



Guidelines Have a Key Role in Driving HCV Elimination by Advocating for Simple HCV Care Pathways

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ABSTRACT

The availability of pangenotypic direct-acting antivirals for treatment of hepatitis C (HCV) has provided an opportunity to simplify patient pathways. Recent clinical practice guidelines have recognised the need for simplification to ensure that elimination of HCV as a public health concern remains a priority. Despite the move towards simplified treatment algorithms, there remains some complexity in the recommendations for the management of genotype 3 patients with compensated cirrhosis. In an era where additional clinical trial data are not anticipated, clinical guidance should consider experience gained in real-world settings.

Although more experience is required for some pangenotypic therapeutic options, on the basis of published real-world data, there is already sufficient evidence to consider a simplified approach for genotype 3 patients with compensated cirrhosis. The coronavirus disease 2019 (COVID-19) pandemic has highlighted the need to minimise the need for complex patient pathways and clinical practice guidelines need to continue to evolve in order to ensure that patient outcomes remain optimised.

Keywords: Elimination; Guidelines; Hepatitis C; Simplification

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Key Summary Points

Simplification of the HCV patient pathway is required to minimise the effect of the COVID-19 pandemic on HCV patient outcomes. Simplification is also a recognised clinical strategy when focusing on HCV elimination.

Clinical practice guidelines have a key role in providing guidance on how to simplify treatment of patients with HCV based on available data and recent national and international guidelines have started to address this.

Despite the move towards simplified treatment algorithms, there remains some complexity in the recommendations for management of genotype 3 patients with compensated cirrhosis despite a wealth of data supporting a simplified approach.

There is a need for guidelines to continue to evolve to reflect data available to ensure elimination remains a priority.

DIGITAL FEATURES

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COMMENTARY

The coronavirus disease 2019 (COVID-19) pandemic has rapidly changed the management of hepatitis C (HCV) [1, 2]. In addition, the disruption of HCV elimination programmes during 2020 is anticipated to have an impact on the ability to achieve the World Health Organization (WHO) elimination goals by 2030 [3]. A recently published model demonstrated that a 1-year delay in HCV treatment initiation could result in 746,000 fewer patients starting

treatment globally before 2030 [4]. The predicted consequence of delaying diagnosis and treatment by 1 year was an additional 44,800 liver cancers and 72,300 HCV-related deaths by 2030. The purpose of this commentary is to describe the need for simplification of the HCV patient pathway in order to achieve HCV elimination and to discuss whether current treatment guideline recommendations are focused sufficiently on simplification.

Simplification of the HCV patient pathway linking infected individuals to care is required in order to minimise the effect of the pandemic on the outcomes of patients with HCV. At a time when face-to-face HCV appointments are decreasing and telemedicine is an increasingly routine part of clinical practice [5]—telehealth visits increased by 57% from the start of the pandemic to July 2020 in the USA [6]—reducing the need for pre-treatment assessments is important. Understanding previous treatment history and identifying decompensated cirrhosis will continue to be key to effective management, but the need to confirm genotype, fibrosis score and the presence of resistance-associated substitutions (RAS) before starting treatment and on-treatment monitoring should no longer be necessary in the current environment.

Simplification was one of the four clinical strategies identified by the American Association for the Study of Liver Diseases, European Association for the Study of the Liver (EASL), Asia-Pacific Association for the Study of the Liver and Asociación Latinoamericana para el Estudio del Hígado in the 2019 Call to Action to broadly implement HCV testing and treatment as part of a focussed effort towards achieving the WHO elimination goals; the other strategies being integration, decentralisation, and task sharing [7]. The need to focus on a simplified approach to HCV management is also increasingly reflected in national and international guidelines. For example, the French Liver Disease Association removed the requirement to document HCV genotype before prescribing the pangenotypic direct-acting antivirals sofosbuvir/velpatasvir (SOF/VEL) and glecaprevir/pibrentasvir (GLE/PIB) in March 2018 [8] and the Australian guidelines released in June 2020

include a similar recommendation [9]. The recent EASL guideline update published in September 2020 is the first of the international recommendations to highlight that treatment with pangenotypic regimens can be initiated without knowledge of genotype and subtype with a high probability of success [10]. The focus on simplification is also clear from the fact that testing for RAS prior to first-line treatment is not recommended by EASL. However, the EASL guideline recommendation committee acknowledges the need for population sequencing or deep sequencing (if available and affordable) in patients at risk of infection with subtype 1l, 4r, 3b, 3g, 6u and 6v (or other subtypes harbouring at least one RAS) known to confer resistance to non-structural protein 5A inhibitors; this recommendation applies to individuals born in sub-Saharan Africa, China or South-East Asia.

People who inject drugs, homeless individuals, migrants, prisoners and individuals with mental health disorders are frequently the groups still waiting to be treated and it is these populations that have been identified by the EASL guideline committee as likely to particularly benefit from a streamlined care pathway [10]. The change in recommendation perspective is an acknowledgment of the need to strive towards elimination while ensuring patient outcomes continue to be optimised. Such a change could only have been considered once there was confidence that pangenotypic agents with known tolerability and drug–drug interaction profiles would result in universally high rates of treatment success.

Despite the move towards simplified management, genotype-specific recommendations remain where genotype/subgenotype assessment is an option [10]. Where most recommendations are in line with the simplified algorithm, they diverge in the recommendation for optimal management of genotype (GT) 3 patients with compensated cirrhosis [10, 11]. In the USA, HCV infection is currently being driven by opioid addiction and these patients are largely infected with GT 3 (D Dieterich, unpublished data). Although only a low proportion of these patients have compensated cirrhosis this in contrast to experience in Italy

where 30% of GT 3 patients (also with a history of drug use) had liver stiffness greater than 12.5 kPa (A Mangia, unpublished data from IRCCS Casa Sollievo della Sofferenza). Previously, GT 3 was more difficult to cure than other genotypes and caution has been required when treating these patients to minimise the risk of treatment failure and disease progression [12]. The consequence of such treatment caution in GT 3 patients with compensated cirrhosis is that genotype-specific recommendations still include pre-treatment assessment of RAS, extended treatment duration or addition of ribavirin (RBV) to limit the potential for treatment failure. From a global elimination perspective, only a very small proportion of GT 3 patients with compensated cirrhosis remain to be treated. Given the high response rates anticipated with pangenotypic agents (Table 1) almost all of them will respond to initial therapy as part of a simplified pangenotypic regimen.

Given that re-treatment with SOF/VEL/voxilaprevir (VOX) results in high rates of sustained virological response irrespective of genotype or RAS profile at baseline [27–30], and that SOF + GLE/PIB provides an effective option for the few patients who fail SOF/VEL/VOX, planning to use effective salvage regimens in the few patients who fail initial therapy could be a more cost-effective approach than genotyping all patients with compensated cirrhosis in order to identify the few remaining HCV GT 3 infections.

If guideline committees are waiting for more data before simplifying the recommendations for GT 3 patients with compensated cirrhosis further, then these data are likely to be based on real-world experience as additional clinical trial data are not anticipated. Currently there remains a lack of consistency on how available real-world data are reflected within the recommendations. The EASL guideline committee acknowledges that more data are required to consolidate the recommendation that GLE/PIB for 8 weeks is an option for treatment-naïve GT 3 patients with compensated cirrhosis [10]. Despite the wealth of real-world experience available for SOF/VEL for 12 weeks in this population (Table 1), the guidelines still

Table 1 Response to the pangenotypic regimens included in the EASL simplified, genotyping/subtyping-free treatment of genotype 3 patients with compensated cirrhosis (treatment-naïve or peginterferon + ribavirin experienced) [6–9]

SOF/VEL for 12 weeks without RBV		GLE/PIB for 8 weeks ^a		GLE/PIB for 12 weeks ^b	
Trial/experience	SVR12, % (n/N)	Trial/experience	SVR12, % (n/N)	Trial/experience	SVR12, % (n/N)
<i>Clinical trial data</i>					
ASTRAL-3 [13]	91 (73/ 80)	EXPEDITION-8 [22]	95 (60/63)		
ASTRAL-5 [14]	100 (3/ 3)				
POLARIS-3 [15]	96 (105/ 109)				
India Regional trial [16]	97 (32/ 33)				
Russia and Sweden [17]	100 (11/ 11)				
Spain Regional [18]	91 (92/101)				
<i>Real-world experience</i>					
German GECCO Cohort [19]	95 (20/ 21)	US Trio Health Network [23]	100 (4/4)	German Hepatitis C- Registry [26]	100 (1/ 1)
Italian Regional Registry—portal hypertension [20]	98 (200/ 205)	International real- world analysis of 7 cohorts [24]	19 patients included; however, response rates according to genotype are not provided		
International real- world cohort [21]	97 (314/ 324)	Spanish HepaC cohort [25]	100 (1/1)		
		German Hepatitis C-Registry [26]	100 (1/1)		

Data shown are not head-to-head comparisons

EASL European Association for the Study of the Liver, GLE/PIB glecaprevir/pibrentasvir, RBV ribavirin, SOF/VEL sofosbuvir/velpatasvir, SVR sustained virological response

^a Treatment-naïve (8 weeks)

^b Treatment-experienced (12 weeks)

recommend addition of RBV in settings where genotype assessments are available, but RAS testing is not.

While awarding the Nobel Prize for Physiology or Medicine to the team behind the discovery of HCV, the Prize Committee put the spotlight on hepatitis C and highlighted that,

for the first time since that discovery, elimination of HCV is a possibility [31]. Management of HCV has come a long way in the 4 years since the WHO published the global health strategy on viral hepatitis [3] and 11 countries are on course to achieve elimination by the 2030 deadline [32]. Simplifying the therapeutic pathway as described by some national and international guidelines [8–10] as well as considering the feasibility of test and treat/rapid treatment start strategies should result in substantial individual and global benefits. In an era where treatment simplicity supports the objective of achieving HCV elimination, these forward-thinking guideline committees have demonstrated that a simplified approach to clinical decision-making is justified on the basis of available data from robust clinical trials and large real-world cohorts. We hope that other clinical practice guidelines follow their lead and continue to evolve to reflect these data to ensure that elimination remains a priority and in reach.

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Compliance with Ethics Guidelines. This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

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REFERENCES

1. Pokorska-Śpiewak M, Śpiewak M. Management of hepatitis C in children and adolescents during COVID-19 pandemic. *World J Hepatol.* 2020;12:485–92.

2. Aghemo A, Masarone M, Montagnese S, et al. Assessing the impact of COVID-19 on the management of patients with liver diseases: a national study by the Italian Association of the Study of the Liver. *Dig Liver Dis.* 2020;52:937–41.
3. World Health Organization. Global health sector strategy on viral hepatitis 2016–21. <https://www.who.int/hepatitis/strategy2016-2021/ghss-hep/en/>. Accessed Jan 2021.
4. Blach S, Kondili LA, Aghemo A, et al. Impact of COVID-19 on global HCV elimination efforts. *J Hepatol.* 2021;74:31–6.
5. Boettler T, Newsome PN, Mondelli MU, et al. Care of patients with liver disease during the COVID-19 pandemic: EASL-SECMID position paper. *J Hep Rep.* 2020;2:100113.
6. Doximity 2020 State of Telemedicine Report. Examining patient perspectives and physician adoption of telemedicine since to COVID-19 pandemic. September 2020. <https://c8y.doxcdn.com/image/upload/v1/Press%20Blog/Research%20Reports/2020-state-telemedicine-report.pdf>. Accessed Jan 2021.
7. American Association for the Study of Liver Diseases. Call to action for liver associations to advance progress towards viral hepatitis elimination: a focus on simplified approaches to HCV testing and cure. <https://www.aasld.org/programs-initiatives/viral-hepatitis-elimination-call-action>. Accessed Jan 2021.
8. Association Francaise pour l'étude du foie. Recommandations AFEF pour l'élimination de l'infection par le virus de l'hépatite C en France. <https://afef.asso.fr/wp-content/uploads/2018/06/VF-INTERACTIF-RECO-VHC-AFEF-v2103.pdf>. Accessed Jan 2021.
9. Gastroenterological Society of Australia. Australian recommendations for the management of hepatitis C virus infection: a consensus statement (June 2020). <https://www.hepcguidelines.org.au/>. Accessed Jan 2021.
10. European Association for the Study of the Liver. EASL recommendations on treatment of hepatitis C: final update to the series. *J Hepatol.* 2020;73:1170–218.
11. American Association for the study of Liver Diseases. <https://www.hcvguidelines.org/>. Accessed Jan 2021.
12. McPhee F. Developments in the treatment of HCV genotype 3 infection. *Exp Rev Anti-infect Ther.* 2019;10:775–85.
13. Foster G, Afdhal N, Roberts S, et al. Sofosbuvir and velpatasvir for HCV genotype 2 and 3 infection. *New Engl J Med.* 2015;373:2608–17.
14. Wyles D, Bräu N, Kottitil S, et al. Sofosbuvir and velpatasvir for the treatment of hepatitis C virus in patients coinfecting with human immunodeficiency virus type 1. An open-label, phase 3 study. *Clin Infect Dis* 2017;65:6–12.
15. Jacobson I, Lawitz E, Gane EJ, et al. Efficacy of 8 weeks of sofosbuvir, velpatasvir, and voxilaprevir in patients with chronic HCV infection: 2 phase 3 randomized trials. *Gastroenterology.* 2017;153:113–22.
16. Sood A, Duseja A, Kabrawala M, et al. Sofosbuvir/velpatasvir single-tablet regimen administered for 12 weeks in a phase 3 study with minimal monitoring in India. *Hepat Int.* 2019;13:173–9.
17. Isakov V, Chulanov V, Abdurakhmanov D, et al. Sofosbuvir/velpatasvir for the treatment of HCV: excellent results from a phase 3, open-label study in Russia and Sweden. *Infect Dis (Lond).* 2019;51:131–9.
18. Esteban R, Pineda JA, Calleja JL, et al. Efficacy of sofosbuvir and velpatasvir, with and without ribavirin, in patients with HCV genotype 3 infection and cirrhosis. *Gastroenterology.* 2018;155:1120–7.
19. Von Felden J, Vermehren J, Ingiliz P, et al. High efficacy of sofosbuvir/velpatasvir and impact of baseline resistance-associated substitutions in hepatitis C genotype 3 infection. *Aliment Pharmacol Ther.* 2018;47:1288–95.
20. Mangia A, Cenderello G, Copetti M, et al. SVR12 higher than 97% in GT3 cirrhotic patients with evidence of portal hypertension treated with SOF/VEL without ribavirin: a nationwide cohort study. *Cells.* 2019;8:313.
21. Mangia A, Milligan S, Khalili M, et al. Global real-world evidence of sofosbuvir/velpatasvir as simple, effective HCV treatment: analysis of 5552 patients from 12 cohorts. *Liver Int.* 2020;40:1841–52.
22. Brown R, Buti M, Rodrigues L, et al. Glecaprevir/pibrentasvir for 8 weeks in treatment-naïve patients with chronic HCV genotypes 1–6 and compensated cirrhosis. *J Hepatol.* 2020;72:441–9.
23. Flamm S, Kort J, Marx SE, et al. Effectiveness of 8-week glecaprevir/pibrentasvir for treatment-naïve, compensated cirrhotic patients with chronic hepatitis C infection. *Adv Ther.* 2020;37:2267–74.
24. Lampertico P, Mauss S, Persico M, et al. Real-world clinical practice use of 8-week glecaprevir/

- pibrentasvir in treatment-naïve patients with compensated cirrhosis. *Adv Ther.* 2020;37:4033–42.
25. Turnes J, Hernández-Guerra M, Souto-Rodríguez R, et al. Effectiveness of 8 weeks of glecaprevir/pibrentasvir in treatment-naïve hepatitis C patients with liver cirrhosis: results from the real-world Spanish HepaC registry. *J Hepatol.* 2020;73:S346–7.
 26. Berg T, Naumann U, Stoehr A, et al. Real-world effectiveness and safety of glecaprevir/pibrentasvir for the treatment of chronic hepatitis C infection: data from the German Hepatitis C-Registry. *Aliment Pharmacol Ther.* 2019;49:1052–9.
 27. Bourlière M, Gordon SC, Flamm SL, et al. Sofosbuvir, velpatasvir and voxilaprevir for previously treated HCV infection. *New Engl J Med.* 2017;376:2134–46.
 28. Degasperi E, Spinetti A, Lombardi A, et al. Real-life effectiveness and safety of sofosbuvir/velpatasvir/voxilaprevir in hepatitis C patients with previous DAA failure. *J Hepatol.* 2019;71:1106–15.
 29. Krajden M, Cook D, Wong S, et al. Real-world effectiveness of sofosbuvir/velpatasvir/voxilaprevir as a hepatitis C virus infection salvage treatment. *Hepatology.* 2019;70(Suppl):914A.
 30. Da BL, Lourdasamy V, Kushner T, Dietrich D, Saberi B. Efficacy of sofosbuvir/velpatasvir/voxilaprevir in direct-acting antiviral experienced patients with hepatitis C virus. *Eur J Gastroenterol Hepatol.* 2020. <https://doi.org/10.1097/MEG.0000000000001786>.
 31. Ward JW. The Nobel Prize for discovery of HCV is a call to end hepatitis. *Lancet.* 2020;396:1733.
 32. Razavi H, Pawlotsky J-M, Lazarus J, et al. Global timing of hepatitis C virus elimination in high-income countries: an updated analysis. *J Hepatol.* 2020;73:S317–9.