

# Effects of Pitavastatin on COVID-19 Incidence and Seriousness Among a Global Cohort of People With HIV

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**Background.** Among people with HIV (PWH), COVID-19 is common and potentially severe. We leveraged REPRIEVE (Randomized Trial to Prevent Vascular Events in HIV) to assess the effects of statin therapy for cardiovascular disease prevention on COVID-19 outcomes (incidence and serious cases) among a global cohort of PWH.

**Methods.** COVID-19 data collection was implemented April 2020 to capture events from January 2020. COVID-19 was defined by positive test result or clinical diagnosis and serious COVID-19 according to the International Conference on Harmonisation definition. Among participants in follow-up on 1 January 2020, Cox proportional hazards modeling was used to estimate the hazard ratio (HR) of COVID-19 (pitavastatin/placebo), stratified by Global Burden of Disease region. Modification of statin effect following COVID-19 vaccination was evaluated via interaction with time-updated vaccination status.

**Results.** Among 6905 PWH, 32% were natal female and 41% were Black or African American. The median age was 53 years and the 10-year atherosclerotic cardiovascular disease risk score 4.5%. Statin therapy did not reduce COVID-19 incidence (HR, 1.05; 95% CI, .95–1.15) but appeared to reduce incidence of serious COVID-19 (HR, 0.75; 95% CI, .52–1.09). Among 1701 PWH with COVID-19, the relative risk (pitavastatin/placebo) for serious COVID-19 was 0.73 (95% CI, .52–1.03). The treatment effect size for serious COVID-19 fell within the hypothesized range, but the 95% CI crossed 1 given fewer-than-anticipated cases (117 vs 200). Furthermore, 83% reported COVID-19 vaccination by end of study, with a strong protective effect on serious COVID-19 (HR, 0.27; 95% CI, .14–.53;  $P < .0001$ ). A protective statin effect was observed prior to vaccination.

**Conclusions.** Among PWH, statin therapy had no effect on COVID-19 incidence but showed potential to reduce risk of serious COVID-19 prior to COVID-19 vaccination.

**Clinical Trials Registration.** NCT02344290 ([ClinicalTrials.gov](https://clinicaltrials.gov)).

**Keywords.** COVID-19; HIV; statin; REPRIEVE; PWH.

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Among people with HIV (PWH), SARS-CoV-2 infection is common and potentially serious. A meta-analysis of 32 studies conducted in North America, Europe, Asia, and Africa suggested that SARS-CoV-2 infection was at least as common among individuals with vs without HIV [1]. Meanwhile, several studies have indicated that outcomes of COVID-19 may be more severe among PWH [2]. For example, data from the World Health Organization's global platform for the clinical characterization of COVID-19 outcomes among hospitalized patients showed that PWH (vs people without known HIV) had 15% increased odds of a severe presentation and 38% increased odds of in-hospital death [3]. Adjustment for antiretroviral therapy (ART) use and suppressed viremia only partially mitigated the increased odds of these adverse outcomes [3]. Thus,

imperatives exist to better understand effects of medical interventions on COVID-19 incidence and seriousness, specifically among PWH.

Select observational studies conducted among individuals without known HIV have suggested links between clinically prescribed statin therapy (eg, for cardiovascular disease and/or dyslipidemia) and lower risk of severe COVID-19 [4–7]. Mechanisms through which statin therapy may confer protection against COVID-19 severity (but not COVID-19 incidence) have been postulated to include suppression of overly robust virus-induced immune activation, antithrombotic effects, and effects to preserve endothelial function [8]. No prior study has assessed whether statin therapy may protect against serious COVID-19 in a relatively healthy global population of PWH treated with ART.

Due to the timing of its conduct, the Randomized Trial to Prevent Vascular Events in HIV (REPRIEVE) offers a unique opportunity to assess the effects of statin therapy on COVID-19 outcomes among a global cohort. REPRIEVE recruited PWH from 12 countries who were being treated with ART, randomized them to either pitavastatin (4 mg daily) or placebo, and followed them for the development of major adverse cardiovascular events [9, 10]. REPRIEVE participant follow-up ran from March 2015 to August 2023, overlapping with the start and peak of the COVID-19 pandemic. COVID-19–related data collection was implemented in April 2020 to capture all events from 1 January 2020 onward. The current investigation leverages REPRIEVE data to assess COVID-19 incidence in PWH globally and evaluate the effects of pitavastatin therapy for the prevention of COVID-19 (incidence and serious disease).

## METHODS

### Trial Design and Participants

REPRIEVE (NCT02344290) enrolled 7769 participants from March 2015 to July 2019 in 12 countries across 5 Global Burden of Disease (GBD) regions [11] in a multicenter phase 3 trial based on a prospective, double-blind, placebo-controlled design to evaluate pitavastatin calcium (4 mg daily) vs placebo among PWH undergoing ART [9, 10]. The key inclusion criteria were PWH  $\geq 40$  and  $\leq 75$  years of age who were undergoing stable ART for  $\geq 6$  months with a CD4+ count  $> 100$  cells/mm<sup>3</sup> [3] and low to moderate risk for atherosclerotic cardiovascular disease. Primary exclusion criteria included known atherosclerotic cardiovascular disease, diabetes mellitus with low-density lipoprotein cholesterol  $\geq 70$  mg/dL, active cancer, renal dysfunction, decompensated cirrhosis, and statin use. REPRIEVE participants were followed until the trial was stopped for demonstrated efficacy in March 2023, with closeout visits completed by August 2023. Analyses were limited to participants who remained in REPRIEVE follow-up at the start of the

COVID-19 pandemic, defined as 1 January 2020; follow-up time to the end of REPRIEVE was included.

### Patient Consent Statement

The study was approved by the Massachusetts General Brigham Human Research Committee, and each participating clinical research site obtained regulatory entity approvals. Informed consent was obtained from study participants. An independent data and safety monitoring board appointed by the National Institutes of Health reviewed the trial every 6 months.

### Outcomes and Characteristics

COVID-19–related data collection, including COVID-19 diagnoses, treatments, and vaccinations, was implemented in April 2020 to capture all events from 1 January 2020 onward. COVID-19 diagnoses were captured as targeted events regardless of grade and included (1) positive results based on SARS-CoV-2 polymerase chain reaction or rapid antigen test (ie, home test) regardless of symptoms and (2) clinical diagnoses. Participant reports of positive testing were accepted, and source documents were not required. Clinical diagnosis by a health care professional without evidence of a positive test result was also accepted. The primary outcome measure was pre-specified as serious COVID-19, defined as COVID-19 that resulted in hospitalization or death or was life-threatening, per guideline E2A of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use [12]. Incidental COVID-19 diagnosis at or during a hospitalization that did not prolong or complicate the hospitalization course was not included as serious. COVID-19 defined as clinical diagnosis or positive test result was a secondary outcome measure. Demographic and clinical characteristics were defined as previously described [13].

### Statistical Analysis

Pitavastatin therapy was a priori hypothesized to reduce serious COVID-19 by 35%. We determined that with 200 anticipated serious COVID-19 events (total information), there would be 80% power to detect such effect. Interim efficacy analyses pre-specified at 50% and 75% information were foregone in agreement with the data and safety monitoring board, given the direction of the pandemic, increased immunity globally, and availability of vaccines and treatments at that time.

The primary treatment effect was estimated via the relative incidence of serious COVID-19 with prescribed pitavastatin as compared with placebo. In the primary analysis, intercurrent events such as treatment discontinuations and COVID-19 vaccinations were ignored (intention-to-treat policy); deaths without a preceding COVID-19 event of interest were censored as competing events. Event incidence was estimated as the number of events divided by the total person-years (PY) of

follow-up at risk, with follow-up time calculated from 1 January 2020 to the first event or last contact, whichever was earlier. The primary treatment effect was estimated by incidence rate ratios from Poisson regression models, adjusted for GBD region to account for regional differences. A supplementary analysis was limited to participants who remained on the study treatment at the start of the COVID-19 pandemic. Given the anti-inflammatory properties of pitavastatin, it was anticipated that while there may not be an effect on COVID-19 infection, serious disease may be mitigated among those infected. In an analysis among participants with COVID-19, a potential mitigation effect was estimated via common relative risk for serious disease with the Mantel-Haenszel method stratified by GBD region.

As a secondary analytic method, stratified Cox proportional hazards regression modeling was conducted with separate cause-specific baseline hazards by GBD region. The relative cause-specific hazard of pitavastatin vs placebo (ie, hazard ratio [HR]) for COVID-19 outcomes was estimated, and the Wald test is presented. This approach was used in the supporting analysis to estimate the pitavastatin effect during treatment (randomized treatment discontinuation was considered a competing risk/censoring event). Modification of the statin effect following COVID-19 vaccination was evaluated via interaction with time-updated vaccination status.

Statistical comparisons were performed with 2-sided significance tests, with a 5% type I error and 2-sided 95% CIs presented. The analysis was conducted with SAS software (version 9.4 for Linux; SAS Institute Inc).

## RESULTS

### Baseline Characteristics

As of 1 January 2020, 6905 REPRIEVE participants remained in follow-up and were included in this analysis (Supplementary Figure 1). Of those, 49% were in North America and Europe (United States [except Puerto Rico], Canada, Spain), 20% in Latin America and the Caribbean (Brazil, Peru, Haiti, Puerto Rico), 16% in sub-Saharan Africa (Botswana, South Africa, Uganda, Zimbabwe), 8% in Southeast/East Asia (Thailand), and 7% in South Asia (India). Treatment groups were even in size and well balanced with respect to all baseline characteristics (Table 1). There were no substantive differences between these participants and the full cohort of 7769 participants enrolled in REPRIEVE [10]. Regional differences (Supplementary Table 1) are as previously described for the full cohort.

### Study Follow-up

Of the 6905 participants, 90% of the pitavastatin group and 89% of the placebo group remained on the study treatment on 1 January 2020 (Supplementary Figure 1). The last REPRIEVE participant enrolled had been receiving treatment for 5.1 months,

and 95% of the participants had been undergoing treatment for over a year. Another 3% in each treatment group discontinued the study treatment after 1 January 2020 but remained in the study follow-up. In total 89% of each treatment group completed the study. The overall median follow-up from 1 January 2020 was 3.3 years. By the end of follow-up, 84% in the pitavastatin group and 83% in the placebo group reported COVID-19 vaccination (Supplementary Figure 2). There were differences in uptake of the COVID-19 vaccine by GBD region, as previously described [14].

### COVID-19 Incidence

Of the 6905 participants, 1701 reported COVID-19. The overall incidence of COVID-19 was 8.57 (95% CI, 8.17–8.98) per 100 PY. The incidence rate varied across GBD regions, with the highest incidence in Southeast/East Asia and the lowest in South Asia and sub-Saharan Africa (Supplementary Table 2). A total of 117 participants reported serious COVID-19: the incidence was 0.53 (95% CI, .44–.63) per 100 PY, with the highest incidence in South Asia. Across regions, nearly all serious COVID-19 events occurred within the first 2 years of the pandemic (Supplementary Figure 3).

### Statin Effects on COVID-19 Outcomes

The incidence of COVID-19 was 8.79 per 100 PY in the pitavastatin group and 8.35 per 100 PY in the placebo group (incidence rate ratio, 1.05; 95% CI, .96–1.16; Table 2, Supplementary Figure 4). Of the 1701 COVID-19 diagnoses, 1684 were symptomatic, including 15 that resulted in death (8 in the pitavastatin group and 7 in the placebo group). The incidence of serious COVID-19 was 0.45 per 100 PY in the pitavastatin group and 0.60 per 100 PY in the placebo group, representing a 25% lower incidence of serious COVID-19 events with pitavastatin (incidence rate ratio, 0.75; 95% CI, .52–1.08). Among the 1701 participants with COVID-19, the risk of serious COVID-19 was 5.75% in the pitavastatin group as compared with 8.05% in the placebo group (relative risk, 0.73; 95% CI, .52–1.03), reflecting a 27% reduction in serious COVID-19 with pitavastatin. In both treatment groups, COVID-19 treatments were reported in about 24% of those with COVID-19 (Supplementary Table 3).

Based on the secondary analytic approach, the estimated HR was 1.05 (95% CI, .95–1.15) for the pitavastatin effect on COVID-19 and 0.75 (95% CI, .52–1.09) for that on serious COVID-19 (Figure 1), consistent with the incidence rate ratio estimates. Results of the supporting analyses while on study treatment were similar, with a slightly larger estimated effect on serious COVID-19. HR estimates within GBD region subgroups were generally consistent with overall estimates (for interaction with treatment,  $P > .70$ ; Supplementary Figure 5). The estimated pitavastatin effect on serious COVID-19 appeared larger among female participants and among participants without select risk factors for serious COVID-19 (ie, those aged <60

**Table 1. Characteristics of the Participants at Baseline**

	Median (Q1-Q3) or No. (%)		
	Total (n = 6905)	Pitavastatin (n = 3451)	Placebo (n = 3454)
Age,* y	53 (48–57)	53 (48–57)	52 (48–57)
40–49	2302 (33)	1139 (33)	1163 (34)
50–59	3536 (51)	1774 (51)	1762 (51)
≥60	1067 (15)	538 (16)	529 (15)
Sex at birth			
Male	4698 (68)	2346 (68)	2352 (68)
Female	2207 (32)	1105 (32)	1102 (32)
Gender identity			
Cisgender	6769 (98)	3391 (98)	3378 (98)
Transgender spectrum	113 (2)	53 (2)	60 (2)
Not reported	23 (<0.5)	7 (<0.5)	16 (<0.5)
Race <sup>a</sup>			
Black or African American	2835 (41)	1386 (40)	1449 (42)
White	2319 (34)	1166 (34)	1153 (33)
Asian	1097 (16)	551 (16)	546 (16)
Other	654 (9)	348 (10)	306 (9)
Ethnicity <sup>b</sup>			
Hispanic or Latino	596 (18)	310 (19)	286 (18)
Not Hispanic or Latino	2601 (81)	1290 (80)	1311 (81)
Unknown	28 (1)	12 (1)	16 (1)
GBD region			
High income	3394 (49)	1696 (49)	1698 (49)
Latin America and Caribbean	1357 (20)	670 (19)	687 (20)
Southeast/East Asia	582 (8)	298 (9)	284 (8)
South Asia	478 (7)	234 (7)	244 (7)
Sub-Saharan Africa	1094 (16)	553 (16)	541 (16)
Smoking status <sup>c</sup>			
Current	1643 (24)	770 (22)	873 (25)
Former	1684 (24)	868 (25)	816 (24)
Never	3570 (52)	1809 (52)	1761 (51)
Substance use <sup>d</sup>			
Current	126 (2)	59 (2)	67 (2)
Former	1886 (27)	941 (27)	945 (27)
Never	4885 (71)	2448 (71)	2437 (71)
Cholesterol, mg/dL <sup>e</sup>			
Total	186 (162–209)	186 (163–210)	185 (162–209)
LDL, calculated	108 (87–128)	109 (87–129)	108 (87–128)
HDL	48 (39–59)	48 (39–59)	48 (39–59)
Nonstatin lipid-lowering therapy*	186 (3)	101 (3)	85 (2)
Hypertension <sup>f,*</sup>	3117 (45)	1528 (44)	1589 (46)
Antihypertensive medication*	1859 (27)	898 (26)	961 (28)
Diabetes*	190 (3)	107 (3)	83 (2)
ASCVD risk score, %	4.5 (2.1–7.0)	4.4 (2.1–7.0)	4.5 (2.2–7.1)
BMI,* kg/m <sup>2</sup>			
<30	5286 (77)	2610 (76)	2676 (78)
≥30	1613 (23)	838 (24)	775 (22)
Time since HIV diagnosis,* y	15 (10–22)	15 (10–22)	15 (10–22)
Nadir CD4, cells/mm <sup>3</sup>			
<200	3446 (50)	1706 (49)	1740 (50)
200–349	1802 (26)	906 (26)	896 (26)
≥350	1456 (21)	731 (21)	725 (21)
Unknown	201 (3)	108 (3)	93 (3)
Total ART use,* y	12.1 (7.9–17.3)	12.0 (7.9–17.4)	12.1 (7.9–17.3)
ART regimen class*			
NRTI + INSTI	2966 (43)	1475 (43)	1491 (43)

**Table 1. Continued**

	Median (Q1-Q3) or No. (%)		
	Total (n = 6905)	Pitavastatin (n = 3451)	Placebo (n = 3454)
NRTI + NNRTI	2540 (37)	1285 (37)	1255 (36)
NRTI + PI	815 (12)	401 (12)	414 (12)
NRTI sparing	225 (3)	112 (3)	113 (3)
Other NRTI containing	359 (5)	178 (5)	181 (5)
CD4 count,* cells/mm <sup>3</sup>			
<500	2056 (30)	1019 (30)	1037 (30)
≥500	4849 (70)	2432 (70)	2417 (70)
HIV-1 RNA, <sup>g,*</sup> copies/mL			
<LLQ	5549 (87)	2754 (86)	2795 (87)
LLQ to <400	645 (10)	341 (11)	304 (9)
≥400	210 (3)	103 (3)	107 (3)

All statistics are calculated out of participants with data collected. Missing data: smoking status (n = 8), substance use (n = 8), BMI (n = 6), time since HIV diagnosis (n = 4), total ART use (n = 2), and HIV-1 RNA (n = 501).

Abbreviations: ART, antiretroviral therapy; ASCVD, atherosclerotic cardiovascular disease; BMI, body mass index; GBD, Global Burden of Disease; HDL, high-density lipoprotein; INSTI, integrase strand transfer inhibitor; LDL, low-density lipoprotein; LLQ, lower limit of quantitation; NNRTI, nonnucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; REPRIEVE, Randomized Trial to Prevent Vascular Events in HIV.

\*Data as of 1 January 2020; otherwise, data are shown as of REPRIEVE study entry.

<sup>a</sup>Other race includes participants self-identifying as native or indigenous to the enrollment region, more than 1 race (with no single race noted as predominant), or unknown.

<sup>b</sup>Ethnicity presented per National Institutes of Health definition for participants in United States (including Puerto Rico) and Canada only; not applicable in other geographic regions.

<sup>c</sup>Smoking is defined as cigarette smoking.

<sup>d</sup>Substance use includes use of cocaine, methamphetamine, and injection drugs.

<sup>e</sup>Screening lipid panel from clinical care used for eligibility is presented. Fasting was not required if random laboratory values to determine eligibility were within the range specified by the protocol.

<sup>f</sup>Hypertension was defined as any of the following: hypertension diagnosis, use of antihypertensive treatment for elevated blood pressure, systolic blood pressure ≥140 mm Hg, or diastolic blood pressure ≥90 mm Hg.

<sup>g</sup>HIV-1 RNA was captured if available through standard of care. The assays used for testing varied, including assays with LLQs between 20 and 400 copies/mL.

**Table 2. COVID-19 Incidence by Treatment Group**

Outcome: Treatment Group	At Risk		No. With Event	Incidence Rate per 100 PY <sup>a</sup> (95% CI)	Incidence Rate Ratio <sup>b</sup> (95% CI)
	No.	Total PY			
<b>COVID-19</b>					
Pitavastatin	3451	9890	869	8.79 (8.22–9.39)	1.05 (.96–1.16)
Placebo	3454	9967	832	8.35 (7.80–8.93)	...
<b>Serious COVID-19</b>					
Pitavastatin	3451	11 099	50	0.45 (.34–.59)	0.75 (.52–1.08)
Placebo	3454	11 080	67	0.60 (.48–.77)	...
<b>Serious COVID-19 on treatment<sup>c</sup></b>					
Pitavastatin	3123	10 138	42	0.41 (.31–.56)	0.73 (.49–1.08)
Placebo	3058	9936	57	0.57 (.44–.74)	...

No. refers to number of participants.

Abbreviation: CI, confidence interval; PY, person-years.

<sup>a</sup>Event incidence was estimated as the number of participants with events divided by the total person-years of follow-up at risk, with follow-up time calculated from 1 January 2020 to the first event or last contact, whichever was earlier.

<sup>b</sup>Incidence rate ratios (reference: placebo) from Poisson models, adjusted for Global Burden of Disease region.

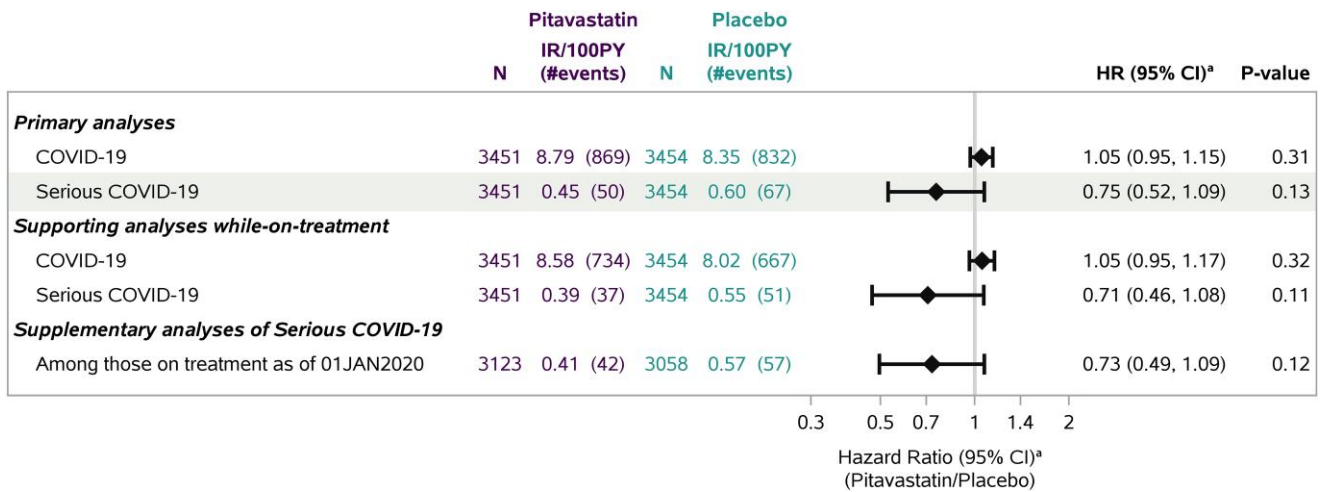
<sup>c</sup>Serious COVID-19 among those on treatment as of 1 January 2020.

years, body mass index <30 kg/m<sup>2</sup>, no hypertension), but with the limited number of events, the confidence intervals were nonconclusive (*P* values >.40; [Supplementary Figure 5B](#)).

In total 83% reported COVID-19 vaccination by end of study, with a 73% reduction in serious COVID-19 events following vaccination (before vs after vaccination: HR, 0.27;

95% CI, .14–.53; *P* < .0001). Of the 117 serious COVID-19 events, 100 (42 in the pitavastatin group, 58 in the placebo group) occurred before COVID-19 vaccination and only 17 following it. In the analysis examining potential statin effect modification following COVID-19 vaccination, there was a 26% reduction in serious COVID-19 events with pitavastatin prior





**Figure 1.** Estimated pitavastatin effect on COVID-19 outcomes. <sup>a</sup>Cause-specific hazard ratio (HR) estimates with 95% CIs from Cox proportional hazards models for time to first event, stratified by Global Burden of Disease region. Deaths without COVID-19 were treated as competing events and censored. In the supporting analyses while on treatment, treatment discontinuations were also treated as competing events and censored. For visual purposes, the HRs with 95% CIs are shown in log scale on the x-axis. 100PY, 100 person-years; IR, incidence rate.

to vaccination (HR, 0.74; 95% CI, .50–1.10) as compared with a 13% reduction following vaccination (0.87; 95% CI, .33–2.25; for interaction,  $P = .77$ ; [Supplementary Figure 6](#)).

## DISCUSSION

Among a global cohort of 6905 PWH randomized to pitavastatin or placebo, the observed overall COVID-19 incidence was 8.57 per 100 PY, varying from 2.80 to 13.74 per 100 PY across regions. The incidence of serious COVID-19 was 0.53 per 100 PY. While statin therapy did not reduce COVID-19 incidence, the incidence of serious COVID-19 was 25% lower. The estimated treatment effect size for serious COVID-19 fell within the hypothesized range, but the fewer-than-anticipated cases (117 vs 200) did not provide sufficient precision to conclude a statin effect. In total 83% reported COVID-19 vaccination by end of study, with a strong protective effect on serious COVID-19. REPRIEVE provides the first randomized comparison assessing statin effects on COVID-19 outcomes among a global cohort of ART-treated HIV, including data during the initial and later years of the COVID-19 pandemic, with findings suggestive of an effect of statins to reduce risk of serious COVID-19. The study also highlights the convincing manner in which vaccination protects against serious COVID-19 among PWH treated with ART globally.

Prior observational studies conducted in the general population assessing statin effects on COVID-19 outcomes have yielded mixed results. Select studies have highlighted a lower risk of severe COVID-19 among individuals with vs without prior statin use [4–7], while other comparative studies have revealed null findings [15, 16]. Overall, however, pooled analysis of

available observational studies favors a protective effect of statins commensurate with what we observed in our randomized trial of PWH. Specifically, a meta-analysis of 48 110 patients enrolled in 9 observational studies showed that prior statin use was associated with a 27% lower risk for severe COVID-19 (pooled adjusted relative risk, 0.83; 95% CI, .57–.94) [17]. Patients enrolled in these observational studies were not known to have HIV but did have clinical indications for statin therapy (including dyslipidemia and established heart disease) [17], in contrast to the population of PWH without clinical indications for statin therapy enrolled in REPRIEVE. The randomized allocation of statin treatment in REPRIEVE (vs clinically driven allocation in prior observational studies) reinforces the validity of our findings.

Experimental studies lend biologic plausibility to the finding that statins may protect against serious COVID-19 [18, 19]. Serious COVID-19 is often associated with an overly robust immune response, triggered when SARS-CoV-2 prompts activation of the NLRP3 inflammasome pathway toward hyperproduction of interleukins 1 $\beta$  and 6. Statins suppress activation of this pathway [18, 19]. Serious COVID-19 is associated with endothelial dysfunction and a prothrombotic state. Statins support salutary endothelial cell function by enhancing endothelial nitric oxide synthase expression, with an attendant increase in nitric oxide production [18, 19]. Statins also help prevent against thrombosis, in part by decreasing expression of tissue factor and other procoagulant proteins [18, 19]. Of note, statins have been shown to protect against serious presentations of other viral illnesses, such as influenza [20, 21]. As to why statins did not appear to reduce COVID-19 incidence in our analysis, this finding, too, has a plausible mechanistic

explanation [18, 19]. On one hand, statins increase expression of ACE2 (angiotensin-converting enzyme 2) [18, 19], which serves as a membrane receptor facilitating SARS-CoV-2 entry. On the other, statin-mediated inhibition of HMGCoA (hydroxymethylglutaryl-coenzyme A) reduces intracellular cholesterol synthesis [18, 19], in turn disrupting the composition of membrane lipid rafts essential to SARS-CoV-2-mediated cellular entry via ACE2 receptors. The net effects of statins on SARS-CoV-2 infection and ensuing COVID-19 incidence may thus be null due to these countervailing influences.

Our study confirmed that among PWH, vaccination had a strong protective effect on serious COVID-19. By the end of the study, 83% reported COVID-19 vaccination, with differences in uptake by GBD region, as previously published [14]. Across regions, nearly all serious COVID-19 events occurred within the first 2 years of the pandemic. That a limited number of serious events occurred later on was related to the uptake of COVID-19 vaccinations and/or COVID-19 treatments, as well as immunity from previous infection. A protective statin effect against serious COVID-19 was observed prior to vaccination. With few serious cases observed following vaccination, statin effect modification by vaccination status could not be evaluated. The aforementioned findings remain relevant 4 years post-pandemic due to recent reports of low COVID-19 booster uptake [22, 23]. Furthermore, although effective treatments are now available to treat potentially serious COVID-19, more serious cases are thought to increase the risk of long COVID or post-COVID-19 conditions (PCCs). Indeed, a meta-analysis including all published studies investigating risk factors and/or predictors of PCCs revealed that patients hospitalized or admitted to the intensive care unit during COVID-19 had a nearly 2.4-fold increased odds of developing PCCs [24]. Meanwhile, COVID-19 vaccination was associated with lower odds of developing PCCs [24]. Thus, prevention of serious COVID-19 through vaccination has ongoing salience.

Overall, in a global cohort of PWH, statin therapy did not affect COVID-19 incidence but showed potential to reduce the risk of serious COVID-19 in the absence of COVID-19 vaccination. Vaccination was protective for serious COVID-19. Potential limitations of our study include the lack of power for meaningful subgroup analyses, as well as ascertainment bias in characterizing COVID-19 incidence due to regional differences in COVID-19 testing and pandemic mitigation strategies. Furthermore, there may have been differences in the availability and uptake of treatment strategies to prevent the progression of COVID-19 to serious COVID-19, as well as in criteria for hospitalization. Given the randomized assignment to statin therapy vs placebo, one would expect access to effective COVID-19 treatments to be balanced between groups. Indeed, our study is unique in illustrating potentially protective effects of randomization to statin therapy vs placebo *prior* to COVID-19 diagnosis among PWH globally. By contrast, other

general-population studies have identified nonsignificant trends toward improved clinical outcomes among individuals randomized to statin therapy vs placebo *after* COVID-19 diagnosis [25, 26], answering a different question. Additional research is needed to understand potential mechanisms of protective statin effects on serious COVID-19, including those among PWH. Mechanistic insights could inform the development of immune-modulatory strategies that are protective against severe systemic sequelae of future novel viral infections. Such research should occur in tandem with systematic public health efforts to maximize access to and uptake of COVID-19 vaccinations and boosters for PWH globally.

### Supplementary Data

**Supplementary materials** are available at *Open Forum 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

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