Tenofovir disoproxil fumarate/emtricitabine and severity of coronavirus disease 2019 in people with HIV infection

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Background: Effective, safe, and affordable antivirals are needed for coronavirus disease 2019 (COVID-19). Several lines of research suggest that tenofovir may be effective against COVID-19, but no large-scale human studies with appropriate adjustment for comorbidities have been conducted.

Methods: We studied HIV-positive individuals on antiretroviral therapy (ART) in 2020 at 69 HIV clinics in Spain. We collected data on sociodemographics, ART, CD4$^+$ cell count, HIV-RNA viral-load, comorbidities and the following outcomes: laboratory-confirmed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, COVID-19 hospitalization, intensive care unit (ICU) admission and death. We compared the 48-week risks for individuals receiving tenofovir disoproxil fumarate (TDF)/emtricitabine (FTC), tenofovir alafenamide (TAF)/FTC, abacavir (ABC)/lamivudine (3TC), and other regimes. All estimates were adjusted for clinical and sociodemographic characteristics via inverse probability weighting.

Results: Of 51 558 eligible individuals, 39.6% were on TAF/FTC, 11.9% on TDF/FTC, 26.6% on ABC/3TC, 21.8% on other regimes. There were 2402 documented SARS-CoV-2 infections (425 hospitalizations, 45 ICU admissions, 37 deaths). Compared with TAF/FTC, the estimated risk ratios (RR) (95% confidence interval) of hospitalization were 0.66 (0.43, 0.91) for TDF/FTC and 1.29 (1.02, 1.58) for ABC/3TC, the RRs of ICU admission were 0.28 (0.11, 0.90) for TDF/FTC and 1.39 (0.70, 2.80) for ABC/3TC, and the RRs of death were 0.37 (0.23, 1.90) for TDF/FTC and 2.02 (0.88−6.12) for ABC/3TC. The corresponding RRs of hospitalization for TDF/FTC were 0.49 (0.24, 0.81) in individuals ≥50 years and 1.15 (0.59, 1.93) in younger individuals.

Discussion: Compared with other antiretrovirals, TDF/FTC lowers COVID-19 severity among HIV-positive individuals with virological control. This protective effect may be restricted to individuals aged 50 years and older.

Introduction

Much research has focused on the repurposing of antivirals for the treatment and prevention of severe COVID-19. Remdesivir, originally developed against the Ebola virus, and molnupiravir, originally developed against the influenza virus, are now used to reduce the risk of hospitalization in high-risk individuals with recently diagnosed coronavirus disease 2019 (COVID-19) [1−5]. More research is needed to determine whether tenofovir, an affordable oral drug with a proven safety record, also prevents severe COVID-19.

Among HIV-positive individuals, two observational studies found lower risk of COVID-19 hospitalization [6] and COVID-19 mortality [6,7] among users of tenofovir disoproxil fumarate/emtricitabine (TDF/FTC) than among users of other antiretroviral regimens. Another observational study found a lower risk of severe COVID-19 in patients with chronic hepatitis B virus (HBV) infection treated with TDF/FTC than among those treated with entecavir [8]. More recently, a large study in male U.S. veterans with HIV has reported that the risk of COVID-19-related hospitalization for TDF/FTC was less than half the risk for other antiretrovirals [9]). Careful adjustment for clinical characteristics, including those associated with risk of severe COVID-19 (e.g. renal disease), had little impact on the association between TDF/FTC and lower risk of severe COVID-19. However, this study included only men with an average age of 59 years.

These findings suggest that TDF/FTC might be used as preexposure prophylaxis or early treatment of COVID-19 [10,11]. This would be especially important for immunosuppressed patients for whom vaccines have suboptimal effectiveness and for individuals for which safety concerns arise with other drugs.

Here, we report the findings from a nationwide cohort study of TDF/FTC and COVID-19 outcomes among men and women of all ages with HIV and on antiretroviral therapy.

Methods

Study population

Individuals with HIV in Spain receive care at specialized hospital outpatient clinics. The CoVIHd Collaboration (COVID-19 in HIV-positive individuals in Spain) includes HIV-positive individuals who were receiving antiretroviral therapy at the HIV clinics of 87 Spanish hospitals between January 1 and December 31, 2020. All clinics collected information on individuals with a history of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, but this analysis is restricted to the 69 clinics that collected information on HIV-positive individuals with and without a history of SARS-CoV-2 infection. These 69 clinics serve approximately 44% of all persons on antiretroviral therapy with virological suppression in Spain [12].

Hospitals transmitted de-identified data to the coordinating center at the Institute of Health Carlos III in Madrid via a secure web-based application specifically designed for this purpose. For each individual, data included sociodemographic characteristics, dates and composition of all antiretroviral therapy regimens received during the study period, latest $CD4^+$ cell count and HIV RNA measurements before a COVID-19 diagnosis, comorbidities (from medical records, see Appendix 2, Supplemental Digital Content, http://links.lww.com/QAD/C628), and date of laboratory-confirmed documented diagnosis of SARS-CoV-2 infection defined as positive results from a polymerase chain reaction (PCR) test (or, in a minority of cases, a SARS-CoV-2 antigen test or antibody test), following the Ministry of Health protocols [13]. The ascertainment of hospitalizations due to COVID-19, intensive care unit (ICU) admissions due to COVID-19, and deaths from COVID-19 was complete, but no protocol was in place to systematically screen for asymptomatic infections and mild cases of COVID-19.

Eligibility criteria and follow-up

We included HIV-positive individuals aged 18 years or older who on February 1, 2020 had not received a diagnosis of SARS-CoV-2 infection and were on antiretroviral therapy, and who had virologically suppression (HIV RNA <50 copies/ml) in 2020. Virological suppression is an indicator of adequate adherence to antiretroviral therapy. For each individual, follow-up started on February 1 and ended on December 31, 2020. The goal was to emulate a (hypothetical) target trial in which individuals are randomly assigned to a particular

nucleos(t)ide reverse transcriptase inhibitor (NRTI) combination before the start of SARS-CoV-2 transmission in their communities.

Antiretroviral therapy regimes

We classified antiretroviral therapy regimes according to their NRTI combination into four categories: tenofovir disoproxil fumarate (TDF)/emtricitabine (FTC), tenofovir alafenamide (TAF)/FTC, abacavir (ABC)/lamivudine (3TC), or other drug regimens excluding TDF, TAF and ABC. Most of the other drugs categories were dual therapies including only one NRTI (3TC) (Appendix Table 1, Supplemental Digital Content, http://links.lww. com/QAD/C628). We also studied regimens with three drugs according to the third drug class used along with the NRTI combination: integrase inhibitor, protease inhibitor, or nonnucleoside reverse transcriptase inhibitor (NNRTI).

Outcomes

The outcomes of interest were any documented laboratory-confirmed diagnosis of SARS-CoV-2 infection and progressively more severe subsets of COVID-19: hospitalization due to COVID-19, ICU admission due to COVID-19, and death due to COVID-19. In supplemental analyses, we also considered documented asymptomatic SARS-CoV-2 infections and mild COVID-19 that did not require hospitalization.

Statistical analysis

We calculated the 48-week risk (cumulative incidence) and 95% confidence interval (CI) for each outcome by NRTI combination. We estimated the risks using a pooled logistic model with indicators for NRTI combination (three indicators, with TAF/FTC as the reference group), week of follow-up (linear and quadratic terms), and product terms between NRTI combination indicators and week of follow-up. To adjust for baseline prognostic factors, we used inverse probability (IP) weighting. To estimate the denominator of the weights we fit a multinomial logistic model for the four NRTI combinations with covariates: age (in years, linear and quadratic terms), sex (male, female), transmission category (heterosexual, homo/bisexual, injecting drug use, other), country of origin (Spain, other), $CD4^+$ cell count (<350, $350-500$, >500 cells/μl), and indicators for hypertension, diabetes, chronic renal disease, cardiovascular disease, and treatment with immunosuppressants or corticosteroids. We compared the risks via risk differences and risk ratios and used a nonparametric percentile-based bootstrap with 500 samples to obtain 95% CIs.

To compare the risks by the non-NRTI drug in the antiretroviral regime, we fit a similar model with indicators for NNRTI, protease inhibitor, and integrase inhibitor. We conducted subgroup analyses by age group (<50, ≥50 years) and sex for documented SARS-CoV-2 infections, and COVID-19 hospitalization.

We also conducted several sensitivity analyses. To evaluate the potential impact of treatment changes regimes, we conducted an analysis in which individuals were censored if/when they switch from their baseline antiretroviral regime to another regime. To evaluate the potential impact of the choice of inverse probability weighting as the method to adjust for confounding, we repeated the analyses with adjustment via standardization and also estimated adjusted hazard ratios via a Cox regression model. To assess the impact of measured confounding due to comorbidities and other factors, we repeated the analysis with no adjustment at all. All analyses were conducted with Stata, version 15.0 (StatCorp, College Station, Texas, USA).

This study was approved by the institutional review board at University Hospital Ramón y Cajal, Madrid, Spain.

Results

Of 51 558 eligible individuals (Fig. 1), 39.6% were receiving TAF/FTC, 11.9% TDF/FTC, 26.6% ABC/3TC, and 21.8% other regimes (see Appendix Table 1, Supplemental Digital Content, http://links.lww.com/QAD/C628 for a description of regimes in each category). The baseline characteristics of individuals in each of the four groups defined by NRTI combination are shown in Table 1. Individuals receiving TDF/FTC and TAF/FTC had similar age, sex, and $CD4^+$ cell counts, and were slightly younger than those receiving ABC/3TC or other regimes. The proportion of injecting drug users was slightly lower in persons on TAF/FTC than in the other groups. Individuals in the TDF/FTC group had a lower prevalence of hypertension, diabetes, and chronic renal disease than individuals in the other groups.

During the 48-week follow-up, there were 2402 documented SARS-CoV-2 infections (425 hospitalizations, 45 ICU admissions, and 37 deaths). Of the 1955 SARS-CoV-2 infections with available information on disease severity, 539 were asymptomatic, 1037 had mild COVID-19, 298 moderate COVID-19 and 81 severe COVID-19. Figure 2 shows the estimated cumulative risks of documented SARS-CoV-2 infection, COVID-19 hospitalization, COVID-19 ICU admission, and COVID-19 death by NRTI combination. Appendix Figure 1, Supplemental Digital Content, http://links. lww.com/QAD/C628 shows the risks of asymptomatic COVID-19 and mild COVID-19.

Table 2 shows the estimated 48-week risks of each outcome by NRTI combination. The estimated risk (95% CI) of documented SARS-CoV-2 infection was 4.3% (4.1, 4.6) for TAF/FTC, 4.5% (3.9, 5.0) for TDF/FTC, and 5.2% (4.8, 5.6) for ABC/3TC. The estimated risks of COVID-19 hospitalization, ICU and death were lowest for TDF/FTC and highest for ABC/3TC (Table
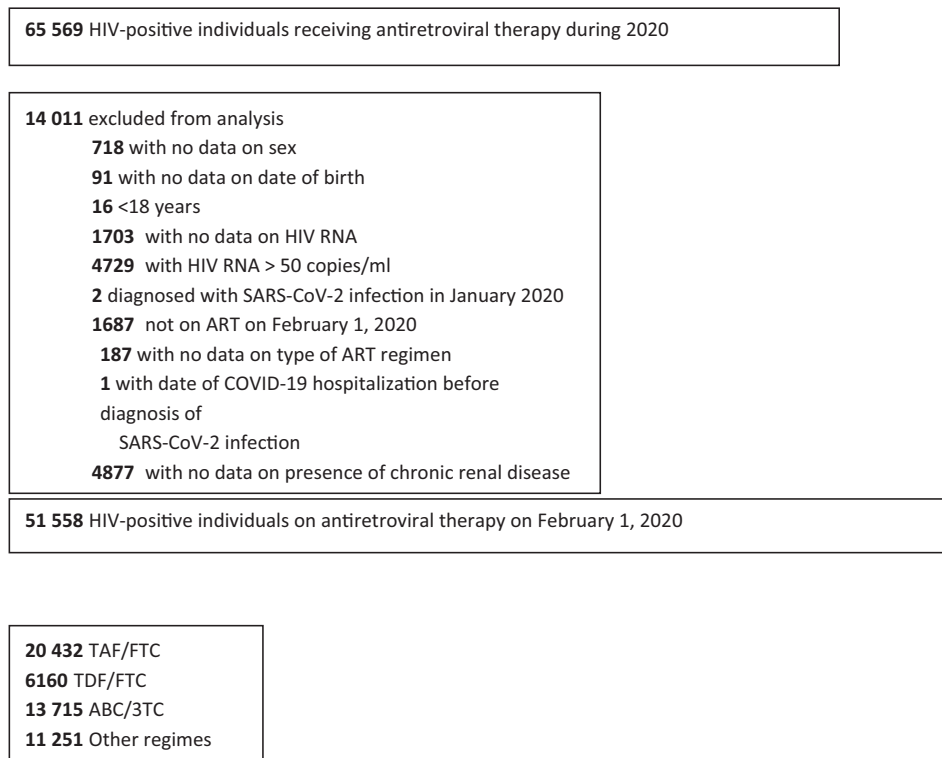
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65 569 HIV-positive individuals receiving antiretroviral therapy during 2020

14 011 excluded from analysis
    718 with no data on sex
    91 with no data on date of birth
    16 <18 years
    1703 with no data on HIV RNA
    4729 with HIV RNA > 50 copies/ml
    2 diagnosed with SARS-CoV-2 infection in January 2020
    1687 not on ART on February 1, 2020
    187 with no data on type of ART regimen
    1 with date of COVID-19 hospitalization before
    diagnosis of
        SARS-CoV-2 infection
    4877 with no data on presence of chronic renal disease

51 558 HIV-positive individuals on antiretroviral therapy on February 1, 2020

20 432 TAF/FTC
6160 TDF/FTC
13 715 ABC/3TC
11 251 Other regimes

Fig. 1. Flowchart of study population among HIV-positive individuals, CoVIHd Collaboration, Spain, February–December 2020.

2). Compared with TAF/FTC, the estimated risk ratio (95% CI) of COVID-19 hospitalization was 0.66 (0.43, 0.91) for TDF/FTC, 1.29 (1.02, 1.58) for ABC/3TC, and 0.81 (0.62, 1.05) for others; the estimated risk ratio (95% CI) of COVID-19 ICU admission was 0.28 (0.11, 0.90) for TDF/FTC, 1.39 (0.70, 2.80) for ABC/3TC, and 0.76 (0.23, 1.77) for others; and the estimated risk ratio (95% CI) of COVID-19 death was 0.37 (0.23, 1.90) for TDF/FTC, 2.02 (0.88−6.12) for ABC/3TC, and 0.99 (0.34, 2.61) for others (Table 2). Compared with TAF/FTC, the estimated risk ratios (95% CI) of asymptomatic SARS-CoV-2 infection and mild COVID-19 were greater than 1 for TDF/FTC and ABC/3TC. (Appendix Table 2, Supplemental Digital Content, http://links.lww.com/QAD/C628).

Compared with TAF/FTC, the 48-week risk difference of hospitalizations per 1000 persons was −2.8 (95% CI −5.2 to −0.8) for TDF/FTC (Table 2). That is, the estimated number needed to treat with TDF/FTC vs. TAF/FTC during the study period would be 357 (192−1250) to prevent one hospitalization. The estimates were similar in sensitivity analyses that censored at treatment switching (Appendix Table 3, Supplemental Digital Content, http://links.lww.com/QAD/C628), that adjusted for confounding via standardization (Appendix Table 4 , Supplemental Digital Content, http://links.lww.com/QAD/C628) or a Cox model (Appendix Table 5, Supplemental Digital Content, http://links.lww.com/QAD/C628), and that

did not adjust for any covariates (Appendix Table 6, Supplemental Digital Content, http://links.lww.com/QAD/C628). The risk of COVID-19 hospitalization was similar across the three classes of third drug (Appendix Table 7, Supplemental Digital Content, http://links.lww.com/QAD/C628).

Compared with TAF/FTC, the estimated risk ratio (95% CI) of COVID-19 hospitalization for TDF/FTC was 0.49 (0.24, 0.81) in individuals aged ≥50 years and 1.15 (0.59, 1.93) in younger individuals (Table 3). The corresponding risk ratio was similar in men and women (Appendix Table 8, Supplemental Digital Content, http://links.lww.com/QAD/C628).

Compared with all NRTI combinations without TDF, the estimated risk ratios (95% CI) of COVID-19 hospitalization, ICU admission and death were 0.64 (0.42−0.89), 0.28 (0.11−0.84) and 0.29 (0.20−1.11), respectively, for TDF/FTC. In individuals aged ≥50 years, these risk ratios were 0.48 (0.24−0.76), 0.24 (0.18−0.88) and 0.22 (0.15−0.97).

Discussion

We studied over 50 000 HIV-positive individuals on antiretroviral therapy with adequate virological control in Spain during 2020, before the start of the SARS-CoV-2

Table 1. Baseline characteristics of 51 558 eligible individuals by NRTI combination in HIV-positive individuals, CoVIHd Collaboration, Spain, February–December 2020.

	TAF/FTC N = 20 432 (39.6%)	TDF/FTC N = 6160 (11.9%)	ABC/3TC N = 13 715 (26.6%)	Other regimes N = 11,251 (21.8%)
Sex [N (%)]				
Men	16 527 (80.9)	4856 (78.8)	10 797 (78.7)	8623 (76.6)
Women	3905 (19.1)	1304 (21.2)	2918 (21.3)	2628 (23.4)
Age, years				
[Median (IQR)]	49 (39–56)	48 (39–55)	51 (41–57)	53 (45–58)
Transmission category [N (%)]				
Heterosexual contact	4652 (22.8)	1463 (23.7)	3218 (23.5)	2726 (24.2)
Homo/bisexual contact	8939 (43.7)	2221 (36.1)	4859 (35.4)	3741 (33.2)
Injecting drug use	3501 (17.1)	1242 (20.2)	2665 (19.4)	2847 (25.3)
Other	503 (2.5)	147 (2.4)	300 (2.2)	328 (2.9)
Unknown	2837 (13.9)	1087 (17.6)	2673 (19.5)	1609 (14.3)
Country of origin [N (%)]				
Spain	12 632 (61.8)	3836 (62.3)	8553 (62.4)	8077 (71.8)
Other	4689 (22.9)	1367 (22.2)	2325 (16.9)	1568 (13.9)
Unknown	3,111 (15.2)	957 (15.5)	2837 (20.7)	1606 (14.3)
CD4$^+$ cell count (cells/μl)				
Median (IQR)	704 (509–933)	700 (511–929)	746 (536–994)	718 (520–948)
<350	2059 (10.1)	619 (10.0)	1179 (8.6)	1014 (9.0)
350–500	2775 (13.6)	834 (13.5)	1735 (12.6)	1504 (13.4)
>500	15 414 (75.4)	4671 (75.8)	10 718 (78.1)	8620 (76.6)
Unknown	184 (0.9)	36 (0.6)	83 (0.6)	113 (1.0)
Hypertension [N (%)]				
No	16 804 (82.2)	5388 (87.5)	10 897 (79.4)	8469 (75.3)
Yes	3091 (15.1)	695 (11.3)	2589 (18.9)	2564 (22.8)
Unknown	537 (2.6)	77 (1.2)	229 (1.7)	218 (1.9)
Diabetes [N (%)]				
No	18 490 (90.5)	5707 (92.6)	12 217 (89.1)	9736 (86.5)
Yes	1486 (7.3)	380 (6.2)	1302 (9.5)	1305 (11.6)
Unknown	456 (2.2)	73 (1.2)	196 (1.4)	210 (1.9)
Chronic renal disease [N (%)]				
No	19 375 (94.8)	5952 (96.6)	12 570 (91.6)	10 028 (89.1)
Yes	1057 (5.2)	208 (3.4)	1145 (8.3)	1223 (10.9)
Cardiovascular disease [N (%)]				
No	16 628 (81.4)	5511 (89.5)	11 759 (85.7)	9568 (85.0)
Yes	1051 (5.1)	302 (4.9)	773 (5.6)	887 (7.9)
Unknown	2753 (13.5)	347 (5.6)	1183 (8.6)	796 (7.1)
Treatment with immunosuppressants or corticosteroids [N (%)				
No	13 631 (66.7)	4313 (70.0)	8768 (63.9)	7805 (69.4)
Yes	174 (0.8)	78 (1.3)	163 (1.2)	142 (1.3)
Unknown	6627 (32.4)	1769 (28.7)	4784 (34.9)	3304 (29.4)

vaccination campaign. The estimated risks of COVID-19 hospitalization and ICU admission were lower among individuals treated with TDF/FTC than among those treated with other antiretrovirals. The potential benefit of TDF/FTC appeared to be restricted to individuals over 50 years of age who have a higher risk of developing severe COVID-19. In this age group, the risk of COVID-19 hospitalization was about 50% lower for TDF/FTC compared with TAF/FTC, the most commonly used NRTI combination. The risk of death from COVID-19 was also lower for antiretroviral regimes based on TDF/FTC, but the estimates were very imprecise. In contrast, individuals on ABC/3TC had a higher risk of severe COVID-19 than those on other NRTI combinations. The estimated risks of documented infection and of mild infection are difficult to interpret because of incomplete ascertainment.

Our estimates are consistent with those from observational studies conducted in Spain [6,14,15], South Africa

[7], and the United States [9]. These studies, which preferentially included COVID-19 cases that were severe enough to be diagnosed, found a lower risk of severe COVID-19 among HIV-positive individuals on TDF/FTC compared with other NRTI combinations. The first study reported in Spain did not collect information on comorbidities, used reported population frequencies of antiretroviral use for noncases (which resulted in a slight overestimation of the proportion of the population on TDF/FTC and an underestimation of the proportion on TAF/FTC), and did not restrict the analyses to persons with virological suppression [6]. The present study improves upon it by including a large population of HIV-positive individuals with adequate antiretroviral control and adjusts for multiple comorbidities. Another study in Spain found a lower SARS-CoV-2 prevalence among TDF/FTC users than in TAF/FTC users [14].

A beneficial effect of TDF for prophylaxis or early treatment of COVID-19 is compatible with the results of
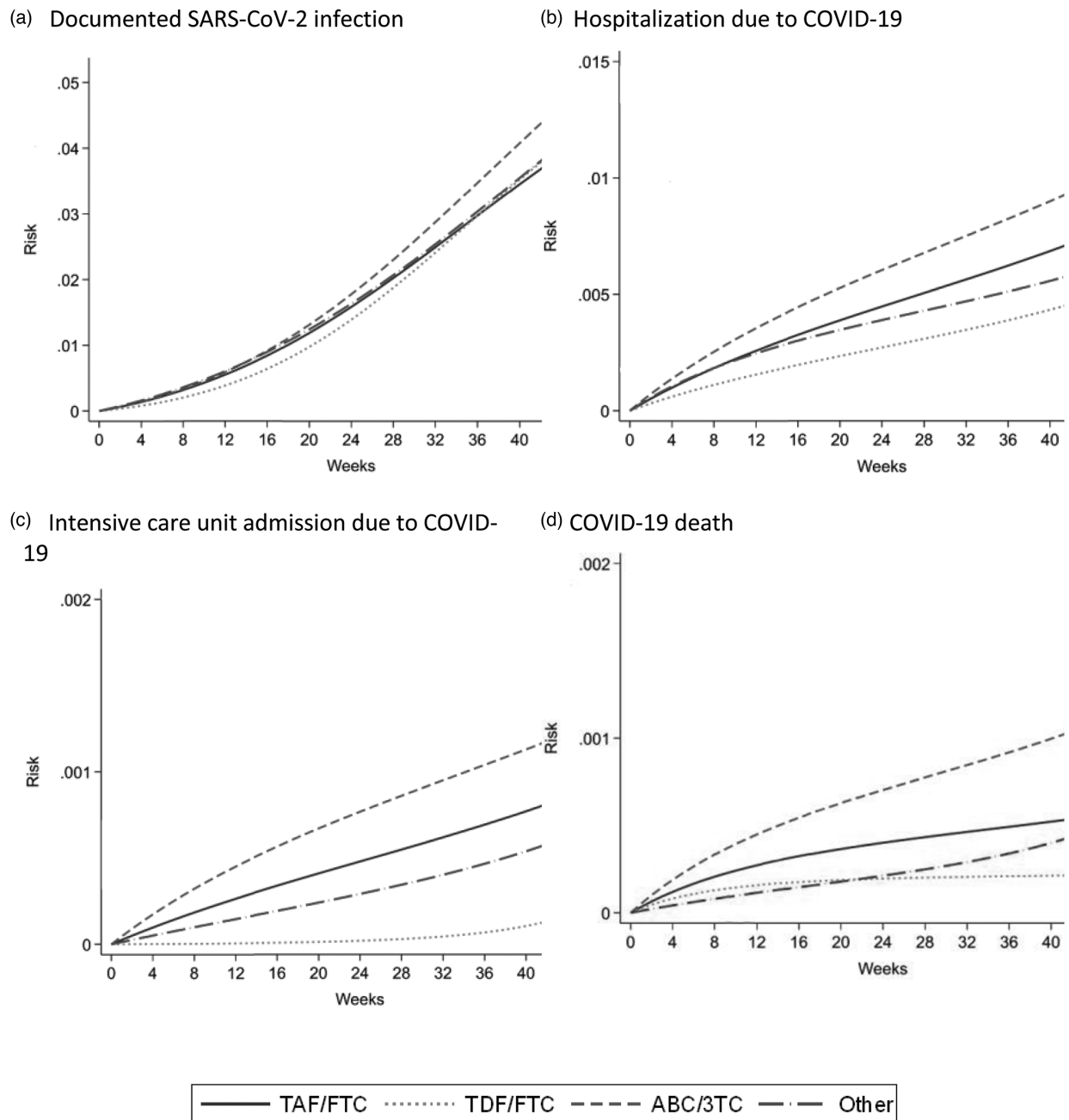
Fig. 2. Estimated risks of COVID-19 outcomes by NRTI combination in HIV-positive individuals, *CoVIHd Collaboration, Spain, February–December 2020. (a) Documented SARS-CoV-2 infection. (b) Hospitalization due to COVID-19. (c) Intensive care unit admission due to COVID-19. (d) COVID-19 death. *Adjusted via inverse probability weighting for age (in years, linear and quadratic terms), sex (male, female), transmission category (heterosexual, homo/bisexual, injecting drug use, other), country of origin (Spain, other), $CD4^+$ cell count (<350, $350–500$, >500 cells/μl), and hypertension, diabetes, chronic renal disease, cardiovascular disease, and treatment with immunosuppressants or corticosteroids. COVID-19, coronavirus disease 2019; NRTI, nucleos(t)ide reverse transcriptase inhibitor; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

Table 2. Estimated 48-week risks, risk differences and risk ratios of COVID-19 outcomes by NRTI combination in HIV-positive individuals,[a] CoVIHd Collaboration, Spain, February–December 2020.

	Documented SARS-CoV-2 infection				Hospitalization due to COVID-19				ICU admission due to COVID-19				COVID-19 death			
	No. events	Risks (95% CI), %	Risk differences (95% CI), %	Risk ratios (95% CI)	No. events	Risks (95% CI), %	Risk differences (95% CI), %	Risk ratios (95% CI)	No. events	Risks (95% CI), %	Risk differences (95% CI), %	Risk ratios (95% CI)	No. events	Risks (95% CI), %	Risk differences (95% CI), %	Risk ratios (95% CI)
TAF/FTC	923	4.3 (4.1, 4.6)	0	1.00	157	0.8 (0.7, 1.0)	0	1.00	17	0.09 (0.05, 0.14)	0	1.00	9	0.06 (0.02, 0.11)	0	1.00
TDF/FTC	300	4.5 (3.9, 5.0)	0.16 (−0.48, 0.69)	1.04 (0.89, 1.17)	35	0.5 (0.4, 0.7)	−0.28 (−0.52, −0.08)	0.66 (0.43, 0.91)	2	0.03 (0.01, 0.08)	−0.07 (−0.12, −0.004)	0.28 (0.11, 0.90)	1	0.02 (0.02, 0.09)	−0.04 (−0.07, 0.03)	0.37 (0.23, 1.90)
ABC/3TC	687	5.2 (4.8, 5.6)	0.89 (0.40, 1.34)	1.21 (1.09, 1.33)	147	1.1 (0.9, 1.2)	0.24 (0.02, 0.45)	1.29 (1.02, 1.58)	18	0.13 (0.08, 0.19)	0.04 (−0.03, 0.12)	1.39 (0.70, 2.80)	18	0.12 (0.07, 0.18)	0.06 (−0.01, 0.12)	2.02 (0.88, 6.12)
Other regimes	492	4.6 (4.1, 5.0)	0.24 (−0.27, 0.77)	1.06 (0.94, 1.18)	86	0.7 (0.5, 0.8)	−0.16 (−0.34, 0.04)	0.81 (0.62, 1.05)	8	0.07 (0.02, 0.12)	−0.02 (−0.09, 0.04)	0.76 (0.23, 1.77)	9	0.06 (0.02, 0.11)	0 (−0.06, 0.06)	0.99 (0.34, 2.61)

[a]Adjusted via inverse probability weighting for age (in years, linear and quadratic terms), sex (male, female), transmission category (heterosexual, homo/bisexual, injecting drug use, other), country of origin (Spain, other), CD4$^+$ cell count (<350, 350–500, >500 cells/μl), and hypertension, diabetes, cardiovascular disease, chronic renal disease, and treatment with immunosuppressants or corticosteroids.
ABC, abacavir ; CI, confidence interval; FTC, emtricitabine ; 3TC, lamivudine ; TAF, tenofovir alafenamide ; TDF, tenofovir disoproxil fumarate.

two randomized trials in nonhospitalized patients. In France, a phase 2 trial in 60 outpatients with early COVID-19 found lower nasopharyngeal shedding of SARS-CoV-2 after initiation of TDF/FTC [16]; in Spain and Latin America, the EPICOS trial could not rule out a beneficial effect of TDF/FTC as preexposure prophylaxis for COVID-19 among healthcare workers, but effect estimates were very imprecise because the target sample size was not met [17]. In contrast, the PANCOVID trial in hospitalized patients with COVID-19 in Spain reported no beneficial effects of TDF/FTC compared with placebo [18]. Note that temdesivir and molnupiravir also had minor or no effects in hospitalized patients [1,2,5], even though they prevented progression to severe COVID-19 in nonhospitalized patients [3,4]. The EPICOS and PANCOVID trials were led by some of the authors of this report.

Our study has some limitations. First, residual confounding by yet to be identified factors cannot be excluded. However, such residual confounding seems unlikely because we adjusted for all known comorbidities that affect both antiretroviral treatment choice and COVID-19 severity and adjustment had little impact on our effect estimates. Therefore, the lowest risk of hospitalization in those receiving TDF/FTC cannot be easily explained by residual confounding. Second, we may have missed some mild (and asymptomatic) SARS-CoV-2 infections because of the lack of systematic testing. However, our main results concern severe outcomes (hospitalization, ICU admissions, and death) that are almost always detected by the health system This study does not allow to draw conclusions on SARS-CoV-2 infection. Third, missing data on comorbidities led to the exclusion of 22% of otherwise eligible individuals. However, estimates did not materially change in unadjusted analyses that included individuals with missing data on comorbidities. Fourth, even a large cohort like this one cannot provide precise estimates for the risks of infrequent events such as ICU admissions and deaths. Fifth, as in the vast majority of COVID-19 studies, data on exposure to the virus were not available. However, it is unlikely that persons on TDF/FTC were less likely to be exposed to SARS-CoV-2 than persons on other regimes.

A protective effect of TDF/FTC is biologically plausible. *In silico* studies suggest that all forms of tenofovir, like other nucleos(t)ide analogues, partly inhibit the SARS-CoV-2 RNA-dependent RNA-polymerase (RNAdR-NAp) [19–21] and some, but not all, *in vitro* studies also suggest that tenofovir inhibits the RNAdRNAp [22–23]. Because of the possible higher bioavailability of TDF than TAF in respiratory cells, TDF might result in greater inhibition of the SARS-CoV-2 RNApRNAp [24–28]. In addition, tenofovir has been reported to have immunomodulatory effects [29–32] and animal models suggest that TDF/FTC increases nasopharyngeal SARS-CoV-2 clearance [33].

Table 3. Estimated 48-week risk, risk differences and risk ratios of COVID-19 outcomes by NRTI combination in HIV-positive individuals, stratified by age group,[a] CoVIHd Collaboration, Spain, February–December 2020.

	Documented SARS-CoV-2 infection				Hospitalization due to COVID-19			
	No. events	Risks (95% CI), %	Risk differences (95% CI), %	Risk ratios (95% CI)	No. events	Risks (95% CI), %	Risk differences (95% CI), %	Risk ratios (95% CI)
<50 years								
TAF/FTC	561	4.9 (4.5, 5.3)	0	1.00	48	0.4 (0.3, 0.6)	0	1.00
TDF/FTC	198	5.3 (4.6, 6.0)	0.45 (−0.43, 1.25)	1.09 (0.91, 1.27)	18	0.5 (0.3, 0.8)	0.06 (−0.21, 0.34)	1.15 (0.59, 1.93)
ABC/3TC	336	5.4 (4.8, 6.0)	0.50 (−0.27, 1.21)	1.10 (0.95, 1.26)	29	0.5 (0.3, 0.6)	0.02 (−0.22, 0.22)	1.03 (0.59, 1.62)
Other regimes	220	5.4 (4.7, 6.0)	0.47 (−0.35, 1.23)	1.10 (0.93, 1.26)	17	0.4 (0.2, 0.6)	−0.04 (−0.26, 0.17)	0.91 (0.49, 1.47)
≥50 years								
TAF/FTC	362	3.8 (3.4, 4.2)	0	1.00	109	1.2 (1.0, 1.4)	0	1.00
TDF/FTC	102	3.6 (2.9, 4.3)	−0.17 (−0.94, 0.64)	0.96 (0.77, 1.18)	17	0.6 (0.3, 0.9)	−0.61 (−1.03, −0.22)	0.49 (0.24, 0.81)
ABC/3TC	351	5.0 (4.6, 5.6)	1.26 (0.62, 1.89)	1.33 (1.15, 1.55)	118	1.7 (1.4, 2.0)	0.47 (0.11, 0.83)	1.40 (1.08, 1.79)
Other regimes	272	3.9 (3.4, 4.3)	0.07 (−0.51, 0.64)	1.02 (0.87, 1.18)	69	0.9 (0.7, 1.1)	−0.29 (−0.62, 0.03)	0.76 (0.54, 1.03)

[a]Adjusted via inverse probability weighting for age (in years, linear and quadratic terms), sex (male, female), transmission category (heterosexual, homo/bisexual, injecting drug use, other), country of origin (Spain, other), CD4$^+$ cell count (<350, 350–500, >500 cells/μl), and hypertension, diabetes, chronic renal disease, cardiovascular disease, and treatment with immunosuppressants or corticosteroids.
ABC, abacavir ; CI, confidence interval; FTC, emtricitabine ; 3TC, lamivudine ; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.

Compared with other drugs repurposed for COVID-19, TDF has several advantages. First, it has a solid safety track record in individuals with normal renal function [34,35], including pregnant women [36], and in fact is used routinely as preexposure prophylaxis for HIV infection. Second, it is administered orally and thus does not need to be administered in a healthcare facility. Third, it is an inexpensive generic drug that could be massively produced in many countries, including in settings with low COVID-19 vaccine coverage.

In summary, our findings suggest that treatment with TDF/FTC results in a lower severity of COVID-19 than treatment with other antiretrovirals among persons with HIV, especially those aged 50 years and older. A protective effect of TDF/FTC has clinical implications for persons with HIV, because TDF/FTC is an effective drug to control HIV infection in individuals without impaired renal function [37,38], and hepatitis B infection. A similar protection for HIV-negative individuals would be especially important for immunosuppressed patients for whom vaccines have suboptimal effectiveness. Confirmatory randomized trials of TDF/FTC for the prophylaxis and early treatment of COVID-19 are warranted.

Conflicts of interest
There are no conflicts of interest.

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