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***Observational Study***

**Factors associated with DAA virological treatment failure and resistance-associated substitutions description in HIV/HCV coinfected patients**

Salmon D *et al.* DAA failure in HIV/HCV coinfected patients

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**Abstract**

***AIM***

To describe factors associated with treatment failure and frequency of resistance-associated substitutions (RAS).

***METHODS***

Human immunodeficiency virus (HIV)/hepatitis C virus (HCV) coinfected patients starting a first direct-acting antiviral (DAA) regimen before February 2016 and included in the French ANRS CO13 HEPAVIH cohort were eligible. Failure was defined as: (1) non-response [HCV-RNA remained detectable during treatment, at end of treatment (EOT)]; and (2) relapse (HCV-RNA suppressed at EOT but detectable thereafter). Sequencing analysis was performed to describe prevalence of drug class specific RAS. Factors associated with failure were determined using logistic regression models (69 mots).

***RESULTS***

Among 559 patients, 77% had suppressed plasma HIV-RNA < 50 copies/mL at DAA treatment initiation, 41% were cirrhotic, and 68% were HCV treatment-experienced. Virological treatment failures occurred in 22 patients and were mainly relapses (17, 77%) then undefined failure (3, 14%) and non-responses (2, 9%). Mean treatment duration was 16 weeks overall. Post-treatment NS3, NS5A or NS5B RAS were detected in 10/14 patients with samples available for sequencing analysis. After adjustment for age, sex, ribavirin use, HCV genotype and treatment duration, low platelet count was the only factor significantly associated with a higher risk of failure (OR: 6.5; 95%CI: 1.8-22.6).

***CONCLUSION***

Only 3.9% HIV-HCV coinfected patients failed DAA regimens and RAS were found in 70% of those failing. Low platelet count was independently associated with virological failure.

**Key words:** Human immunodeficiency virus; Hepatitis C virus; Direct-acting antiviral; Treatment virological failure; Resistant associated mutations

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**Core tip:** In co-infected human immunodeficiency virus-hepatitis C virus (HCV) patients, after adjustment for age, sex, ribavirin use, HCV genotype and treatment duration, low platelets count was the only factor significantly associated with a higher risk of failure.

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**INTRODUCTION**

The treatment of hepatitis C virus (HCV) infection had been revolutionized with the recent development of direct-acting antiviral (DAA) combinations. Cure rates of over 90%, similar to those in HCV monoinfected patients, can now be achieved in human immunodeficiency virus (HIV)/HCV coinfected patients. This has been documented in clinical trials[[1-5](#_ENREF_1)] as well as in real-life cohorts[[6-9](#_ENREF_6)]. For the few patients failing treatment, resistance-associated substitutions (RAS) can emerge and emerging resistant strains appearing at viral rebound are a consequence rather than a cause of failure[[10](#_ENREF_10),[11](#_ENREF_11)].

The real causes of failure to all-oral DAA regimens can be multiple. Several social and medical factors can jeopardize treatment adherence. Some first generation regimens may not be optimal to treat difficult cases of hepatitis C, such as decompensated cirrhosis or genotype 3 HCV infection. In rare circumstances, especially for genotype 1a viruses, baseline mutations in the non-structural-5A (*NS5A*) gene can preexist in the viral species before treatment introduction and may have a potentially deleterious impact on sustained virological response (SVR)[[12](#_ENREF_12)]. Drug-drug interactions between DAA and ARV therapy or other commonly prescribed medications in HIV/HCV coinfected patients are frequent and can decrease drug levels, thereby reducing the efficacy of therapy. Finally, adverse events, although rare with new DAA combinations, can occur and lead to treatment interruption and thus to treatment failure.

We aimed to describe the characteristics of patients failing first-line DAA treatment in the real-life French nationwide ANRS CO13 HEPAVIH cohort of HIV/HCV coinfected patients. Furthermore, we described the emergence of clinically relevant RAS to DAA classes at DAA treatment failure, and report pharmacological drug monitoring results. Finally, we identified factors associated with the occurrence of virological treatment failure.

**MATERIALS AND METHODS**

***Study population***

The ANRS CO13 HEPAVIH cohort (ClinicalTrials.gov Identifier: NCT03324633) is a national multi-centre prospective hospital-based observational study of patients coinfected with HIV and viral hepatitis C, that received approval by an Institutional Review board [Comité de Protection des Personnes (CPP) Ile de France III, Paris, France].

All patients included in the cohort gave their consent for study participation. In addition, patients from the 29 centers participating in the ANRS CO13 HEPAVIH cohort, not included in the cohort but who gave their consent for specific follow-up during and after DAA treatment, were also eligible. For this substudy, patients were included if they had started an all-oral DAA-based regimen before January 2016 (3 mo treatment), February 2016 (2 mo treatment) or October 2015 (6 mo treatment). Patients who participated in completed and published clinical trials were included in the analysis. We did not include patients who were participating in an ongoing clinical trial (including those completed but not yet published), patients who were treated with combinations including Peg-interferon (PegIFN) or with the sofosbuvir (SOF) + ribavirin (RBV) combination. Patients with premature treatment interruption for intolerance or death were also excluded because we were specifically interested in a virological outcome. The DAA regimen was at the discretion of the patient's physician[[13-15](#_ENREF_13)].

### *Data collection and definitions*

The following data were collected prospectively by each participating center, using an eCRF: Age, sex, risk factors for both HIV and HCV infections, HCV genotype, previous anti-HCV treatment, HIV-related characteristics, start and end dates of DAA treatment, initial doses of anti-HCV and anti-HIV drugs and any changes during follow-up, and HCV-RNA at each time point [baseline, week (W)2, W4, W8, W12 if treatment duration was 24 weeks, EOT, follow-up W4 (FU-W4) and FU-W12]. Virological treatment failures were categorized as: (1) Non-response: HCV-RNA never undetectable during treatment; (2) Relapse: HCV-RNA undetectable at EOT and then detectable within the following 12 wk; and (3) Undefined failure: HCV-RNA unknown at end of treatment (EOT) and positive thereafter, without premature discontinuation of treatment. Cirrhotic status was based on liver biopsy (METAVIR fibrosis stage F4), liver stiffness ≥ 12.5 kPa (FibroScan®; Echosens, France), a FibroTest® value ≥ 0.75 (Biopredictive, France) or physical and biological signs of end-stage liver disease, as previously published[[16](#_ENREF_16),[17](#_ENREF_17)].

***Sequencing analysis***

Patients with virological treatment failure, who provided specific consent for HCV genotype testing and who had HCV-RNA > 1000 IU/mL at the sequencing time point were included for HCV testing. Prevalence of drug class specific RAS was evaluated at failure. The HCV NS3, NS5A and/or NS5B domains were amplified by reverse-transcriptase nested PCR (polymerase chain reaction) using genotype and subtype-specific PCR primers to ensure successful amplification of the target gene(s). PCR products were purified and analyzed by population sequencing using an automated sequencer (ABI-3500xL Dx). The cutoff frequency for detecting variants with Sanger sequencing was approximately 15%. Sanger-derived sequences were aligned with Clustal\_W, version 1.74 (Conway Institute UCD, Dublin, Ireland). NS3, NS5A and NS5B RAS were defined as clinically relevant when inducing > 10-fold resistance to DAA[[13](#_ENREF_13),[18-20](#_ENREF_18)].

***Drug concentrations***

Plasma drug concentrations for DAA and RBV were collected, for patients included in the cohort, when available as part of routine therapeutic drug monitoring performed in several centers. Drug concentrations were measured using liquid chromatography coupled with the tandem mass spectrometry method[[21](#_ENREF_21)]. Data were considered as interpretable if concentrations were determined at steady state and information regarding the time of the last drug intake was available.

A suboptimal concentration was defined as below the 2 µg/mL threshold for RBV[[22](#_ENREF_22),[23](#_ENREF_23)], and when concentrations were below the reported expected range for DAA[[24-27](#_ENREF_24)].

***Statistical analysis***

We included all patients who met the inclusion criteria as described in the study population section. Variables are described as number and percentages, or median and IQR [or mean (SD)], as appropriate. Patient characteristics are reported at initiation of DAA treatment. The Wilcoxon-Mann-Whitney test and Fisher’s exact test were used to compare quantitative and qualitative variables between groups, respectively. Factors associated with virological treatment failure were determined using logistic regression models. In order to identify new independent predictors of virological treatment failure, we systematically adjusted for a fixed set of potential confounders based on literature reports. The following variables were thus forced in all models: Age, sex, RBV use, and prescribed treatment duration[[28](#_ENREF_28)]. We then tested the following variables in the model containing the forced variables: HCV genotype (3 *vs* others), cirrhosis (Yes *vs* No), severe cirrhosis (Yes *vs* No, and defined by a B or C or an elastometry value ≥ 20 kPa), plasma HIV-RNA (detectable *vs* undetectable), and platelet count (< 100 Giga/L *vs* ≥ 100 Giga/L). The effect of RBV on virological treatment failure and potential other factors was assessed by a marginal structural model (MSM) in order to consider a potential indication bias for the prescription of RBV. Sensitivity analyses including patients with premature treatment discontinuations for intolerance/death were also performed. The statistical methods of this study were reviewed by Linda Wittkop from Bordeaux Population Health Research Center, Bordeaux. SAS software version 9.4 (SAS Institute Inc., Cary, North Carolina) was used for all analyses.

**RESULTS**

***General characteristics at DAA initiation***

Among 877 patients treated with DAA-combination, 559 met the inclusion criteria and were included in the analysis (318 were not included for the following reasons: treatment with PegIFN (*n* = 30), inclusion in an ongoing clinical trial (*n =* 2), treatment after the period of analysis (*n* = 190), no available treatment result (*n* = 32), treatment with SOF + RBV (*n* = 60), premature treatment interruption for intolerance (*n* = 3), and one patient died while on treatment). Mean treatment duration was 16 weeks overall (15 wk in patients who failed DAA therapy and 16 weeks in those with SVR). The characteristics of the 559 patients are summarized in Table 1.

***Virological treatment failure***

The virological treatment failure rate was 3.9% (95%CI: 2.5-5.9). Overall, 22 virological treatment failures were observed: 2 non-responses, 17 relapses and 3 undefined virological treatment failures (HCV-RNA unknown at EOT). By univariate analysis (Table 1), patients with virological treatment failure had a significantly lower CD4 cell count (median 527 cells/mm3) compared to patients with SVR (619 cells/mm3; *P =* 0.040). They also more frequently had a platelet count below 100 Giga/L (*P =* 0.007) and a trend for having more frequently a prothrombin time < 85% (40% *vs* 17%, *P =* 0.087) and albumin < 35 g/L (25% *vs* 8%, *P =* 0.146). They had also a non-significant trend for less frequent HIV-RNA suppression (77% *vs* 88%, *P =* 0.186).

***Factors associated with treatment failure***

In adjusted models (Table 2), platelet count below 100 Giga/L was significantly associated with a higher probability of virological treatment failure (Model 4). However, clinical cirrhosis status (Model 1), severe cirrhosis status (Model 3) or blood albumin (data not shown) were not associated with a higher probability of failure. Neither HIV-RNA (Model 2) nor CD4 cell count (data not shown) were associated with virological treatment failure. In addition, in the model containing platelet count, a prescribed treatment duration of 24 wk was associated with a lower risk of virological treatment failure (Model 4). RBV use was not associated with the outcome in adjusted logistic regression models and this result was confirmed by an analysis using MSMs (data not shown).

Sensitivity analyses including patients with premature treatment discontinuations for intolerance/death showed similar results (data not shown).

***HCV resistance at virological treatment failure***

The results of RAS analysis in the 14 patients with virological treatment failure in whom either mutation NS3, NS5A or NS5B could be sequenced are presented in Table 3. Almost three quarters of the patients with available data (10/14; 71%) had at least one detectable RAS at the time of virological treatment failure. In patients receiving an NS5A inhibitor-based regimen, 55% (6/11) had NS5A RAS at virological treatment failure. The common substitutions detected at failure were Q30R/H, 30E, 58D and/or Y93C/N, all found in patients with HCV genotype 1. In patients treated with daclatasvir (DCV) and an available NS5A RAS result (*n* = 5), 4 patients developed resistance to DCV, whereas among 6 treated with ledipasvir (LDV) with available NS5A RAS result, 2 developed resistance to LDV. Overall, in all patients with available genotype (*n* = 14), 6 (43%) presented at least one NS5A RAS, leading to a high level of resistance to NS5A inhibitors (> 10-fold resistance). In patients receiving NS3 protease inhibitors, 2/2 patients with available data had NS3 RAS at virological treatment failure. The substitutions detected at failure were 80K, 170T, 174N and 168V, leading to a high level of resistance to most protease inhibitors.

Multiple RAS conferring a higher level of resistance were detected in 3 (21%) patients, including 2 with NS3 + NS5A RAS and one with NS3 + NS5A + NS5B RAS. These three patients were previously treated with PegIFN + RBV and were exposed to NS5A inhibitors butnot exposed to NS3 inhibitors.

***Pharmacological data***

Nine of the 22 (41%) patients who had DAA therapy failure had measurement of DAA and/or RBV concentration at W2 or W4 of treatment, 7 of which were interpretable. Among these 7 patients, suboptimal concentrations were reported in 2 (29%). These low concentrations concerned either DCV (in a patient treated SOF + DCV whose ARV treatment was rilpivirine + raltegravir), or RBV (in a patient treated with SOF/LDV + RBV who was taken rilpivirine + dolutegravir).

**DISCUSSION**

In this cohort of HIV/HCV coinfected patients treated with an interferon-free DAA regimen with or without RBV, we report a low virological treatment failure rate of 3.9%. Our results are similar to those observed in clinical trials[[28](#_ENREF_28)] or previous real-world studies in HIV/HCV coinfection[[6](#_ENREF_6),[7](#_ENREF_7)]. Most of these virological treatment failures were due to relapses (77%) followed by non-responses (9%), while 14% were due to undefined virological treatment failures (HCV-RNA unknown at EOT?).

Due to the very high rates of SVR, it has been difficult, in real-world studies, to identify factors associated with virological treatment failure of DAA, and no study to date has focused on HIV coinfection. In studies of HCV monoinfected patients, three factors have however been found to be associated with virological treatment failure: The main one being the severity of cirrhosis, as assessed by presence of ascites, low albumin, low platelet count or high total bilirubin[[29-35](#_ENREF_29)]; but also male sex[[30](#_ENREF_30),[31](#_ENREF_31)]; and the preexistence of baseline RAS[[34](#_ENREF_34),[36](#_ENREF_36)].

In our study, we found that a low platelet count was significantly associated with a higher rate of virological treatment failure. It is likely that the low platelet count is a surrogate marker of cirrhosis, since we found a tendency for an association with low albumin levels and low PT time by univariate analysis. However, we failed to observe a significant relationship between severe cirrhosis and failure. This might be due to the fact that in case of severe cirrhosis, physicians adapted the treatment to each complex situation by extending the duration or by adding RBV (76% of the patients with Child Pugh B or C cirrhosis received treatment of 24 wk duration *vs* 29% of the other patients in our study), and this less probably might be explained by unreported events of decompensation.

In the first randomized phase 3 clinical trials, assessing the efficacy and safety of DAA, decompensated cirrhosis was an exclusion criterion, which precluded the possibility of assessing this factor as a potential predictor of failure. More recently, several trials have clearly demonstrated that patients with Child Pugh B or C cirrhosis and those with genotype 3 infection have a lower rate of SVR with DAA alone and need the addition of RBV. This was the case for the SOF/LDV combination and for a combination[[37](#_ENREF_37),[38](#_ENREF_38)] of velpatasvir/SOF[[39](#_ENREF_39)].

We observed a trend towards a higher rate of detectable HIV-RNA in patients with virological treatment failure than in those with SVR (*P =* 0.19), by univariate analysis only. This might reflect suboptimal adherence, with patients who are non-compliant for their HIV treatment possibly also being non-adherent to their HCV treatment. Nonetheless, this result did not remain significant by multivariable analysis and thus may also simply reflect a biased estimate.

Moreover, among 7 patients with failure and interpretable pharmacological data, suboptimal blood concentrations of DAA were measured in 2 of them. These results could reflect different situations (drug interactions, suboptimal dosing errors, suboptimal adherence) and warrant further investigation and wider-scale assessment of pharmacological data. Regarding RAS in our study, we did not determine pretreatment RAS and we cannot exclude the possibility that some failures may be due to pre-existing RAS. However, at a population level, the effects of baseline RAS in NS5A, although not rare, are minimal[[10](#_ENREF_10),[36](#_ENREF_36),[40](#_ENREF_40),[41](#_ENREF_41)], and prompted EASL experts[[18](#_ENREF_18),[20](#_ENREF_20)] to recommend that genotyping should not be performed for naïve patients, but rather considered when retreatment is anticipated with a *NS5A* inhibitor regimen, in patients who have previously failed NS5A treatment.

In most of our patients who failed DAA-treatment, RAS were investigated, and we found RAS in 50% of those failing NS5A-based therapy, in the two patients failing NS3, but no major RAS S282T to NS5B. This high prevalence of *NS5A* and -3 RAS at failure in our study confirms the EASL recommendation to evaluate, if resistance testing is available, HCV resistance to NS5A inhibitors (spanning amino acids 24 to 93) as these analyses can guide decisions for a further treatment[[18](#_ENREF_18),[20](#_ENREF_20)].

There are several limitations to this study. Firstly, since the study was an observational cohort, our results must be interpreted with caution, because treatment prescriptions depended on drug availability (with variations over time), and known efficacy with regard to HCV genotypes. Those results were obtained with 2nd generation DAA (LDV, DCV, elbasvir/grazoprevir) and those results may not be entirely applicable to the newer, pangenotypic regimens such as velpatasvir/SOF or pibentasvir/glecaprevir. Our analysis is limited by the low number of subjects with virological treatment failure, and thus, probably has limited power to identify all potential risk factors. All patients with virological treatment failure could not be explored by genotyping to investigate the emergence of RAS due to the need to obtain patient consent. Furthermore, baseline genotyping was not available routinely, since this test is not recommended in France for treatment-naïve patients. Finally, Sanger sequencing assay was used for the detection of RAS, which may not be sensitive enough to detect minor populations of RAS (< 15%). The strengths of our study include prospective data collection with regular monitoring and high quality data.

In conclusion, our study identified that low platelet count was associated with a higher probability of DAA failure. This parameter probably reflects hepatic insufficiency and our results are concordant with the literature in HCV monoinfected patients. We could also speculate that some degree of low adherence could explain some cases of failure since suboptimal drugs levels were observed in 29% of the cases that could be explored and since HIV viral load tended to be often detectable in patients with virological treatment failure to DAA. This study confirms the very low rate of treatment failure with all-oral DAA in HIV/HCV coinfected patients, but a high risk of emergence of non-structural NS3 or NS5A RAS in patients with virological DAA failure.

**ARTICLE HIGHLIGHTS**

***Research background***

In human immunodeficiency virus (HIV)/hepatitis C virus (HCV) coinfection, all-oral direct-acting antiviral (DAA) regimens achieve virological cure in more than 95% of the patients.

***Research motivation***

Risk factors for failure are mainly related to the severity of cirrhosis HCV monoinfected patients but are unknown in the population of HIV HCV coinfected patients. We wanted to know if other factors related to non-adherence or to HIV status could be involved in the occurrence of failures. We thought that knowing risk factors for failure would allow to adapt the treatment to the patients with higher risk for failure.

***Research objectives***

The main objectives were to determine the risk factors for virological treatment failure to DAA in HIV/HCV coinfected patients and to describe the frequency of RAS.

***Research methods***

HIV/HCV coinfected patients starting a first DAA regimen before February 2016 and included in the French ANRS CO13 HEPAVIH cohort were eligible. Failure was defined as: i) non-response (HCV-RNA remained detectable during treatment, at end of treatment (EOT)), ii) relapse (HCV-RNA suppressed at EOT but detectable thereafter). Sequencing analysis was performed to describe prevalence of drug class specific RAS. Factors associated with failure were determined using logistic regression models.

***Research results***

Research findings: Among 559 patients, 77% had suppressed plasma HIV-RNA < 50 copies/mL at DAA treatment initiation, 41% were cirrhotic, and 68% were HCV treatment-experienced. Virological treatment failures occurred in 22 patients and were mainly relapses (17, 77%) then undefined failure (3, 14%) and non-responses (2, 9%). Mean treatment duration was 16 weeks overall. Post-treatment NS3, NS5A or NS5B RAS were detected in 10/14 patients with samples available for sequencing analysis. After adjustment for age, sex, RBV use, HCV genotype and treatment duration, low platelet count was the only factor significantly associated with a higher risk of failure (OR: 6.5; 95%CI: 1.8-22.6); Contributions to the field: In HIV/HCV coinfected patients, the risk factors of failure seem to be related more to the severity of cirrhosis than to HIV immunovirological status or non-adherence issues; Problems that remain to be solved: It remains to be proven that the low platelet count associated with a higher probability of failure reflects the severity of cirrhosis.

***Research conclusions***

In our study of HIV/HCV patients receiving all oral DAA, only 3.9% HIV-HCV coinfected patients failed DAA regimens. RAS were found in 70% of those failing. Low platelet count was independently associated with virological failure. We think that this low platelet count reflects the severity of cirrhosis.

***Research perspectives***

As the number of treatment failure is low, it would be useful to build international collaborations and gather the data of several cohorts in order to gain power. Those results obtained with all oral DAA of 1st generation could be checked with the newer, pangenotypic drug regimen.

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**Table 1 Patients’ characteristics at treatment initiation according to virological response**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | Overall (*n* = 559) | SVR (*n* = 537) | Virological treatment failure  (*n* = 22) | *P*-value |
| **Male sex** | 431 (77) | 414 (77) | 17 (77) | 0.985 |
| **Age (yr)** | 52 (49-56) | 52 (49-56) | 53 (51-57) | 0.586 |
| **CD4 (/mm3) (*n* = 557)** | 618 (426-850) | 619 (429-861) | 527 (346-704) | 0.040 |
| **Undetectable HIV-RNA (*n* = 558)** | 486 (87) | 469 (88) | 17 (77) | 0.186 |
| **ARV treatment** | 549 (98) | 527 (98) | 22 (100) | 1.000 |
| **PI1** | 127 (23) | 122 (23) | 5 (23) |  |
| **NNRTI2** | 98 (18) | 95 (18) | 3 (14) |  |
| **II3** | 204 (37) | 197 (37) | 7 (32) |  |
| **Others** | 120 (22) | 113 (21) | 7 (32) |  |
| **Active tobacco consumption (*n* = 263)** | 153 (58) | 148 (58) | 5 (71) | 0.703 |
| **Active alcohol consumption (*n* = 266)** | 135 (51) | 132 (51) | 3 (43) | 0.719 |
| **Active drug consumption (*n* = 257)** | 7 (3) | 7 (3) | 0 (0) | 1.000 |
| **HCV genotype (*n* = 558)** |  |  |  | 0.475 |
| **1 without precision** | 26 (5) | 24 (5) | 2 (9) |  |
| **1a** | 232 (42) | 221 (41) | 11 (50) |  |
| **1b** | 64 (12) | 64 (12) | 0 (0) |  |
| **2** | 6 (1) | 6 (1) | 0 (0) |  |
| **3** | 62 (11) | 60 (11) | 2 (9) |  |
| **4** | 165 (30) | 158 (30) | 7 (32) |  |
| **5** | 1 (0) | 1 (0) | 0 (0) |  |
| **6** | 2 (0) | 2 (0) | 0 (0) |  |
| **Cirrhosis (*n* = 555)** | 209 (38) | 200 (38) | 9 (41) | 0.748 |
| **Child Pugh, if cirrhosis (*n* = 189)** |  |  |  | 0.537 |
| **A** | 172 (91) | 165 (91) | 7 (88) |  |
| **B/C** | 17 (9) | 16 (9) | 1 (12) |  |
| **FIB-4 (*n* = 405)** | 2.1 (1.4-3.7) | 2.1 (1.4-3.7) | 3.3 (1.9-7.3) | 0.313 |
| **FIB-4 > 3.25 (*n* = 405)** | 120 (30) | 113 (29) | 7 (50) | 0.132 |
| **Elastometry (kPa) (*n* = 115)** | 9 (6-14) | 9 (6-14) | 10 (6-17) | 0.942 |
| **Elastometry ≥ 12.5 kPa (*n* = 115)** | 32 (28) | 30 (27) | 2 (50) | 0.309 |
| **Elastometry ≥ 20 kPa (*n* = 115)** | 17 (15) | 16 (14) | 1 (25) | 0.478 |
| **HCV treatment history** |  |  |  | 0.570 |
| **Naïve** | 210 (38) | 203 (38) | 7 (32) |  |
| **Pretreated** | 349 (62) | 334 (62) | 15 (68) |  |
| **HCV viral load (log10 IU/mL) (*n* = 558)** | 6.09 (5.59-6.51) | 6.09 (5.59-6.51) | 6.04 (5.72-6.49) | 0.886 |
| **Prothrombin rate (*n* = 298)** | 99 (89-100) | 99 (89-100) | 92 (82-100) | 0.116 |
| **Prothrombin rate < 85% (*n* = 298)** | 54 (18) | 50 (17) | 4 (40) | 0.087 |
| **Platelets (Giga/L) (*n* = 408)** | 171 (131-219) | 171 (133-219) | 148 (97-184) | 0.168 |
| **Platelets < 100 Giga/L (*n* = 408)** | 57 (14) | 51 (13) | 6 (43) | 0.007 |
| **Albumin (g/L) (*n* = 301)** | 41 (38-44) | 41 (38-44) | 42 (37-45) | 0.939 |
| **Albumin < 35 g/L (*n* = 301)** | 26 (9) | 24 (8) | 2 (25) | 0.146 |
| **DAA-combination** |  |  |  | NA5 |
| **SOF + DCV ± RBV4** | 240 (43) | 231 (43) | 9 (41) |  |
| **SOF/LDV ± RBV** | 271 (49) | 261 (49) | 10 (46) |  |
| **SOF + SMV ± RBV** | 26 (4) | 23 (4) | 3 (14) |  |
| **Others4** | 22 (4) | 22 (4) | 0 (0) |  |
| **Mean (SD) DAA treatment durationa** | 16 (6) | 15 (5) | 16 (6) |  |

Results are presented as number (as percentages in brackets) or median (IQR in brackets) unless stated otherwise. 1PI was boosted in 98 patients with SVR and in 5 patients with treatment failure; 2NNRTI molecule was rilpivirine in 60 patients with SVR and 3 with failure, and was efavirenz in 25 patients with SVR; 3II molecule was raltegravir in 153 patients with SVR and 4 patients with failure, and was dolutegravir in 38 patients with SVR and 2 with treatment failure; **4**Initial doses of DCV were 30, 60, 90 mg/day in respectively 57, 159 and 21 patients. The dose was unknown for the 5 other patients; 5NA: not applicable, no formal statistical comparison was performed as the prescription of the DAA regimen was chosen by each patient’s physician. SVR: Sustained virological response; ARV: Antiretroviral; PI: Protease inhibitor; NNRTI: Non-nucleoside reverse-transcriptase inhibitor; II: Integrase inhibitor; DAA: All-oral direct-acting antiviral; SOF: Sofosbuvir; RBV: Ribavirin; DCV: Daclatasvir; LDV: Ledipasvir; SMV: Simeprevir.

**Table 2 Adjusted logistic regression for factors associated with virological treatment failure**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Covariables | **Model 1** | | **Model 2** | | **Model 3** | | **Model 4** | |
|  | **OR (95% CI)** | ***P*-value** | **OR (95% CI)** | ***P*-value** | **OR (95% CI)** | ***P*-value** | **OR (95% CI)** | ***P*-value** |
|  | *N =* 538 | | *N =* 538 | | *N =* 526 | | *N =* 395 | |
| **Age at treatment initiation (per 10 yr)** | 1.2  (0.6-2.4) | 0.58 | 1.3 (0.7-2.5) | 0.48 | 1.2 (0.6-2.4) | 0.53 | 1.6 (0.7-4.0) | 0.29 |
| **Ribavirin *vs* no ribavirin** | 1.0 (0.3-3.0) | 0.97 | 1.1 (0.3-3.2) | 0.93 | 1.0 (0.3-3.0) | 0.97 | 1.4 (0.4-5.5) | 0.61 |
| **Male sex *vs* female** | 1.0  (0.4-2.8) | 0.98 | 0.9 (0.3-2.7) | 0.92 | 1.0 (0.3-2.8) | 0.97 | 0.8 (0.2-2.7) | 0.69 |
| **Treatment duration 24 wk *vs* 12 wk** | 0.4  (0.1-1.4) | 0.15 | 0.5 (0.2-1.5) | 0.21 | 0.4 (0.1-1.4) | 0.16 | **0.2 (0.0-1.0)** | **0.05** |
| **Platelet count < 100 Giga/L *vs* ≥ 100** |  |  |  |  |  |  | **6.5  (1.8-22.6)** | **0.004** |
| **Cirrhosis *vs* no cirrhosis** | 1.4  (0.5-3.9) | 0.51 |  |  |  |  |  |  |
| **HIV-RNA detectable *vs* undetectable** |  |  | 2.1 (0.7-5.9) | 0.17 |  |  |  |  |
| **Severe cirrhosis *vs* no severe cirrhosis** |  |  |  |  | 2.1  (0.4-10.3) | 0.35 |  |  |
| **HCV genotype 3 *vs* others** |  |  |  |  |  |  | 0.9 (0.1-7.5) | 0.91 |

HCV: Hepatitis C virus; HIV: Human immunodeficiency virus.

**Table 3 Resistance-associated substitution results in 14 patients with virological treatment failure for whom sequencing was performed in routine care**

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Pat** | **HCV treatment history** | **Treatment received** | **HCV genotype** | | **Cirrhosis** | **ARV treatment** | **RAS** | | |
| **Before treatment** | **After treatment** | **NS3** | **NS5A** | **NS5B** |
| A | Pretreated | SOF + SMV 12 wk | 1a | 1a | Yes | II | Q80K, I170T, S174N | Abs | Abs |
| B | Pretreated | SOF + SMV 12 wk | 1a | 1a | Yes | II | D168V | Abs | Abs |
| C | Pretreated | SOF/LDV 12 wk | 4 | 4a | No | PI | Abs | Abs | Abs |
| G | Pretreated | SOF/LDV + RBV 12 wk | 4 | 4d | No | Others | Abs | Abs | Abs |
| H | Pretreated | SOF + DCV 10 wk3 | 4 | 4 | No | Others | Abs | ND | Abs |
| I | Naive | SOF/LDV 12 wk | 1a | 1a | No | PI | Abs | Abs | Abs |
| J | Pretreated | SOF/LDV 12 wk | 1a | 1a | No | Others | ND | Y93C | Abs |
| L | Naive | SOF + DCV 13 wk2 | 1a | 1a | Yes | NNRTI | Q80K | Abs | Abs |
| M | Pretreated | SOF/LDV 12 wk | 4 | 4a | No | PI | ND | Abs | A421V, M414L |
| N | Pretreated | SOF/LDV + RBV 12 wk | 1a | 1a | Yes | II | A168V | 30E, 58D | Abs |
| P | Pretreated | SOF + DCV + RBV 12 wk1 | 1a | 1a | No | PI | Abs | Y93N | Abs |
| Q | Pretreated | SOF + DCV + RBV 24 wk1 | 1a | 1a | No | Others | T54S | Q30R | Abs |
| R | Pretreated | SOF + DCV 24 wk2 | 1a | 1a | Yes | II | Q80K | Y93C | Y448H |
| W | Pretreated | SOF + DCV 24 wk1 | 1 | 1a | Yes | II | Abs | Q30H | Abs |

1Initial dose of DCV: 30 mg/d; 2Initial dose of DCV: 60 mg/d; 3Initial dose of DCV: 90 mg/d. Pat: Patient; ARV: Antiretroviral; RAS: Resistance-associated substitution; NS3: Non-structural-3; NS5A: Non-structural-5A; NS5B: Non-structural-5B; SOF: Sofosbuvir; RBV: Ribavirin; DCV: Daclatasvir; LDV: Ledipasvir; SMV: Simeprevir; ND: Not done; PI: Protease inhibitor; NNRTI: Non-nucleoside reverse-transcriptase inhibitor; II: Integrase inhibitor; Abs: No RAS found.