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MAJOR ARTICLE

Hepatic Steatosis and Weight Gain During the Coronavirus Disease 2019 Pandemic Among People With Human Immunodeficiency Virus: Impact of Therapy With Tenofovir Alafenamide

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Background. Lockdown due to the coronavirus disease 2019 (COVID-19) pandemic led to increases in weight in part of the population. Weight gain leads to hepatic steatosis (HS). Antiretroviral treatment could also influence HS in people with human immunodeficiency virus (PWH). The impact of lockdown on HS in PWH is unknown. The aim of this study was to analyze the changes in HS, as measured by the controlled attenuation parameter (CAP), during the COVID-19 pandemic in PWH.

Methods. This was a cohort study that included PWH who attended a tertiary care center in southern Spain from January 2018 to December 2021. The CAP was evaluated by transient elastography. Only those who had a valid CAP before and after March 2020 were included. HS was defined as CAP ≥248 dB/m.

Results. Six hundred eighty PWH were attended and 488 (71.8%) were included. Two hundred and fourteen (43.9%) had HS at baseline and 239 (49%) at the end of the follow-up ($P = .036$). The median change in CAP among PWH taking tenofovir alafenamide (TAF) was 8.5 (interquartile range [IQR], −24 to 46.3) dB/m versus −4 (IQR, −35 to 27) dB/m among PWH receiving TAF-free regimens ($P = .003$). After multivariate analysis, adjusted by sex and age, weight gain (adjusted odds ratio [AOR], 1.09 [95% confidence interval {CI}, 1.05–1.14]; $P < .001$), TAF therapy (AOR, 1.59 [95% CI, 1.07–2.35]; $P = .021$), plasma triglycerides (AOR, 1.01 [95% CI, 1–1.01]; $P < .001$), and fasting blood glucose (AOR, 1.01 [95% CI, 1–1.02]; $P = .027$) were associated with HS at the end of follow-up.

Conclusions. The frequency of HS increased during the COVID-19 pandemic among PWH. TAF is associated with HS development, regardless of metabolic factors.

Keywords. HIV infection; liver fibrosis; SARS-CoV-2; steatosis; TAF.

The lockdown period during the coronavirus disease 2019 (COVID-19) pandemic, designed to slow the spread of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has led to a worsening in some health parameters in the general population. Approximately 20% of the population has reported some weight gain, with a higher proportion in people with previous obesity [1], and one-fifth of patients attending weight management programs gained more than 3% of their body weight [2]. People with human immunodeficiency virus (PWH) were less likely to become infected with SARS-CoV-2 during the first waves of COVID-19 [3]. Some possible reasons included greater awareness of the risks of COVID-19 and a greater adherence to stay-at-home mandates. Less physical activity related to lockdown could also have had a greater impact on health among PWH [4].

Progressive weight gain after the achievement of human immunodeficiency virus (HIV) suppression and recovery of CD4 cell counts is worrisome. Weight gain has been associated with some antiretroviral therapy (ART), especially integrase strand inhibitors (INSTIs) [5], although the effect appears to be smaller in subjects of White race. Tenofovir alafenamide (TAF) has also been associated with weight gain in PWH [6]. Hepatic steatosis (HS) is a frequent problem in the setting of HIV infection. In fact, approximately 40% of PWH have HS [7–9]. In the general population, increased weight is correlated to the presence of HS [7]. High body mass index (BMI) is the main predictor of HS in this setting [9]. In fact, ART was not independently

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associated with HS after controlling for BMI in several cross-sectional studies [9–12], conducted when tenofovir disoproxil fumarate was the tenofovir compound most commonly used. In more recent observational studies, exposure to some ART has been associated with HS in PWH, such as INSTIs and TAF [13, 14]. However, there are some conflicting data. In 1 clinical trial, switching from efavirenz to raltegravir resulted in an improvement in HS after 48 weeks [15]. In another study, treatment with INSTIs was not an independent predictor of HS after controlling for TAF exposure and BMI [16]. Other reports have shown that weight gain after switching to INSTIs did not parallel the increase in HS [17].

The impact of the COVID-19 pandemic on weight gain and HS in PWH is unknown. Due to this, we evaluated the changes in HS, measured by the controlled attenuation parameter (CAP) evaluated by vibration-controlled transient elastography (VCTE), in PWH and the factors associated with the persistence or emergence of HS during the SARS-CoV-2 pandemic.

METHODS

Patients and Design

This cohort study included PWH seen in the infectious diseases unit of a tertiary care center in southern Spain from January 2018 to December 2021. Only PWH who self-reported a daily alcohol intake <30 g/day were included. PWH underwent an annual VCTE liver examination. Those with valid VCTE were included. At the same date as the evaluation of VCTE, PWH underwent a clinical examination that included anthropometric measurements and a blood sample draw for laboratory tests.

Transient Elastography Examinations

The CAP was evaluated by VCTE (FibroScan, Echosens, Paris, France), according to a standardized procedure, using the M probe [9]. Examinations were carried out by a trained operator. The CAP is a validated noninvasive tool for the evaluation of HS [18]. To consider the VCTE determinations reliable, the evaluations had to include at least 10 valid measurements, with a success rate ≥60% and an interquartile range (IQR) <30% of the median liver stiffness [19].

Endpoints and Definition Criteria

The primary endpoint was the change in HS measured by CAP. We considered that HS was present if CAP value was ≥248 dB/m [20]. Overweight was defined as BMI ≥25 kg/m^2. The FibroScan-AST (FAST) score is an index that assesses the presence of nonalcoholic steatohepatitis (NASH) and fibrosis stage 2 or greater. A FAST score ≥0.67 is considered to indicate NASH and significant fibrosis [21]. The baseline study period (ie, the period of time before the first COVID-19 lockdown) was January 2018 to March 2020 and the final study period was from April 2020 to December 2021.

Statistical Analysis

Categorical variables were expressed as numbers (percentage) and continuous variables as median (IQR). Ninety-five percent confidence intervals (CIs) were provided for the main rates. We used the χ^2 test for categorical variables and the Student *t* test for continuous variables. The McNemar test was applied for categorical related variables and the Wilcoxon test for continuous related variables. Factors associated with the presence of HS at the end of follow-up in the univariate analysis with a *P* value ≤.1, along with age and sex, were entered into a binary logistic regression model. These analyses were carried out using IBM SPSS 26.0 (IBM Corporation, Chicago, Illinois) and the Stata 16.1 Statistics/Data Analysis package (StataCorp, College Station, Texas).

Patient Consent Statement

The study was approved by the Ethics Committee of the Hospital Universitario Virgen de Valme. All PWH gave their written informed consent before being recruited into this study. This study was conducted in accordance with the Declaration of Helsinki.

RESULTS

Baseline Characteristics of the Population

During the study period, 680 PWH followed clinical visits in our center. A total of 488 (71.8%) PWH were included in the study. The reasons for noninclusion of the rest of the subjects are shown in Figure 1. The baseline characteristics of included and not included PWH in the study are summarized in Table 1. The median time from the baseline visit to the end of follow-up was 16 (IQR, 12–24) months. The median baseline liver stiffness measurement was 5.3 (IQR, 4.3–6.9) kPa, and the median baseline CAP was 240 (IQR, 210–284) dB/m.

Hepatic Steatosis During Follow-up

HS was observed in 214 (43.9%) PWH at baseline and in 239 (49%) PWH at the end of follow-up ($P = .036$). Fifty-three (10.45%) PWH with HS at baseline presented regression of HS. The number of incident HS cases was 78 (16%). Among the overall population, there was no significant difference between the median CAP values at baseline and follow-up visits (Figure 2*A*). PWH who gained weight had an initial CAP of 237 (IQR, 206–277) dB/m and a final CAP of 255 (IQR, 206–277) dB/m ($P < .001$). Among the 294 PWH who gained weight, 127 (43.2%) had HS at baseline and 163 (55.4%) PWH at the follow-up visit ($P < .001$). Sixty (20.4%) PWH without HS at baseline reached a CAP value ≥248 dB/m during the study period. Among those who gained weight, 20 (7.2%) PWH had a FAST score ≥0.67 at baseline and 17 (6.1%) PWH at the follow-up visit ($P = .719$).

The median change in CAP value among PWH taking TAF was 8.5 (IQR, −24 to 46.3) dB/m compared to −4

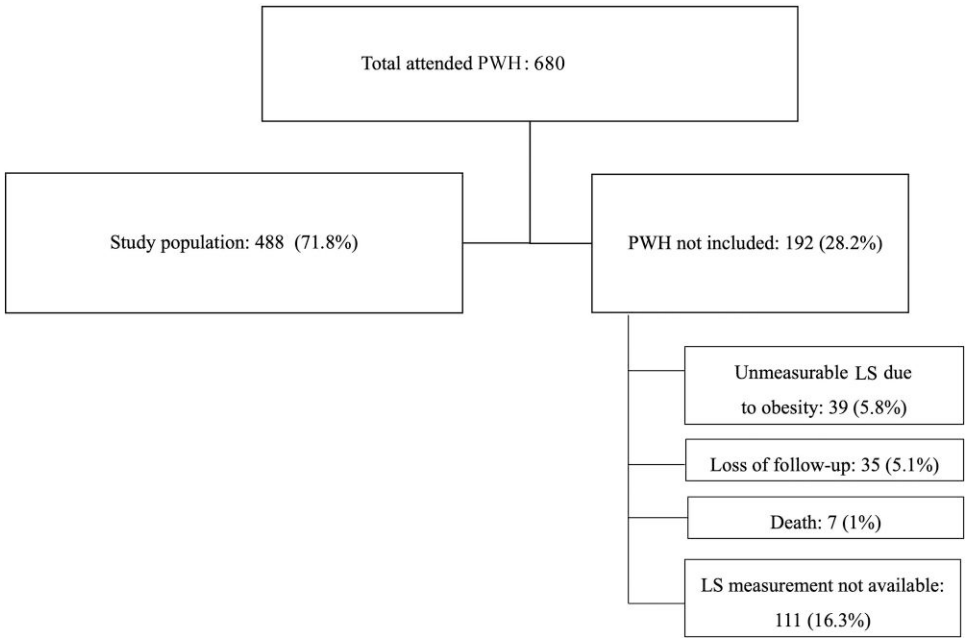

Figure 1. Disposition of the patients. Abbreviations: HIV, human immunodeficiency virus; LS, liver stiffness; PWH, people with human immunodeficiency virus.

Table 1. Baseline Characteristics of Patients Included and Not Included in the Study

Characteristic	Included Patients (n = 488)	Not Included Patients (n = 192)	*P* Value
Male sex	405 (83)	152 (79.2)	.243
Age, y, median (IQR)	55 (49–60)	54 (45–59)	.001
CD4 cell count[a], cells/μL	612 (447–868)	487 (445–715)	.585
Undetectable HIV RNA	428 (89.5)	174 (92.6)	.235
TAF	234 (48)	90 (46.9)	.458
Combinations with TAF/FTC			
Bictegravir	130 (26.6)	41 (21.4)	.153
Dolutegravir	2 (0.4)	1 (0.5)	
Raltegravir	15 (3.1)	5 (2.6)	.744
Elvitegravir	2 (0.4)	5 (2.6)	
Darunavir/cobicistat	81 (16.6)	18 (9.4)	.016
Rilpivirine	5 (1)	20 (10.4)	<.001
Any INSTI	362 (74.2)	119 (62)	.002
Dolutegravir	196 (40.2)	67 (34.9)	.197
Bictegravir	131 (26.8)	41 (21.4)	.138
Raltegravir	33 (6.8)	12 (6.3)	.809
Elvitegravir	2 (0.4)	5 (2.6)	.011
Cabotegravir	1 (0.2)	…	
Weight, kg, median (IQR)	73 (65–80)	76 (67–84)	.008
Overweight	228 (46.9)	91 (56.5)	.035
HDL cholesterol, mg/dL, median (IQR)	50 (42–61)	48 (40–58)	.618
Triglycerides, mg/dL, median (IQR)	112 (77–163)	113 (83–164)	.319
FBG, mg/dL, median (IQR)	93 (86–102)	92 (85–100)	.531

Data are presented as No. (%) unless otherwise indicated.

Abbreviations: FBG, fasting blood glucose; FTC, emtricitabine; HDL, high-density lipoprotein; HIV, human immunodeficiency virus; INSTI, integrase strand inhibitor; IQR, interquartile range; TAF, tenofovir alafenamide.

[a]Only data available for 37 people with HIV.

(IQR, −35 to 27) dB/m among those receiving TAF-free regimens ($P = .003$). The median change in CAP value among PWH taking INSTIs was −1.5 (IQR, −31 to 31) dB/m versus 11 (IQR, −28 to 44) dB/m among PWH not taking INSTIs ($P = .152$). Fifty (21.4%) of those taking TAF developed incident HS compared to 28 (11%) of those on TAF-free regimens

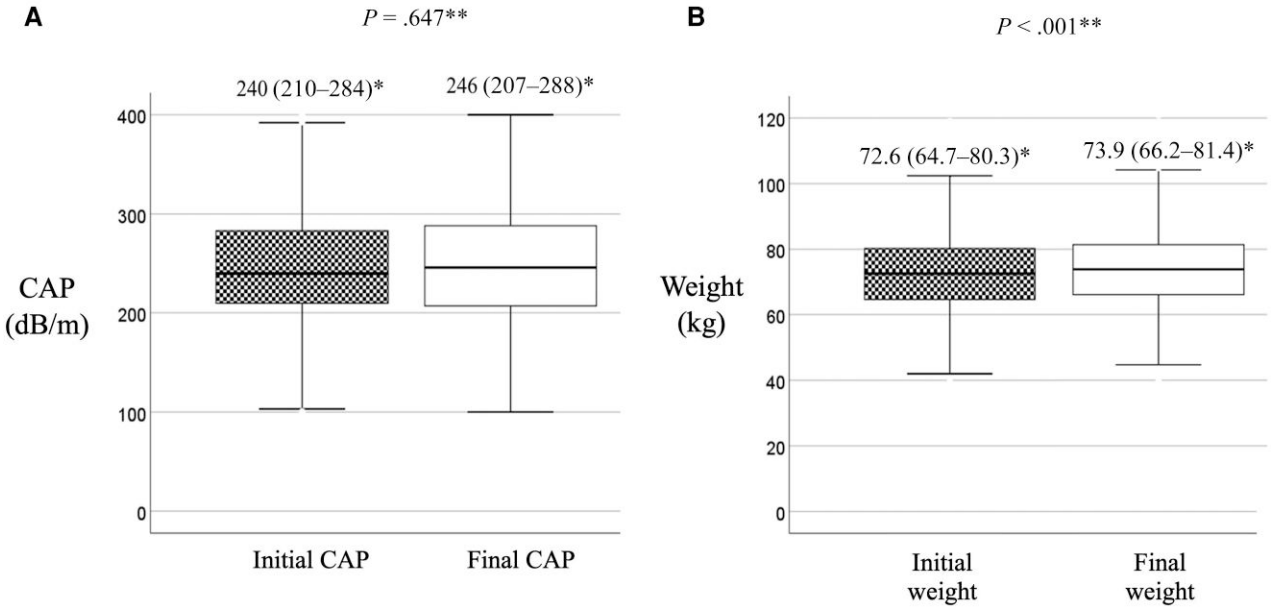

Figure 2. Changes in controlled attenuation parameter (*A*) and weight (*B*) in the overall population. *Median (interquartile range). **Wilcoxon test. Abbreviation: CAP, controlled attentuaion parameter.

Table 2. Characteristics of Patients With and Without Hepatic Steatosis at the End of Follow-up (n = 488)

Characteristic	Patients With HS (n = 239)	Patients Without HS (n = 249)	OR (95% CI)	*P* Value	Adjusted OR (95% CI)[a]	*P* Value
Male sex	198 (82.8)	207 (83.1)	0.98 (.61–1.57)	.933	0.97 (.58–1.63)	.721
Age, y, median (IQR)	56 (52–61)	54 (45–59)	1.03 (1.01–1.05)	.001	1.03 (1.01–1.05)	.007
CD4 count, cells/μL, median (IQR)	659 (462–908)	585 (443–847)	1.00 (1.00–1.00)	.140	…	
Undetectable viral load	206 (89.2)	222 (89.9)	1.08 (.6–1.94)	.802	…	
TAF	128 (53.6)	111 (46.4)	1.56 (1.09–2.24)	.015	1.59 (1.07–2.35)	.021
INSTI	175 (73.2)	64 (26.8)	0.91 (.6–1.36)	.635	…	
Changes in weight, kg, median (IQR)	1.85 (−1.2 to 5.3)	0.25 (−2.3 to 2.32)	−2.47 (−3.42 to −1.52)	<.001	1.09 (1.05–1.14)	<.001
HDL cholesterol, mg/dL, median (IQR)	48 (41–59)	51 (44–62)	0.99 (.98–1.00)	.106	…	
Triglycerides, mg/dL, median (IQR)	127 (91–190)	103 (74–131)	1.00 (1.00–1.01)	<.001	1.01 (1–1.01)	<.001
FBG, mg/dL, median (IQR)	97 (90–107)	93 (86–102)	1.02 (1.01–1.03)	.001	1.01 (1–1.02)	.027

Data are presented as No. (%) unless otherwise indicated.

Abbreviations: CI, confidence interval; FBG, fasting blood glucose; HDL, high-density lipoprotein; HS, hepatic steatosis; INSTI, integrase strand inhibitor; IQR, interquartile range; OR, odds ratio; TAF, tenofovir alafenamide.

[a]Adjusted for sex, age, changes in weight, TAF, HDL, and FBG.

(*P* < .001). Forty-seven (13%) of those taking INSTIs developed incident HS versus 31 (24.6%) of those not taking INSTIs (*P* < .001).

Factors Associated With Hepatic Steatosis at the End of Follow-up

The characteristics of PWH with and without HS at the end of follow-up are shown in Table 2. In the univariate analysis, age, weight gain, TAF, triglycerides, and fasting blood glucose (FBG) were associated with HS at the end of follow-up, emergent or persistent HS. After multivariate analysis, adjusted by sex and age, exposure to TAF, weight gain, hypertriglyceridemia, and FBG at the end of follow-up were associated with the persistence or progression of HS (Table 2). There was no difference in the proportion of PWH with HS at the end of follow-up between regimens according to individual INSTIs (Figure 3).

Fifty-two (10.7%) PWH presented symptomatic SARS-CoV-2 infection. The frequency of HS in the follow-up visit was 29 (55.8%) for PWH who suffered COVID-19, compared with 205 (48.3%) for those without COVID-19 (*P* = .312).

Weight Gain During Follow-up

A total of 294 (60.2%) PWH gained weight. The median weight gain was 1 (IQR, −1.9 to 3.7) kg, and 149 (30.5%) PWH gained >3 kg. In the overall population, weight increased significantly

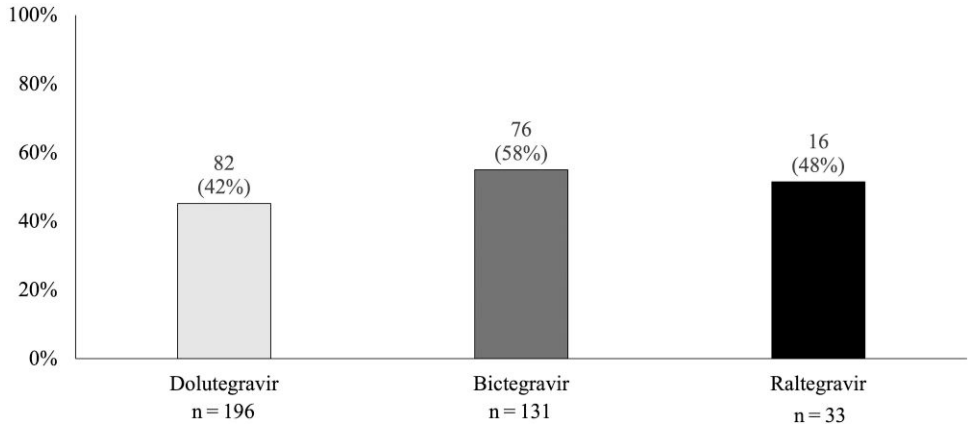

Figure 3. Hepatic steatosis and integrase strand inhibitors at the end of the follow-up.

(Figure 2*B*). PWH who gained weight had an initial weight of 72.1 (IQR, 63.3–79) kg and a final weight of 75.9 (IQR, 68.2–83.2) kg ($P < .001$). The median weight gain was 1.4 (IQR, −1.1 to 5.1) kg among PWH who took TAF compared to 0.6 (IQR, −2.1 to 3) kg for PWH on TAF-free regimens ($P = .010$). Three hundred sixty-two (74.2%) PWH were receiving INSTIs. The median weight gain was 0.9 (IQR, −1.8 to 3.7) kg among PWH taking INSTIs compared with 1 (IQR, −2.1 to 3.5) kg among PWH receiving regimens without INSTIs ($P = .543$).

DISCUSSION

The frequency of HS increased during the COVID-19 pandemic among PWH. This fact was driven by weight gain during this period. However, other relevant factors had an impact on HS emergence independently of metabolic disorders. Among them, the most outstanding one was ART. Thus, exposure to TAF during the study period was associated with persistence of or progression to HS, independent of weight increase, baseline hypertriglyceridemia, or older age.

To date, there have been no studies comparing HS between PWH and the general population during the pandemic. An increase in HS and weight due to poor dietary habits and sedentary lifestyles during the lockdown has been reported in the Spanish general population. The frequency of HS increased by 2% and the median weight gain was 1.6 kg from 2019 to 2020 [22]. Our study is, to the best of our knowledge, the first to evaluate changes in HS during the pandemic in PWH. We reported a 5% increase in the frequency of HS.

In Spain, stay-at-home mandates during the SARS-CoV-2 pandemic, especially during the first and second waves, were more strict and prolonged than in other European countries [23]. A recent meta-analysis that included studies from different countries reported a trend in weight gain worldwide after home confinement, involving 11.1%–72.4% of people. Although weight was self-reported in all studies included in the meta-analysis, surveys conducted later, during or shortly after the lockdown, reported greater weight changes [24]. Fewer infections have been reported in PWH than in the general population in Spain [3]. This may be attributable to a tighter lockdown due to awareness of their vulnerability. PWH may have followed stay-at-home mandates more closely, resulting in more weight gain than the general population [3].

ART regimens based on TAF compared to tenofovir disoproxil fumarate have been associated with increased weight gain, particularly in the context of treatment-naive African women [25]. Starting INSTIs combinations has also been associated with more weight gain than other ART combinations in treatment-naive patients [25]. A lower weight gain has been observed after switching to INSTIs in previously treated PWH [26]. It is possible that weight gain could drive HS over time. In this regard, we found that PWH exposed to TAF were more likely to show evidence of HS, as measured by CAP, at the end of follow-up than those on TAF-free regimens during the pandemic. These differences were not observed for PWH exposed to different INSTIs in this study. This result is in agreement with a previous study that reported a relationship between TAF use and HS, but no independent association with INSTIs exposure [16]. It is noteworthy that weight gain in PWH after switching to INSTI regimens is not associated with changes in HS [17]. These data suggest a possible protective effect of INSTIs on HS that will require further investigation in the future.

The relationship between HS and TAF exposure could be partly explained by weight gain related to TAF-based ART. However, this effect was independent of weight gain. Therefore, in this process not only weight gain should be involved. There may be other unknown factors associated with TAF that drive HS. Mitochondrial toxicity is a potential mechanism for nucleoside analogues. However, newer nucleosides,

such as tenofovir, appear to be free of mitochondrial toxicity due to low affinity for binding to mitochondrial polymerase [27]. One possible explanation could be that TAF produces an alteration in liver lipid metabolism, leading to greater weight increase [28]. More studies are needed to confirm this relationship and understand their mechanisms.

As expected, in this study HS was associated with weight gain and hypertriglyceridemia. In other studies, weight gain was the main predictor of HS [9]. Additionally, PWH evaluated in the present study gained more weight than the Spanish general population during the COVID-19 confinement [22]. It is important to note that in our study weight was measured directly, whereas in some studies on the general population weight was self-reported and could be underestimated [1, 2]. Triglycerides have also been associated with HS. Triglycerides, along with other metabolic factors, are known to increase the risk of HS both in the general population [29] and in PWH [30].

Our study is the first one, to our knowledge, to evaluate clinically evidenced HS and weight changes in PWH after the global SARS-CoV-2 pandemic. Most studies to date were based on self-reported changes in weight in the general population [1, 2]. In the present study, we provide data on the increase in the frequency of PWH with HS after the COVID-19 lockdown. One of the limitations of the study is that we analyzed the use of ART during the pandemic, without taking into account whether ART was previously taken by experienced PWH or started during the lockdown in treatment-naive PWH. Another limitation is that VCTE could not be reliably obtained in obese PWH and other patients due to logistic problems. Nonincluded PWH showed no differences in metabolic parameters with included PWH. Despite this, the rates of HS could have been underestimated in our study. Finally, during the pandemic, access to health services and outpatient clinics has been reduced by the decrease in the number of visits imposed by lockdowns, the fear of PWH to attend healthcare centers, mobility limitations, and selective quarantines. All of these have precluded the scheduled annual VCTE evaluation in some PWH included in the study cohort. Despite these missing data, we were able to recruit a sample of PWH from the cohort large enough to evaluate the evolution and risk factors for HS during the COVID-19 pandemic.

In conclusion, HS rates among PWH have increased during the COVID-19 pandemic. Regardless of the weight gain observed during the lockdown, TAF has been independently associated with the likelihood of HS, but not INSTIs. Identifying PWH at risk of HS is relevant to prevent its progression, facilitate access to targeted treatments when available, and avoid liver complications in the future.

Notes

Author contributions. M. S., J. A. P., and J. M. designed the research study. M. S., A. C.-G., J. M. C., M. P.-G., P. R.-M., and C. M.-S. performed the research and analyzed the data. All authors visualized the results. J. M. provided general supervision to this research. M. S. wrote the original draft of this manuscript. A. C.-G., J. M. C., M. P.-G., P. R.-M., C. M.-S., A. G.-S., J. A. P., L. M. R., and J. M. reviewed and edited this manuscript.

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Data availability. The qualitative data from which this analysis is based are available from the corresponding author upon reasonable request, only if it has undergone ethical review.

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