Treatment of HCV in Patients with HIV Coinfection

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IAS–USA
International AIDS Society–USA

Disclosure

- Dr. Godofsky has received research support from Janssen, AbbVie, Achillion Pharmaceuticals, Inc, Bristol-Myers Squibb, Gilead Sciences, Inc, Boehringer Ingelheim, GSK and Vertex Pharmaceuticals, Inc.
- Dr. Godofsky has served as a scientific advisor or as a consultant to AbbVie, Genetech and Janssen Pharmaceuticals (Past 2 years, updated 6/14)

Lecture Outline

- Evolution of HCV Treatment in Patients with HIV Coinfection
- Timing of Treatment
  - Patient Evaluation and Selection
- Important Drug-Drug Interactions
  - Therapy Considerations for Patients on HIV ART
- Summary of Current AASLD/IDSA/IAS-USA Treatment Recommendations

Evolution of HCV Treatment in HIV Coinfection

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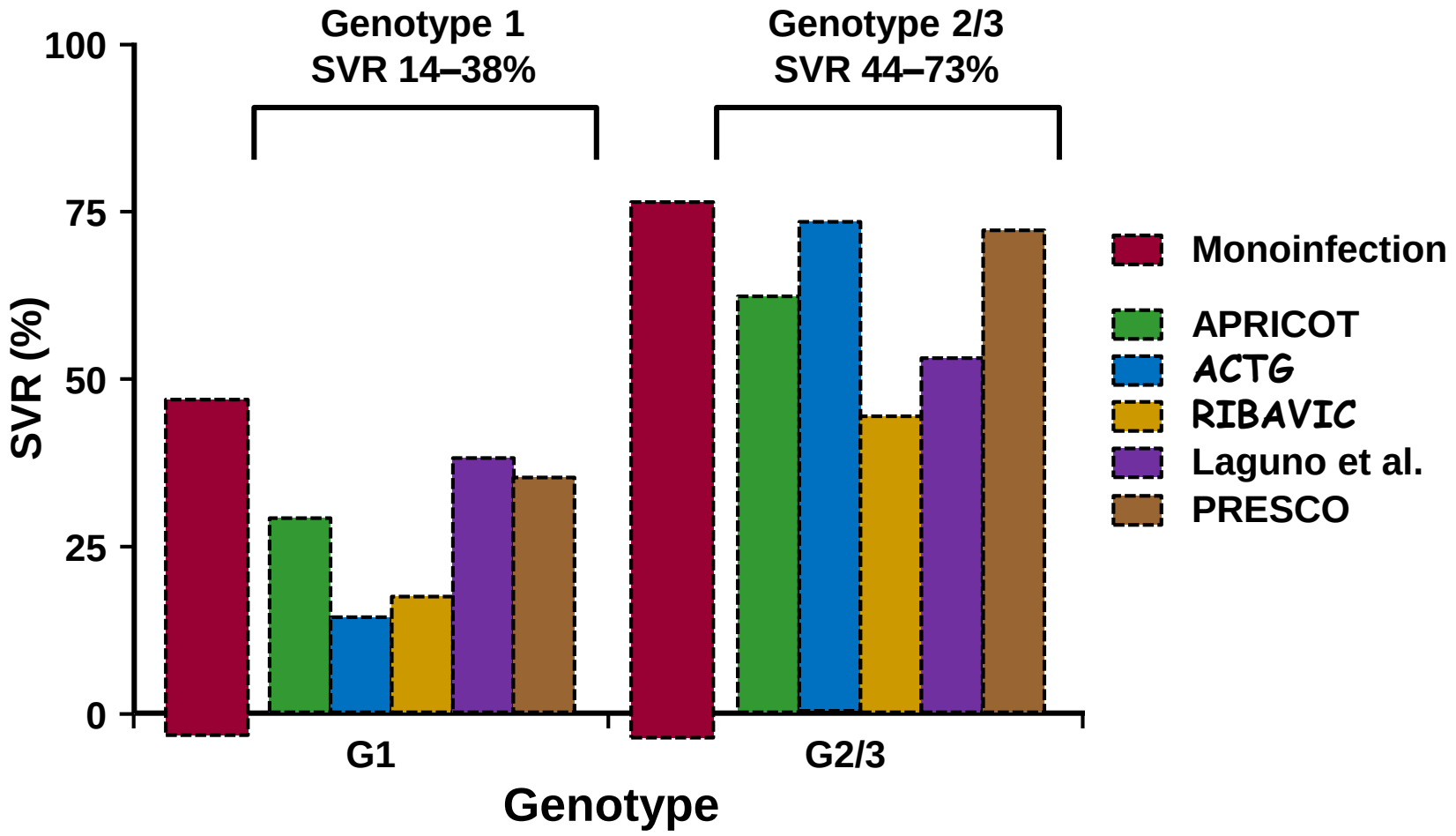
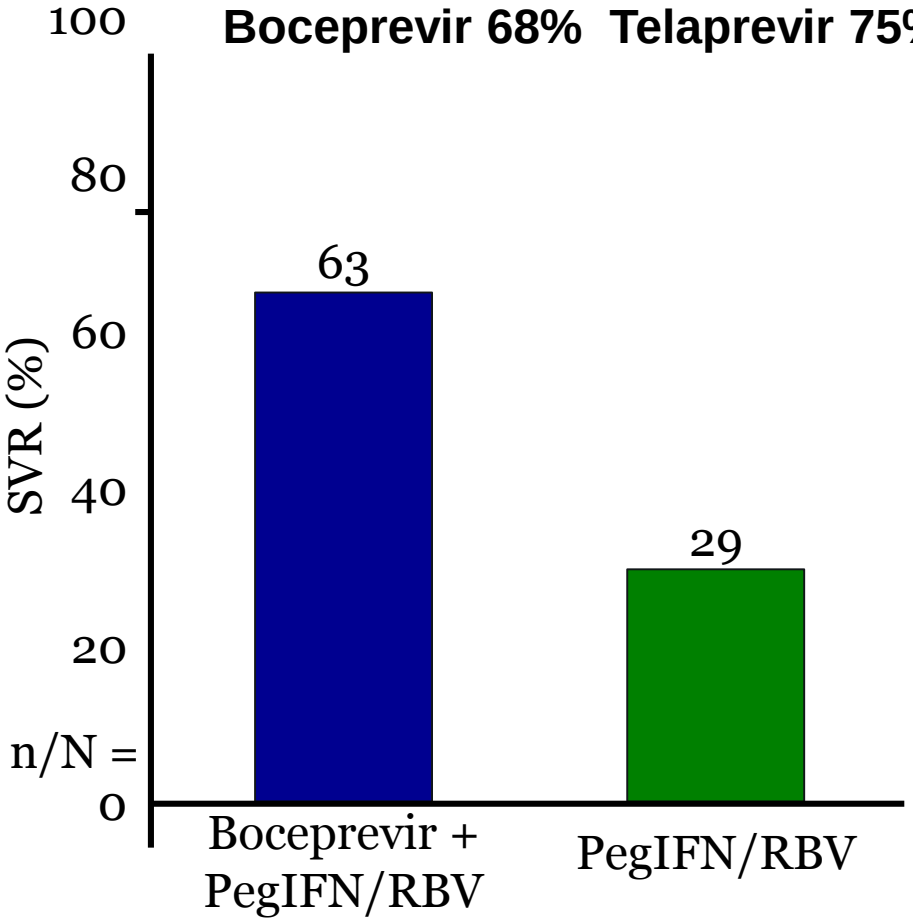
HCV/HIV Treatment Outcomes: PegIFN plus RBV

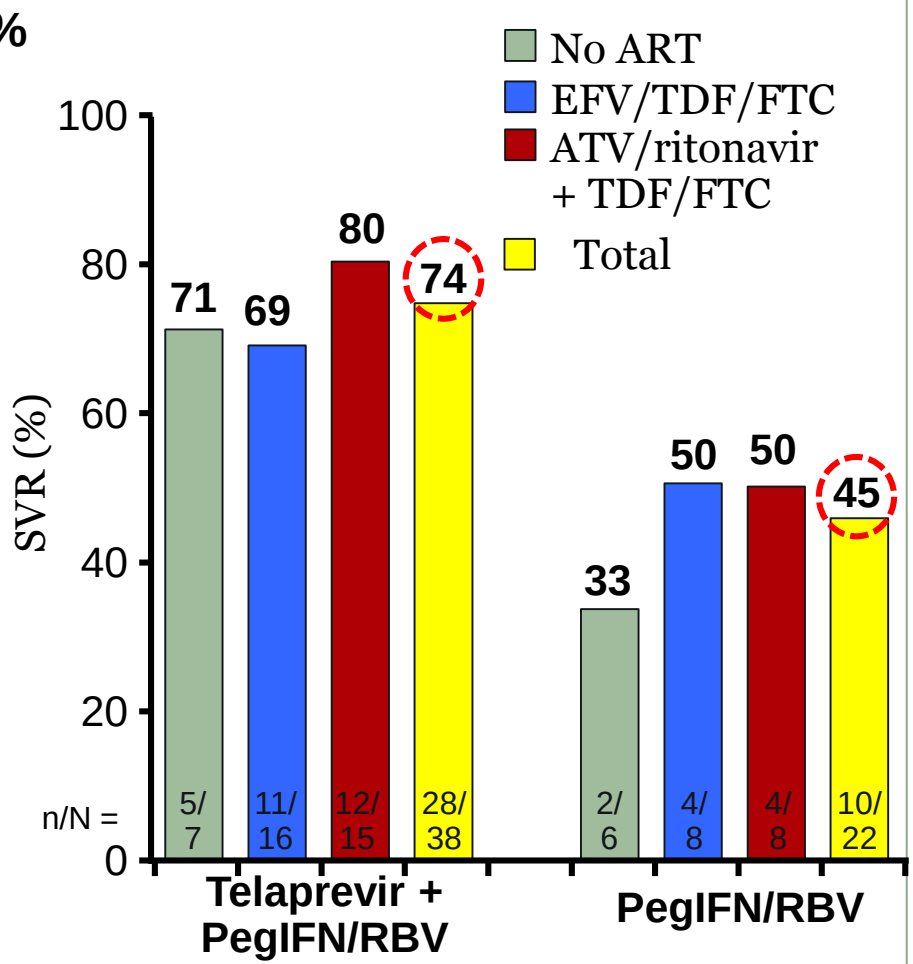


Fried et al, NEJM 2002, 347: 975-982, Torriani et al, NEJM 2004; 351: 438-50, Chung R, et al, NEJM 2004: 351; 451-9, Carrat F, et al, JAMA 2004: 292: 2839-42, Laguno et al, AIDS 2004; 18: F27-F36, Nunez et al, JAIDS 2007: 45: 439-44

First Generation HCV Protease Inhibitors plus PegIFN/RBV in GT 1 Coinfection

SVRs comparable to GT1 HCV-monoinfected patients:
Boceprevir 68% Telaprevir 75%





Sulkowski MS, et al. Ann Intern Med. 2013;159:86-96. Sulkowski M, et al. Lancet Infect Dis. 2013;13:597-605. Poordad F, et al. N Engl J Med. 2011;364:1195-1206. Jacobson IM, et al. N Engl J Med. 2011;364:2405-2416.

Recently Released DAAs

Simeprevir

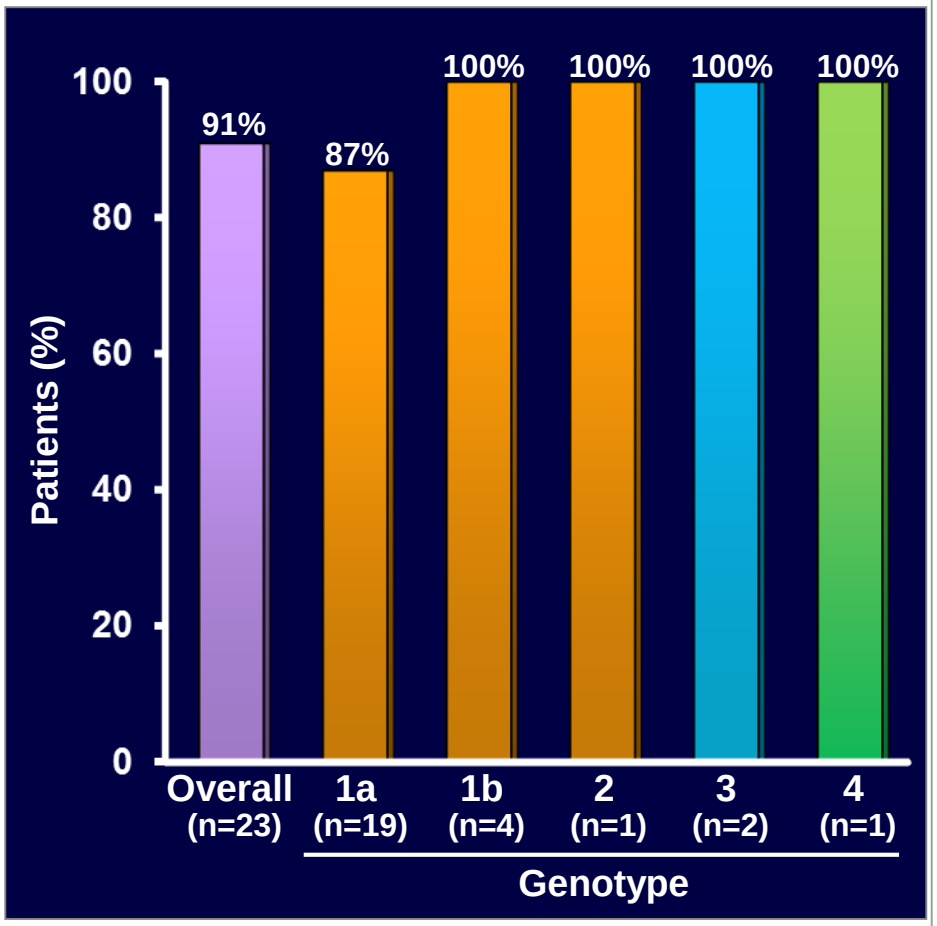
- Multi-genotypic NS3/4A PI
- QD dosing
- Second Wave PI
- Low barrier to resistance
- + DDI with ARVs
- Rash, photosensitivity
- HIV not a special pop

Sofosbuvir

- Pan-genotypic NS5B
- QD dosing
- Nucleotide analogue
- Exceptional barrier to resistance
- No significant DDI
- No AE
- Approved for HIV/HCV as special population

Sofosbuvir + PR for 12 weeks in HCV/HIV Coinfection:Treatment Outcomes

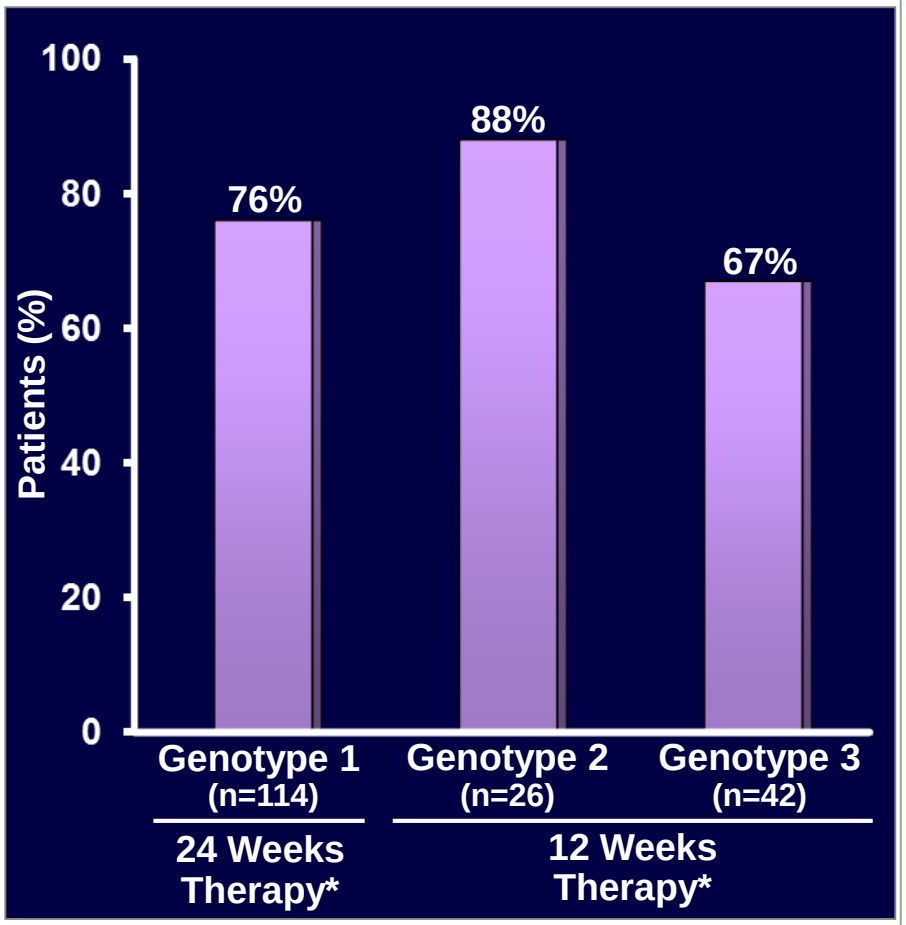
- No change in ART regimens
- SVR12 rates by ART regimen
  - PI: 93%
  - NNRTI: 91%
  - Raltegravir: 100%
- No on-treatment breakthroughs
- Relapse (n=1)
- HIV breakthroughs (n=2)
- Discontinuations due to adverse events: 9%
- Most common adverse events
  - Anemia (52%), fatigue (35%), neutropenia (17%), thrombocytopenia (17%), myalgia (13%)
  - Hyperbilirubinemia (17%)



Rodriguez-Torres M, et al. IDWeek 2013. Abstract 714.

PHOTON-1 Study: Treatment Outcomes

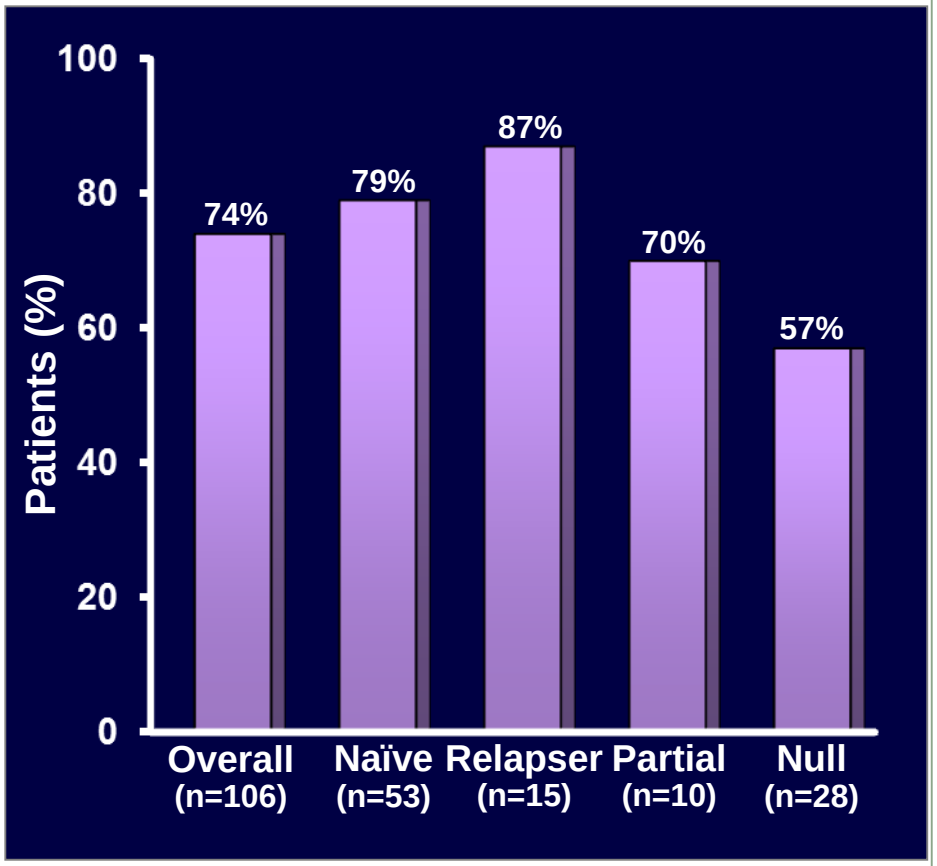
- SVR12 rates in genotype 1
  - Similar regardless of baseline HCV RNA, IL28b genotype, presence of cirrhosis, age, gender, race
  - Lower in genotype 1b versus 1a
- No resistance (deep sequencing) detected in virologic failures
- HIV breakthroughs (n=2)
- Discontinuations due to AEs: 3%
- Most common adverse events
  - Fatigue, insomnia, headache, nausea
  - Grade ≥3 hyperbilirubinemia in patients receiving atazanavir versus no atazanavir (13% versus 1%)
- SVR in treatment experienced pts receiving 24 weeks of therapy: 92% GT2 and 88% GT3



Sulkowski MS, et al. *Hepatology*. 2013;58(suppl 1):313A-314. Abstract 212.

Study C212: Simeprevir + PR in HCV/HIV Infection: GT 1

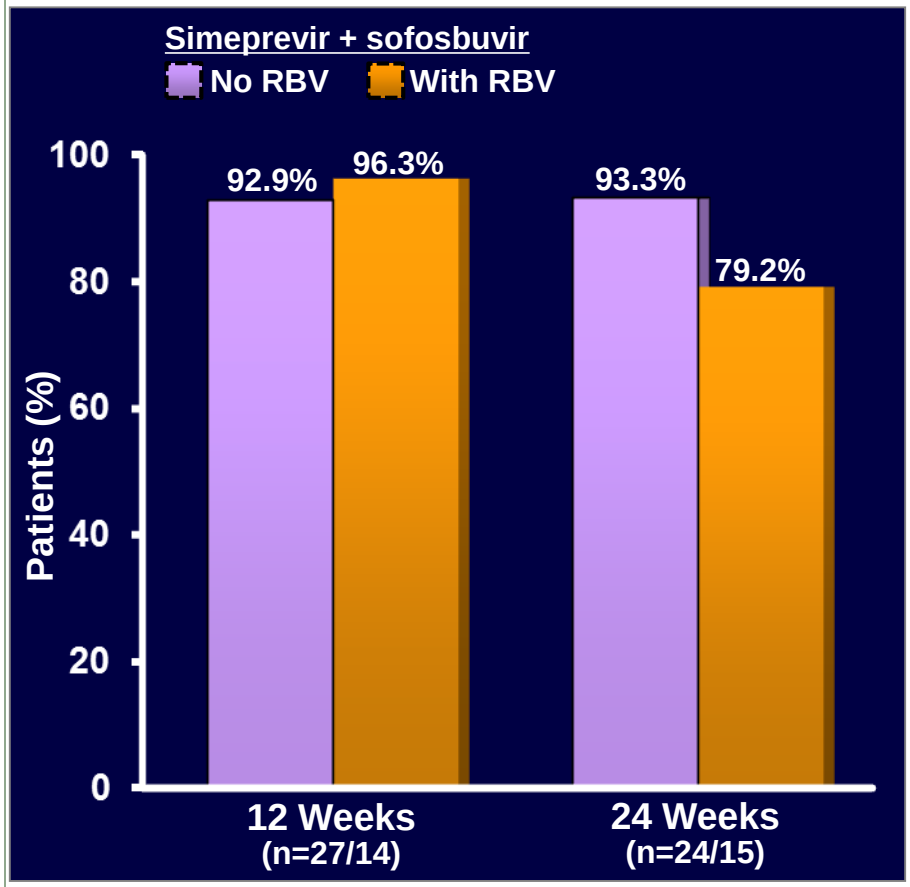
- Phase III open label. Naïve/Relapse (RGT arm) and PR null/partials (48 week tx)
- SVR12 rates in HCV/HIV coinfected were similar to HCV monoinfected trials
  - SVR12 rates were high, regardless of baseline METAVIR fibrosis score
  - SVR12 67% GT1a + Q80k vs. 89% GT1b
- Safety profile similar to monoinfected patients
  - Pruritus and photosensitivity in 20% and 2%, respectively
- Grade 3/4 hemoglobin: 1.9%



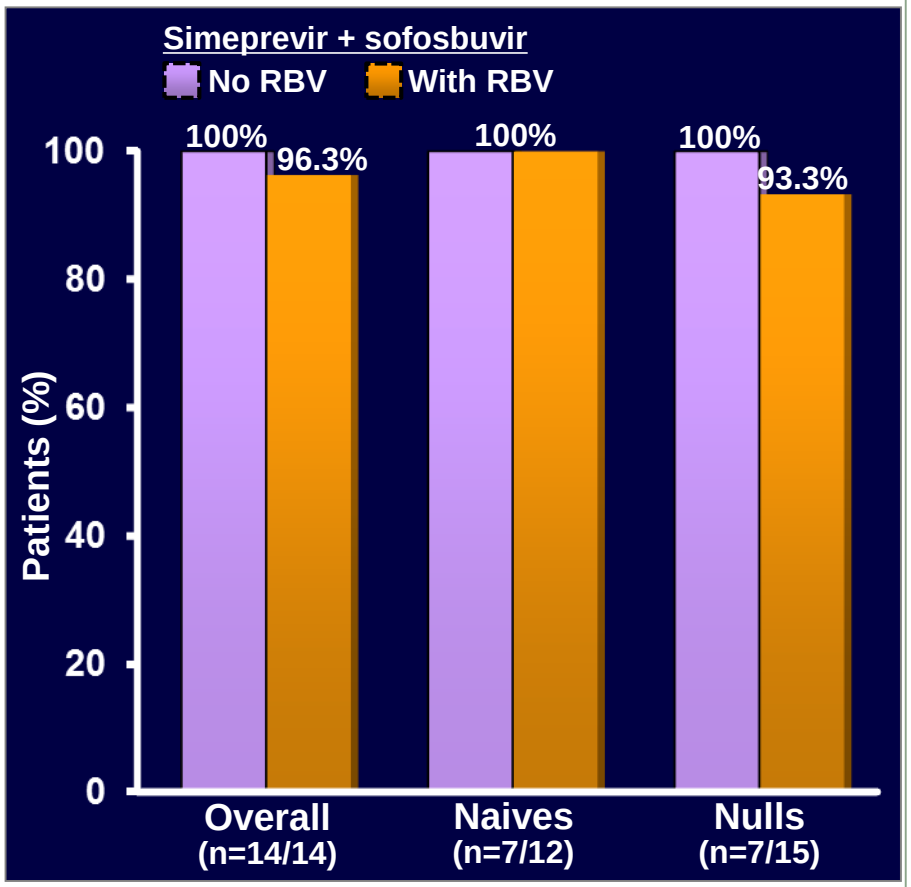
Dieterich D, et al. 14th EACS. Brussels, 2013. Abstract LBPS9/5.

COSMOS Study: Interim Results With Simeprevir + Sofosbuvir ± RBV in HCV Monoinfection

SVR12: No Cirrhosis (F0-F2)
(Prior PR Null Responders)



Cirrhosis (F3-F4)*
(Naives and Prior PR Null Responders)



Jacobson IM, et al. *Hepatology*. 2013;58(suppl 1):73A. Abstract LB-3.

Timing of Treatment

HIV/HCV Coinfection: Who to Treat

- All HCV/HIV coinfected patients are candidates for HCV therapy
- Consider comorbid conditions that limit life expectancy or increase the risks associated with HCV therapy
- HCV cure may decrease risk of ART-associated liver injury
- HIV disease should be stable with or without ART
- IFN-based regimens
  - Defer HCV treatment if CD4 <200 cells/mm^3
  - Interferon can exacerbate pre-existing mental illness
    - Evaluate patients with underlying psychiatric disease before initiating HCV treatment
- Decompensated cirrhosis
  - Refer to medical practitioner with expertise
- Substance abuse
  - Active substance abuse is not a contraindication
  - Associated with high rates of treatment nonadherence and may compromise treatment outcomes

AASLD and IDSA. Available at: http://www.hcvguidelines.org/full-report-view. Version January 29, 2014.
Sulkowski MS, et al. *J Viral Hepatitis*. 2007;14:371-386.

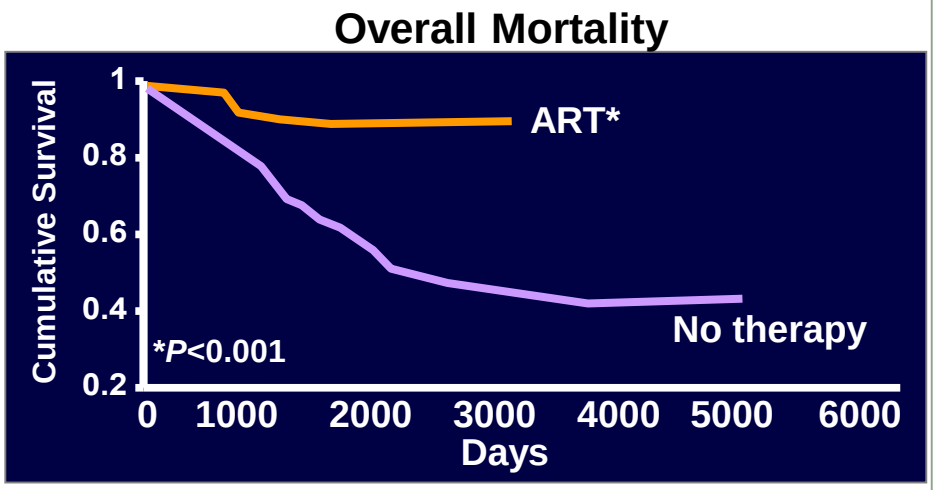
Specific Risks of Deferring Therapy in HIV/HCV-Coinfected Patients

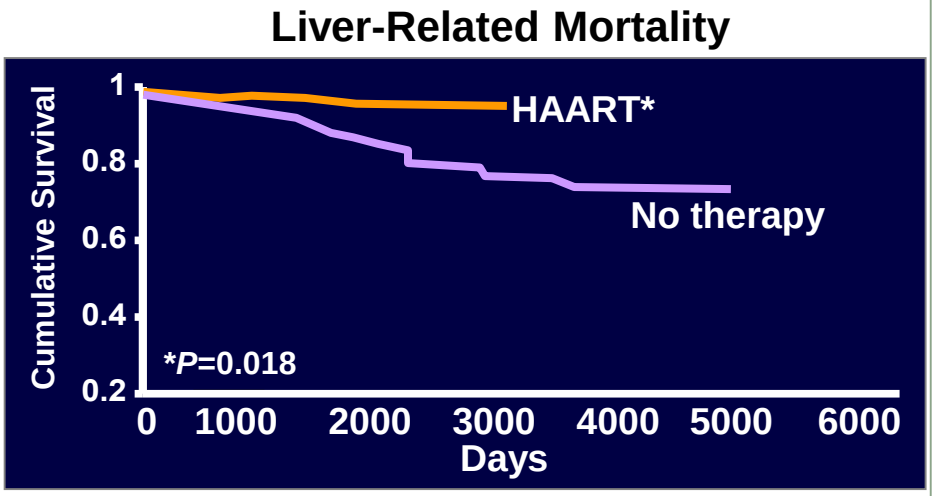
- Accelerated rate of HCV-related hepatic fibrosis progression in coinfected patients with increasing immune deficiency
  - Progression to cirrhosis risk 3-fold higher in coinfected vs HCV-monoinfected patients
  - Relative risk of decompensated liver disease 6-fold higher in coinfected vs HCV-monoinfected patients
  - HCC occurs earlier and more aggressive
- Coinfected patients have reduced access to liver transplantation and reduced survival
- ART may delay liver disease progression

Taylor LE, et al. Clin Infect Dis. 2012;55(suppl 1:S33-42). DHHS Antiretroviral Guidelines for Adults and Adolescents. February 2013. Naggie S, et al. Gastroenterology. 2012;142:1324-1334.
Macías J, et al. Clin Infect Dis. 2013;57:1401-1408.

Bonn Cohort: Benefits of ART on Mortality in HCV/HIV-Coinfection

- HCV/HIV-coinfected patients (n=285)
- Liver-related mortality rates (per 100 person-years)
- With ART: 0.45
  - No ART: 1.70
  - Predictors for increased liver-related mortality
- No ART
  - Low CD4 cell count
  - Increasing age
- ART therapy can slow fibrosis progression and decrease mortality in coinfection

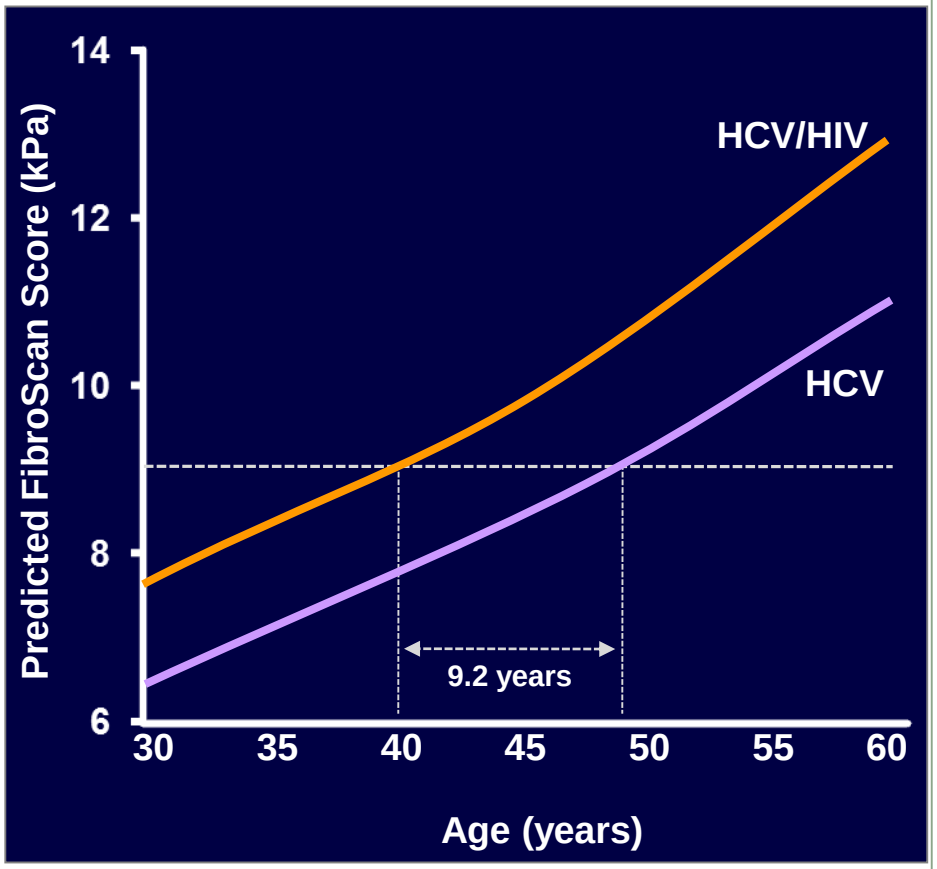




Qurishi N, et al. *Lancet*. 2003:362:1708-1713.

ALIVE Study: HIV, Age, and Severity of HCV-Related Liver Diseases

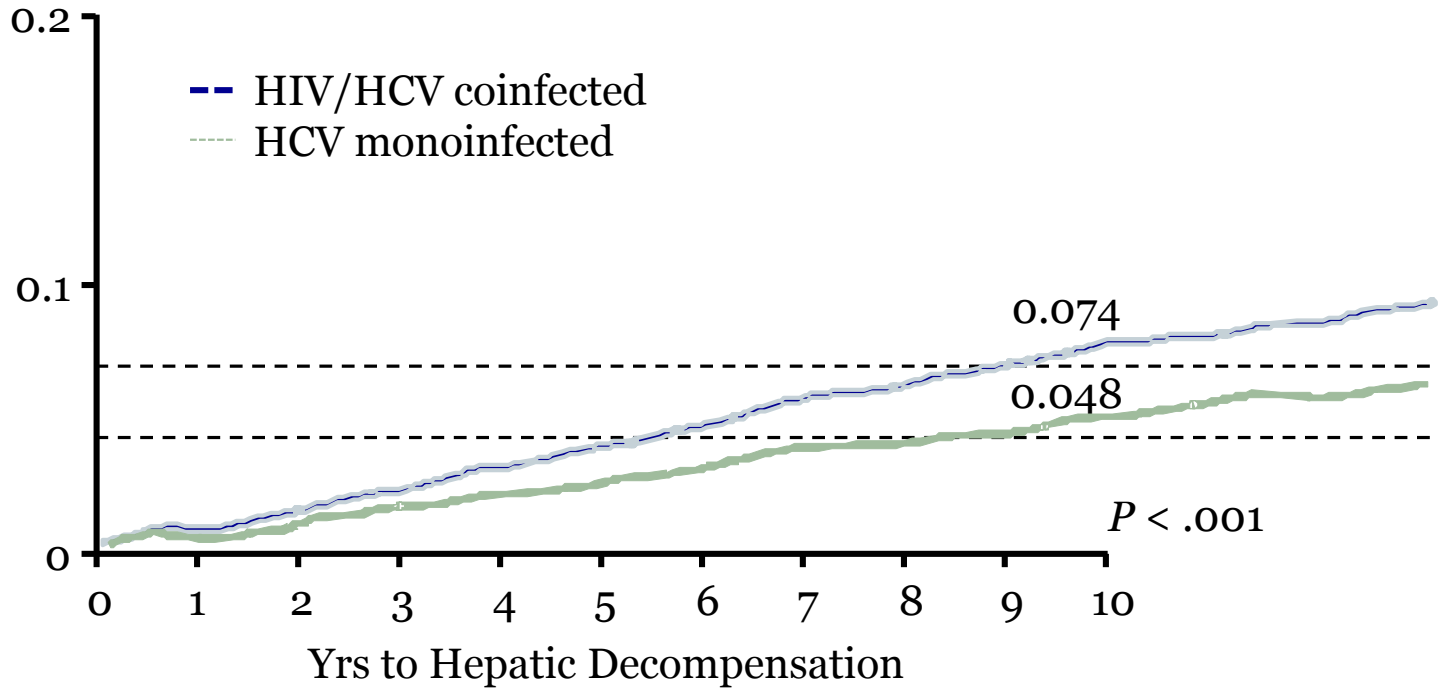
- Prospective cohort of HCV-infected IDUs (2006-2011) (n=1176)
  - HIV co-infected (n=394)
  - Baseline and semi-annual elastography
- Fibrosis was significantly greater in HCV/HIV co-infected versus HCV monoinfection (*P*<0.001)
  - No cirrhosis (12.9% versus 9.5%)
  - With cirrhosis (19.5% versus 11.0%)
  - Independently associated with increasing age and HIV infection
- HCV/HIV patients have liver fibrosis similar to HCV mono-infected patients who are nearly 10 years older



Kirk GD, et al. *Ann Intern Med.* 2013;158:658-666.

HCV Coinfection vs Monoinfection: Cumulative Incidence of Decompensation

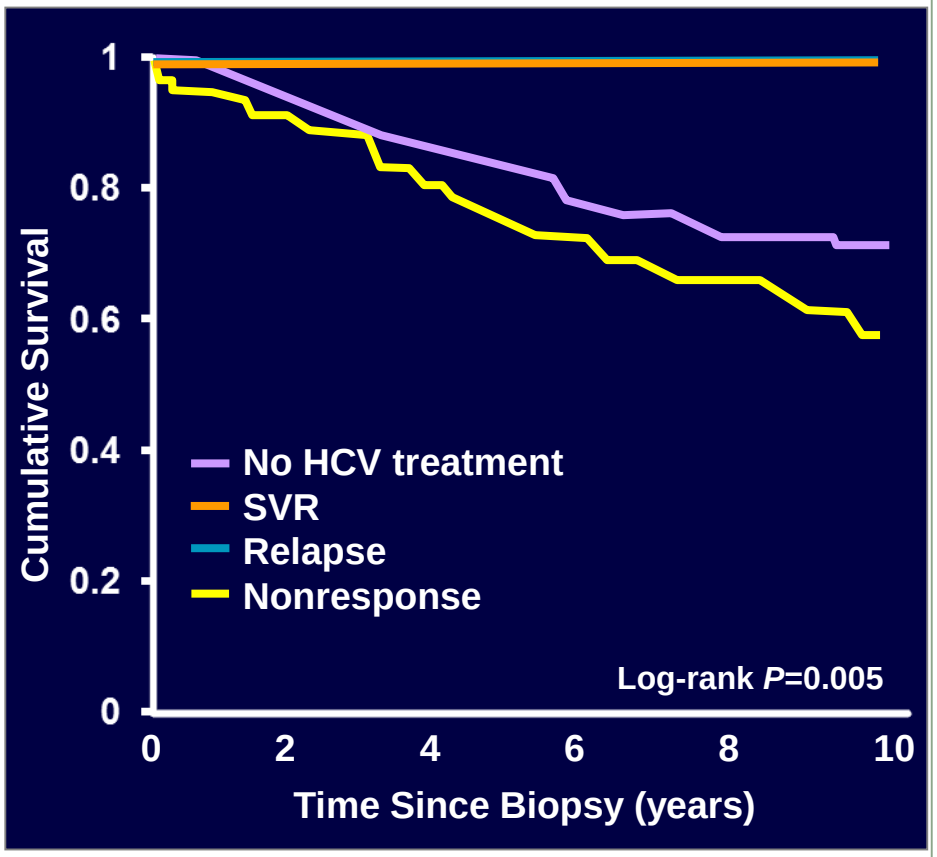
- 10-year hepatic decompensation risk 83% higher in coinfected patients
  - Adjusted HR 1.83 (95% CI: 1.54-2.18)



. Lo Re V, et al. IAC 2012. Abstract WEAB0102.

HCV Treatment and Incidence of ESLD, HCC, and Death

- Prospective US cohort (1993-2011) (n=638)
  - Liver biopsy at baseline
  - 35% underwent HCV treatment with PR
- Baseline ≥F2 versus <F2 fibrosis
  - Higher treatment rates: 54% versus 28% (*P*<0.001)
  - Similar SVR rates: 17% versus 16%
- No clinical events (ESLD, HCC, and death) among patients achieving SVR



Limketkai BN, et al. *JAMA*. 2012;308:370-378.

Assessing HIV+ Patients for Immediate or Deferred HCV Therapy

HCV Therapy in HIV/HCV-Coinfected, HCV Treatment-Naive Patients		
Liver Fibrosis	**Consider HCV Therapy**	**Eligible to Defer HCV Therapy**
No/minimal fibrosis (F0-F2)		●
Advanced fibrosis (F3-F4); cirrhosis[	●	

- Antiretroviral therapy for HIV treatment-naive HIV/HCV-coinfected patients
  - CD4+ cell count < 500 cells/mm^3: initiate antiretroviral therapy for HCV treatment optimization
  - CD4+ cell count > 500 cells/mm^3: may defer antiretroviral therapy until HCV therapy completed

EACS Guidelines, Version 7.0. October 2013. . DHHS Antiretroviral Guidelines for Adults and Adolescents. February 2013.
Macías J, et al. Clin Infect Dis. 2013;2013;57:1401-1408.

Staging of Liver Disease

- Staging is disease assessment with meaningful information for patients and providers
- Liver stage is the CD4 count of HCV
- Who and When to treat (i.e. now or later?)
- Screening for HCC and varices
- Modalities:
  - Liver biopsy
  - Blood markers,
  - Elastography,
  - Combination

Noninvasive Serum-Based Tests for Detection of Fibrosis

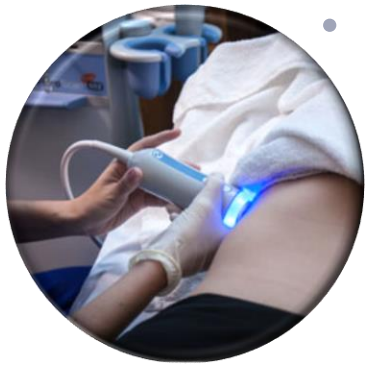
- *FibroTest*
  - Combines 5 markers: α_2-macroglobulin, haptoglobin, GGT, total bilirubin, and apolipoprotein A1
- *FibroSpect II*
  - Combines 3 markers: α2-macroglobulin, hyaluronic acid, and tissue inhibitor of metalloproteinase-1
- APRI
  - AST-to-platelets ratio index
- Forns fibrosis index
  - Age, platelet count, GGT, cholesterol
- FIB-4
  - Combines 4 markers: platelets, ALT, AST, and age

Validity of Noninvasive Methods of Detecting Cirrhosis

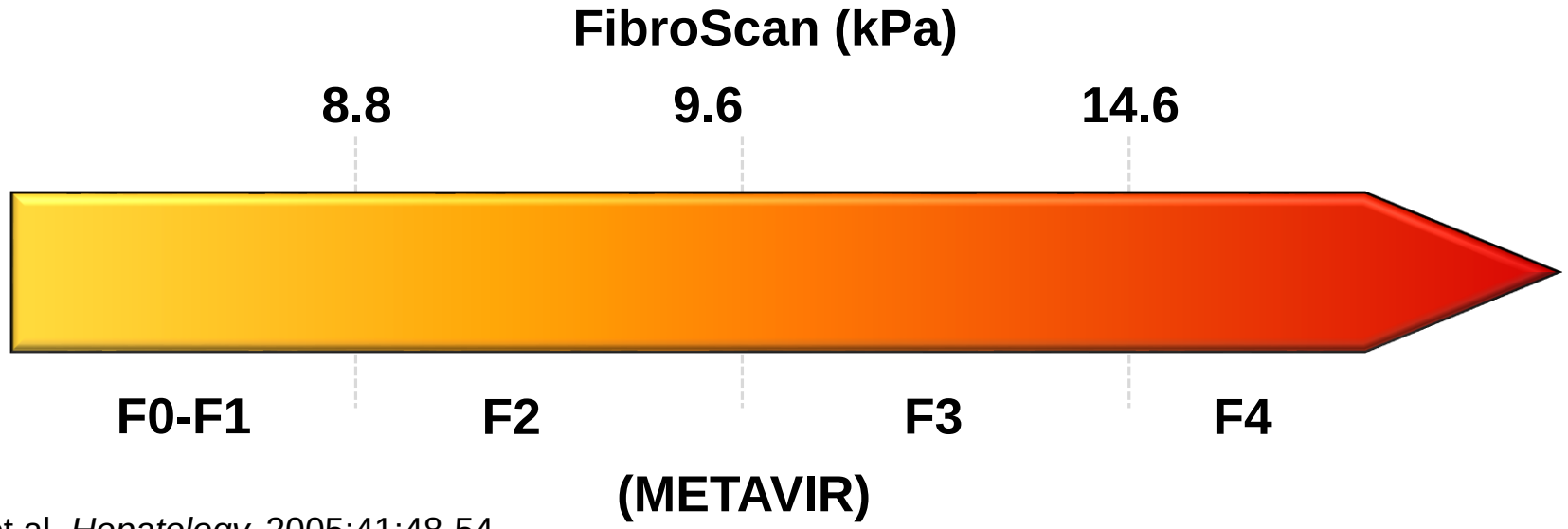
Test	% Sens	% Spec	AUROC	Pos LR	Neg LR
Fibrotest[1] >.56	85	74	.86	3.3	0.2
Fibrotest > .73	56	81	-	2.9	0.54
FIB4[2], >1.45	90	58	.87	2.1	0.17
APRI[3], >1.0	77	75	0.73	3.1	0.31
Forns[4], >4.2	98	27	87	1.3	0.07

Chou Ann Intern Med 2013

FibroScan (Elastography)



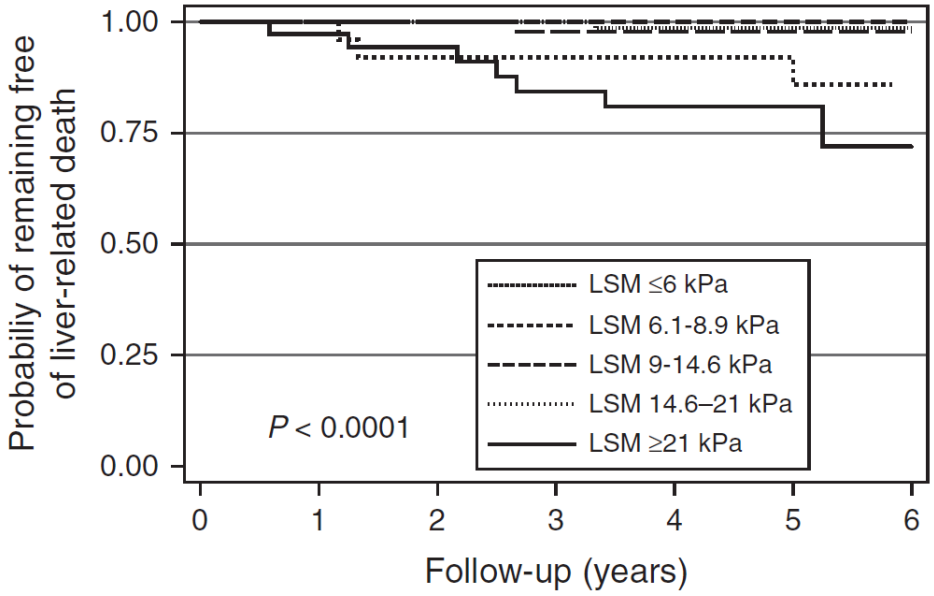
- **The probe induces an elastic wave through the liver**
- **The velocity of the wave is evaluated in a region located from 2.5 to 6.5 cm below the skin surface**
- **Diagnostic accuracy:**
  - **Significant fibrosis: 0.79**
  - **Advanced fibrosis: 0.91**
  - **Cirrhosis: 0.97**

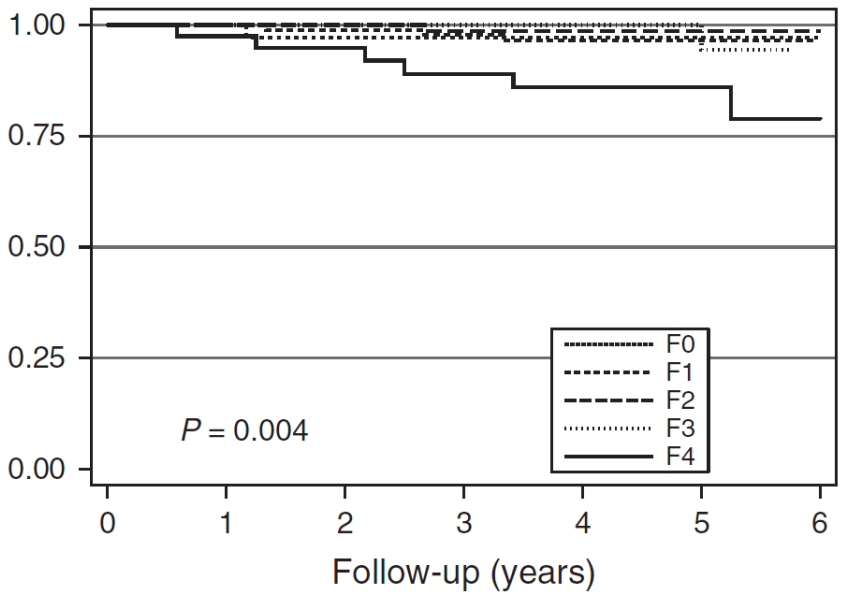


Ziol M, et al. *Hepatology.* 2005;41:48-54.

Which staging test should be done?

- 297 HIV/HCV coinfected patients with Liver Stiffness Model and biopsy within 12 months Dec 2005-Dec 2011.
- LSM-based models performed 8.4% better than liver biopsy prediction survival and liver-decompensation





Which staging test should be done?

- Elastography provides the most, currently useful information when valid
- Elastography and noninvasive can confidently rule out cirrhosis when concordant
- Serum alone may confidently rule out cirrhosis
- Biopsy done by specialists and when discordance or other questions
- Do something

Drug-Drug Interactions

DAA Drug Interactions

ARV	BOC	TPV	SMV	SOF*	DCV	FDV
ATV/r	CAUTION	STAND	CONTRA	STAND	↓ DCV	↓ FDV
DRV/r	CONTRA	CONTRA	CONTRA	STAND	N/A	↓ FDV
EFV	CONTRA	↑ TPV	CONTRA	STAND	↑ DCV	↑ FDV
RPV	STAND	CAUTION	STAND	STAND	STAND	N/A
ETV	CAUTION	CAUTION	CONTRA	STAND	N/A	N/A
RGV	STAND	STAND	STAND	STAND	STAND	STAND
DGV	N/A	N/A	CAUTION	STAND	N/A	N/A
MVC	↓ MVC	↓ MVC	STAND	STAND	STAND	STAND

*Tipranavir CONTRA with SOF

Ouwerkerk-Mahadevan et al. IDSA 2012 Abstract #49; Hulskotte et al. Clin Infect Dis 2013; de Kanter et al. CROI 2012; Bifano et al. CROI 2012; Kirby et al. AASLD 2012

AASLD and IDSA Guidelines: Preferred HCV Regimens in HCV/HIV Coinfection

Genotype 1	
HCV treatment-naïve and prior PR relapsers	
IFN eligible	Sofosbuvir + PR 12 weeks
IFN ineligible	Sofosbuvir + RBV 24 weeks
	Sofosbuvir + simeprevir† + RBV 12 weeks
HCV treatment experienced*	Sofosbuvir + simeprevir† + RBV 12 weeks
Genotype 2	
Regardless of HCV treatment history	Sofosbuvir + RBV 12 weeks
Genotype 3	
Regardless of HCV treatment history	Sofosbuvir + RBV 24 weeks
Genotype 4	
Regardless of HCV treatment history	
IFN eligible	Sofosbuvir + PR 12 weeks
IFN ineligible	Sofosbuvir + RBV 24 weeks
Genotypes 5 or 6	
Regardless of HCV treatment history	Sofosbuvir + PR 12 weeks

Allowable ART: **Sofosbuvir: all except the NRTIs didanosine and zidovudine.**
Simeprevir: INSTI (raltegravir); NNRTI (rilpivirine); Entry/Fusion Inhibitor (maraviroc, enfuvirtide); NRTIs (tenofovir, emtricitabine, lamivudine, abacavir).

AASLD and IDSA. Available at: http://www.hcvguidelines.org/full-report-view. Version January 29, 2014.

AASLD and IDSA Guidelines: Alternative HCV Regimens in HCV/HIV Coinfection

Genotype 1	
HCV treatment-naïve and prior PR relapsers	
IFN eligible	Simeprevir† 12 weeks + PR 24 weeks
IFN ineligible	None
HCV treatment experienced*	
IFN eligible	Sofosbuvir + PR 12 weeks
IFN ineligible	Sofosbuvir + RBV 24 weeks
Genotypes 2 or 3	
HCV treatment-naïve and prior PR relapsers	None
HCV treatment experienced*	
IFN eligible	Sofosbuvir + PR 12 weeks
IFN ineligible	None
Genotypes 4, 5, or 6	None

*Prior PR non-responders.

†For genotype 1a, baseline resistance testing for Q80K should be performed and alternative treatments considered if present.

Allowable ART: Sofosbuvir: all except the NRTIs didanosine and zidovudine.
Simeprevir: INSTI (raltegravir); NNRTI (rilpivirine); Entry/Fusion Inhibitor (maraviroc, enfuvirtide); NRTIs (tenofovir, emtricitabine, lamivudine, abacavir).

AASLD and IDSA. Available at: http://www.hcvguidelines.org/full-report-view. Version January 29, 2014.

AASLD and IDSA Guidelines: HCV Regimens Not Recommended in HCV/HIV Coinfection

Genotype 1

- Telaprevir + PR 24 or 48 weeks (RGT)
- Boceprevir + PR 28 or 48 weeks (RGT)
- PR 48 weeks
- Simeprevir 12 weeks + PR 48 weeks

Genotypes 2 or 3

- Any regimen with telaprevir, boceprevir, or simeprevir
- PR 24 to 48 weeks

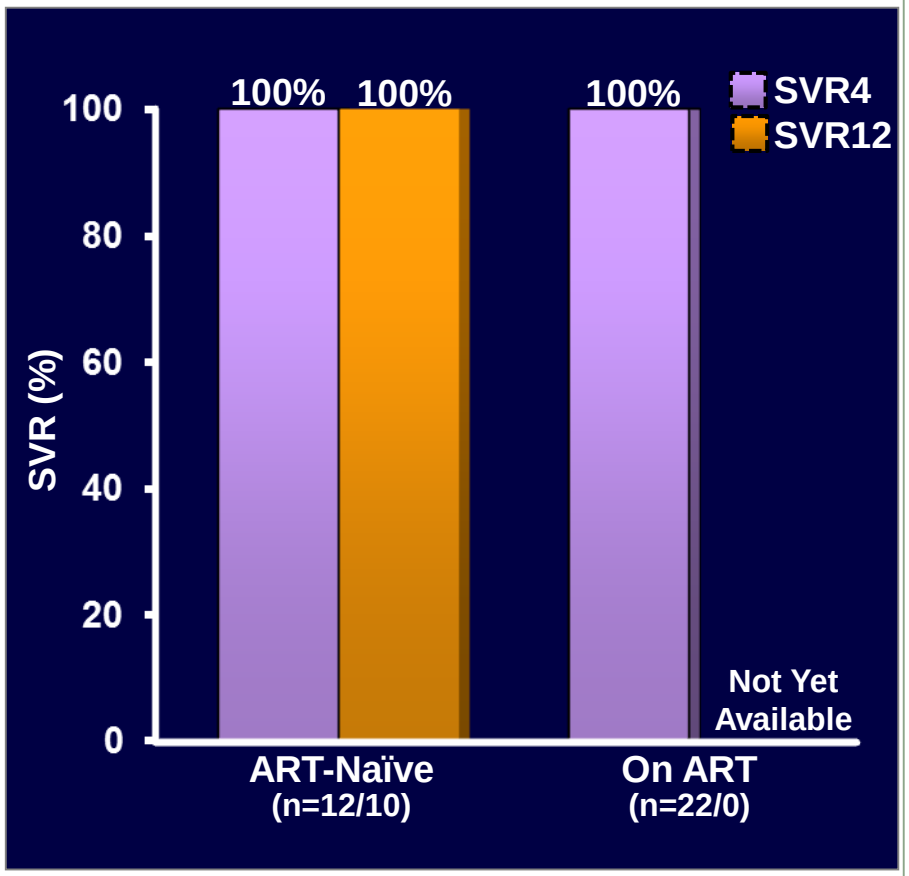
Genotypes 4, 5, or 6

- Any regimen with telaprevir, boceprevir, or simeprevir
- PR 48 weeks

AASLD and IDSA. Available at: http://www.hcvguidelines.org/full-report-view. Version January 29, 2014.

NIAID ERADICATE Study: Sofosbuvir/Ledipasvir in HCV Genotype 1 With HIV Coinfection (Interim Analysis)

- No change within groups
  - CD4 counts or CD4 T-cell percentages
  - Serum creatinine or estimated GFR
- HIV RNA status during HCV treatment
  - ART-naïve: no clinically significant change
  - On ART: transient HIV RNA breakthrough (missed ART for 4 days), re-suppressed
  - No change within groups
- Sofosbuvir/ledipasvir was well tolerated
  - No deaths, grade 4 adverse events or discontinuations due to adverse events
  - Laboratory abnormalities
    - Grade 3: neutropenia (n=1), AST (n=1)
    - Grade 4: creatinine phosphatase (n=1)



Osinusi A, et al. *J Hepatol*. 2014;60(suppl 1):S7. Abstract O14.

HCV/HIV Coinfection: Summary

- Liver disease is a leading cause of morbidity and mortality
- Controlling HIV with ART may slow progression of HCV-related liver disease
- All HIV patients should be screened for HCV
- First-generation PIs + PR regimens present significant challenges and limitations
- Newer, once-daily DAAs
  - Simplify and shorten duration of regimens
  - Improve SVR rates with fewer adverse events
  - Minimize drug-drug interactions