HepHIV 2014
5-7 OCTOBER BARCELONA
HIV and Viral Hepatitis: Challenges of Timely Testing and Care

Hepatitis C virus infection: a systemic disease with the possibility to cure

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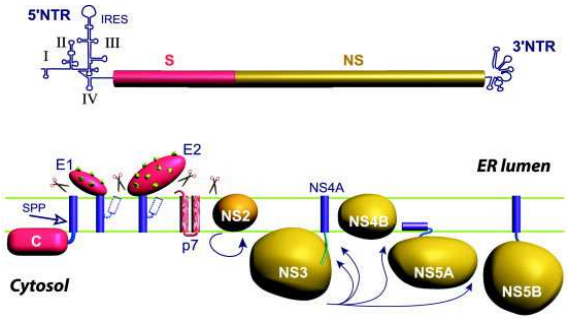
EASL
European Association for the Study of the Liver

Assistance Publique Hôpitaux de Paris
Université Paris Descartes
Instituts thématiques Inserm Institut national de la santé et de la recherche médicale
anrs France REcherche Nord & sud Sida-hiv Hépatites Agence autonome de l'Inserm

Disclosures

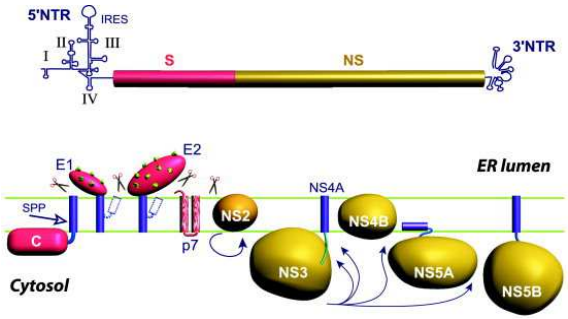
- Consultant: BMS, Boehringer Ingelheim, Janssen, Gilead, Roche, MSD, Abbvie
- Speaker: GSK, BMS, Boehringer Ingelheim, Janssen, Vertex, Novartis, Sanofi, Gilead, Roche, MSD, Abbvie
- Grants: BMS, Gilead, Roche, MSD

Hepatitis C virus infection: a systemic disease with the possibility to cure



- Why to treat?
- The impact of HIV
- How to treat?

Hepatitis C virus infection: a systemic disease with the possibility to cure



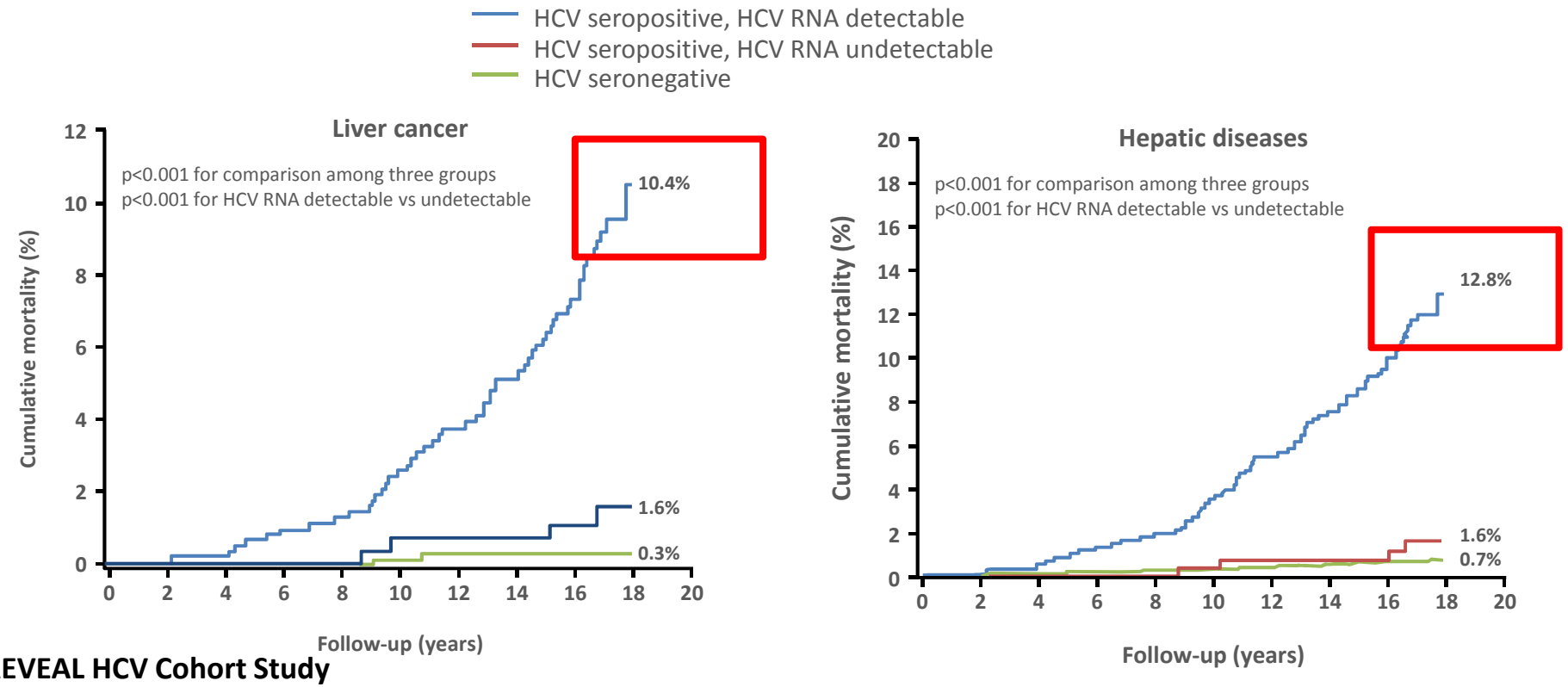
- Why to treat?

- Hepatic manifestations

- Extra-hepatic manifestations
  - Cryoglobulinemic vasculitis or lymphoma

But also general manifestations related to
- "Lymphocytic activation" associated with chronic infection

Persisting detectable HCV RNA is a risk factor for liver-related mortality



The REVEAL HCV Cohort Study

23 820 adults, Taiwan

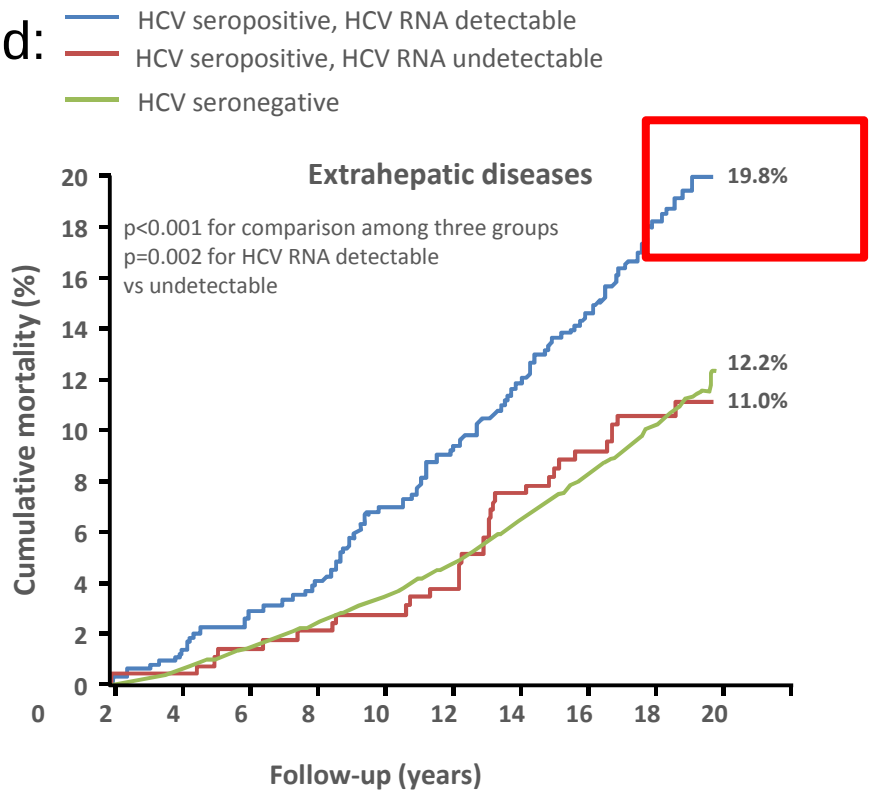
1095 anti-HCV positive; 69.4% with detectable HCV RNA

Lee M-H et al, J Infect Dis 2012;206:469–477

Chronic HCV increases morbi-mortality from non-hepatic diseases

Significant association between HCV and:

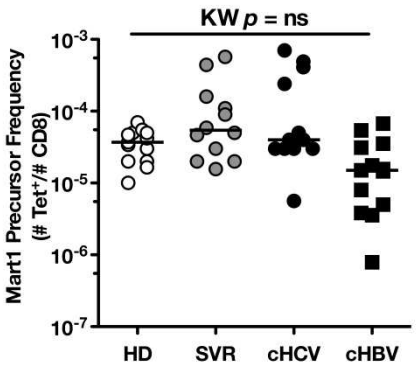
- **diabetes** (OR = 1.8)
- **cardio-vascular morbidity** (OR=2.37)
- **cerebro-vascular mortality** (OR= 2.7)
- **renal disease** (HR for ESRD < 59 y= 7.8 vs. 3.2)
- **extra-hepatic** (breast: OR=2) **cancers**

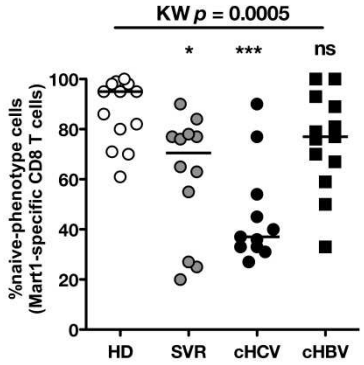


White D et al. J Hepatol 2008;49:831–844
Kakinami L et al. Int J Clin Pract 2013;67:6–13
Lee M-H et al. Stroke 2010;41:2894–2900
Su F-H et al. Am J Kidney Dis 2012;60:553−560
Su F-H et al. BMC Cancer 2011;11:495

Lee M-H et al, J Infect Dis 2012;206:469–477

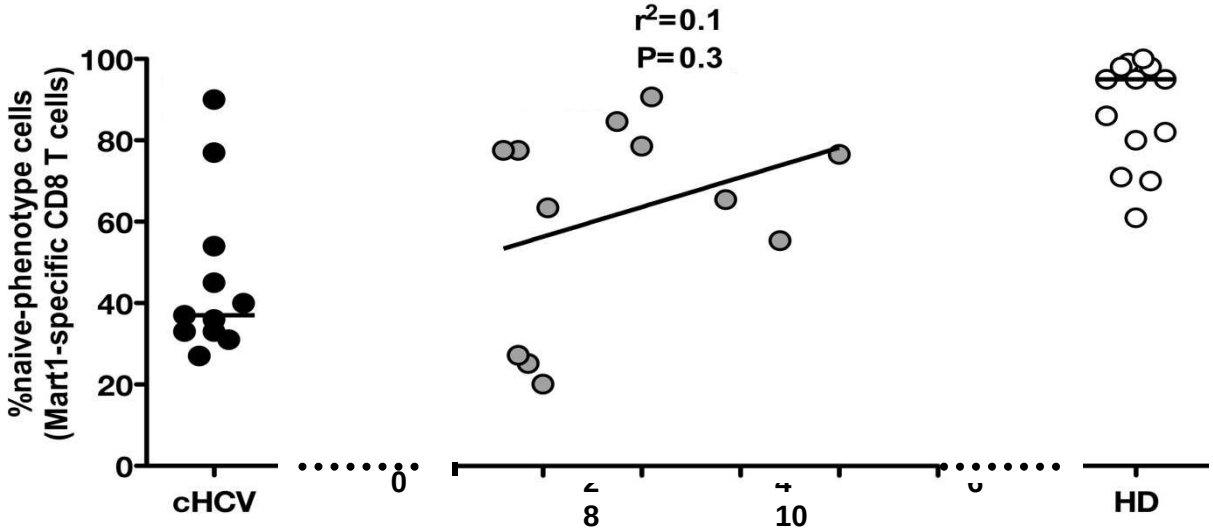
The preimmune repertoire in HCV





Antigen-inexperienced CD8 T cell populations show a memory-phenotype

Qualitative alterations of the preimmune repertoire are slowly reversible



Alanio C et al. Submitted 2014

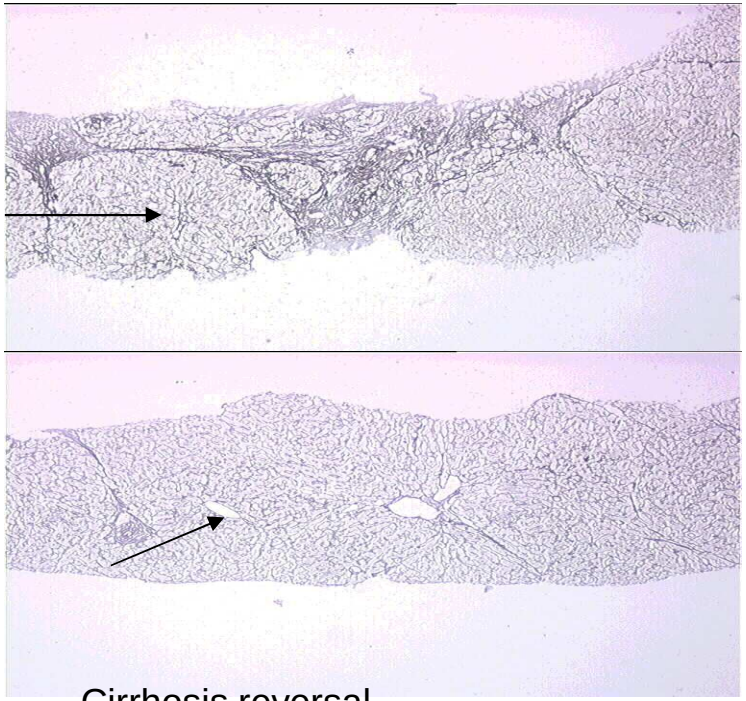
Sustained virologic response (SVR) is the objective of therapy

- HCV is the only chronic viral infection which may be cured (no reservoir, no genomic integration): SVR = no HCV RNA in the serum (and liver/PBMCs) 12weeks after treatment discontinuation
- No viral relapse in patients achieving SVR over time (out of reinfection)
- No viral relapse in transplant (liver and/or kidney) patients who achieved SVR before transplantation

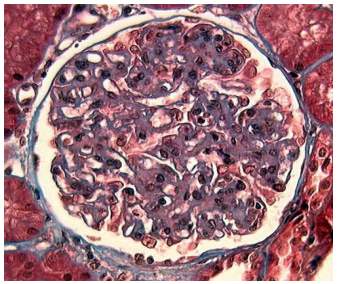
Sustained virologic response (SVR) is the objective of therapy

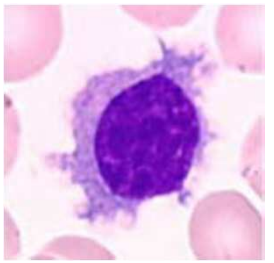
- SVR= virologic cure

- Most of HCV-related manifestations are mainly reversible

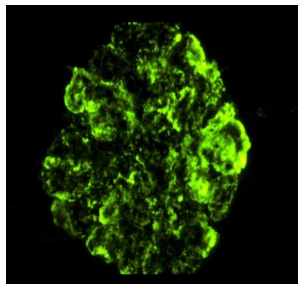


Cirrhosis reversal

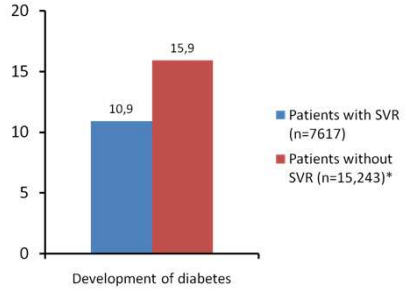




Lymphoma remission

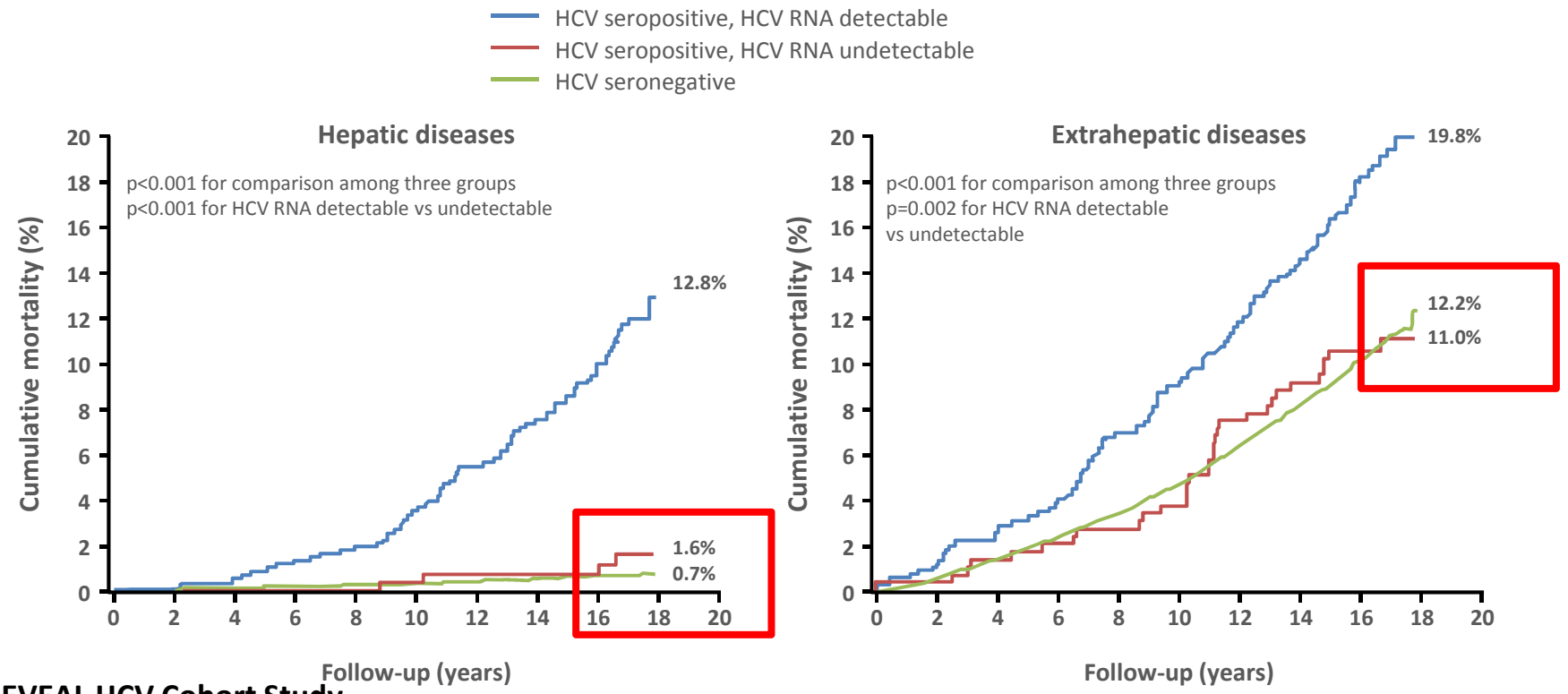


Glomeluronephritis reversal



Diabetes improvement

HCV cure decreases mortality from both hepatic and non-hepatic diseases



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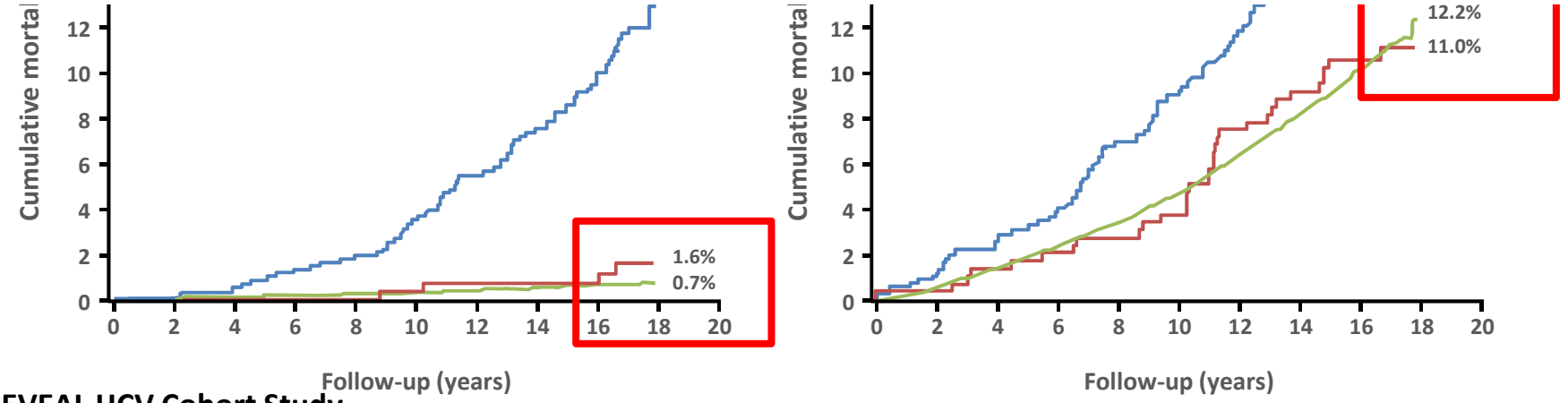
Lee M-H et al, J Infect Dis 2012;206:469–477

HCV cure decreases mortality from both hepatic and non-hepatic diseases

Such a benefit (SVR-related reversal of hepatic and extra-hepatic disease) has to be offered in theory to any HCV-infected patient



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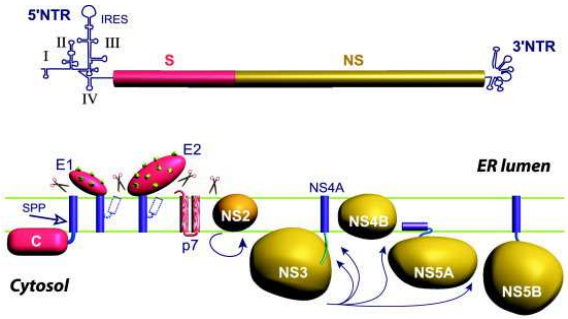
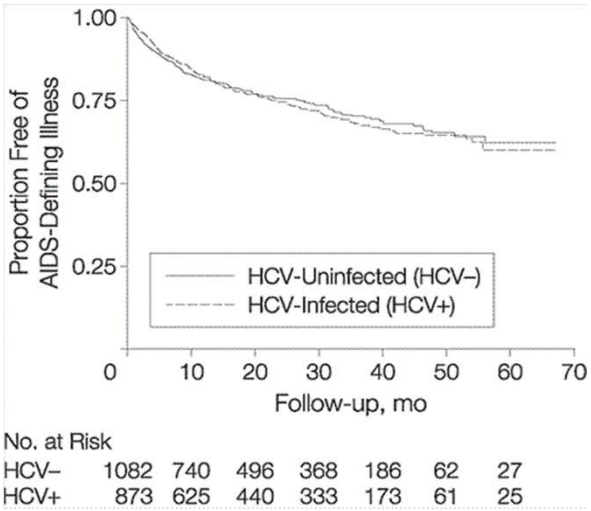
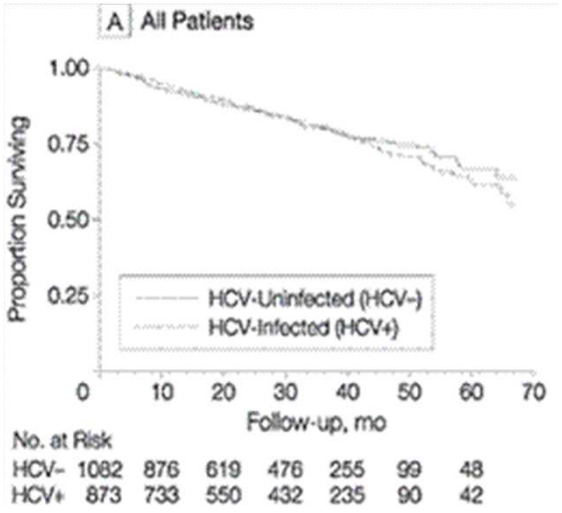


- Why to treat?
- The impact of HIV
- How to treat?

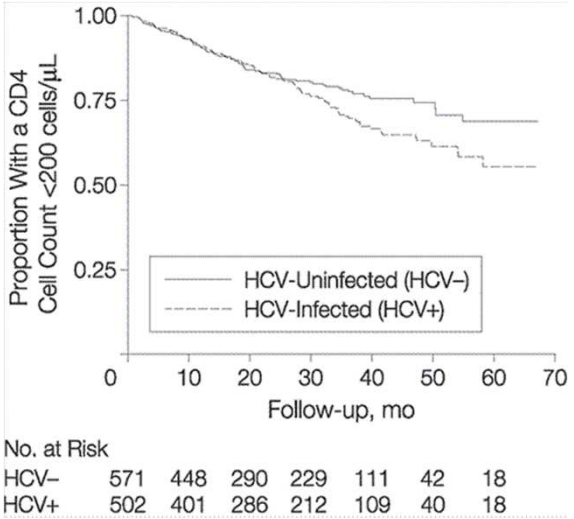
HIV/HCV Co-infection



HR 1.03 (0.86-1.23)



HR 1.05 (0.85-1.30)



HR 1.28 (0.98-1.68)

No modification related to HCV

Sulkowski MS and al. JAMA 2002

HIV/HCV Co-infection: harmfull impact of HIV

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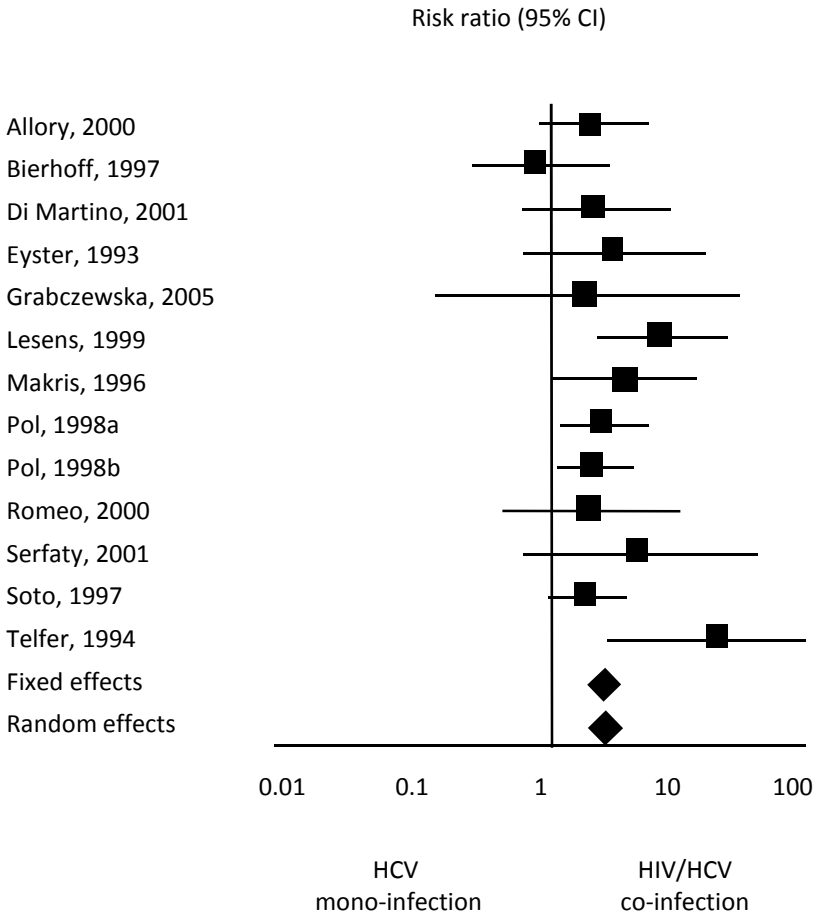
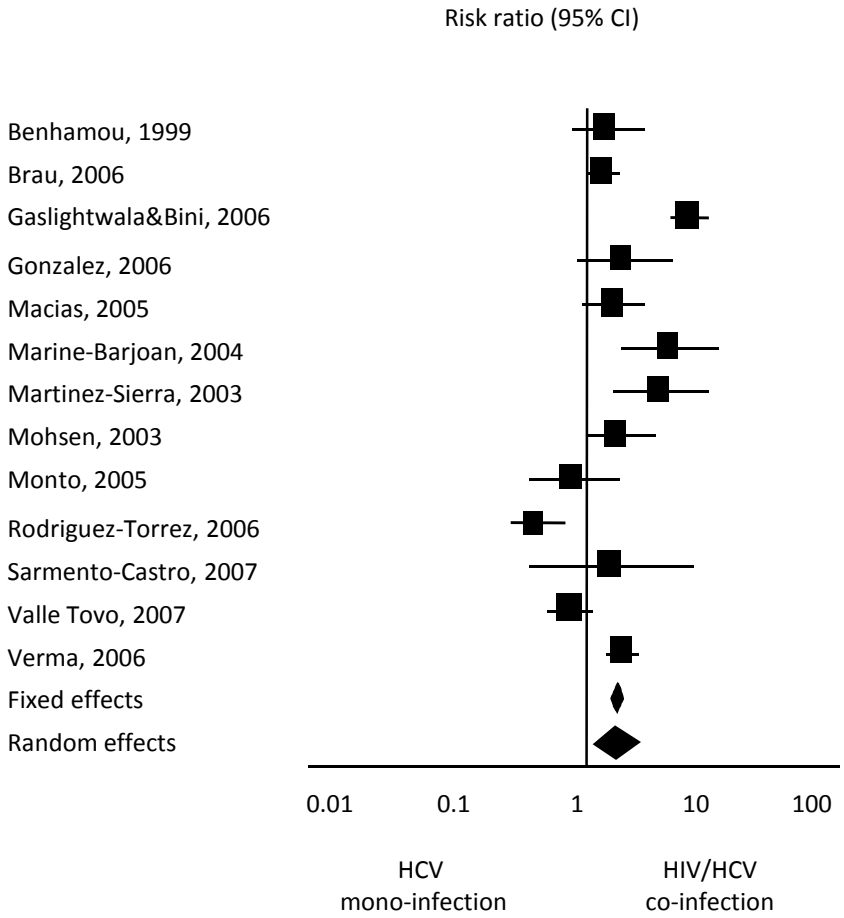
Meta-analysis of 26 studies

No HAART



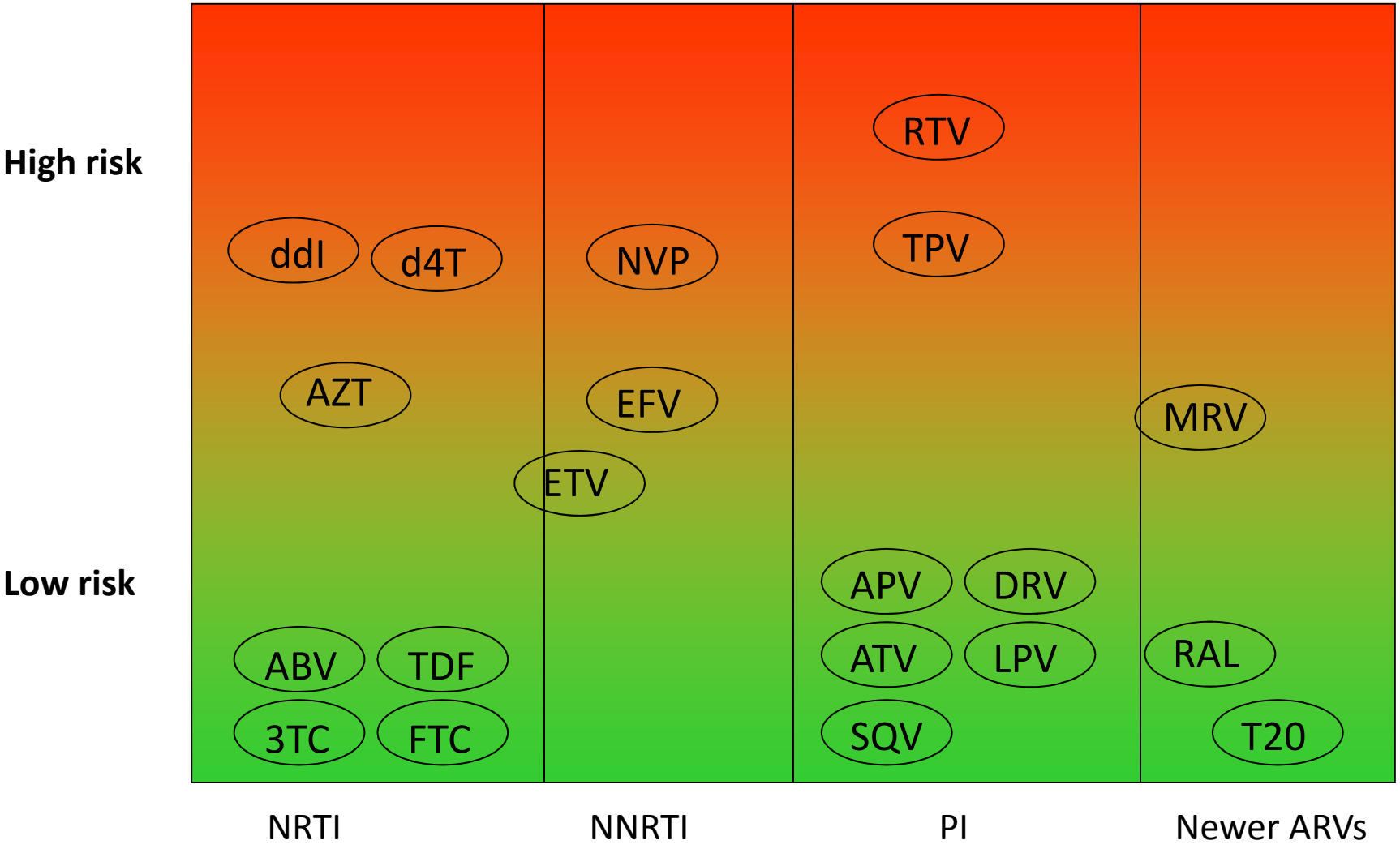
HAART



HAART: highly active antiretroviral therapy

Deng L, et al. World J Gastroenterol2009;15:996–1003

ARV liver toxicity



Soriano V et al. AIDS 2008

HIV/HCV Co-infection: harmfull impact of HIV

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Annals of Internal Medicine
ESTABLISHED IN 1927 BY THE AMERICAN COLLEGE OF PHYSICIANS

From: HIV, Age, and the Severity of Hepatitis C Virus–Related Liver Disease: A Cohort Study

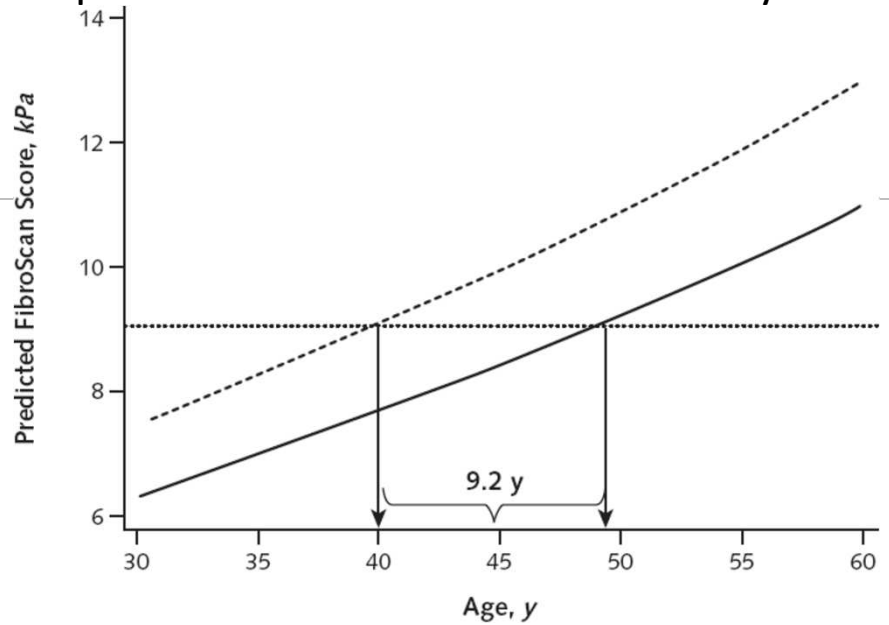
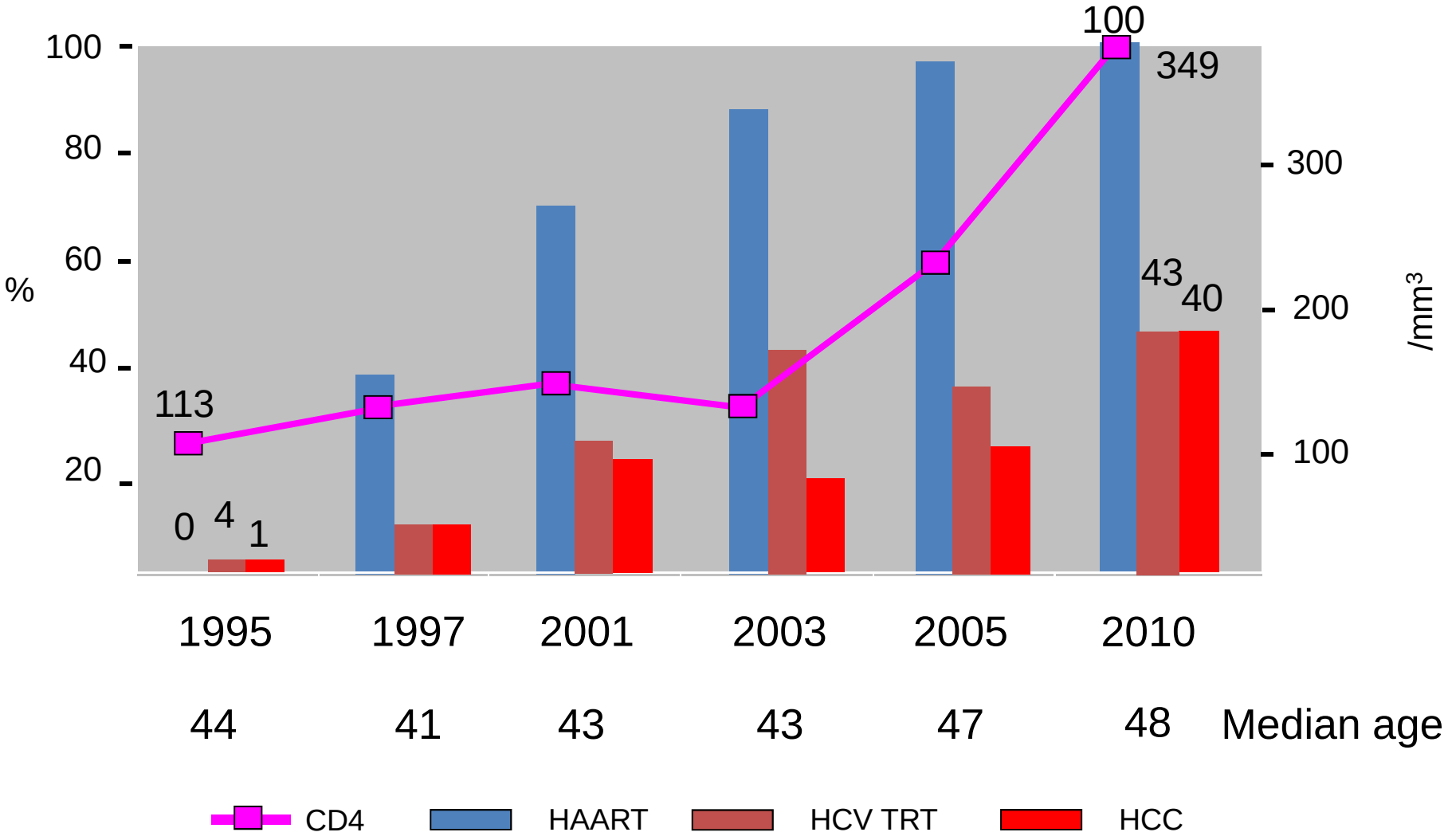


Figure Legend:

Liver fibrosis and age among persons coinfected with HIV and HCV and those with only HCV.

For each age, predicted liver fibrosis scores were calculated using a regression equation that included the race, sex, alcohol use, body mass index, hepatitis B virus surface antigen level status, and HCV RNA level values for a representative participant (black overweight male who has no regular alcohol use, is hepatitis B virus surface antigen–negative, and has high HCV viral load) for persons coinfected with HIV and HCV (dashed line) and for persons with only HCV (solid line). For example, a 40-year-old HIV and HCV coinfected person with these characteristics was calculated to have a predicted FibroScan score of 9.04 kPa. For this same degree of fibrosis, the predicted age in a similar person but with only HCV was 49.2 years. Over the entire age range, the average difference in estimated age between persons coinfected with HIV and HCV and those with only HCV was 9.2 years (90% coverage limit, 5.2 to 14.3 years). HCV = hepatitis C virus.

Liver-related mortality in PLWHIV



Rosenthal E et al. Clin Infect Dis. 2012

HCV infection is a severe disease in PLWHIV

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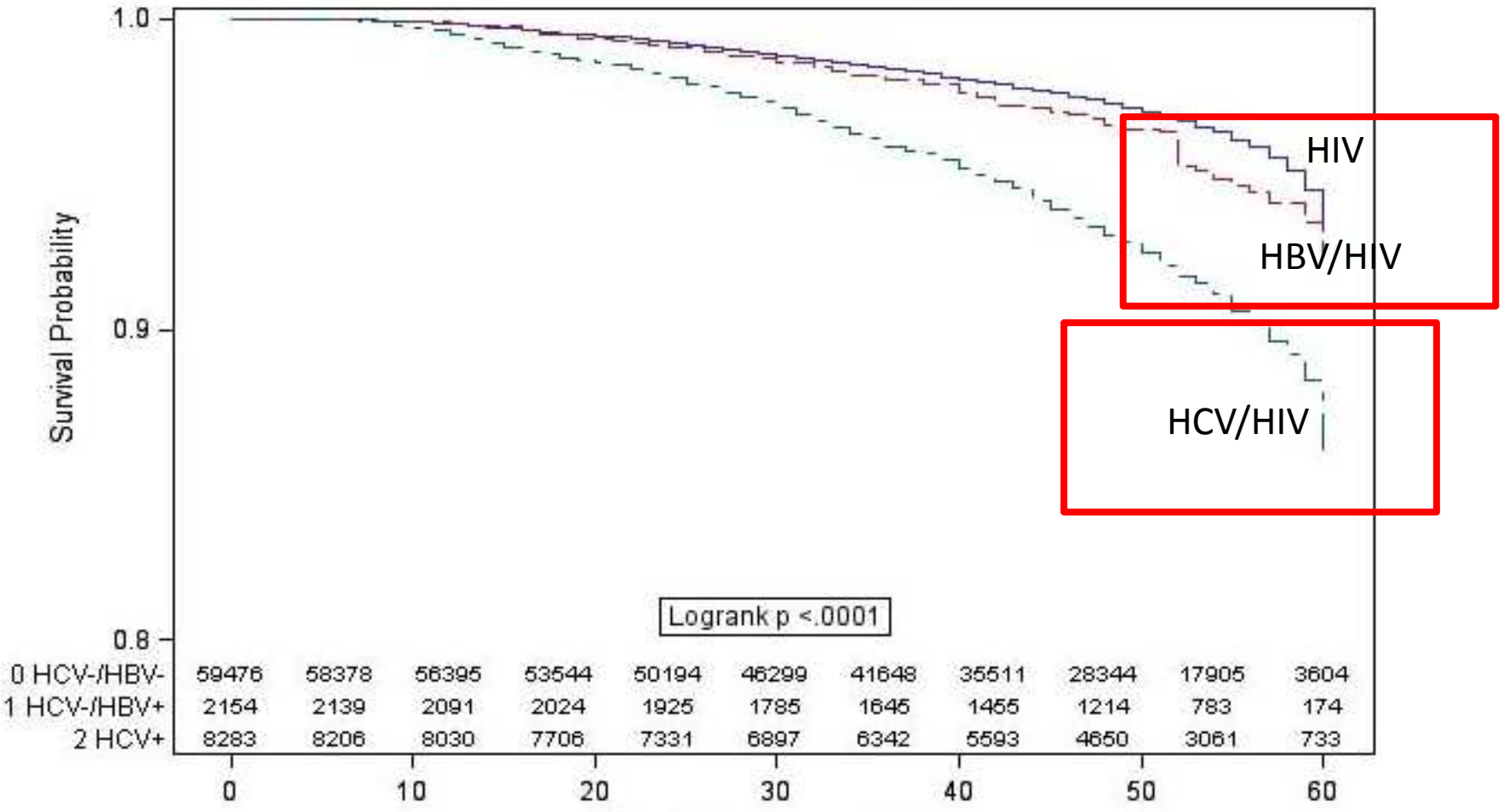
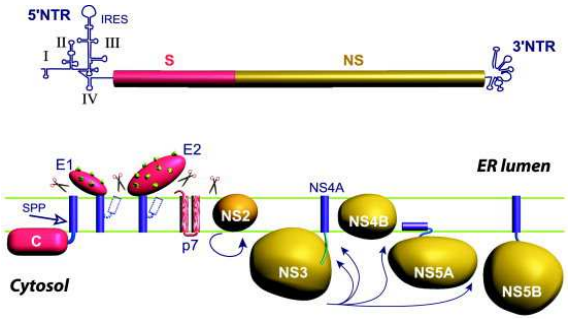
Mortality of 69.913 french PLWHIV (2008-2012)



Adjusted on age, gender, alcohol, decompensated cirrhosis, AIDS

Mallet V et al. CROI 2014

Hepatitis C virus infection: a systemic disease with the possibility to cure



- Why to treat?
- The impact of HIV
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Treatment of HCV infection
Times to treat

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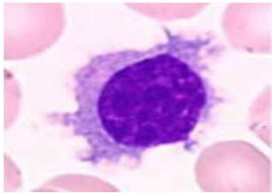


Contamination

Acute Hepatitis

< 30%

Recovery

> 70%

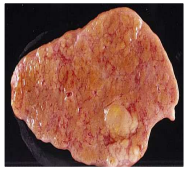
Chronic Infection

> 95%

Chronic Hepatitis

A>1 F>1

> 20%



HCC

Cirrhosis

Lymphotropism

40%

Cryoglobulinemia

1 to 2%

Vasculitis

Lymphoma

EASL guidelines 2011 & 2014

Treatment of chronic hepatitis C

<2011

Combination PEG-IFN – RBV

Treatments with IFN

EASL guidelines 2011

Four pivotal Peg-IFN/RBV studies in HIV/HCV co-infected patients

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Characteristic	APRICOT[1]	ACTG 5071[2]	RIBAVIC[3]	Barcelona[4]
Number enrolled	868	133	412	95
Peg-IFN	2a	2a	2b	2b
RBV	800 mg	600 mg up to 1 g	800 mg	800 mg up to 1.2 g
HIV and CD4 status	>200 cells/mm^3 or 100–200 cells/mm^3 if HIV-RNA <5000 copies/mL	>100 cells/mm^3 + HIV-RNA <10,000 copies/mL or >300 cells/mm^3, tx naïve + not starting ART during trial	>200 cells/mm^3	>250 cells/mm^3 and HIV-RNA <10,000 copies/mL
ALT	"elevated"	NA	NA	>1.5x ULN
Genotype 1, %	60–61	77–78	48	49
Bridging fibrosis or cirrhosis, %	15–16	9–11 (cirrhosis)	39	30
Genotype 1 Peg-IFN/RBV SVR rate, n/N (%)	51/176 (29)	7/51 (14)	21/123 (17)*	22/59 (38)*

*Genotype 1 or 4
ART: ARV therapy; Peg-IFN: peginterferon; RBV: ribavirin
SVR: sustained virologic response; tx: treatment; ULN: upper limit of normal

1.Torriani FJ, et al. N Engl J Med 2004;351:438–50; 2. Chung RT, et al. N Engl J Med 2004;351:451–9; 3. Carrat F, et al. JAMA 2004;292:2839–484
4. LagunoM, et al. AIDS 2004;18:F27–36

Treatment of chronic hepatitis C

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2011-2014

Combination PEG-IFN – RBV

« 2011 » DAAs

Treatments with IFN

	SVR in GT1
	45%
	60-75%

EASL guidelines 2011

Treatment of chronic hepatitis C

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2011-2013

Combination PEG-IFN – RBV

2011 DAAs

Combination PEG-IFN – RBV

New DAAs

Treatments with IFN

	SVR in GT1
	45%
	75%
	75-95%

Sofosbuvir	**1Q14**
Simeprevir	**2Q14**
Daclatasvir	**3Q14**

- Better efficacy (pan-genotypic)
- Better tolerability
- Reduction of duration
- Easier dosing schedule
- Reduced pill burden

Treatment of HCV infection
Times to treat

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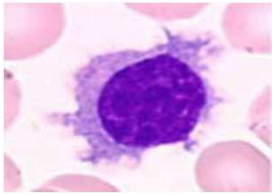


Contamination

Acute Hepatitis

< 30%

> 70%

Recovery

> 95%

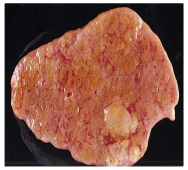
Chronic Infection

Lymphoma

Mandatory in F3-4*
Debatable or recommended in F2**
Wait in F0-1

o 2%

mia



HCC

Cirrhosis

40%

Lymphotropism

*French guidelines: Leroy V et al. Liver Int 2012; online 2013 in co-infected; **EACS Guidelines:Ingiliz P, Rockstroh J. Liver Int. 2012 and French guidelines for HIV/HCV co-infection. Salmon D et al. Liver Int. 2013

Understanding of HCV life cycle revealed several potential innovative drug targets

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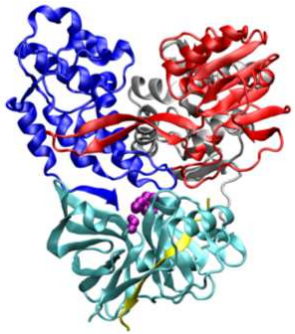
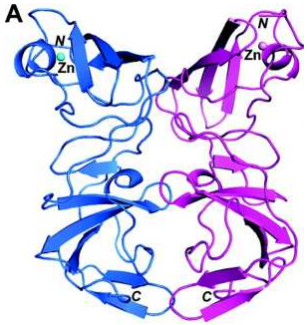
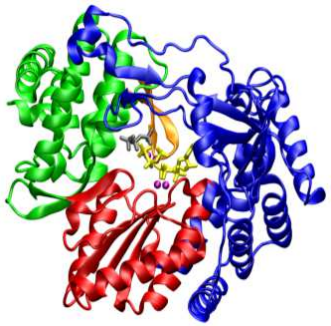
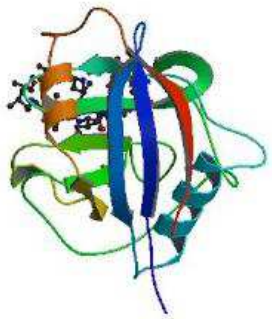
Viral targets







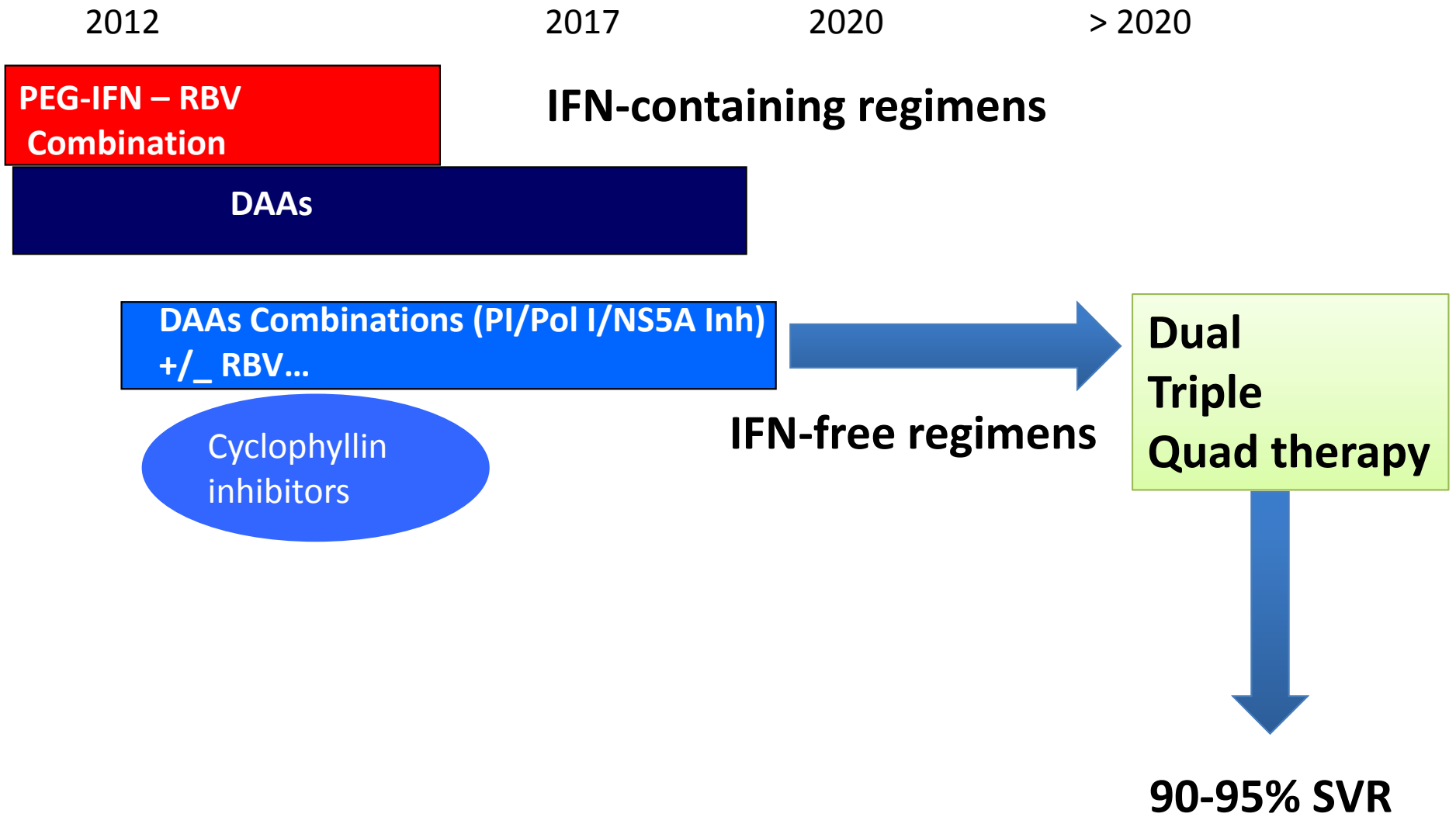
Host targets



NS3	NS5A	NS5B	Cyclophilin A
The NS3/4A serine protease is essential for post-translational processing of HCV polyproteins[1]	Multifunctional membrane-associated phosphoprotein essential component of the HCV-RNA replication complex[2,3]	NS5B is an HCV-specific, RNA-dependent RNA polymerase[1]	Host protein involved in HCV replication through interaction with NS5A and the HCV polymerase[4]
Boceprevir **Telaprevir** ABT-450/r, ACH-1625 Asunaprevir, **Simeprevir**, BI-201335 Danoprevir/r, GS-9451 MK-5172	**Daclatasvir** GS-5885 ABT-267 PPI-668	Nucleos(t)ide analogue **Sofosbuvir**, Mericitabine, IDX-184* Non-nucleoside analogue BI-207127, ABT-333 ABT-072, BMS-791325 Tegobuvir, Setrobuvir VX-222, Filibuvir	Alisporivir** SCY-635

Adapted from 1. Pawlotsky JM, et al. *Gastroenterology* 2007;132:1979–98; 2. Tellinghuisen TL, et al. *Nature* 2005;435:374–9; 3. Gish R & Meanwell NA. *Clin Liver Dis*. 2011;15:627–39; 4. Coelmont L, et al. *PLoS One* 2010;5:e13678.

Treatment of chronic hepatitis C



An almost universal virologic cure

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Phase III studies of the combination by ABT450/r, ombitasvir (ABT 267) & dasabuvir (ABT 333)(3D) in G1

Study	Patients profile	Treatment	SVR12
SAPPHIRE-I (12 weeks)	Treatment Naïve patients (n = 631)	3D + RBV (n = 473)	96 %
SAPPHIRE-II (12 weeks)	Experienced patients (n = 394)	3D + RBV (n = 297)	96 %
PEARL-II (12 weeks)	GT1b Experienced patients (n = 179)	3D + RBV (n = 88)	96 %
		3D (n = 91)	100 %
PEARL-III (12 weeks)	GTb1 Treatment Naïve patients (n = 419)	3D + RBV (n = 210)	99 %
		3D (n = 209)	99 %
PEARL-IV (12 weeks)	GT1a Treatment Naïve patients (n = 305)	3D + RBV (n = 100)	97%
		3D (n = 205)	90%
TURQUOISE-II (12 & 24 weeks)	GT1 with compensated cirrhosis (n = 380)	3D + RBV, 12 w. (n = 208)	92 %
		3D + RBV, 24 w. (n = 172)	96 %

3D = ABT-450/ritonavir (150/100 mg) co-formulated with ombitasvir (ABT-267) (25 mg) QD and dasabuvir (ABT-333) (250 mg) BID with or without weight-based ribavirine

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An almost universal virologic cure

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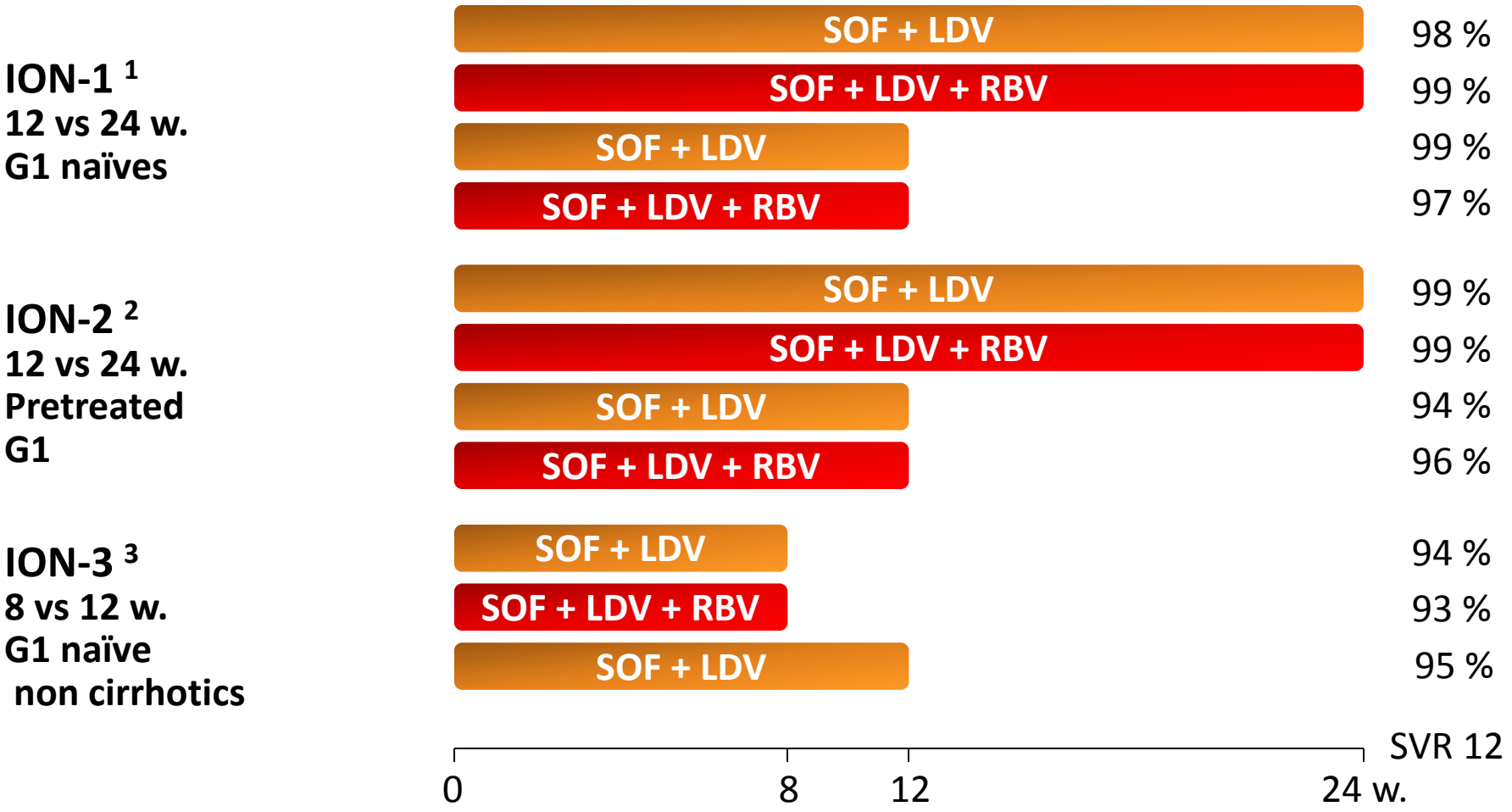
Summary of sofosbuvir/ledipasvir ± RBV studies



[1] Mangia A et al., EASL 2014, Abs. O164;;[2]Afdhal N et al., EASL2014, Abs. O109;
[3] Kowdley KV et al. Etats-Unis, EASL 2014, Abs. O56 actualisé

EASL 2014

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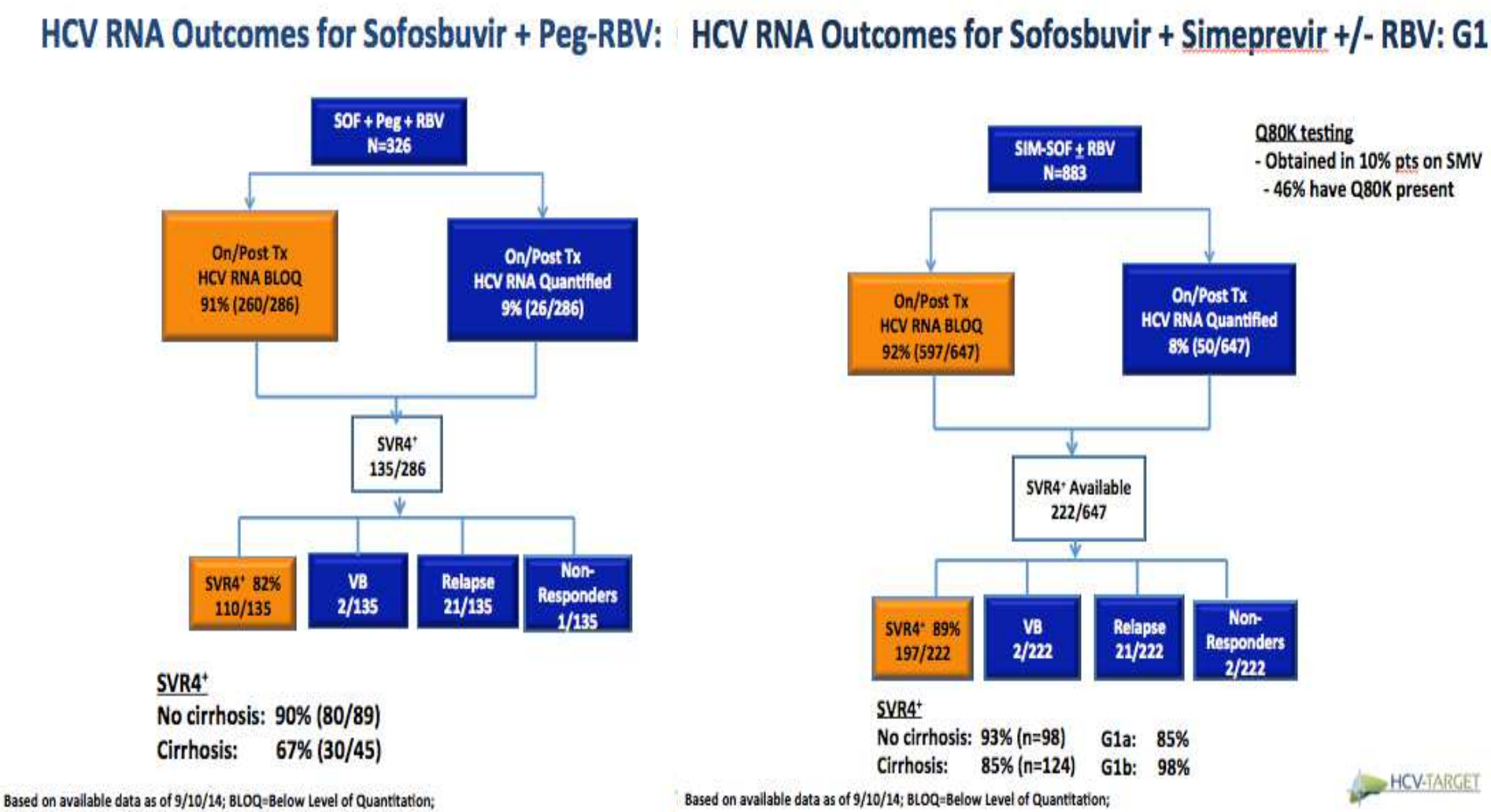
HCV-Target 2.0 study



Nelson D. et al. AASLD/EASL meeting 2014

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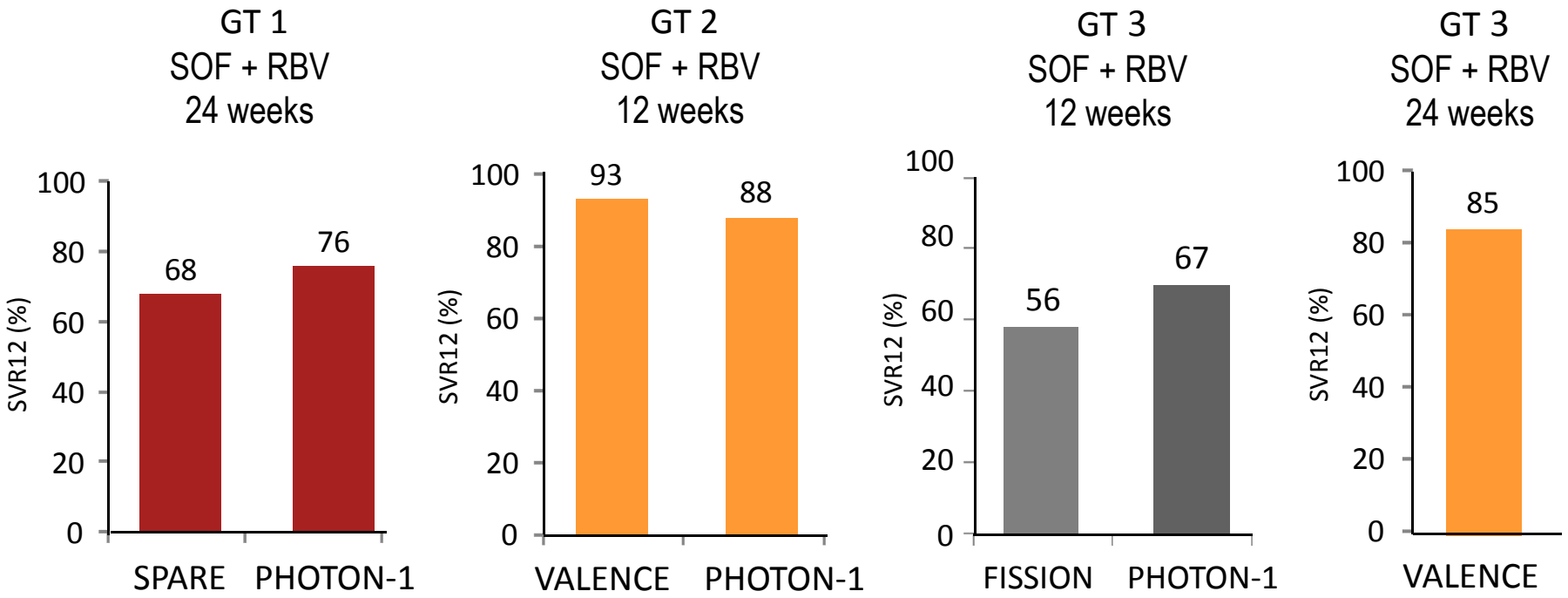
SOF + RBV: Comparison HCV mono- vs. HCV/HIV co-infected



Osinusi A, et al. *JAMA*. 2013;310(8):804-811.
Sulkowski MS, et al. AASLD 2013. #212.
Zeuzem S, et al. AASLD 2013#1085.
Lawitz E, et al. *N Engl J Med*. 2013 May 16;368(20):1878-87.

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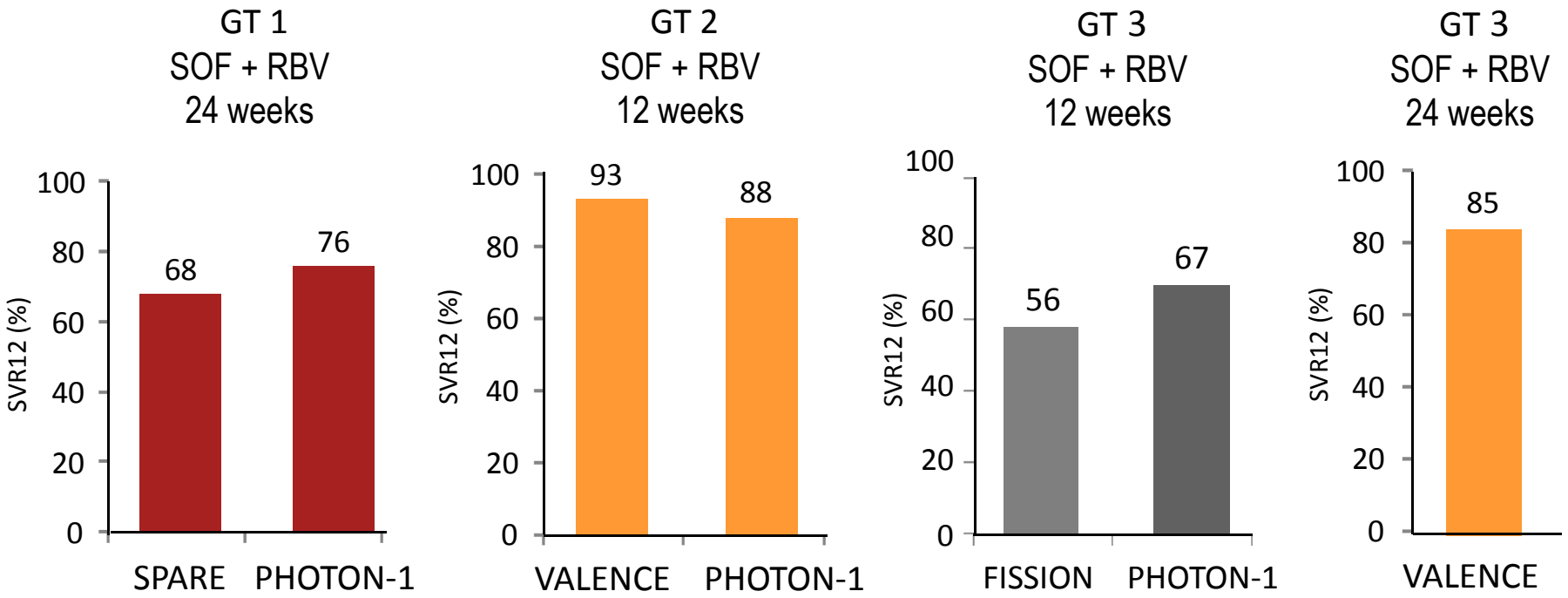
SOF + RBV: Comparison HCV mono- vs HCV/HIV coinfected



The concept of difficult-to-treat population has been removed by the antiviral potency of DAAs

Zeuzem S, et al. AASLD 2013#1085.

Lawitz E, et al. *N Engl J Med*. 2013 May 16;368(20):1878-87.

Hepatitis C : a systemic disease with the possibility to cure
Summary

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- A large number of regimens containing combinations of DAAs (± peg-alfa/RBV) are currently being investigated, appear likely to address many of the current unmet medical needs of HCV patients, especially those who were “difficult-to-treat”

- Dual, Triple or Quad regimen should be tailored to the host- and virus-related factors (subtype, fibrosis, prior therapies, viral resistance and tolerance, co-morbidities, DDI): the best “à la carte” combination

- New therapies should be given to severe patients (F3-4 patients, symptomatic vasculitis, pre- and post-transplant) in priority, but probably should be considered for all patients in the next future