Hepatitis C: Managing Patients, Managing Treatment

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Conflict of Interest Disclosure

Camilla S. Graham, MD, MPH:

-I have no financial relationships with a commercial entity producing healthcare-related products and/or services.

-Member, Drug Utilization Review Board, MassHealth

-Member, Pharmacy and Therapeutics Committee, Tufts Health Plan

Identifying Patients with Hepatitis C

- 4-5 million people in the US have hepatitis C virus (HCV) infection
  - NHANES estimates 3.2 million infected but this national survey excludes people who do not have a permanent address (homeless, incarcerated, nursing home residents), active military, and under-represents most groups outside White, African-American, and Mexican-Hispanic
  - Accounting for under-represented international populations, homeless, and groups that have a high prevalence like IDU and veterans gives the 5+ million estimate
- Most were infected in 1960's through 1980's
  - Up to 250,000 cases per year in 1980's
  - About 50% infected via IDU, rest from blood transfusions, sex, tattoos, medical procedures, and other factors

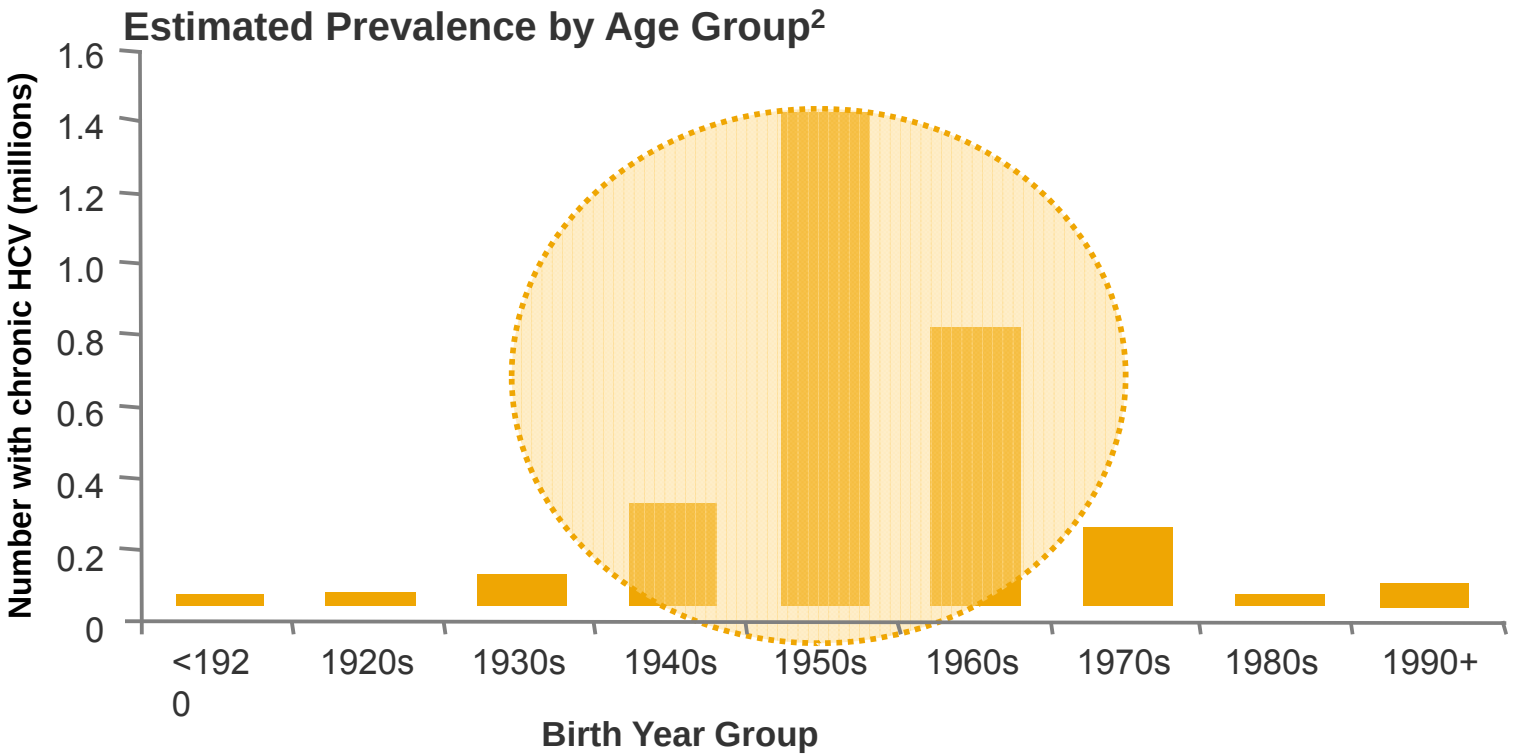
Smith BD et al. MMWR. August 17, 2012/61(RR04);1-18. Armstrong GL et al. Ann Intern Med. 2006 May 16;144(10):705-14. http://www.iom.edu/Reports/2010/Hepatitis-and-Liver-Cancer-A-National-Strategy-for-Prevention-and-Control-of-Hepatitis-B-and-C.aspx; Rein et al. Dig Liver Dis 2011; 43:66

Identifying Patients with Hepatitis C

- Up to 75% of people have not been diagnosed
  - 50% to 75% is estimated
- Risk-based screening misses many people
  - Overburdened primary care
  - Lack of knowledge for patients and providers
  - Stigma associated with IDU, even if decades ago
- Leading cause for liver transplantation and liver cancer (HCC)
  - 37% lifetime risk of HCV-related mortality for patients with chronic HCV

Smith BD et al. MMWR. August 17, 2012/61(RR04);1-18. Armstrong GL et al. Ann Intern Med. 2006 May 16;144(10):705-14. http://www.iom.edu/Reports/2010/Hepatitis-and-Liver-Cancer-A-National-Strategy-for-Prevention-and-Control-of-Hepatitis-B-and-C.aspx; Rein et al. Dig Liver Dis 2011; 43:66

Baby Boomers (Born in 1945–1965) Account for 76.5% of HCV in the US[1]



An estimated 35% of undiagnosed baby boomers with HCV currently have advanced fibrosis (F3-F4; bridging fibrosis to cirrhosis)[3]

1. Centers for Disease Control and Prevention. *MMWR*. 2012;61:1-32; Adapted from Pyenson B, et al. *Consequences of Hepatitis C Virus (HCV): Costs of a baby boomer Epidemic of Liver Disease*. New York, NY: Milliman, Inc; May 18, 2009. http://www.milliman.com/expertise/healthcare/publications/rr/consequences-hepatitis-c-virus-RR05-15-09.php Milliman report was commissioned by Vertex Pharmaceuticals; 3. McGarry LJ et al. *Hepatology.* 2012;55(5):1344-1355.

Who Should Be Tested for HCV

CDC Recommendations

- Everyone born from 1945 through 1965 (one-time)
- Persons who ever injected illegal drugs
- Persons who received clotting factor concentrates produced before 1987
- Chronic (long-term) hemodialysis
- Persons with persistently abnormal ALT levels.
- Recipients of transfusions or organ transplants prior to 1992
- Persons with recognized occupational exposures
- Children born to HCV-positive women
- HIV positive persons

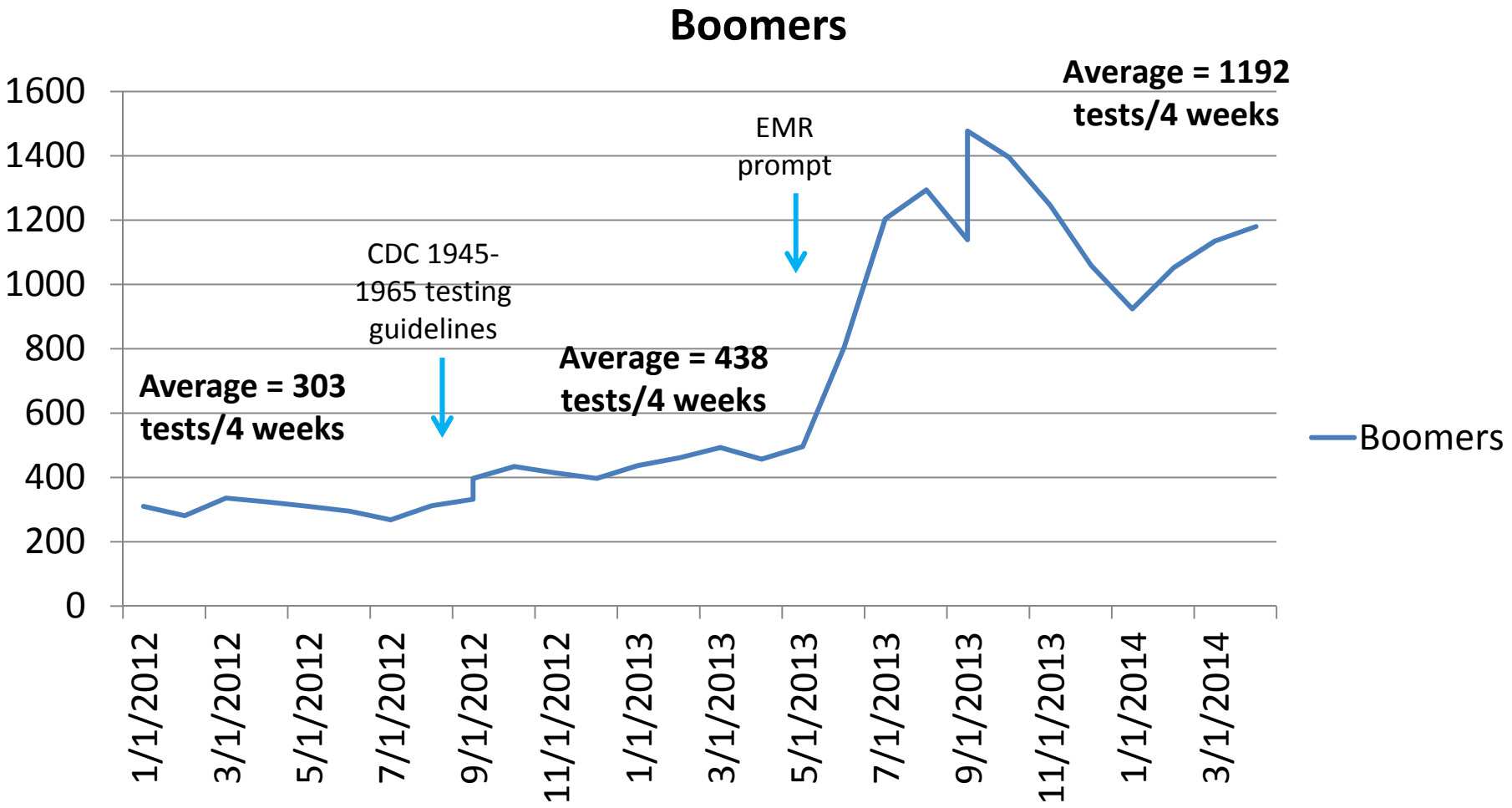
USPSTF Grade B Recs*

- Everyone born from 1945 through 1965 (one-time)
- Past or present injection drug use
- Sex with an IDU; other high-risk sex
- Blood transfusion prior to 1992
- Persons with hemophilia
- Long-term hemodialysis
- Born to an HCV-infected mother
- Incarceration
- Intranasal drug use
- Receiving an unregulated tattoo
- Occupational percutaneous exposure
- Surgery before implementation of universal precautions

*Only pertains to persons with normal liver enzymes; if elevated liver enzymes need HBV and HCV testing

Smith at al. Ann Intern Med 2012; 157:817-822. Moyer et al. Ann Intern Med epub 25 June 2013

HCV Antibody Test Volume Increased after EMR Prompt in CareGroup



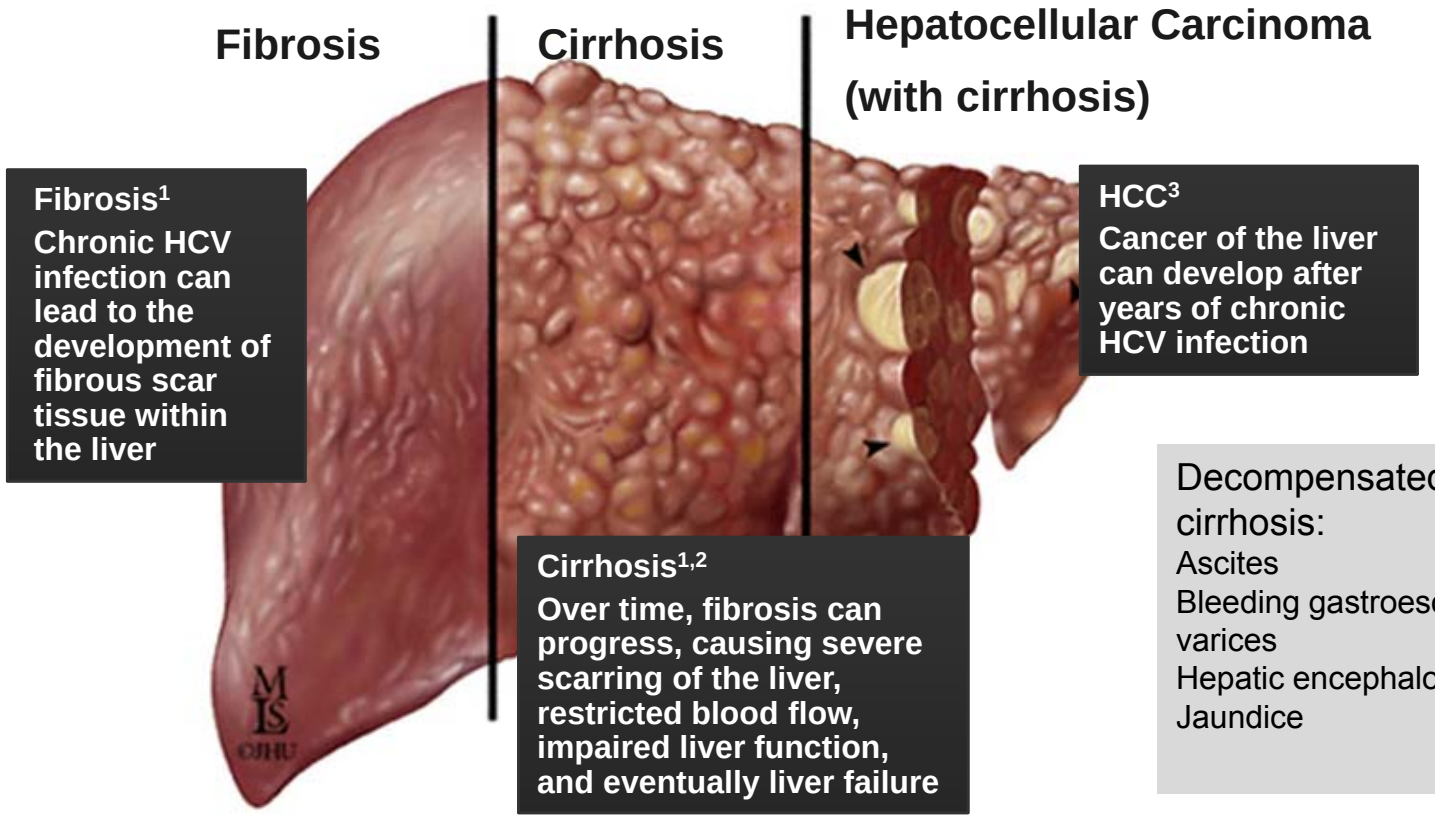
Beth Israel Deaconess Medical Center, Boston, MA, Quality Outcomes Data, 6/5/14

More Women Tested for HCV but More Men are Anti-HCV Positive

Group	Number (%) Tested for HCV Ab	Anti-HCV Seroprevalence (%)
All Boomers	13,107	2.3%
Boomer women	7,555 (58%)	1.4% (34% of HCV Ab+ results)
Boomer men	5,552 (42%)	3.6% (66% of HCV Ab+ results)
All Non-Boomer	7,022	2.6%
Non-Boomer women	4,023 (57%)	1.9% (42% of HCV Ab+ results)
Non-Boomer men	2,999 (43%)	3.5% (58% of HCV Ab+ results)

Beth Israel Deaconess Medical Center, Boston, MA, Quality Outcomes Data, 6/5/14

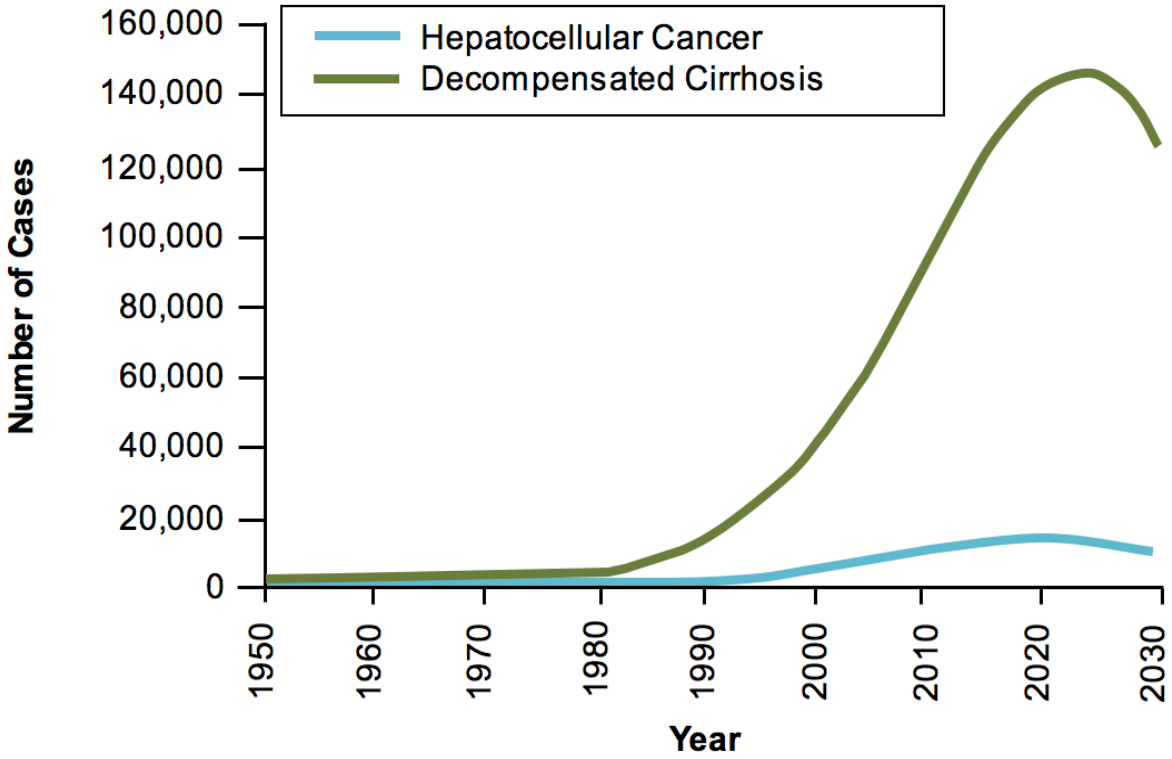
Chronic HCV Infection May Lead to Chronic Liver Disease and Liver Cancer



Chronic liver disease includes fibrosis, cirrhosis, and hepatic decompensation; HCC=hepatocellular carcinoma.

1. Highleyman L. Hepatitis C Support Project. http://www.hcvadvocate.org/hepatitis/factsheets_pdf/Fibrosis.pdf. Accessed August 18, 2011; 2. Bataller R et al. *J Clin Invest*. 2005;115:209-218;
3. Medline Plus. http://www.nlm.nih.gov/medlineplus/enxy.article/000280.htm. Accessed August 28, 2012; 4. Centers for Disease Control and Prevention. http://www.cdc.gov/hepatitis/HCV/HCVfaq.htm. Accessed May 8, 2012.

Projected Numbers of Decompensated Cirrhosis and Cases of HCC to Rise Through 2020

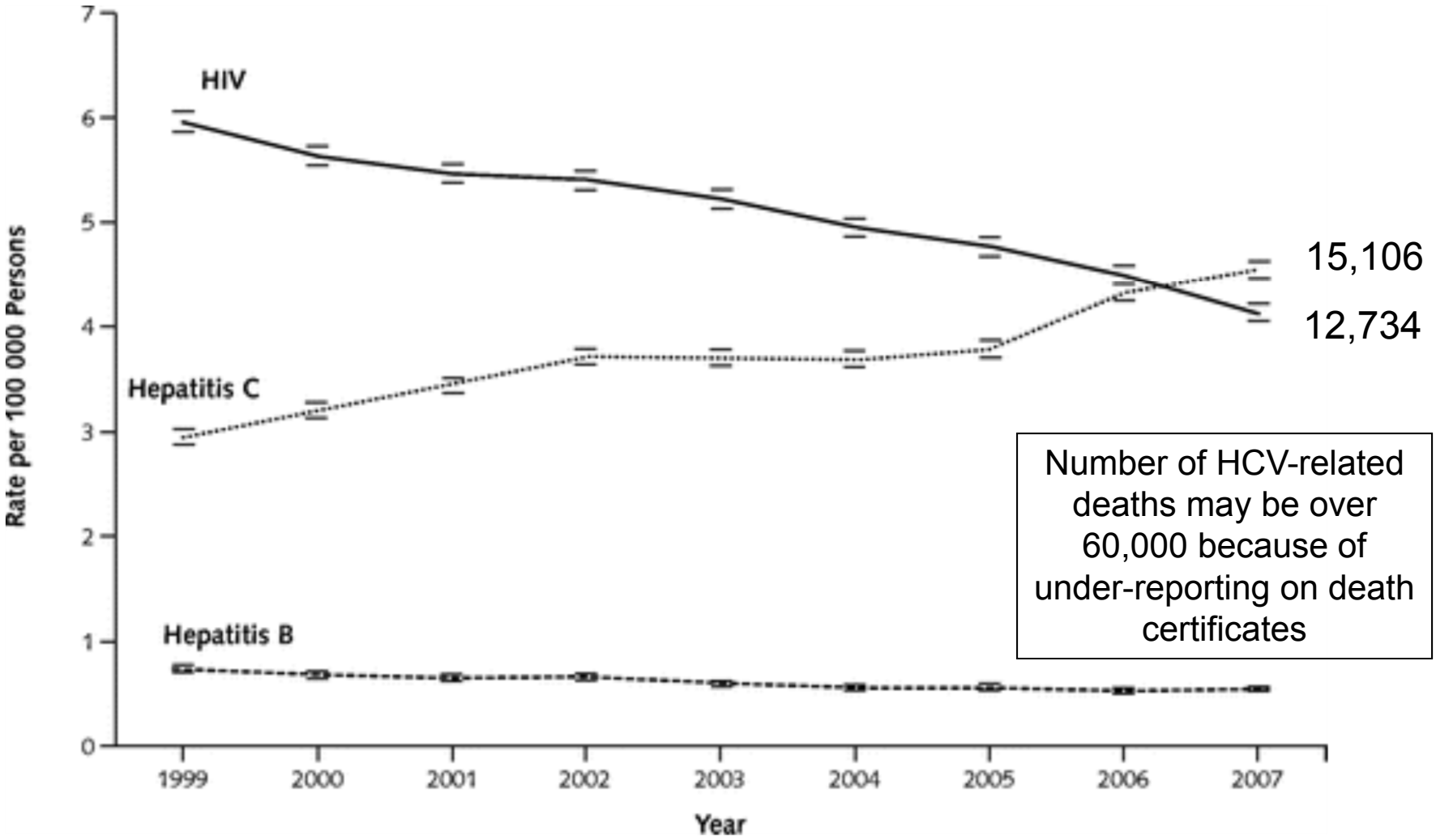


- Decompensated cirrhosis became more common after 1995 and is presently estimated at 11.7% of cirrhosis cases; the number of cases is expected to continue to increase through ~2020-2030
- HCC rose steeply after 1990. Based on the model, the incidence of HCV-related HCC is expected to peak in 2019 at almost 14,000 cases per year if the risk in HCV-infected persons with fibrosis remains the same

HCC=hepatocellular cancer; HCV=hepatitis C virus.

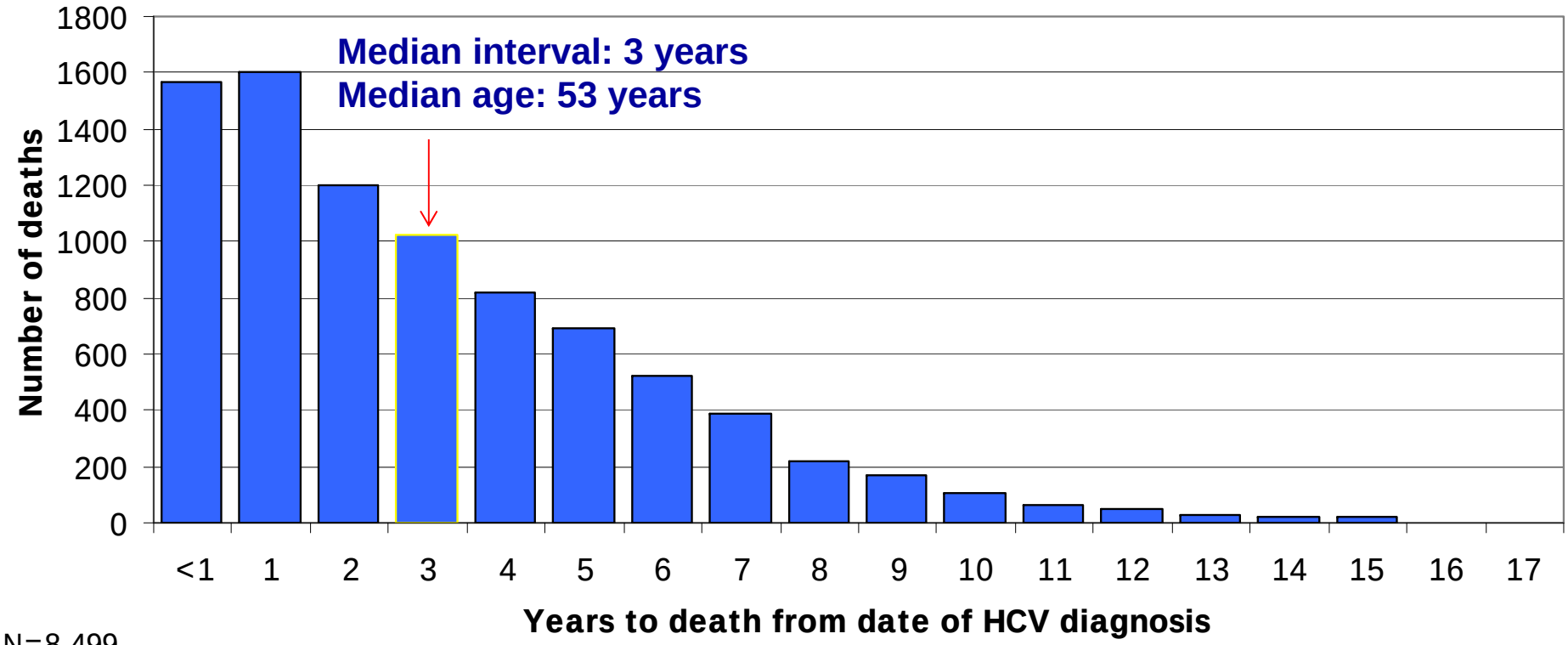
Adapted from Davis GL, et al. *Gastroenterology.* 2010;138(2):513-521

Deaths Due to HCV Infections Now Exceed Those Due to HIV Infection



Ly KN et al. Ann Intern Med. 21 February 2012;156(4):271-278; Mahajan, IDSA 2013

Timing of Mortality Among Known HCV Cases in Massachusetts, 1992-2009



N=8,499

76,122 HCV diagnoses were reported to the MDPH between 1992 and 2009, 8,499 of these reported HCV cases died and are represented in the figure. Data as of 1/11/2011.

Lijewski, et al, 2012

Hepatitis C Diagnosis has been Made: What to Discuss with the Patient

- Do not donate blood, body organs, other tissue, or semen
- Do not share personal items that might have small amounts of blood
  - Toothbrushes, razors, nail-grooming equipment
- HCV is not spread by hugging, kissing, food or water, sharing utensils, or casual contact
- If using illicit drugs, stop using. If continued, get into a treatment program and do not share needles, syringes or works
  - Concern among payers about poor adherence and reinfection after antiviral Rx
- If in short term, multiple or MSM relationships, use latex condoms. No condom use is recommended for long-term monogamous heterosexual couples
  - Maximum incidence rate of HCV sexual transmission estimated about 1 new infection per 190,000 sexual contacts per year (Terrault, Hepatology. 2013; 57(3):881)
- Limit Tylenol to 2 gm a day and discuss all other medications (including OTC and herbal) with a provider
- Check exposure status for hepatitis A and B and vaccinate if needed

Adapted from Winston et al. Management of hepatitis C by the primary care provider: Monitoring guidelines; 2010
http://www.hcvadvocate.org/hepatitis/factsheets_pdf/PCP_web_10.pdf

Address Alcohol Use in HCV

- The CDC recommends brief alcohol intervention for all patients with HCV
- There is no “safe” amount of alcohol consumption
- Insist on absolute abstinence if patient has bridging fibrosis or cirrhosis
- Assess for risky alcohol use
  - Men: >2 drinks/day (>14/week) or more that 4 in one day
  - Women: >1 drink/day (>7/week) or more than 3 in one day
- Screen for alcohol misuse
  - How many times in the past year have you had X or more drinks in a day?”, where X is 5 for men and 4 for women, and a response of >1 is considered positive

http://www.integration.samhsa.gov/images/res/tool_auditc.pdf

Moyer et al. Screening and Behavioral Counseling Interventions in Primary Care to Reduce Alcohol Misuse: USPSTF Recommendation Statement. Annals Int Med; 14 May 2013 online

Baseline Labs in Patients with Newly Diagnosed HCV

- HCV RNA “viral load” (determines active infection)
- Hepatitis C genotype (determines treatment choice)
- Complete blood count (platelets <150,000 assc with cirrhosis)
- INR, Albumin, Total bilirubin (abnormal liver synthetic function often indicates advanced liver disease)
- Creatinine, Glucose, ALT, AST, Alkaline Phosphatase
- Hepatitis A serology: total or IgG (vaccinate if nonreactive)
- Hepatitis B serology: HBsAb, HBcAb, HBsAg (vaccinate if all nonreactive)
- HIV antibody
- Iron studies, ANA
- Assessment of liver fibrosis (such as Hepascore, Fibrotest, APRI, FIB-4, Fibroscan)

BIDMC HCV ECHO Program Recommendations, 2014

Determine Likelihood of Cirrhosis

- Noninvasive test results increase the likelihood of cirrhosis, especially if more than one are present:
  - APRI >1.5 or FIB-4 >3.25 (use on-line calculators)
    - FIB-4 more predictive of ESLD than liver biopsy (CROI 2014)
  - Hepascore or Fibrotest >0.74
  - Fibroscan >12.5
  - Platelets <150,000
  - Albumin < 3.5
- Splenomegaly on exam or ultrasound
- Any signs of liver decompensation
- MELD and Child-Pugh scores (use on-line calculators)

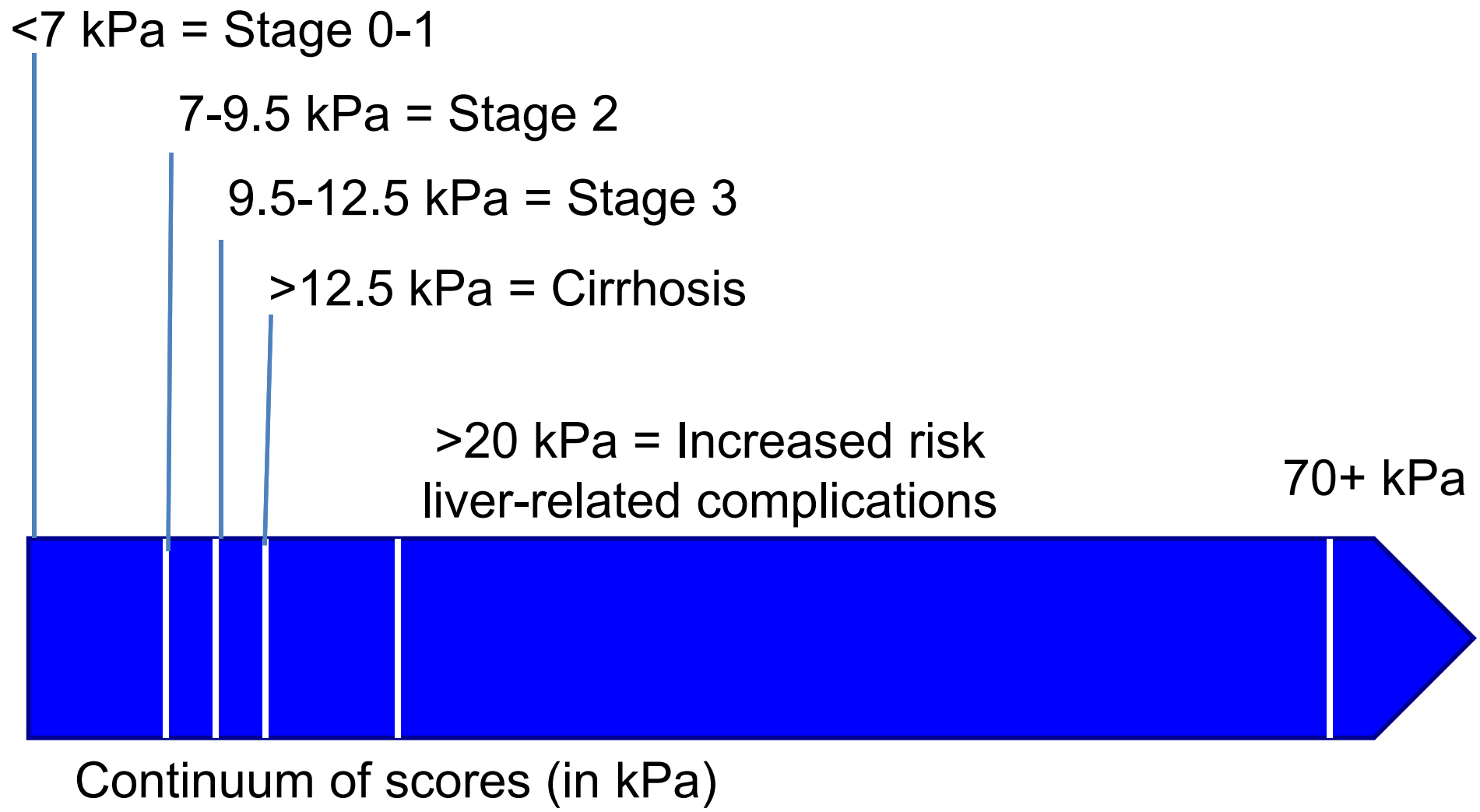
Chou, Annals Int Med 2013; 158:807; Bonder, Curr Gastro Rep 2014; 16:372;
Berenguer #640 and Lo Re #650 CROI 2014

FibroScan - Transient Elastography

- Ultrasound determines velocity of shear wave in m/s, which is proportional to liver stiffness in kilopascal (kPa)
- Entire process requires 15 to 20 minutes, provides immediate results
- Falsely elevated results:
  - High ALT (>100)
  - Eating within 2 hours

Bonder, Curr Gastro Rep 2014; 16:372

Continuum of Fibrosis/Cirrhosis in HCV



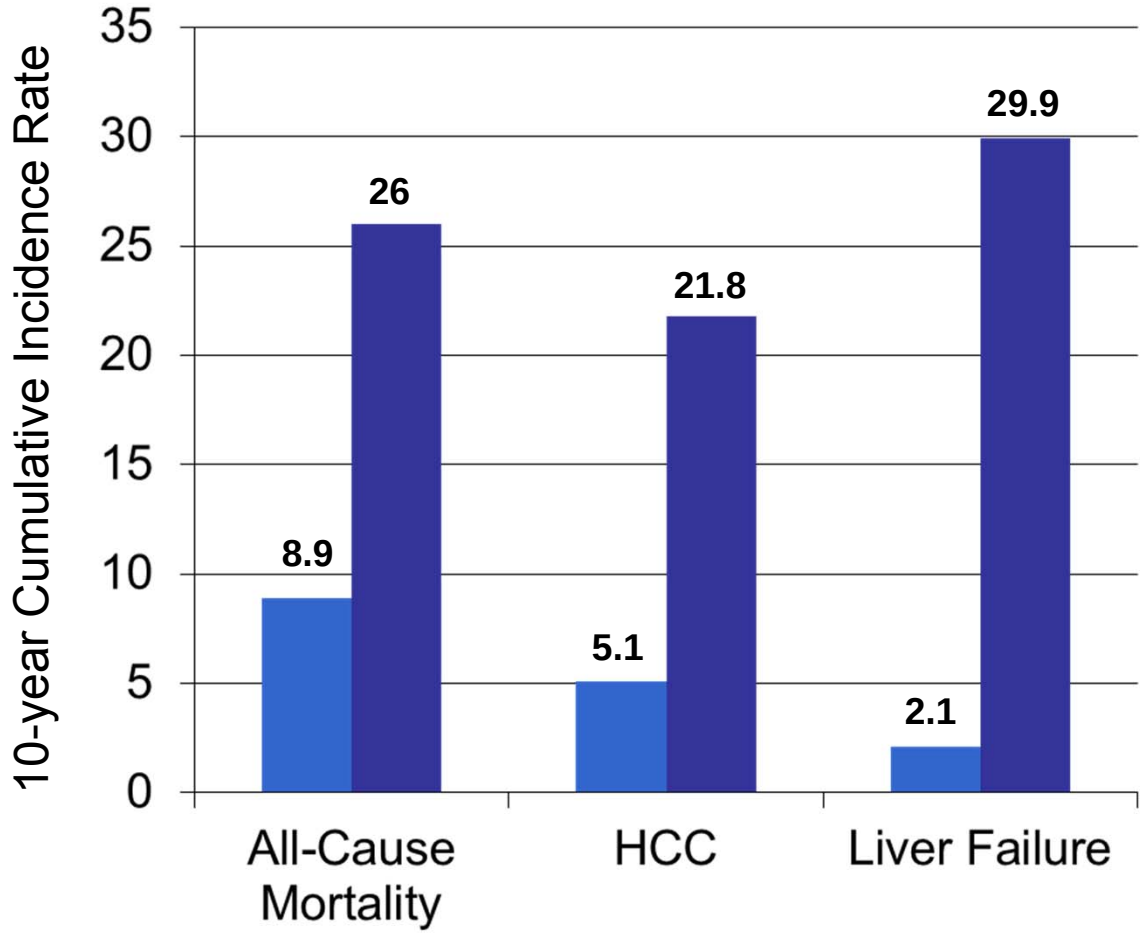
Bonder, Curr Gastro Rep 2014; 16:372

Management of Patients with Hepatitis C and Cirrhosis

- Every 6 month screening for liver cancer
  - Usually ultrasound
  - Consider CT or MRI if highly nodular liver; first exam
- Screening for esophageal varices
  - Repeat every 1 -3 years depending on results
- Counsel on symptoms of hepatic encephalopathy
- Vaccination for pneumococcus
- Counseling around medication use to avoid overdose or adverse events (including common drugs like Tylenol and NSAIDS)
- Counseling about complete abstinence from alcohol
- Evaluation for antiviral treatment
  - Cure of HCV can reduce liver failure and liver cancer, even in patients with cirrhosis (+/- HIV coinfection)
- Possible referral for liver transplant services

http://www.aasld.org/practiceguidelines/pages/guidelinelisting.aspx

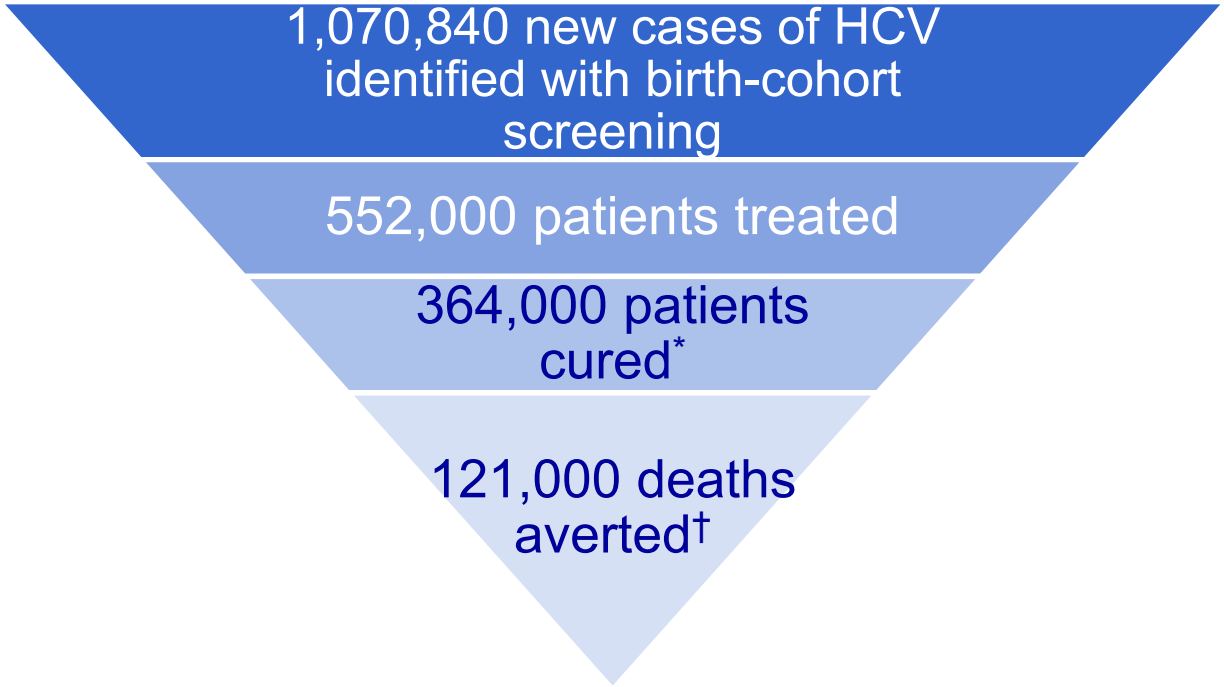
SVR (Cure) Associated with Decreased All-Cause Mortality



530 patients with advanced fibrosis, treated with interferon-based therapy, and followed for 8.4 (IQR 6.4-1.4) years

Van der Meer et al. JAMA 2012; 308:2584

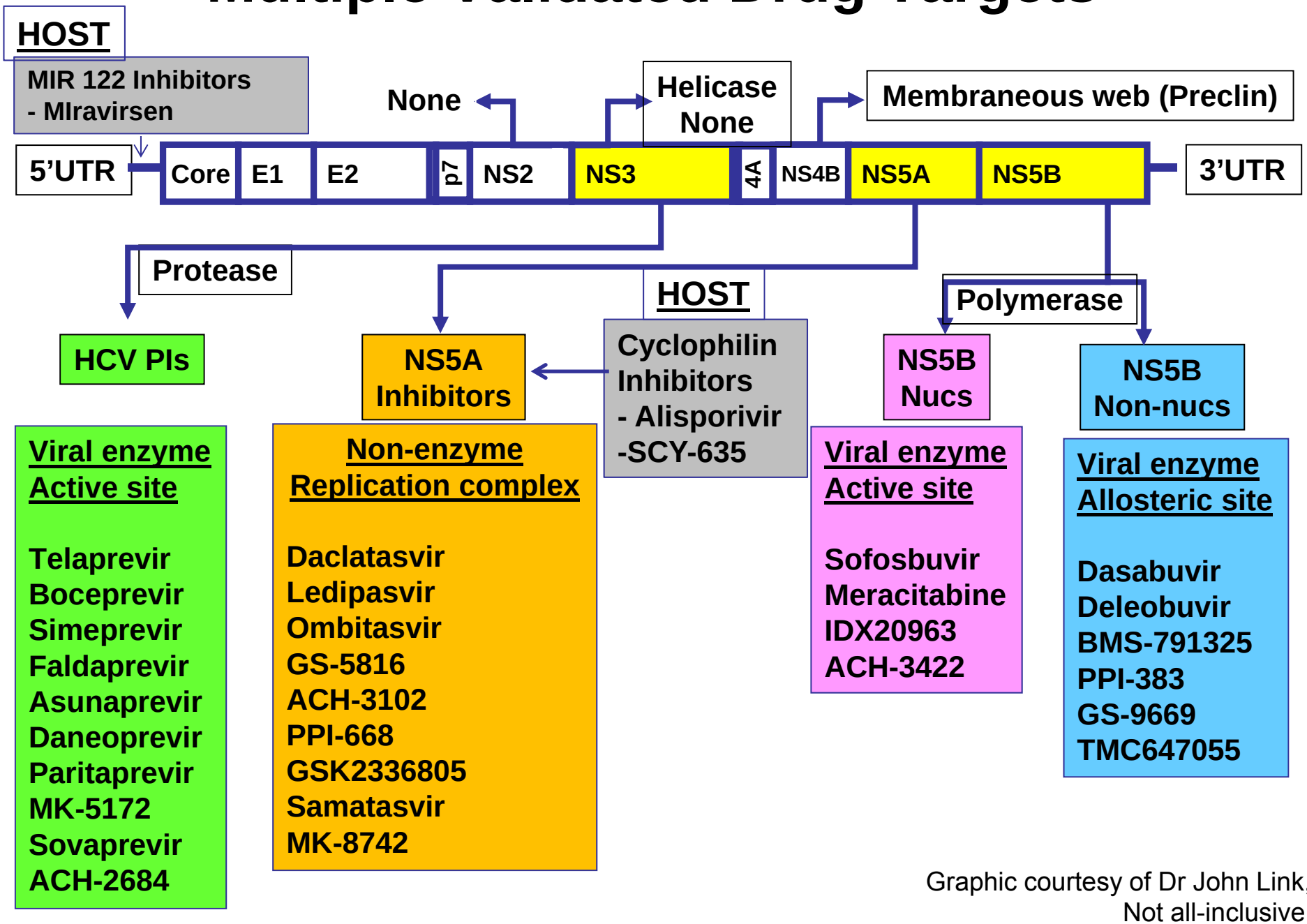
Screening of Baby Boomers May Prevent >120,000 Deaths Due to HCV Infection



- Birth-cohort screening in primary care would identify 86% of all undiagnosed cases in the birth cohort, compared with 21% under risk based screening[1]
- Cost effectiveness of HCV screening is comparable to cervical cancer or cholesterol screening (cost/QALY gained with protease inhibitor+IFN+RBV = $35,700)

Markov chain Monte Carol simulation model of prevalence of hepatitis C antibody stratified by age, sex, race/ethnicity, history of injection drug use, and natural history of chronic hepatitis C.
*With pegylated interferon and ribavirin plus DAA treatment.
†Deaths due to decompensated cirrhosis or hepatocellular carcinoma within 1945-1965 birth cohort. 470,000 deaths under birth cohort screening vs 592,000 deaths under risk-based screening
1. Rein D et al. *Ann Intern Med.* 2012;156(4):263-270; 2. McGarry LJ et al. *Hepatology.* 2012;55(5):1344-1355.

Multiple Validated Drug Targets



Graphic courtesy of Dr John Link,
Not all-inclusive

Current Negative Environment Created By High Price of HCV Drugs

- Confusion and doubt among HCV treaters
- Fear from PCPs about testing and certainly treatment
- Fear/outrage among payers (public and private)
- Hesitation in DPH/public outreach programs
- Questions about integrity of CDC work (research and KNOW MORE HEPATITIS campaign)
- Declarations by prisons, state Medicaids that HCV treatment is not of value
- Difficulty establishing broad baby boomer testing programs
- Rationing of treatment, ie F3-F4
- Conflict between provider, patient and payer over rationing
- No discussion of treatment as prevention
- Justification for overt discriminatory practices like mandating clean urine samples
- Confirmation by patients that they are not “worth” treatment
- Loss of vision about transformative, curative developments

"Standard of Care" Regimens for Hepatitis C Have Been Expensive for Years: Value of Cure

Regimen	SVR rates (Genotype 1, Naïve)	2014 WAC Price	Cost per SVR
Pegasys + Ribavirin x 48 weeks[1]	41%	$41,758	$101,849
Telaprevir + Pegasys + Ribavirin x 24 weeks[2]	75%	$86,843	$115,791
Sofosbuvir + Pegasys + Ribavirin x 12 weeks[3]	90%	$94,421	$104,912

[1]McHutchison, NEJM 2009; [2]Jacobson, NEJM 2011; [3]Lawitz, NEJM 2013

Variables Important in HCV Management and Treatment Decision Making

- Genotype: 1, 2, 3, 4, 5 and 6
- Stage of liver fibrosis: F0-1 (mild), F0-F2 (mild to moderate), F2-F4 (moderate to advanced), F3-F4 (advanced), F4 (cirrhosis)
- Cirrhosis severity: Compensated (Child A), cirrhosis with portal hypertension, Decompensated (Child B/C), Clinical decompensation
- Hepatocellular carcinoma (and stage)
- Pre-Transplant
- Post-Transplant
- Extra-hepatic complications (renal, lymphoma, cryoglobulinemia, etc)
- Psychological distress from HCV infection
- Coinfections: HIV, HBV
- Prevention of transmission: Women pre-pregnancy, MSM, active IDU

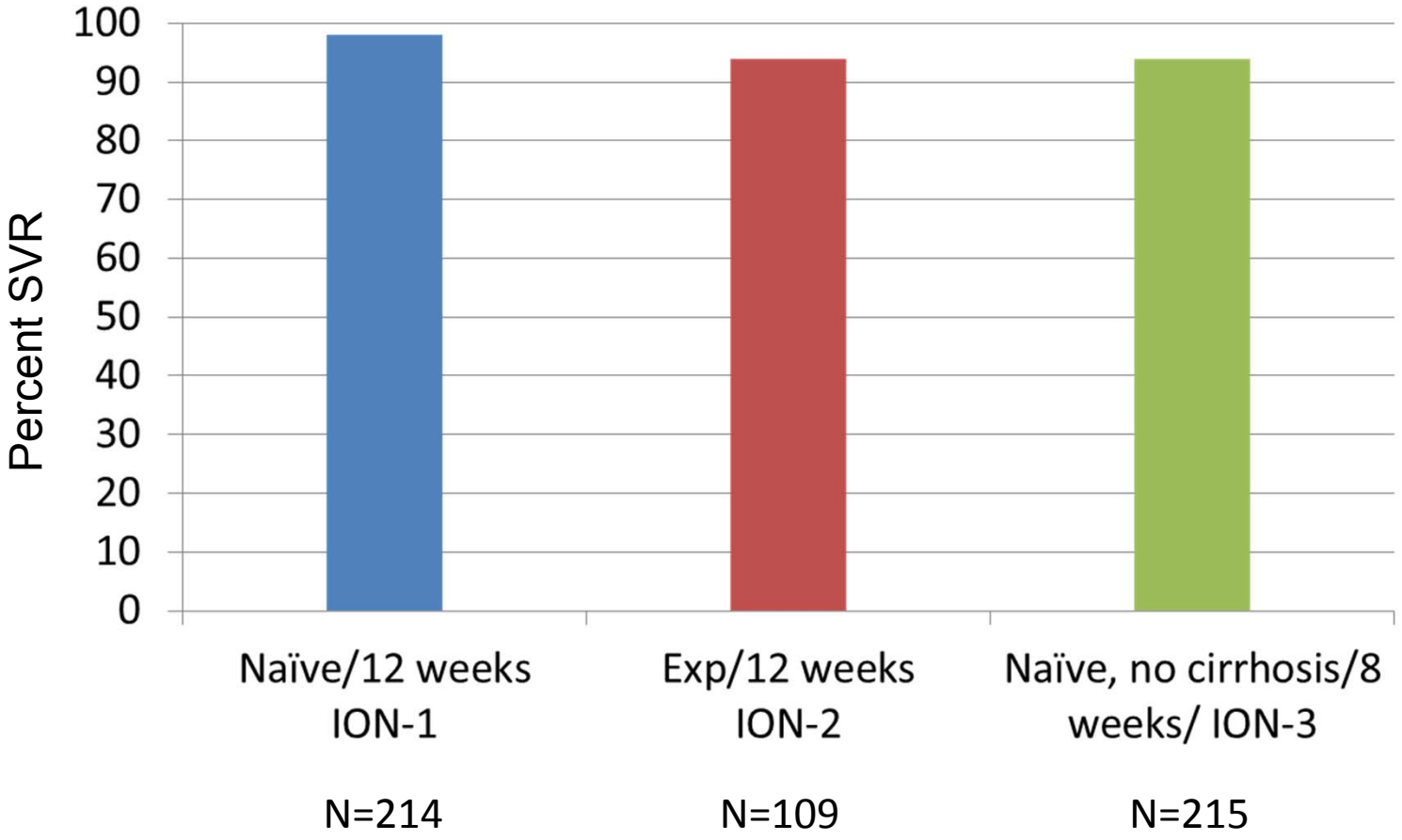
Variables Important in HCV Management and Treatment Decision Making

- Naïve
- Previous treatment:
  - P/R relapse, P/R partial responder, P/R null responder
  - Telaprevir/boceprevir failure (? Importance of relapse vs. nonresponder/breakthrough)
  - Sofosbuvir/RBV +/- IFN failure
  - Sofosbuvir/simeprevir failure
  - Other clinical trial failures

The World is Rapidly Changing in HCV

- ~~Pegylated interferon (Peg-IFN) + ribavirin (RBV)~~
- ~~Peg-IFN + RBV + Telaprevir~~
- ~~Peg-IFN + RBV + Boceprevir~~
- ~~Peg-IFN + RBV + Simeprevir~~
- Sofosbuvir+Ledipasvir x 8 weeks
- Paritaprevir/r/ombitasvir+dasabuvir+/-RBV x 12 weeks
- Sofosbuvir +RBV x 12 weeks
- Sofosbuvir+Ledipasvir x 12 weeks
- Sofosbuvir+Simeprevir x 12 weeks
- Paritaprevir/r/ombitasvir+dasabuvir+/-RBV x 24 weeks (geno 1a cirrhotic [F3-F4] null [non-] responders?)
- Sofosbuvir+RBV x 24 weeks
- Sofosbuvir+Ledipasvir x 24 weeks
- Sofosbuvir+RBV x 48 weeks

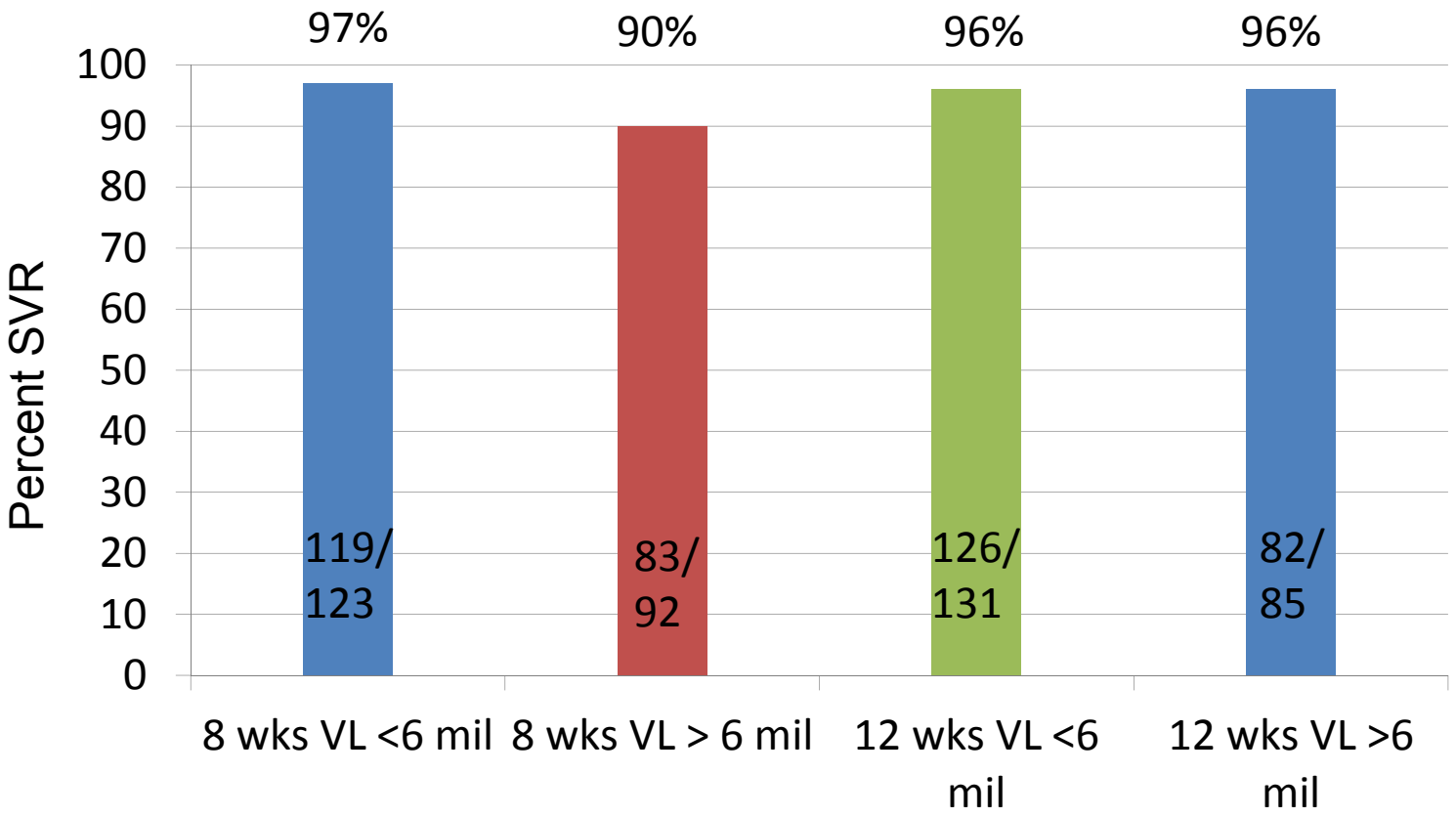
SVR-12 in Genotype 1 Patients Treated with Sofosbuvir+Ledipasvir (FDC)



Gilead Phase 3 Program:
-Genotypes 1a and 1b combined for all studies
-ION-1 with 15.7% cirrhosis
-ION-2 with 20% cirrhosis
-FDA approval anticipated October 10, 2014

EASL 2014

SVR in Genotype 1, Naïve, Non-cirrhotic Patients Treated with Sofosbuvir+Ledipasvir (ION-3)



Harvoni package insert, 10/11/14

Key Points with Sofosbuvir+Ledipasvir

- Most common AEs are fatigue and headache
- Taken with or without food
- Ledipasvir needs acid for solubility/absorption
  - Be careful with OTC acid blockers
- eGFR >30 mL/min/1.73m^2
- No dose adjustment for Child-Pugh Class A, B, or C cirrhosis
- Pregnancy Class B
- Avoid P-gp inducers; see all other DDI data in PI

Harvoni package insert, 10/11/14

Hypothetical Examples for Treatment of Genotype 1, Naïve, Non-Cirrhotic Patients

Regimen	SVR rates	WAC Price	Cost per SVR
Telaprevir + PegIFN + Ribavirin x 24 weeks[2]	75%	$86,843	$115,791
Sofosbuvir + PegIFN + Ribavirin x 12 weeks	90%	$94,421	$104,912
Sofosbuvir+Ledipasvir x 8 weeks	94%	$63,000	$67,021
Sofosbuvir + Ledipasvir x 12 weeks	99%	$94,500	$95,454

Package inserts for products

SOF+LDV: 8 Weeks if VL <6 Million?

- 100 person hypothetical cohorts: Genotype 1 HCV, naive, no cirrhosis, 60% have HCV VL < 6 million, 40% have >6 million.
- #1 Everyone receives 12 weeks:
  - 100 x $94,500 = $9,450,000
  - 3 relapses = 3 x 189,000 = $567,000
  - Total = $10,017,000

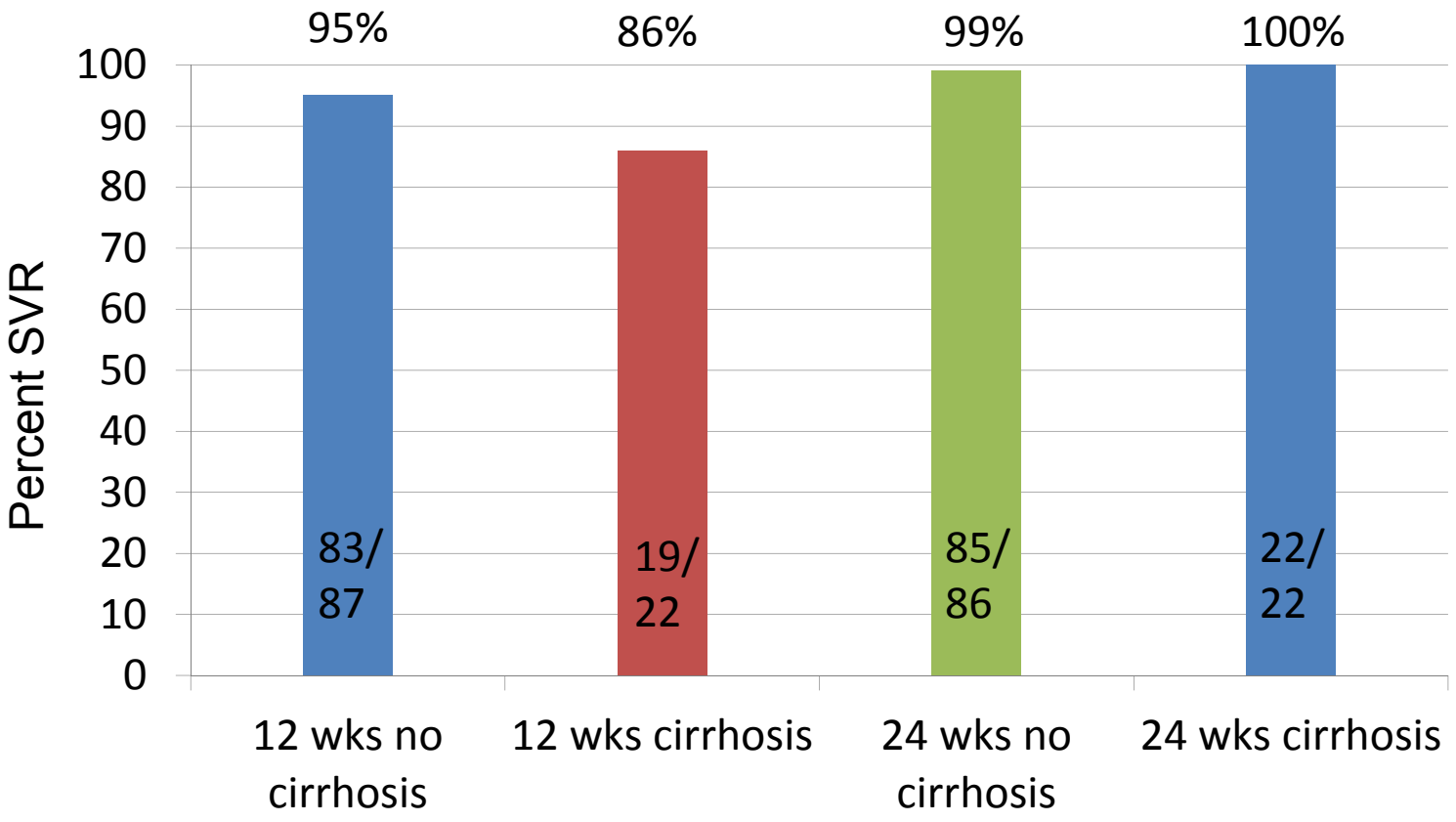
SOF+LDV: 8 Weeks if VL <6 Million?

- #2 If VL <6 million, receive 8 weeks and if VL >6 million receive 12 weeks:
  - 60 x $63,000 = $3,780,000
  - 2 relapse = 2 x $189,000 = $378,000
  - 40 x $94,500 = $3,780,000
  - 1 relapse = 1 x 189,000 = $189,000
  - Total = $8,127,000

SOF+LDV Example

- Convincing providers to use 8 weeks will require:
  - Assurances that retreatment of relapsers will be allowed
  - LOTS of education
  - Not relying on prior authorization alone

SVR in Genotype 1, Treatment-Experienced Patients Treated with Sofosbuvir+Ledipasvir (ION-2)



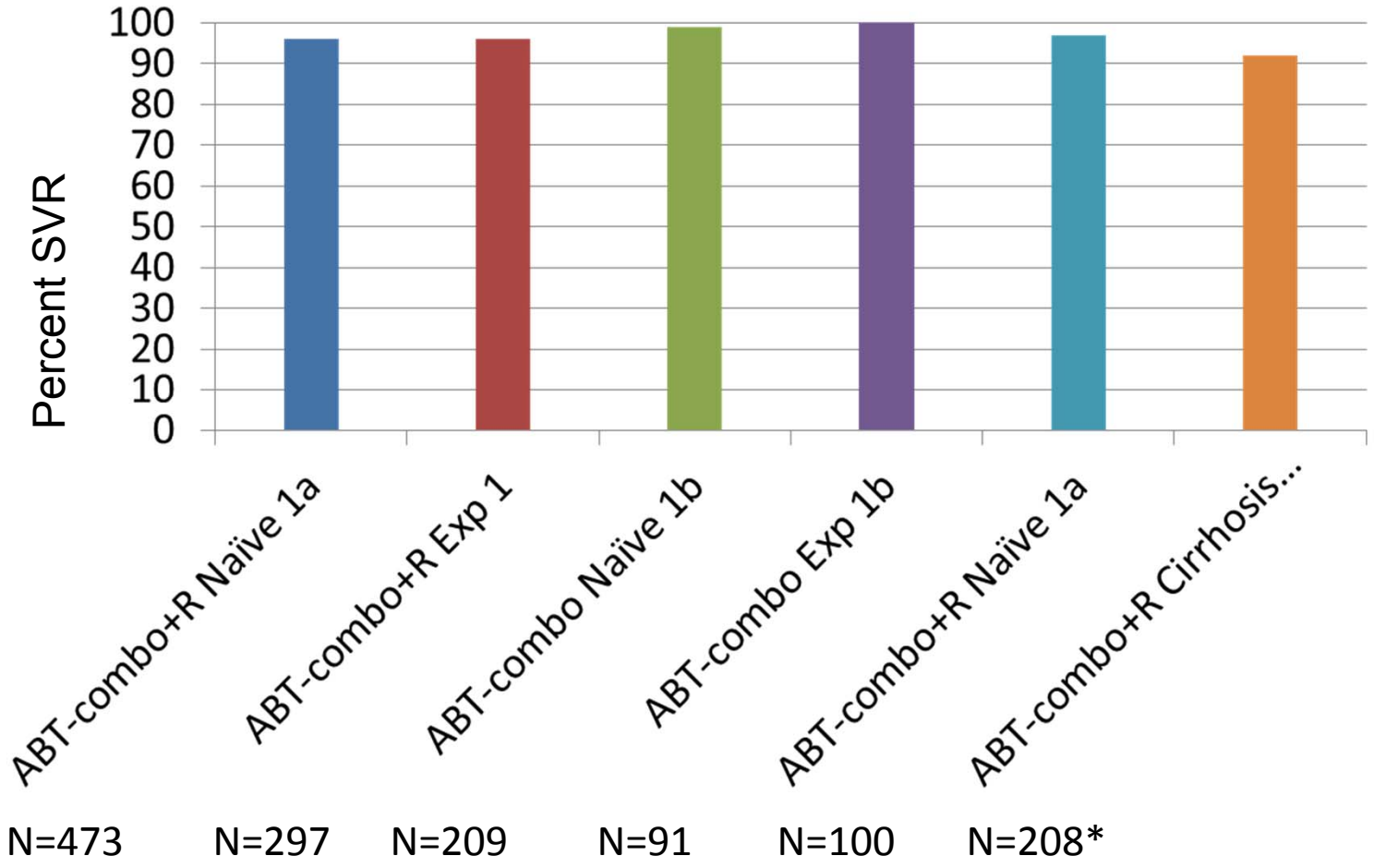
Harvoni package insert, 10/11/14

SOF+LDV in Treatment-Experienced Cirrhotic Patients

- We are making a decision based on 22 patients (!)
- Need real-world data (TARGET, Trio Health)

Regimen	SVR rates	WAC Price	Cost per SVR
Sofosbuvir+Ledipasvir x 12 weeks	86%	$94,500	$109,884
Sofosbuvir + Ledipasvir x 24 weeks	100%	$189,000	$189,000
Sofosbuvir + Simeprevir x 12 weeks (failed P/R)	90%	$150,320	$167,022

SVR-12 in Genotype 1 Patients Treated with Paritaprevir/r+Ombitasvir+Dasabuvir +/- RBV (3-D)

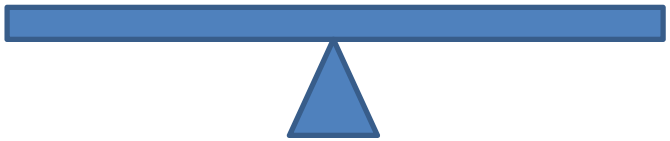


Phase 3 AbbVie program:
-All 12 week treatment arms
-Geno 1b no RBV
-Geno 1a with RBV
-All studies excluded cirrhotic patients expect TURQUOISE-II* (all genotype 1, both naïve and treatment experienced)
-FDA approval anticipated in December, 2014

Feld; NEJM 2014 Apr 11; Zeuzem; NEJM 2014 Apr 10; Poordad NEJM 2014 Apr 12; [e-pub ahead of print]

Relatively Equivalent

Sofosbuvir
+
Ledipasvir

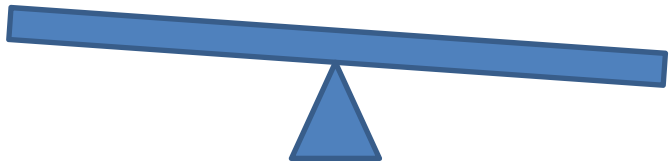


Paritaprevir/r
+
Ombitasvir
+
Dasabuvir
+/-
Ribavirin

- Overall efficacy
- Overall safety
- 24 wks required in treatment experienced, cirrhotic patients (maybe)

Advantage: SOF+LDV

Sofosbuvir
+
Ledipasvir

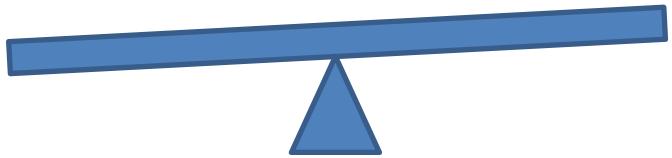


Paritaprevir/r
+
Ombitasvir
+
Dasabuvir
+/-
Ribavirin

- Lower pill count
- Once a day dosing
- 8 week option
- Ribavirin not needed
- Fewer drug-drug interactions
- No ritonavir
- Data in decompensated liver disease
- Retreatment of failures sort of demonstrated

Advantage: “3-D”

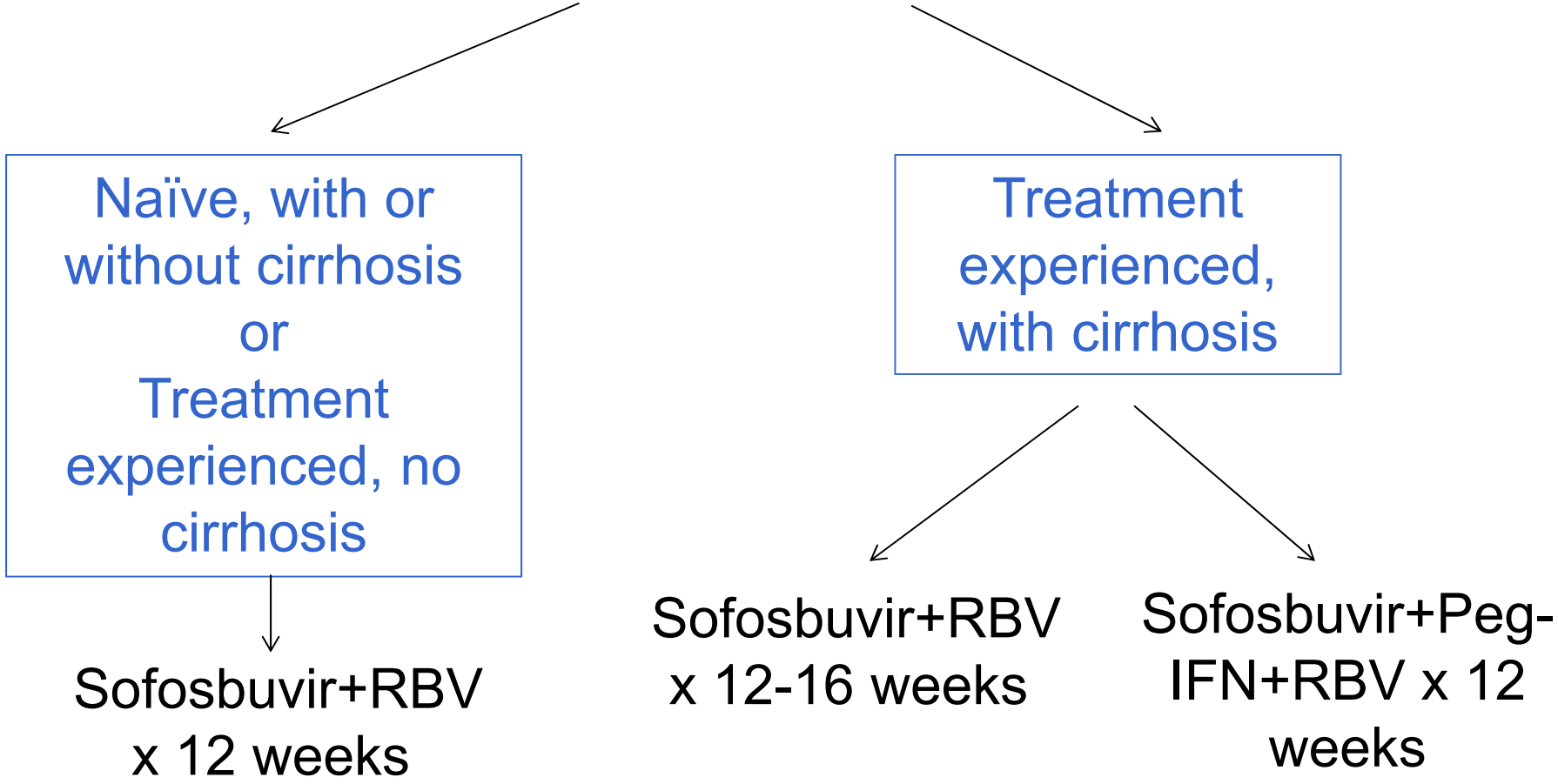
Sofosbuvir
+
Ledipasvir



Paritaprevir/r
+
Ombitasvir
+
Dasabuvir
+/-
Ribavirin

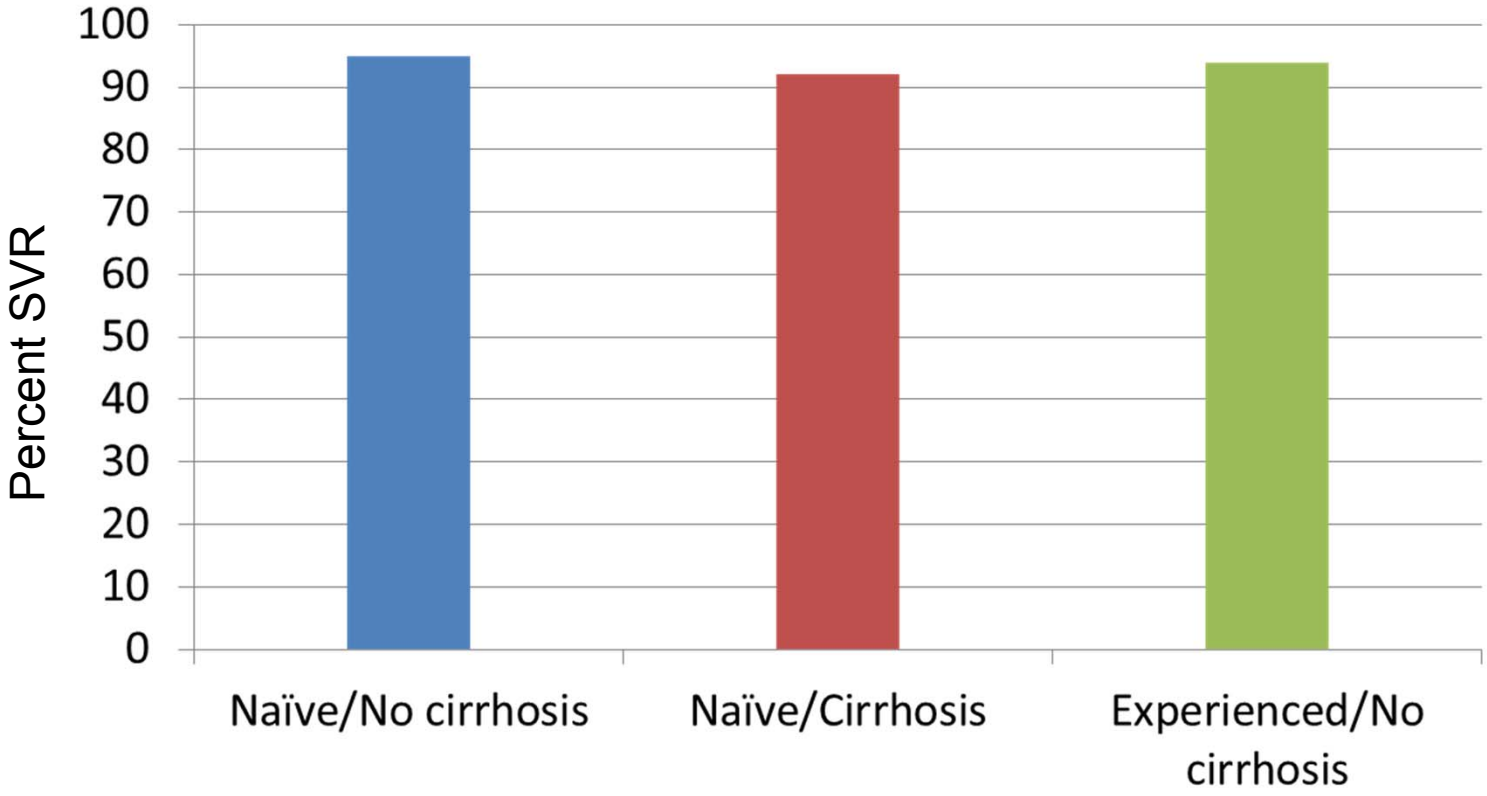
- SVR with 12 weeks treatment in Genotype 1b cirrhotic (F3-F4) null (non-) responders

Genotype 2



2014 IDSA/AASLD Recommendations: www.hcvguidelines.org

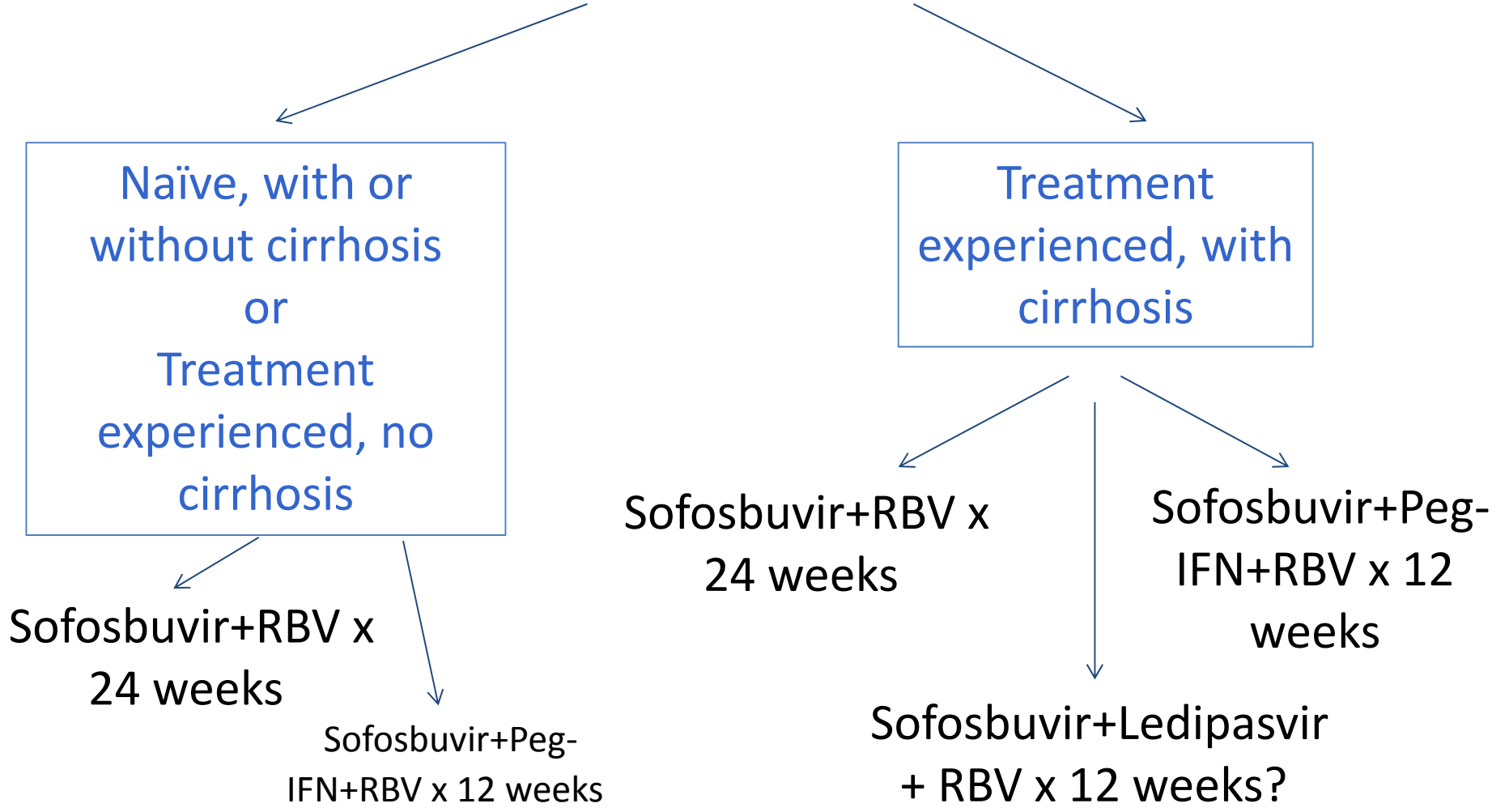
SVR in Genotype 2 Patients Treated with Sofosbuvir+Ribavirin for 12 Weeks



Treatment experienced, cirrhotic patients only had a 78% SVR with 16 weeks SOF+LDV. May wait for sofosbuvir + daclatasvir

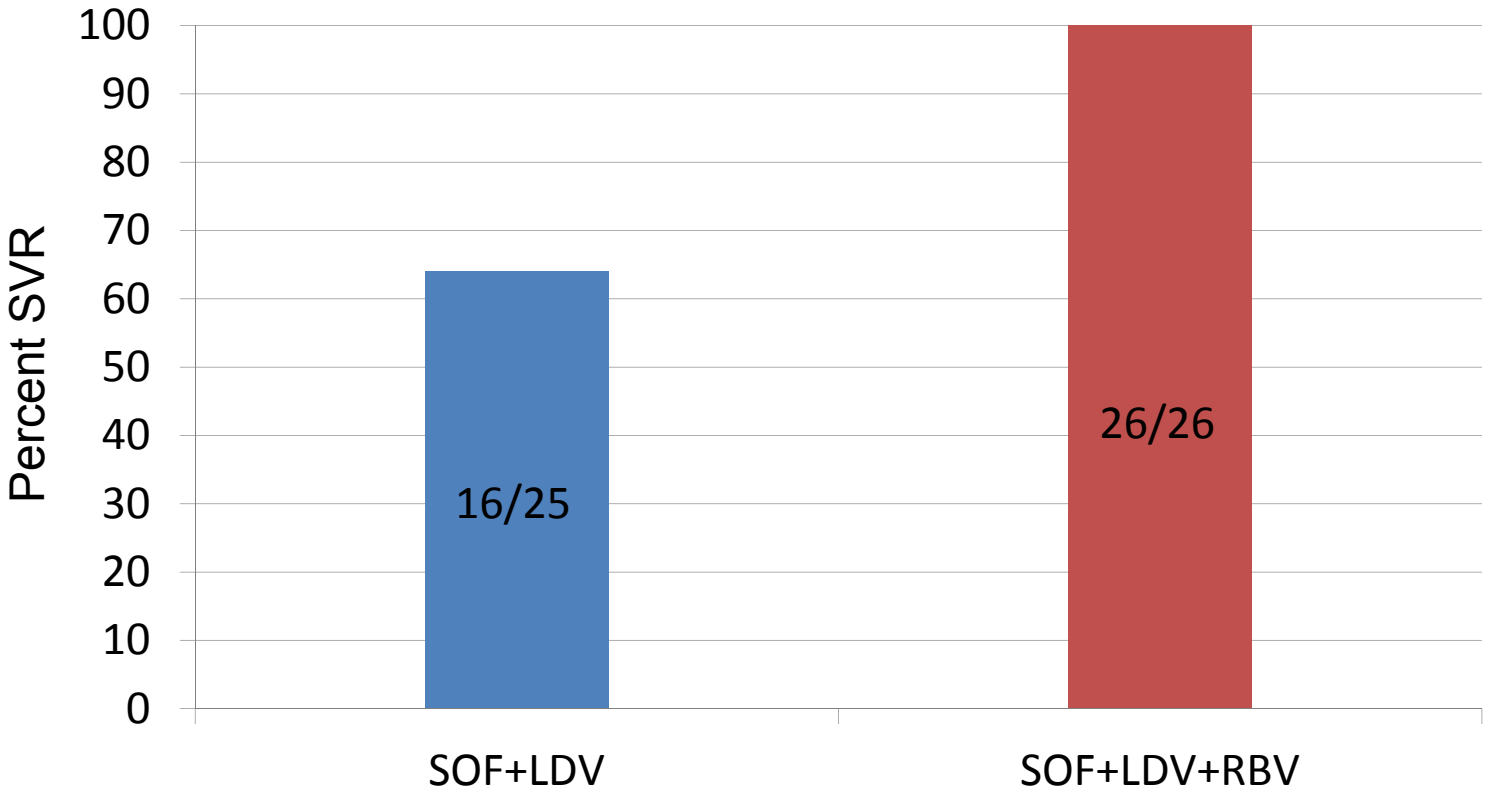
EASL 2014

Genotype 3



www.hcvguidelines.org

SVR in Genotype 3 Naive Patients Treated with Sofosbuvir+Ledipasvir +/- Ribavirin for 12 Weeks



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Prioritization Versus Rationing

- Prioritization involves determining and balancing:
  - Medical needs
    - Immediacy of patient suffering
    - Risk of increasing medical complexity of management
    - Future costs of complications (or not intervening)
    - Public health risks
  - Resource constraints
    - Provider capacity (eg, MA has ~175,000 patients with hepatitis C infection and ~250 HCV providers)
    - Distribution of providers
    - Financial limits (payer horizon typically ~1 to 3 years)
  - Most of us can accept prioritization

Rationing

- Limiting access to medical care
- Often non-attributable in US
  - Lack of or under insurance
  - Lack of access to appropriate providers
  - High co-pays
- Frank denial of medication coverage
  - Usually when a less expensive, “equivalent” alternative is available
- Much of EU, Canada, Australia ration medicine based on urgency of medical needs and anticipated clinical benefit
- Can be based on bias/discrimination

Treatment Priority
Per AASLD/IDSA/IAS–USA HCV Guidelines

1. Patients with highest risk for severe complications
   - Advanced fibrosis or compensated cirrhosis
   - Organ transplant
   - Type 2 or 3 essential mixed cryoglobulinemia with end-organ manifestations (ie, vasculitis)
   - Proteinuria, nephrotic syndrome, or membranoproliferative glomerulonephritis

Treatment Priority
Per AASLD/IDSA/IAS–USA HCV Guidelines

2. Patients with high risk for complications
   - Stage 2 fibrosis
   - HIV coinfection
   - HBV coinfection
   - Other coexistent liver disease (ie, NASH)
   - Debilitating fatigue
   - Type 2 diabetes mellitus (insulin resistant)
   - Porphyria cutanea tarda

Treatment Priority
Per AASLD/IDSA/IAS–USA HCV Guidelines

3. Persons with high transmission risk
   - MSM with high-risk sexual practices
   - Active injection drug users
   - Incarcerated persons
   - Persons on long-term hemodialysis

- "Cure as Prevention"

Medical Need Restriction

- Advanced fibrosis (Metavir F3-F4)
  - Evidenced by liver biopsy, transient elastography, Fibrotest, APRI or FIB-4 score, radiological imaging consistent with cirrhosis, physical findings or clinical evidence consistent with cirrhosis as attested by the prescribing physician

Response to Restricting Treatment to F3/F4

- Cannot require liver biopsy (may be highest risk of death in HCV care with all-oral regimens)
- Since no test can perfectly distinguish F2 from F3 or F3 from F4, limiting access to F3/F4 really means directing treatment to cirrhotic patients
- If we wait until advanced fibrosis, need to do life-long screening for HCC every six months even if cured (expense, logistics, patient anxiety)
- Prioritization of F2-F4 unless other compelling urgency may align with provider capacity

Restrictions Based on Current or History of Substance Abuse

- Prescriber assessment and documentation:
  - 3 to 12 months sobriety/abstinence from EtOH/drug use
  - Completion or enrollment in a treatment center
  - May require drug testing results
- Participate in counseling services
- Engage in care with an addiction specialist

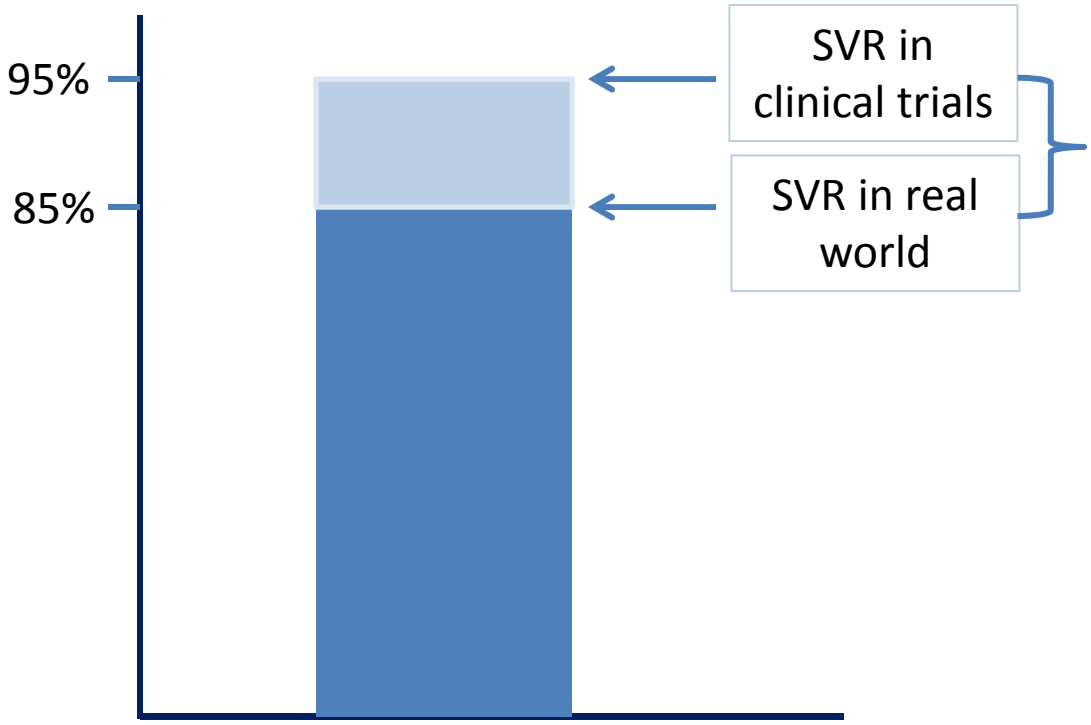
Substance Use

- Biggest concern is potential impact on adherence
  - Many people with substance use issues able to remain adherent
  - Data from peg-IFN/RBV treatment
- Concern about reinfection
- Legal medical marijuana use
  - May improve adherence via management of side effects
- Ongoing hazardous alcohol use has multiple concerns:
  - Impact on adherence with abuse
  - Acceleration of fibrosis
  - Ongoing damage to the liver even if HCV is cured
- Most DAA clinical trials allow methadone +/- buprenorphine – not a concern with adherence
- Ability to study treatment as prevention
- Ask: Would we limit treatment in someone with XX disease?

Approaches for Substance Use

- Use adherence counselors or case managers
- Integrate HCV treatment into buprenorphine programs or methadone treatment
- Look at models to reduce re-infection
  - IDU
  - Sexual (MSM)
- Track rates of re-infection
  - Collaborate with DPH

Hypothetical Costs of Not Optimizing SVR Rates in Clinical Practice



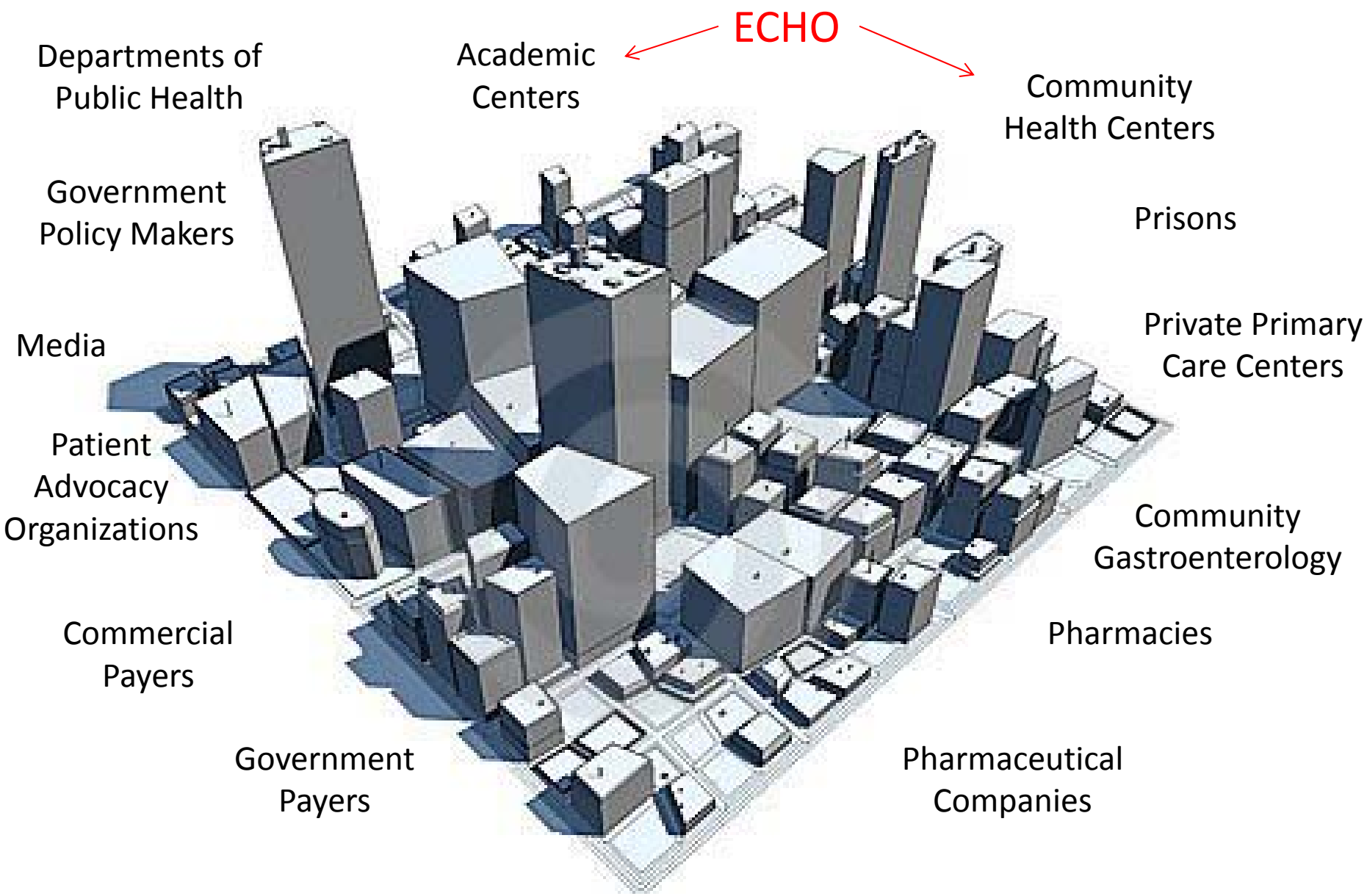
10% difference in SVR rates for a $100,000 regimen result in:

- $12,384 “loss $ per unachieved cure” for each patient
- Cost of retreating all patients who did not achieve SVR
- Costs of liver complications (decompensation, liver cancer, etc.) in those who are not cured and progress

Practice Model for HCV Treatment Initiation: BIDMC Example

- Assess patients for readiness, insurance status, and fill out clinical assessment form
- Deliver the 1st fill of medication to provider office only
- Require teaching visit with clinical staff prior to starting treatment
- Document true start date and inform SP
- Set up ALL follow-up and lab appointments right after teaching visit
- Provide teaching handout and list of appointments to patient
- Utilize pill box / blister pack / smart phone reminder apps to enhance medication compliance
- Specialty pharmacy with weekly or biweekly phone call to patients for follow up assessment
- Adopt a real time tracking system (ie, TrioHealth)
  - Record patient baseline characteristics and treatment regimen
  - Prompt for wk 4, wk 12 viral load and SVR12 due dates
  - Method of communication for provider office and specialty pharmacy

Community Network in HCV



Suggestions

- Create spreadsheets of all patient groups and all potential regimens with costs/cure
- Rank efficacy and safety first (clinicians won't compromise on this), then cost
- Talk to clinicians and advocates about resources, prioritization, and opportunities to treat more patients
- Collaborate on strategies to enhance patient support and adherence