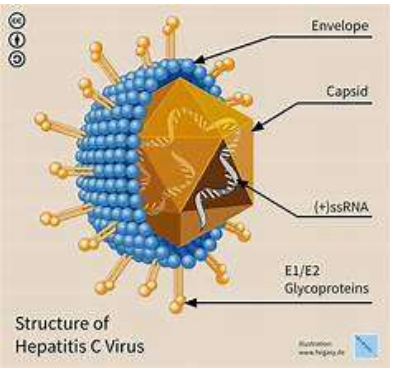


HEPATITIS C

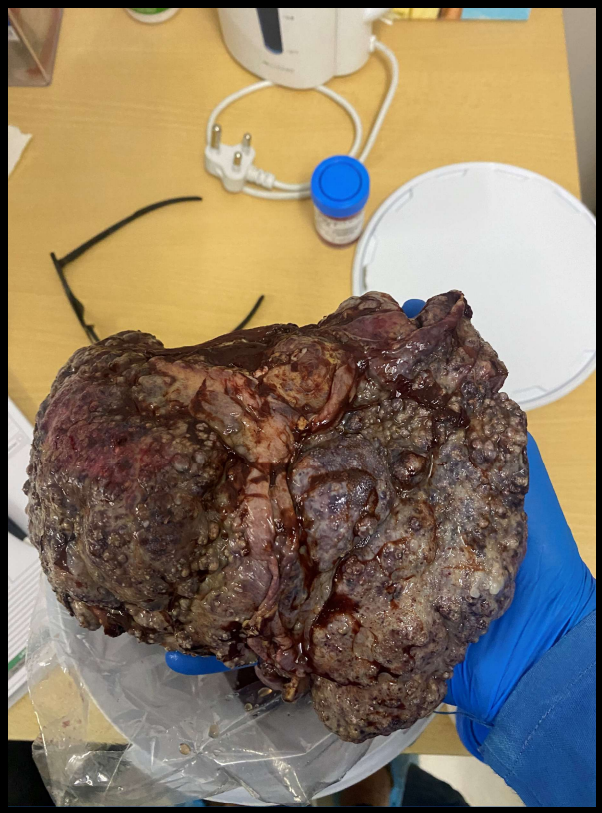
Detect early – Treat Effectively

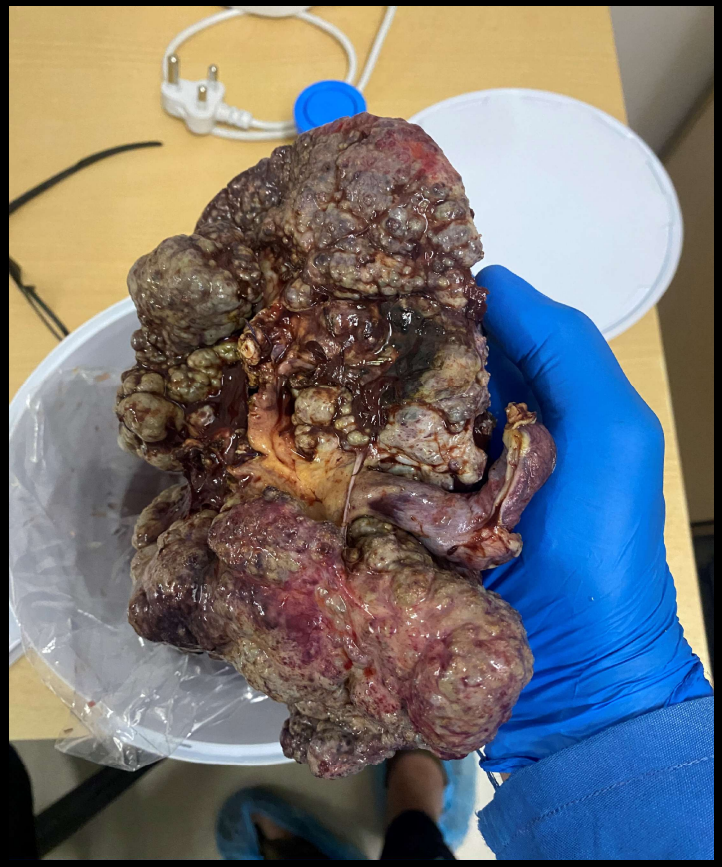
“Cure”

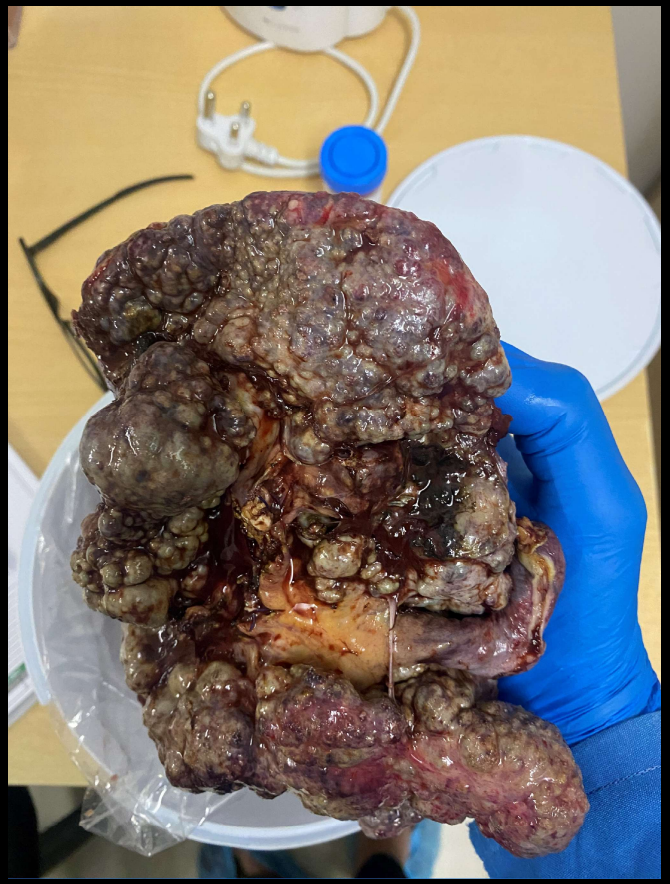
Dr Nnete Nimrod Mokhele

Specialist Physician – Gastroenterologist

EXPLANTED LIVER – CIRRHOTIC







Courtesy of Prof. Mark Sonderup Liver Unit Cape Town

INTRODUCTION

Hepatitis C virus (HCV) infection is a major cause of chronic liver disease, with approximately 71 million chronically infected individuals worldwide.

Clinical care for patients with HCV-related liver disease has advanced considerably thanks to an enhanced understanding of the pathophysiology of the disease, as well as developments in diagnostic procedures and improvements in therapy and prevention.

These therapies make it **possible to eliminate hepatitis C** as a major public health threat, as per the World Health Organization target 2030 although the timeline and feasibility vary from region to region.

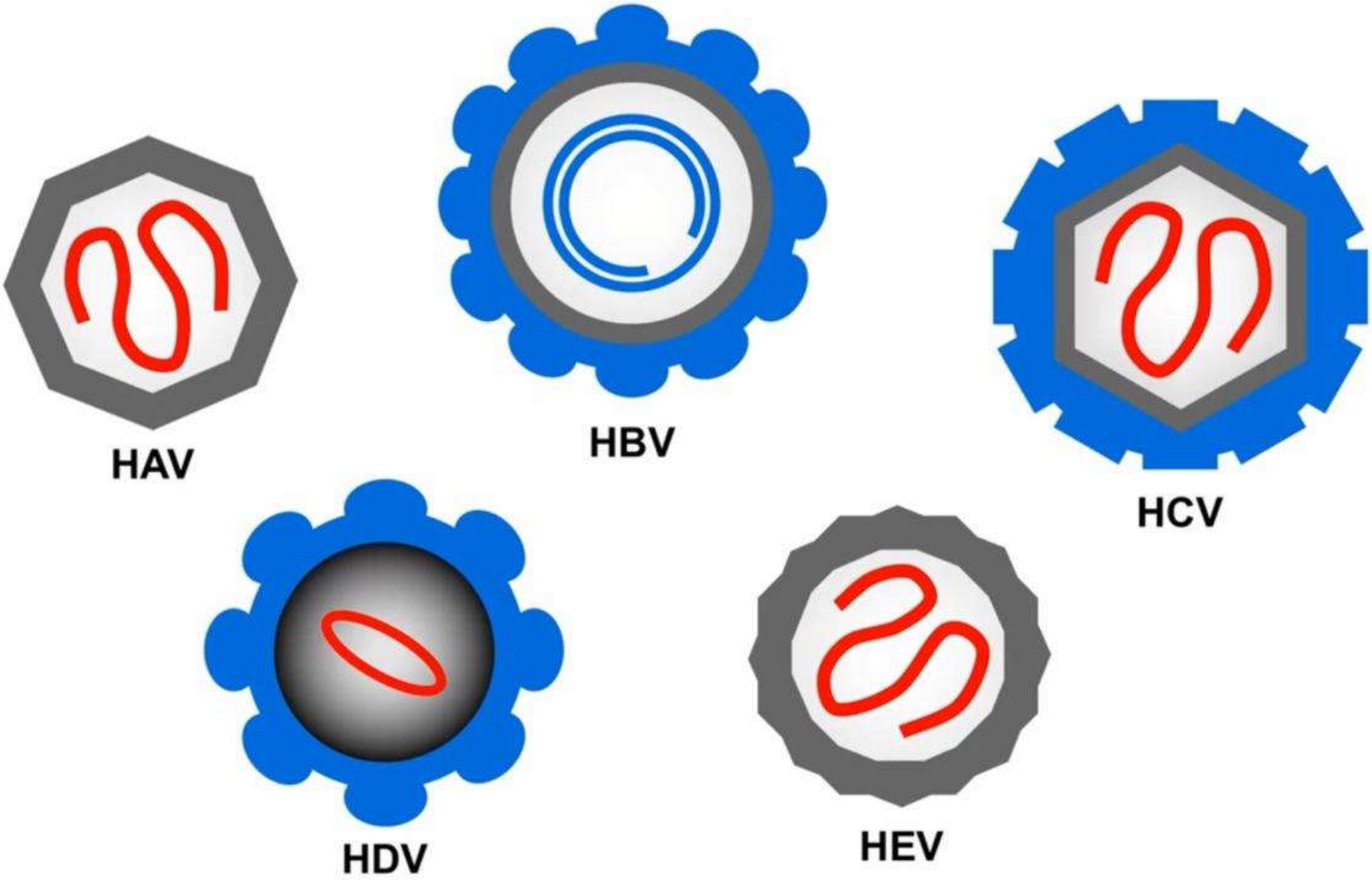
INTRODUCTION

Recognizing that viral hepatitis poses a public health threat on par with human immunodeficiency virus (HIV), malaria, and tuberculosis, in June 2016, the World Health Organization (WHO) published its first global health sector strategy and set forth the goal of elimination of viral hepatitis as a major public health threat by 2030.

❖ SPECIFIC HCV ELIMINATION TARGETS

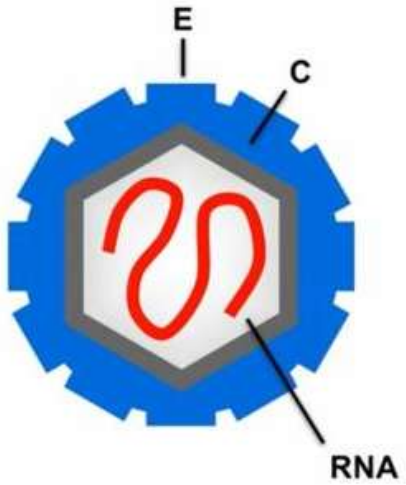
- 90% reduction in incidence and prevalence,
- Treatment of 80% of eligible persons with chronic infection,
- 65% reduction in HCV-related deaths, and
- Universal access to key prevention and treatment services

. World Health Organization. Global health sector strategy on viral hepatitis, 2016–2021. Published June 2016. Available at: https://apps.who.int/iris/bitstream/handle/10665/246177/WHO-HIV-2016.06-eng.pdf. Accessed 28 November 2022

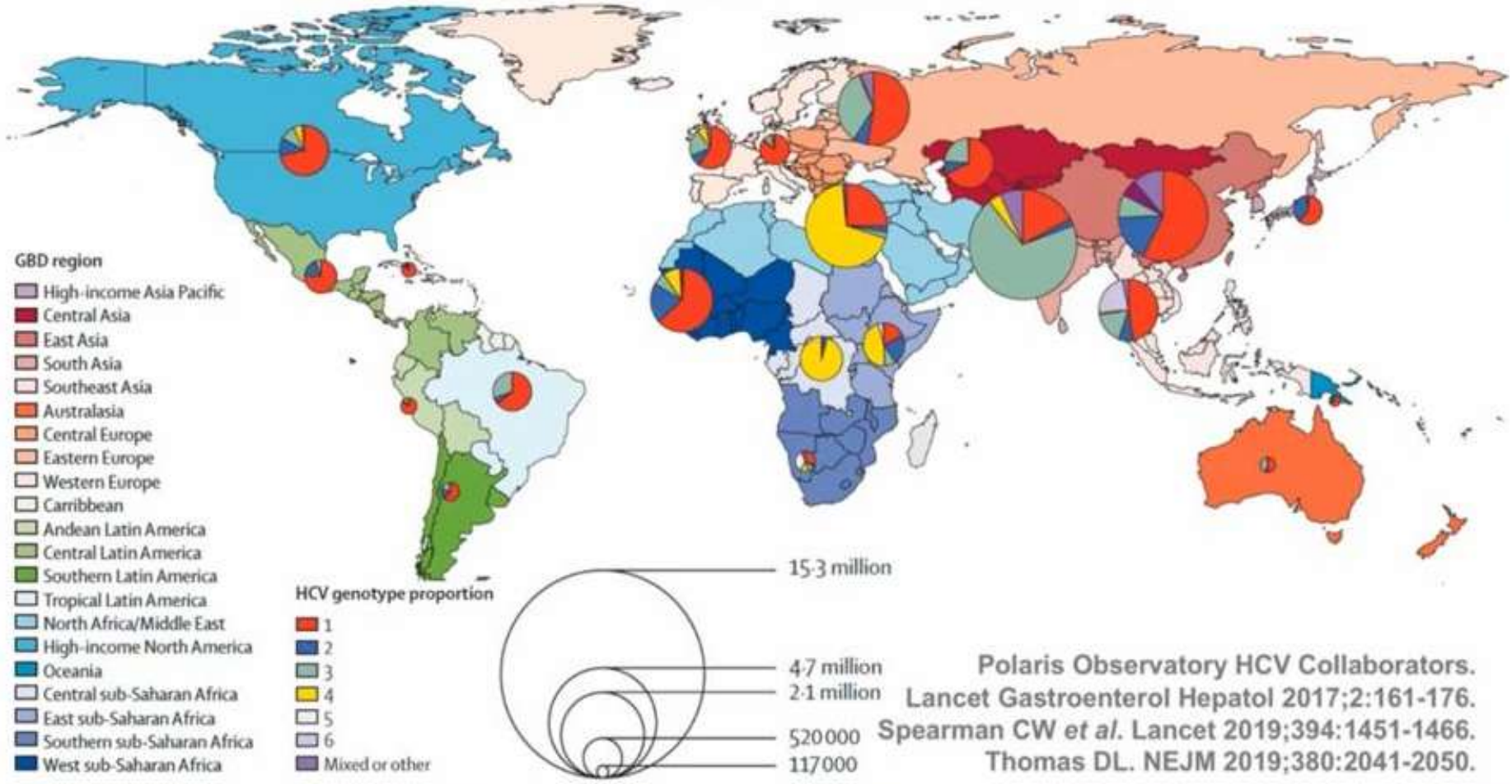

HAV
HBV
HCV
HDV
HEV

Hepatitis C
Virology

- **Hepatitis C virus** (HCV)
- ***Flaviviridae* family**
- **Single-stranded RNA genome**
- **Envelope, capsid**
- **Genetic variability** (7 genotypes)



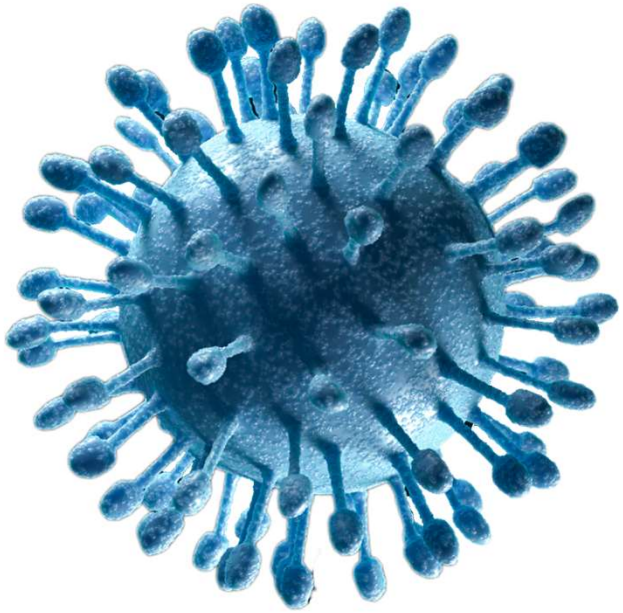
Epidemiology of Hepatitis C



Polaris Observatory HCV Collaborators. Lancet Gastroenterol Hepatol 2017;2:161-176.
Spearman CW *et al*. Lancet 2019;394:1451-1466.
Thomas DL. NEJM 2019;380:2041-2050.

Hepatitis C

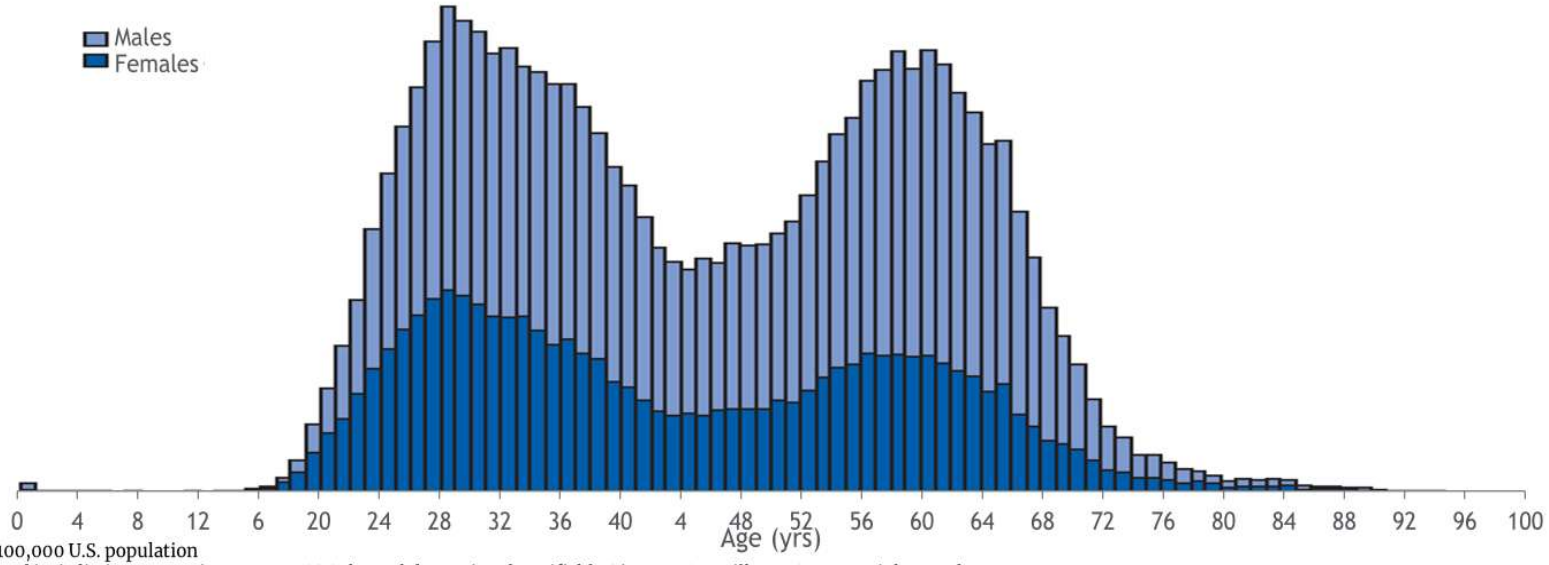
- HCV is a viral infection that can lead to liver disease and has infected ~ 600 000 people in South Africa[1]
- HCV is an RNA virus discovered in 1989[2,3]
  - GT 1-6 are the most common genotypes[2]
- HCV is associated with an increased risk for mortality[4]
- The World Health Organization (WHO) estimated that in 2019, approximately 290 000 people died from hepatitis C[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. Ly KN, et al. *Clin Infect Dis*. 2016;62(10):1287-1288. 5. World Health Organization. Hepatitis C.Updated: 27 July 2021. Available at: https://www.who.int/news-room/fact-sheets/detail/hepatitis-c (Accessed 16 November 2022) 6. CDC website. https://www.cdc.gov/hepatitis/hcv/hcvfaq.htm. Accessed January 10, 2018.

Age Distribution of HCV Infections shows bimodal prevalence



*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 (http://www.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 https://wwwn.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

https://www.cdc.gov/mmwr/volumes/69/wr/mm6914a2.htm

2023 Total Population: 60 414 495

2023 Adult Population: 40 502 250

World Bank Classification: Upper middle income

265 000 (95% UI 205-519) HCV-infected and HCV Seroprevalence: 0.4% (0.3-0.9)

- **Pangenotypic: GT 1-5** **Bimodal distribution: 20 - 39 years and 50 - 70 years**

HCV Infections (2020)†

265,000

<1%

Diagnosed

22%

Annual Treated

<1%

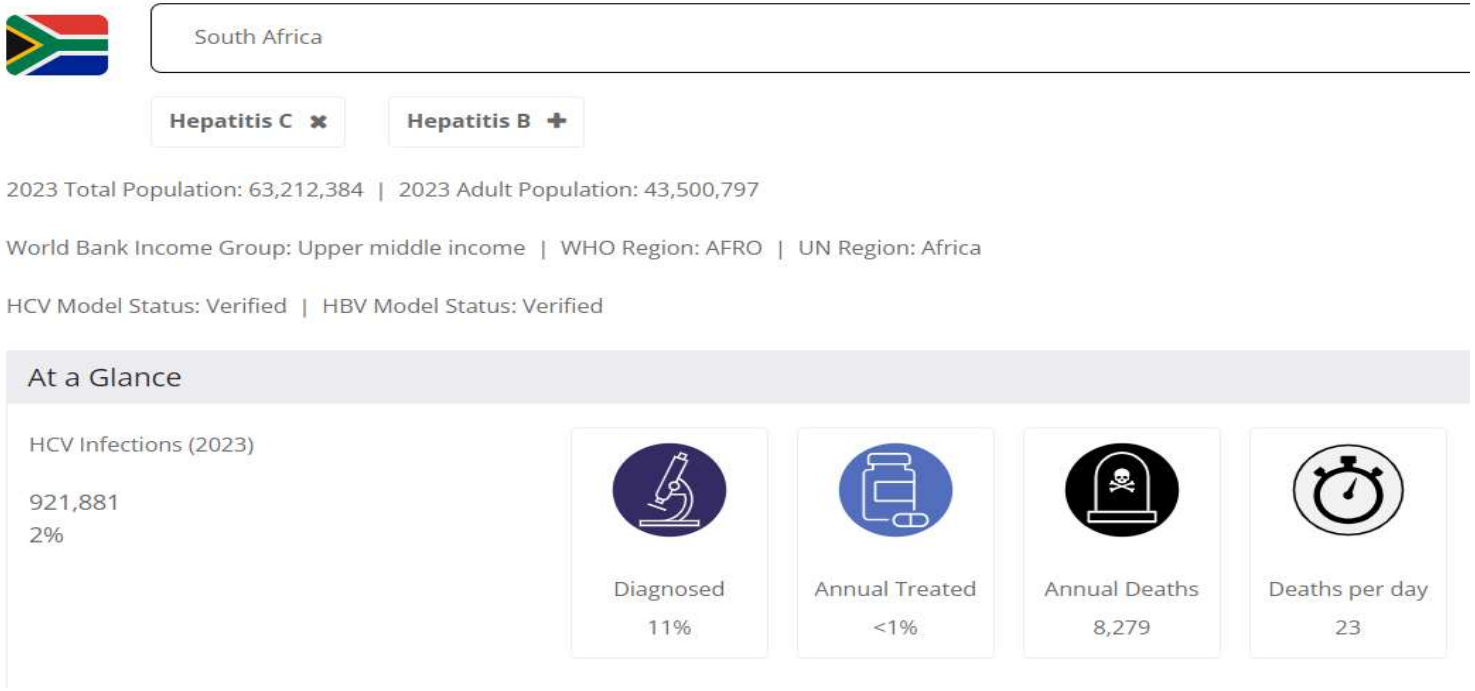
Annual Deaths

2,177

Deaths per day

6

POLARIS ESTIMATE 2023



Polaris Dashboard South Africa; https://cdafound.org/polaris/dashboard/; accessed 11 Nov 2023

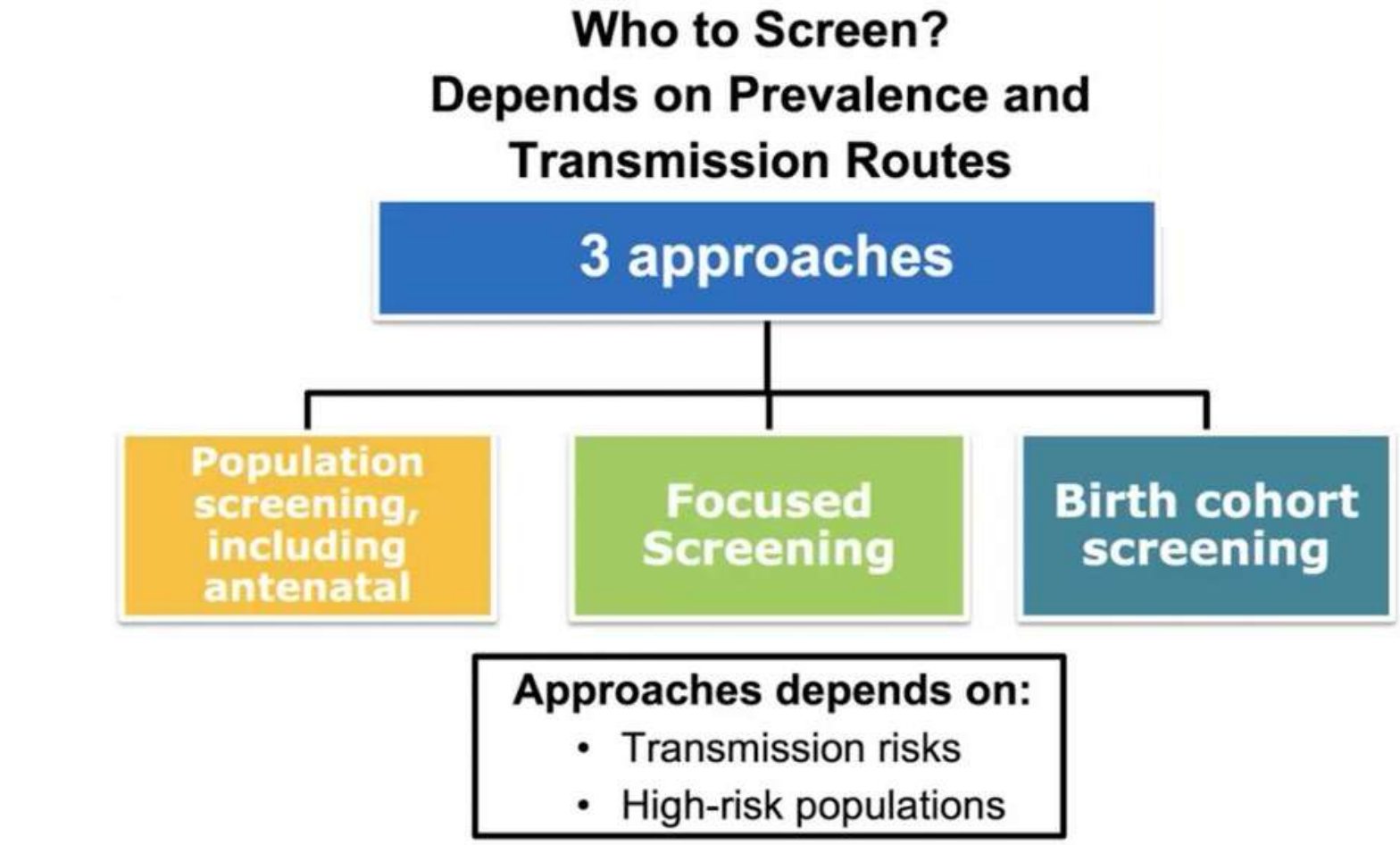
Health Care Provider-Initiated Testing for Chronic HCV Infection

A. **Clinical signs or symptoms of hepatitis**

B. **Risk factors**

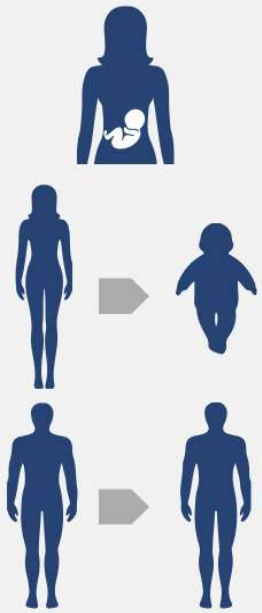
- **Medical** (recipients of blood products or solid organs before 1992, hemodialysis, persons with HBV or HIV infection, ...)
- **Demographic**
- **Behavioural** (injection or intranasal drug use, MSM, sexual partners)
- **Occupational**
- **Others** (imprisonement, piercing or tattoos, children of HCV-infected mothers, ...)

SEVHep - SFOPH | Fretz R *et al*. Swiss Med Wkly 2013;143:w13793.


Who to Screen?
Depends on Prevalence and Transmission Routes
3 approaches
Population screening, including antenatal
Focused Screening
Birth cohort screening
Approaches depends on:
• Transmission risks
• High-risk populations

Other Modes of Transmission

Person to Person



Tissue and organ transplants

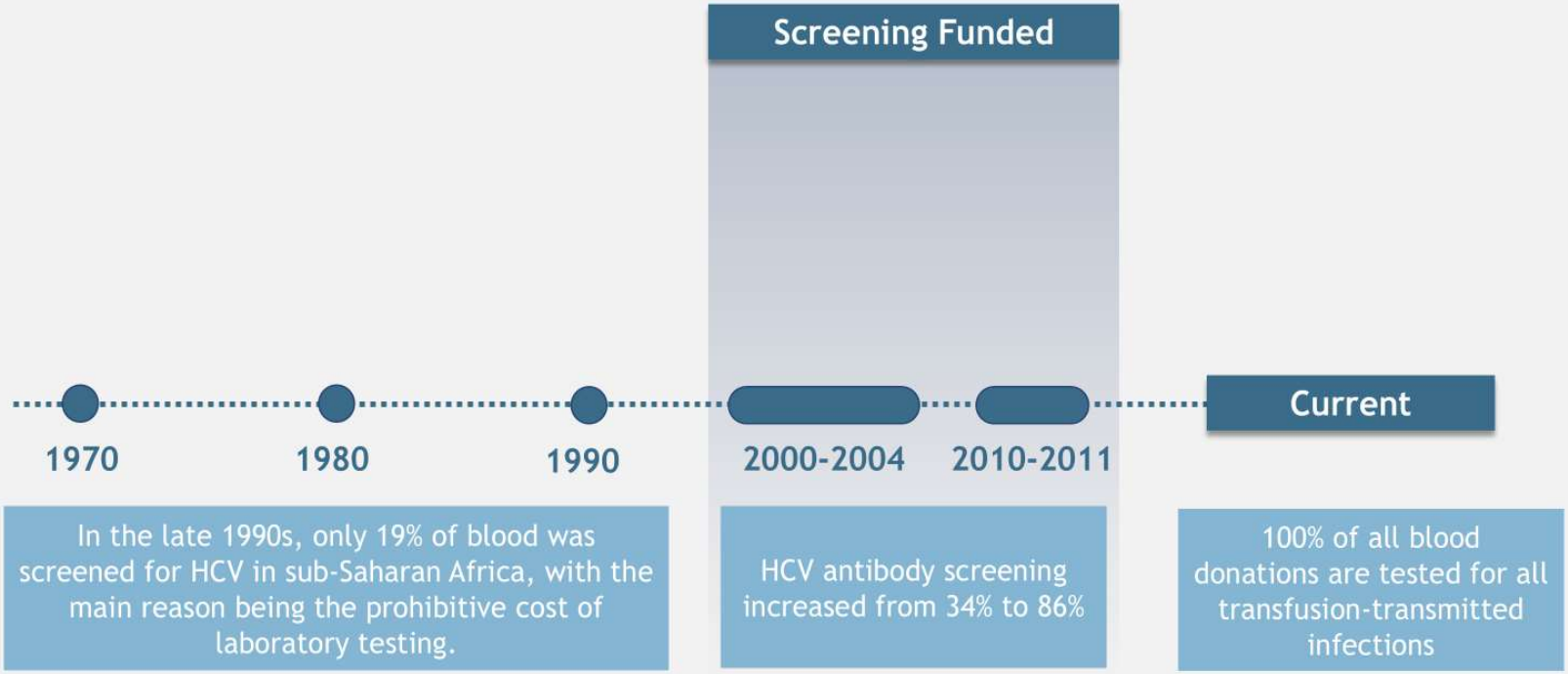
Healthcare worker exposure

Unsafe medical procedures

Body piercing

Blood and blood products

Transmission: Blood Transfusion



Hepatitis C
Risk of Post-Transfusion Hepatitis

1984 **~ 1 : 100**

ALT screening
Anti-HCV screening
Screening by PCR

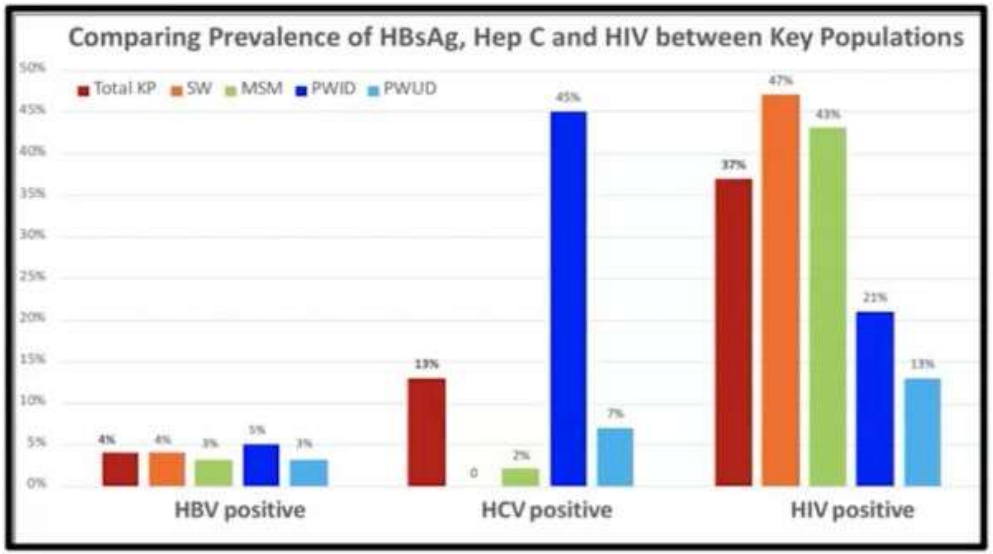
2004 **~ 1 : 2'000'000-10'000'000**

Stramer SL *et al.* N Engl J Med 2004;351:760-768.

South Africa: Key Populations

3439 KPs accessing HIV-related health services: Cape Town, Durban, Pietermaritzburg, Mthatha, Port Elizabeth, Johannesburg and Pretoria

1528 SWs, 746 MSM, 1165 PWUD/ID



HIV prevalence: 37%

- Highest among SWs at 47%

HBsAg prevalence: 4%

- Similar across KPs

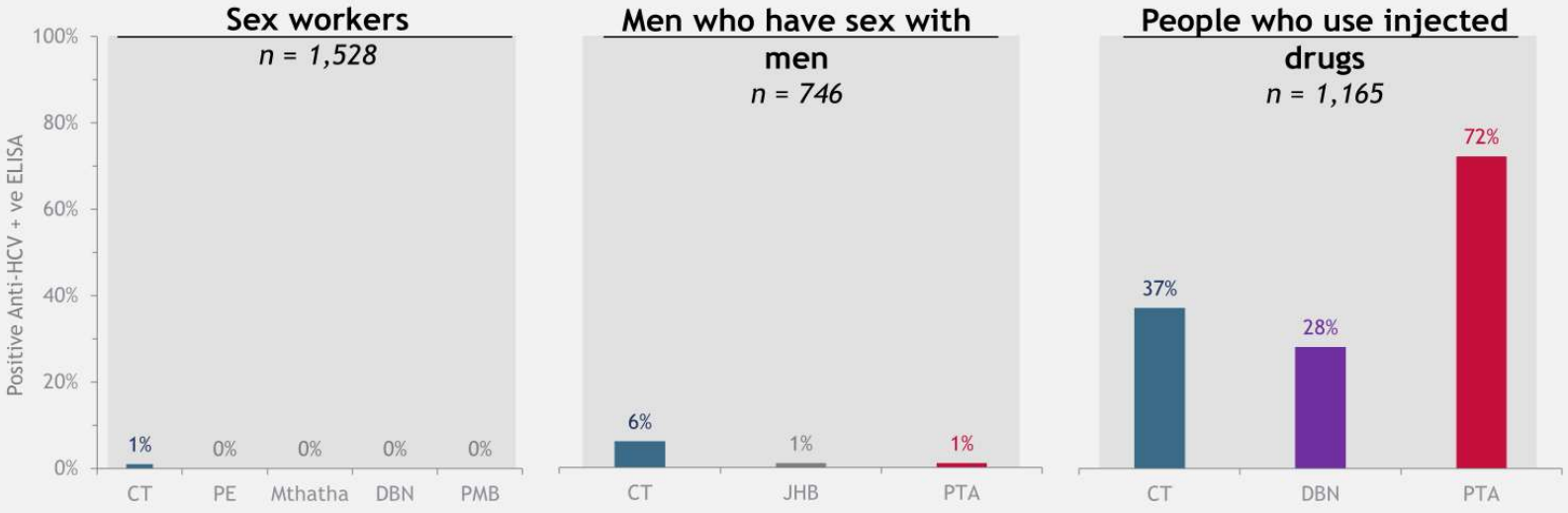
HCV prevalence: 16%

- Highest among PWUD/ID at 46%
  - 75-80% were viraemic
  - GT 1a and 3

Scheibe, A, Young, K; Spearman, W; Sonderup, M et al. BMC Infectious Diseases 2020;20:655

HCV Risk Factors: Results From 7 City Survey

Results from a survey across 7 cities in South Africa found that people who use injected drugs (PWUD) had a higher risk of testing positive for HCV than other high risk groups, including sex workers and men who have sex with men.

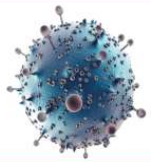


CT = Cape Town; DBN = Durban; JHB = Johannesburg; PE = Port Elizabeth; PMB = Pietermaritzburg; PTA = Pretoria.

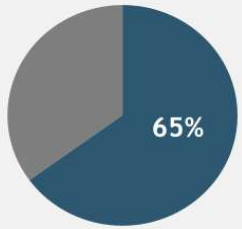
HIV-HCV Coinfection

Coinfection: Infection with at least two different disease-causing organisms

A global systematic review and meta-analysis of the prevalence and burden of HCV co-infection in people living with HIV reported a 6% coinfection prevalence in MSM and 82% in PWID compared to 2% within the general population

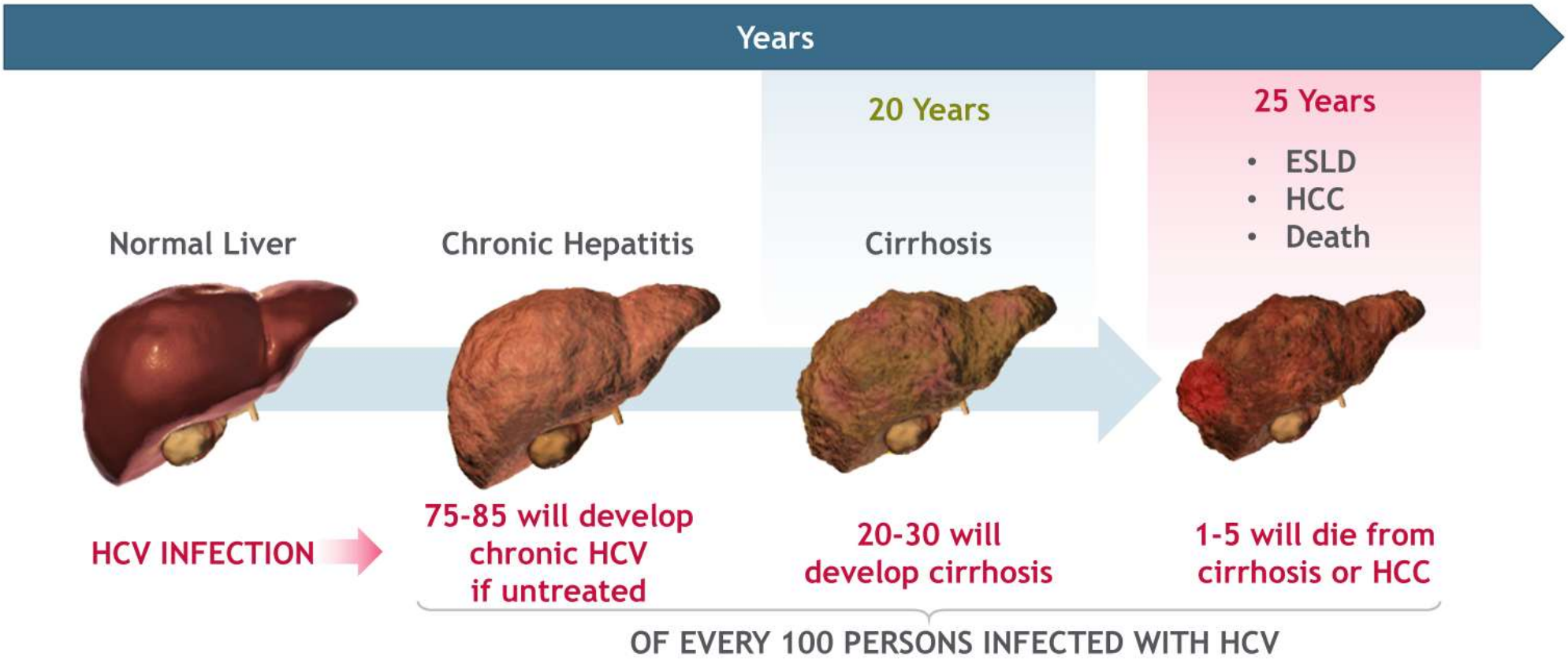


Coinfection increases risk for liver disease, liver failure, and liver-related death



Proportion of HIV-infected PWUD/ID who are likely coinfected with HCV in South Africa

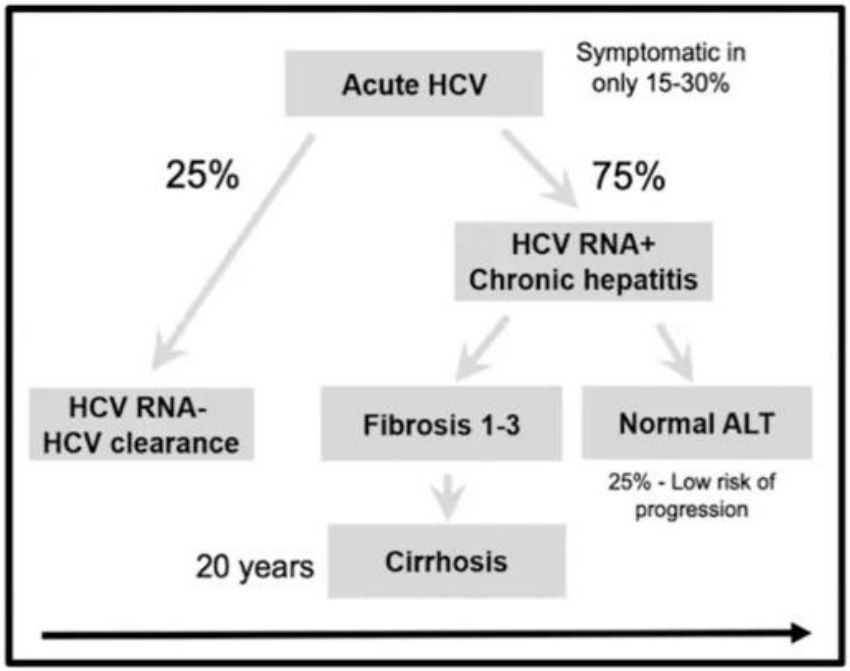
HCV: Disease Progression



NB...Factors associated with an increased rate and earlier occurrence of fibrosis and progression to cirrhosis include **acquisition of HCV at an older age, male sex**, **heavy alcohol use**, **coinfection with HIV or HBV**, **hepatic steatosis**, and **insulin resistance.**

1. ESLD, end-stage liver disease; HCC, hepatocellular carcinoma; Emory University Coalition for Applied Modeling for Prevention (CAMP). www.hepvu.org. Accessed August 2, 2018. Image adapted from Hepatitis C Online. 2015 https://www.hepatitisc.uw.edu/go/evaluation-staging-monitoring/natural-history/core-concept/all. Accessed April 2023.

Hepatitis C: Disease Progression



Determinants of Disease Progression

Host

Modifiable

- Obesity
- MASLD
- Insulin resistance
- Alcohol consumption

Non-modifiable

- Older age at time of infection
- Male sex
- Necroinflammation grade
- Fibrosis stage

Viral

- Co-infection: HIV or HBV
- Genotype 3

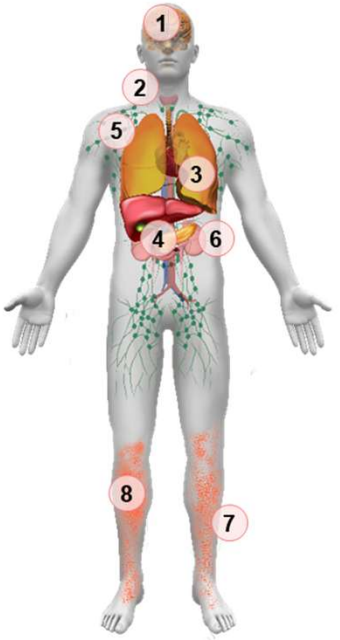
Gastroenterology Clinics of North America 2015; 44: 717; Lancet 2019; 394:1451

https://www.hcvguidelines.org/sites/default/files/full-guidance-pdf/AASLD-IDSA_HCVGuidance_October_24_2022.pdf

HCV Progression and Symptoms

Chronic HCV

- **Often symptom-free**, but if symptoms develop, they may include
  - Fatigue
  - Fever
  - Muscle/joint aches
  - Loss of appetite
  - Abdominal pain
  - Jaundice
  - Dark urine
  - Nausea
  - Vomiting
  - Pale stools
- **Extrahepatic manifestations** (eg, neuropathy, diabetes mellitus, depression)
- **Many patients will have normal liver enzymes**, even though HCV is silently damaging the liver



1. Depression/cognitive impairment
2. Fatigue
3. Cardiovascular disease
4. Type 2 diabetes mellitus/insulin resistance
5. Lymphoproliferative disorders
6. Membranoproliferative glomerulonephritis
7. Mixed cryoglobulinemia vasculitis
8. Skin manifestations

Assess for Extrahepatic Manifestations

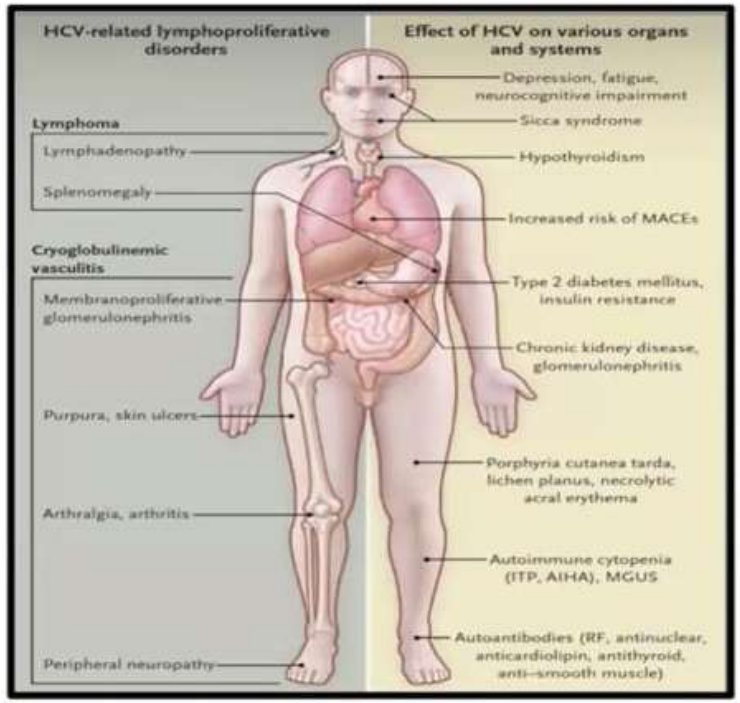
Reported in up to 75% patients

- Independent of degree of liver fibrosis
- **Non-specific symptoms: Neurocognitive impairment underestimated**
  - Fatigue, insomnia, reduced QOL, depression

HCV Cure

- Reduces symptoms and mortality from severe extrahepatic manifestations incl cryoglobinaemia vasculitis
- Non-Hodgkin lymphoma and other lymphoproliferative disorders: Complete or partial remission in up to 75% of cases

J Hepatol. 2016;65:S109-s19; Gastroenterology 2017;152(8):2052-2062.e2;
Am J Gastroenterol. 2017;112(8):1298; Aliment Pharmacol Ther. 2005;21(6):653

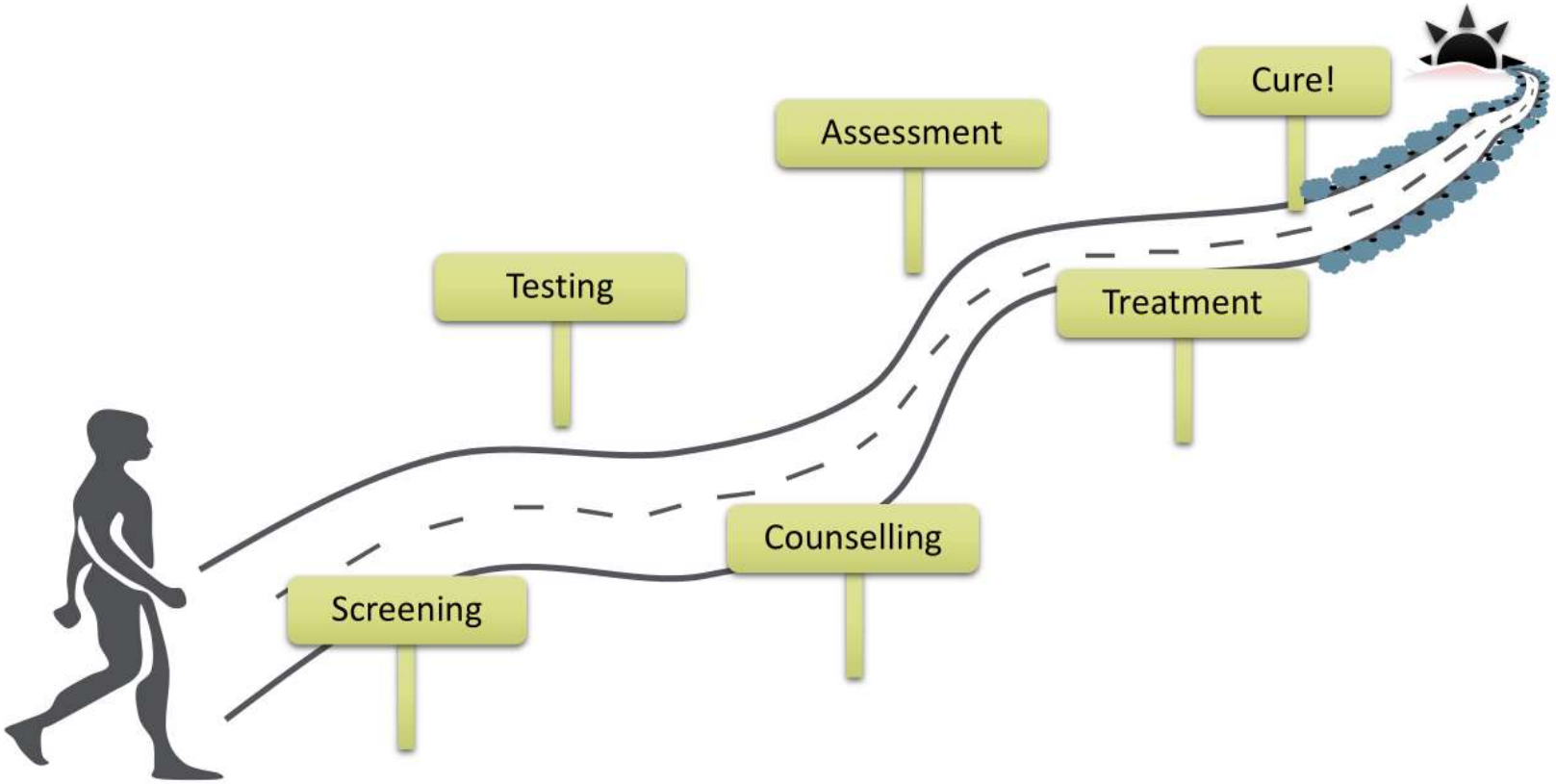


N Engl J Med 2021;384:1038

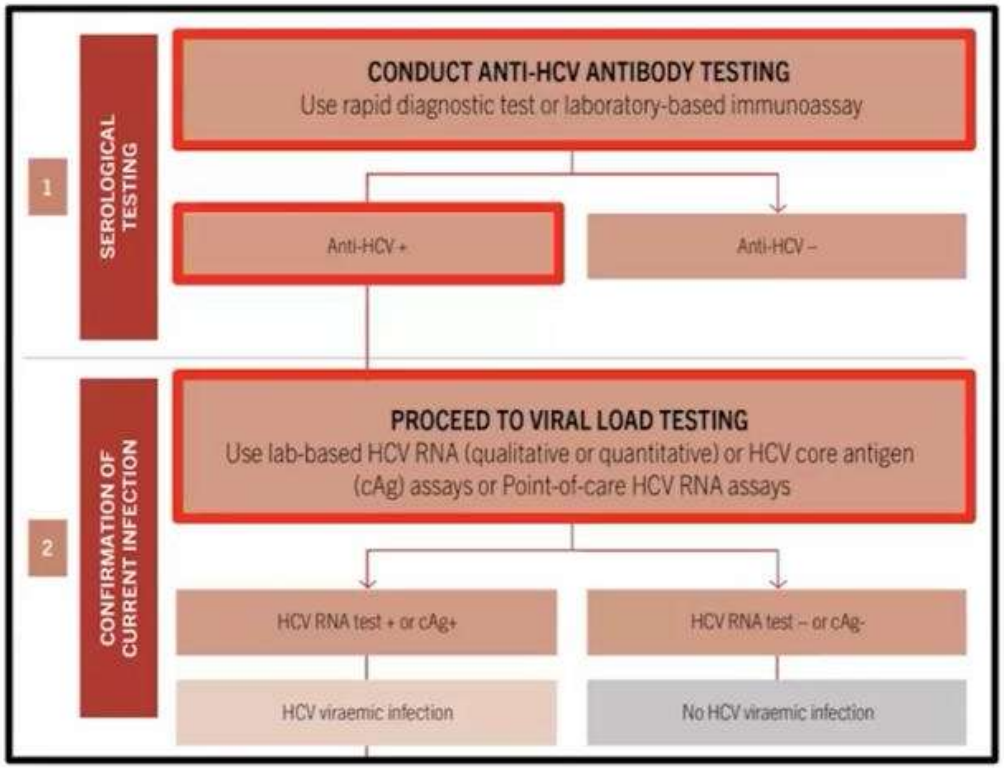
National Guidelines for the Management of Viral Hepatitis

HCV Management

Hepatitis C - the road to cure



Diagnosis of Hepatitis C



HCV PCR: CONFIRM VIRAEMIA

Qualitative or Quantitative

- HCV VL may affect treatment duration with certain regimens

HCV Genotype

- No need if prescribing pangenotypic DAA regimens
- Unless concerned re unusual Genotype 1 and 4 subtypes as seen in SSA

WHO 2022 UPDATED HCV GUIDELINES: https://www.who.int/publications/i/item/9789240052734

Diagnosis of Hepatitis C

Hepatitis C testing should be available in different settings: Increases diagnosis

Healthcare facility-based testing

- Primary healthcare clinics, secondary and tertiary healthcare settings

Community-based testing: Offered through

- Outreach approaches including mobile clinics
  - Workplaces, community centres, shopping malls and harm reduction programmes

Self-testing

- High-risk groups

Once diagnosed, there must be appropriate referral pathways for linkage to care

My patient has hepatitis C: What now?

All HCV-infected individuals require treatment

- Age: WHO 2022 recommendations
  - Adults (≥18 years), adolescents (12–17 years), older children (6–11 years): Strong recommendation
  - Younger children (3–5 years): Conditional recommendation
- Treatment naïve or treatment experienced
- High-risk key populations: PWID or MSM at risk of re-infection & onward transmission
- Remember that anti-HCV does not confer immunity

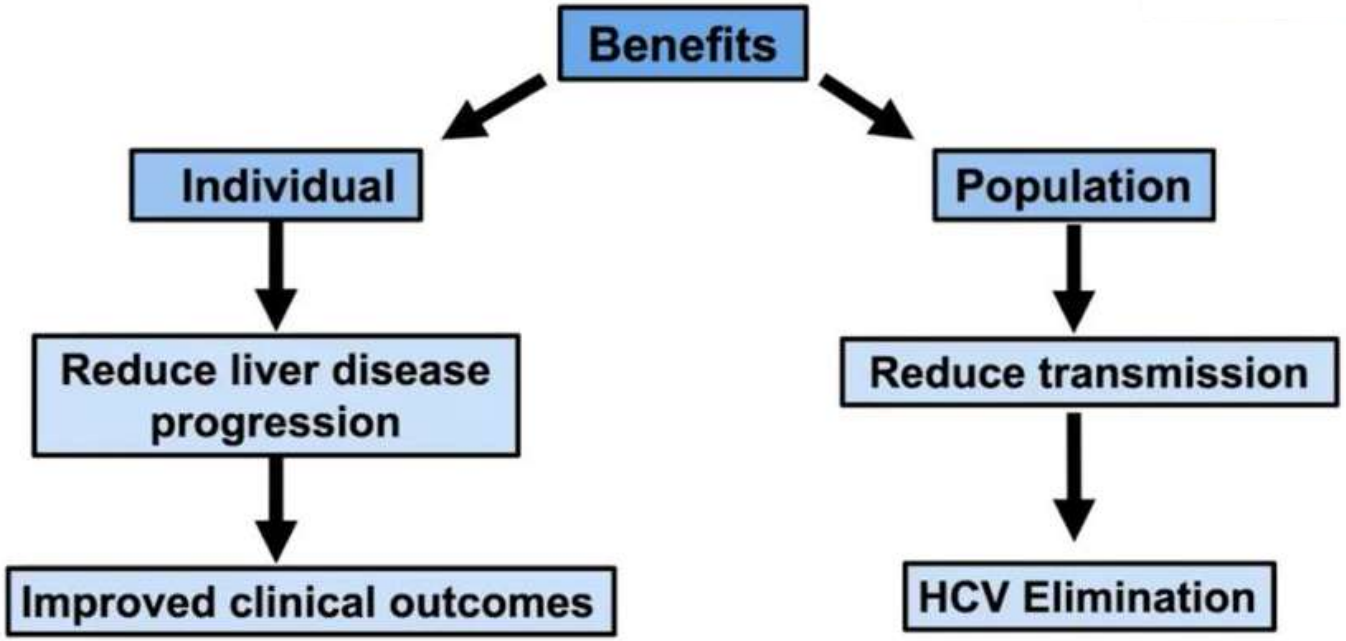
Exception: Limited life expectancy (<12 months): Non-liver-related co-morbid conditions

My patient has hepatitis C: What now?

- Assess necro-inflammation and stage of liver disease
- Assess for extrahepatic manifestations
- Assess for HIV-HCV or HBV-HCV co-infections
- Assess for co-morbid diseases: Type 2 Diabetes, alcohol and iron overload
- Assess renal function
  - Estimated glomerular filtration rate ≥30 mL/min per 1.73 m^2, no DAA dose adjustments necessary
- Assess risk of re-infection
- Exclude pregnancy

EASL recommendations on treatment of hepatitis C: J Hepatology 2020;73:1170
AASLD and IDSA: HCV Guidance: Recommendations for testing, managing and treating Hepatitis C: 24 Oct 2022: www.hcvguidelines.org

Benefits of Treating Hepatitis



Lancet 2019;393:1453; Hepatology 2020;71:1023; Hepatology 2028;67:1683; Lancet Gastroenterol Hepatol 2016; 1: 317
J Viral Hepat 2017; 24: 486; Lancet Infect Dis 2018;18:215; Lancet 2019;394:1451

HCV ELIMINATION

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 & Risk Stratify → **Treat** → **Cure**

HCV RNA positive

98%
Overall SVR Rate§

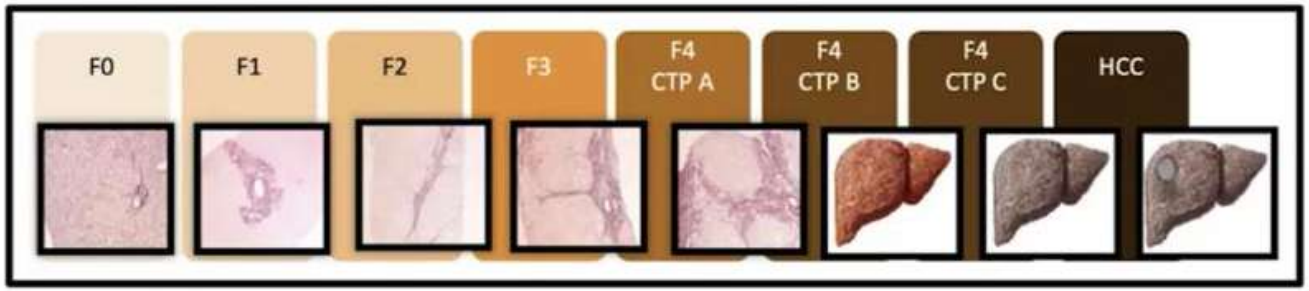
Gilead Sciences Inc. EPCLUSA® US Prescribing Information, Revised November 2017.
DCC: decompensated cirrhosis; F0-F4: fibrosis scores 0-4; GT: genotype
*addition of ribavirin indicated in DCC; †12 weeks; ‡Minimal on-treatment assessments; §In pivotal phase 3 trials

Assessment of Liver Disease Severity

Liver-directed physical exam: Normal in most patients

Why it is important to diagnose advanced fibrosis/cirrhosis

- May determine treatment duration and treatment choice
- Determines if other interventions are needed to prevent complications
  - Upper endoscopy for varices surveillance
  - AFP and Ultrasound liver screening for HCC
- Determines need for ongoing HCC surveillance post SVR



EASL CPG HCV. J Hepatol 2018;69:461

How do we determine the severity of liver disease?

Liver biopsy

- Rarely required
- Consider if other causes of liver disease are suspected

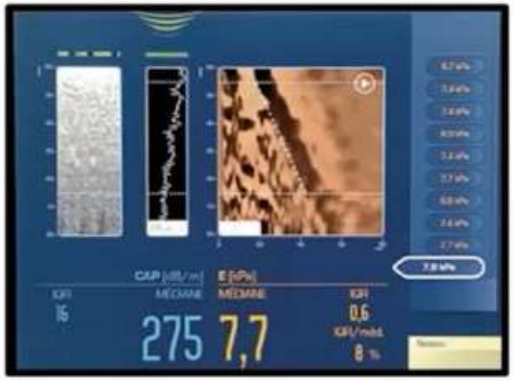
Non-invasive tests

APRI (AST to Platelet Ratio Index) Score

- AST/upper limit of normal)/platelet count

FIB-4

- Age (yrs) × AST (IU/l) /platelet count (×10^9/litre) ×√ALT (IU/l)



Transient elastography

- FibroScan®: ECHOSENS
  - Liver stiffness measurements: Fibrosis & portal hypertension
- AUROC >0·9 for cirrhosis assessment

J Hepatol 2015; 63: 237; Gastroenterology 2017;152:1536
Clin Gastroenterol Hepatol 2015; 13: 772

How do you interpret the NITs?

APRI score: Meta-analysis of 40 studies

APRI score >1.0

- 76% sensitivity and 72% specificity for predicting cirrhosis

APRI score >2.0

- 46% sensitivity and 91% specificity for predicting cirrhosis

APRI score >0.7

- 77% sensitivity and 72% specificity for predicting significant hepatic fibrosis

FIB-4 score

FIB-4 <1.45

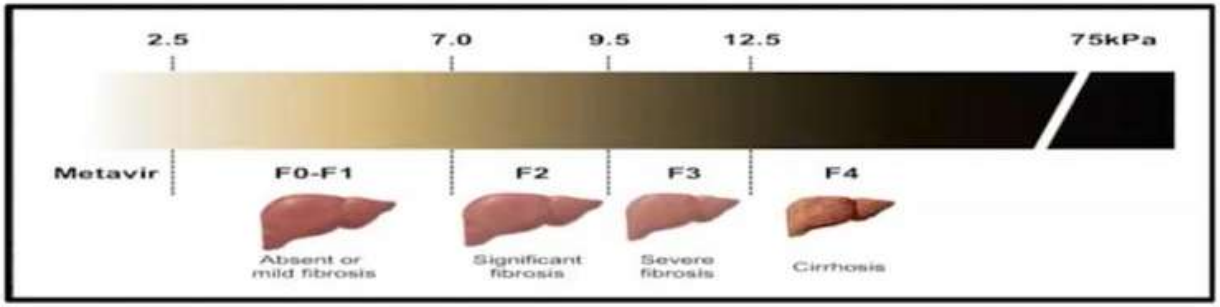
- 90% NPV for advanced fibrosis (Ishak fibrosis score 4-6 which includes early bridging fibrosis to cirrhosis)

FIB-4 >3.25

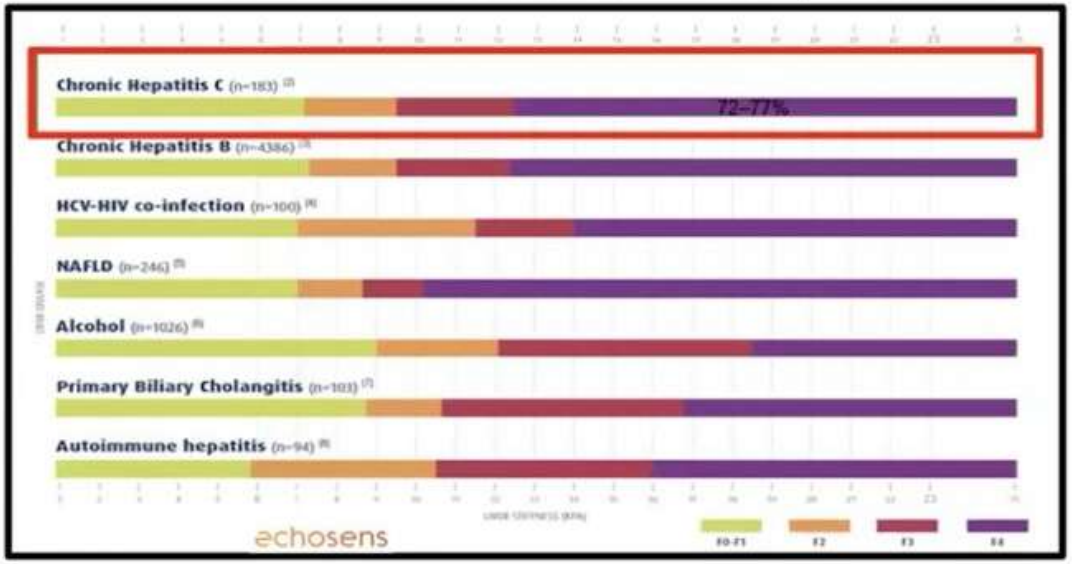
- 97% specificity and positive predictive value of 65% for advanced fibrosis

Hepatology 2011;53:726; Hepatology 2006;43:1317

FIBROSCAN INTERPRETATION



Recommended Fibroscan kPa cut-offs: 7.5 for F2, 9.5-10 kPa for F3 and 12.5-13 kPa for F4



Fibroscan

13 kPa: F4 Cirrhosis

- 72 - 77%: Sensitivity
- 85 - 90%: Specificity

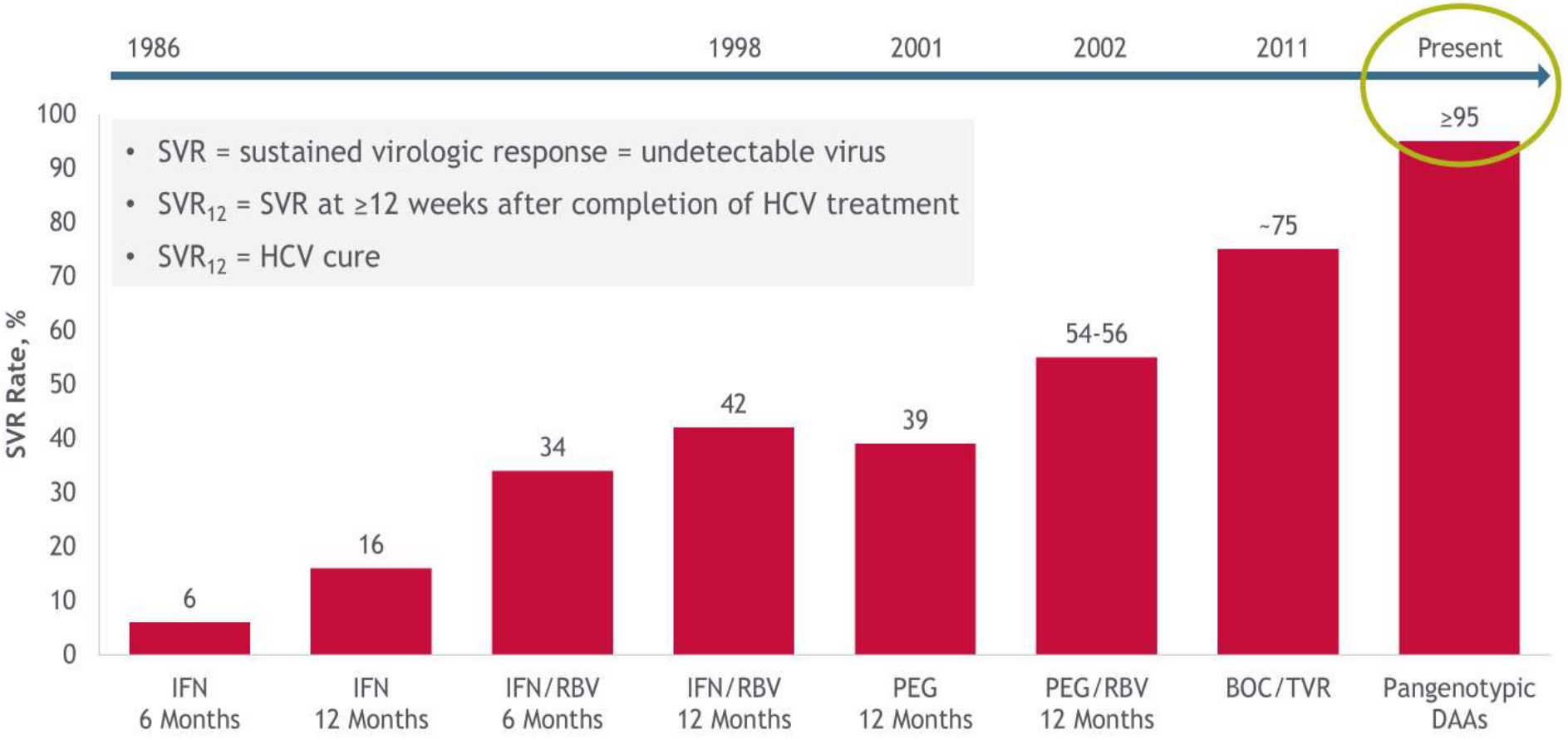
10 kPa: F3 fibrosis

- 72%: Sensitivity
- 80%: Specificity

J Hepatology 2020;73:1170

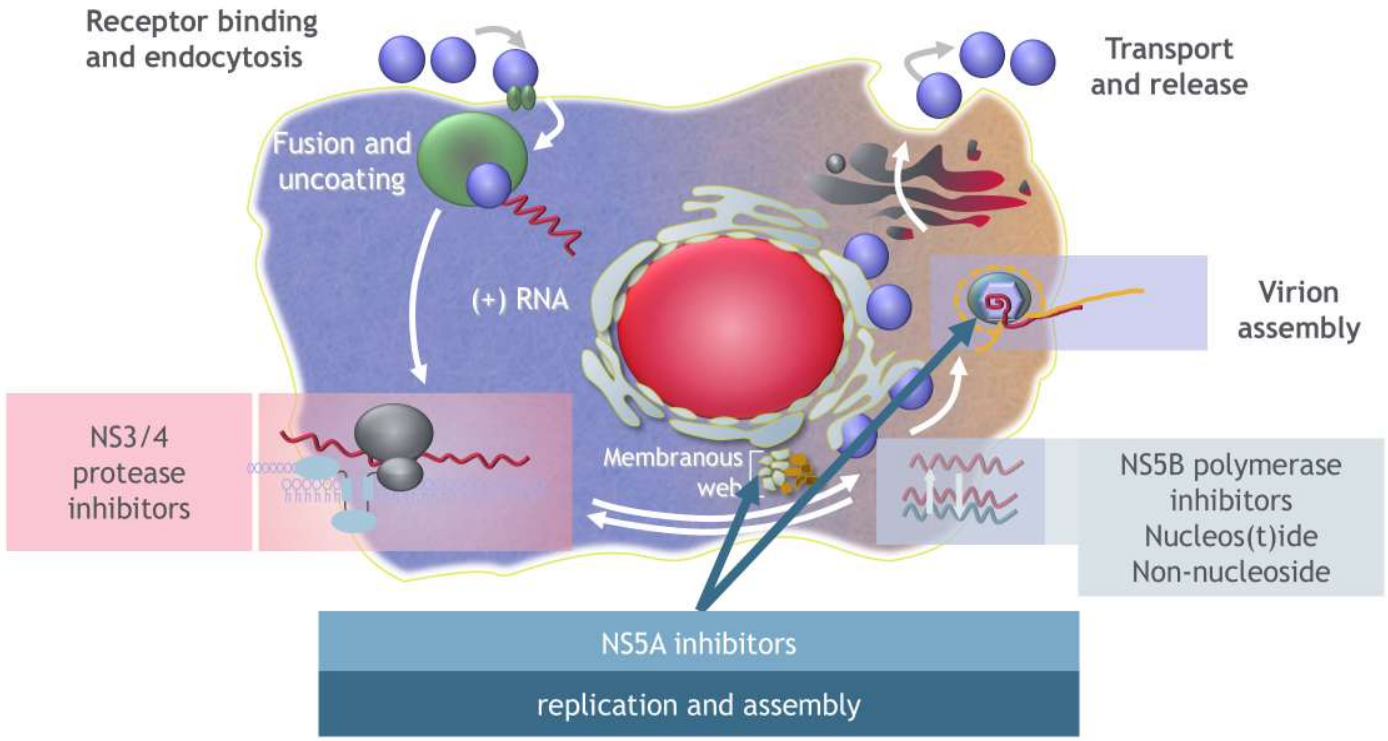
Evolution HCV Treatment

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



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

Treatment of Chronic Hepatitis C in 2021

Class	Generic name	Abbrev.	Fixed-dose combinations
Protease inhibitors	Grazoprevir	GZR	**Zepatier®** GZR EBR
	Glecaprevir	GLE	
	Voxilaprevir	VOX	**Epclusa®** VEL SOF
NS5A inhibitors	Elbasvir	EBR	
	Velpatasvir	VEL	**Vosevi®** VOX VEL SOF
	Pibrentasvir	PIB	
Polymerase inhib.	Sofosbuvir	SOF	**Maviret®** GLE PIB

SASL-SSG-SSI EOS (**www.sasl.ch**, **www.sggssg.ch**, **www.sginf.ch** or Swiss HCV Advisor application).
Sarrazin C *et al*. Z Gastroenterol 2020;58:1110-1131.
EASL Recommendations. J Hepatol 2020;73:1170-1218 (**www.easl.eu**).
AASLD-IDSA Hepatitis C Guidance. Hepatology 2020;71:686-720 (**hcvguidelines.org**).

HCV Treatment

All patients with HCV must be offered therapy unless concomitant co-morbidities will result in short-term mortality.

- **Same DAA regimens** recommended for **chronic and acute HCV infection**, but best DAA initiation timing have not yet been established for acute infection.

The aim of chronic HCV infection treatment is to **achieve a SVR*** that:

- Reduced necro-inflammation and progression to fibrosis, cirrhosis and endstage liver disease
- Reduction in risk of HCC
- Improved liver-related morbidity and mortality
- Improved all-cause mortality
- Prevents onward transmission

*The Sustained virological response (SVR) is defined by undetectable HCV RNA at least 12 weeks after the end of DAA therapy.
DAA, Direct acting antivirals; HCC, Hepatocellular carcinoma.
National Guidelines for the Management of Viral Hepatitis. Department of Health Republic of South Africa Available at: https://sahivsoc.org/Files/SA%20NDOH_Viral%20Hepatitis%20guideilnes%20final_.pdf (Accessed 16 November 2022).

HCV Treatment

Treatment prioritisation (i.e. patients who need to be treated first when the national programme is initiated) target:

- **significant fibrosis (F3) or F4/cirrhosis** (including compensated cirrhosis)
- **HIV or HBV co-infection**
- **extrahepatic manifestations**
- **acute HCV**
- liver transplant and other solid organ transplant recipients
- **PWID/PWUD**

PWID, people who inject drugs.

National Guidelines for the Management of Viral Hepatitis. Department of Health Republic of South Africa Available at: https://sahivsoc.org/Files/SA%20NDOH_Viral%20Hepatitis%20guideilnes%20final_.pdf (Accessed 16 November 2022).

Treating Hepatitis C: Pangenotypic DAA regimens

Type of treatment	Genotype	Cirrhosis status	Prior treatment experience	Sofosbuvir/ velpatasvir	Glecaprevir/ pibrentasvir	Sofosbuvir/ velpatasvir/ voxilaprevir	Grazoprevir/ elbasvir
Genotype/subtype determination-based treatment	Genotype 1a, 1b, 2, 4, 5 and 6	No cirrhosis	Treatment-naïve	12 weeks	8 weeks	No	12 weeks (genotype 1b only)
			Treatment-experienced				
		Compensated (Child-Pugh A) cirrhosis)	Treatment-naïve		12 weeks		
			Treatment-experienced				
	Genotype 3	No cirrhosis	Treatment-naïve	12 weeks	8 weeks	No	No
			Treatment-experienced		12 weeks		No
		Compensated (Child-Pugh A) cirrhosis)	Treatment-naïve	12 weeks with weight-based ribavirin[a]	8-12 weeks[b]	12 weeks[a]	No
			Treatment-experienced		16 weeks		No
	Subtype 1l, 4r, 3b, 3g, 6u, 6v or any other subtype naturally harbouring one or several NS5A RASs[c]	No cirrhosis	Treatment-naïve	Unknown	Unknown	12 weeks	No
			Treatment-experienced				
		Compensated (Child-Pugh A) cirrhosis)	Treatment-naïve				
			Treatment-experienced				

Protease Inhibitors should not be used in decompensated cirrhosis

- GLE/PIB, GZR/EBR, and SOF/VEL/VOX

Sofosbuvir/Velpatasvir can be used in Child-Pugh A, B and C cirrhosis

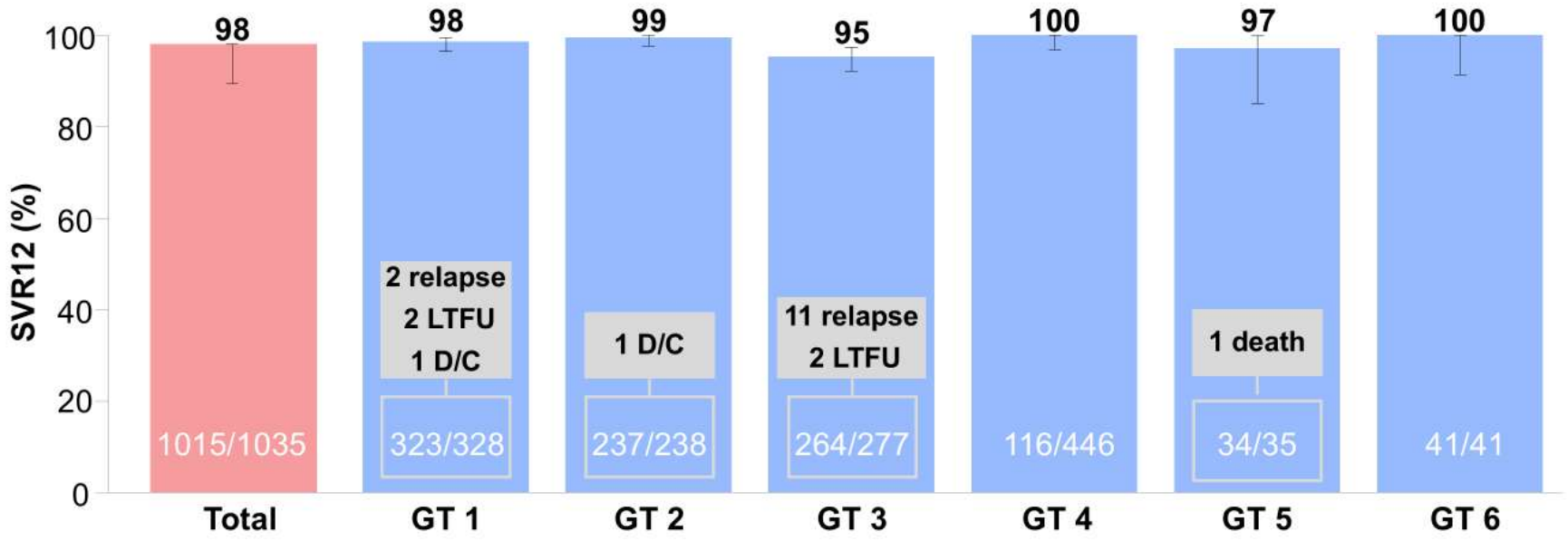
J Hepatol 2020;73:1170

SOFOSBUVIR/VELPATASVIR
SOF/VEL
(Direct Acting Antiviral)
Clinical Trial and Real-World Data

ASTRAL-1, -2, -3

‡

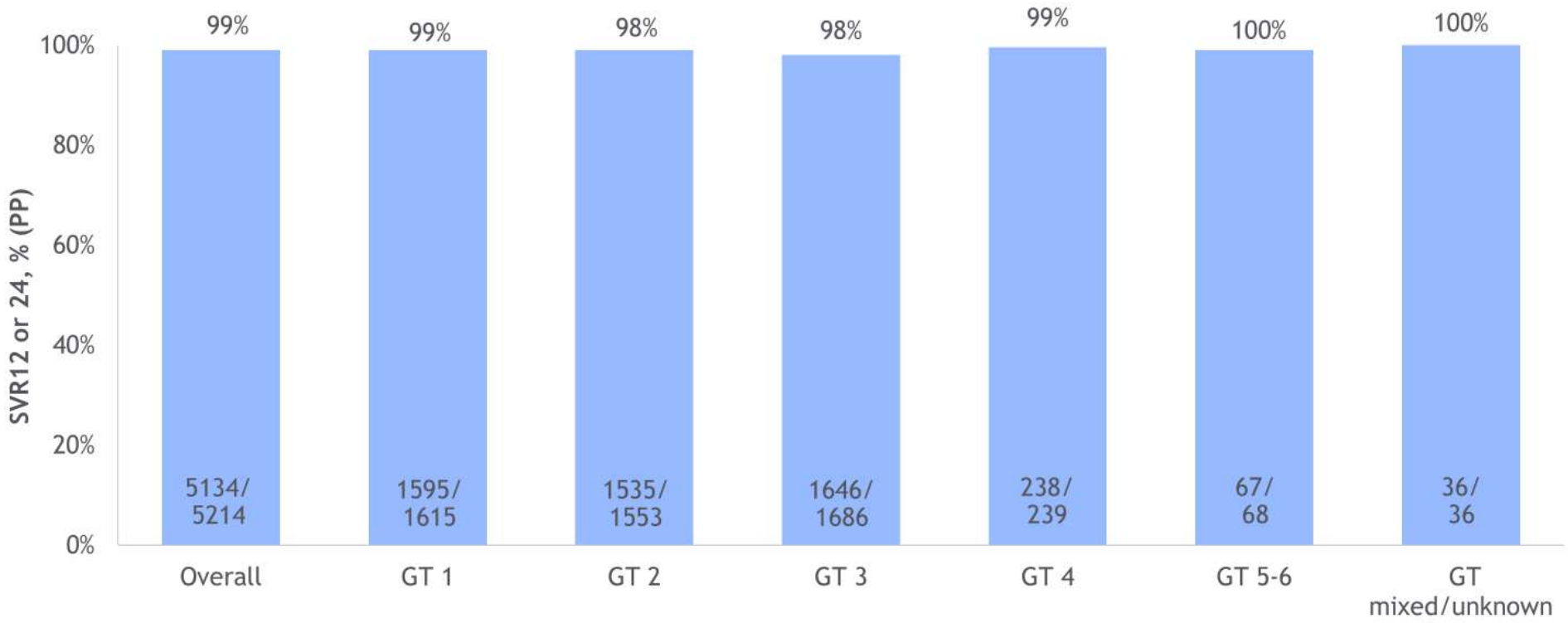
Integrated Efficacy: SVR12



Agarwal, EASL 2016, Poster SAT-195

SOF/VEL for 12 Weeks: SVR by Genotype

Real world analysis of 12 clinical practice cohorts from 7 countries

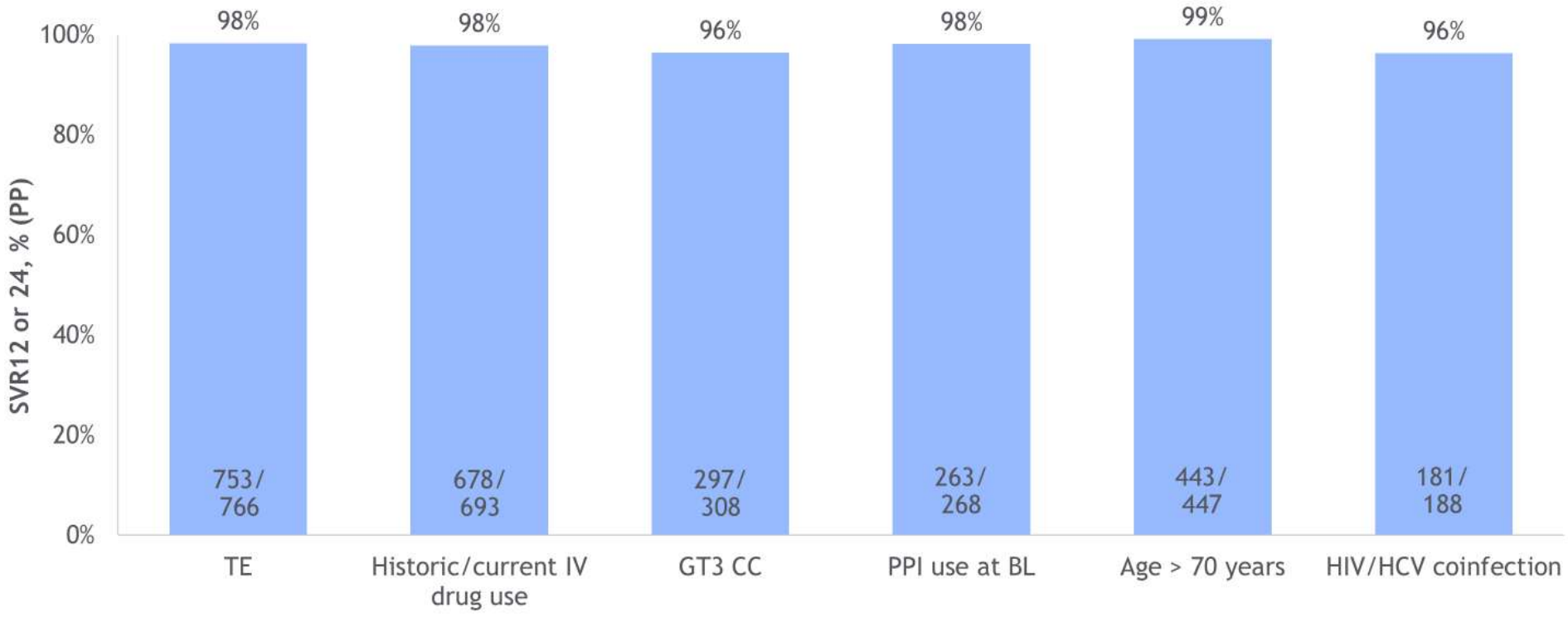


High SVR in the largest real-world cohort across all genotypes

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

‡

Integrated Safety Analysis of SOF/VEL for 12 Weeks

Retrospective integrated analysis of data from 1,035 SOF/VEL patients and control/placebo patients in ASTRAL-1, -2, and -3

Patients, n (%)	SOF/VEL 12 Week N=1035	Placebo 12 Week N=116
AE	821 (79)	89 (77)
Grade 3 or 4 AE	33 (3)	1 (<1)
SAE	23 (2)*	0
AE leading to treatment D/C	2 (<1)^	2 (2)
Death	3 (<1)**	0

*No SAE was assessed as related to SOF/VEL
**None were assessed as related to study treatment
^Two subjects D/C SOF/VEL for AEs; (1 D/C day 1 due to difficulty concentrating, headache, and anxiety and 1 D/C day 13 of due to anxiety)

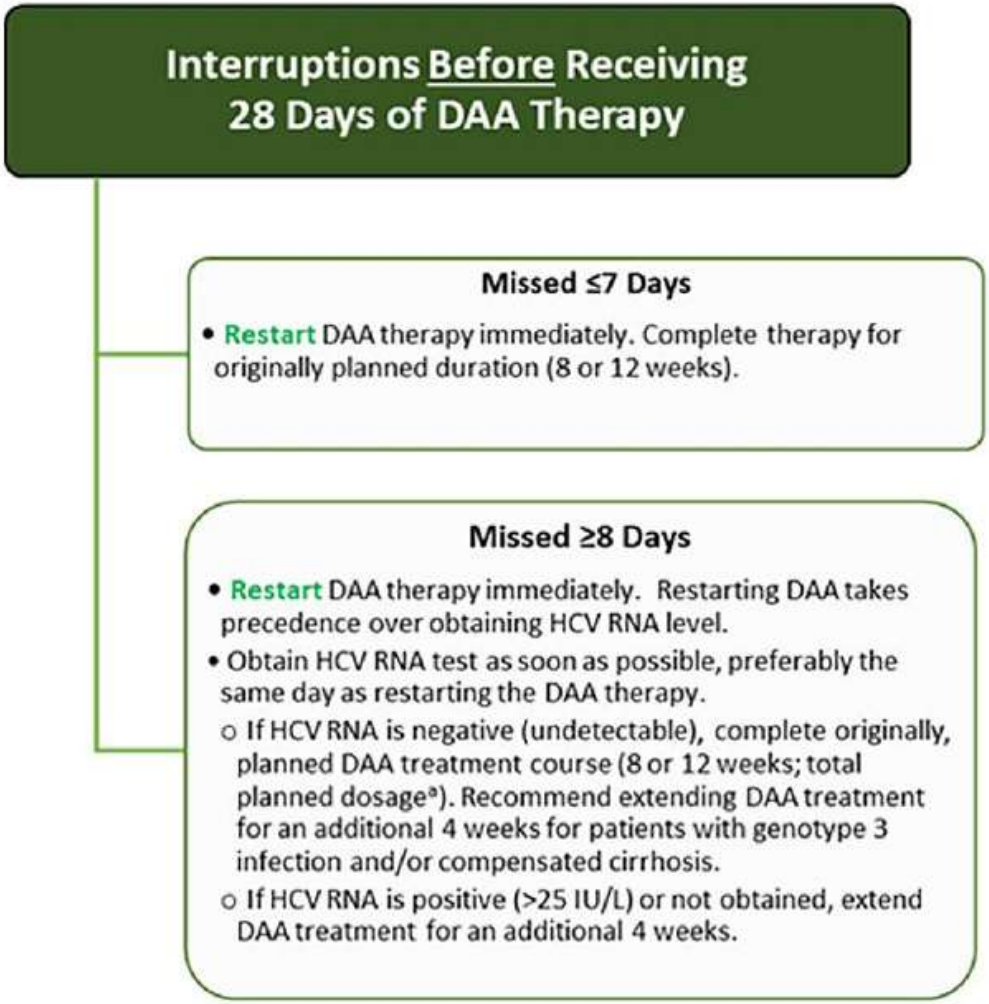
ASTRAL-1, -2, -3

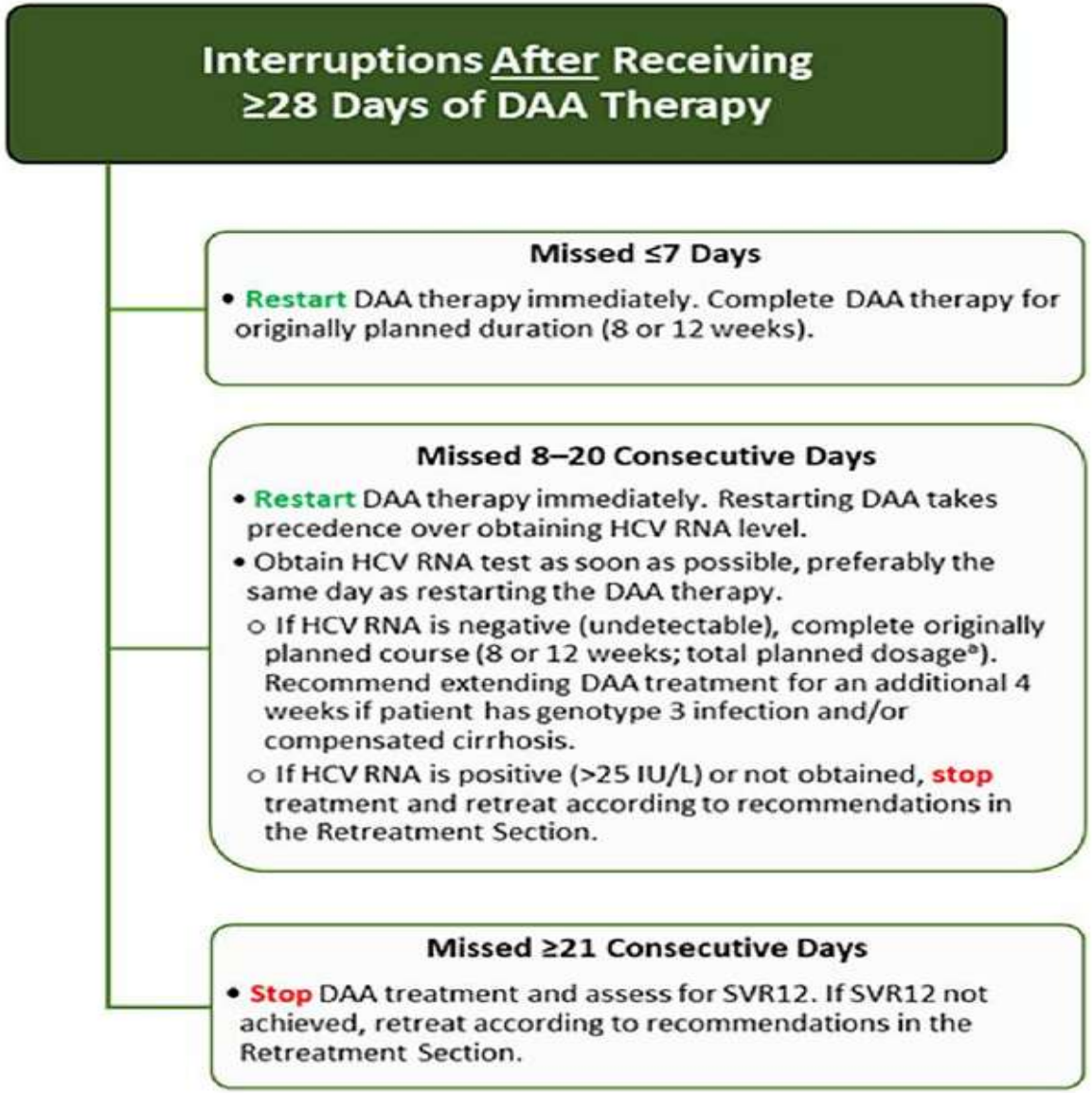
AEs in >10% of Patients

Patients, n (%)	SOF/VEL 12 Week N=1035	Placebo 12 Week N=116
Headache	296 (29)	33 (28)
Fatigue	217 (21)	23 (20)
Nausea	135 (13)	13 (11)
Insomnia	87 (8)	11 (9)
Nasopharyngitis	121 (12)	12 (10)
Cough	57 (6)	4 (3)
Irritability	49 (5)	4 (3)
Pruritus	33 (3)	5 (4)
Dyspepsia	33 (2)	4 (3)

- Severe AEs were rare in SOF/VEL-treated patients, with headache, anxiety, and acute myocardial infarction occurring >1 patient (both cases of acute myocardial infarction were assessed as not related to SOF/VEL treatment by the investigators)

Treatment with SOF/VEL for 12 weeks was well tolerated and had a safety profile similar to that of placebo treatment


Interruptions Before 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 Days
• Restart DAA therapy immediately. Restarting DAA takes precedence over obtaining HCV RNA level.
• Obtain HCV RNA test as soon as possible, preferably the same day as restarting the DAA therapy.
o If HCV RNA is negative (undetectable), complete originally, planned DAA treatment course (8 or 12 weeks; total planned dosage[a]). Recommend extending DAA treatment for an additional 4 weeks for patients with genotype 3 infection and/or compensated cirrhosis.
o 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 DAA therapy for originally planned duration (8 or 12 weeks).
Missed 8–20 Consecutive Days
• Restart DAA therapy immediately. Restarting DAA takes precedence over obtaining HCV RNA level.
• Obtain HCV RNA test as soon as possible, preferably the same day as restarting the DAA therapy.
o If HCV RNA is negative (undetectable), complete originally planned course (8 or 12 weeks; total planned dosage[a]). Recommend extending DAA treatment for an additional 4 weeks if patient has genotype 3 infection and/or compensated cirrhosis.
o If HCV RNA is positive (>25 IU/L) or not obtained, stop treatment and retreat according to recommendations in the Retreatment Section.
Missed ≥21 Consecutive Days
• Stop DAA treatment and assess for SVR12. If SVR12 not achieved, retreat according to recommendations in the Retreatment Section.

Drug-Drug Interactions

Review all prescription drugs, OTC meds, herbal supplements and complimentary medications

Interactions with common drugs

- Proton-pump inhibitors
- Anti-retroviral drugs: EFV; Atazanavir/ritonavir
- Statins
- Anti-epileptics: Carbamazepine
- Amiodarone
- Herbal medications: St John's wart
- Oral contraceptive: Ethinyl-oestrodiol

	SOF	SOF/VEL	SOF/VEL/VOX	GLE/PIB	GZR/EBR
Atorvastatin	◆	■	●	●	■
Bezafibrate	◆	◆	◆	◆	◆
Ezetimibe	◆	◆	■	■	◆
Fenofibrate	◆	◆	◆	◆	◆
Fluvastatin	◆	■	●	■	■
Gemfibrozil	◆	◆	◆	■	■
Lovastatin	◆	■	●	●	■
Pitavastatin	◆	■	●	■	◆
Pravastatin	◆	◆	■	■	◆
Rosuvastatin	◆	■	●	■	■
Simvastatin	◆	■	●	●	■

DAAs, direct-acting antivirals; EBR, elbasvir; GLE, glecaprevir; GZR, grazoprevir; PIB, pibrentasvir; SOF, sofosbuvir; VEL, velpatasvir; VOX, voxilaprevir.

Colour Legend

◆ No clinically significant interaction expected.

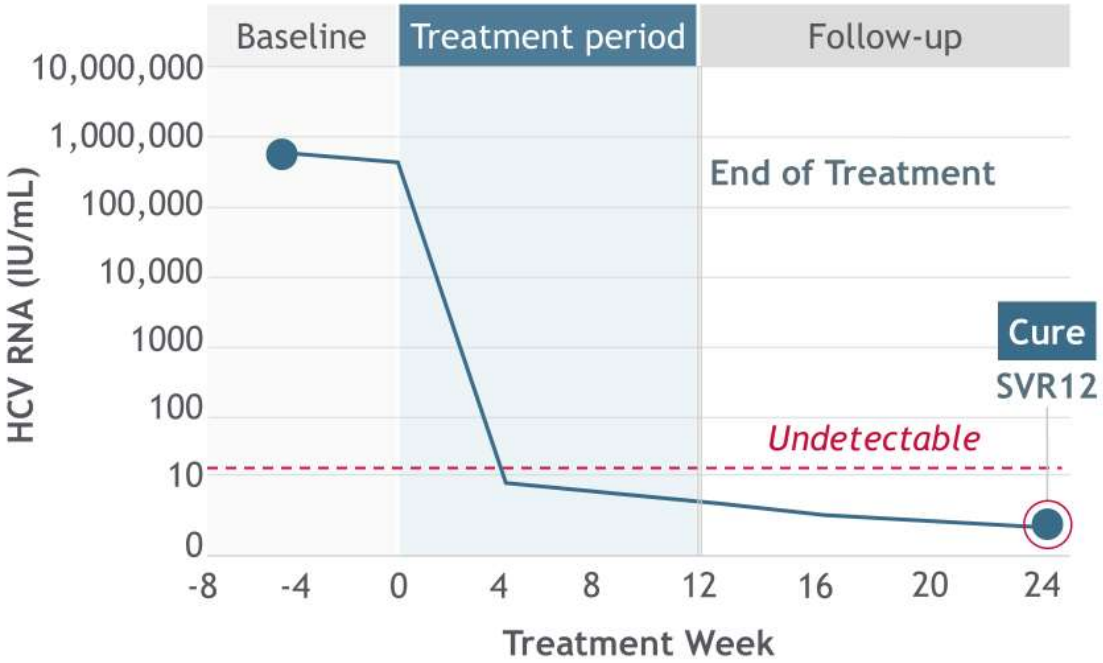
■ Potential interaction which may require a dosage adjustment, altered timing of administration or additional monitoring.

● These drugs should not be co-administered.

J Hepatol 2020;73:1170;
Liverpool DAA interaction online app; www.hep-druginteractions.org/checker

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. http://hcvguidelines.org 2. Hepatitis C Online. Updated October 12, 2020. Accessed July 12, 2021. https://www.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.

Treating Hepatitis C

CURE = Sustained viral response 12 weeks after completion of DAA therapy

SVR corresponds to a definitive cure of HCV infection in >95% cases and is frequently associated with:

- Improvement in extrahepatic manifestations[1]
- Improvement/resolution of liver necroinflammation and fibrosis[1]
- Regression of advanced hepatic fibrosis (F3) or cirrhosis (F4)[2]
- Reduced risk of HCC, hepatic decompensation, non-liver- and liver-related mortality, and liver transplantation[3–7]

If first line DAA therapy fails: Refer to Hepatologist

- Genotype for unusual subtypes in SSA: GT1 and 4
- Resistance-associated substitutions: RAS testing
- Sofosbuvir/Velpatasvir/Voxilaprevir

1. J Hepatol 2016;65:S95; 2. Hepatology 2012;56:532; 3. Gastroenterology 2017;152:142; 4. JAMA 2012;308:2584; 5. J Hepatol 2016;64:1217; 6. J Infect Dis 2012;206:469; 7. Clin Gastroenterol Hepatol 2010;8:280 and EASL CPG HCV. J Hepatol 2020;73:1170

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

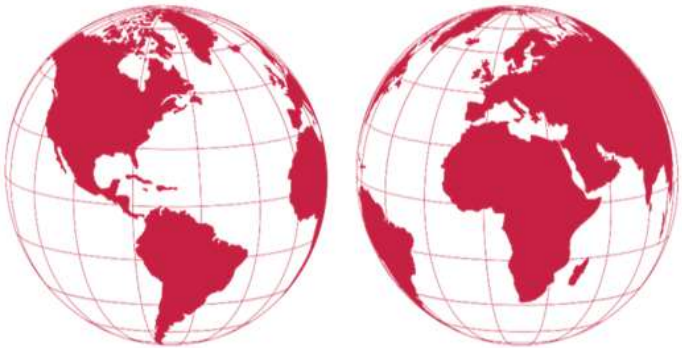
AASLD/IDSA. Updated October 5, 2021. Accessed September 27, 2022. http://hcvguidelines.org

HCV Can be Cured and Potentially Eliminated

The World Health Organization has set an objective to eliminate HCV infection as a public health threat by 2030

2030 Targets for Elimination of HCV

of those with chronic HCV



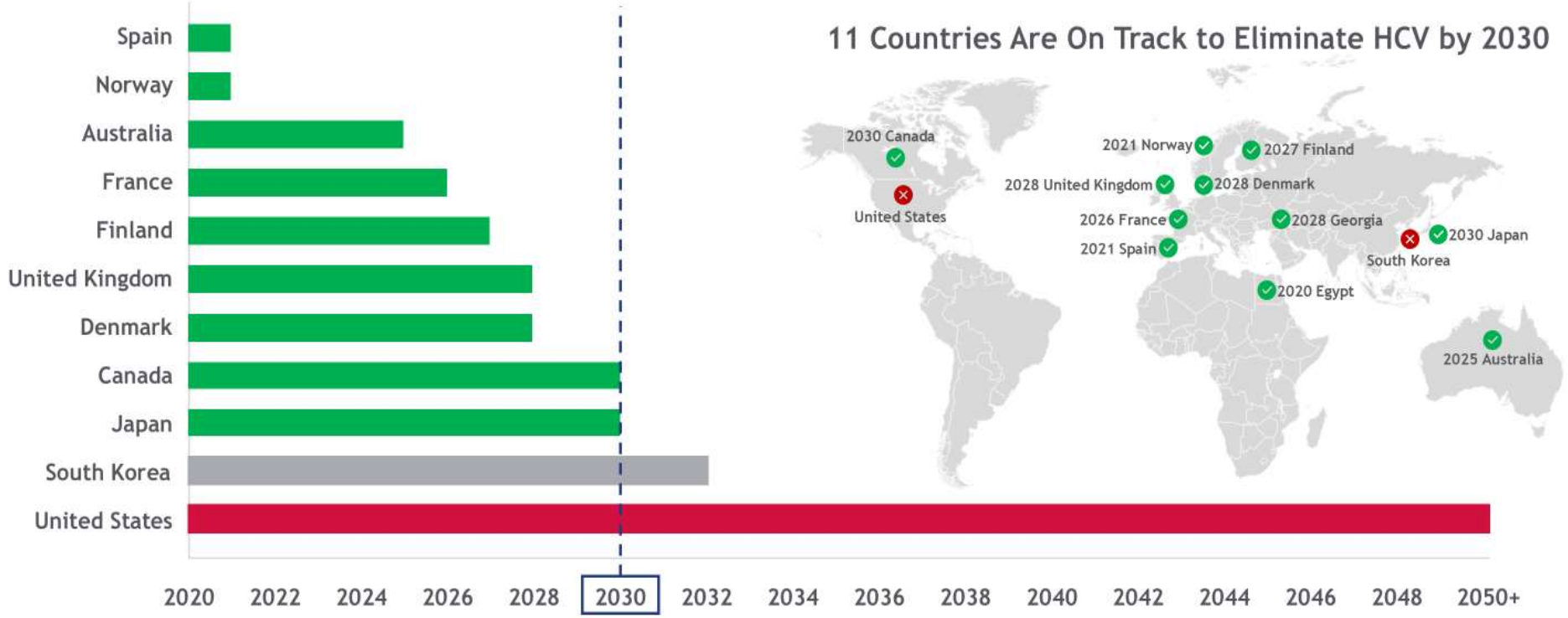
of those diagnosed with chronic HCV

These targets are set to minimize new chronic infections and decrease HCV-related mortality

World Health Organization. Guidelines for the care and treatment of persons diagnosed with chronic hepatitis C virus infection. 2018.

Countries On Track to Meet WHO 2030 HCV Elimination Objectives, Based on Current Treatment Rates[1]

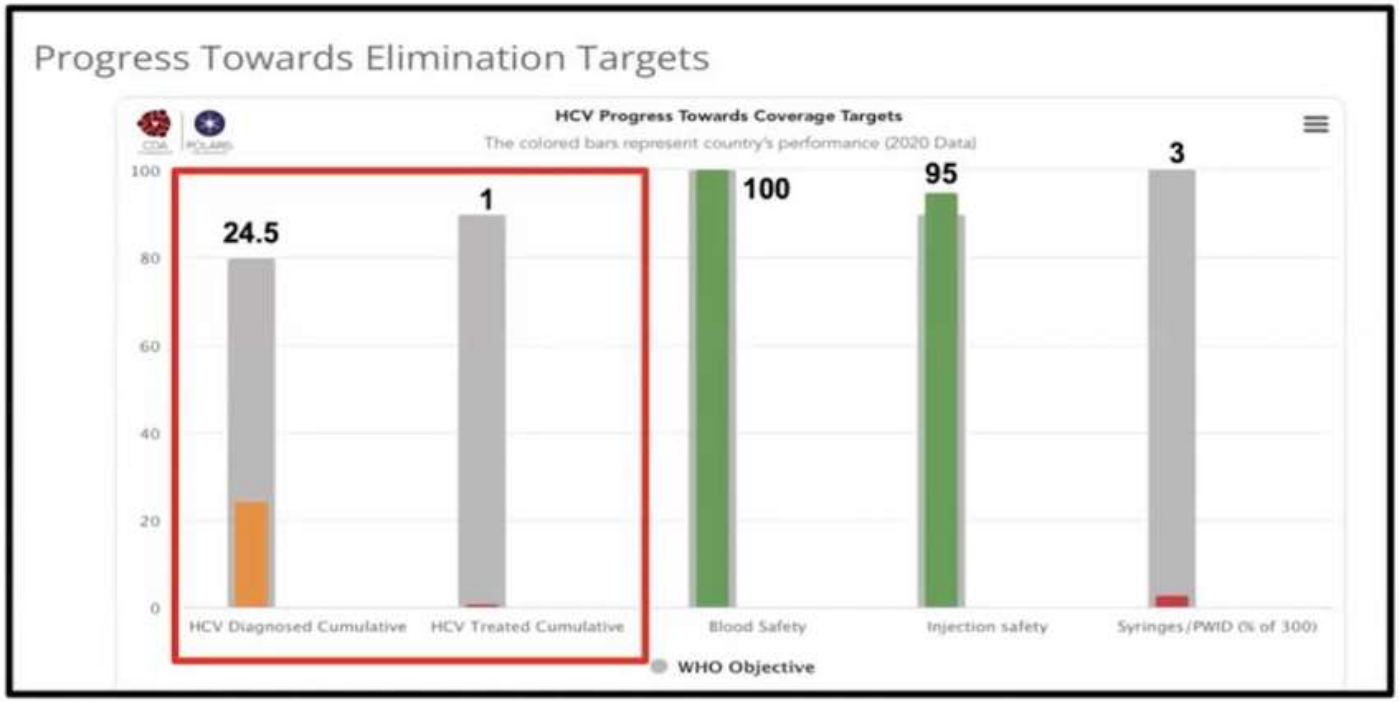
Year Each Country/Region Will Meet WHO Absolute or Relative HCV Targets[a]



[a]Extrapolated from 2020 data using a Markov model predicting achievement of WHO HCV targets.[1,2]

1. CDA Foundation's Polaris Observatory. Accessed January 27, 2023. https://cdafound.org/polaris/ 2. Razavi H. *Antivir Ther*. 2022;27(2):13596535221083179.

Progress towards HCV Elimination: South Africa: 2022



Polaris Observatory: https://cdafound.org/polaris/

Hepatitis C: Diagnosis and Linkage to Care

All HCV-infected individuals require treatment: DAA therapy

- Treatment naïve or treatment experienced
- High-risk key populations: PWID or MSM at risk of re-infection and onward transmission
- Remember that anti-HCV does not confer immunity

Confirm active HCV viraemia

No need for Genotyping or HCV viral load quantification

Assess liver disease severity: Non-invasive tests: APRI, FIB-4 and Fibroscan

Assess conditions that affect disease progression

- HIV-HCV, HBV-HCV and HIV-HBV-HCV-co-infections
- Co-morbid diseases: Type 2 Diabetes, iron overload, alcohol

Determine potential drug-drug interactions

Assess and reduce risk of re-infection

Ongoing HCC surveillance after SVR if cirrhotic

SUMMARY

- Hepatis C can be fatal if left untreated
- Early Detection is key to elimination (Screening –Target high risk)
- Risk stratification minimizes complex drug interaction
- Early effective treatment with DAAs (Sol/Vel) cures Hepatitis C
- Elimination of Hepatitis C is possible and achievable (WHO 2030)

DANKOO