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Human Immunodeficiency Virus Status, Tenofovir Exposure, and the Risk of Poor Coronavirus Disease 19 Outcomes: Real-World Analysis From 6 United States Cohorts Before Vaccine Rollout

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(See the Editorial Commentary by Julia del Amo on pages 1735–7.)

Background. People with human immunodeficiency virus (HIV) (PWH) may be at increased risk for severe coronavirus disease 2019 (COVID-19) outcomes. We examined HIV status and COVID-19 severity, and whether tenofovir, used by PWH for HIV treatment and people without HIV (PWoH) for HIV prevention, was associated with protection.

Methods. Within 6 cohorts of PWH and PWoH in the United States, we compared the 90-day risk of any hospitalization, COVID-19 hospitalization, and mechanical ventilation or death by HIV status and by prior exposure to tenofovir, among those with severe acute respiratory syndrome coronavirus 2 infection between 1 March and 30 November 2020. Adjusted risk ratios (aRRs) were estimated by targeted maximum likelihood estimation, with adjustment for demographics, cohort, smoking, body mass index, Charlson comorbidity index, calendar period of first infection, and CD4 cell counts and HIV RNA levels (in PWH only).

Results. Among PWH (n = 1785), 15% were hospitalized for COVID-19 and 5% received mechanical ventilation or died, compared with 6% and 2%, respectively, for PWoH (n = 189 351). Outcome prevalence was lower for PWH and PWoH with prior tenofovir use. In adjusted analyses, PWH were at increased risk compared with PWoH for any hospitalization (aRR, 1.31 [95% confidence interval, 1.20–1.44]), COVID-19 hospitalizations (1.29 [1.15–1.45]), and mechanical ventilation or death (1.51 [1.19–1.92]). Prior tenofovir use was associated with reduced hospitalizations among PWH (aRR, 0.85 [95% confidence interval, .73–.99]) and PWoH (0.71 [.62–.81]).

Conclusions. Before COVID-19 vaccine availability, PWH were at greater risk for severe outcomes than PWoH. Tenofovir was associated with a significant reduction in clinical events for both PWH and PWoH.

Keywords. HIV; COVID-19; SARS-CoV-2; tenofovir; hospitalization.

Soon after the onset of the coronavirus disease 2019 (COVID-19) pandemic, the US Centers for Disease Control and Prevention designated people with human immunodeficiency virus (HIV) (PWH) as a group more vulnerable to severe clinical outcomes after severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. Initial small cohort studies from Europe and the United States did not show significant differences in severity for PWH compared with people without HIV (PWoH) [1–3]. More recent studies from larger cohorts have reported mixed results for hospitalization [4–7], mechanical ventilation, and intensive care admissions [8, 9]. Several meta-analyses also found an increased risk of death in PWH [10–13], with a reported 80% excess mortality risk among PWH with SARS-CoV-2 [12], although several individual studies show no difference in mortality by HIV status [14, 15]. Previous data from the Corona Infectious Virus Epidemiology Team (CIVET) collaboration indicated low overall rates of

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hospitalizations following vaccine breakthroughs among PWH and PWoH, with the highest rates for those with low or moderate immunosuppression [6]. Others have similarly found poorer outcomes among PWH with low CD4 cell counts [3, 16].

Possible explanations for the heterogeneity of findings may be the potential protective effects of antiretroviral therapy (ART) medications on COVID-19 outcomes [17, 18]. Most observational evidence is supported by early studies in both PWH and PWoH in Spain [19] and France [20], with emerging data from the United States. Among PWH with SARS-CoV-2, cohort studies in both the United States and Spain have found that tenofovir disoproxil fumarate (TDF) may protect against COVID-19–related hospitalizations [18, 21, 22]. Other studies have indicated lower mortality rates for PWH taking TDF compared with other regimens [23]. Among PWoH receiving HIV preexposure prophylaxis (PrEP) containing tenofovir, studies have reported differing SARS-CoV-2 seroprevalence results in both Spanish [19] and French [20] cohorts.

Few studies have evaluated the association of tenofovir-based treatments on COVID-19 severity among PWH [19, 24, 25] and PWoH [26, 27]. Addressing these gaps, our objective was to compare COVID-19 outcomes in individuals with recent SARS-CoV-2 infection by HIV status and use of tenofovir among PWH and PWoH, within 6 diverse cohorts in the United States. Understanding the unique risk and protective factors for COVID-19, including tenofovir use, may help inform continued management of high-risk groups during this and future pandemics.

METHODS

Setting and Population

The CIVET collaboration comprises a subset of cohorts participating in the North American AIDS Cohort Collaboration on Research and Design, including 2 integrated health systems (Kaiser Permanente Northern California, Kaiser Permanente Mid-Atlantic States), 2 academic health centers (Vanderbilt Comprehensive Care Clinic HIV Cohort and the University of North Carolina at Chapel Hill HIV Clinical Cohort), a cohort of all PWH receiving care within the National US Veterans Affairs Healthcare System (the Veterans Aging Cohort Study), and an interval cohort (MACS/WIHS Combined Cohort Study). Details of the CIVET collaboration have been published elsewhere [28].

Similar to methods described for prior CIVET studies [28], eligible participants were PWH and PWoH identified from each cohort who met the following criteria: (1) positive SARS-CoV-2 result between 1 March and 30 November 2020; (2) age 18–80 years at the time of the first positive SARS-CoV-2 result; and (3) enrolled or in care at the time of first positive SARS-CoV-2 result, as operationalized by each individual cohort. The study index date (ie, baseline) was the date of first positive SARS-CoV-2 laboratory result between 1 March and 30 November 2020. All study procedures were reviewed and approved by each site's institutional review board and included waivers of patient informed consent.

Measures

Primary Exposures

There were 2 primary exposures of interest, both measured at the index date. The first was HIV status, determined from history of HIV diagnosis, HIV positive laboratory test result, detectable HIV-1 RNA viral load measurement, or prescription for ART based on inclusion criteria and available data per cohort [29]. The second exposure of interest was exposure to tenofovir, including ART containing TDF or tenofovir alafenamide (TAF) for PWH and an HIV PrEP prescription fill for TDF/emtricitabine (FTC) or TAF/FTC for PWoH in the 6 months before the index date. PrEP analyses were limited to 3 cohorts with larger PWoH comparison groups (Kaiser Permanente Northern California, Kaiser Permanente Mid-Atlantic States, and Vanderbilt Comprehensive Care Clinic HIV Cohort).

Primary Outcomes

The primary outcomes were (1) hospitalization for any reason, defined as hospital admission within 7 days before or 45 days after the first positive SARS-CoV-2 result, regardless of discharge diagnosis; (2) COVID-19 hospitalizations, defined as the subset of all identified hospitalizations with ≥1 discharge diagnosis suggestive of a COVID-19–specific illness (see Supplementary Table 1 for codes); and (3) composite outcome of mechanical ventilation (from 7 days before to 45 days after the first positive SARS-CoV-2 result) (Supplementary Table 1 for codes) or death up to 45 days after the first positive SARS-CoV-2 results. Mortality information was ascertained from administrative and electronic health records (EHRs), the Social Security Administration, and state death certificates.

Covariates

Sociodemographic and clinical data, including laboratory testing and healthcare utilization, were obtained from EHRs or patient surveys (MACS/WIHS Combined Cohort Study only), all measured at or within 1 year before the index date. Sociodemographic variables included age (18–29, 30–39, 40–49, 50–59, 60–69, 70–79 years), sex (male or female), and race/ethnicity (white, black, Hispanic, Asian, other, or unknown). Clinical information included body mass index (BMI) (<18.5 [underweight; BMI calculated as weight in kilograms divided by height in meters squared], 18.5–24.9 [normal weight], 25.0–29.9 [overweight], ≥30.0 [obese], or unknown), self-reported smoking (current, former, never smoker,

unknown), baseline calendar period (March–June, July–September, or October–December 2020), and a modified Charlson comorbidity index (0, 1, 2, or ≥3) that excluded HIV from the calculation. For analyses of PWH, additional covariates considered included CD4 cell count (<200/μL, 200–499/μL, ≥500/μL, or unknown) and HIV RNA levels (<75, 75–499, or ≥500 copies/mL or unknown).

Statistical Analysis

We first determined the prevalence of each of the 3 outcomes within strata defined by HIV status and tenofovir use. Next, we obtained crude risk ratios (RRs) for each outcome and exposures using Poisson regression models with robust standard errors using PROC GENMOD in SAS software, version 9.4. Next, adjusted RRs (aRRs) were estimated by targeted maximum likelihood estimation (TMLE), a semiparametric, doubly robust approach that hedges against model misspecification by relying on machine learning. In particular, TMLE yields unbiased error estimates (ie, correct coverage of the 95% confidence intervals [CIs]) under weak modeling assumptions [30, 31]. Adjusted TMLE models accounted for demographics, cohort, smoking status, BMI, Charlson comorbidity index, and calendar period of first positive SARS-CoV-2 result, as well as for CD4 cell counts and HIV RNA levels in PWH-only analyses. TMLE analyses were performed using the tmle R software package [32] (version 1.5.0.2).

We performed 3 sensitivity analyses. First, for the comparison of COVID-19 severity in PWH and PWoH, we repeated analyses limiting PWH to those prescribed tenofovir (ie, excluding PWH with no ART and those with tenofovir-sparing ART). This analysis helped evaluate whether the potential protective effect of tenofovir attenuates an observed disparity in COVID-19 outcomes by HIV status. Second, among PWH, to further reduce confounding by HIV progression, we restricted subjects to those on ART (ie, excluding PWH not on ART in the prior year). Third, to evaluate medication-specific effects among PWH, we compared those prescribed TAF only (the predominant form of tenofovir used in PWH during the study period) with those on tenofovir-sparing ART (ie, excluding those not on ART or those with ART containing TDF). We also compared PWH with TDF only versus those on tenofovir-sparing ART.

RESULTS

A total of 191 136 SARS-CoV-2–infected patients were included, including 1785 PWH. Among 1785 well-treated PWH (75% with HIV RNA <75 copies/mL and 51% with CD4 cell counts >500/μL), 1139 were prescribed tenofovir (including 1035 on TAF only), 401 were on tenofovir-sparing ART, and 245 were not on ART in the prior year. As shown in Table 1, there were many demographic and clinical differences between PWH and PWoH. Notably, PWH, compared with PWoH, were more likely to be older (60% vs 36% aged ≥50 years), non-Hispanic black (46% vs 14%), and male (86% vs 46%). Differences were also noted, albeit less striking, for recent tenofovir use among PWH and PWoH (Table 1).

COVID-19 Outcomes by HIV Status

Among 1785 PWH with SARS-CoV-2, 422 (24%) were hospitalized, 271 (15%) were hospitalized for COVID-19, and 83 (5%) received mechanical ventilation or died (Table 2). Among 189 351 PWoH, 16 732 (9%) were hospitalized, 11 930 (6%) were hospitalized for COVID-19, and 3037 (2%) received mechanical ventilation or died. Differences by HIV status were statistically significant, with RRs all well above 2 in crude models for all outcomes. The aRRs for HIV status were 1.31 (95% CI: 1.20–1.44), 1.29 (1.15–1.45), and 1.51 (1.19–1.92) (all $P < .001$) for any hospitalization, COVID-19–related hospitalization, and mechanical ventilation or death, respectively. Sensitivity analyses limiting PWH to those treated with tenofovir indicated similar magnitudes of association, with decreased precision, for any hospitalization and COVID-19 hospitalizations but eliminated the association for mechanical ventilation or death (Supplementary Table 2).

COVID-19 Outcomes by Tenofovir Use Among PWH

For tenofovir use among PWH, of 1139 recent tenofovir users, 224 (20%) were hospitalized, 152 (13%) were hospitalized for COVID-19, and 33 (3%) received mechanical ventilation or died. For those without recent tenofovir use, 198 (31%) were hospitalized, 119 (18%) were hospitalized for COVID-19, and 50 (8%) received mechanical ventilation or died. Differences by recent tenofovir use were significant in crude models for all outcomes (Table 2). The aRRs for recent tenofovir use were 0.81 (95% CI: .70–.96; $P = .03$), 0.91 (.72–1.13; $P = .40$), and 0.50 (.33–.75; $P = .002$) for any hospitalization, COVID-19 hospitalization, and mechanical ventilation or death, respectively. Sensitivity analyses restricting to those on ART, and evaluation of TAF only or TDF only did not change inferences for all outcomes (Supplementary Table 2).

COVID-19 Outcomes by HIV PrEP Use Among PWoH

Among PWoH using PrEP (n = 459), 15 (3%) were hospitalized, 14 (3%) were hospitalized for COVID-19, and 3 (1%) received mechanical ventilation or died. For PWoH without PrEP use, 13 324 (8%) were hospitalized, 9278 (5%) were hospitalized for COVID-19, and 2272 (1%) received mechanical ventilation or died. Differences by PrEP use were significant in crude models for any hospitalization and COVID-19 hospitalizations but not for mechanical ventilation or death. The aRRs for PrEP status were 0.71 (95% CI: .62–.81; $P < .001$), 0.86 (74– 1.00; $P = .05$), and 0.91 (.68–1.21; $P = .51$) for any hospitalization,

Table 1. Baseline Characteristics by Human Immunodeficiency Virus Status and Receipt of Tenofovir

Characteristic	Patients, No. (%)[a]					
	HIV Status in Full Cohort		Use of ART With Tenofovir in PWH		Use of HIV PrEP in PWoH (Subset[b])	
	PWH (n = 1785)	PWoH (n = 189 351)	Yes (n = 1139)	No (n = 646)	Yes (n = 459)	No (n = 173 921)
Age, y						
18–29	99 (6)	43 639 (23)	70 (6)	29 (4)	135 (29)	41 252 (24)
30–39	299 (17)	40 006 (21)	206 (18)	93 (14)	171 (37)	37 750 (22)
40–49	314 (18)	36 753 (19)	206 (18)	108 (17)	89 (19)	34 191 (20)
50–59	524 (29)	35 345 (19)	345 (30)	179 (28)	51 (11)	32 258 (19)
60–69	387 (22)	22 958 (12)	228 (20)	159 (25)	13 (3)	19 860 (11)
70–79	162 (9)	10 650 (6)	84 (7)	78 (12)	0 (0)	8610 (5)
Race/ethnicity						
Non-Hispanic white	441 (25)	59 115 (31)	294 (26)	147 (23)	154 (34)	51 221 (29)
Non-Hispanic black	829 (46)	26 106 (14)	493 (43)	336 (52)	62 (14)	21 959 (13)
Hispanic	332 (19)	62 548 (33)	234 (21)	98 (15)	154 (34)	61 474 (35)
Asian	25 (1)	20 270 (11)	19 (2)	6 (1)	53 (12)	20 216 (12)
Other	128 (7)	6383 (3)	86 (8)	42 (7)	10 (2)	4164 (2)
Unknown	30 (2)	14 929 (8)	13 (1)	17 (3)	26 (6)	14 887 (9)
Male	1541 (86)	87 379 (46)	987 (87)	554 (86)	429 (93)	79 803 (46)
BMI[c]						
Underweight	25 (1)	1330 (1)	11 (1)	14 (2)	3 (1)	1264 (1)
Normal	361 (20)	31 033 (16)	216 (19)	145 (22)	133 (29)	30 029 (17)
Overweight	617 (35)	49 942 (26)	384 (34)	233 (36)	162 (35)	48 234 (28)
Obese	673 (38)	73 623 (39)	457 (40)	216 (33)	129 (28)	70 676 (41)
Unknown	109 (6)	33 423 (18)	71 (6)	38 (6)	32 (7)	23 718 (14)
Smoking status						
Current smoker	434 (24)	9870 (5)	264 (23)	170 (26)	32 (7)	8351 (5)
Former smoker	442 (25)	38 729 (20)	281 (25)	161 (25)	113 (25)	35 567 (20)
No history of smoking	894 (50)	126 866 (67)	568 (51)	308 (48)	306 (67)	118 839 (68)
Unknown	15 (1)	13 886 (7)	8 (1)	7 (1)	8 (2)	11 164 (6)
CCI						
0	828 (46)	130 851 (69)	537 (47)	291 (45)	365 (80)	121 005 (70)
1	342 (19)	30 055 (16)	250 (22)	92 (14)	69 (15)	27 828 (16)
2	205 (11)	12 426 (7)	133 (12)	72 (11)	16 (3)	11 382 (7)
≥3	410 (23)	16 019 (8)	219 (19)	191 (30)	9 (2)	13 706 (8)
Calendar period in 2020						
March–June	454 (25)	23 553 (12)	277 (24)	177 (27)	69 (15)	20 668 (12)
July–September	447 (25)	47 027 (25)	289 (25)	158 (24)	117 (25)	42 966 (25)
October–December	884 (50)	118 771 (63)	573 (50)	311 (48)	273 (59)	110 287 (63)
ART use in past 12 mo						
Yes	1540 (86)	…	1139 (100)	401 (62)	…	…
No	245 (14)	…	0 (0)	245 (38)	…	…
CD4 cell count						
< 200/μL	199 (11)	…	92 (8)	107 (17)	…	…
200–499/μL	389 (22)	…	246 (22)	145 (22)	…	…
≥ 500/μL	906 (51)	…	665 (58)	241 (37)	…	…
Unknown	291 (16)	…	136 (12)	155 (24)	…	…
HIV RNA, copies/mL						
< 75	1342 (75)	…	942 (83)	400 (62)	…	…
75–499	80 (4)	…	54 (5)	26 (4)	…	…
≥500	60 (3)	…	32 (3)	28 (4)	…	…
Unknown	303 (17)	…	111 (10)	192 (30)	…	…

Abbreviations: ART, antiretroviral therapy; BMI, body mass index; CCI, Charlson comorbidity index; HIV, human immunodeficiency virus; PrEP, preexposure prophylaxis; PWH, people with HIV; PWoH, people without HIV.

[a]Differences were significant for all variables by χ^2 test ($P < .001$).

[b]Subset limited to Kaiser Permanente Northern California, Kaiser Permanente Mid-Atlantic States, and Vanderbilt Comprehensive Care Clinic HIV Cohort.

[c]BMI calculated as weight in kilograms divided by height in meters squared.

Table 2. Coronavirus Disease 2019 Outcomes by Human Immunodeficiency Virus (HIV) Status, and by Use of Tenofovir Among People With or Without HIV

HIV Status and Use of Tenofovir	All Patients, No.	Patients With Outcome, No. (%)	RR (95% CI)	
			Crude[a]	Adjusted[b]
HIV status				
Hospitalized for any reason				
PWH	1785	422 (24)	2.68 (2.46–2.91)	1.31 (1.20–1.44)
PWoH	189 351	16 732 (9)	Reference	Reference
Hospitalized for COVID-19				
PWH	1785	271 (15)	2.41 (2.16–2.69)	1.29 (1.15–1.45)
PWoH	189 351	11 930 (6)	Reference	Reference
Mechanical ventilation or death				
PWH	1785	83 (5)	2.90 (2.34–3.59)	1.51 (1.19–1.92)
PWoH	189 351	3037 (2)	Reference	Reference
Tenofovir use among PWH				
Hospitalized for any reason				
Tenofovir	1139	224 (20)	0.64 (.54–.76)	0.81 (.70–.96)
No tenofovir	646	198 (31)	Reference	Reference
Hospitalized for COVID-19				
Tenofovir	1139	152 (13)	0.72 (.58–.90)	0.91 (.72–1.13)
No tenofovir	646	119 (18)	Reference	Reference
Mechanical ventilation or death				
Tenofovir	1139	33 (3)	0.37 (.24–.57)	0.50 (.33–.75)
No tenofovir	646	50 (8)	Reference	Reference
Tenofovir use for PrEP among PWoH				
Hospitalized for any reason				
HIV PrEP with tenofovir	459	15 (3)	0.43 (.26–.70)	0.71 (.62–.81)
No HIV PrEP with tenofovir	173 921	13 324 (8)	Reference	Reference
Hospitalized, COVID				
HIV PrEP with tenofovir	459	14 (3)	0.57 (.34–.96)	0.86 (.74–1.00)
No HIV PrEP with tenofovir	173 921	9278 (5)	Reference	Reference
Mechanical ventilation or death				
HIV PrEP with tenofovir	459	3 (1)	0.50 (.16–1.55)	0.91 (.68–1.21)
No HIV PrEP with tenofovir	173 921	2272 (1)	Reference	Reference

Abbreviations: CI, confidence interval; COVID-19, coronavirus disease 2019; HIV, human immunodeficiency virus; PrEP, preexposure prophylaxis; PWH, people with HIV; PWoH, people without HIV; RR, risk ratio.

[a]Crude RRs from Poisson regression models with robust standard errors.

[b]Adjusted RRs estimated by targeted maximum likelihood estimation, accounting for age, sex, race/ethnicity, cohort, smoking status, body mass index, Charlson comorbidity index, and calendar period, as well as CD4 count and HIV viral load for PWH-only analyses.

COVID-19–related hospitalization, and mechanical ventilation or death, respectively.

DISCUSSION

In this large, diverse observational cohort study of well-treated PWH and PWoH with SARS-CoV-2 infection in the United States, PWH were at greater risk for more severe COVID-19 outcomes before rollout of COVID-19 vaccines, especially mechanical ventilation or death. After accounting for demographics, BMI, comorbid conditions and smoking, the risk of hospitalization was 31% greater for PWH compared with PWoH. and the risk of mechanical ventilation or death was 51% greater. Tenofovir use appeared to confer protection against more severe COVID-19 outcomes irrespective of HIV status, with a 19% reduction in hospitalizations for PWH taking ART containing tenofovir and a 48% reduction in mechanical ventilation or death. Similar results were found in PWoH taking PrEP containing tenofovir, with a 29% reduction in hospitalizations for PrEP users but no reduction in mechanical ventilation or death.

Our findings indicated that the increased risk of adverse COVID-19 outcomes among PWH, was attributed in large part to the covariates considered, including age, smoking, and comorbid conditions. In unadjusted models, the risk of hospitalization was 2.7-fold higher and the risk of mechanical ventilation or death 2.9-fold higher for PWH compared with PWoH. In adjusted models, the increased risk was attenuated but remained higher for PWH, with 1.3-fold and 1.5-fold higher risks for hospitalization and mechanical ventilation or death, respectively. In sensitivity analyses that excluded PWH not on tenofovir, the higher risk remained consistent for hospitalization but was no longer seen for mechanical ventilation or death,

suggesting that tenofovir may have a strong association with this more severe outcome specifically. Our results are consistent with earlier work by Hadi et al [29], who found increased rates of COVID-19 hospitalization, and death in PWH compared with PWoH, even after propensity score matching for BMI, smoking, and other comorbid conditions. Our study adds to these findings by evaluating mechanical ventilation as well outcomes across 6 cohorts of PWH throughout the United States. The remaining 30%–50% elevated risk of more severe COVID-19 outcomes likely reflects the impact of HIV immunosuppression on greater COVID-19 severity, consistent with our group's prior findings [6].

Among PWH, those on ART containing tenofovir were 19% less likely to be hospitalized for any reason and 48% less likely to receive mechanical ventilation or die. The majority of PWH on ART containing tenofovir in this sample were receiving prescriptions for TAF; sensitivity analyses restricting to TAF users or TDF users had only a minimal impact on inferences with both formulations showing a protective effect. These results are consistent with others who also demonstrated a potential protective association of ART containing tenofovir against severe COVID-19 outcomes. Del Amo et al [22] reported that, among PWH with COVID-19, those receiving TDF or TAF had a lower risk for hospitalization than those on other treatment regimens, with slightly better outcomes for TDF. Boulle et al [23] reported a lower COVID-19–related mortality rate in PWH on TDF than in those on abacavir-zidovudine. A prior study from the Department of Veterans Affairs noted better COVID-19 outcomes for PWH treated with TDF than for those treated with TAF [18]; however, our sensitivity analyses indicated that the protective effects of TAF and TDF were similar in magnitude.

Consistent with our findings in PWH, we also noted a potential protective association of HIV PrEP and COVID-19 outcomes. Among PWoH, in adjusted models, those with recent PrEP containing tenofovir use were 29% less likely to be hospitalized for any reason and 14% less likely to be hospitalized for COVID-19. Few studies to date have evaluated PrEP use and COVID-19 severity. A randomized control trial of healthcare workers taking TDF/FTC with hydroxychloroquine as PrEP for COVID-19 reported inconclusive results [27]. In Spain, Ayerdi et al [19] noted a higher seroprevalence of SARS-CoV-2 in PrEP users compared with non-PrEP users (15.0% vs 9.2%; $P = .26$), while a French study indicated no difference in SARS-CoV-2 incidence rates comparing PrEP users and the general population [20]. Thus, we are among the first studies to evaluate the association of PrEP use with COVID-19 severity.

A recent review by Zanella and colleagues [33] evaluated available evidence of tenofovir's potential efficacy against SARS-CoV-2. Computer simulation models suggest that tenofovir may inhibit the virus's capacity for cell entry [30, 34] and for fusion, replication, and spread [31, 32], while in vitro studies of animal cells indicated that tenofovir inhibits the release of the SARS-CoV-2 viral genome [35], and an in vivo study in ferrets found a reduction in severity and shorter duration of clinical symptoms [36]. Finally, a pilot randomized control trial in France found a significant reduction in SARS-CoV-2 viral burden after 7 days in patients with nonsevere COVID-19 treated with TDF [37]. Thus, there is evidence of a potential causal protective effect of tenofovir-based therapy against adverse COVID-19 outcomes.

The current study had several limitations. First, data were ascertained from the EHRs, which were collected during routine medical care and not for research purposes. Thus, factors such as smoking status could only be categorized crudely (current, former, or never). Residual confounding is also possible as a result of other measured variables, such as by specific comorbid conditions that contribute to the Charlson comorbidity index, age (given the wide 10-year categories), or non–tenofovir-based ART regimens. There may also be unmeasured confounding for the association of HIV status or tenofovir use; for example, there may have been socioeconomic differences between groups. However, the consistency of the association between tenofovir and COVID-19 severity in PWH and PWoH supports the validity of the findings. A second limitation was that exposure to tenofovir for both PWH and PWoH was based on prescriptions received in the prior 6 months, and we did not consider adherence. Of note, the sites were not able to distinguish daily PrEP users from nondaily or "on-demand" PrEP users, which may have resulted in misclassification (ie, some nondaily users may have used PrEP in the prior 6 months but without a recent prescription fill). We believe that this potential misclassification might only attenuate our study findings.

Another limitation was that results cover only the first 9 months of the COVID-19 pandemic and therefore do not include follow-up during transmission of the Delta or Omicron variants, or after introduction of vaccines. However, an advantage of the design was the ability to focus more directly on potential antiviral effects of tenofovir. COVID-19–related coding conventions were also rapidly evolving early in the pandemic, which may have resulted in some hospitalizations being misattributed to COVID-19. However, all diagnoses were limited to within 90 days of a confirmed SARS-Cov-2 infection, and we limited codes to syndromes (eg, pneumonia) consistent with COVID-19 after review by an infectious disease clinician (author J. S). COVID-19 diagnoses at external institutions may also have been missed, although the misclassification was likely nondifferential with respect to HIV and tenofovir status, and results were therefore likely conservative. Future studies are needed to both confirm our findings and evaluate the potential impact of tenofovir on COVID-19 vaccine effectiveness and any differences with more recent circulating variants.

In summary, the current study represents a unique analysis of COVID-19 outcomes among PWH and PWoH engaged in care within 6 US-based healthcare systems and cohorts. We noted a 30%–50% higher risk of more severe COVID-19 outcomes among PWH compared with PWoH, even after adjustment for key confounders. We also noted a significant potential protective effect of tenofovir therapy against severe COVID-19 outcomes, with similar magnitudes of association for PWH on ART and for PWoH prescribed PrEP. The results have important clinical implications. While COVID-19 vaccines are highly protective against adverse outcomes, they do not completely eliminate risks, and many people remain unvaccinated or have not received timely boosters. Given the lack of many effective treatment options for COVID-19, these findings support further consideration of tenofovir-based treatments, which are widely available at a relatively low cost, to improve outcomes for both PWH and PWoH infected with SARS-CoV-2.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Disclaimer. The views and opinions expressed in this manuscript are those of the authors and do not necessarily represent those of the Department of Veterans Affairs or the United States government.

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