Medical Education Workshops on HIV/AIDS

GreenShoots
FOUNDATION

Updates of Hep C co infection management in co-infected patients

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GreenShoots FOUNDATION

Topics to cover

- Diagnosis of HCV
- Epidemiology
- HCV genotypes
- Goal of HCV therapy
- Natural history of liver disease in HIV coinfection
- Monitoring under HCV therapy
- Antiviral HCV therapy
- Drug drug interactions
- Real world experience
- HCV elemination

How to diagnose acute and chronic HCV?

EASL JOURNAL OF HEPATOLOGY

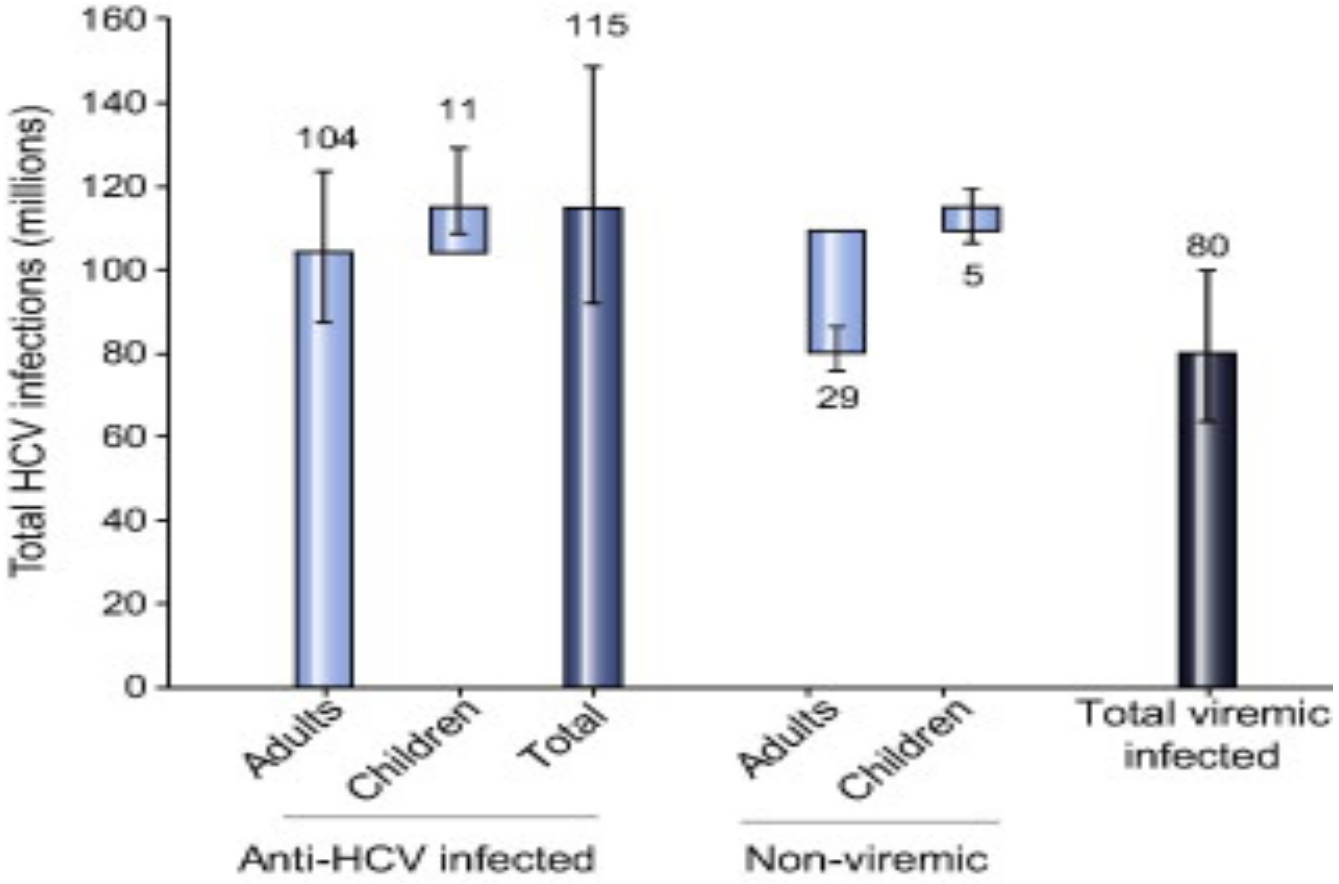
EASL Recommendations on Treatment of Hepatitis C 2015

European Association for the Study of the Liver *

- Anti-HCV antibodies are the first-line diagnostic test for HCV infection **(A1)**
- In the case of suspected acute hepatitis C or in immunocompromised patients, HCV RNA testing should be part of the initial evaluation **(A1)**
- If anti-HCV antibodies are detected, HCV RNA should be determined by a sensitive molecular method **(A1)**
- Anti-HCV-positive, HCV RNA negative individuals should be retested for HCV RNA three months later to confirm true convalescence **(A1)**

Epidemiology of HCV

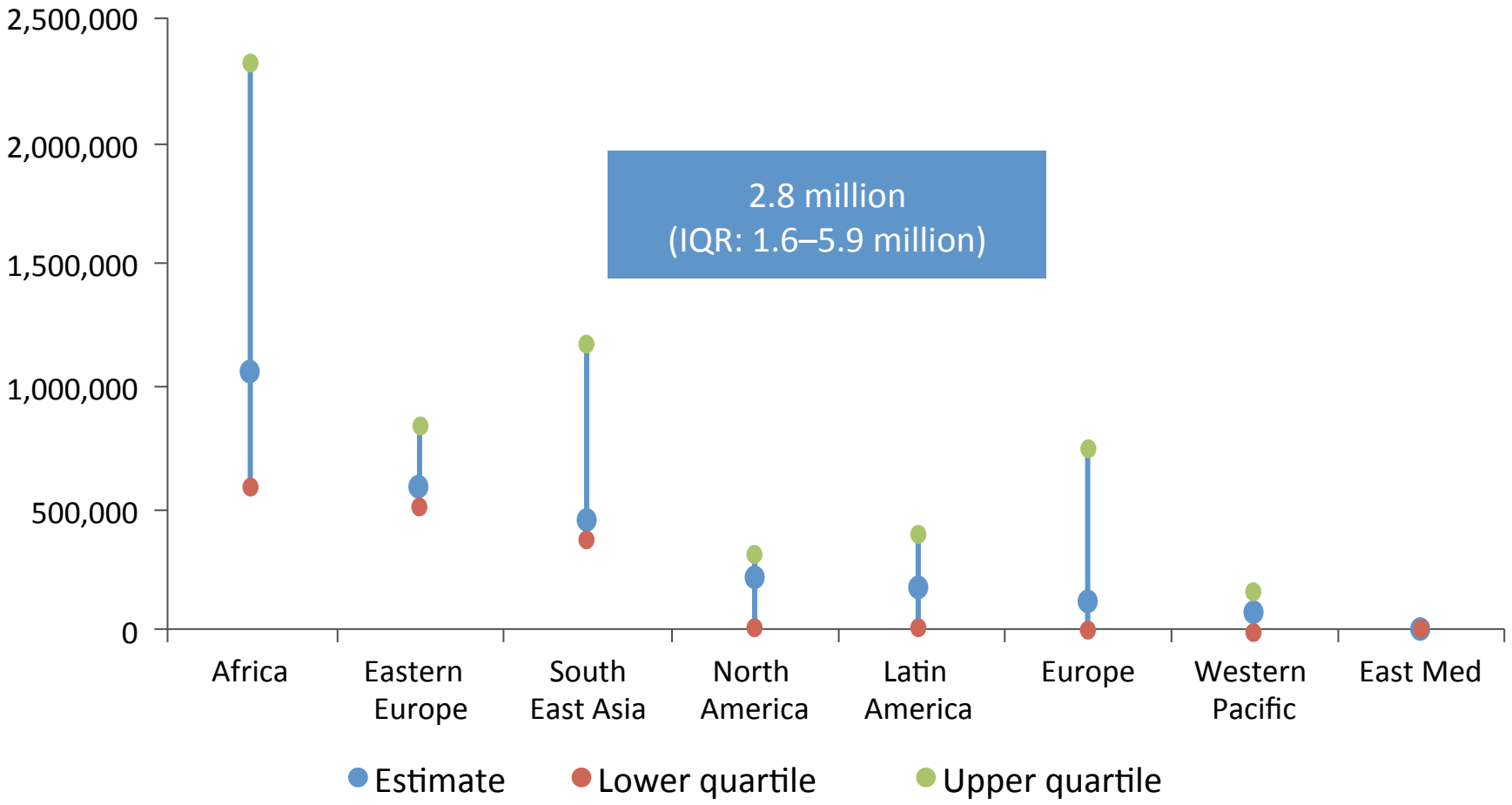
The global number of HCV infections
(anti-HCV and viraemic)



Gower E et al. Global epidemiology and genotype distribution of the hepatitis C virus. J of Hepatology 2014

Global prevalence of HIV/HCV co-infection

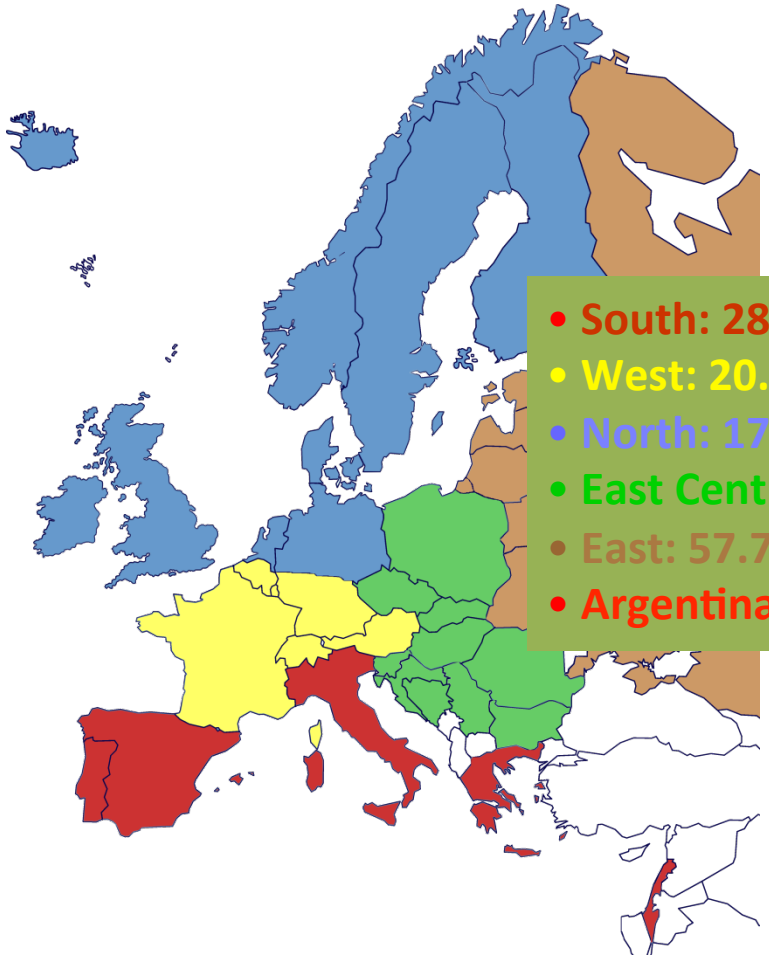
Burden of co-infection with HIV and HCV by region, 2013



Easterbrook P. International HIV/Viral Hepatitis Co-infection Satellite Meeting 2014.

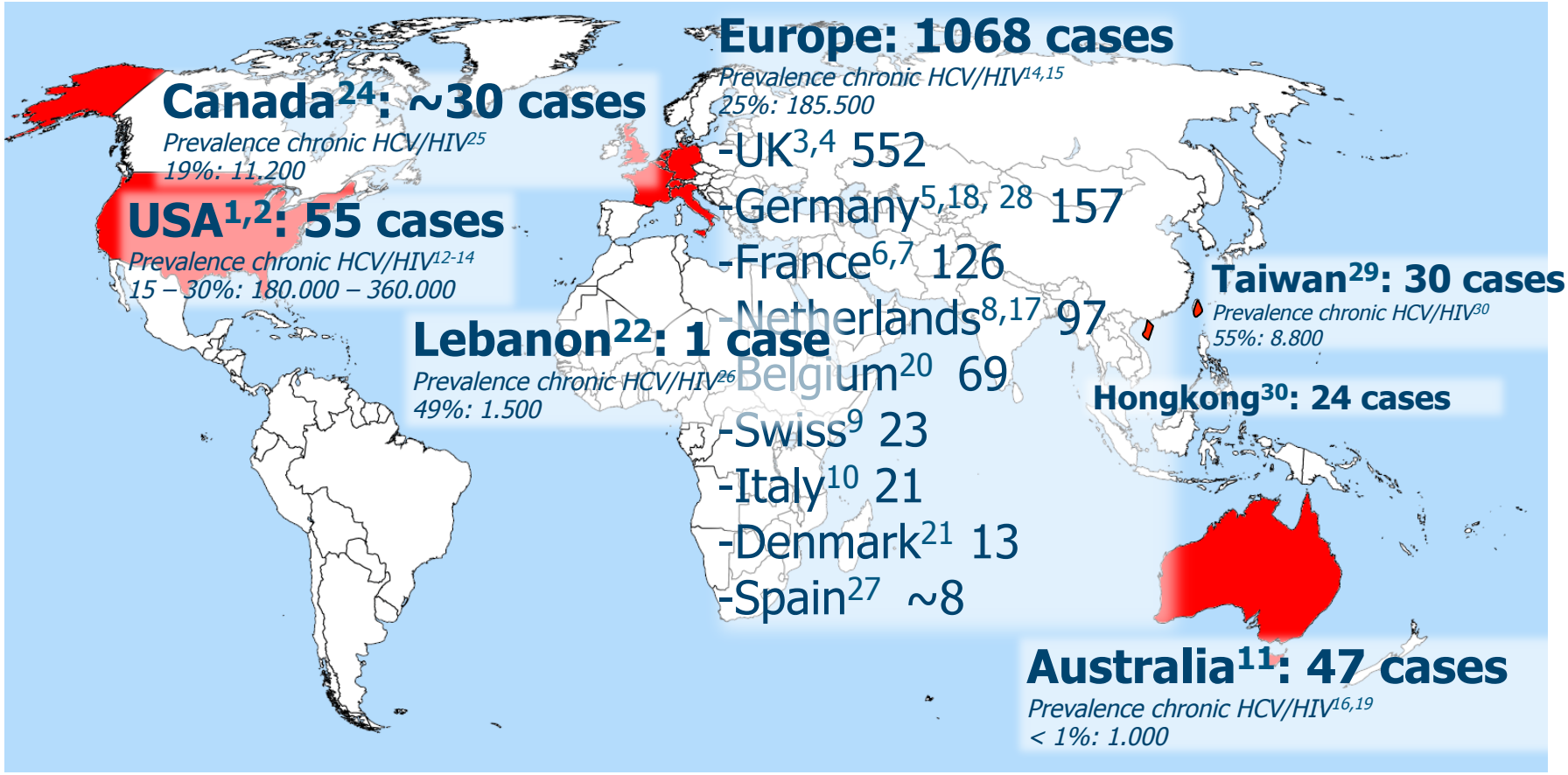
HCV, hepatitis C virus; IQR, inter-quartile ratio

Anti-HCV antibody prevalence in different EuroSIDA regions



Peters L et al., BMC Infect Dis. 2014;14 Suppl 6:S13

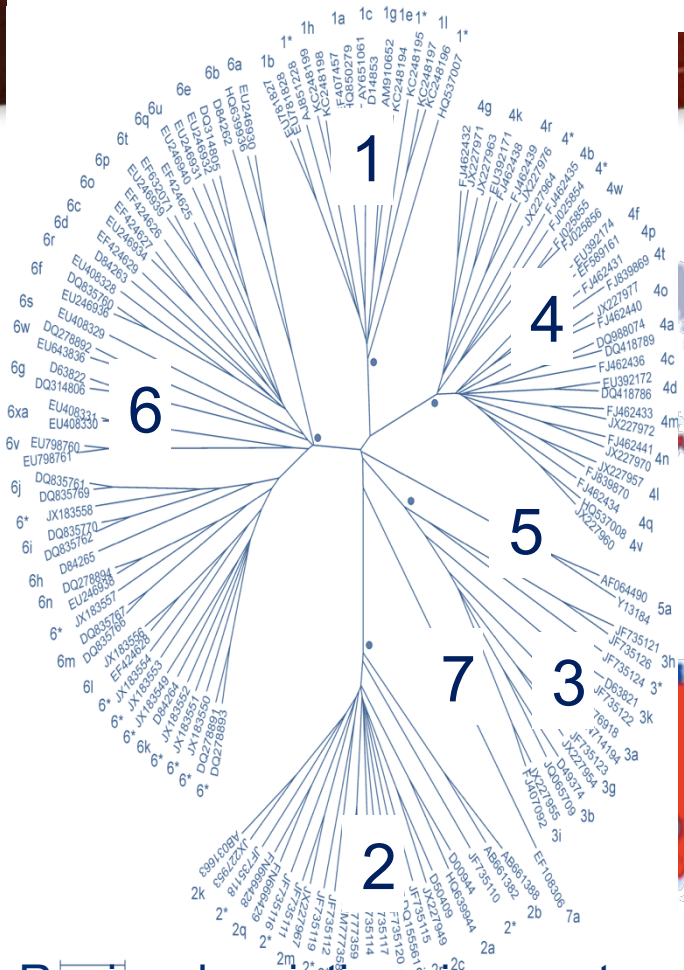
Acute HCV among HIV+ MSM



1:Luetkemeyer JAIDS 2006; 2:Cox Gastroenterology 2008; 3:Giraudon Sex Transm Infect 2008; 4:Ruf Eurosurveill 2008; 5:Vogel CID 2009; 6:Gambotti Euro Surveill 2005; 7:Morin Eur J Gastro Hepat 2010; 8:Urbanus AIDS 2009; 9:Rauch CID 2005; 10:Gallotta 4th Works. HIV & Hep. Coinf. 2008; 11:Matthews CID 2009; 12:Sherman CID 2002; 13:Backus JAIDS 2005; 14:UNAIDS Report 2008; 15:Soriano JID 2008; 16:Matthews CID 2011; 17:Arends Neth J Med 2011; 18:Neukam HIV Med 2011; 19:Pfafferott PLoS One 2011; 20:Bottieau Euro Surveill 2010; 21:Barfod Scand JID 2011; 22:Dionne-Odom Lancet Infect Dis 2009; 23:Taylor Gastroenterology 2009; 24:Hull personal conversation 2011; 25:Remis 1st Canadian HCV Conference 2001; 26:UNGASS Country progress Report 2010; 27:Soriano personal conversation 2011; 28:Boesecke 18thCROI Boston 2011 abstract #113; 29:Sun Liver International 2011; 30:Lee J F Med Assoc 2008;30: Chan DP, Virol J. 2015

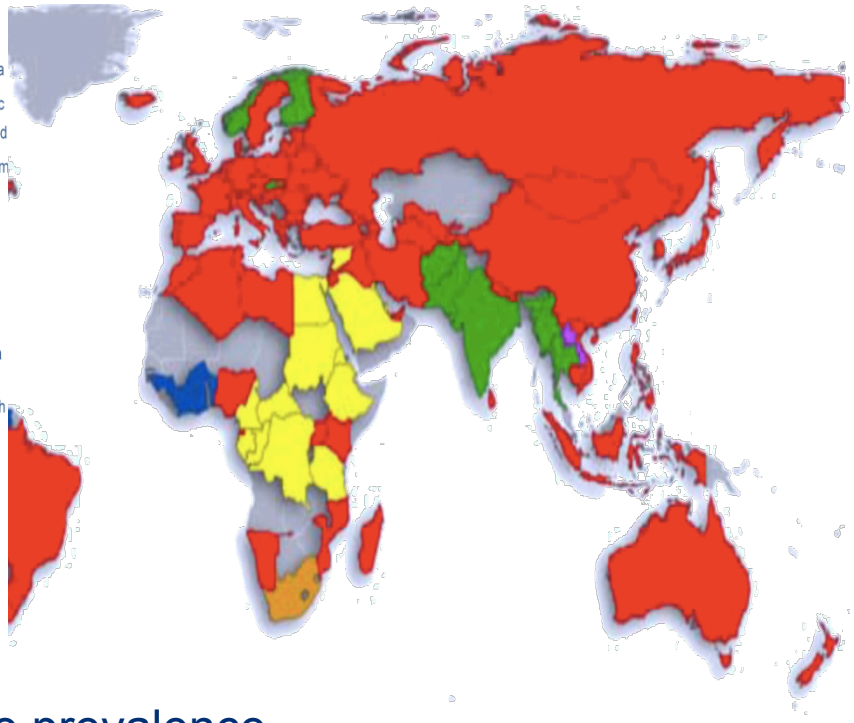
What are HCV genotypes?

HCV Genotypes



HCV genetically diverse

Seven genotypes and many subtypes.



- Regional variations in genotype prevalence
- G1 most common worldwide (44%-48%%) ~50-60 million cases, most in East Asia
- G4 and G5 more prevalent in lower-income countries.

Smith et al. Hepatology, 2014; 59:318-27. Gower, E., et al., J Hepatol 2014; 61:S45–S57. Messina J. et al. Hepatology, 2015;61:77-87

What is the goal of HCV therapy and what does SVR mean for further clinical endpoints?

What do we mean when we talk about 'cure' in HCV?

- Sustained virological response: Undetectable HCV RNA 12 weeks (SVR12) or 24 weeks (SVR24) after treatment completion[1]

- HCV is cured (does not relapse) in > 99% of patients who achieve SVR[1,2]

1. EASL recommendations on treatment of Hepatitis C, 2014.
2. Pearlman BL & Traub N. Clin Infect Dis 2011;52:889–900.

Concordance between SVR4, SVR12, and SVR24 in Phase 3 ION Studies

		SVR12, n	
		Yes	No
SVR4	Yes	1864	8
	No	0	30

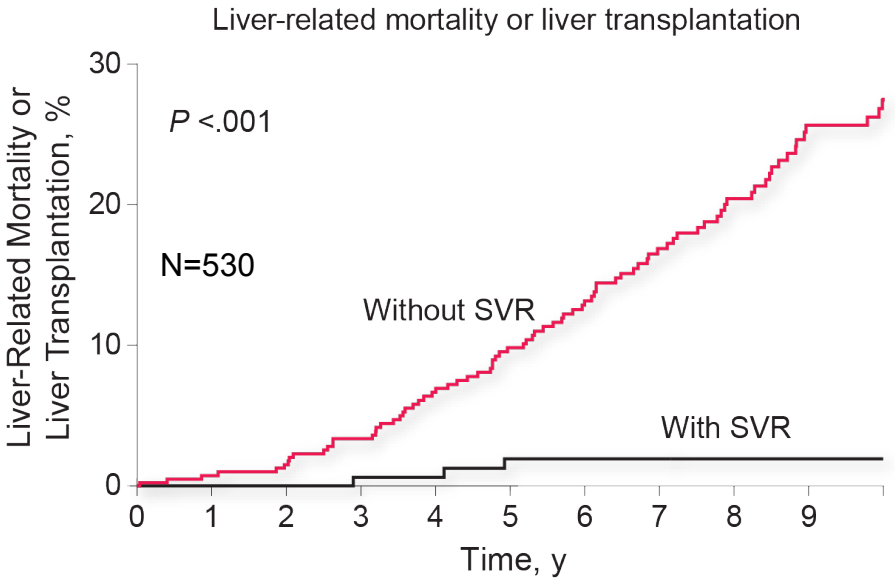
- 99.6% positive predictive value
- 100% negative predictive value

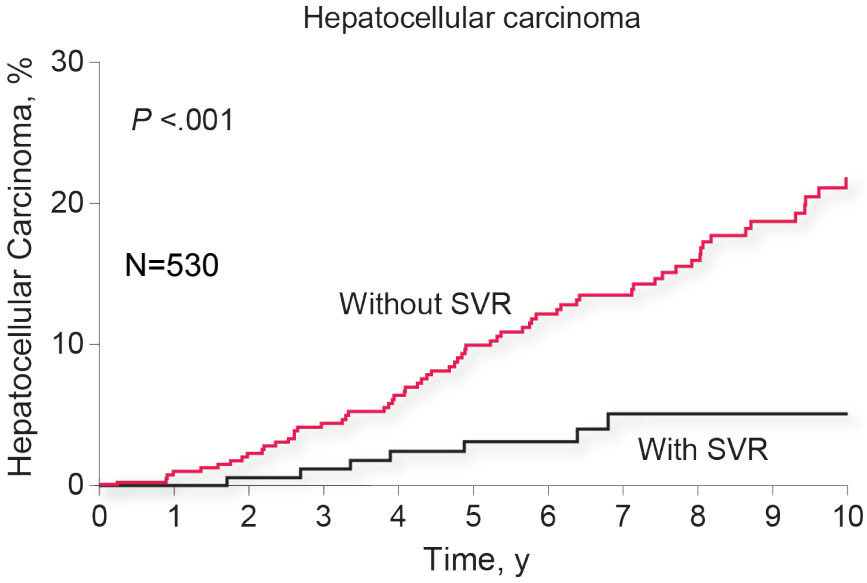
		SVR24, n	
		Yes	No
SVR12	Yes	1850	0
	No	0	3

- 100% positive predictive value
- 100% negative predictive value

Bernstein, AASLD, 2014, Poster #1947

Sustained Virologic Response is associated with a reduction in liver-related mortality and HCC



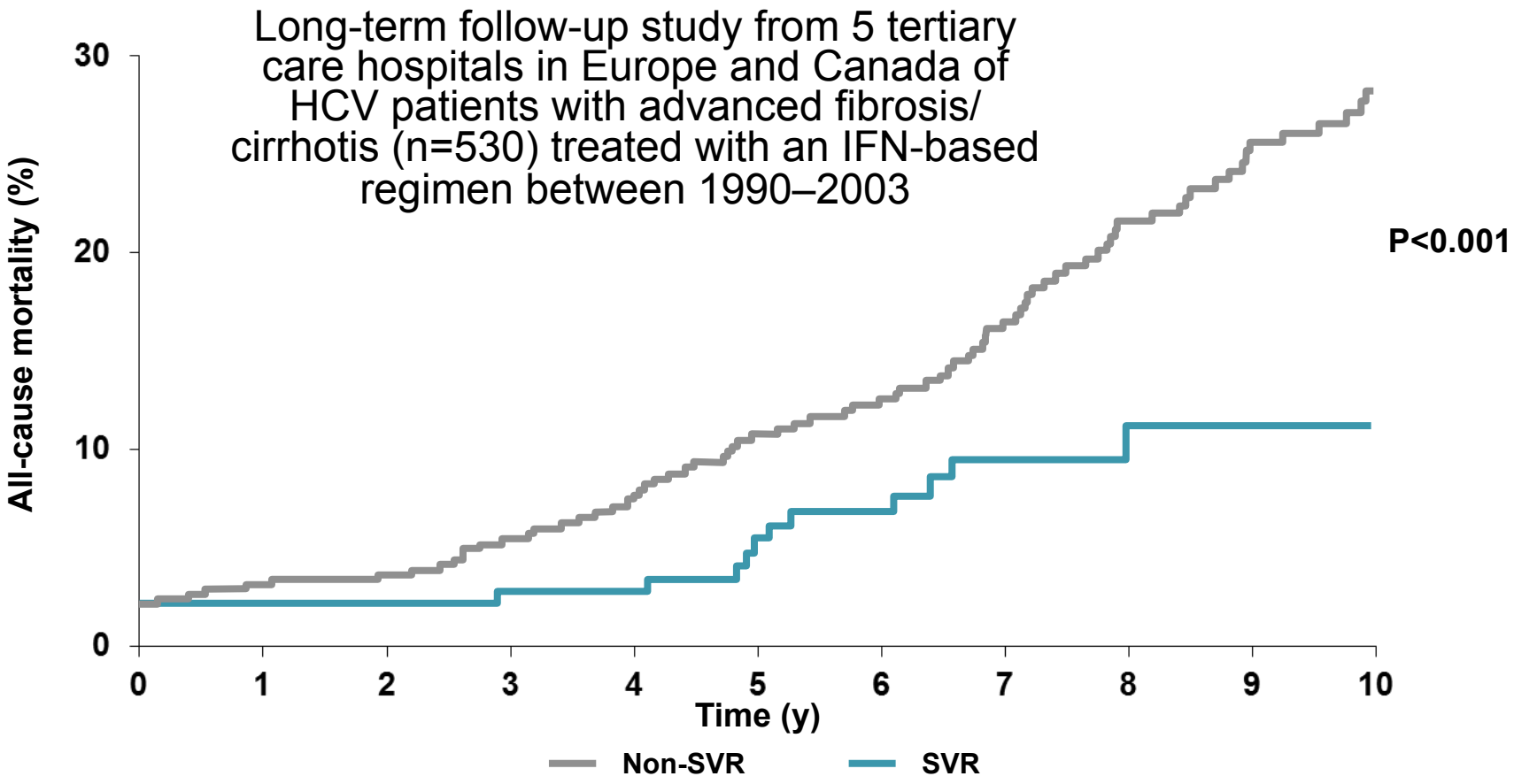


Ten-year cumulative incidence of liver-related mortality or transplantation in HCV patients (n=530) was also calculated in the European/Canadian study within five large tertiary hospitals. All patients had received an interferon-based regimen between 1990 and 2003.

van der Meer AJ, et al. *JAMA*. 2012; 308(24):2584-2593.

SVR reduces all-cause mortality

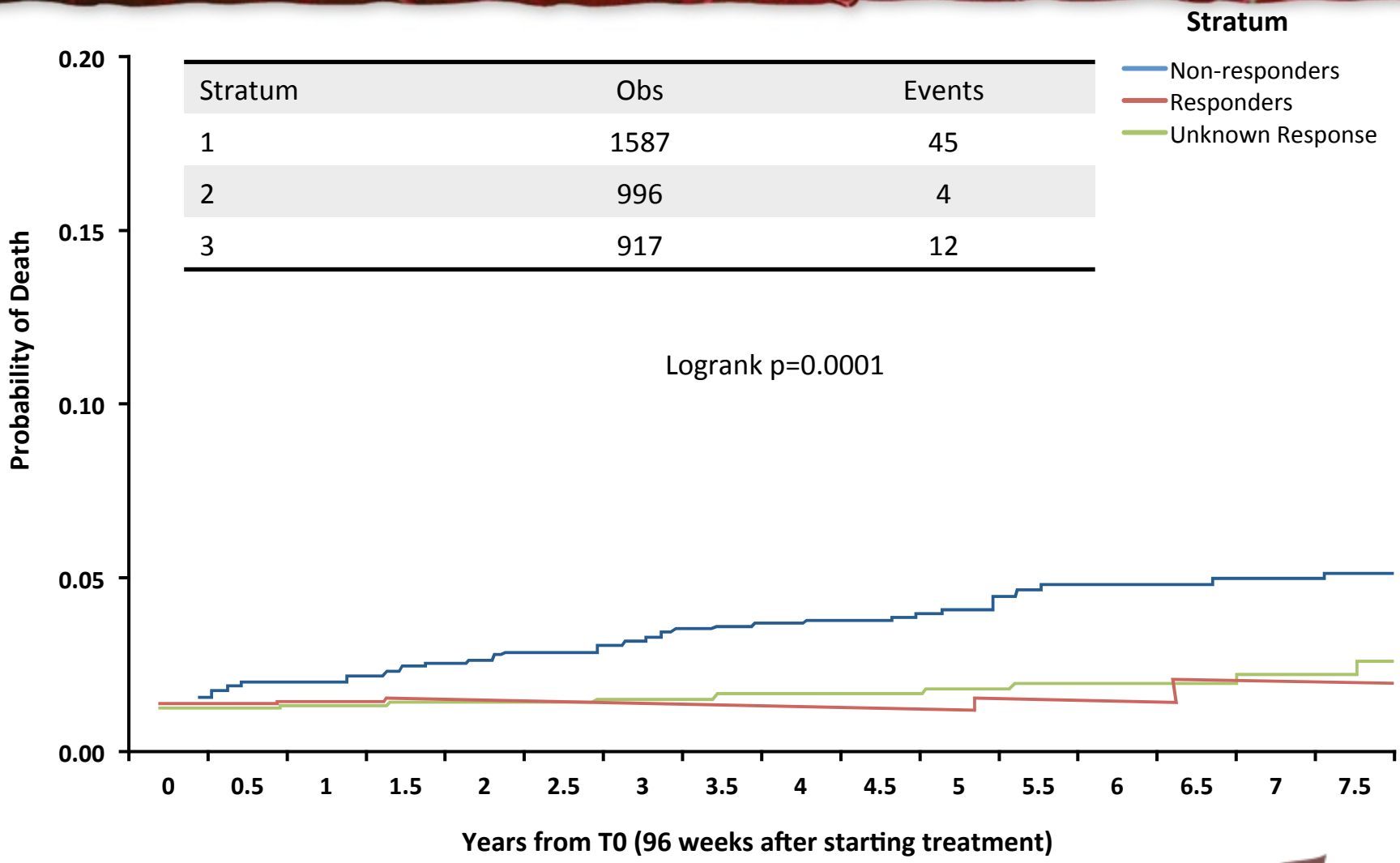
- IFN: interferon



van der Meer AJ, et al. JAMA 2012;308:2584–93.

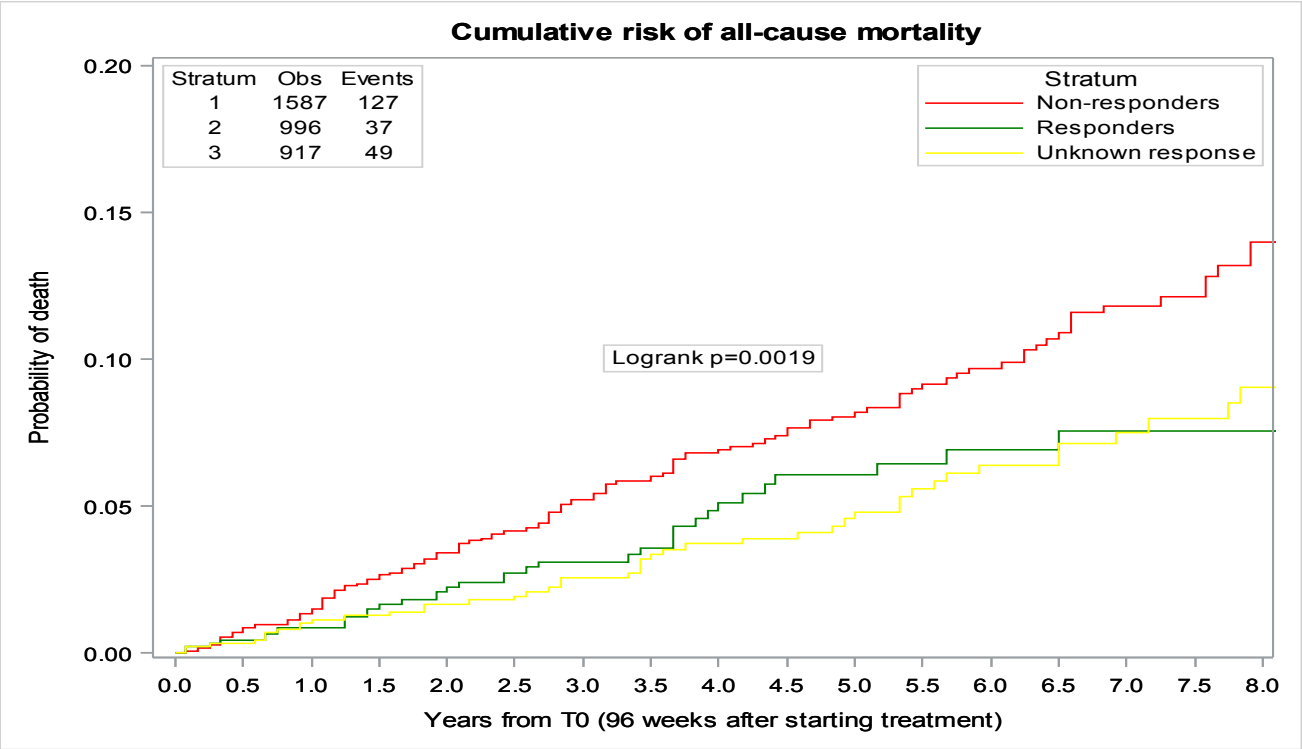
Cumalative Risk of Liver-Related Death after HCV therapy {n=3500} in HIV/HCV coinfected individuals

Stratum	Obs	Events
1	1587	45
2	996	4
3	917	12



Peters L, et al. EACS 2015, abstract 550

Cumulative risk of all-cause mortality after HCV therapy (n=3500)



Non-responders	1587	1428	1222	998	814	626	479	334	201
Responders	996	818	646	472	342	256	174	114	65
Unknown response	917	828	736	632	518	408	308	225	151

Peters L et al., EACS 2015

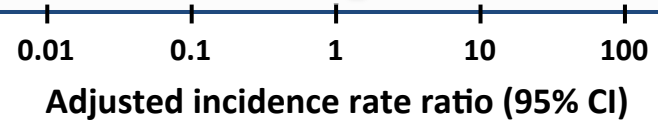
How is the course of HCV different in HIV-coinfection?

HCV co-infection in EuroSIDA

- EuroSIDA: prospective, European study of 18,295 HIV-1–infected patients at 105 centres across Europe, Israel and Argentina
- Prevalence of HCV seropositivity in EuroSIDA is 31% (4,044 patients), 74;2% of which were serum HCV RNA-positive

Progression to liver-related death in HIV-positive population

HCVAb serostatus:	Events (PYFU)	IRR (95% CI; p value)
Negative	43 (66,653)	1
Positive	175 (26,494)	8.90 (5.60–14.14; p<0.0001)
HCV genotype		
GT 1	55 (8122)	1
GT 2	2 (554)	0.27 (0.07–1.13; p=0.073)
GT 3	28 (4503)	0.99 (0.62–1.59; p=0.98)
GT 4	9 (2188)	0.91 (0.44–1.89; p=0.80)
HCV-RNA viremia		
HCVAb-	43 (66,653)	0.18 (0.10–0.32; p<0.0001)
Ab+/RNA-	21 (4838)	1
Ab+/RNA+	86 (11,302)	2.11 (1.30–3.42; p=0.0025)
Ab+/unknown	68 (10,354)	1.42 (0.86–2.35; p=0.17)



Multivariate analysis adjusted for gender, exposure group, race, prior AIDS, region of Europe, CD4+ T-cell nadir, HCV treatment status at baseline, age, and baseline date. Starting cART, HBsAg status, diagnosis of a new AIDS-defining illness and CD4+ T-cell count were included as time-updated variables.

HCVAb, anti-HCV antibodies; PYFU, person years of follow-up; IRR, incidence rate ratio;

Rockstroh J et al. *J Hepatol* 2013;59(2):213-220

HIV/HCV co-infection burden: Accelerated disease progression and morbidity

- ↑ Prevalence, especially in some populations[1–3]
- Compared with HCV mono-infected patients, patients co-infected with HIV display:
  - ↑ viraemia (2–8-fold greater)[1,4]
    - ↑ infectivity increases risk of transmission from mother to child (20% vs 6%) and risk of sexual transmission (3% vs <1%)[1,5]
  - ↓ likelihood of spontaneously clearing HCV[1,4]
  - ↑ hepatic fibrosis (2–5-fold greater), cirrhosis, decompensation, hepatocellular carcinoma and liver-related mortality[1,5]

1. World Health Organization. Protocol 6. Management of hepatitis C and HIV coinfection. WHO Regional Office for Europe 2007;
2. Wiessing L, et al. Euro Surveill 2011;16:pii:20031; 3. Taylor LE, et al. Clin Infect Dis 2012;55(S1):S33–42; 4. Sherman KE, et al. Gastroenterology 2005;128:313–27; 5. Vallet-Pichard A, Pol S. J Hepatol 2006;44(S1):S28–34.

What is the optimal treatment strategy in HIV/HCV co-infected patients?

Treat HCV first?

Treat HIV first?

Treat HIV/HCV simultaneously?

EACS guidelin


The New York Times

F.C.C. CHIEF SEEKS BROADBAND PLAN TO AID THE POOR

AFTER INDICTING 14, U.S. VOWS TO END GRAFT IN SOCCER

Prosecutors Say Charges Against FIFA Officials and Others Are Just the Start

- Initiation of AR
  - ART is always i … mm^3

First, antiretroviral therapy (ART) should be initiated in everyone living with HIV at any CD4 cell count.

	mphocyte count
	>500
HBV requiring	R
HBV not requir	C
HCV for which or given	C
HCV for which	C

Symptomatic HIV disease (CDC B or C conditions, incl. tuberculosis)	Asymptomatic HIV infection	
Any CD4 count	Current CD4 count	
	< 350	≥ 350
SR	SR	R

SR = Strongly Recommended
R = Recommended


Sunnis Fleeing ISIS Find Few Doors Are Open Elsewhere in Iraq

- EACS treatment guidelines, Version 7.1 2014. Acce… …ecommended
  Available at: http://www.europeanaidsclinicalsociety.org

Antiretroviral therapy reduces the rate of hepatic decompensation among HIV- and hepatitis C virus-coinfected veterans

Objective:

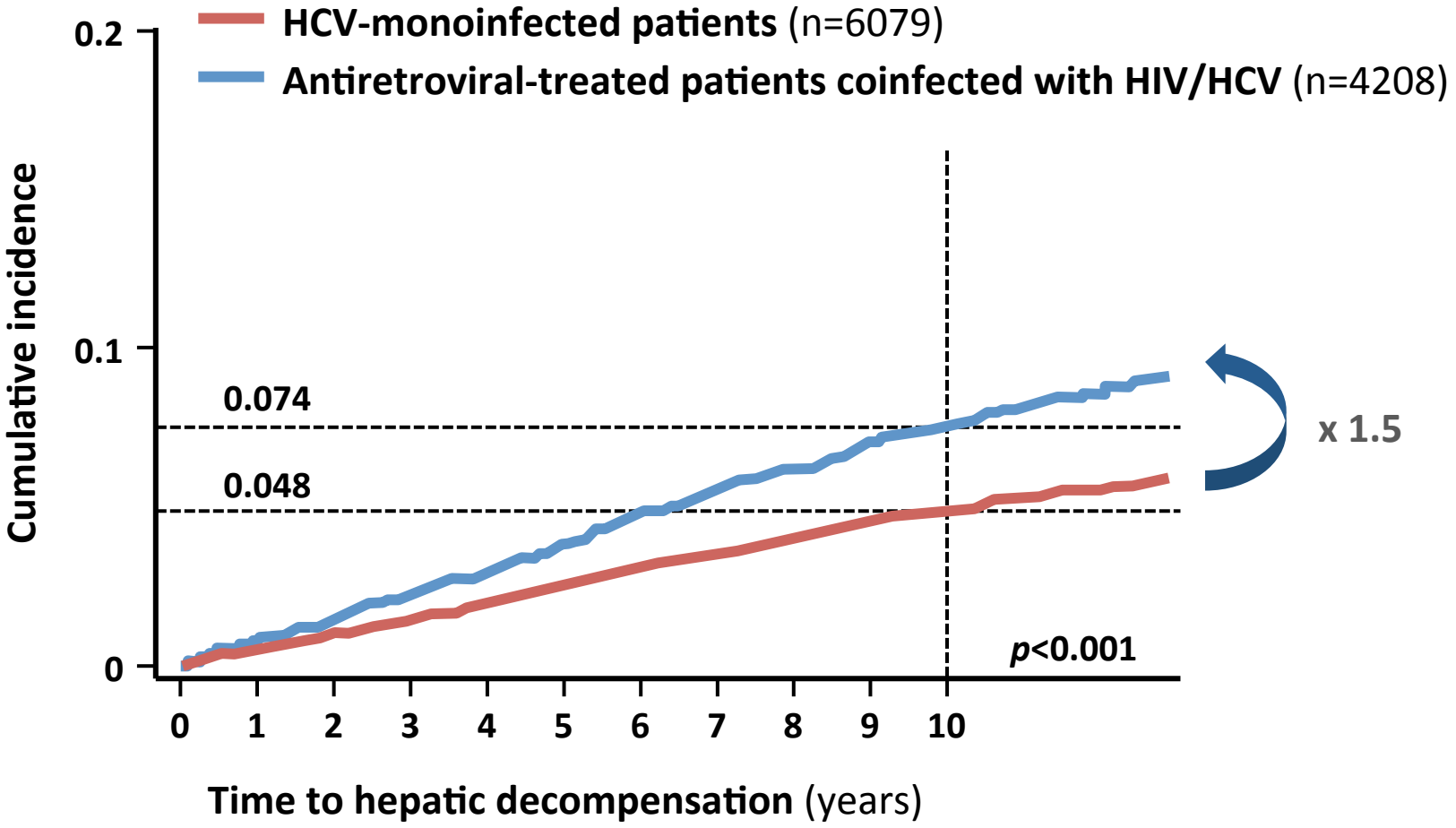
- To evaluate 10,090 HIV/HCV-co-infected males from the Veterans Aging Cohort Study Virtual Cohort, who had not initiated ART at entry, for incident hepatic decompensation between 1996 and 2010

Results:

- Initiation of ART significantly reduced the rate of hepatic decompensation by 28–41% on average

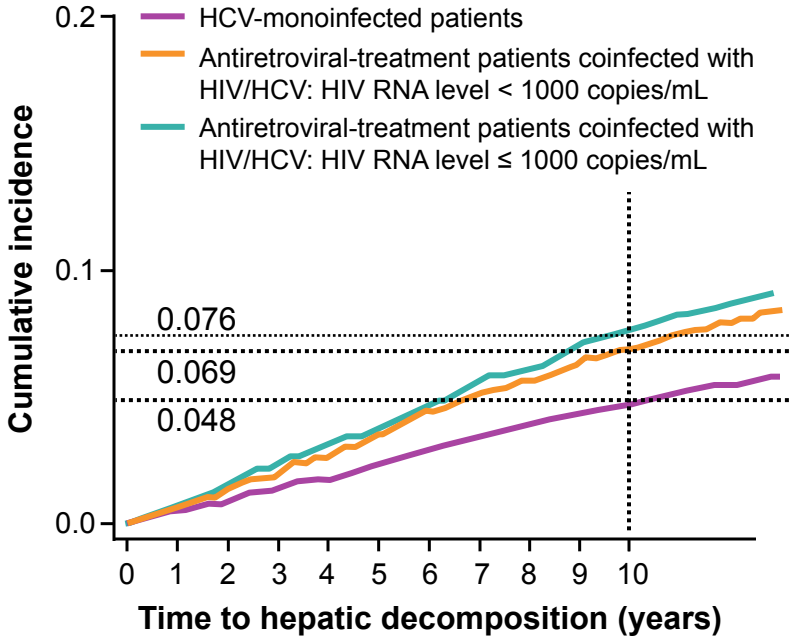
Anderson JP, *et al. Clin Infect Dis* 2014; 58(5): 719–27.

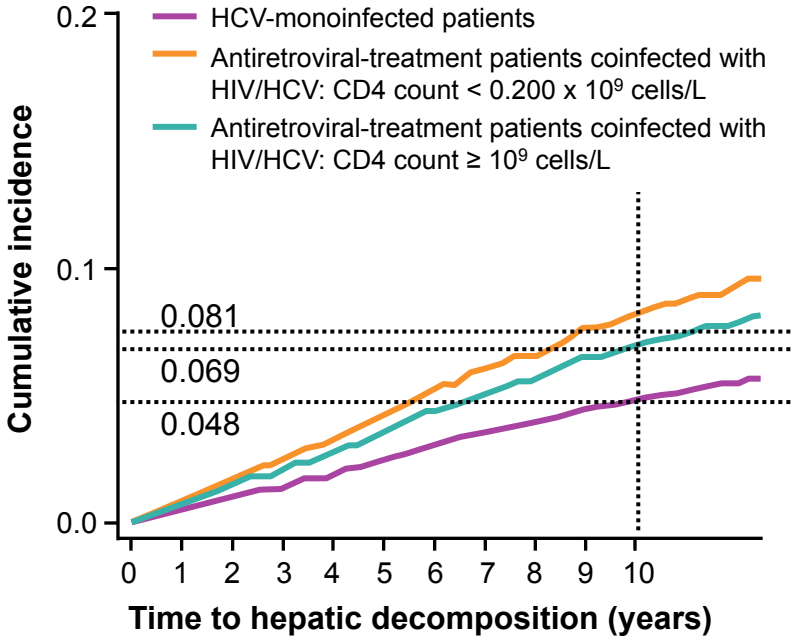
HCV Disease Progression Remains Faster in Coinfected Patients, Despite Effective ART



Adapted from: Lo Re 3rd V, et al. Ann Intern Med 2014;160:369–79.

HCV Disease Progression Remains Faster in Coinfected Patients, Despite Effective ART





If HIV RNA **<1000 copies/mL**: +65% excess risk
If HIV RNA **>1000 copies/mL**: +82% excess risk

If CD4 **< 200/mm²:** +203% excess risk
If CD4 **> 200/mm²:** 56–63% excess risk

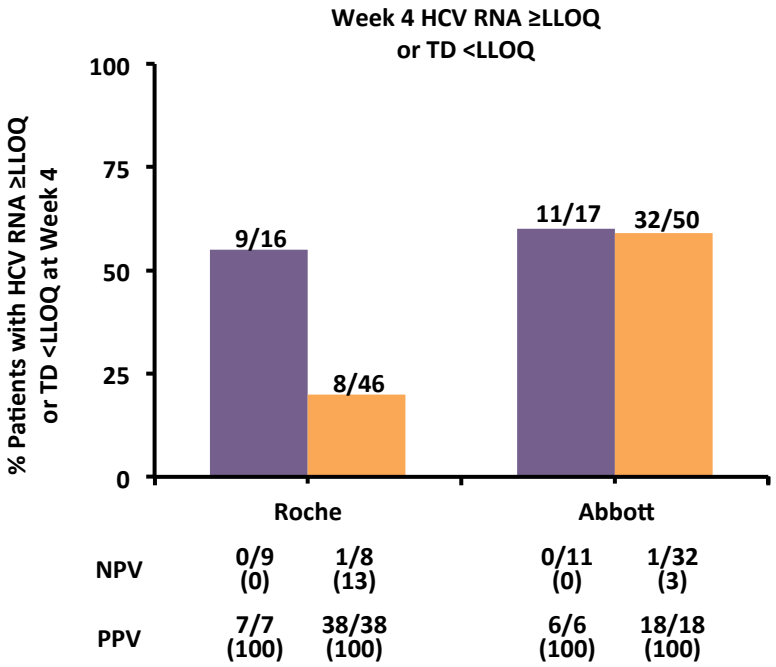
ART, antiretroviral therapy; HCV, hepatitis C virus; HIV, human immunodeficiency virus.

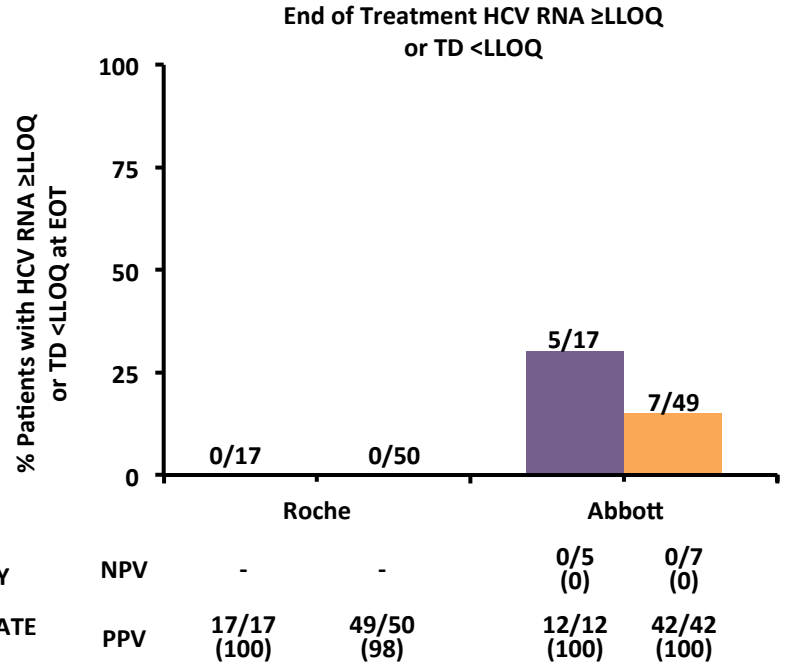
Adapted from: Lo Re 3rd V, et al. Ann Intern Med 2014;160:369–79.

Quantitative HCV-RNA monitoring before and under therapy

Hepatitis C Viral Load Monitoring with Ledipasvir/ Sofosbuvir

Patients with HCV RNA ≥LLOQ or TD <LLOQ at W4 and EOT





SYNERGY

ERADICATE

- The majority of patients with HCV RNA ≥LLOQ or HCV RNA TD <LLOQ at week 4 achieved SVR12 (NPV <13%)
- 5 patients on SYNERGY and 7 patients on ERADICATE had HCV RNA TD <LLOQ at EOT by the Abbott assay
- All 12 patients achieved SVR12
- By the Roche assay, all patients had HCV RNA TND <LLOQ at EOT

Sidharthan S, et al. 22nd CROI; Seattle, WA; February 23-26, 2015. Abst. 689.

Whom to treat?

EASL HCV guidelines 2015

- All treatment-naïve and treatment-experienced patients with compensated or decompensated chronic liver disease due to HCV should be considered for therapy **(A1)**
- Treatment should be prioritized for patients with significant fibrosis or cirrhosis (METAVIR score F3 to F4) **(A1)**
- Patients with decompensated cirrhosis (Child-Pugh B and C) should be urgently treated with an IFN-free regimen **(A1)**
- Treatment should be prioritized regardless of the fibrosis stage in patients with HIV or HBV coinfection, patients in the pre- or post-liver transplant setting, patients with clinically significant extra-hepatic manifestations (e.g. symptomatic vasculitis associated with HCV-related mixed cryoglobulinaemia, HCV immune complex-related nephropathy and non-Hodgkin B cell lymphoma), and patients with debilitating fatigue **(A1)**
- Treatment should be prioritized regardless of the fibrosis stage for individuals at risk of transmitting HCV, including active injection drug users, men who have sex with men with high-risk sexual practices, women of childbearing age who wish to get pregnant, haemodialysis patients, and incarcerated individuals **(B1)**
- Treatment is justified in patients with moderate fibrosis (METAVIR score F2) **(A2)**
- In patients with no or mild disease (METAVIR score F0-F1) and none of the above-mentioned extra-hepatic manifestations, the indication for and timing of therapy can be individualized **(B1)**
- Treatment is not recommended in patients with limited life expectancy due to non-liver-related comorbidities **(B1)**

EASL 2015

Recommendations for Testing, Managing, and Treating Hepatitis C (02/2016)

Summary of Recommendations for When and in Whom to Initiate HCV Therapy

Goal of Treatment

- **The goal of treatment of HCV-infected persons is to reduce all-cause mortality and liver-related health adverse consequences, including end-stage liver disease and hepatocellular carcinoma, by the achievement of virologic cure as evidenced by a sustained virologic response.**
  Rating: Class I, Level A

Recommendations for When and in Whom to Initiate Treatment

- **Treatment is recommended for all patients with chronic HCV infection, except those with short life expectancies that cannot be remediated by treating HCV, by transplantation, or by other directed therapy. Patients with short life expectancies owing to liver disease should be managed in consultation with an expert.**
  Rating: Class I, Level A

Recommendations for Pretreatment Assessment

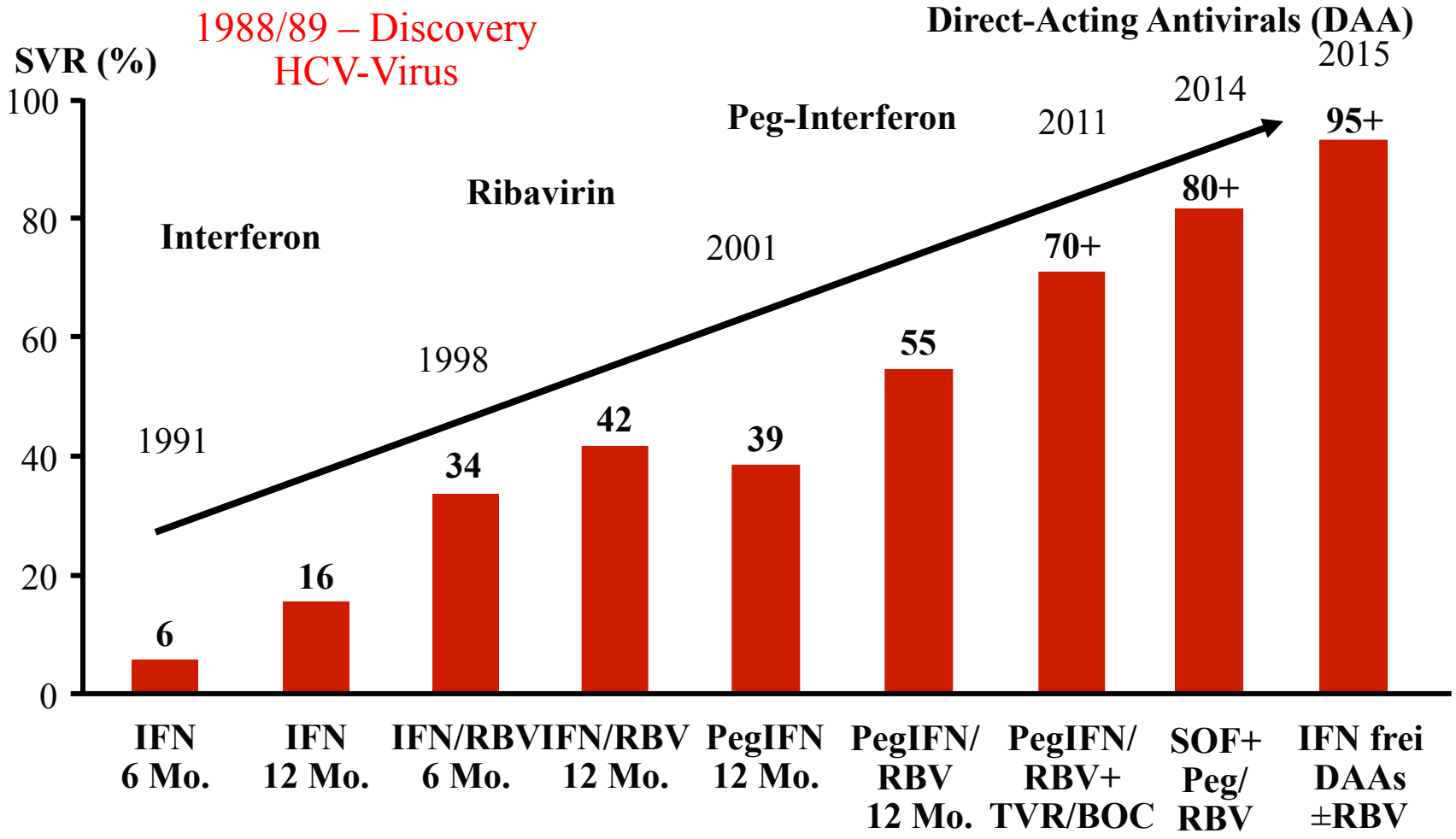
- **Evaluation for advanced fibrosis using liver biopsy, imaging, and/or noninvasive markers is recommended for all persons with HCV infection, to facilitate an appropriate decision regarding HCV treatment strategy and to determine the need for initiating additional measures for the management of cirrhosis (eg, hepatocellular carcinoma screening). (see HCV Testing and Linkage to Care [11])**
  Rating: Class I, Level A

AASLD
AMERICAN ASSOCIATION FOR THE STUDY OF LIVER DISEASES

IDSA
Infectious Diseases Society of America

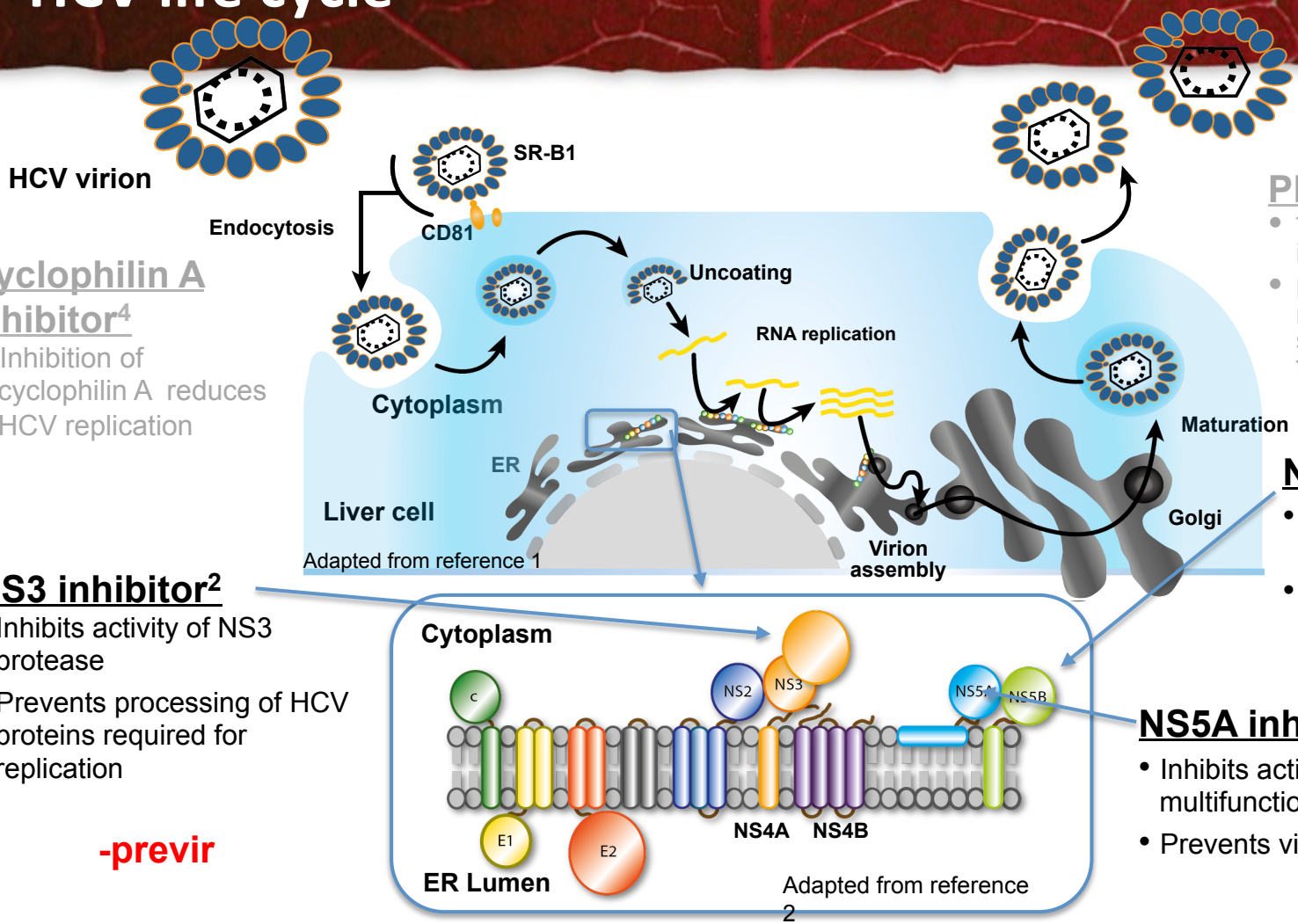
How has HCV therapy changed?

Mile stones in the treatment of HCV Genotype 1 infection



Kronenberger B et al. *Dtsch. Med. Wochenschr*. 2013; **138**: 1796-1800.

HCV life cycle



Cyclophilin A inhibitor[4]

- Inhibition of cyclophilin A reduces HCV replication

PEG-IFN lambda[3]

- Type III pegylated interferon
- Expression of receptor is more limited than Alfa, should lead to improved tolerability and safety

NS3 inhibitor[2]

- Inhibits activity of NS3 protease
- Prevents processing of HCV proteins required for replication

-previr

NS5B inhibitor(s)[2]

- Inhibits NS5B RNA replicase
- Prevents replication of viral genome

-buvir

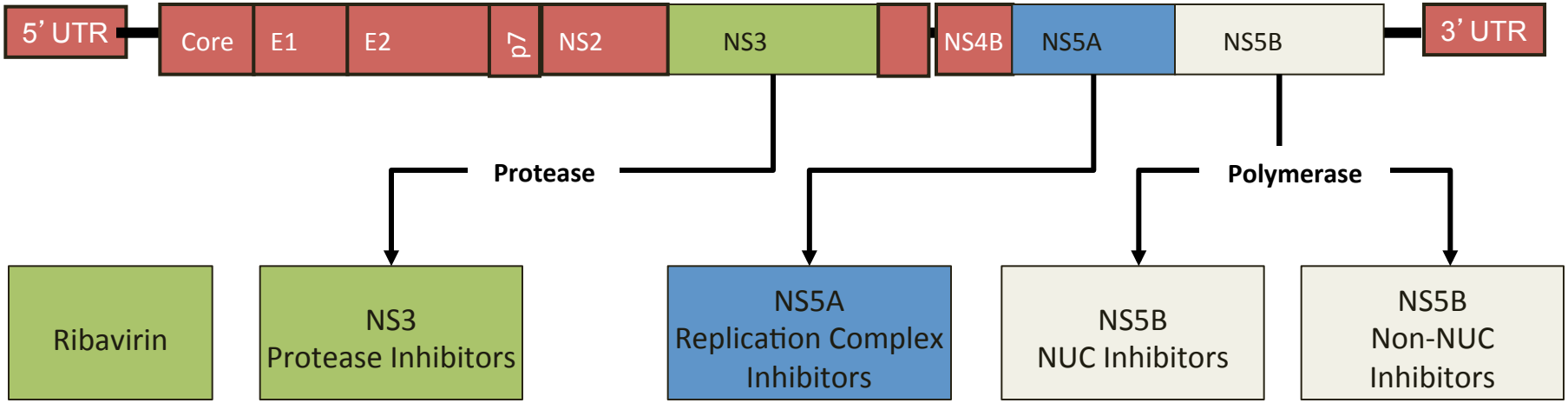
NS5A inhibitor[2]

- Inhibits activity of NS5A, a multifunctional protein
- Prevents viral replication

-asvir

1. Manns MP, et al. Nat Rev Drug Discov 2007;6:991–1000. 2. Rice C. Top Antivir Med 2011;19(3):117–20. 3. Donnelly R, et al. Trends Immunol 2011;32(9):443–50. 4. Gallay P, Lin K. Drug Des Devel Ther 2013;7:105-15.

HCV DAAs



Telaprevir
Boceprevir
Simeprevir
Asunaprevir
Veruprevir
Grazoprevir

Daclatasvir
Ledipasvir
Ombitasvir
Elbasvir
GS-5816

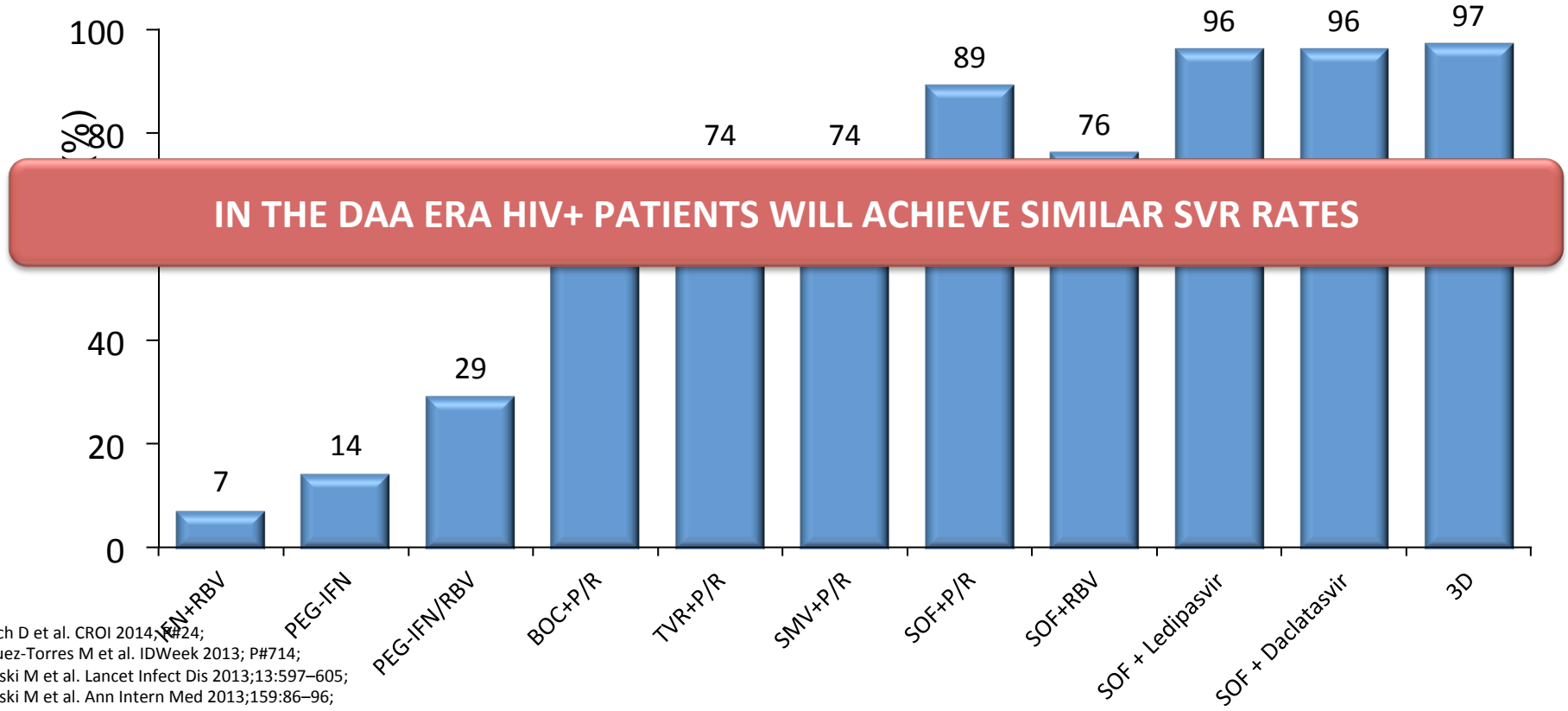
Sofosbuvir
VX-135
IDX21437
ACH-3422

Dasabuvir
Beclabuvir

-previr **-asvir** **-buvir**

Improved SVR12/24 rates over time in HCV GT 1 patients co-infected with HIV

3D, ABT-450/ritonavir/ombitasvir; BOC, boceprevir; DAA, direct-acting antiviral agent; P/R, pegylated interferon/ribavirin; SMV, simeprevir; SOF, sofosbuvir; TVR, telaprevir



IN THE DAA ERA HIV+ PATIENTS WILL ACHIEVE SIMILAR SVR RATES

Dieterich D et al. CROI 2014; P#24;
Rodriguez-Torres M et al. IDWeek 2013; P#714;
Sulkowski M et al. Lancet Infect Dis 2013;13:597–605;
Sulkowski M et al. Ann Intern Med 2013;159:86–96;
Sulkowski M et al Lancet 2014;314:653–61;
Sulkowski M et al. AIDS 2014; P#104 LB;
Torriani FJ, et al. N Engl J Med 2004;351:438–50
Wyles D et al. IAS 2015

Drug-drug Interactions between DAAs and ARVs

HCV drugs		ATV/r	DRV/c	DRV/r	LPV/r	EFV	ETV	NVP	RPV	MVC	DTG	EVG/c	RAL	ABC	FTC	3TC	TDF	ZDV
DAAs	boceprevir	D35%	↓D	↓32%D44%	↓45%D34%	↓19%E20%	↑10%D23%	↓E	↓6%E39%	E	↔	↓D	↔	↔	↔	↔	↔	↔
	daclatasvir	↑110%[ii]	↑	↑40%	↑15%	↓32%[iv]	↓	↓	↔	↔	↔	↑[ii]	↔	↔	↔	↔	↑10%E10%	↔
	ombitasvir/paritaprevir/r/dasabuvir	↑94%[iv]	↑	D[v]	↑	vii	↓E?	↓E?	E[iii]	E	E38%	↑	E134%	↔	↔	↔	↔	↔
	ombitasvir/paritaprevir/r	↑[iv]	↑	↑[vi]	↑	vii	↓E?	↓E?	E[iii]	E	↔	↑	E20%	↔	↔	↔	↔	↔
	simeprevir	↑	↑	↑	↑	↓71%	↓	↓	↑6%E12%	↔	↔	↑	↓11%E8%	↔	↔	↔	↓14%E18%	↔
	sofosbuvir/ledipasvir	↑8/113%[ix]	↑E[ix]	↑34/39%[ix]	↔[ix]	↓-/34%[ix]	↔	↔	↔[ix]	E?	↔	↑36/78E[ix]	D≈20%	↔	↔	↔	E[ix]	↔
	sofosbuvir	↔	↑	↑34%	↔	↓6%D4%	↔	↔	↑9%E6%	↔	↔	↔	↓5%D27%	↔	↓6%	↔	↓6%	↔
	telaprevir	↓20%E17%	↓D	↓35%D40%	↓54%	↓26%D7%	↓16%	↓?	↓5%E	E	E25%	↑13%D16%	E31%	↔	↔	↔	E30%[ix]	↔[i]

Legend

↑ potential elevated exposure of DAA
↓ potential decreased exposure of DAA
↔ no significant effect
D potential decreased exposure of ARV
E potential elevated exposure of ARV

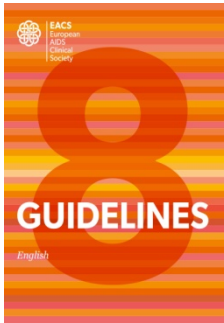
Numbers refer to decreased/increased AUC of DAAs and ARVs as observed in drug interactions studies. Sofosbuvir/ledipasvir: first/second numbers refer to changes AUC sofosbuvir/ledipasvir.

Colour legend

no clinically significant interaction expected.
these drugs should not be co-administered.
potential interaction which may require a dosage adjustment or close monitoring.

Note: the symbol (green, amber, red) used to rank the clinical significance of the drug interaction is based on www.hep-druginteractions.org.

i Potential hematological toxicity
ii Daclatasvir should be reduced to 30 mg qd with ATV/r or EVG/c. No dose reduction with unboosted ATV
iii Daclatasvir should be increased to 90 mg qd
iv Use only with unboosted ATV and in persons without significant HIV PI mutations (ATV increased paritaprevir exposure due to CYP3A4 and OATP1B1/3 inhibition, not recommended without dasabuvir)
v Co-administration is not recommended due to decreased DRV/c trough by 50% when DRV administered 800 mg or 600 mg bid (second dose given with additional RTV)
vi Increase in paritepravir exposure when co-administered with DRV 800 mg given with Viekirax
vii Severe tolerability issues
viii Not recommended unless benefit outweights the risk due to potential for QT interval prolongation with higher concentrations of rilpivirine, co-administration should only be considered in persons without known QT prolongation and without other QT prolongation co-medications
ix Frequent monitoring of kidney function due to increase of TDF if contained in the regimen



Drug Interactions Between Select ARTs and HCV Therapies - *EACS*[1] (1 of 3)

	BOC	DCV	LED/ SOF	OBV/ PTV/r	OBV/ PTV/r +DSV	SMV	SOF	TVR
Integrase Inhibitors								
Raltegravir			D≈20%	E20%	E134%	↓11% E8%	↓5% D27%	E31%
Dolutegravir					E38%			E31%
Elvitegravir/cobicistat	↓D	↑	↑36/78 E	↑	↑	↑		↑13% D16%
NRTIs								
Abacavir								
Emtricitabine							↓6%	
Lamivudine								
Tenofovir		↑10% E10%	E			↓14% E18%	↓6%	E30%
Zidovudine								

↓ = potential decreased exposure of DAA; ↑ = potential increased exposure of DAA;
D = potential decreased exposure of ARV; E = potential elevated exposure of ARV.

	These drugs should not be coadministered
	Potential interaction – may require dosage adjustment or close monitoring
	No clinically significant interaction expected

Drug Interactions Between Select ARTs and HCV Therapies - *EACS*[1] (2 of 3)

	BOC	DCV	LED/ SOF	OBV/ PTV/r	OBV/ PTV/r +DSV	SMV	SOF	TVR
NNRTIs								
Efavirenz	↓19% E20%	↓32%	↓-/34%	Severe*	Severe*	↓71%	↓6% D4%	↓26% D7%
Etravirine	↑10% E12%			↓E?	↓E?	↓		
Nevirapine	↓E	↓		↓E?	↓E?	↓		↓?
Rilpivirine	↓6% E39%			E	E	↑6% E12%	↑9% E6%	↓5% E
Entry Inhibitor								
Maraviroc	E		E?	E	E			E

↓ = potential decreased exposure of DAA; ↑ = potential increased exposure of DAA;
D = potential decreased exposure of ARV; E = potential elevated exposure of ARV.

	These drugs should not be coadministered
	Potential interaction – may require dosage adjustment or close monitoring
	No clinically significant interaction expected

ART = antiretroviral therapy; BOC = boceprevir; DCV = daclatasvir; LED = ledipasvir; OBV/PTV/r + DSV = ombitasvir/paritaprevir/ritonavir + dasabuvir; SMV = simeprevir; SOF = sofosbuvir; TVR = telaprevir; Peg IFN = pegylated interferon; RBV = ribavirin.

1. European AIDS Clinical Society (EACS) Guidelines Version 8.0, Updated October 2015. Available at: http://www.eacsociety.org/guidelines/eacs-guidelines/eacs-guidelines.html. Accessed October 25, 2015.

Drug Interactions Between Select ARTs and HCV Therapies - *EACS*[1] (3 of 3)

- ART = antiretroviral therapy; BOC = boceprevir; DCV = daclatasvir; LED = ledipasvir; OBV/PTV/r + DSV = ombitasvir/paritaprevir/ritonavir + dasabuvir; SMV = simeprevir; SOF = sofosbuvir; TVR = telaprevir; Peg IFN = pegylated interferon; RBV = ribavirin.

	BOC	DCV	LED/ SOF	OBV/ PTV/r	OBV/ PTV/r +DSV	SMV	SOF	TVR
Protease Inhibitors								
Atazanavir/ritonavir	D35%	↑110%	↑8/113%	↑94%	↑	↑		↓20% E17%
Darunavir/cobicistat	↓ D	↑	↑ E	↑	↑	↑	↑	↓ D
Darunavir/ritonavir	↓32% D44%	↑40%	↑34/39%	D	↑	↑	↑34%	↓35% D40%
Lopinavir/ritonavir	↓45% D34%	↑15%		↑	↑	↑		↓54%

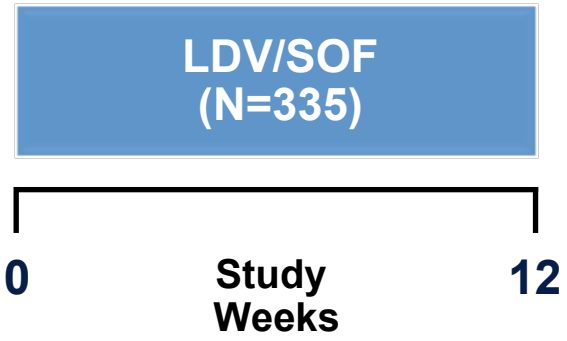
↓ = potential decreased exposure of DAA; ↑ = potential increased exposure of DAA;
D = potential decreased exposure of ARV; E = potential elevated exposure of ARV.

	These drugs should not be coadministered
	Potential interaction – may require dosage adjustment or close monitoring
	No clinically significant interaction expected

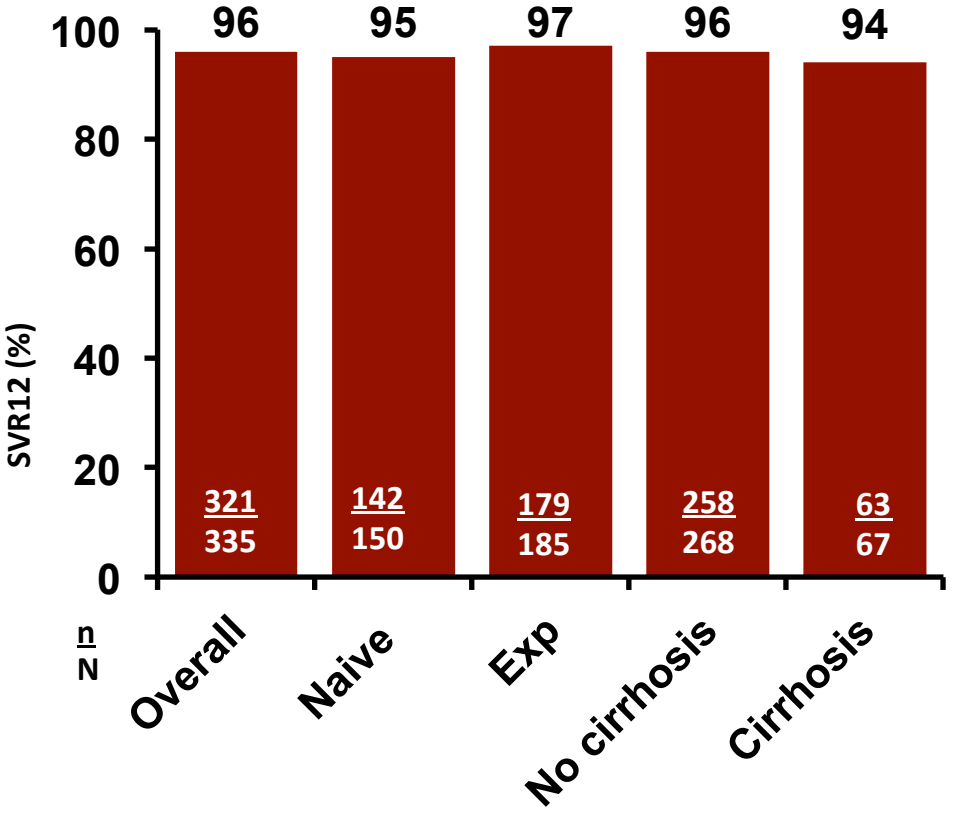
European AIDS Clinical Society (EACS) Guidelines Version 8.0, Updated October 2015. Available at: http://www.eacsociety.org/guidelines/eacs-guidelines/eacs-guidelines.html. Accessed October 25, 2015.

Ledipasvir/sofosbuvir for 12 Weeks in Patients Coinfected with HCV and HIV-1: ION-4

Study Design:
GT1 and 4 with HIV/HCV co-infection*



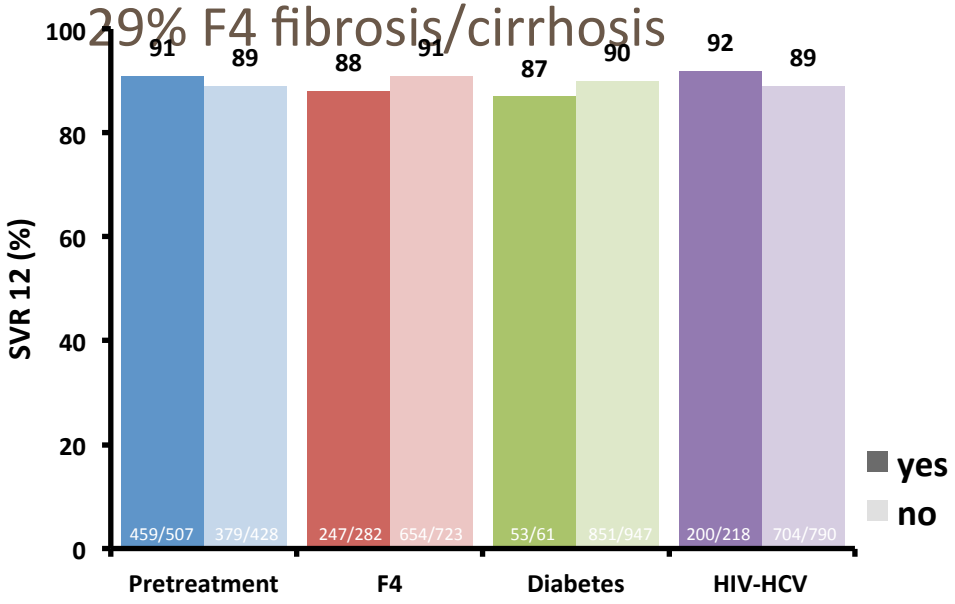
Efficacy Results:
GT1 and 4 with HIV/HCV co-infection

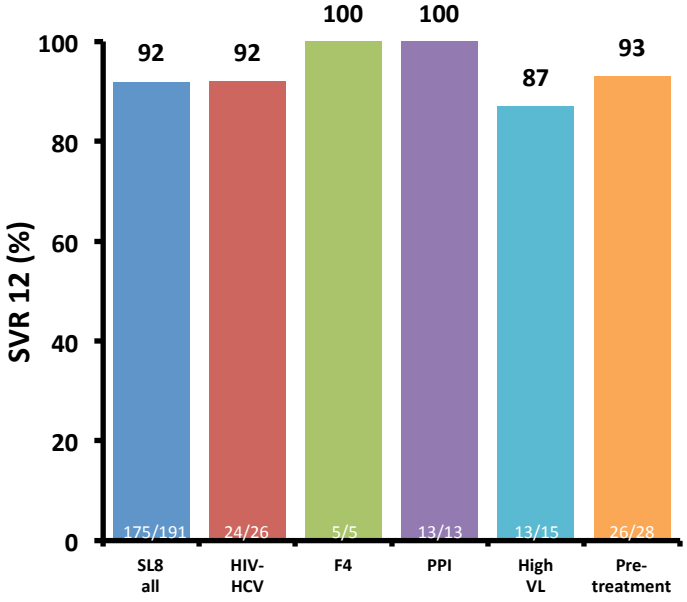


Cooper C, et al; 8th IAS, Vancouver, Canada, July 19-22, 2015; Abst. TUAB0202 and Naggie S, N Engl J Med 2015.

Real Life DAA Data from Germany: GECCO Cohort

- 1346 patients from 9 centres: 21% HIV/HCV co-infected, 29% F4 fibrosis/cirrhosis

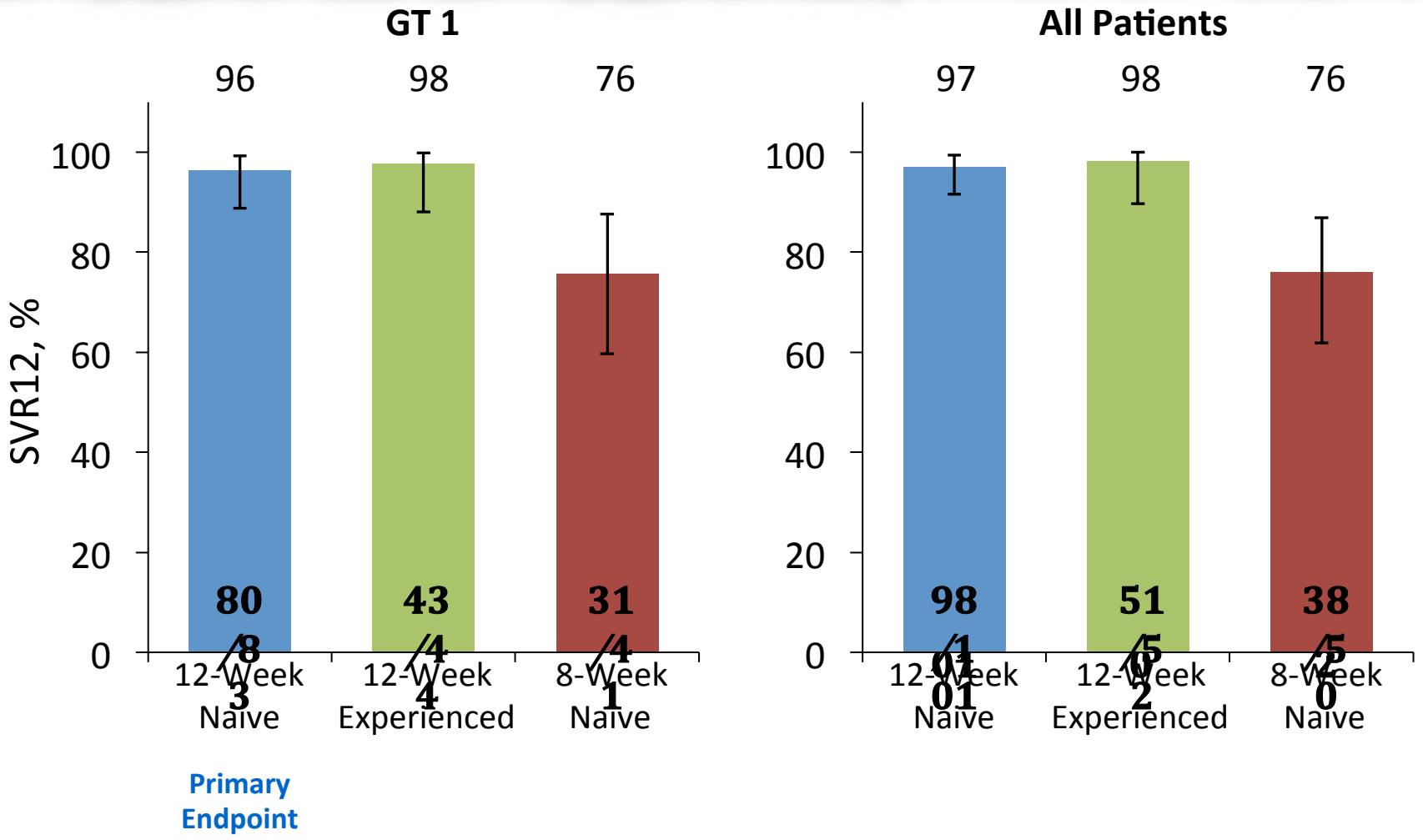




- Good response rates also in Tx experienced, F4, diabetics, co-infected
- 8 weeks of SOF/LDV very effective – even in "problematic" patients

Christensen S, et al. 23rd CROI; Boston, MA; February 22-25, 2016. Abst. 584.

ALLY-2: DCV+SOF in HIV/HCV Coinfection



Wyles D, et al. 50th EASL; Vienna, Austria; April 22-26, 2015. Abst. LP01 and Wyles D, et al. N Engl J Med 2015.

New DAAs, in all four classes, are now approved

	Treatment duration (weeks)
BOC + PEG-IFN + RBV	28–48
TVR + PEG-IFN + RBV	12–48
OMV VPV/RTV + DSV + RBV	12–24
SOF + PEG-IFN + RBV	12
SOF + RBV	24
SOF + SMV ± RBV	12–24
SOF + DCV* ± RBV	12–24
SOF LDV ± RBV	8–24

1. Merck, Sharp & Dohme Ltd. VICTRELIS▼ (boceprevir), SmPc July 2011; 2. Janssen Cilag International. INCIVO▼ (telaprevir), SmPC, September 2011; 3. AbbVie Ltd. VIEKIRAX▼ (ombitasvir/paritaprevir/ritonavir), SmPC, January 2015; 4. AbbVie Ltd. EXVIERA▼ (dasabuvir), SmPC, January 2015; 5. Gilead Sciences Europe Ltd. SOVALDI▼ (sofosbuvir), SmPC, March 2015; 6. Janssen Cilag International. OLYSIO▼(simeprevir), SmPC, May 2014; 7. Bristol-Myers Squibb Pharma. Daklinza▼ (daclatasvir), SmPC, August 2014; 8. Gilead Sciences Europe Ltd. HARVONI▼ (ledipasvir/sofosbuvir), SmPC, November 2014

- *DCV + SOF ist in der Schweiz zugelassen für: Patienten mit HCV-GT1-Infektion ohne Zirrhose (12 oder 24 Wochen Behandlungsdauer)und für Patienten mit HCV-GT3-Infektion mit oder ohne Zirrhose (12 Wochen Behandlungsdauer). Für Patienten mit HCV-GT4 Infektion ist DCV zugelassen in Kombination mit PegInterferon alfa und Ribavirin (24 Wochen Behandlungsdauer).

Treatment Options 2015/2016

IFN-free regimens	GT
Sofosbuvir + RBV	2, 3
Sofosbuvir/Ledipasvir (± RBV)	1, 4, 5, 6
Ombitasvir/Paritaprevir/Ritonavir + Dasabuvir (± RBV)	1
Sofosbuvir + Simeprevir (± RBV)	1, 4
Sofosbuvir + Daclatasvir (± RBV)	All
Ombitasvir/Paritaprevir/Ritonavir (± RBV)	4

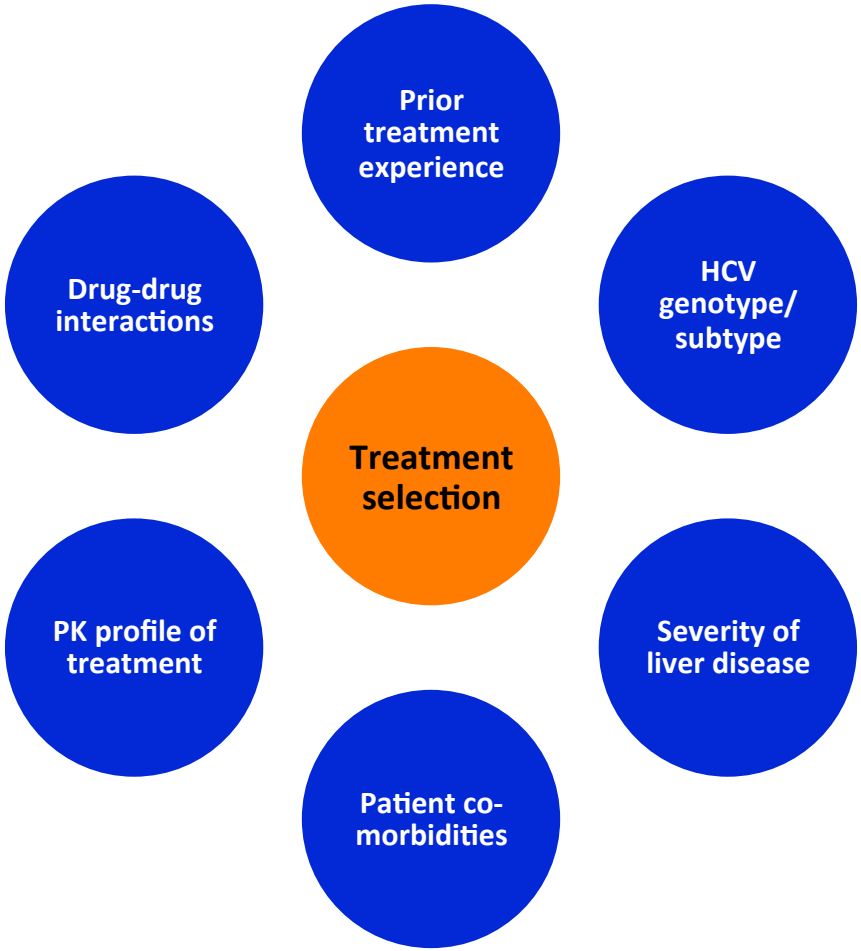
IFN-containing regimens

PegIFNα + RBV + sofosbuvir	All
PegIFNα + RBV + simeprevir	1, 4

*DCV + SOF ist in der Schweiz zugelassen für: Patienten mit HCV-GT1-Infektion ohne Zirrhose (12 oder 24 Wochen Behandlungsdauer)und für Patienten mit HCV-GT3-Infektion mit oder ohne Zirrhose (12 Wochen Behandlungsdauer). Für Patienten mit HCV-GT4 Infektion ist DCV zugelassen in Kombination mit PegInterferon alfa und Ribavirin (24 Wochen Behandlungsdauer).

(J-M Pawlotsky, ILC2015, Vienna, Austria, April 24, 2015. EASL Recommendations on Treatment of Hepatitis C 2015)

Characteristics that Inform Treatment Option Selection



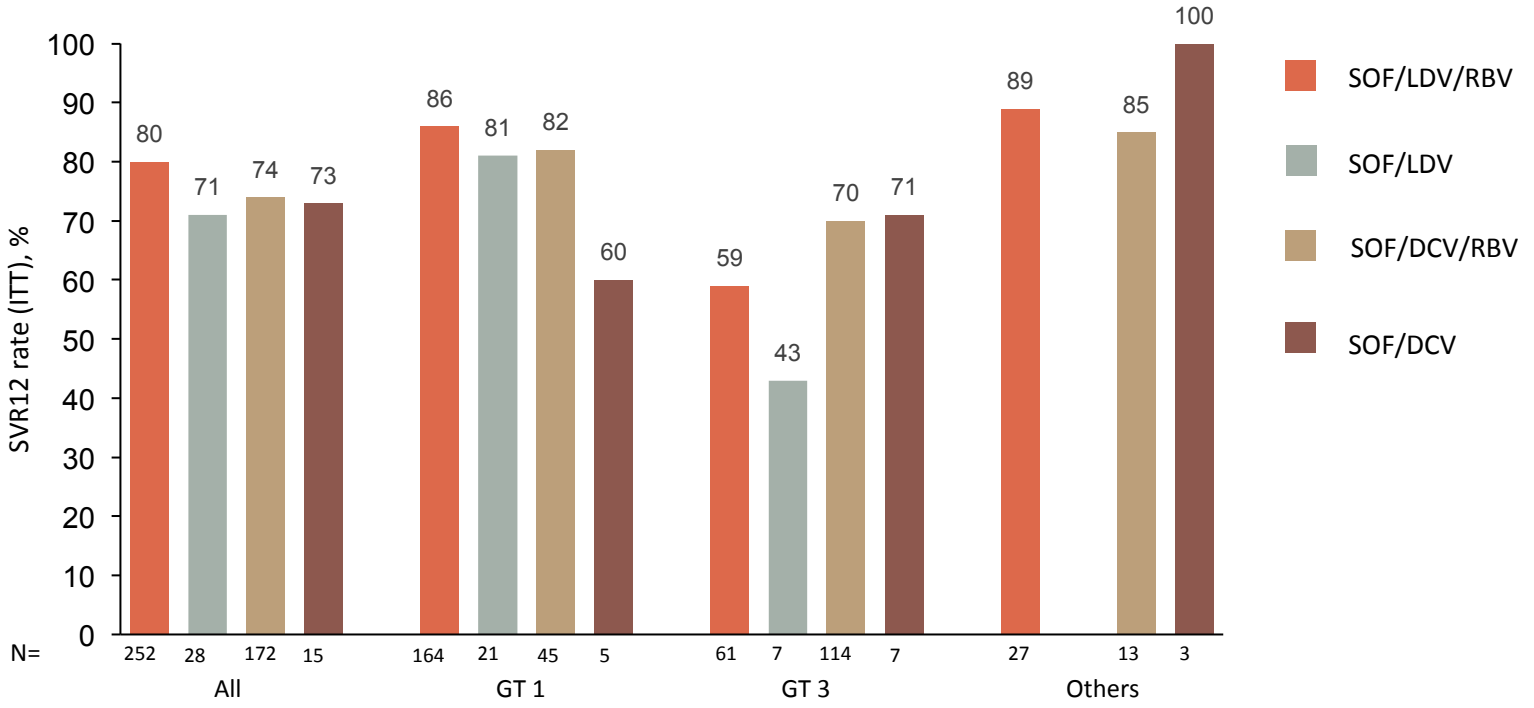
(J-M Pawlotsky, ILC2015, Vienna, Austria, April 24, 2015.

EASL Recommendations on Treatment of Hepatitis C 2015)

Real world experience

SVR12 by genotype and regime from the English EAP study

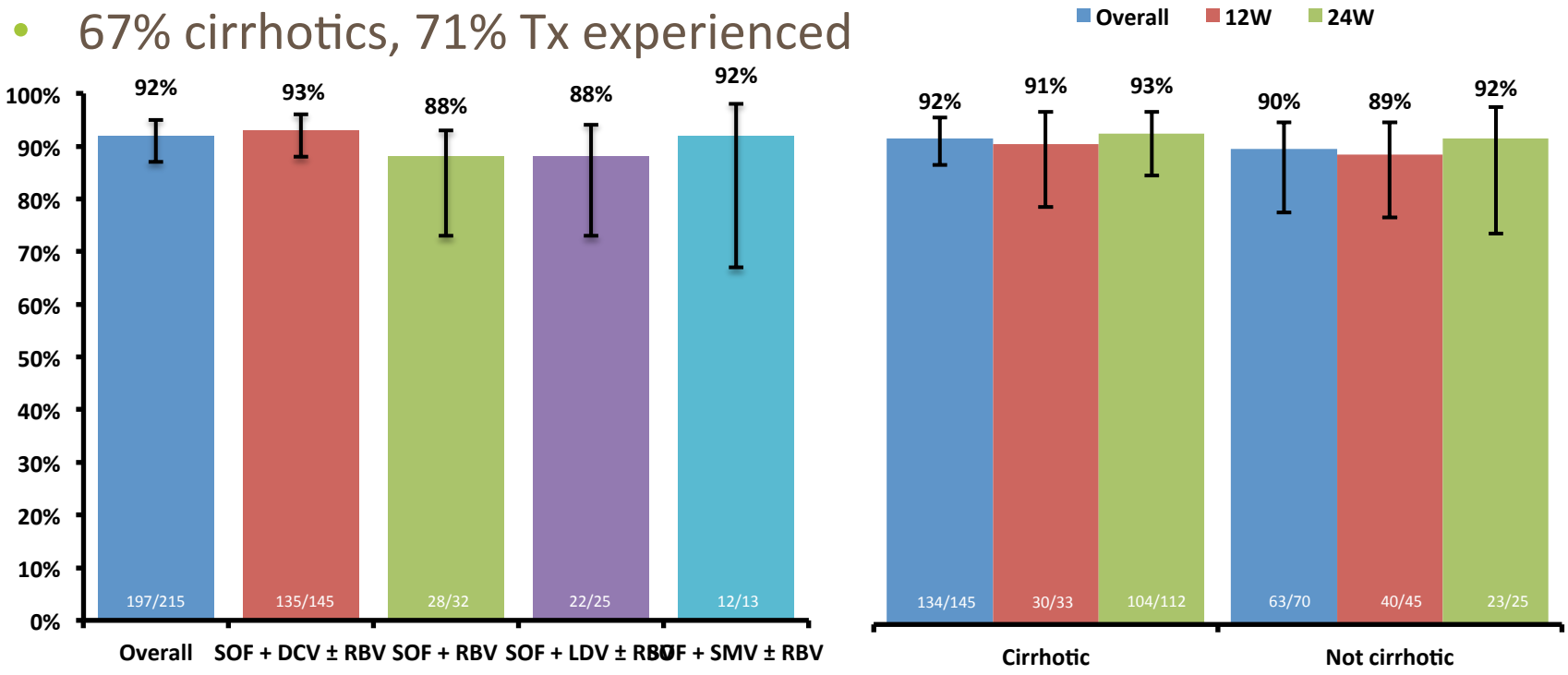
Interesting data on the NHS England Early Access Program (EAP) was presented at EASL which provided 12 weeks of therapy with SOF, with or without RBV and an NS5A inhibitor (provided by Gilead or BMS) to a cohort of ~500 patients with decompensated cirrhosis. In this first analysis, data from 467 HCV patients (235 with GT 1 infection, 189 with GT 3 infection) was presented.



DCV + SOF ist in der Schweiz zugelassen für: Patienten mit HCV-GT1-Infektion ohne Zirrhose (12 oder 24 Wochen Behandlungsdauer)und für Patienten mit HCV-GT3-Infektion mit oder ohne Zirrhose (12 Wochen Behandlungsdauer). Für Patienten mit HCV-GT4 Infektion ist DCV zugelassen in Kombination mit PegInterferon alfa und Ribavirin (24 Wochen Behandlungsdauer).

Real Life DAA Data from France

- 215 HIV HCV co-infected patients from the ANRS HEPAVIH cohort
- 67% cirrhotics, 71% Tx experienced



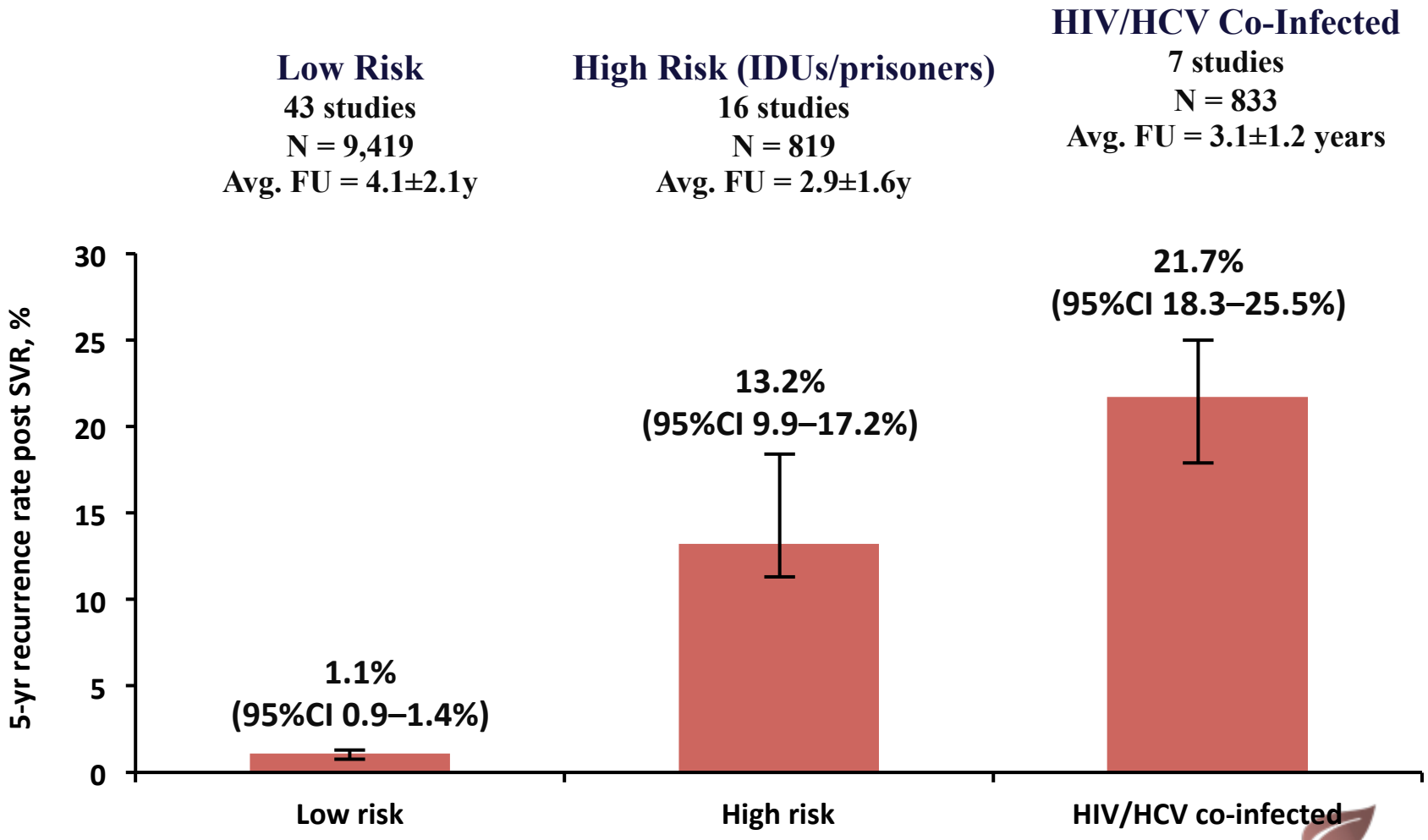
- No influence of cirrhosis or pre-treatment upon SVR

Piroth L, et al. 23rd CROI; Boston, MA; February 22-25, 2016. Abst. 582.

How can we change the HCV epidemic?

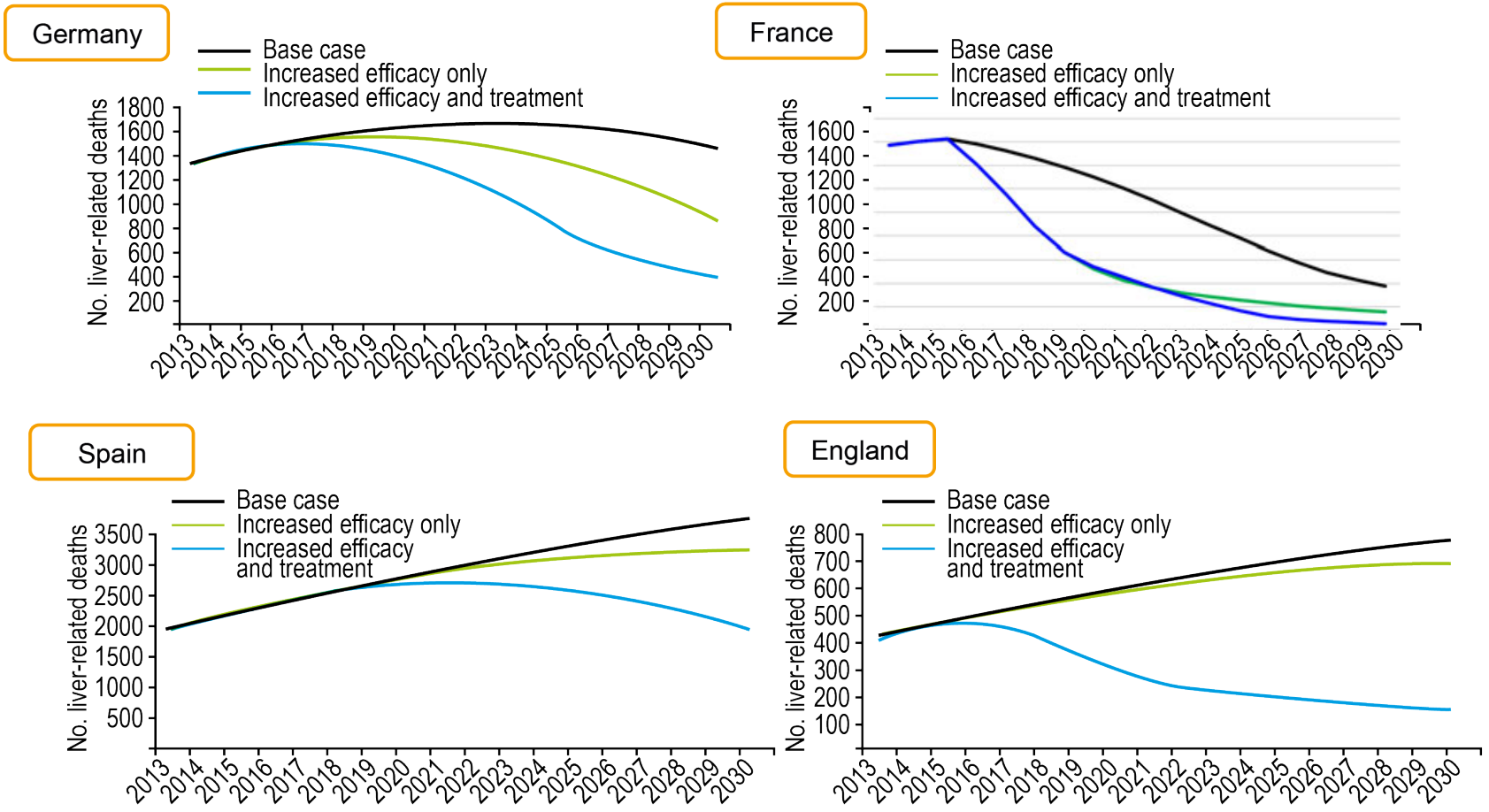
Risk of Late Relapse or Re-Infection with Hepatitis C After Sustained Virological Response: Meta-Analysis of 66 Studies in 11,071 Patients

Five-Year Rate (95%CI) of Recurrence Post-SVR, by Risk Group



Simmons B, et al. Clin Infect Dis. 2016;62:683-94.

Increasing SVR and treatment reduces liver-related mortality



Wedemeyer, J Viral Hepatitis 2014

Summary

- 80 Mill people are HCV viremic worldwide
- Individuals with HCV can now be ‘cured’ due to highly effective and well tolerated DAA-based HCV treatment regimens
- Cure of HCV impacts not only liver disease outcome but also overall mortality
- Elimination of HCV in this population is theoretically possible
- To turn possibility into reality we need to overcome barriers and maximise initiatives already in place to prevent onward transmission and re-infection