Clinical Microbiology and Infection 27 (2021) 1678–1684

Contents lists available at ScienceDirect

Clinical Microbiology and Infection

journal homepage: www.clinicalmicrobiologyandinfection.com

Original article

Prevalence and factors associated with SARS-CoV-2 seropositivity in the Spanish HIV Research Network Cohort

Juan Berenguer [1,*], Cristina Díez [1], María Martín-Vicente [2], Rafael Micán [3], María J. Pérez-Elías [4], Lucio J. García-Fraile [5], Francisco Vidal [6], Inés Suárez-García [7], Daniel Podzamczer [8], Jorge Del Romero [9], Federico Pulido [10], José A. Iribarren [11], Félix Gutiérrez [12], Eva Poveda [13], Carlos Galera [14], Rebeca Izquierdo [15], Víctor Asensi [16], Joaquín Portilla [17], Juan C. López [1], José R. Arribas [3], Santiago Moreno [4], Juan González-García [3], Salvador Resino [2,†], Inmaculada Jarrín [15,†]

[1] *Hospital General Universitario Gregorio Marañón, IiSGM, Madrid, Spain*
[2] *Centro Nacional de Microbiología (ISCIII), Majadahonda, Spain*
[3] *Hospital Universitario La Paz, IdiPaz, Madrid, Spain*
[4] *Hospital Ramón y Cajal, Universidad de Alcalá, IRYCIS, Madrid, Spain*
[5] *Hospital Universitario de La Princesa, Madrid, Spain*
[6] *Hospital Universitari de Tarragona Joan XXIII, IISPV, Universitat Rovira i Virgili, Tarragona, Spain*
[7] *Hospital Universitario Infanta Sofía, FIIB HUIS HHEN, San Sebastián de los Reyes, Universidad Europea de Madrid, Spain*
[8] *Hospital Universitari de Bellvitge, Barcelona, Spain*
[9] *Centro Sandoval, Madrid, Spain*
[10] *Hospital Universitario 12 Octubre, imas12, Universidad Complutense de Madrid, Madrid, Spain*
[11] *Hospital Universitario Donostia, II BioDonostia, San Sebastián, Spain*
[12] *Hospital Universitario de Elche, Universidad Miguel Hernández, Elche, Spain*
[13] *Galicia Sur Health Research Institute (IIS Galicia Sur)-Complexo Hospitalario Universitario de Vigo, SERGAS-UVigo, Spain*
[14] *Hospital Universitario Virgen de la Arrixaca, Murcia, Spain*
[15] *Centro Nacional de Epidemiología (ISCIII), Madrid, Spain*
[16] *Hospital Universitario Central de Asturias, Oviedo, Spain*
[17] *Hospital General Universitario de Alicante, Alicante, Spain*

ARTICLE INFO

Article history:
Received 9 March 2021
Received in revised form
8 June 2021
Accepted 12 June 2021
Available online 26 June 2021

Editor: C. Roy

Keywords:
COVID-19
HIV
SARS-CoV-2
Serology
Seroprevalence

ABSTRACT

Objectives: We aimed to assess the prevalence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and factors associated with seropositivity and asymptomatic coronavirus disease 2019 (COVID-19) among people with HIV (PWH).

Methods: This was a cross-sectional study carried out within the cohort of the Spanish HIV Research Network. Participants were consecutive PWH with plasma collected from 1st April to 30th September 2020. We determined SARS-CoV-2 antibodies (Abs) in plasma. Illness severity (NIH criteria) was assessed by a review of medical records and, if needed, participant interviews. Multivariable logistic regression analysis was used to identify predictors of seropositivity among the following variables: sex, age, country of birth, education level, comorbidities (hypertension, chronic heart disease, diabetes mellitus, non-AIDS-related cancer, chronic kidney disease, cirrhosis), route of HIV acquisition, prior AIDS, CD4+ cell count, HIV viral load, nucleoside/nucleotide reverse transcriptase inhibitor (N [t]RTI) backbone, type of third antiretroviral drug, and month of sample collection.

Results: Of 1076 PWH (88.0% males, median age 43 years, 97.7% on antiretroviral therapy, median CD4+ 688 cells/mm^3, 91.4% undetectable HIV viral load), SARS-CoV-2 Abs were detected in 91 PWH, a seroprevalence of 8.5% (95%CI 6.9–10.3%). Forty-five infections (45.0%) were asymptomatic. Variables independently associated with SARS-CoV-2 seropositivity were birth in Latin American countries versus Spain (adjusted odds ratio (aOR) 2.30, 95%CI 1.41–3.76, p 0.001), and therapy with tenofovir disoproxil

* Corresponding author: Juan Berenguer, Unidad de Enfermedades Infecciosas/VIH (4100), Hospital Gregorio Marañón, Doctor Esquerdo 46, 28007 Madrid, Spain.
E-mail address: jbb4@me.com (J. Berenguer).
† Salvador Resino and Inmaculada Jarrín contributed equally.

https://doi.org/10.1016/j.cmi.2021.06.023

fumarate plus emtricitabine (TDF/FTC) versus tenofovir alafenamide (TAF)/FTC as the N(t)RTI backbone (aOR 0.49, 95%CI 0.26–0.94, p 0.031).
Conclusions: Many SARS-CoV-2 infections among PWH were asymptomatic, and birth in Latin American countries increased the risk of SARS-CoV-2 seropositivity. Our analysis, adjusted by comorbidities and other variables, suggests that TDF/FTC may prevent SARS-CoV-2 infection among PWH. **Juan Berenguer, Clin Microbiol Infect 2021;27:1678**

Introduction

Human immunodeficiency virus (HIV) infection has been an uncommon underlying condition in large case series of coronavirus disease 2019 (COVID-19) associated with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [1–3]. Nevertheless, COVID-19 in people with HIV (PWH) has been the subject of substantial research and controversy [4–22]. Notwithstanding, whether HIV increases the risk of acquiring or dying from COVID-19 remains uncertain.

Seroprevalence studies are essential to better characterize viral infections, including their true prevalence/incidence among populations, geographical distribution, and groups at risk. Besides, seroprevalence studies reflect both clinical and subclinical infection, giving better insight into the disease spectrum and allowing a more reliable estimation of the infection fatality risk [23,24]. SARS-CoV-2 seroprevalence studies have been carried out among the general population in different countries [25–28] or specific populations at risk, such as healthcare workers [29–31] or patients with immune-mediated inflammatory diseases [32].

To the best of our knowledge, two SARS-CoV-2 seroprevalence studies in PWH have been reported so far. The first was a single-centre study carried out in May 2020 in the region of Perugia (Italy) with 270 asymptomatic participants, all of whom tested negative when 4% of the general population in the area was seropositive for SARS-CoV-2 [33]. In the second study, 500 PWH attending an HIV centre in Munich for routine laboratory controls between 29th May and 15th July 2020 were consecutively asked to participate [34]. Nine patients tested positive for SARS-CoV-2 with an IgG immunoassay, two of whom had been diagnosed with COVID-19. The estimated seroprevalence (accounting for the sensitivity and specificity of the test) was 1.5% (95%CI 0.69–3.13).

The objective of our work was to determine the prevalence of SARS-CoV-2 antibodies in a prospective cohort of PWH in Spain under the hypothesis that serological testing provides a suitable approach to assess the frequency of COVID-19 among PWH, to estimate the percentage of asymptomatic infections, and to identify potential risk factors for SARS-CoV-2 infection.

Patients and methods

Design and patient selection

In this cross-sectional study we determined antibodies against SARS-CoV-2 in plasma samples consecutively collected from 1st April 2020 to 30th September 2020 from PWH recruited in the Cohort of the Spanish HIV Research Network (CoRIS).

CoRIS is a prospective cohort of PWH older than 13 years, naive to antiretroviral therapy (ART) at study entry, seen for the first time from 1st January 2004, in 46 participating centres from 13 of 17 regions in Spain. The CoRIS database collects demographic and clinical data, HIV transmission category, ART history, previous opportunistic diseases, specific non-AIDS diseases, and serological and immunovirological data [35]. Blood and other biological samples from PWH in CoRIS are collected yearly and stored in the Spanish HIV BioBank [36]. The Ethics Committee of Hospital General Universitario Gregorio Marañón approved the study (Internal Ref# 162/20).

Data source

The data source for demographics, HIV-related characteristics, and comorbidities in this study was the CoRIS database. COVID-19-related clinical data were retrospectively collected from the electronic hospital and primary-care medical records and, if needed, participant phone interviews. The severity of illness was categorized following the National Institutes of Health (NIH) criteria: asymptomatic infection, and mild, moderate, severe, or critical illness [37].

Laboratory methods

Blood samples were collected at study sites by venepuncture in EDTA tubes, which were then sent the same day to the HIV HGM BioBank where they were processed, and plasma was immediately stored until use at −80°C. For this study, plasma samples were sent to the National Centre for Microbiology, Instituto de Salud Carlos III, where they were tested using the Platelia SARS-CoV-2 Total Ab assay (BioRad, Hercules, CA, USA), following the manufacturer's protocol. This is a qualitative combined enzyme-linked immunoassay (ELISA) for detecting IgG, IgA, and IgM antibodies against the nucleocapsid protein (N protein) of SARS-CoV-2.

Statistics

Descriptive analysis of individuals' characteristics was carried out using frequency tables with percentages for categorical variables and median and quartiles for continuous variables. We calculated the prevalence of SARS-CoV-2 antibodies according to potential risk factors and estimated the magnitude of the association between risk factors and seropositivity by computing odds ratios (ORs) and their 95% confidence intervals (95%CIs). Wald tests were used to derive pairwise p-values for differences in seropositivity between the different categories of each potential risk factor and the reference category. Multivariable models included all the following variables: sex, age, country of birth, education level, comorbidities (hypertension, chronic heart disease, diabetes mellitus, non-AIDS related cancer, chronic kidney disease, cirrhosis), route of HIV acquisition, prior AIDS, CD4+ cell count, HIV viral load, nucleoside/nucleotide reverse transcriptase inhibitors (N [t]RTI) backbone, type of third antiretroviral drug, and month of sample collection. The association of antiretroviral drugs and SARS-CoV-2 seropositivity was investigated because of the protective effect against COVID-19 of the tenofovir disoproxil fumarate plus emtricitabine (TDF/FTC) backbone in two extensive observational studies [14,18]. Given that the number of events (seropositivity) per

covariate was ≤10 in some variables, we used penalization through data augmentation to perform multivariate logistic regression to avoid sparse data bias, setting the prior odds ratio as 1 (uncertain direction) [38]. Statistical analyses were performed by Stata 15.0 software (StataCorp, College Station, TX, USA).

Results

Of 16 178 PWH in active follow-up in CoRIS, plasma samples were collected and stored at the BioBank from 1076 (6.7%) during the study period. These samples are approximately half of those collected during the same period in the preceding year due to circumstances related to the COVID-19 pandemic.

The characteristics of the entire cohort and those PWH included or not in the serosurvey are shown in Table 1. Of the 1076 PWH with plasma samples available for this study, 88.0% were males at birth, their median age was 43 years, 72.3% self-identified as men having sex with men (MSM), 70.0% were native-born Spaniards, 70.9% had high school or university education, 12.3% had had prior AIDS-defining conditions, 97.7% were on ART, their median CD4 cell count was 688 cells/mm^3, and 91.4% had an undetectable HIV viral load. Arterial hypertension was the most common comorbidity (30.5%); less frequent comorbidities (<4.0%) were non-AIDS-defining cancers, diabetes mellitus, chronic heart disease, chronic kidney disease, and liver cirrhosis. Compared with PWH not included in the seroprevalence study, those included were more frequently males at birth, MSM, native Spaniards, and had a higher educational level. Furthermore, they were more frequently diagnosed with arterial hypertension and less frequently had had prior AIDS-defining conditions. Finally, they were more frequently receiving an ART regimen based on tenofovir alafenamide plus emtricitabine (TAF/FTC). The characteristic of PWH included in the serosurvey categorized according to the different N(t)TRI backbones are shown in the Supplementary Material (Table S1). The

Table 1
Characteristics of people with HIV (PWH) in active follow-up in CoRIS during the study period

Variable	Total PWH n = 16 178	PWH included in the serosurvey n = 1076	PWH not included in the serosurvey n = 15 102	p
Male sex at birth: *n*/with data (%)	13 802/16 178 (85.3)	947/1076 (88.0)	12 855/15 102 (85.1)	0.010
Age				
Distribution: *n*/with data (%)				0.279
18–34	3356/16 178 (20.7)	235/1076 (21.8)	3121/15 102 (20.7)	
35–49	7939/16 178 (49.1)	537/1076 (49.9)	7402/15 102 (49.0)	
50–64	4112/16 178 (25.4)	264/1076 (24.5)	3848/15 102 (25.5)	
≥65	771/16 178 (4.8)	40/1076 (3.7)	731/15 102 (4.8)	
Median (Q1; Q3) yr	44 (36; 52)	43 (36; 51)	44 (36:52)	0.101
Mechanism of HIV acquisition: *n*/with data (%)				< 0.001
Men having sex with men	10 013/15 717 (63.7)	745/1030 (72.3)	9268/14 687 (63.1)	
Heterosexual	4430/15 717 (28.2)	258/1030 (25.0)	4172/14 687 (28.4)	
Injection drug use	1118/15 717 (7.1)	20/1030 (1.9)	1098/14 687 (7.5)	
Other	156/15 717 (1.0)	7/1030 (0.7)	149/14 687 (1.0)	
Country of birth: *n*/with data (%)				< 0.001
Spain	9480/16 112 (58.8)	753/1075 (70.0)	8727/15 037 (58.0)	
Latin American countries	3457/16 112 (21.5)	231/1075 (21.5)	3226/15 037 (21.5)	
Other	3175/16 112 (19.7)	91/1075 (8.5)	3084/15 037 (20.5)	
Level of education: *n*/with data (%)				< 0.001
Compulsory education/no education	4688/13 536 (34.6)	257/951 (27.0)	4431/12 585 (35.2)	
High school/university	8581/13 536 (63.4)	674/951 (70.9)	7907/12 585 (62.8)	
Other	267/13 536 (2.0)	20/951 (2.1)	247/12 585 (2.0)	
Comorbidities *n*/with data (%)				
Hypertension	2402/16 178 (14.9)	328/1076 (30.5)	2074/15 102 (13.7)	< 0.001
Chronic heart disease	390/15 969 (2.4)	29/1067 (2.7)	361/14 902 (2.4)	0.546
Diabetes	459/15 969 (2.9)	25/1067 (2.3)	434/14 902 (2.9)	0.282
History of non-AIDS-related cancer	770/15 969 (4.8)	42/1067 (3.9)	728/14 902 (4.9)	0.162
Chronic kidney disease	254/9298 (2.7)	19/890 (2.1)	235/8408 (2.8)	0.251
liver cirrhosis	183/15 969 (1.2)	6/1067 (0.6)	177/14 902 (1.2)	0.064
Prior AIDS-defining conditions *n*/with data (%)	2363/16 178 (14.6)	132/1076 (12.3)	2231/15 102 (14.8)	0.025
Last CD4+ count				
Distribution *n*/with data (%)				*0.606*
<350	1116/9836 (11.4)	100/957 (10.4)	1016/8879 (11.4)	
350–499	1344/9836 (13.7)	136/957 (14.2)	1208/8879 (13.6)	
≥500	7376/9836 (75.0)	721/957 (75.3)	6655/8879 (75.0)	
Median (Q1; Q3) cells/mm^3	702 (499; 921)	688 (500; 909)	702 (499–922)	*0.477*
Last HIV-RNA load ≤50 copies/mm^3 *n*/with data (%)	8996/10 005 (89.9)	918/1004 (91.4)	8078/9001 (89.7)	*0.092*
Antiretroviral therapy (N [t]RTI backbone) *n*/with data (%)				*< 0.001*
TAF/FTC	4289/14 587 (29.4)	416/1062 (39.2)	3873/13 525 (28.6)	
ABC/3TC	3912/14 587 (26.8)	279/1062 (26.3)	3633/13 525 (26.9)	
TDF/FTC	3036/14 587 (20.8)	154/1062 (14.5)	2882/13 525 (21.3)	
Other	1927/14 587 (13.2)	188/1062 (17.7)	1739/13 525 (12.9)	
No antiretroviral therapy	1423/14 587 (9.8)	25/1062 (2.3)	1398/13 525 (10.3)	
Antiretroviral therapy (third drug)				*< 0.001*
NNRTI	3434/14 587 (23.5)	247/1062 (23.3)	3187/13 525 (23.6)	
Protease inhibitor	1451/14 587 (10.0)	63/1062 (5.9)	1388/13 525 (10.3)	
Integrase inhibitor	6322/14 587 (43.3)	530/1062 (49.9)	5792/13 525 (42.8)	
Other	1957/14 587 (13.4)	197/1062 (18.6)	1760/13 525 (13.0)	
No antiretroviral therapy	1423/14 587 (9.8)	25/1062 (2.3)	1398/13 525 (10.3)	

CoRIS, Spanish HIV Research Network Cohort; Q1, 1st quartile; Q3, 3rd quartile; N(t)RTI, nucleoside/nucleotide reverse transcriptase inhibitors; TAF, tenofovir alafenamide; FTC, emtricitabine; ABC, abacavir; 3TC, lamivudine; TDF; tenofovir disoproxil fumarate; NNRTI, non-nucleoside reverse transcriptase inhibitors.

groups were well matched according to baseline characteristics except for arterial hypertension which was more frequent among PWH receiving TAF/FTC.

SARS-CoV-2 antibodies were detected in 91 of 1076 PWH, a prevalence of 8.5% (95%CI 6.9–10.3%). The estimated seroprevalence for the full cohort of 16 178 PWH weighted by sex, age,

Table 2
Prevalence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) antibodies broken down by patient characteristics and factors associated with SARS-CoV-2 seropositivity by univariable and multivariable logistic regression analyses adjusted and non-adjusted for sparse data bias

Variable	Antibody$^+$/total (%)	Univariable logistic regression		Multivariable logistic regression			
				Non-adjusted for sparse data bias		Adjusted for sparse data bias	
		OR (95%CI)	p	OR (95%CI)	p	OR (95%CI)	p
Sex							
Male	85/947 (9.0)	Ref		Ref		Ref	
Female	6/129 (4.6)	0.49 (0.21–1.16)	0.104	0.42 (0.15–1.16)	0.095	0.64 (0.32–1.27)	0.206
Age, years							
18–34	21/235 (8.9)	Ref		Ref		Ref	
35–49	47/537 (8.7)	0.98 (0.57–1.68)	0.934	1.13 (0.63–2.04)	0.685	1.13 (0.64–1.98)	0.677
50–64	20/264 (7.6)	0.84 (0.44–1.58)	0.581	0.96 (0.46–2.01)	0.923	0.99 (0.50 -1.99)	0.984
≥65	3/40 (7.5)	0.83 (0.23–2.91)	0.766	0.81 (0.16–4.04)	0.795	0.99 (0.44–2.23)	0.984
Mechanism of HIV acquisition							
MSM	68/745 (9.1)	Ref		Ref		Ref	
Heterosexual	20/258 (7.7)	0.84 (0.50–1.41)	0.501	1.36 (0.70–2.65)	0.364	1.13 (0.61–2.10)	0.702
IDU	1/20 (5.0)	0.52 (0.07–3.97)	0.532	0.78 (0.09–6.87)	0.827	0.95 (0.40–2.91)	0.912
Other	1/7 (14.3)	1.66 (0.20–13.99)	0.641	2.67 (0.23–30.84)	0.431	1.13 (0.45–2.87)	0.796
Country of birth							
Spain	54/753 (7.2)	Ref		Ref		Ref	
Latin American countries	33/231 (14.3)	2.16 (1.36–3.42)	0.001	2.34 (1.41–3.89)	0.001	2.30 (1.41–3.76)	0.001
Other	4/91 (4.4)	0.60 (0.21–1.68)	0.328	0.64 (0.22–1.89)	0.420	0.82 (0.41–1.64)	0.572
Level of education							
Compulsory education/no education	16/257 (6.2)	Ref		Ref		Ref	
High school/University	65/674 (9.6)	1.61 (0.91–2.83)	0.101	1.45 (0.79–2.68)	0.234	1.43 (0.79–2.61)	0.239
Other	0/20 (0)	—	—	—	—	—	—
Comorbidities							
Hypertension							
No	56/748 (7.5)	Ref		Ref		Ref	
Yes	35/328 (10.7)	1.48 (0.95–2.30)	0.086	1.57 (0.95–2.58)	0.078	1.61 (0.99–2.62)	0.056
Chronic heart disease							
No	88/1038 (8.5)	Ref		Ref		Ref	
Yes	3/29 (10.3)	1.25 (0.37–4.20)	0.723	1.54 (0.39–6.08)	0.540	1.14 (0.51–2.55)	0.750
Diabetes							
No	89/1042 (8.5)	Ref		Ref		Ref	
Yes	2/25 (8.0)	0.93 (0.22–4.01)	0.924	0.77 (0.14–4.24)	0.764	0.94 (0.41–2.16)	0.889
History of non-AIDS-related cancer							
No	88/1025 (8.6)	Ref		Ref		Ref	
Yes	3/42 (7.1)	0.82 (0.25–2.70)	0.743	0.86 (0.25–2.97)	0.810	0.95 (0.44–2.01)	0.884
Chronic kidney disease							
No	70/871 (8.0)	Ref		Ref		Ref	
Yes	3/19 (15.8)	2.15 (0.61–7.54)	0.234	2.61 (0.62–10.95)	0.188	1.37 (0.59–3.18)	0.465
Liver cirrhosis							
No	91/1061 (8.6)	Ref		Ref		Ref	
Yes	0/6 (0)	—	—	—	—	—	
Prior AIDS-defining conditions							
No	80/944 (8.5)	Ref		Ref		Ref	
Yes	11/132 (8.3)	0.98 (0.51–1.90)	0.956	1.01 (0.47–2.17)	0.971	1.04 (0.50–2.17)	0.909
CD4+ count cells/mm^3							
<350	9/100 (9.0)	Ref		Ref		Ref	
350–499	13/136 (9.6)	1.07 (0.44–2.61)	0.884	0.96 (0.37–2.48)	0.933	0.98 (0.50–1.92)	0.947
≥500	62/721 (8.6)	0.95 (0.46–1.98)	0.894	0.87 (0.38–2.00)	0.740	9.90 (0.45–1.83)	0.778
Last HIV-RNA load copies/mm^3							
≤50	80/918 (8.7)	Ref		Ref		Ref	
>50	5/86 (5.8)	0.65 (0.25–1.64)	0.359	0.48 (0.17–1.35)	0.162	0.68 (0.35–1.34)	0.266
Unknown	6/72 (8.3)	0.95 (0.40–2.27)	0.912	2.14 (0.59–7.70)	0.245	2.11 (0.59–7.50)	0.248
Antiretroviral therapy (NRTI backbone)							
TAF/FTC	40/416 (9.6)	Ref		Ref		Ref	
TDF/FTC	5/154 (3.2)	0.32 (0.12–0.81)	0.017	0.25 (0.09–0.70)	0.008	0.49 (0.26–0.94)	0.031
ABC/3TC	23/279 (8.2)	0.84 (0.49–1.44)	0.537	0.91 (0.51–1.62)	0.741	0.97 (0.55–1.73)	0.926
Other	17/188 (9.0)	0.93 (0.52–1.70)	0.824	0.43 (0.05–3.98)	0.458	0.57 (0.07–4.84)	0.607
No antiretroviral therapy	3/25 (12.0)	1.28 (0.37–4.47)	0.697	1.03 (0.24–4.32)	0.970	1.25 (0.31–5.04)	0.756
Antiretroviral therapy (third drug)							
NNRTI	21/247 (8.5)	Ref		Ref		Ref	
Protease inhibitor	4/63 (6.3)	0.73 (0.24–2.21)	0.577	0.53 (0.16–1.74)	0.293	0.80 (0.38–1.66)	0.547
Integrase inhibitor	42/530 (7.9)	0.93 (0.54–1.60)	0.784	0.67 (0.35–1.27)	0.219	0.82 (0.44–1.50)	0.511
Other	18/197 (9.1)	1.08 (0.56–2.09)	0.814	1.51 (0.17–13.56)	0.711	1.48 (1.82–12.20)	0.711

(*continued on next page*)

Table 2 (*continued*)

Variable	Antibody$^+$/total (%)	Univariable logistic regression		Multivariable logistic regression			
				Non-adjusted for sparse data bias		Adjusted for sparse data bias	
		OR (95%CI)	p	OR (95%CI)	p	OR (95%CI)	p
No antiretroviral therapy	3/25 (12.0)	1.47 (0.41–5.31)	0.559	—		—	
Month of sample collection							
April	4/55 (7.3)	Ref		Ref		Ref	
May	23/240 (9.6)	1.35 (0.45–4.08)	0.593	1.39 (0.44–4.40)	0.580	1.36 (0.44–4.27)	0.593
June	26/329 (7.9)	1.09 (0.37–3.27)	0.872	1.12 (0.36–3.50)	0.849	1.14 (0.37–3.51)	0.819
July	12/173 (6.9)	0.95 (0.29–3.08)	0.932	1.00 (0.29–3.40)	0.998	0.96 (0.289–3.21)	0.951
August	7/85 (8.2)	1.14 (0.32–4.11)	0.836	1.44 (0.37–5.55)	0.596	1.32 (0.35–4.98)	0.410
September	19/194 (9.8)	1.38 (0.45–4.25)	0.570	1.49 (0.46–4.81)	0.501	1.42 (0.45–4.50)	0.550

PWH, people with HIV; Q1, 1st quartile; Q3, 3rd quartile; N(t)RTI, nucleoside/nucleotide reverse transcriptase inhibitors; TAF, tenofovir alafenamide; FTC, emtricitabine; ABC, abacavir; 3TC, lamivudine; TDF; tenofovir disoproxil fumarate.

transmission category, country of birth and level of education was 8.1% (95%CI 6.5–10.0%). The seroprevalence remained relatively stable during the study period, being lowest in samples collected in April (4 of 55, 7.3%) and highest in those collected in September (19 of 194, 9.8%).

Forty-one PWH with serologically confirmed COVID-19 had asymptomatic infections; the disease was mild in 43, moderate in four, severe in three, and none had critical disease. Seven PWH were admitted to the hospital, six required oxygen therapy, and three received non-invasive ventilation. Treatment with corticosteroids was administered to three PWH, and no one was treated with remdesivir or cytokine inhibitors. None was admitted to intensive care units or died. Laboratory confirmation of COVID-19 by RT-PCR or antigen testing had been performed in 22 PWH.

The prevalence of SARS-CoV-2 antibodies broken down by patients' characteristics and unadjusted and adjusted OR (95%CI) for the association between each potential risk factor and SARS-CoV-2 seropositivity are described in Table 2. Multivariable analyses adjusted for sparse data bias showed that individuals born in Latin American countries had twice the odds of being SARS-CoV-2-seropositive than native-born Spaniards (adjusted OR (aOR) 2.30, 95%CI 1.41–3.76], p 0.001). In contrast, treatment with the TDF/FTC backbone was associated with half the odds of SARS-CoV-2 seropositivity compared to that based on TAF/FTC (aOR 0.49, 95%CI 0.26–0.94, p 0.031) (Fig. 1). No statistically significant differences in SARS-CoV-2 seropositivity were found concerning age, mechanism of HIV acquisition, level of education, comorbidities, prior AIDS-defining conditions, CD4+ cell counts, HIV detectability, type of third antiretroviral drug used, and month of sample collection.

Discussion

In this study, with plasma samples consecutively collected from 1076 PWH enrolled in a prospective cohort in Spain during the first wave of the pandemic in Spain, the prevalence of SARS-CoV-2 antibodies was 8.5%. Of 91 PWH with serologically confirmed COVID-19, almost half had asymptomatic infections. Birth in Latin American countries was associated with an increased risk of SARS-CoV-2 seropositivity, whereas therapy with TDF/FTC was associated with a lower risk of seropositivity.

The seropositivity against SARS-CoV-2 in our study is somewhat higher than that found in a population-based serosurvey carried out in Spain during the second trimester of 2020 [25]. In this previous study, with 61 075 participants, the seroprevalence was 5.0% by a point-of-care test and 4.6% by a qualitative immunoassay to detect IgG against SARS-CoV-2. Differences in study design must be taken into account when interpreting the results of both studies. First, the nationwide survey was based on a random sampling of households from the national municipal register representative of the Spanish population, whose sociodemographic characteristics differ from individuals in CoRIS who are younger, more frequently male, and less frequently Spanish born than patients in the nationwide survey. Second, the specimens for serological testing were collected in 2 weeks between April and May 2020 in the nationwide survey and over 6 months between April and September in the present study.

Various tests have been used to detect antibodies against SARS-CoV-2, with different diagnostic performances. ELISA tests detecting combined IgG and IgM have shown higher diagnostic sensitivity than ELISA tests for only IgG or IgM [39,40]. The total antibody serological test used in this study has shown excellent diagnostic accuracy for COVID-19, with an AUC of 0.933 and sensitivity and specificity >90% [41], and with a higher sensitivity than other ELISA tests 0–10 days after PCR for detecting SARS-CoV-2-infected patients [42].

The proportion of serologically proved infections in our study that were asymptomatic was 45.0%; this is a noteworthy finding because, to the best of our knowledge, a reliable estimate of the fraction of asymptomatic COVID-19 episodes among PWH has not previously been reported. In the Spanish serosurvey mentioned before, approximately one third of SARS-CoV-2 infections in the general population were asymptomatic [25], a proportion similar to that found in a recently published systematic review on the subject [43].

The association between birth in Latin American countries and a higher risk of SARS-CoV-2 seropositivity is concordant with observations that racial/ethnic minorities or economically disadvantaged people of any background are more susceptible to becoming infected by SARS-CoV-2, most likely due to living or working conditions that increase exposure to the infection, and because of a higher burden of comorbidities [44].

A relevant finding was that TDF/FTC use was associated with a significantly lower risk of serologically confirmed infection after adjustment by demographics, country of birth, education level, comorbidities, and HIV-related variables, including the third drug. Tenofovir diphosphate is a permanent terminator for the SARS-CoV-2 RNA-dependent RNA polymerase [45] with activity against SARS-CoV-2 *in vitro* [46] and in an animal model in ferrets [47]. Besides, the potential beneficial effect of TDF/FTC against COVID-19 has also been found in other large observational studies. In a multicentric cohort in Spain with 77 590 PWH receiving ART, the risk for COVID-19 hospitalization was lower in those receiving TDF/FTC versus those receiving other regimens, although residual confounding by comorbid conditions could not be ruled out [14]. In another study based on real-world data in the Western Cape, South Africa, with 54 0552 PWH of whom 3978 had COVID-19, TDF was associated with lower COVID-19 mortality compared to other antiretrovirals among those on ART, an association that remained when adjusting for kidney disease, viral suppression and ART duration [18]. The association of TDF/TFC but not TAF/FTC with a protective effect against SARS-CoV-2 infection could be related, at

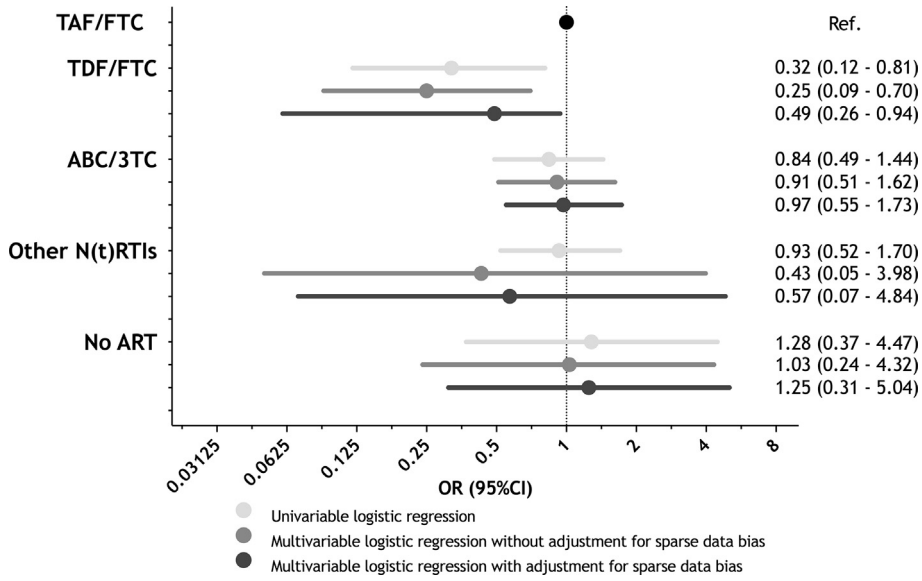

Fig. 1. Association of the nucleoside/nucleotide reverse transcriptase inhibitors (N(t)RTI) backbone with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) seropositivity by logistic regression analysis. Multivariable models were adjusted by sex, age, country of birth, education level, comorbidities, route of HIV acquisition, prior AIDS, CD4+ cell count, HIV viral load, type of third antiretroviral drug used, and month of sample collection. To avoid sparse data bias, we used penalization through data augmentation to perform multivariate logistic regression. TAF, tenofovir alafenamide; FTC, emtricitabine; TDF, tenofovir disoproxil fumarate; ABC, abacavir; 3TC, lamivudine; ART, antiretroviral therapy; OR, odds ratio; CI, confidence interval.

the doses used for HIV, to the fact that TAF yields lower plasma albeit higher intracellular levels of tenofovir than those achieved with TDF [48].

Our study is limited because it was not a random sampling survey among PWH included in CoRIS, and because clinical data related to COVID-19 were collected retrospectively. Another limitation relates to the large number of tests performed in the multivariable model because this increases the probability of finding associations below the significance level of $p < 0.05$. Our study is also limited because socioeconomic factors different from country of birth and education level, such as housing and work, were not available. Finally, some characteristics of the participants in CoRIS (relatively young age, good control of HIV infection, and low frequency of comorbidities) raise a question about the applicability of some of the results of this study to settings where PWH characteristics are less favourable.

Our study's strengths include the leverage within a prospective cohort of PWH, the large sample size, the adjustment for important covariables, including comorbidities, and the adjustment for sparse data bias in the multivariable regression analysis.

In conclusion, the seropositivity against SARS-CoV-2 among PWH in CoRIS was slightly higher than that found in Spain's general population during the first wave of the pandemic, and birth in Latin American countries increased the risk of SARS-CoV-2 seropositivity among PWH. We also found that many SARS-CoV-2 infections among PWH are asymptomatic, as in the general population. Our analysis, adjusted by comorbidities and other variables, further suggests that TDF/FTC may prevent SARS-CoV-2 infection among PWH. We believe that the accumulated evidence justifies randomized trials with TDF/FTC to treat and prevent COVID-19.

Author contributions

JB, CD, SM, JG-G, SR and IJ: study conception and design. MM-V and SR: laboratory procedures. IJ: statistical analyses. JB, IJ and SR: interpretation of data. JB: obtaining funding and drafting of the manuscript. All authors: acquisition of data, critical revision of the manuscript for important intellectual content, and agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Transparency declaration

Juan Berenguer reports honoraria for advice or public speaking from ABBVIE, GILEAD, MSD, JANSSEN, and ViiV Healthcare, and grants from ABBVIE, GILEAD, MSD, and ViiV Healthcare. María J. Pérez-Elías reports honoraria for advice or public speaking from GILEAD, MSD, JANSSEN, and ViiV Healthcare. Lucio J. García-Fraile reports honoraria for advice or public speaking from MSD, and grants from GILEAD. Inés Suárez-García reports honoraria for advice or public speaking from GILEAD, MSD, and ViiV Healthcare. Daniel Podzamczer reports honoraria for advice or public speaking from GILEAD, MSD, JANSSEN, and ViiV Healthcare, and grants from GILEAD, MSD, and ViiV Healthcare. Federico Pulido reports honoraria for advice or public speaking from ABBVIE, GILEAD, MSD, JANSSEN, and ViiV Healthcare. Félix Gutiérrez reports honoraria for advice or public speaking from JANSSEN and ViiV Healthcare. Víctor Asensi reports honoraria for advice or public speaking from ABBVIE, GILEAD, MSD, JANSSEN, and ViiV Healthcare, and grants from JANSSEN and ViiV Healthcare. Juan C. López reports honoraria for advice or public speaking from GILEAD, MSD, JANSSEN, and ViiV Healthcare. José R. Arribas reports honoraria for advice or public speaking from ALEXA, GILEAD, MSD, JANSSEN, SERONO, TEVA, and ViiV Healthcare, and grants from ALEXA, GILEAD, JANSSEN, MSD, SERONO, TEVA, and ViiV Healthcare. Santiago Moreno reports honoraria for advice or public speaking from GILEAD, MSD, JANSSEN, and ViiV Healthcare, and grants from GILEAD, MSD, and ViiV Healthcare. Juan González-García reports honoraria for advice or public speaking from GILEAD, MSD, JANSSEN, and ViiV Healthcare. Inmaculada Jarrín reports honoraria for advice or public speaking from GILEAD, and ViiV Healthcare, and grants from MSD. Cristina Díez, María Martín-Vicente, Rafael Micán, Francisco Vidal, Jorge Del Romero, José A. Iribarren, Eva Poveda, Carlos Galera, Rebeca

Izquierdo, Joaquín Portilla, and Salvador Resino have nothing to disclose. This work was supported by the Instituto de Salud Carlos III (ISCII) (grant number COV20/00108) and the Spanish AIDS Research Network (RD16/0025), which is included in the Spanish I + D + I Plan and is co-funded by ISCIII-Subdirección General de Evaluacion and European Funding for Regional Development (FEDER).

Acknowledgements

We are indebted to all the patients who participated in this research.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cmi.2021.06.023.

References

[1] Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, et al. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med 2020;382:1708–20.
[2] Docherty AB, Harrison EM, Green CA, Hardwick HE, Pius R, Norman L, et al. Features of 20 133 UK patients in hospital with covid-19 using the ISARIC WHO Clinical Characterisation Protocol: prospective observational cohort study. BMJ 2020;369:m1985.
[3] Berenguer J, Ryan P, Rodriguez-Bano J, Jarrin I, Carratala J, Pachon J, et al. Characteristics and predictors of death among 4035 consecutively hospitalized patients with COVID-19 in Spain. Clin Microbiol Infect 2020;26:1525–36.
[4] Blanco JL, Ambrosioni J, García F, Martínez E, Soriano A, Mallolas J, et al. COVID-19 in HIV Investigators. COVID-19 in patients with HIV: clinical case series. Lancet HIV 2020;7:E314–6.
[5] Vizcarra P, Perez-Elias MJ, Quereda C, Moreno A, Vivancos MJ, Dronda F, et al. Description of COVID-19 in HIV-infected individuals: a single-centre, prospective cohort. Lancet HIV 2020;7:e554–64.
[6] Gervasoni C, Meraviglia P, Riva A, Giacomelli A, Oreni L, Minisci D, et al. Clinical features and outcomes of patients with human immunodeficiency virus with COVID-19. Clin Infect Dis 2020;71:2276–8.
[7] Childs K, Post FA, Norcross C, Ottaway Z, Hamlyn E, Quinn K, et al. Hospitalized patients with COVID-19 and human immunodeficiency virus: a case series. Clin Infect Dis 2020;71:2021–2.
[8] Karmen-Tuohy S, Carlucci PM, Zervou FN, Zacharioudakis IM, Rebick G, Klein E, et al. Outcomes among HIV-positive patients hospitalized with COVID-19. J Acquir Immune Defic Syndr 2020;85:6–10.
[9] Collins LF, Moran CA, Oliver NT, Moanna A, Lahiri CD, Colasanti JA, et al. Clinical characteristics, comorbidities and outcomes among persons with HIV hospitalized with coronavirus disease 2019 in Atlanta, Georgia. AIDS 2020;34:1789–94.
[10] Byrd KM, Beckwith CG, Garland JM, Johnson JE, Aung S, Cu-Uvin S, et al. SARS-CoV-2 and HIV coinfection: clinical experience from Rhode Island, United States. J Int AIDS Soc 2020;23:e25573.
[11] Meyerowitz EA, Kim AY, Ard KL, Basgoz N, Chu JT, Hurtado RM, et al. Disproportionate burden of coronavirus disease 2019 among racial minorities and those in congregate settings among a large cohort of people with HIV. AIDS 2020;34:1781–7.
[12] Etienne N, Karmochkine M, Slama L, Pavie J, Batisse D, Usubillaga R, et al. HIV infection and COVID-19: risk factors for severe disease. AIDS 2020;34:1771–4.
[13] Inciarte A, Gonzalez-Cordon A, Rojas J, Torres B, de Lazzari E, de la Mora L, et al. 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. AIDS 2020;34:1775–80.
[14] Del Amo J, Polo R, Moreno S, Diaz A, Martinez E, Arribas JR, et al. Incidence and severity of COVID-19 in HIV-positive persons receiving antiretroviral therapy : a cohort study. Ann Intern Med 2020;173:536–41.
[15] Di Biagio A, Ricci E, Calza L, Squillace N, Menzaghi B, Rusconi S, et al. Factors associated with hospital admission for COVID-19 in HIV patients. AIDS 2020;34:1983–5.
[16] Hadi YB, Naqvi SFZ, Kupec JT, Sarwari AR. Characteristics and outcomes of COVID-19 in patients with HIV: a multicentre research network study. AIDS 2020;34:F3–8.
[17] Shalev N, Scherer M, LaSota ED, Antoniou P, Yin MT, Zucker J, et al. Clinical characteristics and outcomes in people living with human immunodeficiency virus hospitalized for coronavirus disease 2019. Clin Infect Dis 2020;71:2294–7.
[18] Boulle A, Davies MA, Hussey H, Ismail M, Morden E, Vundle Z, et al. Risk factors for COVID-19 death in a population cohort study from the Western Cape Province, South Africa. Clin Infect Dis 2020:ciaa1198.
[19] Geretti AM, Stockdale AJ, Kelly SH, Cevik M, Collins S, Waters L, et al. Outcomes of COVID-19 related hospitalization among people with HIV in the ISARIC WHO Clinical Characterization Protocol (UK): a prospective observational study. Clin Infect Dis 2020. https://doi.org/10.1093/cid/ciaa1605.
[20] Sigel K, Swartz T, Golden E, Paranjpe I, Somani S, Richter F, et al. Coronavirus 2019 and people living with human immunodeficiency virus: outcomes for hospitalized patients in New York City. Clin Infect Dis 2020;71:2933–8.
[21] Bhaskaran K, Rentsch CT, MacKenna B, Schultze A, Mehrkar A, Bates CJ, et al. HIV infection and COVID-19 death: a population-based cohort analysis of UK primary care data and linked national death registrations within the OpenSAFELY platform. Lancet HIV 2021;8:e24–32.
[22] Park LS, Rentsch CT, Sigel K, Rodriguez-Barradas M, Brown ST, Goetz MB, et al. COVID-19 in the largest US HIV cohort 23rd International AIDS Conference. 2020. Abstract # LBPEC23; 6-10 July; Virtual meeting.
[23] Abubakar I, Stagg H, Cohen T, Rodrigues L. Oxford specialist handbook of infectious disease epidemiology. Oxford: Oxford University Press; 2016.
[24] Peeling RW, Wedderburn CJ, Garcia PJ, Boeras D, Fongwen N, Nkengasong J, et al. Serology testing in the COVID-19 pandemic response. Lancet Infect Dis 2020;20:e245–9.
[25] Pollan M, Perez-Gomez B, Pastor-Barriuso R, Oteo J, Hernan MA, Perez-Olmeda M, et al. Prevalence of SARS-CoV-2 in Spain (ENE-COVID): a nationwide, population-based seroepidemiological study. Lancet 2020;396:535–44.
[26] Gudbjartsson DF, Norddahl GL, Melsted P, Gunnarsdottir K, Holm H, Eythorsson E, et al. Humoral immune response to SARS-CoV-2 in Iceland. N Engl J Med 2020;383:1724–34.
[27] Basavaraju SV, Patton ME, Grimm K, Rasheed MAU, Lester S, Mills L, et al. Serologic testing of U.S. blood donations to identify SARS-CoV-2-reactive antibodies: december 2019–January 2020. Clin Infect Dis 2020.
[28] Stringhini S, Wisniak A, Piumatti G, Azman AS, Lauer SA, Baysson H, et al. Seroprevalence of anti-SARS-CoV-2 IgG antibodies in Geneva, Switzerland (SEROCoV-POP): a population-based study. Lancet 2020;396:313–9.
[29] Korth J, Wilde B, Dolff S, Anastasiou OE, Krawczyk A, Jahn M, et al. SARS-CoV-2-specific antibody detection in healthcare workers in Germany with direct contact to COVID-19 patients. J Clin Virol 2020;128:104437.
[30] Mansour M, Leven E, Muellers K, Stone K, Mendu DR, Wajnberg A. Prevalence of SARS-CoV-2 antibodies among healthcare workers at a tertiary academic hospital in New York City. J Gen Intern Med 2020;35:2485–6.
[31] Grant JJ, Wilmore SMS, McCann NS, Donnelly O, Lai RWL, Kinsella MJ, et al. Seroprevalence of SARS-CoV-2 antibodies in healthcare workers at a London NHS Trust. Infect Control Hosp Epidemiol 2020:1–3.
[32] Simon D, Tascilar K, Kronke G, Kleyer A, Zaiss MM, Heppt F, et al. Patients with immune-mediated inflammatory diseases receiving cytokine inhibitors have low prevalence of SARS-CoV-2 seroconversion. Nat Commun 2020;11:3774.
[33] Papalini C, Paciosi F, Schiaroli E, Pierucci S, Busti C, Bozza S, et al. Seroprevalence of anti-SARS-CoV2 antibodies in Umbrian persons living with HIV. Mediterr J Hematol Infect Dis 2020;12:e2020080.
[34] Noe S, Schabaz F, Heldwein S, Mayer W, Ruecker K, Tiller FW, et al. HIV and SARS-CoV-2 co-infection: cross-sectional findings from a German 'hotspot. Infection 2021;49:313–20.
[35] Sobrino-Vegas P, Gutierrez F, Berenguer J, Labarga P, Garcia F, Alejos-Ferreras B, et al. [The Cohort of the Spanish HIV Research Network (CoRIS) and its associated biobank; organizational issues, main findings and losses to follow-up]. Enferm Infecc Microbiol Clin 2011;29:645–53.
[36] Garcia-Merino I, de Las Cuevas N, Jimenez JL, Gallego J, Gomez C, Prieto C, et al. The Spanish HIV BioBank: a model of cooperative HIV research. Retrovirology 2009;6:27.
[37] National Institutes of Health. COVID-19 treatment guidelines. Available from:. 2020. https://www.covid19treatmentguidelines.nih.gov.
[38] Greenland S, Mansournia MA, Altman DG. Sparse data bias: a problem hiding in plain sight. BMJ 2016;352:i1981.
[39] Zhang ZL, Hou YL, Li DT, Li FZ. Diagnostic efficacy of anti-SARS-CoV-2 IgG/IgM test for COVID-19: a meta-analysis. J Med Virol 2021;93:366–74.
[40] Wang H, Ai J, Loeffelholz MJ, Tang YW, Zhang W. Meta-analysis of diagnostic performance of serology tests for COVID-19: impact of assay design and post-symptom-onset intervals. Emerg Microbe. Infect 2020;9:2200–11.
[41] Tre-Hardy M, Wilmet A, Beukinga I, Favresse J, Dogne JM, Douxfils J, et al. Analytical and clinical validation of an ELISA for specific SARS-CoV-2 IgG, IgA, and IgM antibodies. J Med Virol 2021;93:803–11.
[42] Brochot E, Demey B, Handala L, Francois C, Duverlie G, Castelain S. Comparison of different serological assays for SARS-CoV-2 in real life. J Clin Virol 2020;130:104569.
[43] Oran DP, Topol EJ. The proportion of SARS-CoV-2 infections that are asymptomatic : a systematic review. Ann Intern Med 2021:M20–697.
[44] Webb Hooper M, Napoles AM, Perez-Stable EJ. COVID-19 and racial/ethnic disparities. JAMA 2020;323:2466–7.
[45] Chien M, Anderson TK, Jockusch S, Tao C, Li X, Kumar S, et al. Nucleotide analogues as inhibitors of SARS-CoV-2 polymerase, a key drug target for COVID-19. J Proteome Res 2020;19:4690–7.
[46] Clososki G, Soldi R, da Silva R, Guaratini T, Lopes J, Pereira P, et al. Tenofovir Disoproxil Fumarate: new chemical developments and encouraging in vitro biological results for SARS-CoV-2. J Braz Chem Soc 2020;31.
[47] Park SJ, Yu KM, Kim YI, Kim SM, Kim EH, Kim SG, et al. Antiviral efficacies of FDA-approved drugs against SARS-CoV-2 infection in ferrets. mBio 2020;11.
[48] Markowitz M, Zolopa A, Squires K, Ruane P, Coakley D, Kearney B, et al. Phase I/II study of the pharmacokinetics, safety and antiretroviral activity of tenofovir alafenamide, a new prodrug of the HIV reverse transcriptase inhibitor tenofovir, in HIV-infected adults. J Antimicrob Chemother 2014;69:1362–9.