Real-World Liver Outcomes in People With HIV and Hepatitis B Virus Receiving Antiretroviral Therapy

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Conclusions

- This observational study compared the long-term effects of different tenofovir-based and non-tenofovir–based antiretroviral therapy regimens on advanced liver disease in people with HIV and hepatitis B virus
- Tenofovir-based antiretroviral therapy was associated with reduced risk of severe liver-related complications in people with HIV and hepatitis B virus
  - Specifically, tenofovir alafenamide–based antiretroviral therapy was associated with a reduced risk of progression to cirrhosis and hepatocellular carcinoma compared with non-tenofovir–based antiretroviral therapy
  - Tenofovir-based antiretroviral therapy regimens did not negatively affect liver function compared with non-tenofovir–based antiretroviral therapy regimens
- Overall, these findings support guideline recommendations to incorporate tenofovir alafenamide or tenofovir disoproxil fumarate as part of a dual nucleoside reverse transcriptase inhibitor backbone to improve outcomes for people with HIV and hepatitis B virus

Plain Language Summary

- People who have both HIV and hepatitis B virus are more likely to have serious liver problems and die from them than people who have just one of these viruses
- We do not yet know if some HIV treatments work better than others to protect the liver in people who have both HIV and hepatitis B virus
- Tenofovir is a medicine that is often used to treat people who have HIV, hepatitis B virus, or both viruses
- This study looked at how different HIV treatments—some with tenofovir and some without—affected the chances of getting serious liver disease in people with both HIV and hepatitis B virus in the United States
- The study found that people who took HIV treatments that included tenofovir were less likely to develop serious liver disease
- This means that using tenofovir in treatment plans may help protect the liver in people with both HIV and hepatitis B virus

Introduction

- Living with HIV and hepatitis B virus (HIV/HBV) is a serious global health challenge, with as many as 8% of people with HIV in the United States and 16% of people with HIV in other regions worldwide also having HBV[1,2]
- HIV/HBV significantly increases the risk of liver-related complications and is associated with higher morbidity compared with either HIV or HBV alone[3-5]
- Antiretroviral therapy (ART) is crucial for HIV management[6]; however, the impact of different ART regimens on long-term liver disease events in people with HIV/HBV remains uncertain
  - Tenofovir-based therapies, including tenofovir alafenamide (TAF) and tenofovir disoproxil fumarate (TDF), have demonstrated efficacy in suppressing HBV replication while maintaining HIV suppression[7-9]
  - There is a lack of extensive observational evidence comparing the long-term liver outcomes of TAF-, TDF-, and non-tenofovir–based ART regimens in this population

Objectives

- To examine the impact of TAF-, TDF-, and non-tenofovir–based ART regimens on liver disease progression, leveraging a large longitudinal claims dataset from the United States
- To inform clinical decision-making and the development of guidelines for managing living with HIV/HBV simultaneously

Methods

- This retrospective cohort study used deidentified US medical and pharmacy claims data from the HealthVerity database
  - Adults aged ≥18 years who initiated any ART between 1 April 2016 and 31 January 2024 and had both a diagnosis of HIV and a diagnosis of HBV any time during follow-up, but with ≥1 diagnosis of HIV or HBV prior to the index date (ie, the date of ART initiation), were included
    - HIV and HBV diagnoses were determined using *International Classification of Diseases, Tenth Revision* codes
  - People with <168 days of continuous insurance enrolment, with pre-existing liver outcomes of interest, and who had ART any time prior to the index date were excluded from the study
- Eligible people were categorised by the ART regimen they received at initiation:
  - TAF-based regimens
  - TDF-based regimens
  - Non-tenofovir–based regimens (ie, regimens excluding tenofovir but including other nucleoside or nucleotide reverse transcriptase inhibitors or integrase inhibitors)
- Advanced liver disease events (ie, a diagnosis of cirrhosis, liver decompensation, hepatocellular carcinoma [HCC], or liver transplant) and aspartate aminotransferase (AST) and alanine transaminase (ALT) values before and after ART initiation were evaluated
- Time to advanced liver disease events across ART regimen groups was estimated with Kaplan-Meier methods
  - Adjusted hazard ratios (HRs) and corresponding 95% CIs were calculated using Cox proportional hazards models
- AST and ALT levels before and after ART initiation were assessed using adjusted mixed-effects models

Results

- Among 3095 people with HIV/HBV, 76% received TAF-based ART regimens, 13% received TDF-based ART regimens, and 11% received non-tenofovir–based ART regimens (**Table 1**)
- Unweighted baseline comorbidities and demographic characteristics were generally comparable across ART regimen groups, though people on TAF-based ART regimens had a slightly higher prevalence of renal impairment

Table 1. Demographic Characteristics and Comorbidities of People With HIV/HBV Included in the Primary Analysis

	TAF-Based ART (n = 2339)	TDF-Based ART (n = 408)	Non-Tenofovir–Based ART (n = 348)	Overall (N = 3095)
Sex, female, n (%)	592 (25)	128 (31)	75 (22)	795 (26)
Age, y, median (Q1, Q3)	48.0 (38.0, 57.0)	46.5 (37.0, 54.0)	51.0 (39.0, 59.0)	48.0 (38.0, 57.0)
Race/ethnicity, n (%)				
Black	729 (31)	128 (31)	87 (25)	944 (31)
White	490 (21)	70 (17)	75 (22)	635 (21)
Hispanic	194 (8)	40 (10)	41 (12)	275 (9)
Asian	101 (4)	20 (5)	5 (1)	126 (4)
Other/missing	825 (35)	150 (37)	140 (40)	1115 (36)
Insurance type,[a] n (%)				
Medicaid	1188 (51)	226 (55)	201 (58)	1615 (52)
Commercial	402 (17)	91 (22)	67 (19)	560 (18)
Medicare Advantage	141 (6)	15 (4)	25 (7)	181 (6)
Missing/unknown	608 (26)	76 (19)	55 (16)	739 (24)
Initial treatment indication, n (%)				
HIV	2249 (96)	344 (84)	341 (98)	2934 (95)
HBV	87 (4)	63 (15)	7 (2)	157 (5)
HIV/HBV	3 (<1)	1 (<1)	0	4 (<1)
Comorbidity, n (%)				
Mental illness	1284 (55)	213 (52)	169 (49)	1666 (54)
Substance abuse	958 (41)	144 (35)	119 (34)	1221 (39)
Essential hypertension	775 (33)	148 (36)	124 (36)	1047 (34)
Smoking	830 (35)	119 (29)	95 (27)	1044 (34)
Hyperlipidaemia	481 (21)	95 (23)	85 (24)	661 (21)
Medication, n (%)				
Antihypertensives	369 (16)	69 (17)	75 (22)	513 (17)
Antilipids	293 (13)	48 (12)	61 (18)	402 (13)
Calcium channel blockers	225 (10)	51 (13)	39 (11)	315 (10)
Beta-blockers	209 (9)	45 (11)	39 (11)	293 (9)
Antidiabetics	178 (8)	32 (8)	24 (7)	234 (8)
Aspirin	93 (4)	20 (5)	23 (7)	136 (4)
CCI score excluding HIV/AIDS				
Mean (SD)	1.52 (2.05)	1.66 (2.24)	1.56 (2.11)	1.54 (2.08)

[a]Insurance type was determined by the type of insurance an individual was enrolled in for the longest duration at the index date.
ART, antiretroviral therapy; CCI, Charlson Comorbidity Index; HBV, hepatitis B virus; Q1, first quartile; Q3, third quartile; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.

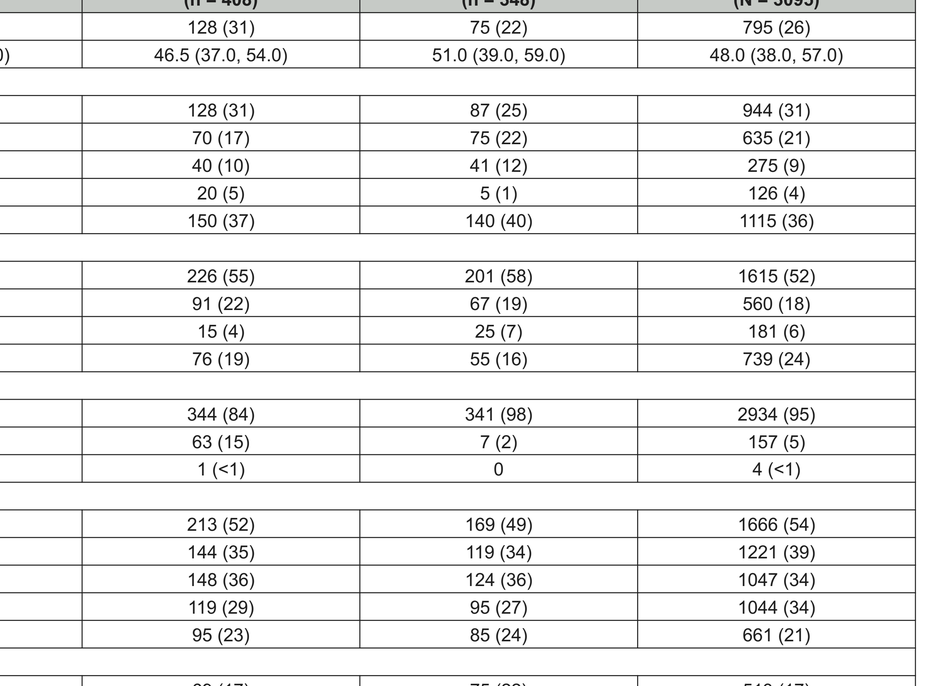
- The most commonly received ART regimens in each of the ART regimen groups are shown in **Table 2**
- People who received TAF- or TDF-based ART regimens experienced a significantly longer time to any advanced liver disease event compared with people who received non-tenofovir–based ART regimens (log-rank P <0.01; **Figure 1**)

Table 2. Most Commonly Received ART Regimens

Initial ART Regimen	Most Commonly Received ART Regimens, n (%)
TAF-based (n = 2339)	B/F/TAF, 1487 (64) EVG/COBI/F/TAF, 403 (17) F/TAF combinations,[a] 151 (6) DRV/COBI/F/TAF, 105 (4) TAF,[b] 87 (4)
TDF-based (n = 408)	F/TDF combinations,[c] 171 (42) EFV/F/TDF, 69 (17) EVG/COBI/F/TDF, 63 (15) TDF,[b] 63 (15) RPV/F/TDF, 35 (9)
Non-tenofovir–based (n = 348)	ABC/3TC/DTG, 227 (65) DTG/3TC, 60 (17) DTG/RPV, 34 (10) ABC/3TC/DRV/r,COBI, 10 (3) CAB+RPV, 10 (3)

[a]F/TAF combinations included F/TAF+DTG, F/TAF+RAL, F/TAF+DRV/r,COBI, and F/TAF+ATV/r,COBI.
[b]Monotherapy for the treatment of HBV.
[c]F/TDF combinations included F/TDF+DTG, F/TDF+RAL, F/TDF+DRV/r,COBI, and F/TDF+ATV/r,COBI.
3TC, lamivudine; ABC, abacavir; ART, antiretroviral therapy; ATV, atazanavir; B, bictegravir; CAB, cabotegravir; COBI, cobicistat; DRV, darunavir; DTG, dolutegravir; EFV, efavirenz; EVG, elvitegravir; F, emtricitabine; HBV, hepatitis B virus; r, ritonavir; RAL, raltegravir; RPV, rilpivirine; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.

Figure 1. Kaplan-Meier Survival Curve for Any Advanced Liver Disease Events by ART Regimen in People With HIV/HBV



Solid lines denote survival curves; dashed lines represent 95% CIs (upper and lower) for each colour-coded survival curve.
ART, antiretroviral therapy; HBV, hepatitis B virus; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.

- The Cox proportional hazards model showed that people on TAF- and TDF-based ART regimens had a 45% and 55% lower risk of advanced liver disease events, respectively, compared with non-tenofovir–based ART regimens (**Table 3**)
- TAF-based ART was associated with a 58% and 72% decrease in the risk of cirrhosis and HCC, respectively, compared with non-tenofovir–based ART

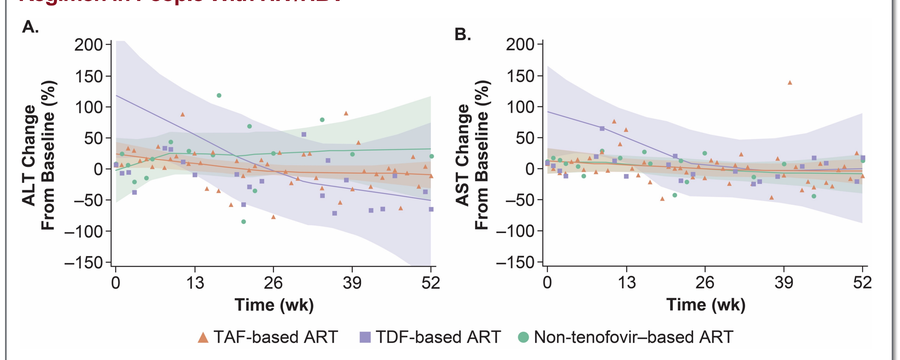
Table 3. HRs for Advanced Liver Disease Events Comparing TAF- and TDF-Based ART Regimens With Non-Tenofovir–Based ART Regimens[a]

Advanced Liver Disease Event	Initial ART Regimen	Events/People	Crude HR (95% CI)	Adjusted HR (95% CI)[b]
All	Non-tenofovir–based	41/311	Reference	Reference
	TAF-based	155/2078	**0.61 (0.43-0.86)**	**0.55 (0.38-0.79)**
	TDF-based	30/368	**0.56 (0.35-0.90)**	**0.45 (0.27-0.74)**
Cirrhosis	Non-tenofovir–based	25/332	Reference	Reference
	TAF-based	77/2184	**0.50 (0.32-0.78)**	**0.42 (0.26-0.68)**
	TDF-based	24/379	0.74 (0.42-1.30)	0.66 (0.36-1.21)
Liver decompensation	Non-tenofovir–based	32/334	Reference	Reference
	TAF-based	129/2186	0.69 (0.47-1.01)	**0.63 (0.42-0.95)**
	TDF-based	23/386	**0.58 (0.34-0.98)**	**0.46 (0.26-0.82)**
HCC	Non-tenofovir–based	7/346	Reference	Reference
	TAF-based	17/2324	**0.40 (0.17-0.98)**	**0.28 (0.11-0.77)**
	TDF-based	7/402	0.75 (0.26-2.15)	0.41 (0.12-1.35)
Liver transplant	Non-tenofovir–based	1/347	Reference	Reference
	TAF-based	1/2328	0.19 (0.01-3.12)	0.50 (NA)[c]
	TDF-based	2/408	1.33 (0.12-14.94)	0.90 (NA)[c]

[a]Bolding denotes an HR with a 95% CI not covering 1 compared with the reference.
[b]HRs were adjusted for age, sex, region, payer type, treatment duration, switching indication, comorbidities, and medications.
[c]The adjusted HR for liver transplant did not converge with valid CIs due to low event counts.
ART, antiretroviral therapy; HCC, hepatocellular carcinoma; HR, hazard ratio; NA, not applicable; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.

- Distinct trajectories of ALT and AST levels were observed with each ART regimen (**Figure 2**)
  - 160 people had ≥1 measurement of ALT and 146 people had ≥1 measurement of AST before and after ART initiation
  - ALT and AST levels in people on TAF- and TDF-based ART regimens generally returned to near-baseline levels in the long term
  - In people on non-tenofovir–based ART regimens, elevated ALT levels were maintained over time, while AST levels returned to near-baseline levels

Figure 2. Trajectories of Liver Function Measured by (A) ALT and (B) AST by ART Regimen in People With HIV/HBV



Mixed models were adjusted for baseline value, race/ethnicity, age, sex, and region. Shaded areas represent 95% CIs.
ALT, alanine transaminase; ART, antiretroviral therapy; AST, aspartate transferase; HBV, hepatitis B virus; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.

Limitations

- In this retrospective, observational study, there were inherent selection biases (eg, inclusion of only individuals in the United States with continuous health insurance enrolment), limited access to laboratory results (eg, markers of HBV activity), and unmeasured confounding factors; for these and other reasons, establishing a cause-effect relationship between tenofovir-based ART and the decrease in advanced liver disease events was not feasible
  - While HBV activity could not be directly assessed due to limited laboratory data, similar ALT/AST levels (~24 U/L) across groups suggest comparable HBV activity and minimise differential confounding
- Some advanced liver disease events are uncommon
  - Relying solely on diagnosis and procedure codes might have resulted in low sensitivity
  - Due to the underreporting of outcomes, the effect of ART might have been overestimated
- Identification of a valid dose-response relationship between ART and the risk of advanced liver disease events may have been limited by the lack of precise measures for ART adherence and cumulative exposures

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Acknowledgements: This study was funded by Gilead Sciences, Inc. Medical writing and editorial support were provided by Patricia Rosell Arevalo, PhD, of Lumanity Communications Inc., and were funded by Gilead Sciences, Inc.

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Disclosures: **CY-C**, **WZ**, **LET**, and **LT** are stockholders and employees of Gilead Sciences, Inc. **MdB** is a stockholder and former employee of Gilead Sciences, Inc.