Is SVR4 Testing an Acceptable Alternative Measure of HCV Cure in Re-Treated Patients Following DAA Failure? An SVR4/12 Concordance Evaluation From the POLARIS Clinical Trials

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Conclusions

- High concordance between sustained virologic response (SVR) at 4 weeks posttreatment (SVR4) and at 12 weeks posttreatment (SVR12) was observed in patients with hepatitis C virus (HCV) infection treated with sofosbuvir/velpatasvir/voxilaprevir (SOF/VEL/VOX) in the Phase 3 POLARIS studies
- SVR4 was highly predictive of HCV cure regardless of SOF/VEL/VOX treatment duration (8 weeks or 12 weeks) or prior direct-acting antiviral (DAA) treatment, supporting the use of SVR4 as a predictor of long-term SVR for patients treated with SOF/VEL/VOX
- Adoption of SVR4 as a measure of HCV cure will simplify the care cascade and may reduce patient loss to follow-up

Plain Language Summary

- Infection with hepatitis C virus causes liver damage and can lead to serious complications, such as liver cancer
- Hepatitis C virus infection is curable with direct-acting antiviral therapies, such as the combination treatment sofosbuvir/velpatasvir/voxilaprevir
- In this study, nearly all patients who were treated with this medication were free of hepatitis C at 4 weeks after completing treatment. Testing done at 12 weeks after treatment showed they were still cured

References: **1.** World Health Organization. Hepatitis C. 2021. Accessed September 16, 2025. https://www.who.int/news-room/fact-sheets/detail/hepatitis-c. **2.** Martinello M, et al. *Lancet*. 2023;402:1085-96. **3.** American Association for the Study of Liver Diseases and the Infectious Diseases Society of America. HCV guidance: recommendations for testing, managing, and treating hepatitis C. 2023. Accessed September 17, 2025. https://www.hcvguidelines.org/sites/default/files/full-guidance-pdf/AASLD-IDSA_HCVGuidance_December_19_2023.pdf. **4.** European Association for the Study of the Liver. EASL recommendations on treatment of hepatitis C: final update of the series. *J Hepatol*. 2020;73:1170-218. **5.** American Association for the Study of Liver Diseases and the Infectious Diseases Society of America. Hepatitis C test and treat initial visit. 2025. Accessed September 17, 2025. https://www.hcvguidelines.org/sites/default/files/full-guidance-pdf/HCV%20Test%20and%20Treat%20Final%20011725.pdf. **6.** Aronsohn A. AASLD/IDSA guidance update: new SVR guidance and test and treat algorithm. Oral presentation at: AASLD, The Liver Meeting; November 15–19, 2024; San Diego, CA, USA. **7.** Bourlière M, et al. *N Engl J Med*. 2017;376:2134-46. **8.** Jacobson I, et al. *Gastroenterology*. 2017;153:113-22.

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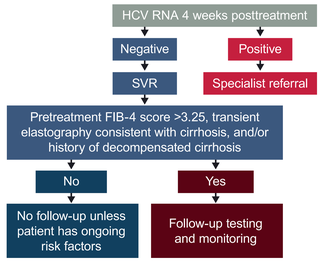
Disclosures: Conflict of interest disclosures may be viewed using the QR code at the top right.

Introduction

- Approximately 50 million people worldwide have chronic HCV infection, which can lead to cirrhosis, decompensated liver disease, and hepatocellular carcinoma[1,2]
- Guidance from the American Association for the Study of Liver Diseases and the Infectious Diseases Society of America (AASLD-IDSA) and the European Association for the Study of the Liver (EASL) have endorsed treatment simplification as part of a global call to action for HCV elimination[3,4]
- Within this simplification strategy, the AASLD-IDSA has recently developed a new algorithm, Hepatitis C Point of Care Test and Treat, in which SVR4 is an acceptable alternative measure of HCV cure for people without cirrhosis or prior DAA exposure[3,5,6]
- We hypothesize that SVR4 could also apply to vulnerable patients with prior DAA exposure, potentially helping to reduce the risk of patients being lost to follow-up
- To investigate this, we evaluated the concordance between SVR4 and SVR12 in the POLARIS-1, -2, -3, and -4 studies. These studies included patients for whom previous DAA treatment failed[7,8]

AASLD-IDSA Hepatitis C Test and Treat Follow-Up Visit Flow Chart



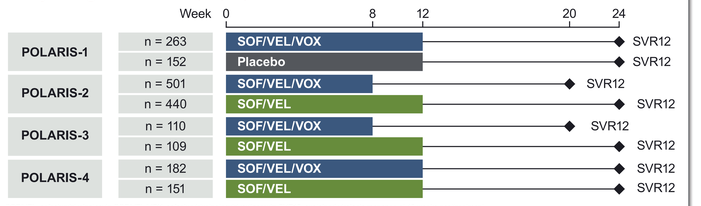
AASLD-IDSA, American Association for the Study of Liver Diseases and the Infectious Diseases Society of America; FIB-4, Fibrosis-4; HCV, hepatitis C virus; SVR, sustained virologic response.

Objectives

- To evaluate the concordance between SVR4 and SVR12 in patients who received SOF/VEL/VOX in the POLARIS-1, -2, -3, or -4 studies and assess the predictive value of SVR4 for HCV cure among patients treated with SOF/VEL/VOX with or without previous DAA exposure

Methods

Study Design: POLARIS-1, -2, -3, and -4



SOF/VEL, sofosbuvir/velpatasvir; SOF/VEL/VOX, sofosbuvir/velpatasvir/voxilaprevir; SVR12, sustained virologic response at 12 weeks posttreatment.

- Patients in this analysis were enrolled in any one of four Phase 3 studies evaluating treatment with SOF/VEL/VOX for 8 or 12 weeks
  - POLARIS-1: double-blind, randomized, placebo-controlled trial; NS5A inhibitor–experienced patients with HCV genotypes 1–6
  - POLARIS-2: open-label, randomized, active-comparator trial; DAA-naïve patients with HCV genotypes 1–6 with or without compensated cirrhosis
  - POLARIS-3: open-label, randomized, active-comparator trial; DAA-naïve patients with HCV genotype 3, all of whom had cirrhosis
  - POLARIS-4: open-label, randomized, active-comparator trial; DAA-experienced, NS5A inhibitor–naïve patients with HCV genotypes 1–6
- HCV RNA data were evaluated
- SVR was defined as a result of HCV RNA less than the lower limit of quantitation (15 IU/mL) using the COBAS TaqMan HCV Test v2.0
- Only patients with both SVR4 and SVR12 data were included in the concordance analysis

Results

Baseline Demographics and Disease Characteristics of All Patients Who Received SOF/VEL/VOX in the POLARIS Studies

	SOF/VEL/VOX, 8 Weeks N = 611	SOF/VEL/VOX, 12 Weeks N = 445
Age, y, mean (SD)	53 (10.7)	58 (8.7)
Sex, n (%)		
Male	329 (54)	343 (77)
Female	282 (46)	102 (23)
Race, n (%)		
Asian	59 (10)	10 (2)
Black or African American	48 (8)	54 (12)
White	491 (80)	371 (83)
Hispanic, n (%)	41 (7)	34 (8)
Region, n (%)		
US	333 (55)	236 (53)
Non-US	278 (46)	209 (47)
HCV GT, n (%)		
GT1	233 (38)	228 (51)
GT2	63 (10)	36 (8)
GT3	202 (33)	132 (30)
GT4	63 (10)	41 (9)
GT5	18 (3)	1 (<1)
GT6	30 (5)	6 (1)
BMI, kg/m², mean (SD)	27.2 (5.68)	28.8 (5.49)
Cirrhosis, n (%)	200 (33)	205 (46)
HCV RNA, log_{10} IU/mL, mean (SD)	6.1 (0.76)	6.3 (0.63)
ALT, U/L, mean (SD)	74 (60.8)	87 (69.2)

ALT, alanine aminotransferase; BMI, body mass index; GT, genotype; HCV, hepatitis C virus; SOF/VEL/VOX, sofosbuvir/velpatasvir/voxilaprevir; y, year.

- Most patients who received SOF/VEL/VOX in the POLARIS studies were White (862/1056, 82%) and male (672/1056, 64%)
- Most patients had HCV genotype 1 (461/1056, 44%) or genotype 3 (334/1056, 32%)
- A greater proportion of patients who received 12 weeks of SOF/VEL/VOX in POLARIS-1 and -4 (205/445, 46%) had cirrhosis at baseline compared with patients who received 8 weeks of treatment (200/611, 33%) in the POLARIS-2 and -3 studies

SVR4 and SVR12 With SOF/VEL/VOX in the POLARIS Studies

	POLARIS-1 N = 263	POLARIS-2 N = 501	POLARIS-3 N = 110	POLARIS-4 N = 182	Total N = 1056
SVR4, n (%)	257 (98)	483 (96)	107 (97)	179 (98)	1026 (97)
SVR12, n (%)	253 (96)	477 (95)	106 (96)	178 (98)	1014 (96)

SOF/VEL/VOX, sofosbuvir/velpatasvir/voxilaprevir; SVR4, sustained virologic response at 4 weeks posttreatment; SVR12, sustained virologic response at 12 weeks posttreatment.

- Overall, 1056 patients who received SOF/VEL/VOX in the POLARIS studies were evaluated for SVR4 and SVR12
  - 611 received 8 weeks of SOF/VEL/VOX in POLARIS-2 and -3
  - 445 received 12 weeks of SOF/VEL/VOX in POLARIS-1 and -4
- At least 96% of patients in each study achieved SVR4; 1026 (97%) patients across all the studies achieved SVR4
- At least 95% of patients in each study achieved SVR12; 1014 (96%) patients across all the studies achieved SVR12

Concordance of SVR4 and SVR12 in the POLARIS Studies

All Patients With Observed SVR4 and SVR12 Data Who Received SOF/VEL/VOX in the POLARIS Studies

	SVR12 Achieved, n	SVR12 Failed, n	PPV, NPV
SVR4 Achieved, n	1001	8	99.2% PPV
SVR4 Failed, n	0	23	100% NPV
Sensitivity, Specificity	100% Sensitivity	74.2% Specificity	

Only patients with both observed SVR4 and SVR12 data available (n = 1032) were included in the concordance analysis; there was no imputation of missing data.
NPV, negative predictive value; PPV, positive predictive value; SOF/VEL/VOX, sofosbuvir/velpatasvir/voxilaprevir; SVR4, sustained virologic response at 4 weeks posttreatment; SVR12, sustained virologic response at 12 weeks posttreatment.

- Of the 1009 patients who achieved SVR4, 1001 also achieved SVR12, yielding a positive predictive value (PPV) of 99.2% for SVR4 in predicting SVR12
  - 8 (0.8%) patients who achieved SVR4 experienced relapse by the SVR12 time point
- Among the 23 patients who did not achieve SVR4, none achieved SVR12, resulting in a negative predictive value (NPV) of 100% for SVR4 in predicting SVR12
- Sensitivity, defined as the ability of SVR4 to correctly identify patients who will also achieve SVR12 (i.e., true positives), was 100% (1001/1001)
- Specificity, defined as the ability of SVR4 to correctly identify patients who will not achieve SVR12 (i.e., true negatives), was 74.2% (23/31)

Concordance of SVR4 and SVR12 in the POLARIS Studies by Duration of SOF/VEL/VOX Treatment

8 Weeks of SOF/VEL/VOX Treatment in POLARIS-2 and -3

	SVR12 Achieved, n	SVR12 Failed, n	PPV, NPV
SVR4 Achieved, n	575	5	99.1% PPV
SVR4 Failed, n	0	18	100% NPV
Sensitivity, Specificity	100% Sensitivity	78.3% Specificity	

12 Weeks of SOF/VEL/VOX Treatment in POLARIS-1 and -4

	SVR12 Achieved, n	SVR12 Failed, n	PPV, NPV
SVR4 Achieved, n	426	3	99.3% PPV
SVR4 Failed, n	0	5	100% NPV
Sensitivity, Specificity	100% Sensitivity	62.5% Specificity	

Only patients with both observed SVR4 and SVR12 data available (n = 1032) were included in the concordance analysis; there was no imputation of missing data.
NPV, negative predictive value; PPV, positive predictive value; SOF/VEL/VOX, sofosbuvir/velpatasvir/voxilaprevir; SVR4, sustained virologic response at 4 weeks posttreatment; SVR12, sustained virologic response at 12 weeks posttreatment.

- In POLARIS-2 and -3, in which DAA-naïve patients received 8 weeks of SOF/VEL/VOX treatment, 575 (96%) patients achieved both SVR4 and SVR12
- In POLARIS-1 and -4, in which DAA-experienced patients received 12 weeks of SOF/VEL/VOX treatment, 426 (98%) patients achieved both SVR4 and SVR12
- The PPV and NPV of SVR4 for predicting SVR12 as well as the sensitivity were similar between patients who received 8 or 12 weeks of SOF/VEL/VOX treatment

Viral Relapse in Patients With Observed SVR4 and SVR12 Data in the POLARIS Studies

	SOF/VEL/VOX, 8 Weeks N = 23	SOF/VEL/VOX, 12 Weeks N = 8
SVR4, n (%)	5 (22)	3 (38)
SVR12, n (%)	0 (0)	0 (0)
Sex, n (%)		
Male	16 (70)	7 (88)
Female	7 (30)	1 (13)
HCV GT, n (%)		
GT1	16 (70)	3 (38)
GT2	2 (9)	0 (0)
GT3	2 (9)	4 (50)
GT4	2 (9)	1 (13)
GT5	1 (4)	0 (0)
GT6	0 (0)	0 (0)
Cirrhosis, n (%)	9 (39)	8 (100)
Prior HCV treatment, n (%)		
PegIFN + RBV	8 (35)	0 (0)
DAA(s) with or without other treatment	0 (0)	8 (100)
Treatment-naïve	15 (65)	0 (0)

DAA, direct-acting antiviral; GT, genotype; HCV, hepatitis C virus; PegIFN + RBV, pegylated interferon and ribavirin; SOF/VEL/VOX, sofosbuvir/velpatasvir/voxilaprevir; SVR4, sustained virologic response at 4 weeks posttreatment; SVR12, sustained virologic response at 12 weeks posttreatment.

- In total, 31 patients experienced viral relapse, and only 8 (26%) of these achieved SVR4
- Most patients who experienced relapse were male (23/31, 74%) and had HCV genotype 1 (19/31, 61%) and cirrhosis (17/31, 55%)
- Slightly over half (16/31, 52%) of patients who relapsed had received prior HCV treatment