Southern African HIV Clinicians Society

3rd Biennial Conference

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Sandton Convention Centre
Johannesburg

Our Issues, Our Drugs, Our Patients

www.sahivsoc.org
www.sahivsoc2016.co.za

HIV and Hepatitis C
Have we finally slayed the beast?

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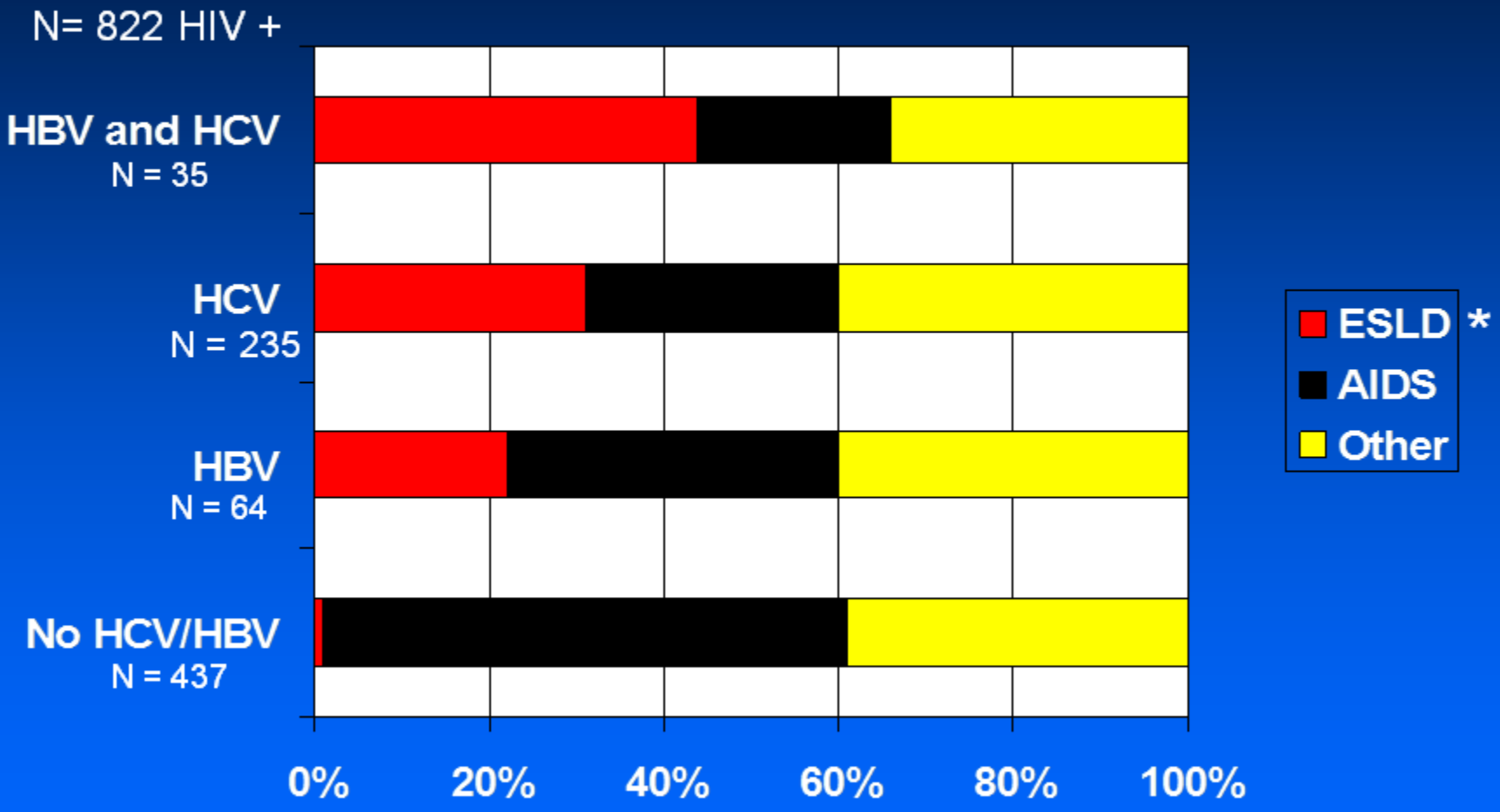
DIVISION OF HEPATOLOGY AND LIVER LABORATORY

2016

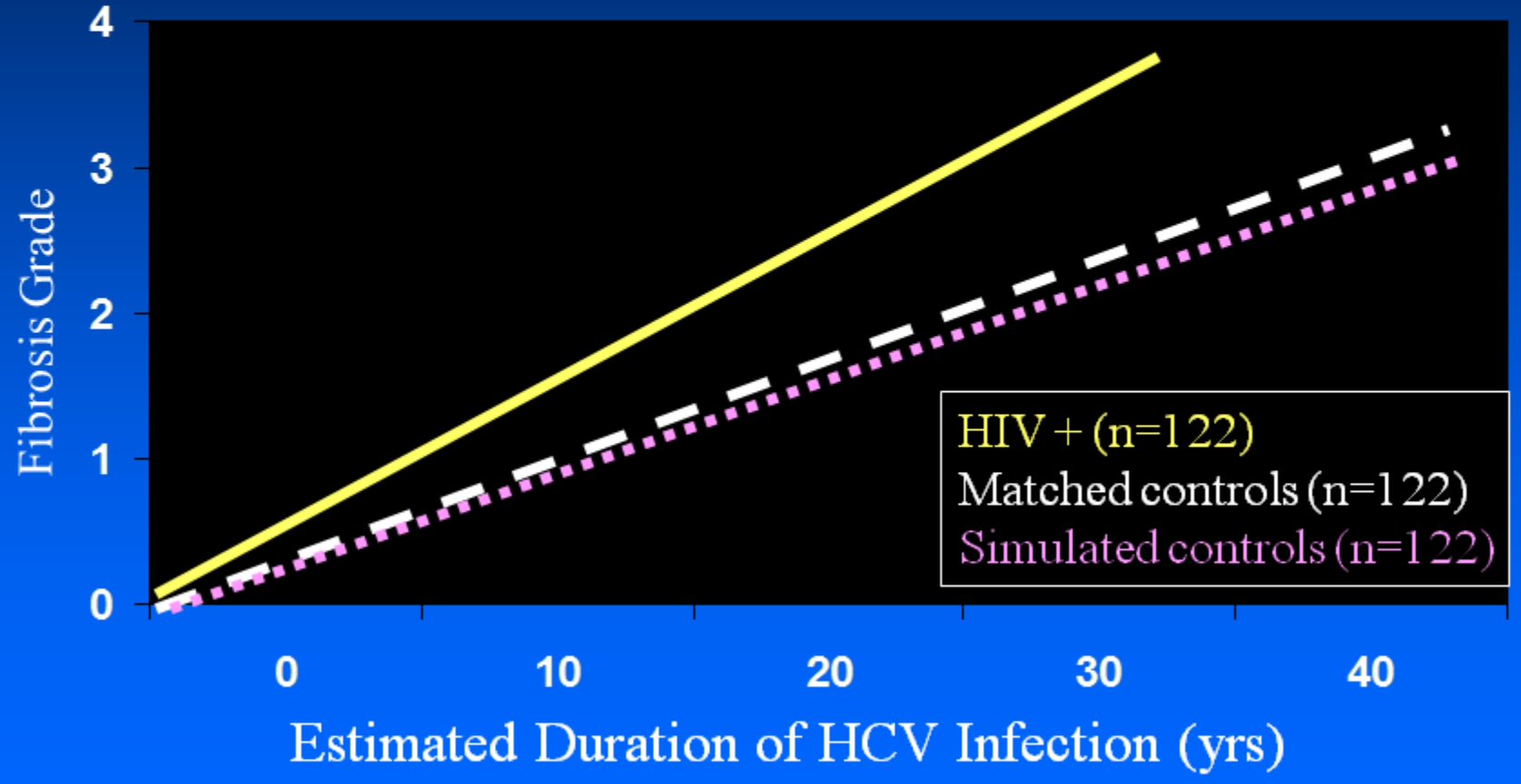
Impact of Viral Hepatitis on Mortality



*50% who died of ESLD had CD4 > 200

Salmon-Ceron et al J Hep 2005;42:799-805

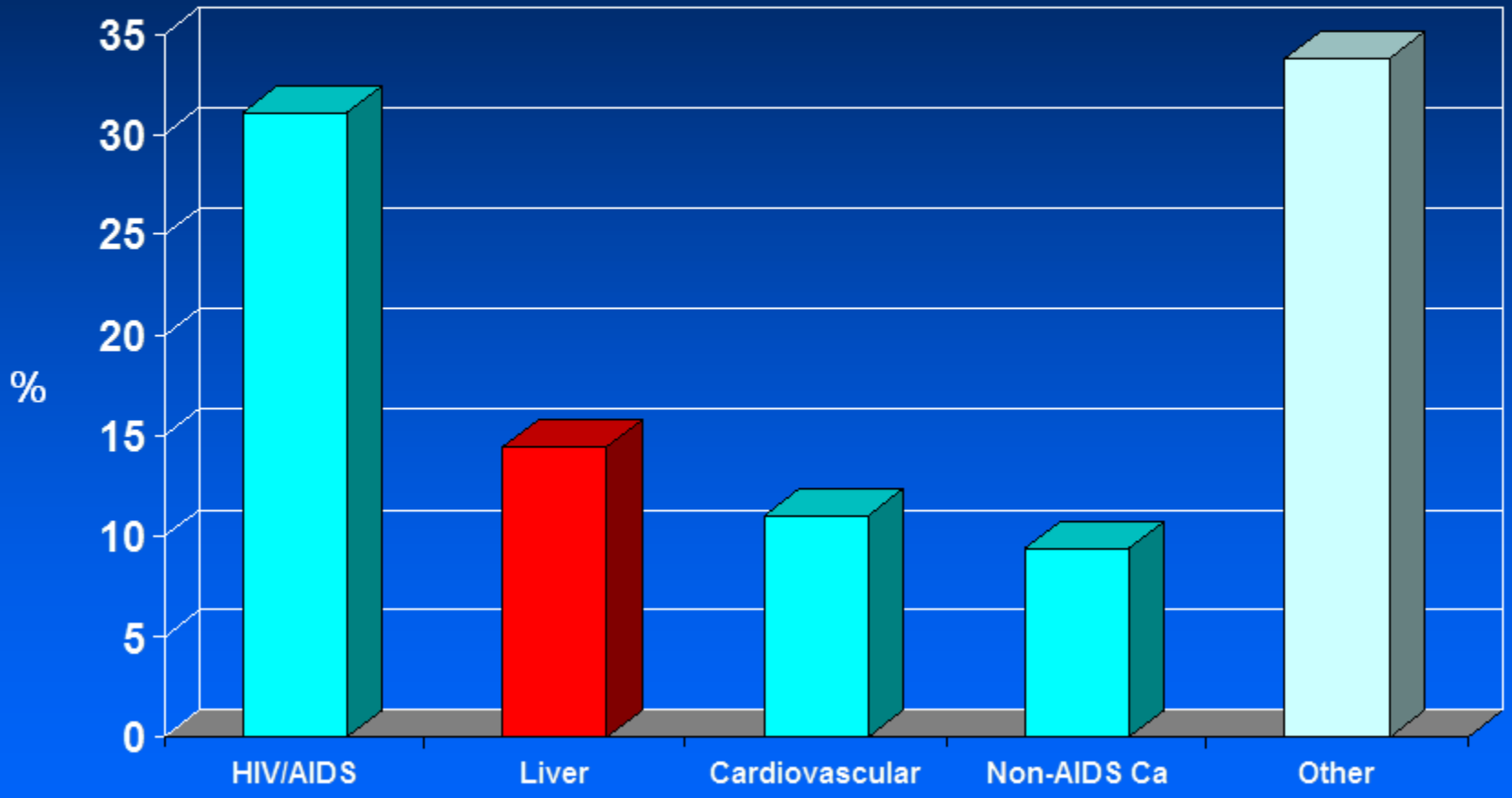
Accelerated Fibrosis in HIV-HCV co-infected patients



Benhamou et al. Hepatology 1999;30:1054-58

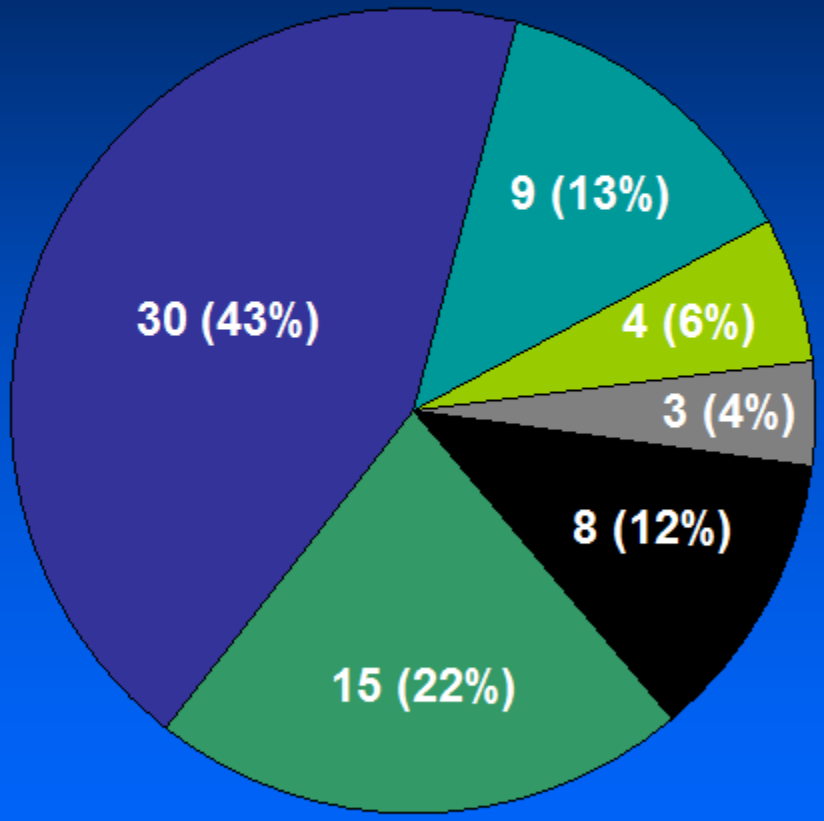
Liver-Related Deaths in HIV

1246 deaths in 23,441 HIV+ pts followed for 3.5 yrs
22% HCV, 8% HBV



D:A:D Study Arch Int Med 2006

Causes of Death in a HIV/HCV Coinfected Population



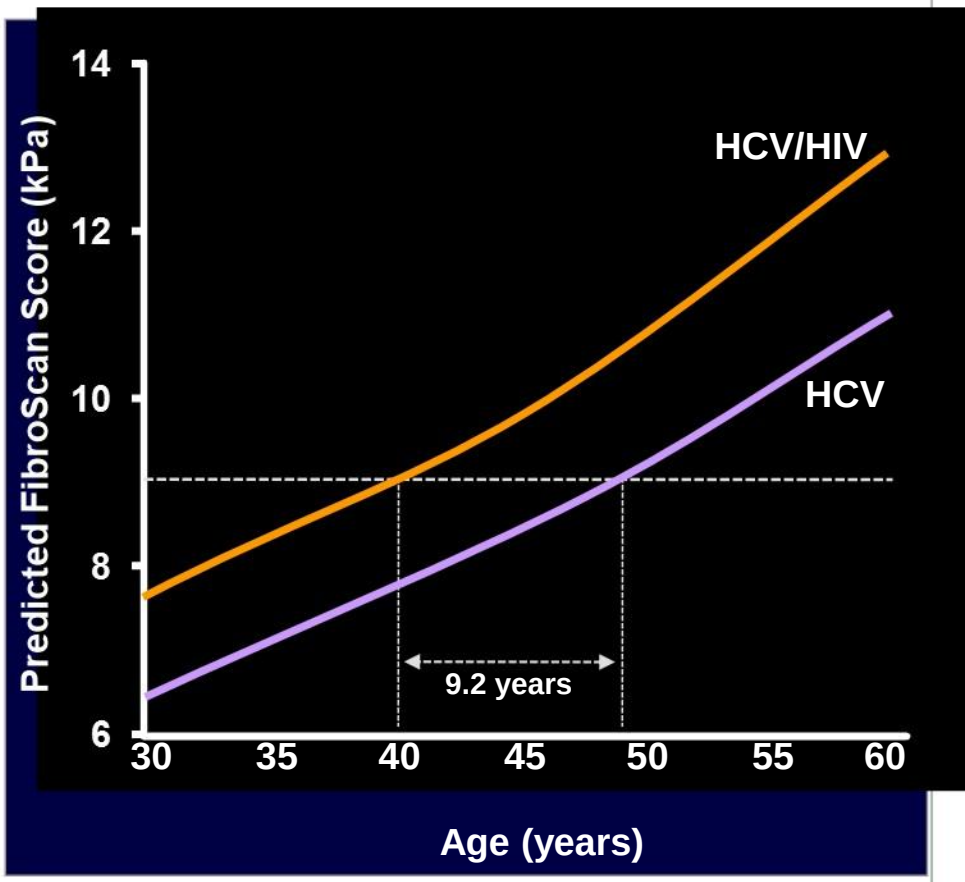
n/N = 69/1011

Twice a likely to die from liver disease than HIV

Pineda JA, et al. *Hepatology.* 2007;46:622-630.

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

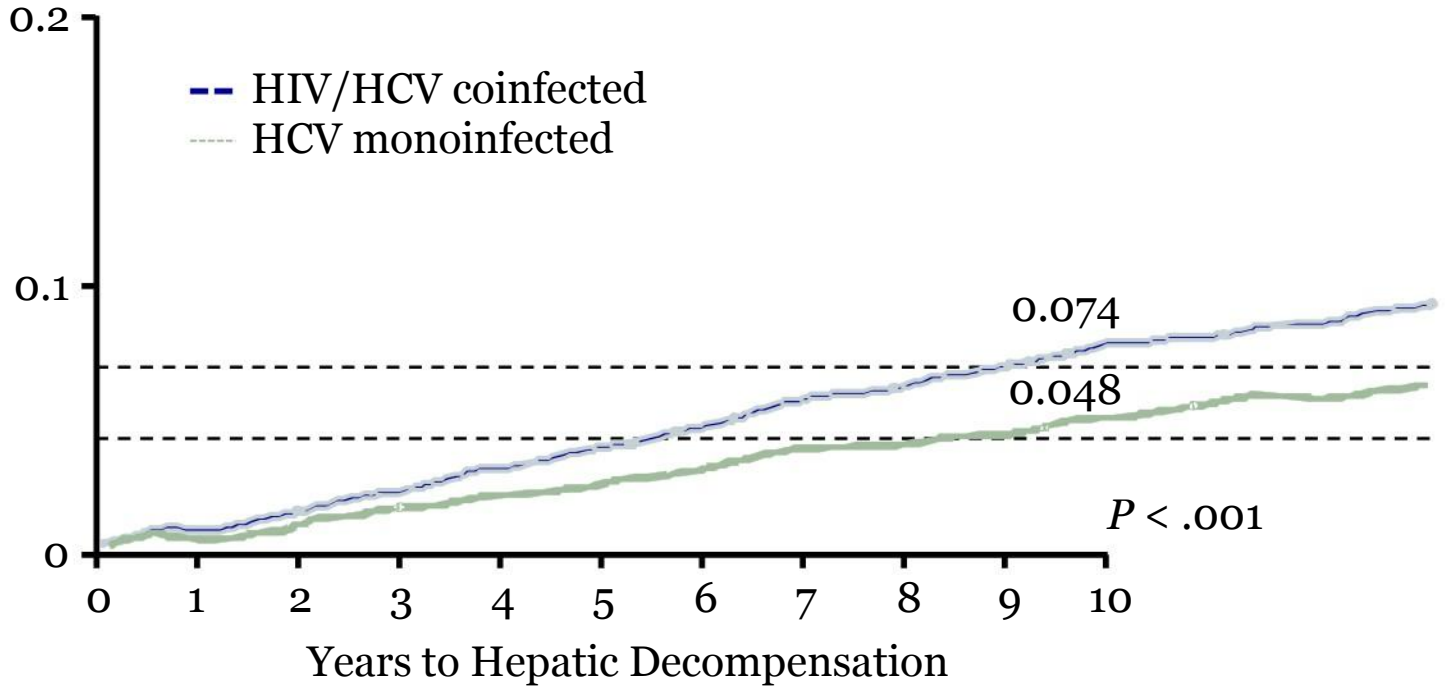
- Prospective cohort of HCV-infected IDUs (2006-2011) (n=1176)
  - HIV co-infected (n=394)
  - Baseline and semi-annual elastography
- Fibrosis was significantly greater in HCV/HIV co-infected versus HCV monoinfection (*P*<0.001)
  - No cirrhosis (12.9% versus 9.5%)
  - With cirrhosis (19.5% versus 11.0%)
  - 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.

Summary of HIV/HCV- co-infection

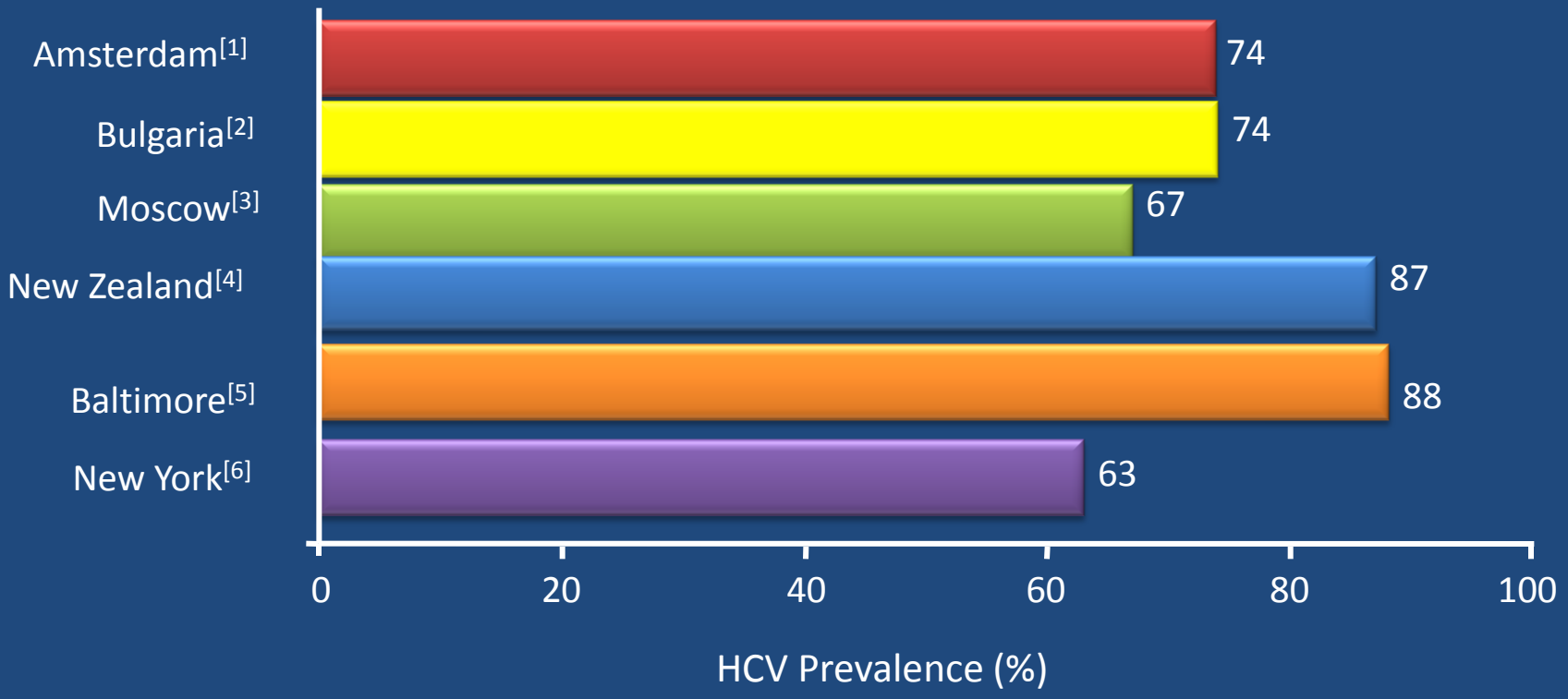
- Accelerated rate of HCV-related liver fibrosis progression in co-infected patients
  - Progression to cirrhosis risk 3-fold higher in co-infected vs HCV-mono-infected patients
  - Relative risk of decompensated liver disease 6-fold higher in co-infected vs HCV-monoinfected patients
  - HCC occurs earlier and more aggressive
- Increased risk of PMTCT of HCV
- Conflicting evidence on whether HCV influences HIV
- HIV confers greater risk of acute HCV infection and reduced rate of spontaneous clearance

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.

HCV transmission – risk factors

Parenteral	Sexual	Perinatal
IDU	Multiple partners	High viral load
Nasal cocaine	Traumatic	HIV (+)
Transfusions	HIV (+)	
Needle stick injury	Use of a CSW	
Tattoos	Rectal contact	
Body piercing	MSM	
Manicures		
Household items		
Toothbrush, razor, nail clipper		
? Scarification		

High Prevalence of HCV Among Injection Drug Users Worldwide



1. van den Hoek JA, et al. J Infect Dis. 1990;162:823-826. 2. Vassilev ZP, et al. Int J STD AIDS. 2006;17:621-626. 3. Rhodes T, et al. Addiction. 2006;101:252-266. 4. Kemp R, et al. N Z Med J. 1998;111:50-53. 5. Thomas DL, et al. Medicine. 1995;74:212-220. 6. Des Jarlais DC, et al. AIDS. 2005;19(suppl 3):S20-S25.

HCV prevalence in low/middle income countries – selected MSF data

- HCV prevalence in blood donors 2012: Centre African Republic: 7.1%, DRC: 8.5%, Nigeria: 7.2% (MSF Operational Center Amsterdam)
- Manipur India: prospective cohort analysis among 468 people infected with HIV, 50.6% are co infected with HCV.(MSF Operational Center Amsterdam)
- HCV screening in Ukraine: 74% of prisoners in MDRTB project are HCV positive. (MSF Ops Brussels)

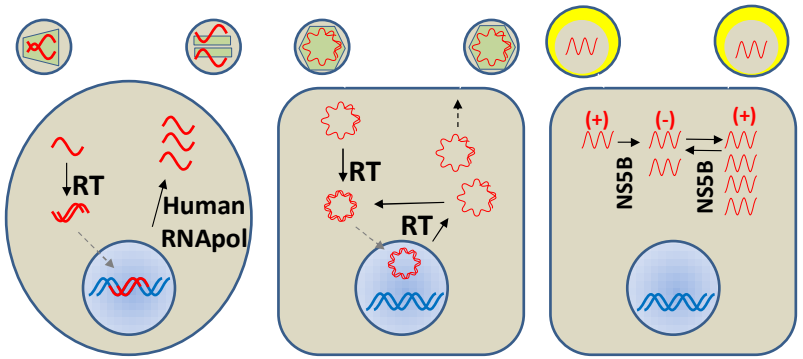
Aim of treatment :
Sustained Virological Response = SVR

= Negative HCV RNA 12 (24) weeks after EOT

= CURE

Aim of Hepatitis C treatment = cure

HCV life Cycle favors resistance development not persistence



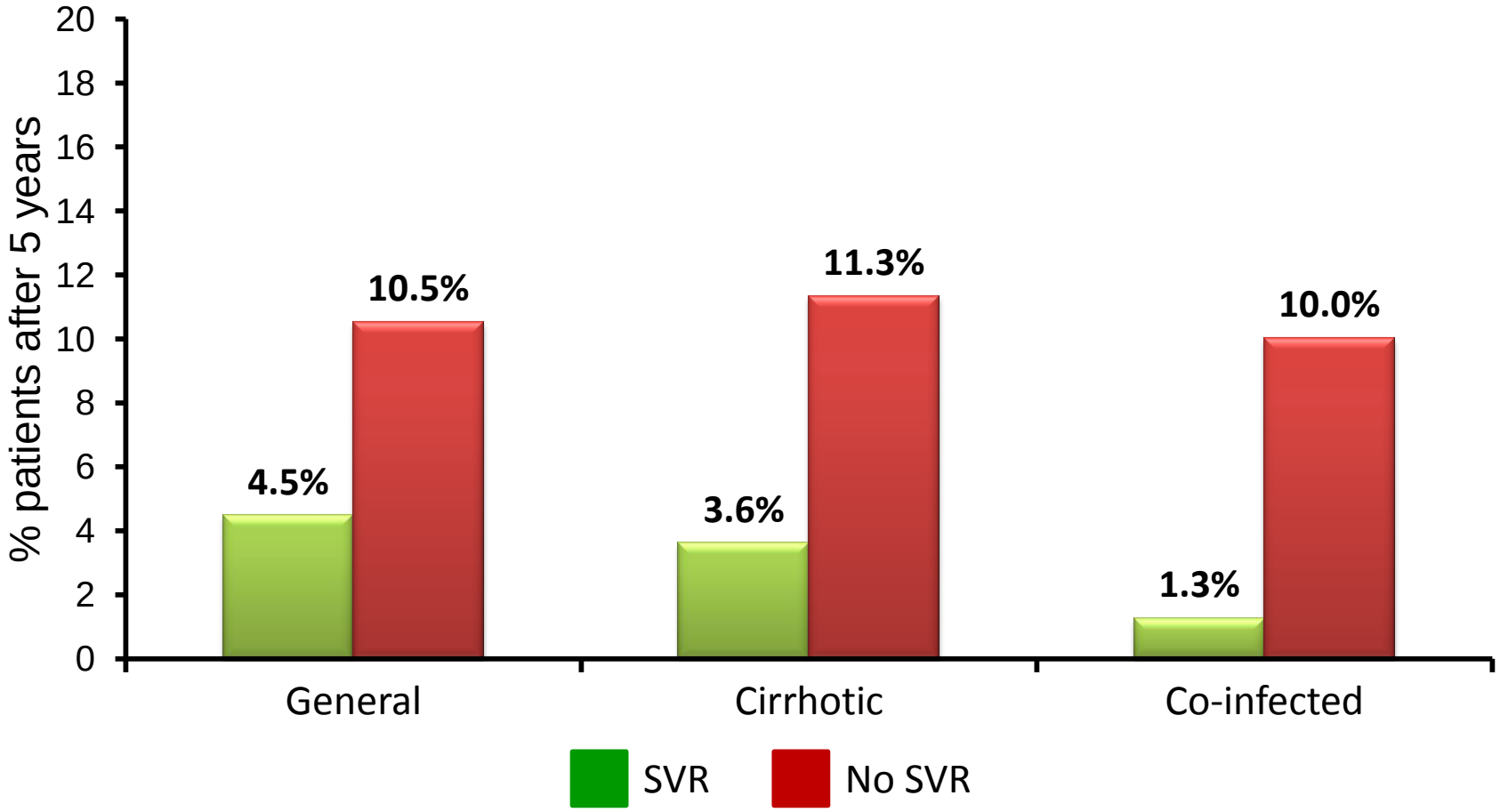
	HIV	HBV	HCV
Stable genome	Provirus	cccDNA	(none)
Virion NA polymerase	Host RNApol	HBV RT	HCV NS5B
Error-prone replications per cell	One	Multiple	Multiple
Plasticity of genome	High	Constrained	Very high
Recombination	Common	Common	Rare

5-year risk of death (all-cause) by SVR

General: 18 studies
n=29,269
Avg. FU=4.6 years

Cirrhotic: 9 studies
n=2,734
Avg. FU=6.6 years

HIV/HCV: 5 studies
n=2,560
Avg. FU=5.1 years

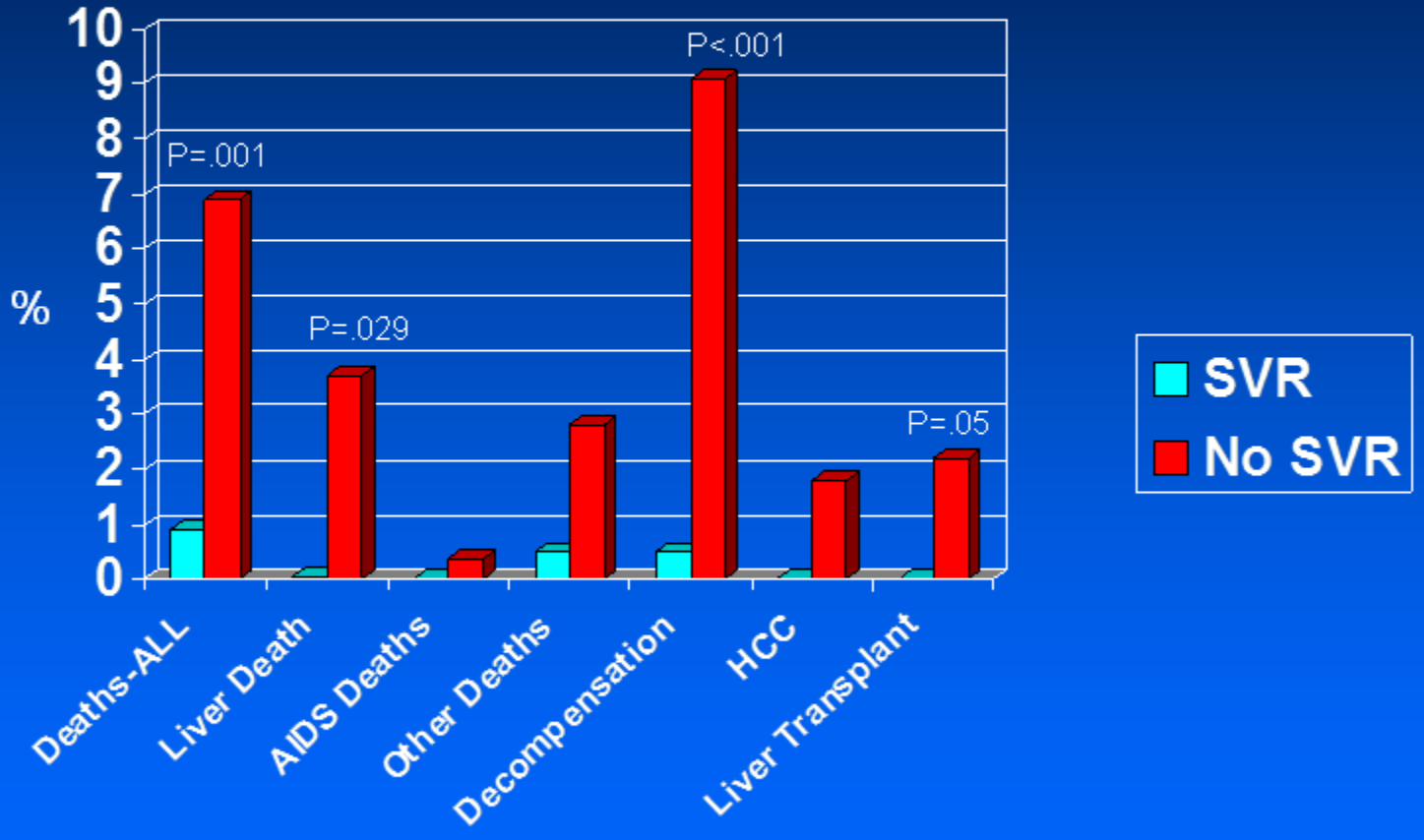


A Hill et al AASLD 2014

Does SVR improve outcomes?

711 HIV-HCV Pts treated 2000-2005

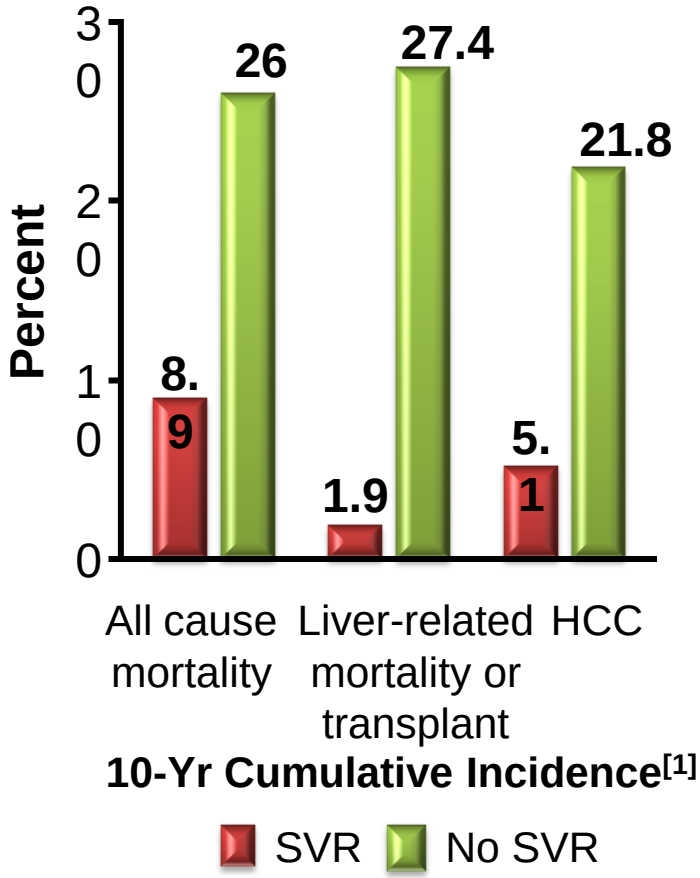
31% had SVR



Berenguer et al. Hepatology 2009;50:407-413

HCV Treatment Improves Health

- **Advanced fibrosis**
  - Multicenter study[1]
    - 5 hospitals (Europe, Canada)
  - 530 pts with HCV
    - IFN regimens 1990-2003
    - Advanced fibrosis or cirrhosis
    - Median follow-up: 8.4 yrs
- **Early-stage disease**
  - Extra-hepatic manifestations[2]
  - Health-related quality of life[3]

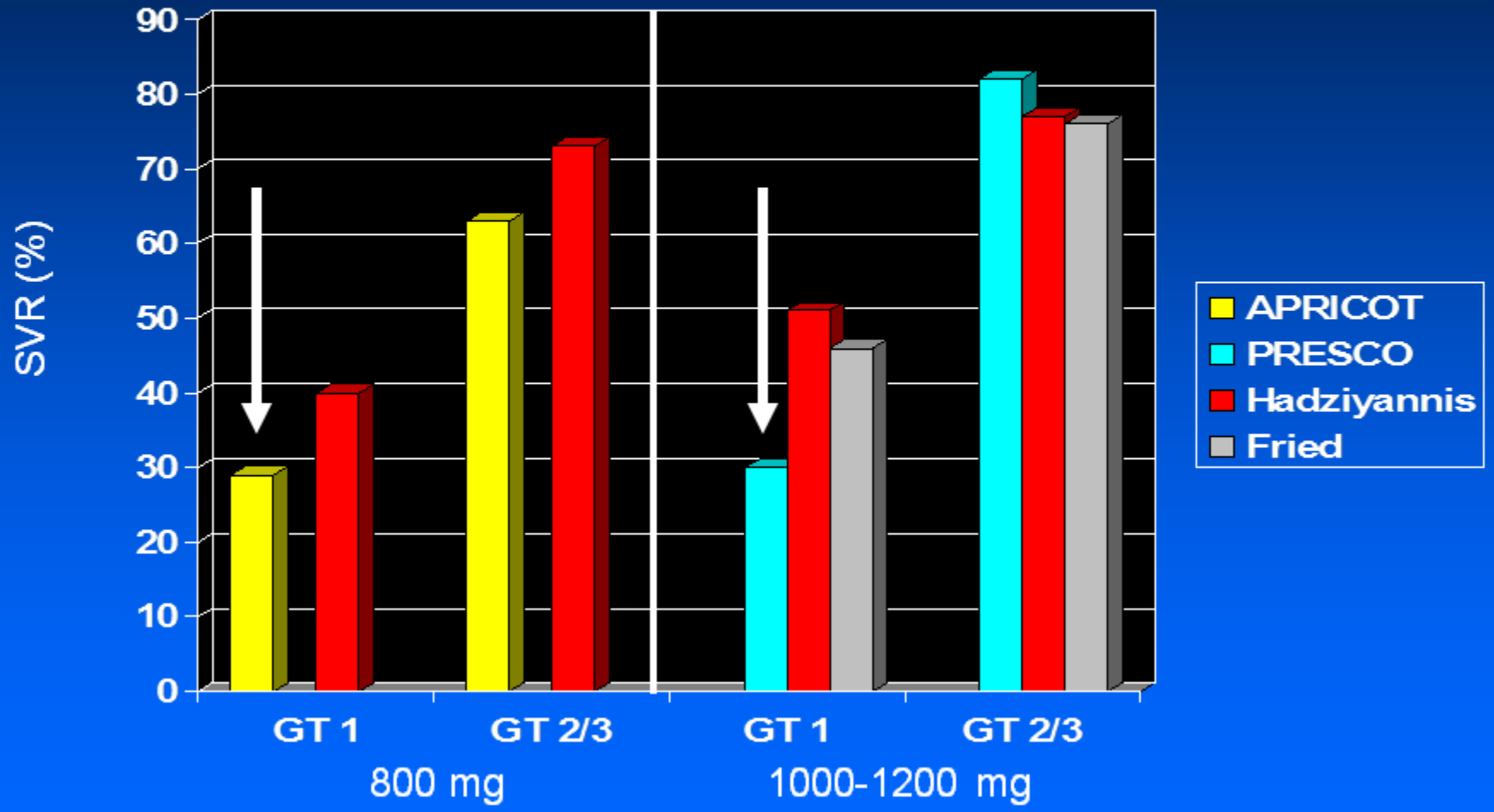


1. van der Meer AJ, et al. JAMA. 2012;308:2584-2593. 2. van der Meer AJ. Expert Rev Gastroenterol Hepatol. 2015;9:559-566. 3. Younossi Z, et al. Clin Gastroenterol Hepatol. 2014;12:1349-1359.

Treatment past and treatment present….

Treatment Past : PEG-Interferon and RIBAVIRIN

MONO- vs. CO-INFECTION outcomes

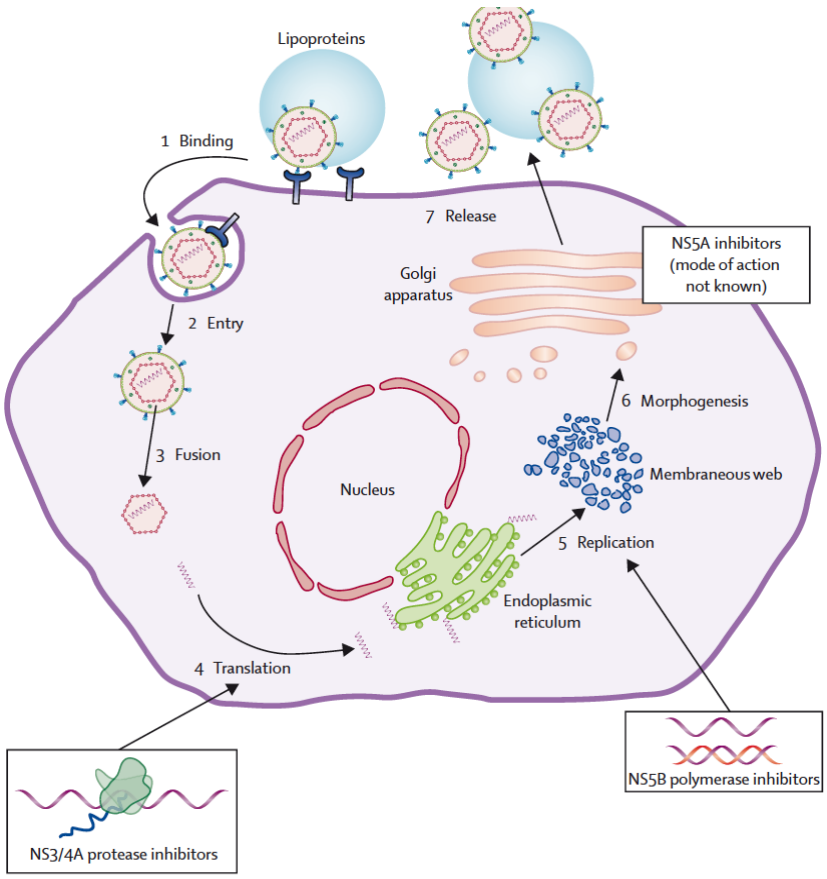


Hadziyannis et al, Ann Int Med 2004
Torriani et al. NEJM 2004

Fried et al. NEJM 2002
Nunez et al (PRESCO) AIDS Res Human Retro 2007

HCV life cycle – the ***D**irect **A**cting **A**ntivirals*

Allows for IFN-free all oral therapy



...previr

Simeprevir
Paritaprevir/r
Asunaprevir
Telaprevir
Boceprevir

...asvir

Daclatasvir
Ledipasvir
Ombitasvir

...buvir

Sofosbuvir
Dasabuvir

Cornberg M and Manns MP, *Lancet* 2014.

DAAs in 2015/16

Protease Inhibitors	Polymerase inhibitors		NS5A inhibitors
	Nucleotide	Non-nucleoside	
Telaprevir/ Boceprevir	Sofosbuvir	Dasabuvir	Daclatasvir
Simeprevir			Ledipasvir
Paritaprevir/ Ritonavir			Ombitasvir
Asunaprevir			Elbasvir
Grazoprevir			Velpatasvir

Guiding principles for all oral DAA regimens

- **Combine drugs from different classes**
  - Protease (NS3/4A) inhibitors
  - Polymerase (NS5B) inhibitors
  - NS5A inhibitors

- Multiple drugs combined to produce greater efficacy and reduce risk of viral resistance (not unlike HAART)

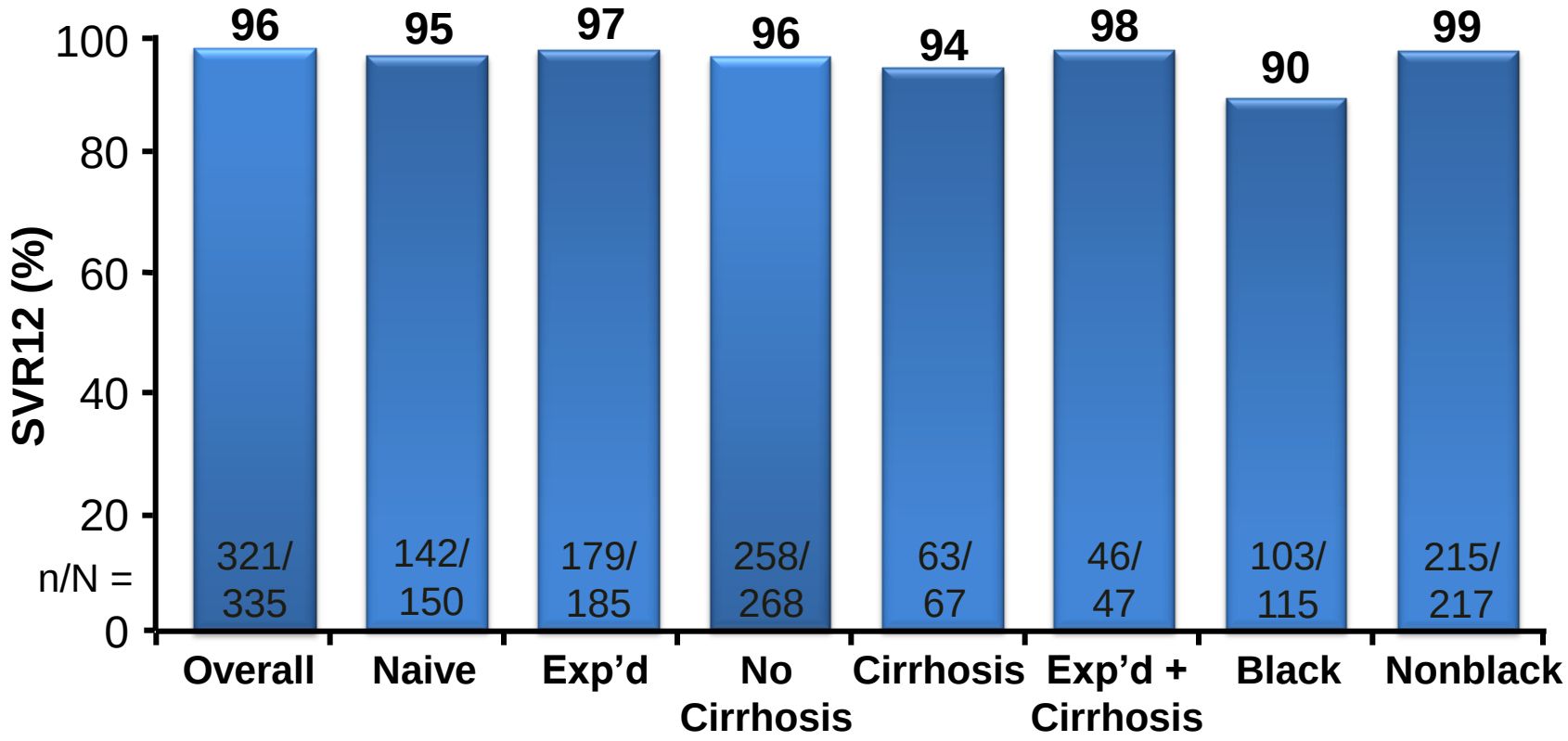
Indications for treatment

- Essentially everyone should be treated
- Treatment prioritization needs to be applied in resource limited settings

Treatment priority	Patient group
Treatment should be prioritized	. Patients with significant fibrosis (F3) or cirrhosis (F4), including decompensated cirrhosis . Patients with HIV coinfection . Patients with HBV coinfection . Patients with an indication for liver transplantation . Patients with HCV recurrence after liver transplantation . Patients with clinically significant extra-hepatic manifestations . Patients with debilitating fatigue . Individuals at risk of transmitting HCV
Treatment is justified	. Patients with moderate fibrosis (F2)
Treatment can be deferred	. Patients with no or mild disease (F0-F1) and none of the above-mentioned extra-hepatic manifestations
Treatment is not recommended	. Patients with limited life expectancy due to non-liver related comorbidities

Adapted from EASL Treatment Recommendations HCV, April 2015

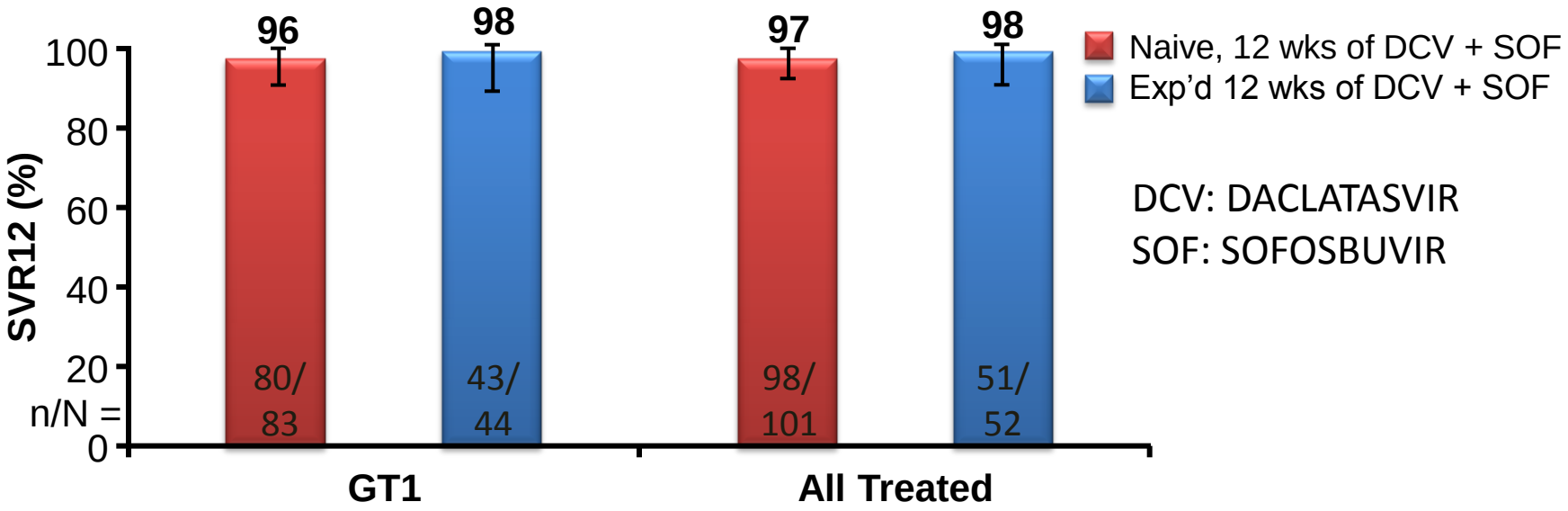
ION-4: LDV/SOF for 12 weeks in GT1/4 HCV/ HIV–coinfected



- Permitted ARTs: TDF/FTC plus efavirenz, raltegravir, or rilpivirine
- Effective across subgroups, but with lowered SVR in black pts
- LDV: LEDIPASVIR
- SOF: Sofosbuvir *(HARVONI)*

Naggie S, et al. CROI 2015

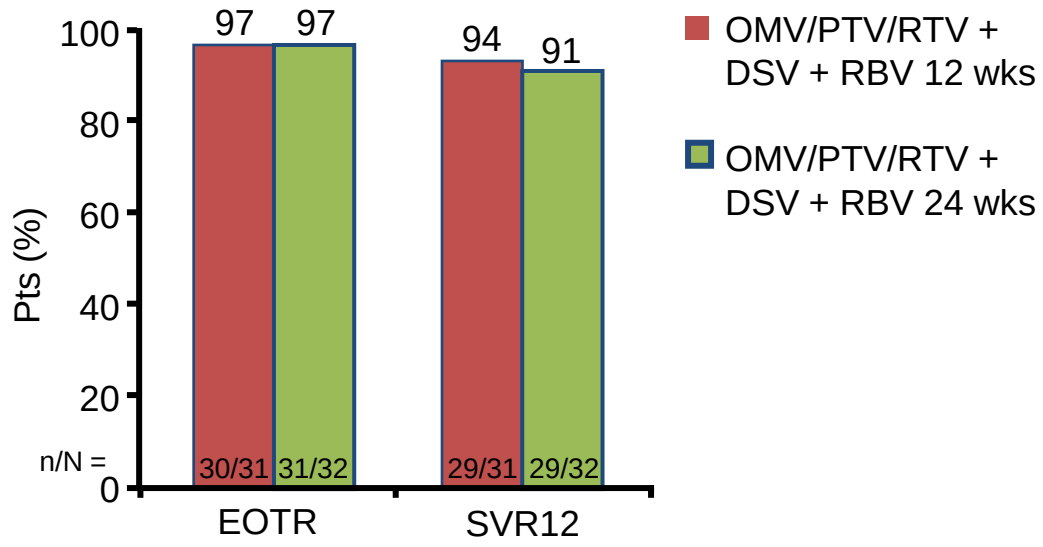
ALLY-2: DCV + SOF for 12 weeks in GT1-4 HCV/HIV–coinfected



- Permitted ARTs: atazanavir/ritonavir, darunavir/ritonavir, lopinavir/ritonavir, efavirenz, nevirapine, rilpivirine, dolutegravir, raltegravir, enfuvirtide, maraviroc, zidovudine, lamivudine, abacavir, tenofovir DF, emtricitabine
- Cirrhosis: 8.9% of naive pts, 28.8% of experienced pts
- No significant difference in SVR12 rates among black vs nonblack pts (92% vs 97%, respectively)
- 8 week arms in ALLY-2 inferior

N Engl J Med. 2015;373:714-25

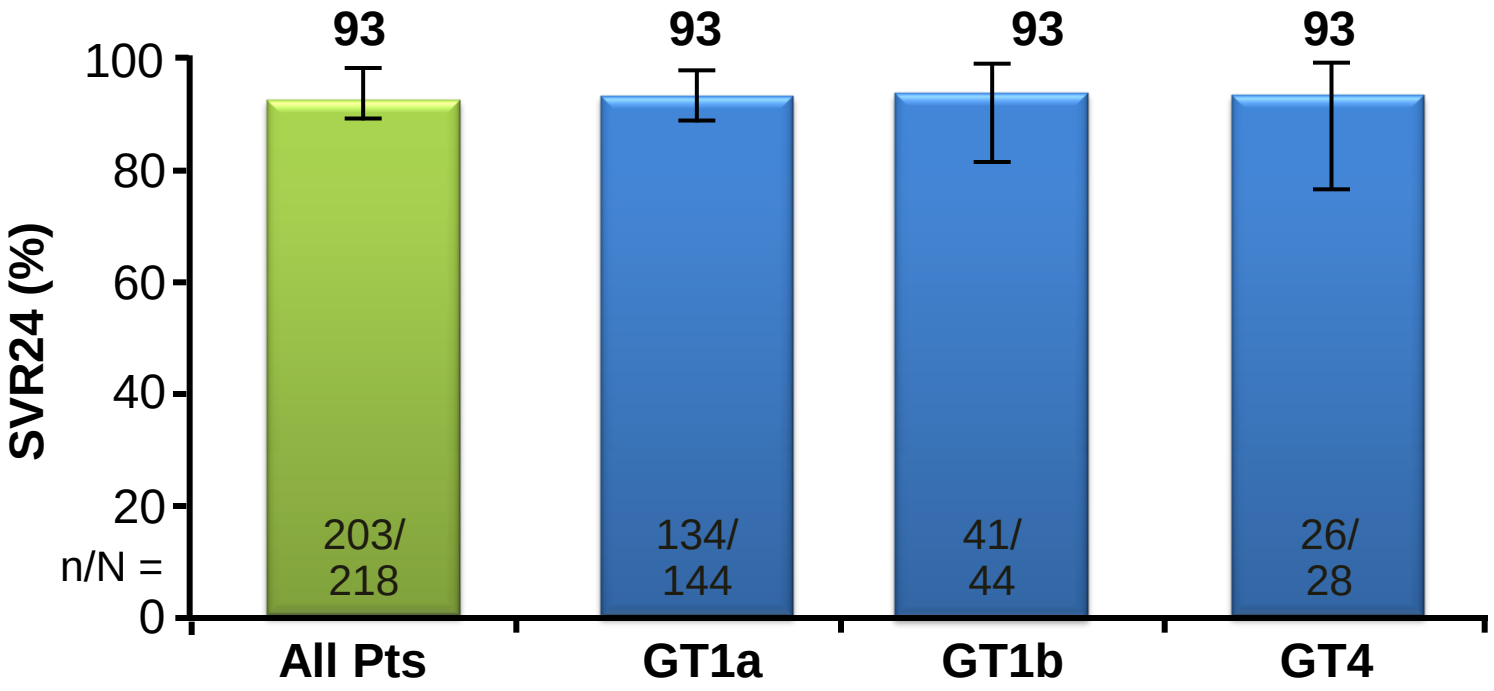
Ombitasvir/Paritaprevir/RTV + Dasabuvir + Ribavirin for 12 vs 24 weeks in GT1 HCV/HIV co-infection



- 65% HCV treatment–naive pts in 12-wk arm, 69% in 24-wk arm
- 19% pts with METAVIR F4 fibrosis

Sulkowski M, et al. JAMA. 2015;313:1223-1231

C-EDGE : Grazoprevir/Elbasvir for 12 weeks in GT1-4 HCV/HIV–coinfection



- SVR rates similar across pt subgroups, including in black pts and pts with cirrhosis
- Tx failure in 2 pts attributable to posttreatment reinfection with GT3 HCV

Rockstroh JK, et al. AASLD 2015. Abstract 210.

Summary – Treatment response

SVR Responses in Treatment naïve GT 1 HCV-HIV Coinfection and HCV Monoinfection						
Regimen	**HCV and HIV Coinfection**			**HCV Monoinfection**		
	Study	**n**	**SVR**	**Study (n)**	**n**	**SVR**
Daclatasvir + Sofosbuvir	ALLY-2	83	96%	AI444040	41	100%
Ledipasvir-sofosbuvir	ION-4	327	96%	ION-1	214	99%
Ombitasvir-Paritaprevir-Ritonavir + Dasabuvir + Ribavirin	TURQUOISE-I	31	94%	PEARL-III, IV	414	99%
Simeprevir + PR	C-212	53	79%	QUEST-1	264	80%
Sofosbuvir + PR	PS7977-1910	19	89%	NEUTRINO	291	90%
Sofosbuvir + Ribavirin	PHOTON-1	114	76%	NIH SPARE	25	68%

PR= Peginterferon + Ribavirin

Drug-Drug-interactions: Antiretrovirals

http://www.hep-druginteractions.org

University of Liverpool *HEP i-chart* (Android/Apple)

		SIM	DCV	SOF	LDV/SOF	3D
NRTIs	Abacavir	◆	◆	◆	◆	◆
	Didanosine	◆	◆	◆	◆	◆
	Emtricitabine	◆	◆	◆	◆	◆
	Lamivudine	◆	◆	◆	◆	◆
	Stavudine	◆	◆	◆	◆	◆
	Tenofovir	◆	◆	◆	■	◆
	Zidovudine	◆	◆	◆	◆	◆
NNRTIs	Efavirenz	●	■	◆	■*	●
	Etravirine	●	■	◆	◆	●
	Nevirapine	●	■	◆	◆	●
	Rilpivirine	◆	◆	◆	◆*	■
Protease inhibitors	Atazanavir; Atazanavir/Ritonavir	●	■	◆	◆*	■
	Darunavir/Ritonavir; Darunavir/Cobicistat	●	◆	◆	◆*	■
	Fosamprenavir	●	■	◆	◆*	■
	Lopinavir	●	◆	◆	◆*	●
	Saquinavir	●	■	◆	◆*	●
Entry/Integrase inhibitors	Dolutegravir	◆	◆	◆	◆	◆
	Elvitegravir/Cobicistat	●	■	◆	■*	●
	Maraviroc	◆	◆	◆	■	■
	Raltegravir	◆	◆	◆	◆	◆

HCV/HIV co-infection

- No longer considered difficult to cure
- Same recommendations as in HCV mono-infected
- Co-infected patients are a treatment priority
- Consider drug–drug interactions
- DCV + SOF ± RBV is recommended when ART regimen changes cannot be made to accommodate other DAAs

AASLD/IDSA. HCV guidelines.