Dr Curtis Cooper

The Ottawa Hospital, Canada

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COMPETING INTEREST OF FINANCIAL VALUE ≥ £1,000:	
Speaker Name	**Statement**
Curtis Cooper	TBC
Date	**22 September 2012**

HIV-HCV Co-Infection: When to Treat and When to Wait

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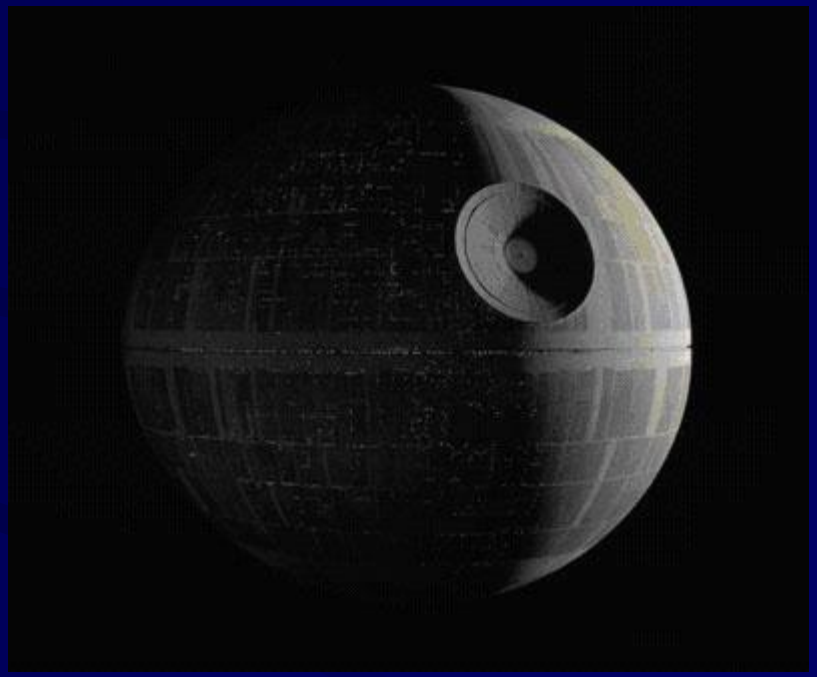
Division of Infectious Diseases

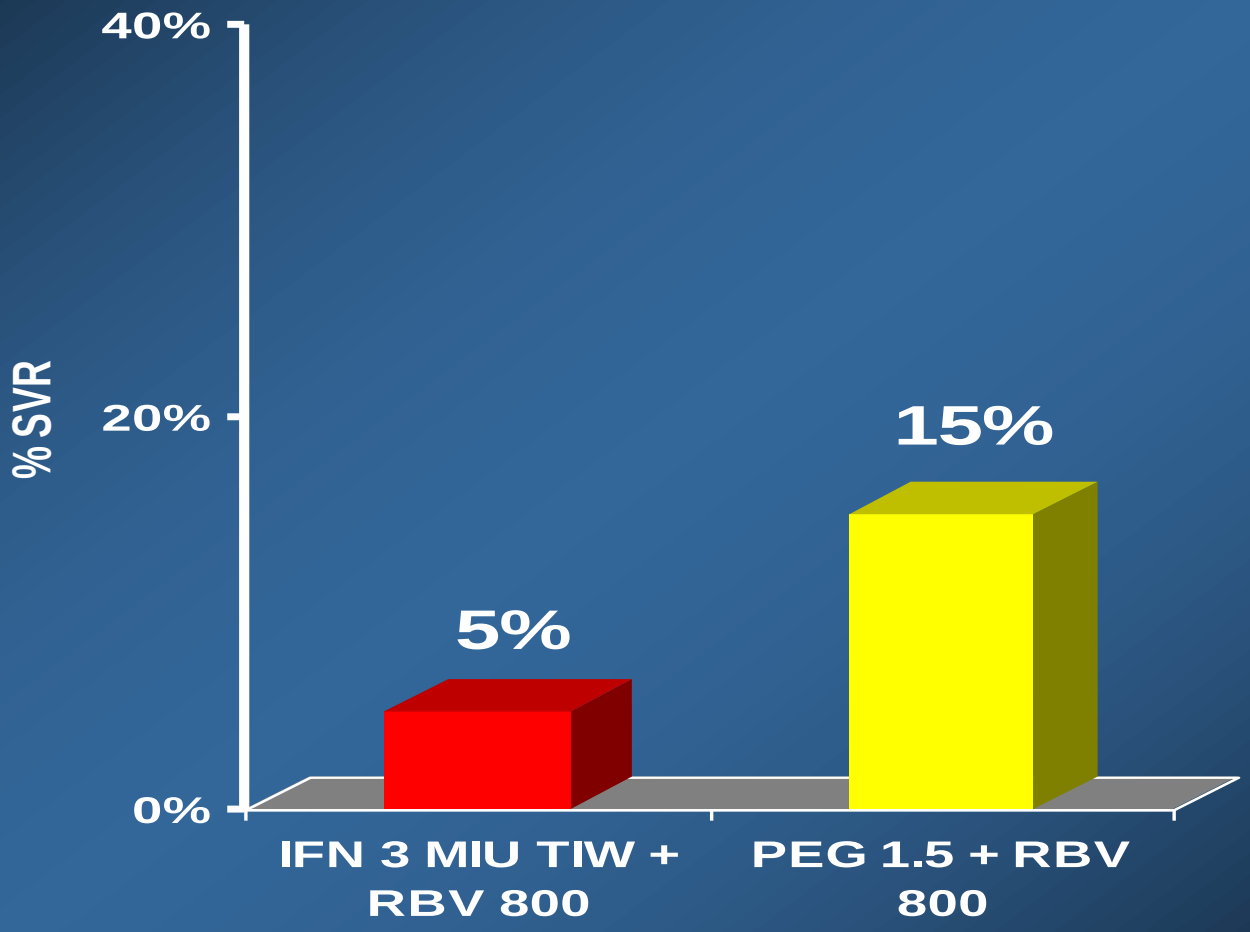
October 3, 2012

Disclosures

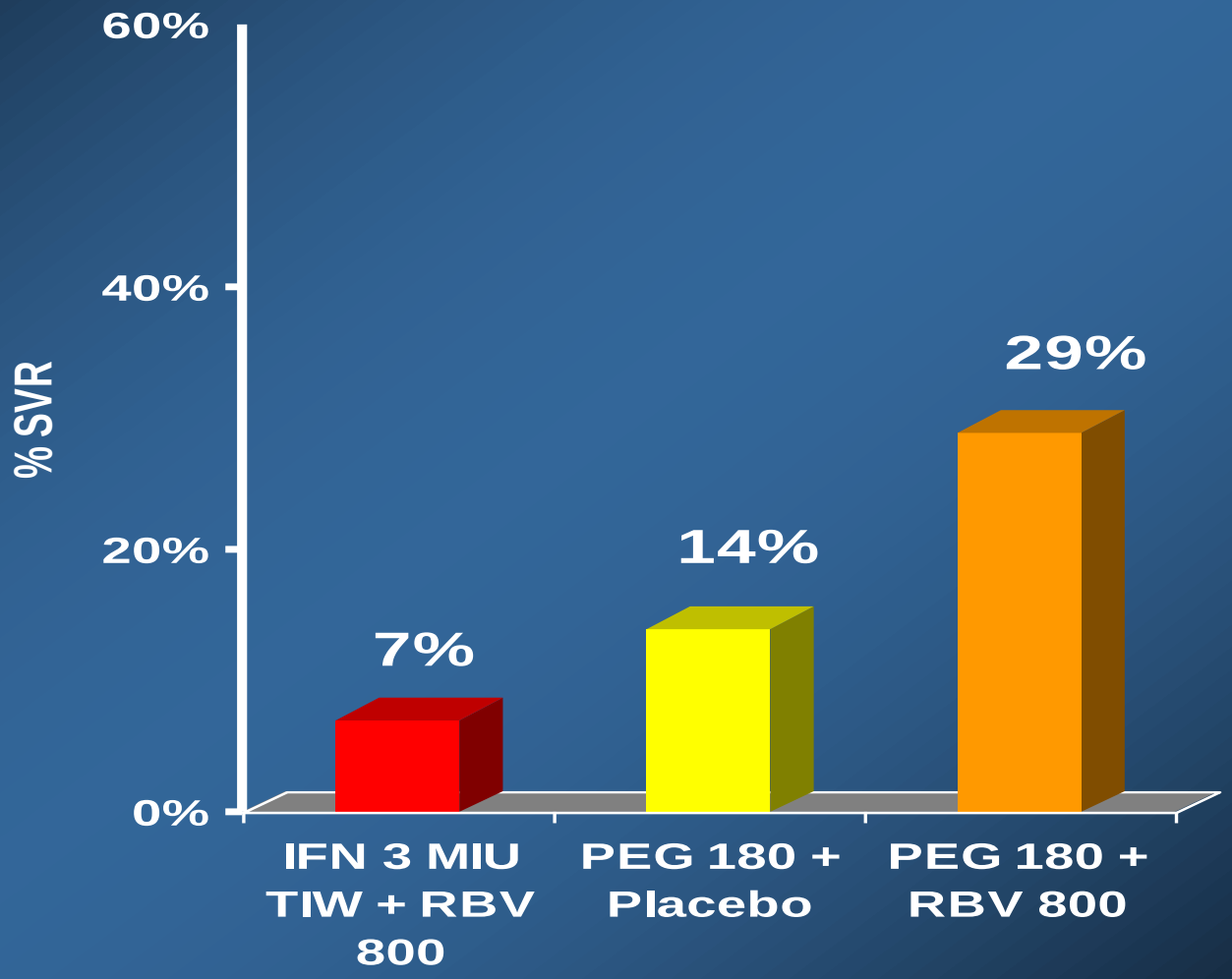
- Industry
  - Investigator: Merck, Vertex, Roche, BI, Tibotec, GS, BMS
  - Consultant /Advisor: Merck, Vertex, Roche, BI
  - Speaker: Merck, Roche, BI, ViiV, BMS
- Government
  - OHTN
  - CIHR
  - PCIRN
  - Health Canada



RIBAVIC:
ITT SVR Genotype 1

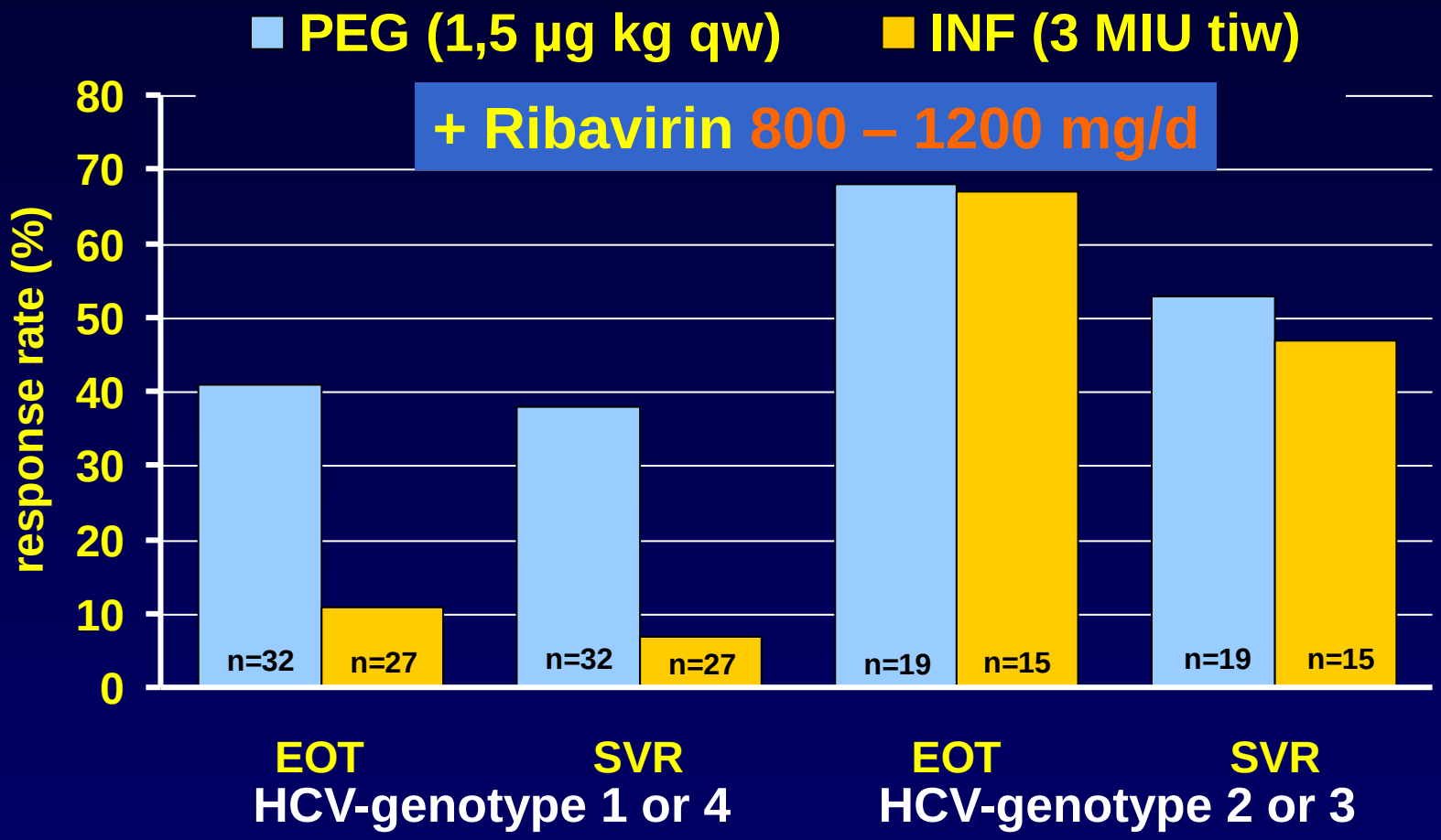


APRICOT: Genotype 1 PROTOCOL SVR



Hospital Clínic Barcelona

Peginterferon α-2b vs. Interferon α-2b



EOT: p=0.033

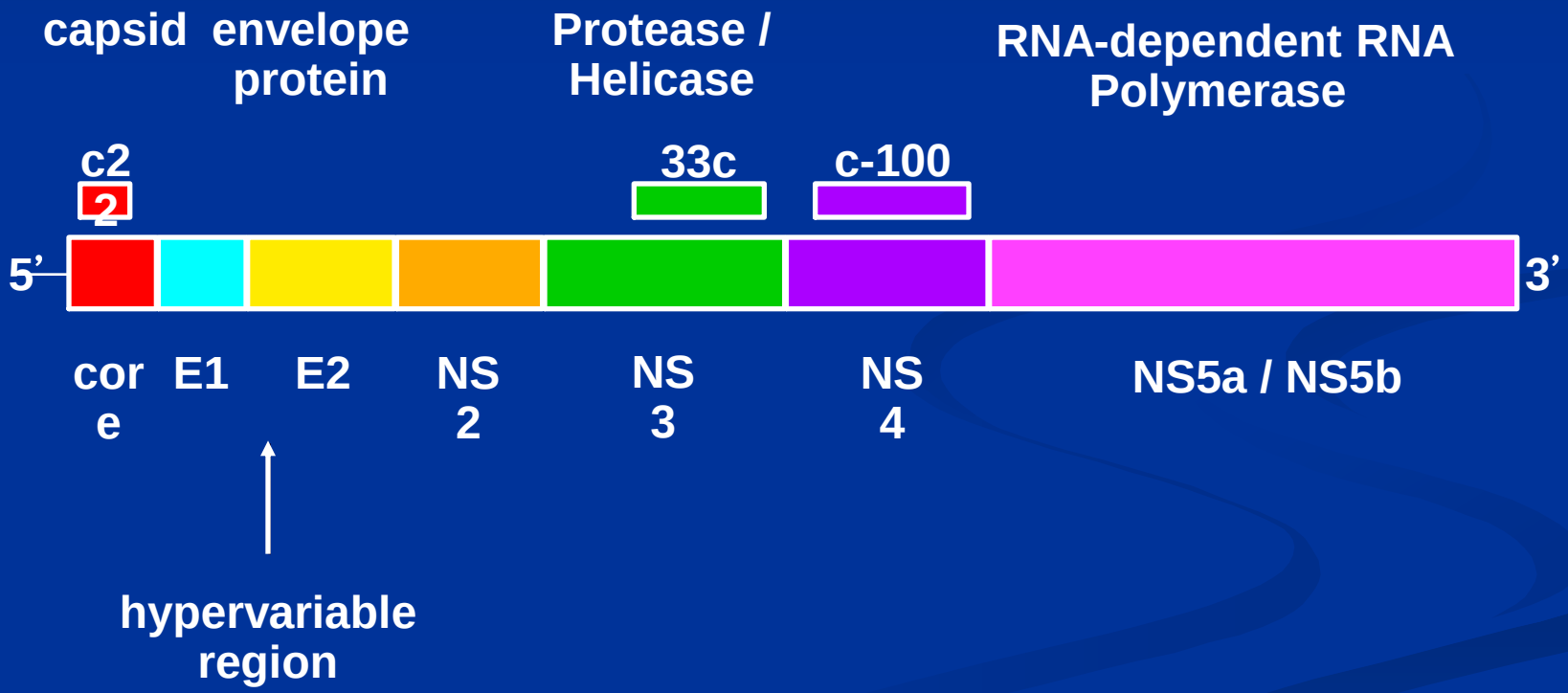
SVR: p=0.007

EOT: p=0.914

SVR: p=0.730

Laguno M et al. AIDS 2004, 18: F27-F36

Can we hope for more?



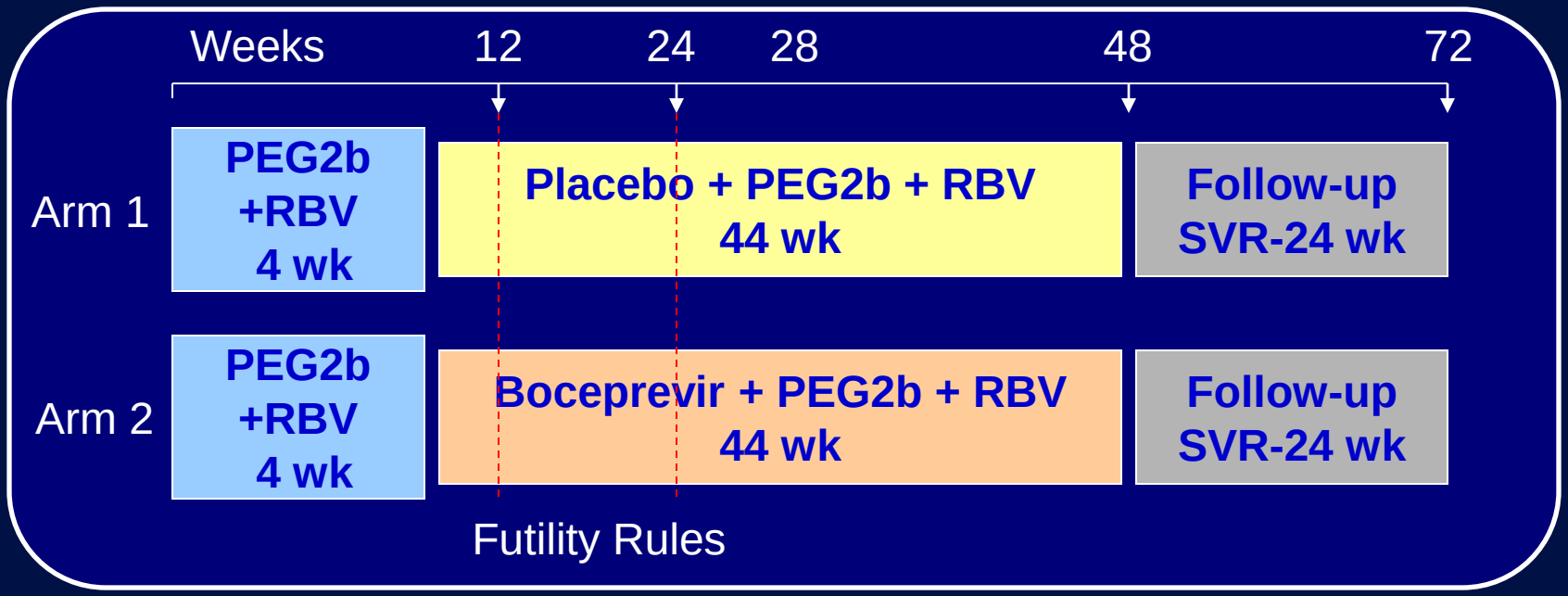
Boceprevir Plus Peginterferon/Ribavirin for the Treatment of HCV/HIV Co-Infected Patients

M Sulkowski[1], S Pol[2], C Cooper[3], H Fainboim[4], J Slim[5], A Rivero[6], M Laguno[7], S Thompson[8], J Wahl[8], W Greaves[8]

[1]John Hopkins University School of Medicine, Baltimore, MD; [2]Hopital Cochin, Paris, France; [3]The Ottawa Hospital, Ottawa, ON, Canada; [4]F. J. Muñiz Hospital De Infecciosas, Buenos Aires, Argentina; [5]Saint Michael's Medical Center, Newark, NJ; [6]Hospital Universitario Reina Sofia, Córdoba, Spain, [7]Hospital Clinic i Provincial Barcelona, Spain; [8]Merck Sharp & Dohme, Whitehouse Station, NJ.

Oral Abstract Q-175
19th Conference on Retroviruses and Opportunistic Infections (CROI)
Seattle, WA
March 6, 2012

Study Design



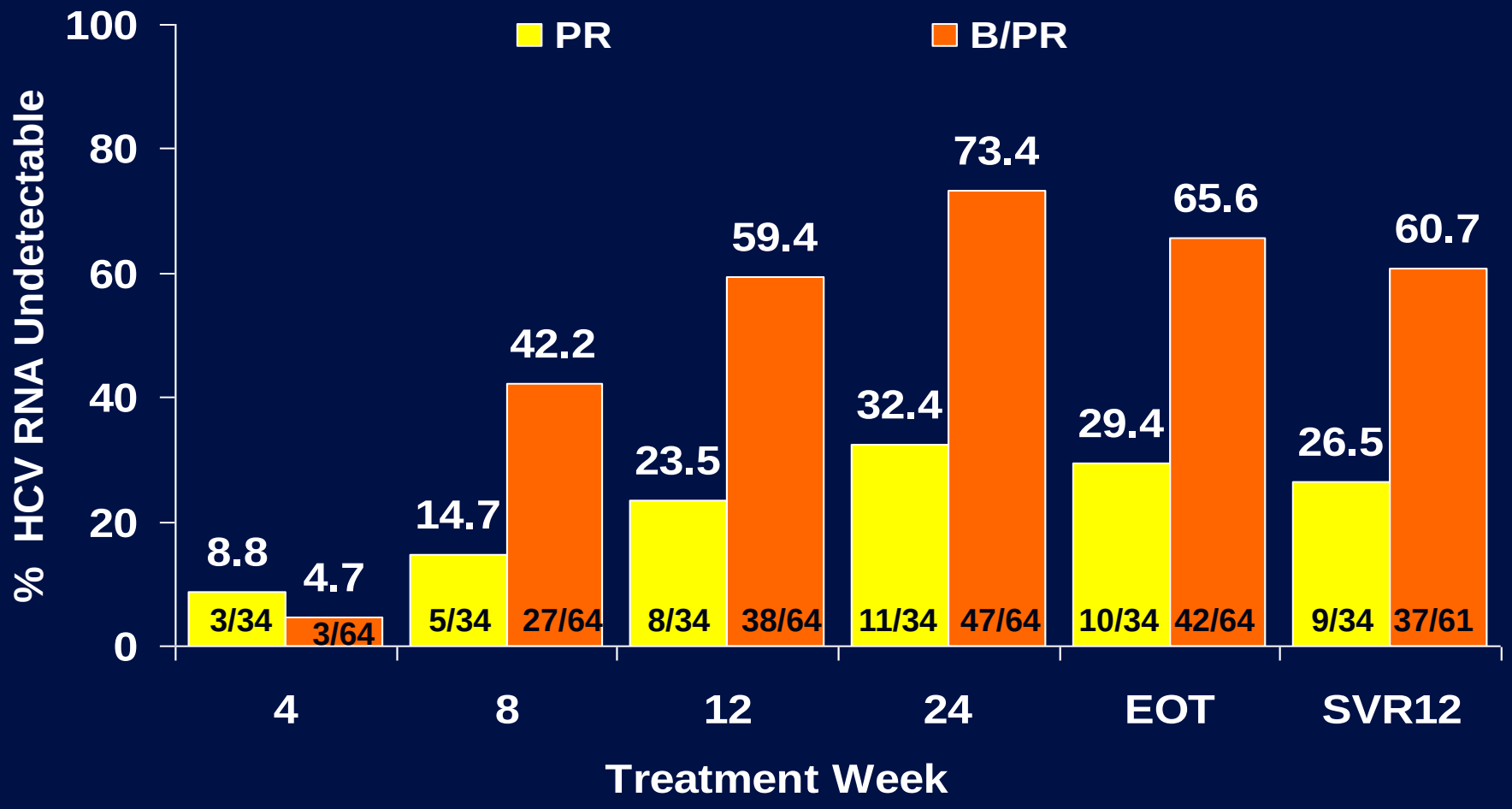
- Two-arm study, double-blinded for BOC, open-label for PEG2b/RBV
  - 2:1 randomization (experimental: control)
  - Boceprevir dose 800 mg TID
- 4-week lead-in with PEG2b/RBV for all patients
  - PEG-2b 1.5 µg/kg QW; RBV 600-1400 mg/day divided BID
- Control arm patients with HCV-RNA ≥ LLOQ at TW 24 were offered open-label PEG2b/RBV+BOC via a crossover arm

Demographics and Baseline Characteristics

	PR (N=34)	B/PR (N=64)
Age (years), mean (SD)	45 (9.8)	43 (8.3)
Male, n (%)	22 (65)	46 (72)
Race, n (%)		
White	28 (82)	52 (81)
Non-white	6 (18)	12 (19)
Body mass index, mean (SD)	26 (4)	25 (4)
Cirrhosis, n (%)	1 (3)	4 (6)
HCV genotype subtype, n (%)*		
1a	22 (65)	42 (66)
1b	10 (29)	15 (23)
HCV RNA level >800,000 IU/mL, n (%)	30 (88)	56 (88)
HIV RNA <50 copies/mL, n (%)	33 (97)	62 (97)
CD4 count (cells/mm^3), median (range)	586 (187-1258)	577 (230-1539)

*Subtyping not reported for 9 patients with Genotype 1.

Virologic Response Over Time†



† Three patients undetectable at FW4 have not yet reached FW12 and were not included in SVR12 analysis.

Summary of Safety

	PR (N=34)	B/PR (N=64)
Any AE	34 (100)	63 (98)
Serious AEs	7 (21)	11 (17)
Death	0	0
Treatment-related treatment-emergent AEs	34 (100)	61 (95)
Study discontinuation due to an AE	3 (9)	13 (20)
Any drug modification due to an AE	8 (24)	18 (28)

All data shown as number (%) of patients.

Most Common Adverse Events With a Difference of ≥10% Between Groups

	PR (N=34)	B/PR (N=64)
Anemia	26%	41%
Pyrexia	21%	36%
Asthenia	24%	34%
Decreased appetite	18%	34%
Diarrhea	18%	28%
Dysgeusia	15%	28%
Vomiting	15%	28%
Flu-like illness	38%	25%
Neutropenia	6%	19%

Interim Analysis Summary

- HCV-HIV co-infected HCV treatment naïve patients had high rates of HCV response on BOC
  - SVR-12: 61% of patients on B/PR vs. 27% of patients on PR

- Preliminary safety data of B/PR in co-infected patients showed a profile consistent with that observed in mono-infected patients

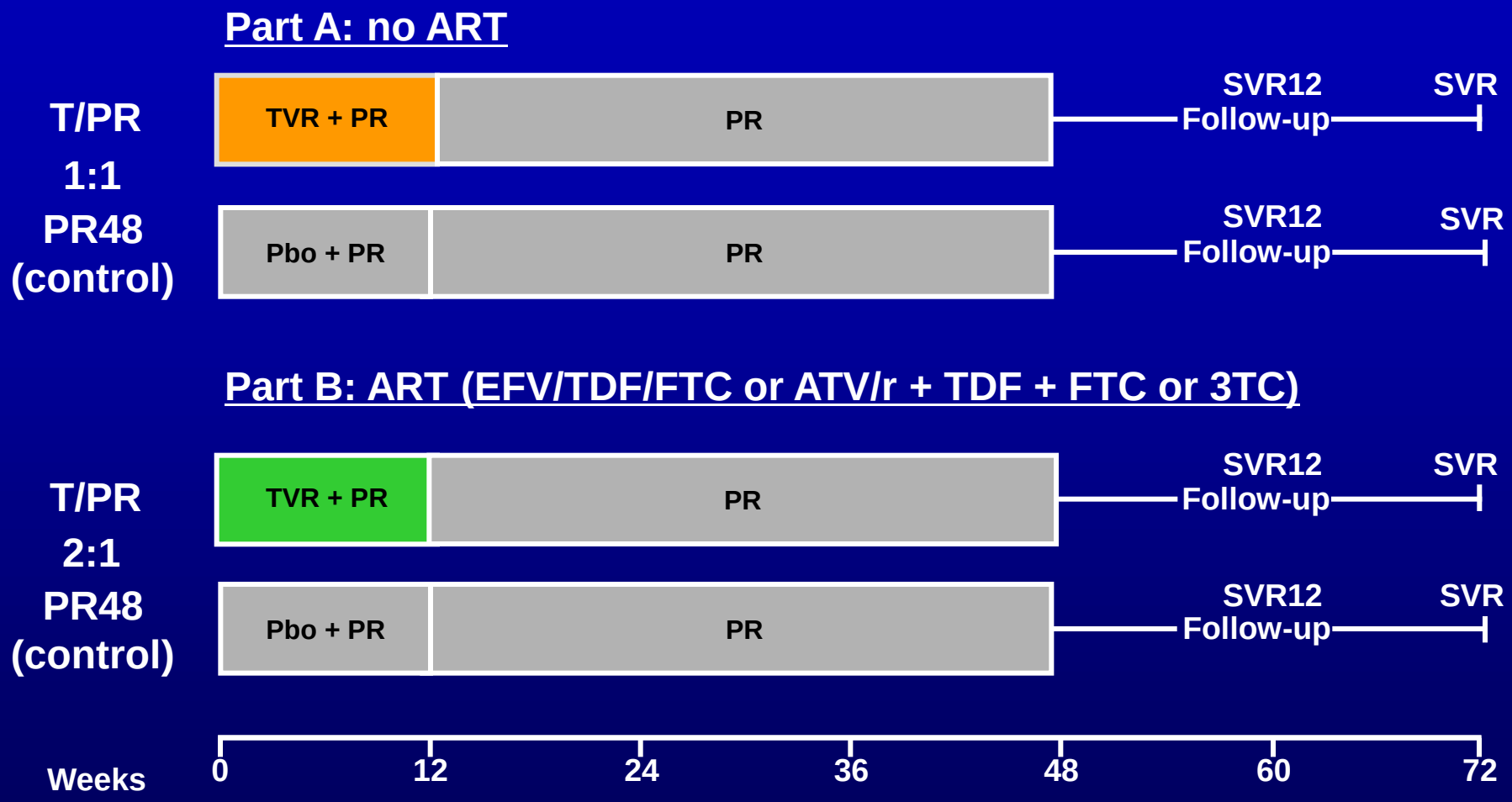
Telaprevir in Combination with Peginterferon Alfa-2a/Ribavirin in HCV/HIV Co-infected Patients: SVR12 Interim Analysis

Douglas T. Dieterich[1], Vincent Soriano[2], Kenneth E. Sherman[3], Pierre-Marie Girard[4], Jürgen K. Rockstroh[5], Joshua Henshaw[6], Raymond Rubin[6], Mohammad Bsharat[6], Nathalie Adda[6], Mark S. Sulkowski[7]

On behalf of the Study 110 Team

[1]Mount Sinai School of Medicine, New York, NY, United States, [2]Hospital Carlos III, Madrid, Spain, [3]University of Cincinnati College of Medicine, Cincinnati, OH, United States, [4]Hôpital St Antoine, Paris, France, [5]University of Bonn, Bonn, Germany, [6]Vertex Pharmaceuticals Incorporated, Cambridge, MA, United States, and [7]Johns Hopkins University School of Medicine, Baltimore, MD, United States.

Study 110 Design: Randomized, Double-blind, Placebo-controlled Trial



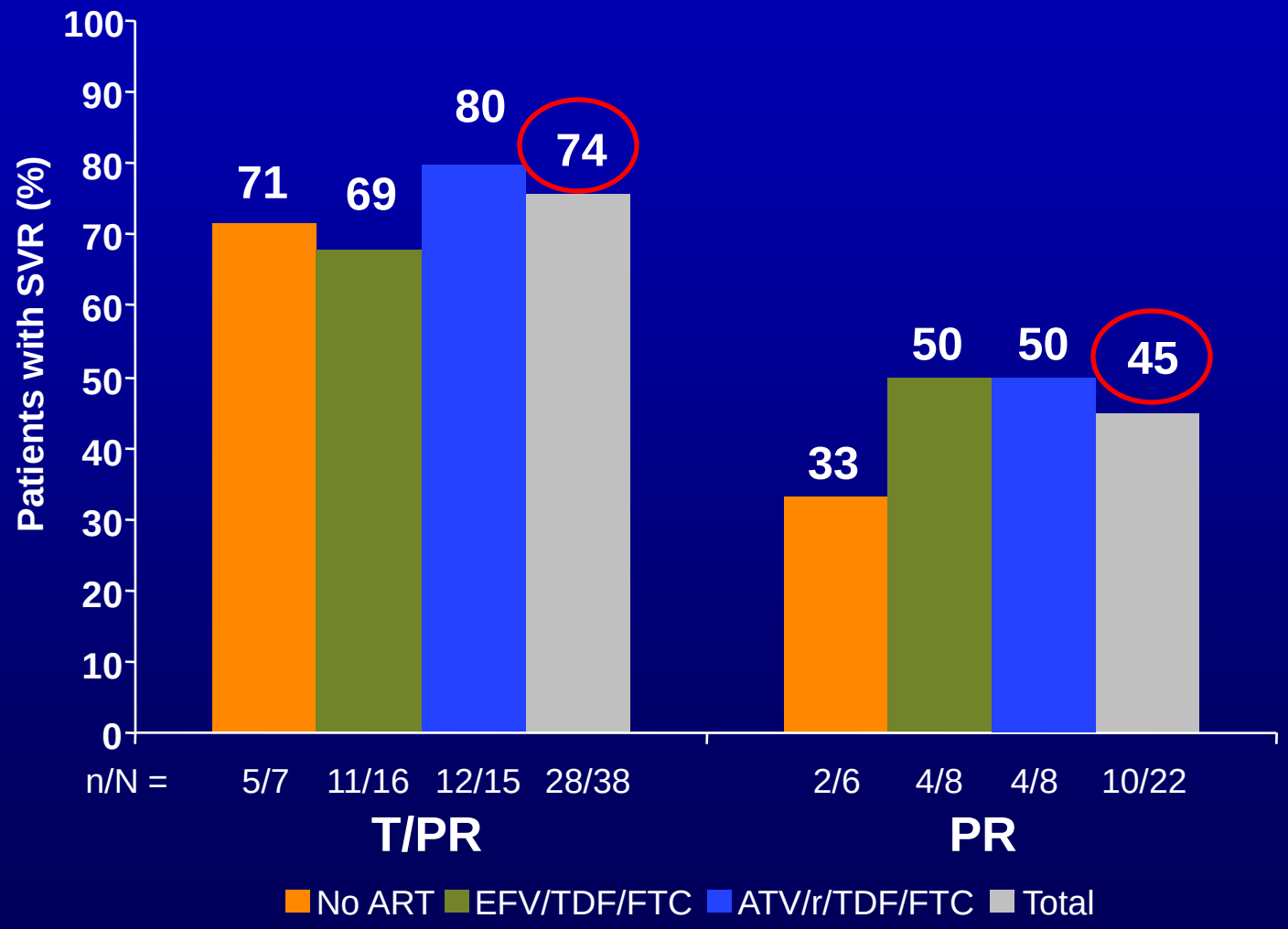
(EFV)=efavirenz; (TDF)=tenofovir; (FTC)=emtricitabine; (ATV/r)=ritonavir-boosted atazanavir; (3TC)=lamivudine;
(T) TVR=telaprevir 750 mg q8h or 1125 mg q8h (with EFV); Pbo=Placebo; (P) Peg-IFN=pegylated interferon alfa-2a (40 kD) 180 µg/wk;
(R) RBV=ribavirin 800 mg/day or weight-based (1000 mg/day if weight <75 kg, 1200 mg/day for if weight ≥75 kg; France, Germany, n=5 patients)
Roche COBAS® TaqMan® HCV test v2.0, LLOQ of 25 IU/mL, LOD of <10 IU/mL

Patient Demographics and Baseline Characteristics

	Part A		Part B			
	No ART		EFV/TDF/FTC		ATV/r + TDF + FTC or 3TC	
	T/PR N=7	PR N=6	T/PR N=16	PR N=8	T/PR N=15	PR N=8
Gender, n (%): Male	6 (86)	4 (67)	16 (100)	7 (88)	13 (87)	7 (88)
Caucasian†, n(%) Black/African American, n(%)	2 (29) 4 (57)	3 (50) 3 (50)	12 (75) 3 (19)	5 (62) 3 (38)	13 (87) 2 (13)	7 (88) 1 (12)
Ethnicity†: Hispanic, n (%)	3 (43)	2 (33)	5 (31)	1 (12)	3 (21)	3 (38)
Age, median years (range)	39 (34-50)	48 (42-65)	48 (31-57)	47 (31-53)	52 (36-59)	39 (26-53)
BMI, median kg/m^2 (range)	29 (22-37)	31 (26-37)	24 (21-32)	23 (19-28)	24 (23-33)	25 (22-30)
HCV RNA ≥ 800,000 IU/mL**, n (%)	7 (100)	5 (83)	13 (81)	7 (88)	12 (80)	7 (88)
HCV Genotype Subtype*, n (%) 1a 1b Other	 3 (43) 4 (57) 0 (0)	 3 (50) 2 (33) 1 (17)	 12 (75) 4 (25) 0 (0)	 6 (75) 1 (12) 1 (12)	 12 (80) 3 (20) 0 (0)	 5 (62) 3 (38) 0 (0)
Bridging Fibrosis, n(%) Cirrhosis, n (%)	1 (14) 0 (0)	0 (0) 0 (0)	2 (12) 2 (12)	1 (12) 0 (0)	0 (0) 0 (0)	1 (12) 0 (0)
HIV RNA median copies/mL (range)	1495 (193-53,450)	267 (25-21,950)	25 (25-25)	25 (25-25)	25 (25-25)	25 (25-25)
CD4+ median cells/mm^3 (range)	604 (496-759)	672 (518-1189)	533 (299-984)	514 (323-1034)	514 (254-874)	535 (302-772)

†Race and ethnicity were self-reported *5'NC InnoLipa line probe assay
**Roche COBAS® TaqMan® HCV test v2.0, LLOQ of 25 IU/mL and LLOD of 10-15 IU/mL

SVR Rates 12 Weeks Post-Treatment (SVR12*)



*Patient was defined as SVR12 if HCV RNA was < LLOQ in the visit window

HCV Treatment Outcome

	Total	
Virologic Outcome n/N (%)	T/PR	PR
SVR	28/38 (74)	10/22 (45)
Patients without SVR	10/38 (26)	12/22 (55)
On-treatment virologic failure	3/38 (8)	8/22 (36)
Not suppressed at EOT	5/37* (14)	9/22 (41)
Patients with relapse	1/32 § (3)	2/13 (15)
Other	6/38 (16)	2/22 (3)

Relapse was defined as HCV RNA ≥LLOQ relative to the actual end-of-treatment (EOT) window. Number of patients with values <LLOQ at EOT visit window, or those whose next value observed after the actual EOT window is <LLOQ was used as denominator for relapse calculations.
*N=37, 1 patient did not have EOT HCV RNA
§ T/PR patient from Part A

Events of Special Interest: Overall Treatment Phase

	T/PR N=38 n (%)	PR N=22 n/N (%)
Severe rash	0 (0)	0 (0)
Mild and moderate rash	13 (34)	5 (23)
Anemia	7 (18)	4 (18)
Grade 3 hemoglobin shifts* (7.0-8.9 g/dL)	11 (29)	5 (23)
Use of erythropoietin stimulating agent	3 (8)	1 (5)
Blood transfusions	4 (11)	1 (5)

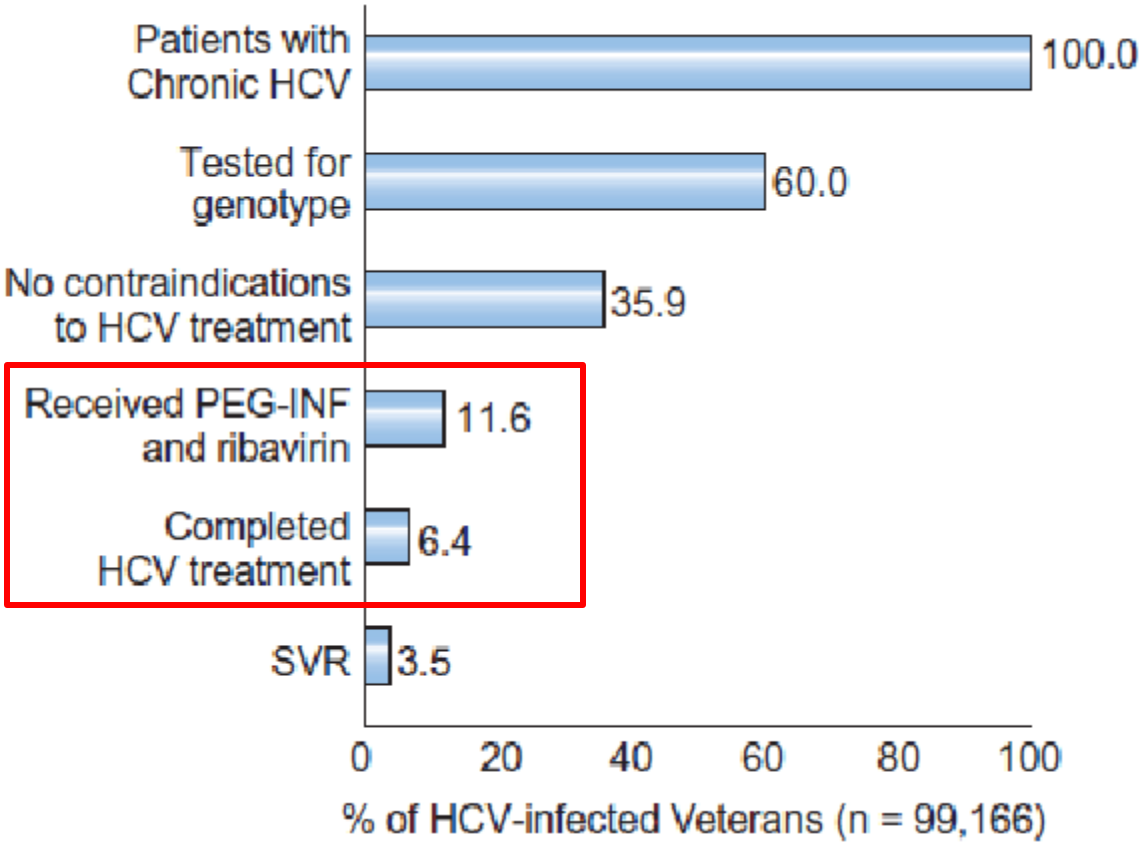
- CD4 counts declined in both T/PR and PR groups; CD4% remained unchanged

*DAIDS HIV-negative scale

Conclusions

- Higher SVR12 rates were observed in chronic genotype 1 HCV/HIV co-infected patients treated with telaprevir combination treatment
  - T/PR 74%
  - PR 45%
- In patients treated with telaprevir combination treatment, overall safety and tolerability profile was comparable to that previously observed in chronic genotype 1 HCV mono-infected patients

Low Rates of Treatment Initiation and Completion of HCV Therapy in US VA System



- Among individuals not receiving HCV therapy HIV coinfection cited as the reason for 6.3%

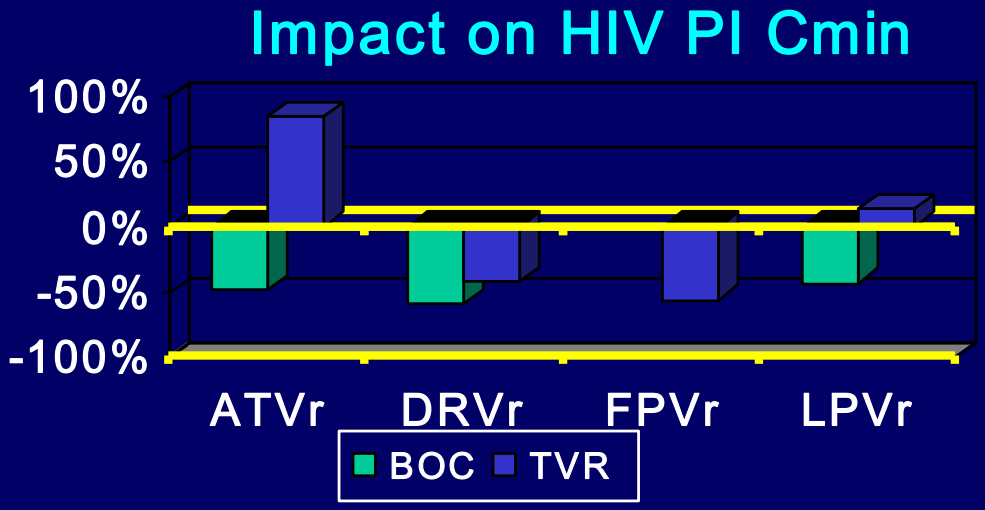
Kramer JR, et al. J Hepatol. 2012;56:320-325.

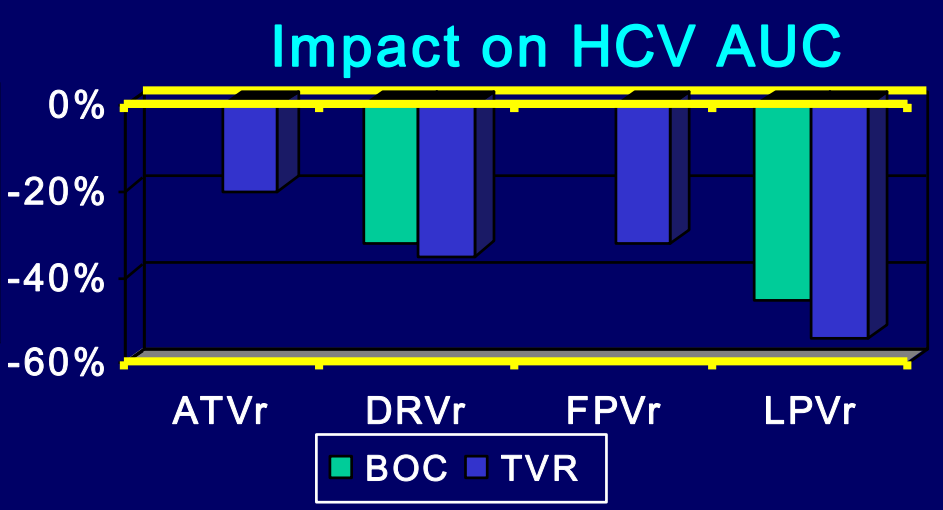
Issues with HCV Therapy Influencing Treatment Decisions in HIV

- Polypharmacy
- Side Effect Profile
- Interferon-based
- DDI

PK Issues and Clinical Consequences

Interactions Between HCV and HIV PIs
Summary of Healthy Volunteer Studies



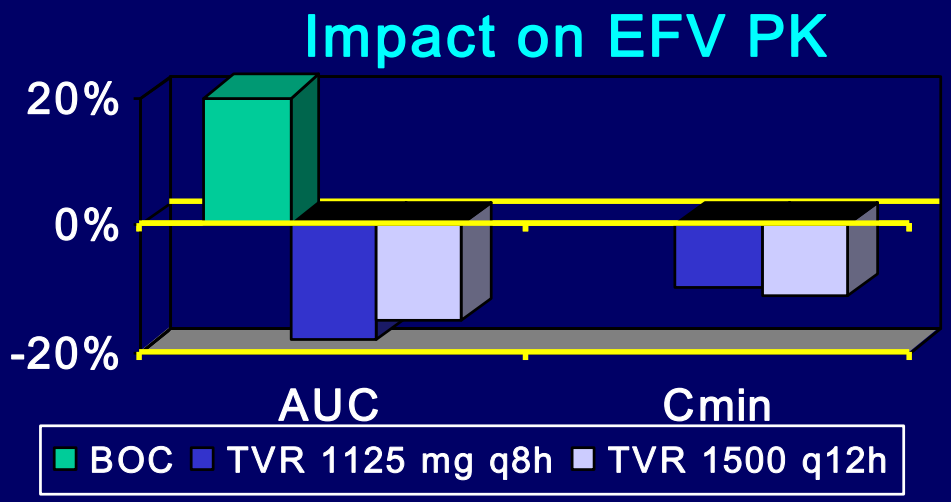


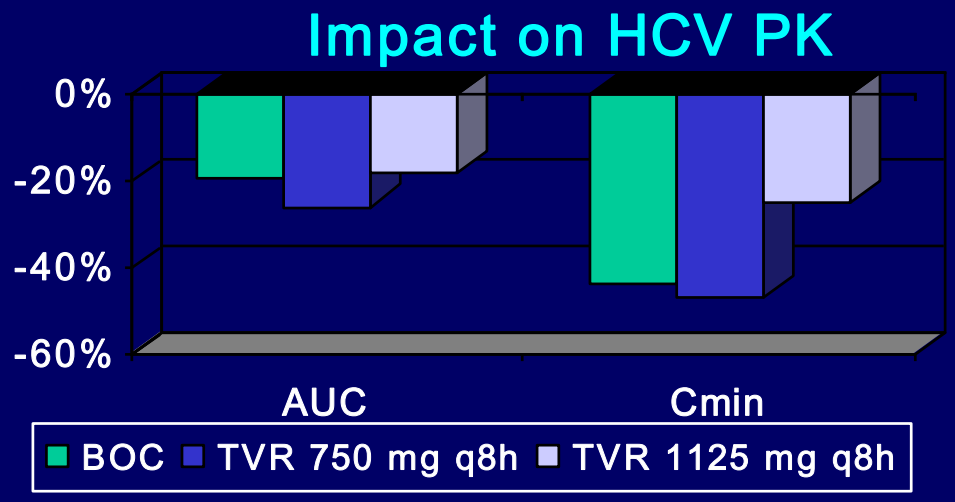
- Dosing recommendations:
  - Boceprevir: coadministration with ritonavir-boosted PIs is not recommended
  - Telaprevir: do not administer with DRVr, FPVr or LPVr; ongoing evaluation with ATVr

[van Heeswijk et al. CROI 2011, #119. Hulskotte et al. CROI 2012, #771LB]

Interactions Between HCV DAA & EFV

Summary of Healthy Volunteer Studies



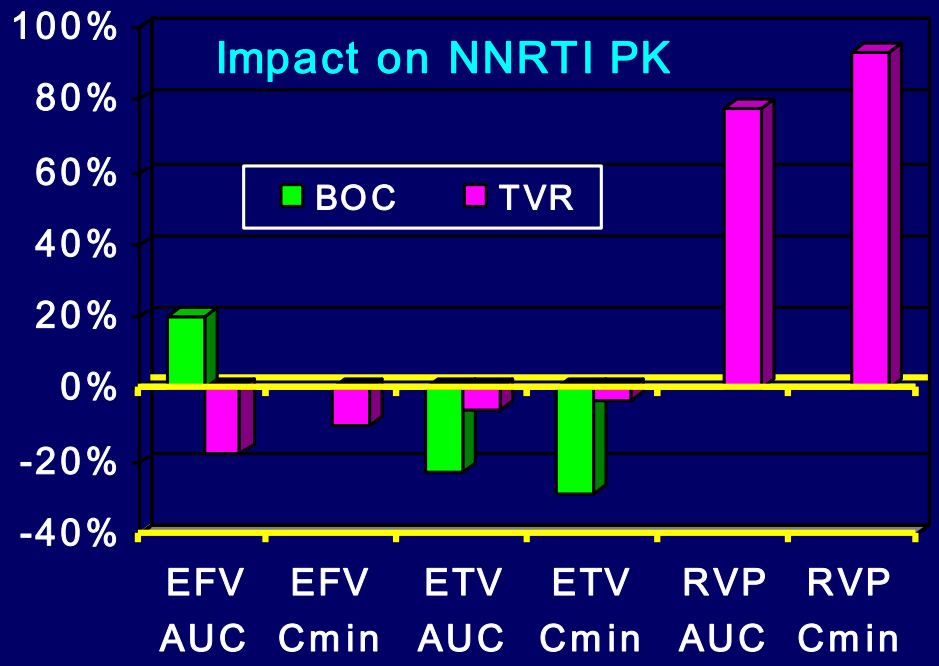


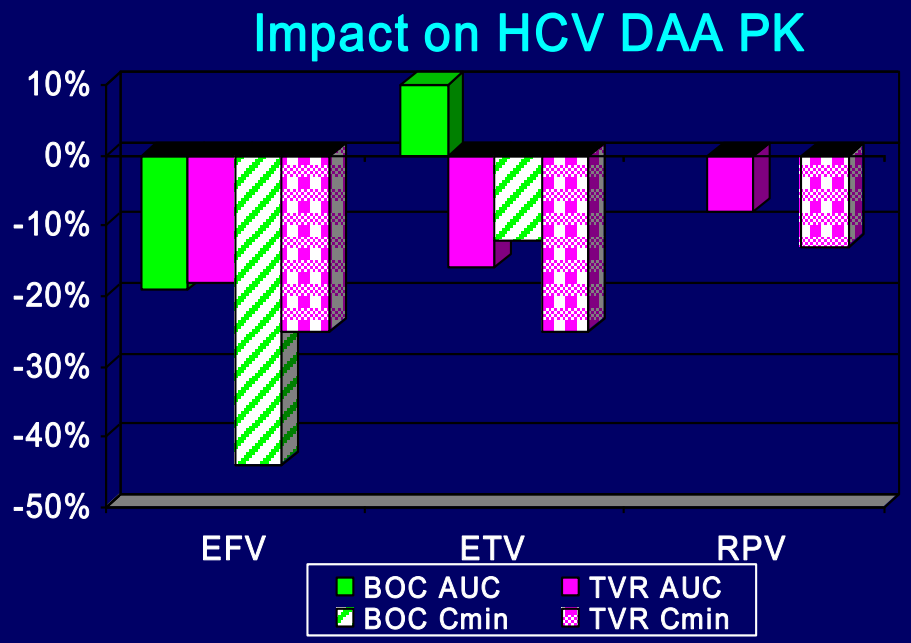
- Dosing recommendations:
  - **Boceprevir**: coadministration EFV is not recommended
  - **Telaprevir**: use 1125 mg TID with EFV

[van Heeswijk et al. CROI 2011, #119. Garg et al. 6th HCV PK Wksp 2011, #PK_13. Victrelis Monograph 2011]

Interactions Between HCV DAA & NNRTIs

Summary of Healthy Volunteer Studies





- Dosing recommendations:
  - **Efavirenz:** avoid with BOC, use 1125 mg TID telaprevir
  - **Etravirine**: ? with BOC, OK with telaprevir
  - **Rilpivirine**: OK with telaprevir

[van Heeswijk et al. CROI 2011, #119. Garg et al. 6th HCV PK Wksp 2011, #PK_13. Victrelis Monograph 2011. Hammond et al. IWCPHT 2012 O-15. Kakuda et al. IWCPHT 2012 O_18]

Integrase Inhibitors- Raltegrevir

	RAL + BOC	RAL	GMR (90% CI)		paired sample t-test
$AUC_{0\text{-}12h}$ (mg*h/L)	4.27 (3.22-5.66)	4.22 (3.19-5.59)	1.01	(0.85-1.20)	0.664
C_{max} (mg/L)	1.06 (0.76-1.49)	0.98 (0.73-1.31)	1.09	(0.89-1.33)	0.471

De Kanter. Poster #772LB CROI 2012

Figure 2: Mean (SD) PK Profile of TVR

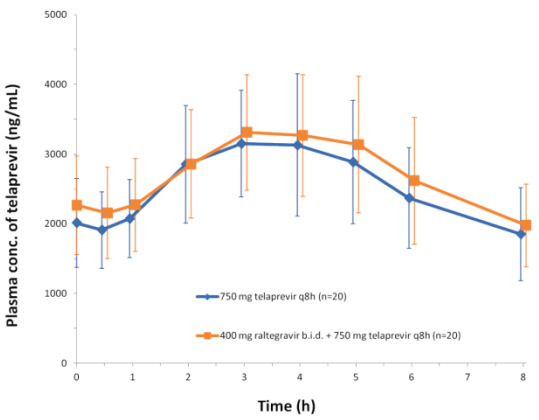
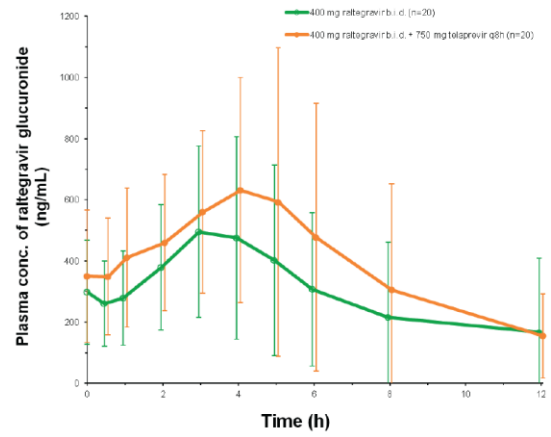


Figure 5: Mean (SD) PK Profiles of RAL-gluc



Van Heeswijk. ICAAC 2011. Poster #1738

Clinical Relevance

- Boceprevir
  - 7 patients had HIV breakthrough (>50 copies HIV RNA at 2 consecutive visits):
    - 3/64 randomized to B/PR
    - 4/34 to PR
- Telaprevir
  - There were no HIV RNA breakthroughs
  - 3 T/PR patients experienced HCV RNA breakthrough:
    - 1 receiving EFV/TDF/FTC and 1 receiving ATV/r + TDF/FTC at W4
    - 1 receiving EFV/TDF/FTC at W12

Issues with HCV Therapy Influencing Treatment Decisions in HIV

- Expense
- Do the studies reflect your population?
- Complexity of delivery
- Lack of expertise
- Is this a true priority?

When not to Treat?

- HIV Status
- Psychosocial-Economic Conditions currently exist to support treatment?
- Substance Abuse

When to Treat?

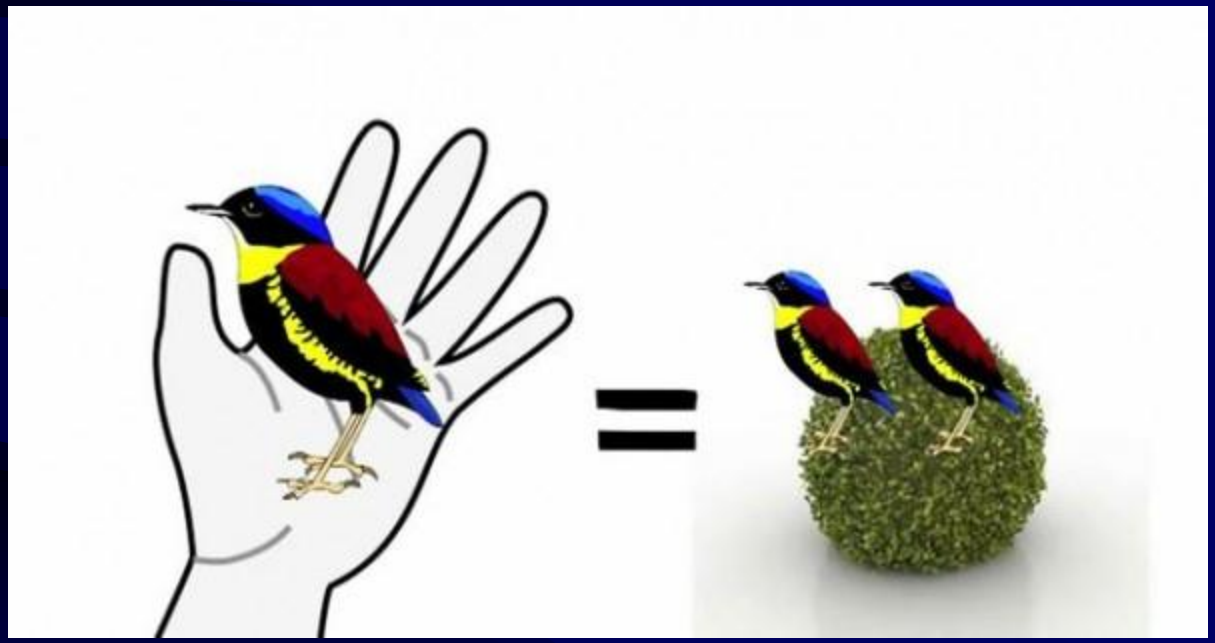
- HIV in check
- Young and healthy without advanced liver disease
- Compensation but advanced fibrosis

When to Treat?

- Sexual Transmission
- Acute Infection

- Vogel M, Dominguez S, Bhagani S, Azwa A, Page E, Guiguet M, Valantin MA, Katlama C, Rockstroh JK, Nelson M. Treatment of acute HCV infection in HIV-positive patients: experience from a multicentre European cohort. Antivir Ther. 2010;15(2):267-79.

Present versus Future



Research Needs

- Treatment of HIV-HCV co-infection in more advanced disease
- RGT
- IFN-sparing regimens
- DDI
- HCV treatment post OLT

Concluding Statement

- The majority of issues are not unique to
- HIV-HCV co-infection.
- The same general approach to work-up, treatment and long-term follow-up is appropriate in this population as in HCV mono-infection.

Thank You