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## Grazoprevir/elbasvir for the immediate treatment of recently acquired HCV genotype 1 or 4 infection in MSM

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1 **Grazoprevir/elbasvir for the immediate treatment of recently acquired hepatitis C virus genotype 1**  
2 **or 4 infection in men having sex with men**

3

4 Anders BOYD<sup>1</sup>, Patrick MIALHES<sup>2</sup>, Julie CHAS<sup>3</sup>, Marc-Antoine VALANTIN<sup>4</sup>, Yazdan YAZDANPANA<sup>5</sup>,  
5 Eric ROSENTHAL<sup>6</sup>, Stephane CHEVALIEZ<sup>7</sup>, Lionel PIROTH<sup>8</sup>, Hayette ROUGIER<sup>9</sup>, Gilles PEYTAVIN<sup>10</sup>, Gilles  
6 PIALOUX<sup>3,11</sup>, Pierre-Marie GIRARD<sup>12,13</sup>, Karine LACOMBE\*<sup>12,13</sup>

7

8 **Institutional affiliations:**

9 <sup>1</sup>INSERM, Institut Pierre Louis d'Epidémiologie et de Santé Publique, F-75012, Paris, France;

10 <sup>2</sup>Hôpital de la Croix-Rousse, Hospices Civils de Lyon, Service de Maladies Infectieuses et Tropicales,  
11 Lyon, France

12 <sup>3</sup>AP-HP, Hôpital Tenon, Service de Maladies Infectieuses et tropicales, Paris, France

13 <sup>4</sup>AP-HP, Groupe Hospitalier Pitié-Salpêtrière, Service de Maladies Infectieuses et tropicales, Paris,  
14 France

15 <sup>5</sup>AP-HP, Hôpital Bichat-Claude Bernard, Service de Maladies Infectieuses et tropicales, Paris, France

16 <sup>6</sup>Hôpital de l'Archet, Service de médecine interne, Nice, France

17 <sup>7</sup>AP-HP, département de Virologie, Hôpital Henri Mondor; National Reference Center for Viral  
18 Hepatitis B, C and delta; INSERM U955, Créteil, France

19 <sup>8</sup>Département d'infectiologie, CHU de Dijon, 21079 Dijon, France; Inserm CIC 1432, Université de  
20 Bourgogne, 21079 Dijon, France

21 <sup>9</sup>Institut de Médecine et d'Epidémiologie Appliquée, Paris

22 <sup>10</sup>AP-HP, Hôpital Bichat-Claude Bernard, Laboratoire de Pharmacologie-Toxicologie and IAME, UMR  
23 1137, Université Paris Diderot, Sorbonne Paris Cité and INSERM, Paris, France

24 <sup>11</sup>Sorbonne Université, Paris, France

25 <sup>12</sup>Service de maladies infectieuses et tropicales Hôpital St Antoine, AP-HP, Paris, France

26 <sup>13</sup>Sorbonne Université, Inserm UMR-S1136, Institut Pierre Louis de Santé Publique, Paris, France

27

28 **Corresponding Author:**

29 Prof. Karine Lacombe, MD, PhD

30 Service de maladies infectieuses et tropicales

31 Hôpital Saint-Antoine

32 184 rue du Faubourg Saint-Antoine

33 75012 Paris – FRANCE

34 Tel: +33 1 49 28 24 38

35 Fax: +33 1 49 28 21 49

36 Email: karine.lacombe2@aphp.fr

37

38 **Running Title:** GZR/ EBR for acute HCV infection

39 **SYNOPSIS**

40

41 **Background:** Men having sex with men (MSM) belong to the most at-high risk populations that fuel  
42 the epidemic of recently acquired hepatitis C in Europe. Alternative associations of direct antiviral  
43 agents against hepatitis C virus (HCV) need to be assessed.

44 **Patients and methods.** In this pilot trial, MSM with recently acquired genotype 1-4 HCV infection  
45 were prospectively included and received 8 weeks of oral grazoprevir 100 mg and elbasvir 50 mg in a  
46 fixed-dose combination administered once daily. The primary endpoint was sustained virological  
47 response evaluated 12 weeks after end of treatment (SVR12). Secondary endpoints were the  
48 virological characterization of failures, the quality of life before, during and after treatment and the  
49 rate of reinfection.

50 **Results.** In a 15 months period 30 patients were enrolled, all of whom were men who have sex with  
51 men. Of the 29 patients completing follow-up, 28 (96%, 95%CI=82-99%) achieved SVR12. One patient  
52 interrupted follow-up (suicide) but had undetectable plasma HCV-RNA at the end of treatment. One  
53 patient with suboptimal adherence confirmed by plasma drug monitoring relapsed and developed  
54 NS3, NS5A and NS5B RASs at positions V36M, M28V, and S556G. The most common adverse events  
55 related to study drug were diarrhoea ( $n=4$ , 13%), insomnia ( $n=2$ , 7%), and fatigue ( $n=2$ , 7%), although  
56 no patient discontinued treatment. No HIV-RNA breakthrough was reported in the 28 patients with  
57 HIV co-infection. At week 48, reinfection was diagnosed in 3 patients.

58 **Conclusions.** Our data support the use of grazoprevir/elbasvir for immediate treatment against HCV  
59 in order to reduce HCV transmission in MSM.

## 60 INTRODUCTION

61

62 With the use of direct-acting antivirals (DAAs), clearance of hepatitis C virus (HCV) can be achieved  
63 with short-course treatment for all HCV-infected individuals.<sup>1</sup> This success has prompted the World  
64 Health Organization to target HCV elimination by 2030.<sup>2</sup>

65

66 In Western European countries, outbreaks of recently acquired HCV among HIV-positive MSM have  
67 begun since 1996<sup>3</sup> and HCV incidence has failed to decline over the past decade.<sup>4</sup> With the increased  
68 use of pre-exposure prophylaxis against HIV, clustering of recently acquired HCV infections has also  
69 been observed between HIV-positive and HIV-negative MSM.<sup>5</sup> Although most settings delay  
70 treatment for 6 months in order to assess spontaneous HCV clearance, HIV-positive MSM with  
71 recently acquired HCV infection could still be engaging in at risk activity and continue to transmit  
72 HCV.<sup>6</sup> Short-course DAA treatment during recently acquired HCV infection could therefore be  
73 beneficial to reduce HCV transmission. Modelling studies have indeed suggested that treating HCV  
74 early-on is an essential part of the interventions needed to curb HCV incidence and reach  
75 elimination.<sup>7-9</sup>

76

77 Few DAA combinations exploring diverse durations of treatment, mostly involving the NS5B inhibitor  
78 sofosbuvir, have been studied for individuals with acute HCV infection. In two one-arm, open label  
79 trials, sustained virological response 12 weeks after treatment (SVR12) was achieved with 6- or 8-  
80 week sofosbuvir/ledipasvir in 77% and 100% of HCV genotype 1-4 HIV-positive individuals.<sup>10, 11</sup> In the  
81 SWIFT-C trial, a 12-week sofosbuvir/ritonavir regimen led to 59% with SVR12, which is clearly sub-  
82 optimal.<sup>12</sup> An 8-week course of the non-sofosbuvir based DAA regimen,  
83 paritaprevir/ritonavir/ombitasvir/dasabuvir±ribavirin, was examined in acute HCV genotype 1  
84 infection, resulting in 97% with SVR12.<sup>13</sup> These trials were limited in that patients with acute or early  
85 chronic HCV infection were combined.

86 Grazoprevir and elbasvir are potent NS3/4 and NS5A inhibitors for the treatment of chronic HCV  
87 genotype 1/4 infection and have resulted in high proportions of SVR12.<sup>14, 15</sup> SVR12 of 96%-99% after  
88 12-week grazoprevir/elbasvir have also been observed among HIV and chronic HCV co-infected  
89 patients harbouring HCV genotypes 1, 4 and 6 in both clinical trials<sup>16, 17</sup> and real-life settings.<sup>18</sup> Only  
90 one trial has evaluated the efficacy of this combination in individuals recently infected with hepatitis  
91 C genotype 1 or 4 in the Netherlands and after a shorter 8-week duration of treatment, reported an  
92 SVR12 of 99%.<sup>19</sup> Further confirmation of these results are needed. We present herein the results of a  
93 clinical pilot trial conducted in France that included MSM with a recently acquired HCV genotype 1 or  
94 4 infection undergoing eight-week grazoprevir/elbasvir.

95

96

## 97 **PATIENTS AND METHODS**

98

### 99 **Study design**

100

101 The SAHIV study is an open-label, single-arm, interventional, pilot trial evaluating the efficacy and  
102 safety of 8-week grazoprevir 100 mg and elbasvir 50 mg for the treatment of recently acquired  
103 genotype 1 or 4 HCV infection. Recruitment of study participants occurred at 6 university hospitals in  
104 France (Paris – Hôpital Saint-Antoine, Hôpital La Pitié-Salpêtrière, Hôpital Bichat, Hôpital Tenon; Lyon  
105 – Hôpital de la Croix-Rousse, Lyon; Nice – CHU de Nice). The protocol was approved in accordance  
106 with the Helsinki Declaration. The trial was registered at clinicaltrials.gov (identifier: NCT02886624).

107

### 108 **Participants**

109

110 Inclusion criteria were: age  $\geq 18$  years, recently acquired HCV genotype 1 or 4 infection (defined in  
111 the Supplementary methods), plasma HCV-RNA  $\geq 1000$  IU/mL, body weight 40-125 kg, and health

112 coverage under the French national health system. If HIV-positive, infection had to be confirmed with  
113 a positive western blot. HIV-positive individuals were allowed to either follow an ART combination  
114 not contraindicated with grazoprevir and elbasvir or remain untreated with ART while taking the  
115 study drug. All patients signed written informed consent prior to participating in the trial.

116

117 Non-inclusion criteria were: active or recent (<6 months) opportunistic infection; primary HIV  
118 infection; hepatitis B surface antigen-positive without treatment containing a third-generation  
119 nucleoside/nucleotide analogue [tenofovir, tenofovir alafenamide, entecavir] within 2 weeks of  
120 participating; confirmed cirrhosis prior to acute HCV diagnosis; any other known causes of acute  
121 hepatitis; pregnant or breast-feeding; liver transplant recipient; progressive malignancy; history of  
122 non-adherence; participation in another clinical trial with experimental treatment; under legal  
123 guardianship or incarcerated; haemoglobin <10 g/dL (female) or <11 g/dL (male); platelet count  
124 <50,000/mm<sup>3</sup>; neutrophil count < 750/mm<sup>3</sup>; or contraindication to grazoprevir and/or elbasvir or to  
125 any of the excipients.

126

## 127 **Study procedures**

128

129 Participants received an oral, fixed-dose, once-daily combination of grazoprevir (100 mg) and elbasvir  
130 (50 mg) for eight weeks. HCV genotype and HCV-RNA viral load were obtained either at screening  
131 visit or from a previous biological test performed 1-4 weeks before treatment initiation. RAS testing  
132 was not performed prior to treatment initiation.

133

134 After treatment initiation, patients were followed at week 4 (W4) and week 8 (W8) and post-  
135 treatment at week 4 (PTW4) and week 12 (PTW12). Blood samples were drawn at each visit to assess  
136 ALT, AST, total and conjugated bilirubin,  $\gamma$ -glutamyl transferase, alkaline phosphatase, full blood and  
137 platelet count, and creatinine levels. HCV-RNA viral load was measured using a commercially-

138 available PCR assay at the study centre (TaqMan 2.0 Assay Roche diagnostic or Abbott Realtime;  
139 lower limit of detection: 15 IU/mL and 12 IU/mL, respectively). Genotyping was performed using  
140 Versant® HCV Genotype 2.0 Assay (LiPA) (Siemens Healthcare Diagnostics Inc., Tarrytown, USA). For  
141 HIV-positive individuals, HIV-RNA viral load was measured using a commercially-available PCR assay.  
142 Patients were asked to fill in questionnaires on adherence at W4 and W8 and on quality of life [using  
143 the Short Form (SF)-12v2] at treatment initiation and PTW12.

144

145 If SVR12 was not achieved, drug concentrations were quantified on stored plasma samples obtained  
146 during treatment (W4 and W8) using UPLC coupled with tandem MS (Acquity-TQD, Waters  
147 Corporation; Milford, MA, USA).<sup>20,21,22</sup>

148

149 For post-treatment study visits at which HCV-RNA levels were detectable, HCV drug resistance  
150 profiles were determined from stored serum samples at baseline and the study visit where failure  
151 was recorded<sup>23, 24</sup> NS3, NS5A and NS5B sequencing analysis were performed by in-depth  
152 phylogenetic analysis. The phylogenetic trees were visualized using Dendroscope (version 3.5.9) and  
153 used to differentiate between late relapse of the same infection or reinfection with another HCV  
154 strain. HCV-RNA testing continued until 48 weeks post-treatment to assess HCV re-infection.

155

## 156 **End-points**

157

158 The primary outcome was SVR12, defined by undetectable plasma HCV-RNA twelve weeks after end  
159 of treatment (EOT). The secondary outcomes included virological failure at the end of follow-up, as  
160 determined by the number of patients harbouring HCV (NS5A, NS5B and NS3/4) resistance  
161 mutations, and reinfection. For HIV-positive individuals, the median levels of HIV-RNA and CD4+ T  
162 cell count at baseline and PTW12 were also evaluated.

163



164 **Statistical analysis**

165

166 Given the single-arm, non-comparative design, the sample size calculation was based on statistical  
167 precision and not on a comparative statistical test. Assuming an absolute precision of <30% between  
168 lower and upper bounds of the Clopper-Pearson 95% CIs for a binomial end-point and an SVR12 in  
169 ITT analysis at ≥80%, a total 30 patients were necessary.

170 In PP analysis, all available HCV-RNA data at PTW12 were used to calculate SVR12. In ITT analysis, all  
171 available HCV-RNA data were used to calculate SVR12, yet individuals lost to follow-up prior to  
172 PTW12 were considered as not achieving SVR12.

173

174 Scores from the SF-12 were calculated for each of the eight quality of life domains. All scores were  
175 transformed to range from 0 to 1 with higher scores indicating better mental or physical health.

176 Scores were compared between treatment initiation and PTW12 using a fractional probit model with  
177 cluster-adjusted variance estimators.

178

179 Statistical analysis was conducted using STATA v15.0 (College Station, TX, USA). Significance was  
180 determined using a *p*-value <0.05.

181

182 **Role of funding source**

183

184 This was an investigator-initiated study funded by Merck Sharp & Dohme Corp. The funding source  
185 was not involved in any part of data collection, interpretation of data or writing of the manuscript.

186

187

188 **RESULTS**

189

190 **Description of the study population**

191 Between 31 May 2017 and 20 August 2018, of 33 individuals assessed for eligibility, 3 did not meet  
192 inclusion criteria (Figure 1). Thirty individuals were allocated to study treatment, all of whom  
193 received eight-week grazoprevir/elbasvir. The distribution of criteria sets used to define acute HCV  
194 infection at inclusion is provided in Table S1.

195

196 Patient characteristics at grazoprevir/elbasvir initiation are described in Table 1. Median time  
197 between suspected presentation of acute HCV symptoms and treatment initiation was 85 days  
198 (IQR=63-130). Illicit drug use over the past 12 months was found in 18 (75%) patients (Table S2). Ten  
199 patients (33%) were diagnosed as re-infected, either by change in HCV genotype from previous  
200 known infection ( $n=4$ ) or positive HCV-RNA viral load from previously successful treatment ( $n=6$ ).  
201 Eight (27%) patients had an STI within 12 months prior to inclusion, with the most common STIs  
202 being *Neisseria gonorrhoea* (5 infections) and syphilis (4 infections).

203

204 Median HCV-RNA was 5.71  $\log_{10}$  IU/mL (IQR=5.08-6.44) and patients harboured genotype 1a ( $n=15$ ),  
205 genotype 1b ( $n=1$ ) or genotype 4 ( $n=14$ ). Of note, 8 patients had an HCV-RNA viral load  $>800,000$   
206 IU/mL and genotype 1a. Median ALT and AST levels were 282 IU/L (IQR=100-202) and 128 IU/L  
207 (IQR=100-202), respectively, and 3 (10%) presented with ALT or AST levels  $\leq 2x$  upper limit of normal.

208

209 The large majority of patients were HIV-positive ( $n=28$ ), all of whom were undergoing ART with  
210 either undetectable HIV-RNA ( $n=26$ ,  $<40$  copies/mL) or low-level replication ( $n=2$ , at 51 and 90  
211 copies/mL). No patient was on an agent having possible drug interactions with study medication.

212 Immunosuppression was largely mild with only 3 (11%) HIV-positive patients having a previous AIDS-  
213 defining illness and median CD4+ cell count at 580/mm<sup>3</sup> (IQR=467-706).

214

215 **Virological and biochemical response**

216

217 Of the 30 included patients, all completed 8 weeks of grazoprevir/elbasvir. During post-treatment  
218 follow-up, one patient died (suicide occurring 3 weeks after the W8 visit). In total, 29 completed the  
219 PTW12 visit. The proportion of detectable HCV-RNA at each follow-up visit is given for both PP and  
220 ITT analysis in Figure 2A. The proportion of patients achieving SVR12 was 93% (95%CI=78-99%) in ITT  
221 analysis and 96% (95%CI=82-99%) in PP analysis. SVR12 was not different between individuals with or  
222 without re-infection ( $n=10/10$ , 100% and  $n=18/19$ , 95%; respectively) or between individuals with  
223 baseline HCV-RNA  $\leq 800,000$  IU/mL or  $>800,000$  IU/mL ( $n=16/16$ , 100% and  $n=12/13$ , 92%;  
224 respectively).

225

226 As shown in Figure 2B, most patients were able to normalize transaminase levels at the PTW12 visit.  
227 One patient had increasing ALT levels from 78 IU/L at baseline to 109 IU/L PTW4, then decreasing to  
228 37 IU/L at PTW12. This patient had undetectable HCV-RNA at all visits during and post-treatment.  
229 Two patients had ALT levels  $>40$  IU/L at their PTW12 visit: one with undetectable HCV-RNA at all  
230 visits after W4 and the other failing treatment (described below). No patient had a flare in ALT or AST  
231  $>250$  IU/L during or post-treatment.

232

233 One patient with GT1a experienced virological failure. Virological and biological evolution of this  
234 patient is described in Figure 3. At W4, both plasma GZR and EBR concentrations were undetectable  
235 ( $<5$  ng/mL) and concomitant plasma antiretroviral concentrations were low (FTC, 111 ng/mL; TDF, 48  
236 ng/mL; RPV 78 ng/mL). At W8, plasma concentrations of study drug were normal (GZR, 144 ng/mL;  
237 EBR, 105 ng/mL) including those of the antiretroviral regimen (FTC, 1074 ng/mL; TDF, 213 ng/mL;  
238 RPV, 90 ng/mL). HCV-RNA level was undetectable at PTW4 but rebounded to  $6.57 \log_{10}$  IU/mL at  
239 PTW12. Phylogenetic analysis indicated the same HCV viral strain compared to baseline, ruling out  
240 HCV re-infection. Genotypic resistance analysis at PTW12 revealed the V36M amino acid  
241 substitution in NS3, M28V in NS5A, and S556G in NS5B regions of the HCV genome.

242

243 **Self-reported adherence and quality of life**

244

245 At the W4 and W8 visits, respectively, 1 (4%) and 2 (7%) patients declared missing  
246 grazoprevir/elbasvir within the last 4 days and 2 (7%) and 1 (3%) forgot to take grazoprevir/elbasvir  
247 at least once during the weekend. The level of grazoprevir/elbasvir adherence was comparable to  
248 that of ART, for which 4 (15%) and 3 (11%) patients reported missing  $\geq 1$  pills included in their  
249 regimen within the last 4 days and 1 (3%) and 1 (3%) forgetting to take their medication at least once  
250 during the weekend at the W4 and W8 visits, respectively.

251

252 Based on scores from the SF-12 (Table S3), significant improvement between treatment initiation and  
253 PTW12 were observed in role physical ( $p=0.02$ ) and role emotional ( $p=0.02$ ) domains. No significant  
254 differences between treatment initiation and PTW12 were observed in the other six domains:  
255 physical functioning, bodily pain, general health, vitality, social functioning, and mental health. At  
256 baseline, when compared to the overall average SF-12 across domains in the entire study population  
257 (0.61), the only patient failing treatment had an average SF-12 of 0.58 and the two patients with  
258 completed and attempted suicide, respectively, had an average SF-12 of 0.79 and 0.40.

259

260 **Control of HIV-infection during follow-up**

261

262 At PTW12, all 27 HIV-positive participants with available data had HIV-RNA  $< 50$  copies/mL and  
263 median CD4+ T cell count was  $655/\text{mm}^3$  (IQR=488-829). After treatment with grazoprevir/elbasvir, 3  
264 patients switched from TDF/FTC/RAL ( $n=2$ ) or TDF/FTC/DTG ( $n=1$ ) to TAF/FTC/elvitegravir/COBI  
265 (unrelated to HIV virological failure or toxicity). No HIV virological failure was reported during  
266 treatment or post-treatment.

267

268 **Adverse events and serious adverse events**

269

270 During treatment and post-treatment, 60 clinical adverse events were reported and  $\geq 1$  clinical  
271 adverse event occurred in 23 (77%) participants. Only 3 serious clinical adverse events occurred: one  
272 patient had a panic attack with underlying suicidal ideation and another patient committed suicide.  
273 None of the serious clinical adverse events was related to study treatment. All other possible and  
274 probable drug-related adverse events are listed in Table 2.

275

276 **Reinfection rate**

277

278 No HCV re-infections were observed within 12 weeks after EOT. However, HCV-RNA was detected in  
279 3 patients after PTW12. One patient with previous GT1a infection acquired a GT4d strain 48 weeks  
280 after PTW12, the second patient with a previous GT4 infection acquired an HCV GT1b strain 24 weeks  
281 after PTW12, and the third patient with a previous GT1a infection acquired a GT1a strain 28 weeks  
282 after PTW12, but phylogenetic analysis showed that it was a different strain from baseline. In total, the  
283 reinfection rate was 3/28 (10.7/100 patient-month). All have successfully been retreated with various  
284 DAA combinations for 8 to 16 weeks.

285

286 **DISCUSSION**

287

288 In this multicentre pilot study of MSM with recently acquired HCV infection, we observed that 96%  
289 (28/29) were able to achieve SVR12 after an eight-week course of treatment with  
290 grazoprevir/elbasvir. This proportion was 93% (28/30) assuming those lost to follow-up did not  
291 achieve SVR at the end of follow-up. These SVR rates are comparable to chronically HCV-infected  
292 individuals undergoing the same treatment combination for 12-weeks, regardless of HIV status.<sup>15-18</sup>  
293 Of those completing the PTW12 visit, only one exhibited RAS associated with grazoprevir/elbasvir

294 treatment failure. These data provide strong evidence that eight-week grazoprevir/elbasvir is  
295 appropriate for the treatment of acute HCV infection genotype 1 and 4, and particularly in HIV-  
296 positive patients.

297

298 In chronic HCV infection, the C-WORTHY trial showed that higher SVR12 rates were achieved in  
299 patients treated with 12-week versus 8-week grazoprevir/elbasvir.<sup>17</sup> Nevertheless, more recent  
300 clinical trials evaluating 8-week grazoprevir/elbasvir have demonstrated high SVR in HCV genotype  
301 1b or 4 infected patients with liver fibrosis levels at METAVIR F0-F2<sup>25,26</sup> or in genotype 1b when  
302 plasma HCV-RNA is low.<sup>27</sup> Given that MSM recently acquiring HCV are unlikely to have severe liver  
303 fibrosis<sup>28</sup>, 8-week duration of grazoprevir/elbasvir could be sufficient for treating acute HCV. The  
304 recent DAHHS2 trial conducted in the Netherlands demonstrated that short-term duration of  
305 grazoprevir/elbasvir is possible in acutely infected individuals, reporting SVR12 of 99% in 80 patients  
306 with acute HCV genotype 1 (all with genotype 1a or 4 infection after 8-week grazoprevir/elbasvir).<sup>19</sup>  
307 Our data confirm this finding with high SVR12 in both ITT and PP analysis. Furthermore, as reported  
308 by Boerekamps *et al.*, SVR12 was also able to be achieved in all patients harbouring HCV genotype  
309 1a (one of the most prevalent genotypes among European MSM<sup>3</sup>) and all but one genotype 1a-  
310 infected patient with plasma HCV-RNA >800,000 IU/mL at baseline, which is also associated with  
311 virologic failure during chronic HCV infection.<sup>29</sup>

312

313 Of note, there were four patients with detectable plasma HCV-RNA at EOT, 3 of whom eventually  
314 achieved SVR12. This phenomenon has been described in chronic HCV infected individuals enrolled in  
315 registration trials of peg-IFN-free DAA containing regimens.<sup>30</sup> The other patient with detectable HCV-  
316 RNA at EOT eventually developed virological failure with the emergence of 28V and 36M RAS, both of  
317 which have been previously identified in HCV mono-infected patients with virological failure.<sup>31</sup> This  
318 patient might not have been consistently using study medication, as indicated by the undetectable  
319 plasma grazoprevir/elbasvir and ARV concentrations at W4. Emergence of these substitutions would

320 likely be the result of selective pressures from poor adherence and not necessarily insufficient  
321 treatment duration.

322

323 Poor quality of life has been associated with suboptimal adherence and early treatment  
324 discontinuation<sup>32, 33</sup>, thereby increasing the risk of virologic failure. In our study, we were able to  
325 observe improvements in both role physical and role emotional domains. Studies on patient-  
326 reported outcomes during and after grazoprevir/elbasvir treatment for chronic HCV have observed  
327 improvements in many domains, including mental health and role physical, but not with role  
328 emotional.<sup>34</sup> Differences between studies could be the result of included study populations (acute  
329 versus chronic HCV infection) and Quality of Life inventories (SF-36 versus SF-12). Yet considering the  
330 limited data on quality of life during DAA-treated acute infection, it is difficult to explain these  
331 discrepancies any further.

332

333 Despite some improvements in quality of life, no change in the mental health domain was observed.  
334 It is also noteworthy that, after EOT, one patient attempted suicide and another committed suicide.  
335 Illicit drug use within the 12 months prior to baseline was observed in 75% of patients with available  
336 data. Half of these individuals had consumed drugs that are known to be associated with high risk  
337 sexual behaviour and STI acquisition<sup>35</sup> and whose use could be potentially driven by internalizing  
338 mental health disorders.<sup>36</sup> These observations underscore the need to incorporate mental health and  
339 addiction services when treating HCV in this key population.

340

341 The proportion with a probable or possible drug-related adverse event was low and in line with  
342 previous studies using grazoprevir/elbasvir in HCV mono-infection or HIV/HCV co-infected  
343 populations.<sup>15,18,19</sup> Besides the serious mental health problems identified during follow-up, no other  
344 serious adverse events and no serious laboratory abnormalities were observed. Other studies have  
345 included STIs as a part of adverse events, reported in roughly 24% of MSM twelve weeks after

346 grazoprevir/elbasvir treatment.<sup>19</sup> We did not consider this as an adverse event; nevertheless, 27% of  
347 included patients reported at least one bacterial STI within the year prior to treatment initiation and  
348 among them, 88% reported having at least one adverse event during follow-up. Assuming that STIs  
349 were only to occur in patients with previously detected infections, the proportion with adverse  
350 events during treatment would not have changed.

351

352 In HIV-positive individuals, potential drug-drug interactions between grazoprevir/elbasvir and certain  
353 antiretroviral agents are problematic and reconsideration of ART regimen might be required for a  
354 number of patients planning to initiate grazoprevir/elbasvir.<sup>37</sup> ART regimens had to be modified in  
355 only one of the twenty-eight HIV-positive individuals without concern and no rebounds in plasma  
356 HIV-RNA or changes in CD4+ T cell count were observed in ART-experienced patients during  
357 grazoprevir/elbasvir treatment.

358

359 There are certain limitations to our study. First, treatment efficacy was not assessed using a non-  
360 inferior study design. Nevertheless, we argue that any non-inferiority limit assuming an SVR12 rate  
361 below 90% would be uninformative given the efficacy of current DAA treatments. Second, we included  
362 a limited number of acute HCV infected individuals, reducing the potential numbers of virological  
363 failures and hence our ability to determine reasons for failure. There were also few HIV-negative  
364 participants enrolled, which limits generalizability to this group. Finally, data on baseline RAS were  
365 not collected and thus we cannot conclude on the efficacy of grazoprevir/elbasvir in the presence of  
366 these substitutions. NS5A RAS appear to mostly affect virologic response in patients with high HCV  
367 viral loads<sup>27</sup> or those infected with HCV genotype 1a and less so with genotype 1b or 4.<sup>15,38-40</sup> Half of  
368 included patients were infected with genotype 1a, which would make data on RAS particularly  
369 helpful. Nevertheless, in the DAHHS2 study, where sequencing was performed at baseline for all  
370 patients, no one harbouring a strain with RAS experienced virological failure.<sup>19</sup>

371



372 In conclusion, given the 96% SVR12 rate and the single patient with RAS, eight-week  
373 grazoprevir/elbasvir is an efficacious treatment option for recently acquired HCV infection. As  
374 adverse events were uncommon, particularly those related to the study drug, this treatment would  
375 appear well-tolerated. These data support the use of grazoprevir/elbasvir for rapid treatment against  
376 HCV, appropriate for reducing ongoing HCV transmission in the current epidemic of HCV infection  
377 among European MSM with genotypes 1 and 4. The suicide attempt and completed suicide coupled  
378 with frequent illicit drugs use observed in this study population stress the need for mental health  
379 services in MSM at risk for HCV infection.

380

381

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406

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408

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412

413

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524 participants with hepatitis C virus genotype 1b infection. *J Gastroenterol* 2018; **53**: 679-88.

525

526

527

528

529 **TABLES**

530

531 **Table 1. Description of the study population at treatment initiation**

532

| <b>General characteristics</b>                | <b>N=30</b>      |
|---|------------------|
| Male gender*                                  | 30 (100)         |
| Birth country/region*                         |                  |
| France  | 22 (73)          |
| Europe (outside of France)                    | 3 (10)           |
| Asia  | 3 (10)           |
| Other   | 2 (7)            |
| Age, years <sup>†</sup>                       | 44 (34-52)       |
| BMI, kg/m <sup>2</sup> <sup>†</sup>           | 22.4 (20.6-25.4) |
| Hypertension* <sup>‡</sup>                    | 10 (33)          |
| Diabetes* <sup>§</sup>                        | 1 (3)            |
| Co-infection with HIV*                        | 28 (93)          |
| <b>HCV-related characteristics</b>            | <b>N=30</b>      |
| Transmission route* <sup>¶</sup>              |                  |
| Nasal drug-use                                | 6 (20)           |
| Injection drug-use                            | 5 (17)           |
| Sexual contact                                | 23 (77)          |
| Unknown                                       | 2 (7)            |
| Involved first HCV reinfection*               | 9 (30)           |
| Involved second HCV reinfection*              | 1 (10)           |
| Time since last infection, years <sup>†</sup> | 2.8 (1.2-3.8)    |

533



534 **Table 1 (con't).**

| <b>HIV-related characteristics</b>           | <b>N=28</b>      |
|--|------------------|
| Known duration of HIV infection <sup>†</sup> | 8.5 (4.5-14.0)   |
| AIDS-defining illness*                       | 3 (11)           |
| Undergoing ART**μ                            | 28 (100)         |
| HIV RNA viral load >50 copies/mL*            | 2 (7)            |
| HIV RNA viral loads, copies/mL**             | (51, 90)         |
| CD4+ T cell count, /mm <sup>3†</sup>         | 580 (467-706)    |
| CD8+ T cell count, /mm <sup>3†</sup>         | 644 (508-964)    |
| CD4:CD8 ratio <sup>†</sup>                   | 0.84 (0.55-1.24) |

535 \*n (%) <sup>†</sup>Median (IQR)536 <sup>†</sup>Systolic blood pressure >130 mm/Hg or diastolic blood pressure >80 mm/Hg.537 <sup>§</sup>Declared by treating physician.538 <sup>¶</sup>More than one transmission route can occur within individuals.

539 \*\*For individuals with HIV RNA &gt;50 copies/mL.

540 μ TDF/emtricitabine (FTC)/rilpivirine (RPV), n=9; abacavir/lamivudine/dolutegravir (DTG), n=9;

541 TDF/FTC/DTG, n=6; TDF/FTC/raltegravir (RAL), n=3; or TDF/FTC dual therapy, n=1. Of note, one

542 patient switched from TDF/FTC/cobicistat (COBI)-boosted darunavir to TDF/FTC/DTG at treatment

543 initiation (following recommendations for concomitant antiretroviral agents).

544 **Table 2. Adverse and serious adverse events during follow-up**

|  |         |
|--|---------|
| All clinical adverse events, <i>n</i>                        | 60      |
| Patients with $\geq 1$ clinical adverse event, <i>n</i> (%)  | 23 (77) |
| Serious clinical adverse events, <i>n</i>                    | 3       |
| Panic attack   | 1       |
| Suicidal ideation (without suicide)                          | 1       |
| Suicide  | 1       |
| Serious drug-related clinical adverse events, <i>n</i>       | 0       |
| Discontinuation due to clinical adverse events, <i>n</i> (%) | 0 (0)   |
| Deaths, <i>n</i> (%)   | 1 (3)   |
| Cause of death   |         |
| Suicide  | 1       |
| All possible drug-related adverse events                     | 8       |
| Diarrhoea  | 2       |
| Abdominal distension   | 1       |
| Stomach spasms   | 1       |
| Myalgia  | 1       |
| Xerostomia   | 1       |
| Hyperhidrosis  | 1       |
| Osteoarthritis of knee and hands                             | 1       |
| All probable drug-related adverse events                     | 8       |
| Insomnia   | 2       |
| Diarrhea   | 2       |
| Fatigue  | 2       |
| Binge eating   | 1       |

546 **Table 2 (con't).**

---

|   |         |
|---|---------|
| Dysgeusia   | 1       |
| Patients with $\geq 1$ grade 2 laboratory abnormality*, <i>n</i> (%)      | 12 (40) |
| Creatinine clearance 60-90 mL/min/1.73m <sup>2</sup>                      | 12      |
| Patients with $\geq 1$ grade 3 or 4 laboratory abnormality*, <i>n</i> (%) | 0 (0)   |

---

547 \*Specifically during treatment.

548 **FIGURE LEGENDS**

549

550 **Figure 1. Patient flow during the study**

551

552 **Figure 2. Hepatitis C virus (HCV) and alanine transaminase levels during and after treatment with**  
553 **grazoprevir/elbasvir**

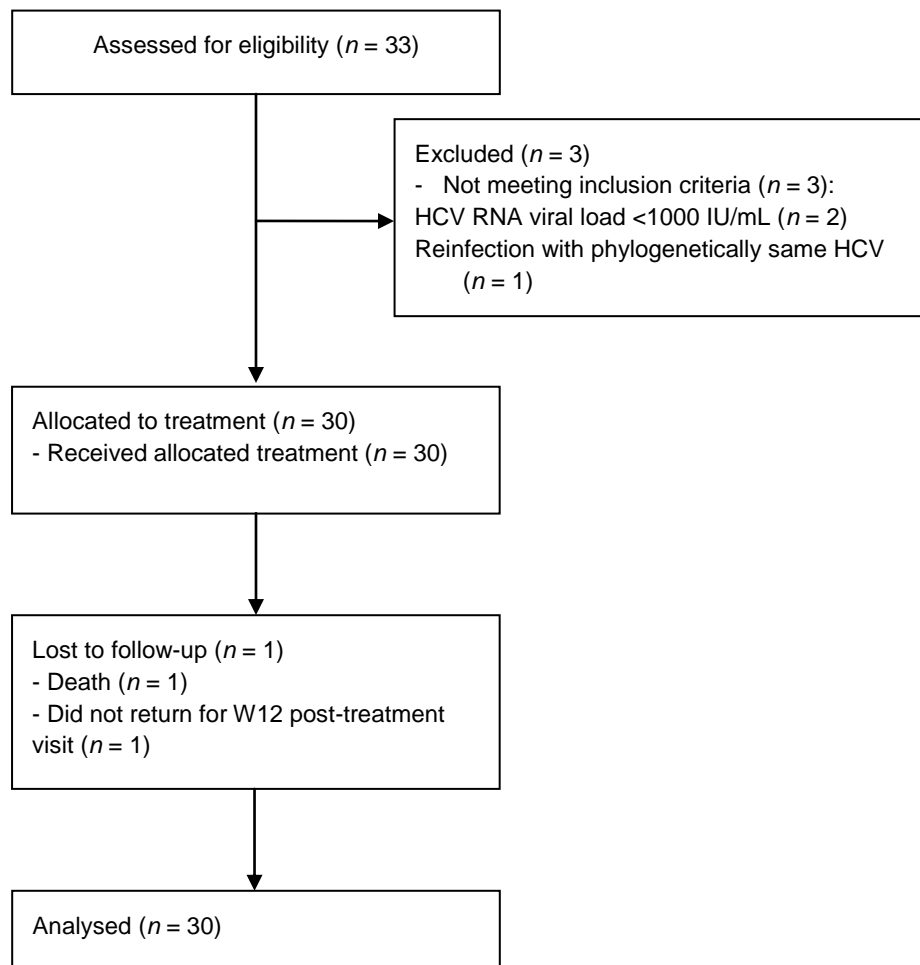
554

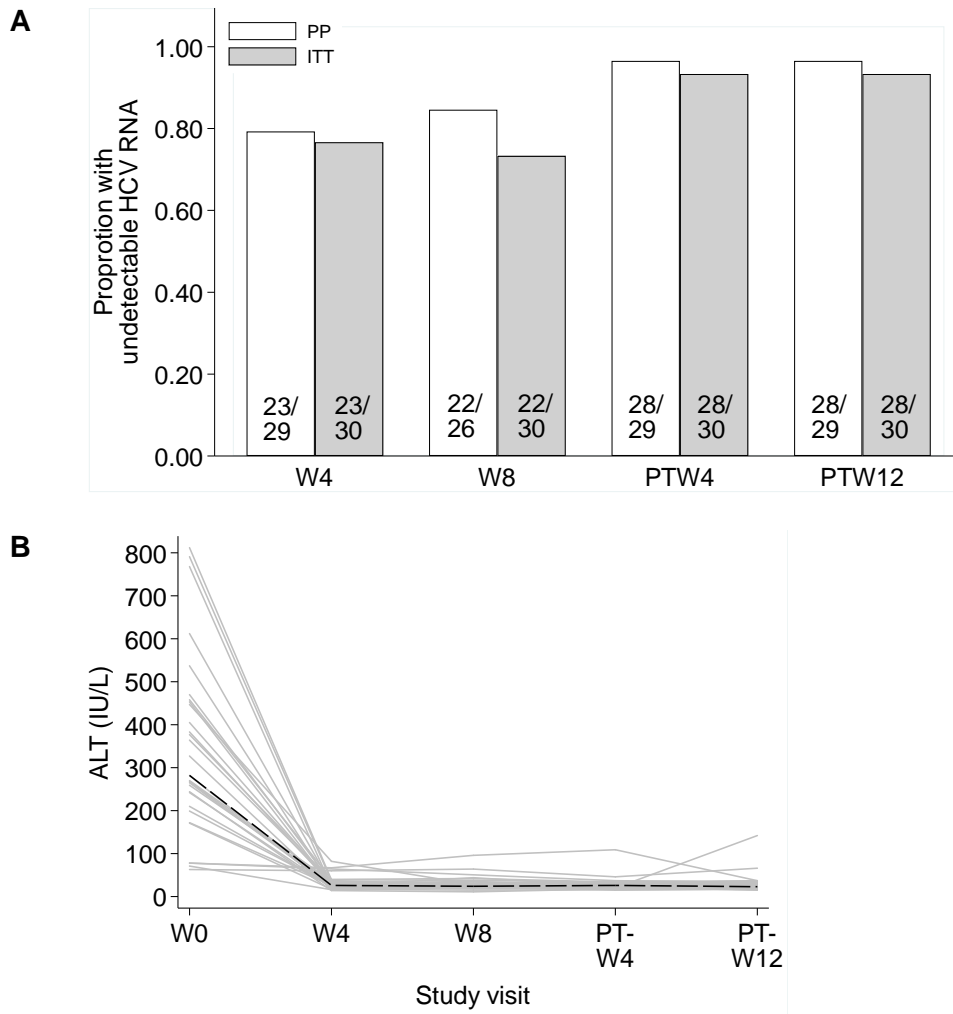
555 Number of patients with undetectable HCV over total number of patients are given during treatment  
556 at week 4 (W4) and week 8 (W8) as well as post-treatment at week 4 (PTW4) and week 12 (PTW12)  
557 in PP and ITT analysis (A). Individual (grey lines) and median (black line) ALT levels are given at each  
558 study visit in (B).

559

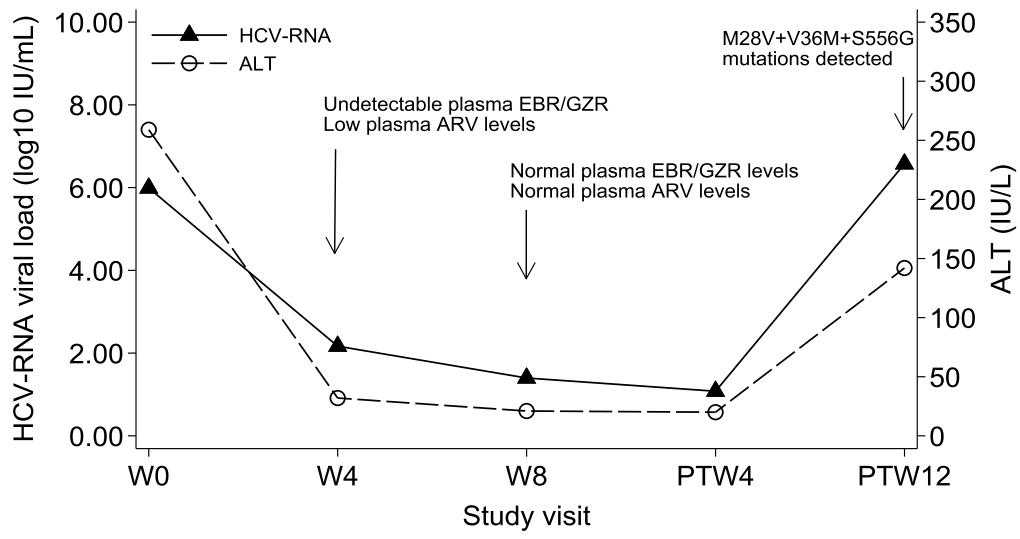
560 **Figure 3. Virological and biochemical evolution of the patient with treatment failure**

561 Hepatitis C virus (HCV)-RNA (genotype 1a) and ALT levels during treatment at week 4 (W4) and week  
562 8 (W8) as well as post-treatment at week 4 (PTW4) and week 12 (PTW12) for the only patient with  
563 treatment failure. Antiretroviral (ARV), elbasvir (EBR) and grazoprevir (GZR) plasma levels were  
564 quantified at W4 and W8 and RASs were determined at PTW12.





568 **Figure 3.**



569