Hepatitis C

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Hepatitis C

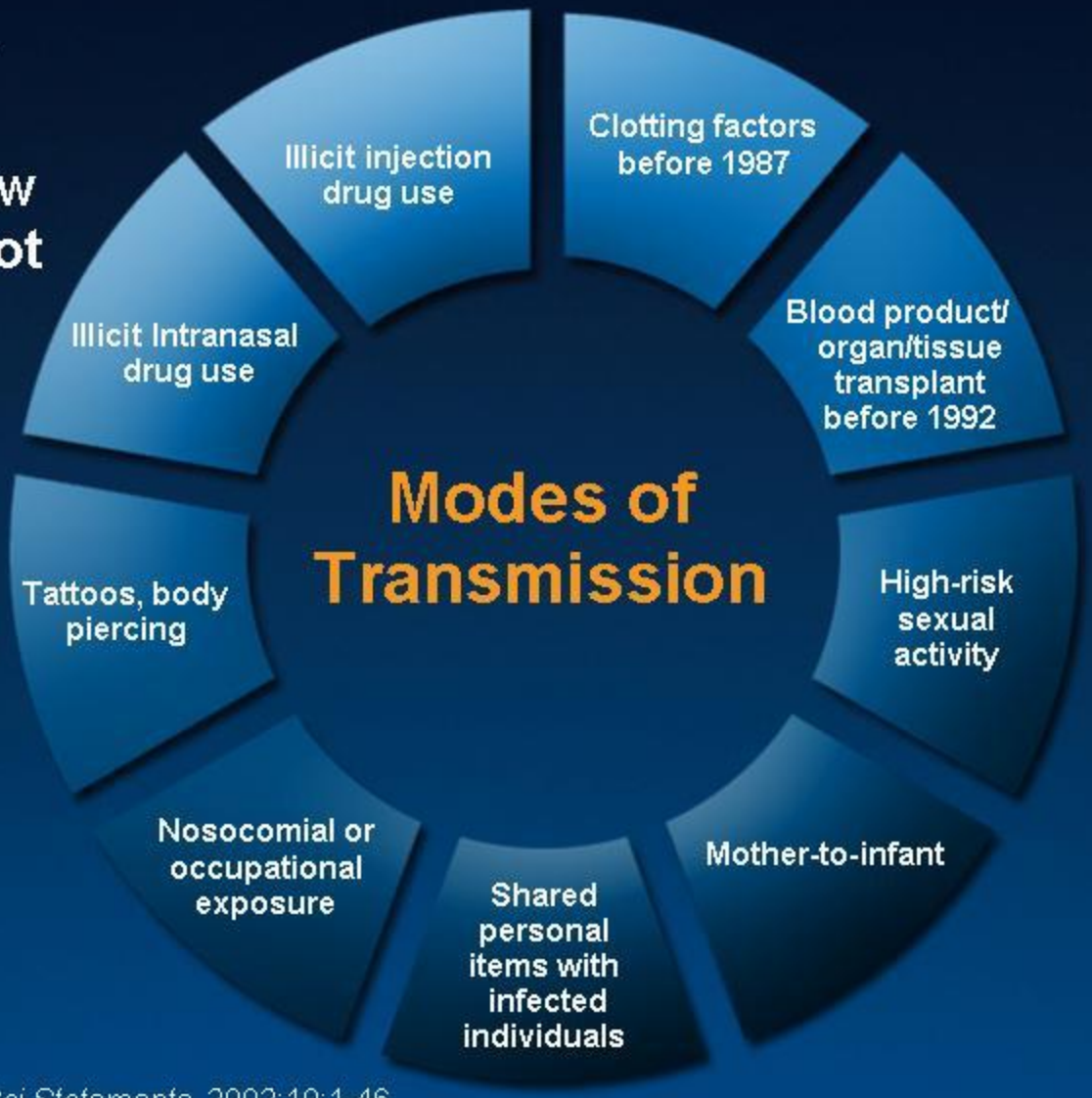
- 50 nm enveloped, positive-sense, single-stranded RNA hepacivirus.
- Seven genotypes and > 100 subtypes.
- 170 million infected worldwide;
- 4 million in USA (1.8%);
- 18,000 new infections/year.
  - 56% recent IVDU
  - 34% had =/> 2 sexual partners in last 6 months
  - 16% had recent sex with HCV (+) partner

Prevalence,

Transmission
&
Disease Burden

Transmission of HCV

~ 30% of patients do not know how they got HCV



NIH. *NIH Consens State Sci Statements*. 2002;19:1-46.

Hepatitis C Disease Burden: US

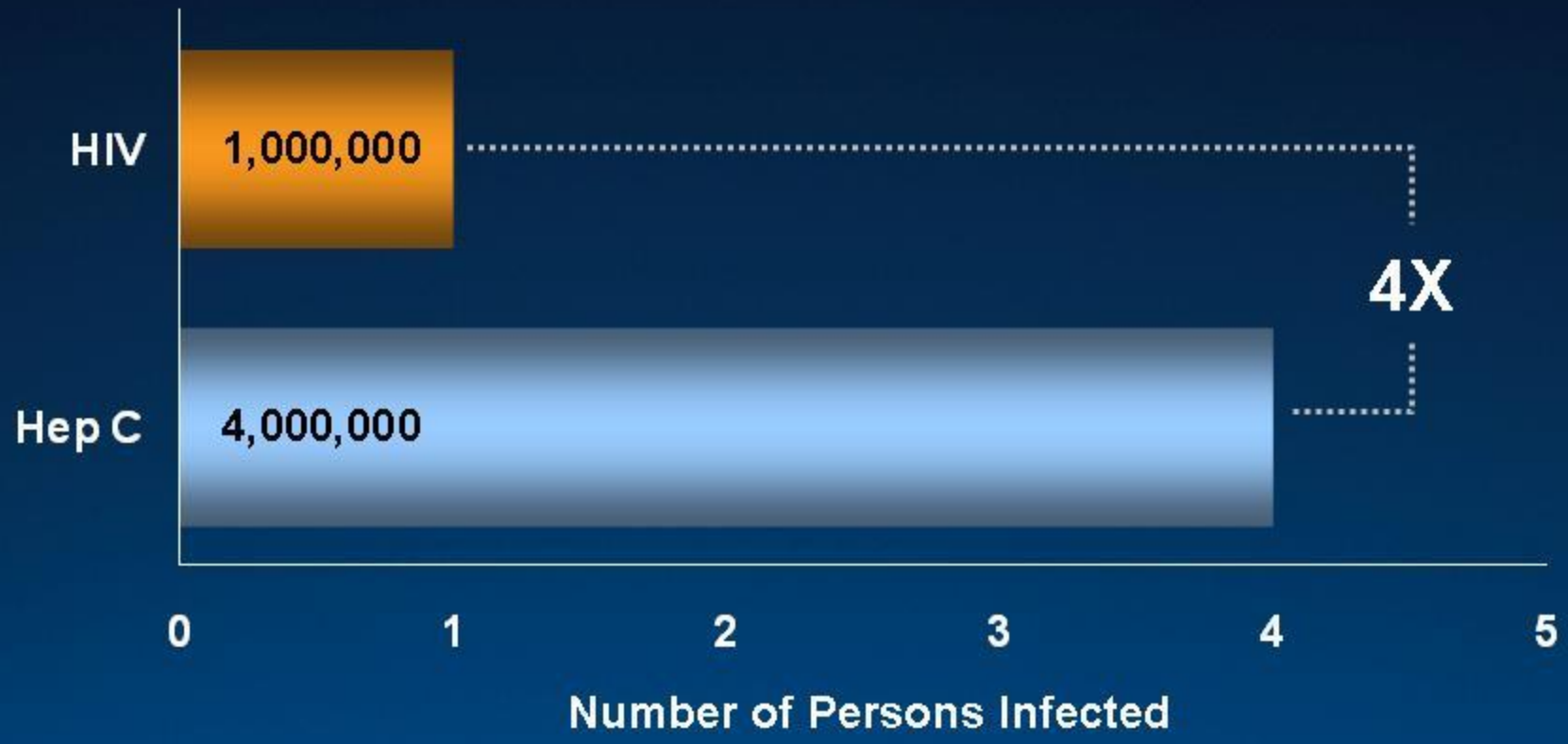
- Hepatitis C is the most common chronic blood-borne viral infection in the US[1]
  - ~ 1/2 of cirrhotic patients[2]
  - ~ 1/3 of HCC patients[3]
  - #1 reason for liver transplants[4]
  - #1 cause of death in HIV patients[5,6]

It is estimated that 4 million Americans are infected with HCV[7]

1. Alter M, et al. *N Engl J Med*. 1999;341:556-562; 2. NDDIC, 2006. Available at http://digestive.niddk.nih.gov/ddiseases/pubs/chronichepc; 3. NIH. *NIH Consens State Sci Statements*. 2002;19:1-46; 4. CDC Hepatitis Fact Sheet. http://www.cdc.gov/ncidod/diseases/hepatitis/c/fact.htm. Updated December 8, 2006; 5. Bica I et al. *Clin Infect Dis*. 2001;32:492-497; 6. Salmon-Ceron D et al. J Hepatol 2005;42:700-805; 7. Edlin B, et al. Presented at AASLD 2005. November 11-15, 2005; San Francisco, CA. Oral Presentation #44.

Prevalence of Hepatitis C

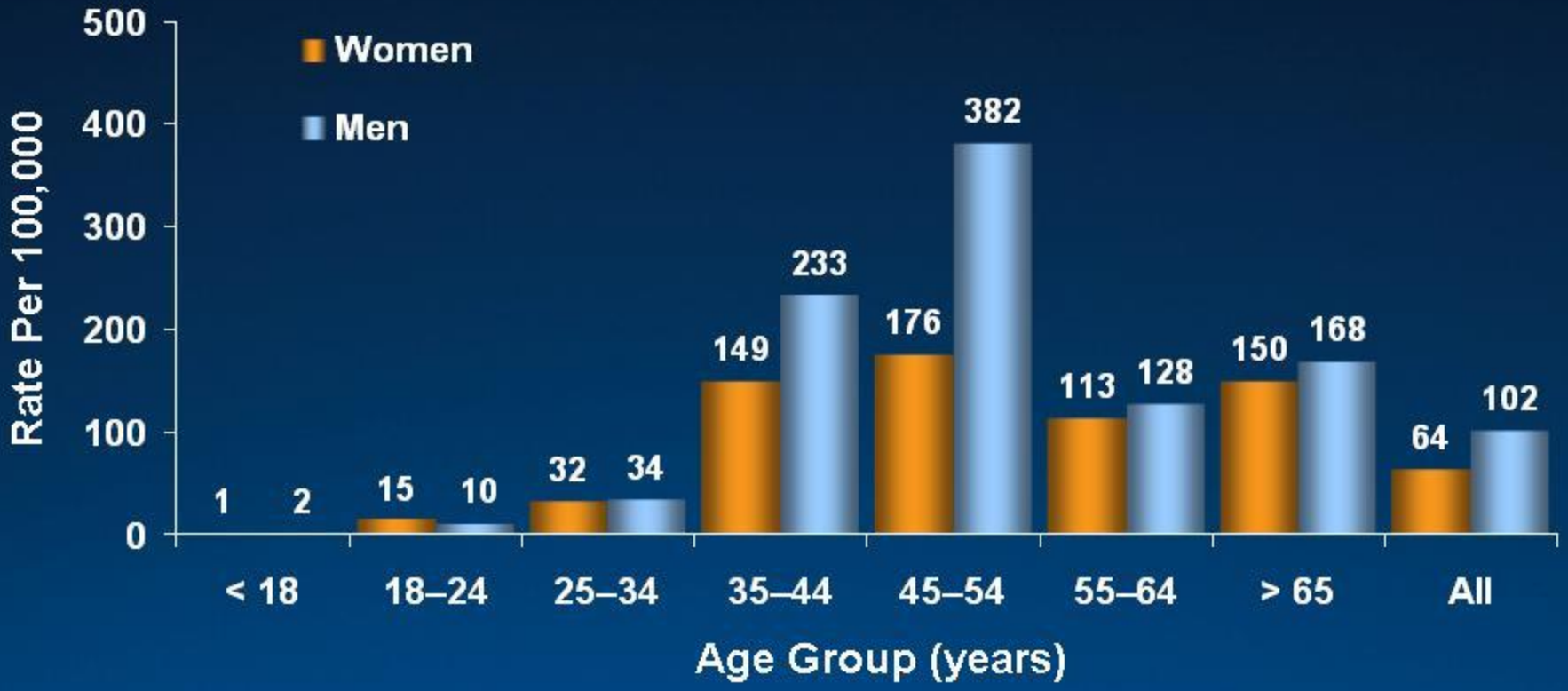
- Hepatitis C is 4 times more prevalent than HIV[1,2]



1. NIAID HIV/AIDS fact sheet. 2007. Available at: www.niaid.nih.gov/factsheets/hivinf.htm; 2. Edlin B, et al. Presented at AASLD 2005. November 11-15, 2005; San Francisco, CA. Oral Presentation #44.

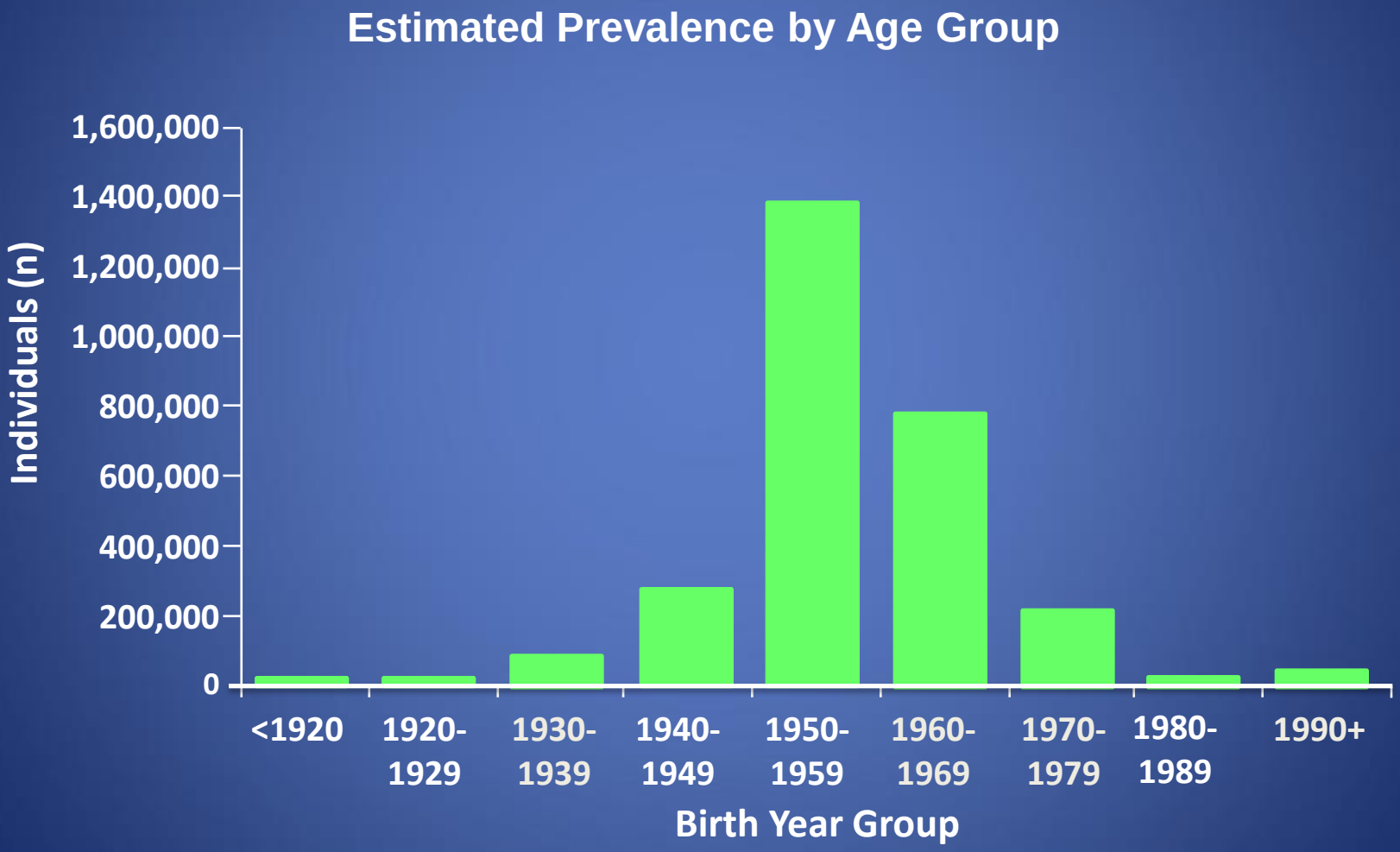
Prevalence of Hepatitis C by Age and Sex

Retrospective review of claims from 1997–1999 in US Health Plan with 3.9 million members



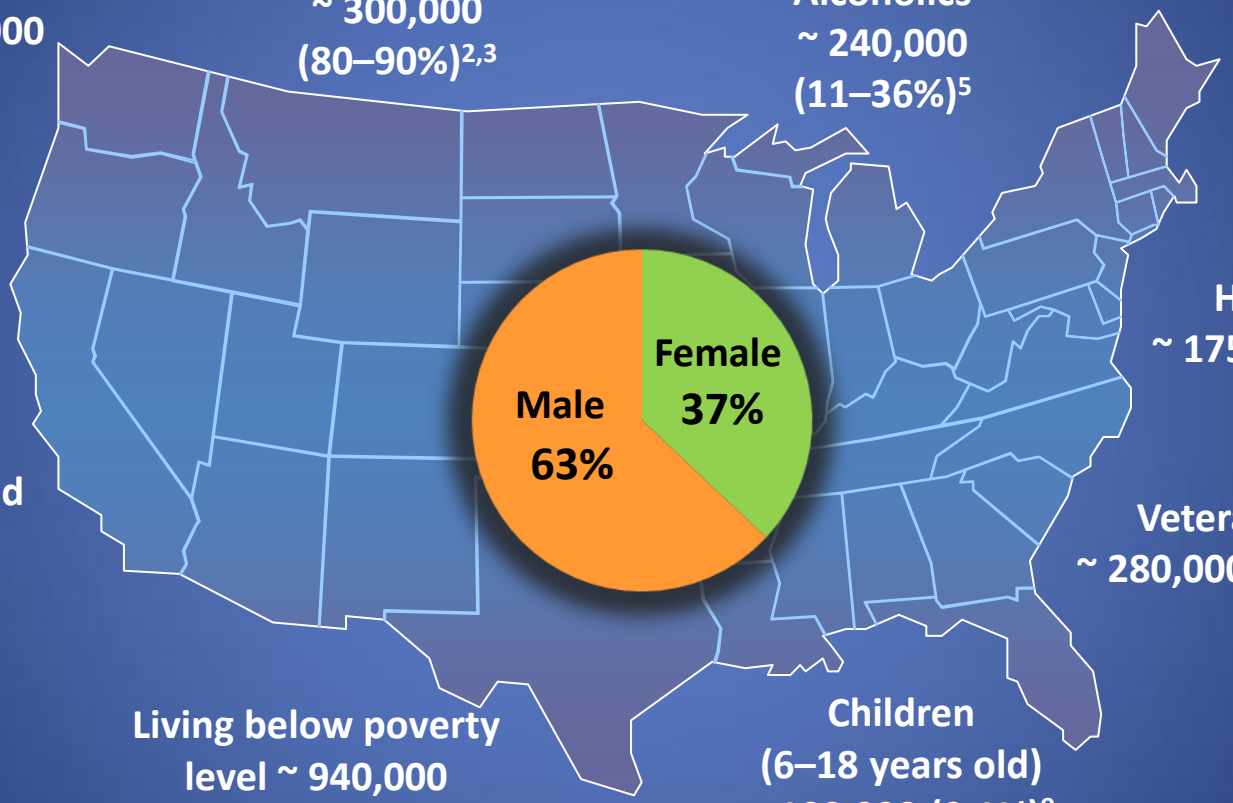
Shatin D, et al. *Am J Manag Care*. 2004;10:250-256.

Two-Thirds of Those With Chronic HCV in the US Were Born Between 1946 and 1964



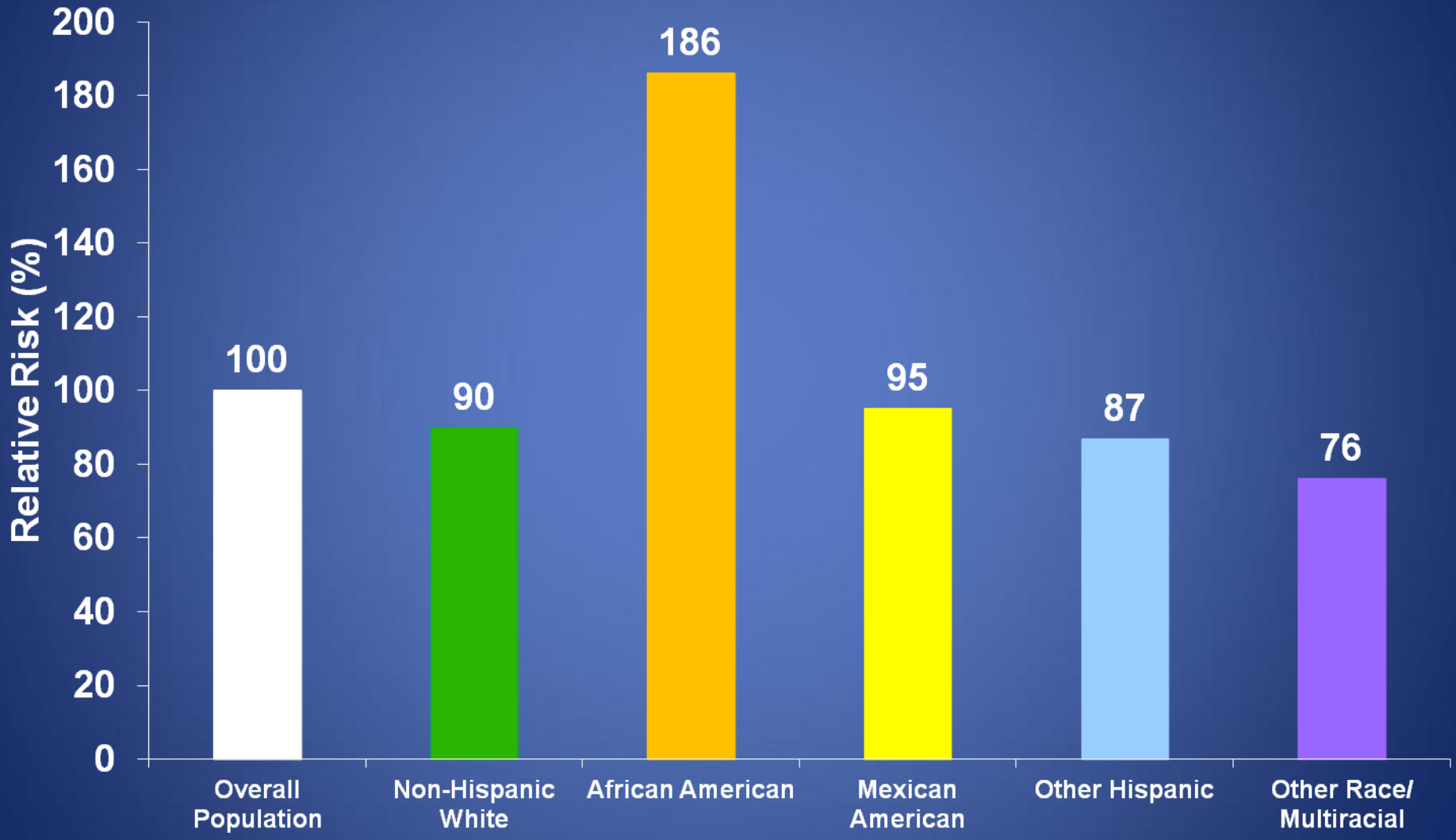
Pyenson B, et al. *Consequences of Hepatitis C Virus (HCV): Costs of a Baby Boomer Epidemic of Liver Disease.* New York, NY: Milliman, Inc; 2009.

Prevalence of HCV in Select Populations



Adapted from: 1. CDC. *MMWR*. 2003;52(RR-1):1-33; 2. Edlin B. *Hepatol*. 2002;36(5 suppl 1):S210-S219; 3. NHSDA Report 2003; 4. Poles M, et al. *Clin Infect Dis*. 2000;31:154-161; 5. LaBrecque D, et al. *Hepatitis C Choices*. 2002:7-15; 6. Alter M, et al. *N Engl J Med*. 1999;341:556-562; 7. Nyamathi A, et al. *J Gen Intern Med*. 2002;17:134-143; 8. Dominitz J, et al. *Hepatology*. 2005;41:88-96; 9. Jonas M. *Hepatol.* 2002;36(5 suppl 1):S173-S178.

Relative Risk of Being HCV Positive by Race



Pyenson B, et al. *Consequences of Hepatitis C Virus (HCV): Costs of a Baby Boomer Epidemic of Liver Disease.* New York, NY: Milliman, Inc; 2009.

HCV Prevalence Hemodialysis Patients

	general=	HD=
Egypt	18.1%	80%
Moldavia	4.9%	75%
Bulgaria	1.1%	66%
Saudi Arabia	1.8%	57%
Turkey	1.5%	31%
Italy	0.5%	22%
France	1.1%	16%
Belgium	0.9%	9%
USA	***1.8%***	***9%***
Netherlands	0.1%	3%

HCV Transmission
Dialysis Unit

- Sharing medications (heparin)
- Poor hand washing / not changing gloves
- Reuse of dialyzer after disinfection (rare)
- Internal contamination of HD machine (very rare)
- ***Must use "Universal Precautions";*** *consider room, machine & staff separation and separate dialyzer disinfection-room*

Source and Risk
HCV infection in ESRD

SOURCE	***Degree of RISK***
Breakdown of "Universal Precautions" in Dialysis Unit	Very High
Contaminated HD equipment	High
Blood Tx before 1992	Moderate
Peritoneal Dialysis	Low
Blood Tx after 1992	Very low
Illicit drug use	As general population

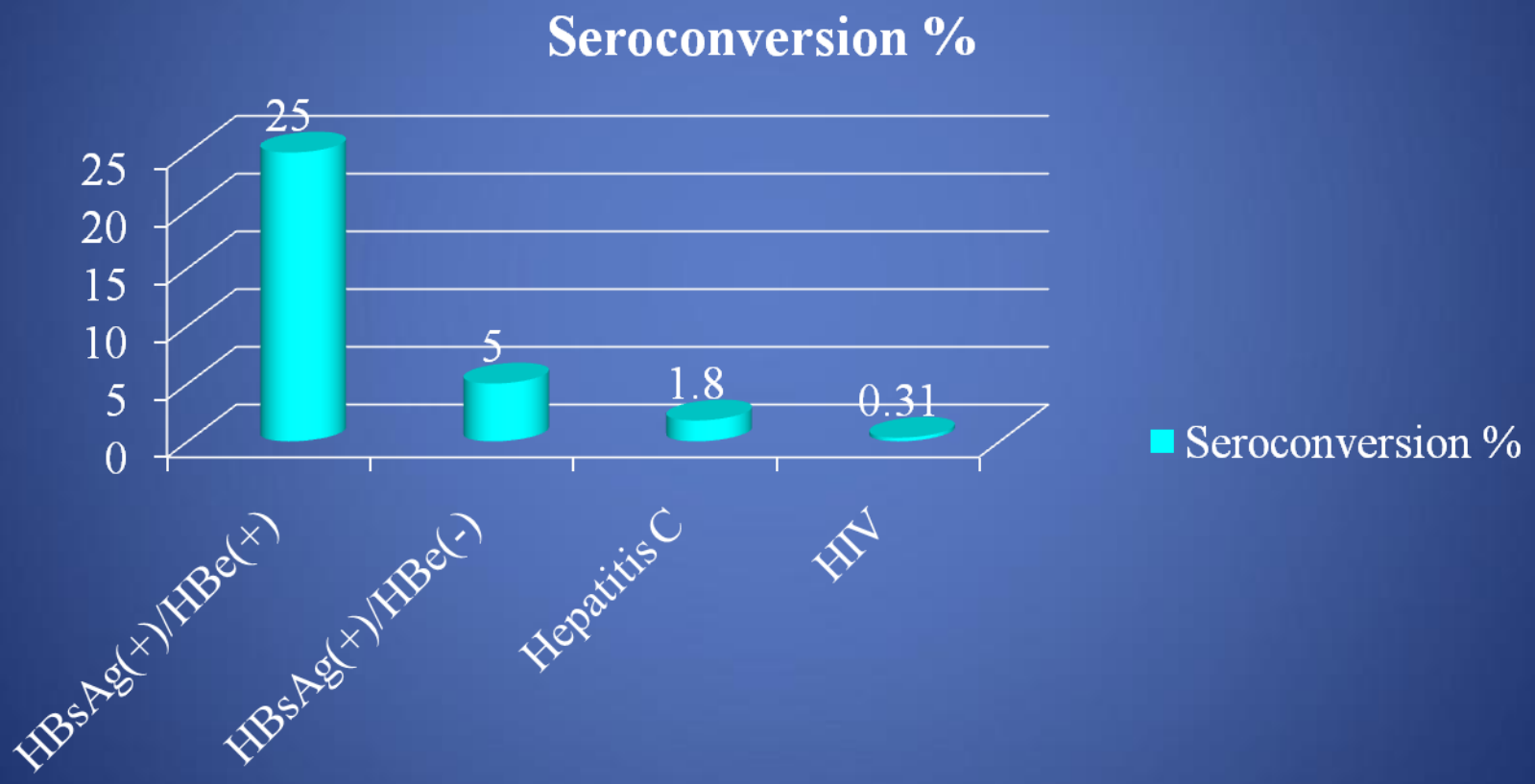
Hepatitis C and Healthcare Workers (HCWs)

HCW exposure to HCV

- Prevalence of HCV in HCWs is similar to that of the general population.
- Testing for HCV in HCWs should be done after percutaneous, mucosal, and nonintact skin exposure to HCV(+) blood and potentially infectious body fluids.
- HCV can survive in environmental surfaces for > 16 hours, but < than 4 days.
- Baseline testing: anti-HCV, HCV-RNA quant, ALT
- F/U testing: ALT, HCV-RNA, anti-HCV @ wk 4, 12 & 24.
- If infection occurs and persists for >/= 12 weeks, treat as acute HCV.

Risk of Seroconversion after percutaneous exposure to infected source (without prophylaxis)

Epidemiol Rev 1994;16:437-450 & MMWR 1998;47(RR-19):1-39



Worldwide Cases of HCW-to-Patient HIV, HBV, or HCV Transmission 1991-2005

Am J Infect Control 2006;34:313-319

	# HCW	# Infected Patients	# Patients tested in look-back	% Infected Patients
HIV	3	3	3527	0.09%
HBV	12	91	3079	2.96%
HCV	11	38	9678	0.36%

Risk of Infection by Mode of Exposure to HCWs

	HBV	HCV	HIV
Percutaneous	6-30%	1.8%	0.2-0.5%
Mucosal	Transmission documented	Transmission documented	0.09%
Nonintact Skin	Transmission NOT documented	Transmission NOT documented	< 0.1%
Human Bite	Transmission documented	Transmission documented	Transmission documented

Infective Material Causing HCWs Infection

	HBV	HCV	HIV
Documented	Blood Blood products	Blood Immunoglobulins	Blood Blood products Body fluids
Possible	Semen Vaginal fluid Bloody fluids Saliva	Blood products Bloody fluids Semen Vaginal Fluids	Semen Vaginal fluid Cerebrospinal fluid Breast milk Serosal fluids Amniotic fluid Exudates Saliva in dental exam
Unlikely	Urine Feces	Saliva Urine Feces	Saliva Urine Feces

Vertical Transmission of HCV

(Obstet Gynecol Surv 2006; 61:666-72)

- Risk if mother anti-HCV(+) is approximately 2%;
  - If mother is HCV-RNA (+), risk is 4-5%.
  - Scalp electrodes increase risk of transmission.
- Up to 30% of infected neonates may have acquired HCV “in utero” (Arch Dis Child Fetal Neonatal Ed 2005;90:F156-60)
- In HCV/HIV co-infection the risk is higher (15-18%) but HAART may decrease the risk.
- There is no association between vertical transmission of HCV, gestational age at delivery, nor chorioamnionitis.
- Data are conflicting about duration of ruptured membranes and risk of HCV transmission (increased after 6 h ?)

Vertical Transmission of HCV
Cesarean Section vs Vaginal Delivery

- The “Cochrane Pregnancy and Childbirth Group’s Trial Register”, and the “Cochrane Central Register of Controlled Trials” were analyzed until April 2006.
- No randomised controlled trials were found (Cochrane Database Syst Rev 2006; Oct 18).
- Systematic review of observational studies (subject to biases) or RCT’s are needed.

Vertical Transmission of HCV

(Obstet Gynecol Surv 2006; 61:666-72)

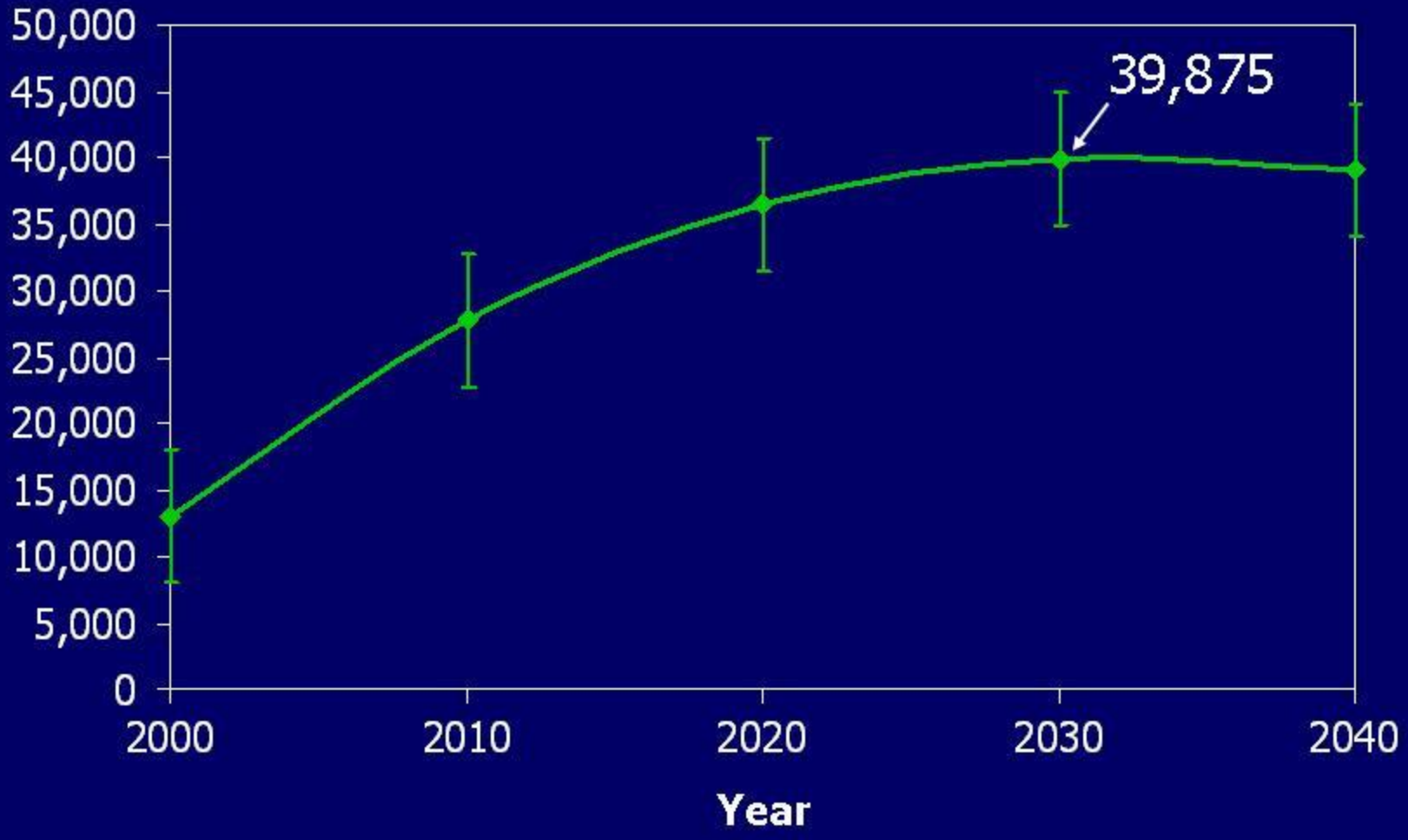
- **In HCV(+)/HIV(-) mothers:**
  - Route of delivery does not influence vertical transmission.
  - There is no need to discourage breast feeding.
- **In HCV(+)/HIV(+) mothers:**
  - Mode of delivery should be based in HIV status.
  - Breast feeding should be discouraged.

Measures to Avoid Transmission of HCV
What an Infected Person Should Do

- Avoid sharing toothbrushes and dental or shaving equipment.
- Cover any bleeding wound in order to prevent contact of their blood with others
- Stop using illicit drugs.
- If continue to inject drugs should:
  - 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
- Do not donate blood, body organs, other tissue or semen
- Know that the risk of sexual transmission is low, and that the infection itself is not a reason to change sexual practices (i.e., those in long-term relationships need not start using barrier precautions and others should always practice “safer” sex)

Table adapted from “Recommendations for prevention and control of hepatitis C virus (HCV) infection and HCV-related chronic disease.” Centers for Disease Control and Prevention. MMWR Recomm Rep 1998;47(RR-19):1-39

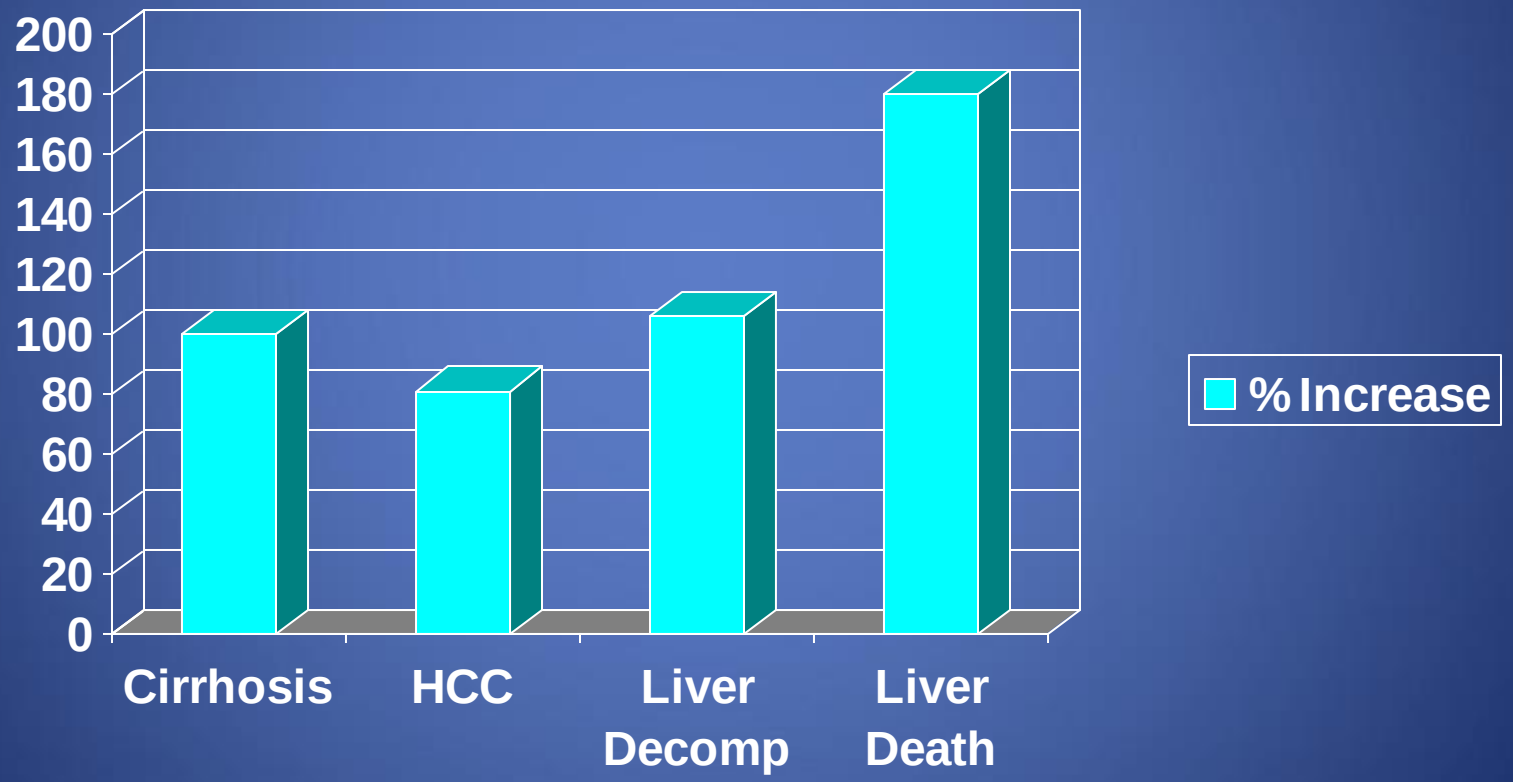
Projected HCV Mortality



Adapted from Davis et al. *Liver Transpl.* 2003;9:331-338.

Future Disease Burden: Estimated Increases from 2000-2020

(Davis GL Liver Transpl 2003:9:331-338)

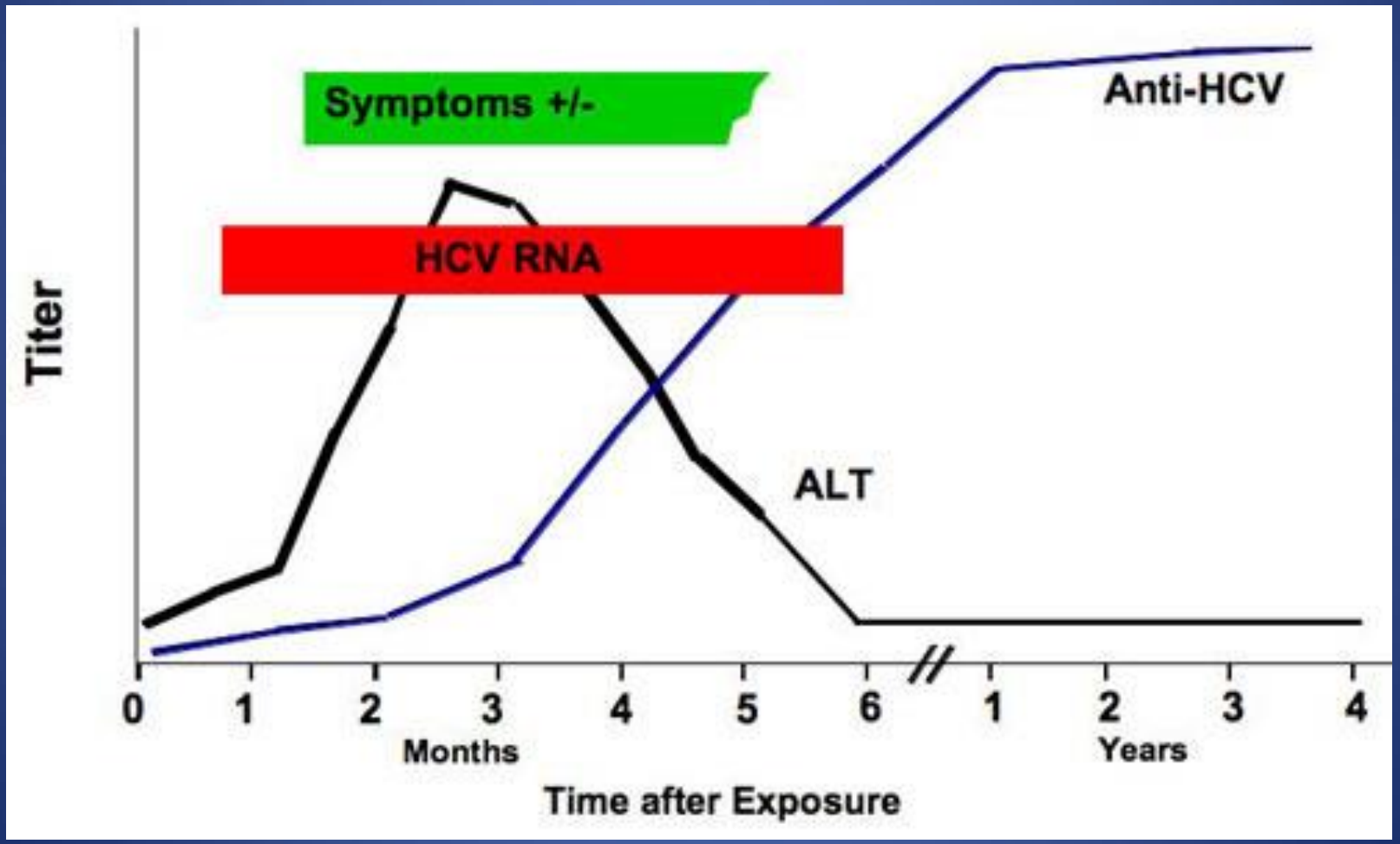


Acute HCV

Acute HCV

- **Incubation**: 2-26 weeks (usually 7-8)
- **Symptoms:** in < 30%, mild & last < 1month;
  - Usually: anorexia, arthralgia, myalgia, fatigue;
  - Rarely: jaundice, fever, or skin rash.
  - Extremely rare: FHF.
- **DX**: HCV-RNA (+) days to weeks after acquisition ; anti-HCV (+) in 6 weeks.
- **Spontaneous HCV clearance**: (within 12 weeks in adults)
  - Children < 2 y.o. & young women = 45%;
  - Others = 23%
  - HIV co-infection = 20%

Acute Hepatitis C

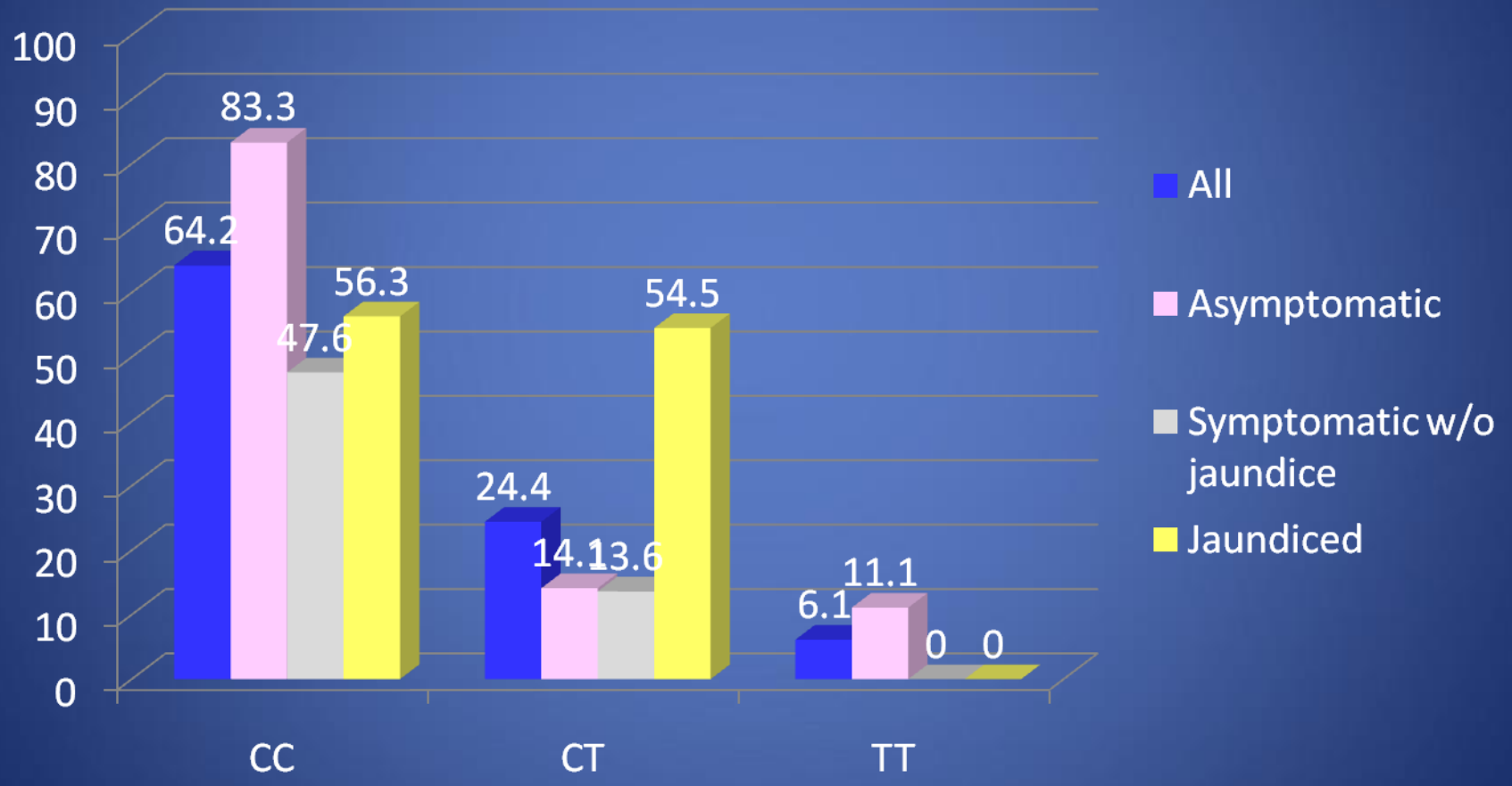


Interpretation of Tests During Diagnosis of Acute HCV

TEST	Interpretation in Acute HCV
HCV antibody	•May be negative in the first 6 weeks after exposure •May be delayed or absent when the individual is immunosuppressed •Presence alone does not distinguish between acute and chronic infection •Low signal-to-cutoff ratio may be present during acute HCV infection or represent a false-positive result
HCV RNA	•Viral fluctuations greater than 1 log10 IU/mL may indicate acute HCV infection •May be transiently negative during acute HCV infection •Alone does not distinguish between acute and chronic infection
Alanine aminotransferase (ALT)	•Fluctuating peaks during acute HCV infection suggest acute infection •May be normal during acute HCV infection •May be elevated due to other liver insults such as alcohol consumption

Spontaneous HCV Clearance in Acute HCV in 136 Young Women (25+/-4 y/o) by IL28B Genotype

Gastroenterology 2010;139:1586-1592



Recommendations for medical management and monitoring in acute HCV infection

- **Regular laboratory monitoring is recommended in the setting of acute HCV infection until the ALT level normalizes and HCV RNA becomes undetectable. Rating:** Class I, Level B
- **Monitoring HCV RNA (eg, every 4 weeks to 8 weeks) for 6 months to 12 months is recommended to detect spontaneous clearance of HCV infection. Rating:** Class I, Level B
- **Counseling is recommended for patients with acute HCV infection to avoid hepatotoxic insults including hepatotoxic drugs (eg, acetaminophen) and alcohol consumption and to reduce the risk of HCV transmission to others. Rating:** Class I, Level C
- **Referral to an addiction medicine specialist is recommended for patients with acute HCV infection related to IDU. Rating:** Class I, Level B

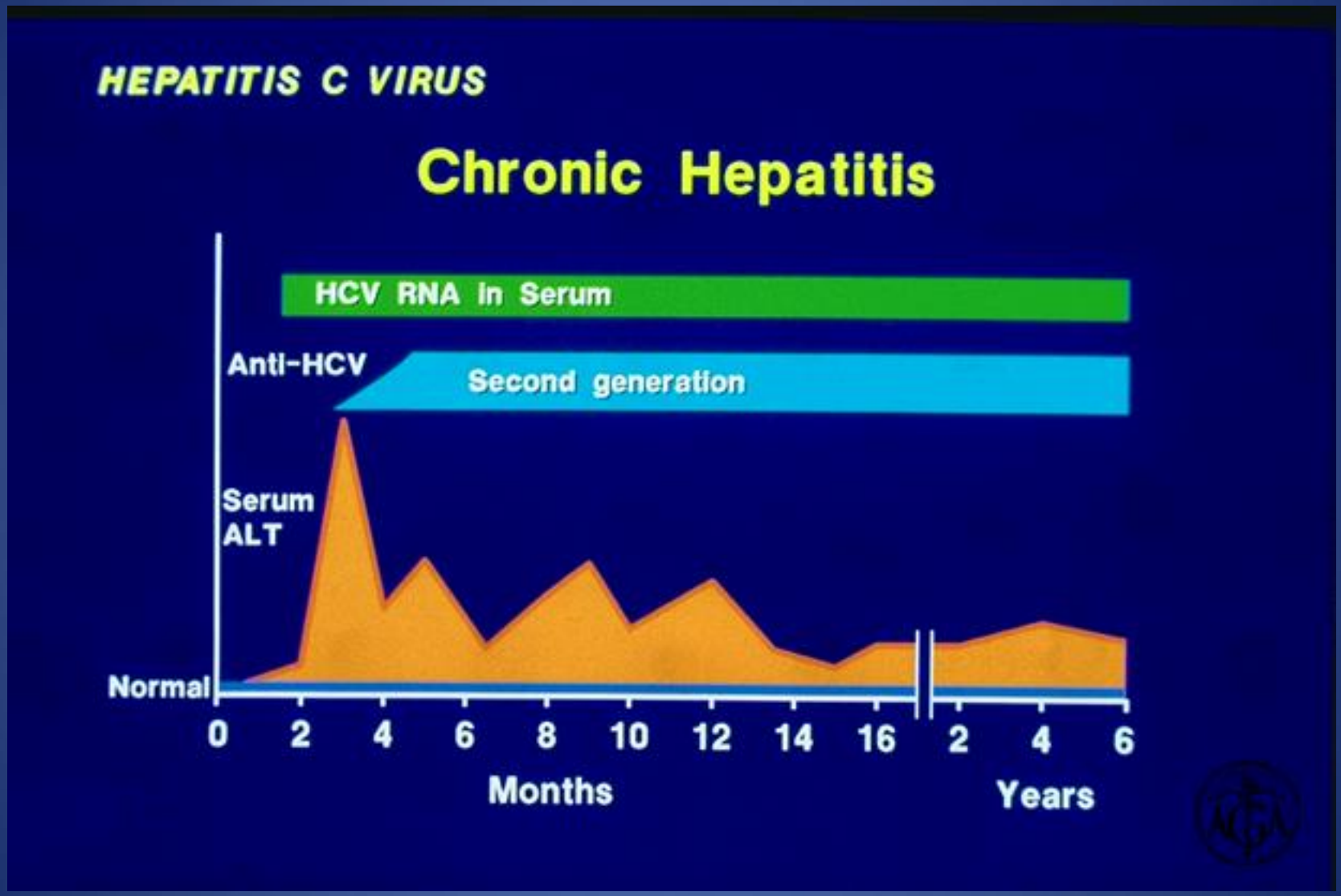
Recommended treatment for patients with Acute HCV infection

- **If the practitioner and patient have decided that a delay in treatment initiation is acceptable, monitoring for spontaneous clearance is recommended for a minimum of 6 months. When the decision is made to initiate treatment after 6 months, treating as described for chronic hepatitis C is recommended. Rating:** Class IIa, Level C
- **If a decision has been made to initiate treatment during the acute infection period, monitoring HCV RNA for at least 12 weeks to 16 weeks is recommended to allow for spontaneous clearance before starting treatment. Rating:** Class IIa, Level C
- ***Recommended regimens for patients with acute HCV infection:*** **Owing to high efficacy and safety, the same regimens recommended for chronic HCV infection are also recommended for acute infection. Rating:** Class IIa, Level C
- ***Alternative regimen for patients with acute HCV infection who are eligible to receive IFN:*** **PEG-IFN with or without RBV:**
  - **for 16 weeks (for those with genotype 2 or 3 HCV who have a rapid virologic response [RVR])**
  - **for 24 weeks (for those with genotype 1 HCV). Rating:** Class II, Level A

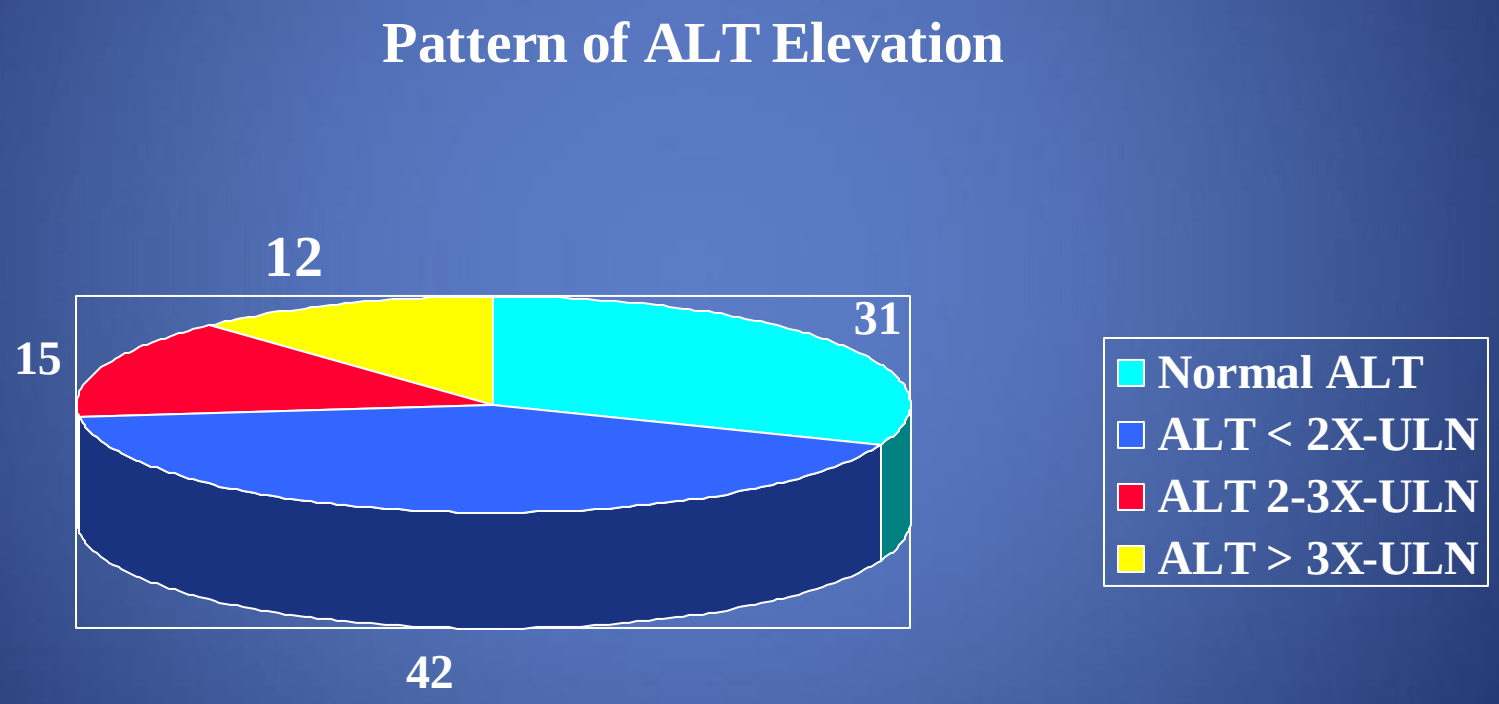
Chronic HCV

Chronic HCV

- Most are asymptomatic; 6% symptomatic before diagnosis.
- **Symptoms**: fatigue, RUQ discomfort, anorexia, nausea, itching, arthralgia, myalgia.
- **Extrahepatic**: mixed cryoglobulinemia, purpura, mononeuritis multiplex, PCT, membrano-proliferative glomerulonephritis, xerostomy, low-grade B-cell lymphoma, corneal ulcers and idiopathic pulmonary fibrosis, lichen planus.

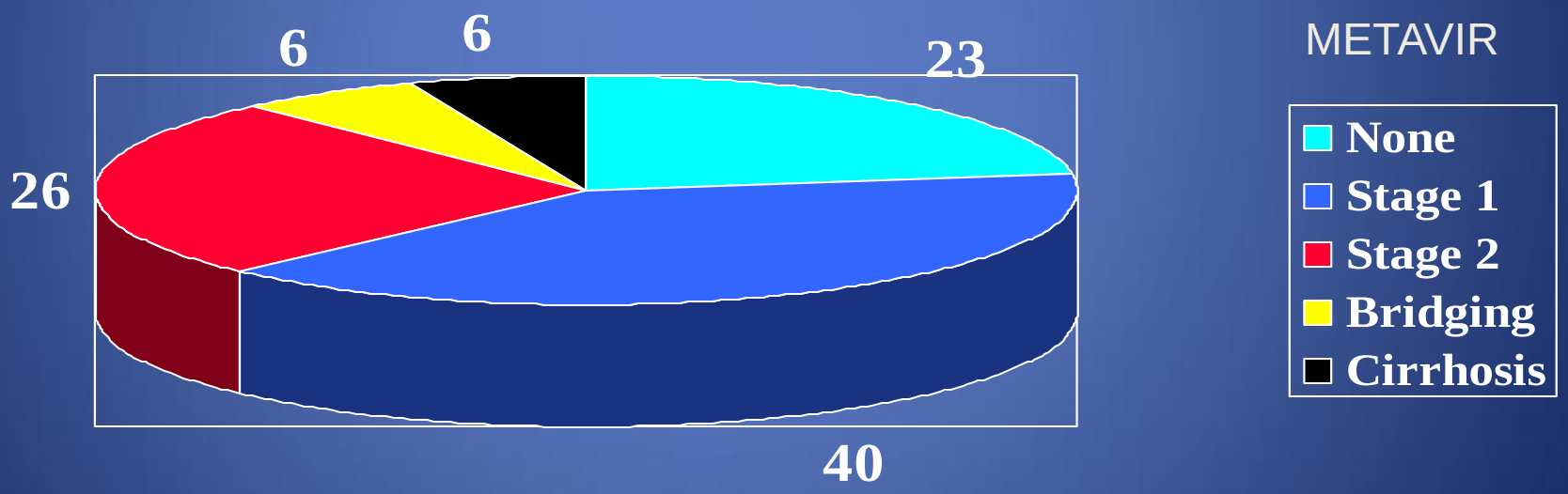

HEPATITIS C VIRUS
Chronic Hepatitis
HCV RNA in Serum
Anti-HCV
Second generation
Serum ALT
Normal
0 2 4 6 8 10 12 14 16 2 4 6
Months
Years

Pattern of ALT Elevation in Chronic HCV



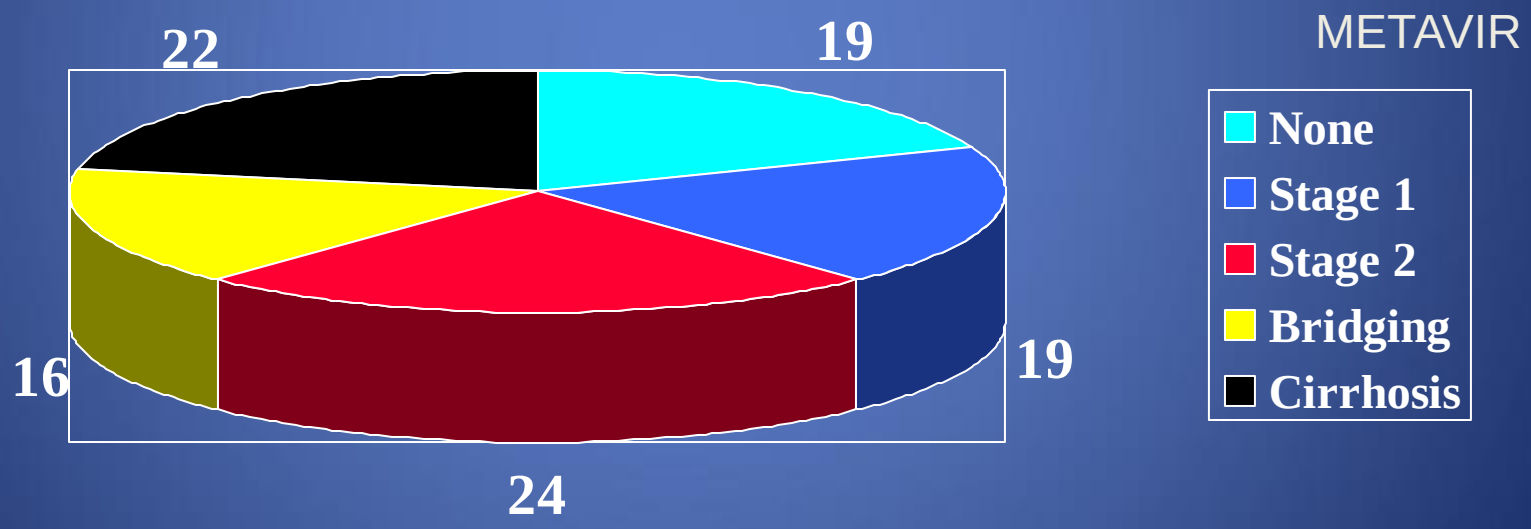
Degree of Fibrosis in Chronic HCV With Normal ALT

(Schiffman et al. J Infect Dis. 2000; 182:1595-1601)



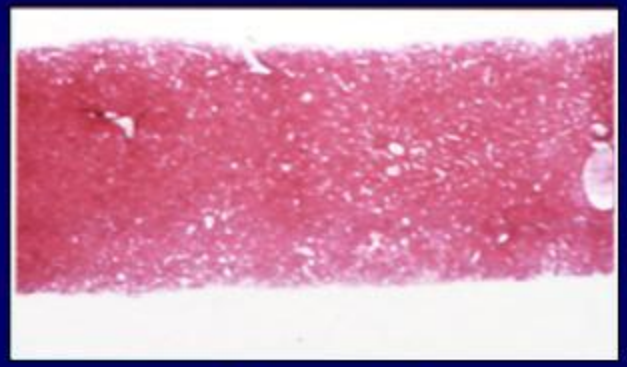
38% qualify for therapy (METAVIR >/= 2)

Degree of Fibrosis in Chronic HCV With Elevated ALT

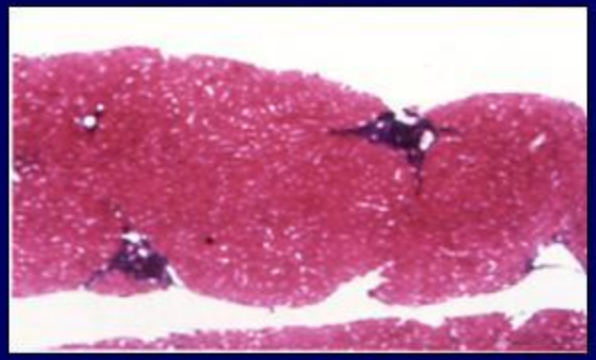


68% qualify for therapy (METAVIR >/= 2)

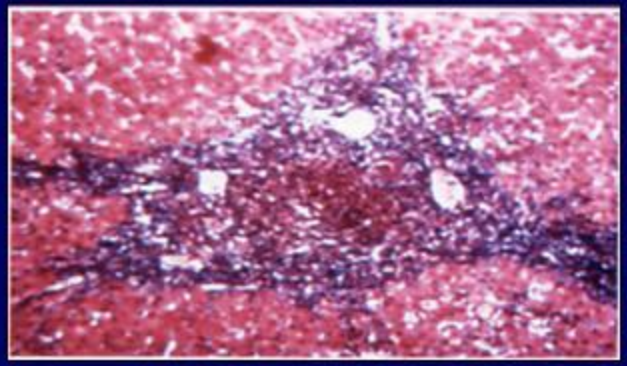
Histologic Progression of HCV on Biopsy



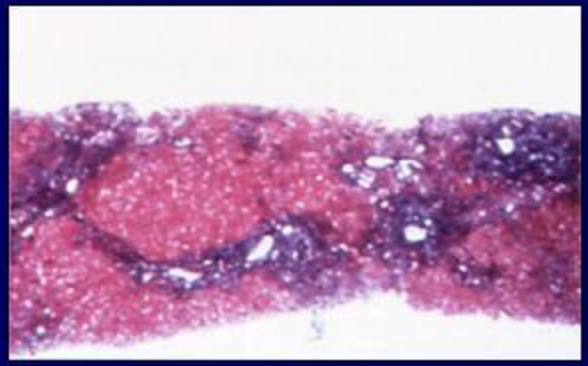
Normal



Mild Chronic Hepatitis



Moderate Chronic Hepatitis



Cirrhosis

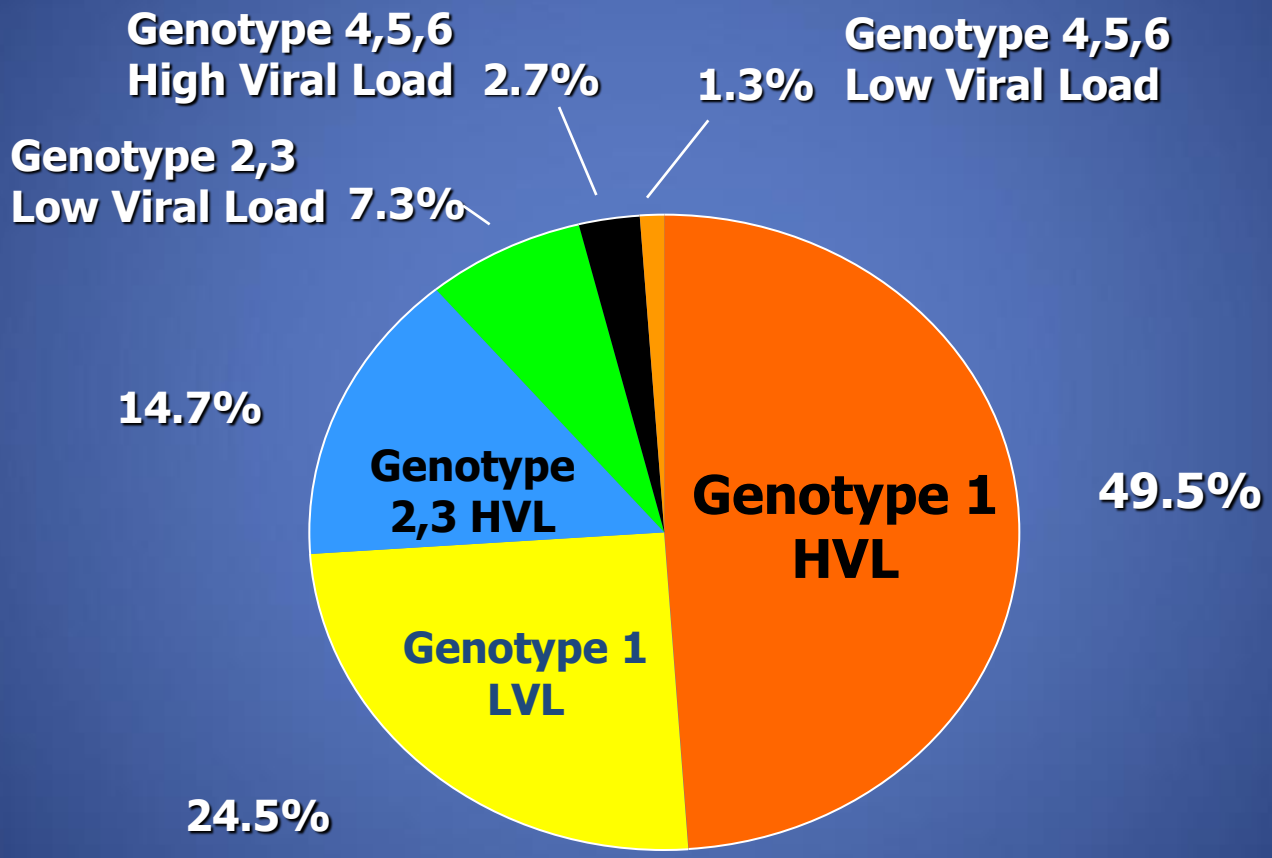
Slide Courtesy of Bennett, MD.

Relation of “Fibrosis Stage” to “Mean Area of Fibrosis” by Imaging Analysis

Bedossa P et al. Hepatology 2003;38;1449-1457

Metavir Stage	Mean Area of Fibrosis (range)
F0	**2** (0.7-2.7)
F1	**3.4** (2.7-4.6)
F2	**5.8** (4.6-10.2)
F3	**14.7** (10.2-19.9)
F4	**25.1**(19.9-30.2)

Genotype and Viral Load in US Patients



Alter et al. *N Engl J Med.* 1999;341;556-562.
Blatt et al. *J Viral Hepatitis.* 2000;7:196-202.

Hepatitis C

Diagnostic Tests

Diagnostic Tests for HCV

EIA (enzyme immunoessay)	Recommended screening test for HCV – Tests for antibodies against infection – 98.8–100% sensitivity
Qualitative HCV RNA	Recommended to confirm HCV diagnosis – May be more sensitive than quantitative test
Quantitative HCV RNA	Obtain viral load and confirm HCV diagnosis – May be less sensitive than qualitative test
Genotype	Used to determine HCV genotype after confirmation of diagnosis
Liver biopsy	May be used by specialist to determine extent of liver fibrosis and guide treatment decisions

Kuritzky L, et al. *Family Practice Recertification*. 2006;28(2):41-57.

Markers of Viral Hepatitis C: ***Anti-HCV***

- Usually ELISA-3
- False (+) in low prevalence population without risk factors (40%) and hypergammaglobulinemia
- Rare false (-) [HIV(+), hemodialysis, transplant]
- Acute HCV turns (+) at week 4 in 74%; 98% at week 20. ***(average "window" is 8-12 weeks)***

Markers of Viral Hepatitis C: ***Anti-HCV,*** *continued*

- Not a protective antibody
- May remain (+) up to 10 years post-acute infection
- **Almost all patients with chronic HCV are anti-HCV (+)**

Markers of HCV infection:
HCV-RNA Quantitation

- Uses Real-time PCR, Transcription mediated amplification (TMA), or TaqMan
- Appears 1-2 weeks after infection
- In perinatal infection:
  - 70% (+) @ 3 months; many clear spontaneously.
  - Better test @ 18 months if anti-HCV is (+).
- **Variations of up to 0.5 log (3-fold) have no clinical meaning.**

Markers of Viral Hepatitis C: ***HCV-RNA Quantitation***

- Fall of < 2-log at week 12 of therapy predicts lack of response to PEG-interferon + Ribavirin
- Fall > 2-log at week 12 of therapy predict SVR in 68% [90% if PCR(-) & 26% if PCR(+)]
- Low viral load ($\leq$ 400,000 IU/ml) respond better to therapy than High viral load (HVL);
- HVL patients respond similarly independently of how high is the load.
- Infrequent false (+) or false (-)

Quantitative HCV-RNA ASSAYS

	Conversion Factor IU/mL	Dynamic Range IU/mL	FDA Approved
Amplicor HCV Monitor	0.9 copies/mL	600-500,000	Yes
COBAS Amplicor HCV Monitor V2	2.7 copies/mL	600-500,000	Yes
Versant HCV RNA 3 Assay (bDNA)	5.2 copies/mL	615-7'700,000	Yes
LCX HCV RNA-Quantitative Assay	3.8 copies/mL	25-2'630,000	No
SuperQuant	3.4 copies/mL	30-1'470,000 **LLD 8 IU/mL**	No
COBAS Taqman HCV Test		43-69'000,000 **LLD 10 IU/mL**	Yes
Abbott RealTime		12-100'000,000	No

HCV in ESRD

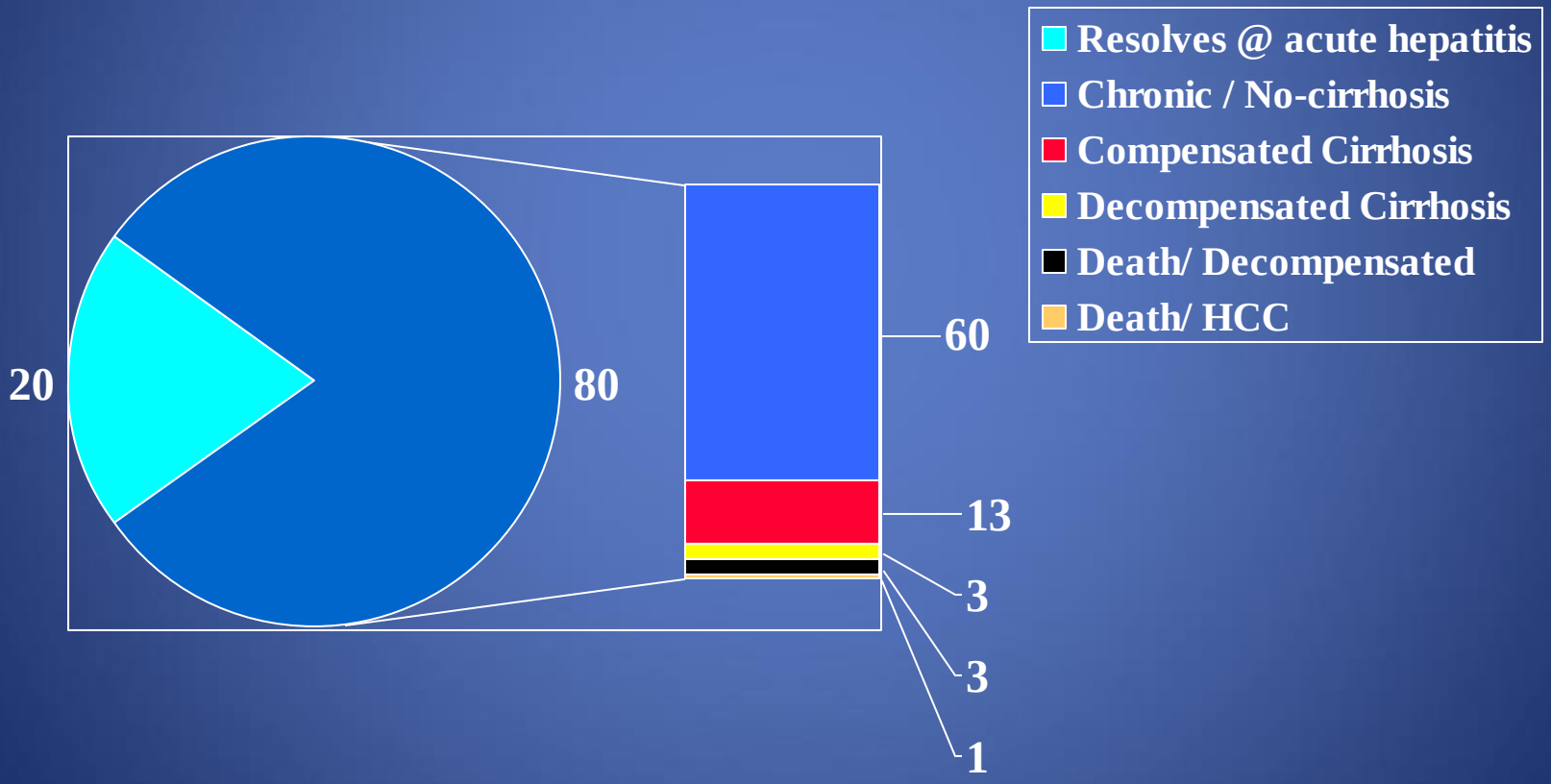
Problems with Diagnosis

- False (-) anti-HCV by ELISA-2 = 2.60 %
- False (-) anti-HCV by ELISA-3 = 0.23 %
- Delayed sero-conversion (>7 mo) and short-lived elevation of ALT after acute infection.
- ALT frequently normal in chronic HCV (+) patients with ESRD and/or in hemodialysis
- Heparin in dialysis interferes with PCR
- Hemodialysis decreases HCV-RNA load.

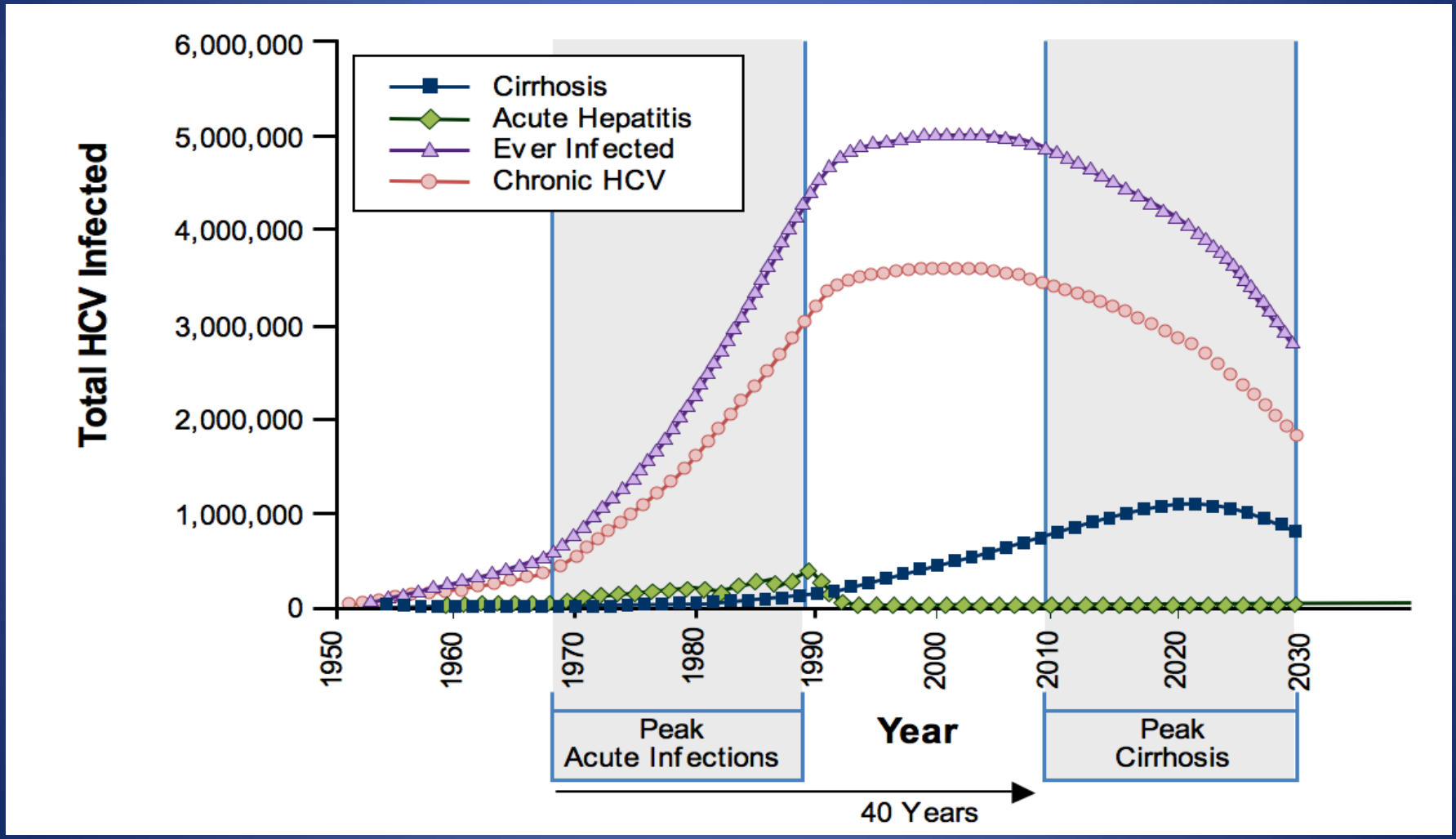
Immunocompetent Host

Natural History

Outcome of HCV
25-30 year Follow-up



Aging of HCV-Infected Persons in the US: Disease Progression



Davis G, et al. *Gastroenterology*. 2010;138:513-521.

Factors Associated With Disease Progression

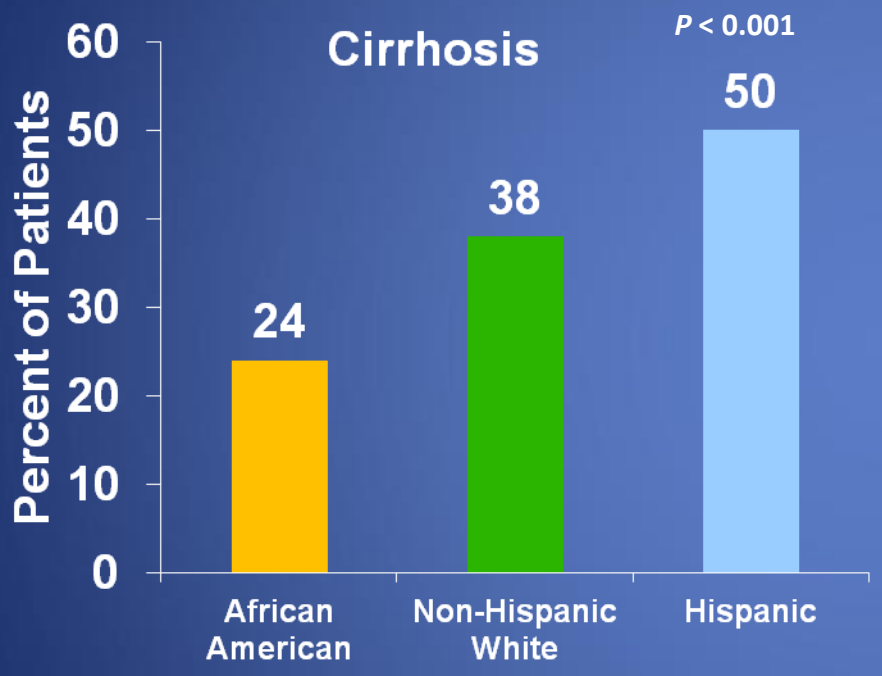
Associated with disease progression[1]	Not Associated with disease progression[1]
Alcohol consumption 30 g/day for males 20 g/day for females } ~2 drinks/day	Alanine aminotransferase level
	Viral load
	Transmission mode
Disease acquisition at >40 years	Genotype
Male gender	
Coinfection: HIV or HBV[2]	
Immunosuppression[2]	

Metabolic factors (steatosis, obesity, diabetes)

[1]Poynard et al. *Lancet.* 1997;349:825-832.

[2]NIH. *NIH Consens State Sci Statements.* 2002;19(3):1-46.

Ethnicity and Cirrhosis on Liver Biopsy



Clinical Factors Associated with Cirrhosis–Multivariate Analysis

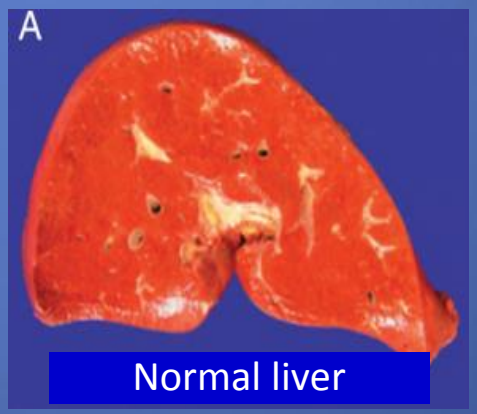
Factor	OR	95% CI	*P*-value
Hispanic*	2.4	1.27-4.42	0.007
Non-Hispanic White*	1.6	0.95-2.79	0.076
BMI	1.1	1.03-1.10	0.001
Duration of infection	1	1.00-1.06	0.062
Diabetes mellitus	1.8	1.00-3.13	0.05
Past alcohol	2	1.22-3.24	0.006

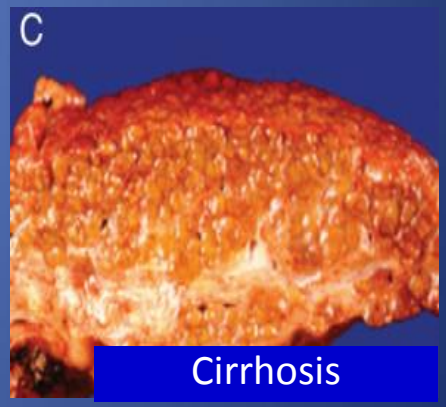
*Compared with African Americans as the reference group

Kallwitz ER, et al. *Clin Gastro Hepatol.* 2010; 8:72-78.

Factors Associated with Fibrosis in HCV

- Age at infection
- Duration of infection
- Metabolic factors (steatosis, obesity, diabetes)
- Compromised immune system
- Genetic factors
- HIV co-infection
- HBV co-infection
- Heavy alcohol use





Poynard T, et al. *Lancet.*1997;349:825-832.
Monto A, et al. *Hepatology.* 2002;36:729-736.
Marcolongo M, et al. *Hepatology*. 2009;50:1038-1044.
Cecil Medicine 23rd edition. Saunders Elsevier, Philadelphia, PA 2008.

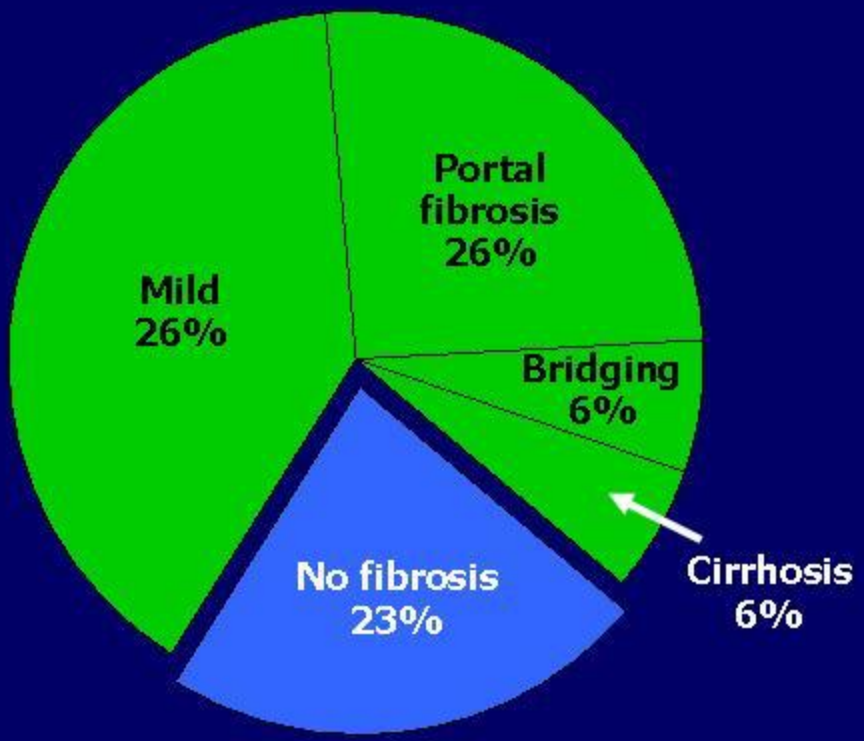
Histological Scoring of Fibrosis

Description	Modified HAI (Ishak)	HAI (Knodell)	Batts-Ludwig, Scheuer, or IASL	METAVIR
None	0	0	0	0
Mild-Portal fibrosis (some p. areas)	1	1	1	1
Moderate-Periportal Fibrosis (most p. areas, or occasional portal-portal septa)	2	3	2	2
Severe-Bridging fibrosis (few / occasional bridges, any portal-central)	***3***	***3***	***3***	***2***
Severe-Bridging fibrosis (many portal-central bridges)	**4**	**3**	**3**	**3**
Incomplete cirrhosis	**5**	**4**	**4**	**4**
Cirrhosis	**6**	**4**	**4**	**4**

Treat METAVIR =/> 2, or Ishak/Batts-Ludwig/Scheuer/Knodell =/> 3

HCV Disease Progression in Patients With Normal ALT

Despite 'persistently normal' ALT levels, >75% have some degree of liver damage on biopsy, with 32% having portal and bridging fibrosis

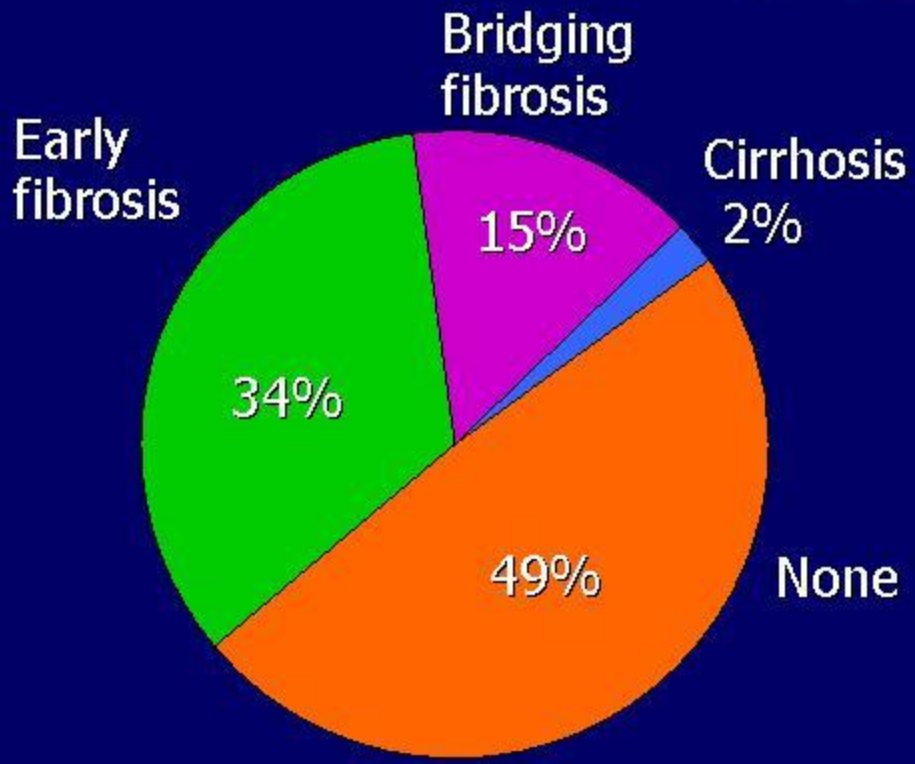


38% qualify for therapy (METAVIR >/= 2)

Shiffman et al. *J Infect Dis.* 2000;182:1595-1601.

Liver Fibrosis After 17 Years of Infection in Nonalcoholic Young Women

N=363

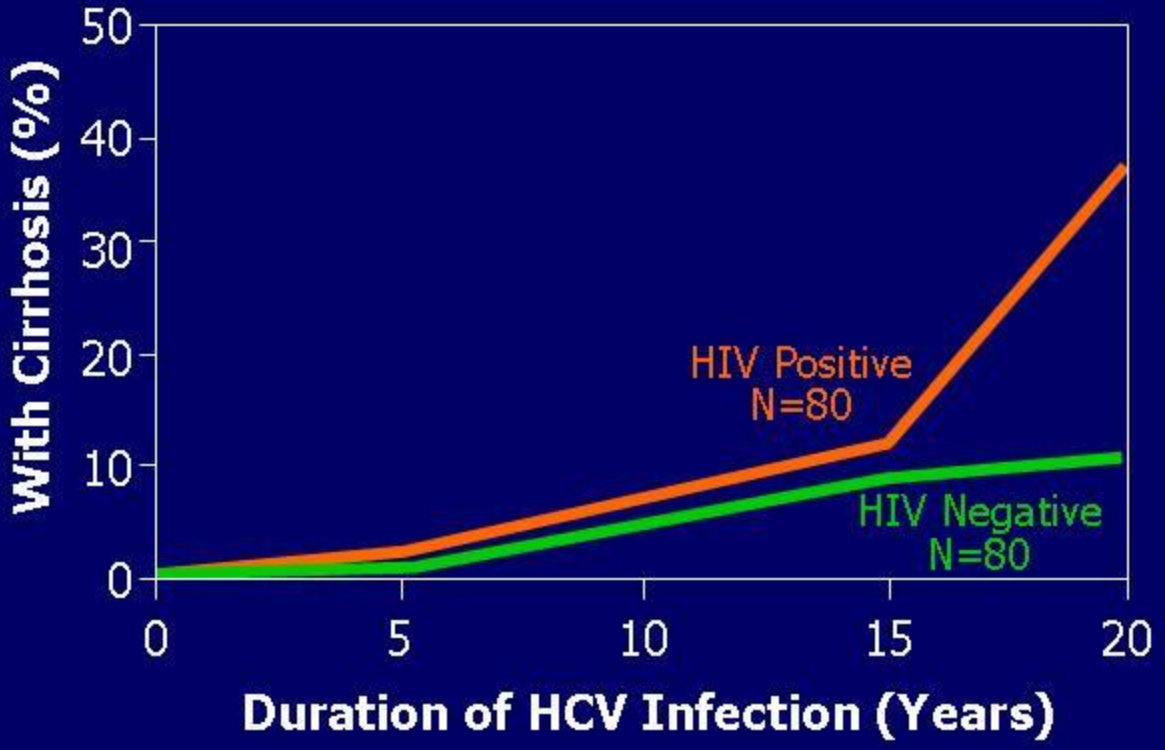


- Young women at infection
- Nonalcoholic
- Not immunosuppressed
- Not coinfected
  - HIV or HBV

Kenny-Walsh et al. *N Engl J Med.* 1999;340:1228-1233.

Profile of Patients at Higher Risk for Disease Progression

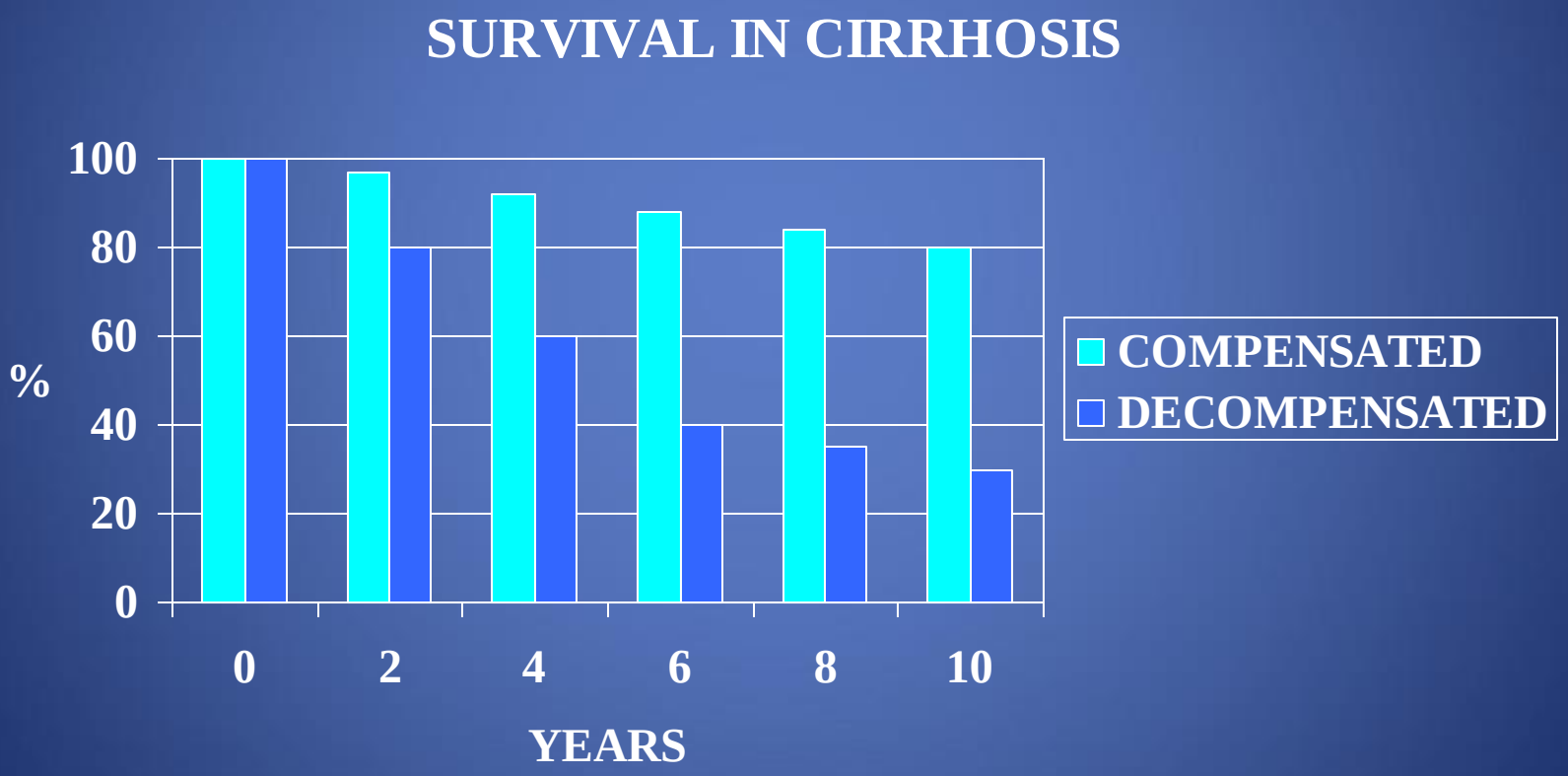
N=160



- 73% male overall
- Coinfected with HIV
- Immunocompromised
- Alcohol abuse

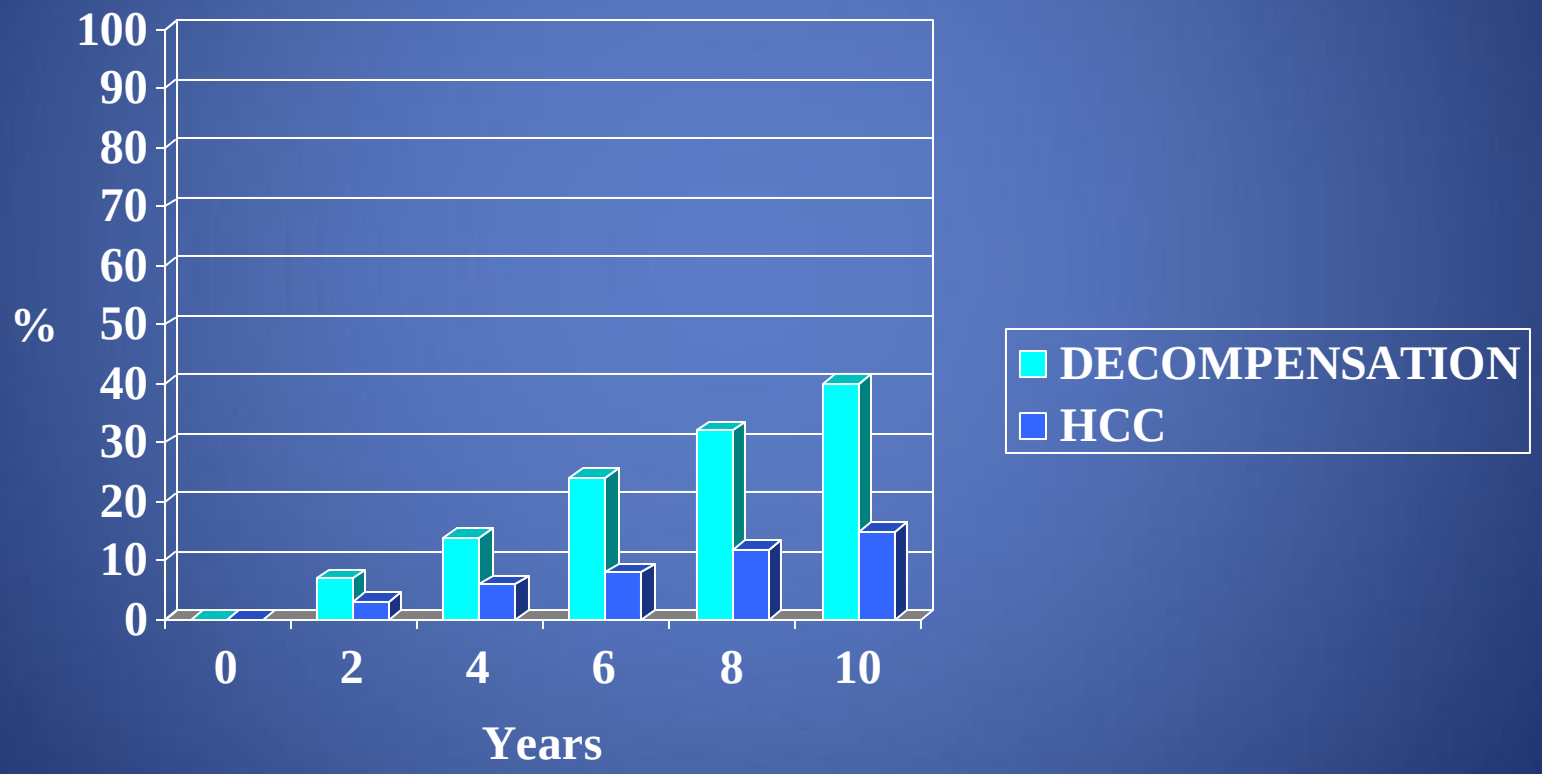
Adapted from Di Martino et al. *Hepatology*. 2001;34(6):1193-1199.

HCV Cirrhosis Survival

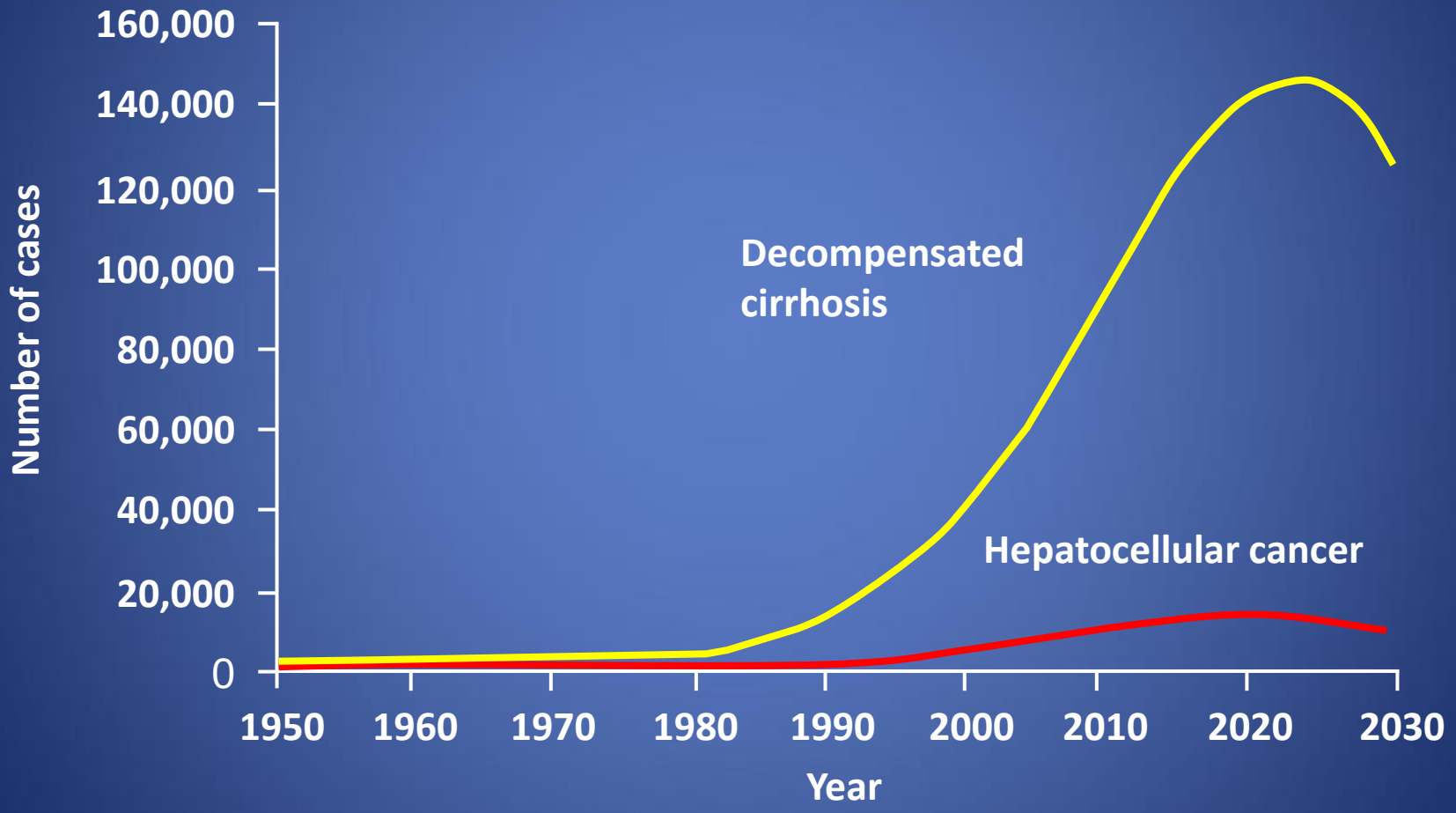


HCV Cirrhosis

Decompensation & Hepatocellular CA



Projected Cases of Hepatocellular Carcinoma and Decompensated Cirrhosis Due to HCV



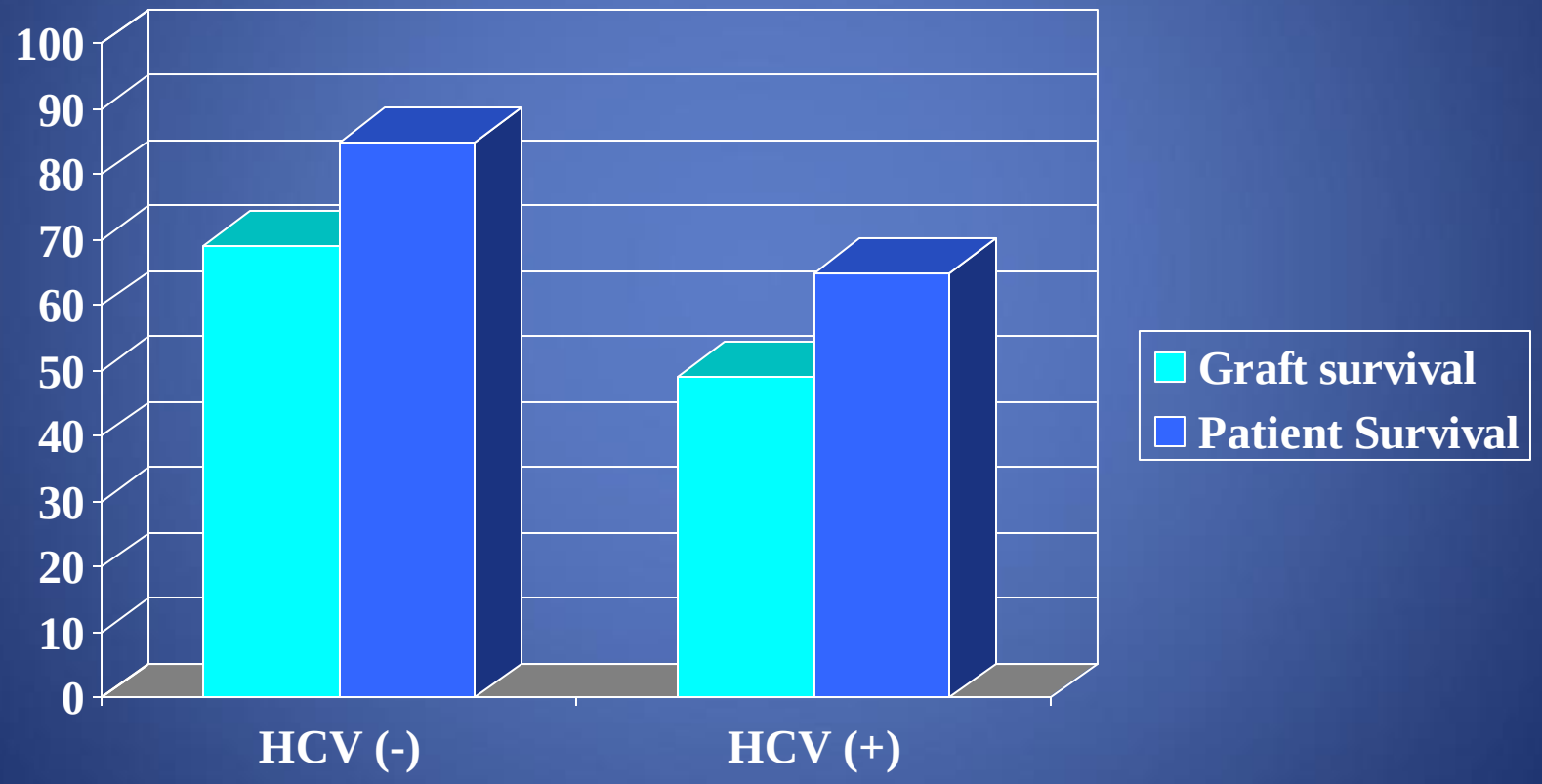
Davis GL, et al. *Gastroenterology*. 2010;138(2):513-521

Chronic HCV in ESRD
Natural History

Chronic HCV in ESRD
Natural History

- Indolent & asymptomatic; normal liver enzymes
- Advanced fibrosis (F3-F4) in 22-32%
- Death rate 35% higher in HCV cirrhosis
- Risk of Liver Ca 50% higher in HCV (+)
- Mortality of HCV (+) kidney Tx is 40% higher than HCV (-) kidney Tx.
- Mortality of HCV (+) who receive kidney Tx is 50% lower than those who continue in hemodialysis.

HCV in Renal Tx
Natural History (10 years)



HCV in Renal Transplant

- Survival: same 5-year but lower @ 10-years
- Survival better than if continue on HD
- Liver damage accelerated by Azathioprine and anti-lymphocyte globulin
- Higher risk of membranous and membranoproliferative glomerulonephritis.
- Decreased renal graft function

Immunocompromised Host

HCV Recurrence Post Liver Transplant

Natural History

Post-OLTx HCV Recurrence

- Infection occurs during graft reperfusion.
- Negative-strand HCV-RNA (replication) as early as 48h post-LTx.
- 25% have HCV core Ag in hepatocyte 10 d post-LTx, & > 90% @ 3 months post-LTx
- Pre-LTx HCV-RNA level may be reached by day 4.
- Peak titers reached at 1-3 mo post-Tx.
- 1-y post-LTX, HCV-RNA level are 10-100X pre-LTx
- Failure to develop a HCV-specific MHC-complex class II-restricted $CD4^+$ T-cell response contributes to graft-injury.

Post-OLTx HCV Recurrence

- Risk of death (hazard ratio 1.23) & of graft-loss (hazard ratio 1.3) is higher in HCV(+) than in HCV(-), at 1, 3, & 5 years.
- Fibrosis progression in HCV:
  - **LTx = 0.3-0.8 stage/y vs**
  - **Immunocompetent = 0.1-0.2 stage/year.**
- Median time to cirrhosis:
  - **LTx = 10y;**
  - **Immunocompetent = 20-40 y.**

Post-OLTx HCV Recurrence

- Cirrhosis:
  - **6-23% in 3-4 y,**
  - **30% by 5 y.**
- Risk of decompensation:
  - **1y = 42% (< 5% immunocompetent) &**
  - **3y = 62% (< 20% in Immunocompetent)**
- Approximately 10-25% of post-LTx HCV-liver disease will need re-Tx or will be dead within initial 5 years.

Post-OLTx HCV Recurrence
Factors That Affect Outcome

- Pre-OLTx HCV-RNA > 600000 IU (1 M copies)
- Advanced Donor Age (increase 1%/y after age 25; poor if > 65 y)
- Treatment of ACR
- High-average daily steroid dose
- T-cell depleting therapy
- CMV disease
- Non-caucasian recipient
- Year of OLTx (?); (worse in recent years)

Acute Post-OLTx HCV Recurrence

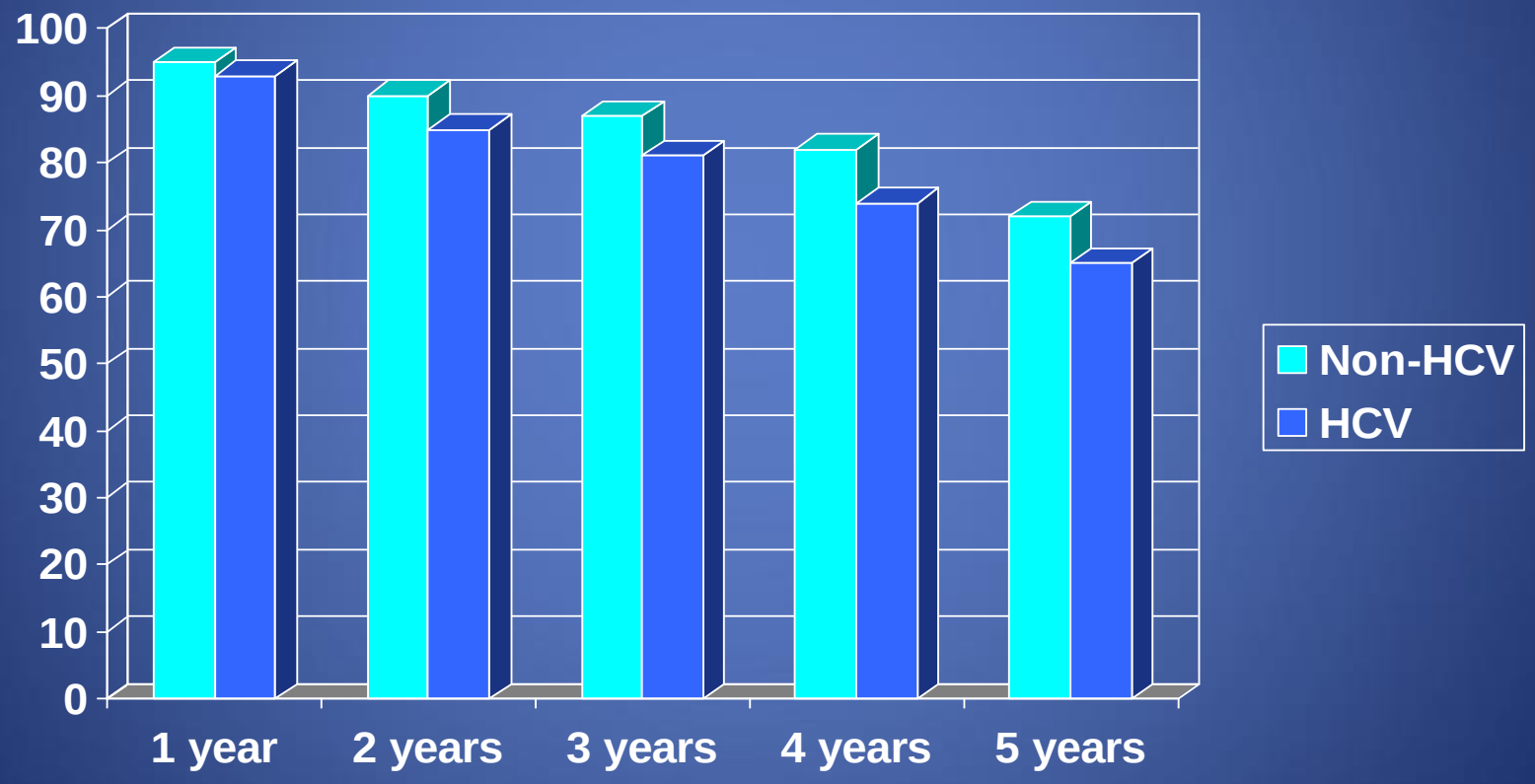
- Mild to moderate ALT/AST elevation
- **Total bilirubin < 6 mg/dL**
- Liver Bx in HCV recurrence: mononuclear lobular infiltrate, variable hepatocyte necrosis, and fatty infiltration;(Il-2, IFN-gamma, and TNF dominate).
- Liver Bx in Acute Cellular Rejection: endothelitis, severe bile duct damage, and *mixed-cell* infiltrate;(Il-4 & Il-10 gene expression dominate).
- Portal lymphocytic infiltrate and lymphocyte aggregates are seen in both HCV & ACR.

Chronic HCV Recurrence

- There is portal-portal bridging fibrosis and portal & lobular infiltration; variable degrees of hepatocyte necrosis.
- Progressive, non-specific Th^1 inflammatory response.

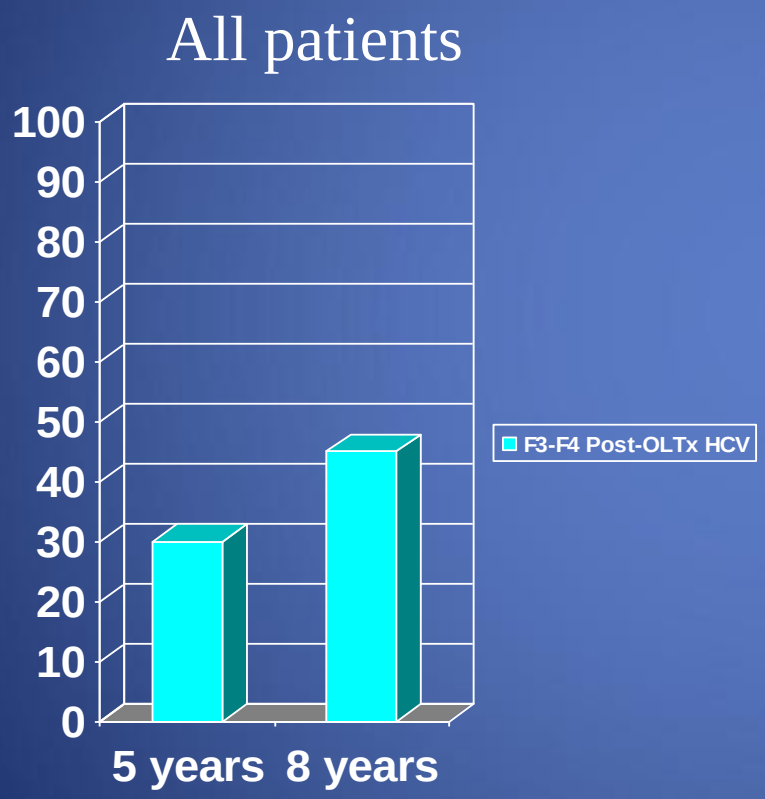
Survival After Liver Transplantation

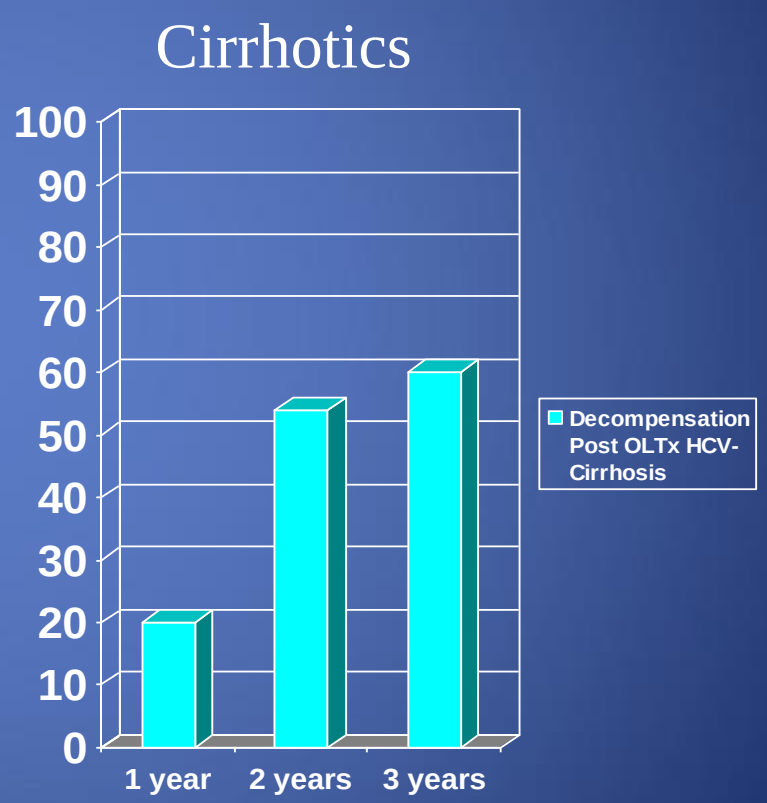
UNOS (1992-98) Gastroenterol 2002;122:889-896



Progression to F3-F4 Fibrosis and to Decompensated Cirrhosis Post OLTx HCV

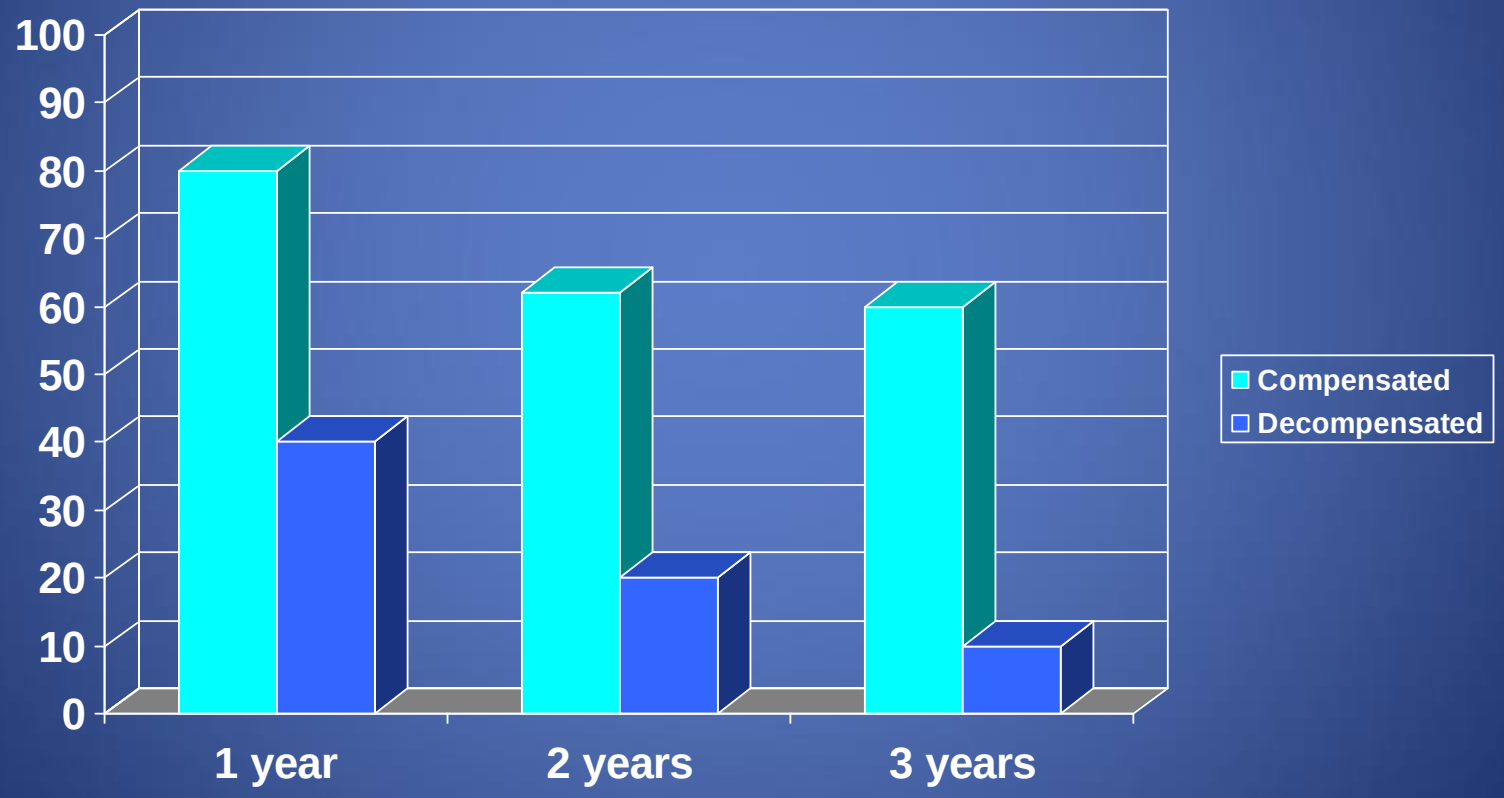
Berenguer et al J. Hepatol 2000;32:673-684 & Hepatology 2000;32:852-858





Survival in Post-OLTx HCV-Cirrhosis

Berenguer et al. Hepatology 2000;32:852-858



Fibrosing Cholestatic Hepatitis C

- **Bilirubin > 6 mg/dL without biliary or vascular complications.**
- ALT & AST elevated 2-5X; **alk. phosph. > 500 U/L & GGT > 1000 U/L**
- Very high serum & intrahepatic HCV-RNA
- Begins about 1 mo post LTx; liver failure in 3-6 months.
- **Liver Bx**: severe perivenular hepatocyte ballooning, intrahepatic cholestasis, pericellular & portal fibrosis, ductular proliferation, and paucity of inflammation.
- Probably due to high immunosuppression; stable quasispecies; $T_H2 > T_H1$ cytokine response; direct cytotoxic injury.

Predictors of Poor Outcome in HCV Re-Transplantation

- Bilirubin > 10 mg/dL
- Creatinine > 2 mg/dL
- Creatinine clearance < 40 mL/min
- Recipient > 55 years
- Cirrhosis < 1 year post-LTx
- Donor > 40 years

HCV + HIV Co-Infection

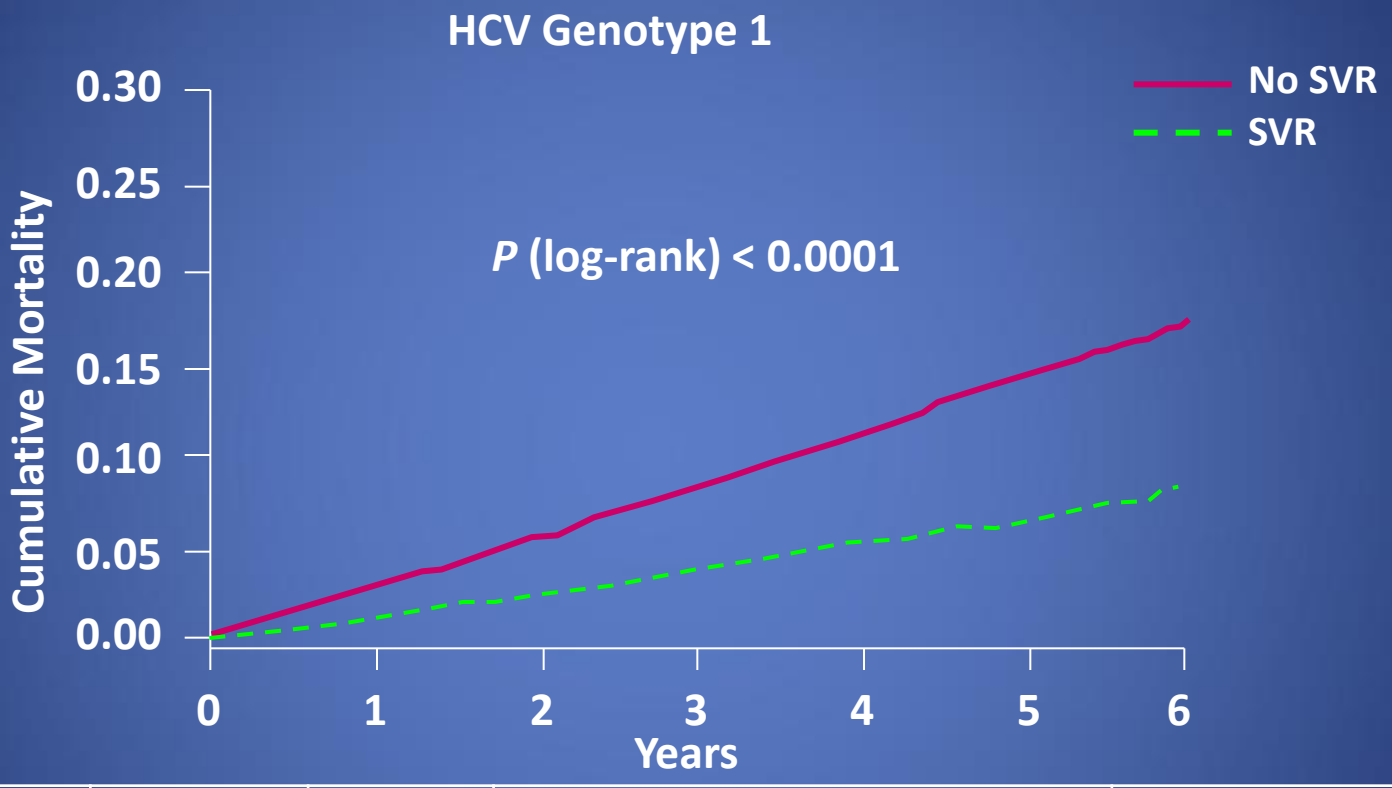
- 43% of HIV deaths are liver related.
- Relative risk of cirrhosis:
  - In antiretrovirals = 1.72
  - Without antiretrovirals = 2.49
- Relative risk of decompensation = 6
- Causes of increased fibrosis:
  - HIV related inflammatory response activates stellate cells.
  - The HIV envelope gp 120 protein signaling activates stellate cells
  - Depleted intestinal lymphocytes increase bacterial translocation.
  - Antiretroviral toxicity.
  - Metabolic syndrome due to ART and/or HIV
  - Excessive alcohol comsuption.

Chronic Hepatitis C

Treatment

SVR and Reduced Risk of All-Cause Mortality

US VA Study: Treatment with Pegylated Interferon/Ribavirin



Genotype	N	SVR	Hazard Ratio for Death with SVR	*P*-value
1	12,166	35%	0.70	< 0.0001
2	2904	72%	0.64	0.006
3	1794	62%	0.51	0.0002

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

Who should be treated for HCV

Highest Priority due to Highest Risk for Severe Complications

- **Advanced fibrosis (Metavir F3) or compensated cirrhosis (Metavir F4)**
  - **Rating:** Class I, Level A
- **Organ transplant**
  - **Rating:** Class I, Level B
- **Type 2 or 3 essential mixed cryoglobulinemia with end-organ manifestations (eg, vasculitis)**
  - **Rating:** Class I, Level B
- **Proteinuria, nephrotic syndrome, or membranoproliferative glomerulonephritis**
  - **Rating:** Class IIa, Level B
- *Transient Liver Elastograpy (TLE) & serum fibrosis markers:*
  - *A cutoff value of 8.7 kPa correlates with Metavir F2 or higher fibrosis stage;*
  - *greater than 9.5 kPa with F3; and*
  - *14.5 or higher kPa with F4 or cirrhosis.*
  - *The measurement range does overlap between stages. If serum fibrosis markers (e.g.: Fibrosure) are discordant with TLE, do liver biopsy.*

Who should be treated for HCV

High Priority

Owing to High Risk for Complications

- **Fibrosis (Metavir F2)**
  - **Rating:** Class I, level B
- **HIV-1 coinfection**
  - **Rating:** Class I, Level B
- **HBV coinfection**
  - **Rating:** Class IIa, Level C
- **Other coexistent liver disease (eg, NASH)**
  - **Rating:** Class IIa, Level C
- **Debilitating fatigue**
  - **Rating:** Class IIa, Level B
- **Type 2 Diabetes mellitus (insulin resistant)**
  - **Rating:** Class IIa, Level B
- **Porphyria cutanea tarda**
  - **Rating:** Class IIb, Level C

Owing to Transmission Risk

- **MSM with high-risk sexual practices**
- **Active injection drug users**
- **Incarcerated persons**
- **HCV-infected women of child-bearing potential wishing to get pregnant**
- **Persons on long-term hemodialysis**
  - **Rating:** Class IIa, Level C
  - Should be counseled on ways to decrease transmission and minimize the risk of reinfection.

Factors Associated with Accelerated Fibrosis in HCV

Host Factors

- **Non-Modifiable**
  Fibrosis stage
  Inflammation grade
  Older age at time of infection
  Male sex
  Organ transplant
- **Modifiable**
  Alcohol consumption
  Nonalcoholic fatty liver disease
  Obesity
  Insulin resistance

Viral Factors

- Genotype 3
- Coinfection with HBV or HIV

Histological Scoring of Fibrosis

Description	Modified HAI (Ishak)	HAI (Knodell)	Batts-Ludwig, Scheuer, or IASL	METAVIR
None	0	0	0	0
Mild-Portal fibrosis (some p. areas)	1	1	1	1
Moderate-Periportal Fibrosis (most p. areas, or occasional portal-portal septa)	2	3	2	2
Severe-Bridging fibrosis (few / occasional bridges, any portal-central)	***3***	***3***	***3***	***2***
Severe-Bridging fibrosis (many portal-central bridges)	**4**	**3**	**3**	**3**
Incomplete cirrhosis	**5**	**4**	**4**	**4**
Cirrhosis	**6**	**4**	**4**	**4**

Treat METAVIR =/> 2, or Ishak/Batts-Ludwig/Scheuer/Knodell =/> 3

Multiple Direct Acting Antivirals

Protease

Polymerase

HCV PIs	NS5A Inhibitors	NS5B Nucs	NS5B Non-nucs
Viral enzyme Active site	Non-enzyme Replication complex	Viral enzyme Active site	Viral enzyme Allosteric site
Telaprevir	Daclatasvir	Sofosbuvir	ABT-333
Boceprevir	Ledipasvir	VX-135	Deleobuvir
Simeprevir	ABT-267	IDX20963	BMS-791325
Faldaprevir	GS-5816	ACH-3422	PPI-383
Asunaprevir	ACH-3102		GS-9669
ABT-450	PPI-668		TMC647055
MK-5172	GSK2336805		
Sovaprevir	Samatasvir		
ACH-2684	MK-8742		

Direct-Acting Antiviral Profiles

	Direct-Acting Antiviral					
	NS3[1]	NS3[2]	NS5A[1]	NS5A[2]	Non Nuc NS5B	Nuc NS5B
Resistance profile						
Pan-genotypic efficacy						
Efficacy						
Adverse events						
Drug-drug interactions						

 Good profile  Average profile  Least favorable profile

[1] 1st generation.
[2] 2nd generation.

	Simeprivir (OLYSIO)	Sofosbuvir (SOVALDI)
Drug Group	NS3/4A Protease inhibitor	NS5B polymerase inhibitor Nucleotide analog
Genotypes affected	1a Q80K(-); 1b; (2, 4, 5, 6)	1,2,3,4 (5 & 6)
Dose	150 mg/d with food	400 mg a day
Associated drugs; dose reduction	Peg-IFN; standard RBV (as in RBV prescribing info)	Peg-IFN; standard RBV 1200/1000 by weight; 600 dose reduction
Regimens approved by FDA (see effectiveness in tables; some non-approved regimens may be superior)	G1 Naïve or Relapser: S+P+R x 12 w + PR x 12 w G1 NR, Part R & Null: S+P+R x 12w + PR x 36 w	**G1 & 4: S+P+R 12 w**, G1: S+R x 24 w (IFN Ineligible) **G1 & 4 pre-OLTx: S+R x 48 w** **G2: S+R x 12 w** **G3: S+R x 24 w *(Cirrhosis: S+P+R x 12 is superior but no FDA approved).*** ***HIV: S+P+R x 12 w (all G) is best regimen but no FDA approved.*** HIV G1 & 3: S+R x 24 HIV G2: S+R x 12 w
Renal impairment	No dose change. Not studied in GFR < 30	No if GFR < 30
Stop Rules and Precautions	STOP: if >/= 25 @ 4, 12, or 24 w Precaution: East Asian ancestry.	None
Liver Impairment	No in C-P B or C or decompensation.	MELD</= 14; Compensated C-P A, B, or C. No in decompensation.
Pregnancy	2 anti-conceptives during & until 6 months after.	2 anti-conceptives during &until 6 months after
Ages	19-73	19-75

	Simeprivir	Sofosbuvir
DAA increases drug levels **but can be used with caution and monitoring**	**Antiarrhytmics:** Digoxin, Amiodarone, Disopyramide, Flecainide, Mexiletine, Propafenone, Quinidine **Ca Channel blockers:** Amlodipine, Diltiazem , Felodipine, Nicardipine, Nifedipine, Nisoldipine, Verapamil **Statins:** Rosuvastatin max 10 mg, Atorvastatin max 40 mg, Simvastatin lowest possible dose, Pitavastatin lowest possible dose, Pravastatin lowest possible dose, Lovastatin lowest possible dose **Phosphodiesterase 5 inh:** Sildenafil , Tadalafil , Vardenafil all need dose adjustment when treating pulmonary hypertension **Sedatives:** Oral Midazolam and Triazolam	
DAA increases drug levels and **SHOULD NOT BE USED**	Erythromycin, Cisapride	
Drug **increases DAA** level and **SHOULD NOT BE USED**	**Milk Thistle** **Antibiotics:** Erythromycin, Clarithromycin, Telithromycin, **Antifungals (systemic):** Itraconazole, Ketoconazole, Posaconazole, Fluconazole , Voriconazole, **Anti-retrovirals:** Cobicistat-containing product (elvitegravir/cobicistat/ emtricitabine/tenofovir disoproxil fumarate), Darunavir, Ritonavir	
Drug **decreases DAA** level and **SHOULD NOT BE USED**	**St John's wort** **Anticonvulsants:** Carbamazepine, Oxcarbazepine, Phenobarbital, Phenytoin **Antibiotics:** Rifampin, Rifabutin, Rifapentine **Corticosteroids:** Dexamethasone. **Antiretrovirals:** Efavirenz	**St John's wort** **Anticonvulsants:** Carbamazepine, Oxcarbazepine, Phenobarbital, Phenytoin **Antibiotics:** Rifampin, Rifabutin, Rifapentine **Antiretrovirals:** tipranavir//ritonavir
Drug has **variable effect in DAA** and **SHOULD NOT BE USED**	**Antiretrovirals:** Atazanavir, Fosamprenavir, Lopinavir, Indinavir, Nelfinavir, Saquinavir, Tipranavir, Delavirdine, Etravirine, Nevirapine	
DAA has modest effect that requires monitoring	Cyclosporine, Tacrolimus, Sirolimus, Warfarin	

Concomitant Medications	Ledipasvir	Paritaprevir / Ritonavir / Ombitasvir + Dasabuvir	Simeprevir	Sofosbuvir
Acid-reducing agents*	X	X		
Alfuzosin/tamsulosin		X		
Anticonvulsants	X	X	X	X
Antiretrovirals*	Coming Soon	Coming Soon	Coming Soon	tipranavir / ritonavir only
Azole antifungals*		X	X	
Buprenorphine/naloxone		X		
Calcineurin inhibitors*		X	X	
Calcium channel blockers*		X	X	
Cisapride		X	X	
Digoxin	X		X	
Ergot derivatives		X		
Ethinyl estradiol–containing products		X		
Furosemide		X		
Gemfibrozil		X		
Glucocorticoids		X (inhaled, intranasal	X	
Herbals St. John's wort Milk thistle		X	X X	X
Macrolide antimicrobials*			X	
Other antiarrythmics*		X	X	
Phosphodiesterase type 5 inhibitors*		X	X	
Pimozide		X		
Rifamycin antimicrobials*	X	X	X	X
Salmeterol		X		
Sedatives*		X	X	
Simeprevir	X			
Statins*	X	X	X	

Concomitant Medications	Ledipasvir	Paritaprevir / Ritonavir / Ombitasvir + Dasabuvir	Simeprevir	Sofosbuvir
Acid-reducing agents*	-Decrease Omeprazole not to exceed 20 mg a day.	-Increase Omeprazole but do not exceed 40 mg a day ; decreases effect of Omeprazole.		
Alfuzosin/tamsulosin		-Do not take with Viekira; can cause hypotension.		
Anticonvulsants	-AVOID: Carbamazepine, Phenytoin; decrease Ledispavir	-Do not take with Carbamazepine, phenytoin, Phenobarbital. Loss of effectiveness of Viekira.	-DO NOT USE; DECREASES SIMEPREVIR EFFECT: Carbamazepine, Oxcarbazepine, Phenobarbital, Phenytoin.	-DO NOT USE; DECREASES SOFASBUVIR EFFECT: Carbamazepine, Oxcarbazepine, Phenobarbital, Phenytoin
Antiretrovirals*	-with tenofovir only if CrCl >/= 60; -DO NOT USE with cobicistat, elvitegravir nor tipranavir	-Atazanavir without Ritonavir: give only 300 mg and only in am. Likely to elevate bilirubin. -Do not give Darunavir/Ritonavir -Do not give Lopinavir/Ritonavir -Do not give Rilpivirine (QT prolongation) -Do not give with Efavirenz (liver enzyme elevation).	-DO NOT USE; INCREASES SIMEPREVIR LEVELS: Cobicistat-containing product (elvitegravir/cobicistat/ emtricitabine/tenofovir disoproxil fumarate), Darunavir, Ritonavir -DO NOT USE; DECREASES SIMEPREVIR EFFECT: Efavirenz -DO NOT USE; VARIABLE EFFECT ON SIMEPREVIR: Atazanavir, Fosamprenavir, Lopinavir, Indinavir, Nelfinavir, Saquinavir, Tipranavir, Delavirdine, Etravirine, Nevirapine	-DO NOT USE; DECREASES SOFOSBIVIR EFFECT: tipranavir / ritonavir only.
Azole antifungals*		-Do not exceed Fluconazole 200 mg a day. -Avoid using Voriconazole.	-DO NOT USE; INCREASES SIMEPREVIR LEVELS: Itraconazole, Ketoconazole, Posaconazole, Fluconazole , Voriconazole.	
Buprenorphine/naloxone		-No dose modification, BUT monitor closely for sedation and cognitive effects.		

Concomitant Medications	Ledipasvir	Paritaprevir / Ritonavir / Ombitasvir + Dasabuvir	Simeprevir	Sofosbuvir
Calcineurin inhibitors*		-Reduce CSA to 1/5th of original dose and monitor levels; readjust by blood levels at EOT. Monitor renal function. -Tacrolimus: do not give in day 1 of Viekira; start day 2 with 0.5 mg a week adjusting dose and frequency by blood levels. Monitor renal function.	-MODEST EFFECT AND REQUIRES MONITORING: Cyclosporine, Tacrolimus, Sirolimus	
Calcium channel blockers*		- Dose reduce Amlodipine and monitor BP.	-USE WITH CAUTION AND MONITORING: Amlodipine, Diltiazem , Felodipine, Nicardipine, Nifedipine, Nisoldipine, Verapamil	
Cisapride		X	-Increases Cisapride level	
Digoxin	-AVOID: increases Digoxin levels.		-Increases Digoxin levels; reduce dose and monitor levels.	
Ergot derivatives		-Do not give with Ergotamine, dihydroergotamine, methylergonovine.; can cause ergot toxicity (vasospasm + ischemia).		
Ethinyl estradiol–containing products		-Do not give with BCPs or patches (Lo Estrin, FE, Norinyl, Ortho Tri-Cyclen Lo, Ortho Evra), or Rings (NuvaRing), or hormone replacement (FEM HRT); Causes ALT elevation.		
Furosemide		-Increases effect of furosemide; reduce dose or monitor.		

Concomitant Medications	Ledipasvir	Paritaprevir / Ritonavir / Ombitasvir + Dasabuvir	Simeprevir	Sofosbuvir
Gemfibrozil		-Do not take with Gemfibrozil (Lopid); causes QT prolongation.		
Glucocorticoids		-Inhaled, or Intranasal Fluticasone is absolved in excess and causes decreased cortisol levels.	-Decreases Simeprivir effect: Dexamethasone.	
Herbals **St. John's wort** **Milk thistle**		-Causes loss of activity of Viekira: St. John's wort	-DO NOT USE; DECREASES SIMEPREVIR LEVEL: St John's wort. -DO NOT USE; INCREASE SIMEPREVIR LEVEL: Milk Thistle	-DO NOT USE; DECREASES SOFOSBUVIR EFFECT: St. John's wort
Macrolide antimicrobials*			-DO NOT USE: Erythromycin, Clarithromycin, Telithromycin; increases Simeprivir levels. -Simeprevir also increases antibiotic level.	
Other antiarrythmics*		-USE WITH CAUTION AND MONITORING: Amiodarone, Bepridil, Disipyramide, Flecainidine, Lidocaine (systemic), Mexiletine, Propafenone, Quinidine; increases antiarrhythmic effect; follow drug levels.	-USE WITH CAUTION AND MONITORING: Digoxin, Amiodarone, Disopyramide, Flecainide, Mexiletine, Propafenone, Quinidine	
Phosphodiesterase type 5 inhibitors*		-Revatio CONTRAINDICATED because effect is increased; risk of visual disturbance, hypotension, priapism, and syncope.	-USE WITH CAUTION AND MONITORING: Sildenafil , Tadalafil , Vardenafil all need dose adjustment when treating pulmonary hypertension.	

Concomitant Medications	Ledipasvir	Paritaprevir / Ritonavir / Ombitasvir + Dasabuvir	Simeprevir	Sofosbuvir
Pimozide		-Do not give Pimozide with Viekira; risk of cardiac arrhythmias.		
Rifamycin antimicrobials	-AVOID; Decreases Ledipasvir level.	-Rifampin causes loss of effect of Viekira.	-DO NOT USE; Decrease Simeprivir level: Rifampin, Rifabutin, Rifapentine	-DO NOT USE; DECREASES SOFOSBUVIR EFFECT: Rifampin, Rifabutin, Rifapentine
Salmeterol		-Not recommended due to increased risk of QT prolongation and sinus tachycardia.		
Sedatives		- Do not give with Oral Midazolam nor Triazolam; prolonged sedation and respiratory depression. -Alprazolam : consider dose reduction; effect is increased.	-USE WITH CAUTION AND MONITORING: Oral Midazolam and Triazolam	
Simeprevir	-AVOID: Increases levels of both drugs.			
Statins	-Rosuvastatin: AVOID; Increases rosuvastatin level and risk of myopathy and rhabdomyolysis.	-CONTRAINDICATED with Lovastatin and Simvastatin ; risk of myopathy and rhabdomyolysis. -Limit Rosuvastatin to 10 mg/d . -Limit Pravastatin to 40 mg/d.	-Rosuvastatin max 10 mg, -Atorvastatin max 40 mg, -Simvastatin lowest possible dose, -Pitavastatin lowest possible dose, -Pravastatin lowest possible dose, -Lovastatin lowest possible dose	

Treatment of HCV
AASLD/IDSA Guidelines

Who should be Tested for HCV?

- **HCV testing is recommended at least once for persons born between 1945 and 1965. Rating:** Class I, Level B
- **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
  - ***Risk behaviors***
    - **Injection-drug use (current or ever, including those who injected once)**
    - **Intranasal illicit drug use**
  - ***Risk exposures***
    - **Long-term hemodialysis (ever)**
    - **Getting a tattoo in an unregulated setting**
    - **Healthcare, emergency medical, and public safety workers after needle sticks, sharps, or mucosal exposures to HCV-infected blood**
    - **Children born to HCV-infected women**
    - **Prior recipients of transfusions or organ transplants, including persons who:**
      - **were notified that they received blood from a donor who later tested positive for HCV infection**
      - **received a transfusion of blood or blood components, or underwent an organ transplant before July 1992**
      - **received clotting factor concentrates produced before 1987**
      - **were ever incarcerated**
  - ***Other medical conditions***
    - **HIV infection**
    - **Unexplained chronic liver disease and chronic hepatitis including elevated alanine aminotransferase levels**

Recommendations for patients with HCV

- Avoid sharing toothbrushes and dental or shaving equipment, and cover any bleeding wound to prevent the possibility of others coming into contact with their blood.
- Stop using illicit drugs and enter substance abuse treatment. If continue to inject drugs should avoid reusing or sharing syringes, needles, water, cotton, and other drug preparation equipment; use new sterile syringes and filters and disinfected cookers; clean the injection site with a new alcohol swab; and dispose of syringes and needles after one use in a safe, puncture-proof container.
- Do not donate blood and discuss HCV serostatus prior to donation of body organs, other tissue, or semen.
- MSM with HIV infection and those with multiple sexual partners or sexually transmitted infections should use barrier precautions to prevent sexual transmission. Other persons with HCV infection should be counseled that the risk of sexual transmission is low and may not warrant barrier protection.
- Household surfaces and implements contaminated with visible blood from an HCV-infected person should be cleaned using a dilution of 1 part household bleach to 9 parts water. Gloves should be worn when cleaning up blood spills.

Interferon Ineligible
Definition

- Intolerance to IFN
- Autoimmune hepatitis and other autoimmune disorders
- Hypersensitivity to PEG or any of its components
- Decompensated hepatic disease
- History of depression
- Clinical features consistent with depression
- A baseline neutrophil count below 1500/µL
- A baseline platelet count below 90,000/µL
- A baseline hemoglobin below 10 g/dL
- A history of preexisting cardiac disease

Ribavirin and Teratogenicity

- Patients should be informed that Ribavirin is teratogenic.
- Ribavirin should not be started unless a pre-treatment pregnancy test has been negative.
- Women of childbearing potential and all males should use 2 methods of contraception during treatment and for 6 months after therapy.
- If pregnancy occurs, they should be advised of the significant teratogenic risk to the fetus.
- Physicians are strongly encouraged to report any pregnancy in a patient or partner, during treatment or 6 months after treatment to: Ribavirin Pregnancy Registry @ 1-800-593-2214

Grading of the Evidence

Classification	Description
Class I	Conditions for which there is evidence and/or general agreement that a given diagnostic evaluation, procedure, or treatment is beneficial, useful, and effective
Class II	Conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness and efficacy of a diagnostic evaluation, procedure, or treatment
Class IIa	Weight of evidence and/or opinion is in favor of usefulness and efficacy
Class IIb	Usefulness and efficacy are less well established by evidence and/or opinion
Class III	Conditions for which there is evidence and/or general agreement that a diagnostic evaluation, procedure, or treatment is not useful and effective or if it in some cases may be harmful
Level of Evidence	**Description**
Level A	Data derived from multiple randomized clinical trials or meta-analyses
Level B	Data derived from a single randomized trial, or nonrandomized studies
Level C	Consensus opinion of experts, case studies, or standard of care

Treatment Naïve or Relapsers after Peg-IFN/RBV

Genotype	Recommended	Alternative	NOT Recommended
1	-**SOF 400 + SMV* 150 ± RBV** 1-1.2g x 12 weeks (24 weeks in cirrhosis) (all: 93%-96%) -**SOF/LED 400/90** (Naive F0-2, < 6 Million x 8 weeks: 97%); (Naive F0-2,> 6 Million x 12 weeks: 96%); (F3-4 x 12w: 94%) -**VIEKIRA +/- RBV**: **1a** F0-2 with RBV 1-1.2 x 12 weeks (96%);F3-4 with RBV 1-1.2 x 24 weeks (95%); **1b** F0-2 (without RBV) x 12 weeks (100%);F3-4 with RBV 1-1.2 x 12 weeks (99%).	-None	-SOF 400 + PEG/RBV 1-1.2g x 12 weeks (Cir:80%; NCir:92%) -TVR + PEG/RBV x 24 or 48 weeks (RGT) -BOC + PEG/RBV x 28 or 48 weeks (RGT) -PEG/RBV x 48 weeks -Monotherapy with PEG, RBV, or a DAA -Do not treat decompensated cirrhosis with PEG or SMV
2	-**SOF 400 + RBV** 1-1.2g x 12 weeks (Naive:94%)	-None	-PEG/RBV x 24 weeks -Monotherapy with PEG, RBV, or a DAA -Any regimen with TVR, BOC, or SMV
3	-**SOF 400 + RBV** 1-1.2g x 24 weeks (Naive:93%; Rlap:77%)	-**SOF 400 + PEG/RBV** 1-1.2g x 12 weeks (compensated F3/F4 cirrhosis) (Naive:97%; if C:92%)	-PEG/RBV x 24-48 weeks -Monotherapy with PEG, RBV, or a DAA -Any regimen with TVR, BOC, or SMV
4	-**SOF 400 + RBV** 1-1.2g x 24 weeks (Naive: 92-100%) -**SOF/LED 400/90** x 12 weeks (95-100%) -**VIEKIRA + RBV** 1-1.2g/d x 12 weeks (100%)	-**SOF 400 + SIM 150* +/- RBV** 1-1.2 g/d x 12 weeks (unknown; in study) -IFN eligible Naive**:** -**SOF 400 + PEG/RBV** 1-1.2g x 12 weeks (Naive:96%)	-PEG/RBV x 48 weeks -Monotherapy with PEG, RBV, or a DAA -Any regimen with TVR or BOC
5	-**SOF 400 + PEG/RBV** 1-1.2g x 12 weeks	-**PEG/RBV** 1-1.2g x 48 weeks	Monotherapy with PEG, RBV, or a DAA -Any regimen with TVR or BOC
6	-**SOF/LED 400/90** x 12 weeks (SVR: 96%)	-**SOF 400 + PEG/RBV** 1-1.2g x 12 weeks (100 %)	

* No in Q80K polymorphism (add RBV if with SOF)

Previous Peg-IFN/RBV Failures (Non-responders or Null-Responders)

Genotype	Recommended	Alternative	NOT Recommended
1	-**SOF/LED 400/90 +/- RBV**: In 1a or b: F0-2: SOF/LED 400/90 x 12 weeks (95%);F3-4: SOF/LED 400/90 **+ RBV** 1-1.2 g x 12 weeks (SVR 96%), or SOF/LED 400/90 x 24 weeks (100%) -**SOF 400 + SMV* 150 ± RBV** 1-1.2g x 12 weeks (24 weeks in cirrhosis) (all:93%-96%) -**VIEKIRA +/- RBV**: **1a** F0-2 with RBV 1-1.2 x 12 weeks (96%);F3-4 with RBV 1-1.2 x 24 weeks (95%); **1b** F0-2 (without RBV) x 12 weeks (100%); F3-4 with RBV 1-1.2 x 12 weeks (99%)	-None -In previous **SOFOSBUVIR FAILURES with ADVANCED FIBROSIS**: **SOF/LED 400/90 +/- RBV** 1-1.2 x 24 weeks (unknown SVR)	-PEG/RBV ± telaprevir or boceprevir -Monotherapy with PEG, RBV, or a DAA -Do not treat **decompensated cirrhosis** with PEG or SMV -SOF x 12 weeks + PEG/RBV 1-1.2g x 12-24 weeks (C:80%; NC:92%) -SOF 400 + RBV 1-1.2g x 24 weeks (all:70%) -SIM x 12 weeks + PEG/RBV 1-1.2 x 48 weeks (null:53%,Partl:65%)
2	-**SOF 400 + RBV** 1-1.2g x 12-16 weeks (88%-91%)	-**SOF 400 + PEG/RBV** 1-1.2g x 12 weeks (96%)	-PEG/RBV ± telaprevir or boceprevir -Monotherapy with PEG, RBV, or a direct-acting antiviral agent -Do not treat decompensated cirrhosis with PEG
3	-F0-2: **SOF 400 + RBV** 1-1.2g x 24 weeks (87%) -F3-4: **SOF 400 + Peg/RBV** 1-1.2 g/d x 12 weeks (83%) -**SOF/LED 400/90 + RBV 1-1.2** x 12 weeks (F0-2: 89%; F3-4: 73%)	-F0-2: **SOF 400 + PEG/RBV** 1-1.2g x 12 weeks (83%) -F3-4: **SOF 400 + RBV** 1-1.2g/d x 24 weeks (60%)	-PEG/RBV ± any current protease inhibitor -Monotherapy with PEG, RBV, or a DAA -Do not treat decompensated cirrhosis with PEG
4	-**Viekira + RBV** 1-1.2 g x 12 weeks (100%) -**SOF/LED 400/90** x 12 weeks (95%) -**SOF 400 + PEG/RBV** 1-1.2g x 12 weeks (96%) -**SOF 400 + RBV** 1-1.2g x 24 weeks (89%)		-PEG/RBV ± any current HCV protease inhibitor -Monotherapy with PEG, RBV, or a DAA -Do not treat decompensated cirrhosis with PEG
5	-**SOF 400 + PEG/RBV** 1-1.2g x 12 weeks	-**PEG/RBV** 1-1.2 g/d x 48 weeks	-PEG/RBV ± any current HCV protease inhibitor -Monotherapy with PEG, RBV, or a DAA -Do not treat decompensated cirrhosis with PEG
6	-**SOF/LED 400/90** x 12 weeks (SVR: 96%)	-**SOF + Peg/RBV** 1-1.2 g/d x 12 weeks (100%)	

* No in Q80K polymorphism (add RBV if with SOF)

Previous Failure with Peg-IFN/RBV + Telaprevir or Boceprevir

Genotype	Recommended	Alternative	NOT Recommended
1a or b	-F0-2: **SOF/LED 400/90** x 12 weeks (SVR 96%) -F3-4: **SOF/LED 400/90 + RBV** 1-1.2 g/d x 12 weeks, or **SOF/LED 400/90** x 24 weeks (SVR 97%)	-None	-PEG/RBV ± telaprevir or boceprevir or SMV -Monotherapy with PEG, RBV, or a DAA -Do not treat decompensated cirrhosis with PEG or SMV

Treatment in Cirrhosis

- **Treatment-naive patients with compensated cirrhosis, including those with hepatocellular carcinoma**: should receive the same treatment as recommended for patients without cirrhosis. **Rating: Class I, Level A**
- ***Patients with decompensated cirrhosis (moderate or severe hepatic impairment; CTP class B or C):*** *should be referred to a medical practitioner with expertise in that condition (ideally in a liver transplant center).* **Rating: Class I, Level C**
- ***Patients with any HCV genotype who have decompensated cirrhosis (moderate or severe hepatic impairment; CTP class B or C)*** *who may or may not be candidates for liver transplantation,* ***including those with hepatocellular carcinoma****. This regimen should be used only by highly experienced HCV providers*
  - **Daily sofosbuvir (400 mg) plus weight-based RBV** (with consideration of the patient's creatinine clearance and hemoglobin level) **for up to 48 weeks. Rating: Class IIb, Level B**
  - **Daily SOF/LED 400/90 + RBV 600 escalated up as tolerated x 12 weeks (SVR 86%)** (Treatment naïve or experienced; Child-Pugh A, B, and C up to CPT 12; MELD up to 20; most had PSE and/or ascites). MELD and CPT improved in most patients during therapy.
- *The following regimens are* ***NOT recommended for patients with decompensated cirrhosis*** *(moderate or severe hepatic impairment; CTP class B or C):*
  - Any IFN-based therapy. **Rating: Class III, Level A**
  - Monotherapy with PEG, RBV, or a DAA. Rating: **Class III, Level A**
  - Telaprevir-, boceprevir-, or simeprevir-based regimens. **Rating: Class III, Level A**
  - Viekira regimens

Child-Pugh Classification (non-Cholestatic)

"Decompensated Cirrhosis" = Child-Pugh B or C

	Class A	Class B	Class C
Total points	5–6	7–9	10–15
Factor	**1 Point**	**2 Points**	**3 Points**
Total bilirubin (mg/dL)	< 2	2 to 3	> 3
Serum albumin (g/L)	>35	28–35	<28
Prothrombin time/international normalized ratio	<1.7	1.71–2.30	>2.30
Ascites	None	Mild	Moderate to Severe
Hepatic encephalopathy	None	Grade I–II (or suppressed with medication)	Grade III–IV (or refractory)

Treatment Post-Liver Transplant

Genotype	Recommended	Alternative	NOT Recommended
1, & 4 (including compensated cirrhosis)	**-For Genotype 1 or 4:** -**SOF/LED 400/90 + RBV 1-1.2g x 12 weeks (96%)** (in decompensated, increasing dose weekly as tolerated from 600 mg) Rating: Class I, Level B -**SOF/LED 400/90 x 24 weeks**	-None	-Monotherapy with PEG, RBV, or a DAA Rating: Class III, Level A -Telaprevir- or boceprevir- based regimens should not be used for patients with compensated allograft hepatitis C infection. Rating: Class III, Level A
	-For genotype 1 only: **-SOF 400 + SIM 150 +/- RBV 1-1.2 g x 12 weeks (92%)** (weight-based dose of 1000 mg [<75 kg] to 1200 mg [≥75 kg] 1200 mg). Rating: Class IIb, Level C -**For F0-2 only: VIEKIRA + RBV 1-1.2 g/day x 24 weeks** (start at 600-800 and increase weekly as tolerated) (1a: 97%; 1b: 100%) [CSA 1/5 of daily dose when starting Viekira; TAC none on 1st Viekira day, 0.5 mg/week starting day-after starting Viekira] Rating: Class I, Level B		
2 (including compensated cirrhosis)	**Daily sofosbuvir (400 mg) and RBV 1-1.2 g x 24 weeks** (if decompensated, initial dose 600 mg/day, increased weekly by 200 mg/day as tolerated to weight-based dose of 1000 mg [<75 kg] to 1200 mg [≥75 kg] 1200 mg) with consideration of the patient's CrCL value and hemoglobin level. Rating: Class IIb, Level C		
3 (including compensated cirrhosis)	**Daily sofosbuvir (400 mg) and RBV 1-1.2 g x 24 weeks** (if decompensated, initial dose 600 mg/day, increased weekly by 200 mg/day as tolerated to weight-based dose of 1000 mg [<75 kg] to 1200 mg [≥75 kg] 1200 mg) with consideration of the patient's CrCL value and hemoglobin level. Rating: Class I, Level B	-SOF/LED + RBV (?) no enough data	
Any with decompensated cirrhosis	Treatment-naive patients with decompensated allograft HCV infection should receive the same treatment as recommended for patients with decompensated cirrhosis (moderate or severe hepatic impairment; CTP class B or C). Rating: Class I, Level C		

Treatment of HIV/HCV Co-infection

Genotype	Recommended	Alternative	NOT Recommended	Allowable Antiretroviral Therapy
1 Treatment Naïve or PEG/RBV Relapsers	**SOF 400 + SMV* 150 ± RBV** 1-1.2g x 12 weeks (24 weeks in cirrhosis) (all: 93%-96%) -**SOF/LED 400/90** (N F0-2 <6M; 8w: 97%); (N F0-2,>6M; 12w: 96%); (F3-4 12w: 94%) -**VIEKIRA +/- RBV**: **1b** F0-2 x 12 weeks (100%);F3-4 with RBV 1-1.2 x 12 weeks (99%); **1a** F0-2 with RBV 1-1.2 x 12 weeks (96%);F3-4 with RBV 1-1.2 x 24 weeks (95%)	-None	-TVR + PEG/RBV x 24 or 48 weeks (RGT) -BOC + PEG/RBV x 28 or 48 weeks (RGT) -PEG/RBV x 48 weeks -SMV x 12 weeks + PEG/RBV x 48 wks	**For SOF use:** ALL except didanosine, zidovudine, tipranavir **For SMV use:** Only in raltegravir, rilpivirine, maraviroc, enfuvirtide, tenofovir, emtricitabine, lamivudine, abacavir. NO with efavirenz, etravirine nevirapine, cobicistat or any HIV protease inhibitor **For LED use:** with tenofovir only if CrCl >/= 60; NO with cobicistat, elvitegravir nor tipranavir **For Viekira use:** NO with efavirenz,rilpiviride, darunavir, nor ritonavir-boosted lopinavir NO IN PATIENTS NOT TAKING HAART **For RBV use:** NO in didanoside, stavudine, nor zidovudine
1 PEG/RBV Nonresponders	-**SOF/LED 400/90 +/- RBV**: In 1a or b: F0-2: SOF/LED 400/90 x 12 weeks (95%);F3-4: SOF/LED 400/90 **+ RBV** 1-1.2 g x 12 weeks (SVR 96%), or SOF/LED 400/90 x 24 weeks (100%) -**SOF 400 + SMV* 150 ± RBV** 1-1.2g x 12 weeks (24 weeks in cirrhosis) (all:93%-96%) -**VIEKIRA +/- RBV**: **1a** F0-2 with RBV 1-1.2 x 12 weeks (96%);F3-4 with RBV 1-1.2 x 24 weeks (95%); **1b** F0-2 x 12 weeks (100%); F3-4 with RBV 1-1.2 x 12 weeks (99%)	-None -In previous **SOFOSBUVIR FAILURES with ADVANCED FIBROSIS**: **SOF/LED 400/90 +/- RBV** 1-1.2 x 24 weeks		Same as above
4	-**SOF 400 + RBV** 1-1.2g x 24 weeks (Naive: 84 %) -**SOF/LED 400/90** x 12 weeks -**SOF 400 + PEG/RBV** 1-1.2g x 12 weeks -**VIEKIRA + RBV** 1-1.2g/d x 12 weeks	-None	-PEG/RBV x 48 weeks -Any regimen with TVR or BOC	**For SOF/RBV:** ALL except didanosine, zidovudine, stavudine, tipranavir **For Viekira use:** NO with efavirenz,rilpiviride, darunavir, nor ritonavir-boosted lopinavir NO IN PATIENTS NOT TAKING HAART
5	**Regardless of treatment history:** -**SOF 400 + PEG/RBV 1-1.2g** x 12 weeks	-**PEG/RBV** 1-1.2g x 48 weeks	-Any regimen with TVR, BOC, or SMV	**For SOF/RBV:** ALL except didanosine, zidovudine, stavudine, tipranavir
6	-**SOF/LED 400/90 x 12 weeks**	-**SOF + Peg/RBV** 1-1.2 g/d x 12 weeks		**For SOF/RBV:** ALL except didanosine, zidovudine, stavudine, tipranavir

Treatment of HIV/HCV Co-infection

Genotype	Recommended	Alternative	NOT Recommended	Allowable Antiretroviral Therapy
2 Treatment Naïve or Peg/RBV Relapsers	-**SOF 400 + RBV** 1-1.2g x 12 weeks (94%)	-None	-PEG/RBV x 24-48 weeks -Any regimen with TVR, BOC, or SMV	ALL except didanosine, zidovudine, stavudine, nor tripanavir
2 Peg/RBV Nonresponders	**SOF 400 + RBV** 1-1.2 g/d x 12-16 weeks (91%)	-**SOF 400 + PEG/RBV** 1-1.2g x 12 weeks (96%)		-SOF cannot be used with tipranavir -RBV cannot be used with didanoside, stavudine, nor zidovudine.
3 Treatment Naïve or Peg/RBV Relapsers	-**SOF 400 + RBV** 1-1.2 x 24 weeks regardless of treatment history	-**SOF 400 + PEG/RBV** 1-1.2g x 12 weeks (compensated F3/F4 cirrhosis) (Naive:97%; if C:92%)	-PEG/RBV x 24 - 48 weeks -Any regimen with TVR, BOC, or SMV	ALL except didanosine, zidovudine, stavudine, nor tripanavir
3 Peg/RBV Nonresponders	-F0-2: **SOF 400 + RBV** 1-1.2g x 24 weeks (87%) -F3-4: **SOF 400 + Peg/RBV** 1-1.2 g/d x 12 weeks (83%) -SOF/LED 400/90 + RBV 1-1200 x 12 weeks (?)	-F0-2: **SOF 400 + PEG/RBV** 1-1.2g x 12 weeks (83%) -F3-4: **SOF 400 + RBV** 1-1.2g/d x 24 weeks (60%)		-SOF cannot be used with tipranavir -RBV cannot be used with didanoside, stavudine, nor zidovudine.

Dose Adjustment for Renal Impairment

Renal Impairment	eGFR/CrCl level (mL/min/ 1.73 m^2)	Interferon	Ribavirin	Sofosfovir	Simeprevir
Mild	50-80	180 µg PEG (2a); PEG (2b) 1.5 µg/kg	Standard	Standard	Standard
Moderate	30-50	180 µg PEG (2a); PEG alfa-2b1 µg/kg or 25% reduction	Alternating doses 200 and 400 mg every other day	Standard	Standard
Severe	<30	135 µg PEG (2a); PEG (2b)1 µg/kg or 50% reduction	200 mg/d	Data not available	Standard
ESRD/HD		PEG (2a) 135 µg/wk or PEG (2b) 1 µg/kg/wk or standard IFN 3 mU 3x/wk	200 mg/d	Data not available	Data not available

Dose Adjustment for Renal Impairment

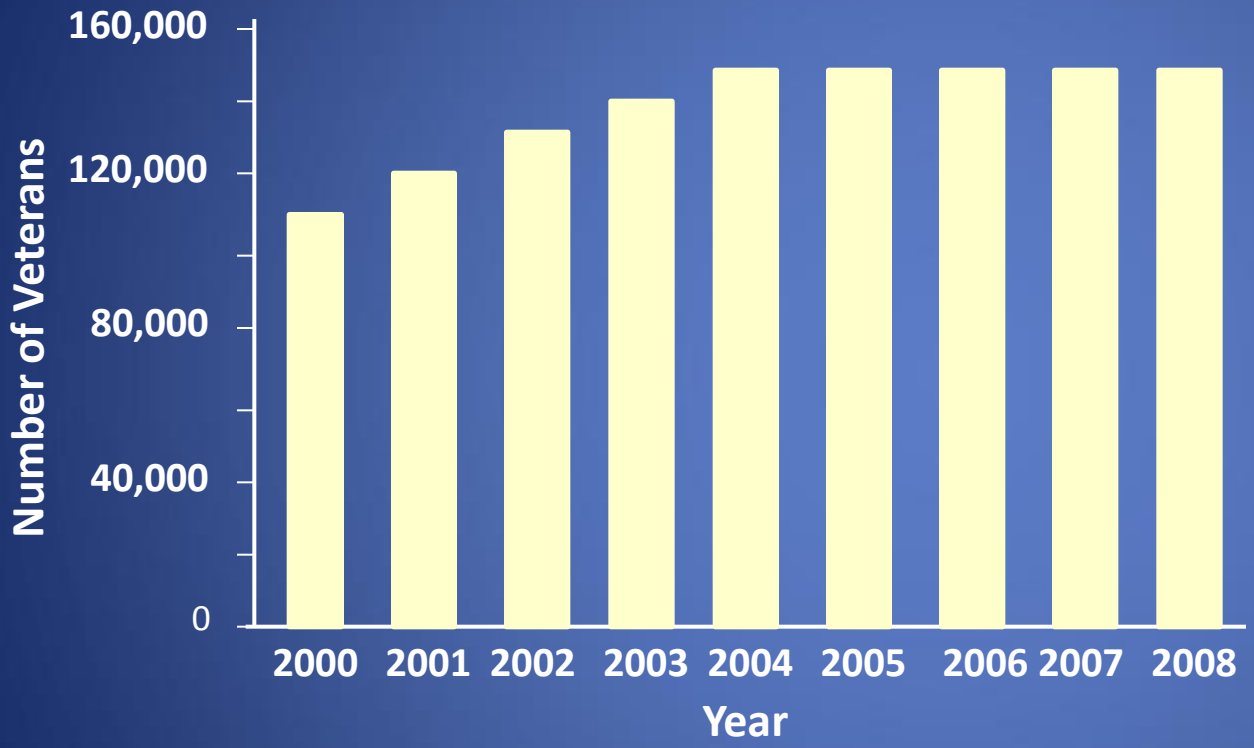
- When using sofosbuvir to treat or retreat HCV infection in patients with appropriate genotypes, no dosage adjustment is required for patients with mild to moderate renal impairment (CrCl ≥30 mL/min). Sofosbuvir is not recommended in patients with severe renal impairment/ESRD (CrCl <30 mL/min) or those who require hemodialysis, because no dosing data are currently available for this patient population. **Rating: Class IIa, level B**
- When using simeprevir in treatment/retreatment of HCV-infected patients, no dosage adjustment is required for patients with mild to moderate to severe renal impairment. Simeprevir has not been studied in patients with ESRD, including those requiring hemodialysis. **Rating: Class IIa, level B**
- In patients with renal impairment/ESRD/HD, dosing of PEG and RBV should follow updated FDA recommendations or package insert recommendations based on calculated GFR. Caution should be used in administering RBV to these patients, and close monitoring of hemoglobin is required. **Rating: Class IIa, level B**

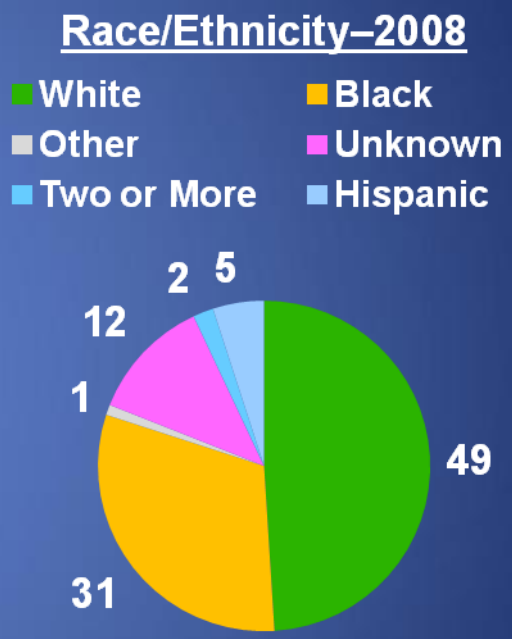
Suggested RBV dose by Creatinine Clearance

Kamar N et al. Am J Kidney Dis. 2004;43:140-146 &
Bruchfeld A et al. Drug Monit. 2002;24:701-708

Creatinine Clearance (Cockcroft-Gault)	>/= 100 mL/min	80 mL/min	60 mL/min	40 mL/min	20 mL/min	< 20 mL/min
RBV (mg/day)	1200	1000	800	600	400	200

Veterans with Chronic HCV in VHA Care





Among the 20,477 veterans who initiated their 1st course of PegIFN + ribavirin between 2002 and 2006, SVR was:

- 26% for genotype 1
- 62% for genotype 2
- 52% for genotype 3

US Dept of Veterans Affairs. http://www.hepatitis.va.gov/provider/policy/HCV-state-of-care-2010.asp. Accessed June 2011.

Special Groups

Indolent B-Cell Non-Hodgkin Lymphoma

Treatment of HCV-related Indolent B-Cell Non-Hodgkin Lymphoma

- **Indolent NHL** has reasonable long-term survival of several years.
- Usually not curable with conventional therapy.
- Indolent HCV-related NHL treatable with Peg-IFN/RBV:
  - Follicular (stage I & II)
  - Plasmacytoid
  - Marginal Zone (Splenic, Nodal, or Extra-nodal)
- Up to 80% of those with SVR have a sustained hematological response.
- Non-Responders to Peg-IFN/RBV: Rituximab + CHOP

Ann-Arbor Classification of NHL

Stage I	Involvement of a single lymph node region (I), or a single extralymphatic organ or site (IE)
Stage II	Involvement of two or more lymph node regions or lymphatic structures on the same side if the diaphragm alone (II), or with involvement of limited, contiguous extralymphatic organ or tissue (IIE)
Stage III	Involvement of lymph node regions on both sides of the diaphragm (III), which may include the spleen (IIIS) or limited, contiguous extralymphatic organ or site (IIIE), or both (IIIES)
Stage IV	Diffuse or disseminated foci of involvement of one or more extralymphatic organs or tissues, with or without associated lymphatic involvement.

A: no systemic symptoms;
B: unexplained fever, night sweats, or weight loss > 10% during 6 months before diagnosis

HCV-related Mixed (IgG/IgM) Cryoglobulinemia

HCV-related Mixed (IgG/IgM) Cryoglobulinemia

- Type II mixed: 95% of patients have HCV infection.
- Some cases of type-III mixed cryoglobulinemia are also HCV-related.
- Palpable purpura, skin necrosis in exposed areas, hepatosplenomegaly, hypocomplementemia C3, C4, C1q (C4 < C 3), & IgM kappa Rheumatoid Factor.
- Renal disease: hematuria, proteinuria (nephritic range), hypertension (80%), moderate renal insufficiency (50%).
- HCV-containing immune complexes cause the renal disease.

HCV-related Mixed (IgG/IgM) Cryoglobulinemia

- Plasmapheresis: one plasma volume TIW replaced with warmed 5% albumin x 2-3 weeks. Indicated for:
  - Progressive renal failure
  - Distal necrosis requiring amputation
  - Advanced neuropathy.
- Peg-Ifn + RBV: Not appropriate when plasmapheresis is needed (but can be used 2-4 months after plasmapheresis)
  - SVR is 40-50%.
  - Decreases cryoglobulin levels.
  - Improves vasculitis, skin rash and arthritis/arthralgia, proteinuria.
  - Polyneuropathy & renal function do not reliably improve.
  - Treatment may be preceded by Plasmapheresis, and/or Rituximab
  - Cryoglobulinemia may persist or recur even after SVR.

HCV-related Mixed (IgG/IgM) Cryoglobulinemia

- Rituximab: When other options not indicated. Once a week IV for 4 weeks.
  - Improves vasculitis, skin rash, indolent B-cell NHL, arthralgia, MPGN, arthritis/arthralgia.
  - HCV-RNA increases 2-fold.

HCV-Related Renal Disease

HCV-Related Renal Disease
Peg-IFN + RBV Treatment

- **Mixed Cryoglobulinemia** (good data; treat)
- **Membranoproliferative Glomerulonephritis**, even without detectable cryoglobulins (good data; treat)
- **Membranous Nephropathy** (conflicting data; consider treatment)
- **Crescentic Glomerulonephritis** associated to the previous three disorders (good data; treat with Plasmapheresis followed by Rituximab; 2-4 months later Peg-IFN/RBV).
- Give ACE inhibitor or ARB to control proteinuria y blood pressure.
- Uncommon (no good data available):
  - Focal Segmental Glomerular Sclerosis
  - Proliferative Glomerulonephritis
  - Fibrillary Glomerulopathy
  - Immunotactoid Glomerulopathy
  - Post-transplant Thrombotic Microangiopathy

Treatment of Chronic HCV in ESRD on Dialysis

HCV in ESRD & post-KTx Treatment

- Risk of Interferon use post-KTx is high: 15-64% vascular rejection / tubulo-interstitial lesion.(not recommended)
- Difficult to use Ribavirin in ESRD b/o toxicity (dose is 150-300 mg/d) ; severe hemolysis.
- Lower efficacy of Interferon (18-27% SVR) in ESRD.
- Dose: PEG-Intron 1 mcg/kg/week; PEGASYS 135-180 mcg/week.
- Erythropoietin is usually needed

Peg-IFN-a2a in ESRD
Pharmacokinetics

- Peg-Ifn-a2a is not significantly cleared by dialysis (hemodialysis or peritoneodialysis).
- In a 12 weeks study, Peg-Ifn-a2a 135 or 180 mcg once weekly gave safe and constant concentration on patients with ESRD on hemodialysis.
- The dose of 135 mcg/wk in ESRD gives levels similar to those of patients with normal renal function receiving 180 mcg/wk (13000 pg/mL).
- Safety of 135 vs 180 mcg per week in ESRD is similar.

Peg-Ifn-a2a Monotherapy in ESRD (hemo- or peritoneo- dialysis)

Author	Treatment	Result
Kokoglu (J Gastroenterol Hepatol 2006;21:575-580)	Rp(12): Peg 135 x 48w C(13): no therapy	Rp: EOT(-) 84%, SVR 75% C: EOT(-) 8%, SVR 8%
Sporea (World J Gastroenterol 2006;12(26):4191-4194)	Rp(10): Peg 180 x 48w	SVR: ITT 30%, PP 50%
Chan (Nephrology 2007;12:11-17)	Rp(6): Peg 135 x 48 w	EOT(-) 83%, SVR 33%
Teta (Nephrol Dial Transplant 2005;20:991-993)	Rp(3): Peg 90-180 x 24-48 w	SVR 66%
Peck-Radosavljevic (EASLD Abstr. April 2007)	Rp(38): Peg 135 x 48 w Rp(43): peg 90 x 48 w	Interim wk 24: HCV-RNA(-) 58% vs 49%
Ionita-Radu (EASLD Abstr. April 2007)	Rp(29): Peg 135	SVR 41%

Peg-Inf-a2a + RBV in ESRD (hemo- or peritoneo- dialysis)

Author	Treatment	Result
Rendina (Journal of Hepatology 2007:768-774)	Rp(35): Peg 135/RBV 200qd x 48 w(g-1) or 24 w (g-no-1)+EPO C(35): no therapy	Rp: SVR 97% (93% g-1, 100% g-non-1)
Hakim (DDW Abstr. May 2006)	Rp(20): Peg 135/RBV 200 TIW x 48 w	Interim 12 w: HCV-RNA(-) 45%
Deltenre (AASLD Abstr. Oct 2006)	Rp(14): Peg 180/RBV 800 per w x 24-48 w + EPO	EOT(-): 79%, SVR 63%
Carriero (AASLD Abstr. Oct 2006)	Rp(15): Peg 135-180/RBV 200 qd x 4-76 w + EPO	SVR 31%
Bruchfeld (J Viral Hepatitis 2006;13:316-321)	Rp(2): Peg 135/RBV 1400-2000 mg per w + EPO	SVR 100%

Treatment According to Stages of Chronic Kidney Diseases

Stage	Description	GFR (ml min1 1.73 m2)	Recommended Treatment
1.	Kidney damage with normal or increased GFR	90	A
2.	Kidney damage with mild decrease GFR	60-90	A
3.	Moderate decrease GFR	30-59	B
4.	Severe decrease GFR	15-29	B
5.	Kidney failure	15	B
5D.	Dialysis (hemo-or peritoneal)		C

A: Routine combination therapy according to viral genotype.

B: Peginterferon alfa-2b, 1 mcg/kg subcutaneously once weekly, or Peginterferon alfa-2a, 135 mcg subcutaneously once weekly plus Ribavirin, 200-800 mg/day in two divided does starting with low dose and increasing gradually

C: Controversial: Standard interferon (2a or 2b) 3mU three times weekly, or Pegylated interferon alfa-2b, 1 mcg/kg/week, or Pegylated interferon alfa-2a, 135 mcg/week ? Ribavirin in markedly reduced daily dose.

Questions ?