GILEAD | Medical Information

Epclusa® (sofosbuvir/velpatasvir) Use in Patients Co-Infected With HIV

This document is in response to your request for information regarding the use of Epclusa® (sofosbuvir/velpatasvir [SOF/VEL]) for the treatment of chronic HCV in people with HIV (PWH).

This document includes content from, or references to, clinical practice guidelines, and inclusion 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]

Key drug interactions are summarized below.

Clinical Data on SOF/VEL Use for HCV in PWH

The phase 3 ASTRAL-5 study evaluated 12 weeks of SOF/VEL treatment in PWH and HCV GTs 1 to 4 who were suppressed on a TDF-based or 3TC/ABC-containing ARV regimen.[2] The overall SVR12 rate was 95%. SOF/VEL was well tolerated.[2,3]

An open-label study in China evaluated 12 weeks of SOF/VEL treatment in PWH and HCV. The SVR12 rate was 97%, and SOF/VEL was well tolerated.[4]

Real-World Data on SOF/VEL Use for HCV in PWH

Four real-world studies examined the outcomes of treatment with SOF/VEL in PWH and those with HCV.

- In a Canadian cohort (N=1801), the SVR12 rates ranged from 92% to 96% across GT 1 to 3 subgroups. In the GT 1 subgroup, PWH had a lower SVR rate compared with those without HIV (86% vs 94%, respectively).[5]
- In a prospective Mexican cohort that compared outcomes between participants with both HIV and HCV and participants with HCV monoinfection, SVR rates were 81.6% and 86.4%, respectively (*P*=0.128).[6]
- In a study that included African American patients with HCV GT 1, SVR12 was achieved in 95% of all patients, including 2 individuals with HIV.[7]
- In a Spanish cohort of adult MSM or transsexual women who acquired HCV in the previous 12 months (N=133), SVR12 rates were 90.7% and 94.7% in the ITT and PP analyses, respectively.[8]

Clinical Practice Guidelines

Guideline recommendations for the treatment of patients with HIV and HCV can be found below.

Product Labeling

Drug Interactions

Established and potentially significant drug Interactions[1]

Clearance of HCV infection with DAAs may lead to changes in hepatic function, which may impact the safe and effective use of concomitant medications.

Table 1 provides a listing of established or potentially clinically significant drug interactions. The drug interactions described are based on studies conducted with either SOF/VEL, the components of SOF/VEL (SOF and VEL) as individual agents, or are predicted drug interactions that may occur with SOF/VEL.

Table 1. Potentially Significant Drug Interactions With HIV ARVs[1]

Concomitant Drug Name	Effect on Concentration	Clinical Effect/Recommendation
EFV[a]	Decreased VEL	Coadministration of SOF/VEL with EFV-containing regimens is not recommended.
Regimens containing TDF	Increased TFV	Monitor for TFV-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.
TPV/RTV	Decreased SOF Decreased VEL	Coadministration is not recommended.

Abbreviations: EFV=efavirenz; TFV=tenofovir; TPV=tipranavir.
[a]These interactions have been studied in healthy adults.

Drugs without clinically significant interactions with SOF/VEL

Based on drug interaction studies conducted with the components of SOF/VEL (SOF or VEL) or SOF/VEL, no clinically significant drug interactions have been observed or are expected with the following drugs: ATV/RTV, DRV/RTV, DTG, E/C/F/TAF, FTC, RAL, or RPV.[1]

Based on drug interaction studies conducted with BIC/FTC/TAF or the components of BIC/FTC/TAF, no clinically significant drug interactions have been observed when BIC/FTC/TAF is combined with SOF/VEL.[9]

Clinical Data on SOF/VEL Use for HCV in PWH

ASTRAL-5: SOF/VEL for HCV GTs 1 to 4 in PWH[2,3,10]

Study design and demographics[2]

ASTRAL-5 was a phase 3, single-arm, open-label, multicenter study that evaluated 12 weeks of SOF/VEL treatment in 106 TN or TE participants with HCV GTs 1 to 4 and HIV. PWH with a CD4 count ≥100 cells/mcL and HIV RNA ≤50 copies/mL, who received a stable ARV regimen for ≥8 weeks (boosted protease inhibitor regimen, n=50; NNRTI, n=13; integrase-inhibitor based, n=36; other, n=7), and had a CrCl >60 mL/min were eligible for inclusion. HIV therapy consisted of E/C/F/TDF, FTC/TDF/RPV, or FTC/TDF or ABC/3TC and one of the following RTV-boosted agents: ATV, DRV, LPV, RAL, or RPV. The primary endpoint was SVR12, defined as HCV RNA <15 IU/mL at 12 weeks after EOT.

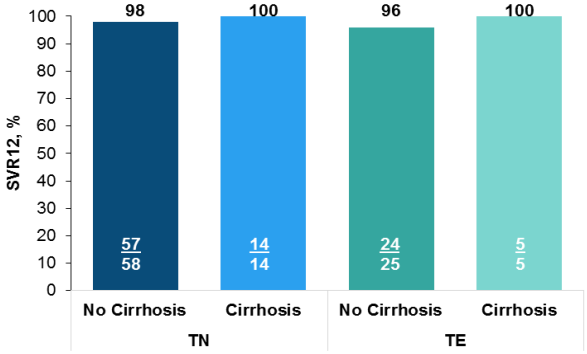
Table 2. ASTRAL-5: Baseline Demographics and Disease Characteristics[2]

Key Demographics and Disease Characteristics		SOF/VEL (N=106)
Age, mean (range), years		54 (25–72)
Male, n (%)		91 (86)
Race, White/Black, n (%)		54 (51)/48 (45)
HCV GT, 1a/1b/2/3/4, n (%)		66 (62)/12 (11)/11 (10)/12 (11)/5 (5)
Cirrhosis, n (%)		19 (18)
TE, n (%)		31 (29)
CD4 count, mean (range), cells/mcL		598 (183–1513)
ARV by TDF use, n (%)	Boosted TDF-based	56 (53)
	Non-boosted TDF-based	35 (33)
	Non–TDF-based	15 (14)

Efficacy[2,3]

Overall, the SVR12 rate was 95% (101/106). SVR12 rates by GT were as follows: GT 1a, 95% (63/66); GT 1b, 92% (11/12); GT 2, 100% (11/11); GT 3, 92% (11/12); and GT 4, 100% (5/5). Achievement of SVR12 was also evaluated according to treatment history and cirrhosis status (Figure 1).[2]

Figure 1. ASTRAL-5: SVR12 by Treatment History and Cirrhosis Status[2]



Two participants were LTFU, and 1 participant with GT 3 discontinued SOF/VEL due to vomiting.[3] Two participants with GT 1a relapsed: both were Black females without cirrhosis; one participant was TE (PEG-IFN + RBV) and received RTV + LPV and FTC/TDF, and the

other TN participant received RTV + DRV and ABC/3TC. On-treatment adherence was confirmed by pill counts and blood levels, and no RASs were detected at baseline or at post-treatment Week 4.[2]

The presence of baseline NS5A RASs did not impact SVR12 rates. Of the 103 participants who had available data on virologic outcomes by deep sequencing, 13 had detectable NS5A RASs at baseline with a 15% deep sequencing cut-off, and 100% (12/12) achieved SVR12.[2] Of the 91 participants without NS5A baseline RASs, 98% (89/91) achieved SVR12. Three participants without post-treatment samples were excluded from the resistance analysis.[3]

PK parameters[2]

Exposures to SOF, its metabolite (GS-331007), and VEL following SOF/VEL administration were similar for all ARV regimens evaluated, regardless of whether they were boosted or un-boosted, and were similar to prior phase 2/3 study results. Tenofovir PK levels were similar in boosted or un-boosted TDF regimens, and to levels observed in PWH without HCV.

Safety

Treatment with SOF/VEL for 12 weeks was well tolerated. The most common AEs (≥5%) were fatigue (25%), headache (13%), arthralgia (8%), URTI (8%), diarrhea (8%), insomnia (7%), and nausea (7%). The majority of AEs were mild in severity (Grade 1 or 2). Two participants experienced serious AEs, neither of which were deemed related to study drug. Another participant withdrew consent after vomiting on Day 4.[2] Grade 3 or 4 AEs or laboratory abnormalities were experienced by 8% and 18% of participants, respectively.[3] Elevated bilirubin was the most common laboratory abnormality in participants who received ATV/RTV, which is a common AE associated with ATV. Three participants who received TDF-based ART experienced a change from baseline SCr levels of ≥0.4 mg/dL.[2]

Comparison to ASTRAL-1 to -3 studies[10]

Wyles et al conducted a comparison of the efficacy and safety outcomes of ASTRAL-5 to those seen in the ASTRAL-1, -2, and -3 studies, which excluded PWH (N=1035). The SVR12 rate was 98% in participants with HCV (1015/1035) and 95% in participants with HIV and HCV. Nearly all ASTRAL-1 to -3 participants who did not have baseline RASs (n=709) achieved SVR12 (99%, 701/709), and 98% (89/91) of those with baseline RASs (n=12) achieved SVR12. The most common AEs seen in participants with HCV (ASTRAL-1 to -3) were similar to those seen in PWH and HCV (ASTRAL-5).

Open-Label Chinese Study[4]

Study design and demographics

A single-arm, multicenter, open-label study in China evaluated the efficacy and safety of SOF/VEL in 243 participants with HCV and HIV-1 who were being treated with E/C/F/TAF. Participants who were naive to DAAs, receiving stable ART, and had HIV RNA below the lower limit of detection for ≤12 months of screening were included in this study. All participants received SOF/VEL once daily for 12 weeks regardless of HCV GTs. The primary endpoints were SVR12 (HCV RNA <15 IU/mL at 12 weeks after EOT) and the proportion of participants who discontinued treatment early due to AEs.

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

Key Demographics and Disease Characteristics	SOF/VEL (N=243)
Age, median (IQR), years	45 (41–48)
Male, n (%)	189 (78)
HCV RNA, median (IQR), log_{10} IU/mL	6 (5.4–6.5)
HCV GT, 1a/1b/2a/3a/3b/6a/6e/6n/6v, n (%)	10 (4)/60 (25)/4 (2)/36 (15)/53 (22)/ 65 (27)/2 (1)/11 (5)/2 (1)
Previous HCV treatment, n (%)	23 (9)
IFN + RBV/PEG-IFN + RBV, n (%)	21 (91)/2 (9)
Relapse or breakthrough with prior HCV treatment, n/N (%)	12/23 (52)
FIB-4 categories, <1.45/1.45–3.25/>3.25, n (%)	126 (52)/97 (40)/20 (8)
CD4 count, median (IQR), cells/mm^3	452 (313–623)

Efficacy

All 243 participants completed 12 weeks of SOF/VEL and achieved serum HCV RNA <15 IU/mL at EOT. The SVR12 rate was 97% in both the ITT population (235/243) and the PP population (227/233). The SVR12 rates by GT were as follows: GT 1, 100% (63/63); GT 2, 67% (2/3); GT 3, 95% (84/88); and GT 6, 99% (78/79). Among participants with FIB-4 index scores, SVR12 was achieved in 99% of participants (213/215) with FIB-4 ≤3.25 and in 78% of participants (14/18) with FIB-4 >3.25 (*P*<0.001). The SVR24 rate was 93% in the ITT population and 98% (225/230) in the PP population.

At 12 weeks after EOT, 6 participants with HCV relapsed. After adjusting for potential confounders in an exploratory analysis, an 18-fold risk of HCV relapse was found in patients with FIB-4 >3.25 compared with those who had FIB-4 ≤3.25.

Safety

AEs were reported in 29% of participants (70/243). Five of these participants experienced severe AEs; however, all 5 participants achieved and maintained SVR12 and SVR24 during the study. The most common AEs were URTI (5%), cough (3%), abnormal liver function (2%), abnormal renal function (2%), constipation (2%), sleep disorders (2%), and urinary tract infection (2%). No participants discontinued SOF/VEL due to AEs, and no deaths were reported.

Real-World Data on SOF/VEL Use for HCV in PWH

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 GTs 1 to 3 (N=1801), including PWH (Table 4). To allow for variations in clinical practice, SVR was defined as undetectable HCV RNA at ≥10 weeks, instead of 12 weeks, after EOT.

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

Key Demographics and Characteristics	SOF/VEL (N=1801)
Age, median (IQR), years	58 (51–63)
Male, n (%)	1148 (64)

Key Demographics and Characteristics	SOF/VEL (N=1801)
TE, n (%)	236 (13)
HCV GT, 1/2/3, %	625/351/725
Cirrhosis, n (%)	90 (5)
HIV-positive, n (%)	172 (10)
Diabetes, n (%)	125 (7)
Recent/past IDU, n (%)	322 (18)/309 (17)

Effectiveness and safety

SVR rates were 93% (584/628), 96% (338/351), and 92% (670/725) in the GT 1, GT 2, and GT 3 subgroups, respectively.

In the GT 1 subgroup, PWH had a lower SVR rate (86%) compared with those without HIV (94%). The overall odds ratio (95% CI) of achieving SVR among those with HIV was 1.24 (0.69–2.22) and varied by GT: GT 1, 1.49 (0.58–3.88); GT 3, 0.88 (0.36–2.15). A multivariate analysis indicated that IDU was associated with lower SVR rates. SOF/VEL + RBV was also associated with lower SVR rates. Safety results were not reported.

Prospective Mexican Cohort[6]

Study design and demographics

A prospective cohort study in Mexico assessed the effectiveness of DAA treatment in the achievement of SVR12 in patients with both HIV and HCV compared with HCV monoinfection (N=278). Adults aged ≥18 years, with or without HIV, with functional cure or under nucleos(t)ide analog treatment for HBV were included; DAA-experienced participants were included in cases of reinfection and were excluded in cases of previous DAA failure. In the group of participants with both HIV and HCV, all were receiving ART and had undetectable HIV-1 RNA (<40 c/mL).

Table 5. Baseline Demographics and Disease Characteristics (Lopez et al)[6]

Key Demographics and Characteristics	HIV/HCV (n=130)	HCV (n=148)
Age,[a] median (IQR), years	35 (29–41)	58 (47–69)
Male,[a] n (%)	119 (91.5)	61 (41.2)
Cirrhosis[a], n (%)	12 (9.2)	84 (56.7)
FIB-4,[a] median (IQR)	0.96 (0.56–1.36)	3.75 (1.18–6.32)
CD4 count, median (IQR), cells/mm^3	572 (413–731)	N/A
HCV RNA,[a] median (IQR), IU/mL	1,687,026 (843,516–2,530,542)	793,125 (198,734–1,190,593)

[a]Between-group difference, *P*<0.001.

Effectiveness and safety

HCV RNA levels were undetectable in both groups at EOT, and there was no significant difference in SVR12 rates between participants with both HIV and HCV and those with HCV monoinfection (*P*=0.128). In the HIV/HCV group, SVR12 was achieved by 81.6% of participants (106/130), including 45 participants treated with SOF/VEL and 3 participants treated with SOF/VEL + RBV. In the HCV monoinfection group, the SVR12 rate was 86.4% (128/148), including 28 participants treated with SOF/VEL and 58 participants treated with SOF/VEL + RBV.

AEs were reported in 81 participants (62.3%) with both HIV and HCV and in 129 participants (87.1%) with HCV monoinfection (*P*<0.001). Severe AEs were reported in 4 participants with HCV monoinfection and led to DAA discontinuation in 1 participant.

Treatment of HCV GT 1 in African American Patients[7]

Study design and demographics

A retrospective cohort study compared the safety, efficacy, and tolerability of SOF-based regimens in African American patients with HCV GT 1 and evaluated variables that impacted the achievement of SVR12, including the presence of HIV. Of the 278 patients included in the study, 78 received SOF/VEL, and 14 of those patients (18%) were PWH. In the SOF/VEL group, the mean (range) age was 61 (28–94) years, 68% were male, 15% were TE, and 86% and 14% were Child-Pugh Class A and B, respectively.

Effectiveness and safety

SVR12 was achieved in 95% of all patients (263/278). Ninety-seven percent of patients treated with SOF/VEL (76/78), 100% of PWH (2/2), and 94% of patients (34/36) without HIV achieved SVR12. Per univariate analysis, HIV status was not significantly associated with SVR12 achievement (*P*=0.425).

Nearly half of all patients included in this study (46%, 128/278) experienced ≥1 AE; no severe AEs were reported. The most common AEs among patients who received SOF/VEL were fatigue (24% [n=19]), nausea (6% [n=5]), headache (5% [n=4]), and arthralgia (4% [n=3]).

Spanish Observational Cohort[8]

Study design and demographics

A multicenter, ambispective, observational study in Madrid assessed the rate of spontaneous cure in patients who did not start HCV treatment early as well as SVR12 rates in patients who received any DAA treatment, including SOF/VEL (N=133). Eligible patients were MSM or transsexual women aged ≥18 years with HIV who had acquired HCV in the previous 12 months. Overall, the median (IQR) age was 40 (34.3–46.1) years, the median (IQR) duration of time since HIV diagnosis was 8 (4–12) years, 126/133 patients (96.2%) were receiving ART, and 43/133 (33.6%) had a history of previous HCV infection.

Effectiveness

Spontaneous cure was evaluated in 90 patients who had 2 HCV viral load assays separated by 1 month before HCV treatment was initiated; 10 of these patients (11%; 95% CI: 0.6–20) spontaneously cleared HCV. Overall, 119 patients initiated DAA treatment at a median (IQR) of 1.8 (0.7–4.6) months after HCV diagnosis, including 31 patients who received SOF/VEL. The overall SVR12 rate was 90.7% (108/119) in the ITT population and 94.7% (108/114) in the PP population. SVR12 was achieved by 24/31 patients who received SOF/VEL; 3 had virologic failure (possible reinfections, n=2; bad adherence, n=1), and 3 were LTFU. Two patients had HCV GT 3 and were both treated with SOF/VEL: 1 patient achieved SVR12, and the other was LTFU.

Safety data were not reported.

Clinical Practice Guidelines

The inclusion of these guidelines should not be interpreted as a treatment recommendation or an endorsement of the guidelines by Gilead Sciences, Inc.

The AASLD/IDSA Recommendations for Testing, Managing, and Treating Hepatitis C, which includes recommendations regarding HCV/HIV co-infected patients, may be found at: https://www.hcvguidelines.org/.

The EASL Recommendations on Treatment of Hepatitis C, which includes guidance regarding HCV/HIV co-infected patients, may be found at: https://easl.eu/wp-content/uploads/2020/10/EASL-recommendations-on-treatment-of-hepatitis-C.pdf

References

1. Enclosed. Gilead Sciences Inc, EPCLUSA® (sofosbuvir and velpatasvir) tablets, for oral use. US Prescribing Information. Foster City, CA.
2. Wyles D, Brau N, Kottilil S, et al. Sofosbuvir and Velpatasvir for the Treatment of Hepatitis C Virus in Patients Coinfected with Human Immunodeficiency Virus Type 1: An Open-Label, Phase 3 Study. *Clin Infect Dis.* 2017;65(1):6-12.
3. Brau N, Wyles D, Kottili S, et al. Sofosbuvir/Velpatasvir for 12 Weeks in Patients Coinfected With HCV and HIV-1: The ASTRAL-5 Study [Presentation]. Paper presented at: International AIDS Society (IAS); 18-22 July, 2016; Durban, South Africa.
4. Lin W, Wang X, Zhang J, et al. A simple, feasible, efficient and safe treatment strategy of sofosbuvir/velpatasvir for chronic HCV/HIV-1 coinfected patients regardless of HCV genotypes: a multicenter, open-label study in China. *Lancet Reg Health West Pac.* 2023;36:100749.
5. Janjua NZ, Wong S, Yu A, et al. Effectiveness of Sofosbuvir / Velpatasvir in Treating Hepatitis C Virus Infection in Real-World Setting [Poster 608]. Paper presented at: AASLD; 09-13 November, 2018; San Francisco, CA.
6. Roman Lopez CG, Triana Gonzalez S, Cano Diaz AL, Lopez DDF, Mata Marin JA, Gaytan Martinez JE. Effectiveness of Direct Antiviral Agents in People with HCV-Monoinfection Compared to HCV/HIV Coinfection in a Real Life Setting. *Viruses.* 2024;16(11):1724. https://www.ncbi.nlm.nih.gov/pubmed/39599839
7. Gayam V, Tiongson B, Khalid M, et al. Sofosbuvir Based Regimens in the Treatment of Chronic Hepatitis C Genotype 1 Infection in African-American Patients: A Community-Based Retrospective Cohort Study. *Eur J Gastroenterol Hepatol.* 2018;30(10):1200-1207. https://www.ncbi.nlm.nih.gov/pubmed/30096090
8. Martin-Carbonero L, Gutierrez A, Bisbal O, et al. Recently acquired hepatitis C: Epidemiological characteristics and treatment response in a large cohort of MSM living with HIV in Madrid. *Enferm Infecc Microbiol Clin.* 2024;42(8):414-419. https://www.ncbi.nlm.nih.gov/pubmed/37945463
9. Enclosed, Gilead Sciences Inc. BIKTARVY® (bictegravir, emtricitabine, and tenofovir alafenamide) tablets, for oral use. US Prescribing Information. Foster City, CA.
10. Wyles D, Brau N, Naggie S, et al. SOF/VEL Single-Tablet Regimen in HCV Mono-Infected and HIV/HCV Co-Infected Patients: Comparison of Efficacy and Safety Data from Phase 3 Clinical Trials [Abstract]. Paper presented at: International Congress of Drug Therapy in HIV Infection 23-26 October 2016; Glasgow, United Kingdom.

Abbreviations

3TC=lamivudine
ABC=abacavir
AE=adverse event
ART=antiretroviral therapy
ARV=antiretroviral
ATV=atazanavir
BIC=bictegravir
CD4=cluster of differentiation 4

DAA=direct-acting antiviral
DRV=darunavir
DTG=dolutegravir
E/C/F/TAF=elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide
EOT=end of treatment
FIB-4=fibrosis 4 score
FTC=emtricitabine
GS-331007=predominant metabolite of SOF
GT=genotype
IDU=injection drug use
IFN=interferon
LPV=lopinavir
LTFU=lost to follow-up
MSM=men who have sex with men
NNRTI=non-nucleos(t)ide reverse transcriptase inhibitor
PEG=pegylated
PK=pharmacokinetic(s)
PP=per-protocol
PWH=people with HIV
RAL=raltegravir
RAS=resistance-associated substitution
RBV=ribavirin
RPV=rilpivirine
RTV=ritonavir
SOF=sofosbuvir
SVR=sustained virologic response
SVR12/24=SVR 12/24 weeks after end of treatment
TAF=tenofovir alafenamide
TDF=tenofovir disoproxil fumarate
TE=treatment-experienced
TN=treatment-naive
URTI=upper respiratory tract infection
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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Gilead Global Patient Safety ☎ 1-800-445-3235, option 3 or
🖱 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

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