Detectable HBV viraemia in HIV/HBV co-infected patients undergoing HBV active antiretroviral therapy

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Background

Approximately 33 million people globally are infected with HIV and are coinfected with hepatitis B virus (HBV) on average 10 – 20% . HIV infection has a significant impact on the natural history of chronic HBV infection, with increased levels of HBV DNA, accelerated progression of liver disease, and increased liver associated mortality. Tenofovir disoproxil fumarate (TDF) and tenofovir alafenamide (TAF), approved for the treatment of both HIV and HBV, are very effective in suppressing both their replication in participants with HIV– HBV coinfection. TDF and TAF are active against wild-type HBV and HBV strains that contain lamivudine (LMV) resistance polymerase gene mutations. In addition, TAF improves the renal and bone safety profile compared to TDF while maintaining similar virological efficacy and safety. Therefore, elderly people living with HIV (PLWH)/HBV or those with long-term use of TDF may have a benefit in switching from TDF to TAF. Cases of resistance to TDF and TAF have not been reported, while few data are available on TDF or TAF suboptimal response(1,2). However, the reasons for HBV-DNA detectability during HBV/HIV active ART are unclear.

Aim of the study

We investigated the frequency of HBV detectable viremia and possible clinical related factors in PLWH and HBV coinfection.

HBV Treatment Indication (EACS 2021)

1. *All PLWH with HBV/HIV co-infection should receive ART that includes TDF or TAF unless history of tenofovir intolerance.*
2. *Stopping anti-HBV active ART should be avoided in persons with HIV/ HBV co-infection because of the high risk of severe hepatitis flares and decompensation following HBV reactivation hepatitis.*

Methods

Study Participants

145 PLWH, HBsAg positive, followed as outpatients at San Raffaele Hospital with available HBV-DNA quantitation in years 2020-21 and currently receiving ART, including TDF or TAF, were enrolled. Anonymized clinical and laboratory data were collected or extracted from the Infectious Diseases Department database (CSLHIV Cohort). Written informed consent was obtained from all participants, and the study was approved by the ethics committee of the San Raffaele Hospital, Milan, Italy.

Virological Assays

HBV DNA and HIV RNA were measured by real-time PCR (Cobas 6800 system, Roche diagnostic, Italy); HBV DNA was classified as detectable ≥10 IU/mL or undetectable <10 IU/mL. HIV RNA was classified as detectable (≥50 copies/mL) or undetectable (<50 copies/ml).

Resistance mutations within the polymerase gene of HBV were detected by population sequencing.

Statistical Analysis

Results were reported as median (interquartile range, IQR) or frequency (%). Categorical variables were compared using the χ^2 test, or Fisher's exact test. Continuous variables were compared using the Mann–Whitney test. A p value < 0.05 was considered statistically significant. Analysis was completed using R software, version 4.1.2 (2021-11-01).

Results

Characteristics of PLWH/HBV under ART active on HIV/HBV according to HBV-DNA detectability or not are summarized in Table 1.

Overall

Most patients were males and the main route of transmission was the sexual route.

The comparison of HBV DNA positive participants with those HBV DNA negative showed a different immune status profile:

- Higher CD8 cells count in the HBV DNA positive group (1060 [886;1313] *vs* 876 [583;1189]) with a trend towards significance (p=0.054),
- Lower CD4/CD8 ratio in the HBV DNA positive group (0.32 [0.24;0.52] *vs* 0.81 [0.58;1.06], p=0.003),

while CD4 cells count were similar in the two groups.

Concerning HIV load, HBV DNA positive participants with respect to HBV DNA negative participants had:

- Higher frequency of HIV-RNA positivity (≥50 copies/mL), 35.7%, compared to HBV DNA negative participants who had a 9.92% positivity. (p=0.041)
- Higher HIV viral load (23.5 [5.42;73.5]) compared to HBV DNA negative participants (0.90 [0.90;26.0]) (p=0.017).

Concerning necroinflammatory activity assessed by transaminases and gamma glutamyl transpeptidase (GGT) levels, HBV DNA positive PLWH had:

- Higher aspartate aminotransferase (AST) (44.5 [34.0;54.8]), alanine aminotransferase (ALT) (53.5 [38.2;63.0]), both with p<0.001, and GGT (47.0 [31.0;109]) levels (p=0.006).

HBeAg was positive in a higher percentage in the HBV DNA positive group than in the HBV DNA negative one, as described in Figure 1. Anti-HBeAg antibodies were present in higher proportion in the HBV DNA negative group, as described in Figure 2.

In HBV DNA positive participants the median period from the most recent positive HBV DNA evaluation was 262 days [IQR: 32.5;475], while in HBV negative participants the median period from the most recent negative HBV DNA evaluation was 2528 days [IQR: 997;3702].

Table 1. Characteristics of HBV DNA positive and HBV DNA negative subjects in the cohort

		[ALL] N=145	Negative (or unknown) N=131	Positive N=14	P value
Age years		54.9 [50.1;60.3]	55.3 [50.4;60.3]	53.3 [49.1;58.5]	0.343
Sex female/male		14 (9.66%)/131 (90.3%)	12 (9.16%)/119 (90.8%)	2 (14.3%)/12 (85.7%)	0.627
Risk Factors for HIV infection					0.061
	Unknown	36 (24.8%)	29 (22.1%)	7 (50.0%)	
	Sexual Exposure	89 (61.4%)	84 (64.1%)	5 (35.7%)	
	Drug (or Ex) Users	20 (13.8%)	18 (13.7%)	2 (14.3%)	
CD4 cells count number/mmc		676 [464;865]	678 [488;862]	511 [291;893]	0.308
CD8 cells count number/mmc		893 [592;1203]	876 [583;1189]	1060 [886;1313]	0.054
CD4/CD8 ratio		0.80 [0.53;1.05]	0.81 [0.58;1.06]	0.32 [0.24;0.52]	0.003
AST IU/L		26.0 [22.0;34.0]	26.0 [21.2;32.0]	44.5 [34.0;54.8]	<0.001
ALT IU/L		27.0 [19.8;42.2]	26.0 [19.0;37.8]	53.5 [38.2;63.0]	<0.001
GGT IU/L		25.0 [18.0;41.0]	25.0 [18.0;36.0]	47.0 [31.0;109]	0.006
Birilubin mg/dL		0.55 [0.40;0.87]	0.54 [0.38;0.90]	0.63 [0.49;0.74]	0.313
Anti HDV neg/pos/unknown		76 (52.4%)/13 (8.97%)/56 (38.6%)	68 (51.9%)/12 (9.16%)/51 (38.9%)	8 (57.1%)/1 (7.14%)/5 (35.7%)	1.000
Anti HCV neg/pos/unknown		104 (71.7%)/25 (17.2%)/16 (11.0%)	95 (72.5%)/22 (16.8%)/14 (10.7%)	9 (64.3%)/3 (21.4%)/2 (14.3%)	0.727
HBV DNA IU/mL		120 [22.2;1408]	. [.;.]	120 [22.2;1408]	.
HIV RNA copies/mL:					0.041
	Neg (<50)	120 (82.8%)	111 (84.7%)	9 (64.3%)	
	Pos (>=50)	18 (12.4%)	13 (9.92%)	5 (35.7%)	
	Unknown	7 (4.83%)	7 (5.34%)	0 (0.00%)	
HIV RNA num. values		0.90 [0.90;35.2]	0.90 [0.90;26.0]	23.5 [5.42;73.5]	0.017
HIV RNA num. values only for positive		110 [82.5;424]	106 [93.0;351]	114 [74.0;449]	0.805
Years of ART		12.3 [7.64;14.7]	12.2 [7.74;14.7]	12.5 [6.20;14.8]	0.629

Results described by median (IQR) or frequency (%). Abbreviations: AST : aspartate aminotransferase (normal values (NV) <35 IU/L); ALT :alanine aminotransferase (NV <59 IU/L); GGT gamma glutamyl transpeptidase (NV <68 IU/L) HDV: hepatitis D virus; HCV: hepatitis C virus; HBV: hepatitis B virus; HIV: human immunodeficiency virus; ART: antiretroviral therapy.

Concerning HBV resistance pattern:

- 2/9 of HBV-DNA positive PLWH tested had resistance to lamivudine and entecavir, L180M and M204V, but none had resistance to TAF or TDF.
- One other participant previously found to harbor a resistant strain to lamivudine had a reversion to wild type, although HBV-DNA was positive at high levels (35800000 IU/mL). This patient was on ART including TAF 10 mg + FTC and treatment was changed to TDF + FTC with a dramatic reduction of HBV viremia (127.000 IU/mL). This case is described in Figure 4.

Concerning adherence to treatment, poor treatment adherence was recorded in 4/14 HBV-DNA positive participants.

About antiretroviral therapy, compared to the HBV DNA undetectable group, patients with detectable HBV DNA had:

- More prescription of TAF10 and TDF.
- Way less prescription of TAF25 .

As described in Figure 3.

Figure 1. Serology HBsAg in HBV DNA positive (A) and negative (B) participants.

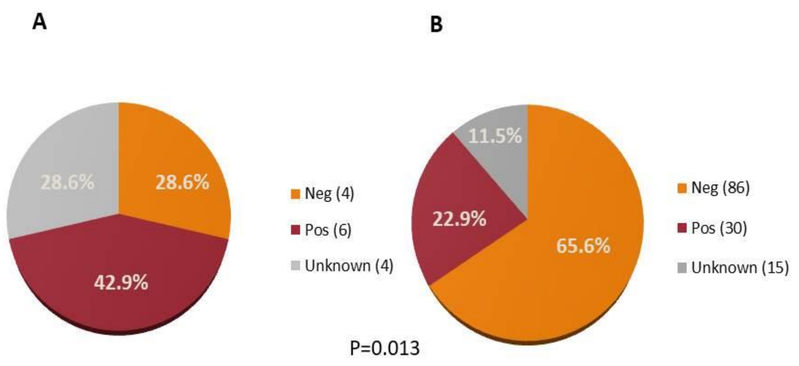


Figure 2. Anti-HBsAg antibodies in HBV DNA positive (A) and negative (B) participants.

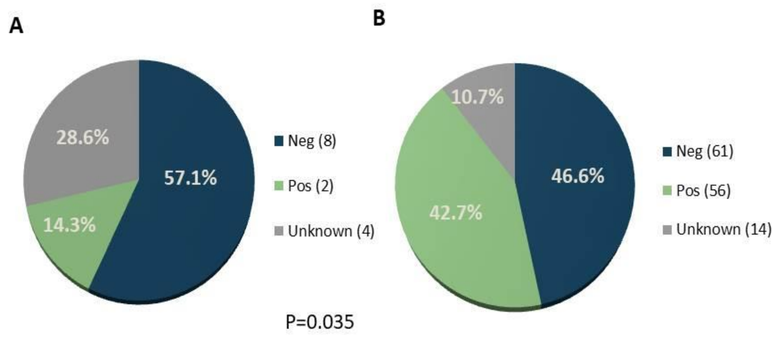


Figure 3. Antiretroviral therapy according to HBV DNA.

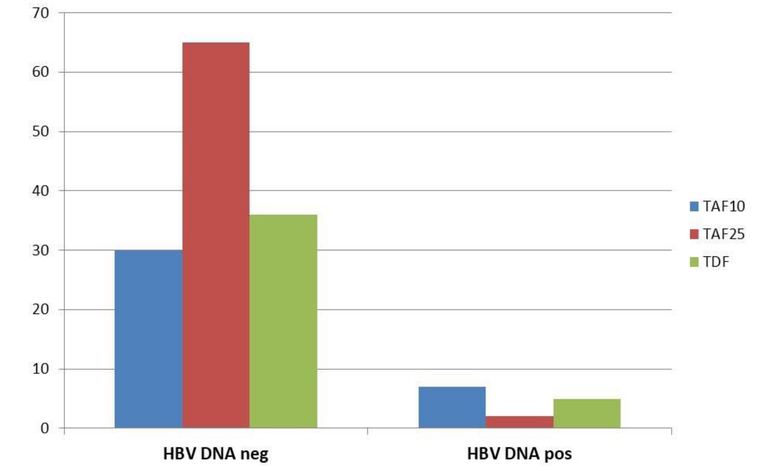
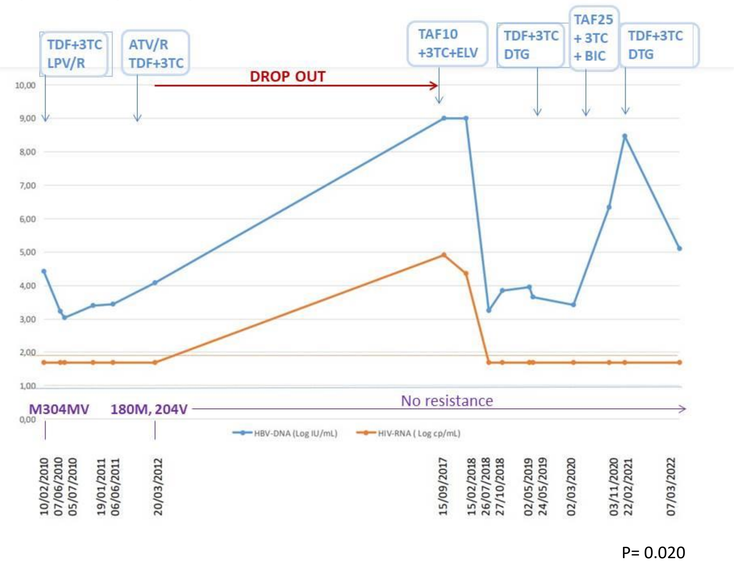


Figure 4. Longitudinal virological evaluation of a HBV DNA positive participant.



Summary

In this group of PLWH with concomitant HBV infection under ART active on both viruses we found that HBV DNA positive participants respect to the counterpart of HBV DNA negative had

- A less preserved immune status (< CD4/CD8 ratio)
- Higher necroinflammatory activity assessed by transaminases and GGT levels
- Higher frequency of HIV-RNA positivity and higher HIV viral load
- Were more frequently HBeAg positive and anti-HBeAg negative
- Were more frequently on ART including TAF10 and TDF

Despite HBV DNA positive viremia, no resistance to TAF or TDF was detected in tested specimens (9/14). However, 2/9 (22.2%) cases had resistance to lamivudine and entecavir. In one other case an interesting HBV mutational profile was detected with also viral load dynamic changing in relation to ART change.

Discussion and conclusion

The finding that about 10% of participants had positive HBV viremia, 5 with concomitant positive HIV viremia suggests in some cases a poor adherence to treatment.

Importantly none of PLWH had resistance to TDF or TAF, while in 2/9 cases was identified a dominant strain resistant to nucleoside analogs (NA) lamivudine and entecavir. Most of HBV DNA positive participants were on ART including TAF 10 and TDF. Therefore, we could form the hypothesis of a better forgiveness for HBV (that is the difference between the duration of beneficial action after dosing and the prescrived dosing interval, F=D-I) of TAF 25 respect to TAF10 and TDF (3,4).

In conclusion, over than poor adherence, a relatively less preserved immune status, ART regimen and resistance to AN lamivudine and entecavir, may have contributed to HBV-DNA detectability.

References

1.Audsley J, Bent SJ, Littlejohn M, Avihingsanon A, Matthews G, Bowden S, Bayliss J, Luciani F, Yuen L, Fairley CK, Locarnini S, Lewin SR, Sasadeusz J. Effects of long-term tenofovir-based combination antiretroviral therapy in HIV-hepatitis B virus coinfection on persistent hepatitis B virus viremia and the role of hepatitis B virus quasispecies diversity. AIDS. 2016 Jun 19;30(10):1597-606. doi: 10.1097/QAD.0000000000001080. PMID: 26950313.

2. Boyd A, Gozlan J, Maylin S, Delaugerre C, Peytavin G, Girard PM, Zoulim F, Lacombe K. Persistent viremia in human immunodeficiency virus/hepatitis B coinfected patients undergoing long-term tenofovir: virological and clinical implications. Hepatology. 2014 Aug;60(2):497-507. doi: 10.1002/hep.27182. Epub 2014 Jun 20. PMID: 24752996.

3. Chen R, Pei S, Chen Y, Tan L, Xue Y, Liu S, Huang Y, Fan X. Suboptimal Response to Tenofovir Alafenamide in Two Patients With HBeAg-Positive Hepatitis B: A Case Report. Front Med (Lausanne). 2021 Jul 8;8:701061. doi: 10.3389/fmed.2021.701061. PMID: 34307428; PMCID: PMC8295557.

4. Matthews GV, Seaberg EC, Avihingsanon A, Bowden S, Dore GJ, Lewin SR, Sasadeusz J, Revill PA, Littlejohn M, Hoy JF, Finlayson R, Ruxrungtham K, Saulynas M, Locarnini S, Thio CL. Patterns and causes of suboptimal response to tenofovir-based therapy in individuals coinfected with HIV and hepatitis B virus. Clin Infect Dis. 2013 May;56(9):e87-94. doi: 10.1093/cid/cit002. Epub 2013 Jan 11. PMID: 23315316; PMCID: PMC3693490.