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Similar Risk of Severe Acute Respiratory Syndrome Coronavirus 2 Infection and Similar Nucleocapsid Antibody Levels in People With Well-Controlled Human Immunodeficiency Virus (HIV) and a Comparable Cohort of People Without HIV

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Background. Within the ongoing AGE_hIV Cohort Study in Amsterdam, we prospectively compared the incidence of and risk factors for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection between human immunodeficiency virus (HIV)–positive and HIV-negative participants. Moreover, we compared SARS-CoV-2 nucleocapsid antibody levels between participants with incident infection from both groups.

Methods. Starting in September 2020, consenting HIV-positive and HIV-negative participants were assessed every 6 months for incident SARS-CoV-2 infection, using combined immunoglobulin (Ig) A/IgM/IgG SARS-CoV-2 nucleocapsid antibody assay. Cumulative incidence of SARS-CoV-2 infection and associated risk factors were assessed from 27 February 2020 through 30 April 2021, using complementary log-log regression. In those with incident SARS-CoV-2 infection, nucleocapsid (N) antibody levels were compared between groups using linear regression.

Results. The study included 241 HIV-positive (99.2% virally suppressed) and 326 HIV-negative AGE_hIV participants. The cumulative SARS-CoV-2 incidence by April 2021 was 13.4% and 11.6% in HIV-positive and HIV-negative participants, respectively ($P = .61$). Younger age and African origin were independently associated with incident infection. In those with incident infection, only self-reported fever, but not HIV status, was associated with higher N antibody levels.

Conclusions. HIV-positive individuals with suppressed viremia and adequate CD4 cell counts had similar risk of SARS-CoV-2 acquisition and similar SARS-CoV-2 N antibody levels after infection compared with a comparable HIV-negative cohort.

Clinical Trial Registration. NCT01466582.

Keywords. SARS-CoV-2; HIV; COVID-19; incidence; serology.

Since the first case of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection was diagnosed in the Netherlands on 27 February 2020, >2.0 million Dutch people have become infected and >18 000 have died of coronavirus disease 2019 (COVID-19) as of 12 October 2021 [1]. Established risk factors for polymerase chain reaction (PCR)–confirmed SARS-CoV-2 infection include older age, male sex, obesity, comorbid conditions, such as diabetes, hypertension, and other cardiovascular diseases, as well as certain conditions characterized by immunodeficiency [2–4].

With respect to people with human immunodeficiency virus (HIV) (PWH), studies investigating the acquisition of SARS-CoV-2 infection and COVID-19 severity conducted in different parts of the world have reported contrasting findings [5–18]. Most studies report a similar [8, 10, 11, 14, 15] or even lower [9, 13] incidence of PCR-confirmed SARS-CoV-2 infection among HIV-positive compared with HIV-negative groups. However, some

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studies have compared the incidence in PWH with data from the general population [8, 9, 13], whereas others have compared it with data from individuals without HIV using population-based surveillance registers [10, 11, 14]. Only one study has compared SARS-CoV-2 incidence in PWH with that in a group of age-, race-, sex- and site-matched HIV-negative people [15].

In the general population, the majority of people with symptomatic SARS-CoV-2 infection, with or without PCR confirmation, develop detectable antibodies against the nucleocapsid (N), spike (S) and receptor-binding domain protein [19–21]. N antibodies are detectable in >91% of individuals after a symptomatic SARS-CoV-2 infection [22, 23]. Vaccination with the currently European Medicines Agency–approved vaccines all trigger an immune response to the SARS-CoV-2 S-protein but do not elicit N antibodies [24–27]. SARS-CoV-2 N antibodies are thus an appropriate marker to detect past SARS-CoV-2 infection, including infection acquired despite partial or complete vaccination. Several studies found that SARS-CoV-2 N antibodies remained detectable for ≥8 months after infection, although levels may decline over time [28, 29].

SARS-CoV-2 S- and N antibody titers are each correlated with disease severity, titers being higher in patients with moderate to severe COVID-19 than in those with asymptomatic or mild symptomatic infection [21, 29–31]. Moreover, one general population study reported that older age and higher body mass index (BMI) were also associated with higher N antibody titers [32]. Few studies have addressed the potential impact of HIV on the antibody response to SARS-CoV-2 infection. One small cross-sectional study reported no significant difference in SARS-CoV-2 N antibody titers between 47 PWH and 35 HIV-negative healthcare workers [33]. Another small study in 28 PWH found no difference in SARS-CoV-2 immunoglobulin (Ig) G N antibody titers between PWH with CD4 cell counts ≥500/μL or <500/μL [8].

To our knowledge, no study has prospectively compared the acquisition of symptomatic or asymptomatic SARS-CoV-2 and the antibody response to infection between people with well-controlled HIV and comparable HIV-negative individuals. We therefore conducted a study of this design nested within our ongoing AGE_hIV cohort study in Amsterdam.

METHODS

Study Design and Participants

The AGE_hIV Cohort Study is a prospective observational cohort study assessing the prevalence and incidence of age-related comorbid conditions and their risk factors in HIV-positive and HIV-negative participants aged ≥45 years. Between 2010 and 2012, HIV-positive participants were recruited at the outpatient HIV clinic of the Amsterdam University Medical Centers, Academic Medical Center location, and HIV-negative participants from either the sexual health clinic or the Amsterdam Cohort Studies on HIV/AIDS at Public Health Service Amsterdam, resulting in a control group with highly similar sociodemographic and behavioral characteristics. At baseline and every 2 years thereafter, patients undergo standardized screening for age-related comorbid conditions, and collection of blood, urine, and stool samples for cryopreservation. Details have been described elsewhere [34].

In August 2020, after the first SARS-CoV-2 epidemic wave in the Netherlands, all AGE_hIV Cohort participants in active follow-up and residing in the Netherlands were asked to participate in a COVID-19 substudy, which includes 5 planned study visits at 6-month intervals between September 2020 and October 2022. During each visit, a blood sample is obtained to assess SARS-CoV-2 humoral and cellular immune responses, and participants complete a standardized study questionnaire.

For the current analysis, data from the first and second study visits (September–October 2020 and March–April 2021) were used. These data capture approximately up to 14 months of possible exposure to SARS-CoV-2 in the Netherlands: from 27 February 2020 (when the first case of COVID-19 was identified in the Netherlands) until 30 April 2021 (end of second COVID-19 substudy visit). Written informed consent was obtained from all participants. The study was approved by the ethics committee of the Amsterdam University Medical Centers, Academic Medical Center location, and is registered at www.clinicaltrials.gov (NCT01466582).

Data Collection

Participant Characteristics

Date of birth, sex at birth, and ethnic origin obtained at the time of enrollment into the AGE_hIV Cohort Study were used for all participants. Other baseline characteristics were obtained from the last available parent cohort study visit before 27 February 2020 and included data on number of prevalent comorbid conditions, lifestyle (ie, smoking, alcohol use, recreational drug use, and other behavioral characteristics), BMI, CD4 and CD8 cell count measurements, last HIV test result for HIV-negative participants, and antiretroviral treatment (ART) and HIV-1 RNA for HIV-positive participants. BMI (calculated as weight in kilograms divided by height in meters squared) was categorized as underweight (<18.5), normal weight (18.5–24.9), overweight (25.0–29.9), or obese (≥30.0). Undetectable HIV-1 plasma viral load was defined as <50 copies/mL, while viral blips up to 200 copies/mL were also considered undetectable.

Questionnaire Data

At each substudy visit, participants were asked to complete a standardized questionnaire (Supplementary Data 1). This questionnaire assessed whether participants had, since the start of the pandemic or the previous study visit, possibly experienced any particular COVID-19–related symptoms and/or had been tested for or received a diagnosis of SARS-CoV-2 infection. Furthermore, questions were included on changes in substance

use, sexual behavior and use of combination ART (cART) in HIV-positive participants or preexposure prophylaxis (PrEP) for HIV in HIV-negative individuals since the start of the coronavirus outbreak and the implementation of social distancing measures in March 2020. Finally, participants were also asked about their self-perceived adherence to and experiences with social distancing measures.

SARS-CoV-2 N Antibody Measurements

SARS-CoV-2–specific N antibodies were measured to determine which participants had become infected with SARS-CoV-2. At each substudy visit, SARS-CoV-2 N antibody levels were measured using the semiquantitative INgezim COVID-19 double recognition assay (Eurofins Ingenasa), which captures the combined IgA, IgM, and IgG antibody response to the SARS-CoV-2 nucleocapsid protein (sensitivity, 100%; specificity, 98.2% [35]). N antibody levels were expressed as a ratio of the sample to positive control for each sample, calculated as follows: [(OD) sample − OD blank)/(OD positive control − OD blank)) × 10, where OD represents optical density. A sample–positive control ratio ≥6 was considered a positive SARS-CoV-2 N antibody response, in accordance with the manufacturer's instructions, and was used to define SARS-CoV-2 infection.

Statistical Analysis

Baseline was defined as 27 February 2020. Follow-up continued until the date of the last available SARS-CoV-2 N antibody measurement, loss to follow-up, or death, whichever occurred first. Baseline characteristics and clinical course of SARS-CoV-2 infection were compared between HIV-positive and HIV-negative participants using Pearson χ^2, Fisher exact, or Wilcoxon rank sum tests, as appropriate.

The cumulative incidence of SARS-CoV-2 infection was estimated during 2 time intervals (from 27 February to 31 October 2020 and from 1 November 2020 to 30 April 2021) and was compared between HIV-positive and HIV-negative participants using a log-rank test. Hazard ratios comparing the incidence of SARS-CoV-2 infection across levels of risk factors, along with their 95% confidence intervals, were estimated using complementary log-log regression with discrete-time survival, while accounting for within-participant correlation with a clustered variance estimator. Included risk factors were age, sex, ethnic origin, BMI, number of concomitantly prevalent comorbid conditions, possible COVID-19–related symptoms, substance use (smoking, alcohol, and recreational drugs), number of sexual contacts, number of household contacts, self-reported compliance with social distancing measures, baseline CD4 and CD8 cell counts and CD4/CD8 ratio, use of PrEP in HIV-negative participants, and HIV-negative participants, and HIV-specific parameters in HIV-positive participants (nadir CD4 count, years since HIV diagnosis and years since start of first ART). The multivariable log-log regression model was built using a backward stepwise selection procedure, including all variables associated with a *P* value <.20 in univariable analyses and subsequently removing all those with a *P* value ≥.05. Biologically plausible interactions between significant variables in the final multivariable model and HIV status were also assessed.

Differences in SARS-CoV-2 N antibody levels across levels of risk factors and their 95% confidence intervals were estimated using linear regression. Risk factors considered in this analysis were HIV status, age, sex, ethnic origin, BMI, number of comorbid conditions, presence of COVID-19–related symptoms, hospitalization for COVID-19, baseline CD4 and CD8 cell counts and CD4/CD8 ratio, use of PrEP in HIV-negative participants, and HIV-specific parameters in HIV-positive participants (nadir CD4 count and years since HIV diagnosis and since start of first ART). The multivariable linear regression model was built using a backward stepwise selection procedure, including all variables associated with a *P* value <.20 in univariable analyses and subsequently removing all those with a *P* value ≥.05. Statistical significance was defined as a 2-sided *P* value <.05. Statistical analyses were carried out using Stata/IC software (version 15.1; StataCorp).

RESULTS

A total of 824 participants were eligible for participation in the AGE_hIV COVID-19 substudy and were invited to participate. Initially, 548 participants provided consent and were included in the first substudy visit. Between the first and second visits, 77 participants dropped out and 19 new consenting participants were included, resulting in 490 individuals participating in the second study visit (Figure 1). In total, 567 participants were included: 326 HIV-negative controls and 241 HIV-positive participants. Compared with AGE_hIV participants who declined participation (n = 257), included participants were significantly more often HIV negative and white and had higher educational levels (Supplementary Table 1). Reasons for declining participation did not differ between HIV-positive and HIV-negative participants (Supplementary Table 2).

The characteristics of included participants are shown in Table 1. The majority were white men (83.4%), and the median age was 60.9 years. HIV-positive participants were more often male and had more comorbid conditions. The median time since HIV diagnosis was 21.4 years, with a median CD4 cell count nadir of 190/μL. At baseline, all HIV-positive participants were receiving cART, except for 1 elite controller. Of those with an available HIV-1 viral load measurement (n = 237), 99.2% were virologically suppressed (<50 copies/mL, n = 235; 50–200 copies/mL, n = 1; >200 copies/mL, n = 1). The current median CD4 cell count of HIV-positive participants was 680/μL; 79.7% had counts ≥500/μL.

At the time of their second study visit, 19 of 202 HIV-positive participants (9.4%) and 8 of 288 HIV-negative participants (2.8%) had received 1 or 2 doses of a COVID-19 vaccine.

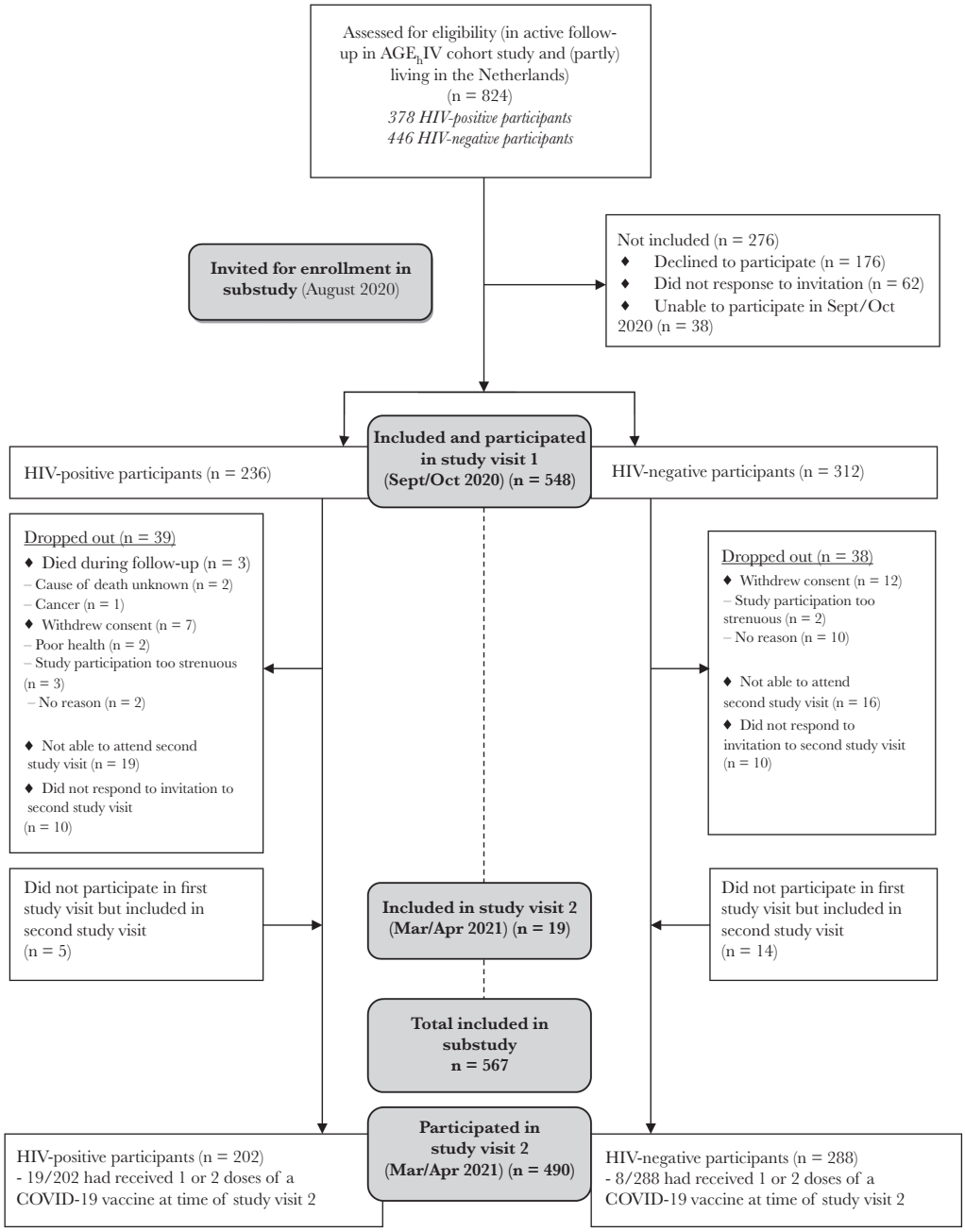

Figure 1. Overview of inclusion and participation during the first (September–October 2020) and second (March–April 2021) study visits of the AGE$_h$IV coronavirus disease 2019 (COVID-19) substudy. Abbreviation: HIV, human immunodeficiency virus.

Because vaccination involves only the SARS-CoV-2 spike protein and does not affect the N antibody assay used in our study, vaccinated participants were not excluded from the analyses.

Cumulative Incidence of SARS-CoV-2 Infection

Between 27 February 2020 and 30 April 2021, a total of 61 participants had positive N antibody responses, indicative of incident SARS-CoV-2 infection. Three additional HIV-positive participants without a detectable N antibody response, but who reported a positive PCR result in the 6 months before the study visit (all 3 also reported possible COVID-19–related symptoms), were also considered to have acquired SARS-CoV-2 infection.

This resulted in an overall cumulative incidence of SARS-CoV-2 infection of 6.2% (n = 34) by 31 October 2020 and 12.3% (n = 64) by 30 April 2021. The cumulative incidence did not differ significantly between HIV-positive and HIV-negative participants (Figure 2). In a sensitivity analysis, in which we considered the 3 above-mentioned participants as not having acquired SARS-CoV-2 infection, the conclusions remained largely unchanged (Supplementary Data 2).

Table 1. Characteristics of Participants Included in the AGE$_n$IV Coronavirus Disease 2019 Substudy (September–October 2020 and March–April 2021), by Human Immunodeficiency Virus Status

	Participants, No. (%)[b]		
Characteristic[a]	HIV Negative (n = 326)	HIV Positive (n = 241)	*P* Value
Age, median (IQR), y	60.3 (56.8–65.9)	61.9 (57.7–66.9)	.06[c]
Age category			
53–59 y	158 (48.5)	97 (40.3)	.12[d]
60–64 y	77 (23.6)	62 (25.7)	
65–69 y	44 (13.5)	48 (19.9)	
≥70 y	47 (14.4)	34 (14.1)	
Male sex at birth	271 (83.1)	221 (91.7)	.003[d]
MSM	231/323 (71.5)	204/240 (85.0)	<.001[d]
Ethnic origin			
White	309 (94.8)	229 (95.0)	.08[e]
African	9 (2.8)	11 (4.6)	
Asian	8 (2.5)	1 (0.4)	
Educational level			
Lower education (primary and secondary)	130/319 (40.8)	111/239 (46.4)	.12[d]
Higher vocational or university education	184/319 (57.7)	120/239 (50.2)	
Other	5/319 (1.6)	8/239 (3.4)	
BMI category[f,g]			
Underweight	2 (0.6)	2 (0.8)	.64[e]
Normal weight	163 (50.0)	133 (55.2)	
Overweight	124 (38.0)	81 (33.6)	
Obese	37 (11.4)	25 (10.4)	
Total comorbid conditions[g]			<.001[d]
0	197 (60.4)	104 (43.2)	
1–2	113 (34.7)	113 (46.9)	
≥3	16 (4.9)	24 (9.9)	
Smoking[g,h]	72 (22.1)	46 (19.1)	.39[d]
Alcohol consumption[g,h]	283 (86.8)	191 (79.3)	.02[d]
Recreational drug use[g,h]	105/306 (34.3)	74/225 (32.9)	.73[d]
Use of PrEP[g,h]	31 (9.5)	NA	…
Time since HIV diagnosis, median (IQR), y	NA	21.4 (15.1–26.9)	…
Time since ART initiation, median (IQR), y	NA	18.6 (12.6–23.7)	…
Use of cART[g]	NA	240 (99.6)	…
Undetectable HIV-1 viral load[g]	NA	235/237 (99.2)	…
Cell count, median (IQR), cells/μL[g]			
CD4 cell count	840 (660–1130)	680 (530–830)	<.001[c]
CD4 cell count nadir	NA	190 (90–260)	…
CD8 cell count	470 (320–630)	730 (520–1000)	<.001[c]
CD4/CD8 cell count ratio[g]	1.90 (1.36–2.51)	0.93 (0.67–1.25)	<.001[c]

Abbreviations: ART, antiretroviral therapy; BMI, body mass index; cART, combination ART; HIV, human immunodeficiency virus; MSM, men having sex with men; NA, not applicable; PrEP, preexposure prophylaxis.

[a]Characteristics at time of invitation to enrollment in the coronavirus disease 2019 substudy (August 2020). '

[b]Data represent no. (%) unless otherwise specified. Denominators are specified where they vary from those in the column heads.

[c]*P* value based on Wilcoxon rank sum test.

[d]*P* value based on Pearson χ^2 test.

[e]*P* value based on Fisher exact test.

[f]BMIs were calculated as was calculated as weight in kilograms divided by height in meters squared and categorized as underweight (<18.5), normal weight (18.5–24.9), overweight (25.0–29.9), or obese (≥30.0).

[g]Last available data before baseline (defined as 27 February 2020).

[h]During the last 6 months.

Self-Reported SARS-CoV-2 Test Results and Potential COVID-19–Associated Signs and Symptoms

Study questionnaire data were available from 60 of the 64 participants with incident SARS-CoV-2 infection (32 HIV-negative and 28 HIV-positive participants) (Table 2). Of these 60 participants, 49 (81.7%) reported having experienced signs or symptoms since the start of the pandemic or the previous study visit, and 11 (18.3%) reported no signs or symptoms. Eighteen of the 60 (30%) had a positive PCR test result, 17 of whom also reported signs or symptoms. In the 49 symptomatic participants,

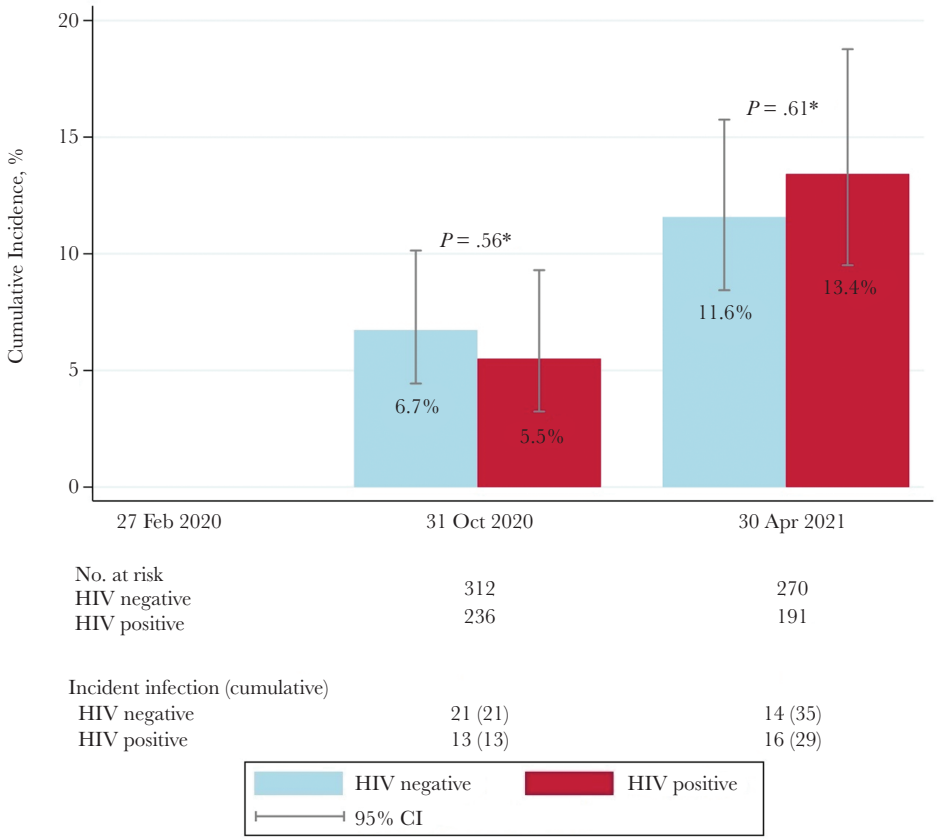

Figure 2. Cumulative incidence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection from 27 February 2020 until 30 April 2021 among participants in the AGE_nIV coronavirus disease 2019 substudy, Amsterdam. Follow-up started on 27 February 2020 and continued until the date of the last SARS-CoV-2 nucleocapsid antibody measurement, loss to follow-up, or death, whichever occurred first. Numbers of participants at risk and numbers with incident infection at the end of each time interval are shown. *P* values are based on log-rank test. Abbreviations: CI, confidence interval; HIV, human immunodeficiency virus.

the most frequently reported symptoms were fatigue, cough, rhinorrhea, muscle ache, headache, and fever. There was no significant difference between both groups, except for "confusion," which was reported more often by HIV-positive participants. Only 2 participants, both HIV negative, reported that they had been admitted for >1 day to a general hospital ward for treatment of COVID-19 with supplemental oxygen.

Factors Associated With Incident SARS-CoV-2 Infection

HIV status was not independently associated with incidence of SARS-CoV-2 infection in both univariable (Supplementary Table 3) and multivariable (Table 3) analyses. In the univariable analysis, the association with self-reported compliance to social distancing did not reach statistical significance. In the multivariable analysis, incident SARS-CoV-2 infection was significantly associated with younger age and being of African origin, with none of these risk factors showing a statistically significant interaction with HIV status.

Factors Associated With SARS-CoV-2 N Antibody Levels

In the 61 participants with incident SARS-CoV-2 infection and detectable N antibody levels, HIV status was not independently associated with SARS-CoV-2 N antibody levels ($P = .53$) at the moment of the first N antibody positive test result. The median N antibody level was 34.2 (IQR, 17.8–37.7) in HIV-positive and 27.6 (15.7–36.0) in HIV-negative participants. In the 57 of 61 participants with available information on self-reported COVID-19 symptoms, HIV status was not associated with N antibody levels in univariable (Supplementary Table 4) or multivariable (Table 4) analyses. Experiencing fever in the 6 months before the positive SARS-CoV-2 N antibody test was the only variable significantly associated with a higher N antibody level in multivariable analysis.

DISCUSSION

During 14 months of possible SARS-CoV-2 exposure, we found no significant difference in the cumulative incidence of infection between HIV-negative participants in our study and those who were HIV-positive and—with few exceptions—were on cART with suppressed viremia and a reasonably high CD4 cell count. Having HIV also did not significantly impact the SARS-CoV-2 N antibody level, as measured by INgezim COVID-19 double recognition assay. Only 2 of our participants, both HIV negative, had been admitted to the hospital for COVID-19, with neither progressing to severe disease or death.

Table 2. Self-Reported PCR Test Results and Possible COVID-19-Associated Signs and Symptoms Since the Start of the COVID-19 Pandemic or the Previous Study Visit in 60 Participants of the AGE$_h$IV COVID-19 Substudy

	Participants		
Outcome or symptoms[a]	HIV-negative (n = 32)	HIV-positive (n = 28)	*P value*[b]
Self-reported SARS-CoV-2 PCR-positive test result	9 (28.1%)[c]	9 (32.1%)[d]	>.99
Symptomatic SARS-CoV-2			.74
Asymptomatic	5 (15.6%)	6 (21.4%)	
Symptomatic	27 (84.4%)	22 (78.6%)	
Experienced symptoms			
Fever	16 (50.0%)	7 (25.0%)	.055
Chills	13 (40.6%)	9 (32.1%)	.79
Rhinorrhoea	18 (56.3%)	15 (53.6%)	>.99
Ear pain	2 (6.3%)	3 (10.7%)	0.83
Cough	18 (56.3%)	15 (53.6%)	.79
Phlegm	12 (37.5%)	11 (39.3%)	>.99
Bloody phlegm	0 (0.0%)	0 (0.0%)	>.99
Sore throat	12 (37.5%)	10 (35.7%)	.78
Shortness of breath	14 (43.8%)	12 (42.9%)	>.99
Loss of smell	9 (28.1%)	8 (28.6%)	.91
Loss of taste	9 (28.1%)	7 (25.0%)	.89
Fatigue	16 (50.0%)	19 (67.9%)	.26
Muscle ache	14 (43.8%)	13 (46.4%)	.35
Headache	12 (37.5%)	15 (53.6%)	.16
Confusion	0 (0.0%)	5 (17.9%)	.03
Nausea	5 (15.6%)	5 (17.9%)	>.99
Vomiting	1 (3.1%)	2 (7.1%)	0.79
Abdominal pain	5 (15.6%)	5 (17.9%)	>.99
Diarrhoea	6 (18.8%)	10 (35.7%)	.15
Skin rash	3 (9.4%)	2 (7.1%)	>.99
Chest pain	5 (15.6%)	4 (14.3%)	>.99
Other	5 (15.6%)	0 (0.0%)	.06
Admitted to the hospital	2 (6.3%)	0 (0.0%)	.50

Abbreviations: *P*, *P*-value; PCR, polymerase chain reaction.

[a]Since the start of the COVID-19 pandemic or the previous study visit.

[b]*P* values based on Fisher's exact test.

[c]Of 9 HIV-negative participants with PCR-positive test results, 8 were symptomatic.

[d]Of 9 HIV-positive participants with PCR-positive test result, 9 were symptomatic.

Table 3. Factors Associated With Severe Acute Respiratory Syndrome Coronavirus 2 Infection Acquired Between 27 February 2020 and 30 April 2021 Among 567 Participants of the AGE$_h$IV COVID-19 Substudy

		Univariable Analysis		Multivariable Analysis	
Factor	Participants, No./Total (%)[a]	HR (95% CI)	*P* Value	aHR (95% CI)[b]	*P* Value
HIV status					
HIV negative	35/326 (10.7)	Reference	.62	Reference	.41
HIV positive	29/241 (12.0)	1.14 (.69–1.86)		1.23 (.75–2.03)	
Age[c]					
53–59 y	39/246 (15.9)	3.69 (1.32–10.32)	.01	3.61 (1.25–10.40)	.02
60–64 y	16/143 (11.2)	2.58 (.86–7.69)		2.57 (.84–7.87)	
65–69 y	5/95 (5.3)	1.19 (.32–4.42)		1.16 (.31–4.33)	
≥70 y	4/83 (4.8)	Reference		Reference	
Ethnic origin					
White	57/538 (10.6%)	Reference	.008	Reference	.02
African	6/20 (30.0%)	3.71 (1.63–8.45)		3.11 (1.40–6.90)	
Asian	1/9 (11.1%)	1.06 (.16–7.10)		1.76 (.29–10.60)	

Abbreviations: aHR, adjusted hazard ratio; CI, confidence interval; HIV, human immunodeficiency virus; HR, hazard ratio.

[a]Number and percentage of participants with incident infection per total amount of participants for each variable category.

[b]aHRs are adjusted for HIV status, age, ethnic origin, and body mass index.

[c]Age at time of severe acute respiratory syndrome coronavirus 2 nucleocapsid antibody test.

Table 4. Factors Associated With Severe Acute Respiratory Syndrome Coronavirus 2 Nucleocapsid (N) Antibody Level at the Time of First N Antibody–Positive Measurement (September–October 2020 or March–April 2021) Among 57 Participants in the AGE$_h$IV Coronavirus Disease 2019 Substudy

	Univariable Analysis		Multivariable Analysis[a]	
Factor	Coefficient (95% CI)	*P* Value	Coefficient (95% CI)	*P* Value
HIV status				
HIV negative	Reference	.53	Reference	.25
HIV positive	2.03 (−4.46 to 8.52)		3.67 (−2.66 to 10.00)	
Self-reported fever[b]				
No	Reference	.005	Reference	.003
Yes	9.07 (2.82– 15.33)		9.73 (3.39–16.06)	

Abbreviations: CI, confidence interval; HIV, human immunodeficiency virus.

[a]Values represent regression coefficients with 95% confidence interval, adjusted for HIV status and reported fever.

[b]In the 6 months prior to the first positive severe acute respiratory syndrome coronavirus 2 nucleocapsid antibody test.

In our cohort, the cumulative incidences on 31 October 2020 and 30 April 2021 were 6.2% and 12.3%, respectively. This is similar to the SARS-CoV-2 seroprevalence for those 50–70 years old in the general Dutch population, which ranged between 4%–6% and 10%–15% in September 2020 and February 2021, respectively [36].

We found no difference in the incidence of SARS-CoV-2 infection between HIV-positive and HIV-negative participants. This is in line with findings from various cross-sectional studies comparing the prevalence of PCR-confirmed SARS-CoV-2 in PWH with that in the general population [8, 10, 11, 14, 18]. In contrast, a systematic review and meta-analysis of the epidemiology and outcomes of COVID-19 in PWH showed that the risk of a PCR-confirmed SARS-CoV-2 infection was significantly higher in HIV-positive than in HIV-negative individuals (risk ratio, 1.24) [37]. Importantly however, the influence of CD4 cell count, current ART use and the degree of HIV suppression on the incidence of COVID-19 in PWH could not be determined in this meta-analysis, as this information was not available for all included studies.

An important limitation of using PCR-based test results in those studies is the possibility that people with asymptomatic SARS-CoV-2 are missed. In a matched case-control observational study, Spinelli et al [38] found that the seroprevalence of SARS-CoV-2 was about 2 times lower among PWH than among HIV-negative people. Of note, participants were matched only for age and date of sampling; the 2 groups were not comparable with regard to sex, ethnic origin, and prevalence of comorbid conditions, which likely affects the observed difference in seroprevalence between the groups. In our study, participants in both groups were highly comparable, which might explain why we found no difference between the groups.

We found that living with HIV was not independently associated with an increased risk of SARS-CoV-2 infection. We did not find an association between incident SARS-CoV-2 infection and HIV-specific parameters. Of note, almost all HIV-positive participants in our study (99.2%) were virologically suppressed, with almost 80% having CD4 cells counts ≥500/μL and virtually none having clinically relevant immunodeficiency. This limits our ability to assess the associations between HIV viral load, CD4 cell count, and acquisition of SARS-CoV-2. However, other studies found no association between HIV viral load or current CD4 cell count and SARS-CoV-2 seropositivity [38, 39]. Moreover, most PCR-based prevalence studies also found no association between HIV-specific factors and SARS-CoV-2 infection [11, 13, 15, 16]. One study from Wuhan suggested a higher risk of SARS-CoV-2 infection in PWH who reported or were inferred to have had interrupted access to cART during the lockdown in the early stage of the epidemic [8].

Younger age and being of African origin were each associated with an increased risk of SARS-CoV-2 infection in our analysis, without a significant interaction between these factors and HIV status. These findings corroborate the higher seroprevalence of SARS-CoV-2 in younger adults observed in other studies [38, 40, 41] and are similar to observations in the general Dutch population [36]. A study among 6 ethnic groups living in Amsterdam likewise showed SARS-CoV-2 seroprevalence to be significantly higher in individuals of Ghanaian origin, compared with those of Dutch origin [42]. This increased risk in individuals of African origin might be associated with socioeconomic factors, including lower income, dependence on public transport, or work in a contact-based profession. Unfortunately, data on such factors were not available for our study.

In participants with an incident SARS-CoV-2 infection, N antibody levels did not differ significantly between HIV-positive and HIV-negative participants, similar to findings reported by another study in which HIV-positive participants (median age, 52 years) all had undetectable viral load [33]. Moreover, in that study antibody titers were similar in HIV-positive participants with CD4 cell counts ≥500/μL and those with counts <500/μL. In contrast, Spinelli et al [38] found significantly lower IgG receptor binding domain antibody levels in participants with HIV than in HIV-negative participants, after adjustment for age and sex. In HIV-positive participants, significantly lower titers

were seen in those with CD4 cell counts <200/μL. Furthermore, Huang et al [8] observed lower SARS-CoV-2 S- and N antibody titers in HIV-positive participants with an HIV viral load >20 copies/mL than in those with a viral load ≤20 copies/mL. Inadequately treated HIV and thus possibly diminished immune responses might explain why both studies found lower SARS-CoV-2 antibody titers in PWH and why our study—in which 99.2% of HIV-positive participants were virologically suppressed—did not find a difference between HIV-positive and HIV-negative participants.

In the current study, participants who reported fever in the 6 months before their N antibody positive test had higher SARS-CoV-2 N antibody levels. These results are in line with observations in several other studies, where both fever [43] and disease severity were correlated with levels of SARS-CoV-2 antibodies [21, 29–31].

To our knowledge, the current study is the first prospective longitudinal systematic comparative assessment of SARS-CoV-2 incidence, irrespective of symptoms, comparing HIV-positive and HIV-negative individuals. A strength of our study is the inclusion of individuals >50 years old with significant comorbid conditions, which may increase their risk of symptomatic SARS-CoV-2 infection.

Furthermore, both HIV-positive and HIV-negative participants—highly comparable with respect to demographic, lifestyle, and behavioral characteristics—have been extensively characterized for the presence of comorbid conditions and their risk factors for ≥10 years. This allows for an unbiased assessment of the potential association between HIV-positive status and acquisition of SARS-CoV-2 infection. Moreover, the additional standardized collection of data on household size and self-reported compliance with social distancing measures allowed us to take these into account in the analysis.

However, the current study also has a number of limitations. First, our findings apply to HIV-positive participants in an urban setting with good access to healthcare and well-controlled HIV infection on cART with a reasonably high CD4 cell count. Thus, findings may not be generalizable to all individuals with HIV. Second, although reasons to decline participation in our COVID-19 substudy were similar for both groups of AGE_hIV Cohort participants, those who declined were more often HIV positive, of African origin, and with a lower educational level. Individuals of African origin were underrepresented in our substudy and at greater risk of acquiring SARS-CoV-2, so our observed incidence may represent an underestimation. Third, with only 2 participants reporting hospitalization for COVID-19, we could not address the extent to which HIV-positive status in our cohort may affect the risk of COVID-19 disease severity. Finally, although we were able to consider many factors in our analysis, we cannot rule out potential unmeasured confounders, such as employment in professions which may have influenced the risk of SARS-CoV-2 exposure.

In conclusion, the risk of SARS-CoV-2 acquisition and N antibody levels after infection in our cohort of HIV-positive individuals with suppressed viremia and adequate CD4 cell counts were similar to those in a comparable cohort of HIV-negative people. This may be different in other populations and parts of the world, including in resource-limited settings, where significant numbers of PWH do not yet have access to or have less immune restoration on cART. Not only should this be investigated in such settings, but it also once more reinforces the urgency for global access to early diagnosis and treatment of HIV.

Supplementary Data

Supplementary materials are available at *The Journal of 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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