

# Clinical characteristics, risk factors, and incidence of symptomatic coronavirus disease 2019 in a large cohort of adults living with HIV: a single-center, prospective observational study

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**Background:** It is unclear how characteristics, risk factors, and incidence of coronavirus disease 2019 (COVID-19) in people living with HIV (PLWH) differ from the general population.

**Methods:** Prospective observational single-center cohort study of adult PLWH reporting symptoms of COVID-19. We assessed clinical characteristics, risk factors for COVID-19 diagnosis and severity, and standardized incidence rate ratio for COVID-19 cases in PLWH cohort and in Barcelona.

**Results:** From 1 March 2020 to 10 May 2020, 53 out of 5683 (0.9% confidence interval 0.7–1.2%) PLWH were diagnosed with COVID-19. Median age was 44 years, CD4<sup>+</sup> T cells were 618/ $\mu$ l and CD4<sup>+</sup>/CD8<sup>+</sup> was 0.90. All but two individuals were virologically suppressed. Cough (87%) and fever (82%) were the most common symptoms. Twenty-six (49%) were admitted, six (14%) had severe disease, four (8%) required ICU admission, and two (4%) died. Several laboratory markers (lower O<sub>2</sub> saturation and platelets, and higher leukocytes, creatinine, lactate dehydrogenase, C reactive protein, procalcitonin, and ferritin) were associated with COVID-19 severity. No HIV or antiretroviral-related factors were associated with COVID-19 diagnosis or severity. Standardized incidence rate ratios of confirmed or confirmed/probable COVID-19 in PLWH were 38% (95% confidence interval 27–52%,  $P < 0.0001$ )

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and 33% (95% confidence interval 21–50%,  $P < 0.0001$ ), respectively relative to the general population.

**Conclusion:** PLWH with COVID-19 did not differ from the rest of the HIV cohort. Clinical presentation, severity rate, and mortality were not dependent on any HIV-related or antiretroviral-related factor. COVID-19 standardized incidence rate was lower in PLWH than in the general population. These findings should be confirmed in larger multicenter cohort studies.

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**Keywords:** coronavirus disease 2019, HIV, prospective observational trial, severe acute respiratory syndrome coronavirus 2

## Introduction

Risk for severe coronavirus disease 2019 (COVID-19) increases with age, male sex, and comorbidities [1–3]. Although individuals with immunosuppression have higher fatality rates [4], there is no clear evidence for a higher COVID-19 infection rate or different disease course in people living with HIV (PLWH) than in the general population [5–10]. In hospitalized patients with COVID-19, less than 1% involved PLWH and HIV did not adversely impact survival [3,11,12].

Low ( $<200/\mu\text{l}$ )  $\text{CD4}^+$  cell counts or not being on antiretroviral therapy have been suggested as contributing factors for a higher severity of COVID-19 in PLWH [13,14]. Moreover, other general factors may be over-represented in PLWH. In Spain more than three quarters of PLWH are men [15], and among PLWH over 50 years of age more than 50% have comorbidities [16].

Alternatively, some factors in PLWH might be protective for COVID-19. Antiretroviral therapy was suggested as a protective factor during the severe acute respiratory syndrome epidemic in 2003 [17]. Some antiretroviral agents such as lopinavir/ritonavir are currently being tested for COVID-19 in major trials such as RECOVERY (ClinicalTrials.gov: NCT04381936) or SOLIDARITY (ISRCTN83971151). In-vitro studies have shown that some nucleoside reverse transcriptase inhibitors used as anti-HIV therapy may inhibit the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) RNA-dependent RNA polymerase [18,19]. Moreover, the persistent immune dysregulation that accompanies HIV infection despite effective antiretroviral therapy could play a role in preventing the cytokine storm that is characteristic of severe COVID-19 [20], although this point remains speculative.

We aimed to assess the clinical characteristics and outcome, the risk factors, and the incidence of COVID-19 in a large cohort of PLWH.

## Methods

### Study design and participants

Prospective observational study carried out at Hospital Clinic of Barcelona (Spain). All consecutive PLWH 18 years or older reporting symptoms suggestive of COVID-19 from 1 March 2020 to 10 May 2020 were included. A check-list of COVID-19 symptoms was assessed in each patient [1,21–24]. Demographics, HIV characteristics, and COVID-19-related clinical, laboratory, radiology, treatment, and outcome data were obtained from the hospital database. The study was approved by the local Research Ethics Committee (HCB/2020/0331) and individuals provided informed consent.

### Procedures and definitions

According to the hospital COVID-19 Standard Operating Procedure (SOP), criteria for admission included respiratory rate more than 20 bpm, room air oxygen saturation less than 95%, and any comorbidity; having  $\text{CD4}^+$  T cell counts less than  $350/\mu\text{l}$  was also a criterion for PLWH admission. PLWH had no restrictions regarding therapeutic resources including ICU admission. SARS-CoV-2, influenza A and B, and syncytial respiratory virus were assessed in nasal and pharyngeal swabs by real-time reverse-transcriptase-PCR (RT-PCR). ELISA IgM/IgA/IgG blood test performed 3 weeks or longer after the onset of the symptoms was used to confirm COVID-19 whenever SARS-CoV-2 RT-PCR had not been done.

Confirmed and probable COVID-19 cases were defined according to the European Centre for Disease Prevention and Control (ECDC) Case Definition for COVID-19 [25]. The degree of severity of COVID-19 was defined according to the American Thoracic Society guidelines for community-acquired pneumonia [26]. Last  $\text{CD4}^+$  T-cell count and plasma HIV RNA (viral load) were the most recent values registered at the clinical database, usually within the last 6 months period.

**Statistical analysis**

We calculated absolute frequencies and proportions for categorical variables and median and interquartile range (IQR) or mean and SD for quantitative variables. No imputation was made for missing data. Fisher’s exact or Chi-squared and Wilcoxon Rank Sum tests were used for comparisons. Standardized incidence rates of COVID-19 were estimated along with 95% confidence interval (CI) using a Poisson regression model with robust standard errors. The standardized incidence rate ratio represents the ratio of the number of observed COVID-19 cases in the cohort of PLWH to the number that would be expected if this cohort had the same age and sex-specific rates as in Barcelona. The number of new COVID-19 cases during the period of study was obtained from the Government of Catalonia registry [27] and the age and sex of Barcelona population from the Statistical Institute of Catalonia [28]. All tests were two-tailed and the significance level was set at 0.05. We used REDCap for data storage and STATA (version 15; Stata Corp LLC, College Station, Texas, USA) for statistical analyses.

**Results**

**People living with HIV with symptoms suggestive of coronavirus disease 2019**

By 10 May 2020, 62 PLWH out of 5683 (1.09%) in the cohort had contacted the hospital reporting symptoms suggestive of COVID-19. Nine patients tested negative for SARS-CoV-2 RT-PCR and alternative causes were: pneumococcal pneumonia (*n* = 2), syphilis (*n* = 2), urinary tract infection (*n* = 2), tuberculosis (*n* = 1), acute tonsillitis (*n* = 1), and diabetic ketoacidosis (*n* = 1). COVID-19 was confirmed in 42 cases and probable in 11 cases. No other viral respiratory infections concomitant to SARS-CoV-2 were found.

**Clinical characteristics of coronavirus disease 2019 people living with HIV and outcome**

Characteristics of COVID-19 PLWH are summarized in Table 1. Median age was 44 years; 15 (28%) were older than 50 years and only five (9%) older than 65 years. Eight (15%) were healthcare workers and 17 (46%) had a recent history of a close contact with COVID-19 patients. Twenty-three (43%) patients had at least one comorbidity, 16 (31%) were current smokers, and 11 (21%) were recreational drug users in the context of group sex. Median last CD4<sup>+</sup> T-cell counts and CD4<sup>+</sup>/CD8<sup>+</sup> ratio were 618 cells/μl and 0.90, respectively. Eight (15%) and two (4%) individuals had CD4<sup>+</sup> T-cell counts below 350 and 200 cells/μl, respectively. All but two individuals were on antiretroviral therapy and those treated were virologically suppressed. Forty-four (83%) patients were receiving triple therapy: 15 (28%) a boosted-protease inhibitor-regimen (all of them cobicistat-boosted darunavir), and 35 (66%) a tenofovir-containing regimen.

**Table 1. Characteristics of coronavirus disease 2019 patients.**

Age (years)	44 (36–52)
Female sex, <i>n</i> (%)	8 (15)
BMI (kg/m <sup>2</sup> )	25 (23–27)
Drug addiction	
Tobacco smoking, <i>n</i> (%)	16 (31)
Alcohol abuse, <i>n</i> (%)	24 (48)
Chemsex, <i>n</i> (%)	11 (21)
Comorbidities	
Any, <i>n</i> (%)	23 (43)
≥2, <i>n</i> (%)	21 (40)
Cardiovascular disease, <i>n</i> (%)	2 (9)
Hypertension, <i>n</i> (%)	9 (39)
Diabetes mellitus, <i>n</i> (%)	5 (22)
Chronic renal disease, <i>n</i> (%)	2 (9)
Chronic obstructive pulmonary disease, <i>n</i> (%)	3 (13)
Fatty liver syndrome, <i>n</i> (%)	3 (13)
Neoplasia, <i>n</i> (%)	6 (12)
Prior opportunistic infections, <i>n</i> (%)	13 (25)
HIV characteristics	
Nadir CD4 <sup>+</sup> cells/μl	266 (140–414)
Last CD4 <sup>+</sup> cells/μl	618 (449–834)
Nadir CD4 <sup>+</sup> /CD8 <sup>+</sup> ratio	0.40 (0.19–0.60)
Last CD4 <sup>+</sup> /CD8 <sup>+</sup> ratio	0.90 (0.66–1.20)
Last plasma HIV RNA < 50 copies/l, <i>n</i> (%)	49 (96)
Antiretroviral therapy	
Any, <i>n</i> (%)	51 (96)
Triple therapy, <i>n</i> (%)	44 (83)
InSTI-based, <i>n</i> (%)	29 (55)
PI-based, <i>n</i> (%)	15 (28)
NNRTI-based, <i>n</i> (%)	13 (25)
Tenofovir (TAF or TDF), <i>n</i> (%)	35 (66)
Abacavir, <i>n</i> (%)	9 (17)
Clinical presentation	
Cough, <i>n</i> (%)	45 (87)
Fever, <i>n</i> (%)	42 (82)
Malaise, <i>n</i> (%)	29 (59)
Headache, <i>n</i> (%)	28 (56)
Myalgia, <i>n</i> (%)	27 (54)
Fatigue, <i>n</i> (%)	25 (50)
Diarrhea, <i>n</i> (%)	16 (31)
Anosmia, <i>n</i> (%)	15 (29)
Odynophagia, <i>n</i> (%)	11 (22)
Dyspnea, <i>n</i> (%)	10 (20)
Nausea/vomiting, <i>n</i> (%)	4 (8)
Vital signs at admission	
Heart rate (per minute)	88 (80–96)
SBP (mmHg)	121 (119–132)
DBP (mmHg)	74 (70–80)
Respiratory rate (per minute)	18 (16–23)
Oxygen saturation (%)	98 (96–99)
Laboratory data	
Leukocytes (10 <sup>9</sup> /l), <i>n</i> (%)	6.48 (5.04)
Lymphocytes (10 <sup>9</sup> /l), <i>n</i> (%)	13.11 (7.44)
Platelets (10 <sup>9</sup> /l), <i>n</i> (%)	189 (85)
C-reactive protein (mg/dl), <i>n</i> (%)	8.7 (10.0)
D-dimer (ng/ml), <i>n</i> (%)	873 (1744)
Procalcitonin (ng/ml), <i>n</i> (%)	0.31 (0.66)
Creatinine (mg/dl), <i>n</i> (%)	1.10 (0.33)
AST (U/l), <i>n</i> (%)	36 (15)
ALT (U/l), <i>n</i> (%)	44 (32)
LDH (U/l), <i>n</i> (%)	273 (120)
High-sensitivity troponin I (ng/l), <i>n</i> (%)	886 (2676)
Ferritin (ng/ml), <i>n</i> (%)	467 (516)
Chest radiograph	
Performed, <i>n</i> (%)	38 (72)
Abnormal, <i>n</i> (%)	26 (40)
Bilateral involvement, <i>n</i> (%)	18 (69)
Alveolar pattern, <i>n</i> (%)	7 (25)
Interstitial pattern, <i>n</i> (%)	12 (43)
Opacities, <i>n</i> (%)	8 (29)
Consolidation, <i>n</i> (%)	1 (4)

Data are (median, IQR) unless otherwise stated. AST, aspartate aminotransferase; ALT, alanine aminotransferase; InSTI, integrase strand transfer inhibitor; IQR, interquartile range; LDH, lactate dehydrogenase; NNRTI, nonnucleoside reverse transcriptase inhibitor; PI, protease inhibitor; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.

The median (IQR) time from the onset of the symptoms to medical consultation was 4 (3–7) days. Cough ( $n=45$ , 87%) and fever ( $n=42$ , 82%) were the most common symptoms, while gastrointestinal symptoms including nausea or vomiting ( $n=4$ , 8%) or diarrhea ( $n=16$ , 31%) were rare. Of 38 (72%) patients with a chest radiograph at admission, 26 (70%) had bilateral involvement ( $n=18$ , 69%) or interstitial pattern in ( $n=12$ , 43%) as the most common radiological features.

Twenty-six (49%) patients were admitted. The median (IQR) duration of hospitalization was 4 days (1–9). Four (7.5%) patients required ICU admission and two (4%) died. Among the PLWH admitted ( $n=26$ , 49%), all but two received any specific COVID-19 therapy: 21 received triple therapy with a combination of lopinavir/ritonavir, azithromycin, and hydroxychloroquine, and five received dual therapy with a combination of two of the previous three drugs. Two (8%) individuals also received IFN-1 $\beta$ , seven (28%) systemic glucocorticoids, or eight (32%) tocilizumab. Mechanical ventilation was used in two patients and extracorporeal membrane oxygenation in one patient. Of the PLWH not admitted to hospital ( $n=27$ , 51%), only one received specific COVID-19 treatment (azithromycin and hydroxychloroquine) and none switched their antiretroviral regimen.

### Factors associated with severity among people living with HIV with coronavirus disease 2019

There were six (11%) severe COVID-19 cases. They had more commonly neoplasia ( $n=4$ , 67% vs.  $n=2$ , 4%;  $P=0.0008$ ) among comorbidities, more commonly dyspnea ( $n=5$ , 83% vs.  $n=5$ , 11%;  $P=0.0006$ ) and less commonly headache ( $n=0$ , 0% vs.  $n=28$ , 64%;  $P=0.0047$ ) at presentation, lower median (IQR) O<sub>2</sub> saturation (93% (93–96) vs. 98% (96–99);  $P=0.0121$ ), lower median (IQR) platelets [135 (80–163–13.04) vs. 5.93 (4.10–7.29)  $\times 10^9/L$ ;  $P=0.0489$ ], higher median (IQR) leukocytes (8.91 (6–51–13.04) vs. 5.93 (4.10–

7.29)  $\times 10^9/L$ ;  $P=0.0489$ ), higher creatinine [1.45 (1.30–1.63) vs. 1.01 (0.85–1.13) mg/dl;  $P=0.0062$ ], higher lactate dehydrogenase [332 (316–357) vs. 239 (172–270) U/l;  $P=0.0232$ ], higher median (IQR) C reactive protein [16.99 (5.46–30.00) vs. 3.01 (0.45–10.21) mg/dl;  $P=0.0186$ ], higher procalcitonin [0.72 (0.12–1.63) vs. 0.03 (0.03–0.08) ng/ml;  $P=0.0016$ ], and higher ferritin [905 (595–1101) vs. 200 (84–311) ng/ml;  $P=0.0020$ ]. We were unable to find any HIV or antiretroviral factors significantly associated with COVID-19 severity.

### Factors associated with coronavirus disease 2019 in the people living with HIV cohort

We did not identify any demographic, HIV, or antiretroviral factor significantly associated with the diagnosis of COVID-19 in PLWH (Table 2).

### Incidence of coronavirus disease 2019 in the people living with HIV cohort compared with the incidence of coronavirus disease 2019 in the city of Barcelona

The standardized incidence rates of confirmed COVID-19 were 107 (95% CI 72–141) cases per 10 000 in the PLWH cohort and 282 (282–282) cases per 10 000 Barcelona inhabitants. The standardized incidence rate ratio was 0.38 (95% CI 0.27–0.52,  $P < 0.0001$ ) indicating that confirmed COVID-19 cases in the PLWH cohort were 62% lower than those in Barcelona.

Similarly, the standardized incidence rates of confirmed/probable COVID-19 cases were 136 (95% CI 78–193) cases per 10 000 PLWH and 417 (417–417) cases per 10 000 Barcelona inhabitants. The standardized incidence rate ratio was 0.33 (95% CI 0.21–0.50,  $P < 0.0001$ ), which means that confirmed/probable COVID-19 cases in the PLWH cohort were 67% lower than those in Barcelona.

**Table 2. Factors associated with severe coronavirus disease 2019 in the Hospital Clinic Barcelona people living with HIV cohort.**

	COVID-19 cases, $n=53$	Rest of HCB cohort, $n=5630$	Total, $n=5683$	$P$ value
Age (years)	44 (36–52)	47 (38–55)	47 (38–55)	0.1832
Female sex, $n$ (%)	10 (19)	928 (16)	938 (17)	0.6416
MSM, $n$ (%)	39 (74)	3619 (67)	3658 (67)	0.3193
Years HIV infection	11 (7–16)	12 (7–21)	12 (7–21)	0.2772
Prior opportunistic infection, $n$ (%)	10 (19)	785 (14)	795 (14)	0.3036
Nadir CD4 <sup>+</sup> cells/ $\mu$ l	303 (140–434)	277 (149–416)	278 (149–416)	0.6598
Last CD4 <sup>+</sup> cells/ $\mu$ l	624 (462–838)	662 (483–880)	662 (483–880)	0.6727
On ART, $n$ (%)	51 (96)	5551 (99)	5604 (99)	0.3852
Triple ART, $n$ (%)	44 (83)	4711 (85)	4755 (85)	0.7087
PI-based ART, $n$ (%)	15 (28)	1133 (20)	1148 (20)	0.1566
InSTI-based ART, $n$ (%)	29 (55)	3498 (63)	3527 (63)	0.2131
NNRTI-based ART, $n$ (%)	13 (25)	1293 (23)	1306 (23)	0.8323
Tenofovir (TAF or TDF)-based ART, $n$ (%)	35 (66)	3406 (61)	3441 (61)	0.4861
Abacavir-based ART, $n$ (%)	9 (17)	1262 (23)	1271 (23)	0.3195

Data are (median, IQR) unless otherwise stated. ART, antiretroviral therapy; COVID-19, coronavirus disease 2019; InSTI, integrase strand transfer inhibitor; IQR, interquartile range; NNRTI, nonnucleoside reverse transcriptase inhibitor; PI, protease inhibitor; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.

## Discussion

To our knowledge, this is the first prospective study assessing clinical characteristics and outcome, risk factors, and incidence of symptomatic COVID-19 in a large cohort of PLWH. During the COVID-19 epidemics in Barcelona (Spain), approximately 1% of PLWH sought help for clinical symptoms suggestive of COVID-19. Although the vast majority of them had COVID-19 confirmed, 15% had other causes that may also affect PLWH.

Clinical characteristics of COVID-19 did not differ from those already described in the general population [1,3,11,12,23,29,30]. However, cough, fever, bilateral lung infiltrates, and lymphocytopenia should prompt differential diagnosis with opportunistic diseases such as *Pneumocystis jirovecii*, mycobacterial or cryptococcal pneumonia. The 4% rate of mortality we saw in PLWH is similar to that reported for the general population aged 50–59 years in patients with COVID-19 admitted to a major Spanish hospital [12].

Because anti-COVID-19 therapy was protocolized in the SOP, in general PLWH received similar anti-COVID-19 therapy as other non-HIV-infected patients. This meant that antiretroviral therapy was temporarily switched to a regimen that included lopinavir/ritonavir unless otherwise contraindicated. We are unable to provide further data on the efficacy of this strategy against COVID-19 in PLWH. As in the general population, some PLWH with a worse clinical evolution also received other drugs including IFN-1 $\beta$ , glucocorticoids, and tocilizumab according to SOP [31,32].

We were unable to identify any HIV or antiretroviral factors associated with COVID-19 severity. As reported in the general population [32], several laboratory parameters best distinguished between severe and nonsevere COVID-19 in PLWH. These results suggest that HIV characteristics including CD4<sup>+</sup>, CD4<sup>+</sup>/CD8<sup>+</sup> ratio, or plasma viral load, or the type of antiretroviral therapy do not seem to play a major influence on the severity of COVID-19 in PLWH. In addition, we were unable to identify any epidemiological, HIV, or antiretroviral factor associated with the diagnosis of COVID-19 in PLWH.

The incidence of COVID-19 seen in this cohort of PLWH was much lower than that of the general population adjusted by age and sex living the same geographical area. This finding needs further confirmation in larger cohort studies. Whether it may be due to HIV, antiretroviral therapy, or other factors should be subject of further research.

The current study is limited by the low number of PLWH diagnosed with symptomatic COVID-19. Only symptomatic PLWH were included in this study, but we now

know that asymptomatic COVID-19 is not unusual [33]; we are systematically performing ELISA IgM/IgA/IgG blood tests to know the real incidence of COVID-19 in the PLWH cohort. This cohort of PLWH had universal standardized HIV and COVID-19 care and this situation may not be extrapolated to other settings. The lack of identification of HIV or antiretroviral factors associated with a higher risk or severity of COVID-19 in PLWH does not rule out that they may exist. Although probable cases in the general population fulfilled the ECDC Case Definition for COVID-19 [24], they could be due to causes other than SARS-CoV-2 that were not so thoroughly investigated as we did in the PLWH cohort and therefore the comparison of incidences between PLWH and the general population should be taken with caution (Supplementary Figure, <http://links.lww.com/QAD/B797>).

In summary, COVID-19 in PLWH had similar clinical characteristics and outcome but a lower incidence than in the general population. We were unable to identify any major role of HIV or antiretroviral factors on the risk or severity. These findings should be confirmed in larger multicenter cohort studies.

## Acknowledgements

### Conflicts of interest

There are no conflicts of interest.

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