Similar risk of SARS-CoV-2 infection and similar nucleocapsid antibody levels in people with well-controlled HIV and a comparable cohort of people without HIV

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BRIEF SUMMARY

HIV-positive individuals with suppressed viremia and adequate CD4 cell counts were not at increased risk of acquiring SARS-CoV-2 and had similar nucleocapsid antibody levels after infection, compared to a comparable cohort of people without HIV.

FOOTNOTES

Conflicts of interests

FWNMW has served on scientific advisory boards for ViiV Healthcare and Gilead sciences. MFSvdL has received independent scientific grant support from Sanofi Pasteur, MSD Janssen Infectious Diseases and Vaccines, and Merck & Co; has served on advisory boards of GlaxoSmithKline and Merck & Co; and has received non-financial support from Stichting Pathologie Onderzoek en Ontwikkeling. MvdV through his institution has received independent scientific grant support and consultancy fees from AbbVie, Gilead Sciences, MSD, and ViiV Healthcare, for which honoraria were all paid to his institution. PR through his institution has received independent scientific grant support from Gilead Sciences, Janssen Pharmaceuticals Inc, Merck & Co and ViiV Healthcare, and has served on scientific advisory boards for Gilead Sciences, ViiV Healthcare, and Merck & Co honoraria for which were all paid to his institution. AB, MB, NAK, LvdH and MLV declare no competing interests.

Part of these data were presented during the 18th European AIDS Conference, London, UK, October 27-30, 2021, abstract number BPD3/8; and during the 14th Netherlands Conference on HIV Pathogenesis, Epidemiology, Prevention and Treatment, November 23, 2021, abstract number O.02.

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ABSTRACT

Background. Within the ongoing AGE$_h$IV Cohort Study in Amsterdam, we prospectively compared the incidence of and risk factors for SARS-CoV-2 infection between HIV-positive and -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 6-monthly for incident SARS-CoV-2 infection, using combined IgA/IgM/IgG SARS-CoV-2 nucleocapsid antibody assay. Cumulative incidence of SARS-CoV-2 infection and associated risk factors were assessed from February 27, 2020 through April 30, 2021 using complementary log-log regression. In those with incident SARS-CoV-2 infection, N-antibody levels were compared between groups using linear regression.

Results. 241 HIV-positive (99.2% virally suppressed) and 326 HIV-negative AGE$_h$IV participants were included in this study. Cumulative SARS-CoV-2 incidence by April 2021 was 13.4% and 11.6% in HIV-positive and HIV-negative participants, respectively (p=0.61). 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 were had similar risk of SARS-CoV-2 acquisition, and had similar SARS-CoV-2 N-antibody levels following infection compared to a comparable cohort of HIV-negative people.

Clinical Trial Registration. NCT01466582.

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

BACKGROUND

Since the first case of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection was diagnosed in the Netherlands on February 27, 2020, over 2.0 million Dutch people have become infected and more than 18,000 people have died of COVID-19 as of October 12, 2021.[1] Established risk factors for PCR-confirmed SARS-CoV-2 infection include older age, male sex, obesity, comorbidities, such as diabetes, hypertension and other cardiovascular diseases, as well as certain conditions characterized by immunodeficiency [2-4]. With respect to people with 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 to HIV-negative groups. However, some studies have compared incidence in PWH to data from the general population[8, 9, 13], whereas others have compared it to individuals without HIV using population-based surveillance registers[10, 11, 14]. Only one study has compared SARS-CoV-2 incidence in PWH to 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 confirmation by PCR, develop detectable antibodies against the nucleocapsid (N), spike (S) and receptor binding domain (RBD) protein.[19-21] N-antibodies are detectable in more than 91% of individuals following 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 at least 8 months after infection, although levels may decline over time.[28, 29]

SARS-CoV-2 S- and N-antibody titres each correlate with disease severity, titres 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 older age and higher BMI to also be associated with higher N-antibody titres.[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 titres between 47 PWH and 35 HIV-negative health care workers.[33] Another small study in 28 PWH found no difference in SARS-CoV-2 IgG N-titres between PWH with CD4 cell counts ≥500 or <500 cells/mm^3.[8]

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$_h$IV cohort study in Amsterdam.

METHODS

Study design and participants

The AGE$_h$IV Cohort Study is a prospective observational cohort study assessing the prevalence and incidence of age-related comorbidities and their risk factors in HIV-1-positive and HIV-negative participants aged 45 years or older. Between 2010 and 2012, HIV-positive participants were recruited at the outpatient HIV-clinic of the Amsterdam University Medical Centers (UMC), location Academic Medical Center (AMC), and HIV-negative participants from either the sexual health clinic or the Amsterdam Cohort Studies on HIV/AIDS at the Public Health Service Amsterdam, resulting in a control group with highly similar socio-demographic and behavioural characteristics. At baseline and every 2 years thereafter, patients undergo standardized screening for age-related comorbidities, and collection of blood, urine and stool for cryopreservation. Details have been described previously.[34]

In August 2020, following the first SARS-CoV-2 epidemic wave in the Netherlands, all AGE$_h$IV Cohort participants in active follow-up and residing in the Netherlands were asked to participate in a COVID-19 substudy, which includes five planned, six-monthly study visits between September 2020 and October 2022. During each visit, blood 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 six-monthly 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 February 27, 2020 (the date at which the first case of COVID-19 was identified in the Netherlands) until April 30, 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 UMC, location AMC and is registered at www.clinicaltrials.gov (NCT01466582).

Data collection

Participant characteristics

Date of birth, sex at birth and ethnic origin obtained at time of enrolment into the AGE$_h$IV Cohort Study were used for all participants. Other baseline characteristics were obtained from the last available parent cohort study visit prior to February 27, 2020, and included data on number of prevalent co-morbidities, lifestyle (i.e., smoking, alcohol use, recreational drug use, other behavioural characteristics), BMI, CD4 and CD8 cell count measurements, last HIV test result for HIV-negative participants and antiretroviral treatment and HIV-1 RNA for HIV-positive participants.

BMI was categorized as underweight (<18.5 kg/m^2), 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 as 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 diagnosed with a SARS-CoV-2 infection. Furthermore, questions were included on changes in substance use, sexual behaviour and use of cART (in HIV-positive participants) or pre-exposure prophylaxis for HIV (PrEP) (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 nucleocapsid (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 semi-quantitative INgezim® COVID-19 double recognition assay (Eurofins Ingenasa, Madrid, Spain), 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 (S/Co) for each sample, which was calculated as *((optical density (OD) sample-OD blank) / (OD positive control-OD blank)) x 10*. An S/Co ratio ≥6 was considered a positive SARS-CoV-2 N-antibody response in accordance with the manufacturer's instructions, and used to define SARS-CoV-2 infection.

Statistical analysis

Baseline was defined as February 27, 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's χ^2 test, Fisher's exact test or Wilcoxon's rank-sum test, as appropriate.

The cumulative incidence of SARS-CoV-2 infection was estimated during two time intervals (i.e., from February 27, 2020 to October 31, 2020 and from November 1, 2020 to April 30, 2021) and was compared between HIV-positive and -negative participants using a log-rank test. Hazard ratios (HR) comparing incidence of SARS-CoV-2 infection across levels of risk factors, along with their 95% confidence intervals (CI), 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 comorbidities, having experienced possible COVID-19 related symptoms, substance use (smoking, alcohol, recreational drugs), number of sexual contacts, number of household contacts, self-reported compliance with social distancing measures, baseline CD4 and CD8 cell counts and CD4/8 ratio, use of PrEP (in 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 $p<0.20$ in univariable analyses and subsequently removing all those with a $p\geq0.05$. 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% CI were estimated using linear regression. Risk factors considered in this analysis were HIV status, age,

sex, ethnic origin, BMI, number of comorbidities, presence of COVID-19 related symptoms, hospitalization for COVID-19, baseline CD4 and CD8 cell counts and CD4/8 ratio, use of PrEP (in 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 linear regression model was built using a backward stepwise selection procedure, including all variables associated with a $p<0.20$ in univariable analyses and subsequently removing all those with a $p\geq0.05$.

Statistical significance was defined as a two-sided $p<0.05$. Statistical analyses were carried out using Stata/IC (version 15.1, College Station, Texas, USA).

RESULTS

A total of 824 participants were eligible for participation in the AGE$_h$IV 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 to AGE$_h$IV participants who declined participation (n=257), included participants were significantly more often HIV-negative, Caucasian and had attained higher education levels (Supplementary Table 1). Reasons for declining participation did not differ between HIV-positive and –negative participants (Supplementary Table 2).

The characteristics of included participants are shown in Table 1. The majority were Caucasian males (83.4%) and the median age was 60.9 years. HIV-positive participants were more often male and had more comorbidities. The median time since HIV diagnosis was 21.4 years, with a median CD4 nadir of 190 cells/mm^3. At baseline, all HIV-positive participants were on cART, except for one 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 cells/mm^3; 79.7% had ≥500 cells/mm^3.

At the moment of their second study visit, 19 of 202 (9.4%) HIV-positive and 8 of 288 (2.8%) HIV-negative participants had received one or two doses of a COVID-19 vaccine. As vaccination only involves 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 February 27, 2020 and April 30, 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-test in the six months prior to the study visit (all three also reported having had possible COVID-19 related symptoms), were also considered as having acquired SARS-CoV-2 infection.

This resulted in an overall cumulative incidence of SARS-CoV-2 infection of 6.2% (n=34) by October 31, 2020 and 12.3% (n=64) by April 30, 2021. The cumulative incidence was not significantly different between HIV-positive and HIV-negative participants (Figure 2).

In a sensitivity analysis, in which we considered the three above mentioned participants as not having acquired SARS-CoV-2 infection, the conclusions remained largely unchanged (Supplementary Data 2).

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 and 11 (18.3%) reported none, since the start of the pandemic or the previous study visit. Eighteen of the 60 (30%) reported having had a positive PCR-test result, 17 of whom also reported having had signs or symptoms. In the 49 symptomatic participants, the most frequently reported symptoms

were fatigue, cough, rhinorrhoea, 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 two participants, both HIV-negative, reported that they had been admitted for >1 day to a general hospital ward with COVID-19 for treatment 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 the univariable (Supplementary Table 3) and multivariable analysis (Table 3). 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=0.53) 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 [IQR 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 both the univariable (Supplementary Table 4) and multivariable analysis (Table 4). Having experienced fever in the six months prior to 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 two of our participants, both HIV-negative, had been admitted to the hospital for COVID-19, with neither having progressed to severe disease or death.

In our cohort, the cumulative incidence on October 31, 2020 and April 30, 2021 was 6.2% and 12.3%, respectively. This is similar to the SARS-CoV-2 seroprevalence for those 50 to 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 to 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 compared to HIV-negative individuals (risk ratio 1.24).[37] Importantly however, the influence of CD4 cell count, current ART use and 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. found that the seroprevalence of SARS-CoV-2 was about two times lower

among PWH compared to HIV-negative people.[38] Of note, participants were only matched for age and date of sampling; the two groups were not comparable with regards to sex, ethnic origin and prevalence of comorbidities, 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 were virologically suppressed (99.2%), with almost 80% having ≥500 CD4 cells/mm^3 and virtually none had a clinically relevant degree of immunodeficiency. This limits our ability to assess the associations between HIV viral load, CD4 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 six ethnic groups living in Amsterdam likewise showed SARS-CoV-2 seroprevalence to be significantly higher in individuals of Ghanaian origin, compared to those of Dutch origin.[42] This increased risk in individuals of African origin might be associated with socio-economic factors, including lower income, being dependent of public

transport or working 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 were not significantly different between HIV-positive and –negative participants, similar to what was reported by another study in which HIV-positive participants (with a median age of 52 years) all had undetectable viral load.[33] Moreover, in that study antibody titres were similar in HIV-positive participants with CD4 cell counts ≥500 cells/mm^3 compared to those with <500 cells/mm^3. In contrast, Spinelli et al. found significantly lower IgG RBD-antibody levels in participants with HIV compared to HIV-negative participants, after adjustment for age and sex. In HIV-positive participants, significantly lower titres were seen in those with CD4 cell counts <200 cells/mm^3.[38] Furthermore, Huang et al. observed lower SARS-CoV-2 S- and N-antibody titres in HIV-positive participants with an HIV viral load >20 copies/mL compared to those with a viral load ≤20 copies/mL.[8] Inadequately treated HIV and thus possibly diminished immune responses might explain why both studies found lower SARS-CoV-2 antibody titres in PWH and why our study - where 99.2% of the HIV-positive participants were virologically suppressed - did not find a difference between HIV-positive and –negative participants.

In our study, participants who reported fever in the six months prior to 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, this is the first prospective longitudinal systematic comparative assessment of SARS-CoV-2 incidence, irrespective of symptoms, between HIV-positive and HIV-negative individuals. A strength of our study is the inclusion of individuals over the age of fifty with significant comorbidity which may increase their risk of symptomatic SARS-CoV-2 infection.

Furthermore, both the HIV-positive and HIV-negative participants – the latter being highly comparable with respect to demographic, lifestyle and behavioural characteristics – have been extensively characterized for the presence of comorbidities and their risk factors for 10-plus 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 also take these into account in the analysis.

However, this 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 had 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$_h$IV Cohort participants, those who declined were more often HIV-positive, of African origin and lower educated. Individuals of African origin were underrepresented in our substudy and at greater risk of acquiring SARS-CoV-2, therefore our observed incidence may represent an underestimation. Third, with only two participants reporting having been hospitalized for COVID-19, we were not able to address to which extent HIV-positive status in our cohort may affect the risk of COVID-19 disease severity. Lastly, although we were able to take a large number of factors into account 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, risk of SARS-CoV-2 acquisition and N-antibody levels following infection in our cohort of HIV-positive individuals with suppressed viremia and adequate CD4 cell counts were similar to 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.

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Conflicts of interests

FWNMW has served on scientific advisory boards for ViiV Healthcare and Gilead sciences. MFSvdL has received independent scientific grant support from Sanofi Pasteur, MSD Janssen Infectious Diseases and Vaccines, and Merck & Co; has served on advisory boards of GlaxoSmithKline and Merck & Co; and has received non-financial support from Stichting Pathologie Onderzoek en Ontwikkeling. MvdV through his institution has received independent scientific grant support and consultancy fees from AbbVie, Gilead Sciences, MSD, and ViiV Healthcare, for which honoraria were all paid to his institution. PR through his institution has received independent scientific grant support from Gilead Sciences, Janssen Pharmaceuticals Inc, Merck & Co and ViiV Healthcare, and has served on scientific advisory boards for Gilead Sciences, ViiV Healthcare, and Merck & Co honoraria for which were all paid to his institution. AB, MB, NAK, LvdH and MLV declare no competing interests.

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FIGURE 1: Overview of inclusion and participation during the first (September/October 2020) and second (March/April 2021) study visit of the AGE$_h$IV COVID-19 substudy.

FIGURE 2: Cumulative incidence of SARS-CoV-2 infection from February 27, 2020 until April 30, 2021 in participants of the AGE$_h$IV COVID-19 substudy, Amsterdam.

Follow-up started on February 27, 2020 and continued until the date of the last SARS-CoV-2 N-antibody measurement, loss to follow-up or death, whichever occurred first. The Y-axis and percentages inside the bars represent the cumulative incidence of SARS-CoV-2 infection. Number of participants at risk and number of those with incident infection at the end of each time interval are given.

* *P* value of log-rank test.

TABLE 1: Characteristics of participants included in the AGE$_h$IV COVID-19 substudy (September/October 2020 and March/April 2021), by HIV status.

	HIV-negative (n = 326)	HIV-positive (n = 241)	*P*
Age in years	60.3 (56.8 – 65.9)	61.9 (57.7 – 66.9)	.063*
Age category			.12**
53 to 59 years	158 (48.5%)	97 (40.3%)	
60 to 64 years	77 (23.6%)	62 (25.7%)	
65 to 69 years	44 (13.5%)	48 (19.9%)	
70 years and older	47 (14.4%)	34 (14.1%)	
Male sex at birth	271 (83.1%)	221 (91.7%)	.003**
MSM	231/323 (71.5%)	204/240 (85.0%)	< .001**
Ethnic origin			.083***
Caucasian	309 (94.8%)	229 (95.0%)	
African	9 (2.8%)	11 (4.6%)	
Asian	8 (2.5%)	1 (0.4%)	
Educational level			.12**
Lower education	130/319 (40.8%)	111/239 (46.4%)	
Higher vocational or university	184/319 (57.7%)	120/239 (50.2%)	
education	5/319 (1.6%)	8/239 (3.4%)	
Other			
BMI category [a, b]			.64***
Underweight	2 (0.6%)	2 (0.8%)	
Normal weight	163 (50.0%)	133 (55.2%)	
Overweight	124 (38.0%)	81 (33.6%)	
Obese	37 (11.4%)	25 (10.4%)	
Total comorbidities [b]			<.001**
0 comorbidities	197 (60.4%)	104 (43.2%)	

1 – 2 comorbidities	113 (34.7%)	113 (46.9%)	
3 or more comorbidities	16 (4.9%)	24 (9.9%)	
Smoking [b, c]	72 (22.1%)	46 (19.1%)	.39**
Alcohol consumption [b, c]	283 (86.8%)	191 (79.3%)	.016**
Recreational drug use [b, c]	105/306 (34.3%)	74/225 (32.9%)	.73**
Use of PrEP [b, c]	31 (9.5%)	NA	…
Time since HIV diagnosis in years	NA	21.4 (15.1 – 26.9)	…
Time since ART initiation in years	NA	18.6 (12.6 – 23.7)	…
CD4 nadir in cells/mm^3 [b]	NA	190 (90 – 260)	…
Use of cART [b]	NA	240 (99.6%)	…
Undetectable HIV-1 viral load [b]	NA	235/237 (99.2%)	…
CD4 cell count in cells/mm^3 [b]	840 (660 – 1130)	680 (530 – 830)	<.001*
CD8 cell count in cells/mm^3 [b]	470 (320 – 630)	730 (520 – 1000)	<.001*
CD4/8 ratio [b]	1.90 (1.36 – 2.51)	0.93 (0.67 – 1.25)	<.001*

Characteristics at time of being invited for enrolment in the COVID-19 substudy (August, 2020). All values are n. (%) or median (interquartile range). a. BMI was categorized as underweight (<18.5 kg/m^2), normal weight (18.5-24.9), overweight (25.0-29.9) or obese (≥30.0). b. Last available data prior to baseline (defined as February 27, 2020). c. During the last 6 months.

Abbreviations: ART, antiretroviral therapy; BMI, body mass index; cART, combination antiretroviral therapy; MSM, men having sex with men; NA, not applicable; P, p-value; PrEP, pre-exposure prophylaxis

* Wilcoxon rank-sum test

** Pearson χ^2 test

*** Fisher's exact test

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.

	HIV-negative (n = 32)	HIV-positive (n = 28)	*P*
Self-reported SARS-CoV-2 PCR-positive test result [a]	9 (28.1%)[b]	9 (32.1%)[b]	1.0
Symptomatic SARS-CoV-2 [a]			.74
Asymptomatic	5 (15.6%)	6 (21.4%)	
Symptomatic	27 (84.4%)	22 (78.6%)	
Experienced symptoms [a]			
Fever	16 (50.0%)	7 (25.0%)	.055
Chills	13 (40.6%)	9 (32.1%)	.79
Rhinorrhoea	18 (56.3%)	15 (53.6%)	1.0
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%)	1.0
Bloody phlegm	0 (0.0%)	0 (0.0%)	1.0
Sore throat	12 (37.5%)	10 (35.7%)	.78
Shortness of breath	14 (43.8%)	12 (42.9%)	1.0
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%)	.028
Nausea	5 (15.6%)	5 (17.9%)	1.0
Vomiting	1 (3.1%)	2 (7.1%)	0.79

Abdominal pain	5 (15.6%)	5 (17.9%)	1.0
Diarrhoea	6 (18.8%)	10 (35.7%)	.15
Skin rash	3 (9.4%)	2 (7.1%)	1.0
Chest pain	5 (15.6%)	4 (14.3%)	1.0
Other	5 (15.6%)	0 (0.0%)	.06
Admitted to the hospital [a]	2 (6.3%)	0 (0.0%)	.50

All values are n. (%). Fisher's exact test was used to compare both groups. a. Since the start of the COVID-19 pandemic or the previous study visit. b. Of 9 HIV-negative participants with PCR-positive test result, 8 were symptomatic. c. Of 9 HIV-positive participants with PCR-positive test result, 9 were symptomatic. Abbreviations: P, p-value; PCR, polymerase chain reaction.

TABLE 3: Factors associated with SARS-CoV-2 infection acquired between February 27, 2020 and April 30, 2021 among 567 participants of the AGE$_h$IV COVID-19 substudy.

		Univariable analysis		Multivariable analysis [a]	
	n/N (%) [b]	HR (95% CI)	*P*	aHR (95% CI)	*P*
HIV status			.62		.41
HIV-negative	35/326 (10.7%)	REF		REF	
HIV-positive	29/241 (12.0%)	1.14 (0.69-1.86)		1.23 (0.75-2.03)	
Age [c]			.012		.018
53 to 59 years	39/246 (15.9%)	3.69 (1.32-		3.61 (1.25-	
60 to 64 years	16/143 (11.2%)	10.32)		10.40)	
65 to 69 years	5/95 (5.3%)	2.58 (0.86-7.69)		2.57 (0.84-7.87)	
70 years and	4/83 (4.8%)	1.19 (0.32-4.42)		1.16 (0.31-4.33)	
older		REF		REF	
Ethnic origin			.008		.018
Caucasian	57/538 (10.6%)	REF		REF	
African	6/20 (30.0%)	3.71 (1.63-8.45)		3.11 (1.40-6.90)	
Asian	1/9 (11.1%)	1.06 (0.16-7.10)		1.76 (0.29-	
				10.60)	

a. Values represent adjusted hazard ratios (aHR) with 95% confidence interval. HR are adjusted for HIV status, age, ethnic origin and BMI. b. Number and percentage of participants with incident infection per total amount of participants for each variable category. c. At moment of SARS-CoV-2 N-antibody test. Abbreviations: aHR, adjusted hazard ratio; CI, confidence interval; HR, hazard ratio; P, p-value; REF, reference group.

TABLE 4: Factors associated with SARS-CoV-2 N-antibody level at the time of first N-antibody positive measurement (either September/October 2020 or March/April 2021) in 57 participants of the AGE$_h$IV COVID-19 substudy.

	Univariable analysis		Multivariable analysis [a]	
	Coeff (95% CI)	*P*	Coeff (95% CI)	*P*
HIV status		.53		.25
HIV-negative	REF		REF	
HIV-positive	+2.03 (-4.46 to +8.52)		+3.67 (-2.66 to +10.00)	
Self-reported fever [b]		.005		.003
No	REF		REF	
Yes	+9.07 (+2.82 to +15.33)		+9.73 (+3.39 to +16.06)	

a. Values represent regression coefficients with 95% confidence interval, adjusted for HIV status and reported fever. b. In the six months prior to the first positive SARS-CoV-2 N-antibody test.

Abbreviations: CI, confidence interval; Coeff, regression coefficient; P, p-value; REF, reference group.

Figure 1

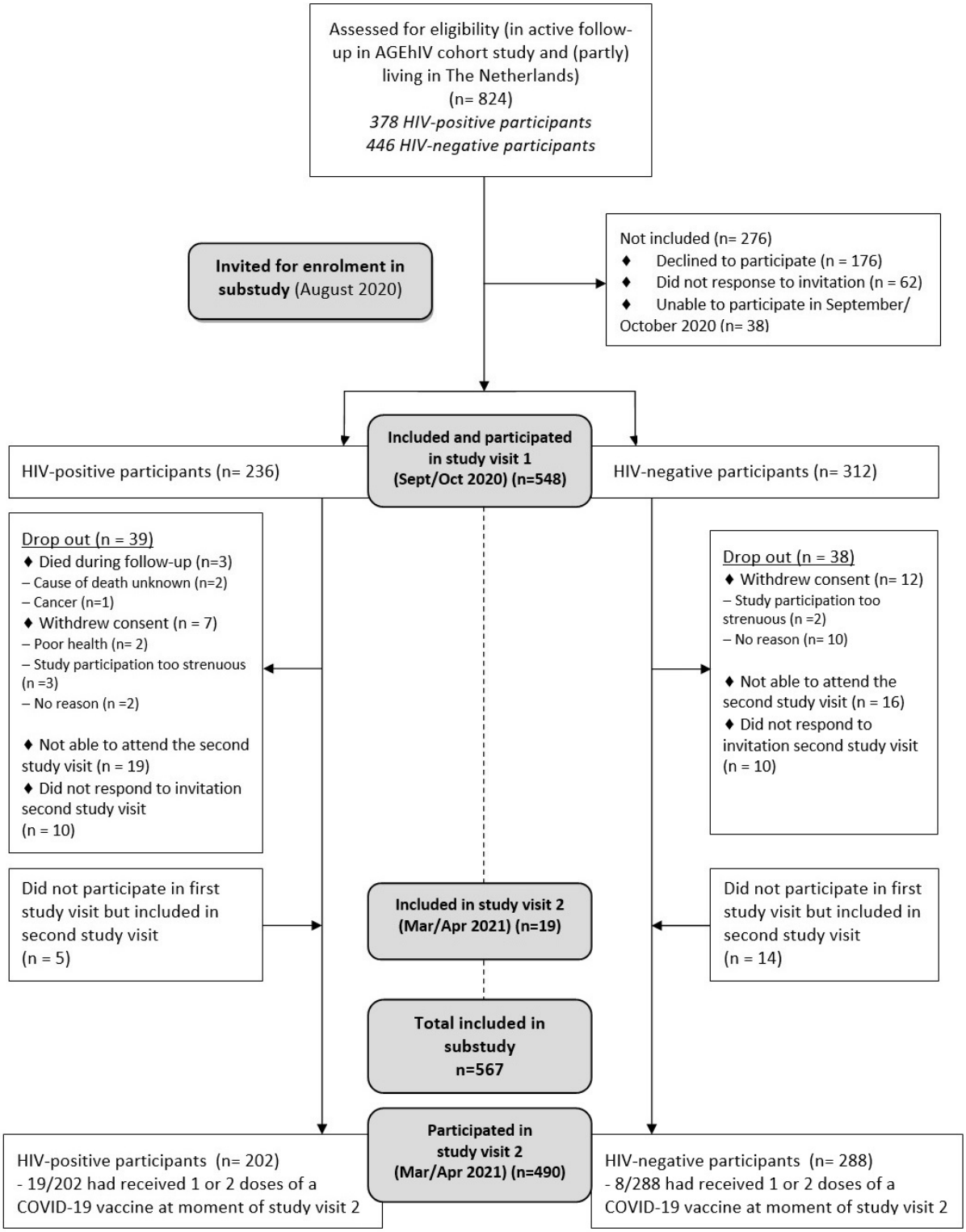
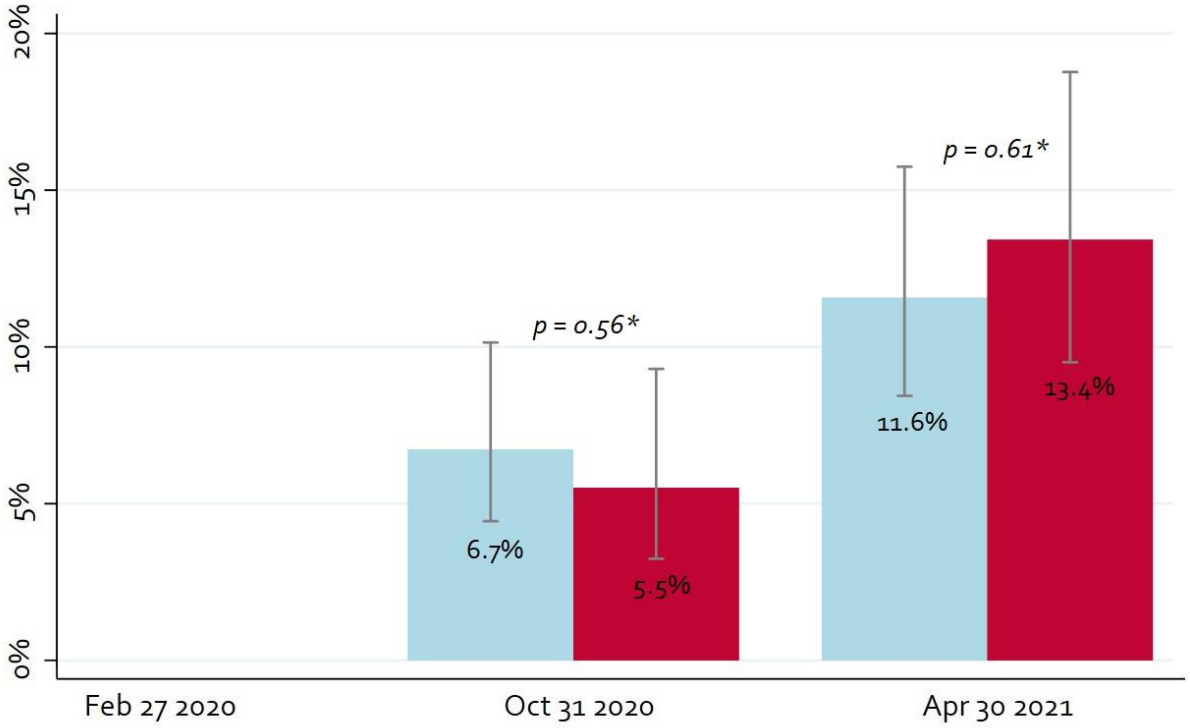

Assessed for eligibility (in active follow-up in AGEhIV cohort study and (partly) living in The Netherlands)
(n= 824)
378 HIV-positive participants
446 HIV-negative participants
Invited for enrolment in substudy (August 2020)
Not included (n= 276)
♦ Declined to participate (n = 176)
♦ Did not response to invitation (n = 62)
♦ Unable to participate in September/ October 2020 (n= 38)
Included and participated in study visit 1 (Sept/Oct 2020) (n=548)
HIV-positive participants (n= 236)
HIV-negative participants (n= 312)
Drop out (n = 39)
♦ Died during follow-up (n=3)
– Cause of death unknown (n=2)
– Cancer (n=1)
♦ Withdrew consent (n = 7)
– Poor health (n= 2)
– Study participation too strenuous (n =3)
– No reason (n =2)
♦ Not able to attend the second study visit (n = 19)
♦ Did not respond to invitation second study visit (n = 10)
Drop out (n = 38)
♦ Withdrew consent (n= 12)
– Study participation too strenuous (n =2)
– No reason (n= 10)
♦ Not able to attend the second study visit (n = 16)
♦ Did not respond to invitation second study visit (n = 10)
Did not participate in first study visit but included in second study visit (n = 5)
Included in study visit 2 (Mar/Apr 2021) (n=19)
Did not participate in first study visit but included in second study visit (n = 14)
Total included in substudy n=567
Participated in study visit 2 (Mar/Apr 2021) (n=490)
HIV-positive participants (n= 202)
- 19/202 had received 1 or 2 doses of a COVID-19 vaccine at moment of study visit 2
HIV-negative participants (n= 288)
- 8/288 had received 1 or 2 doses of a COVID-19 vaccine at moment of study visit 2

Figure 2



	Feb 27 2020	Oct 31 2020	Apr 30 2021
Number at risk			
HIV-negative		312	270
HIV-positive		236	191
Incident infection (cumulative)			
HIV-negative		21 (21)	14 (35)
HIV-positive		13 (13)	16 (29)

HIV-negative HIV-positive
95% confidence interval