

Exploring the New Landscape of Hepatitis C Therapy

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Disclosure Information

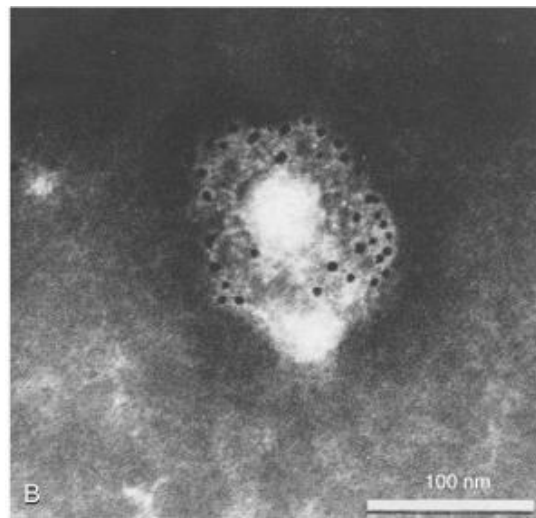
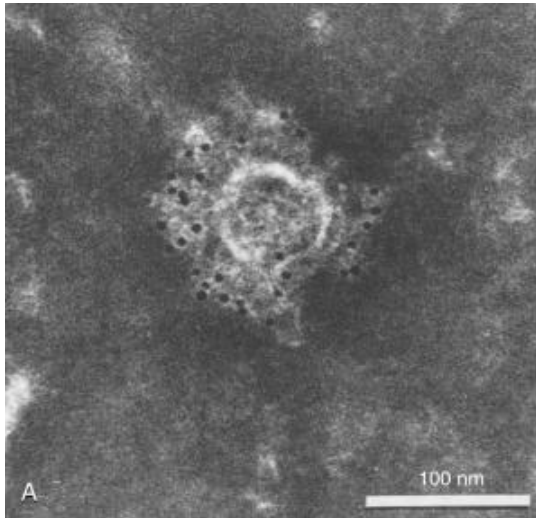
ACOI Annual Convention and Scientific Sessions

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HCV Virus



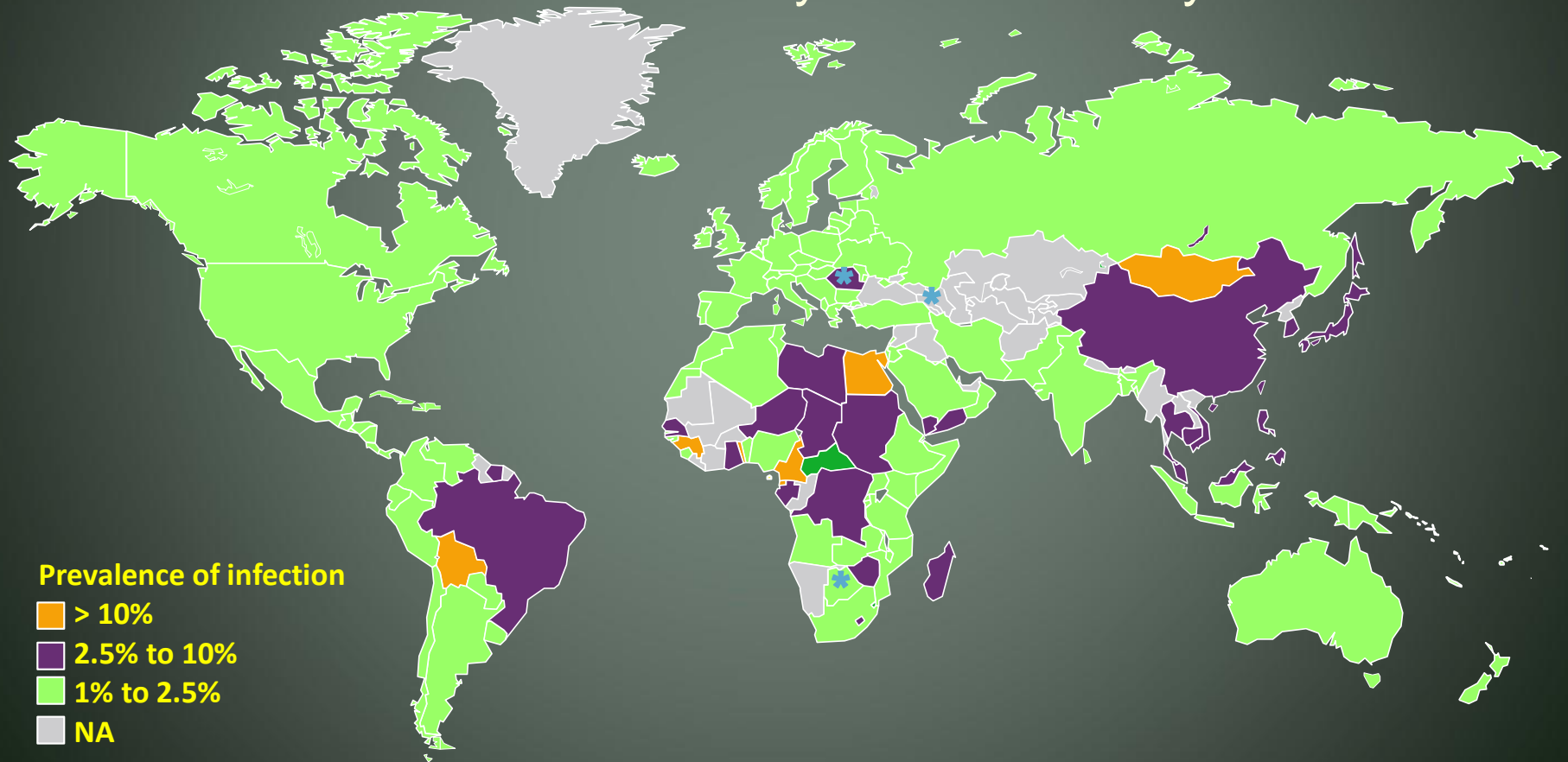
- RNA virus
 - Positive strand
 - 55nm diameter
 - Family Flaviviridae,
Genus Hepacivirus
 - Related genus Flavivirus-
Dengue, Yellow Fever
 - In vivo replication: liver
and lymphocytes

A and B, Electron microscopic images of hepatitis C virus (HCV) virions concentrated from human plasma by high-speed centrifugation. The virions are identified by staining with gold-labeled antibodies to the HCV envelope proteins.

(From Kaito M, Watanabe S, Tsukiyama-Koham K, et al. Hepatitis C virus particle detected by immunoelectron microscopic study. J Gen Virol. 1994;75:1755-1760.)

HCV Infection Worldwide

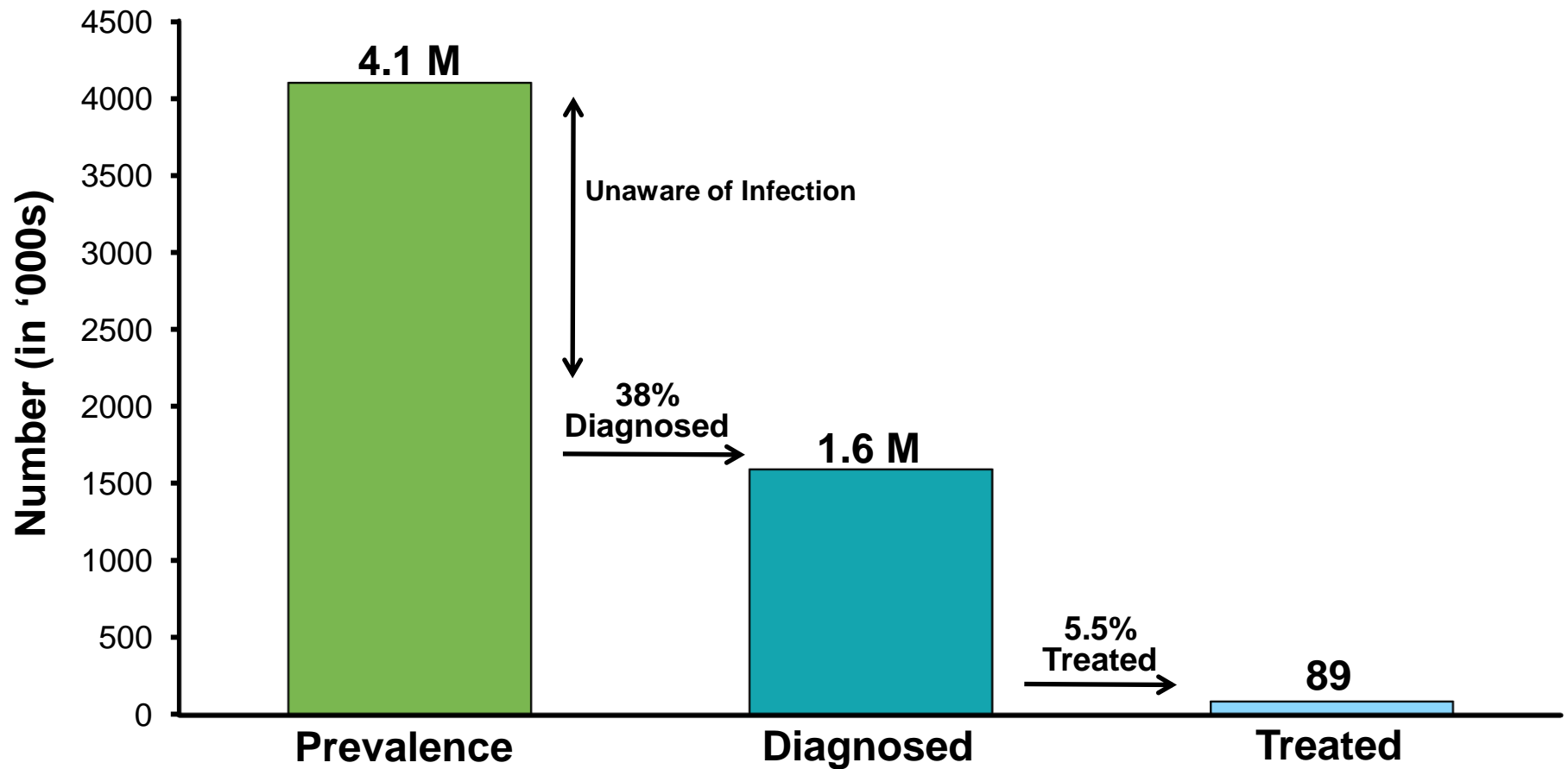
- 200 million persons with HCV
- 3-4 million newly infected each year



HCV Infection

- 200 million Chronic Infections Worldwide
 - 2% of worlds population
 - 75% of people unaware of status
- ~5 millions Americans infected with HCV
 - 45-85% are unaware they are infected

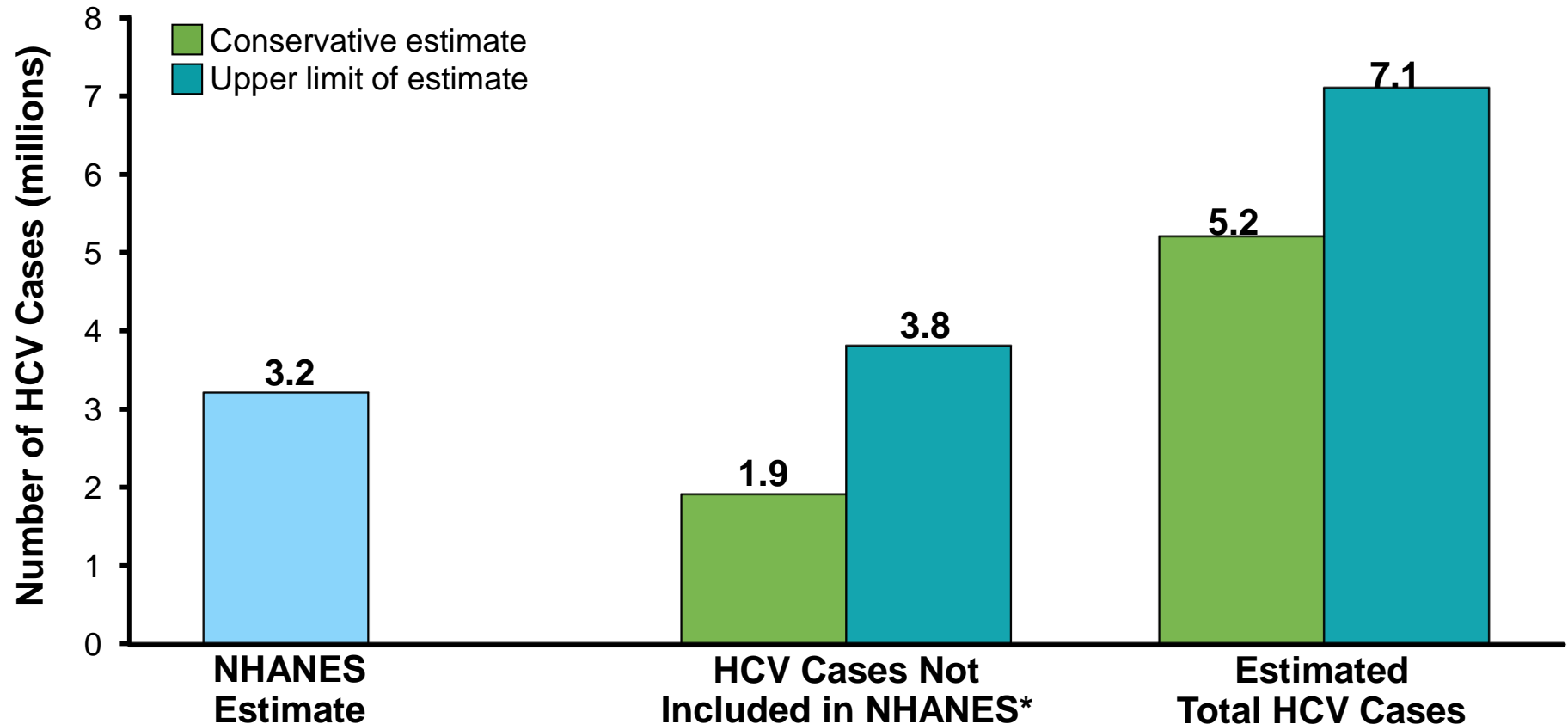
Chronic HCV in the US: Underdiagnosed and Untreated



Estimated treatment rate is based on Q2 and Q4 2011 chart audits.

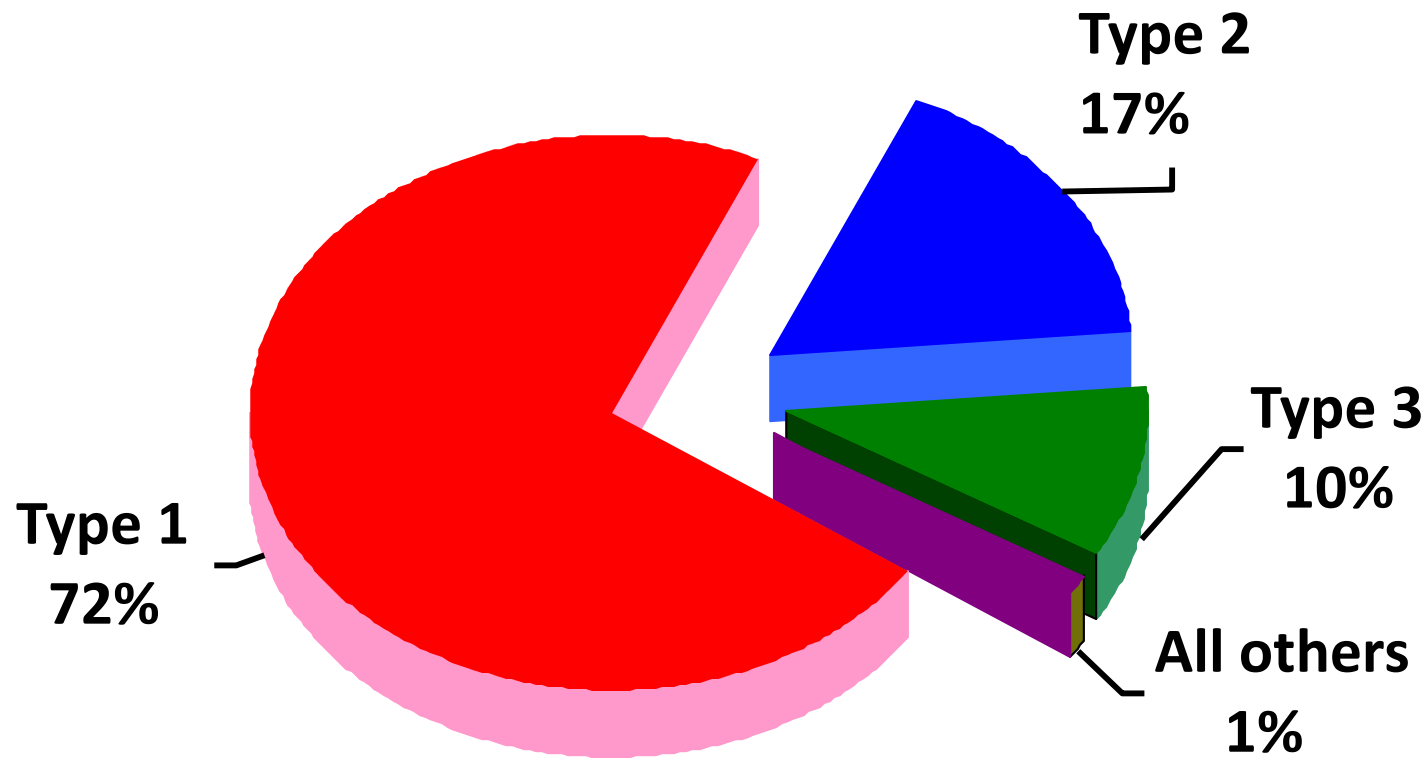
Hepatitis C Monitor. Ipsos Healthcare.

Over 5.2 Million People Living With Chronic HCV in the US

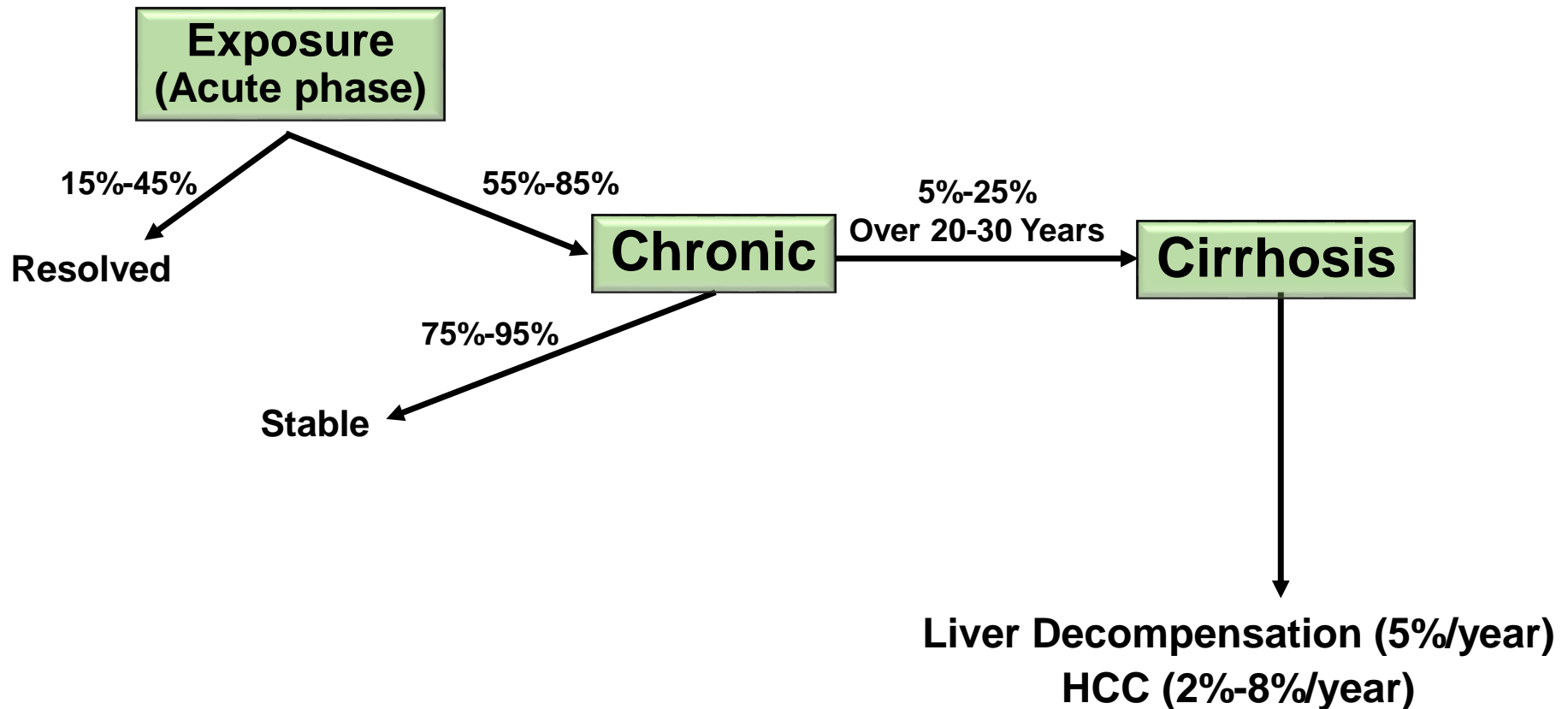


*Homeless (n=142,761-337,6100); incarcerated (n=372,754-664,826); veterans (n=1,237,461-2,452,006); active military (n=6805); healthcare workers (n=64,809-259,234); nursing home residents (n=63,609); chronic hemodialysis (n=20,578); hemophiliacs (n=12,971-17,000).

Hepatitis C Virus *Genotypes in the USA*



Chronic HCV Infection: Natural History



Clinical Considerations on the Progression of HCV Infection

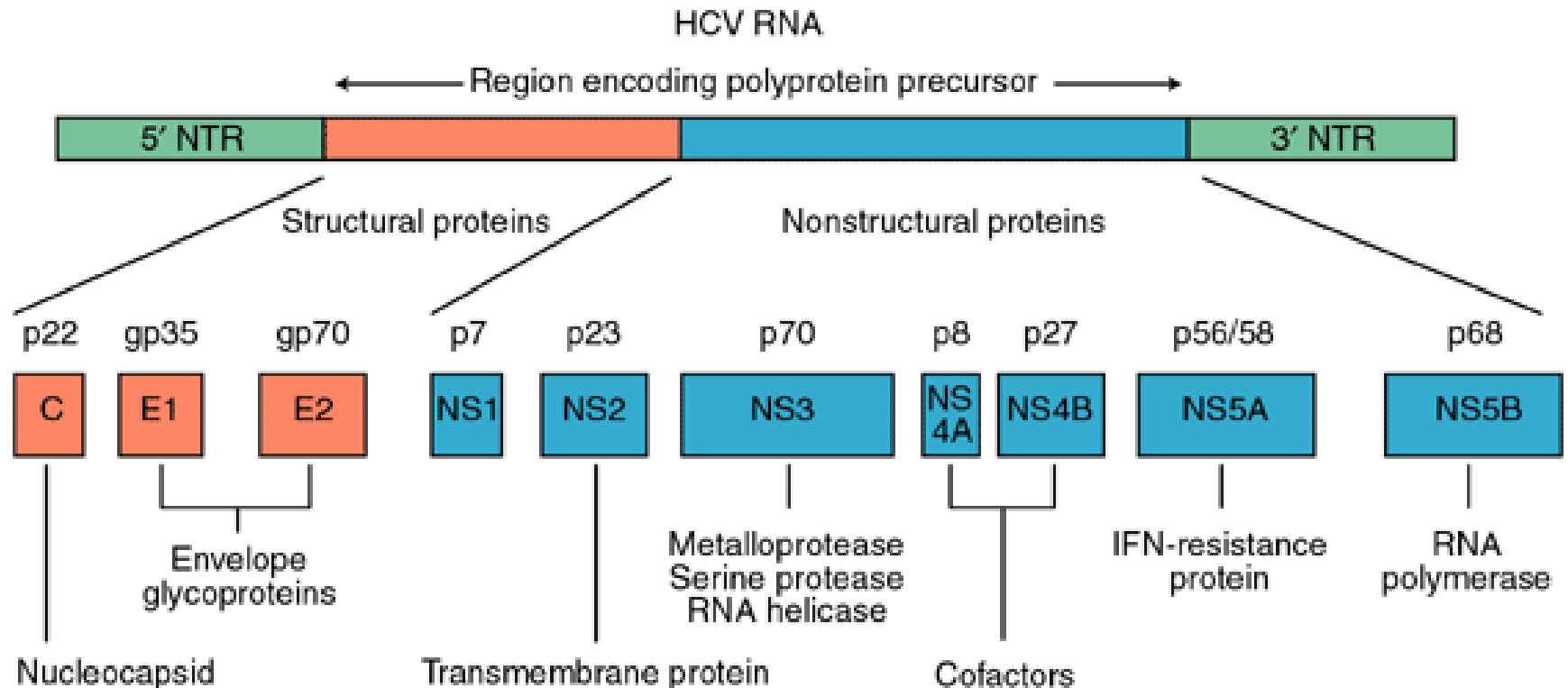
- Of every 100 persons infected with HCV, approximately
 - 75% to 85% will develop chronic infection
 - 60% to 70% will develop chronic liver disease
 - 5% to 20% will develop cirrhosis in 20 to 30 years
 - 1% to 5% will die from the consequences of chronic infection (liver cancer or cirrhosis)

Risk Factors for Progressive Fibrosis and Cirrhosis

- Persistently elevated ALT levels
- Longer duration of infection
- Alcohol excess (>50 g/day)
- Age >40 years at time of infection
- HIV or HBV coinfection
- High BMI
- Male gender

HCV genome

b Proteins encoded by the HCV genome

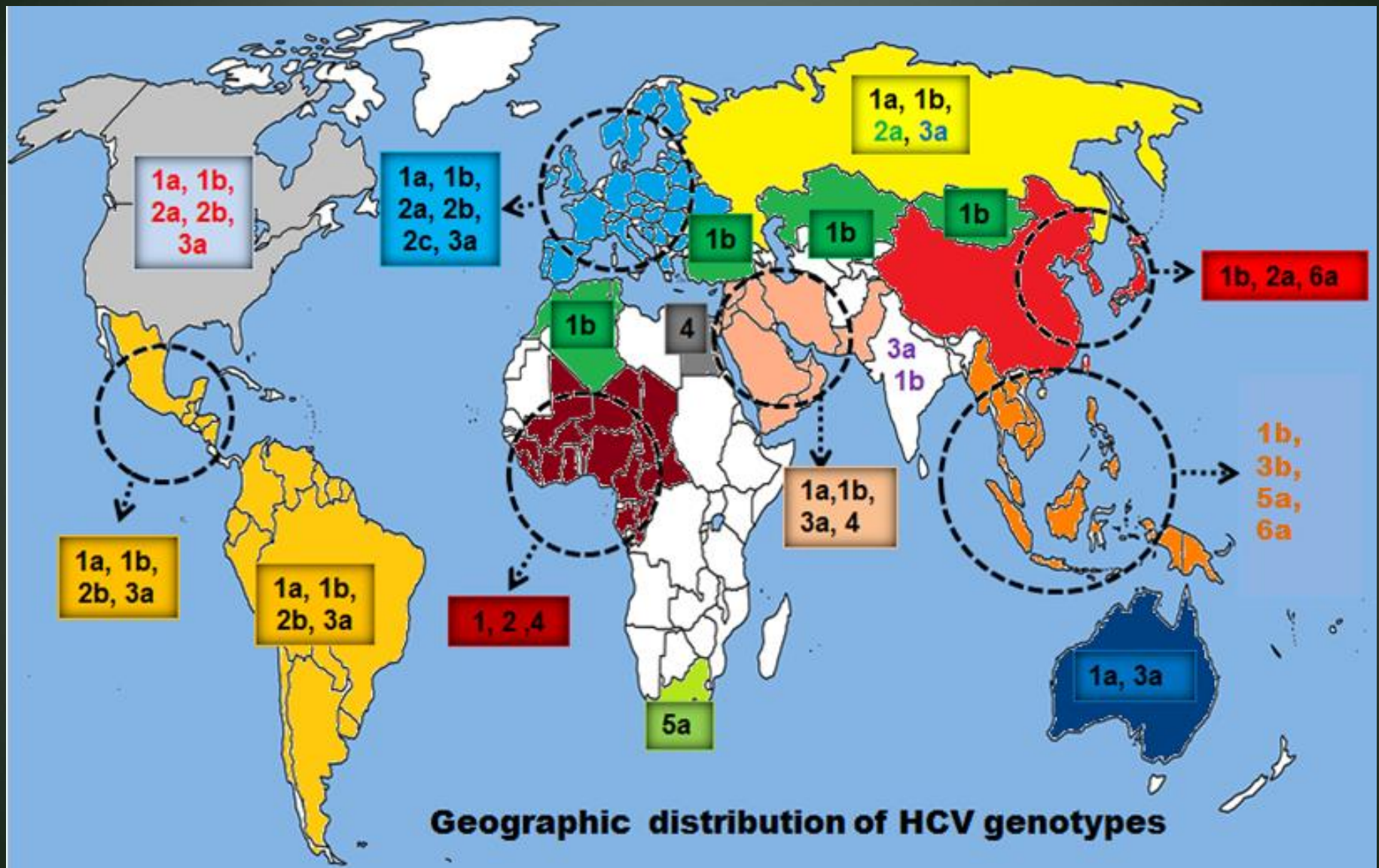


Hepatitis C virus (HCV): model structure and genome organisation

Expert Reviews in Molecular Medicine ©2003 Cambridge University Press

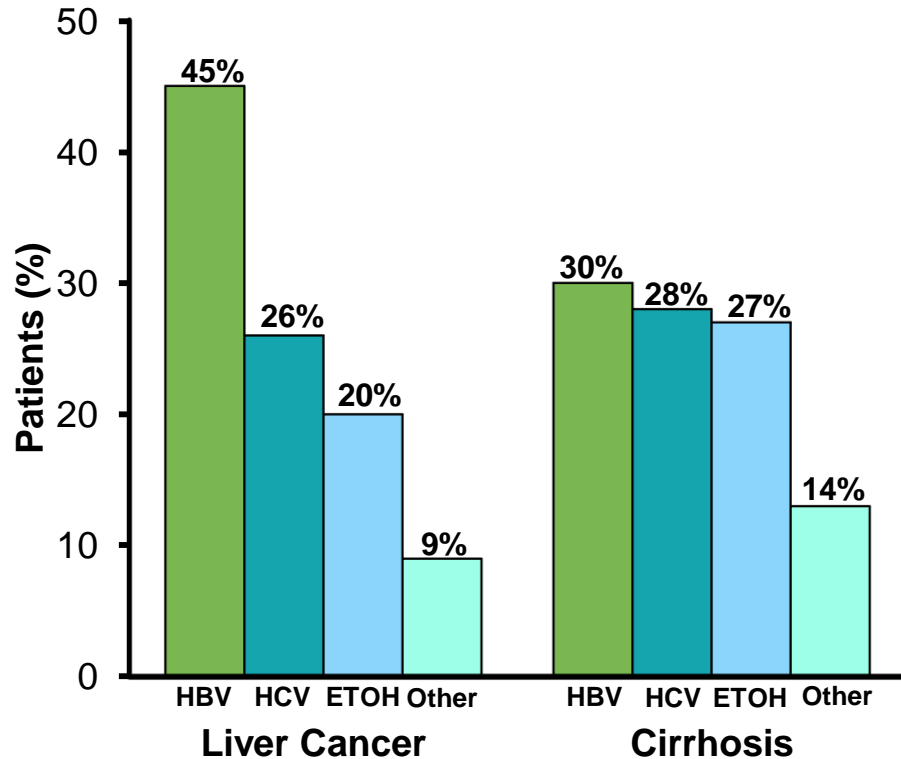
Hepatitis C Has High Viral Diversity

- HCV replicates at high levels (>10 trillion virions/day)
- Lack of error correction leads to drift
- Drift is observed in two forms
 - Quasispecies
 - Genotypes (1-7)

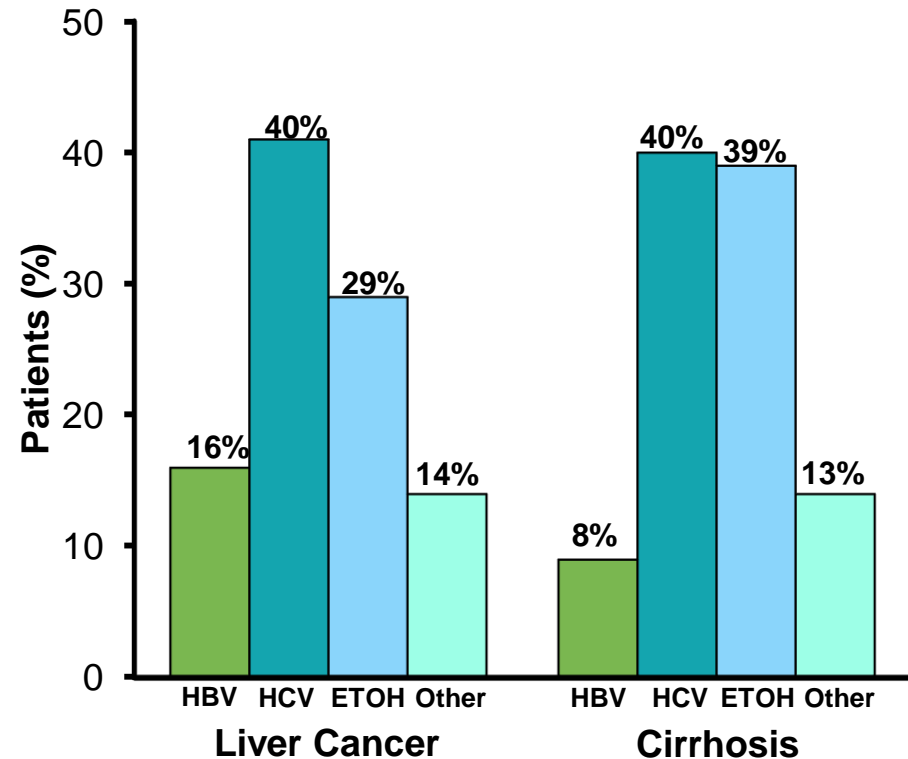


Global Burden of Disease Study 2010: Causes of Death From Chronic Liver Disease

Global 2010



USA 2010



Increase in liver-cancer deaths (past 20 years):
Globally (from 1.25 to 1.75 million/year); USA (45,000 to 70,000/year).

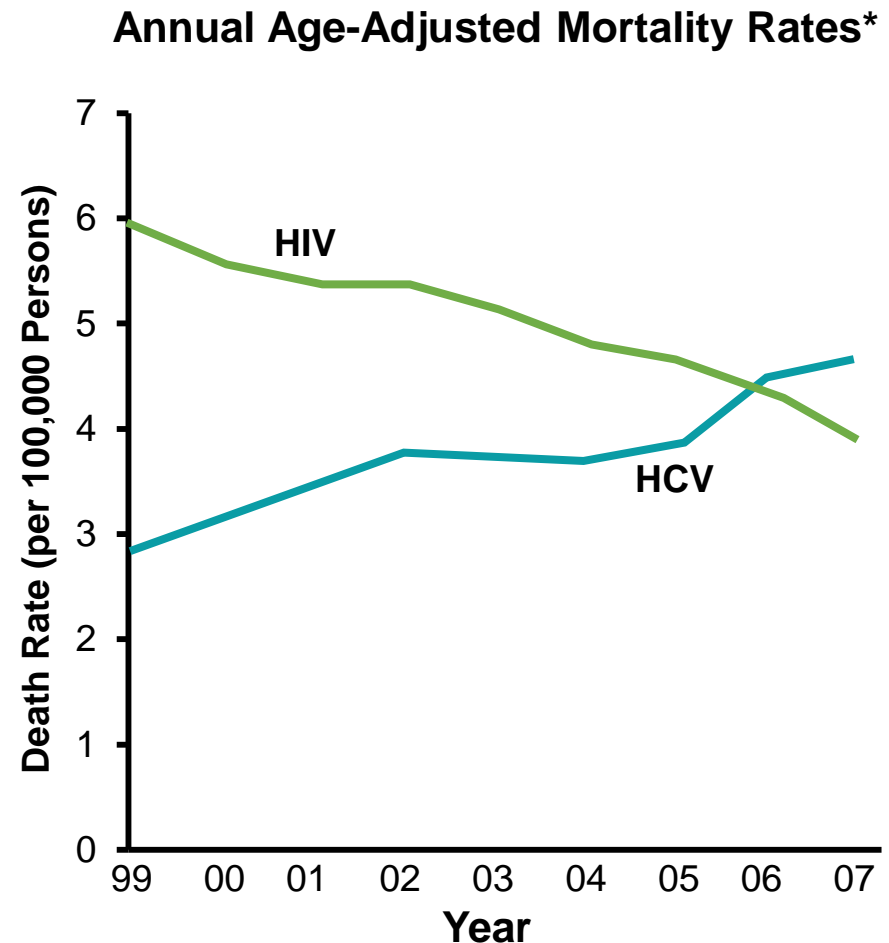
Cowie BC, et al. *Hepatology*. 2013;58(suppl 1):218A-219A. Abstract 23.

Extrahepatic Manifestations of Chronic HCV Infection

- Arthralgia
- Arthritis
- Behcet's disease
- Canities
- Cerebral vasculitis
- Cryoglobulinemia
- Diabetes
- Fatigue
- Fibromyalgia
- Hypertrophic cardiomyopathy
- Immune thrombocytopenic purpura
- Insulin resistance
- Lichen myxoedematosus and planus
- Lung abnormalities
- Membranoproliferative glomerulonephritis
- Membrane nephropathy
- Mooren corneal ulceration
- Multiple myeloma
- Neutropenia
- Non-Hodgkin's lymphoma
- Paresthesia
- Porphyria cutanea tarda
- Pruritus
- Raynaud's syndrome
- Sialadenitis
- Sjogren's syndrome
- Spider nevi
- Systemic lupus erthematosus
- Thrombocytopenia
- Thyroid disease
- Vasculitis
- Vitiligo
- Waldenstrom macroglobulinemia

HCV and HIV Mortality in the US (1999-2007)

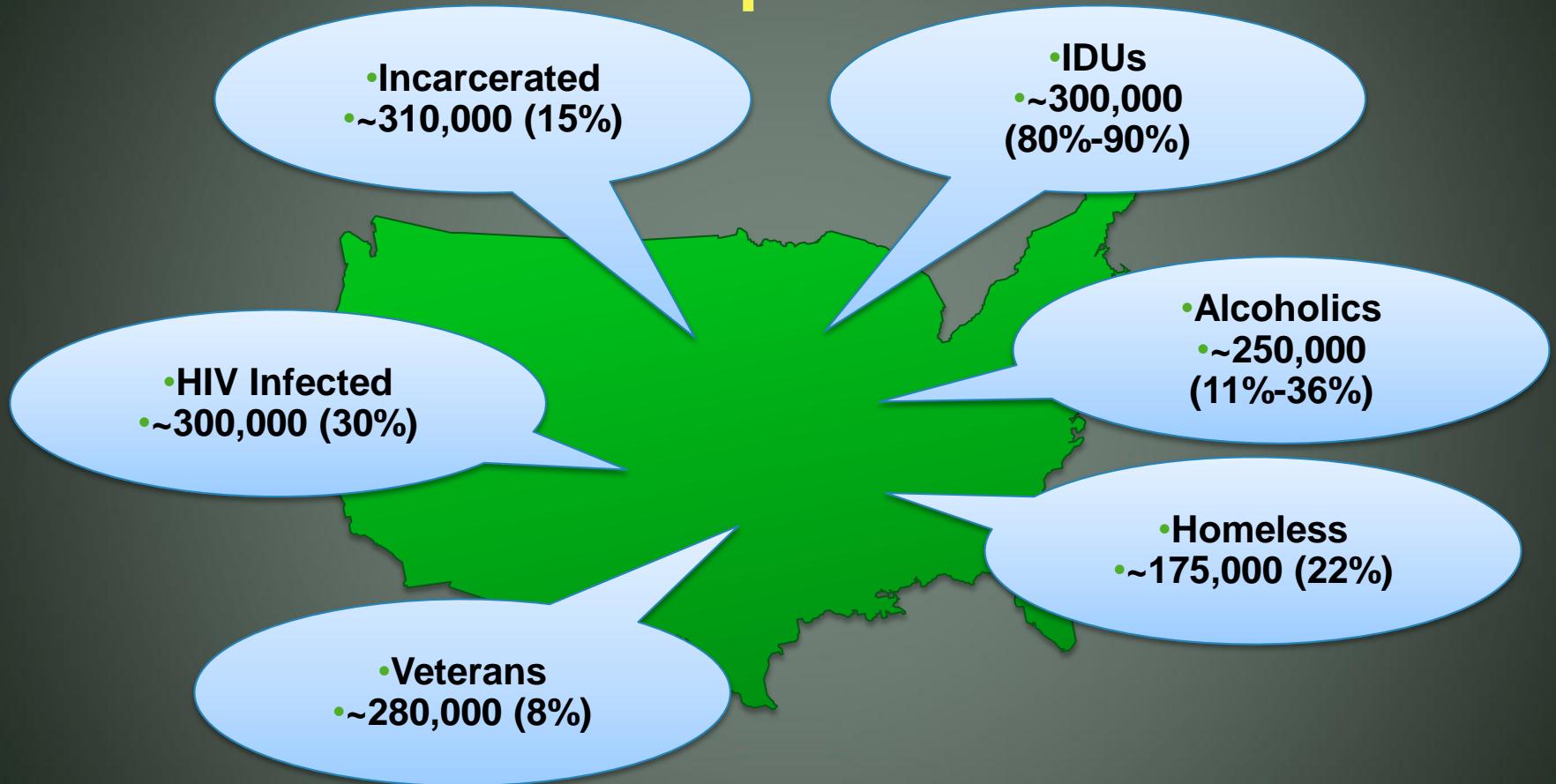
- US multiple-cause mortality data (NCHS, 50 states plus DC)
 - Death certificate data
 - Approximately 21.8 million decedents
- Change in age-adjusted mortality rates (per 100,000 person-years)
 - HCV: increased 0.18 ($P=0.002$)
 - HIV: decreased 0.21 ($P=0.001$)
- **New policy initiatives are needed to detect and link HCV patients to care and treatment**



NCHS: National Center for Health Statistics.

*A record listing >1 type of infection was counted for each type of infection.

HCV Prevalence in High-Risk US Populations



• Weinbaum C, et al. MMWR Recomm Rep. 2003;52(RR-1):1-36. Edlin BR. Hepatology. 2002;36(5 suppl 1):210-219. National Survey on Drug Use & Health (NSDUH). NSDUH Report. 2003. Khalili MA, et al. Clin Inf Dis. 2000;31:154-161. LaBreck DR, et al. In: Hepatitis C Choices. 2002. Alter MJ, et al. N Engl J Med. 1999;341(8):556-562. Nyamathi AM, et al. J Gen Intern Med. 2002;17(2):134-143. Bräu N, et al. Am J Gastroenterol. 2002;97(8):2071-2078. Jonas MM. Hepatology. 2002;36(5 suppl 1):S173-S178.

HCV Screening and Testing Recommendations (CDC and AASLD/IDSA)

- HCV testing is recommended at least once for **persons born between 1945 and 1965 (“Baby Boomers”)**
- Other persons should be screened for **risk factors** for HCV infection
- 1-time testing should be performed for all persons with behaviors, exposures, and conditions associated with an increased risk of HCV infection
- Annual HCV testing is recommended
 - Persons who inject drugs
 - HIV-positive MSMs who have unprotected sex
- Periodic testing should be offered to other persons with ongoing risk factors for exposure to HCV

HCV Screening: Behaviors, Exposures, and Conditions Associated With Increased Risk of HCV Infection

- Adults born between 1945 and 1965
- Risk behaviors
 - Past or current injection drug use
 - Intranasal illicit drug use
- Risk exposures
 - Chronic hemodialysis
 - Getting tattoo in an unregulated setting
 - Persons with recognized exposures (needle-sticks, mucosal exposures)
 - Birth to an infected mother
 - Recipients of transfusions or organ transplants before 1992
 - Recipients of clotting factors (prior 1987)
 - Ever incarcerated
- Other medical conditions
 - HIV infection
 - Unexplained chronic liver disease and chronic hepatitis including persistently abnormal ALT

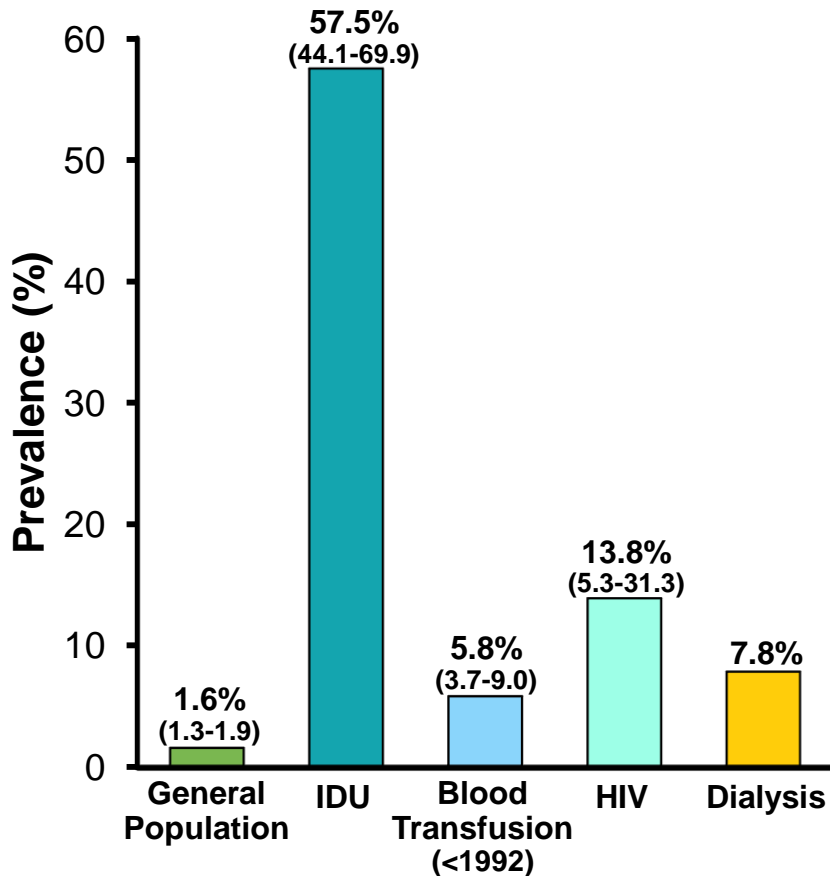
<http://www.cdc.gov/hepatitis/HCV/HCVfaq.htm>.

Centers for Disease Control and Prevention. *MMWR*. 2012;61(RR-4):1-33.

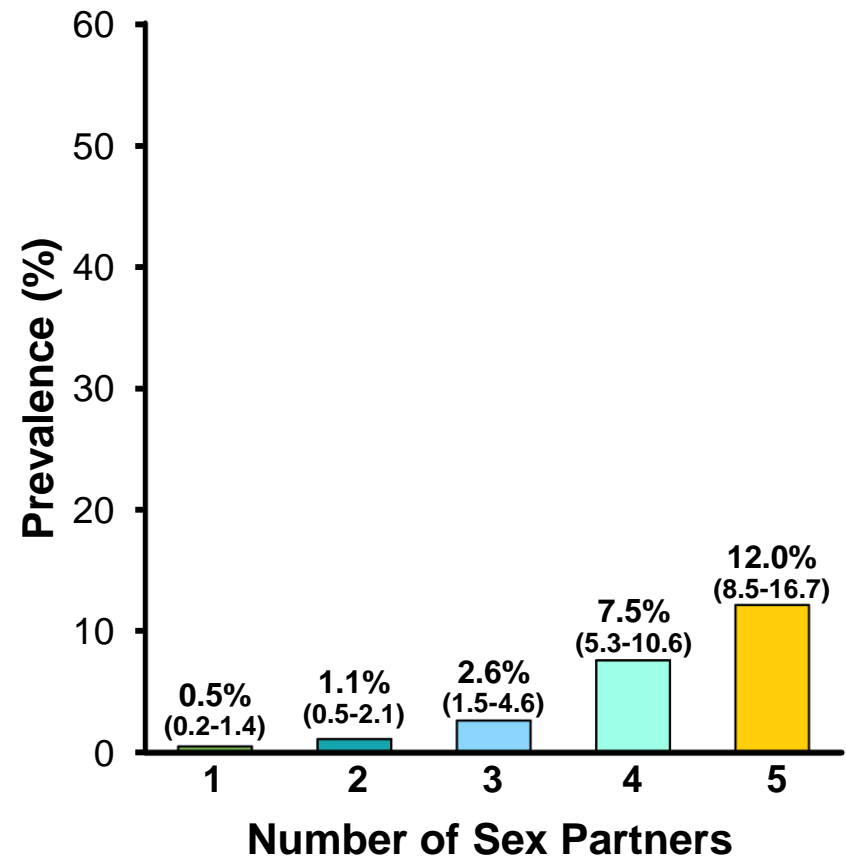
AASLD and IDSA. <http://www.hcvguidelines.org/full-report-view>. Version December 19, 2014.

Prevalence of Antibody to HCV: NHANES (1999-2002)

General Risk Factors



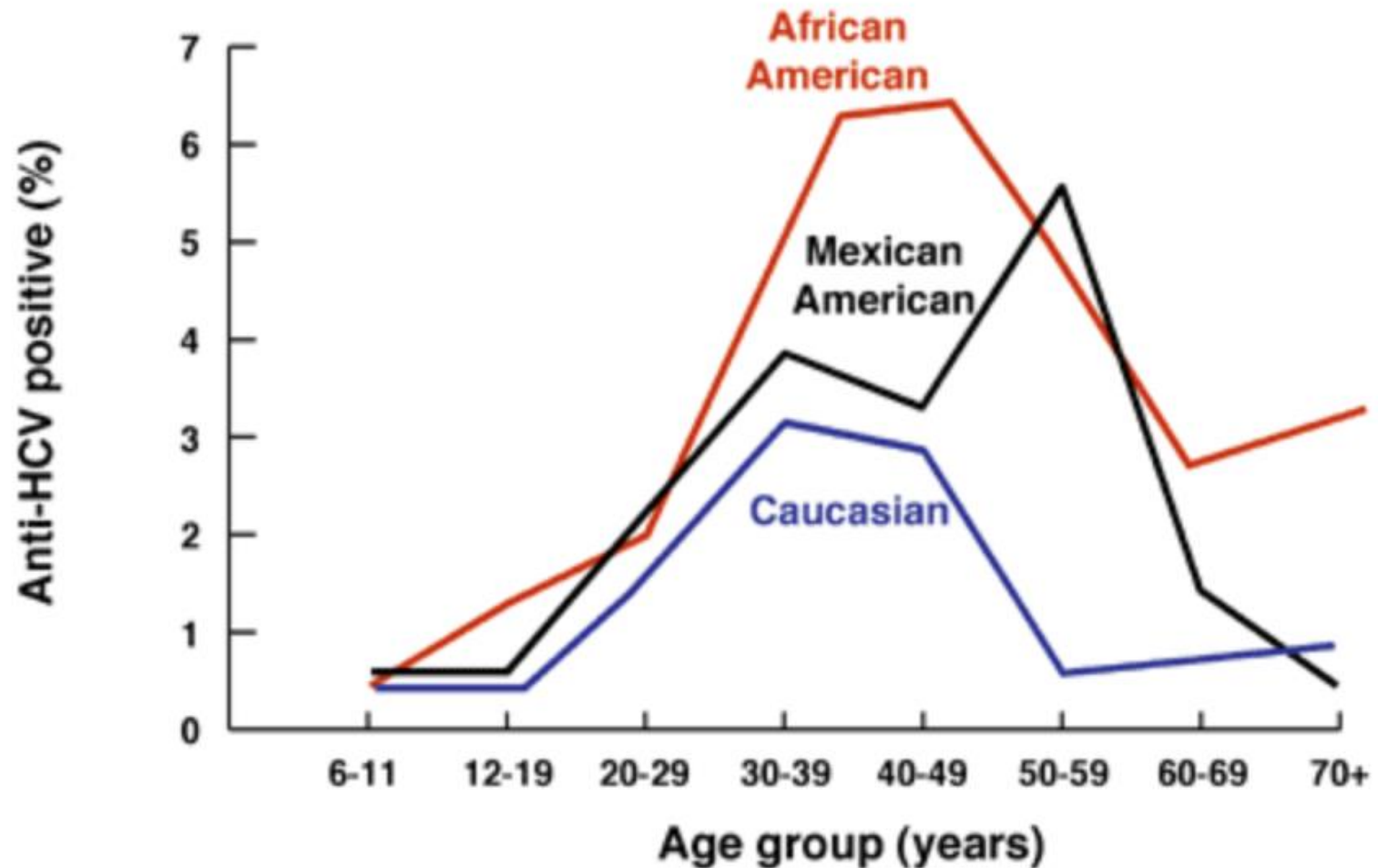
Number of Sex Partners



Recommended Laboratory Tests for Chronic HCV Infection

Test Application	
Hepatitis C antibody by enzyme immunoassay (EIA)	Screening for past or present HCV infection Sensitive and inexpensive
PCR for HCV RNA	Confirmation of positive EIA Medical evaluation and management

Prevalence of HCV Infection by Age and Race/Ethnicity in the United States, 1988-1994



HCV Testing and Linkage to Care

- **US Preventive Services Task Force** Guidelines expanded screening

HCV testing is recommended at least once for persons born between 1945 and 1965.

Rating: Class I, Level B



Accounts for 75% of all HCV infections

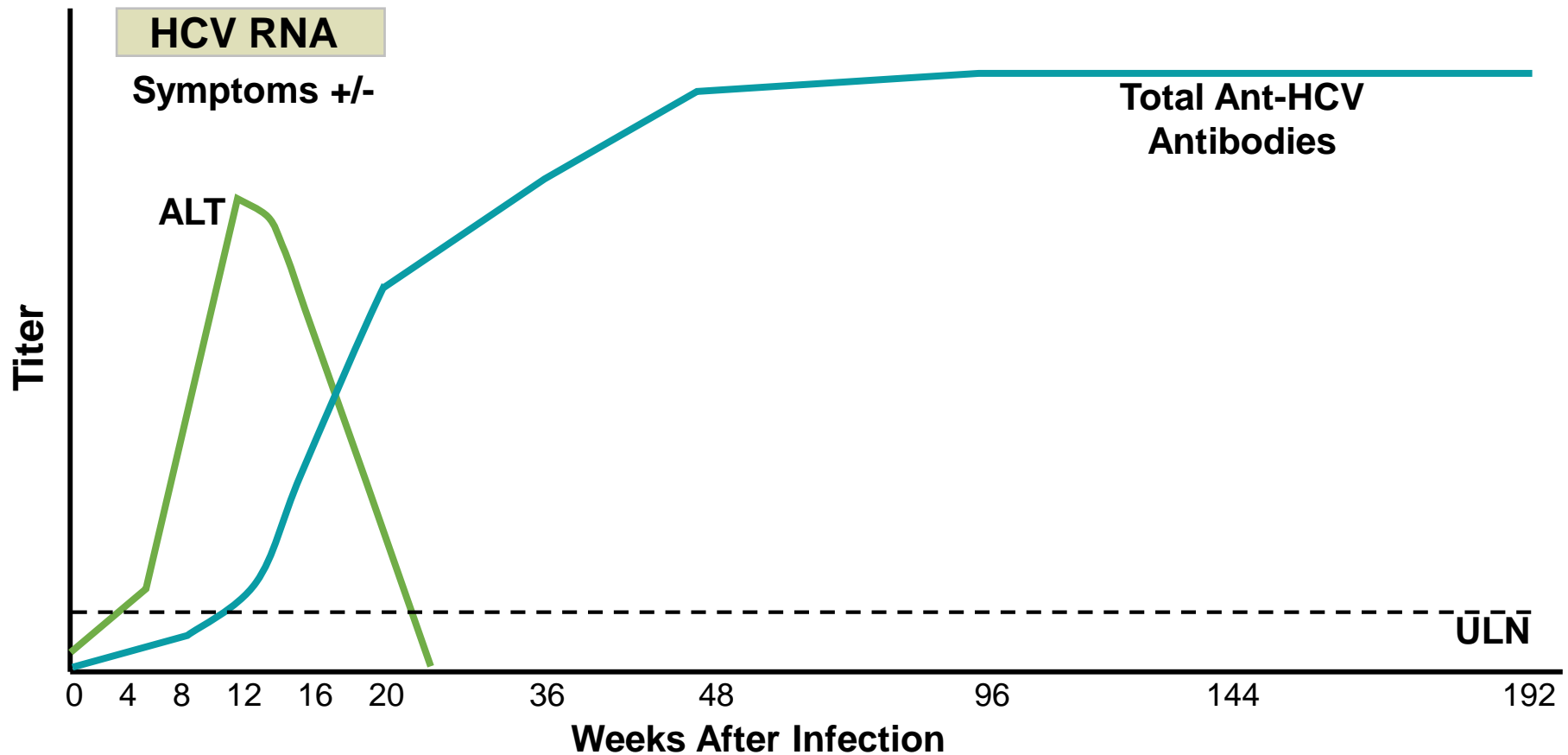
Other persons should be screened for risk factors for HCV infection, and one-time testing should be performed for all persons with behaviors, exposures, and conditions associated with an increased risk of HCV infection.

Rating: Class I, Level B

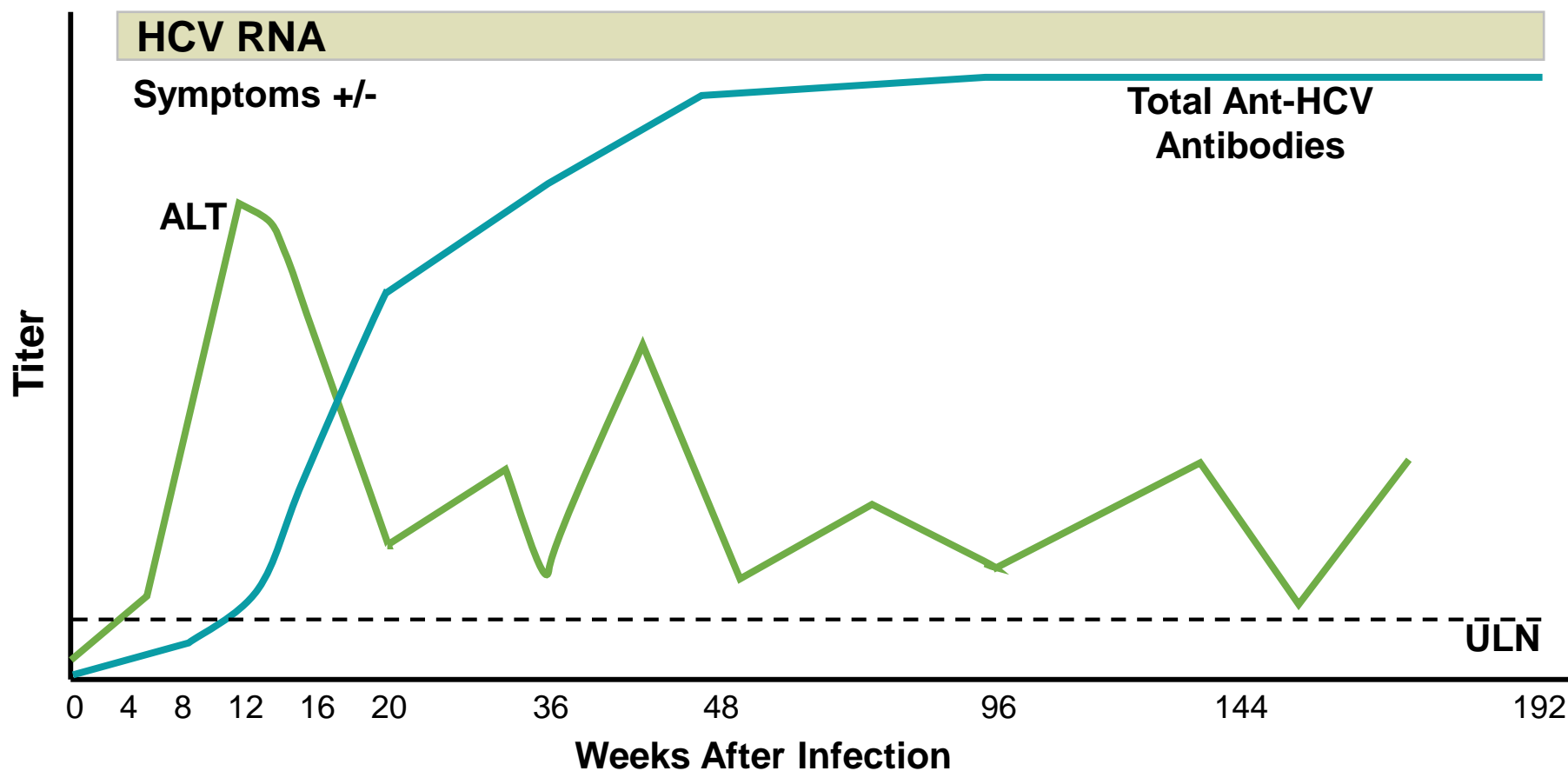
Annual HCV testing is recommended for persons who inject drugs and for HIV-seropositive men who have unprotected sex with men. Periodic testing should be offered to other persons with ongoing risk factors for exposure to HCV.

Rating: Class IIA, Level C

Markers for Acute HCV Infection



Markers for Chronic HCV Infection



ELISA Screening Tests for HCV

- Serologic assays to detect circulating HCV antibodies
- Sensitivity (97% to 100%)
- Positive predictive value
 - 95% with risk factors and elevated ALT
 - 50% without risk factors and normal ALT
- False positives now rare
 - More likely in patients with low risk of HCV infection
- False negatives
 - More likely in severely immunocompromised patients, transplant recipients, patients with chronic renal failure on dialysis, HIV-positive patients

When to Test for HCV RNA (AASLD Recommendation)

- Positive anti-HCV antibody test
- Considering antiviral treatment
 - Use sensitive quantitative assay
- Unexplained liver disease and negative anti-HCV antibody test and who are
 - Immunocompromised
 - Suspected of having acute HCV infection (HCV RNA becomes positive well before anti-HCV antibody test): Consider for known HCV exposures (IVDU, needle sticks, etc.)
- Lab can “reflex” to HCV RNA PCR with positive anti-HCV test
- If HCV RNA positive, consider or refer for treatment

HCV Assays: What the Results Mean

Anti-HCV	HCV RNA	Interpretation
+	+	Acute or chronic HCV depending on the clinical context
+	—	False positive HCV antibody (rare) Resolved infection Low-level intermittent viremia
—	+	Early acute HCV infection Chronic HCV in setting of immunosuppressed state False positive HCV RNA test (rare)
—	—	Absence of HCV infection (no vaccination available)

Counseling HCV-Infected Patients: Avoiding Transmitting HCV to Others

- Items to avoid
 - Sharing toothbrushes and dental or shaving equipment
 - Using illicit drugs
 - Those who continue to inject drugs, avoid reusing or sharing syringes, needles, water, cotton or other paraphernalia. Clean the injection site with a new alcohol swab and dispose of syringes and needles after one use in a safe, puncture-proof container
- Bandage bleeding wounds to prevent contact with others
- Do not donate blood, body organs, other tissue or semen
- Safe, sexual practices
 - Encourage barrier protection for HIV-positive MSMs and those with multiple sexual partners or STIs
 - For others with HCV infection, the risk of sexual transmission of HCV is low

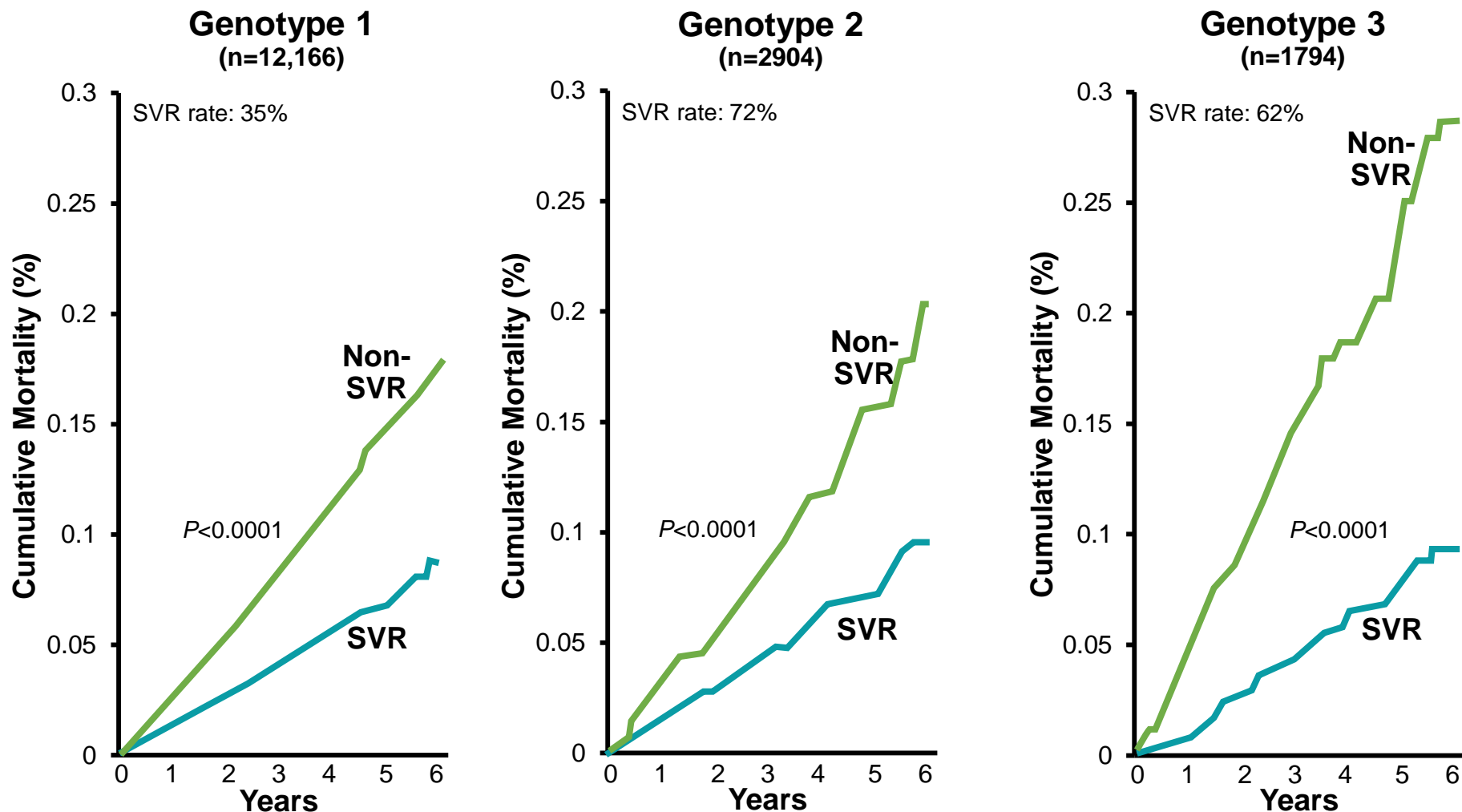
Counseling HCV-Infected Patients: Minimizing Disease Progression

- Avoid alcohol
 - HCV-related fibrosis progression is increased with alcohol consumption >50 g/day
 - Alcohol consumption is associated with increases in HCV RNA levels
- Administer HAV and HBV vaccines as needed
- Consider treatment for chronic HCV infection in ALL patients: Since cure rates are approaching 100% and therapy is relatively brief and generally well tolerated, **there is usually no medical justification for delaying treatment!**
- Some patients with advanced liver disease may need to delay treatment as directed by their liver program.

Achieving a Sustained Virologic Response is Associated With Improved Outcomes

- Sustained viral response
 - Durable
 - 99% stay HCV negative for >10 years
 - Leads to improved histology
 - Leads to clinical benefits
 - Decreased decompensation
 - Prevents de novo esophageal varices
 - Decreased hepatocellular carcinoma
 - Decreased mortality
 - Improves transplant outcomes
 - Prolongs life

SVR is Significantly Associated With Reduction in All-Cause Mortality



Retrospective analysis of veterans who received pegIFN + RBV at any VA medical facility (2001-2008).

Backus LI, et al. *Clin Gastroenterol Hepatol*. 2011;9:509-516.

Advanced Liver Disease: Basic Principles

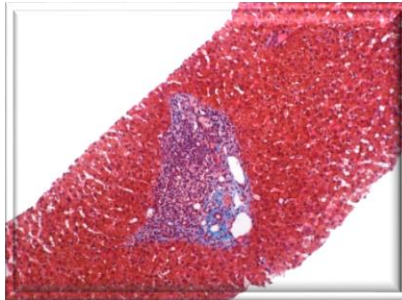
- Hepatic fibrosis is not reliably diagnosed by ultrasound or other imaging modalities
- Liver Biopsy no longer routinely recommended for Hepatitis C therapy decisions
- Liver fibrosis rates are not predictable or linear
- Cirrhosis can be suspected based on imaging and labs (especially platelet count); as many as 40% of HCV patients may be cirrhotic by 2020.
- Progression from compensated cirrhosis to decompensated liver disease occurs in 5% of patients per year
- Hepatocellular carcinoma (HCC) develops in 1% to 2% of patients with hepatitis-related cirrhosis each year
- Patients who are cirrhotic or nearly cirrhotic need long term surveillance even when cured of their HCV (US and AFP q 6 months)

Progression of Fibrosis in Viral Hepatitis on Biopsy (Metavir)

No Fibrosis

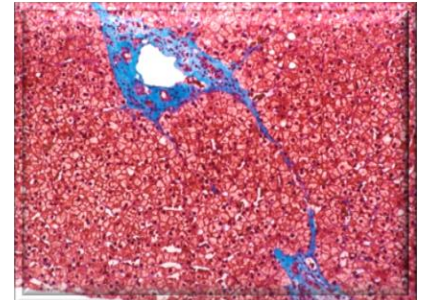


Stage 1



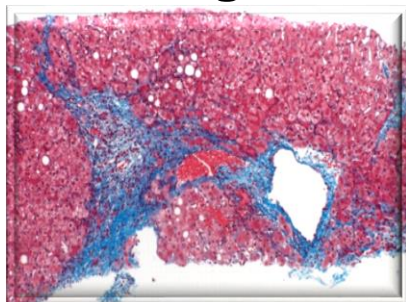
Fibrous expansion of some portal areas

Stage 2



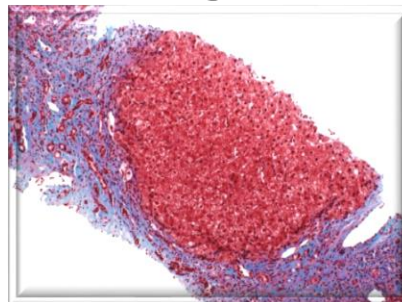
Fibrous expansion of most portal areas with occasional portal to portal bridging

Stage 3



Fibrous expansion of portal areas with marked bridging (portal-to-portal and portal-to-central)

Stage 4



Cirrhosis



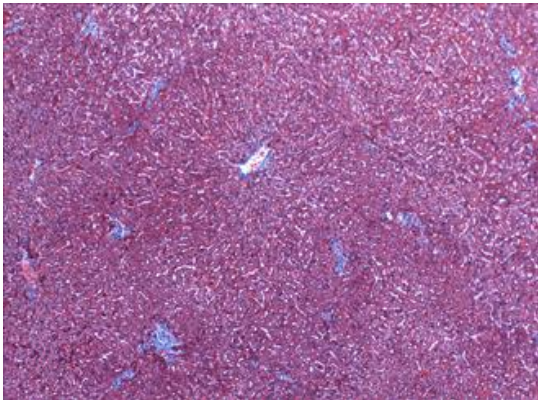
Cirrhotic Liver

Unfortunately, some payers and guidelines are still improperly restricting access to only F3 and F4 patients

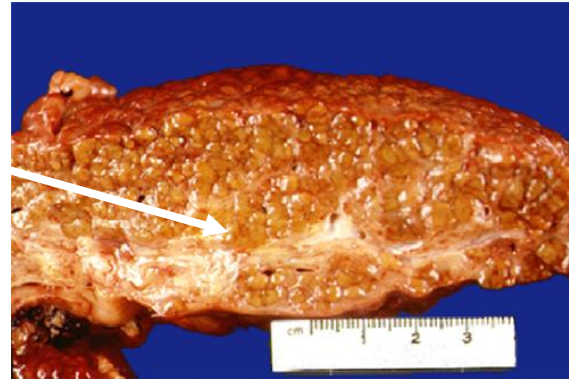
Normal (F0)



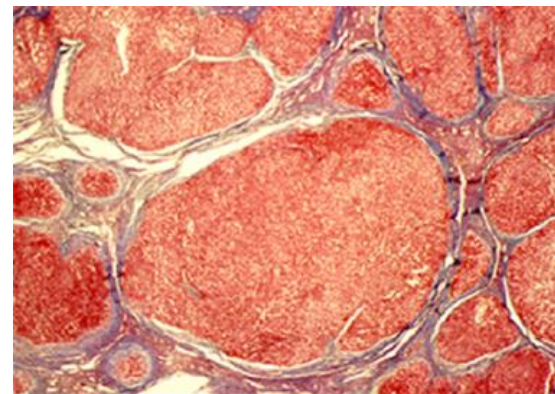
Nodules



Cirrhosis (F4)



Irregular
surface



Nodules
surrounded by
fibrous tissue

Transient Elastography (Fibroscan®)



- Non invasive liver stiffness measurement
- Received 510(k) clearance from FDA on April 5, 2013
- Manufactured by Echosens (Paris)
- Distributed in the United States by Sandhill Scientific, Inc.

Transient Elastography (Fibroscan®)

- Works by measuring deformation of tissue caused by mechanical compression
- Non-invasive
- High concordance with biopsy
- Fibroscan® eliminates the need for biopsy in some patients

Transient Elastography (Fibroscan®)

- Technical limitations of transient elastography
 - Testing cannot be performed in all patients
 - Either the test cannot be performed or the results are unreliable in patients who:
 - Have ascites
 - Are morbidly obese
 - Have large amounts of chest wall fat

FibroScan “Elastography”

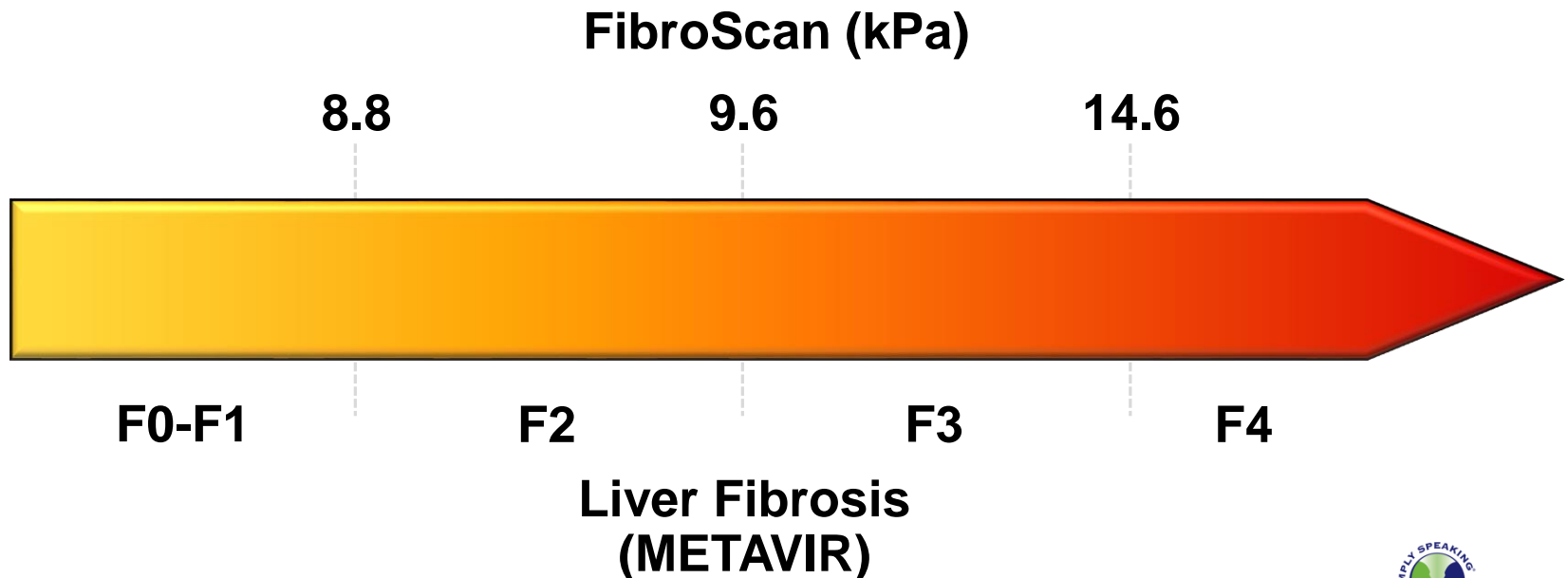


The probe induces an elastic wave through the liver

The velocity of the wave is evaluated in a region located from 2.5 to 6.5 cm below the skin surface

Diagnostic accuracy:

- Significant fibrosis: 0.79
- Advanced fibrosis: 0.91
- Cirrhosis: 0.97





SuperSonic Aixplorer Ultrasound

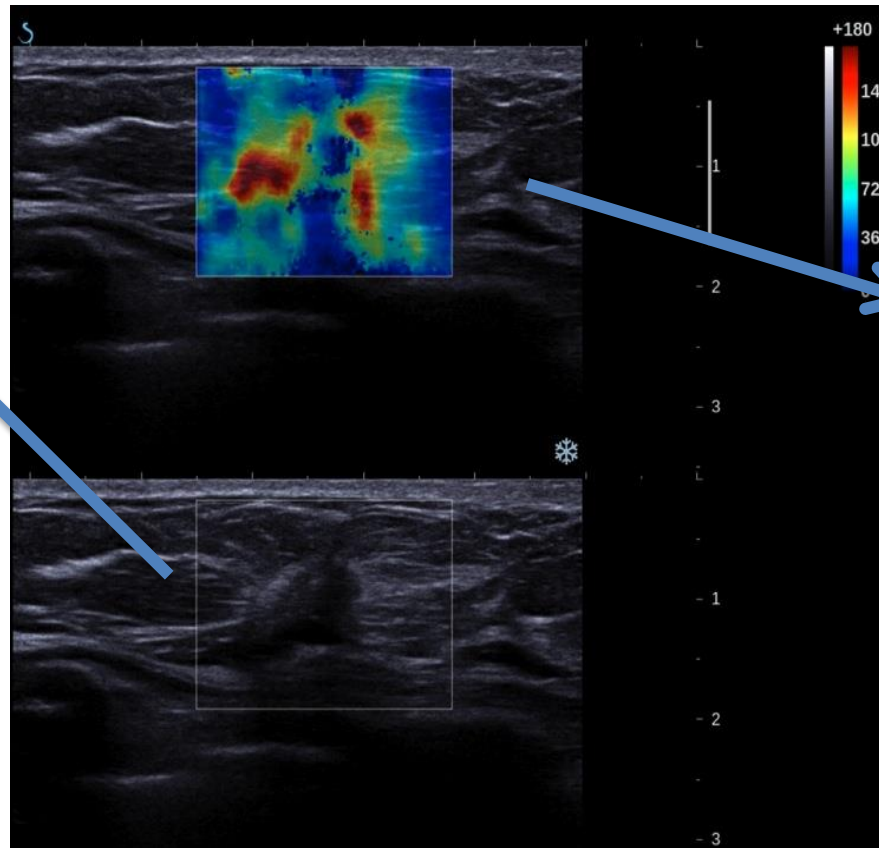


MultiWave™ Technology

Two waves to better characterize tissue :

**One
Ultrasound
Wave :**

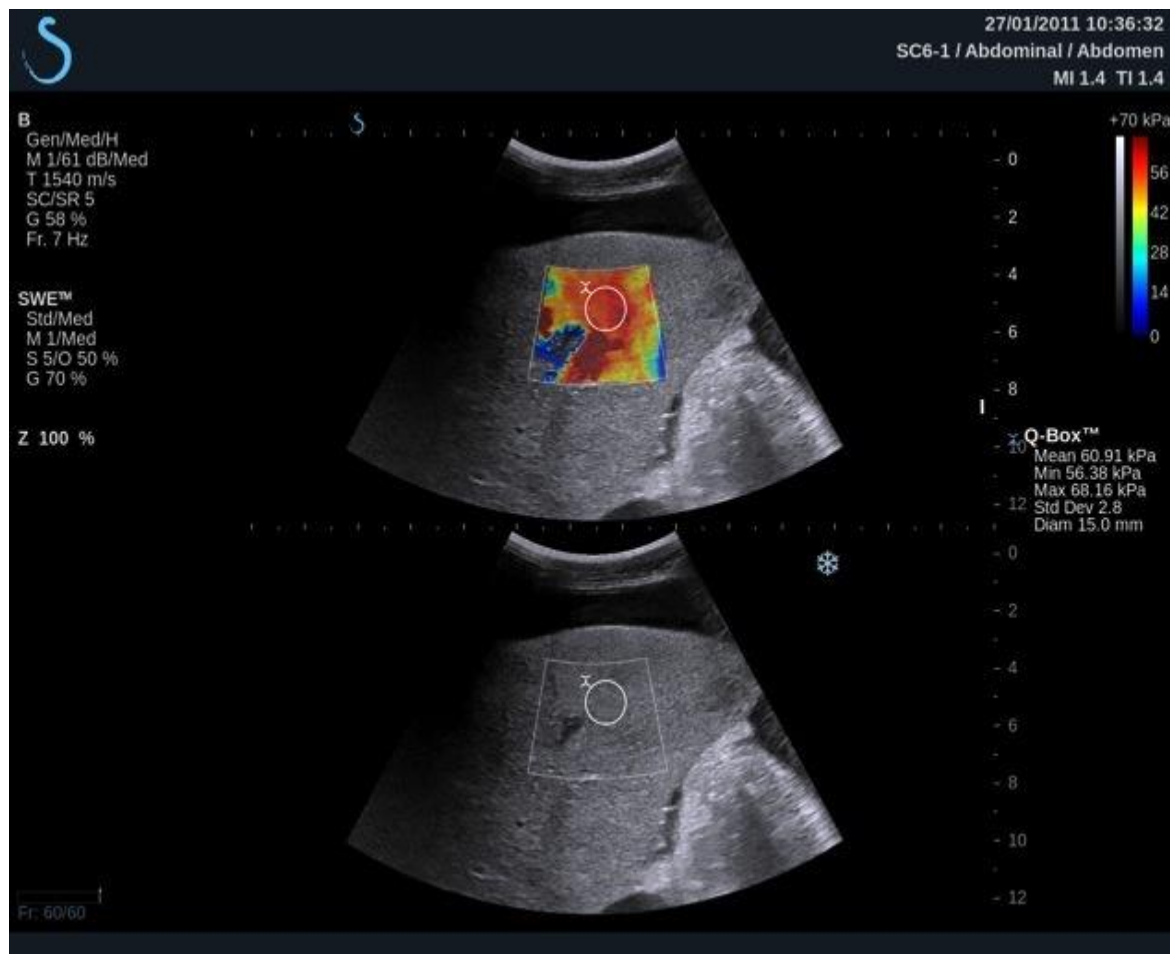
Impeccable
image quality
in B-mode



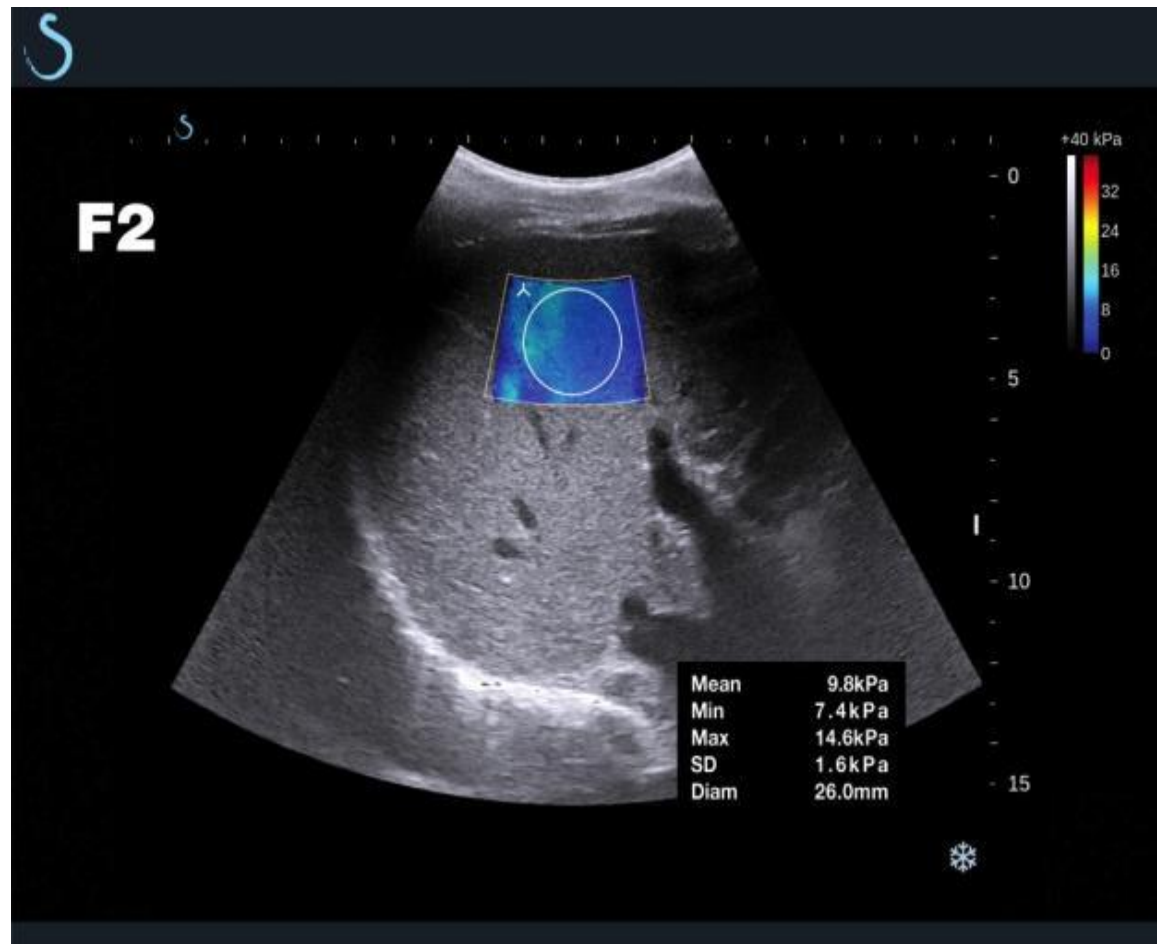
**One Shear
Wave :**

Measures and
displays, in real
time, local
tissue elasticity
in kilopascals

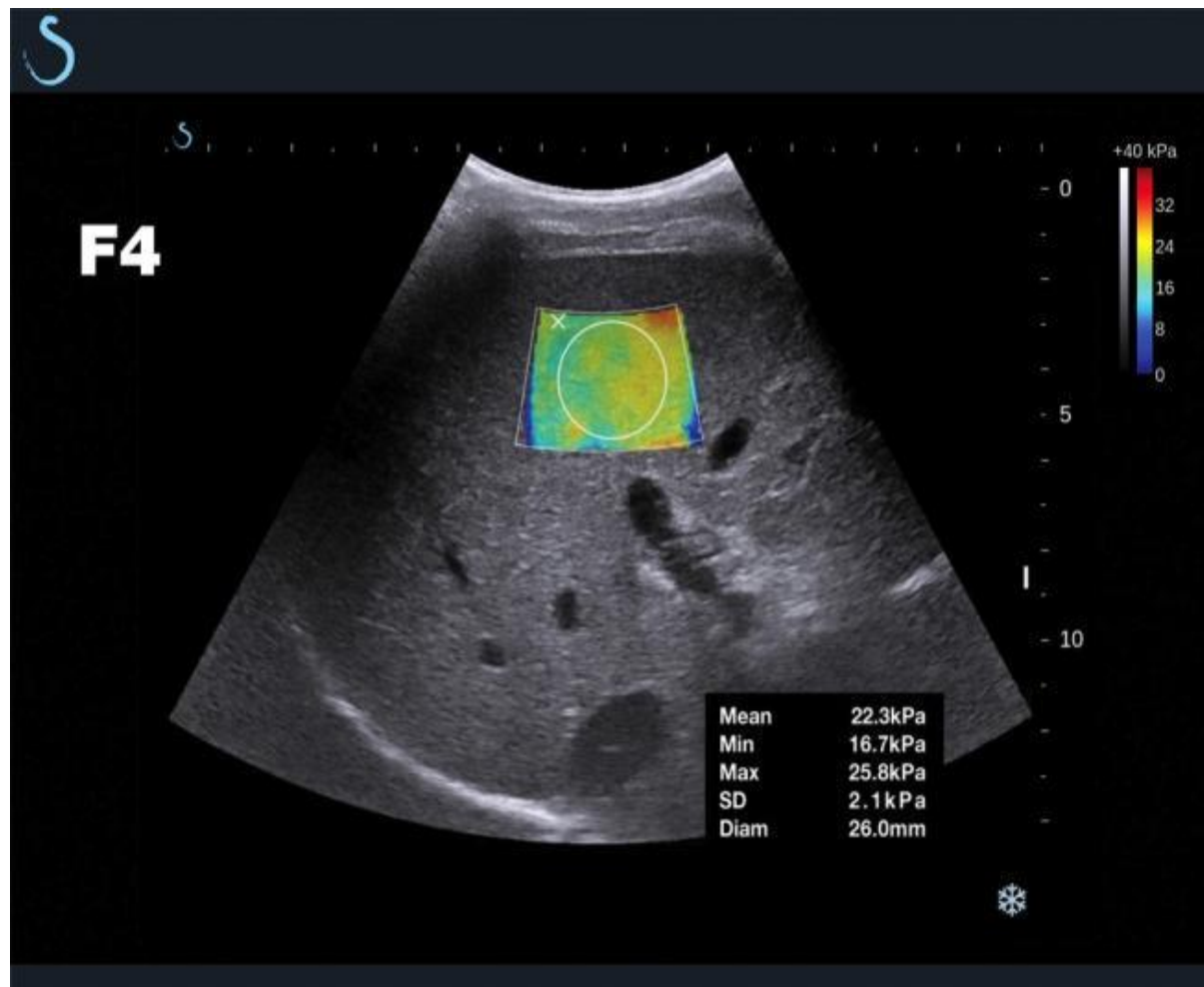
Abdomen - Liver



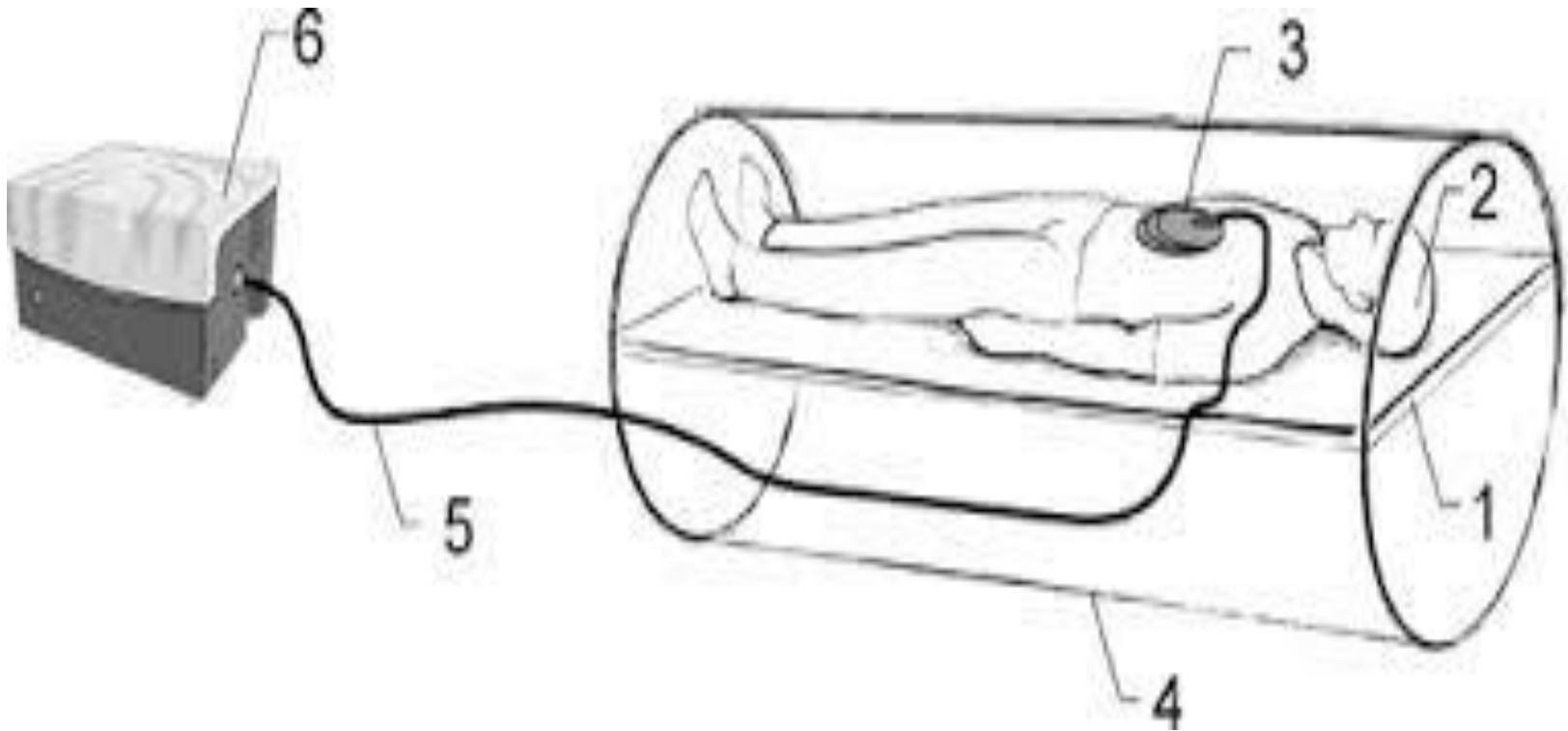
Liver Fibrosis F2



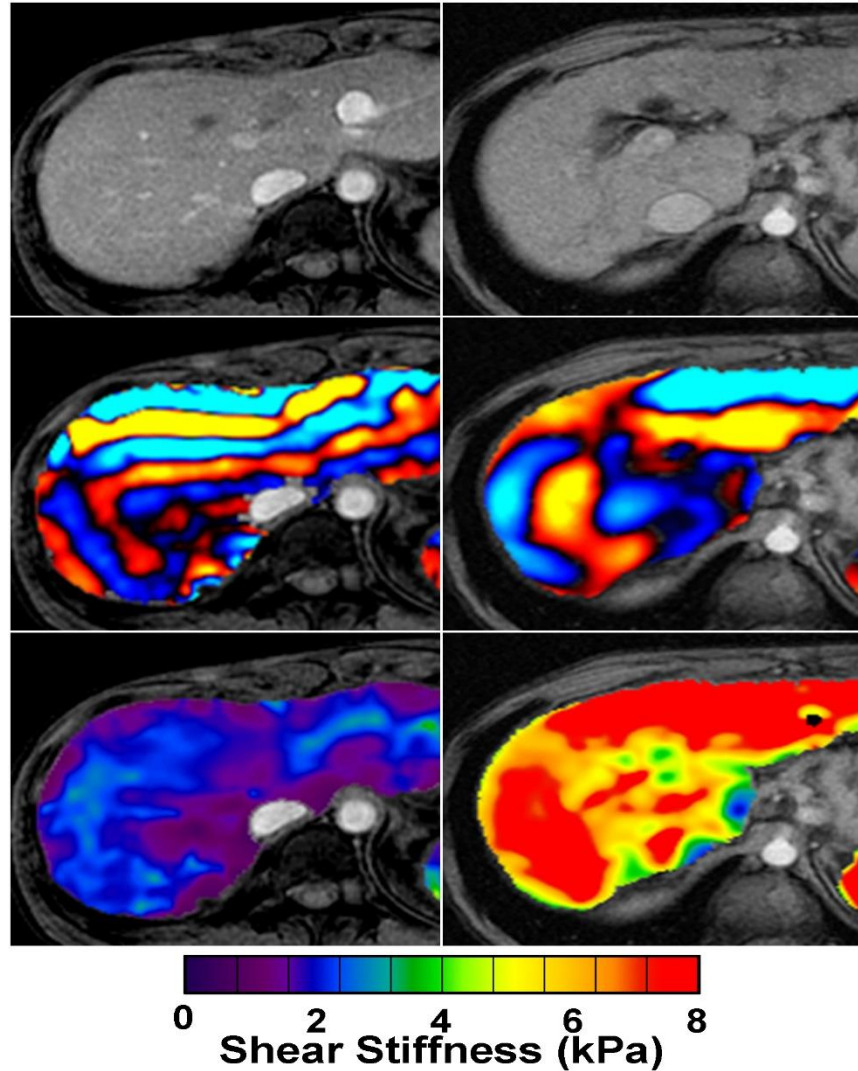
Liver Fibrosis F4



MAGNETIC RESONANCE IMAGING (MRE)



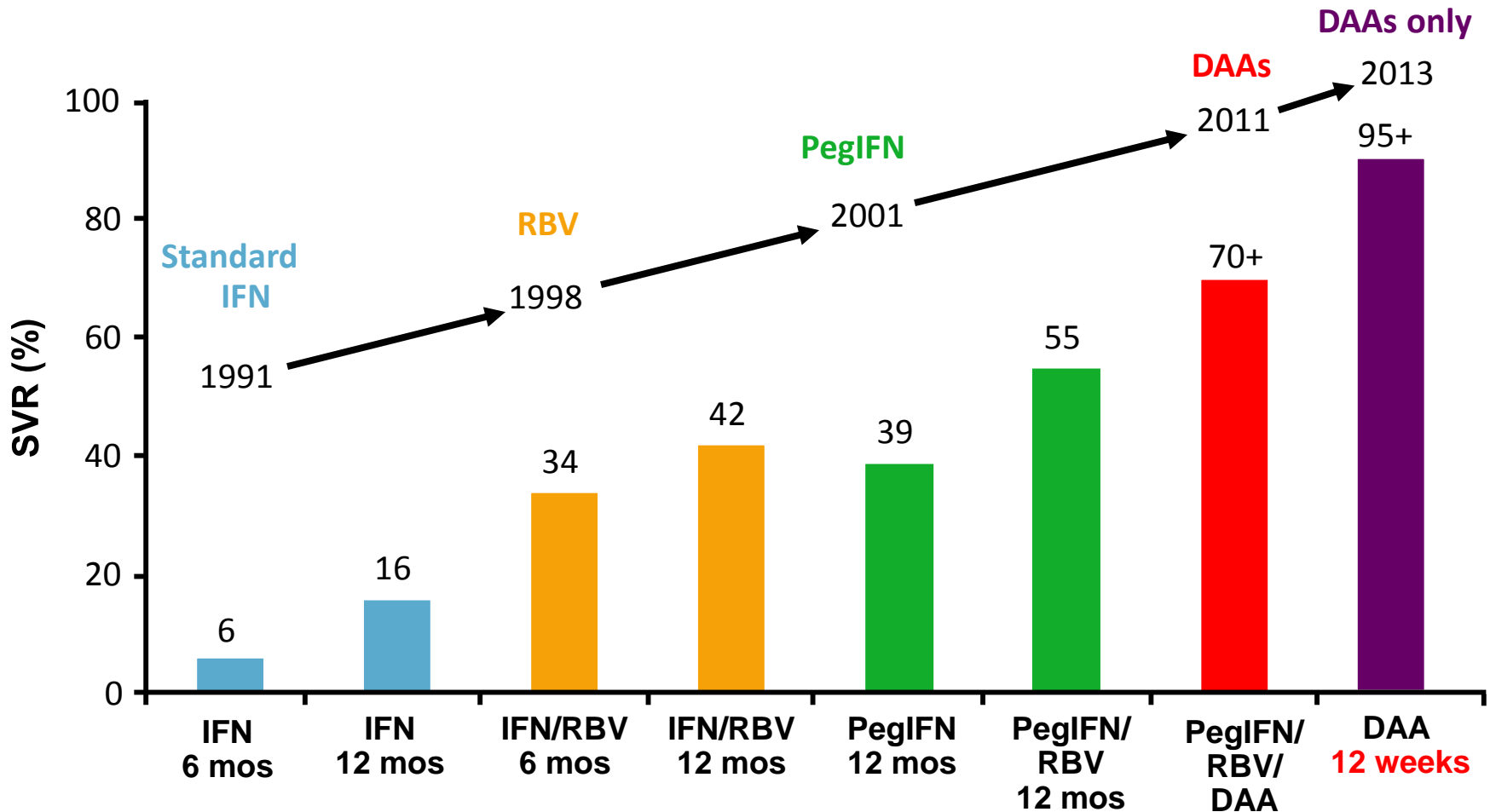
MAGNETIC RESONANCE IMAGING (MRE)



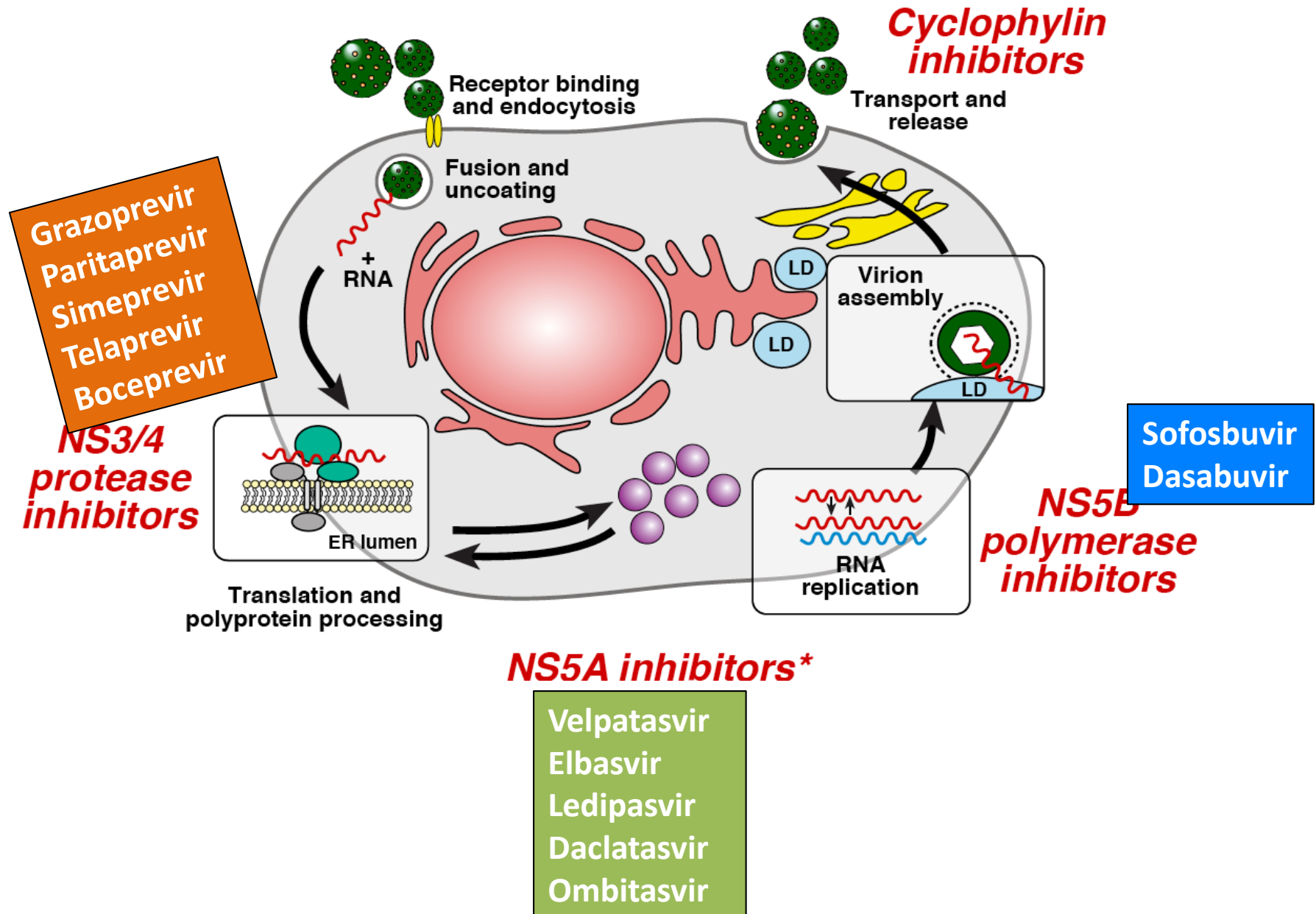
HCV Therapy Goal: CURE HCV=SVR

- **SVR = undetectable 12 weeks post therapy**
- **SVR = “Sustained Virological Response”**
- **Improve liver histology and clinical outcomes:**
 - **Decreased Decompensation**
 - **Decreased Esophageal Varices**
 - **Decreased Hepatocellular carcinoma**
 - **Decreased Mortality**

Changing Treatment Paradigms for HCV: Most patients care now CURED with simple and brief all-oral regimens



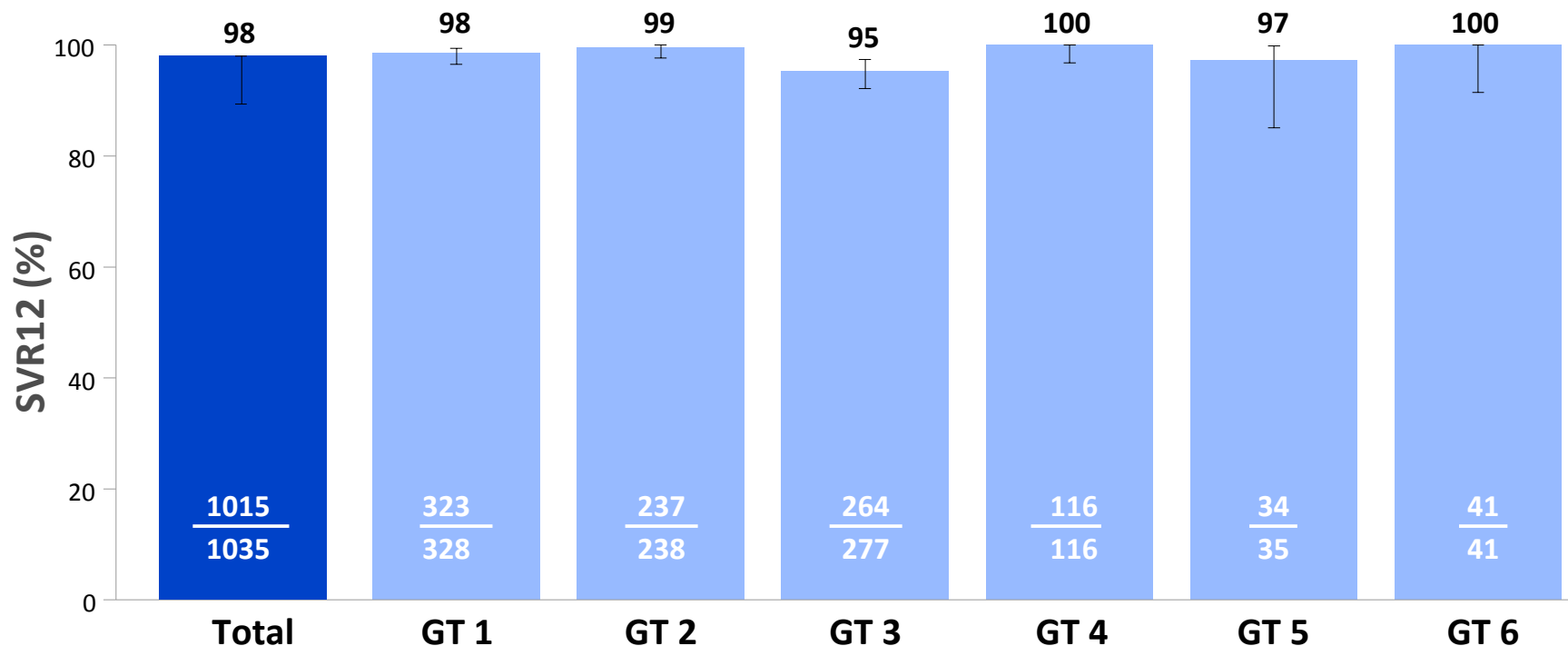
DAA Targets: Many Therapies Available



The “Ideal” HCV Antiviral

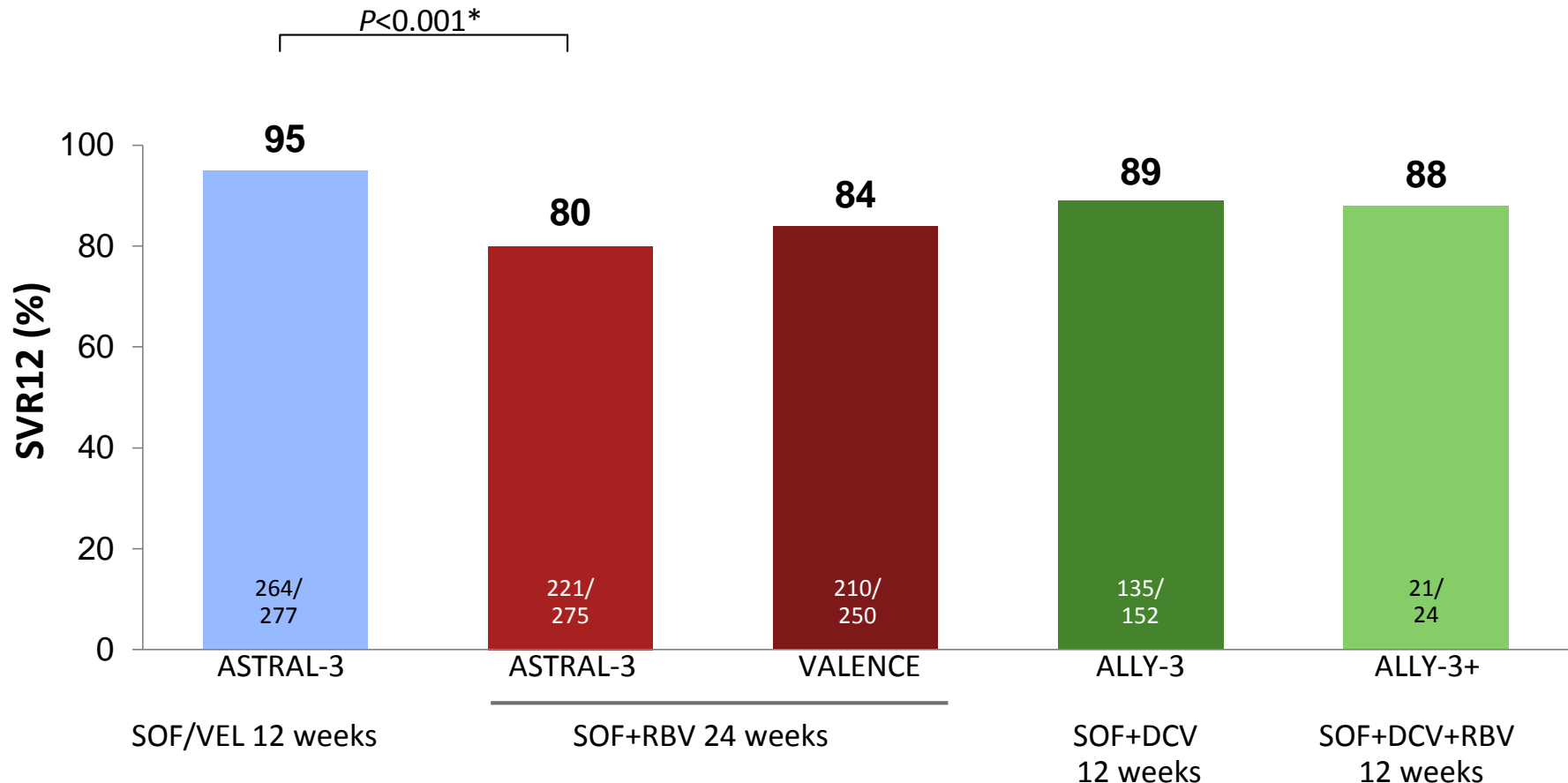
- High Antiviral Activity
- Activity against all genotypes
- High barrier to resistance
- Simple application (few pills, QD dosing)
- Highly favorable safety profile
- No Drug-Drug interactions
- Short and finite duration of therapy
- Efficacious in all patient populations
- Cure (very high SVR rates)
- High value

HCV SVR12 (CURE) Rates: Sofosbuvir/Velpatasvir



Summary of Genotype 3 (TN, TE, NC, C) SVR Results from ASTRAL-3, VALENCE, ALLY-3 and ALLY-3+

Overall SVR of SOF-Based Regimens for HCV Genotype 3 (GT 3 is the most difficult genotype to cure)



**SOF/VEL for 12 weeks yielded high SVR12 rates without the need for RBV
in HCV GT 3 subjects**

*P-value for superiority of SOF/VEL compared with SOF+RBV.

Foster GR, et al. *N Engl J Med* 2015;373(27):2608-2617; SOVALDI® [PI]. Gilead Sciences, Inc. Foster City, CA August 2015; Daklinza™ US PI April 2016; Nelson, *Hepatology* 2015;61(4):1127-1135; Leroy V. et al. *Hepatology* 2016;63(5):1430-1441

Important Points About Current HCV Treatment

- **The vast majority of patients can be cured with 8-12 weeks of all-oral therapy.**
 - **95+% cure rates**
 - **Well-tolerated regimens**
- **Cost of medications is still high (\$74,000 “retail” for the latest medication)**
 - **Some restrictions by insurers persist on types of patients that can be treated**
 - **Pricing now heavily discounted; challenges remain with Medicaid payers in most states**

IDSA/AASLD Guidelines Overview

AMERICAN ASSOCIATION FOR
THE STUDY OF LIVER DISEASES



HCV Guidance: Recommendations for Testing, Managing, and Treating Hepatitis C



- 1. HCV Testing and Linkage to Care**
- 2. When to Treat**
- 3. Initial Treatment**
- 4. Retreatment**
- 5. Monitoring Patients On or Post Therapy**
- 6. Unique Patient Populations**
- 7. Management of Acute HCV Infection**

Important Points When Interpreting HCV Guidelines

- **Treatment for HCV is rapidly changing with the development and approval of directly acting antivirals (DAAs)**
- **Guidance provides up-to-date recommendations and are up dated regularly**

Who will still need specialist care?

- **HIV/HCV Coinfection**
- **Decompensated Cirrhosis**
- **Organ Transplant patients**
- **Comorbidities like HBV, Autoimmune hepatitis, HIV/HBV/HCV**
- **Renal Failure Patients**
- **Hepatocellular Carcinoma**
- **Multiple Failures of HCV Therapy**

Conclusions

- **Treatment for hepatitis C has evolved rapidly in the past 3 years to simple, all oral regimens with very high cure rates**
- **Increased screening and linkage to care is required as most patients with hepatitis C do not know they are infected**
- **Political and social will required to improve patient access to drugs**
- **Possibilities ahead for global eradication/elimination, with pilot projects being done**