

# Rio Update

3<sup>rd</sup> International AIDS Society Conference  
on HIV Pathogenesis and Treatment



**July 24-27, 2005**

**Rio de Janeiro, Brazil**

**Report Back for Community  
Consortium**

**Brad Hare, MD**

**August 17, 2005**

Special acknowledgement for slide preparation to :

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# **Treatment Experienced Patients and Resistance**

Brad Hare, M.D.

# Predictors of TPV/r Response

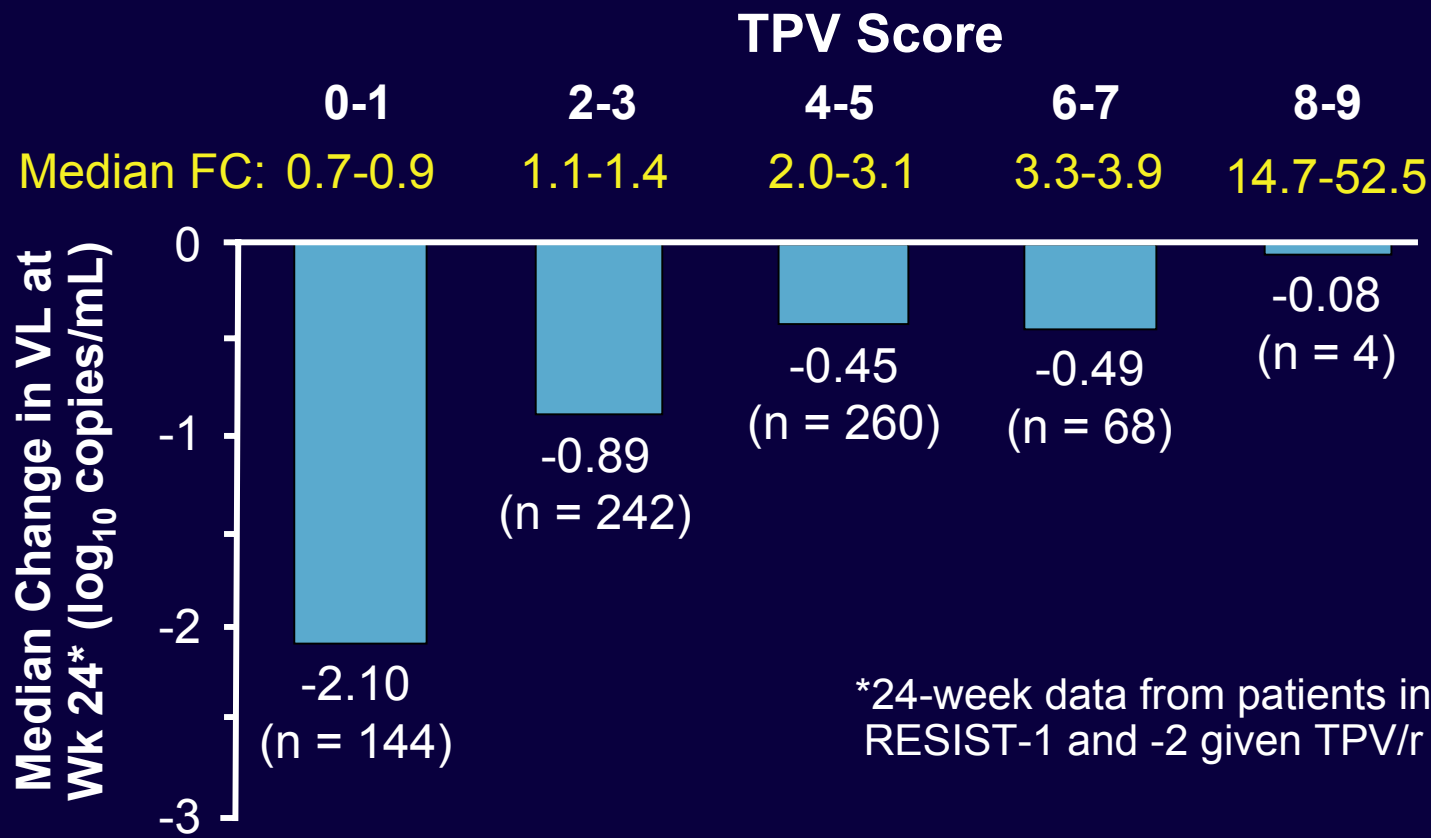
- 400 Randomly selected samples of TPV/r recipients in RESIST-1 and -2 evaluated (multiple regression model)

Predictors	Estimated Response at 24 Weeks (log <sub>10</sub> copies/mL)	P Value
TPV/r use	-1.25	< .01
ENF use (all subjects on ENF)	-0.91	< .01
Per active drug in OBR	-0.24	< .01
TPV score (per mutation)*	+0.17	< .01

\* 21 mutations at 16 protease codons associated with ↓ TPV susceptibility/response in phase 2 and 3 trials: 10V, 13V, 20M/R/V, 33F, 35G, 36I, 43T, 46L, 47V, 54A/M/V, 58E, 69K, 74P, 82L/T, 83D, and 84V (Note: No L90M, N88D)

	L	I	K		L	E	M	K	M	I		I	Q		H		T		V	N	I
TPV	10	13	20		33	35	36	43	46	47		54	58		69		74		82	83	84
	V	V	M		F	G	I	T	L	V		A	E		K		P		L	D	V
			R									M							T		
			V									V									

# Relationship of TPV Score to TPV Phenotype Results and Response



# TPV/r More Effective in Combination with T-20

- Week 24 viral load changes:

Viral load Parameter	All patients N=329	With T-20 N=99	Without T-20 N=230	With T-20 and TPV IQ* $\geq$ 60 N=57
<400 copies	35%	44%	30%	60%
< 50 copies	24%	27%	22%	37%

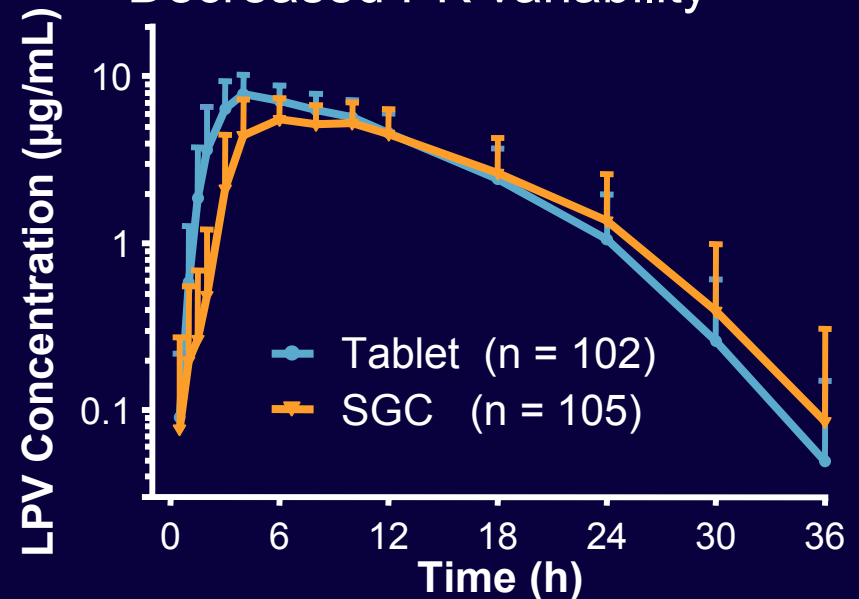
\* Inhibitory Quotient (IQ) = Cmin / TPV Fold-change

# Pharmacokinetics of New Lopinavir/Ritonavir Formulation

- LPV/r (200/50 mg) tablet created by melt-extrusion technology
  - ↓ pill count from 6 to 4 /day
  - No refrigeration
  - No oleic acid



- Phase 1, open-label, randomized, cross-over, single dose studies in healthy adults
- Moderate-fat meal
- Decreased PK variability



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# Lack of PI Resistance After Boosted PI Failure

- No primary PI resistance mutations in pts with failure of SQV/r regimen
  - Staccato trial: Of 10 patients failing SQV/r 1600/100 mg QD + d4T/ddI (or TDF/3TC), none had primary PI mutations at failure; 3 had NRTI mutations <sup>[1]</sup>
- Consistent with previous reports on FPV/r, LPV/r
  - SOLO trial: Of 32 pts failing FPV/r + ABC + 3TC, none developed primary or secondary PI mutations at failure <sup>[2]</sup>
  - M98-863 trial: Of 51 pts failing LPV/r + d4T + 3TC, none had primary PI mutations at failure <sup>[3]</sup>

1. Ananworanich J, et al. IAS 2005. Abstract WePe4.4C12.

2. MacManus S, et al. AIDS. 2004;18:651-655.

3. Kempf DJ, et al. J Infect Dis. 2004;189:51-60.

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# Pharmacokinetics of Dual-boosted PI Regimens

- Substantial reductions in APV and LPV levels previously shown when FPV and LPV/r coadministered [1]
- Current study showed no apparent adverse PK effect with ATV (300 or 400 QD) + LPV/r (400/100 BID) [2]
  - 20 treatment-experienced pts; 3 PI naive; 14 LPV/r naive
  - Median ATV and LPV C<sub>min</sub> in target range
  - 69% < 400 copies/mL at Week 24
  - 25% Grade 2/3 hyperbilirubinemia
- Further formal drug interaction studies and clinical trials are warranted

1. Kashuba A, et al. AIDS. 2005;19:145-152.

2. Duvivier C, et al. IAS 2005. Abstract WePe3.2C10.

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# Polymorphisms Associated with CD4+ Response

- 3 genes involved in T-cell proliferation, survival, and apoptosis had haplotypes associated with more favorable CD4+ increase on HAART
  - Interferon alpha
  - Interleukin 2
  - Interleukin 15 receptor, alpha
- Factors associated with  $< 200$  cells/mm<sup>3</sup> increase in CD4+ cell count (multivariate analysis):
  - Older age, male sex, lower pre-treatment viral load, lower pre-therapy CD4+, hepatitis B antigen positivity

# Immune Effects of Growth Hormone

AACTG 5174 [1]

Wk 24

Wk 48

On HAART > 1 yr  
CD4+ < 350  
VL < 400  
(N = 60)

Arm A: HAART + rGH (1.5 mg SC QD)

Arm B: HAART

HAART + rGH (3.0 mg SC QD)

- Growth hormone ↑ naive and total CD4+ cell count [1]

Parameter	Arm A	Arm B
Total CD4 count		
Week 24	+19 (0.03)	+16 (0.16)
Week 48	+36 (0.001)	+55 (<0.001)
Naïve CD4 %		
Week 24	0 (0.5)	-2 (0.07)
Week 48	+8 (<0.0001)	+4 (0.003)
Grade 3/4 Clinical AEs	13%	23%
Grade 3/4 Labs	23%	17%

- Clinical implications unknown; follow-up off rGH pending
- Similar results with longer growth hormone treatment in a small pilot study [2]

1. Smith K, et al. IAS 2005. Abstract TuOa0203.

2. Napolitano LA, et al. IAS 2005. Abstract MoPpLB0104.

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# The “New York Case” Revisited: “Patient Zero”

- Potential transmission source identified through resistance mutation profile matching
  - Possible source: long-term, HIV(+) MSM couple in Connecticut
    - **Both reported unprotected anal intercourse with NY case**
    - **No evidence of rapid progression in either source patient**
    - **Viruses 98-99.5% related by phylogenetic analysis; same mutational pattern**
  - Transmission possible via other NY case partners
- Discordance in viral replication capacity and viral tropism
  - NY case: RC 136% (86-215%); R5/X4-tropic virus
  - CT01: RC 41% (21-65%); R5-tropic virus
- No evidence of epidemic of highly virulent HIV
- Host factors are likely explanation of rapid course of NYC case

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# Resistance and Progression

- Traditional dogma is that drug resistant virus may cause slower disease progression due to impaired fitness. NYC case challenged that.
- From SPREAD cohort in Europe – 1415 newly diagnosed HIV+ patients in 2003. 16 month follow-up. 20% with <1 year infection.
  - 78 Patients with initial drug resistant virus by genotype
  - Randomly selected 77 patients with drug susceptible virus
  - Proportion reaching CD4+ count < 200, start of ART, or clinical AIDS was the same in drug resistant cases (44%) vs. drug-susceptible cases (55%). HR = 0.7 (0.3 – 1.1)
    - Proportion with endpoint at time of diagnosis was the same in both groups, OR = 1.3 (0.6-2.6)

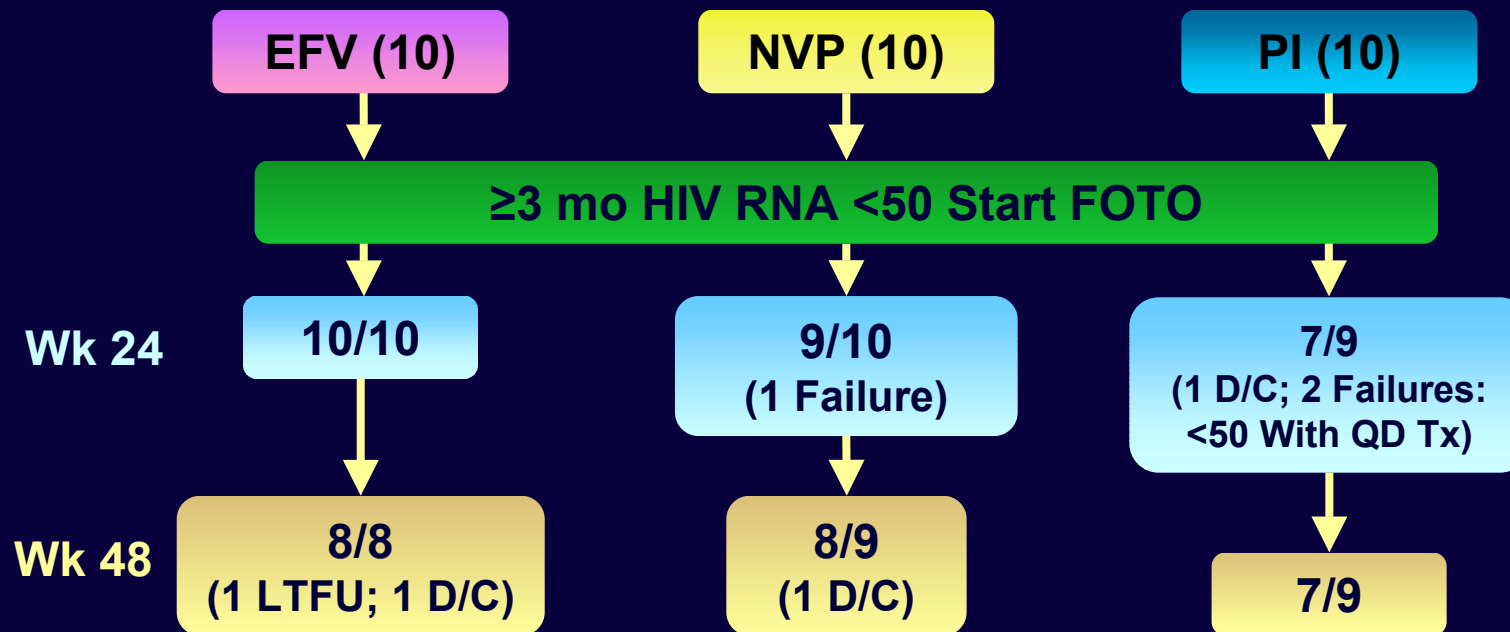
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# Methamphetamine Use and Risk of Transmission of Drug Resistance

- 189 patients from SF General Hospital's SCOPE study with detectable viremia and confirmed genotypic drug resistance
  - 77% MSM, 9% MSW, 14% women
  - 38% with triple-class resistance
  - 29% Reported unprotected anal or vaginal sex with HIV negative/unknown partner in previous 4 months
  - Predictors of high risk sex:
    - **Methamphetamine use: OR = 4.2 (1.6 - 11.3)**
    - **Viagra use: OR = 3.7 (1.7 - 8.3)**
    - **Younger age: OR = 3.2 per 10-year decrease (1.8 – 5.7)**
    - **Depression and homelessness were marginally significant**

# Five Days On, Two Days Off (FOTO) Results at 48 Wk: <50 c/mL

Open-Label, Single-Arm Prospective Pilot Study



- **CD4 Count:** No significant differences
- **Resistance:** None observed
- **Safety/Tolerability:** Decrease in LDL cholesterol, 116 -> 103
- **Adherence:** 15/378 visits, pts reported taking less doses than prescribed; 2/378 reported taking more doses than prescribed
- **Preference:** Mean Likert score regarding preferred therapy was 9.7/10
- **Costs:** Reduced by 28%

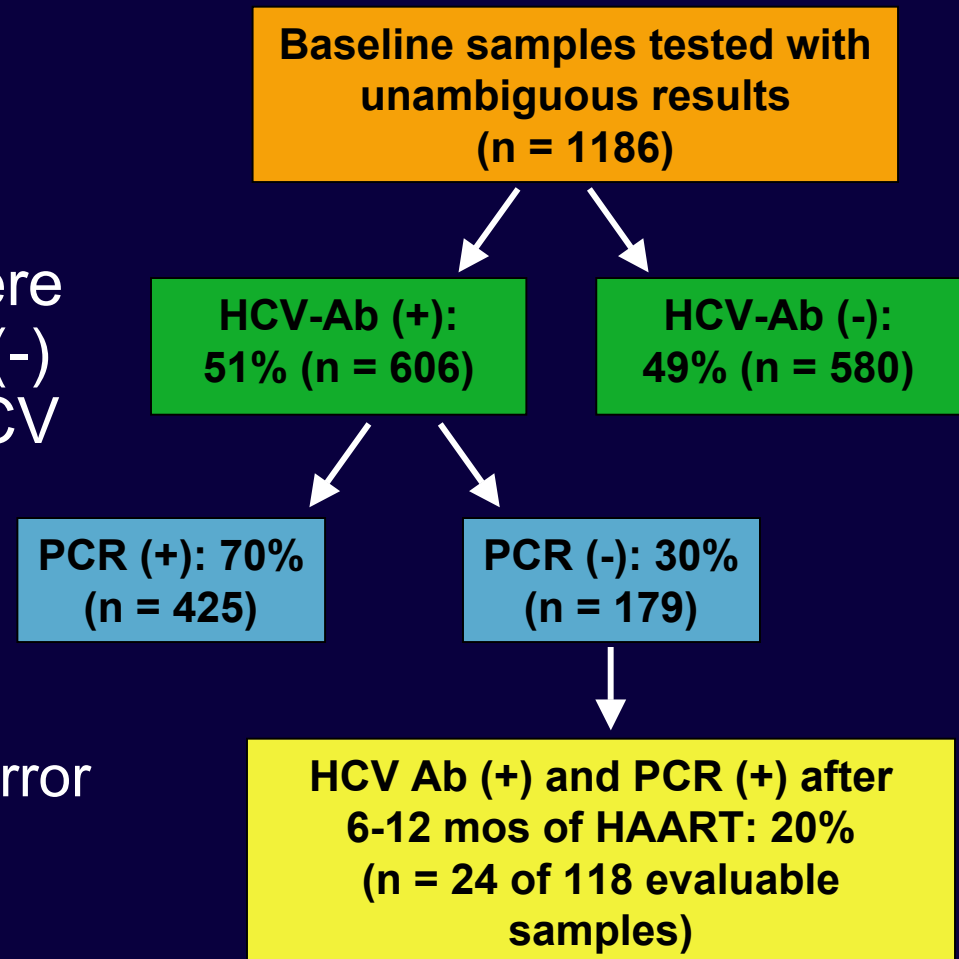
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# Hepatitis Co-Infections

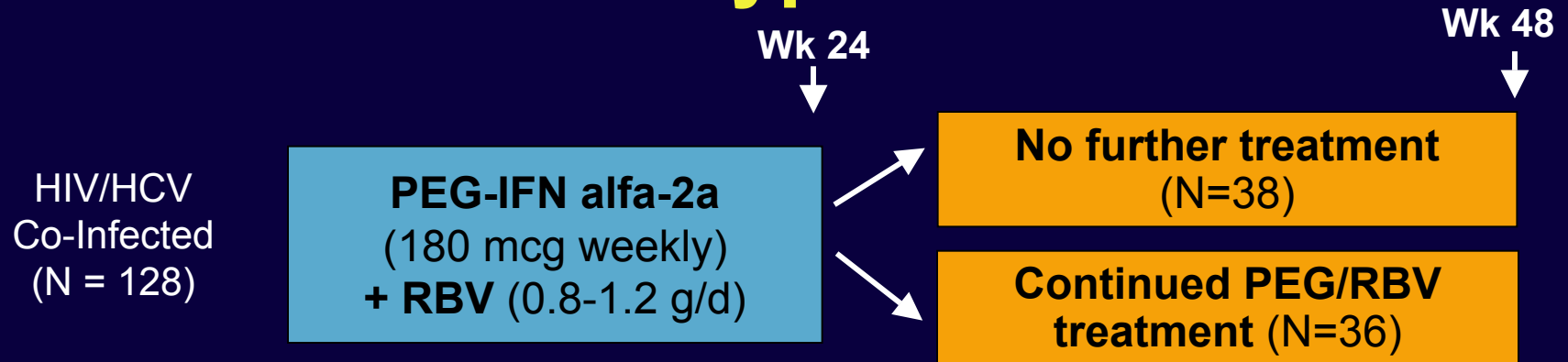
Brad Hare, M.D.

# Increase in HCV RNA Detection After HAART Initiation

- Analysis of HCV/HIV-coinfected pts in the HOMER cohort
- 20% of patients who were HCV-Ab (+)/HCV RNA (-) pre-HAART became HCV RNA (+) after HAART
- Possible explanations
  - Blips
  - Laboratory variation, error
  - Immune restoration



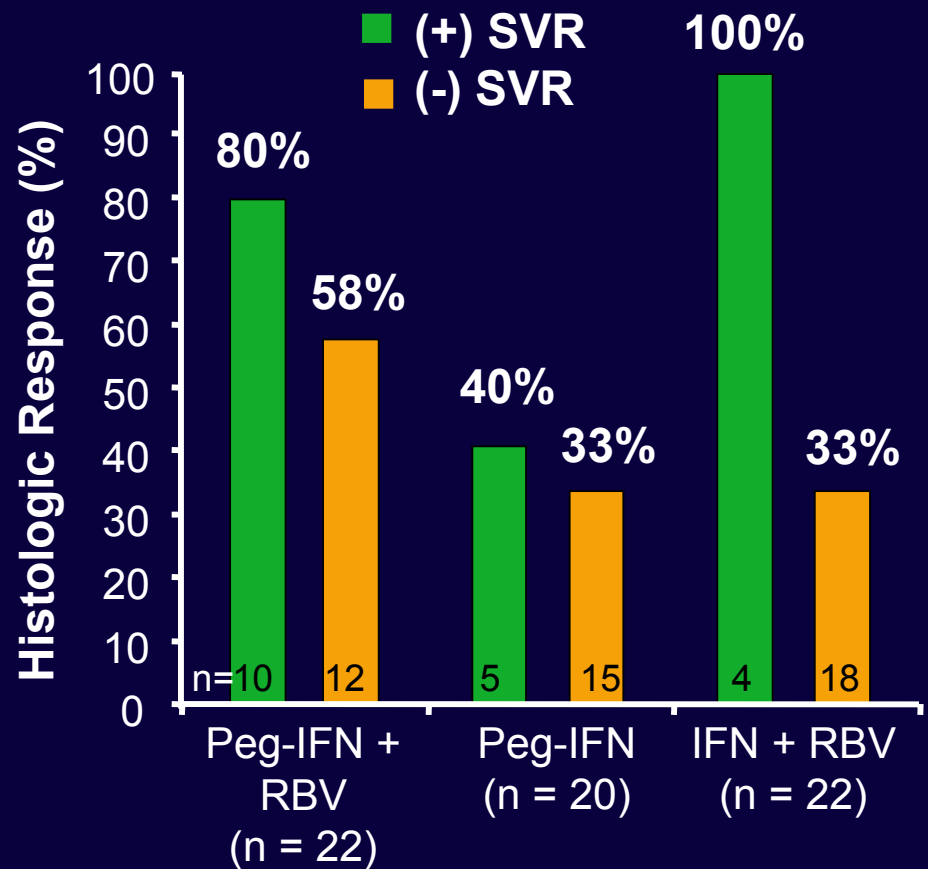
# 48 Weeks of HCV Therapy Superior to 24 Weeks in Genotype 2/3 Co-Infection



- 74 Treatment responders with negative HCV RNA at week 24 randomized to continue or stop treatment
  - Per protocol analysis:
    - 24-week treatment, SVR = 60%
    - 48-week treatment, SVR = 90%

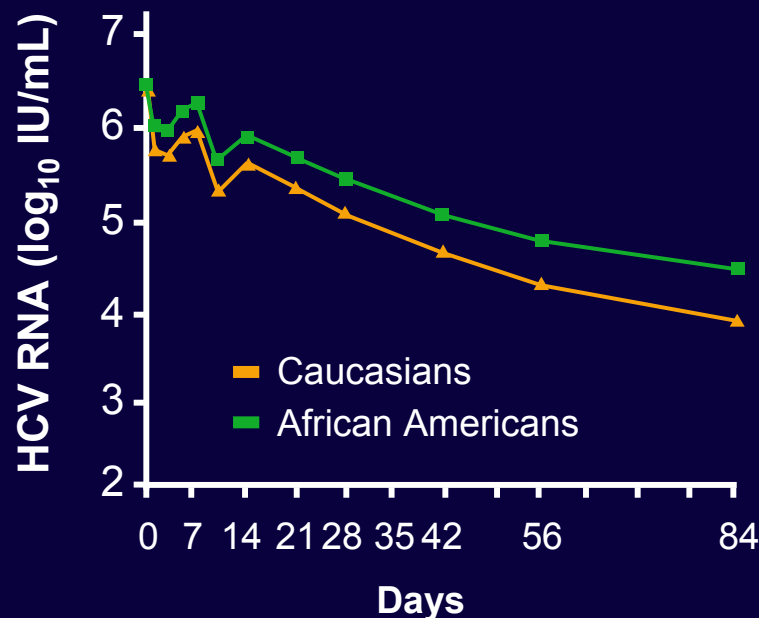
# Histologic Benefits of HCV Treatment in Virologic Nonresponders

- Histologic response possible even in patients who do not achieve SVR in APRICOT study
- Prospective study of treatment for HCV/HIV co-infected nonresponders ongoing (SLAM-C)



# Differences in HCV Viral Kinetics in HIV-Coinfected Patients

- Steeper decline in HCV viral kinetics while on peg-IFN + ribavirin seen in Caucasians vs African Americans and in Genotype 2 vs 1
  - Viral kinetics as early as 3 days predicted SVR
    - 100% PPV for no SVR if HCV RNA >5 log on both Day-3 and Day-28

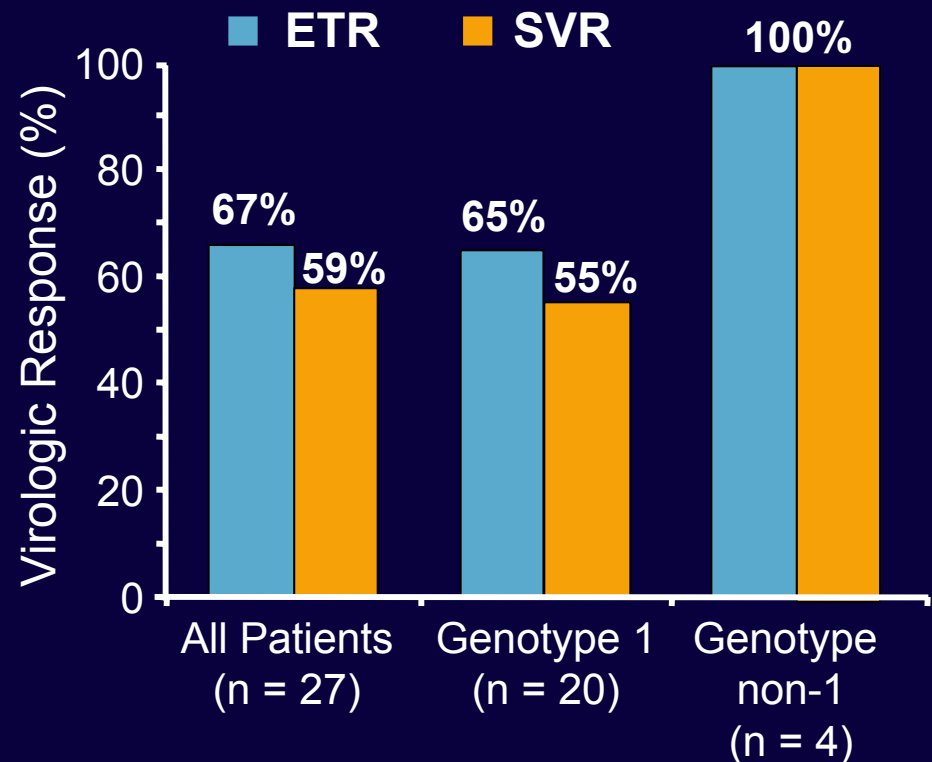


	Cauc	AA	P value
n	10	12	
1 <sup>st</sup> Phase	-0.96	-0.51	< .01
2 <sup>nd</sup> Slope	-0.52	-0.24	< .01
HCV	6.3	6.3	NS
ALT	90	76	NS
CD4	647	553	NS
HIV	2.4	2.1	NS
ETR	8/10	4/12	
SVR	4/10	1/12	

# Response to Treatment During Acute HCV in HIV-Coinfected Patients

- 50 Patients with HCV Ab seroconversion
  - 12/50 (24%) spontaneously cleared within 12 weeks
    - Associated with low HCV RNA and higher baseline CD4 count
  - 11/50 (22%) did not clear, but declined therapy
  - 27/50 (54%) treated with 24 wks Peg-IFN alfa 2b + RBV
- 59% SVR overall
  - 55% Genotype 1
  - 100% Genotype non-1
  - Associated with higher CD4 count and higher peak ALT

Peg-IFN (1.5 µg/kg/wk) + RBV (800-1200 mg/day) for 24 weeks



# Progression to HCC in HCV/HIV-Coinfected Patients

- HCC Cases retrospectively reviewed from 1992-2004 in 15 US and Canadian centers

	HIV/HCV (n = 41)	HCV (n = 119)	P Value
Mean duration of HCV infection at time of HCC diagnosis, yrs	26.4 (n = 30)	35.2 (n = 62)	< .001
Mean age, yrs	52.4	61.1	< .001
Median AFP level, ng/mL	1274	192	.002
Excessive alcohol use, %	48.7 (n = 39)	71.0 (n = 100)	.005
Receive HCC therapy, %	56	36	.025