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Impact of tenofovir on SARS-CoV-2 infection and severe outcomes among people living with HIV: a propensity score-matched study

Daniel K. Nomah[1,2,3]†, Juliana Reyes-Urueña [1,3,4]*†, Yesika Díaz[1,3], Sergio Moreno[1,3], Jordi Aceiton[1,3],
Andreu Bruguera[1,2,3], Rosa M. Vivanco-Hidalgo[5], Jordi Casabona[1,2,3,4], Pere Domingo [6], Jordi Navarro [7],
Arkaitz Imaz[8], Elisabet Deig[9], Gemma Navarro[10], Josep M. Llibre [11] and Jose M. Miro[12] on behalf of the PISCIS study group‡

[1]Centre Estudis Epidemiològics sobre les Infeccions de Transmissió Sexual i Sida de Catalunya (CEEISCAT), Dept Salut, Generalitat de Catalunya, Badalona, Spain; [2]Departament de Pediatria, d'Obstetrícia i Ginecologia i de Medicina Preventiva i de Salut Publica, Universitat Autònoma de Barcelona, Bellaterra, Spain; [3]Institut d'Investigació Germans Trias i Pujol (IGTP), Barcelona, Spain; [4]CIBER Epidemiologia y Salud Pública (CIBERESP), Barcelona, Spain; [5]Agència de Qualitat i Avaluació Sanitàries de Catalunya, Barcelona, Spain; [6]Hospital de la Santa Creu i Sant Pau, Barcelona, Spain; [7]Vall d'Hebron Research Institute (VHIR), Hospital de Vall d'Hebron, Barcelona, Spain; [8]Hospital Universitari de Bellvitge, Bellvitge Biomedical Research Institute (IDIBELL), University of Barcelona, L'Hospitalet de Llobregat, Spain; [9]Hospital General de Granollers, Granollers, Spain; [10]Unitat de VIH/SIDA, Corporació Sanitària i Universitària Parc Taulí-Universitat Autònoma de Barcelona, Sabadell, Spain; [11]Hospital Universitari Germans Trias i Pujol, Badalona, Spain; [12]Hospital Clínic-Institut d'Investigacions Biomèdiques August Pi i Sunyer, University of Barcelona, Barcelona, Spain

*Corresponding author. E-mail: jmreyes@iconcologia.net
†These authors contributed equally to this manuscript.
‡Members are listed in the Acknowledgements.

Background: Reports on the impact of some antiretrovirals against SARS-CoV-2 infection and disease severity are conflicting.

Objectives: We evaluated the effect of tenofovir as either tenofovir alafenamide/emtricitabine (TAF/FTC) or tenofovir disoproxil fumarate/emtricitabine (TDF/FTC) against SARS-CoV-2 infection and associated clinical outcomes among people living with HIV (PLWH).

Methods: We conducted a propensity score-matched analysis in the prospective PISCIS cohort of PLWH ($n = 14$ 978) in Catalonia, Spain. We used adjusted Cox regression models to assess the association between tenofovir and SARS-CoV-2 outcomes.

Results: After propensity score-matching, SARS-CoV-2 diagnosis rates were similar in TAF/FTC versus ABC/3TC recipients (11.6% versus 12.5%, $P = 0.256$); lower among TDF/FTC versus ABC/3TC recipients (9.6% versus 12.8%, $P = 0.021$); and lower among TDF/FTC versus TAF/FTC recipients (9.6% versus 12.1%, $P = 0.012$). In well-adjusted logistic regression models, TAF/FTC was no longer associated with reduced SARS-CoV-2 diagnosis [adjusted odds ratio (aOR) 0.90; 95% confidence interval (CI), 0.78–1.04] or hospitalization (aOR 0.93; 95% CI, 0.60–1.43). When compared with ABC/3TC, TDF/FTC was not associated with reduced SARS-CoV-2 diagnosis (aOR 0.79; 95% CI, 0.60–1.04) or hospitalization (aOR 0.51; 95% CI, 0.15–1.70). TDF/FTC was not associated with reduced SARS-CoV-2 diagnosis (aOR 0.79; 95% CI, 0.60–1.04) or associated hospitalization (aOR 0.33; 95% CI, 0.10–1.07) compared with TAF/FTC.

Conclusions: TAF/FTC or TDF/FTC were not associated with reduced SARS-CoV-2 diagnosis rates or associated hospitalizations among PLWH. TDF/FTC users had baseline characteristics intrinsically associated with more benign SARS-CoV-2 infection outcomes. Tenofovir exposure should not modify any preventive or therapeutic SARS-CoV-2 infection management.

Introduction

Tenofovir has been postulated as a treatment candidate for COVID-19.[1] This nucleotide analogue is very prominent in antiretroviral treatment (ART) and is available as the prodrugs tenofovir alafenamide (TAF) and tenofovir disoproxil fumarate (TDF). The two medicines are also efficacious as HIV pre-exposure prophylaxis (PrEP) in high-risk populations without HIV infection.[2] The repurposing of TAF and TDF is due to their well-established safety profile, the wide availability of the generic forms, and the low cost of TDF.[3] In pre-clinical studies, tenofovir showed some *in vitro* activity against SARS-CoV-2, inhibiting its RNA-dependent RNA polymerase (RdRp).[4] Furthermore, triphosphate forms of tenofovir are believed to be incorporated by SARS-CoV-2 RdRp and retard polymerase extension, which could explain why the nucleotide analogue could inhibit SARS-CoV-2.[5] However, a recent comprehensive set of *in vitro* analyses performed by the drug manufacturer has finally indicated that neither TAF, TDF, nor emtricitabine (FTC) are inactive against SARS-CoV-2.[6] These results are corroborated by the lack of interaction between tenofovir triphosphates and SARS-CoV-2 RdRp observed both in biochemical assays and in structural modelling analyses.[6]

A study of people living with HIV (PLWH) receiving ART in Spain suggested that individuals receiving TDF/FTC were at a lower risk of COVID-19 and related hospitalization than those receiving other antiretroviral regimens.[7] However, the analysis was not adjusted for baseline co-morbidities and important sociodemographic characteristics, and could be overestimating the protective effect of TDF/FTC because recipients of TDF/FTC are likely to be younger and without comorbidities such as renal and cardiovascular diseases, which have been established as risk factors for COVID-19 and severe outcomes.[8–10] In another study, from South Africa, TDF/FTC (versus abacavir or zidovudine) was again associated with lower mortality among PLWH after adjusting for kidney disease, viral suppression, and antiretroviral treatment duration.[11] Zidovudine, a second-line regimen, is however associated with prior virological failure or presence of tuberculosis, both of which were not adjusted for in that study. Similarly, among HIV-negative individuals with chronic hepatitis B infection, lower rates of severe COVID-19, ICU admission, need for respiratory support, and shorter hospitalization duration were found among patients receiving TDF/FTC compared with entecavir.[12] However, again, the prevalence of chronic comorbidities was significantly lower among those receiving TDF/FTC, establishing again a channelling prescription bias.[12]

A study that assessed the protective effects of tenofovir against SARS-CoV-2 infection among HIV-negative individuals found just the opposite: a higher SARS-CoV-2 seroprevalence among PrEP (tenofovir) users compared with persons not receiving tenofovir (15.5% versus 9.2%, $P = 0.026$).[13] The study found no statistically significant differences in COVID-19 clinical manifestations between users of PrEP, TDF/FTC or TAF/FTC and the control group.[13] Similarly, the PREVENIR-ANRS and SAPRIS-Sero study from France also showed no reduction in SARS-CoV-2 seroprevalence among TDF/FTC PrEP users.[14] That study is particularly relevant as there were no baseline patient characteristics biasing the analysis through a channelling prescription.

There are several on-going clinical trials assessing the potential of tenofovir as prophylaxis against SARS-CoV-2 infection and treatment for COVID-19.[3] Understanding the preventive effect of tenofovir is very relevant given the rapidly changing COVID-19 situation and the surge of new variants with potential to escape vaccine- or infection-induced immune protection.

We evaluated the association between TAF/FTC and TDF/FTC exposure against SARS-CoV-2 infection and severe COVID-19 among PLWH, mitigating the limitations in existing studies by adjusting adequately for potential baseline confounders.

Patients and methods

Study population and design

We performed a retrospective study using data from the Populational HIV Cohort from Catalonia and Balearic Islands (PISCIS). PISCIS is a prospective, multicentre, population-based cohort which follows PLWH aged ≥16 years accessing care at 15 hospitals in Catalonia, Spain.[15] We linked PISCIS data with data from several administrative official public health databases to obtain information about chronic comorbidities, SARS-CoV-2 diagnosis, and related clinical outcomes. Data were managed through the Analytical Data for Research and Innovation in Health Project of Catalonia (PADRIS) so as to ensure anonymization in accordance with current data protection legislation.[16] The study period was from 1 March 2020 to 18 July 2021. We excluded patients who were reported dead before 1 March 2020, those without information on ART, and those who had at any point switched their ART regimen since cohort entry.

Study definitions and outcomes

We divided the study population into three groups according to nucleos(t)ide reverse transcriptase inhibitor (NRTI) exposure: (i) TAF/FTC; (ii) TDF/FTC; and (iii) abacavir/lamivudine (ABC/3TC). The primary outcome variables of interest were SARS-CoV-2 diagnosis confirmed by a positive reverse transcription polymerase chain reaction (RT-PCR) and/or antigen detection; and COVID-19 outcomes graded as asymptomatic, symptomatic requiring community management (mild symptoms managed as outpatients or at the emergency department for <24 h), and hospital admissions (>24 h with any of the following signs: dyspnoea, tachypnoea, hypoxaemia, asphyxia or hyperventilation). Among hospitalized patients, we also assessed admission to the ICU (suffered a respiratory failure or sepsis) and death.

Independent variables in the study included patient sociodemographic characteristics: age; sex; socioeconomic deprivation based on the Catalonian Government socioeconomic deprivation index classified as least deprived, mildly deprived, and moderately/severely deprived;[17] and country of origin (Spanish and non-Spanish origin). The HIV-associated variables we included in the study were HIV acquisition risk groups as stated in Table 1; duration since HIV diagnosis in years; CD4 cell count (categorized <350 cells/mm³, 350–499 cells/mm³, and ≥500 cells/mm³) and CD4/CD8 cell ratio; plasma HIV-RNA [detectable and undetectable (≤50 copies/mL)]; and duration on ART in years. We included chronic comorbidities extracted using the International Classification of Diseases, ninth revision, Clinical Modification (ICD-9-CM) and tenth revision (ICD-10-CM) and grouped them into 11 groups (Table S1, available as Supplementary data at *JAC* Online).

Statistical analysis

Continuous variables are presented as median with interquartile ranges (IQR) and frequencies with percentages for categorical variables. Proportions for categorical variables were compared using the χ^2 or Fisher's exact test where appropriate. Continuous variables were

Table 1. Propensity score-matched[a] baseline characteristics of people living with HIV receiving (i) TAF/FTC versus ABC/3TC, (ii) TDF/FTC versus ABC/3TC, or (iii) TAF/FTC versus TDF/FTC

Characteristic	TAF/FTC versus ABC/3TC				TDF/FTC versus ABC/3TC				TAF/FTC versus TDF/FTC			
	Total (n=7024)	TAF/FTC (n=3512)	ABC/3TC (n=3512)	P value	Total (n=3052)	TDF/FTC (=763)	ABC/3TC (n=2289)	P value	Total (n=3080)	TAF/FTC (n=2310)	TDF/FTC (n=770)	P value
Sex, n (%)				0.926				1.000				0.557
Male	5678 (80.8)	2841 (80.9)	2837 (80.8)		2476 (81.1)	619 (81.1)	1857 (81.1)		2504 (81.3)	1884 (81.6)	620 (80.5)	
Female	1346 (19.2)	671 (19.1)	675 (19.2)		576 (18.9)	144 (18.9)	432 (18.9)		576 (18.7)	426 (18.4)	150 (19.5)	
Age, years, median (IQR)	48.2 (39.6–55.4)	48.0 (39.4–55.2)	48.4 (39.8–55.6)	0.117	45.2 (38.0–53.1)	45.0 (38.3–52.4)	45.3 (37.9–53.2)	0.803	45.0 (38.3–52.5)	45.1 (38.3–52.6)	44.9 (37.9–52.3)	0.542
Age category, years				0.642				0.893				0.587
16–39	1832 (26.08)	932 (26.54)	900 (25.63)		1014 (33.2)	250 (32.8)	764 (33.4)		988 (32.1)	730 (31.6)	258 (33.5)	
40–64	4706 (67)	2346 (66.8)	2360 (67.2)		1907 (62.5)	480 (62.9)	1427 (62.3)		1957 (63.5)	1477 (63.9)	480 (62.3)	
65–74	393 (5.6)	192 (5.47)	201 (5.72)		97 (3.2)	26 (3.4)	71 (3.1)		113 (3.7)	88 (3.8)	25 (3.3)	
≥75	93 (1.32)	42 (1.2)	51 (1.45)		34 (1.1)	7 (0.9)	27 (1.2)		22 (0.7)	15 (0.7)	7 (0.9)	
Country of origin, n (%)				0.007				0.608				0.621
Spain	4354 (62.0)	2121 (60.4)	2233 (63.6)		1838 (60.2)	453 (59.4)	1385 (60.5)		1794 (58.3)	1339 (58.0)	455 (59.1)	
Outside Spain	2669 (38.0)	1390 (39.6)	1279 (36.4)		1214 (39.8)	310 (40.6)	904 (39.5)		1285 (41.7)	970 (42.0)	315 (40.9)	
Socioeconomic deprivation, n (%)				0.001				0.978				0.032
Least deprived	3361 (47.9)	1754 (49.9)	1607 (45.8)		1443 (47.3)	361 (47.3)	1082 (47.3)		1559 (50.6)	1196 (51.8)	363 (47.1)	
Mildly deprived	1372 (19.5)	659 (18.8)	713 (20.3)		597 (19.6)	137 (18.0)	460 (20.1)		559 (18.2)	421 (18.2)	138 (17.9)	
Moderately/severely deprived	2123 (30.2)	1021 (29.1)	1102 (31.4)		933 (30.6)	237 (31.1)	696 (30.4)		884 (28.7)	643 (27.8)	241 (31.3)	
Missing	168 (2.4)	78 (2.2)	90 (2.6)		79 (2.6)	28 (3.7)	51 (2.2)		78 (2.5)	50 (2.2)	28 (3.6)	
HIV acquisition risk group, n (%)				0.058				0.938				0.266
PWID	853 (12.1)	442 (12.6)	411 (11.7)		291 (9.5)	71 (9.3)	220 (9.6)		335 (10.9)	264 (11.4)	71 (9.2)	
MSM	3631 (51.7)	1835 (52.3)	1796 (51.1)		1663 (54.5)	408 (53.5)	1255 (54.8)		1663 (54.0)	1255 (54.3)	408 (53.0)	
Male heterosexual	978 (13.9)	469 (13.4)	509 (14.5)		427 (14.0)	111 (14.6)	316 (13.8)		401 (13.0)	290 (12.6)	111 (14.4)	
Female hetero/homo/bisexual	1032 (14.7)	526 (15.0)	506 (14.4)		448 (14.7)	111 (14.6)	337 (14.7)		451 (14.6)	336 (14.6)	115 (14.9)	
Other	397 (5.7)	175 (5.0)	222 (6.3)		171 (5.6)	46 (6.0)	125 (5.5)		175 (5.7)	126 (5.5)	49 (6.4)	
Missing	133 (1.9)	65 (1.9)	68 (1.9)		52 (1.7)	16 (2.1)	36 (1.6)		55 (1.8)	39 (1.7)	16 (2.1)	
Years since HIV diagnosis, median (IQR)	11.7 (6.3–18.1)	11.6 (6.6–18.1)	11.8 (6.0–18.1)	0.877	11.1 (5.8–16.9)	11.7 (7.4–17.2)	10.8 (5.0–16.8)	<0.001	11.0 (6.3–17.0)	10.7 (6.0–16.8)	11.7 (7.3–17.1)	0.001
CD4 count (cells/mm³) category				0.057				0.869				0.983
<350	781 (11.1)	424 (12.1)	357 (10.2)		303 (9.9)	79 (10.4)	224 (9.8)		335 (10.9)	254 (11.0)	81 (10.5)	
350–499	981 (14.0)	482 (13.7)	499 (14.2)		431 (14.1)	105 (13.8)	326 (14.2)		428 (13.9)	320 (13.9)	108 (14.0)	
≥500	5262 (74.9)	2606 (74.2)	2656 (75.6)		2318 (76.0)	579 (75.9)	1739 (76.0)		2317 (75.2)	1736 (75.2)	581 (75.5)	
CD4 count (cells/mm³), median (IQR)	695.5 (499.0–926.0)	680.0 (490.0–904.0)	711.0 (506.0–950.0)	<0.001	707.0 (509.8–937.0)	690.0 (508.0–918.5)	712.0 (510.0–944.0)	0.103	686.0 (500.0–910.0)	684.5 (500.0–906.0)	688.5 (505.3–917.5)	0.681
CD4/CD8 ratio, median (IQR)	0.9 (0.6–1.2)	0.9 (0.6–1.2)	0.9 (0.6–1.2)	0.323	0.9 (0.6–1.3)	0.9 (0.7–1.3)	0.9 (0.6–1.2)	0.030	0.9 (0.6–1.3)	0.9 (0.6–1.2)	0.9 (0.7–1.3)	0.011
Plasma HIV-RNA, n (%)				0.581				0.840				1.000

Continued

Table 1. *Continued*

Characteristic	TAF/FTC versus ABC/3TC				TDF/FTC versus ABC/3TC				TAF/FTC versus TDF/FTC			
	Total (n=7024)	TAF/FTC (n=3512)	ABC/3TC (n=3512)	P value	Total (n=3052)	TDF/FTC (=763)	ABC/3TC (n=2289)	P value	Total (n=3080)	TAF/FTC (n=2310)	TDF/FTC (n=770)	P value
Detectable[b]	511 (7.3)	262 (7.5)	249 (7.1)		219 (7.2)	53 (7.0)	166 (7.3)		220 (7.1)	165 (7.1)	55 (7.1)	
Undetectable[b]	6513 (92.7)	3250 (92.5)	3263 (92.9)		2833 (92.8)	710 (93.1)	2123 (92.8)		2860 (92.9)	2145 (92.9)	715 (92.9)	
Number of comorbidities, n (%)				0.715				0.983				0.978
0	2041 (29.1)	1048 (29.8)	993 (28.3)		1150 (37.7)	291 (38.1)	859 (37.5)		1218 (39.6)	920 (39.8)	298 (38.7)	
1	1651 (23.5)	818 (23.3)	833 (23.7)		792 (26.0)	193 (25.3)	599 (26.2)		754 (24.5)	561 (24.3)	193 (25.1)	
2	1244 (17.7)	613 (17.5)	631 (18.0)		507 (16.6)	126 (16.5)	381 (16.6)		507 (16.5)	381 (16.5)	126 (16.4)	
3	773 (11.0)	383 (10.9)	390 (11.1)		253 (8.3)	66 (8.7)	187 (8.2)		264 (8.6)	198 (8.6)	66 (8.6)	
≥4	1315 (18.7)	650 (18.5)	665 (18.9)		350 (11.5)	87 (11.4)	263 (11.5)		337 (10.9)	250 (10.8)	87 (11.3)	
Type of comorbidities, n (%)												
Respiratory disease	1596 (22.7)	811 (23.1)	785 (22.4)	0.477	554 (18.2)	149 (19.5)	405 (17.7)	0.278	539 (17.5)	390 (16.9)	149 (19.4)	0.132
Cardiovascular disease	1220 (17.4)	612 (17.4)	608 (17.3)	0.925	378 (12.4)	93 (12.2)	285 (12.5)	0.899	360 (11.7)	267 (11.6)	93 (12.1)	0.746
Autoimmune disease	840 (12.0)	393 (11.2)	447 (12.7)	0.051	295 (9.7)	72 (9.4)	223 (9.7)	0.860	311 (10.1)	239 (10.4)	72 (9.4)	0.468
Chronic kidney disease	374 (5.3)	136 (3.9)	238 (6.8)	<0.001	116 (3.8)	9 (1.2)	107 (4.7)	<0.001	70 (2.3)	61 (2.6)	9 (1.2)	0.026
Chronic liver disease	1393 (19.8)	722 (20.6)	671 (19.1)	0.135	467 (15.3)	127 (16.6)	340 (14.9)	0.258	506 (16.4)	379 (16.4)	127 (16.5)	1.000
Neuropsychiatric	2128 (30.3)	1077 (30.7)	1051 (29.9)	0.516	746 (24.4)	207 (27.1)	539 (23.6)	0.052	771 (25.0)	564 (24.4)	207 (26.9)	0.187
Diabetes	464 (6.6)	210 (6.0)	254 (7.2)	0.039	140 (4.6)	37 (4.9)	103 (4.5)	0.764	126 (4.1)	89 (3.9)	37 (4.8)	0.294
Metabolic disease	1839 (26.2)	878 (25.0)	961 (27.4)	0.026	598 (19.6)	134 (17.6)	464 (20.3)	0.114	558 (18.1)	424 (18.4)	134 (17.4)	0.589
Cancer	789 (11.2)	381 (10.9)	408 (11.6)	0.326	262 (8.6)	67 (8.8)	195 (8.5)	0.881	228 (7.4)	161 (7.0)	67 (8.7)	0.131
Hypertension	1630 (23.2)	790 (22.5)	840 (23.9)	0.166	526 (17.2)	120 (15.7)	406 (17.7)	0.223	504 (16.4)	384 (16.6)	120 (15.6)	0.536
Obesity	699 (10.0)	342 (9.7)	357 (10.2)	0.577	234 (7.7)	60 (7.9)	174 (7.6)	0.875	230 (7.5)	170 (7.4)	60 (7.8)	0.752
Years on ART, median (IQR)	9.9 (5.4–15.3)	9.8 (5.7–14.9)	10.1 (5.3–15.5)	0.213					9.5 (5.6–13.7)	9.3 (5.4–13.6)	10.4 (6.1–14.1)	0.003

Abbreviations: IQR, interquartile range; PWID, people who inject drugs; MSM, men who have sex with men; ART, antiretroviral therapy; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate; FTC, emtricitabine; ABC/3TC, abacavir/lamivudine.

a: Propensity score-matching ratio is 1:1 for TAF/FTC versus ABC/3TC, 1:3 for TDF/FTC versus ABC/3TC, and 1:3 for TDF/FTC versus TAF/FTC.

b: HIV-RNA viral load (detectable: ≥50 copies per mL, undetectable: <50 copies per mL).

Table 2. SARS-Cov-2 diagnosis and clinical severity in propensity score-matched groups of PLWH based on antiretroviral therapy (ART) and results from Cox regression models that evaluated the effect of ART regimens on SARS-CoV-2 diagnosis and associated hospitalization

	Total[a]	TAF/FTC[a]	ABC/3TC[a,b]	P value[c]	uOR (95% CI)	aOR (95% CI)
TAF/FTC versus ABC/3TC						
SARS-CoV-2 diagnosis						
Positive	848 (12.1)	408 (11.6)	440 (12.5)	0.256	0.92 (0.80–1.05)	0.90 (0.78–1.04)
Negative	6176 (87.9)	3104 (88.4)	3072 (87.5)			
Clinical severity				0.838		
Asymptomatic	380 (44.8)	186 (45.6)	194 (44.1)			
Symptomatic mild community management	370 (43.6)	172 (42.3)	198 (45.0)			
Hospitalization[d]	98 (11.6)	50 (12.3)	48 (10.9)		1.04 (0.70–1.55)	0.93 (0.60 –1.43)
ICU admission	4 (0.5)	2 (0.5)	2 (0.5)			
Death[e]	17 (2.0)	9 (2.2)	8 (1.8)			

	Total	TDF/FTC	ABC/3TC[b]	P value[c]	uOR (95% CI)	aOR (95% CI)
TDF/FTC versus ABC/3TC						
SARS-CoV-2 diagnosis						
Positive	369 (12.0)	74 (9.6)	295 (12.8)	0.021	**0.74 (0.57–0.95)**	0.79 (0.60–1.04)
Negative	2704 (88.0)	697 (90.4)	2007 (87.2)			
Clinical severity				0.352		
Asymptomatic	172 (46.6)	40 (54.1)	132 (44.8)			
Symptomatic mild community management	170 (46.1)	31 (41.9)	139 (47.1)			
Hospitalization[d]	27 (7.3)	3 (4.1)	24 (8.1)		0.37 (0.11–1.24)	0.51 (0.15–1.70)
ICU admission	2 (0.5)	0 (0)	2 (0.7)			
Death[e]	3 (0.8)	0 (0)	3 (1.0)			

	Total	TAF/FTC[b]	TDF/FTC	P value[c]	uOR (95% CI)	aOR (95% CI)
TAF/FTC versus TDF/FTC						
SARS-CoV-2 diagnosis						
Positive	377 (12.2)	303 (13.1)	74 (9.6)	0.012	**0.72 (0.56–0.93)**	0.79 (0.60–1.04)
Negative	2703 (87.8)	2007 (86.9)	696 (90.4)			
Clinical severity				0.274		
Asymptomatic	190 (50.4)	150 (49.5)	40 (54.1)			
Symptomatic mild community management	150 (39.8)	119 (39.3)	31 (41.9)			
Hospitalization[d]	37 (9.8)	34 (11.2)	3 (4.1)		**0.26 (0.08–0.86)**	0.33 (0.10–1.07)
ICU admission	3 (0.8)	3 (1.0)	0 (0)			
Death[e]	6 (1.6)	6 (2.0)	0 (0)			

Adjusted model: Adjusted for country of origin, socioeconomic status, CD4 count (continuous variable), time in years on ART, CD4/CD8 ratio, diabetes, chronic kidney disease, chronic liver disease, and metabolic disease.
Abbreviations: TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate; FTC, emtricitabine; ABC/3TC, abacavir/lamivudine; ICU, intensive care unit, SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; OR, odds ratio; uOR, unadjusted odds ratio; aOR, adjusted odds ratio; CI, confidence interval.
[a]Data in this category is presented as n (%).
[b]Reference group for odds ratios.
[c]Numbers in bold indicate significant differences (P < 0.05).
[d]Including ICU admissions.
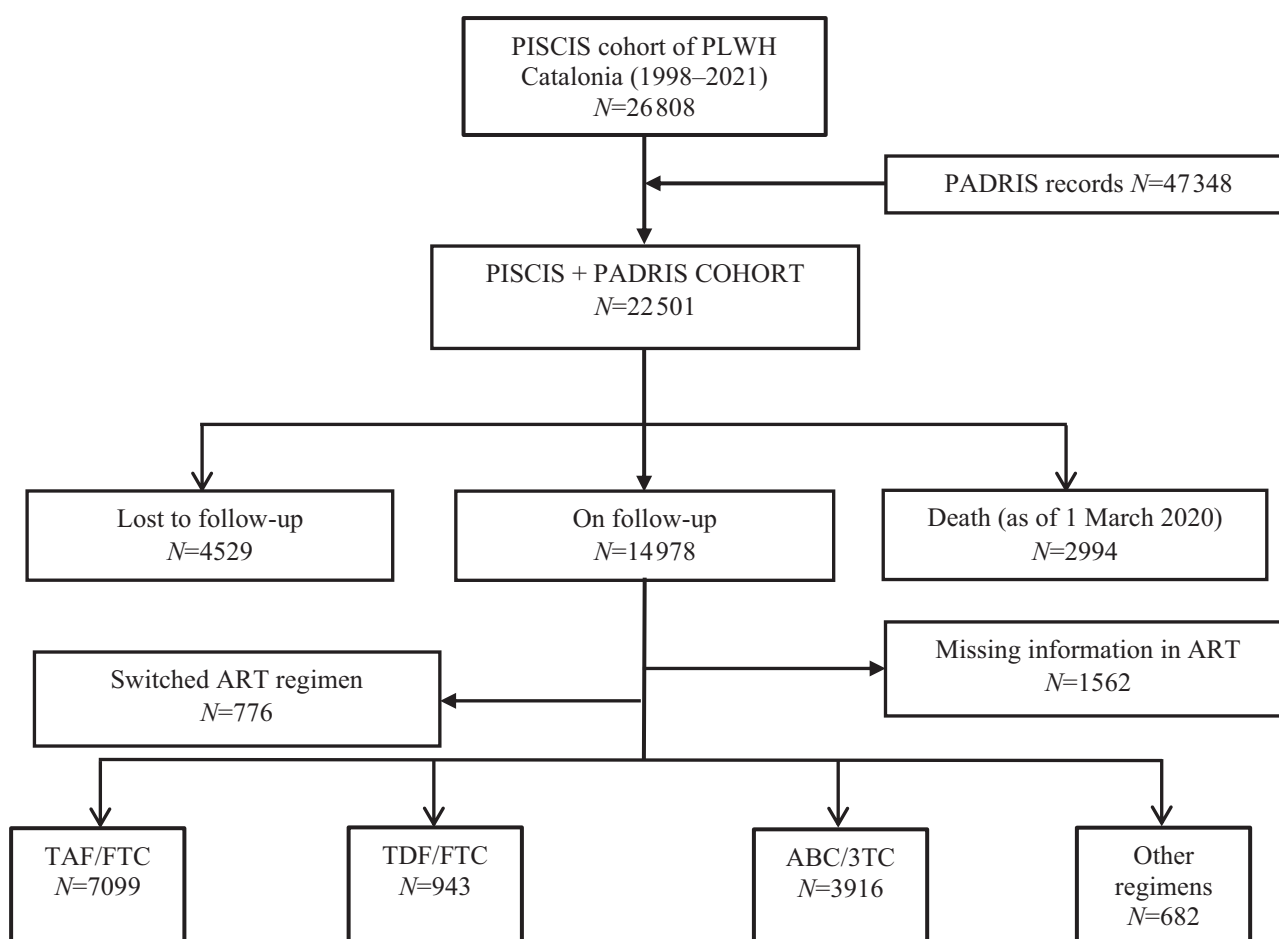[e]Also included in hospitalized patients.

Figure 1. Flow diagram of people living with HIV in the PISCIS cohort in Catalonia showing the reception ART regimens and inclusion into the analysis. Abbreviations: PADRIS, Analytical Data for Research and Innovation in Health Project of Catalonia; ART, antiretroviral therapy; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate; FTC, emtricitabine; ABC/3TC, abacavir/lamivudine.

compared using the Kruskal Wallis test. We performed four rounds of propensity-score matching for TAF/FTC versus ABC/3TC and a single round for TDF/FTC versus ABC/3TC and TAF/FTC versus TDF/FTC using nearest-neighbour algorithms with a calliper width of 0.1 of the pooled standard deviations to ensure that key baseline characteristics of the groups were adequately balanced. We matched patients by sex, age, plasma HIV-RNA [detectable and undetectable (HIV RNA <50 copies/ mL)], and number of comorbidities (none, one, two, three, four or more). We did three separate propensity score matches in a ratio 1:1 for TAF/FTC versus ABC/3TC, and 1:3 for TDF/FTC versus ABC/3TC, and TDF/FTC versus TAF/FTC. To evaluate the effect of ART regimens on SARS-CoV-2 diagnosis and severe outcomes, we used Cox regression models and provided adjusted odds ratios (aOR) and unadjusted odds ratios (uOR) along with their 95% confidence intervals (95% CI) to remove residual confounding.[18] We adjusted for the factors that were significantly different after propensity score matching. We adjusted for country of origin, socioeconomic status, CD4 count (continuous variable), time in years on ART, CD4/CD8 ratio, diabetes, chronic kidney disease, and metabolic disease. In multivariable analysis, we removed the time since HIV diagnosis due to collinearity with the time in years on ART (Table S2). Records of missing values for adjustment covariates were excluded in adjusted analyses, as they were few and not expected to affect estimates significantly. A two-sided *P* value <0.05 was considered

statistically significant. We performed all statistical analyses using R Statistical Software version 4.0.2.

Ethics

The PISCIS cohort study was approved by the Ethics Committee of the Germans Trias i Pujol University Hospital, Badalona, Spain (EO-11–108). Data collection was also approved by the ethics committees of participating hospitals. Patient-level information obtained from PADRIS was anonymized and de-identified before the analysis. This study follows the Strengthening the Reporting of Observational studies in Epidemiology (STROBE) guidelines.[19] The planning, conduct, and reporting of the study was in line with the Declaration of Helsinki, as revised in 2013.

Access to data

The study protocol is available from Dr Juliana Reyes-Urueña (e-mail: jmreyes@iconcologia.net). Statistical code for the analysis can be requested from Yesika Díaz, Sergio Moreno, and Jordi Aceiton (ydiazr@ iconcologia.net, smorenof@iconcologia.net, jaceiton@igtp.cat). The data for this study is available at the Centre for Epidemiological Studies of Sexually Transmitted Diseases and HIV/AIDS in Catalonia (CEEISCAT),

the coordinating centre of the PISCIS cohort and from each of the collaborating hospitals upon request via https://pisciscohort.org/contacte/.

Results

Out of 14 978 PLWH (median age: 46.4 years, male sex: 82.1%) on follow-up in our cohort, 1562 had missing information on ART, 776 had switched their ART regimen at least once during the study period, and 11 958 were included in the present analysis. Of them, 7099 were treated with TAF/FTC, 943 with TDF/FTC, 3916 with ABC/3TC, and 682 were receiving other regimens (Figure 1). PLWH receiving TDF/FTC were younger (median age 44.6 years) compared with those receiving TAF/FTC (45.6 years) or ABC/3TC (48.2 years) ($P < 0.001$). Individuals receiving TDF/FTC had a lower number of comorbidities than those receiving TAF/FTC or ABC/3TC ($P < 0.001$) and significantly different socioeconomic deprivation (Table S3).

Of the patients included in the analysis, 1445 (12.1%) individuals had tested positive for SARS-CoV-2 as of 18 July 2021, of whom 670 (46.4%) were asymptomatic, 630 (43.6%) were symptomatic with mild disease requiring community management, and 145 (10.0%) were hospitalized. In the latter, 7 (0.5%) were admitted to the ICU, and 20 (1.4%) died.

Out of 7099 PLWH receiving TAF/FTC, 3512 were matched 1:1 to an equal number of ABC/3TC recipients ($n = 3512$). Out of 943 TDF/FTC recipients, 763 were matched 1:3 to 2289 ABC/3TC recipients; and 770 TDF/FTC recipients were matched 1:3 to 2310 TAF/FTC recipients. No key covariates exhibited major imbalances (standard mean difference <0.1) (Figure S1). The baseline characteristics of the propensity score-matched groups are presented in Table 1.

TAF/FTC was not associated with a reduction in SARS-CoV-2 diagnosis (aOR 0.90; 95% CI, 0.78–1.04) or associated hospitalization (aOR 0.93; 95% CI, 0.60–1.43) compared with ABC/3TC in adjusted analysis. TDF/FTC compared with ABC/3TC was not associated with a reduction in SARS-CoV-2 diagnosis (aOR 0.79; 95% CI, 0.60–1.04) or hospitalization (aOR 0.51; 95% CI, 0.15–1.70). We finally compared the association between TDF/FTC and TAF/FTC in adjusted analysis. TDF/FTC was not associated with a reduction in SARS-CoV-2 diagnosis (aOR 0.79; 95% CI, 0.60–1.04) or associated hospital admissions (aOR 0.33; 95% CI, 0.10–1.07) compared with TAF/FTC (Table 2).

Discussion

We assessed the association between current TAF/FTC and TDF/FTC treatment and SARS-CoV-2 diagnosis and COVID-19 outcomes in a prospective multicentre cohort of PLWH using a propensity score-matched approach. TAF/FTC and TDF/FTC were not significantly associated with a reduction in SARS-CoV-2 diagnosis and poorer COVID-19-related outcomes including hospitalizations, ICU admissions, and death among PLWH. We found no significant association either when TAF/FTC or TDF/FTC were compared with ABC/3TC or against each other.

Importantly, we found significantly lower rates of SARS-CoV-2 infection and associated hospitalizations in unadjusted analyses among those receiving TDF/FTC. Compared with patients receiving TAF/FTC and ABC/3TC, those receiving TDF/FTC were significantly younger, and had a lower number and prevalence of comorbidities. When the analysis was adjusted for these variables, the potential protective effect disappeared. This finding supports that the differences in baseline factors intrinsically associated with lower SARS-CoV-2 infection rates and more benign SARS-CoV-2 infection outcomes constitute a channelling bias that could have influenced many previous analyses that indicated that TDF could have a protective role against SARS-CoV-2 infection, but lacked an adequate adjustment of these variables that are directly correlated with the primary outcome.[7,11]

Analyses performed in PrEP studies with TDF/FTC, such as PREVENIR-ANRS and SAPRIS-Sero[14] sub-study from France, where these biases do not exist, found no reduced risk in SARS-CoV-2 infection among TDF/FTC PrEP users.

Similarly, TDF/FTC in our study reduced COVID-19-associated hospitalizations in unadjusted analysis but not in adjusted analysis, which is contrary to previous large studies.[7,11] As previously discussed, the lack of adjustment for baseline patient characteristics probably influenced the results of the study from del Amo et al.[7] by confounding and channelling bias. In the subsequent large study from the Western Cape, South Africa,[11] there was an adjustment for kidney disease, viral suppression, and antiretroviral treatment. Zidovudine use (the alternative to TDF), however, was preferentially prescribed to individuals with prior virologic failure as per the WHO guidelines[20] and can be associated with higher rates of tuberculosis, both of which were not adjusted for in that study.

The rationale behind the possible protective benefits of tenofovir was a result of the potential activity that the nucleotide analogue showed against SARS-CoV-2 in pre-clinical studies and animal models (ferrets)[4,21] and the more potent immunomodulatory effects of TDF[22] including the decreased production of interleukin-8 and -10,[23] and the higher penetration into mucosal tissues.[24] However, in a recent analysis, none of these drugs (TAF, TDF or FTC) showed any significant in vitro anti-SARS-CoV-2 effect at concentrations up to 100-fold higher than the clinically relevant levels.[6] These results are corroborated by the lack of interaction between the respective NRTI-triphosphates and SARS-CoV-2 RdRp observed both in biochemical assays and in structural modelling analyses.[6]

Our finding that TAF does not prevent SARS-CoV-2 diagnosis or severe disease is in-line with a report from Ayerdi et al.[13] who actually found a higher SARS-CoV-2 seroprevalence among HIV-negative PrEP users receiving TAF or TDF versus those without PrEP. That study also demonstrated no differences in terms of clinical manifestations between people receiving tenofovir (TAF or TDF) and those not on tenofovir.[13]

The study by del Amo et al.[7] found a lower risk for SARS-CoV-2 diagnosis among persons receiving TDF/FTC compared with those on other regimens. SARS-CoV-2 diagnosis in Spain has also been disproportionately affected by sociodemographic factors including country of origin and socioeconomic status in both the general population[25] and among PLWH.[15] The del Amo et al.[7] study did not adjust for these sociodemographic factors.

In recent findings from a clinical trial involving 30 participants on TDF/FTC and a control group of 30 participants on standard of care therapy, TDF/FTC did not expedite the natural clearance of nasopharyngeal SARS-CoV-2 viral load at day 4 (primary endpoint), there were no differences in the time to symptom recovery nor in the hospitalization rates.[26] However, there was a

significantly greater increase in the Ct RT-PCR on the seventh day, with an effect corresponding to approximately 0.8 $\log_{10}$ decrease of SARS-CoV-2 RNA, a reduction of unknown microbiological or clinical relevance.

Our study is limited by its epidemiological nature, depriving us of having information on treatment adherence and exposure to SARS-CoV-2, which are both relevant given the objectives of our study. Secondly, assessing the association between ART and SARS-CoV-2 infection is challenging in a scenario where not everyone is tested equally for SARS-CoV-2. For example, testing could be more frequent among patients with higher risks of poor COVID-19 outcomes. The identification of a higher incidence of SARS-CoV-2 infection and associated hospitalizations in un-adjusted analyses that disappears in the propensity score matching and adjusted Cox regression models suggests that indeed subjects treated with TDF have intrinsic characteristics that lend them a lower risk for SARS-CoV-2 infection or poorer COVID-19 outcomes. Our analyses demonstrate that failure to evaluate potential sociodemographic and clinical confounding factors can bias observational study results and lead to erroneous inferences.

In conclusion, the use of TAF/FTC or TDF/FTC among PLWH was not associated with a reduction in SARS-CoV-2 diagnosis or poorer COVID-19 outcomes including hospital and ICU admissions or death. Until well-designed randomized clinical trials reveal new robust evidence, existing preventive measures and treatment approaches for PLWH against SARS-CoV-2 infection should be maintained, independent of tenofovir exposure.

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Supplementary data

Figure S1 and Tables S1 to S4 are available as Supplementary data at *JAC* Online.

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