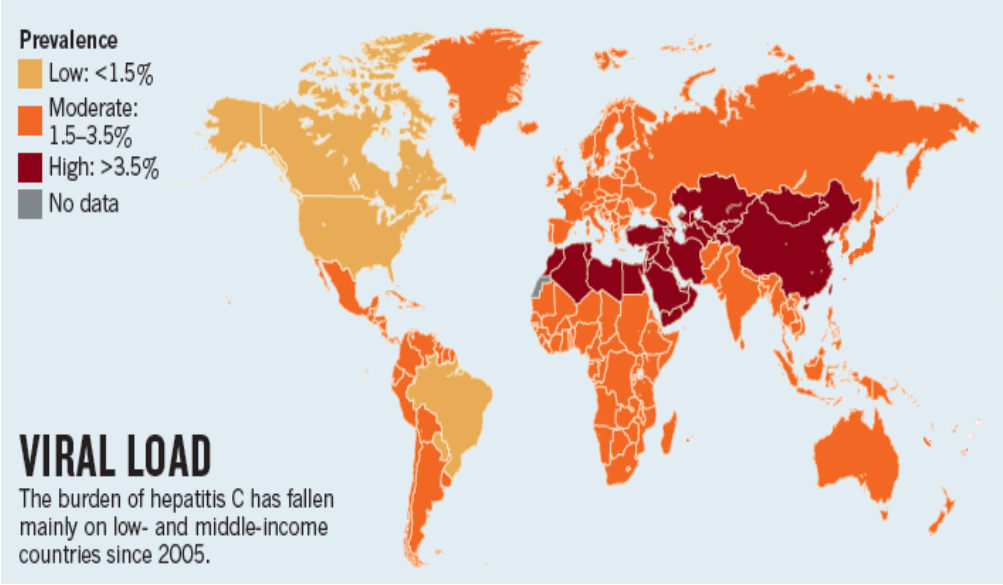
The Changing Landscape of Hepatitis C Testing and Therapy

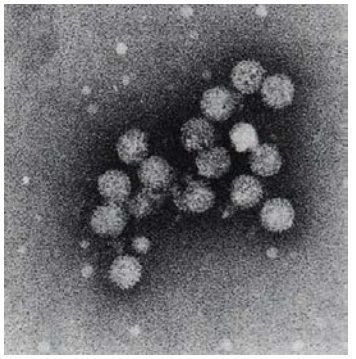
David R Hillyard MD
Professor, Pathology
University of Utah School of Medicine
9-30-2015

Hepatitis C Virus (HCV)

- Flaviviridae family
- Recent widespread human transmission
  - Transfusion services
  - ID drug use
- Chronic HCV Infection
  - 3.8 million U.S.
  - >130 million worldwide
- Most chronic infection undiagnosed

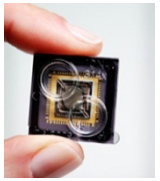


Discovery HCV



- Search for basis of non-A, non-B hepatitis
  - 85% of blood transfusion hepatitis
  - DNA or RNA virus?
- Purify nucleic acid from infected chimpanzee
- Copy and clone into bacteriophage λgt11
- Identify clones expressing viral proteins using antibodies from non-A, non-B patient

Ron Davis



Ion Torrent and much much more!

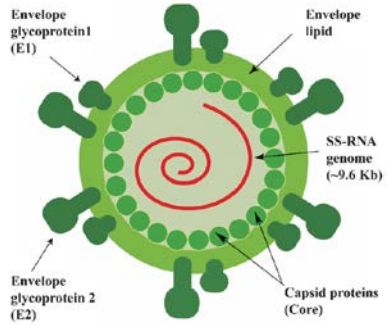
"It is not unrealistic to expect that other elusive agents may now be recognized using similar approaches"

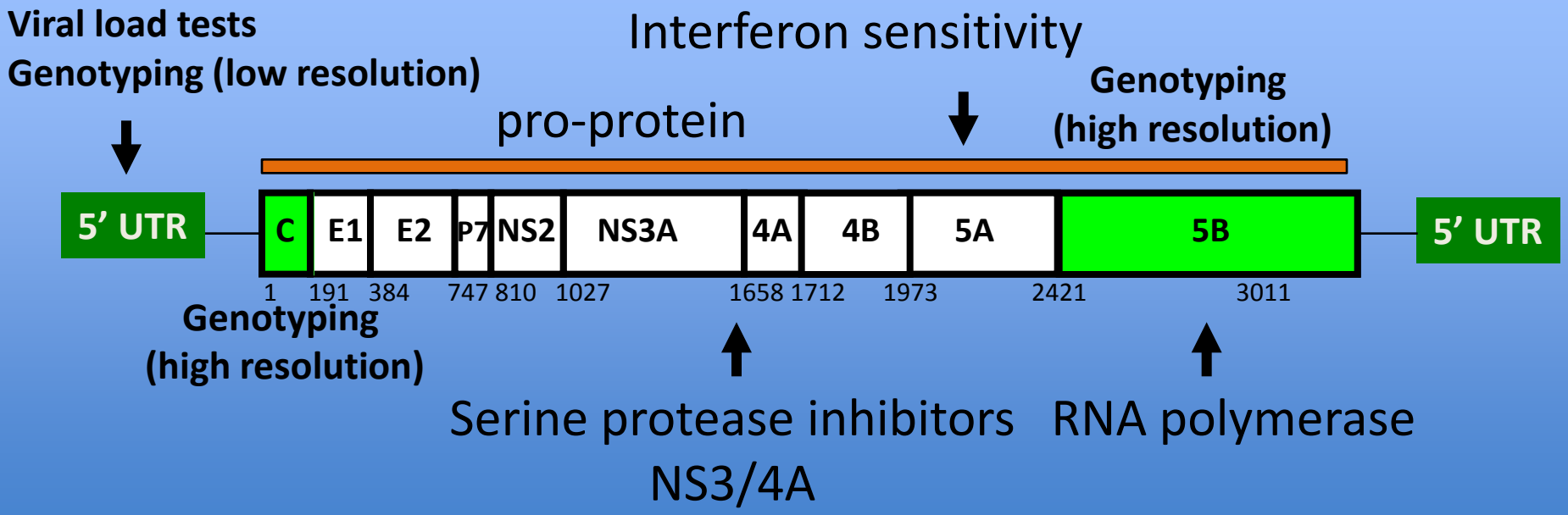
Harvey Alter Annals of Internal Medicine 1991

-Genome ssRNA

-Replicates in hepatocytes

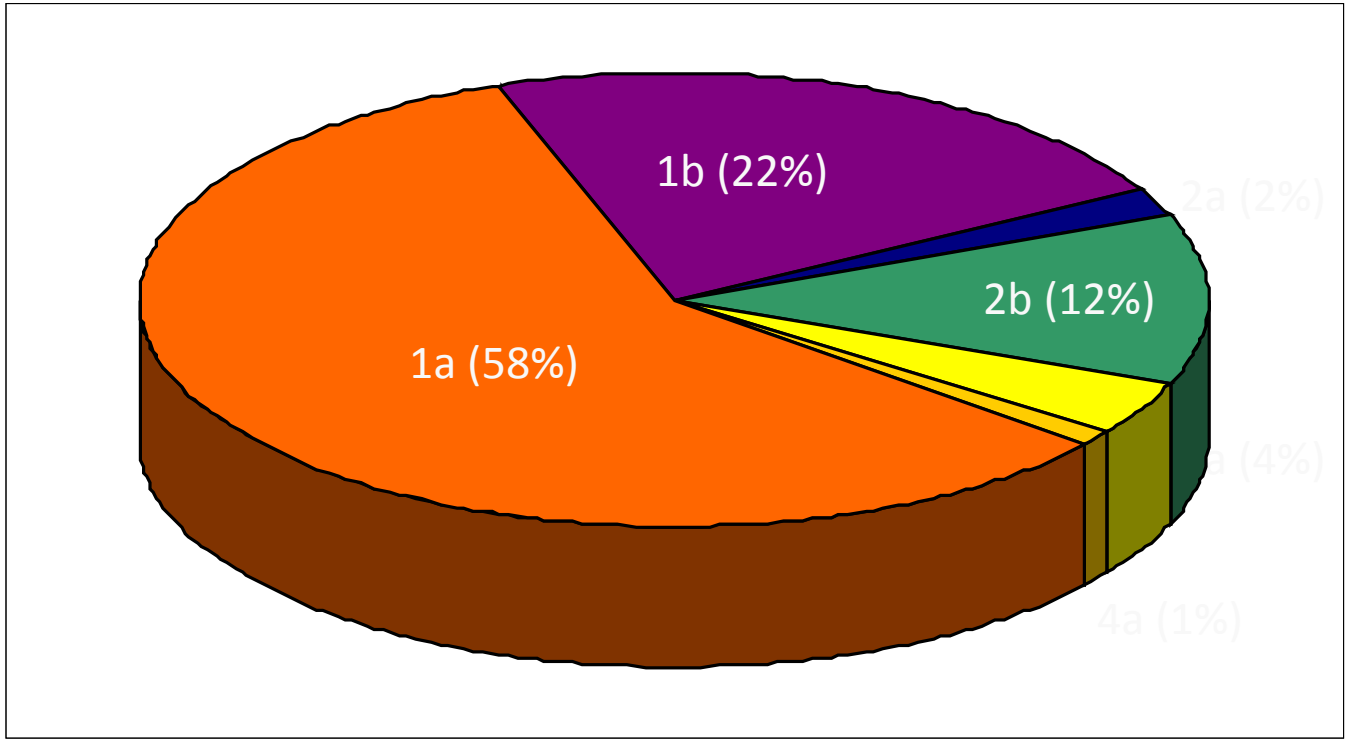
-HCV genome does not integrate into host genome allowing spontaneous clearance and therapeutic cures





HCV Genotypes 1-7

-Multiple Subtypes (a,b,c …)
-Type 1 virus most common in the US and most challenging to treat
-Assays and therapies optimized to type 1 virus



Genotype and subtype used to inform:

-Selection of therapy
-Length/duration of therapy
-Likelihood of resistance mutations

GENOTYPE	SUBTYPE (total=84)
1	a,b c,d,e,f,g,h,i,j,k,l,m (13)
2	a,b,c,d,e,f,g,h,i,j,k,l,m,n,o,p,q,r (18)
3	a,b,c,d,e,f,g,h,i,k (10)
4	a,b,c,d,e,f,g,h,i,j,k,l,m,n,o,p,q,r,s,t,u (21)
5	a (1)
6	a,b,c,d,e,f,g,h,i,j,k,l,m,n,o,p,q,r,s,t (20)
7	a (1)

Confirmed subtypes Provisional subytpes

Provisional subtypes added since 2005

Combet et al. 2007; http://euhcvdb.ibcp.fr/euHCVdb

Natural History of Hepatitis C

Acute Hepatitis C
(rarely diagnosed)

↓ 85%

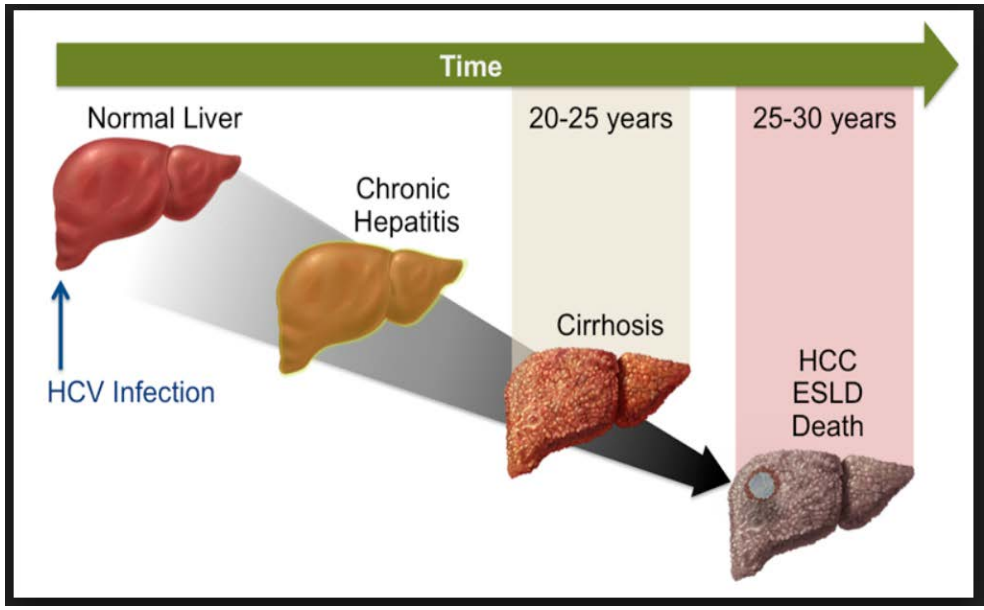
Chronic Hepatitis C

↓ 20%

Cirrhosis

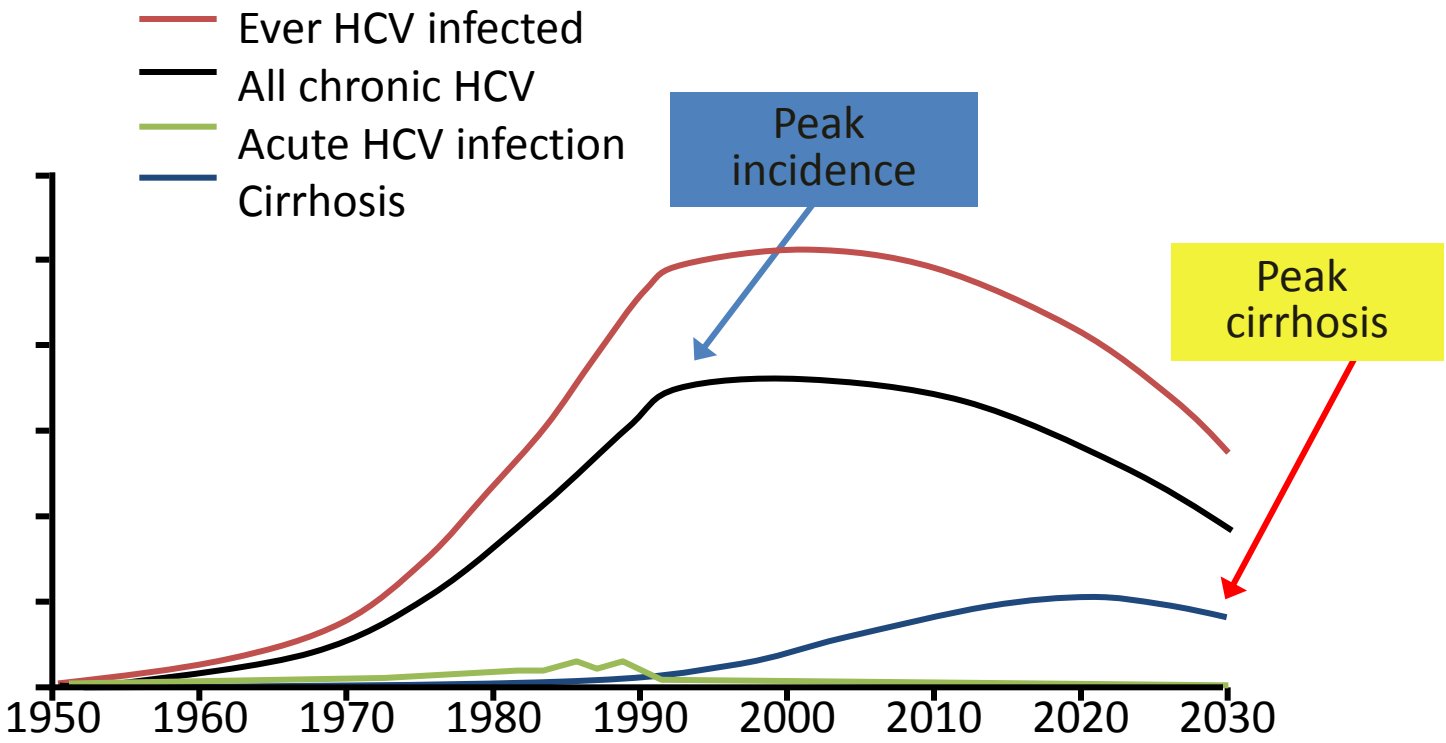
↓ 1-5%

Liver cancer



- #1 cause of cirrhosis
- #1 cause of liver failure
- 10,000 death per year
- #1 cause for liver transplant in the US

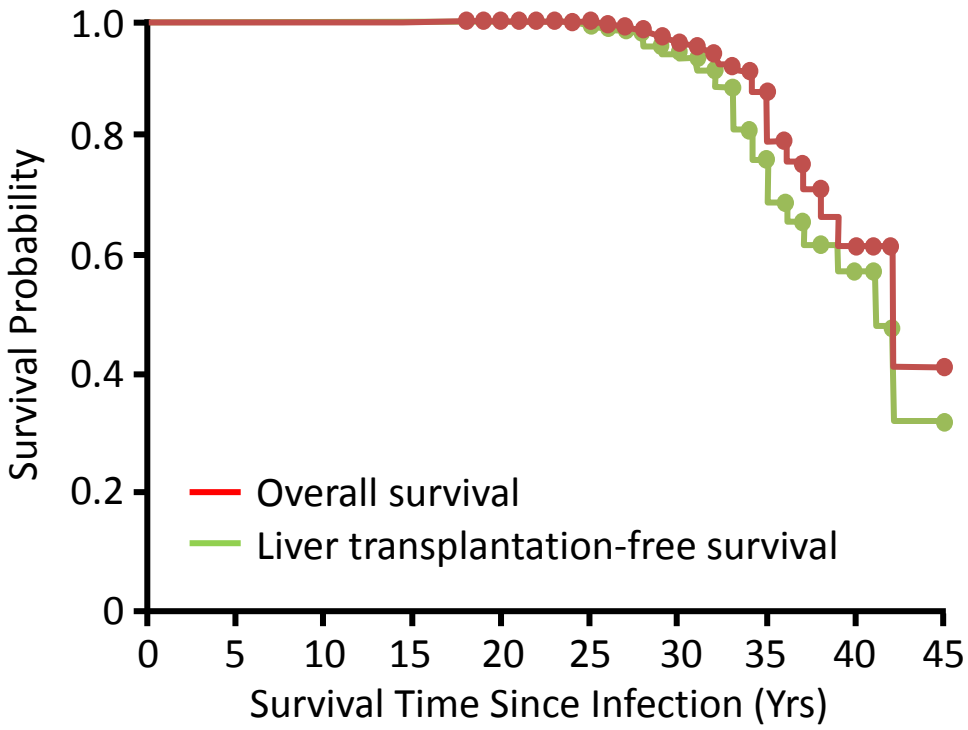
The Changing Face of HCV in the US



Reprinted from Gastroenterology, 138, Davis GL, et al, Aging of hepatitis C virus (HCV)-infected persons in the United States: a multiple cohort model of HCV prevalence and disease progression, 513-521, Copyright 2010, with permission from Elsevier. **Clinical Care Options 2010.**

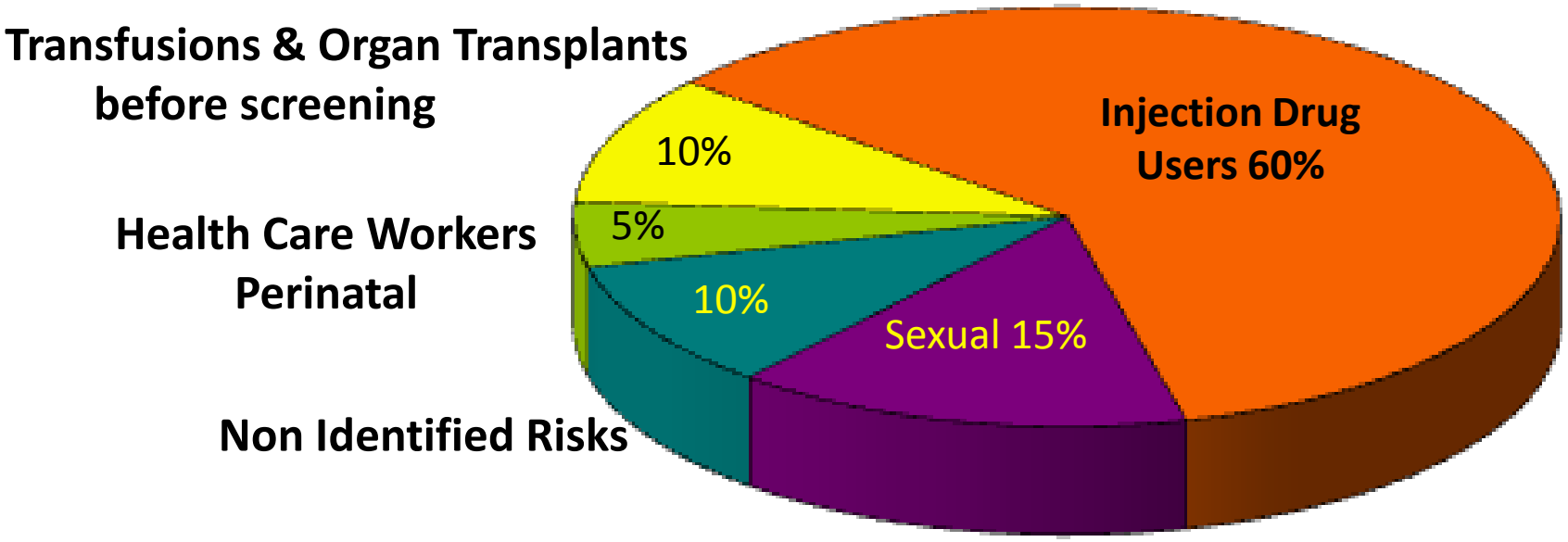
Natural History of Chronic HCV Progression

- Chart review of 485 plasma donors infected in Austria during 1970s (mean follow-up: 31 yrs)



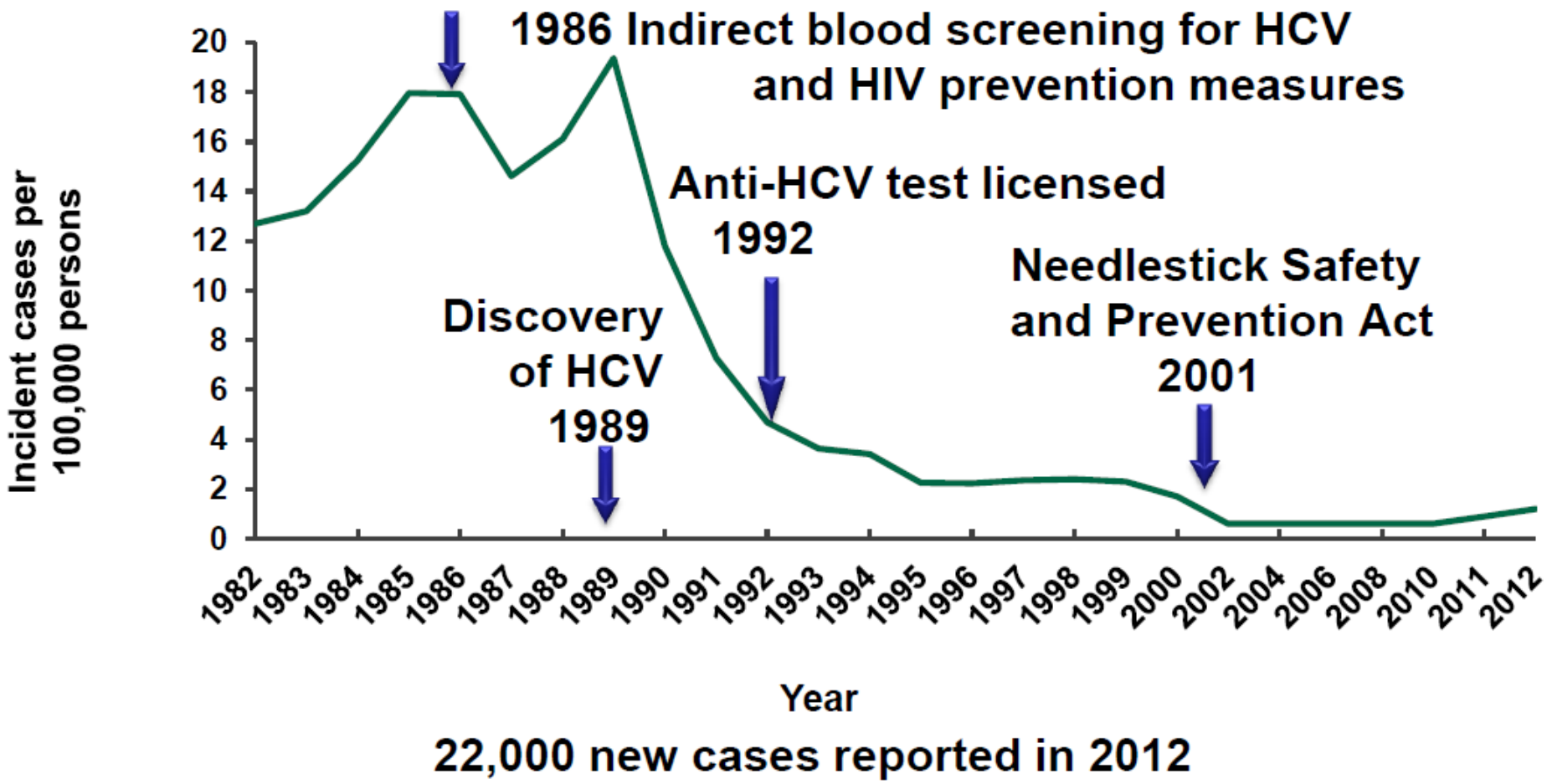
- First liver transplant: 18 yrs after infection
- First death: 28 yrs after infection

Risk Factors - HCV Transmission



Source: Centers for Disease Control and Prevention

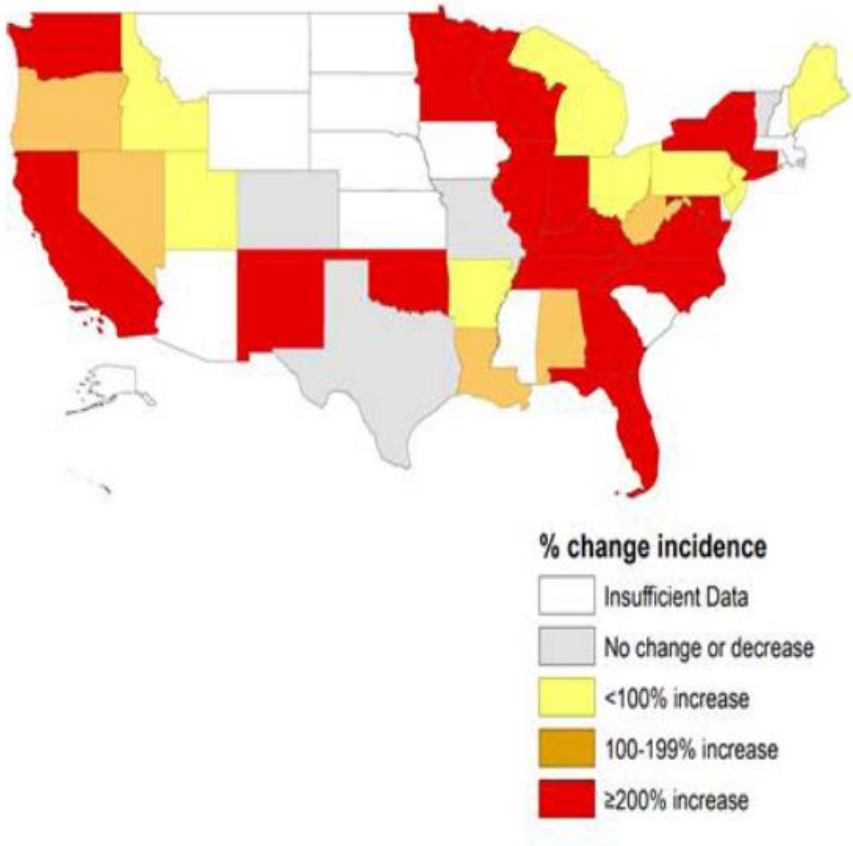
HCV Prevention



Jagger J, *J Infect Dis Pub Health* 2008. Ward JW. *Clin Liver Dis,* 2013. CDC.gov/hepatitis

Recent Increase in HCV Infection

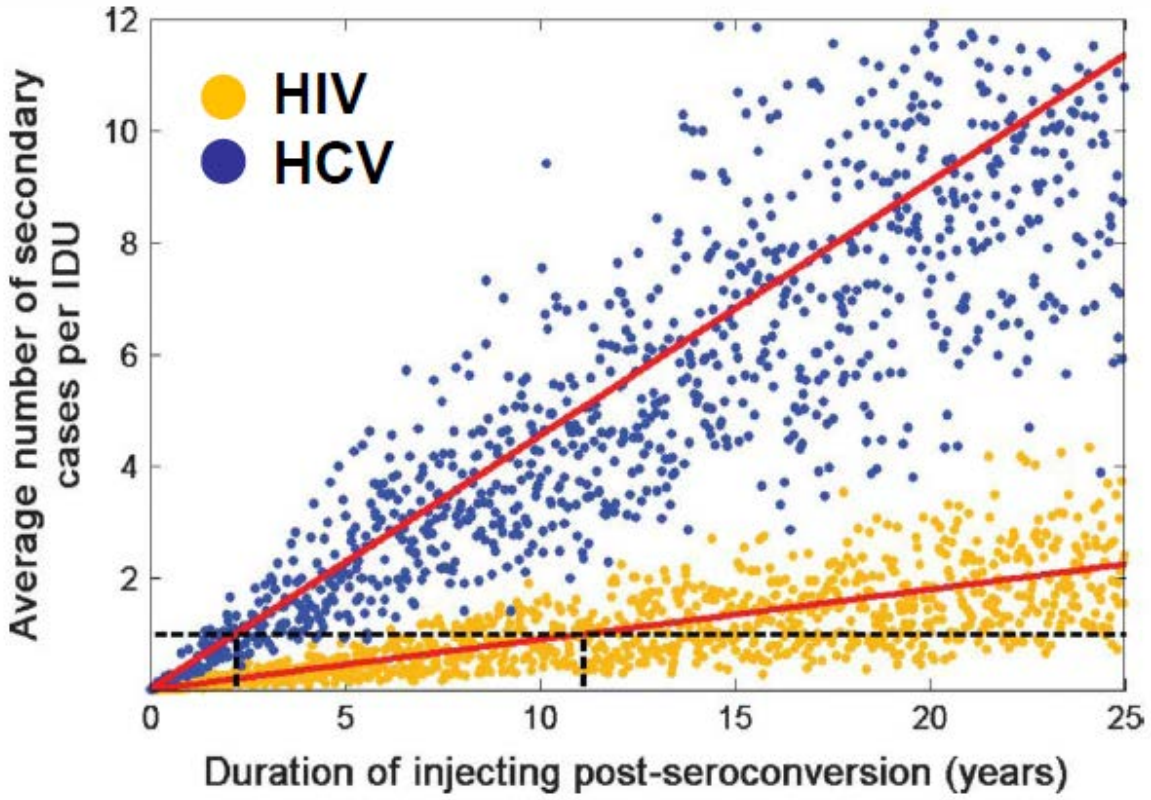
- Between 2007 to 2012
  - 50% increase in case reporting
  - 200% increase in 17 states
- Risk factors
- ~ 70% persons who inject drugs
- Previous oral prescription narcotic use
- Equally male to female
- Young, ages 18-29 years
- Rural and suburban
- White



J. Ward http://www.cdc.gov/cdcgrandrounds/archives/2014/june2014.htm

Transmission Among Persons Who Inject Drugs

- Transmission risks
  - injection duration
  - Injection frequency
  - Equipment sharing
- HCV prevalence
  - 27 to 51%
- Incidence declined in response to HIV harm reduction (syringe access programs)



Burt, *J Urban Health* 2007. Garfein R, *J Urban Health* 2013. Keen L, *Addict Behav* 2014. Amon JJ, *Clin Infect Dis* 2008 Kwon J, *AIDS* 2009.

Other Modes HCV Transmission

- **Accidental needle stick in healthcare setting**
  - HCV risk is 1.3%, HIV risk is 0.3%
- **18 healthcare-associated outbreaks from 2008 to 2013**
  - 223 cases involving over 90,550 at-risk persons notified
- **Non-injecting drug use (e.g., intranasal cocaine use)**
- **Perinatal-infants born to HCV infected mothers**
  - ~4% risk if mother infected with HCV
  - ~25% risk if mother co-infected with HCV and HIV
- **Sexual transmission is rare**
  - HIV infected MSM at highest risk
- **Miscellaneous reported**
  - Unregulated tattooing

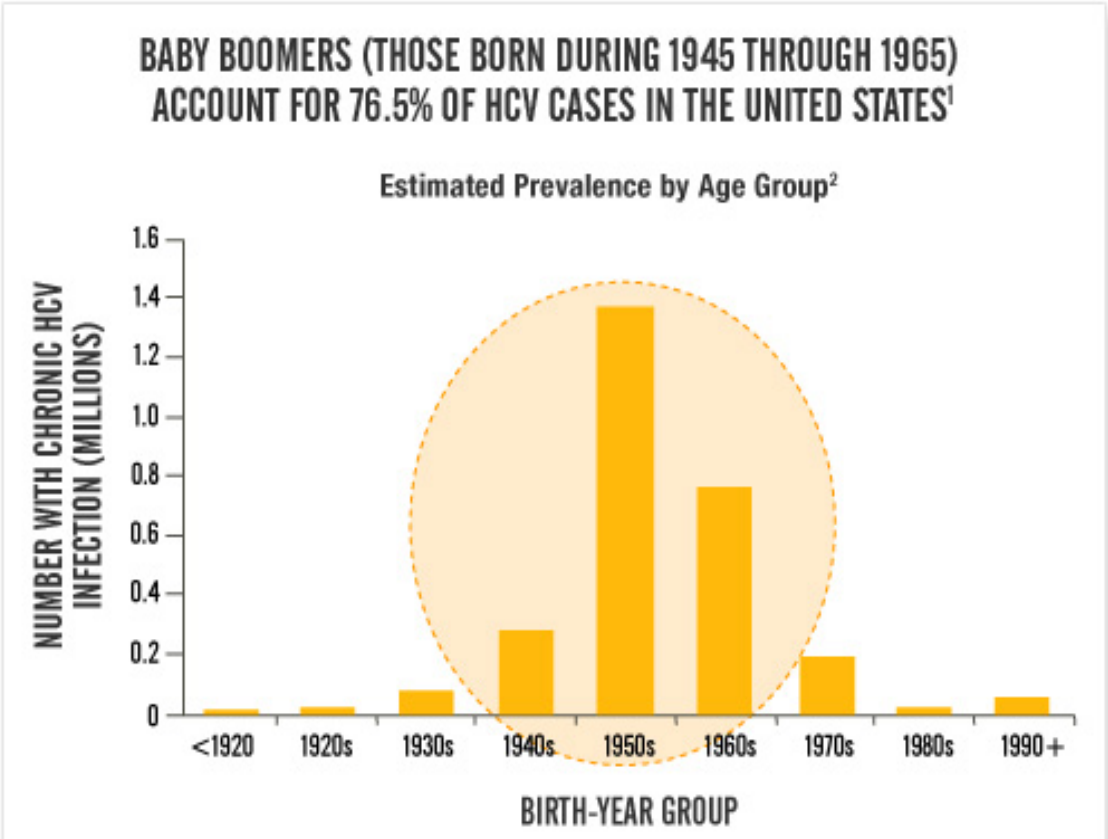
From J. Ward http://www.cdc.gov/cdcgrandrounds/archives/2014/june2014.htm
Scheinmann, *Drug and Alcohol Dependence* 2006. Weinbaum, *MMWR* 2003. Gough, *BMC Public Health* 2010. Mast, *J Infect Dis,* 2005. Marincovich B, *Sex Transm Infect* 2003. Yaphe S, *Sex Transm Inf* 2012. Bottieau, *Eurosurveillance* 2010. Ackerman Z, *J Viral Hepat* 2000. Tohme RA, *CID* 2012. *MMWR* 2001. CDC/hepatitis.gov

Bending the HCV Outcomes Curve

- Estimated 45% to 85% of HCV persons with chronic HCV are unaware of infection
- Screening strategies have been based on risk*
  - Blood transfusion before 1992, IV drug exposure
  - Many in highest risk cohort do not identify themselves
- Recent treatments only ~ 50% effective, expensive
  - Many identified persons have elected to wait for better drugs which are now available (Combination DAAs)

MMWR Rep. 1998;47(RR-19):1-39. [PMID: 9790221 *

- In 2012 the CDC issued guidelines recommending a one-time anti-HCV antibody test for all baby boomers (those born during 1945 through 1965), although those at high risk should be tested regularly MMWR Recomm Rep. 2012;61(RR-4):1-32.



Other Screening Indications

- Persons who have injected drugs (once)
- Persons with conditions associated with HCV
  - HIV
- Elevated aminotransferase (ALT)
- Hemodialysis
- Transfusions/organ transplants prior to 1992
- Children of HCV infected mothers
- Exposed healthcare workers
- Sexual partners of HCV infected individuals *

Laboratory Testing for HCV Infection

- Serology - anti-HCV antibodies

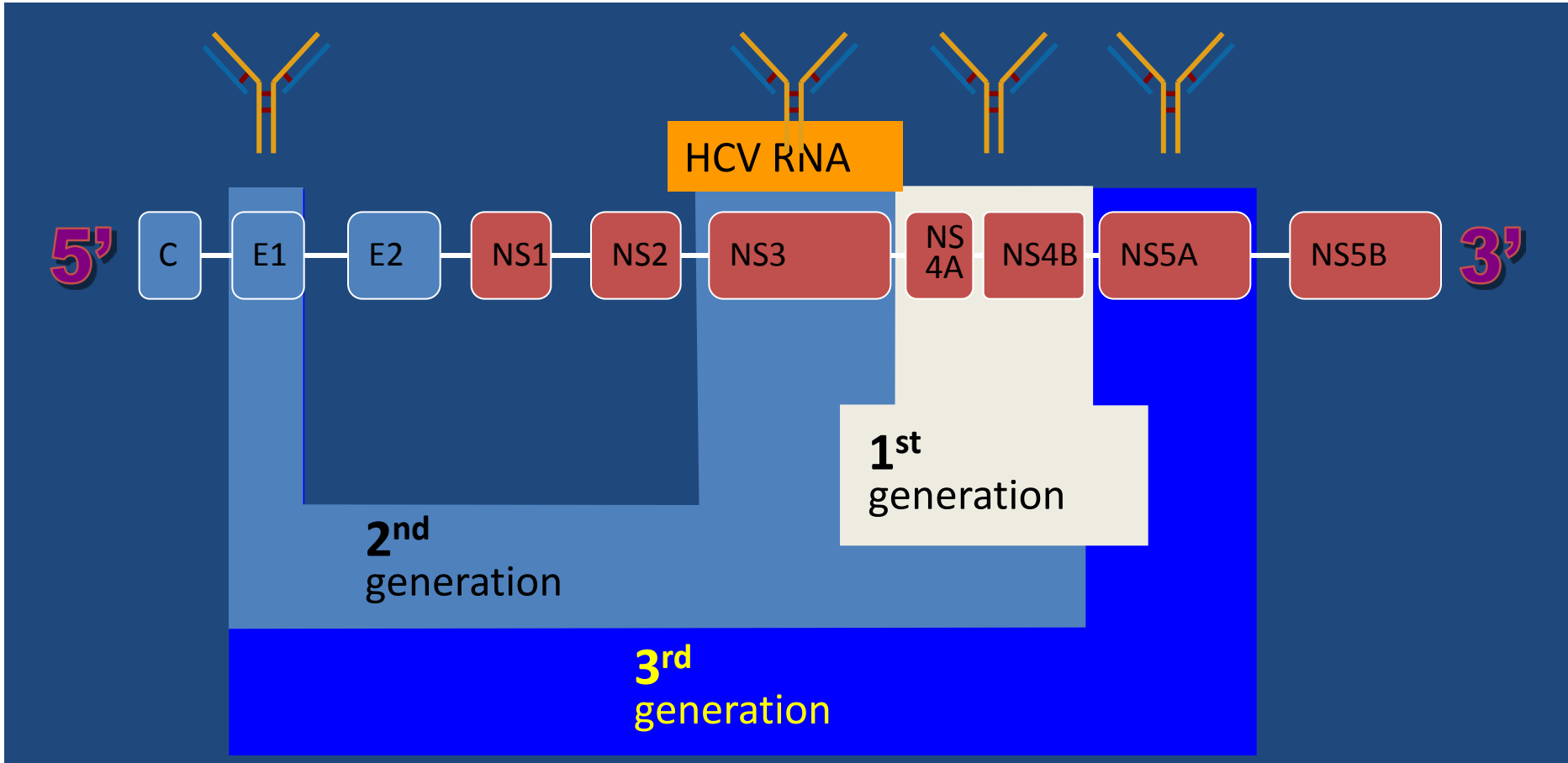
  screening test (EIA or CIA)

Virus Detection - HCV RNA

qualitative PCR or TMA

quantitative real-time PCR

HCV Immunoassay (IA)



HCV IA detects antibodies to 3 or more viral proteins

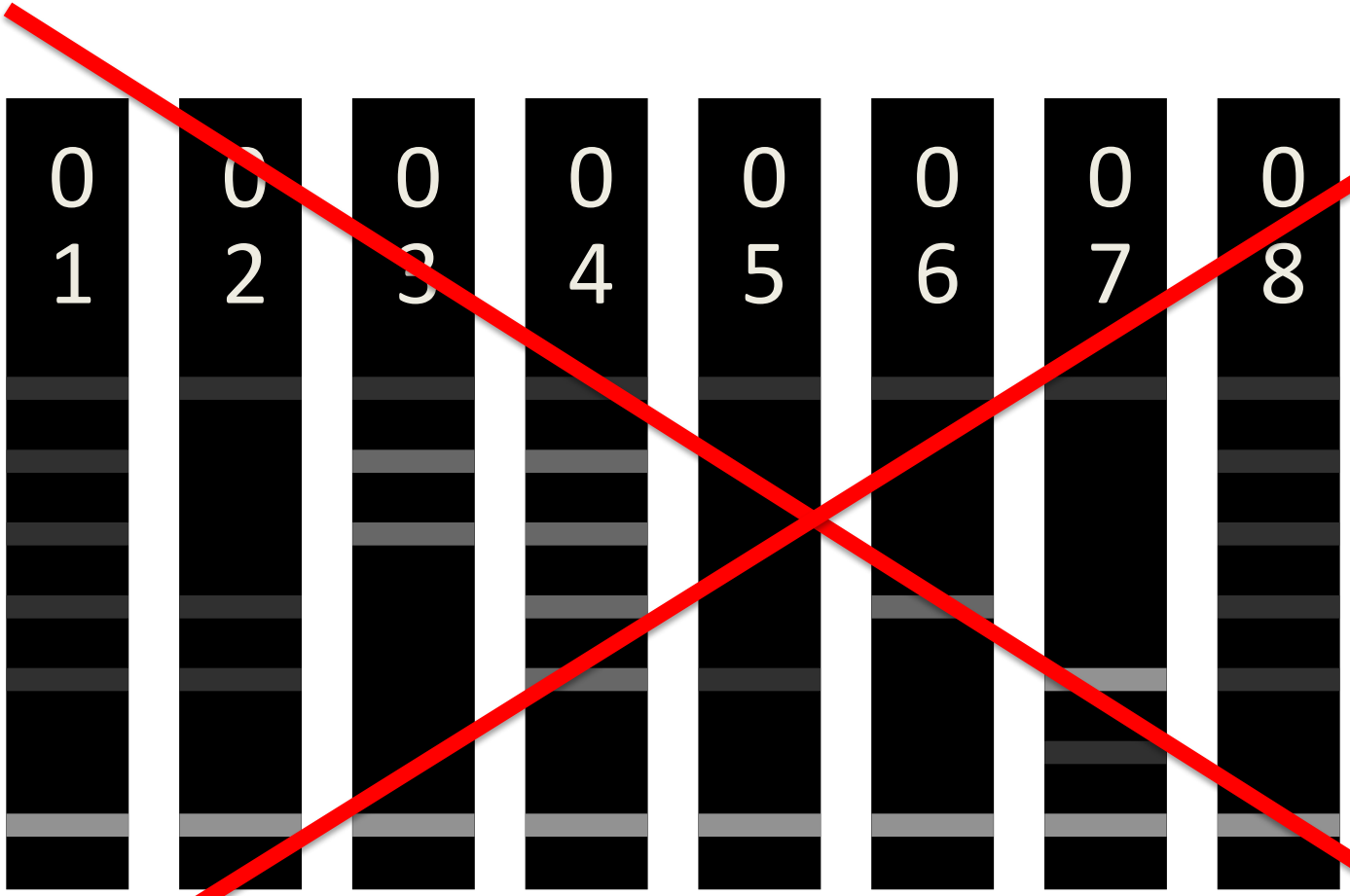
Signal to Cutoff Ratios (S/Co)

Screening Test Kit Name	Manufacturer	Assay Format	Signal-to-cut-off ratio predictive true positive ≥ 95% of the time
Ortho HCV Version 3.0 ELISA Test System	Ortho	EIA	≥ 3.8
Abbott HCV EIA 2.0	Abbott	EIA	≥ 3.8
VITROS Anti-HCV	Ortho	CIA	≥ 8.0
AxSYM Anti-HCV	Abbott	MEIA	≥ 10.0
Architect Anti-HCV	Abbott	CMIA	≥ 5.0
Advia Centaur HCV	Siemens	CIA	≥ 11.0

S/CO predicts HCV viremia
S/CO guide to choosing screening confirmation (RIBA vs PCR) testing algorithm now obsolete

anti-HCV RIBA 3.0

Reagent manufacture discontinued 2013



3+ Control

5-1-1 & c100p

c33c

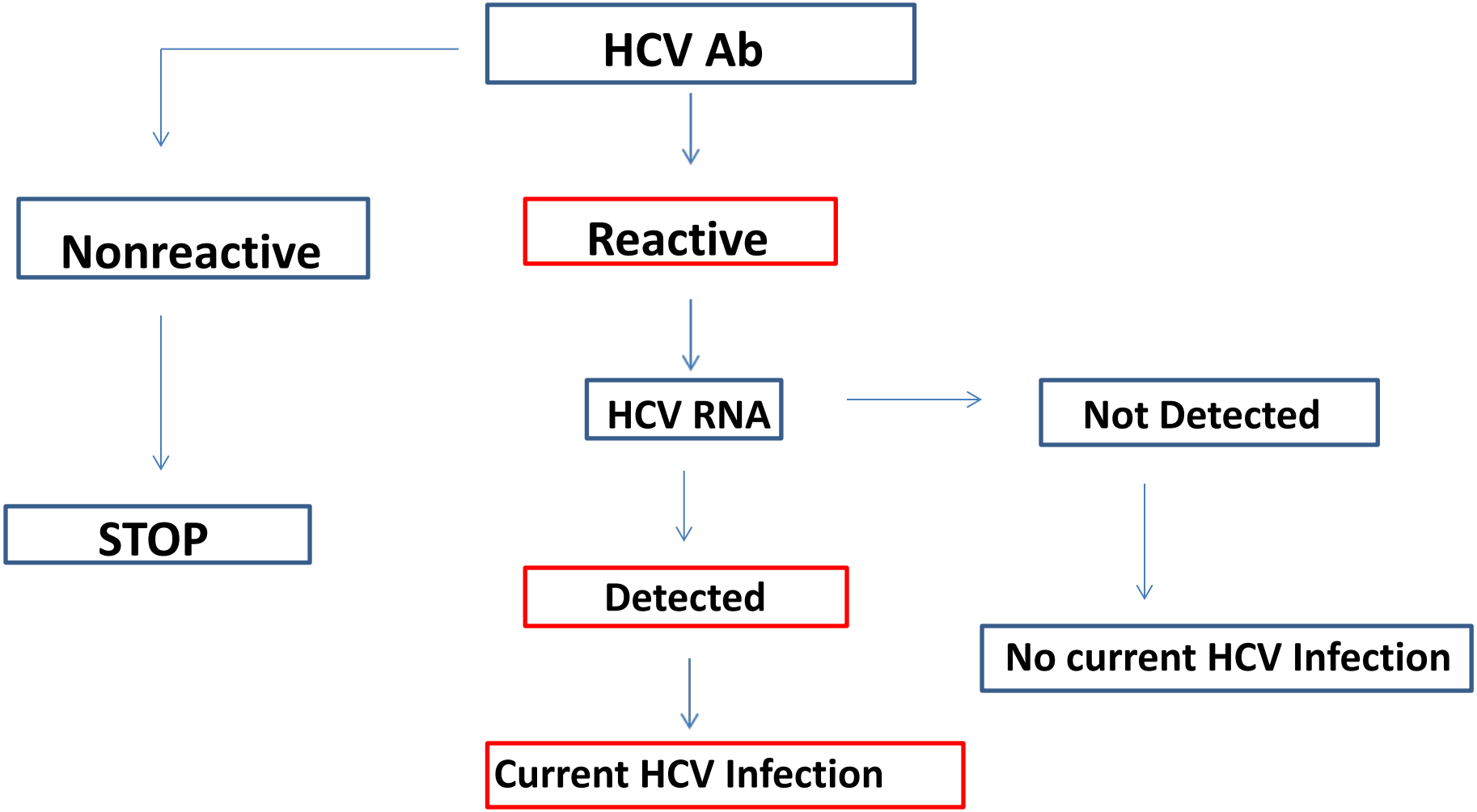
c22p

NS5

SOD

1+ Control

HCV Algorithm (2013)



Result Interpretation

Anti-HCV	HCV RNA	Interpretation
Positive	Positive	Acute or chronic HCV depending on clinical context
Positive	Negative	Past, resolved HCV infection; False Positive Screen
Negative	Positive	Early acute HCV infection; chronic HCV in setting of immunosuppressed state; false positive HCV RNA test
Negative	Negative	Absence of HCV infection

HCV Molecular Confirmation Issues

- Confirm with “sensitive” HCV RNA test
  - COBAS AmpliPrep/ COBAS Taqman, quantitative (Roche)
  - RealTime HCV, quantitative (Abbott)
  - APTIMA HCV RNA, qualitative (Hologic) FDA approved for diagnosis HCV
- Both HCV Viral Load tests are very sensitive but none are FDA approved for diagnosis (still confirmation standard)
- Confirmation with quantitative assay is both process and cost efficient (baseline for therapeutic monitoring)

Issues for Timely Confirmatory Testing

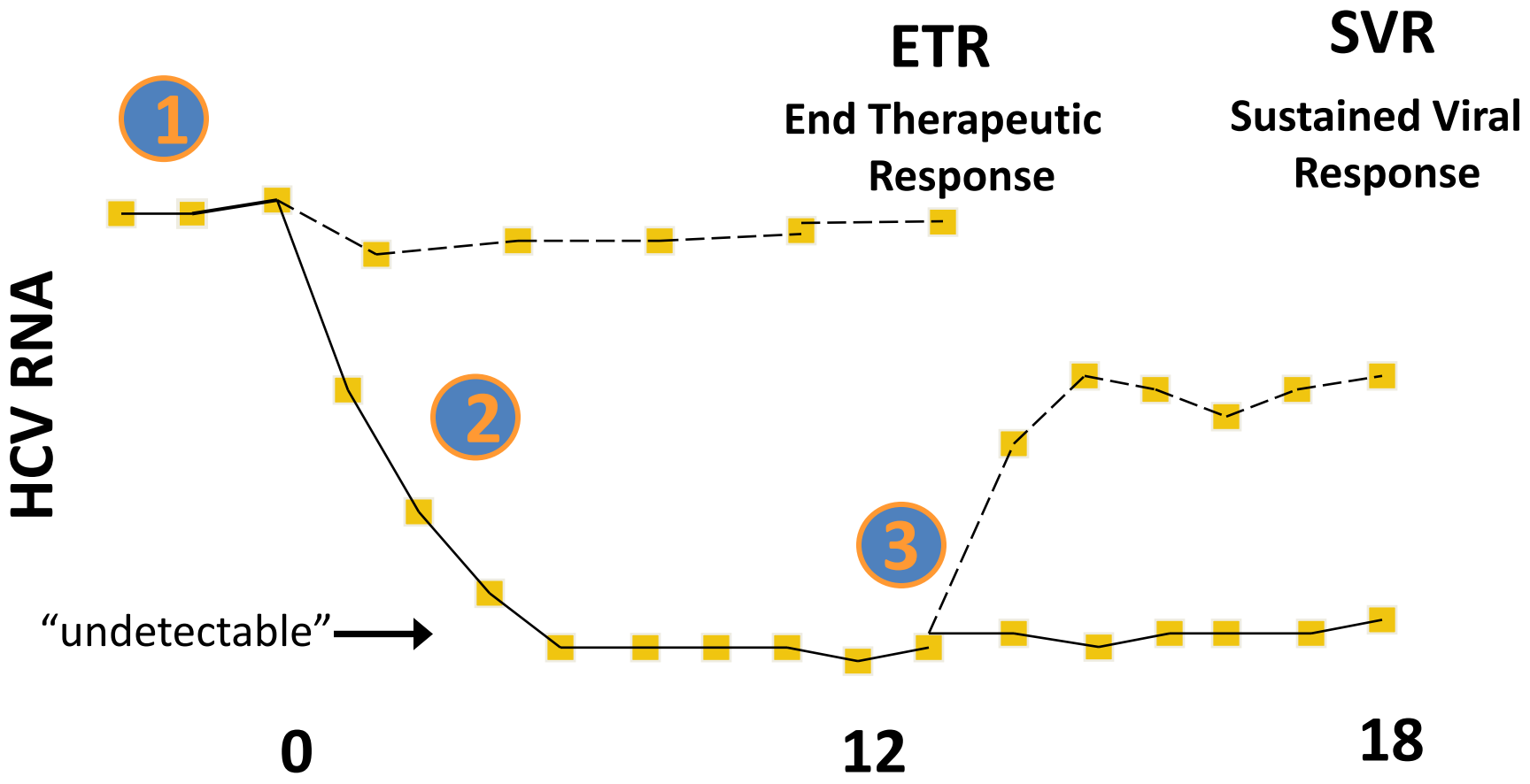
- Time gap in Screening vs PCR confirmation
  - Patients at risk for follow up.
- Re-testing screening sample by PCR condoned by CDC, however, potential contamination risk?
  - Reflex PCR testing of 2nd tube for sero-positives?
  - Pre-aliquoting samples prior to serologic and potential molecular testing?
- Unmet need: Rapid, unified screening/assay process (POC?)

Candidates for Therapy and Outcome Predictors

- >18 years
- Antibody & RNA +
- Liver bx (chronic hepatitis), not required
- Stage of disease appropriate
- No Rx contraindications

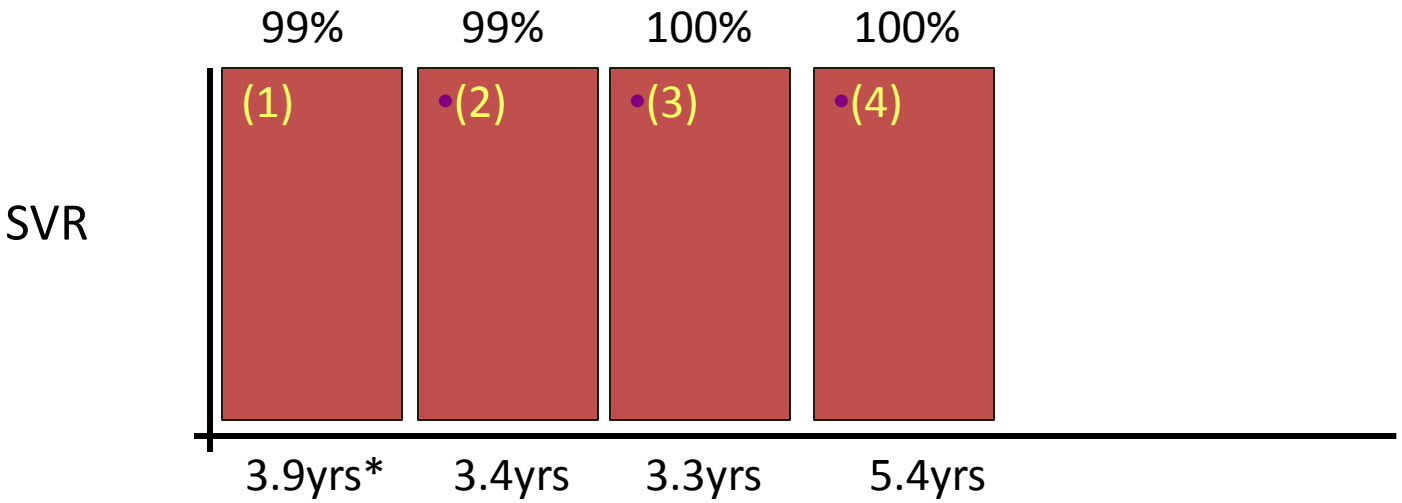
- VL < 400,000 I.U./ml
- Age
- Sex
- Race
- Weight
- Fibrosis
- Steatosis
- Insulin resistance
- Alcohol consumption
- **All less predictive than IL28 (traditional intereferon Rx)***
- **New treatment options (DAAs) effective for previous difficult to treat patients**

HCV Treatment:
Goal is Sustained Viral Response (SVR)



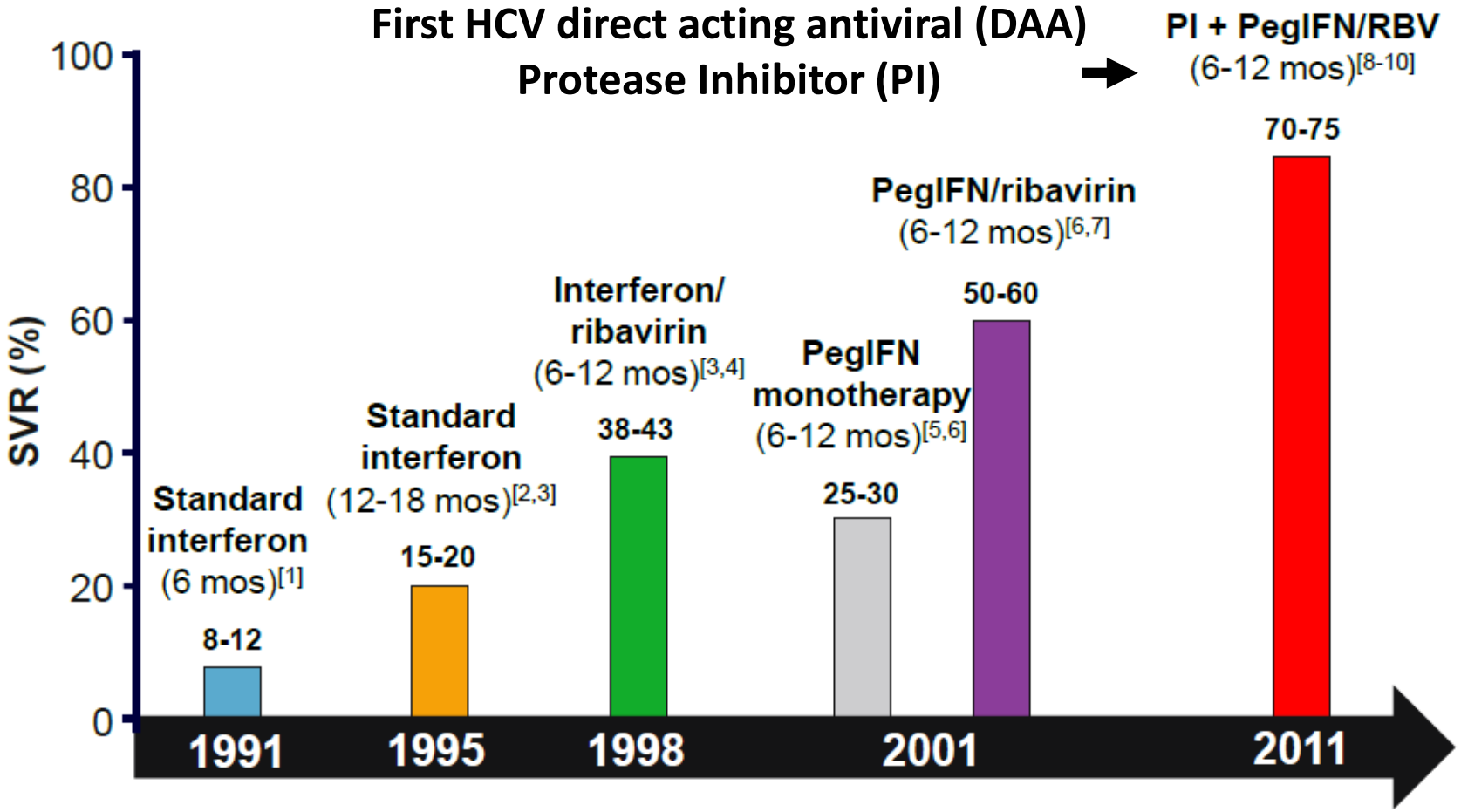
SVR = Improved Outcomes!

- SVR – virologic "cure"
  - Durable
  - Leads to improved histology
  - Leads to clinical benefits
    - Decreases decompensation
    - Decreases risk of hepatocellular carcinoma
    - Decreases mortality



Bruno S, et al. Hepatology. 2010;51:2069-2076. Veldt BJ, et al. Ann Intern Med. 2007;147:677-684.
Maylin S, et al. Gastroenterology. 2008;135:821-829. 1. Swain MG, et al. Gastroenterology. 2010;139:1593-1601. 2. Giannini EG, et al. Aliment Pharmacol Ther. 2010;31:502-508. 3. Maylin S, et al. Gastroenterology. 2008;135:821-829. 4. George SL, et al. Hepatology. 2009;49:729-738.

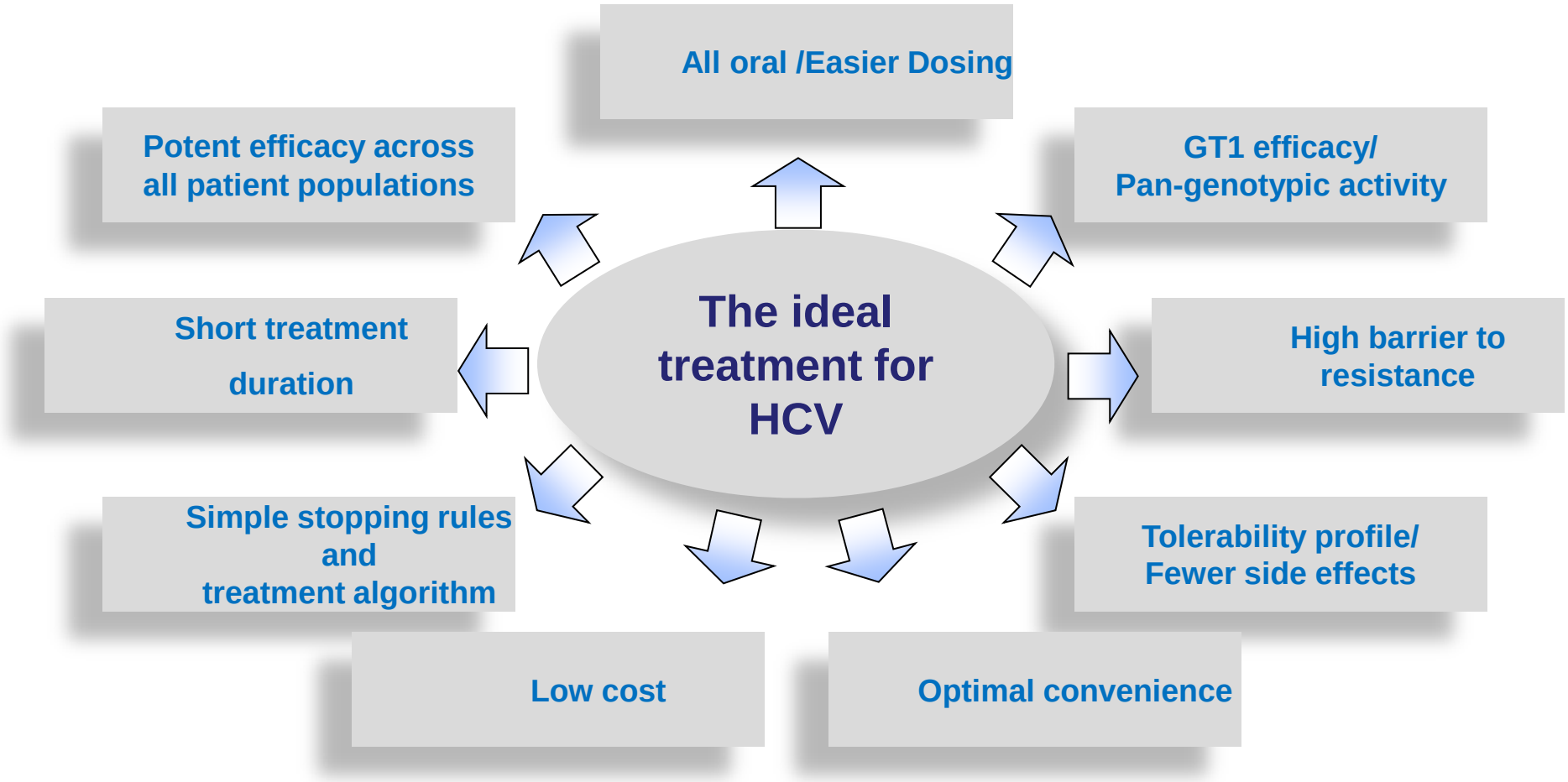
Treatment of Chronic Hepatitis C (Pre-2011)



1. Carithers RL Jr., et al. Hepatology. 1997;26(3 suppl 1):83S-88S. 2. Zeuzem S, et al. N Engl J Med. 2000;343:1666-1672. 3. Poynard T, et al. Lancet. 1998;352:1426-1432. 4. McHutchison JG, et al. N Engl J Med. 1998;339:1485-1492. 5. Lindsay KL, et al. Hepatology. 2001;34:395-403. 6. Fried MW, et al. N Engl J Med. 2002;347:975-982. 7. Manns MP, et al. Lancet. 2001;358:958-965. 8. Poordad F, et al. N Engl J Med. 2011;364:1195-1206. 9. Jacobson IM, et al. N Engl J Med. 2011;364:2405-2416. 10. Sherman KE, et al. N Engl J Med. 2011;365:1014-1024.

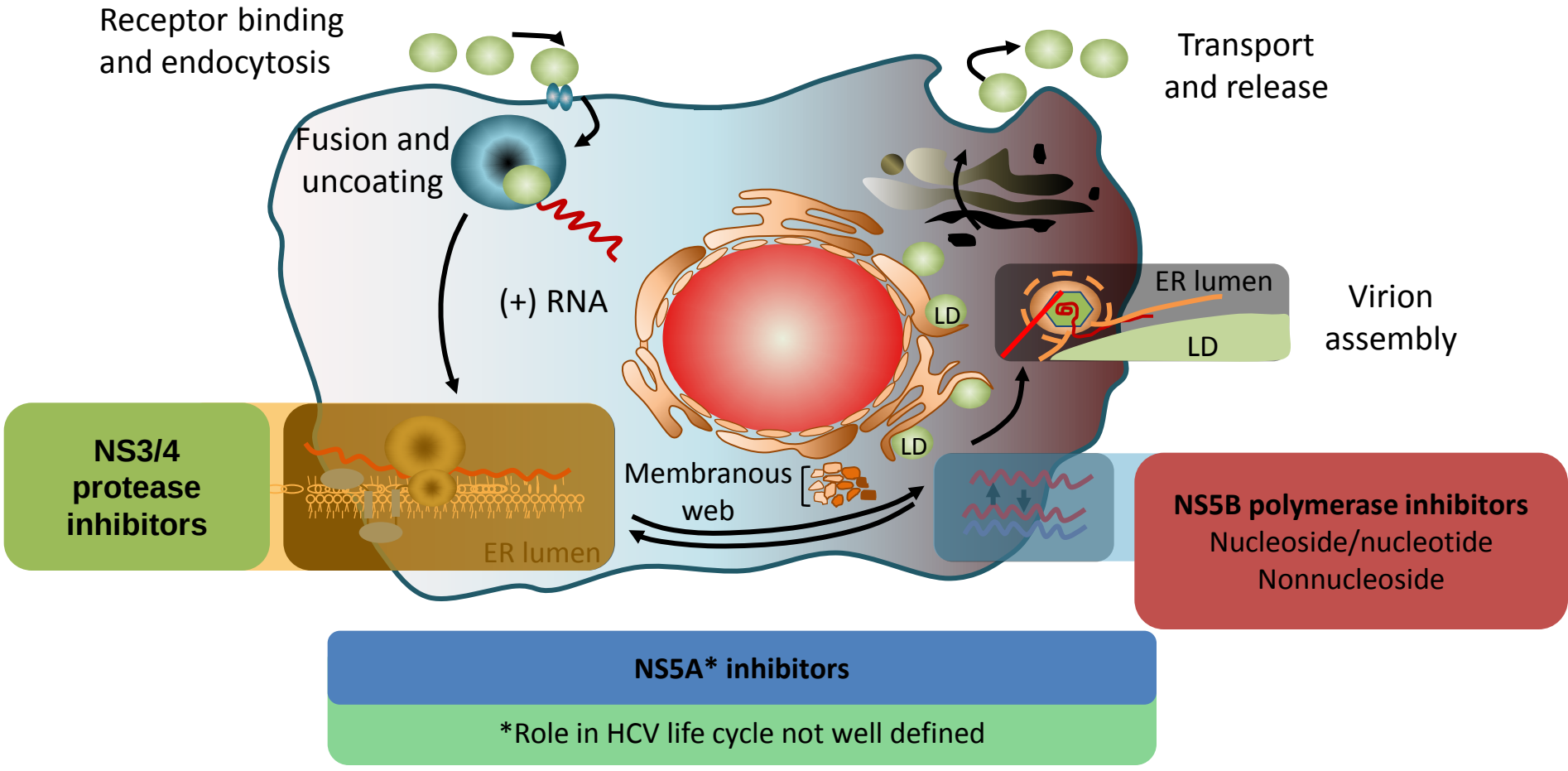
HCV Therapies Continue to Evolve:

Unmet needs driving drug development



Direct Acting Antivirals (DAA)

Basis for New Therapies



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

DAA Class Characteristics

Characteristic	Protease inhibitors	Nucleos(t)ide Polymerase inhibitors	Nonnucleoside Polymerase inhibitors	NS5A inhibitors
Potency	High; Variable among HCV genotypes	Moderate-high; Consistent across genotype, subtype	Variable; Variable among HCV genotypes	High; multiple HCV genotypes
Barrier to Resistance	Low 1a < 1b	High; 1a = 1b	Very Low 1a < 1b	Low 1a < 1b
Drug Interaction Potential	High	Low	Variable	Low to moderate
Toxicity	Rash Anemia ↑Bilirubin	Mitochondrial Nuc interactions (ART, RBV)	Variable	Variable
Pharmacokinetics	Variable; QD to TID	QD	Variable; QD to TID	QD
Comments	2nd gen PIs: better barrier, pangenotypic	Single target Active site	Allosteric; Many targets	Multiple antiviral MOA

Paul Pockros 2013

New Therapies (Post-2011)

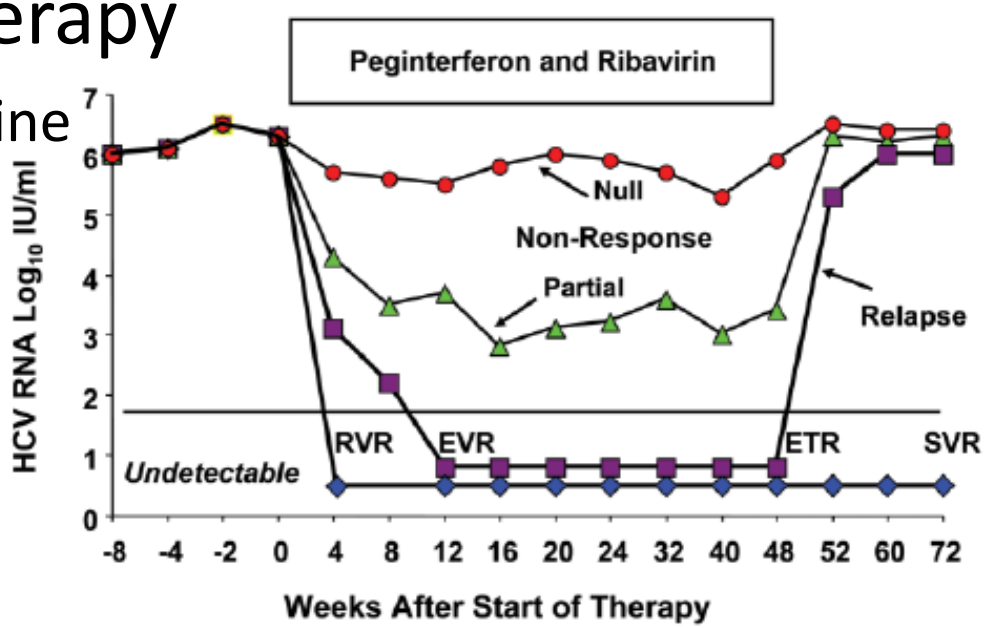
- Greatly increased likelihood of sustained viral response (SVR)
- Better Tolerated
- Shorter Treatment Regimens
- Simpler Treatment and Monitoring Algorithms
- More Drug Options
- Expensive

HCV Treatment: Tests for Selection and Guidance of Therapy

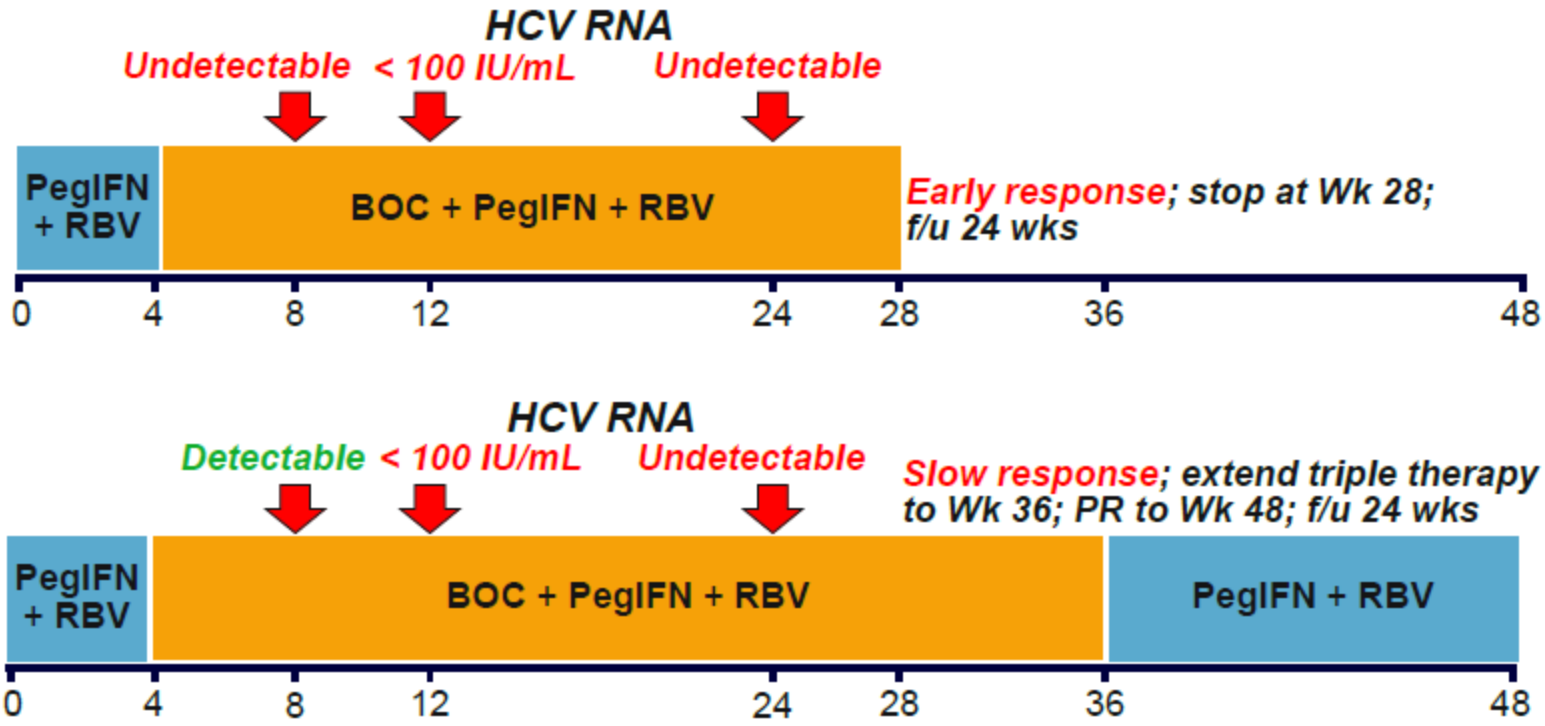
- Selection
  - Genotype and subtype
  - Stage of disease
  - Past treatment history
- Guidance
  - Genotype and subtype guided
    - how long to treat
  - Response guided
    - How long to treat/when to stop

Two Approaches to Guided Therapy

- Genotype Guided Therapy
  - Rx some genotypes shorter
    (GT2,3 interferon ribavirin therapy)
  - Rx other genotypes longer
    (GT1, 4, 5, 6 interferon ribavirin therapy)
- Response Guided Therapy
  - Rx based on rate VL decline
  - Treatment duration
  - Stopping rules



Response-Guided Therapy
"First Generation Direct Acting Antivirals"



Boceprevir [package insert]. May 2011. Ghany MG, et al. Hepatology. 2011;54:1433-1444.

Recommended Regimens for Treatment-Naive GT1 HCV Pts

Subtype	Noncirrhotic		Compensated Cirrhotic	
	Regimen	Duration, Wks	Regimen	Duration, Wks
GT1a or 1b	LDV/SOF	12*	LDV/SOF	12
GT1a	OMV/PTV/RTV + DSV + RBV	12	OMV/PTV/RTV + DSV + RBV	24
GT1b	OMV/PTV/RTV + DSV	12	OMV/PTV/RTV + DSV + RBV	12
GT1a	SMV + SOF ± RBV	12	SMV + SOF ± RBV	24
GT1b	SMV + SOF	12	SMV + SOF	24

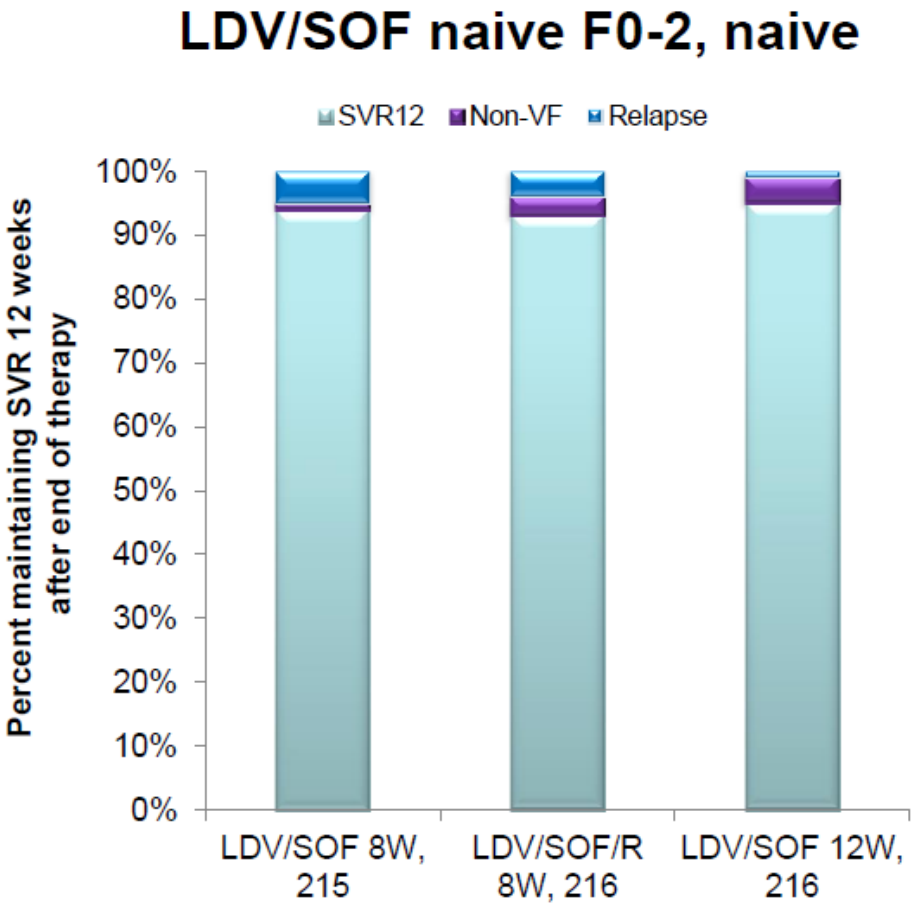
*Shorter course can be considered in pts with pretreatment HCV RNA < 6 million IU/mL at provider's discretion but should be done with caution.

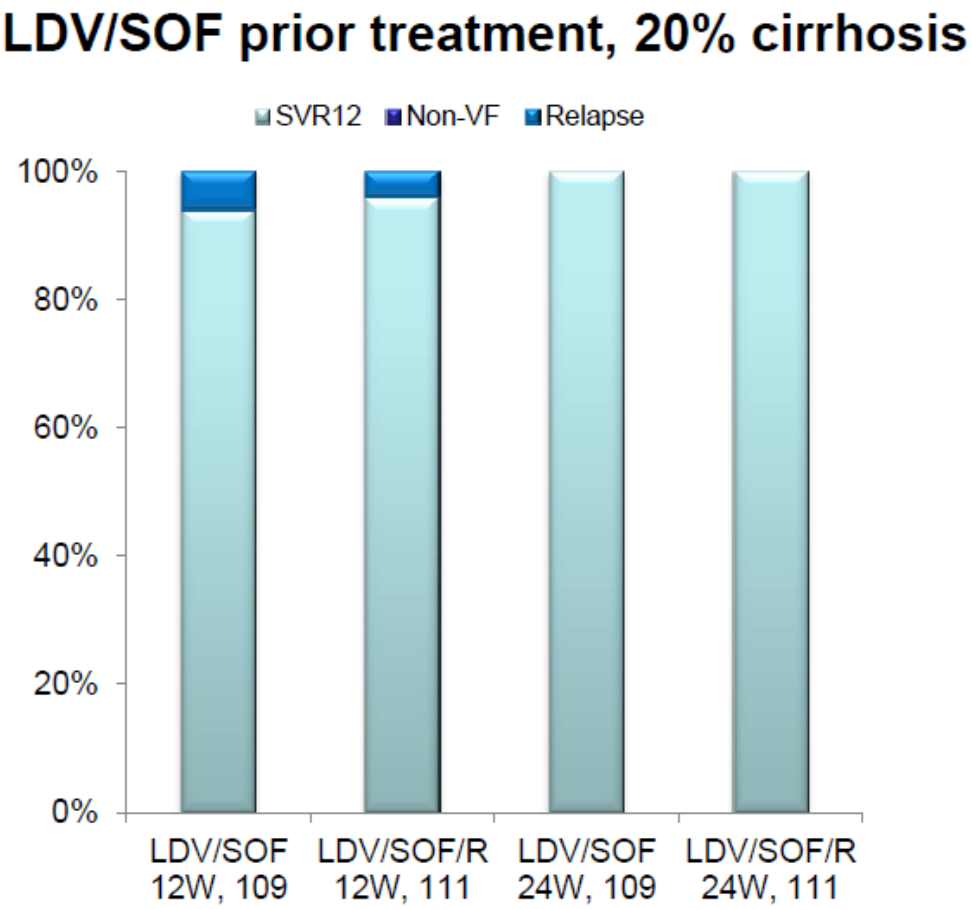
DSV dasabuvir ABT-333 NS5AI
LDV ledipasvir GS-5885 NS5AI
OMV ombitasvir ABT-267 PI
PTV paritaprevir *ABT-450* *PI*

RBV ribavirin
RTV ritonavir
SMV simeprevir TMC435 PI
SOF sofosbuvir. GS-331007 *NS5BI*

From Sulkowski Clinical Care Options 2015

Genotype 1 HCV Ledipasvir (LDV) and Sofosbuvir (SOF)

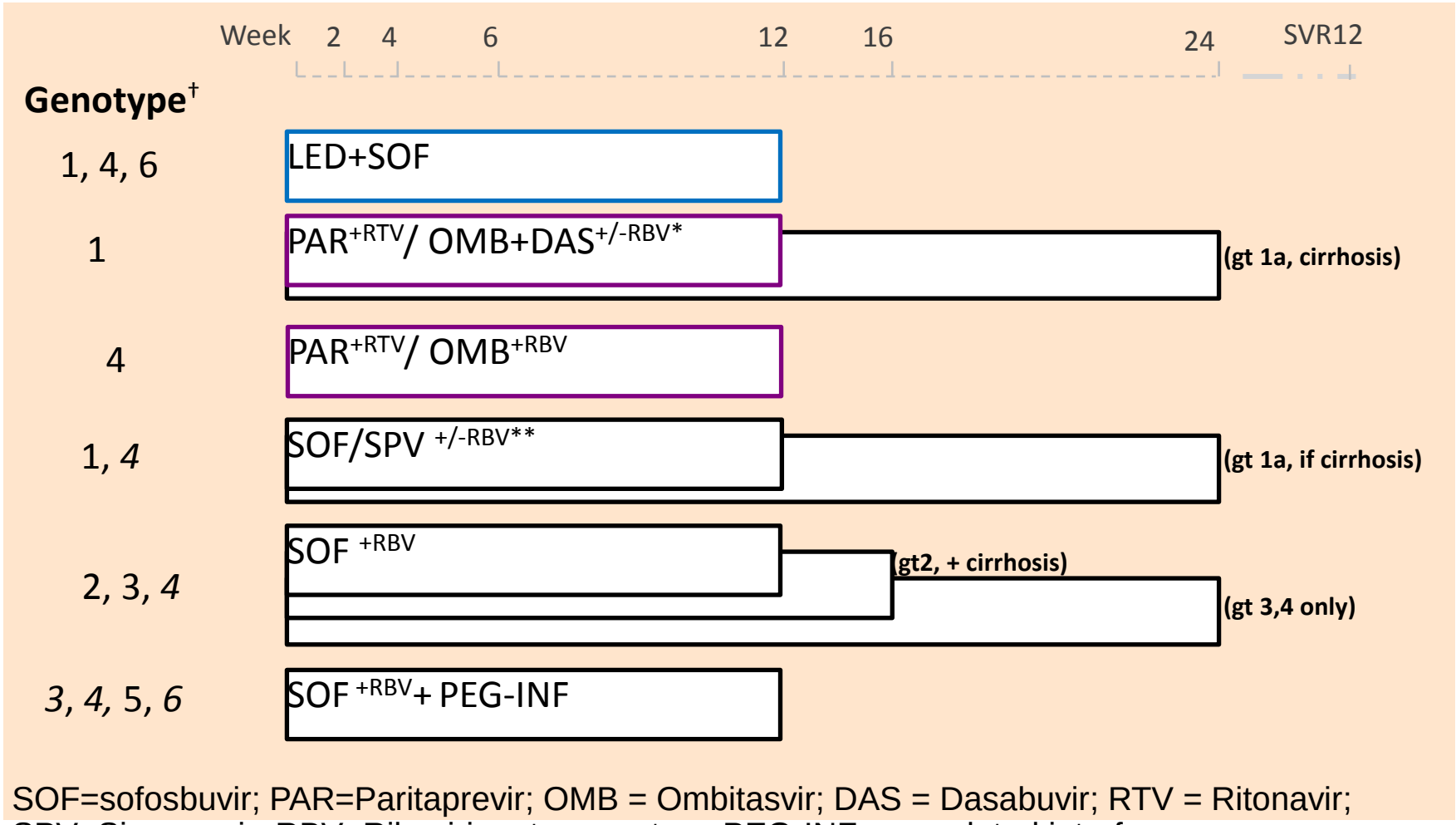




Kowdley *NEJM* 2014. Afdhal, *NEJM* 2014

HCVCurrent Recommendations, New All Oral Therapies:

Treatment Naïve patients: HCV genotype, duration important



SOF=sofosbuvir; PAR=Paritaprevir; OMB = Ombitasvir; DAS = Dasabuvir; RTV = Ritonavir; SPV=Simeprevir; RBV=Ribavirin; gt = genotype PEG-INF = pegylated interferon

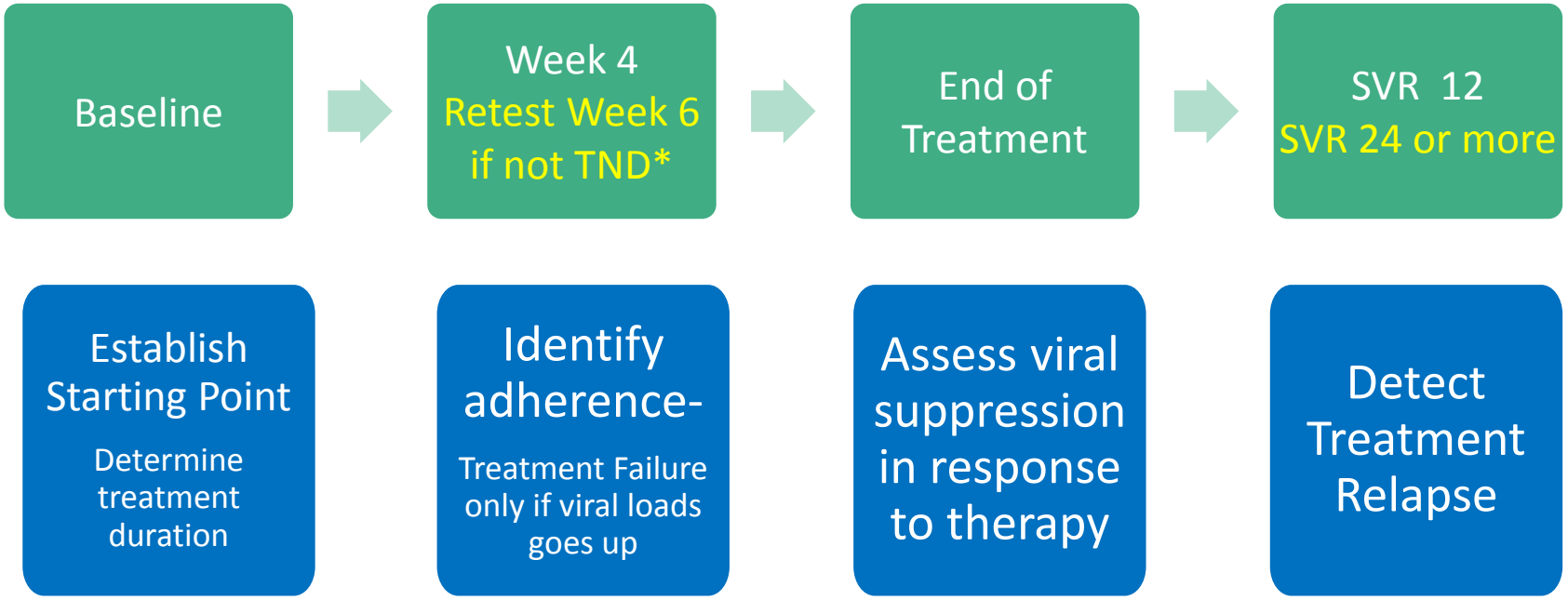
† *Italics* indicates alternative regimen recommendation * Genotype 1b: +RBV only if cirrhosis, 12 wks ** -RBV only for genotype 4

Note: For genotype 5, PEG-INF+RBV can be used as an alternative

AASLD-IDSA Recommendations on Treatment of Hepatitis C 2014, http://www.hcvguidelines.org/full-report/initial-treatment-hcv-infection accessed 5/19/2015

Evolving Landscape of HCV

Updated 2014 AASLD Guidelines



***If quantitative HCV viral load has increased by greater than 10-fold (>1 $\log_{10}$ IU/mL) on repeat testing at week 6 (or thereafter), then discontinuation of HCV treatment is recommended.**

AASLD Guidelines www.HCVguidelines.org accessed May 19,, 2015

HCV Genotyping Considerations

- Patients with HCV genotype 1a tend to have higher relapse rates than patients with HCV genotype 1b with certain regimens.
- Genotype 1a patients may receive more aggressive therapy
- Genotype 1 HCV infection that cannot be subtyped should be treated as genotype 1a infection

AASLD/IDSA HCV Guidance 05-29-15c

HCV Genotyping Methods

- LiPA (reverse hybridization line probe)
  - (5'UTR, Core)
- Nucleic Acid Sequencing (Sanger or NGS)
  - (5'UTR, Core, NS5)
- Primer specific PCR (Abbott TaqMan) FDA approved
  - (5'UTR, NS5)
- GenMark
  - (5'UTR, Core)

HCV Genotyping Test Issues

- Tests targeting only 5’ UTR do not reliably discriminate types 1a vs 1b or type 1 vs rare type 6 HCV
- Interrogation of core and NS5B associated with low percentage of no calls due to sequence variability of targets

HCV Genotyping for Drug Resistance

- **R**esistance **A**ssociated **V**ariation (RAVs) arise due to selection (previous failed therapies)
- Spontaneous RAVs also present in untreated populations
- Mutations may confer fitness cost
- Barrier to resistance varies with drug class
- Evolving recommendations for resistance testing

HCV GT1a Infections with NS3 (protease) Q80K Polymorphism

- Efficacy of SMV/PEG/RBV substantially reduced*
- Sofosbuvir plus simeprevir**
  - 1a patients with Q80K mutation have lower rates of SVR
- Recommendations for testing for NS5A and other mutations are now emerging

***Simeprevir (OLYSIO™) Prescribing Information. Janssen Therapeutics, Titusville, NJ. November, 2013.**

**Lawitz E, Matusow G, DeJesus E et al EASL 2015;S264 AASLD/IDSA HCV Guidance 05-29-15

New Indications for RAV Testing

- NS5A mutations likely detected in setting of virologic breakthrough post DAA treatment
  - ledipasvir, ombitasvir, and daclatasvir
- NS5A inhibitor mutations likely stable and detectable as long as 2 years after treatment.
- NS3 region mutations may also occur (protease inhibitors)
  - Paritaprevir and simeprevir
- Treatment examples
  - ledipasvir/sofosbuvir
  - ombitasvir/paritaprevir/ritonavir/dasabuvir
  - Daclatasvir/sofosbuvir

- Indication for RAV testing: Treatment is urgent and previous treatment with NS5A/NS3 inhibitors has failed
- Test NS5A and NS3 regions
- Indications NS5B polymerase testing less clear
- Testing currently limited to a few specialty labs
- Field new and rapidly evolving

Evaluating the Cost Effectiveness of New Therapies

- In 2011, average wholesale acquisition costs of drugs alone were $32,000 to over $100,000
- Quality adjusted life years for those regimens considered reasonable
- New regimens are $100,000 to $175,000 in U.S.
- Incremental cost benefits have been demonstrated
- Evaluating cost effectiveness of new regimens also has to reflect the increased efficacy of the treatment (cost/cure)
- Will competition and or regulation bend the cost curve?

Rein *Ann Intern Med* 2012 and unpublished data. Younoussi, *J Hepatol* 2014. Hagan, *Hepatology* 2014. Linas, *AIDS* 2014. Deuffic-Burban, *J Hepatol* 2014. Brogan, Plos One 2014 .

The HCV Revolution

- Viral discovery
- Advancing therapeutics
- Evolving laboratory technology
- Convergence on use of high quality molecular tests for detection and genotyping (VL considered)
- Broad population screening
- Education, screening, resource availability, team based management
- Economic models to bring affordable care for chronic HCV infection

ARUP LABORATORIES

UNIVERSITY OF UTAH
SCHOOL OF MEDICINE

Department of Pathology