HCV Treatment for New Providers

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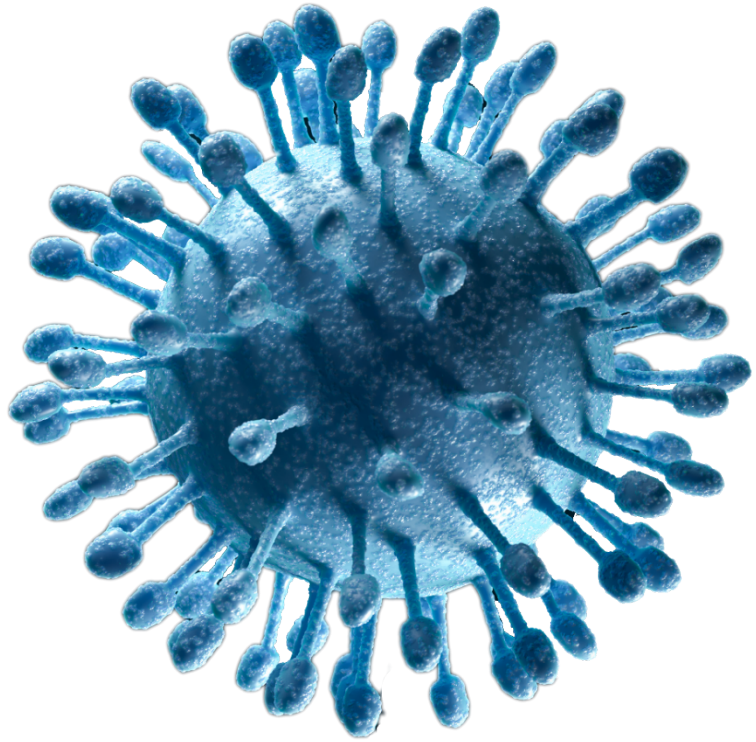
History and Epidemiology of Chronic HCV Infection

Hepatitis C

- HCV is a viral infection that can lead to liver disease and has infected ~2.7 million Americans[1]
- HCV is an RNA virus discovered in 1989[2,3]
  - GT 1-6 are the most common genotypes[2]
- HCV is the most common chronic blood-borne infection in the United States[4]
- HCV is associated with an increased risk for mortality[5]
- There is no vaccine available[6]
- HCV is curable with currently available therapies[2]



DAA, direct-acting antiviral; GT, genotype; RNA, ribonucleic acid; *Derived from PubMed-archived papers (N=85) published between 1989 and 2013 containing the terms “HCV” or “hepatitis C virus” and “genotype” or “subtype”. [3]

1. Chhatwal J et al. Aliment Pharmacol Ther. 2019;00:1-9.. 2. US Department of Health and Human Services, Center for Drug Evaluation and Research. Draft Guidance for Industry. Chronic Hepatitis C Virus Infection: Developing Direct-Acting Antiviral Drugs for Treatment. November 2017. 3. Messina JP, et al. *Hepatology*. 2015;61(1):77-87. 4. Ditah I, et al. *J Hepatol*. 2014;60(4):691-698. 5. Ly KN, et al. *Clin Infect Dis*. 2016;62(10):1287-1288. 6. CDC website. **********.cdc.gov/hepatitis/hcv/hcvfaq.htm. Accessed January 10, 2018.

HCV: Disease Progression

Years

20-25 Years

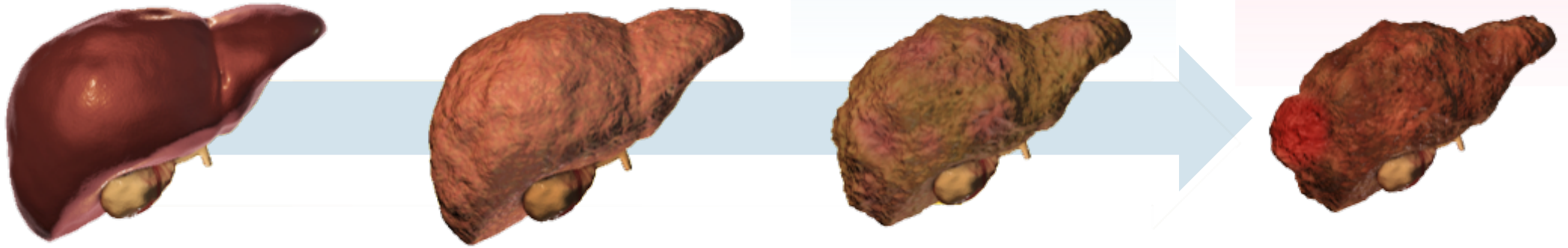
25-30 Years

- ESLD
- HCC
- Death

Normal Liver

Chronic Hepatitis

Cirrhosis



HCV INFECTION

75-85 will develop chronic HCV if untreated

5-20 will develop cirrhosis

1-5 will die from cirrhosis or HCC

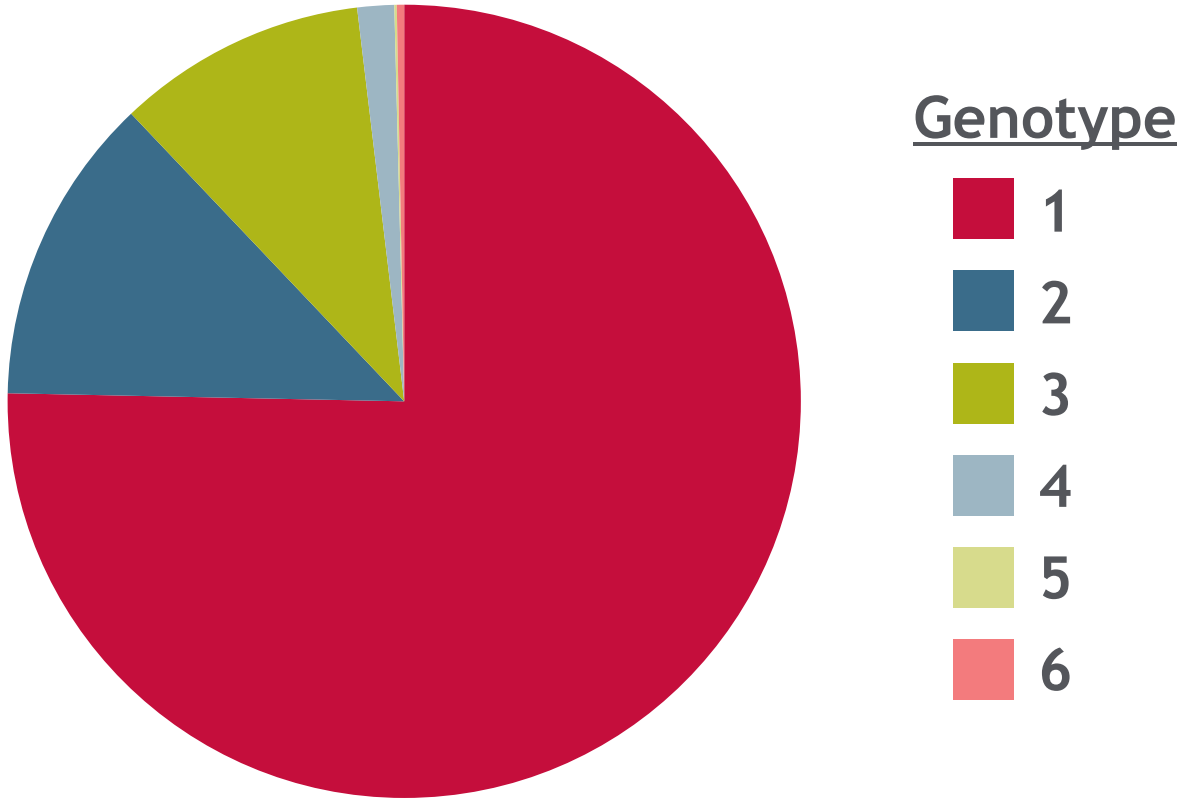
OF EVERY 100 PERSONS INFECTED WITH HCV

ESLD, end-stage liver disease; HCC, hepatocellular carcinoma; Emory University Coalition for Applied Modeling for Prevention (CAMP). ***.hepvu.org. Accessed August 2, 2018. Image adapted from Hepatitis C Online. 2015 **********.hepatitisc.uw.edu/go/evaluation-staging-monitoring/natural-history/core-concept/all. Accessed August 2, 2018.

HCV Genotypes

- 6 HCV genotypes[2]
- Genotypic prevalence varies by geography[2]
- Genotype 1 is the most common in the US and accounts for approximately 70% of HCV infections[2]
- GT 1a and GT 3 have a significantly greater prevalence among the PWID population than the general population

Distribution of HCV Genotypes in the US

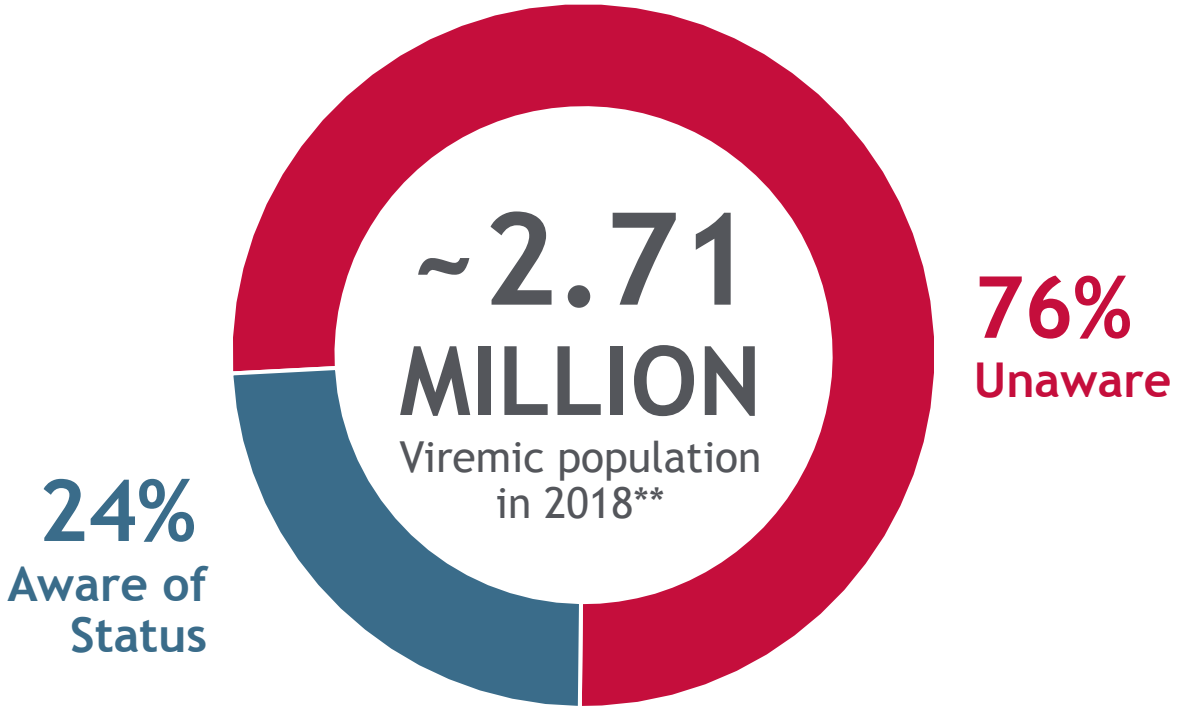


PWID, people who inject drugs.

1. Gordon SC et al, J Clin Gastroenterol. 2019 January ; 53(1): 40-50; 2. Manos MM et al. J Med Virol. 2012 Nov;84(11):1744-50; 3. Robaeys G, et al. J Hepatol 2016;65:1094-103

HCV Epidemiology: US Prevalence

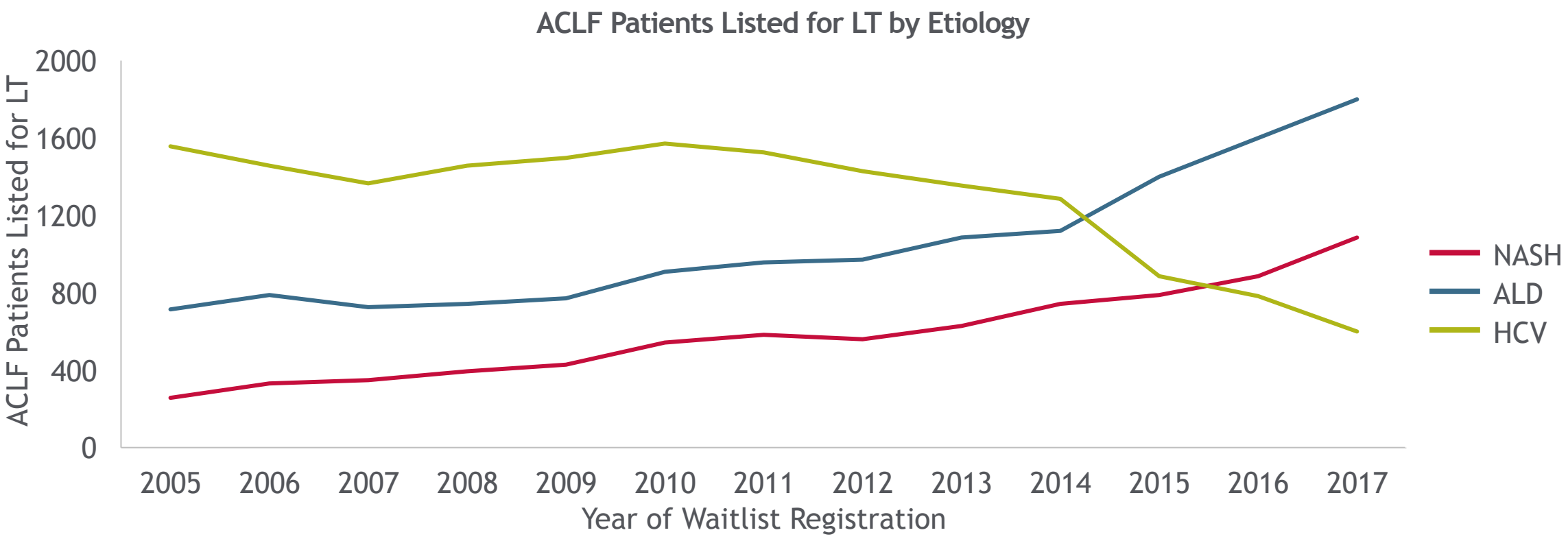
- By the end of 2018, of 4.29 million HCV persons alive*, 2.71 million (63%) were actively viremic, 2.24 million (52%) aware and 1.58 million (37%) cured
- Approximately 76% of those viremic remain unaware of their disease
- By 2030, 1.87 million people could remain viremic under current screening and treatment practices



*Both viremic and non-viremic persons; **1.41 million in NHANES and 1.3 million in non-NHANES population; Chhatwal J et al. *APT*. 2018

Curative HCV therapy has impacted care: HCV is no longer the leading etiology for Liver Transplants

Trends from UNOS on proportion of patients with NASH, ALD, and HCV listed for LT with ACLF

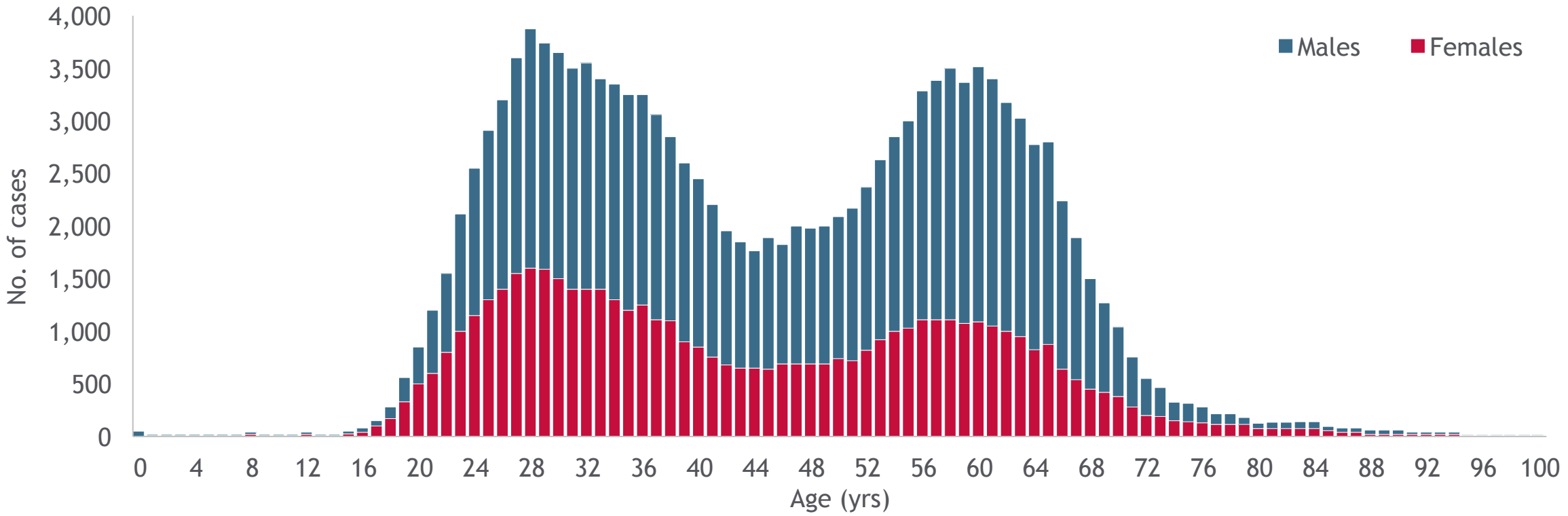


Achieving HCV SVR is no longer the key etiology of LT, leading to cost savings to healthcare system

ALD, alcoholic liver disease; UNOS, United Network for Organ Sharing; ACLF, acute on chronic liver failure; Sundaram V, et al. AASLD 2019. 1072

Age Distribution of New HCV Infections in the US Skews Toward Young Adults

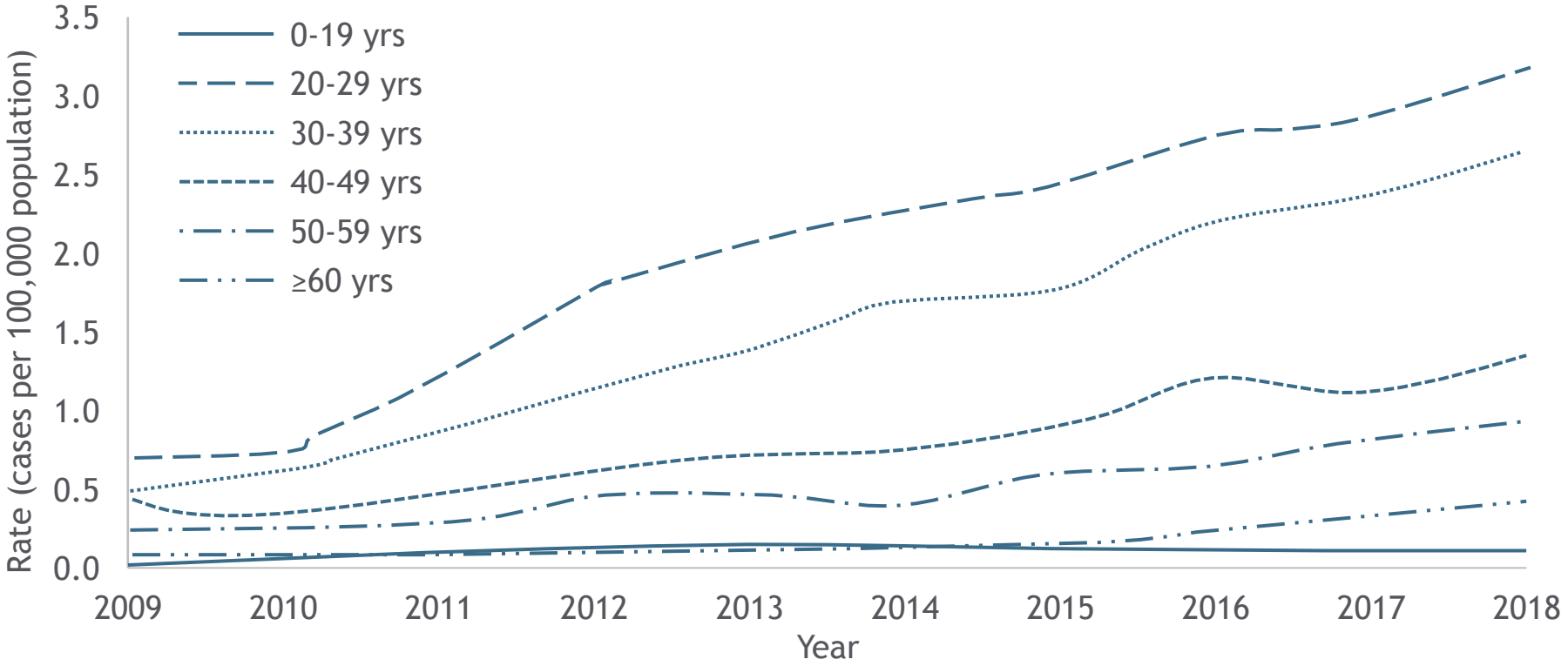
Figure 2. Number of newly reported* chronic hepatitis C cases,† by sex and age – National Notifiable Diseases Surveillance System, United States, 2018



*Cases per 100,000 U.S. population; †The states and jurisdictions reporting cases to CDC through he National Notifiable Diseases Surveillance System might vary by year (**********.cdc.gov/hepatitis/statistics/2017surveillance/index.htm). During 2018, cases of acute hepatitis C were either not reportable by law, statute, or regulation; not reported; or otherwise unavailable to CDC from Alaska, Arizona, Delaware, District of Columbia, Hawaii, Iowa, Mississippi, and Rhode Island; §Only confirmed, acute hepatitis C cases are included. Complete case definitions by year are available at **********n.cdc.gov/nndss/conditions/hepatitis-c-acute/; *Vital Signs:* Newly Reported Acute and Chronic Hepatitis C Cases — United States, 2009–2018; *Weekly* / April 10, 2020 / 69(14);399–404 Blythe Ryerson et al; **********.cdc.gov/mmwr/volumes/69/wr/mm6914a2.htm

From 2009-2018: HCV Increased Significantly Among People Aged 20-39

Figure 1. Rate* of reported† acute hepatitis C cases,§ by year and age group - National Notifiable Diseases Surveillance System, United State, 2009-2018



Among people aged 20-29 years

300%

3.1 Rate/100,00 of Acute HCV

Among people aged 30-39 years[1]:

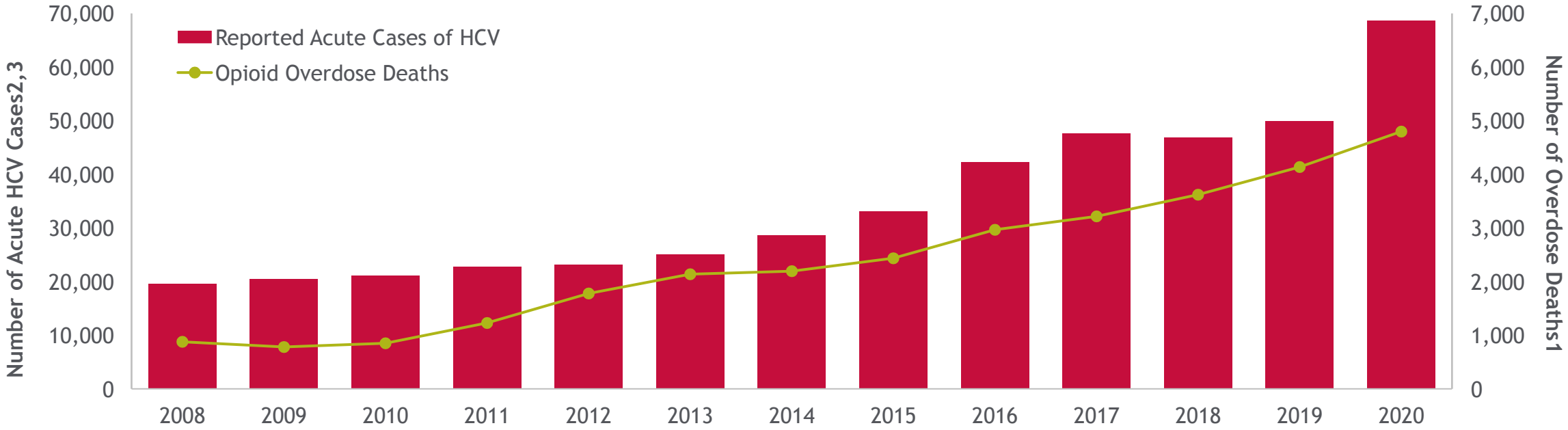
400%

2.6 Rate/100,00 of acute HCV

*Cases per 100,000 U.S. population; †The states and jurisdictions reporting cases to CDC through he National Notifiable Diseases Surveillance System might vary by year (**********.cdc.gov/hepatitis/statistics/2017surveillance/index.htm). During 2018, cases of acute hepatitis C were either not reportable by law, statute, or regulation; not reported; or otherwise unavailable to CDC from Alaska, Arizona, Delaware, District of Columbia, Hawaii, Iowa, Mississippi, and Rhode Island; §Only confirmed, acute hepatitis C cases are included. Complete case definitions by year are available at **********n.cdc.gov/nndss/conditions/hepatitis-c-acute/; *Vital Signs:* Newly Reported Acute and Chronic Hepatitis C Cases — United States, 2009–2018; *Weekly* / April 10, 2020 / 69(14);399–404 Blythe Ryerson et al; **********.cdc.gov/mmwr/volumes/69/wr/mm6914a2.htm

New HCV infections are on the rise due to the opioid Epidemic and injection drug use

Opioid-related Overdose Deaths and Reported Acute Cases of HCV



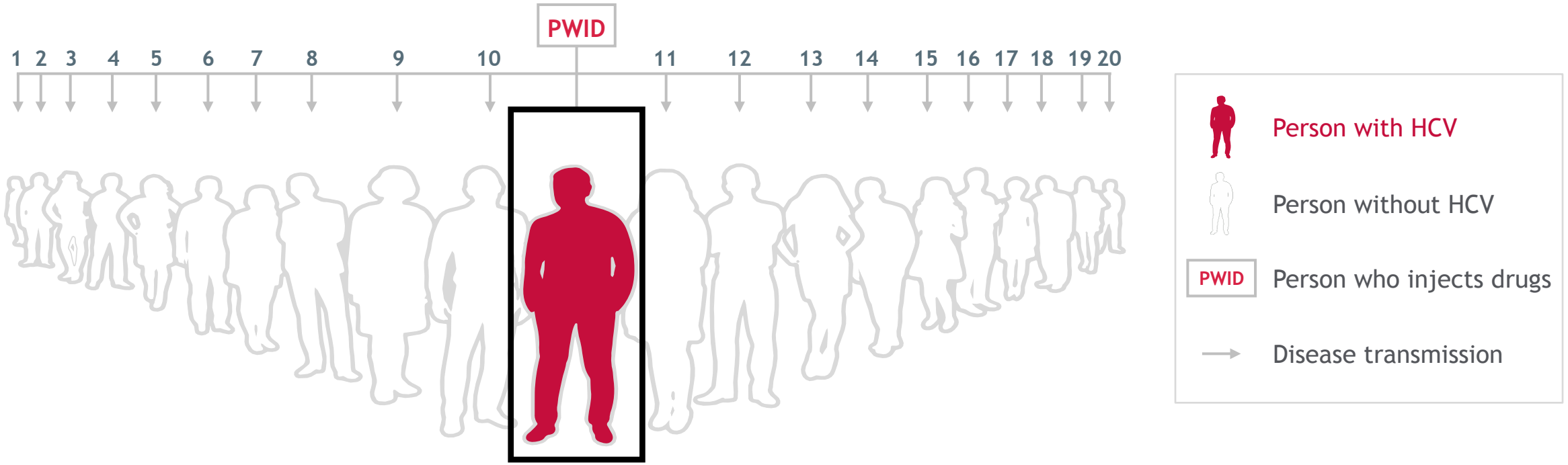
Acute HCV infection becomes chronic in more than 50% of acute cases.[4]
EPCLUSA (sofosbuvir/velpatasvir) is not indicated for the treatment of acute HCV.[5]

Overdose deaths **exceeded 100,000** in 2021, mainly driven by fentanyl or another synthetic opioid[6,7]

CDC=Centers for Disease Control and Prevention; **1.** CDC. Published December 2021. Accessed September 27, 2022. **********.cdc.gov/nchs/data/databriefs/db428-tables.pdf **2.** CDC. Accessed September 27, 2022. **********.cdc.gov/hepatitis/statistics/2020surveillance/index.htm **3.** CDC. Accessed September 28, 2022. **********.cdc.gov/hepatitis/statistics/2012surveillance/index.htm **4.** CDC. Accessed November 18, 2021. **********.cdc.gov/hepatitis/statistics/2019surveillance/index.htm **5.** EPCLUSA US full Prescribing Information. Gilead Sciences, Inc. Foster City, CA. April 2022. **6.** Ahmad FB, et al. National Center for Health Statistics. 2022. Accessed May 27, 2022. **********.cdc.gov/nchs/nvss/vsrr/drug-overdose-data.htm **7.** News release. CDC. May 11, 2022. Accessed June 16, 2022. **********.cdc.gov/nchs/pressroom/nchs_press_releases/2022/202205.htm

Each person who injects drugs with HCV is likely to infect 20 other people within the first 3 years of initial infection[1,2]

Based on the 2021 NIH National Institute on Drug Abuse Heroin Research Report

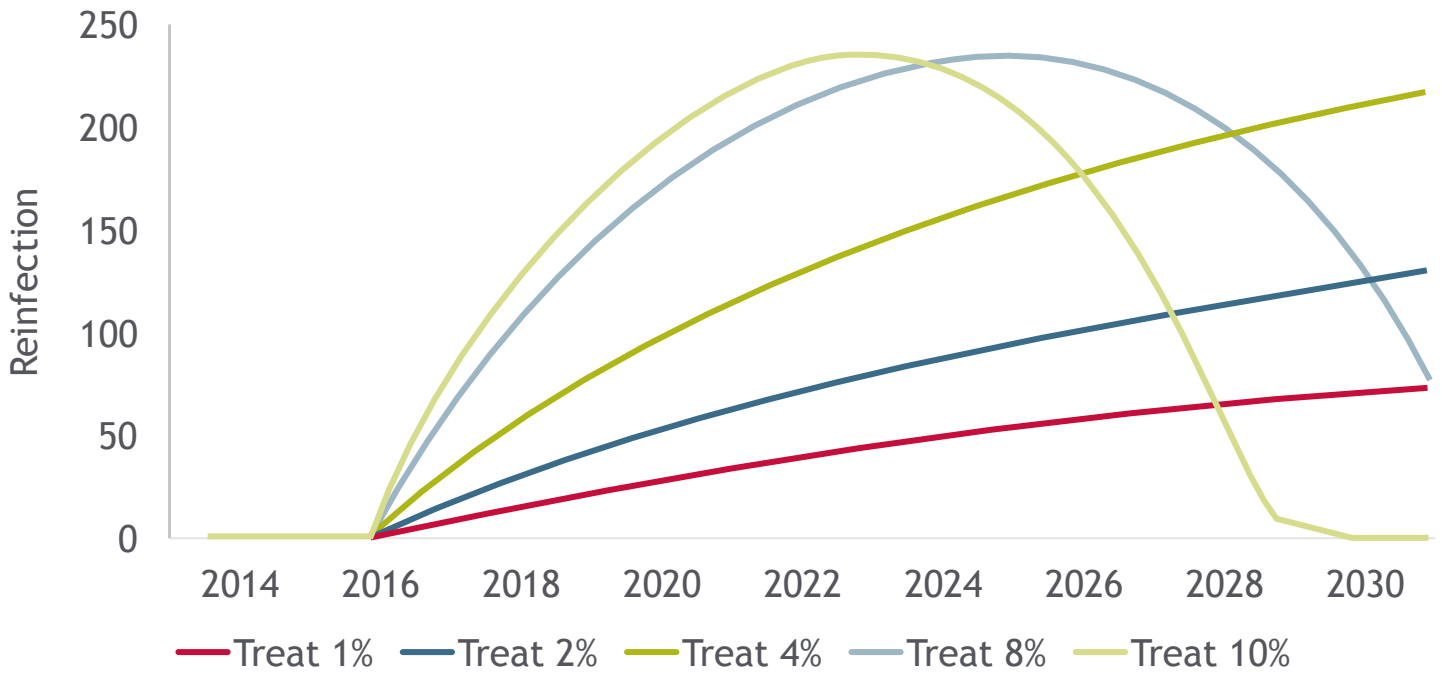


NIH=National Institutes of Health; **1.** NIH National Institute on Drug Abuse. Updated June 2021. Accessed November 2, 2021. **********.drugabuse.gov/download/37596/heroin-research-report.pdf **2.** NIH National Institute on Drug Abuse. Updated August 3, 2020. Accessed November 9, 2021. **********.drugabuse.gov/drug-topics/viral-hepatitis-very-real-consequence-substance-use

HCV Treatment as Prevention

Harm Reduction is an Essential Component

The More PWID Treated, the Faster We Get to HCV Elimination[1]



BUT we must concomitantly scale up harm reduction measures

- Medication-assisted treatment
- Syringe services programs
- Increased intensity of HCV management; eg, directly observed therapy
- Patient education and counseling

AND

- Increase HCV treater workforce

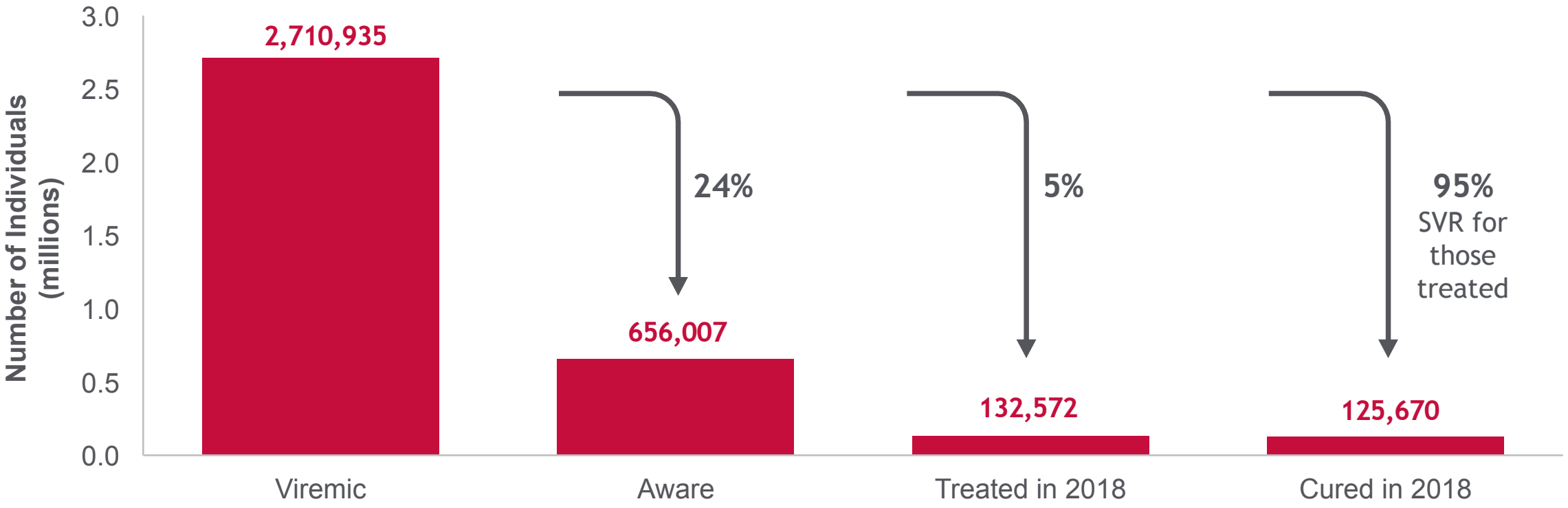
Harm-reduction services and patient education are essential to HCV elimination

1. Grebely J, et al. *Nat Rev Gastroenterol Hepatol*. 2017;14(11):641-651;

Screening

HCV is Underdiagnosed and Undertreated[1]

Cascade of Care in 2018 in the United States[1,2,a,b]

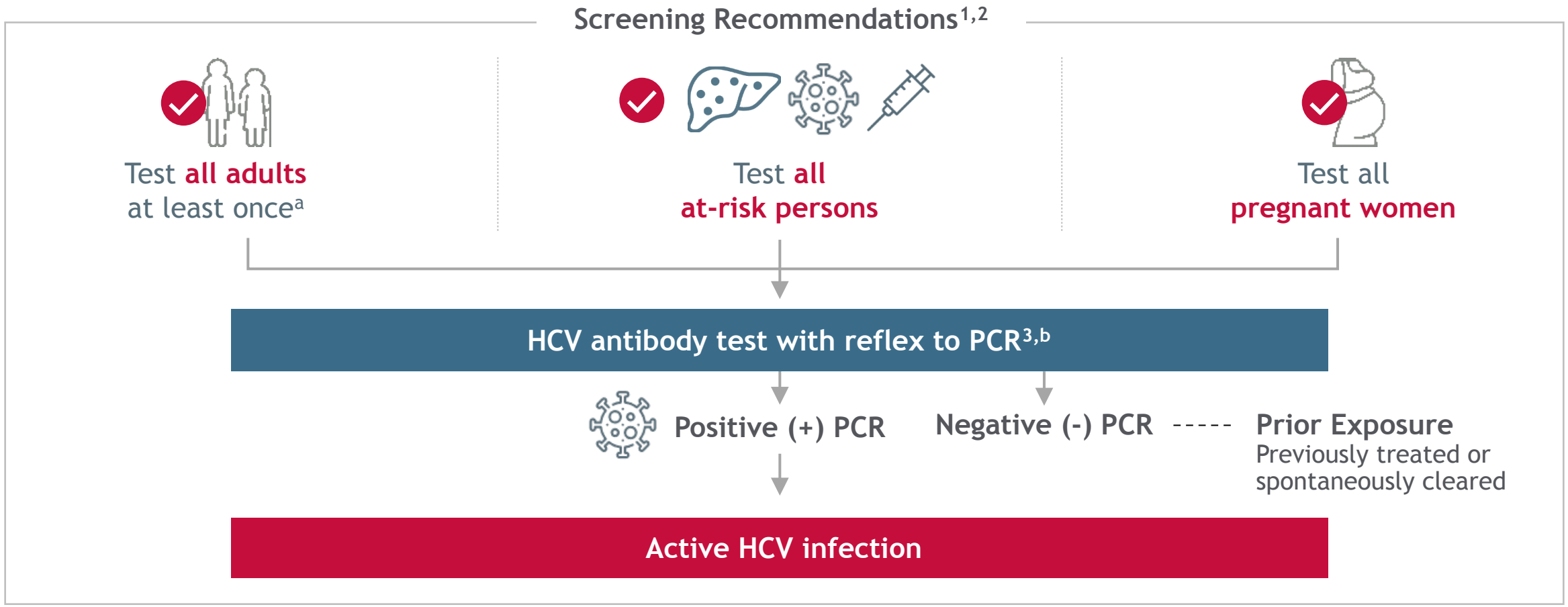


Given the accuracy of the screening test and the availability of effective DAAs for HCV infection, the USPSTF determined that the magnitude of the benefit of screening and treatment is substantial for adults aged 18 to 79 y.[2]

[a]All numbers are approximate. [b]This HCV care cascade shows data of viremic patients only. The number of persons alive who had or have ever had HCV is estimated to be 4.29 million in 2018. [a]

1. Chhatwal J et al. APT. 2019; 2. Zibbell JE, et al. Am J Public Health. 2018;108(2):175-181. 2.USPSTF.https://***.uspreventiveservicestaskforce.org/uspstf/document/RecommendationStatementFinal/hepatitis-cscreening#practice-considerations Accessed March 2, 2020

CDC and AASLD/IDSA recommend universal screening for Chronic HCV



"At-risk" refers to patients with characteristics that increase risk of HCV infection, including those with a history of drug use (current and past) and all persons living with HIV infection.

PCR=polymerase chain reaction; [a]Except in settings where the prevalence of HCV infection is <0.1%. [b]For those without access to reflex testing, conduct an HCV antibody test followed by an HCV RNA PCR test.

1. AASLD/IDSA. Updated October 5, 2021. Accessed September 27, 2022. **********.hcvguidelines.org 2. Schillie S, et al. *MMWR Recomm Rep*. 2020;69(2):1-17. 3. Dieterich DT, et al. *Gastroenterol Hepatol (NY)*. 2019;15(5 suppl 3):1-12.

Assessment and Simplified Approach to HCV Treatment

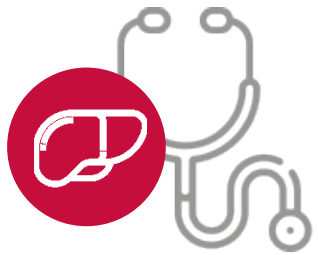
AASLD/IDSA Recommends Immediate Treatment for People with Chronic HCV

Treatment Guidance[1]

Treat all patients with chronic HCV infection, including those with active or recent injection drug use or a concern for reinfection

Patients with a short life-expectancy that cannot be remediated by HCV treatment, liver transplantation, or another directed therapy should be excluded

Refer to a Specialist[2]



Patients who have any of the following characteristics:

- Prior hepatitis C treatment without cure
- HIV-positive or HBsAg-positive
- Decompensated cirrhosis
- Severe renal impairment[a]
- Known or suspected HCC[b]
- Liver transplantation candidates
- Uncontrolled comorbidities
- Children and adolescents

eGFR=estimated glomerular filtration rate; HBsAg=hepatitis B surface antigen; HCC=hepatocellular carcinoma.
[a]eGFR <30 mL/min/1.73 m^2 or renal replacement therapy.[2] [b]Abnormal ultrasound result and/or an elevated alpha fetoprotein concentration.[2]
1. AASLD/IDSA. Updated October 5, 2021. Accessed September 27, 2022. **********.hcvguidelines.org 2. Dieterich DT, et al. *Gastroenterol Hepatol (NY)*. 2019;15(5 Suppl 3):1-12.

Simplified HCV Treatment for Treatment-Naïve Patients Without Cirrhosis

ELIGIBLE

Patients with chronic hepatitis C who do not have cirrhosis and have not previously received Hepatitis C treatment

PRETREATMENT ASSESSMENT

Cirrhosis Assessment
- Biopsy not required
- Cutoffs suggesting cirrhosis
  - FIB-4 >3.25
  - APRI >2.0
  - Platelets <150,000/mm^3
  - FibroScan >12.5 kPa

Medication Reconciliation
- Current Rx and OTC

DDI Assessment

Education
- Tx administration, adherence, avoidance of alcohol, and reinfection

Pretreatment Lab Testing
Within 6 months
- CBC
- Hepatic function panel
- eGFR

Prior to starting antiviral therapy
- Quantitative HCV RNA (HCV viral load)
- HIV antigen/antibody test
- HBsAg

Before initiating Tx
- Serum pregnancy testing and counseling about pregnancy risks of HCV medication should be offered to women of childbearing age.

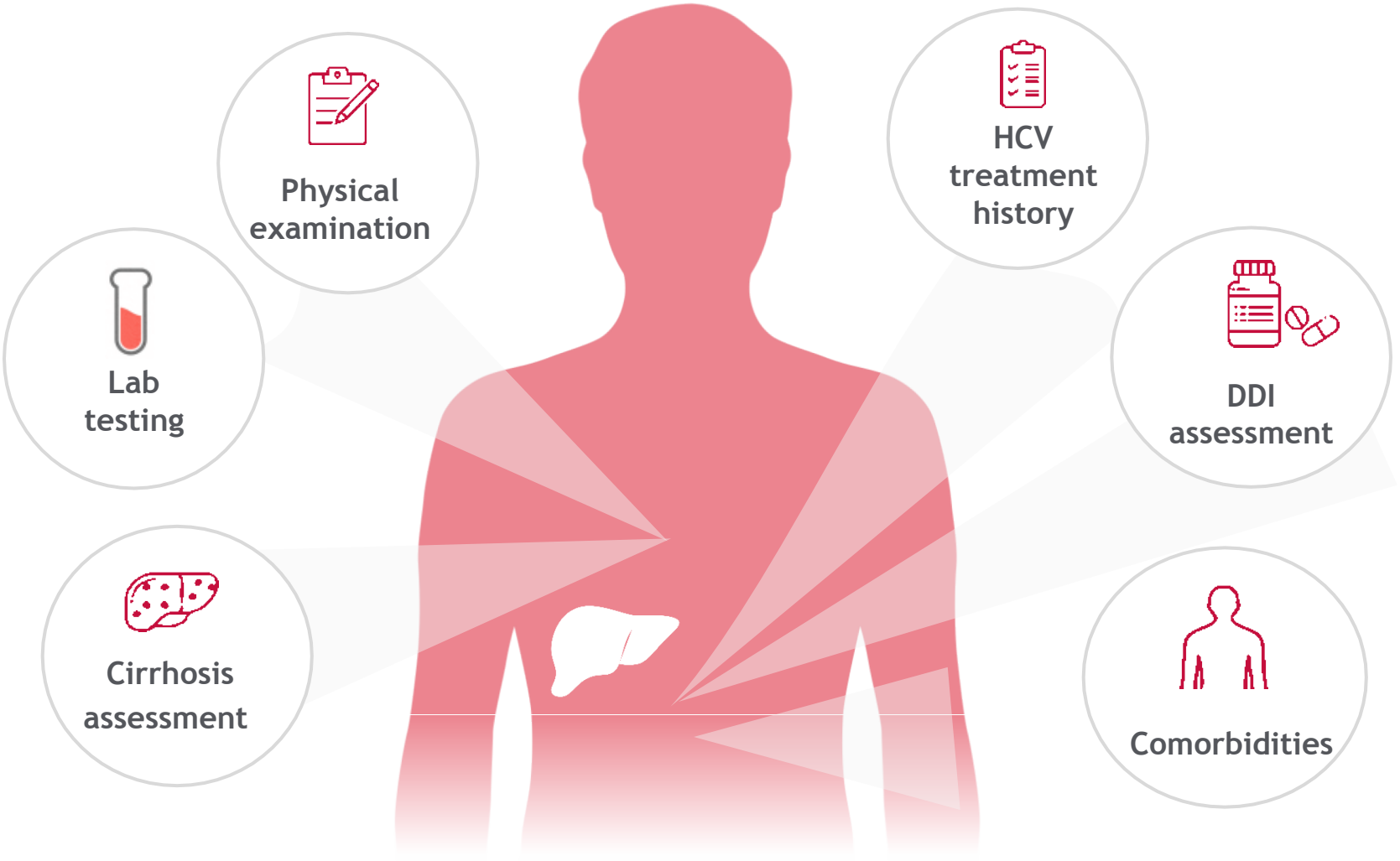
NOT ELIGIBLE

Patients who have any of the following characteristics:
- Prior hepatitis C treatment
- Cirrhosis
- Prior liver transplant
- HIV or HBsAg positive
- End-stage renal disease (ie, eGFR <30 mL/min/m^2)
- Currently pregnant

APRI, aspartate aminotransferase (AST) to platelet ratio index; CBC, complete blood count; DDI, drug–drug interaction; FIB-4, Fibrosis-4; GLE, glecaprevir; OTC, over-the-counter; PIB, pibrentasvir; RNA, ribonucleic acid.

AASLD/IDSA HCV Guidance: Recommendations for Testing, Managing, and Treating Hepatitis C, updated January 21, 2021
Available at: **********.hcvguidelines.org/sites/default/files/full-guidance-pdf/AASLD-IDSA_HCV-Guidance_TxN-Simplified-Treatment_a.pdf.

Pre-treatment assessments: Clinical and physical examination



AASLD/IDSA. Updated October 5, 2021. Accessed September 27, 2022. **********.hcvguidelines.org

Stages of Liver Fibrosis

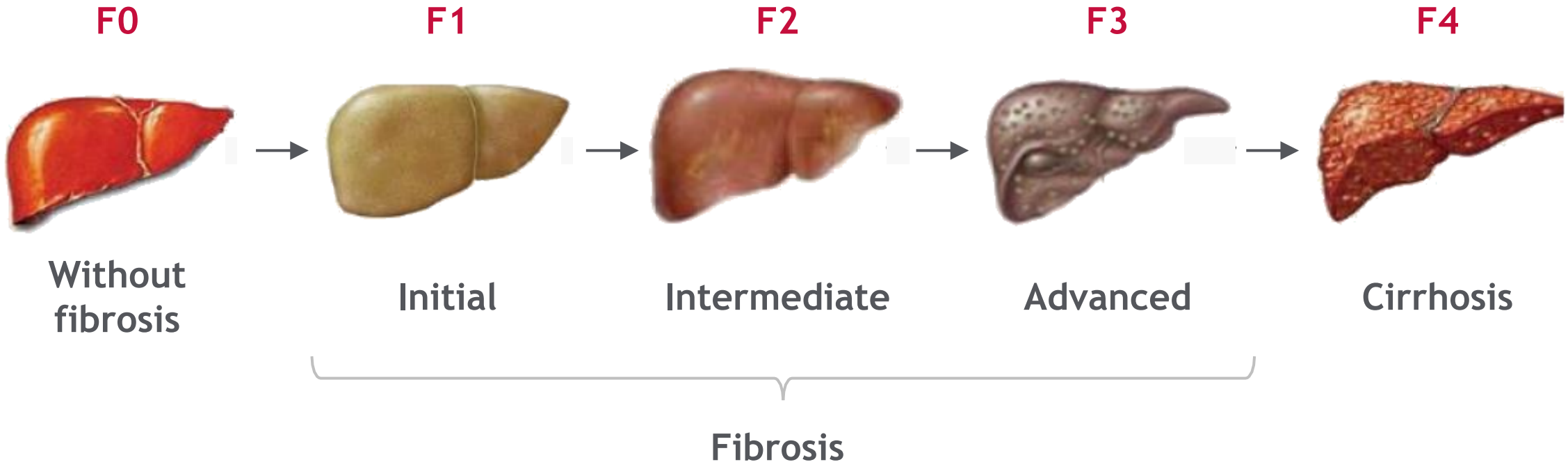
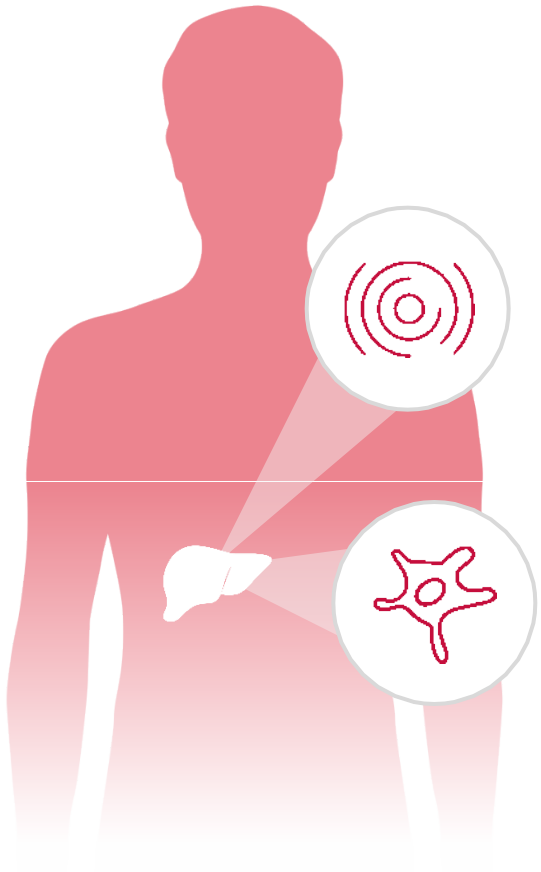


Image adapted from World J Gastroenterol. Nov 7, 2015; 21(41): 11552-11566

PRE-TREATMENT ASSESSMENTS: LIVER FIBROSIS ASSESSMENT



Fibrosis can be assessed by any one or more of the following:

Elastography[1]
Transient elastography (FibroScan®): estimation based on detection of ultrasound-propagated shear waves

Biomarkers[1-4]
FIB-4: Estimation based on patient's age, ALT, AST, and platelet count

FibroSure®: Estimation based on 6 biomarkers[a]

APRI: Estimation based on AST and platelet count

Platelets: Low levels predictive of advanced liver disease

Accurate assessment of fibrosis is recommended for all patients with chronic HCV[5]

Liver biopsy not required[5]

Individuals with clinically evident cirrhosis do not require additional staging[5]

Cutoffs suggesting cirrhosis (F4)[2,6]	
FIB-4	>3.25
FibroSure®	>0.73
APRI	>2.0
Platelets	<150,000/mm³
FibroScan®	>12.5 kPa

For patients with cirrhosis (F4)[5]:

- Calculate CTP score
- Perform ultrasound of the liver (conducted within 6 months prior to treatment initiation)
  - Evaluate to exclude HCC and subclinical ascites

APRI=aspartate aminotransferase to platelet ratio index; CTP=Child-Turcotte-Pugh; FIB-4=Fibrosis-4; [a]Alpha-2-macroglobulin, haptoglobin, apolipoprotein A1, gamma-glutamyl transpeptidase, total bilirubin, alanine transaminase.[4]

1. Papastergiou V, et al . *Ann Gastroenterol*. 2012;25(2):218-231. 2. Chou R, et al. *Ann Intern Med*. 2013;158(11):807-820. 3. Northwell Health Laboratories. Accessed June 15, 2021. *******nslijlab.testcatalog.org/show/FIBROSURE 4. eviCore Healthcare. Accessed July 8, 2021. **********.evicore.com/-/media/files/evicore/clinical-guidelines/solution/lab-management/healthplan/fibrotest-fibrosure.pdf 5. AASLD/IDSA. Updated October 5, 2021. Accessed September 27, 2022. **********.hcvguidelines.org 6. AASLD/IDSA. Updated November 6, 2019. Accessed June 14, 2021. **********.hcvguidelines.org/sites/default/files/full-guidance-pdf/AASLD-IDSA_HCV-Guidance_TxN-Simplified-Tx-No-Cirr_e.pdf

Scoring parameters for determining severity of Cirrhosis

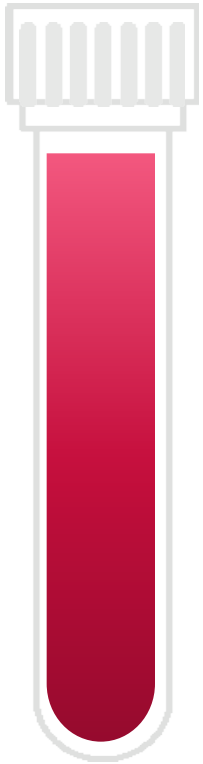
Parameter	Points Scored for Observed Findings		
	1 Point	2 Points	3 Points
Encephalopathy	None	Grade 1 or 2 (or precipitant-induced)	Grade 3 or 4 (or chronic)
Ascites	None	Mild/Moderate (diuretic responsive)	Severe (diuretic refractory)
Serum bilirubin (mg/dL)	<2	2 to 3	>3
Serum albumin (g/dL)	>3.5	2.8 to 3.5	<2.8
PT (sec prolonged) **or international Normalized Ratio** (INR)	<4 <1.7	4 to 6 1.7 to 2.3	>6 >2.3

The Child-Turcotte-Pugh (CTP) score is obtained by adding the score for each parameter

- CTP class A = 5-6 points
- CTP class B = 7-9 points
- CTP class C = 10-15 points

US Department of Veterans Affairs. Child-Turcotte-Pugh Calculator. **********.hepatitis.va.gov/cirrhosis/background/child-pugh-calculator.asp. Accessed November 17, 2021.

Pre-treatment assessments: Blood tests



BLOOD TESTS

- **HCV genotype**
- **HCV RNA viral load**
- **CBC/platelets**
- **INR**
- **Hepatic function panel**
  - Albumin
  - Total and direct bilirubin
  - ALT
  - AST
- **HBV serology**
  - HBsAb
  - HBsAg
  - HBcAb
- **HIV test**
- **eGFR**
- **Pregnancy serum test**
- **HAV test**

ALT=alanine aminotransferase; AST=aspartate aminotransferase; CBC=complete blood count; HBcAb=hepatitis B core antibody; HBsAb=hepatitis B surface antibody.
AASLD/IDSA. Updated October 5, 2021. Accessed September 27, 2022. **********.hcvguidelines.org
Dieterich et al, Gastroenterology & Hepatology; volume 15, issue 5, supplement 3, May 2019

Potential for HBV Reactivation During DAA Therapy

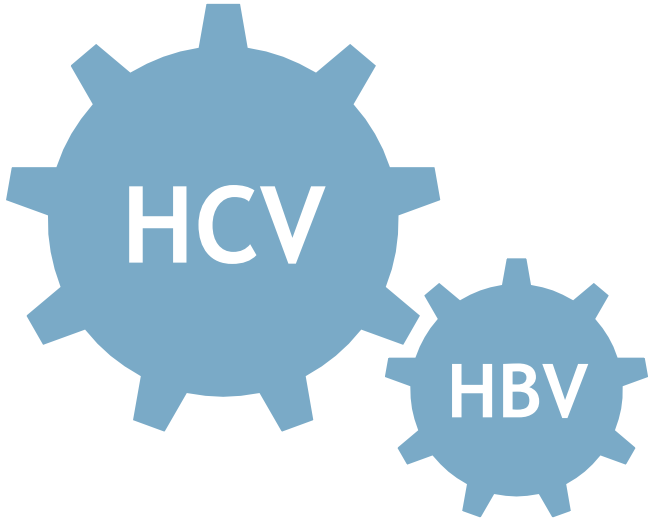
In October 2016, the FDA sent out a safety announcement

- 24 cases of HBV reactivation in HBV/HCV coinfected patients treated with DAAs (from 11/22/2013 through 07/18/16)
- Warned of the risk of HBV becoming an active infection in any patients with current or previous HBV infection and who are treated with certain HCV DAAs.
- All patients should be screened for HBV prior to DAA treatment and monitored for HBV flare-ups or reactivation during treatment and after treatment follow-up

In February 2017, the FDA updated all HCV DAA labels with a warning regarding the risk of HBV reactivation in patients coinfected with HCV and HBV

Boxed Warning:

Hepatitis B virus (HBV) reactivation has been reported, in some cases resulting in fulminant hepatitis, hepatic failure, and death

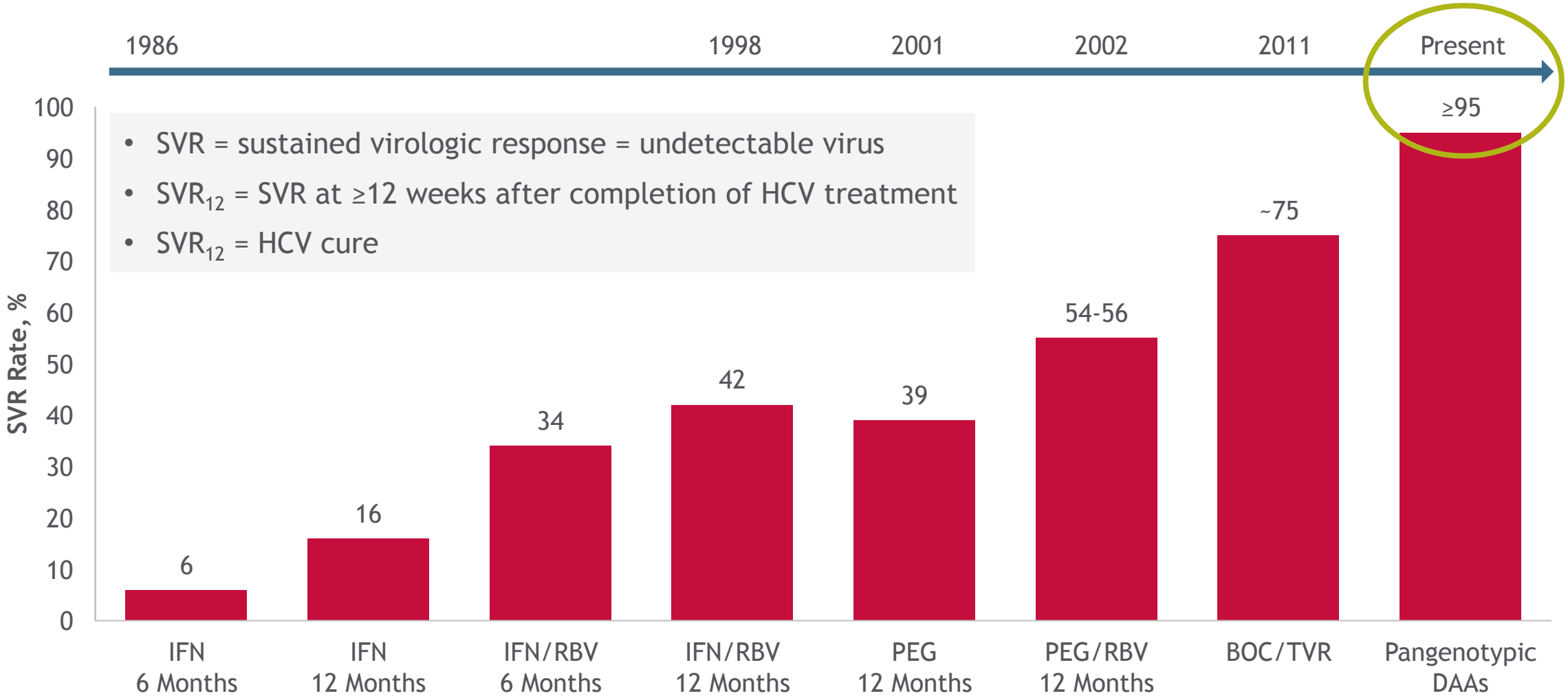


1. Wang et al. Clin Gastro and Hepatol. 2017.; 2. Bersoff-Matcha S, et al. Annals of Internal Medicine. 2017; 166:792-798; 3. Delaney W. Antiviral Research. 2013; 4. Aggeletopoulou et al. World J Gastroenterol. 2017; 23(24):4317-4323; 5. Doi et al. Hepatology Research. 2017; 6. Caccamo G, Saffioti F, Raimondo G. World J Gastroentrol. 2014; 20(40):14559-14567; 7. Terrault NB et al. Hepatology 2015; Published online November 13, 2015: doi:10.1002/hep.28156

HCV Treatment

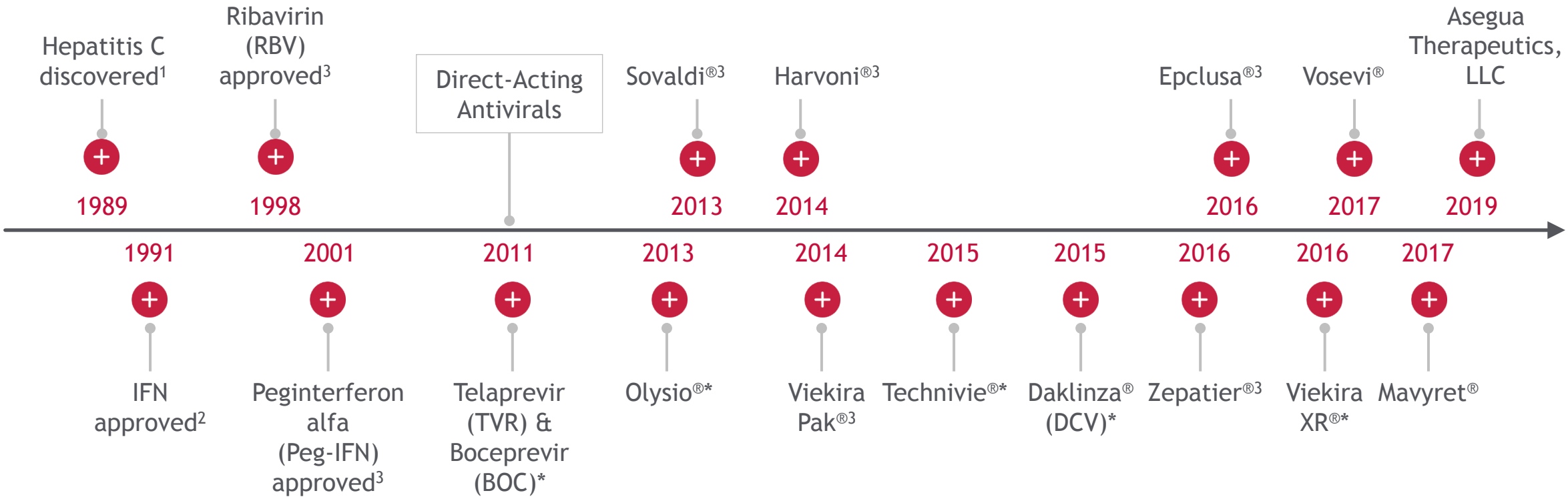
Evolution HCV Treatment

It's Come a Long Way



BOC, boceprevir; DAA, direct-acting antiviral (drug); IFN, interferon; PEG, pegylated interferon; RBV, ribavirin; SVR, sustained virologic response; TVR, telaprevir.
Adapted from Strader DB, Seeff LB. *Clin Liver Dis.* 2012;1(1):6-11.

HCV Treatment Timeline

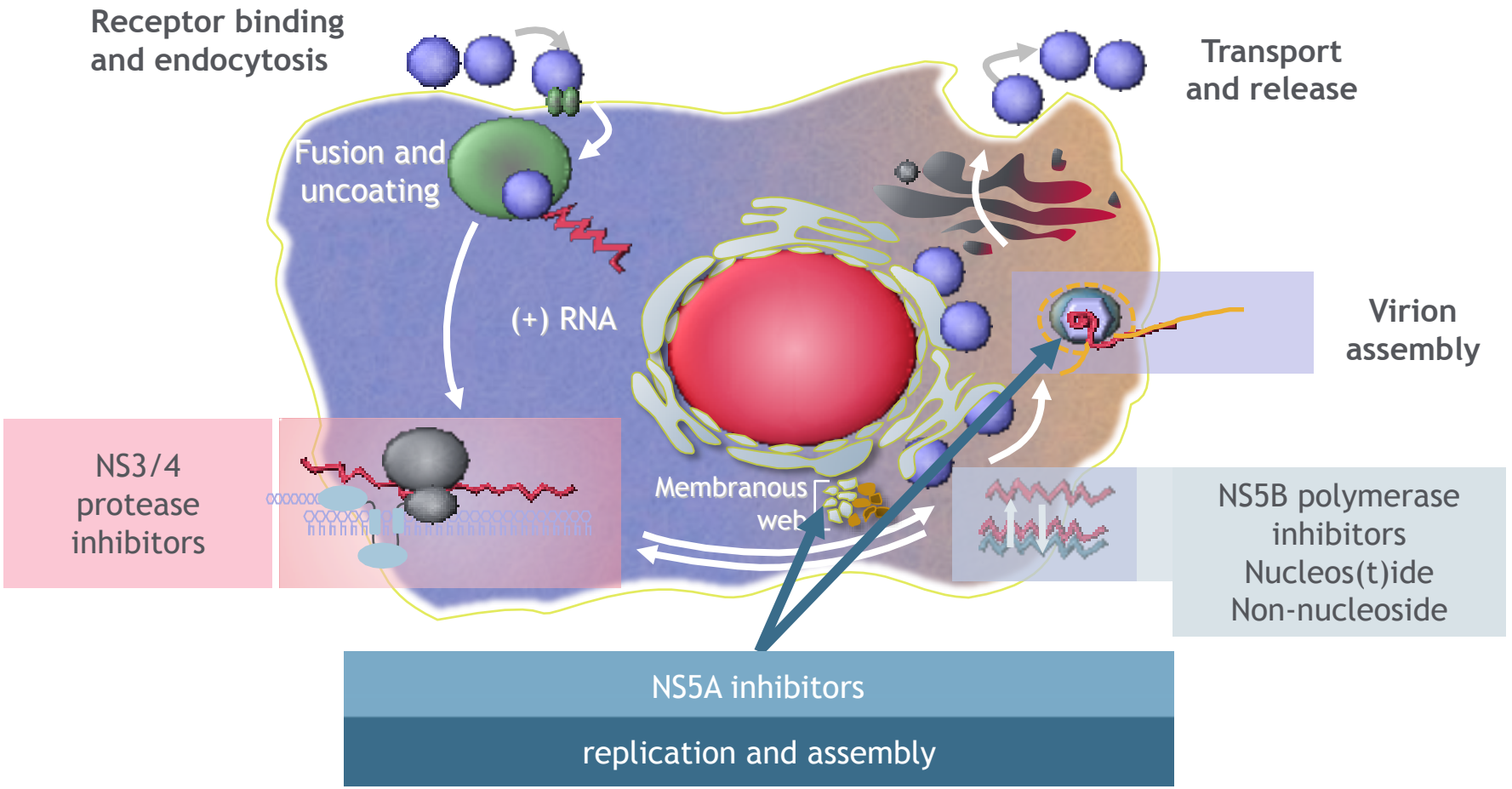


Recent advances in HCV therapeutic options provide high cure rates (>95%) with direct-acting antiviral options that are IFN-free[4]

Timeline not to scale

* = Discontinued therapeutic; 1. CDC. Hepatitis C: 25 Years of Discovery. **********.cdc.gov/knowmorehepatitis/timeline.htm. Accessed March 2, 2020; 2. Friedman RM and Contente S. Treatment of Hepatitis C Infections with Interferon: A Historical Perspective. Hep Res Treat. 2010; DOI: 10.1155/2010/323926; 3. Hepatitis C Online. **********.hepatitisc.uw.edu/page/treatment/drugs . HCV Advocate site. March 2020; 4. FDA. Chronic Hepatitis C Virus Infection: Developing Direct-Acting Antiviral Drugs for Treatment Guidance for Industry. **********.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm225333.pdf. Accessed March 2, 2020.

HCV Life Cycle and Targets for Direct-Acting Antivirals (DAAs)



Adapted from Manns MP, et al. *Nat Rev Drug Discov*. 2007;6:991-1000.

Gilead's Commitment to HCV Elimination

2013	2014	2016	2017
Sovaldi Sofosbuvir	Harvoni Ledipasvir/ Sofosbuvir	Epclusa Sofosbuvir/ Velpatasvir	Vosevi Sofosbuvir/ Velpatasvir/ Voxilaprevir
400 mg	90 mg/400 mg	400 mg/100 mg	400 mg/100 mg/100 mg
			
GT1,2,3,4 interferon-free treatment option for GT2,3	**STR, licensed in adults and adolescents***	**pangenotypic STR****	**pangenotypic STR for DAA treatment failure**

DAA: direct-acting antiviral agent; GT: genotype;
STR: single tablet regimen
*LDV/SOF is licensed for the treatment of adults and adolescent patients ≥12 years of age with GT1, 4, 5 or 6 CHC
**SOF/VEL is licensed for the treatment of adults and pediatric patients ≥3 years of age with GT1-6. See Epclusa FDA package insert for pediatric dosing formulations.

THE ONLY PROTEASE INHIBITOR-FREE, PANGENOTYPIC, PANFIBROTIC HCV REGIMEN

SOFOSBUVIR	A nucleotide analog NS5B polymerase inhibitor
VELPATASVIR	An NS5A inhibitor

In Adult NC/CC Patients

Pill not actual size

1
PILL
ONCE A DAY

12
WEEKS
FOR ALL PATIENTS

NO FOOD REQUIREMENT

Dosing for pediatric patients aged 3 years and older is based on weight

- Lower-dose formulations are recommended for certain pediatric patients
- In pediatric patients less than 6 years of age, administer the oral pellets with food to increase tolerability related to palatability

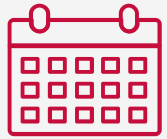
See EPCLUSA full Prescribing Information, including Instructions for Use for oral pellets, for details on dosing for pediatric patients.

CC=compensated cirrhosis; NC=non-cirrhotic.
EPCLUSA US full Prescribing Information. Gilead Sciences, Inc. Foster City, CA. June 2021.

Gilead's Commitment to HCV Elimination with EPCLUSA

Simple delivery of care for HCV control and ultimately elimination

Pan-genotypic	Pan-fibrotic	1 Pill*	1 Duration†	Minimal Monitoring‡	High SVR Rates
1 2 3 4 5 6	F0 F1 F2 F3 F4				
	Including DCC				



Test → **Treat** → **Cure**

HCV RNA positive

98%
Overall SVR Rate§

Gilead Sciences Inc. EPCLUSA® US Prescribing Information, Revised November 2017.
DCC: decompensated cirrhosis; F0-F4: fibrosis scores 0-4; GT: genotype
*addition of ribavirin indicated in DCC; †12 weeks; ‡Minimal on-treatment assessments; §In pivotal phase 3 trials

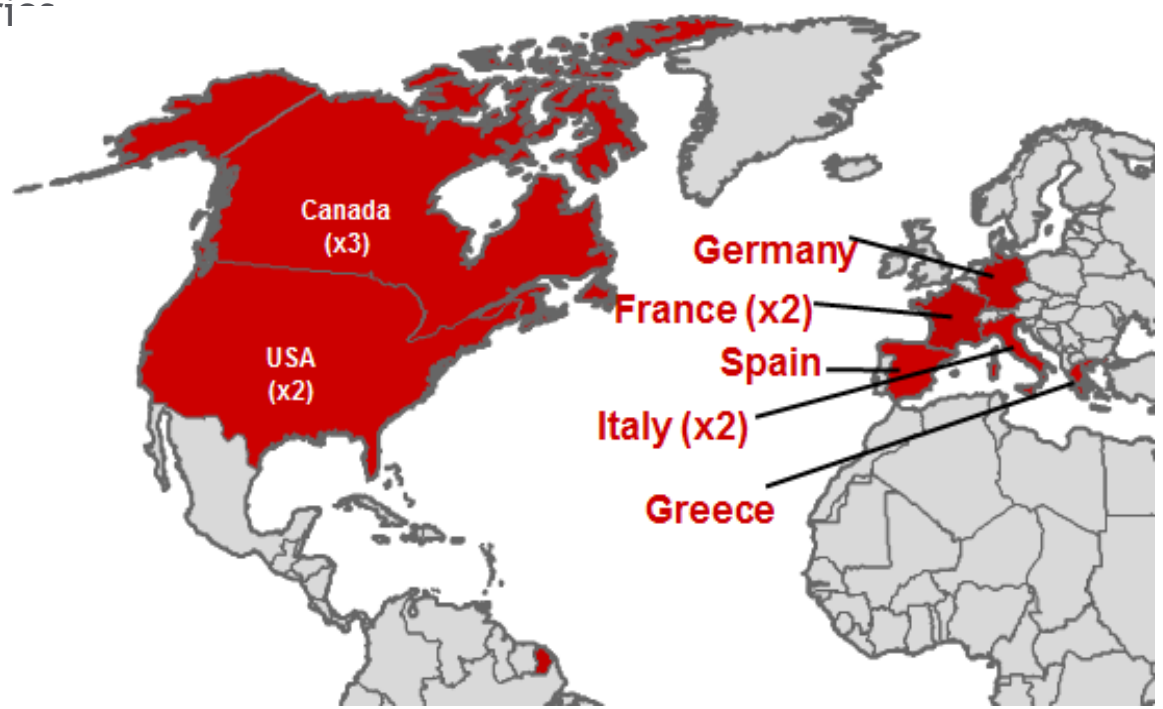
SOF/VEL Real-World Data

Global real-world evidence of SOF/VEL for 12 weeks

Real world analysis of 12 clinical practice cohorts from 7 countri--

5541 patients were included, without use of RBV §

Baseline Characteristics	N=5340 (%)
Age – mean (SD)	54 (13%)
Male	2822 (53%)
Genotype, % **1**/ **2**/ **3**/ 4/ 5/ 6/ unknown	**30**/ **30**/ **33**/ 5/ 1/ 1
Fibrosis, % F0-F2/ **F3**/ **F4**/ unknown	54/ **13**/ **21**/ 12
HIV/HCV coinfection	196 (4%)
Former or ongoing IVDU	706 (13%)
PPI use at Baseline	287 (5%)
TE (pegIFN + RBV ± PI)	660 (12%)



Trio Health REAL WORLD EVIDENCE

anrs France REcherche Nord & sud Sida-hiv Hépatites

HCV-TARGET Hepatitis C Therapeutic Registry and Research Network

HELIOS HEpatitis C real-Life study for patients On Sofosbuvir

DHC-R Deutsches Hepatitis C-Register

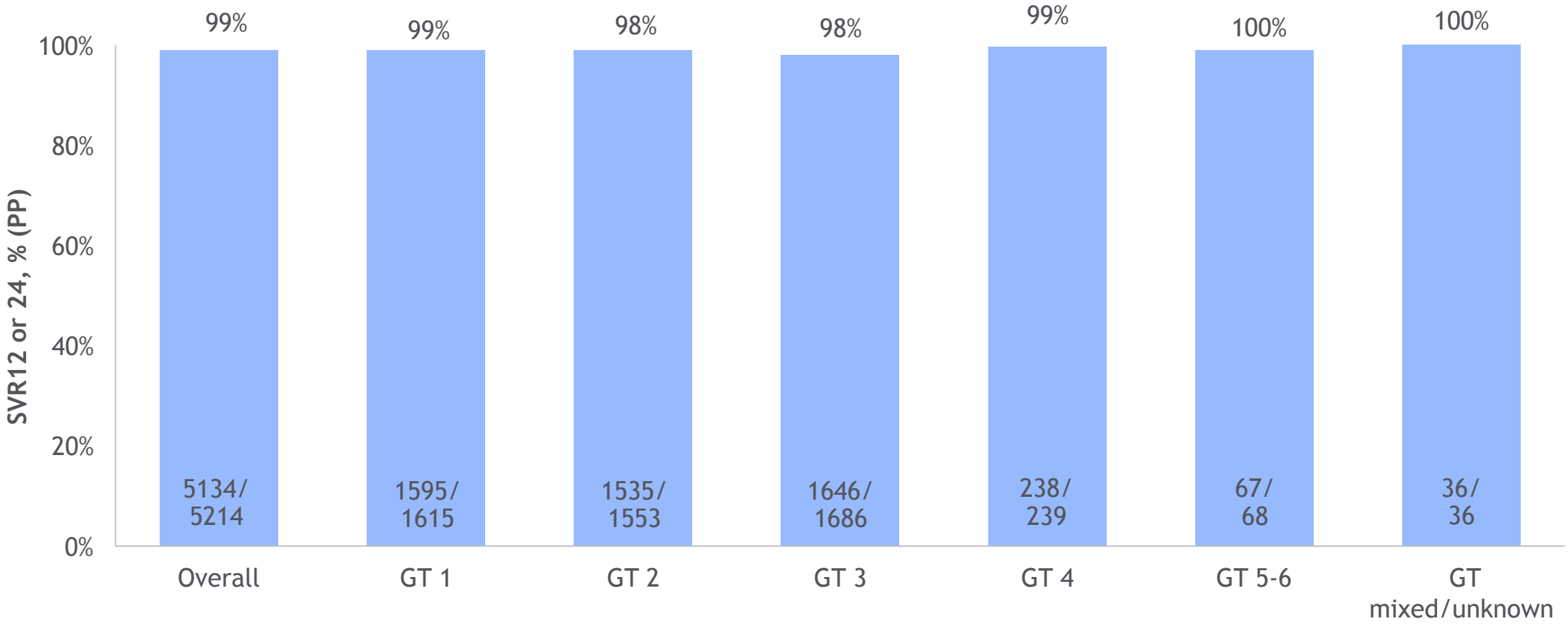
§Total number of patients varies across the characteristics, due to missing data

* Data from 1 cohort were not included in the ITT characteristics analysis due to missing data

Mangia et al.Liver International 2020;40:1841-1852

SOF/VEL for 12 Weeks: SVR by Genotype

Real world analysis of 12 clinical practice cohorts from 7 countries

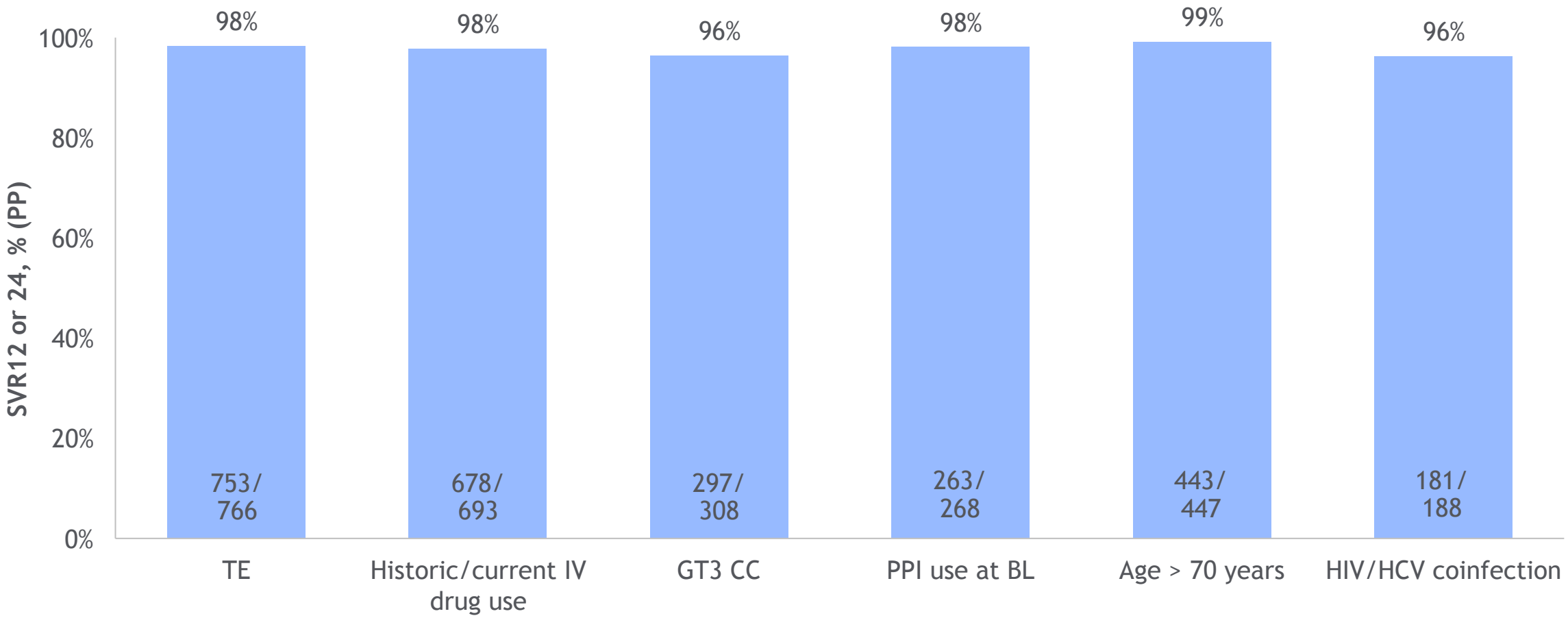


High SVR in the largest real-world cohort across all genotypes

Mangia et al.Liver International 2020;40:1841-1852

SOF/VEL for 12 Weeks: SVR by Subpopulations

Real world analysis of 12 clinical practice cohorts from 7 countries



High SVR in the largest real-world cohort of diverse patients

Mangia et al.Liver International 2020;40:1841-1852

Conclusion: Largest Real-World Cohort With SOF/VEL

Real world analysis of 12 clinical practice cohorts from 7 countries

- **High effectiveness of SOF/VEL** in diverse patient populations, regardless of:
  - Genotype
  - Fibrosis stage
  - Prior treatment (pegIFN + RBV ± PI)
  - Patient characteristics (IV drug use, PPI use, older age, HIV/HCV Co-infection)
- **Simplification** of HCV Care Cascade is possible with SOF/VEL
- A **Test and Treat** strategy with SOF/VEL may further improve HCV care

Mangia et al.Liver International 2020;40:1841-1852

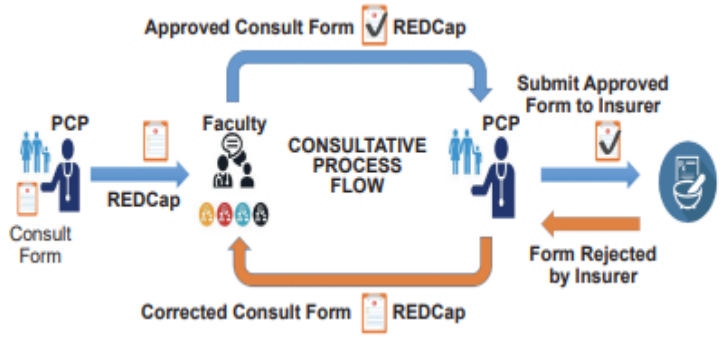
New HCV Treaters

PCPs New to HCV Treatment Achieve High Response Rates

Rural PCPs (33 NPs, 12 MDs/DOs and 7 PAs) new to HCV treatment underwent web-based training by expert faculty and began HCV treatment in their community

Patient Demographics	
Age (yrs), median (range)	40 (22-79)
Gender, female (%)	44.1%
Payer (%)	Medicaid, 87.7% Medicare, 8.0% Private, 5.3% Uninsured, 1.3%
History of IVDU (%)	82.1%
Genotype (%)	GT1, 64% GT2, 12% GT3, 25% Other, 0.6%
Fibrosis Score (%)	F0-F1, 65.1% F2, 17.1% F3-F4,10.9% Unknown, 6.8%
Naïve/Experienced (%)	97.6%/2.4%

Expert Faculty and PCP Process



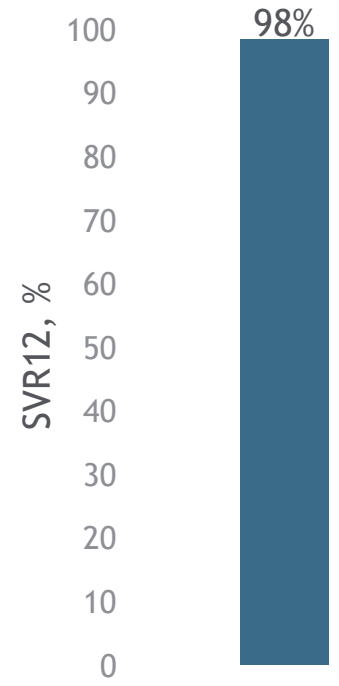
Automatic Email Alerts:

- To faculty that new/updated consult is ready for review
- To PCP that consult has been approved or requires revision/response

Downloadable PDF:

- Serves as a PA request and contains all elements of work-up in one place for insertion into PCP's EMR

Response Rate



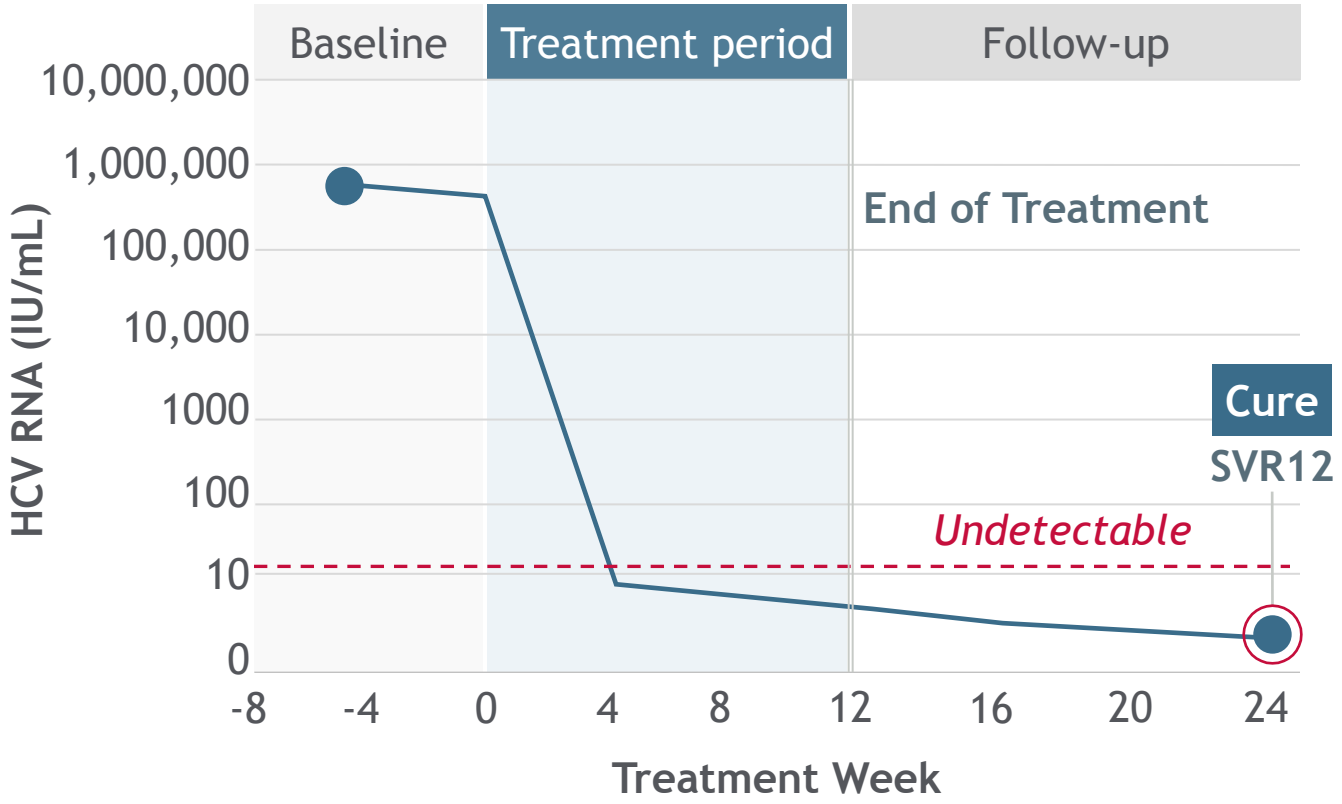
New HCV Treaters in Rural PCP Setting Achieve Similarly High Response Rates to Specialists

Feinberg et al. Mobilizing PCP to Treat CROI 2023 Poster #594

Monitoring

TREATMENT AND MONITORING:
ASSESSMENT OF CURE (SVR12)

Viral load testing is recommended ≥12 weeks after completion of therapy to document SVR12 (cure)[1,2]



Pivotal Clinical Trials

98% **OVERALL CURE RATE**

(n=1015/1035; ASTRAL -1, -2, -3)

in GT 1-6 adult patients without cirrhosis or with compensated cirrhosis[a]

SVR12 was the primary endpoint and was defined as HCV RNA <15 IU/mL at 12 weeks after the end of treatment. Achieving SVR12 is considered a virologic cure.[3,4]

[a]Patients included in all ASTRAL trials were TN or TE.[3]

1. AASLD/IDSA. Updated October 5, 2021. Accessed September 27, 2022. *******hcvguidelines.org 2. Hepatitis C Online. Updated October 12, 2020. Accessed July 12, 2021. **********.hepatitisC.uw.edu/go/treatment-infection/monitoring/core-concept/all 3. EPCLUSA US full Prescribing Information. Gilead Sciences, Inc. Foster City, CA. April 2022. 4. US Department of Health and Human Services, Center for Drug Evaluation and Research. Guidance for industry. Chronic hepatitis C virus infection: developing direct-acting antiviral drugs for treatment. November 2017.

TREATMENT AND MONITORING: POST-CURE MANAGEMENT

Patients Without Cirrhosis

No special monitoring or follow-up specifically for HCV or liver care is recommended

Patients With Cirrhosis

Due to persistent risk for developing HCC, conduct continued surveillance for HCC with an abdominal ultrasound (with or without alpha fetoprotein) every 6 months

Persistently Abnormal Liver Tests

Evaluate for possible other causes of liver disease, including HBV

Ongoing Risk of HCV Reinfection

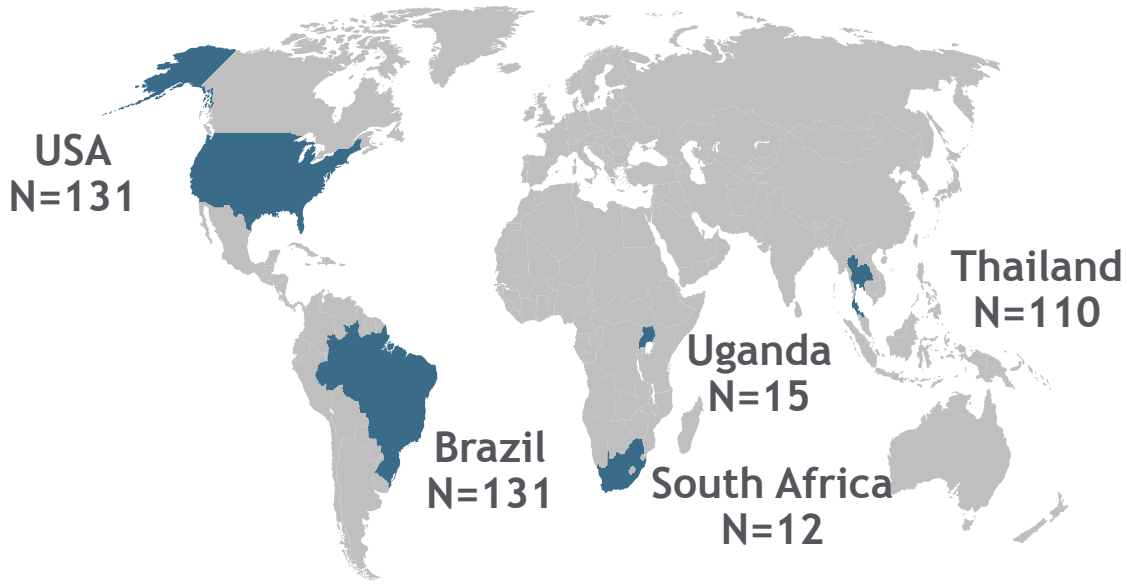
All persons with ongoing risk for reacquiring HCV should have periodic assessment for HCV reinfection and counseling on prevention of reinfection. At least annual HCV RNA screening is recommended for persons who inject drugs and for men with HIV who have unprotected sex with men

AASLD/IDSA. Updated October 5, 2021. Accessed September 27, 2022. *******hcvguidelines.org

SOF/VEL Minimal Monitoring (MinMon) Strategy for HCV treatment

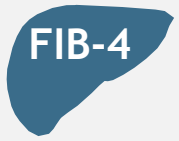
Phase IV multi-national, open-label, prospective, single-arm, interventional study

A broad population of 399 participants from 5 countries



Compensated cirrhosis	PWID (former/ current)	Women	HIV coinfection
9%	34%	35%	42%

Treatment with SOF/VEL for 12 weeks in a simplified, minimal monitoring approach



FIB-4 liver assessment and no pre-treatment genotyping

SOF/VEL 12 weeks

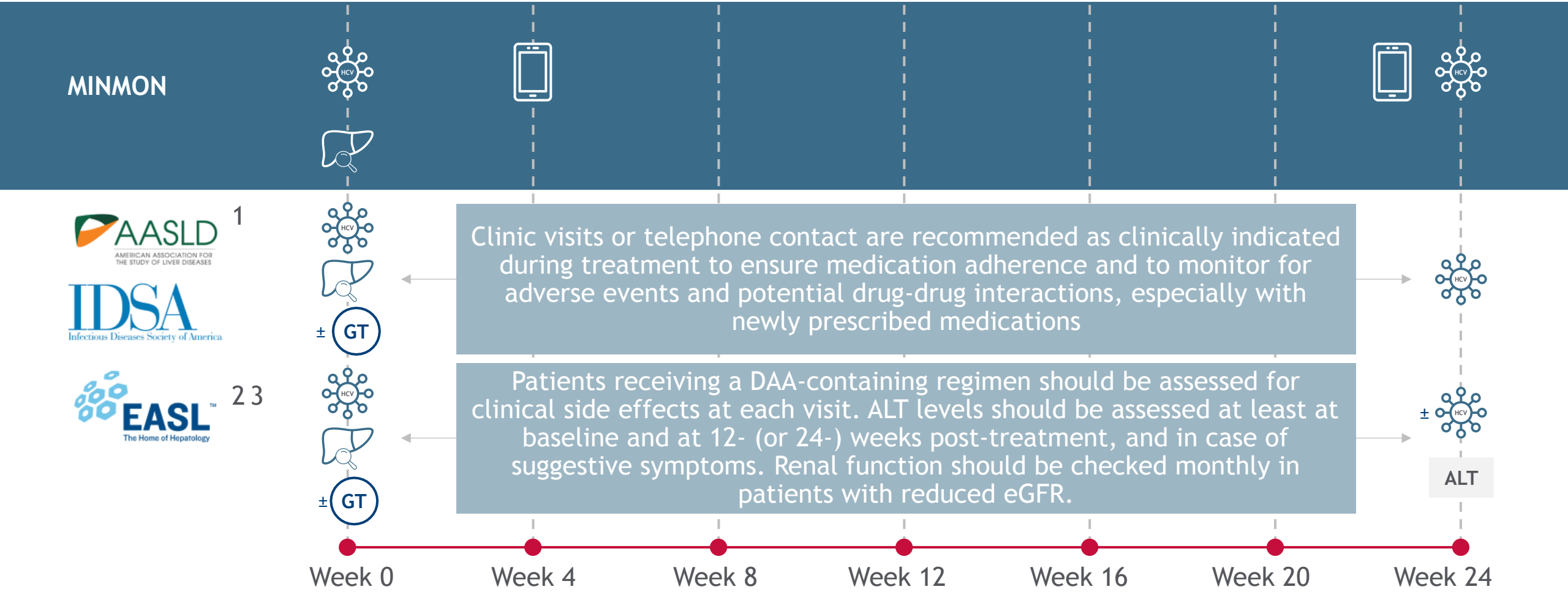
All 84 tablets dispensed at initiation

Remote contact at Week 4 and 22 (SVR scheduling) – no on-treatment clinic visits/labs

ACTG=AIDS Clinical Trials Group

Solomon S, et al. Lancet Gastroenterology Hepatology 2022. ********doi.org/10.1016/S2468-1253(21)00397-6

SOF/VEL Minimal Monitoring (MinMon) Strategy for HCV treatment

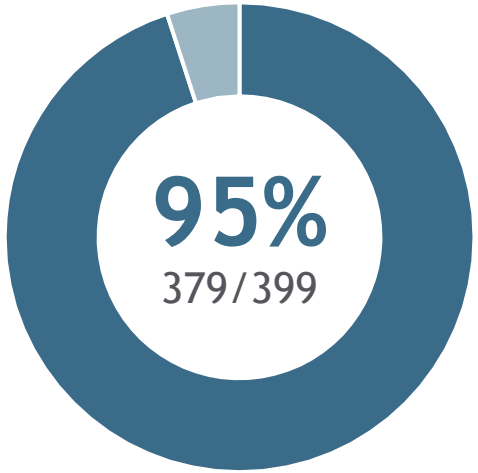


ACTG=AIDS Clinical Trials Group

1. AASLD/IDSA. HCV Guidance: Recommendations for Testing, Managing, and Treating Hepatitis C. Available at: **********.hcvguidelines.org/evaluate/monitoring. (Accessed November 2020); 2. EASL CPG HCV. J Hepatol 2020; ********doi.org/10.1016/j.jhep.2020.08.018; 3. Solomon S, et al. Lancet Gastroenterology Hepatology 2022. ********doi.org/10.1016/S2468-1253(21)00397-6

SOF/VEL Minimal Monitoring (MinMon) Strategy for HCV treatment

Sustained virological response*



- 17 with virological non-response**
- 1 sample prior to SVR window opening and no follow-up after
- 2 lost to follow-up

2x

Remote contact:
- Week 4: 99% (396/399)
- Week 22: 84% (335/399)

Unplanned visits
- 15 (3.8%) participants recorded 21 unplanned visits†

Adverse and serious adverse events

AE

23 participants (5.8%) reported AEs
- 5 attributed to SOF/VEL
- 1 resulted in SOF/VEL discontinuation

SAE

14 participants (3.5%) reported SAEs
- 0 attributed to SOF/VEL
- 0 resulted in SOF/VEL discontinuation

The MinMon approach to HCV treatment delivery with SOF/VEL was simple, safe and achieved SVR comparable to current clinical standards in treatment naïve persons without decompensated cirrhosis

*SVR defined as HCV ≤LLOQ in the first sample obtained from participant from Week 22–Week 76; †8=abnormal lab values at baseline; 6=non-AE clinical events; 3=adverse events. **Investigator reinfection analysis pending. ACTG=AIDS Clinical Trial Group; Solomon S, et al. Lancet Gastroenterology Hepatology 2022. ********doi.org/10.1016/S2468-1253(21)00397-6

Adherence

Recommendations for the Management of DAA Treatment Interruptions

Interruptions During First 28 Days of DAA Therapy

Missed ≤7 Days

- **RESTART** DAA therapy immediately. Complete therapy for originally planned duration (8 or 12 weeks)

Missed ≥8 Days

- **RESTART** DAA therapy immediately. Restarting takes precedence over obtaining an HCV RNA level
- Obtain HCV RNA test as soon as possible, preferably the same day as restarting DAA therapy
- If HCV RNA is negative (undetectable) complete originally planned DAA treatment course (8 or 12 weeks)
  Recommend extending DAA treatment for an additional 4 weeks for patients with GT 3 and/or cirrhosis
- If HCV RNA is positive (>25 IU/L), or not obtained, extend DAA treatment for an additional 4 weeks

Interruptions After Receiving ≥28 Days of DAA Therapy

Missed ≤7 Days

- **RESTART** DAA therapy immediately. Complete therapy for originally planned duration (8 or 12 weeks)

Missed 8-20 Consecutive Days

- **RESTART** DAA therapy immediately. Restarting takes precedence over obtaining an HCV RNA level
- Obtain HCV RNA test as soon as possible, preferably the same day as restarting DAA therapy
- If HCV RNA is negative (undetectable) complete originally planned DAA treatment course (8 or 12 weeks)
  Recommend extending DAA treatment for an additional 4 weeks for patients with GT 3 and/or cirrhosis.
- If HCV RNA is positive (>25 IU/L), or not obtained, **STOP** treatment and retreat according to retreatment recommendations

Missed ≥21 Consecutive Days

- **STOP** DAA treatment and assess for SVR12. If SVR12 not achieved, retreat according to retreatment recommendations.

AASLD_IDSA. Incomplete Adherence. Recommendations for testing, managing, and treating hepatitis C. **********.hcvguidelines.org/evaluate/monitoring#incomplete-adherence . [Accessed on 5/2/2022]

Simplify: Efficacy and Safety of SOF/VEL for 12 Weeks in People Who Inject Drugs

The Phase 4 SIMPLIFY clinical trial was evaluated in those with recent injection drug use (within the past 6 months), naïve to NS5A-based HCV therapy, with or without compensated cirrhosis

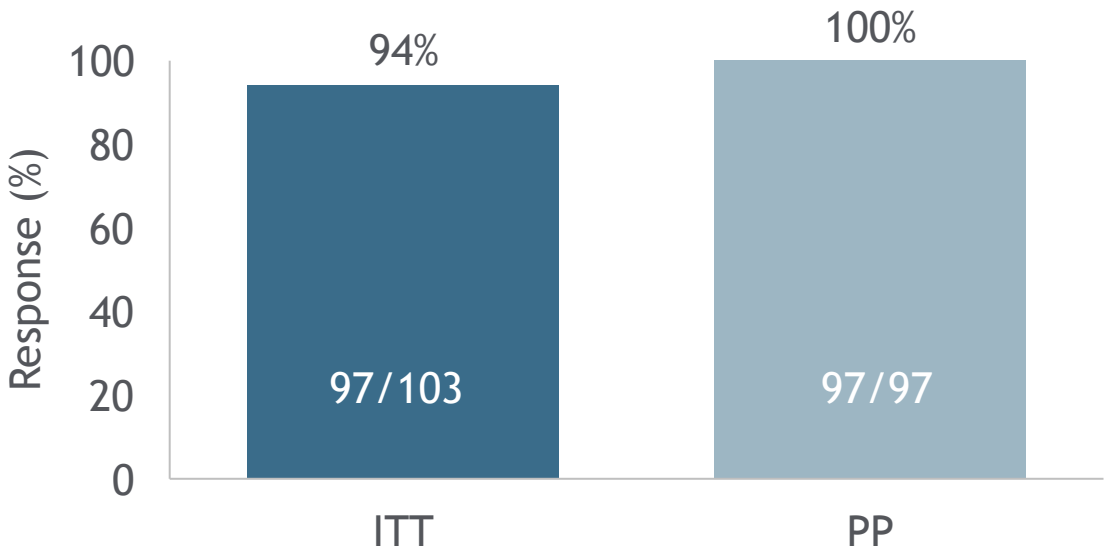
Baseline Characteristics	N=103
Median age, years (SD)	48 (41-53)
Male sex, n (%)	74 (72)
Genotype, n (%)	
• 1	36 (35)
• 2	5 (5)
• 3	60 (58)
• 4	2 (2)
F4 (cirrhosis), n (%)	9 (9)
Any injection drug use in the past 6 months, n (%)	103 (100)
Any injection drug use in the past 30 days, n (%)	76 (74)
At least daily injection drug use in the past 30 days, n (%)	27 (26)
Alcohol use in the past 30 days, n (%)	62 (60)
History of OST use, n (%)	84 (82)
Current OST, n (%)	
• Methadone	45 (44)
• Buprenorphine	4 (4)
• Buprenorphine-naloxone	12 (12)
Unstable housing, n (%)	24 (23)

OST, opioid substitution therapy; SD, standard deviation.

1. Grebely J, et al. Lancet Gastroenterol Hepatol. 2018;3(3):153-161. 2. Grebely J, et al. Clin Infect Dis. 2016;63(11):1479-1481.

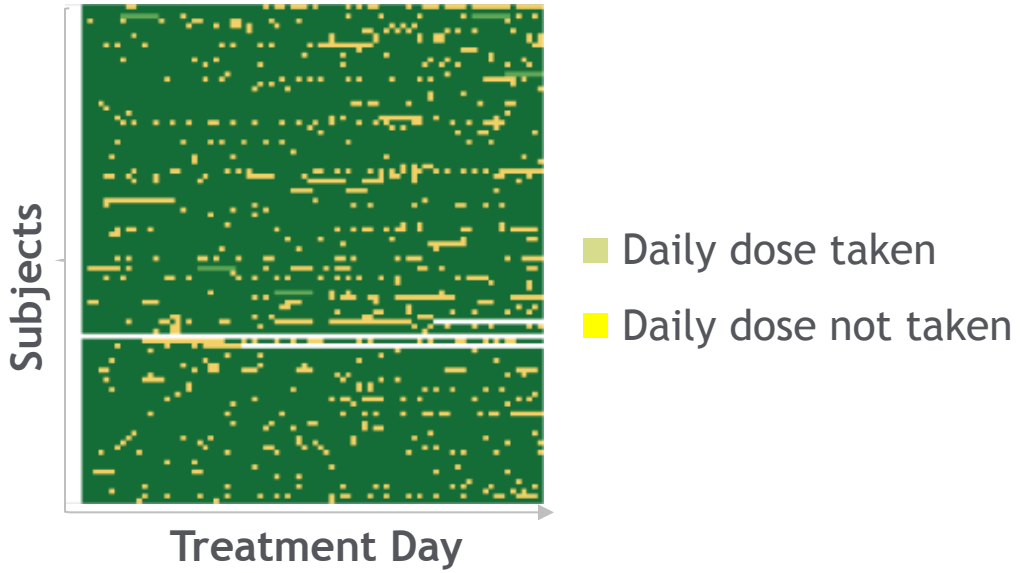
Efficacy of SOF/VEL for 12 Weeks in People with HCV GT 1-6 and Recent Injection Drug Use

Efficacy Results (SVR12)[1]



LTFU: loss to follow-up; RI: re-infection
n=3 did not complete treatment
(2 LTFU, 1 overdose death)
n=3 did not have an SVR12 (2 LTFU, 1 reinfection)

Daily Adherence of Patients[2]



34% of the patients non-adherent[1,*]
SVR rates were similar for adherent and non-adherent groups (94%) and no virologic failure observed in both groups[2]

SOF/VEL for 12 weeks in patients with recent injecting drug use led to high SVR12 rates despite ongoing drug use

*Non-adherent: missed >8 doses

1. Grebely J, et al. Lancet Gastroenterology Hepatology 2018 Mar;3(3):153-161; 2. Cunningham EB, et al. *Int J Drug Policy.* 2018;62:14-23.

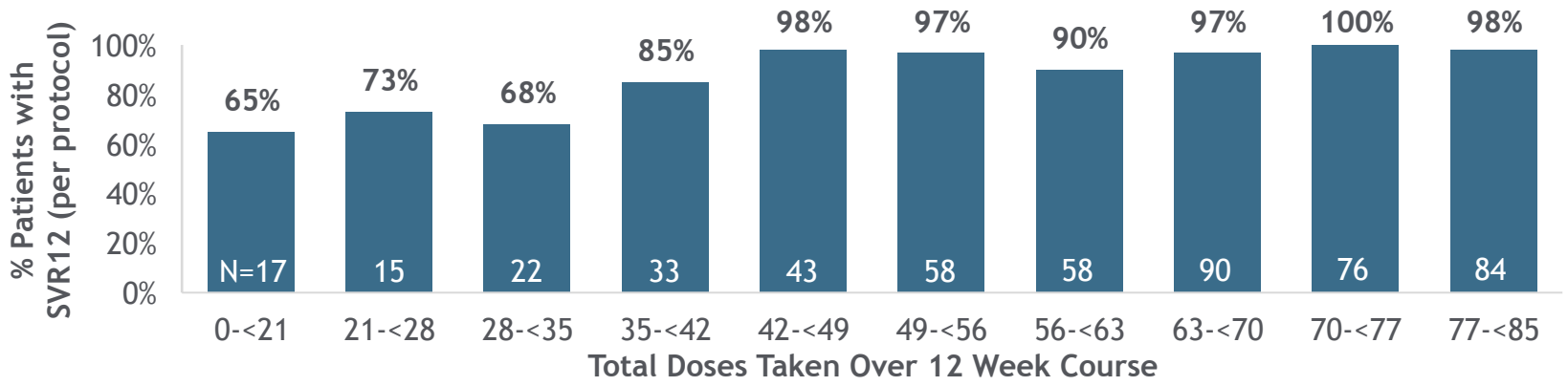
Impact of Adherence to SOF/VEL on SVR12 in PWUD

Prospective, multi-center pragmatic trial of community-based SOF/VEL therapy

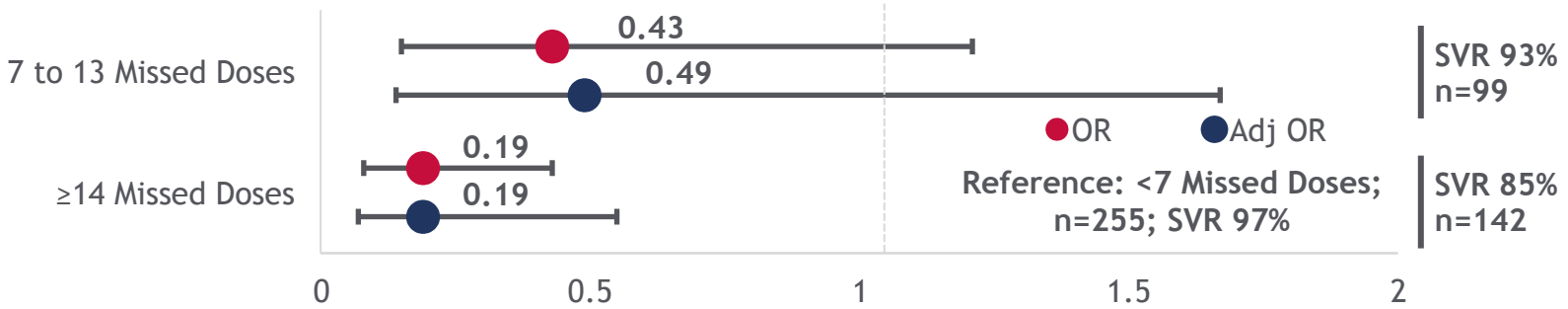
Baseline Characteristics

Patients, n (%)	N=755
Age <40	334 (44)
Unstable living situation	399 (54)
Genotype 1	368 (72)
2	45 (9)
3	94 (18)
HIV coinfection	102 (20)
Last drug injection within 3 months of screening	
0-4 weeks	572 (76)
5-12 weeks	182 (24)
Number of drug injections/day	
≤2	355 (52)
>2	325 (48)
Urine drug screen results at baseline – any drug	576 (85)

SVR12 Rate by Total SOF/VEL Doses Taken Over 12 Weeks*



Impact of Consecutive Missed Doses on SVR12 Rates*



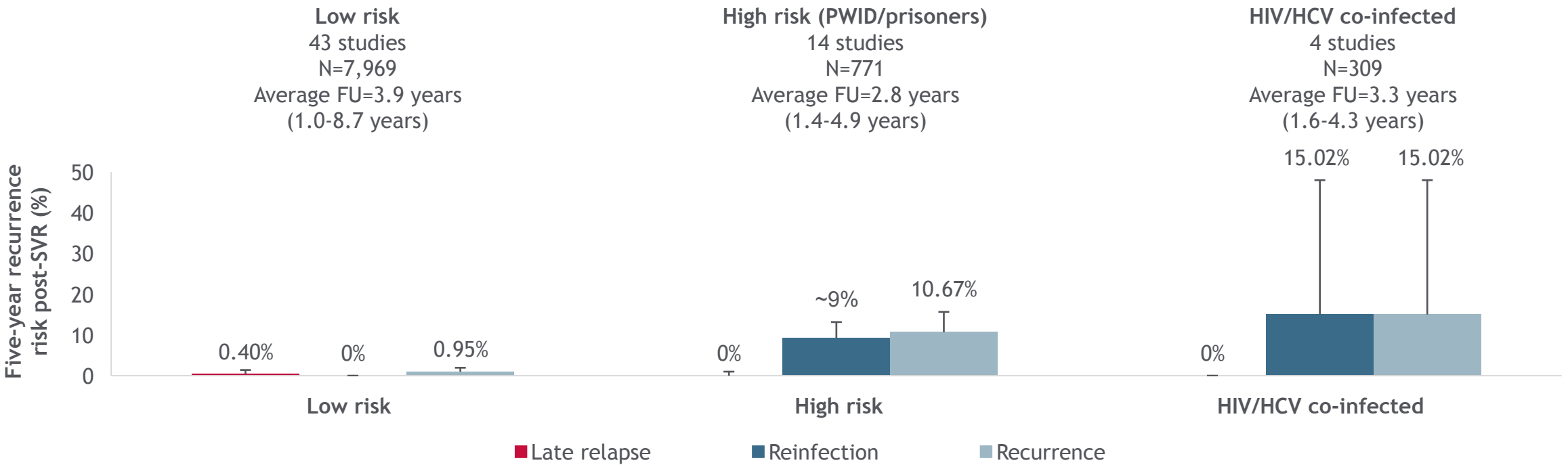
Despite suboptimal adherence, SVR was achieved by a high proportion of participants receiving SOF/VEL

*Per protocol population: 502 patients who were randomized, initiated treatment, and had an SVR12 result. Adj, adjusted; OR, odds ratio; PWUD, people who use drugs; SOF, sofosbuvir; SVR12, sustained virologic response 12 weeks after treatment completion; VEL, velpatasvir.; Litwin A, et al. Presented at AASLD 2022 during the session: VHE Community Conversation: Hepatitis Elimination and Health Equity – Reaching Marginalized Populations ; Litwin AH, et al. Lancet Gastroenterol Hepatol 2022;7:1112-1127

Reinfection

Risk of Late Relapse or Reinfection with HCV in Low and High Risk Groups and HIV/HCV Co-infection

Meta-analysis of 61 studies in 9,049 patients



Differences in rates suggest reinfection is more common than relapse

Harm reduction measures such NSP and counselling prevent reinfection among persons who inject drugs

Error bars represent 95% CI.; FU, follow-up; NSP, needle/syringe programme; Simmons B, et al. Clin Infect Dis 2016;62:683-94

HCV REINFECTION RATES ARE RELATIVELY LOW, EVEN AMONG PEOPLE WITH RECENT INJECTION DRUG USE

Meta-analysis of 36 Studies With 6311 PY Follow-up[a]

HCV reinfection following treatment among people with recent drug use (injecting or non-injecting) or those receiving MAT

6.2 per 100 PY
(6.2% per year)

among people with **recent injection drug use**

5.9 per 100 PY
(5.9% per year)

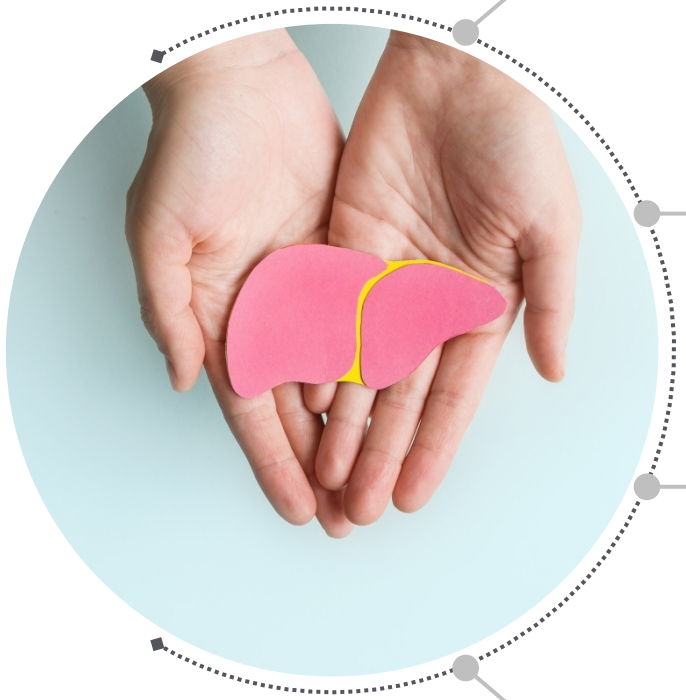
among people with **recent drug use (injecting or non-injecting)**

3.8 per 100 PY
(3.8% per year)

among people **receiving MAT**

DAA=direct-acting antiviral; PY=person-years.
[a]The 36 studies were prospective and retrospective studies that met all of the following criteria: 1) Study population included defined populations of people with recent drug use or people receiving MAT; 2) Reinfection following treatment-induced HCV clearance (interferon-based or DAA therapy) was assessed; and 3) Reinfection rate, including PY follow-up, was reported.; Hajarizadeh B, et al. *J Hepatol*. 2020;72(4):643-657.

A National Plan to Eliminate Hepatitis C



The White House Office of Science Technology Policy outlining the steps in the development a national Hepatitis C elimination program

Development of a model of the expected health benefits and cost savings with a scale-up of hepatitis C prevention, care and treatment

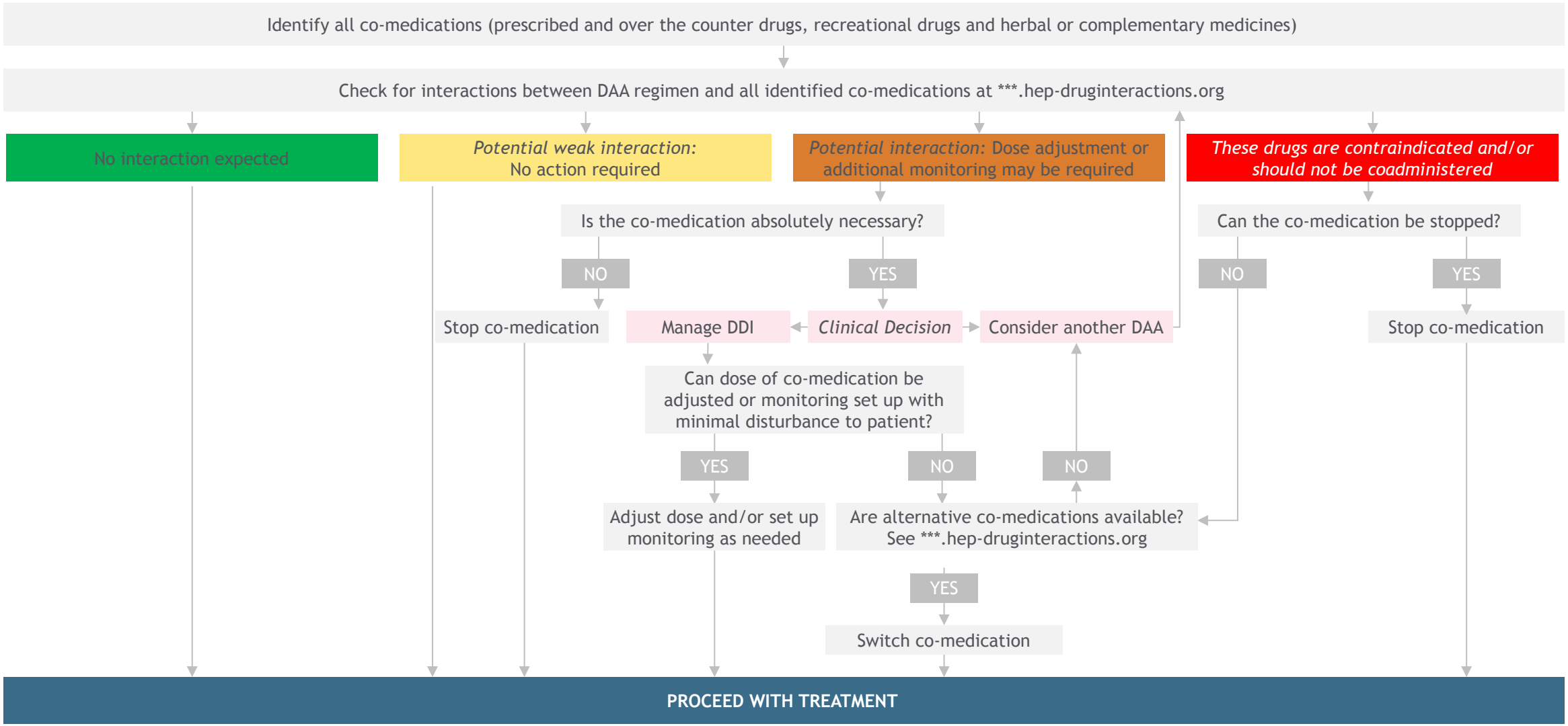
Insight from clinician and community perspectives of programs goals, implementation and impact

Includes Centers for Disease Control and Prevention, Substance Abuse and Mental Health Services Administration, the Indian Health Service, Food and Drug Administration and the Federal Bureau of Prisons

Drug-Drug Interactions (DDIs)

University of Liverpool HEP Drug Interaction Checker data

Interpreting the Liverpool HEP Interactions Checker



DAA=direct-acting antiviral; DDI=drug-drug interaction
***.hep-druginteractions.org

DDIs Between HCV DAAs and Anti-Psychotics

ANTI-PSYCHOTICS		
MEDICATION	**EPCLUSA (SOF/VEL) – PI-Free**	**Mavyret (GLE/PIB) – PI-Containing**
Amisulpride (Solian[a])		
Aripiprazole (Abilify)		
Chlorpromazine (Thorazine[a])		
Clozapine (Clozaril[a])		
Flupentixol (Depixol[a])		
Haloperidol (Haldol)		
Lurasidone (Latuda)		
Olanzapine (Zyprexa[a])		
Paliperidone (Invega)		
Quetiapine (Seroquel)		
Risperidone (Risperdal)		
Ziprasidone (Geodon)		
Zuclopenthixol (Clopixola)		

No clinically significant interaction Potential weak interaction Potential interaction Should not be coadministered

[a]Brand name may vary.; DAA=direct-acting antiviral; DDI=drug-drug interaction; GLE=glecaprevir; PI=protease inhibitor; PIB=pibrentasvir; SOF=sofosbuvir; VEL=velpatasvir

HEP Drug Interactions. University of Liverpool. Accessed July 30, 2022. **********.hep-druginteractions.org/checker

DDIs Between HCV DAAs and MAT and Illicit Drugs

MAT AND ILLICIT DRUGS		
MEDICATION/ILLICIT DRUG	**EPCLUSA (SOF/VEL) - PI-Free**	**Mavyret (GLE/PIB) - PI-Containing**
Amphetamine		
Buprenorphine		
Cannabis		
Carfentanil		
Cocaine		
Diazepam		
Fentanyl (Prescribed)		
Fentanyl (Recreational)		
Gamma-hydroxybutyrate		
Ketamine		
MDMA (Ecstasy/Molly)		
Mephedrone		
Methadone		
Methamphetamine		
Naltrexone		
Oxycodone		
PCP		
Temazepam		

No clinically significant interaction Potential weak interaction Potential interaction Should not be coadministered

DAA=direct-acting antiviral; DDI= drug-drug interaction; GLE=glecaprevir; MAT= medication-assisted treatment; PCP=phencyclidine; PI=protease inhibitor; PIB=pibrentasvir; SOF=sofosbuvir; VEL=velpatasvir

Hep Drug Interactions. University of Liverpool. Accessed July 28, 2022. **********.hep-druginteractions.org/checker

DDIs Between HCV DAAs and Oral Contraceptive Therapy

ORAL CONTRACEPTIVE THERAPY		
MEDICATION	**EPCLUSA (SOF/VEL) – PI-Free**	**Mavyret (GLE/PIB) – PI-Containing**
Desogestrel/ethinyl estradiol		
Drospirenone/ethinyl estradiol		
Ethinyl estradiol/levonorgestrel		
Ethinyl estradiol/norgestimate		
Norethisterone/ethinyl estradiol		

No clinically significant interaction Potential weak interaction Potential interaction Should not be coadministered

DAA=direct-acting antiviral; DDI=drug-drug interaction; GLE=glecaprevir; PI=protease inhibitor; PIB=pibrentasvir; SOF=sofosbuvir; VEL=velpatasvir

Hep Drug Interactions. University of Liverpool. Accessed July 28, 2022. **********.hep-druginteractions.org/checker

DDIs Between HCV DAAs and Anti-Seizure Medications

ANTI-SEIZURE THERAPY		
MEDICATION	**EPCLUSA (SOF/VEL) – PI-Free**	**Mavyret (GLE/PIB) – PI-Containing**
Carbamazepine (Tegretol)		
Phenytoin (Dilantin)		
Oxcarbazepine (Trileptal)*		
Ethosuximide (Zarontin)		
Valproic acid (Depakote, Depakene)		
Topiramate (Topamax)		
Lamotrigine (Lamictal)		
Primidone (Mysoline)		
Phenobarbital		

No clinically significant interaction Potential weak interaction Potential interaction Should not be coadministered

*FDA package insert does not list oxcarbazepine having a drug-drug interaction with Epclusa; DAA=direct-acting antiviral; DDI=drug-drug interaction; GLE=glecaprevir; PI=protease inhibitor; PIB=pibrentasvir; SOF=sofosbuvir; VEL=velpatasvir
Hep Drug Interactions. University of Liverpool. Accessed July 28, 2022. **********.hep-druginteractions.org/checker

DDIs Between HCV DAAs and Lipid-Lowering Agents

LIPID-LOWERING AGENTS		
MEDICATION	**EPCLUSA (SOF/VEL) – PI-Free**	**Mavyret (GLE/PIB) – PI-Containing**
Atorvastatin (Lipitor)		
Bezafibrate (Bezalip[a])		
Ezetimibe (Zetia[a])		
Fenofibrate (Triglide[a])		
Fluvastatin (Lescol)		
Gemfibrozil (Lopid)		
Lovastatin (Altoprev[a])		
Pitavastatin (Livalo)		
Pravastatin (Pravachol)		
Rosuvastatin (Crestor)		
Simvastatin (Zocor[a])		

No clinically significant interaction | Potential weak interaction | Potential interaction | Should not be coadministered

[a]Brand name may vary.; DAA=direct-acting antiviral; DDI=drug-drug interaction; GLE=glecaprevir; PI=protease inhibitor; PIB=pibrentasvir; SOF=sofosbuvir; VEL=velpatasvir

Hep Drug Interactions. University of Liverpool. Accessed July 28, 2022. **********.hep-druginteractions.org/checker

DDIs Between HCV DAAs and Acid-Reducing Agents

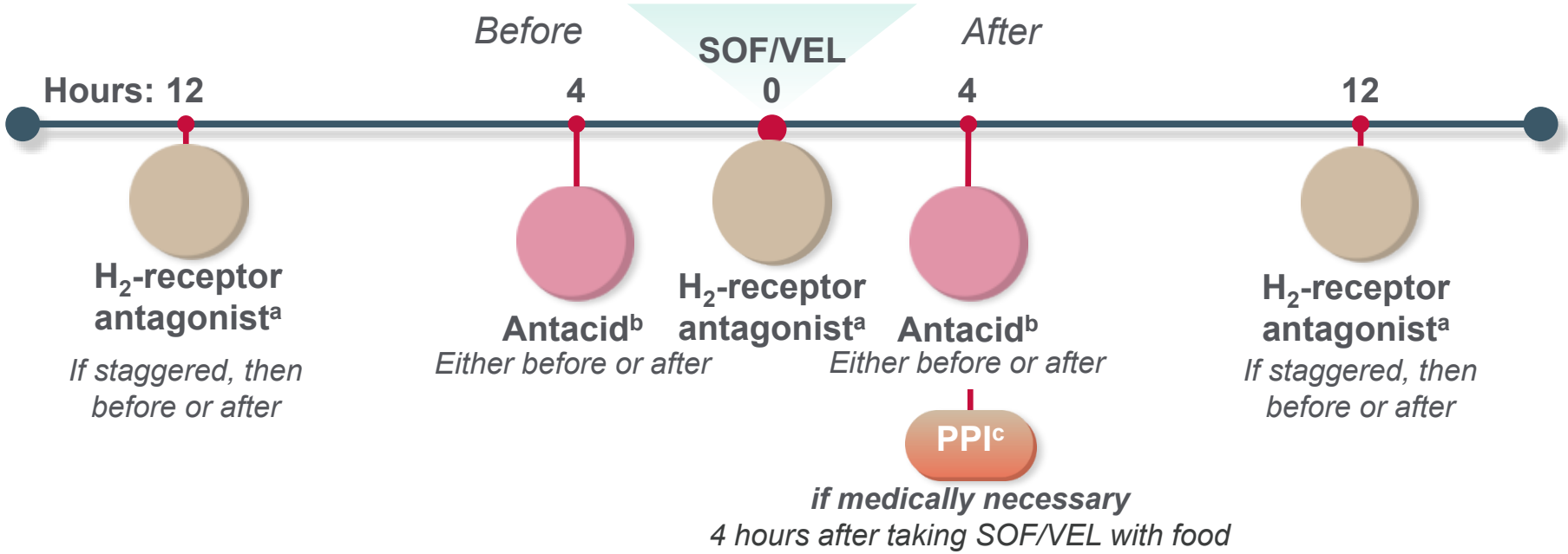
ACID-REDUCING AGENTS		
MEDICATION	**EPCLUSA (SOF/VEL) – PI-Free**	**Mavyret (GLE/PIB) – PI-Containing**
Cimetidine (Tagamet[a])		
Esomeprazole (Nexium)		
Famotidine (Pepcid)		
Lansoprazole (Prevacid)		
Omeprazole (Prilosec[a])		
Pantoprazole (Protonix)		
Rabeprazole (AcipHex)		

No clinically significant interaction | Potential weak interaction | Potential interaction | Should not be coadministered

[a]Brand name may vary.; DAA=direct-acting antiviral; DDI=drug-drug interaction; GLE=glecaprevir; PI=protease inhibitor; PIB=pibrentasvir; SOF=sofosbuvir; VEL=velpatasvir

Hep Drug Interactions. University of Liverpool. Accessed July 28, 2022. **********.hep-druginteractions.org/checker

Co-administration of SOF/VEL With Acid-reducing Agents



- H2-receptor antagonists should be used at a dose that does not exceed doses comparable to famotidine 40 mg twice daily
- Coadministration of omeprazole or other PPIs is not recommended with SOF/VEL
  - If it is considered medically necessary to coadminister, SOF/VEL should be administered with food and taken 4 hours before omeprazole 20 mg
  - Use with other PPIs has not been studied
- Velpatasvir solubility decreases as pH increases. Drugs that increase gastric pH are expected to decrease concentration of velpatasvir

[a]eg, famotidine. [b]eg, aluminum and magnesium hydroxide. [c]eg, omeprazole.

EPCLUSA US full Prescribing Information. Gilead Sciences, Inc. Foster City, CA. December 2021.