10TH ANNUAL

DIGESTIVE DISEASES: NEW ADVANCES

September 29–30, 2023

Hyatt Regency Jersey City On The Hudson

This activity is supported by educational grants from Cook Medical, CymaBay Therapeutics, Inc., Grifols, Mallinckrodt Pharmaceuticals, Olympus, and Salix Pharmaceuticals.

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What Is New in Hepatitis C

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Disclosures

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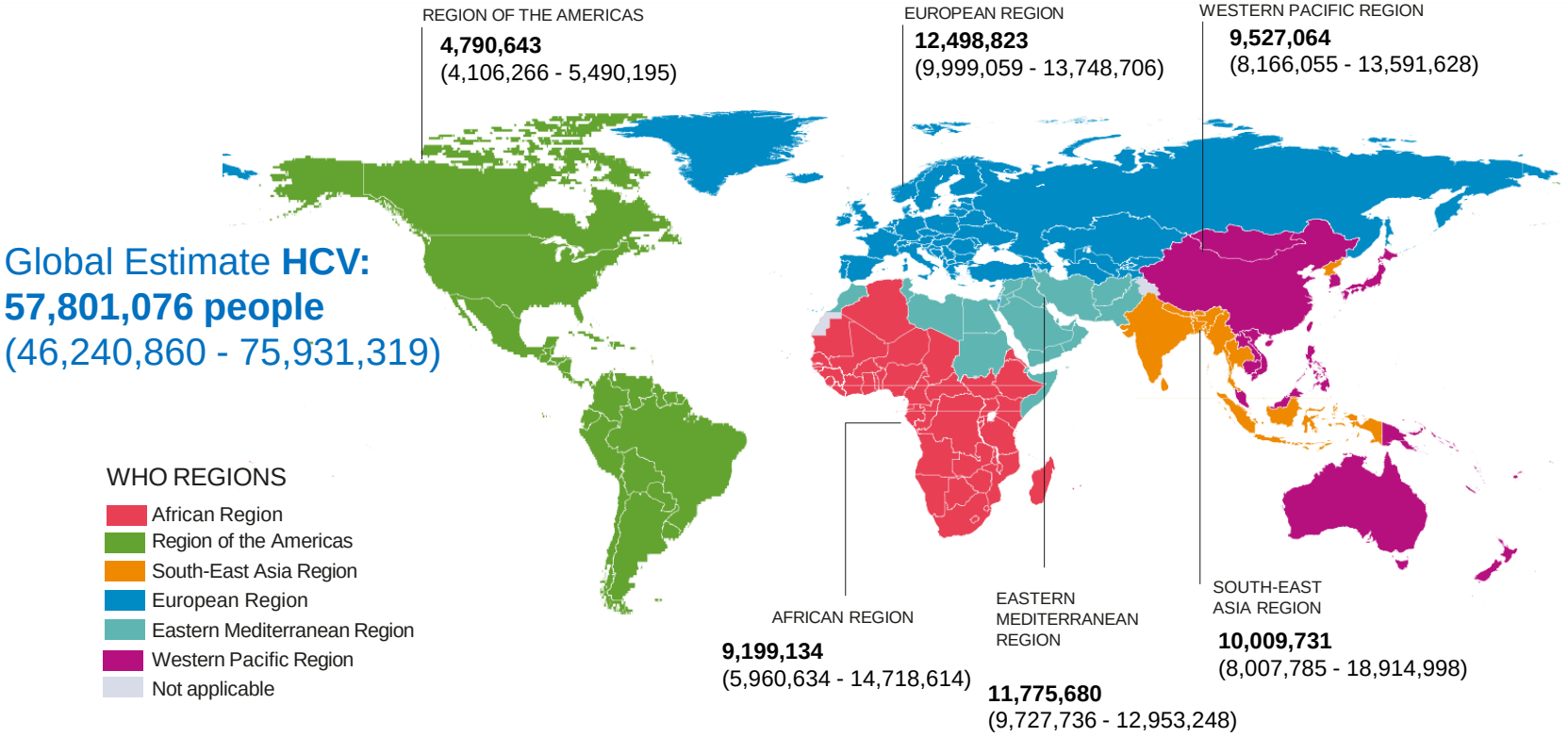
Abbvie: Consultant; Aligos: Consultant; Altimmune: Research Grant; Antios: Consultant; Arrowhead:Research Grant; Bristol-Myers Squibb: Research Grant; Drug Farm: Consultant; Durect: Consultant, Stockholder; Eiger: Research Grant Consultant; Enanta:; Gilead: Consultant, Research Grant; HepQuant: Consultant; Inventiva: Consultant; Mallinckrodt: Novo Nordisk: Research Grant; Ultragenyx: Research Grant

Off lablel use: Lonafarnib, PEG Lambda, Bulivertide

Prevalence of Hepatitis C Virus Infection by WHO Region, 2019



Source: WHO, 2021.

Global Call for HCV Elimination

- **WHO vision**[1]**:** "*Eliminate viral hepatitis as a major global public health threat by 2030*"

2030 Targets

90% Diagnosed

80% Treated

65% Reduced mortality

- **US HBV/HCV Elimination Strategy** (National Academies of Sciences, Engineering, and Medicine)[2]
  - "Elimination" = 90% reduction in incidence by 2030
- **HCV elimination in US not feasible without engaging, treating PWID**
  - 30.5% of all HCV infections in North America are among people with recent IDU[3]
  - Incarceration: a venue to identify and cure HCV infection

1. WHO. Global Health Sector Strategy on Viral Hepatitis, 2016-2021; 2. NASEM. A national strategy for the elimination of hepatitis B and C. Washington, DC: *The National Academies Press*; 2017; 3. Grebely. *Addiction*. 2019;114:150.

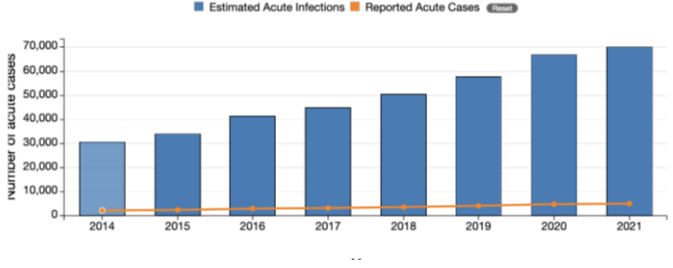
Eradication Versus Elimination

- Eradication
  - Permanent reduction to zero worldwide incidence
  - Intervention measures no longer required
  - Ex: Smallpox
- Elimination
  - Reduction to zero incidence of an infection in a certain geographical area
  - Intervention measures are required
  - Ex: Poliomyelitis

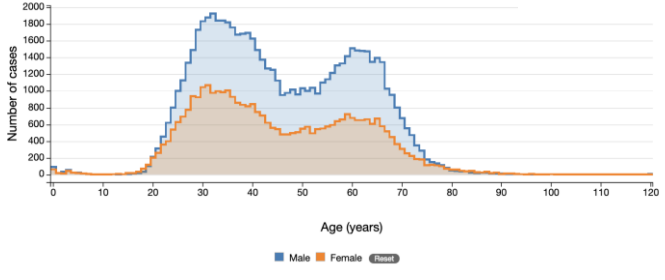
Most infections that have been eradicated/eliminated have been as a result of effective vaccines
Exception is onchocerciasis (river blindness)
Over one hundred million individuals treated
Eliminated in many countries with ivermectin
Despite effective hepatitis B vaccine, we have not been able to eliminate hepatitis B

Hepatitis C Epidemiology

Number of reported cases* of acute Hepatitis C virus infection and estimated infections† — United States, 2014–2021

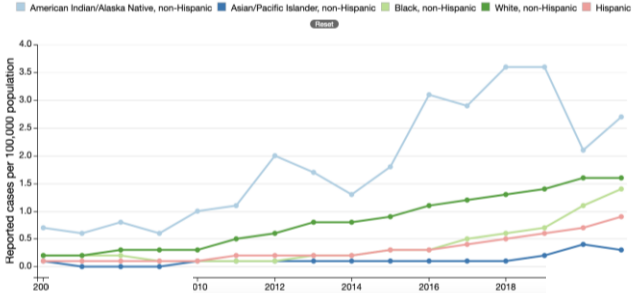


Number of newly reported* chronic Hepatitis C virus infection cases† by sex and age — United States, 2021

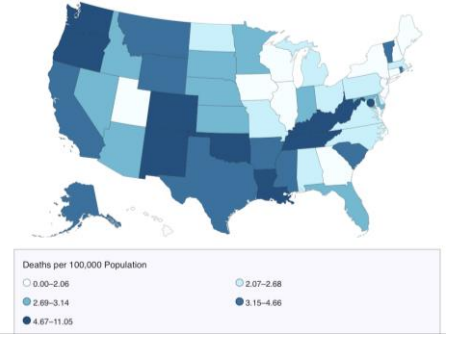


https://www.cdc.gov/hepatitis/statistics/2021surveillance/hepatitis-c.htm.

Rates* of reported cases† of acute Hepatitis C virus infection, by race/ethnicity — United States, 2006–2021



Number of newly reported* chronic Hepatitis C virus infection cases† by sex and age — United States, 2021



USPS Task Force: Hepatitis C Virus Infection in Adolescents and Adults: Screening

CDC has also released broadened screening recommendations

Recommendation Summary

Population	Recommendation	Grade (What's This?)
Adults aged 18 to 79 years	The USPSTF recommends screening for hepatitis C virus (HCV) infection in adults aged 18 to 79 years.	B

To read the recommendation statement in *JAMA*, select here.

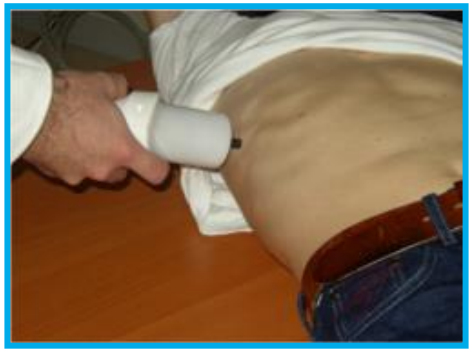
To read the evidence summary in JAMA, select here.

See the Clinician Summary for a more detailed summary of the recommendation for clinicians.

https://www.uspreventiveservicestaskforce.org/Page/Document/UpdateSummaryFinal/hepatitis-c-screening1.

Staging of Hepatic Fibrosis Is Essential Prior to HCV Treatment: Do Not Miss Cirrhosis

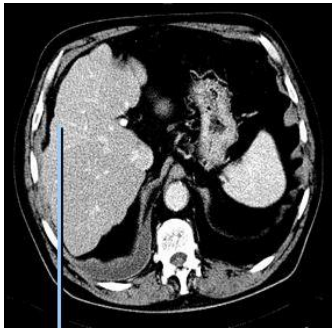
Liver biopsy:
Gold standard
Rarely done



Elastography (> 12.5 kPa =cirrhosis

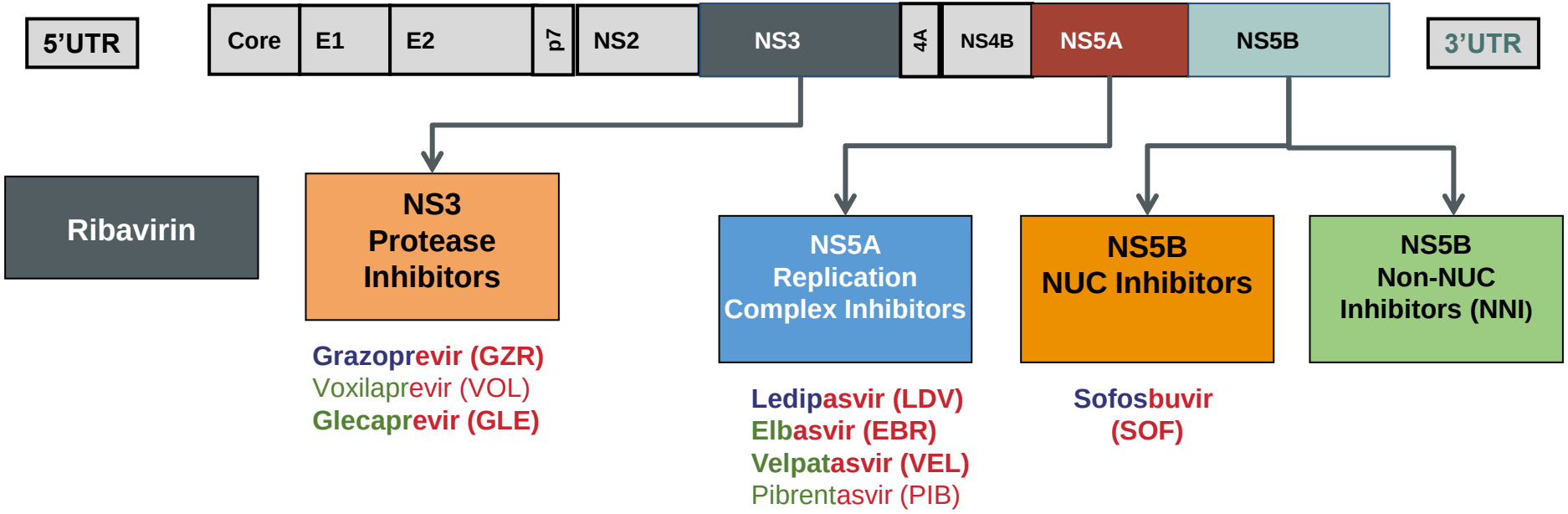
Serum Biomarkers

Serum Markers of Fibrosis:
APRI, FIB-4: Very good negative predictive value
APRI<0.5, FIB-4 < 1.45 rule out cirrhosis
Commercial serum fibrosis tests also available in US (FIBROSpect®, FibroSURE ®)



Axial CT/MRI, US can demonstrate cirrhotic morphology, portal hypertension

Approved Direct-Acting Antiviral Agents (DAAs) From Multiple Classes Are Combined to Achieve SVR



All First Line Treatment Options Lead to Sustained Response Rates ≥ 95%

HCV Genotype	No Cirrhosis		Compensated Cirrhosis	
1	SOF/VEL GLE/PIB LDV/SOF EBR/GZR*	12 W 8 W 8 or 12 W 12 W	SOF/VEL GLE/PIB LDV/SOF EBR/GZR*	12 W 8 W 12 W 12 W
2/3	GLE/PIB SOF/VEL	8 W 12 W	GLE/PIB SOF/VEL**	8 W 12 W
4	EBR/GZR GLE/PIB LDV/SOF SOF/VEL	12 W 8 W 12 W 12 W	EBR/GZR GLE/PIB LDV/SOF SOF/VE	12 W 8 W 12 W 12 W
5/6	GLE/PIB LDV/SOF SOF/VEL	8 W 12 W 12 W	GLE/PIB LDV/SOF SOF/VEL	8 W 12 W 12 W

* Alternative therapy for GT1a No NS5a RAS, **No Y93H

https://www.hcvguidelines.org.

Almost All Unique Populations Achieve High SVR Rates

Population	SVR Rate	Comments
DAA failures	>95%	SOF/VEL/VOX± RBV pangenotypic option
HIV/HCV Coinfection	>95%	Must do drug drug interactions
Post Orthotopic Liver Transplant	>95%	Must do drug drug interactions
With Renal Impairment/Dialysis	>95%	GLE/PIB and SOF/VEL are pangenotypic options
Kidney Transplant Patients	>95%	Must do drug drug interactions
Management of Acute HCV Infection	>95% if treated for 8 weeks	20-50% of acute infections clear
HCV in Pregnancy	No treatment during pregnancy	Screen at risk women, treating before pregnancy preferred
HCV in Children	>95%	Treatment approved for those ≥ 3 years of age

- Drug-Drug interactions are essential to evaluate, particularly with HIV/HCV coinfection and transplant patients
- use available resources (https://aidsinfo.nih.gov/guidelines/htmltables/1/5536 is an example for HIV)
- Antiretroviral drug switches, when needed, should be done in collaboration with the HIV practitioner

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]

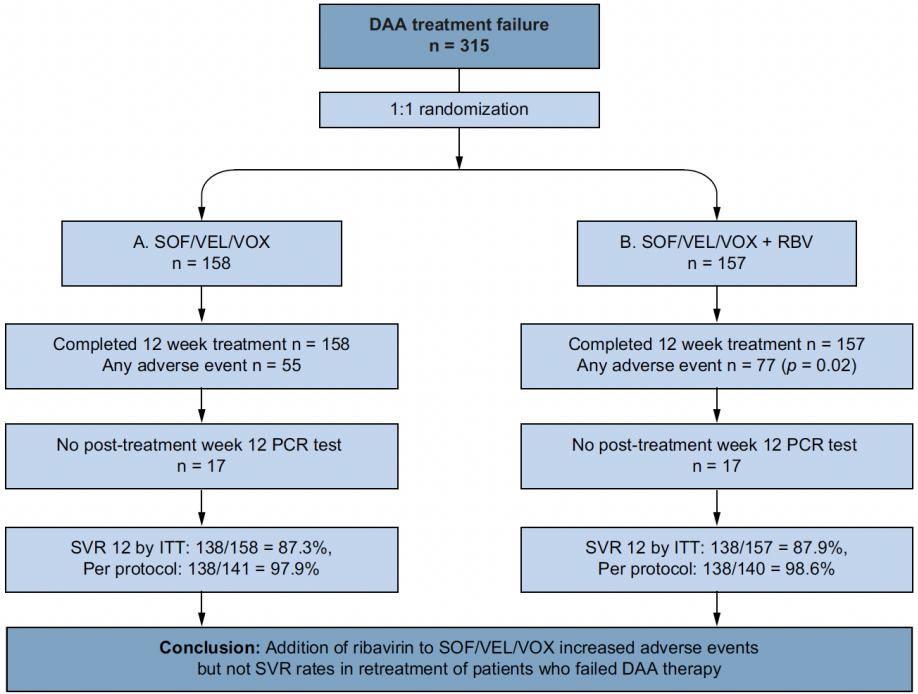
RECOMMENDED	DURATION	RATING
Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) plus daily sofosbuvir (400 mg) and weight-based ribavirin	16 weeks[b]	IIa, B
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)/voxilaprevir (100 mg) plus weight-based ribavirin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

A Randomized-Controlled Trial of SOF/VEL/VOX With or Without Ribavirin for Retreatment of Chronic Hepatitis C



Treatment received	Sex	Age	Tobacco use	Genotype
SOF/VEL/VOX	M	45	Yes	4a
SOF/VEL/VOX	F	60	No	4a
SOF/VEL/VOX	M	40	Yes	4a
SOF/VEL/VOX/RBV	M	36	Yes	4a
SOF/VEL/VOX/RBV	F	51	No	4a

DCV, daclatasvir; RBV, ribavirin; SOF, sofosbuvir; SVR12, sustained virologic response at 12 we

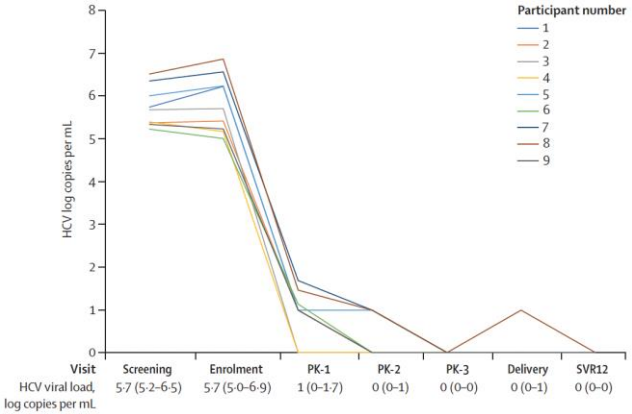
- *High efficacy of both regimens for the retreatment of previous DAA failures*
- *Ribavirin was associated with more AEs, one DC for anemia*

Journal of Hepatology. 2023. vol. 79 j 314–320.

Ledipasvir Plus Sofosbuvir in Pregnant Women With Hepatitis C Virus Infection: A Phase 1 Pharmacokinetic Study

- Genotypes 1, 4, 5, 6
- All received ledipasvir/sofosbuvir for 12 weeks
- All the patients achieved SVR
- No changes in pK due to pregnancy

HCV viral response to ledipasvir–sofosbuvir during pregnancy



Maternal adverse events and pregnancy outcomes

	HCV-infected pregnant women (n=9)
Maternal adverse events related to ledipasvir-sofosbuvir*	5 (56%)
Maternal adverse events >grade 2 related to ledipasvir-sofosbuvir	0
Discontinuation of ledipasvir-sofosbuvir because of adverse events	0
Gestational age at delivery, weeks + days	39 + 2 (36 + 6 to 41 + 0)
Vaginal delivery	5 (56%)
Scheduled caesarean section	3 (33%)
Emergent caesarean section†	1 (11%)
Apgar score at 1 min	8 (6 to 9)
Apgar score at 5 min	9 (8 to 9)
Male infants	7 (78%)
Infant birthweight, kg	3·29 (2·60 to 4·16)
Detectable HCV RNA in cord blood	0
Length of stay in hospital, days	3 (2 to 12)
Admission to the neonatal intensive care unit‡	3 (33%)

Data are n (%) or median (range). HCV=hepatitis C virus. *Four were grade 1 (three nausea or vomiting and one diarrhoea) and one was grade 2 (fatigue). †Due to umbilical cord prolapse. ‡Reasons for neonatal intensive care admission: one shoulder dystocia and two neonatal opioid withdrawal syndromes.

https://doi.org/10.1016/S2666-5247(20)30062-8.

First Line Treatment Options Lead to Good SVR Rates (>85%) in Childs B/C Patients (Special Population)

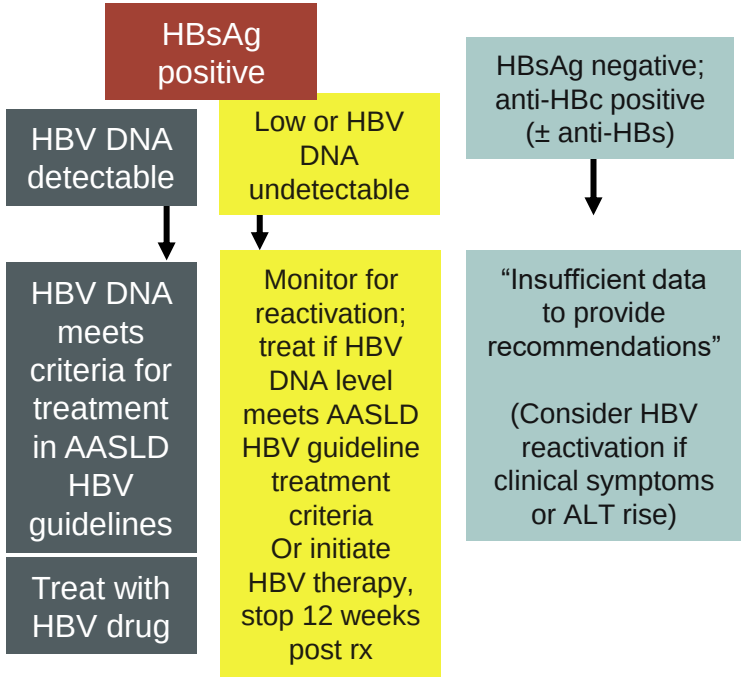
HCV genotype	Decompensated Cirrhosis, RBV tolerant		Decompensated Cirrhosis, RBV intolerant	
1,4	LDV/SOF/RBV SOF/VEL/RBV	12 W 12W	LDV/SOF SOF/VEL	24 W 24 W
2/3	SOF/VEL/RBV	12W 12 W	SOF/VEL	24 W 24W
5, 6	LDV/SOF/RBV SOF/VEL/RBV	12 W 12 W	LDV/SOF SOF/VEL	24 W 24 W

Those with decompensated cirrhosis who have failed therapy remain one of the final special populations in need of additional therapies

Protease inhibitors cannot be given in decompensated cirrhosis

HBV Testing/Monitoring During HCV DAA Therapy to Prevent Reactivation

- Cases of **Hepatitis B reactivation** have been reported in predominantly HBsAg+/HCV coinfected with extremely rare HCV/Anti HBc individuals developing reactivation
- **Test all pts initiating HCV therapy for HBsAg, anti-HBc, and anti-HBs**
  - **Vaccinate** if **no HBV markers**; **follow flow chart** below **if HBV markers present**



AASLD/IDSA. HCV Guidelines 2017. Graphic adapted from Ira M. Jacobson, MD.

Simplified Regimens

No Cirrhosis

GLE/PIB 8 weeks
SOF/VEL 12 weeks

Who Is Eligible for Simplified Treatment

Adults with chronic hepatitis C (any genotype) who do not have cirrhosis and have not previously received hepatitis C treatment

Who Is *NOT* Eligible for Simplified Treatment

Patients who have any of the following characteristics:

- Prior hepatitis C treatment
- Cirrhosis (see simplified treatment for treatment-naive adults with compensated cirrhosis)
- End-stage renal disease (ie, eGFR <30 mL/min/m^2) (see Patients with Renal Impairment section)
- HIV or HBsAg positive
- Current pregnancy
- Known or suspected hepatocellular carcinoma
- Prior liver transplantation

Labs prior to treatment: Complete blood count (CBC), International normalized ratio (INR) Hepatic function panel Calculated glomerular filtration rate (eGFR), Quantitative HCV RNA (HCV viral load), HIV, HBsAg

Assessment of potential drug-drug interactions
Many good resources (https://www.hep-druginteractions.org/ , http://www.hcvdruginfo.ca/tables.html are 2 examples)

Assess Compliance, pregnancy testing in child-bearing aged women

Compensated cirrhosis

GLE/PIB 8 weeks
SOF/VEL 12 weeks GT 1,2, 4,5,6

Who Is Eligible for Simplified Treatment

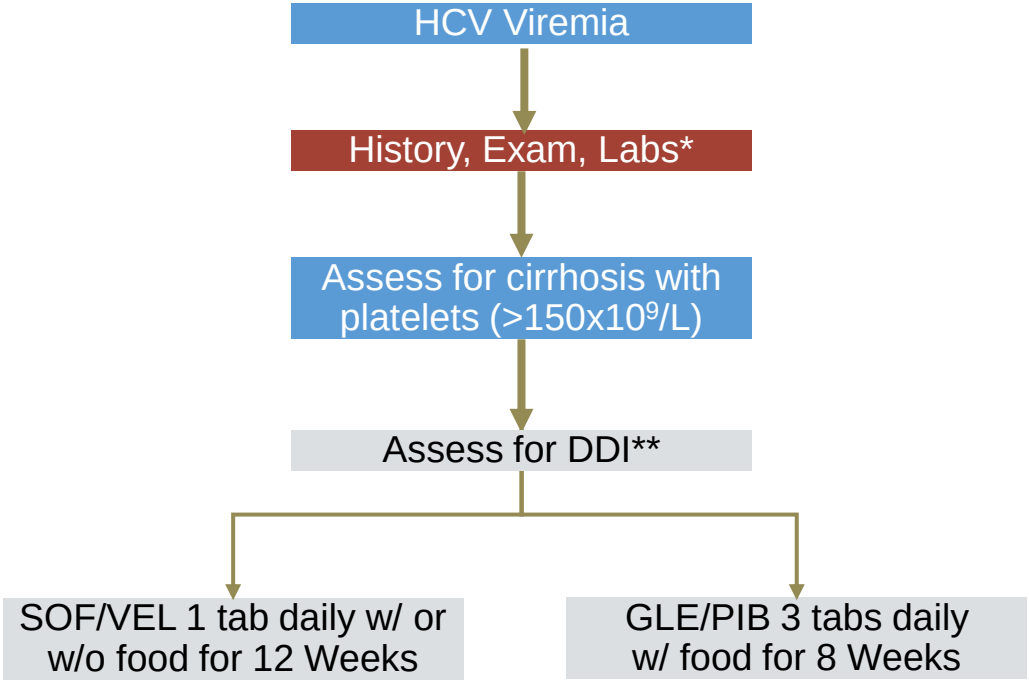
Adults with chronic hepatitis C (any genotype) who have compensated cirrhosis (Child-Pugh A) and have not previously received hepatitis C treatment
Liver biopsy is not required. For the purpose of this guidance, a patient is presumed to have cirrhosis if they have a FIB-4 score >3.25 or any of the following findings from a previously performed test.

- Transient elastography indicating cirrhosis (eg, FibroScan stiffness >12.5 kPa)
- Noninvasive serologic tests above proprietary cutoffs indicating cirrhosis (eg, FibroSure, Enhanced Liver Fibrosis Test, etc)
- Clinical evidence of cirrhosis (eg, liver nodularity and/or splenomegaly on imaging, platelet count <150,000/mm^3, etc)
- Prior liver biopsy showing cirrhosis

Cirrhosis adds CPT assessment
US/HCC assessment
HCV Genotype if using SOF/VEL
For GT 3 should obtain RAS assessment
If Y93 present add RBV to SOF/VEL or use SOF/VEL/VOX

https://www.hcvguidelines.org/treatment-naive/simplified-treatment; https://www.hcvguidelines.org/treatment-naive/simplified-treatment-compensated-cirrhosis.

How Simple Can Treatment Become for Most Patients?



*Assessment labs: CBC, AST, ALT, bilirubin, albumin, creatinine, HBV, HIV, HAV; eGFR

**HCPs should consult prescribing information, their local pharmacist and/or online tools (eg, HEP Drug Interactions; http://www.hep-druginteractions.org) to confirm interaction or lack of interaction for specific drugs within a class, as exceptions may exist.

Recommended Follow-Up for Patients Who Achieved a Sustained Virologic Response (SVR)

- For patients who do not have advanced fibrosis (Metavir stage F0-F2), recommended follow-up is the same as if they were never infected with HCV
  - Verify that ALT normalizes (risk of NAFLD or alcohol related liver disease, and others may persist)
  - Assessment of other causes of liver disease is recommended for patients who develop persistently abnormal liver tests after achieving SVR
- Assessment for HCV recurrence or reinfection only if the patient has ongoing risk for HCV infection or otherwise unexplained hepatic dysfunction develops with HCV RNA testing
- Surveillance for hepatocellular carcinoma: twice-yearly ultrasound for patients with advanced fibrosis (ie, Metavir F4) who achieve SVR
- A baseline endoscopy is recommended to screen for varices if cirrhosis is present. Patients in whom varices are found should be treated and followed as indicated.

AASLD/IDSA Guidelines: Acute HCV Infection

Pharmacologic Prophylaxis Not Recommended

NOT RECOMMENDED	RATING
Pre-exposure or post-exposure prophylaxis with antiviral therapy is not recommended.	III, C

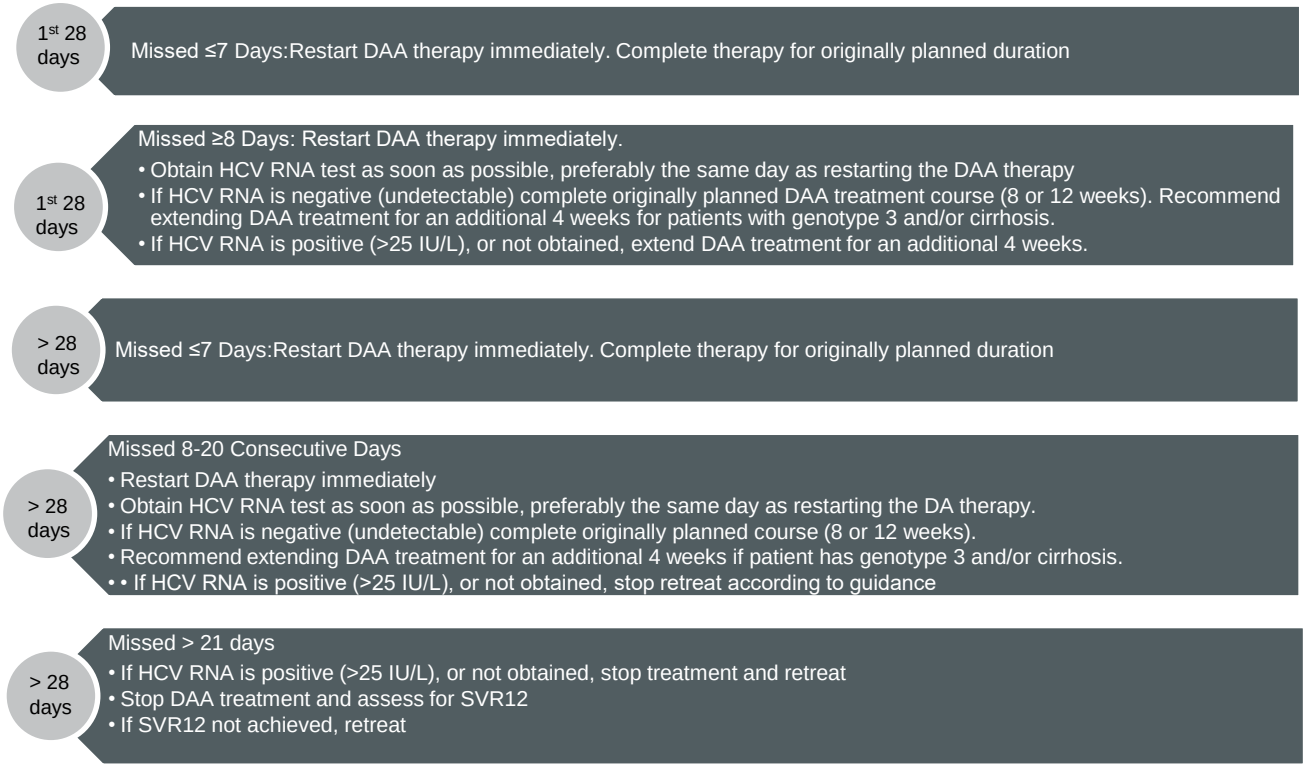
Recommendations for Medical Management and Monitoring of Acute HCV Infection

RECOMMENDED	RATING
After the initial diagnosis of acute HCV with viremia (defined as quantifiable RNA), HCV treatment should be initiated without awaiting spontaneous resolution.	I, B
Counseling is recommended for patients with acute HCV infection to avoid hepatotoxic insults, including hepatotoxic drugs (eg, acetaminophen) and alcohol consumption, and to reduce the risk of HCV transmission to others.	I, C
Referral to an addiction medicine specialist is recommended for patients with acute HCV infection related to substance use.	I, B

Recommended Regimens for Patients With Acute HCV Infection

RECOMMENDED	RATING
Owing to high efficacy and safety, the same regimens that are recommended for chronic HCV infection are recommended for acute infection.	IIa, C

Recommended Management of DAA Treatment Interruptions Receiving Glecaprevir/Pibrentasvir or Sofosbuvir/Velpatasvir



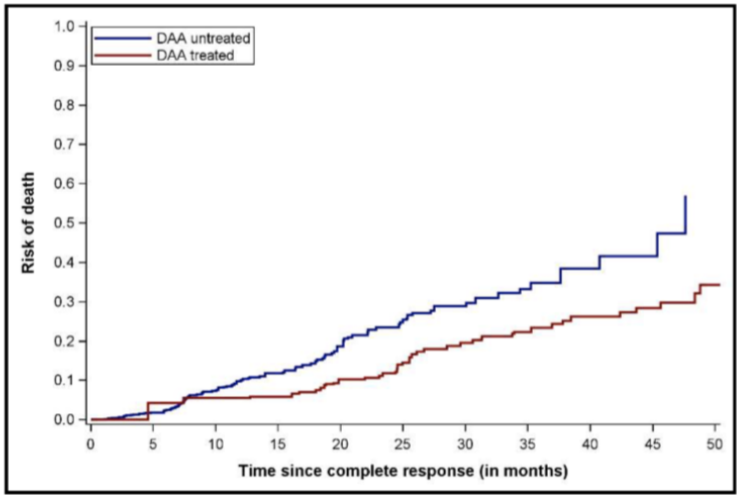
https://www.hcvguidelines.org/evaluate/monitoring.

Direct-Acting Antiviral (DAA) Therapy Is Associated With Improved Survival in Patients With a History of Hepatocellular Carcinoma and HCV Infection

Results:

DAA Treated:
4.6 deaths per 100 person-years follow-up

DAA Untreated:
19.6 deaths per 100 person-years follow-up



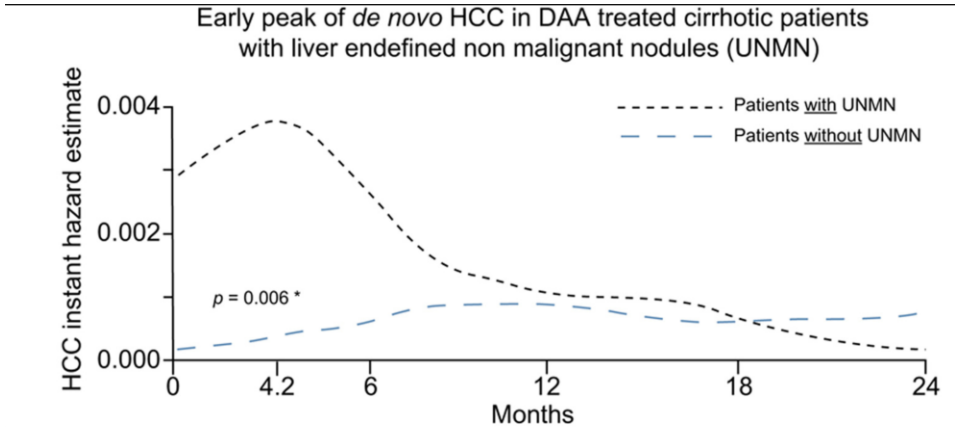
Multivariable analysis
- Adjusted for site, age, sex Child Pugh score, AFP, tumor burden and HCC treatment modality

→ **DAA therapy associated with lower mortality: HR: 0.54; 95%CI: 0.33 – 0.90**

Singal AG et al. *Gastroenterology*. 2019.

HCV/HCC Risk in DAA-Treated Patients With Cirrhosis

- Evaluate all elevated AFP and characterize indeterminate nodules prior to treatment
- Undefined non-malignant nodules, ascites and AFP were independently associated with the incidence of *de novo* HCC

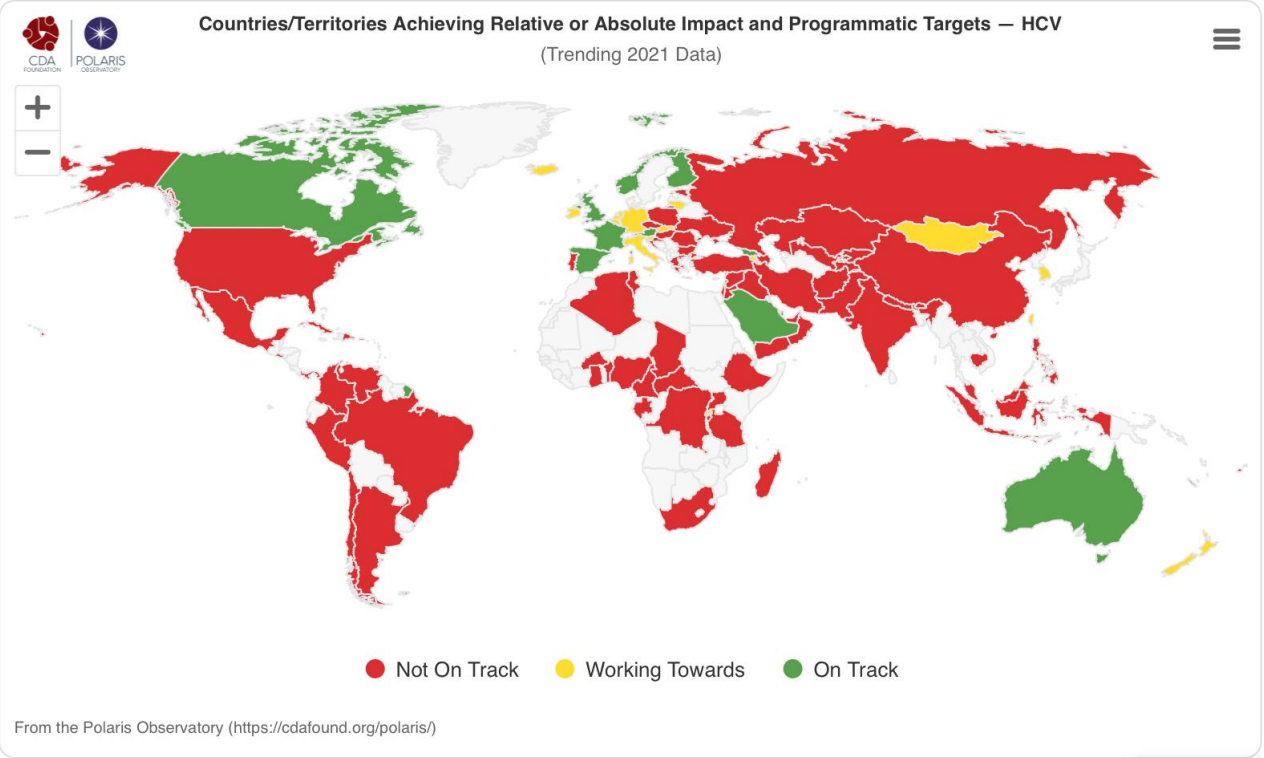


N° at risk						
- - - - - - -	73	69	63	52	40	18
— — —	1,088	1,038	974	734	471	190

(*) Time dependent effect of the presence of nodules with the development of HCC in patients with vs without UNMN, proportional hazard test.

https://doi.org/10.1016/j.jhep.2020.03.030.

Countries/Territories Achieving Relative or Absolute Impact and Programmatic Targets — HCV



White House Hopes to Eliminate HCV

Viewpoint

March 9, 2023

A National Hepatitis C Elimination Program in the United States

A Historic Opportunity

Rachael L. Fleurence, MSc, PhD[1]; Francis S. Collins, MD, PhD[1]

» Author Affiliations | Article Information

JAMA. 2023;329(15):1251-1252. doi:10.1001/jama.2023.3692

Our Approach to Hepatitis C Must Evolve to a Decentralized Model of Care

Improved access to HCV testing
Improved education about testing
Prompts for testing

Access to HCV care providers
Improved access to care (universal access)
Co-localized testing and treatment facilities

Education about Importance of treatment
Psychological and harm reduction services for comorbid conditions
Resources for primary care to treat HCV

Treatment of opioid addiction
Psychological and harm reduction services for comorbid conditions
Directly observed therapy

Many success stories in the US: Cherokee Nation elimination program
VA healthcare system has treated over 100,000 individuals, ECHO HCV projects.