

Longitudinal evaluation of hepatitis B, C and/or D viremia in HIV-HBV co-infected patients: virological interactions and effects of treatment

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Abstract (Updated)

Introduction: In the context of HIV-infected patients, virological interactions of hepatitis B (HBV), hepatitis C (HCV), and hepatitis D (HDV) viruses have been poorly characterized and treatment influences have not been analyzed.

Methods: Viral fluctuations were prospectively studied during a 3-year period in a cohort of 308 HIV-HBV co-infected patients. In a first analysis, undetectability rates of HBV-DNA, HCV-RNA, and HDV-RNA were summarized and compared using GEE models with calculation of OR adjusted for age, serum HIV-RNA, CD4 cell count, concurrent treatment with lamivudine/emtricitabine and adefovir/tenofovir, and concurrent or prior treatment with interferon. In an alternative analysis, the changes of viral detection were evaluated in the presence of treatment.

Results: Hepatic co-infection in HIV-infected patients (age in years, SD) was as follows: 265 HBV (40.7, 8.2); 19 HBV-HCV (39.7, 4.1); 12 HBV-HDV (35.2, 9.9); and 12 HBV-HCV-HDV (39.2, 5.2). Lamivudine and tenofovir were prescribed before inclusion in 87.0% and 17.5% of patients, respectively, and did not differ across co-infection groups ($p=0.2$, $p=0.7$). HDV co-infected patients used interferon therapy more frequently ($p=0.02$). Hepatitis B virus suppression was significantly associated with the presence of HDV (aOR=3.85, 95% CI 1.13-13.10, $p=0.03$) and HCV co-infection (aOR=2.65, 95% CI 1.03-6.81, $p=0.04$), whereas marginal suppression was found in the presence of HCV/HDV co-infection (aOR= 2.32, 95% CI 0.94-5.74, $p=0.07$ respectively). HBV-HCV-HDV infection tended to have a modest suppression of HCV replication ($p=0.1$), with an increase in HDV replication ($p=0.2$). HIV-replication was associated with diminished HBV replication ($p<0.001$), an effect not observed on HCV or HDV replication. Adefovir/tenofovir had a more suppressive effect on HBV replication (aOR=3.24, 95% CI 2.27-4.63, $p<0.001$) while interferon had a suppressive effect on HCV ($p=0.04$). HDV-replication was more uncontrolled by treatment than HCV.

Conclusion: In comparing detection between hepatic viruses, it appears that HDV plays a dominating influence on HBV and HCV replication, independent of the influences of treatment, CD4 cell count and HIV-replication. Future studies must consider the viral detectability under the influence of treatment, which can only be assessed in longitudinal evaluation.

Introduction

• Due to the similar transmission modes of human immunodeficiency virus (HIV), hepatitis B virus (HBV), hepatitis C virus (HCV), and hepatitis D virus (HDV), co-infection occurs relatively frequently.^{1,2}

• Viral interactions in such co-infected HIV-infected patients have only been studied cross-sectionally; a more recent study has concluded viral suppression of HDV on HBV replication.³

• Fluctuating replication profiles between HBV and HCV have been found in HIV-negative patients,⁴ yet have not been sufficiently examined in the context of HIV, where antiviral treatment is largely used and may interfere with viral interactions.

Objective

To examine interactions between hepatitis viruses in HIV-HBV co-infected patients with respect to HCV and/or HDV co-infection, HIV-disease indicators, and antiviral treatment.

Methods and Patients

Study Design

• 3-year, prospective, longitudinal study with baseline and every 12-months clinical and virological assessment

Patients

- Recruited from the French 2002 – 2006 HIV-HBV Cohort Study and enrolled in the present study according to the following inclusion criteria:
 - HIV enzyme linked immunoabsorbant assay (ELISA) positivity confirmed by a Western-Blot
 - HBsAg seropositivity
 - Available HCV and HDV serology at baseline

Methods and Patients (con't)

Co-infection groups

- Defined by positive HCV and/or HDV serology (>6 months) every 12 months.

Standardized detection limit

- Undetectable thresholds arbitrarily chosen as the following:
 - HBV-DNA < 600 UI/mL
 - HCV-RNA < 615 UI/mL
 - HDV-RNA < 1000 copies/mL

Modeling detectable hepatic viremia during follow-up

- Proportion of detectable HBV, HCV and HDV compared across co-infection groups using adjusted, multivariable GEE models (with exchangeable working correlation structure).

Treatment influence on viral hepatitis detection

- Stabilizations/fluctuations of replicating virus in the presence of treatment evaluated every 12 months (in patients with complete follow-up).

Results

Description of Study Population

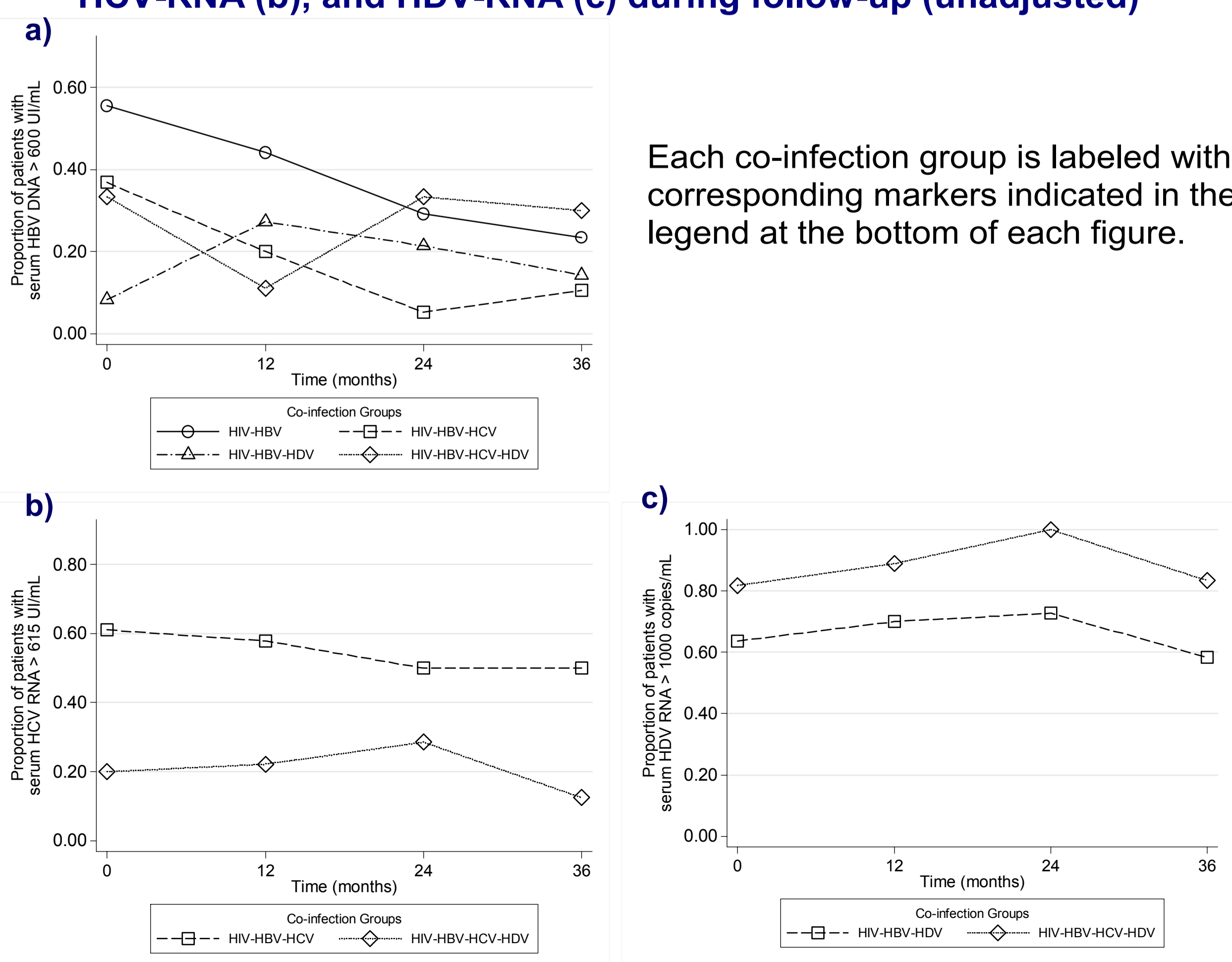
Table 1: Patients according to viral hepatitis subgroups at baseline

	HIV-HBV (n=265)	HIV-HBV w/ HCV (n=19)	HIV-HBV w/ HDV (n=12)	HIV-HBV w/ HCV-HDV (n=12)	Sign
Demographics					
Sex Ratio, m/f (% male)	224/41 (84.5)	16/3 (84.2)	8/4 (66.6)	11/1 (91.7)	ns
Age years, mean (SD)	40.7 (8.2) ^a	39.7 (4.1) ^{ab}	35.2 (9.9) ^b	39.2 (5.2) ^{ab}	*
HIV and Hepatitis Infection					
Estimated duration of HIV infection years, mean (SD)	8.6 (5.5) ^a	13.5 (3.9) ^b	8.1 (6.4) ^a	13.4 (5.4) ^b	*
AIDS-defining event, nb (%)	67 (25.3)	6 (31.6)	2 (16.7)	4 (33.3)	ns
CD4+ cell count /mm ³ , mean (SD)	445 (262)	413 (235)	414 (135)	297 (155)	ns
Treatment Characteristics Before Inclusion					
Nb (%) of patients treated w/ lamivudine	217 (81.9)	17 (89.5)	10 (83.3)	12 (100)	ns
Nb (%) of patients treated w/ tenofovir	49 (18.5)	2 (10.5)	0	3 (25.0)	ns
Nb (%) of patients treated w/ interferon	48 (18.1) ^a	3 (15.8) ^{ab}	4 (33.3) ^{ab}	5 (41.7) ^b	ns

Means were compared horizontally between co-infected groups. For each comparison, means or numbers with different letters indicate significant differences ($p < 0.05$), while those sharing the same letter are indistinguishable.

Overall Effect of Co-infection on Replicative Viral Hepatitis

Fig 1. Proportion of patients with detectable serum HBV-DNA (a), HCV-RNA (b), and HDV-RNA (c) during follow-up (unadjusted)



Each co-infection group is labeled with corresponding markers indicated in the legend at the bottom of each figure.

Results (con't)

Overall Effect of Co-infection on Replicative Viral Hepatitis (con't)

Table 2. Determinants of viral interaction, HIV-disease indicators, and antiviral treatment on the proportion of HBV-DNA, HCV-RNA, and HDV-RNA undetectability

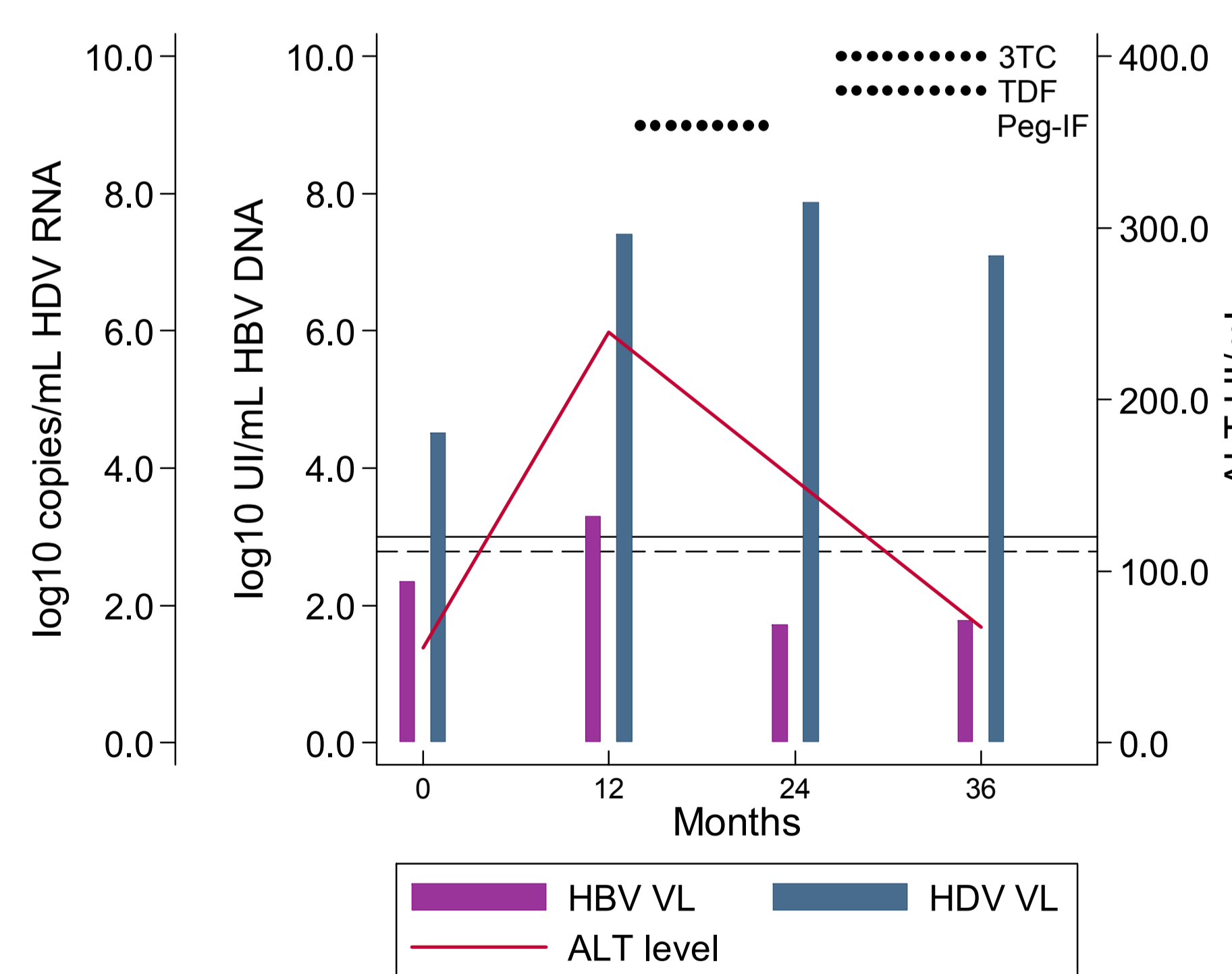
	Unadjusted			Adjusted ¹		
	OR	95% CI	p	aOR	95% CI	p
a) HBV-DNA undetectability (<600 IU/mL)						
Co-infection group ² [vs. HIV-HBV (n=265)]						
w/ HCV (n=19)	3.08	(1.21-7.87)	0.01	2.65	(1.03-6.81)	0.04
w/ HDV (n=12)	2.70	(0.91-8.03)	0.07	3.85	(1.13-13.10)	0.03
w/ HCV-HDV (n=12)	1.58	(0.62-4.02)	0.3	2.32	(0.94-5.74)	0.07
Concurrent treatment with lamivudine and/or emtricitabine	1.69	(1.18-2.43)	0.004	0.97	(0.65-1.46)	0.9
Concurrent treatment with adefovir and/or tenofovir	3.79	(2.74-5.25)	<0.001	3.24	(2.27-4.63)	<0.001
Prior and current treatment with standard and/or peg-interferon	2.28	(1.09-4.76)	0.02	1.58	(0.61-4.07)	0.3
b) HCV-RNA undetectability (<615 IU/mL)						
Co-infection group ² [vs. w/ HCV (n=19)]						
w/ HCV-HDV (n=12)	7.78	(1.37-44.25)	0.02	5.65	(0.65-48.86)	0.1
Concurrent treatment with lamivudine and/or emtricitabine	1.60	(0.78-3.29)	0.2	2.10	(0.86-5.14)	0.1
Concurrent treatment with adefovir and/or tenofovir	1.14	(0.91-1.42)	0.3	0.88	(0.58-1.32)	0.5
Prior and current treatment with standard and/or peg-interferon	1.91	(0.89-4.12)	0.1	3.53	(1.07-11.66)	0.04
c) HDV-RNA undetectability (<1000 copies/mL)						
Co-infection group ² [vs. w/ HDV (n=12)]						
w/ HCV-HDV (n=12)	0.30	(0.05-1.98)	0.2	0.30	(0.04-2.24)	0.2
Concurrent treatment with lamivudine and/or emtricitabine	0.87	(0.28-2.70)	0.8	1.15	(0.40-3.26)	0.8
Concurrent treatment with adefovir and/or tenofovir	0.78	(0.22-2.74)	0.7	0.68	(0.21-2.20)	0.5
Prior and current treatment with standard and/or peg-interferon	1.18	(0.54-2.59)	0.7	1.41	(0.60-3.29)	0.4

¹ Multivariable models were adjusted for age, indicators of HIV-infection (serum HIV-RNA > 250 copies/mL and CD4+ cell count > 200 cells/mm³) and anti-hepatic viral treatment (concurrent treatment with lamivudine and/or emtricitabine, concurrent treatment with adefovir and/or tenofovir, and prior and current treatment with interferon and/or peg-interferon).

² The number of each co-infection group is at baseline. Four HIV-HBV co-infected patients seroconverted to either HCV (n=2) or HDV (n=2) during follow-up.

Treatment Influence on Viral Hepatitis Replication Profiles

Fig 2. Example of a treatment-response profile in a tri-infected patient



This patient had pre-controlled HBV from treatment with lamivudine prior to inclusion. HBV viremia "blipped" at the 12-month visit. HDV-RNA was uncontrolled throughout follow-up, even under treatment.

- HBV profiles were similarly pre-controlled or controlled across co-infection groups [HIV-HBV = 142 (77.6%), HIV-HBV-HCV = 12 (85.7%); HIV-HBV-HDV = 5 (62.5%), HIV-HBV-HCV-HDV = 2 (50.0%); $p = 0.3$]
- HBV profiles tended to blip more frequently under quad-infection vs all other co-infection groups [2 (50.0%) vs. 13 (6.3%), $p=0.0008$]
- HDV profiles remained more uncontrolled than those of HCV regardless of co-infection group [7/12 (58.3%) vs. 7/18 (38.9%), respectively].

Conclusion

When comparing HBV, HCV, and HDV detection in HIV-infected patients:

- An overall significant suppression of HBV was observed under HCV and HDV co-infection.
- HDV was more dominant over HCV replication in quad-infection, which may have resulted in a less potent suppression of HBV.
- Concurrent treatment with Adefovir or Tenofovir also induces a significant suppression of HBV over time, whereas HCV and HDV replications are not influenced by antiviral treatment.
- Fluctuations of viral interactions can persist throughout the course of infection, even under anti-hepatic treatments.

Because of the confounding action of antiviral treatment and the fluctuating viral interactions between HBV, HCV and HDV, it is essential that future studies longitudinally evaluate hepatic viral interactions, especially in the context of HIV infection.

References and Acknowledgements

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