Dually Active HIV/HBV Antiretrovirals Protect Against Incident Hepatitis B Infections

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

Background

- Hepatitis B virus (HBV) has a detrimental effect on HIV natural course, and HBV vaccination in HIV infected individuals is less likely to elicit a protective immune response compared to HIV uninfected ones.
- 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 (MSM), and intravenous drug users (IDU); who are HIV-infected yet susceptible to HBV, with comprehensive follow-up data about risky sexual behavior and immunological status.

Methods

- We defined an incident HBV infection as the presence of any of HBV serological markers (HBsAg, AntiHBc, or HBV-DNA) following a negative baseline test. We excluded patients who only developed positive AntiHBs response (i.e. vaccinated). Both univariate and multivariate Cox proportional hazard models were utilized, with an incident case of HBV infection as the outcome variable. The multivariable model was adjusted for proportion of observation time on treatment (ART/DAART), age, sex/transmission risk group combination, ethnicity, registration year, baseline √CD4, √CD4 and √CD8 at test time.

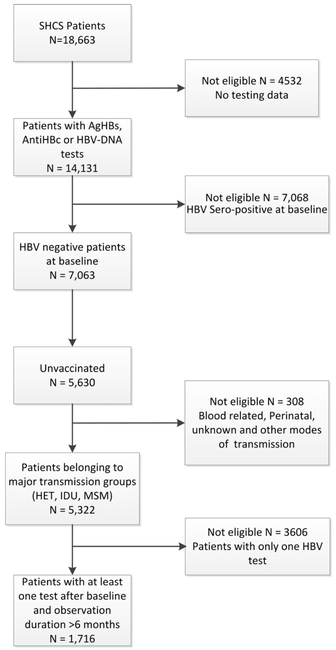


Figure 1. Patients selection flowchart.

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

	Patients with an incident HBV infection (N. = 177)	Patients with no incident HBV infection (N. = 1539)
Age at registration in years ,median (IQR)	33 (27-38)	33 (28-40)
Sex		
Male, n (%)	141 (80)	971 (63)
Female, n (%)	36 (20)	568 (37)
Transmission group		
HET, n (%)	49 (28)	887 (58)
IDU, n (%)	42 (24)	178 (12)
MSM, n (%)	86 (48)	474 (31)
CD4+ cell count, cells/mm3, median (IQR)	429 (265-636)	432 (271-625)
HIV-1 RNA, log10 copies/mL, median (IQR)	3.5 (2.1-4.7)	3.4 (2.0-4.4)
Ethnicity		
White, n (%)	151 (85)	1246 (81)
Black, n (%)	10 (6)	170 (11)
Hispano-American, n (%)	6 (3)	52 (3)
Asian, n (%)	6 (3)	30 (2)
Other/Unknown, n (%)	4 (3)	41 (3)
Percentage of observation time on DAART, median (IQR)	35 (0-80)	60 (15-94)
Percentage of observation time on ART, median (IQR)	0 (0-28)	0 (0-14)
Year of enrollment, median (IQR)	1996 (1992-2001)	1998 (1994-2003)
N. of tests, median (IQR)	2 (2-2)	2 (2-3)
Observation time in months, median (IQR)	59 (32-99)	66 (34-111)
History of drug use (%) , n (%)	2 (1%)	16 (1%)

Results

- We analyzed 1,716 eligible patients from the Swiss HIV Cohort Study with 177 incident HBV cases and 10,682 person years (Figure 1, Table 1).
- Both in the bivariate and in the adjusted models time on DAART was strongly and negatively associated with incident HBV infection, adjusted hazard ratio (HR) 0.3, (95 C.I 0.2-0.5) while other ART type had no significant effect HR 1.12 (95 C.I 0.55-2.30).
- Condomless sex (HR 1.9, 95 C.I 1.4-2.6), belonging to MSM (HR 2.7, 95 C.I 1.7-4.2) or IDU (HR 3.8, 95 C.I 2.4-6.1) transmission risk groups as well as registration year (HR 1.06 ,95 C.I 1.03-1.10) were all associated with higher HBV acquisition hazard (Figure 2).
- Additionally, the hazard of HBV acquisition for patients on two DAART (TDF/3TC and TDF/FTC) was lower as compared to patients on a single DAART (TDF alone or 3TC alone, FTC was not prescribed alone), (adjusted HR two DAART 0.1, 95% CI 0.0-0.3; adjusted HR single DAART 0.4, 95%CI 0.2-0.6).

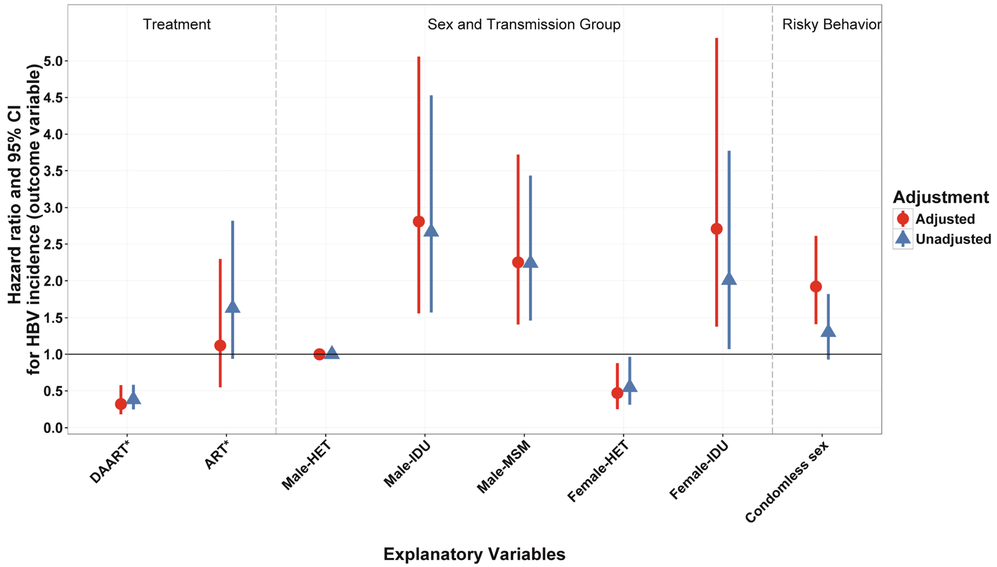


Figure. 2 The hazard ratios of the different factors associated with HBV incidence. *Proportion of observation time. DAART: Dually Active Antiretrovirals, ART: HIV only Antiretrovirals (ART).

Conclusions

- Our study suggests that DAART might be an additional tool in the arsenal of fighting HBV infections in HIV patients in general, and especially in settings where HBV vaccination uptake is low.
- Early antiretroviral therapy initiation, regardless of CD4 counts, can have a strong beneficial public health impact, including pre-exposure prophylaxis of HBV co-infections.