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Letter to the Editor

Seroprevalence of SARS-CoV-2 in HIV patients

High SARS-CoV-2 seroprevalence in HIV patients originating from sub-Saharan Africa in the Ile-de-France area

Dear Editors

As reported in this journal, a recent study in South Africa suggest that HIV is not a risk factor for moderate or severe COVID-19 disease neither is it a risk factor for mortality[1] However other studies described that HIV could be associated with a similar or a higher risk of acquiring COVID-19 and/or worse outcomes.[2,3] To date, no longitudinal studies have been conducted in PLWHIV. Thus, we aimed to determine the SARS-CoV-2 seroprevalence in our PLWHIV and to identify factors potentially associated with COVID-19 infection, and then to evaluate the kinetics of anti-SARS-CoV-2 antibodies.

Our study is a longitudinal prospective cohort conducted between April 2020 and September 2021. All HIV-1 patients followed in the Pitié-Salpétrière hospital were invited to participate in this study. Residual plasma samples obtained from plasma HIV-RNA viral load measurements were used to perform SARS-COV-2 serologies.

IgG was measured using the Abbott Alinity instrument. It is a chemiluminescent microparticle immunoassay for semi-qualitative detection of IgG against nucleoprotein (N) and quantitative detection of IgG against the receptor-binding domain (RBD) of spike (S) protein. IgA against the S1 domain of the S protein was measured using enzyme-linked immunosorbent assays (ELISA, EuroImmun). At inclusion, all plasma samples were screened for IgG anti-N and all samples that were confirmed positive for IgG anti-N were tested to detect IgG anti-S and IgA anti-S. Patients with positive serology were evaluated at 6 and 12 months (M).

Table 1
Patients characteristics at baseline.

	All patients N		n (%) / Median (IQR)	Seropositive SARS-CoV-2 (IgG anti-N) N	n (%) / Median (IQR)
Age (years)	1901		53 (44–60)	254	50 (43–57)
Sex	1901	Female	677 (35.6%)	254	118 (46.5%)
		Male	1224 (64.4%)		136 (53.5%)
Country of origin	1892	France	865 (45.7%)	253	47 (18.6%)
		Europe	80 (4.2%)		6 (2.4%)
		North Africa	77 (4.1%)		4 (1.6%)
		Sub Saharan Africa	724 (38.3%)		184 (72.7%)
		America	65 (3.5%)		6 (2.4%)
		Asia	81 (4.3%)		6 (2.4%)
Active smoking	1286	No	944 (73.4%)	166	148 (89.2%)
		Yes	342 (26.6%)		18 (10.8%)
BMI (kg/m2)	1838		24.9 (22.3–28.6)	243	27.5 (23.9–30.5)
Duration of HIV infection (years)	1900		17.0 (9.1–26.0)	254	14.6 (8.0–19.7)
Duration of ARV treatment (years)	1891		13.9 (7.5–22.2)	252	11.5 (6.5–18.9)
CD4 (cells/mm^3)	1710		588 (429 - 772)	224	518 (381–670)
CD4/CD8	1698		0.93 (0.61 - 1.38)	223	0.87 (0.60–1.39)
HIV-1 RNA viral load (cp/ml)	1784	<50 (cp/ml)	1594 (89.4%)	234	202 (86.3%)
		>50 (cp/ml)	190 (10.6%)		32 (13.7%)
Previous COVID-19 infection	636	No	579 (91.0%)	90	53 (58.9%)
		Yes	57 (9.0%)		37 (41.1%)
ART regimen	1884	2 NRTI + 1 NNRTI	480 (25.5%)	248	73 (29.4%)
		2 NRTI + 1 INSTI	681 (36.2%)		100 (40.3)
		2 NRTI + 1 PI	144 (7.6%)		19 (7.7%)
		1 INSTI+1 NRTI	22 (1.2%)		0 (0.0%)
		1 INSTI+1 NNRTI	164 (8.7%)		16 (6.5%)
		Others	393 (20.9%)		40 (16.1%)

Categorical variables were summarised with frequency and percentages whereas continuous variables were summarised with median and interquartile range (IQR); *N*= number of patients; ARV= Antiretroviral; ART = Antiretroviral therapy; NRTI= Nucleoside Reverse Transcriptase Inhibitor; NNRTI= Non-Nucleoside Transcriptase Inhibitor; PI= Protease Inhibitor; INSTI= Integrase Strand Transfer Inhibitor.

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Table 2
Factors associated with the risk of a positive serology SARS-CoV-2 (IgG anti-N) at baseline.

			N	COVID-19	Univariate		Multivariate	
Variables	N				OR (95% CI)	p value	OR (95% CI)	p value
Age (years)	1901	<50	714	125 (17.5%)	1	<0.0001	1	0.6492
		>=50	1187	129 (10.9%)	0.57 (0.44, 0.75)		0.93 (0.67, 1.29)	
Sex	1901	Male	1224	136 (11.1%)	1	<0.0001	1	0.0666
		Female	677	118 (17.4%)	1.69 (1.29, 2.21)		0.74 (0.54, 1.02)	
Country of origin	1901	Others	1175	70 (5.9%)	1	<0.0001	1	<0.0001
		Sub Saharan Africa	726	184 (25.3%)	5.36 (3.99, 7.19)		4.78 (3.39, 6.73)	
Department	1901	Paris	919	118 (12.9%)	1	0.5978		
		Others	982	135 (13.8%)	1.08 (0.82, 1.42)			
BMI (Kg/m^2)	1901	<30	1559	182 (11.7%)	1	<0.0001	1	0.2024
		>=30	342	71 (20.9%)	2.00 (1.47, 2.73)		1.25 (0.89, 1.75)	
Smoking	1901	No	1395	220 (15.8%)	1	<0.0001	1	0.0176
		Yes	506	34 (6.7%)	0.38 (0.25, 0.59)		0.57 (0.36, 0.90)	
Duration of HIV infection (years)	1901			14.6 (7.9 – 19.7)	0.97 (0.96, 0.98)	<0.0001	0.99 (0.95, 1.02)	0.4424
Duration of ARV treatment (years)	1901			11.5 (6.6 – 18.8)	0.97 (0.96, 0.99)	0.0003	1.01 (0.95, 1.07)	0.7988
Time on ongoing ARV therapy (years)	1901			1.5 (0.8 – 2.4)	0.94 (0.89, 1.01)	0.0757	1.01 (0.94, 1.08)	0.8653
CD4 ($cells/mm^3$)	1901	<350	290	53 (18.3%)	1	0.0127	1	0.2357
		>350	1611	201 (12.5%)	0.64 (0.45, 0.91)		0.79 (0.53, 1.17)	
CD8 ($cells/mm^3$)*	1901			612 (390 – 816)	0.80 (0.67, 0.96)	0.0179	0.87 (0.70, 1.06)	0.1695
CD4/CD8 ratio	1901			0.9 (0.6 – 1.4)	1.00 (0.97, 1.04)	0.8507		
HIV-1 RNA viral load (cp/ml)	1901	<50	1698	219 (12.9%)	1	0.1371	1	0.6097
		>50	203	34 (16.8%)	1.36 (0.91, 2.04)		1.12 (0.72, 1.75)	
Abacavir + Lamivudine	1901	No	1822	246 (13.5%)	1	0.2730		
		Yes	79	7 (9.2%)	0.64 (0.29, 1.41)			
Emtricitabine + Tenofovir	1901	No	1681	222 (13.2%)	1	0.6741		
		Yes	220	31 (14.3%)	1.09 (0.73, 1.64)			
Emtricitabine + Tenofovir-alafenamide	1901	No	1166	142 (12.2%)	1	0.0724	1	0.8820
		Yes	735	111 (15.2%)	1.28 (0.98, 1.68)		0.97 (0.65, 1.45)	
Efavirenz	1901	No	1837	245 (13.4%)	1	0.9791		
		Yes	64	8 (13.3%)	0.99 (0.47, 2.10)			
Etravirine	1901	No	1844	248 (13.5%)	1	0.3214		
		Yes	57	5 (8.9%)	0.63 (0.25, 1.58)			
Rilpivirine	1901	No	1395	182 (13.1%)	1	0.5510		
		Yes	506	71 (14.1%)	1.09 (0.81, 1.47)			
Doravirine	1901	No	1827	242 (13.3%)	1	0.4686		
		Yes	74	12 (16.2%)	1.26 (0.67, 2.38)			
Nevirapine	1901	No	1839	248 (13.5%)	1	0.2479		
		Yes	62	5 (8.3%)	0.58 (0.23, 1.46)			
Atazanavir	1901	No	1829	243 (13.3%)	1	0.7509		
		Yes	72	10 (14.7%)	1.12 (0.56, 2.21)			
Darunavir	1901	No	1696	226 (13.4%)	1	0.9589		
		Yes	205	27 (13.3%)	0.99 (0.64, 1.53)			
Raltegravir	1901	No	1784	236 (13.3%)	1	0.6908		
		Yes	117	17 (14.6%)	1.11 (0.65, 1.90)			
Dolutegravir	1901	No	1352	196 (14.6%)	1	0.0196	1	0.4894
		Yes	549	57 (10.4%)	0.68 (0.50, 0.94)		0.87 (0.59, 1.28)	
Elvitegravir	1901	No	1786	239 (13.4%)	1	0.7289		
		Yes	115	14 (12.3%)	0.9 (0.51, 1.61)			
Bictegravir	1901	No	1540	196 (12.8%)	1	0.1249	1	0.3779

Univariable and multivariable logistic regression models were used to assess factors associated with the risk of a positive serology (IgG anti-N) at baseline. Multiple imputation approach with Fully Conditional Specification method was used to fill in missing data. Analyses were run on each of the 10 data sets, including the imputed values, and the results were combined with Rubin's rules. Variables with a univariate p-value <0.20 were included in the multivariable logistic regression model. The significance level of the p-value in the multivariable model was set at 0.05.

Univariable and multivariable logistic regression models were used to assess factors associated with the risk of a positive serology at baseline. We used a multiple imputation approach with Fully Conditional Specification method to fill in missing data. The change from baseline in antibodies levels overtime were compared using mixed models for repeated measures with random effects and unstructured covariance matrix.

A total of 1901 PLWHIV were enrolled in the study. 64.4% of them were male with median age of 53 years (44–60). Only 57 patients reported previous COVID-19 infection without any complications. Among the participants, 26.6% were active smokers and 38.3% were from sub-Saharan Africa.

At inclusion, 254 patients were seropositive, corresponding to a seroprevalence rate in PLWHIV of 13.4% (95% IC 11,9%, 15%). Median age was 50 years (43–57), 53.5% men, 72.7% Sub-Saharan African, only 37 previous COVID-19 infection and 10.8% were active smokers. The main characteristics of the study population are summarized in Table 1.

Among seropositive patients, 88.2% and 64.1% had positive IgG anti-S and IgA anti-S respectively at baseline. The mean levels of antibody concentrations were 3.95 (Standard error (SE) 0.16) for IgG anti-N, 199.4 BAU/mL (SE 28.3) for IgG anti-S and 3.14 (SE 0.21) for IgA anti-S. At M6, 51.9%, 87.3% and 75.4% patients had positive IgG anti-N, IgG anti-S and IgA anti-S respectively. At M12, 35.2%, 87.6%, and 81.2% patients had positive IgG anti-N, IgG anti-S and IgA anti-S respectively. Over one year, levels of IgG anti-N and anti-S decreased significantly (−2.83 (SE 0.20) $p<0.0001$ and −94.9 BAU/mL (SE 28.3) $p<0.0001$ respectively), while IgA anti-S level increased significantly (+2.97 (SE 0.95) $p<0.0001$).

Univariable et multivariable logistic regression analyses were performed to assess independent factors associated with positive serology at baseline (Table 2). Fourteen factors were retained for

the multivariable analysis showed that the geographical origin and smoking were independently associated with positive SARS-CoV-2 antibodies. Sub-Saharan African patients were more likely to have positive IgG anti-N in comparison with patients originating from France and other countries (OR: 4.78 [95% CI 3.39;6.73], $p<0.0001$), while active smoking was a protective factor (OR: 0.57 [95% CI 0.36; 0.90], $p = 0.0176$).

To our knowledge, this is the first study evaluating the seroprevalence and assessing the kinetics of SARS-CoV-2 antibodies during one year in the HIV population. Our findings show a higher seroprevalence of SARS-CoV-2 in PLWHIV in comparison to that reported in general population in France in the same period.[4] This result could be explained by social and behavioural determinants of health associated with COVID-19 transmission in different communities especially in PLWHIV. Indeed, we found a higher seroprevalence of SARS-CoV-2 in African Sub-Saharan HIV patients, which may reflect social inequalities in health and healthcare in France for people of sub-Saharan African origin.

We showed that levels of IgG anti-N and IgG anti-S decreased significantly while levels of IgA anti-S increased significantly over one year. Our results reinforce previous studies of evolution of antibody immunity to SARS-CoV-2 showing the decrease of antibody levels with time.[5–7] Previous works have shown that anti-RBD IgA levels decreased in a less proportion compared to the anti-RDB IgG levels over a time period of 6 to 9 months.[7] Antibody kinetics suggest that HIV patients don't exhibit an efficient immune response in case of virus re-exposure. However, direct conclusions about protective immunity cannot be made only on the basis of humoral immunity. Other investigations in memory B and T cells are needed.

We showed also that active smoking was associated with a lower rate of IgG anti-N antibodies. Our result is in line with other studies showing that active smoking was associated with a lower rate SARS-CoV-2 antibodies and supporting the role of nicotine as protective for SARS-CoV-2 infection.[4,8] Many authors hypothesize that this protective role is associated with the nicotine regulation of angiotensin-converting enzyme-2 receptor expression which is involved in SARS-CoV-2 entry.[8] However, data on whether COVID-19 has a greater incidence in non-smokers is still contradictory and the causal role of tobacco in lung cancer and chronic obstructive pulmonary disease should not encourage smoking to limit the risk of developing COVID-19.

In conclusion, the higher seroprevalence observed in sub-Saharan Africa patients highlights the need of an implementation of health and prevention system taking care of vulnerable people especially PLWHIV. More investigations are needed to understand the association between smoking and COVID-19.

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Authors contribution

Conceptualization, BA., VP., A.G.M., LA. and VC; Methodology, ALN., LA., BA., VP. and A.G.M.; Software, ALN. and LA.; Validation, BA., VP., A.G.M., LA. and VC.; Formal Analysis, ALN. and LA.,.; Investigation, SD., RP., KZ., SM., ET., CS., MAV., CK., LS., RT.,MW. and SS.; Data Curation, BA., ALN., LA.; Writing – Original Draft Preparation, BA., VP., ALN. and LA.; Writing – Review & Editing, all authors reviewed and accepted the final version of the article.; Supervision, VP., A.G.M., VC. and LA.; Project Administration, BA., VP. and YD.; Funding Acquisition, A.G.M., VC. and VP.

Declaration of Competing Interest

None to declare.

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