

HIV/STD/TB/Hepatitis Symposium April 11, 2012

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Overview

- History of the virus
- Disease burden
- Natural history of the virus
- Risk factors
- Issues related to acute infection
- Issues related to chronic infection
- Treatment

History of hepatitis C virus

- 1970's
 - Labeled as Non-A, Non-B hepatitis- cause of 90% of transfusion ass. hepatitis

- 1988
 - HCV discovered by molecular cloning- cause of 90% of transfusion ass. hepatitis

Disease burden

HEPATITIS C: A GLOBAL HEALTH PROBLEM

About 170 million carriers worldwide, 3 – 4 million new cases each year



Source: World Health Organization

Why is hepatitis C infection so important?

- The most common chronic blood-borne infection in the US
- 4x more common than HIV
- 10th leading cause of death
- The cause of 40% of chronic liver disease

Why is hepatitis C infection so important?

- 3.9 million US population
- ~30,000 new infections/year
- Most frequent indication for liver transplant.
($>1/2$ of transplants)
- Costs over \$600 million each year

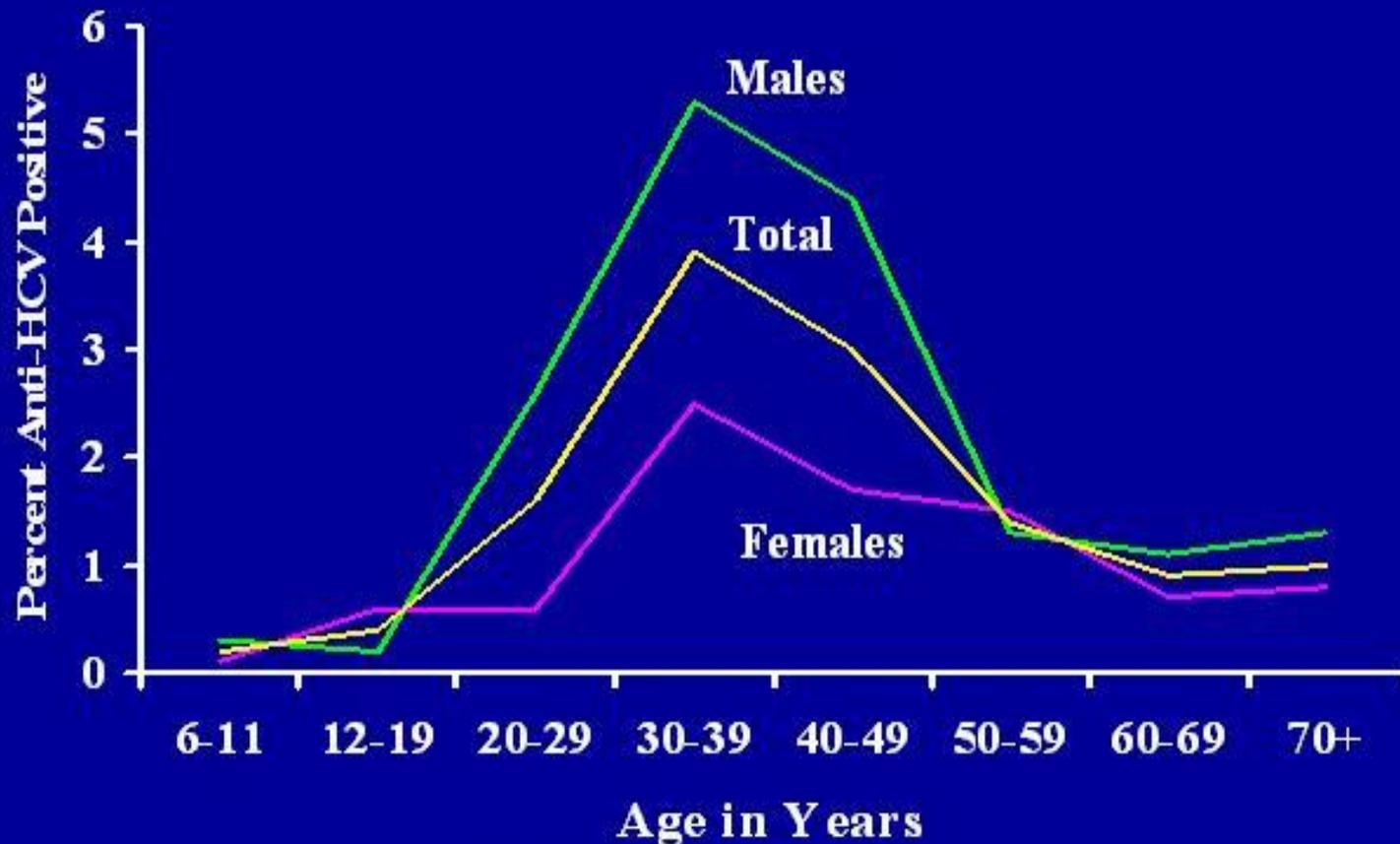
Special population

- Incarcerated population (1.8 million) ~ 30-40%
- 42% of 597 homeless veterans were anti-HCV positive
- Institutionalized population

Special population-Veterans

- Shockingly high rates of HCV among United States veterans
 - 6.6-17.7% (versus 1.8% general pop.)
- Over 90% of veterans surveyed had at least one risk factor not directly related to military service
- Homeless shelters for veterans
 - seroprevalence 41.7%

Prevalence of HCV Infection by Age and Gender, United States, 1988-1994



Source: CDC, NHANES III, NEJM 1999



Figure 4.1. Reported and adjusted* number of acute hepatitis C cases — United States, 1992–2009

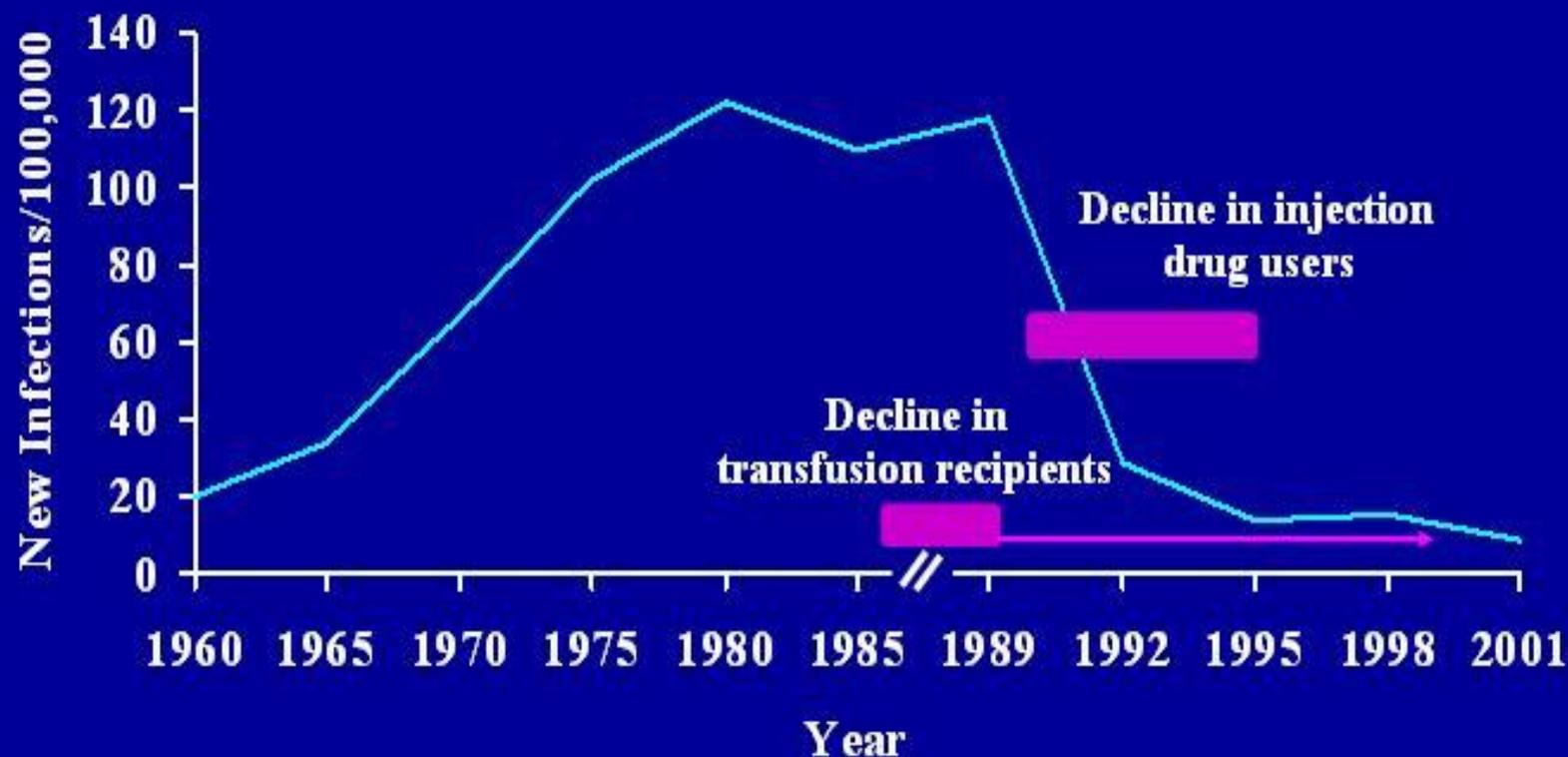


* Adjusted for underreporting.

Note: Until 1995, acute hepatitis C was reported as “acute hepatitis, non-A /non-B.”

Source: National Notifiable Diseases Surveillance System (NNDSS)

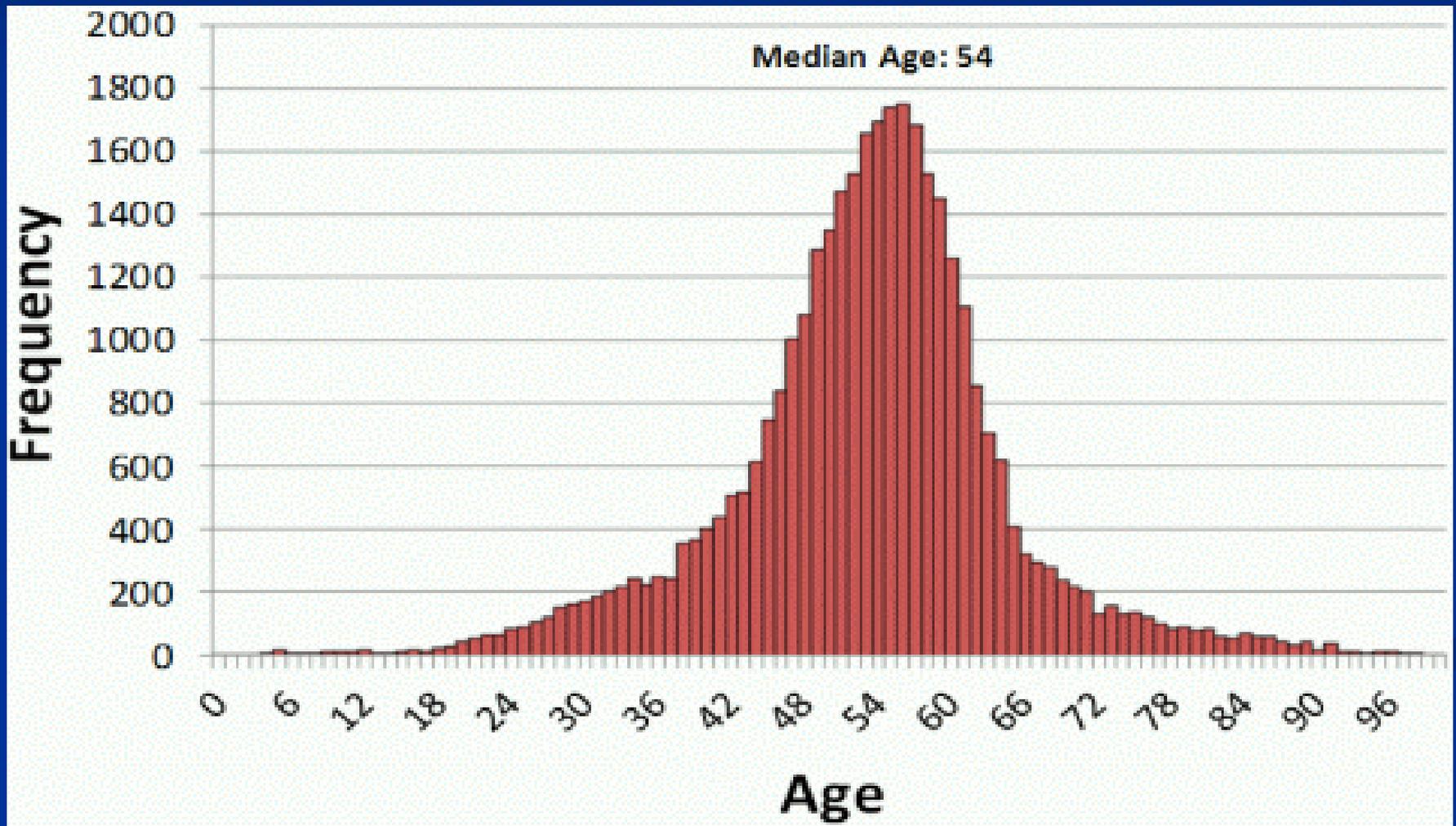
Estimated Incidence of Acute HCV Infection United States, 1960-2001



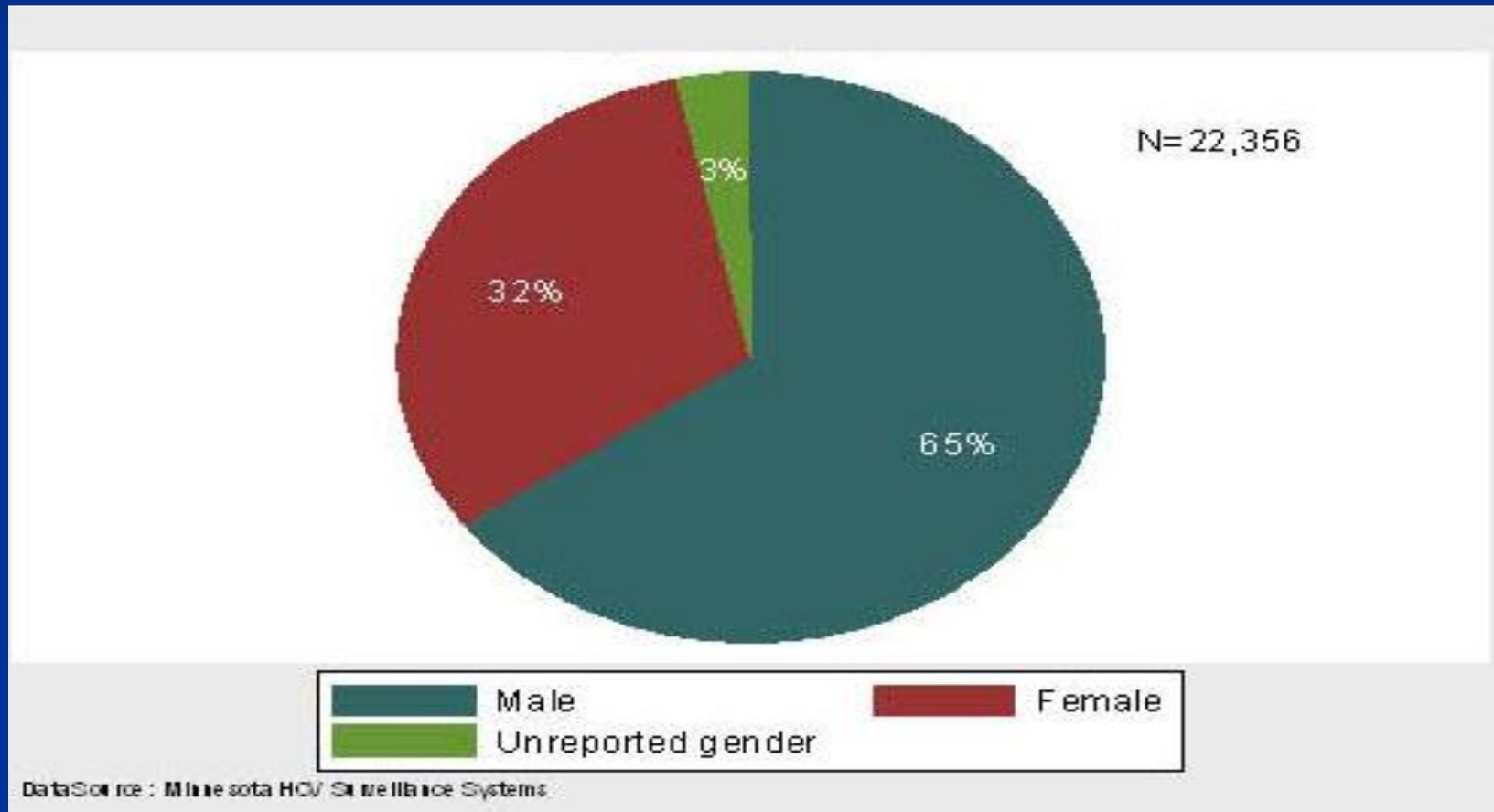
Source: *Hepatology* 2000;31:777-82; *Hepatology* 1997;26:62S-65S;
CDC, unpublished data



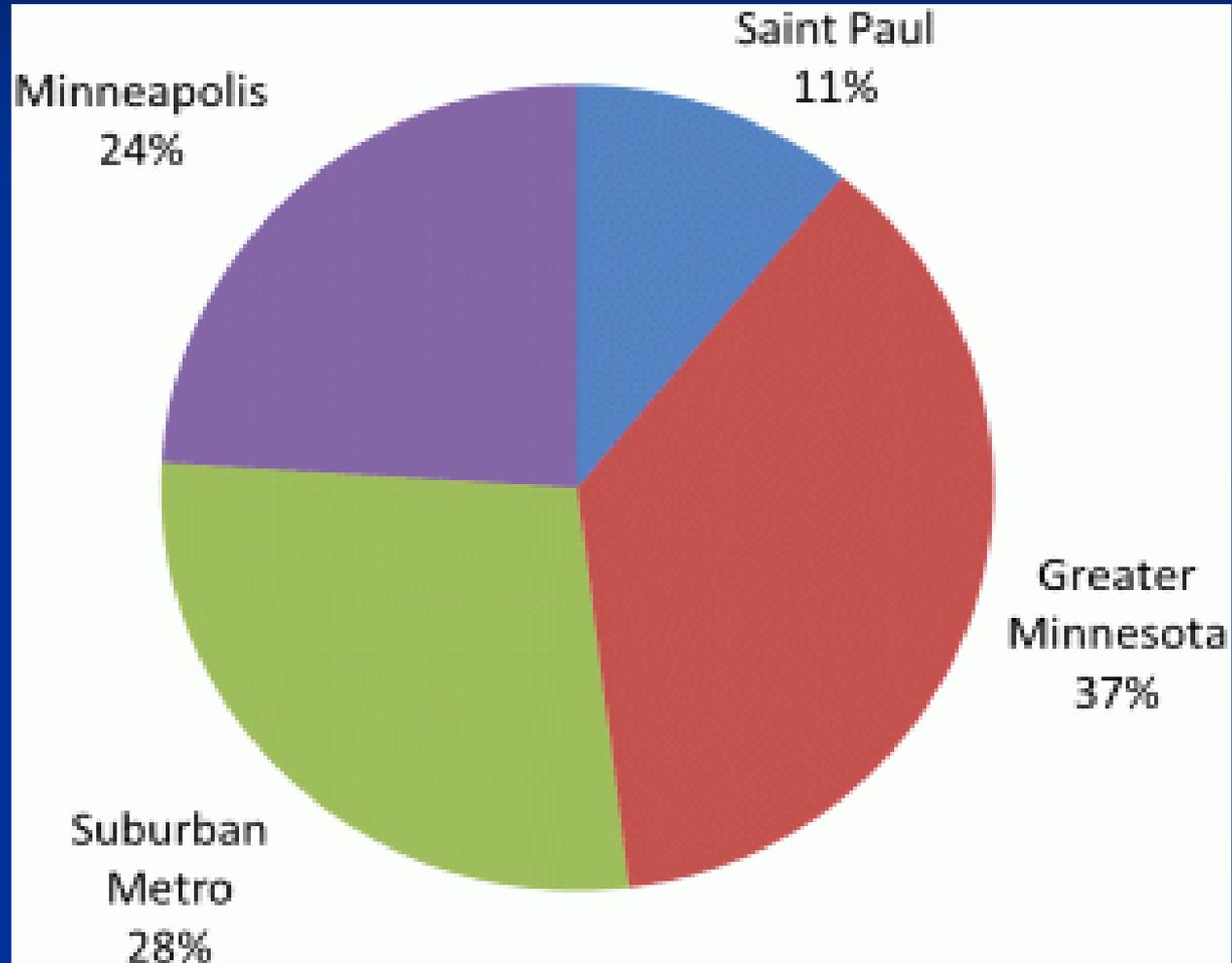
Persons living with HCV in MN by age, 2010



Persons living with HCV in MN by gender, 2010

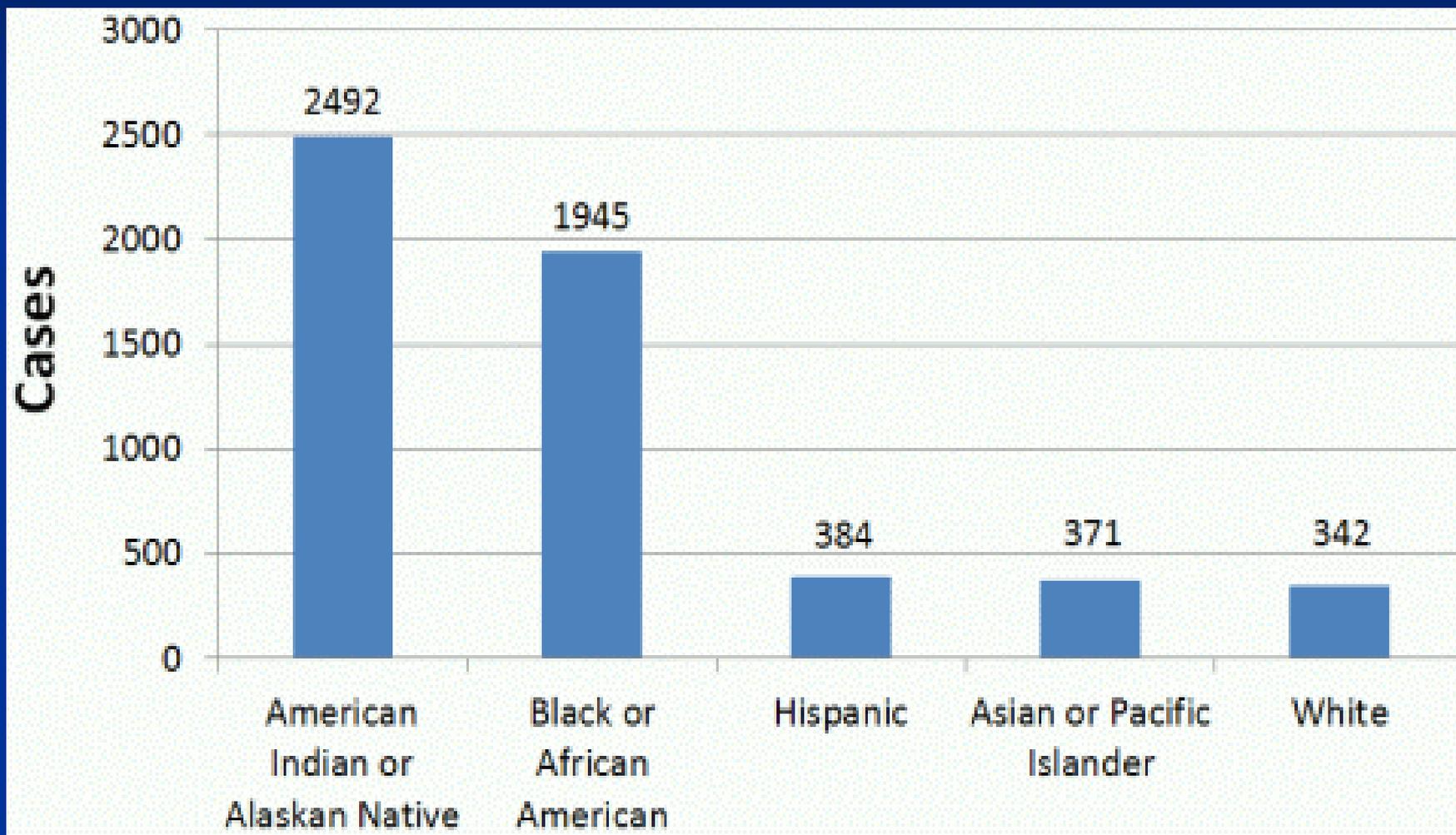


Person living with HCV in MN by current residence, 2010 (total number of residence information- 18657)

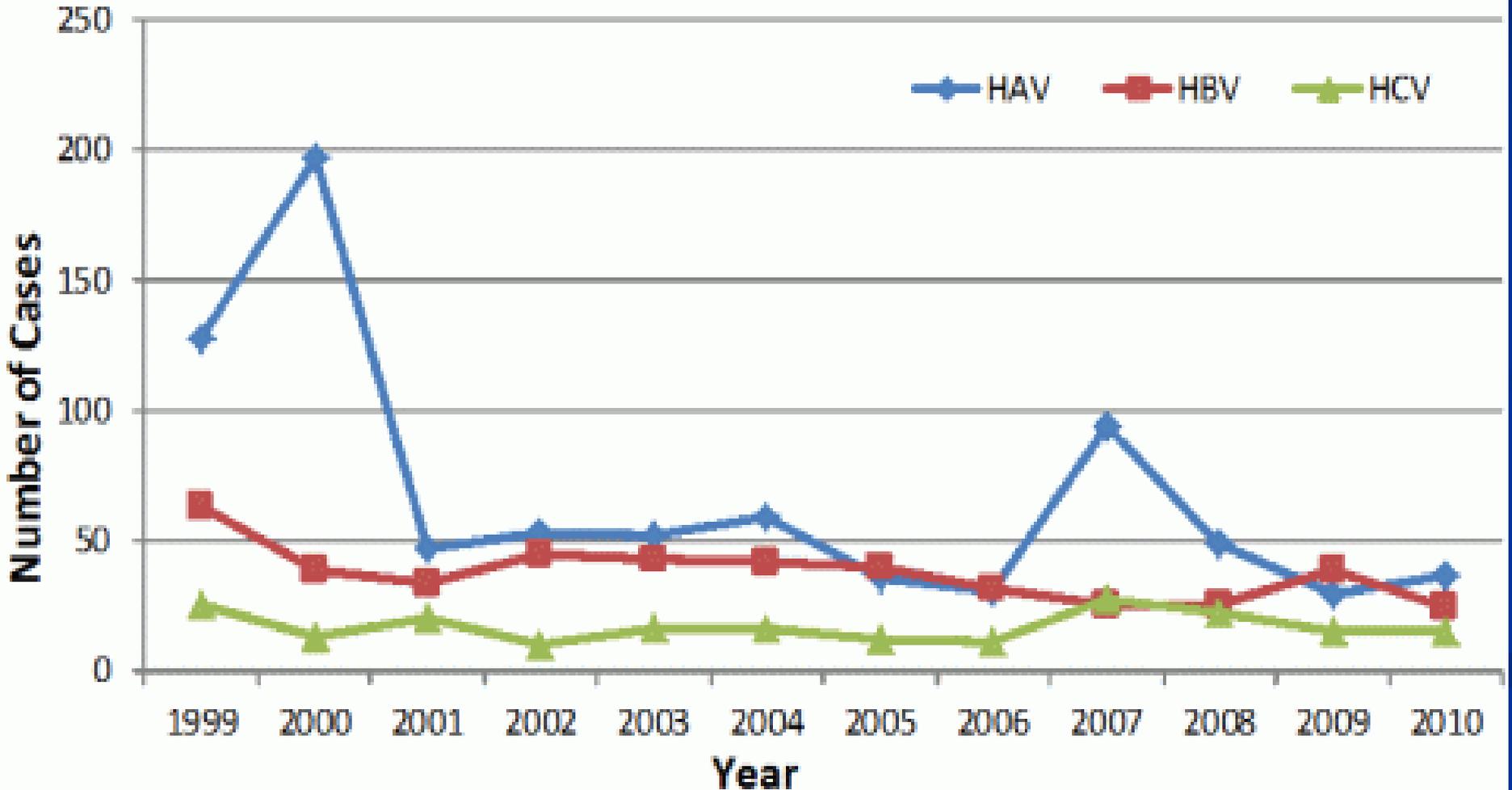


Source: MN Dept of Health, web site accessed: April 7, 2012

Persons Living with HCV in MN by Race Rates (per 100,000 persons*), 2010



Number of acute cases per year, 1999-2010

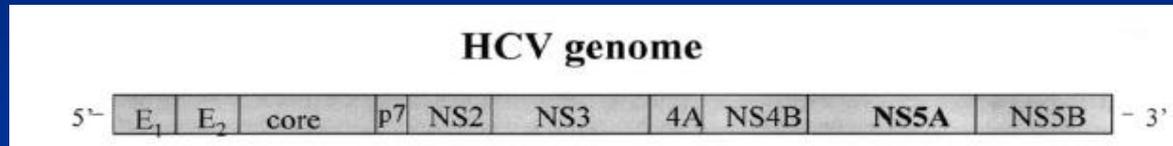


What is the natural history of hepatitis C?

- Single stranded RNA virus of the Flaviviridae family
- 'error prone' replication
- 7 HCV genotypes and > 50 subtypes



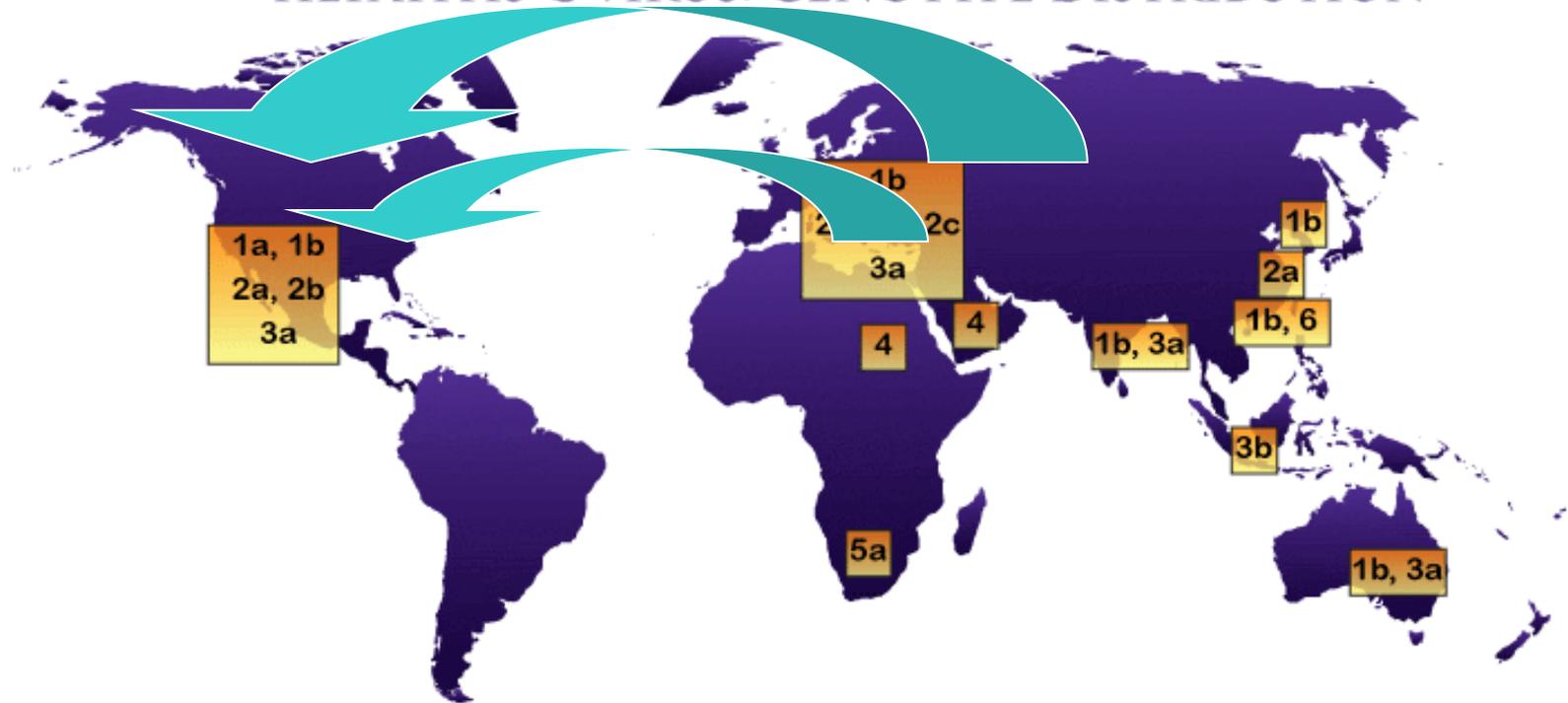
HCV Genome



- *HCV core protein* :
 - this structural protein is implicated in the nucleocapsid assembly

- *The NS5A protein*:
 - it has a variety of functions, including participation in polyprotein cleavage and interaction with host proteins and modulation of host homeostasis

HEPATITIS C VIRUS: GENOTYPE DISTRIBUTION



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**HCV Infection
100%**

**Subclinical Course
~75%**

**Acute Hepatitis
~25%**

**Persistent Infection
85-100%**

**Fulm. Hepatitis
Very Rare**

**Chronic Hepatitis
50-70%**

Extrahepatic Problems ~7%
• Arthritis
• Skin Problems
• Glomerulonephritis
• Cryoglobulinemia

**Liver Cirrhosis
12-25% after ~20 ys**

**Liver Cancer
1-5%**

**HCV
Course**

Risk Factors

➤ Common causes

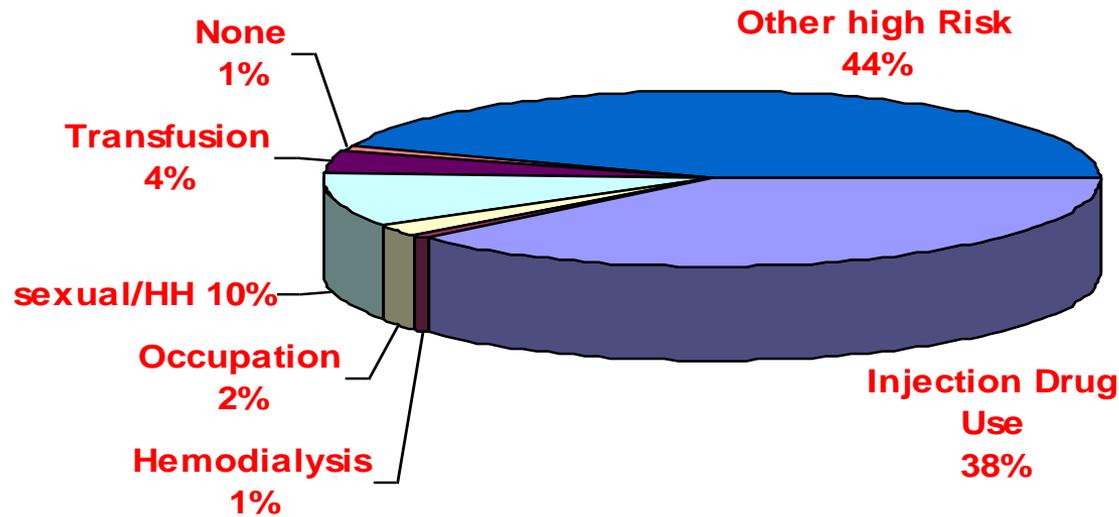
- IVDU
- contaminated blood products (prior to 1990)
- Hemodialysis
- Mother to infant transmission
- Sexual transmission

➤ Uncommon causes

- Occupational
- Intranasal cocaine
- Razors
- Toothbrushes
- Tattoos
- Body piercing

What are the risk factors?

**Risk Factors for Acute Hepatitis C:
United States 1990-1993**



Tattoos & risk of hepatitis C infection

- In prison populations the OR:3.4 (95% CI 1.6 - 7.5)
- A systematic review and meta-analysis of 124 studies from 30 countries
 - Pooled OR 2.74 (95% CI 2.38-3.15) for hepatitis C comparing those with and without tattoos



IVDU- (up to 65%)
main risk factor



Other transmission issues

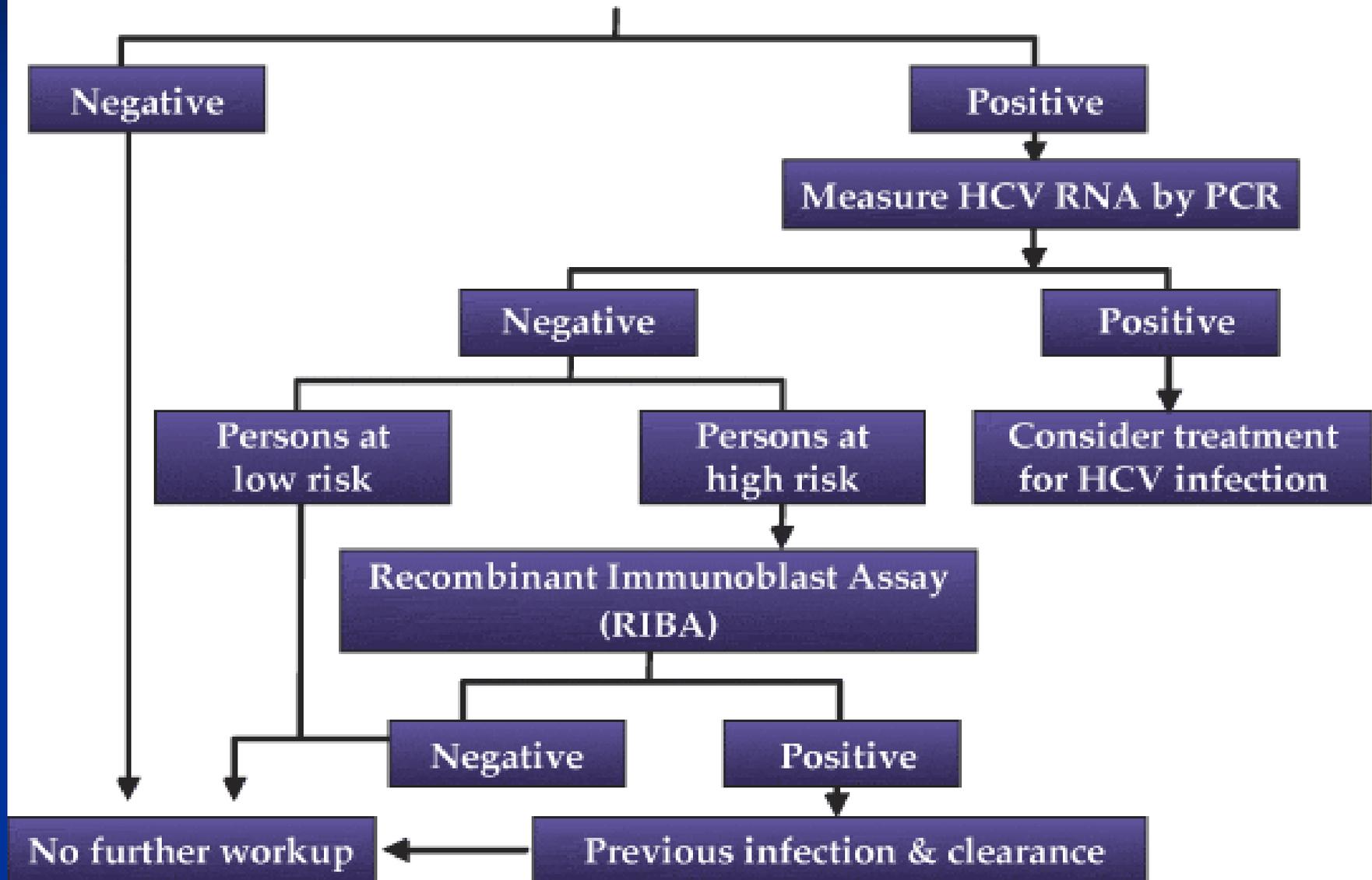
- **HCV not spread by kissing, hugging, sneezing, coughing, food or water, sharing eating utensils or drinking glasses, or casual contact**
- **Do not exclude from work, school, play, childcare or other settings based on HCV infection status**

What is the approach to diagnose hepatitis C?

- HCV antibody
 - EIA 2 or EIA3- 97% specific
 - RIBA- useful in low-risk population
 - Hepatitis C Rapid Antibody Test (OraQuick), FDA approved 6/2010, ~ 20 min results
- HCV RNA – positive in 1-3 weeks of exposure
- Genotyping- for prognosis
- Imaging
- HIV & hepatitis A & B screening

TESTING FOR HEPATITIS C

SECOND OR THIRD-GENERATION EIA



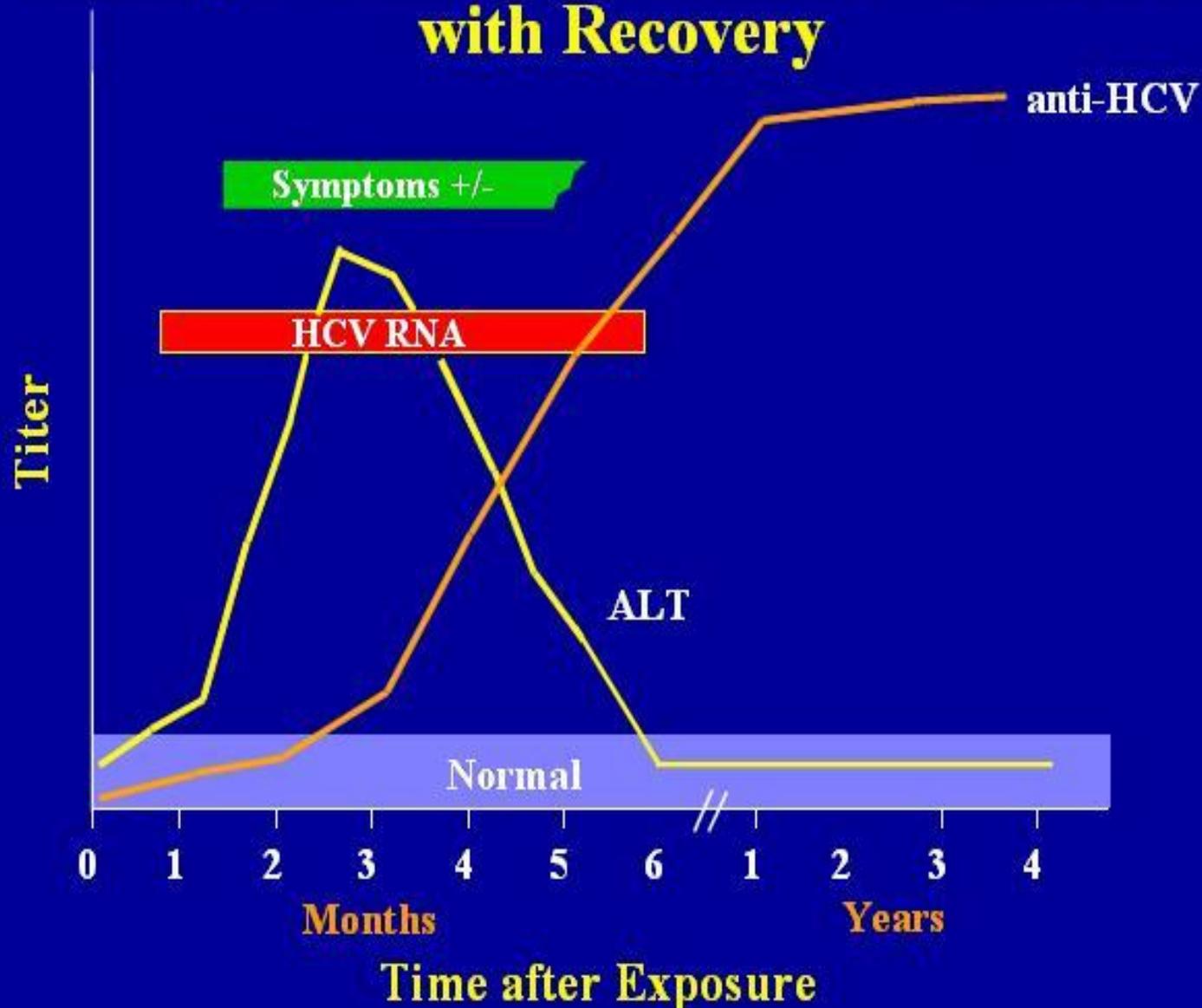
Test	Use	Comments	Approximate Cost, \$
Serum alanine aminotransferase	Screening	Widely available; reproducible results; nonspecific	35
HCV enzyme immunoassay	Screening	Reproducible; requires confirmation	100
Recombinant immunoblot assay	Confirmation	Most useful in low-risk blood donor situations	300
HCV RNA by PCR	Confirmation, quantitation of viremia	Sensitive and specific; technically demanding	250 to 700
HCV quantification by branched-chain DNA	Confirmation, quantitation of viremia	Reproducible; inaccurate with viral loads < 3200 copies/mL	250 to 350
HCV genotyping	Treatment prognosis	Can shorten course of antiviral therapy	350 to 750

* HCV = hepatitis C virus; PCR = polymerase chain reaction.

Acute Infection

- Asymptomatic (70-85%)
- If symptomatic (within 50 days of exposure)
 - Jaundice
 - Fatigue
 - Abdominal pain
 - Nausea
- Diagnosis:
 - Seroconversion
 - Positive PCR
 - Elevated liver enzymes
- Anti-viral therapy indicated after week 12

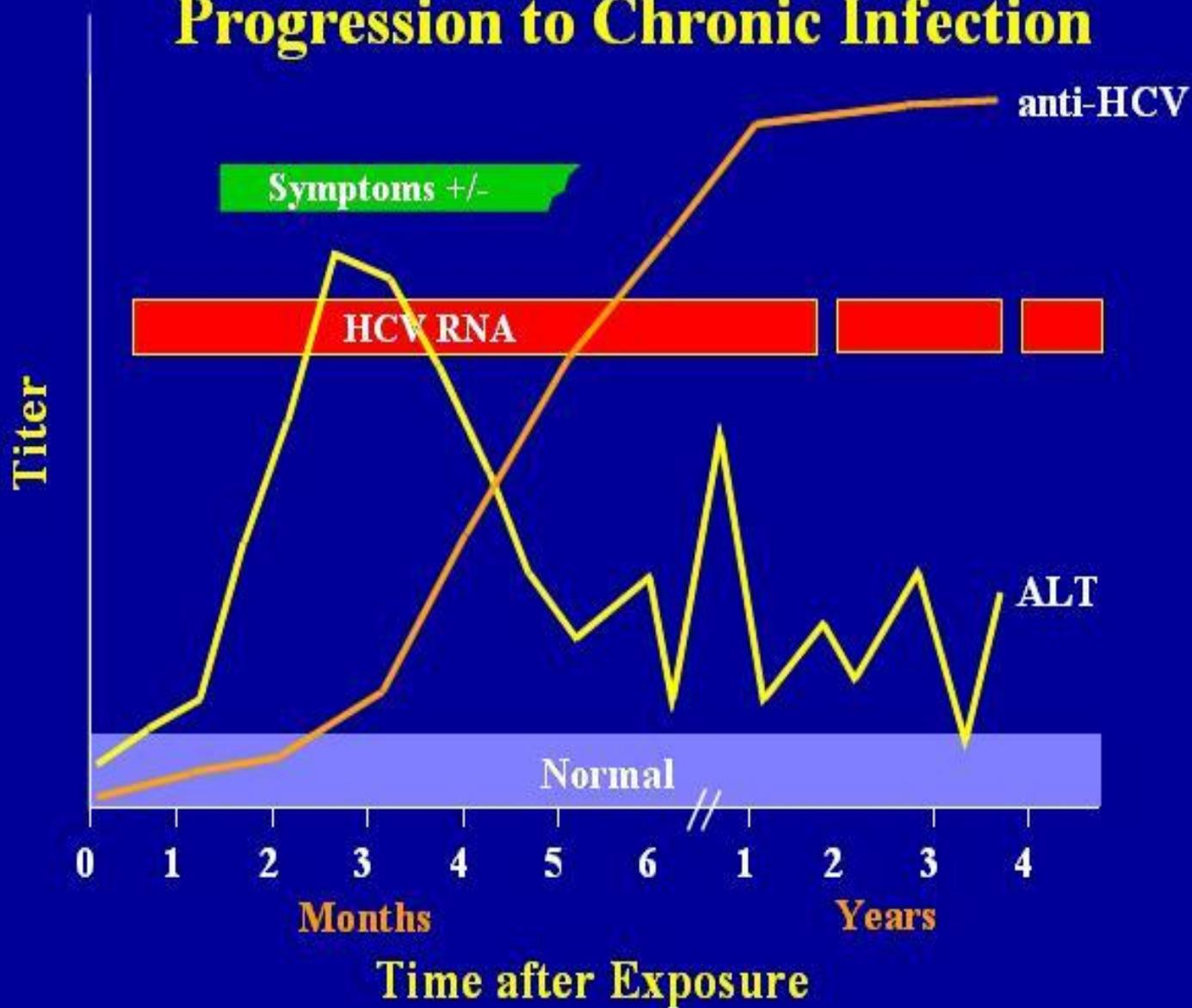
Serologic Pattern of Acute HCV Infection with Recovery



Chronic Infection

- Most common sequelae acute infection (60-85%)
- Insidious, progressive disease
- Diagnosis made on blood donor screen or elevated ALT on physical

Serologic Pattern of Acute HCV Infection with Progression to Chronic Infection



Extra-hepatic manifestations

- Cryoglobulinemia
- Membranoproliferative glomerulonephritis
- Porphyria cutanea tarda
- seronegative arthritis
- lichen planus
- B-cell lymphoma



Porphyria Cutanea Tarda

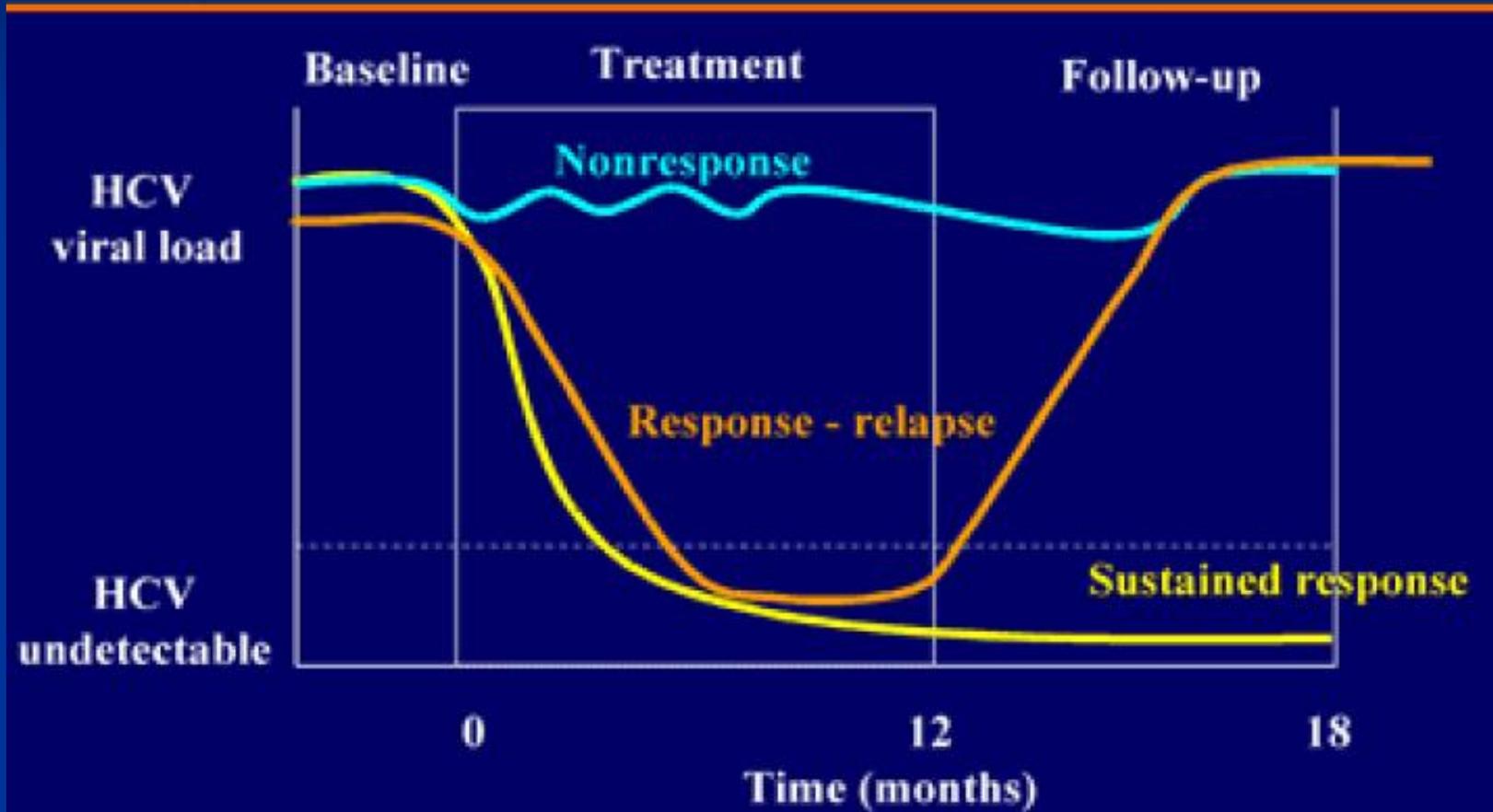


Mixed Cryoglobulinemia

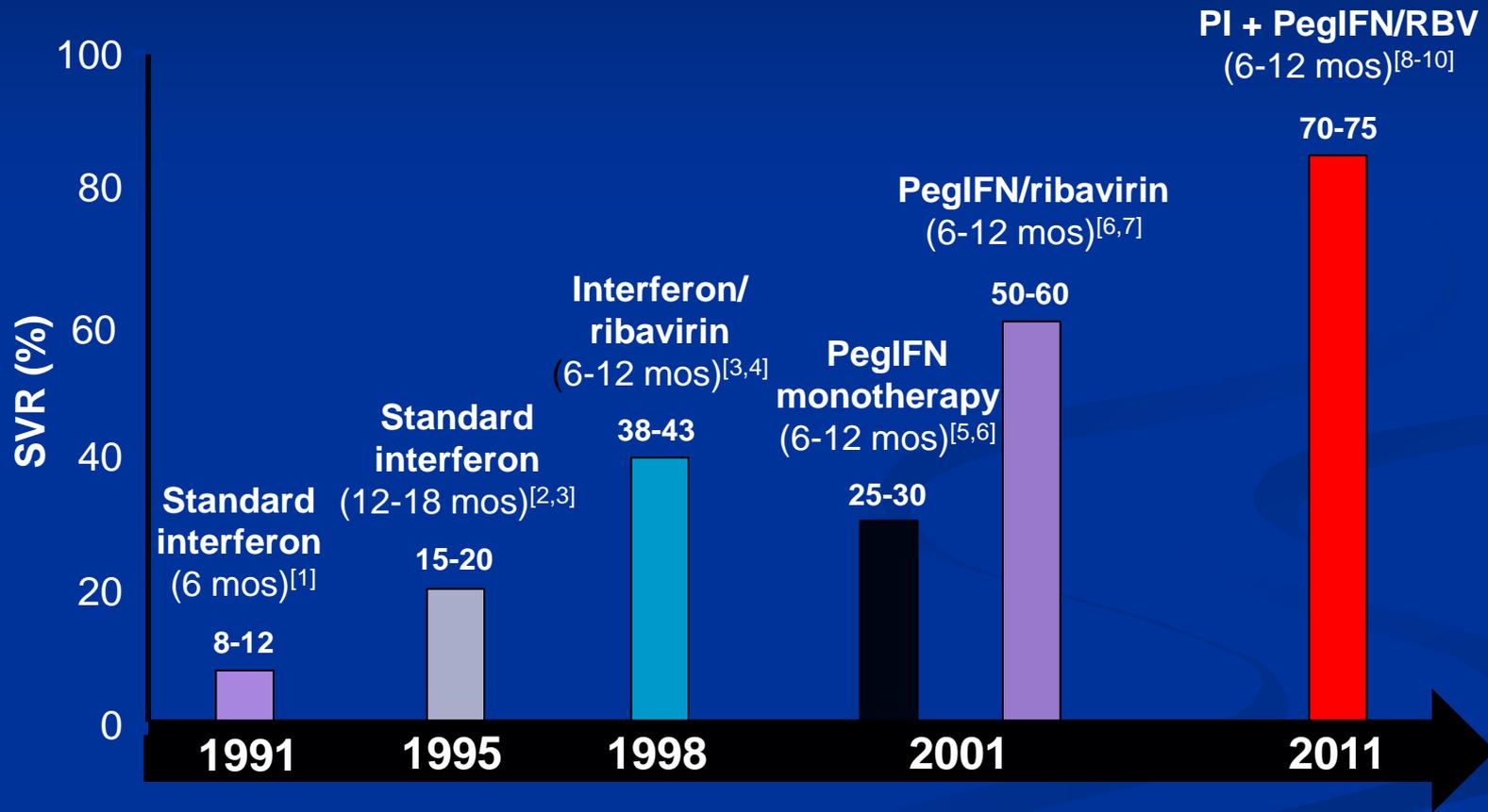
Who Needs Treatment?

- Acute hepatitis C
- Increased risk for cirrhosis
 - Advanced fibrosis
 - Prior to transplantation
- Patients with symptoms
- HIV-HCV coinfecting patients

Clinical course on anti-viral therapy



Treatment of Chronic Hepatitis C



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.

2 Protease Inhibitors Approved for Genotype 1 HCV Infection

Protease Inhibitor	Additional Regimen Components	Considerations
Boceprevir 800 mg TID (q7-9hrs) ^[1,2]	PegIFN alfa + weight-based RBV	<ul style="list-style-type: none">■ Naive to previous therapy■ Previous treatment failure■ Compensated cirrhosis■ RGT■ Take with food
Telaprevir 750 mg TID (q7-9hrs) ^[2,3]	PegIFN alfa + weight-based RBV	<ul style="list-style-type: none">■ Naive to previous therapy■ Previous treatment failure■ Compensated cirrhosis■ RGT■ Take with food (not low fat)

For patients with genotype 2/3 infection, HCV therapy with pegIFN/RBV remains the standard of care

1. Boceprevir [package insert]. 2011.
2. Ghany MG, et al. Hepatology. 2011;54:1433-1444.
3. Telaprevir [package insert]. 2011.

Phase III Protease Inhibitor Studies

■ Telaprevir

■ Treatment-naïve

- ADVANCE^[1]

- ILLUMINATE^[2]

■ Treatment-experienced

- REALIZE^[3]

■ Boceprevir

– Treatment-naïve

- SPRINT-2^[4]

– Treatment-experienced

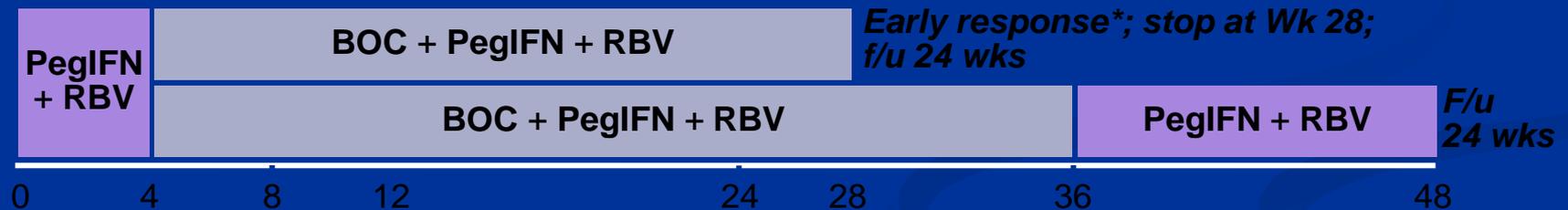
- RESPOND-2^[5]

Treatment-Naive Patients

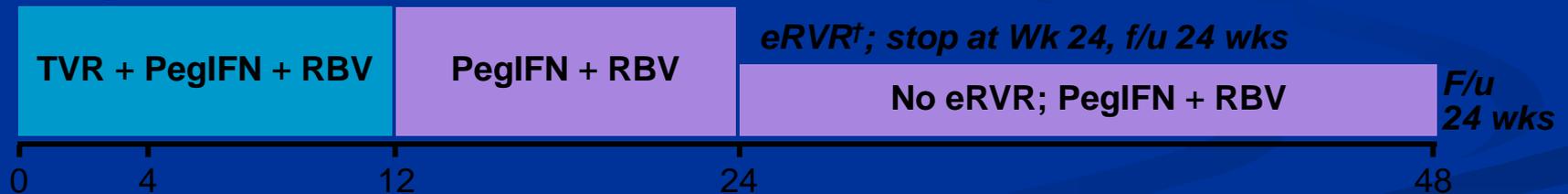
New Standard of Care for Genotype 1 Treatment-Naive Patients

- Recommendation:** Optimal treatment for all genotype 1 treatment-naive patients is BOC or TVR + pegIFN/RBV
 - BOC and TVR should not be used without pegIFN/RBV

Boceprevir^[1,2]



Telaprevir^[2,3]



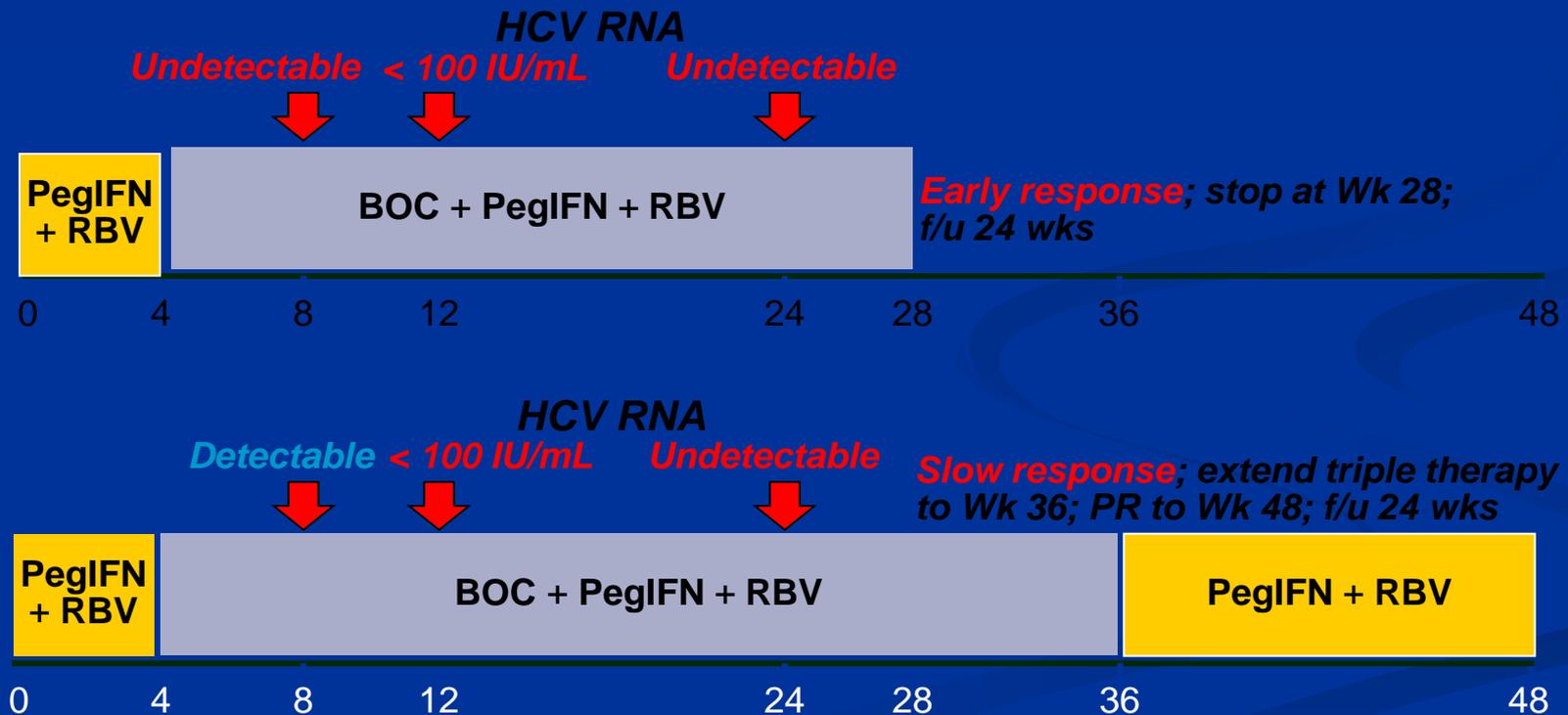
*Undetectable HCV RNA at Wk 8 of therapy (Wk 4 of triple therapy).

†Undetectable HCV RNA at Wks 4 and 12 of triple therapy.

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

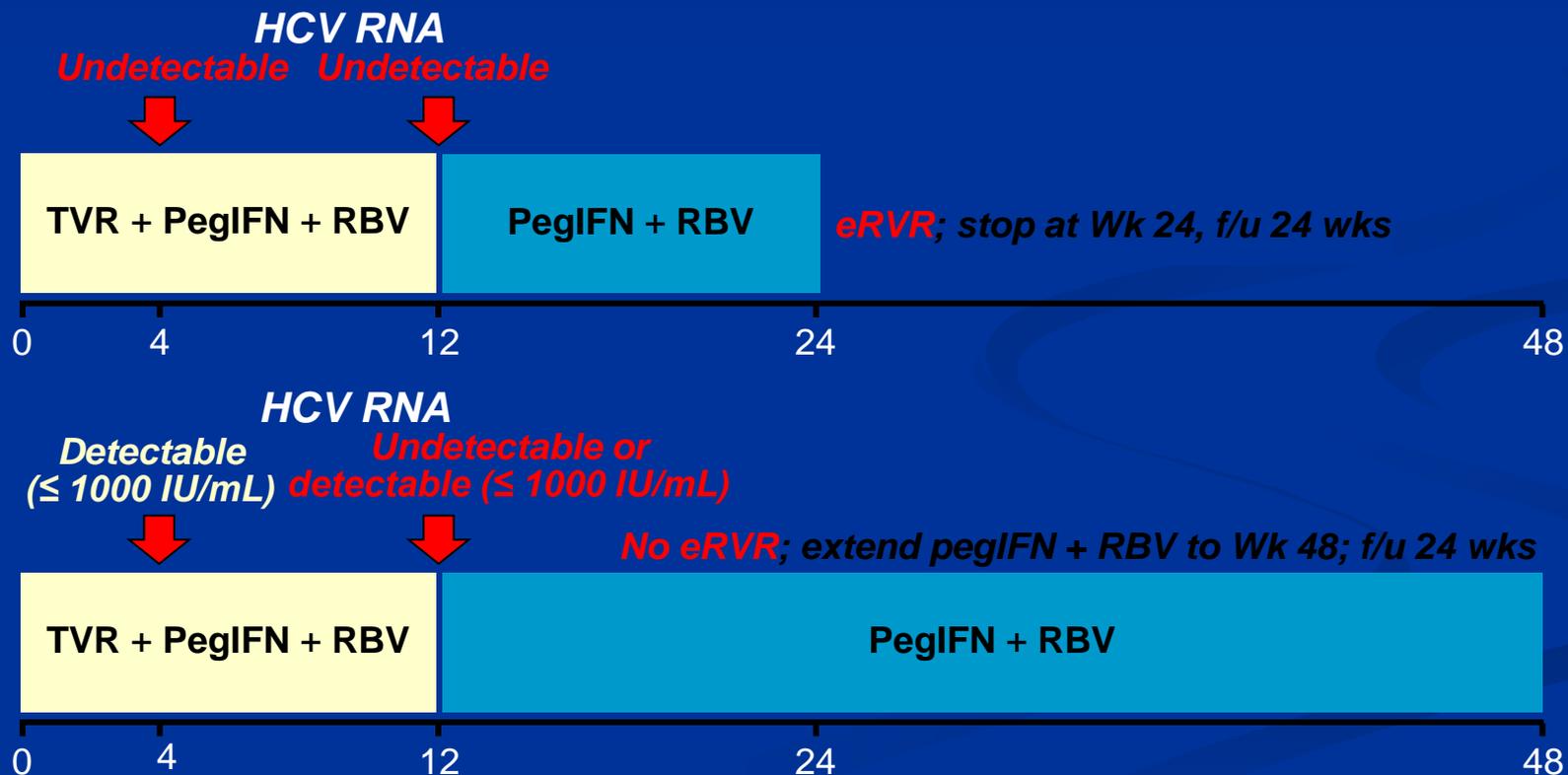
Response-Guided Therapy Paradigm With BOC + PegIFN/RBV in Tx-Naive Patients

- **Recommendation:** Noncirrhotic patients can be considered for response-guided therapy with BOC



Response-Guided Therapy Paradigm With TVR + PegIFN/RBV in Tx-Naive Patients

- **Recommendation:** Noncirrhotic patients can be considered for response-guided therapy with TVR



Futility Rules for BOC or TVR + PegIFN/RBV in Tx-Naive Patients

- **Recommendation:** All therapy should be discontinued in patients with the following:

BOC^[1,2]

Time Point	Criteria	Action
Wk 12	HCV RNA \geq 100 IU/mL	Discontinue all therapy
Wk 24	HCV RNA detectable	Discontinue all therapy

TVR^[1,3]

Time Point	Criteria	Action
Wk 4 or 12	HCV RNA > 1000 IU/mL	Discontinue all therapy
Wk 24	HCV RNA detectable	Discontinue pegIFN/RBV

Assay should have a lower limit of HCV RNA quantification of \leq 25 IU/mL and a limit of HCV RNA detection of approximately 10-15 IU/mL.

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

Care of patients with hepatitis C

- Herbs and natural treatment
 - Milk Thistle
 - Liver aid
- Caffeine use
- Marijuana use
- Vaccination for hepatitis A and B

What are the contra-indications to Hepatitis C therapy?

➤ Therapy

➤ Interferon

Decompensated liver disease
Severe psychiatric disease, especially severe depression
Autoimmune disease
Active substance abuse, including alcohol
Pregnancy
Comorbid disease
Unstable coronary artery disease
Uncontrolled seizure disorder
Uncontrolled diabetes
Uncontrolled hypertension

➤ IFN + Ribavarin

Anemia
Hemolysis
Renal insufficiency
Coronary artery disease
Cerebral vascular disease
Gout
Inability to practice contraception

What are the contra-indications to Hepatitis C therapy?

➤ Therapy

➤ Boceprevir & Telaprevir

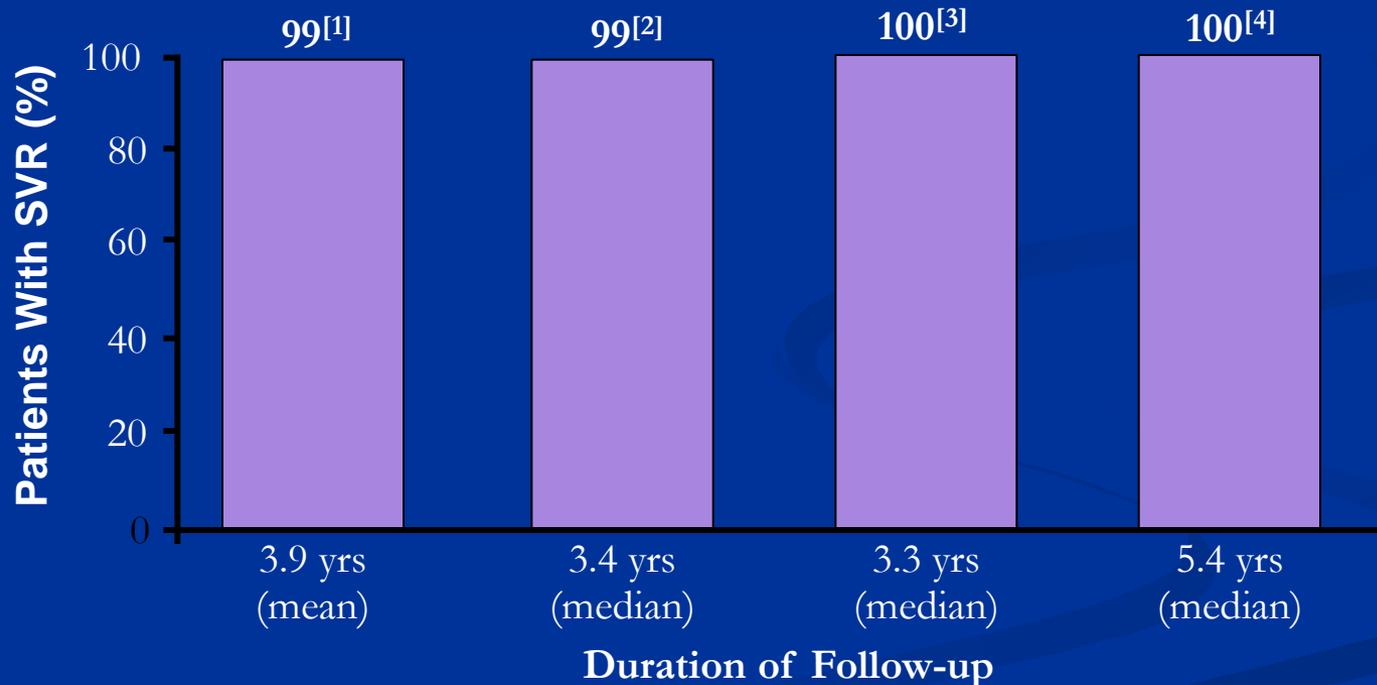
- Pregnancy & men whose female partner is pregnant
- Co-administration with other drugs (potent CYP3A4/5 inducers)
- Co-administration with drugs that are highly dependent on CYP3A for clearance

Complications of hepatitis C infection

- Cirrhosis (10-25%)
- Portal hypertension
 - Ascites
 - Encephalopathy
 - Variceal bleeding
 - Spontaneous bacterial peritonitis
- HCC (1-5%)

SVR Equivalent to Viral Cure

- Nearly 100% of patients who achieve SVR remain undetectable during long-term follow-up^[1-4]



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.

Side Effects of Triple Therapy

Telaprevir and Boceprevir- safety (no head-to-head data)

	ADVANCE (TVR)		SPRINT-2 (BOC)	
	TVR12/PR	PR	BOC RGT	PR
Discontinue due to AE	10%	7%	12%	16%
Discontinue due to Rash	7%	1%		
Anemia (<10/<8.5 gm/dl)	36%/ 9%	14%/ 2%	45%/ 5%	26%/ 4%
Use of Epo	Not permitted		43%	24%

Drug Side Effects are additive

- Peg- IFN alfa:
 - Flu-like symptoms, bone marrow suppression (**anemia**, leukopenia, thrombocytopenia), depression, fatigue
 - Hemolytic **anemia**, GI side effects, rash
- Ribavarin:
 - **Anemia**, dysgeusia
- Boceprevir:
 - Rash, **anemia**, anorectal symptoms
- Telaprevir:
 - Rash, **anemia**, anorectal symptoms

Management of Side Effects

Management of Anemia

- Check frequent hemoglobin levels; avoid iatrogenic anemia
- Patient with liver cirrhosis-especially vulnerable
- Never (!!) dose reduce the protease inhibitor
- Use stepwise dose reduction of RBV
- Start RBV dose reduction early
- Consider the use of erythropoietin and blood transfusions
- Reduced efficacy of erythropoietin in patients with cirrhosis? (no studies)

Telaprevir-associated rash

- Rash primarily eczematous and resolves slowly upon cessation of therapy
- Moderate and severe rash with progression are managed by sequentially discontinuing of Tx:
 - TVR → RBV → Peg-IFN
- Rash severity: mainly grade 1-2
 - grade 3 ~ 3%
- Drug Rash with Eosinophilia and Systemic Symptoms (DRESS) and Stevens-Johnson Syndrome (SJS) in < 1% of patients
- Biomarker required

Grading of TVR-associated rash severity

Description

- Grade 1 (mild): localized skin eruptions and/ or localized skin eruption with limited distribution, w/wo associated pruritus
- Grade 2 (moderate): Diffuse skin eruption involving up to 50% of BSA, w/wo superficial skin peeling, pruritus or mucous membrane involvement with no ulceration

Management

- Telaprevir interruption generally not necessary
- Telaprevir interruption generally not necessary
- For progressive eruption, TVR should be discontinued first
- Consider interrupting ribavirin and/or peginterferon if no improvement in eruption in 7 days or if rash worsens

Role of switching PI during therapy

- No role of switching PI in case of resistance
- Switch from TVR to BOC in case of severe rash- safety not assessed

Grading of TVR-associated rash severity

Description

- Grade 3 (severe): generalized rash involving >50% of BSA or rash presenting with any of the following:
 - Vesicles or bullae
 - Superficial ulceration of mucous membranes
 - Epidermal detachment
 - Atypical or typical target lesions
 - Palpable purpura/non-blanching erythema
- Life threatening or systemic lesions:
Steven Johnson Syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS), erythema multiforme (EM), acute generalized exanthematous pustulosis (AGEP), rash that requires therapy with systemic corticosteroids

Management

- Telaprevir must be stopped
- Interrupt RBV and/or PegIFN if no improvement in rash within 7 days or earlier if rash worsens
- Careful monitoring of skin, mucosa, CRP, CBC with eosinophils counts
- Steroid treatment
- Experienced dermatologist
- Permanent discontinuation of all treatment is required
- Steroid treatment
- admission

Telaprevir- associated rash

- Inform patient of the likelihood of rash
- Explain 9% rule of estimating body surface area
- Explain potential severities and the respective need for treatment discontinuation at > grade 2
- Inform about potential risks of SJS and DRESS
- Pre-emptive prescription for anti-histamines like allegra and potent steroids ointments
- Establish collaboration with a dermatologist

Telaprevir rash-grade 3



Telaprevir rash



Telaprevir rash



Practical considerations concerning PI

- Check necessity of concurrent medications:
 - Herbal products
 - Sildenafil
- Stopping any concurrent medication:
 - Statins
 - PDE5 inhibitors
- Study full prescribing information

Drugs within class that are contraindicated with TVR and BOC

- Alpha 1 adrenoreceptor antagonist: alfuzosin
 - Increased alfuzosin concentrations can result in hypotension
- Antimicrobials: Rifampin & Anticonvulsants: phenytoin
 - May lead to loss of virologic response to Victrelis
- Ergot derivatives:
 - Potential for acute ergot toxicity
- GI motility agent: Cisapride
 - Potential for cardiac arrhythmias.
- Herbal products: St' John's Wort
 - May lead to loss of virologic response to Victrelis

Drugs that are contraindicated with TVR and BOC

- HMG Co-A reductase inhibitors: atorvastatin, lovastatin, simvastatin
 - Potential for myopathy, including rhabdomyolysis
- Neuroleptic: pimozide
 - Potential for cardiac arrhythmias
- PDE5 inhibitor: sildenafil, tadalafil
 - hypotension, prolonged erection and syncope
- Sedatives/Hypnotics: orally administered midazolam, triazolam
 - Prolonged or increased sedative effect or respiratory depression

future

- Hepatitis C vaccine
- Interferon free therapy

Hepatitis C virus is curable!