TREATMENT OF HEPATITIS C: 2015 UPDATE

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Disclosures

Company	Type of Relationship	Product(s)
AbbVie, Gilead, Janssen, Salix	Speakers Bureau	*VieKira Pak* (paritaprevir with ritonavir, ombitasivr and dasabuvir), *Harvoni* (ledipasvir and sofosbuvir), *Sovaldi* (sofosbuvir) and *Olysio* (simeprevir), *Xifaxin* (rafaximin)
AbbVie, BMS, Gilead, Merck, Novartis, Boehringer Ingelheim, Salix	Clinical Research Support	As above and daclatasvir

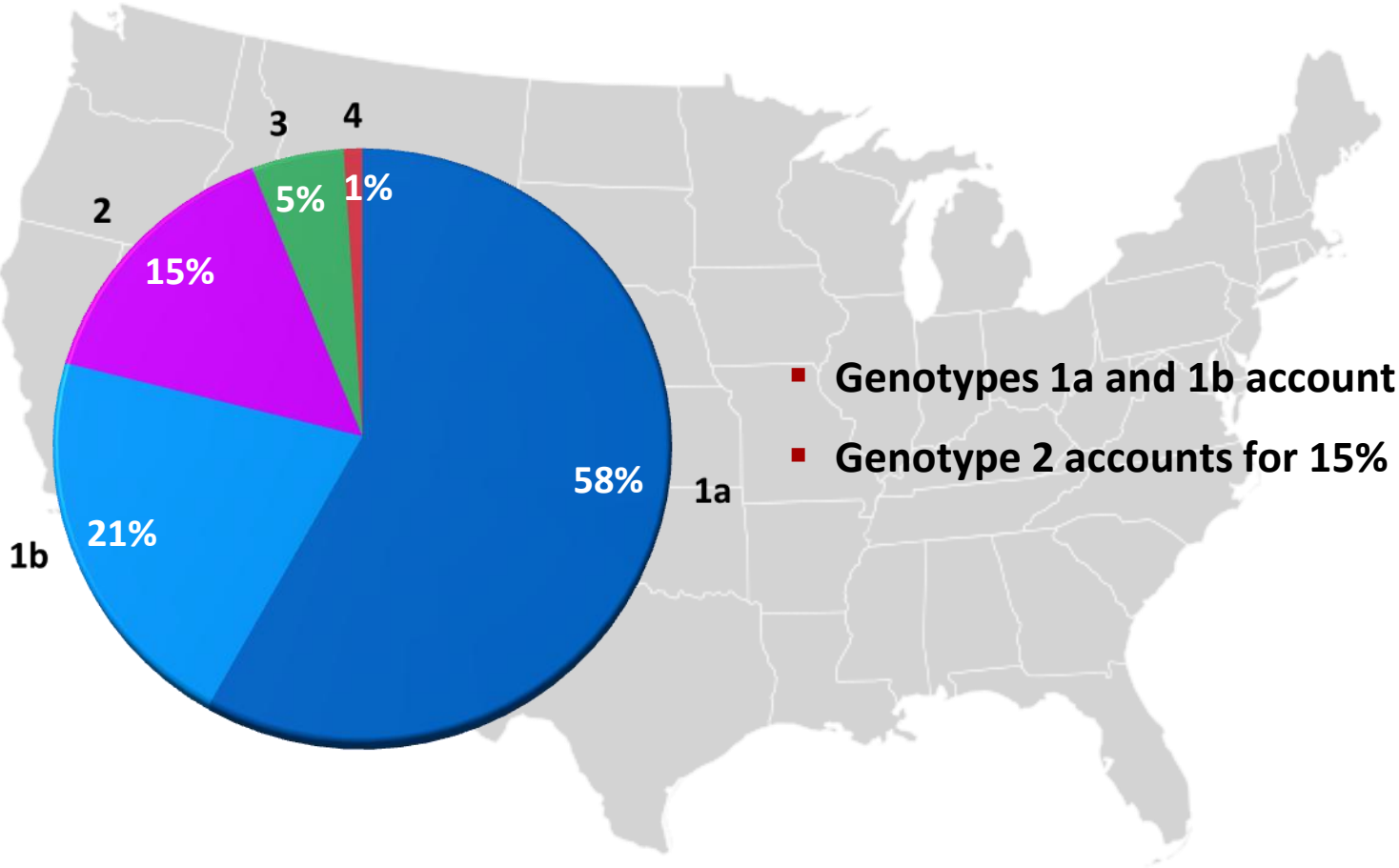
Epidemiology and Natural History of HCV Infection

Approximately 3.2 Million People in the US Have Chronic HCV Infection

- **~3.2 million people are chronically infected with HCV based on NHANES (1999-2002) population[1,2]**
  - ~70% born 1945-1964[1]
- **The number chronically infected with HCV in the US may be even higher[3]**
  - Accounting for populations not sampled in NHANES
    - Incarcerated
    - Homeless
    - Nursing home residents
    - Hospitalized
    - Those on active military duty

1. Armstrong GL, et al. *Ann Intern Med.* 2006;144:705-714; 2 . http://www.cdc.gov/hepatitis/HCV/HCVfaq.htm; 3. Chak E, et al. *Liver Int.* 2011;31:1090-1101.

Distribution of HCV Genotypes in the US



- Genotypes 1a and 1b account for 79%
- Genotype 2 accounts for 15%

Zein NN, et al. *Ann Intern Med*. 1996;125:634-639.

Transmission of Hepatitis A, B, and C Virus

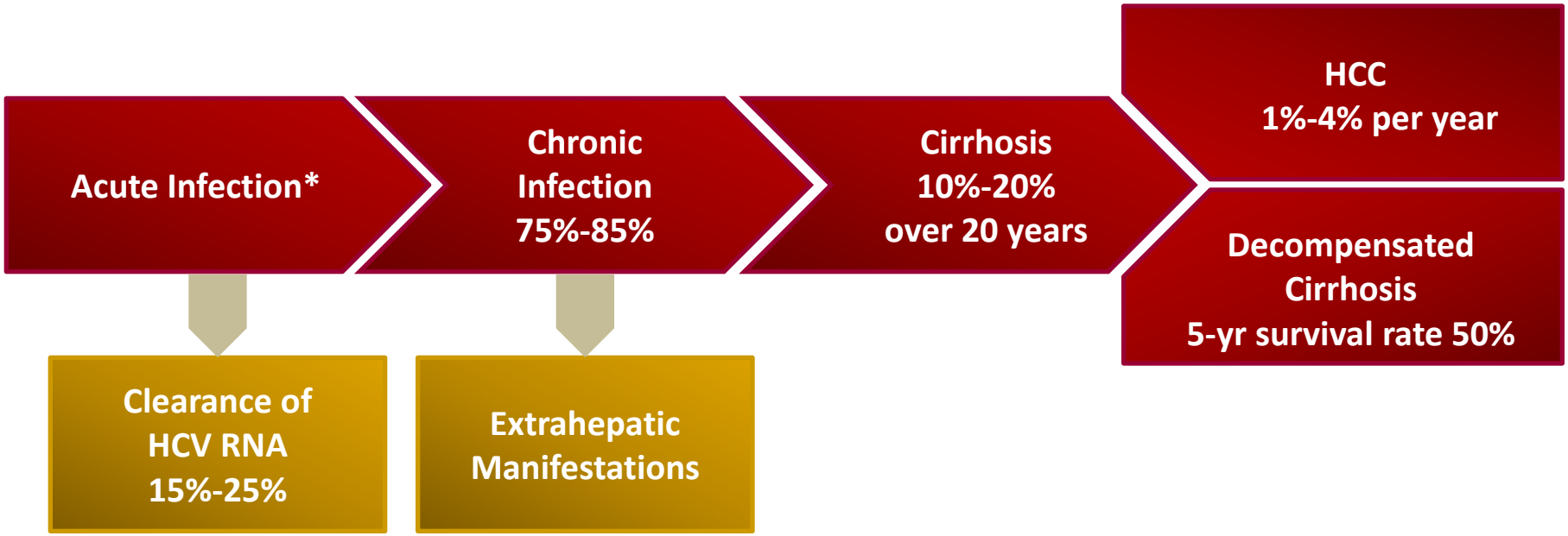
Route	Hepatitis A	Hepatitis B	Hepatitis C
IV drug use	▲	●	●
Transfusion	▲	●	●
Hemodialysis	■	●	●
Intra-institutional	●	●	●
Sexual	▲	●	▲
Household	●	▲	▲
Mother-to-newborn	▲	●	▲
Oral-oral contact	●	▲	■
Food-borne	●	■	■
Fecal (oral)	●	■	■
Water-borne	●	■	■
Raw shellfish	●	■	■

● Common ▲ Infrequent ■ Never

IV=intravenous.

Adapted from Dartmouth College. www.epidemic.org/thefacts/hepatitisc/transmission.php.

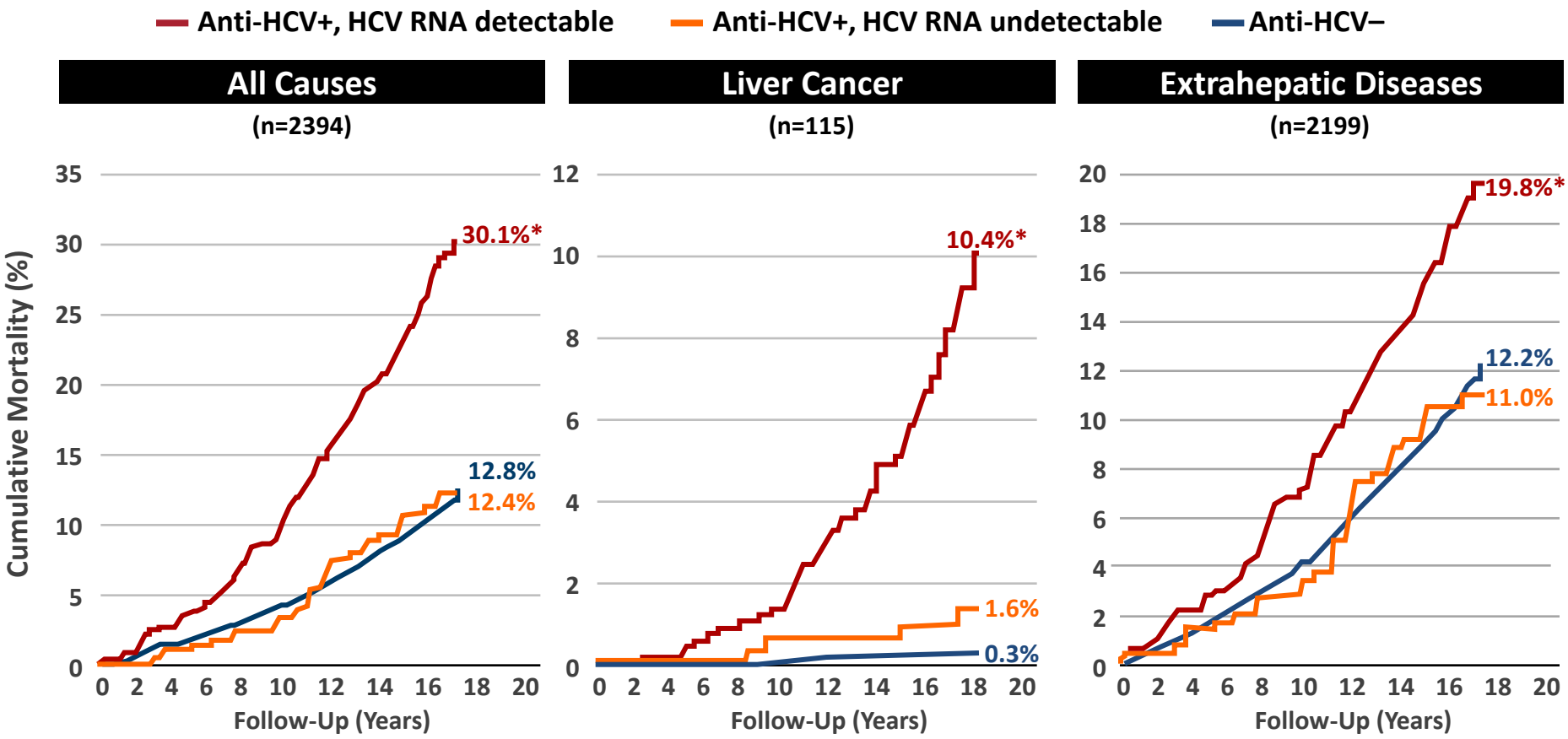
Natural History of HCV Infection



*20%-30% of individuals are symptomatic.
HCC=hepatocellular carcinoma.

Adapted from Chen SL, Morgan TR. *Int J Med Sci*. 2006;3:47-52.

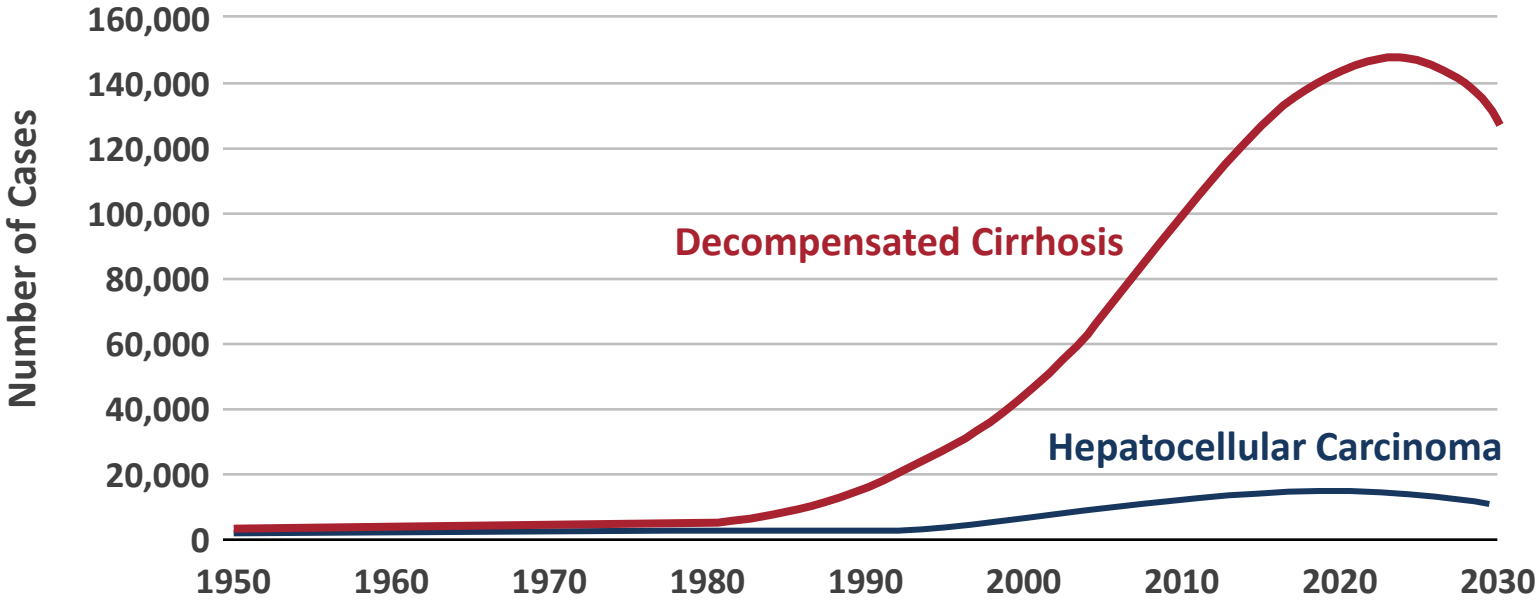
HCV Viremia Was Associated With Increased Mortality in a Prospective Taiwanese Cohort Study



REVEAL HCV: Risk Evaluation of Viral Load Elevation and Associated Liver Disease/Cancer (1991-2008).
Anti-HCV seronegative (n=18,541); anti-HCV seropositive (n=1095; detectable HCV RNA: 69.4%). Average follow-up: 16.2 years.
Among extrahepatic causes of death, 68.5% and 69.3% were noncancer deaths for HCV seronegative and seropositive, respectively.
*P<.001 for comparison among all 3 groups and P<.001 for HCV RNA detectable vs undetectable.

Lee M-H, et al. *J Infect Dis*. 2012;206:469-477.

HCV-Related Decompensated Cirrhosis and HCC Projected to Rise in the US

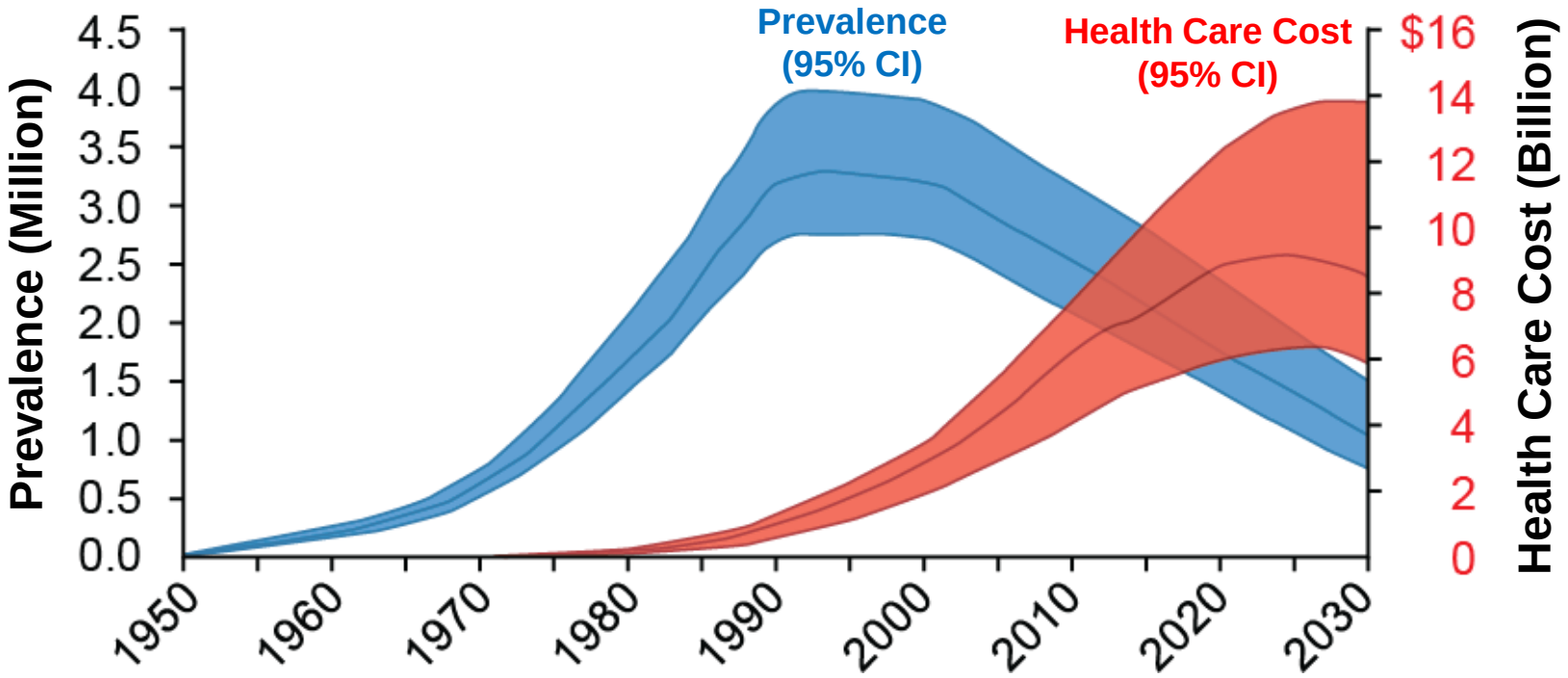


- **HCV-related decompensated cirrhosis and HCC are rising as manifestations of liver disease in aging population[1]**
- **73.4% of HCV-related deaths occurred among persons 45-64 years of age**
  - **Median age was 57 years; ~20 years less than the average lifespan of persons living in the US[2,*]**

Projection based on a dynamic, multicohort, natural history model of data from the CDC, NHANES, and a review of the medical literature, with conservative estimates of disease progression and complications. Model assumes first-year mortality of 80%-85% for HCC.
*During the period from 1999 to 2007.

1. Davis GL, et al. *Gastroenterology.* 2010;138:513-521; 2. Smith BD, et al. *MMWR Recomm Rep*. 2012;61(RR-4):1-32.

Increasing Health Care Costs Associated With Progressive Liver Disease in the Aging HCV-Infected Population

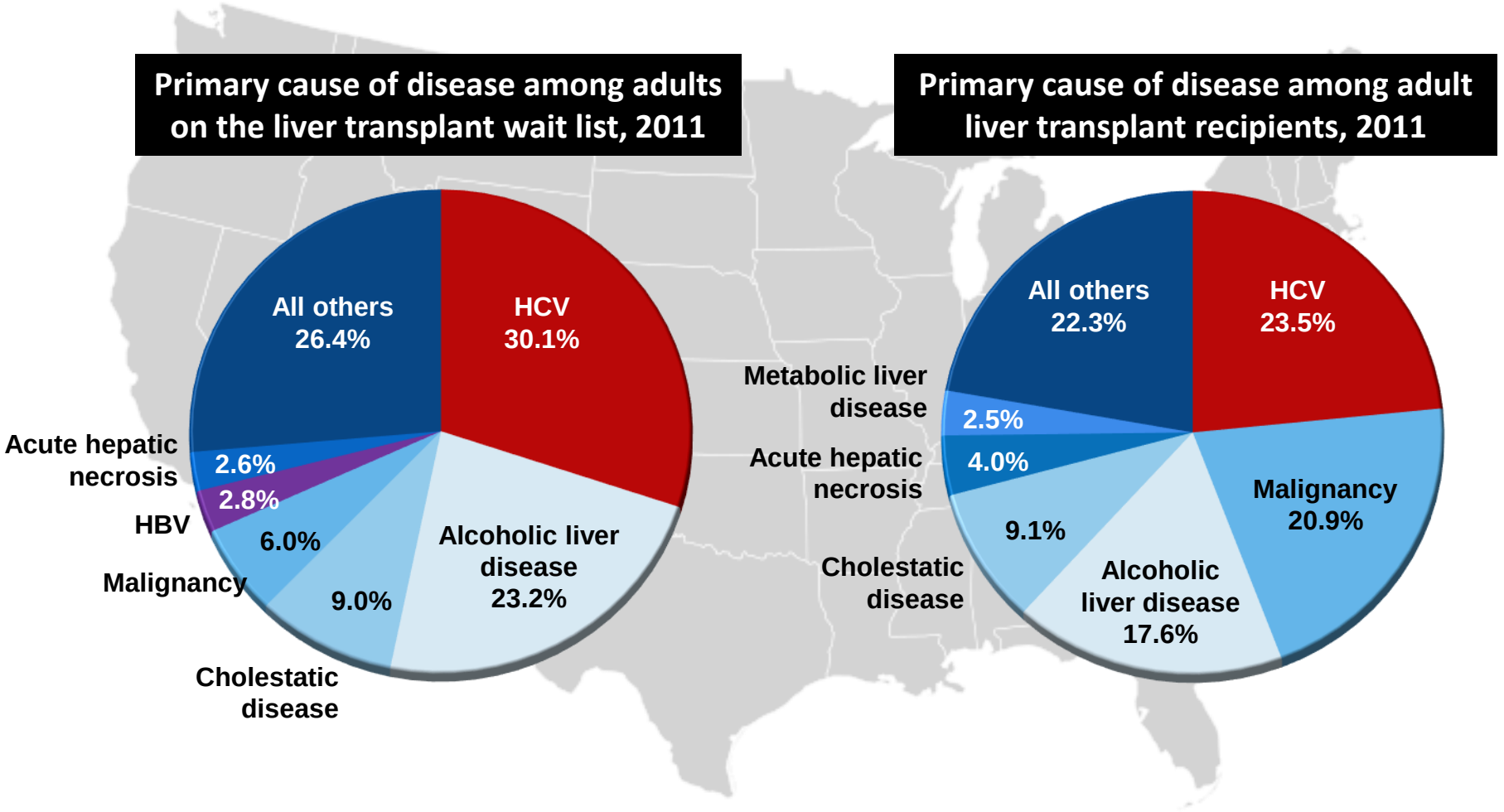


- **While the prevalence of HCV infection is declining from its peak, the incidence of advanced liver disease and associated health care costs continue to rise**
- **Modeling does not take into account any impact of birth cohort screening**

A system dynamic modeling framework was used to quantify the HCV-infected population, the disease progression, and the associated cost from 1950-2030.
CI=confidence interval.

Razavi H, et al. *Hepatology*. 2013. Epub ahead of print.

HCV Is Leading Cause of Liver Transplants in the US

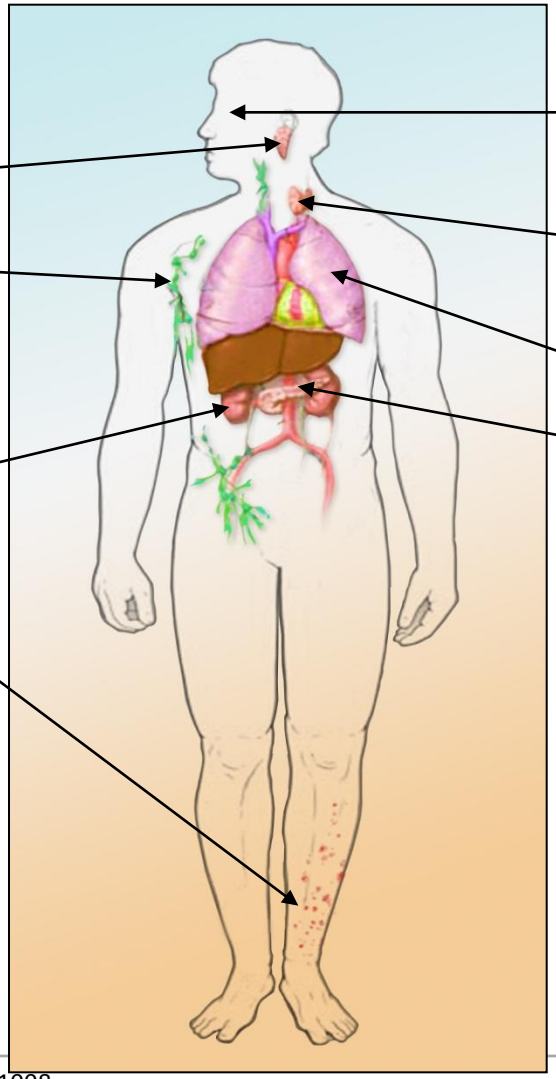


Available at: http://srtr.transplant.hrsa.gov/annual_reports/2011/pdf/03_%20liver_12.pdf.

Extrahepatic Manifestations of HCV

Strongly associated

- Mixed cryoglobulinemia
- Sjögren (sicca) syndrome
- Lymphoproliferative disorders
- Porphyria cutanea tarda
- Neuropathy
- Membranoproliferative glomerulonephritis
- Cryoglobulinemic vasculitis

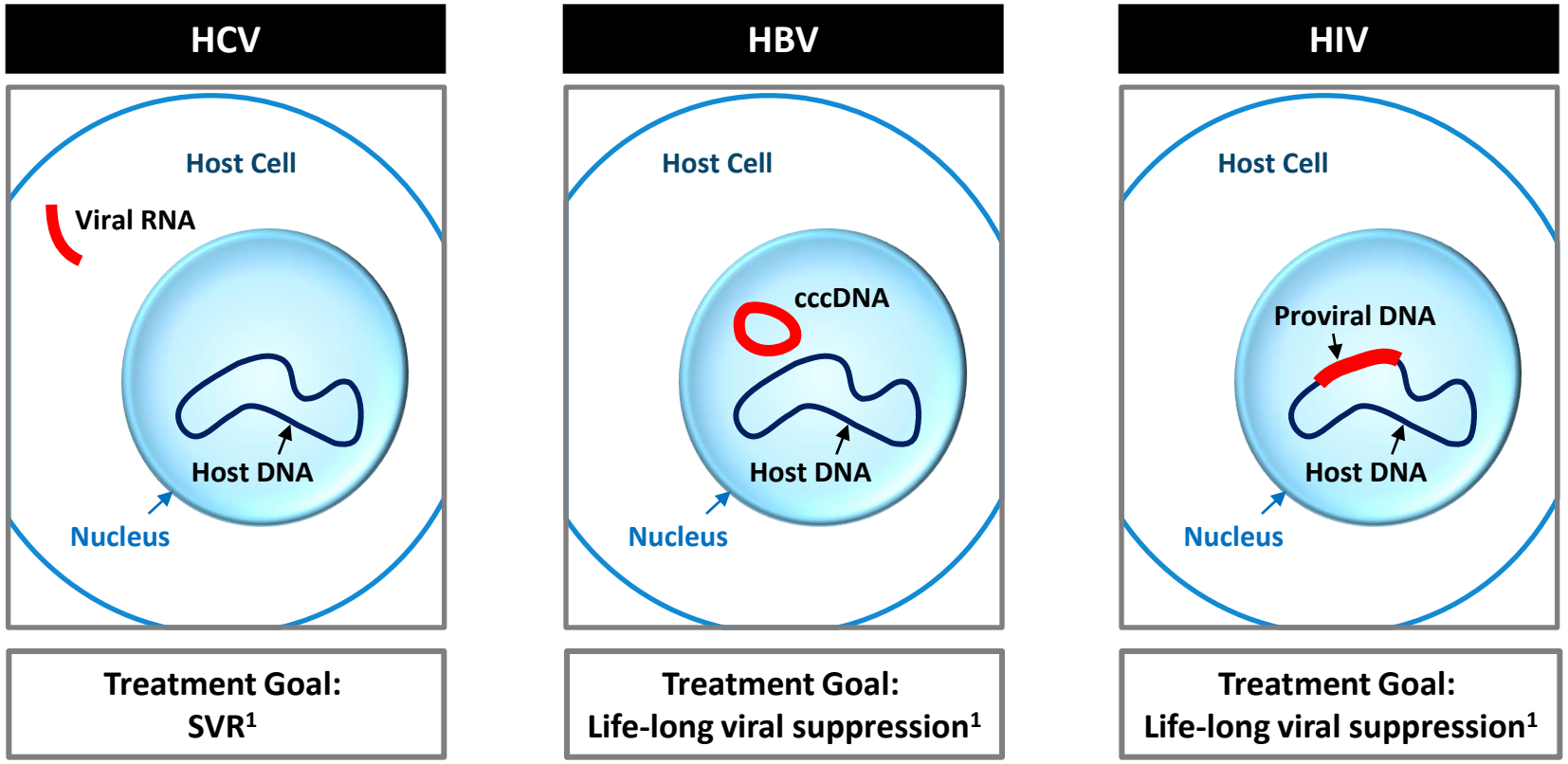


Possibly associated

- Corneal ulcers (Mooren ulcers)
- Thyroid disease
- Lichen planus
- Pulmonary fibrosis
- Type 2 diabetes
- Systemic vasculitis (polyarteritis nodosa, microscopic polyangiitis)
- Arthralgias, myalgias, inflammatory polyarthritis
- Autoimmune thrombocytopenia

Adapted from Ali A, Zein NN. *Cleve Clin J Med.* 2005;72:1005-1008.

Treatment Goal in HCV Is SVR



- **Majority of patients who achieve an SVR do not experience viral recurrence[2]**

cccDNA=covalently closed circular DNA; HBV=hepatitis B virus.

Images adapted from Soriano V, et al.[1]

1. Soriano V, et al. *J Antimicrob Chemother*. 2008;62:1-4; 2. Swain MG, et al. *Gastroenterology.* 2010;139:1593–1601.

Definitions of Virologic Response to Treatment

Response Term	Definition
Rapid virologic response (RVR)	HCV RNA negative at treatment week 4 by a sensitive PCR-based quantitative assay
Early virologic response (EVR)	≥2 log reduction in HCV RNA level compared with baseline (partial EVR) or HCV RNA negative at treatment week 12 (complete EVR). Predictive of SVR
End-of-treatment response (ETR)	HCV RNA negative by a sensitive test at the end of treatment
Sustained virologic response (SVR)	HCV RNA negative at 24 weeks (SVR24) after cessation of treatment. Best predictor of long-term outcomes
Breakthrough	Reappearance of HCV RNA in serum while on therapy
Relapse	Reappearance of HCV RNA in serum after therapy is discontinued
Nonresponder	Failure to clear HCV RNA from serum after 24 weeks of therapy
Null responder	Failure to achieve a 2 log reduction in HCV RNA after 24 weeks of therapy
Partial responder	2-log reduction in HCV RNA but still HCV RNA positive at week 24

Adapted from Ghany MG, et al. *Hepatology*. 2009;49:1335-1374.

Sustained Virologic Response (SVR) Achieved After Treatment Is Durable

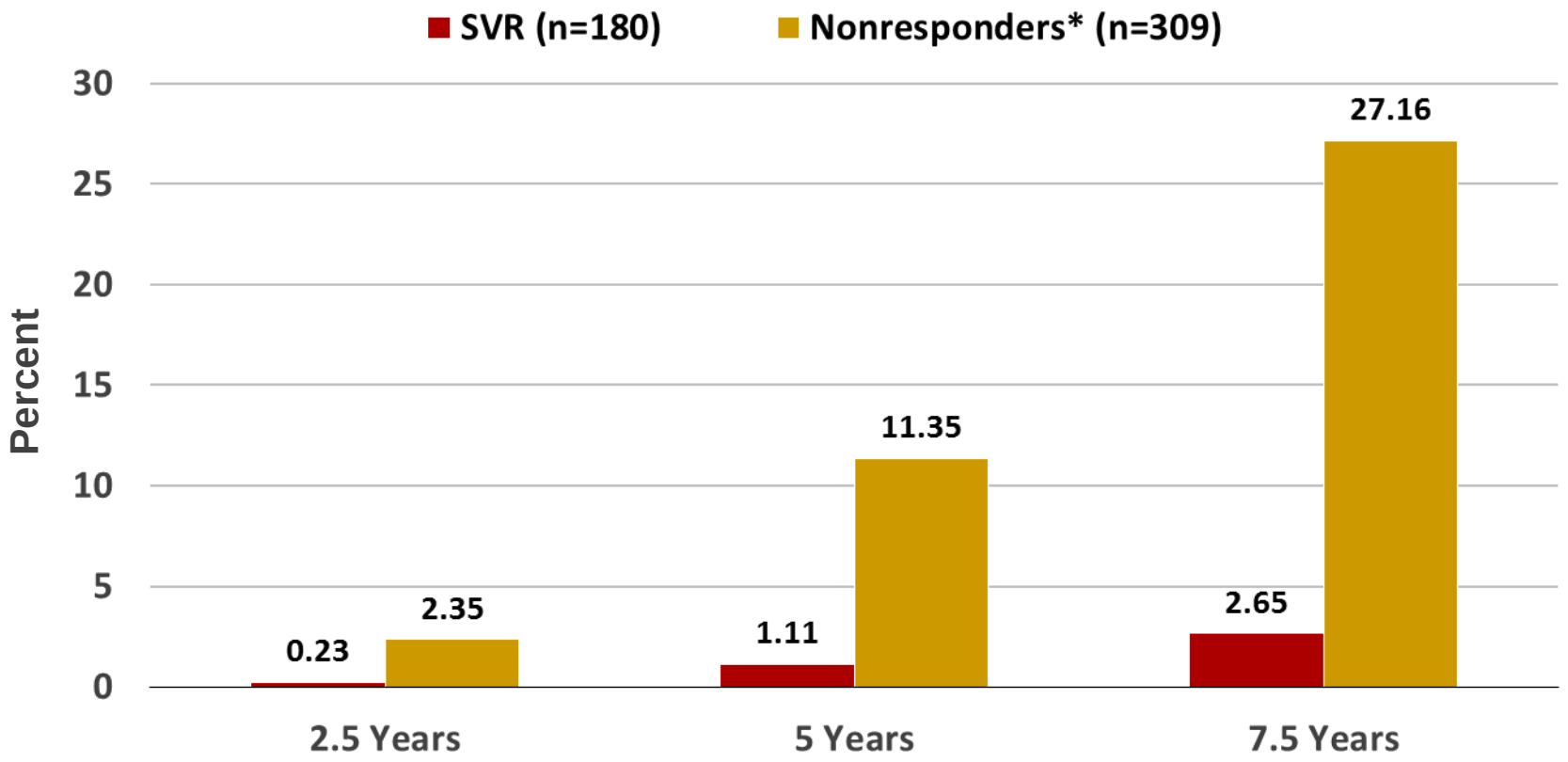
- **SVR = HCV RNA negative (by a sensitive assay, <25 IU/mL) at 12weeks after cessation of treatment[1]**
- **99% of patients who achieved an SVR had undetectable levels of HCV RNA in serum samples throughout the follow-up period[2,*]**
  - "These data suggest that the recurrence of HCV RNA is extremely rare in patients who achieve an SVR, and it now appears likely that such patients may be considered "cured" from a virologic standpoint"[2]
- **For patients with cirrhosis, current guidelines recommend monitoring those who have achieved an SVR at 6- or 12-month intervals for the development of HCC[1]**

*After treatment with peginterferon alfa-2a ± ribavirin; mean follow-up, 3.9 years (range, 0.8–7.1 years).

1. Ghany MG, et al. *Hepatology*. 2009;49:1335-1374; 2. Swain MG, et al. *Gastroenterology.* 2010;139:1593–1601.

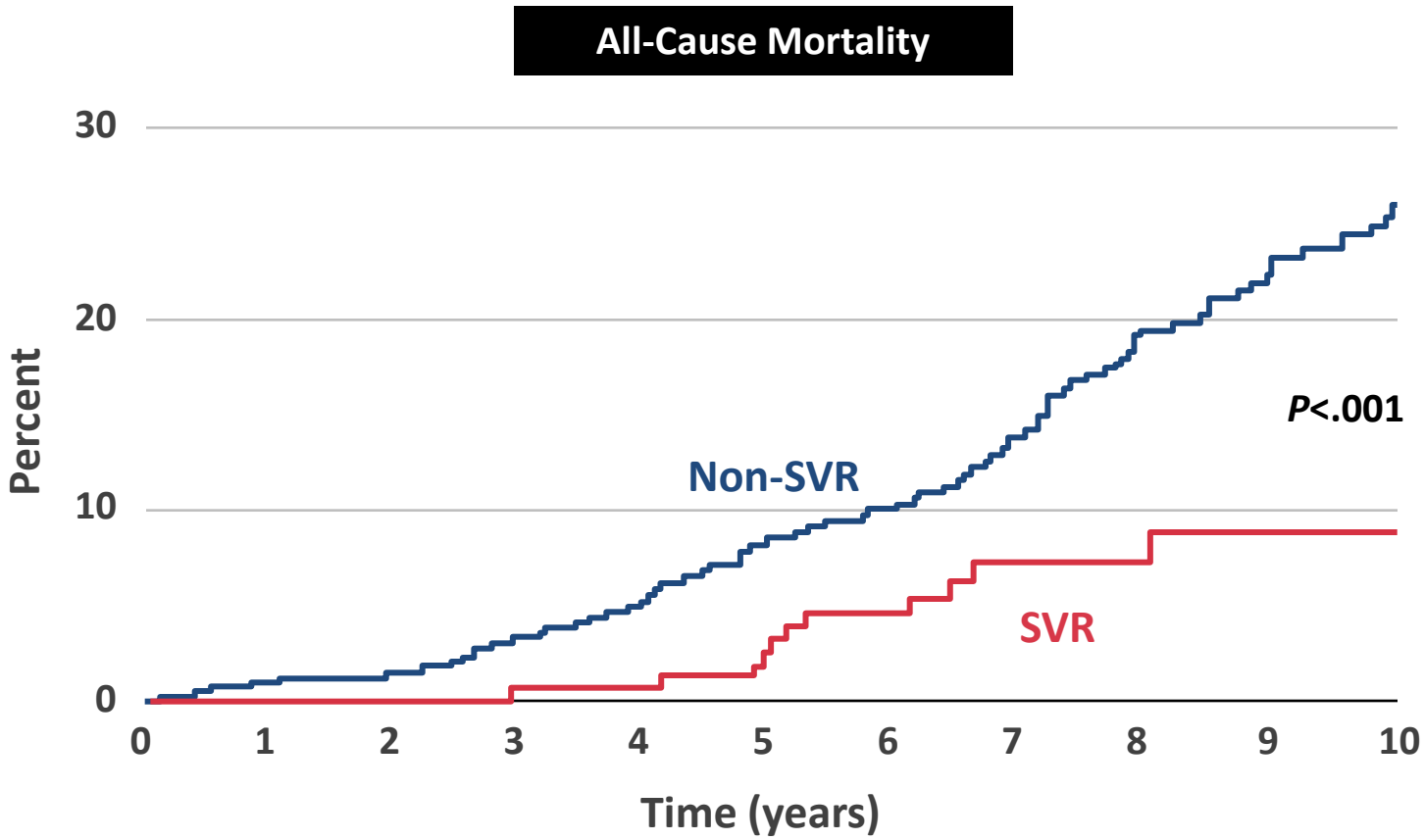
SVR Was Associated With Improved Long-Term Liver-Related Outcomes in the HALT-C Trial Database

Cumulative Incidence of Any Liver-Related Outcome Among Patients With Bridging Fibrosis or Cirrhosis



Analysis of liver outcomes (decompensation, HCC, or death) in the HALT-C trial database. All comparisons *P*<.0001.
*Detectable HCV RNA at treatment week 20 (combination therapy was discontinued at week 24).
HALT-C=Hepatitis C Antiviral Long-Term Treatment against Cirrhosis.
Morgan TR, et al. *Hepatology.* 2010;52:833-844.

SVR Was Associated With Reduced Long-Term Risk of All-Cause Mortality in an International, Multicenter Study



International, multicenter, long-term follow-up study from 5 large tertiary care hospitals in Europe and Canada. Patients with chronic HCV infection started an interferon-based treatment regimen between 1990 and 2003 (n=530).

van der Meer AJ, et al. *JAMA*. 2012;308:2584-2593.

Screening Recommendations for HCV

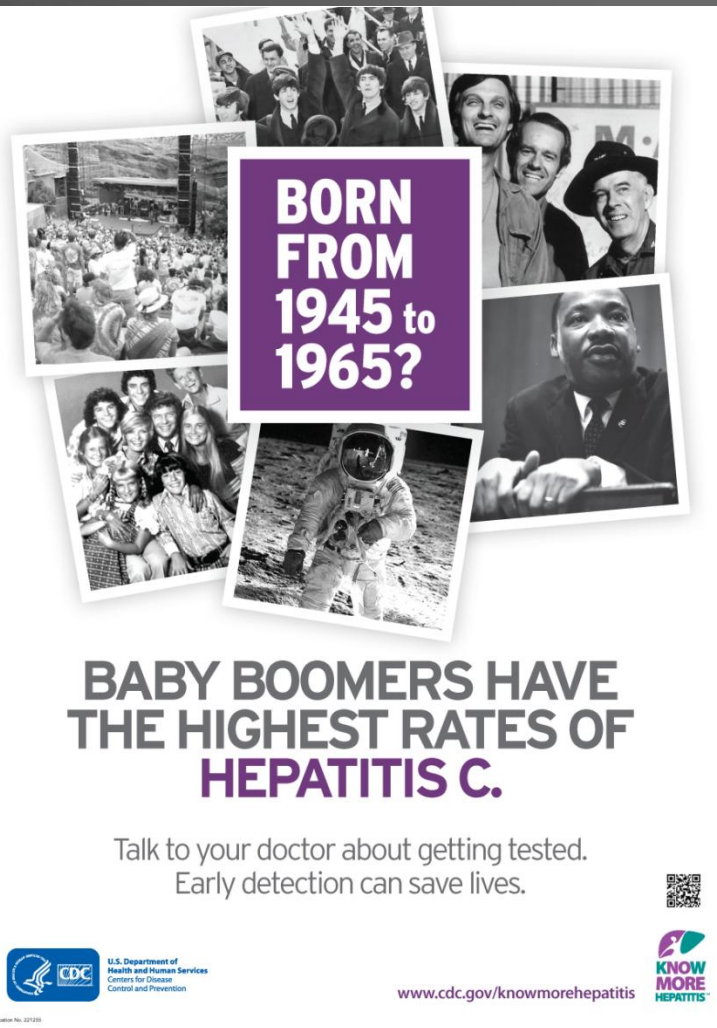
2012 CDC Recommendations for Birth Cohort (1945–1965) Screening

- **Recommendation 1**
  - Adults born from 1945 to 1965 should receive one-time testing for HCV without prior ascertainment of HCV risk

    Grade: strong recommendation
    Evidence: moderate-quality

- **Recommendation 2**
  - All persons identified with HCV infection should receive a brief alcohol screening and intervention as clinically indicated, followed by referral to appropriate care and treatment services for HCV infection and related conditions as indicated

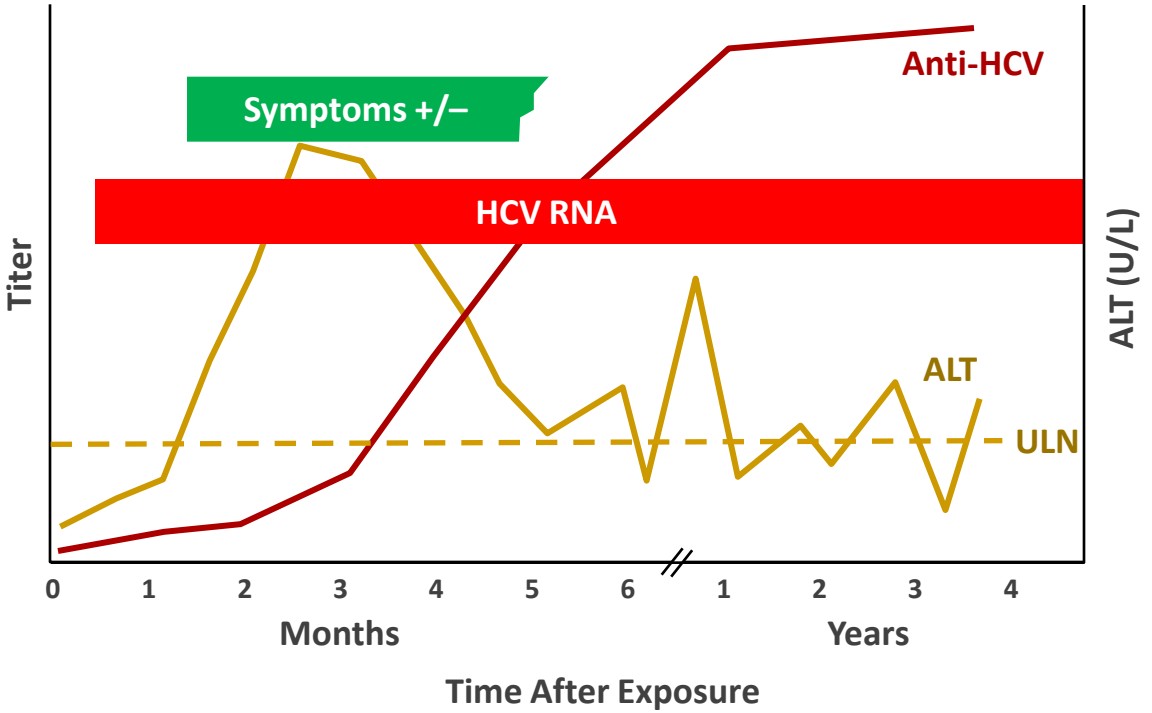
    Grade: strong recommendation
    Evidence: moderate-quality



Smith BD, et al. *Ann Intern Med*. 2012;157:817-822.

Laboratory Diagnosis of Chronic HCV Infection

- **RNA testing identifies active disease in HCV-seropositive patients**
- **HCV antibodies appear by 6–8 weeks following infection[1]**
  - Can be detected by EIA[2]
- **Serum ALT is not a reliable indicator of liver damage[1]**
- **FDA-approved rapid point-of-care testing is available[3]**
  - OraQuick® HCV Test

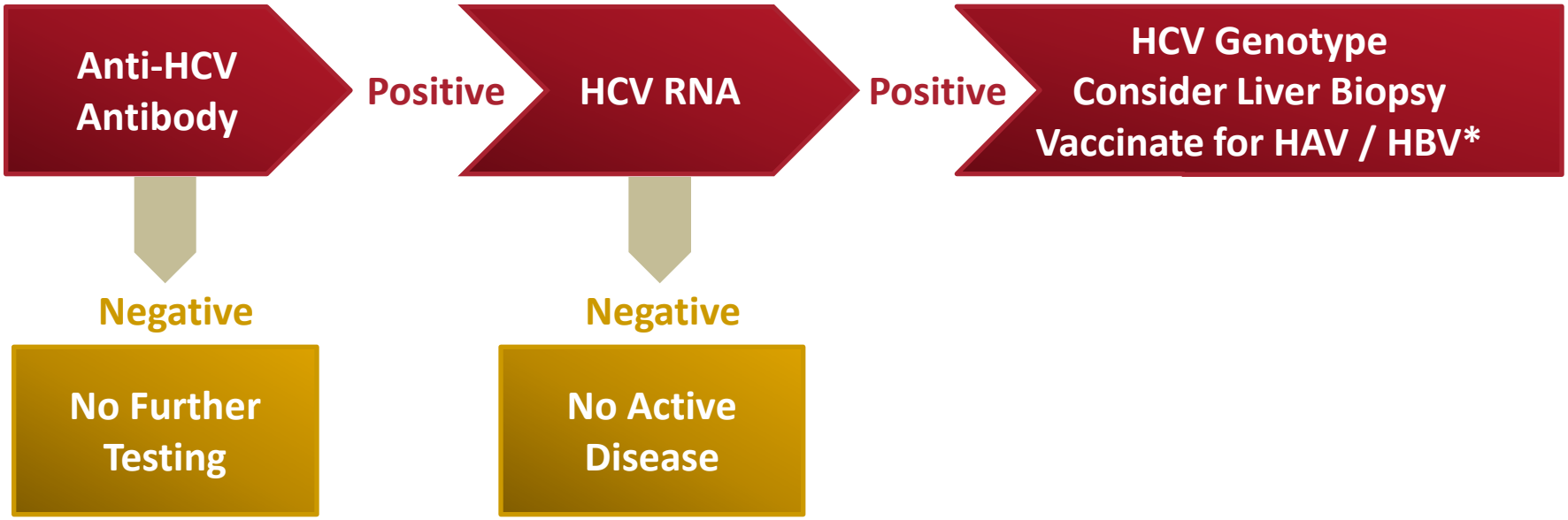


ALT=alanine aminotransferase; EIA=enzyme immunoassay; RNA=ribonucleic acid; ULN=upper limit of normal.

Image adapted from MicrobiologyBytes:Virology:HCV[1]

1. www.microbiologybytes.com/virology/HCV.html; 2. Alter MJ, et al. *MMWR Recomm Rep*. 2003;52(RR-3):1-13, 15;
3. Shivkumar S, et al. *Ann Intern Med*. 2012;157:558-566.

HCV Diagnostic Algorithm Based on Serologic Testing



*If patient lacks pre-existing antibodies to HAV or HBV.
HAV=hepatitis A virus, HBV=hepatitis B virus.

Ghany MG, et al. *Hepatology*. 2009;49:1335-1374.

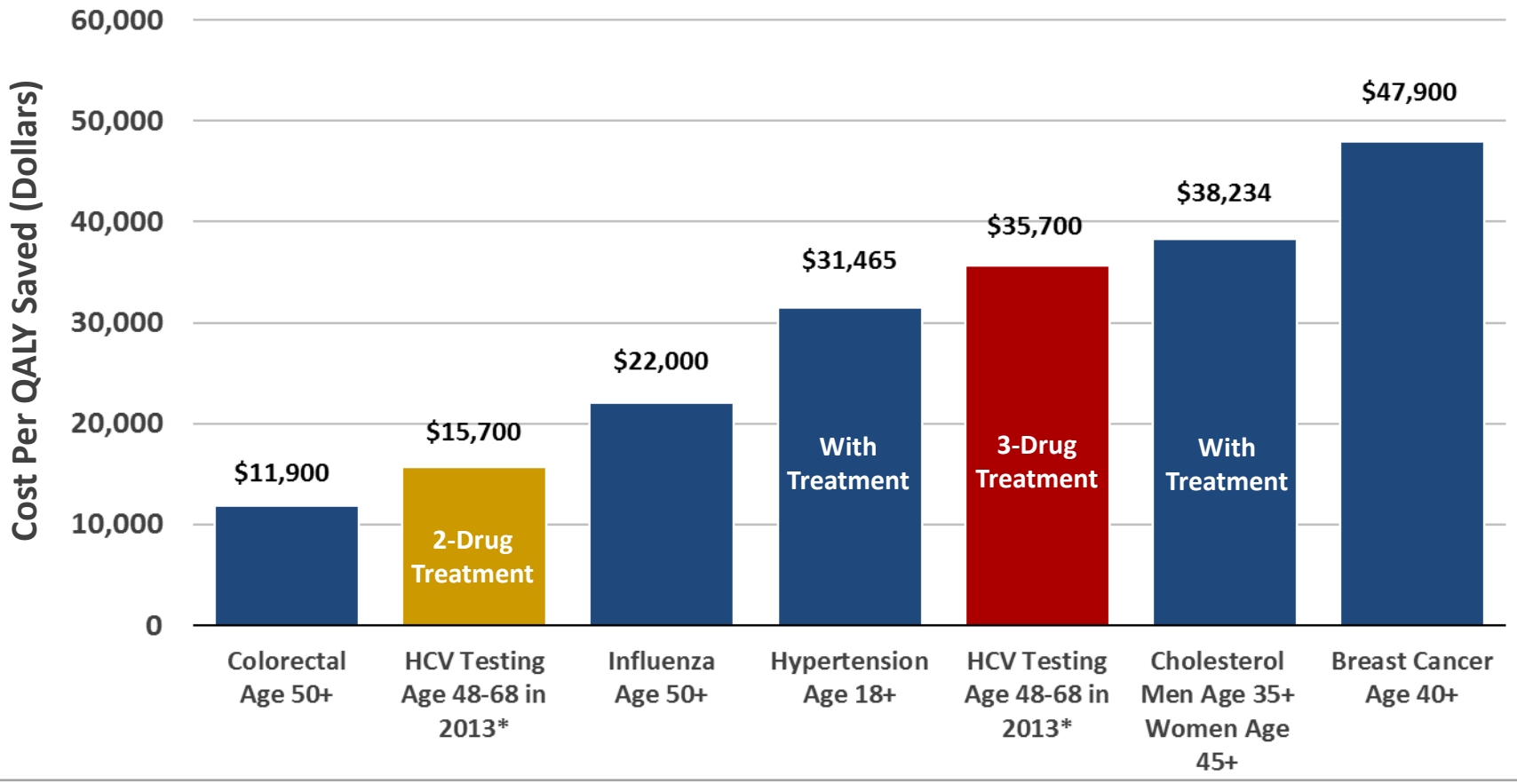
2013 Updated USPSTF HCV Screening Recommendations

- **In June 2013, the USPSTF issued its Grade B recommendations regarding HCV screening[1]:**
  - Those at high risk for HCV infection
  - Those born from 1945 to 1965 (one-time screening of "Baby Boomers," regardless of risk)
- **For this update, the USPSTF reviewed the indirect chain of evidence showing benefits of screening through[1]:**
  - Improvements in SVR with current treatments
  - Reductions in all-cause and liver-related mortality, and HCC associated with SVR
- **The USPSTF gave this recommendation a Grade B[1]:**
  - Grade B means there is high certainty that the net benefit is moderate or there is moderate certainty that the net benefit is moderate to substantial
- **The Affordable Care Act[1,2]:**
  - Requires non-grandfathered private health plans to cover clinical preventive services given an A or B Grade by USPSTF without cost sharing
  - Provides incentives for Medicaid programs to cover these services

USPSTF=United States Preventive Services Task Force.

1. Moyer VA; on behalf of the USPSTF. *Ann Intern Med*. 2013 Jun 11. [Epub ahead of print]; 2. Ngo-Metzger, Q et al. *Ann Intern Med*. 2013 Jun 11. [Epub ahead of print].

Cost-Effectiveness of HCV Testing vs Other Routine Preventive Services



*Birth cohort testing, 1945-1965.

2-drug treatment=PegIFN+RBV; 3-drug treatment=PegIFN+RBV+PI.

QALY=quality-adjusted life-year.

www.prevent.org/National-Commission-on-Prevention-Priorities/Rankings-of-Preventive-Services-for-the-US-Population.aspx.

Rein DB, et al. *Ann Intern Med*. 2012;156:263-270.

Patient Counseling for HCV Precautions and Treatment Expectations

Counseling Recommendations for HCV-Infected Individuals

To Prevent HCV Transmission

- Avoid sharing toothbrushes and dental or shaving equipment
- Prevent blood contact with others
- Stop using illicit drugs; those who continue to inject drugs should take precautions to avoid viral transmission
- Risk of sexual transmission is low, but practice "safe sex"

Additional Recommendations

- Avoid alcohol consumption
  - Excess alcohol may lead to progressive liver disease, increased HCV RNA replication, and reduced response to treatment
- Consider treatment for hepatitis C*
- Vaccinate for hepatitis A and B
- Get tested for HIV
- Encourage family members to get screened

*If patient meets generally accepted indications for HCV treatment.

Adapted from Ghany MG, et al. *Hepatology*. 2009;49:1335-1374.

Summary

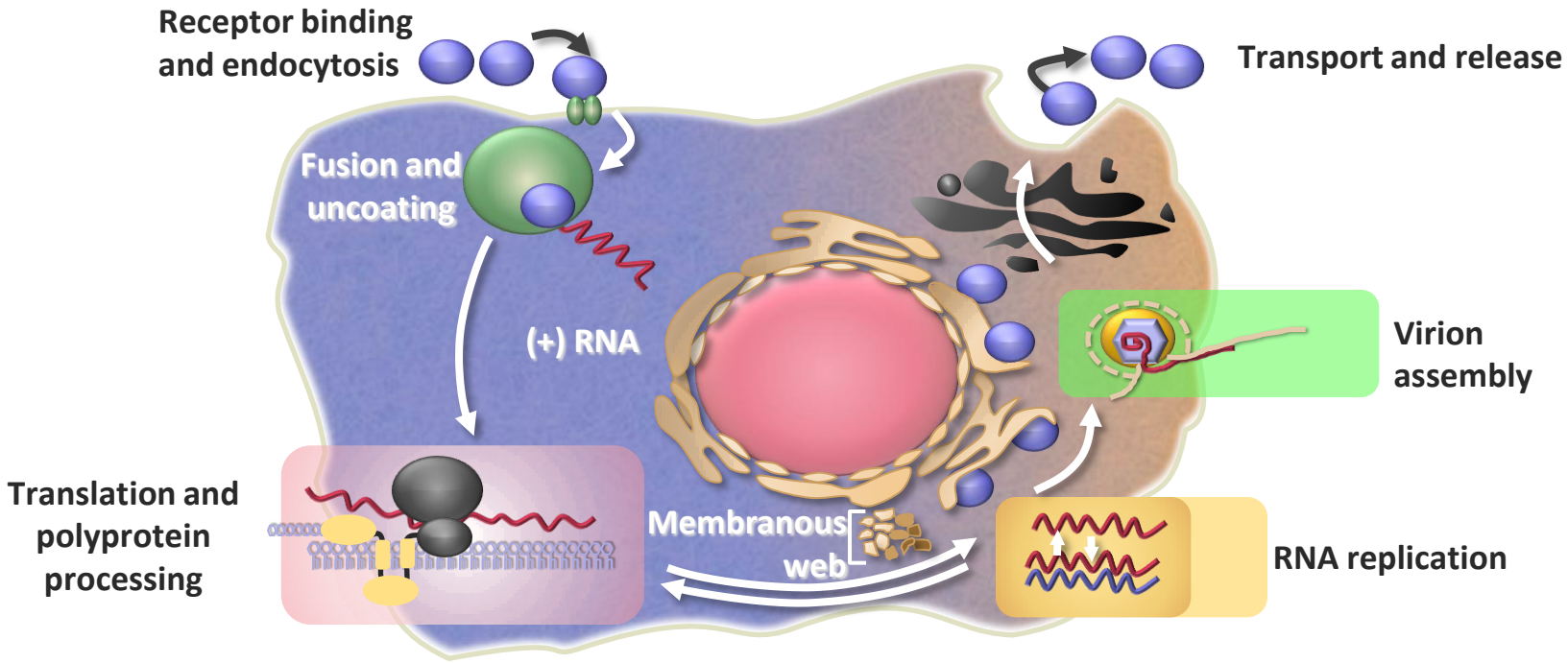
- **Approximately 3.2 million people in the US have chronic HCV infection[1,2,*]**
- **If left untreated, HCV infection can lead to advanced liver disease**
  - Patients often asymptomatic in early stages of HCV infection[3]
  - There is an increasing burden of liver disease in aging baby boomers due to manifestations of HCV infection acquired 20-30 years ago[3]
- **CDC and USPSTF recommend screening all baby boomers in addition to those with other specific risk factors[4,5]**
- **HCV infection is curable (SVR=virologic cure)[6,†]**
  - SVR reduces the risk of mortality and of developing advanced liver disease[7,8]
  - Patients with cirrhosis who achieved an SVR should continue to be monitored at 6- or 12-month intervals for the development of HCC[9]

*Prevalence estimate based on NHANES data from 1999 through 2002.[1,2]
†Outcomes based on 2-drug therapy with PegIFN and RBV.

1. Armstrong GL, et al. *Ann Intern Med.* 2006;144:705-714.
2. http://www.cdc.gov/hepatitis/HCV/HCVfaq.htm.
3. Davis GL, et al. *Gastroenterology.* 2010;138:513-521.
4. Smith BD, et al. *Ann Intern Med*. 2012;157:822.
5. Moyer VA; on behalf of the USPSTF. *Ann Intern Med*. 2013 Jun 11. [Epub ahead of print.]
6. Swain MG, et al. *Gastroenterology.* 2010;139:1593–1601.
7. van der Meer AJ, et al. *JAMA*. 2012;308:2584-2593.
8. Morgan TR, et al. *Hepatology.* 2010;52:833-844.
9. Ghany MG, et al. *Hepatology*. 2009;49:1335-1374.

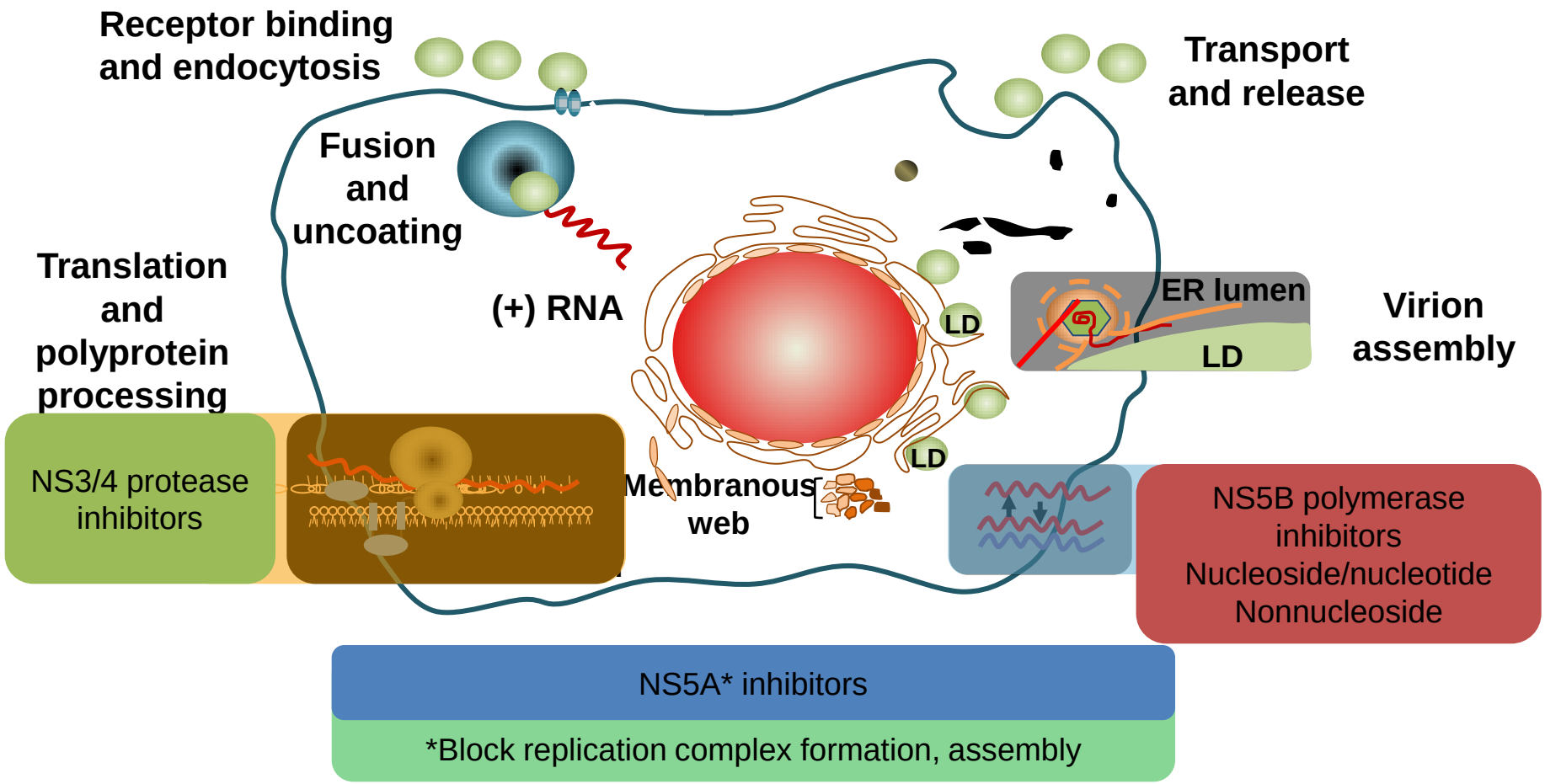
HCV Life Cycle

HCV Life Cycle



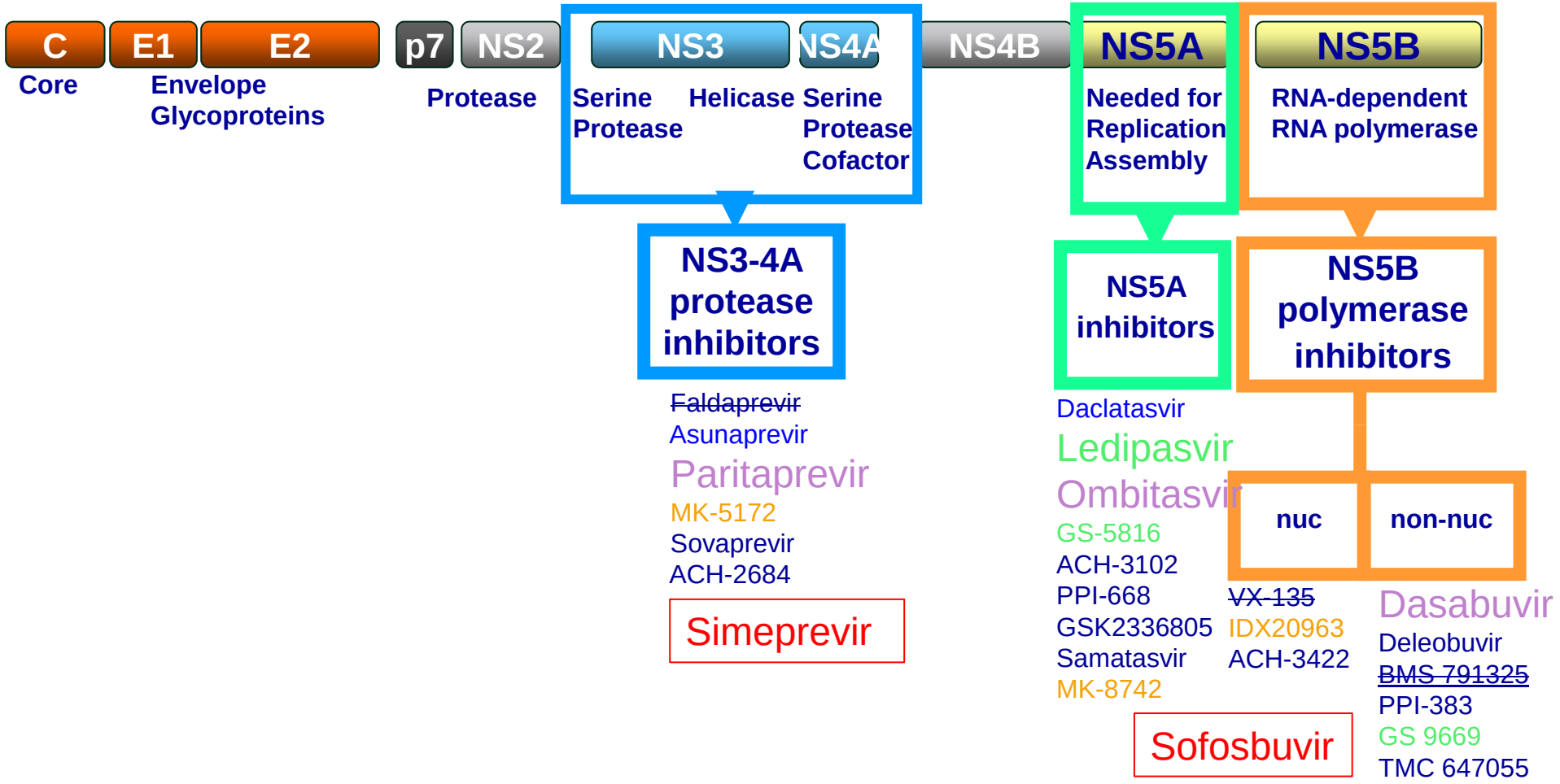
Adapted from Manns MP, et al. *Nat Rev Drug Discov*. 2007;6:991-1000 and McGovern B, et al. *Hepatology*. 2008;48:1700-1712.

HCV Life Cycle and DAA Targets



Adapted from Manns MP, et al. Nat Rev Drug Discov. 2007;6:991-1000.

Targets for Direct-Acting Antiviral (DAA) Agents



Adapted from: McGovern B, Abu Dayyeh B, and Chung RT. Hepatology. 2008; 48:1700-12

Comparison of DAA Profiles

	DAA				
	PI, 1st Generation	PI, 2nd Generation	NS5A Inh	Nuc NS5B Inh	Nonnuc NS5B Inh
Resistance Profile					
Pangenotypic Efficacy					
Efficacy					
Adverse Events					
Drug–Drug Interactions					

 Good profile  Average profile  Least favorable profile

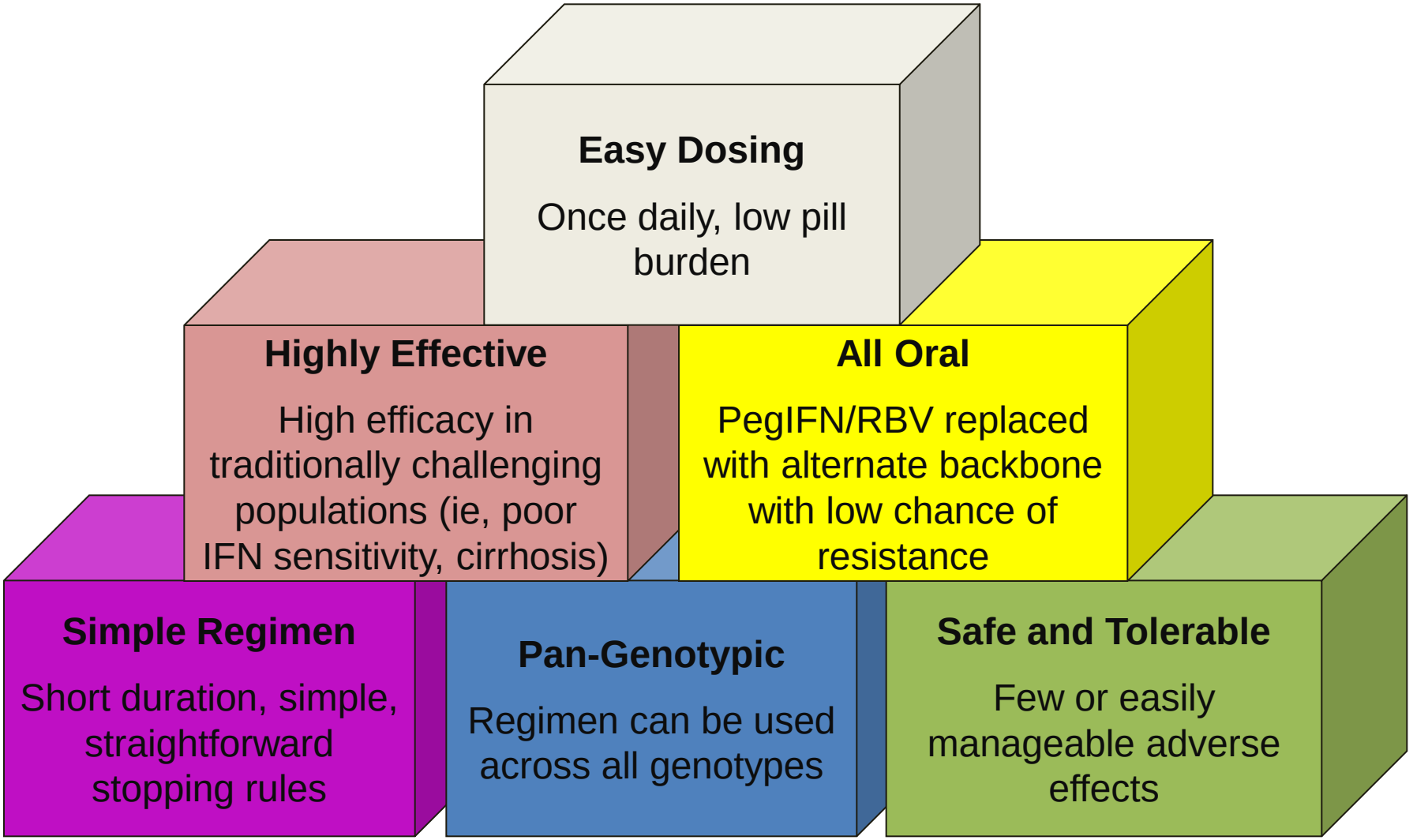
Adapted from: Farnik H, et al. Antivir Ther. 2012;17:771-783.

Treatment Evolution:
The Era of Direct Acting Anti-virals

FDA Approved Treatment Regimens

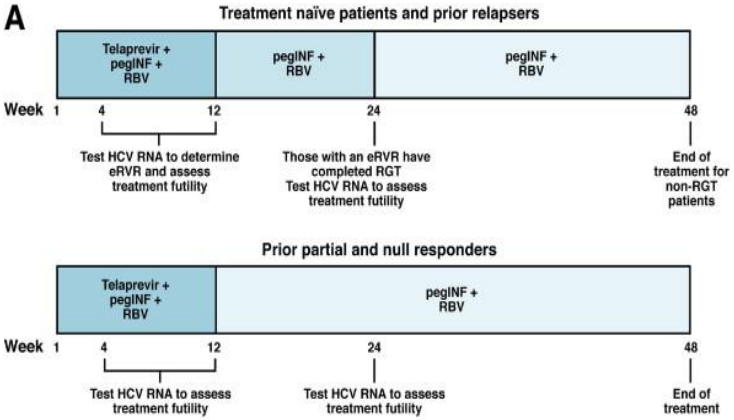
- 2001: PEG-IFN + RBV 24-48 weeks
- 5/2011: PEG-IFN + RBV + Boceprevir or Telaprevir
- 11/2013: PEG-IFN + RBV + Simeprevir (Olysio®)
- 12/2013: PEG-IFN + RBV + Sofosbuvir (Sovaldi®) (Gt 1)
- 12/2013: Sofosbuvir + RBV (Gt 2 & 3)
- 10/2014: Ledipasvir-sofosbuvir (Harvoni®)
- 11/2014: Simeprevir + sofosbuvir ± RBV
- 12/2014: Paritaprevir/r-ombitasvir + dasabuvir (Viekira Pak®) ± RBV

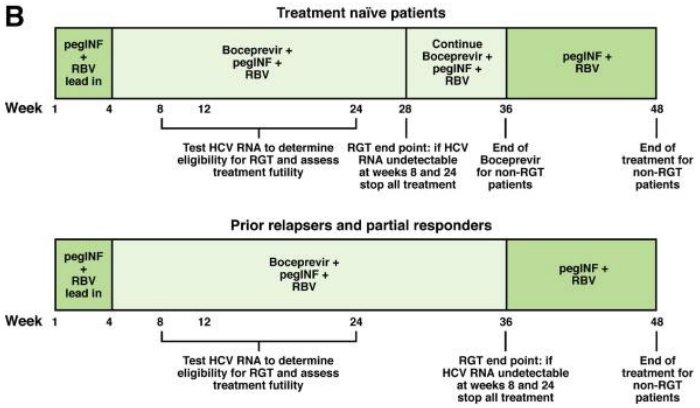
What Are the Key Elements of an Ideal HCV Regimen?



“The Good Old Days” —Many Challenges

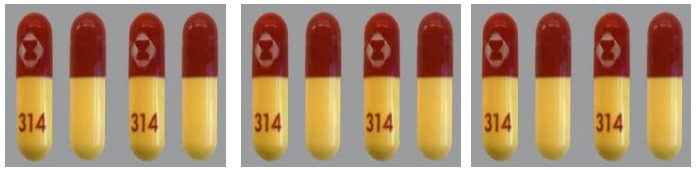
For us—lead-in, response-guided therapy . . .





For our patients . . .

Pill Burden



BOC = 12/day
RBV = 4-7/day

TVR = 6/day
RBV = 4-7/day

Food Requirement

Treatment Options in 2015

- **Sovaldi^{R}** (sofosbuvir without/with ribavirin)
  - Genotypes 1,2,3,4
- **Harvoni^{R}** (ledipasvir/sofosbuvir single tablet regimen)
  - Genotype 1
- **Olysio^{R} +Sovaldi^{R}** (simeprevir/sofosbuvir)
  - Genotype 1
- **VieKira Pak^{R}** (paritaprevir/ritonavir, dasabuvir and ombitasvir without/with ribavirin)
  - Genotype 1
- **hcvguidelines.org**

Harvoni[R] Product Information

HARVONI[R] INDICATIONS AND USAGE

- HARVONI is a fixed-dose combination of ledipasvir, a hepatitis C virus (HCV) NS5A inhibitor, and sofosbuvir, an HCV nucleotide analog NS5B polymerase inhibitor
- Indicated for the treatment of chronic hepatitis C (CHC) genotype 1 infection in adults

------DOSAGE FORMS AND STRENGTHS------

- Tablets: 90 mg ledipasvir and 400 mg sofosbuvir
- Dose- 1 pill Daily

HARVONI® WARNINGS AND PRECAUTIONS

- Use with other drugs containing sofosbuvir, including SOVALDI, is not recommended (5.2)

---------ADVERSE REACTIONS----------

- The most common adverse reactions (incidence greater than or equal to 10%, all grades) observed with treatment with HARVONI for 8, 12, or 24 weeks are
  - Fatigue
  - Headache
  - Nausea
  - Insomnia
  - Diarrhea

HARVONI® DRUG INTERACTIONS

- P-gp inducers (e.g., rifampin, St. John's wort):
  - May alter concentrations of ledipasvir and sofosbuvir.

- Use of HARVONI with P-gp inducers is not recommended

Severe Renal Impairment and End Stage Renal Disease and Harvoni®

- No dose recommendation can be given for patients with severe renal impairment (estimated Glomerular Filtration Rate [eGFR] <30 mL/min/1.73m2)
- or with end stage renal disease (ESRD) due to higher exposures (up to 20-fold) of the predominant sofosbuvir metabolite

Recommended Treatment Duration for HARVONI® in Patients with CHC Genotype 1

Patient Population	Recommended Treatment Duration
▪ Treatment-naïve with or without cirrhosis	▪ 12 weeks*
▪ Treatment-experienced** without cirrhosis	▪ 12 weeks
▪ Treatment-experienced** with cirrhosis	▪ 24 weeks

* **HARVONI for 8 weeks** can be considered in treatment-naïve patients without cirrhosis who have pre-treatment HCV RNA less than 6 million IU/mL [see Clinical Studies].

**Treatment-experienced patients who have failed treatment with either peginterferon alfa + ribavirin or an HCV protease inhibitor + peginterferon alfa + ribavirin.

HARVONI® LABORATORY ABNORMALITIES

- *Bilirubin Elevations*: Bilirubin elevations of greater than 1.5xULN were observed in 3%, <1%, and 2% of subjects treated with HARVONI for 8, 12, and 24 weeks, respectively.
- *Lipase Elevations*: Transient, asymptomatic lipase elevations of greater than 3xULN were observed in <1%, 2%, and 3% of subjects treated with HARVONI for 8, 12, and 24 weeks, respectively.
- *Creatine Kinase*: Creatine kinase was not assessed in Phase 3 trials of HARVONI. Isolated, asymptomatic creatine kinase elevations (Grade 3 or 4) have been previously reported in subjects treated with sofosbuvir in combination with ribavirin or peginterferon/ribavirin in other clinical trials.

VieKira Pak[R] Product Information

VIEKIRA PAK[R] INDICATIONS AND USAGE

- VIEKIRA PAK with or without ribavirin is indicated for the treatment of patients with genotype1 chronic hepatitis C virus (HCV) infection including those with compensated cirrhosis.
- Limitation of Use:

  VIEKIRA PAK is not recommended for use in patients with decompensated liver disease

VIEKIRA PAK[R] DOSAGE FORMS AND STRENGTHS

Tablets:

- Ombitasvir/paritaprevir/ritonavir: 12.5/75/50 mg
- Dasabuvir: 250 mg

CONTRAINDICATIONS

- If VIEKIRA PAK[R] is administered with ribavirin, the contraindications to ribavirin also apply to this combination regimen.
- Patients with severe hepatic impairment.
- Co-administration with drugs that are: highly dependent on CYP3A for clearance; strong inducers of CYP3A and CYP2C8; and strong inhibitors ofCYP2C8. (4)
- Known hypersensitivity to ritonavir (e.g. toxic epidermal necrolysis Stevens-Johnson syndrome).

VIEKIRA PAK[R] DOSAGE AND ADMINISTRATION

- **Recommended Dosage in Adults**
- VIEKIRA PAK[R] is ombitasvir/paritaprevir/ritonavir fixed dose combination tablets co-packaged with dasabuvir tablets.
- The recommended oral dosage of VIEKIRA PAK[R]:
  - ***Two ombitasvir/ paritaprevir/ritonavir tablets QD*** (in the morning) and
  - ***One dasabuvir tablet BID*** (morning and evening).
- *Take VIEKIRA PAK[R] with a meal* without regard to fat or calorie content.
- VIEKIRA PAK[R] is used in combination with ribavirin (RBV) in certain patient populations.
  - When administered with VIEKIRA PAK, the recommended dosage of RBV is based on weight: 1000 mg for subjects <75 kg and
  - 1200 mg/day for those ≥75 kg
  - divided and administered twice-daily with food.
- For ribavirin dosage modifications, refer to the ribavirin prescribing information.

VIEKIRA PAK[R] ADVERSE REACTIONS

- VIEKIRA PAK[R] *with ribavirin*: the most commonly reported adverse reactions (greater than 10% of subjects)
  - fatigue
  - nausea
  - pruritus and other skin reactions
  - Insomnia
  - asthenia
- VIEKIRA PAK *without ribavirin*, the most commonly reported adverse reactions (greater than or equal to 5% of subjects)
  - nausea
  - pruritus
  - insomnia

VIEKIRA PAK® Treatment Regimen and Duration by Patient Population

Patient Population	Treatment*	Duration
Genotype 1a *w/o cirrhosis*	VIEKIRA PAK + ribavirin	12 weeks
Genotype 1a *with cirrhosis*	VIEKIRA PAK + ribavirin	24 weeks**
Genotype 1b *w/o cirrhosis*	VIEKIRA PAK	12 weeks
Genotype 1b with cirrhosis	VIEKIRA PAK + ribavirin	12 weeks

- *Note: Follow the genotype 1a dosing recommendations in patients with an unknown genotype 1 subtype or with mixed genotype 1 infection.
- **VIEKIRA PAK administered with ribavirin for 12 weeks may be considered for some patients based on prior treatment history who had a partial response or relapse to PEG/riba.
- HCV/HIV-1 co-infection: For patients with HCV/HIV-1 co-infection, follow the dosage recommendations in the table above.
- Liver Transplant Recipients: In liver transplant recipients with normalhepatic function and mild fibrosis (Metavir fibrosis score ≤2), therecommended duration of VIEKIRA PAK with ribavirin is 24 weeks.

VIEKIRA PAK[R] WARNINGS AND PRECAUTIONS

- ALT Elevations:
  - Discontinue ethinyl estradiol-containing medications prior to sarting VIEKIRA PAK (alternative contraceptive methods are recommended).
  - Perform hepatic laboratory testing on all patients during the first 4 weeks of treatment.
  - For ALT elevations on VIEKIRA PAK, monitor closely and follow recommendations in full prescribing information.
- Risks Associated With Ribavirin Combination Treatment:
  - If VIEKIRA PAK[R] is administered with ribavirin, the warnings and precautions for ribavirin also apply to this combination regimen.
- Drug Interactions:
  - The concomitant use of VIEKIRA PAK[R] and certain other drugs may result in known or potentially significant drug interactions, some of which may lead to loss of therapeutic effect of VIEKIRA PAK[R].

Olysio[R] Product Information

OLYSIO® INDICATIONS AND USAGE

- OLYSIO® (simeprevir) is a hepatitis C virus (HCV) *NS3/4A protease inhibitor* indicated for the treatment of chronic hepatitis C (CHC) genotype 1 infection as a ***component of a combination antiviral treatment regimen***. (1)
- Limitations of Use:
  - OLYSIO® monotherapy is not recommended.
  - OLYSIO® combination with peginterferon alfa and ribavirin: Screening patients with HCV genotype 1a infection for the presence of virus with the NS3 Q80K polymorphism is strongly recommended and alternative therapy should be considered if HCV genotype 1a with Q80K is detected.
  - OLYSIO® is not recommended in patients who have previously failed therapy with a treatment regimen that included OLYSIO® or other HCV protease inhibitors.

OLYSIO® DRUG INTERACTIONS

- Co-administration of OLYSIO® with drugs that are moderate or strong inducers or inhibitors of CYP3A may significantly affect the plasma concentrations of simeprevir.
- The potential for drug-drug interactions must be considered priorto and during treatment.

OLYSIO® WARNINGS AND PRECAUTIONS

- Photosensitivity:
  - Serious photosensitivity reactions have been observed during combination therapy with OLYSIO.
  - Use sun protection measures and limit sun exposure during OLYSIO combination therapy.
  - Consider discontinuation if a photosensitivity reaction occurs.
- Rash:
  - Rash has been observed during OLYSIO combination therapy.
  - Discontinue OLYSIO if severe rash occurs.

OLYSIO[R] DOSAGE AND ADMINISTRATION

DOSAGE FORMS AND STRENGTHS

Capsule: 150 mg

- One 150 mg capsule taken once daily with food.
- OLYSIO[R] should be *administered in combination with other antiviral drugs for the treatment of CHC infection.*

RECOMMENDED TREATMENT DURATION

- **OLYSIO[R] with sofosbuvir** 400 mg (irrespective of previous Rx):
  - ***Without* Cirrhosis:** **12 weeks**
  - ***With* Cirrhosis:** **24 weeks.**

OLYSIO[R] ADVERSE REACTIONS

- Most common reported adverse reactions (incidence greater than 20%)
- OLYSIO[R] with peginterferon and ribavirin during first 12 weeks of treatment (>3% vs. PEG/riba placebo arm):
  - rash (including photosensitivity)
  - pruritus
  - nausea
- OLYSIO with sofosbuvir during 12 or 24 weeks of treatment:
  - fatigue
  - headache
  - nausea

Getting down to business.
Treatment of chronic HCV in 2015

What Truly Matters in 2015

- **Genotype**
  - No universally applied pan-genotypic regimen
- **Fibrosis**
  - Minimal to mild
  - Advanced/cirrhotic
- **Previous Treatment Experience**
  - Any response vs. Null response
  - Did failed treatment include DAA?
- **HCV RNA titer (viral load)**
  - Threshold for shorter treatment duration?

Treatment Considerations:

- **Treatment Duration**
  - 8 wks
  - 12 wks
  - 16 wks
  - 24 wks
- **Treatment Adjuncts**
  - Ribavirin
  - Ritonavir
- **Challenging Populations**
  - HIV/HCV co-infected
  - Post transplant
- **Safety and Tolerance**
  - Renal insufficiency limits use
  - Advanced hepatic failure requires careful monitoring
- **Drug-Drug Interactions**
  - Marked improvement over 1st generation DAA's
  - Use of online tools helpful
- **Resistance**
  - Prohibition of monotherapy with DAA diminishes likelihood
  - Very low probability of on treatment virologic failure

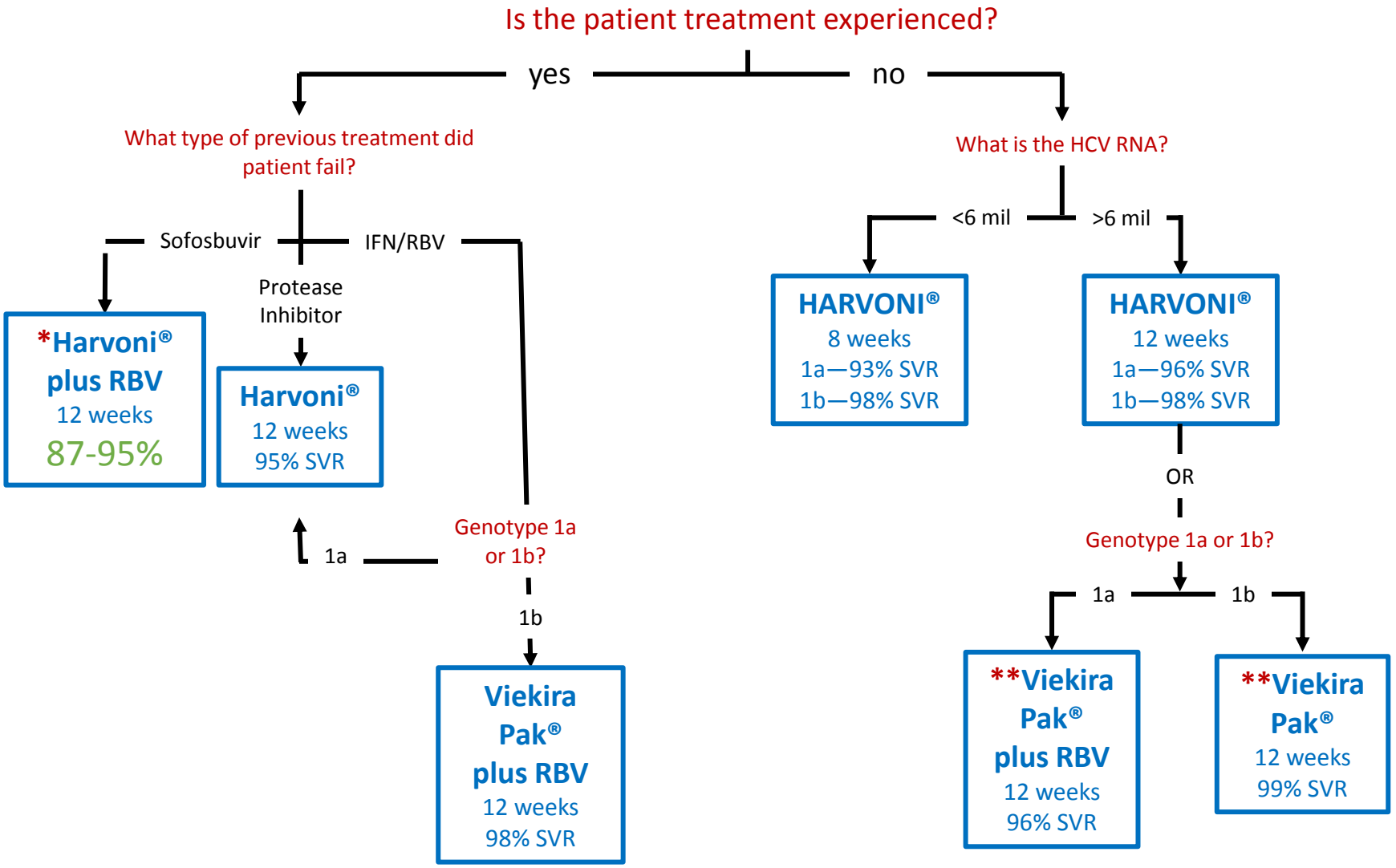
Treatment Efficacy:

Overall SVR for Genotype 1

>95% !

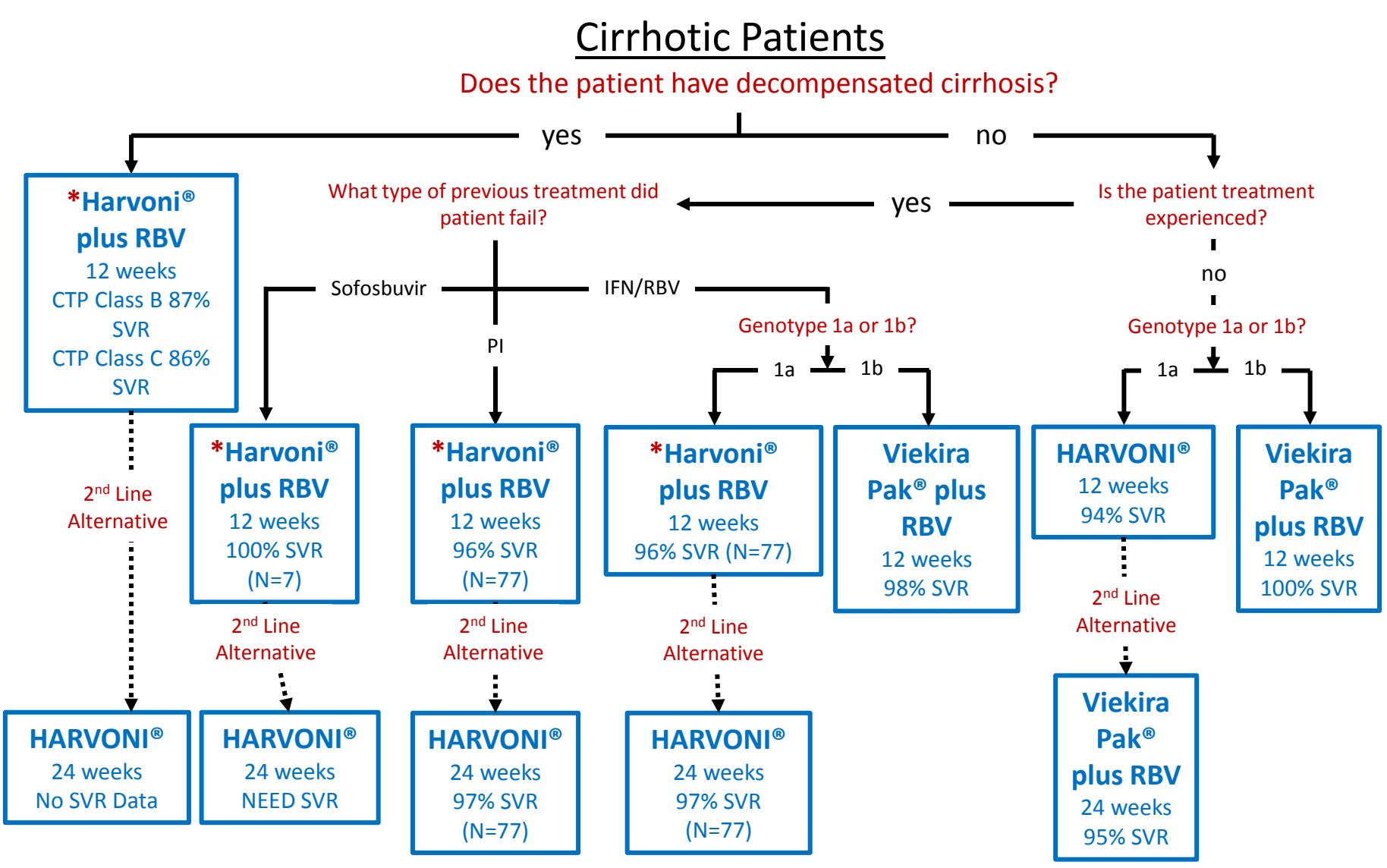
Hepatitis C Genotypes 1 or 4 Treatment Regimen Decision Tree

Non-cirrhotic Patients



*Non-FDA approved regimen; may be challenging to obtain prior auth. Seek alternate treatment regimen, as indicated, if unable to obtain.
**Treatment has similar efficacy—select treatment based on accessibility.

Hepatitis C Genotypes 1 or 4 Treatment Regimen Decision Tree



*Non-FDA approved regimen; may be challenging to obtain prior authorization. Seek alternate treatment regimen, as indicated, if unable to obtain.

Hepatitis C Genotypes 2 and 3 Treatment Regimen Decision Tree

Genotype 2 Patients

Does patient have cirrhosis?

yes

Sovaldi® plus RBV
16 weeks
78% SVR

no

Sovaldi® plus RBV
12 weeks
94% SVR

Genotype 3 Patients

Does patient have cirrhosis?

yes

***Harvoni® plus RBV**
12 weeks
**TE 73% SVR (N=22)
TN 100% SVR (N=4)

Alternative regimen if unable to obtain prior authorization

Sovaldi® plus RBV
24 weeks
**TE 60% SVR (N=45)
TN 92% SVR (N=13)

no

***Harvoni® plus RBV**
12 weeks
TE 89% SVR (N=28)
TN 100% SVR (N=22)

Alternative regimen if unable to obtain prior authorization

Sovaldi® plus RBV
24 weeks
TE 85% SVR (N=85)
TN 93% SVR (N=92)

Key
TE—Treatment Experienced
TN—Treatment Naive

*Non-FDA approved regimen; may be challenging to obtain prior authorization. Seek alternate treatment regimen, as indicated, if unable to obtain.

**For *treatment experienced, cirrhotic* patients, Solvadi®/IFN/RBV may be considered for 12 weeks with expected SVR of 83%.

Where Do We Go From Here?

What Hopefully Improves in 2015

- **"Retail" cost is very high**
  - Patient support programs have kept direct costs to patients affordable
  - Competition has already had beneficial impact on cost to payers
- **Fibrosis stipulation limiting access to treatment**
  - Extrahepatic manifestations/all cause mortality of chronic HCV not related to degree of fibrosis
- **Only 6-7 % of hose with chronic HCV have been successfully treated**
  - Access to care is bottleneck

Questions?