GILEAD | Medical Information

Epclusa® (SOF/VEL) Risk of HBV Reactivation

This document is in response to your request for information regarding Epclusa® (sofosbuvir/velpatasvir [SOF/VEL]) and the risk of HBV reactivation during and after treatment for HCV with direct-acting antivirals (DAAs).

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

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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]

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.

Real-World Data on HBV Reactivation During and After DAA Treatments for HCV

In a retrospective, European cohort study that included 10,152 patients (HBsAg+, n=111; HBsAg-, n=10,041) with chronic HCV, HBV reactivation occurred during and after DAA treatment more frequently in patients who were HBsAg+ (5.9%) than in patients who were HBsAg- (0.16%).[2]

In a retrospective cohort study of 17,779 US Veterans (HBsAg+, n=137; HBsAg-/HIV-, n=17,266), HBV reactivation occurred in 17 patients. Reactivations occurred more frequently in patients who were HBsAg+ (n=13) than who were HBsAg- and HIV- (n=4) and more frequently after treatment completion (n=12) than during treatment (n=5).[3]

Guideline Recommendations Regarding Monitoring for HBV Reactivation

The AASLD and IDSA recommend that all patients who initiate HCV DAA therapy should be assessed for HBV co-infection with HBsAg testing and assessed for evidence of prior infection with HBsAb and HBcAb testing. HBsAg positivity does not represent a contraindication to HCV DAA therapy.[4]

Real-World Data on HBV Reactivation During and After DAA Treatments for HCV

Retrospective, European Cohort Study[2]

Study design and demographics

A real-world, retrospective, European cohort study consisted of 10,152 patients (HBsAg+, n=111; HBsAg-, n=10,041) with chronic HCV and evaluated the prevalence and clinical characteristics of HCV/HBV co-infection and the rate of HBV reactivation associated with DAA therapy for HCV.

The following criteria constituted HBV reactivation: reappearance of HBsAg in a patient who was HBsAg- and HBcAb+, detection of HBV DNA in patients who were previously HBV DNA-, or a sudden ≥100-fold rise in HBV DNA in patients with prior detection of HBV DNA.

Of the patients who were HBsAg+ and were tested, 46/102 had detectable HBV DNA (all <2000 IU/mL) prior to DAA treatment. Of the patients who were HBsAg- and were tested, 1239/6139 were HBcAb+.

Table 1. Baseline Demographics and Disease Characteristics (Jaroszewicz et al)[2]

Key Demographics and Characteristics		HBsAg+ (n=111)	HBsAg- (n=10,041)
Age,[a] mean (SD), years		44.6 (13.9)	53 (27.3)
Male,[a] n (%)		66 (59)	4847 (48)
HCV GT, n (%)	1/1a/1b	2 (1.8)/7 (6.3)/81 (73)	196 (1.9)/330 (3.3)/7990 (79.6)
	2/3/4	0/15 (13.5)/6 (5.4)	13 (0.1)/1048 (10.4)/462 (4.6)
Prior failure with HCV treatment, n (%)		39 (35.1)	3179 (31.7)
Fibrosis (Metavir scoring),[a] n (%)	F0–2	51 (45.9)	5629 (56.8)
	F3–4	57 (51.3)	4190 (42.3)
HIV co-infection,[a] n (%)		13 (11.7)[b]	447 (4.4)
SOF-based DAA regimens,[c] n (%)	SOF-based, non-pangenotypic	42 (37.8)	3454 (34.4)
	SOF/VEL ± RBV	4 (3.6)	420 (4.2)

[a]*P*<0.05, for HBsAg+ vs HBsAg-.
[b]All patients with HIV, HBV, and HCV received highly active antiretroviral therapy with an anti-HBV backbone.
[c]Other DAA regimens included GLE/PIB, EBR/GZR ± RBV, and PrO ± DSV ± RBV.

Results

SVR12 was achieved in 96% of patients who were HBsAg+ and in 95% of patients who were HBsAg- (*P*=0.7).

HBV reactivation occurred in 8 patients: 6 (5.9%) were HBsAg+ and 2 (0.16%) were HBsAg-/HBcAb+. HBV reactivation occurred during the treatment phase in 5 of the 6 patients who were HBsAg+ and occurred 12 weeks after therapy completion in the other patient who was HBsAg+; no significant HBV reactivation risk factors were observed. The rate of HBV reactivation was also not significantly different in patients who had detectable HBV DNA than in those who had undetectable HBV DNA.

Patients who were HBsAg+ and experienced HBV reactivation were between the ages of 28 and 59 years and had HCV GT 1. Two patients experienced ALT flare, and DAA therapy (PrOD ± RBV) was discontinued in 1 of these patients. Of the 2 patients who were HBsAg- and HBcAb+, HBV reactivation occurred 12 and 24 weeks after therapy completion;

both patients had low levels of fibrosis, were receiving immunosuppressive therapy, and had significant elevations in ALT levels. One of these patients was receiving lamivudine.

No HBV reactivation resulted in decompensated liver function or death. Two patients who experienced HBV reactivation were receiving treatment with LDV/SOF + RBV; 1 patient had reactivation at Week 8, and 1 patient had reactivation at Week 12.

VA Retrospective Cohort Study[3]

Study design and baseline demographics

A retrospective cohort study utilizing the VA administrative database was conducted in 17,779 US Veterans who were HBcAb+ to evaluate the incidence of ALT flares, clinically significant hepatic events (defined as increase in ALT level >100 IU/L and increase in bilirubin level >2.5 mg/dL), and HBV reactivation (>1 $\log_{10}$ increase in HBV DNA or >4 $\log_{10}$ absolute increase in HBV DNA) or HBsAg reverse seroconversion while on DAA treatment and up to 12 months after DAA treatment. Of these patients, most were HBsAg- and HIV- (n=17,266) prior to DAA therapy.

Table 2. Baseline Demographics and Disease Characteristics (Serper et al)[3]

Key Demographics and Characteristics		HBsAg+[a] (n=137)	HBsAg- and HIV- (n=17,266)
Age, median, years		61	63
Male, n (%)		135 (99)	16,902 (98)
Race, White/Black/other/unknown, n (%)		81 (59)/54 (39)/0/1 (1)	7882 (46)/8097 (47)/ 271 (2)/976 (6)
GT, 1/2/3/4–6, n (%)		111 (81)/10 (7)/11 (8)/1 (1)	14,372 (83)/1444 (8)/ 838 (5)/171 (1)
Cirrhosis, n (%)		37 (27)	4148 (24)
Decompensated cirrhosis, n (%)		2 (1)	509 (3)
Hepatocellular carcinoma, n (%)		0	37 (<1)
Alcoholism, n (%)		9 (7)	1386 (8)
SOF-based DAA regimens,[b] n (%)	LDV/SOF	84 (61)	10,737 (62)
	SOF + RBV	23 (17)	1802 (11)
	SOF + SMV	6 (4)	914 (5)
	SOF/VEL	6 (4)	502 (3)
	SOF + DCV	1 (1)	242 (1)

[a]Included 3 patients with HIV.
[b]Other DAA regimens included EBR/GZR and PrOD.

Results

The SVR12 rate among those tested was 93% (9944/10,675). Overall, 17 patients experienced HBV reactivation. Reactivation occurred more often in patients who were HBsAg+ than who were HBsAg- and HIV- and more frequently after treatment completion than during treatment (Table 3 and Table 4). Reverse seroconversion (from HBsAg- to HBsAg+) occurred in 1 of 4 patients with HBV reactivation. Six patients experienced HBV reactivation with >4 $\log_{10}$ increases in HBV DNA.

Table 3. Outcomes in Patients Who Were HBsAg+ (Serper et al)[3a]

Outcomes, n (%)		HBsAg+			
		During Treatment		After Treatment	
		No Cirrhosis (n=100)	Cirrhosis (n=37)	No Cirrhosis (n=77)	Cirrhosis (n=36)
HBV reactivation		4 (4)	0	3 (4)	6 (17)
ALT flare	ALT ≥2 × ULN	3 (3)	1 (3)	25 (32)	16 (44)
	ALT ≥4 × ULN	8 (8)	4 (11)	11 (15)	8 (22)
	ALT >300 IU/mL	2 (2)	1 (3)	2 (2)	1 (3)
	ALT >1000 IU/mL	1 (1)	1 (3)	1 (1)	0
Significant hepatic events		0	1 (3)	0	1 (3)

[a]Included 3 patients with HIV; all of whom were non-cirrhotic, and none experienced HBV reactivation.

Table 4. Outcomes in Patients Who Were HBsAg- and HIV- (Serper et al)[3]

Outcomes, n (%)		HBsAg- and HIV-	
		During Treatment (n=17,266)	After Treatment (n=13,390)
HBV reactivation		1 (<0.1)	3 (<0.1)
ALT flare	ALT ≥2 × ULN	2336 (14)	1264 (9)
	ALT ≥4 × ULN	577 (3)	387 (3)
	ALT >300 IU/mL	31 (<0.1)	85 (0.6)
	ALT >1000 IU/mL	3 (<0.1)	10 (0.1)
Significant hepatic events		4 (<0.1)	35 (0.3)

References

1. Enclosed. Gilead Sciences Inc, EPCLUSA® (sofosbuvir and velpatasvir) tablets, for oral use. US Prescribing Information. Foster City, CA.
2. Jaroszewicz J, Pawlowska M, Simon K, et al. Low risk of HBV reactivation in a large European cohort of HCV/HBV coinfected patients treated with DAA. *Expert Rev Anti Infect Ther.* 2020;18(10):1045-1054.
3. Serper M, Forde KA, Kaplan DE. Rare clinically significant hepatic events and hepatitis B reactivation occur more frequently following rather than during direct-acting antiviral therapy for chronic hepatitis C: Data from a national US cohort. *J Viral Hepat.* 2018;25(2):187-197.
4. 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.

Abbreviations

DAA=direct-acting antiviral
DCV=daclatasvir
DSV=dasabuvir
EBR=elbasvir
GLE=glecaprevir
GT=genotype
GZR=grazoprevir
HBcAb=hepatitis B core antibody
HBsAg=hepatitis B surface antigen
LDV=ledipasvir
PIB=pibrentasvir
PrO=paritaprevir/ritonavir + ombitasvir
PrOD=paritaprevir/ritonavir + ombitasvir + dasabuvir
RBV=ribavirin
SMV=simeprevir
SOF=sofosbuvir
SVR12=sustained virologic response 12 weeks after end of treatment
ULN=upper limit of normal
VA=Veterans Affairs
VEL=velpatasvir

Product Label

For the full indication, important safety information, and boxed warning(s), please refer to the Epclusa US Prescribing Information available at: 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

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