect 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], Roger Kouyos[1,2] and The Swiss HIV Cohort Study

[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

[8]Department of Infectious Diseases, Inselspital, Bern University Hospital, University of Bern, Switzerland

Contact information: Prof. Roger Kouyos, PhD, University Hospital Zurich, Division of Infectious Diseases and Hospital Epidemiology, Rämistrasse 100, CH-8091 Zürich, Switzerland, +41 44 255 36 10, roger.kouyos@usz.ch

Alternative corresponding author: Mohaned Shilaih, University Hospital Zurich, Division of Infectious Diseases and Hospital Epidemiology, Rämistrasse 100, CH-8091 Zürich, Switzerland, +41 44 255 1816, Mohaned.shilaih@usz.ch

This work was presented in part in February 2016 at CROI 2016, Boston, USA, abstract number 567.

List of Abbreviations

HIV: Human immunodeficiency virus

HBV: Hepatitis B virus

DAART: Dually active antiretroviral therapy

HBsAg: Hepatitis B Surface Antigen

TDF: Tenofovir

3TC: Lamivudine

FTC: Emtricitabine

AntiHBc: Anti-Hepatitis B core antibodies

HBV-DNA: Hepatitis B DNA

SHCS: Swiss HIV cohort study

HET: Heterosexuals

MSM: Men who have sex with men

IDU: Intravenous drug use

Potential conflicts of interest: H.F.G. has been an adviser and/or consultant for the following companies: GlaxoSmithKline, Abbott, Gilead, Novartis, Boehringer Ingelheim, Roche, Tibotec, Pfizer and Bristol-Myers Squibb, and has received unrestricted research and educational grants from Roche, Abbott, Bristol-Myers Squibb, Gilead, Astra-Zeneca,

GlaxoSmithKline, and Merck Sharp & Dohme (all money went to institution). DLB received travel grants from Pfizer and from Astellas and has been an adviser for Gilead. RDK received travel grants from Gilead.

Author's contributions

MS RDK HFG conceived and designed the study; MS RDK performed the experiments and analyzed the data; HFG and DLB provided clinical advisory; contributed to reagents/materials/analysis tools/data collection/early draft: AM, AUC, DLB, HK, MR, KD, MB, MH, EB, CH, HFG. Wrote the paper: MS and RDK. All authors reviewed and approved the paper.

Abstract

Background

Hepatitis-B virus (HBV) has a detrimental effect on 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/Emtricitabine) in a large cohort encompassing heterosexuals, men-who-have-sex-with-men (MSM), and intravenous drug users (IDU), who are HIV-infected yet susceptible to HBV, with comprehensive follow-up data about risky behavior and immunological profile.

Methods

We defined an incident HBV infection as the presence of any of HBV serological markers (HBsAg/AntiHBc/HBV-DNA) following a negative baseline AntiHBc test. Patients with positive AntiHBs were excluded. Cox proportional hazard models were utilized, with an incident case of HBV infection as the outcome variable.

Results

We analyzed 1,716 eligible patients from the Swiss HIV Cohort Study with 177 incident HBV cases. DAART was negatively associated with incident HBV infection (hazard ratio 0.4, 95%CI 0.2-0.6). This protective association was robust to adjustment (0.3, 0.2-0.5) for condomless sex, √CD4 count, drug use, and patients' demographics. Condomless sex (1.9,1.4-2.6), belonging to MSM (2.7,1.7-4.2) or IDU (3.8,2.4-6.1) were all associated with higher HBV hazard.

Conclusions

Our study suggests that DAART, independently of CD4 count and risky behavior, has a potentially strong public health impact including pre-exposure prophylaxis of HBV co-infection.

The prevention of Hepatitis B virus (HBV) transmission in HIV infected individuals is important as both viruses share common transmission modes and both HIV and HBV 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 one half of hepatocellular carcinoma deaths, and one third of liver cirrhosis related mortality [4]. It is estimated that globally, HBV affects 10% of all HIV-1 infected individuals [5,6]. In addition, HBV and hepatitis C virus taken together are responsible for ~15% of mortality in HIV 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 HIV's effect on the immune system, mounting and maintaining a protective immune response against HBV is sometimes unattainable with a success rate between 18% and 71% [8, 9, 10].

Taken together with the unfavorable course of HIV/HBV co-infections, it is of great public health value to prevent HBV acquisition in HIV patients. 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] and that intravenous drug use (IDU) is responsible of 30% of HIV cases outside of sub-Saharan Africa [16], and that the highest HBV burden lies in sub-Saharan Africa and south east Asia [17], it is of great importance to evaluate the protective effect of DAART in all of these three major

transmission groups. Consequently, in this study we examine the effect of dually acting HIV/HBV antiretrovirals (DAART) containing regimens (TDF, 3TC, and FTC) in protecting against incident HBV infections in HET, MSM, and IDU. Our study has one of the largest number of HBV susceptible HIV-positive individuals and incident cases examined so far in the context of ART protective effect and it is unique in its generalizability as it considers the three main transmission-groups. Using the SHCS's comprehensive longitudinal data on patients' sexual behavior, drug use, immunological and antiretroviral treatment status, we aim to quantify DAART's effect and discern the effects of the aforementioned factors from DAART's direct one, which would provide a more concrete estimate on 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 vaccination rates or vaccination success are low and where 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

The Patients

The Swiss HIV Cohort Study (SHCS) is an ongoing, prospective, national observational cohort study with biannual follow-ups that started in 1988. Written informed consent was obtained from all patients. CD4 and CD8 cell count, and HIV-1 viral load are collected continuously (during follow up visits, in general every 3 months). In addition, antiretroviral treatment history is recorded since the first ART drugs are available in Switzerland. Age, transmission group and ethnicity are recorded as well as condom usage. In particular, at each of the biannual follow-up visits, individuals were asked if in the preceding 6 months (a) they

had occasional partners, (b) they had sex with an occasional partner, and (c) how often they used condoms. The SHCS has an excellent coverage with more than 70% of patients on 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 for at least one of the following HBV markers: Hepatitis B surface Antigen (HBsAg), Anti-Hepatitis B core antibodies (AntiHBc), or Hepatitis B Virus-DNA. Next, patients positive for any of the aforementioned HBV markers at baseline were excluded from the analysis (borderline tests were considered positive). Successful vaccination is highly protective against HBV infection. Accordingly, patients with positive AntiHBs antibodies at baseline were excluded. For patients who developed positive AntiHBs antibodies during their follow-up time, only the time at risk before the first positive AntiHBs test was included. An incident case was then defined to be a person in whom any of the three HBV markers of interest turned positive following at least a negative AntiHBc at baseline.

An isolated antiHBc 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 isolated antiHBc serology to assess the robustness of the associations.

In all analyses only patients with an observation time longer than 6 months were examined.

Statistical Methods

Both univariable and multivariable Cox-proportional-hazard regression models were utilized 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 on ART

calculated by dividing the number of months the patients was on ART over the number of months the patient was observed (later further subdivided into individual DAART and ART regimens). In a sensitivity analysis we also examined the proportion of observation time on ART while an individual is suppressed (i.e. viral load <400 copies/ml) and non-suppressed. Given the longitudinal nature of the data and the fact that outcome variable (HBV infection) cannot be observed exactly (contrary for example to death), a sensitivity analysis was performed using a parametric interval censored model with time varying covariates [19] (see supplementary material for method, R-code, and simulated data).

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

Results

Starting with all SHCS patients registered (December 2014) (N = 18,663), we kept only patients with a negative baseline HBV serology, at least another test after baseline, and who belonged to one of the major transmission groups (MSM, HET, and IDU) (N = 1,716), Figure 1. The risk group distribution was 936 HET (54%), 220 IDU (13%) and 612 MSM (33%). 4,532 individuals were excluded due to the unavailability of their HBV tests, said patients were mostly recruited early in the cohort (median 1990, IQR 1988-1992) and 95% died or were lost to follow up by 1996.

The total number of incident HBV cases was 177 of which 49% (86 cases) were in MSM. Patients' observation time started from the date of the first negative test and ended at the last time the patient was tested or if an event occurred. Most patients had only two tests (N = 1,129, 66%) (IQR 2-3), and the median time between tests was 29 months (IQR 12-58), Table 1. The total observation time was 10,682 person years. The overall incidence rate (IR) per thousand person years was (16, 95%CI 14-19). The transmission group incidence rate was as follows: HET (IR 9, 95%CI 6-11), IDU (IR 28, 95%CI 21-38), and MSM (IR 25, 95%CI 21-31) per thousand person years.

Both univariable and multivariable analysis showed a strong risk reduction of acquiring HBV for patients on DAART. In univariable analysis DAART had a protective effect against HBV acquisition with a Hazard ratio (HR) of 0.4 (95%CI 0.2-0.6), while other ART regimens had none (HR 1.63, 95%CI 0.94-2.81) (Figure 2 and Table 2). Furthermore, the exclusion of patients with isolated positive antiHBc serology did not affect the associations (HR 0.4,

95%CI 0.2-0.8). The proportion of time on DAART while HIV-RNA viral load is below 400 showed similar protective effect (HR 0.4, 95%CI 0.2-0.6), while being on DAART but not suppressed had no significant protection (HR 0.6, 95%CI 0.2-1.7). Other non-DAART antiretrovirals showed no protective effect even with suppression (HR 1.4, 95%CI 0.70-2.7), moreover being on non-DAART regimens and not suppressed was associated with higher HBV incidence (HR 3.4, 1.2-10.0), but this association was not significant in the multivariable model (multivariable HR 2.0, 95%CI 0.5-7.5). The log-likelihood ratio test showed no significant difference between the unadjusted model with DAART only and the model with DAART conditional on suppression (P-Value: 0.3), however the difference was borderline significant when comparing the adjusted models (P-Value: 0.055).

The univariable analysis also demonstrated a higher burden of incident cases in MSMs and IDU compared to HET (Table 2). Compared to heterosexual males, heterosexual females had lower odds of acquiring HBV (HR 0.5, 95%CI 0.3-1.0).

Self-reported risky sexual behavior was associated with higher risk of acquiring HBV. History of condomless sex was associated with higher HBV acquisition risk (HR 1.9, 95%CI 1.4-2.6), while having used intravenous drugs at any point during the observation time did not play a role (HR 1.0, 95%CI 0.2-3.8).

We examined the closest √CD4 count value to the HBV co-infection date as a proxy for immune-mediated effect of ART on HBV, and a protective association was observed, yet not statistically significant (HR 0.98, 95%CI 0.96-1.002). Neither the baseline √CD4 cell count

nor √CD8 cell count had an influence on the risk of HBV acquisition. Using non square root transformed values of CD4 and CD8 cell counts did not alter the associations.

One notable observation was the stronger protective effect of DAART in patients with CD4 nadir >=200 x 10^6 cells/ml (635 patients, 38%). In those patients DAART's protective effect was (HR 0.2, 95%CI 0.1-0.5) in the univariable model and (HR 0.1, 95%CI 0.1-0.4) in the multivariable one. DAART also had a protective effect in patients with CD4 nadir <200 10^6 cells/ml (1062 patients, 62%) yet only significant in the univariable model (univariable HR 0.5, 95%CI 0.3-0.8; multivariable HR 0.5, 95%CI 0.2-1.1). The difference in DAART's effect between patients with CD4 nadir => 200 and <=200 was not statistically significant in a multivariable Cox model with an interaction term between the proportion of time on DAART and nadir CD4.

The adjusted analysis displayed the same direction of association in terms of the protective effect of DAART (HR 0.3, 95%CI 0.2-0.6) (Table 2). √CD4 was not significant in the multivariable model (HR 1.0, 95%CI 0.98-1.03), while condomless sex remained significant (HR 1.9, 95%CI 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, evident by 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 0.3-0.6, adjusted HR 0.5, 95% CI 0.4-0.7).

In univariable analysis, the hazard of HBV acquisition for patients on two DAART (TDF/3TC and TDF/FTC) was half that of patients on one DAART (TDF alone or 3TC alone, FTC was not prescribed alone) (unadjusted HR two DAART 0.2, 95%CI 0.1-0.6; unadjusted HR one DAART 0.4, 95%CI 0.3-0.7). The protective effect of dual therapy was further strengthened after adjustment (adjusted HR two DAART 0.1, 95%CI 0.0-0.3; adjusted HR one DAART 0.4, 95%CI 0.2-0.6). We tested the statistical significance of the reduction of risk for two versus one DAART regimens by the likelihood-ratio test, and obtained P-Values of 0.2 and 0.01 for the univariable and the adjusted model respectively.

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 0.0-0.4) and (adjusted HR 0.2, 95%CI 0.1-0.5) 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 containing regimens had wide confidence intervals because of the short observation time patients were on TDF monotherapy. In the unadjusted model there was no statistically significant difference in the log-likelihood ratio test comparing all DAART combined versus individual DAART regimens (P-value: 0.1), while the difference was statistically significant in the adjusted model P-Value: 0.01).

Discussion

In this study we analyzed a large cohort of HIV-1 infected individuals at risk of acquiring HBV, in order to evaluate the protective effect of DAART in the three major HIV transmission groups (HET, IDU, MSM). We confirm earlier reports about the protective effect of dually acting anti-retroviral drugs 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 as it independently increases the risk even in patients on 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 was not a main actor in influencing the risk of acquiring HBV for patients on DAART. However, patients with a better long term immunological status (represented by nadir CD4 >= 200) had a higher protective effect of DAART.

Our study confirms 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 where individuals were not virologically suppressed. This further underlines a direct effect of DAART since treatment failure is associated with poor adherence [22,23] and generally with low plasma levels of drugs. For non-DAART regimens we found an increase in the hazard of an HBV infection in non-suppressed individuals, however this association was not robust to adjustment (multivariable HR 2.0, 95% CI 0.5-7.5). 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 model with suppression and without could indicated a power issue given the short periods patients are usually not suppressed (and on DA/ART). This is further supported by the fact that the likelihood ratio test was borderline significant (P-Value 0.055) in comparing the adjusted models. Fortunately, 96% of patients on ART in the SHCS are suppressed, consequently, this problem is less concerning in our setting [26]. The UNAIDS Gap Report shows that 76% of patients on ART achieved viral suppression, yet the bigger problem remains that 47% of the HIV-infected are unaware of their positive status[16].

Our findings also suggest that dual DAART regimens (i.e. TDF plus FTC or 3TC) are superior to single DAART regimens in protecting against incident HBV. This finding my be relevant for optimizing ART-regimes in settings where HBV incidence is high and vaccination coverage or response is low. One caveat to be aware of is that the majority of observation time on one drug was on 3TC, with the observation time on 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 only present in the adjusted model implying that other factors (such as immunological status and risk behavior) could have confounded the association in the unadjusted model.

Previous studies [12,14] suggest a superior protection of TDF over 3TC containing regimens. We did not observe a clear superiority of TDF over 3TC regimens in our data, evident by the likelihood ratio test and the overlapping confidence intervals 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+FTC regimens along with other TDF regimens and

did not encode the treatment as proportion of observation time, while Heuft et al. [12] adopted treatment averaging with categorization (detailed in the following paragraph).

As with all observational studies there are limitations to ours. The longitudinal and periodic nature of the data collection gives rise to uncertainty in knowing the precise infection date of HBV (Figure S1). Interval censored models with time varying covariates account for this varying exposure (i.e. treatment changes). However, these models are scarcely described or used in the literature [19]. Heuft et al. shared the same concerns about the interval censored nature of the data [12], yet they circumvented this problem by coding for the different treatments as proportion of observation time on the respective treatments with <20% equaling to no treatment, and larger is equivalent to being on a certain treatment. This method of handling treatment indeed avoids some of the problems of the treatment changes and interruptions, but remains problematic as patients on 21% DAART are treated as those on 100% (as discussed in [12]).

In order 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 the Cox proportional hazard model. The estimates of both models are in line with earlier reports [11–14].

Data on HBV incidence in Switzerland remains scarce, however it is plausible that it is on the decline as vaccination against HBV ramped up and better harm reduction interventions were employed for IDU, particularly needle exchange programs [27]. In order 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 0.2-0.6; adjusted HR 0.3, 95%CI 0.2-0.5).

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 majorly white population while that of Gatanaga et al [14] and Sheng et al. [13] are both comprised of an Asian majority. The consistency of the findings in previously conducted studies and ours suggest 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 evident by an isolated antiHBc serology only. The exclusion of those patients did not alter the protective DAART association (data not shown), suggesting that this serological profile is probably caused by HIV co-infection [18,28] and not by false positive lab tests as some studies suggested [18]. The isolated antiHBc in the HIV infected usually alludes to a recently resolved infection with low or undetected AntiHBs.

One interesting population that we were not able to examine, is patients who were vaccinated but did not mount an immune response. Such an analysis was not possible using the SHCS dataset, as the SHCS does not collect vaccination records of the patients.

One modeling study concluded [29] that even if vaccination uptake were to be 100% by all susceptible patients, a large fraction of patients would remain at risk of HBV acquisition, namely owing to the lower vaccination response in HIV 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 weapon in the arsenal of fighting HBV infections in HIV patients in general, and especially in settings where HBV vaccination uptake is low. Moreover, our study adds to the growing body of evidence that early antiretroviral therapy initiation [30], regardless of CD4 counts, has a strong beneficial public health impact, including pre-exposure prophylaxis of HBV co-infections.

Funding: this work was supported by the Swiss HIV Cohort Study, supported by the Swiss National Science Foundation [SNF grant #33CS30-134277 and 324730-112594] and the SHCS projects #470, 528, 569, 683, 760 the SHCS Research Foundation, the Swiss National Science Foundation [grant # 24730-112594 and -130865 (to HFG)], the European Community's Seventh Framework Program [grant FP7/ 2007–2013), under the Collaborative HIV and Anti-HIV Drug Resistance Network [CHAIN; grant 223131, to HFG], and by a further research grant of the Union Bank of Switzerland, in the name of an anonymous donor to HFG, an unrestricted research grant from Gilead, Switzerland to the SHCS research foundation, and by the University of Zurich's Clinical research Priority Program "Viral infectious diseases: Zurich Primary HIV Infection Study" (to HFG and DLB). RDK was supported by [SNF # PZ00P3-142411 and SNF #BSSGI0_155851]. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Acknowledgements: Special thanks for Bruno Ledergerber for his input on the analysis. We thank the patients who participate in the SHCS; the physicians and study nurses for excellent patient care; the resistance laboratories for high-quality genotypic drug-resistance testing; SmartGene, Zug, Switzerland, for technical support; Brigitte Remy, Martin Rickenbach, F.

Schoeni-Affolter, and Yannick Vallet from the SHCS Data Center in Lausanne for data management; and Danièle Perraudin and Mirjam Minichiello for administrative assistance.

The members of the Swiss HIV Cohort Study are: Aubert V, Battegay M, Bernasconi E, Böni J, Braun DL, Bucher HC, Burton-Jeangros C, Calmy A, Cavassini M, Dollenmaier G, Egger M, Elzi L, Fehr J, Fellay J, Furrer H (Chairman of the Clinical and Laboratory Committee), Fux CA, Gorgievski M, Günthard H (President of the SHCS), Haerry D (deputy of "Positive Council"),Hasse B, Hirsch HH, Hoffmann M, Hösli I, Kahlert C, Kaiser L, Keiser O, Klimkait T, Kouyos R, Kovari H, Ledergerber B, Martinetti G, Martinez de Tejada B, Metzner K, Müller N, Nadal D, Nicca D, Pantaleo G, Rauch A (Chairman of the Scientific Board), Regenass S, Rickenbach M (Head of Data Center), Rudin C (Chairman of the Mother & Child Substudy), Schöni-Affolter F, Schmid P, Schüpbach J, Speck R, Tarr P, Trkola A, Vernazza P, Weber R, Yerly S.

References

1. Thio CL, Seaberg EC, Skolasky R, et al. HIV-1, hepatitis B virus, and risk of liver-related mortality in the Multicenter Cohort Study (MACS). Lancet. **2002**; 360(9349):1921–1926.
2. Wandeler G, Gsponer T, Bihl F, et al. Hepatitis B virus infection is associated with impaired immunological recovery during antiretroviral therapy in the Swiss HIV cohort study. J Infect Dis. **2013**; 208(9):1454–8.
3. Konopnicki D, Mocroft A, Wit S de, et al. Hepatitis B and HIV: prevalence, AIDS progression, response to highly active antiretroviral therapy and increased mortality in the EuroSIDA cohort. AIDS. **2005**; 19(6):593–601.
4. Lozano R, Naghavi M, Foreman K, et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet. **2012**; 380(9859):2095–128.
5. Puoti M, Airoldi M, Bruno R, et al. Hepatitis B virus co-infection in human immunodeficiency virus-infected subjects. AIDS Rev. **2002**; 4(1):27–35.
6. Kourtis AP, Bulterys M, Hu DJ, Jamieson DJ. HIV-HBV coinfection--a global challenge. N Engl J Med. **2012**; 366(19):1749–52.
7. Schoeni-Affolter F, Ledergerber B, Rickenbach M, et al. Cohort profile: the Swiss HIV Cohort study. Int J Epidemiol. **2010**; 39(5):1179–89.
8. Chang JJ, Wightman F, Bartholomeusz A, et al. Reduced hepatitis B virus (HBV)-specific CD4+ T-cell responses in human immunodeficiency virus type 1-HBV-coinfected individuals receiving HBV-active antiretroviral therapy. J Virol. **2005**; 79(5):3038–51.
9. Okwen MP, Reid S, Njei B, Mbuagbaw L. Cochrane Database of Systematic Reviews. Cochrane database Syst. Rev. Chichester, UK: John Wiley & Sons, Ltd; 1996.

10. González R, Castro P, García F, et al. Effects of highly active antiretroviral therapy on vaccine-induced humoral immunity in HIV-infected adults. HIV Med. **2010**; 11(8):535–9.

11. Falade-Nwulia O, Seaberg EC, Snider AE, et al. Incident Hepatitis B Virus Infection in HIV-Infected and HIV-Uninfected Men Who Have Sex With Men From Pre-HAART to HAART Periods: A Cohort Study. Ann Intern Med. American College of Physicians; **2015**; 163(9):673–680.

12. Heuft MM, Houba SM, Berk GEL van den, et al. Protective effect of hepatitis B virus-active antiretroviral therapy against primary hepatitis B virus infection. AIDS. **2014**; .

13. Sheng W-H, Chuang Y-C, Sun H-Y, et al. Prophylactic effect of lamivudine-based antiretroviral therapy on incident hepatitis B virus infection among HIV-infected patients. Clin Infect Dis. **2013**; 57(10):1504–6.

14. Gatanaga H, Hayashida T, Tanuma J, Oka S. Prophylactic effect of antiretroviral therapy on hepatitis B virus infection. Clin Infect Dis. **2013**; 56(12):1812–9.

15. Beyrer C. HIV epidemiology update and transmission factors: risks and risk contexts--16th International AIDS Conference epidemiology plenary. Clin Infect Dis. **2007**; 44(7):981–7.

16. United Nations Programme on HIV/AIDS (UNAIDS). The Gap Report [Internet]. [cited 2016 Feb 17]. Available from: http://www.unaids.org/sites/default/files/en/media/unaids/contentassets/documents/unaidspublication/2014/UNAIDS_Gap_report_en.pdf

17. Schweitzer A, Horn J, Mikolajczyk RT, Krause G, Ott JJ. Estimations of worldwide prevalence of chronic hepatitis B virus infection: a systematic review of data published between 1965 and 2013. Lancet (London, England). **2015**; .

18. Pondé RAA, Cardoso DDP, Ferro MO. The underlying mechanisms for the “anti-HBc alone” serological profile. Arch Virol. **2010**; 155(2):149–58.

19. Sparling YH, Younes N, Lachin JM, Bautista OM. Parametric survival models for interval-censored data with time-dependent covariates. Biostatistics. **2006**; 7(4):599–614.

20. Lascar RM, Gilson RJ, Lopes AR, Bertoletti A, Maini MK. Reconstitution of hepatitis B virus (HBV)-specific T cell responses with treatment of human immunodeficiency virus/HBV coinfection. J Infect Dis. **2003**; 188(12):1815–9.

21. Lascar RM, Lopes AR, Gilson RJ, et al. Effect of HIV infection and antiretroviral therapy on hepatitis B virus (HBV)-specific T cell responses in patients who have resolved HBV infection. J Infect Dis. **2005**; 191(7):1169–79.

22. Cadosch D, Bonhoeffer S, Kouyos R. Assessing the impact of adherence to anti-retroviral therapy on treatment failure and resistance evolution in HIV. J R Soc Interface. **2012**; 9(74):2309–20.

23. Bangsberg DR. Preventing HIV antiretroviral resistance through better monitoring of treatment adherence. J Infect Dis. **2008**; 197 Suppl (Supplement_3):S272–8.

24. Kalichman SC. Co-occurrence of treatment nonadherence and continued HIV transmission risk behaviors: implications for positive prevention interventions. Psychosom Med. **2008**; 70(5):593–7.

25. Diamond C, Richardson JL, Milam J, et al. Use of and adherence to antiretroviral therapy is associated with decreased sexual risk behavior in HIV clinic patients. J Acquir Immune Defic Syndr. **2005**; 39(2):211–8.

26. Kohler P, Schmidt AJ, Cavassini M, et al. The HIV care cascade in Switzerland: reaching the UNAIDS/WHO targets for patients diagnosed with HIV. AIDS. **2015**; .

27. Niederhauser C, Schneider P, Fopp M, Ruefer A, Lévy G. Incidence of viral markers and evaluation of the estimated risk in the Swiss blood donor population from 1996 to 2003. Euro Surveill. **2005**; 10(2):14–6.

28. Witt MD, Lewis RJ, Rieg G, Seaberg EC, Rinaldo CR, Thio CL. Predictors of the

isolated hepatitis B core antibody pattern in HIV-infected and -uninfected men in the multicenter AIDS cohort study. Clin Infect Dis. **2013**; 56(4):606–12.

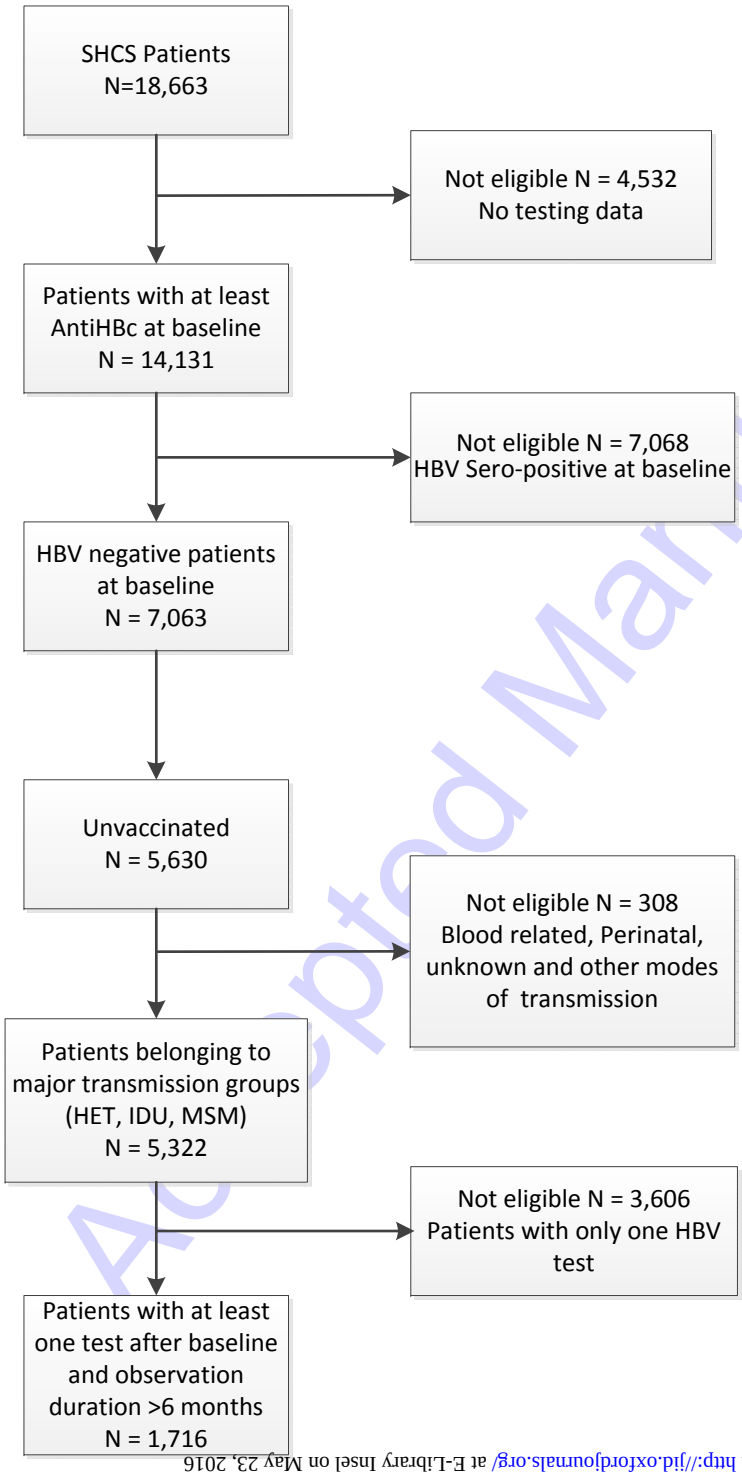
29. Calisti G, Capocci SJ, Ware A, et al. Impact of hepatitis B-active combination antiretroviral therapy on hepatitis B susceptibility in newly diagnosed HIV patients. Clin Infect Dis. **2014**; 58(1):137–9.

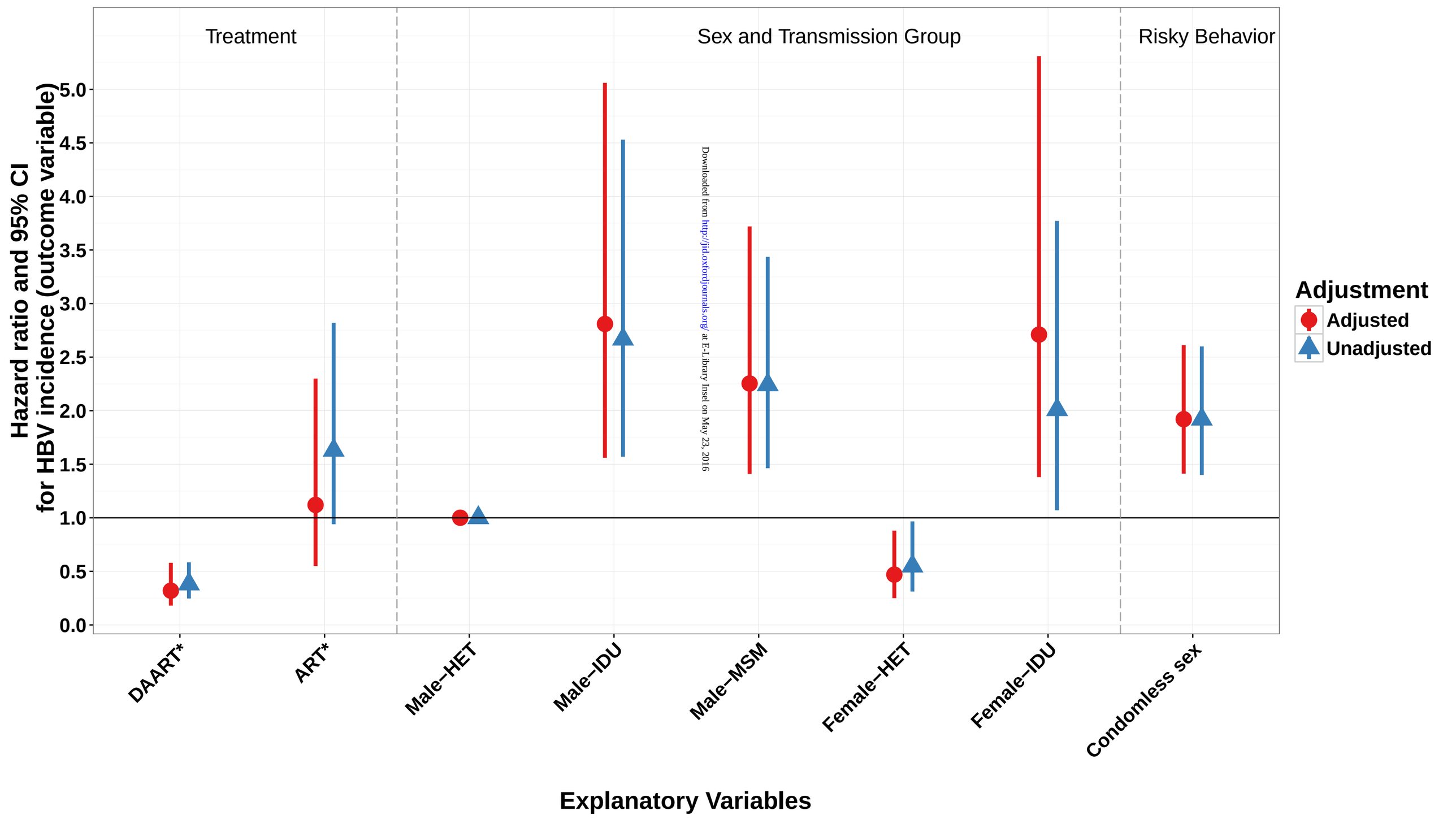
30. Bärnighausen T, Eyal N, Wikler D. HIV treatment-as-prevention research at a crossroads. PLoS Med. Public Library of Science; **2014**; 11(6):e1001654.

Figures captions

Figure. 1 **Patients selection flowchart**

Figure. 2 **The hazard ratios of the different factors influencing HBV incidence. Adjusted models co-variates shown in Table 2, column 2.** *Proportion of observation time. DAART: Dually Active Antiretrovirals, ART: HIV only Antiretrovirals (ART).





Tables

Table 1 Baseline characteristics of the 1716 patients eligible for the study based on their HBV status

	Patients with an incident HBV infection (N. = 177)	Patients with 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, cells/mm3, median (IQR)	429 (265-636)	432 (271-625)
Age at registration in years , median (IQR)	33 (27-38)	33 (28-40)
HIV-1 RNA, log10 copies/mL, median (IQR)	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)
Percentage 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)
N. of tests, media (IQR)	2 (2-2)	2 (2-3)
Observation time in months, media (IQR)	59 (32-99)	66 (34-111)
History of drug use (%)	2 (1%)	16 (1%)
ART start year, median (IQR)	1997 (1996-2002)	1998 (1996-2004)
Infection year, median (IQR)	2006 (2002-2010)	-

Table 2. Univariable and Multivariable Cox proportional hazard models for the effect of DAART and ART on the acquisition of HBV (bold signifies a P-Value < 0.05)

	Univariable Analysis	Multivariate Analysis Complete cases only (N. = 1,697)
Proportion of observation time on treatment		
DAART	**0.38 (0.25-0.58)**	**0.32 (0.18-0.58)**
ART	1.63 (0.94-2.81)	1.12 (0.55-2.30)
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 (0.31-0.97)**	**0.47 (0.25-0.88)**
Female-IDU	**2.01 (1.07-3.77)**	**2.71 (1.38-5.31)**
Ethnicity		
White	1 (Reference)	1 (Reference)
Black	0.62 (0.33-1.18)	1.52 (0.71-3.26)
Hispano-American	1.03 (0.46-2.34)	1.53 (0.66-3.53)
Asian	1.77 (0.78-4.01)	2.37 (0.96-5.85)
Other/Unknown	1.38 (0.51-3.74)	1.18 (0.42-3.31)
Age at cohort enrollment	1.00 (0.98-1.02)	1.01 (0.99-1.03)
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)**
√CD4 count at test time	0.98 (0.96-1.00)	1.00 (0.98-1.03)
√CD8 count at test time[b]	1.01 (0.99-1.03)	1.00 (0.98-1.03)
√baseline CD4 count	1.00 (0.92-1.01)	0.98 (0.95-1.00)
History of Intravenous drug use[d]	0.92 (0.23-3.73)	-

a (17 missing values)
b (3 missing values)
d Excluded for possible collinearity with IDU transmission group

Table 3 Univariable and Multivariable Cox regression of the effect of different ART regimens on the acquisition of HBV (bold signifies a P-Value < 0.05)

	Univariable Analysis	Multivariate Analysis Complete cases only (N. = 1,697)
Proportion of observation time on treatment		
TDF	0.56 (0.12-2.56)	0.23 (0.04-1.14)
3TC	**0.42 (0.28-0.68)**	**0.41 (0.22-0.75)**
TDF+3TC	**0.02 (0.00-0.34)**	**0.03 (0.00-0.43)**
TDF+FTC	0.42 (0.14-1.22)	**0.16 (0.05-0.55)**
Other ART regimens	1.02 (0.57-1.80)	1.17 (0.57-2.40)
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 (0.31-0.97)**	**0.47 (0.25-0.88)**
Female-IDU	**2.01 (1.07-3.77)**	**2.69 (1.37-5.26)**
Ethnicity		
White	1 (Reference)	1 (Reference)
Black	0.62 (0.33-1.18)	1.50 (0.70-3.22)
Hispano-American	1.03 (0.46-2.34)	1.55 (0.67-3.60)
Asian	1.77 (0.78-4.01)	2.35 (0.95-5.81)
Other/Unknown	1.38 (0.51-3.74)	1.18 (0.42-3.29)
Age at cohort enrollment	1.00 (0.98-1.02)	1.01 (0.99-1.03)
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)**
√CD4 count at test time	0.98 (0.96-1.00)	1.00 (0.97-1.03)
√CD8 count at test time[b]	1.01 (0.99-1.03)	1.00 (0.98-1.02)
√baseline CD4 count	1.00 (0.92-1.01)	0.98 (0.96-1.00)

a (17 missing values)
b (3 missing values)