Transaminase decrease upon switch from TDF to TAF in PWH is modulated by HBV status

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BACKGROUND

Among HBV mono-infected individuals, switching from tenofovir disoproxil fumarate (TDF) to tenofovir alafenamide (TAF) has been associated with unexpected reductions in transaminase levels, even among those with normal baseline values. [*Lampertico 2020*] Observational studies have shown similar trends among people with HIV (PWH). [*Squillace 2020, Kovari 2021, Sarowar 2022*] Notably, the largest of these studies found no significant effect modifications across the variables examined; however, the effect of HBV co-infection status was not explored. [*Kovari 2021*]

The underlying mechanisms and the reason of these findings remain unclear. One hypothesis suggests that TAF's enhanced intracellular concentrations may lead to better suppression of HBV replication, indirectly improving liver function. Alternatively, TDF has been associated with metabolic side effects, such as hepatic steatosis, which may resolve upon switching to TAF.

We therefore aimed to assess whether the effect of switching from TDF to TAF on transaminase levels varied based on the baseline HBV status.

METHODS

We conducted a longitudinal study on PWH enrolled in the San Gerardo Hospital (HSG) HIV Cohort Study. Patients who switched from TDF to TAF between 2016 and 2023 were selected and categorized based on their Hepatitis B surface antigen (HBsAg) and Hepatitis B core antibody (HBcAb) status before the switch. They were classified as chronically HBV-infected (CHBV) if HBsAg-positive, potential occult HBV infection (pOBI) if HBsAg-negative and HBcAb-positive, and uninfected if both HBsAg and HBcAb negative.

To assess the effect of the switch on transaminase levels, a mixed-effects model with random intercepts at the patient level was used. An interaction term between the switch and HBV status was included to determine whether the effect varied across the three mutually exclusive HBV categories. Additionally, multivariable models were performed to adjust for other potential factors influencing transaminase levels.

Switching from TDF to TAF leads to a **significant transaminase decrease** in PWH, with a **greater effect in those with chronic HBV infection**, suggesting enhanced viral suppression beyond plasma HBV DNA measurement.

RESULTS

- Among 727 PWH switching from TDF to TAF, 8.1% had CHB and 37.7% pOBI. **Table 1** summarizes other patient characteristics.
- Using a mixed model with random intercepts at the patient level, we observed a significant decrease in ALT levels following the switch to TAF (β -3.5 U/L, 95%CI -5.2 to -1.9, P<0.001). ALT levels also showed gradual decline over time, with a mean reduction of 0.9 U/L per year (P<0.001), independent of the treatment status. However, there was no evidence that the rate of ALT decline differed before and after the switch (interaction term: P=0.229)
- A significant interaction between HBV serostatus and the switch was observed. Compared with patients without HBV, those with CHB experienced a additional, significant steeper ALT decrease upon switch (β -7.5, 95%CI -11.8 to -3.2; P=0.001) while pOBI showed smaller, non-significant reduction (β -2; 95%CI -4.5 to 0.5; P=0.112).
- **Figure 1** shows the estimated ALT trend, overall and by HBV serostatus, based on marginal effects from the mixed model adjusted for time, switch, and their interaction.
- The significant interaction between HBV serostatus and the switch to TAF was confirmed in an additional multivariable model, adjusted for age, gender, calendar year, HIV risk factor and diabetes.
- In such model, male gender (β +10, 95%CI 6.5 to 13.4, P <0.001) and diabetes (β +5.1, 95%CI 0.2 to 10, P=0.042) were additional factors associated with higher ALT levels. In contrast, older age (β -0.2 per year increase, 95%CI -0.3 to -0.1, P=0.021) and later calendar years (*versus* 2016-2017, β -7.1, 95%CI -13 to -1.5, P=0.012 for 2020-2023 and β -3.7, 95%CI -7.2 to -0.2, P=0.037 for 2018-19) were associated with lower ALT levels.
- Consistent results with AST were obtained.

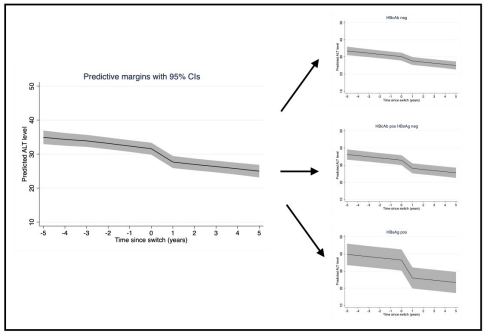
CONCLUSIONS

- Switching from TDF to TAF is associated with significant transaminase decrease in PWH.
- Such effect is partially dependent of HBV status,as individuals with CHB and, to a lesser extent, those with pOBI experienced a greater decline in transaminase levels after switching compared to those without HBV infection.
- This suggests that enhanced viral suppression, beyond what is captured by plasma HBVDNA measurements, may play a role

Table 1 Patients' characteristics	n (%)
Age, years, median (IQR)	49 (41-55)
Sex, male	540 (74.3%)
Risk factor for HIV acquisition	
MSM	196 (27%)
Heterosexual intercourses	322 (44.3%)
Injecting drug use	90 (12.4%)
Other/unknown	119 (16%)
Place of birth, Foreign born	139 (19.1%)
Antiretroviral drugs in the switch regimen	
Non-nucleoside reverse-trascriptase inhibitor	292 (40.2%)
Protease inhibitor	131(18%)
Integrase-strand inhibitor	310 (42.6%)
Ritonavir or cobicistat as booster	257 (35.3%)
HBV serostatus ^	
Chronic hepatitits B (HBsAg+)	8.1% (7.7-8.6)
Possible occult hepatitis B (HBsAg-/HBcAb+)	37.7% (35.9-39.5)
No Hepatits B exposure (HBsAg-/HBcAb-)	54.2% (52.3-56)
Diabetes	104 (14.3%)
Year of the switch from TDF to TAF	
2016-2017	392 (53.9%)
2018-2019	237 (32.6%)
2020-2023	98 (13.5%)

^ HBV status values were imputed for 38 missing observations (24 with negative HBsAg and missing HBcAb, 14 with missing HBsAg and HBcAb) using chained equations across 20 datasets. Results were pooled for Rubin's rules and presented as percentage with 95%CI.

Figure 1 Predicted ALT values, based on marginal effects from mixed models



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