# Update in Viral Hepatitis and Chronic Liver Disease

Sammy Saab, MD, MPH, AGAF, FACG, FAASLD
Professor of Medicine and Surgery
Head, Outcomes Research in Hepatology
David Geffen School of Medicine at UCLA
Adjunct Professor of Nursing
UCLA School of Nursing
Associate Editor for Liver, *Journal of Clinical Gastroenterology*

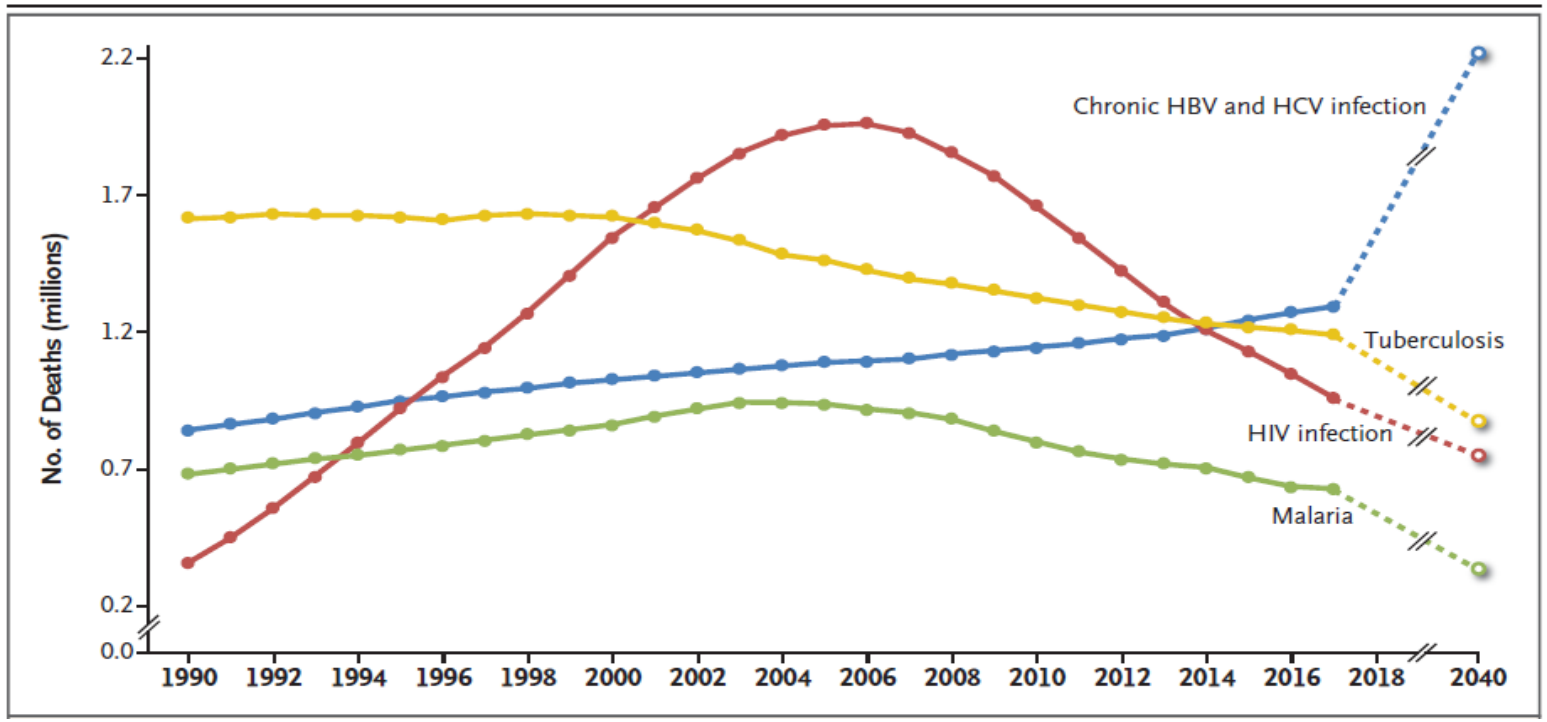
# Disclosures

| | |
|---|---|
| Speaker Bureau: | AbbVie, BMS, Eisai, Exelixis, Gilead, Intercept, Salix |
| Consultant: | AbbVie, Dova, Eisai, Exelixis, Gilead, Intercept, Salix, Mallinckrodt |

# Objectives

1. Describe why eliminating hepatitis C (HCV) is important for public health
2. Review progress in the US for eliminating HCV, and identify drivers of new HCV infection
3. Detail novel strategies to improve the rate of testing and managing HCV infection
4. Highlight current HCV treatments, and management of patients who do not respond to initial therapy
5. Link patients with diagnosed HCV infection to timely and appropriate HCV therapy
6. Describe cardiac advantages to curing HCV
7. Understand the changing burden of fatty liver as a cause of chronic liver disease
8. Be able to differentiate among different types of fatty liver
9. Review how patients with HIV are particular risk of fatty liver
10. Review potential upcoming therapies and understand FDA goals for drug approval

# Worldwide Deaths From Chronic Viral Hepatitis as Compared with Deaths from Tuberculosis, HIV, and Malaria




Data on deaths from 1990 to 2017 are from the Institute for Health Metrics and Evaluation as of November 14, 2018.

Thomas D. *N Engl J Med*. 2019

# WHO Vision: Eliminate Viral Hepatitis as a Major Health Threat by 2030

World Health Organization

*"A world where viral hepatitis transmission is halted and everyone living with hepatitis has access to safe, affordable and effective care and treatment services"*

**90% reduction in new chronic HCV infections**

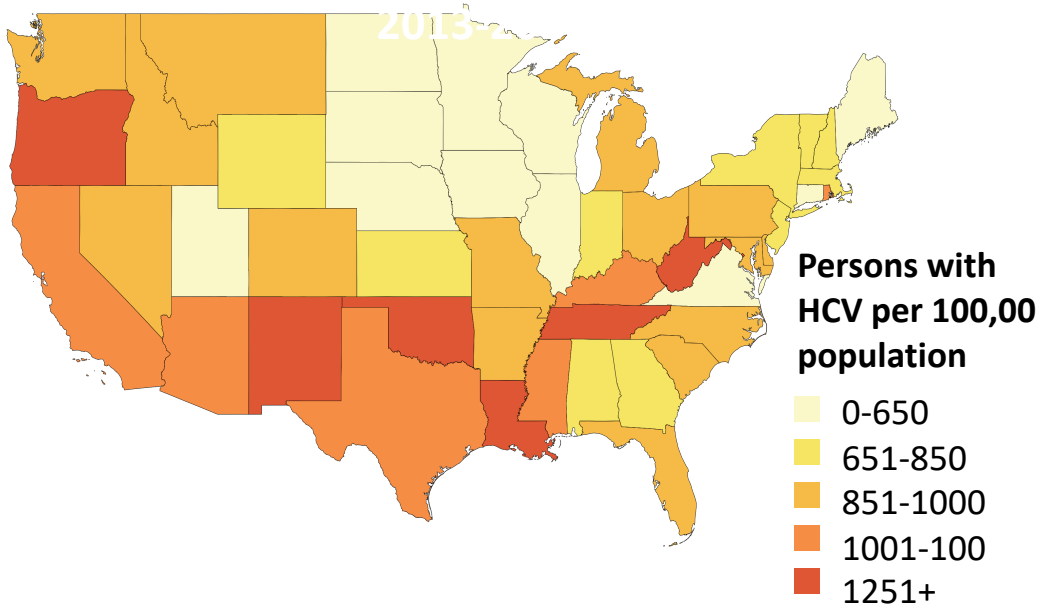
**Treatment of 80% of eligible persons with chronic HCV infection**

**65% reduction in mortality rates**

WHO. https://www.who.int/hepatitis/strategy2016-2021/ghss-hep/en/. Accessed November 17, 2020.

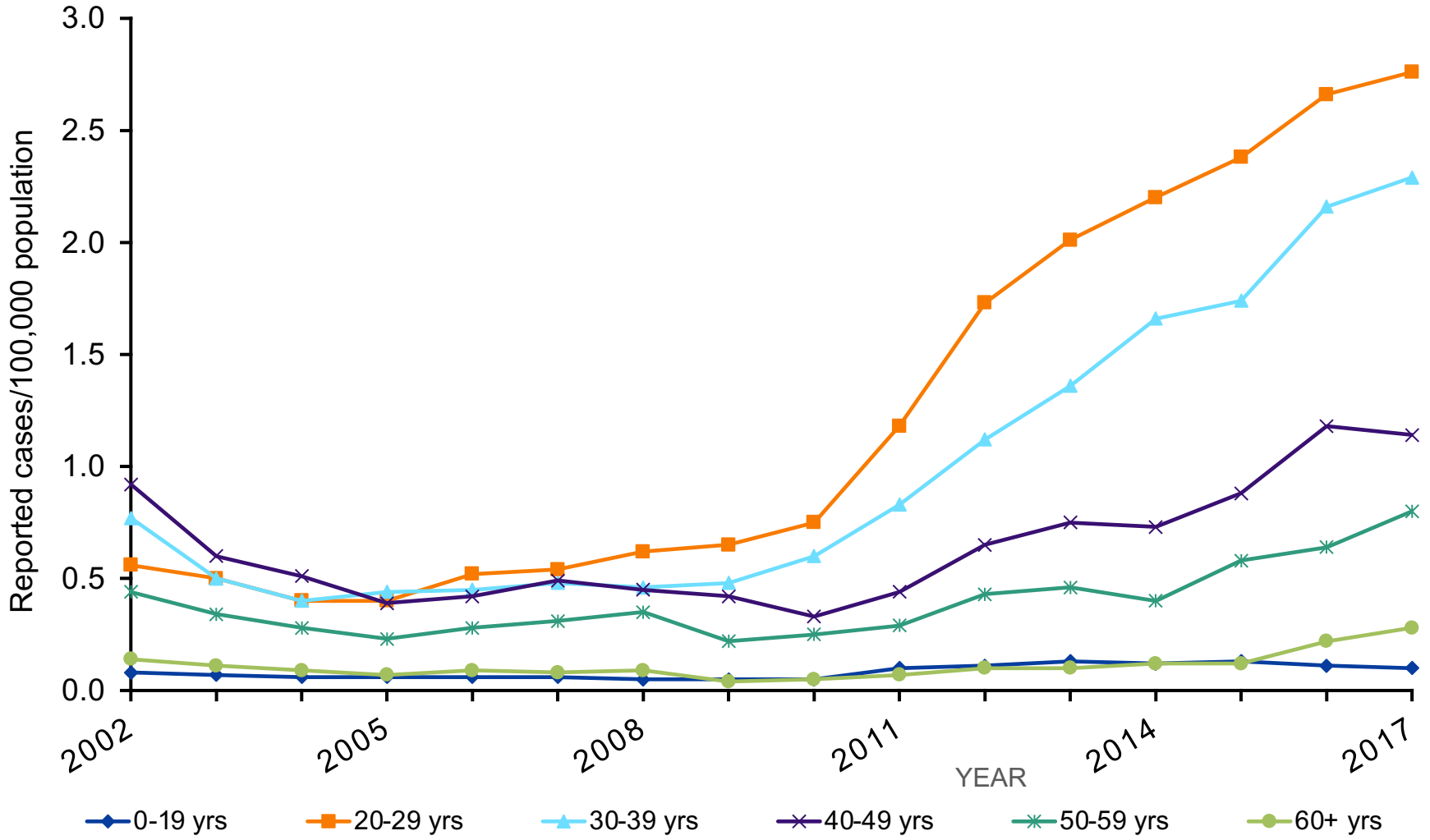
# Epidemiology of HCV in the United States

- ~ 2.4 million Americans living with HCV in 2013-2016
- Nearly 50% unaware of their infection



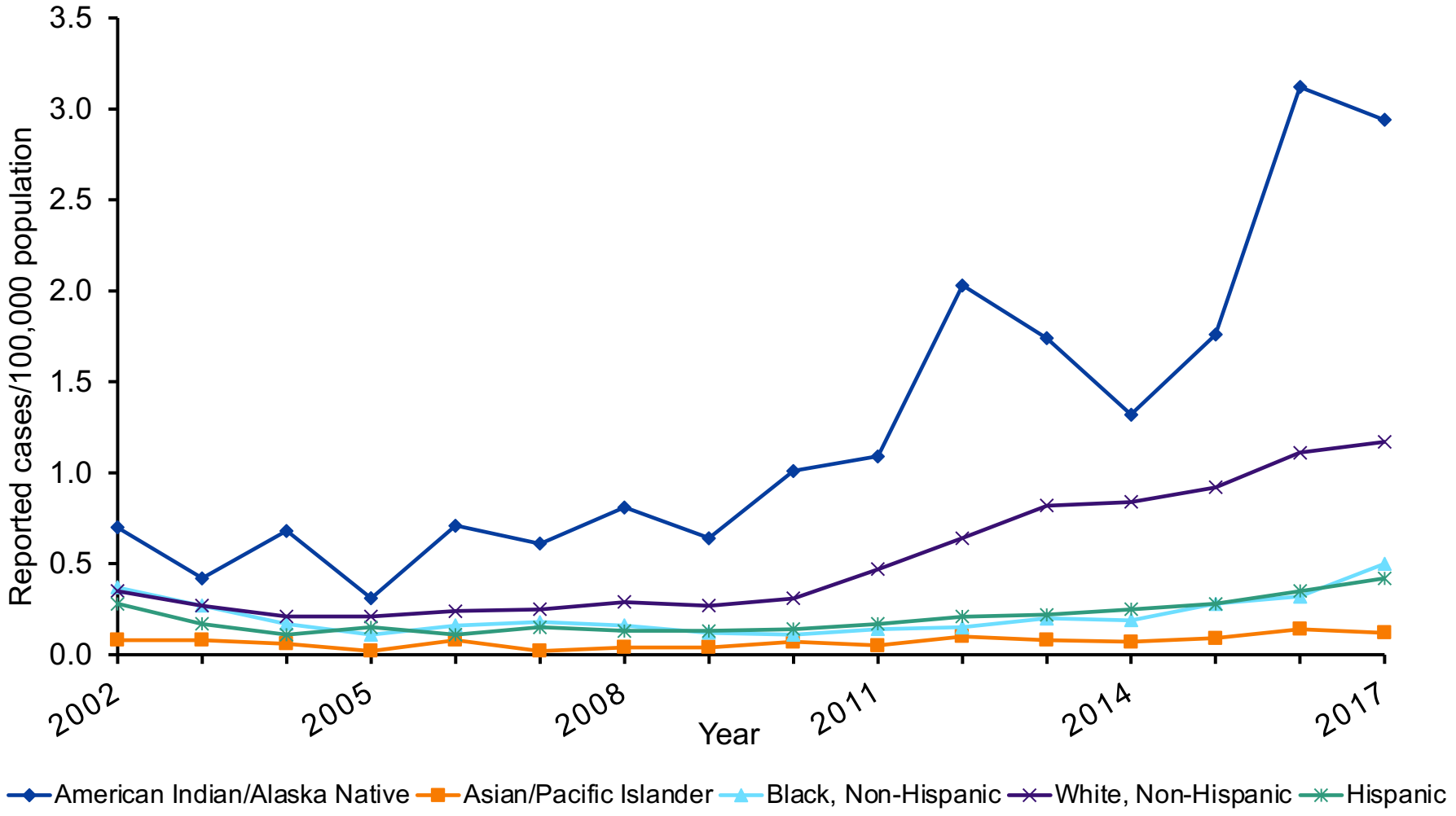

1. Ryerson. MMWR Morb Mortal Wkly Rep. 2020;69:399. 2. HepVu. https://map.hepvu.org/map. Accessed November 17, 2020.

# Rates of Reported Acute Hepatitis C, by Age Group — United States



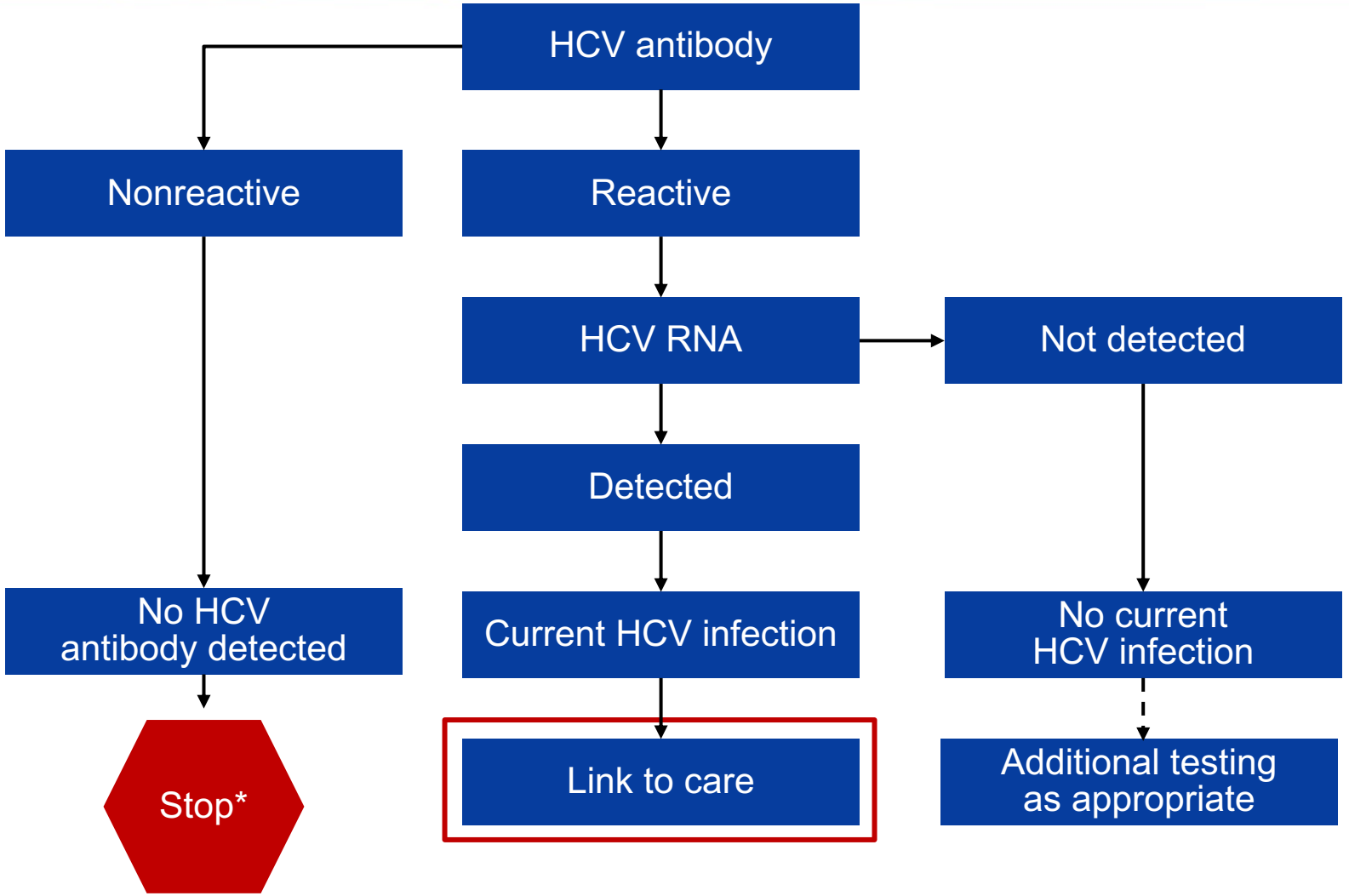

Source: CDC, National Notifiable Diseases Surveillance System.

# Rates of Reported Acute Hepatitis C, by Race/Ethnicity — United States




Source: CDC, National Notifiable Diseases Surveillance System.

# CDC Recommended Testing Sequence for Identifying Current HCV Infection




www.hcvguidelines.org. Adapted from Centers for Disease Control and Prevention (CDC), 2013.

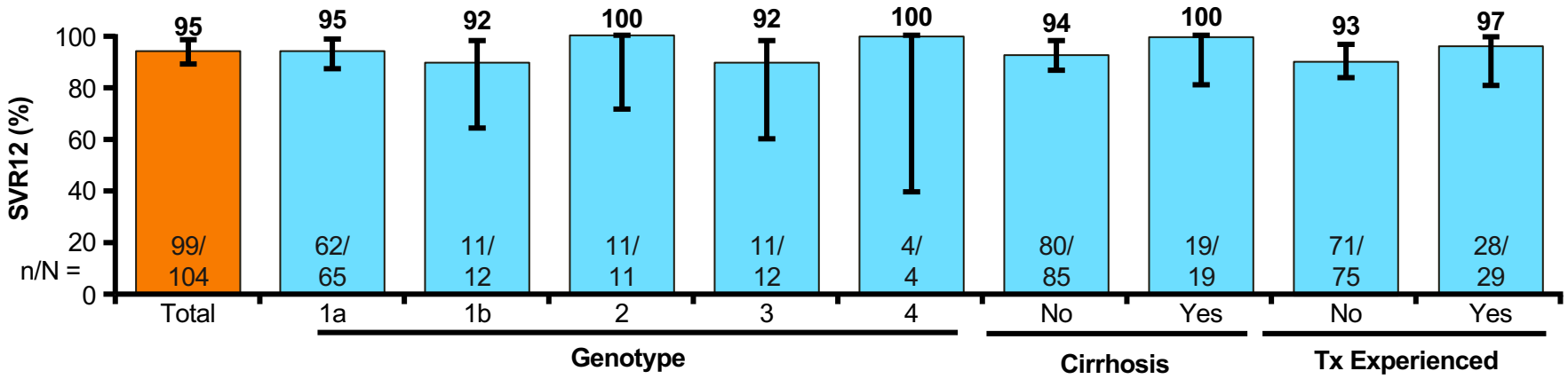
# Rapid Finger Stick Testing and Multiple Home Testing ELISA Kits are Available to Diagnose Hepatitis C


The information provided on this website is intended only for the residents of the U.S. The products discussed herein may have different labeling in different countries and may not be for sale in all other countries.

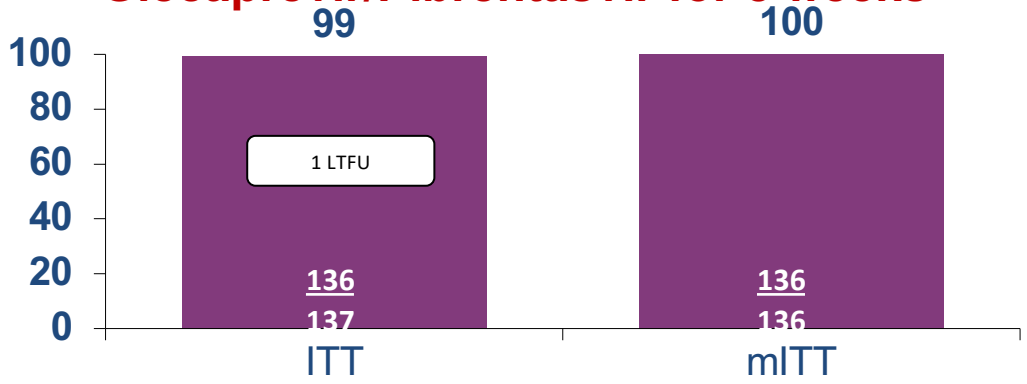
https://www.orasure.com/products-infectious/products-infectious-oraquick-hcv.asp

# HIV/HCV Co-infected Individuals Have Similar Cure Rates

## Sofosbuvir/Velpatasvir x 12 weeks

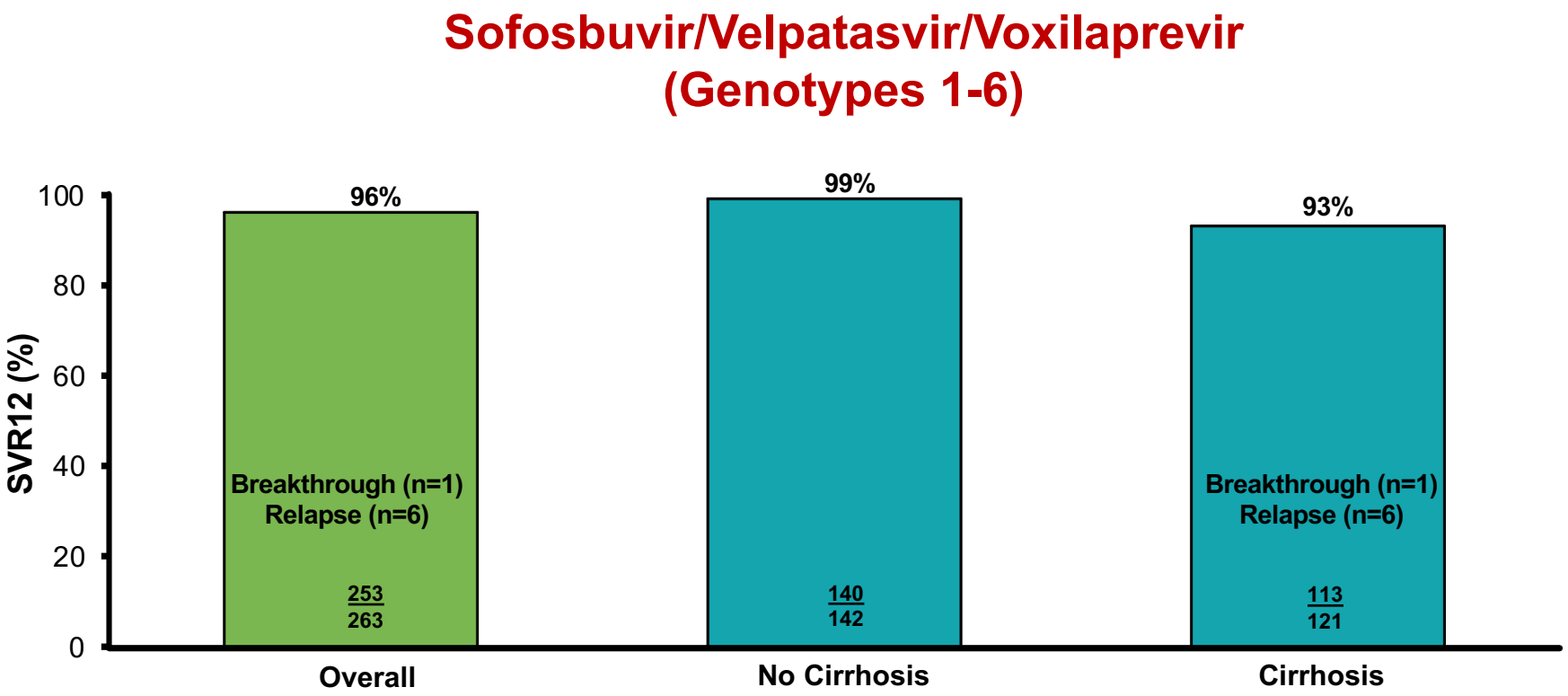



## Glecaprevir/Pibrentasvir for 8 weeks




Wyles D, et al. EASL 2016. Abstract PS104.

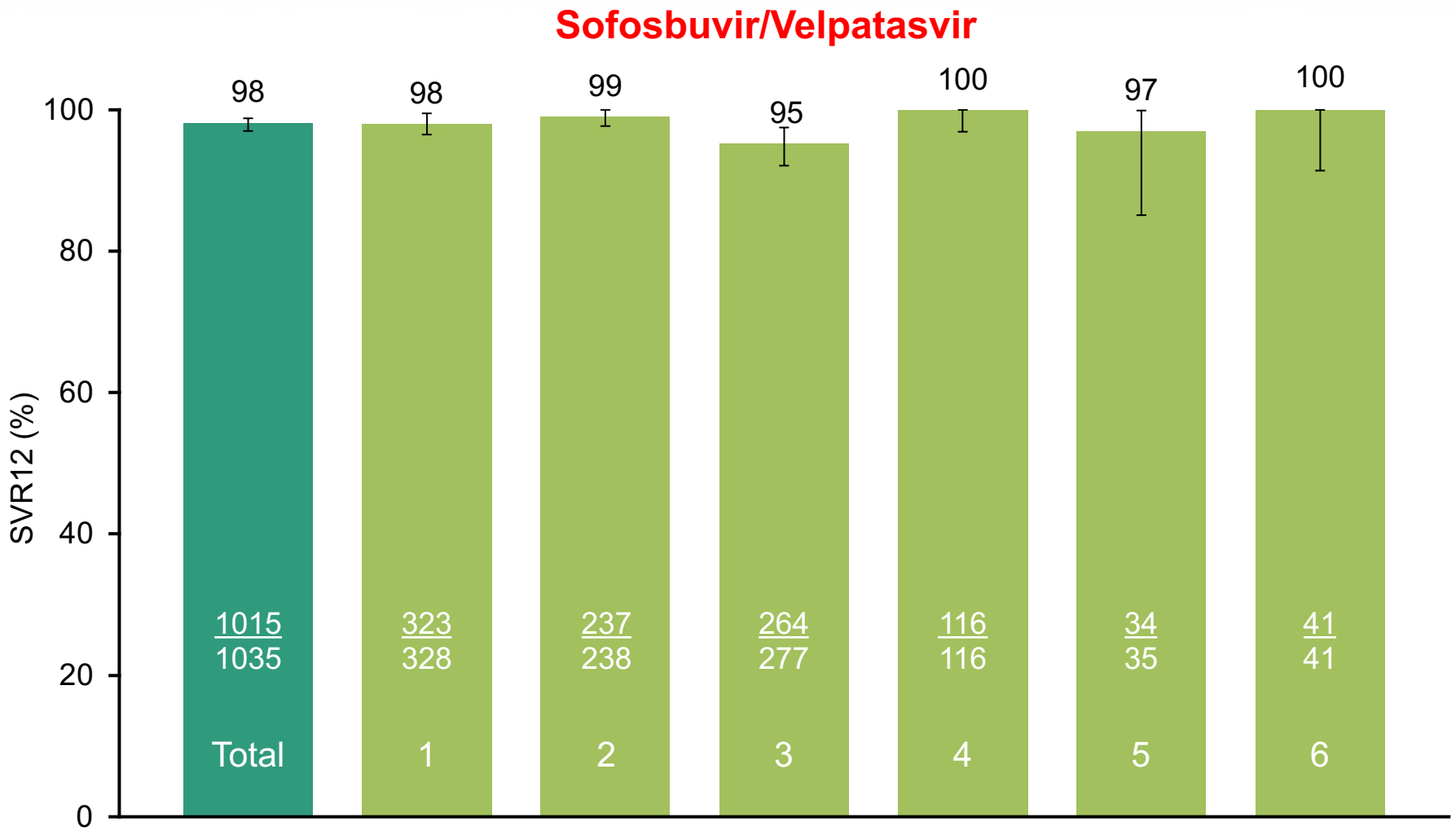
# Overall Cure Rates in NS5A inhibitor – Experienced patients




No placebo patients achieved an SVR12.
*$P$<0.001 for superiority versus pre-specified goal of 85% for sofosbuvir/velpatasvir/voxilaprevir.

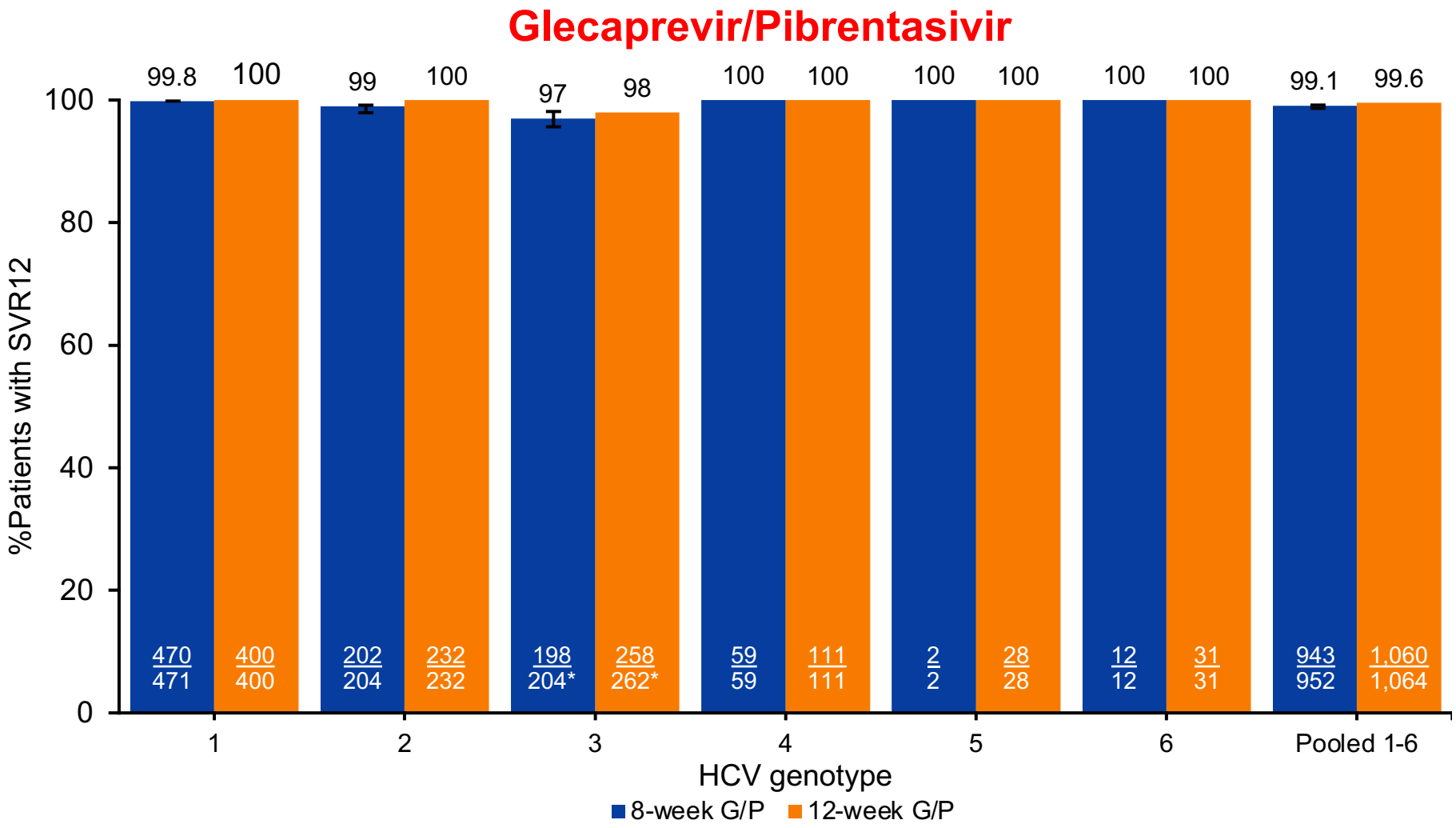
Bourlière M, et al. *Hepatology*. 2016; Abstract 194.

# Persons With HCV Genotype 1, 2, 3, 4, 5, or 6 Infection Can Be Effectively Treated With One Tablet Daily for 12 Weeks



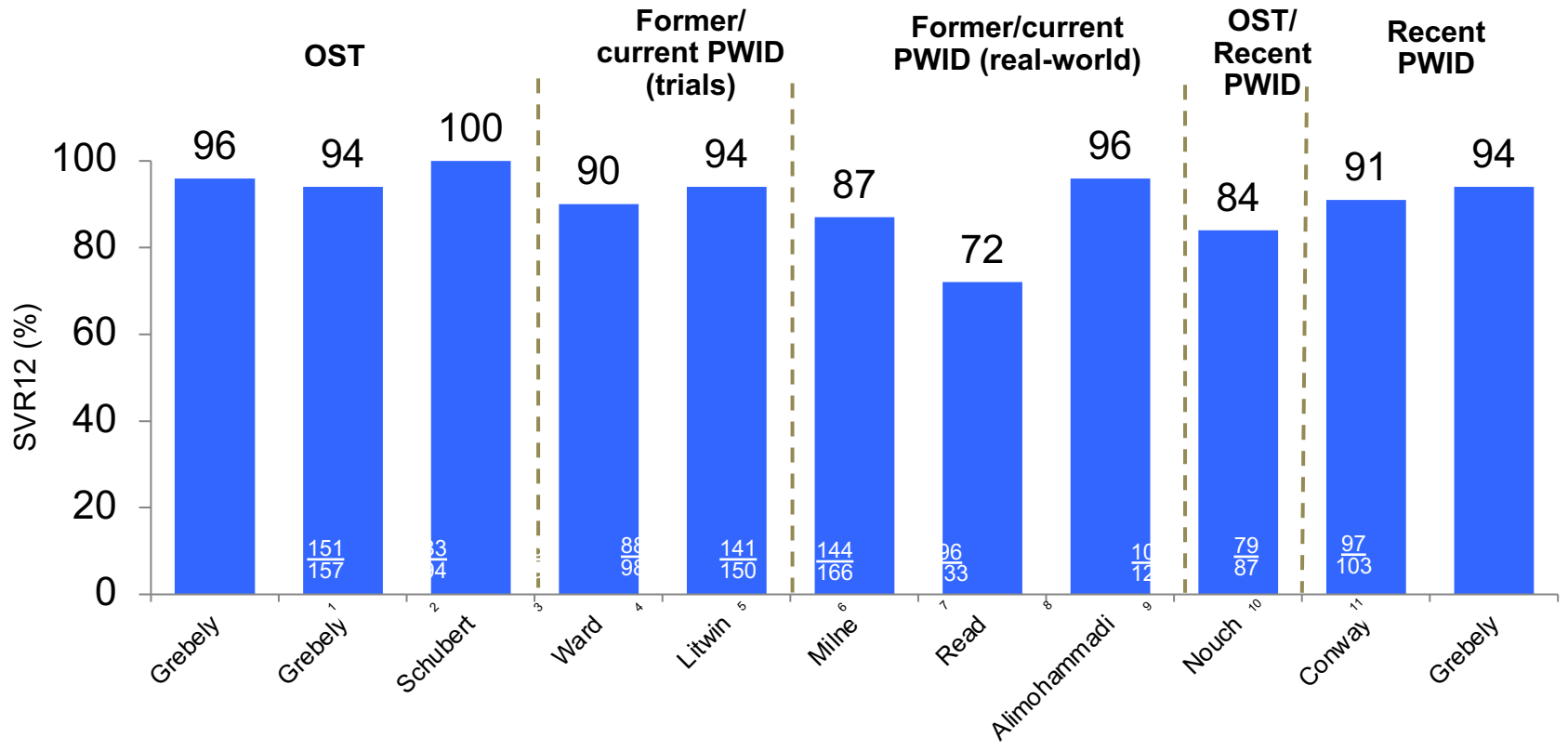

Feld JJ et al. *NEJM* 2016; Foster G et al *NEJM* 2016

# Persons with HCV Genotype 1, 2, 3, 4, 5, or 6 Infection Can Be Effectively Treated with Three Tablets Daily for 8 Weeks

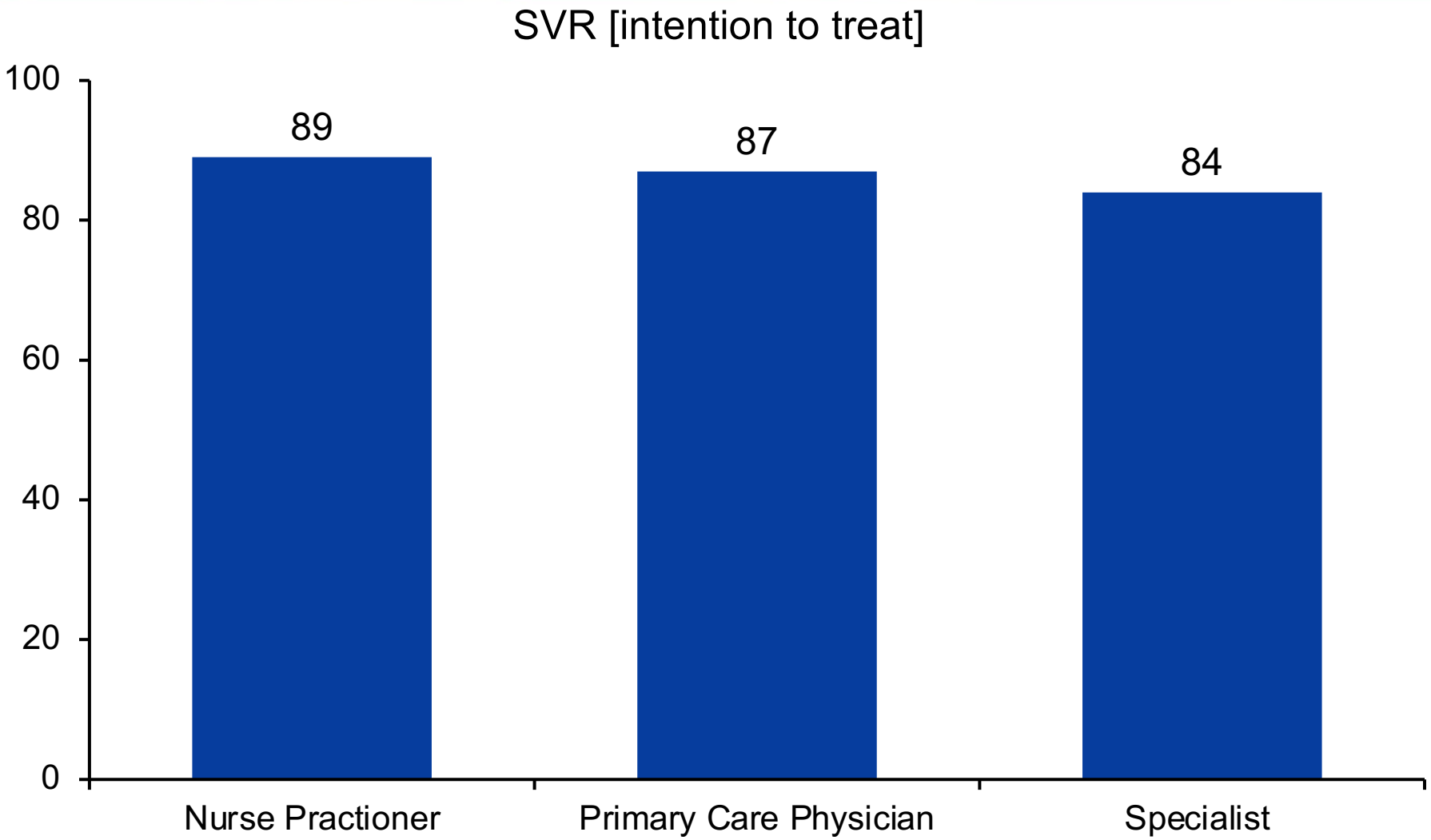



Puoti M et al. J Hepatol 2018; Brown RS et al. J Hepatol 2019

# Hepatitis C DAA Therapy Among People on OST and PWID



# Expansion of HCV Treatment to Beyond Physicians and Specialists




Kattakuzhy Ann Intern Med 2017

# Management of G/P or SOF/VEL Interruptions For Treatment-Naïve Patients

## Interruptions during first 28 days of DAA therapy

**Missed ≤ 7 days**

**Restart** DAA therapy immediately. Complete therapy for originally planned 8-week duration.

**Missed ≥ 8 days**

- **Restart** DAA therapy immediately.
- Obtain HCV RNA test as soon as possible, preferably the same day as restarting DAA therapy.
- If HCV RNA is negative complete originally planned DAA treatment course (8 or 12 weeks). Recommend extending DAA treatment for an additional 4 weeks for patients with GT3 and/or CC.
- 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 DAA therapy.
- If HCV RNA is negative complete originally planned course (8 or 12 weeks). Recommend extending DAA treatment for an additional 4 weeks for patients with GT3 and/or CC.
- If HCV RNA is positive (>25 IU/L), or not obtained, **STOP** treatment and retreat according to AASLD-IDSA retreatment guidelines.

**Missed ≥ 21 days**

**STOP** DAA treatment and assess for SVR12. If SVR12 not achieved, retreat according to recommendations in the AASLD-IDSA retreatment guidelines.

DAA, direct-acting antiviral; CC, compensated cirrhotic; G/P, glecaprevir/pibrentasvir; GT, genotype; NC, non-cirrhotic; SOF, sofosbuvir; VEL, velpatasvir

https://www.hcvguidelines.org/evaluate/monitoring/incomplete-adherence.

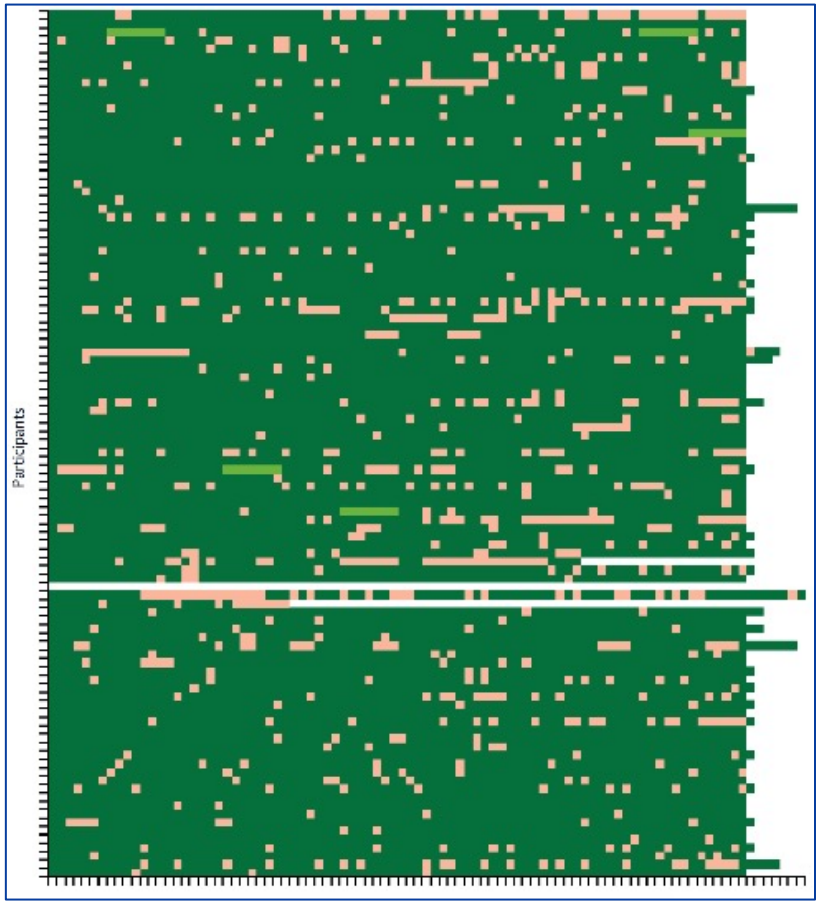
# HCV Treatment With SOF/VEL Was Effective in Active PWID

103 HCV infected individuals receiving OST or with recent injection drug use 97/103 (94%) achieved SVR, 2 lost to F/U, 1 death

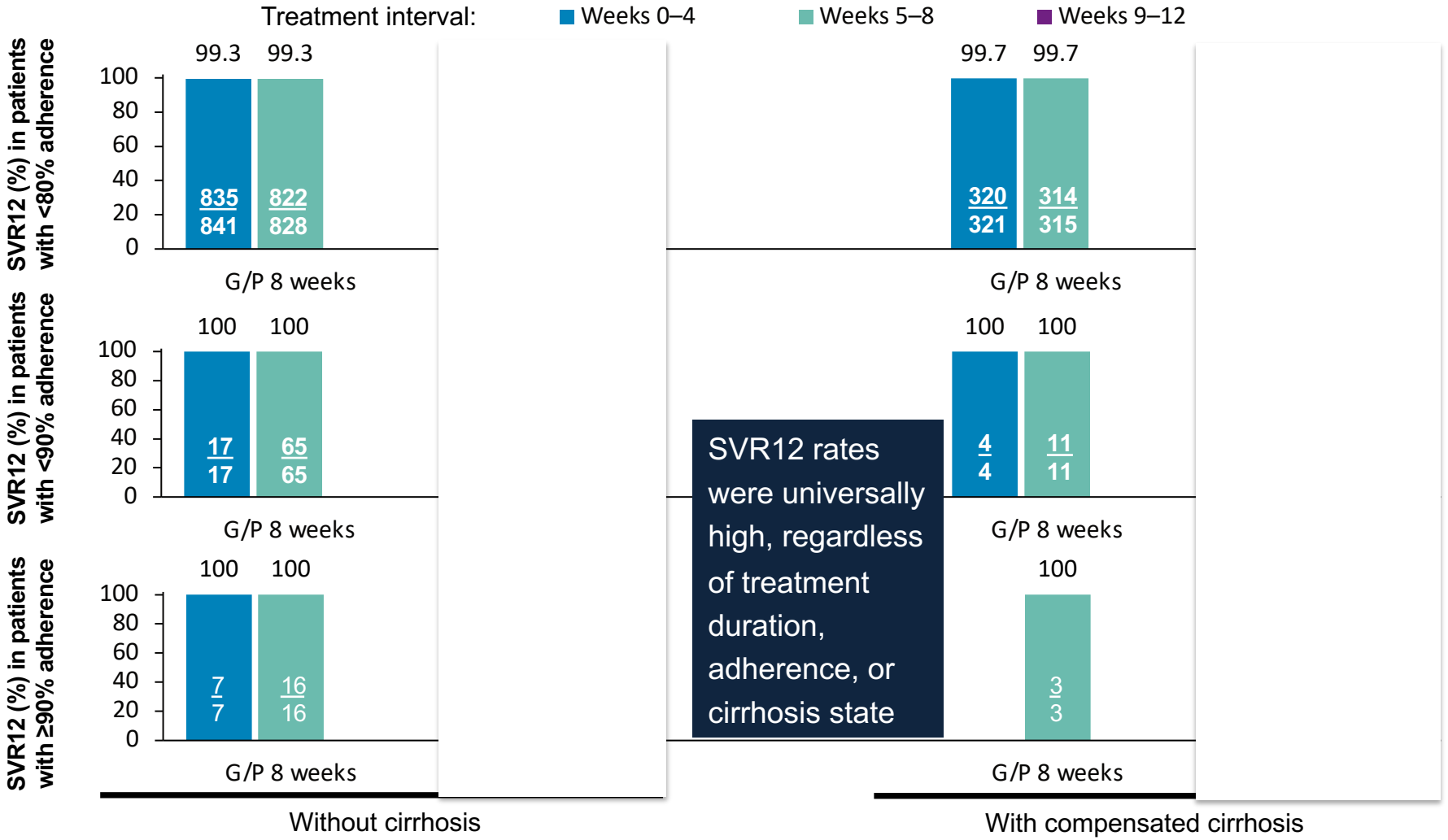
| | Sofosbuvir-velpatasvir for 12 weeks (n=103) |
|---|---|
| Age (years) | 48 (41-53) |
| Sex | |
| Male | 74 (72%) |
| Female | 29 (28%) |
| High school or higher education | 50 (49%) |
| Unstable housing* | 24 (23%) |
| Any drug use in the past 6 months | 103 (100%) |
| Any injecting drug use in the past 6 months | 103 (100%) |
| Any non-injecting drug use in the past 30 days | 56 (54%) |
| Any injecting drug use in the past 30 days | 76 (74%) |
| Heroin | 57 (55%) |
| Cocaine | 13 (13%) |
| Methamphetamines | 31 (30%) |
| Other opioids | 22 (21%) |
| Other | *7 (7%)* |

Grebly J et al. *Lancet Gastroenterol Hepatol*, 2018

Daily adherence to therapy with SOF/VEL in 103 participants, measured by weekly electronic blister packs



# Patients Receiving G/P
# SVR12 Rates by Treatment Adherence




G/P, glecaprevir/pibrentasvir; SVR12, sustained virologic response at posttreatment Week 12.

Zamor P, et al. *Am J Gastroenterol* 2021;116:1896–1904

# Drug-Drug Interactions With HCV Treatments

- No clinically significant interaction expected
- Potential interaction that may require dose adjustment, altered administration timing, or additional monitoring
- Should not becoadministered

| Lipid-Lowering Drug | SOF | SOF/VEL | SOF/VEL/VOX | GLE/PIB | GZR/EBR |
|---|---|---|---|---|---|
| Atorvastatin | | | | | |
| Bezafibrate | | | | | |
| Ezetimibe | | | | | |
| Fenofibrate | | | | | |
| Fluvastatin | | | | | |
| Gemfibrozil | | | | | |
| Lovastatin | | | | | |
| Pitavastatin | | | | | |
| Pravastatin | | | | | |
| Rosuvastatin | | | | | |
| Simvastatin | | | | | |

| Illicit/Recreational Drug | SOF | SOF/VEL | SOF/VEL/VOX | GLE/PIB | GZR/EBR |
|---|---|---|---|---|---|
| Amphetamine | | | | | |
| Cannabis | | | | | |
| Cocaine | | | | | |
| Diamorphine | | | | | |
| Diazepam | | | | | |
| Fentanyl | | | | | |
| γ-hydroxybutyrate | | | | | |
| Ketamine | | | | | |
| MDMA | | | | | |
| Mephedrone | | | | | |
| Methadone | | | | | |
| Methamphetamine | | | | | |
| Oxycodone | | | | | |
| Phencyclidine | | | | | |
| Temazepam | | | | | |

Pawlotsky. *J Hepatol.* 2020;73:1170.

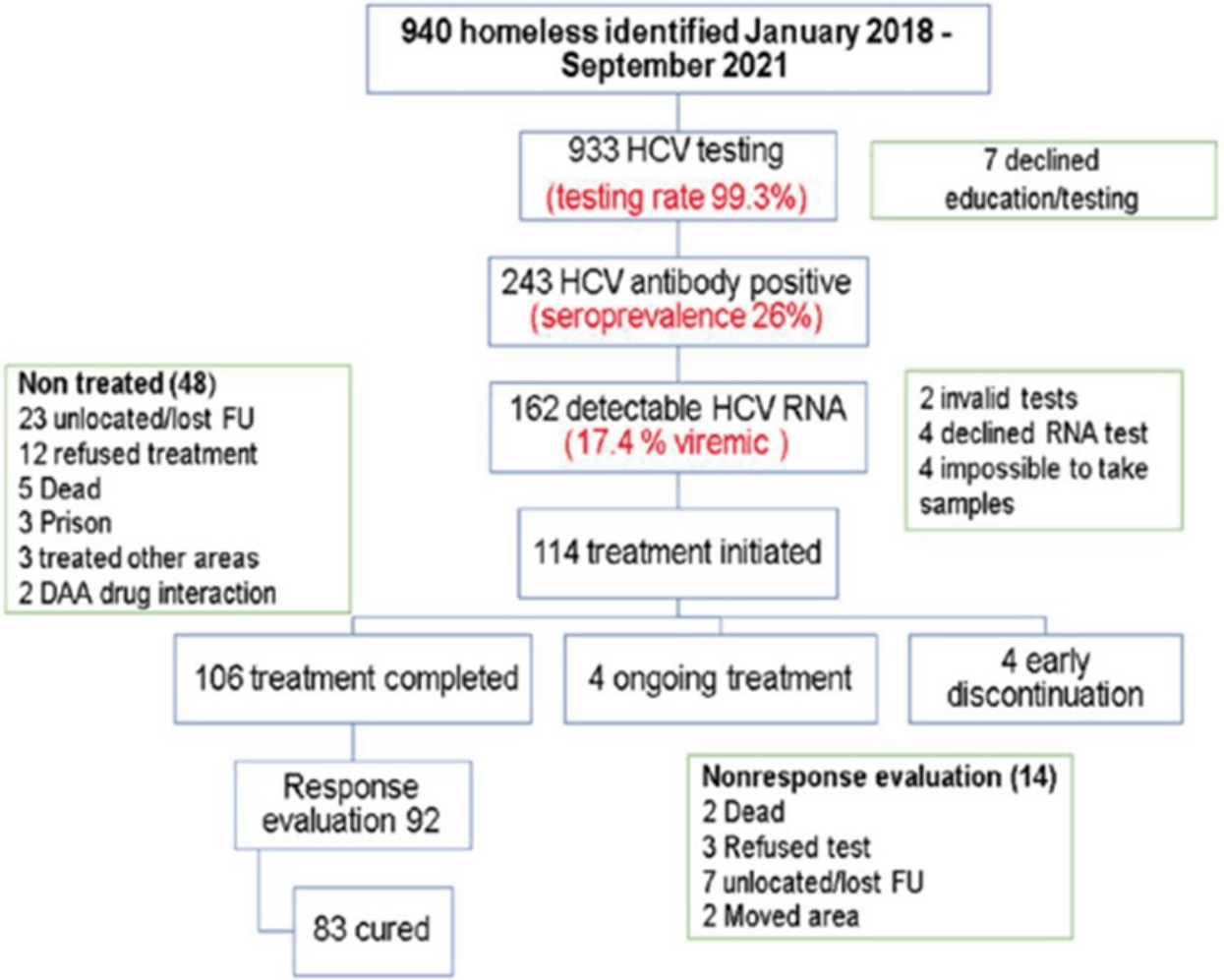
# Drug-Interaction Potential Between Selected HIV Antiretroviral and Preferred HCV Direct-Acting Antiviral Agents

| | Glecaprevir/ Pibrentasvir | Sofosbuvir/ Velpatasvir | Ledipasvir/ Sofosbuvir | Elbasvir/ Grazoprevir | Sofosbuvir/Velpatasvir/ Voxilaprevir |
|---|---|---|---|---|---|
| Atazanavir + RTV or COBI | x | √ | √ | x | x |
| Darunavir + RTV or COBI | x | √ | √ | x | ≈ |
| Lopinavir/ritonavir | x | ≈ | √ | x | x |
| Doravirine | √ | √ | √ | √ | √ |
| Efavirenz | x | x | ≈ | x | x |
| Rilpivirine | √ | √ | √ | √ | √ |
| Raltegravir | √ | √ | √ | √ | √ |
| Elvitegravir/COBI/FTC/TAF | √ | √ | √ | x | √ |
| Dolutegravir | √ | √ | √ | √ | √ |
| Bictegravir/FTC/TAF | | √ | √ | √ | √ |
| Tenofovir DF | √ | ≈ | ≈ | √ | ≈ |
| Tenofovir AF | √ | √ | √ | √ | √ |
| Abacavir | √ | √ | √ | √ | √ |
| Lamivudine | √ | √ | √ | √ | √ |

No clinically significant interaction expected | Potential weak interaction | Potential interaction | Do not coadminister

HEP Drug Interactions. https://www.hep-druginteractions.org/.

# HCV Homeless Mobile Van with Rapid Xpert Cepheid RNA Test




Guerra-Veloz MF, et al. EASL 2022

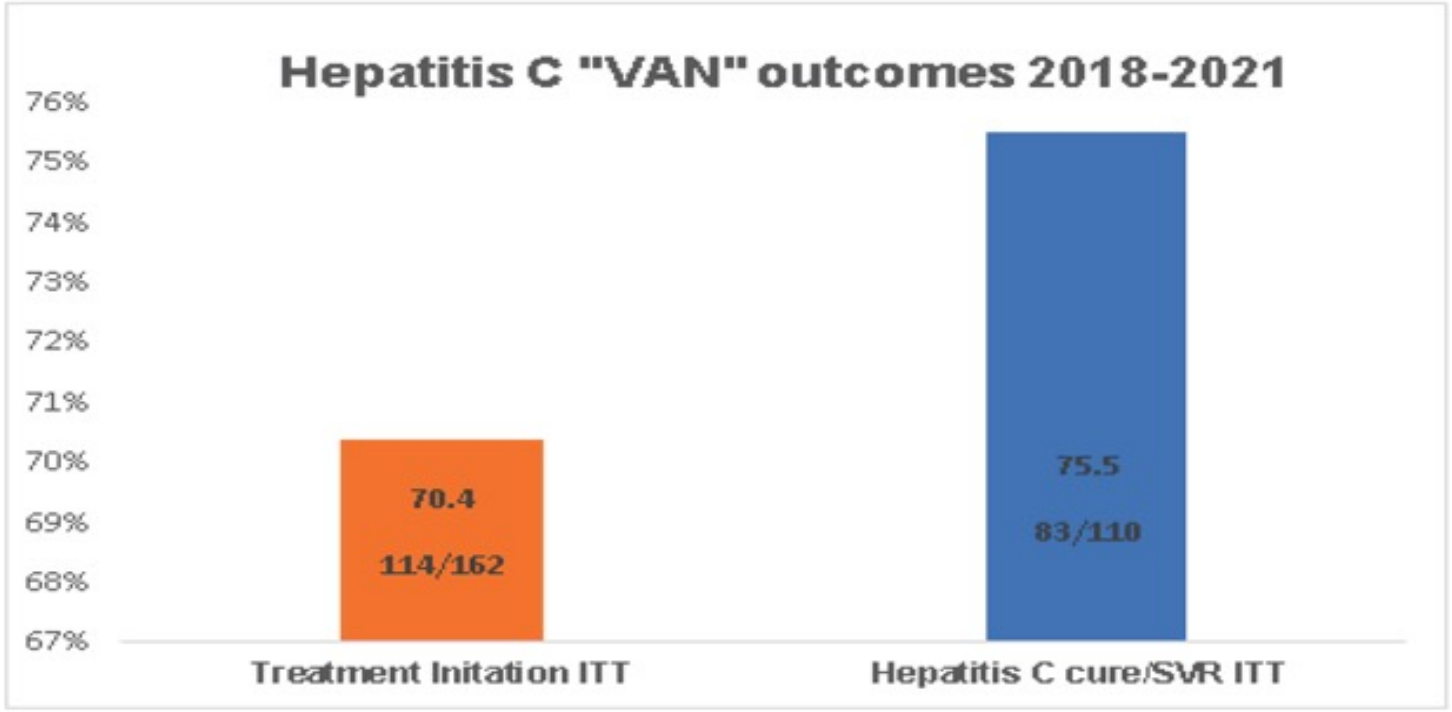
# HCV Homeless Mobile Van with Rapid Xpert Cepheid RNA Test

Multivariate analysis of variables associated with treatment initiation and treatment SVR

| | Multivariate analysis OR (CI 95%) | p | Multivariate analysis OR (CI 95%) | p |
|---|---|---|---|---|
| | Treatment initiation | | Treatment cure | |
| Gender (males n (%) | | | | |
| Age (years), median (IQR) | | | | |
| Race n (%) | | | | |
| Type house | | | | |
| Hotel/hostel based | | | | |
| Street/daily kitchen Based | 2.755(1.356-5.600) | 0.005(ref) | | |
| OST, n (%) | 2.288 (1.041-5.026) | 0.039 | | |
| Active drug user, n (%) | 1.557 (0.699-3.470) | 0.278 | | |
| Active alcohol user, n (%) | | | 0.627 (0.156-2.517) | 0.510 |
| History of previous incarceration n (%) | | | 1.180 (0.305-4.568) | 0.811 |
| History of previous test | | | 0.358 (0.102-1.260) | 0.760 |
| History of previous treatments | | | | |
| Psychiatric disorders | 1.140 (0.524-2.476) | 0.741 | 1.742 (0.489-6.203) | 0.345 |
| Presence of advanced fibrosis (LSM >10kpa and/or Fib-4 >3.25) yes | | | 2.348 (0.399-13.830) | 0.458 |
| Adherence treatment > 75% vs <75% | | | 26.552 (7.299-96.587) | <0.001 |

Guerra-Veloz MF, et al. EASL 2022

# HCV Homeless Mobile Van with Rapid Xpert Cepheid RNA Test




## Results

- 940 clients were identified as homeless and 933 (99.3%) participated. Of them 56.2% who were screened were street-based, 243 (26%) tested positive for HCV antibody and of these, 162 (67%) had detectable viremia (figure 1).
- Treatment initiation was 70.4% and SVR 12 week was 75.5%.

Guerra-Veloz MF, et al. EASL 2022

# Point of care [Cepheid GeneXpert assay] testing for hepatitis C in mental health, prison and drug & alcohol settings

**Aims**

PROMPt aimed to provide HCV point-of-care (POC) testing and direct linkage in the settings of mental health, prisons and alcohol & other drugs (AOD) services.

**Methods**

*Sites*:

- Remand Prison, SA
- Inpatient Alcohol & Other Drug Service, SA
- Mental Health Inpatient Unit, SA

*HCV POC testing*:

- POC HCV diagnostic testing using SD Bioline fingerstick Antibody assay
- Participants HCV Ab positive offered Cepheid fingerstick HCV RNA GeneXpert assay
- Peer educator, HCV education, pre/post test counselling and linkage to care.

*Linkage to care*:

- HCV RNA positive underwent counselling, and were linked to treatment
- Participants details being sent to the local nurse for management.

Ferguson C, et al. EASL 2022

# Point of care [Cepheid GeneXpert assay] testing for hepatitis C in mental health, prison and drug & alcohol settings

**Results**

Participant characteristics total 1549.

83% (1,290) male, 17% (256) female, 0.2% (3) other, median age 37 (30-46), Aboriginal/Torres Strait Islander 25% (379)

**Table 1. HCV Ab and RNA POC test results and RNA positivity N = 1,549.**

| POC test outcomes | Remand Prison | Inpatient AoD | Inpatient Mental Health Unit | Total |
|---|---|---|---|---|
| HCV Ab test (n) | 877 | 496 | 176 | 1549 |
| % Ab positive | 17% (150/877) | 19% (96/496) | 10% (18/176) | 17% (246/1549) |
| HCV RNA test (n) | 150 | 96 | 18 | 264 |
| % RNA positive | 5% (39/877) | 2% (10/496) | 3% (6/196) | 4% (55/1549) |
| RNA positivity | 26% (39/150) | 10% (10/96) | 33% (6/18) | 21% (55/264) |

**Table 3. Linkage to care outcomes N = 55**

| Linkage to care | Remand Prison | Inpatient AoD | Inpatient Mental Health Unit | Total |
|---|---|---|---|---|
| RNA positive, n | 39 | 10 | 6 | 55 |
| Linked to care, n (%) | 37/39 (95%) | 7/10 (70%) | 6/6 (100%) | 50 (90%) |
| Commenced Treatment, n(%) | 37/39 (95%) | 6/10 (60%) | 4/6 (67%) | 47 (85%) |
| Days from referral to treatment, median (IQR) | 14 (5-43) | 20 (5-27) | 2 (1.5-2) | 14 (5-30) |

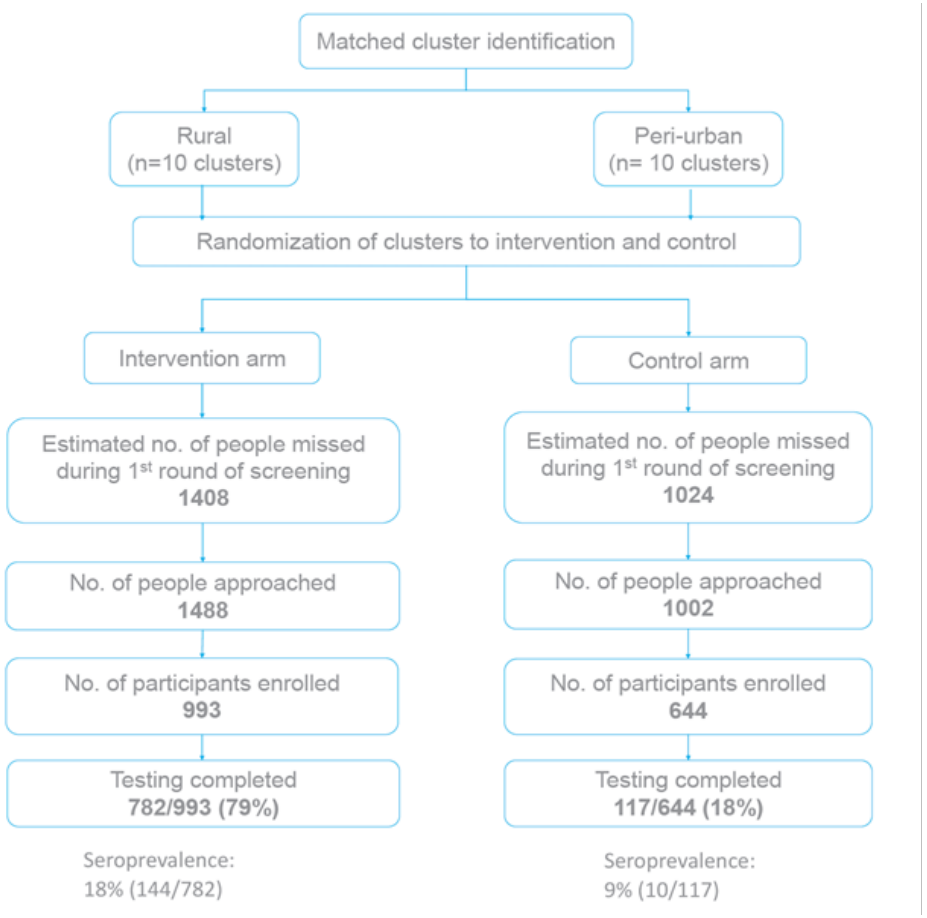
Ferguson C., et al. EASL 2022

# Hepatitis C Self-Testing

## A cluster randomized controlled study of secondary distribution of HCV self-test to support micro-elimination in Karachi, Pakistan

**Methods**

- This ongoing cluster randomized control study targets persons missed during house-to-house screening done
- Target sample size is 1000 participants in each group.
- intervention group, an HCV self-test is left with instructions for use explained to a senior household member.
- control group, a pamphlet is left with directions to visit the nearest clinic for HCV screening.
- Both groups are followed up within 4 weeks to inquire if testing was completed and a brief acceptability survey is conducted with the tester. Results report are incentivized and individuals with positive tests are linked for further management.

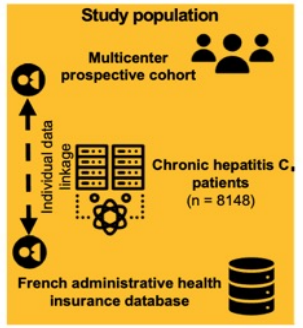



Hasnain A, et al. EASL 2022

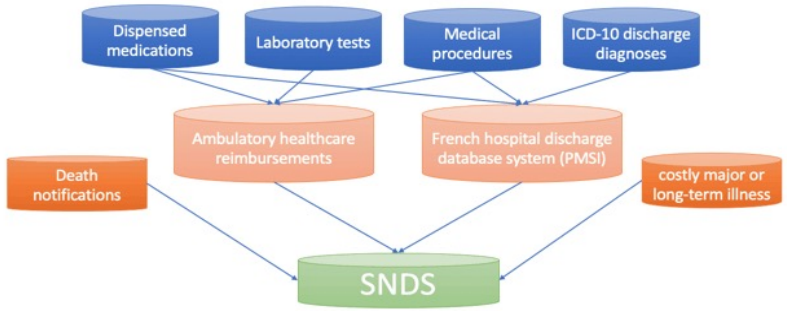
# Impact of Direct-Acting Antiviral Treatment for Hepatitis C on Cardiovascular Disease

**The Prospective ANRS CO22 HEPATHER Cohort Was Enriched With Individual Data From the French National Health Insurance Database (SNDS)**

- Chronic hepatitis C (CHC) patients enrolled between August 2012 and December 2015 in 32 French hepatology centers.
- Enrichment with SNDS data until December 2018.
- Linkage procedure:
  - deterministic approach : 93.8%
  - probabilistic approach : 6.2%




**The French Health Insurance System (SNDS) Covers 99% of the French Population**




**DAAs Were Associated With a Decreased Risk of Cardiovascular Outcomes in Patients With Advanced Fibrosis (n = 3586)**

| Outcomes | Adjusted hazard ratios associated with DAAs (95% Confidence Interval) |
|---|---|
| Acute stroke | 0.58 (0.29, 1.18) |
| Acute coronary syndrome | 0.59 (0.29, 1.19) |
| Acute pulmonary embolism | 0.79 (0.16, 3.97) |
| Acute heart failure | 0.47 (0.27, 0.81) |
| Arrhythmias and conduction disorders | 1.02 (0.57, 1.84) |
| Peripheral arterial disease | 0.36 (0.17, 0.73) |
| Major cardiovascular events | 0.50 (0.36, 0.71) |
| Any cardiovascular events | 0.58 (0.42, 0.79) |
| Any extrahepatic solid cancers | 0.39 (0.09, 1.71) |

Lam L, et al. EASL 2022

# Distinct hepatocellular carcinoma risks in treated chronic hepatitis C patients with different definitions of advanced chronic liver disease

- CHC achieved SVR by direct acting anti-viral agents (DAA), whose LMS by transient elastography (Fibroscan) and FIB-4 index were both available before DAA therapy were enrolled.
- The ACLD was define as **LSM >10 kPa** and/or **FIB-4 >3.25** and/or **ultrasound** sign or cirrhosis.
- Predictabilities for HCC and 3-year cumulative HCC incidences compared among four groups of ACLD patients diagnosed by different non-invasive assessments
  - **group A**: FIB-4>3.25 but LSM≤10
  - **group B**: FIB-4 ≤3.25 but LSM>10
  - **group C**:FIB-4>3.25 + LSM>10
  - **group D: FIB-4** ≤3.25 and LSM ≤10 but ultrasonography showed cirrhosis

**Table 1: Comparisons of characteristics among the group A-D**

| | Group A | Group B | Group C | Group D | P Value |
|---|---|---|---|---|---|
| **Age (yr)** | 70±11 | 61±11 | 67±10 | 60±12 | <0.01 |
| **Male, n(%)** | 47 (37) | 183 (50) | 160 (39) | 9 (47) | 0.01 |
| **Genotype 1, n(%)** | 84 (66) | 235 (64) | 280 (69) | 9 (47) | 0.14 |
| **ALT (U/L)** | 60 (5-1290) | 62 (12-711) | 92 (11-642) | 45 (20-139) | <0.01 |
| **MELD score** | 6.9 (5.9-12.7) | 6.9 (5.9-13.1) | 7/3 (6..4-12.3) | 6.9 (6.4-8.7) | <0.01 |
| **Platelet ($10^3$ /uL)** | 134 (32-326) | 192(100-747) | 110(20-263) | 157(102-374) | <0.01 |
| **HbA1c ≥6.5, n(5)** | 15(14) | 92(30) | 77(23) | 4(24) | <0.01 |

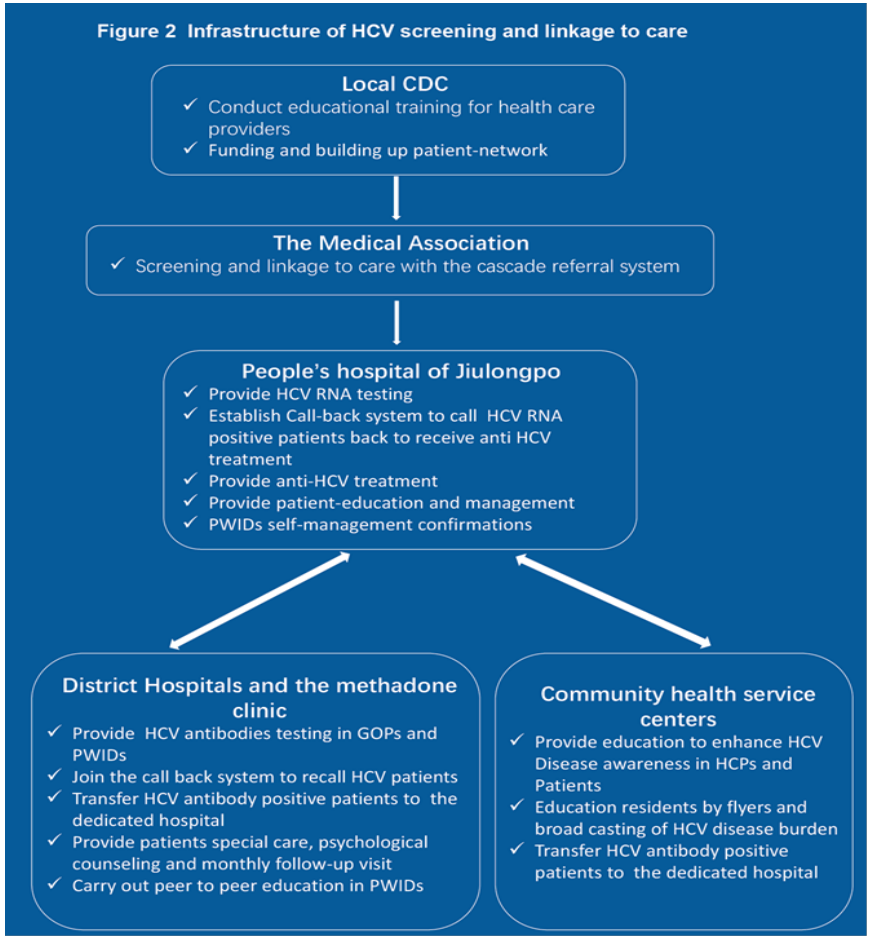
**Table 2: Predictability of HCC on different definitions for ACLD**

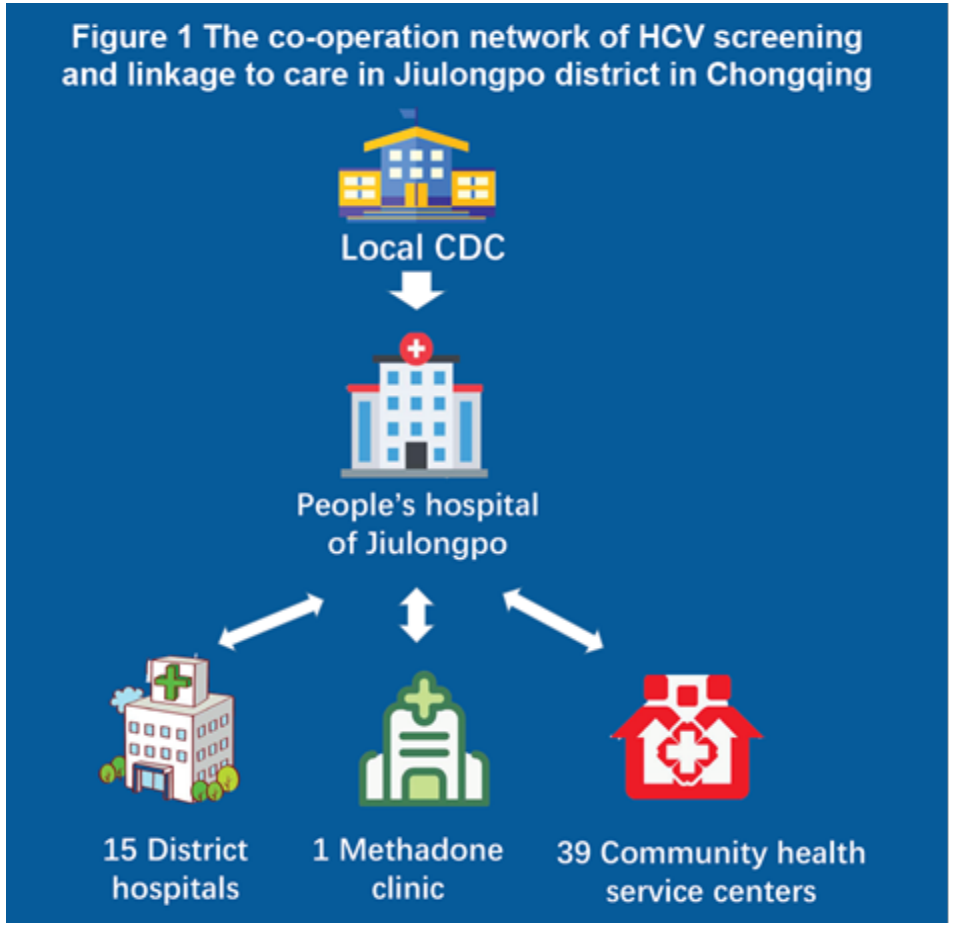
| ACLD definition | Annual incidence | Sensitivity | Specificity | PPV | NPV |
|---|---|---|---|---|---|
| **Group A** | 0.3% | 1.4% | 91.7% | 0.8% | 95.2% |
| **Group B** | 2.2% | 27.8% | 77.2% | 5.4% | 95.8% |
| **Group C** | 3.8% | 62.5% | 76.4% | 11.1% | 97.7% |
| **Group D** | 3.9% | 2.8% | 98.9% | 10.5% | 95.6% |

Liu YC, et al. EASL 2022

# Elimination of Hepatitis C Possible through Co-Operative Model

**From extensive to intensive screening, co-operation model of HCV elimination in out-patients and PWID population in southwest of China**




Lin Q, et al. EASL 2022

# Elimination of Hepatitis C Possible through Co-Operative Model

## Conclusions

- The co-operation model was effective in HCV elimination in GOPs (general outpatients) and PWIDs.
- HCV prevalence of PWIDs was significantly higher than GOPs in the direct scale.
- Although PWIDs had lower treatment adherence, the treatment rate in PWIDs were improved significantly by intensive follow-up. Both groups achieved high SVR with good safety profile by SOF/VEL treatment.
- The co-operations model with intensive and extensive screening was an optimal option for GOP and PWID to eliminate HCV.

Lin Q, et al. EASL 2022

# Treating HCV Nonresponders Using **Glecaprevir/Pibrentasvir & Sofosbuvir**

**Glecaprevir/pibrentasvir & sofosbuvir for 16 weeks without ribavirin is safe and highly effective retreatment for patients who have failed an NS5A inhibitor containing antiviral regimen**

## Retreatment of DAA Treatment Failures in New Zealand


- Inclusion criteria
  - Written informed consent and over 18 years of age
  - Previous NS5A inhibitor-based DAA therapy
  - Confirmed failure as demonstrated by positive viral load at 12 weeks after end of treatment and no history to suggest reinfection
  - Confirmed NS5A resistance (National Reference Virology Laboratory)
- Exclusion criteria
  - Decompensated cirrhosis (Child Pugh Class C)
  - Hepatocellular carcinoma
  - Pregnant or breast-feeding

## Retreatment of DAA Treatment Failures in New Zealand


- Patient characteristics (n=66)
  - 50 male (76%)
  - Mean age 56 years (38-80);
  - 24 cirrhotic (36%) - 23 CTP A; 1 CTP-B (7)
  - 8 (12%) on opioid substitution (methadone)
  - 9 (14%) still injecting
  - 1 HIV coinfection; 1 HBV coinfection;
  - 64 had confirmed NS5A RAS present, 2 sequencing failures (GT-2)

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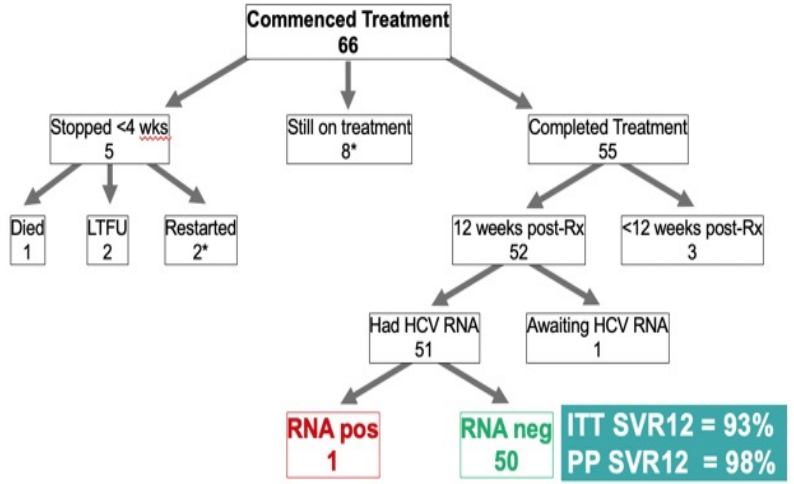
# Treating HCV Nonresponders Using **Glecaprevir/Pibrentasvir & Sofosbuvir**

**Glecaprevir/pibrentasvir & sofosbuvir for 16 weeks without ribavirin is safe and highly effective retreatment for patients who have failed an NS5A inhibitor containing antiviral regimen**

Retreatment of DAA Treatment Failures in New Zealand




Retreatment of DAA Treatment Failures in New Zealand

**Interim Safety Results**

- Serious Adverse Events
  - 1 drug overdose (died); 1 HCC (resected); no decompensation
- 3 non-virologic failures
  - All active PWID
    - 1 overdose at Week 4
    - 2 lost to follow-up at Weeks 2 and 4
- 1 confirmed virologic failure
  - 53 year old woman with HCV GT 1a, noncirrhotic, previous PrOD+RBV
    - RAS profile pre-GLE/PIB+SOF : M28V, Q30R
  - Retreated with GLE/PIB+SOF for 16 weeks
    - RAS profile post-GLE/PIB+SOF: M28V only
  - ⇨Awaiting retreatment with GLE/PIB+SOF+RBV for 16 weeks

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# Early post liver transplant rescue treatment with sofosbuvir/velpatasvir/voxilaprevir in patients experienced to NS5A-inhibitors

**Conclusions**

- From January 2019 to March 2022, 492 patients underwent LT in our Center. Among 50 patients who were HCV viremic at LT, 6 (12%) were experienced to NS5A inhibitors.

- The early post-LT use of SOF/VEL/VOX was successful in all patients (SVR 100%)

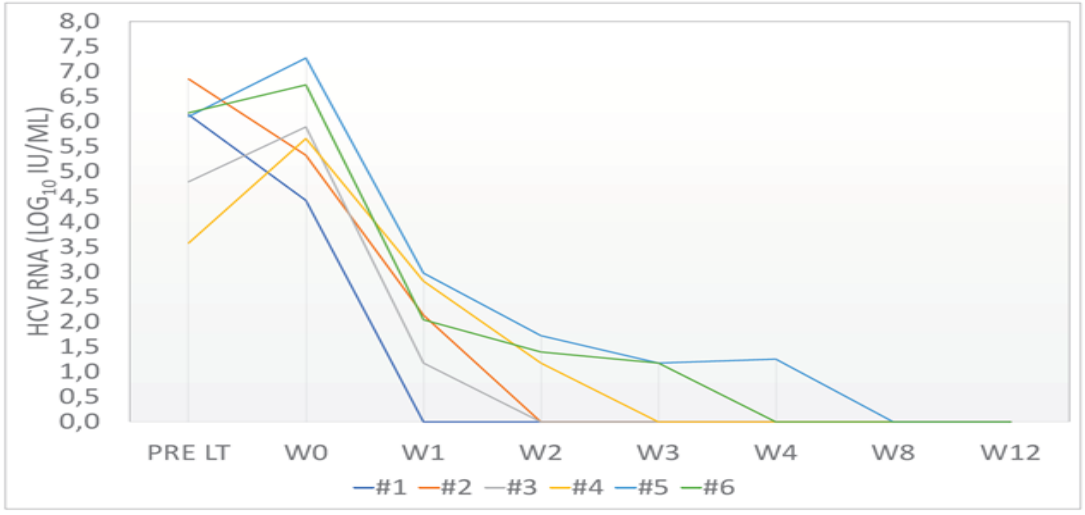



**Figure 1**. HCV RNA kinetic during SOF/VEL/VOX therapy

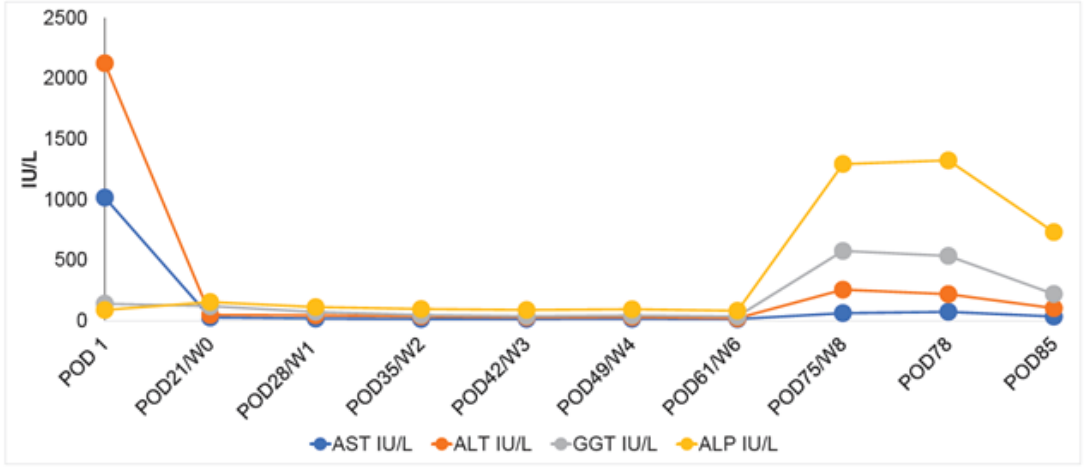
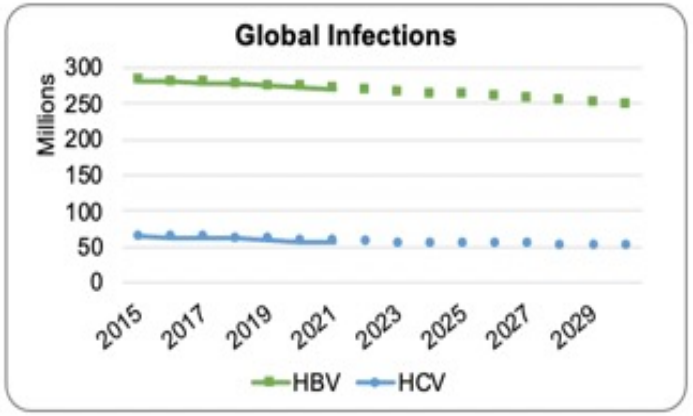
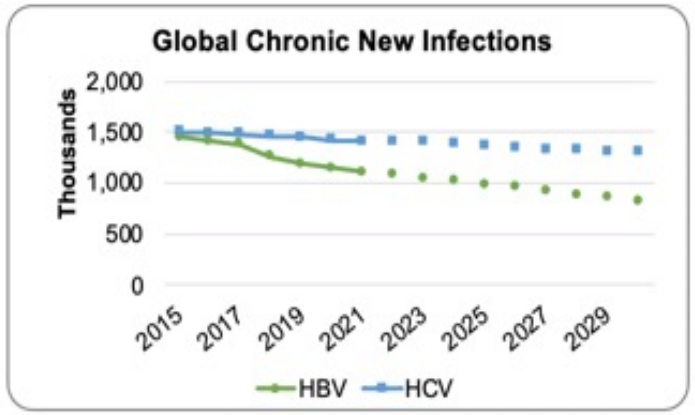



**Figure 2**. Liver tests of patient #3 who experienced a cholestatic hepatitis at W8 of SOF/VEL/VOX. (POD = post-operative day; W= week of DAA therapy)

Saraccol M, et al. EASL 2022

# The disease burden of hepatitis B and C from 2015- 2030: The long and winding road towards elimination




HBV infections are expected to increase in North America as the result of immigration.

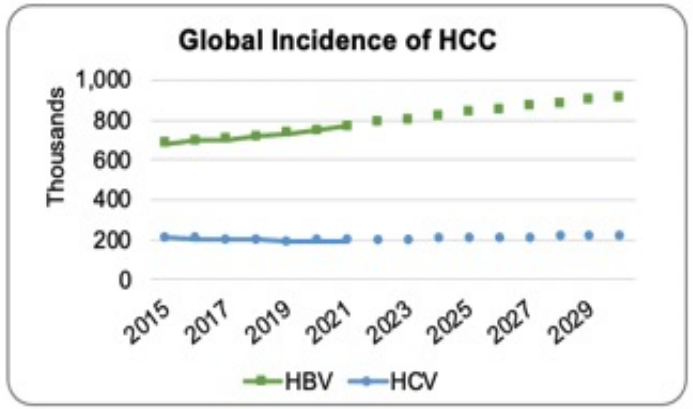
HCV infections in Oceania are expected to grow as the result of low treatment rate while in Africa the decline is due to Egypt's program.

HBV vaccination is reducing new chronic HBV infections – less in Africa & Oceania who don't have access to birth dose.

HCV treatment & harm reduction programs will reduce new viremic HCV infections – exception is the United State where access to harm reduction programs are limited.

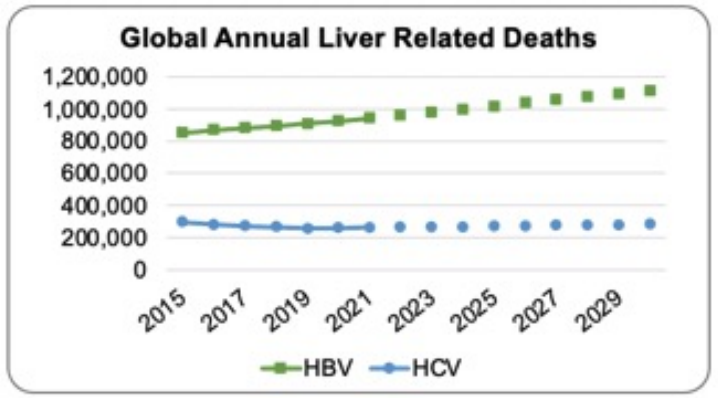
Razavi-Shearer D, et al. EASL 2022

# The disease burden of hepatitis B and C from 2015- 2030: The long and winding road towards elimination




HBV related HCC cases are expected to increase the most in Africa and Asia which have a very high prevalence.

HCV related HCC are projected to decrease in all regions with a high treatment rate – Australia, Europe & N America. Egypt's program brings down the numbers for Africa.




HBV related deaths are expected to increase in all regions without substantial increase in diagnosis and treatment.

HCV related deaths are projected to decrease in all regions with a high treatment rate – Australia, Europe & N America. Egypt's program brings down the numbers for Africa.

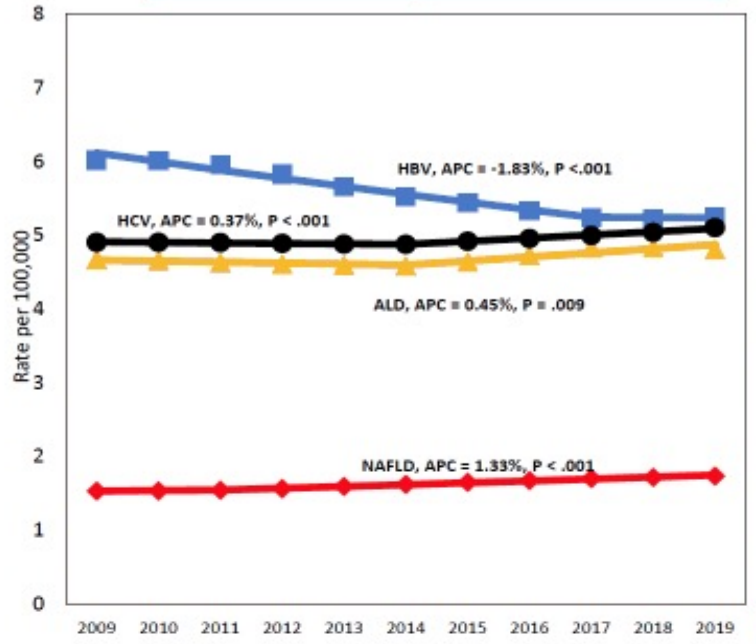
Razavi-Shearer D, et al. EASL 2022

# Drivers of Global Burden of Liver Cancer and Chronic Liver Disease

## Annual Percent Change in Chronic Liver Disease Death Rate by Each Liver Disease from 2009 to 2019

INOVA Join the future of health.

### Global Change in CLD Death




### Regional Change in CLD Death

| | CLD Death | | | | |
|---|---|---|---|---|---|
| | All | HBV | HCV | ALD | NAFLD |
| Global | -0.18 | -1.83 | 0.37 | 0.45 | 1.33 |
| 21 GBD Regions | | | | | |
| High-income North America | 1.49 | -0.86 | 1.52 | 0.69 | 2.97 |
| Caribbean | 2.73 | 1.21 | 2.64 | 3.06 | 2.95 |
| South Asia | -0.19 | -0.85 | -0.50 | 1.28 | 2.51 |
| Tropical Latin America | 0.15 | -1.81 | 0.03 | 0.34 | 2.18 |
| Central Latin America | 1.68 | 1.11 | 1.67 | 1.83 | 1.78 |
| East Asia | -1.16 | -4.9 | 0.42 | 0.43 | 1.73 |
| Southern Latin America | 1.04 | -3.25 | 1.44 | 1.53 | 1.71 |
| High-income Asia Pacific | 0.24 | 1.14 | -0.45 | 0.18 | 1.71 |
| Southeast Asia | 0.60 | -0.86 | 0.92 | 1.58 | 1.64 |
| North Africa and Middle East | 0.47 | -0.83 | 1.09 | 1.17 | 1.56 |
| Central Asia | -0.03 | -3.34 | 1.01 | 1.23 | 1.40 |
| Australasia | 0.97 | 0.40 | 0.95 | 0.51 | 1.33 |
| Andean Latin America | 0.23 | -2.79 | 0.25 | 0.59 | 0.72 |
| Central Sub-Saharan Africa | -0.94 | -3.23 | 0.40 | 0.39 | 0.67 |
| Oceania | 0.14 | -0.24 | 0.36 | 0.59 | 0.57 |
| Eastern Europe | -0.70 | -5.93 | 0.19 | -0.06 | 0.44 |
| Eastern Sub-Saharan Africa | -0.66 | -3.10 | 0.12 | 0.01 | 0.35 |
| Western Europe | -0.48 | -2.05 | -0.57 | -0.48 | 0.01 |
| Central Europe | -0.78 | -1.90 | -0.69 | -0.36 | -0.15 |
| Western Sub-Saharan Africa | -1.77 | -2.66 | -1.13 | -1.09 | -0.66 |
| Southern Sub-Saharan Africa | -2.02 | -3.14 | -1.75 | -1.21 | -1.47 |

Improving (APC< 0%)
Worsening (APC> 0%)

Data displayed APC
* Region is ordered by APC for CLD Death due to NAFLD

- Similarly, NAFLD-related CLD deaths increased for most GBD regions
- NAFLD-related CLD deaths had the highest APC from 2009-2019

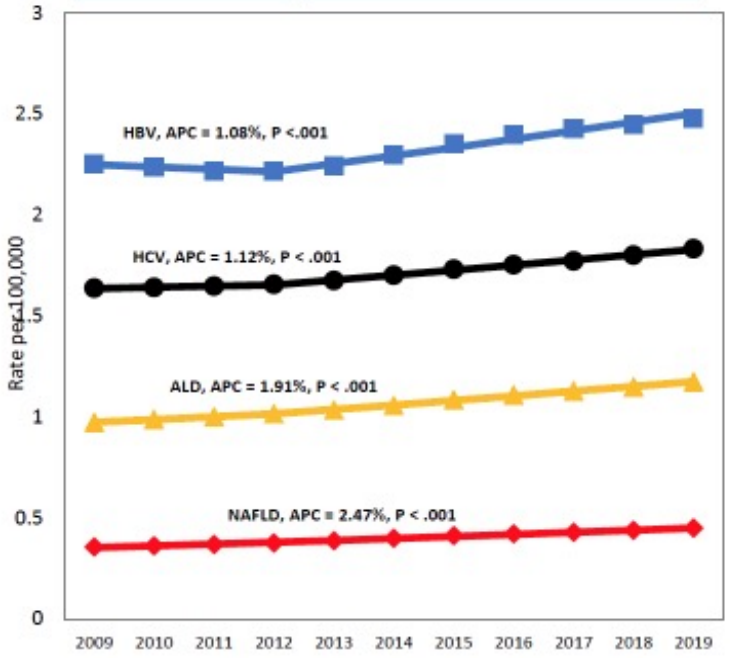
Paik J, et al. EASL 2022

# Drivers of Global Burden of Liver Cancer and Chronic Liver Disease

## Annual Percent Change in Liver Cancer Death Rate by Each Liver Disease from 2009 to 2019

INOVA Join the future of health.

### Global Change in Liver Cancer Death




### Regional Change in Liver Cancer Death

| | Liver Cancer Death | | | | |
|---|---|---|---|---|---|
| | All | HBV | HCV | ALD | NAFLD |
| Global | 1.33 | 1.08 | 1.12 | 1.91 | 2.47 |
| 21 GBD Regions | | | | | |
| Central Latin America | 3.61 | 2.96 | 3.42 | 4.15 | 4.19 |
| East Asia | 2.54 | 2.09 | 3.00 | 4.13 | 4.07 |
| Tropical Latin America | 2.65 | 2.00 | 2.90 | 2.75 | 4.02 |
| Caribbean | 3.10 | 2.77 | 2.79 | 3.50 | 3.40 |
| High-income North America | 3.35 | 2.48 | 2.77 | 4.30 | 3.28 |
| Southern Latin America | 2.46 | 1.58 | 2.61 | 2.86 | 2.90 |
| Australasia | 2.38 | 1.67 | 3.12 | 1.91 | 2.88 |
| Southeast Asia | 1.83 | 1.21 | 2.14 | 2.55 | 2.79 |
| North Africa and Middle East | 1.06 | 1.70 | 0.43 | 1.40 | 2.62 |
| Eastern Europe | 1.36 | 0.53 | 1.97 | 1.14 | 2.51 |
| South Asia | 1.51 | 0.53 | 2.25 | 2.24 | 2.26 |
| Andean Latin America | 1.39 | 0.87 | 1.45 | 2.06 | 2.24 |
| Western Europe | 1.25 | 1.02 | 1.40 | 1.06 | 1.61 |
| Central Asia | 0.66 | 0.29 | 0.36 | 1.16 | 1.27 |
| Eastern Sub-Saharan Africa | 0.39 | 0.07 | 0.88 | 0.62 | 1.22 |
| Central Sub-Saharan Africa | -0.29 | -0.47 | 0.03 | 1.05 | 1.03 |
| High-income Asia Pacific | 0.24 | -0.01 | 0.13 | 0.75 | 0.98 |
| Central Europe | 0.30 | -0.66 | 0.46 | 0.61 | 0.92 |
| Oceania | 0.42 | 0.27 | 0.45 | 0.91 | 0.62 |
| Western Sub-Saharan Africa | -0.33 | -0.65 | -0.36 | -0.02 | 0.31 |
| Southern Sub-Saharan Africa | -0.49 | -0.84 | -0.25 | -0.23 | 0.08 |

Improving (APC< 0%)
Worsening (APC> 0%)

Data displayed APC
* Region is ordered by APC for Liver Cancer Death due to NAFLD

- NAFLD-related LC deaths increased for each GBD region
- NAFLD-related LC deaths had the highest APC from 2009-2019

Paik J, et al. EASL 2022

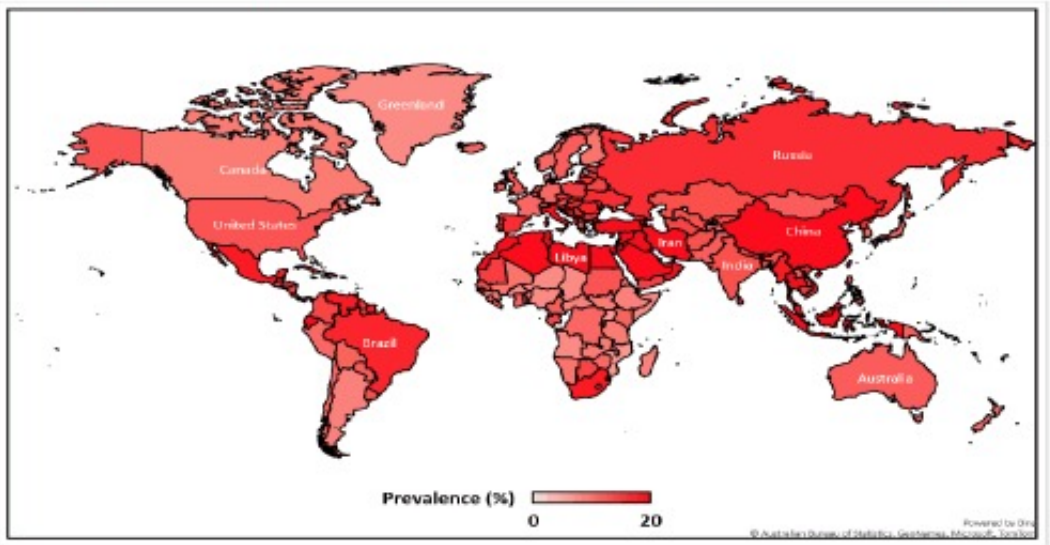
# Drivers of Global Burden of Liver Cancer and Chronic Liver Disease

## Focusing on NAFLD: The Global and Regional Prevalence of NAFLD

INOVA
Join the future of health.

- In 2019 globally, there were
  - 1.24 billion NAFLD prevalent cases (16.0%),
  - 172.3K incidental cases of NAFLD
  - 168.9K deaths due to NAFLD
  - 4.42 million DALYs due to NAFLD
  - NAFLD global DALYs accounted for 0.2% of total global DALYs.

Maps of NAFLD Prevalence (%) in 2019

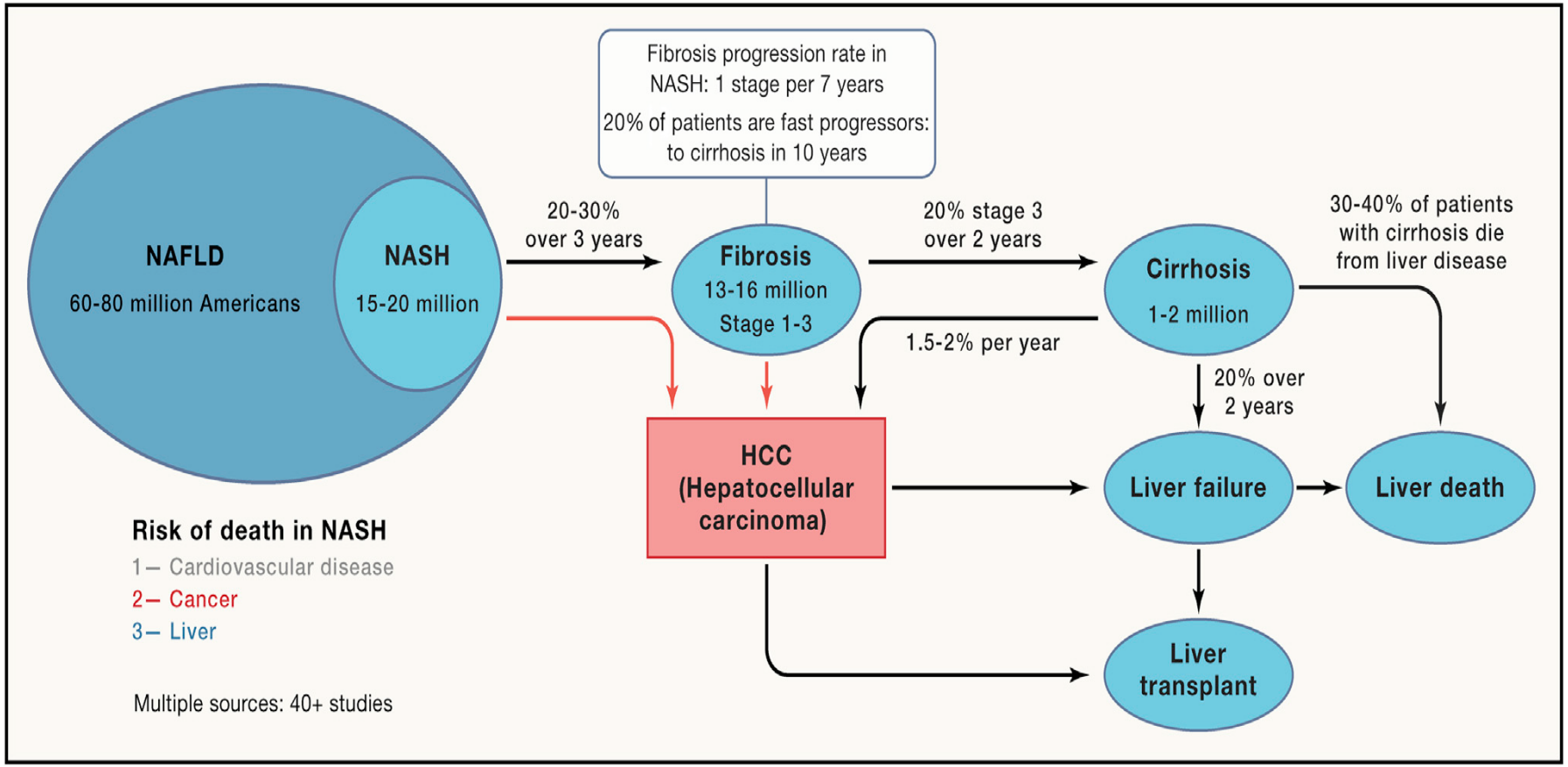



- The highest NAFLD prevalence occurred in Middle East North Africa and North Africa (MENA) (26.5%) which was primarily driven by high numbers of cases in Egypt, Iran, and Turkey.

- Furthermore, East Asia (20.6%) had the next highest NAFLD prevalence largely driven by China.

Paik J, et al. EASL 2022

# Natural history of NAFLD




Loomba R, et al. *Cell*. 2021

# Conditions associated with NAFLD

| Condition | Prevalence | |
|---|---|---|
| | NAFLD (%) | NASH (%) |
| Obesity | 51 | 82 |
| Type 2 diabetes mellitus | 23 | 44 |
| Dyslipidemia | 69 | 72 |
| Hypertriglyceridemia | 41 | 83 |
| Hypertension | 39 | 68 |
| Metabolic syndrome | 43 | 71 |
| CKD | 20-55 | NA |
| HIV | 30 | NA |

CKD, chronic kidney disease; NA, not available; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis.

Ferguson D, Finck BN. *Nat Rev Endocrinol*. 2021; Younossi Z, et al. *Hepatol* 2016; Bren CD, Targher G, *J Hepatol* 2020; Maurice JB *AIDS* 2017

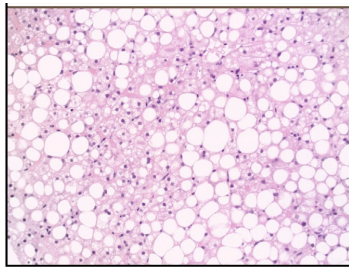
# Classification of Fatty Liver Disease

**Fatty Liver Disease**
**≥5% hepatic steatosis**

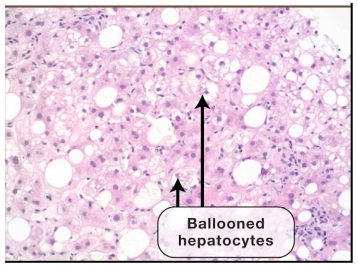
**Alcoholic (ALD)**
Over a 2-year period
Men: >21 drinks/week
Women: >14 drinks/week

**Nonalcoholic Fatty Liver Disease (NAFLD)**

**Nonalcoholic Fatty Liver (NAFL)**



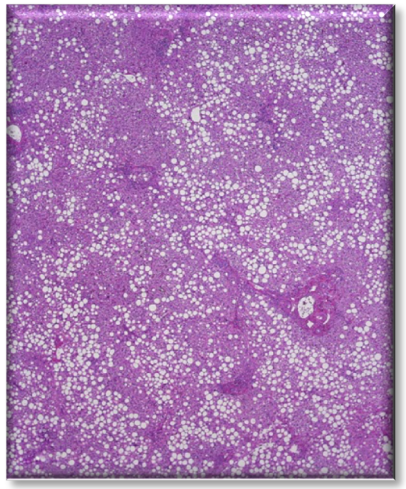
**Nonalcoholic Steatohepatitis (NASH)**




Loomba R, et al. *Cell*. 2021

# Histopathology of NASH: Necessary Components for a Diagnosis

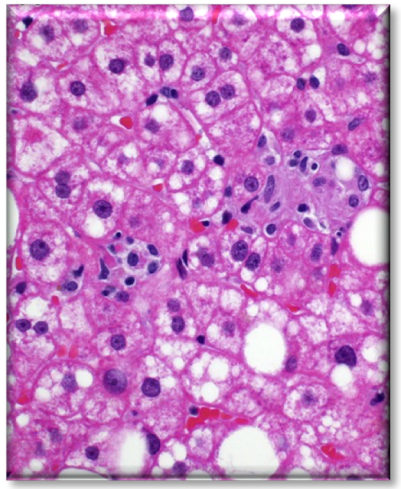
**Steatosis (≥5%)**



Macro>Micro
Accentuated in zone 3
Periportal areas usually spared in early disease

+

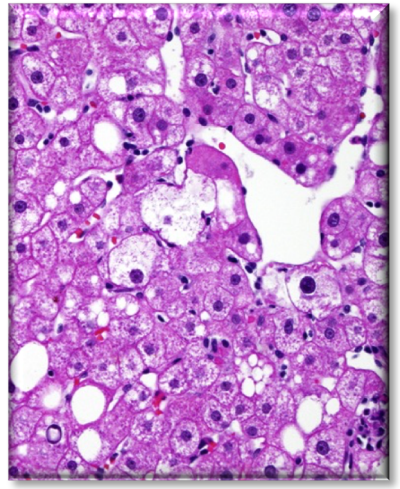
**Lobular Inflammation**



Any degree (mixed, mild)
Scattered polymorphonuclear leukocytes as well as mononuclear cells

+

**Hepatocellular Ballooning**

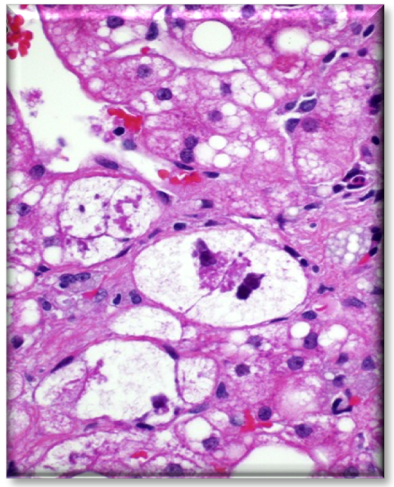


Most apparent near steatotic liver cells
Typically zone 3

Chalasani N, et al. *Hepatology.* 2012. Takahashi Y, et al. *World J Gastroenterol.* 2014. Kleiner DE, et al. *Clin Liver Dis.* 2016.

# Histopathology of NASH: Supportive Components for a Diagnosis

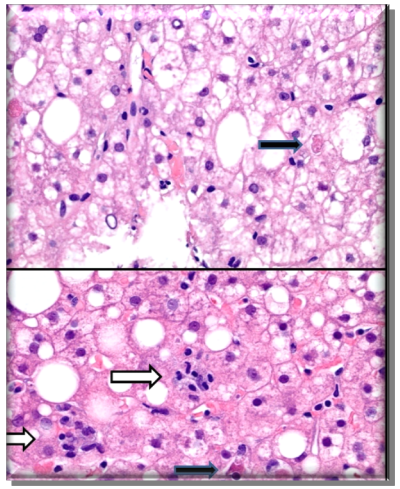
## Mallory-Denk Bodies



Large cytoplasmic inclusions seen in ballooned hepatocytes

Protein aggregates comprising misfolded keratins

## Apoptotic Bodies

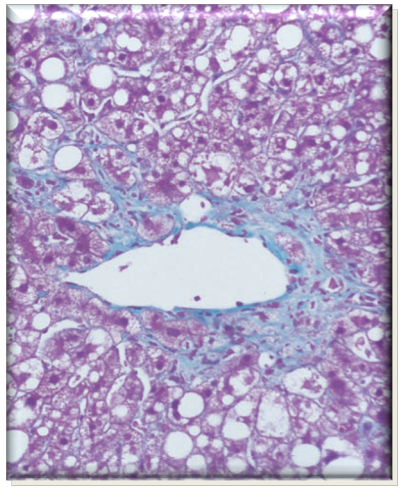


Also known as acidophil bodies

Correlate with disease activity

Commonly present with ballooned hepatocytes and lobular infiltrates (white arrows)

## Perisinusoidal Fibrosis



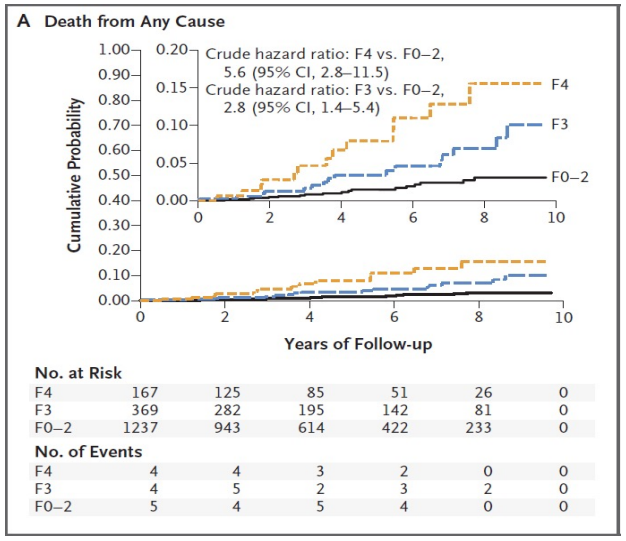
Typically zone 3

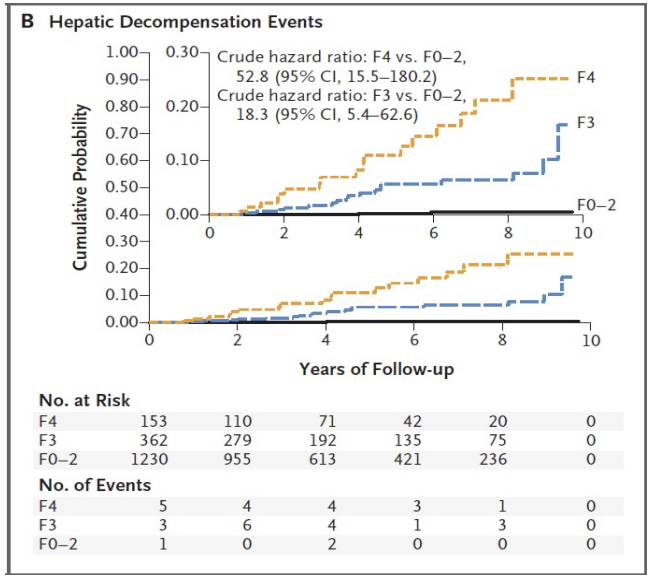
Delicate collagen strands between ballooned hepatocytes

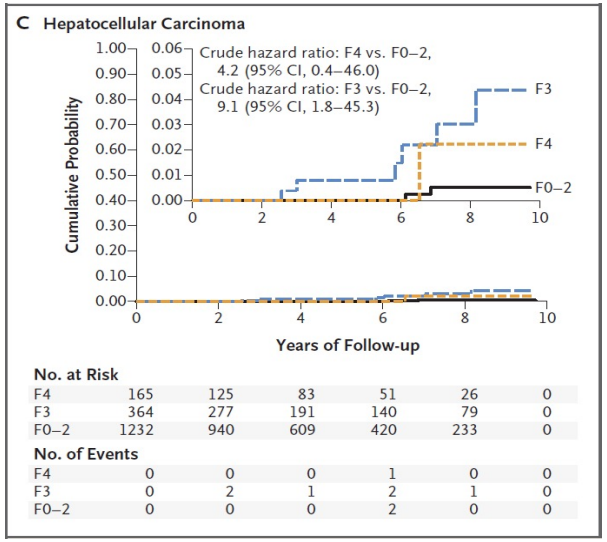
Chalasani N, et al. *Hepatology.* 2012. Takahashi Y, et al. *World J Gastroenterol.* 2014. Kleiner DE, et al. *Clin Liver Dis.* 2016.

# Outcomes in NAFLD

## Kaplan-Meier time-to-event analysis




Sanyal AJ et al. *NEJM* 2021

# Diagnostic Modalities for NAFLD, NASH and Fibrosis

## Serum Biomarkers

- FIB-4 index
- NFS
- APRI
- ELF®
- Hepascore®
- FibroSure®
- FibroMeter®

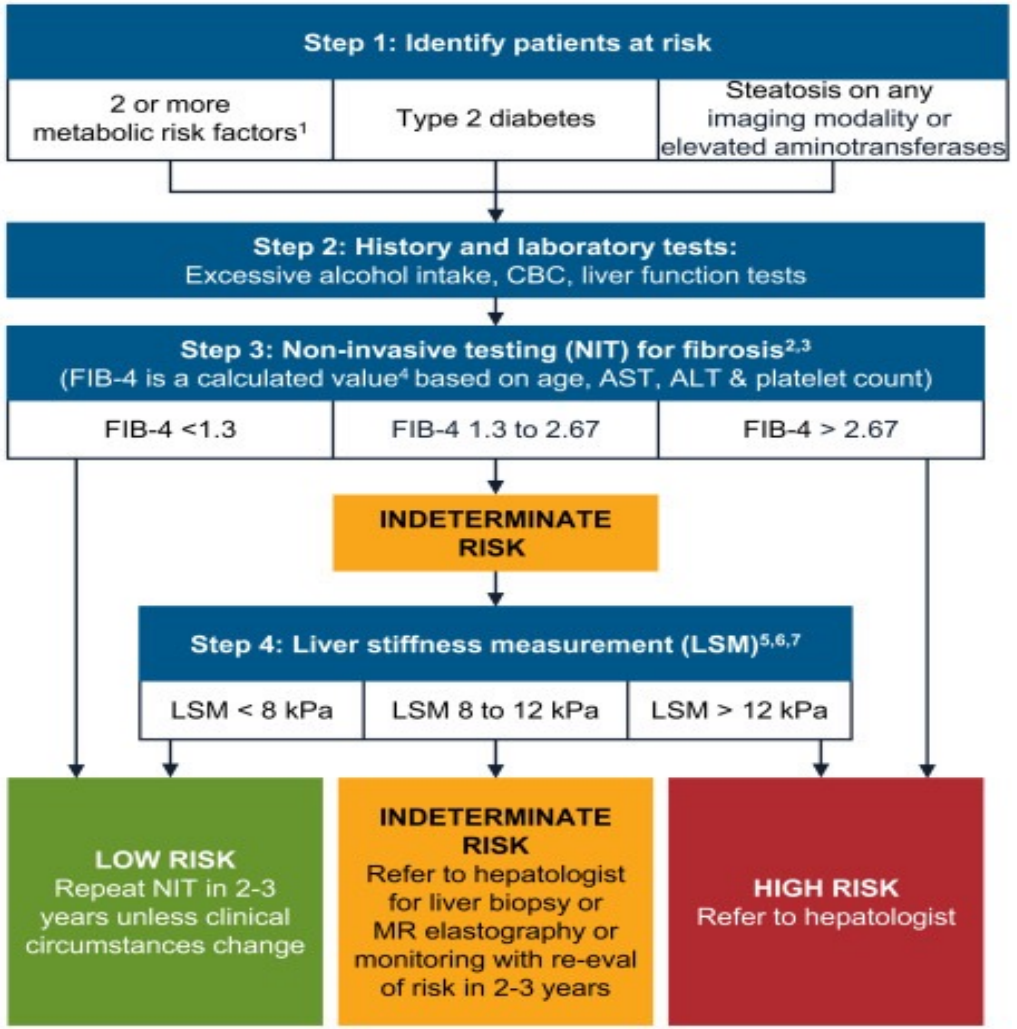
## Imaging Biomarkers

- Transient elastography
- Shear wave elastography
- Magnetic resonance techniques

FIB-4, Fibrosis-4 Index; NFS, NAFLD Fibrosis Score; ELF, Enhanced Liver Fibrosis.

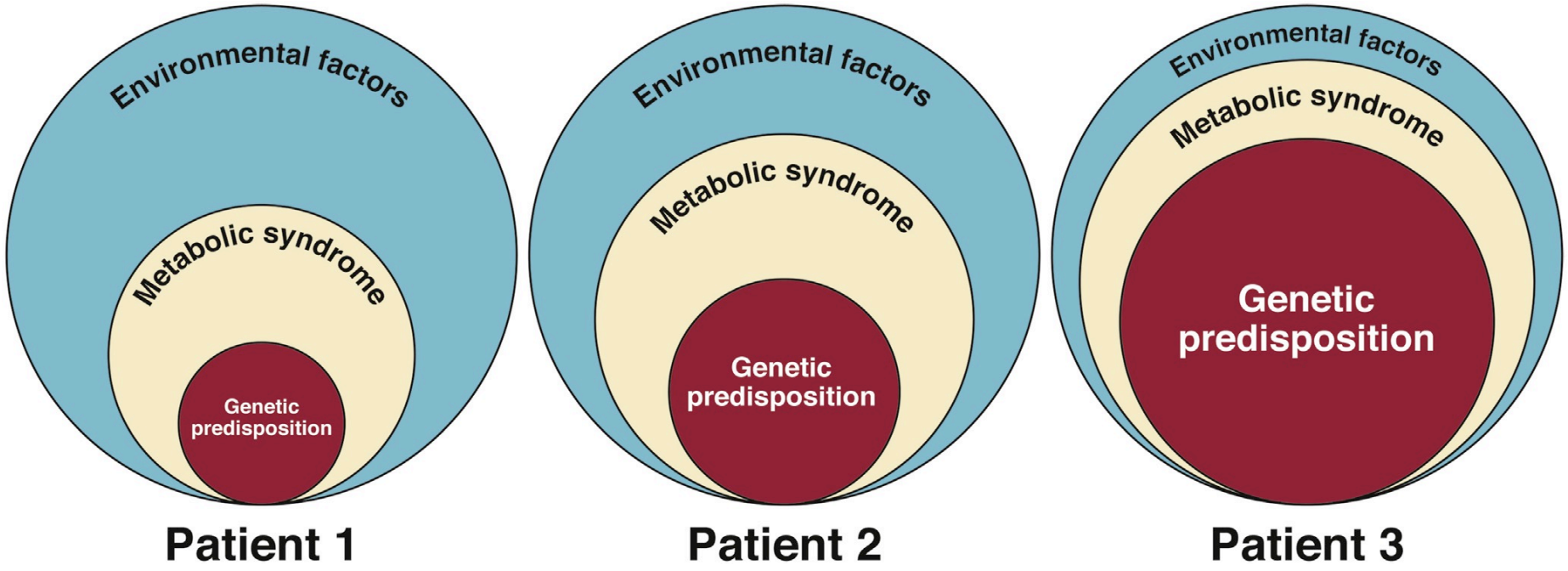
Papagianni M, et al. *World J Hepatol*. 2015; Golabi P, et al. *Expert Rev Gastroenterol Hepatol*. 2016.

# Screening for advanced fibrosis related to NAFLD/NASH




Kanwal et al. *Gastroenterology*. 2021

# Inter-individual variation in the predominant drivers of MAFLD

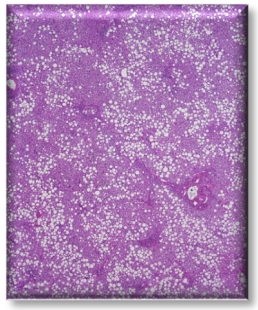



Eslam M, et al. *Gastroenterology* 2020

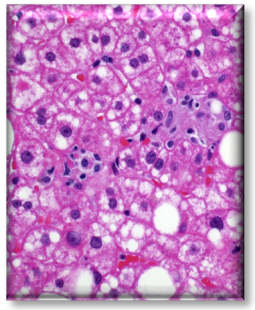
# FDA Clinical Trial Goals for Patients with NASH and no Cirrhosis

**NASH**

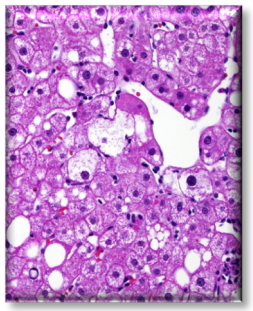
**Steatosis (≥5%)**



**Lobular Inflammation**

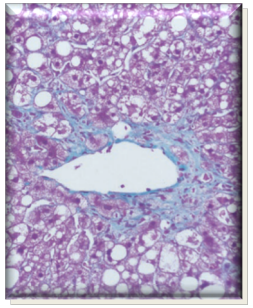


**Hepatocellular Ballooning**



**Fibrosis**

**Perisinusoidal Fibrosis**



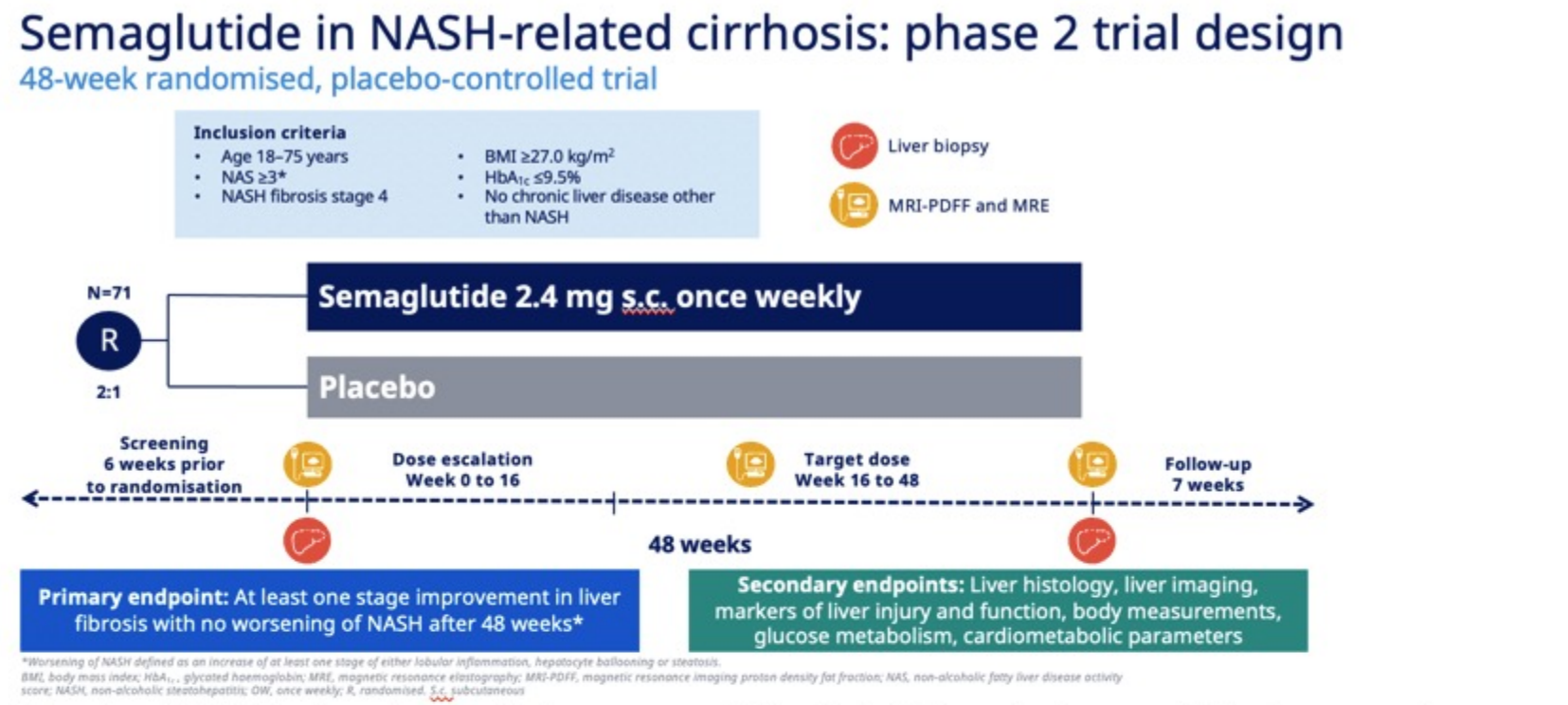
FDA Goal ~ Resolution of NASH and/or improvement of fibrosis

# Potential Treatment for NASH

## NASH agents in clinical development

| Agent | Target(mechanism) | Trial, patients and primary endpoint(s) |
|---|---|---|
| Aramchol | Lipotoxicity (SCD1 inhibitor) | **ARMOR (n=2000, fibrosis stage 2-3)**<br>• Reversal of NASH without worsening of fibrosis |
| Resmetirom (MGL-3196) | Lipotoxicity (TRß agonist) | **MAESTRO-NASH (n=2000, fibrosis stage 2–3)**<br>• NASH resolution with at least a 2-point improvement in NAS without worsening of fibrosis |
| Obeticholic acid | Lipotoxicity/oxidative stress (FXR agonist) | **REGENERATE (n=2370, fibrosis stage 1–3)**<br>• Fibrosis improvement ≥1 stage without NASH worsening<br>**FLINT (n=283, fibrosis stage 0–3)**<br>• Decrease in NAS of ≥2 without worsening of fibrosis from baseline |
| Semaglutide | Lipotoxicity/Steatosis (GLP1-RA) | **ESSENCE**<br>• Resolution of steatohepatitis and no worsening of liver fibrosis<br>• Improvement in liver fibrosis and no worsening of steatohepatitis<br>• Time to first liver-related clinical event |

# Semaglutide as Potential Treatment for Non-alcoholic Steatohepatitis (NASH)




**Worsening of NASH defined as an increase of at least one stage of either lobular inflammation, hepatocyte ballooning or steatosis.*
*BMI, body mass index; $HbA_{1c}$, glycated haemoglobin; MRE, magnetic resonance elastography; MRI-PDFF, magnetic resonance imaging proton density fat fraction; NAS, non-alcoholic fatty liver disease activity score; NASH, non-alcoholic steatohepatitis; OW, once weekly; R, randomised. S.c. subcutaneous*

Loomba R, et al. EASL 2022

# Semaglutide as Potential Treatment for Non-alcoholic Steatohepatitis (NASH)

## Imaging and biomarker measures at baseline

| | Semaglutide 2.4 mg OW | | Placebo | |
|---|---|---|---|---|
| **Number of patients – N** | 47 | | 24 | |
| **Scans – geometric mean (CV)** | | | | |
| MRE | 6.4 | (27.9) | 5.8 | (30.7) |
| MRI-PDFF | 10.0 | (58.3) | 10.4 | (54.7) |
| **Liver enzymes – geometric mean (CV)** | | | | |
| ALT | 47.6 | (59.0) | 36.4 | (57.3) |
| AST | 47.2 | (45.7) | 39.0 | (46.0) |
| **Exploratory biomarkers** | | | | |
| ELF – mean (SD) | 10.7 | (0.8) | 10.6 | (0.7) |
| Pro-C3 – geometric mean (CV) | 20.4 | (31.3) | 17.9 | (26.1) |
| FIB-4 – geometric mean (CV) | 2.4 | (38.3) | 2.2 | (54.2) |
| Adiponectin – geometric mean (CV) | 3.3 | (69.0) | 4.2 | (94.9) |
| **Liver safety** | | | | |
| MELD – mean (SD) | 7.6 | (1.2) | 7.7 | (2.6) |

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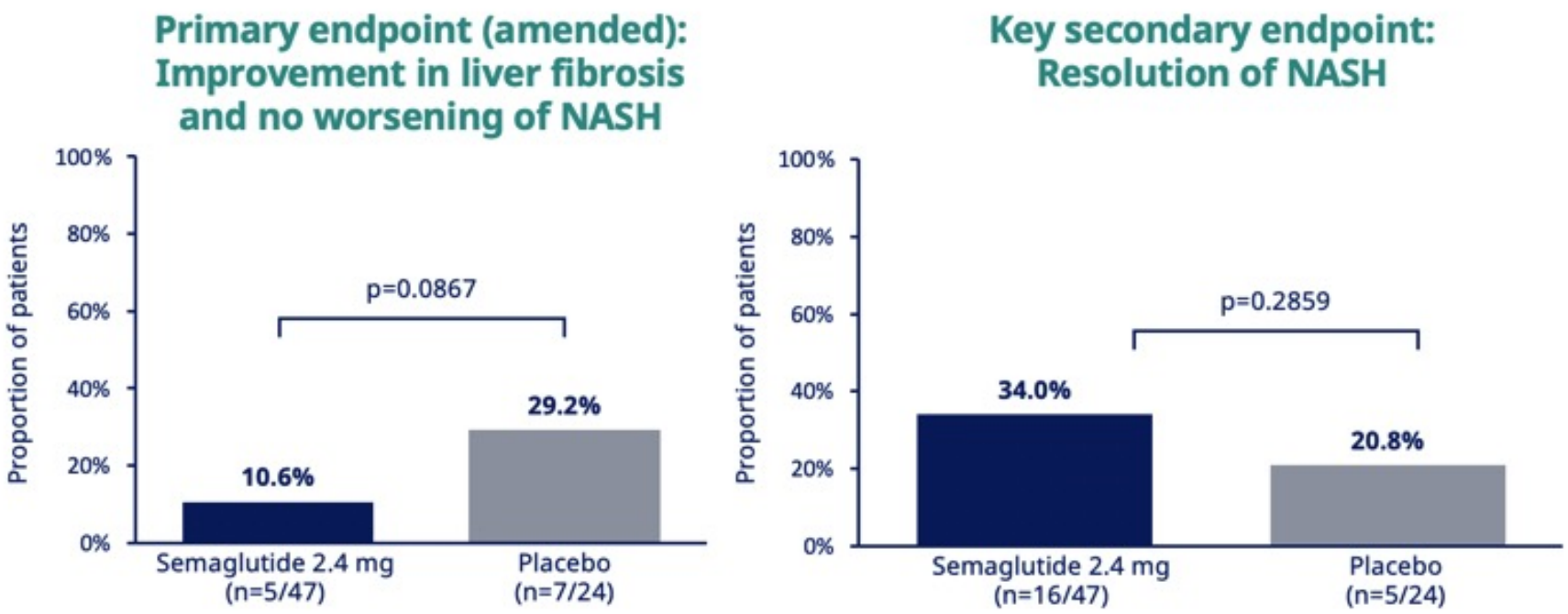
# Semaglutide as Potential Treatment for Non-alcoholic Steatohepatitis (NASH)

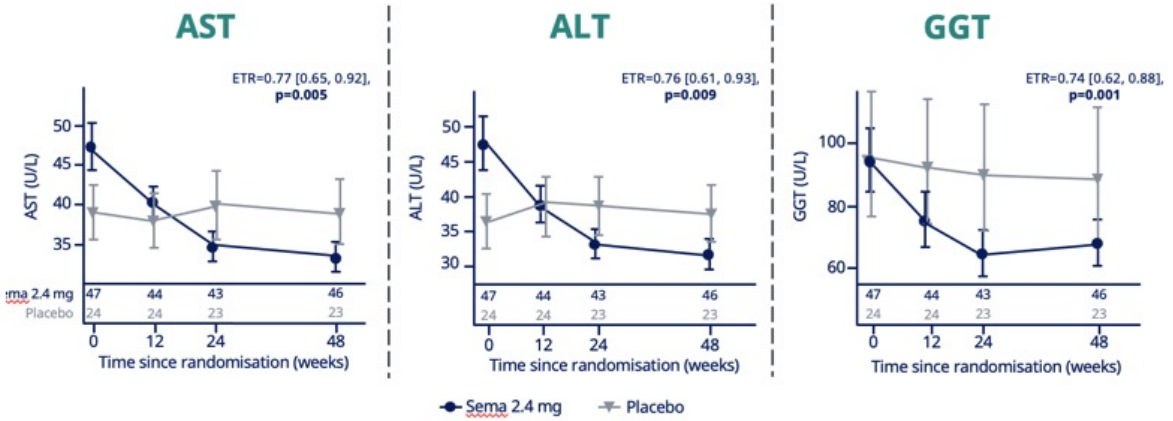
## Primary histologic endpoint and key secondary endpoint



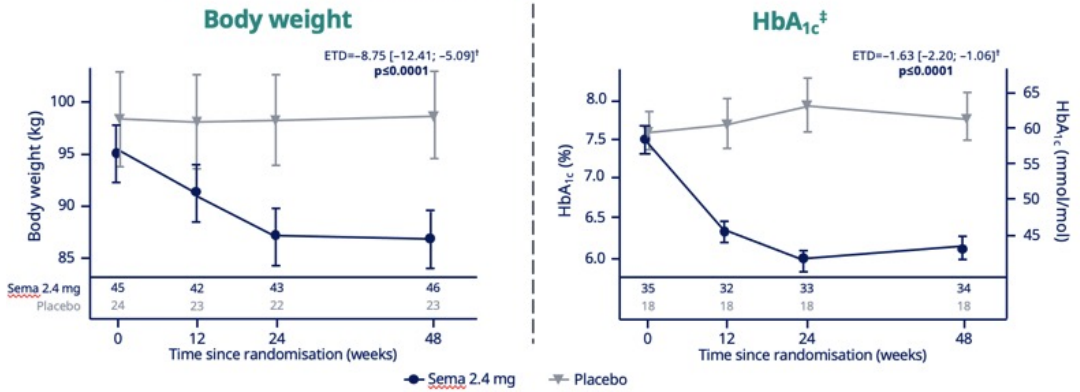

Loomba R, et al. EASL 2022

# Semaglutide as Potential Treatment for Non-alcoholic Steatohepatitis (NASH)

## Semaglutide treatment significantly improved liver enzyme levels

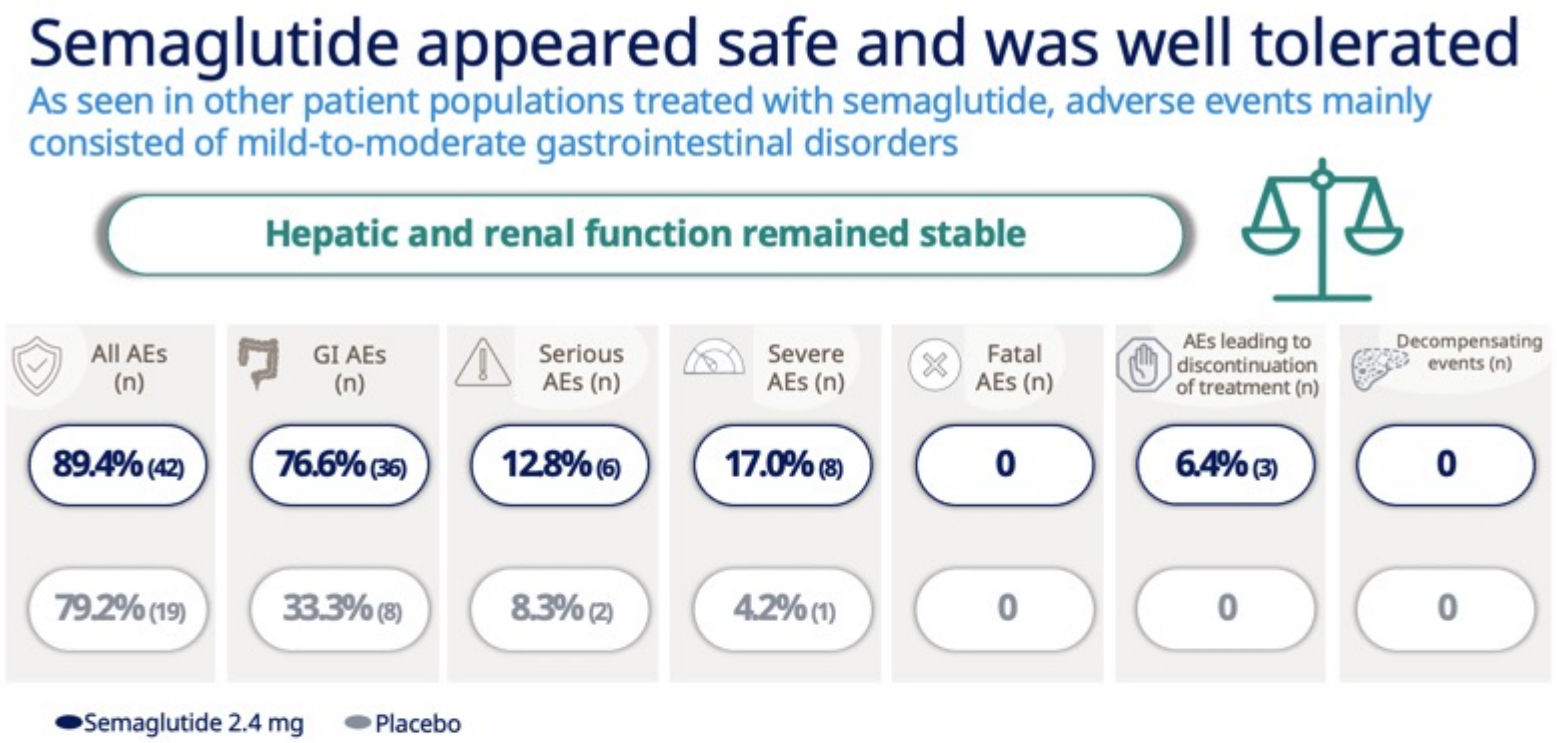



## Semaglutide significantly reduced body weight and improved glycaemic control




Loomba R, et al. EASL 2022

# Semaglutide as Potential Treatment for Non-alcoholic Steatohepatitis (NASH)



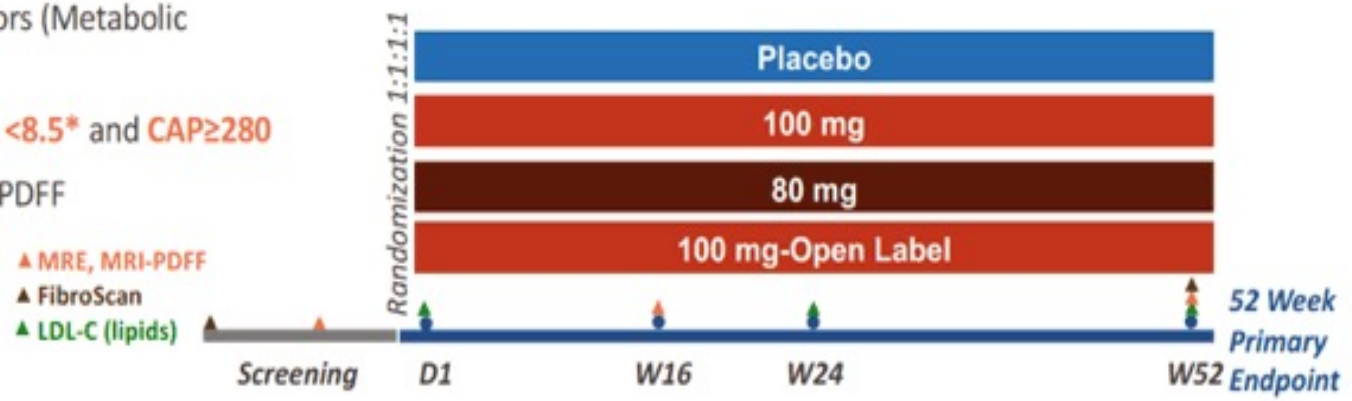

Loomba R, et al. EASL 2022

# Thyroid-Receptor Agonist for Fatty Liver

## Phase 3 MAESTRO-NAFLD-1 (presumed NASH) Study Design: Randomized, Double-Blind, PBO Controlled with 100 mg Open Label Arm

**Inclusion/Exclusion**

- ≥3 metabolic risk factors (Metabolic Syndrome)
- FibroScan kPa ≥ 5.5 & <8.5* and CAP≥280
- ≥8 % liver fat on MRI-PDFF



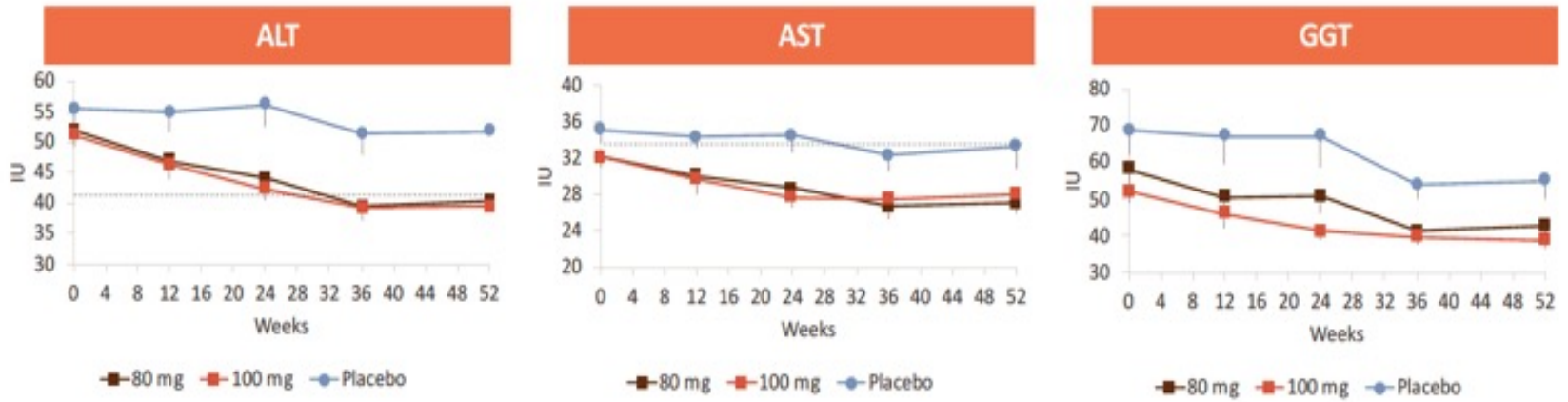

- 1143 presumed NASH patients enrolled in the USA (~80 sites)
  - 972 randomized to double-blind arms
  - 171 open label patients (recruitment completed July 1, 2020)

*A "Real-life" NASH Study with Non-invasive Monitoring of Patient Response*

Harrison SA, et al. EASL 2022

# Thyroid-Receptor Agonist for Fatty Liver

## Liver Enzymes in the subgroup of patients with baseline ALT ≥30
## 80 mg (n=172) - 100 mg (n=164) - placebo (n=159)



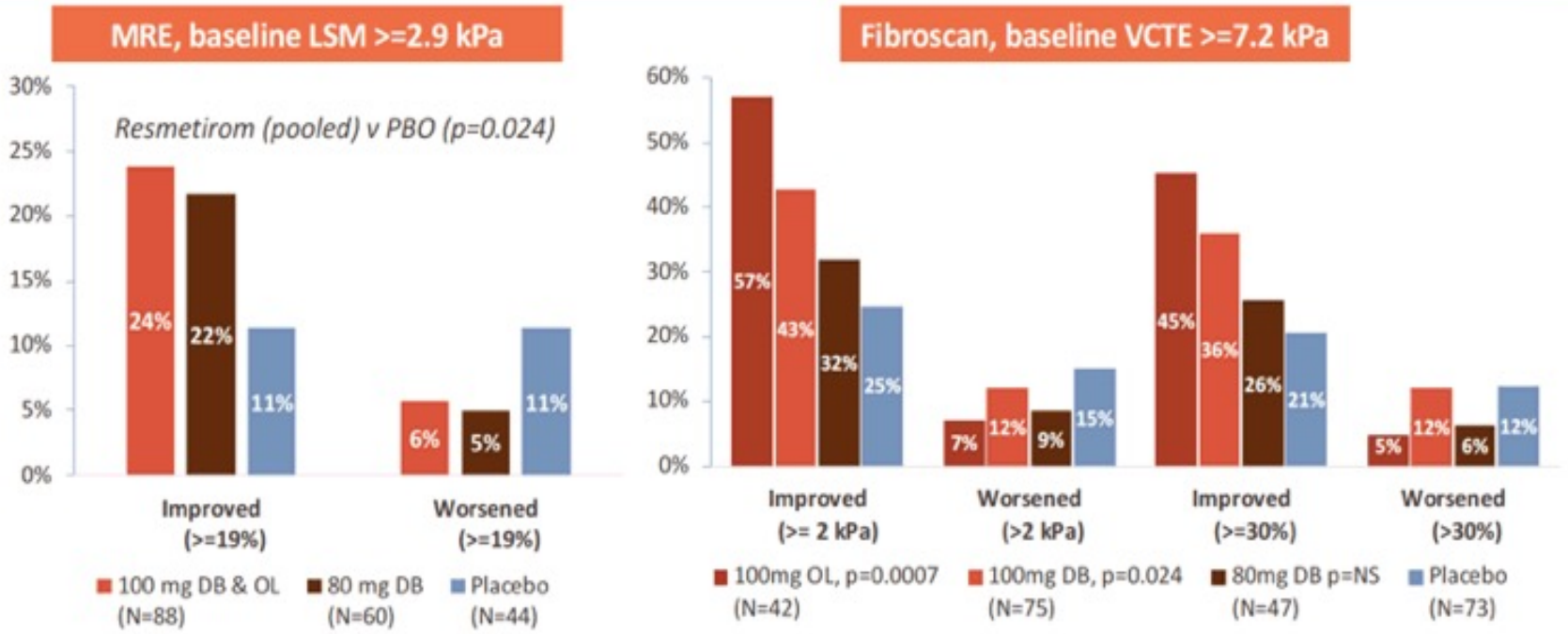

- Patients in the resmetirom 80 mg and 100 mg (double-blind) achieved reductions relative to placebo in:
  - ALT (p=0.002; <0.0001)
  - AST (p=0.028; 0.074)
  - GGT (p=0.039;0.021)
  - This was consistent with the 100 mg OL arm
- ALT increases ≥3 times the upper limit of normal occurred in 0.61% in the resmetirom 80 mg group, 0.31% in the 100 mg group and 1.6% of patients in the placebo group

Madrigal

Harrison SA, et al. EASL 2022

# Thyroid-Receptor Agonist for Fatty Liver

## Fibroscan and MRE, Liver Stiffness Measure (LSM), Change at Week 52




- In this study most patients did not have baseline LSM on FibroScan or MRE that met criteria for analysis
- Although directionally showing a resmetirom treatment effect at 100 mg, mean change was not significantly different for FibroScan LSM
- Responder analyses were conducted to reduce the influence of highly variable (inaccurate) measurements and showed statistically significant response in resmetirom compared with placebo

Madrigal

Harrison SA, et al. EASL 2022

# Thyroid-Receptor Agonist for Fatty Liver

## Safety Double-Blind Arms

| Safety population | Resmetirom 80 mg n=327 | Resmetirom 100 mg n=324 | Placebo n=318 |
|---|---|---|---|
| **At least one TEAE** | **289 (88.4)** | **279 (86.1)** | **260 (81.8)** |
| Grade 1 | 99 (30.3) | 99 (30.6) | 92 (28.9) |
| Grade 2 | 164 (50.2) | 151 (46.6) | 139 (43.7) |
| TEAE ≥ Grade 3 Severity | 25 (7.6) | 29 (9.0) | 29 (9.1) |
| Related TEAE >= Grade 3 Severity | 1(0.3) | 1(0.3) | 2 (0.6) |
| **At least one Serious TEAE** | **20 (6.1)** | **24 (7.4)** | **20 (6.3)** |
| **AE discontinuations from study** | **8 (2.4)** | **9 (2.8)** | **4 (1.3)** |
| **Related AE discontinuations from study** | **5 (1.5)** | **6 (1.9)** | **3 (0.9)** |
| GI AE discontinuations from study | 5 (1.5) | 6 (1.9) | 2 (0.6) |

- In the 100 mg resmetirom open-label arm, 94% & 89% completed key efficacy endpoints at Weeks 24 & 52, respectively
- Drop-out rate due to AEs was 1.2%
- Most frequent AEs- GI Related (Diarrhea and Nausea)- Consistent with the Phase 2 study & MAESTRO-NAFLD-1 open-label arm, no increase in incidence of GI-related AEs after first 12 weeks of resmetirom treatment. Females had higher incidence of early nausea
- Consistent with Phase 2 data, minimal reduction in prohormone free T4 (due to liver effect) & no effect on active hormone free T3 or TSH

Madrigal

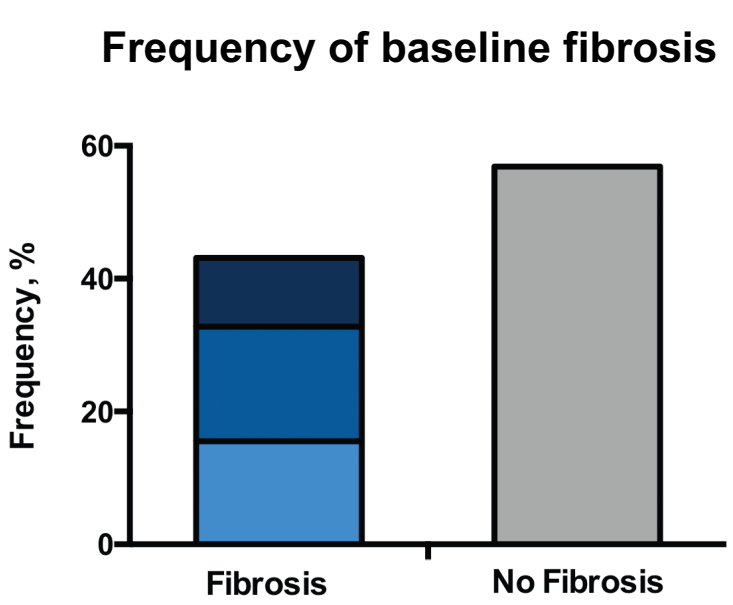
Harrison SA, et al. EASL 2022

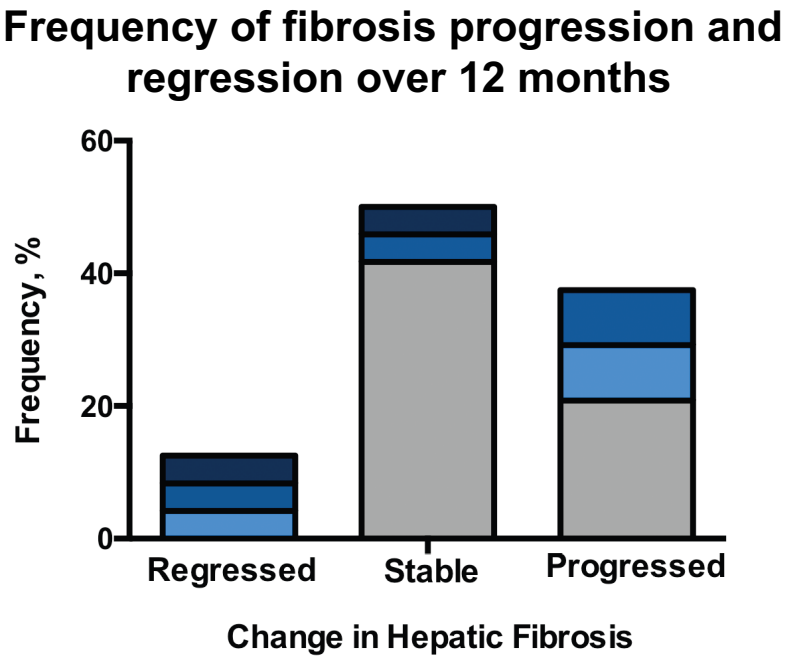
# Risk Factors for HIV-Specific Nonalcoholic Fatty Liver Disease

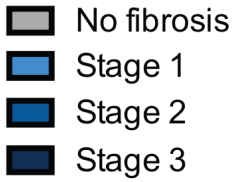
- Metabolic syndrome (hypertension, dyslipidemia, increased waist circumference, insulin resistance)
- HIV-related lipodystrophy
- Hyperuricemia
- Combination antiretroviral therapy
- HIV virus
- Gut microbiome

Seth A & Sherman KE. *Topics in Antiviral Medicine* 2019

# Frequency of liver fibrosis presence and progression in HIV - NAFLD



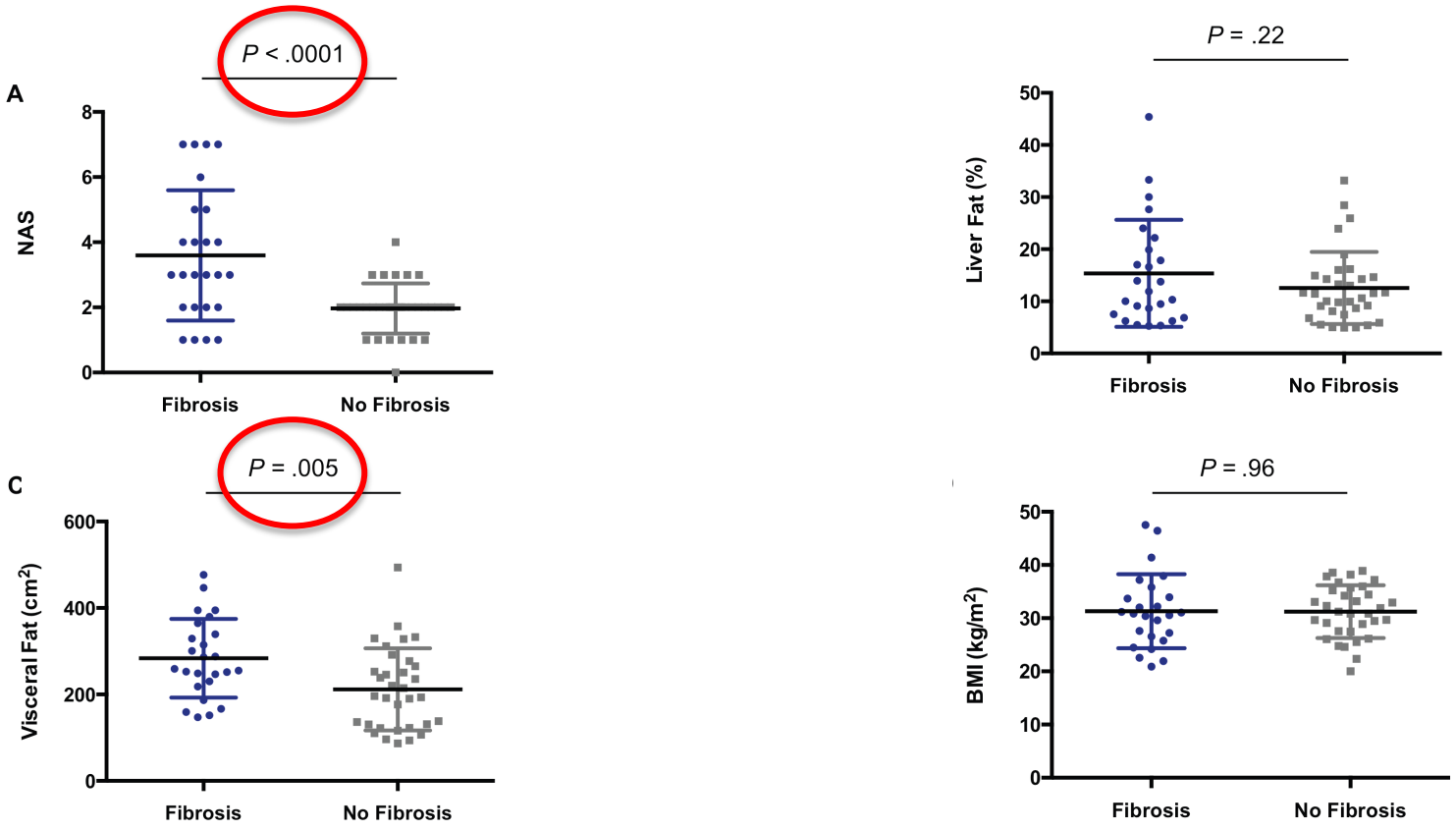




Participants with stage 4 fibrosis or clinical cirrhosis were excluded from study participation.

Fourman LT, et al. *Clinical Infectious Diseases* 2021

# Relationship of key baseline characteristics to presence of liver fibrosis in HIV–NAFLD

Baseline NAFLD Activity Score (**NAS**) higher in individuals with vs without baseline hepatic fibrosis (3.6 ± 2.0 vs 2.0 ± 0.8; *P* < .0001). **Baseline visceral fat** content higher in individuals with vs without baseline hepatic fibrosis (284 ± 91 cm2 vs 212 ± 95 cm2; *P* = .005).

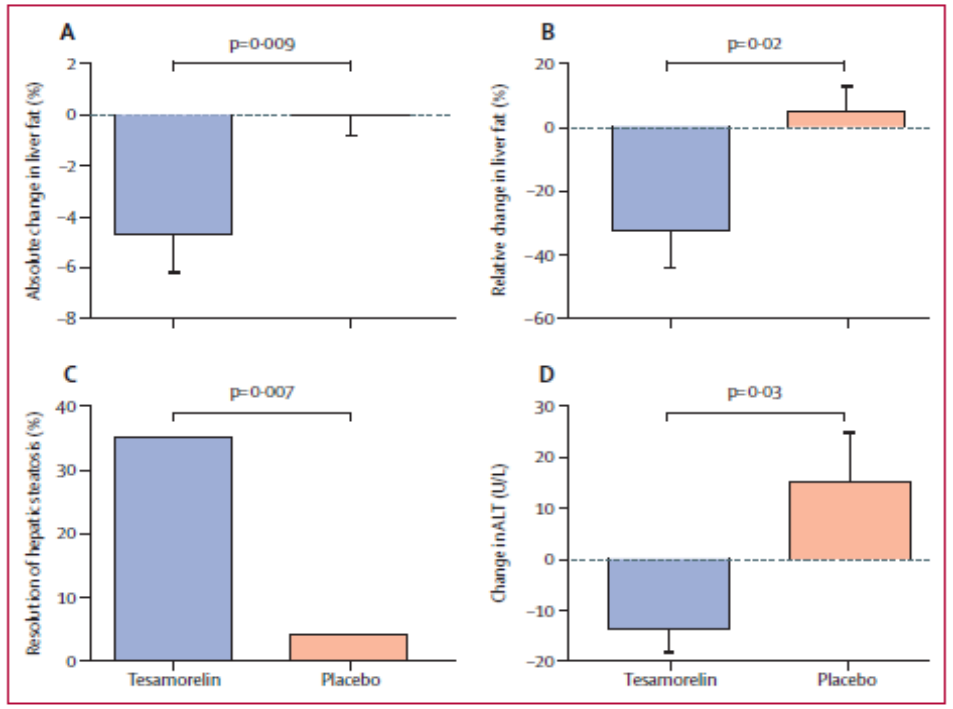



Fourman LT, et al. *Clinical Infectious Diseases* 2021

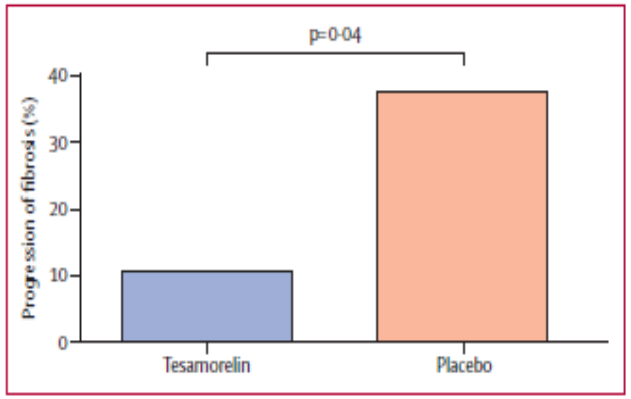
# Tesamorelin may play a major role in treating HIV-fatty liver

- **Tesamorelin is a growth hormone-releasing hormone (GHRH)**
- **Participants randomly assigned (1:1) to receive either tesamorelin 2 mg subcutaneously once daily or placebo once daily for 12 months.**

**Change in Hepatic Fat Fraction, ALT, and resolution of steatosis between baseline and 12 months**




**Proportion of patients with Any progression of fibrosis**




Stanley T, et al. *Lancet HIV* 2019

# Conclusions

1. Innovative strategies will help us eliminate hepatitis C, but it will take a multidisciplinary approach
2. Hepatitis C treatment is highly effective and tolerable.  Strategies exist to retreat those uncommon individuals who do not respond to initial therapy. Describe why eliminating hepatitis C (HCV) is important for public health
3. The relative importance of fatty liver disease as a major cause of liver cancer and chronic liver disease continues to emerge
4. Routine blood work can identify who among those with fatty liver are at risk of progressive liver disease
5. Patients with HIV are increased risk of fatty liver
6. Therapies for fatty liver are expected next year