

Research Letter

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HIV infection and COVID-19: risk factors for severe disease

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We performed an observational prospective monocentric study in patients living with HIV (PLWH) diagnosed with COVID-19. Fifty-four PLWH developed COVID-19 with 14 severe (25.9%) and five critical cases (9.3%), respectively. By multivariate analysis, age, male sex, ethnic origin from sub-Saharan Africa and metabolic disorder were associated with severe or critical forms of COVID-19. Prior CD4⁺ T cell counts did not differ between groups. No protective effect of a particular antiretroviral class was observed.

In France, the Paris area, where more than 51 000 patients are living with HIV (PLWH), was highly affected by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) pandemic between February and May 2020. However, in most series, PLWH usually account for less than 1% of patients requiring hospitalization [1,2]. Only a few cases series are available concerning coronavirus disease 2019 (COVID-19) occurring in PLWH [1,3–5]. Several risk factors have been well described as associated with severe forms of COVID-19, such as age, male sex, metabolic disorders, cardiovascular and chronic respiratory diseases, while the role of immunosuppression remains unclear [2,6–11]. As PLWH are often carriers of this comorbidities, our objectives were to determine which factors most likely involved in the development of severe forms of COVID-19 in PLWH.

We performed an observational prospective monocentric cohort study of PLWH diagnosed with SARS-CoV2 infection from 1 March to 30 April 2020. Consecutive PLWH taken in care in our department and having developed COVID-19 clinical symptoms and/or hospitalized for COVID-19 in our hospital were included in the study. Data were collected through telephone interviews or from the hospital charts on a questionnaire filled at least 14 days after the first symptoms. Ethics demand of approval was registered with number 2020-A01550-39 with favorable response number 20053-67751.

Qualitative variables were described as numbers and percentages, and quantitative variables as the median and interquartile range (IQR). To assess potential differences between the three ‘moderate’, ‘severe’ and ‘critical’ cases, the Kruskal–Wallis and chi-squared tests were used, as appropriate. Given the small number of critical diseases, we pooled the ‘critical’ and ‘severe’ patients. The Wilcoxon–Mann–Whitney test, chi-squared or Fisher’s exact tests were used to compare quantitative and qualitative variables between the ‘moderate’ and ‘severe/critical’ groups, respectively. Risk factors associated with severe and critical disease were determined using multivariable logistic regression models. In order to identify new independent predictors, we adjusted for age and sex. Statistical significance was considered for *P* value less than 0.05. As ethnic origin and BMI were highly correlated, we could not test those two variables into the same model. Analyses were performed using Stata software (version 14.2; StataCorp, College Station, Texas, USA).

A total of 54 PLWH with COVID-19 were included for analysis, of whom 61.1% were men. Median age was 54 (IQR: 47–60) years. Prior to COVID-19, all were treated by combined antiretroviral drugs and 51 out of 53 (96.2%) had RNA HIV less than 40 copies/ml with last median CD4⁺ T cell counts at 583 cells/ μ l (IQR: 474–773). Compared with the whole out-patient population of 4000 PLWH, the proportion of COVID-19 patients was higher in those from sub-Saharan Africa origin (44.6 vs. 29.7%) and did not differ in patients treated with a protease inhibitor (16.7 vs. 19.7%). The diagnosis of COVID-19 was confirmed in 38 cases (70.3%) and judged to be probable according to the association of clinical criteria in 16 cases (29.6%). All cases were followed-up for at least 14 days and for a median duration of 29 days (29–45 days). Clinical course of COVID-19 was moderate in 35 cases (64.8%), severe in 14 cases (25.9%) and critical in five cases (9.3%). One patient died. As summarized in Table 1, patients with critical COVID-19 tended to be older than those with severe disease, and those with a moderate disease (*P* = 0.06). In severe and critical forms, 13 out of 19 patients were from sub-Saharan Africa origin vs. 11 out of 35 in moderate form. Those who developed severe or critical disease had more frequently metabolic disorders (*P* = 0.004), hypertension (*P* = 0.002) and/or renal insufficiency (*P* = 0.006). By multivariate analysis, increased age, male sex and being from sub-Saharan Africa origin were independently associated with severe and critical forms of COVID-19 in PLWH. Furthermore, the presence of a metabolic disorder (obesity and/or diabetes) was independently

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Table 1. Comparison of moderate vs. severe and critical forms of COVID-19 in patients living with HIV (n = 54).

	All patients N = 54	Moderate N = 35	Severe N = 14	Critical N = 5	P
Clinical characteristics					
Age (years)	54 (47–60)	51 (42–58)	57 (55–60)	62 (56–64)	0.06
Age >65	6 (11.1)	4 (11.4)	1 (7.1)	1 (20)	0.64
Male, No. (%)	33 (61.1)	19 (54.3)	10 (71.4)	4 (80)	0.38
Female, No. (%)	21 (38.9)	16 (45.7)	4 (28.6)	1 (20)	
Ethnic origin					
European no. (%)	25 (46.3)	20 (57.1)	5 (35.7)	0	0.08
Sub-Saharan Africa, no. (%)	24 (44.4)	11 (31.4)	8 (57.1)	5 (100)	
North Africa, no. (%)	2 (3.7)	2 (5.7)	0	0	
South America, no. (%)	3 (5.6)	2 (5.7)	1 (7.1)	0	
BMI (kg/m ²)	25.2 (22.5–28.4)	24.8 (21.8–27.9)	24.6 (23.9–27.7)	32.1 (27.9–33.2)	0.03
BMI ≥30, no. (%)	N = 54 11 (20.4)	5 (14.3)	3 (21.4)	3 (60)	0.09
Metabolic disorder					
Active Smoking, no. (%)	14 (25.9)	5 (14.9)	5 (35.7)	4 (80)	0.004
	7 (13.0)	6 (17.1)	1 (7.1)	0	0.70
Comorbidities					
Diabetes, no. (%)	5 (9.3)	0	3 (21.4)	2 (40)	0.002
Arterial hypertension, no. (%)	16 (29.6)	7 (20)	4 (28.6)	5 (100)	0.002
ACEI	4 (7.4)	0	2 (14.3)	2 (40)	0.02
ARB	8 (14.8)	6 (17.1)	1 (7.1)	1 (20)	
Other cardiac disease, no. (%)	4 (7.4)	1 (2.9)	2 (14.3)	1 (20)	0.14
Renal insufficiency (creatinin clearance <60 ml/min), no. (%)	3 (5.6)	0	1 (7.1)	2 (40)	0.006
Respiratory disease (asthma, chronic bronchitis) no. (%)	5 (9.3)	3 (8.6)	1 (7.1)	1 (20)	0.58
Cirrhosis, no. (%)	1 (1.9)	0	1 (7.1)	0	0.35
Active cancer, no. (%)	2 (3.7)	0	2 (14.3)	0	0.12
Cardiovascular comorbidities	25 (46.3)	13 (37.1)	7 (50.0)	5 (100)	0.03
Overall comorbidities	30 (55.6)	15 (42.9)	10 (71.4)	5 (100)	0.02
Immunovirological status prior to COVID-19					
Nadir CD4 ⁺ T cell count/μl	N = 51 215 (100–340)	N = 34 217.5 (162–323)	N = 13 188 (100–440)	N = 4 206 (42–333)	0.84
Last CD4 ⁺ T cell count/μl	N = 52 583 (474–773)	N = 52 643 (475–840)	N = 13 535 (420–700)	N = 4 501 (386–547)	0.08
Last CD4%	N = 44 33.1 (26–40.8)	N = 31 34.4 (28.7–43)	N = 9 32.8 (24.8–37)	N = 4 23.9 (22.4–25.5)	0.10
Last CD8 T cell count/μl	N = 43 687 (508–958)	N = 31 647 (508–958)	N = 8 693 (523–958)	N = 4 768 (534–930)	0.96
Last CD8%	N = 37 41.1 (28.8–49.4)	N = 27 44 (28.8–51.8)	N = 8 37.2 (29–44.8)	N = 2 26.9 (18.8–34.9)	0.15
HIV viral load <40 no. (%)	N = 53 51 (96.2)	N = 35 35 (100)	N = 12 12 (85.7)	N = 4 4 (100)	0.11
Last antiretroviral regimen	54 (100)	35 (100)	14 (100)	5 (100)	
Protease inhibitors based, no. (%)	9 (16.7)	3 (8.6)	4 (28.6)	2 (40)	0.06
Darunavir	6 (11.1)	2 (5.7)	3 (21.4)	1 (20)	
Atazanavir	2 (3.7)	1 (2.9)	0	1 (20)	
Lopinavir	1 (1.9)	0	1 (7.1)	0	
Non-nucleoside inhibitors based no. (%)	25 (46.3)	17 (48.6)	6 (42.9)	2 (40)	0.92
Nucleoside inhibitors based no. (%)	43 (79.6)	27 (77.1)	13 (92.9)	3 (60)	0.27
Integrase inhibitors based	33 (61.1)	23 (65.7)	7 (50)	3 (60)	0.58
Clinical outcome					
Cure	N = 50 43 (86)	N = 35 32 (91.4)	N = 12 9 (75.0)	N = 3 2 (66.7)	0.06
Still hospitalized	1 (2)	NA	1 (8.3)	0	
Not cure	5 (10)	3 (8.6)	2 (16.7)	0	
death	1 (2)	0	0	1 (33.3)	

Values are median (interquartile range) or number (percentage %). Cardiovascular comorbidities: arterial hypertension, obesity, diabetes and others cardiac disease. Overall comorbidities: arterial hypertension, obesity, diabetes, others cardiac pathology, renal insufficiency, respiratory disease, cirrhosis and active cancer. *P* value: Kruskal–Wallis or chi-square for quantitative or qualitative variables. Confirmed COVID-19: (1) virological confirmation of SARS-CoV-2 infection, using a semi-quantitative RT-PCR assay; and/or (2) CT scan showing a typical COVID-19 pneumonia; and/or (3) prior contact with a virologically confirmed case in the 14 days prior to onset of symptoms and at least two major symptoms of COVID-19 (fever ≥38°C, cough, pulmonary parenchymal disease, shortness breath, anosmia without nasal obstruction, agueusia). Probable COVID-19: (1) at least three major symptoms or (2) two major and two minor symptoms (headaches, sore throat, runny nose, headache, prolonged asthenia, chills, odynophagia, diarrhoea, vomiting, cutaneous signs) or (3) one major and three minor symptoms. Moderate COVID-19 disease: outpatient care. Severe COVID-19 disease: oxygen requirement. Critical COVID-19 disease: admission in ICU for respiratory decompensation or multiple organ failure. ACEI/ARB, angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers.

associated with the occurrence of severe and critical forms. There was no significant difference (for data prior COVID-19), between severe/critical disease and moderate/minor disease for CD4⁺ T cell count, proportion of patients with HIV RNA less than 40 copies/ml or receiving a protease inhibitor based treatment.

As in the general population, the severity of COVID-19 in PLWH was associated with older age, male sex and metabolic disorders, such as obesity and diabetes [2,6–11]. We also found that patients who originated from sub-Saharan Africa possibly were at an increased risk of disease severity. Black ethnicity has already been suggested to be associated with poor outcome of COVID-19 in at least two studies [12,13]. One explanation for this finding could be a higher frequency of metabolic disorders and social deprivation in this population as observed in the UK [13]. Poor outcome could be related to particular genetic traits in these populations. It is very important to confirm (or not) these data and explain this finding, especially as epidemiological trends raise fears that the COVID-19 epidemic is expanding in Africa [14,15]. On the basis of low level of evidence-based data, international recommendations state that PLWH are not at higher risk than the general population, provided that CD4⁺ T cell count are greater than 200 cells/ μ l and viral replication is controlled by antiretroviral treatment [16,17]. Our study did not allow us to assess the risk linked to immune deficiency, especially as all patients were taking antiretroviral treatment. We found a trend for lower CD4⁺ T cell counts in severe forms as suggested in a previous study based on low-level evidence [4]. As elevated IL-6 levels are associated with older age and higher BMI in PLWH, higher viral replication and low nadir CD4⁺ T cell count could be associated with poor outcome [18]. Larger prospective cohort studies, including patients under and not yet taking antiretroviral drugs, are warranted in order to fully assess the determinants of health outcomes in PLWH with COVID-19. Finally, we did not find any protective effect of protease inhibitors, but these results may be biased by the fact that protease inhibitors are usually prescribed as second-line antiretrovirals. Larger studies are also needed on this topic.

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DS, NE, FC, LW and JPV conceived and designed the study. All the members of the COVID-19 ID Team were responsible for patient inclusion, clinical follow-up and helped to write the manuscript. RU, MM, MK and VL collected the data. FC and LS took responsibility for the integrity of the data and the accuracy of the data analysis. All authors critically revised the manuscript and gave final approval for the final version.

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Conflicts of interest

None.

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