Attualità nella gestione clinica della epatite cronica HCV

Il paziente coinfetto HIV/HCV

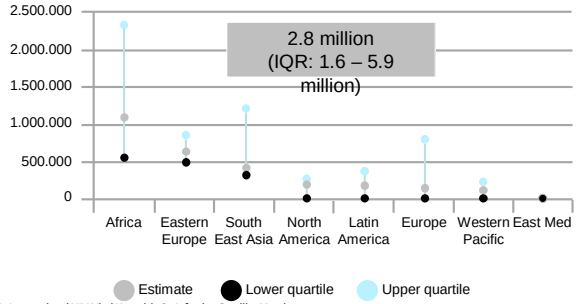
G. Verucchi - DIMEC - Università di Bologna

Ferrara 19 settembre 2015

Prevalence of HIV/HCV co-infection by region,

WHO global systematic review of prevalence of HIV/HCV Ab co-infection based on prevalence studies in HIV+ persons stratified by risk group (where available) or general population surveys reporting HIV/HCV or HBV co-infection: burden of co-infection HIV/HCV accounts for 2.8 million people

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

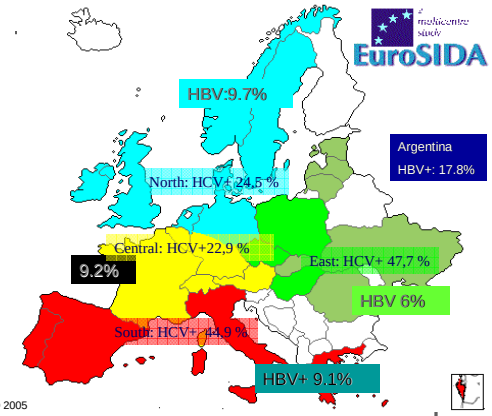


Easterbrook P, International HIV/Viral Hepatitis Co-Infection Satellite Meeting 2014

Prevalence of HCV and HBV Co-infection in persons living with HIV in EuroSIDA cohort

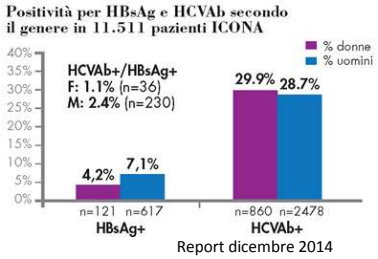
- **Among 9803 subjects in the EuroSIDA Cohort:**
  - **5883 had a HBsAg test available at time of enrollment**
    - **530 (9%) were positive**
  - **5957 had a HCVAb test available**
    - **1960 (33%) were positive**

Regions:
South
Central
North
East



Konopnicki D et al.; AIDS. 2005 Rockstroh J et al.; JID 2005

Prevalenza HIV/HCV in Italia



Report dicembre 2014

Italia

Stimati 94.146 soggetti HIV+

ISS2014

Stimati HIV/HCV+ 27.303

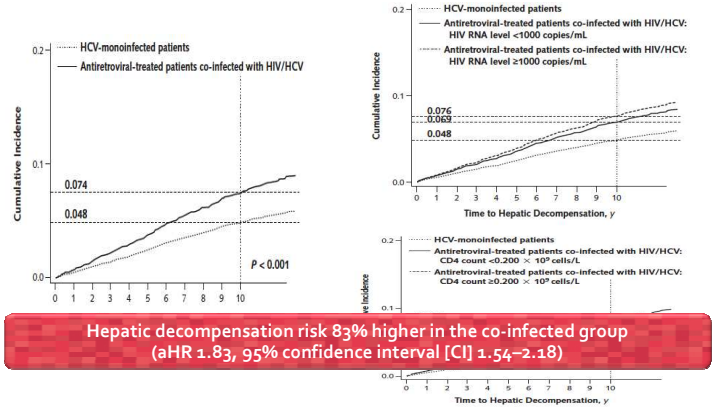
Impact of HCV Exposure/ Coinfection on HIV disease

Issue	HCV exposure (HCVAb+ vs HCVAb-)	HCV active replication (HCVAb+ HCVRNA+ vs HCVAb+ HCVRNA-)
Faster HIV disease progression	Yes[1]	
Impaired CD4 recovery on cART	Yes[2]	Yes[3]
Impaired HIVRNA suppression on cART	Yes [4]	
Worsened renal function	Yes[5]	Yes[6]
Higher incidence of osteopor. fractures	Yes[7]	
Higher incidence of Cardiovascular related events	Yes [8]	
Higher incidence of Diabetes	Yes [9]	
Higher non AIDS non liver related mortality	Yes[10]	Yes[11]

1. Greub, Lancet, 2000, Piroth, J Viral Hepat, 2000 De Luca et al, Arch Intern Med, 2002), Herrero Martinez E JID 2002, Dorrucci AIDS 2004; Braitsein JID 2006;
2. Lincoln, HIV Med, 2003
3. Potter M AIDS 2010
4. Pulido AIDS Review 2012; Hsu L AIDS 2013
5. Izzedine AIDS 2009; Lucas JID 2013
6. Peters AIDS 2012; Macrofr A PLOS One 2012; Lucas JID 2013
7. Lo Re Hepatology 2012; Maalouf J Bon Min Res 2013, Casado Osteopos Int 2014
8. Erqou S CROI 2014
9. Howard AA JAIDS 2014; Butt AA AIDS 2009; Jain MK HIV Med 2007; Butt AA Hepatology 2004
10. Mallet V CROI 2014
11. Grint D CROI 2014

ART and hepatic de-compensation in HCV/HIV vs. HCV alone

Cohort study, 4,286 cART-treated HIV/HCV-coinfected and 6,639 HCV-monoinfected patients in the Veterans Aging Cohort Study Virtual Cohort (1997-2010)



Hepatic decompensation risk 83% higher in the co-infected group (aHR 1.83, 95% confidence interval [CI] 1.54–2.18)

Le Re III, et al. Ann Intern Med 2014; 160: 369

Sustained Virological Response to Interferon Plus Ribavirin ReducesOverall, Liver Related and Non–Liver-Related Mortality in 1599 Patients Coinfected With HIV and Hepatitis C Virus

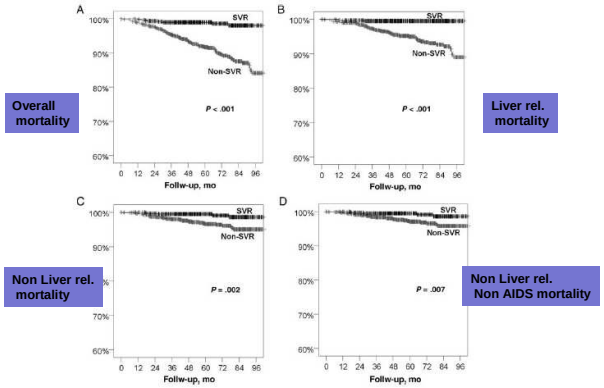
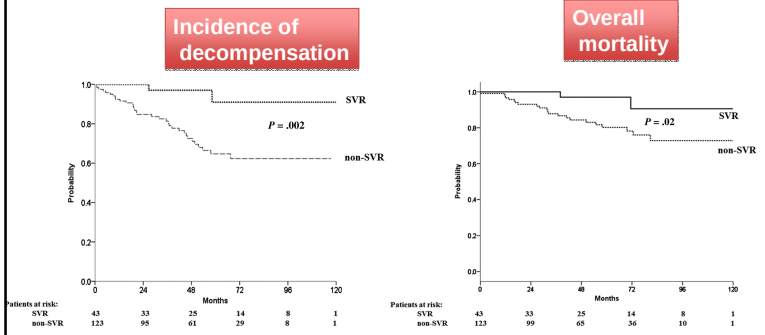


Figure 1. Kaplan-Meier curves showing the occurrence of overall deaths (*A*), liver-related deaths (*B*), non–liver related deaths (*C*), and non–liver-related, non–AIDS-related deaths (*D*) in 1599 patients coinfected with human immunodeficiency virus and hepatitis C virus, with or without sustained virological response after therapy with interferon plus ribavirin. Abbreviation: SVR, sustained virological response.

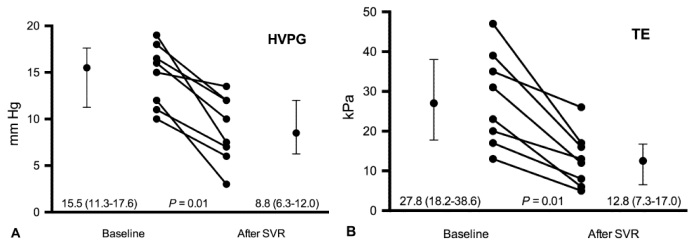
Berenguer Clin Inf Dis 2012; 55: 728-36

Benefits From Sustained Virologic Response to Pegylated Interferon Plus Ribavirin in 166 HIV/HCV Coinfected Patients With Compensated Cirrhosis



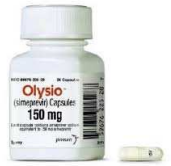
Mira J CID 2013;56:1646-53

Effect of Eradication of HCV on Hepatic Venous Pressure Gradient in HIV-Infected Patients With Compensated HCV-Related Cirrhosis

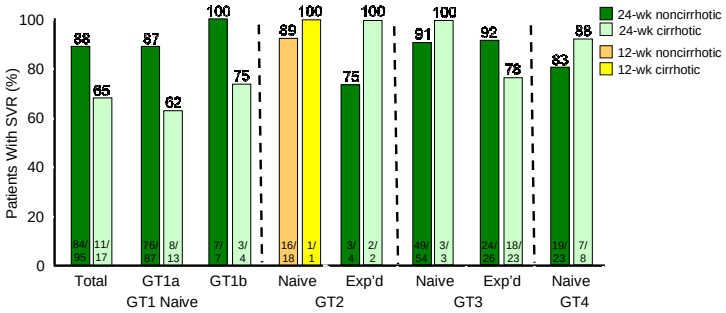


Sánchez-Conde M et al J Acquir Immune Defic Syndr 69,4, August 1, 2015

Approved HCV drugs in Europe in 2015



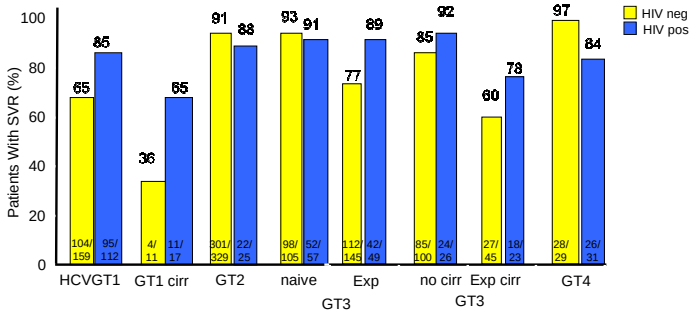
PHOTON-2 SOF+RBV: SVR12 by Genotype and Cirrhosis



- Absolute CD4+ count—but not CD4%—decreased, consistent with effect of RBV on lymphocytes

Molina JM, et al. The Lancet v 385 March 2015

Comparison of SVR in HCV monoinfected and HIV/HCV co-infected



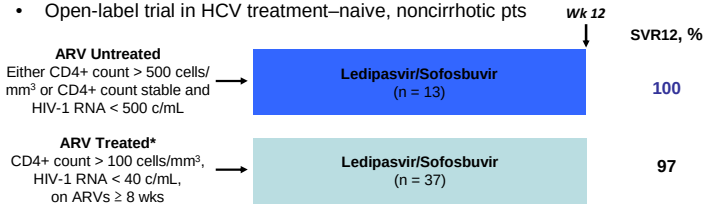
- Sulkowski et al Ann.Int.Med 2014; Molina et al AIDS 2014

Real life data on Sofosbuvir+ Simeprevir (± RBV) in HIV/HCV: CROI 2015

Author/ Pts Character.	Abstract n°	SVR/ total
Grant J all	649	18/20 (90%)
Marks K (PI exp)	644	12/13 (92%)
Gilmore (cirrhotics)	647	22/29 (76%)
Del Bello D (all)	645	26/29 (90%)
All		78/91 (86%)

NIAID ERADICATE: LDV/SOF in GT1 HCV Pts Coinfected With HIV

- Open-label trial in HCV treatment–naive, noncirrhotic pts

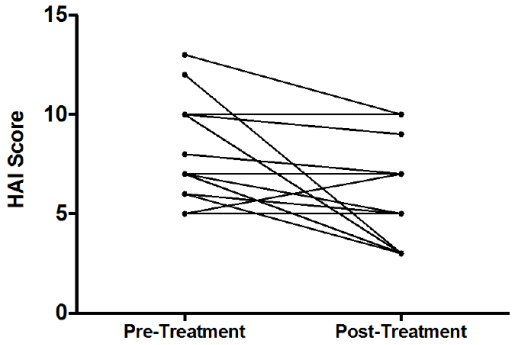


- 1 HCV relapse at posttreatment Wk 36 in 45-yr-old male with HAI fibrosis 1, IL23B CC, IFNL4 TT/TT, receiving raltegravir + tenofovir/emtricitabine
- No renal impairment observed

Ledipasvir 90 mg/sofosbuvir 400 mg
*ARVs included rilpivirine, raltegravir, efavirenz, and tenofovir/emtricitabine.

NIAID ERADICATE: LDV/SOF in GT1 HCV Pts Coinfected With HIV

Knodell-HAI Scores From Liver Biopsies Pre- and Post-Treatment



ION-4: LDV/SOF for 12 Wks in HCV/HIV-Coinfected Patients

- Phase III open-label study in HIV virologically suppressed HIV/HCV coinfected pts (N = 335)
  - 20% with compensated cirrhosis
  - n = 8 with HCV GT4
- ART regimens
  - TDF/FTC/EFV (n = 160)
  - TDF/FTC + RAL (n = 146)
  - TDF/FTC/RPV (n = 29)
- HCV treatment experienced: 55%
  - Previous HCV PI therapy: 29%
- Very high SVR12 rate
  - No differences based on HCV tx experience or cirrhosis status
  - Black (vs nonblack) race associated with significantly lower SVR12 rate in multivariate analysis
  - 10 relapses, all in black pts

Cooper C, et al. EASL 2015. Abstract P1353.

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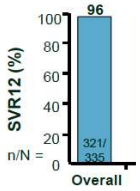
SVR Rates According to BL Characteristics



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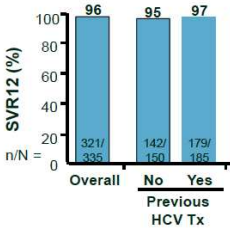

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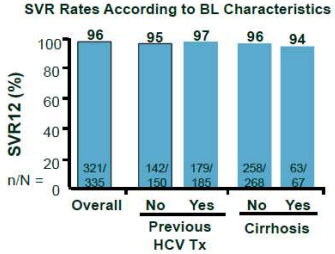

Cooper C, et al. EASL 2015. Abstract P1353.

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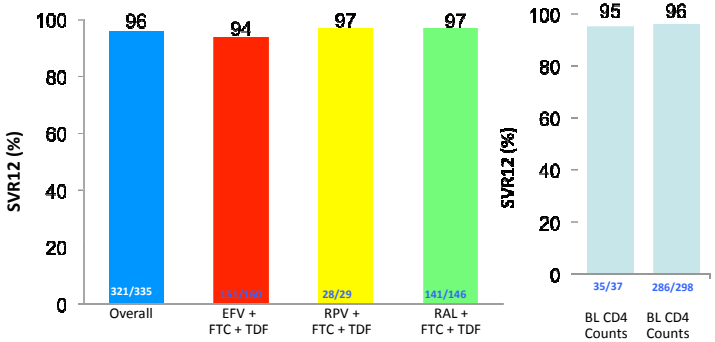
ION-4: LDV/SOF in HIV/HCV

SVR12 by HIV ARV Regimen and BL CD4 Count



- No patient had confirmed HIV virologic rebound
- Stable CD4 counts through treatment and follow-up phase

EFV, efavirenz; FTC, emtricitabine; RAL, raltegravir; RPV, rilpivirine; TDF, tenofovir disoproxil fumarate

Cooper C, et al. EASL 2015. Abstract P1353.

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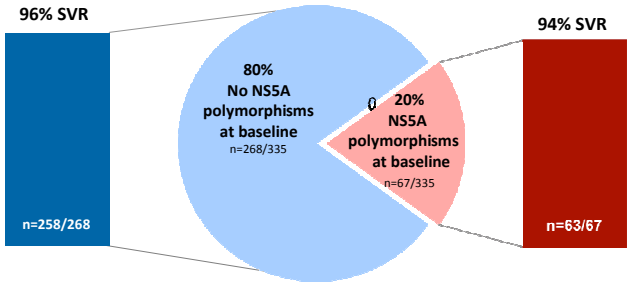
ION-4: LDV/SOF in HIV/HCV

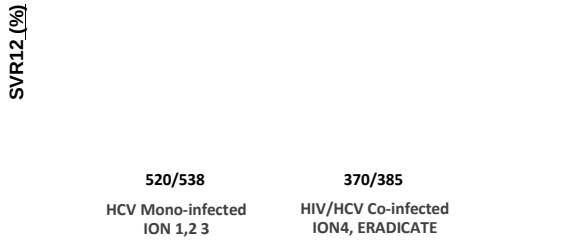
SVR12 by Baseline NS5A Substitutions



- NS5A RAVs were observed in 10 of the 12 patients with virologic failure
- No NS5B S282T was observed in any patient at baseline or virologic failure

Naggie S, et al. CROI 2015, Oral #LB-152

LDV/SOF x 12 Weeks
SVR12 in HCV Mono-infected and HCV/HIV Co-infected

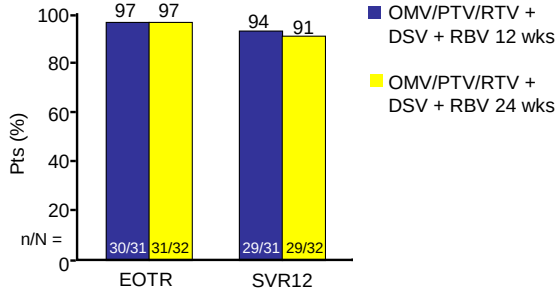


Similar response rates in HCV/HIV co-infected patients compared to HCV mono-infected patients

Afdhal N, et al. *N Engl J Med* 2014; 370: 1889-98. Afdhal N, et al. *N Engl J Med* 2014; 370: 1483-93. Kowdley K, et al. *N Engl J Med* 2014; 370: 1879-88. Naggie et al, CROI 2015, Oral #LB-152; Osinusi A, et al *JAMA* February 23, 2015

TURQUOISE-1: OMV/PTV/RTV + DSV+ RBV for 12 vs 24 Wks in GT1 HCV/HIV Coinfection

Open-label phase II/III trial in GT1, DAA-naive, coinfected pts
HIV-1 RNA < 40 c/mL on ATV or RAL regimen; CD4+ count ≥ 200 or CD4+% ≥ 14%

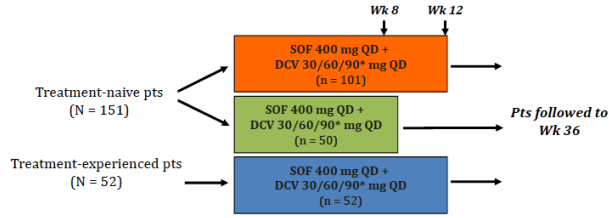


- 65% HCV treatment-naive pts in 12-wk arm, 69% in 24-wk arm
- 19% patients with METAVIR F4 fibrosis

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

Daclatasvir in Combination With Sofosbuvir for HIV/HCV Coinfection: ALLY-2 Study

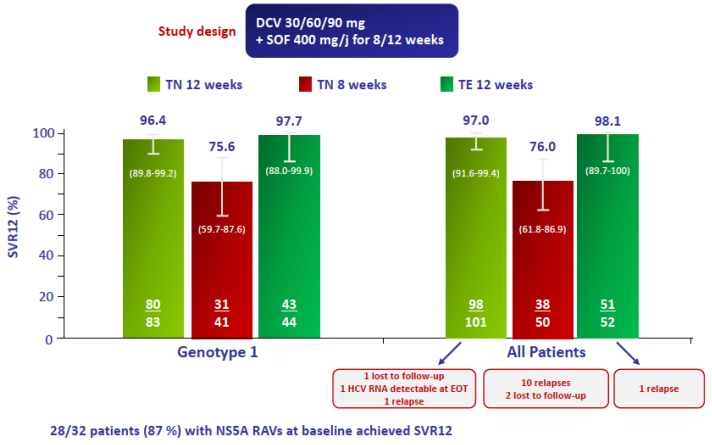
- Phase III open-label study
  - Non GT1 < 20% in each cohort; compensated cirrhosis < 50% overall; HIV-1 RNA < 50 c/mL and CD4+ ≥ 100 in pts on ART; CD4 ≥ 350 in pts not on ART
  - ART allowed: PI/RTV, NRTIs, NNRTIs, INSTIs, MVC, ENF
- Primary endpoint: SVR12 in GT1 naive pts treated for 12 wks



*Standard dose of 60 mg adjusted for ART: 30 mg with RTV; 90 mg with NNRTIs except RPV.

Wyles DL, et al. CROI 2015. Abstract 151LB.

Daclatasvir in Combination With Sofosbuvir for HIV/HCV Coinfection: ALLY-



28/32 patients (87 %) with NS5A RAVs at baseline achieved SVR12

Wyles DL. et al. EASL 2015, Abstract LP01

DACLATASVIR PLUS SOFOSBUVIR WITH OR WITHOUT RIBAVIRIN IN PATIENTS WITH HIV-HCV COINFECTION:INTERIM ANALYSIS OF A FRENCH MULTICENTER COMPASSIONATE USE PROGRAM

Parameter	All Patients (N = 727)*
Age, median years (range)	52.3 (27-74)
Sex ratio, M/F	2.62
Fibrosis stage, n	
F0–F2	36
F3[a]	164
F4	508
Child-Pugh class B/C among patients with F4	81
Treatment experienced	573
CD4 cells/mm³, mean (SD)	591 (348)
HIV viremia, n (%)[b]	
Undetectable	649 (98)
Detectable	12 (2)
< 200 copies/mL	600 (98)
≥ 200 copies/mL	12 (2)
Copies/mL: patients with detectable HIV, mean (SD)[c]	32,246 (70,777)

Fontaine et al EASL 2015 LP23

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DACLATASVIR PLUS SOFOSBUVIR WITH OR WITHOUT RIBAVIRIN IN PATIENTS WITH HIV-HCV COINFECTION:INTERIM ANALYSIS OF A FRENCH MULTICENTER COMPASSIONATE USE PROGRAM

Fontaine et al EASL 2015 LP23

Figure 1. SVR Rates by Treatment Duration and HCV Genotype

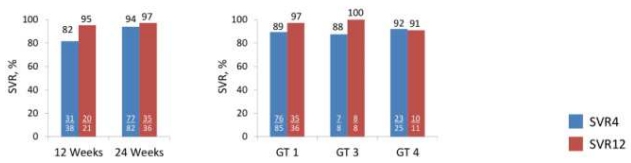
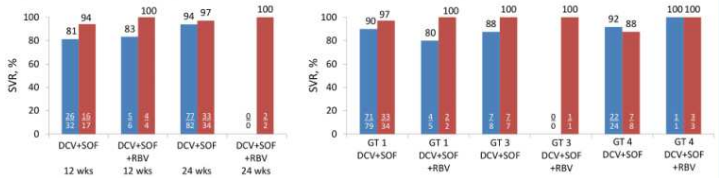


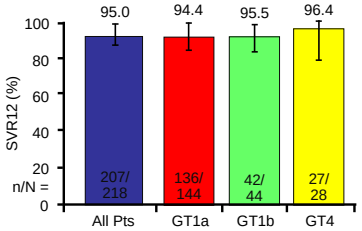
Figure 2. SVR Rates by Regimen, Treatment Duration, and HCV Genotype



Treatment discontinuations occurred in 14 patients (1.9%) and were related to an adverse event (n=4), death (n=3), patient decision (n=3), contra-indication (n=3) and unknown reason (n=1).

C-EDGE Coinfection: Grazoprevir/Elbasvir for Pts Coinfected With HCV/HIV

- Multicenter, single-arm, open-label phase III trial; HCV treatment-naive pts coinfected with HIV and GT1, 4, or 6 HCV
  - Treatment: Grazoprevir/elbasvir for 12 wks
  - ART regimen components: ABC: 21.6%; TDF: 75.2%; RAL: 51.8%; DTG: 27.1%; RPV: 17.4%



- No subgroup provided an efficacy advantage or disadvantage
- New NS3, NS5A RAVs detected at failure in 5 of 6 pts who relapsed
- Short-lived HIV-1 RNA increases occurred in 2 pts on ART during treatment: both resuppressed HIV-1 RNA without ART change
- Grazoprevir/elbasvir well tolerated: no pt discontinued for AEs and no serious treatment-related AEs

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

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No more difference between HCV monoinfected patients and HIV/HCV co-infected patients

New online EASL HCV recommendations

Same treatment regimens can be used in HIV/HCV patients as in patients without HIV infection, as the virological results of therapy are identical (A1)

American Association for the Study of Liver Diseases
AASLD

HCV Guidance: Recommendations for Testing, Managing, and Treating Hepatitis C

IDSA Infectious Diseases Society of America

August 2015

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…….

Rating: Class I, Level B

New online EASL HCV recommendations

Table 5. Treatment recommendations for HCV-monoinfected or HCV/HIV coinfected patients with chronic hepatitis C without cirrhosis, including treatment-naïve patients and patients who failed on a treatment based on PegIFN-α and ribavirin (RBV)

Patients	PegIFN-α, RBV and sofosbuvir	PegIFN-α, RBV and simeprevir	Sofosbuvir and RBV	Sofosbuvir and ledipasvir	Ritonavir-boosted paritaprevir, ombitasvir and dasabuvir	Ritonavir-boosted paritaprevir, and ombitasvir	Sofosbuvir and simeprevir	Sofosbuvir and daclatasvir
Genotype 1a	12 wk	12 wk, then PegIFN-α and RBV 12 wk (treatment-naïve or relapsers) or 36 wk (partial or null responders)	No	8-12 wk, without RBV	12 wk with RBV 12 wk without RBV	No	12 wk without RBV	12 wk without RBV
Genotype 1b								
Genotype 2	12 wk	No	12 wk	No	No	No	No	12 wk without RBV
Genotype 3	12 wk	No	24 wk	No	No	No	No	12 wk without RBV
Genotype 4	12 wk	12 wk, then PegIFN-α and RBV 12 wk (treatment-naïve or relapsers) or 36 wk (partial or null responders)	No	12 wk without RBV	No	12 wk with RBV	12 wk without RBV	12 wk without RBV
Genotype 5 or 6	12 wk	No	No	12 wk without RBV	No	No	No	12 weeks without RBV

New online EASL HCV recommendations

Table 6. Treatment recommendations for HCV-monoinfected or HCV/HIV coinfected patients with chronic hepatitis C with compensated (Child-Pugh A) cirrhosis, including treatment-naïve patients and patients who failed on a treatment based on PegIFN-α and ribavirin (RBV)

Patients	PegIFN-α, RBV and sofosbuvir	PegIFN-α, RBV and simeprevir	Sofosbuvir and RBV	Sofosbuvir and ledipasvir	Ritonavir-boosted paritaprevir, ombitasvir and dasabuvir	Ritonavir-boosted paritaprevir, and ombitasvir	Sofosbuvir and simeprevir	Sofosbuvir and daclatasvir
Genotype 1a	12 wk	12 wk (treatment-naive or relapsers) or 24 wk (partial or null responders)	No	12 wk with RBV, or 24 wk without RBV, or 24 wk with RBV if negative predictors of response	24 wk with RBV	No	12 wk with RBV, or 24 wk without RBV	12 wk with RBV, or 24 wk without RBV
Genotype 1b					12 wk with RBV			
Genotype 2	12 wk	No	16-20 wk	No	No	No	No	12 wk without RBV
Genotype 3	12 wk	No	No	No	No	No	No	24 wk with RBV
Genotype 4	12 wk	12 wk (treatment-naive or relapsers) or 24 wk (partial or null responders)	No	12 wk with RBV, or 24 wk without RBV, or 24 wk with RBV if negative predictors of response	No	24 wk with RBV	12 wk with RBV, or 24 wk without RBV	12 wk with RBV, or 24 wk without RBV
Genotype 5 or 6	12 wk	No	No	12 wk with RBV, or 24 wk without RBV, or 24 wk with RBV if negative predictors of response	No	No	No	12 wk with RBV, or 24 wk without RBV

HCV Guidance: Recommendations for Testing, Managing, and Treating Hepatitis C

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The following regimens are NOT recommended for treatment-naive or -experienced HIV/HCV-coinfected patients.

- **Treatment courses shorter than 12 weeks, such as the use of 8 weeks of ledipasvir/sofosbuvir**

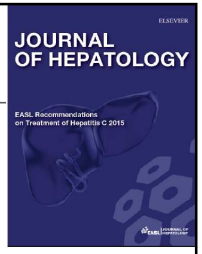
  Rating: Class IIb, Level C

- **Monotherapy with PEG-IFN, RBV, or a direct-acting antiviral**

  Rating: Class III, Level A

- **PEG-IFN and RBV with or without simeprevir, telaprevir, or boceprevir for 24 weeks to 48 weeks**

  Rating: Class IIb, Level A



Potential drug-drug interactions with antiretroviral drugs should be taken into account

Drug–drug interactions

		SIM	DCV	SOF	LDV/SOF	3D
NRTIs	Abacavir	◆	◆	◆	◆	◆
	Didanosine	◆	◆	◆	◆	◆
	Emtricitabine	◆	◆	◆	◆	◆
	Lamivudine	◆	◆	◆	◆	◆
	Stavudine	◆	◆	◆	◆	◆
	Tenofovir	◆	◆	◆	■	◆
	Zidovudine	◆	◆	◆	◆	◆
NNRTIs	Efavirenz	●	◆ 90 mg	◆	■*	●
	Etravirine	●	◆ 90 mg	◆	◆	●
	Nevirapine	●	◆90 mg	◆	◆	●
	Rilpivirine	◆	◆	◆	◆*	■
Protease inhibitors	Atazanavir; Atazanavir/Ritonavir	●	◆30 mg	◆	◆*	■ no RTV
	Darunavir/Ritonavir; Darunavir/Cobicistat	●	◆	◆	◆*	■ no RTV low Dar Cthrough
	Fosamprenavir	●	◆ 30 mg	◆	◆*	■ no RTV
	Lopinavir	●	◆	◆	◆*	●
	Saquinavir	●	◆ 30 mg	◆	◆*	●
Entry/Integrase inhibitors	Dolutegravir	◆	◆	◆	◆	◆
	Elvitegravir/Cobicistat	●	◆30 mg	◆	■*	●
	Maraviroc	◆	◆	◆	■	■ 150 mg MVC
	Raltegravir	◆	◆	◆	◆	◆

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Drug-Drug interactions

	SMV	SOF	LDV	DCV	OMV/PTV/RTV + DSV
ATV/RTV	No data	No data	LDV ↑; ATV ↑	DCV ↑	PTV ↑; ATV ↑
DRV/RTV	SMV ↑; DRV↔	SOF ↑; DRV↔	LDV ↑; DRV↔	DCV ↑; DRV↔	PTV ↓/↑; DRV ↓
LPV/RTV	No data	No data	No data	DCV ↑; LPV↔	PTV ↑; LPV↔
Tipranavir/RTV	No data	No data	No data	No data	No data
EFV	SMV ↓; EFV↔	SOF↔; EFV↔	LDV ↓; EFV ↓	DCV ↓	No PK data
RPV	SMV↔; RPV↔	SOF↔; RPV↔	LDV↔; RPV↔	No data	PTV ↑; RPV ↑
Etravirine	No data	No data	No data	DCV ↓	No data
RAL	SMV↔; RAL↔	SOF↔; RAL↔	LDV↔; RAL↔	No data	OMV/PTV/RTV + DSV↔; ↑ RAL
EVG/COBI	No data	COBI ↑; SOF ↑	COBI ↑; LDV ↑	No data	No data
DTG	No data	No data	LDV↔; DTG↔	DCV↔; DTG ↑	PTV ↓ DTG ↑
Maraviroc	No data	No data	No data	No data	No data
TDF	SMV↔; TDF↔	SOF↔; TDF↔	LDV↔; TDF ↑	DCV↔; TDF↔	OMV/PTV/RTV + DSV↔; TDF↔

AASLD/IDSA Guidance for HIV/HCV Coinfection

- Same recommendations as in HCV-monoinfected patients, but consider drug–drug interactions
  - Need to adjust or withhold RTV if receiving a boosted PI with OMV/PTV/RTV + DSV
  - Potential for LDV-mediated increase in tenofovir levels, especially if tenofovir used with RTV
    - Avoid LDV if CrCl < 60 mL/min or if receiving tenofovir with RTV-boosted PI
  - OMV/PTV/RTV + DSV can be used with raltegravir (and probably dolutegravir), enfuvirtide, tenofovir, emtricitabine, lamivudine, atazanavir
  - SMV can be used with: raltegravir (and probably dolutegravir), rilpivirine, maraviroc, enfuvirtide, tenofovir, emtricitabine, lamivudine, abacavir
- Other interactions at aidsinfo.nih.gov/guidelines, hiv-druginteractions.org

AASLD/IDSA/IAS–USA. Recommendations for testing, managing, and treating hepatitis C.

Check for drug–drug interactions between HCV and HIV drugs!

- **Drug interactions**
  - http://www.drugs.com/drug_interactions.html
  - http://www.medscape.com/druginfo/druginterchecker
  - http://www.drugstore.com/pharmacy/drugchecker/
  - http://drugchecker.aol.com
  - http://hcvdruginfo.ca
- **List of CYP substrates, inhibitors, inducers**
  - http://medicine.iupui.edu/clinpharm/ddis
- **HIV drug interactions**
  - http://www.hiv-druginteractions.org
  - http://www.hep-druginteractions.org

CYP = cytochrome.

Khoo S. 15th International Workshop on Clinical Pharmacology of HIV & Hepatitis Therapy; May 2014

Progression to advanced liver fibrosis in HIV–HCV-coinfected patients and prioritization of new hepatitis C therapies

Antiviral Therapy 2014; 19:799–803

Pablo Labarga[1], Jose V Fernández-Montero[1], Mariola López[1], Pablo Barreiro[1], Carmen de Mendoza[1,2], Rocío Sierra-Enguita[1], Ana Treviño[1], Vincent Soriano[1]*

Table 2. Main characteristics of untreated HIV–HCV-coinfected patients with baseline null/mild liver fibrosis

	LFP (*n*=25)	No LFP (*n*=114)	*P*-value
Mean age, years (SD)	41.1 (4.7)	41.1 (6.7)	0.9
Male gender, %	64	61	0.8
Mean body mass index, kg/m² (SD)	22.3 (4.4)	22.7 (3.3)	0.6
Intravenous drug use, %	96	81.8	0.1
Mean CD4⁺ T-cell count, cells/μ			0.003
Mean CD4⁺ T-cell nadir, cells/μ			0.006
Antiretroviral therapy, %			0.3
Plasma HIV RNA<50 copies/ml, %	56	69.8	0.1
HCV genotypes 1 or 4, %	81.8	80.9	0.4
Mean serum HCV RNA, log IU/ml (SD)	6.6 (0.7)	5.2 (1.9)	0.04
Mean baseline liver stiffness, kPa (SD)	7.4 (1.4)	5.8 (1.4)	<0.001
IL28B CC alleles, %	47.4	40.4	0.5
Mean LDL cholesterol, mg/dl (SD)	86.2 (27.2)	104.9 (31.4)	0.007
Mean AST, IU/ml (SD)	80 (55)	44 (26)	0.004
Mean GGT, IU/ml (SD)	123.4 (142.8)	78.2 (89.6)	0.04
Positive HBsAg, %	15.4	3.4	0.1
Alcohol intake >60 g/day, %	22.7	14.3	0.2
Mean follow-up, months (SD)	49.7 (15.7)	50.6 (16.6)	0.8

45% versus 8%; p<0.003

AST, aspartate aminotransferase; GGT, gamma-glutamyl transpeptidase; HBsAg, hepatitis B surface antigen; LDL, low-density lipoprotein; LFP, liver fibrosis progression.

Overall Deaths, Liver-Related Deaths, and Liver Decompensation Rate According to Fibrosis Classified by Liver Biopsy Stage (n5683) and by Liver Stiffness Measurement (n51024): Sensitivity Analyses Including Only Patients With Length of Biopsy 15 mm (n5527) or Liver Stiffness IQR <30% (n5971)

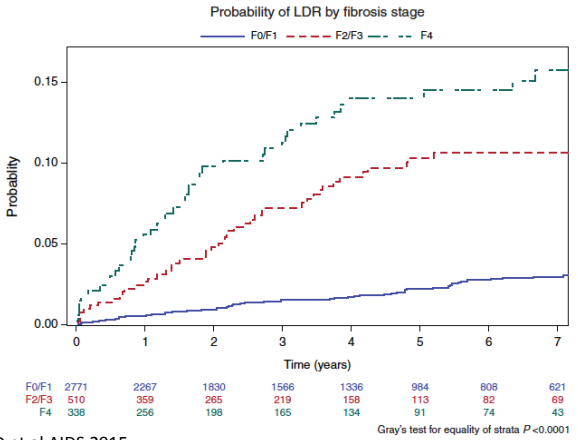
	Overall Deaths			Liver-Related Deaths			Liver Decompensations		
	No.	Rate*(95% CI)	P†	No.	Rate*(95% CI)	P†	No.	Rate*(95% CI)	P†
Fibrosis by biopsy, all patients									
Stage 0	5	0.69 (0.29-1.67)	Reference	1	0.13 (0.02-0.99)	Reference	1	0.13 (0.02-0.99)	Reference
Stage 1	10	0.91 (0.49-1.69)	0.644	5	0.46 (0.19-1.09)	0.289	6	0.55 (0.25-1.22)	0.194
Stage 2	14	1.71 (1.01-2.89)	0.077	6	0.73 (0.33-1.63)	0.098	8	0.98 (0.49-1.96)	0.034
Stage 3	15	1.77 (1.06-2.91)	0.065	8	0.94 (0.47-1.87)	0.039	11	1.29 (0.71-2.33)	0.008
Stage 4	34	3.94 (2.82-5.52)	<0.0001	16	1.85 (1.14-3.03)	0.0005	39	4.52 (3.3-6.19)	<0.0001
Fibrosis by biopsy, length ≥15 mm									
Stage 0	4	0.66 (0.25-1.76)	Reference	1	0.17 (0.02-1.18)	Reference	1	0.17 (0.02-1.18)	Reference
Stage 1	5	0.53 (0.22-1.28)	0.742	2	0.21 (0.05-0.85)	0.780	3	0.32 (0.10-0.99)	0.521
Stage 2	13	2.09 (1.21-3.59)	0.036	6	0.95 (0.43-2.12)	0.048	8	1.27 (0.64-2.54)	0.013
Stage 3	12	1.61 (0.91-2.83)	0.117	8	1.10 (0.55-2.20)	0.022	11	1.5 (0.84-2.73)	0.004
Stage 4	29	3.35 (2.33-4.83)	0.0003	14	1.72 (1.02-2.91)	0.001	34	4.19 (2.99-5.86)	<0.0001

- ✓ The mortality rate for liver disease was 0.95 (95% CI 0:43 to 2:12) to 100 aa / pp follow-up and the rate of decompensation was 1.27 (95% CI 0,64-2.54) to 100 aa / pp
- ✓ The treatment of 1000 patients HIV F2 should prevent 47 deaths and 63 liver decompensation in 5 years

*Rate per 100 person-years.
†P value for the comparison between the incidence of events of the reference category and that of each other category.

Macias J et al Hepatology 2015

Cumulative incidence functions of liver-related death Stratified by liver fibrosis staging



Grint D et al AIDS 2015

EASL Recommendations on Treatment of Hepatitis C 2015

JOURNAL OF HEPATOLOGY

Indications for treatment of chronic hepatitis C in 2015: Who should be treated and when?

Treatment priority	Patient group
Treatment is indicated	• All treatment-naïve and treatment-experienced patients with compensated and decompensated liver disease
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 (active injection drug users, men who have sex with men with high-risk sexual practices, women of child-bearing age who wish to get pregnant, haemodialysis patients, incarcerated individuals)
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

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When and in Whom to Initiate HCV Therapy Table 1. Settings of Liver-Related Complications and Extrahepatic Disease in Which HCV Treatment is Most Likely to Provide the Most Immediate and Impactful Benefits

Highest Priority for Treatment Owing to Highest Risk for Severe Complications

Advanced fibrosis (Metavir F3) or compensated cirrhosis (Metavir F4)
Rating: Class I, Level A

Organ transplant
Rating: Class I, Level B

Type 2 or 3 essential mixed cryoglobulinemia with end-organ manifestations (eg, vasculitis)
Rating: Class I, Level B

Proteinuria, nephrotic syndrome, or membranoproliferative glomerulonephritis
Rating: Class IIa, Level B

HCV Guidance: Recommendations for Testing, Managing, and Treating Hepatitis C

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When and in Whom to Initiate HCV Therapy Table 1. Settings of Liver-Related Complications and Extrahepatic Disease in Which HCV Treatment is Most Likely to Provide the Most Immediate and Impactful Benefits

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

Hepatitis C and HIV Co-infection
Closing the Gaps