Epclusa® (sofosbuvir/velpatasvir) Use in Patients With HCV and HBV

This document is in response to your request for information regarding the use of Epclusa® (sofosbuvir/velpatasvir [SOF/VEL]) in patients with HCV and HBV.

This document includes content from or references to clinical practice guidelines, and the inclusion of these guidelines should not be interpreted as a treatment recommendation or an endorsement of the guidelines by Gilead Sciences, Inc.

Some data may be outside of the US FDA-approved prescribing information. In providing this data, Gilead Sciences, Inc. is not making any representation as to its clinical relevance or to the use of any Gilead product(s). For information about the approved conditions of use of any Gilead drug product, please consult the FDA-approved prescribing information.

The full indication, important safety information, and boxed warnings are available at: www.gilead.com/-/media/files/pdfs/medicines/liver-disease/epclusa/epclusa_pi.

Summary

Product Labeling[1]

The FDA issued a boxed warning and monitoring recommendations for all HCV DAAs about the risk of HBV reactivation.

Test all patients for evidence of current or prior HBV infection before initiating treatment with SOF/VEL. HBV reactivation has been reported in HCV/HBV co-infected patients who were undergoing or had completed treatment with HCV DAAs and were not receiving HBV antiviral therapy. Some cases have resulted in fulminant hepatitis, hepatic failure, and death. Monitor HCV/HBV co-infected patients for hepatitis flare or HBV reactivation during HCV treatment and post-treatment follow-up. Initiate appropriate patient management for HBV infection as clinically indicated.

SOF/VEL has been shown to increase tenofovir exposure.

Monitor for tenofovir-associated adverse reactions in patients receiving SOF/VEL concomitantly with a regimen containing TDF. Refer to the prescribing information of the TDF-containing product for recommendations on renal monitoring.

Clinical Data on SOF/VEL Use in HCV and HBV

- In a prospective, multicenter study of SOF/VEL treatment and prophylaxis with TAF in Chinese participants, the overall SVR12 rate was 97.6%, and rates were high across HCV GTs and in those with or without cirrhosis.[2]
- In a prospective, multicenter study of SOF/VEL in TN Chinese participants with HCV GTs 1 to 6 and HBV who received prophylactic TAF, the overall SVR12 rate was 98.3%.[3]

Real-World Data on SOF/VEL Use in HCV and HBV

- In a real-world study in Singapore that included a cohort of community and incarcerated patients treated with SOF/VEL ± RBV, the SVR12 rate was 100% in the 10 patients with HCV and HBV.[4]

- In a Canadian study, among patients with HCV GTs 1, 2, or 3 and HBV who were treated with SOF/VEL ± RBV, SVR rates ranged from 91.5% to 100%. Overall, the aOR (95% CI) for the association of HBV with non-SVR was 0.74 (0.37–1.49).[5]

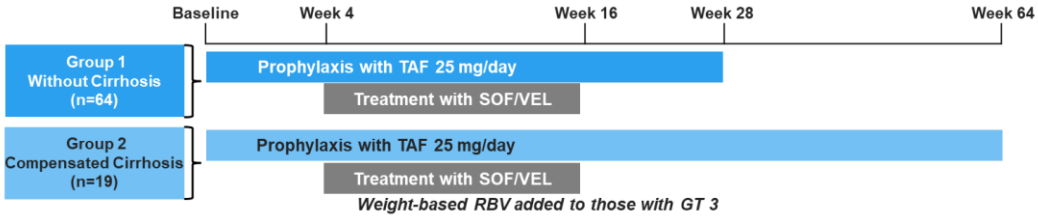
Clinical Data on SOF/VEL Use in HCV and HBV

Prospective, Multicenter Study in China[2]

Study design

A multicenter, prospective, single-arm study evaluated the efficacy and safety of SOF/VEL treatment with TAF prophylaxis in 83 participants with HCV GTs 1 to 6 and HBV. all received TAF prophylaxis and 12 weeks of SOF/VEL; participants were grouped by the presence or absence of compensated cirrhosis (Figure 1). Distribution of HCV GTs in the overall study population was as follows: GT 1, 26.5%; GT 2, 14.5%; GT 3, 21.7%; GT 6, 21.7%; not available, 15.6%.

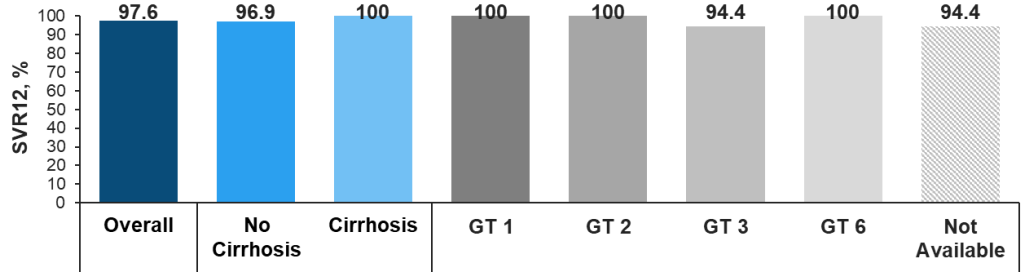
Figure 1. Prospective, Multicenter Study: Study Design[2]



Results

The overall SVR12 rate was 97.6%, and high SVR12 rates were observed for both groups and across GTs, including an SVR12 rate of 100% among those with cirrhosis (Figure 2). Overall, levels of HCV RNA and HBV DNA decreased from baseline to Week 28 (*P*-values not provided). One participant with GT 3 in Group 1 had HBV reactivation; their HBV DNA level was 2.15 $\log_{10}$ IU/mL at EOT with SOF/VEL but was <LLoQ at the SVR12 timepoint.

Figure 2. SVR12 Rates Overall, by Cirrhosis Status, and by HCV GTs (Lin et al)[2]



In Group 1, significant changes in laboratory parameters were observed from baseline to Week 28: ALT, 41.4 vs 17 IU/mL, respectively (*P*<0.001); AST, 38 vs 22 IU/mL (*P*<0.001); total bilirubin, 14.3 vs 13.6 mcmol/L (*P*=0.006); albumin, 42.4 vs 45.1 g/L (*P*<0.001). In Group 2, significant changes were observed from baseline to Week 64: ALT, 59 vs 22 IU/mL (*P*<0.001); AST, 60 vs 26 IU/mL (*P*<0.001); albumin, 41.3 vs 42.5 g/L (*P*=0.002); platelets, 114 vs 127.2 $\times 10^9$/L (*P*<0.001).

Generally, numerical decreases in LSM, APRI, and FIB-4 from baseline to Week 28 were observed in Group 1 (*P*=nonsignificant). In Group 2, significant decreases in liver fibrosis assessments were observed from baseline to Week 64: 19.4 vs 16.7 kPa, respectively (*P*=0.003); APRI, 1.6 vs 0.6 (*P*=0.007); FIB-4, 4.3 vs 1.3 (*P*=0.004). No drug-related adverse events were reported.

Prospective, Multicenter Study in TN Chinese Patients[3]

Study design and demographics

A multicenter, prospective, single-arm, open-label study evaluated the safety and efficacy of SOF/VEL in TN Chinese participants with HCV GTs 1 to 6 and HBV who received prophylactic TAF to prevent HBV reactivation. Participants received TAF from Day 0 to Week 28 and SOF/VEL from Week 4 to Week 16. Of the 60 participants, 47 did not have cirrhosis, and 13 had compensated cirrhosis. The primary endpoint was SVR12 for HCV, which was assessed at Week 28.

Table 1. Baseline Demographics and Disease Characteristics (Chen et al)[3]

Key Demographics and Characteristics		No Cirrhosis (n=47)	Compensated Cirrhosis (n=13)	Total (N=60)
Age, mean (range), years		49 (32–76)	56 (36–73)	51 (32–76)
Female, n (%)		19 (43.1)	3 (25)	22 (39.3)
HCV RNA	Mean (SD), log_{10} IU/mL	5.8 (1.1)	5.8 (0.9)	5.8 (1.2)
	≥5 log_{10} IU/mL, n (%)	36 (76.6)	11 (84.6)	47 (78.3)
HCV GT, n (%)	GT 1	12 (25.5)	5 (38.5)	17 (28.3)
	GT 2	9 (19.1)	2 (15.4)	11 (18.3)
	GT 3a	6 (12.8)	1 (7.7)	7 (11.7)
	GT 3b	8 (17)	2 (15.4)	10 (16.7)
	GT 6	13 (27.7)	2 (15.4)	15 (25)
HBsAg mean (range), log_{10} IU/mL		2.1 (0.8–3.1)	1.6 (0.3–2.5)	2 (0.8–3)
HBsAb+, n (%)		3 (6)	0	3 (4.7)
HBeAg+, n (%)		1 (2)	1 (7.1)	2 (3.1)
HBV DNA	Mean (range), log_{10} IU/mL	2.7 (2.1–3.2)	2.9 (2.1–3.7)	2.7 (2.1–3.4)
	≥LLoQ, n (%)	25 (50)	5 (35.7)	30 (46.9)
LSM, mean (range), kPa		6.9 (5.6–9.8)	20.5 (16.4–37.1)	9.3 (6.5–13.2)

Abbreviation: HBeAg=hepatitis B envelope antigen.

Results

Overall, SVR12 was achieved by 98.3% of participants (59/60; Table 2); the 1 participant who did not achieve SVR12 did not have cirrhosis and had HCV GT 1b. The SVR12 rate was 100% for HCV GTs 2, 3a, 3b, and 6; the SVR12 rate for GT 1 was 94.11%.

Table 2. SVR Rates at Study Weeks 4, 16, and 28 (Chen et al)[3]

	No Cirrhosis (n=47)			Compensated Cirrhosis (n=13)			Total (N=60)		
	Week 4	Week 16	Week 28 (SVR12)	Week 4	Week 16	Week 28 (SVR12)	Week 4	Week 16	Week 28 (SVR12)
SVR, %	4.3	97.9	97.9	7.7	100	100	5	98.3	98.3

Of the 28 participants who were HBV DNA+ at baseline, 2 participants remained HBV DNA+ at Week 28, and no participants experienced HBV reactivation. There was no significant difference in LSM between baseline and Week 16 in participants without cirrhosis (*P*=0.69) or with compensated cirrhosis (*P*=0.246).

Most participants did not experience significant adverse effects. No further safety data were reported.

Real-World Data on SOF/VEL Use in HCV and HBV

Incarcerated and Community Asian Cohort[4]

Study design and demographics

A retrospective, observational study evaluated the safety and efficacy of SOF/VEL ± RBV for 12 weeks in a cohort of community and incarcerated patients with HCV who were treated in a Singapore hospital between January 2018 and December 2019 (N=779). Overall, 16 patients also had HBV or HIV; 1 patient had HIV, HBV, and HCV; 10 patients had HCV and HBV. The primary endpoint was SVR12 in patients with HCV GT 3.

Table 3. Baseline Demographics and Disease Characteristics (Wong et al)[4]

Key Demographics and Characteristics	Incarcerated Patients (n=662)	Community Patients (n=117)
Age, median (IQR),[a] years	51 (43–58)	55 (51–60)
Male, n (%)	607 (91.7)	102 (87.2)
GT, 1/2/3/4/6/indeterminate, %	25.7/1.7/68.1/0.6/0.3/3.6	29.1/0/67.5/0.9/0.9/1.7
TE, n (%)	27 (4.1)	7 (6)
Fibrosis stage, F1/F2/F3/F4/not available,[a] %	33.3/11.2/12.7/25.8/17.1	24.7/11.1/12/42.7/9.4
Hepatocellular carcinoma, n (%)	10 (1.5)	4 (3.4)
Comorbid HBV/HIV, n (%)	9 (1.4)/5 (0.8)	1 (0.9)/2 (1.7)

[a]*P*≤0.005 for comparison between groups.

Efficacy and safety

SVR12 rates in the overall cohort were 98.3% in the ITT analysis, which included those who were lost to follow-up or who discontinued treatment early, and 99.5% in the PP analysis, which included all patients in the ITT population who completed treatment and had available SVR12 data. Four patients with GT 3 had virologic failures (decompensated cirrhosis, n=2; no cirrhosis, n=2), and no deaths occurred during treatment.

All 10 patients with HBV in the ITT and PP populations achieved SVR12. Five of the 10 patients with HBV received HBV prophylaxis with nucleos(t)ide analogs; of these patients, 3 had compensated HBV cirrhosis, 1 had advanced fibrosis, and 1 had HIV. Of the 5 patients who did not receive HBV prophylaxis, all were HBsAg+ and had undetectable HBV DNA levels at baseline. One of these patients experienced HBV virological relapse, but none developed clinical hepatitis during the median 8 months of follow-up.

Canadian Cohort[5]

Study design and demographics

The British Columbia Hepatitis Testers Cohort was used to evaluate the effectiveness of SOF/VEL ± RBV in patients with HCV. The cohort consisted of patients who tested positive for HCV, HIV, HBV, or active tuberculosis from 1990 through 2015. Patients who were HCV+ as of the end of 2015, had received SOF/VEL ± RBV treatment through December 2018, and underwent HCV RNA testing through April 9, 2019, were included in

the study. SVR was defined as undetectable HCV RNA at ≥10 weeks after EOT and was assessed in a modified ITT analysis, which excluded patients with no HCV RNA test after treatment initiation or HCV RNA-status on their last test but no HCV RNA test ≥10 weeks after EOT. A multivariable regression analysis assessed characteristics associated with non-SVR (defined as any detectable HCV RNA after EOT, HCV RNA+ status during treatment and no VL test after EOT, or detectable HCV RNA on the last HCV VL test during treatment or within 10 weeks of EOT).

Table 4. Baseline Demographics and Disease Characteristics (Wilton et al)[5]

Key Demographics and Characteristics	SOF/VEL ± RBV (N=2821)
Age, median (IQR), years	58 (50–63)
Male, n (%)	1766 (62.6)
Race, White/other, %	90.6/9.5
GT 1/2/3, n (%)	1076 (38.1)/531 (18.8)/1072 (38)
Co-infection, HBV/HIV, n (%)	187 (6.7)/248 (8.8)
Concomitant RBV, n (%)	278 (9.9)
TE, n (%)	310 (11)
Cirrhosis/decompensated cirrhosis, n (%)	105 (3.7)/66 (2.3)
History of injecting drugs, n (%)	1021 (36.1)

Results

Overall SVR rates were high across GTs: GT 1, 94.5% (n/N=1017/1076); GT 2, 96.4% (n/N=512/531); and GT 3, 93.7% (n/N=1004/1072). Among patients with HBV, the SVR rate was 91.5% in patients with GT 1 (n/N=54/59), 100% in patients with GT 2 (n/N=36/36), and 93.4% in patients with GT 3 (n/N=71/76).

The aOR (95% CI) for the association of HBV with non-SVR was 0.76 (0.26–2.22) in the GT 1 subgroup, 1.16 (0.43–3.14) in the GT 3 subgroup, and 0.74 (0.37–1.49) in all patients treated with SOF/VEL. Safety data were not reported.

Guideline Recommendations on SOF/VEL Use in HCV and HBV

AASLD/IDSA Recommendations for Management of Patients With HCV and HBV[6]

All patients initiating HCV DAA therapy should be assessed for HBV co-infection with HBsAg testing, and for evidence of prior infection with HBsAb and HBcAb testing. HBsAg positivity does not represent a contraindication to HCV DAA therapy. Recommended actions are summarized in Table 5.

Table 5. AASLD/IDSA Recommendations for Management of Patients With HCV and HBV Treated with DAAs[6]

		Recommended Action
HBsAg+	Meets AASLD criteria for HBV treatment	Initiate HBV therapy at the same time or before initiation of HCV DAA therapy.
	Does not meet AASLD criteria for HBV treatment (low or undetectable HBV DNA and normal ALT levels)	Initiate prophylactic HBV treatment and continue until 12 weeks after completion of DAA therapy. OR Monitor HBV DNA levels during and immediately after HCV DAA therapy (usually no more frequently than every 4 weeks). Start HBV treatment if there is a rise in HBV DNA >10-fold above baseline or if >1000 IU/mL in those with previously undetectable or unquantifiable HBV DNA.
Isolated HBcAb+ or HBsAb+/HBcAb+ (immune recovery)	Insufficient data to provide clear recommendations. However, the possibility of HBV reactivation should be considered in these groups in the event of unexplained increases in liver enzymes during and/or after completion of DAA therapy.	

References

1. Enclosed. Gilead Sciences Inc, EPCLUSA® (sofosbuvir and velpatasvir) tablets, for oral use. US Prescribing Information. Foster City, CA.
2. Lin N, Han Y, Chen H, et al. Evaluating the safety and efficacy of SOF/VEL treatment and prophylactic use of TAF in patients with chronic HBV/HCV coinfection: A multicenter study [Poster]. Paper presented at: AASLD The Liver Meeting; November 15-19, 2024; San Diego, CA.
3. Chen H, Kang Q, Pan J, Zeng Z, Yu Y, Xu X. The efficacy and safety of 12 week SOF/VEL regimen combined with prophylactic use of TAF for treatment naive genotype1 6 HCV/HBV co infection adult patients with or without compensated cirrhosis in China: a multi center prospective, single arm, open label trial. [Poster 1896-A]. Paper presented at: AASLD - The Liver Meeting; November 10-14, 2023; Boston, MA.
4. Wong YJ, Thurairajah PH, Kumar R, et al. Efficacy and safety of sofosbuvir/velpatasvir in a real-world chronic hepatitis C genotype 3 cohort. *J Gastroenterol Hepatol.* 2020.
5. Wilton J, Wong S, Yu A, et al. Real-World Effectiveness of Sofosbuvir/Velpatasvir for Treatment of Chronic Hepatitis C in British Columbia, Canada: A Population-Based Cohort Study. *Open Forum Infect Dis.* 2020;7(3):ofaa055. https://www.ncbi.nlm.nih.gov/pubmed/32154326
6. American Association for the Study of Liver Diseases (AASLD), Infectious Disease Society of America (IDSA). HCV Guidance: Recommendations for Testing, Managing, and Treating Hepatitis C. Available at: https://www.hcvguidelines.org. Last Updated: 05 October. 2021.

Abbreviations

AASLD=American Association for the Study of Liver Diseases
aOR=adjusted odds ratio
APRI=AST to platelet ratio index
DAA=direct-acting antiviral
EOT=end of treatment
FIB-4=Fibrosis-4
GT=genotype
HBcAb=hepatitis B core antibody
HBsAb=hepatitis B surface antibody
HBsAg=hepatitis B surface antigen
IDSA=Infectious Diseases Society of America
LLoQ=lower limit of quantification
LSM=liver stiffness measurement
PP=per protocol
RBV=ribavirin
SOF=sofosbuvir
SVR=sustained virologic response
SVR12=sustained virologic response 12 weeks after end of treatment
TAF=tenofovir alafenamide
TE=treatment experienced
TN=treatment naïve
VEL=velpatasvir
VL=viral load

Product Label

For the full indication, important safety information, and boxed warning(s), please refer to the Epclusa US Prescribing Information available at: https://www.gilead.com/-/media/files/pdfs/medicines/liver-disease/epclusa/epclusa_pi.

Follow Up

For any additional questions, please contact Gilead Medical Information at:

☎ 1-866-MEDI-GSI (1-866-633-4474) or 🖱 www.askgileadmedical.com

Adverse Event Reporting

Please report all adverse events to:

Gilead Global Patient Safety ☎ 1-800-445-3235, option 3 or
🖱 https://www.gilead.com/utility/contact/report-an-adverse-event

FDA MedWatch Program by ☎ 1-800-FDA-1088 or ✉MedWatch, FDA, 5600 Fishers Ln, Rockville, MD 20852 or 🖱 www.accessdata.fda.gov/scripts/medwatch

Data Privacy

The Medical Information service at Gilead Sciences may collect, store, and use your personal information to provide a response to your medical request. We may share your information with other Gilead Sciences colleagues to ensure that your request is addressed appropriately. If you report an adverse event or concern about the quality of a Gilead or Kite product, we will need to use the information you have given us in order to meet our regulatory requirements in relation to the safety of our medicines.

It may be necessary for us to share your information with Gilead's affiliates, business partners, service providers, and regulatory authorities located in countries besides your own. Gilead Sciences has implemented measures to protect the personal information you provide. Please see the Gilead Privacy Statement (www.gilead.com/privacy-statements) for more information about how Gilead handles your personal information and your rights. If you have any further questions about the use of your personal information, please contact privacy@gilead.com.