PRESIDENZA DEL CONSIGLIO DEI MINISTRI
Dipartimento Politiche Antidroga

REGIONE VENETO
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Dipartimento delle Dipendenze

Screening and treatment of HIV and drug related diseases among drug users: a scientific update

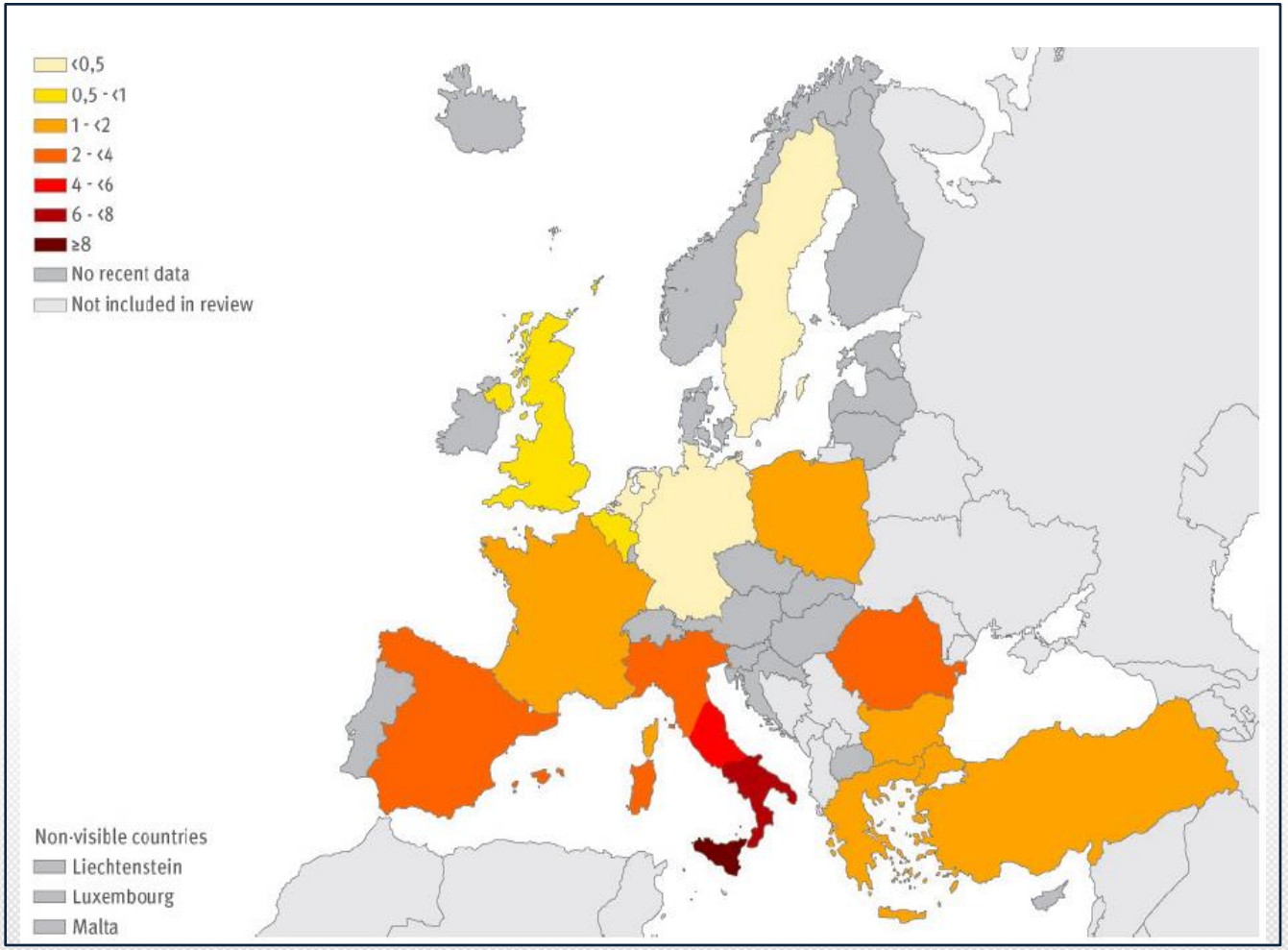
Hepatitis treatment among drug users and HIV infected patients

Stefano Nardi

Centro di Medicina Comunitaria

Verona 3rd April 2014

HCV - Scenario Attuale



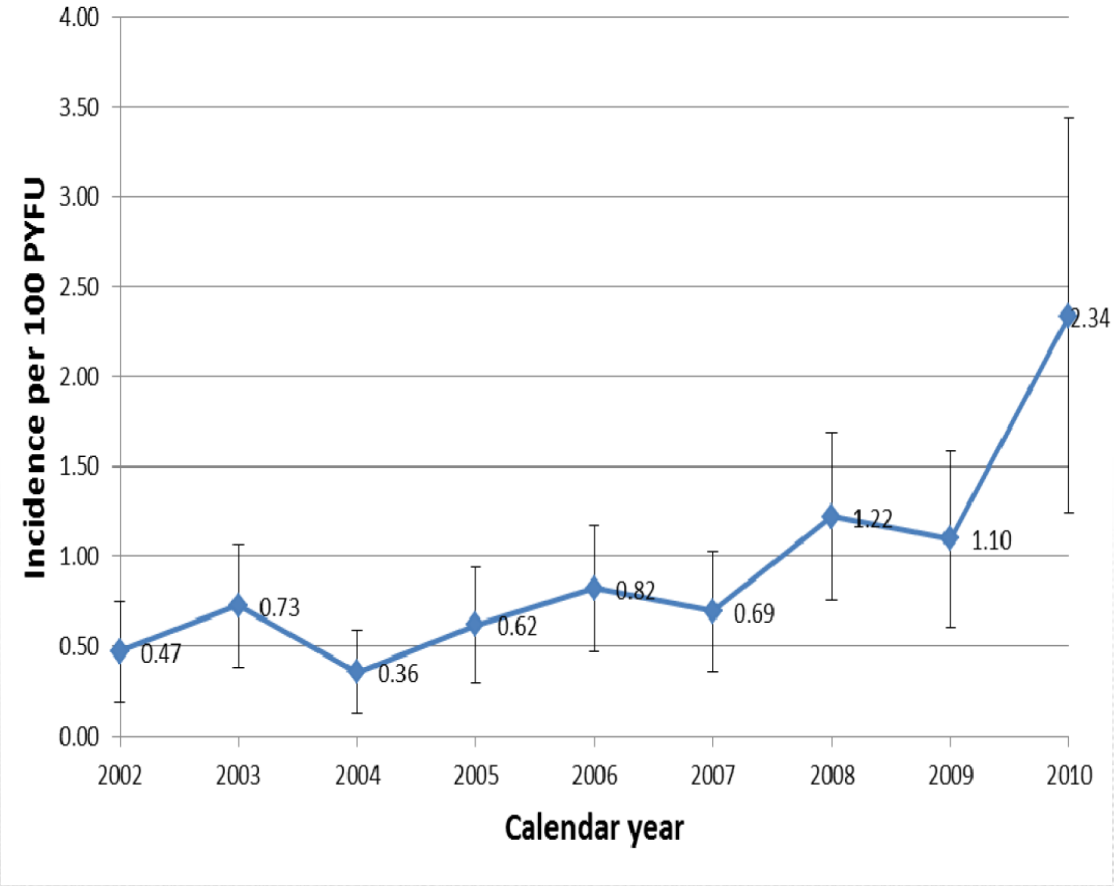
TECHNICAL REPORT Hepatitis B and C in the EU neighbourhood: prevalence, burden of disease and screening policies September 2010

Epidemiology

Hepatitis C is a disease of significant global impact. According to the World Health Organization there are 130-170 million people infected with hepatitis C virus (HCV). There are considerable regional differences: in some countries, e.g., Egypt, the prevalence is as high as 22% (WHO 2011). In Africa and the Western Pacific prevalence is significantly higher than in North America and Europe (CDC 2012). It is estimated that there are 2-5 million HCV-positive persons in Europe. Certain groups are preferentially affected, like injection drug users. In Europe and the United States chronic hepatitis C is the most common chronic liver disease. The majority of liver transplants performed in these regions are for chronic HCV. It is difficult to determine the number of new HCV infections, as most acute cases are not noticed clinically. Recent numbers from Europe still show an ongoing epidemic of acute HCV especially among IVDU and MSM (Rockstroh 2012).

Epidemiology

Increase in acute HCV infection incidence across Europe



Rockstroh J, et al. HIV11 2012. O242,

Transmission

Parenteral exposure to hepatitis C is the most efficient means of transmission. The majority of patients infected with HCV in Europe and the United States acquired the disease through intravenous drug use or blood transfusion, which has become rare since routine testing of the blood supply for HCV began. The following possible routes of infection have been identified in blood donors (in descending order of transmission risk):

- **Injection drug use**
- **Blood transfusion**
- **Sex with an intravenous drug user**
- **Having been in jail more than three days**
- **Religious scarification**
- **Having been struck or cut with a bloody object**
- **Pierced ears or body parts**
- **Immunoglobulin injection**

Very often in patients with newly diagnosed HCV infection no clear risk factor can be identified.

Disease progression

Chronic HCV progression may differ depending on several factors. Other factors not yet identified may also be important.

Age and gender: More rapid progression is seen in males older than 40-55 (Svirtlih 2007), while a less rapid progression is seen in children (Child 1964).

African-Americans (Sterling 2004).

HCV-specific cellular immune response: Genetic determinants like HLA expression (Hraber 2007) probably guide the inflammatory response.

Alcohol intake: Even moderate amounts of alcohol increase HCV replication, enhance the progression of chronic HCV, and accelerate liver injury (Gitto 2009).

Daily use of marijuana: may cause a more rapid progression.

Other host factors: TGF B1 phenotype or PNPLA-3 (adiponutrin) and fibrosis stage are correlated with fibrosis progression rate (Zimmer 2011). Moderate to severe steatosis correlates with developing hepatic fibrosis.

Viral coinfections: HCV progression is more rapid in HIV-infected patients. Acute hepatitis B in a patient with chronic hepatitis C may be more severe. Liver damage is usually worse and progression faster in patients with dual HBV/HCV infections.

Geography and environmental factors: Clear, but not understood (Lim 2008).

Use of steroids: increases HCV viral load.

Viral factors: There seems to be no significant role of different genotypes and quasispecies on fibrosis progression or outcome. However, coinfection with several genotypes may have a worse outcome as compared to monoinfection. Liver biopsy is the best predictor of disease progression (Gebo 2002).

On the other hand, new parameters seem to be more important such as HCV subtypes 1a and 1b. Patients with HCV GT1a have a higher risk of developing resistance during PI-based therapy compared to HCV GT1b because HCV GT1a requires an exchange of only one nucleotide versus two for HCV GT1b at position 155 to develop resistance (reviewed in Sarrazin and Zeuzem 2010b).

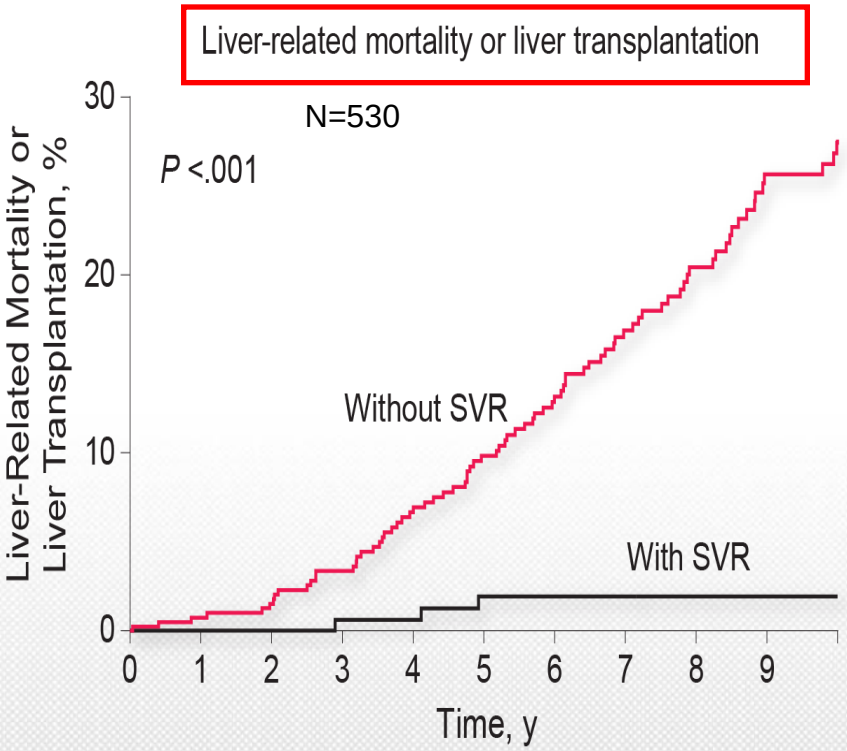
During treatment, the kinetics of the HCV RNA decline is a strong predictor of response. HCV RNA measurements at weeks 4, 12 and 24 are important for a response-guided treatment approach for PEG-IFN/RBV but also for the new triple therapy including BOC and TLV.

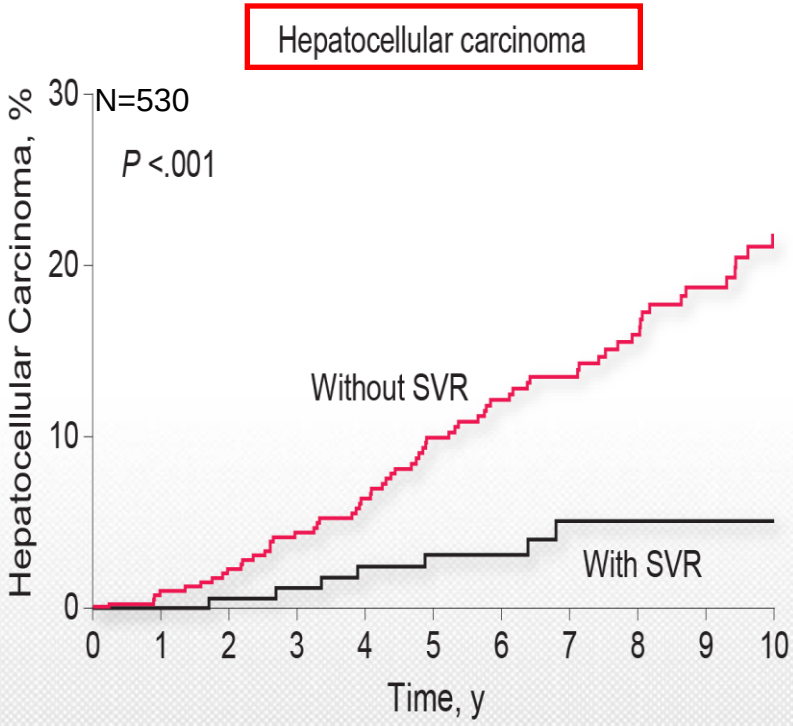
Recently, genome-wide association studies have identified host genetic polymorphisms (i.e., rs12979860, rs8099917) located on chromosome 19 located upstream to the region coding for IL28B (or IFN λ3) associated with SVR to treatment with PEG-IFN/RBV in HCV GT1 patients (Ge 2009, Rauch 2010, Suppiah 2009, Tanaka 2009) but also to a lesser extent for HCV GT2/3 (Mangia 2010c, Sarrazin 2011b).

Data on IL28B explain the different responses to PEG-IFN/RBV between ethnic groups, i.e., the low SVR in African Americans and the high SVR in Asian patients. However, the negative predictive value is not strong enough to recommend general testing (EASL 2011). Viral kinetics, especially response at week 4, have a higher predictive value (Sarrazin 2011a) (Poordad 2012) and the relevance of IL28B as a predictive marker for the success of triple therapy with PEG-IFN/RBV/PI is less significant (Jacobson 2011a, Pol 2011a, Poordad 2012). However, IL28B testing may be useful to determine the IFN responsiveness and the likelihood of achieving RVR with PEG-IFN/RBV before starting triple therapy. It may be of relevance to discuss treatment options with the individual patient.

Additional predictive markers are being evaluated. For example, low serum levels of interferon γ inducible protein 10 (IP-10) are associated with SVR and may improve the predictive value for discrimination between SVR and non-response (Darling 2011, Fattovich 2011).

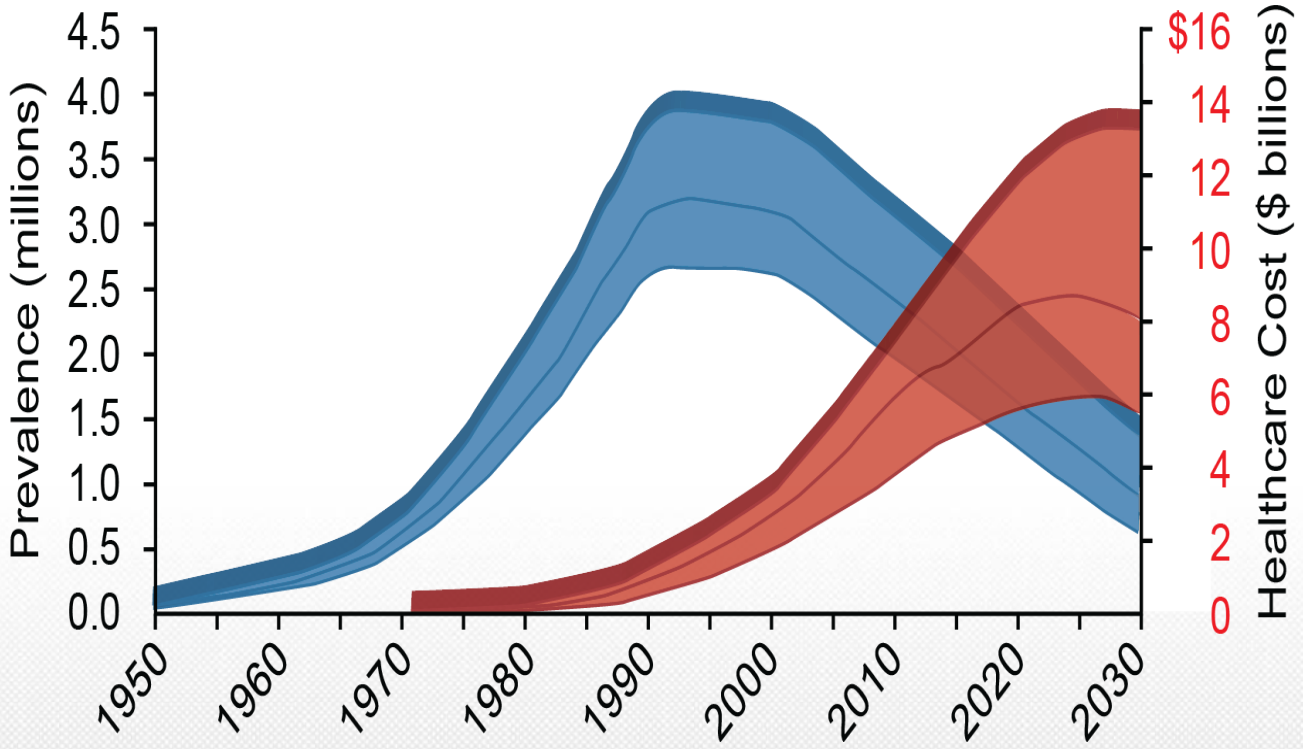
Sustained Virologic Response is associated with a reduction in liver-related mortality and HCC





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

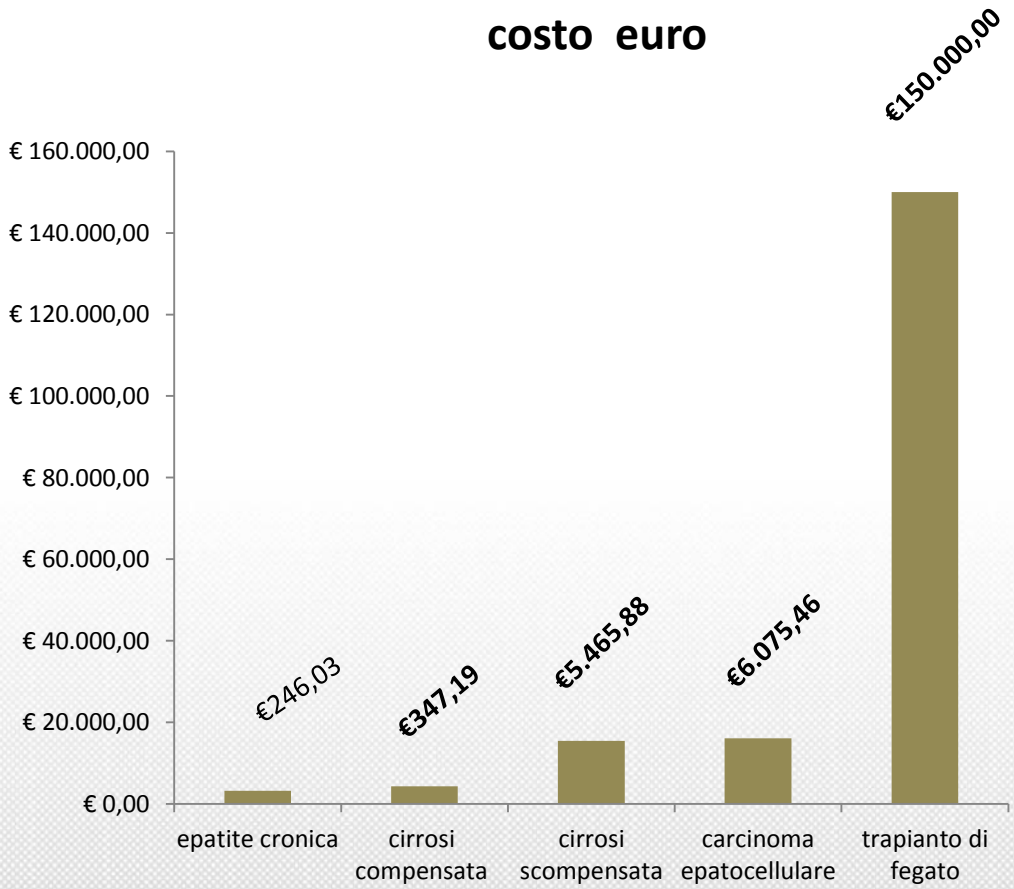
Healthcare costs are climbing due to HCV patient progression to more advanced liver disease



HCV population is ageing
Serious liver disease associated with HCV will have a greater healthcare system impact as the infected population ages

Razavi H, et al. *Hepatology.* 2013. Epub ahead of print

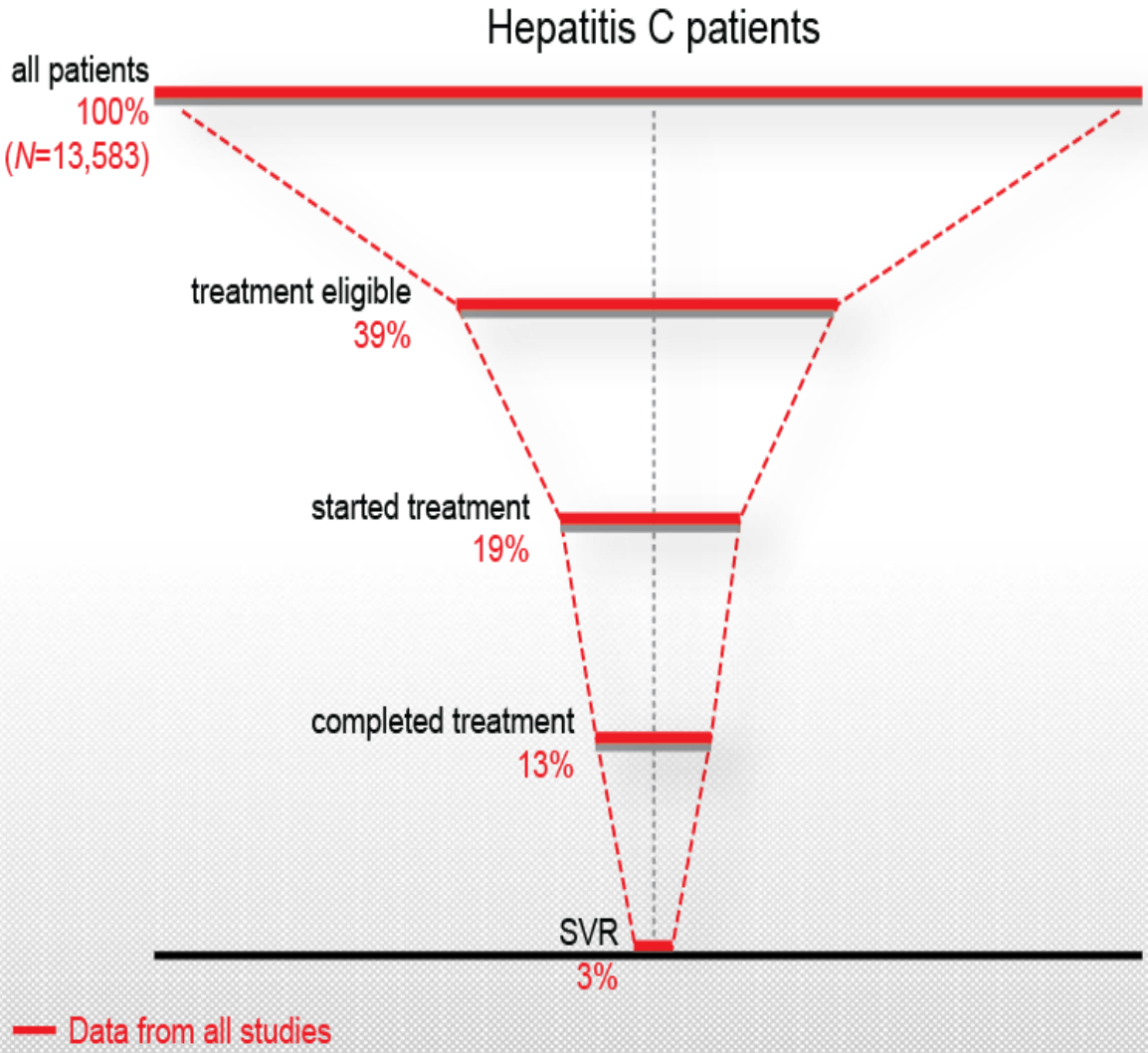
HCV scenario attuale costi



Global costs of HCV Gt1 therapy in naïves (assuming treatment of F2 to F4)

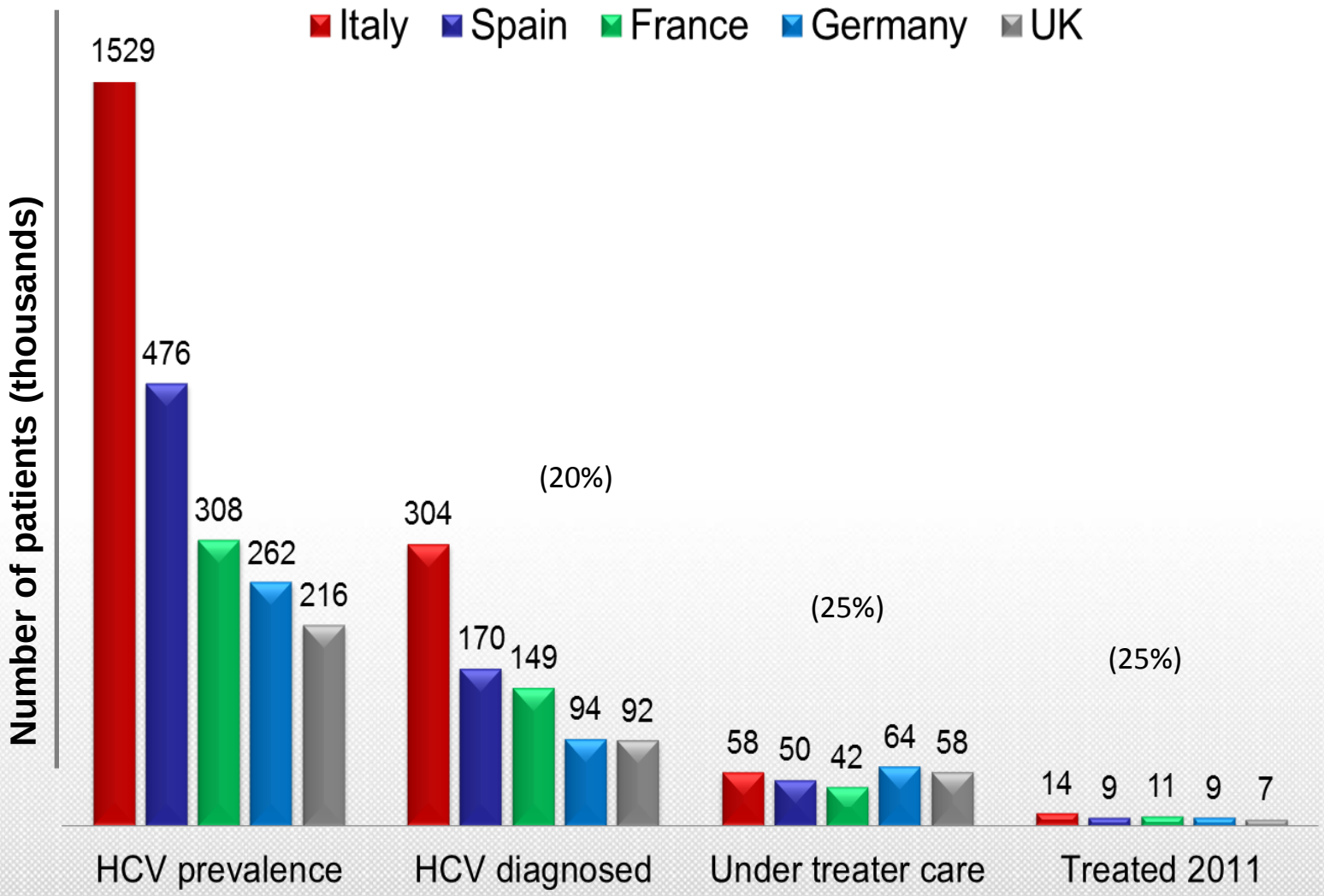
Cost	PegIFN/ RBV 48 wks	BOC/ TPV + P/R 36-48 wks	SFBV + P/R 12 wks	SMPV+ P/R 12 wks	SFBV + RBV 24 wks	SFBV + SMPV ± RBV 12 wks
drugs	6-9.000	25-30.000	66.000	44.000	121.000	100.000
monitoring	8.000	10-12.000	4.000	4.000	6.000	5.000
EPO, G-CSF, blood tx, others	1.000	20-25.000	500	500	≈ 0	≈ 0
TOTAL	15-18.000	55-67.000	70.500	48.500	131.000	105.000
Expected efficacy	≈ 40%	≈ 65%	>90%	>90%	>90%	>95%
Euros for 1 SVR	≈ 38-45.000	≈ 85-103.000	≈ 78.000	≈ 54.000	≈ 145.000	≈ 110.000

Sixty one percent of patients are not eligible for currently available treatments – implying 97% have minimal chance of cure



North CS, et al. *Gen Hosp Psych.* 2013; 35: 122-128

A small proportion of HCV patients are being treated



Data on file. Ipsos Healthcare HCV Therapy Monitor Q2 and Q4 2011. Permission granted for use.

The Prevention and Management of Hepatitis C Virus Infection Among People Who Inject Drugs

The majority of hepatitis C virus (HCV) occurs among people who inject drugs (PWID), and the burden of HCV-related liver disease is still increasing. HCV treatment is safe and effective among PWID, and international guidelines encourage HCV treatment in this group, but HCV treatment uptake remains low among PWID, mainly due to patient- practitioner- and systems-related barriers to care.

•Hajarizadeh B, Grebely J, Dore GD . Epidemiology and natural history of hepatitis C virus infection [published online ahead of print 2 July 2013]. Nat Rev Gastroenterol Hepatol 2013.
•Grebely J, Dore GJ . What is killing people with hepatitis C virus infection? Semin Liver Dis 2011;31:331-9.
• Dimova RB, Zeremski M, Jacobson IM, Hagan H, Des Jarlais DC, Talal AH .Determinants of hepatitis C virus treatment completion and efficacy in drug users assessed by meta-analysis. Clin Infect Dis 2013;56:806-16.
•Ghany MG, Strader DB, Thomas DL, Seeff LB . Diagnosis, management, and treatment of hepatitis C: an update. Hepatology 2009;49:1335-74.
• European Association for the Study of the Liver. EASL clinical practice guidelines: management of hepatitis C virus infection. J Hepatol 2011;55:245-64.
•Iversen J, Grebely J, Topp L, et al . Uptake of hepatitis C treatment among people who inject drugs attending Needle and Syringe Programs in Australia, 1999–2011 [published online ahead of print 1 July 2013]. J Viral Hepat 2013.
• Grebely J, Raffa JD, Lai C, et al . Low uptake of treatment for hepatitis C virus infection in a large community-based study of inner city residents. J Viral Hepat2009;16:352-8.

HCV PREVENTION AMONG PWID

It is estimated that 10 million PWID (people who inject drugs) were HCV antibody positive in 2010, with a global HCV prevalence of 67% among PWID.
HCV incidence also remains high among PWID

Data from many studies suggest that large reductions (>45%) in HCV chronic prevalence over 10 years requires HCV antiviral treatment, with the scale-up of combined interventions, including OST (opiate substitution treatment) and NSPs (needle and syringe programs)

An alternative way of preventing HCV infection would be through the availability of an HCV vaccine.
There are recent advancements in HCV vaccine research, including recent phase 1/2 trials of an HCV candidate vaccine among PWID

ENHANCING HCV ASSESSMENT AMONG PWID

Although HCV treatment is successful among PWID, assessment and uptake remain low. Understanding the barriers and facilitators of HCV care is critical in the design of strategies and programs for effectively increasing the proportion of PWID assessed and treated for HCV.

ENHANCING HCV ASSESSMENT AMONG PWID

HCV care models among PWID:

"one size does not fit all"

when HCV nursing and specialist support are integrated into existing OST or community health clinics, a high proportion of PWID with chronic HCV assessed by a nurse can be engaged in HCV care

ENHANCING HCV ASSESSMENT AMONG PWID

HCV assessment and treatment in prisons is important for involving community-based groups early into the design and for implementation of these programs to achieve the greatest opportunity for engagement by PWID.

ENHANCING HCV TREATMENT AMONG PWID

Populations studied are often heterogeneous (combination of current and former PWID) and there are few data on HCV treatment outcomes among active PWID

Aspinall et al demonstrate an overall sustained virologic response (SVR) of 56%. This is the first systematic review of HCV treatment among those with ongoing drug use at the time of treatment and illustrates that active PWID can respond favorably to therapy

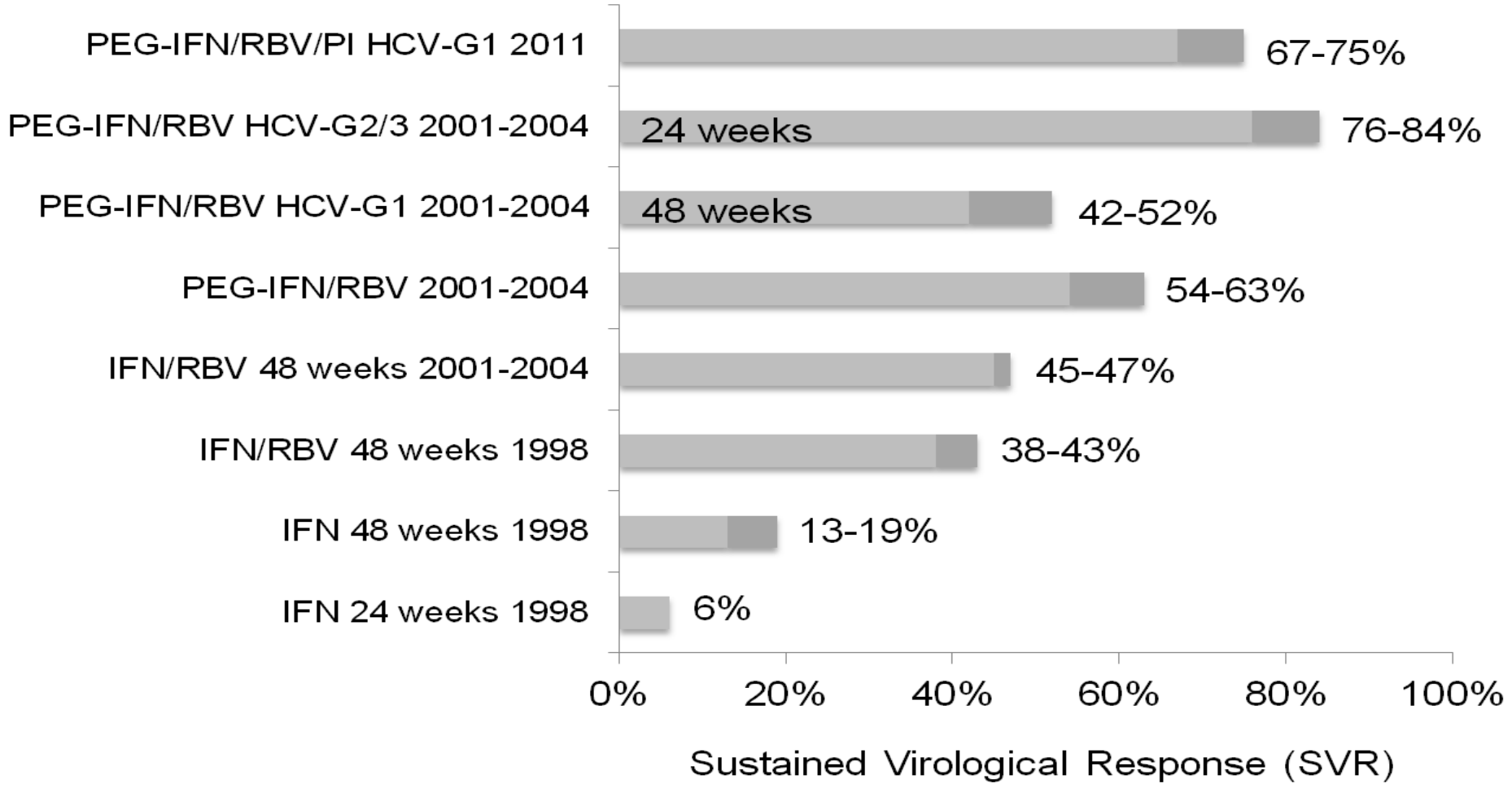
Aspinall E, Corson S, Doyle J, et al . Treatment of hepatitis C virus infection among people who are actively injecting drugs: a systematic review and meta-analysis. Clin Infect Dis 2013;57 2:S80-9.

ENHANCING HCV TREATMENT AMONG PWID

Directly observed pegylated interferon and self-administrated ribavirin can lead to a high proportion of patients with SVR among active drug users, but delaying treatment may compromise subsequent engagement in HCV treatment

Hilsden RJ, Macphail G, Grebely J, et al . Directly observed pegylated interferon plus self-administered ribavirin for the treatment of hepatitis C virus infection in people actively using drugs: A randomized controlled trial. Clin Infect Dis 2013;572:S90-6.

Development of chronic hepatitis C therapy



IFN trials

USA trial: McHutchison et al., NEJM 1998
Int. trial: Poynard et al., Lancet 1998

PEG-IFN trials

PEG-IFN2b: Manns et al., Lancet et al., 2001
PEG-IFN2a: Friedet al., NEJM 2002
PEG-IFN2a: Hadziyannis et al., Ann Int Med. 2004

PI trials

Boceprevir: Poordad et al., NEJM 2011 (non-black cohort)
Telaprevir: Jacobson et al., NEJM 2011

Treatments for HCV: the present

PEG IFN + RBV + TEL/BOC

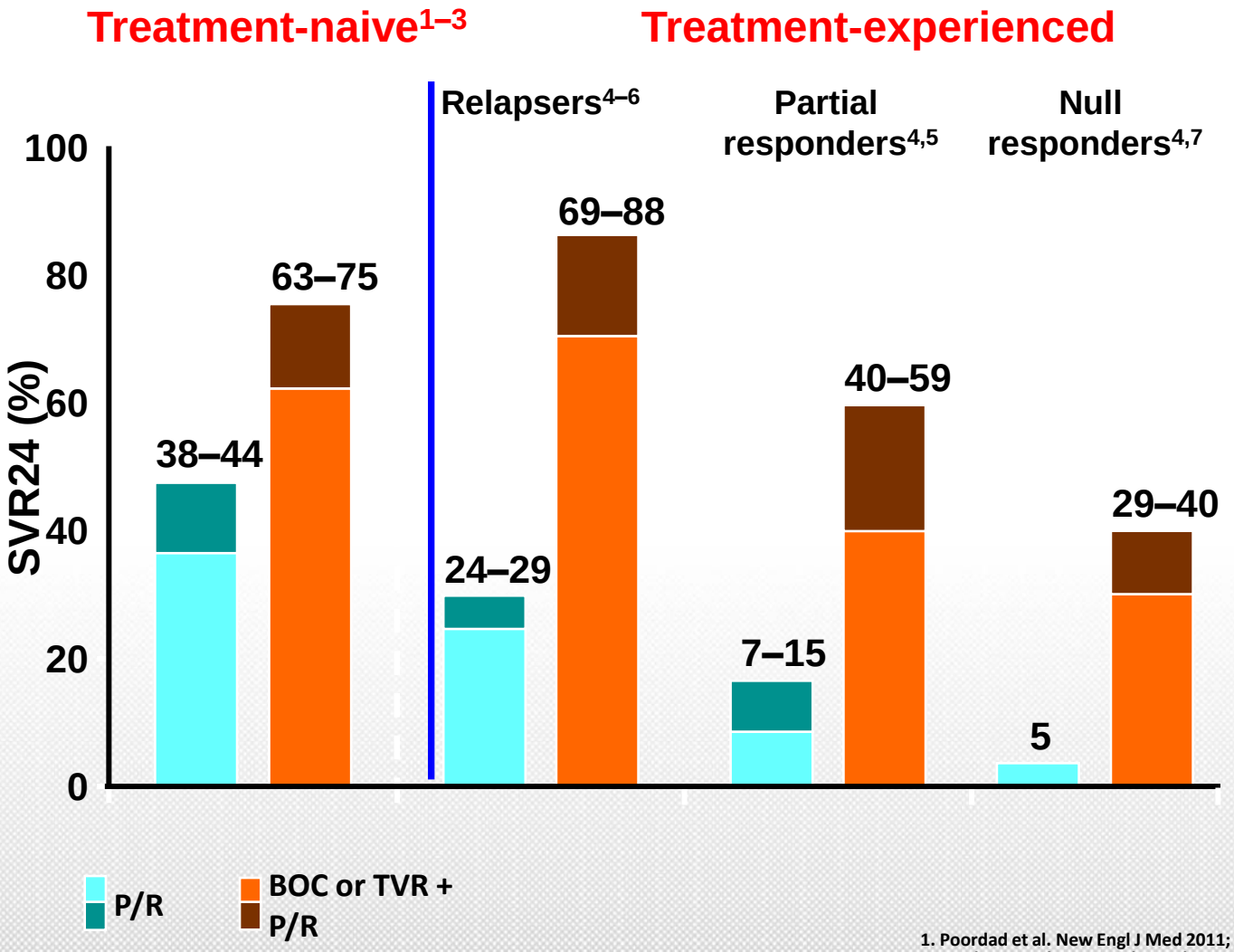
(low potency low genetic barrier less convenience more side effects)

- New standard of care efficacy related to PEG + RBV backbone :
  - 63-88% naive & relapsers
  - < 50% in partial & null response
- Increased response rate and shorter Tx duration than PEG+RBV
- Several challenges (AE, DDI, complex schedules, adherence, resistance)

Approved drugs for the treatment of chronic hepatitis C (2011)

Medication	Dosing
Pegylated interferon α-2a (Pegasys®)	180 µg once weekly
Pegylated interferon α-2b (PEGIntron ®)	1.5 µg/kg once weekly
Interferon α-2a (Roferon®)	3 - 4.5 Mill IU three times weekly
Interferon α-2b (Intron A®)	3 Mill IU three times weekly
Consensus Interferon (Infergen®)	9 µg three times weekly
Ribavirin (Copegus®) Ribavirin (Rebetol®)	800 - 1200 mg daily (200 mg or 400 mg tablets) 600 - 1400 mg daily (200 mg capsules or solution)
Boceprevir (Victrelis®) Telaprevir (Incivek®, Incivo®)	800 mg (4 x 200 mg capsules) every 7-9 hours 750 mg (2 x 375 mg tablets) every 7-9 hours* *3 x 375 mg every 12 hours is as effective in treatment-naïve patients (Buti 2012)

Addition of BOC or TVR to PegIFN/RBV improves SVR in G1 Patients



BOC = boceprevir; P/R = peginterferon/ribavirin; TVR = telaprevir

1. Poordad et al. New Engl J Med 2011; 364: 1195–206;
2. Jacobson et al. New Engl J Med 2011; 364: 2405–16;
3. Sherman et al. New Engl J Med 2011; 365: 1014–24;
4. Zeuzem et al. New Engl J Med 2011; 364: 2417–28;
5. Bacon et al, New Engl J Med 2011; 364: 1207–17;
6. Flamm et al. Clin Gastroenterol Hepatol 2013; 11: 81–87;
7. Bronowicki et al. EASL 2012; abstract 11

AASLD/IDSA HCV guidelines recommended regimen

	G1	G2	G3	G4	G 5,6
NAIVE/ RELAPSER	SOF + PegIFN + RBV x 12 weeks (I, B)	SOF + RBV x 12 weeks (I, B)	SOF + RBV x 24 weeks (I, B)	SOF + PegIFN + RBV x 12 weeks	SOF + PegIFN + RBV x 12 weeks
IFN inelegible	SOF + RBV x 24 weeks (I, B) SOF + SMV ± RBV x 12 weeks (IIa, C)			SOF + RBV x 24 weeks	?
EXPERIENCED	SOF + SMV ± RBV x 12 weeks (IIa, C)	SOF + RBV x 12 weeks (I, B)	SOF + RBV x 24 weeks (I, B)	SOF + PegIFN + RBV x 12 weeks	SOF + PegIFN + RBV x 12 weeks
IFN inelegible				SOF + RBV x 24 weeks	?

NOT recommended
PegIFN + RBV x 24-48 weeks

http://www.hcvguidelines.org/

Global costs of HCV Gt1 therapy in naïves (assuming treatment of F2 to F4)

Cost	PegIFN/ RBV 48 wks	BOC/ TPV + P/R 36-48 wks	SFBV + P/R 12 wks	SMPV+ P/R 12 wks	SFBV + RBV 24 wks	SFBV + SMPV ± RBV 12 wks
drugs	6-9.000	25-30.000	66.000	44.000	121.000	100.000
monitoring	8.000	10-12.000	4.000	4.000	6.000	5.000
EPO, G-CSF, blood tx, others	1.000	20-25.000	500	500	≈ 0	≈ 0
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Future HCV treatment strategies

Peg IFN a Containing Regimens

Phase III

2nd. Generation PI Triple

Faldaprevir
Simeprevir

NUC Triple

Sofosbuvir

triple quadruple regimens

- Asunaprevir (2nd gen PI)
- MK 5172 (3rd gen PI)
- Daclatasvir (1st gen NS5A)
- Asunaprevir (2nd gen PI) + Daclatasvir
- GS 5885 (NS5A) + GS59451 (PI)

2013 2014 2015 2016 2017

IFN free regimens

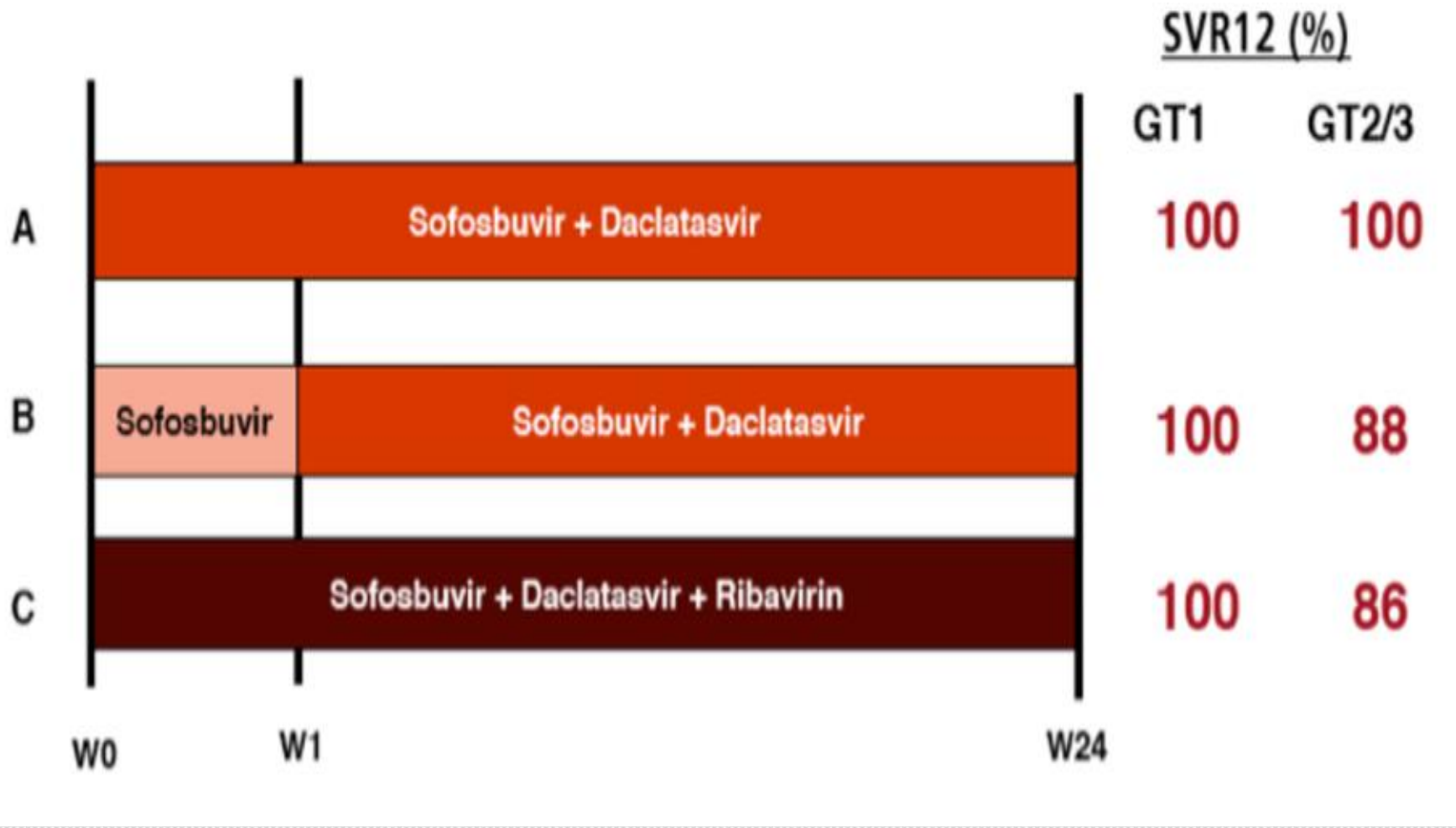
Phase III

Sofosbuvir + RBV

HCV G2 & G3 (?)

- **ABT45o/r (3rd g PI) + ABT 267 (NS5A) + ABT 333 (NNUC) + RBV**
- **Faldaprevir (3rd g PI) + BI 207127(NNUC) + RBV**
- **Simeprevir (3rd g PI) + Sofosbuvir (NUC) + RBV**
- **Daclatasvir(NS5A) + Sofosbuvir (NUC) + RBV**
- **Ledipasvir (NS5A) + Sofosbuvir (NUC) + RBV**
- **Asunaprevir (2nd gen PI) Daclatasvir (NS5A) + GS 791385**

Dual Combination : Daclatasvir (NS5A) +Sofosbuvur (Nuc) ± RBV



Sulkowski MS et al EASL 2012,

Goal of antiviral therapy

The goal of antiviral therapy is to cure hepatitis C via a sustained elimination of the virus. A sustained elimination of HCV is achieved if the HCV RNA remains negative six months after the end of treatment (sustained virological response, SVR).

Follow-up studies document that more than 99% of patients who achieve an SVR remain HCV RNA negative 4-5 years after the end of treatment and no signs of hepatitis have been documented (Manns 2008, Swain 2010).

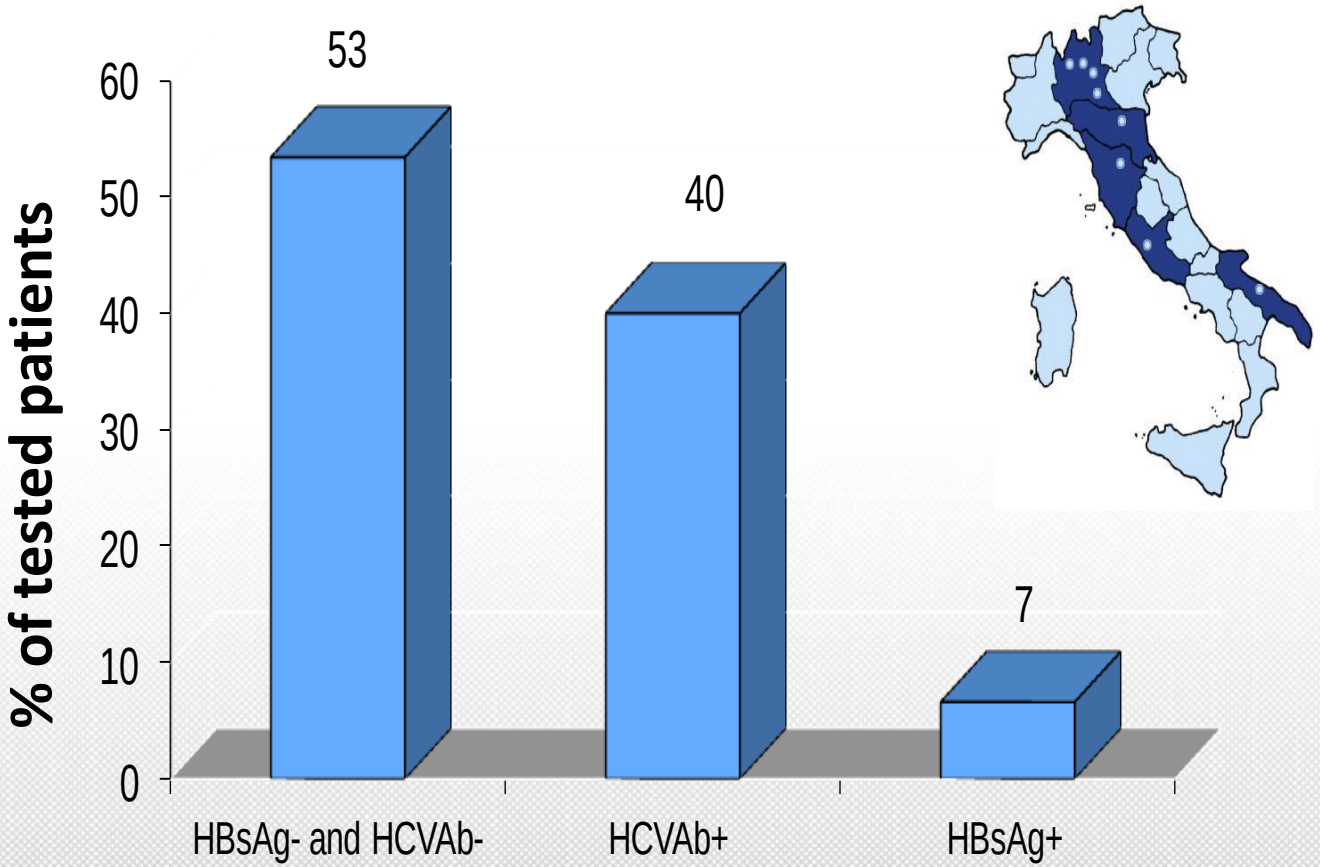
Importantly, long-term benefits of SVR are the reduction of HCV-related hepatocellular carcinoma and overall mortality (Backus 2011, Veldt 2007, van der Meer 2013).

In 2011, the FDA accepted SVR-12 as endpoint for future trials because HCV relapse usually occurs within the first 12 weeks after the end of treatment. However, virologic relapses at later time points may appear in rare cases (Lawitz 2012).

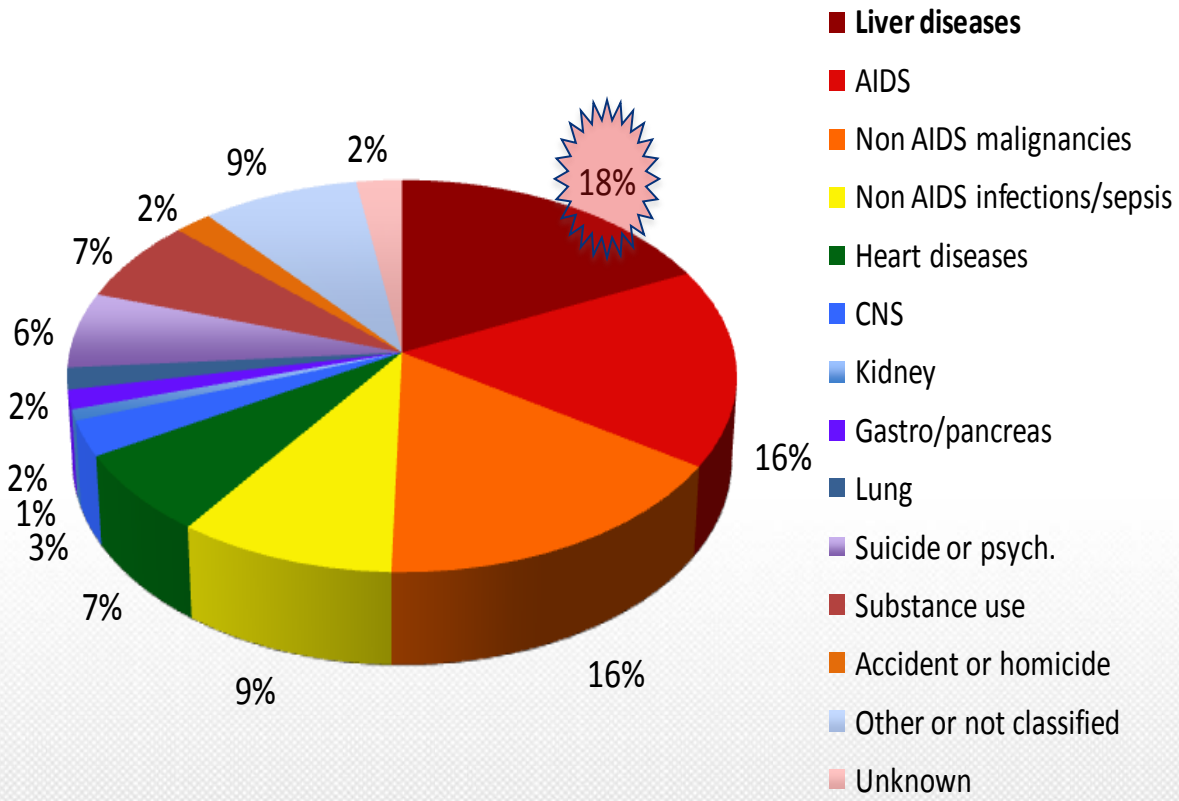
In addition to liver disease, several other hepatic manifestations such as cryoglobulinemia, non-Hodgkin'slymphoma, membrano-proliferative glomerulo nephritis or porphyria cutanea tarda have been reported in the natural history of hepatitis C virus infection. Antiviral treatment may improve symptoms even if an SVR is not acheived. On the other hand, antiviral therapy may worsen extrahepatic manifestations (Pischke 2008, Zignego 2007).

Co-infezioni

Epidemiology
Prevalence of hepatitis markers in the MASTER observational database (N=9098)



Epidemiology
Causes of death in the Swiss HIV Cohort study 2005–2009



Ruppik M. et al. CROI 2011; Boston, MA, USA. Poster 789

Clinical Management and Treatment of Chronic HCV Co-infection in HIV-positive Persons

In persons with chronic HCV, ART initiation is recommended when CD4 cell counts drop below 500 cells/µL. Stopping ART has been associated with enhanced risk for AIDS and non-AIDS related events; indeed, the risk for non-AIDS events was particularly enhanced for persons with hepatitis co-infection

EACS october 2013

Patient Population	Recommended Regimens	Alternative Regimens	Regimens Not Recommended
Treatment-naive-patients and prior relapsers *	**Interferon eligible:** Sofosbuvir + ribavirin + peginterferon for 12 w **Interferon ineligible:** Sofosbuvir + ribavirin for 24 w Sofosbuvir + simeprevir + ribavirin for 12 w Note: When coadministered with ART, simeprevir should be used only with agents with which it does not have significant interactions: abacavir, enfuvirtide, lamivudine, maraviroc, raltegravir, rilpivirine, tenofovir#	**Interferon eligible:** Simeprevir + ribavirin + peginterferon for 24 w† **Interferon ineligible:** None Note: When coadministered with ART, simeprevir should be used only with agents with which it does not have significant interactions: abacavir, enfuvirtide, lamivudine, maraviroc, raltegravir, rilpivirine, tenofovir#	Peginterferon +ribavirin ± telaprevir or boceprevir for 24 to 48 w Monotherapy with peginterferon, ribavirin or a DAA
Treatment-experienced patients with prior nonresponse to peginterferon + ribavirin	Sofosbuvir + simeprevir ± ribavirin for 12 w Note: When coadministered with ART, simeprevir should be used only with agents with which it does not have significant interactions: abacavir, enfuvirtide, lamivudine, maraviroc, raltegravir, rilpivirine, tenofovir#	**Interferon eligible:** Sofosbuvir + ribavirin + peginterferon for 12 w **Interferon ineligible:** Sofosbuvir + ribavirin for 24 wks	

Recommended dosing: sofosbuvir 400 mg once daily; simeprevir 150 mg once daily. Dosing of ribavirin is weight based: 1000 mg (< 75 kg) to 1200 mg (> 75 kg) daily. Peginterferon is dosed weekly according to the package insert.
*Relapsers are patients who have achieved an undetectable HCV RNA during a prior treatment course of peginterferon/ribavirin and relapsed subsequently.
†This regimen may be considered only in patients with genotype 1b infection or in patients with genotype 1a infection in whom the Q80K mutation is not detected at baseline.#Interactions between simeprevir and newer antiretrovirals may not have been evaluated.

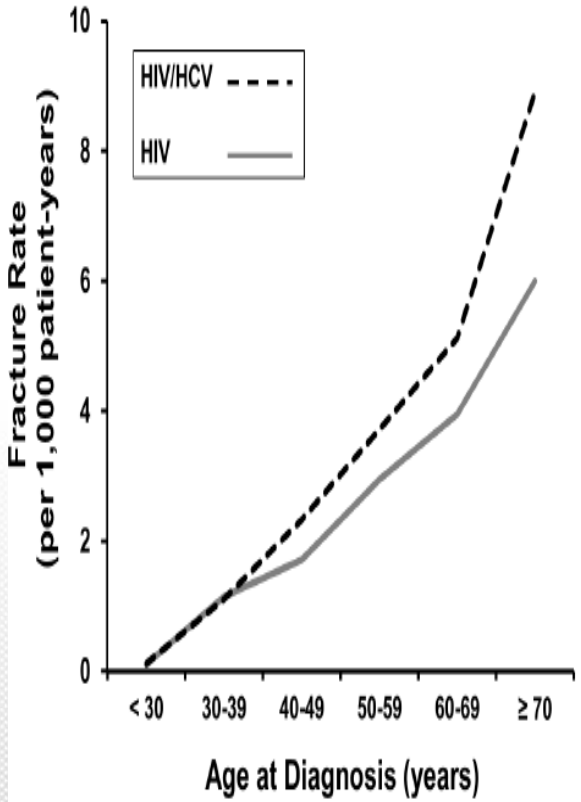
AASLD/IDSA Recommended Regimens for HCV Treatment of HIV/HCV-Coinfected Patients Infected With Genotype 1 HCV

HCV Genotype	Recommended Regimens	Alternative Regimens	Regimens That Are Not Recommended
2	Sofosbuvir + ribavirin for 12 wks*	Treatment naive and prior relapsers†: ▪None Interferon eligible prior nonresponders to peginterferon + ribavirin: ▪Sofosbuvir + ribavirin + peginterferon for 12 wks	▪Peginterferon + ribavirin ±telaprevir or boceprevir for 24 to 48 wks ▪Monotherapy with peginterferon, ribavirin or a DAA
3	Sofosbuvir + ribavirin for 24 wks		
4	▪Interferon eligible: Sofosbuvir + peginterferon + ribavirin for 12 wks ▪Interferon ineligible: Sofosbuvir + ribavirin for 24 wks	None	
5 or 6	Sofosbuvir + peginterferon +ribavirin for 12 wks		

AASLD/IDSA Recommended Regimens for HCV Treatment of HIV/HCV-Coinfected Patients Infected With Genotype non-1 HCV

Hepatitis C Co-infection and Severity of Liver Disease as Risk Factors for Osteoporotic Fractures among HIV-infected Patients†

NM Maalouf[1*], S Zhang[1], H Drechsler[1,2], GR Brown[1,2], P Tebas[3], R Bedimo[1,2]



	HR for Fracture in Entire Cohort (95% CI; p-value)	HR for Fracture in HCV/HIV co-infected (95% CI; p-value)	HR for Fracture in HIV mono-infected (95% CI; p-value)
Controlling for APRI score			
HCV +ve	1.30 (1.09 – 1.54; p= 0.003)	N/A	N/A
APRI score			
Per unit change	1.006 (1.001 – 1.011; p=0.013)	1.008 (1.002 – 1.014; p=0.015)	1.005 (0.99 – 1.02; p=0.5)
0.5–1.49 vs. <0.50	1.08 (0.90 – 1.30; p=0.41)	0.91 (0.71 – 1.17; p=0.46)	1.26 (0.97 – 1.65; p=0.086)
≥1.50 vs. <0.50	1.61 (1.26 – 2.06; p=0.0002)	1.31 (0.97 – 1.76; p=0.074)	2.40 (1.56 – 3.69; p<0.0001)
≥1.50 vs. 0.5–1.49	1.49 (1.16 – 1.90; p=0.002)	1.44 (1.07 – 1.94; p=0.02)	1.90 (1.19 – 3.01; p=0.007)

J **Bone** Miner Res. 2013 May 15..

Tossicità ossea : conclusioni

- **Dati non omogenei da meta analisi indicative di un rischio aumentato di riduzione della BMD nel paziente con HIV/HCV > HIV+ ≥HIV-**
- **Assenza di meta analisi mirate a identificare il ruolo di molecole specifiche sulla riduzione del danno osseo**

Tossicità renale: conclusioni

- **Meta analisi conclusive di un rischio aumentato di danno renale nel paziente con HIV/HCV > HIV+ >HIV-**
- **Dati conclusivi sull'effetto nefrotossico di tenofovir se pur lieve**
- **Studi in corso (future meta analisi) sull'impatto dello switch da TDF containing a TDF sparing regimen**

Insulin resistance is associated with progression to hepatic fibrosis in a cohort of HIV/HCV co-infected patients

Mark W. Hull[a], Kathleen Rollet[b], Erica E.M. Moodie[c], Sharon Walmsley[d], Joseph Cox[c,e], Martin Potter[f], Curtis Cooper[g], Neora Pick[h], Sahar Saeed[b], and Marina B. Klein[b] the Canadian Co-infection Cohort Study Investigators

Table 2. Multivariate Cox proportional hazards model of factors associated with development of APRI score >1.5 during follow-up (n = 85).

Variables	Adjusted Hazard Ratio	95% Confidence Interval
A. Insulin Resistance modeled as HOMA-IR≥2 vs. HOMA-IR < 2		
HOMA–IR > 2	7.72	2.55–23.36
Age (years)	0.98	0.88–1.09
Female Gender	0.85	0.27–2.63
Duration of HCV infection (per year)	1.05	0.99–1.12
BMI ≥25	0.73	0.24–2.28
Baseline APRI (ln)	7.92	1.94–32.42
Time updated CD4 cell count (per 100 cells/μL)	0.92	0.81–1.06
Time updated HIV viral load < 50 copies/mL	0.74	0.24–2.29
B. Insulin Resistance modeled with HOMA-IR as a continuous variable		
HOMA–IR (log-base 2)	1.48	1.12–1.86
Age (years)	1.00	0.91–1.09
Female Gender	0.82	0.26–2.55
Duration of HCV infection (per year)	1.02	0.97–1.10
BMI ≥25	0.83	0.29–2.34
Baseline APRI (ln)	5.20	1.31–20.69
Time updated CD4 cell count (per 100 cells/μL)	0.92	0.79–1.08
Time updated HIV viral load <50 copies/mL	0.77	0.20–2.99

The population (n = 85) is defined as those with no baseline history of fibrosis or ESLD and confirmed presence of HCV RNA. Median follow-up period was 1.4 years (IQR: 1.0, 1.7 years). Abbrev. APRI, AST-to-platelet ration index; BMI, body mass index; HOMA-IR, homeostasis model for assessment of insulin resistance.

50 YEARS ICAAC
BOSTON | SEPTEMBER 12–15, 2010
H 1673

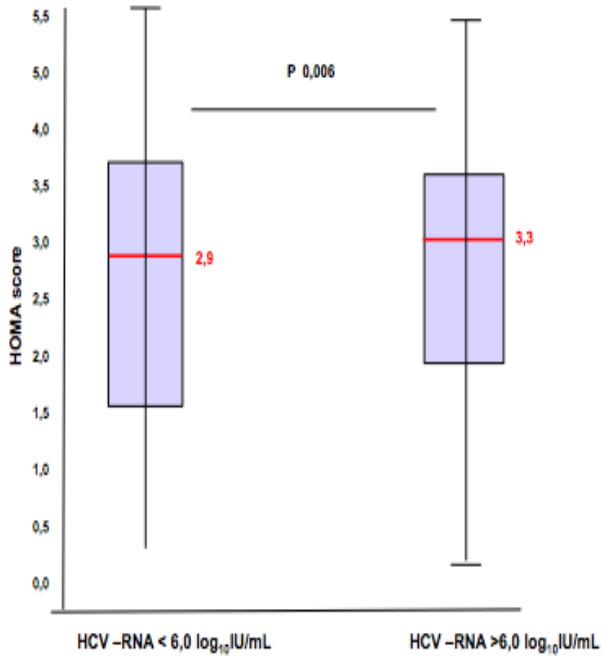
Insulin Resistance is Associated with Hepatitis C Viremia and Reduces the Success of Peginterferon alfa2a plus Ribavirin in HIV/HCV Co-infected Patients

P. Nasta,, F. Gatti, F. Borghi M. Mendeni, K. Prestini and G. Carosi Prof.

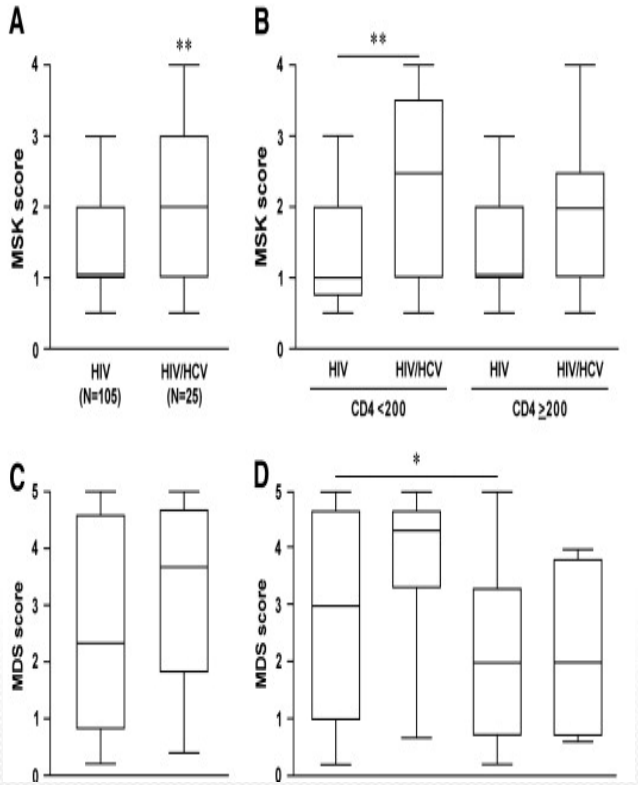
Institute of Infectious and Tropical Diseases, University of Brescia, Italy

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Figure 2: HOMA score in patients with HCV-RNA load > or < 6,0 log_{10} IU/mL



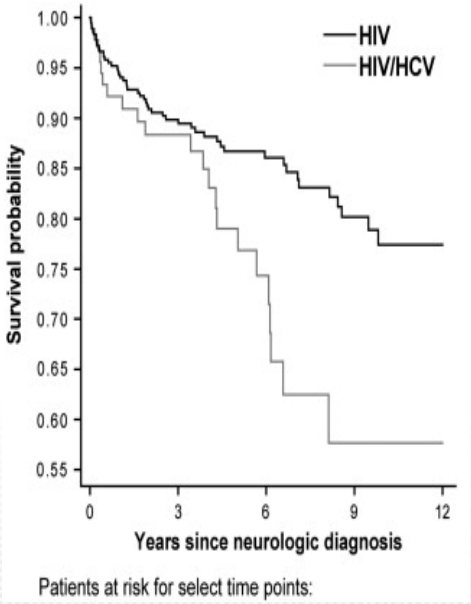
Neurocognitive disorders



Hepatitis C virus co-infection increases neurocognitive impairment severity and risk of death in treated HIV/AIDS

Pornpun Vivithanaporn[a,b], Krista Nelles[a], Leah DeBlock[a], Stephen C. Newman[c], M. John Gill[d,e,f], Christopher Power[a,c,f]

Journal of the Neurological Sciences
Volume 312, Issues 1–2, 15 January 2012, Pages 45–51



The presence of HCV co-infection among HIV-infected individuals increased neurologic disease burden and risk of death. This underscores HCV's capacity to affect the nervous system and survival of HIV-infected persons

Vivithanaporn P, et al. J Neurol Sci. 2012; 312:45–51

Liver toxicity and fibrosis progression

Drug (Reference)	Severe ALT Elevation* (%)	Increased Risk in HCV/HBV Coinfection	Other Groups with High Risk of Hepatotoxicity	Hepatic Failure/ Liver Fatalities	Liver-Related Black Box Warning
NRTIs					
Abacavir ([10])	6%	-	-	Yes[1,2]	Yes[1,2]
Didanosine ([11])	6%	Yes	+HU,+D4T, pregnancy	Yes[2,3]	Yes[2]
Emtricitabine ([12])	2%-5%	-	-	No	Yes[2]
Lamivudine ([13])	3.7%-3.8%	-	-	Yes[2]	Yes[2]
Stavudine ([14])	6%-13%	Yes	+DDI ± D4T, pregnancy	Yes[2,3,4]	Yes[2]
Tenofovir ([15])	4%	-	-	No	Yes[2]
Zidovudine ([16])	3.1%	-	-	Yes[2]	Yes[2]
NNRTIs					
Delavirdine ([17])	4.1%-5.1%	-	-	Yes[5]	No
Efavirenz ([18])	2%-8%	20%	+Other hepatotoxic drugs	Yes[5]	No
Etravirine ([19])	2.6%	Yes	-	Yes[1,5]	No
Nevirapine (20)	5.3%-14%¶	Yes	Higher CD4counts, F>M	Yes[1,3,6]	Yes[1]
Protease inhibitors¶¶					
Atazanavir/ritonavir ([21])	3%-9%	15%	-	No	No
Darunavir ([22])	5.6%-6.9%**	Yes	-	Yes[3]	No
Fosamprenavir/ritonavir ([23])	4%-8%	Possibly	Non-HIV postexposure prophylaxis	No	No
Indinavir ([24])	2.6%-4.9%	-	-	Yes	No
Lopinavir/ritonavir ([25])	3%-11%¶¶¶	Possibly	-	Yes[3]	No
Nelfinavir ([26])	1%-2%***	-	-	No	No
Ritonavir ([27])	5.3%-8.5%	Possibly	-	Yes[3]	No
Saquinavir ([28])	Not provided	Yes	+Rifampin	Unclear	No
Tipranavir/ritonavir ([29])	9.7%	10.3-20.3%	-	Yes[3,6]	Yes
Fusion inhibitors					
Enfuvirtide ([30])	5.3%-6.2%	-	-	No	No
CCR5 blockers					
Maraviroc ([31])	2.4%	Insufficient data	-	Yes[1]	Yes[1]
Integrase inhibitors					
Raltegravir ([32])	4%	27%**	-	No	No

Epatotossicità : Review & expert opinion

- **Jones M, Nunez M. Liver toxicity of antiretroviral drugs.Semin Liver Dis 2012;32:167-76**
- **Puoti M. Moioli MC, Travi G, Rossotti R The burden of liver disease in human immunodeficiency virus-infected patients.**
  Semin Liver Dis,2012 ;32:103-13
- **Ambrosioni J, Negro F, Calmy A. The challenges of HIV-HCV co-infection. Rev Med Suisse . 2012; 8:905-10**
- **Nasta P, Cattelan AM, Maida I,Gatti F,Chiari E,Puoti M and Carosi G on behalf the Italian HIV/HCV coinfection working group. Antiretroviral Therapy in HIV/HCV Co-Infection Italian Consensus Workshop *Advances in Infectious Diseases, 2013, 3, 105-114***

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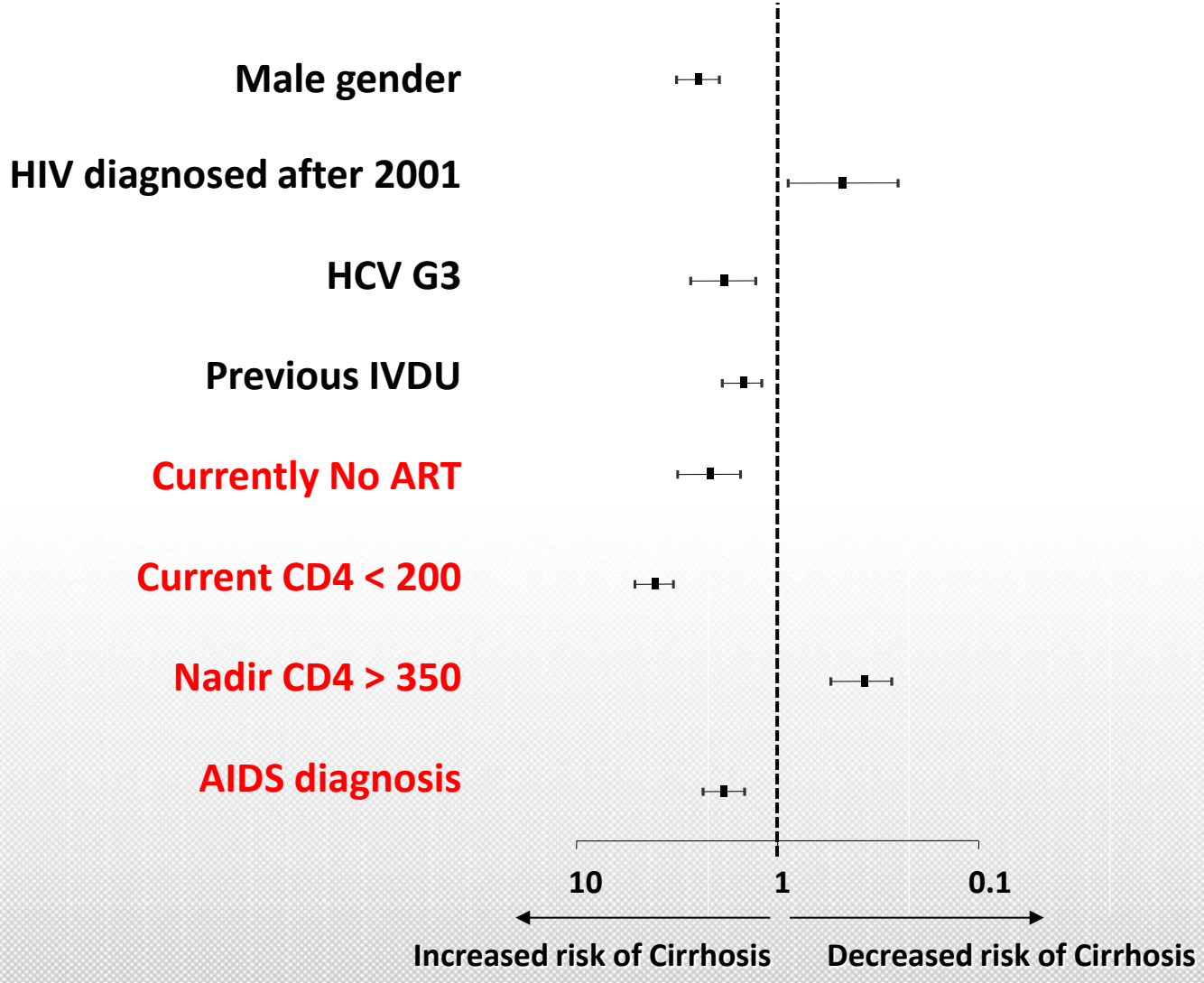
Kivexa

abacavir/lamivudina

Poiché abacavir e ribavirina (RBV) condividono la stessa via di fosforilazione, è stata ipotizzata una possibile interazione intracellulare tra questi farmaci, che potrebbe portare ad una riduzione dei metaboliti fosforilati intracellulari della ribavirina e, come possibile conseguenza, ad una ridotta possibilità di risposta virologica sostenuta (*sustained virological response* - SVR) per l'epatite C (HCV) nei pazienti con infezione concomitante da HCV trattati con interferone pegilato più RBV. In letteratura sono riportati risultati clinici contrastanti sulla co-somministrazione di abacavir e ribavirina. Alcuni dati suggeriscono che i pazienti con infezione concomitante da HIV/HCV in trattamento con terapia antiretrovirale (ART) contenente abacavir possono essere a rischio di un tasso di risposta inferiore alla terapia con interferone pegilato/ribavirina. Deve essere usata cautela quando entrambi i farmaci sono somministrati contemporaneamente (vedere paragrafo 4.5).

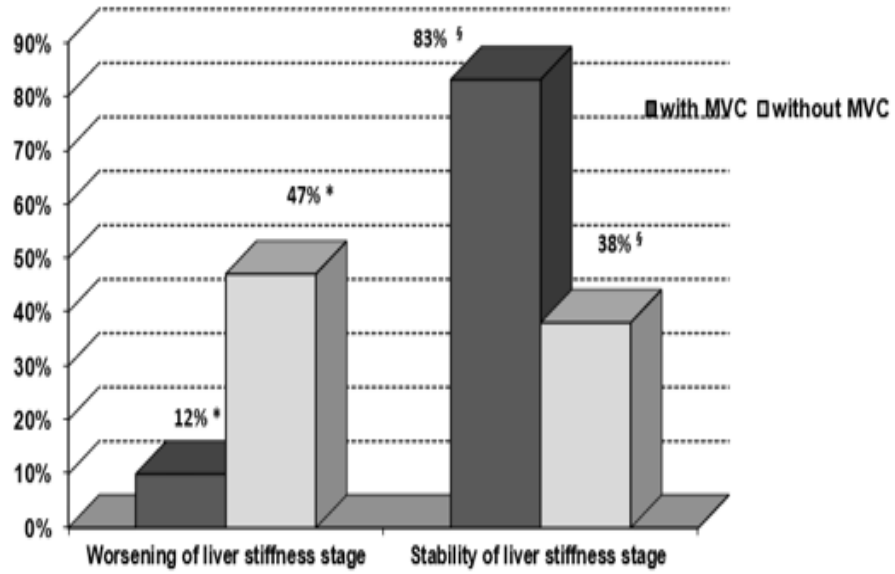
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Factors associated with risk of cirrhosis in HIV/HCV co-infected patients in MASTER cohort

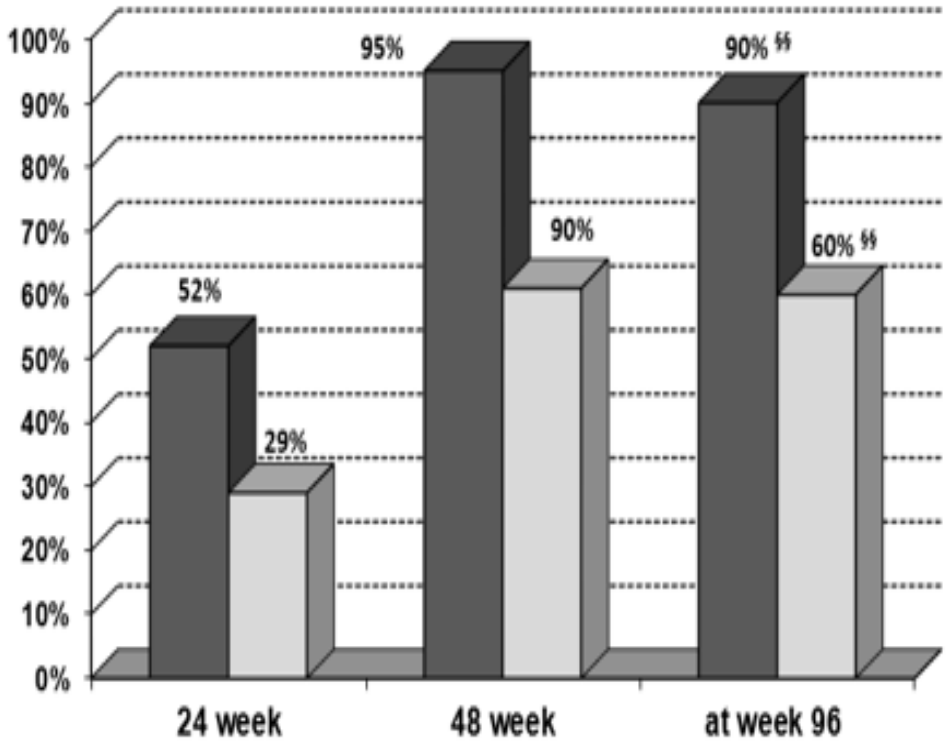


Maraviroc may contribute to reduce the liver stiffness progression when added to atazanavir/r + truvada antiretroivral regimen in HIV/HCV-RNA positive patients with undetctable viral load at baseline

Liver stiffness variation



Hyaluronic acid variation



*[AOR 4.6 (1.1–10.5), p 0.02].

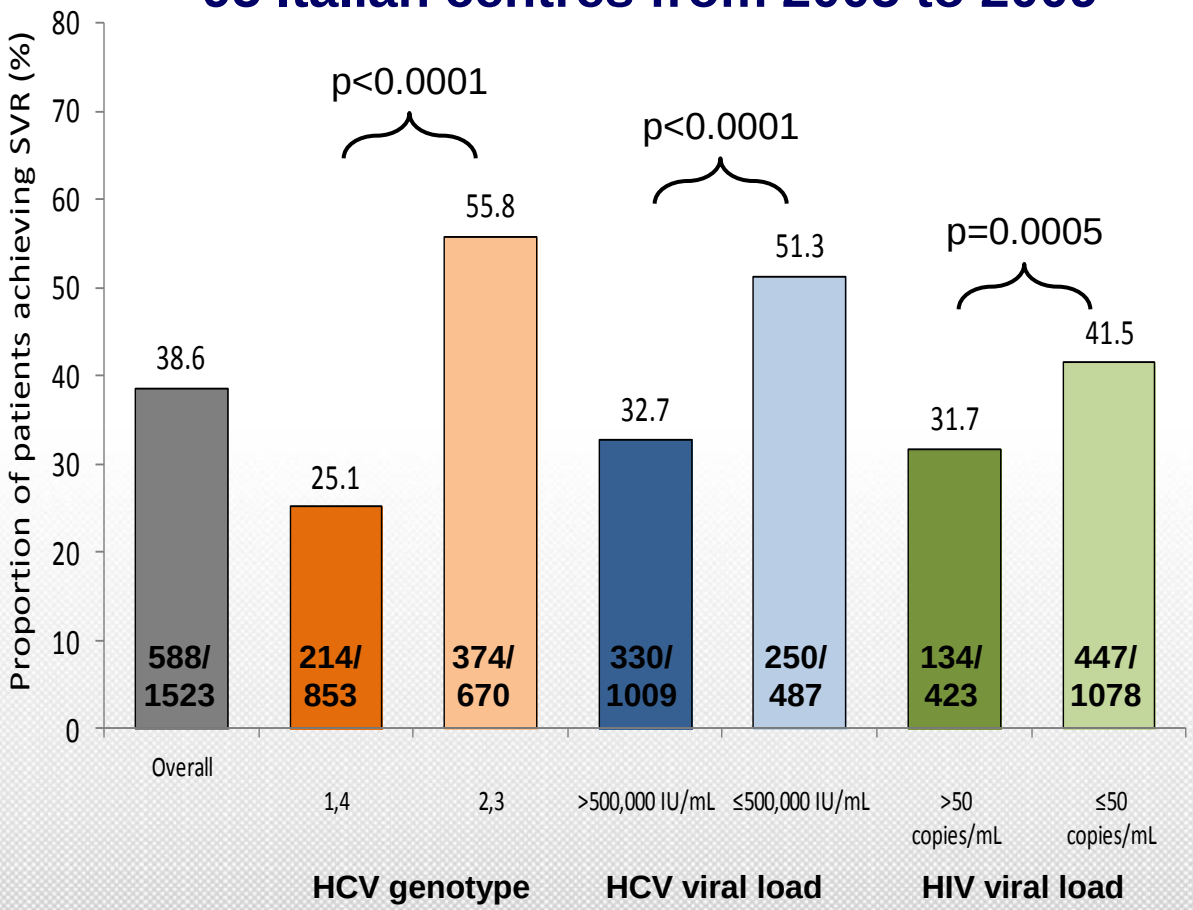
§[AOR 0.01 (0.02–0.7), p 0.002].

[AOR 0.06 (0.005–0.6), p 0.01].

Anti HCV treatment: Opera study: SVR response

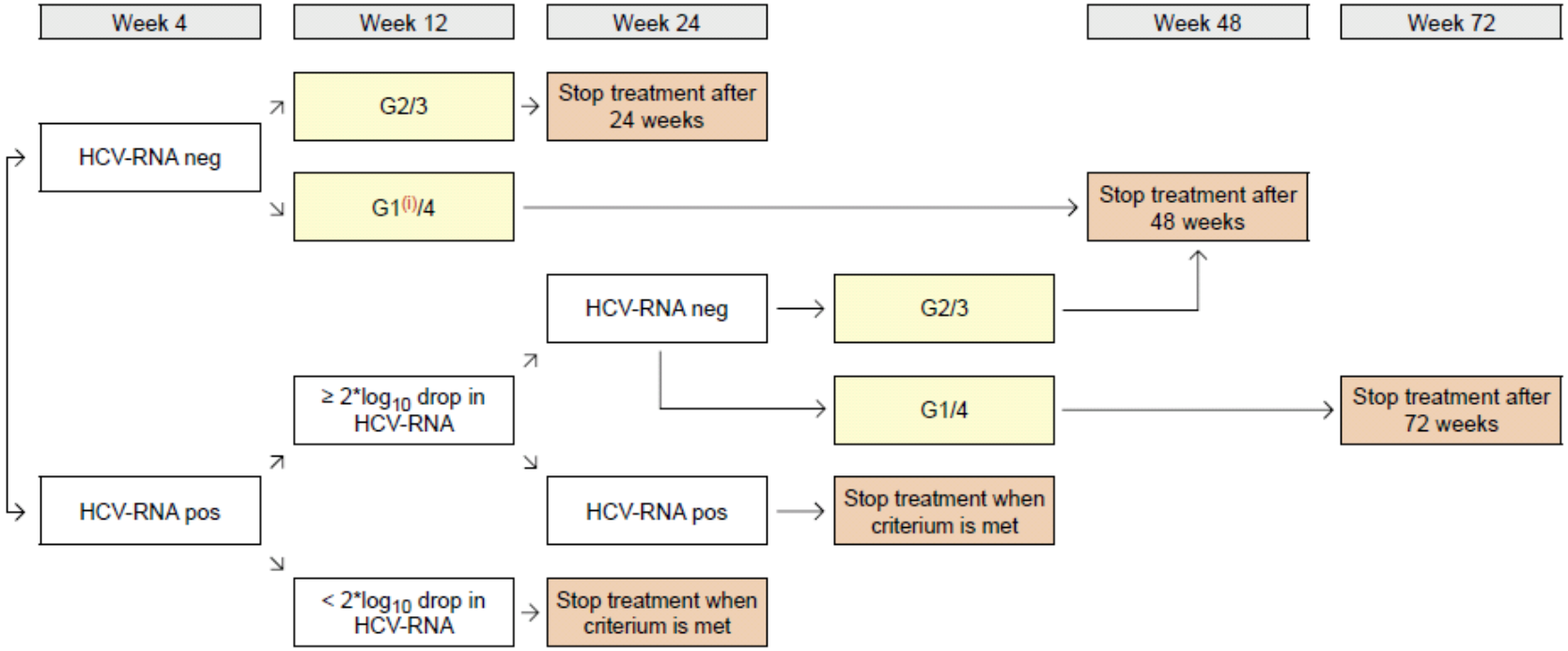
by baseline characteristics from co-infection trials

Italian observational cohort of 1523 HIV/HCV co-infected patients from 95 Italian centres from 2005 to 2009



Puoti M et al. Antivir Ther. 2014; in press

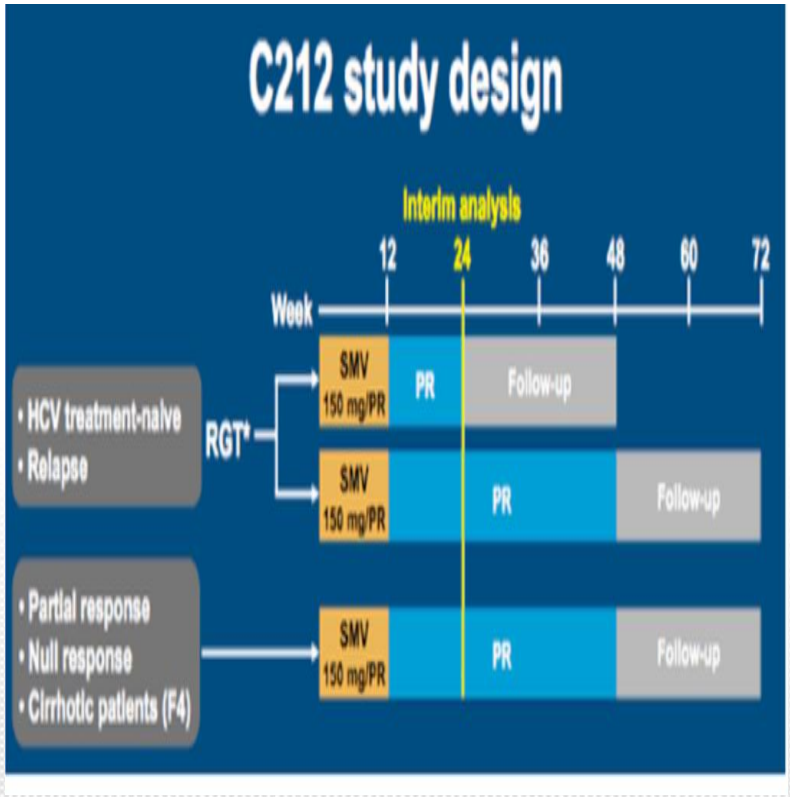
Optimal duration of dual therapy in HIV/HCV not eligible for triple therapy

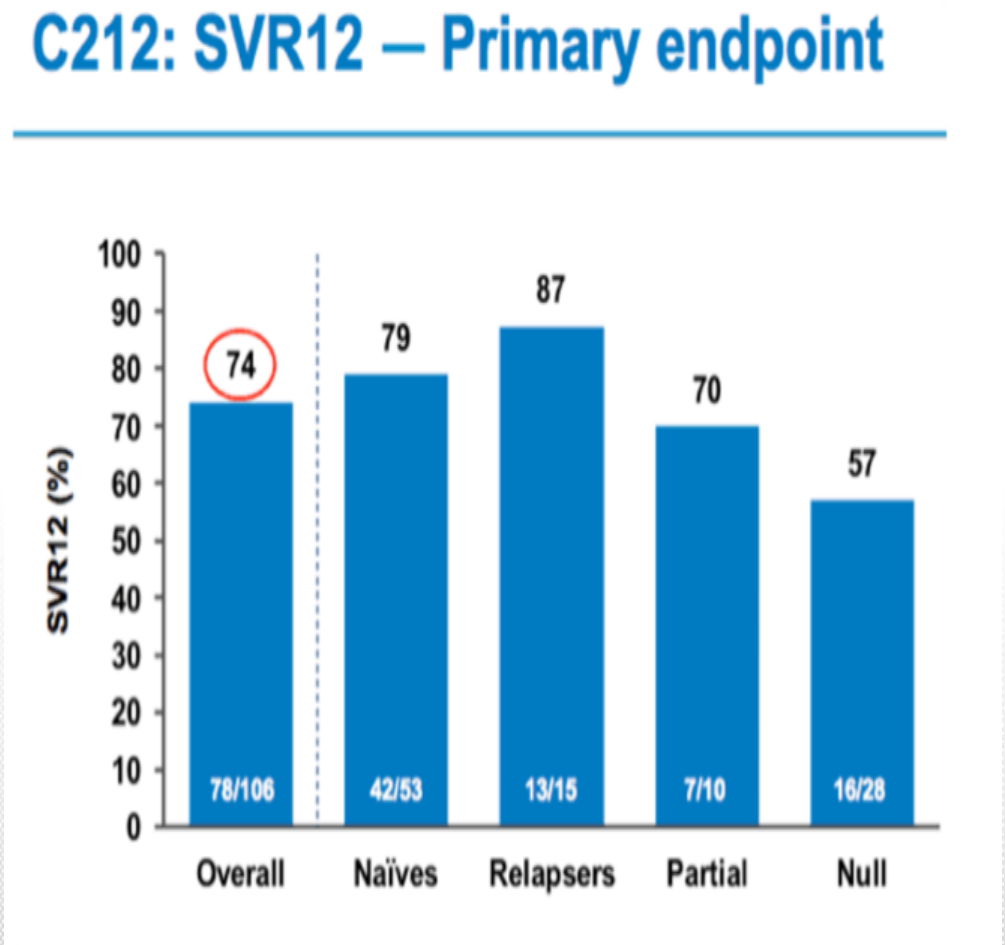


i Where no access to DAAs available or high chances of cure even with dual therapy (favourable IL28B GT, low HCV-RNA and no advanced fibrosis)

EACS october 2013

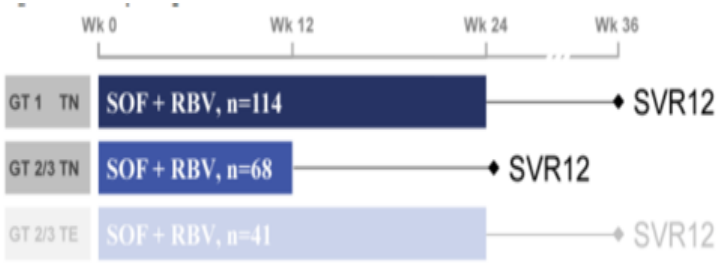
Simeprevir (TMC435) in combination with peginterferon/ribavirin in patients co-infected with HCV genotype-1 and HIV-1: Primary analysis of the C212 study



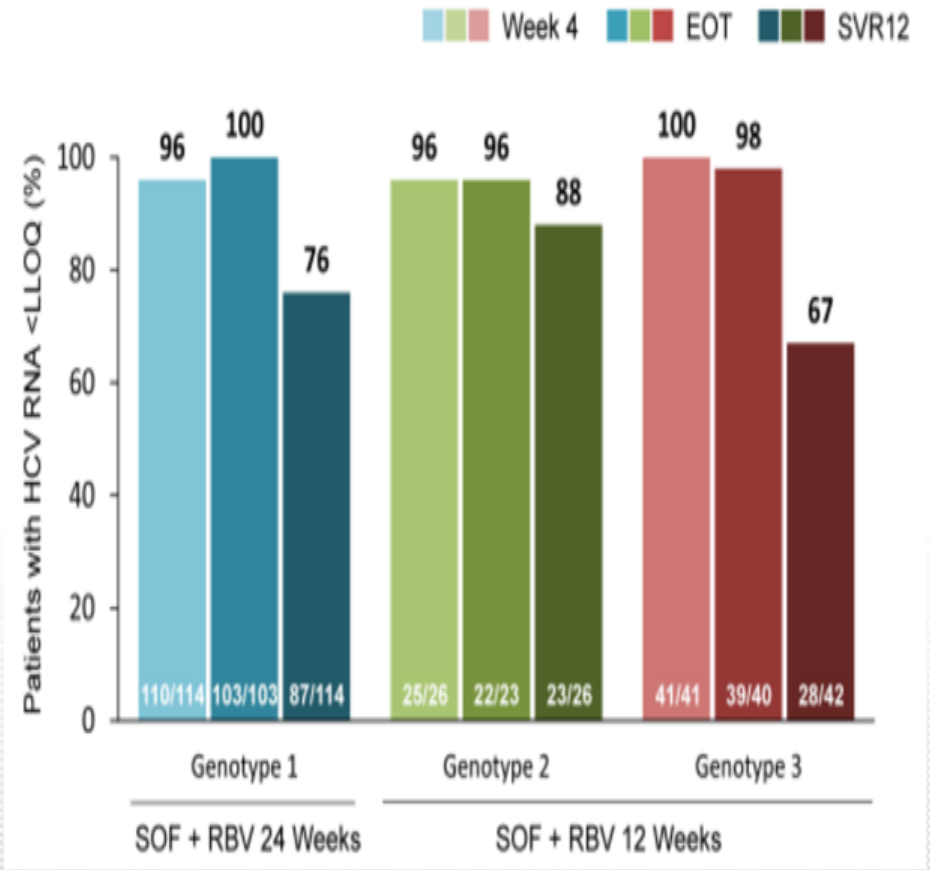


Dieterich D et al, et al. EACS 2013, Abstract P59/5

All-Oral Therapy With Sofosbuvir Plus Ribavirin For the Treatment of HCV Genotype 1, 2, and 3 Infection in Patients Co-infected With HIV (PHOTON-1)



Patients, %	SOF + RBV	
	GT1 TN 24 Weeks (n=114)	GT2/3 TN 12 Weeks (n=68)
AEs	93	84
AEs in ≥ 10% of patients		
Fatigue	36	35
Insomnia	13	21
Headache	14	13
Nausea	16	18
Diarrhea	11	9
Irritability	12	10
URI	11	12
Grade 3–4 AEs	13	10
Serious AEs	7	7
Treatment D/C due to AEs*	3	4
Death	0	1†
Hemoglobin††		
<10 mg/dL	22 (19)	7 (10)
<8.5 mg/dL	2 (2)	1 (1)



Sulkowski M et al.,AASLD 2013 , Abs 212

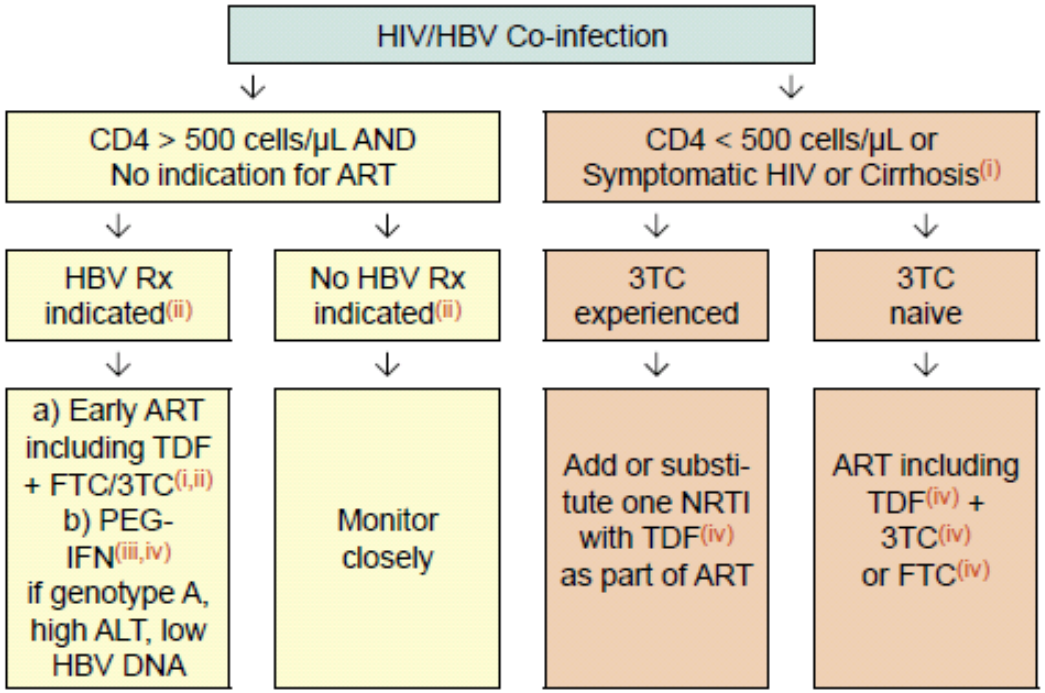
Clinical Management and Treatment of Chronic HBV Co-infection in HIV-positive Persons

HIV-positive persons with HBV and/or HCV co-infection benefit from early ART because liver fibrosis progression is reduced with immune reconstitution and suppression of HIV-VL.

ART initiation with a TDF-based regimen is recommended in all persons with HBV coinfection needing anti-HBV therapy irrespective of CD4 cell count, and in all HBsAg positive persons with less than 500 CD4 cells irrespective of HBV disease status to prevent transition to a more active HBV disease state due to immune suppression

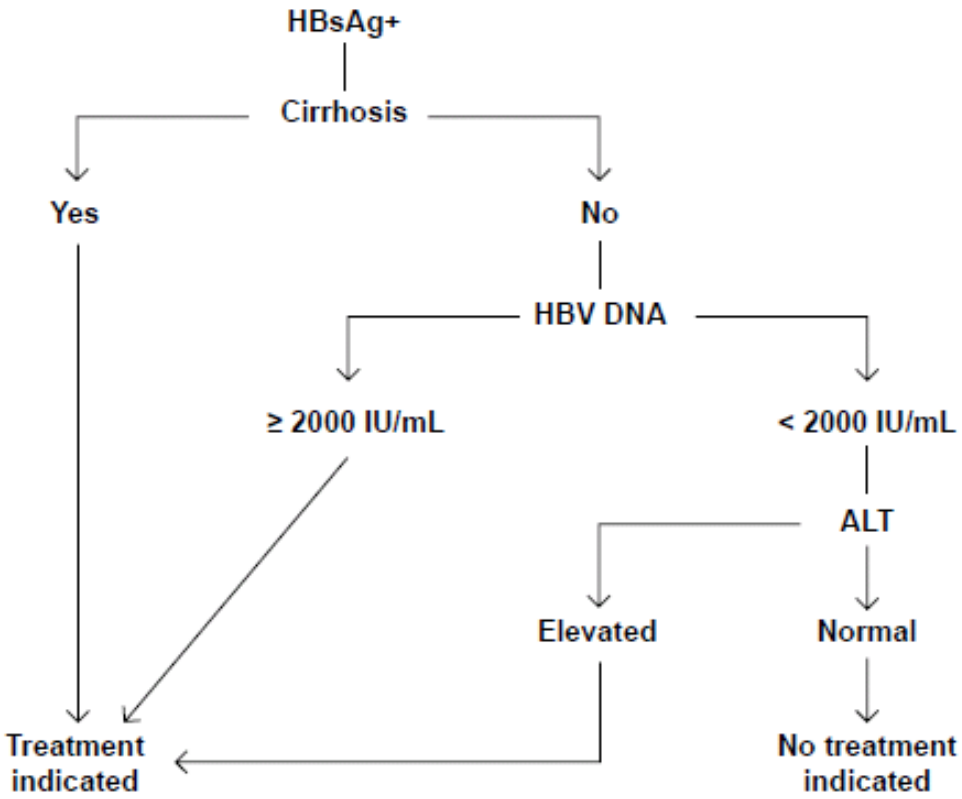
EACS october 2013

Treatment of chronic HBV in HIV/HBV co-infection



EACS october 2013

Assessment of Treatment indications for HBV in Persons with HBV/HIV Co-infection



EACS october 2013

Clinical Management and Treatment of Chronic HBV or HCV Co-infection in HIV-positive Persons

HIV-positive persons require the same measures for the treatment of oesophageal varices, hepatorenal syndrome, hepatic encephalopathy or ascites as HIV-negative persons

EACS october 2013

Liver transplantation

Persons with HCC or a MELD-score > 15*, CD4 cell count > 100 cells/µL and options for efficacious and durable ART should be evaluated for liver transplantation (OLTX). OLTX outcomes in persons with HIV/HBV co-infection are particularly promising, whereas post-transplant survival in persons with HIV/HCV co-infection has been somewhat lower than in persons with HCV mono-infection mainly due to the complicated course of HCV re-infection after transplantation.

EACS october 2013

Grazie per l'attenzione !