Challenging aspects in the management of persons with HIV-HCV coinfection

Mark Sulkowski, MD
Professor of Medicine

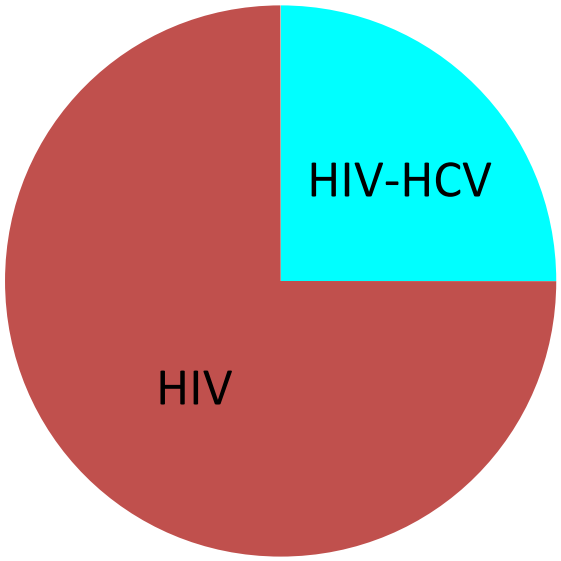
JOHNS HOPKINS
MEDICINE

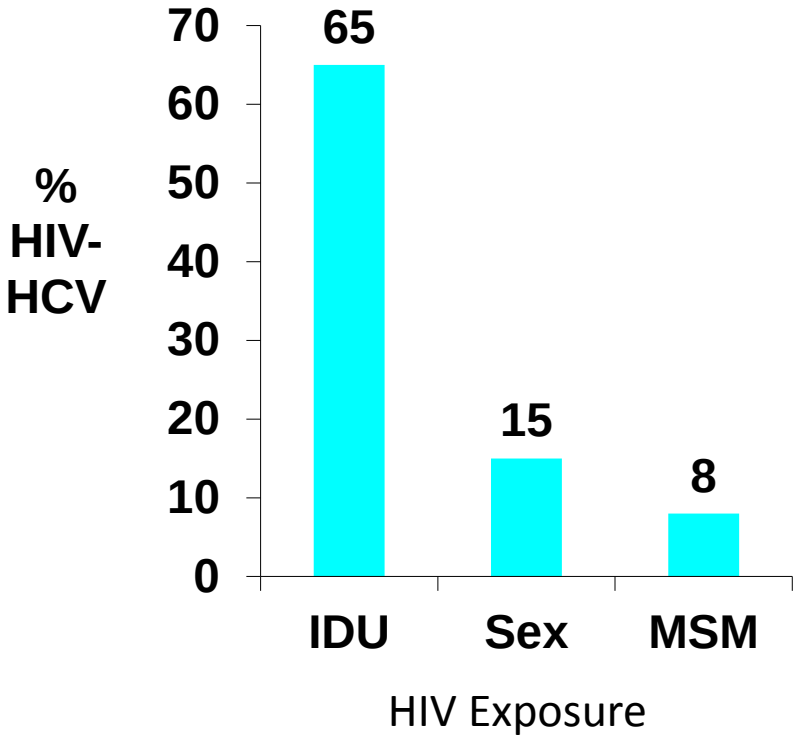
Challenging aspects of HIV/HCV coinfection: Epidemiology/Natural History

- Epidemiology
  - High prevalence of chronic HCV infection
    - However, MOST are diagnosed
  - Acute HCV infection especially among MSMs
  - HCV is associated with many comorbid conditions
- Natural history
  - Rapid progression to cirrhosis
  - Limited access to liver transplantation
    - However, effective ART is associated with 66% reduction in liver mortality/ESLD/HCC

HCV Infection ~ 25% of HIV-infected Persons

Prevalence differs by HIV risk group



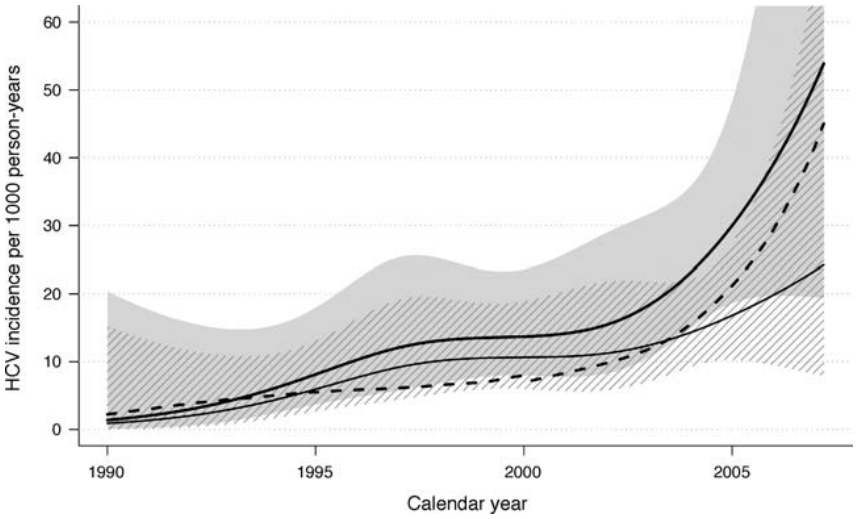


Sherman K et al. *Clin Infect Dis* 2002; Sulkowski M et al. *Ann Intern Med* 2003.

HCV is a sexually transmitted disease among HIV-infected MSMs

- 74 HIV-positive MSM diagnosed with recent HCV between 2005 and 2010
  - No IDU
  - Antiretroviral therapy, 74%
  - HCV associated with receptive anal intercourse (AOR = 23) and sex while on methamphetamine (AOR 28.56)
- NS5B sequences were obtained in 50 men
  - Phylogenetic analysis revealed 5 clusters of genotype 1a

Incidence of HCV in HIV-infected MSM from 12 cohorts within CASCADE



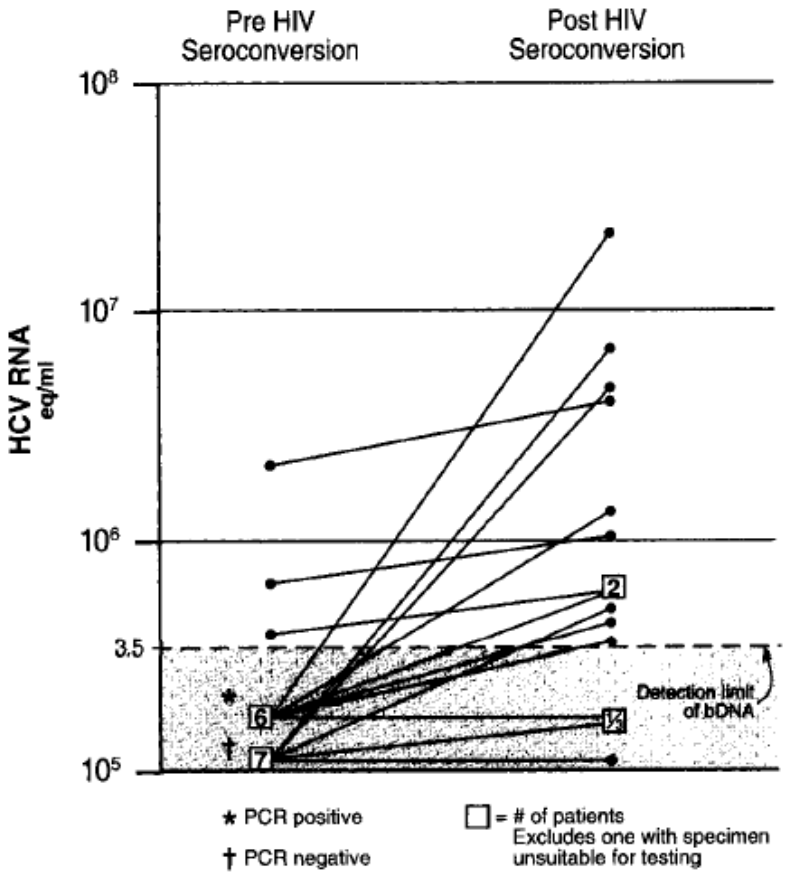
Fierer DS et al. MMWR July 22, 2011; van der Helm JJ et al. AIDS 2011, 25*:1083–1091*

HIV/HCV coinfected patients have more comorbid medical and psychiatric conditions that may complicate HCV care

	HCV (n =114,005)	HIV/HCV (n = 6,502)
Drug use	39%	56%
Alcohol use	44%	48%
Depression (major)	18%	23%
Bipolar	10%	10%
Anemia	12%	24%
Hepatitis B	3%	9%
Received HCV treatment	12%	7%

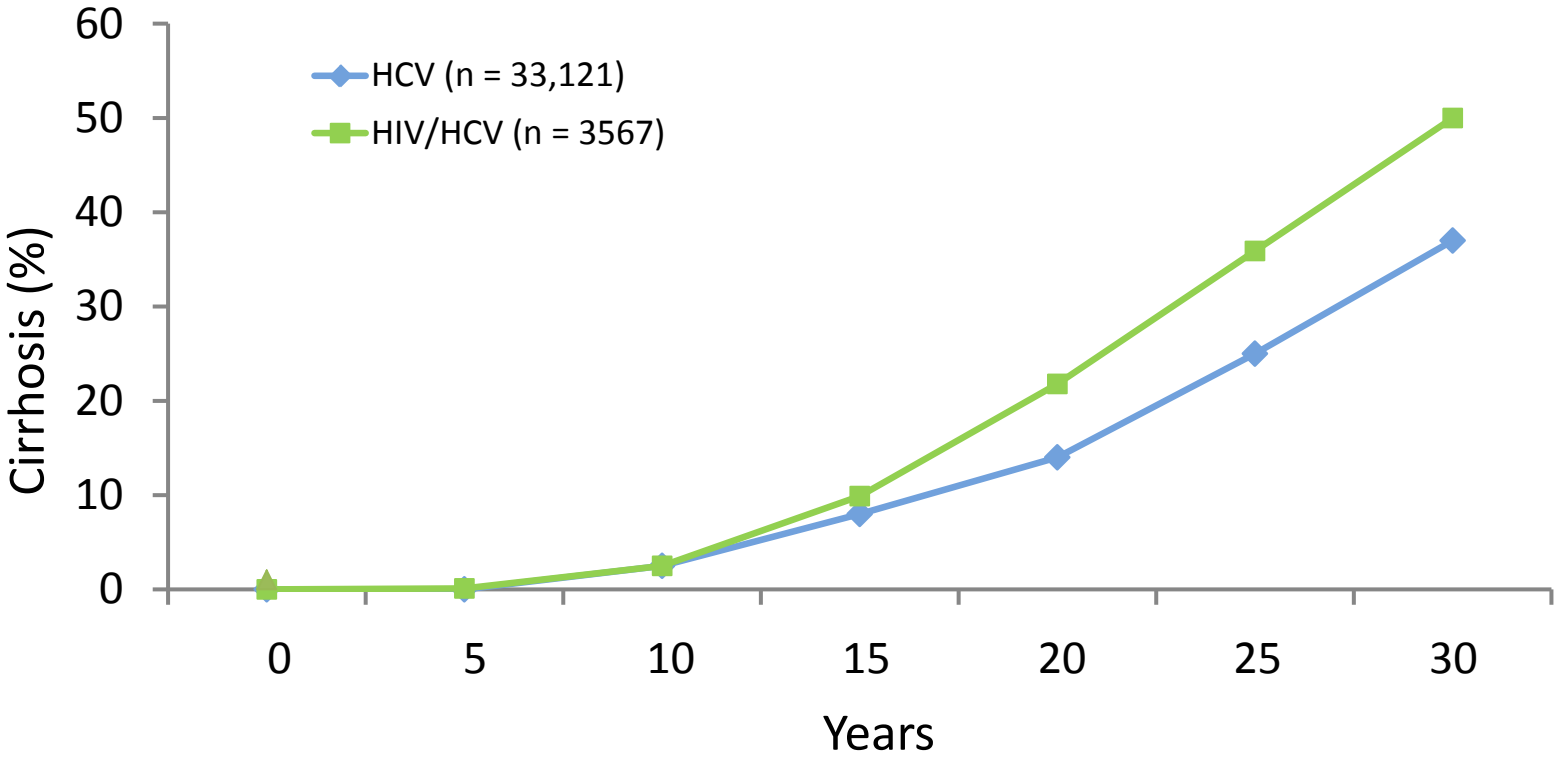
Butt A. Alimentary Pharmacology & Therapeutics
Volume 24, Issue 4, Pages 585-591. 2006

HIV coinfection leads to higher levels of HCV RNA



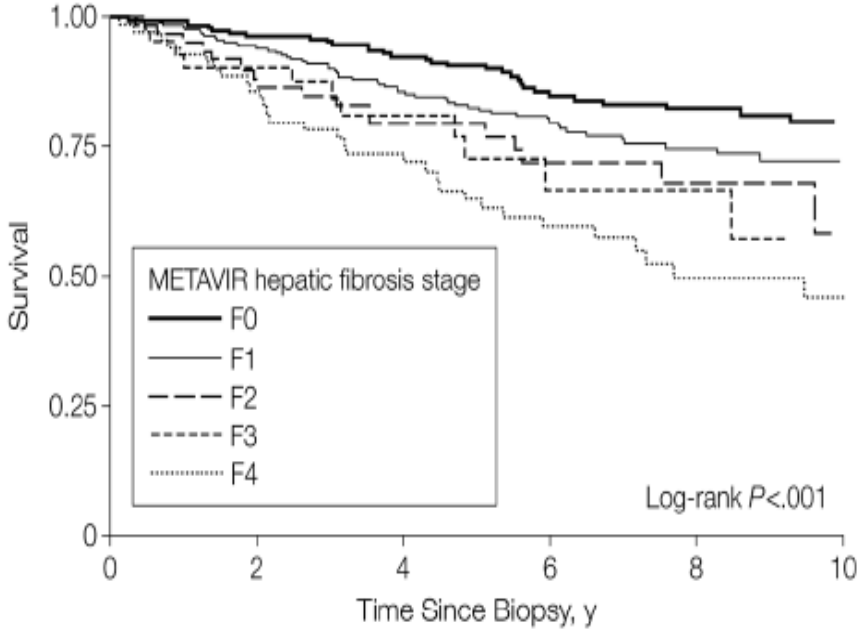
ME Eyster, MW Fried, AM Di Bisceglie and JJ Goedert. Blood. 1994 84: 1020-1023

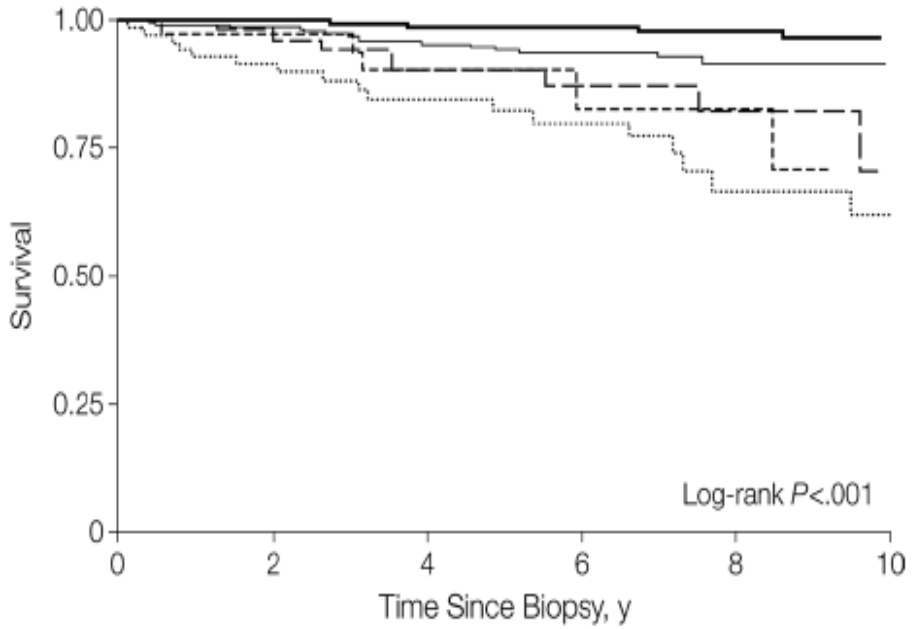
HIV coinfection is associated with accelerated liver disease progression



Thein H-H et al. AIDS. 2008;22:1979-1991.
Thein H-H et al. Hepatology. 2008;48:418-431.

METAVIR Fibrosis stage is associated with time to death, ESLD or HCC among 638 HIV/HCV coinfected adults prospectively followed after liver biopsy





Limketkai et al. JAMA. July 25, 2012,308(4):370-378

Antiretroviral therapy was associated with reduced risk of liver outcomes

Table 3. Crude and Adjusted Incidence Rate Ratios[a]

	No. of Events[b]	Person-Years[b]	ESLD, HCC, or All-Cause Mortality, Incidence RR (95% CI) Crude	ESLD, HCC, or All-Cause Mortality, Incidence RR (95% CI) Adjusted[c]	No. of Events[b]	Person-Years[b]	ESLD, HCC, or Liver-Related Mortality, Incidence RR (95% CI) Crude	ESLD, HCC, or Liver-Related Mortality, Incidence RR (95% CI) Adjusted[c]
METAVIR fibrosis stage[d]								
F0	33	1363	1 [Reference]	1 [Reference]	4	1363	1 [Reference]	1 [Reference]
F1	57	1511	1.53 (0.97-2.41)	1.59 (0.99-2.55)	16	1511	3.86 (1.21-12.24)	3.53 (1.08-11.48)
F2	18	330	2.25 (1.22-4.16)	2.31 (1.23-4.34)	9	330	9.60 (2.72-33.90)	9.34 (2.60-33.58)
F3	11	194	2.50 (1.21-5.19)	3.18 (1.47-6.88)	5	194	10.03 (2.46-40.84)	11.15 (2.63-47.35)
F4	31	388	3.19 (1.88-5.40)	3.57 (2.06-6.19)	17	388	16.02 (5.01-51.25)	16.82 (5.13-55.16)
Race								
Black	124	3098	1 [Reference]	1 [Reference]	39	3098	1 [Reference]	1 [Reference]
White	26	687	1.01 (0.64-1.58)	1.01 (0.62-1.65)	12	687	1.51 (0.74-3.06)	1.38 (0.62-3.06)
Sex								
Men	100	2531	1 [Reference]	1 [Reference]	34	2531	1 [Reference]	1 [Reference]
Women	50	1254	0.99 (0.69-1.43)	0.86 (0.59-1.27)	17	1254	1.00 (0.53-1.87)	0.75 (0.38-1.46)
Age, y								
≤50	112	3064	1 [Reference]	1 [Reference]	35	3064	1 [Reference]	1 [Reference]
>50	38	721	1.46 (0.98-2.17)	1.71 (1.13-2.60)	16	721	1.95 (1.02-3.75)	2.05 (1.02-4.10)
Injection drug use								
No	18	956	1 [Reference]	1 [Reference]	10	956	1 [Reference]	1 [Reference]
Yes	131	2829	2.54 (1.52-4.24)	2.41 (1.41-4.12)	40	2829	1.46 (0.69-3.07)	1.66 (0.76-3.63)
CD4 cell count/μL[e]								
<200	67	594	1 [Reference]	1 [Reference]	14	594	1 [Reference]	1 [Reference]
200-350	28	824	0.29 (0.18-0.46)	0.27 (0.16-0.44)	11	824	0.57 (0.24-1.35)	0.54 (0.22-1.31)
>350	55	2364	0.22 (0.15-0.32)	0.21 (0.14-0.31)	26	2364	0.53 (0.26-1.08)	0.52 (0.25-1.09)
HIV-1 RNA measures <400 copies/mL, %[e,f]								
≥75	45	1891	1 [Reference]		20	1891	1 [Reference]	
26-75	43	981	1.87 (1.20-2.90)		12	981	1.16 (0.54-2.48)	
0-25	62	908	3.00 (1.98-4.54)		19	908	2.13 (1.07-4.25)	
ART exposure[e]								
No	74	929	1 [Reference]	1 [Reference]	22	929	1 [Reference]	1 [Reference]
Yes	76	2856	0.27 (0.19-0.39)	0.27 (0.19-0.38)	29	2856	0.36 (0.19-0.66)	0.34 (0.18-0.66)

Abbreviations: ART, antiretroviral therapy; ESLD, end-stage liver disease; HCC, hepatocellular carcinoma; RR, rate ratio.

[a] Incidence RRs were estimated using negative binomial regression.

[b] Events, person-years, and incidence rate ratios were calculated from the data set including time-varying covariates. Twenty-nine persons who had missing CD4 cell count, HIV-1 RNA measurements, or both at the time of biopsy entered the analysis and accumulated person-time from the date of the first available CD4 cell count rather than the date of the first biopsy (median, 2.78 years after biopsy).

[c] Adjusted for age, sex, race, injection drug use, time-varying CD4 cell count, and current ART exposure.

[d] METAVIR fibrosis stages: F0, no fibrosis; F1, portal fibrosis without septa; F2, portal fibrosis with few septa; F3, numerous septa without cirrhosis; F4, cirrhosis.

[e] Time-varying measures.

[f] Because of collinearity, HIV RNA suppression and receipt of ART were not included in the same multivariable model; current ART was retained in the final model over viral suppression because it demonstrated a stronger statistical association with the outcomes.

Limketkai et al. JAMA. July 25, 2012,308(4):370-378

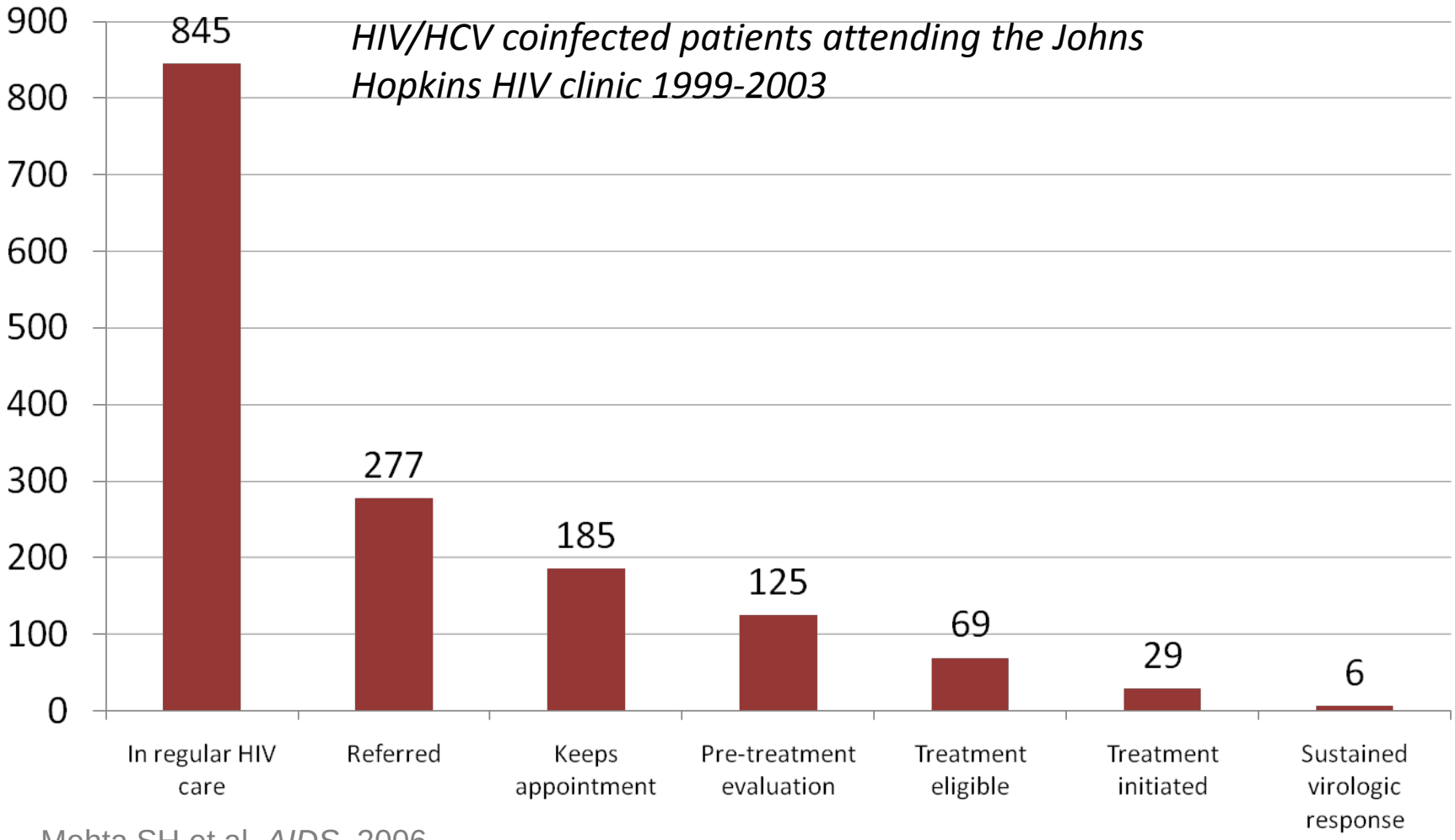
Challenging aspects of HIV/HCV coinfection: HCV Treatment

- Most take concurrent antiretroviral therapy
  - Overlapping toxicity is possible
  - Drug interactions are likely and difficult to predict
    - CYP3A4 inhibition (ritonavir); induction (Efavirenz)
    - Must study the DAA regimen + ART regimen in healthy volunteers
- However, long-term adherence to ART/clinic visits predicts adherence to HCV therapy
  - And pharmacy coverage is widespread

Challenging aspects of HIV/HCV coinfection: HCV Treatment **Efficacy**

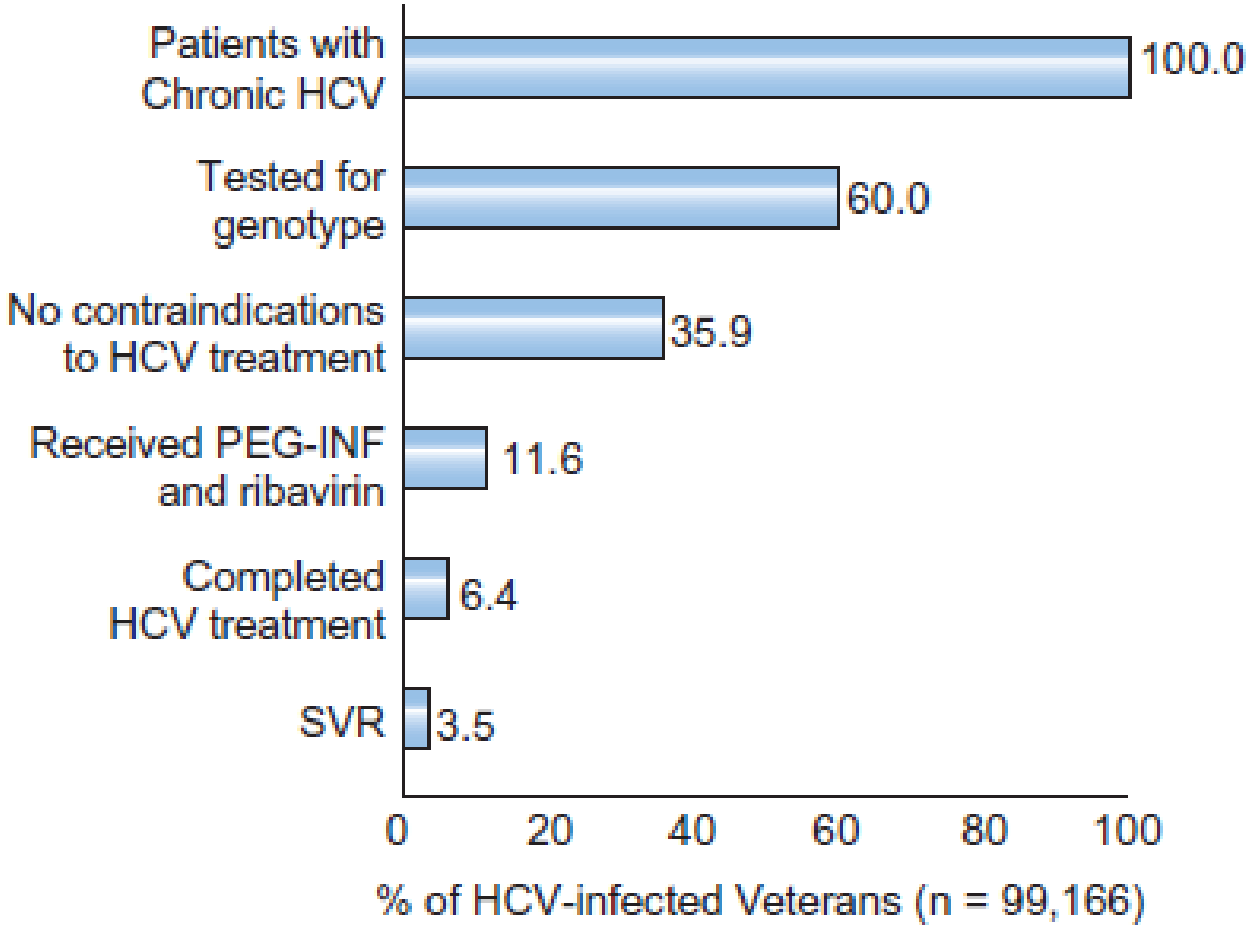
- Interferon is a problem in this population
  - HIV providers and patients are not enthusiastic
  - Prevalent mental health disorders
    - However, most have access to treatment
  - Poor IFN response present in some – but not all – HIV+ persons
    - Cure is less common with PegIFN/RBV
- However, cure leads to survival benefits
- And interferon is on the verge of extinction and the response to oral HCV DAAs may be independent of HIV

HCV treatment cascade is not unique – HIV/HCV Baltimore (Population based cascade)

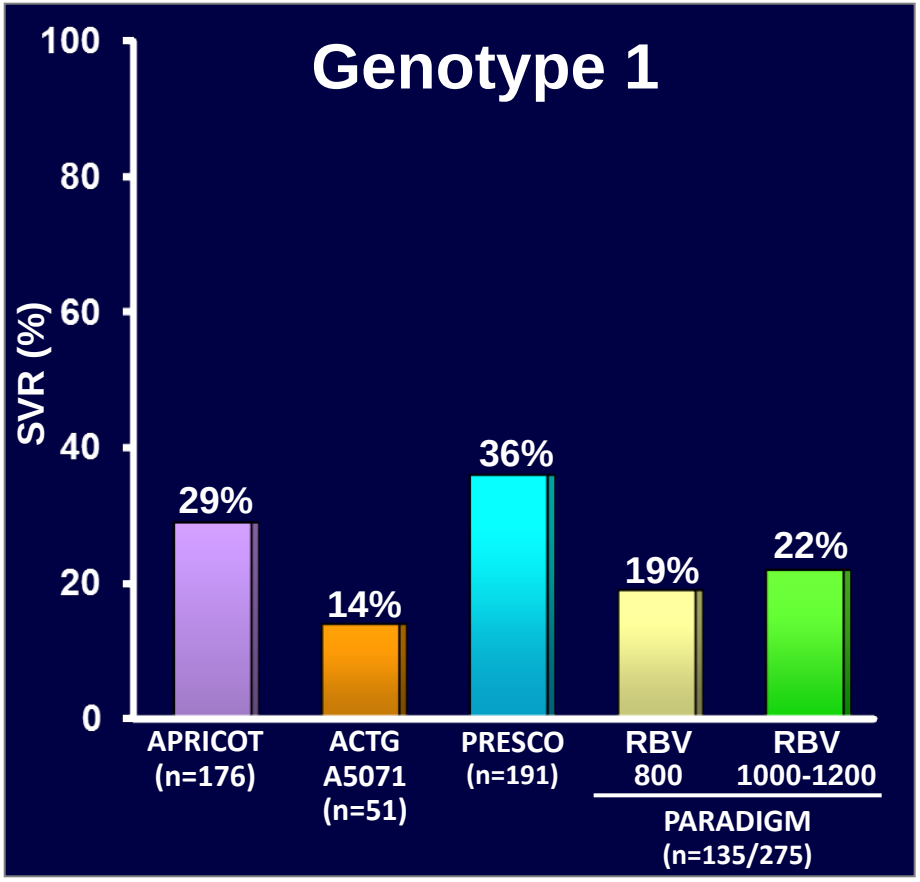


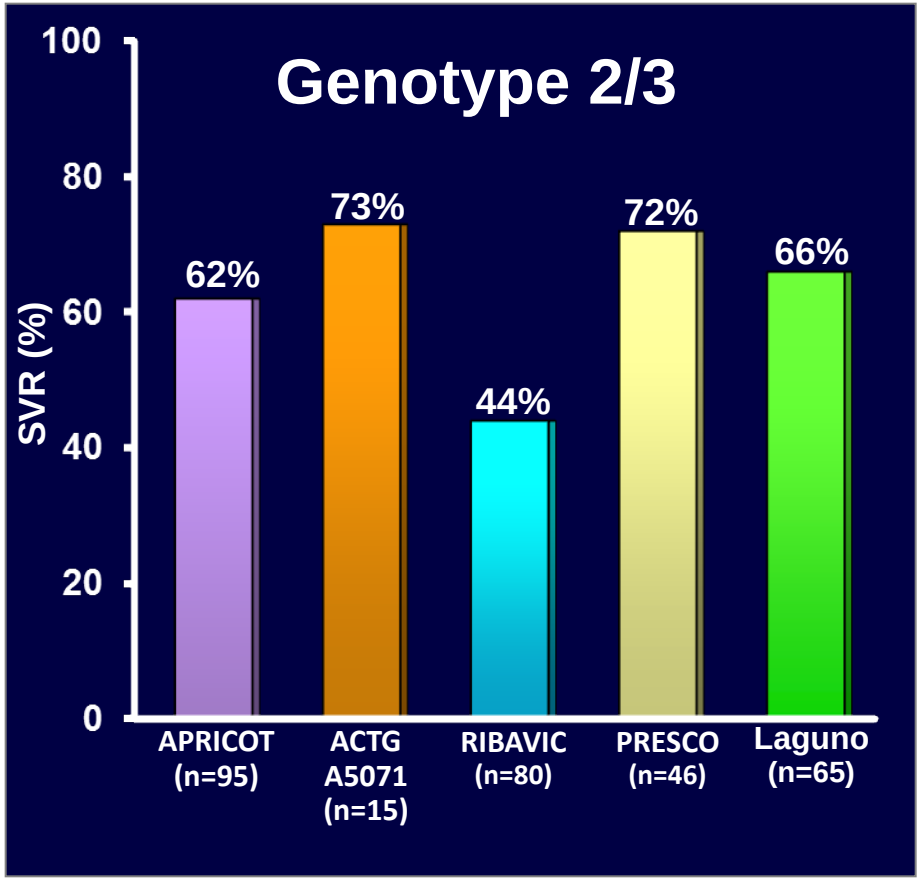
Mehta SH et al, *AIDS*, 2006

HCV treatment cascade is not unique – HCV Veterans, USA (Population based)



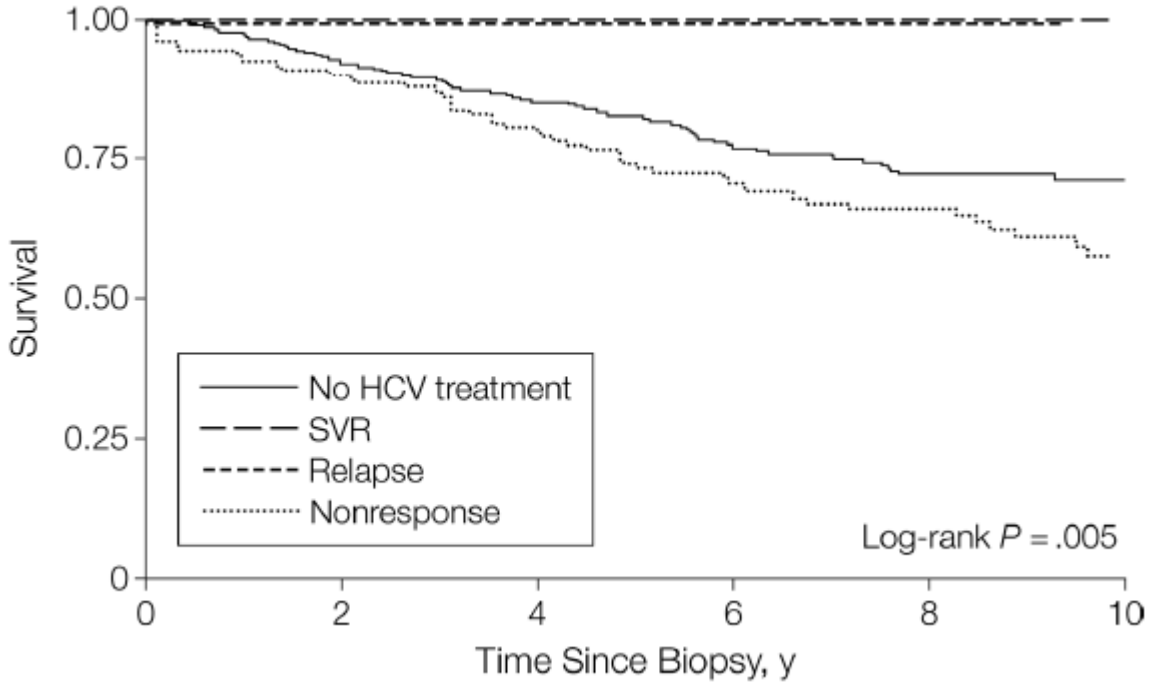
HIV/HCV coinfection leads to lower cure rates with PegIFN/RBV





Torriani FJ, et al. *N Engl J Med.* 2004;351:438-450; Chung R, et al. *N Engl J Med.* 2004;351:451-459; Carrat R, et al. *JAMA.* 2004;292:2839-2848; Nunez M, et al. *AIDS Res Human Retrovir*. 2007;23:972-982; Rodriguez-Torres M, et al. *HIV Clin Trials.* 2012;13:142-152; Laguno M, et al. *Hepatology.* 2009;49:22-31.

HCV cure is associated with survival in HIV/HCV coinfected patients



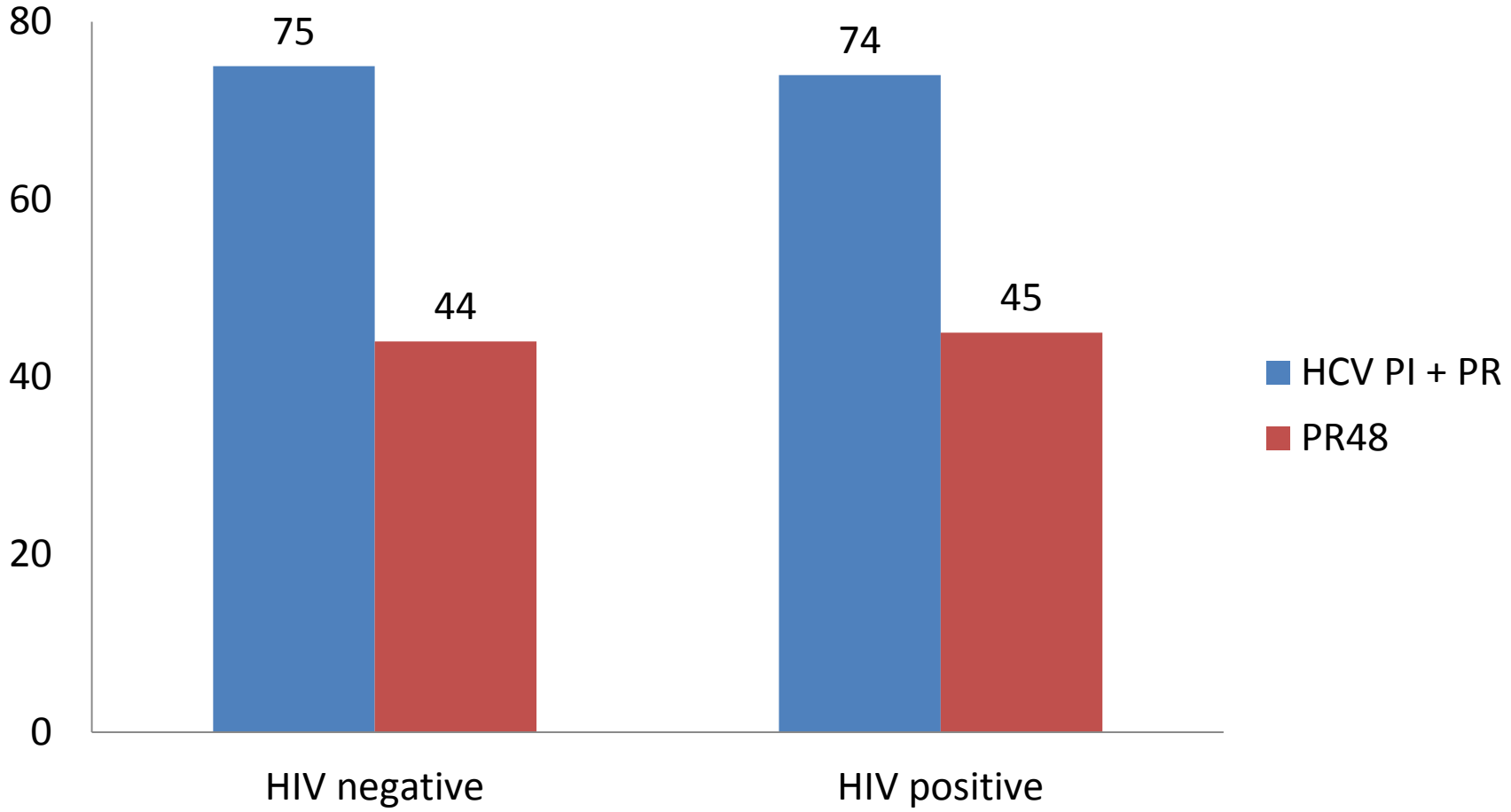
Limketkai et al. JAMA. July 25, 2012,308(4):370-378

Hypothesis: HCV response to DAAs will be similar in persons with and without HIV coinfection

- HCV DAAs will improve SVR in HIV-infected persons by directly targeting the virus (HCV) and circumventing host-related pathways to viral eradication
- Increase of DAA over control (placebo or PR) will be similar in patients with HIV/HCV to that observed in patients with HCV alone*
    - $\Delta VR_{HIV/HCV} \approx \Delta VR_{HCV}$

*After adjustment for baseline differences in psychiatric disease and/or socioeconomic instability

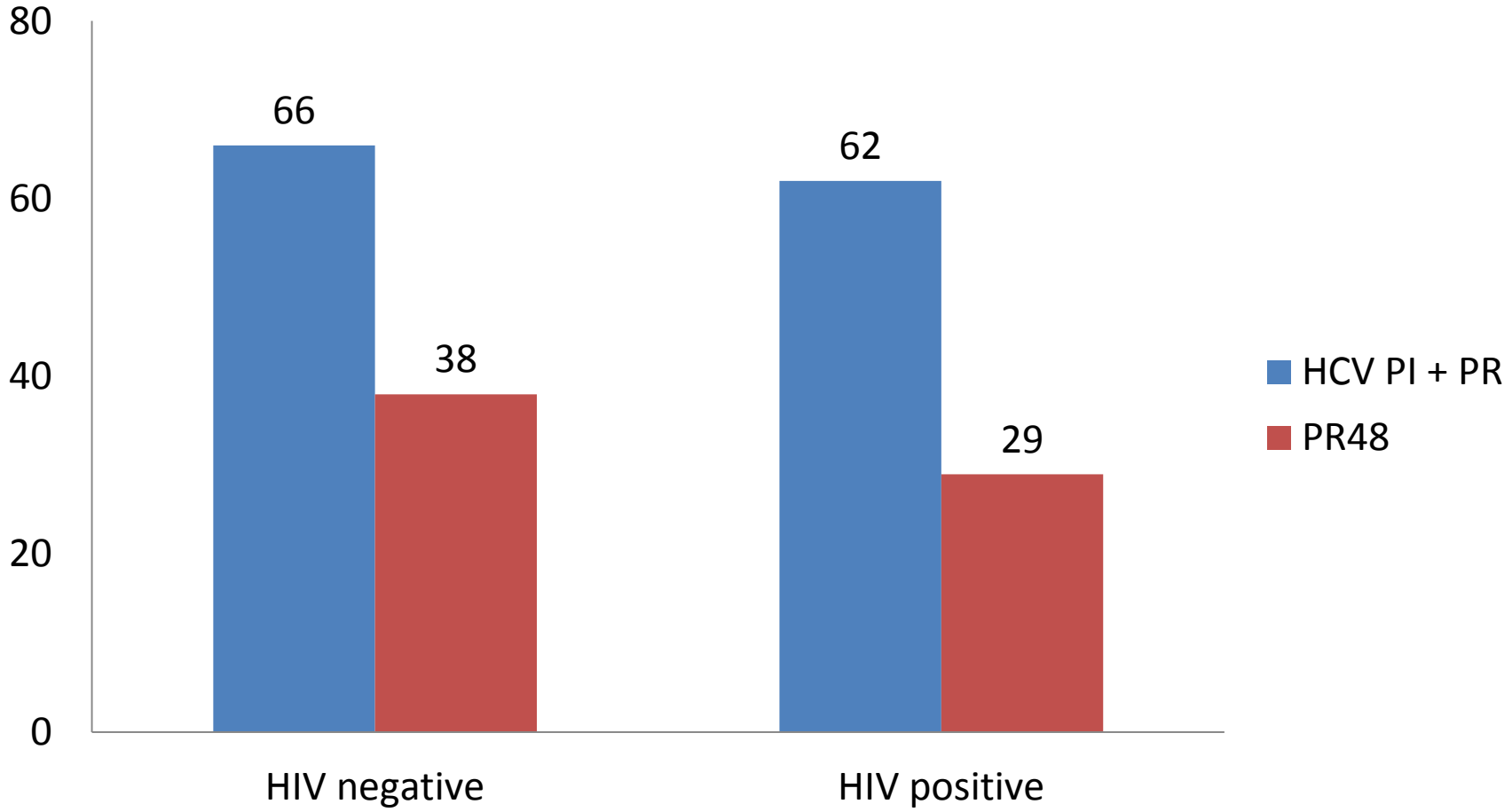
Telaprevir/PR for HCV genotype 1 treatment naïve HIV negative and positive patients



.

Sulkowski et al AASLD 2012. Jacobson et al. New Eng j Med 2011

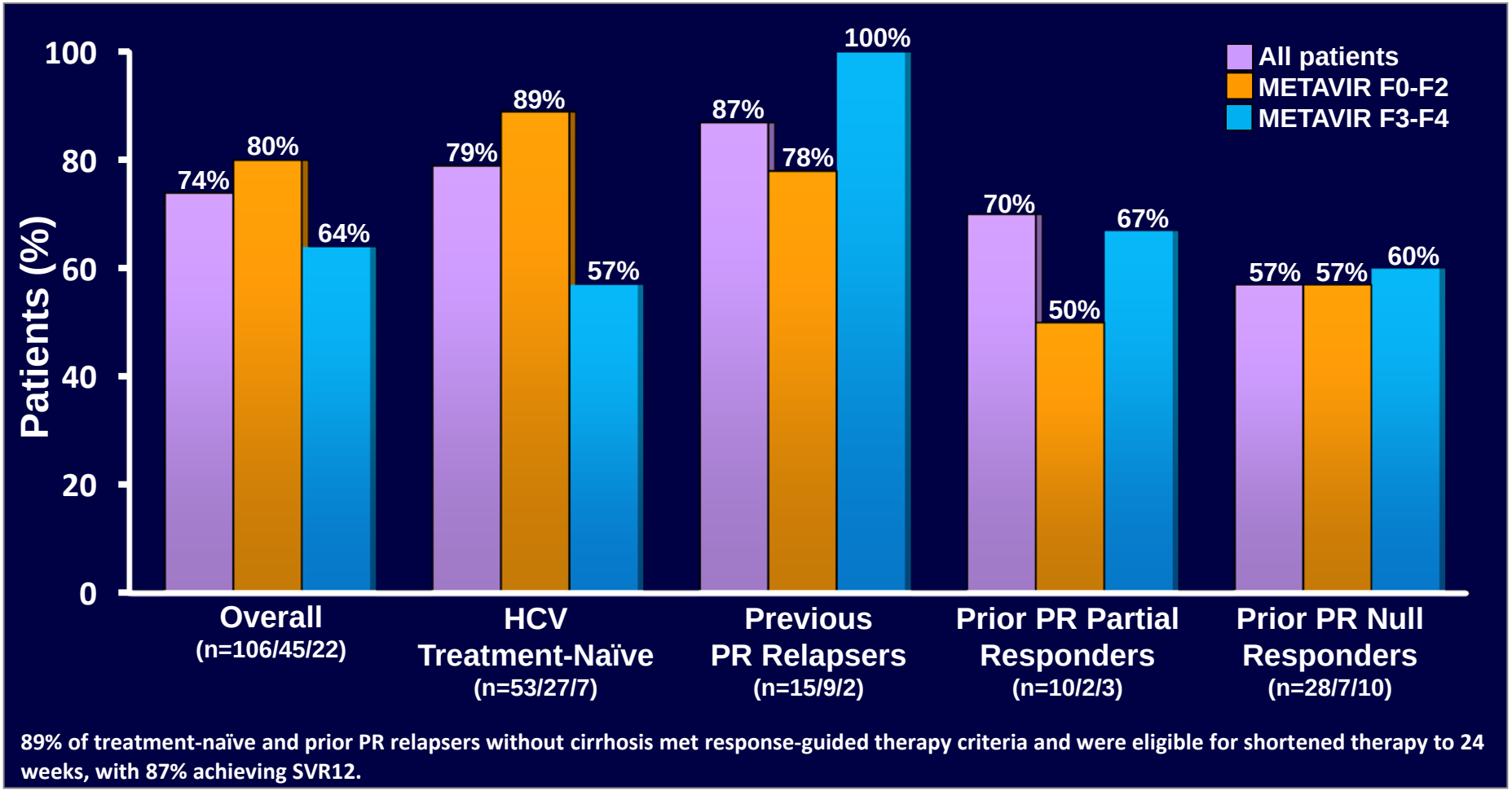
Boceprevir/PR for HCV genotype 1 treatment naïve HIV negative and positive patients



.

Sulkowski et al 2012. Poordad et al. New Eng j Med 2011

Study C212: SVR12 With Simeprevir + PR in HIV/HCV Coinfection

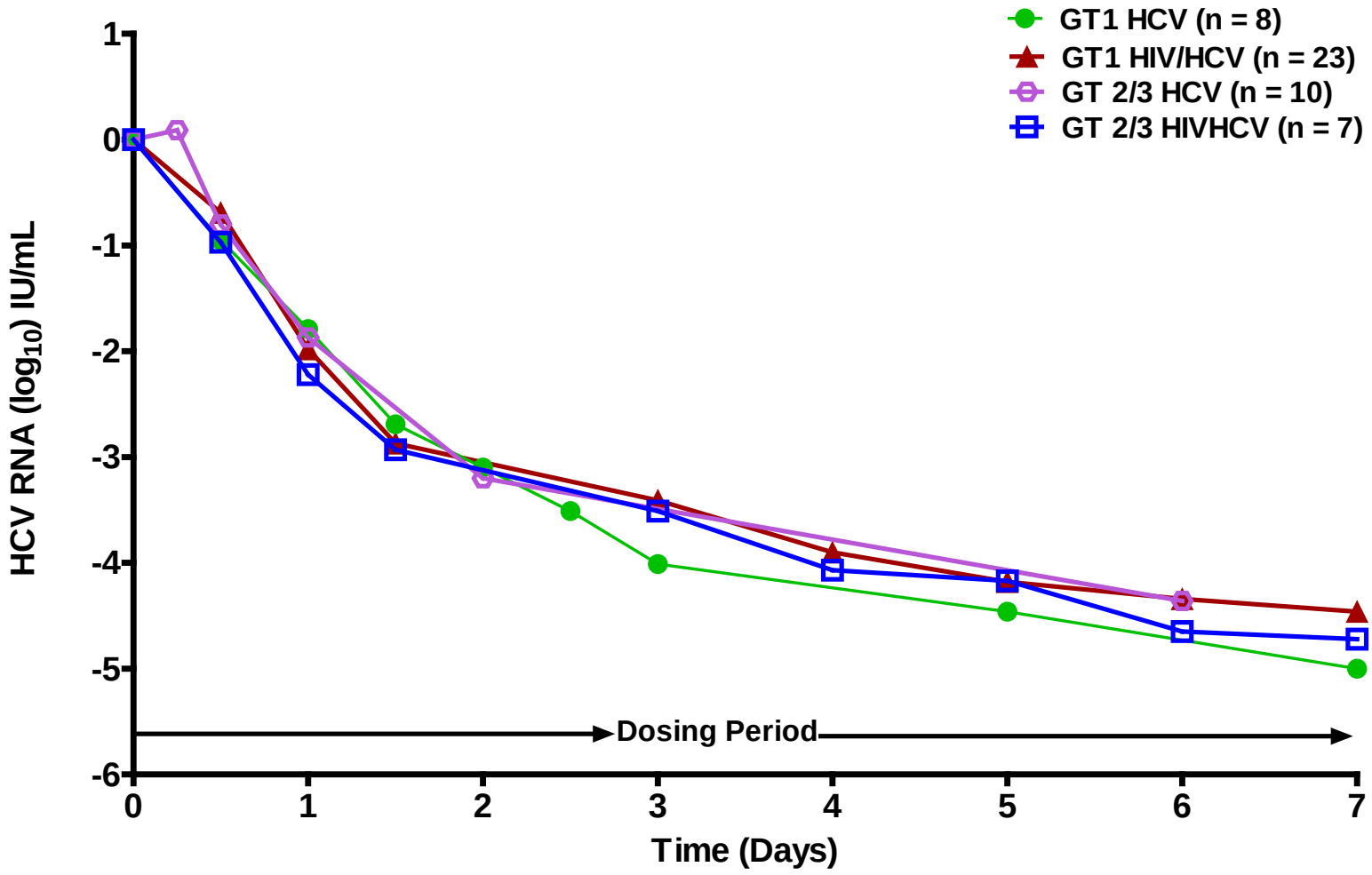


89% of treatment-naïve and prior PR relapsers without cirrhosis met response-guided therapy criteria and were eligible for shortened therapy to 24 weeks, with 87% achieving SVR12.

PR: peginterferon + ribavirin.

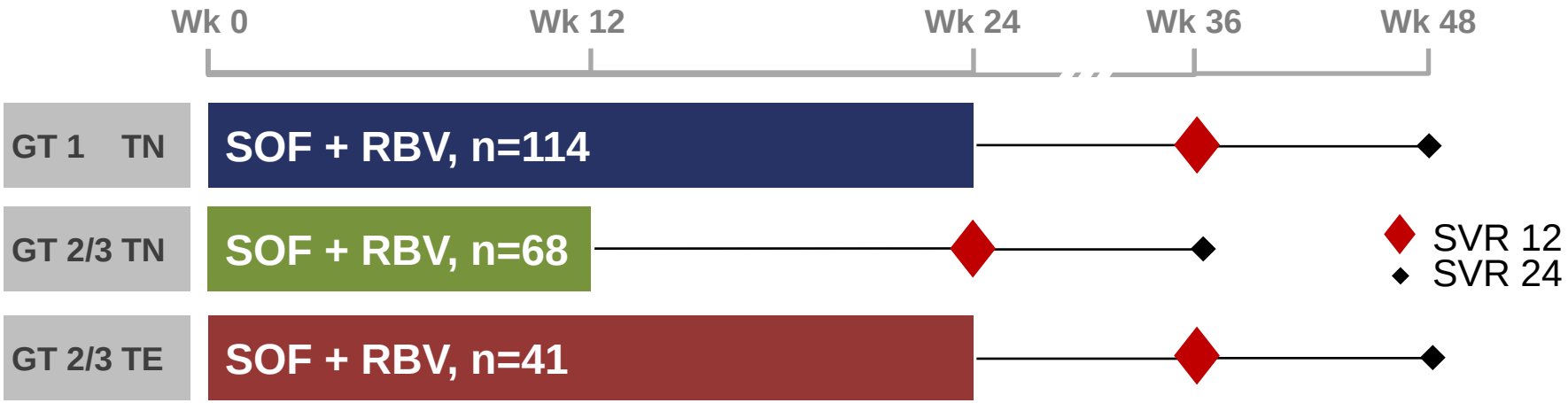
Dieterich D, et al. 21st CROI. Boston, 2014. Abstract 24.

Sofosbuvir for 7 days in patients with HCV monoinfection and HIV/HCV coinfection (n=30)



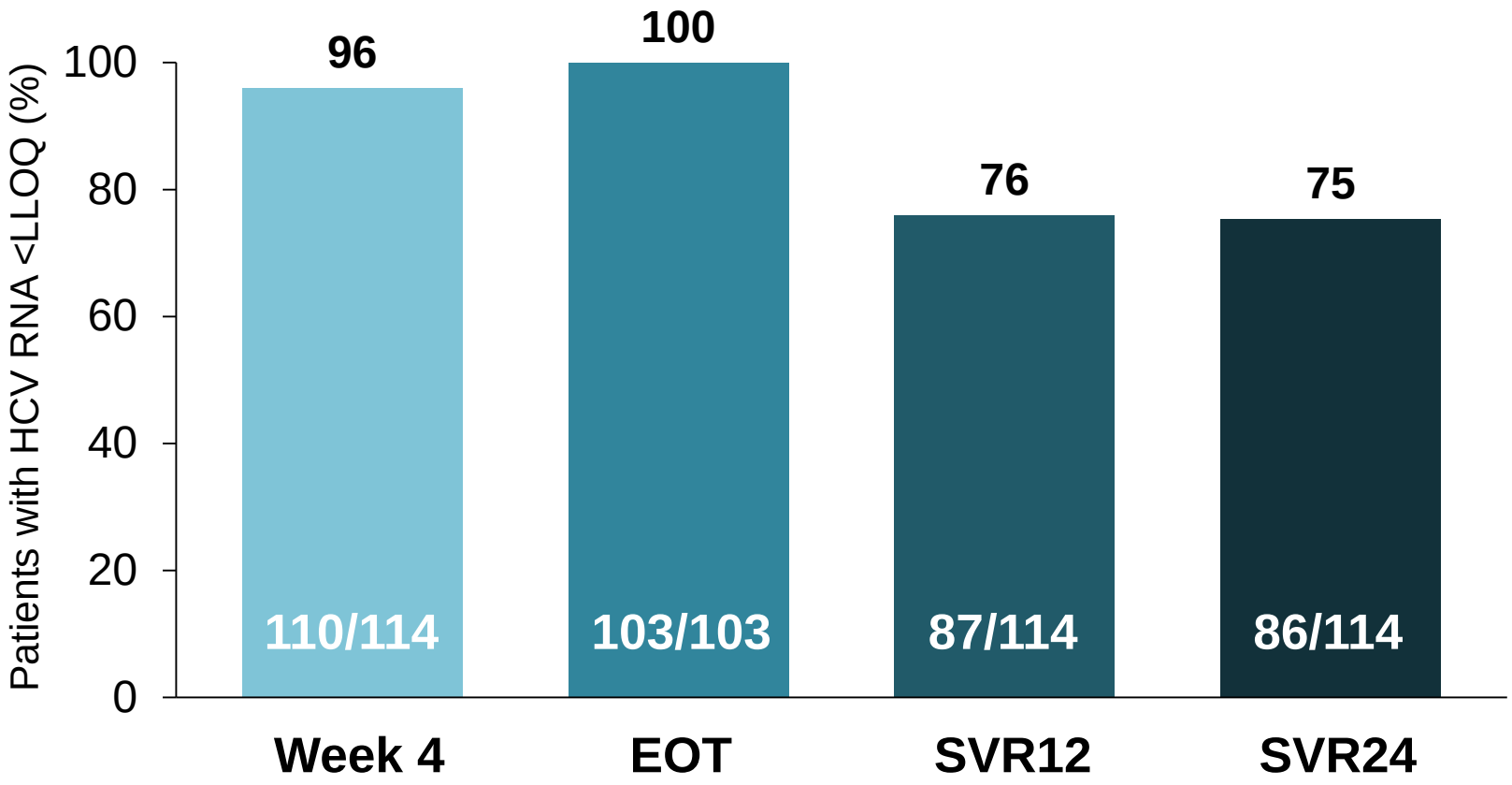
Lawitz E, et al. EASL 2012; Gane E, et al. AASLD 2011; Rodriguez-Torres et al ICAAC 2012

Study Design

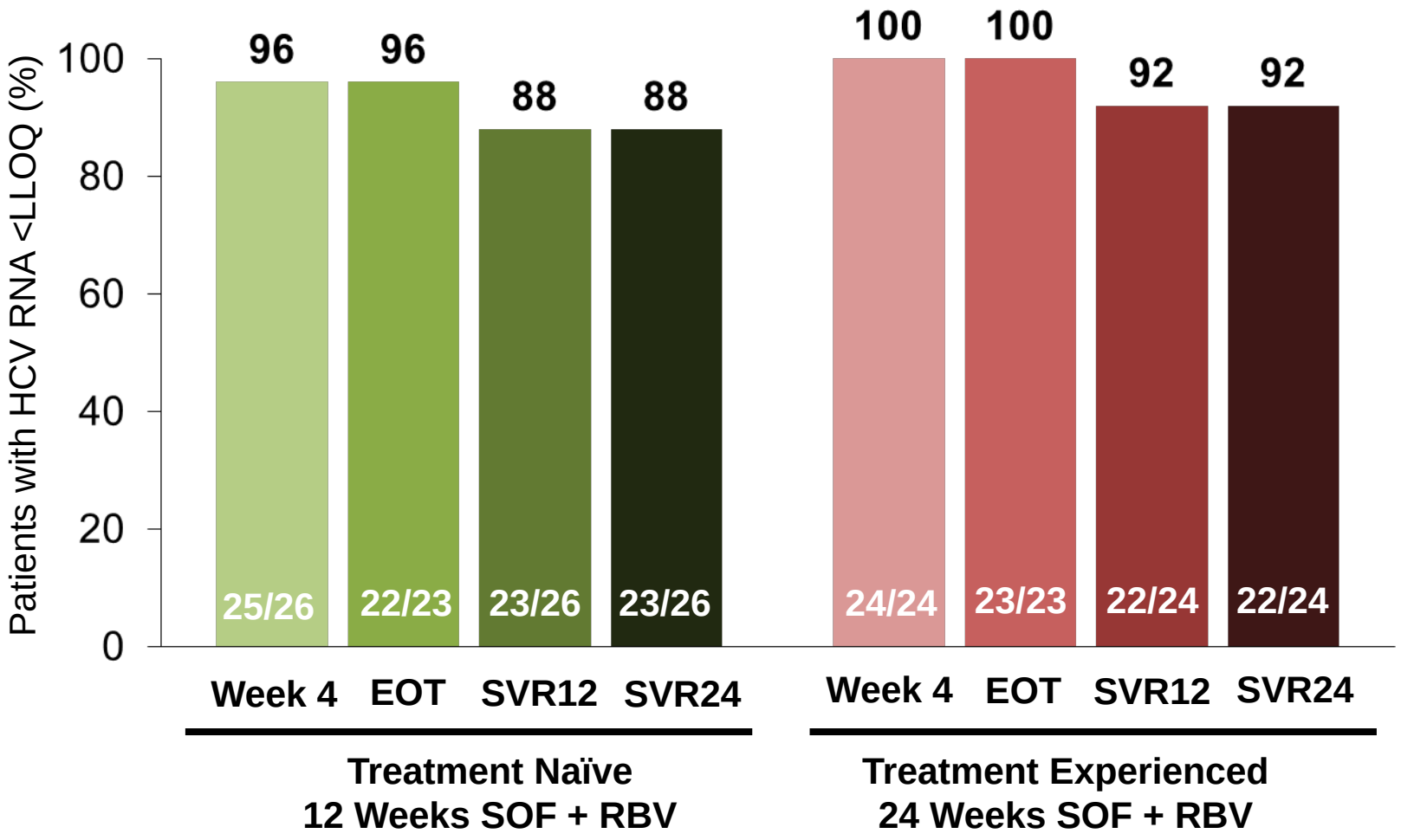


- Broad inclusion criteria
  - Cirrhosis permitted with no platelet cutoff
  - Hemoglobin: ≥12 mg/dL (males); ≥11 mg/dL (females)
- Wide range of ART regimens allowed
  - Undetectable HIV RNA for >8 weeks on stable ART regimen
- Baseline CD4 count
  - ART treated: CD4 T-cell count >200 cells/mm^3 and HIV RNA < 50 c/mL
  - ART untreated: CD4 T-cell count >500 cells/mm^3

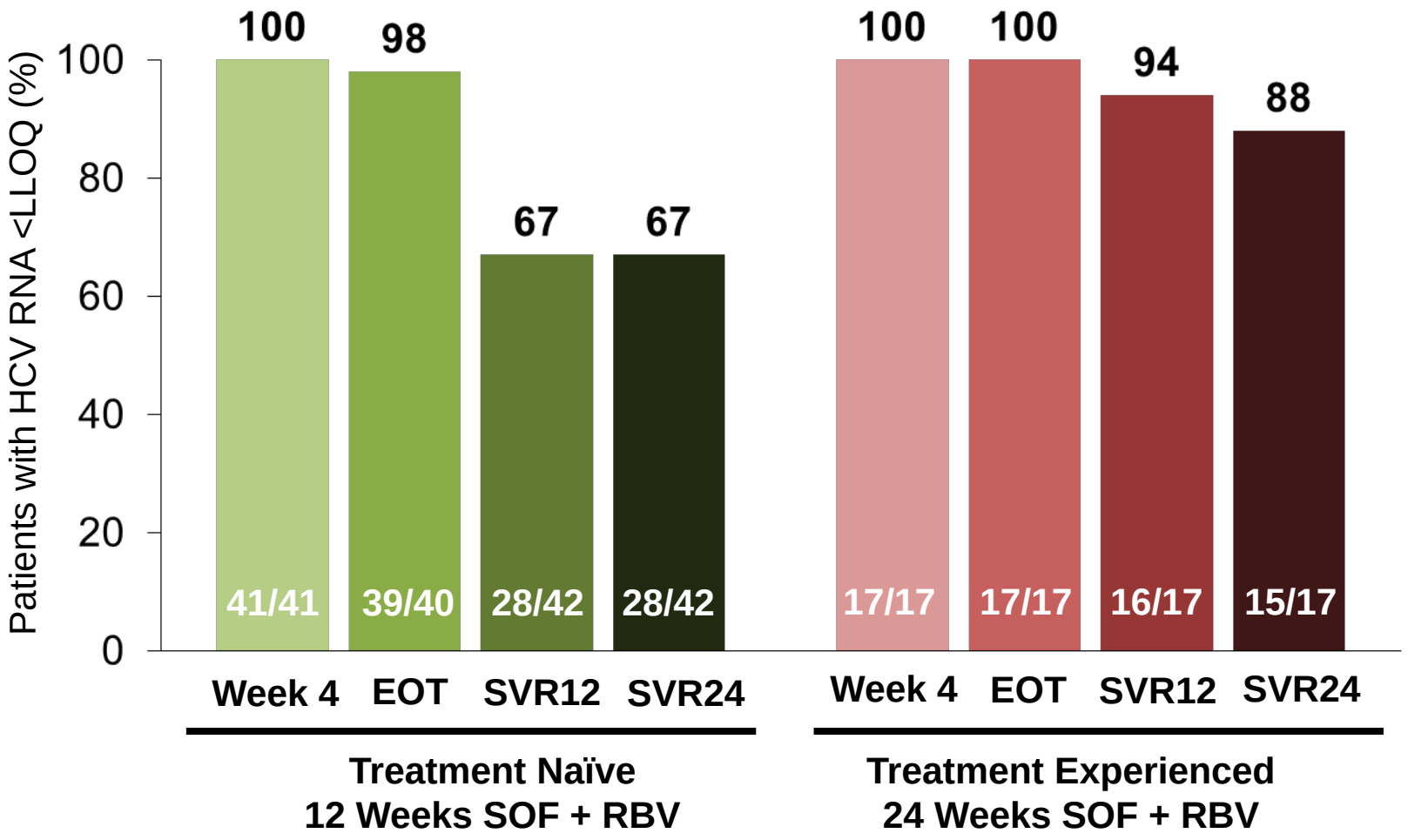
Virologic Response: Genotype 1



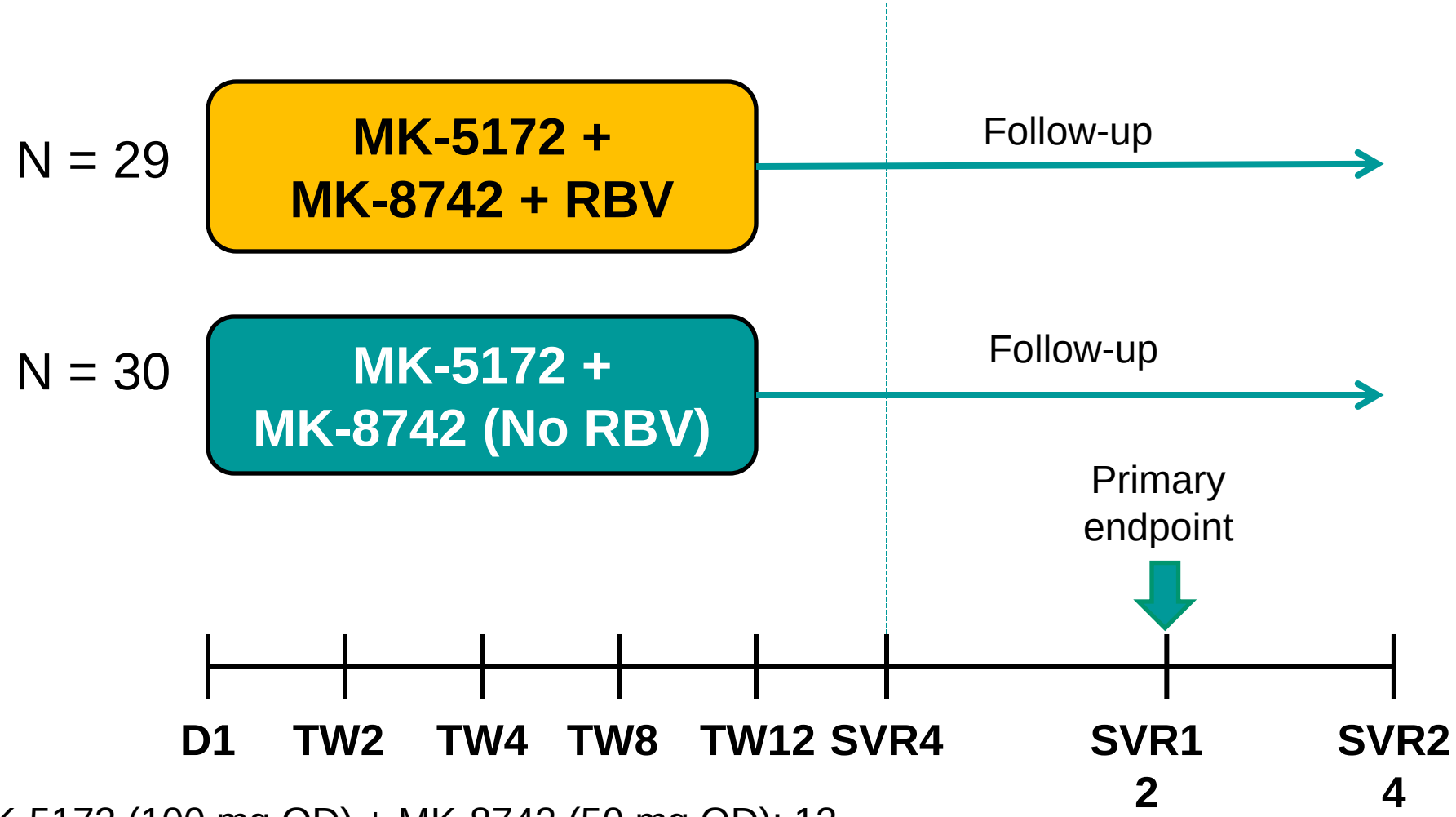
Virologic Response: Genotype 2



Virologic Response: Genotype 3

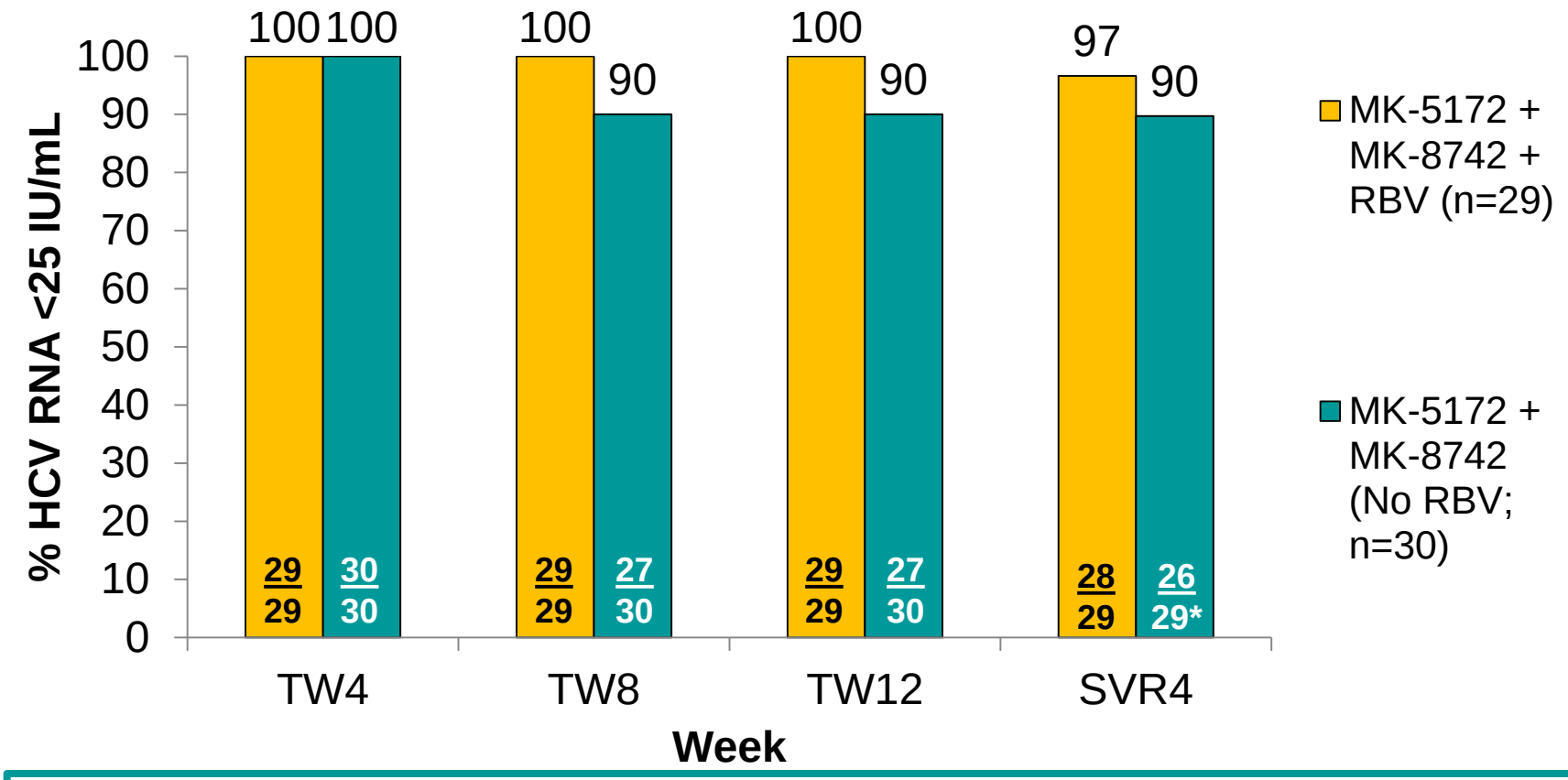


HIV/HCV Co-infected Non-cirrhotic Patients



MK-5172 (100 mg QD) + MK-8742 (50 mg QD); 12

Virologic Responses
ITT Population



Virologic Failures: 1 relapse in +RBV arm;
2 breakthrough and 1 lost to follow up in No RBV arm

* One patient has not yet reached FU4

Challenging aspects of HIV/HCV coinfection: **Drug interactions – HCV DAAs and HIV ART**

- Drug interactions are likely and difficult to predict
  - CYP3A4 inhibition (ritonavir); induction (Efavirenz)
  - Must study the DAA regimen + ART regimen in healthy volunteers
- However, long-term adherence to ART/clinic visits predicts adherence to HCV therapy

HCV NS3/4A Protease Inhibitors and ART

AB450/ritonavir -- will be coformulated with NS5A		?	?
Asunaprevir		?	?
Simeprevir (SIM)	DRV/r	May increase SIM concentration	All other HIV PIs – not evaluated in PK studies, but likely similar to DRV/r TDF; RPV; RAL – no significant PK interaction have been identified to date. DTG – not evaluated in PK studies, but not expected to alter the PK of SIM; SIM not expected to alter PK of DTG
	EFV	Significant reduction in SIM exposure	
	ETR, NVP	Reduction in SIM exposure expected	
	EVG/cobi/TDF/FTC	Increase in SIM exposure expected	
Faldaprevir	DRV/r	DRV AUC increase 15%; FDV AUC increase 129%	DRVr; Reduce FDV dose to 120 mg once daily
	EFV	FDV AUC decrease 35%	EFV; FDV 240 mg once daily
	TFV	TFV AUC increased by 22%; FDV AUC decreased 22%	TDF; no dose adjustment

HCV NS5A Inhibitors and ART

Ledipasvir – coformulated with SOF			
Ombitasvir – coformulated withABT450/-r			
Daclatasvir	ATV/r	ATVr increases DCV	Reduce DCV to 30 mg once daily
	EFV	EFV decreases DCV	Increase DCV to 90 mg once daily

HCV NS5B Polymerase Inhibitors and ART

BMS 325 -- Coformulated with Asunaprevir and Daclatasvir			
Dasabuvir – Only with ABT450/r/ombitasvir			
Sofosbuvir	TPV/r	May decrease SOF levels	TDF; RPV; EVG/cobi; RAL – No significant PK interaction have been identified to date. DTG – not evaluated in PK studies, but not expected to alter PK of SOF; SOF not expected to alter PK of DTG
	ATV/r	Elevated total bilirubin (grade 3 or 4) was observed in 30/32 (94%) subjects receiving ATV as part of ARV regimen.	

Challenging aspects of HIV/HCV coinfection Down to one?!

- Drug interactions with ART
  - HCV DAAs alone
  - HCV DAA combination regimens
- 12 week duration of HCV treatment is beneficial
  - What magnitude of interaction is “clinically acceptable” for short duration?
  - Switch or hold ART for 12 weeks?