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ORIGINAL ARTICLE

Predictive factors of hepatitis C virus eradication after interferon-free therapy in HIV coinfection

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Abstract

Real-life cohorts have shown that the effectiveness of all-oral, direct-acting antivirals (DAA) for HCV treatment is > 90%. We aimed to explore the predictive factors of DAA success in HIV coinfection. This is an observational prospective study within the cohort "VIH-DOC", Madrid, Spain. HIV/HCV-coinfected patients were included if they had been treated with DAAs between 9 January 2015 and 31 August 2016. The sustained virological response (SVR) was analysed in the intention-to-treat population. Binary logistic regression was used to study the impact of cirrhosis, anti-HCV therapy experience and the IL28B polymorphism on SVR, besides factors with a p value < 0.15 from the univariate analysis. DAA were prescribed to 423 patients. SVR was confirmed in 92.9%. The univariate analysis showed higher proportion of patients with SVR among those with DAA adherence ≥ 95% (difference + 10.3%, 95% CI 3.5–19.6) and a baseline CD4+ cell count ≥ 200/μL (difference + 14.7%, 95% CI 4.1–31.0). Logistic regression evinced that both DAA adherence and baseline CD4+ cell counts predicted the SVR (OR 3.9, 95% CI 1.8–8.8, and OR 5.2, 95% CI 1.9–13.9, respectively). Moreover, men who reported having sex with other men (MSM) were less likely to achieve SVR (OR 4.2, 95% CI 1.1–16.1). Among MSM, three of three patients without SVR were suspected to have experienced HCV reinfection. DAA for HCV in HIV-coinfected patients is highly effective. DAA adherence ≥ 95% and a baseline CD4+ count ≥ 200/μL predicted a higher probability of SVR. A lower rate of SVR was found in MSM, presumably due to a higher frequency of HCV reinfection.

Keywords HIV/HCV coinfection · Direct-acting antivirals · Sustained virological response · Treatment adherence · HCV reinfection

Introduction

Interferon-free regimens with all-oral, direct-acting antivirals (DAA) have improved virological outcomes for chronic hepatitis C virus (HCV) infection treatment in HIV-coinfected patients. Different clinical trials have shown high efficacy for the first available DAA in this difficult-to-treat population [1–6].

Many cohorts have demonstrated the high effectiveness of DAA for HCV therapy in HIV-coinfected subjects [7]. However, some of these observational studies either included a small number of patients [8] or were restricted to HCV genotype 1 [9–12]. Data on three larger cohorts have been published. A French cohort described a sustained virological response (SVR) of 93.5% in 323 HIV/HCV-coinfected subjects without genotype restrictions, although some patients had been treated as part of clinical trials [13]. Bischoff et al. demonstrated an SVR of 91.2% in 488 HIV/HCV-coinfected patients in a German cohort, but 10.5% had been treated using

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interferon-based treatment regimens [14]. Finally, the Madrid-CoRe cohort confirmed an SVR of 94.1% in 2369 HIV/HCV-coinfected subjects treated with DAA in public hospitals in Madrid, Spain [15].

Nevertheless, there are few studies focusing on potentially predictive factors of SVR with DAA in HIV/HCV-coinfected patients. Moreover, given the complexity of data collection in multicentre observational studies, detailed data are not currently available. Therefore, the aim of this study was to evaluate the predictive variables of DAA therapy effectiveness in HIV/HCV coinfection.

Methods

Design and patients

This was a prospective observational study run within the VIH-DOC cohort, at the HIV Unit of the University Hospital *12 de Octubre*, Madrid (Spain). Subjects who were HCV coinfected and treated with DAA between 9 January 2015 and 31 August 2016 were eligible for inclusion in the study.

Epidemiological, clinical and laboratory variables were collected at the time of treatment onset. Virological response, adverse events and adherence were prospectively evaluated during subsequent visits: treatment week 4 (W4), end of treatment (EOT: depending on the scheduled duration of therapy, this could be at treatment week 8, 12 or 24) and weeks 12 and 24 post-treatment. Patients treated with a 24-week scheme also had an appointment at treatment week 12.

Variables

Dependent variable Sustained virological response was the dependent variable. SVR confirmation required undetectable HCV RNA at least 24 weeks after the last DAA dose was taken (SVR24). Some studies have, however, validated undetectable HCV RNA 12 weeks post-treatment as the criterion defining HCV eradication in HCV-monoinfected patients treated with both interferon-based and interferon-free regimens [16–19]. We used SVR24 as primary endpoint rather than SVR12 due to the lack of data regarding SVR12 as an HCV cure criterion in HIV-coinfected patients. Nevertheless, SVR12 data were also analysed.

Non-response was considered when undetectable HCV RNA was not achieved while on treatment.

Recurrence was defined as detectable HCV RNA after undetectable HCV RNA had been confirmed at EOT. Whenever the genotype in the post-treatment sample was the same as the pretreatment one, and there was no risk factor for reinfection, the recurrence was considered as a relapse. Otherwise, it was considered as a suspected reinfection if there was no difference between the HCV genotypes before and after therapy, but the patient recognised a clear risk exposure. Reinfection was confirmed if a difference in the genotype was found.

Independent variables There were four categories of independent variables: (a) epidemiological data: age, gender and HIV/HCV infection transmission mechanism; (b) comorbidities: alcohol consumption >25 g per day [20], type 2 diabetes mellitus, HBV coinfection (positive HBsAg), liver cirrhosis (defined by either a liver stiffness ≥ 14.6 kPa [21, 22] or a clinical liver decompensation history), estimated glomerular filtration rate (eGFR) impairment or cryoglobulinemia; (c) HIV-related factors: baseline HIV RNA, clinical classification according to the CDC disease staging system (1993) and both nadir and baseline CD4+ cell count; and (d) HCV-related factors: baseline HCV RNA, HCV genotype (most often uncovered some years before treatment onset and obtained from patients' records), IL28B polymorphism, interferon treatment experience, DAA regimen and DAA adherence.

DAA adherence estimation was obtained through patient accounts and the hospital pharmacy registry. The latter specified the delivery date of each DAA bottle, which was given every 4 weeks to each patient (each bottle contained the necessary pills for exactly 28 days of therapy).

Two aspects of adherence were considered: (a) the proportion of pills actually taken by the patient (adherence rate_1: the number of DAA pills taken divided by the number of DAA pills scheduled to be taken) and (b) the regularity with which the patient took the pills (adherence rate_2: the scheduled treatment's duration (in days) divided by the actual treatment's duration (in days)). The scheduled treatment's duration (in days) was equal to 56 days for 8 weeks of treatments, 84 days for 12 weeks of treatments and 168 days for 24 weeks of treatments. The actual treatment's duration (in days) was equal to the days between the date when the patient started to take the DAA pills and the date when the patient reported having stopped taking them.

Whenever the adherence was incomplete ($\text{adherence rate}_1 < 1$ = early interruption, taking a fewer number of pills than scheduled) and irregular ($\text{adherence rate}_2 < 1$ = treatment duration longer than scheduled due to oversight), the global adherence rate was estimated as follows: $[\text{adherence rate}_1 - (1 - \text{adherence rate}_2)]$ = global adherence rate.

Analysis

SVR24 was analysed in the intention-to-treat population (ITT SVR24), taking into account every patient who received at least one dose of a DAA. It was also analysed using on-treatment analysis (OT SVR24), which considered only those patients whose treatment and follow-up were completed.

ITT SVR24 proportions in every two subgroups defined by the independent variables were compared by Fisher's exact test. A binary logistic regression model (*backward stepwise*) was used to detect predictive factors independently associated with DAA success in the entire population. Factors included in this model were some of those traditionally associated with a lower SVR after interferon-based treatment regimens (i.e., cirrhosis, previous interferon-based therapy and IL28B polymorphism), as well as factors with a Fisher exact test p value < 0.15 in the univariate analysis. Regarding the subgroup with cirrhosis, owing to the low number of patients without SVR24, the binary logistic regression model included only those factors with a Fisher exact p value < 0.05. The strength of association was estimated using Nagelkerke pseudo-R squared. Moreover, a sensibility analysis was performed, which applied the same test for the OT SVR24 data.

The proportion of patients with treatment compliance ≥ 95% in the different subgroups defined by some of the described independent variables were compared using Fisher's exact test. A binary logistic regression model (*backward stepwise*) was used to detect predictive factors independently associated with adherence ≥ 95%, including factors with a Fisher exact test p value < 0.15.

Both the difference of proportions (Diff%) in every two subgroups and the *odds ratio* result (OR) from the binary logistic regression models were described with a 95% confidence interval (95% CI).

Ethics

Patients signed an informed consent approved by the Ethics Committee of the Biomedical Research Institute *Imas12* (University Hospital *12 de Octubre*) when included in the VIH-DOC cohort. This document allows clinical data recollection and analysis for observational study purposes.

Data were anonymised and managed according to the Good Clinical Practice Guidelines published by the World Medical Association Declaration of Helsinki.

Results

A total of 423 HIV/HCV-coinfected patients were treated with DAAs in our centre between 9 January 2015 and 31 August 2016. Baseline characteristics are shown in Table 1. Subjects were mostly male (75%), and the main transmission mechanism was intravenous drug use (85%).

Regarding HCV infection, almost a third of the population had received interferon-based anti-HCV therapy. The median value of liver stiffness (LS) was 10.0 kPa (IQR 7.6–17.6), and 131 patients met the clinical or elastographic criteria for liver cirrhosis. HCV genotypes most frequently found were 1a (41%) and 4 (21%). A combination of sofosbuvir plus ledipasvir in a single tablet regimen was the most common DAA regimen used (69%).

With respect to HIV infection, HIV RNA was undetectable (< 50 copies/mL) in 95% of the subjects, and the median value of the CD4+ cell count was 573/μL (IQR 393–835). Antiretroviral therapy (ART) had to be changed in 18% of the patients to avoid drug-drug interactions.

DAA therapy effectiveness

Sustained virological response was confirmed in 393/423 subjects (92.9%, 95% CI 90.0–95.2) who had taken at least one DAA dose (ITT SVR24).

Absence of SVR24 was due to different causes, which are detailed in Online Resource 1.

Five subjects had withdrawn DAA therapy prematurely, with detectable HCV RNA occurring after the withdrawal. Another ten patients were lost to follow-up without HCV RNA data having been collected. These 15 patients were not included in the OT SVR24 analysis, nor were subjects with SVR24 despite an early DAA withdrawal (n = 10). Therefore, OT SVR24 was confirmed in 383/398 patients (96.2%, 95 CI 93.9–97.9).

The remaining 15 subjects without SVR24 had completed their DAA therapy and had HCV RNA data at week 24 after EOT, which was detectable. There was one case of non-response, ten patients with relapse and four recurrences that were considered reinfections. There were three recurrences among the subgroup of men who reported having sex with men (MSM) as their HCV transmission mechanism, and all of them were considered as belonging in this latter subgroup of reinfections.

When analysing HCV RNA data at week 12 after EOT within the entire cohort, there were two patients for whom SVR12 had been confirmed but who had detectable HCV RNA at week 24 after EOT.

Regarding the subgroup with liver cirrhosis, ITT SVR24 was confirmed in 120/131 subjects who had taken at least one DAA dose (91.6%, 95% CI 85.5–95.7). OT SVR24 was found in 117/121 patients (96.7%, 95% CI 91.8–99.1).

Predictive factors of DAA effectiveness

Table 2 shows ITT SVR24 frequency comparisons between the different subgroups. No difference was found when analysing cirrhotic vs. non-cirrhotic patients (Diff% 1.9, 95% CI − 3.1–8.3), or in subgroups defined by gender, age or associated diseases. There was a higher proportion of patients with SVR24 among those with baseline CD4+ cell count ≥ 200/μL (Diff% 14.7, 95% CI 4.1–31.0), as well as those with DAA adherence ≥ 95% (Diff% 10.3, 95% CI 3.5–19.6).

Table 1 Baseline characteristics ($n = 423$)

Epidemiological data	
Age: mean (years old) (SD)	50.1 (5.6)
Gender: *n* (%) male/female	316 (74.7) / 107 (25.3)
Transmission mechanism: *n* (%)	359 (84.9) / 44 (10.4) / 19 (4.5) / 1 (0.2)
Intravenous drug users/heterosexual/men who have sex with men/vertical	
Baseline HIV infection data	
Time since diagnosis: median (years) (IQR)	23.9 (19.9–26.5)
CDC (93) clinical group C: *n* (%)	140 (33.1)
Nadir CD4+ cell count (/μL): *n* (%) < 200 / 200–500 /> 500	246 (58.2) / 153 (36.2) / 24 (5.7)
Baseline CD4+ cell count: median (/μL) (IQR)	573 (393–835)
Baseline HIV RNA < 50 copies/mL: *n* (%)	400 (94.6)
Change of ARV to prescribe DAA: *n* (%)	76 (18.0)
ARV coadministered with DAA: *n* (%)	67 (15.8) / 132 (31.2) / 86 (20.3)
2 NRTI + 1 NNRTI / 2 NRTI + 1 PI / 2 NRTI + 1 INSTI / PI-based dual or monotherapy / other / neither	100 (23.6) / 30 (7.1) / 8 (1.9)
Baseline HCV infection data	
Time since diagnosis: median (years) (IQR)	28.6 (23.3–32.4)
Baseline HCV RNA: median (IU/mL) (IQR)	1,896,346 (650,018–4,860,784)
Genotype: *n* (%)	21 (5.0) / 175 (41.4) / 62 (14.7) /3 (0.7) / 62 (14.7) / 90 (21.3) / 10 (2.4)
1 without subtype or mixed 1a and 1b / 1a / 1b / 2 / 3 / 4 / mixed no. 1a and 1b	
Interferon regimen experience: *n* (%)	125 (29.6)
DAA regimen experience: *n* (%)	0 (0.0)
Baseline liver stiffness: median (kPa) (IQR)	10.0 (7.6–17.6)
Baseline FIB4 score: median (IQR)	2.06 (1.37–3.49)
Clinical liver decompensation history: *n* (%)	37 (8.7)
Hepatocellular carcinoma history: *n* (%)	9 (2.1)
Liver transplant: *n* (%)	4 (0.9)
Current DAA regimen (±RBV): *n* (%)	292 (69.0) / 83 (19.6) / 40 (9.5) / 2 (0.5) / 6 (1.4)
SOF + LDV / OTV + PTVr ± DSV / SOF + DCV / SOF + SMV / SOF + RBV	

SD standard deviation, *IQR* interquartile range, *CDC* Centers for Disease Control, *HIV RNA* human immunodeficiency virus viral load, *ARV* antiretroviral therapy, *DAA* direct-acting antiviral, *NRTI* nucleoside/nucleotide reverse transcriptase inhibitor, *NNRTI* non-nucleoside reverse transcriptase inhibitor, *PI* ritonavir-boosted protease inhibitor, *INSTI* integrase inhibitor, *HCV* RNA hepatitis C virus viral load, *FIB4* fibrosis-4 score, *RBV* ribavirin, *SOF* sofosbuvir, *LDV* ledipasvir, *OTV* ombitasvir, *PTVr* ritonavir-boosted paritaprevir, *DSV* dasabuvir, *DCV* daclatasvir, *SMV* simeprevir

The logistic regression model (Fig. 1) indicated that DAA success was independently predicted by a baseline CD4+ cell count ≥ 200/μL (OR 5.2, 95% CI 1.9–13.9) and a DAA adherence ≥ 95% (OR 3.9, 95% CI 1.8–8.8). Infection transmission risk groups other than MSM also independently predicted a higher rate of ITT SVR24 (OR 4.2, 95% CI 1.1–16.1). The model's Nagelkerke pseudo-*R* squared was 0.130.

The HCV RNA measure at W4 (W4 HCV RNA) was included in the analysis when available. Considering the subgroup with this measure ($n = 417$), alongside baseline CD4+ cell count, DAA adherence and the transmission mechanism, undetectable W4 HCV RNA predicted a higher rate of SVR24 (OR 3.9, 95% CI 1.7–8.8) (Table 3). The positive predictive value of detectable W4 RNA HCV for SVR24 absence was 18.5% (95% CI 9.9–30.0).

When analysing OT SVR24 in the entire population, both baseline CD4+ cell count ≥ 200/μL and transmission mechanisms other than sex in MSM were found to independently predict a greater probability of SVR24, but not DAA adherence (see Online Resource 2). Moreover, we analysed the OT SVR24 in the population with the W4 HCV RNA measurement, and undetectable W4 HCV RNA remained an independent predictive factor for SVR24 (see Online Resource 3).

Table 2 Univariate analysis of sustained virological response in the intention-to-treat population ($n = 423$)

Analysis subgroups (n)	SVR24 (% patients, 95% CI)	Diff% (95% CI)	Fisher's test p value
Male (316) Female (106)	92.7 (89.3–95.3) 93.5 (87.0–97.3)	− 0.7 [(− 5.5)–6.0]	1.000
< 50 years old (200) ≥ 50 years old (223)	92.5 (87.9–95.7) 93.3 (89.2–96.2)	− 0.8 [(− 6.0)–4.2]	0.850
No MSM (404) MSM (19)	93.3 (90.4–95.6) 84.2 (60.4–96.6)	*+ 9.1 [(− 1.6)–31.0]*	*0.144*
Without diabetes mellitus (361) With diabetes mellitus (62)	93.6 (90.6–95.9) 88.7 (78.1–95.3)	+ 4.9 [(− 1.5)–15.4]	0.179
≤ 25 g alcohol/day (365) > 25 g alcohol/day (58)	93.7 (90.7–96.0) 87.9 (76.7–95.0)	+ 5.8 [(− 1.0)–16.8]	0.161
Without HBV coinfection (415) With HBV coinfection (8)	92.8 (89.8–95.1) 100.0 (63.1–100.0)	− 7.2 [(− 10.1)–25.3]	1.000
Without liver cirrhosis (292) With liver cirrhosis (131)	93.5 (90.0–96.0) 91.6 (85.5–95.7)	+ 1.9 [(− 3.1)–8.3]	0.540
eGFR ≥ 60 mL/min/1.73 m^2 (400) eGFR < 60 mL/min/1.73 m^2 (23)	92.8 (89.8–95.1) 95.7 (78.1–99.9)	− 2.9 [(− 7.6)–13.9]	1.000
Negative/unknown cryoglobulina (377) Positive cryoglobulina (46)	93.4 (90.4–95.7) 89.1 (76.4–96.4)	+ 4.2 [(− 2.6)–16.6]	0.354
Baseline HIV RNA < 50 cp/mL (400) Baseline HIV RNA ≥ 50 cp/mL (23)	93.3 (90.3–95.5) 87.0 (66.4–97.2)	+ 6.3 [(− 2.7)–25.5]	0.218
CDC clinical category A/B (283) CDC clinical category C (140)	93.6 (90.1–96.2) 91.4 (85.5–95.5)	+ 2.2 [(− 2.8)–8.5]	0.424
Nadir CD4+ cell count ≥ 200/μL (177) Nadir CD4+ cell count < 200/μL (246)	95.5 (91.3–98.0) 91.1 (86.8–94.3)	*+ 4.4 [(− 0.7)–9.2]*	*0.087*
Baseline CD4+ count ≥200/μL (389) Baseline CD4+ count < 200/μL (34)	94.1 (91.3–96.2) 79.4 (62.1–91.3)	*+ 14.7 (4.1–31.0)*	*0.006*
Baseline HCV RNA < 10^6 IU/mL (146) Baseline HCV RNA ≥ 10^6 IU/mL (277)	94.5 (89.5–97.6) 92.1 (88.2–95.0)	+ 2.5 [(− 3.2)–7.1]	0.428
HCV genotype ≠ 1 (165) HCV genotype = 1 (258)	90.9 (85.5–94.8) 94.2 (90.6–96.7)	− 3.3 [(− 9.1)–1.7]	0.244
IL28B polymorphism CC (154) IL28B polymorphism CT/TT (269)	90.3 (84.4–94.5) 94.4 (91.0–96.9)	− 4.2 [(− 10.3)–0.9]	0.118
Without interferon experience (298) With interferon experience (125)	92.0 (88.3–94.8) 95.2 (89.9–98.2)	− 3.3 [(− 7.7)– 2.6]	0.301
DAA regimen with SOF (340) DAA regimen without SOF (83)	92.4 (89.0–94.9) 95.2 (88.1–98.7)	− 2.8 [(− 7.3)–4.5]	0.478
DAA regimen with ribavirin (143) DAA regimen without ribavirin (280)	93.7 (88.4–97.1) 92.5 (88.8–95.3)	1.2 [(− 4.6)–5.9]	0.695
DAA adherence ≥ 95% (338) DAA adherence < 95% (85)	95.0 (92.1–97.0) 84.7 (75.3–91.6)	*+ 10.3 (3.5–19.6)*	*0.003*

The italic entries are referring to statistically significant results

SVR24 sustained virological response (undetectable HCV RNA 24 weeks after the end of treatment), *95% CI* 95% confidence interval, *MSM* men who reported having sex with men, *HBV* hepatitis B virus, *eGFR* estimated glomerular filtration rate, *HIV RNA* human immunodeficiency virus viral load, *CDC* Centers for Disease Control, *HCV RNA* hepatitis C virus viral load, DAA direct-acting antiviral, *SOF* sofosbuvir

With regard to cirrhotic patients, factors independently associated with a higher rate of ITT SVR24 included a baseline Child-Turcotte-Pugh score A (OR 10.3, 95% CI 2.1–50.0), baseline liver stiffness < 25 kPa (OR 9.1, 95% CI 1.0–83.3) and a DAA adherence ≥ 95% (OR 8.9, 95% CI 1.8–43.5) (see Online Resource 4). OT SVR24 could not be analysed in the multivariate model owing to few events.

DAA adherence

Median adherence was 100% (IQR 97.7–100.0). Table 4 shows that factors independently associated with adherence < 95% were current alcohol consumption > 25 g per day (OR 2.7, 95% CI 1.5–5.1), absence of anti-HCV treatment experience (OR 3.3, 95% CI 1.7–5.0) and a

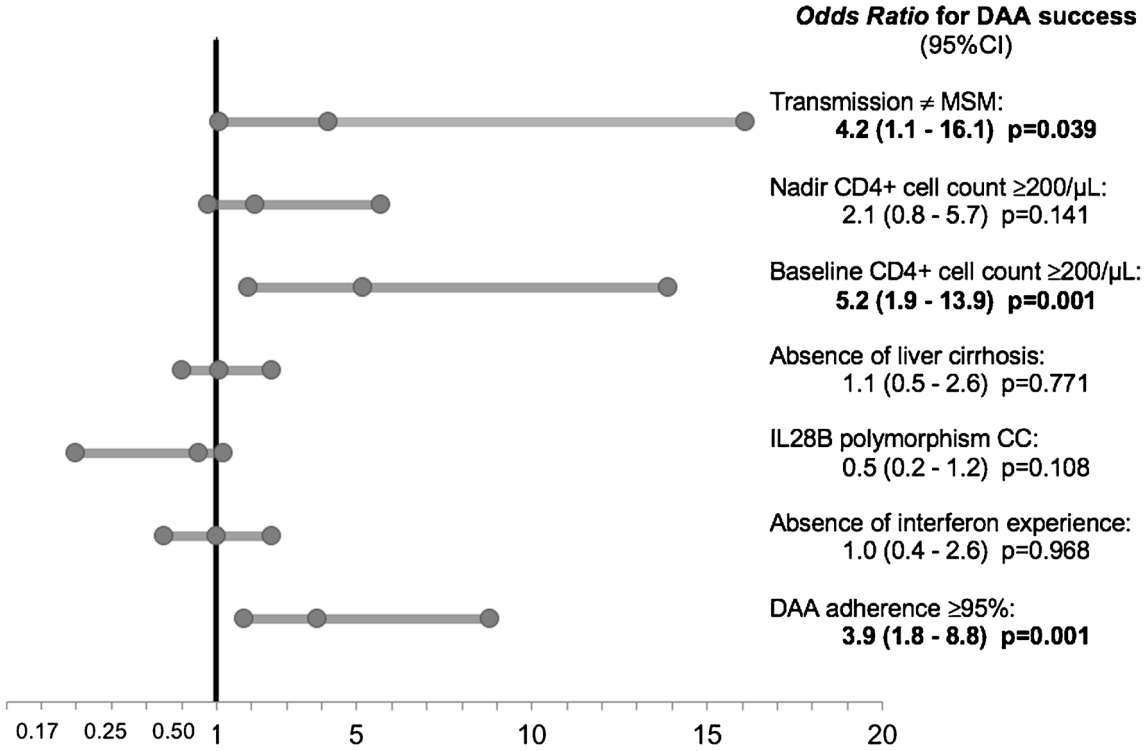

Fig. 1 Multivariate analysis of sustained virological response rate in the intention-to-treat population ($n = 423$). DAA direct-acting antiviral, MSM men who reported having sex with men

DAA regimen with a scheduled duration of 24 weeks (OR 1.8, 95% CI 1.1–3.0). The model's Nagelkerke pseudo-*R* squared was 0.135.

There was no difference in the proportion of patients with adherence ≥ 95% when comparing treatment durations of 8 vs. 12 weeks (data not shown).

Safety

The most frequent clinically adverse events were asthenia (23.2%) and headache (18.8%).

Eighteen patients (4.3%) prematurely withdrew from DAA therapy. Five of the interruptions (27.8%) were considered as

Table 3 Univariate and multivariate analysis of sustained virological response in the intention-to-treat population with HCV RNA measured at week 4 (W4) on treatment ($n = 417$)

Analysis subgroups (*n*)	SVR24 (% patients, 95% CI)	Dif% (95% CI)	Fisher's test *p* value	OR[a] (95% CI)	OR *p* value
No MSM (398) MSM (19)	93.5 (90.6–95.7) 84.2 (60.4–96.6)	*+ 9.3 [(− 1.4)–31.1]*	*0.138*	*4.2 (1.1–16.7)*	*0.040*
Without liver cirrhosis (286) With liver cirrhosis (131)	93.7 (90.2–96.2) 91.6 (85.5–95.7)	+ 2.1 [(− 2.9)–8.5]	0.416	1.1 (0.5–2.5)	0.881
Nadir CD4+ cell count ≥ 200/µL (176) Nadir CD4+ cell count < 200/µL (241)	95.5 (91.2–98.0) 91.3 (87.0–94.5)	+ 4.2 [(− 0.9)–9.0]	0.120	1.9 (0.7–5.2)	0.213
Baseline CD4+ count ≥ 200/µL (384) Baseline CD4+ count < 200/µL (33)	94.0 (91.2–96.2) 81.8 (64.5–93.0)	*+ 12.2 (2.2–28.5)*	*0.019*	*3.9 (1.4–11.4)*	*0.012*
HCV RNA W4 < 15 IU/mL (352) HCV RNA W4 ≥ 15 IU/mL (65)	95.2 (92.4–97.2) 81.5 (70.0–90.1)	*+ 13.6 (5.6–24.9)*	< 0.001	*3.9 (1.7–8.8)*	*0.001*
DAA adherence ≥ 95% (338) DAA adherence < 95% (79)	95.0 (92.1–97.0) 84.8 (75.0–91.9)	*+ 10.2 (3.3–19.9)*	*0.005*	*3.5 (1.5–8.1)*	*0.003*

The italic entries are referring to statistically significant results

SVR24 sustained virological response (undetectable HCV RNA 24 weeks after the end of treatment), *95% CI* 95% confidence interval, *MSM* men who reported having sex with men, *HCV RNA* hepatitis C virus viral load, *DAA* direct-acting antiviral

[a] *Odds ratio* (OR) value for the sustained virological response probability in the first subgroup with respect to the second one in each row

Table 4 Univariate and multivariate analysis of DAA adherence in the intention-to-treat population ($n = 423$)

Analysis subgroups (n)	Adherence ≥ 95% (% patients, 95% CI)	Diff% (95% CI)	Fisher's test p value	OR[a] (95% CI)	OR p value
Male (316) Female (107)	81.7 (76.9–85.8) 74.8 (65.5–82.7)	*+ 6.9 [(− 1.8)–16.7]*	*0.127*	1.6 (0.9–2.7)	0.104
< 50 years old (200) ≥ 50 years old (223)	75.5 (68.9–81.3) 83.9 (78.4–88.4)	*− 8.4 [(− 16.0)–(− 0.7)]*	*0.039*	0.6 (0.4–1.0)	0.065
No PWID (64) PWID (359)	82.8 (71.3–91.1) 79.4 (74.8–83.5)	*+ 3.4 [(− 8.3)–12.0]*	*0.614*	–	–
≤ 25 g alcohol/day (365) > 25 g alcohol/day (58)	83.3 (79.1–87.0) 58.6 (44.9–71.4)	*+ 24.7 (12.2–38.0)*	*< 0.001*	*2.7 (1.5–5.1)*	*0.001*
Without liver cirrhosis (292) With liver cirrhosis (131)	81.2 (76.2–85.5) 77.1 (69.0–84.0)	+ 4.1 [(− 4.0)–13.0]	0.359	–	–
Without interferon experience (298) With interferon experience (125)	75.2 (69.9–80.0) 91.2 (84.8–95.5)	*− 16.0 [(− 22.5)–(− 8.3)]*	*< 0.001*	*0.3 (0.2–0.6)*	*0.001*
DAA regimen with SOF (340) DAA regimen 2D/3D (83)	79.4 (74.7–83.6) 81.9 (72.0–89.5)	− 2.5 [(− 10.7)–7.9]	0.650	–	–
DAA regimen without ribavirin (280) DAA regimen with ribavirin (143)	80.4 (75.2–84.9) 79.0 (71.4–85.4)	+ 1.3 [(− 6.4)–9.9]	0.798	–	–
DAA regimen duration 8–12 weeks (273) DAA regimen duration 24 weeks (150)	82.4 (77.4–86.7) 75.3 (67.6–82.0)	*+ 7.1 [(− 0.9)–15.6]*	*0.099*	*1.8 (1.1–3.0)*	*0.026*

The italic entries are referring to statistically significant results

95% CI 95% confidence interval, *PWID* people who inject(ed) drugs, *DAA* direct-acting antiviral, *SOF* sofosbuvir, *2D* ombitasvir plus ritonavir-boosted paritaprevir, *3D* 2D plus dasabuvir

[a] *Odds ratio* (OR) value for the probability of DAA adherence ≥ 95% in the first subgroup with respect to the second one in each row

possibly or probably attributable to the DAA treatment: two patients deliberately withdrew from the sofosbuvir/ledipasvir regimen due to constipation and headache, respectively, without telling us or waiting for alternative remedies. Another subject interrupted sofosbuvir/ledispasvir owing to constipation aggravated by opioid therapy prescribed in the context of a metastatic hepatocellular carcinoma that had been diagnosed while on treatment. A fourth patient withdrew when an itchy rash developed after 5 weeks of therapy with dasabuvir plus ombitasvir/ritonavir-boosted-paritaprevir. It was clinically diagnosed by our dermatologist colleague as a pigmented purpuric dermatosis, which progressively resolved after treatment discontinuation and the application of topical corticosteroids. The fifth subject was on the fifth week of sofosbuvir/ledipasvir therapy when progressive liver failure developed and obliged the patient to interrupt both the DAA and antiretroviral therapy. At first, improvement in laboratory data was detected after the drug withdrawal, but the patient's clinical status did not and the patient died. A liver biopsy was not performed, so a definitive mechanism for the liver failure remains unknown.

Discussion

In our HIV/HCV coinfection cohort, DAA therapy effectiveness was high and similar to that found in other real-life cohorts [8–15].

The influence of baseline CD4+ cell count on SVR has been studied in HIV/HCV-coinfected patients treated with interferon [23, 24], with no associations found. Moreover, Del Bello et al. [11] studied 89 HIV/genotype 1 HCV-coinfected subjects treated with sofosbuvir plus simeprevir, with or without ribavirin and with sofosbuvir plus ribavirin. No association was found between baseline CD4+ cell count and SVR.

Nevertheless, Berenguer et al. [15] focused on every type of interferon-free regimen available until 2016, without HCV genotype exclusion, within the Madrid-CoRe cohort and found that baseline CD4+ cell count < 200/μL was independently associated with a lower rate of SVR in HIV/HCV coinfection. Notwithstanding that this result could be due to the higher number of patients included in this cohort, we corroborate this finding with a smaller population.

Pawlotsky's biphasic model for HCV eradication during therapy can explain this finding [25]. The first phase shows a fast reduction in HCV RNA owing to the direct effect of drugs on viral replication. In the second, slower phase, there are immunological mechanisms that destroy any remaining infected cells. Therefore, this latter phase is likely to be impaired in HIV-positive patients with lower CD4 cell count.

With regard to sexual transmission in MSM as a predictive factor for DAA failure, the three cases of HCV recurrence among the 19 MSM subjects included in our cohort were considered as HCV reinfections. One of them was confirmed by the change in the HCV genotype, while there was a high suspicion

of HCV reinfection for the other two patients, as described in Online Resource 1. Simmons et al. [26] published a systematic review that included four post-SVR follow-up studies in 309 HIV/HCV-coinfected patients treated with interferon regimens. Globally, the HCV recurrence rate was higher in HIV/HCV-coinfected patients than in HCV-monoinfected ones, even if the latter had been identified as "high risk of reinfection". They found the highest number of cases in a cohort that exclusively included MSM subjects. Furthermore, the NEAT Study Group analysed data from a follow-up of 6006 HIV-positive MSM with documented HCV cures (either after interferon regimen treatment, or spontaneously) [27]. The reinfection rate was 7.3/100 py (95% CI 6.2–8.6). Reinfection data after all-oral DAA therapy is also known from the GECCO cohort [28], in which 32 reinfections were detected among 1533 treated patients, with 26/32 in HIV-positive MSM.

Therefore, our findings probably reflect the consequences of precocious reinfections in this population. While these are not actual DAA failures, these reinfections diminish the practical effectiveness of this therapy.

Another factor associated with the rate of SVR24 was HCV RNA at treatment week 4 (W4 HCV RNA). In HIV/HCV-coinfected patients treated with interferon-based regimens, undetectable W4 HCV RNA predicted SVR [29]. Two other observational studies with HCV-infected subjects treated with all-oral DAA have shown similar findings [9, 30] but were restricted to a particular HCV genotype, and included both HCV-monoinfected and HIV/HCV-coinfected patients, without analysis by multivariate models. Further data are needed in order to confirm this finding, as increasing treatment duration and/or adding ribavirin to the treatment regimens used in our cohort could be outlined in presence of detectable W4 HCV RNA.

In regard to the role of DAA adherence on the SVR24 rate, a review suggests that two virologic rebounds while on DAA treatment within the OPTIMIST trial were attributable to dose omission [31]. However, to the best of our knowledge, there is no real-life study, apart from ours, that has investigated the effect of DAA compliance on SVR.

We analysed factors that could affect DAA adherence and found independent associations with current alcohol consumption, DAA therapy duration and interferon treatment experience. Alcohol was the only factor associated with DAA dose omission in a Canadian study, which included 74 patients in social exclusion and/or active drug users [32]. Moreover, it has been shown that estimated adherence significantly diminishes after 4 weeks of treatment in both monoinfected and in HIV/HCV-coinfected patients [33, 34]. Finally, and contrary to our data, Puenpatom et al. [35] found an association between sofosbuvir plus ledipasvir discontinuation and treatment experience, with no explanation by the authors. We believe that our findings (higher proportion of interferon-naïve patients with DAA adherence < 95%) could be explained by two facts. First, our study has a selection bias; patients who did not have access to interferon therapy, mainly due to psychiatric aspects, did have access to all-oral DAA. This type of population could have problems with adherence. On the other hand, the motivation for a much shorter, safer and more effective therapy could be higher in patients who had been previously treated with interferon.

Therefore, efforts to guarantee adherence must be directed to patients with this described profile. In this way, the chances for an SVR would also be increased.

It is worth noting that the influence of DAA adherence was lost in the on-treatment analysis. Insofar as patients with an adherence rate$_1$ < 100% (pills taken in fewer number than the scheduled prescription) are not included in the on-treatment analysis, this finding could mean that what actually impacts SVR is the early withdrawal of treatment, but not when it is taken completely though to the end, albeit irregularly. Therefore, we believe that it is important to insist that patients finish their treatment with the scheduled number of pills, even though their actual treatment duration would be longer.

We detected no association between SVR24 and classic factors such as HCV RNA, IL28B polymorphism, cirrhosis, interferon treatment experience and genotype 1, which is consistent with other observational studies [8, 13]. In contrast, Berenguer et al. [15] found that male gender, CDC clinical category C, baseline HCV RNA ≥ 800,000 IU/mL, liver cirrhosis, decompensated liver disease and the use of specific DAA regimens (as well as a baseline CD4+ cell count < 200/μL) were independently associated with a lower rate of SVR in HIV-coinfected patients. Perhaps the large number of patients included in the Madrid-CoRe cohort could justify this discordance. Given that some of those factors are taken into account to modify treatment (adjusting duration, adding ribavirin or using different DAA combinations), the possible influence they exert could be lost in a smaller cohort.

When considering only cirrhotic patients, it was found that, besides DAA adherence, a baseline Child-Turcotte-Pugh score of B or C and liver stiffness ≥ 25 kPa were associated with a lower SVR24 rate. While there was no difference according to a baseline Child-Turcotte-Pugh score in the French cohort [36], the Madrid-CoRe cohort also showed a worse SVR in decompensated cirrhotic patients with a baseline Child-Turcotte-Pugh score of C [15]. Additionally, Montes et al. [37] found a higher risk of DAA failure for greater baseline liver stiffness in cirrhotic subjects.

In our cohort, this could be explained by the fact that patients who died before SVR24 confirmation (50% due to liver events, data not shown) were considered as DAA failures. Moreover, advanced liver disease might alter immunological mechanisms working on the second phase of HCV eradication during treatment.

Our study has some limitations. First, as mentioned above, there could be some selection bias due not only to easier

access to DAA for patients to whom interferon-based regimens were contraindicated but also because, when DAA became available in Spain (and when this study began), cirrhotic patients had to be prioritised. Although the DAA regimen was prescribed and strictly guided by both local and European Guidelines, it could be expected that effectiveness and safety would improve even more in ongoing and future studies, especially with a lower prevalence of advanced liver disease and new DAA drugs which are pangenotypic (so genotypic mistakes are not as relevant) and allow for a shorter duration and less ribavirin use. Thus, this bias may not diminish the value of our findings. Second, the predominance of injected drug users could impair the generalisation of these results, especially taking into account the recent increase of sexually transmitted HCV infections in MSM. However, even with a low number of MSM subjects, we were able to show the impact of reinfection in the MSM population in our study. Third, there were a scarce number of events (absence of SVR24), so we could not introduce more factors into the multivariate analysis model. Finally, we could not perform phylogenetic analyses in cases of HCV recurrence to confirm relapse vs. reinfection, a problem shared with other observational studies.

Nevertheless, this analysis presents a considerable number of HIV/HCV-coinfected patients with the inclusion of important variables, some of which have not been taken into account in published works to date.

In conclusion, the treatment of HCV infection in HIV-coinfected patients is highly effective and secure, even in cirrhotic subjects. DAA adherence ≥ 95%, baseline CD4+ count ≥ 200/μL and undetectable W4 HCV RNA are all predictive of a higher probability of SVR. Additionally, a lower rate of SVR was found in MSM, presumably due to the higher frequency of HCV reinfection, which needs to be addressed from a public health standpoint.

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Compliance with ethical standards

Conflict of interest - LDD has received payment for lectures from Abbvie, Gilead and Janssen, and she has received financial support for expert courses and congress by Merck Sharp and Dome, Gilead and Abbvie.

- OB has received payments for lectures from AbbVie, Merck Sharp and Dome and Janssen, and she has received scholarship for expert courses and congress by Merck Sharp and Dome, Janssen, Bristol-Myers-Squibb, Gilead and Abbvie. Her work is currently supported by the Spanish AIDS Research Network (RD16/0025/0017) that is included in the Spanish I+D+I Plan and is cofinanced by ISCIII-Subdirección General de Evaluación and European Funding for Regional Development (FEDER).

- MM reports honoraria for advisory boards from Abbvie and has received payment for lectures from AbbVie, Bristol-Myers-Squibb and Merck Sharp and Dome.

- ML reports honoraria as speaker in educational programs sponsored by Janssen, ViiV, Gilead, Bristol-Myers-Squibb, Merck Sharp and Dome and Abbvie; has received scholarship for expert courses by Merck Sharp and Dome, Janssen and Abbvie; and has received financial support for national and international HIV courses (registration and travel assistance).

- AH, OP and CL have no conflict of interest.

- RR reports grants and payment for lectures from Abbott, Boehringer Ingelheim, Bristol-Myers-Squibb, Gilead, Janssen, Merck Sharp and Dome and ViiV.

- FP has received honoraria for lectures and advisory boards from Abbvie, Gilead, Janssen and ViiV.

Ethical approval and informed consent Patients signed an informed consent approved by the Ethics Committee belonging to the Biomedical Research Institute *Imas12* (University Hospital *12 de Octubre*) when included in the VIH-DOC cohort. This document allows clinical data recollection and analysis for observational study purposes.

Data were anonymised and managed according to the Good Clinical Practice Guidelines published by the World Medical Association Declaration of Helsinki.

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