AETC AIDS Education & Training Center Program Southeast

HIV/HCV Coinfection:

Why It Matters and What To Do About It

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Disclosures

- I have no relevant financial disclosures.

Objectives

At the end of this lecture, the learner will be able to:

- Understand how HIV coinfection impacts the natural history of hepatitis C virus (HCV)
- Describe appropriate HCV direct-acting antiviral (DAA) therapies for the treatment of HIV/HCV coinfection
- Recognize the potential for DAA drug-drug interactions, particularly with HIV antiretroviral therapy
- Participate in case discussions regarding HCV therapy in HIV/HCV coinfection

Outline

- Impact of HCV Coinfection in HIV
- DAA Review
- Prescribing DAA Therapy for HIV/HCV Coinfection
- Cases

Outline

- **Impact of HCV Coinfection in HIV**
- DAA Review
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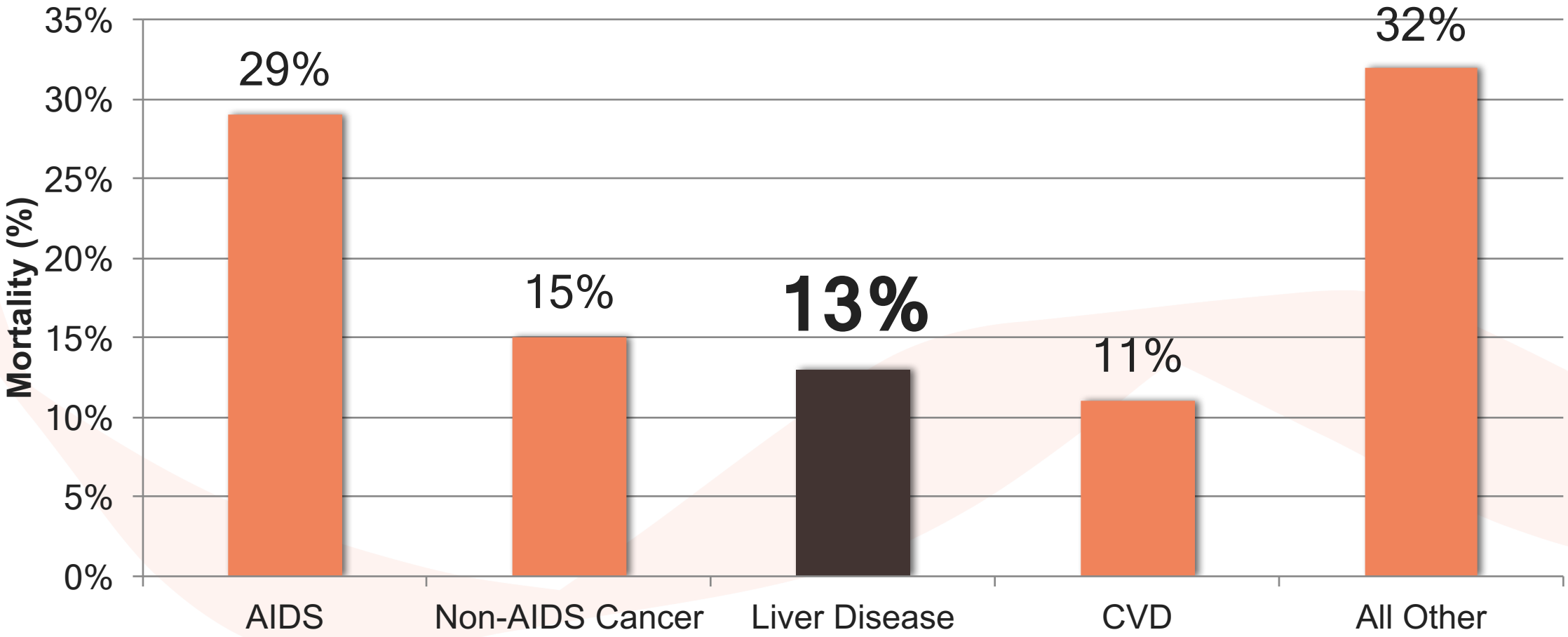
- Cases

Cause of Death in D:A:D Cohort



Smith CJ et al. *Lancet* 2014.

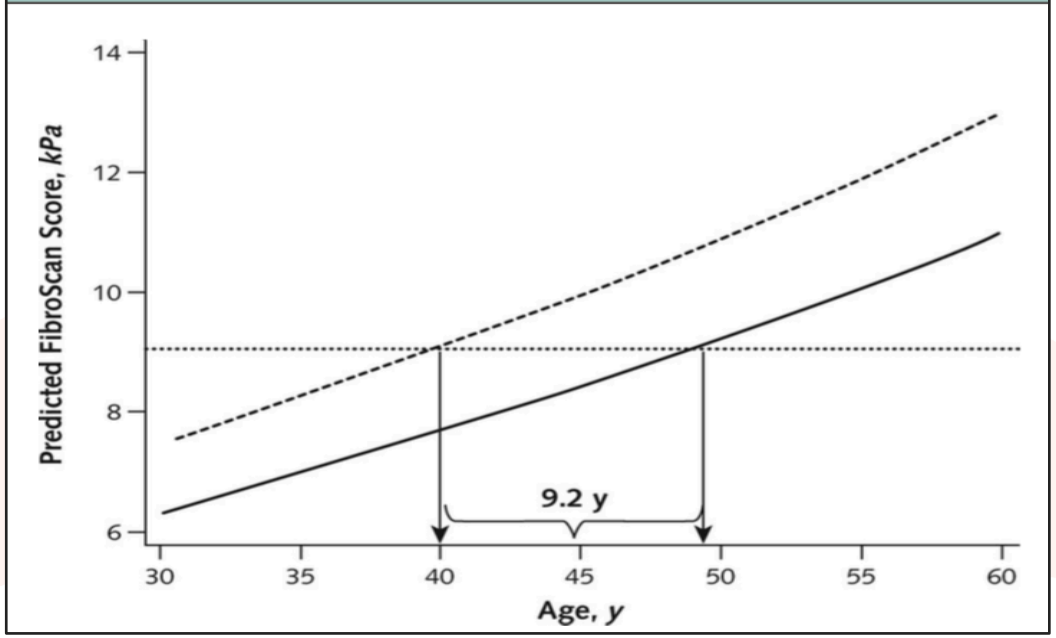
Factors Associated with HCV Accelerated Fibrosis Progression

Host	Viral
Nonmodifiable	HCV genotype 3
Fibrosis stage	Coinfection with hepatitis B virus or HIV
Inflammation grade	
Older age at time of infection	
Male sex	
Organ transplant	
Modifiable	
Alcohol consumption	
Nonalcoholic fatty liver disease	
Obesity	
Insulin resistance	

Fibrosis and Cirrhosis in HIV/HCV Coinfection

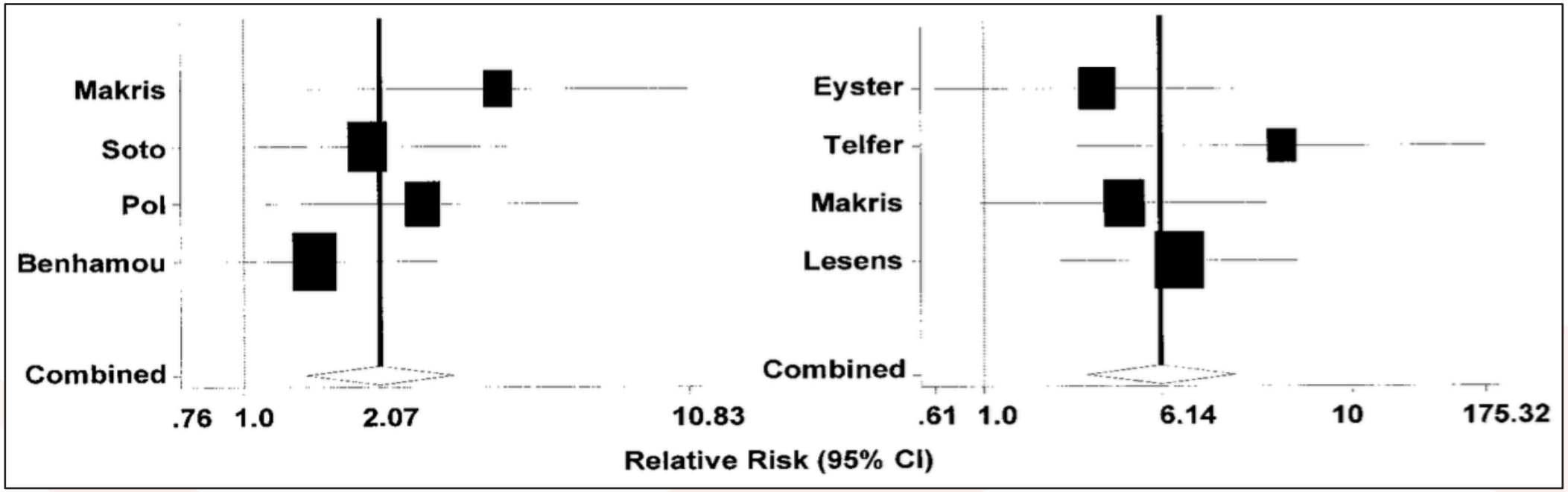
- Fibrosis and cirrhosis develop **more quickly** in HIV/HCV coinfected patients.
  - HIV is **independently associated** with advanced liver fibrosis and cirrhosis in HCV patients.
  - In one study, persons with HIV-HCV coinfection had liver fibrosis stages similar to persons with HCV monoinfection **a decade older**.
  - Severe cases of rapid decline to ESLD in HIV patients with recent HCV infection have been reported.

Figure 3. **Liver fibrosis and age among persons coinfected with HIV and HCV (*dashed line*) and those with only HCV (*solid line*).**



De Ledinghen et al. *J Viral Hepatitis* 2008.
Kirk GD et al. *Ann Int Med* 2013. // Fierer DS et al. *Clin Infect Dis* 2013.

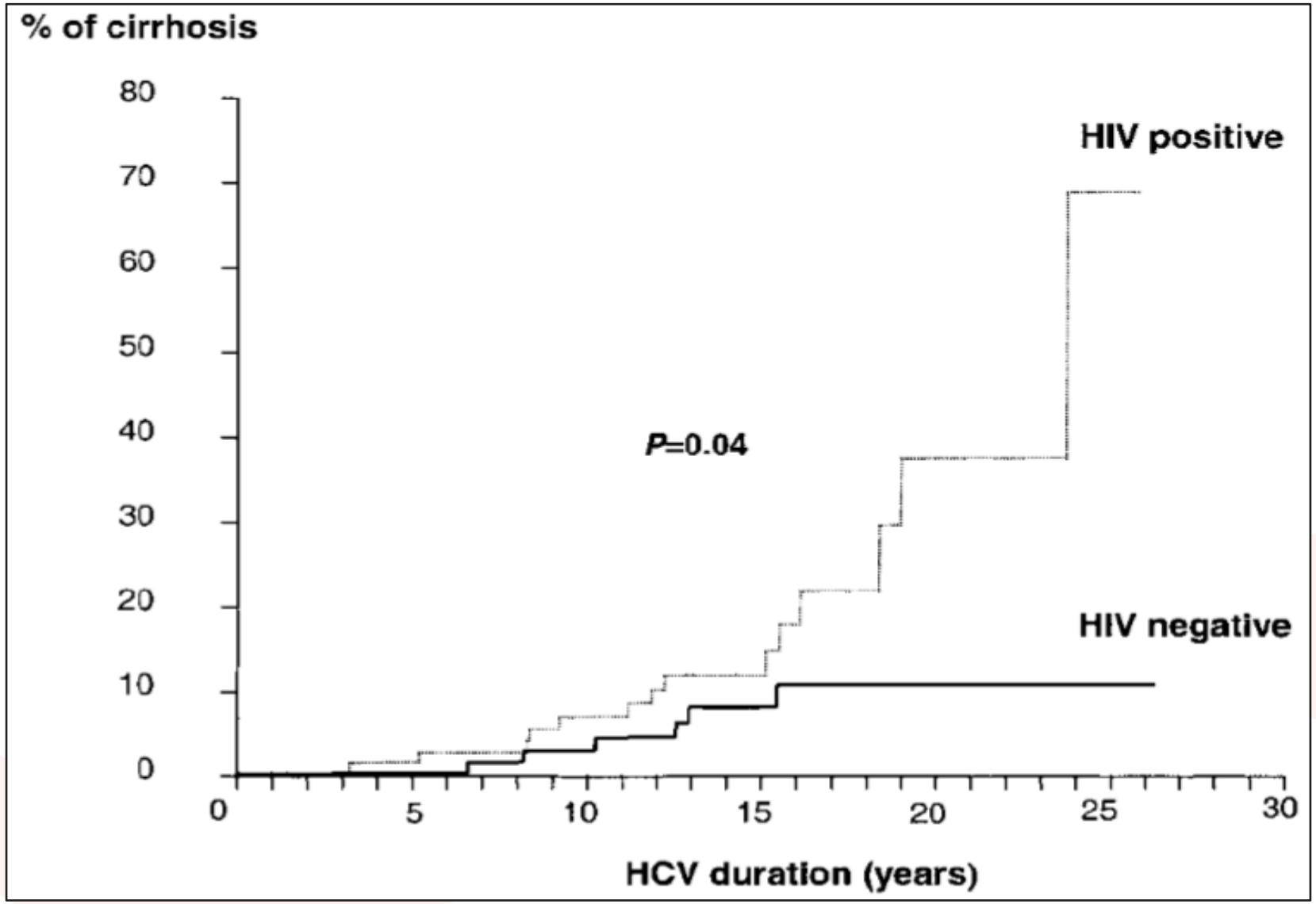
Meta-analysis of Impact of HIV on HCV Natural History



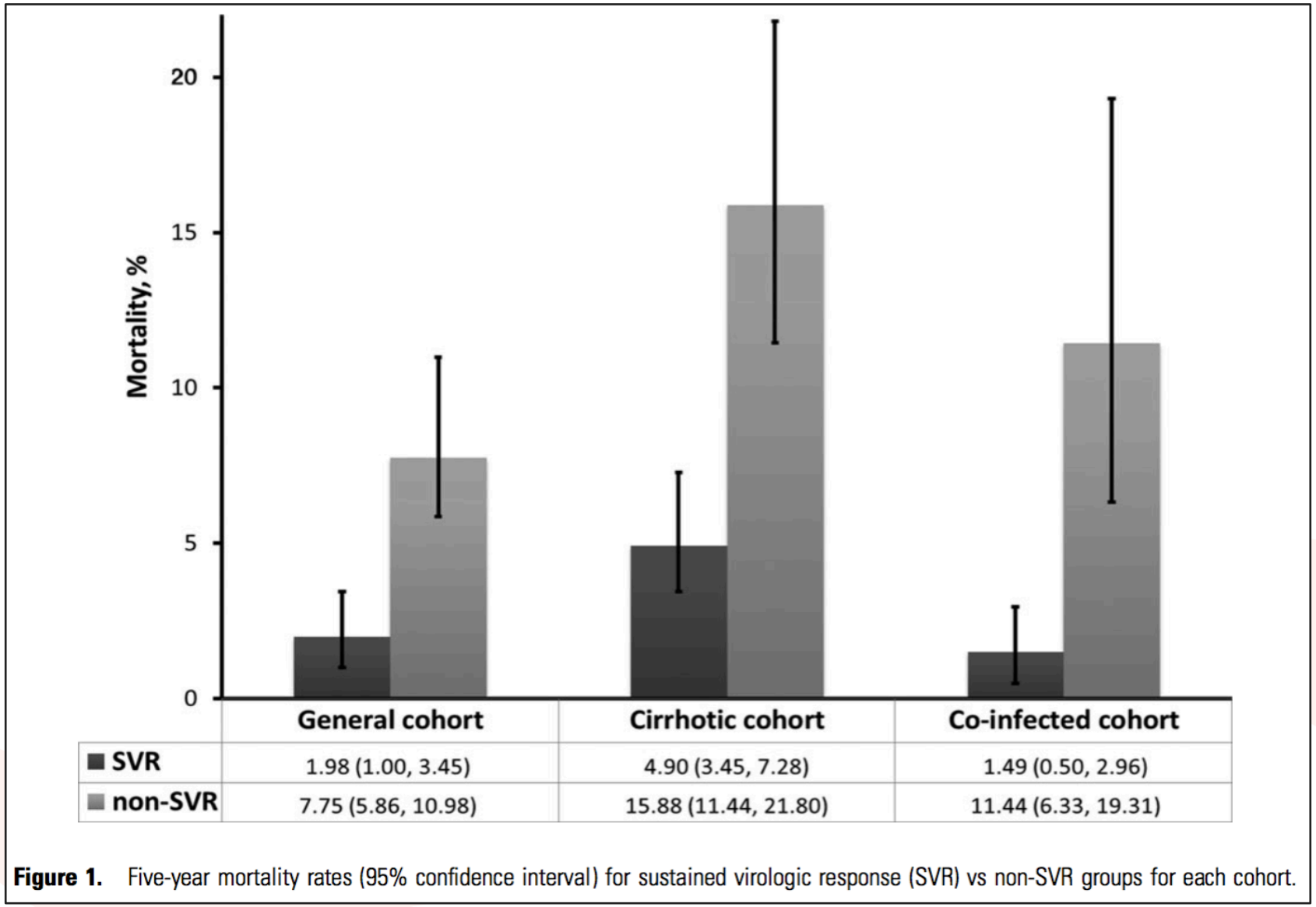
RR of Cirrhosis

RR of End Stage Liver Disease

Graham CS et al. *Clin Infect Dis* 2001.



Di Martino V et al. *Hepatology* 2001.

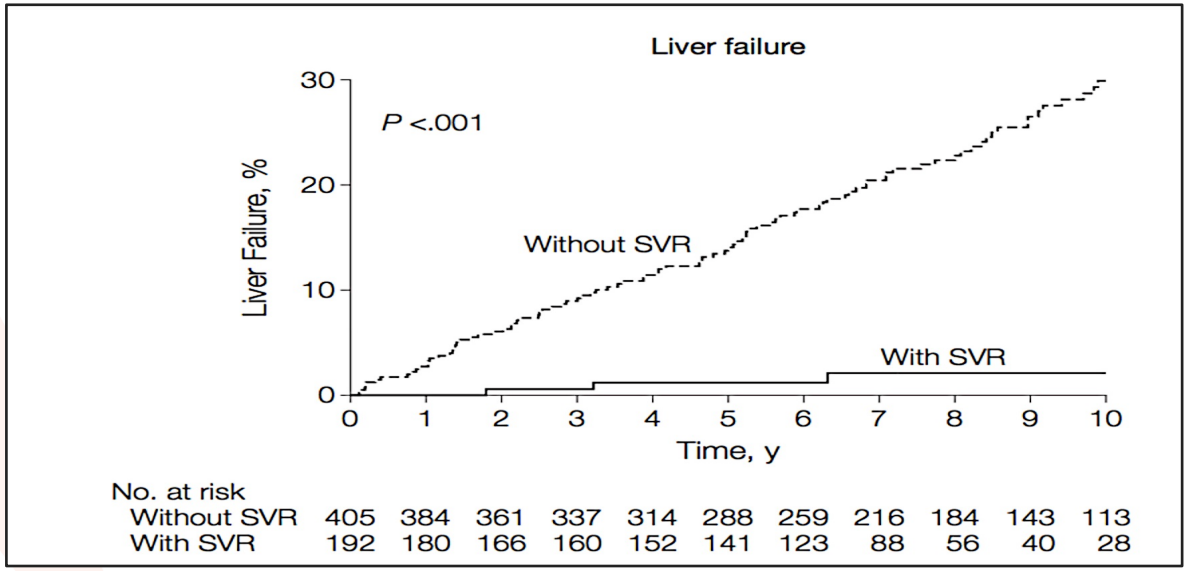


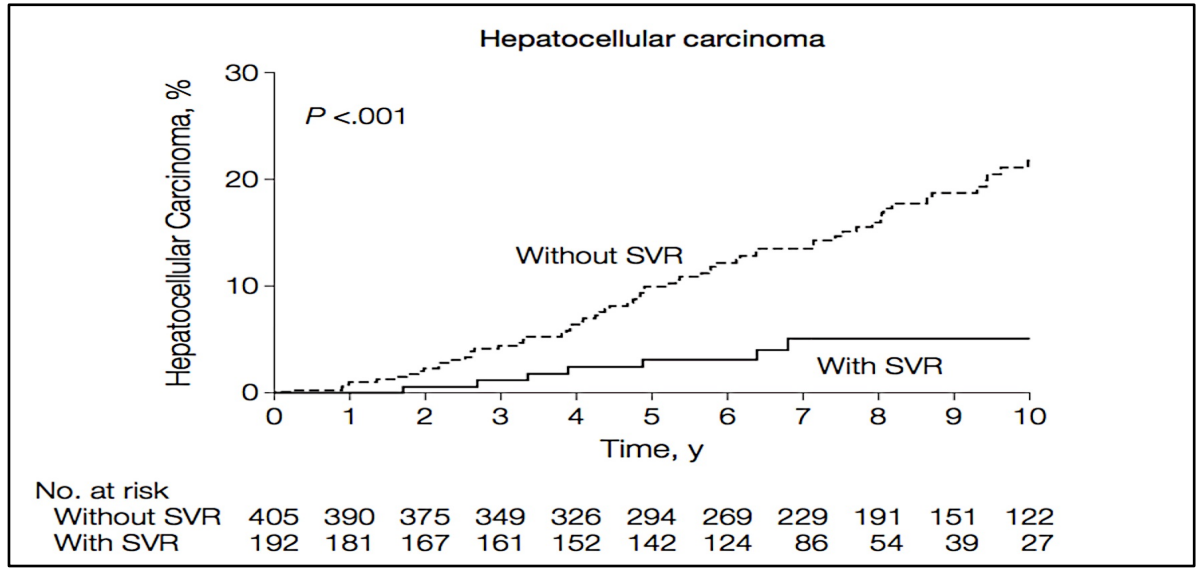
	General cohort	Cirrhotic cohort	Co-infected cohort
SVR	1.98 (1.00, 3.45)	4.90 (3.45, 7.28)	1.49 (0.50, 2.96)
non-SVR	7.75 (5.86, 10.98)	15.88 (11.44, 21.80)	11.44 (6.33, 19.31)

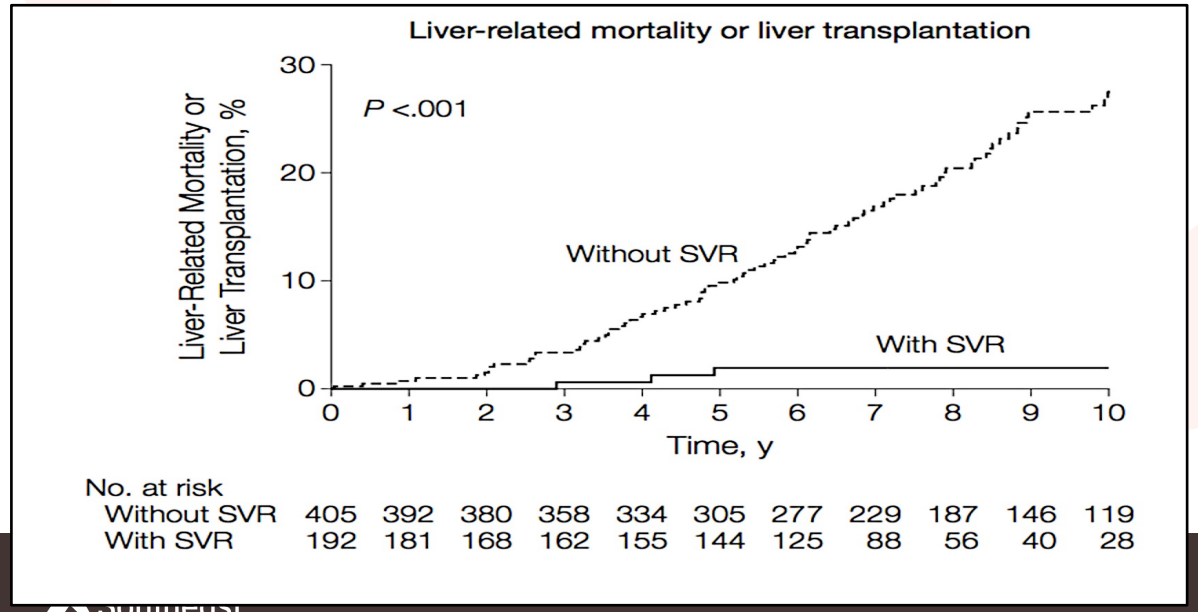
Figure 1. Five-year mortality rates (95% confidence interval) for sustained virologic response (SVR) vs non-SVR groups for each cohort.

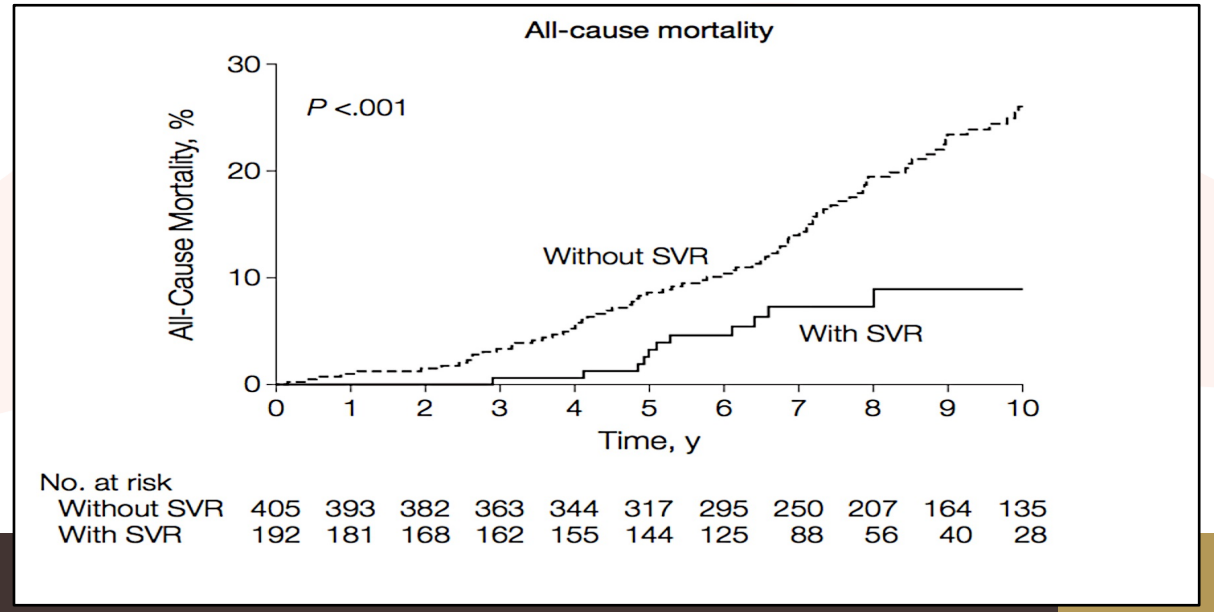
Simmons B et al. *Clin Infect Dis* 2016.

Why Should We Treat HCV?









Van der Meer AJ et al. *JAMA* 2012.

Why Should We Treat HIV/HCV Coinfection?

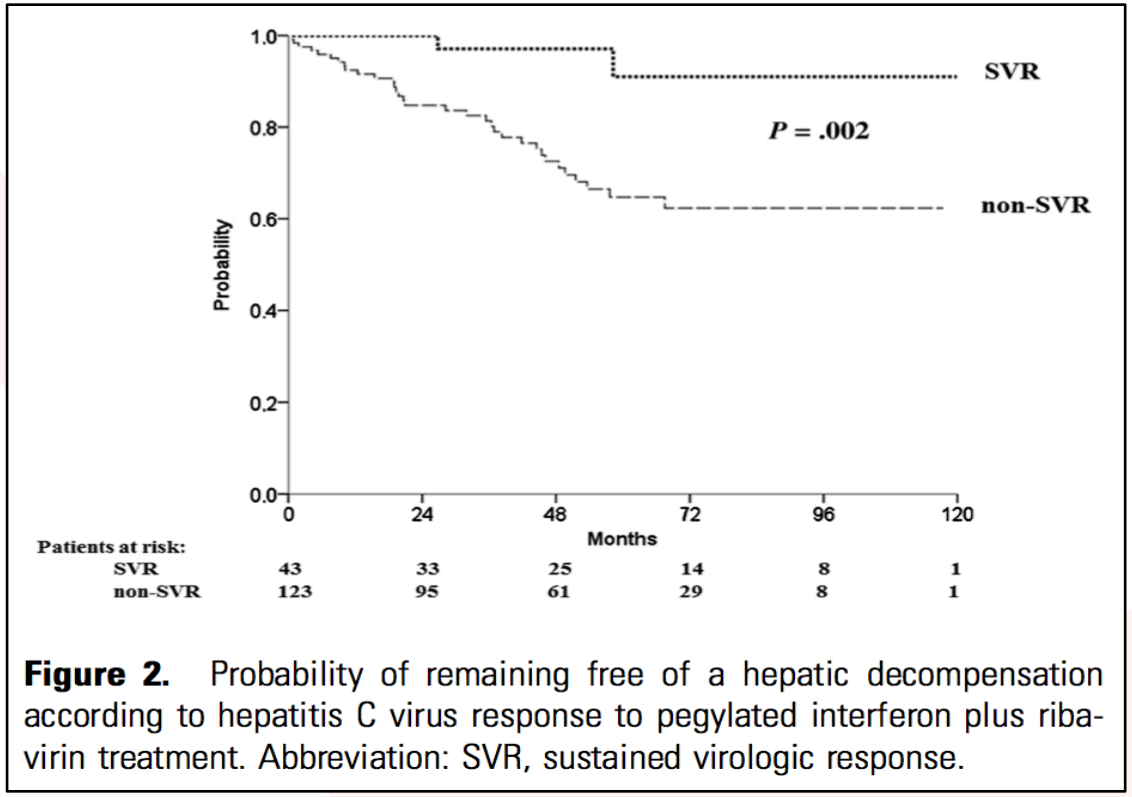


Figure 2. Probability of remaining free of a hepatic decompensation according to hepatitis C virus response to pegylated interferon plus ribavirin treatment. Abbreviation: SVR, sustained virologic response.

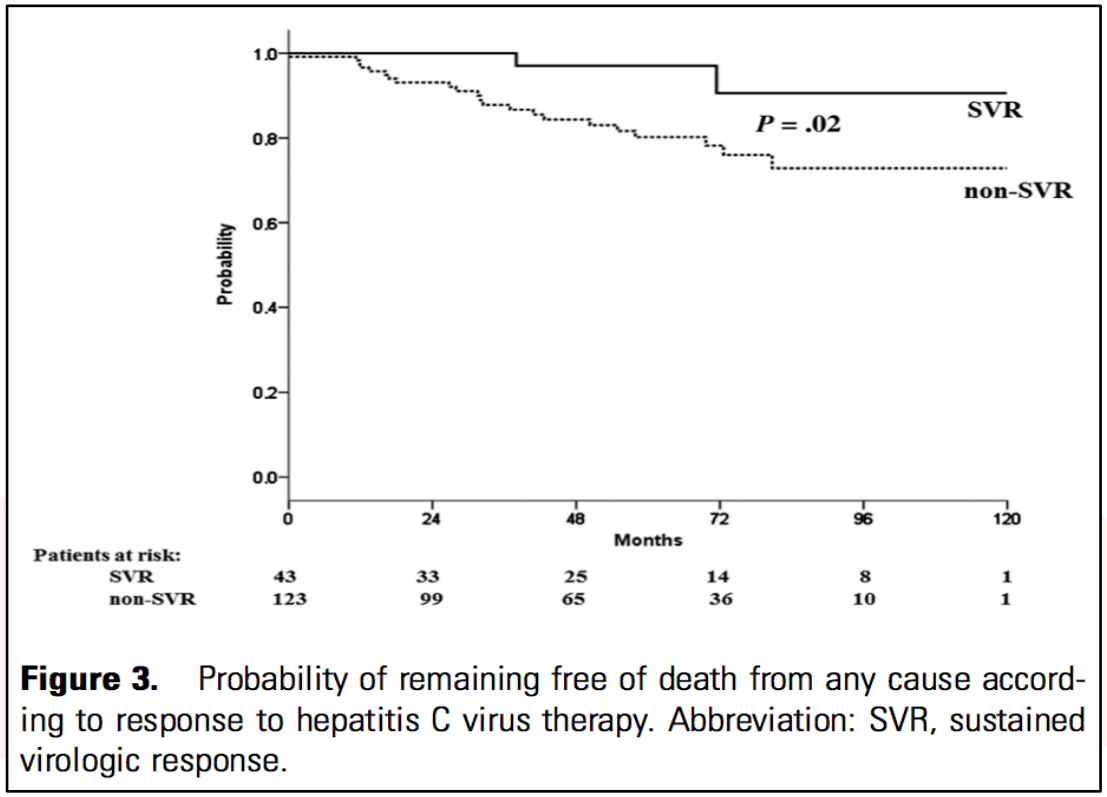


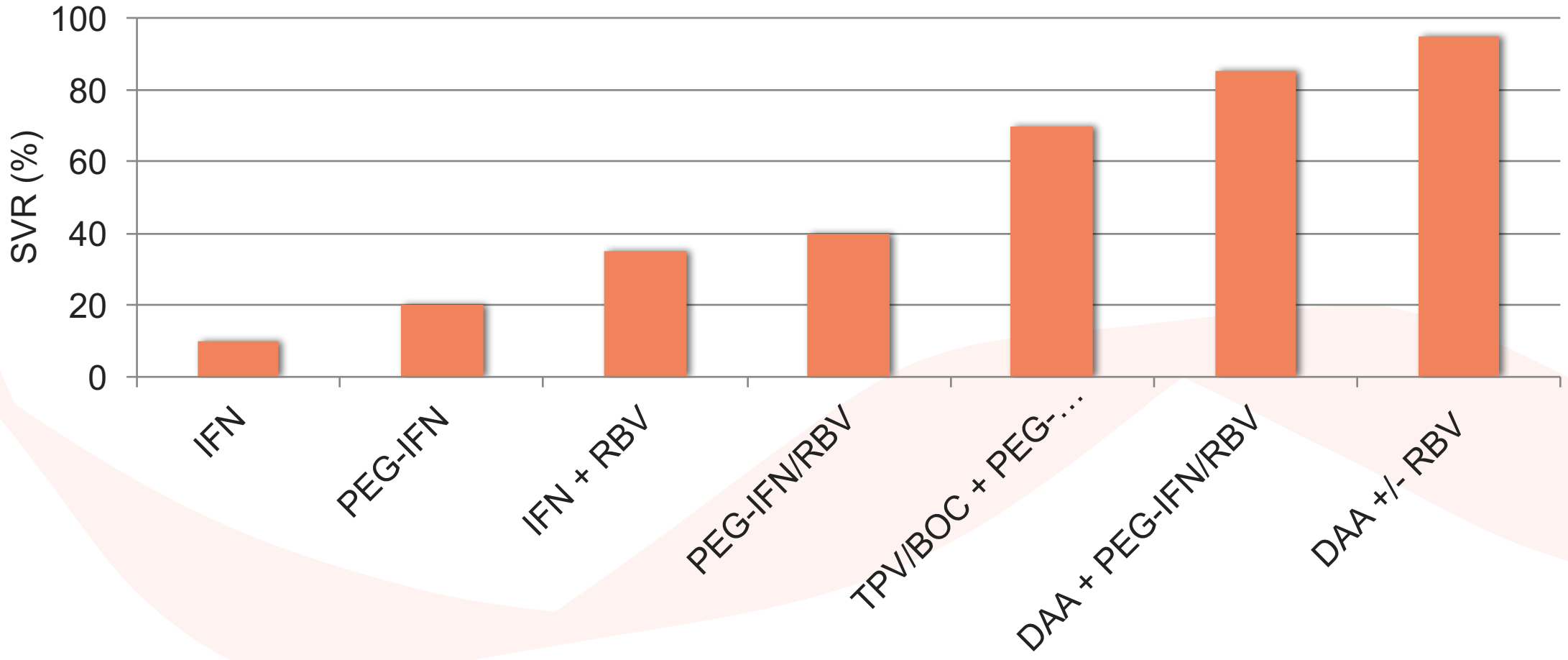
Figure 3. Probability of remaining free of death from any cause according to response to hepatitis C virus therapy. Abbreviation: SVR, sustained virologic response.

Mira JA et al. *Clin Infect Dis* 2013.

Outline

- Impact of HCV Coinfection in HIV
- **DAA Review**
- Prescribing DAA Therapy for HIV/HCV Coinfection
- Cases

Treatment Response in Direct Acting Antiviral (DAA) Era



HCV Therapies: The Past, Present, and Future

Pre-2011

IFN
PEG-IFN
RBV

July 2011

IFN
PEG-IFN
RBV
Telaprevir
Boceprevir

Nov-Dec 2013

IFN
PEG-IFN
RBV
Telaprevir
Boceprevir
Simeprevir
Sofosbuvir

Oct-Dec 2014

IFN
PEG-IFN
RBV
~~**Telaprevir**~~
Boceprevir
Simeprevir
Sofosbuvir
Ledipasvir
Paritaprevir
Ombitasvir
Dasabuvir

July 2015

IFN
PEG-IFN
RBV
~~Telaprevir~~
~~**Boceprevir**~~
Simeprevir
Sofosbuvir
Ledipasvir
Paritaprevir
Ombitasvir
Dasabuvir
Daclatasvir

Jan-Jun 2016

IFN
PEG-IFN
RBV
~~Telaprevir~~
~~Boceprevir~~
Simeprevir
Sofosbuvir
Ledipasvir
Paritaprevir
Ombitasvir
Dasabuvir
Daclatasvir
Elbasvir
Grazoprevir
Velpatasvir

FDA Approved HCV Therapies (10/2016)

NS3/4 Protease Inhibitors

~~Telaprevir (TPV)~~

~~Boceprevir (BOC)~~

Simeprevir (SMV)

Paritaprevir (PTV)

Grazoprevir (GZP)

NS5A Inhibitors

Ledipasvir (LDV)

Ombitasvir (OBV)

Daclatasvir (DCV)

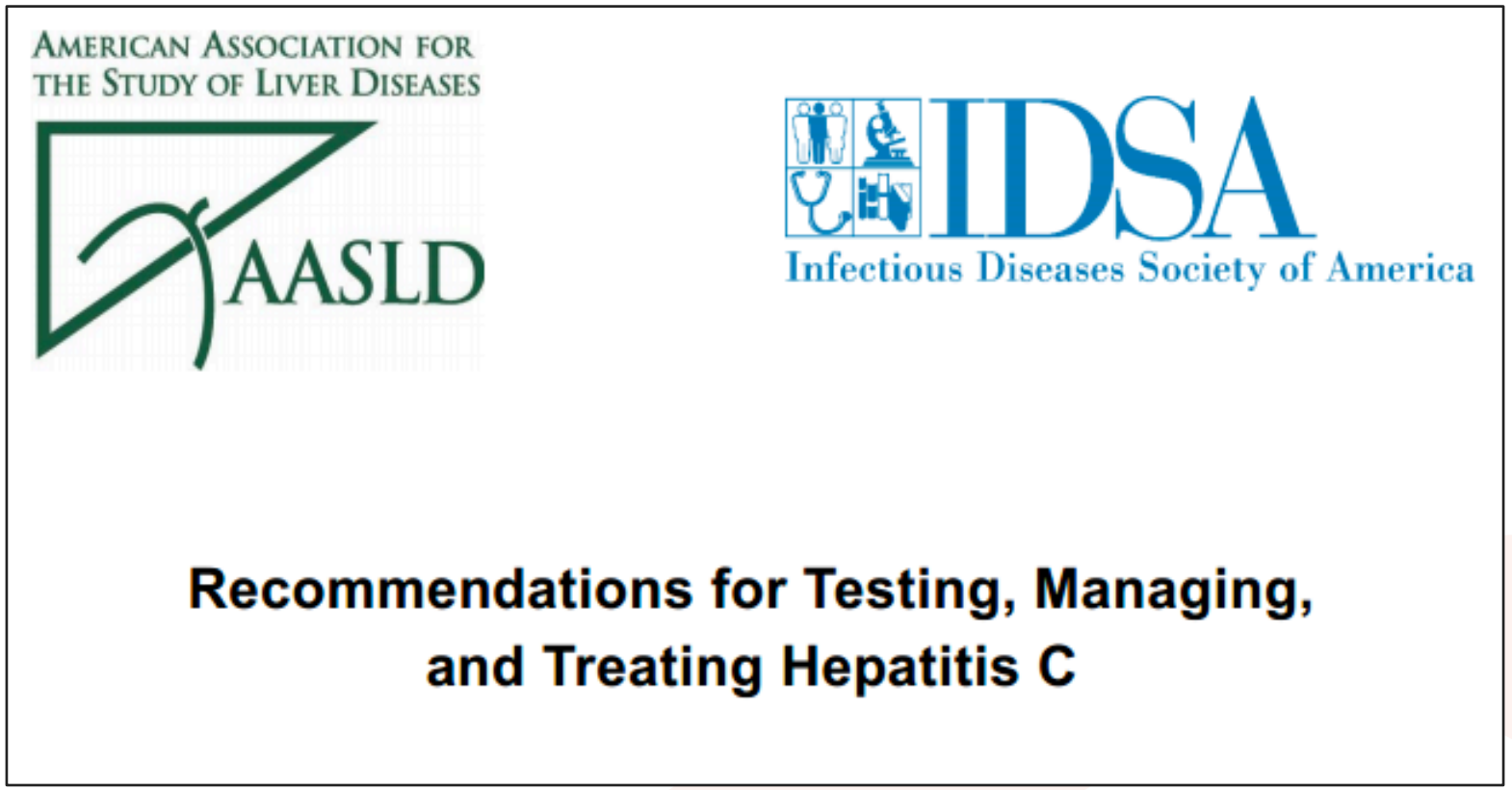
Elbasvir (EBR)

Velpatasvir (VEL)

NS5B Polymerase Inhibitors

Sofosbuvir (SOF)

Dasabuvir (DBV)



Released January 29, 2014, frequently updated, and available at www.hcvguidelines.org.

FDA Approved DAA Regimens for HCV Genotype (GT) 1

Elbasvir + Grazoprevir (Zepatier®) +/- RBV x 12-16 weeks

Paritaprevir/ritonavir + Ombitasvir + Dasabuvir (Viekira Pak®) +/- RBV x 12-24 weeks

Sofosbuvir (Sovaldi®) + Daclatasvir (Daklinza®) +/- RBV x 12-24 weeks

Sofosbuvir + Ledipasvir (Harvoni®) +/- RBV x 8-24 weeks

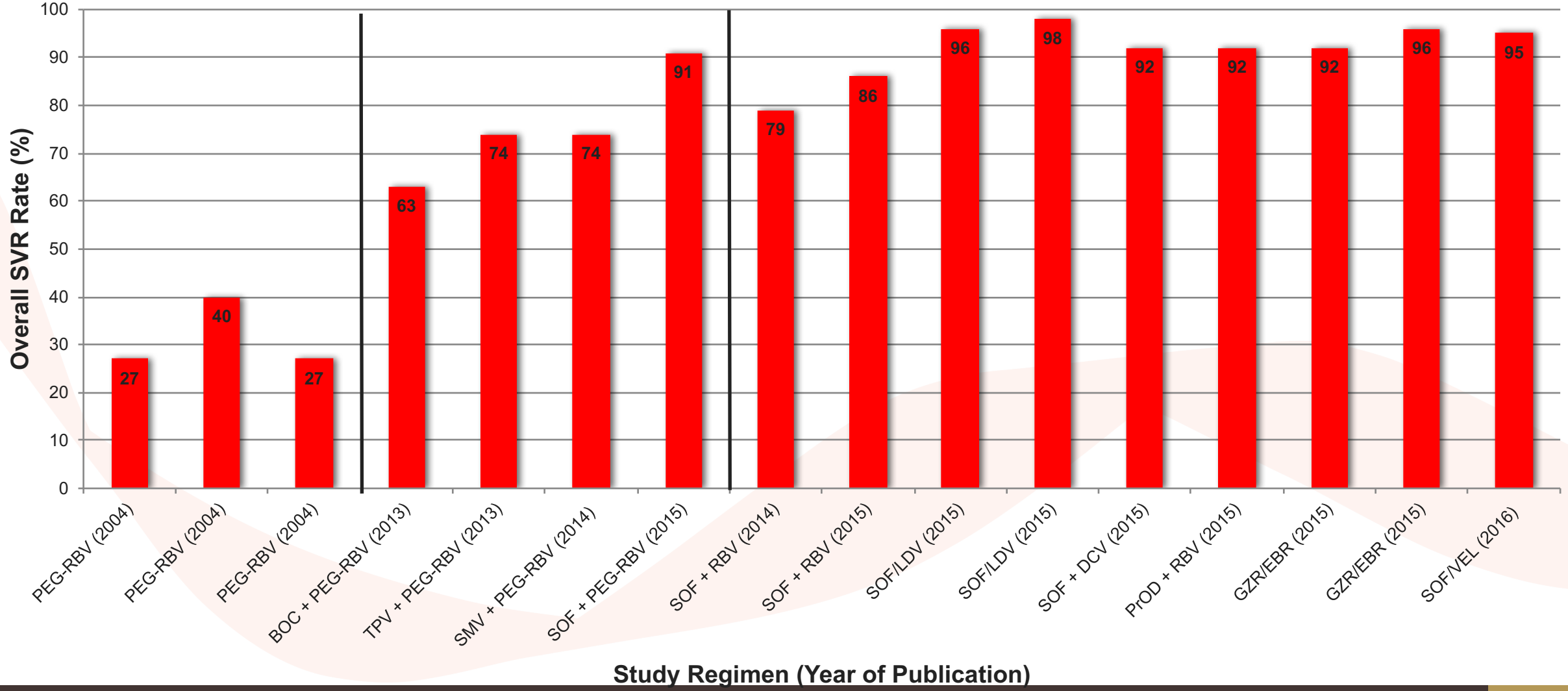
Sofosbuvir (Sovaldi®) + Simeprevir (Olysio®) +/- RBV x 12-24 weeks

Sofosbuvir + Velpatasvir (Epclusa®) +/- RBV x 12 weeks

FDA Approved DAA Regimens for HCV GT 2 and 3

- GT 2
  - **Sofosbuvir (Sovaldi®) + Daclatasvir (Daklinza®) x 12 weeks**
  - **Sofosbuvir + Velpatasvir (Epclusa®) +/- RBV x 12 weeks**
- GT 3
  - **Sofosbuvir (Sovaldi®) + Daclatasvir (Daklinza®) +/- RBV x 12-24 weeks**
  - **Sofosbuvir + Velpatasvir (Epclusa®) +/- RBV x 12 weeks**

Sustained Virologic Response (SVR) Rates in HIV/HCV Coinfection Trials



Bagwell A and Chastain CA. *Curr Treat Options Infect Dis* 2016.

Outline

- Impact of HCV Coinfection in HIV
- DAA Review
- **Prescribing DAA Therapy for HIV/HCV Coinfection**
- Cases

Treating HIV/HCV Coinfection

- Selection of DAA Therapy
- Drug-Drug Interactions
- Access

Selecting DAA Therapy for HIV/HCV Coinfection

- Same regimens as used for HCV monoinfection
- Efficacy similar between HCV monoinfection and HIV/HCV coinfection populations
- Selection based on genotype, stage, treatment history, and secondary factors (i.e. drug-drug interactions)

Drug-Drug Interactions

- Major issue for HIV/HCV coinfection
- Watch Out:
  - Ritonavir (used for both HIV and HCV treatment regimens)
  - Daclatasvir (dose adjustment may be necessary)
  - Tenofovir disoproxil fumarate (TDF)
    - Boosted protease inhibitors, dolutegravir, efavirenz, rilpivirine
    - Additional renal function monitoring
  - Older ART not studied with DAA therapy

	Sofosbuvir	Ledipasvir	Velpatasvir	Simeprevir	Daclatasvir	Elbasvir/ grazoprevir	Paritaprevir, ritonavir, ombitasvir plus dasabuvir (PrOD)	Paritaprevir, ritonavir, ombitasvir (PrO)
Ritonavir-boosted atazanavir	No data	Ledipasvir ↑; atazanavir ↑[a]	Velpatasvir ↑; atazanavir ↑[a]	No data	Daclatasvir ↑[b]	Elbasvir ↑; grazoprevir ↑; atazanavir ↑	Paritaprevir ↑; atazanavir ↑	Paritaprevir ↑; atazanavir ↔
Ritonavir- boosted darunavir	Sofosbuvir ↑; darunavir ↔	Ledipasvir ↑; darunavir ↔[a]	Velpatasvir ↔; darunavir ↔[a]	Simeprevir ↑; darunavir ↔	Daclatasvir ↑; darunavir ↔	Elbasvir ↑; grazoprevir ↑; darunavir ↔	Paritaprevir ↓/↑; darunavir ↓	Paritaprevir ↑; darunavir ↔
Ritonavir-boosted lopinavir	No data	No data[a]	Velpatasvir ↔; lopinavir ↔[a]	No data	Daclatasvir ↑; lopinavir ↔	Elbasvir ↑; grazoprevir ↑; lopinavir ↔	Paritaprevir ↑; lopinavir ↔	Paritaprevir ↑; lopinavir ↔
Ritonavir-boosted tipranavir	No data	No data	No data	No data	No data	No data	No data	No data
Efavirenz	Sofosbuvir ↔; efavirenz ↔	Ledipasvir ↓; efavirenz ↓[a]	Velpatasvir ↓; efavirenz ↓	Simeprevir ↓; efavirenz ↔	Daclatasvir ↓[b]	Elbasvir ↓; grazoprevir ↓; efavirenz ↓	No pharmacokinetic data[c]	No data
Rilpivirine	Sofosbuvir ↔; rilpivirine ↔	Ledipasvir ↔; rilpivirine ↔	Velpatasvir ↔; rilpivirine ↔	Simeprevir ↔; rilpivirine ↔	No data	elbasvir ↔; grazoprevir ↔; rilpivirine ↔	Paritaprevir ↑; rilpivirine ↑	No data
Etravirine	No data	No data	No data	No data	Daclatasvir ↓[b]	No data	No data	No data

	Sofosbuvir	Ledipasvir	Velpatasvir	Simeprevir	Daclatasvir	Elbasvir/ grazoprevir	Paritaprevir, ritonavir, ombitasvir plus dasabuvir (PrOD)	Paritaprevir, ritonavir, ombitasvir (PrO)
Raltegravir	Sofosbuvir ↔; raltegravir ↔	Ledipasvir ↔; raltegravir ↔	Velpatasvir ↔; raltegravir ↔	Simeprevir ↔; raltegravir ↔	No data	Elbasvir ↔; grazoprevir ↔; raltegravir ↑	PrOD ↔; ↑ raltegravir	PrO ↔; raltegravir ↑
Cobicistat-boosted elvitegravir	Sofosbuvir ↑[a]; cobicistat ↑	Ledipasvir ↑; cobicistat ↑[a]	Velpatasvir ↑; cobicistat ↑	No data	No data	Elbasvir ↑; grazoprevir ↑; cobicistat ↑	No data	No data
Dolutegravir	No data	Ledipasvir ↔; dolutegravir ↔	Velpatasvir ↔; dolutegravir ↔	No data	Daclatasvir ↔; dolutegravir ↑	Elbasvir ↔; grazoprevir ↔; dolutegravir ↑	Paritaprevir ↓; dolutegravir ↑	No data
Maraviroc	No data	No data	No data	No data	No data	No data	No data	No data
Tenofovir disoproxil fumarate	Sofosbuvir ↔; tenofovir ↔	Ledipasvir ↔; tenofovir ↑	Velpatasvir ↔; tenofovir ↑	Simeprevir ↔; tenofovir ↔	Daclatasvir ↔; tenofovir ↔	Elbasvir ↔; grazoprevir ↔; tenofovir ↑	PrOD ↔; tenofovir ↔	Pro ↔; tenofovir ↔
Tenofovir alafenamide	Sofosbuvir ↑; tenofovir ↑[d]	Ledipasvir ↔; tenofovir ↑[d]	Velpatasvir ↔; tenofovir ↑[d]	No data	No data	No data	No data	No data

Drug-Drug Interactions Continued

- Consider sofosbuvir plus daclatasvir +/- ribavirin if ART cannot be modified
- Places to assess drug-drug interactions:
  - hcvguidelines.org
  - aidsinfo.nih.gov/guidelines
  - hiv-druginteractions.org
  - hep-druginteractions.org

Access

- HIV/HCV coinfection may or may not impact prioritization of treatment depending on payer
- Ryan White programs may or may not provide DAA treatment for HIV/HCV coinfection depending on formulary

Outline

- Impact of HCV Coinfection in HIV
- DAA Review
- Prescribing DAA Therapy for HIV/HCV Coinfection
- **Cases**

Case 1

- Alvin is a 45 y/o man with HIV (CD4 850, VL<20) who is referred for HCV evaluation.
- He is treatment naïve.
- Workup reveals:
  - HCV RNA VL 4,000,000
  - GT 1b
  - CT findings consistent with nodular cirrhosis
  - HIV ART: 3TC/ABC + ATV
    - He is reticent to change his regimen but willing to if no other options are available.

Case 1 Continued

- Does the patient need further staging?
- Do you want to treat?
- Does the patient need ART changes?

Case 1: What treatment strategy would be BEST for this scenario?

A. EBV/GZP x 12 weeks
B. PTV/r/OBV + DBV x 12 weeks
C. PTV/r/OBV + DBV + RBV x 12 weeks
D. SOF + SMV x 12 weeks
E. SOF/LDV x 8 weeks
F. SOF/LDV x 24 weeks
G. SOF/VEL x 8 weeks

Case 1: What treatment strategy would be BEST for this scenario?

A. EBV/GZP x 12 weeks
B. **PTV/r/OBV + DBV x 12 weeks**
C. PTV/r/OBV + DBV + RBV x 12 weeks
D. SOF + SMV x 12 weeks
E. SOF/LDV x 8 weeks
F. SOF/LDV x 24 weeks
G. SOF/VEL x 8 weeks

Case 1 Strategies

- SOF/LDV
  - 8 weeks is appropriate for select patients:
    - Treatment naïve, HCV RNA VL <6,000,000, no cirrhosis
  - 12 weeks is appropriate for most other treatment naïve patients
  - 24 weeks of therapy is needed for certain treatment experienced cirrhotics or decompensated cirrhotic patients
- SOF + SMV
  - Difficult to obtain for GT 1
  - Short course (i.e. 12 weeks) may be appropriate for non-cirrhotics
  - Extension to 24 weeks may increase SVR rates in cirrhotics
  - Role of adding RBV unclear
  - Significant drug-drug interactions with HIV protease inhibitors
- EBV/GZP x 12 weeks
  - Significant drug-drug interactions with HIV protease inhibitors
- SOF/VEL
  - Not approved for 8 weeks of therapy

Case 1 Strategies Continued

- PTV/r/OBV + DBV +/- RBV
  - All patients with GT 1a require RBV
  - Patients with GT 1b do equally well with or without RBV, with or without cirrhosis, for 12 or 24 weeks
  - 12 weeks is appropriate for GT 1a treatment naïve, non cirrhotics
  - 24 weeks may be beneficial for GT 1a treatment experienced and/or cirrhotics
  - Lots of DDI with ART (including HIV PIs), but not with ATV or typical NRTI backbone therapies

Case 2

- Beth is a 55 y/o woman with DM (A1c 8.5%), CAD (s/p PCI 6 months ago) and HIV (CD4 550, VL <20) who presents for HCV evaluation.
- Previously treated with pegylated interferon/ribavirin, but therapy discontinued for suicidal ideation
- Workup reveals:
  - AST 85, ALT 125, Platelets 135,000
  - HCV RNA VL 9,500,000
  - GT 2a
  - Liver biopsy reveals grade 1 hepatitis, stage 2 fibrosis
  - HIV ART: FTC/TDF + DRV/r + DTG

Case 2: What treatment strategy would be BEST at this time?

A. EBV/GZP x 12 weeks
B. SOF + DCV x 12 weeks
C. SOF + SMV x 12 weeks
D. SOF + RBV x 24 weeks
E. SOF/LDV x 12 weeks
F. SOF/VEL x 12 weeks

Case 2: What treatment strategy would be BEST at this time?

A. EBV/GZP x 12 weeks
B. **SOF + DCV x 12 weeks**
C. SOF + SMV x 12 weeks
D. SOF + RBV x 24 weeks
E. SOF/LDV x 12 weeks
F. **SOF/VEL x 12 weeks**

Case 2 Strategies

- GT 2 most likely genotype to achieve SVR12 with prior or current ***appropriate*** treatment strategies.
- LDV, SMV, and PTV/r/OBV/DBV have minimal GT 2 activity.
- SOF + DCV or SOF/VEL are both reasonable strategies for treatment.
  - Extended therapy of SOF + DCV may be needed in GT 2, cirrhotic, treatment experienced patients.
- If SOF/VEL considered, would d/c TDF and switch to alternative therapy (i.e. TAF) to minimize risk of toxic TDF exposure.
- SOF + RBV is no longer recommended for GT 2.

Case 3

- Carl is a 60 y/o man with PMH of HTN, HIV (CD4 650, VL <20), and ESRD on HD.
- The patient is referred for HCV evaluation and is treatment naïve.
- Workup reveals:
  - AST 60, ALT 75, Platelets 195,000
  - HCV RNA VL 850,000
  - GT 1a
  - Liver biopsy 2 years ago consistent with grade 1 hepatitis, stage 1 fibrosis.
  - HIV ART: 3TC + TDF + RAL

Case 3: What treatment strategy would be BEST for this scenario?

A. EBV/GZP x 12 weeks
B. PTV/r/OBV + DBV + RBV x 12 weeks
C. SOF + SMV x 12 weeks
D. SOF/LDV x 8 weeks
E. SOF/LDV x 12 weeks
F. SOF/LDV x 24 weeks
G. SOF/VEL x 12 weeks

Case 3: What treatment strategy would be BEST for this scenario?

A. **EBV/GZP x 12 weeks**
B. **PTV/r/OBV + DBV + RBV x 12 weeks**
C. SOF + SMV x 12 weeks
D. SOF/LDV x 8 weeks
E. SOF/LDV x 12 weeks
F. SOF/LDV x 24 weeks
G. SOF/VEL x 12 weeks

Case 3 Strategies

- ESRD limits therapy options.
- SOF efficacy and safety in ESRD is not well established.
  - Small case series of SOF used in HD patients with varying strategies.
- Clinical data available for both EBV/GZP and PTV/r/OBV + DBV + RBV in ESRD.
  - Duration of EBV/GZP dependent on baseline NS5A resistance status.

Case 4

- David is a 38 y/o man referred for HCV evaluation and treatment, who was diagnosed at time of HIV diagnosis in 2005.
- His PMH includes HIV (last CD4 950 with HIV viral load <20), bipolar disorder, and prior IVDU.
- Workup reveals:
  - AST 35, ALT 65, Platelets 315,000
  - HCV RNA VL 12,500,000
  - GT 1a
  - Elastography consistent with F1-F2 fibrosis
  - Meds: FTC/TDF + DRV/r, oxcarbazepine, quetiapine

Case 4: Which medication is most concerning for potential drug-drug interactions with DAAs?

A. Tenofovir DF
B. Darunavir
C. Ritonavir
D. Oxcarbazepine
E. Quetiapine

HCV DAAs and DDIs

- Watch out for:
  - Anticonvulsants
  - Antipsychotics
  - Antimycobacterials
  - HIV protease inhibitors
  - Immunosuppressants
  - Herbs/supplements

HIV/HCV Coinfection Management Pearls

- Use same regimens as indicated in HCV monoinfection
- Special attention to drug-drug interactions
  - Avoid “double dosing” RTV when using RTV-boosted DAA therapy (i.e. paritaprevir)
  - Adjust DCV dose based on concomitant ART
  - Monitor impact of DAA and ART on TDF
- Consider SOF + DCV +/- RBV when constrained by complex ART drug-drug interactions

Summary

- HIV/HCV coinfection is a significant cause of morbidity and mortality in people infected with HIV.
- HCV should be treated aggressively in people infected with HIV.
- DAA therapy is selected in the same way in HIV/HCV coinfection as in HCV monoinfection, with special attention to drug-drug interactions.

AETC AIDS Education & Training Center Program Southeast

Thank You!

Questions?

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