

Association Between CD4 Count and COVID-19 Severity in a Cohort of People Living with HIV in Marseille, France

Assane Diouf^{1,2*}, Ngo Ngai Christine^{1,3}, Dudouet Pierre³, Ngom Ndèye Fatou^{4,5}, Lagier Jean-Christophe³, Million Mathieu³ and Seydi Moussa^{1,2}

¹Service des Maladies Infectieuses et Tropicales (SMIT), Centre Hospitalier National Universitaire de Fann, Dakar, Sénégal

²Faculté de Médecine, de Pharmacie et d'Odontostomatologie, Université Cheikh Anta Diop, Dakar, Sénégal

³Institut Hospitalier Universitaire Méditerranée Infections, Marseille, France

⁴Outpatient Treatment Center, Fann Hospital, Dakar, Senegal

⁵Department of Medicine, UFRSDD, University Alioune Diop, Bambey, Senegal

*Corresponding author

Assane Diouf, Service des Maladies Infectieuses et Tropicales, Université Cheikh Anta Diop, Dakar, Sénégal, Faculté de Médecine, de Pharmacie et d'Odontostomatologie, Université Cheikh Anta Diop, Dakar, Sénégal.

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ABSTRACT

COVID-19 can cause severe forms, especially in the presence of acknowledged risk factors. However, the few published results on COVID-19 in PLHIV appear conflicting, particularly regarding the evolution of the disease.

Objective: To describe the characteristics of COVID-19, and to assess the association between the CD4 cell count and COVID-19 severity in PLHIV.

Methods: We conducted a cross-sectional study including all PLHIV followed at the IHU Méditerranée Infections with a confirmed diagnosis of COVID-19 between March 2020 and March 2022. The association between COVID-19 severity and CD4 count was analysed using a logistic regression model.

Results: We included 71 patients with a median (IQR) age of 53 (42 - 58) years including 53.5% of men. Risk factors for severe disease were found in 32.4%. A proportion of 93% were on triple ARV therapy, including 12.5% on protease inhibitors (PIs); 39.2% had CD4 count $\geq 500/\text{mm}^3$, and for 36.8%, plasma HIV RNA was < 1 log copies/ml at the time of COVID-19 diagnosis. In our study population, 16.9% had a News 2 score > 4 , while 25.4% were hospitalized. Among these, three were admitted in intensive care unit, but no deaths occurred. The probability of being hospitalized was 5.8 times higher for a patient with a CD4 count $< 500/\text{mm}^3$ than in a patient with a CD4 count $\geq 500/\text{mm}^3$.

Conclusion: Among PLWH coinfecting with SARS-CoV-2 in Marseille, we found that hospitalization was associated with a CD4 count $< 500/\text{mm}^3$.

Keywords: COVID-19, HIV infection, CD4 cell count, France

Background

Coronavirus disease 2019 (COVID-19) emerged in the city of Wuhan, Hubei District, China. In January 2020, it was declared a public health emergency of international concern and then a pandemic on March 11, 2020 by the World Health Organization (WHO). As of October 05 2025, 778 781 579 confirmed cases including 39 047 823 in France with 7 102 784 deaths have been reported worldwide i.e. a lethality of 0.9% which may be higher in the presence of certain conditions recognized as risk factors for death in patients infected with the 2nd severe

acute respiratory syndrome coronavirus (SARS-CoV-2). These conditions include high blood pressure, diabetes, chronic renal disease, cardiovascular diseases, chronic obstructive pulmonary disease (COPD), and obesity. However, discordant results have been reported on the prognostic role of HIV infection during COVID-19 and there are other uncertainties about SARS-CoV-2 infection in people living with human immunodeficiency virus (PLHIV)[4–10]. The objectives of our study were to describe the characteristics of COVID-19, and to assess the association between CD4 cell count and the severity of COVID-19 in PLHIV [1-10].

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Methods

We conducted a cross-sectional study at the Institut hospitalo-universitaire (IHU) Méditerranée Infections in Marseille including all the PLHIV followed up with a PCR-confirmed diagnosis of COVID-19 between March 2020 and March 2022. The main explanatory variable was CD4 cell count at COVID-19 diagnosis, measured by flow cytometry. The primary outcome was the type of care offered upon diagnosis of COVID-19. Management was ambulatory for patients with a News 2 score ≤ 4 and a clinical assessment deemed compatible with outpatient care, whereas for a News 2 score > 4 and severe clinical features, patients were admitted in hospitalization.

Descriptive statistics were used to compare hospitalization frequencies according to CD4 cell count and other exposure variables, using χ^2 tests. The association between inpatient care admission and CD4 cell count was analyzed by a logistic regression model. We estimated crude and adjusted odds ratios (ORs) with 95% confidence intervals (95% CIs).

Confounding was controlled using a 10% change in estimate method (variables that change the estimate by $\geq 10\%$ were included in the model) among the following potential confounders: age ($<35/35-45/46-55/>55$), sex (male/female), BMI ($<18.5/18.5-25/>25$), time to consult after the onset of symptoms ($\leq 2/>2$), HIV infection duration ($<10/10-30/>30$), CD4 cell count at the time of COVID-19 diagnosis ($<500/\geq 500$), HIV RNA at the time of COVID-19 diagnosis ($<1 \log_{10}/\geq 1 \log_{10}$), risk factors of severe COVID-19 (yes/no), oxygen saturation ($<90\%/\geq 90\%$), News 2 score ($\leq 4/>4$), CT value ($<20/20-30/>30$), CRP (normal/high), Radiological findings at CT scan (minimal/moderate/severe/atypical), drug use (yes/no) and SARS-CoV-2 variant (Alpha/Delta/Marseille 4/Omicron/Wuhan). Ethical approval was obtained from the Ethics Committee of IHU Méditerranée Infections in France on August 8, 2022 (N° 2022-037) (Appendix I).

Results

Between March 2020 and March 2022, among the 2,100 PLHIV monitored at the IHU Méditerranée Infection in Marseille, 71 were co-infected with SARS-CoV-2 ie. a cumulative incidence of 3.4%. The characteristics of the study population are summarized in table 1. The median age (IQR) was 53 (42-58) years, with 53.5% of men. The median duration of HIV infection was 24 years (10-30), and 32.4% had risk factors for severe COVID-19. A proportion of 93% were on antiretroviral therapy (ART) including 12.5% on protease inhibitors (PI); 39.2% had a CD4 cell count $\geq 500/\text{mm}^3$ and for 36.8%, plasma HIV RNA $< 1 \log$ copies/ml at COVID-19 diagnosis. Two patients were vaccinated against COVID-19.

In this population, 9.8% (95% CI = 4% - 19.3%) were asymptomatic. Among the others, the median time (IQR) to consult after the onset of symptoms was 4 days (2-7). General signs as fever, fatigue were present in 80.6% (95% CI = 69.5% - 89.9%), respiratory signs (cough, dyspnea, rhinorrhea) in 72.2% (95% CI = 59.2% - 82.4%), otolaryngological signs (dysgeusia, anosmia) in 29.2% (95% CI = 18.9% - 42.4%) and digestive signs in 22.2% (95% CI = 12.5% - 34%).

Table 1: Characteristics of the PLHIV co-infected with SARS-CoV-2 between March 2020 and March 2022 at the Institut hospitalo-universitaire Méditerranée Infections in Marseille

Variables (N = 71)	%	95% CI
Age		
< 35	16.9	09.0 - 27.7
35-45	11.3	05 - 21.0
46 – 55	35.2	24.2- 47.5
>55	36.6	25.5 - 48.9
Sex		
Female	46.5	34.5 - 58.7
Male	53.5	41.3 - 65.4
Risk factors for severe disease 2		
Yes	32.4	21.8 - 44.5
No	67.6	55.4 -78.2
Drug use		
Yes	26.8	16.9 - 38.6
No	73.2	61.4 -83.1
BMI (Kg/m¹)		
<18.5	05.6	1.6 - 13.8
18.5 – 25	46.5	34.5 - 58.7
> 25	47.9	35.9 - 60.1
HIV infection duration (years)		
< 10	23.9	14.6 - 35.585
10 – 30	53.5	41.3 - 65.4
> 30	22.5	13.5 - 34.0
HIV treatment		
Yes	93.0	84.3 - 97.7
No	07.0	02.3 -15.7
CD4 count at COVID-19 diagnosis		
≥ 500	39.2	25.8 - 53.9
< 500	60.8	46.1 - 74.1
HIV viral load (log₁₀ copies/ml)		
< 1	36.8	16.3 - 61.6
≥ 1	63.2	38.4 - 83.7
Time before consultation (day)		
≤ 2	27.9	17.7 - 40.1
> 2	72.1	59.8 - 82.3
COVID-19 vaccination		
Yes	02.8	00.3 - 29.8
No	97.2	90.2 - 99.7
Variant Marseille 4		
Alpha	31.2	16.1 - 50.0
Delta	18.7	07.2 - 36.4
Wuhan	15.6	05.3 - 32.8
Omicron	09.4	02.0 - 25.0
O2 saturation (%)		
≥ 90	97.2	90.2 - 99.7

< 90	02.8	0.3 - 9.8
News 2 score		
0-4	83.1	72.3 - 90.9
> 4	16.9	09.0 - 27.7
CT value		
< 20	22.6	12.9 - 35.0
20-30	56.4	43.3 - 69.0
> 30	21.0	11.7 - 33.2
CRP		
Normal	50.0	31.9 - 68.1
High	50.0	31.9 - 68.1
Radiological findings at CT scan		
Minimal	33.3	18.0 - 51.8
Moderate	27.3	13.3 - 45.5
Severe	12.1	03.4 - 28.2
Atypical	27.3	13.3 - 45.5
Outcome		
Outpatient care	74.6	62.9 - 84.2
Inpatient care	25.4	15.8 - 37.1

¹Severity risk factors include hypertension, diabetes, active cancer, immunodepression (excluding HIV), COPD, renal failure, obesity, heart failure.

Eighteen patients were hospitalized. Of these, 3 were admitted to intensive care, but no deaths occurred. The most frequently found COVID-19 variants were Marseille 4 (25%), Alpha (31.2%), Delta (18.7%) and Wuhan (15.6%). Patient characteristics by type of management are presented in Table 2. The proportion of patients hospitalized was higher in case of CD4 cell count < 500/mm³ or HIV viral load ≥ 1 log copies/ml or News 2 score > 4. It was different according the radiological findings at CT scan; higher in case of severe impairment (62.5%; 95% CI =24.5% – 91.5%).

Table 2: Proportions of participants managed as outpatients or hospitalized according to age, sex, existence of risk factors for severe form, drug use, BMI, HIV infection duration, CD4 count, plasma HIV RNA, time to consultation, vaccination against COVID-19, SARS-Cov-2 variant, oxygen saturation, News 2 score, extent of lesions and treatment protocol.

Variables	Outpatient care N = 53 % (95% CI)	Inpatient care N = 18 % (95% CI)	p-value
Age			
< 35	83.3 (51.6 - 97.9)	16.7 (02.1 - 48.4)	0.173
35-45	87.5 (47.3 - 99.7)	12.5 (03.2 - 52.6)	
46-55	80 (59.3 - 93.2)	20 (06.8 - 40.7)	
>55	57.7 (36.9 - 76.6)	42.3 (23.3 - 63.1)	
Sex			

Male	71.0 (54.1 - 84.6)	29.0 (15.4 - 45.9)	0.556
Female	78.8 (61.1 - 91.0)	21.2 (09.0 - 38.9)	
Risk factors of severe disease			
No	79.2 (65.0 - 89.5)	20.8 (10.5 - 35.0)	0.206
Yes	65.2 (42.7 - 83.6)	34.8 (16.4 - 57.3)	
Drug use			
No	73.1 (59.0 - 84.4)	26.9 (15.6 - 41.0)	0.615
Yes	78.9 (54.4 - 93.9)	21.1 (06.0 - 45.6)	
BMI			
<18.5	50 (06.8 - 93.2)	50 (06.8 - 93.2)	0.325
18.5 - 25	69.7 (51.3 - 84.4)	30.3 (15.6 - 48.7)	
> 25	82.3 (65.5 - 93.2)	17.7 (06.8 - 34.5)	
HIV infection duration (years)			
< 10	88.2 (63.5 - 98.5)	11.8 (01.5 - 36.4)	0.342
10 – 30	71.1 (54.1 - 84.6)	28.9 (15.4 - 45.9)	
> 30	68.8 (41.3 - 89.0)	31.2 (11.0 - 58.7)	
CD4 cell count (cell/μl)			
≥ 500	96.4 (81.6 - 99.9)	03.6 (00.9 - 18.3)	< 0.001
< 500	60.5 (44.4 - 75.0)	39.5 (25.0 - 55.6)	
HIV viral load (log10 copies/ml)			
< 1	96.1 (80.4 - 99.9)	3.9 (00.9 - 19.6)	0.010
≥ 1	62.2 (46.5 - 76.2)	37.8 (23.8 - 53.5)	
Time to consultation (days)			
≤ 2	90.0 (68.3 - 98.8)	10.0 (12.4 - 31.7)	0.164
> 2	68.6 (54.1 - 80.9)	31.4 (19.1 - 45.9)	
Vaccination			
No	75.4 (63.5 - 84.9)	24.6 (15.0 - 36.5)	0.451
Yes	50.0 (12.61 - 98.7)	50 (12.61 - 98.7)	
Variant			
Alpha	72.3 (49.8 - 89.3)	27.3 (10.7 - 50.2)	0.781
Delta	69.2 (38.6 - 90.9)	30.8 (09.0 - 61.4)	

Omicron	85.7 (42.1 - 99.6)	14.3 (03.6 - 57.9)	
Wuhan	81.8 (48.2 - 97.7)	18.2 (02.3 - 51.8)	
Marseille 4	72.2 (46.5 - 90.3)	27.8 (09.7 - 53.5)	
O2 saturation (%)			
≥ 90	75.4 (63.5 - 84.9)	24.6 (15.0 - 36.5)	0.451
< 90	50.0 (12.6 - 98.7)	50.0 (12.6 - 98.7)	
News 2 score			
≤ 4	84.7 (73.0 - 92.8)	15.3 (07.2 - 27.0)	< 0.001
> 4	25.0 (05.5 - 57.2)	75.0 (42.8 - 94.5)	
Radiological findings at CT scan			
Minimal	79.2 (57.9 - 92.9)	20.8 (07.1 - 42.1)	0.004
Moderate	70.0 (45.7 - 88.1)	30.0 (11.9 - 54.3)	
Severe	37.5 (08.5 - 75.5)	62.5 (24.5 - 91.5)	
Atypical	89.5 (66.9 - 98.7)	10.5 (01.3 - 33.1)	

After adjustment for age, sex, radiological findings at CT scan, and News 2 score, CD4 count < 500/mm³ was associated with hospitalization. The probability of hospitalization was 5.8 times higher in a patient with CD4 count < 500/mm³ compared with a patient whose CD4 cell count was ≥ 500/mm³ (Table 3).

Table 3: Crude and adjusted* odds ratios of CD4 count on type of care for PLHIV co-infected with SARS-CoV-2 between March 2020 and March 2022 at the Institut hospitalo-universitaire Méditerranée Infections in Marseille using logistic regression models age, sex, News 2 score, radiological findings at CT-scan

Characteristics	Univariate analysis N = 51	P-value	Multivariate analysis N = 51	
	ORb (IC95%)		c OR* (IC95%)	P-value
CD4 value ≥ 500	1		1	
CD4 value < 500	5,74 (2,44-6,37)	0,002	5,82 (2,68-7,24)	0,011

Discussion

In this cohort of PLHIV followed at IHU Méditerranée Infections in France during two years, the cumulative incidence of SARS-CoV-2 infection was 3.4% and COVID-19 severity was associated with CD4 cell count < 500/mm³. Sociodemographic, clinical and paraclinical data were collected, and the model

was adjusted for potential confounders. The study population (size and distribution of main exposures and event of interest) allowed us to demonstrate an association between low CD4 cell count and hospitalization, with an ORa ≥ 2.5, a α risk of 5% and power ≥ 80%.

In our study population, hospitalization was 5.8 times more frequent for CD4 counts < 500/mm³. These results are in line with those reported by Guo et al. A Brazilian study reported an association between disease severity, and a low CD4/CD8 ratio [10]. Mnguni et al suggested a higher risk of death in HIV-immunocompromised patients, associated with opportunistic infections such as tuberculosis in their study population. Boswell et al. found the only factors associated with a higher risk of hospitalization to be elevated biological markers, notably creatinine in the context of HIV [7,10-12].

Three large studies have suggested an increased incidence of severe COVID-19 outcomes for PLHIV. In these different studies, additional factors taken into account in the HIV context were other comorbidities, systemic stress related to chronic infection and social determinants of COVID-19 severity. In addition, it was reported from South Africa the development of more than ten new SARS-CoV-2 variants in an individual with untreated HIV-1 infection who had been co-infected with SARS-CoV-2. The authors hypothesized that untreated HIV-1 infection may provide an environment that favors intra-host viral mutagenesis of SARS-CoV-2 with, in particular, a significant rate of quasispecies [13-16].

The main limitation of our study lies in the assessment of severity: the decision to hospitalize was based on the News 2 score and clinical assessment, which does not exclude an investigator bias. In such a case, where PLHIV were being followed up, clinicians with knowledge of patients' immunological status might choose to hospitalize immunosuppressed patients (CD4 count < 500/mm³) more frequently. This could contribute to optimal (patient-centered) management, as evidenced by the absence of deaths in our study whereas they have been reported in most of the published studies [5-7,14]. Another limitation is the completeness of the data, which did not allow the associations studied to be adjusted for potential confounding factors, including plasma HIV RNA hence the possibility of residual confounding.

Conflicts of Interest

No Author Declares Potential Competing Interests

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Data availability

Data are available on reasonable request. Aggregate data can be obtained through a formal request procedure. Researchers interested in obtaining access to the data are advised to contact the corresponding author (DA). Data will be shared in accordance with applicable data protection regulations and ethical considerations.

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