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EL drafted, wrote and approved this letter; DL, BK, EL reviewed, added content, wrote and approved this letter; BP, AF, SH, MJ, SK, MM, JO, EP & ES critically reviewed and approved this letter.

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Non-responders to sofosbuvir/velpatasvir/voxilaprevir in the treatment of chronic hepatitis C infection

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To the Editor:
Although direct-acting antivirals (DAAs) for the treatment of chronic HCV infection are effective with over 95% sustained

virological response (SVR) rates, a minority of patients do not achieve SVR.[1,2] Virologic failure may be associated with the development of resistance-associated substitutions (RASs) in HCV non-structural (NS) regions.[3] Therefore, efficient re-treatment may need to target the NS5A, NS5B, and NS3 proteins. The combination of the second-generation NS3/4A protease-inhibitor (PI) voxilaprevir (VOX), the NS5A-inhibitor velpatasvir (VEL), and the nucleotide polymerase inhibitor sofosbuvir (SOF) are recommended as the preferred salvage regimen following treatment failure with an initial NS5A inhibitor-based DAA regimen, regardless of the presence of RASs.[4,5] As Dietz *et al.* noted, virological failure after SOF/VEL/VOX treatment is uncommon and therefore limited data are available to guide management of non-responders.[1] We summarized available data regarding the characteristics of SOF/VEL/VOX non-responders and the efficacy of salvage antiviral therapy after SOF/VEL/VOX failure.

We searched the literature indexed in PubMed, Scopus, and Web of Science databases on April 17, 2022, without time or language restrictions. Detailed methods are described in the supplement. Of 319 studies identified, 76 met potential eligibility for full-text screening (Fig. S1). Excluding 46 ineligible full-text records, 30 studies with 244 SOF/VEL/VOX non-responders remained for manual data extraction (Table S3).

Characteristics of SOF/VEL/VOX non-responders included mean age of 58.5 years (min–max age: 35–77 years) and male sex in 78.2%. The HCV genotype (GT) was GT1 in 57.7% (1a: 43, 1b: 22, and unspecified: 66), GT2 in 3.1%, GT3 in 33.5%, GT4 in 5.3%, and GT5 in 0.4% of patients. Complete data regarding prior treatment were available in 226 patients, 71.7% and 4% of whom were DAA- and PEGylated interferon/ribavirin-experienced, respectively. Patients were treated with SOF/VEL/VOX for 4 (n = 11), 6 (n = 29), 8 (n = 39), 12 (n = 144), 16 (n = 1), and 24 weeks (n = 2). Fifteen patients (6.6%) received ribavirin. The individual characteristics of these 244 patients are shown in Table S6.

Among 144 patients with NS5A RAS testing prior to SOF/VEL/VOX therapy, 101 (70.1%) had a documented NS5A RAS. Among 150 patients with NS5A RAS data after SOF/VEL/VOX treatment failure, 109 (72.7%) had a documented NS5A RAS. NS3 RASs were present in 54 (47.4%) of 114 patients at baseline and 66 (45.5%) of 145 patients at the time of failure (Table S4).

There are no randomized controlled trials and few published reports (6 studies with 38 patients) addressing rescue treatment after SOF/VEL/VOX failure (Table 1). Of 32 SOF/VEL/VOX non-responders treated in 6 studies[1,3,6–9] with glecaprevir/pibrentasvir (GLE/PIB) (± sofosbuvir (SOF) and/or ± ribavirin for 12, 16, or 24 weeks), 28 (87.5%) achieved SVR12 (1 patient achieved SVR4 and died prior to SVR 12, 2 patients relapsed, and 1 other patient died). One patient had RAS testing after unsuccessful rescue treatment with GLE/PIB +SOF +ribavirin for 16 weeks; NS5A RASs (A30K, L31F, Y93H) were detected, no NS3 or NS5B RASs were detected.[1] All 4 patients in 1 cohort[1] who were re-treated with SOF/VEL/VOX (± ribavirin for 24 weeks) achieved SVR. Re-treatment with SOF/VEL + ribavirin for 24 weeks in 2 other SOF/VEL/VOX non-responders resulted in virologic relapse.[1,9] One subsequently achieved SVR after further re-treatment with GLE/PIB + SOF + ribavirin for 12 weeks.[9] The other SOF/VEL + ribavirin retreatment virologic relapse had an NS5A RAS (Y93H), no NS3 or NS5B RASs were detected.[1]

Due to incomplete individual patient data, we were limited in examining predictors of response *vs.* non-response to SOF/VEL/VOX. Also, adverse events associated with SOF/VEL/VOX therapy

Table 1. The characteristics of 38 re-treated sofosbuvir/velpatasvir/voxilaprevir non-responder patients.

First author	Sex	Age, yr	HCV genotype	Cirrhosis	Re-treatment regimen	Outcome
D. Garcia-Cehic[3]	2: Male	70 60	1: 1b 1: 3a	1: No 1: Yes	1: GLE/PIB + RBV (12 w) 1: GLE/PIB + SOF + RBV (12 w)	1: Relapse 1: SVR
B. Bernhard[6]	1: Female	50	3a	No	GLE/PIB + SOF + RBV (24 w)	1: SVR
M. Meszaros[7]	4: Males 1: Female	56.5†	1: 1b 3: 3 1: 4d	4: Yes 1: No	5: GLE/PIB + SOF + RBV (16 w)	5: SVR‡
M. T. Martin[8]	5: Male 1: Female	67 60 61 68 68 58	1b 3a 3 1a 1b 1a	5: Yes	4: GLE/PIB + SOF (16 w) 2: GLE/PIB + SOF (24 w)	6: SVR
T. L. Tergast[9]	2: Females	63 52	2: 3	2: Yes	1: SOF/VEL + RBV (24 w) then GLE/PIB + SOF + RBV (12 w) 1: GLE/PIB + SOF (12 w)	1: Relapse then SVR 1: SVR
J. Dietz[1,10]	22: ND	59.0†	6: 1a 3: 1b 12: 3a 1: 4d	15: Yes 7: No	1: GLE/PIB (12 w) 1: GLE/PIB + RBV (12 w) 4: GLE/PIB + SOF (12 w) 1: GLE/PIB + SOF (16 w) 2: GLE/PIB + SOF (24 w) 2: GLE/PIB + SOF + RBV (12 w) 4: GLE/PIB + SOF + RBV (16 w) 2: GLE/PIB + SOF + RBV (24 w) 3: SOF/VEL/VOX (24 w) 1: SOF/VEL/VOX + RBV (24 w) 1: SOF/VEL + RBV (24 w)	17: SVR 2: Relapse 1: Pending* 1: Death 1: SVR4, death

Data are the number of patients (n:) and their characteristics.
GLE, glecaprevir; HCC, hepatocellular carcinoma; ND, not determined; PIB, pibrentasvir; RBV, ribavirin; SOF, sofosbuvir; SVR, sustained virological response; VEL, velpatasvir; VOX, voxilaprevir.
†Mean age of the study population.
‡Two patients died post-SVR (one HCC metastasis, one non-liver-related cause).
*The authors mentioned SVR12 in an updated report.

and its rescue treatment regimens were not evaluated in this study. However, we identified that among 244 SOF/VEL/VOX non-responders, a majority were infected with HCV genotypes GT1 (58%) and GT3 (34%), nearly two-thirds (60%) had cirrhosis, more than two-thirds had a previous history of treatment with DAAs, and a few had received ribavirin. Despite the contraindication to use of PIs according to current treatment guidelines,[4,5] the SOF/VEL/VOX regimen was prescribed in a small number of patients with decompensated cirrhosis.

Pre-treatment evaluation for re-treatment in SOF/VEL/VOX treatment failures should include an assessment for potential drug-drug interactions. Consideration should also be given to adding weight-based ribavirin to regimens of GLE/PIB ± SOF or SOF/VEL/VOX, and extension of treatment duration as these may increase the chance of successful rescue treatment. Consistent with available evidence, EASL and AASLD guidelines recommend adding weight-based ribavirin for patients with cirrhosis with HCV GT3 infection previously treated with NS5A inhibitors.[4,5] Further investigations into the role of RAS testing to guide individualized approaches to salvage therapy are needed to support evidence-based guidelines. Available data support current guidelines for the re-treatment of SOF/VEL/VOX non-responders with SOF + GLE/PIB ± ribavirin or SOF/VEL/VOX ± ribavirin for 12–24 weeks.[4,5]

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Authors' contributions
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Internet search engines and social media are improving awareness on non-alcoholic fatty liver disease in Brazil

To the Editor:

The authors read with great interest the recently published manuscript by Lazarus *et al.*,[1] highlighting that no nation is properly tackling the emerging global challenge of non-alcoholic fatty liver disease (NAFLD). To our knowledge, this is

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