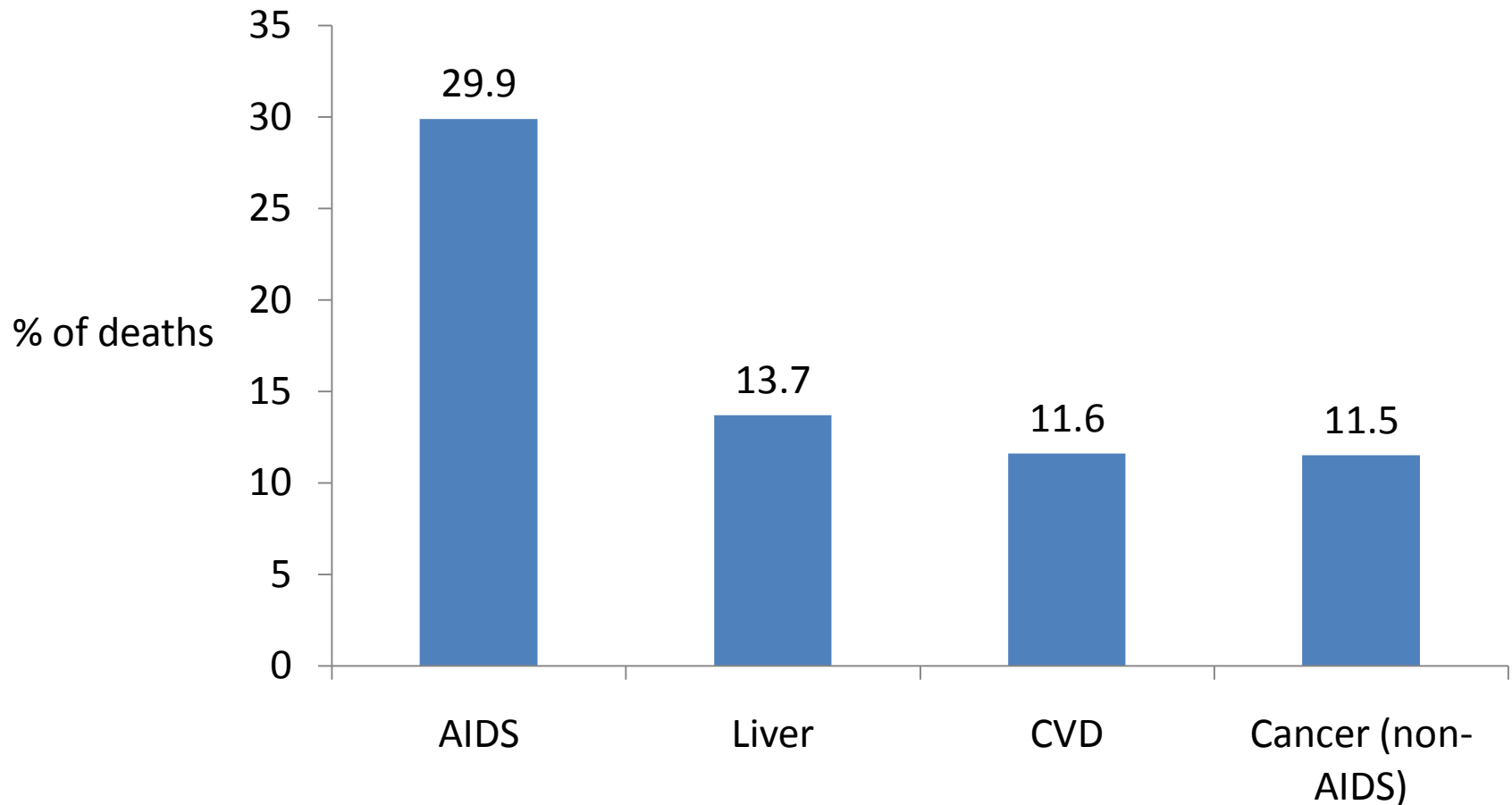


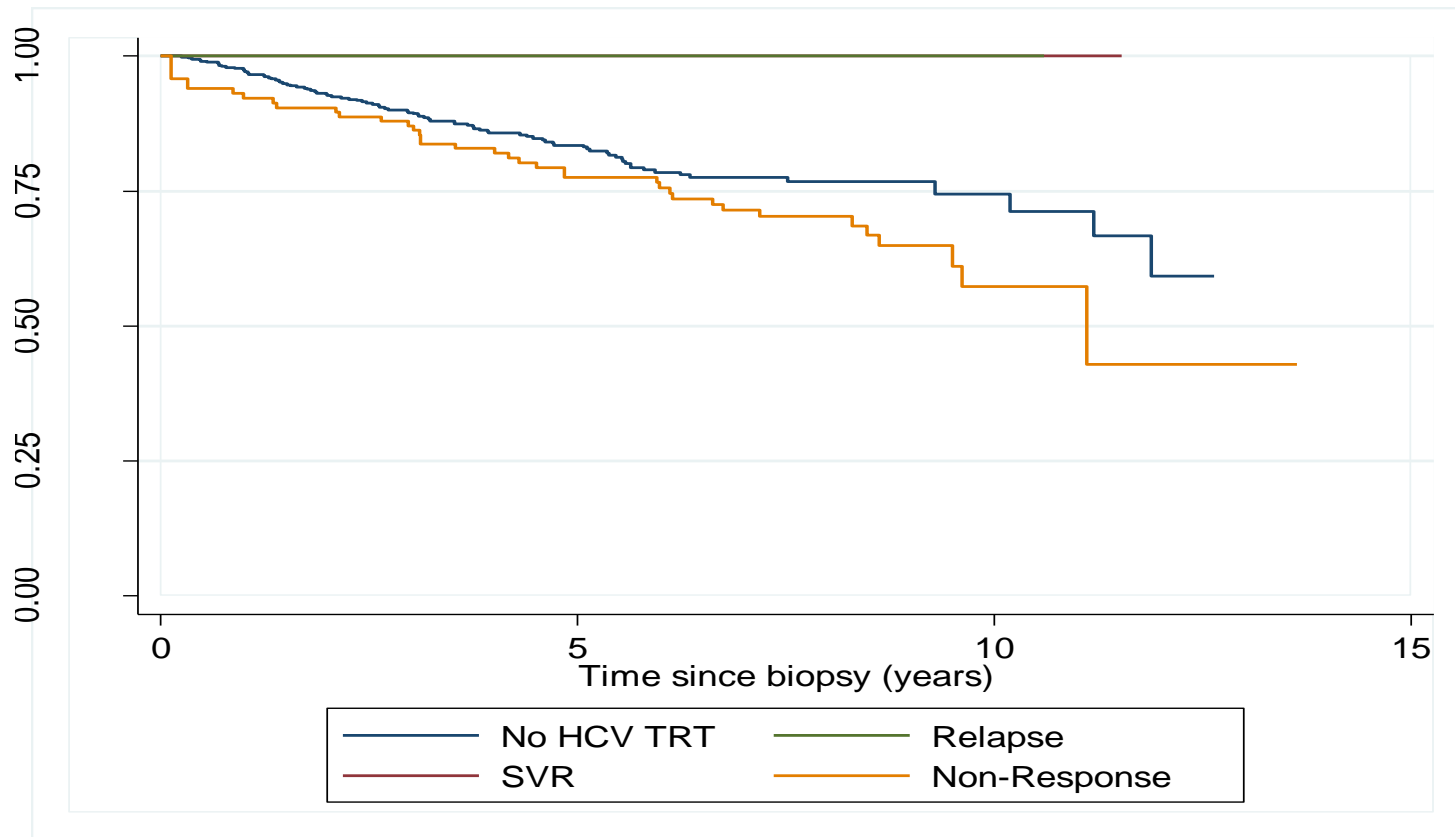
# Safety and Efficacy of DAA + PR in HCV/HIV co-infected patients

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# Liver disease is the second leading cause of death amongst HIV-positive patients in the D:A:D study



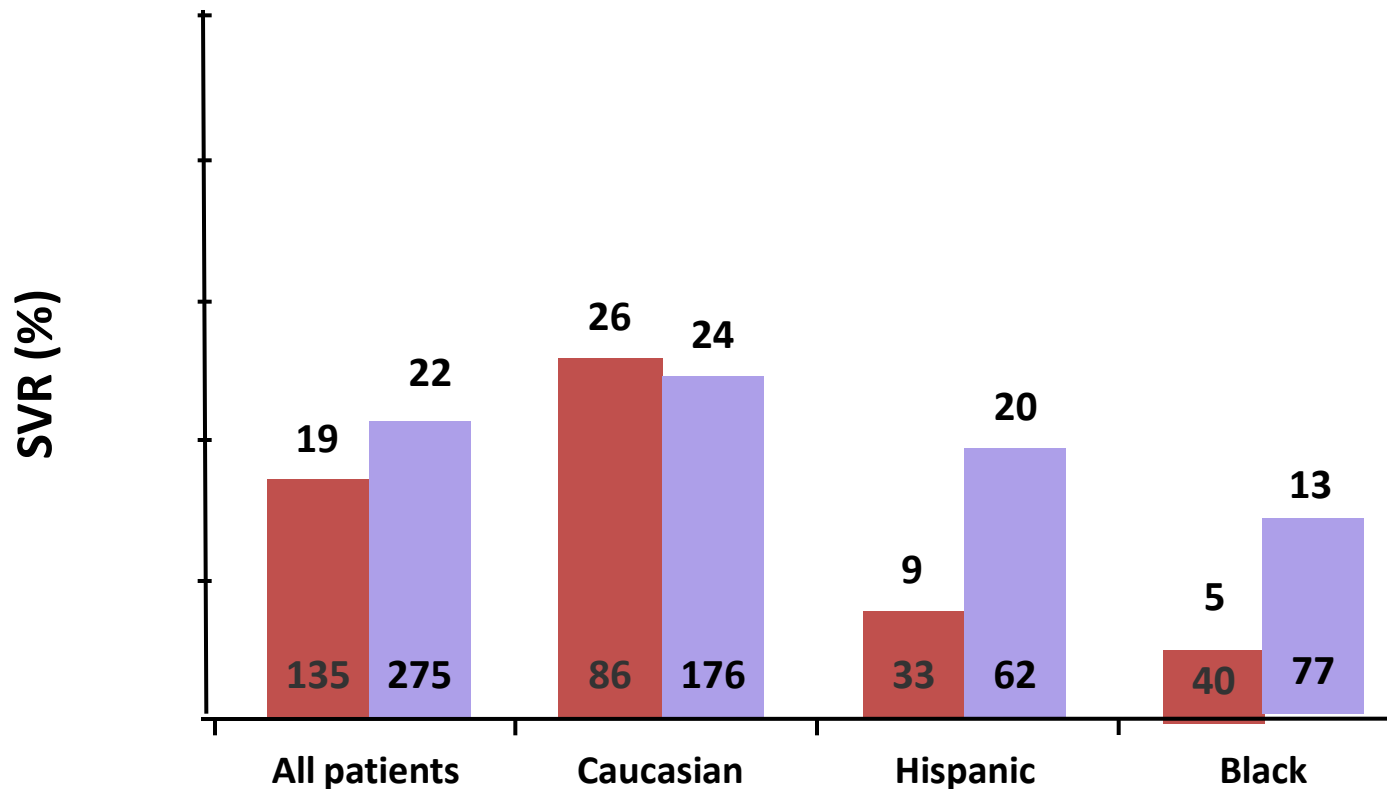
# SVR or virologic relapse following HCV treatment was associated improved liver disease free survival



# PegIFN/RBV: SVR rates are low among HCV genotype 1 patients confection with HIV

■ Ribavirin 800 mg/day (n=135)

■ Ribavirin 1000/1200 mg/day (n=275)

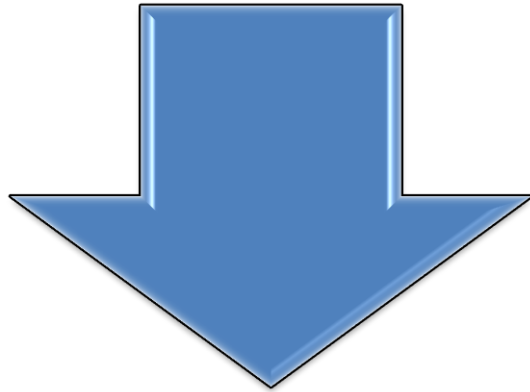


# HCV/HIV-coinfected Patients have Significant Comorbidities

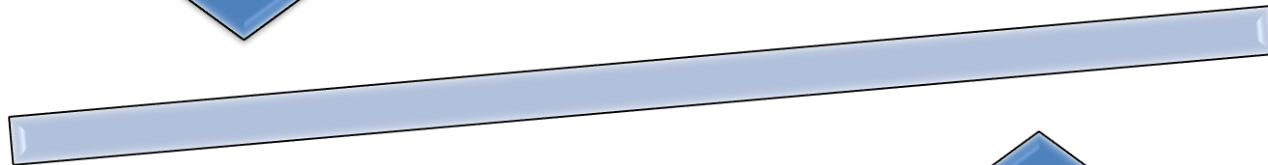
*HIV-infected Veterans with and without HCV*

	HIV	HIV/HCV
Drug disorder	22%	58%
Alcohol disorder	24%	56%
Depression	28%	43%
Bipolar	6%	12%
Anemia	19%	27%
COPD	17%	21%
Hypertension	37%	42%

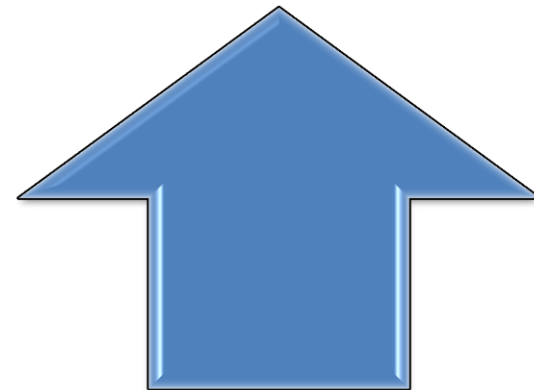
# Should current DAAs + PR be used to treat HCV in HIV-infected patients?



AEs with DAA/PR  
Frequent DDIs w/DAAs + ARVs  
Safety/Efficacy not established  
High cost



High HCV disease burden  
ESLD/HCC  $\approx$  death  
Poor response to PR  
DDIs = manageable

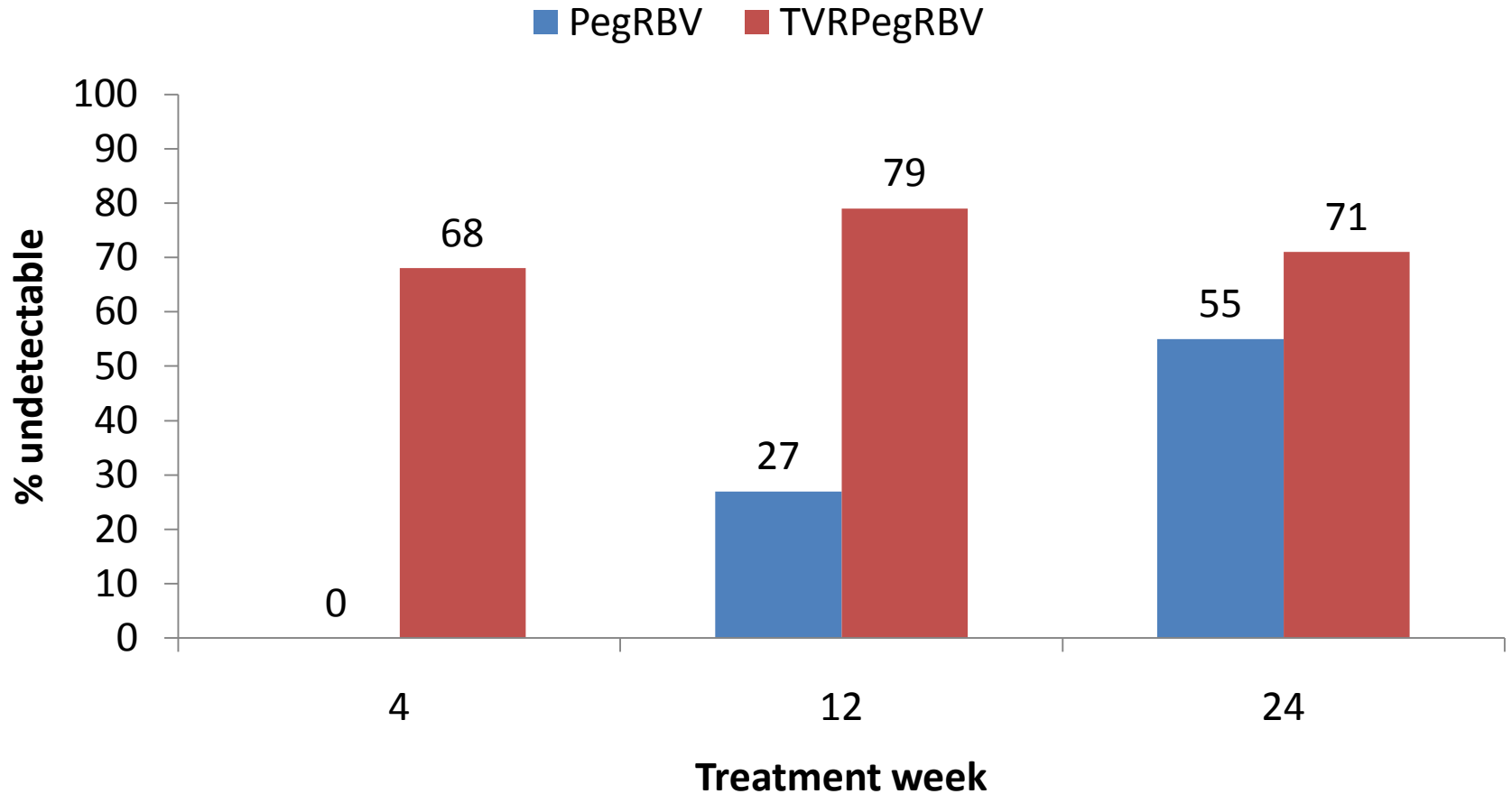


# Phase 2 studies of HCV PI + PR

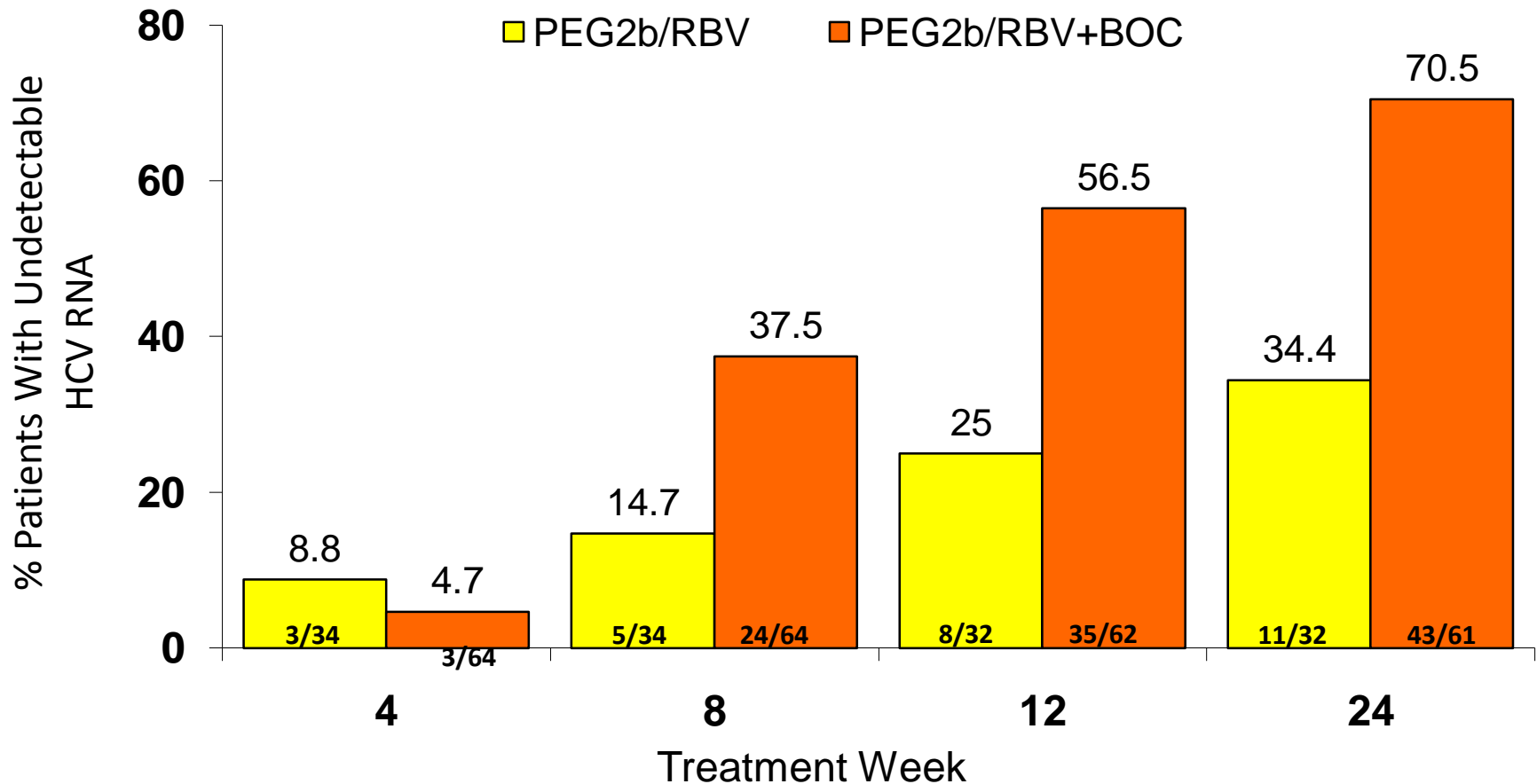
	Telaprevir	Boceprevir
Number of patients	<b>TVR, 38</b> ; Control, 22	<b>BOC, 64</b> ; Control, 34
HCV population	Naïve, genotype 1	Naïve, genotype 1
HIV population	CD4 $\geq$ 500; HIV $\leq$ 100,000 c/mL CD4 $\geq$ 300; HIV $\leq$ 50 c/mL	CD4 $\geq$ 200 cells/mm <sup>3</sup> HIV RNA <50 c/mL
Antiretroviral therapy	None (n=7) EFV (n=16) or ATV/r (n=15) + TDF/FTC	No NNRTIs ATV/r, (n=20); DVR/r (n=16); DRV/r (n=12); RAL(n=11)
HCV regimen	TLV 750 mg Q8H or 1125 mg Q8H (if EFV co-admin) + pegIFN-2a + RBV 800 mg/day	BOC 800 mg Q8H + pegIFN-2b + weight based RBV (600–1400 mg/day)
PR Lead-in	No	Yes
Duration of PI	12 weeks	44 weeks
Duration of PR (no RGT)	48 weeks	48 weeks
Virologic futility rules	Week-4/8/12 HCV RNA >1000 IU/mL Week-24 Detectable HCV RNA	Week-12 <2 log <sub>10</sub> decline Week-24 Detectable HCV RNA
HCV PI PK measured	Yes	Yes
ART PK measured	Yes	No

Interim Efficacy: Week 24 HCV  
RNA undetectable not SVR

# Proportion with undetectable HCV RNA over 24 weeks Telaprevir x 12 weeks/PegIFN/RBV Vs. PegIFN/RBV



# Proportion with undetectable HCV RNA over 24 weeks Boceprevir/PegIFN/RBV Vs. PegIFN/RBV



# Interim Safety and Tolerability

# Telaprevir + PR

Table 3: Most Common Adverse Events*		
%	T/PR (N=38)	PR (N=22)
Fatigue	42	41
<b>Pruritus</b>	<b>40</b>	<b>9</b>
<b>Headache</b>	<b>37</b>	<b>27</b>
<b>Nausea</b>	<b>34</b>	<b>23</b>
Diarrhea	24	18
<b>Dizziness</b>	<b>21</b>	<b>9</b>
<b>Pyrexia</b>	<b>21</b>	<b>9</b>
<b>Depression</b>	<b>21</b>	<b>9</b>
Neutropenia	21	23
Anorexia	10	4
Vomiting	18	9
Myalgia	16	23
Chills	16	18
Weight Decreased	10	23
Insomnia	13	23

\*Reported in >15% of patients regardless of severity in any treatment arm, in bold event occurring at >10% points in any T/PR group vs PR. Abdominal pain occurred more frequently in the T/PR groups ( $\geq 10\%$  difference) compared to PR as well.

- No severe rash report with TVR
- TVR/PR - bilirubin AEs 27% (4/15) versus none of control (0/8)

# Telaprevir + PR

**Table 4: Adverse 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=15	PR N=8
Any AE, n (%)	7 (100)	6 (100)	16 (100)	8 (100)	15 (100)	8 (100)
Serious AE <sup>*†</sup> , n (%)	1 (14)	0	1 (6)	0	5 (33)	1 (12)
Discontinuation of all study drugs due to AE, n (%)	0	0	0	0	2 (13)	0
Due to jaundice	0	0	0	0	1 (6.7)	0
Due to cholelithiasis	0	0	0	0	1 (6.7)	0
Due to hemolytic anemia <sup>*</sup>	0	0	0	0	1 (6.7)	0

<sup>\*</sup>Hemolytic anemia was reported as a serious adverse event.

<sup>†</sup> One additional patient had a serious AE of pneumococcal pneumonia reported after the Week 4 safety follow-up visit.

# TVR/PR: Virologic Breakthrough

- No HIV RNA breakthrough
- HCV RNA breakthrough, 7 patients
  - Efavirenz, 4 of 16 at weeks 4 (n=1), 8 (1), 12 (2)
  - Atazanavir/ritonavir, 3 of 15 at weeks 4 (n=1), 8 (1), 12 (1)

# Boceprevir + PR: Most Common Adverse Events With a Difference of $\geq 10\%$ Between Groups

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	PEG2b/RBV (N=34)	PEG2b/RBV + BOC (N=64)
Days on study, median	166	211
Neutropenia, (%)	3%	13%
Dysgeusia, (%)	15%	25%
Vomiting, (%)	15%	25%
Pyrexia, (%)	21%	34%
Headache, (%)	12%	28%
Decreased Appetite, (%)	18%	30%

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# Safety Boceprevir + PR

	<b>PEG2b/RBV (N = 34)</b>	<b>PEG2b/RBV + BOC (N = 64)</b>
Days on study, median	166	211
Any AE, n (%)	34 (100)	63 (98)
Serious AEs, n (%)	7 (21%)	5 (8%)
Treatment-related Treatment-emergent AEs, n (%)	34 (100%)	61 (95%)
Study Discontinuation Due to an AE, n (%)	3 (9%)	9 (14%)
Any Drug Modification Due to an AE, n (%)	7 (21%)	12 (19%)

# Boceprevir + PR: Hematologic Adverse Events

	PEG2b/RBV (N=34)	PEG2b/RBV + BOC (n=64)
<b>Anemia</b>		
AEs, n (%)	9 (26)	19 (30)
SAEs, n (%)	2 (6)	1 (2)
AEs leading to discontinuation, n (%)	1 (3)	1 (2)
Grade 2 (8.0 to <9.5 g/dL), n (%)	7 (21)	10 (16)
Grade 3 (6.5 to <8.0 g/dL), n (%)	1 (3)	3 (5)
Erythropoietin use, n (%)	7 (21)	17 (27)
Transfusions, n (%)	2 (6)	4 (6)
<b>Neutropenia</b>		
AEs, n (%)	1 (3)	8 (13)
Grade 3 (<0.75x10 <sup>9</sup> /L), n (%)	3 (9)	10 (16)
Grade 4 (<0.5x10 <sup>9</sup> /L), n (%)	*	*

# BOC/PR: Virologic Breakthrough

- HIV RNA breakthrough, 4 patients
  - 2 on placebo
  - 2 on BOC + ATV/r with HIV RNA transient increase  
HIV RNA from  $< 50$  c/mL and no change in ART
- No HCV RNA breakthrough reported

# Interim Drug Interactions

# Telaprevir – ARV Interactions

TVR dose	ARV	TVR AUC <sub>tau</sub>	TVR C <sub>min</sub>	ARV AUC <sub>tau</sub>	ARV C <sub>min</sub>	Comments
TVR 750 mg every 8 hours	ATV/r 300/100 mg qd	↓20%	↓15%	↑17% (NS)	↑85%	Dose: TVR 750mg q8h + ATV/r 300/100 mg qd.
	DRV/r 600/100 mg bid	↓35%	↓32%	↓40%	↓42%	Avoid co-administration
	FPV/r 700/100 mg bid	↓32%	↓30%	↓47%	↓56%	Avoid co-administration
	LPV/r 600/100 mg bid	↓54%	↓52%	↑6% (NS)	↑14% (NS)	Avoid co-administration
TVR 1125 mg every 8 hours	EFV 600 mg qhs (w/ TDF)	↓18%	↓25%	↓18%	↓10%	Dose: TVR 1125mg q8h + EFV 600 mg qhs.
	TDF 300 mg qd (w/EFV)			↑10%	↑17%	Dose: TDF 300 mg qd
TVR 750 mg every 8 hours	TDF 300 mg qd	No change	↑3% (NS)	↑30%	↑41%	Dose: TVR 750 mg q8h + TDF 300 mg qd
TVR 750 mg every 8 hours	RAL 400 mg bid	↑7% (NS)	↑14%	↑31%	↑78%	Dose: TVR 750 mg q8h + RAL 400 mg bid

# Change in Antiretroviral concentration after TVR administration in HIV/HCV infected patients

ART Medication	Median C <sub>min</sub> before HCV treatment (ng/mL)		Median (10 <sup>th</sup> - 90 <sup>th</sup> percentiles) ratio of C <sub>min</sub> before and after HCV treatment*	
	+TVR/PR	+PBO/PR	+TVR/PR	+PBO/PR
Atazanavir (ATV)	1230	1890	122% (54% - Undef)	81% (16% - 220%)
Efavirenz (EFV)	1441	1925	86% (53% - 165%)	66% (52% - 148%)
Tenofovir (+EFV)	61.2	67.6	90% (60% - 422%)	59% (42% - 201%)
Tenofovir (-EFV)	128.1	139	83% (35% - 353%)	74% (53% - 170%)

EFV= efavirenz-based ART regimen

ATV= atazanavir/ritonavir-based ART regimen

- Telaprevir concentration were similar in all patient groups and comparable to other populations
- Dose adjustment of TVR with EFV was successful

# Boceprevir Drug Interactions with ART (limited data)

<b>Boceprevir</b>	<b>Effect on Concentration of PI or Concomitant Drug</b>
<b>Efavirenz</b>	↓ boceprevir •Plasma trough concentrations of BOC decreased when coadministered, which may result in loss of therapeutic effect •Avoid combination
<b>Ritonavir</b>	↓ boceprevir ↑ or ↓ HIV protease inhibitors •Boceprevir concentrations decreased with ritonavir; effect of ritonavir-boosted HIV PIs on BOC exposure is unknown •The effect of BOC on HIV PI concentrations is unknown

# Change in Antiretroviral concentration after BOC administration in HIV/HCV infected patients

- ARV concentration not assessed
  - Patient took ATV/r, DRV/r, LPV/r and RAL (and other ARVs) in phase 2 trial
- Healthy volunteer drug interactions studies underway
- Phase 3 trial (ACTG 5294) will permit most ARVs and carefully assess PK

# Provisional Recommendations for HCV treatment in HIV-infected patients (late 2011)

- Treat in clinical trials *when feasible* (no control group)
- PegIFN + Ribavirin is appropriate many coinfecting patients
- *If available*, interim data support the cautious use of telaprevir or boceprevir + PR in carefully selected patients
  - No antiretroviral therapy → TVR or BOC
  - ATV/r or RAL → TVR or BOC
  - EFV → TVR (requires increase TVR dose)
  - DRV/r or LPV/r → BOC?
  - Other ARVs → Change ARVs or treat with PR
- Major limitations to DAA + PR therapy
  - Cost (> 6000 HIV + patients on ADAP wait lists for ART in 12 states)
  - Need for PegIFN

# IFN-free clinical trials exclude HIV/HCV coinfected patients (late 2011)

- Multiple IFN-free studies found on [clinicaltrials.gov](http://clinicaltrials.gov) or press releases, none enroll HIV/HCV
- IFN-free trials should be prioritized:
  - Interaction studies with ART are needed
  - Data from phase 2 studies of BOC and TVR do not indicate differences in safety and tolerability in HIV/HCV
  - Regulatory agencies have not required controlled trials