TDF and TAF in HBV/HIV co-infected individuals in the United States: monitoring practices and incidence of HBV reactivation or hepatitis flare

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OPERA® The Longitudinal Cohort

Background

- In the absence of a suppressive HBV treatment, people with HBcAb+ with HIV or on immunosuppressive therapy are at risk for HBV reactivation, and possibly fulminant or fatal hepatitis.[1]
- HBV/HIV co-infection: HIV antiretroviral therapy should include either TDF or TAF plus either 3TC or FTC to maintain HBV viral suppression.[2]
  - 3TC without TDF or TAF: high risk of HBV resistance.[1]
  - ETV without TDF or TAF: high risk of HIV resistance.[1]

Objectives

Among HBV/HIV co-infected individuals:

1) **Describe TDF and TAF interruptions**
2) **Describe HBV monitoring practices**
3) **Assess the incidence of HBV reactivation and hepatitis flares during TDF and TAF interruptions**

Methods

- **OPERA cohort:** Electronic health records from >142K people with HIV in the US (96 clinics, 22 states, 1 US territory)
- **Study inclusion:**
  - HIV/HBV co-infection (HBsAg+ and/or HBcAb+)
  - Interruption: stopped TDF or TAF for ≥45 days (16APR2001-10MAY2023)
  - ≥1 ALT, HBsAg or HBV DNA during the interruption
- **Stratification:** Serology-based HBV reactivation risk (**Table 1**)

Table 1. HBV reactivation risk based on HBV serology

	HBsAg	HBcAb	HBsAb
High	+	+ / – / ?	+ / – / ?
Moderate	– / ?	+	– / ?
Low	– / ?	+	+

- **HBV reactivation** (AASLD definition)[1]
  - **High** risk
    - ≥100-fold increase in HBV DNA (if detectable at BL)
    - HBV DNA ≥1,000 IU/mL (if undetectable at BL)
    - HBV DNA ≥10,000 IU/mL (if missing at BL)
  - **Moderate**/**low** risk: Any detectable HBV DNA or HBsAg+
- **Hepatitis flare** (AASLD definition)[1]
  - ALT >100 U/L & ≥3-fold ALT increase (if available at BL)
  - ALT >5X ULN (if missing at BL)
- **Analyses**
  - Presence of testing within ≤12 months before (HBV DNA, ALT) and during the interruption (HBV DNA, ALT, HBsAg)
  - Incidence rate of HBV reactivation or hepatitis flare: univariate Poisson regression

Results

Figure 1. HBV/HIV co-infected population with TDF or TAF interruptions

5343 people with HIV/HBV and ≥1 TDF or TAF interruption
- 14% with ≥2 interruptions

6252 TDF or TAF interruptions across 5343 people
- Median duration: 23 months (IQR: 7, 53)
- 79% lasting ≥180 days

Table 2. Anti-HBV agents during TDF or TAF interruptions[a]

	High Risk	Moderate Risk	Low Risk
# interruptions	685	1219	4348
No anti-HBV agent	385 (56%)	630 (52%)	2154 (50%)
Any anti-HBV agent[a]	300 (44%)	589 (48%)	2194 (50%)
3TC	258 (86%)	569 (97%)	2157 (98%)
FTC	15 (5%)	26 (4%)	57 (3%)
ETV	92 (31%)	3 (<1%)	3 (<1%)

[a] All anti-HBV agents used in any regimen throughout the interruption.

Table 3. Monitoring within 12 months before or during TDF or TAF interruptions

	High Risk (685 interruptions)	Moderate Risk (1219 interruptions)	Low Risk (4348 interruptions)
Within 12 months before the interruption			
Any HBV DNA test	302 (44%)	78 (6%)	354 (8%)
Any ALT test	622 (91%)	1115 (91%)	4055 (93%)
Last ALT ≤ ULN	456 (73%)	911 (82%)	3450 (85%)
During the interruption			
Any HBV DNA test	359 (52%)	109 (9%)	236 (5%)
Median (IQR) weeks to first HBV DNA test	19 (8, 48)	48 (16, 121)	65 (15, 233)
Any ALT test	677 (99%)	1216 (100%)	4338 (100%)
Any HBsAg test	170 (25%)	373 (31%)	1207 (28%)

Figure 2. Incidence of HBV reactivation

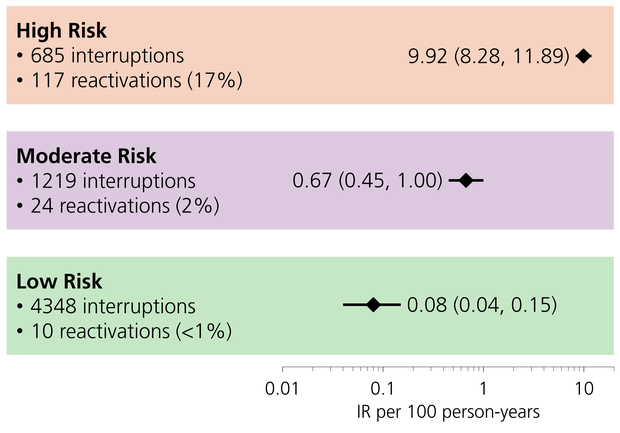
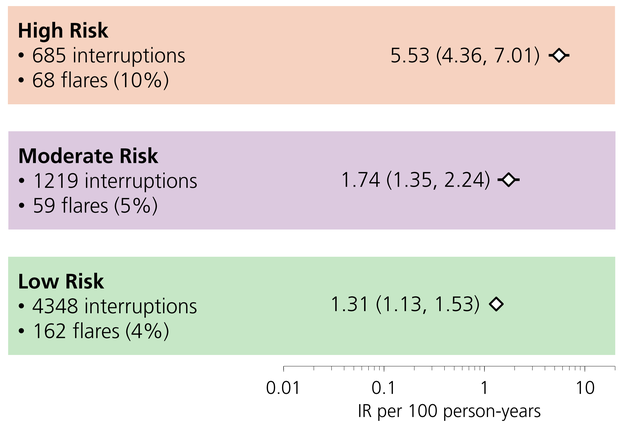


Figure 3. Incidence of hepatitis flare



Abbreviations
3TC, lamivudine; **AASLD**, American Association for the study of liver disease; **ALT**, alanine transaminase; **BL**, baseline; **ETV**, entecavir; **FTC**, emtricitabine; **HBcAb**, HBV core antibody; **HBsAb**, HBV surface antibody; **HBsAg**, HBV surface antigen; **HBV**, hepatitis B; **HIV**, human immunodeficiency; **IR**, incidence rate; **TAF**, tenofovir alafenamide; **TDF**, tenofovir disoproxil fumarate; **ULN**, upper limit of normal

Discussion

- Primary and HIV care providers in the US may be focusing on HIV control and overlooking HBV monitoring and management:
  - TDF or TAF interruptions were common and lengthy (**Fig 1**).
  - Less than half of TDF or TAF interruptions covered by another anti-HBV agent (**Table 2**).
  - No HBV DNA monitoring before or during most interruptions (**Table 3**).
- All were at risk for HBV reactivation and hepatitis flare, regardless of baseline risk level; highest risk if HBsAg+ (**Fig 2-3**)
- Strengths
  - Large sample size from the OPERA cohort, which represents routine clinical care and included ~13% of people with diagnosed HIV infection in the US at the time of this study.[3]
- Limitations
  - HBV serology was sometimes incomplete or dated; misclassification of risk level is possible.
  - HBV DNA and HBsAg labs were missing for a large proportion of the population; reactivations and flare were therefore likely missed.

Key Findings

- **HBV management was often overlooked during routine HIV care in the US, resulting in 151 HBV reactivations and 289 hepatitis flares.**
- **Primary and HIV care providers need to incorporate HBV monitoring in their standard of care and proceed with caution if considering a TDF or TAF interruption for people with HBV/HIV co-infection.**

References

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