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Long-term trajectories of hepatic and metabolic biomarkers after switching from tenofovir disoproxil fumarate to tenofovir alafenamide in antiretroviral therapy-experienced people with HIV with and without hepatic coinfection: Data from the ICONA cohort

Mariacristina Poliseno[1,*], Sergio Lo Caputo[2], Alessandro Tavelli[3,4], Roberta Gagliardini[5], Lidia Gazzola[6], Annalisa Saracino[1], Teresa Antonia Santantonio[2], Nicola Squillace[7], Massimo Puoti[8], Valentina Mazzotta[5], Adndrea Antinori[5], Antonella d'Arminio Monforte[3], Alessandro Cozzi-Lepri[9]

[1] Clinic of Infectious Diseases, Dep artment of Precision Medicine and Jonian Area (DiMePre-J), University of Bari "Aldo Moro", Bari, Italy
[2] Unit of Infectious Diseases, University of Foggia, Foggia, Italy
[3] ICONA Foundation, Milan, Italy
[4] National PhD Programme in One Health Approaches to Infectious Diseases and Life Science Research, Department of Public Health, Experimental and Forensic Medicine, University of Pavia, Pavia, Italy
[5] National Institute for Infectious Diseases "L. Spallanzani", IRCCS, Rome, Italy
[6] Clinic of Infectious Diseases, San Paolo Hospital, ASST Santi Paolo e Carlo, Italy
[7] Infectious Disease Unit, Fondazione IRCCS San Gerardo dei Tintori, Monza, Italy
[8] Division of Infectious Diseases, Department of Medicine, ASST Grande Ospedale MetropolitanoNiguarda, University of Milan Bicocca, Milan, Italy
[9] Institute for Global Health, UCL, University College London, London, UK

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ABSTRACT

Objectives: Long-term effects of switching from tenofovir disoproxil fumarate (TDF) to tenofovir alafenamide (TAF) on hepatic, renal, and metabolic parameters remain poorly characterized, especially in people with HIV (PWH) and hepatitis B virus coinfection.

Methods: We analyzed 24-month trajectories before and after the switch to TDF/TAF in antiretroviral therapy-experienced, virologically suppressed participants from the ICONA cohort, excluding those who started antiviral treatment or had detectable hepatitis C virus-RNA during the study period. Mean values at 18 (T_{-18}) and 6 months (T_{-6}) pre-switch, at switch, and 6, 12, and 24 months post-switch (T_{+6}, T_{+12}, T_{+24}) were assessed using adjusted mixed linear models.

Results: At 6 months, alanine aminotransferase (ALT) decreased modestly by −3.05 (−6.42, 0.31) U/l, remaining stable at T_{+24}; similar toother liver damage markers. In participants with chronic liver enzyme elevation, ALT reductions were more marked (−20.5 to −22.6 U/l from T_{+6} to T_{+24}). Total cholesterol, low-density lipoprotein cholesterol (LDL-Chol), and triglycerides increased by 14.46, 10.70, and 11.56 mg/dl, respectively, at T_{+6}, and then stabilized thereafter. PWH with baseline LDL-Chol <100 mg/dl showed larger LDL increases. Compared with HIV-monoinfected individuals, hepatitis B surface antigen+ individuals had higher ALT and lower estimated glomerular filtration rate on TDF; differences attenuated after switching to TAF (P <0.001 and P = 0.002). No lipid trajectory differences emerged by coinfection status.

Conclusions: Greater hepatic improvement was noticed after TDF-to-TAF switch in PWH with hepatitis B virus coinfection, with no differences in lipid increases compared with monoinfected patients.

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Introduction

Over the past decade, tenofovir alafenamide (TAF), a prodrug of tenofovir disoproxil fumarate (TDF), has increasingly replaced its predecessor in antiretroviral therapy (ART) regimens due to its

* Corresponding author.
E-mail address: polisenomc@gmail.com (M. Poliseno).

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improved safety profile, while maintaining comparable efficacy in HIV-RNA suppression and its known efficacy against hepatitis B virus (HBV) [1].

Although the renal function and bone mineral density benefits of switching from TDF to TAF are well established [2], a less extensively investigated effect of this switch is the reduction in serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels—key biomarkers of hepatocellular injury.

Although these changes are generally modest and remain within the normal range, they have been reported across various populations, including individuals with HIV monoinfection [3], HBV monoinfection [4], and those coinfected with HBV and/or hepatitis C virus (HCV) [5,6]. However, these observations are limited by small sample sizes, short follow-up periods, or both.

Conversely, some studies have associated TAF-based regimens with increases in lipid parameters, particularly triglycerides (TGL) and low-density lipoprotein cholesterol (LDL-Chol), both of which are established markers of cardiovascular risk [7,8].

It has been demonstrated that, compared with TDF, TAF achieves higher intracellular concentrations in hepatocytes and lymphocytes, due to its distinct chemical properties [9].

Although this pharmacokinetic advantage may contribute to more effective suppression of HBV DNA of TAF compared with TDF in people with HIV (PWH) coinfected with HBV [10], there is an ongoing debate regarding the possible impact of TAF on hepatic and metabolic parameters in individuals with pre-existing liver disease.

To date, although other cohorts have examined several metabolic or hepatic markers in separate publications [3,11], no HIV cohort to date has systematically assessed all markers (hepatic, renal, and lipid changes) in the same analysis after controlling for a common set of potential confounders and has addressed potential differences in the trajectories pre/post a switch to TAF between PWH who are monoinfected and those coinfected with HBV.

Indeed, although TAF-associated metabolic and hepatic changes have been extensively documented in HBV-monoinfected populations [12], no comparable body of literature exists for individuals coinfected with HIV and HBV, a population with a potentially dual source of hepatic injury due to both viral infections and, possibly, ART-related metabolic effects.

This study aims to address this knowledge gap by evaluating longitudinal trends in liver enzymes, renal function, and lipid profiles in a large cohort of PWH with and without HBV, who have been followed up for a period of 24 months before and 24 months after switching from TDF- to TAF-based regimens.

Methods

Patient selection and data collection

The ICONA Foundation Study is a multicenter, prospective, observational cohort that has been collecting sociodemographic and clinical data from over 22,000 PWH enrolled across 62 Italian Infectious Diseases centers since 1997 [13]. Eligible participants are ≥18 years old, ART-naïve, and provide written informed consent following the Helsinki Declaration (1983 revision) and local ethical regulations. Each center obtained approval from its own Ethics Committee, while the latest amendment to the study protocol was centrally approved by the Lazio Area 4 Territorial Ethics Committee on July 1, 2024 (approval no. 83-2024).

In this analysis, we included ART-experienced PWH of ICONA who underwent a TDF-to-TAF switch in combination with any anchor drug and who

i) were virologically suppressed at the time of switch (HIV-RNA ≤50 copies/ml)
ii) have been followed for 24 months before the switch from TDF to TAF, as well as an additional 24 months after this switch, and
iii) had at least two clinical visits with laboratory markers measured over this observation period.

We excluded PWH with evidence of active HCV infection—defined as HCV-RNA >15 copies/µl, those who started direct antiviral agent (DAA) treatment during the whole study period of 48 months, and those with evidence of coinfection with both HBV and HCV during the study period window (Flowchart in Figure 1). We also excluded ALT values that were measured around episodes of acute viral hepatitis. These criteria were applied to remove the direct effect of active hepatitis viral replication and of DAA on some of the studies' biomarkers (especially ALT), which could be mistakenly attributed to the TDF-to-TAF switch. Participants' follow-up after the switch was censored at the time of discontinuing TAF, at 24 months after the switch, or December 31, 2024 (administrative censoring), whichever occurred first.

We evaluated the following laboratory markers, with normal ranges defined according to international guidelines [14–16], both within 24 months before and 24 months after the TDF-to-TAF switch: ALT (≤50 UI/l for males and ≤35 UI/l for females), aspartate aminotransferase (AST, <34 UI/l), gamma-glutamyl transferase (GGT, <73 UI/l), and alkaline phosphatase (ALP, 46-116 UI/l). Chronic liver enzyme elevation (cLEE) was defined as at least two ALT levels above these thresholds, persisting for ≥6 months. Lipid profile normality was defined as fasting total cholesterol (Tot-Chol, 50-200 mg/dl), high-density lipoprotein cholesterol (HDL-Chol, >40 mg/dl), LDL-Chol (<116 mg/dl), Tot-/HDL-Chol ratio (<3.5), and TGL (<150 mg/dl). Normal fasting glucose was defined as <100 mg/dl, normal serum creatinine (0.67-1.17 mg/dl), and normal kidney function as an estimated glomerular filtration rate (eGFR, >90 ml/min/1.73 m^2).

Information regarding participants' sociodemographic, clinical, and immunovirological characteristics collected before ART initiation was retrieved from the ICONA study electronic database.

Our main area of interest was coinfection with HBV. Specifically, we compared markers' trajectories between HCV antibody (HCVAb)-negative and HBV surface antigen (HBsAg)-negative (HIV-monoinfection) vs HCVAb-negative and HBsAg-positive (chronic HBV coinfection). We also included a third group: the HCVAb-positive with HCV-RNA ≤15 IU/ml (who cleared HCV either naturally or after treatment with DAA). Although this group was also of some interest (because of their residual hepatic risk despite the cure), the sample size was too small to evaluate them beyond the descriptive analyses.

Statistical analyses

We performed a descriptive analysis of the study population. Categorical variables were expressed as counts and percentages and compared across hepatitis coinfection groups using the chi-square test. Continuous variables were reported as medians with interquartile ranges (IQR) and compared between groups using the non-parametric Mann-Whitney test.

We conducted an initial analysis to assess the trends over time of all the considered metabolic parameters in the overall study population. Distributions of all markers have been checked and did not deviate from the normality assumption. We used a regression discontinuity analysis within a linear mixed-effects modeling framework to describe the trajectories of metabolic biomarkers over 24 months before and after the TDF-to-TAF switch. For convenience, we calculated and reported the model predictions in windows around 18 (T_{-18}) and 6 (T_{-6}) months before the switch, at the time of switch (T_0), and 6 (T_6), 12 (T_{12}), and 24 (T_{24}) months after treatment switch. To provide an estimate of the magnitude of

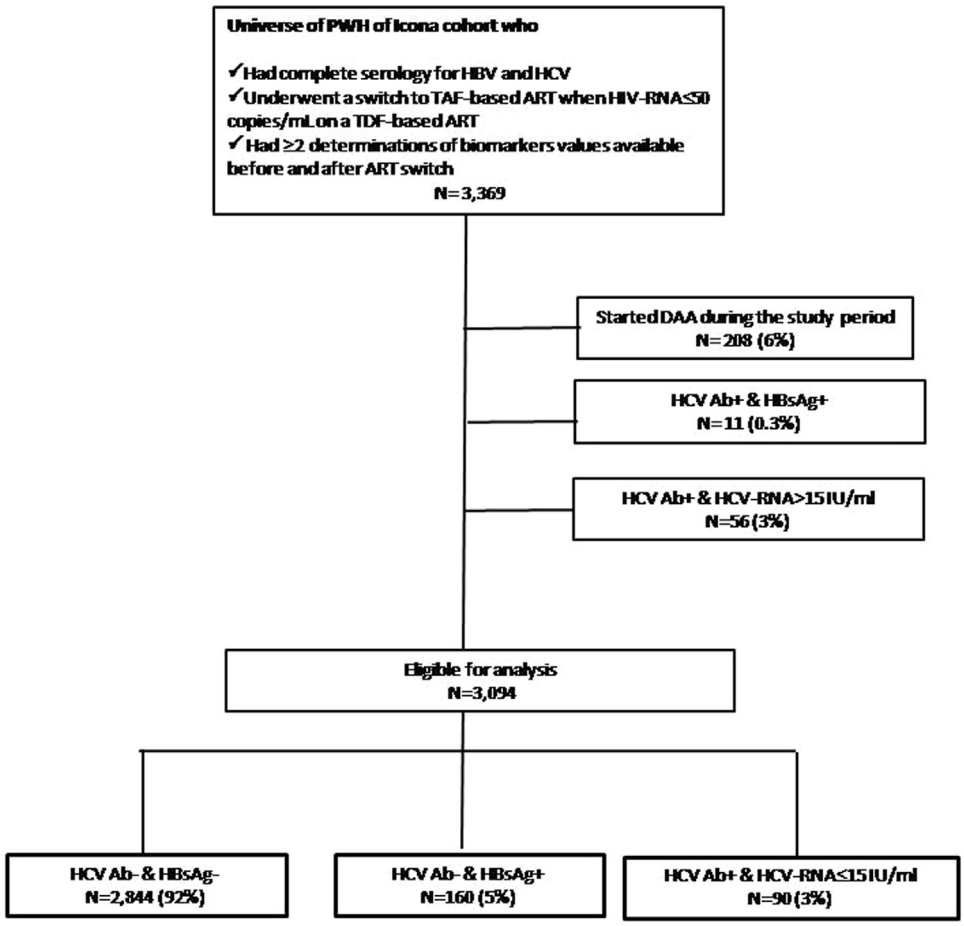


Figure 1. Flowchart of patient selection and inclusion criteria. Abbreviations: ART, antiretroviral therapy; HCVAb, hepatitis C virus antibodies; HBsAg, hepatitis B virus surface antigen; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.

the change over the study period, we also modeled the differences over time using T_0 values as the comparator.

For a subset of biomarkers (ALT, total and LDL-Chol, TGL, and eGFR), we fitted separate mixed linear models with random intercepts and slopes, including an interaction term between exposure to chronic HBV coinfection and time, and we used the model to predict mean biomarker values. Interaction between coinfection and time was formally tested, and *P*-values were provided both for the interaction tests and for individual contrasts between exposed and unexposed individuals at each predefined time point. Models for all outcomes were adjusted for age, cisgender sex, mode of HIV transmission, nationality, and for the drug class of the anchor regimen associated with TDF: non-nucleoside reverse transcriptase inhibitors, protease inhibitors, or integrase strand transfer inhibitors.

To replicate previous published research [3,11] and explore the consistency of results in sub-groups, we decided at the outset to repeat these analyses in subsets of the cohort: those with cLEE as previously defined, LDL-Chol levels $<$100 mg/dl at T_0, and those with eGFR values $<$90 ml/min/1.73 m^2 at T_0.

All statistics were performed using StataCorp 2025. *Stata Statistical Software: Release 19*. College Station, TX: StataCorp LLC and SAS version 9.4 (Cary, North Carolina, USA).

Results

Main participants' characteristics

A total of 3369 ART-experienced PWH of ICONA who had completed serology tests for HBV and HCV and underwent TDF-to-TAF switch and who satisfied the other inclusion criteria described in the Methods were initially extracted for this analysis. Of these, 208 (6%) were excluded because they started DAA during the study period, 11 (0.3%) were excluded due to coinfection with both HBV and HCV, and 56 (3%) were HCV+ with HCV-RNA $>$15 IU/ml (Figure 1).

The final analysis included 3094 PWH, mainly males (80%), of Italian nationality (83%), median age of 45 (IQR 37-52) years. Among them, 2844 were classified as HIV-monoinfected, whereas 160 (5%) had chronic HBV coinfection (HBsAg-positive, HCVAb-negative). The remaining 90 PWH (3%) were people with cured HCV infection. Among them, 59 (66%) spontaneously cleared the HCV infection, whereas the remaining 31 individuals achieved viral eradication through DAA treatment administered before the study period. In the HIV-monoinfected group, 535 patients (24%) showed evidence of previous HBV exposure, as indicated by hepatitis B core antibody (HBcAb) positivity. Overall, participants included in this analysis had been receiving TDF for a median duration of 969 months (IQR 598, 1496), most commonly in combination with a non-nucleoside reverse transcriptase inhibitor (50%) or an integrase strand transfer inhibitor (39%).

Table 1 presents the full clinical and immunovirological characteristics of the study population at the time of switching to TAF (T_0), also stratified by coinfection status. Older age, longer duration of ART, a higher number of previous ART regimens, lower CD4 cell nadir, and higher prevalence of AIDS-defining conditions were observed among PWH with HCVAb+/HCV-RNA $\leq$15 IU/ml /HBsAg– compared with the other groups. No evidence for a difference was observed instead either in median exposure to TDF at T_0 (median

Table 1
Baseline clinical and immunovirological characteristics of study population according to coinfection groups.

Characteristics	HCVAb/ HBsAg– N = 2844	HCVAb/ HBsAg+ N= 160	HCVAb+/ HBsAg– N= 90	Total N = 3094	*P*-value[a]
Gender, n (%)					
Female	568 (20)	19 (12)	22 (24)	609 (20)	0.022
Nationality, n (%)					
Not Italian	506 (18)	38 (24)	11 (12)	555 (18)	0.017
Age, years, median (IQR)	44 (37-52)	49 (42-56)	53 (45-56)	45 (37-52)	<.001
Hepatitis coinfection, n (%)					
HBcAb+	535 (24)	119 (84)	44 (59)	692 (28)	<.001
HCV RNA log10 I/UI, median (IQR)			0.0 (0.0, 1.1)	1.0 (0.0, 1.1)	0.164
HBV DNA log10 I/UI, median (IQR)		1.0 (1.0, 1.3)			
Mode of HIV transmission, n(%)					<.001
IDU	56 (2)	7 (5)	49 (55)	112 (4)	
Homosexual contacts	1376 (48)	71 (44)	21 (23)	1468 (47)	
Heterosexual contacts	1227 (43)	74 (46)	19 (21)	1320 (43)	
Other/Unknown	185 (7)	8 (5)	1 (1)	194 (6)	
AIDS diagnosis, n (%)	383 (13)	29 (18)	18 (20)	430 (14)	0.060
Time to first cART, months, median (IQR)	68 (39, 114)	84 (41, 143)	186 (66, 314)	70 (40, 118)	<.001
Calendar year of ART start, median (IQR)	2013 (2011, 2015)	2012 (2009, 2014)	2011 (2022, 2014)	2013 (2011, 2015)	<.001
CD4 count, cells/mmc, median (IQR)	694 (505, 1061)	636 (408, 831)	652 (429, 844)	691 (500, 888)	0.015
CD4 count nadir, cells/mmc, median (IQR)	302 (164, 430)	256 (123, 395)	205 (103, 320)	297 (158, 425)	<.001
CD4 count, n (%)					
≤200 cells/mmc	88 (3)	7 (4)	6 (7)	101 (3)	0.123
Viral load, log10 copies/ml					
Median (IQR)	0.00 (0.00, 6.41)	1.28 (0.00, 6.44)	0.00 (0.00, 5.16)	0.00 (0.00, 6.44)	0.016
Median (range)	0.00 (0.00, 1.56)	1.38 (0.00, 1.58)	0.00 (0.00, 1.45)	0.00 (0.00, 1.56)	
Time on ART, year, median (IQR)	4 (3, 7)	5 (3, 9)	7 (4, 16)	4 (3, 7)	<.001
Number of previous regimens, median (IQR)	1 (1, 2)	2 (1, 3)	3 (2, 5)	2 (1, 3)	<.001
Time on TDF, months, median (IQR)	966 (599, 1484)	1022 (553, 2077)	1040 (613, 1600)	969 (598, 1496)	0.270
Anchor drug class TDF regimen, n (%)					0.109
NNRTIs	1404 (45)	63 (39)	43 (48)	1510 (49)	
Boosted PIs	512 (15)	84 (24)	15 (17)	565 (18)	
INSTIs	1130 (40)	57 (36)	31 (34)	1017 (33)	
Calendar year of switch to TAF median, IQR	2017 (2017, 2018)	2017 (2017, 2017)	2018 (2017, 2018)	2017 (2017, 2018)	0.479
Time on TAF, months, median (IQR)	868 (616, 1232)	803 (586, 1189)	799 (622, 1242)	867 (615, 1228)	0.360
Anchor drug class TAF regimen, n (%)					0.006
NNRTIs	1291 (45)	48 (30)	43 (44)	1510 (48)	
Boosted PIs	512 (15)	27 (17)	14 (16)	565 (18)	
INSTIs	1130 (40)	84 (53)	31 (34)	1017 (40)	
Metabolic profile at T_0					
Aspartate aminotransferase, IU/l, median (IQR)	23 (19, 29)	25 (10, 33)	24 (21,29)	24 (19, 29)	0.002
Alanine aminotransferase, IU/l, median (IQR)	26 (19, 35)	28 (20, 33)	23 (18, 37)	26 (19, 35)	0.108
Alkaline phosphatase, U/l, median (IQR)	76 (63, 95)	80 (64, 97)	27 (16, 47)	77 (63, 95)	0.546
Gamma-glutamyl transpeptidase, IU/l, median (IQR)	23 (16, 37)	25 (18, 42)	27 (16, 47)	23 (16, 38)	0.053
Fasting glucose, mg/dl, median (IQR)	86 (80, 94)	77 (54, 83)	76 (67, 83)	77 (59, 82)	0.472
Tot-Chol, mg/dl, median (IQR)	179 (155, 204)	176 (153, 200)	175 (153, 196)	178 (155, 203)	0.163
HDL-Chol, mg/dl, median (IQR)	46 (38, 54)	44 (39, 55)	45 (36, 57)	46 (38, 54)	0.726
Low-density lipoprotein cholesterol, mg/dl, median (IQR)	132 (109, 158)	134 (112, 154)	129 (106, 152)	132 (109, 158)	<0.001
Triglycerides, mg/dl, median (IQR)	180 (127, 266)	196 (134, 280)	248 (168, 383)	178 (155, 203)	0.163
Tot-Chol/HDL ratio, median (IQR)	3.9 (3.1, 4.7)	3.7 (3.2, 4.6)	3.9 (3.2, 4.6)	3.9 (3.1, 4.7)	0.695
Creatinine, mg/dl, median (IQR)	0.9 (0.8, 1.1)	1.0 (0.9, 1.1)	0.9 (0.8, 1.0)	0.9 (0.8, 1.1)	0.011
Estimated glomerular filtration rate, ml/min/1.73 m^2, median (IQR)	89 (77, 102)	88 (73, 97)	84 (75, 92)	89 (76, 101)	0.003
Chronic liver enzymes elevation[b], n (%)	298 (10)	20 (12)	9 (10)	327 (11)	0.709

[a] Chi-square or Kruskal-Wallis test as appropriate.
[b] Defined as two or more elevated ALT values (males >50 U/L, females >35 U/L) over at least 6 months.
HBsAg, hepatitis B surface antigen; HBcAb, hepatitis B core antibodies; HCVAb, hepatitis C virus antibodies; HDL-Chol, high-density lipoprotein cholesterol; IDU, intravenous drug user; INSTIs, integrase strand transfer inhibitors; IQR, interquartile range; NRTIs, nucleoside reverse transcriptase inhibitors; NNRTI, non-NRTIs; PIs, protease inhibitors; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate; Tot-Chol, total cholesterol.

966 [IQR 599-1484] vs median 1022 [IQR 533-2077] vs median 1040 [IQR 613-1600] months, $P = 0.27$) or in the distribution of third-agent drug classes combined with TDF according to coinfection status.

Biomarker levels at T_0

At the time of switch (T_0), median levels of liver damage markers were within the normal range in our population (Table 1). As

Table 2
Unadjusted trend over time of differences in means of all biomarkers from time of switch.

Markers	Months from the switch from tenofovir disoproxil fumarate to tenofovir alafenamide					
	Unadjusted differences in means over time (raw scale) - reference date of switch					
	-18 95% CI	-6 95% CI	0 REF	+6 95% CI	+12 95% CI	+24 95% CI
Alanine aminotransferase, UI/l	-0.90 (-4.22, 2.43)	-0.46 (-3.87, 2.95)		-3.05 (-6.42, 0.31)	-4.14 (-7.61, -0.67)	-2.11 (-5.79, 1.56)
Aspartate aminotransferase, UI/l	-0.65 (-3.71, 2.40)	-0.18 (-3.28, 2.92)		-2.19 (-5.26, 0.89)	-2.64 (-5.86, 0.59)	0.50 (-3.01, 4.00)
Gamma-glutamyl transpeptidase, UI/l	-0.37 (-5.58, 4.84)	0.42 (-4.69, 5.54)		-4.03 (-9.13, 1.06)	-4.65 (-9.91, 0.61)	1.85 (-4.00, 7.71)
Alkaline phosphatase, UI/l	7.57 (3.29, 11.85)	3.26 (-1.07, 7.59)		-12.9 (-17.2, -8.66)	-13.3 (-17.7, -8.87)	-9.73 (-15.0, -4.44)
Triglycerides, mg/dl	-3.17 (-9.40, 3.06)	-4.05 (-10.2, 2.15)		11.56 (5.39, 17.72)	9.02 (2.69, 15.36)	2.29 (-4.74, 9.31)
Total cholesterol, mg/dl	-2.01 (-4.34, 0.33)	-0.36 (-2.69, 1.96)		14.46 (12.14, 16.78)	16.14 (13.75, 18.52)	12.69 (10.05, 15.32)
Low-density lipoprotein cholesterol, mg/dl	-0.53 (-3.19, 2.13)	0.66 (-1.77, 3.09)		10.70 (8.36, 13.04)	13.94 (11.49, 16.39)	11.15 (8.21, 14.10)
Total/high-density lipoprotein cholesterol, mg/dl	0.15 (0.02, 0.27)	0.21 (0.09, 0.33)		0.09 (-0.03, 0.21)	0.10 (-0.02, 0.22)	-0.09 (-0.23, 0.05)
Fasting glucose, mg/dl	-0.73 (-2.10, 0.64)	-1.11 (-2.51, 0.29)		0.08 (-1.32, 1.47)	2.42 (0.97, 3.87)	1.29 (-0.32, 2.90)
Creatinine, mg/dl	0.07 (-0.02, 0.16)	0.11 (0.02, 0.21)		-0.02 (-0.11, 0.07)	0.02 (-0.08, 0.11)	-0.00 (-0.11, 0.10)
Estimated glomerular filtration rate, ml/min/1.73 m^2	3.81 (3.04, 4.59)	0.69 (-0.11, 1.49)		0.72 (-0.07, 1.50)	-0.78 (-1.60, 0.04)	-1.59 (-2.47, -0.71)

CI, confidence interval.

expected, slightly higher median values—although still within normal limits—were observed in the subgroups with positive HBsAg or HCVAb compared with HIV-monoinfected individuals for AST (25 [IQR 20-33] in PWH with HBsAg+ and 24 [IQR 21-29] in PWH with HCVAb+ vs 23 [IQR 19-29] UI/l in participants with HIV monoinfection, $P = 0.002$), but not for ALT (28 [IQR 20-37] in PWH with HBsAg+ and 23 [IQR 18-37] in PWH with HCVAb+ vs 26 [IQR 19-35] UI/l in participants with HIV monoinfection, $P = 0.11$), GGT (25 [IQR 18-42] in PWH with HBsAg+ and 27 [IQR 16-47] in PWH with HCVAb+ vs 23 [IQR 16-37] UI/l in participants with HIV monoinfection, $P = 0.05$), or ALP (80 [IQR 64-97] in PWH with HBsAg+ and 82 [IQR 67-99] in PWH with HCVAb+ vs 76 [IQR 63-95] UI/l in participants with HIV monoinfection, $P = 0.55$) Notably, 327 PWH (11%) were defined as cLEE at T_0, with no evidence for a difference by coinfection status (10% in mono vs 12% in PWH with positive HBsAg and 10% in those with positive HCVAb, $P = 0.71$).

Altered fasting lipid profiles were detected at the time of switch in the overall population, with TGL and LDL-Chol levels exceeding the upper normal limits. Specifically, at T_0, 1856 individuals (55%) had LDL-Chol levels >100 mg/dl, of whom 1210 (65%) had values exceeding 116 mg/dl. Higher TGL levels at T_0 were detected in patients with positive HCVAb compared with PWH with positive HBsAg and with HIV-monoinfected individuals (median 248 [IQR 168-383] in PWH and HCVAb+ vs 196 [IQR 134-280] in PWH and HBsAg+ and 180 [IQR 127-266] mg/dl in participants with HIV monoinfection, $P < 0.001$), whereas LDL-Chol levels were more similar between groups (median 129 [IQR 106-152] in PWH and HCVAb+ vs 134 [IQR 112-154] in PWH and HBsAg+ and 132 [IQR 109-158] mg/dl in participants with HIV monoinfection, $P = 0.600$). Notably, 328 individuals (111%) were receiving statin therapy before the switch, with a similar proportion between the three subgroups.

Fasting glucose and Tot-/HDL-Chol ratios were within normal ranges in all exposure groups. A slightly lower GFR was observed among PWH with past HCV compared with other subgroups (median 84 [IQR 75-92] in PWH and HCVAb+ vs 88 IQR 73-98] in PWH and HBsAg+ and 89 [IQR 77-102] mg/dl in participants with HIV monoinfection, $P = 0.003$) at the time of switching to TAF, although the difference in serum creatinine levels between groups was negligible (median 0.9 [IQR 0.8-1.0] in PWH and HCVAb+ vs 1.0 [IQR 0.9-1.1] in PWH and HBsAg+ and 0.9 [IQR 0.8-1.1] mg/dl in participants with HIV monoinfection, $P = 0.011$).

Overall trends over time

A modest upward trend in mean levels of liver damage markers and serum creatinine was observed during treatment with TDF, although of small clinical significance. A similar trend could be observed for lipid biomarkers over the same period of exposure to TDF, whereas a modest downward trajectory was noticed for fasting glucose and TGL.

Mean differences over time for all laboratory parameters in the overall population, compared with mean values at the time of switch, as predicted by the models, are summarized in Table 2, and, for ALT, Tot- and LDL-Chol, TGL, and eGFR, a graphical illustration of these predictions is reported in Supplementary Figure 1.

Following the switch from TDF to TAF, a decline in ALT levels was observed, with a mean change of −3.05 (IQR−6.42, 0.31) U/L at T_6 compared with T_0, which remained stable up to 12 and 24 months after the switch. Similar downward trends were observed for AST and GGT levels (Table 2). The reduction in liver enzyme levels was more pronounced when the analysis was restricted to individuals with cLEE, particularly for ALT, which decreased by −20.5 (IQR −49.2, 8.32) UI/l at T_6, −39.8 (IQR −70.5, −9.15) UI/l at T_{12}, and −22.6 (IQR −53.6, 8.39) UI/l at T_{24}. A substantial reduction was also seen in GGT levels, which declined by −37.2 (IQR −67.7, −6.68) UI/l at T_6, −29.5 (IQR −60.1, 1.12) UI/l at T_{12}, and −22.9 (IQR −54.2, 8.41) UI/l at T_{24}.

In contrast, fasting T-Chol, LDL, and TGL increased in the overall population at T_6 by 14.46 (IQR 12.14, 16.78) mg/dl, 10.70 (IQR 8.36, 13.04) mg/dl, and 11.56 (IQR 5.39, 17.72) mg/dl, respectively, followed by a plateau or slight decrease at T_{12} and T_{24}.

Notably, a greater increase in total and LDL-Chol levels—by 19.72 (IQR 15.38, 24.07) mg/dl and 15.49 (IQR 11.66, 19.32) mg/dl, respectively—was observed at T_6 among PWH with baseline LDL-Chol ≤100 mg/dl. In addition, in this subgroup, values plateaued

Table 3
Mean differences in laboratory parameters over time according to coinfection status from fitting a linear mixed model.

	Months from the switch from tenofovir alafenamide to tenofovir disoproxil fumarate						
	Adjusted[b] differences in means by exposure groups (raw scale) - comparator mono-HIV group *P*-value						
Markers	-12 95% CI	-6 95% CI	0 95% CI	+6 95% CI	+12 95% CI	+24 95% CI	*P*-value[a]
Alanine aminotransferase							
HBsAg-/HCVAb-	**REF**						<0.001
HBsAg+/HCVAb-	6.96 (2.53, 11.40) 0.002	3.56 (-1.24, 8.35) 0.146	12.11 (6.36, 17.85) <.001	3.61 (-1.09, 8.32) 0.132	0.03 (-4.60, 4.66) 0.990	-0.92 (-5.62, 3.77) 0.700	
Total cholesterol							
HBsAg-/HCVAb-	**REF**						0.207
HBsAg+/HCVAb-	-7.44 (-14.8, -0.10) 0.047	-5.84 (-13.3, 1.66) 0.127	-6.71 (-15.4, 1.95) 0.129	-9.11 (-16.7, -1.51) 0.019	-3.22 (-10.6, 4.18) 0.394	-7.83 (-15.3, -0.34) 0.040	
Low-density lipoprotein cholesterol							
HBsAg-/HCVAb-	**REF**						0.160
HBsAg+/HCVAb-	-3.09 (-11.3, 5.10) 0.460	-1.52 (-9.29, 6.25) 0.702	-10.4 (-19.1, -1.63) 0.020	-4.95 (-12.6, 2.74) 0.207	1.74 (-5.76, 9.24) 0.649	-6.39 (-14.0, 1.23) 0.100	
Triglycerides							
HBsAg-/HCVAb-	**REF**						0.980
HBsAg+/HCVAb-	-14.1 (-32.9, 4.72) 0.142	-11.0 (-30.3, 8.26) 0.262	-16.0 (-38.9, 6.85) 0.170	-10.4 (-30.0, 9.25) 0.299	-15.3 (-34.3, 3.72) 0.115	-19.3 (-38.7, 0.04) 0.050	
Estimated glomerular filtration rate							
HBsAg-/HCVAb-	**REF**						0.002
HBsAg+/HCVAb-	-0.59 (-3.22, 2.04) 0.658	-1.88 (-4.64, 0.88) 0.183	-0.18 (-3.31, 2.96) 0.913	-3.52 (-6.23, -0.81) 0.011	-1.70 (-4.41, 1.01) 0.220	-0.05 (-2.78, 2.68) 0.973	

[a] F-test type 3 interaction *P*-value.
[b] Adjusted for age, cisgender sex, mode of HIV transmission, nationality, and class of anchor drug used in the TDF-based regimen.
HBsAg, hepatitis B surface antigen; HCVAb, hepatitis C virus antibodies.

between T_{+12} and T_{+24}. The proportion of individuals receiving lipid-lowering and antihypertensive medications remained stable over the study period, with only a slight increase from 10% at the beginning of the study period to 13% at the end of follow-up, with higher prevalences consistently observed among PWH with positive HBsAg.

Overall, a reduction in eGFR was observed, as reported in Table 2. However, in a sub-analysis of 1765 subjects (52%) with eGFR <90 ml/min/1.73 m² at time of switching to TAF, an improvement in eGFR was observed shortly after the switch, with increases of 3.37 (IQR 2.28, 4.46) ml/min/1.73 m² at T_6, followed by a plateau around a value of 2.45 (IQR 1.32, 3.59) ml/min/1.73 m² by T_{12} and 1.69 (IQR 0.49, 2.89) at T_{24}.

Notably, the estimated average values of all biomarkers remained within normal ranges over the whole study period, except for LDL-Chol, with mean population values that increased above the upper limit of normality after the date of switching to TAF-based ART (Table 1 and Figure 1 of the Supplementary Materials).

Trends over time by hepatitis B surface antigen-positive/hepatitis C virus antibodies-negative status

Adjusted mean differences in ALT, Tot- and LDL-Chol, TGL, and eGFR between monoinfected and HBsAg+ HCVAb– PWH, after controlling for the potential confounding effect of age, cisgender sex, mode of HIV transmission, nationality, and drug class of the anchor drug included in the TDF regimen, are reported in Table 3. The estimated trends in mean differences of laboratory parameters in the exposure strata mirrored those observed in the overall population. However, strong evidence for a difference in the trajectories of ALT and eGFR was observed comparing the HIV-monoinfected and HBsAg+ group. Specifically, ALT on average was higher and eGFR lower in the HBsAg+ group vs HIV-monoinfected in the period in which participants were treated with TDF, but these differences tended to attenuate after the switch to TAF (interaction *P*-values <0.001 and 0.002, respectively, Table 3 and Figure 2). In contrast, we found no evidence for a difference in lipid profile trajectories by hepatitis coinfection group.

Discussion

This study has shown a modest but consistent decline in ALT, accompanied by parallel reductions in AST, ALP, and GGT over 24 months after switching from TDF- to TAF-based regimens. Notably, despite the changes, all values remained within normal ranges throughout follow-up.

These findings align with those of previous studies. Kovari et al. reported a modest ALT reduction after TDF discontinuation, regardless of TAF introduction. Notably, authors found that transaminase reduction was particularly marked in individuals with elevated baseline transaminases, but minimal in those with normal baseline ALT [4]. Similarly, the Surveillance Cohort Long-term Toxicity Antiretrovirals/Antivirals study observed ALT decreases 6 months post-TDF replacement with TAF in PWH—with or without HBV/HCV coinfection—more pronounced in those with elevated baseline ALT [8].

TAF achieves higher intracellular concentrations than TDF in hepatocytes and lymphocytes [12], raising concerns about hepatotoxicity and lipid disturbances, particularly in patients with pre-existing liver disease and baseline dyslipidemia.

Our cohort included small proportions of participants with chronic HBV coinfection or cured HCV coinfection. Although modest and of limited clinical relevance, we observed differences in ALT trajectories following the switch from TDF to TAF according to coinfection status. Specifically, much higher ALT levels in HBsAg+ vs HIV-monoinfected during treatment with TDF, which were somewhat attenuated after the switch to TAF. Furthermore, individuals with cLEE at baseline—who were evenly distributed

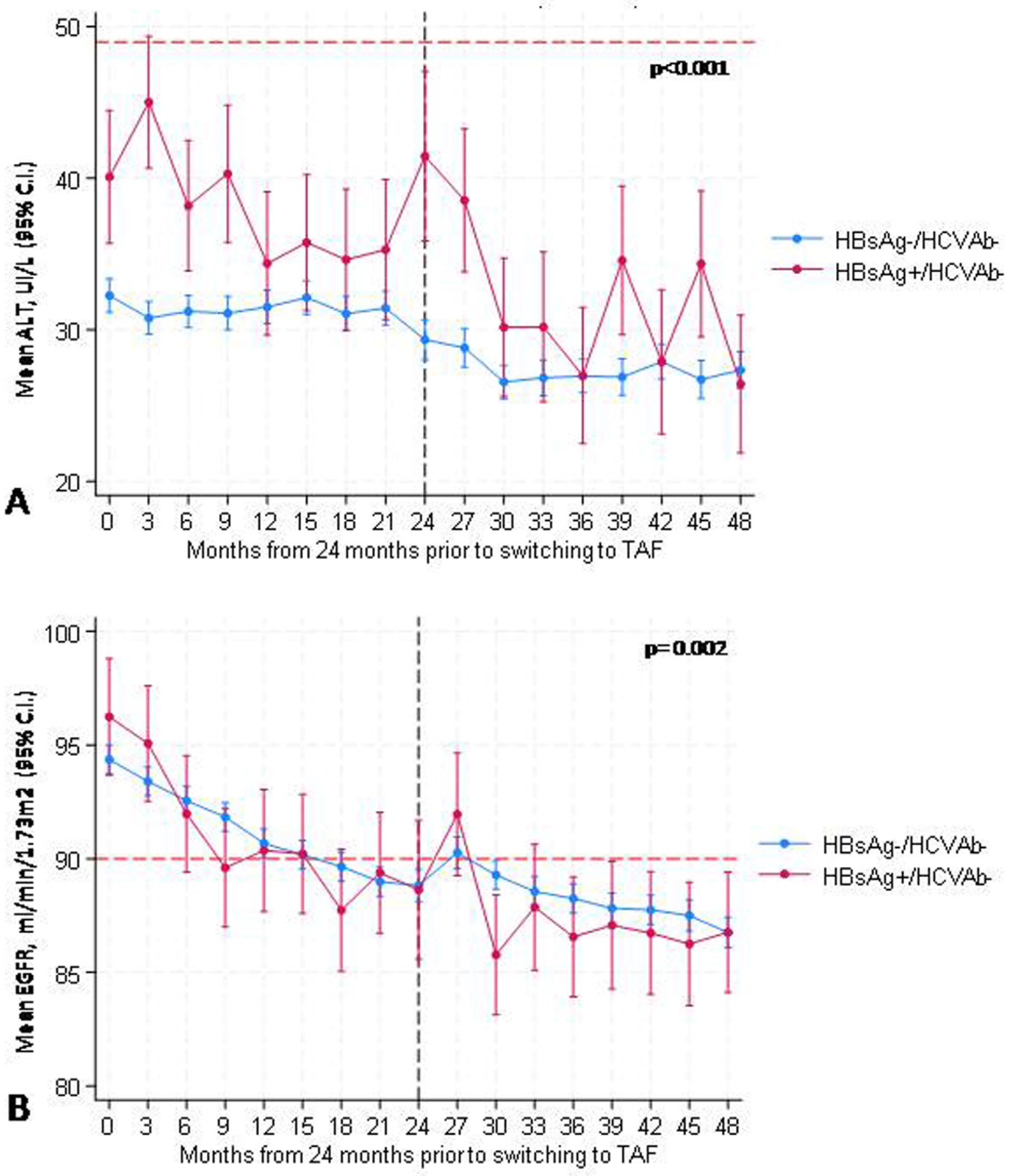


Figure 2. Trends in mean values and 95% CIs of ALT (a) and eGFR (b) from 24 months before to 24 months after the switch from tenofovir disoproxil fumarate to TAF according to HBsAg-positive/HCVAb-negative status. Red dotted lines indicate the thresholds of normal values.
ALT, alanine aminotransferase; CIs, confidence intervals; eGFR, estimated glomerular filtration rate; HCVAb, hepatitis C virus antibodies; HBsAg, hepatitis B virus surface antigen; TAF, tenofovir alafenamide.

across all groups—experienced a more pronounced reduction in ALT levels after the switch. This improvement may stem from TDF discontinuation rather than TAF initiation, as TDF is associated with reversible transaminase elevations likely due to its higher mitochondrial toxicity observed in animal studies [17]. Regardless of the underlying biological mechanism, the improvement in transaminase levels observed after switching from TDF to TAF, consistently reported not only in our study but also across the literature, has a remarkable clinical significance and supports the use of TAF in special populations such as HIV/HBV-coinfected patients, including those without contraindications to TDF.

At the time of the TDF-to-TAF switch, fasting lipid values were largely within normal ranges. Following the switch, all lipid parameters increased significantly, though generally remained within normal limits—except for LDL-Chol, whose increased exceeded the normal threshold. No evidence for a difference in trajectories over time was observed according to HBV coinfection status.

It should be emphasized that the increase in LDL-Chol levels was mainly observed in individuals with baseline values <100 mg/dl, whereas levels did not worsen significantly in those who already had elevated LDL-Chol at baseline. This is reassuring, as it indicates that switching from TDF to TAF does not further com-

promise the lipid profile in patients already at higher cardiovascular risk. At the same time, the switch may selectively increase cardiovascular risk markers in patients with initially low LDL-Chol, underscoring the importance of careful lipid monitoring and preventive management in this subgroup.

LDL-Chol is increasingly recognized as a key surrogate marker for cardiovascular disease [8], particularly in PWH who exhibit higher cardiovascular risk than age- and sex-matched individuals, due to chronic inflammation, persistent immune activation despite viral suppression, ART effects, and HIV-related endothelial and metabolic dysfunction [18].

The association between TAF and the onset or worsening of dyslipidemia has been observed, particularly among both mono- and HBV-coinfected individuals switching from TDF- to TAF-based regimens [19,20]. In contrast, switching to TAF-sparing regimens has shown minimal impact on lipid and weight parameters, with most studies reporting either slight lipid increases or overall metabolic stability [21,22]. These findings suggest that, like changes in ALT, the observed lipid alterations are likely driven primarily by TDF discontinuation rather than TAF initiation. The lipid-lowering and weight-reducing effects of TDF have been linked to mechanisms, including intestinal villi damage [23], downregulation of adipogenic pathways in enterocytes [24], and inhibition of fibroblast-to-adipocyte differentiation [25]. However, despite these metabolic benefits, such mechanisms may adversely affect body composition, notably through reductions in lean mass and bone mineral density [26]. Recent data from the REPRIEVE trial demonstrate that low-dose statins provide cardiovascular protection to PWH, including those at moderate or low risk, through lipid-lowering and anti-inflammatory effects [27]. Consequently, ART selection based solely on lipid impact is being reconsidered, with greater focus on lifestyle modification and adjunctive lipid-lowering therapies, in line with current international guidelines [28].

Finally, our findings reinforce the renal safety profile of TAF. Although renal function was preserved during TDF exposure, coinfected individuals showed slightly lower eGFR, possibly due to unquantified end-stage liver disease, longer TDF exposure, or higher median age, given eGFR's age dependency, as serum creatinine remained within normal limits in both groups. However, in patients with baseline eGFR $<$90 ml/min, a slight but stable increase post-switch was observed, supporting TAF use in vulnerable populations. To note, comparable results were reported in a prospective analysis of 106 HIV/HBV-coinfected patients with renal dysfunction in the Swiss HIV Cohort [14]. Importantly, our data not only confirms previous findings but also extends the observation to a much longer time after the switch to TAF. In addition, to our knowledge, this is the first paper in which all markers have been analyzed simultaneously in the same study population and after controlling for a common set of potential confounding factors.

Our study has several limitations. First, although the ICONA cohort enrolls a relatively large number of PWH, the proportion of individuals with HBsAg or HCVAb positivity was relatively small, which may have limited the precision of our results.

Moreover, we relied on plasma surrogate markers of liver function rather than more precise diagnostic tools like elastography, which are less accessible in routine practice. Second, important parameters such as waist circumference and proteinuria that could provide more detailed insights into cardiovascular risk and renal impairment were not measured. Indeed, proteinuria is a more sensitive marker of TDF-related nephrotoxicity, and it has been shown that it often improves after switching to TAF despite stable or slightly decreased eGFR [29]. In addition, lipid-lowering therapy use was likely underestimated, with insufficient detail on treatment type and duration, limiting the interpretation of LDL changes. Third, it is important to note that some of the large changes observed in subset analyses restricting to participants with marker values below a certain threshold at T_0 may be partly due to regression to the mean. Finally, despite adjusting for confounders in analyzing hepatitis coinfection effects, residual confounding cannot be excluded. More generally, our basic analysis is mainly descriptive, not geared towards estimating the causal effect of discontinuing TDF or initiating TAF on the measured parameters.

Conclusion

In the ICONA cohort, liver enzyme improvements and eGFR increases were observed over 2 years after switching from TDF to TAF, especially in individuals with chronic HIV/HBV coinfection, supporting TAF's hepatic safety. Lipid increases were mostly limited to the first 6 months and stabilized thereafter, with no differences by coinfection status, confirming TAF's overall metabolic safety.

Declaration of competing interest

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Authors Contributions

Conceptualization, M.P., S.L.C., A.T., A.D.M. and A.C.L.; methodology, M.P., S.L.C., A.T., A.D.M. and A.C.L.; formal analysis, A.C.L.; investigation, M.P, R.G., L.G., A.S., T.A.S., N.S., M.P., V.M., A.A.; resources, A.T.; data curation, A.T, A.C.L..; writing—original draft preparation, M.P. and A.C.L.; writing—review and editing, M.P., and A.C.L.; visualization, M.P., S.L.C., A.T., A.D.M. and A.C.L.; supervision, A.D.M. and A.C.L.; project administration, M.P., S.L.C., A.T., A.D.M. and A.C.L . All authors have read and agreed to the published version of the manuscript.

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Data sharing agreement

The datasets generated during the current study are not publicly available because they contain sensitive data that must be treated under data protection laws and regulations. Appropriate agreement of data sharing can be arranged after a reasonable request to the corresponding author.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijid.2025.108081.

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