GILEAD | Medical Information

Epclusa® (sofosbuvir/velpatasvir) Treatment Interruption/Adherence

This document is in response to your request for information regarding Epclusa® (sofosbuvir/velpatasvir [SOF/VEL]) and the effect of adherence on the achievement of sustained virologic response (SVR) in participants with HCV infection.

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]

Take SOF/VEL once daily with or without food for the duration recommended by the physician. It is important not to miss or skip doses.[1]

The median terminal half-lives of SOF and its primary circulating metabolite GS-331007 following administration of SOF/VEL were 0.5 and 25 hours, respectively. The median terminal half-life of VEL following administration of SOF/VEL was 15 hours.[1] Since drugs are generally eliminated in 3 to 5 half-lives,[2] approximately 4 to 6 days after stopping therapy, systemic levels of SOF, GS-331007, and VEL would be predicted to be very low. This can vary based on patient-specific parameters.

Clinical Studies on SOF/VEL Adherence and SVR

In a pooled, post hoc analysis of six phase 3 RCTs (ASTRAL-1 to -5 and POLARIS-4), the average SVR12 rate was 97.6% in participants with ≥80% adherence (N=1382) and 78.1% in participants with <80% adherence.[3]

In a pooled analysis of the ANCHOR and ASCEND studies (N=628), SVR was achieved by >75% of participants with imperfect DAA treatment adherence. Gaps ≤7 days and the timing of gaps were not associated with significant differences in SVR12 rates.[4]

In the HERO study of participants with active IDU, the overall SVR rate was 92.7% in the PP population, with a median adherence rate of 75%. The SVR rate among participants with >14 consecutive missed treatment days was 85.25%, compared with 96.9% among participants with <7 consecutive missed days.[5]

- In a secondary analysis of self-reported adherence and objective adherence, the SVR rate was 96% among participants with a self-reported overall adherence of 100% and an objective adherence of 83%. The SVR rate among those with ≥80% overall objective

adherence was 98%, compared with 89% among participants with <80% overall objective adherence.[6]

In the MINMON adherence analysis at Week 4, 96.5% of participants (n=355) with early optimal adherence (100% adherence) and 77.8% of participants (n=21) with early suboptimal adherence (<100% adherence) achieved SVR12 (*P*<0.001). The lowest rates of early optimal adherence were among participants <30 years of age (75% [24/32]), participants in the US (84% [108/128]), participants in Uganda (87% [13/15]), participants with ongoing psychoactive medication use (87% [52/60], and participants who reported active IDU (87% [13/15]).[7]

In the SIMPLIFY study, the overall SVR12 rate was 94% (97/103) in participants who reported recent IDU.[8] Missed doses (93% adherence) were not associated with significant differences in SVR12 rates (*P*=0.359).[9] Common AEs (≥10%) were fatigue, headache, and nausea.[8]

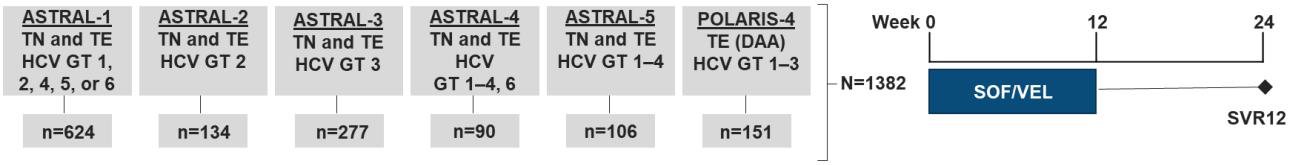
Clinical Studies on SOF/VEL Adherence and SVR

Post Hoc Analysis of ASTRAL-1 to -5 and POLARIS-4 RCTs[3]

Study design and demographics

A total of 1382 participants treated with SOF/VEL without RBV were included in a pooled, post hoc analysis of six phase 3 RCTs (ASTRAL-1 to -5 and POLARIS-4) that explored virologic suppression and the association of adherence with the on-treatment rate of HCV RNA undetectability during 12 weeks of SOF/VEL treatment. Participants reporting SOF/VEL adherence of ≥80% and ≥90% were evaluated, and pill counts were used to measure <80% adherence. The proportions of participants with HCV RNA less than the lower limit of quantitation (15 IU/mL) were pooled from Weeks 2, 4, 8, and 12, and SVR12 at Week 24 was reported as a weighted average.

Figure 1. Post Hoc Analysis: Study Designs of Phase 3 RCTs of SOF/VEL Without RBV[3]



Abbreviation: TE=treatment experienced.
Note: ASTRAL-4 included participants with decompensated cirrhosis; ASTRAL-5 included participants with HIV and HCV.

For the overall population, the mean ± SD) age was 54±3.3 years old, 65% were male, 26% had GT 3, 29% had cirrhosis, and 7% had decompensated cirrhosis.

Results

Rates of undetectable HCV RNA were 57.2% at Week 2, 90.3% at Week 4, 99.6% at Week 8, and 99.9% at Week 12.

Table 1. Post Hoc Analysis: Adherence and Associated SVR12 Rate[3]

Trial	N	Adherence ≥80%		Adherence <80%	
		%	SVR12 Rate, %	n	SVR12 Rate, %
ASTRAL-1	624	96.5	99.3	22	90.9
ASTRAL-2	134	97	100	4	75
ASTRAL-3	277	95.3	95.5	13	92.3
ASTRAL-4	90	92.2	86.7	7	28.6
ASTRAL-5	106	91.5	97.9	9	66.7
POLARIS-4	151	95.1	98.3	9	77.8
Total	1382	95.5	97.6	64	78.1

Pooled Analysis of Participants in the ANCHOR and ASCEND Studies

Study design and demographics

Data were pooled (N=628) from the ANCHOR study[10] and the ASCEND study[11] to evaluate the impact of non-adherence (frequency and timing) to DAA treatment including SOF/VEL on SVR. Participants who were treated for 12 weeks with ≥1 month of dispensed medication and had an available posttreatment SVR assessment were included in the analysis. Adherence was measured by the number of pill bottles that were dispensed (medication receipt), the number of days between the expected and actual receipt of pill bottles, (medication gap), and on-treatment detectable VL (defined as VL >1000 IU/mL at Week 4 or >100 IU/mL at Week 12).[4]

Study participants were a median of 59 years of age, 69% were male, and 94% were Black. Seventy percent of participants (n=440) had stable housing, 25% (n=160) had unstable housing, and 4% (n=28) had an unknown housing status. Current opioid and cocaine use was reported by 28% and 16% of participants, respectively. DAA treatments included LDV/SOF in 75% of participants (n=472), SOF/VEL in 15% (n=93), and EBR/GZR in 10% (n=63).[4]

Adherence[4]

A total of 570 participants (91%) received all 3 bottles of DAA treatment; 37% (n=211) had a medication gap of ≥1 day, with an overall median (range) gap of 7 (1–197) days. There was no association between medication receipt and gender, race, or substance use. Current cocaine (P=0.05) or opioid (P<0.001) use had a statistically significant association with on-treatment detectable VL; however, race, gender, and housing status did not.

Table 2. Pooled Data From ANCHOR and ASCEND: Adherence Results[4]

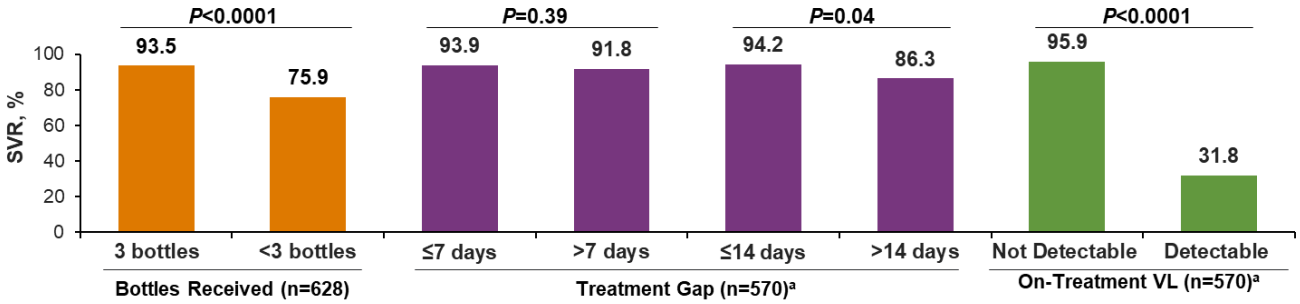
	n (%)
Medication receipt (N=628), 1/2/3 bottles	15 (2)/43 (7)/570 (91)
Medication gap (n=570),[a] no/any gap	359 (63)/211 (37)
Gap length, 1–6/>7/>14 days	92 (44)/78 (37)/41 (19)
Gap timing, between Months 1 and 2/between Months 2 and 3/between both	89 (42)/79 (37)/43 (20)
On-treatment detectable VL (n=570),[a,b] no/any detectable VL	545 (96)/22 (4)

[a]Only included participants who received 3 bottles of DAA.
[b]VL was not obtained for 3 of these participants.

Impact of adherence on SVR[4]

There was a significantly higher rate of SVR achievement for participants who received 3 bottles of DAA medication (*P*<0.0001), had a medication gap of ≤14 days (*P*=0.037), or had no detectable VL while on treatment (*P*<0.0001) than for participants who received <3 bottles, had a medication gap of >14 days, or had detectable VL while on treatment, respectively (Figure 2). Medication gaps of <7 days and the timing of medication gaps, however, were not associated with achievement of SVR. Overall, SVR was achieved by >75% of participants with imperfect DAA treatment adherence.

Figure 2. Pooled Data From ANCHOR and ASCEND: Impact of Adherence on SVR[4]



[a]Only included participants who received 3 bottles of DAA.

HERO Study

Study design and demographics

A pragmatic, randomized, multicenter study compared outcomes between two patient-centered treatment models for the treatment of HCV in participants with active IDU in the US.[5] Eligibility criteria included active IDU, with last use within 90 days of study enrollment; no prior DAA treatment; and current HCV infection and HCV VL test within the past 12 months. Participants in both arms received 12 weeks of SOF/VEL, and adherence was measured using electronic blister packs. Participants had monthly follow-ups for the 12 weeks of treatment, an SVR12 check at Week 24, and quarterly follow-ups thereafter until Week 168.[12] The primary and secondary outcomes were SVR (HCV RNA ≤15 IU/mL determined between 70 and 365 days after treatment completion) and adherence, respectively.[5]

A total of 755 participants were randomized, and 496 were included in the PP analysis (primary analysis population), which included those who were randomized, initiated treatment, did not cross over to a different treatment arm, and had available SVR12 outcomes. The mITT population included the 593 participants who initiated treatment and had data from ≥1 blister pack. The baseline demographics of participants in the PP population were the following: male, 72.6%; median (IQR) age, 42.6 (35.3–53.7) years; White race, 63.6%; non-Hispanic ethnicity, 77.2%; and stable housing, 51.7%.[5]

Efficacy and impact of adherence on SVR12

The SVR rates were 92.7% (460/496; 95% CI: 90.5–95%) in the PP population and 77.4% (461/593; 95% CI: 74.2–81%) in the mITT population, with overall median adherence rates of 75% and 70%, respectively. A higher number of total adherent days was significantly associated with SVR in the PP population (aOR=1.07; 95% CI: 1.04–1.1; *P*<0.001). The

SVR rate was ≥90% in the PP population with as few as 42/84 total adherent days (50%) and in the mITT population with ≥63/84 total adherent days.[5]

When the PP population was stratified by <50% and ≥50% adherence rates, among participants with <50% adherence, a greater number of total adherent days during Weeks 9 through 12 was significantly associated with SVR (aOR=1.15; 95% CI: 1.01–1.3). Among participants with <50% adherence in the mITT population, total adherent days (aOR=1.09; 95% CI: 1.04–1.15), total adherent days during Weeks 5 through 8 (aOR=1.12; 95% CI: 1.03–1.21), and total adherent days during Weeks 9 through 12 (aOR=1.12; 95% CI: 1.04–1.22) were significantly associated with SVR. Total adherent days were not significantly associated with SVR among participants with ≥50% adherence in either population.[5]

The number of consecutive missed treatment days was inversely associated with SVR in both the PP population (aOR=0.93; 95% CI: 0.91–0.96; *P*<0.001) and the mITT population (aOR=0.94; 95% CI: 0.92–0.95). In the PP population, the SVR rate was 85.25% among participants with >14 consecutive missed treatment days and 96.9% among those with <7 consecutive missed days (aOR=0.19; 95% CI: 0.07–0.55; *P*=0.02); in the mITT population, it was 58.9% among participants with >14 consecutive missed treatment days and 89.2% among those with <7 consecutive missed days (aOR=0.22; 95% CI: 0.13–0.39; *P*<0.001).[5]

Secondary analysis of self-reported adherence and objective adherence[6]

A secondary analysis was conducted that included all participants from the PP population who had data at all time points for objective and self-reported adherence (N=493) to examine the association of self-reported adherence (via a visual analog scale at Weeks 4, 8, and 12) and objectively measured adherence (using blister packs) with SVR.

A total of 203 participants (41%) reported an overall adherence of 100% for the 12-week treatment period; the mean ± SD objective adherence for that group was 83%±14%, with an SVR rate of 96%. Compared with participants with 100% overall self-reported adherence, the odds of achieving SVR were lower for those with <80% overall self-reported adherence (aOR=0.07; 95% CI: 0.02–0.24; *P*<0.001). The overall objective adherence was ≥80% for 222 participants (45%), and the SVR rate for that group was 98%, compared with 89% (240/271) among participants with <80% overall objective adherence. The odds of achieving SVR was higher among participants with overall objective adherence ≥80% than among those with <80% (aOR=5.91; 95% CI: 1.84–18.98; *P*=0.003).

MINMON Trial[7]

Study design and demographics

MINMON was a phase 4, open-label, international (Brazil, South Africa, Thailand, Uganda, and US) single-arm trial that evaluated the safety and efficacy of 12 weeks of SOF/VEL in TN adult participants (N=399) using the minimal monitoring strategy. Participants with and without HIV, with and without drug use, and without decompensated cirrhosis or active HBV infection were enrolled between October 2018 and July 2019. Participants were given all 84 SOF/VEL tablets in three 28-pill bottles, and the first dose taken was observed. Adherence and tolerability were assessed using a standardized questionnaire during treatment; adherence was self-reported at Week 4 and was stratified as either early optimal adherence (100% adherence, no missed doses) or early suboptimal adherence (<100%

adherence). At Week 24, participants reported the date they completed the 84-pill regimen, with timely treatment completion defined as finishing the regimen within 84±7 days.

Of the 400 participants who enrolled, 399 initiated treatment. The median (IQR) age was 47 (37–57) years, 35% were female at birth, 41% were co-infected with HIV, and 14% reported current drug use at baseline.

Results

Of the 395 participants who had follow-up data at Week 4, 368 (93%) reported early optimal adherence, and 355 (96.5%) of those with early optimal adherence achieved SVR12, compared with the 21/27 participants (77.8%) with early suboptimal adherence (P<0.001). Over the entire course of treatment, 334/346 participants (96.5%) with overall optimal adherence and 42/46 (91.3%) who reported overall suboptimal adherence achieved SVR12 (P=0.1).

The lowest rates of early optimal adherence were among participants <30 years of age (75% [24/32]), participants in the US (84% [108/128]), participants in Uganda (87% [13/15]), participants with ongoing psychoactive medication use (87% [52/60], and participants who reported active IDU (87% [13/15]). In a multivariate analysis, participants <30 years of age and participants in the US were factors that were independently associated with early suboptimal adherence.

Safety data were not reported.

SIMPLIFY Study

Study design and demographics[8]

SIMPLIFY was an open-label, multicenter, phase 4 study that assessed the efficacy and safety of SOF/VEL in 103 participants infected with HCV who reported IDU within 6 months. Eligible participants were ≥18 years of age, had HCV GTs 1 to 6, and were naive to NS5As; participants with HIV and/or decompensated liver disease were excluded. At each weekly visit, participants received a weekly supply of SOF/VEL (dosed daily) in an electronic blister pack with an integrated sensor grid for a 12-week course, were assessed for adherence (secondary endpoint), underwent HCV RNA VL testing and laboratory assessments, completed questionnaires and physical examinations, and reported AEs. SVR12 was assessed at Week 24.

Included participants were mostly male (72%) and had a median (IQR) age of 48 (41–53) years and an HCV RNA level of 6.1 (5.3–6.7) log IU/mL. GTs included GT 1a, 34%; GT 1b, 1%; GT 2, 5%; GT 3, 58%; and GT 4, 2%. Most participants had F0 to F1 liver disease (<7 kPa), 61%; 28% had F2 to F3 (7.1–12.49 kPa), and 9% had F4 (≥12.5 kPa). All participants reported drug use in the past 30 days; IDU and non-IDU were reported by 74% and 54%, respectively. IDU frequency in the past 30 days ranged from less than daily (48%) to at least daily (26%); 26% never used IV drugs in the past 30 days. Within the past 30 days, use of heroin, methamphetamine, opioids, cocaine, and other drugs was reported by 55%, 30%, 21%, 13%, and 7%, respectively. Sixty percent reported any alcohol use, and 17% reported hazardous alcohol use in the past 30 days. A total of 82% of participants reported a history of OST use; current OST use with methadone, buprenorphine + naloxone, and buprenorphine was reported by 44%, 12%, and 4% of participants, respectively. One hundred participants completed 12 weeks of treatment.

Efficacy[8]

The following factors did not affect SVR12: IDU within the past month at baseline, baseline frequency of recent IDU, baseline OST, ongoing IDU during HCV treatment, stable housing situation, liver fibrosis, and alcohol consumption frequency.

Participants were followed for a median (IQR) of 12 (12–24) weeks after treatment completion. The end-of-treatment response rate was 96% (99/103; 95% CI: 90–99%), and the SVR12 rate was 94% (97/103; 95% CI: 88–98%). Three participants did not complete treatment (2 were LTFU [1 following baseline and 1 at Week 8], and 1 died of a drug overdose at Week 3). Of the 100 participants who completed 12 weeks of SOF/VEL, 3 did not meet SVR12 (2 were LTFU [including 1 who did not have a final sample post treatment], and 1 participant who continued to inject morphine during treatment [non-viremic following SOF/VEL treatment but had recurrent viremia at Week 24] experienced HCV reinfection). No instances of virologic failure or relapse were noted.

Safety[8]

The most common AEs (≥10%) were fatigue (22%; n=23), headache (18%; n=19), and nausea (14%; n=14). One SAE of rhabdomyolysis was deemed to be possibly related to treatment and resolved. One death was due to illicit drug overdose and was deemed unrelated to treatment, and 1 participant discontinued treatment due to an AE.

Table 3. SIMPLIFY Study: Safety Outcomes[8]

Safety Outcomes, n (%)	SOF/VEL (N=103)
Experienced ≥1 AE	85 (83)
Grade 1–2/3/4[a]	78 (76)/6 (6)/1 (1)
Treatment-related AE	48 (47)
Grade 1–2/3/4[a]	47 (46)/1 (1)/0
SAEs	7 (7)

[a]AE occurred ≤28 days of last dose.

Adherence[9]

An analysis of adherence to SOF/VEL (≥90% of doses; overall, daily, and weekly), factors that led to adherence, consistency of dose timing, changes in adherence over the 12-week treatment course, and self-reported adherence compared with adherence measured with the electronic blister packs was conducted. Median (IQR) adherence rates for the following arms were noted: self-reported, 99% (98–100%); weekly blister pack, 98% (94–100%); daily blister pack, 94% (88–98%).

Table 4. SIMPLIFY Study: Additional Adherence Outcomes[9]

Outcomes	SOF/VEL (N=103)
Missed doses, none/1–4/5–8/9–17/≥18, %	12/35/19/17/17
Longest non-adherent episode,[a] 1/2/3/4/5/6/≥7 days, %	43/18/3/9/2/3/11
Dose timing consistency,[a] <120/≥120 to <240/≥240 minutes, n (%)	24 (24)/43 (42)/35 (34)
Reason for non-adherence,[b] forgot/inaccessible at time of dose/ lost pill/other, n (%)	54 (67)/14 (17)/ 7 (9)/6 (7)

[a]n=102 (participants with available blister pack data). [b]n=81.

SVR12 rates were not significantly different between participants with adherence <90% and those with adherence ≥90% (SVR12 of 94% for both; *P*=0.944) or between participants with missed doses and those without missed doses (93% vs 100%; *P*=0.359). SVR12 rates

differed significantly between participants who completed 12 weeks of SOF/VEL and those who did not complete the treatment course (97% vs 0%; *P*<0.001).

Overall, 32% of participants were considered non-adherent (<90% adherence); however, adherence did not appear to negatively affect SVR12. Factors associated with <90% adherence included baseline injection of stimulants within the past month (odds ratio: 2.77; *P*=0.019), stimulant injection during SOF/VEL treatment (aOR: 3.33; *P*=0.023), timing of dosing deviated by ≥240 minutes (aOR: 12.57; *P*<0.001), and late vs early study visits (aOR: 1.08; *P*<0.001). Factors associated with inconsistent dose administration (deviation by ≥240 minutes) included less than a high school education (aOR: 2.77; *P*=0.025) and recent injection of stimulants (aOR: 2.43; *P*=0.048).

Guideline Recommendations on SOF/VEL and Treatment Interruptions

AASLD/IDSA: Management of Treatment Interruptions

The following recommendations are applicable to TN patients with or without compensated cirrhosis who are receiving either SOF/VEL or glecaprevir/pibrentasvir. The recommendations are the opinion of the AASLD/IDSA HCV Treatment Guidance Panel and are based in large part on SOF/VEL data (see SIMPLIFY above). The recommendations can be found here: https://www.hcvguidelines.org/evaluate/monitoring#incomplete-adherence.[13]

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Abbreviations

AASLD=American Association for the Study of Liver Disease
AE=adverse event
aOR=adjusted odds ratio
DAA=direct-acting antiviral
EBR=elbasvir
GT=genotype
GZR=grazoprevir
HERO=Hepatitis C Real Options
IDSA=Infectious Disease Society of America
IDU=injection drug use
LDV=ledipasvir
LTFU=lost to follow-up
MINMON=minimal monitoring
mITT=modified intent-to-treat
OST=opioid substitution therapy
PP=per protocol
RBV=ribavirin
RCT=randomized controlled trial
SAE=serious adverse event
SOF=sofosbuvir
SVR=sustained virologic response
SVR12=SVR 12 weeks after end of treatment
TN=treatment-naive
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: 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
🖱 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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