

Update on Pathobiology and
Treatment of Hepatitis C in HIV
Coinfection

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HCV Progression and End Stage Liver Disease in African Americans

Blacks have a higher rate of cirrhosis, HCC, and death due to HCV

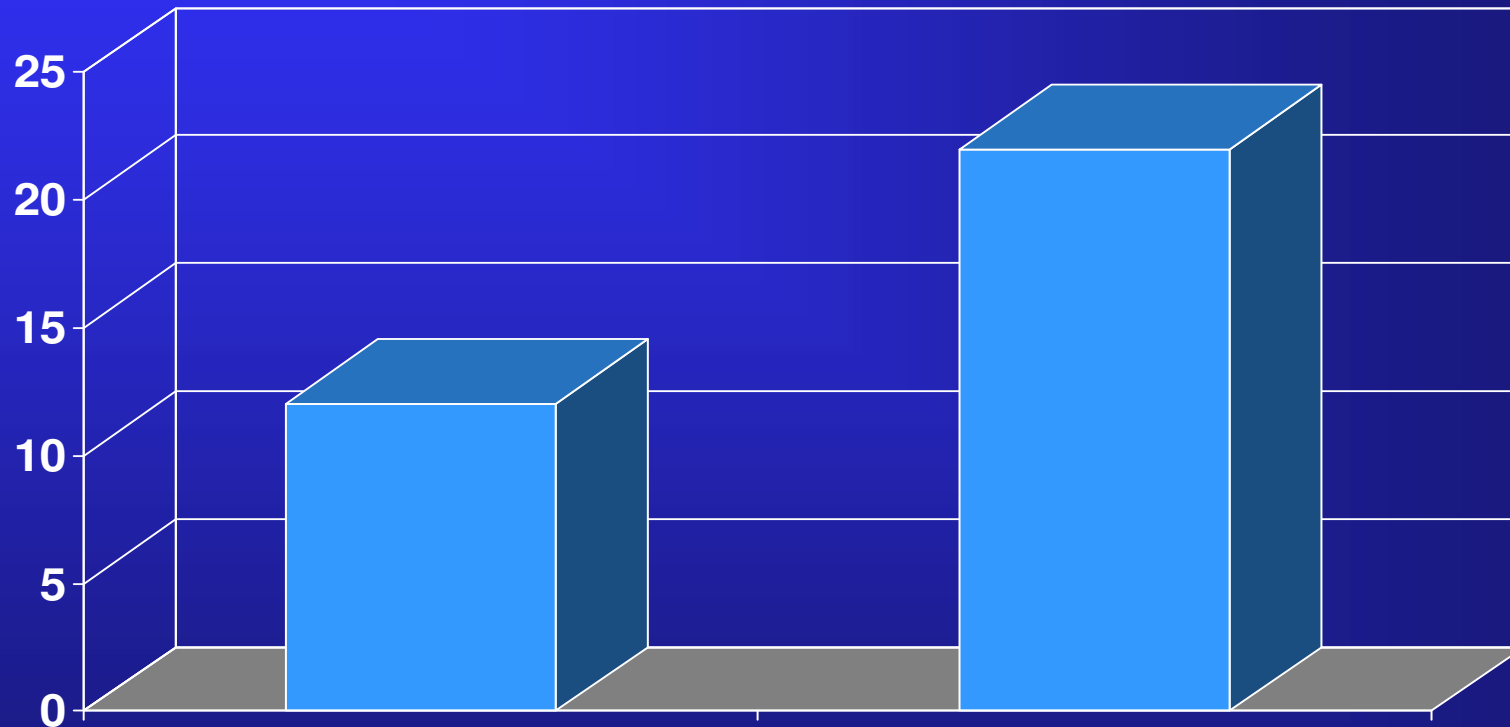
Although African Americans represent 12.8% of the U.S. population and are more likely to have chronic liver disease than whites, they are less likely to undergo liver transplantation

HCV disproportionately affects both the Latino and African-American communities in the U.S

- **HCV is 2- to 3-fold more common among African-Americans and Latinos than non-Hispanic whites**
 - 1.8% of the adult, civilian, non-institutionalized U.S. population had anti-HCV
 - Rates of anti-HCV were higher among African American (3.2%) and Hispanic (2.1%) populations as compared with non-Hispanic white populations (1.8%)
 - African Americans, who represent 12%–13% of the population, account for 22% of the estimated 2.7 million people in the United States with chronic HCV
- **The peak prevalence of anti-HCV was found in the 4th and 5th decades in African Americans, but peaked in the 4th decade in whites, declining thereafter**
 - On average, African American patients were older than whites (49 vs. 45 years) and had a longer duration of infection (27 vs. 23 years) at the time of liver biopsy

Chronic Hepatitis C in African Americans

Percent

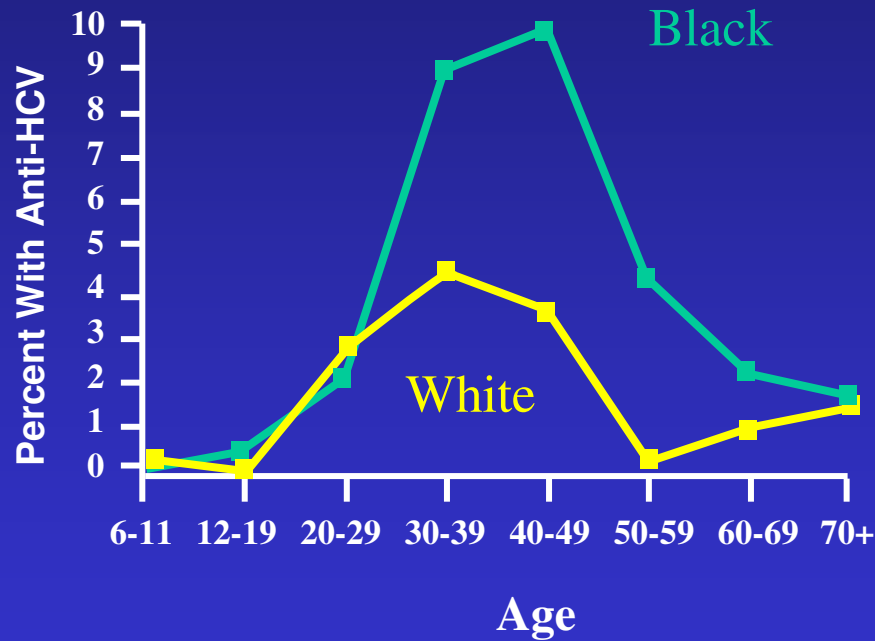


Percent of Population

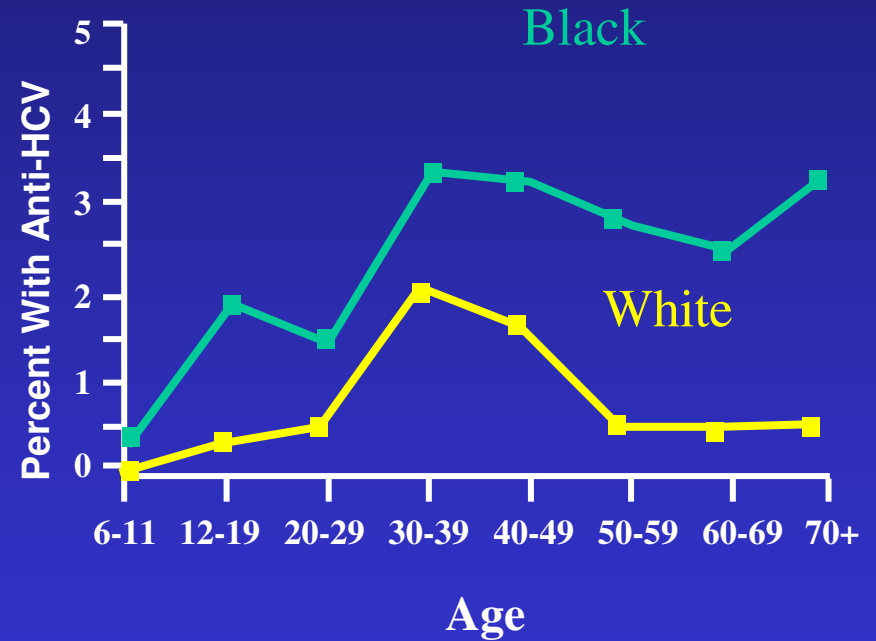
Percent of HCV Positive

Prevalence of HCV by Gender and Race

Males



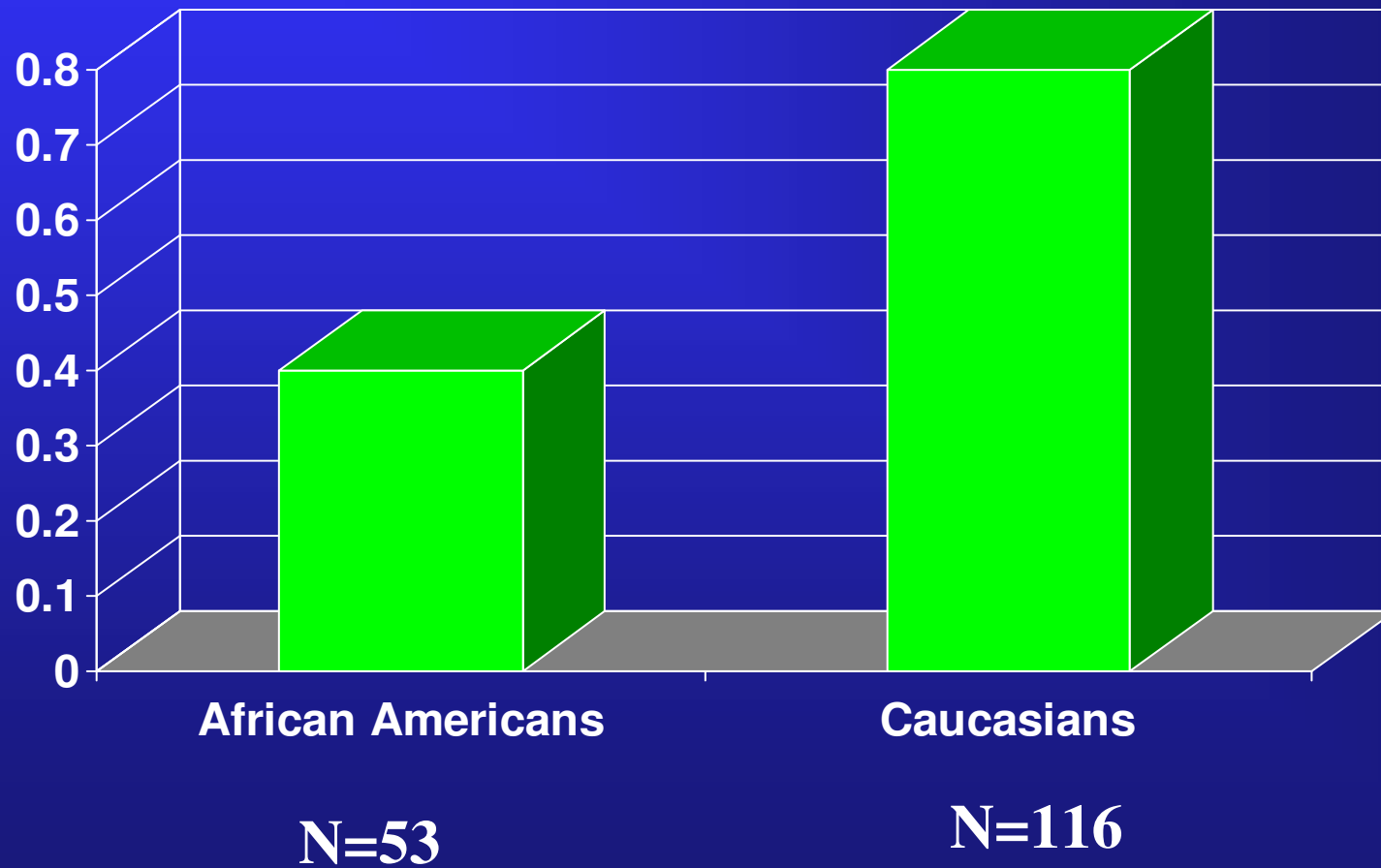
Females



Source: NHANES III

Progression of Fibrosis in Patients with Chronic Hepatitis C

Stages per Year



HCV and HIV: The two most prevalent blood-borne infections in the US

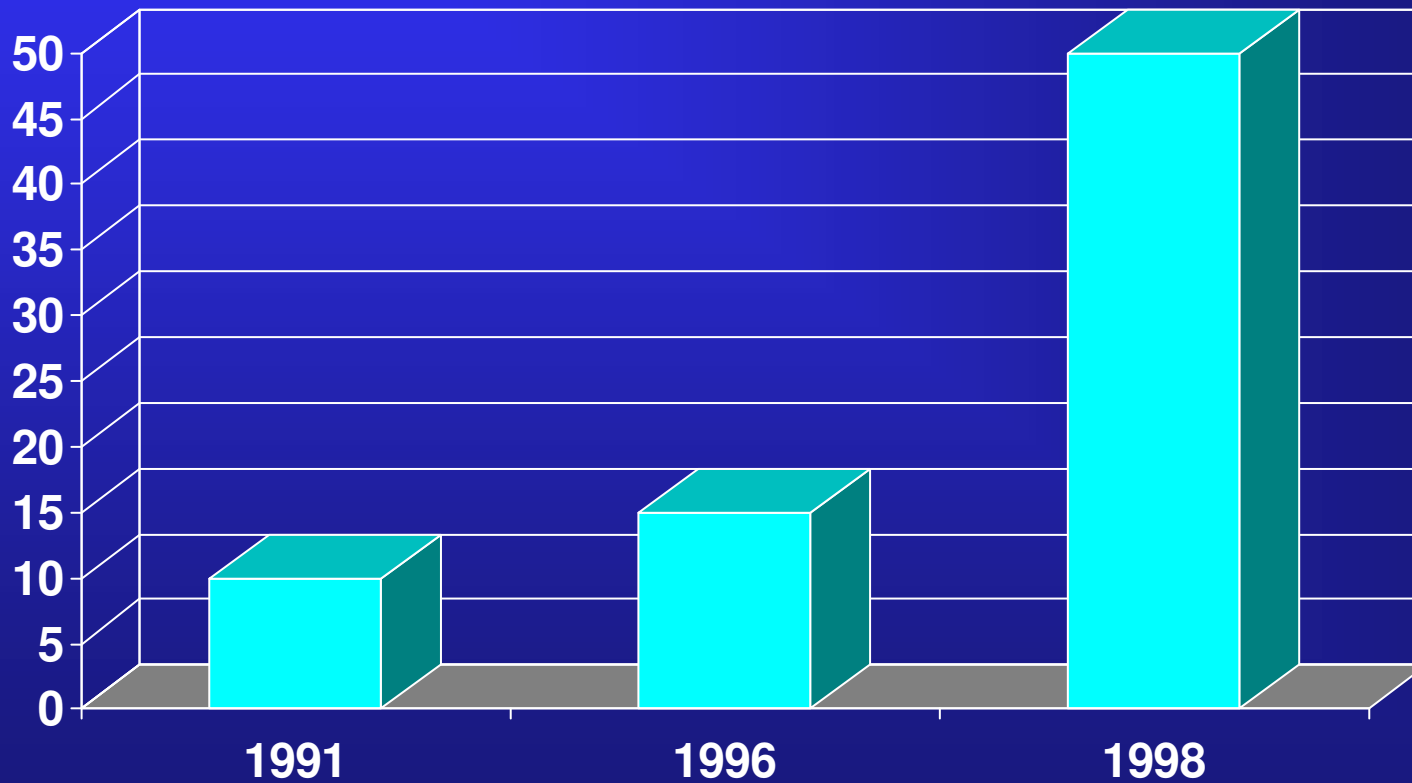
- **Chronic hepatitis C affects approximately four million Americans and HIV almost one million.**
- **Nationally, 30 percent of HIV-infected individuals are co-infected with HCV.**
- **It is also estimated that 60-90 percent of individuals infected with HIV through intravenous drugs use have HCV.**
- **In total, it is estimated that 300,000 individuals in the United States have co-infection.**

Modifiers of HCV Infection
New Jersey Medical School

	<u>VIREMIA</u>	<u>CIRRHOSIS</u>	<u>HCC</u>
<u>AIDS</u>	+ 300%	+30%	+20%
ALCOHOLISM	+50%	+300%	+200%

Death From End-Stage Liver Disease Among Patients with HIV Infection

Percent Mortality

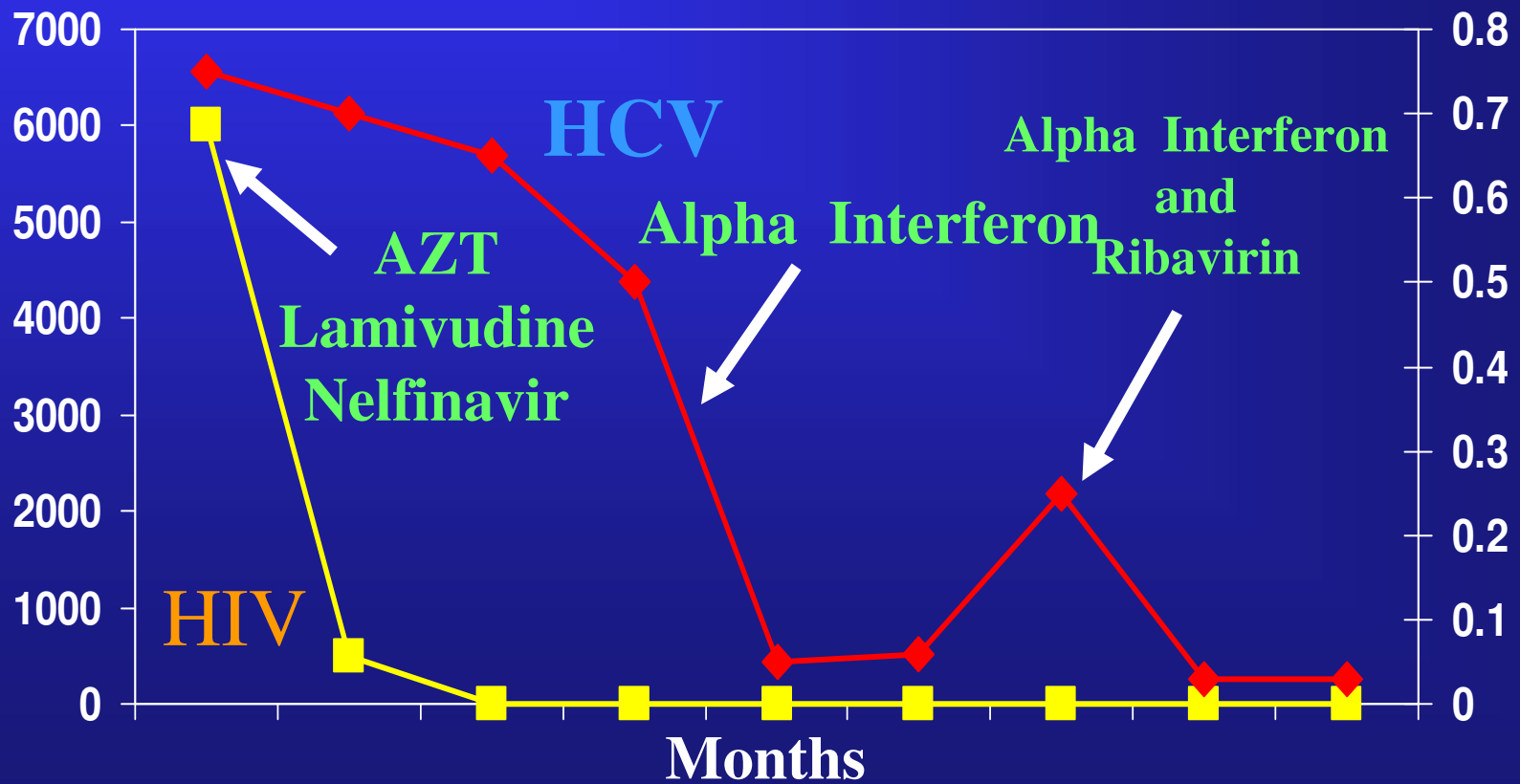


McGoven et. al

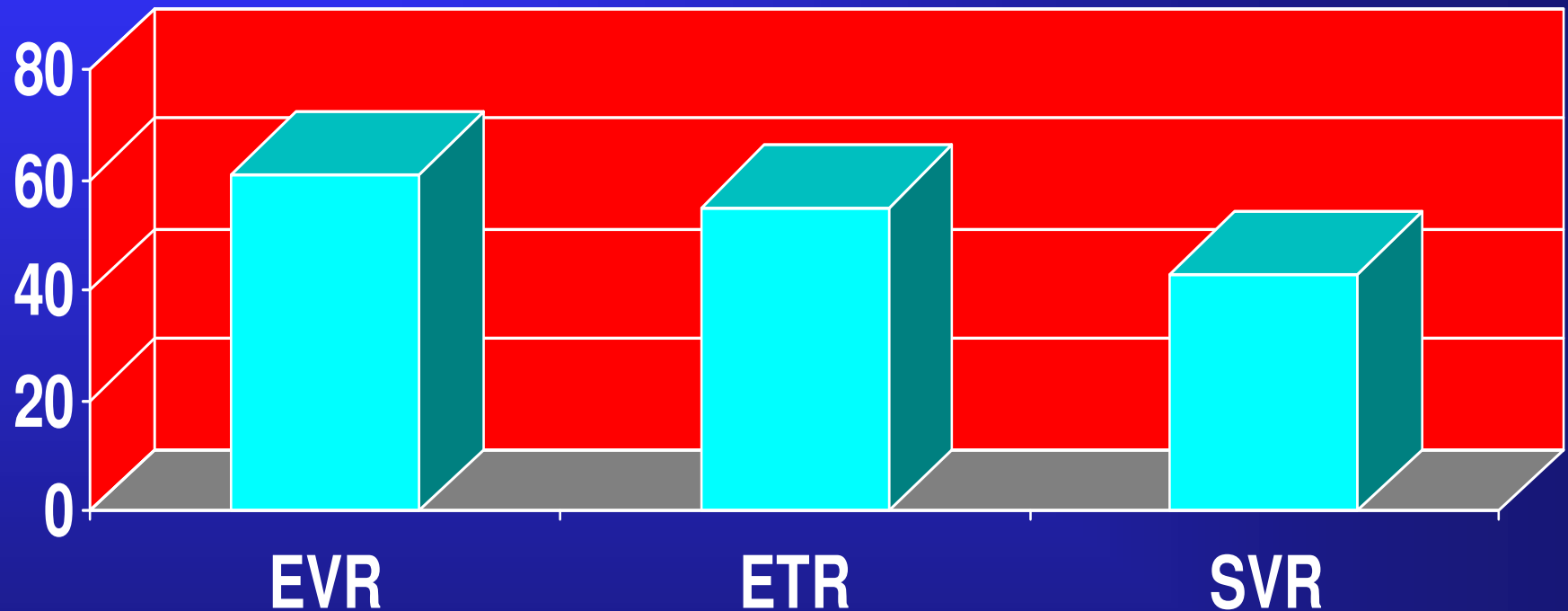
Addition of Ribavirin to Interferon for Treatment of Recurrent HCV in Combined Treatment for AIDS and Hepatitis C

HIV Copies / ml

HCV Million Copies / ml



Treatment at UMDNJ-Liver Center with Pegasys and Copegus in Coinfected Patients Using Growth Factors

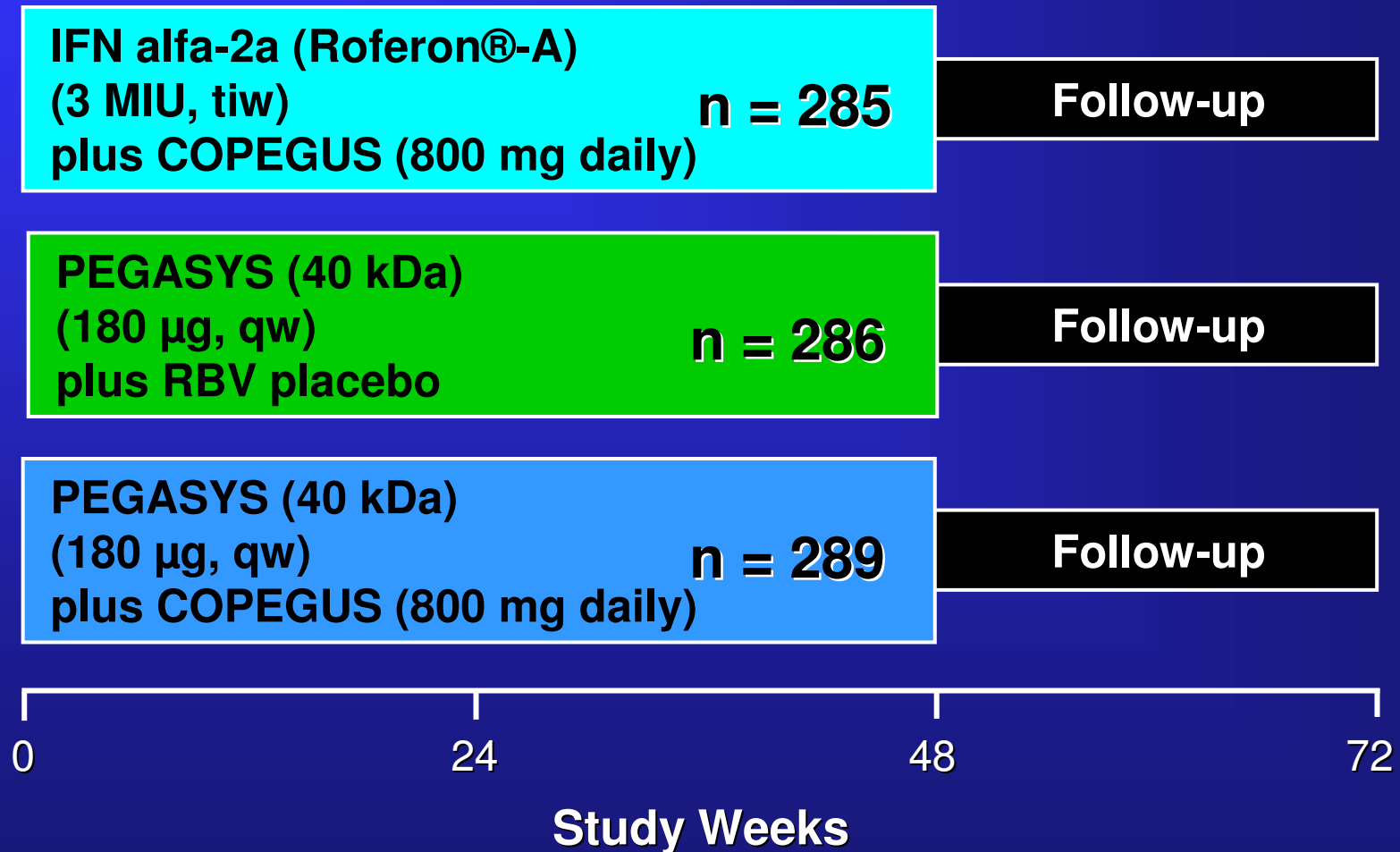


N=211 35% Cirrhotic 52% required Growth Factors 84% Genotype 1 and 4

APRICOT Study Design

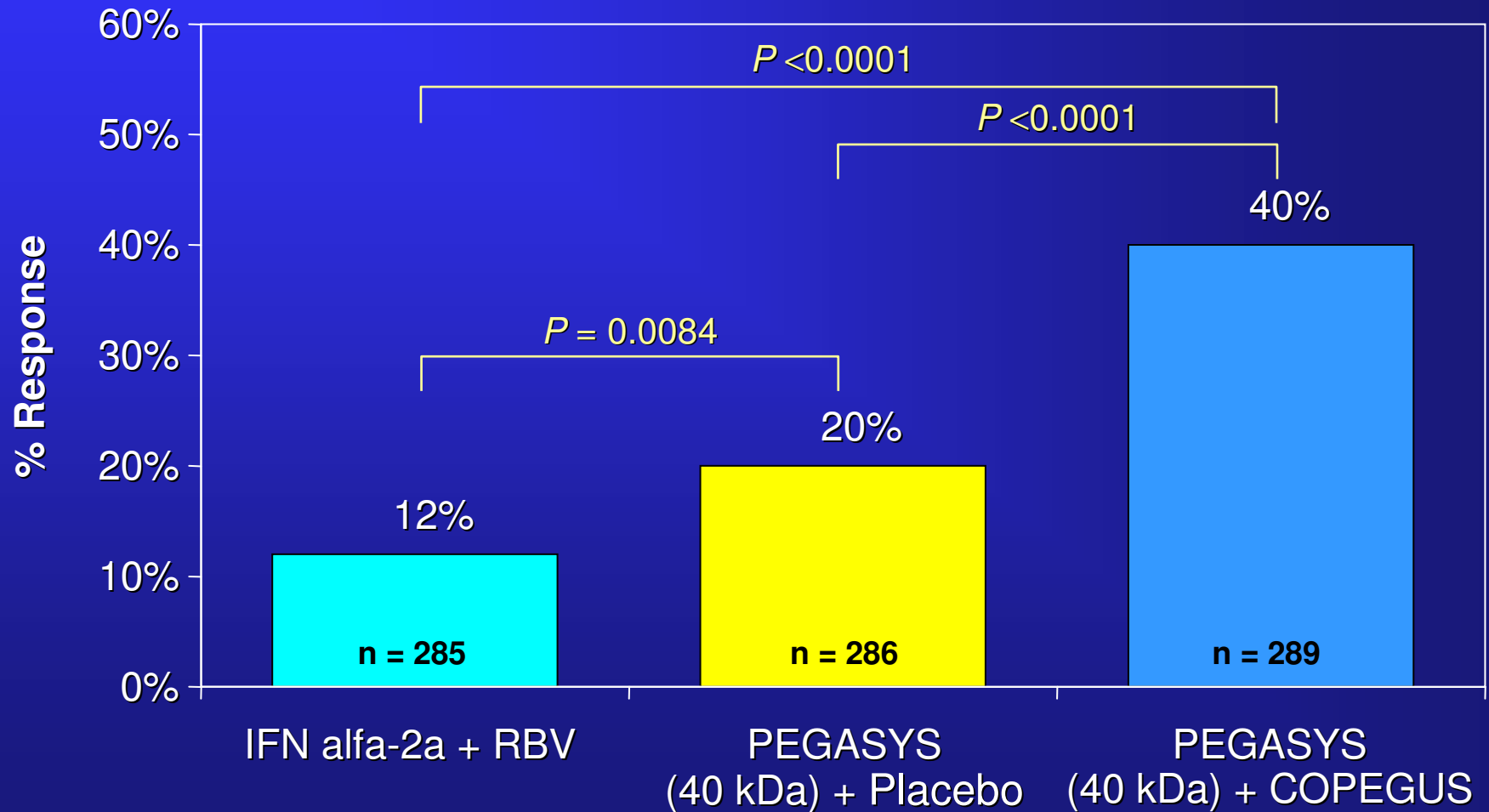
- PEGASYS combination therapy blinded (COPEGUS vs placebo)
- Stratified
 - Genotype 1 vs non-1
 - CD4⁺ 100 to <200/ μ L vs \geq 200/ μ L
 - ART vs no ART
 - Cirrhotic vs non-cirrhotic
 - Geographic region

APRICOT Study Design



860 received at least one dose

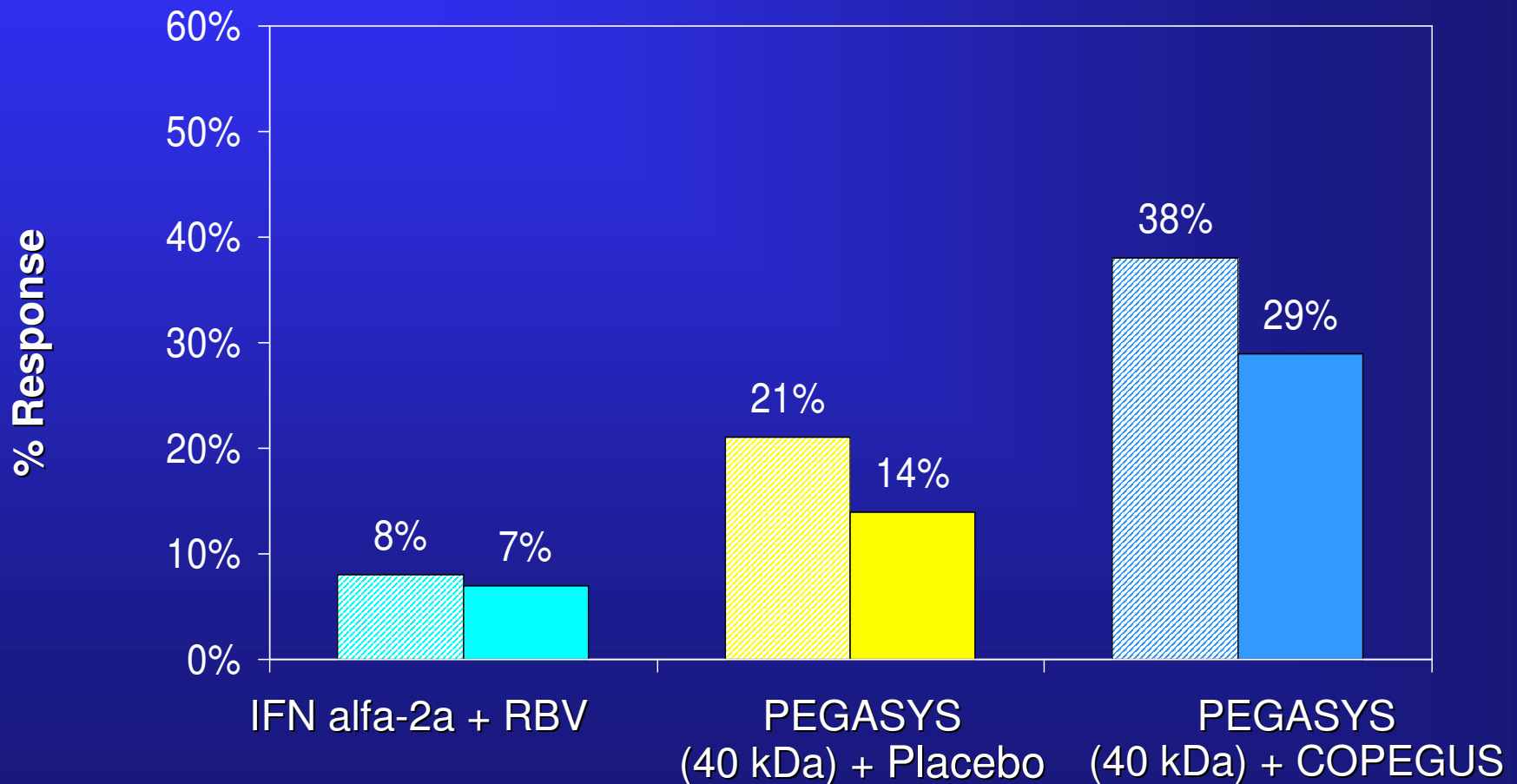
Sustained Virologic Response*



* Defined as <50 IU/mL HCV RNA at week 72; ITT

Virologic Response* – End of Treatment vs End of Follow-up (Genotype 1)

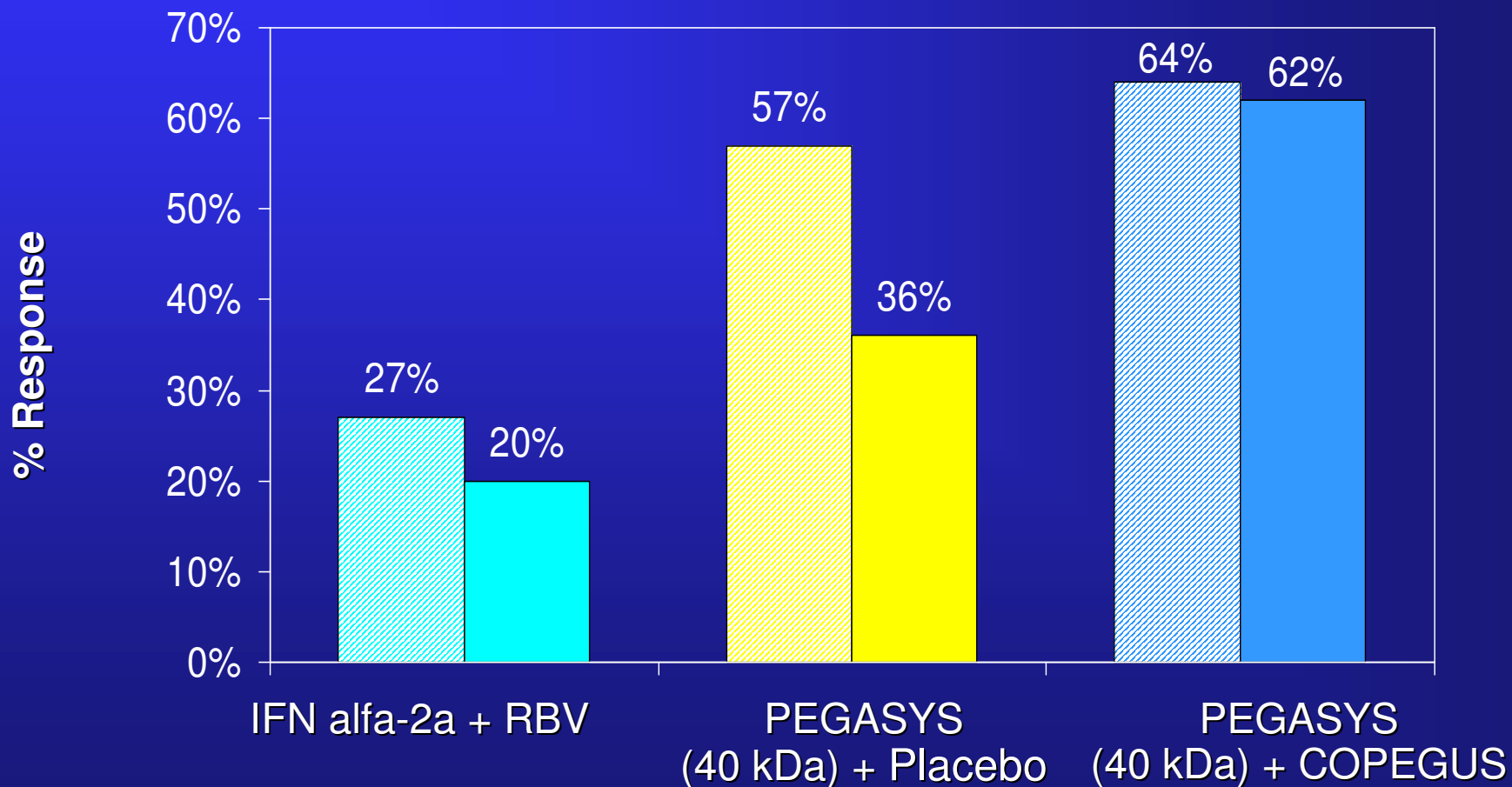
▨ End of treatment ■ End of follow-up



* Defined as <50 IU/mL HCV RNA

Virologic Response* – End of Treatment vs End of Follow-up (Genotype 2 and 3)

▨ End of treatment ■ End of follow-up

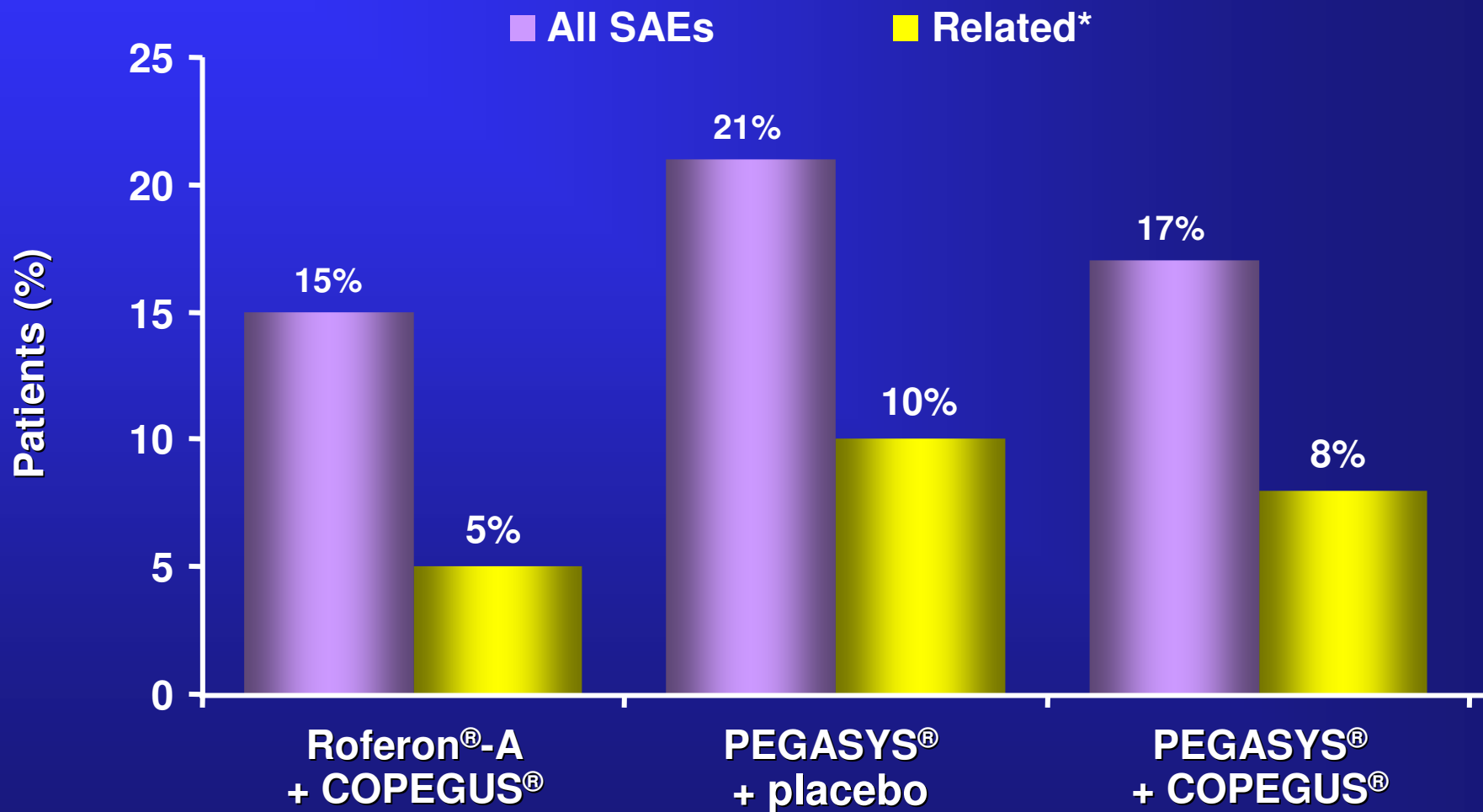


* Defined as <math><50\text{ IU/mL HCV RNA}</math>

Adverse events $\geq 20\%$ irrespective of causality

	Roferon [®] -A + COPEGUS [®] (n = 285)	PEGASYS [®] + placebo (n = 286)	PEGASYS [®] + COPEGUS [®] (n = 288)
Fatigue	40%	41%	44%
Pyrexia	35%	43%	44%
Headache	41%	38%	39%
Myalgia	29%	33%	36%
Nausea	25%	27%	30%
Diarrhoea	24%	26%	28%
Insomnia	29%	21%	26%
Asthenia	24%	22%	28%
Depression	22%	20%	26%
Arthralgia	18%	20%	20%
Weight decreased	14%	18%	20%

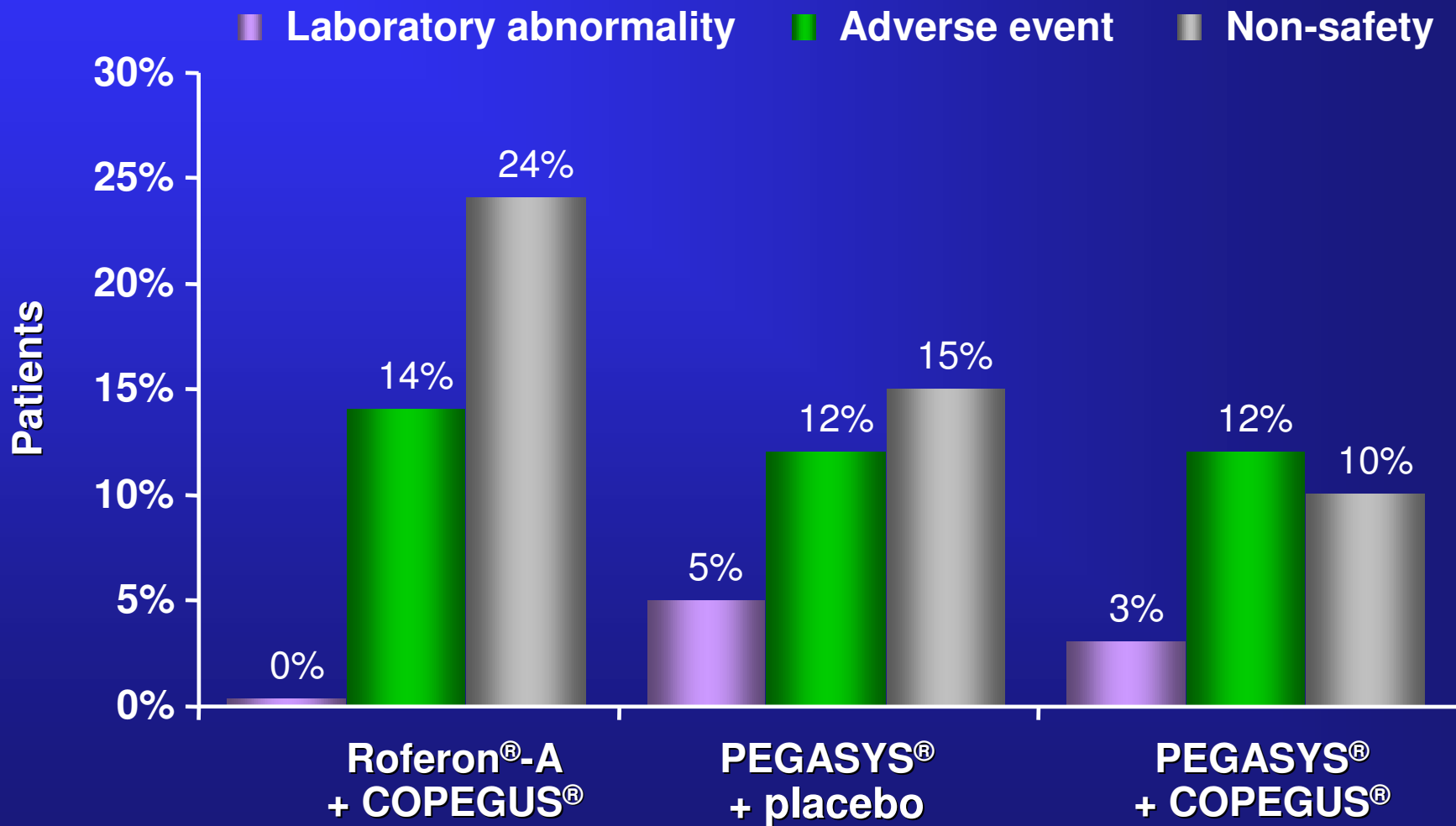
Patients with serious adverse events (SAEs)



*Possibly or probably related

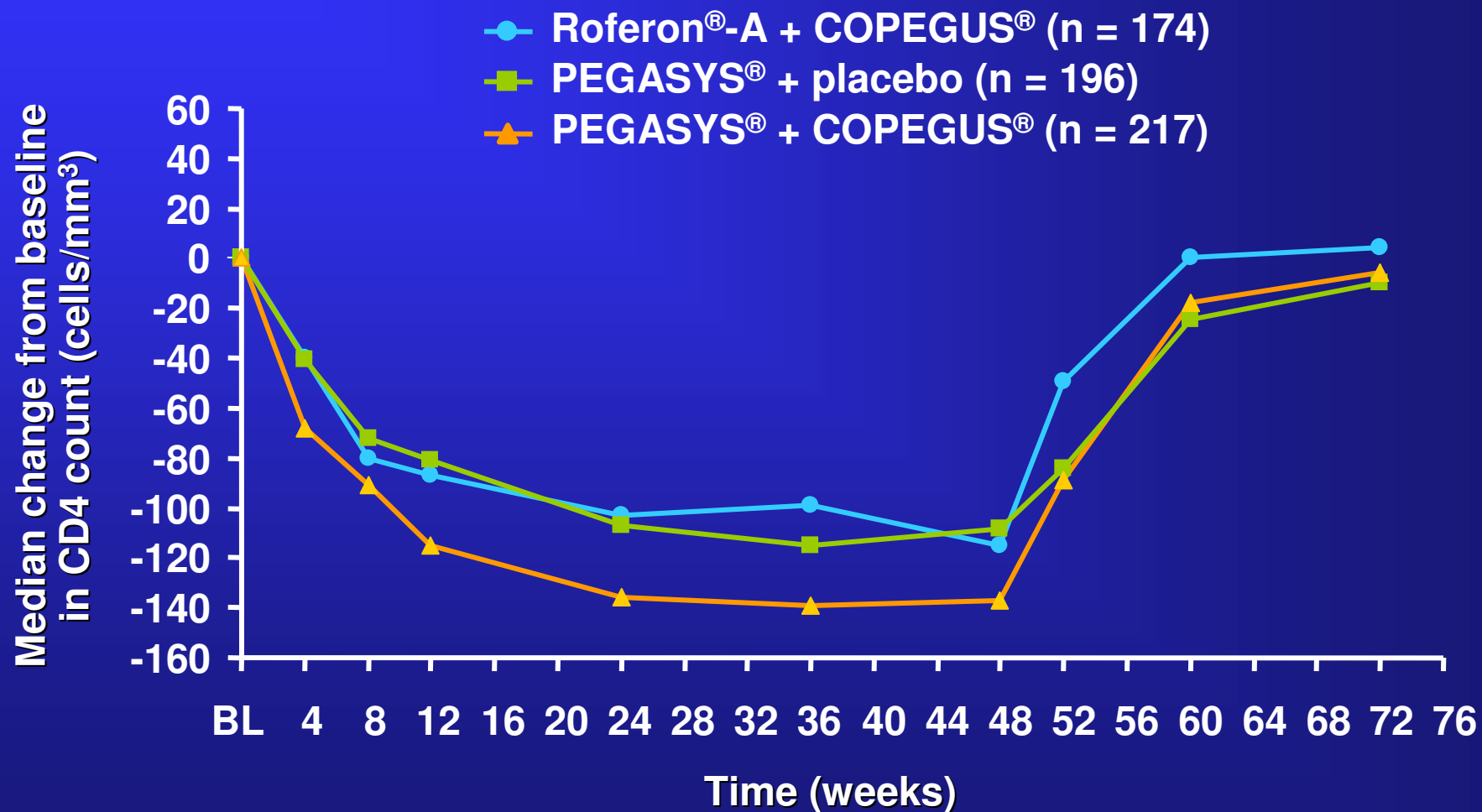
Torriani *et al.* 11th CROI, 2004; abstract 112

Withdrawal from treatment



Torriani et al. 11th CROI, 2004; abstract 112

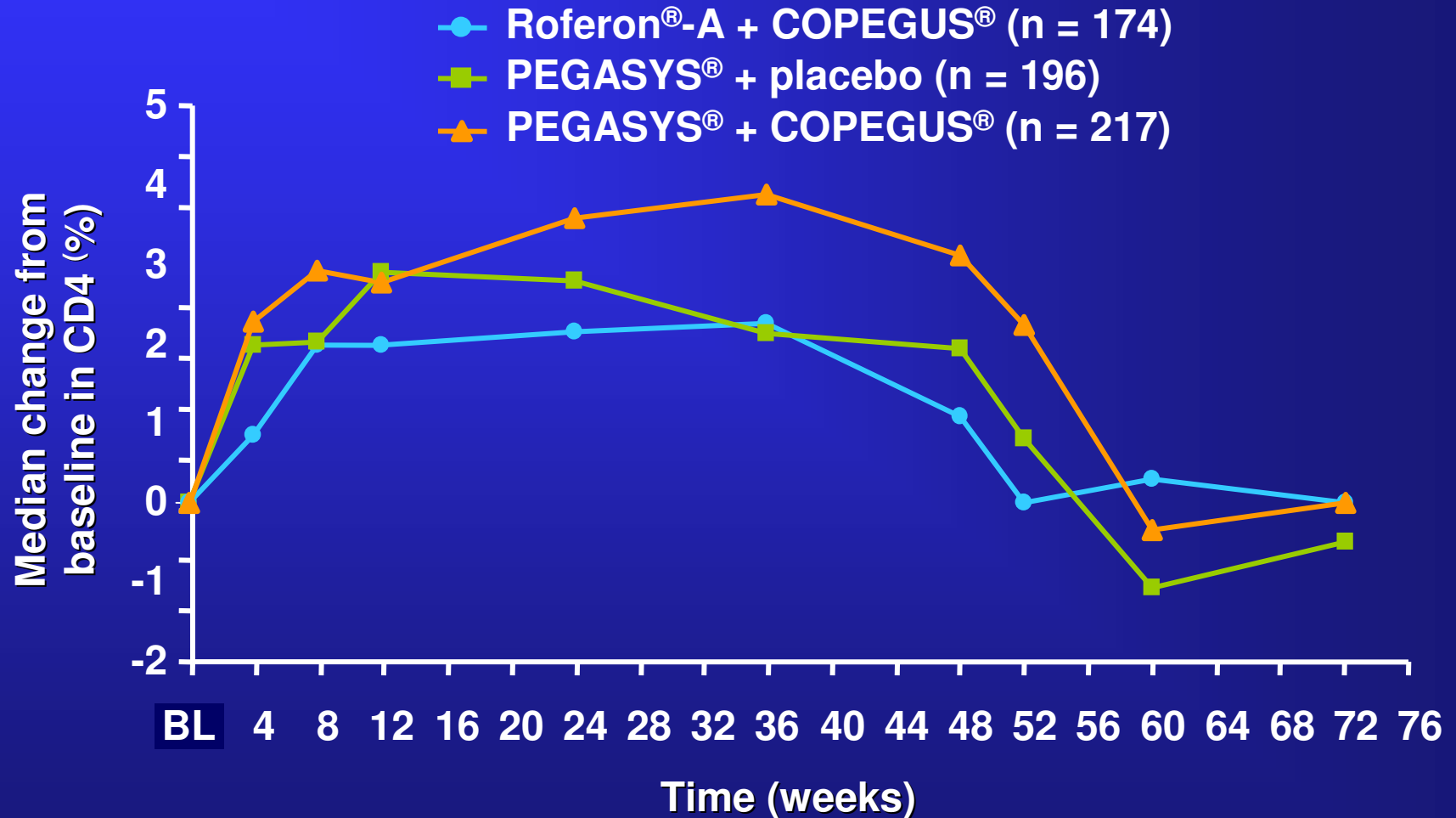
Median change from baseline in CD4 counts



Patients receiving 48 weeks of treatment

Torriani *et al.* 11th CROI, 2004; abstract 112

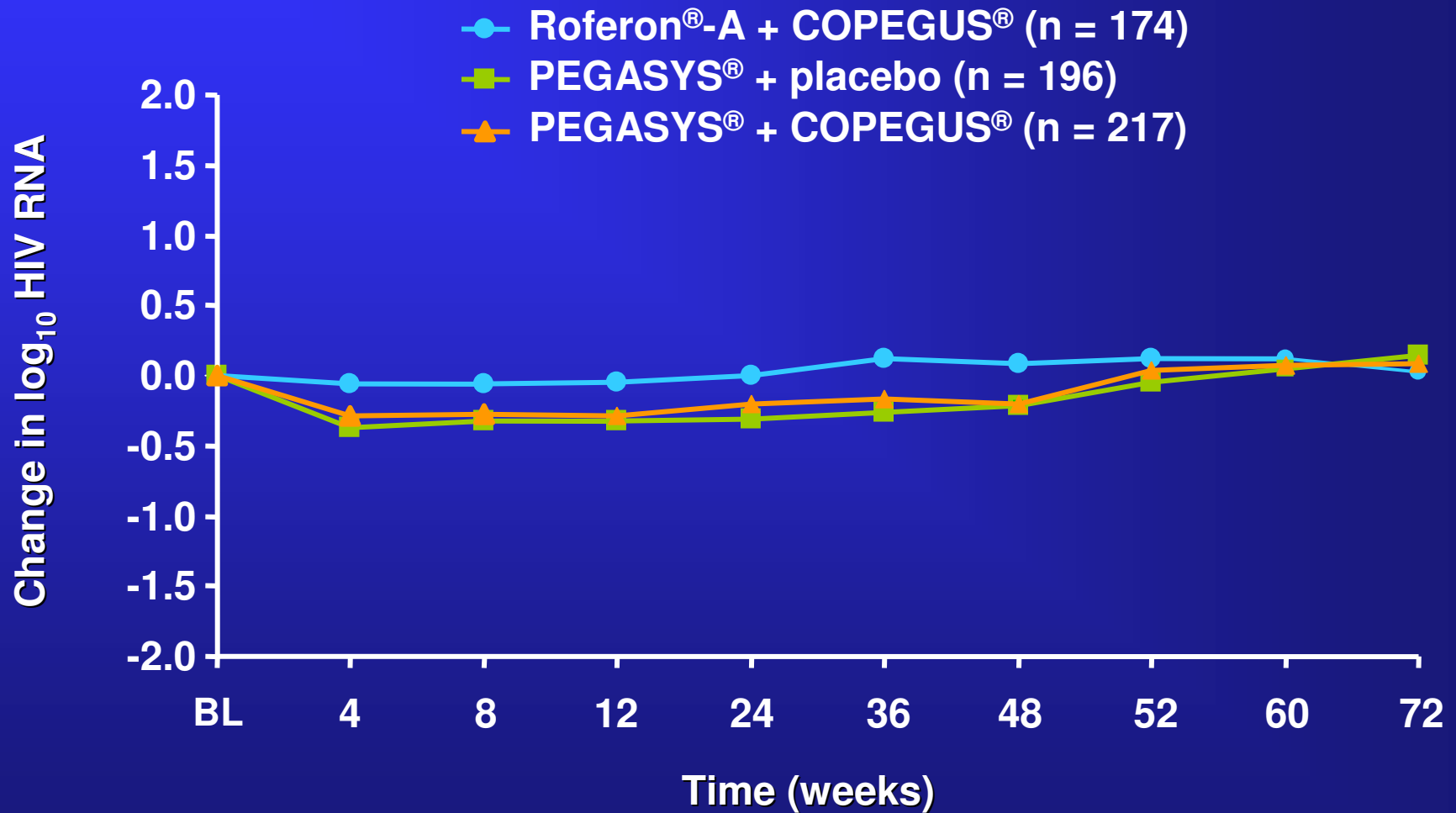
Median change from baseline in CD4 percentage of lymphocytes



Patients receiving 48 weeks of treatment

Torriani *et al.* 11th CROI, 2004; abstract 112

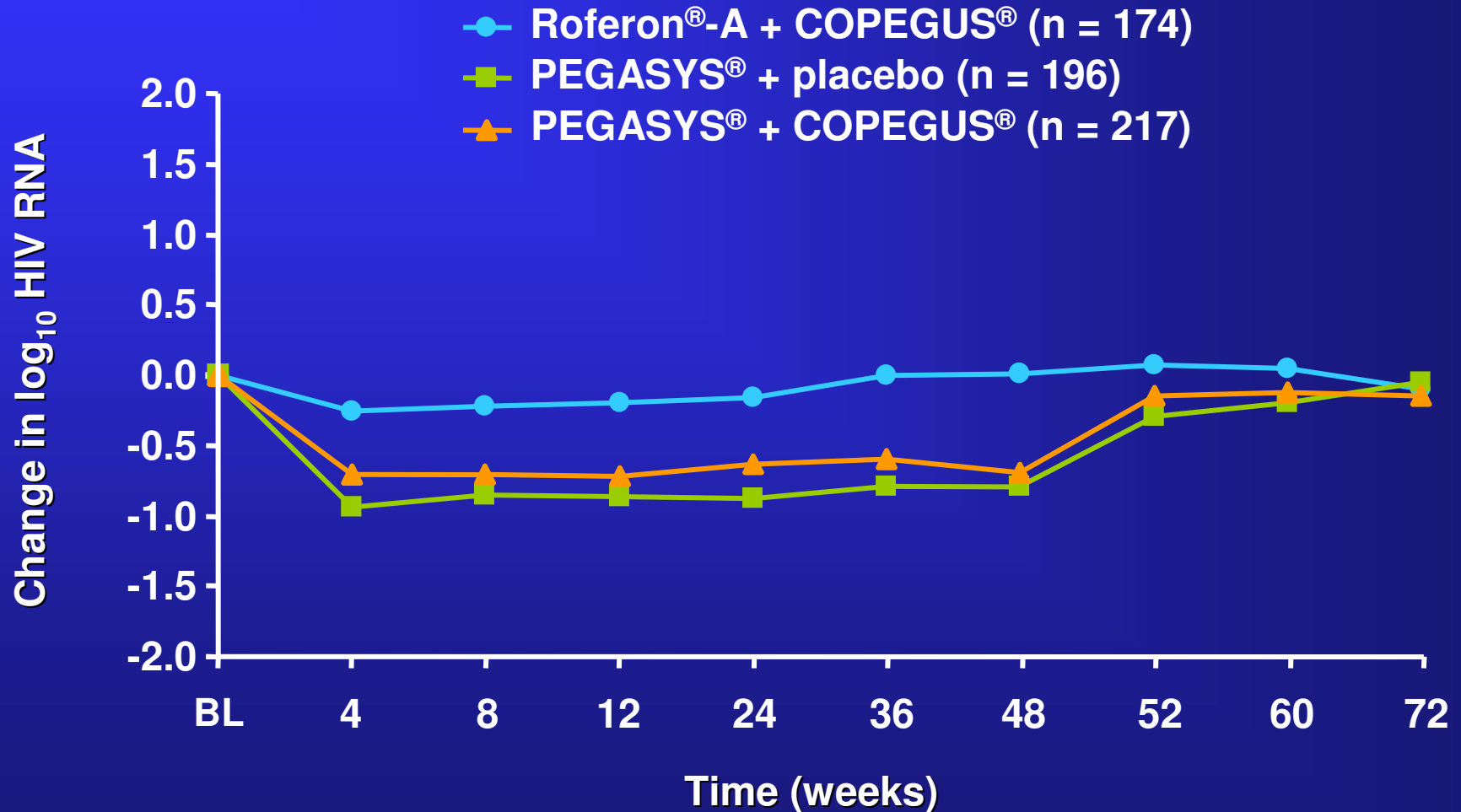
Mean change from baseline in HIV RNA: all patients treated



Patients receiving 48 weeks of treatment

Torriani *et al.* 11th CROI, 2004; abstract 112

Mean change from baseline in HIV RNA: patients with detectable HIV RNA at baseline



Patients receiving 48 weeks of treatment

Torriani *et al.* 11th CROI, 2004; abstract 112

Effects of HCV treatment on HIV therapy

- In APRICOT, PEGASYS® plus COPEGUS® did not negatively affect the control of HIV infection:
 - Absolute CD4 counts decreased during treatment
(a known effect of interferon therapy)
 - Absolute CD4 counts returned to baseline levels during follow-up
 - Percentage CD4 count increased during therapy
 - HIV RNA levels remained almost unchanged during treatment
 - Patients with detectable HIV RNA at baseline had a 0.7 log₁₀ copies/ml reduction in HIV RNA during treatment

Nested pharmacokinetics

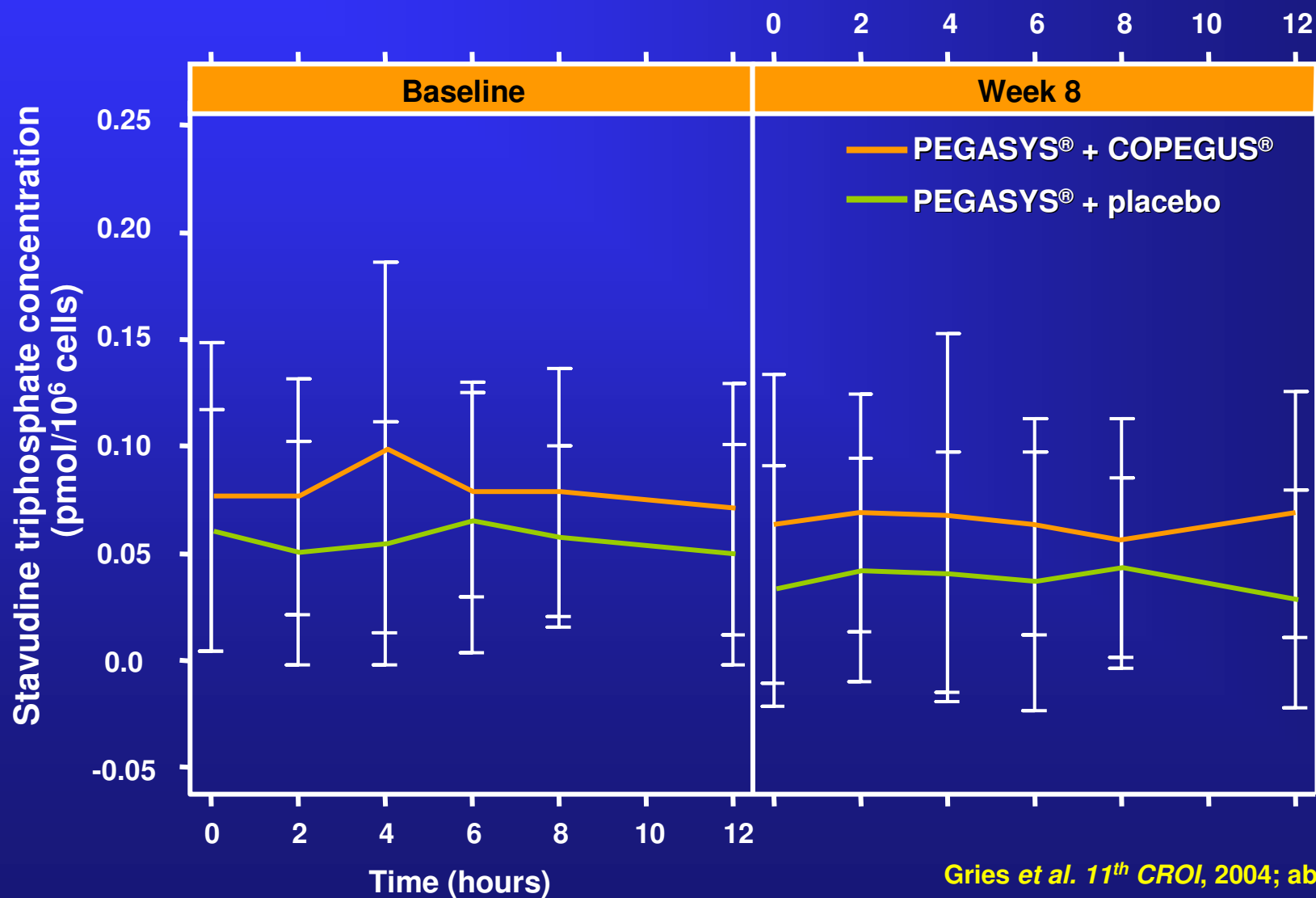
- **Rationale:**

- Ribavirin affects intracellular nucleotide pools
- Ribavirin reduces phosphorylation of pyrimidine analogues (lamivudine, stavudine, zidovudine)

- In patients with HIV–HCV co-infection:

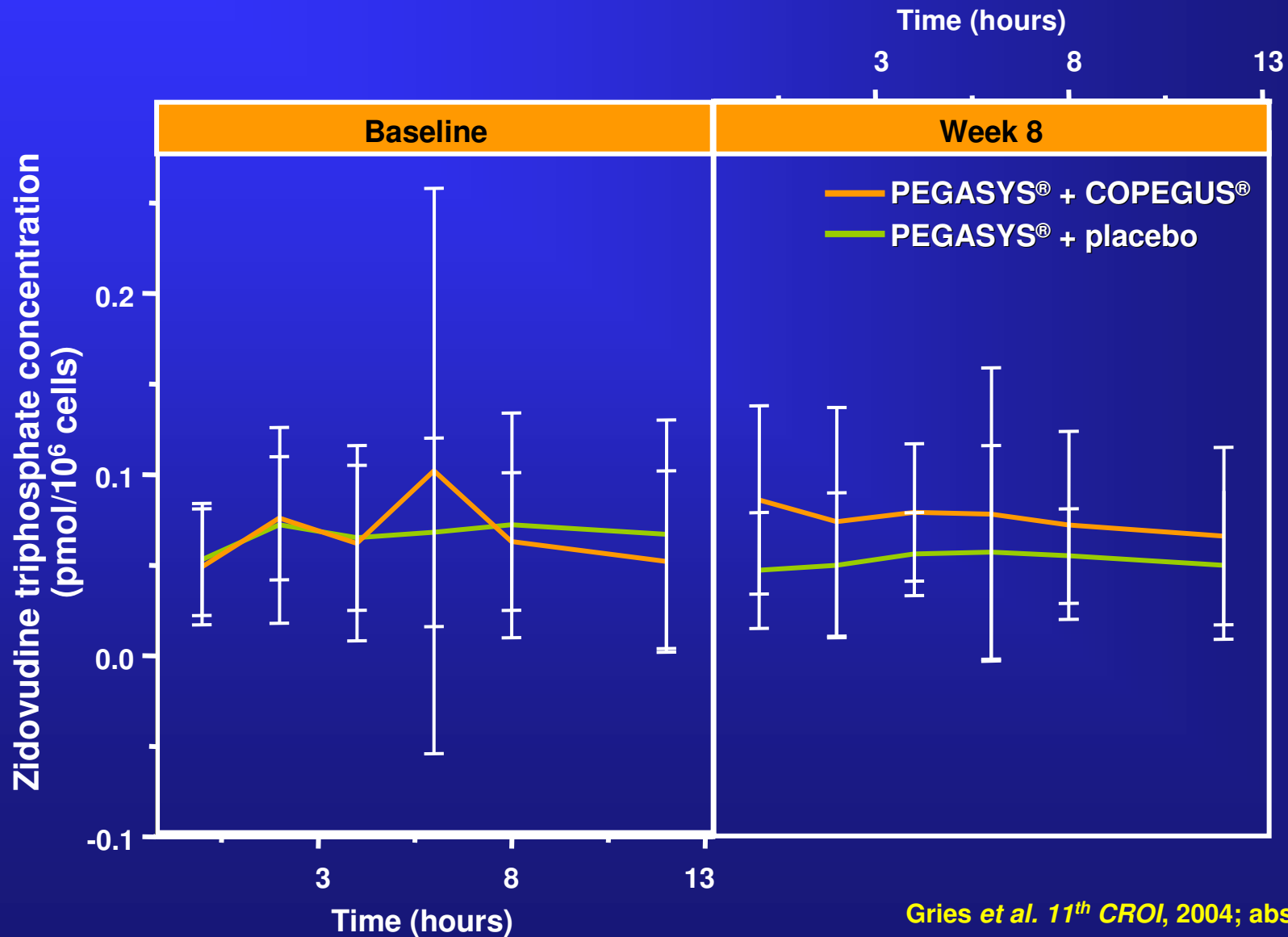
- COPEGUS[®] did not appear to disrupt the intracellular metabolism of lamivudine, stavudine or zidovudine or their corresponding nucleoside triphosphates
- COPEGUS[®] did not appear to modify the plasma concentration-time profile of lamivudine, stavudine or zidovudine (data not shown)
- PEGASYS[®] plus COPEGUS[®] at 800 mg/day can be prescribed in HIV–HCV co-infected patients receiving antiretroviral therapy without undue concern for pharmacokinetic interactions between COPEGUS[®] and lamivudine, stavudine and/or zidovudine

Intracellular stavudine triphosphate time profile



Gries et al. 11th CROI, 2004; abstract 136LB

Intracellular zidovudine triphosphate time profile



Gries et al. 11th CROI, 2004; abstract 136LB

Summary

Combination therapy with PEGASYS® plus COPEGUS® appears to have a favourable benefit-to-risk ratio in patients with HIV–HCV co-infection

- **SVR was significantly higher for PEGASYS (40 kDa) + COPEGUS compared to conventional combination therapy**
 - Overall: 40% vs 12%; $P < 0.0001$
 - Genotype 1: 29% vs 7%
 - Genotype 2/3: 62% vs 20%
- **Adverse event profile of PEGASYS (40kDa) + COPEGUS is generally similar to IFN + RBV therapy**
- **Only 15% of patients discontinued for adverse events or laboratory abnormalities**