

Treatment of Chronic Hepatitis C in HIV infection

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Disclosures

The following disclosures are my reported disclosures related to this presentation:

- Vertex: Research support; speakers' bureau, advisor
- Merck: Research support; advisor
- Boehringer: Review panel member
- Genentech: Speaker's bureau; research support
- Pfizer: Review panel member.

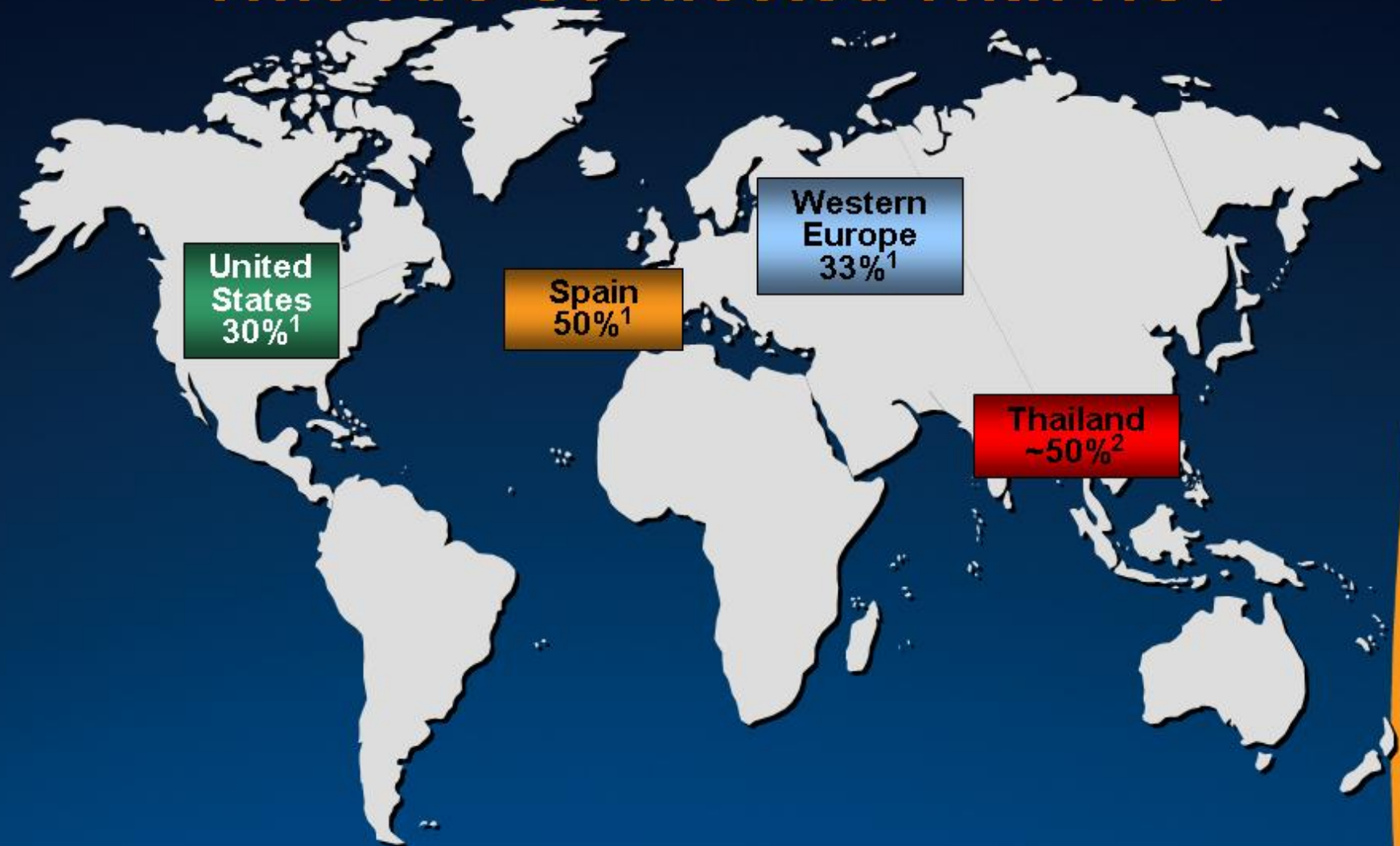
Presentation outline

- Epidemiology and evaluation of HCV in HIV/HCV coinfection
- Limited data on direct acting antivirals for HCV in HIV-infected people.
- Limited data on drug-drug interactions between telaprevir and antiretroviral medication.

HCV: A Global Challenge



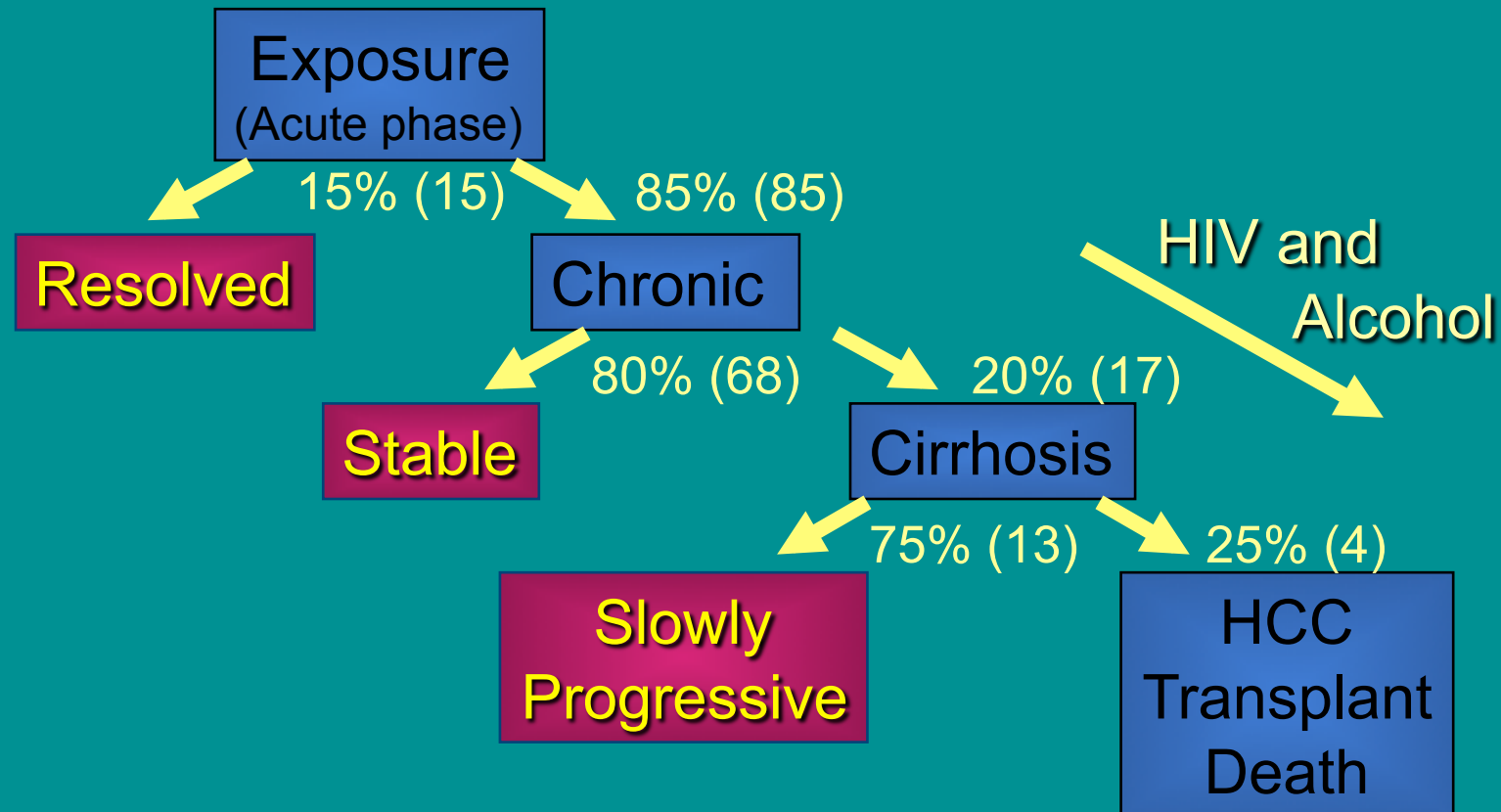
Worldwide Prevalence: % of HIV Patients Who Are Coinfected With HCV



¹Soriano V, et al. *AIDS*. 2002;16:813-826.

²Chanbancherd P, et al. *Southeast Asian J Trop Med Public Health*. 2003;Sept;34:580-582.

Natural History of HCV Infection



HCV: Who Should Be Tested?

- Unexplained liver disease
- Unexplained abnormal ALT
- Blood transfusion before 1992
- Past or present IV drug use
- Unequivocal blood exposure of skin or mucous membrane
- History of or current hemodialysis
- History of intranasal cocaine use
- Heavy alcohol use^{*}
- History of multiple sexual partners[†]
- Vietnam-era service[‡]
- Tattooing or repeated body piercing

^{*}Defined as more than 50 grams of alcohol per day for 10 or more years.(an average drink contains 10-12 grams of alcohol).

Adapted from <http://www.hepatitis.va.gov/vahep?page=tp03-01-04-02>. Accessed 12/30/04.

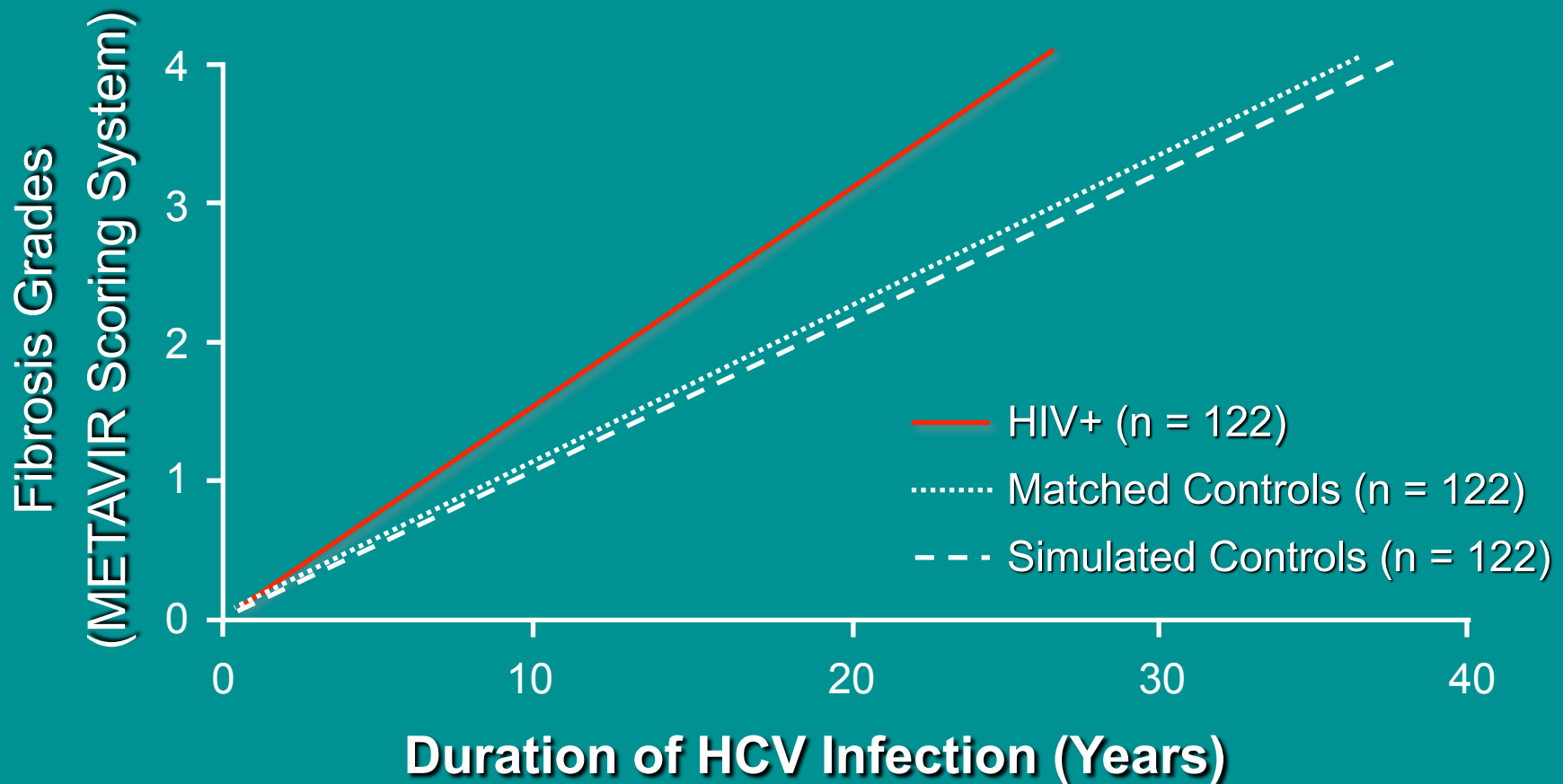
[†]Defined as more than 10 lifetime partners.

[‡] Dates of service between 1961-1975.

HCV Antibody Test

- False-positives may occur in patients with:
 - Autoimmune hepatitis
 - Hypergammaglobulinemia
 - Normal liver enzymes and no risk factors for HCV
 - Uncommon with 2nd/3rd generation tests
- False-negatives may occur in:
 - Immunosuppressed patients (e.g., organ transplant recipients)
 - Chronic dialysis patients
 - Very uncommon in 2nd /3rd generation tests

Effect of HIV Coinfection on Fibrosis Progression Rates



Increase with CD4 <200/mm³, EtOH, Age

Benhamou Y, et al. *Hepatology*. 1999;30:1054.

Diagnostic Evaluation of Viral Hepatitis

History and Physical Examination

- Duration & potential route of infection
- Alcohol consumption
- Symptoms and signs of liver disease

Laboratory evaluation

- Albumin, bilirubin, PT, ALT:AST, CBC, platelets
 - Quantitative HBV DNA or HCV RNA
 - HCV: Genotype
- HBV: surface Ag, sAb, core Ab, eAg and eAb

Assessment of liver histology-Is it still necessary?

- Liver biopsy
- Noninvasive markers of hepatic fibrosis

Viral Hepatitis Extrahepatic Manifestations

- Glomerulonephritis
- Cryoglobulinemia
 - Vasculitis
 - ?Lymphoma
- Porphyria cutanea tarda
- Lichen planus
- Association with type 2 diabetes mellitus.

Liver Biopsy

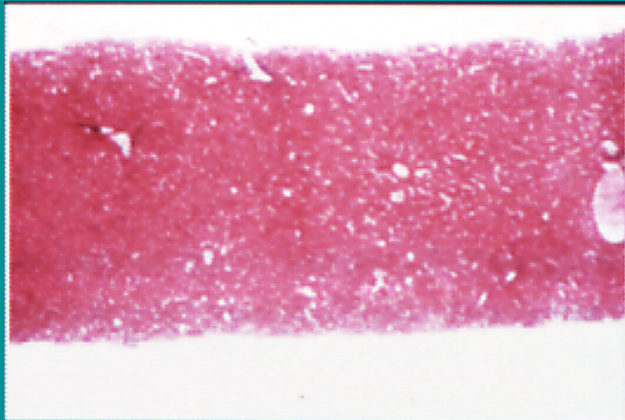
Assess liver injury

- Inflammation
- Fibrosis
- HBV: Stain for surface antigen and core

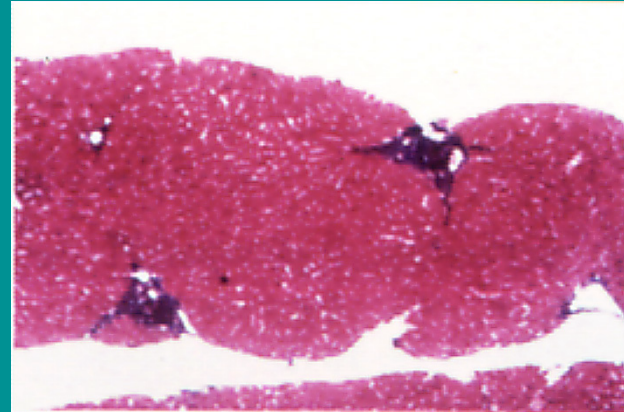
Relationship to treatment

- Urgency
- Necessity to complete therapy
- Influence retreatment and maintenance therapy

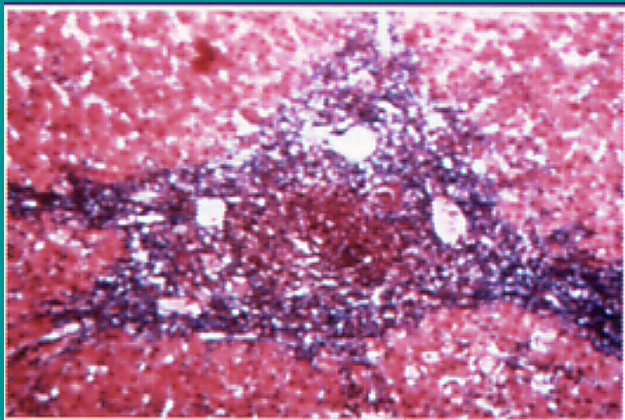
Fibrosis Progression in HCV



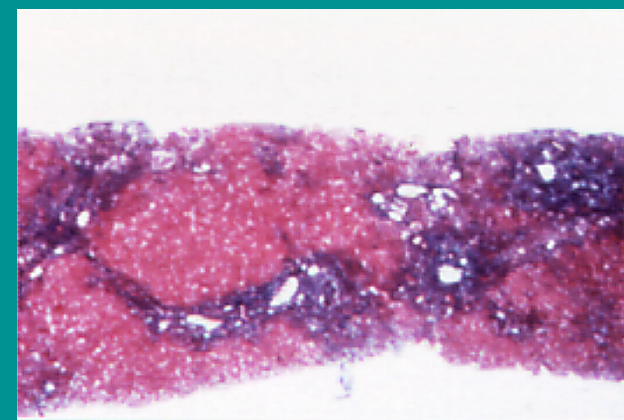
Normal



Mild Chronic Hepatitis



Moderate Chronic Hepatitis



Cirrhosis

Assessment of fibrosis: Scheuer

<u>Grade/Stage</u>	<u>Histology</u>
0	No or minimal activity
1	Portal inflammation
2	Mild piecemeal necrosis
3	Mod piecemeal necrosis
4	Severe piecemeal necrosis

Liver biopsy limitations

Invasive
procedure

Morbidity

Limited number of measurements

Mortality

Sampling
error

1/50,000 of liver

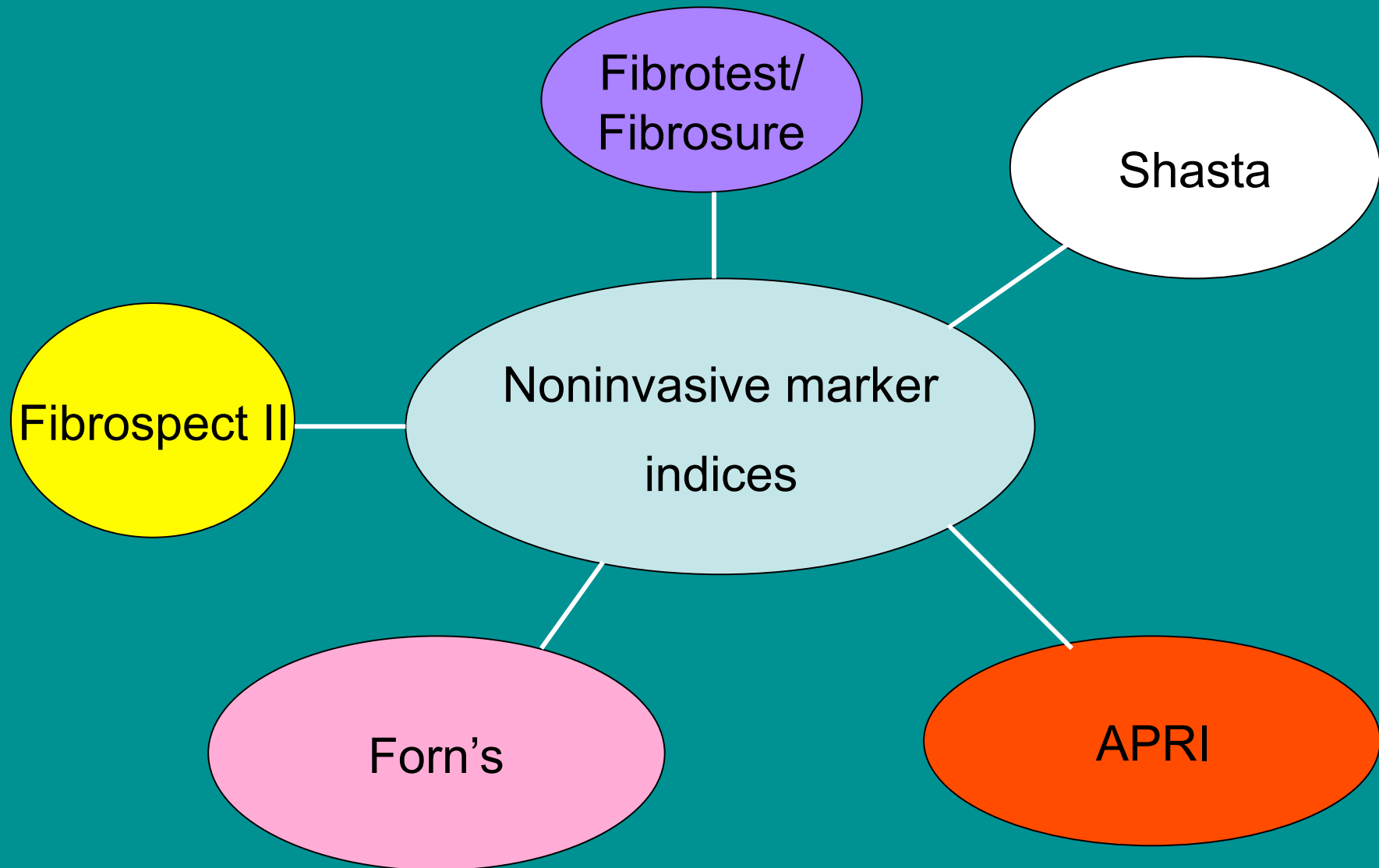
Biopsy size matters-2.5 cm

Fibrosis
assessment
variability

Pathologist

Different scoring systems

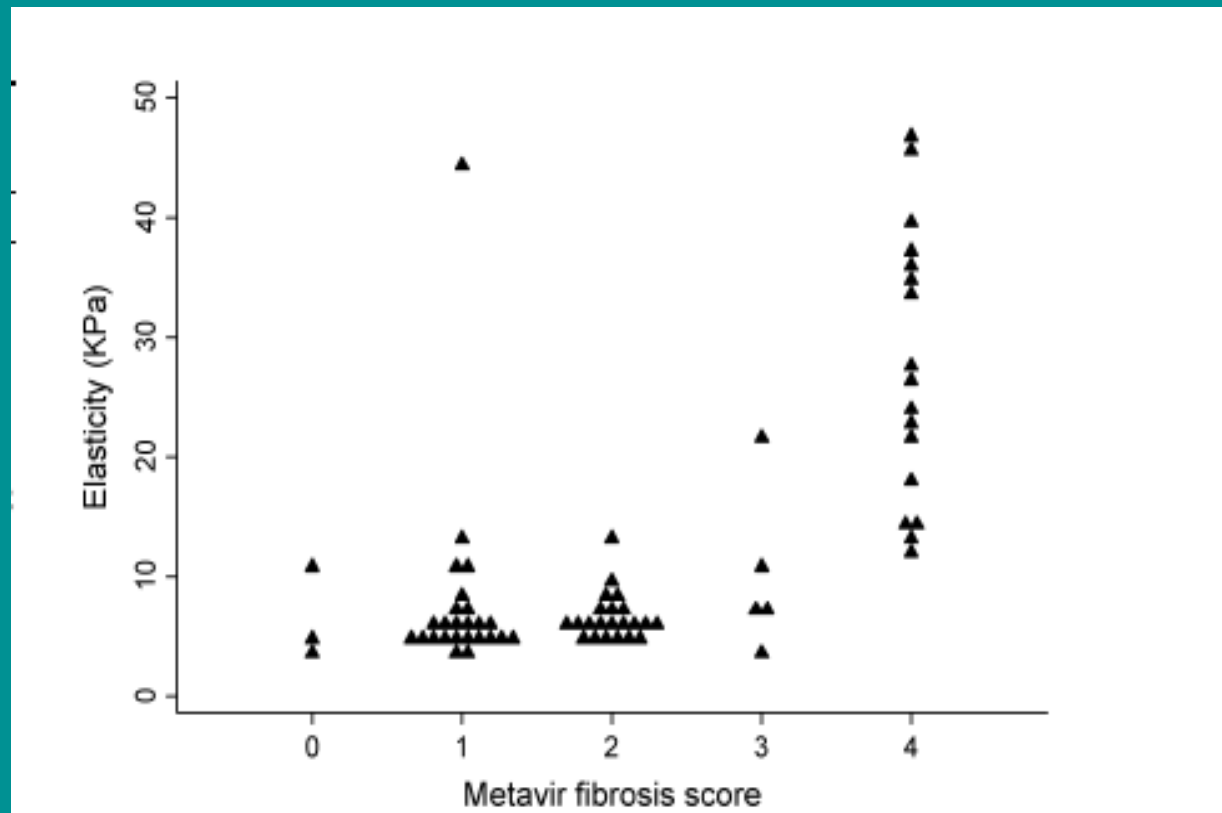
Liver biopsy alternatives



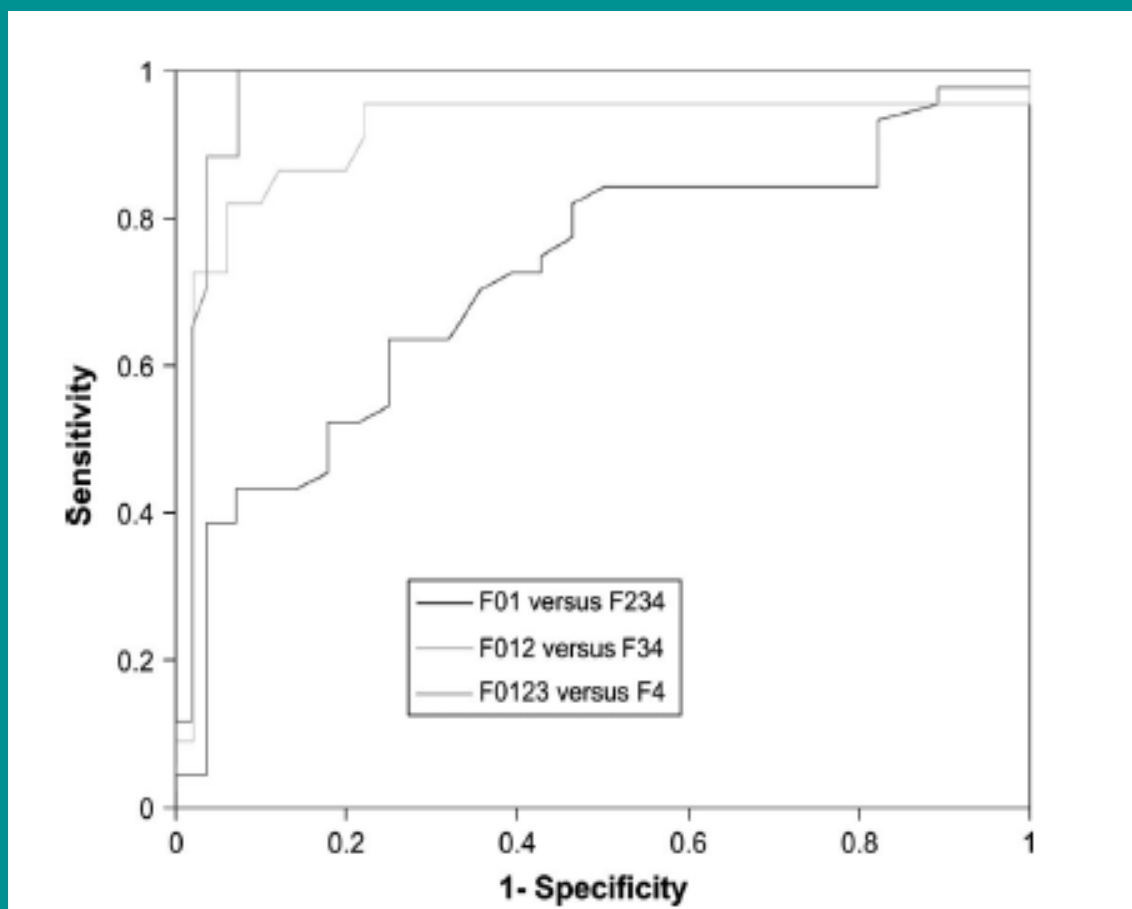
Transient elastography

Modified ultrasound based technique

Measure of liver stiffness



Transient elastography: Reliable detection of advanced fibrosis



Hepatic histology assessment- 2011

HCV antibody positive

HCV RNA detectable
(HCV genotype)

Platelets >70K
PT < 13.7
No ascites

Bleeding
diathesis

Percutaneous liver biopsy

Transjugular liver biopsy

2.5 cm length
Experienced hepatopathologist

Alternatives to liver biopsy

HCV antibody positive

HCV RNA detectable
(HCV genotype)

Fibrotest/Fibrosure (LabCorp)
Fibrospect (Prometheus)

Low value

Moderate values

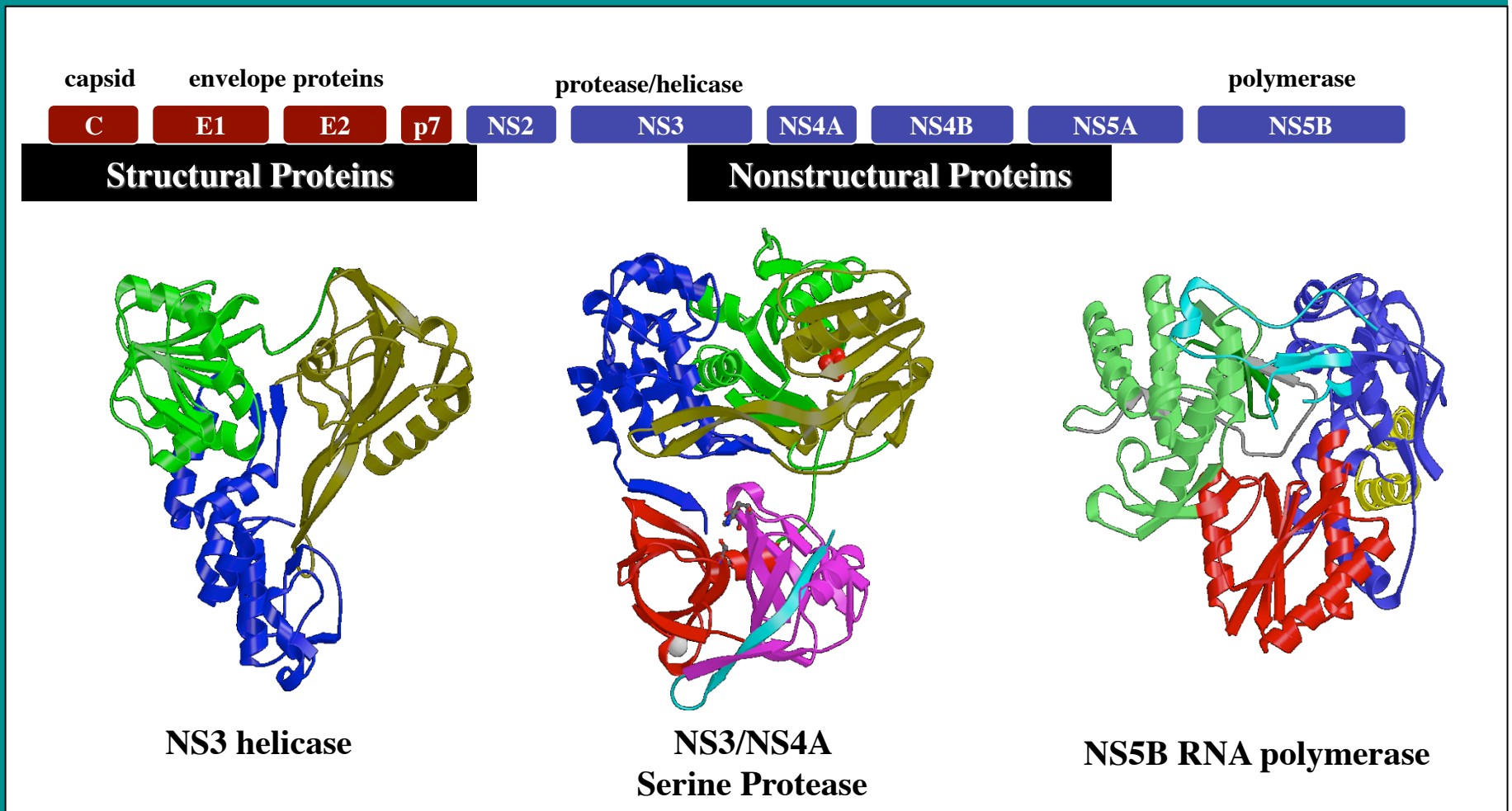
High values
Other lab abnormalities

Follow-up
Liver biopsy?
Treatment

Liver biopsy

Treatment?
Upper GI endoscopy?
HCC surveillance

Selected Targets for HCV Antivirals



Personal communication, Pat Weber, Schering Plough.

Why Treat HCV? A Curable Infection

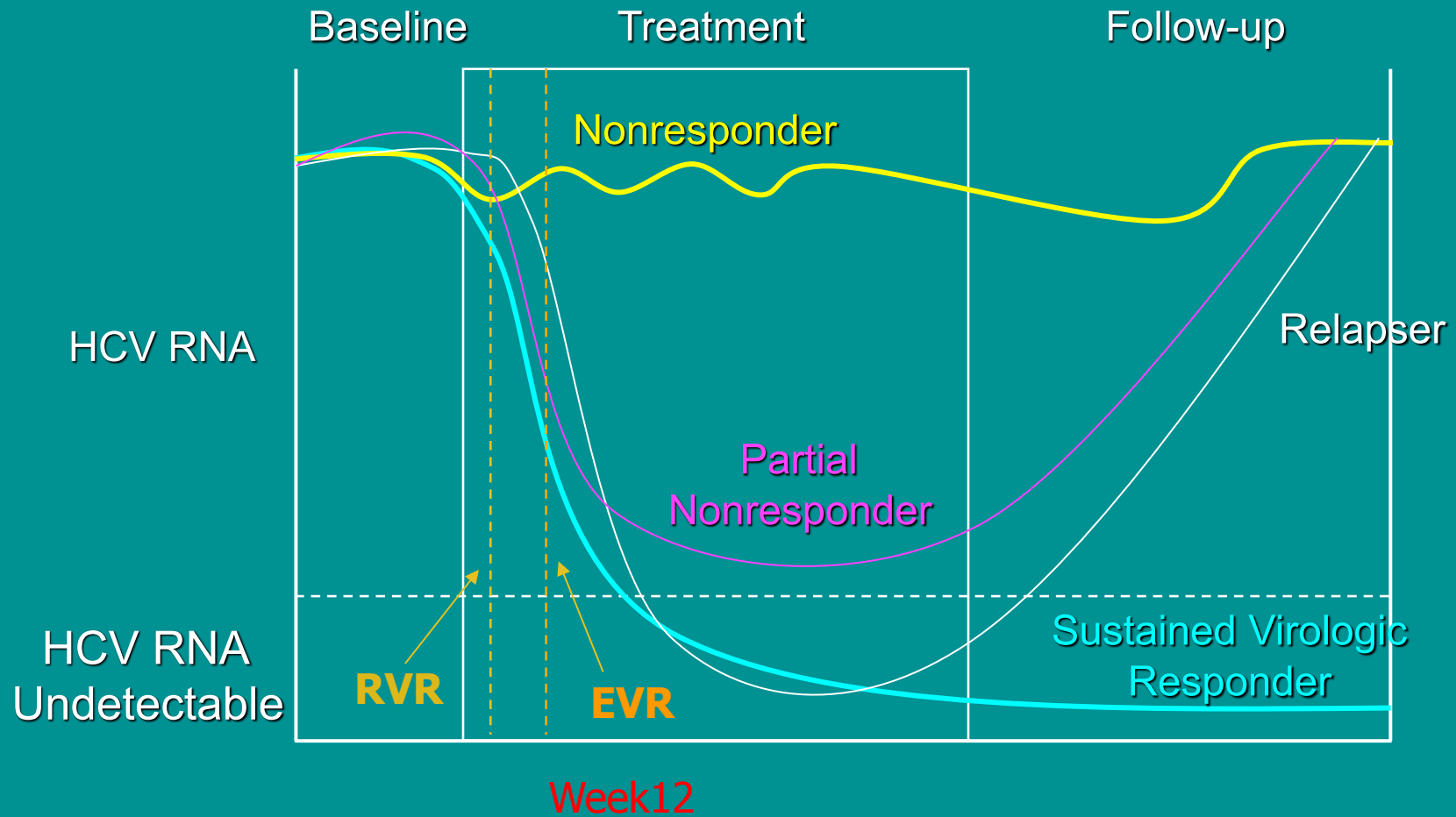
Primary goal-Viral Eradication

- Eradication possible-Viral replication extranuclear
- Sustained viral response-Absence of detectable serum or hepatic HCV RNA three or six months post treatment

Secondary goal-Halt Disease Progression

- Viral eradication enhances but not absolutely required for fibrosis regression.
- In absence of viral eradication, can decrease:
 - Fibrosis progression
 - Hepatocellular carcinoma
 - Development of end stage liver disease

Patterns of HCV Response



PEG-IFN/RBV Efficacy in HIV/ HCV Co-infection

Study	N	SVR		Geno 1		Geno non-1	
		#	%	#	%	#	%
Apricot ¹	860	116/289	40	51/176	29	59/ 95	62
ACTG ²	133	18/ 66	27	7/51	14	11/15	73
Ribavic ³	412	56/206	27	21/125	17	35/80	44
Total	1405	190/561	34	79/352	22	105/190	55

¹Torriani et al, NEJM 2004;351:438-50, ²Chung et al, NEJM 2004;351:451-9, ³Carrat et al, JAMA 2004;292:2839-48.

PEG-IFN/RBV Efficacy in HCV-infection

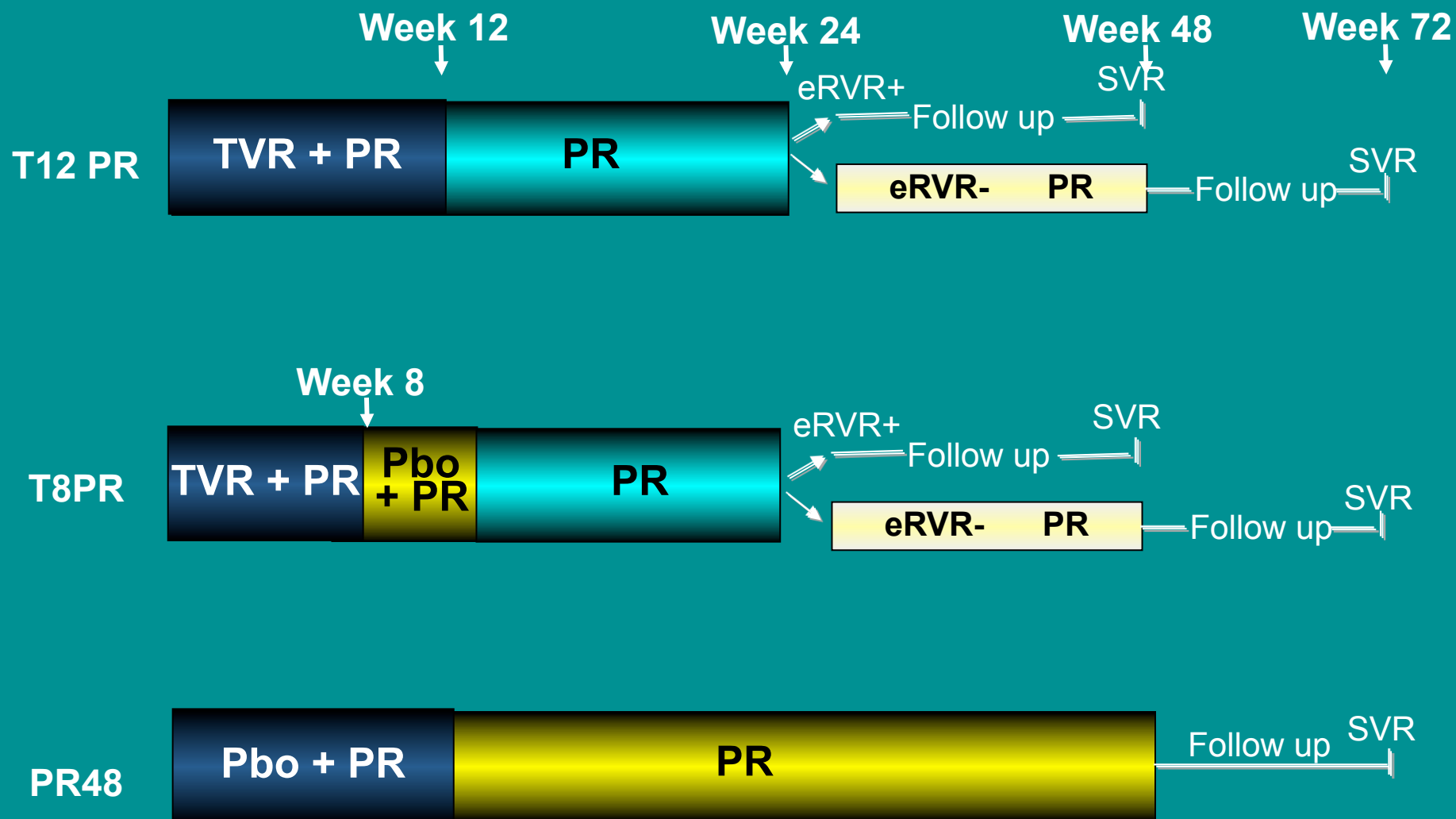
Study	N	SVR		Geno 1		Geno non-1	
		#	%	#	%	#	%
Manns ¹	1530	274/571	54	145/348	42	121/147	82
Fried ²	1121	255/453	56	136/298	46	106/140	76
Total	2651	529/1024	52	281/646	43	227/287	79
HIV/ HCV	1405	190/561	34	79/352	22	105/190	55

¹Manns et al, Lancet 2001;358:958-65, ²Fried et al, NEJM 2002;347:975-82

Advance

- Objectives
 - 12 or 8 weeks of telaprevir in combination with PEG-IFN/RBV in response guided treatment to standard treatment for 48 weeks.

Advance: Study Design



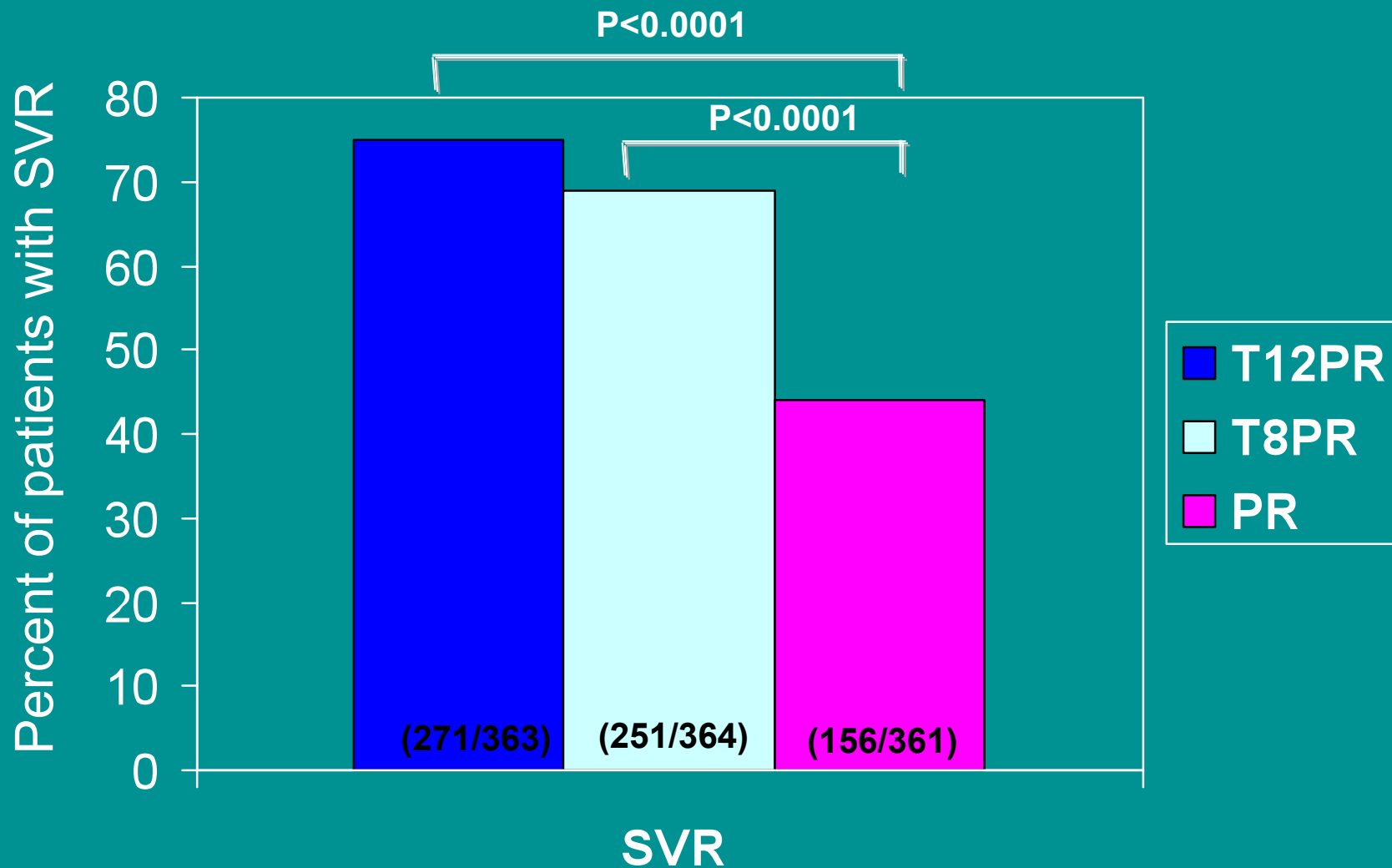
(T) TVR = telaprevir 750 mg q8hrs; Pbo = Placebo; PEG-IFN (P) = pegylated interferon plus ribavirin (R) 1000 or 1200 mg/d

Advance: Stopping rules

Timepoint	Criteria for Stopping	Action
Week 4*	HCV RNA > 1000 IU/ml	D/c TVR, cont. PR
Week 12		D/c all treatment
Week 24-40	HCV RNA detectable	D/c all treatment

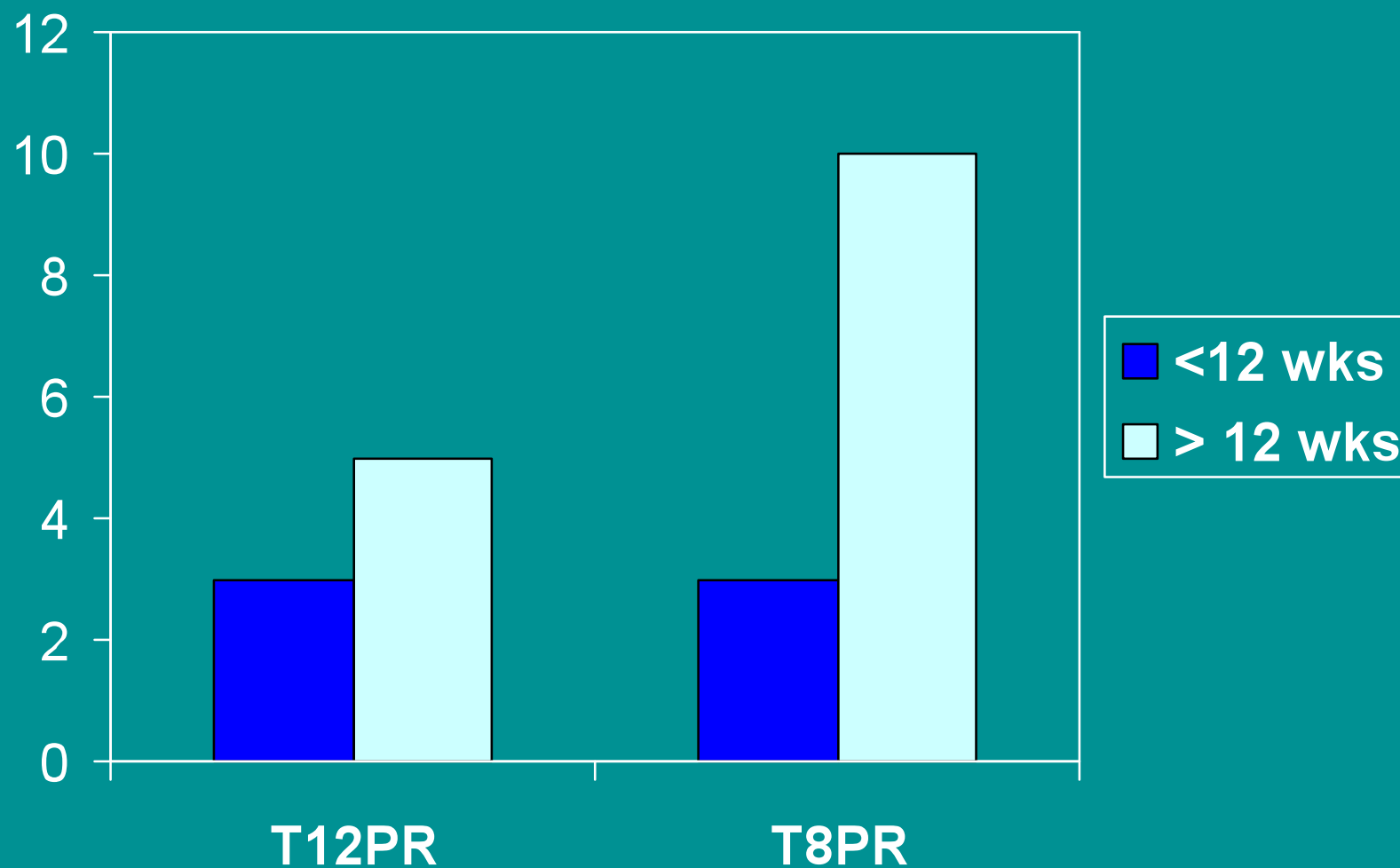
*Applies to telaprevir-treated patients only

SVR in TVR vs. PEG-RBV

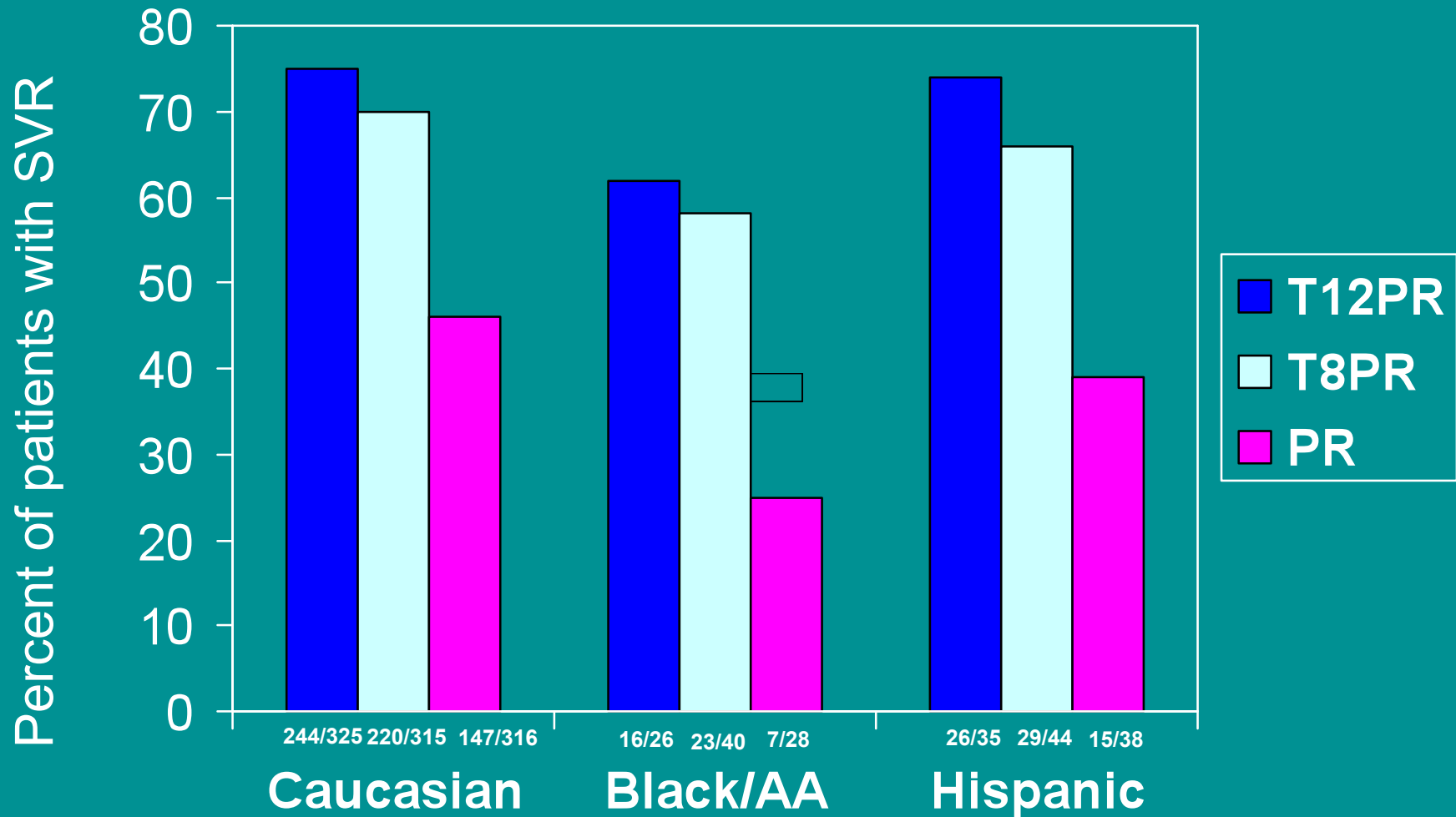


Virologic failure: Wk 8 vs. 12

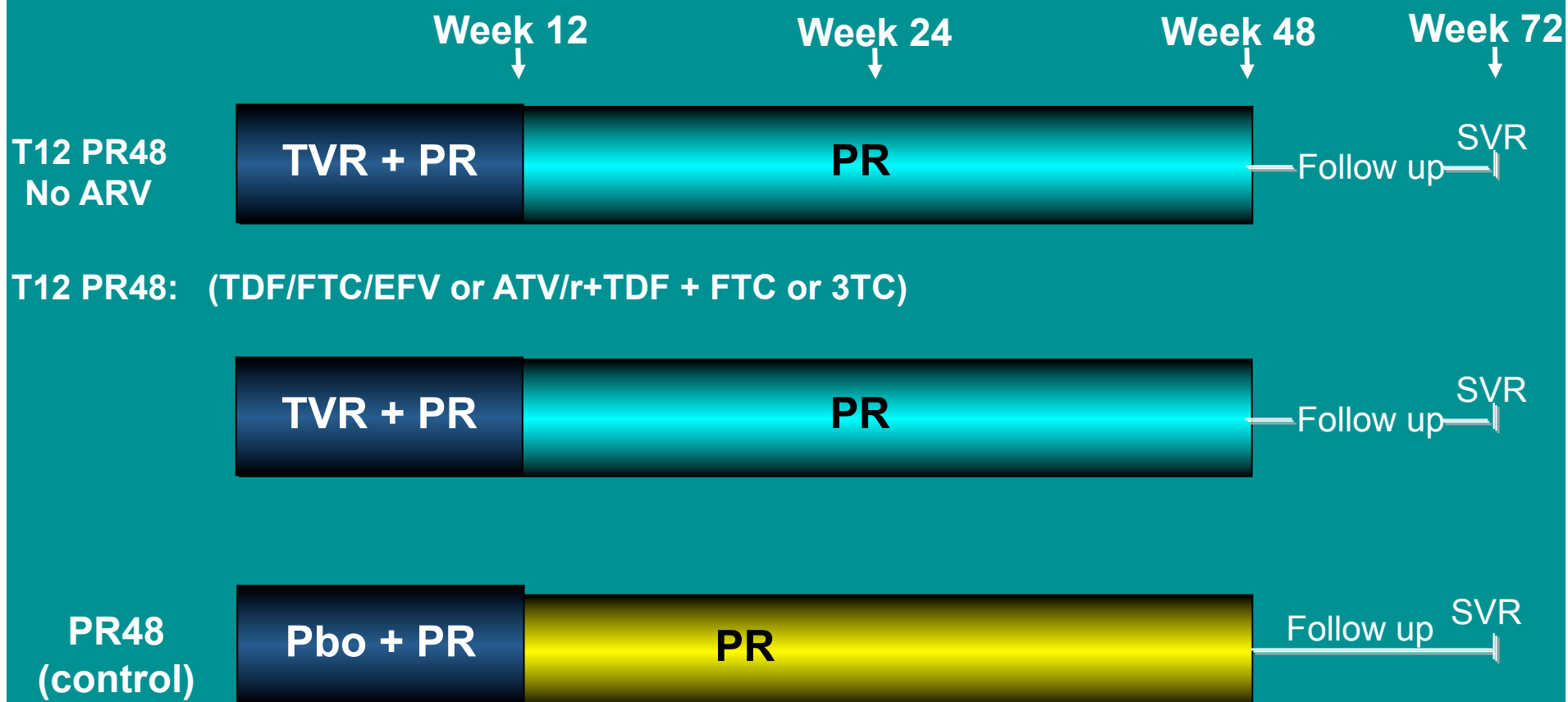
Percent of patients with virologic failure



SVR rates by Race or Ethnicity



TVR/PEG-IFN/RBV in HIV/HCV

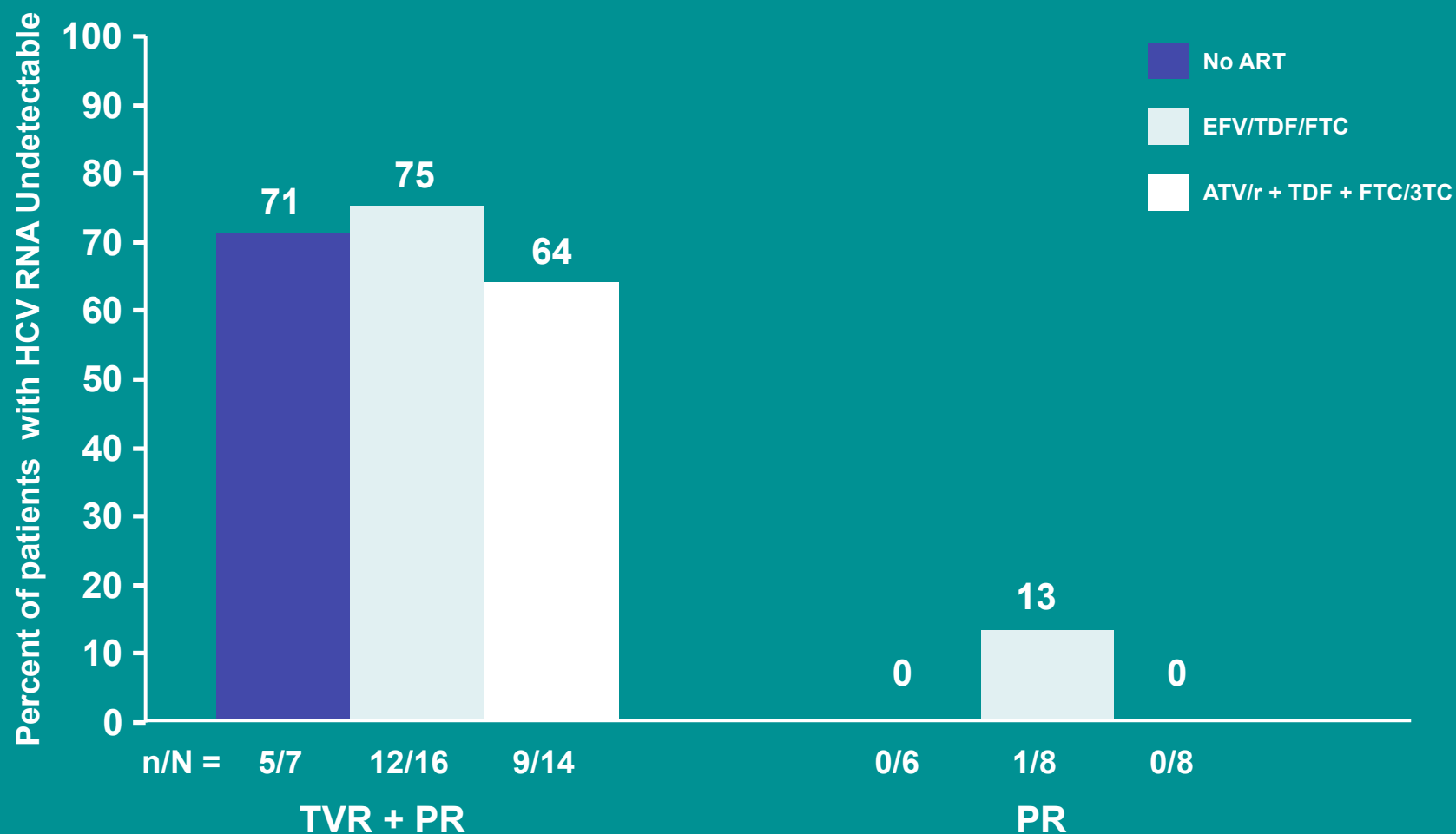


(T) TVR = telaprevir 750 mg q8hrs; PEG-IFN (P) = pegylated interferon plus ribavirin (R) 1000 or 1200 mg/d

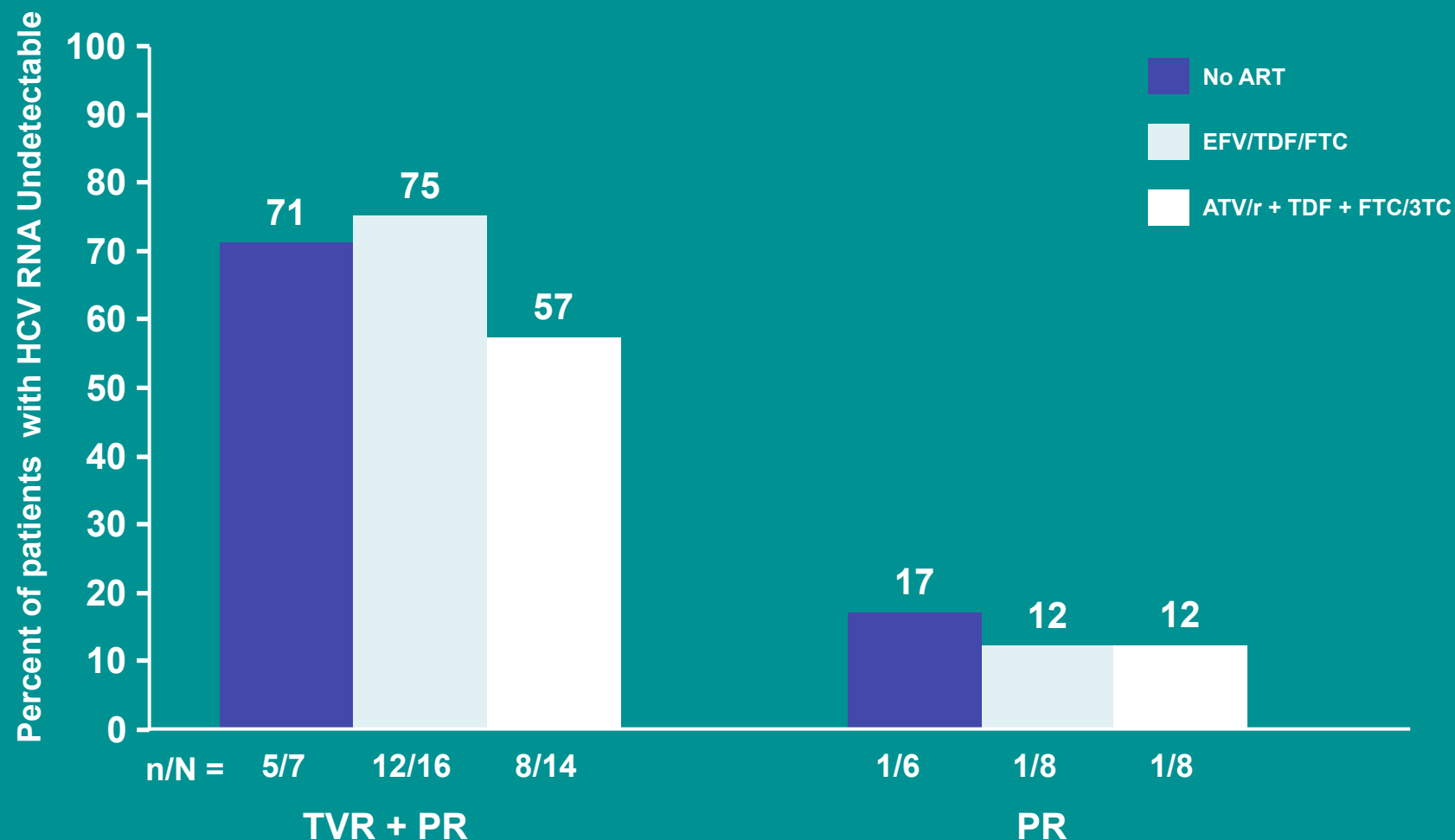
Demographics and Baseline Characteristics

	Part A		Part B			
	No ART		EFV/TDF/FTC		ATV/r + TDF + FTC/ 3TC	
	T/PR N=7	PR N=6	T/PR N=16	PR N=8	T/PR N=14	PR N=8
Gender, n (%): Male	6 (86)	4 (67)	16 (100)	7 (88)	12 (86)	7 (88)
Race†, n(%)						
Caucasian	2 (29)	3 (50)	12 (75)	5 (62)	12 (86)	7 (88)
Black/African American	4 (57)	3 (50)	3 (19)	3 (38)	2 (14)	1 (12)
Ethnicity†, n (%)						
Hispanic	3 (43)	2 (33)	5 (31)	1 (12)	3 (21)	3 (38)
Age, median years (range)	39 (34-51)	48 (43-65)	48 (31-57)	47 (31-53)	54 (37-60)	39 (26-53)
BMI, median kg/m² (range)	29 (22-37)	31 (26-37)	24 (21-32)	23 (19-29)	24 (23-33)	25 (22-30)
HCV RNA ≥ 800,000 IU/mL**, n (%)	7 (100)	5 (83)	13 (81)	7 (88)	10 (71)	7 (88)
HCV Genotype Subtype*, n (%)						
1a	3 (43)	3 (50)	12 (75)	6 (75)	11 (79)	5 (62)
1b	4 (57)	2 (33)	4 (25)	1 (12)	3 (21)	3 (38)
HIV RNA median copies/mL (range)	1495 (155-53,450)	267 (25-21,950)	<50	<50	<50	<50
CD4+ median cells/mm³ (range)	604 (496-759)	672 (518-1189)	533 (299-1075)	514 (323-1034)	492 (279-874)	535 (302-772)

Undetectable HCV RNA at Week 4 (RVR)



Undetectable HCV RNA at Week 12 (cEVR)



Serious Events and Treatment Discontinuation

	Part A		Part B			
	No ART		EFV/TDF/FTC		ATV/r + TDF + FTC/ 3TC	
	T/PR (N=7)	PR (N=6)	T/PR (N=16)	PR (N=8)	T/PR (N=14)	PR (N=8)
Any AE	100%	83%	94%	88%	100%	100%
Serious AE	14%	0	0	0	21%	0
Discontinuation of all study drugs						
Due to AE	0	0	0	0	14%	0
Due to anemia	0	0	0	0	7%	0
Due to rash	0	0	0	0	0	0

- Mild and moderate rash events occurred in 16% and 11% of T/PR patients, respectively and in 14% and <1% of PR patients

Drug-drug interactions: ARV and TVR

- Inhibitors of CYP3A
 - Atazanavir/ritonavir (ATV/r), darunavir/r (DRV/r), fosamprenavir/r (fAPV/r), lopinavir/r (LPV/r).
- Inducer of CYP3A
 - Efavirenz
- Inhibitor of CYP3A
 - Telaprevir
 - Boceprevir

Drug-drug interactions: ARV and TVR

- Neither TVR nor BOC are increased by ritonavir boosting.
- EFV decreases BOC concentration by 44% and also decrease TVR conc.
- All ritonavir boosted PIs decrease TVR conc-20% for ATV/r to 54% for LPV/r.
- Doses of TVR to 1125 mg TID might be needed for patients on ATV/r.

HCV Treatment in HIV/HCV coinfection

- Recent approval of first direct acting antivirals (boceprevir and telaprevir).
 - Opportunities for off-label use in HIV/HCV coinfection
 - Need depends upon urgency-fibrosis stage, extrahepatic manifestations, patient desire
- New opportunities for research studies:
 - Need data on optimal management in HIV/HCV coinfection.
 - New treatment regimens with easier side effect profiles and dosing regimens.