HIV/HCV Co-Infection

2015 Kentucky Conference on Viral Hepatitis

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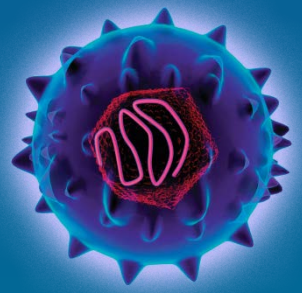
Disclosures / Acknowledgment

- This seminar contains off-label and investigational medications.
- Industry Relationships: DiaPharma, Conatus, Intercept, Lumena, Zeon Chemicals, Merck, Gilead, Janssen, Genentech, Kadmon, Vertex, Abbvie.
- Current Government Grants and Contracts: NIH 1R01ES021375, K23AA18399, 1R13ES024661, CDC/ATSDR#200-2013-M-57311.

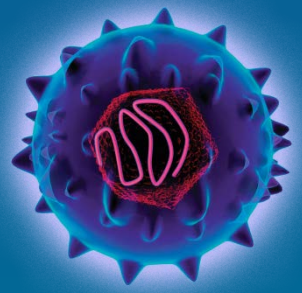
Dr. Cave would like to acknowledge Susanna Naggie, MD, Assistant Professor of Medicine - Infectious Disease, Duke University, for her assistance with this presentation.



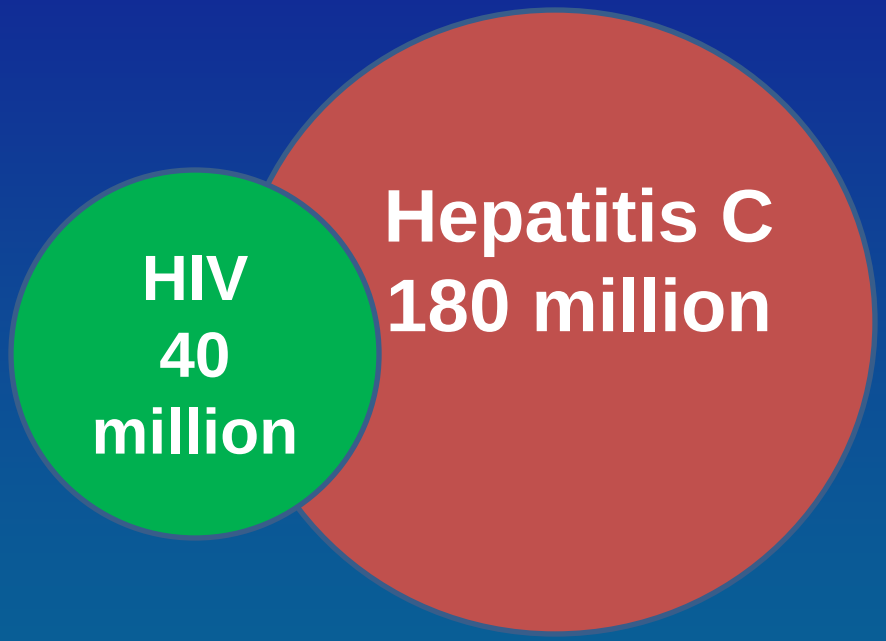
Learning Objectives

After attending this presentation, participants will be able to:

- Discuss the epidemiology and natural history of HCV in HIV-infected patients
- Discuss the AASLD/IDSA Guideline recommendations for management and treatment of HIV/HCV Patients
- Discuss response rates and phase III trials of DAA in HIV/HCV
- Discuss the drug interactions with antiretrovirals and HCV direct acting antivirals (DAAs)



HIV & HCV



- 10 million people worldwide
- 30% of US patients with HIV have HCV
- Epidemic in HIV+ MSM

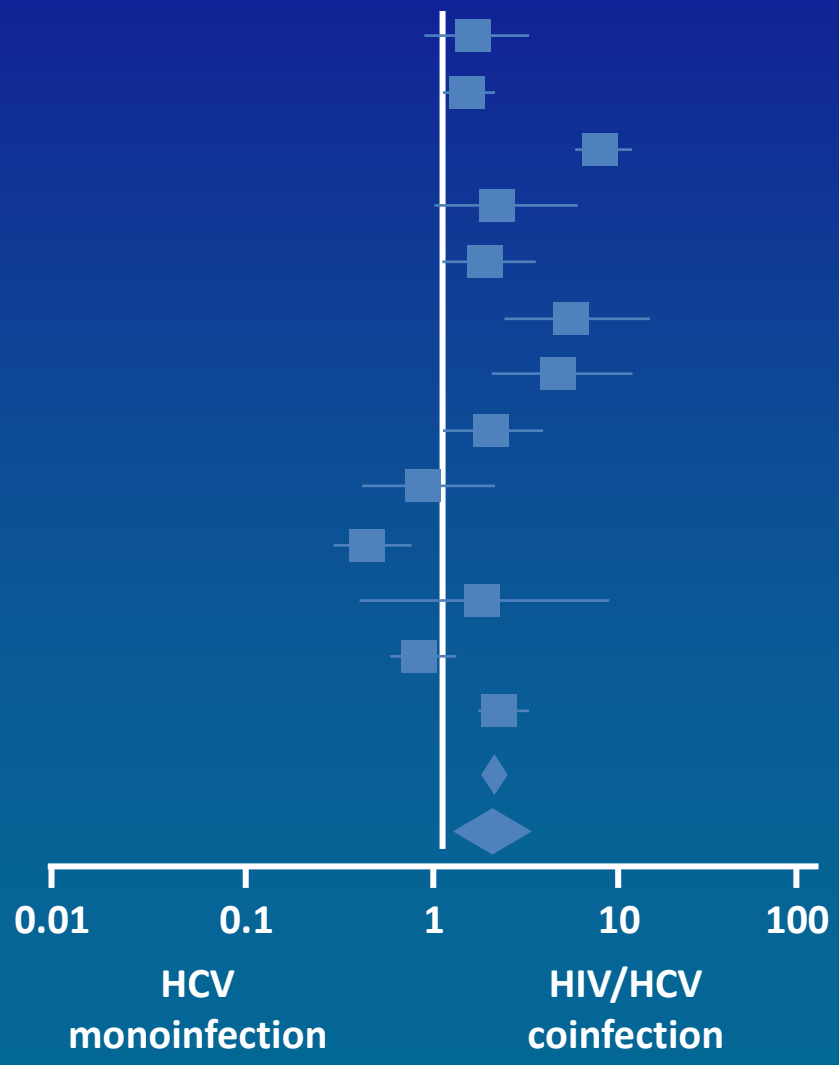
Staples CT. Clin Infect Dis 1999
DAD Study Group, Arch Intern Med 2006

Annual HCV screening in high risk HIV+ Patients

Annual HCV testing is recommended for persons who inject drugs and for HIV-seropositive men who have unprotected sex with men. Periodic testing should be offered to other persons with ongoing risk factors for exposure to HCV.

Rating: Class IIA, Level C

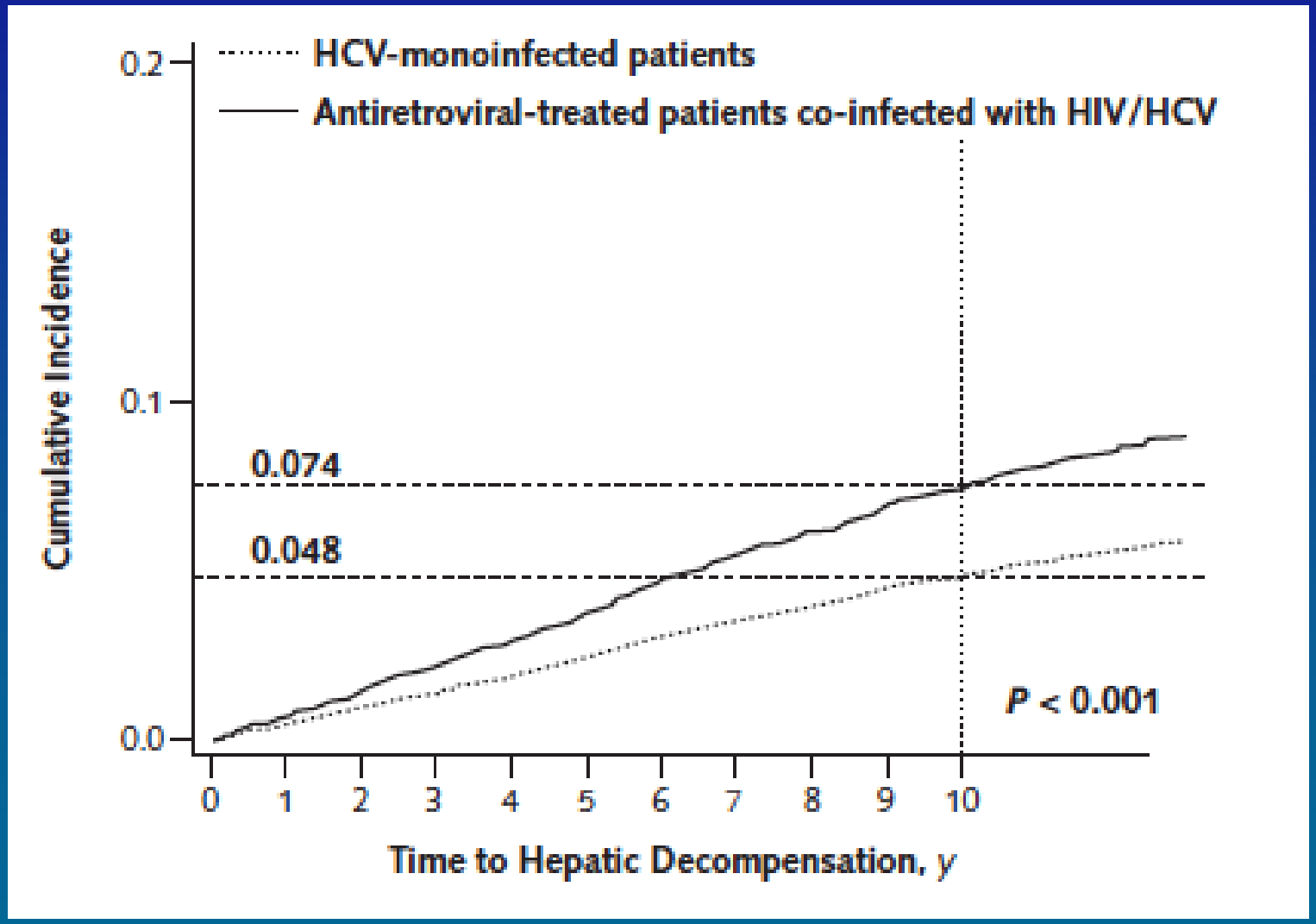
The Effect of HIV on Development of HCV Cirrhosis



- Overall RR 2.11
- Pre-HAART era
  - RR 2.49
- HAART era
  - RR 1.72
- 20-year, 30-year rates
  - 25%, 54%

Thein et al. AIDS 2008; 22:1979

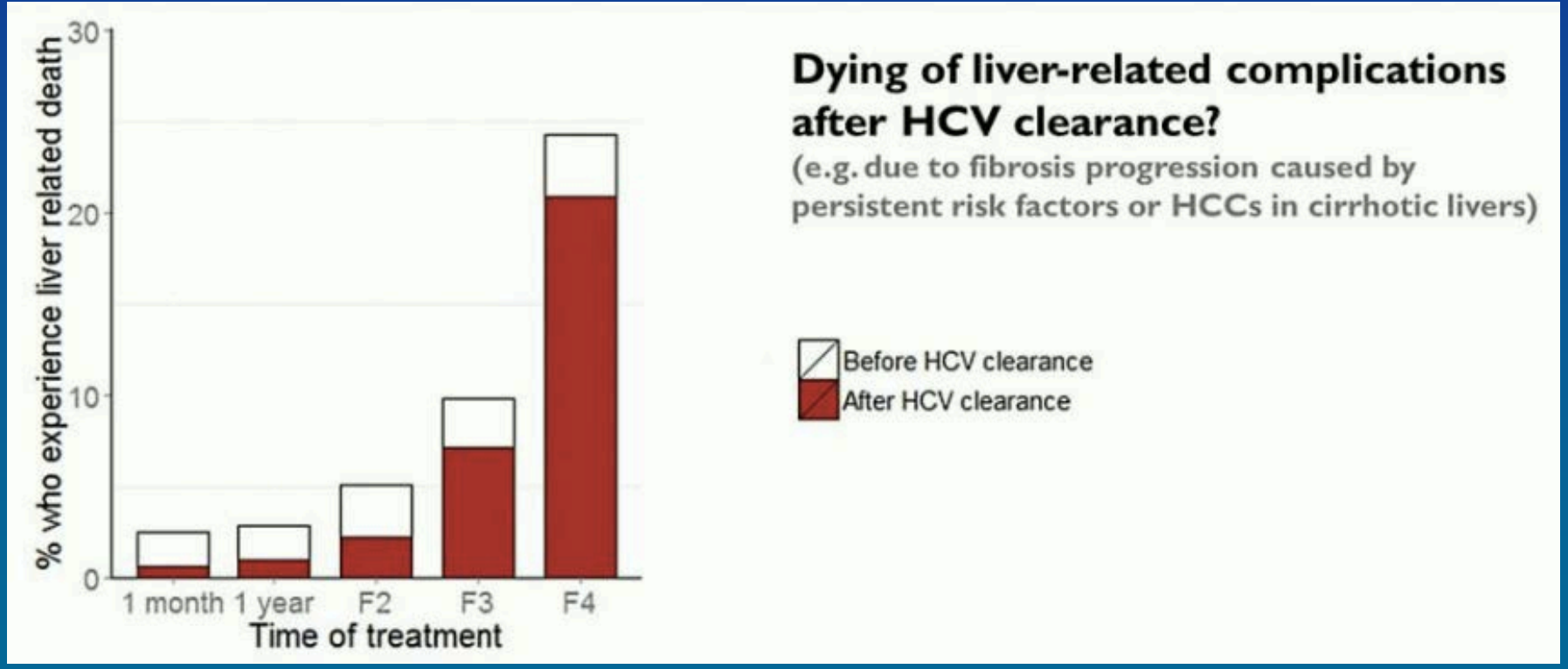
Hepatic Decompensation



Lo Re et al. Ann Intern Med 2014; 160

Delaying HCV Treatment in HIV Co-infection Impacts Survival

: Delaying treatment until 1 year after diagnosis or until F2, F3 or F4 led to 14, 43, 142 and 418 additional cases of liver-related deaths per 1000 HCV infections as compared with treating all patients one month after diagnosis



Impact of Deferring HCV Treatment on Liver-Related Events in HIV+ Patients. Cindy Zahn et al. CROI 2015#150.

High Priority for Treatment Owing to High Risk for Complications

Fibrosis (Metavir F2)

Rating: Class I, level B

HIV-1 coinfection

Rating: Class I, Level B

Hepatitis B virus (HBV) coinfection

Rating: Class IIa, Level C

Other coexistent liver disease (eg, [NASH])

Rating: Class IIa, Level C

Debilitating fatigue

Rating: Class IIa, Level B

Type 2 Diabetes mellitus (insulin resistant)

Rating: Class IIa, Level B

Porphyria cutanea tarda

Rating: Class IIb, Level C

American Association for the Study of Liver Diseases

AASLD

HIV/HCV Co-infection (Dec 2014)

IDSA

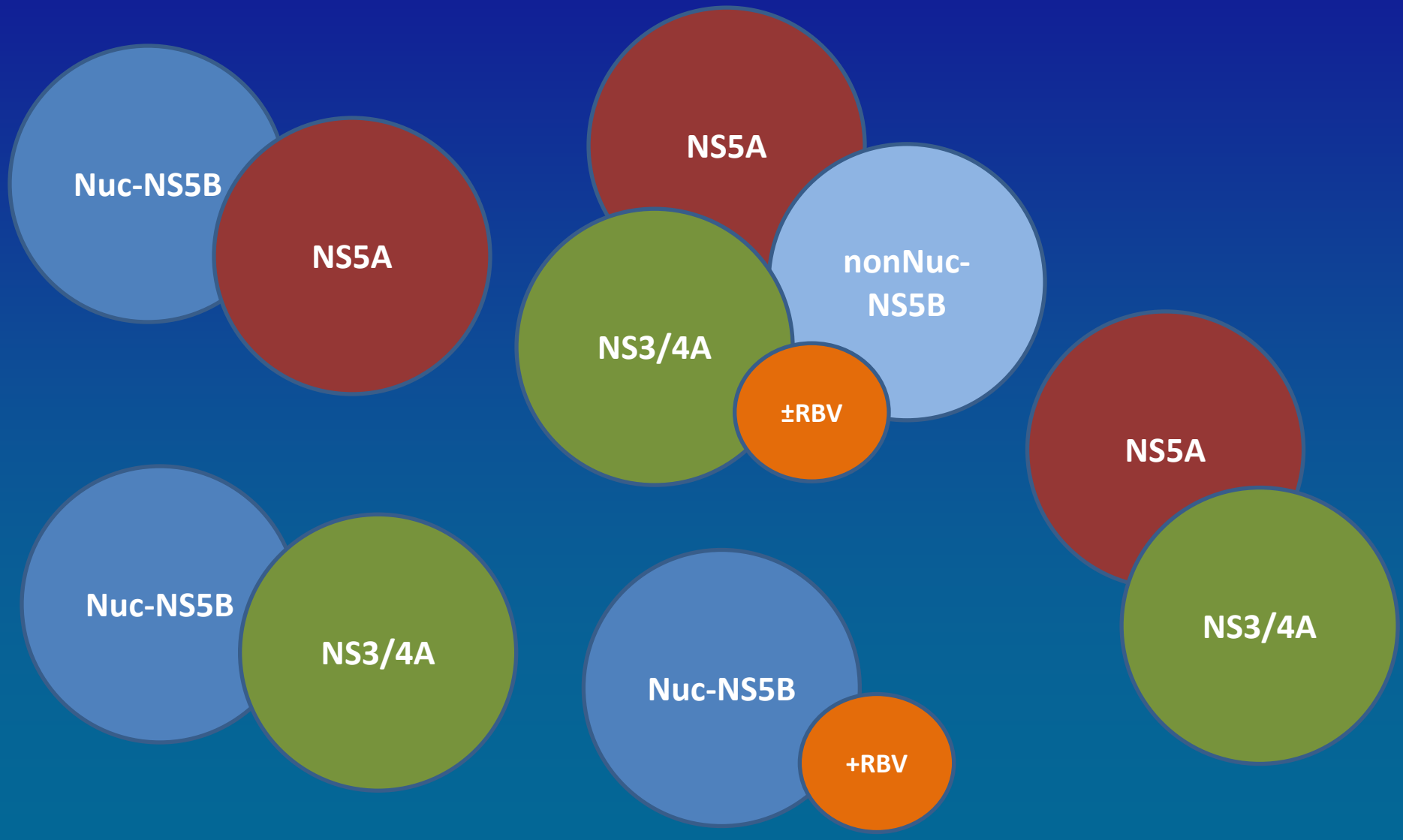
Infectious Diseases Society of America

Recommended regimens for HIV/HCV-coinfected individuals.

HIV/HCV-coinfected persons should be treated and retreated the same as persons without HIV infection, after recognizing and managing interactions with antiretroviral medications (see Initial Treatment of HCV Infection and Retreatment of Persons in Whom Prior Therapy Has Failed sections).

Rating: Class I, Level B

The new treatment paradigm



Agents and Regimens

	Antiviral				
	NS3	NS5A	Non-Nuc NS5B	Nuc NS5B	RBV
Ledipasvir/sofosbuvir FDC		⊙		⊙	
Paritaprevir/r/ombitasvir FDC + dasabuvir	⊙	⊙	⊙		⊙ 1a only
Simeprevir + sofosbuvir	⊙			⊙	
Sofosbuvir + ribavirin				⊙	⊙
Daclatasvir* + sofosbuvir		⊙		⊙	

*pending FDA approval; approved in EU

The State of HIV/HCV data (Geno 1)

Regimen	Phase	Size	Design	SVR
FDA Approved				
Ledipasvir/sofosbuvir	II	50	Single arm: 12 weeks	98%
	III	327	Single arm: 12 weeks	96%
Paritaprevir/r/ombitasvir + dasabuvir + ribavirin	II	63	RCT: 12 vs 24 weeks	92%
Simeprevir + sofosbuvir	N/A	19/31	Observational	95/77%
Investigational				
Daclatasvir + sofosbuvir	III	168	RCT: 8 vs 12 (N=127) weeks	97%
Grazoprevir + elbasvir	III	218	Single arm: 12 weeks	95%

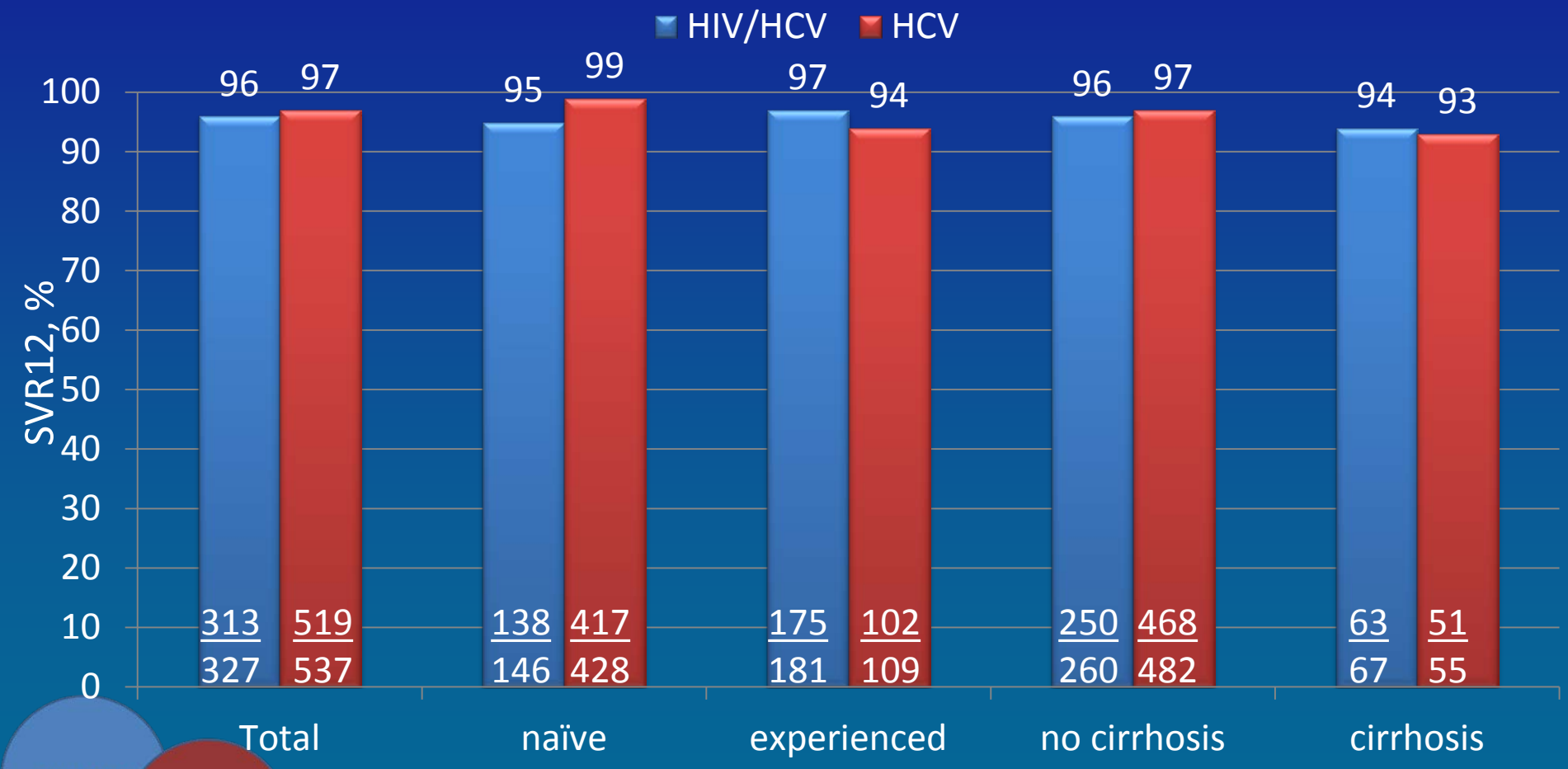
Osinusi et al, JAMA 2015; Naggie et al, CROI 2015 LB152; Sulkowski et al, JAMA 2015; Wyles et al, CROI 2015 LB151; Rockstroh et al, EASL 2015 P0887; Grant et al, CROI 2015 649; Gilmore et al, CROI 2015 645

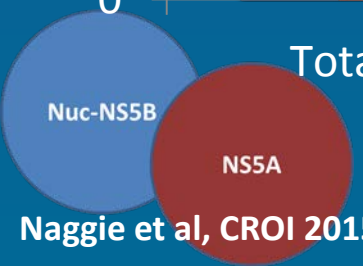
Recommended regimens for treatment-naïve and experienced patients with HIV/HCV genotype 1 infection and without cirrhosis

Regimen	Weeks	Rating
Ledipasvir + sofosbuvir	12*	I, A
Simeprevir + sofosbuvir ± ribavirin (subtype)	12	IIa, B
Paritaprevir/r/ombitasvir + dasabuvir + ribavirin , GT 1a	12	I, A
Paritaprevir/r/ombitasvir + dasabuvir, GT 1b	12	I, A

*8 weeks considered in patients without cirrhosis with HCV RNA <6 million IU/mL although I would not recommend this approach in patient with HIV

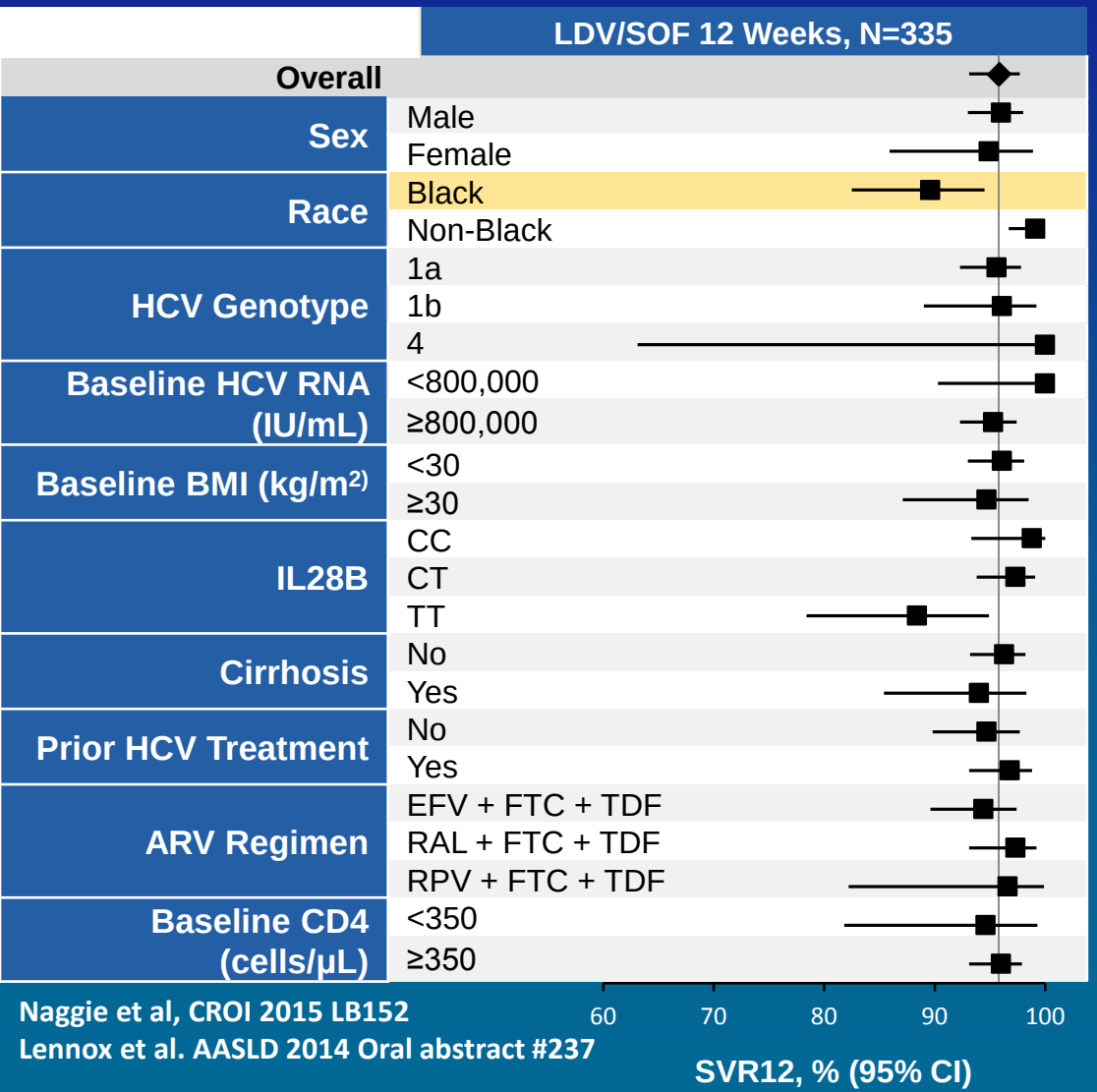
Question #1: Do GT-1 HIV patients achieve same SVR with 12W of LDV/SOF?





Naggie et al, CROI 2015 LB152; Afdhal et al. NEJM 2014

ION-4 LDV/SOF X 12W in HIV/HCV
Predictors of relapse



- No difference in SVR in HCV mono-infected ION program (12 weeks) for black (89/90, 99%) versus non-black (431/448, 96%)
- LDV and SOF population PK levels
  - Similar across the different ARV regimens, black and non-black patients, relapse and SVR
- GWAS and whole genome sequencing analysis underway

Naggie et al, CROI 2015 LB152
Lennox et al. AASLD 2014 Oral abstract #237

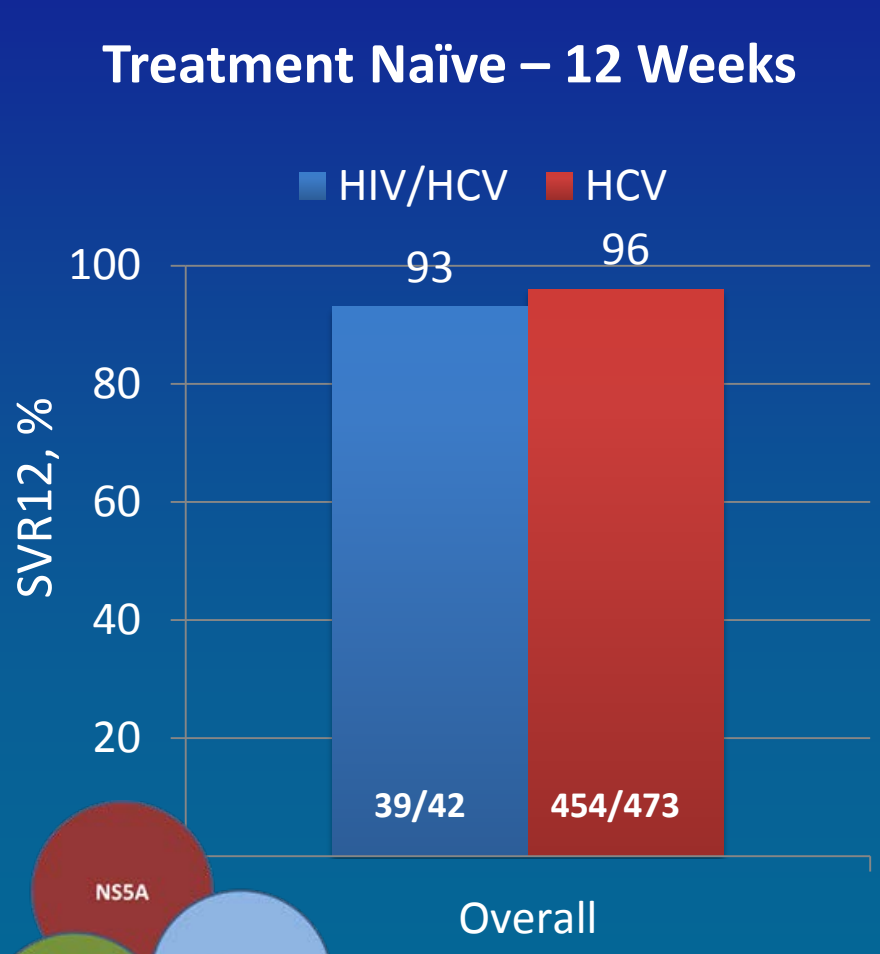
Characteristics of Relapsers
HIV-HCV (ION-4)

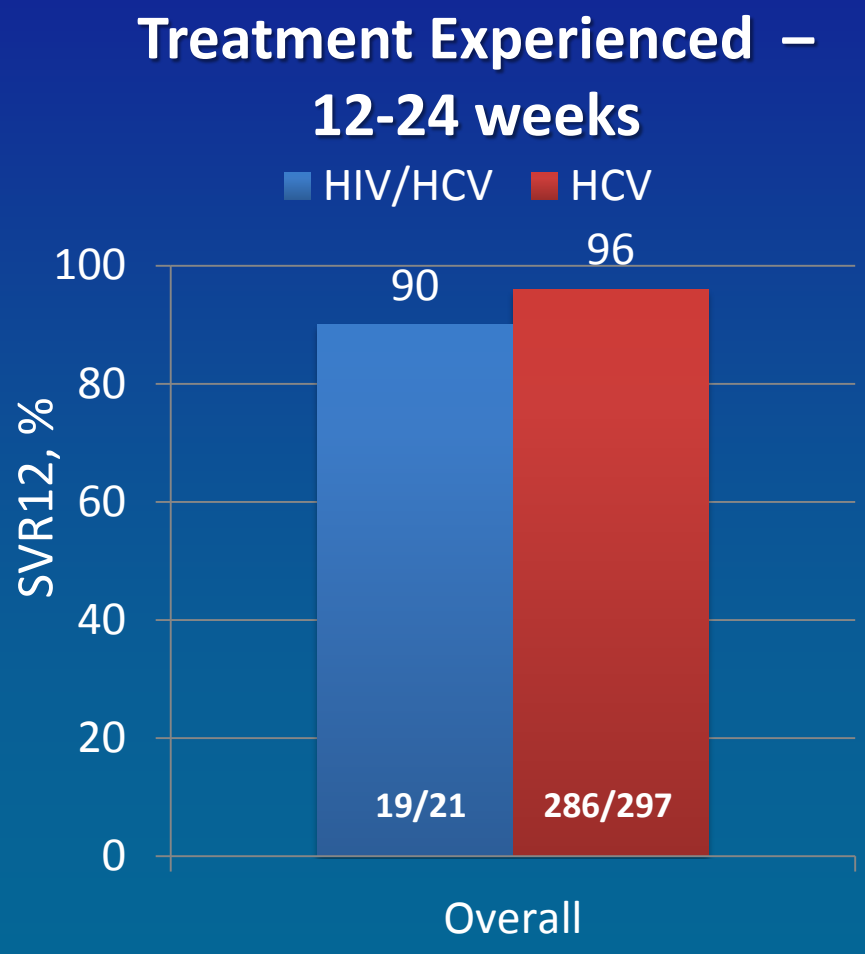
Age	Sex	Race	BMI (kg/m²)	HCV GT	BL CD4 Count (cells/µL)	Cirrhosis	IL28B GT	BL HCV RNA (log_{10} IU/mL)	HCV RNA <LLOQ (Wk)	Timing of VF (FU wk)	Prior HCV Treatment	ARV Regimen
35	M	Black	24.1	1a	308	No	CT	7.3	2	4	N/A	EFV+FTC+TDF
58	M	Black	28.2	1a	553	No	TT	7.5	2	4	PEG+RBV	EFV+FTC+TDF
61	M	Black	22.4	1a	504	Yes	TT	7.0	4	4	N/A	EFV+FTC+TDF
61	F	Black	26.8	1a	144	Yes	CT	6.4	1	12	PEG+RBV	RAL+FTC+TDF
51	M	Black	30.0	1a	964	No	TT	6.5	2	4	NS5A+PEG +RBV*	EFV+FTC+TDF
65	F	Black	24.8	1b	904	Yes	TT	7.0	2	4	N/A	EFV+FTC+TDF
60	M	Black	32.3	1a	435	No	TT	7.4	2	4	N/A	RAL+FTC+TDF
63	M	Black	42.7	1a	690	No	TT	7.3	4	12	PEG+RBV	EFV+FTC+TDF
55	M	Black	32.5	1a	933	No	CT	6.7	1	4	PEG+RBV	EFV+FTC+TDF
58	M	Black	24.8	1b	2069	No	TT	7.3	4	4	PEG+RBV	EFV+FTC+TDF

*Prohibited regimen (protocol violation).
BL, baseline; FU, follow-up; VF, virologic failure.

Naggie et al, CROI 2015 LB152

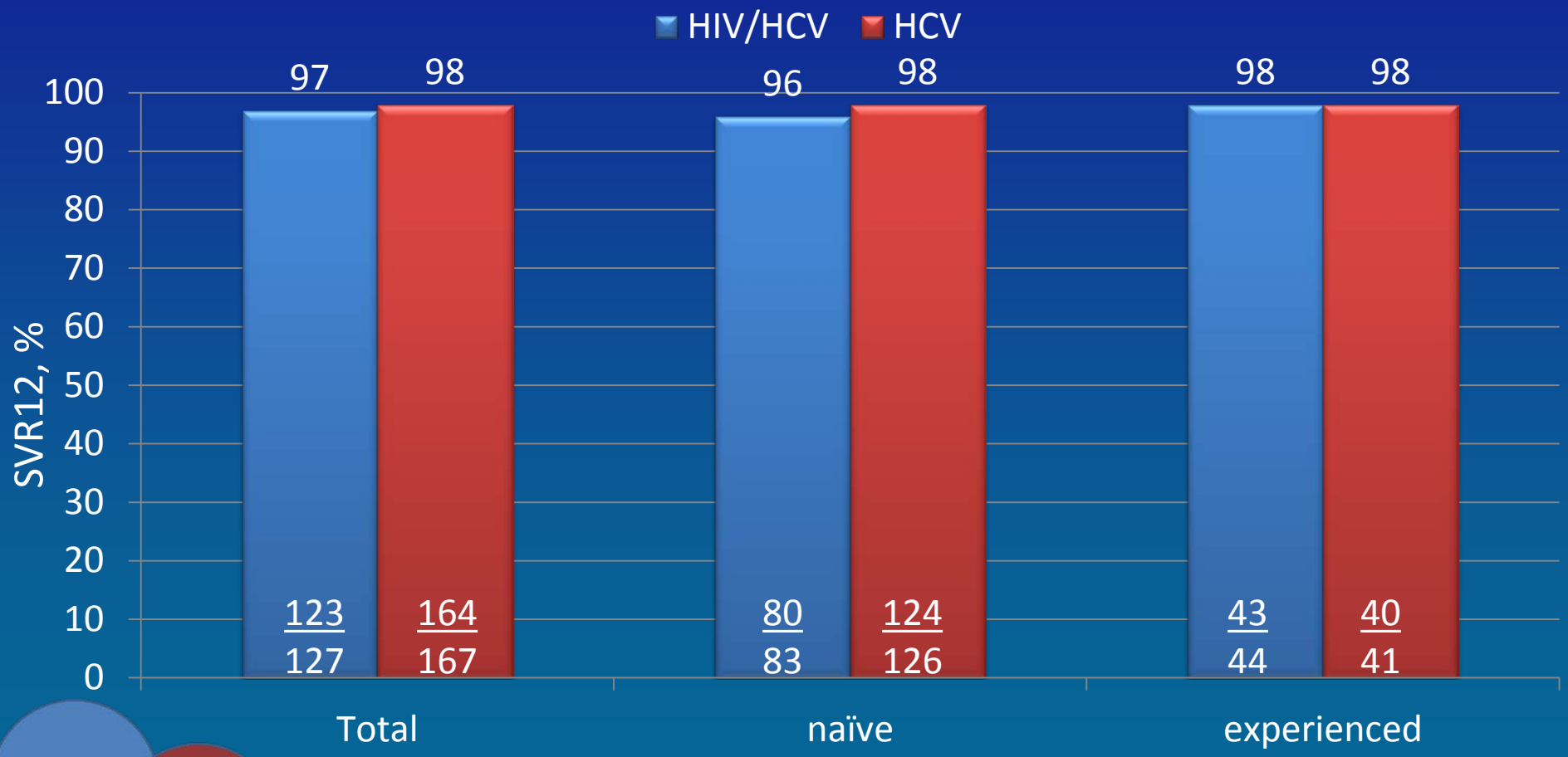
Question #2: Do GT-1 HIV patients achieve same SVR with P/r/O+D+RBV?

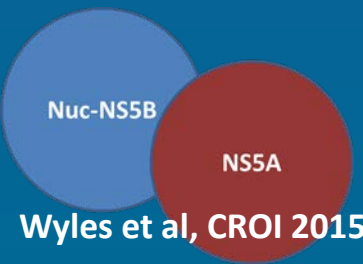




Sulkowski et al, JAMA 2015; Feld et al, NEJM 2014.

Question #3: Do GT-1 HIV patients achieve same SVR with 12W of DCV/SOF?

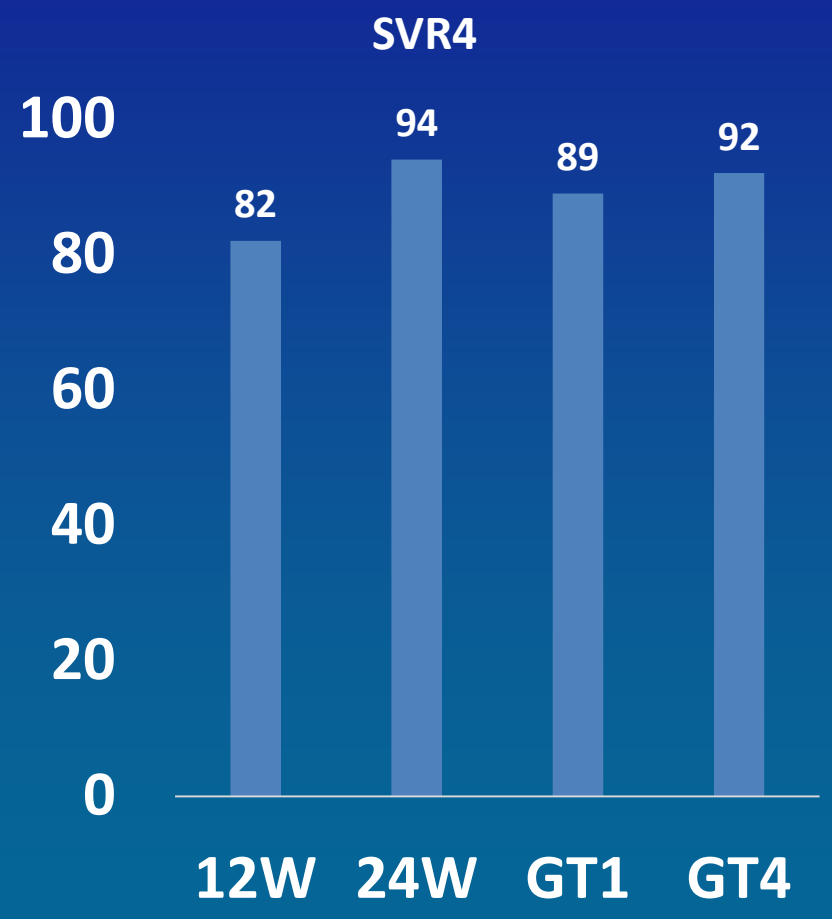




Wyles et al, CROI 2015 LB151; Sulkowski et al. NEJM 2014

French Compassionate Use Program for HIV/HCV: DCV/SOF

- 733 Co-infected
- 12 vs 24 weeks
  - 80% 24W
- 70% cirrhosis
- 78% Treatment exp

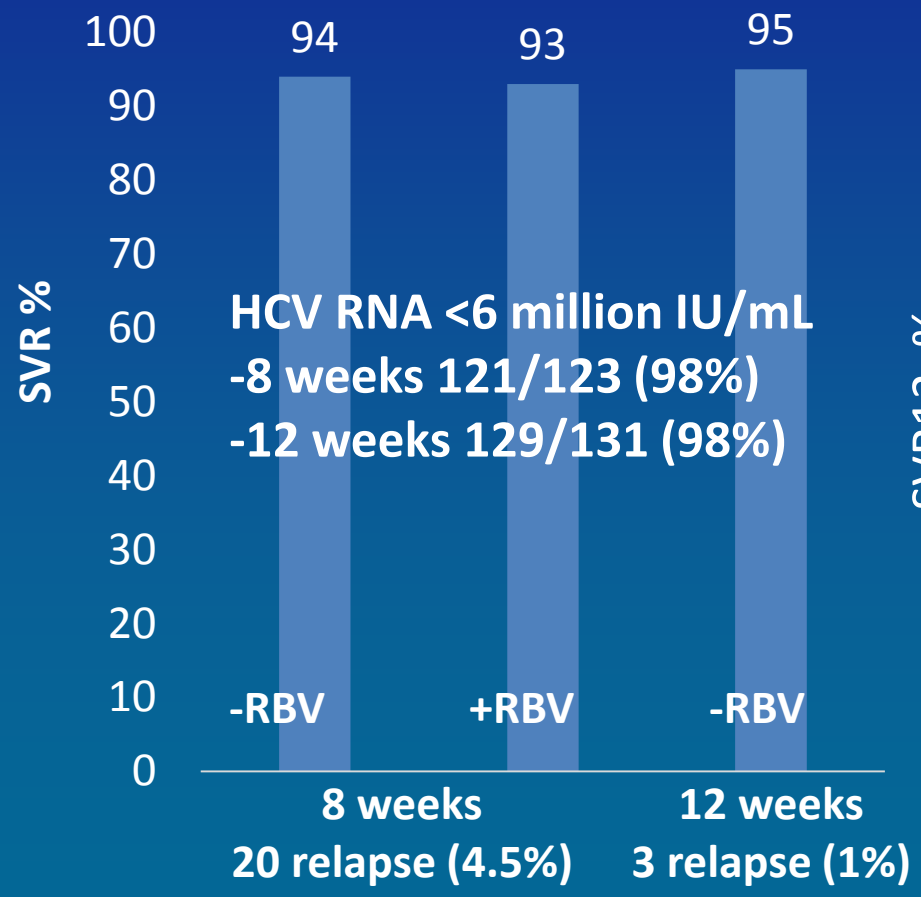


Fontaine et al. EASL 2015 LP23

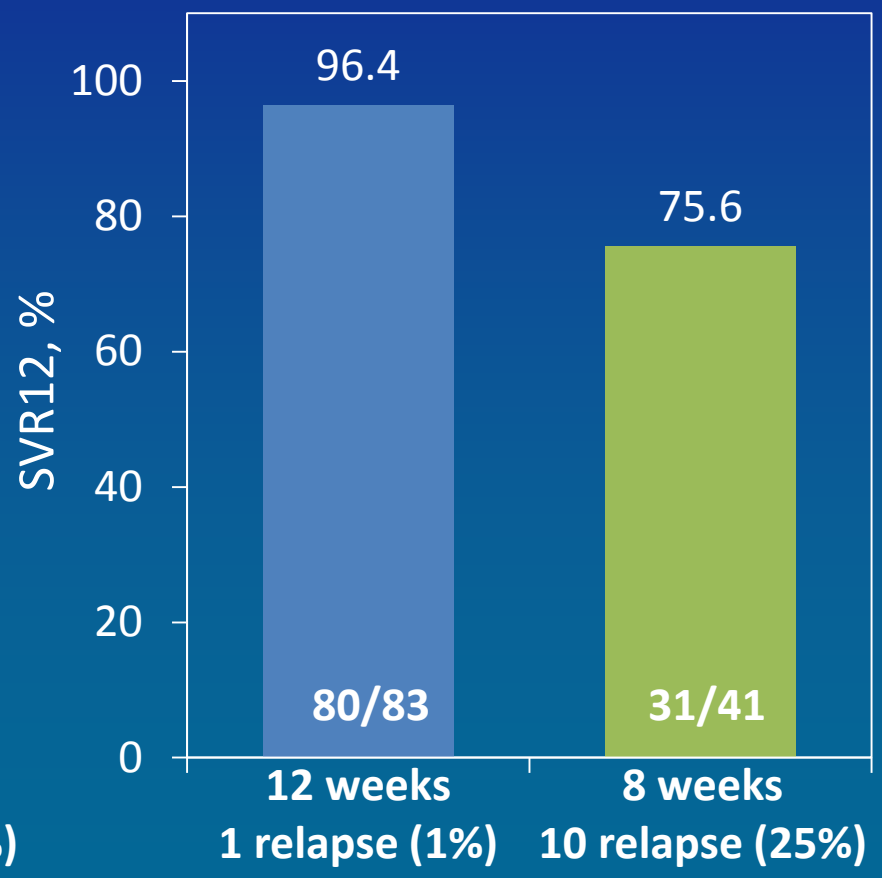
Question #4: Should we use 8 weeks of LDV/SOF in HIV/HCV?

Tx

HCV MONO
Tx Naïve, No cirrhosis: ION-3



HIV/HCV COINFECTION
Naïve : ALLY-2 (DCV/SOF)

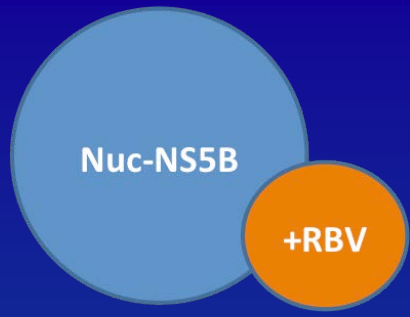


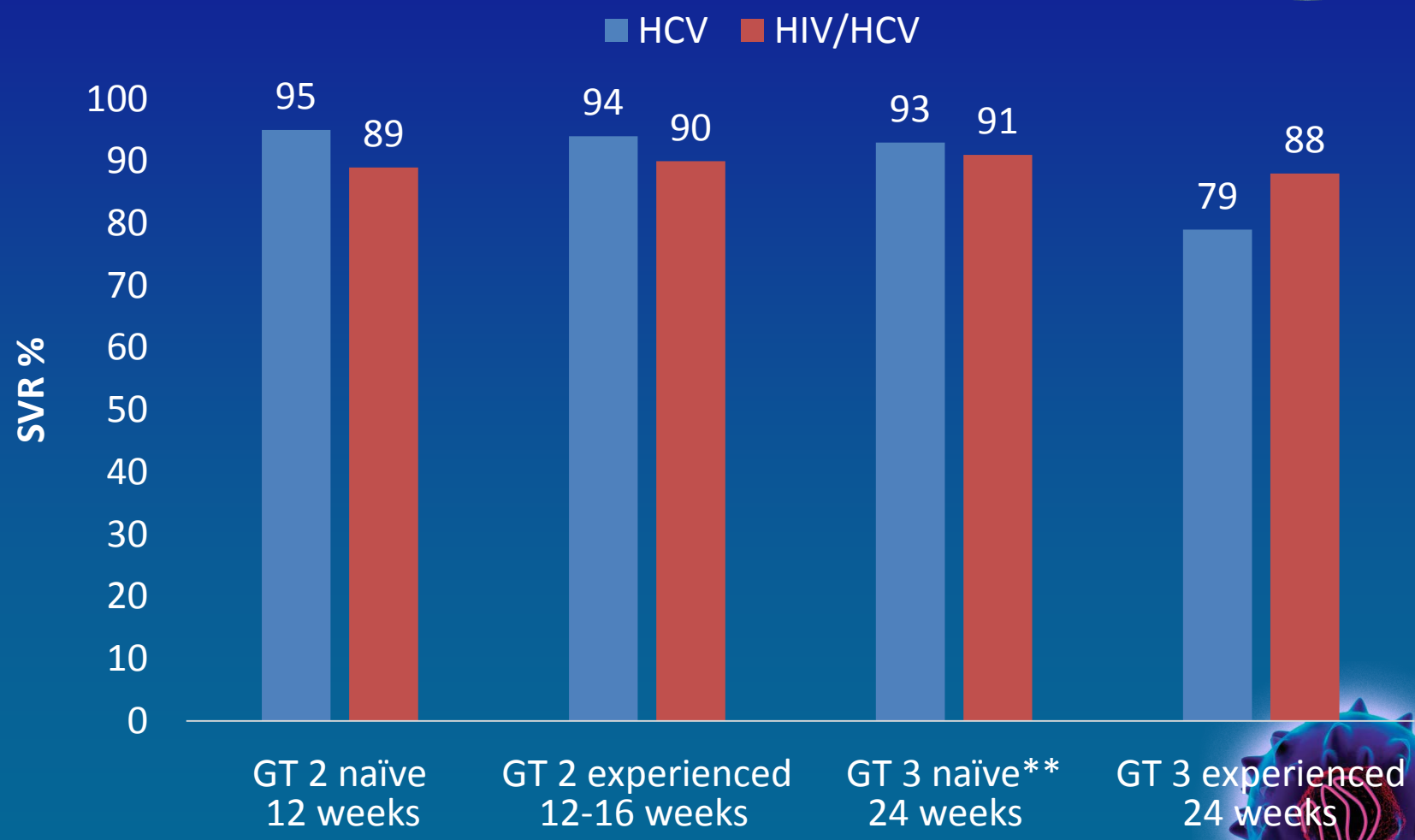
ION-3 Kowdley et al. NEJM; Wyles et al. CROI 2015 LB151

Recommended regimens for HCV genotype 1 infection and cirrhosis

Regimen	Weeks	Rating
Treatment Naïve or Experienced		
Simeprevir + sofosbuvir ± ribavirin	24	IIa, B
Paritaprevir/r/ombitasvir + dasabuvir + ribavirin , GT 1a	24	I, A
Paritaprevir/r/ombitasvir + dasabuvir + ribavirin, GT 1b	12	I, A
Treatment Experienced Only		
Ledipasvir + sofosbuvir + ribavirin	12	I, A
Ledipasvir + sofosbuvir	24	I, A

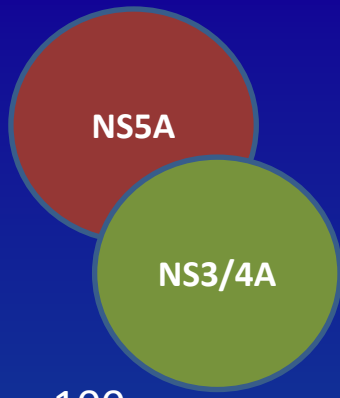
Treating Genotype 2 or 3

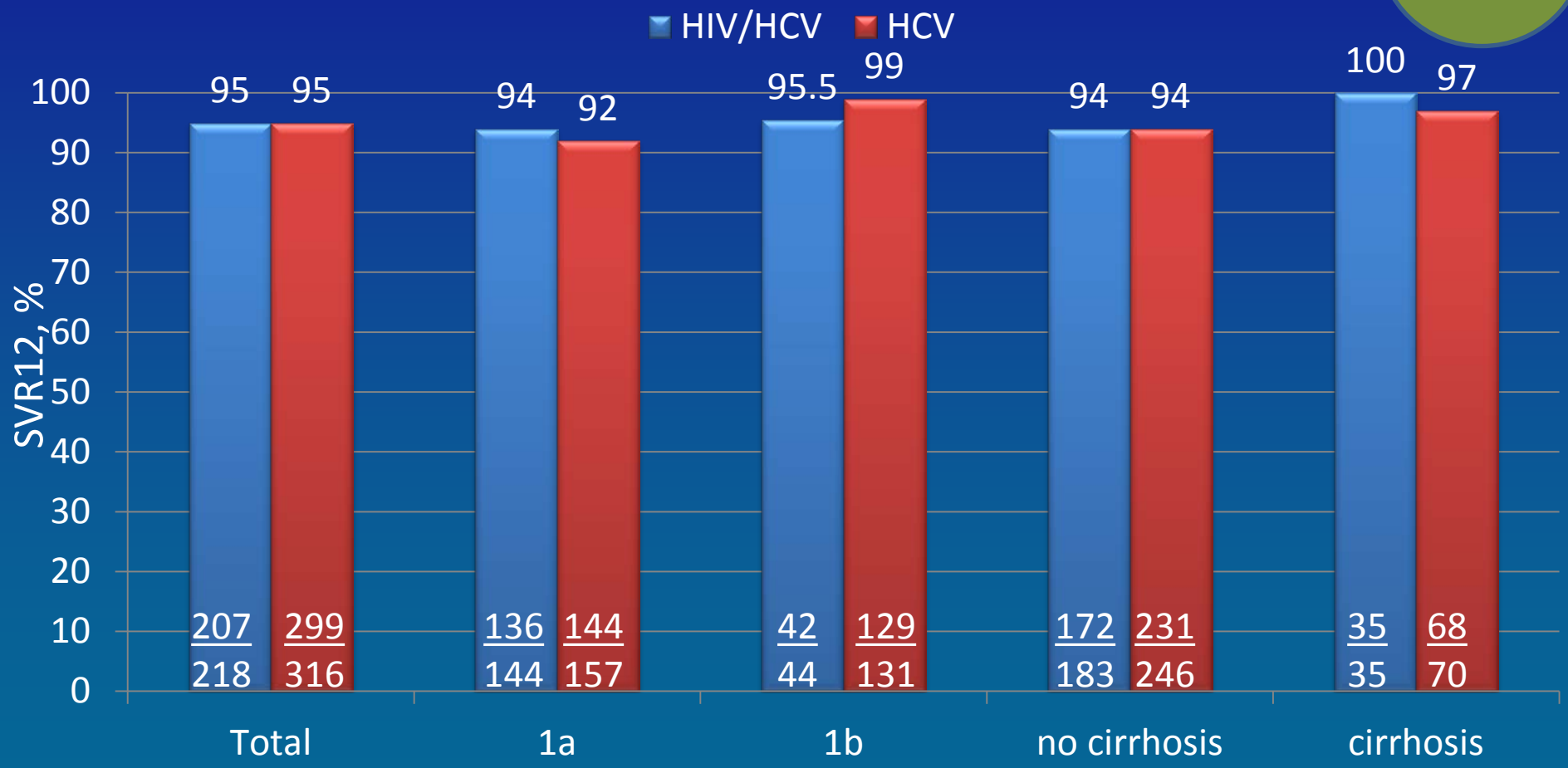




Sulkowski et al. JAMA 2014 (PHOTON-1), Lawitz et al. NEJM April 2013; Zeuzem et al NEJM May 2014, Rockstroh et al, AASLD 2014 (pooled PHOTON 1 and 2)

Merck Grazoprevir/Elbasvir 12 Wks





Rockstroh et al. EASL 2015 Abstract P0887, Zeuzem et al. EASL 2015

	Simeprevir	Sofosbuvir	Ledipasvir	Daclatasvir	P/r/O + D
DDI	**Substrate of CYP3A4, OATP1B1/3**	**Substrate of P-gp and BCRP**	**Inhibitor/ Substrate of P-gp and BCRP**	**Inhibitor of OATP1B1/3, BCRP, Substrate of P-gp and CYP3A4**	**Inhibit/Sub of UGT1A1,OATP1B1/ 3, BCRP, CYP3A4, CYP2C8, P-gp**
ATV/r	No data	No data	LDV ↑; ATV ↑	DCV ↑*	ATV ↔; ABT450 ↑
DRV/r	SIM ↑; DRV ↔	SOF ↑; DRV ↔	LDV ↑; DRV ↔	ALLY-2 ↔	DRV ↓; 3D ↓
LPV/r	No data	No data	No data	ALLY-2 ↔	LPV ↔; ABT450 ↑
TPV/r	No data	No data	No data	No data	No data
EFV	SIM ↓; EFV ↔	SOF ↔; EFV ↔	ION-4 ↔	DCV ↓*	No PK data**
RPV	SIM ↔; RPV ↔	SOF ↔; RPV ↔	LDV ↔; RPV ↔	ALLY-2 ↔	ABT450 ↑; RPV ↑
ETV	No data	No data	No data	No data	No data
RAL	SIM ↔; RAL ↔	SOF ↔; RAL ↔	LDV ↔; RAL ↔	ALLY-2 ↔	3D ↔; ↑ RAL
ELV/cobi	No data	No data	No data	No data	No data
DLG	No data	No data	No data	ALLY-2 ↔	No data
MVC	No data	No data	No data	No data	No data
TDF	SIM ↔; TFV ↔	SOF ↔; TFV ↔	LDV ↔; ↑TFV	DCV ↔; TFV ↔	3D ↔; TFV ↔

Slide courtesy of Jennifer Kiser

* Decrease DCV dose to 30mg QD, Increase DCV dose to 90mg QD, ** 3D + EFV led to premature study discontinuation/toxicities

Allowed HIV Meds in Clinical Trials

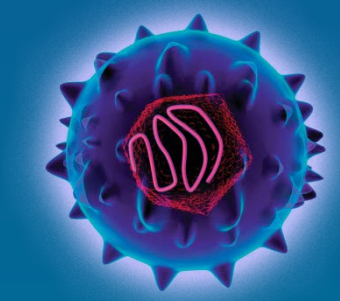
- Harvoni (ION-4): tenofovir/emtricitabine (Truvada) plus either efavirenz (Sustiva), raltegravir (Isentress), or rilpivirine (Edurant).
- Viekira Pak (Turquoise I): atazanavir (Reyataz) or raltegravir plus 2 nucleos(t)ide RTI (e.g. Truvada).
- Sofosbuvir/Daclatasvir (Ally-2): Only exclusion was ritonavir-boosted PI Plus NNRTI (e.g. efavirenz/Sustiva, nevirapine/Viramune, delavirdine/Resriptor, etravirine/Intelence. Rilpivirine OK.
- Grazoprevir/elbasvir (C-EDGE): Truvada or abacavir/emtricitabine or abacavir/lamivudine plus either raltegravir, dolutegravir, rilpivirine.

<u>Comon Regimen Cheat Sheet</u>

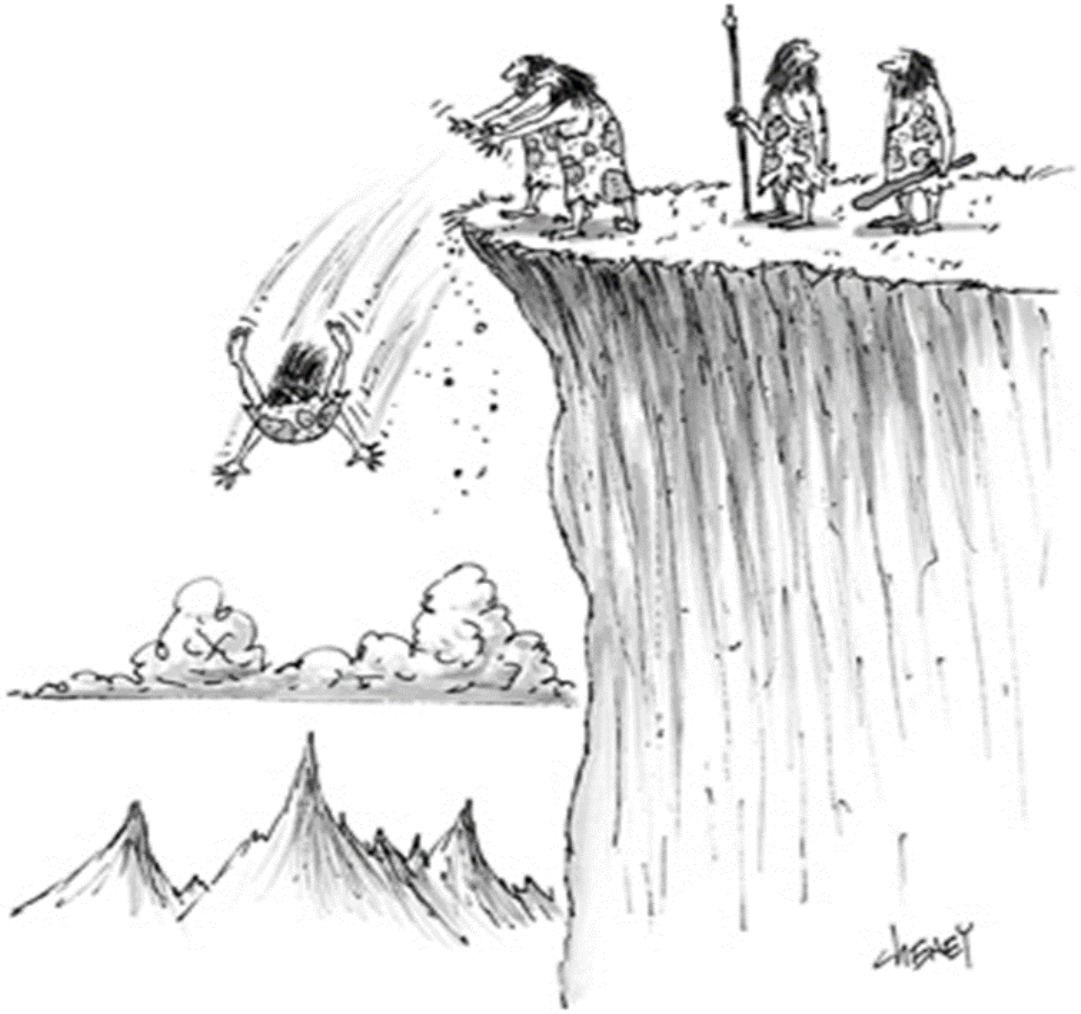
Truvada+Isentress: anything (harvoni, sim/sof, dca/sof, Merck)

Truvada+Reyataz/r: Viekira Pak (hold r) or sofosbuvir/daclatasvir (90mg)

Atripla: Harvoni or sofosbuvir/daclatasvir (30mg)



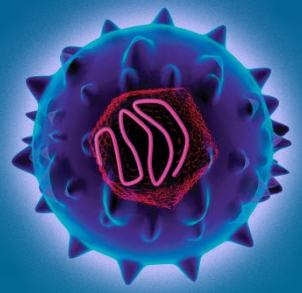
The real challenge isn't the HIV…



"It's the only treatment option he has under his current health plan."

Conclusions

- Co-infection is common and the natural history of HCV is aggressive in HIV.
- Discussed the AASLD/IDSA Guideline recommendations for management and treatment of HIV/HCV Patients.
- Discussed response rates and phase III trials of DAA in HIV/HCV including investigational agents awaiting FDA approval in 2015-2016.
- Discussed the drug interactions with antiretrovirals and HCV direct acting antivirals (DAAs)



Questions