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Factors associated with COVID-19 infection in People Living with HIV. A case-control study nested in a Colombian cohort

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Abstract

Objective: People living with HIV (PLWH); can be especially vulnerable to the effects of SARS-Co V-2 and COVID-19. In this study, we evaluate the factors associated with acquiring COVID-19 and the severity of the infection among PLWH.

Materials and methods: Through a case-control study nested in a cohort, where cases were PLWH diagnosed with COVID-19; and controls were PLWH without the infection, 476 people were evaluated between May 1, 2020, and February 28, 2021. A univariate analysis was performed with the variables considered candidates. Binary logistic regression models were conducted for the COVID-19 outcome, and among those diagnosed with the infection, regression models for the outcome of hospitalization vs. outpatient treatment.

Results: Among 238 PLWH diagnosed with COVID-19, receiving integrase inhibitors p < 0.001 (CI 95% 0.27,0.72) or protease inhibitors p 0.034 (CI 95%0.42,0.97) within their antiretroviral regime, was associated with a lower probability of developing COVID-19. 196 (82,35%) of the 238 cases received outpatient treatment, and 42 (17,64%) required hospitalization. In this case, being older than 50 years p < 0.001 (CI 95% 1.8,9.64) and having obesity as a comorbidity p 0.017 (CI 95% 1.34,17.93) increased the possibility of requiring hospitalization, while receiving antiretroviral treatment or having received vaccination against influenza, decreased the likelihood of this outcome.

Conclusions: There are still many questions regarding whether there is a differential risk of acquiring COVID-19 among PLWH. Antiretroviral treatment with integrase or protease inhibitors; was associated with a lower probability of developing the co-infection. Some factors related to comorbidities, such as older age and obesity, draw attention to possible risk factors for hospitalization in this population. Discussing the feasibility of new studies with proposed causal hypotheses that allow directing the research designs toward a more precise answer to these questions is essential.

Key Words: COVID-19, HIV, case and control studies.

Factores asociados a la infección por COVID-19 en personas que viven con el VIH. Un estudio de casos y controles anidado en una cohorte colombiana.

Resumen

Objetivo: Las personas que viven con el VIH (PVV) pueden ser especialmente vulnerables a los efectos del SARS-CoV-2 y a la COVID-19. En el presente estudio, evaluamos los factores que se asocian a la presentación y severidad en esta población.

Materiales y métodos: A través de un estudio de casos y controles anidado en una cohorte, donde los casos fueron PVV, con diagnóstico de COVID-19 y los controles, PVV sin este diagnóstico, se evaluaron 476 personas entre el 1 de mayo de 2020 y el 28 de febrero de 202. Se realizó un análisis univariado y con las variables que se consideraron candidatas, se construyeron modelos de regresión logística binaria para el desenlace de COVID-19 y entre quienes presentaron esta infección, para el desenlace de hospitalización vs manejo ambulatorio.

Resultados: Entre 238 PVV diagnosticadas con COVID-19, el recibir tratamiento con inhibidores de integrasa p < 0.001 (CI 95% 0.27,0.72) o inhibidores de proteasa p 0.034 (CI 95%0.42,0.97) fueron asociados con una menor posibilidad de presentar COVID-19. De los 238 casos, 196 (82,35%) fueron atendidos ambulatoriamente y 42 (17,64%) requirieron hospitalización. En este caso, la edad mayor de 50 años p < 0.001 (CI 95% 1.8,9.64) y la obesidad p 0.017 (CI 95% 1.34,17.93) fueron factores que aumentaron la posibilidad de ser hospitalizado, mientras que el recibir tratamiento antirretroviral o haber recibido previamente vacunación contra influenza, disminuyeron la posibilidad de este desenlace.

Conclusiones: Aunque existen aún muchas preguntas acerca de si existe un riesgo diferencial de presentar COVID-19 en PVV y un riesgo aumentado de severidad en estas, algunos factores relacionados con la edad, tipo de antirretrovirales recibidos, vacunación previa con influenza y comorbilidades como la obesidad, llaman la atención sobre un posible rol como factores de riesgo aumentado o disminuido para estos desenlaces en esta población. Es importante discutir la factibilidad de realizar nuevos estudios con hipótesis causales planteadas que permitan dirigir los diseños de investigación hacia una respuesta más clara a estas preguntas.

Palabras clave: COVID-19, VIH, estudios de casos y controles.

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Introduction

The SARS-CoV-2 infection was declared a global health emergency and categorized as a pandemic by the World Health Organization (WHO)[1]. As we learn more about the infection, it has been established that severity and mortality rates are associated with underlying health conditions, such as hypertension, diabetes, and cardiovascular diseases[2]. Given these circumstances, many health institutions worldwide have questioned; whether there is an increased risk of morbidity and complications in immunocompromised patients[3].

Understanding susceptibility to SARS-CoV-2 infection among people living with HIV (PLWH) or propensity to develop a critical condition are crucial questions for health providers worldwide. The rapid and globally progressive spread of the COVID-19 pandemic occurs among the last great pandemic of our era, HIV[16]. Evidence to date does not suggest a higher incidence of the infection among PLWH, but once exposed, they have a greater risk of severe COVID-19[4]. PLWH can be disproportionately impacted by social determinants of health that may increase the risk of developing the infection and the severity of the disease[4]. In countries like Colombia, with high rates of late HIV presentation and still significant mortality[8], PLWH can be especially vulnerable to the effects of SARS-CoV-2. They also have increased rates of comorbidities, such as cardiovascular disease, pulmonary disease, cancer, obesity, and diabetes, which can raise the risk of severe COVID-19[4]. For this reason, it is a priority to maintain close surveillance of this population and to evaluate the impact of COVID-19 on them and, above all, the factors associated with its susceptibility, the different clinical stages, and the presence of possible protective factors that could be later evaluated in another type of population.

Our objective was to evaluate the factors associated with the propensity of developing the infection in PLWH and differentiated by the patient's clinical condition.

Materials and methods

Study design

We conducted an analytical observational study, nested case-control in a cohort. Cases were PLWH with an incident diagnosis of COVID-19, carried out using RT-PCR, and controls were PLWH randomly selected from this cohort, but who at the time of the selection had not acquired the infection. In a nested case-control study, cases are patients with the disease in a defined cohort. For each case, a specified number of matched controls is selected among those in the cohort who have not developed the disease by the time of disease occurrence in the case. For many research questions, the nested case-control design potentially offers impressive reductions in costs and efforts of data collection and analysis; and a relatively minor loss in statistical efficiency[6]; when compared to the complete cohort approach. This study was considered exploratory because we did not pre – hypothesize an associated factor but instead explored which of a few plausible factors were associated with COVID-19 infection in this population.

Setting

This study was conducted in a cohort of patients from Colombian health institutions providing attention to PLWH. These institutions are part of the VIHCOL group. The VIHCOL group is a research group that began its activities on February 2016, intending to establish an inclusive group of health institutions that offers integral attention to PLWH and generates a reliable and adequate information system. All centers report their indicators to the high-cost account of the Colombian Ministry of Health under its regulations and following the definitions of the Colombian clinical practice guideline. The institutions that took part in this study are located in Bogotá, Cali, and Medellín.

Participants

The criteria for selecting the participants and reviewing their medical history were: people older than 13 years with a confirmed diagnosis of HIV infection based on the recommendations of the Colombian clinical practice guideline for HIV[9]. Data from people who had declined authorization for research participation before the start of this study or during was excluded. When the study began, we did not know the prevalence of COVID-19 in PLWH or the risk of developing this comorbidity in our country. For this reason, the sampling was incidental and convenient; in a 1:1 ratio of cases and controls. Due to the analysis being carried out through a multiple logistic regression model, it was proposed to have at least ten events per variable[7].

Variables of study

Based on the knowledge of the researchers, the following variables were defined for analysis as possible associated factors: i) Biological sex of the person, male or female; ii) Age in years at the time of inclusion in the study; iii) Category of the residency area: urban, semi-urban or rural; iv) Clinical stage of the HIV infection at the time of inclusion in the study according to the classification revised by the Centers for Disease Control (CDC) in 2008[11]; v) CD4+ T lymphocyte count, CD8+ and CD4/CD8 index; vi) Viral load count in copies/ml of HIV RNA at the time of the diagnosis of COVID-19 or inclusion in the study; vii) Description of the type of antiretroviral combination and drug classes included in the regime; viii) If the patient has had their first antiretroviral treatment modified during the clinical follow-up, a description of the causes and the number of months since the modification until the study entry; ix) Comorbidities present by each participant (obesity and diabetes); x) Habits of the participants (active smoking); xi) Vaccination status against influenza, pneumococcus and hepatitis B and xii) Immigration status in the country.

Analysis of data

The data was collected from each health institution, and personnel from each center was responsible for completing the database based on the electronic medical record. A Microsoft Excel spreadsheet was provided to share the database with the principal investigator. Patients' data were coded to avoid sharing personal identities. The missing data was less than

5%, except for the CD8+ TL variable, which was greater than 20%, for which it was decided not to analyze and not to impute the missing values for other variables. The information was analyzed using the R programming language, version 4.1.0, and the RStudio integrated development environment. The normal distribution of the variables was evaluated using the Shapiro – Wilk test, reporting the median and the range when these variables did not present a normal distribution. Using the Mann-Whitney U test, the difference in medians for quantitative variables was evaluated when these variables had two categories; when they had more than two categories, the Kruskal-Wallis test was used. About qualitative variables, the hypothesis of independence was evaluated using the chi-square test or Fisher's F test in case of having expected values less than 5 in more than 25% of the values. To analyze both factors associated with the acquisition of COVID–19 and disease severity, multivariate analyzes were performed using binary logistic regressions with all the variables that were considered associated with the outcome in the bivariate analysis for plausibility and statistical criteria (in this case, a value of conservative p of 0,2 was the criterion). The best model was chosen after evaluating its AIC value, R2, and the area under the curve. This final selected model was assessed for its adjustment with the Hosmer-Lemeshow test, and the variables were considered significant if their p-value was less than 0.05.

Results

Data collected between May 1, 2020, and February 28, 2021, included 476 patients; 238 cases, and 238 controls, were analyzed. The characteristics of the participants are presented in Table 1. The median evolution time of the HIV infection was 4.52 years (range 0.04 to 23.10), and there was no difference between cases and controls. Among the patients with COVID-19, 31 (13%) were women, and 207 (87%) were men. Most patients lived in urban areas and were classified in stages 2 or 3 of HIV infection. No differences were found between the association of CD4 count and COVID-19 incidence, but instead were observed among patients under antiretroviral treatment (ART), receiving integrase and protease inhibitors, and for the variables smoking, migrant status, and diabetes (Table 1).

Of the 238 patients who acquired COVID-19, 196 (82,35%) received outpatient treatment, and 42 (17,64%) were hospitalized. Differences were observed between these outcomes regarding age, CD4 count, clinical stage of HIV infection, ART, vaccination status, causes of ART modification, obesity, and diabetes (Table 2).

Multivariate analysis: Regarding the diagnosis of COVID-19, the use of integrase inhibitors or protease inhibitors within the antiretroviral regime remained as factors that decreased the risk of acquiring COVID-19 by 56% and 46%, respectively (Table 3). Concerning hospitalization or outpatient treatment, age remains a factor that increases the possibility of being hospitalized as the person gets older; however, we are aware that PLWH and older than 50 years have a higher risk of cardiovascular comorbidity and that is the reason why this variable was categorized above this limit (50 years), with this analysis, the variable was significant between outpatient and hospitalized patients ($p < 0,0001$). Patients under antiretroviral treatment were 83% less likely to be hospitalized, similar to those vaccinated against influenza had 86% fewer possibilities for the same outcome. Finally, patients with obesity were associated with a 389% higher risk of hospitalization (Table 4).

Discussion

This study was conducted in a cohort of PLWH from 3 health institutes located in the three main cities of Colombia. We described the factors associated with the COVID-19 acquisition and severity; based on a series of variables considered of interest by knowledge and prior experience of clinical experts. Regarding the acquisition of COVID-19, integrase or protease inhibitors used within the antiretroviral regime were associated with decreased risk, adjusted to active smoking, immigration status, and TLCD4+ count. Patients co-infected with SARS-CoV-2 and HIV, who are 50 years or older, and obese were more likely to be hospitalized. In contrast, receiving antiretroviral treatment and vaccination against influenza were protective factors for this outcome.

As the pandemic continues, the susceptibility of PLWH to SARS-CoV-2 infection remains a concern; due to a higher burden of some comorbidities and a weakened adaptive immune response[8]. A cohort study from 60 health institutions that care for 77.590 PLWHs in Madrid (Spain); estimated a higher risk of acquiring COVID-19 and requiring hospitalization among PLWHs aged 70 years or older. On the contrary, receiving Tenofovir Disoproxil Fumarate/ Emtricitabine (TDF/FTC) within the antiretroviral treatment; resulted in a lower risk for both outcomes when compared with other drugs[9]. On the other hand, a multicenter cohort of 286 PLWH in the United States; observed that having three or more comorbidities was associated with both hospitalization and severe outcomes[10]. The authors of a systematic review reported that age and comorbidities appear to be the strongest predictors of severity and mortality in PLWH. Most patients that developed symptomatic COVID-19; had at least one comorbidity, more commonly hypertension, dyslipidemia, or type 2 diabetes[11]. However, these same authors concluded that, although prior case series and cohort studies did not find an increased risk of SARS-CoV-2 infection or severe COVID-19 outcomes among PLWH, recent studies have pointed out an increased risk of severity even in the context of virologically controlled patients. Although, it is unknown whether this is due to a higher prevalence of comorbidities and other social determinants of health among PLWH[11].

In contrast to other studies, our results suggest a protective effect of protease inhibitors. This outcome can be related to the findings of studies that have analyzed the effect of inhi-

Table 1. Demographic and clinical characteristics of the participants.

COVID-19 (Absolute Frequency (%))			
Variable	**YES (n = 238)**	**NO (n = 238)**	***P value***
Years since HIV diagnosis*	4.61 [0.038, 23.1]	4.40 [0.043, 23.1]	0.7032
No data	13 (5.5%)	9 (3.8%)	
Biological sex			
Female	31 (13.0%)	32 (13.4%)	0.8494
Male	207 (87.0%)	206 (86.6%)	
Age (years)*	36 [15, 73]	35 [19, 72]	0.6063
Residency area**			
Urban	234 (98.3%)	231 (97.1%)	0.5078
Semi-urban	3 (1.3%)	3 (1.3%)	
Rural	1 (0.4%)	4 (1.7%)	
HIV stage at the time of COVID-19 diagnosis			
1***	34 (14.3%)	28 (11.8%)	0.6854
2***	104 (43.7%)	104 (43.7%)	
3***	100 (42.0%)	106 (44.5%)	
TL $CD4^+$ count (cel/µL)*	434 [16, 1530]	426 [8, 1080]	0.3011
CD4 stage			
≥ 500 cel/µL	95 (39.9%)	80 (33.6%)	0.3189
≥ 200 y < 500 cel/µL	105 (44.1%)	120 (50.4%)	
< 200 cel/µL Variable	38 (16.0%) YES (n = 238)	38 (16.0%) NO (n = 238)	*P value*
CD4 percentage	26.0 [3.43, 67.9]	24.2 [2.20, 62.9]	0.2916
No data	4 (1.7%)	6 (2.5%)	
CD4/CD8 Index*	0.670 [0.0400, 2.46]	0.630 [0.0300, 3.52]	0.2605
No data	8 (3.4%)	3 (1.3%)	
Index stage CD4CD8			
≥ 1	64 (26.9%)	51 (21.4%)	0.1259
< 1	166 (69.7%)	184 (77.3%)	
No data	8 (3.4%)	3 (1.3%)	
Viral load HIV (copies/ml)*	20.0 [20.0, 1180000]	20.0 [20.0, 333000]	0.1312
No data	1.00 (0.4%)	2.00 (0.8%)	
Viral load stage HIV**			
< 50 copies/ml	186 (78.2%)	193 (81.1%)	0.725
≥ 50 y < 200 copies/ml	14.0 (5.9%)	11.0 (4.6%)	
≥ 200 y < 1000 copies/ml	7.00 (2.9%)	6.00 (2.5%)	
≥ 1000 y < 100000 copies/ml	23.0 (9.7%)	23.0 (9.7%)	
≥ 100000 copies/ml	7.00 (2.9%)	3.00 (1.3%)	
No data	1.00 (0.4%)	2.00 (0.8%)	
Receives ART			
No	14 (5.9%)	3 (1.3%)	0.0065
Yes Variable	224 (94.1%) YES (n = 238)	235 (98.7%) NO (n = 238)	*P value*
Receives Tenofovir			
No	83 (34.9%)	83 (34.9%)	0.6991
Yes	141 (59.2%)	152 (63.9%)	
No ART	14 (5.9%)	3 (1.3%)	

Table 1 (continued). Demographic and clinical characteristics of the participants.

COVID-19 (Absolute Frequency (%))			
Variable	**YES (n = 238)**	**NO (n = 238)**	***P value***
Receives integrase inhibitor			
No	165 (69.3%)	199 (83.6%)	0.0035
Yes	59 (24.8%)	36 (15.1%)	
No ART	14 (5.9%)	3 (1.3%)	
Receives protease inhibitor			
No	149 (62.6%)	170 (71.4%)	0.1756
Yes	75 (31.5%)	65 (27.3%)	
No ART	14 (5.9%)	3 (1.3%)	
Type of regime ART**			
Backbone (2 ITRN) + third drug	208 (87.4%)	230 (96.6%)	0.0199
Dual Therapy IP-INSTI	8 (3.4%)	1 (0.4%)	
Other regimes	8 (3.4%)	4 (1.7%)	
No ART	14 (5.9%)	3 (1.3%)	
Months with the actual ART regime*	25.8 [0, 252]	25.8 [0.06, 233]	0.8839
No data Variable	24 (10.1%) YES (n = 238)	13 (5.5%) NO (n = 238)	
Months with the actual ART regime category			
≤ 6 months	32 (13.4%)	38 (16.0%)	0.5798
> 6 months	182 (76.5%)	187 (78.6%)	
No data	24 (10.1%)	13 (5.5%)	
Previous changes in the ART regime			
No changes	102 (42.9%)	119 (50.0%)	0.395
With changes	107 (45.0%)	106 (44.5%)	
No data	24 (10.1%)	13 (5.5%)	
Active smoking			
No	208 (87.4%)	195 (81.9%)	0.12
Yes	30 (12.6%)	42 (17.6%)	
No data	0 (0%)	1 (0.4%)	
Obesity			
No	223 (93.7%)	228 (95.8%)	0.3043
Yes	15 (6.3%)	10 (4.2%)	
Diabetes			
No	230 (96.6%)	235 (98.7%)	0.1272
Yes	8 (3.4%)	3 (1.3%)	
Previous vaccination			
Influenza and pneumococcus	54 (22.7%)	68 (28.6%)	0.391
Influenza only	62 (26.1%)	59 (24.8%)	
Pneumococcus only Variable	18 (7.6%) YES (n = 238)	12 (5.0%) NO (n = 238)	
None	104 (43.7%)	99 (41.6%)	
Immigration status			
No	218 (91.6%)	226 (95.0%)	0.1431
Yes	20 (8.4%)	12 (5.0%)	
Country of origin			
Colombia	218 (91.6%)	226 (95.0%)	0.1607
Venezuela	19 (8.0%)	11 (4.6%)	
South America other than Venezuela	0 (0%)	1 (0.4%)	
Central America	1 (0.4%)	0 (0%)	

*Median and range. ** *p-value* calculated with Fisher test *** According to the classification revised by the Centers for Disease Control (CDC) in 2008.

Table 2. Demographic and clinical characteristics of patients with COVID-19.

Condition of the patient with COVID-19 (Absolute frequency (%))			
Variable	**Outpatient treatment (n = 196)**	**Hospitalized (n = 42)**	***P value***
Years since HIV diagnosis*	4.29 [0.0384, 22.0]	5.79 [0.0877, 23.1]	0.3281
Biological sex			
Female	26 (13.3%)	5 (11.9%)	0.8121
Male	170 (86.7%)	37 (88.1%)	
Age (years)*	34.0 [15.0, 73.0]	44.5 [20.0, 72.0]	0.0001
Residency area**			
Urban	193 (98.5%)	41 (97.6%)	0.5425
Semi-urban	2 (1.0%)	1 (2.4%)	
Rural	1 (0.5%)	0 (0%)	
HIV stage			
1***	30 (15.3%)	4 (9.5%)	0.1716
2***	89 (45.4%)	15 (35.7%)	
3***	77 (39.3%)	23 (54.8%)	
TL $CD4^+$ count (cel/µL)*	439 [68.0, 1530]	376 [16.0, 1480]	0.1023
CD4 stage			
≥ 500 cel/µL	81 (41.3%)	14 (33.3%)	0.0031
≥ 200 y < 500 cel/µL	91 (46.4%)	14 (33.3%)	
< 200 cel/µL	24 (12.2%)	14 (33.3%)	
CD4 percentage*	26.6 [6.92, 60.3]	22.0 [3.43, 67.9]	0.0447
No data	1 (0.5%)	3 (7.1%)	
CD4/CD8 Index*	0.700 [0.100, 2.33]	0.500 [0.0400, 2.46]	0.1545
No data	2 (1.0%)	6 (14.3%)	
Index stage CD4CD8			
≥ 1	55 (28.1%)	9 (21.4%)	0.6803
< 1	139 (70.9%)	27 (64.3%)	
No data	2 (1.0%)	6 (14.3%)	
Viral load HIV (copies/ml)*	20.0 [20.0, 394000]	20.0 [20.0, 1180000]	0.1647
No data	0 (0%)	1 (2.4%)	
Viral load stage HIV**			
< 50 copies/ml	155 (79.1%)	31 (73.8%)	0.0569
≥ 50 y < 200 copies/ml	13 (6.6%)	1 (2.4%)	
≥ 200 y < 1000 copies/ml	7 (3.6%)	0 (0%)	
≥ 1000 y < 100000 copies/ml	18 (9.2%)	5 (11.9%)	
≥ 100000 copies/ml	3 (1.5%)	4 (9.5%)	
No data	0 (0%)	1 (2.4%)	
Viral load stage HIV ****			
< 1000 copies/ml	175 (89.3%)	32 (76.2%)	0.0498
≥ 1000 copies/ml	21 (10.7%)	9 (21.4%)	
No data	0 (0%)	1 (2.4%)	
Receives ART			
No	7 (3.6%)	7 (16.7%)	0.0043
Yes	189 (96.4%)	35 (83.3%)	
Receives Tenofovir			
No	69 (35.2%)	14 (33.3%)	0.6944
Yes	120 (61.2%)	21 (50.0%)	
No ART	7 (3.6%)	7 (16.7%)	

Table 2 (continued). Demographic and clinical characteristics of patients with COVID-19.

Condition of the patient with COVID-19 (Absolute frequency (%))			
Variable	**Outpatient treatment (n = 196)**	**Hospitalized (n = 42)**	***P value***
Receives integrase inhibitor			
No	140 (71.4%)	25 (59.5%)	0.7441
Yes	49 (25.0%)	10 (23.8%)	
No ART	7 (3.6%)	7 (16.7%)	
Receives protease inhibitor			
No	124 (63.3%)	25 (59.5%)	0.5027
Yes	65 (33.2%)	10 (23.8%)	
No ART	7 (3.6%)	7 (16.7%)	
Type of regime ART**			
Backbone (2 ITRN) + third drug	177 (90.3%)	31 (73.8%)	0.2137
Dual Therapy IP-INSTI	7 (3.6%)	1 (2.4%)	
Other regim	5 (2.6%)	3 (7.1%)	
No ART	7 (3.6%)	7 (16.7%)	
Months with the actual ART regime*	25.8 [0, 252]	28.0 [0.700, 183]	0.9455
No data	12 (6.1%)	12 (28.6%)	
Months with the actual ART regime category			
≤ 6 months	26 (13.3%)	6 (14.3%)	0.4105
> 6 months	158 (80.6%)	24 (57.1%)	
No data	12 (6.1%)	12 (28.6%)	
Previous changes in the ART regime			
No changes	89 (45.4%)	13 (31.0%)	0.5172
With changes	90 (45.9%)	17 (40.5%)	
No data	17 (8.7%)	12 (28.6%)	
Active smoking			
No	168 (85.7%)	40 (95.2%)	0.0915
Yes	28 (14.3%)	2 (4.8%)	
Obesity			
No	189 (96.4%)	34 (81.0%)	0.0012
Yes	7 (3.6%)	8 (19.0%)	
Diabetes			
No	191 (97.4%)	39 (92.9%)	0.1505
Yes	5 (2.6%)	3 (7.1%)	
Previous vaccination			
Influenza and pneumococcus	40 (20.4%)	14 (33.3%)	0.0012
Influenza only	60 (30.6%)	2 (4.8%)	
Pneumococcus only	14 (7.1%)	4 (9.5%)	
None	82 (41.8%)	22 (52.4%)	
Immigration status**			
No	180 (91.8%)	38 (90.5%)	0.7611
Yes	16 (8.2%)	4 (9.5%)	
Country of origin			
Colombia	180 (91.8%)	38 (90.5%)	0.7969
Venezuela	15 (7.7%)	4 (9.5%)	
South America other than Venezuela	0 (0%)	0 (0%)	

*Median and range. ** *p-value* calculated with Fisher test *** According to the classification revised by the Centers for Disease Control (CDC) in 2008.

biting the protease on SARS CoV2 viral isolates, realizing that drugs such as ritonavir have in vitro activity against the virus[12]. However, several studies on this medication, including randomized control trials, systematic reviews, and meta-analyses, have failed to demonstrate benefits on mortality, hospital admission, or mechanical ventilation[8,13]. Distinctively, this effect has not been reported for integrase inhibitors, whereby our results regarding these drugs have to be deeply analyzed; before dropping out conclusions on this association.

Our study has various limitations. Despite being a case-control study nested in a cohort, the sample was selected from a cohort of patients located in the three main cities of the country; for this reason, patients may not represent the majority of sociodemographic contexts along Colombia. Additionally, the study is exploratory; since it was not developed from a previous hypothesis; other than the reports of variables that decreased the risk of severe COVID-19 (such as the use of TDF, for example). The variables analyzed were established by experts on the attention of PLWH and infectious diseases specialists, avoiding considering the analysis only based on statistical significance. Furthermore, bias surveillance may exist due to the possibility of undiagnosed cases within controls, for example, patients with an asymptomatic course of COVID-19 disease. This bias can overestimate some associations. The acquisition of COVID-19 was the principal outcome, and the sample was calculated for a logistics regression model for this result. Rates of hospitalization were evaluated to recognize variables that could be controlled to avoid this outcome. However, the small sample size could still be insufficient to find differences between variables and could affect the precision of the inferences.

On the other hand, the period in which the study was conducted had some specific epidemiological characteristics, including SARS-CoV2 variants and no access to effective vaccines; these factors added to a short follow-up limits the generalizability of the results.

Despite its limitations, this study is the first report providing a glance at the COVID-19 pandemic among PLWH in Colombia. The analysis and conclusions should be taken as an initial approach to this coinfection, not as confirmatory of associations and much less as causality. Our results would be helpful to generate hypotheses around variables associated with COVID-19, both for its acquisition and its severity, helping to propose new research designs that will help in their solving.
In conclusion, although, there are still many questions regarding whether there is a differential risk of acquiring COVID-19 among PLWH. Antiretroviral treatment with integrase or protease inhibitors was associated with a lower probability of developing the co-infection. Some factors related to comorbidities, such as older age and obesity, draw attention to possible risk factors for hospitalization in this population. Discussing the feasibility of new studies with proposed causal hypotheses that allow directing the research designs toward a more precise answer to these questions is essential.

Table 3. Binary logistic regression model for the diagnosis of COVID-19.

	Raw OR (IC95%)	Adjusted OR (IC95%)	P value
Integrase inhibitor			
No (Reference)			
Yes	0.51 (0.32,0.81)	0.44 (0.27,0.72)	< 0.001
Protease inhibitor			
No (Reference)			
Yes	0.75 (0.5,1.12)	0.64 (0.42,0.97)	0.034
Active smoking			
No (Reference)			
Yes	1.53 (0.91,2.57)	1.65 (0.97,2.82)	0.065
Immigrant status			
No (Reference)			
Yes	0.55 (0.26,1.16)	0.54 (0.25,1.16)	0.115
TLCD4⁺ count			
≥ 500 cel/µL (Reference)			
≥ 200 y < 500 cel/µL	1.37 (0.92,2.04)	1.41 (0.94,2.13)	0.099
< 200 cel/µL	1.36 (0.77,2.4)	1.58 (0.87,2.84)	0.131

Hosmer-Lemeshow p- value= 0.4013. R2 Nagelkerke = 6.19% AUC = 62.1%

Table 4. Binary logistic regression model for the severity (outpatient or hospital care) of COVID-19.

	Raw OR (IC95%)	Adjusted OR (IC95%)	P value
Age			
< 50 years (Reference)			
≥ 50 years	3.92 (1.88,8.14)	4.16 (1.8,9.64)	< 0.001
Receives ART			
No (Reference)			
Yes	0.19 (0.06,0.56)	0.17 (0.05,0.58)	0.005
Vaccination status			
None (Reference)			
Influenza	0.12 (0.03,0.55)	0.14 (0.03,0.64)	0.011
Streptococcus pneumoniae	1.06 (0.32,3.56)	1.27 (0.33,4.84)	0.724
Influenza and pneumococcus	1.3 (0.6,2.82)	1.03 (0.42,2.54)	0.951
Obesity			
No (Reference)			
Yes	6.35 (2.16,18.67)	4.89 (1.34,17.93)	0.017

Hosmer-Lemeshow p- value= 0.9718. R2 Nagelkerke = 27.01% AUC = 79.4%

Ethical considerations

This study was conducted considering Resolution 8439 of 1993, which regulates ethical aspects of research in Colombia and allows the classification of it as having no risk for the participants. The data from patients who had declined authorization for research participation was excluded, considering the Declaration of Helsinki of 2005 and the principle of beneficence and autonomy. The Research Ethics Committee of the Biological Research Corporation (CIB) approve this study, act number 43 (June 17, 2020).

Conflicts of interest. The authors of this manuscript declare not having any potential conflict of interest.

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MG, BH: Collected the data
JA, EM: Conceived and designed the analysis
All the authors declare that the requirements for the authorship have been fulfilled and approve the present version of the manuscript.

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