HIV-HCV coinfection

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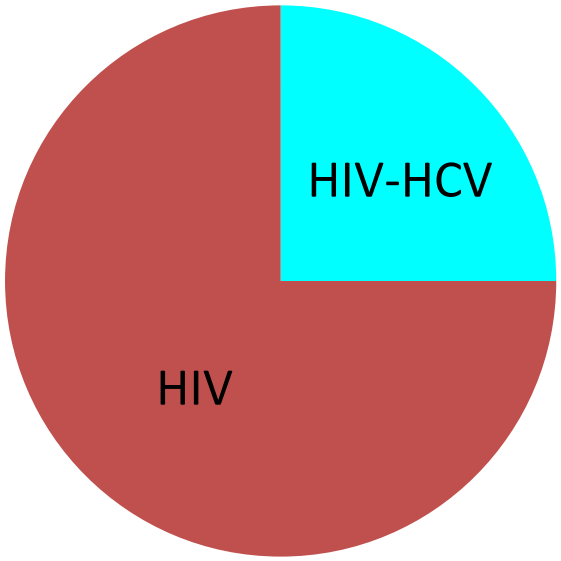
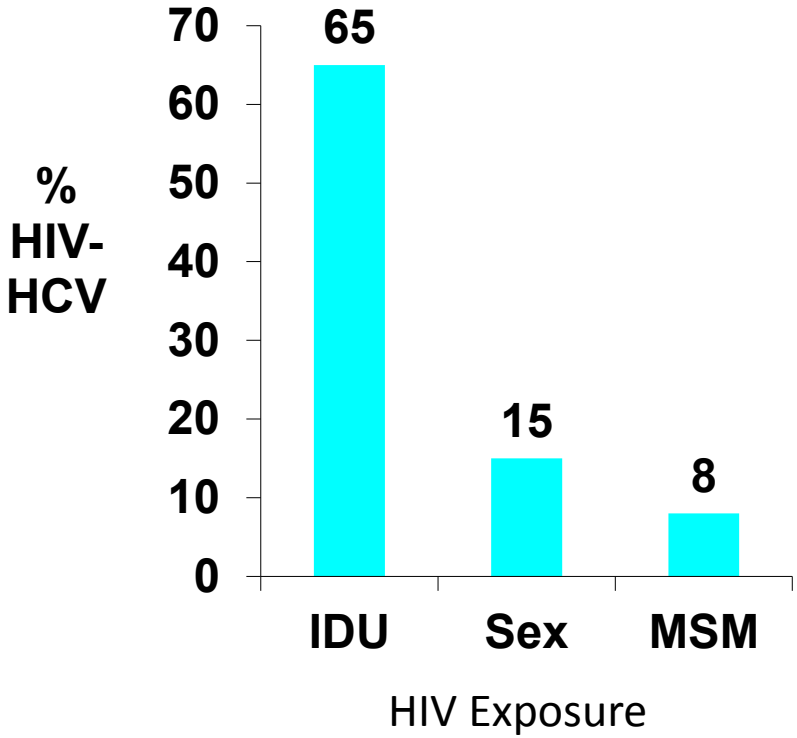
HCV Infection ~ 25% of HIV-infected Persons

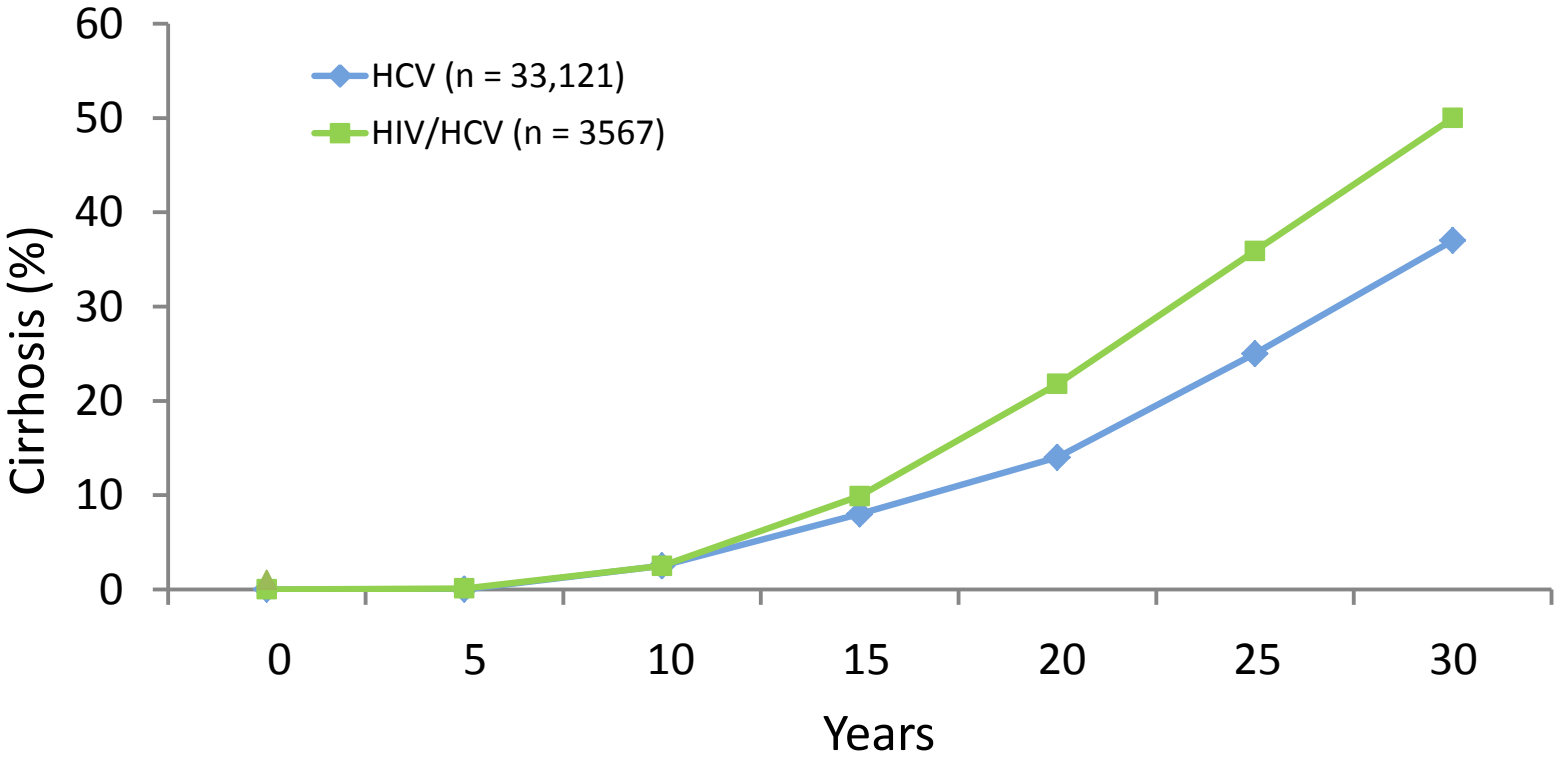
Prevalence differs by HIV risk group





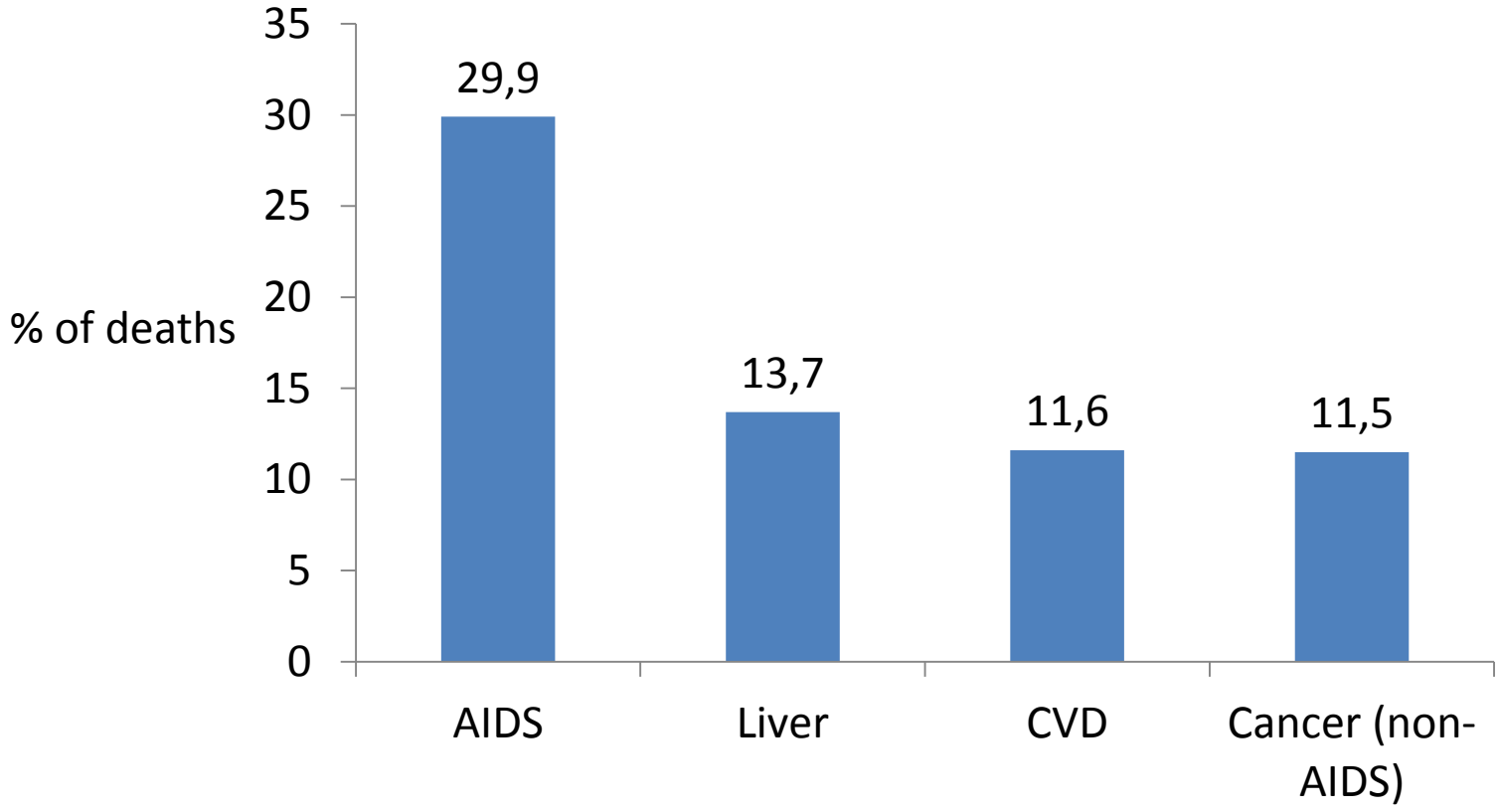
Sherman K et al. *Clin Infect Dis* 2002; Sulkowski M et al. *Ann Intern Med* 2003.

Impact of HIV on HCV-related Liver Disease Progression



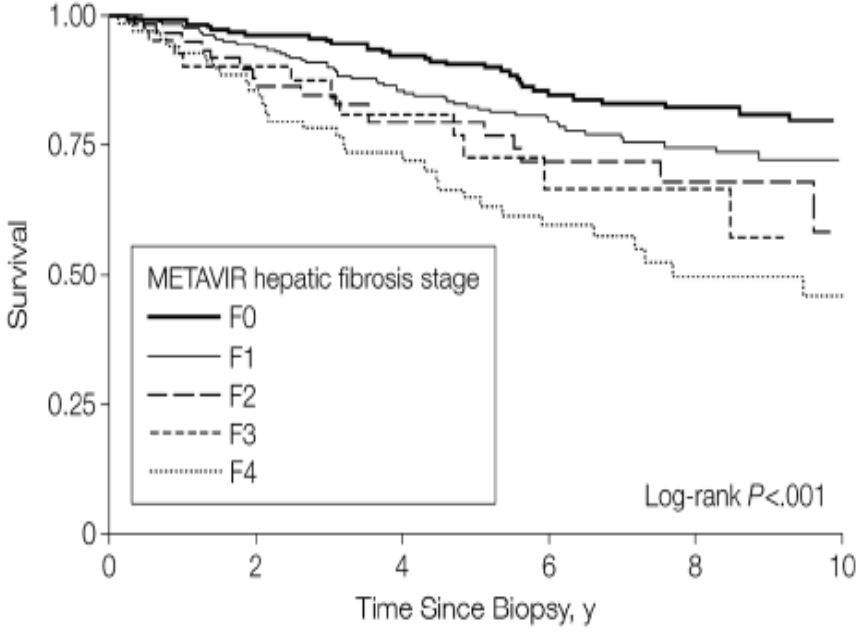
Thein H-H et al. AIDS. 2008;22:1979-1991.
Thein H-H et al. Hepatology. 2008;48:418-431.

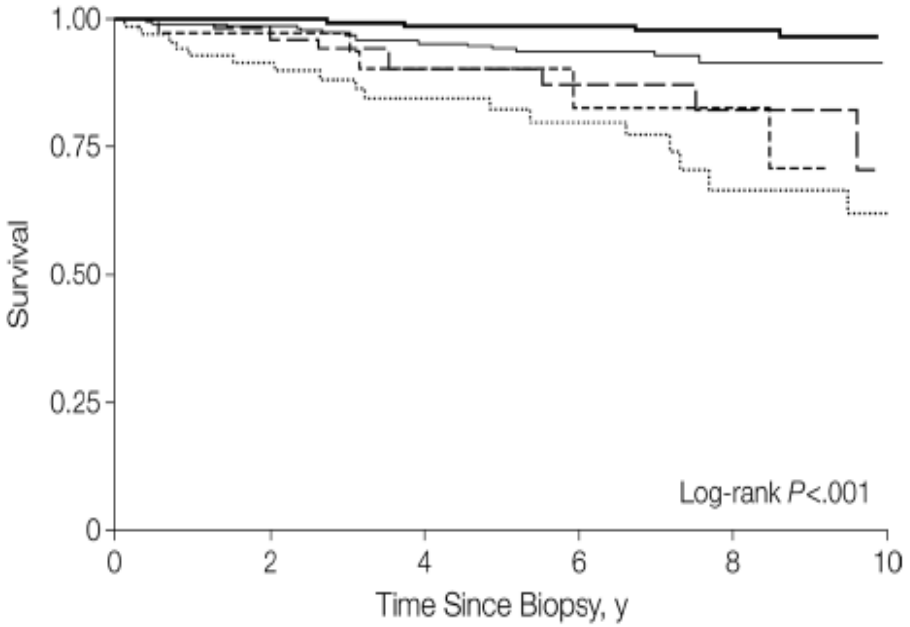
Liver disease is the second leading specific causes of death amongst HIV-positive individuals in the D:A:D study



AIDS. 2010 Jun 19;24(10):1537-48.

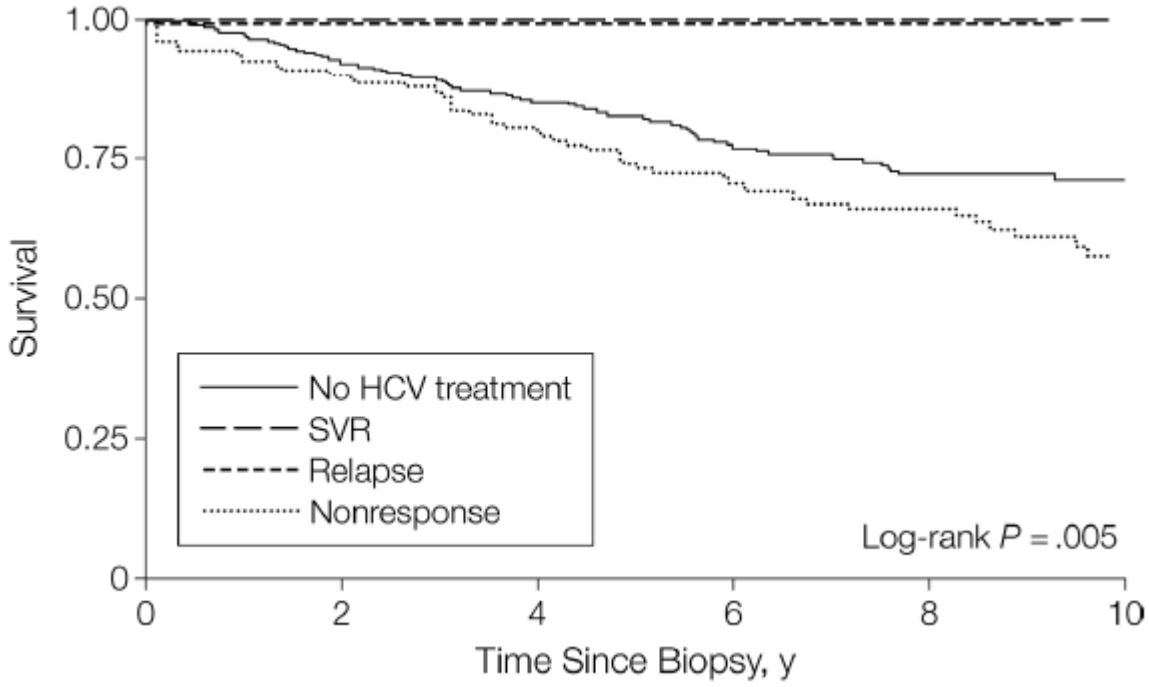
Time to death, ESLD or HCC among 638 HIV/HCV coinfected adults prospectively followed after liver biopsy





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

HCV suppression during or eradication following treatment was associated with survival

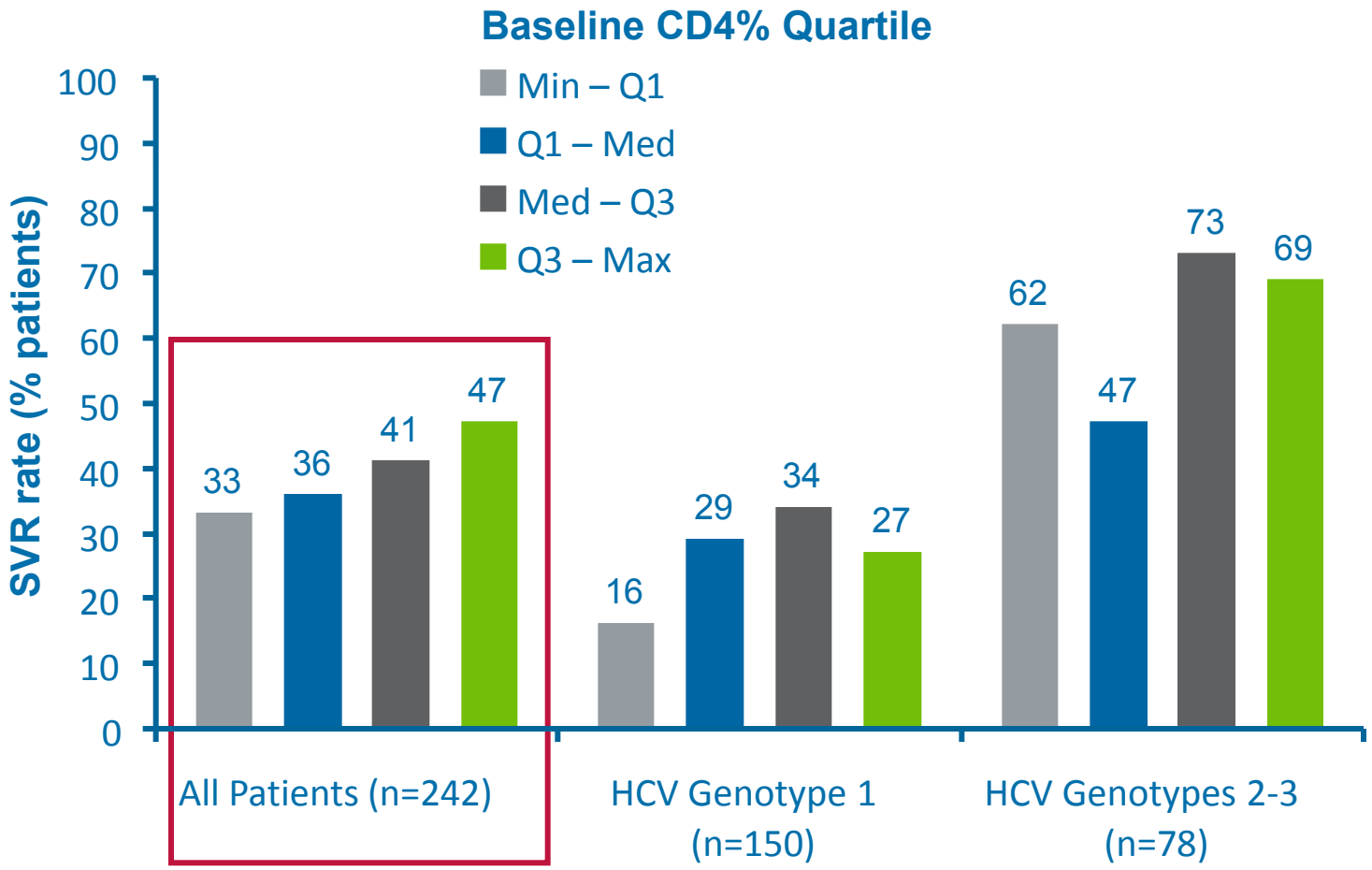


JAMA. July 25, 2012,308(4):370-378

PegIFN/RBV for HCV infection in HIV-coinfected patients

Study	Regimen	SVR (%) G1 or G4	SVR (%) G2 or G3	Take home observations
RIBAVIC[1] France (N = 412)	Peg-IFN α-2b RBV 800 mg	17	44	Low-dose RBV Toxicity with ddI + RBV Failure to suppress HCV RNA at week 4 <460,000 IU/mL → 100% NPV
Laguno et al[2] Spain (N =182)	Peg-IFN α-2b RBV 800 – 1200 mg	28	62	Weight-based RBV → higher SVR Short (24-week) therapy for genotype 2/3 not effective
ACTG A5071[3] USA (N = 133)	Peg-IFN α-2a RBV 600 - 1000 mg	14	73	Low-dose RBV Failure to achieve week 12 EVR → 100% NPV ZDV + RBV → more anemia
APRICOT[4] International (N = 868)	Peg-IFN α-2a RBV 800 mg	29	62	Low-dose RBV Decompensation with advanced fibrosis Genotype 1/High HCV RNA –18% SVR
PRESCO[5] Spain (N = 389)	Peg-IFN α-2a RBV 1000 – 1200 mg	35	72	Weight-based RBV → higher SVR No increase in anemia Long (72-week) therapy not well tolerated

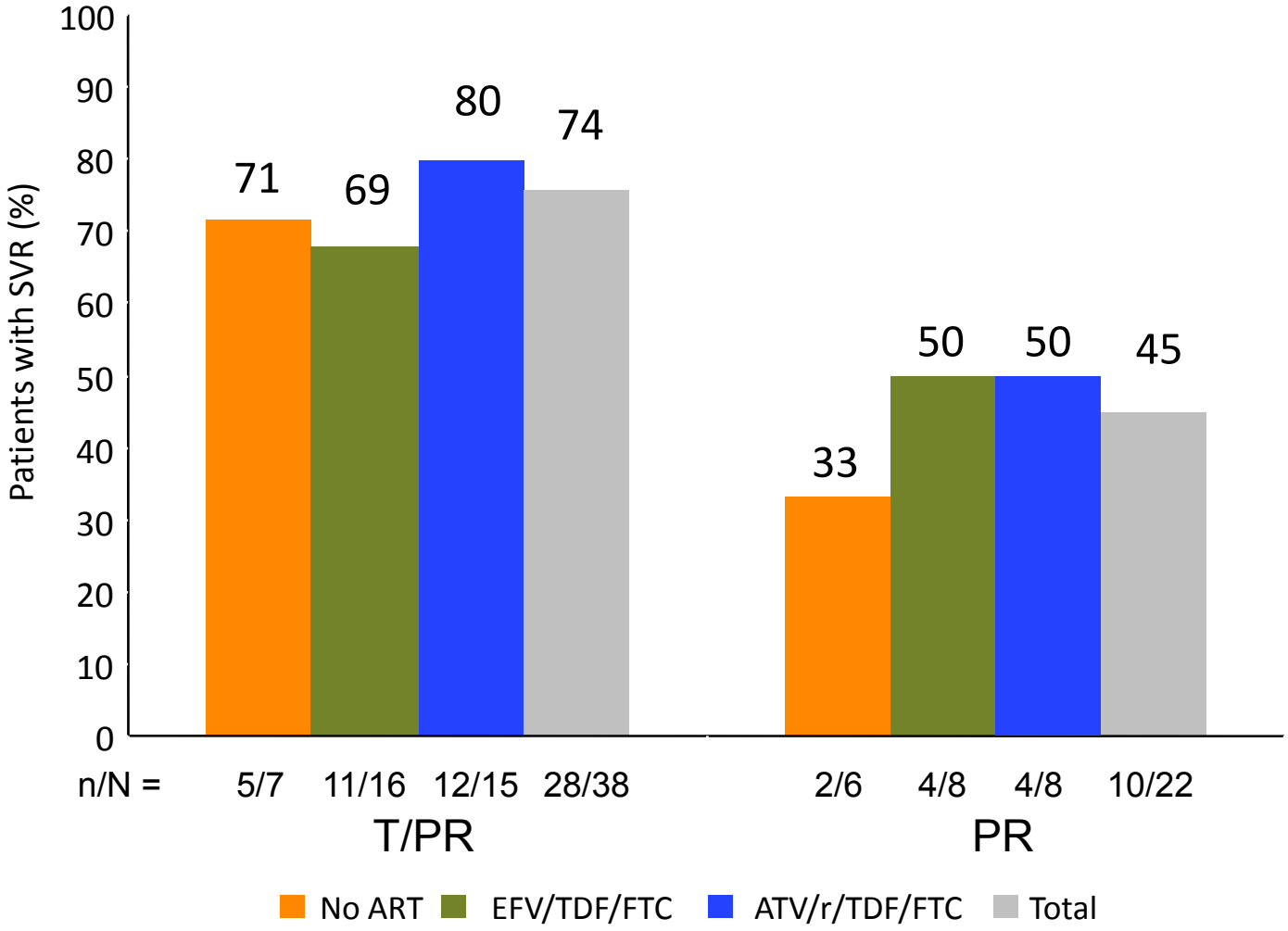
Rate of SVR increases with higher CD4% at baseline: APRICOT Study



Phase 2 studies of HCV PI + PR

	Telaprevir	Boceprevir
Number	TVR, 38; Control, 22	BOC, 64; Control, 34
HCV population	Naïve, genotype 1	Naïve, genotype 1
HIV population	CD4 ≥500; HIV ≤100,000 c/mL CD4 ≥ 300; HIV ≤50 c/mL	CD4 ≥ 200 cells/mm^3 HIV RNA <50 c/mL
ART	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)
Lead-in	No	Yes
Duration of PI	12 weeks	44 weeks
Duration of PR	48 weeks	48 weeks

Telaprevir + PegIFN/RBV: SVR Rates (SVR24)



Sulkowski et al. AASLD 2012

Most Common Adverse Events in >15% Patients: TVR Treatment Phase (Weeks 1-12)

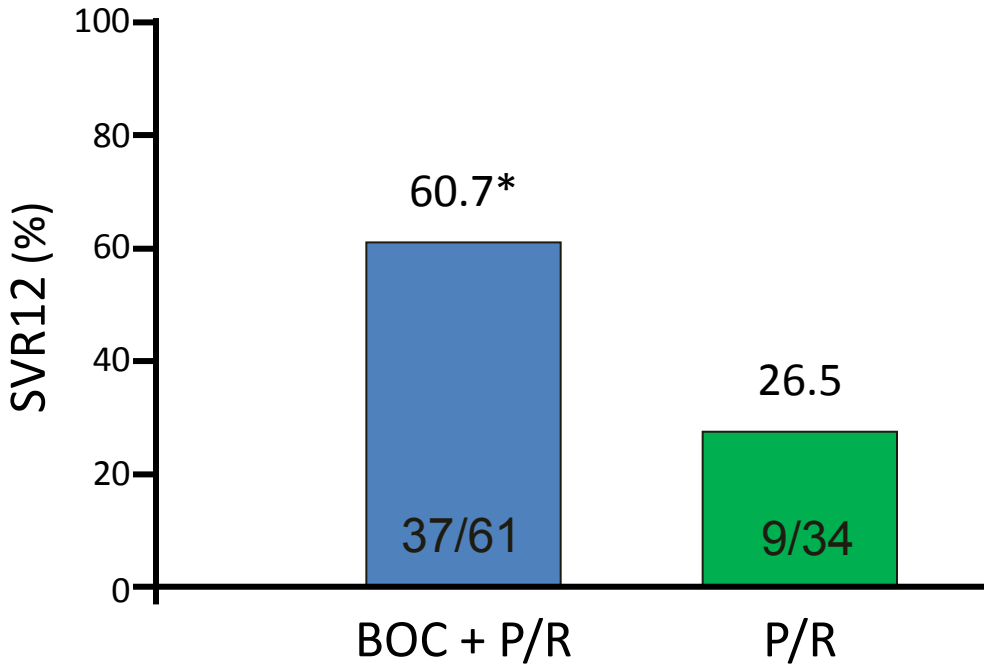
N (%)	T/PR N=38	PR N=22
Fatigue	15 (39)	9 (41)
Pruritus	**13 (34)**	**1 (5)**
Headache	**13 (34)**	**5 (23)**
Nausea	**12 (32)**	**4 (18)**
Rash†	**11 (29)**	**4 (18)**
Diarrhea	8 (21)	3 (14)
Dizziness	**8 (21)**	**2 (9)**
Pyrexia	7 (18)	2 (9)
Depression	6 (16)	2 (9)
Anemia†	5 (13)	4 (18)
Vomiting	6 (16)	2 (9)
Myalgia	**5 (13)**	**5 (23)**
Chills	5 (13)	4 (18)
Insomnia	5 (13)	4 (18)

Sulkowski et al. AASLD 2012

Boceprevir + PegIFN/RBV: SVR Rates 12 Weeks Post-Treatment (SVR12)

– Interim efficacy analysis

- 3 BOC pts had not yet reached SVR12 time point



Mallolas J, et al. EASL 2012. Abstract 50.

Boceprevir + PegIFN/RBV: Adverse effects

	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%

Pharmacokinetic Interactions Between Telaprevir and ART

ART	Effects on ART		Effects on TVR		Recommendations
	AUC	C_{min}	AUC	C_{min}	
Efavirenz	No change		↓ 26%	↓ 47%	↑ telaprevir dose to 1,125mg q8h
Atazanavir/r	-	↑ 85%	↓ 20%	↓15%	Use standard doses
Darunavir/r	↓ 40%	↓ 42%	↓ 35%	↓ 32%	Do Not Co-Administer
FPV/r	↓ 47%	↓ 56%	↓ 32%	↓ 30%	Do Not Co-Administer
Lopinavir/r	↓ 34%	↓ 43%	↓ 54%	↓ 52%	Do Not Co-Administer
Raltegravir	↑ 31%	-	No significant changes		Use standard doses

Pharmacokinetic Interactions Between Boceprevir and ART

ART	Effects on ART		Effects on BOC		Recommendations
	AUC	C_{min}	AUC	C_{min}	
Efavirenz	↑ 20%	-	↓ 19%	↓ 44%	Do Not Co-Administer
ETR, NVP, RPV	No PK Data, Interaction Possible				Do Not Co-Administer
Atazanavir/r	↓ 35%	↓ 49%	No change		Do Not Co-Administer
Darunavir/r	↓ 44%	↓ 59%	↓ 29%	↓ 35%	Do Not Co-Administer
Lopinavir/r	↓ 34%	↓ 43%	↓ 44%	↓ 35%	Do Not Co-Administer
Raltegravir	No significant changes				Use standard doses

AASLD recommendation for HCV treatment in HIV-infected patients (2011)

"*Pharmacokinetic interactions have particular implications in HIV-coinfected, where drug–drug interactions will complicate treatment paradigms, so that any use of BOC or TVR in transplant or HIV coinfected populations of patients with HCV should be done with caution and under close clinical monitoring*"

Ghany et al. HEPATOLOGY, October 2011

New Treatment Options for HIV/HCV Genotype 1 Patients: EACS Guidelines

- EACS guidelines include the option to treat HIV/HCV GT 1 coinfected patients with telaprevir*[1]
- Updated guidelines will also include option to treat with boceprevir as interim results became available

*With efavirenz, telaprevir dose should be increased to 1150mg every 8 hours. Data on coadministration of telaprevir with raltegravir is anticipated, but clinicians are advised to check www.hep-druginteractions.com for further information.

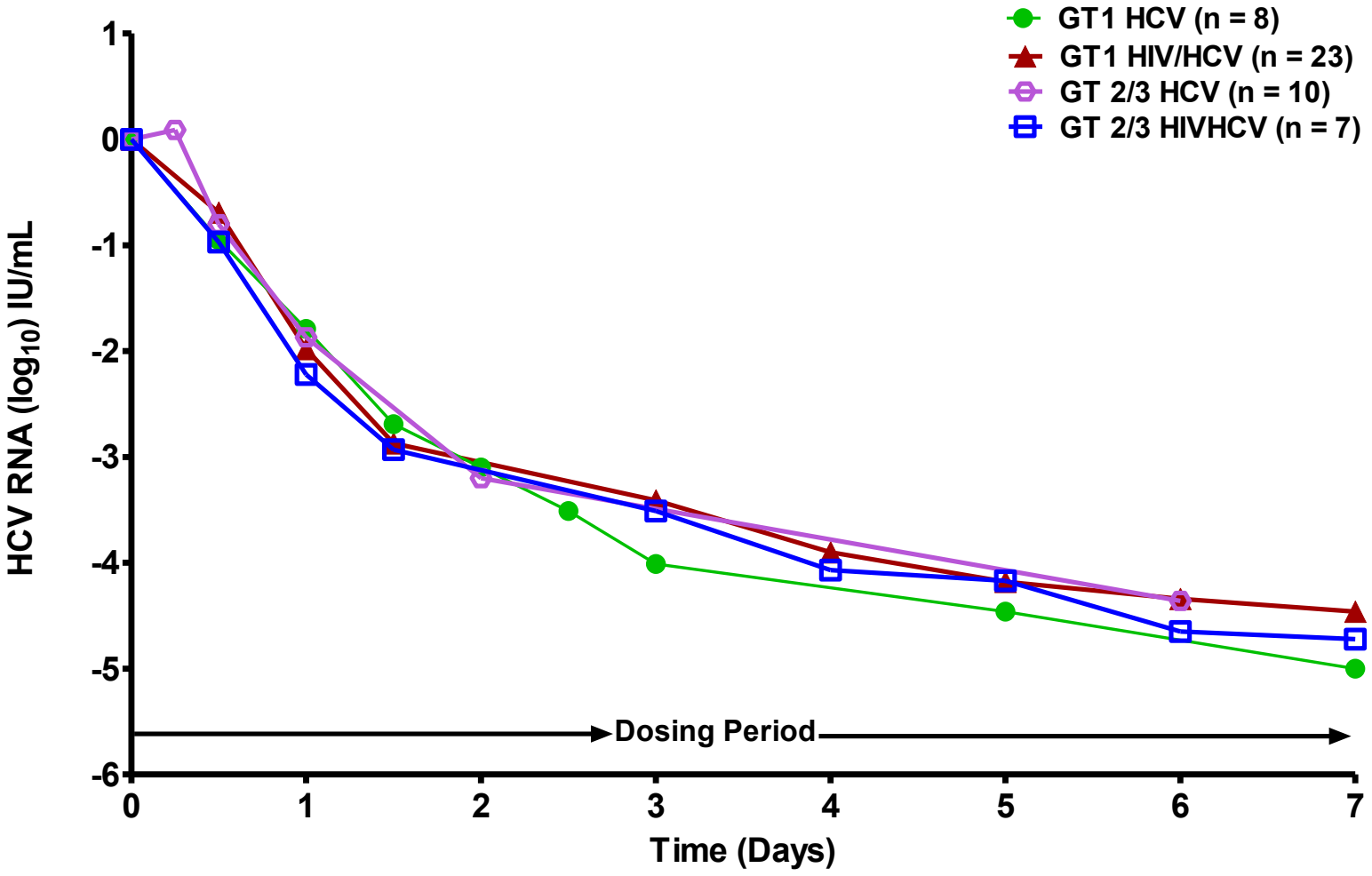
1. EACS Guidelines, October 2011, Version 6.0.

Clinical Trials of Novel DAAs for HCV Treatment in HIV-infected Patients

- Simeprevir (PI) once daily + PegIFN/RBV
- Faldaprevir (PI) once daily + PegIFN/RBV
- Daclatasvir (NS5A) once daily + PegIFN/RBV
- Sofosbuvir (nucleotide analogue polymerase inhibitor) once daily + RBV
  - Genotype 2 or 3 – 12 weeks
  - Genotype 1 – 24 weeks

Sofosbuvir 400 mg daily for 7 days in Patients with HIV/HCV Coinfection

Viral kinetics according to HIV Coinfection and HCV genotype



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

No or Minimal Hepatic Fibrosis

- Genotype 2 or 3 or 4, consider PegIFN/RBV
- Genotype 1, IL28B CC, consider PegIFN/RBV
- Other patients
  - Treat with antiretroviral therapy (even high CD4)
  - No alcohol
  - Achieve or maintain a normal BMI
  - Defer HCV therapy pending more effective DAA regimens

Moderate to Severe Hepatic Fibrosis

- Genotype 2 or 3 or 4, treat with PegIFN/RBV
- Genotype 1
  - If available, data support the cautious use of telaprevir or boceprevir + PegIFN/RBV R in carefully selected patients based on ARV regimens and ability to tolerate therapy
  - Cost is major factor in use of HCV PIs