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Original article

Major cardiovascular events after COVID-19 in people with HIV

Raquel Martín-Iguacel [1, 2, *], Sergio Moreno-Fornés [1], Andreu Bruguera [1, 3, 4], Jordi Aceitón [1], Daniel Kwakye Nomah [1, 5], Ana González-Cordón [6], Pere Domingo [7], Adrian Curran [8], Arkaitz Imaz [9], David Dalmau Juanola [10], Joaquim Peraire [11, 12], Beatriz Borjabad [13], Laia Arbones Fernandez [14], Isik Somuncu Johansen [2], José M. Miró [6, 12], Jordi Casabona [1, 4, 5], Josep M. Llibre [15, 16], on behalf of the PISCIS study group

[1] Centre of Epidemiological Studies of HIV/AIDS and STI of Catalonia (CEEISCAT), Health Department, Generalitat de Catalunya, Badalona, Spain
[2] Department of Infectious Diseases, Odense University Hospital, Odense, Denmark
[3] CIBER Epidemiologia y Salud Pública (CIBERESP), Spain
[4] Department of Paediatrics, Obstetrics and Gynecology and Preventive Medicine, Universitat Autònoma de Barcelona, Badalona, Spain
[5] Fundació Institut D'investigació en Ciències de la Salut Germans Trias I Pujol (IGTP), Badalona, Spain
[6] Department of Infectious Diseases, Hospital Clínic-Institut d'Investigacions Biomèdiques August Pi I Sunyer, University of Barcelona, Barcelona, Spain
[7] Infectious Diseases Unit, Hospital Universitari de la Santa Creu i Sant Pau, Barcelona, Spain
[8] Department of Infectious Diseases, Hospital Universitari de la Vall d'Hebron, Barcelona, Spain
[9] Department of Infectious Diseases, Hospital Universitari de Bellvitge-Bellvitge Biomedical Research Institute (IDIBELL), University of Barcelona, L'Hospitalet de Llobregat, Barcelona, Spain
[10] Department of Internal Medicine, Hospital Universitari Mútua Terrassa, Barcelona, Spain
[11] Department of Internal Medicine, Hospital Universitari de Tarragona Joan XXIII, IISPV, Universitat Rovira i Virgili, Tarragona, Spain
[12] CIBERINFEC, Instituto de Salud Carlos III, Madrid, Spain
[13] Department of Internal Medicine, Consorci sanitari integral, Hospitalet del Llobregat, Barcelona, Spain
[14] Department of Internal Medicine, Hospital de Mataró, Mataró, Spain
[15] Infectious Diseases Department, University Hospital Germans Trias i Pujol, Badalona, Barcelona, Spain
[16] Fight Infections Foundation, Badalona, Barcelona, Spain

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ABSTRACT

Objectives: To assess the effect of COVID-19 on the postacute risk of cardiovascular events (CVEs) among people with HIV (PWH).
Methods: Population-based matched cohort, including all PWH ≥16 years in the Catalan PISCIS HIV cohort. We estimated the incidence rate of the first CVE after COVID-19, analysed it a composite outcome (2020–2022). We adjusted for baseline differences using inverse probability weighting and used competing risk analysis.
Results: We included 4199 PWH with and 14 004 PWH without COVID-19. The median follow-up was 243 days (interquartile range [IQR]: 93–455), 82% (14 941/18 203) were men, with a median age of 47 years. Overall, 211 PWH with COVID-19 and 621 without developed CVE, with an incidence rate of 70.2 and 56.8/1000 person-years, respectively. During COVID-19 infection, 7.6% (320/4199) required hospitalization and 0.6% (25/4199) intensive care unit admission, 97% (4079/4199) had $CD4^{+}$T-cell ≥200 cells/μL, 90% (3791/4199) had HIV-RNA<50 copies/mL and 11.8% (496/4199) had previous CVE at baseline. The cumulative CVE incidence was higher among PWH after COVID-19 compared with PWH without COVID-19 during the first year (log-rank p=0.011). The multivariable analysis identified significantly increased CVE risk with age, heterosexual men, previous cardiovascular disease (CVD), and chronic kidney or liver disease. COVID-19 was associated with increased subsequent risk of CVE (adjusted hazard ratio 1.30 [95% CI, 1.09–1.55]), also when only including individuals without previous CVD (1.60 [95% CI, 1.11–2.29]) or nonhospitalized patients (1.34 [95% CI, 1.11–1.62]).

* Corresponding author. Raquel Martin-Iguacel, Department of Infectious Diseases, Odense University Hospital, J. B. Winsløws Vej 4, 5000 Odense C, Denmark.
E-mail address: raquel@bisaurin.org (R. Martín-Iguacel).
(R. Martín-Iguacel)

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Discussion: COVID-19 was associated with a 30% increased risk of major CVE in PWH during the subsequent year, suggesting that COVID-19 should be considered an additional CVD risk in PWH in the short term. **Raquel Martín-Iguacel, Clin Microbiol Infect 2024;30:674**

Introduction

Since the advent of antiretroviral therapy (ART) in 1996, HIV-related morbidity and mortality have dropped drastically, and today, people with HIV (PWH) timely diagnosed and starting treatment with preserved CD4$^+$T-cell count have a life expectancy close to the general population [1–3]. However, improved survival has translated into an increased burden of age-related noninfectious comorbidities, such as cardiovascular disease (CVD), which tends to occur at younger ages [1,4] and whose risk is estimated to be 1.5–2-fold increase compared with the general population [5,6].

Acute COVID-19, caused by SARS-CoV-2, emerged in late 2019 and has caused more than 450 million cases worldwide [7]. Several studies have linked COVID-19 infection with an increased risk of adverse cardiovascular outcomes in the general population, both in the acute phase and after recovery from the infection [8–13]. However, the effect of COVID-19 on CVD among PWH, with an a priori elevated risk of cardiovascular events (CVEs), has not yet been explored.

We aimed to assess the effect of COVID-19 on incident major CVE among PWH in a population-based prospective cohort study.

Methods

Setting

In July 2023, Catalonia had a population of 7.98 million citizens and an estimated adult prevalence of HIV infection of 0.4%. The Catalan healthcare system provides universal, tax-funded healthcare to all citizens.

Study design and data sources

We conducted a population-based matched cohort study in Catalonia, Spain. Data were retrieved from the PISCIS HIV cohort (Catalonian and Balearic Islands) and PADRIS (Public Data Analysis for Health Research and Innovation Program). The design of PISCIS is described elsewhere [14]. Briefly, PISCIS is an ongoing, prospective, multicentre, population-based cohort that includes all PWH aged ≥16 years followed in one of the 16 collaborating hospitals, representing 84% of all PWH in Catalonia, from 1998 to 2023. Data are updated yearly.

PADRIS is a central research-oriented database that gathers and crossmatches real-world health data generated by the public health systems (SISCAT). The database includes individual-level laboratory, microbiology, prescription, disease surveillance data, and comorbidity data from hospital discharge and primary healthcare diagnoses from 2005 [15].

We linked PISCIS with PADRIS to obtain data on SARS-CoV-2 diagnosis, comorbidities, hospitalization, and clinical and mortality outcomes (Supplementary methods and Table S1).

Study period

March 1, 2020, through July 1, 2022.

Ethics approval

The PISCIS cohort has been approved by Germans Trias University Hospital's Clinical Research Ethics Committee (EO-11-108). Patient data extraction is allowed by the 203/2015 Decree from the Catalan Health Department. All data are anonymized.

Study population

In the COVID-19 group, we included all PWH aged ≥16 years from PISCIS who had been diagnosed with COVID-19 in the study period (Fig. S1).

COVID-19 was defined by a positive SARS-CoV-2 nucleic acid amplification, or antigen detection from respiratory samples and the date of the first positive test was assigned as the index date. This group was compared with the rest of PWH from PISCIS without evidence of COVID-19 infection during the study period.

To ensure similar follow-up times in both groups, we randomly generated an index date in the control group based on the distribution of index dates in the COVID-19 group. To have balanced groups regarding COVID-19 vaccination, comorbidity and risk factors, a logistic regression obtained the weights of having a COVID-19 diagnosis of the inverse probability weighting (IPW). Variables included in the model were sex, age at COVID-19 diagnosis, HIV risk groups, CD4$^+$T-cell count at index date (<200 vs. ≥200 cells/μL), COVID-19 vaccination (≥1 dose), and baseline CVD-related comorbidities (chronic kidney, liver or lung disease, diabetes, solid and haematological neoplasms, hypertension, and dyslipidaemia).

Charlson comorbidity scores at baseline were calculated in both groups [16], excluding cardiovascular-related comorbidities. The socioeconomic status, based on the socioeconomic deprivation level index created by the Catalan Government (Supplementary methods) was described [17].

Outcome measures

The primary outcome was time to first incident CVE, analysed as a composite outcome, including ischaemic heart disease, cerebrovascular disease, dysrhythmias, heart failure, inflammatory heart disease (myocarditis and pericarditis), peripheral vascular disease, thromboembolic event (pulmonary thromboembolism and deep venous thrombosis), and other cardiac disorders (Supplementary methods). Only the first event was considered if the individuals experienced more than one outcome.

Covariates

We adjusted for the following baseline covariates in the multivariable model: age, previous CVD, baseline CVD-related comorbidities (as described above), HIV risk groups, region of birth (Spain and migrant), CD4$^+$T-cell count, AIDS-defining event before index date, and COVID-19 diagnosis.

Statistical analysis

Continuous variables were described as the median and interquartile range (IQR), whereas categorical variables were presented as the frequency and percentage of available data.

Individuals were followed from index date to the first CVE hereafter, loss-to-follow-up, death, or end of the observation period (July 1, 2022), whichever occurred first.

The cumulative incidence of the first CVE in the two groups was compared using the Log-rank test.

We estimated the incidence rate (IR) of incident CVE in PWH experiencing COVID-19 compared with PWH without evidence of COVID-19 and estimated the excess burden of CVD based on the difference of IR in both groups.

We performed univariable and multivariable Cox proportional hazards regression models. We adjusted for differences in baseline characteristics described above using IPW, including the weighting in the competing risk model. We provided hazard ratios (HRs) and their corresponding 95% CI. We performed the multivariable analysis for subgroups of individuals (according to age, ethnicity, transmission group, $CD4^{+}$T-cell count, and comorbidity).

In sensitivity analyses, we stratified the regression analysis by the requirement of hospitalization for any cause, defined as the need for hospitalization >1 day from 7 days before to 28 days after the COVID-19 diagnosis. Furthermore, we repeated the analyses excluding patients with a previous history of CVD before the index date. All analyses were performed using R software (version 4.3.0).

Results

We included 4199 PWH with and 14 004 PWH without confirmed COVID-19 (Fig. S1, Table S2). The median follow-up time was 243 days (IQR: 93–0455). Overall, 211/4199 (5.0%) and 621/14 004 (4.4%) PWH with and without COVID-19 developed a CVE during the study period. This corresponded to an IR of 70.2 (95% CI, 69.9–70.5) and 56.8 (95% CI, 56.7–57.0) per 1000 person-years, respectively, with an excess burden of CVE of 13.3 (95% CI, 2.9–23.9) per 1000 person-years in PWH with COVID-19. Most individuals were males (14 941/18 203, 82%), with a median age of 47 years (IQR: 39–55) and 11% (1962/18 203) had a previous CVE at baseline. During the COVID-19 episode, 320/4199 PWH (7.6%) were hospitalized, and 25/4199 (0.6%) required intensive care unit (ICU) admission (Table 1).

The Kaplan-Meier curves for CVE showed a significant difference in cumulative incidence between COVID-19 positive and negative PWH (log-rank p 0.011), with a shorter time to CVE in PWH experiencing COVID-19 (Fig. 1). The curves between groups overlapped after the first year.

In multivariable analysis, COVID-19 was associated with increased subsequent risk of CVE (adjusted HR [aHR] 1.30 [95% CI, 1.09–1.55]) (Fig. 1 and Table S3). Other risk factors significantly associated with an increased risk for developing CVE included older age (40–59 years aHR 2.11 [95% CI, 1.44–3.10], ≥60 years 3.15 [95% CI, 2.08–4.78]), heterosexual men compared with men who have sex with men (aHR 1.33 [95% CI, 1.04–1.71]), chronic kidney or liver disease (aHR 1.80 [95% CI, 1.28–2.53], and 1.36 [95% CI, 1.04–1.77], respectively), previous CVE (aHR 26.16 [95% CI, 20.61–33.22]), and malignancy (aHR 1.27 [95% CI, 0.99–1.62]; p = 0.057) (Fig. 2).

Overall, the most frequent CVE were ischaemic heart disease (n = 295, 1.6%), heart failure (n = 166, 1.0%), and cerebrovascular events (n = 162, 0.9%). There was a significantly higher rate of thrombotic disorders (0.5% vs. 0.2%; p 0.007), heart failure (1.3% vs.0.8%; p 0.009), and other cardiac disorders (0.7% vs. 0.3%; p 0.001) in PWH with COVID-19 (Table 2).

In sensitivity analysis, the higher incidence of CVE after COVID-19 was present in all subgroups (Fig. 3). Besides, we performed the analysis excluding individuals with previous CVE before study entry, which yielded similar results. The IR of CVE was 16.29/1000 person-years (95% CI, 16.14–16.44) and 12.38/1000 person-years (95% CI, 12.32–12.45) for PWH with and without COVID-19, respectively, and COVID-19 was still associated with an increased risk of CVE in individuals with no previous CVE (aHR 1.60 [95% CI, 1.11–2.29]) (Tables S4–S6).

Furthermore, we stratified the analysis by hospitalization requirement in the COVID-19 population. The comorbidity distribution in these subgroups compared with COVID-19 negative PWH were no longer evenly balanced (Table S7). People with HIV with COVID-19 requiring hospitalization had a shorter time to CVE (log-rank p < 0.001), with the highest event rate occurring in the first 6 months after the COVID-19 episode (Fig. S2). In the univariable Cox analysis, COVID-19 infection was associated with a higher risk of any CVE (HR 2.61 [95% CI. 1.84–3.71]); however, in the adjusted model, only a trend was observed (aHR 1.21 [95% CI, 0.80–1.82]; p 0.089). However, the total number of CVEs was low (n = 43) (Tables S9 and S10).

We also found an increased risk of CVE when comparing PWH with COVID-19 not requiring hospitalization with PWH without COVID-19 (aHR 1.34 [95% CI, 1.11–1.62]) (Tables S10 and S11).

Discussion

This population-based prospective cohort study compared PWH with COVID-19 vs. a control population of PWH without COVID-19 adjusting for baseline characteristics using IPW. After the COVID-19 episode, PWH had a significant 30% increased relative risk of major CVE, assessed as a composite outcome. Although the risk was highest in the early postacute period (first 6 months), it remained increased for a year. Sensitivity analysis identified an increased risk in individuals without previous CVE, indicating that the increased risk also involves PWH who are at a lower risk of CVD. The increased risk after COVID-19 was observed in all PWHs regardless of the need for hospitalization.

To the best of our knowledge, no studies have evaluated the risk of major CVE among PWH after COVID-19. Other studies have described similar findings in the general population both in the acute phase [8–10,18] and in the postacute phase following COVID-19 [11–13]. Two nationwide cohort studies from Sweden and Denmark found an increased short-term risk of myocardial infarction and stroke following COVID-19 in the first 30 days after diagnosis [8,9]. A US cohort of 153 760 individuals with COVID-19 surviving the first 30 days found that beyond the first 30 days after infection, there was a significant 1.5–2-fold increased risk and 1-year burden of any incident CVE, regardless of hospitalization requirement [11]. In another study from the United Kingdom, with 428 650 individuals with COVID-19 without previous diabetes mellitus or CVD and compared with a matched control group, authors found a 6-fold increased risk of CVD in the first 4 weeks after COVID-19, a 50% increased risk from week 5 to 12, returning to premorbid risk thereafter [12].

Another study from the UK Biobank including 17 871 COVID-19 cases and matched controls, reported significantly increased rates of thromboembolic events in both hospitalized and nonhospitalized cases (HR 27.6 [95% CI, 14.5–52.3] and 2.74 [95% CI, 1.38–5.45], respectively), and increased risk for other CVE among hospitalized individuals [13].

The short follow-up time after the COVID-19 event of some of these studies raised questions about the possibility of delayed notifications of the CV outcomes occurring during the acute COVID-19 episode. The study by Xie et al. [11] unequivocally confirmed

Table 1
Characteristics of the study population included after inverse probability weighting

Description of PWH with and without COVID-19 (n = 18 203)				
	PLWH with COVID-19	PLWH without COVID-19	p	SMD
Total	4199 (23.07)	14 004 (76.93)		
Age (y)			<0.001	0.213 (0.179 ± 0.248)
<40	1486 (35.39)	3688 (26.34)		
40-59	2310 (55.01)	8407 (60.03)		
≥60	403 (9.6)	1909 (13.63)		
Age (y), median (IQR)	45.19 (37.32–53.94)	48.85 (40.29–56.46)	<0.001	
Male, *n* (%)	3457 (82.33)	11 484 (82.01)	1	0.008 (−0.026 ± 0.043)
HIV risk groups, *n* (%)			<0.001	0.205 (0.171 ± 0.24)
MSM	2500 (59.54)	7120 (50.84)		
Heterosexual men	483 (11.5)	2125 (15.17)		
Women infected through sex	580 (13.81)	1882 (13.44)		
IDU	384 (9.15)	1867 (13.33)		
Other	105 (2.5)	428 (3.06)		
Unknown	147 (3.5)	582 (4.16)		
Birth area, *n* (%)			<0.001	0.173 (0.138 ± 0.207)
Spain	2329 (55.47)	8668 (61.9)		
Migrant	1870 (44.53)	5261 (37.57)		
Unknown	0 (0)	75 (0.54)		
CD4 cell count at COVID-19 diagnosis			0.085	0.032 (−0.003 ± 0.066)
<200	120 (2.86)	478 (3.41)		
≥200	4079 (97.14)	13 526 (96.59)		
CD4 cell count at COVID-19 diagnosis, median (IQR)	688 (510–909.5)	698 (498.75–937)	0.174	
Viral load at COVID-19 diagnosis			0.003	0.061 (0.026 ± 0.095)
Undetectable (<50 copies/mL)	3791 (90.28)	12 520 (89.4)		
Detectable	270 (6.43)	1096 (7.83)		
Unknown	138 (3.29)	388 (2.77)		
AIDS before COVID-19, *n* (%)	586 (13.96)	2290 (16.35)	<0.001	0.067 (0.032 ± 0.101)
Income, *n* (%)			<0.001	0.645 (0.61 ± 0.68)
None economic deprivation	2184 (52.01)	5371 (38.35)		
Mild economic deprivation	694 (16.53)	2133 (15.23)		
Moderate/Severe economic deprivation	1203 (28.65)	3232 (23.08)		
Unknown	118 (2.81)	3268 (23.34)		
ART backbone at COVID-19 diagnosis			<0.001	0.098 (0.064 ± 0.133)
TAF/TDF	2260 (53.82)	7557 (53.96)		
ABC	669 (15.93)	2637 (18.83)		
Other	579 (13.79)	1596 (11.4)		
Unknown	691 (16.46)	2214 (15.81)		
Anchor treatment at COVID-19 diagnosis			0.012	0.063 (0.029 ± 0.098)
InSTI	1895 (45.13)	6017 (42.97)		
PI	479 (11.41)	1759 (12.56)		
NNRTI	561 (13.36)	2089 (14.92)		
Other	278 (6.62)	927 (6.62)		
Unknown	986 (23.48)	3212 (22.94)		
Modified Charlson comorbidity score, *n* (%)			<0.001	0.167 (0.132 ± 0.202)
0	2494 (59.4)	8924 (63.72)		
1	675 (16.08)	1531 (10.93)		
2-3	791 (18.84)	2924 (20.88)		
≥4	239 (5.69)	625 (4.46)		
CVD risk comorbidities				
Chronic kidney disease	106 (2.52)	365 (2.61)	0.812	0.005 (−0.029 ± 0.04)
Chronic liver disease	454 (10.81)	1606 (11.47)	0.25	0.021 (−0.014 ± 0.055)
Chronic lung disease	85 (2.02)	375 (2.68)	0.021	0.043 (0.009 ± 0.078)
Diabetes	43 (1.02)	174 (1.24)	0.288	0.021 (−0.014 ± 0.055)
Haematological neoplasm	572 (13.62)	1566 (11.18)	<0.001	0.074 (0.04 ± 0.109)
Obesity	203 (4.83)	586 (4.18)	0.077	0.031 (−0.003 ± 0.066)
Dyslipidaemia	431 (10.26)	1723 (12.3)	<0.001	0.064 (0.03 ± 0.099)
Hypertension	257 (6.12)	484 (11.53)	<0.001	0.125 (0.091 ± 0.16)
Solid neoplasm	171 (4.07)	490 (3.5)	0.09	0.03 (−0.004 ± 0.065)
Previous CVD at baseline, *n* (%)				
Ischaemic heart disease	116 (2.76)	458 (3.27)	0.109	0.03 (−0.005 ± 0.064)
Cerebrovascular disease	142 (3.38)	417 (2.98)	0.201	0.023 (−0.011 ± 0.058)
Dysrhythmia	92 (2.19)	249 (1.78)	0.096	0.03 (−0.005 ± 0.064)
Heart failure	141 (3.36)	348 (8.29)	0.003	0.052 (0.017 ± 0.086)
Thrombotic disorders	38 (0.9)	83 (0.59)	0.038	0.036 (0.002 ± 0.071)
Inflammatory heart disease	36 (0.86)	64 (0.46)	0.003	0.05 (0.015 ± 0.084)
Peripheral vascular disease	63 (1.5)	199 (1.42)	0.761	0.007 (−0.028 ± 0.041)
Other cardiac disorders	73 (1.74)	174 (1.24)	0.018	0.041 (0.006 ± 0.075)
Any previous CVD at baseline	496 (11.81)	1466 (10.47)	0.015	0.043 (0.008 ± 0.077)
>1 episodes of COVID-19	553 (13.17)			
Hospitalization during COVID-19, *n* (%)	320 (7.62)			
Hospitalization in ICU, *n* (%)	25 (0.6)			
Tobacco consumption			<0.001	0.302 (0.268 ± 0.337)

(*continued on next page*)

Table 1 (*continued*)

Description of PWH with and without COVID-19 (n = 18 203)				
Nonsmoker	1066 (25.39)	2177 (15.55)		
Smoker	1008 (24.01)	3363 (24.01)		
Former smoker	393 (9.36)	935 (6.68)		
Unknown	1732 (41.25)	7529 (53.76)		
COVID-19 vaccination before COVID-19 diagnosis			<0.001	0.33 (0.295 ± 0.365)
No	2181 (51.94)	9508 (67.89)		
Yes	2018 (48.06)	4496 (32.11)		

ABC, abacavir; AIDS, AIDS-defining event; ART, antiretroviral therapy; CVD, cardiovascular disease; CVE, cardiovascular events; ICU, intensive care unit; IDU, injection drug use; IQR, interquartile range; INSTI, integrase strand transfer inhibitor; MSM, men who have sex with men; NNRTI, non-nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; PWH, people with HIV; SMD, standardized mean differences; TAF/TDF, tenofovir Alafenamide/tenofovir disoproxil fumarate.

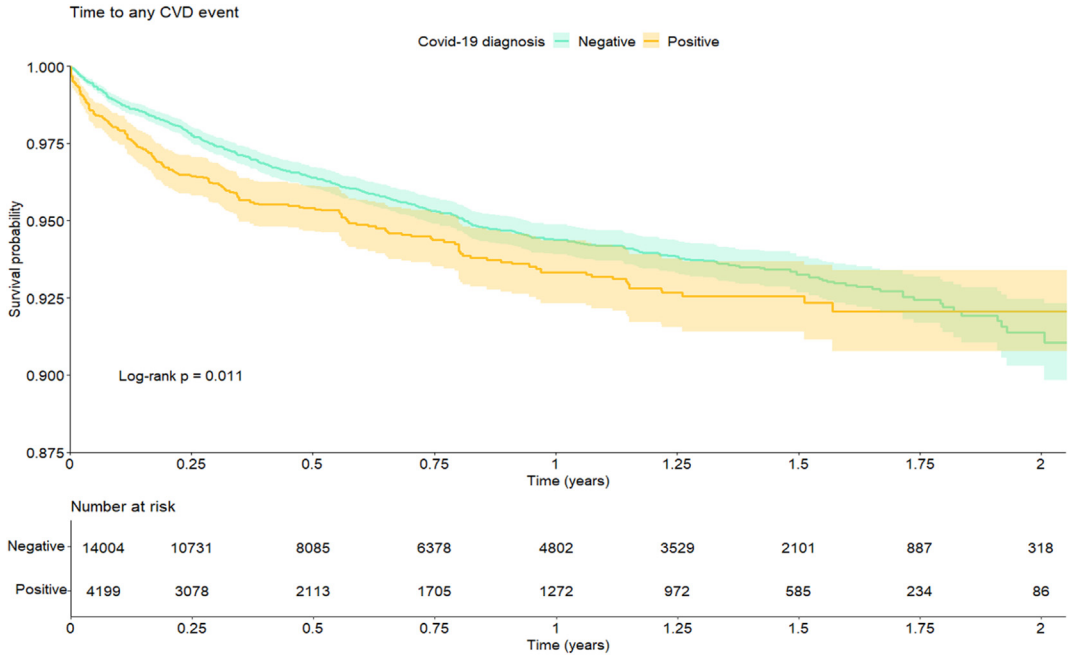

Fig. 1. Kaplan-Meier curves of event-free survival for cardiovascular events in people with HIV (PWH) with and without COVID-19.

that the incidence of CVE truly increased for one year following COVID-19 in the general population [13]. Our study in PWH also shows that the risk of incident CVE extends well beyond the acute phase of COVID-19 and cannot be explained by delayed notifications of CVE.

We found that PWH with COVID-19 had an increased CV risk, even if not requiring hospitalization, especially regarding thromboembolic disorders, heart failure and other CVEs. Even though the absolute rates of CVE in PWH have significantly declined in recent years, they continue to have a 1.5–2-fold greater relative risk compared with individuals without HIV [19,20]. Therefore, the confirmation that the incidence of major CVE is increased the year following COVID-19 in PWH, including those nonhospitalized or without previous CVE, deserves major awareness. As life expectancy in PWH has improved, the burden of age-related comorbidities, such as CVD, is rising in this population. CVD represents one of the leading causes of mortality among PWH, with approximately 10% of deaths being attributed to CVD as the underlying cause [21]. Based on our results, treating physicians should be aware of the additional increased CV risk after COVID-19, regardless of COVID-19 severity or presence of previous CVD, and therefore should be cognizant of this risk in PWH considered as having a low CV risk. These findings have important clinical implications, highlighting the importance of COVID-19 immunization as prevention in PWH and populations at risk for CVD and worse CVD outcomes and the necessity of assessing and managing CVD risk among PWH recovering from COVID-19 and initiating timely prevention and treatment options for these individuals. Current guidelines recommend anticoagulation in moderate-to-severe COVID-19 cases [22]. Anticoagulant prophylaxis after hospital discharge should be weighed against the risk of bleeding in individuals at high risk of thromboembolic events. Some studies are currently evaluating the benefit of long-term anticoagulation prevention in individuals recovering from COVID-19, with results expected in a short timeframe [23,24].

The mechanisms behind the increased CV risk after COVID-19 are not fully elucidated. Direct viral invasion of cardiomyocytes or endothelial cells that may cause cell injury, coagulopathy associated with increased thromboembolic risk, cytokine-mediated plaque destabilization, persistent immune activation, and autoimmunity are some of the proposed mechanisms [25–28]. Although the mechanisms underlying postacute sequelae of SARS-CoV-2 infection in PWH have yet to be fully delineated, early studies have suggested that PWH have increased proportions of PD-1+CD4$^+$-T-cells and levels of certain inflammatory markers (IL-6, TNF-α, and IP-10) and immune dysregulation even in the presence of ART, that place them at increased risk of persistent symptoms. However, the effect on major CVE has not yet been explored [29].

Our study has some strengths. This is a large population-based, prospective multicentre cohort of PWH, including 84% of all PWH

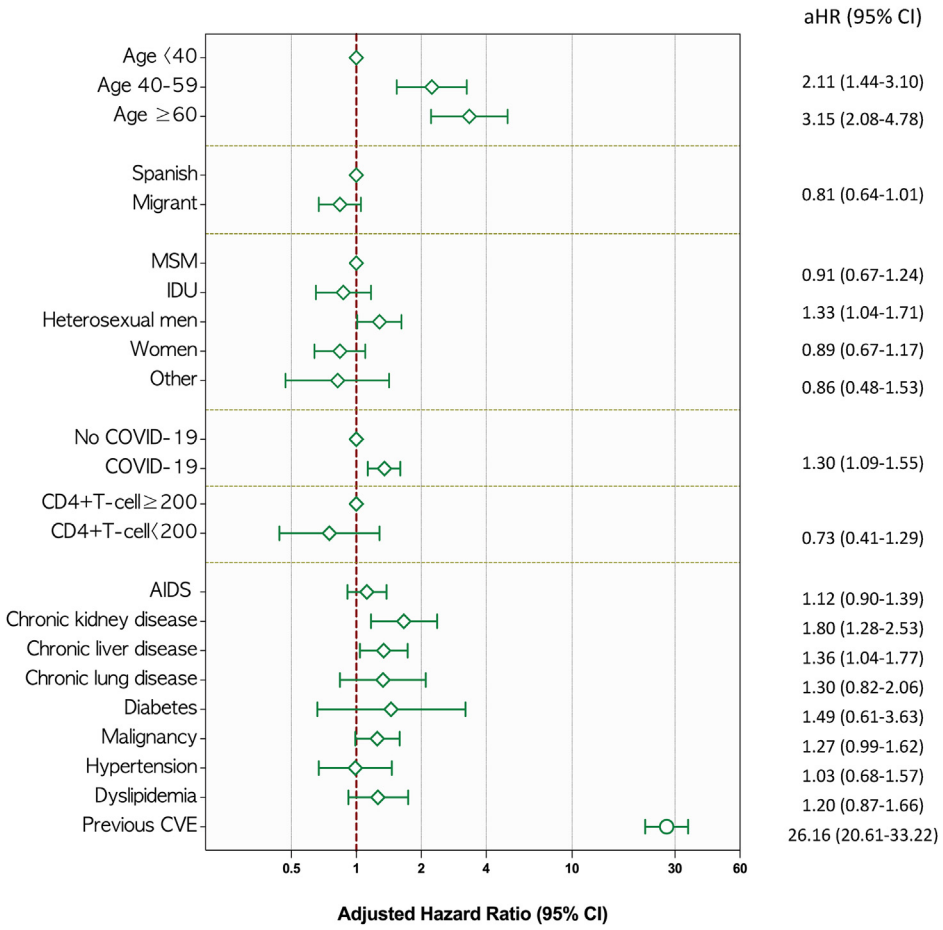

Fig. 2. Multivariable analysis of risk factors for developing incident cardiovascular events during the study period. Adjusted hazard ratios and 95% CIs are presented. aHR, adjusted hazard ratio; AIDS, AIDS-defining event; CVE, cardiovascular events; IDU, injection drug use; MSM, men who have sex with men. Hazard ratio adjusted for age, birthplace, HIV transmission group, COVID-19, $CD4^+$T-cell count at index date, and comorbidities.

Table 2
Cardiovascular events in the study population during the study period

Cardiovascular events in people with HIV			
	COVID-19 positive	COVID-19 negative	p
Any cardiovascular event, *n* (%)	211 (5.03)	621 (4.43)	0.118
Dysrhythmia, *n* (%)	31 (0.74)	101 (0.72)	0.992
Cerebrovascular disease, *n* (%)	40 (0.95)	122 (0.87)	0.69
Ischaemic heart disease, *n* (%)	54 (1.29)	241 (1.72)	0.059
Heart failure, *n* (%), *n* (%)	53 (1.26)	113 (0.81)	0.009
Thrombotic disorders, *n* (%)	21 (0.5)	32 (0.23)	0.007
Inflammatory heart disease, *n* (%)	4 (0.1)	8 (0.06)	0.616
Peripheral vascular disease, *n* (%)	28 (0.67)	90 (0.64)	0.951
Other cardiac disorders[a], *n* (%)	30 (0.71)	47 (0.34)	0.001

[a] Nonischemic cardiomyopathy, cardiac arrest, cardiogenic shock, unspecified atherosclerosis, cardiac and vascular implants and grafts, aneurism of aorta, aortic aneurism and dissection, other aneurism and dissection, and aneurism of pulmonary artery and aortitis.

in active follow-up in Catalonia. We performed adjustment of baseline characteristics, including COVID-19 vaccination using IPW to obtain more comparable groups of PWH when assessing the effect of COVID-19 on CVD. We had access to high-quality, real-world health data, including accurate information on CVE, comorbidities, and mortality. We had information about smoking and although many patients had unknown smoking status, the proportion of current or former smokers did not differ significantly between groups.

Our study also has several limitations. We did not consider the effect of calendar time, or new COVID-19 variants in our study, which might have an effect on CV risk. Viral variants of concern are in constant evolution. The number of different CVE was low with risk for type II errors. Thus, conclusions for specific CVE should be drawn with caution. Among PWH hospitalized with COVID-19, the trend for an increased risk of CVE did not achieve statistical significance.

Despite adjusting for known risk factors the influence of residual confounders, such as lifestyle factors, alcohol consumption, and substance abuse other than injection drug use cannot be ruled out.

People with HIV without COVID-19 could have contracted COVID-19 without being tested, resulting in an underestimation of the risk differential. Finally, the need for hospitalization in PWH with COVID-19 could be due to any cause, and thus, COVID-19 could have been only a secondary diagnosis. Therefore, hospital admission might not indicate the severity of COVID-19 itself, but rather a marker of baseline comorbidity burden.

In conclusion, the first year after COVID-19, we found a significant 30% increased risk for major CVE assessed as a composite outcome in PWH. This higher risk was also confirmed in PWH without previous CVD and in those not requiring hospitalization. COVID-19 in PWH should be considered an additional CVD risk in the short term, emphasizing the importance of prevention through

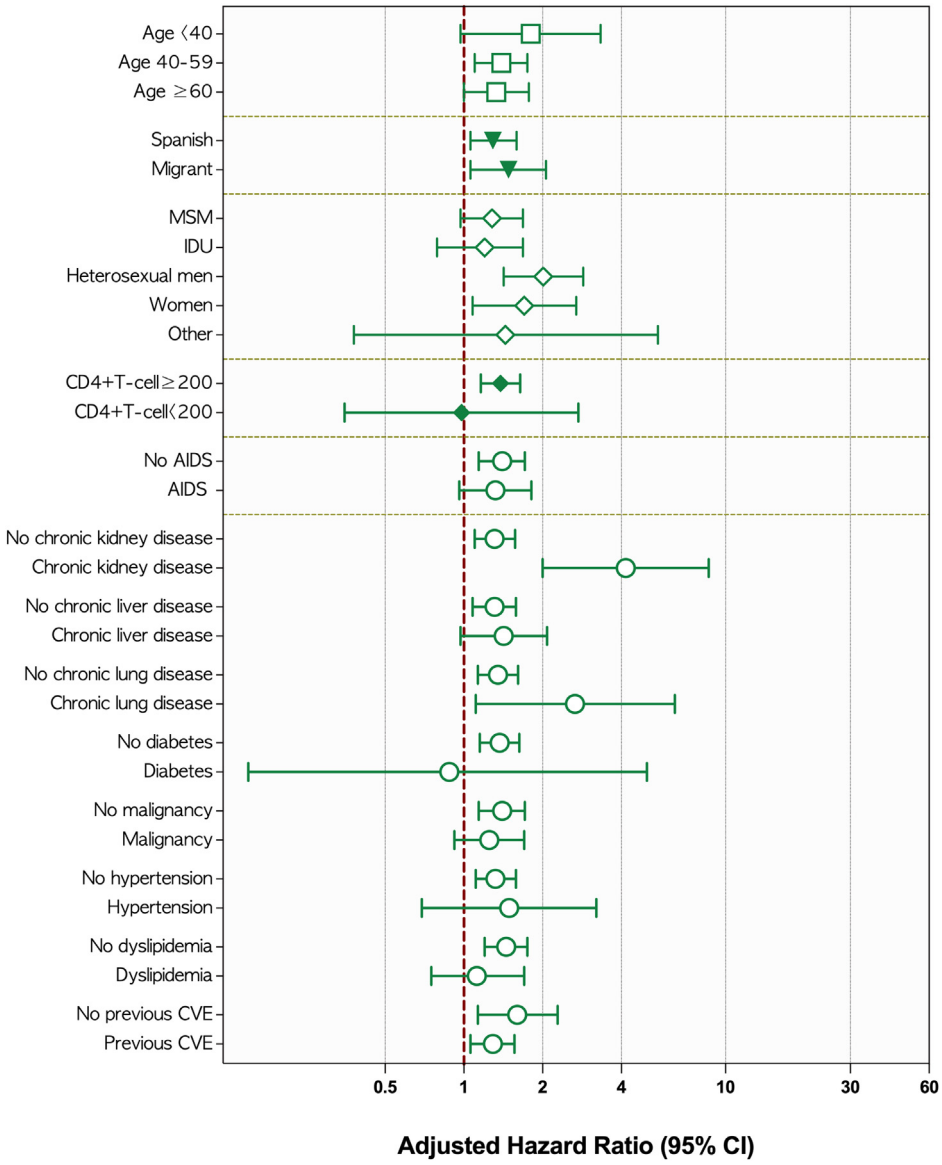

Fig. 3. Subgroup analysis of the risk of incident cardiovascular events after COVID-19 in people with HIV compared with people with HIV without a COVID-19 diagnosis. Adjusted hazard ratios and 95% CIs are presented. AIDS, AIDS-defining event; CVE, cardiovascular events; IDU, injection drug use; MSM, men who have sex with men.

immunization in this population with an a priori elevated CV risk, and the urgent need to leverage CV preventative interventions during this period. CV health should be a major care focus for PWH recovering from COVID-19.

Author contributors

RMI conducted the research and SM analysed the data. RMI, SM and JML wrote the first draft of the manuscript and all authors contributed to the interpretation of the results and revision of the manuscript and gave their final approval to the manuscript.

Transparency declaration

We hereby declare that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as originally planned have been explained.

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organization for the submitted work; no financial relationships with any organizations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cmi.2024.02.006.

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