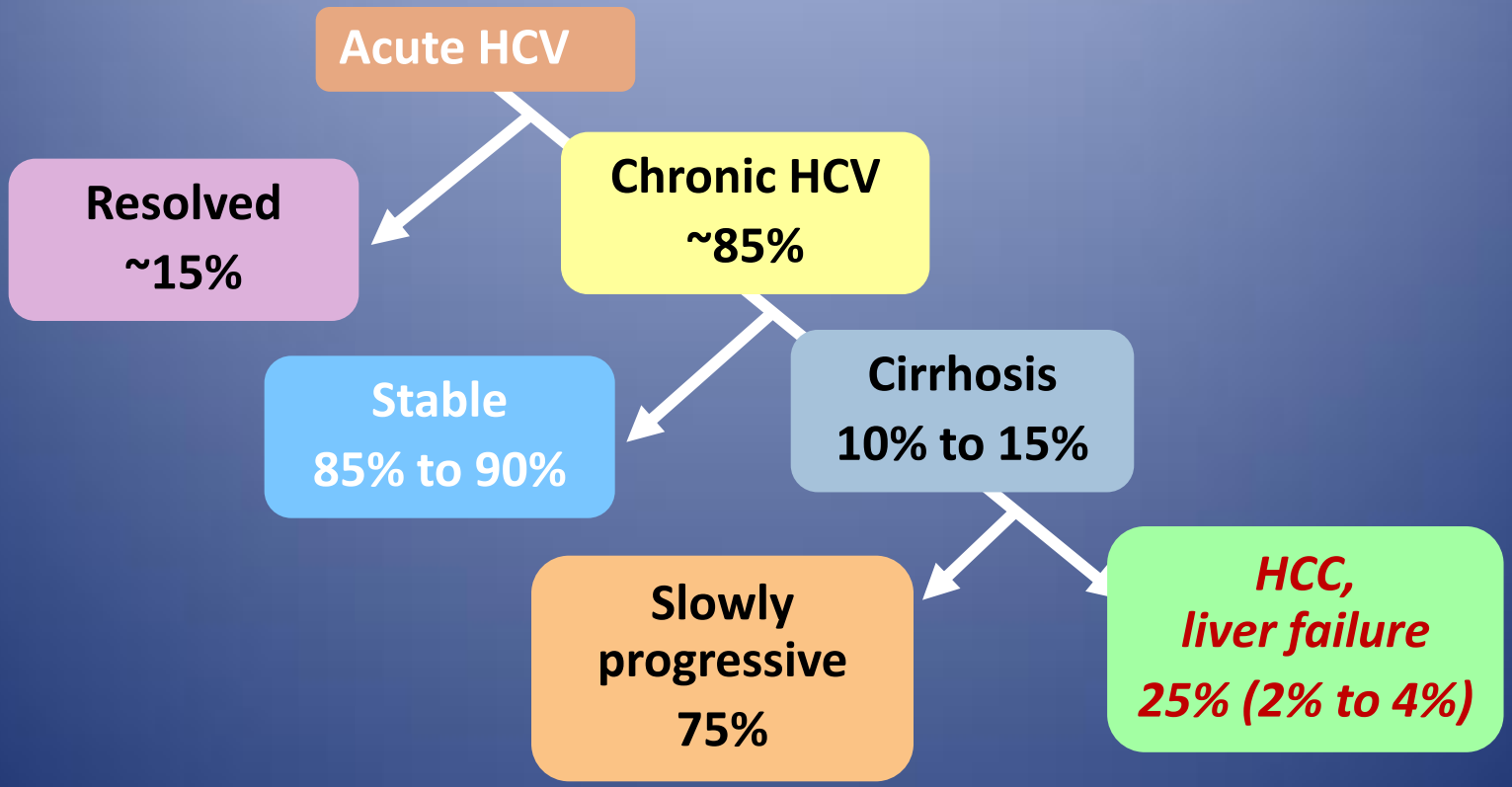
Hepatitis C

Michael J. Surdy, PharmD, AAHIVP

FINANCIAL DISCLOSURE

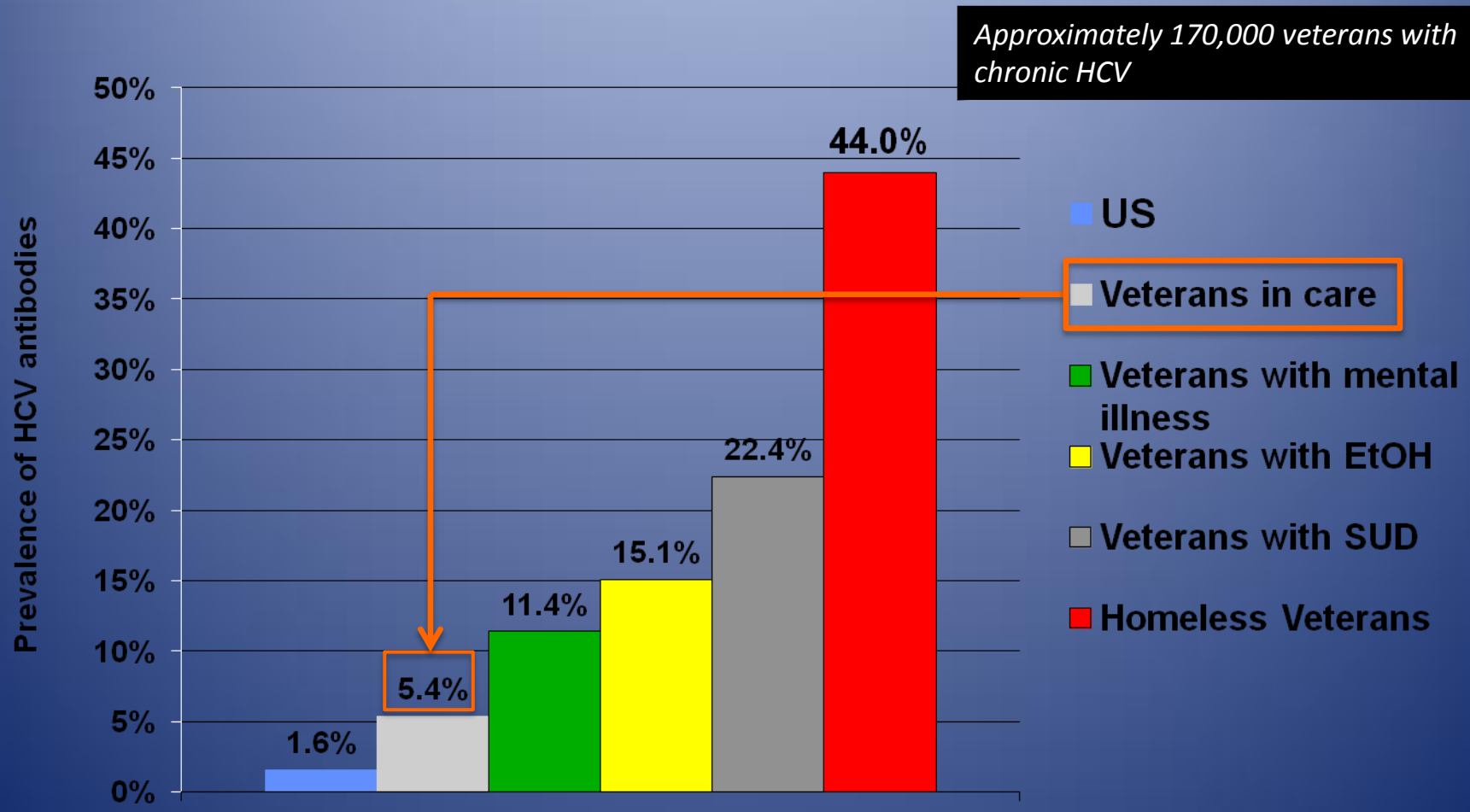
- I have no financial interests concerning any products mentioned in this presentation

NATURAL HISTORY



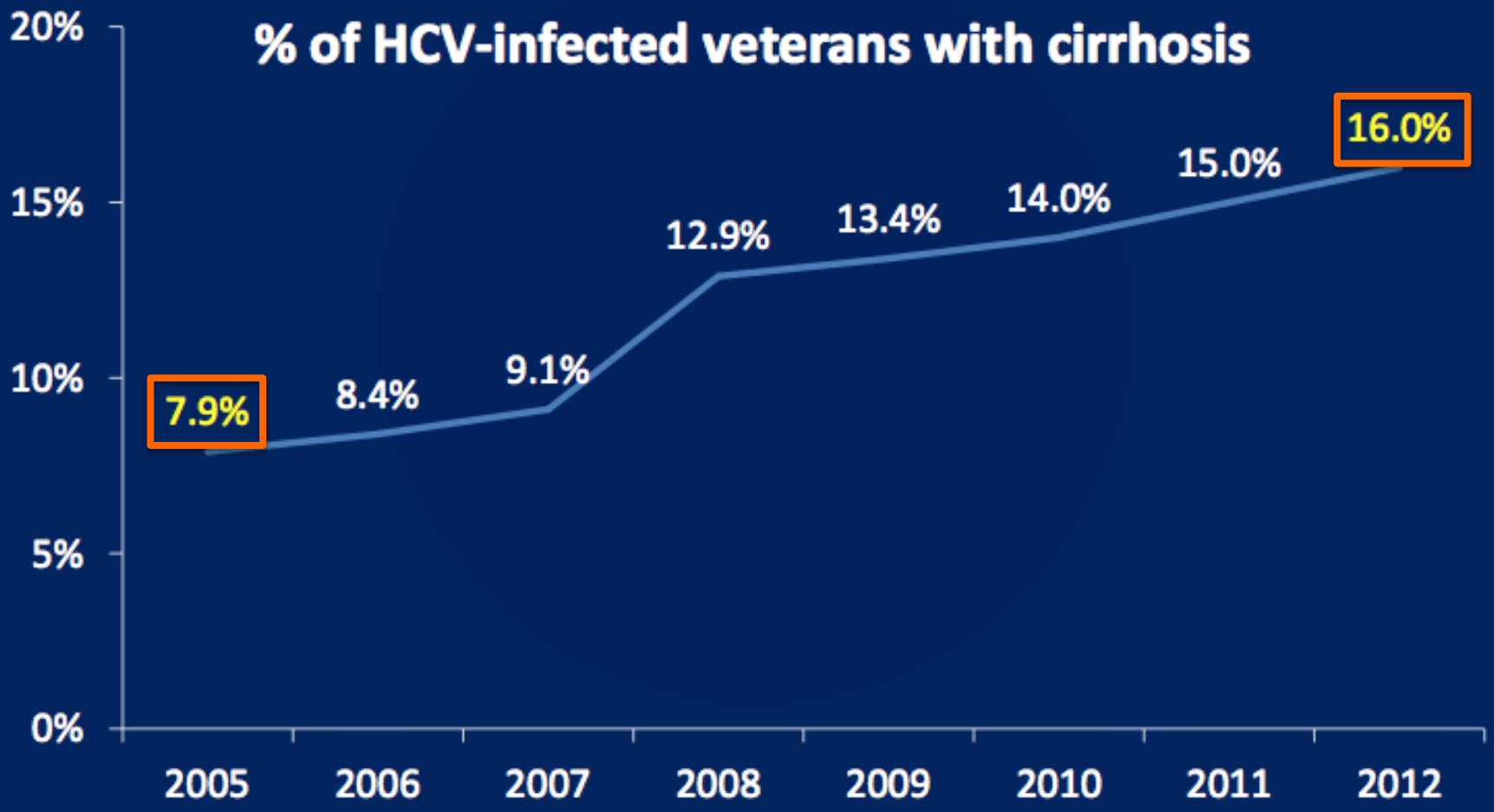
NIH Management of Hepatitis C Consensus Conference Statement. June 10-12, 2002.

HEPATITIS C IN VA



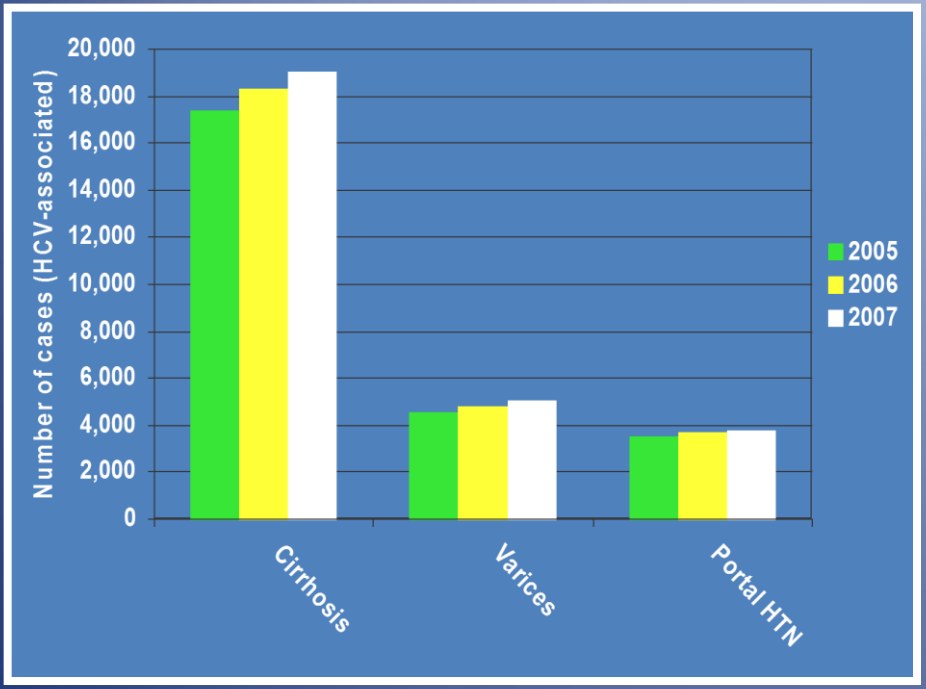
Dominitz JA, *et al*, Hepatology 2005;41:88-96
Desai RA, *et al*. Soc Psychiatry Psychiatr Epidemiol. 2003; 38:396-401

Aging Cohort



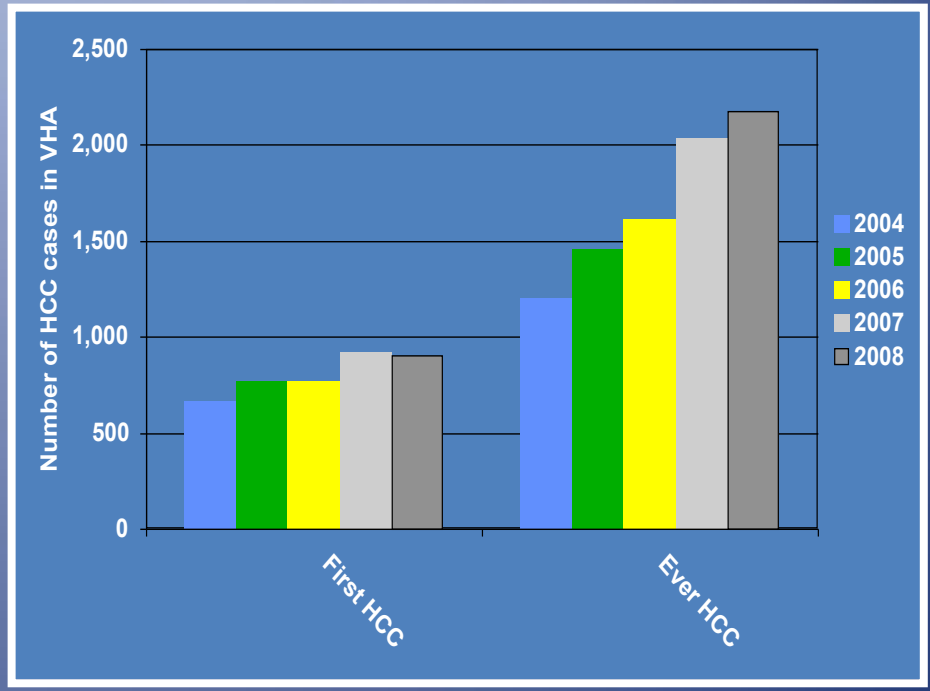
http://vaww.hepatitis.va.gov; accessed 4/13

END STAGE LIVER DISEASE IN VA



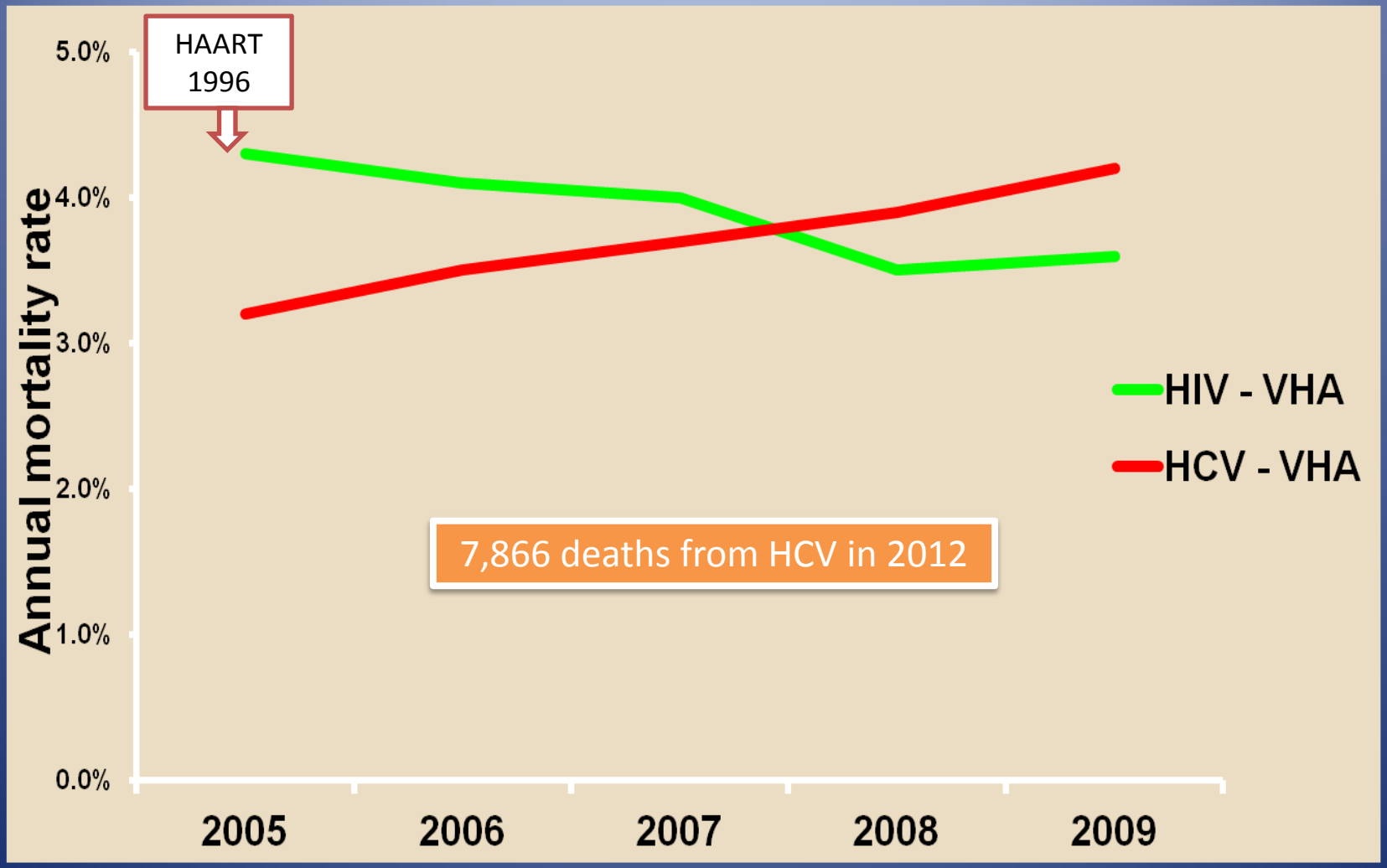
VHA Center for Quality Management in Public Health
http://vaww.hepatitis.va.gov/vahep?page=prin-cqm-01#t-1

INCIDENCE OF HCC IN VA



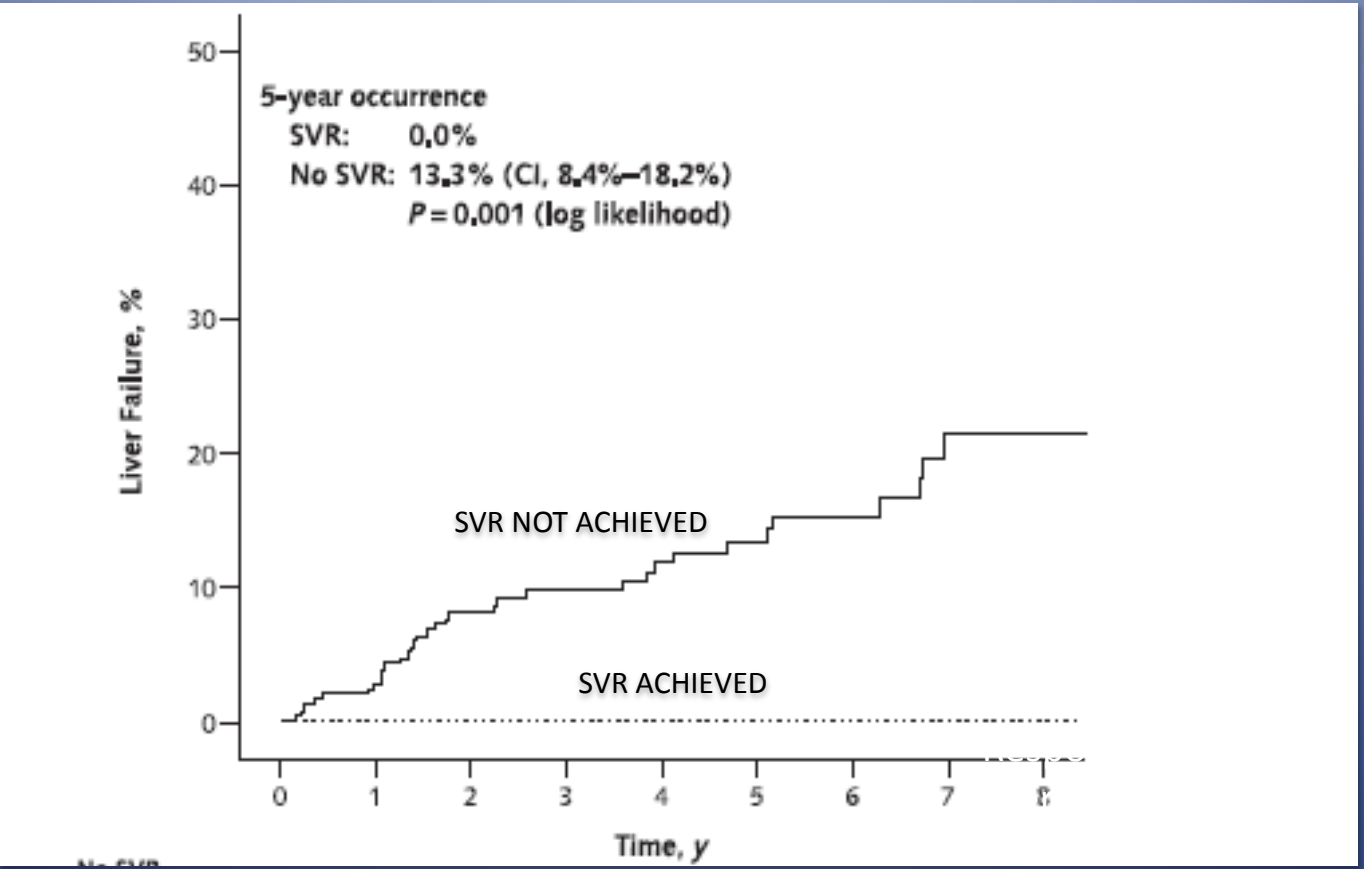
VHA Center for Quality Management in Public Health
http://vaww.hepatitis.va.gov/vahep?page=prin-cqm-01#t-1

Mortality in HCV+ Veterans in VHA is increasing



http://vaww.hepatitis.va.gov/vahep?page=prin08-Demo-Deaths-HCVVir-2009-All

Anti-viral treatment of HCV can reduce the risk of liver failure (and death)…

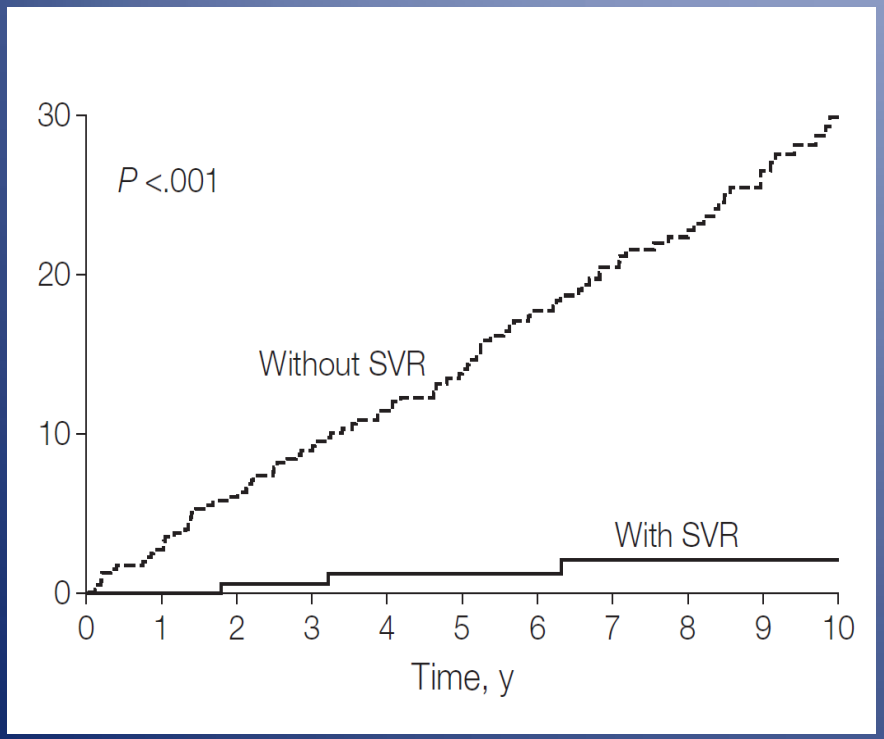


Veldt BJ, et al. Ann Int Med 2007; 147:677

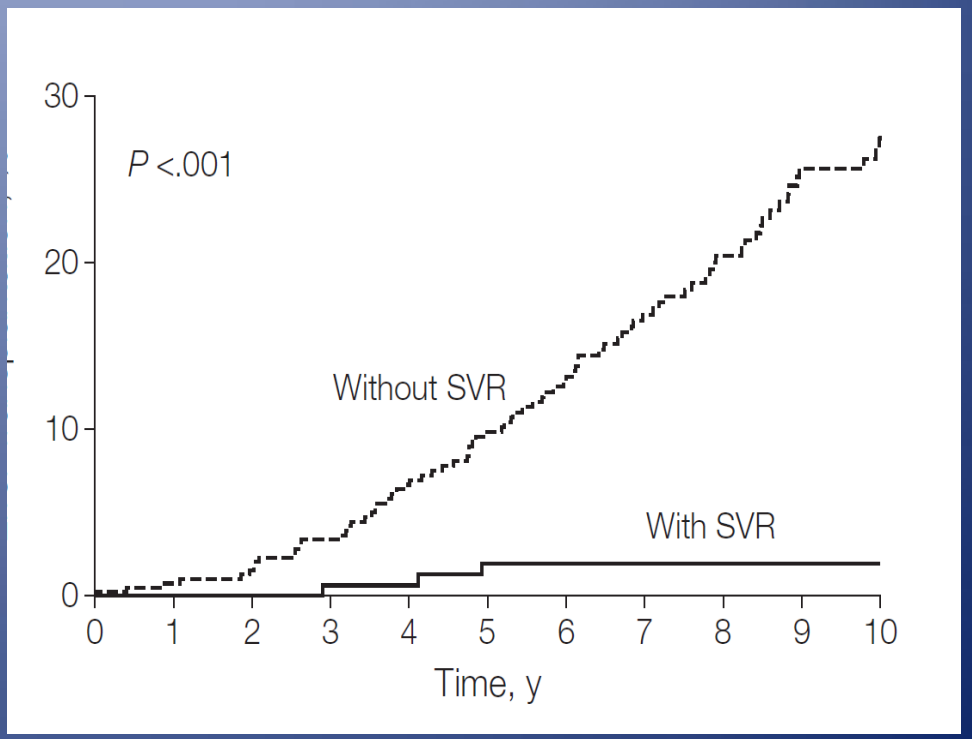
However, only 22% of veterans have ever been treated as of 2009.

SVR leads to lower rates of decompensation and death in HCV related cirrhosis

Decompensation

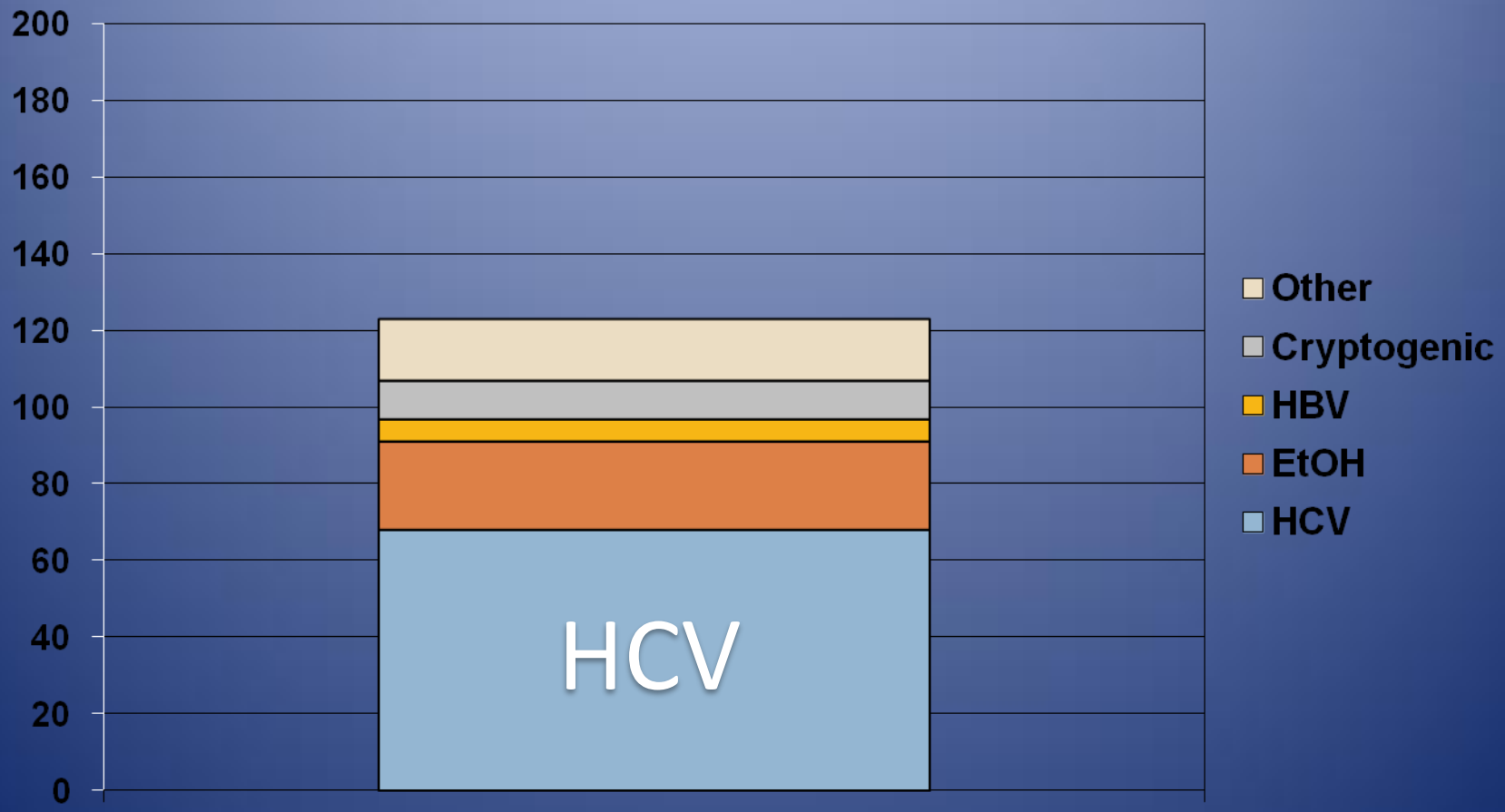


Liver-related death or transplant



Van der Meer et al. JAMA. 2012; 26;308:2584-93.

The average VA primary care provider has over 100 liver disease patients…



Data from Portland VAMC transplant program and Dominitz JA et al. Hepatology 2005; 41:88 - 96

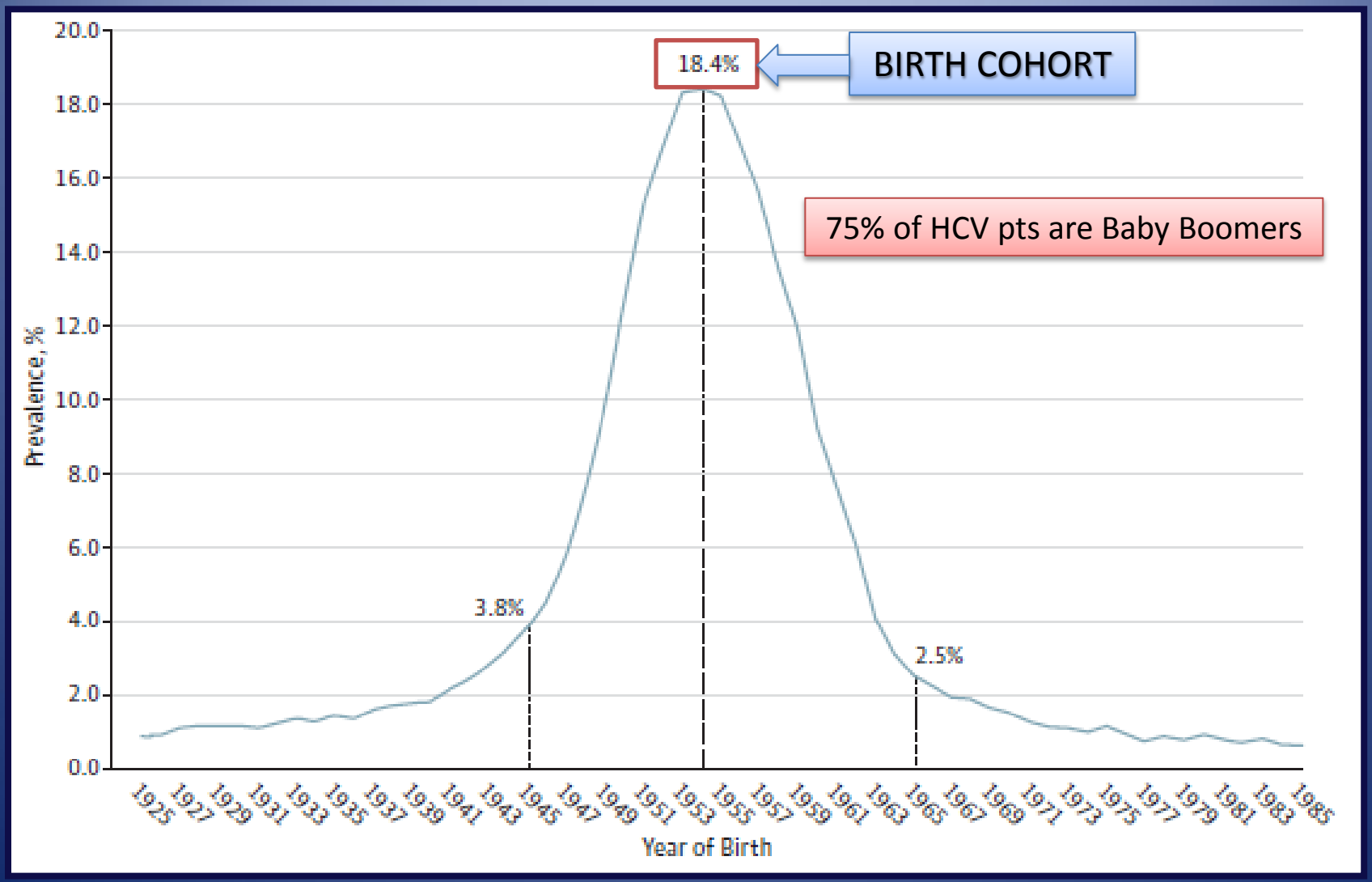
Who Should We Screen for HCV?

- ***Persons for Whom Testing is Recommended***
- ***Adults born during 1945 through 1965*** should be tested once (without prior ascertainment of HCV risk factors)
- HCV-testing is recommended for those who:
  - *Currently inject drugs*
  - *Ever injected drugs, including those who injected once or a few times many years ago*
  - Have certain medical conditions, including persons:
    - Who received clotting factor concentrates produced before 1987
    - Who were ever on long-term hemodialysis
    - With persistently abnormal alanine aminotransferase levels (ALT)
    - Who have HIV infection
  - Were 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, blood components or an organ transplant before July 1992*

- ***Persons for Whom Routine Testing is Uncertain***
  - Recipients of transplanted tissue (e.g., corneal, musculoskeletal, skin, ova, sperm)
  - Intranasal cocaine and other non-injecting illegal drug users
  - Persons with a history of tattooing or body piercing
  - Persons with a history of multiple sex partners or sexually transmitted diseases
  - Long-term steady sex partners of HCV-positive persons

Centers for Disease Control and Prevention

PREVALENCE OF HEPATITIS C VIRUS INFECTION BY BIRTH YEAR



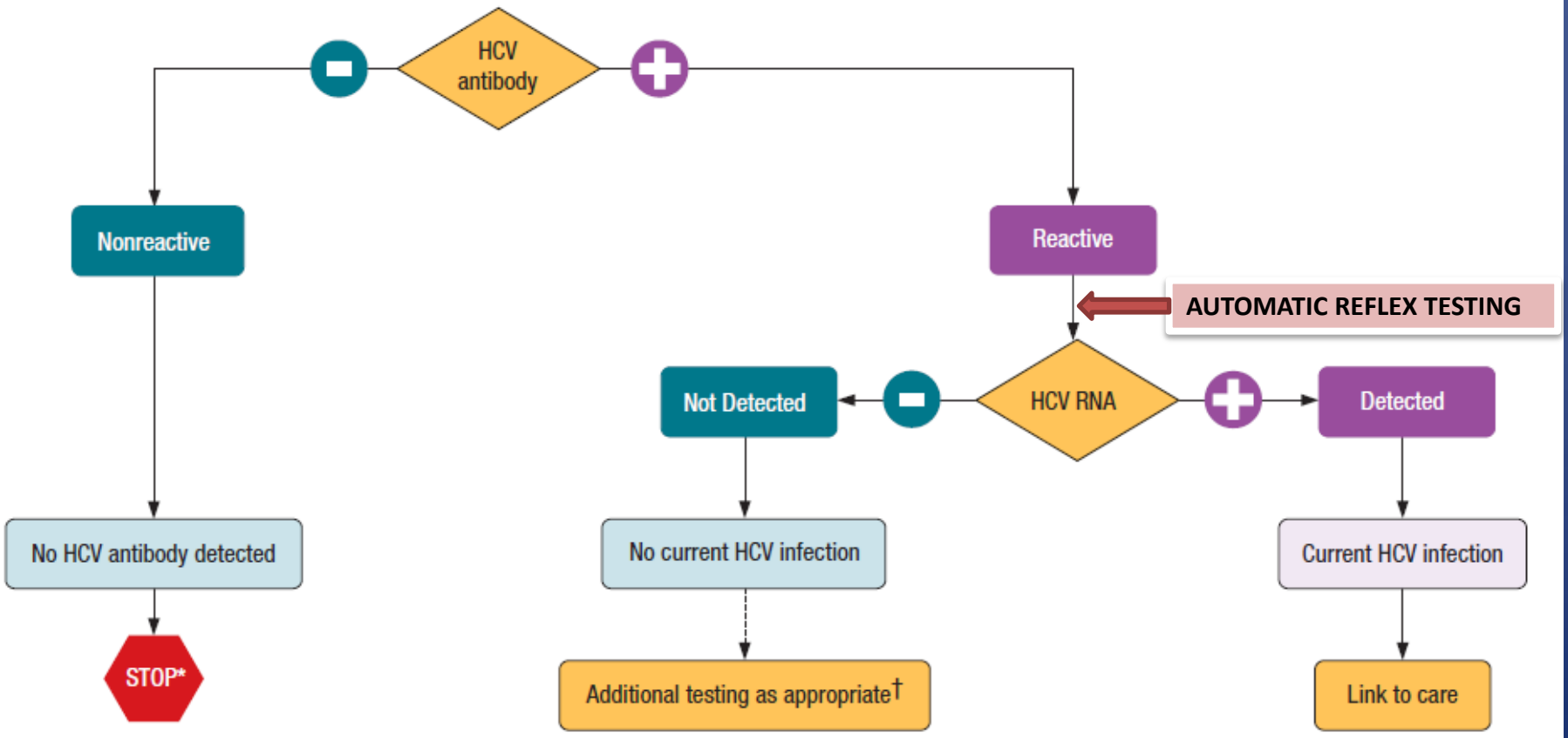
Backus L, et al. JAMA Intern Med . 2013.

VISN 4 SCREENING OF BIRTH COHORT PATIENTS

	Overall Screening Rate	Born Before 1945	Born 1945-1965	Born After 1965
NATIONAL			66.3%	
VISN 4	49.0%	30.1%	61.1%	63.1%
Altoona	64.2%	54%	75.0%	66.4%
Butler	32.1%	18.7%	42.1%	51.8%
Clarksburg	53.2%	39.2%	62.0%	58.9%
Coatesville	39.0%	14.3%	59.6%	67.1%
Erie	48.2%	30.1%	57.6%	75.6%
Lebanon	49.8%	31.5%	63.5%	67.4%
Philadelphia	56.0%	31.1%	70.7%	66.5%
Pittsburgh	51.5	31.5%	63.1%	66.1%
Wilkes-Barre	38.1%	26.3%	43.1%	50.3%
Wilmington	44.7%	28.7%	55.1%	53.0%

Recommended Testing Sequence for Identifying Current Hepatitis C Virus (HCV) Infection

U.S. Department of Health and Human Services
Centers for Disease Control and Prevention



* For persons who might have been exposed to HCV within the past 6 months, testing for HCV RNA or follow-up testing for HCV antibody is recommended. For persons who are immunocompromised, testing for HCV RNA can be considered.

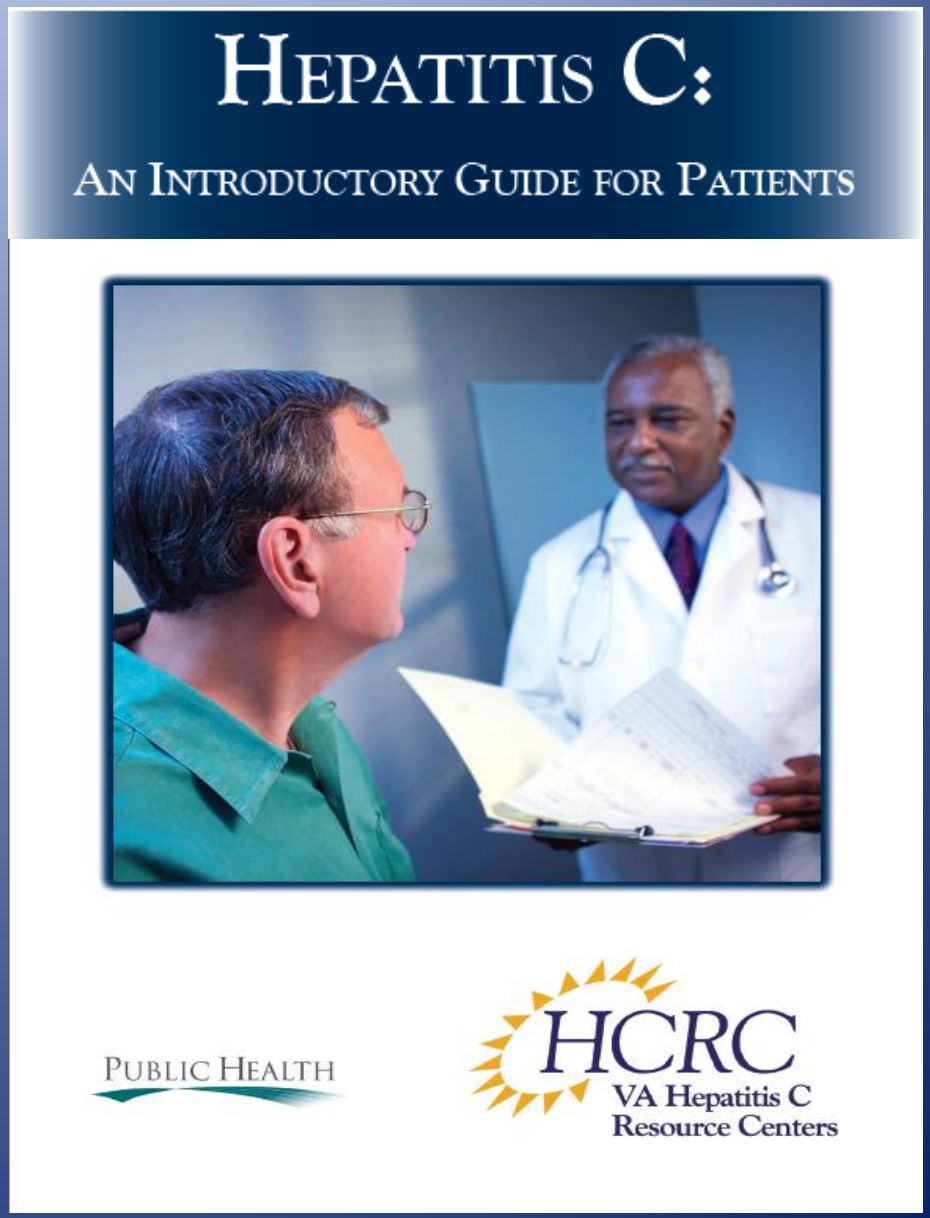
† To differentiate past, resolved HCV infection from biologic false positivity for HCV antibody, testing with another HCV antibody assay can be considered. Repeat HCV RNA testing if the person tested is suspected to have had HCV exposure within the past 6 months or has clinical evidence of HCV disease, or if there is concern regarding the handling or storage of the test specimen.

Source: CDC. Testing for HCV infection: An update of guidance for clinicians and laboratorians. MMWR 2013;62(18).

Counsel on Preventing HCV Transmission

- DO NOT
  - Donate blood, organs
  - Donate body fluids
  - Share tooth brushes
  - Share razors, needles
- DO
  - Cover exposed/bleeding wounds
  - Use sharps containers
  - Practice safe sex

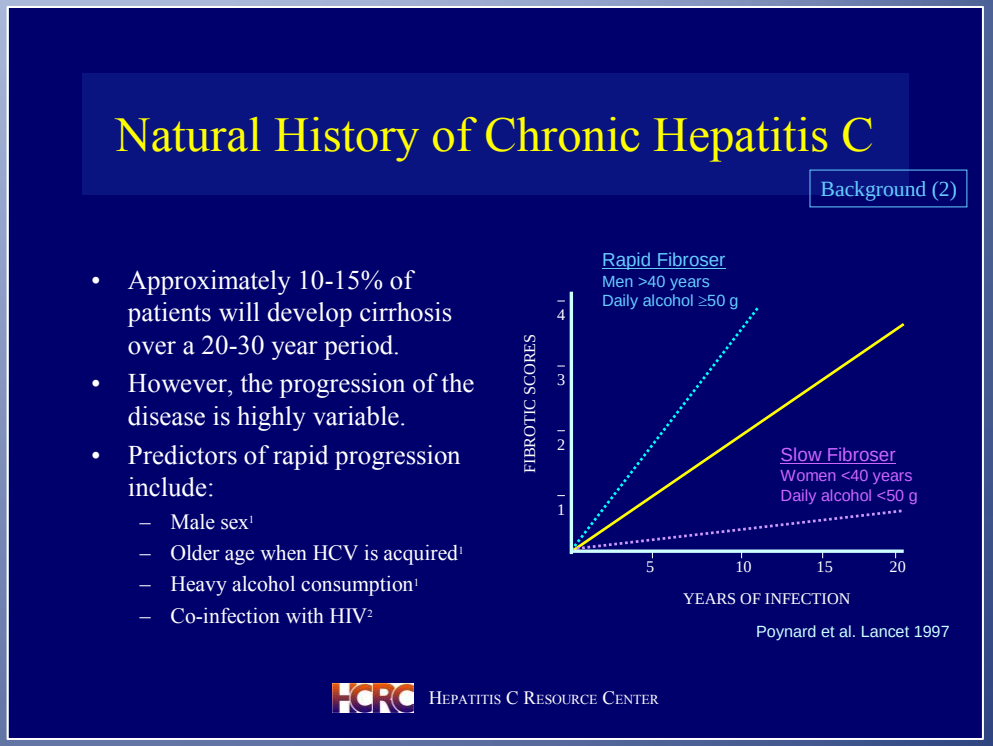
Hepatology. 2009;49(4):1335 – 1374.



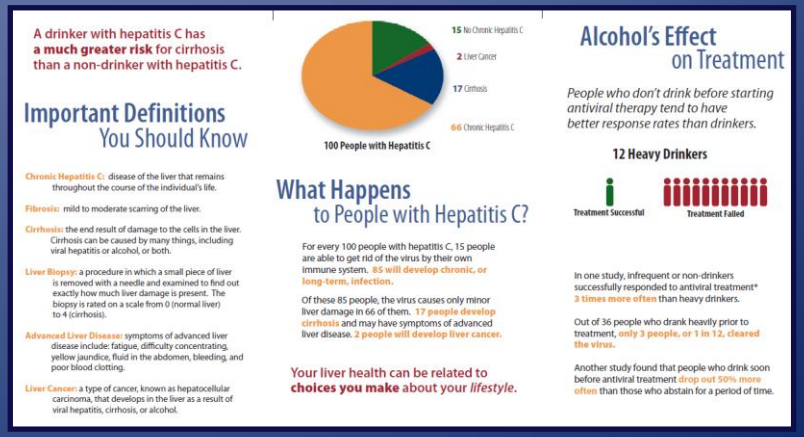
www.hepatitis.va.gov

Provide Guidance on Alcohol Use

- Avoid Alcohol
  - 50 g/day is the amount determined to significantly increase HCV-fibrosis progression
  - ➢ How much alcohol is 50g
    - 48 ounces beer(4 cans)
    - 4.5 ounces 80 proof alcohol (4 shots)
    - 15 ounces wine(2.5 glasses)
  - ◆ Educational tools
    - http://www.hepatitis.va.gov
    - http://vawww.hepatitis.va.gov



Centers for Disease Control and Prevention.



www.hepatitis.va.gov

Additional Screening

- HIV
  - 25% of HIV infected patients have HCV
- Hepatitis A
  - Can cause acute liver failure in HCV infected patients
  - Determine prior infection and/or need for vax
  - HAV vaccine 0, 6 months
- Hepatitis B
  - Determine prior infection and/or need for vax
  - HBV vaccine 0, 1, 6 months
- Cirrhotics
  - Upper endoscopy
  - Abdominal ultrasound and AFP

Pre-Treatment Assessment

LAB/TEST	ASSESSMENT
SCr	Adjust doses of antivirals
AST, ALT	AST>ALT may be a sign of cirrhosis*
Albumin	Marker of advanced liver disease
INR	Marker of advanced liver disease
t. bilirubin	Marker of advanced liver disease
PLT	<150,000: marker of cirrhosis, portal HTN ▪ 75% of cirrhotic patients have PLT<150K
Pregnancy test	Contraindication to ribavirin
HIV test	ID referral
HAV/HBV serology	Provide vaccinations if no immunity
HCV viral load	Confirm active infection
HCV genotype	Determines treatment regimen
Abdominal ultrasound	May suggest cirrhosis

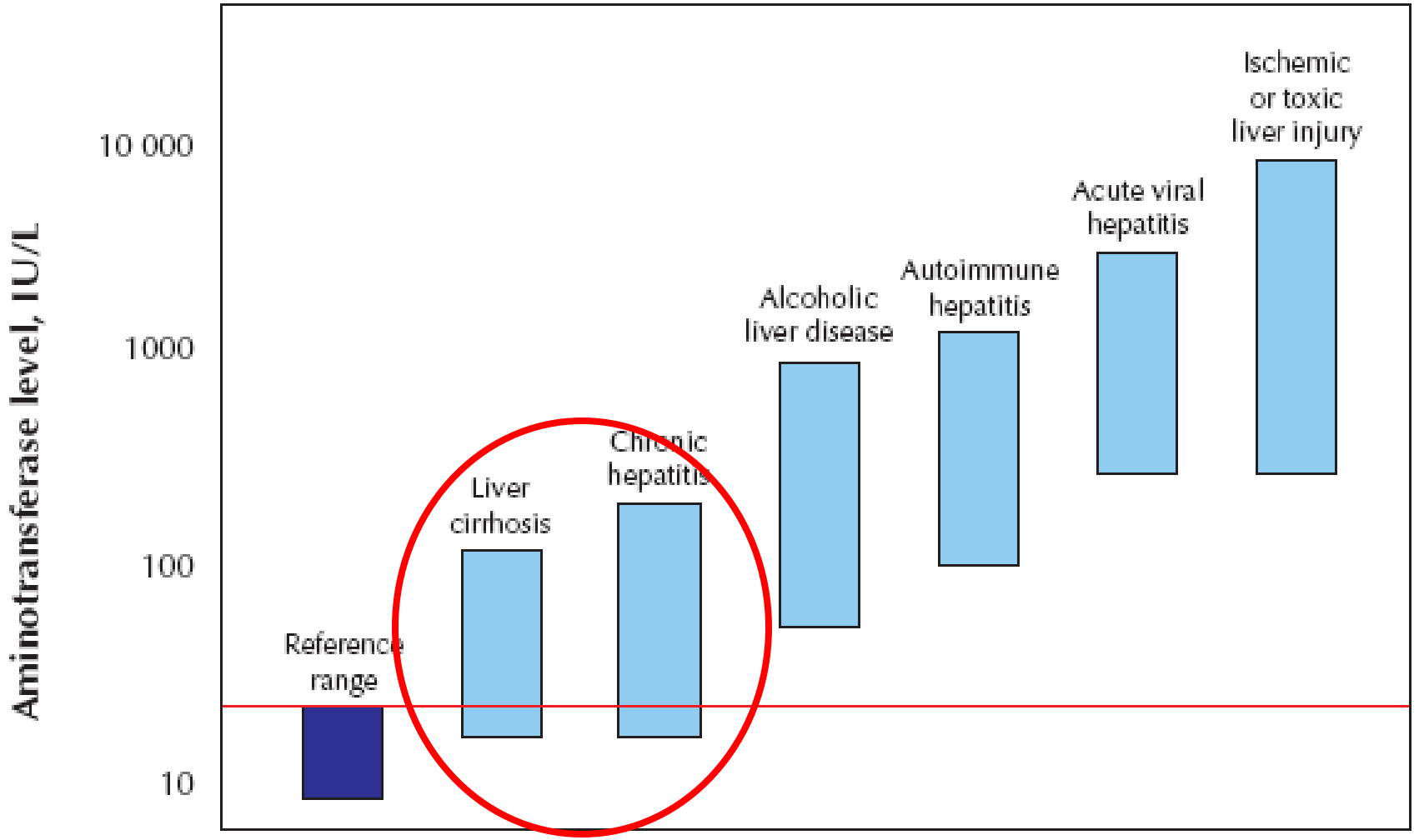
** Absence of elevation does not rule out liver disease*

Utility of Ultrasound

- Useful to determine size and morphology of liver
  - Findings:
    - Irregular surface/borders, nodular surface
    - Parenchymal texture becomes more coarse
- Can help determine severity of liver disease
- Can sometimes diagnose HCC or fatty liver

Nishiura T, et al. British Journal of Radiology 2007. Feldman M, et al. Sleisenger & Fordtran's Gastrointestinal and Liver Disease. 6th Ed. Philadelphia, PA: WB Saunders; 1998.

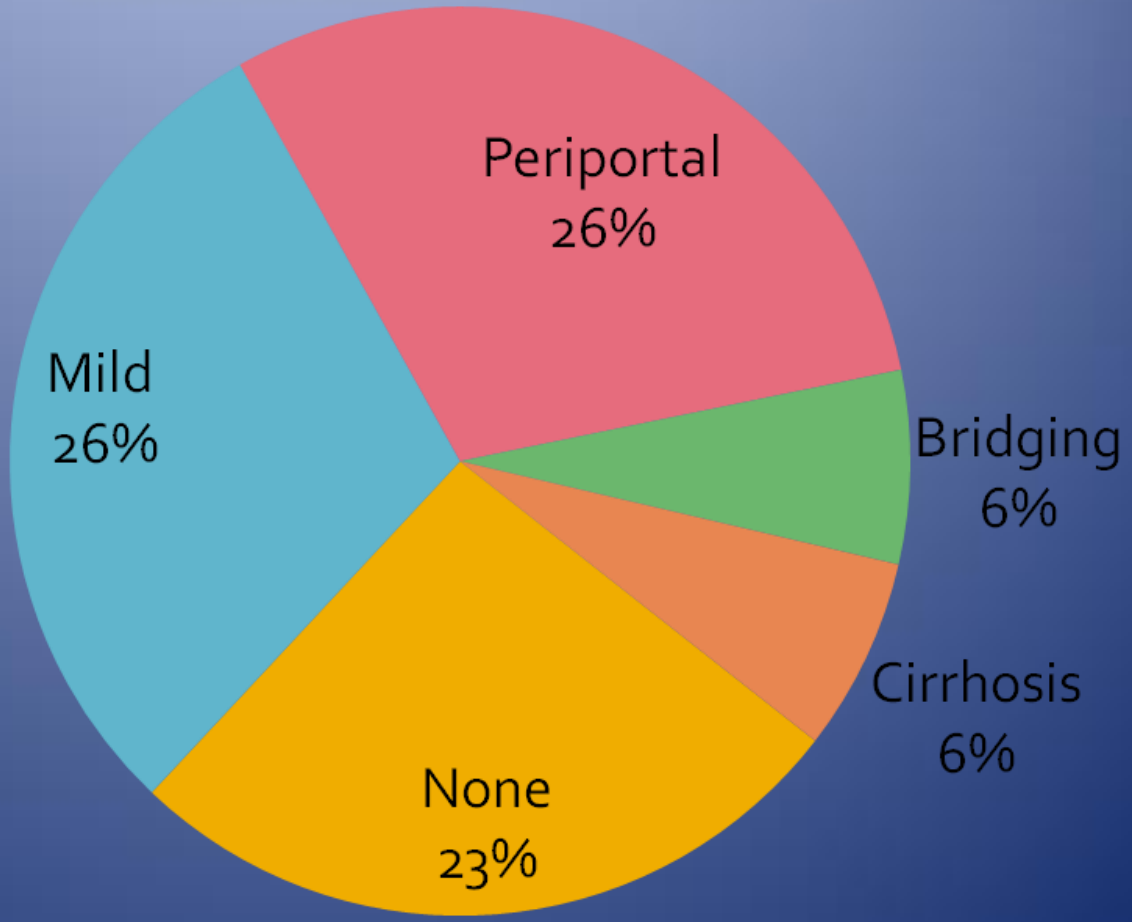
LFT Patterns in Liver Disease



From Giannini EG et al, CMAJ 2005;172

Don’t Rely on LFTs

Disease progression can occur despite apparently “normal” LFT’s



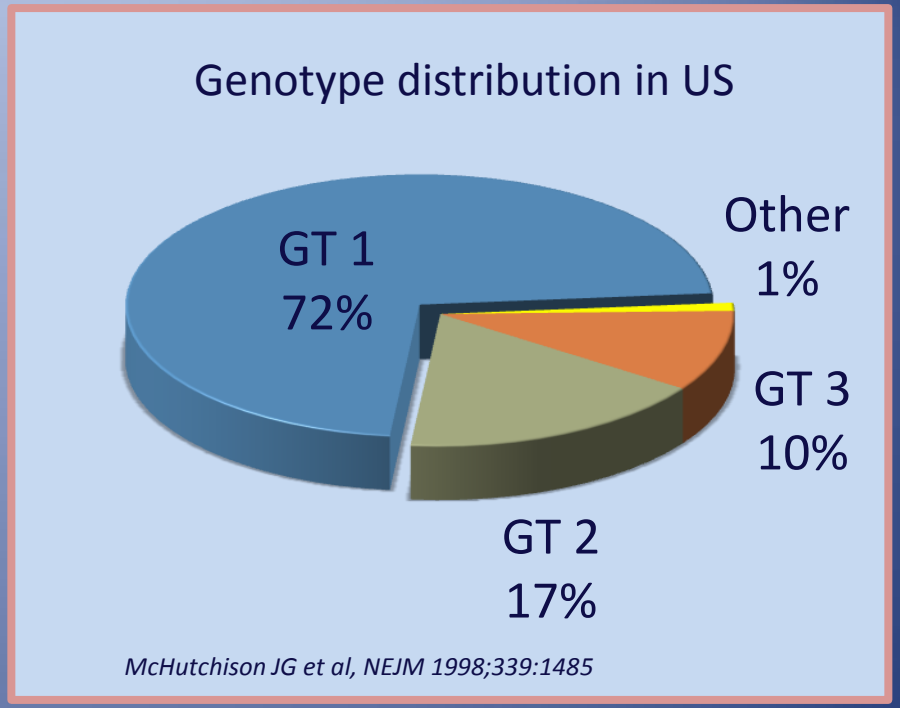
Shiffman ML, et al J Infect Dis. 2000;182:1595 – 1601.

HCV Viral Load

- **No indication to repeat viral load to assess severity of liver disease**
- **Indications**
  - **Diagnosis of chronic HCV**
  - **Assessment of response in patients on treatment**
- Routine monitoring of HCV viral load in patients not on treatment is not warranted
  - HCV RNA did not change significantly in 25 patients followed for 5 years
- HCV RNA levels do not correlate with degree of inflammation and fibrosis on liver biopsy

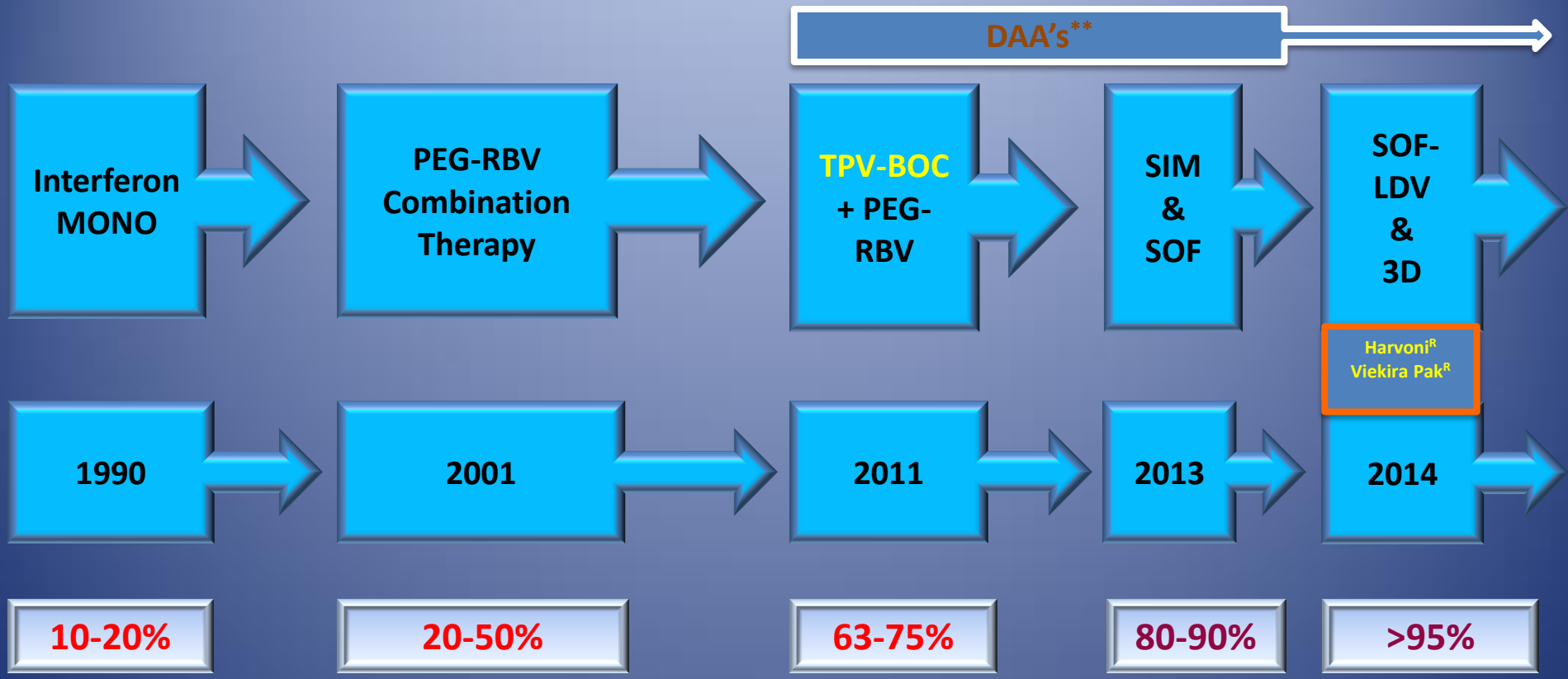
HCV GENOTYPE

- 6 major Genotypes
  - GT1-3: Worldwide
  - GT 4: Middle East, Africa
  - GT 5, 6: South Africa, SE Asia
- Multiple subtypes
  - GT 1a,b,c; GT 2a,b,c; GT 3a,b
- Utility of genotype:
  - Predicts treatment regimen
  - Predicts treatment response
  - Determines treatment duration
- HCV genotyping should only be done **ONCE**



Nov 24, 2014 09:35	TYPE 1A
Jul 21, 2014 09:26	TYPE 1a
Aug 12, 2013 09:02	TYPE 1A
Jun 19, 2012 09:55	TYPE 1a
Nov 04, 2009 09:07	TYPE 1a
Oct 27, 2009 09:02	
Aug 20, 2009 10:57	
Jul 23, 2009 09:13	
Jun 25, 2009 12:22	
Mar 04, 2009 09:17	TYPE 1a
Mar 04, 2009 09:17	TYPE 1a
Jan 20, 2009 09:12	
Dec 31, 2008 08:50	TYPE 1a
Dec 31, 2008 08:50	

HCV Therapy & SVR*: Past-Present- Future



SVR* rates in treatment naïve genotype 1 patients

SVR = Sustained Virologic Response or "cure"

***DAA = Direct Acting Antiviral*

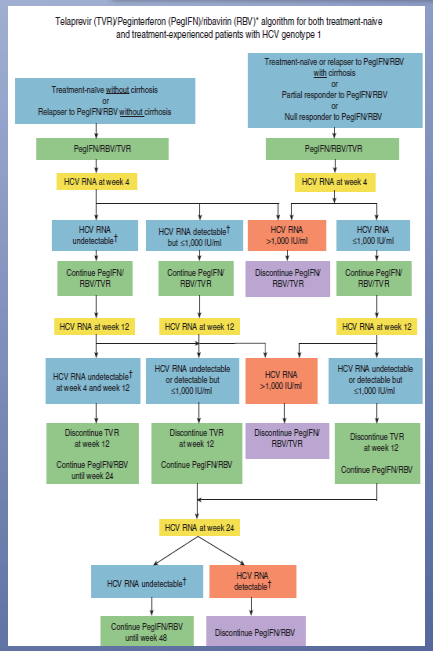
Past Regimens Very Complicated

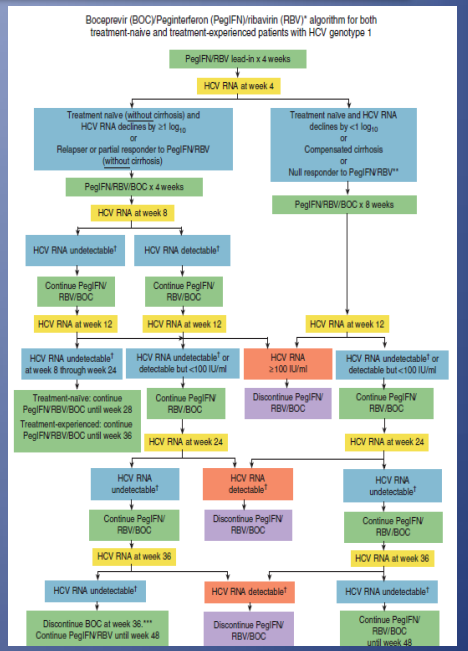
Pill Burden

TID Dosing

Boceprevir = 12/d + RBV = 4-7/d		Telaprevir = 6/d + RBV = 4-7/d	
Morning 6 : 30 am	2 # ribavirin	Morning 6 : 30 am	2 # ribavirin
Afternoon 2 : 30 pm	2 # ribavirin	Afternoon 2 : 30 pm	2 # ribavirin
Night 10 : 30 pm		Night 10 : 30 pm	
Peginterferon		Peginterferon	

Response-Guided Therapy



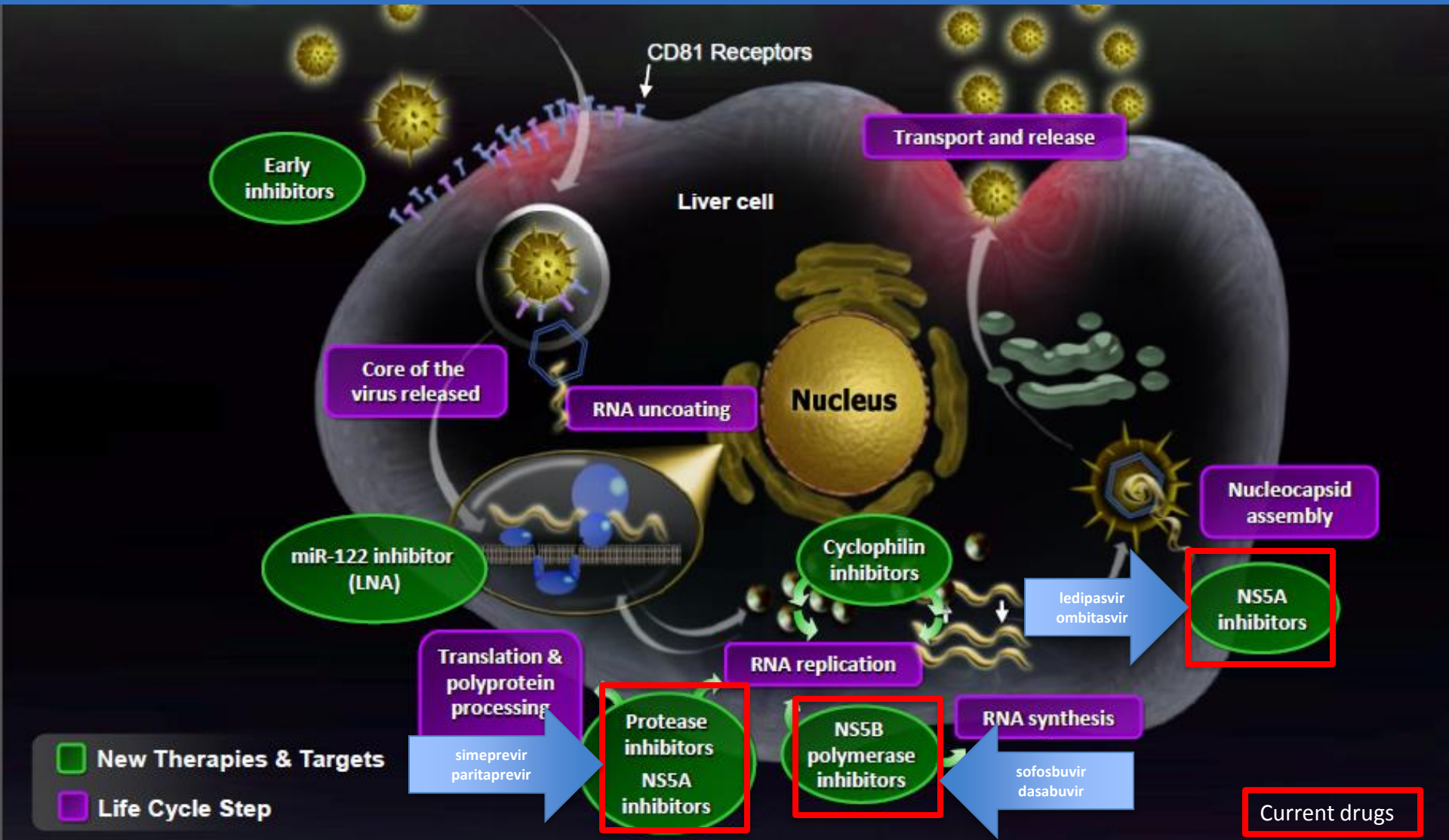


Yee et al. *Am J Gastroenterol*. 2012;107:669-689.

Food Requirement

AEs

HCV Life Cycle and New HCV Treatment Targets



From: Philippe Halfon presented at: Workshop sur la prise en charge des patients infectes VIH-VHC; November 2012.

GOALS OF TREATMENT

- ***Primary goals***
  - Eliminate detectable HCV-RNA 12 weeks after completion of treatment(SVR)
    - "cure"
    - Durability: 99% remain HCV negative for >10 years
- ***Secondary goals***
  - Prevent HCV-related complications
    - ESLD
    - Liver transplant
    - HCC

DRUG THERAPY

FDA APPROVED AGENTS

DRUG	DOSE
PEG-INF alfa-2a(PEGASYS)	180mcg SC once weekly
PEG-INF alfa-2b(PEG-INTRON)	1.5mcg/kg SC once weekly
Boceprevir	***800mg po every 7-9 hours po with food***
Telaprevir	***750mg po every 7-9 hours po with 20g fat***
Simeprevir	150mg po once daily
Ribavirin*	**1,000-1,200mg/day po**
Sofosbuvir(Sovaldi^{R})*	**400mg once daily po**
Sofosbuvir/lepdipasvir(Harvoni^{R})*	**400mg/90mg once daily po**
r-ombitasvir/paritaprevir/dasabuvir(Viekira Pak^{R})*	**r-ombitasvir/parateprevir po QD dasabuvir 250mg po BID**

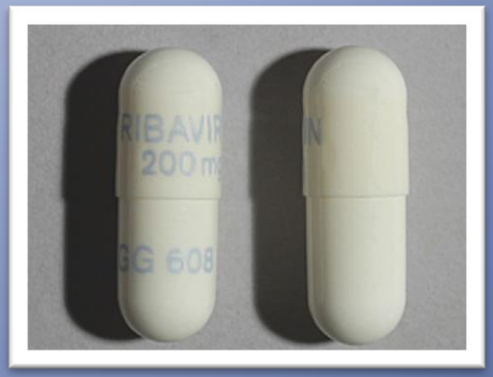
**Primary Drugs*

INTERFERON

- Pharmacology
  - Backbone of prior treatment regimens
  - Numerous contraindications
- Adverse Events
  - Flu-like symptoms
    - Fever, chills
    - HA
    - Myalgias/arthralgias
  - Fatigue
  - Anorexia, N/V/D
  - Thyroid alterations
  - Thrombocytopenia
  - Neutropenia
  - Anemia
  - Depression
  - Mood swings, irritability

RIBAVIRIN

- Pharmacology
  - Limited antiviral activity when used as monotherapy
  - Decreases relapse rates
  - Not used in all regimens

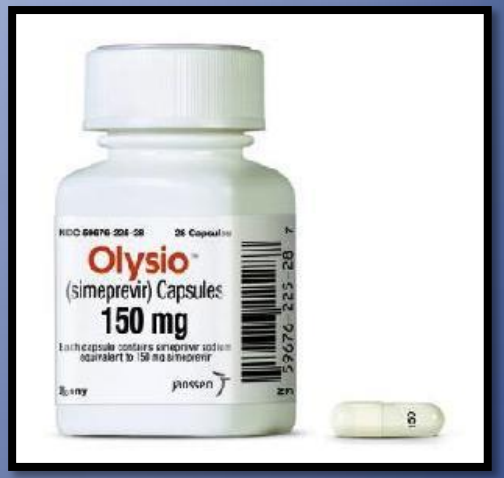


- Adverse effects
  - ***Hemolytic anemia***
    - ***Dose dependent***
  - Cough, rash
  - ***Teratogenicity (Primary and partner)***
    - ***Dual contraception until 6 months after ribavirin d/c'd***
    - ***Baseline & monthly pregnancy test for women***

- Dosing
  - <75kg: 1,000mg day
    - 400mg AM & 600mg PM
  - ≥75kg: 1,200mg/day
    - 600mg AM & 600mg PM

SIMEPREVIR(Olysio^{R})

- Mechanism of action: protease inhibitor
- Used in genotype 1 only
- Low barrier to resistance
  - Cannot use if previously treated with a PI

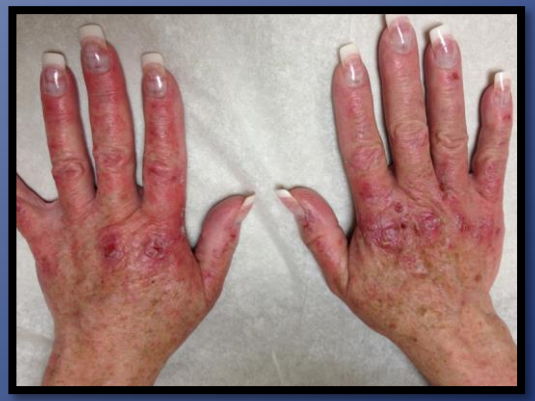


- Not a 1st line agent
- Used in combination with sofosbuvir in cirrhotic patients prior to FDA approval of sofosbuvir/ledipasvir(Harvoni^{R}) and *ritonavir-ombitasvir/paritaprevir/dasabuvrir* (Viekira Pak^{R})

- Dose: 150mg po daily with food

ADVERSE EVENTS & DRUG INTERACTIONS

- Adverse Events
  - Anemia, neutropenia
  - Rash, pruritis
  - ***Photosensitivity***
    - ***Most common in 1st 4 weeks***
    - ***Appears as an exaggerated sunburn in áreas exposed to light***
  - Dyspnea
  - Hyperbilirubinemia
- Drug Interactions
  - Inhibits intestinal CYP3A4
  - Metabolized by hepatic CYP3A4
  - Caution with CYP3A4 inhibitors/inducers



SOFOSBUVIR(Sovaldi^{R})

- MOA: NS5B polymerase inhibitor
- Efficacy established in HCV GT 1, 2, 3, & 4
- Not used as monotherapy
- One 400mg tablet daily with or without food
- No CYP450 involvement
- Eliminated primarily via renal clearance
  - Safety/efficacy not established in CrCl<30ml/min
- Adverse events: fatigue, headache
- Drug interactions
  - Sofosbuvir is a substrate of P-gp
  - Anticonvulsants, rifampin, St. John's Wort, tipranavir/ritonavir

Sofosbuvir/Ledipasvir(Harvoni^{R})

- Class/Mechanism of Action
  - Ledipasvir: NS5A inhibitor
  - Sofosbuvir: NS5B polymerase inhibitor
- Dosage
  - Once-daily, oral fixed-dose (400/90 mg) combination tablet
  - Take with or without food
- Adverse effects: fatigue, headache
- ≥95% SVR rate with 12 weeks of treatment
  - Can consider 8 weeks of treatment in treatment naïve patients w/out cirrhosis who have a pretreatment viral load < 6,000,000 IU/ml

Drug Interactions

- **Acid reducing agents:**
  - H2RA: Do not exceed the equivalent of famotidine 40 mg twice daily and administer simultaneously with SOF/LDV or separate by 12 hours
  - PPI: Dose comparable to omeprazole 20 mg may be administered simultaneously with SOF/LDV under fasted conditions
  - Antacids should be separated by 4 hours
- Almost all seizure medications are contraindicated
- LDV is a substrate of P-gp in addition to being a weak P-gp inhibitor and OATP inhibitor
  - Caution warranted for narrow therapeutic index drugs, such as digoxin
  - Rosuvastatin is not recommended
  - St. Johns Wort
  - Rifampin
- Caution with
  - Antiarrhythmics
  - Antimycobacterials
  - HIV antiretrovirals

CLINICAL TRIALS SUBMITTED TO FDA
Sofosbuvir-Ledipasvir

STUDY	POPULATION	REGMENS	SVR12
ION-1	Treatment naïve GT-1 w or w/out cirrhosis	LDV/SOF x 12 WKs	99% (210/213)
ION-2	Treatment experienced GT-1 w/ or w/out cirrhosis who failed PEG/RBV +/- PI	LDV/SOF x 12 WKs LDV/SOF x 24 WKs	94% (102/109) 99% (108/109)
ION-3	Treatment naïve GT-1 w/out cirrhosis	LDV/SOF x 8 WKs LDV/SOF x 12 WKs	94% (202/215) 96% (208/216)

Ombitasvir-Paritaprevir-Ritonavir + Dasabuvir (Viekira Pak^{R})

- Regimen components
  - Ombitasvir: NS5A inhibitor
  - Paritaprevir: protease inhibitor
  - Ritonavir: HIV protease inhibitor used as pharmacologic booster
    - No HCV activity
  - Dasabuvir: NS5B polymerase inhibitor
- Dosage form
  - ombitasvir/-paritaprevir-ritonavir(fixed dose 12.5/75/50mg)
  - Dasabuvir: 250mg tablet
- Dosing
  - 2 ombitasvir/-paritaprevir-ritonavir(fixed dose 12.5/75/50mg) tablets in the AM with food
  - 1 dasabuvir 250mg tablet BID with food
  - Weight-based ribavirin dosing: 1,000 mg if ≤ 75 kg, 1,200 mg if > 75 kg
    - Dosage divided and taken BID with food
  - No dose adjustment for hepatic or renal impairment
  - No dosage adjustment needed in patients with CrCl ≥ 15 mL/min
- **SVR rates >95% in treatment naïve, non-cirrhotic patients**

ADVERSE EVENTS & DRUG INTERACTIONS

- Adverse events
  - Nausea
  - Pruritus
  - Insomnia

- Drug interactions
  - Contraindicated with
    - Drugs dependent on CYP3A for clearance
    - Strong CYP3A and CYP2C8 inducers
    - Strong CYP2C8 inhibitors

    - Common contraindicated drugs(not a complete list)
      - Carbamazepine, phenytoin, phenobarbital
      - Ethinyl-estradiol containing products
        - » Discontinue prior to use of Viekira Pak^{R}
        - » Resume 2 weeks after completing Viekira Pak^{R}
      - Lovastatin, simvastatin
      - St. John's Wort

- UGT1A1 inhibitors
  - OMB, PAR, DSB
- OATP inhibitors
  - PAR
- BRCP inhibitors
  - PAR, RTV, DSB
- 3A4 substrates
  - PAR, RTV
- 2C8 substrates
  - DAS
- P-gp substrates
  - OMB-PAR-DAS- RTV
- BRCP substrates
  - OMB-PAR-DAS
- OATP substrates
  - PAR

DRUG INTERACTION RESOURCES

CLINICAL TRIALS SUBMITTED TO FDA

Ombitasvir-Paritaprevir-Ritonavir + Dasabuvir

STUDY	POPULATION	REGIMEN	SVR12		
SAPHIRE-I	Treatment naïve GT-1 w/out cirrhosis	Viekira Pak + RBV x 12 wks	GT1a:	96%	(308/322)
SAPHIRE-II	Treatment experienced GT-1 w/out cirrhosis	Viekira Pak + RBV x 12 wks	GT1a:	96%	(166/173)
PEARL-II	Treatment experienced GT-1b w/out cirrhosis	Viekira Pak + RBV x 12 wks	Not provided		
		Viekira Pak x 12 wks	GT1b:	100%	(91/91)
PEARL-III	Treatment naive GT-1b w/out cirrhosis	Viekira Pak + RBV x 12 wks	Not provided		
		Viekira Pak x 12 wks	GT1b:	100%	(209/209)
PEARL-IV	Treatment naïve GT-1a w/out cirrhosis	Viekira Pak + RBV x 12 wks	GT1a:	97%	(97/100)
		Viekira Pak x 12 wks	Not provided		
TURQUOISE-II	Treatment naïve & experienced GT-1 w/ cirrhosis	Viekira Pak + RBV x 12 wks	GT1a: GT1b:	89% 99%	(124/140) (67/68)
		Viekira Pak + RBV x 24 wks	GT1a:	95%	(115/121)

CURRENT TREATMENT REGIMENS

GT	SVR*(%)	REGIMEN	TREATMENT DURATION
1	>95%	• sofosbuvir-ledipasvir • r-ombitasvir/paritaprevir/dasabuvir ± ribavirin	8-12* weeks
2	97%	sofosbuvir + ribavirin	12 weeks
3	63% 100%	• sofosbuvir + ribavirin • sofosbuvir + ledipasvir + ribavirin	24 weeks 12 weeks
4	97	PEG-INF + RBV + sofosbuvir	12 weeks

**treatment naïve patients w/out cirrhosis with a pretreatment viral load < 6,000,000 IU/ml can be treated for 8 weeks*

PATIENT MEDICATION HANDOUTS

Taking Your Hepatitis C Therapy: SOFOSBUVIR

Sofosbuvir

GSI

- Dose: 1 tablet (400 mg), taken at the same time each day, with or without food
- Store at room temperature (<86° F) away from direct sunlight

Ribavirin

riba 200 | riba 200

- You will be given 200 mg capsules or tablets; your dose will be based on your weight and may change during the course of treatment
- Take with food to minimize stomach upset such as nausea and vomiting
- Use sunscreen and limit sun exposure
- Do not consider pregnancy until at least 6 months after treatment for either partner has ended

Do You Need to Take Peginterferon? Yes ☐ No ☐

- You may or may not be prescribed Peginterferon
- If Peginterferon is prescribed, you will be given prefilled syringes or pens; store in the refrigerator
- Dose: ☐ Pegasys® _____mcg/week or ☐ Peg-Intron® _____mL (_____mcg)/week
- This medication is injected once weekly–take it the same day, same time

My Medication Schedule

Start Date: _____ End Date: _____ Total Expected Treatment Duration: _____ weeks

Morning	Evening	Inject weekly Yes ☐ No ☐
Time: _____ am	Time: _____ pm	Day_____ Time: _____ am/pm
Ribavirin Take ____ ribavirin with food	Ribavirin Take ____ ribavirin with food	Peginterferon _____ mcg per week
GSI Sofosbuvir Take 1 tablet		

Note: You can choose to take **sofosbuvir** together with **ribavirin** or at a separate time of day, but be sure to take it at the same time each day.

If You Miss a Dose:

Sofosbuvir:

- If you miss a dose, TAKE THE MISSED DOSE THE SAME DAY as soon as you remember; take your next dose of sofosbuvir at your regular time the next day
- Do not take more than 1 tablet of sofosbuvir in a day
- If you miss multiple doses, call your prescriber/clinic listed below

Ribavirin:

- If you miss more than 1-2 days of ribavirin, call your prescriber/clinic listed below

Prescriber/Clinic Contact: _____

For Refills: _____

TAKING YOUR HEPATITIS C MEDICATIONS

VIEKIRA PAK(ombitasvir/parataprevir/ritonavir) ☐

Pink tablet: ombitasvir-paritaprevir-ritonavir

Beige tablet: dasabuvir

EVERY MORNING*(about the same time)*

- Take 2 pink tablets and 1 beige tablet **WITH FOOD**

EVERY EVENING*(about the same time)*

- Take 1 beige tablet with or without food.

- **MISSED DOSES**

Pink Tablets(ritonavir-ombitasvir-paritaprevir)

- If you miss a dose and it is less than 12 hours from your last dose, **TAKE THE MISSED DOSE** with a meal and resume your normal schedule.
- If you miss a dose and it is more than 12 hours from your last dose, **SKIP THE MISSED DOSE** and resume your normal schedule.

Beige Tablets(dasabuvir)

- If you miss a dose and it is less than 6 hours from your last dose, **TAKE THE MISSED DOSE** with a meal and resume your normal schedule.
- If you miss a dose and it is more than 6 hours from your last dose, **SKIP THE MISSED DOSE** and resume your normal schedule.

Never take more than your prescribed dose of either medication to make up for a missed dose.

Start date: __/__/_____ Stop date: __/__/_____ Duration: _____ weeks

RIBAVIRIN ☐

- You will be given 200mg capsules. Your dose may change during the course of treatment.
- *Take 1 2 3 capsule(s) every morning along with the 2 pink tablets and 1 beige tablet.*
- *Take 1 2 3 capsule(s) every evening along with the beige tablet.*
- Take with food to minimize stomach upset such as nausea and vomiting.
- *If you miss more than 1-2 doses, call your prescriber/clinic listed below.*

WB GI/HEP PharmD. Clinic Michael J. Surdy, PharmD. 570-824-3521 ext 4995 or 4150