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Antiretrovirals and risk of COVID-19 diagnosis and hospitalization in HIV-positive persons

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To the Editor

In a recently published report, we describe the incidence and severity of COVID-19 in HIV-positive persons receiving antiretroviral therapy.[1] We showed estimated risks of COVID-19 diagnosis and hospitalization between 1 February and 15 April 2020 in Spain. Here we present rate ratios and a discussion about confounding as a potential explanation for the findings.

Briefly, 60 hospital-based HIV clinics providing care for 77,590 HIV-positive individuals on antiretroviral therapy (ART) identified 236 COVID-19 diagnoses confirmed via polymerase chain reaction (PCR) and 151 COVID-19 hospitalizations. ART regimes were classified according to their nucleos(t)ide reverse transcriptase inhibitor (NRTI) backbone into four classes: tenofovir disoproxil fumarate/emtricitabine (TDF/FTC), tenofovir alafenamide/ emtricitabine (TAF/FTC), abacavir/lamivudine (ABC/3TC), and others (including 3TC in dual therapies and protease inhibitor monotherapy). We used the 2019 National HIV Hospital Survey to obtain the distribution of ART regimes of the HIV-positive individuals without a diagnosis of COVID-19 and supplemented it with information from hospitals' pharmacies.[2] We combined the information from the 60 HIV clinics and the National HIV Hospital Survey to estimate the 75-day risk of COVID-19 diagnosis and hospitalization by ART regime in HIV-positive individuals. We found that individuals on TDF/FTC had the

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lowest COVID-19 risks: the risk of diagnosis was 16.9% for TDF/FTC, 39.1% for TAF/FTC, 28.3% for ABC/3TC, and 29.7% for others; the risk of hospitalization was 10.5% for TDF/FTC, 20.3% for TAF/FTC, 23.4% for ABC/3TC, and 20.0% for others. However, we did not report formal comparisons of these risks. Here we show age-adjusted incidence rate ratios (and their 95% confidence intervals) by NRTI backbone estimated via Poisson regression. This study was approved by the institutional review board at University Hospital Ramón y Cajal, Madrid, Spain. We conducted analyses in Stata software (version 15.0; Stata Corporation, College Station, Texas, USA).

The Table shows the age-adjusted rate ratios of COVID-19 diagnosis and of hospital admissions by NRTI backbone among HIV-positive individuals. The rate ratio of diagnosis was 0.44 (0.27, 0.70) and of hospitalization was 0.53 (0.29, 0.97) for individuals on TDF/FTC compared with those on TAF/FTC. During the period of the study, diagnosis of COVID-19 in Spain was confirmed by PCR only in cases severe enough to require medical attention.

As in all observational studies, our estimates may be partly explained by confounding. It is possible that persons with comorbidities, and thus more likely to develop severe COVID-19, are the least likely to be on TDF/FTC. While we could not adjust for comorbidities, the between-hospital heterogeneity in the proportion of patients on TDF/FTC suggests that treatment choice was largely driven by the preferred treatment at each hospital, which is consistent with previous studies.[3] We also conducted three sensitivity analyses to explore the possible impact of confounding by comorbidities.

First, we restricted the analysis to individuals younger than 60 years, who have the lowest prevalence of comorbidities. Compared with individuals on TAF/FTC, the rate ratios (95% CI) of diagnosis were 0.46 (0.28–0.75) for those on TDF/FTC, 0.62 (0.43–0.91), for those on ABC/3TC, and 0.59 (0.39–0.87) for those on other regimes; the corresponding rate ratios for hospitalization were 0.55 (0.29–1.04) for those on TDF/FTC, 0.92 (0.58–1.48) for those on ABC/3TC, and 0.76 (0.46–1.26) for those on other regimes.

Second, we restricted the analysis to the region of Madrid, the region with the largest between-hospital heterogeneity in use of TDF/FTC and the highest COVID-19 burden. Compared with individuals on TAF/FTC, the rate ratios (95% CI) of diagnosis were 0.43 (0.22–0.85) for those on TDF/FTC, 0.73 (0.46–1.14) for those on ABC/3TC, and 1.15 (0.77–1.72) for those on other regimes; the corresponding rate ratios for hospitalization were 0.70 (0.28–1.76) for those on TDF/FTC, 1.48 (0.81–2.71) for those on ABC/3TC, and 1.87 (1.05–3.34) for those on other regimes.

Third, we explored the possibility of confounding for the comparative effect of tenofovir-based regimes (either TDF/FTC or TAF/FTC) by comparing the risks of COVID-19 diagnosis and hospitalization between individuals who receive their care in hospitals which used >70% of tenofovir as TDF/FTC versus hospitals which used >70% of tenofovir as TAF/FTC. Since the distribution of HIV comorbidities across hospitals' health districts is expected to be similar and unrelated to the choice of tenofovir type, any differences in risk at the hospital level could not be readily explained by individual-level confounding due to

comorbidities. We found lower incidences in hospitals with a predominant use of TDF/FTC. The rate ratios (95% CI) of diagnosis and hospitalization were 0.63 (0.36–1.12) and 0.80 (0.41– 1.56), respectively, in 3 hospitals which used predominantly tenofovir as TDF/FTC compared with 27 hospitals which used predominantly TAF/FTC, but the 95% confidence intervals were wide.

The above results suggest that confounding by individual clinical characteristics cannot completely explain our finding of a lower risk of COVID-19 diagnosis and hospitalization among HIV-positive individuals receiving TDF/FTC. A large magnitude of confounding due to the third drug in the ART regime seems also unlikely because about two thirds of both TDF/FTC and TAF/FTC regimes were supplemented with integrase inhibitors and no evidence supports an effect of either integrase inhibitors or protease inhibitors on COVID-19.[4–5]

In summary, the risk of COVID-19 diagnosis and hospitalization among HIV-positive individuals is lower in those receiving treatment with TDF/FTC than in those receiving other ART regimes. This association does not seem to be explained by confounding due to unmeasured clinical characteristics. Our finding is compatible with accumulating evidence on a potential effect of TDF/FTC against SARS-CoV-2 infection.[6–8]

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table.

Age-adjusted rate ratios of PCR-confirmed COVID-19 diagnosis and hospital admission by NRTI regimes among 77,590 HIV-positive persons on ART, February 1-April 15, 2020, Spain.

NRTI backbone	Estimated persons at risk[a]	COVID-19 diagnosis		COVID-19 hospital admission	
		N	Rate ratio (95% CI)	N	Rate ratio (95% CI)
TAF/FTC	25,571	100	1 (ref.)	52	1 (ref.)
TDF/FTC	12,395	21	0.44 (0.27–0.70)	13	0.53 (0.29–0.97)
ABC/3TC	20,105	57	0.68 (0.49–0.94)	47	1.0 (0.69–1.5)
Other regimes[b]	19,520	58	0.73 (0.50–1.01)	39	0.89 (0.59–1.4)

[a] Distribution derived from the 2019 National HIV Hospital Survey

[b] Other regimes include only 3TC in dual therapies or no NRTI in patients treated with PI monotherapy

Nucleos(t)ide reverse transcriptase inhibitor (NRTI)

Tenofovir disoproxil fumarate (TDF)/emtricitabine (FTC)

Tenofovir alafenamide (TAF)/FTC

Abacavir (ABC)/lamivudine (3TC)