2015 8th Paris Hepatitis Conference
Organised by Pr Patrick Marcellin
12 & 13 January 2015
Palais des Congrès, Paris

universitäts klinikum bonn

Special populations: HIV coinfected patients

8th Paris Hepatitis Conference, 12.-13. January 2015, Palais des Congrès, Paris, France

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Conflict of interest

I have received honoraria for speaking at educational events or consulting from:

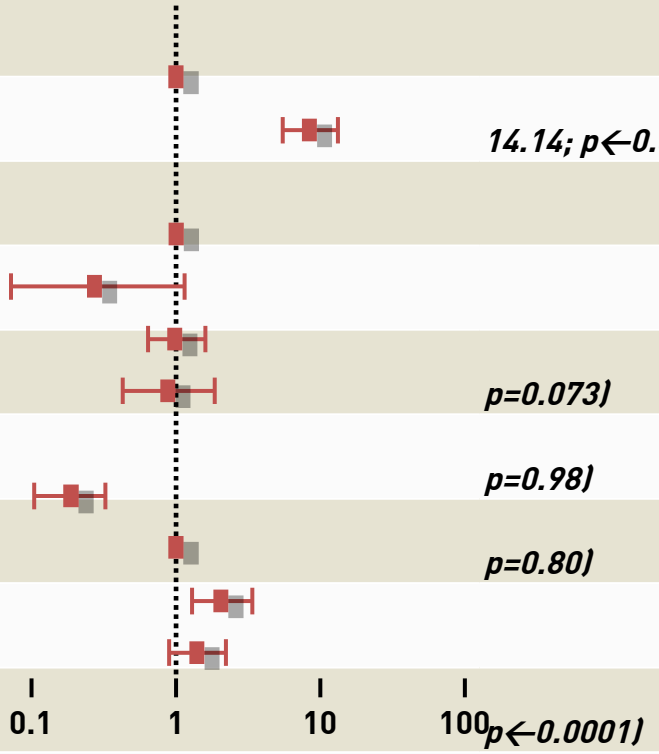
Abbott, Abbvie, Bionor, BMS, Boehringer, Gilead, Janssen, Merck, Novartis, Pfizer, Roche, Tibotec, Tobira and ViiV

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)	Ev	IRR (95% CI; p value)
Negative	*(66,653)*	*43*	*1*
Positive	*5 (26,494)*	*17*	*8.90 (5.60–14.14; p<0.0001)*
HCV genotype			
GT 1	*(8122)*	*55*	*1*
GT 2	*(554)*	*2*	*0.27 (0.07–1.13; p=0.073)*
GT 3	*(4503)*	*28*	*0.99 (0.62–1.59; p=0.98)*
GT 4	*(2188)*	*9*	*0.91 (0.44–1.89; p=0.80)*
HCV-RNA viremia			
HCVAb-	*(66,653)*	*43*	*0.18 (0.10–0.32; p<0.0001)*
Ab+/RNA-	*(4838)*	*11*	*1*
Ab+/RNA+		*86*	*2.11 (1.30–3.42;*

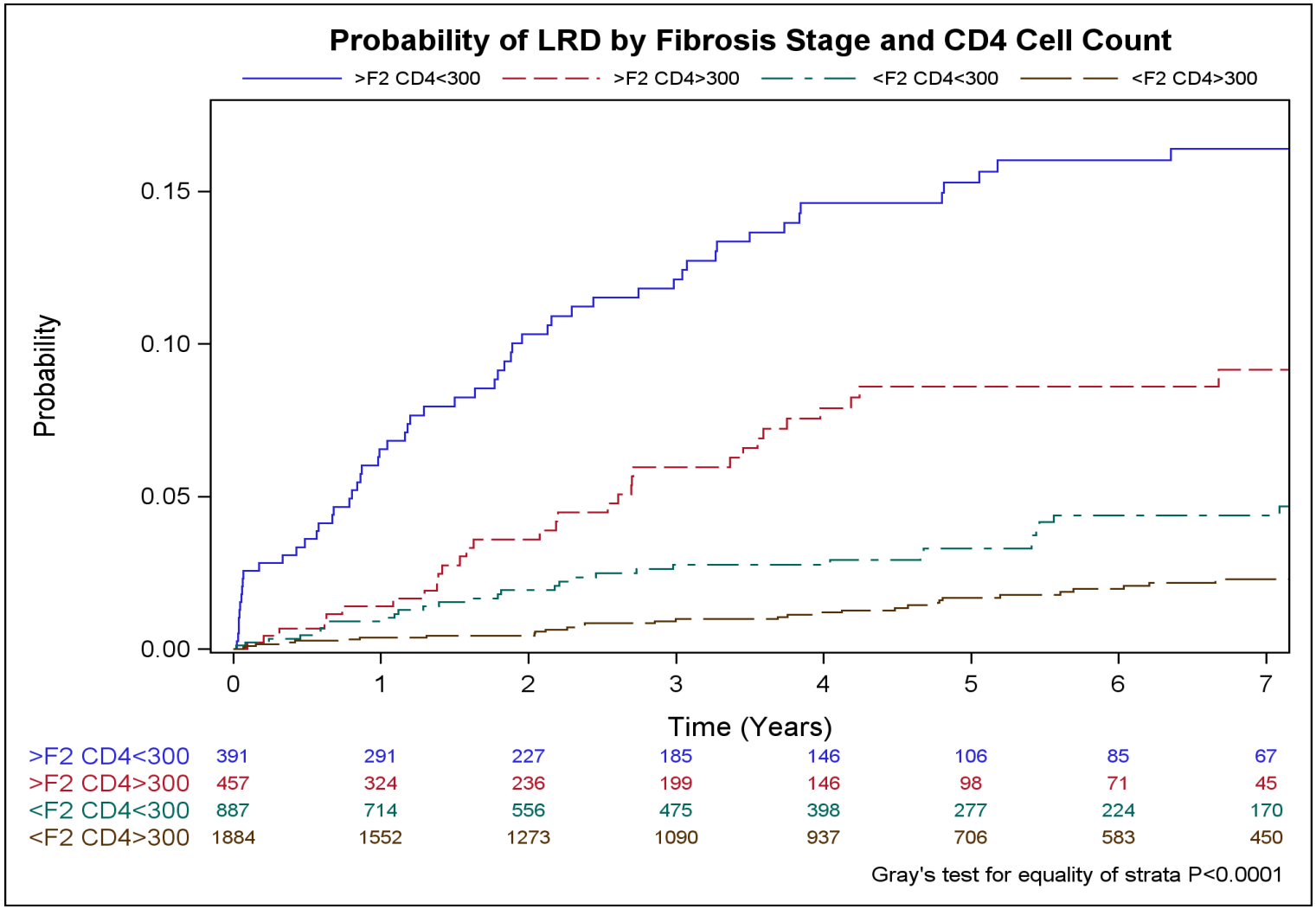


Multivariate a
race, prior AI
treatment sta
cART, HBsAg
and CD4+ T-c
variables.

person
e ratio;
3-220

Cumulative incidence of LRD by fibrosis staging and CD4 cell count

145 LRD among 3941 HIV/HCV pts from EuroSIDA



Grint et al CROI 2014

HIV/HCV – double-trouble for the liver

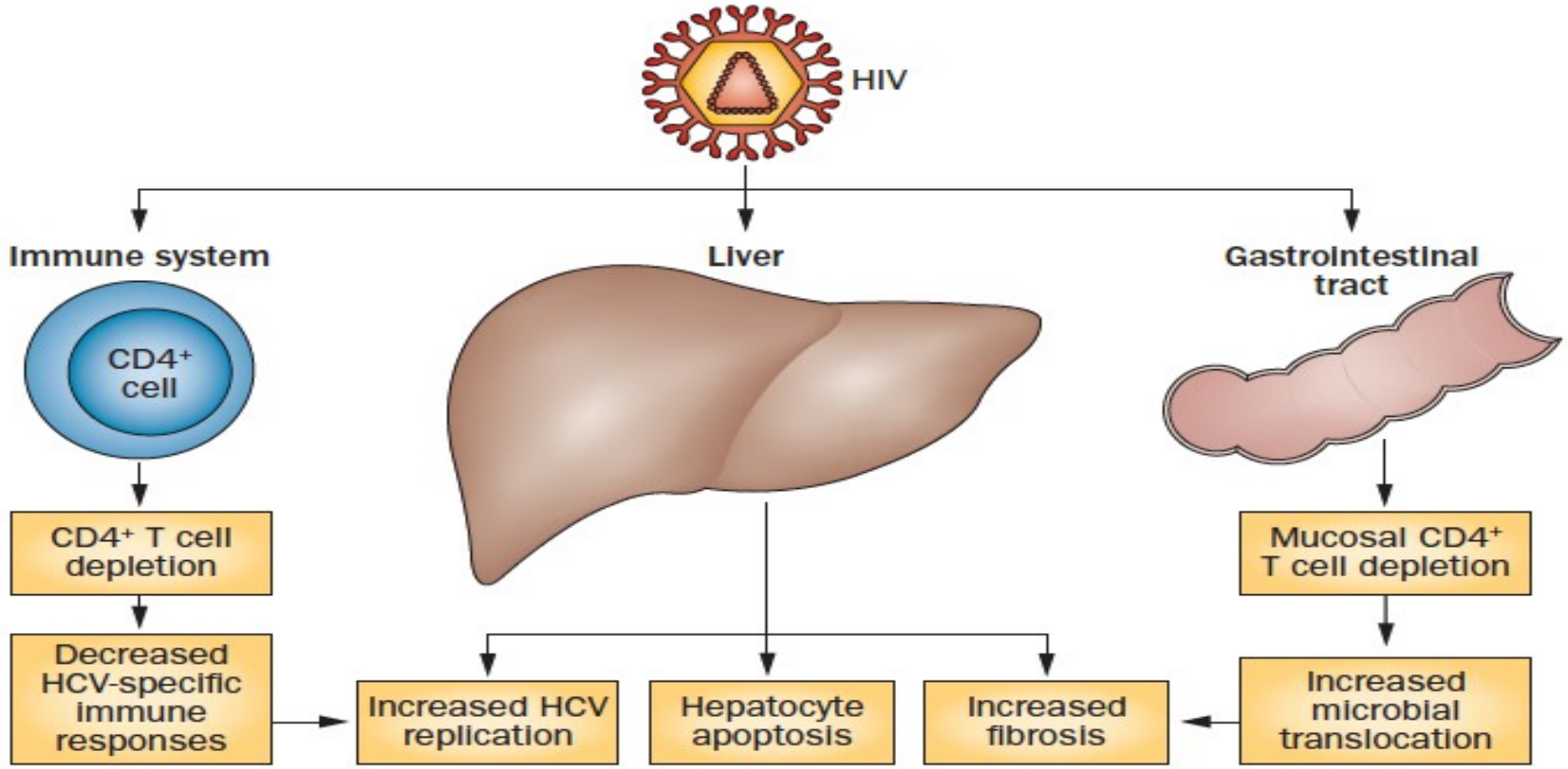


Figure 1 | Driving factors underlying liver disease pathogenesis in HCV–HIV co-infection. HIV infection leads to an impaired immune response against HCV, increased HCV replication, hepatic inflammation and apoptosis, increased microbial translocation from the gastrointestinal tract and increased fibrosis.

Chen J Nat Rev Gastroenterol Hep 2014
doi:10.1038/nrgastro.2014.17

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

Treat HCV first?

Treat HIV first?

Treat HIV/HCV simultaneously?

EACS guidelines: when to start

- Initiation of ART
  - ART is always recommended if CD4 count <350 cells/mm^3

Condition	Current CD4+ lymphocyte count	
	350–500	>500
HBV requiring anti-HBV treatment	R	R
HBV not requiring anti-HBV treatment	R	C
HCV for which anti-HCV treatment is being considered or given	R	C
HCV for which anti-HCV treatment not feasible	R	C

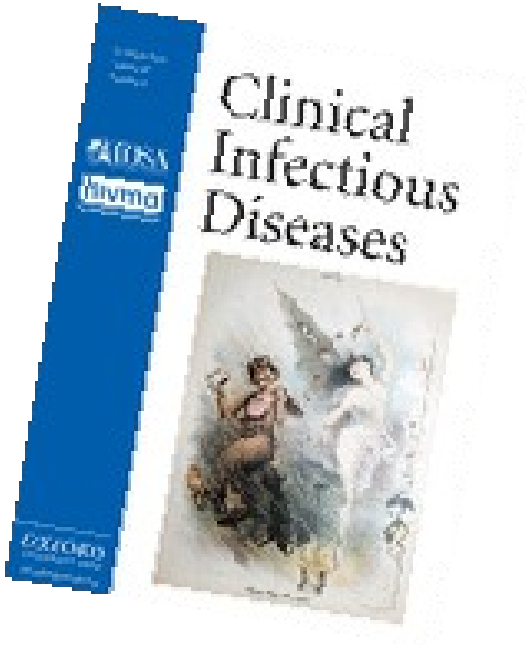
EACS treatment guidelines, Version 7.0 2013. Accessed November 2013. . Available at: http://www.europeanaidsclinicalsociety.org

C, consider; D, defer; R, recommended

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

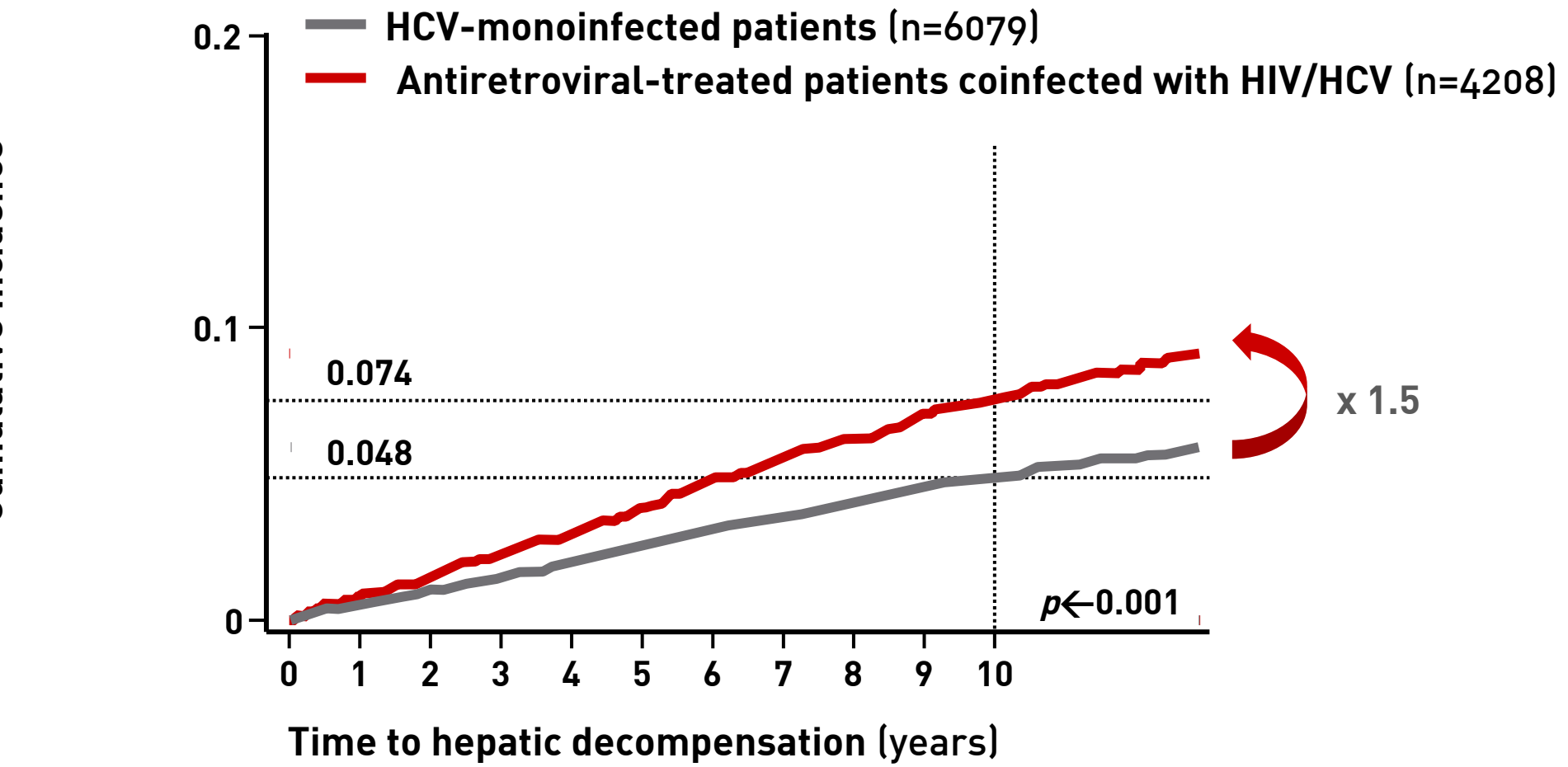


Results:

- 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

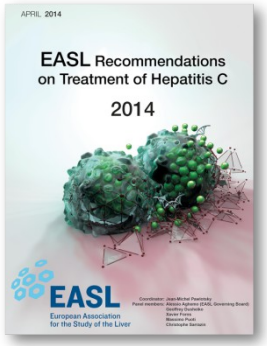


ART, antiretroviral therapy

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

EASL and AASLD/IDSA/IAS-USA HCV recommendations

- Indications for HCV treatment in HIV/HCV co-infected patients are identical to those in HCV mono-infection (Recommendation A1) (EASL)
- Same treatment regimens can be used in HIV/HCV patients as in patients without HIV infection, as the virological results of therapy are identical (Recommendation A1) (EASL)



High Priority for Treatment Owing to High Risk for Complications

- HIV-1 coinfection (AASLD/IDSA)
- Rating: Class I, Level B

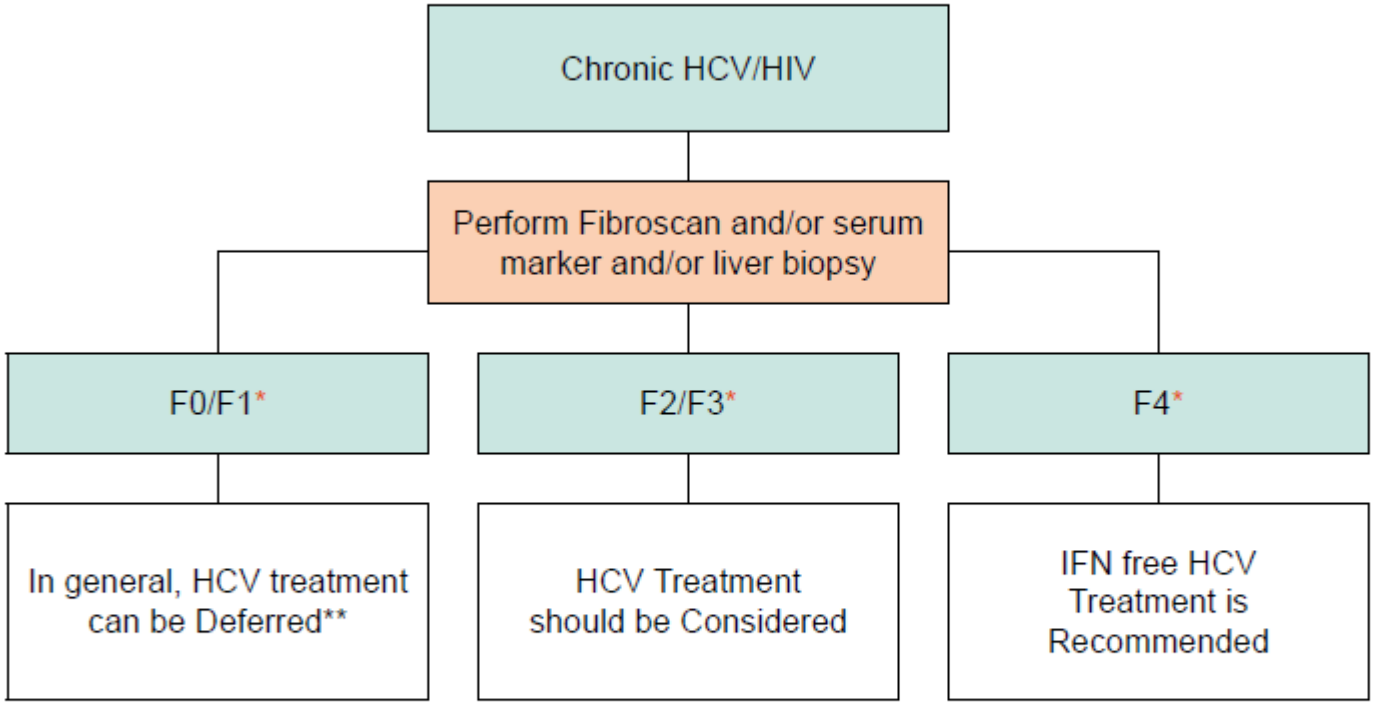
AMERICAN ASSOCIATION FOR THE STUDY OF LIVER DISEASES
AASLD

IDSA
Infectious Diseases Society of America

Collaborating Partner
IAS–USA
International Antiviral Society–USA

EASL recommendations April 2014. Accessed October 2014. Available at: http://files.easl.eu/easl-recommendations-on-treatment-of-hepatitis-c-summary.pdf

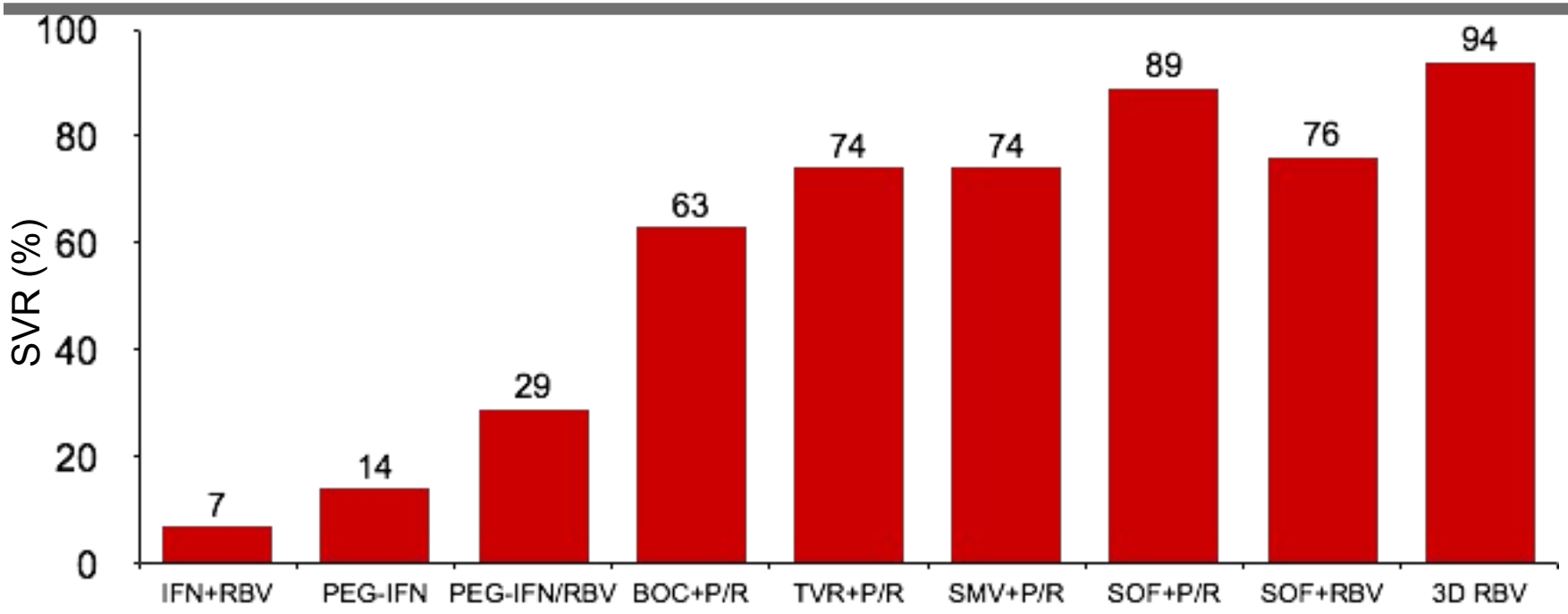
Management of Persons with Chronic HCV/HIV Co-infection



* Metavir fibrosis score: F0=no fibrosis; F1= portal fibrosis, no septae; F2= portal fibrosis, few septae, F3=bridging fibrosis, F4=cirrhosis.

** Monitor fibrosis stage annually, preferably with two established methods. Consider Treatment, if rapid progression.

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



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

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

ARV Interaction Score Card

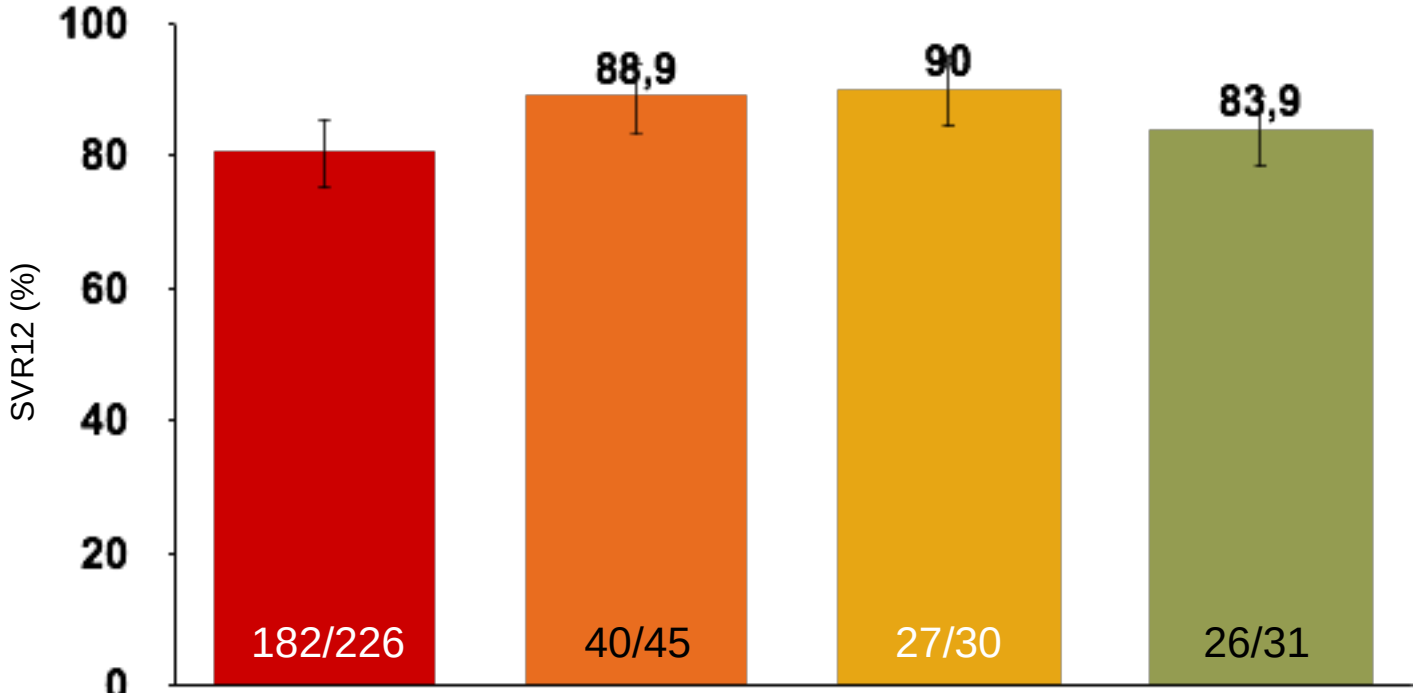
	Simeprevir	Sofosbuvir	Ledipasvir	Daclatasvir	AbbVie 3D
TV/r	No data	ATV SOF	No data	DCV ↑*	ATV ; ABT450 ↑
RV/r	SIM ↑; DRV	SOF ↑; DRV	No data	DCV (↑)	DRV ↓; 3D ↓
PV/r	No data	No data	No data	DCV	LPV ; ABT450 ↑
PV/r	No data	No data	No data	No data	No data
FV	SIM ↓; EFV	SOF ; EFV	LDV ↓; EFV ↓	DCV ↓*	No PK data**
PV	SIM ; RPV	SOF ; RPV	LDV ; RPV	No data	ABT450 ↑; RPV ↑
TV	No data	No data	No data	No data	No data
AL	SIM ; RAL	SOF ; RAL	LDV ; RAL	No data	3D ; ↑ RAL
LV/cobi	No data	No data	No data	No data	No data
LG	No data	No data	No data	No data	No data

* Decrease DCV dose to 30mg QD, Increase DCV dose to 90mg QD, ** 3D + EFV led to premature study discontinuation due to toxicit
***when TDF is administered with a boosted HIV-PI and LDV significantly higher TDF levels can be expected warranting closer renal monitorin

Personal communication Jennifer Kiser, University of Colorado, Denver, USA

PHOTON-1 and 2: Results

Overall SVR12 by HCV Genotype

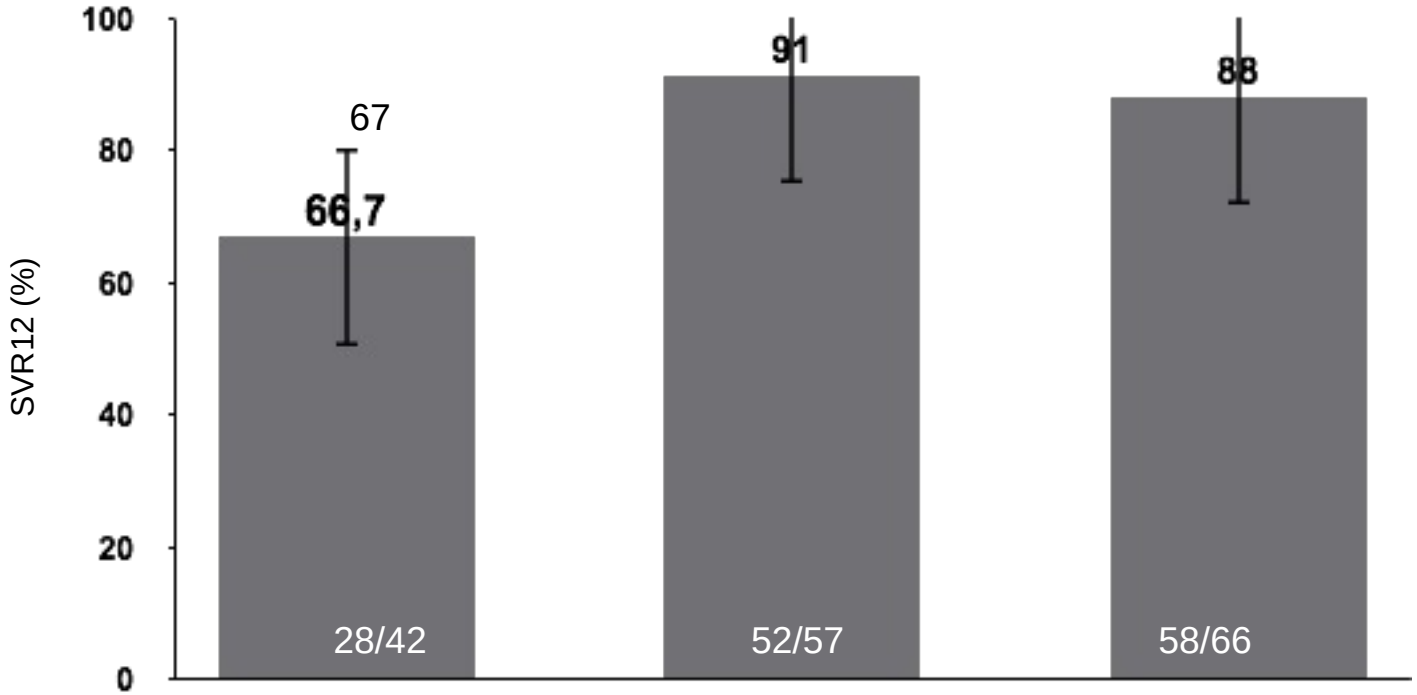


	GT 1 TN 4 Weeks	GT 2 TN 2 Weeks	GT 2 TE 4 Weeks	GT 4 TN 4 Weeks
Relapse, n (%)	*9 (17)*	*1 (2)*	*2 (7)*	*5 (16)*
Breakthrough, n (%)	*1 (<1)*	*1 (2)*	*0*	*0*

Rockstroh J, et al. 65th AASLD; Boston, MA; November 7-11, 2014. Abst. 195.

PHOTON-1 and 2: Results

SVR12 by HCV Genotype 3



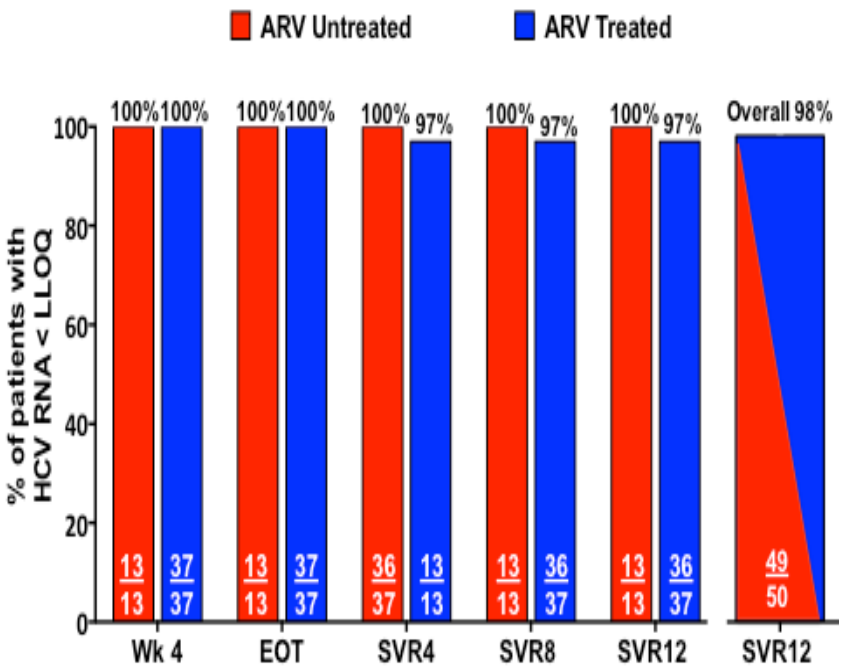
	GT 3 TN 1 2 Weeks	GT 3 TN 2 4 Weeks	GT 3 TE 2 4 Weeks
Relapse, n (%)	*1 2 (29)*	*4 (7)*	*7 (11)*
Breakthrough, n (%)	*0*	*0*	*1 (<1)*

Rockstroh J, et al. 65th AASLD; Boston, MA; November 7-11, 2014. Abst. 195.

NIAID ERADICATE: SOF/LDV in TN GT 1 HIV/HCV co-infected patients

In this Phase 3 study, 50 GT 1 TN (n=13) or TE (n=37) patients were treated with SOF/LDV for 12 weeks

Treatment Response:



Safety data:

Event, n (%)	SOF/ LDV ART naïve (n=13)	SOF/ LDV ART experienced (n=37)
D/C due to AEs	*0*	*0*
Grade 4 AEs	*0*	*0*
Death	*0*	*0*
Grade ≥2 lab abnormality in >5% of population		
Hypophosphataemia	*1 (8)*	*7 (19)*
Decreased ANC	*2 (15)*	*4 (11)*
Elevated ALT	*1 (8)*	*3 (8)*
Elevated AST	*1 (8)*	*3 (8)*

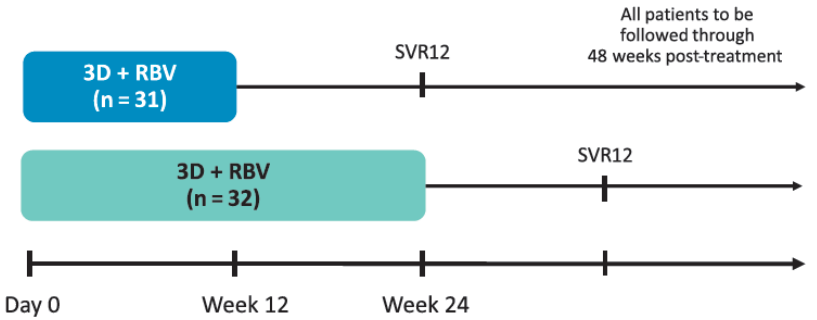
ANC, absolute neutrophil count; AST, aspartate aminotransferase

Osinusi A et al. J Hepatol 2014;60(Suppl):S7 and Osinusi A, et al. 65th AASLD; Boston, MA; November 7-11, 2014. Abst. 84

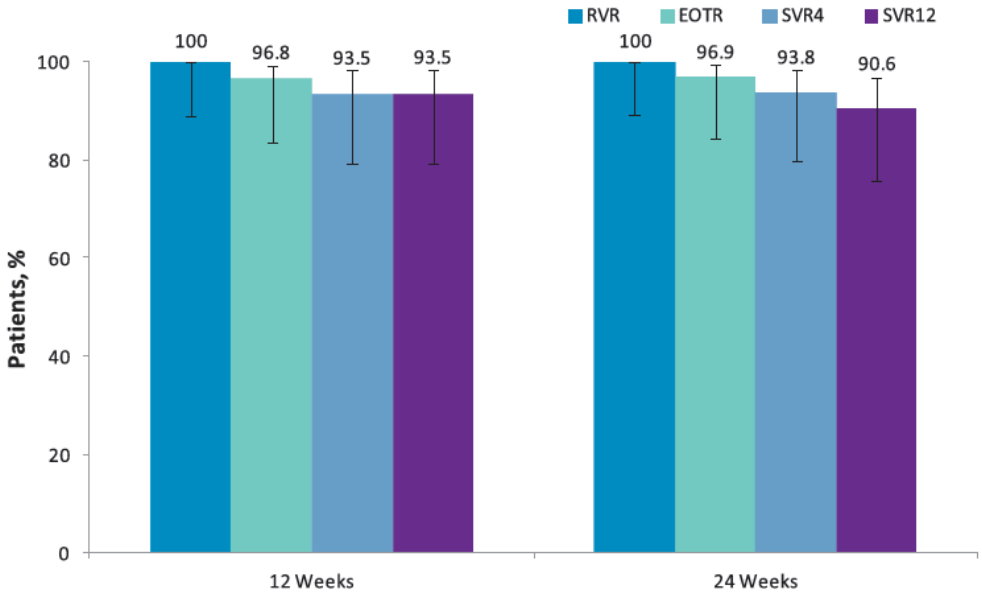
HIV-HCV Coinfection study: TURQUOISE-I: 3 DAAs + RBV

Characteristic	3D + RBV	
	12-Week Group (n = 31)	24-Week Group (n = 32)
Male, n (%)	29 (93.5)	29 (90.6)
Race, n (%)		
White	24 (77.4)	24 (75.0)
Black	7 (22.6)	8 (25.0)
Age, y (mean ± SD)	50.9 ± 6.0	50.9 ± 8.3
BMI, kg/m^2 (mean ± SD)	26.4 ± 3.9	27.2 ± 4.3
HCV RNA level, $\log_{10}$ IU/mL (mean ± SD)	6.54 ± 0.57	6.6 ± 0.78
CD4+ T-cell count/mm^3 (mean ± SD)	633 ± 236	625 ± 296
IL28B genotype, n (%)		
CC	5 (16.1)	7 (21.9)
Non-CC	26 (83.9)	25 (78.1)
HCV GT/subtype, n (%)		
1a	27 (97.1)	29 (90.6)
1b	4 (12.9)	3 (9.4)
Cirrhosis present, n (%)	6 (19.4)	6 (18.8)
Prior HCV treatment history		
Treatment-naïve, n (%)	20 (64.5)	22 (68.8)
Treatment-experienced	11 (35.5)	10 (31.3)
Prior pegIFN/RBV response, n (%)		
Relapser	1 (3.2)	3 (9.4)
Partial responder	5 (16.1)	2 (6.3)
Null responder	5 (16.1)	5 (15.6)
HIV-1 ART regimen, n (%)		
Atazanavir	16 (51.6)	12 (37.5)
Raltegravir	15 (48.4)	20 (62.5)

3D, ABT-450/r/ombitasvir and dasabuvir; ART, antiretroviral therapy; BMI, body mass index; HCV, hepatitis C virus; IL, interleukin; pegIFN/RBV, pegylated interferon plus ribavirin; r, ritonavir; RBV, ribavirin.



3D, co-formulated ABT-450/r/ombitasvir (150/100/25 mg) administered once daily; dasabuvir 250 mg administered twice daily. RBV, ribavarin, weight-based dosing (1000 or 1200 mg), administered twice daily. SVR12, sustained virologic response 12 weeks after the last dose of study drug.



EOTR, end of treatment response; RBV, ribavirin; RVR, rapid virologic response (week 4); SVR4, sustained virologic response at 4 weeks after the end of treatment; SVR12, sustained virologic response at 12 weeks after the end of treatment.

Wyles, AASLD 2014 #1939

IFN free HCV treatment options

HCV genotype	Treatment	Treatment duration in treatment-naive patients	Treatment duration in treatment-experienced patients
1 & 4	SOF + RBV	24 weeks	24 weeks
	SOF + SMP	12 weeks (possible extension up to 24 weeks and/or addition of RBV)	12 weeks (possible extension up to 24 weeks and/or addition of RBV)
	SOF + DCV	12 weeks in non-cirrhotics, 24 weeks in compensated cirrhotics +/- RBV	12 weeks in non-cirrhotics, 24 weeks in compensated cirrhotics +/- RBV
	SOF/Ledipasvir	8-12 weeks in non-cirrhotics, 12-24 weeks in cirrhotics +/- ribavirin	24 weeks +/- ribavirin
	Ombitasvir/ Paritaprevir/Ritonavir + Dasabuvir + /- RBV (only for GT 1)	12 weeks in non-cirrhotics; RBV for GT1a but not GT 1b; 24 weeks in cirrhotics + RBV for GT1a and 12 weeks + RBV in GT1b	12 weeks in non-cirrhotics; RBV for GT1a but not GT 1b; 24 weeks in cirrhotics + RBV for GT1a and 12 weeks + RBV in GT1b

RBV: Ribavirin, SOF: Sofosbuvir, SMP: Simeprevir, DCV: Daclatasvir

Summary

- In the DAA era, HIV/HCV-coinfected patients show the same high cure rates (over 90%) under IFN-free DAA combinations –therefore, guidelines no longer separate between mono- and co-infected patients
- Indication for HCV therapy as well as DAA drug selection has become the same for all patients
- The only special consideration in HIV/HCV-coinfected patients is the need to check for DDIs between HIV and HCV drugs
- Considering the faster fibrosis progression and higher risk for hepatic decompensation in coinfected patients (even in the era of ART), the uptake of modern HCV therapy needs to be encouraged and HCV therapy should be discussed with all coinfected patients

ART, antiretroviral therapy; DAA, direct-acting antiviral; DDI, drug–drug interaction; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IFN, interferon.