Hepatitis C Overview

Viral Hepatitis Summit
September 17, 2015

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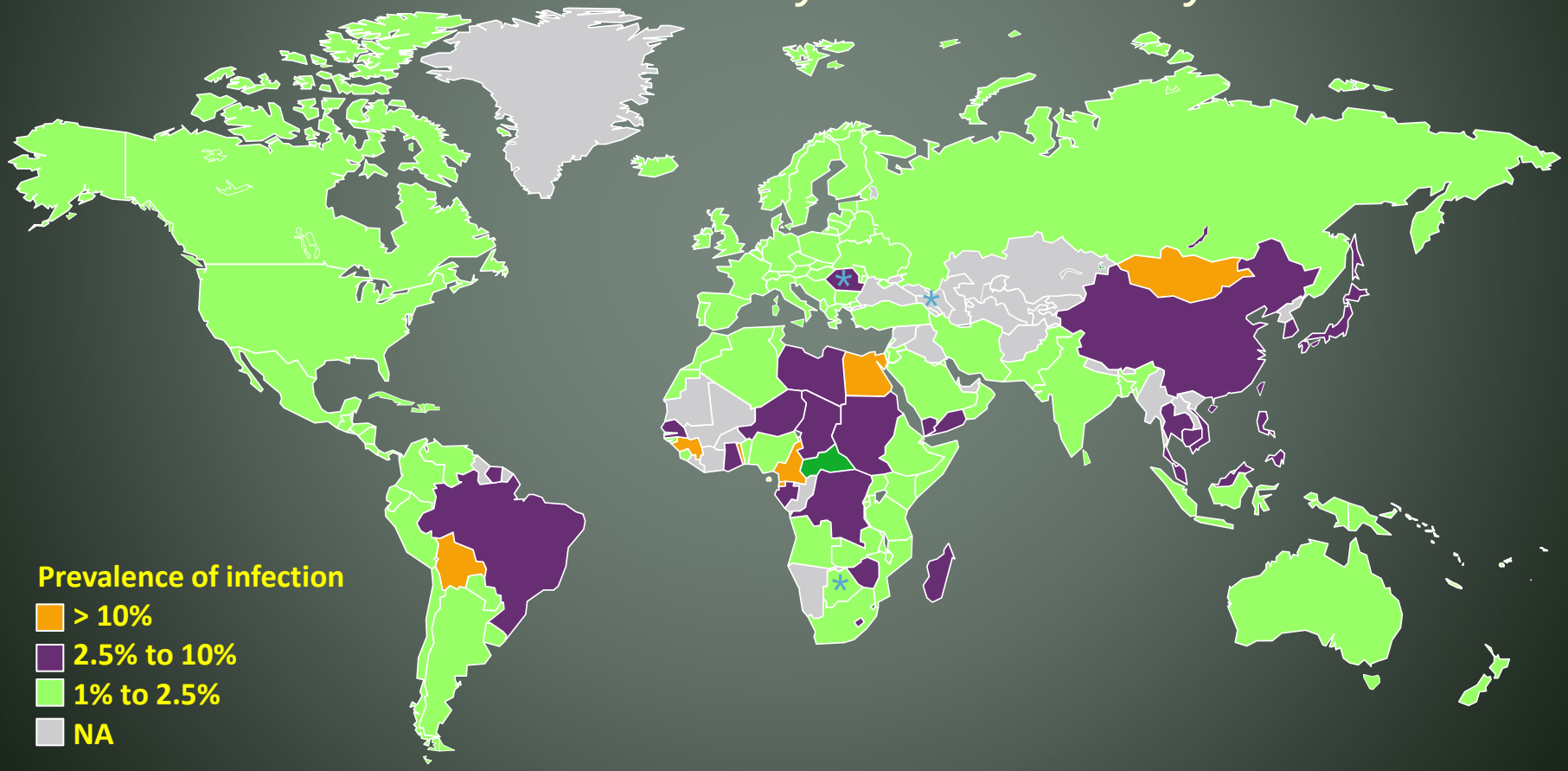
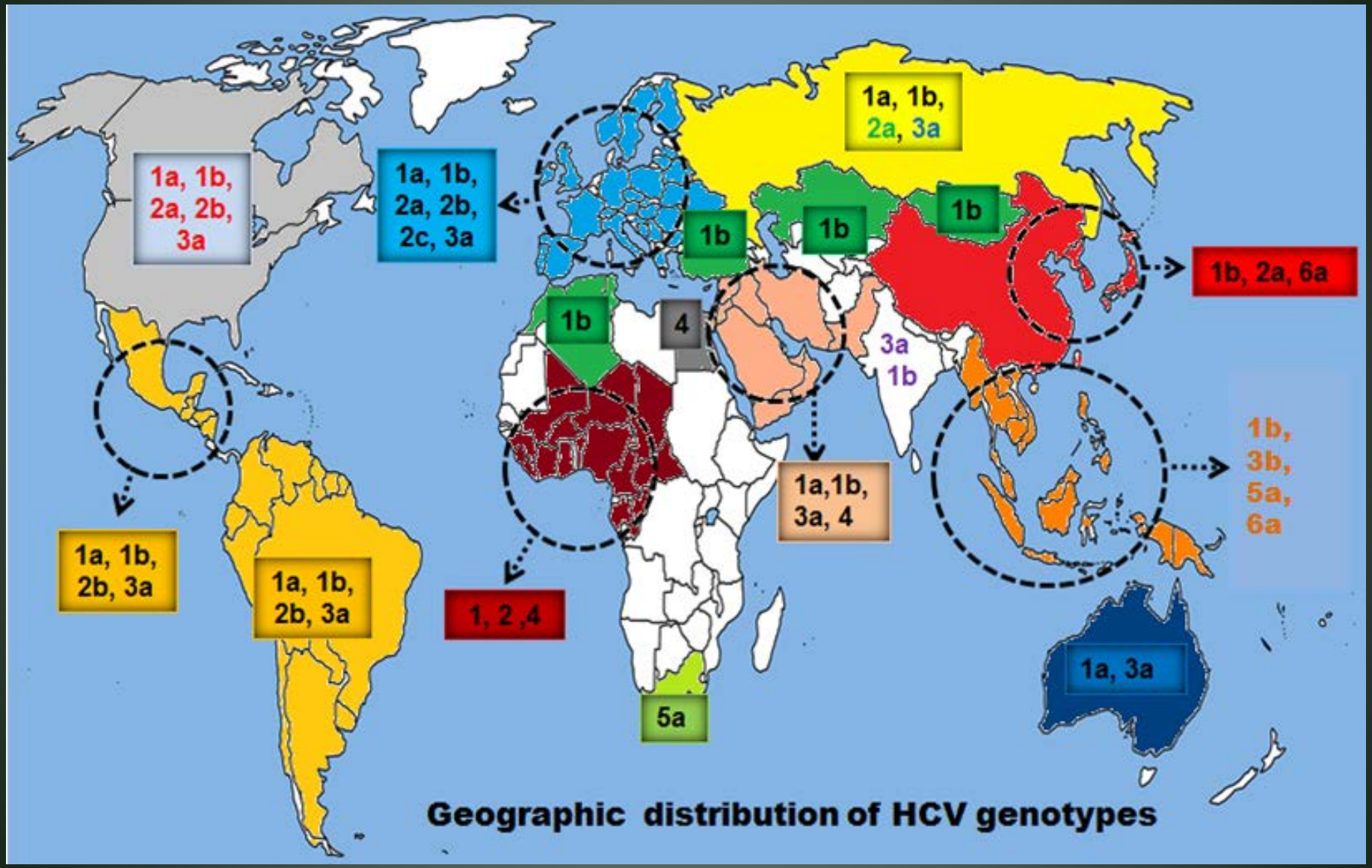
HCV Infection Worldwide

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



•World Health Organization 2008. Available at: http://www.who.int/ith/es/index.html. Accessed October 8, 2010.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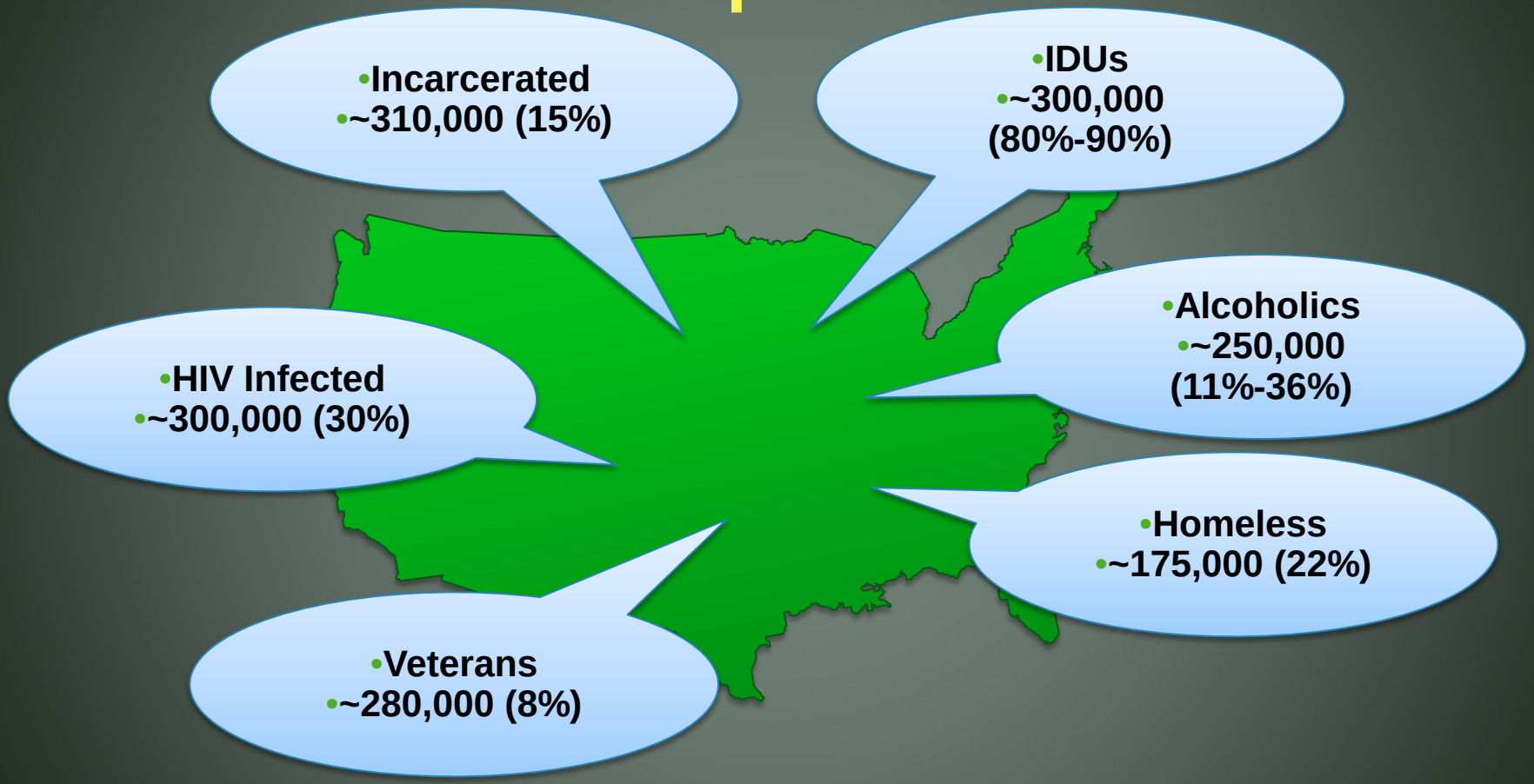
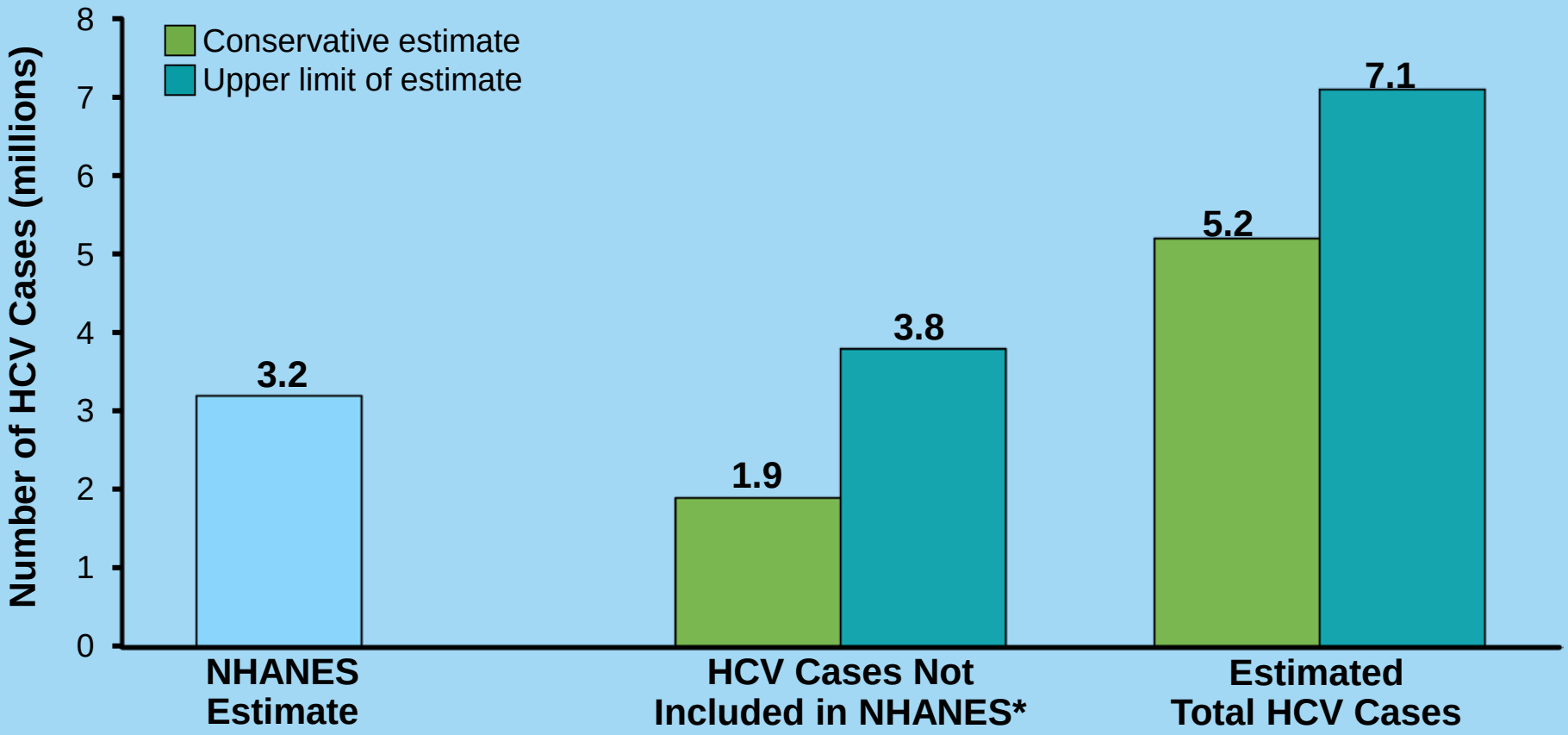
Geographic distribution of HCV genotypes

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. LaBreque DR, et al. In: Hepatitic 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.

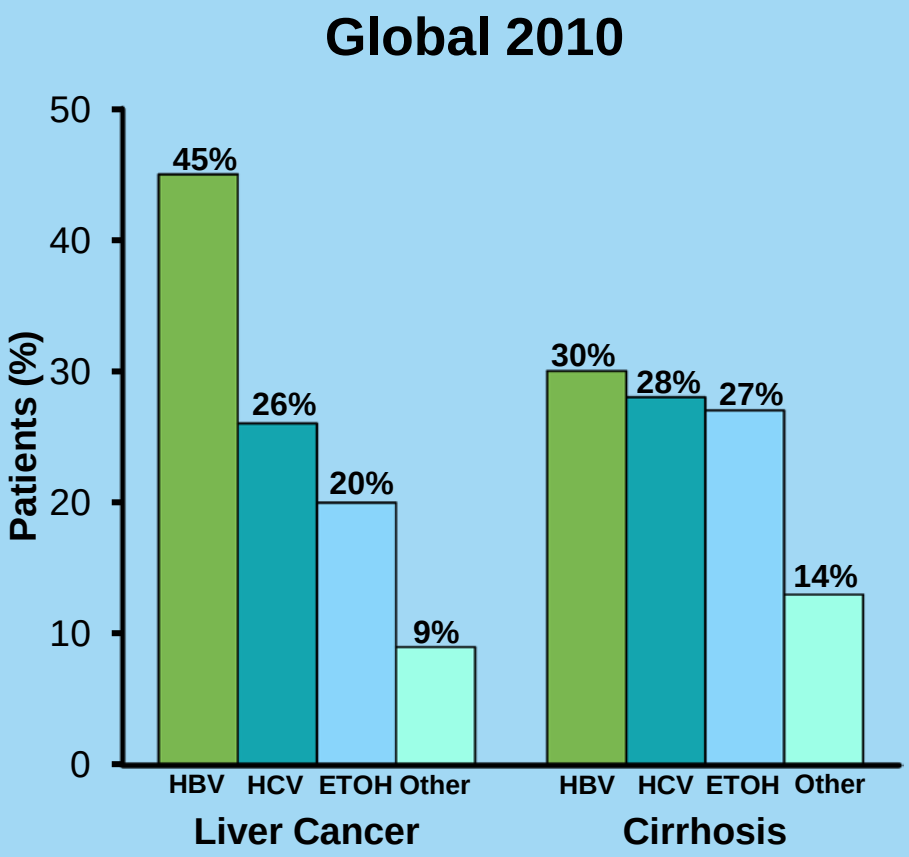
Over 5.2 Million People Living With Chronic HCV in the US

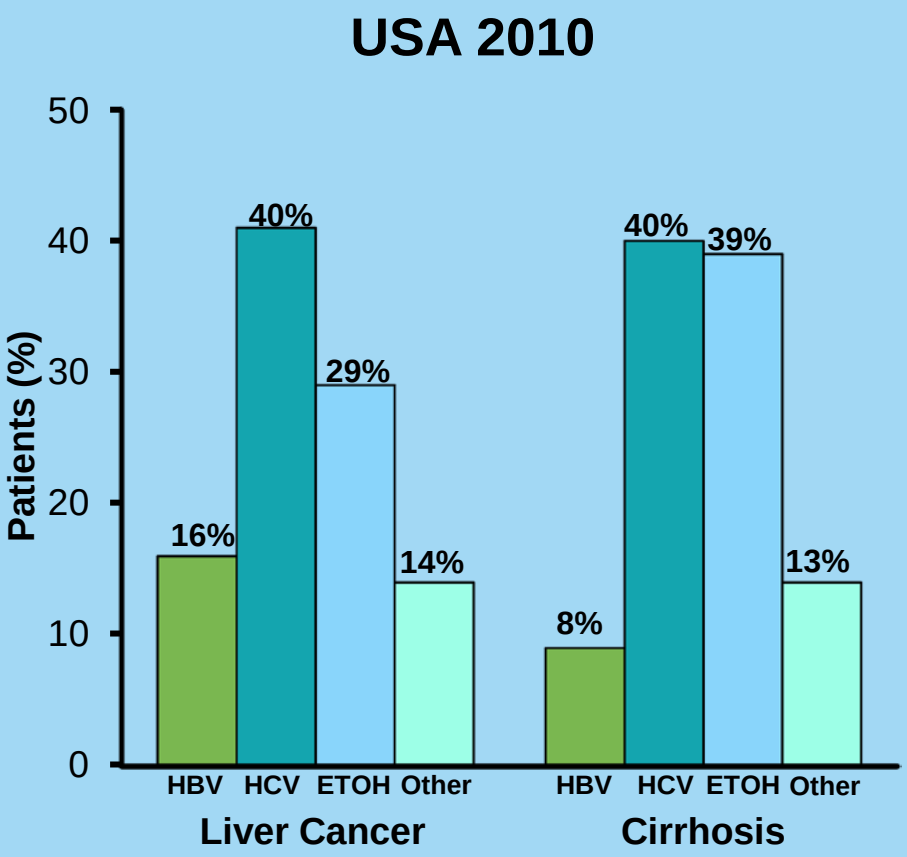


*Homeless (n=142,761-337,6100); incarcerated (n=372,754-664,826); veterans (n=1,237,461-2,452,006); active military (n=6805); healthcare workers (n=64,809-259,234); nursing home residents (n=63,609); chronic hemodialysis (n=20,578); hemophiliacs (n=12,971-17,000).

Chak E, et al. *Liver Int.* 2011; 31:1090-1101.

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





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.

Clinical Considerations on the Progression of HCV Infection

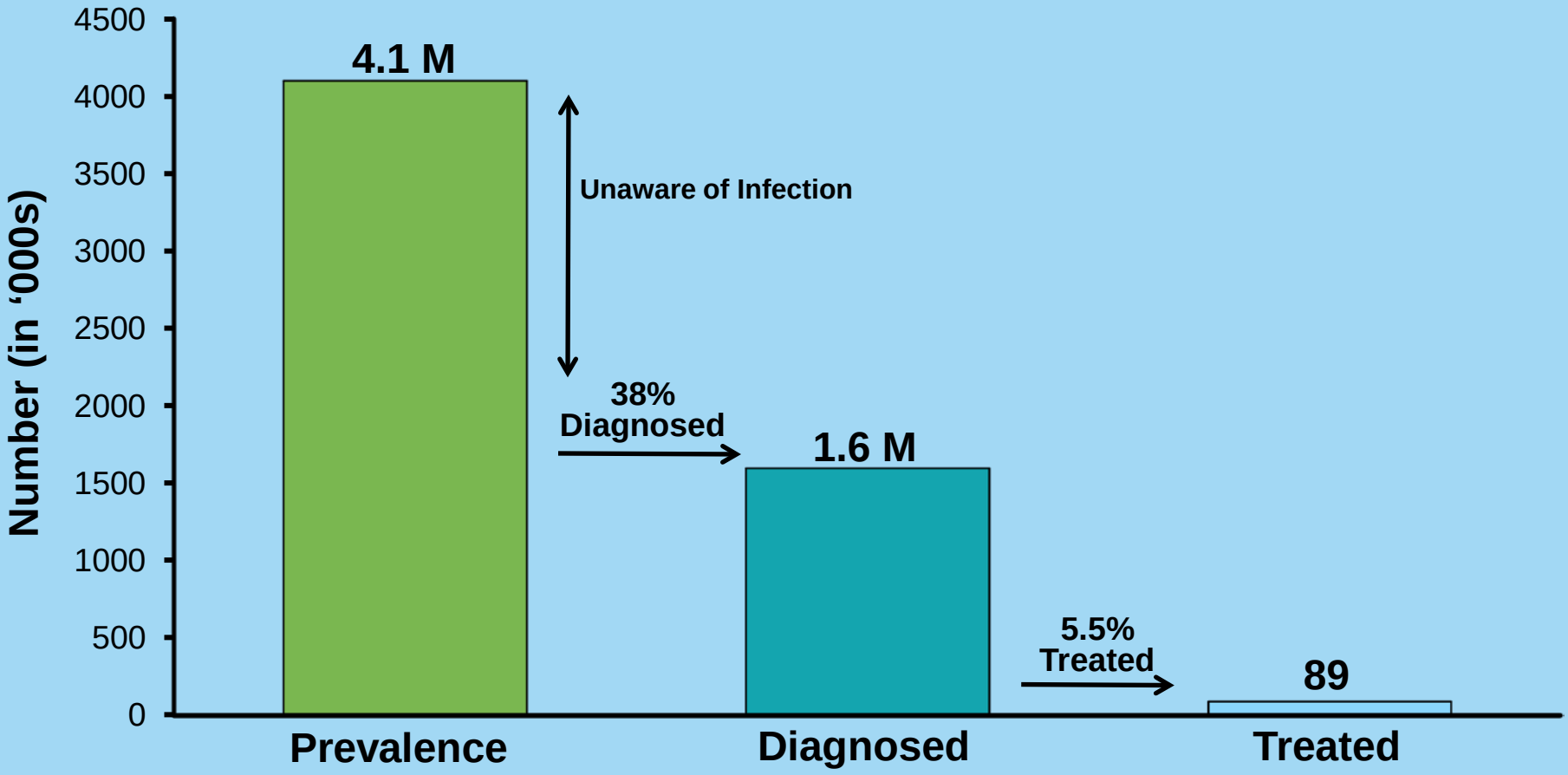
- Of every 100 persons infected with HCV, approximately
  - 75% to 85% will develop chronic infection
  - 60% to 70% will develop chronic liver disease
  - 5% to 20% will develop cirrhosis in 20 to 30 years
  - 1% to 5% will die from the consequences of chronic infection (liver cancer or cirrhosis)

http://www.cdc.gov/hepatitis/HCV/HCVfaq.htm#section2.

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

Chronic HCV in the US: Underdiagnosed and Untreated

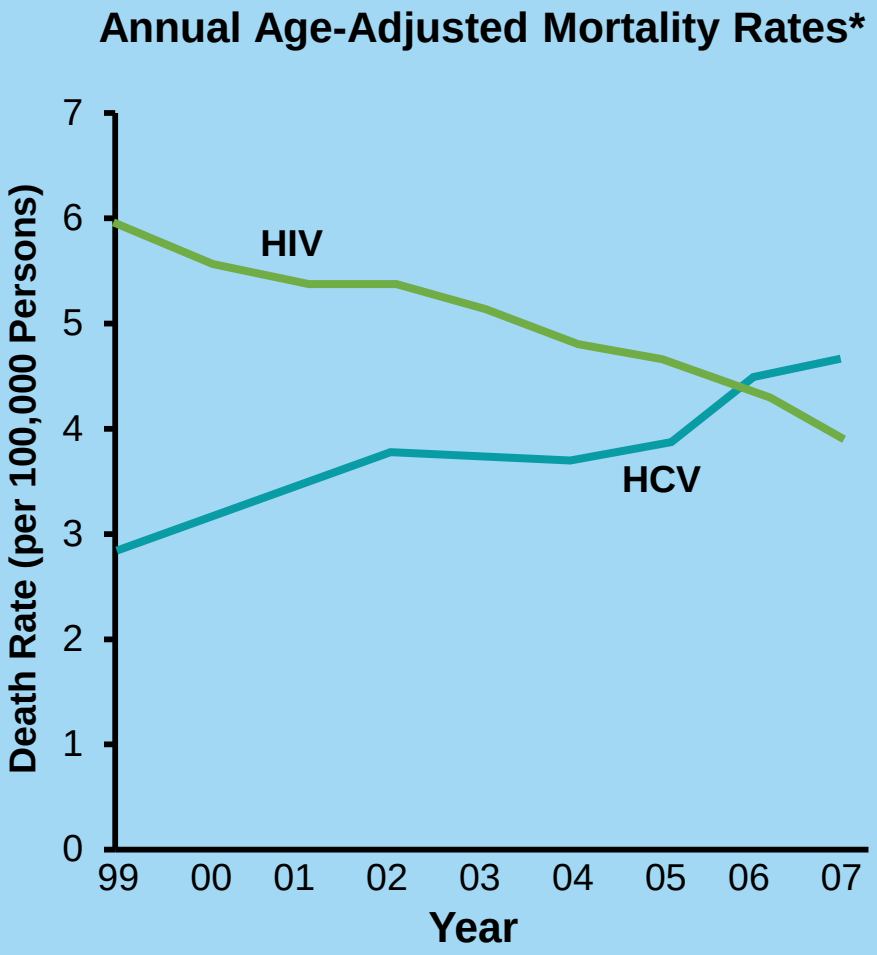


Estimated treatment rate is based on Q2 and Q4 2011 chart audits.

Hepatitis C Monitor. Ipsos Healthcare.

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.

Ly KN, et al. *Ann Intern Med*. 2012;156:271-278.

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

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

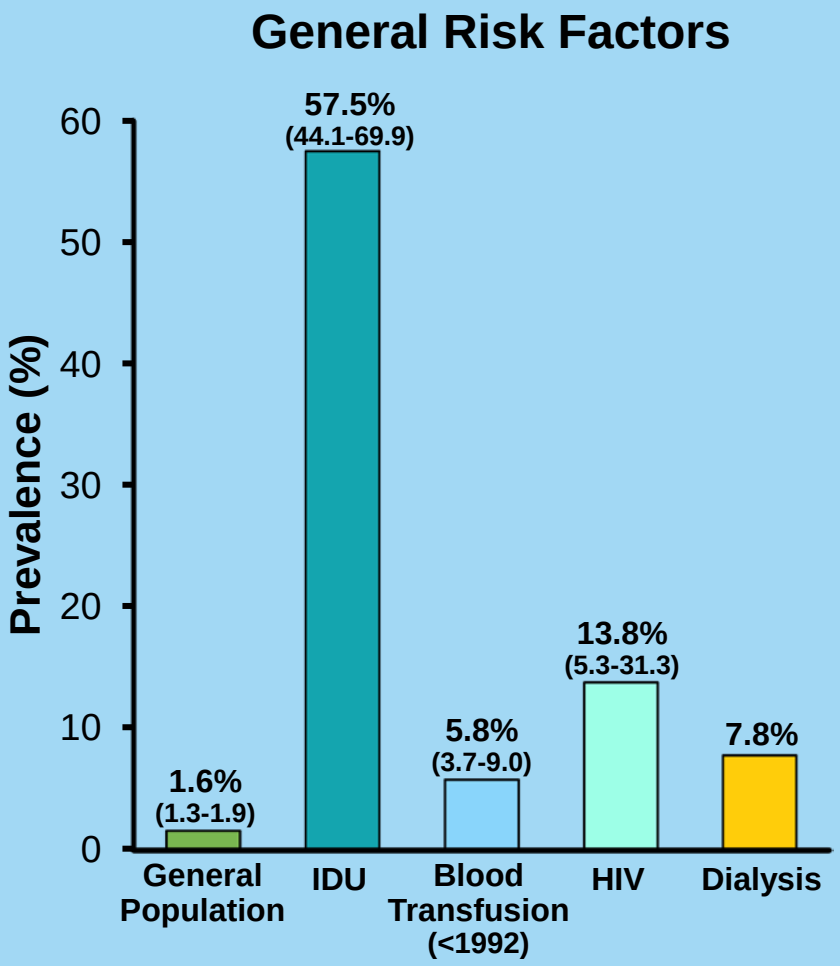
Centers for Disease Control and Prevention. *MMWR*. 2012;61(RR-4):1-33.
AASLD and IDSA. http://www.hcvguidelines.org/full-report-view. Version December 19, 2014.

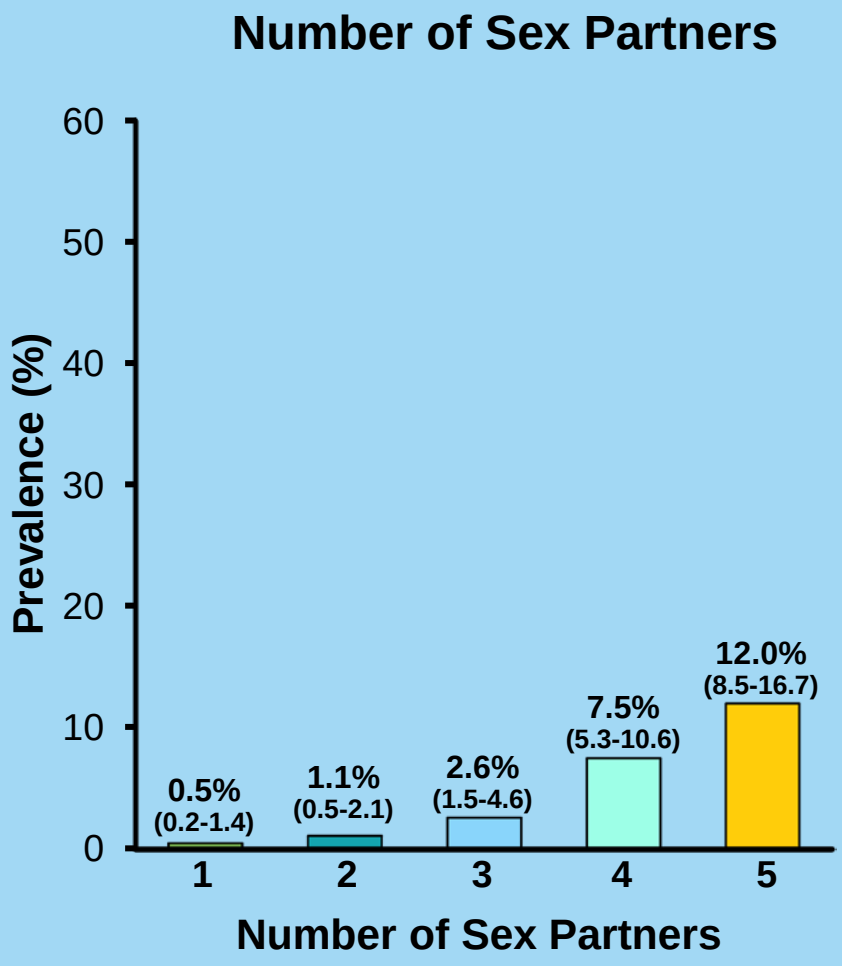
HCV Screening: Behaviors, Exposures, and Conditions Associated With Increased Risk of HCV Infection

- 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
  - 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)





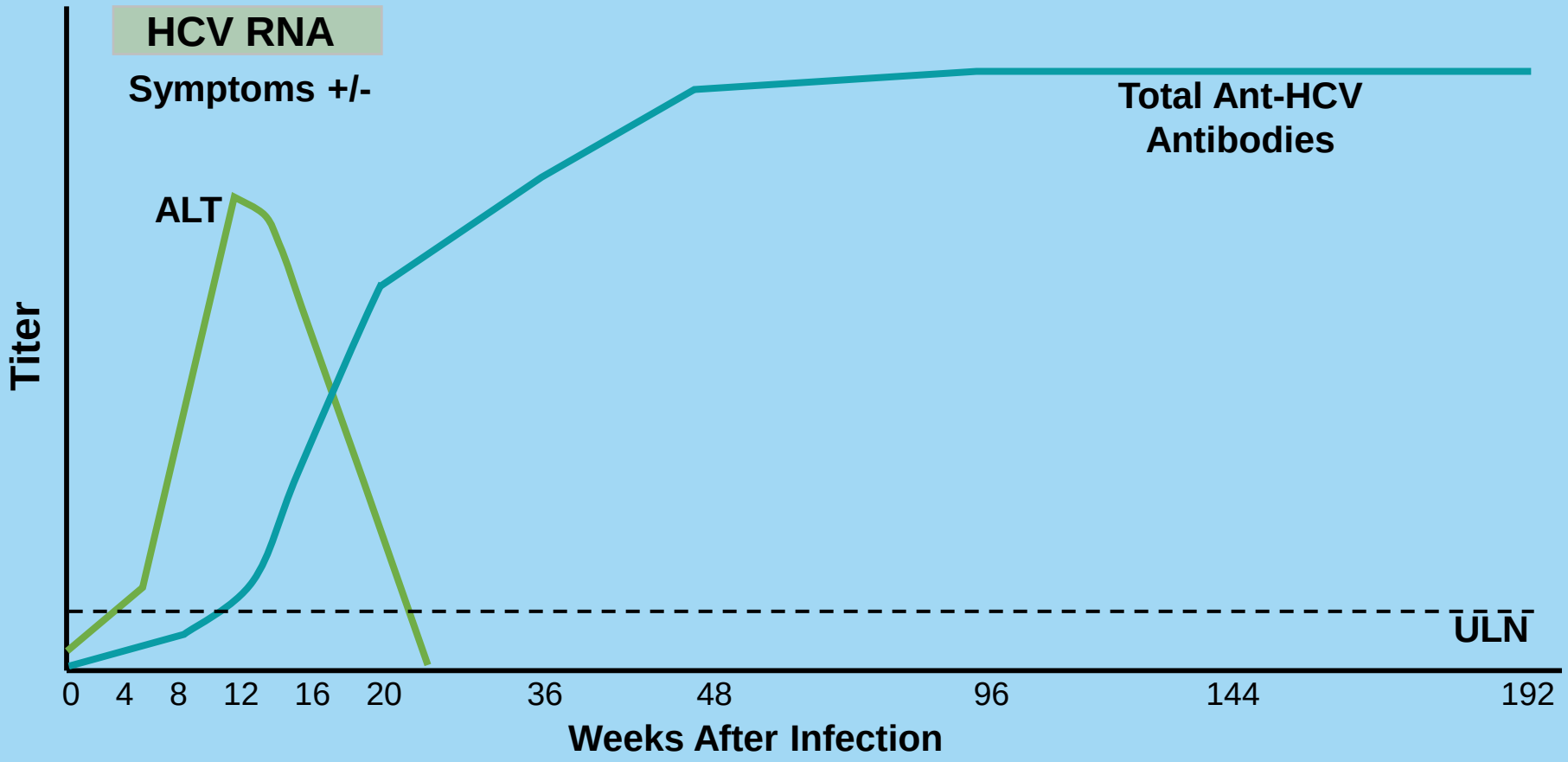
Armstrong GL, et al. *Ann Intern Med*. 2006;144:705-714.
Finelli L, et al. *Semin Dial*. 2005;18:52-61.

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

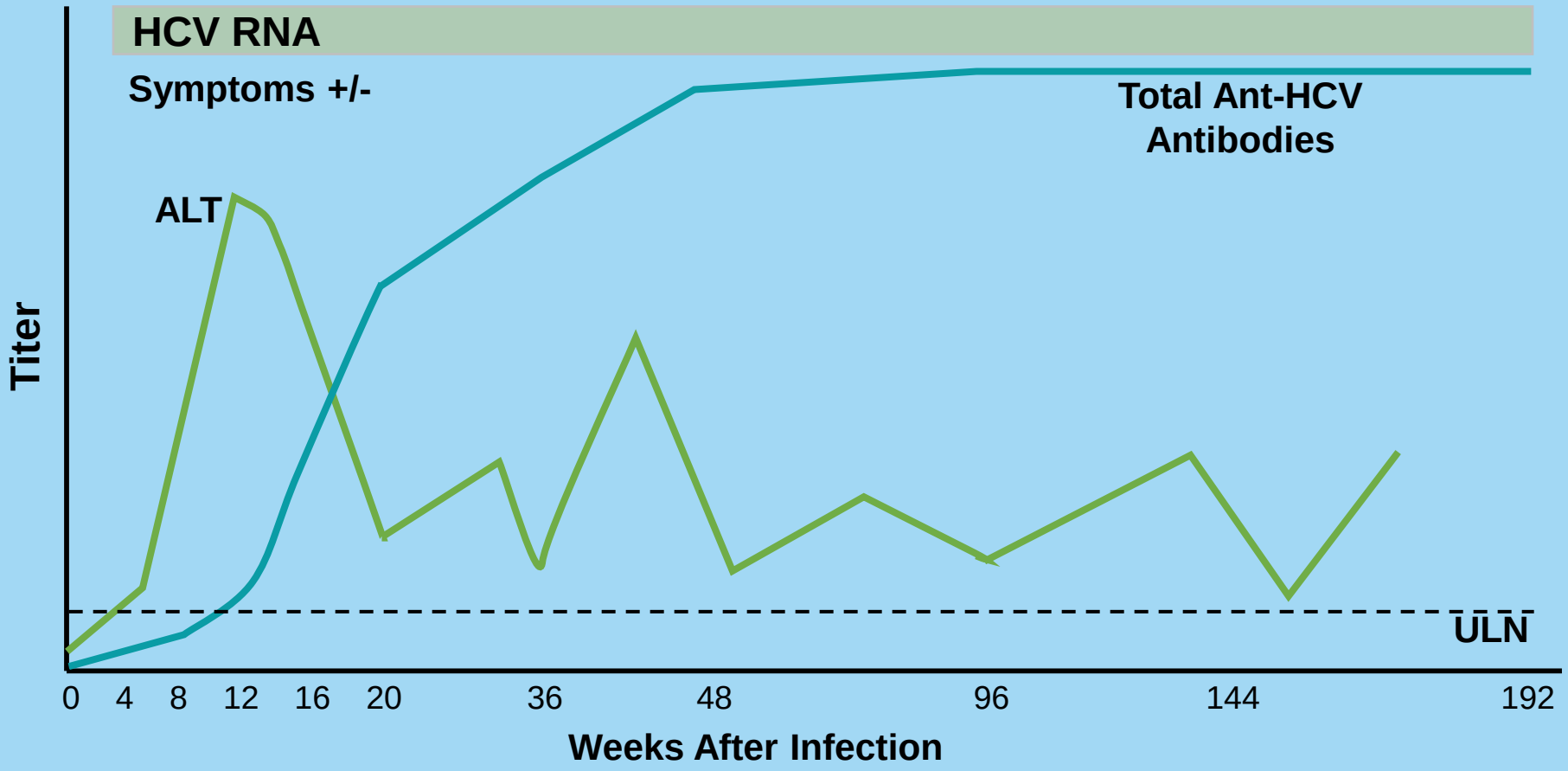
AASLD and IDSA. http://www.hcvguidelines.org/full-report-view. Version December 19, 2014.

Markers for Acute HCV Infection



Chevaliez S, et al. *Liver Int.* 2009;29:9-16.
Pawlotsky JM, et al. *Hepatology.* 2002;36:S65-S73.

Markers for Chronic HCV Infection



Chevaliez S, et al. *Liver Int.* 2009;29:9-16.

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
  - 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

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

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

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

HCV Assays: What the Results Mean

Anti-HCV	HCV RNA	Interpretation
+	+	Acute or chronic HCV depending on the clinical context
+	–	False positive HCV antibody Resolved infection Low-level intermittent viremia
–	+	Early acute HCV infection Chronic HCV in setting of immunosuppressed state False positive HCV RNA test
–	–	Absence of HCV infection

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

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

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

Counseling HCV-Infected Patients: Minimizing Disease Progression

- Avoid alcohol
  - HCV-related fibrosis progression is increased with alcohol consumption >50 g/day
  - Lower levels of alcohol consumption is associated with increases in HCV RNA levels
- Administer HAV and HBV vaccines as needed
- Consider treatment for chronic HCV infection

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

Vitamin D and Coffee: Role in Chronic HCV Infection

- Vitamin D levels (HCV genotype 1 [n=197] versus age- and sex-matched healthy controls [n=49])
  - 25(OH) D levels significantly lower in HCV versus controls (25 versus 43 µg/L; $P<0.001$)
  - Low levels significantly associated with female sex, increased liver inflammation, increased liver fibrosis, and decreased SVR (n=167)
- Coffee consumption $\geq$3 cups/day (HALT-C trial, serial liver biopsies every 2 years)
  - Lower rates of disease progression (relative risk 0.47 [$P=0.0003$])
  - Lower insulin and HOMA-2 score
  - Independent predictor of improved virologic response to PR (adjusted* odds ratio 1.80 [$P=0.034$])

*Adjusted for age, race/ethnicity, sex, alcohol, cirrhosis, AST/ALT ratio, IL28B polymorphism rs12979860, and dose reduction in peginterferon. PR: pegIFN + RBV.

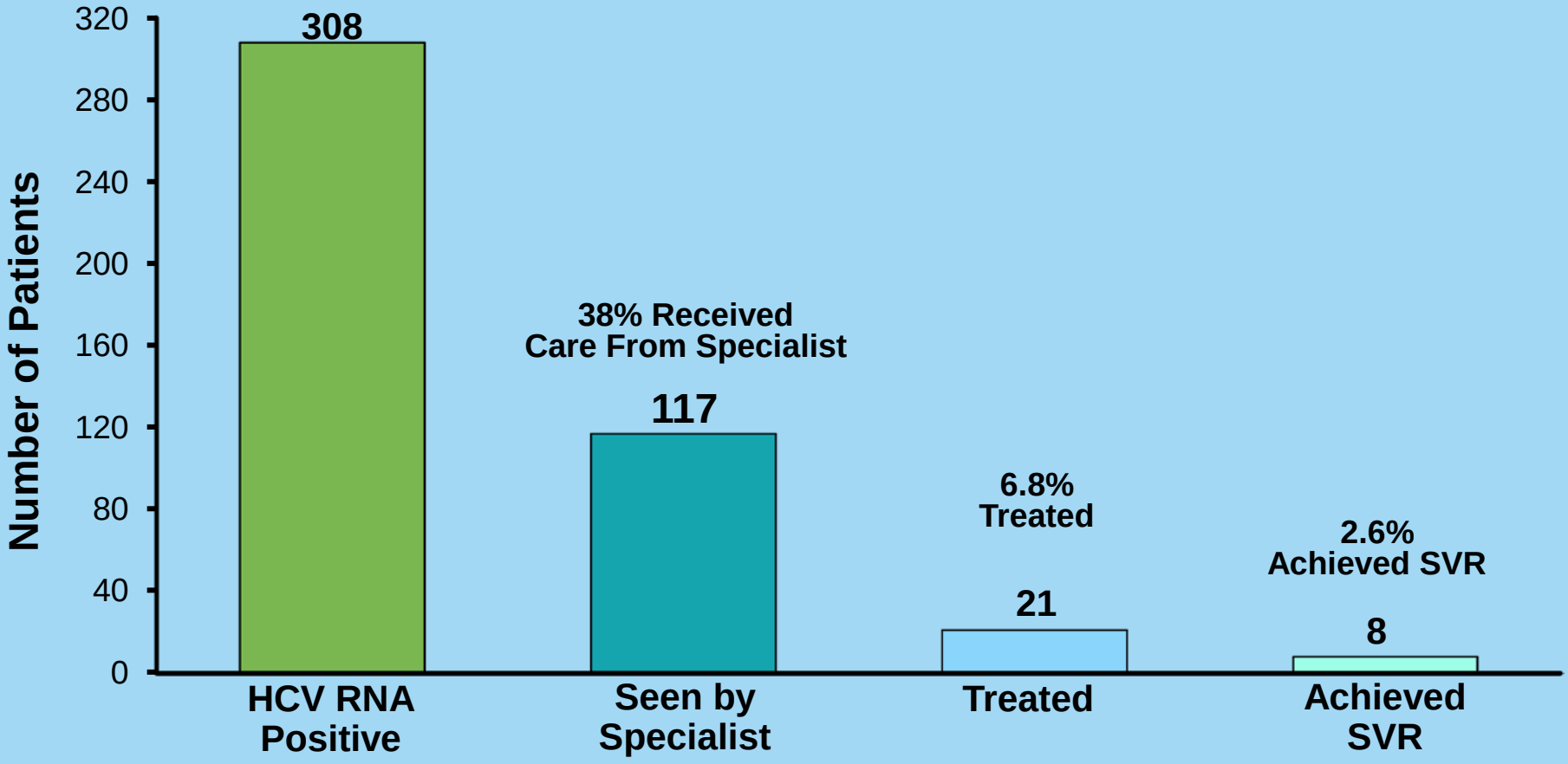
Petta S, et al. *Hepatology.* 2010;51:1158-1167.
Freedman ND, et al. *Hepatology.* 2009;50:1360-1369.
Freedman ND, et al. *Gastroenterology.* 2011;140:1961-1969.

Tobacco and HCC Risk

- The relationship between cigarette smoking and HCC has been examined in >60 studies (both areas of high and low incidence of HCC)
  - Both positive associations and no associations have been reported
- Studies with positive associations
  - Effects limited to subgroups defined by HCV or HBV status
  - Meta-analysis of 16 publications
    - HBV and cigarette smoking: more than additive interaction
    - HCV and cigarette smoking: more than multiplicative interaction

El-Serag HB. *Gastroenterology*. 2012;142:1264-1273.
Chuang SC, et al. *Cancer Epidemiol Biomarkers Prev*. 2010;19:1261-1268.

HCV Linkage-to-Care: Missed Opportunities in a Large Primary Care Setting (2005-2010)



Patients with a positive anti-HCV antibody test and visit to primary care from 2005-2010 (n=566).
Of these patients, 458 underwent HCV RNA testing.

Brown KA, et al. *Hepatology.* 2013;58(suppl 1):1291A. Abstract 2240.

Stepwise Barriers to Hepatitis C Treatment

HCV Infection → **Diagnosis**

Barriers
Asymptomatic disease
Poor awareness/education
Lack of medical coverage
MD failure to screen/test

Diagnosis → **Referral to Specialist**

Barriers
Non-adherence
MD failure to identify need for referral
Logistical concerns
Limited specialists availability

Referral to Specialist → **Treatment Initiation**

Barriers
Patient fears/misunderstandings
Stigmatization
Substance abuse
Psychiatric comorbidity
Financial concern
Transportation/logistical concern
Communication difficulties

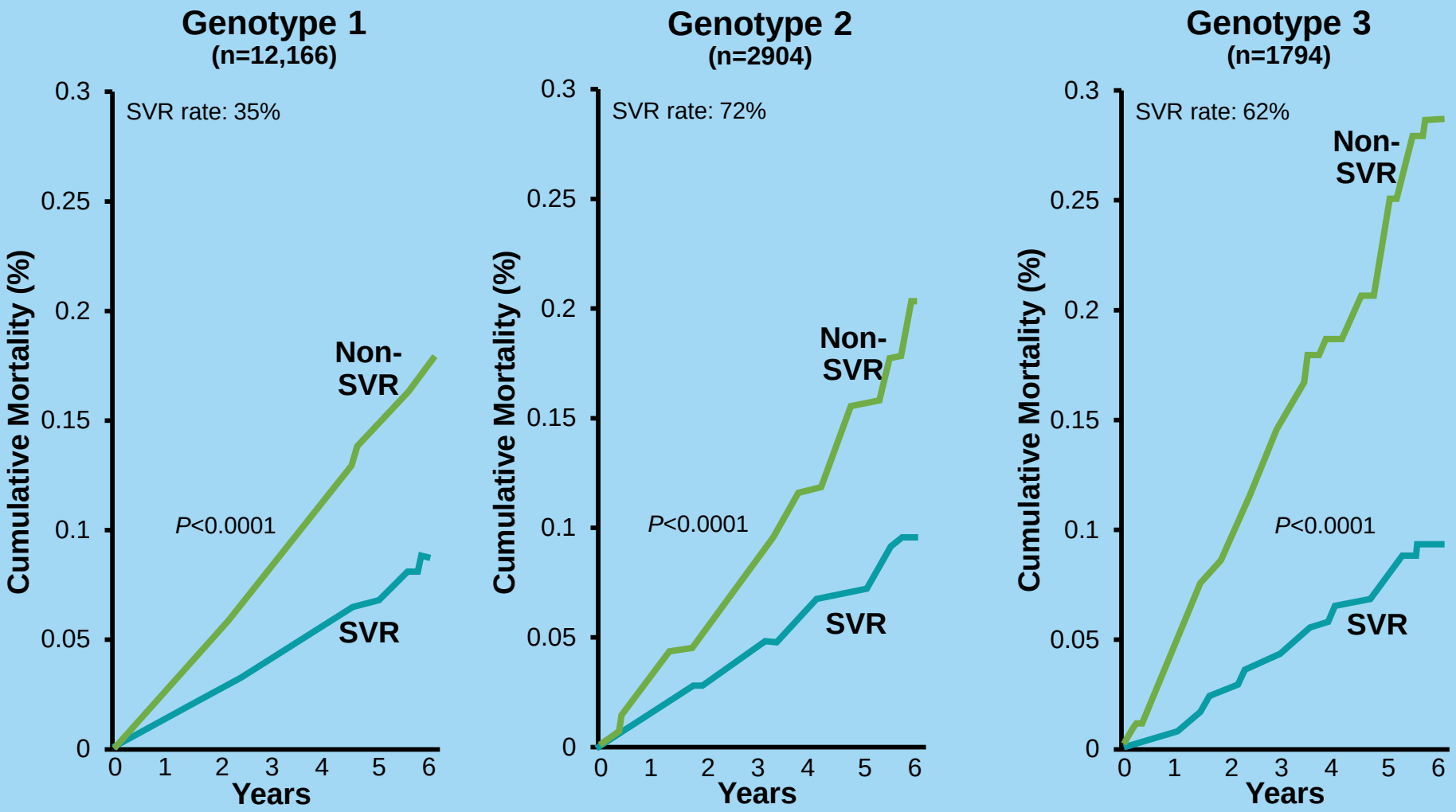
McGowan CE, et al. *Liver Int.* 2012;32(suppl 1):151-156.

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

Bruno S, et al. *Hepatology*. 2010;51:2069-2076.
Veldt BJ, et al. *Ann Intern Med*. 2007;147:677-684.
Maylin S, et al. *Gastroenterology*. 2008;135:821-829.

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

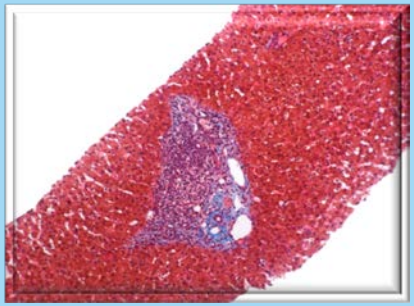
- Hepatic fibrosis
  - Not reliably diagnosed by ultrasound or other imaging modalities
- Liver fibrosis rates
  - Not predictable or linear
- Progression from compensated cirrhosis to decompensated liver disease
  - Occurs in 5% of patients per year
- Hepatocellular carcinoma
  - Develops in 1% to 2% of patients with hepatitis-related cirrhosis each year
- <u>Liver Biopsy no longer routinely recommended for Hepatitis C therapy decisions</u>

Sherman KE. *Top HIV Med*. 2011;19:121-125.

Progression of Fibrosis in Viral Hepatitis on Biopsy (Metavir)

No Fibrosis

Stage 1

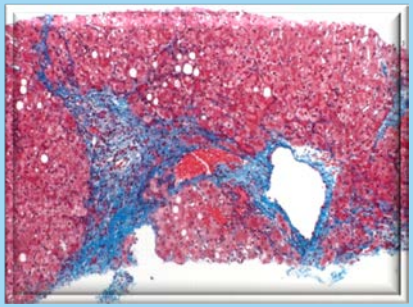


Fibrous expansion of some portal areas

Stage 2

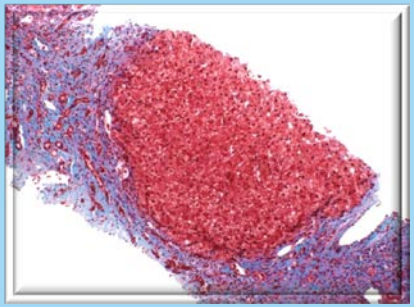
Fibrous expansion of most portal areas with occasional portal to portal bridging

Stage 3



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

Stage 4

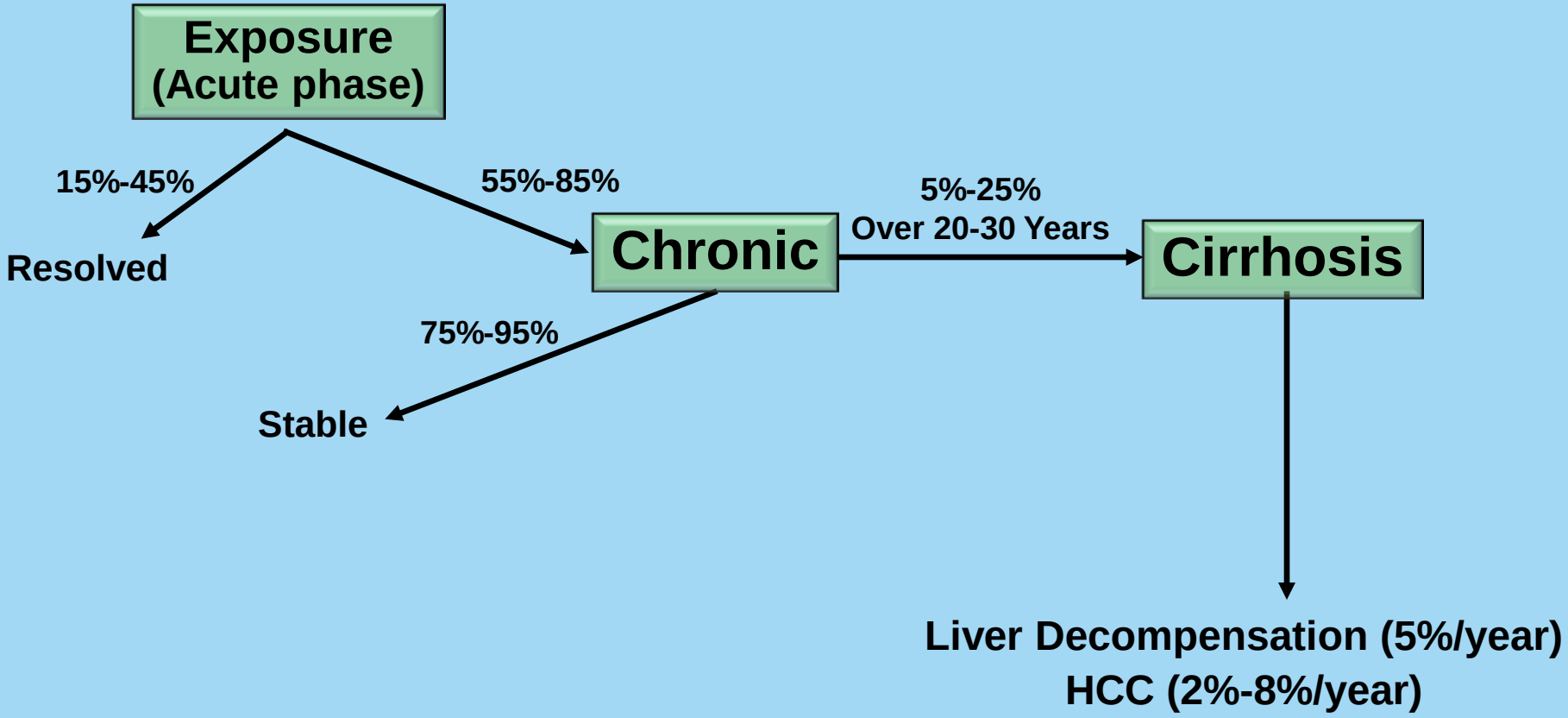


Cirrhosis

Cirrhotic Liver

Faria SC, et al. *Radiographics.* 2009;29:1615-1635. Adapted from Everson GT.

Chronic HCV Infection: Natural History



Poynard T, et al. *Lancet.* 1997;349:825-832.

Risk Factors for Progressive Fibrosis and Cirrhosis

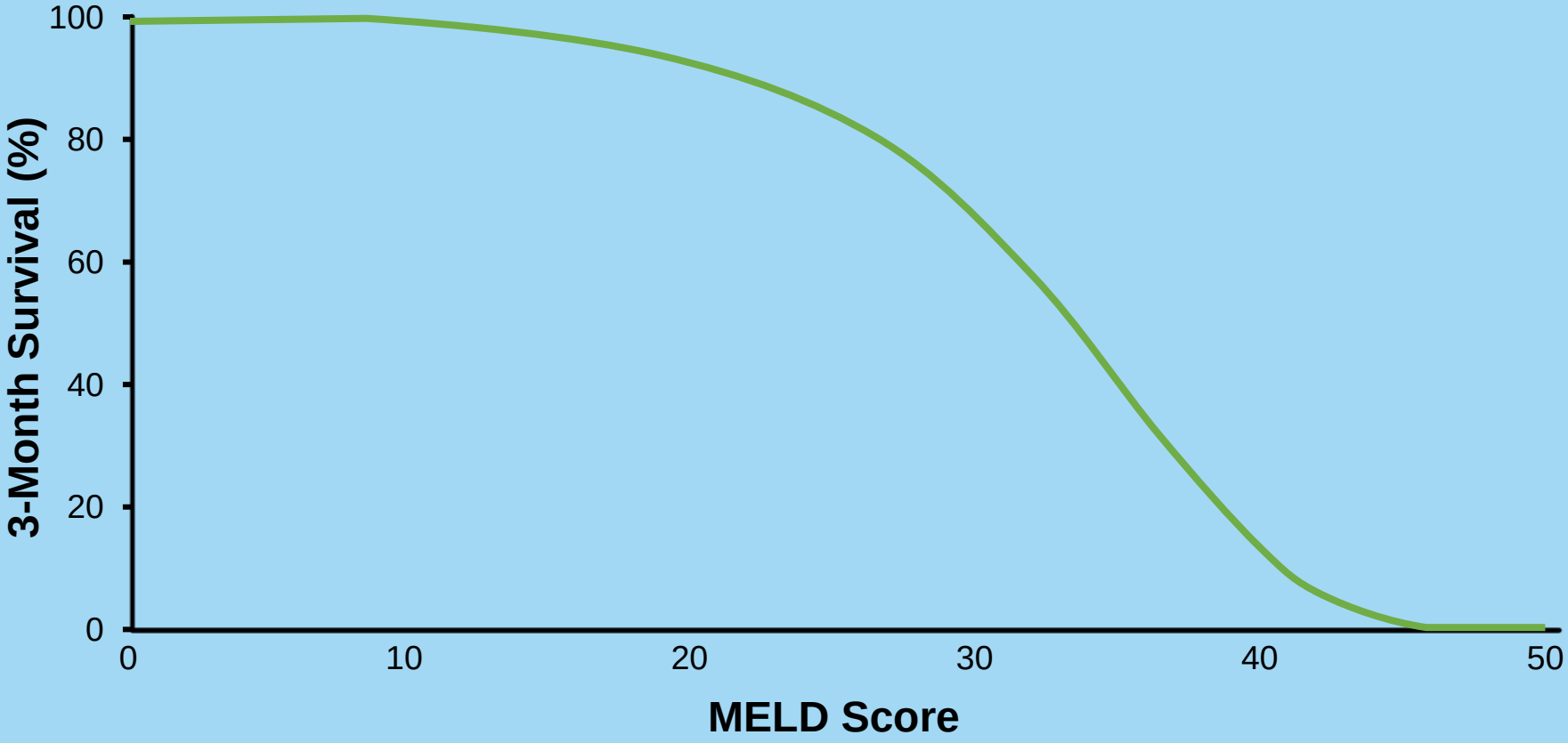
- Persistently elevated ALT levels
- Longer duration of infection
- Alcohol excess (>50 g/day)
- Age >40 years at time of infection
- HIV or HBV coinfection
- High BMI
- Male gender

Poynard T, et al. *Lancet.* 1997;349:825-832.
Kim WR, et al. Gastroenterology. 2004;127:749-755.

Health Maintenance of the Cirrhotic Patient

- Vaccinations
- Bone disease screening, surveillance, and management
- HCC screening and surveillance
- Varices screening and surveillance
- Nutritional support
  - Vitamin assessment for vitamin A and D deficiency
  - Mineral assessment: zinc and magnesium (Mg++)
- Review medication list

Estimated 3-Month Survival as a Function of MELD



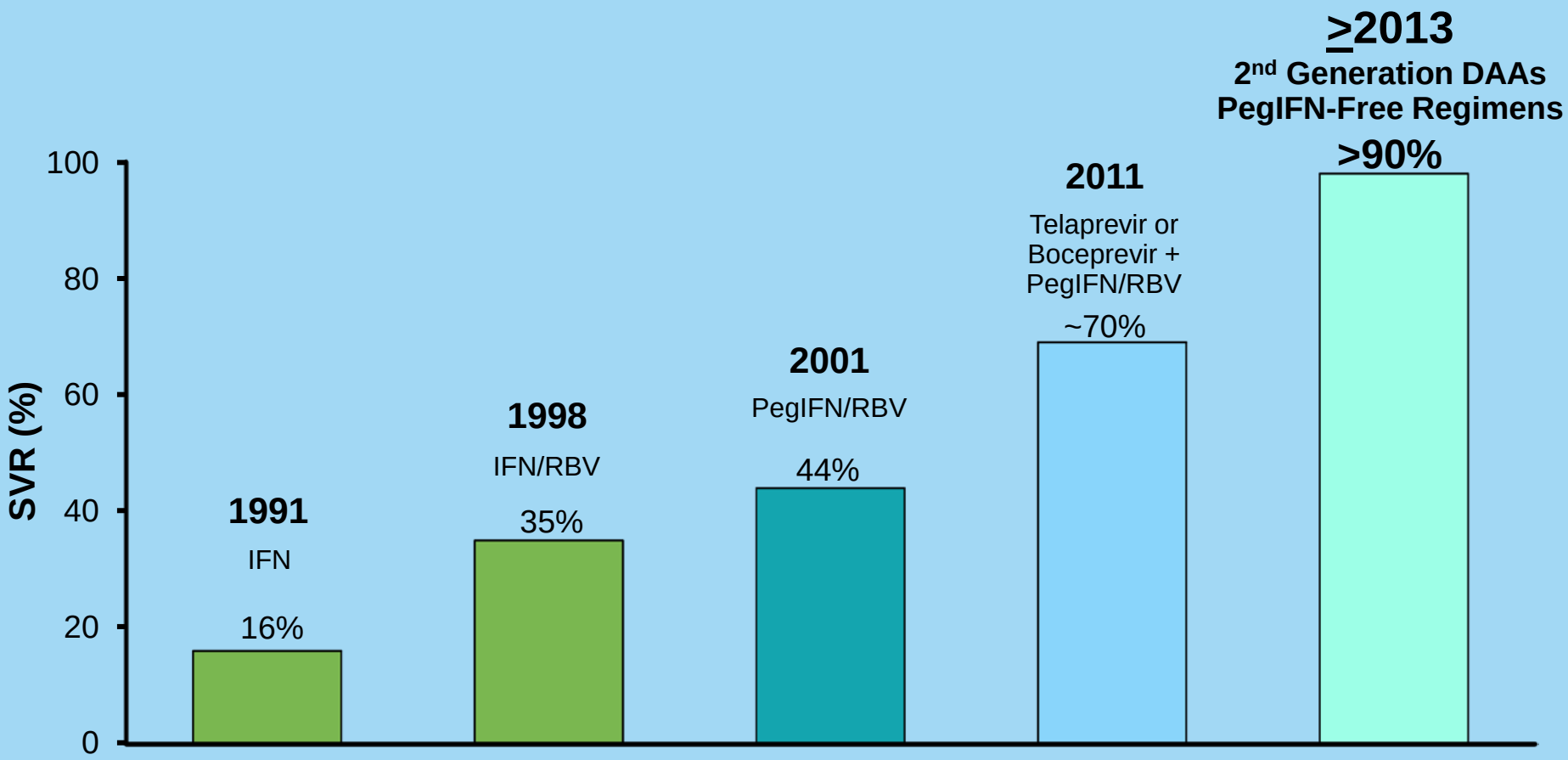
MELD = 3.8[Ln serum bilirubin (mg/dL)] + 11.2[Ln INR] + 9.6[Ln serum creatinine (mg/dL)] + 6.4

Wiesner R, et al. *Gastroenterology.* 2003;124:91-96.

When to Refer to Hepatology

- Any hepatic decompensation
  - Ascites
  - Jaundice
  - Encephalopathy
  - Variceal bleeding
- MELD >10
- Hepatocellular carcinoma

Chronic HCV Therapy: Advances in Raising Cure Rates



Schaefer EA, et al. *Gastroenterology.* 2012;142:1340-1350.
AASLD and IDSA. http://www.hcvguidelines.org/full-report-view. Version December 19, 2014.

Thank You

Richard.Manch@dignityhealth.org

What to know even more about HCV?

4th Annual Current Trends in Liver Disease

Hepatitis C From A to Z

CME Conference

Friday, October 9
11:30 a.m. – 5 p.m.

Sonntag Pavilion
St. Joseph's Hospital and Medical Center

Course Director:
Richard A. Manch, MD, FACP, FACG
Chief of Hepatology
St. Joseph's Hospital and Medical Center

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