Hepatitis C; Progressing towards elimination

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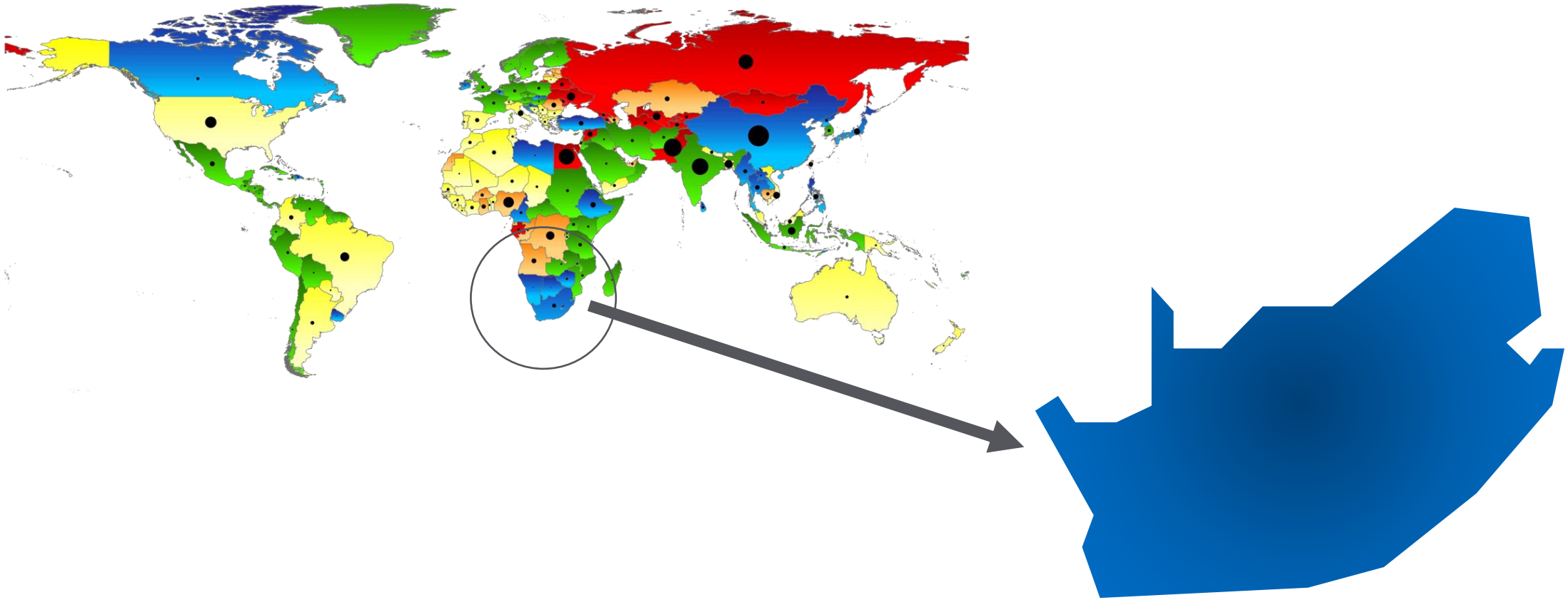
FOCUS ON HCV

History and Epidemiology of Chronic HCV Infection

Hepatitis C in South Africa

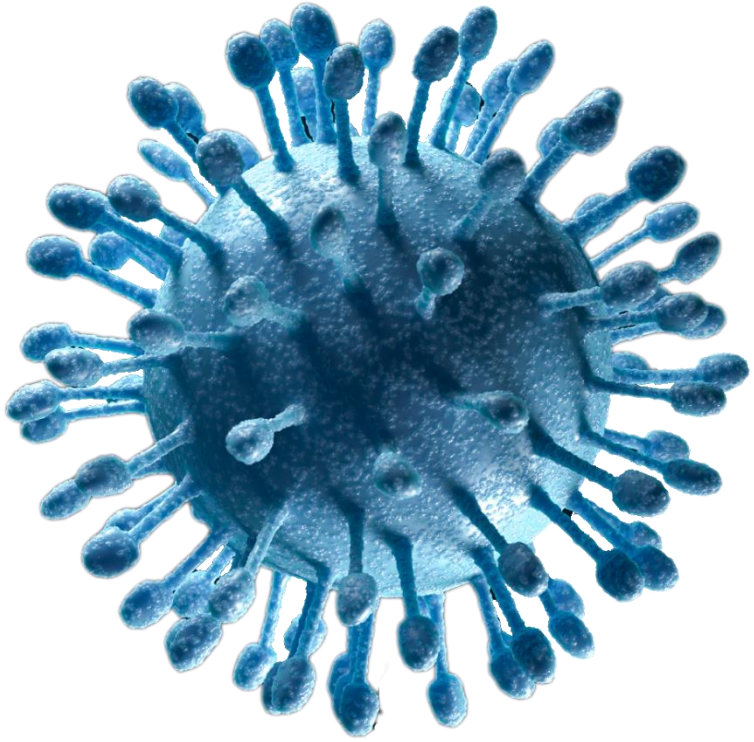


~600 000 HCV viraemic in SA [UI 400 000 -800 000]

Blach S, Zeuzem S, Manns M, Altraif I, Duberg A-S, Muljono DH, et al. Global prevalence and genotype distribution of hepatitis C virus infection in 2015: a modelling study. The Lancet Gastroenterology & Hepatology. 2017;2(3):161-76

Hepatitis C

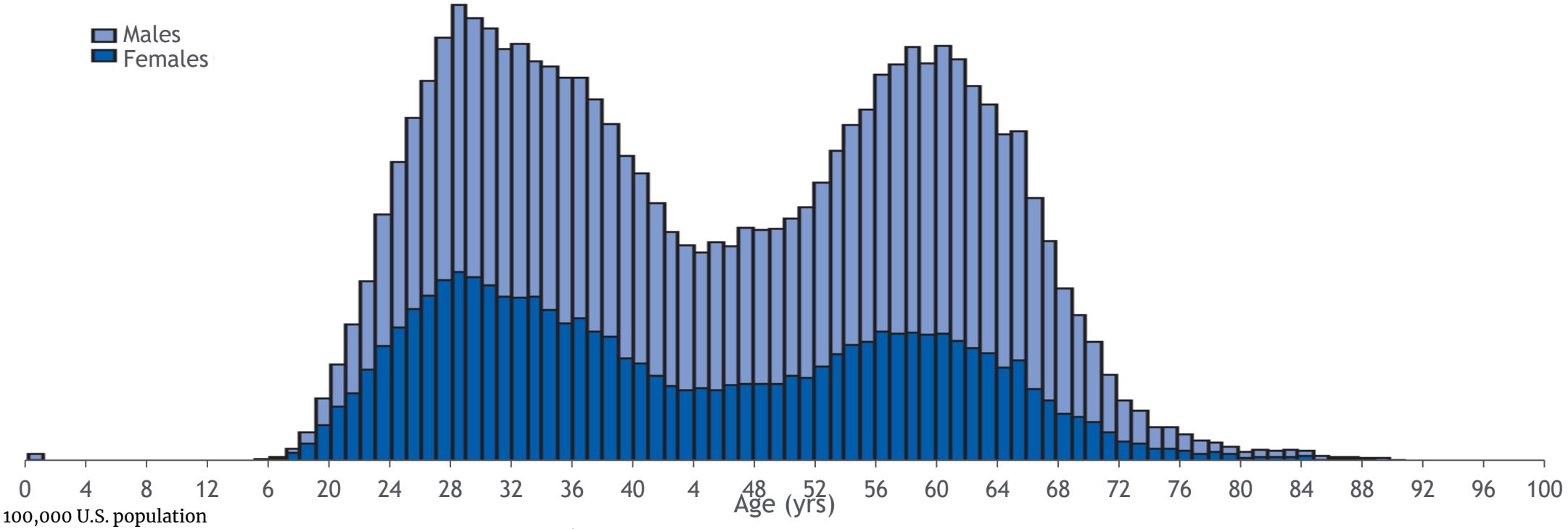
- HCV is a viral infection that can lead to liver disease and has infected ~ 600 000 people in South Africa[1]
- HCV is an RNA virus discovered in 1989[2,3]
  - GT 1-6 are the most common genotypes[2]
- HCV is associated with an increased risk for mortality[4]
- The World Health Organization (WHO) estimated 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 Draft Guidance for Industry.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

Modes of Transmission and Risk Factors

Transmission: Blood Transfusion

Screening Funded

1970 — 1980 — 1990 — 2000-2004 — 2010-2011 — **Current**

In the late 1990s, only 19% of blood was screened for HCV in sub-Saharan Africa, with the main reason being the prohibitive cost of laboratory testing.

HCV antibody screening increased from 34% to 86%

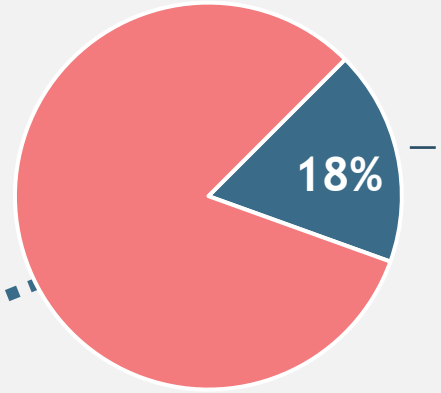
100% of all blood donations are tested for all transfusion-transmitted infections

Transmission: Injection Drug Use

Injection Drug Use

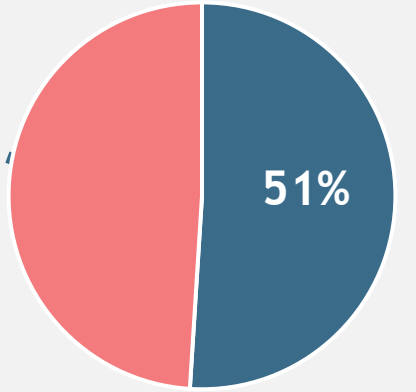
Increased Risk for HCV Infection

Unsafe needle usage



Therapeutic injections with re-used syringes or unsterilised needles

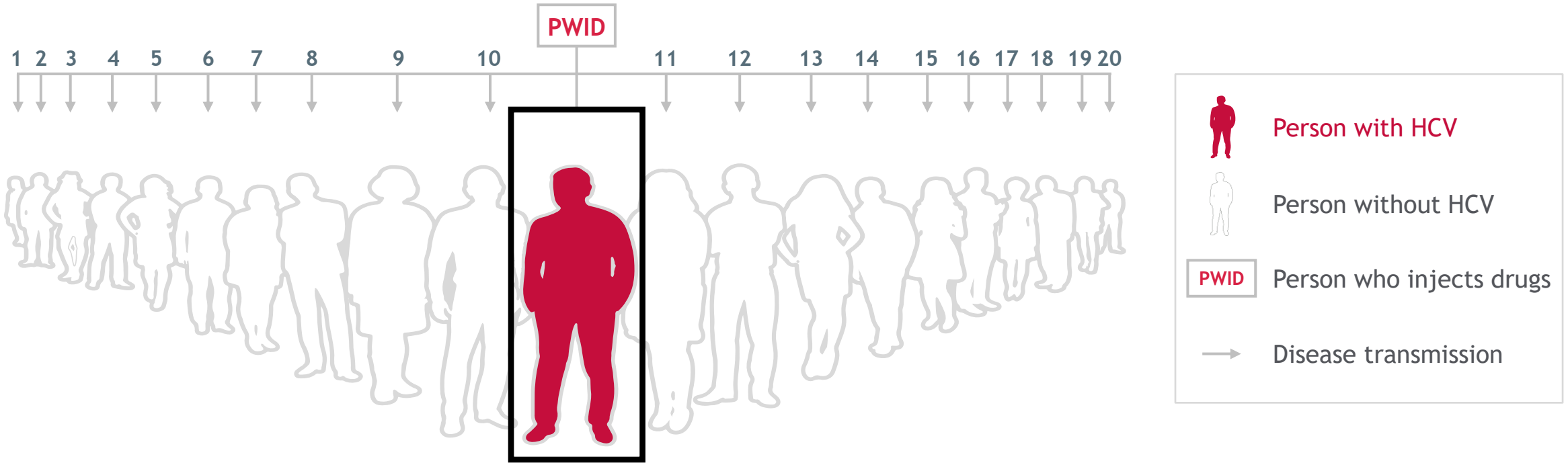
HCV antibodies



PWUD with anti-HCV antibodies in South Africa

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

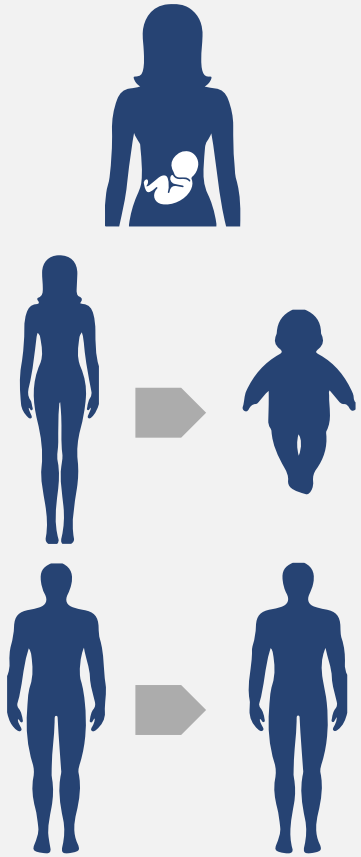
Based on the 2021 NIH National Institute on Drug Abuse Heroin Research Report



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

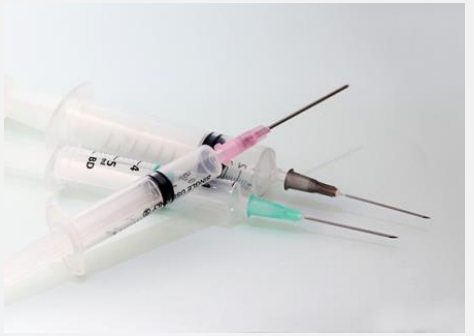
Other Modes of Transmission

Person to Person



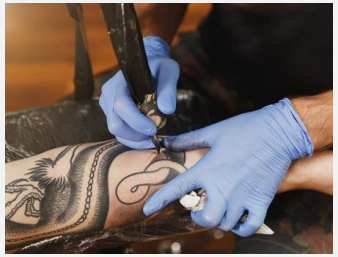
Tissue and organ transplants

Healthcare worker exposure



Unsafe medical procedures

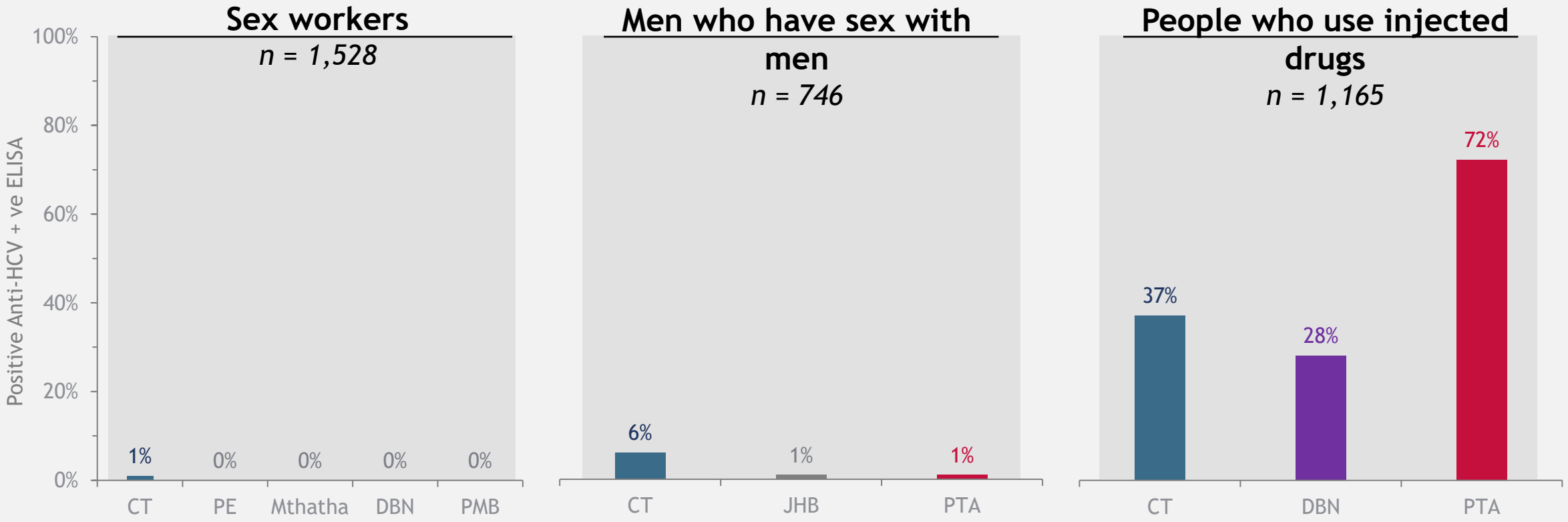
Body piercing



Blood and blood products

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.

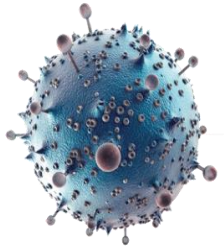


CT = Cape Town; DBN = Durban; JHB = Johannesburg; PE = Port Elizabeth; PMB = Pietermaritzburg; PTA = Pretoria.

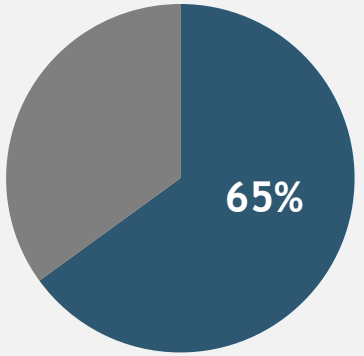
HIV-HCV Coinfection

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

HCV: Disease Progression

Years

20 Years

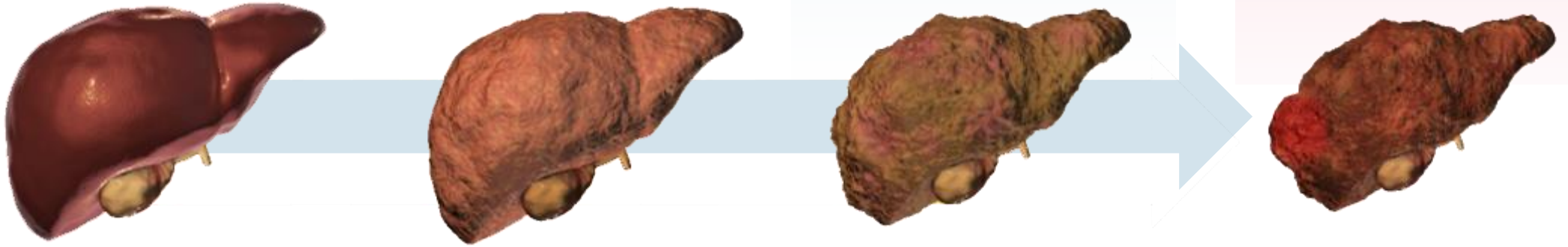
25 Years

- ESLD
- HCC
- Death

Normal Liver

Chronic Hepatitis

Cirrhosis



HCV INFECTION

75-85 will develop chronic HCV if untreated

20-30 will develop cirrhosis

1-5 will die from cirrhosis or HCC

OF EVERY 100 PERSONS INFECTED WITH HCV

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.

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		

Types of Hepatic Cell Injury Response: Inflammation and Degeneration

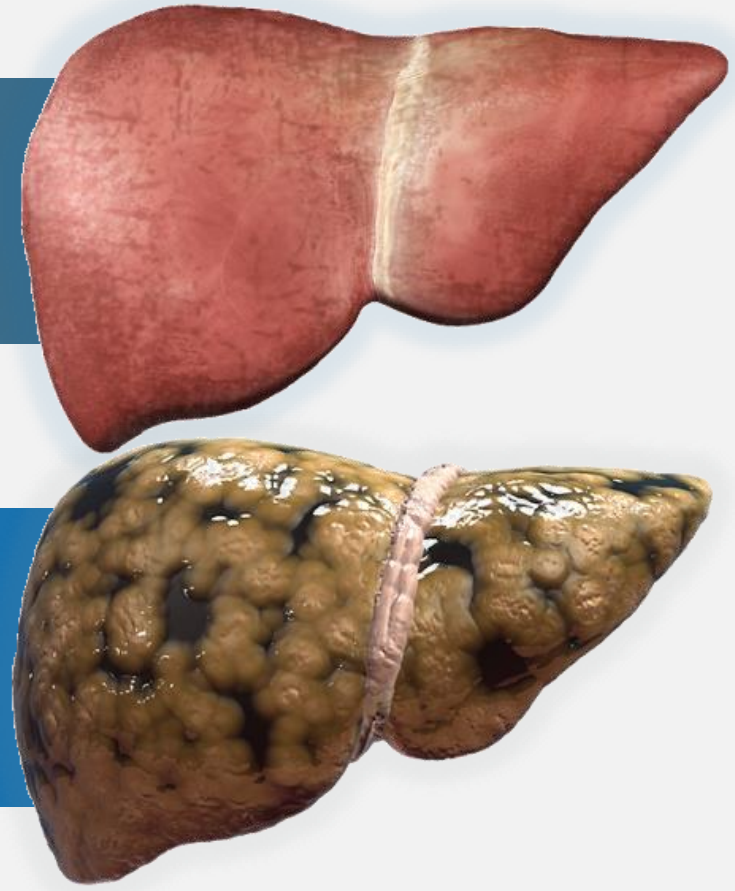
Inflammation

Injury associated with influx of proinflammatory cells – hepatitis

Most hepatic injury involves necrosis (cell death) + inflammation

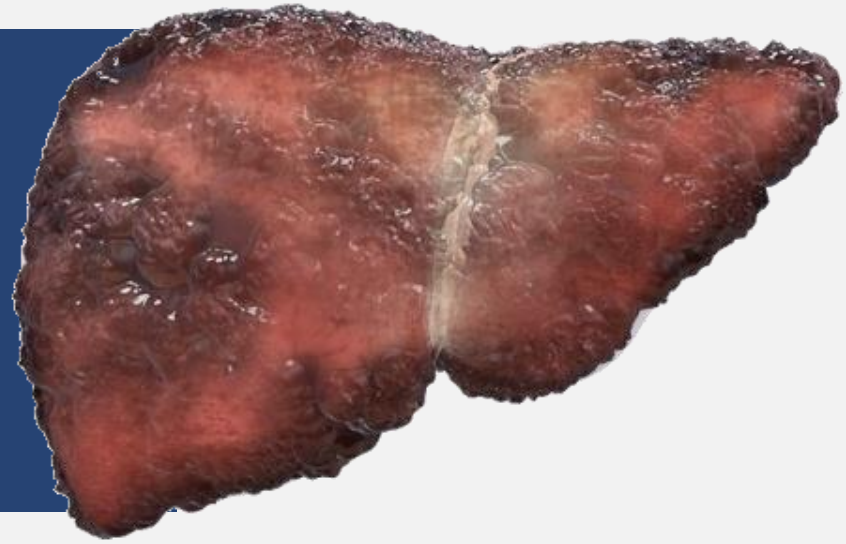
Degeneration

- Ballooning degeneration – water
- Feathery degeneration – bile
- Steatosis (“fatty liver”) – lipids



Stages of Hepatic Cell Injury Response: Fibrosis

- Fibrosis
- Characterized by
  - Deposition of collagen
  - Formation of fibrous tissue within the liver
- Often occurs in response to inflammation/direct toxic injury to liver
- Over time, bridging fibrosis may occur



Types of Hepatic Cell Injury Response: Cirrhosis

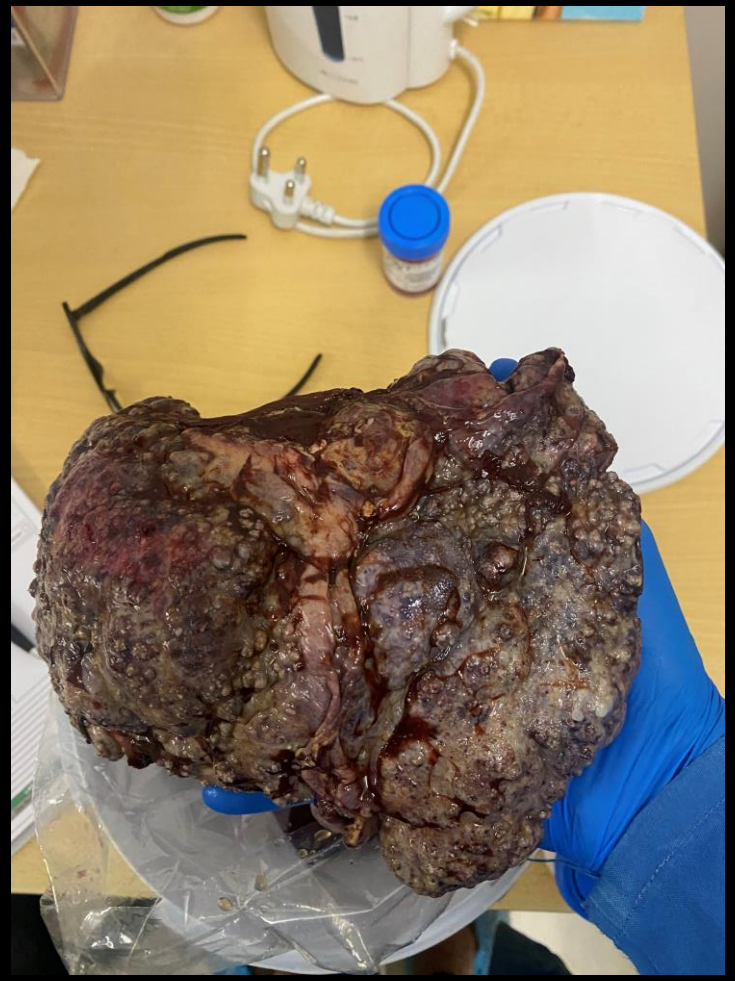
End-stage form of liver disease

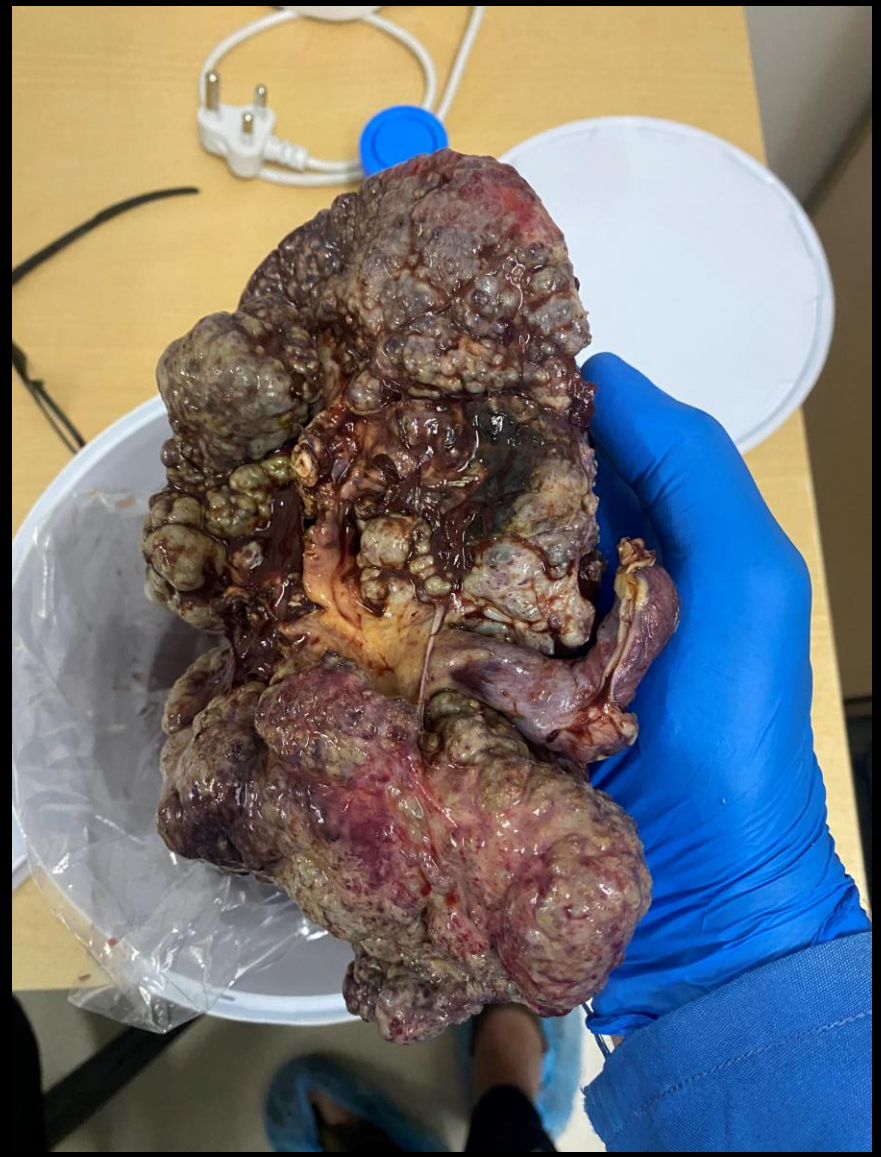
Compensated
- **Heavily scarred**
- Still able to carry out important bodily functions
- Patients may live many years with no symptoms

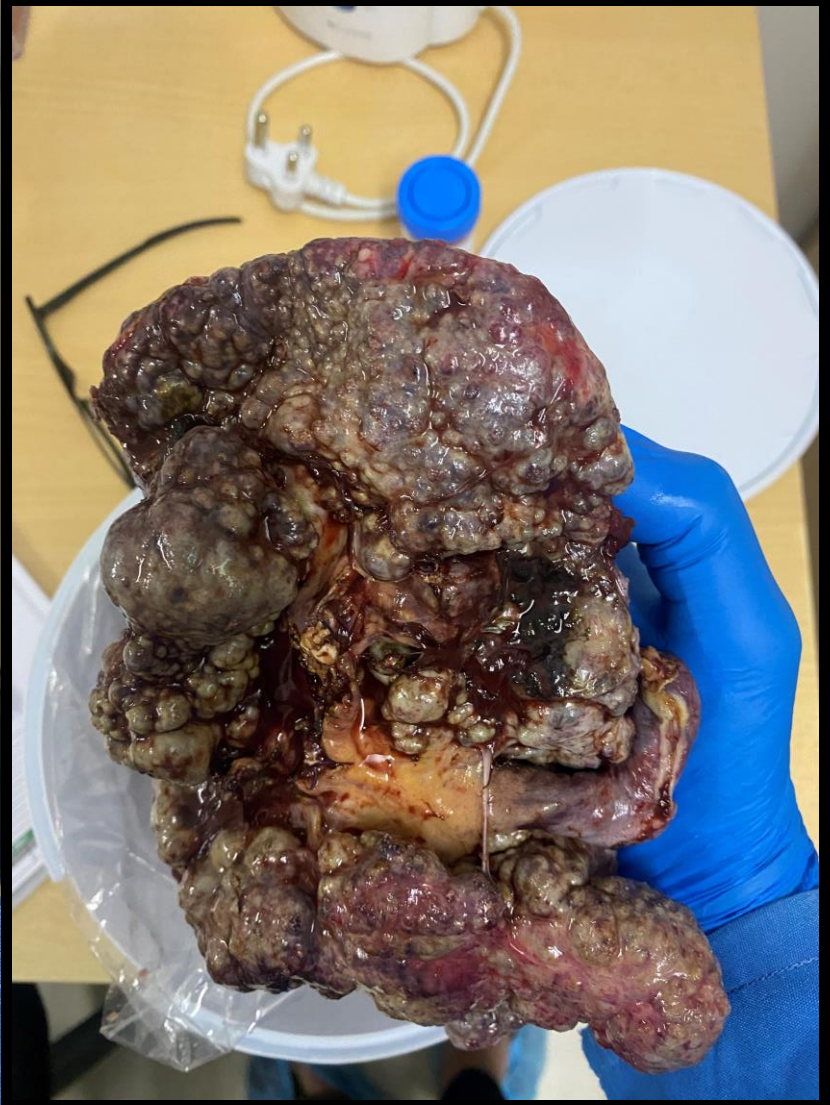
Decompensated
- **Extensively scarred**
- Unable to function adequately
- Patients develop symptoms and experience life-threatening complications

Potential Symptoms:
- Ascites
- Upper GI bleeding
- Hepatorenal syndrome
- Hepatic encephalopathy

Explanted cirrhotic liver – liver removed during transplant



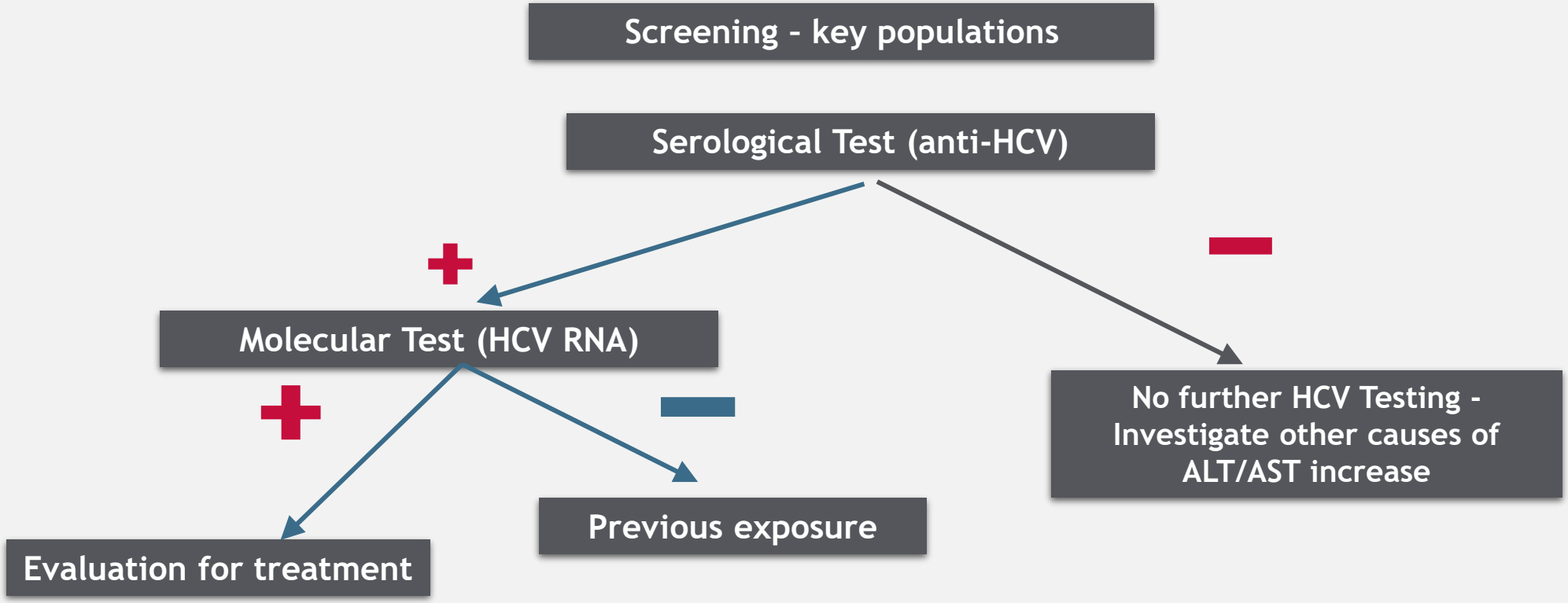




Courtesy of Dr.Mark Sonderup Liver Unit Cape Town

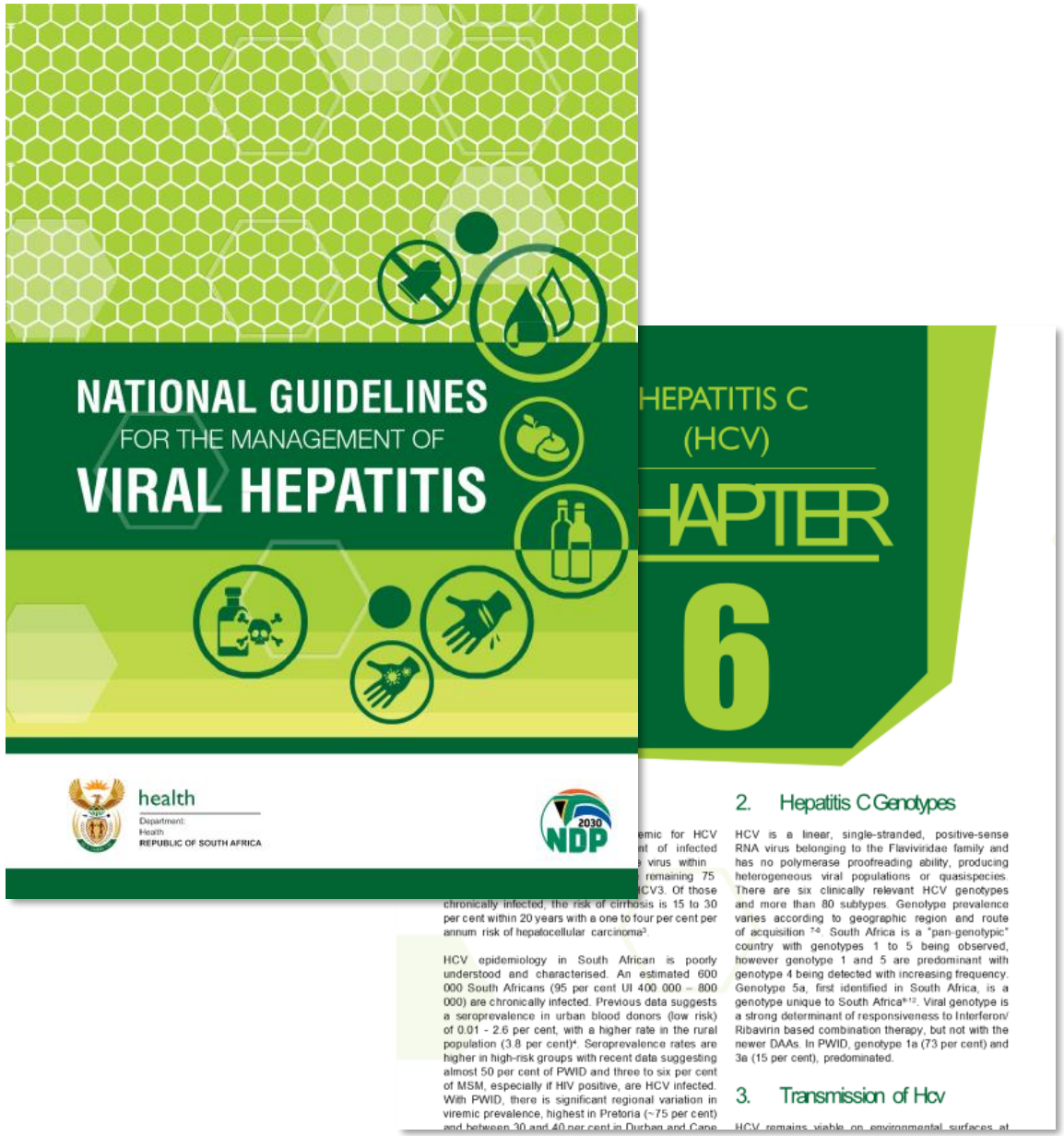
Assessment and Simplified Approach to HCV Treatment

Typical Sequence of Diagnosis for HCV Infection

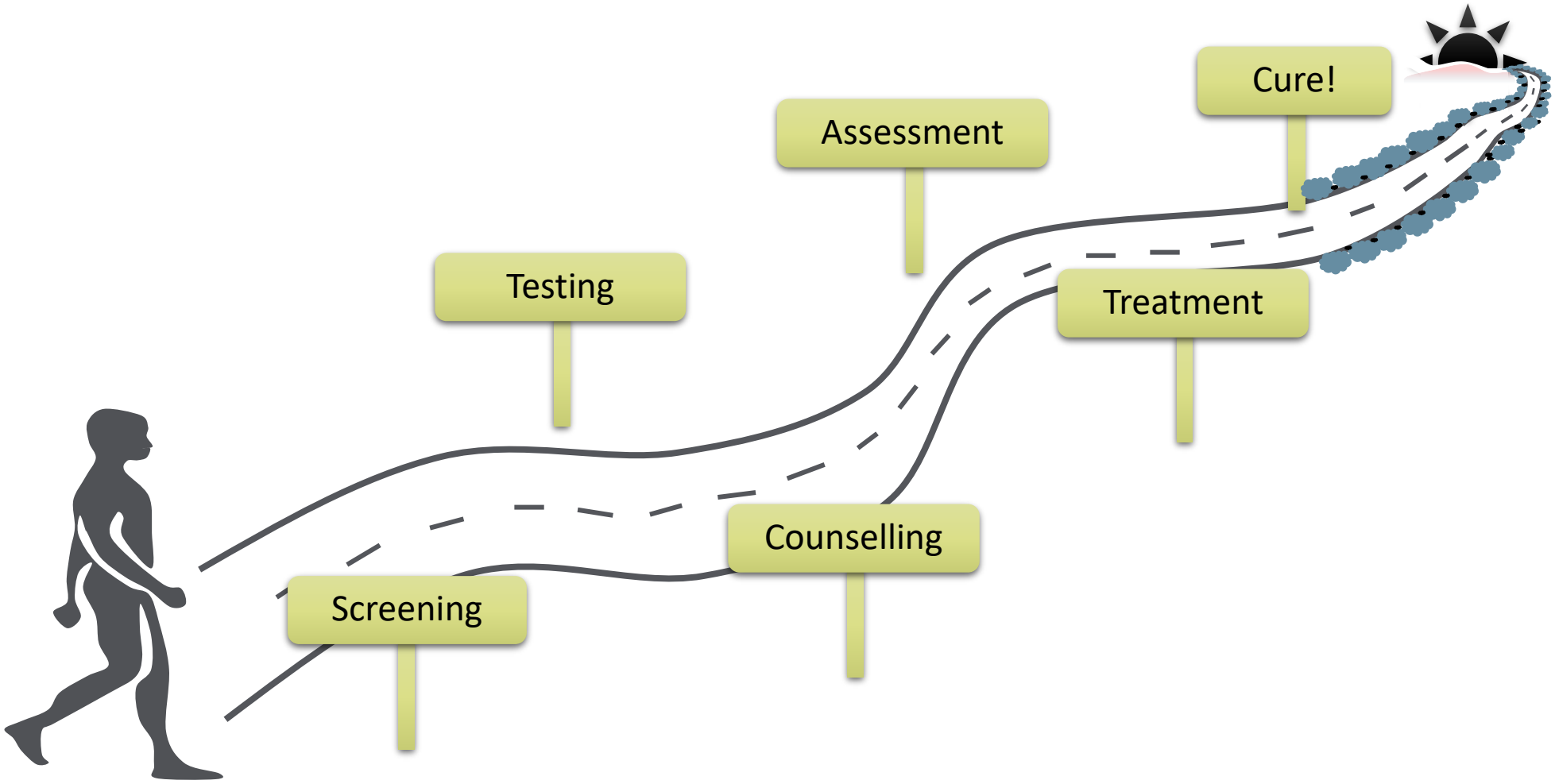


National Guidelines for the Management of Viral Hepatitis

HCV Management

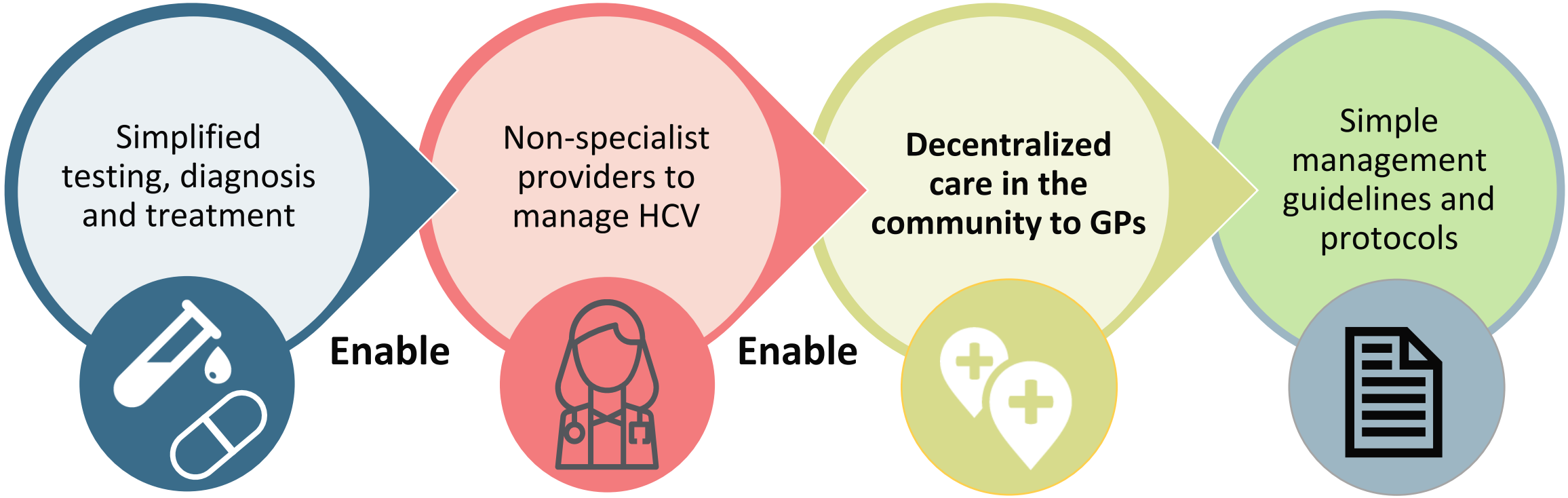


Hepatitis C - the road to cure



Primary approach is for simplified care !!

Simplified care delivery in those who are Hep C RNA positive

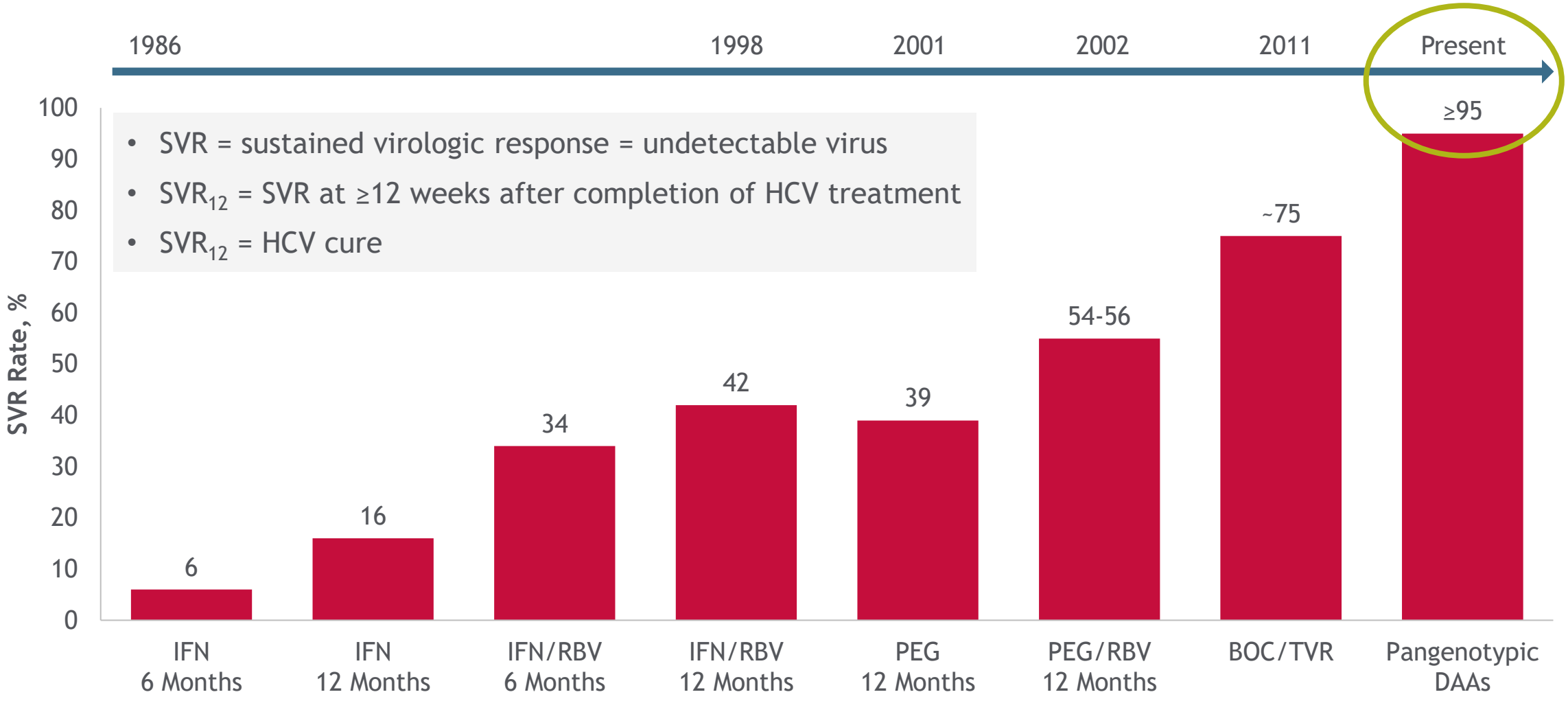


J Hepatol 2018;68:383. Cooke. Lancet Gastroenterol Hepatol 2019;4:135.

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

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:

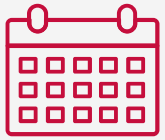
- **significant fibrosis (F3) or F4/cirrhosis** (including compensated cirrhosis)
- **HIV or HBV co-infection**
- **extrahepatic manifestations**
- **acute HCV**
- liver transplant and other solid organ transplant recipients
- **PWID/PWUD**

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).

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
	 Including DCC				

Test → **Treat** → **Cure**

HCV RNA positive

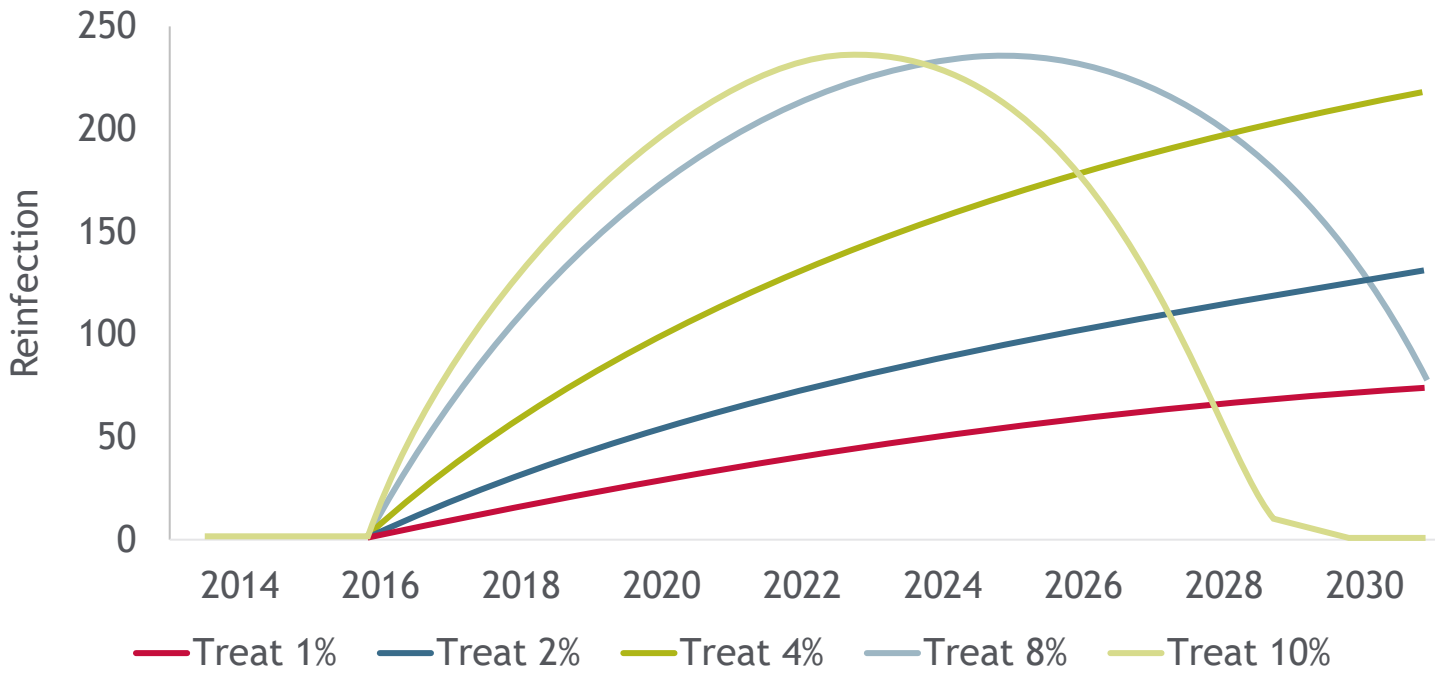
98%
Overall SVR Rate§

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

HCV Treatment as Prevention

Harm Reduction is an Essential Component

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



BUT we must concomitantly scale up harm reduction measures

- Increased intensity of HCV management; eg, directly observed therapy
- Patient education and counseling

AND

  - Increase HCV treater workforce

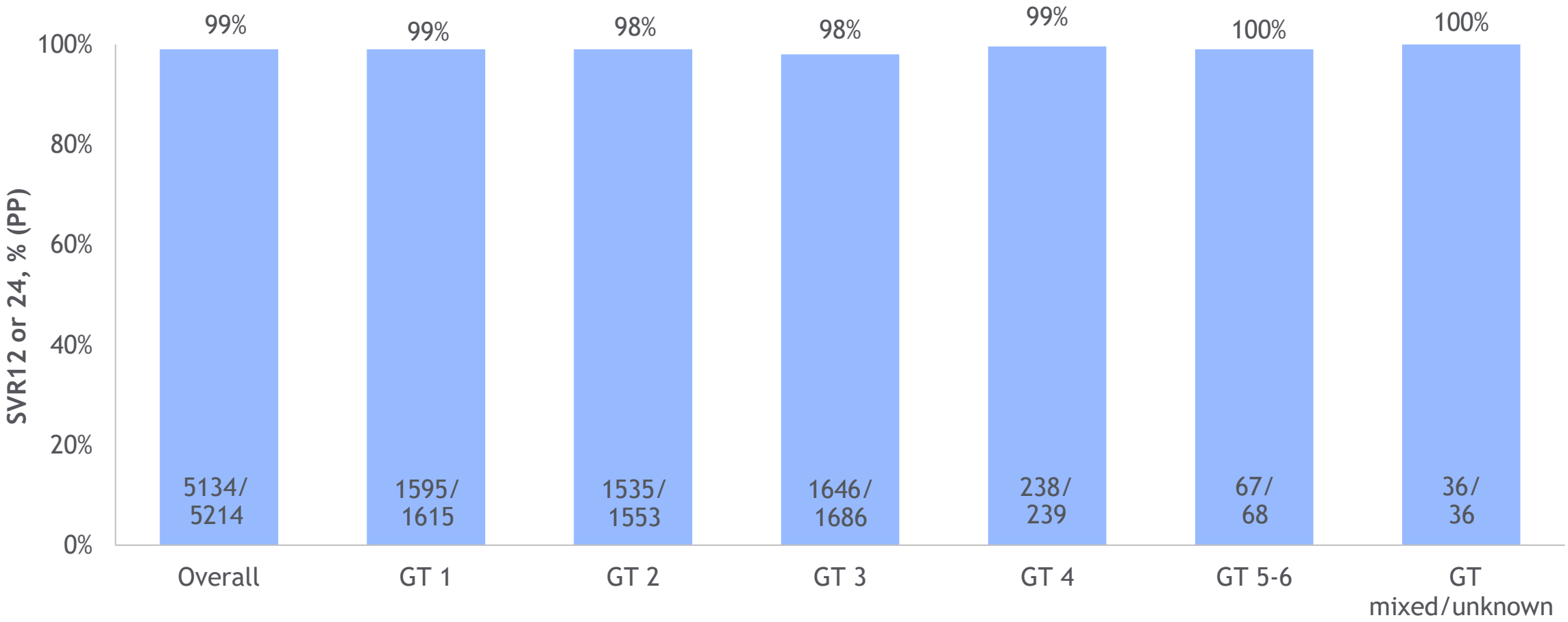
Harm-reduction services and patient education are essential to HCV elimination

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

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

SOF/VEL for 12 Weeks: SVR by Genotype

Real world analysis of 12 clinical practice cohorts from 7 countries

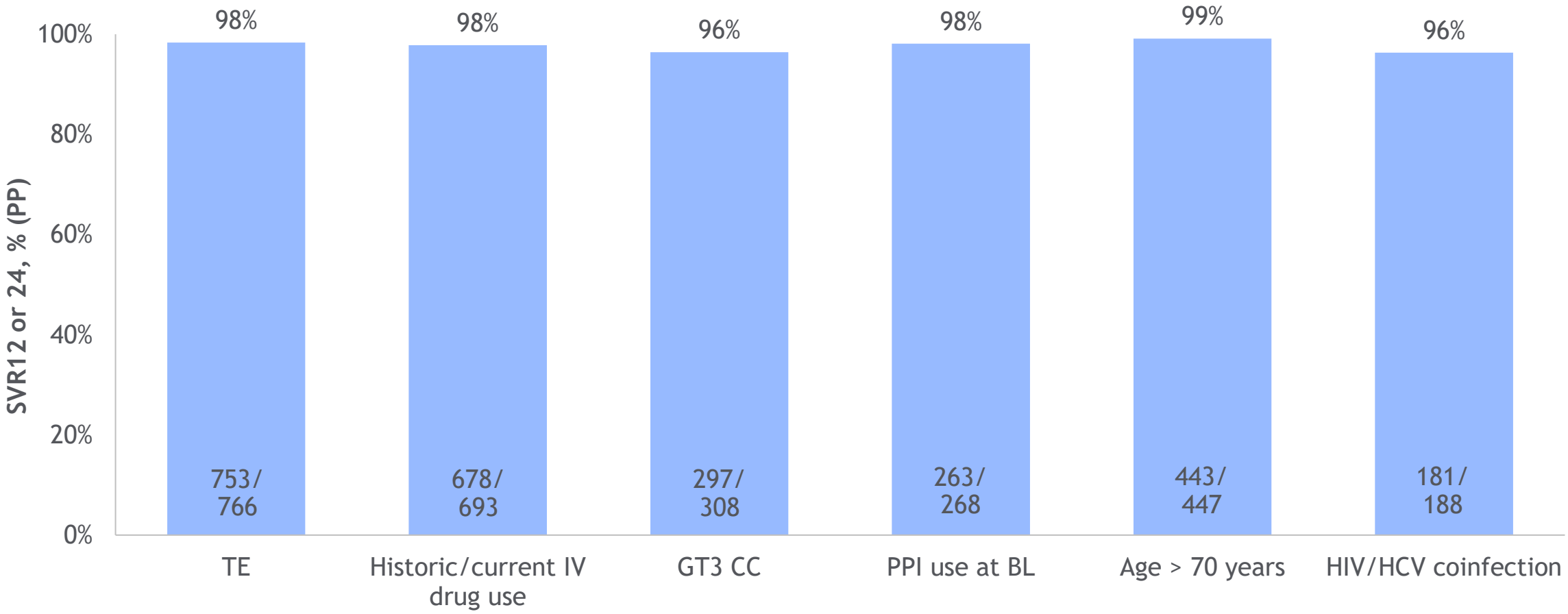


High SVR in the largest real-world cohort across all genotypes

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 Sofosbuvir/Velpatasvir** 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

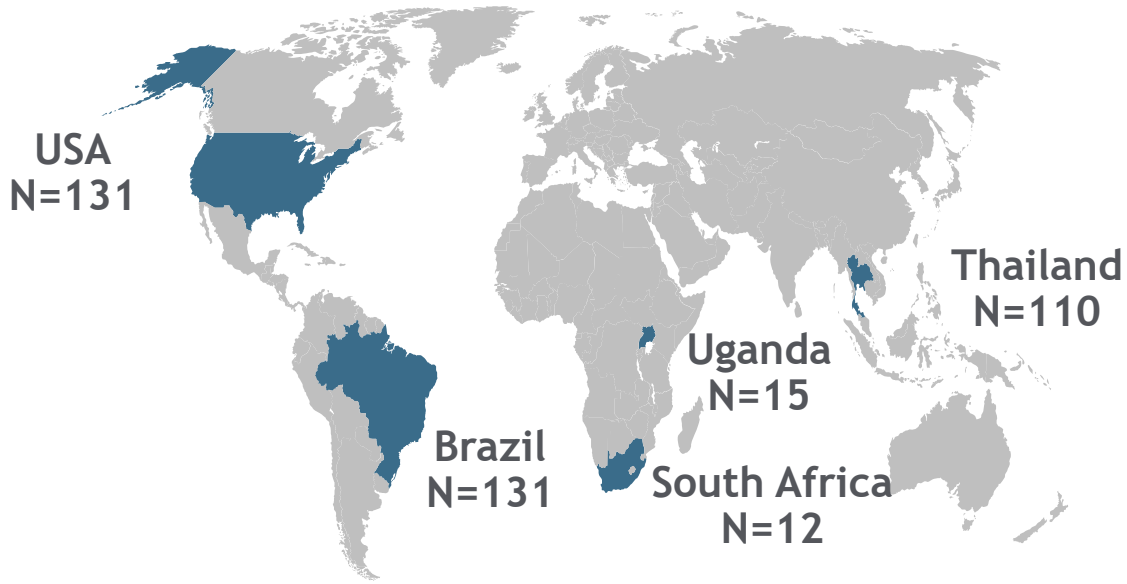
Mangia et al.Liver International 2020;40:1841-1852

Monitoring

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

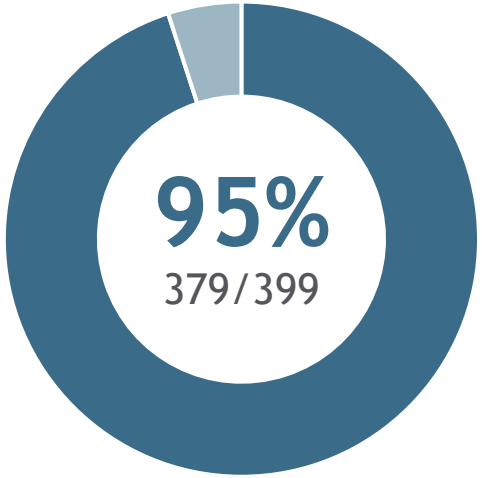
Remote contact at Week 4 and 22 (SVR scheduling) – no on-treatment clinic visits/labs

ACTG=AIDS Clinical Trials Group

Solomon S, et al. Lancet Gastroenterology Hepatology 2022. https://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

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

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. https://doi.org/10.1016/S2468-1253(21)00397-6

Elimination

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

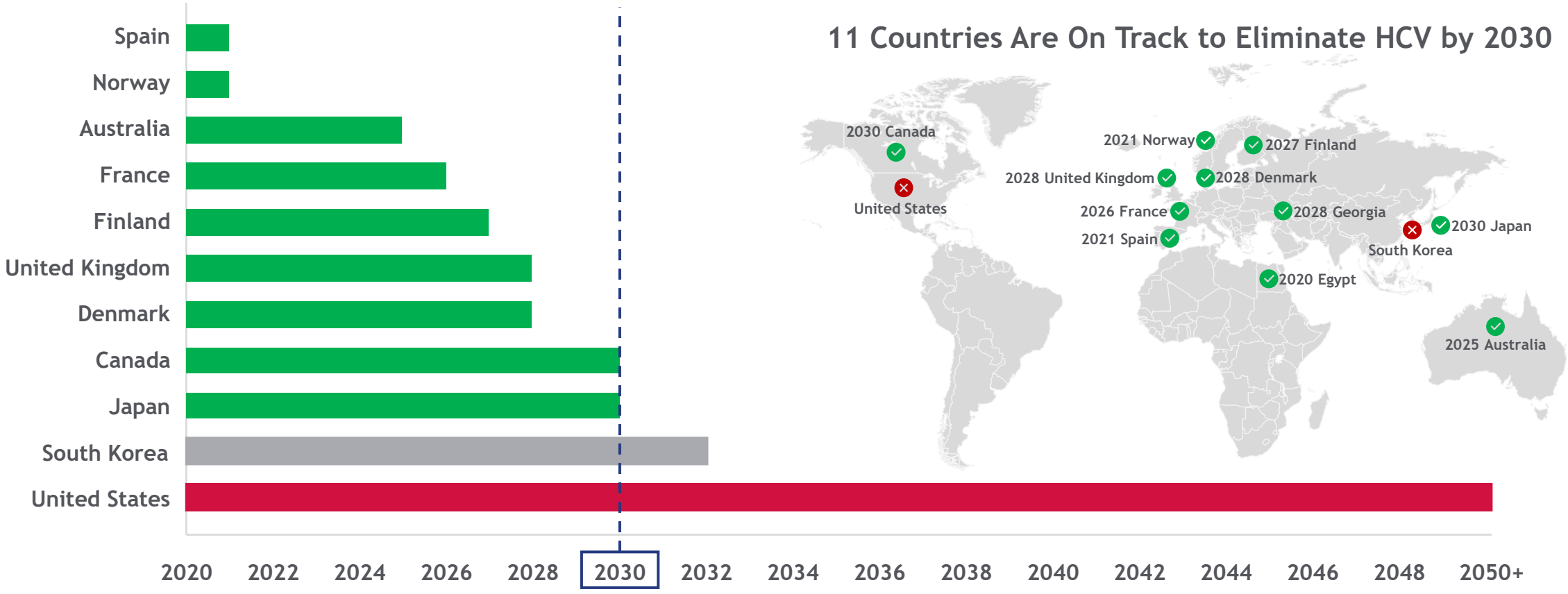
of those diagnosed with chronic HCV

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.

SUMMARY OF CHANGES TO THE NEMLC TERTIARY AND QUATERNARY LEVEL ESSENTIAL MEDICINES LIST (JULY 2023)

ATC CODE	MEDICINE	INDICATION	NEMLC OUTCOMES	REVIEW INDICATORS	DATE RATIFIED
J ANTI-INFECTIVES FOR SYSTEMIC USE					
J05AP55	**Sofosbuvir-velpatasvir**	Viral Hepatitis C	**Approved**	New evidence of efficacy and safety (particularly local evidence), pricing changes	20 July 2023
L ANTINEOPLASTIC AND IMMUNOMODULATING AGENTS					
L01BA01	**Methotrexate**	Crohn's Disease	**Approved**	n/a	20 July 2023
L01BB02	**Mercaptopurine**	Crohn's Disease	**Approved**	n/a	20 July 2023
L04AB04	**TNF inhibitor: Adalimumab**	Juvenile Idiopathic Arthritis (with or without uveitis)	**Approved** Approved for use in patients who are refractory to conventional disease modifying anti-rheumatic drugs (DMARDs)	• Change in price of adalimumab comparable to other TNF-inhibitors	20 July 2023
L04AD02	**Tacrolimus extended-release formulation**	• Primary therapy in high immunological risk renal allograft recipients. • Renal allograft recipients on ciclosporin who experience steroid resistant acute allograft rejection.	**Not Approved**	• Price reduction (comparable to immediate release formulation)	20 July 2023
L04AX01	**Azathioprine**	Crohn's Disease	**Approved**	n/a	20 July 2023
N NERVOUS SYSTEM					
N05CM18	**Dexmedetomidine**	Sedation of patients in intensive care requiring mechanical ventilation	**Not Approved**	• Price reduction • new evidence of safety or efficacy	20 July 2023

https://knowledgehub.health.gov.za/elibrary/hospital-level-tertiary-quaternary-medicine-recommendations-medicine-reviews-and-costing. Accessed October 2023

National Strategic Plan for HIV/TB/STIs

Viral hepatitis prevention, treatment and care objectives and interventions have been included in this NSP as a neglected infection of high prevalence that is also associated with HIV and STIs

	KEY POPULATIONS	OTHER PRIORITY POPULATIONS
STIs	• Sex workers and their clients • Transgender persons • MSM	• Adolescents and young people, especially AGYW • Survivors of SGBV • Pregnant women
Viral hepatitis	**For HBV:** • People in prisons • PWUD • MSM • Sex workers **For HCV:** • PWUD • MSM • People in prisons	• Health workers • Pregnant women

Thank you