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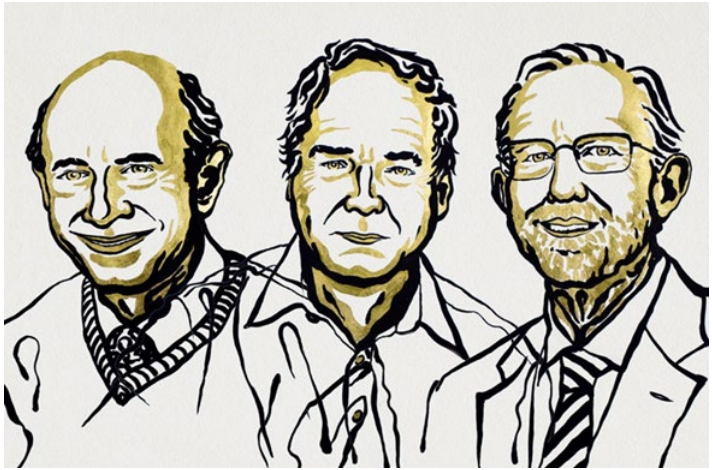
LIFE CHANGING MEDICINE

2024 UPMC Annual Update in Medical Hepatology

Hepatitis B; Hepatitis C – Management Dilemmas

Kapil Chopra, MD
Professor Of Medicine

2020: Nobel Prize in Medicine - Hepatitis C



Harvey Alter, MD, Michael Houghton, Ph.D., Charles Rice, Ph.D.

Awarded to three scientists who made a pivotal contribution to the discovery of the **hepatitis C virus**

Hepatitis B (D)

Hepatitis B - Pregnancy

Early vs Late Postpartum Cessation of TDF Initiated for Prevention of Vertical HBV Transmission

- Single-center prospective study of pregnant women with chronic HBV infection in large, tertiary care center in Shenzhen, China, with >6000 births annually
- HBV prevalence among mothers: 6.04%
- Inclusion criteria: HBsAg confirmed at antenatal test, HBV DNA >200,000 IU/mL, normal LFT, treatment naive

- TDF started at 24-28 wk of pregnancy if HBV DNA >200,000 IU/mL
- TDF treatment discontinued at delivery (early withdrawal) or ≥4 wk after delivery (late withdrawal)
- Primary outcome: viral rebound defined as >1 log increase in HBV DNA after TDF treatment cessation

Mak. AASLD 2023. Abstr 59

Early vs Late Postpartum Cessation of TDF Initiated for Prevention of Vertical HBV Transmission

No cases of vertical HBV

Birth Outcome	Live Births
Male sex, %	53
Birth before 37 wk of gestation, n/N (%)	18/326 (5.5)
Birth weight <2.5 kg, n/N (%)	14/326 (4.3)
APGAR score ≥9, n (%)	310/326 (95.1)
HBsAg+, n/N	0/299
Anti-HBc+, n/N (%)	69/299 (23.1)
Anti-HBs ≥10 IU/L, n/N (%)	295/299 (98.7)
Anti-HBs ≥1000 IU/L, n/N (%)	98/299 (32.8)

No significant difference in TDF retreatment based on time of TDF withdrawal (log-rank *P* = .087)

Early vs Late Postpartum Cessation of TDF Initiated for Prevention of Vertical HBV Transmission

- In single-center prospective study of pregnant women with chronic HBV infection initiating TDF to prevent vertical HBV transmission, no significant difference in viral rebound or clinical relapse rates with early (at delivery) vs late (≥4 wk after delivery) postpartum TDF withdrawal

No significant difference in viral rebound or clinical relapse rates with early vs late postpartum TDF withdrawal

Hepatitis B - Hepatocellular Carcinoma; Mortality: TDF vs ETV

Kaiser Permanente Northern California: HCC or Death With TDF vs ETV for Chronic Hepatitis B

- Kaiser Permanente Northern California: large HMO with ~4 million insured, deemed representative of insured Americans (no income extremes)
- Retrospective chart study of HCC or death in persons with HBV infection
- Included adults with chronic HBV infection treated with TDF or ETV for ≥1 yr between 2006 and 2021 with >90% adherence by on-time prescription refills

Seo. AASLD 2023. Abstr 64.

Kaiser Permanente Northern California: HCC or Death With TDF vs ETV for Chronic Hepatitis B

- Evaluated overall TDF and ETV cohort as well as 1:1 propensity score–matched TDF and ETV cohort to adjust for cohort differences
- Propensity score matched by age, sex, race/ethnicity, BMI, DM, hyperlipidemia, HTN, alcohol abuse, cirrhosis, HIV, serum creatinine, previous 3TC, HBV DNA, HBeAg, HBeAb

Kaiser Permanente Northern California: HCC Screening Adherence and Viral Breakthrough With TDF vs ETV

- In overall cohort (N = 3368), those treated with ETV (n = 2342) had significantly higher rates of DM, hyperlipidemia, HTN, and cirrhosis at baseline vs TDF (n = 1026)

- PS-matched cohort: n = 1938 (ETV, n = 969; TDF, n = 969)

- In both overall and PS-matched cohorts, HCC screening adherence was higher with ETV vs TDF and viral breakthrough rates were similar with ETV and TDF

Kaiser Permanente Northern California: HCC and All-Cause Mortality With TDF vs ETV

Outcome	HR for TDF vs ETV (95% CI)	*P* Value
HCC		
▪ Unadjusted model	0.61 (0.40-0.93)	.020
▪ Adjusted model*	0.81 (0.52-1.26)	.348
▪ PS-matched model	0.80 (0.41-1.54)	.506
All-cause mortality		
▪ Unadjusted model	0.60 (0.43-0.85)	.004
▪ Adjusted model*	0.56 (0.38-0.84)	.005
▪ PS-matched model	0.72 (0.42-1.23)	.227

*Adjusted and PS models controlled for baseline age, sex, race/ethnicity, DM, BMI, hyperlipidemia, HTN, alcohol abuse, HIV, cirrhosis, previous 3TC, creatinine, HBV DNA, HBeAg status, HBeAb status.

In PS-matched cohort, no significant difference in HCC or all-cause mortality between TDF and ETV
(matched by age, sex, race/ethnicity, BMI, DM, hyperlipidemia, HTN, alcohol abuse, cirrhosis, HIV, serum creatinine, previous 3TC, HBV DNA, HBeAg, HBeAb)

Hepatitis B – “Gray Zone”

HBV Guidelines: Treatment Indications

Criteria	AASLD[1] 2018	APASL[2] 2016	EASL[3] 2017	
HBeAg Positive				
HBV DNA, IU/mL	>20,000	>20,000	>20,000	>2000
ALT	≥2x ULN	≥2x ULN	>2x ULN	>ULN
Liver biopsy				≥ moderate necroinflammation ± fibrosis
HBeAg Negative				
HBV DNA, IU/mL	>2000	>20,000	>20,000	>2000
ALT	≥2x ULN	≥2x ULN	>2x ULN	>ULN
Liver biopsy				≥ moderate necroinflammation ± fibrosis

1. Terrault. Hepatology 2018;67:1560. 2. Sarin. Hepatol Int 2016;10:1. 3. EASL. J Hepatol 2017; 67:370.

Missed HBV Treatment Opportunities

- Suboptimal HBV treatment uptake
- Complexity of treatment criteria and clinical monitoring
- Conflicting recommendations between guidelines
- Large portion of patients left uncategorized and considered to be in the "gray zone"

  - **Indeterminate phase** where **HBV DNA or ALT levels are borderline** between inactive CHB and immunoreactive
  - **~75% of patients** in the "gray zone" are **HBeAg negative**

Tétrault. Hepatology 2018;67:1560. Wong. Clin Infect Dis. 2023;76:e791. Yao. J Viral Hepat. 2021;28:1025.

WHO HBV Guidelines: Anticipated Changes

- Expanded treatment criteria
- Updated treatment indications for non-cirrhotic patients
- Possible expansion in HBeAg-positive patients (immune tolerant)
- Address treatment criteria for HBeAg negative patients in the "gray zone" (borderline HBV DNA or ALT levels)

Lee. Clin Mol Hepatol. 2023;29:825.
who.int/news/item/29-04-2023-who-announces-the-update-of-hepatitis-b-guidelines-on-testing-and-treatment.

Antiviral Treatment in Patients With CHB in the Indeterminate Phase

- Retrospective cohort study of 855 treatment-naive patients with CHB without advanced fibrosis in the indeterminate phase from 14 centers (US, Europe, and Asia)
- Indeterminate phase: not meeting standard criteria for immune tolerant, immune-active, or inactive CHB
- Baseline characteristics balanced by inverse probability of treatment weighting

- 10-yr HCC risk:
- No antiviral therapy: 15%
- Antiviral therapy: 4%

Antiviral therapy reduced HCC risk by 70%

Huang. Hepatology. 2023;78:1558.

Hepatitis B – "Gray Zone"

- Large portion of patients with CHB left uncategorized, in the "gray zone"
- Gray zone: HBV DNA or ALT levels borderline between inactive CHB and immunoreactive
- ~75% of patients in the "gray zone" are HBeAg negative
- Many patients with negative HBeAg and HBV DNA <2000 IU/mL have significant histologic disease and subsequently increased risk of HCC1-3
- In gray zone patients, antiviral therapy has histologic benefits by reducing fibrosis and necroinflammation progression
- ATTENTION trial: antiviral therapy reduced liver-related clinical events of patients in gray zone

Expanding indications for treatment of HBV would benefit more patients by **reducing risk of HCC**

1. Deng. Zhonghua Gan Zang Bing Za Zhi. 2020;28:1013. 2. Sheng. J Clin Transl Hepatol. 2022;10:972.
3. Wang. Aliment Pharmacol Ther. 2023;57:464. 4. Teng. Hepatol Int. 2021;15:1421. 5. Lim. AASLD 2022. Abstr 1162.

Hepatitis B – “Functional Cure”

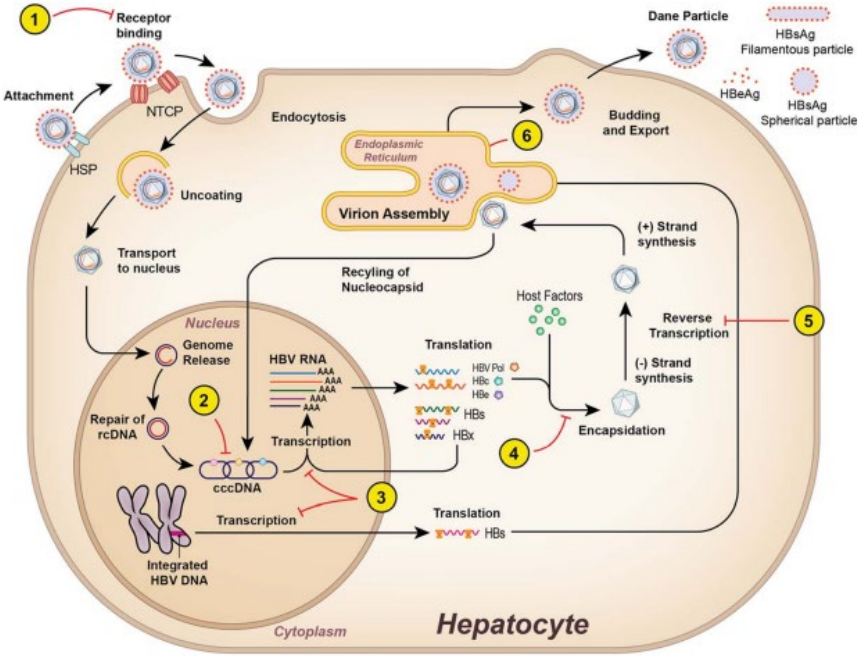
Definitions

- “Functional” cure, defined as sustained HBsAg loss and HBV DNA less than the lower limit of quantitation(LLOQ) 24 weeks off-treatment

- “Partial cure”defined as sustained HBsAg level < 100 IU/mL and HBV DNA < LLOQ24 weeks off-treatment

Marc Ghany et al. *Hepatology*. 2023;78:1654–1673

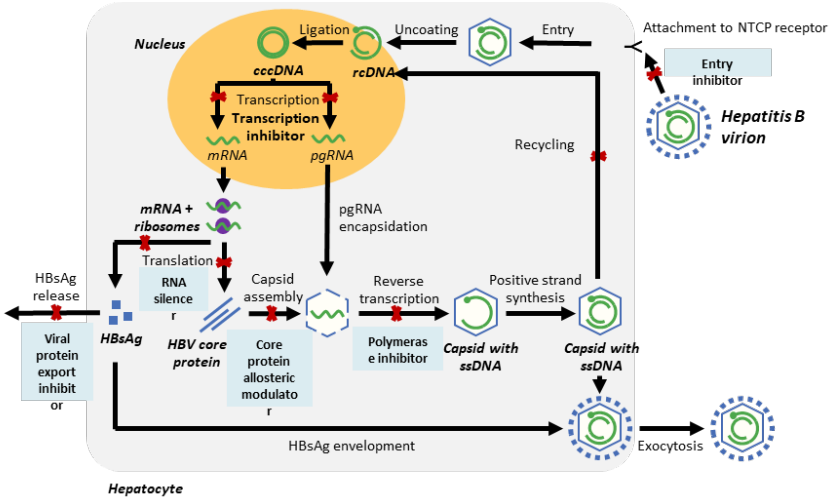
HBV life cycle and drug targets



Marc Ghany et al. *Hepatology*. 2023;78:1654–1673

HBV Treatment Pipeline

Potential Strategies to Achieve Functional Cure



Replication inhibition	±	Antigen reduction	±	Immune modulation
Entry inhibitor: Bulevirtide **HBV polymerase:** HS-10234 **Capsid inhibitors:** GLS4, Canocapavir, EDP-514, ABI-H3733, ALG-000184, ABI-4334		**HBsAg release:** REP 2139 **ASO:** Bepirovirsen **siRNAs:** JNJ-3989, VIR-2218, RG6346, AB-729, ALG-125755		**Immune invigoration:** Selgantolimod, RG7854, Envafolimab **Immune stimulation:** Hep Tcell, TG-1050/T101, GSK3528869A, VTP300 **mAb against HBV:** VIR-3434

1. Hui. Expert Opin Emerg Drugs. 2022;27(2):127.
2. Feld. Clin Gastroenterol Hepatol. 2023;21(8):2040.

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Hepatitis D

AASLD Recommendations for HDV Testing in Clinical Practice

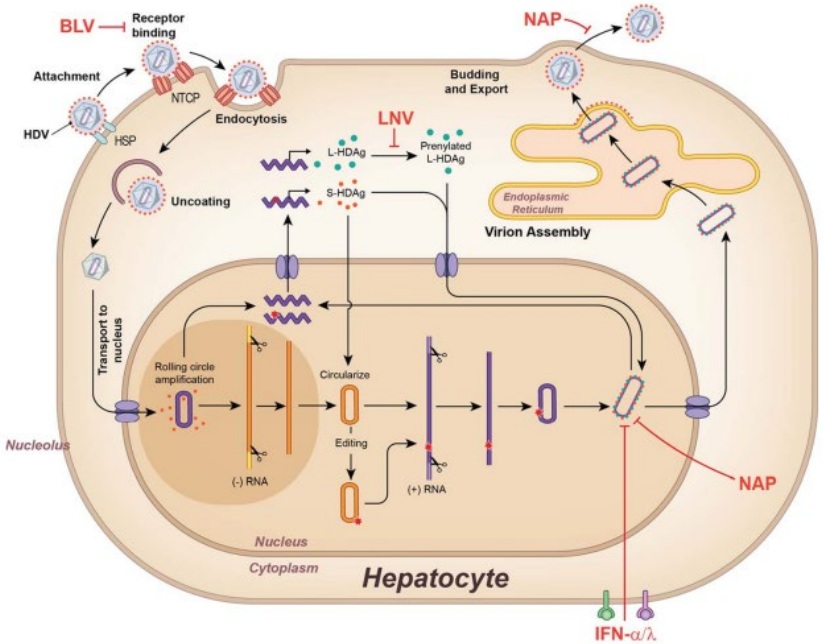
HBsAg-positive persons at high risk for HDV infection who should be screened

- Persons born in regions with reported high HDV endemically, such as:
- Africa (West Africa, Horn of Africa)
- Asia (Central and Northern Asia, Vietnam, Mongolia, Pakistan, Japan, Taiwan)
- Middle East (all countries)
- Eastern Europe (Eastern Mediterranean regions, Turkey)
- South America (Amazonian basin)
- Persons who have ever injected drugs
- MSM
- Individuals infected with HCV or HIV
- Persons with multiple sexual partners or any history of sexually transmitted disease
- Individuals with elevated ALT or AST with low or undetectable HBV DNA

HDV Testing: Comparison of Guidelines

Guideline	Whom to Test	How to Test
AASLD 2018[1]	▪ HBsAg+ patients with HDV risk factors ▪ Low/undetectable HBV DNA and high ALT	▪ Anti-HDV ▪ HDV RN
EASL 2017[2]	▪ All patients infected with HBV	▪ Not specified
APASL 2016[3]	▪ Patients with chronic HBV and chronic liver disease	▪ HDAg or anti-HDV ▪ HDV RNA
WHO 2015[4]	▪ Not specified	▪ Anti-HDV ▪ HDV RNA

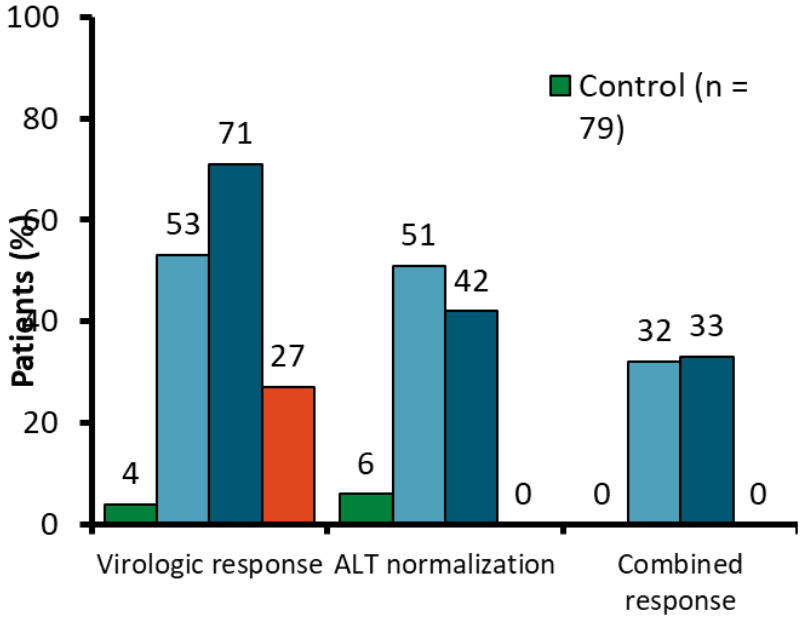
HDV life cycle and drug targets



Marc Ghany et al. *Hepatology*. 2023;78:1654–1673

Bulevirtide Monotherapy in HDV

- Pooled analysis of 2 phase II and 1 phase III, randomized, open-label trials
- 4 comparator groups: BLV 2 mg, BLV 10 mg, pegIFN-α, and control (placebo)
- Primary outcome: combined response at 24 wk
- ALT normalization and virologic response (ie, undetectable HDV RNA or a decrease in ≥2 log10 IU/mL from baseline)



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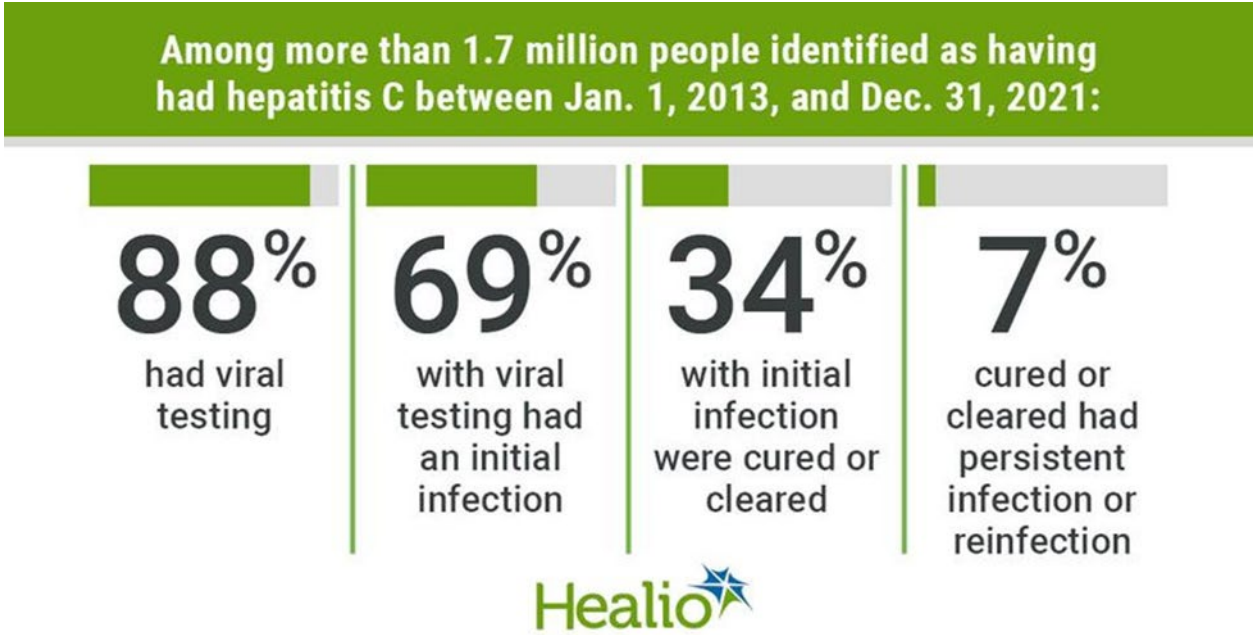
Hepatitis C

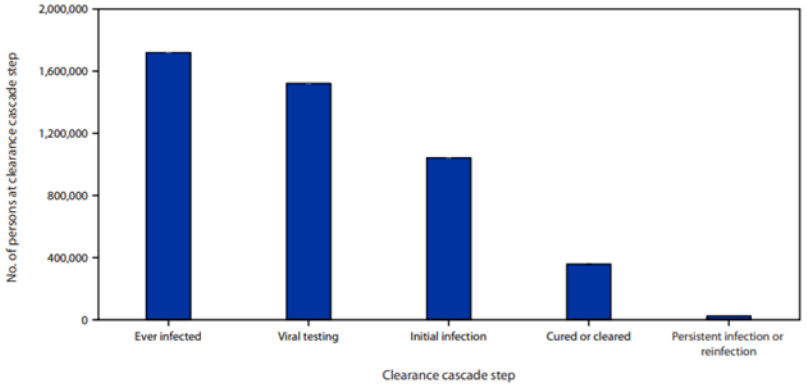
Hepatitis C: Access To Care

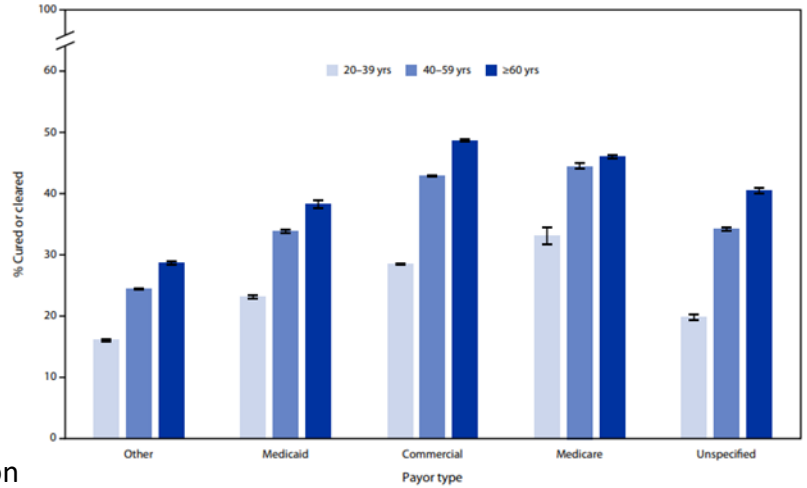
Hepatitis C cure rates ‘jarringly low’ as many lack access to treatment



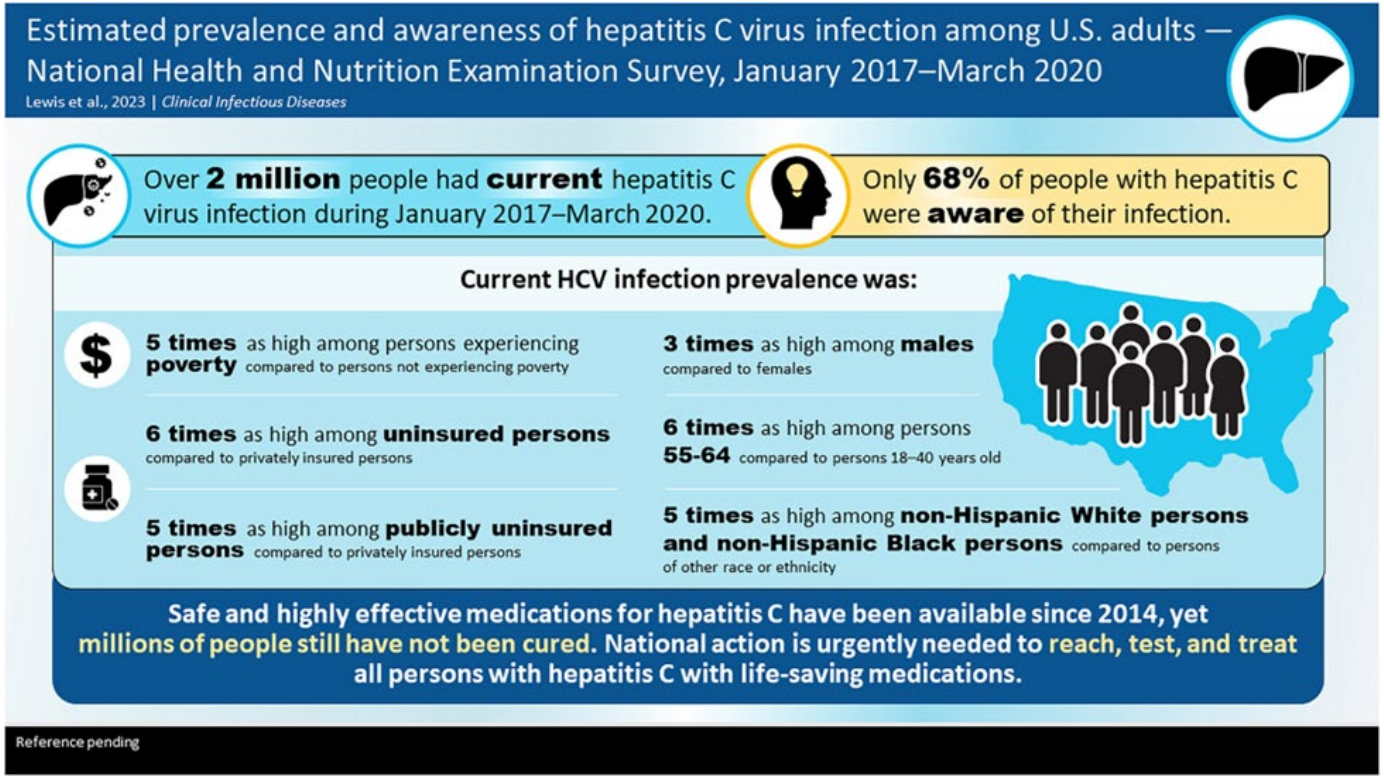
Hepatitis C Virus Clearance Cascade — United States, 2013–2022

An analysis of the HCV clearance cascade using 2013–2022 national HCV testing data found that the prevalence of viral clearance among persons with diagnosed hepatitis C was only 34% overall and was even lower (16%) among persons aged 20–39 years with other payor (client or self-pay) insurance





Carolyn Wester, MD et al. Centers for Disease Control and Prevention
MMWR | June 30, 2023 | Vol. 72 | No. 26



Clin Infect Dis, Volume 77, Issue 10, 15 November 2023,
Pages 1413–1415, https://doi.org/10.1093/cid/ciad411

National Strategic Plan

- The Viral Hepatitis National Strategic Plan for the United States calls for ≥80% of persons with hepatitis C to achieve viral clearance by 2030

HCV Decompensated Cirrhosis: Direct-Acting Anitvirals

HCV: Decompensated Cirrhosis DAA Therapy

Recommended for All Patients With HCV Infection Who Have Decompensated Cirrhosis	
RECOMMENDED	RATING
Patients with HCV infection who have decompensated cirrhosis—moderate or severe hepatic impairment, ie, Child-Turcotte-Pugh (CTP) class B or class C—should be referred to a medical practitioner with expertise in that condition, ideally in a liver transplant center.	I, C

https://www.hcvguidelines.org/unique-populations/decompensated-cirrhosis

HCV: Decompensated Cirrhosis DAA Therapy

- Improvement in clinical and biochemical indicators of liver disease between baseline and posttreatment week 12, including patients with CTP class C cirrhosis. **Improvements - insufficient to avoid liver-related death or the need for liver transplantation**

- Predictors of improvement or decline have not been clearly identified, patients with a **Model for End-Stage Liver Disease (MELD) score >20 or severe portal hypertension complications** may be less likely to improve and might be better served by transplantation than antiviral treatment

- DAA-induced SVR was associated with reduced risk of clinical disease progression in patients with Child-Pugh A cirrhosis but not in those with Child-Pugh B/C cirrhosis. **A ≥2 point decrease in MELD score among patients with Child-Pugh B/C cirrhosis was not associated with improved clinical outcome**

HCV: Decompensated Cirrhosis DAA Therapy

- Patients with advanced cirrhosis (defined as cirrhosis and MELD score ≥10) treated with a variety of DAA regimens, the **overall SVR12 rate was 90.5%.** Age <60, male sex, ascites, serum albumin <3.5 mg/dL, hepatocellular carcinoma, proton-pump inhibitor use, MELD score >16, and CTP class B/C were significantly associated with decreased odds of SVR12

- Long-term follow-up at a median of 4 years after the end of treatment, **a clinically meaningful decrease in MELD score of ≥3 occurred in 29% and a final MELD score of <10 was achieved in 25%.** A proportion of patients with advanced cirrhosis who receive DAA therapy may not achieve significant long-term improvement in liver function

- **DAA therapy was associated with reduced all-cause mortality and non-liver related deaths. In the 88% of patients who achieved SVR, the risk of mortality, hepatocellular carcinoma and liver transplantation - reduced**

Hepatitis C – DAA Failures

AASLD: New Simplified HCV Treatment Approach

Eligible Patients:
Chronic hepatitis C without cirrhosis and no previous HCV therapy

- **Assess cirrhosis (liver biopsy not required)**
  - Treat as though cirrhotic if any of the following suggest cirrhosis: FIB-4 > 3.25, platelet count < 150,000/mm^3, APRI > 2.0, *FibroScan* > 12.5 kPa
- **Record medications and supplements, assess DDIs**
- **Conduct recommended baseline labs**
- **Provide patient education**

Treatment Options:
GLE/PIB 3 pills/day for 8 wks (with food) or **SOF/VEL** 1 pill/day for 12 wks

Glecaprevir/Pibrentasvir Treatment Failures

Recommended regimens listed by evidence level and alphabetically for:

Glecaprevir/Pibrentasvir Treatment Failures (All Genotypes), With or Without Compensated Cirrhosis[a]

RECOMMENDED	DURATION	RATING
Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) plus daily sofosbuvir (400 mg) and weight-based ribavirin	16 weeks	IIa, B
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)/voxilaprevir (100 mg)	12 weeks	IIa, B
For patients with compensated cirrhosis, addition of weight-based ribavirin is recommended.	12 weeks	IIa, C

[a] For decompensated cirrhosis, please refer to the appropriate section.

https://www.hcvguidelines.org/treatment-experienced/g-p-failures

Multiple DAA Treatment Failures (All Genotypes), Including Sofosbuvir/Velpatasvir/Voxilaprevir or Sofosbuvir Plus Glecaprevir/Pibrentasvir

Recommended regimens listed by evidence level and alphabetically for:

Sofosbuvir/Velpatasvir/Voxilaprevir Treatment Failures, With or Without Compensated Cirrhosis[a]

RECOMMENDED	DURATION	RATING
Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) plus daily sofosbuvir (400 mg) and weight-based ribavirin	16 weeks[b]	IIa, B
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)/voxilaprevir (100 mg) plus weight-based ribavirin	24 weeks	IIa, B

[a] For decompensated cirrhosis, please refer to the appropriate section.

[b] Extension of treatment to 24 weeks should be considered in extremely difficult cases (e.g., genotype 3 with cirrhosis) or failure following sofosbuvir plus glecaprevir/pibrentasvir.

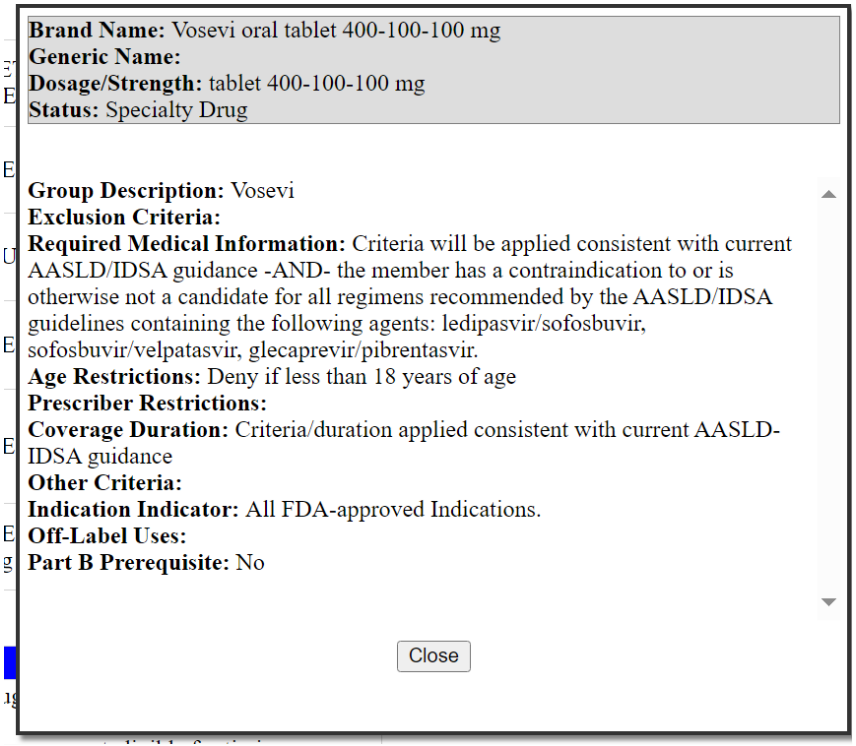
https://www.hcvguidelines.org/treatment-experienced/multiple-daa-failure

DAA Failures

Results

Brand Name generic name	Therapeutic Class *Sub-Class*	Dose/Strength	Status	Notes & Restrictions
Epclusa Oral Pellets In Packet 150-37.5 Mg	ANTIVIRALS *ANTI-HEPATITIS C (HCV) AGENTS*	PELLETS IN PACKET 150-37.5 mg	SP Specialty Product	QL Quantity Limit PA Prior Auth
Epclusa Oral Pellets In Packet 200-50 Mg	ANTIVIRALS *ANTI-HEPATITIS C (HCV) AGENTS*	PELLETS IN PACKET 200-50 mg	SP Specialty Product	QL Quantity Limit PA Prior Auth
Epclusa Oral Tablet 200-50 Mg	ANTIVIRALS *ANTI-HEPATITIS C (HCV) AGENTS*	TABLET 200-50 mg	SP Specialty Product	QL Quantity Limit PA Prior Auth
Epclusa Oral Tablet 400-100 Mg	ANTIVIRALS *ANTI-HEPATITIS C (HCV) AGENTS*	TABLET 400-100 mg	SP Specialty Product	QL Quantity Limit PA Prior Auth
Harvoni Oral Pellets In Packet 33.75-150	ANTIVIRALS *ANTI-HEPATITIS C*	PELLETS IN PACKET 33.75-150	SP Specialty Product	QL Quantity Limit PA Prior Auth

DAA Failures



Brand Name: Vosevi oral tablet 400-100-100 mg
Generic Name:
Dosage/Strength: tablet 400-100-100 mg
Status: Specialty Drug

Group Description: Vosevi
Exclusion Criteria:
Required Medical Information: Criteria will be applied consistent with current AASLD/IDSA guidance -AND- the member has a contraindication to or is otherwise not a candidate for all regimens recommended by the AASLD/IDSA guidelines containing the following agents: ledipasvir/sofosbuvir, sofosbuvir/velpatasvir, glecaprevir/pibrentasvir.
Age Restrictions: Deny if less than 18 years of age
Prescriber Restrictions:
Coverage Duration: Criteria/duration applied consistent with current AASLD-IDSA guidance
Other Criteria:
Indication Indicator: All FDA-approved Indications.
Off-Label Uses:
Part B Prerequisite: No

Close

Questions