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università di ferrara
DA SEICENTO ANNI GUARDIAMO AVANTI.

HIV HCV

Epatite da HCV e HIV in nefrologia

Laura Sighinolfi

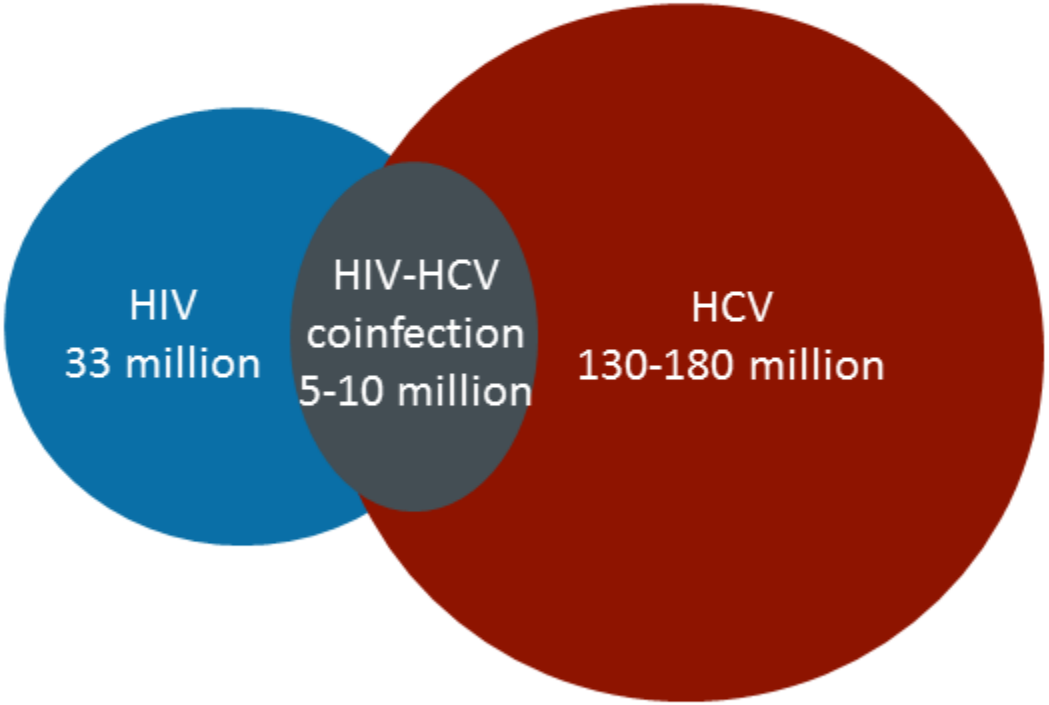
U.O.Malattie Infettive

Azienda Ospedaliero Universitaria - Ferrara

Ferrara, 26 maggio 2017

HCV and HIV Coinfection

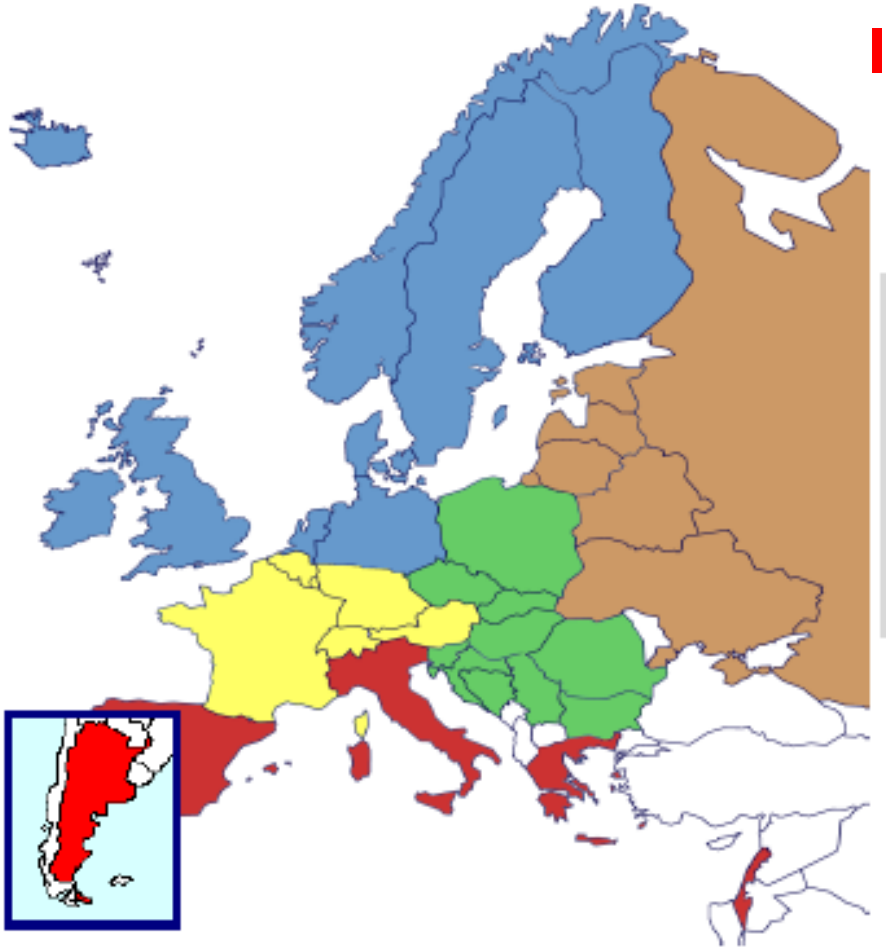
Prevalence Worldwide[a]



- HCV/HIV coinfection treated same as HCV monoinfection[b]

a. Clausen LN, et al. *World J Gastroenterol*. 2014;20:12132-12143.
b. EASL. EASL Recommendations on Treatment of Hepatitis C 2015.

Anti-HCV antibody prevalence in HIV positive individuals from different EuroSIDA regions



Italia 30.000 HIV/HCV

- South: 28.8%
- West: 20.1%
- North: 17.3%
- East Central: 34.0%
- East: 57.7%
- Argentina: 20.6%

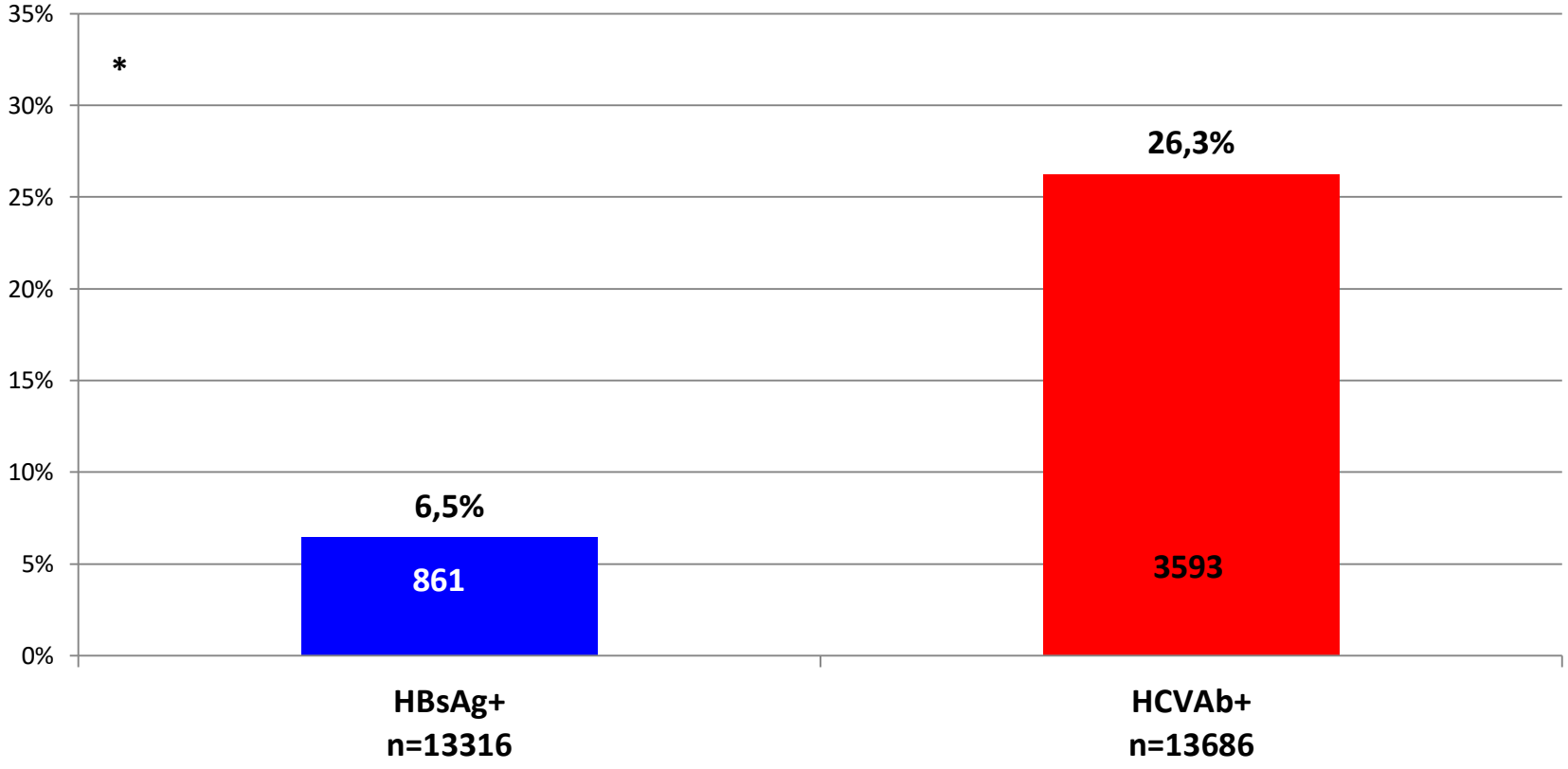
Peters et al, BMC Infect Dis, 2014

HEPAicona Hepatitis Icona Cohort

Fondazione Icona
ITALIAN COHORT NAIVE ANTIRETROVIRALS

Italian Cohort I.C.O.N.A. Naive Antiretrovirals

HBsAg and HCVAb positivity in 13.934 patients enrolled in ICONA



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HIV/HCV

- **Fattore di rischio principale: tossicodipendenza**

- **Problema emergente:**

  trasmissione sessuale in MSM

HIV e nefropatia

Anni ‘80 nefropatia HIV correlata

- **HIVAN –** glomerulosclerosi con flogosi tubulo interstiziale e fibrosi

  Razza nera - Polimorfismo apolipoproteina L1 – APOL1sul cromosoma 22

- **HIVICK** – nefropatia da immunocomplessi
- **HIV –TMA** micorangiopatia trombotica

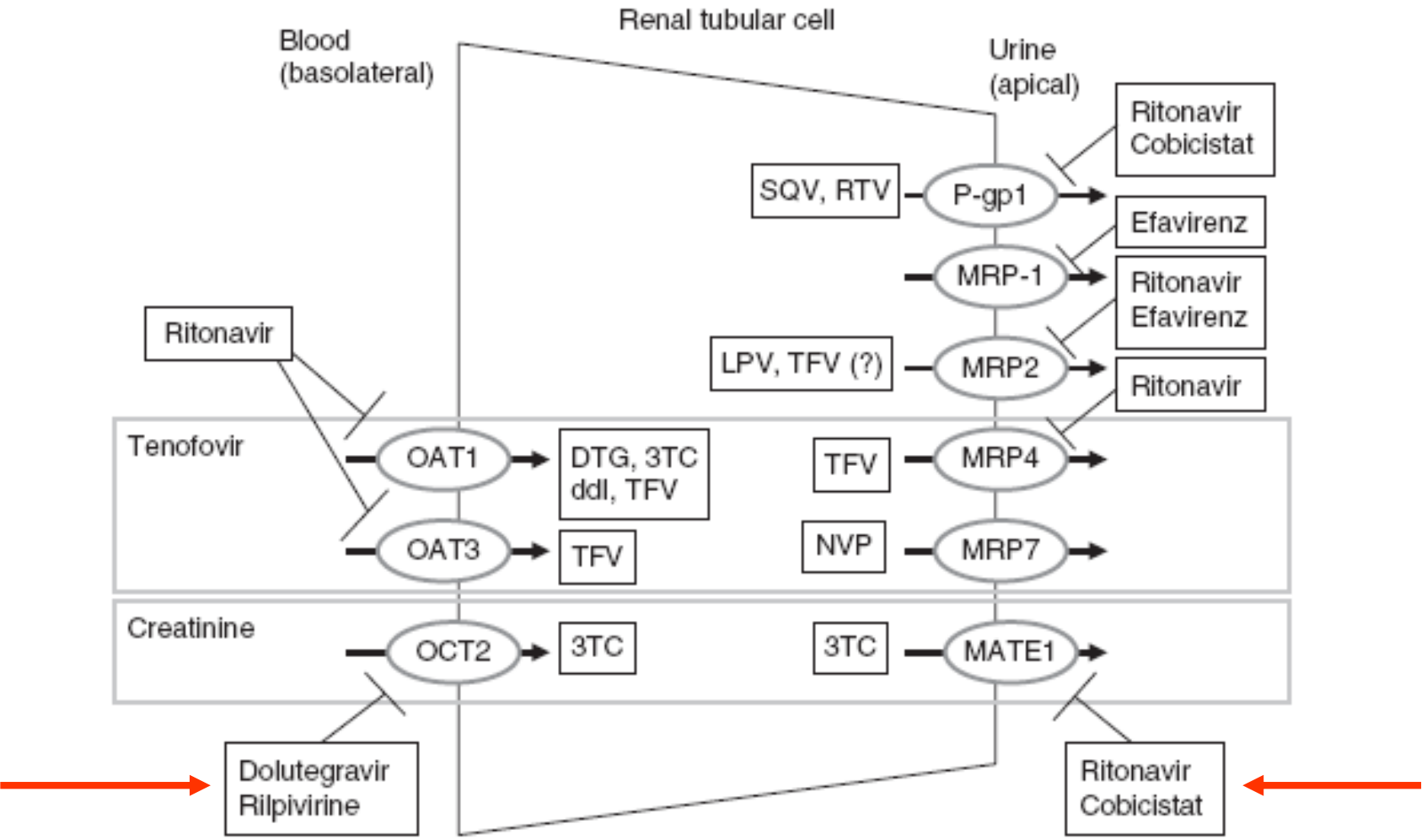
HIV e nefropatia

Anni 2000 comorbilità dovuta a :

- **Infiammazione cronica**
- **Invecchiamento**
- **Patologie concomitanti : diabete, ipertensione, HCV**
- **Terapia antiretrovirale (TDF, inibitori proteasi)**

Interazione con trasportatori di membrana, aumento della creatinina serica e < eGFR

Antiretrovirals and the kidney Yombi *et al.* *AIDS* 2014,



HCV e patologia renale

- Crioglobulinemia mista (crioglobulinemia tipo II)[1]
- Glomerulonefrite membranoproliferativa (MPGN)[1]
- Poliarterite nodosa [2]

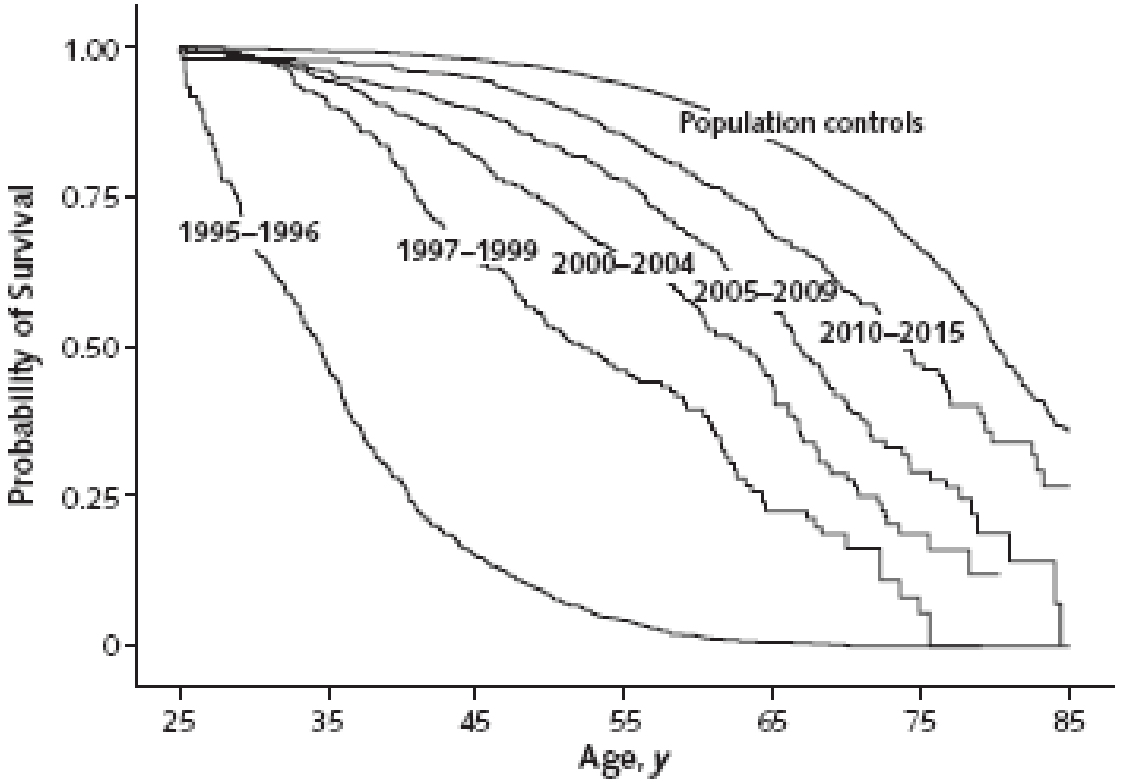
- **Nei paesi industrializzati la prevalenza di HCV varia dal 2.6% al 23.0% in pazienti ESRD (mean: 13.5%)[2]**
- **HCV è associato in maniera indipendente ad un aumento di mortalità dei pazienti in dialisi.**

1. Ozkok A, et al. World J Gastroenterol. 2014;20:7544-7554. 2. Saadoun D, et al. Arthritis Care Res (Hoboken). 2011;63:427-435. 3. Satapathy SK, et al. J Clin Exp Hepatol. 2014;4:8-13.

Update of Survival for Persons With HIV Infection in Denmark

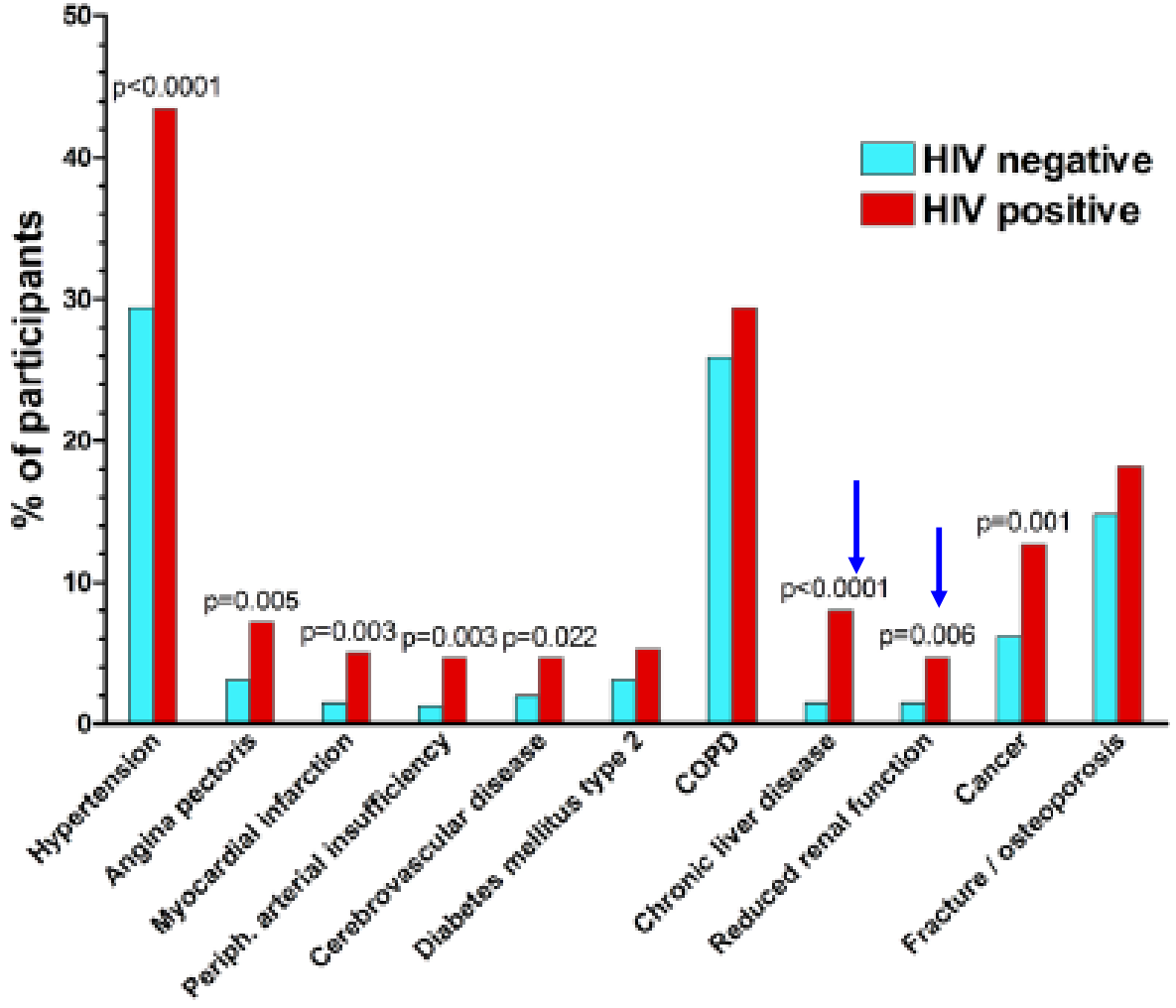
***Lohse et al* .**

Data 1995-2015



Comorbidity distribution

CROI 2016



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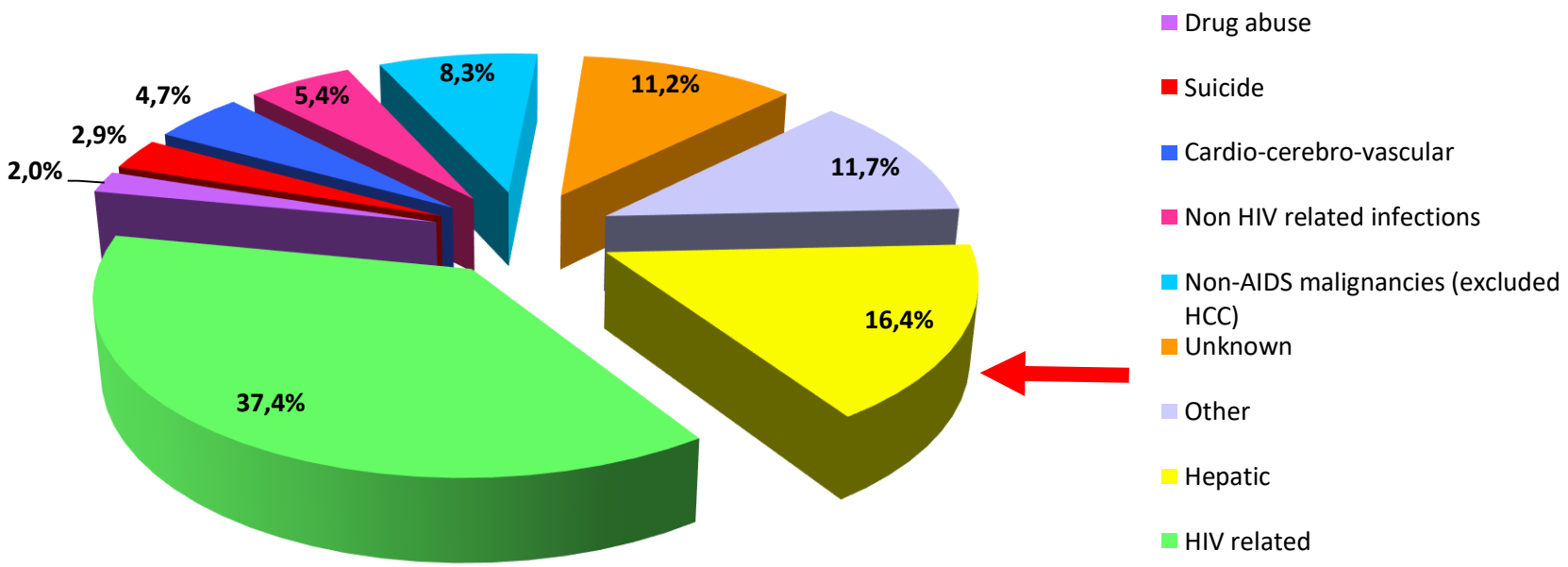
ITALIAN COHORT NAIVE ANTIRETROVIRALS

Italian Cohort I. C. O. N. A. Naive Antiretrovirals

Cause of death, n= 848



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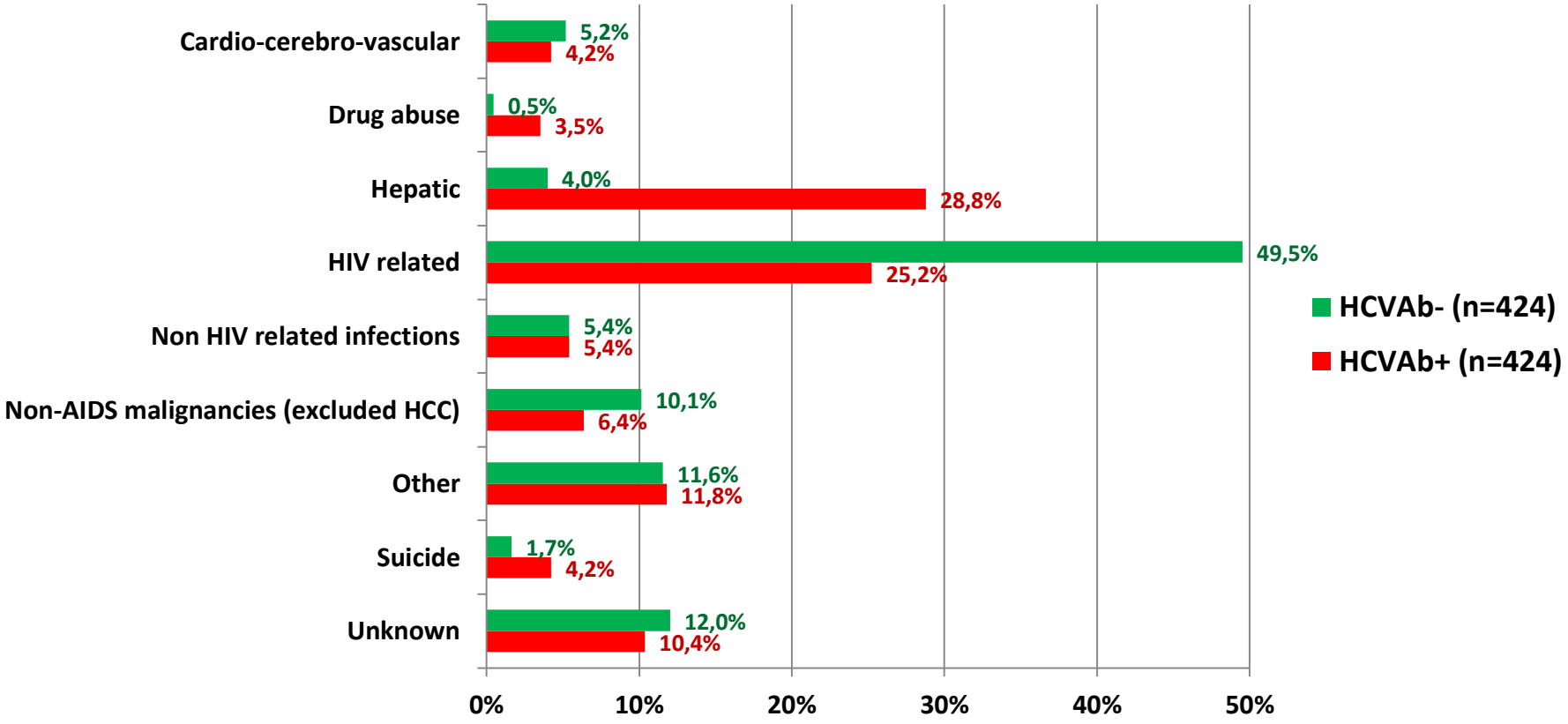
ITALIAN COHORT NAIVE ANTIRETROVIRALS

Italian Cohort I.C.O.N.A. Naive Antiretrovirals

Cause of death according to HCVAb status



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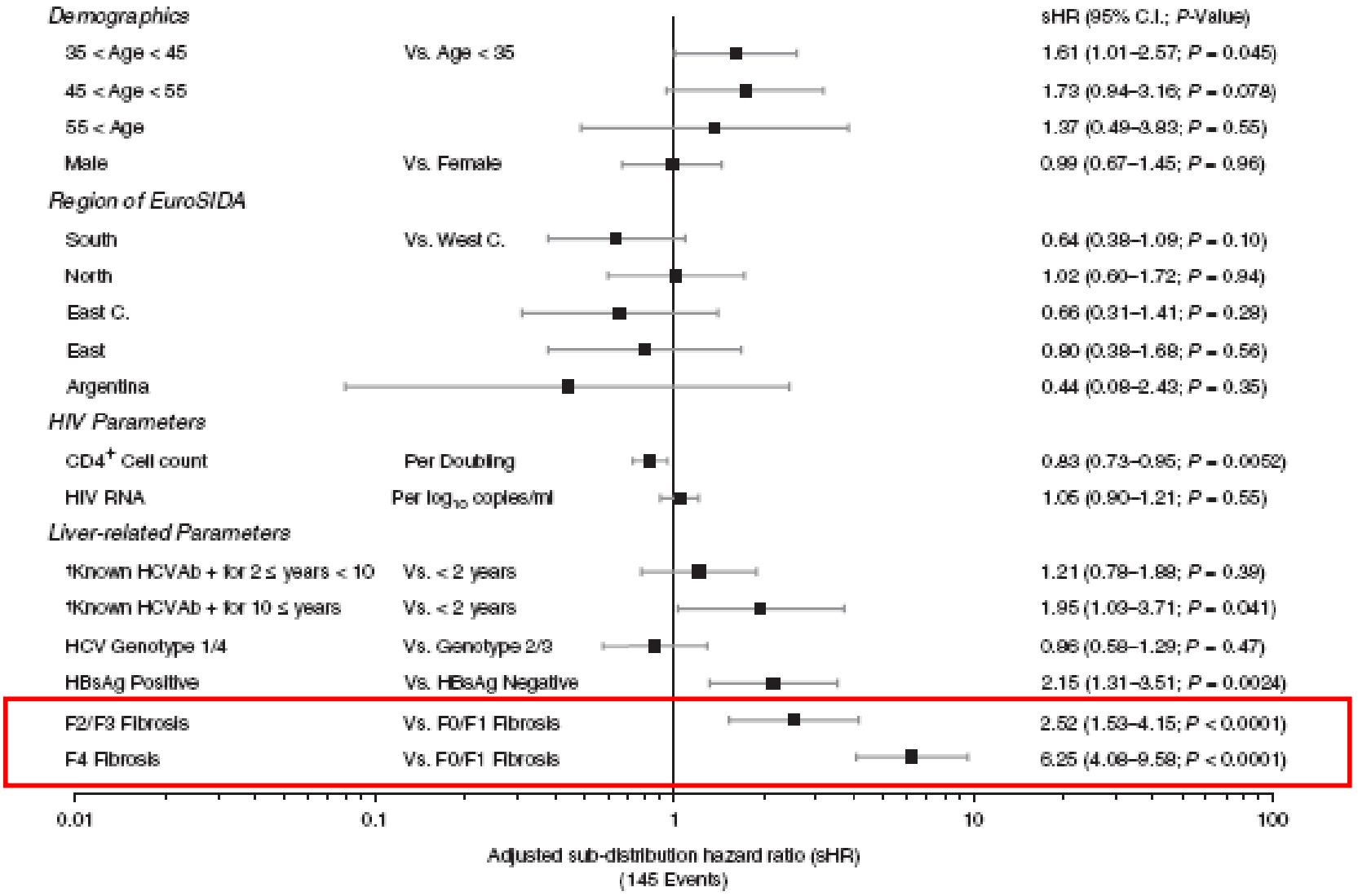
Fattori correlati alla mortalità per cause epatiche: dati EUROSIDA

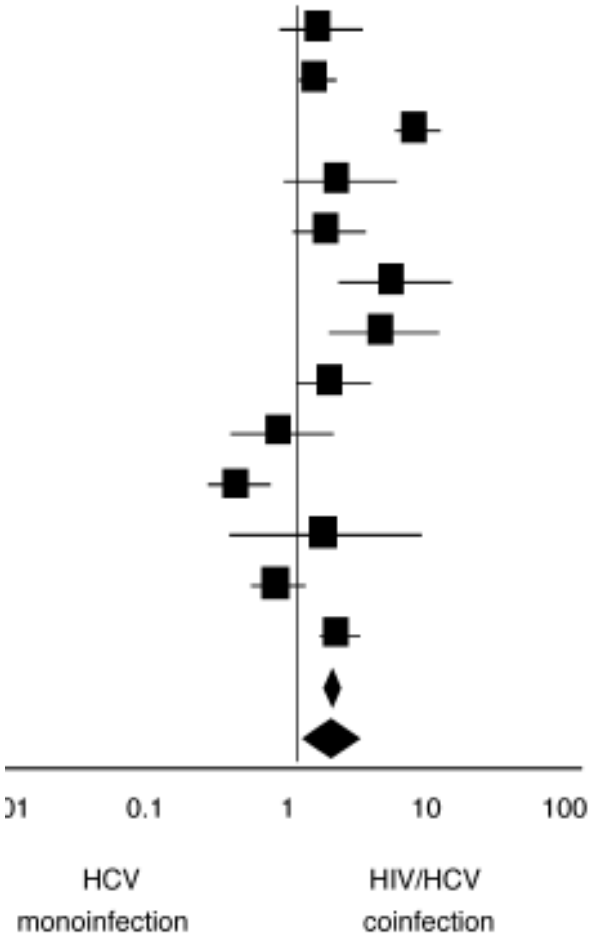
(Grint. D AIDS 2015)



HIV/HCV

- HIV accelera la progressione di HCV
- Rischio di evoluzione in cirrosi maggiore HIV/HCV

- Cirrosi a 10-15 anni:
  15-25% HIV/HCV
  2.6-6.5% HCV



•***(Thein H AIDS 2008 al.)***

Risk of End-Stage Liver Disease in HIV-Viral Hepatitis Coinfected Persons in North America From the Early to Modern Antiretroviral Therapy Eras

CID • Klein et al

2016

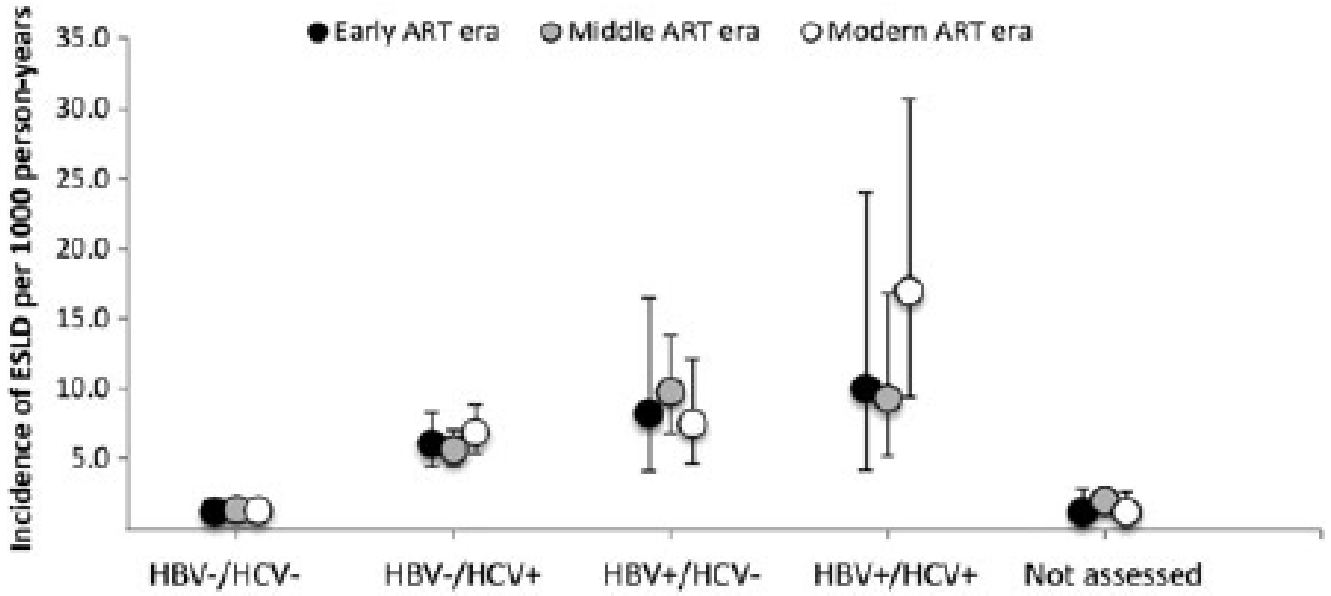


Figure 1. End-stage liver disease (ESLD) incidence rates and 95% confidence intervals by viral hepatitis coinfection status and antiretroviral therapy (ART) era, North American AIDS Cohort Collaboration on Research and Design, January

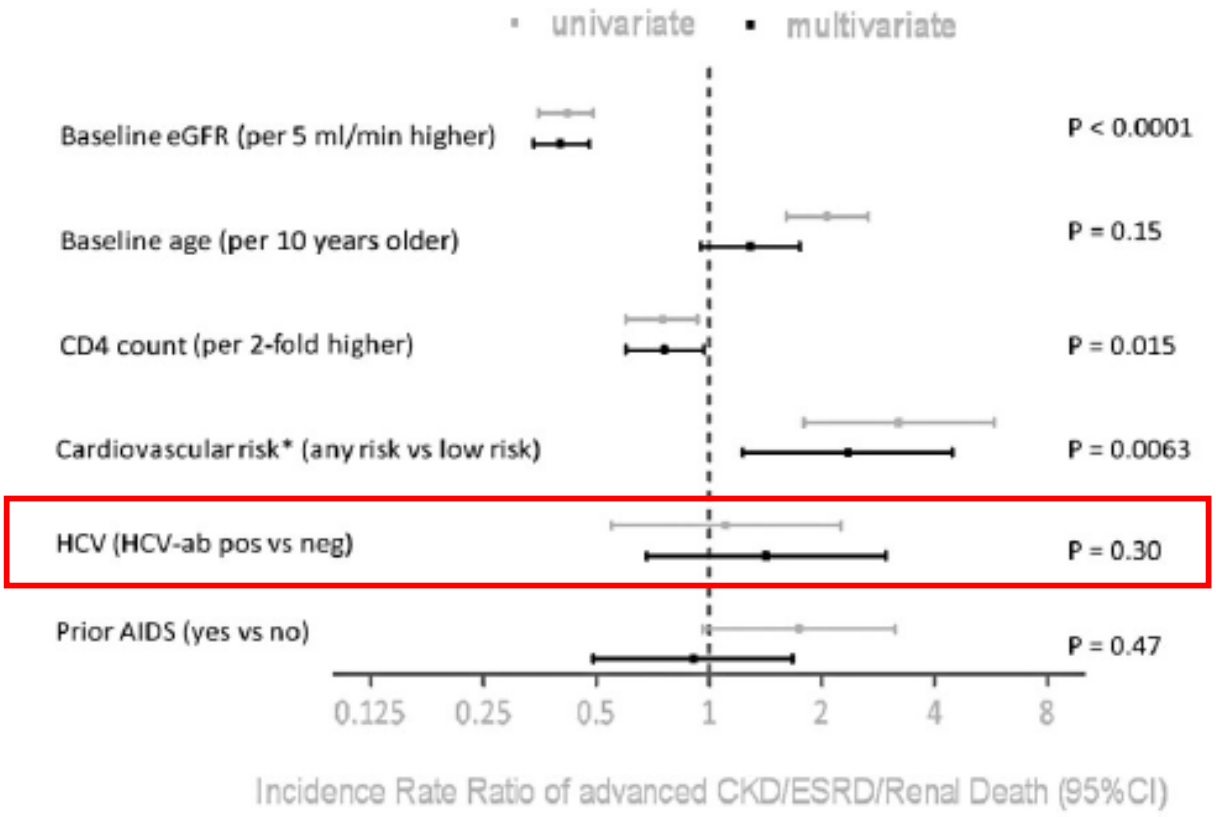
Advanced chronic kidney disease, end-stage renal disease and renal death among HIV-positive individuals in Europe

L Ryom,[1] O Kirk,[1,2] JD Lundgren,[1,2] P Reiss,[3] C Pedersen,[4] S De Wit,[5] S Buzunova,[6] J Gasiorowski,[7] JM Gatell[8] and A Mocroft[9] on behalf of EuroSIDA in EuroCoord*

HIV Medicine (2013),

9044 soggetti

eGFR < 30 ml/ dialisi/ trapianto/morte 58 (0.64%)



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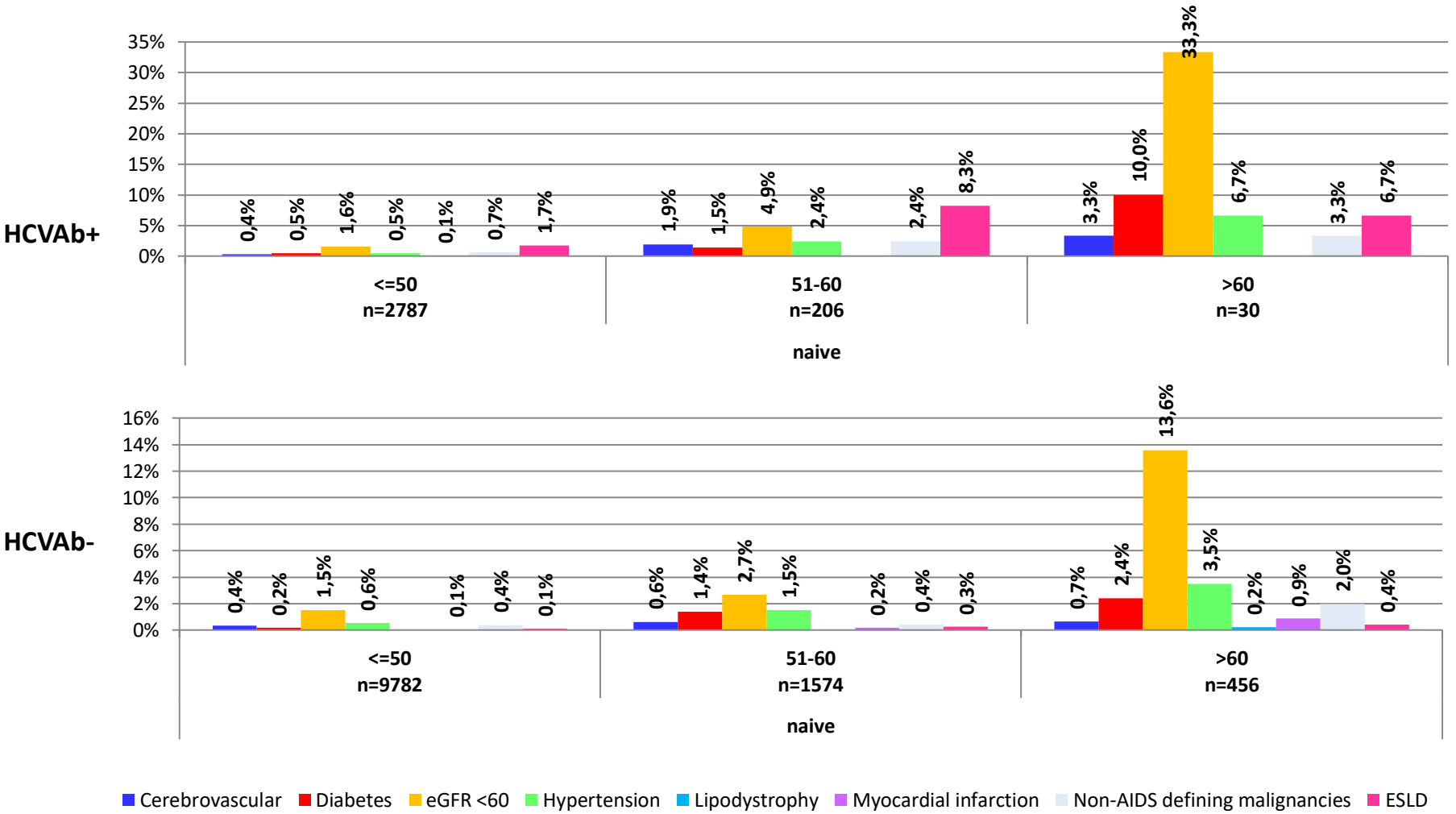
ITALIAN COHORT NAIVE ANTIRETROVIRALS

Prevalence of different non-AIDS related co-morbidities at different age strata in naive patients, according to HCVAb positivity



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HIV/HCV
Terapia DAAs

- **% risposta uguale ai monoinfetti**
- **risposta non condizionata dal valore CD4**
- **Scarsi effetti collaterali**

La coinfezione HIV/HCV

L'efficacia dei DAAs è equivalente negli HCV monoinfetti e HIV/HCV coinfetti

Study	HCV direct-acting antiviral regimen	Study size (*n*)	SVR 12 weeks proportion (95% confidence interval)
C-EDGE CO-INFECTION (12)	Grazoprevir/ Elbasvir	218	96% (93–98)
TURQUISE-I (10)	Ombitasvir/ Paritaprevir/ ritonavir + Dasabuvir + Ribavirin	31	94% (79–98)
ION-4 (9)	Ledipasvir/ Sofosbuvir	335	96% (93–98)
ALLY-2 (11)	Daclatasvir + Sofosbuvir	127	96.4% (90–99)

HCV-HIV co-infected patients: no longer a 'special' population?

Mark S. Sulkowski Liver Int. 2016; **36** (Suppl. S1): 43–46

EASL HCV recommendations

Hepatology 2015

- Indications for HCV treatment in HCV/HIV coinfected persons are identical to those in patients with HCV-monoinfection **(A1)**

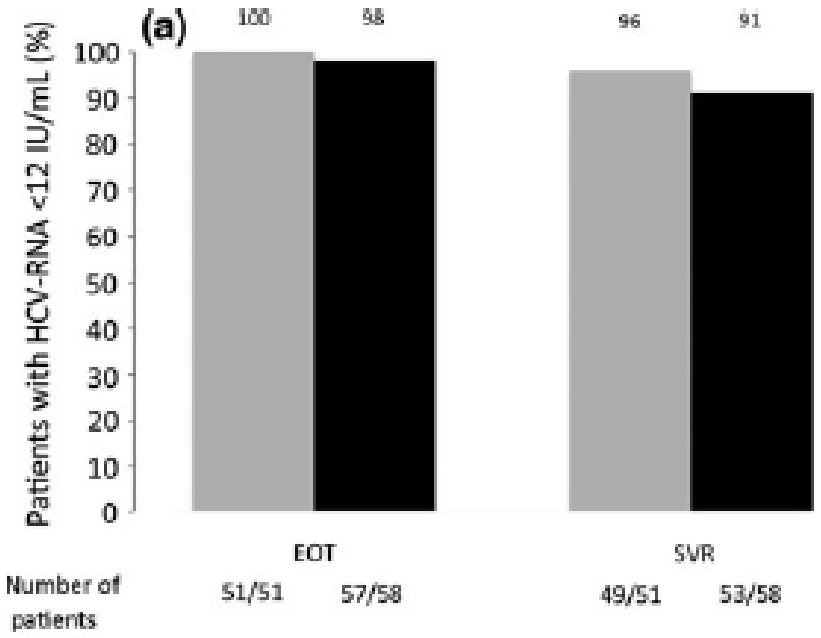
- Notwithstanding the respective costs of these options, IFN-free regimens are the best options when available in HCV-monoinfected and in HIV-coinfected patients without cirrhosis or with compensated (Child-Pugh A) or decompensated (Child-Pugh B or C) cirrhosis, because of their virological efficacy, ease of use and tolerability **(A1)**

- The same IFN-free treatment regimens can be used in HIV-coinfected patients as in patients without HIV infection, as the virological results of therapy are identical **(A1)**

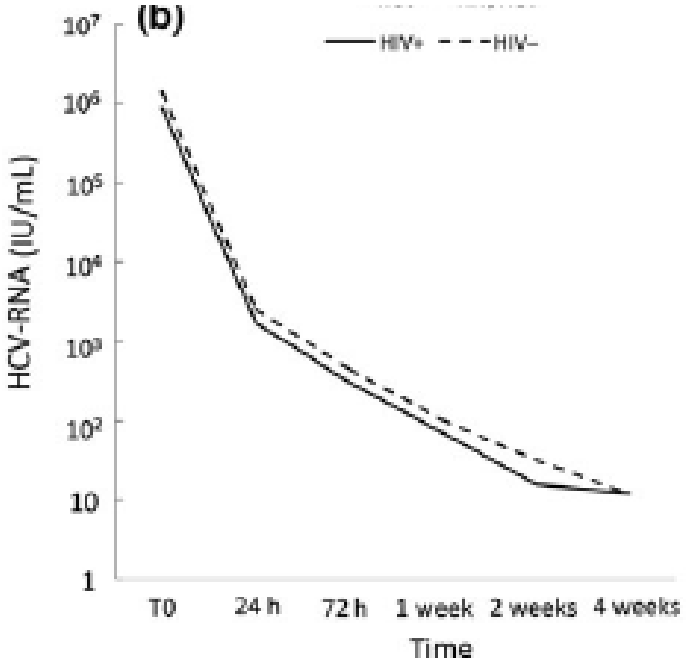
Direct-acting antivirals in hepatitis C virus (HCV)-infected and HCV/HIV-coinfected patients: real-life safety and efficacy

HIV Medicine (2016)

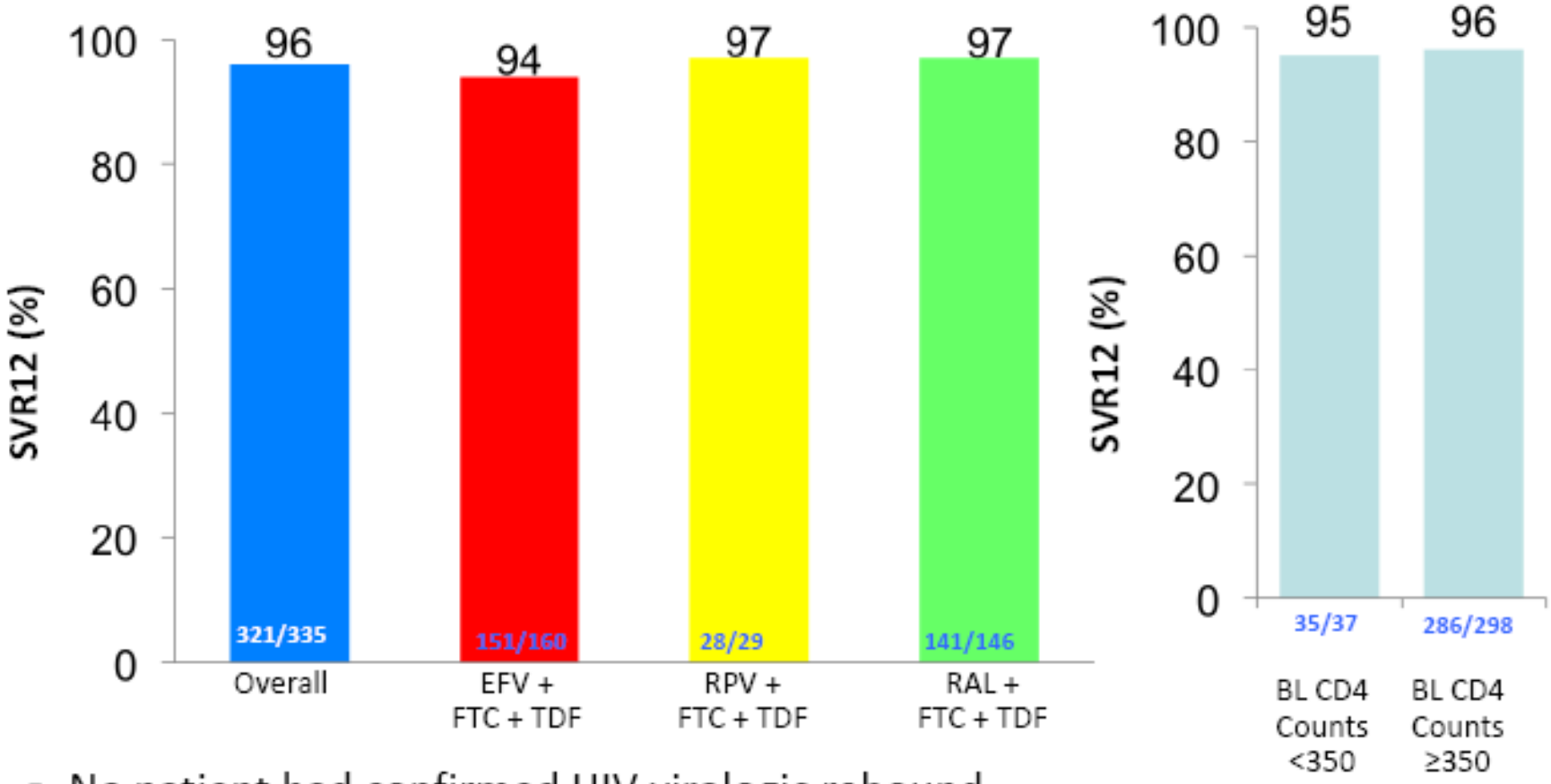
L. Milazzo,[1,*] A. Lai,[1] E. Calvi,[1] P. Ronzi,[1] V. Micheli,[2] F. Binda,[1] A.L. Ridolfo,[1] C. Gervasoni,[1] M. Galli,[1] S. Antinori[1] and S. Sollima[1]



Cirrosi 60%



SVR12 by HIV ARV Regimen and BL CD4 Count



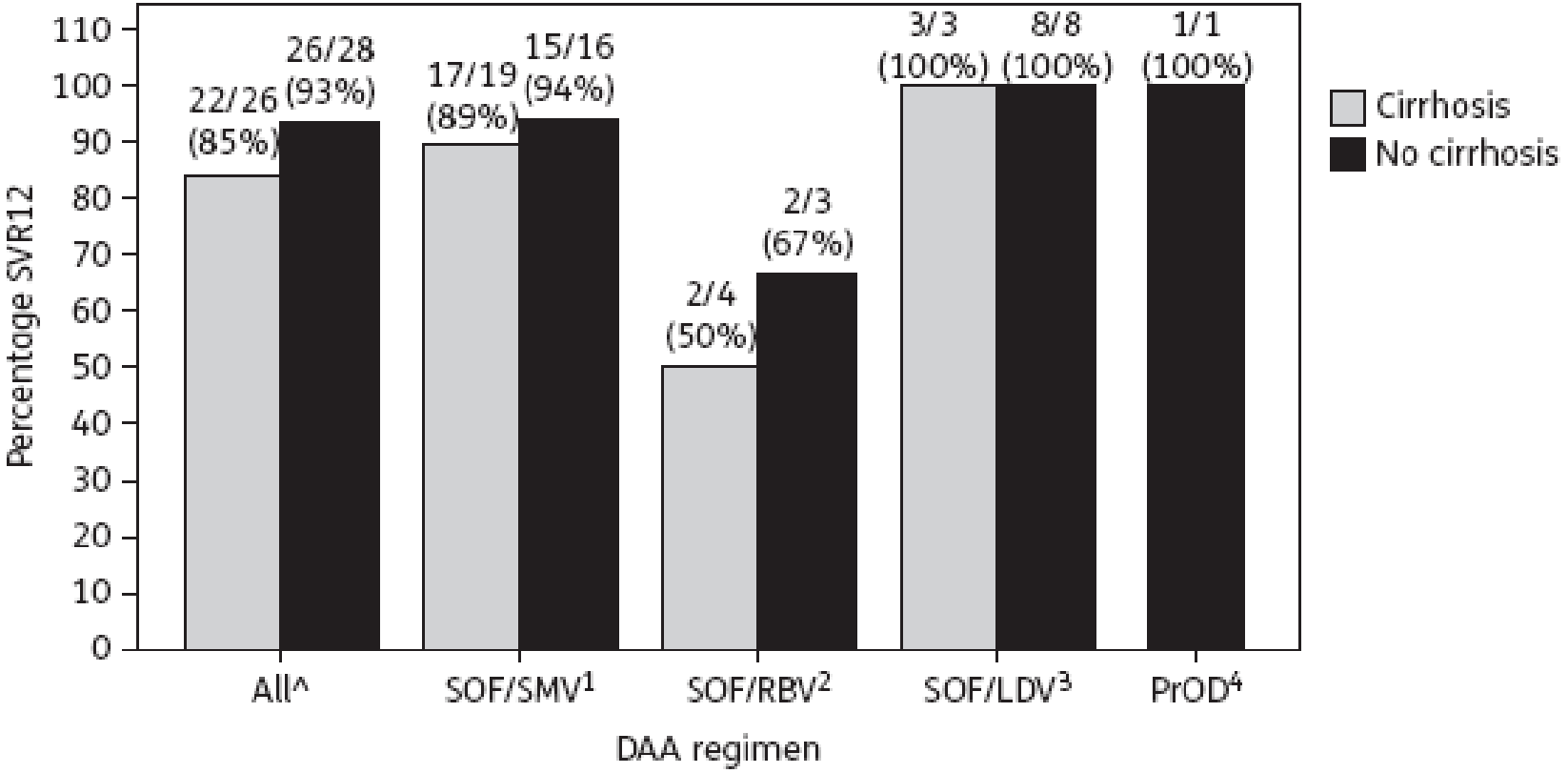
- No patient had confirmed HIV virologic rebound
- Stable CD4 counts through treatment and follow-up phase

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

High rates of hepatitis C virus (HCV) cure using direct-acting antivirals in HIV/HCV-coinfected patients: a real-world perspective

Claudia Hawkins[1]*, Jennifer Grant[1], Lauren Rose Ammerman[2], Frank Palella[1], Milena Mclaughlin[3,4], Richard Green[5], Donna Mcgregor[1] and Valentina Stosor[1]

J Antimicrob Chemother **2016**



L'associazione Exviera eViekirax nel trattamento di pazienti con confezione HIV-HCV:
risultati preliminari di un programma per uso compassionevole.
(Andreoni M. et al, SIMIT 2015)

- **213 pazienti HIV/HCV con fibrosi F2**
- **62,7% HCV gen 1°**
- **Risposta EOT 96,9%**
- **6 pazienti con viremia rilevabile**
- **Nessun evento avverso di grado 3-4**

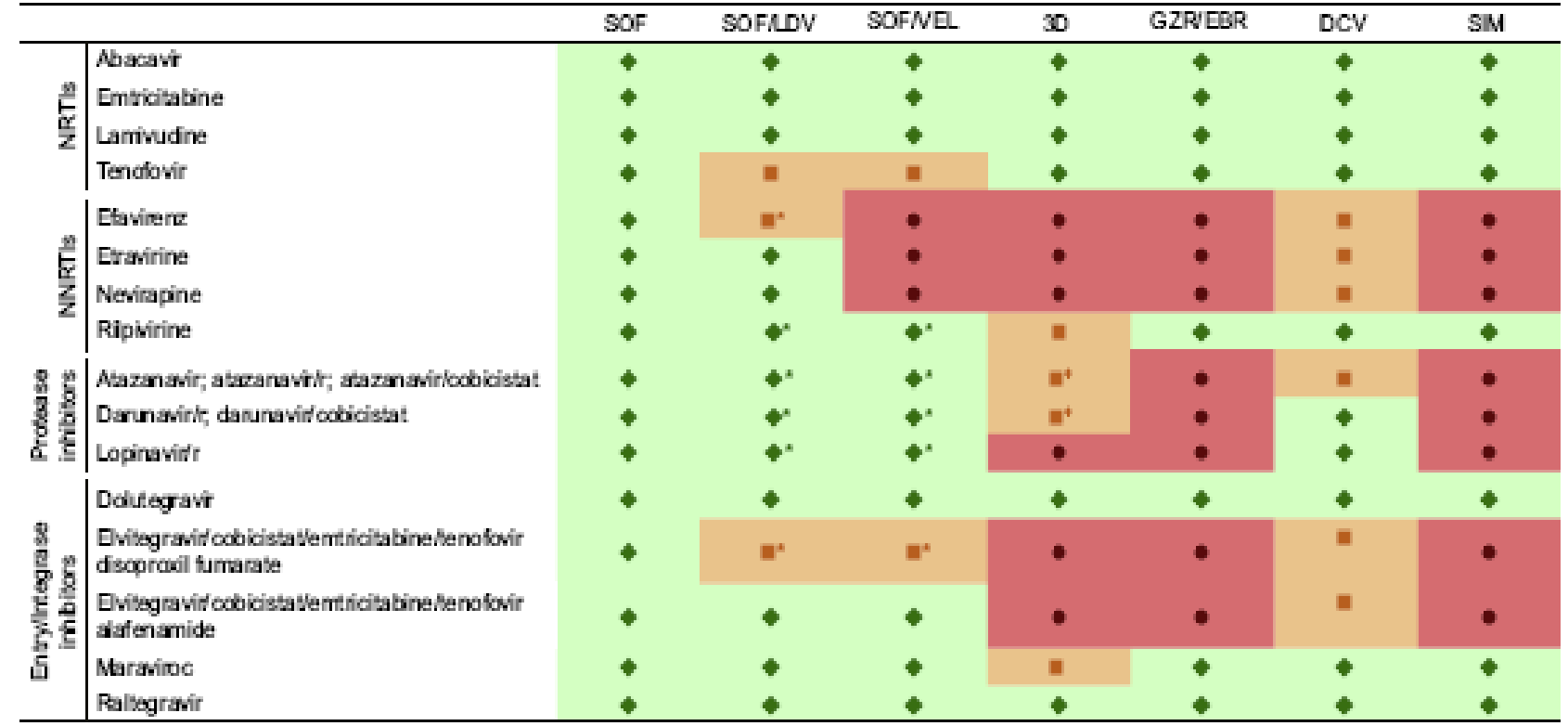
- **59,5% ha modificato ART pre-terapia**

HIV/HCV
terapia DAAs: criticità

- **Interazioni con terapia antiretrovirale**
- **Durata della terapia**

EASL Recommendations on Treatment of Hepatitis C 2016☆

EASL JOURNAL OF HEPATOLOGY



		SOF	SOF/LDV	SOF/VEL	3D	GZR/EBR	DCV	SIM
NRTIs	Abacavir	◆	◆	◆	◆	◆	◆	◆
	Emtricitabine	◆	◆	◆	◆	◆	◆	◆
	Lamivudine	◆	◆	◆	◆	◆	◆	◆
	Tenofovir	◆	■	■	◆	◆	◆	◆
NNRTIs	Efavirenz	◆	■*	●	●	●	■	●
	Etravirine	◆	◆	●	●	●	■	●
	Nevirapine	◆	◆	●	●	●	■	●
	Rilpivirine	◆	◆*	◆*	■	◆	◆	◆
Protease inhibitors	Atazanavir; atazanavir/r; atazanavir/cobicistat	◆	◆*	◆*	■*	●	■	●
	Darunavir/r; darunavir/cobicistat	◆	◆*	◆*	■*	●	◆	●
	Lopinavir/r	◆	◆*	◆*	●	●	◆	●
Entry/Integrase inhibitors	Dolutegravir	◆	◆	◆	◆	◆	◆	◆
	Elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate	◆	■*	■*	●	●	■	●
	Elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide	◆	◆	◆	●	●	■	●
	Maraviroc	◆	◆	◆	■	◆	◆	◆
	Raltegravir	◆	◆	◆	◆	◆	◆	◆

Interazioni DAAs e terapia antiretrovirale

Dosing Considerations for Pts With Renal Impairment

- **OBV/PTV/RTV + DSV**: no dose adjustment required with mild, moderate, or severe renal impairment (CrCl: ≥ 15 mL/min)[1,2]
- **LDV/SOF and SMV + SOF**: no dose adjustment required with mild or moderate renal impairment (CrCl ≥ 30 mL/min)[3,4]
  - Safety and efficacy not established in severe renal impairment or hemodialysis
  - TARGET data demonstrate feasibility of SOF-containing regimens but renal and urinary AEs increased across decreasing eGFR strata[5]
- **DCV**: no dose adjustment required with any degree of renal impairment (studied in subjects with CrCl: ≥ 15 mL/min)[6]
- **RBV**: dose adjustment required for CrCl < 50 mL/min[7]

CrCl	RBV Dose
30-50 mL/min	Alternating 200 mg and 400 mg every other day
< 30 mL/min	200 mg/day
Hemodialysis	200 mg/day

1. OBV/PTV/RTV + DSV [package insert]. 2. Pockros PJ, et al. EASL 2015. Abstract L01. 3. LDV/SOF [package insert].
4. AASLD/IDSA. HCV Management. http://www.hcvguidelines.org. 5. Saxena V, et al. EASL 2015. Abstract LP08.
6. DCV [European package insert]. 7. RBV [package insert].

Interazioni DAAs e ART

- **Ledipasvir e velpatasvir possono aumentare la concentrazione di TDF in particolare se usati con PI/b**
  - Non usare LDV o VEL con tenofovir se CrCl < 60 mL/min ed in associazione con PI/b

- **OBV/PTV/RTV + DSV e PI/b : considerare uso PI senza booster**

AASLD/IDSA. HCV Management. http://www.hcvguidelines.org

TURQUOISE 1b: DRV in HIV/HCV-Coinfected Pts With OBV/PTV/RTV + DSV

- Sustained HCV virologic response achieved in 22/22 pts[1]

Least Square Means Ratios vs DRV Alone (90% CI)[1]	DRV QD + OBV/PTV/RTV + DSV + RBV (n = 10)[1]	DRV BID + OBV/PTV/RTV + DSV + RBV (n = 12)[1]
C_{max}	0.924 (0.723-1.181)	0.921 (0.755-1.122)
AUC	0.833 (0.711-0.975)	0.876 (0.732-1.048)
C_{trough}	0.643 (0.443-0.934)	0.730 (0.578-0.921)

- 5 pts with detectable HIV-1 RNA (42-79 copies/mL) during coadministration[2]
  - No HIV-1 RNA > 200 copies/mL
  - No apparent association with DRV PK (3 pts on BID, 2 pts on QD DRV)

1. Wyles D, et al. CROI 2016. Abstract 574.
2. Ruane PJ, et al. EACS 2015. Abstract LBPS7/1.

Slide credit: clinicaloptions.com

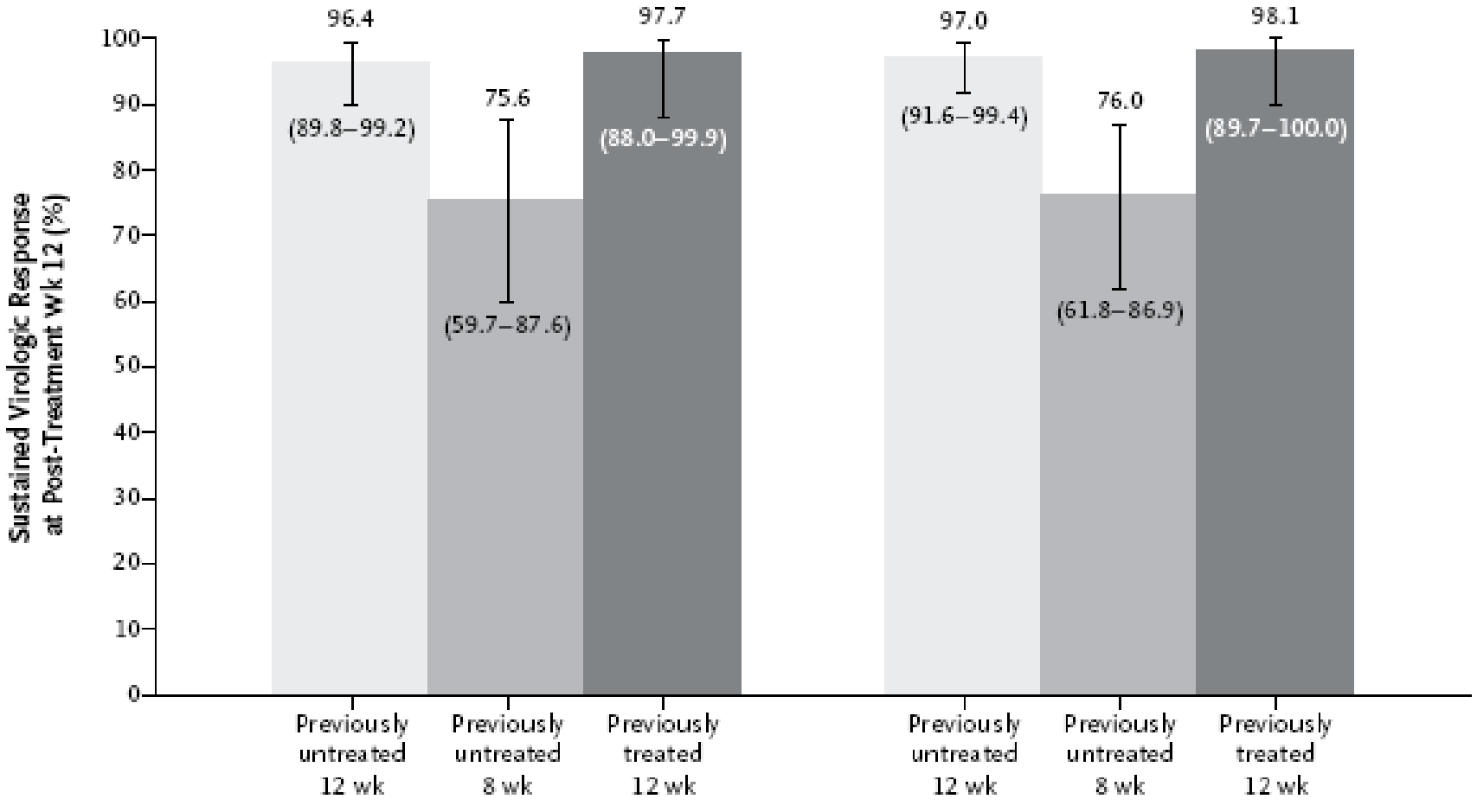
HIV/HCV
terapia DAAs: criticità

- **Interazioni con terapia antiretrovirale**
- **Durata della terapia**

Daclatasvir plus Sofosbuvir for HCV in Patients Coinfected with HIV-1

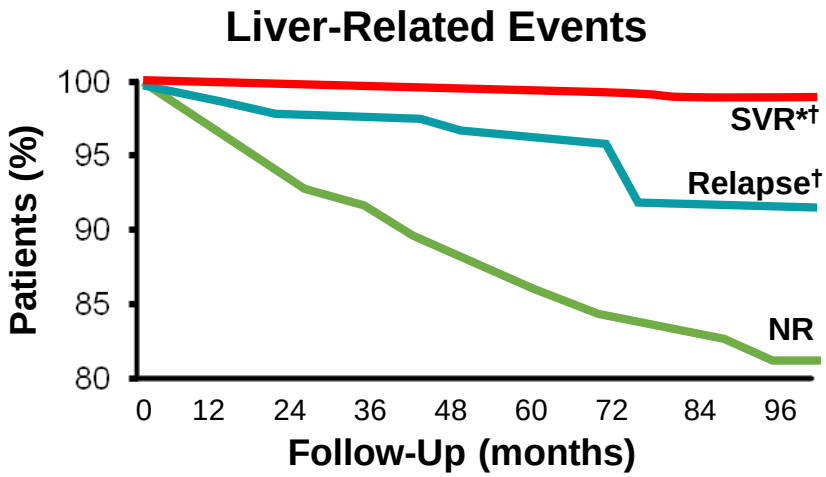
ALLY-2 Investigators*

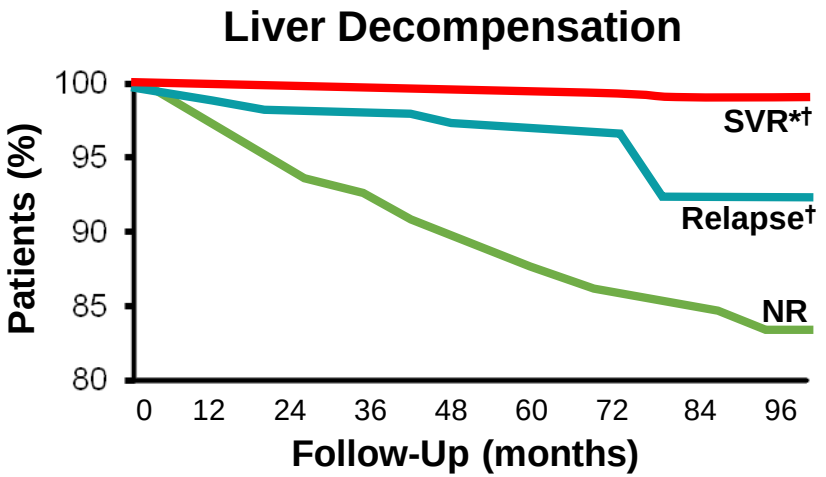
N ENGL J MED 373;8 NEJM.ORG AUGUST 20, 2015

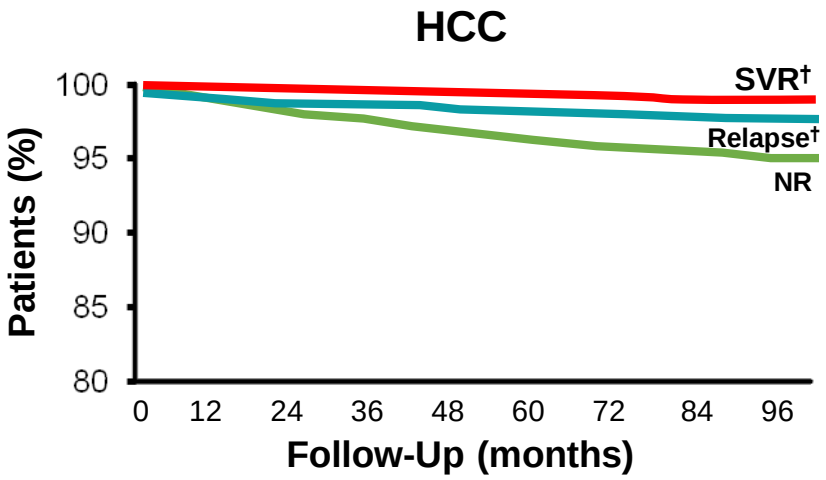


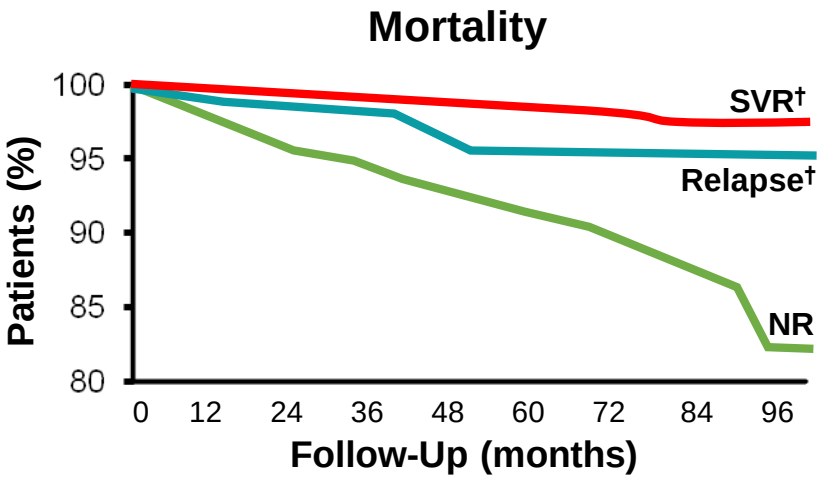
	Genotype 1			Genotypes 1 to 4		
No. of Events	80	31	43	98	38	51
Total No. of Patients	83	41	44	101	50	52

GESIDA HIV/HCV Cohort: HCV Eradication Reduces Liver-Related Outcomes









*P<0.05 versus NR and relapse; †P<0.05 versus NR.

Berenguer J, et al. *J Hepatol*. 2013;58:1104-1112.

Eradication of HCV and non–liver-related non–AIDS-related events in HIV/HCV coinfection

GESIDA HIV/HCV Cohort Study

Hepatology in press

Table 4. Crude and adjusted hazards for events during follow-up for 997 non-responders to interferon plus ribavirin compared with 628 responders

	Univariate analysis[a]		Multivariate analysis[a,b]	
	HR (95% CI)	***P***	**HR (95% CI)**	***P***
Overall deaths	0.35 (0.24 - 0.52)	<.001	0.36 (0.24 - 0.54)	<.001
	sHR (95% CI)	***P***	**sHR (95% CI)**	***P***
Cause-specific deaths				
Liver-related deaths	0.12 (0.05 - 0.28)	<.001	0.13 (0.06 - 0.28)	<.001
Non–liver-related deaths	0.69 (0.43 - 1.1)	.119	0.73 (0.44 - 1.20)	.214
AIDS-related deaths	0.45 (0.09 - 2.22)	.325	0.37 (0.09 - 1.43)	.148
NLR-NAR deaths	0.73 (0.44 - 1.19)	.204	0.79 (0.47 - 1.35)	.388
New AIDS-defining events	0.34 (0.16 - 0.72)	.004	0.37 (0.17 - 0.79)	.010
Liver-related events				
Liver decompensation	0.09 (0.04 - 0.2)	<.001	0.10 (0.05 - 0.21)	<.001
Hepatocellular carcinoma	0.12 (0.03 - 0.5)	.004	0.13 (0.03 - 0.50)	.003
Liver transplantation	0.10 (0.01 - 0.77)	.027	0.12 (0.02 - 0.78)	.027
NLR-NAR events				
Diabetes mellitus *	0.54 (0.34 - 0.87)	.011	0.57 (0.35 - 0.93)	.024
NLR-NAR Cancer	0.91 (0.6 - 1.38)	.650	0.91 (0.58 - 1.45)	.703
Cardiovascular events	1.41 (0.93 - 2.13)	.105	1.57 (0.99 - 2.50)	.056
NAR-Infections	0.55 (0.33 - 0.92)	.024	0.65 (0.37 - 1.14)	.131
Bone events	1.39 (0.82 - 2.35)	.225	1.28 (0.69 - 2.38)	.433
Renal events *	0.41 (0.17 - 0.99)	.049	0.43 (0.17 – 1.09)	.075

HIV HCV

Grazie per l'attenzione