Transaminase elevations among patients with occult HBV infection on two-drug antiretroviral regimens

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BACKGROUND

- Concerns have been raised about hepatitis B reactivation among people with HIV (PWH) with occult HBV infection (OHBVI) who discontinue agents with anti-HBV activity.
- This occurrence has been reported sporadically, mostly in PWH with low CD4+ cell counts or during immunosuppressive treatment.
- It is worth investigating whether OHBVI increases the risk of transaminase elevation, which could indicate hepatitis B reactivation, among PWH who switch to two-drug regimens (2DR) and discontinue tenofovir (TFV) and/or lamivudine (3TC).

METHODS

- We selected antiretroviral-experienced patients from the HSG cohort, a prospective cohort enrolling PWH at Fondazione IRCCS San Gerardo de' Tintori of Monza (Italy), who:
  - Switched for the first time to a 2DR between Jan 2018 and Oct 2023, discontinuing ≥1 drug with anti-HBV activity;
  - Tested negative for HBV surface antigen;
  - Had measured anti-HBV core antibody (HBcAb) and transaminase levels before the switch.
- A reactive HBcAb serum indicated the presence of OHBVI.
- Two cohorts were enrolled in the study. Cohort 1 consisted of patients who discontinued TFV but continued 3TC. Cohort 2 consisted of patients who switched to a regimen that did not include either TFV or 3TC.

- Time to grade ≥1 liver function test increase (LFTI), defined as aspartate (AST) or alanine aminotransferase (ALT) ≥1.25 the upper limit of normality, was compared between patients with or without OBHVI, using log-rank test and Cox regression.
- Follow-up time was calculated from the date of the switch to the occurrence of LFTI. Patients were censored if they changed the switch regimen.
- The effect of the following possible confounders was explored: age, gender, HIV risk factor, HCV Ab status, hepatits B surface antibody (HBsAb), alcohol abuse, diabetes, baseline AST/ALT, and CD4 count. Multiple imputation by chained equations (MICE) was used to address missingness.
- Mixed linear regression models with random intercepts and slopes were used to compare transaminase trajectories and Generalized Estimating Equation (GEE) model with a random intercept to compare rates of grade≥1 LFTI across follow-up, in those with and without OHBVI.
- We herein present an updated analysis based on the January 2024 version of the database.

Occult HBV infection is not significantly associated with transaminase elevation among PWH switching to two-drug regimens and discontinuing anti-HBV agents.

RESULTS

- A total of 167 patients switched to a 2DR containing 3TC (Cohort 1). Among them 33 patients (19.8%) had discontinued TDF and 134 (80.2%) discontinued TAF.
- 118 switched to a 2DR without TFV and 3TC (Cohort 2), of whom 11 (9.3%) discontinued TDF and FTC, 61 (51.7%) TAF and FTC and 46 (39%) only 3TC.
- Table 1 shows their characteristics grouped by OHBVI
- Grade ≥1 LFTI was observed in 20 (12%) of those in Cohort 1 and in 13 (11%) of those in Cohort 2. No grade ≥3 LFTI was observed.

Table 1. Patient characteristics grouped by presence of absence of OHBVI

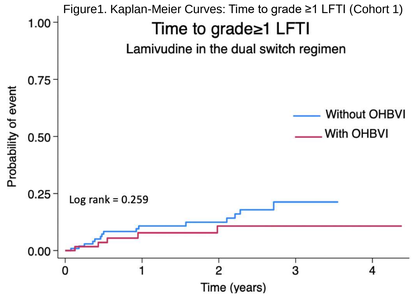
	Cohort 1 Dual regimens including 3TC (N= 167)			Cohort 2 Dual regimens with no anti-HBV agents (N= 118)		
Parameter	**No OHBVI (108)**	**OHBVI (59)**	**p**	**No OHBVI (78)**	**OHBVI (40)**	**p**
Male gender (n, %)	85 (78.7)	50 (84.8)	0.343	53 (68)	29 (72.5)	0.611
Age (mean; SD)	45.6 (11.1)	54.6 (11.9)	<0.001	48.7 (12.4)	56 (8.5)	0.001
Born in Italy (n, %)	96 (88.9)	46 (78)	0.059	64 (82.1)	34 (85)	0.686
Risk Factors (n, %)*			0.019			0.005
Heterosexual	53 (53.5)	22 (44)		40 (62.5)	15 (42.8)	
MSM	44 (44.4)	22 (44)		22 (34.4)	10 (28.6)	
Intravenous drug use	1 (1.01)	6 (12)		2 (3.1)	7 (20)	
Other	1 (1.01)	0		0	3 (8.6)	
HCV Ab positive (n, %)▲	10 (9.3)	10 (17.5)	0.037	6 (8)	10 (26.3)	0.008
Alcohol abuse (n, %)*	13 (14.1)	11 (22.9)	0.349	13 (20.6)	6 (15.8)	0.089
Diabetes (n, %)	11 (10.2)	8 (13.6)	0.512	5 (6.4)	6 (15)	0.180
BMI (median; IQR)*	24.6 (22.2-27.9)	25.9 (23.5-29.1)	0.099	25 (21.3-27.7)	26.1 (21.5-28.1)	0.611
Grade≥1 LFTI within 2 years (n, %)	15 (13.9)	5 (8.5)	0.455	8 (10.3)	5 (12.5)	0.760
Calendar year (n, %)			0.058			0.185
2018-2019	2 (1.9)	6 (10.2)		6 (7.7)	5 (12.5)	
2020-2021	64 (59.3)	34 (57.6)		23 (29.5)	17 (42.5)	
2022-2023	42 (38.9)	19 (32.2)		49 (62.8)	18 (45)	
Baseline CD4 count (median cells/mm3; IQR)	781 (562-970)	764 (429-938)	0.389	808 (514-1120)	721 (367-1055)	0.264
Type of therapy (n; %)	3TC+DTG (108; 100)	3TC+DTG (59; 100)		RPV + DTG (29; 37.2%) RPV + CAB (38; 48.7) Others (11; 14.1)	RPV + DTG (19; 47.5) RPV + CAB (13; 32.5) Others (8; 20)	

❖ Risk factor: N=149 (Cohort 1) and N=99 (Cohort 2); ▲ HCV Ab status: N=165 (Cohort 1) and N=115 (Cohort 2);
* Alcohol abuse: N=140 (Cohort 1) and N=101 (Cohort 2); * BMI: N=161 (Cohort 1) and N=114 (Cohort 2)
Alcohol abuse: Self-reported consumption >10 units of alcohol/week or binge-drinking (>5 units/24h)

Risk of grade ≥1 transaminase elevation

- Among patients on 3TC-including 2DR, the incidence of grade≥1 LFTI was 4.59 and 7.47 per 100 person-years of follow-up in those with and without OHBVI.
- Time to the event did not significantly differ according to OHBVI (log-rank test P=0.259, Figure 1).

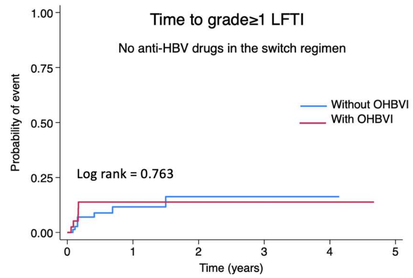
Figure1. Kaplan-Meier Curves: Time to grade ≥1 LFTI (Cohort 1)



- Among those with no anti-HBV agents in the regimen (Cohort 2), the incidence of grade ≥1 LFTI was 8.04 and 8.68 per 100 patient-years of follow-up, based on the presence or absence of OHBVI.

- Rates were not significantly different in the time to the event based on OHBVI status (log-rank test P=0.763, Figure 2).

Figure 2. Kaplan-Meier Curves: Time to grade ≥1 LFTI (Cohort 2)

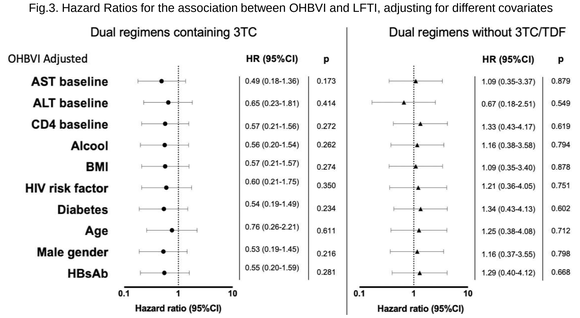


Multivariable Cox regression

- Using Cox regression analysis, OHBVI was not associated with risk of LFTI, either in Cohort 1 (HR 0.56; 95%CI 0.2-1.5; p=0.266) or in Cohort 2 (HR 1.18; 95%CI 0.4-3.6; p=0.769).

- After adjusting for possible confounders, the forest plot in Figure 3 shows no significant change in the lack of association between OHBVI and the outcome for Cohort 1 (left panel) or Cohort 2 (right panel).

Fig.3. Hazard Ratios for the association between OHBVI and LFTI, adjusting for different covariates



Transaminase dynamics after switch

- Figure 4 and Figure 5 show mean ALT levels after the switch to a 2DR including 3TC (Cohort 1) or not including TFV and 3TC (Cohort 2), respectively.

Figure 4. Mean ALT levels after the switch to 2DR including 3TC

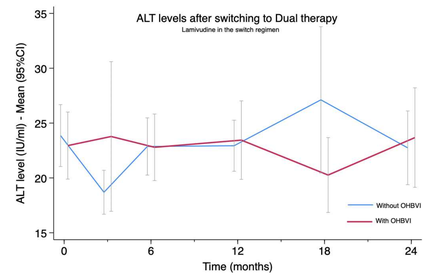
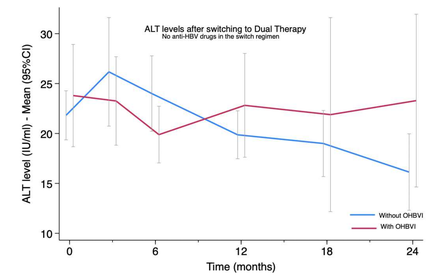


Figure 5. Mean ALT levels after the switch to 2DR without 3TC and TFV



- Using a mixed-effects model, after adjusting for baseline levels, there was no significant difference in ALT levels between patients with and without OHBVI in Cohort 1 (coeff 1.64; 95% CI -0.46-3.73).
- Surprisingly, among PWH included in Cohort 2, OHBVI was significantly associated with lower mean ALT levels (coeff -2.57; 95%CI -4.99 to -0.13).
- In both cases, no evidence was found of any effect of time or interaction with OHBVI.
- The same outcomes were observed when the AST level was used as the result.
- Using GEE models, OHBVI was not significantly associated with grade ≥1 LFTI, either in Cohort 1 (OR 0.77; 95%CI 0.15-3.99) or in Cohort 2 (OR 0.55; 95%CI 0.10-2.56).

CONCLUSIONS

Presence of OHBVI infection was not significantly associated with transaminase elevation among PWH treated with 2DR lacking anti-HBV agents.

This real-life observation provides reassurance regarding the safety of transitioning to dual therapy in patients with OHBVI.

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