Access to care and response to HCV treatment in Europe

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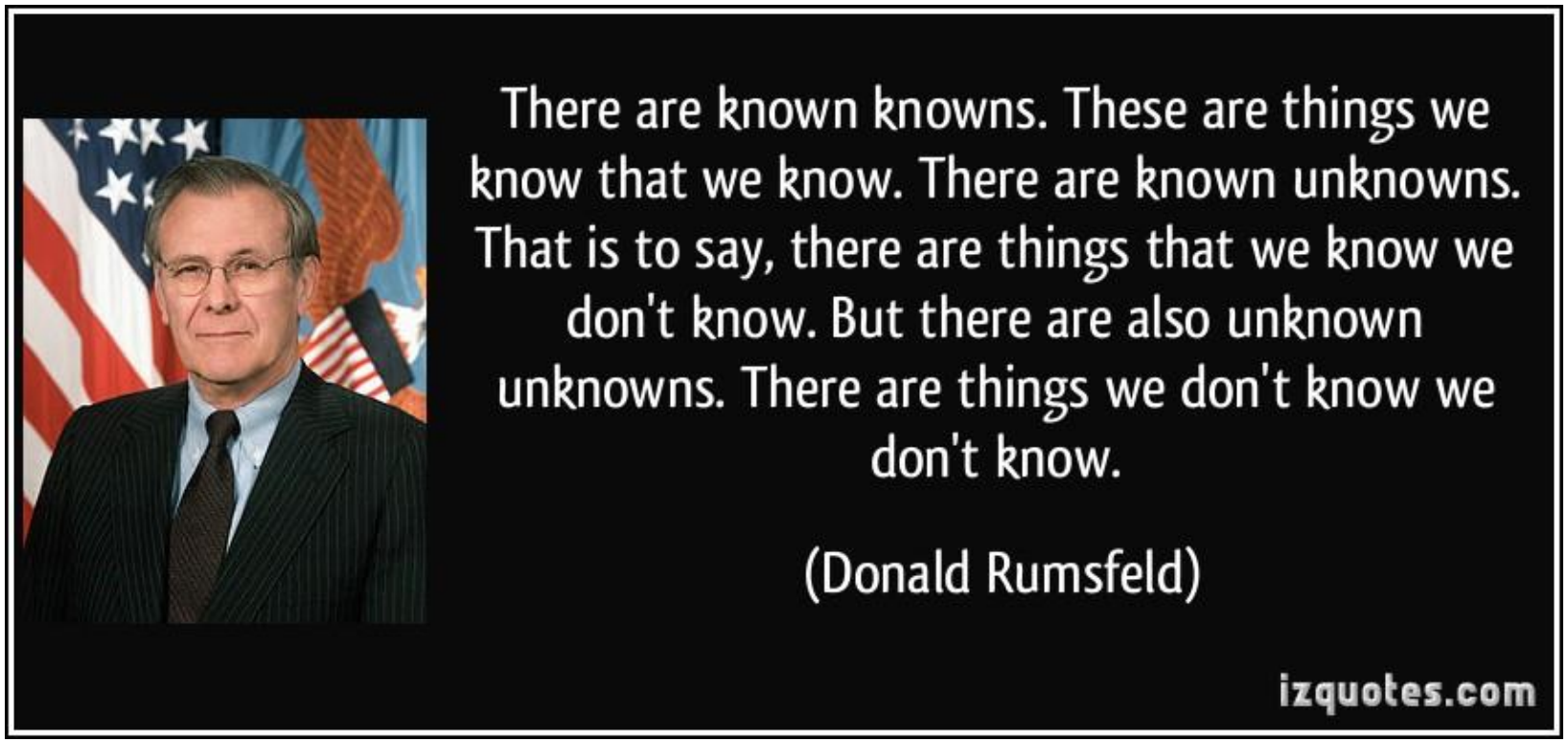
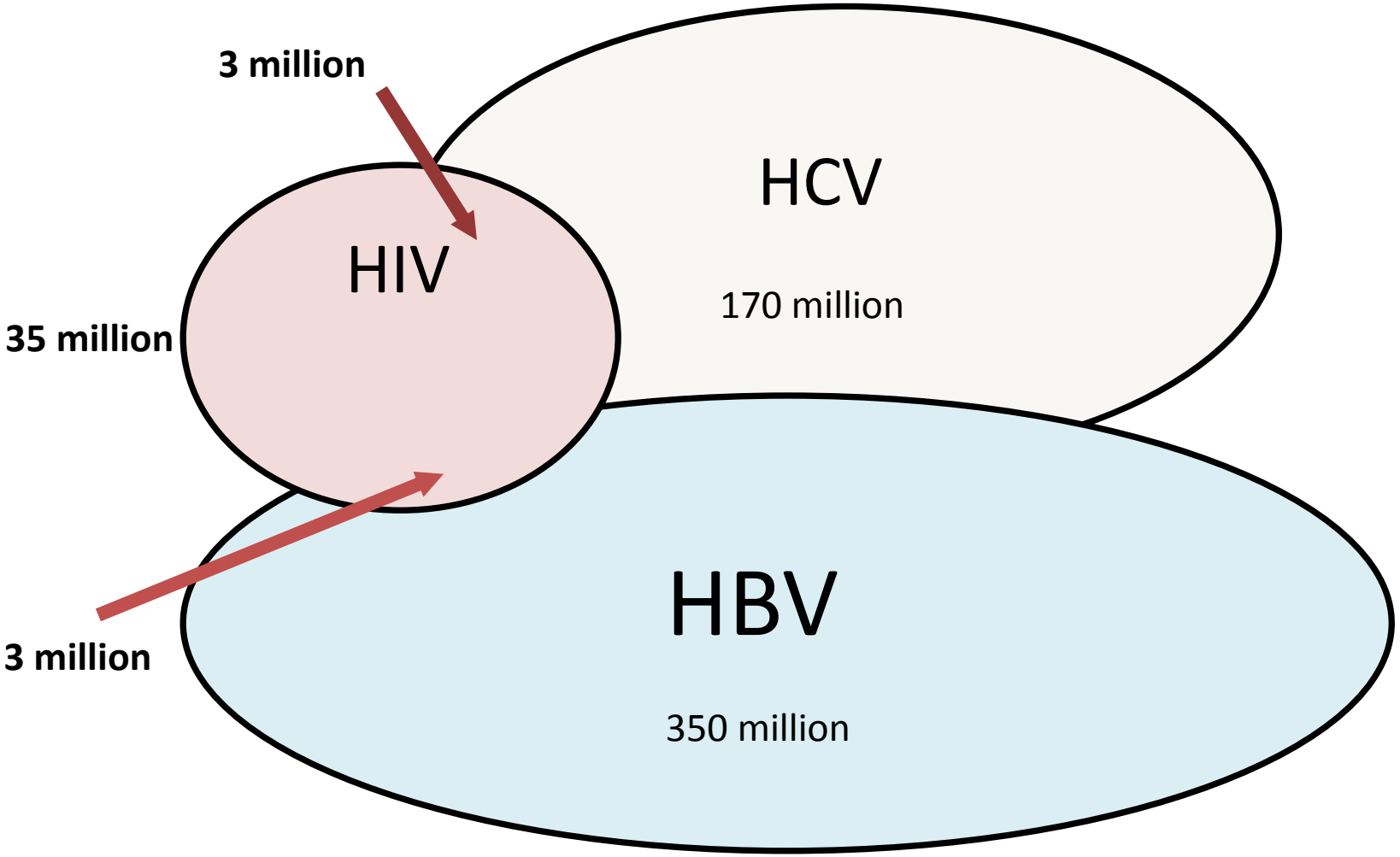
Access to care and response to HCV treatment in Europe……



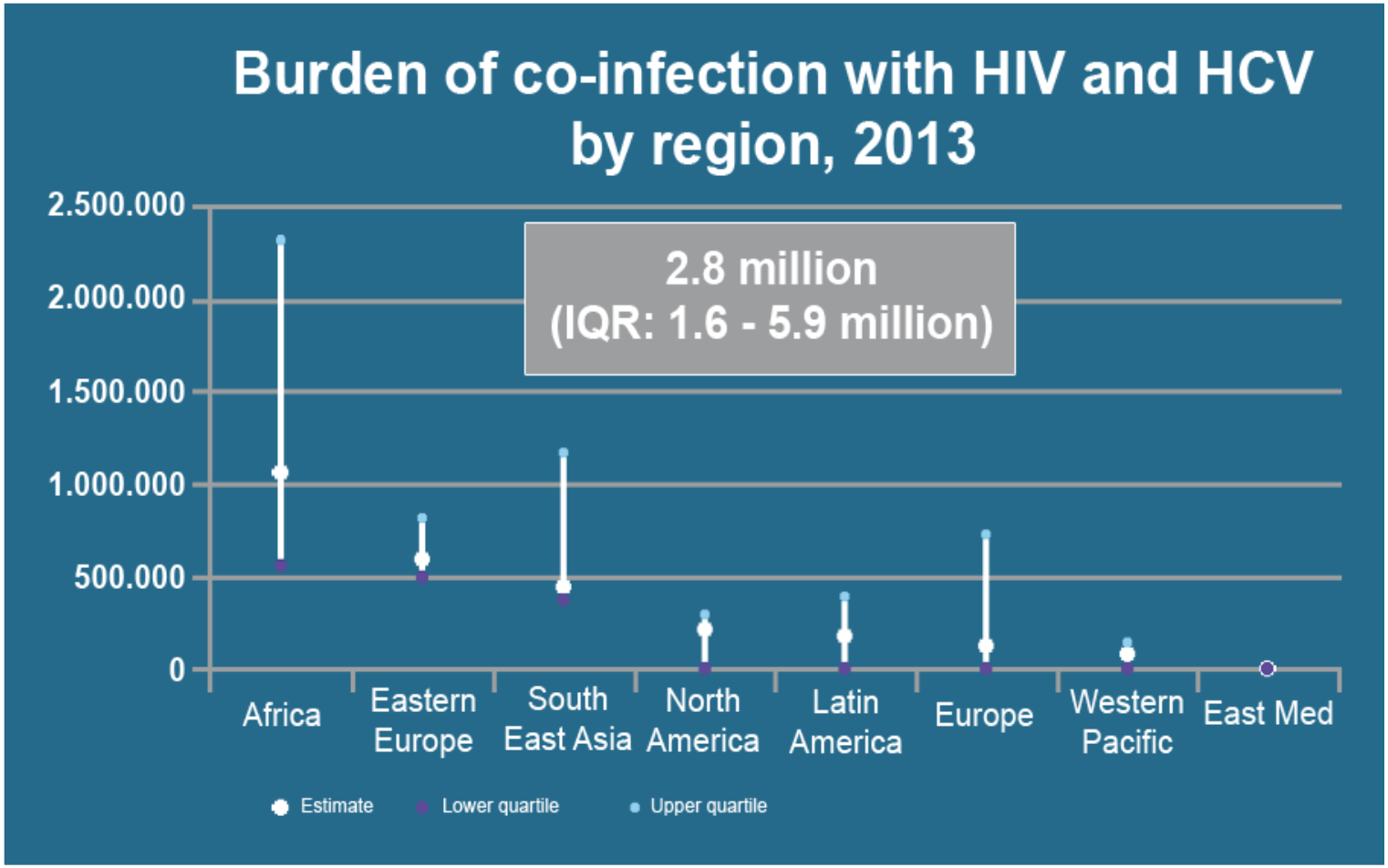
Overview

- HCV/HIV co-infection in Europe
- Current guidelines and data on current Rx
- Who should we Rx, and who should we prioritise
- Access to DAAs

Overlapping epidemics

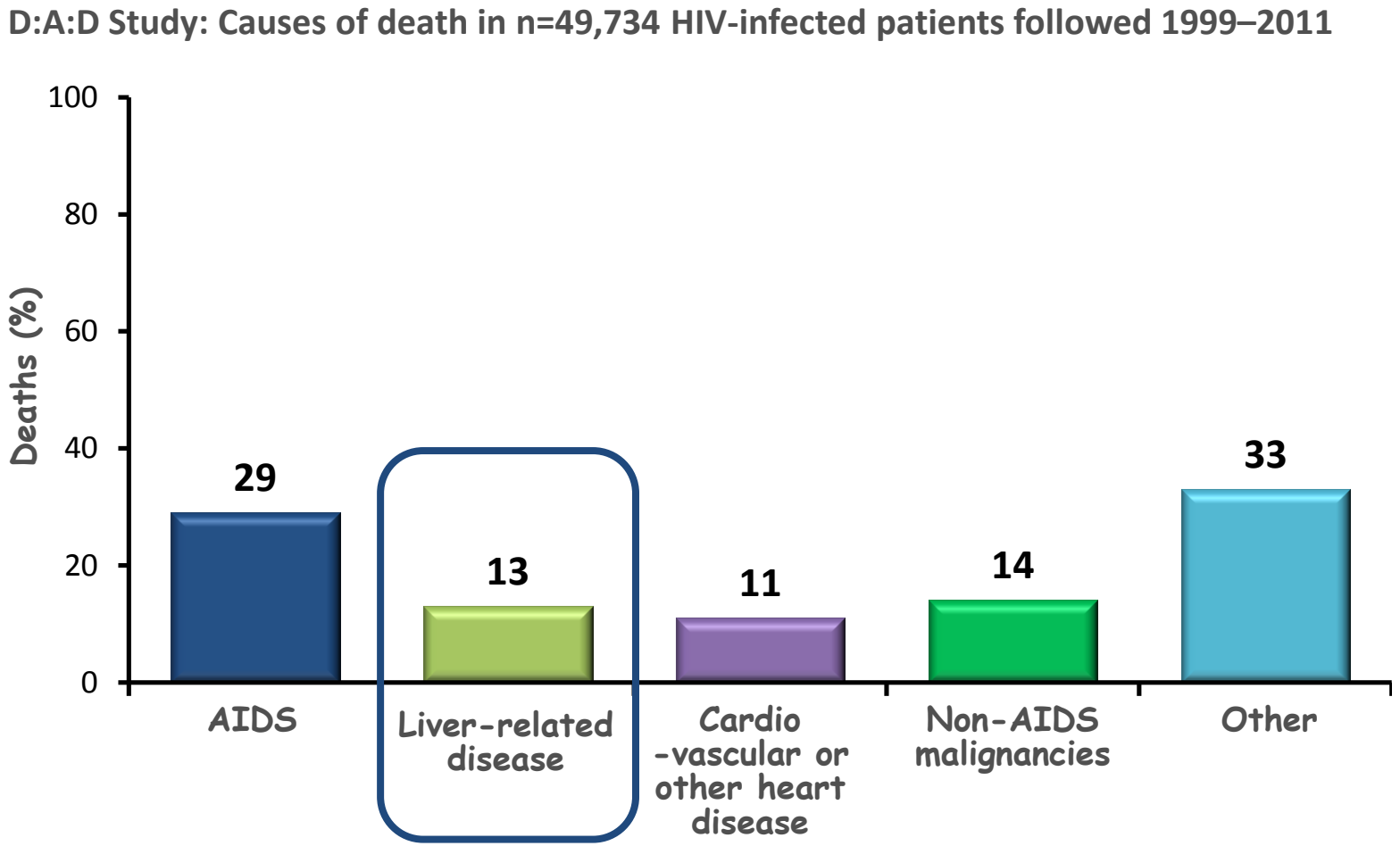


Burden of HCV in HIV populations



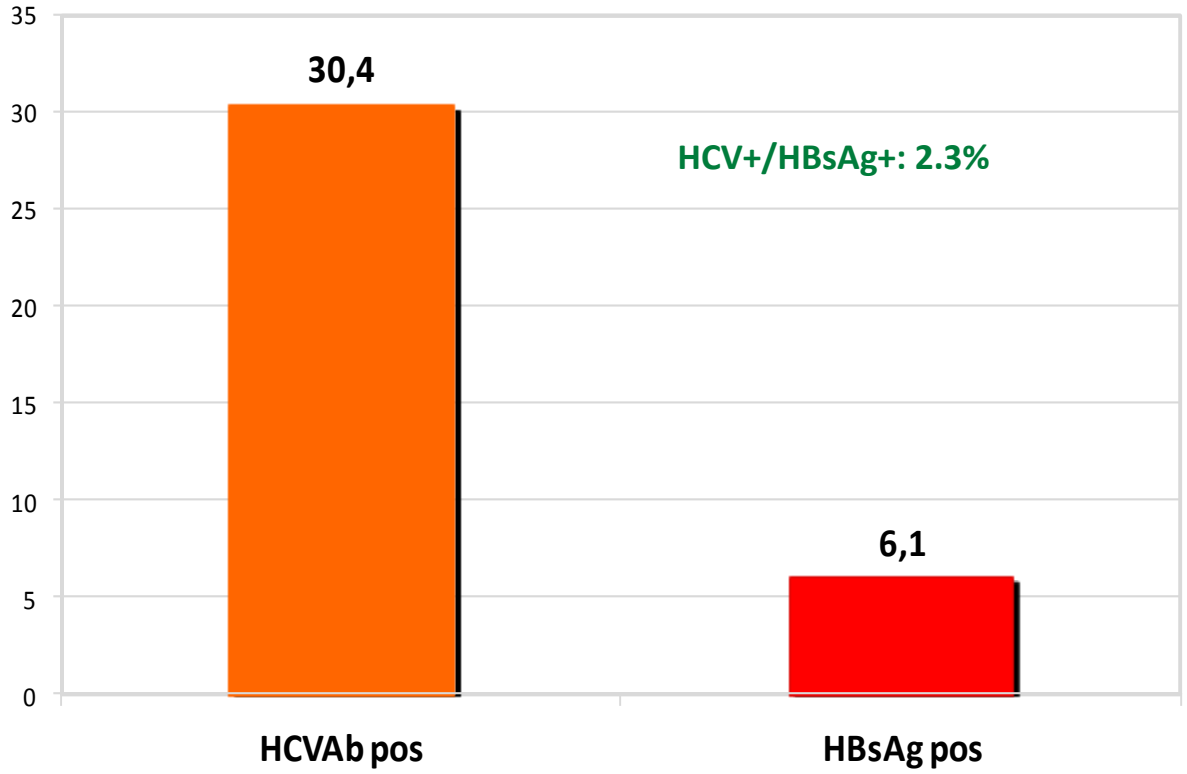
WHO 2013

D:A:D: Liver-related death is a frequent cause of non-AIDS death in HIV-infected patients



Weber R, et al. AIDS 2012. Washington USA. Oral presentation THAB0304.

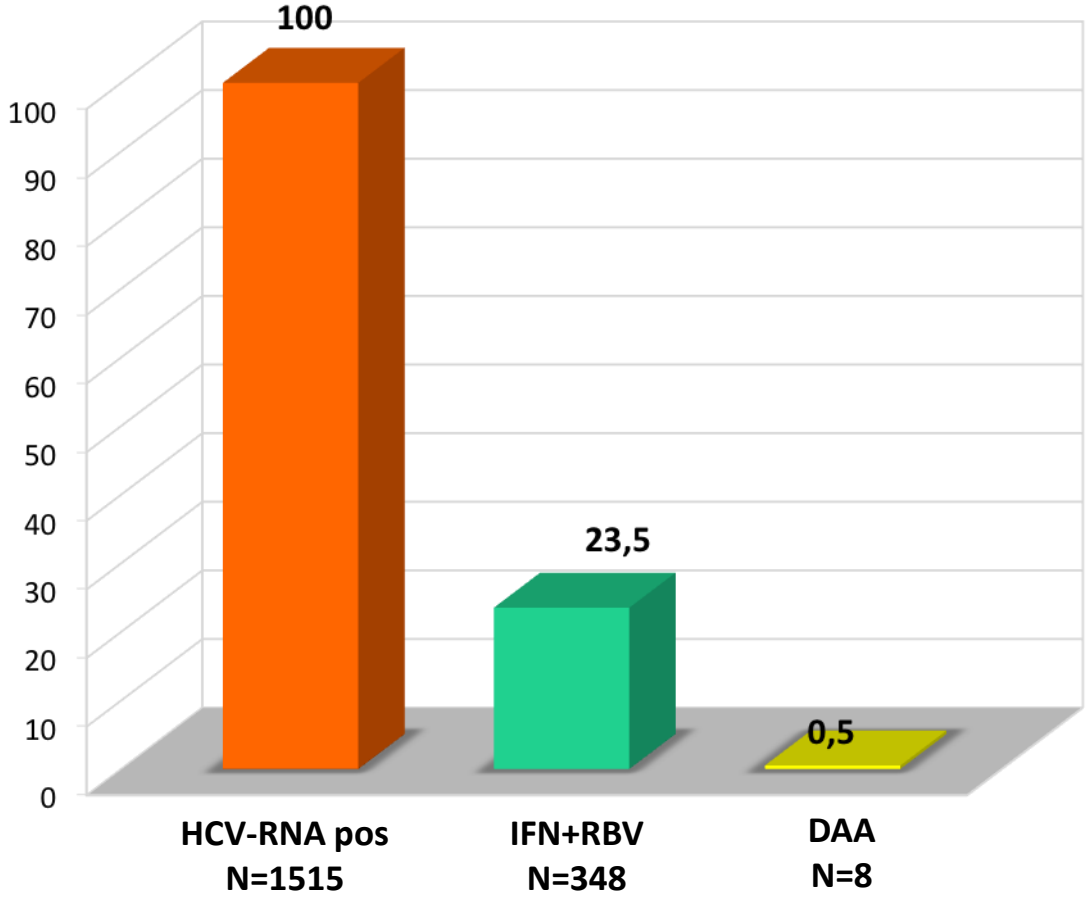
HBsAg and HCV Ab positivity in 10,665 patients



for 2014, 6 months

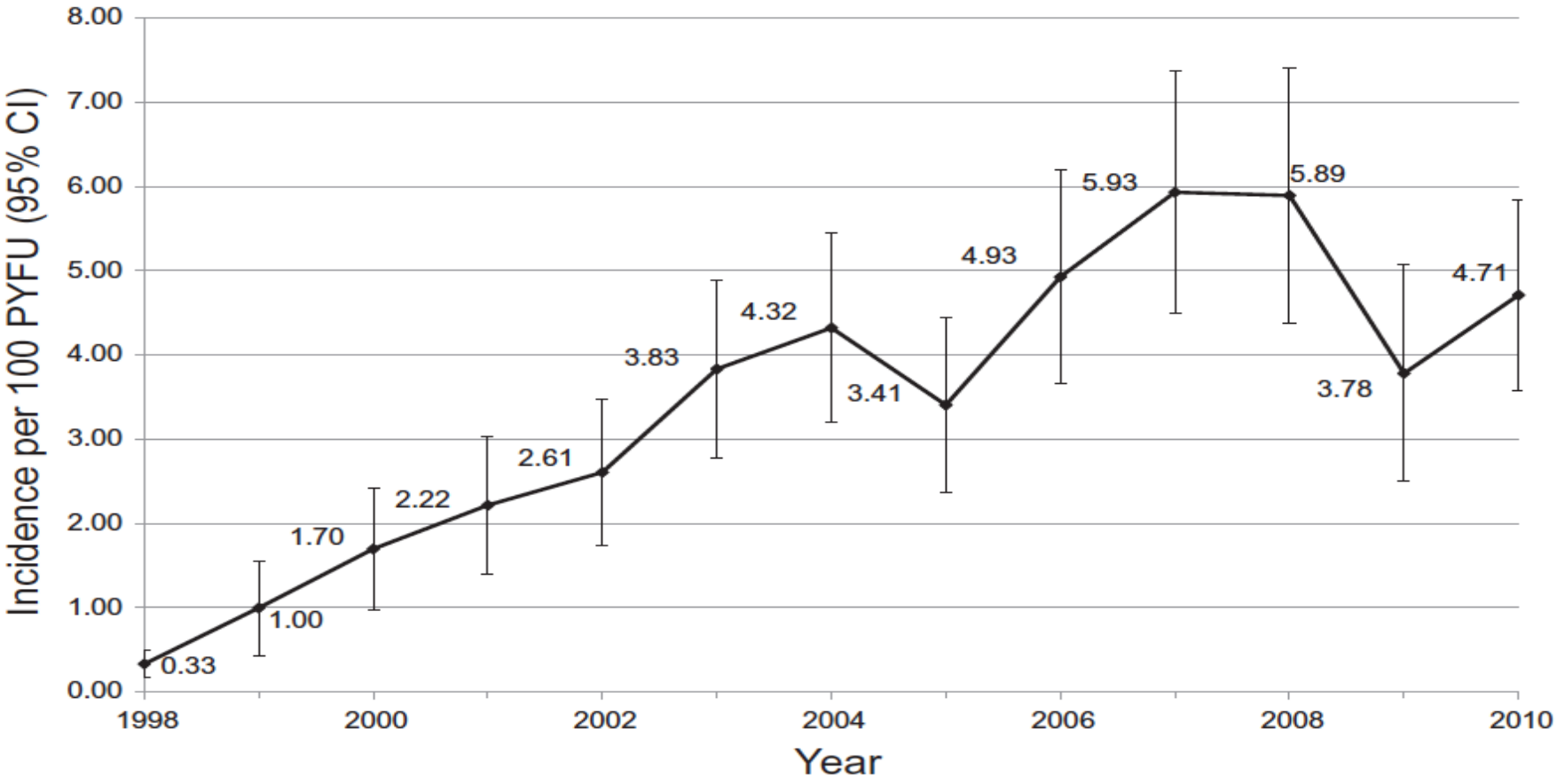
Fondazione Icona
ITALIAN COHORT NAIVE ANTIRETROVIRALS

Proportion of HCV-RNA positive patients starting any anti-HCV treatment



for 2014, 6 months

HCV Rx uptake EuroSIDA

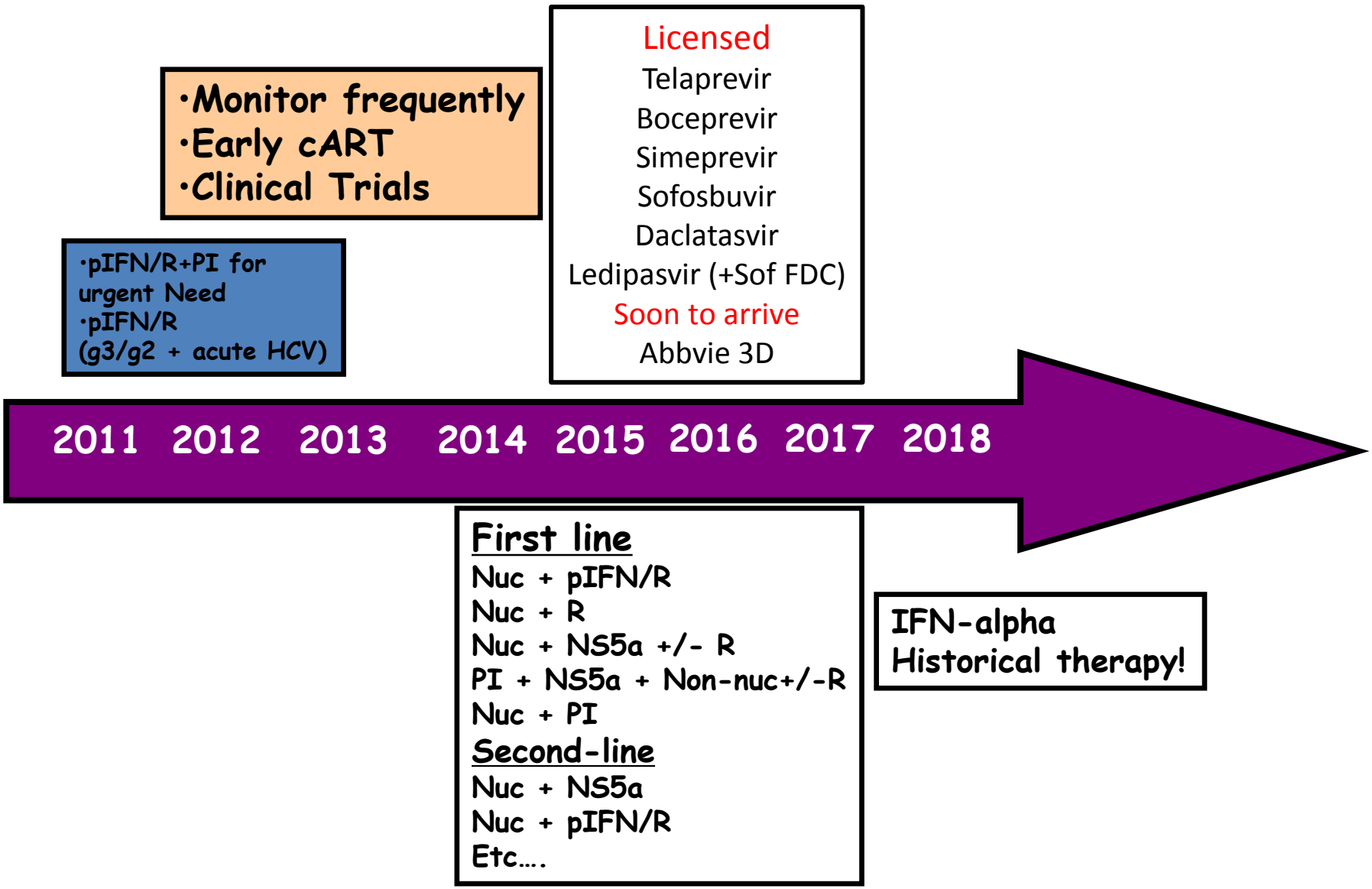


1998–2007: unadjusted IRR 1.27 (95% CI 1.23–1.31; P < 0.0001) per year

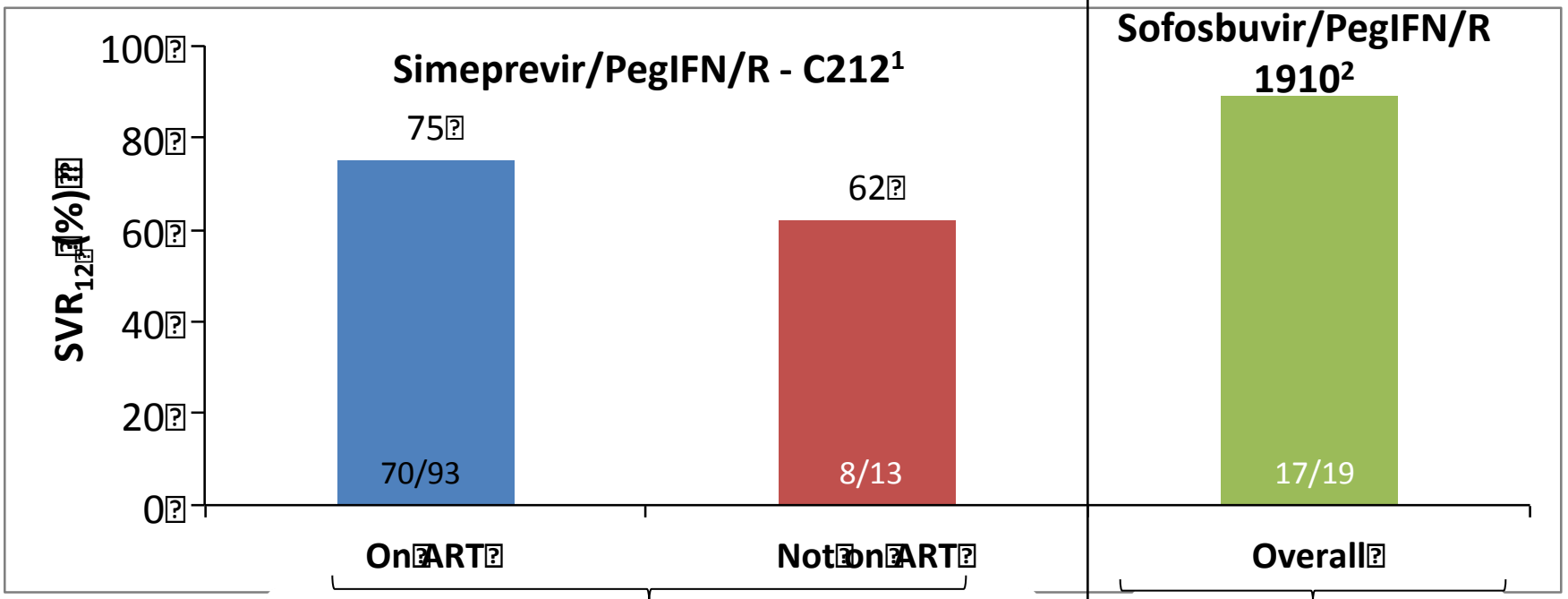
2007–2010: unadjusted IRR 0.88 (95% CI 0.79–0.98; P = 0.020) per year

Grint D, et al. HIV Medicine 2013

HCV Rx landscape – the DAA era has arrived..



HCV/HIV co-infection: pegIFNα-containing regimens in GT-1 patients



- Incidence/profile of AEs in coinfected patients comparable to that in HCV monoinfected patients
- With SMV + PR, 33% patients had grade 3/4 AE, 5.7% had SAEs, 3.8% discontinued SMV due to an AE
- In patients on ART, 35.5% had grade 3/4 AEs, 6.5% had SAEs, 4.3% discontinued SMV due to an AE

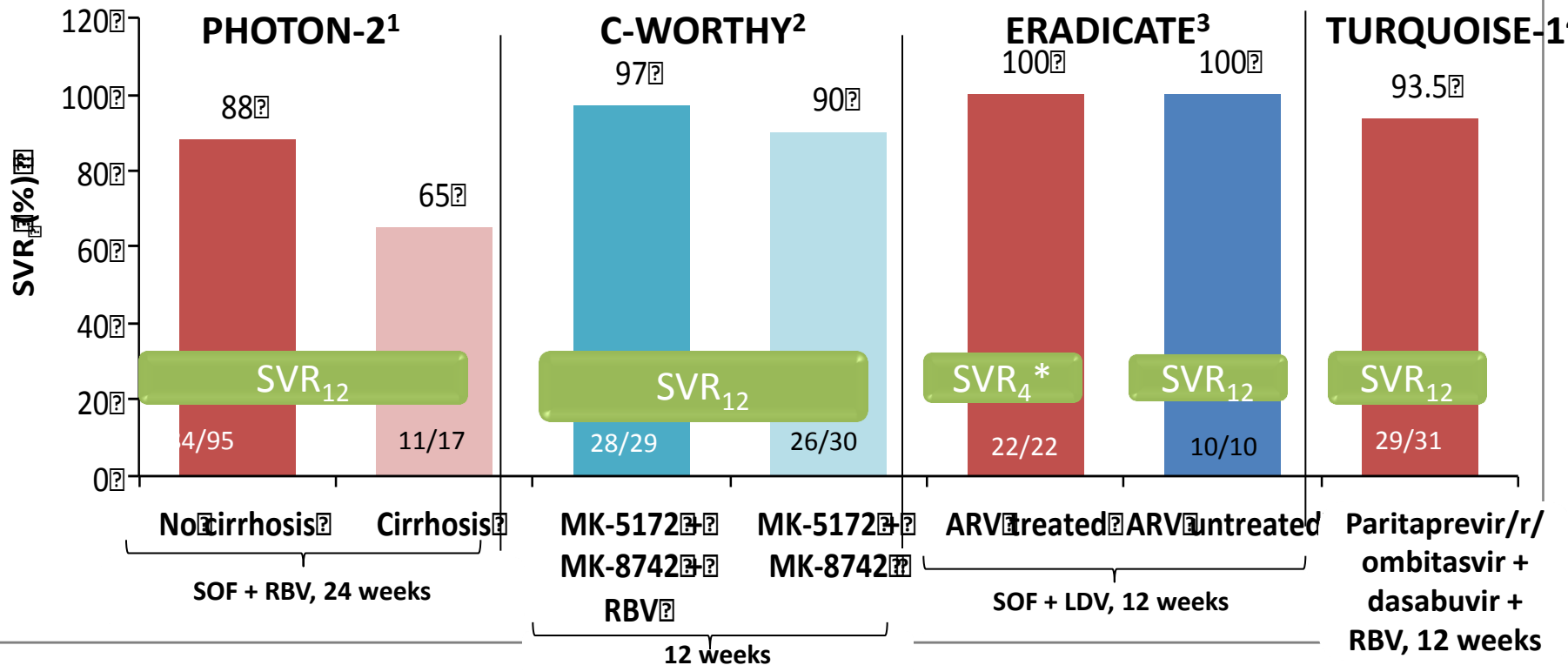
- The most frequently reported AEs (> 15%) were anaemia (52%), fatigue (35%), hyperbilirubinemia (17%), neutropenia (17%) and thrombocytopenia (17%)

NOTE: not head-to-head comparisons.

AE, adverse event; ART, antiretroviral therapy; GT, genotype; HCV, hepatitis C virus; HIV, human immunodeficiency virus; pegIFNα, pegylated interferon alfa; PR, pegylated interferon alfa + ribavirin; SAE, serious adverse event; SMV, simeprevir; SOF , sofusbuvir; SVR, sustained virologic response.

1. Dieterich D, et al. CROI 2014, Abstract 24.
2. Rodriguez-Torres M, et al. ID Week 2013, Poster 714.

HCV/HIV co-infection: pegIFNα-free regimens GT-1



- Treatment discontinuations due to AEs: 2%
- Grade 3/4 AEs: 6%
- Stable CD4+ T-cell counts
- 4 patients had an HIV RNA rebound

- Most common AEs: fatigue, headache, back pain and asthenia
- Supressed HIV and stable CD4+ T-cell counts
- No early discontinuations due to AEs

- No significant CD4+ T-cell count or HIV RNA changes
- No renal toxicity
- No discontinuations

- Most common AEs: fatigue, insomnia, headache
- No SAEs
- Most common laboratory abnormality: elevation in total bilirubin

*Awaiting SVR_{12} for ARV treated.

Ledipasvir, MK-5172, MK-8742, paritaprevir, ombitasvir and dasabuvir are investigational, unlicensed compounds.

1. Molina J, et al. AIDS 2014, MOAB0105LB2. 2. Sulkowski M, et al. AASLD 2014. 3. Osinusi A, et al. EASL 2014, O14. 4. Sulkowski M, et al. AIDS 2014, MOAB0104LB.

NOTE: not head-to-head comparisons.

AE, adverse event; ARV, antiretroviral; HCV, hepatitis C virus; HIV, human immunodeficiency virus; LDV, ledipsavir; pegIFNα, pegylated interferon alfa; RBV, ribavirin; SAE, serious adverse event; SOF, sofosbuvir; SVR, sustained virologic response.

	VICTIM of DDI	PERPETRATOR of DDI	DDI potential
Teleprevir	Substrate for CYP 3A4, PgP	Inhibits CYP 3A4, PgP, OATP1B1/2 ? Protein binding	Significant
Boceprevir	Substrate for aldoketoreductase, CYP 3A4, PgP, BCRP	Inhibits CYP 3A4, PgP, OCT 1&2	Significant
Simeprevir	Substrate for CYP 3A4, PgP	Inhibits OATP1B1, MRP2 Mild inhibitor gut CYP 3A4, PgP	Moderate
Sofosbuvir	cathepsin A, esterases, kinases PgP & BCRP substrate (parent)	Weak inhibitor of gut PgP & BCRP	Low
Ledipasvir	Primarily excreted unchanged (>98% faeces), PgP / BCRP substrate	Weak inhibitor of PgP/BCRP, ?OATP1B1/3	?Low
ABT450r	Substrate for CYP 3A4, PgP, OATP1B1/3	Weak inhibitor PgP/BCRP (gut), ?OATP1B1/3	
Ombitasvir (ABT-267)	Substrate for PgP, BCRP (CYP 3A4)	Weak inhibitor of UGT1A1	Moderate to Significant (RTV)
Dasabuvir (ABT-333)	Substrate of CYP 2C8 > 3A4 > 2D6, Substrate of PgP, BCRP	Weak inhibitor of UGT1A1	
Daclatasvir	Substrate for CYP 3A4, PgP	Inhibits OATP1B1/3 & PgP	Moderate
MK-5172	Substrate for CYP 3A4, PgP, ? OATP1B1	Inhibits CYP 2C8, weak inhibitor of UGT1A1, ? BCRP	Moderate
MK-8742	Substrate for CYP 3A4, PgP, ?OATP1B1	weak inhibitor of UGT1A1	Moderate

Slide courtesy of S Khoo, 2014

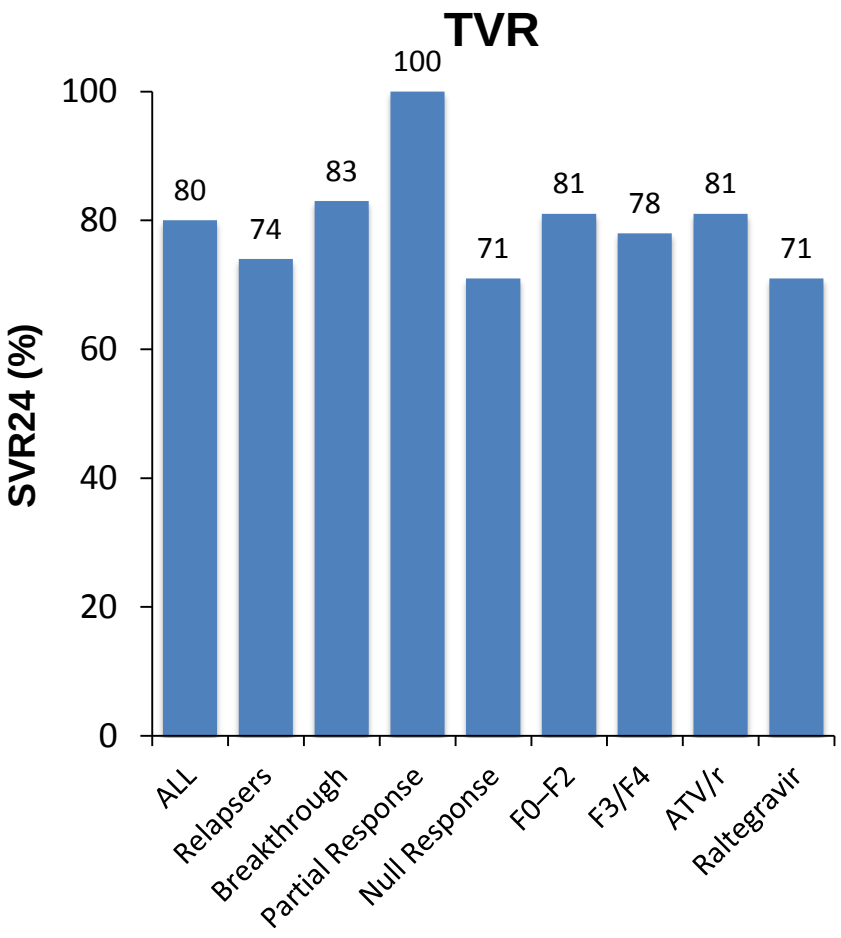
New online EASL HCV recommendations

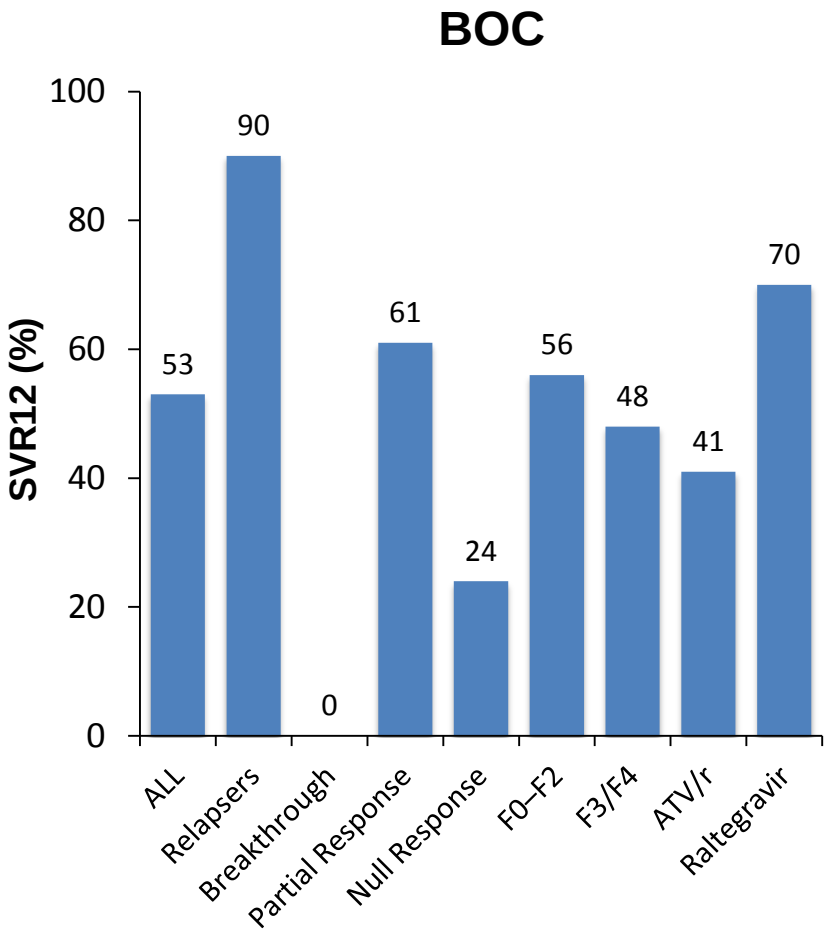
Same treatment regimens can be used in HIV/HCV patients as in patients without HIV infection, as the virologic results of therapy are identical (A1)

EASL recommendations April 2014. Available from: http://files.easl.eu/easl-recommendations-on-treatment-of-hepatitis-c-summary.pdf (Accessed September 2014).

EASL, European Association for the Study of the Liver; HCV, hepatitis C virus; HIV, human immunodeficiency virus.

ANRS studies TelapreVIH and BocepreVIH in TE HCV GT 1 HIV/HCV co-infected patients



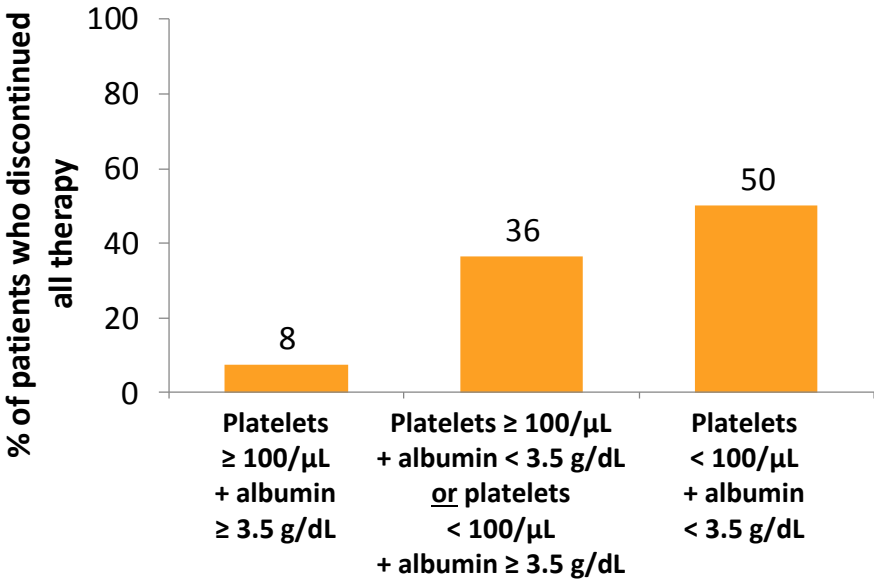


SVR24 in HIV/HCV PEG-IFN/RBV experienced treated with PEG-IFN/RBV + TVR (69) or BOC (64); 4 weeks lead in + 44 weeks standard + 24 additional weeks if HCV RNA at Week 8 >15IU/mL.
ATV/r: ritonavir boosted atazanavir; TE: treatment-experienced

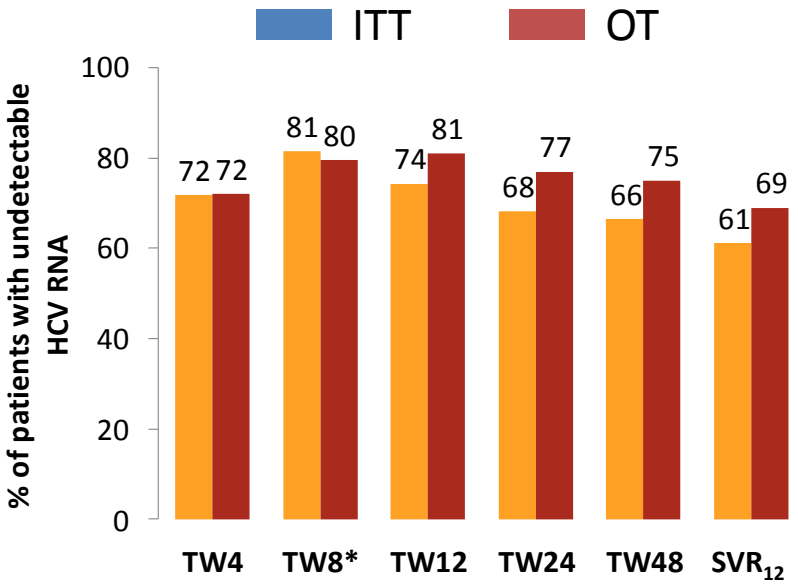
1. Cotte L, et al. CROI 2014; Oral #668;
2. Poizot Martin I, et al. CROI 2014. Oral #659.

‘Real-life’ experience pegIFNα/RBV + TVR/BOC – pan-European data

Treatment discontinuation



Treatment response ITT and OT



Neukam K, et al. 21st CROI 2014, Abstract 660.

BOC, boceprevir; HCV, hepatitis C virus; ITT, intention to treat; OT, on-treatment; pegIFNα, pegylated interferon alfa; RBV, ribavirin; SVR, sustained virologic response; TVR, telaprevir; TW, treatment week.

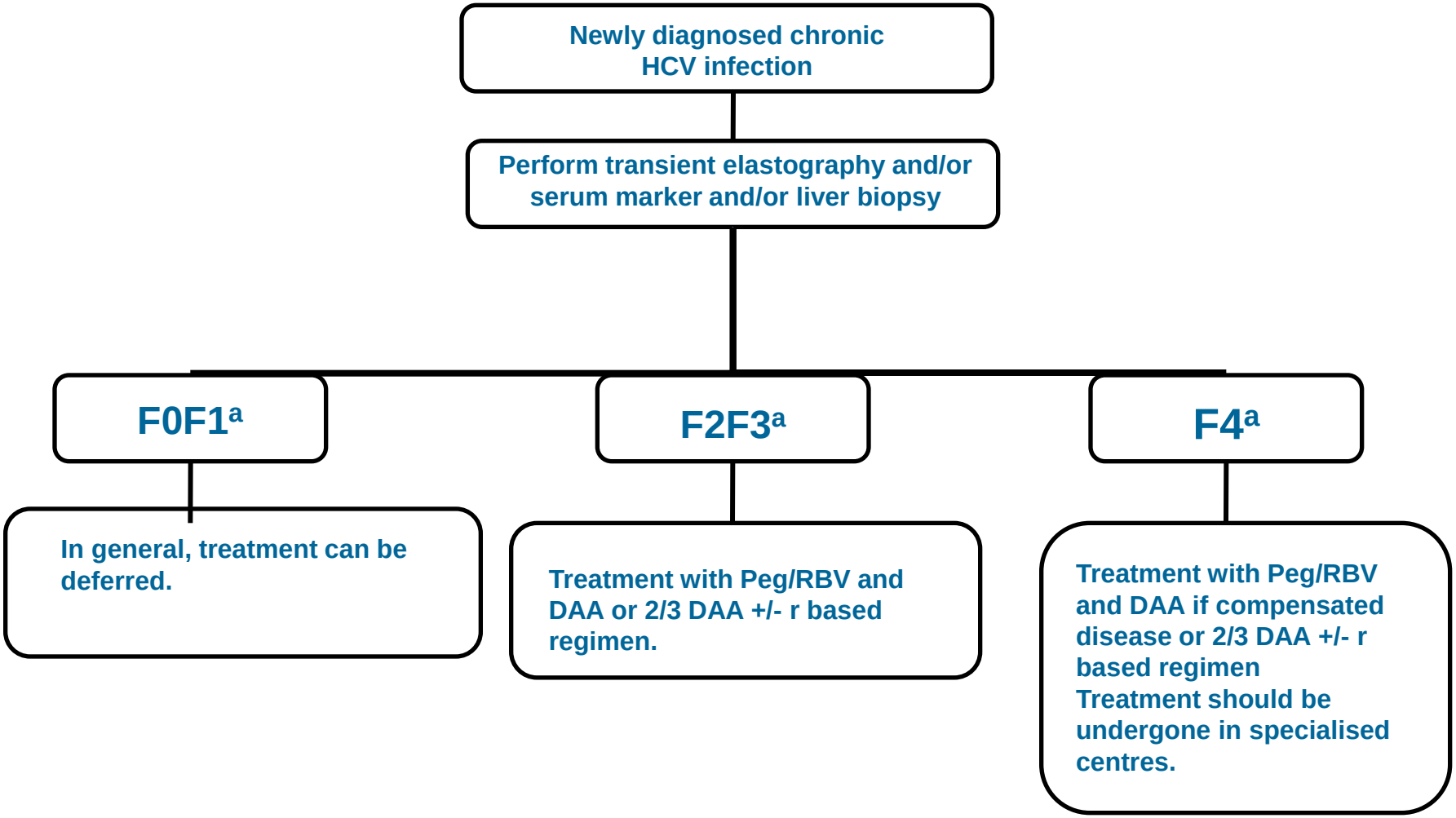
Management HCV/HIV GT 1: BHIVA 2014

	Naive	Relapser/ Partial Res.	Non-responder
F0/F1	Defer/Triple therapy/ Offer trial	Defer/Triple therapy/ Offer trial	Defer/Triple therapy/ Offer trial
F2	Defer/Triple therapy/ Offer trial	Defer/Triple therapy/ Offer trial	Defer/Triple therapy/ Offer trial
F3	Defer/Triple therapy/ Offer trial	Defer/Triple therapy/ Offer trial	Defer/Triple therapy/ Offer trial
F4	Triple therapy	Triple therapy	Triple therapy

BHIVA 2014 – updated November

- DAA-based Rx new ‘standard of care’
  - PegIFN based or IFN-free
- Rx should be offered to ALL co-infected patients
- Patients with de-compensated cirrhosis should be treated in centres or within networks with access to liver transplantation

Management of HIV/HCV Co-infected Patients (EACS 2014)



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

But Rx is expensive….and may not yet be available

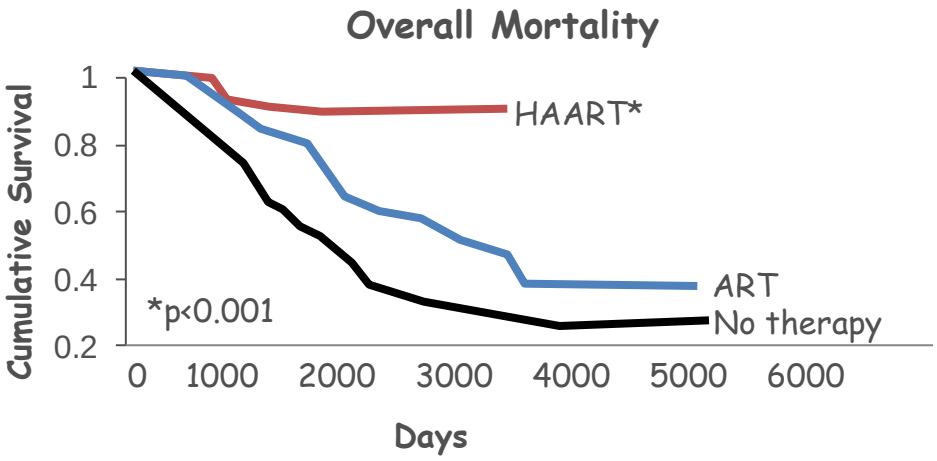
Drug	$ per dose	$ treatment course
Sofosbuvir	1000	84000
Simeprevir	785	66000
Telaprevir	117	59000
Daclatasvir	??	??
Boceprevir	15.7	52000
Peg-IFN-alpha	566	33500
Ribavirin	10	20600

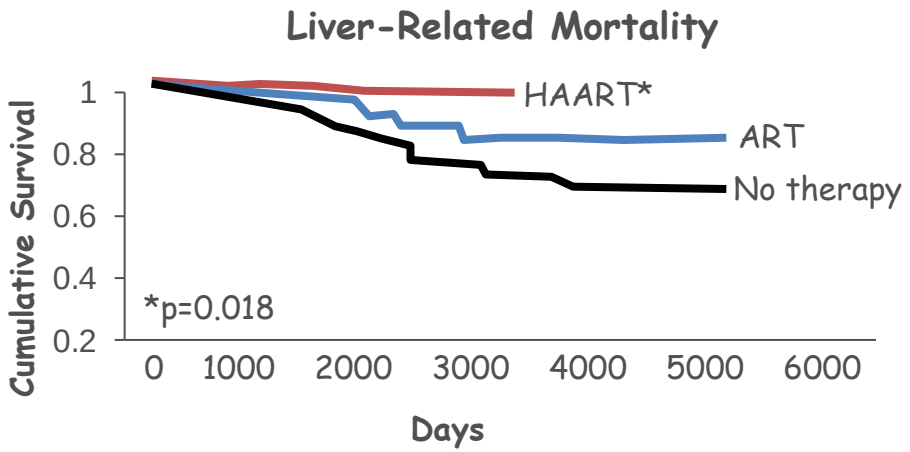
So are the guidelines correct?

- Early cART
- Rx F2+
- Prioritise F4

HAART reduces mortality in HIV/HCV-co-infected patients

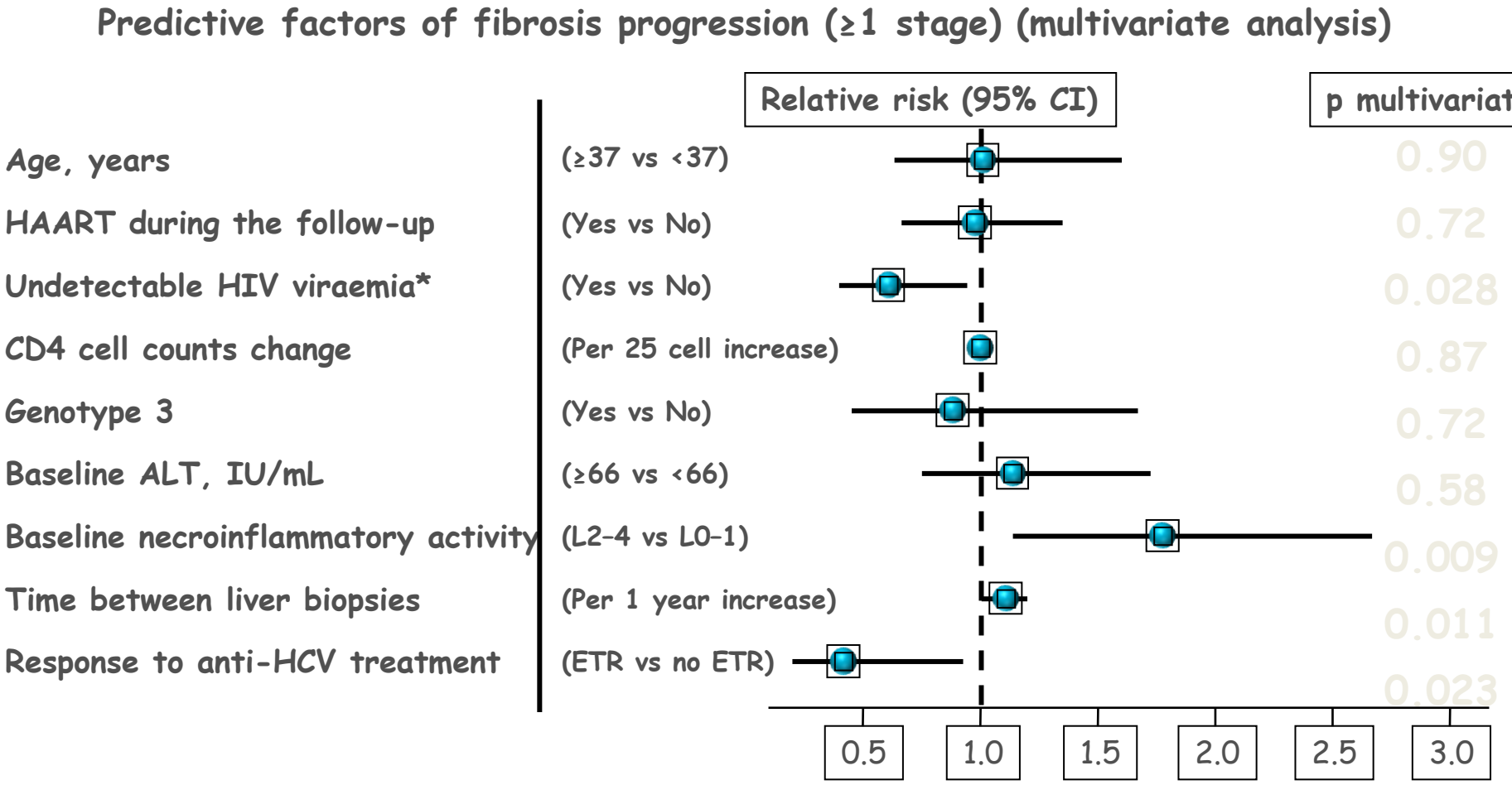
- Bonn cohort (1990–2002)
  - 285 HIV/HCV-coinfected patients
- Liver-related mortality rates per 100 PY:
  - HAART: 0.45
  - ART: 0.69
  - No therapy: 1.70
- Predictors of liver-related mortality:
  - No HAART
  - Low CD4 cell count
  - Increasing age





Adapted from Qurishi N, et al. Lancet. 2003:362:1708–13.

Effective treatment of HIV infection reduces fibrosis risk in HIV/HCV-coinfected patients

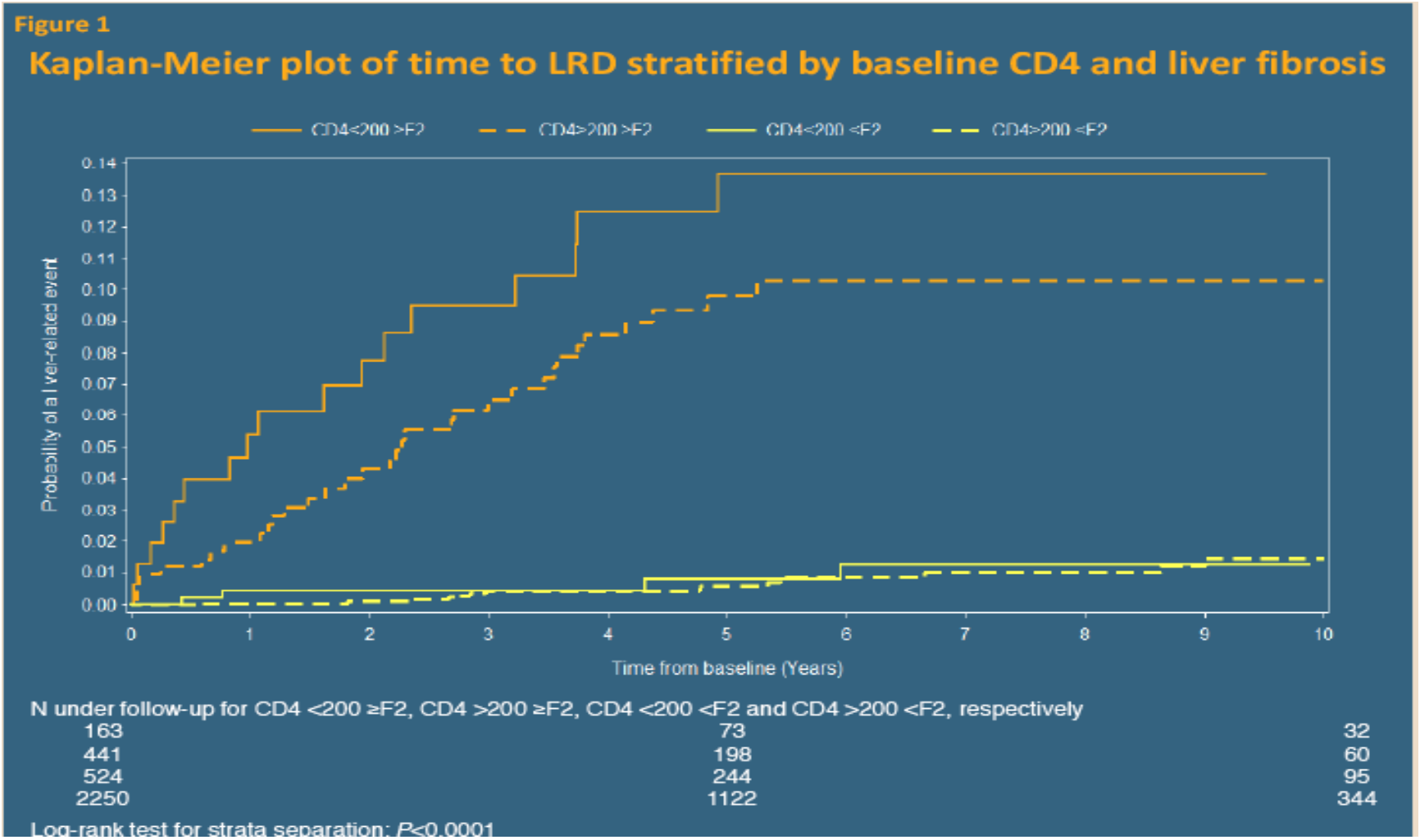


Data collected from 135 coinfected patients with 2 liver biopsies >1 year apart.
Specimens were centrally read and scored blindly by 2 independent pathologists using the Scheuer classification.

RR (95% CI)=relative risk (95% confidence interval); ETR=end-of-treatment response;
HAART=highly active antiretroviral therapy; *Undetectable HIV RNA in ≥70% determinations during the follow up.

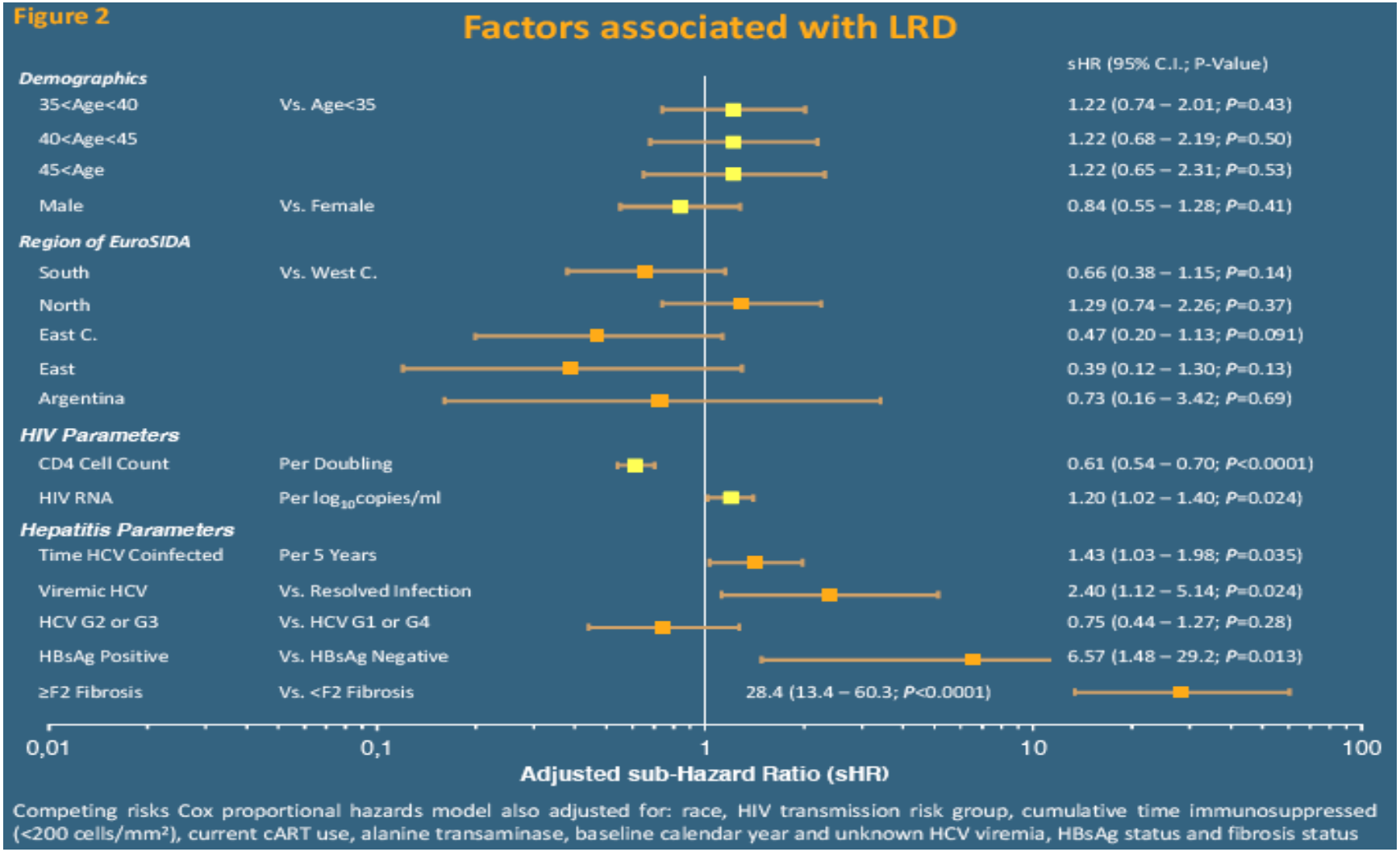
Created from Macias J, et al. Hepatology 2009;50:1056–63.

Liver-related events EuroSIDA – effect of CD4 and hepatic fibrosis



D Grint, et al. CROI 2013

Liver-related Death

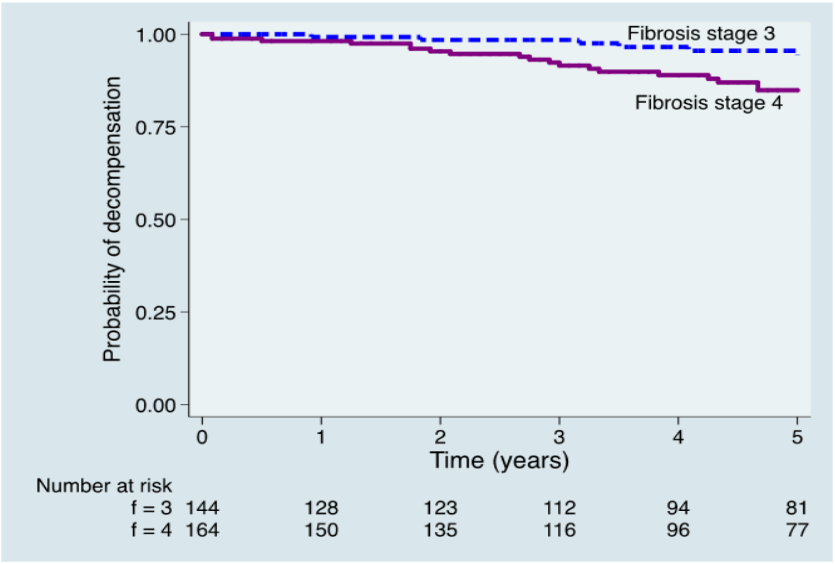


D Grint, et al. CROI 2013

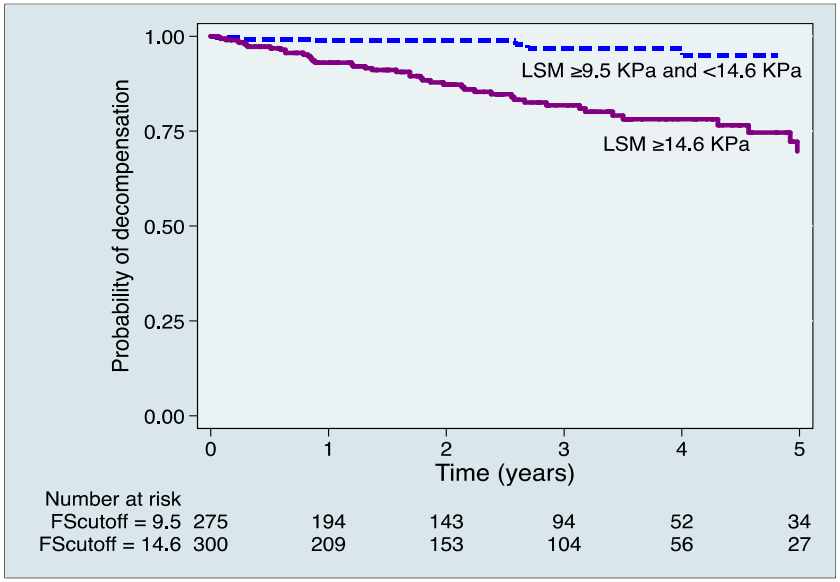
Probability of de-compensation for F3/F4 disease

the risk of decompensation events among HIV-infected individuals with chronic hepatitis C and advanced liver fibrosis.

- Retrospective multi-centre cohort study~575patients
- HCV/HIV with F3/F4 fibrosis
  - 317 biopsy assessed
- 45% previous anti-HCV treatment
- 12 year follow-up



Macias, et al. Clin Infect Dis 2013

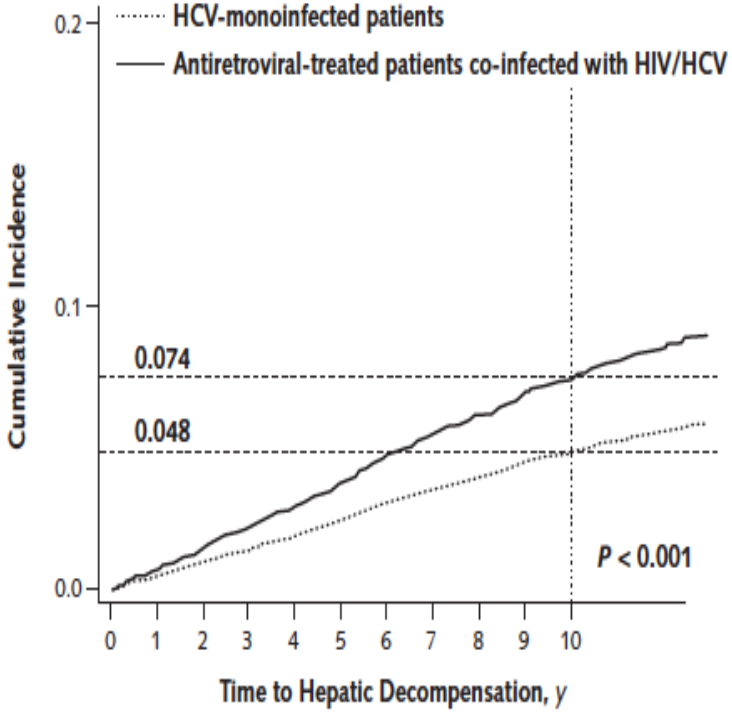


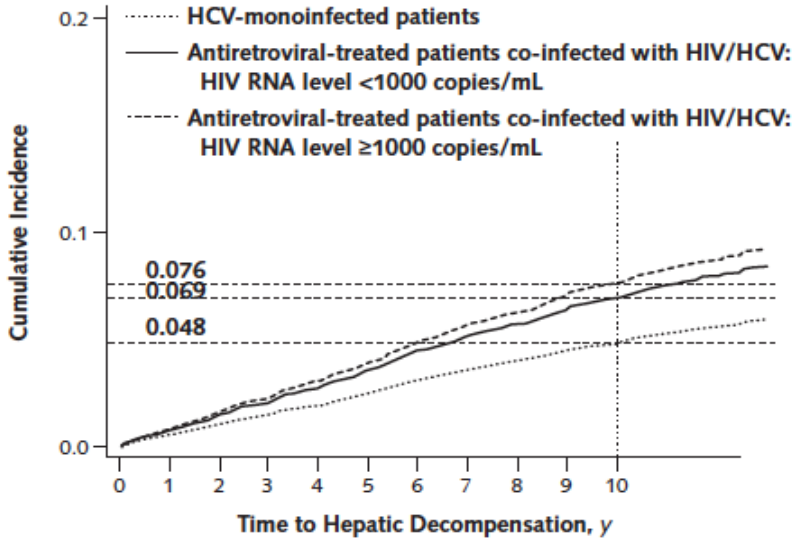
Risk of de-compensation:

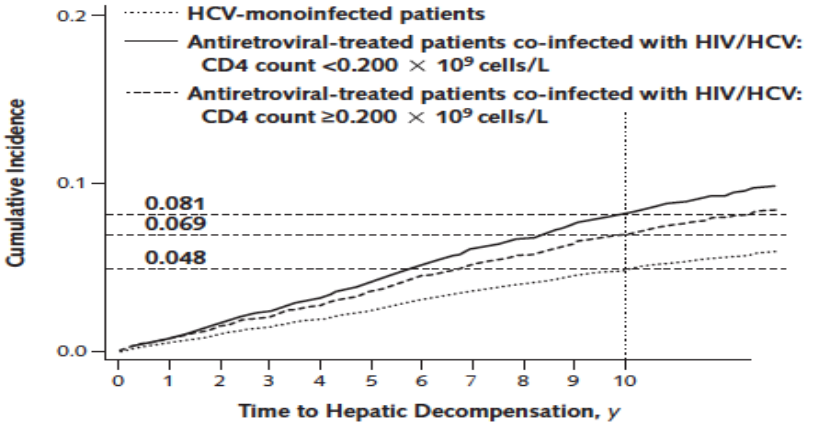
a) Fibrosis stage
   F4 on biopsy or LSM >14.6

b) Platelet count
   <105

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

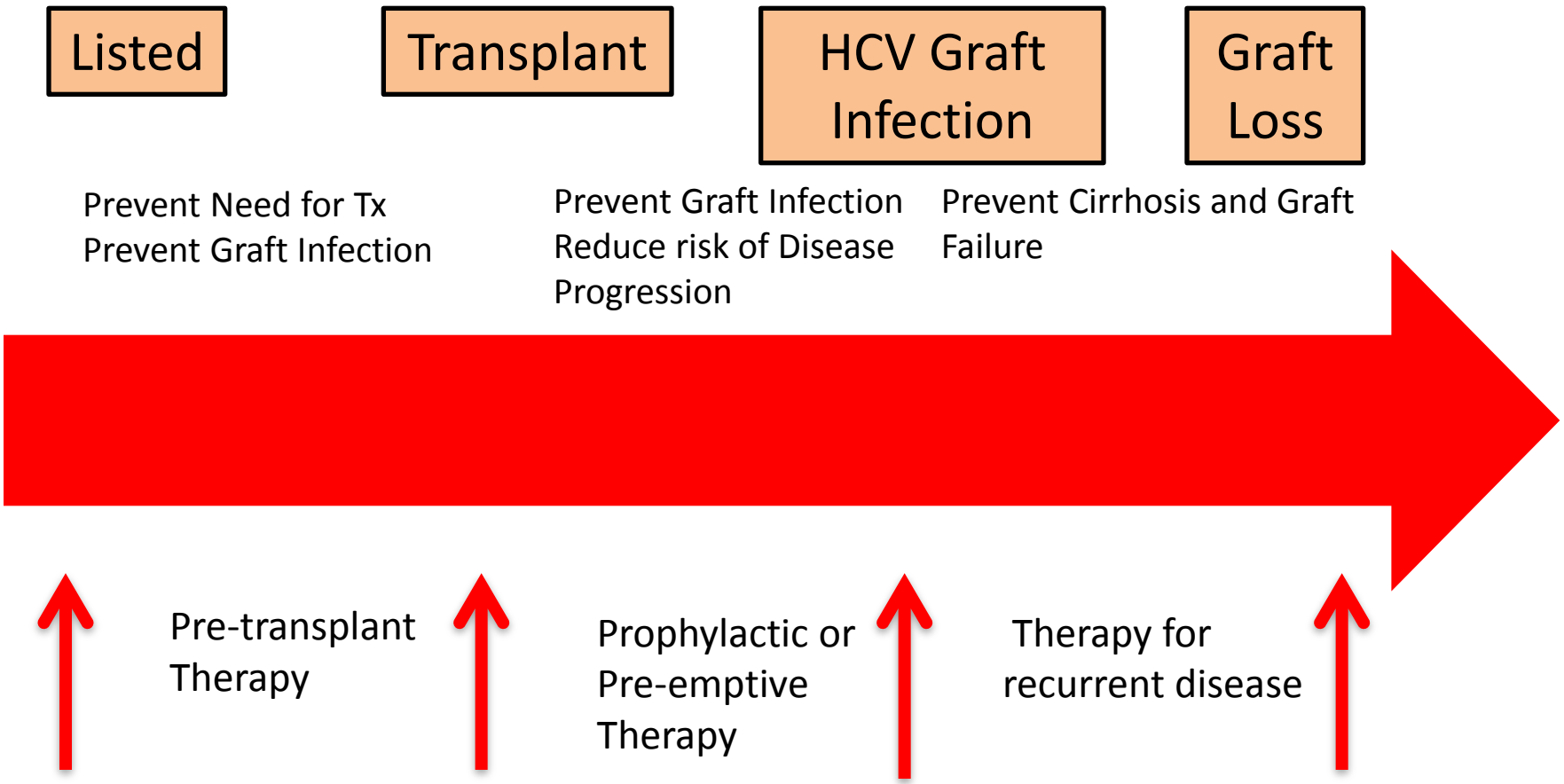






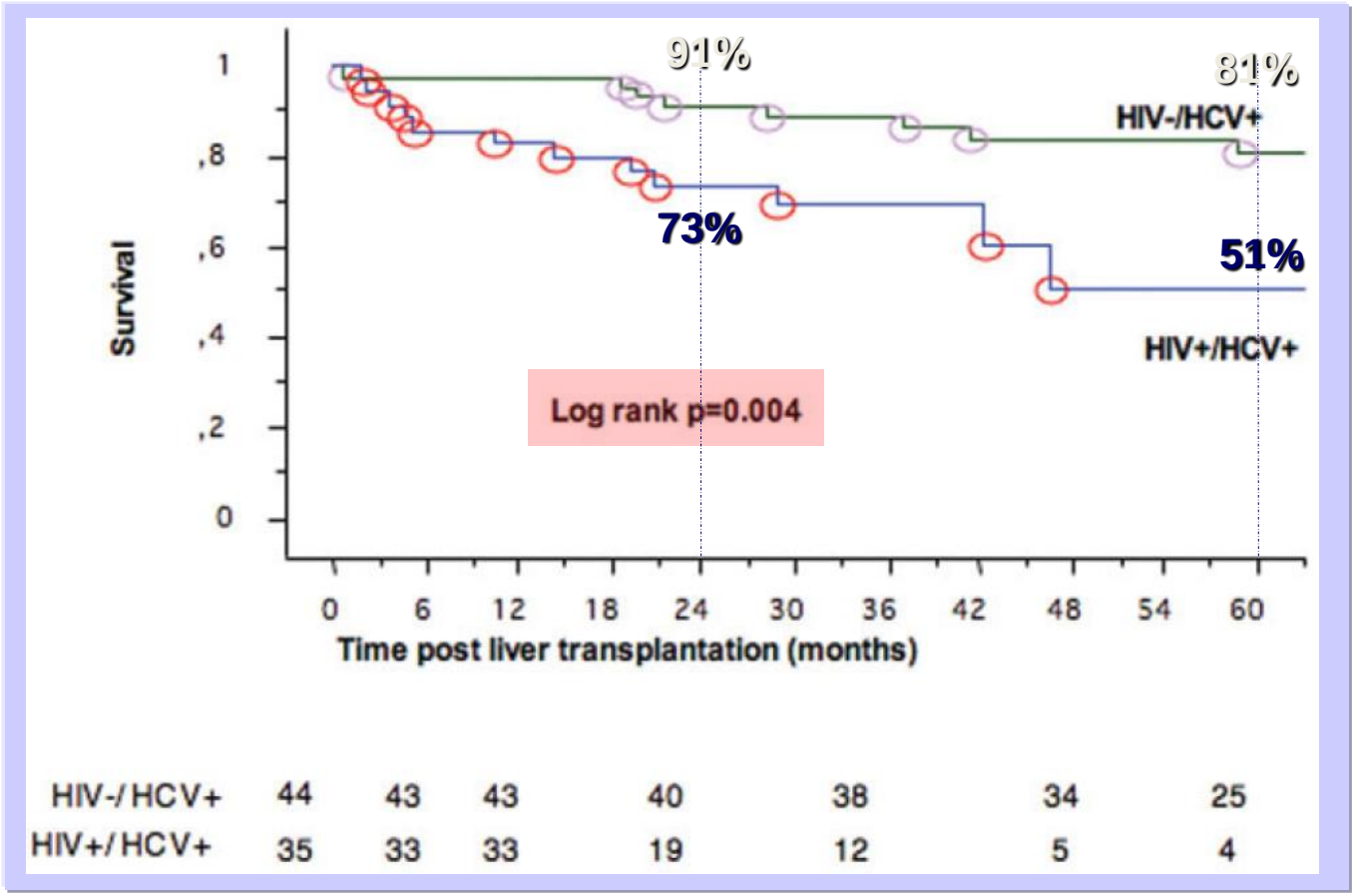
Le Ro III, et al. Ann Intern Med 2014; 160: 369

DAA based HCV Rx – opportunities to influence natural history?



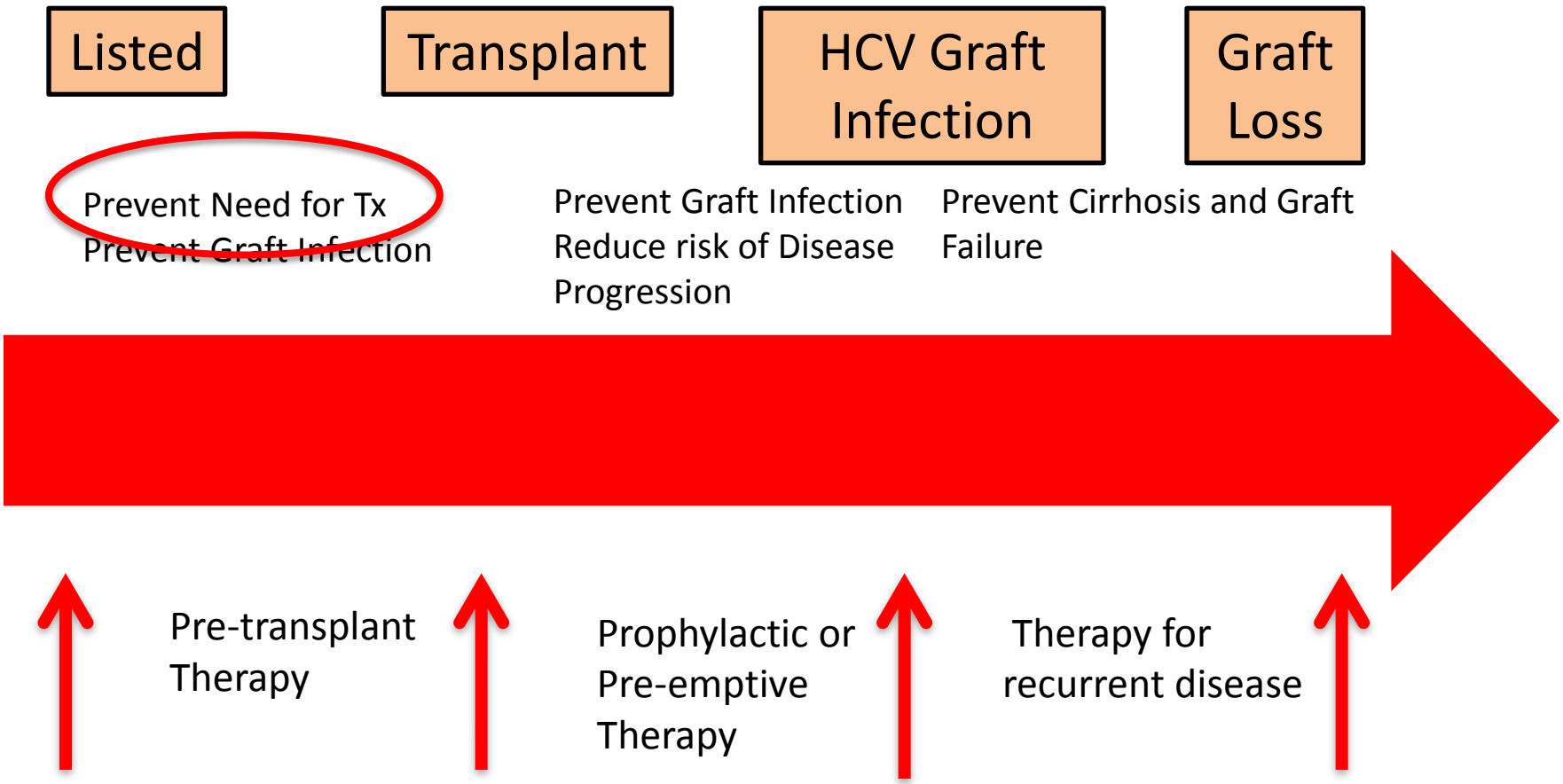
HIV (+) patients: post-OLT survival

Survival:
HIV-HCV co-infected vs HCV mono-infected recipients



Duclos-Vallèe J-C, Féray C *et al.* *Hepatolog* 2008; 47 (2):407-417

DAA based HCV Rx – opportunities to influence natural history?



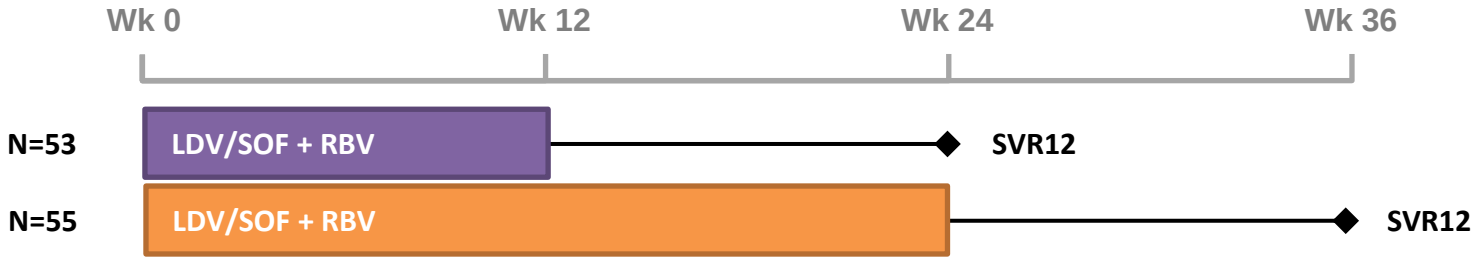
PK Changes with Advancing Liver Disease

	Liver Impairment			Notes
	mild	*moderate*	*severe compensated*	
Teleprevir	↓ 0.85	↓ 0.54		*SS, HCV-*
Boceprevir	↔	1.32	1.45	
Simeprevir		↑2.44	↑5.22	*SS, HCV-*
Sofosbuvir		↑1.26 (↑1.18**)	↑1.43 (↔1.09**)	*Parent (SS, HCV+)* *GS 331007 metabolite*
Ledipasvir	no adjustment	no adjustment		*SS, HCV-*
ABT 450r	↓ 0.71	↑1.62	↑10.23	*Single dose, HCV-*
Ombitasvir (ABT-267)	0.92	0.70	0.45	
Dasabuvir (ABT-333)	1.17	0.84	4.19	
Faldeprevir		↔	↔	*No change in cirrhosis*
Asunaprevir	↓ 0.79	↑ 9.8	↑ 32	*SS, HCV-, concentrates in liver,* *↑PK in >60 years*
Daclatasvir	↓ 0.57	↓ 0.62 unbound ↔	↓ 0.64 unbound ↔	*Single dose, HCV-*
MK5172	↑1.62	↑4.88		*SS, 100mg/200mg (HCV-)*
MK8742	↔	↔		*Single dose*

SOLAR-1

LDV/SOF + RBV for HCV Patients with Decompensated Cirrhosis

Prospective, multicenter study of 12 or 24 weeks of LDV/SOF + RBV in TN and TE HCV GT 1 and 4 patients with CTP B (N=59) or CTP C (N=49) clinically decompensated cirrhosis

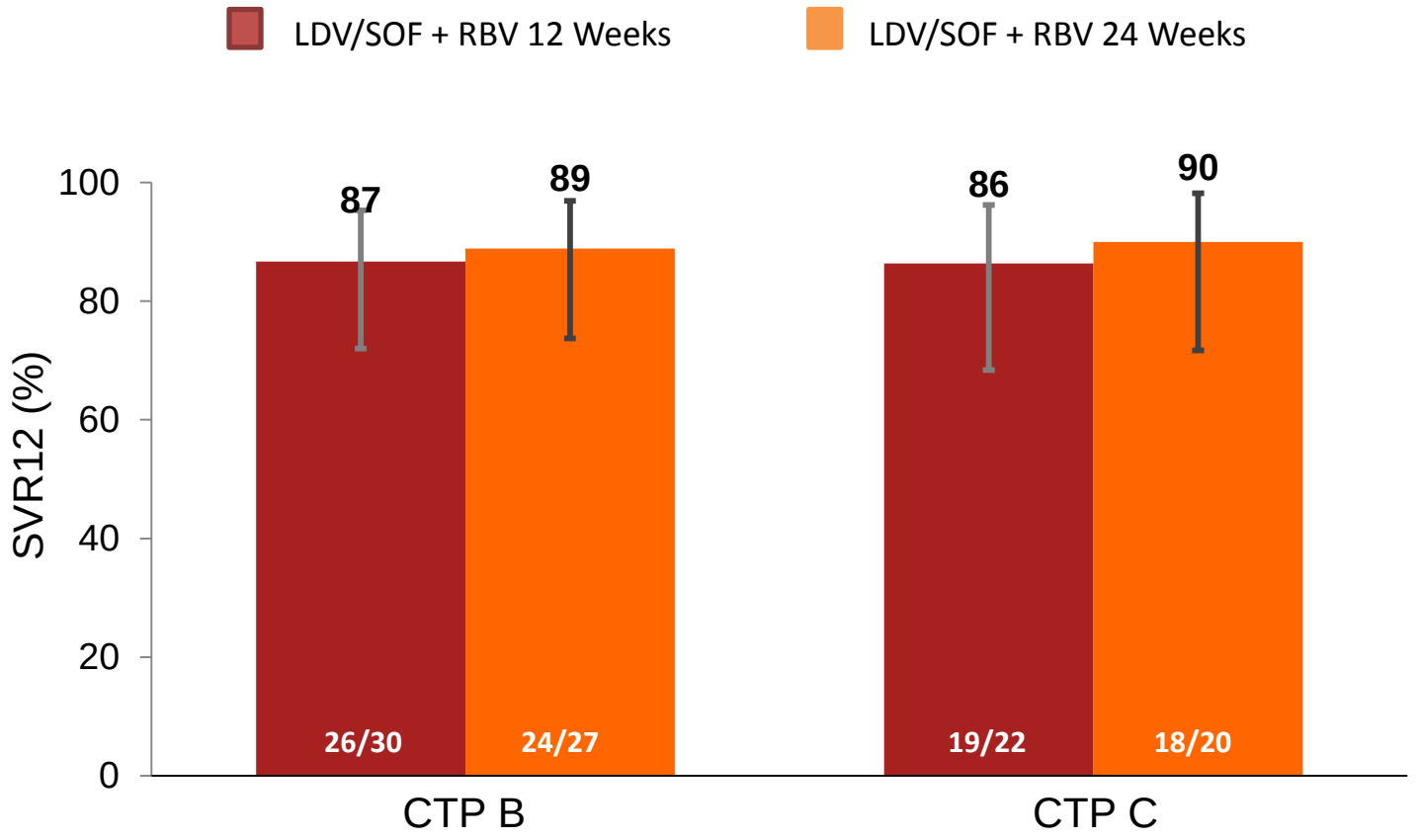


- 108 patients randomized 1:1 to 12 or 24 weeks of treatment
- Stratified by CTP class B [7-9] or C [score 10–12]*
- Broad inclusion criteria:
  - No history of major organ transplant, including liver
  - No hepatocellular carcinoma (HCC)
  - Total bilirubin ≤10 mg/dL, Hemoglobin ≥ 10 g/dL
  - CrCl≥ 40 mL/min, Platelets > 30,000
- RBV dosing: dose escalation, 600–1200 mg/d

Flamm, AASLD, 2014, Oral #239

*Patients with CTP scores 13-15 were excluded

Results: SVR12



SVR rates were similar with 12 or 24 weeks of LDV/SOF + RBV

Error bars represent 90% confidence intervals.

Flamm, AASLD, 2014, Oral #239

Liver Cancer and HCV

HCC incidence – SVR /non-SVR

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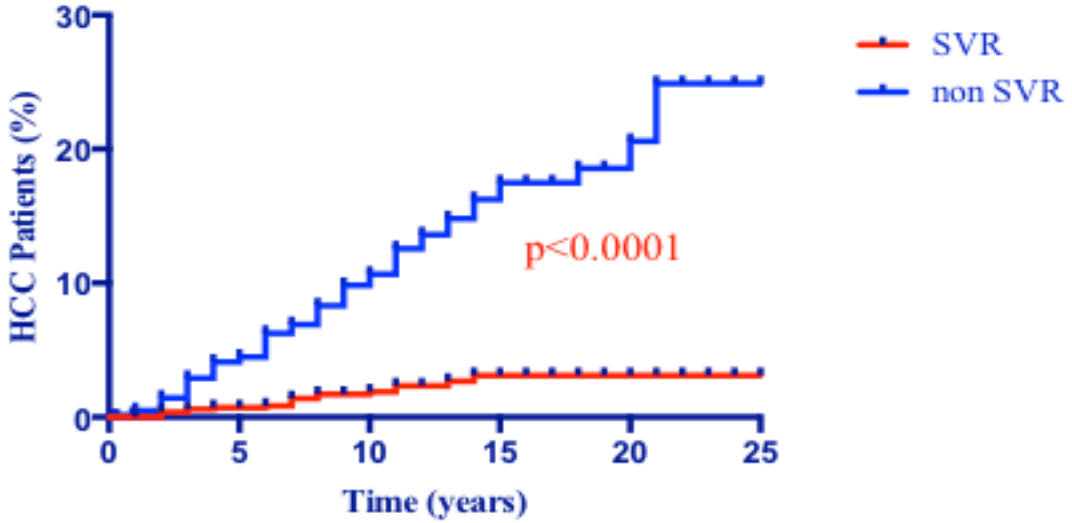
SVR group = **1.8% vs. Non-SVR = 12.1%,** p<0.0001



Liver Cancer in cirrhotic patients despite viral clearance

HCC incidence overtime in F4 patients according SVR

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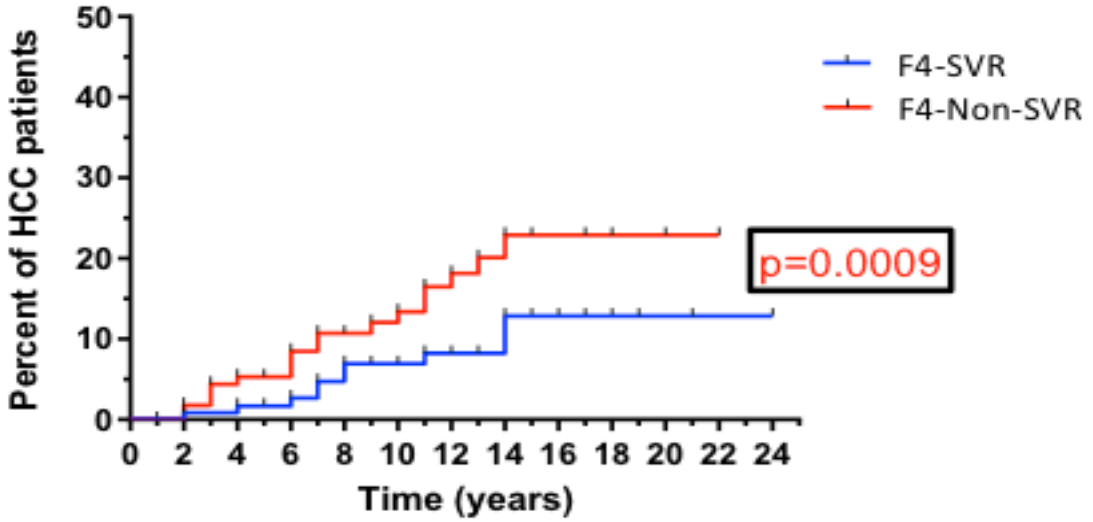
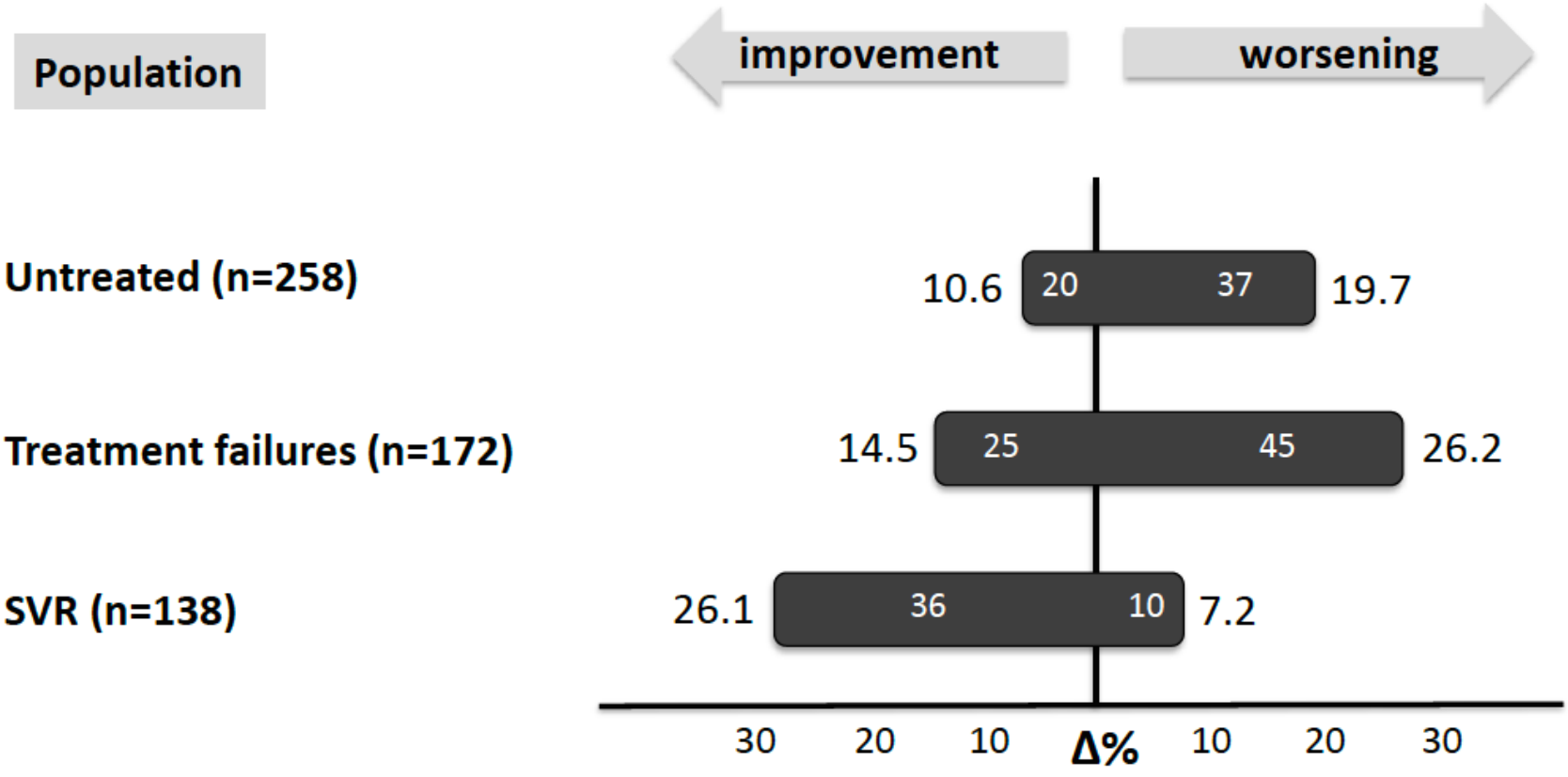
HCC-Incidence: SVR 7.7% *vs.* Non-SVR 15.6%

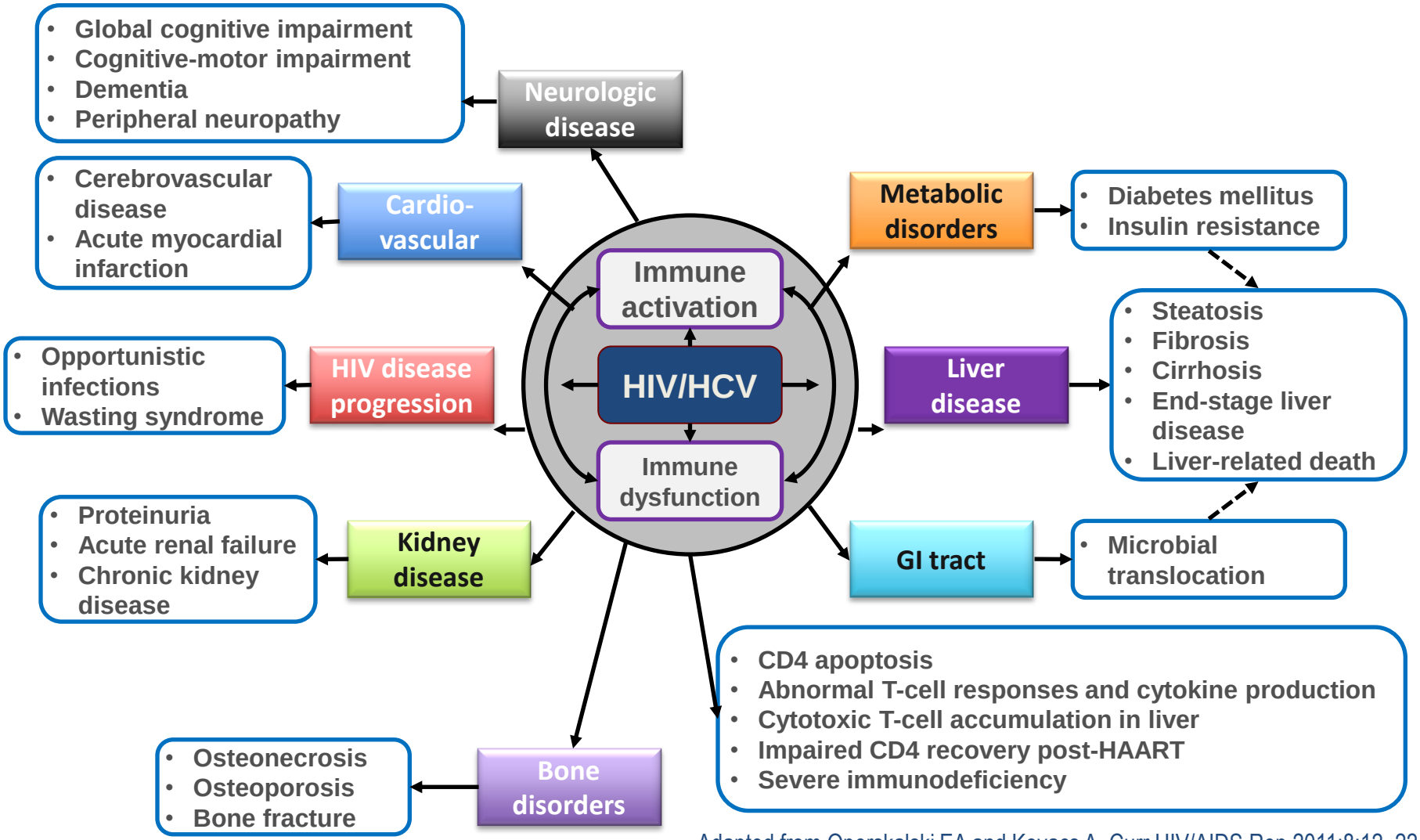


Fibrosis progression/regression post SVR – the Madrid experience



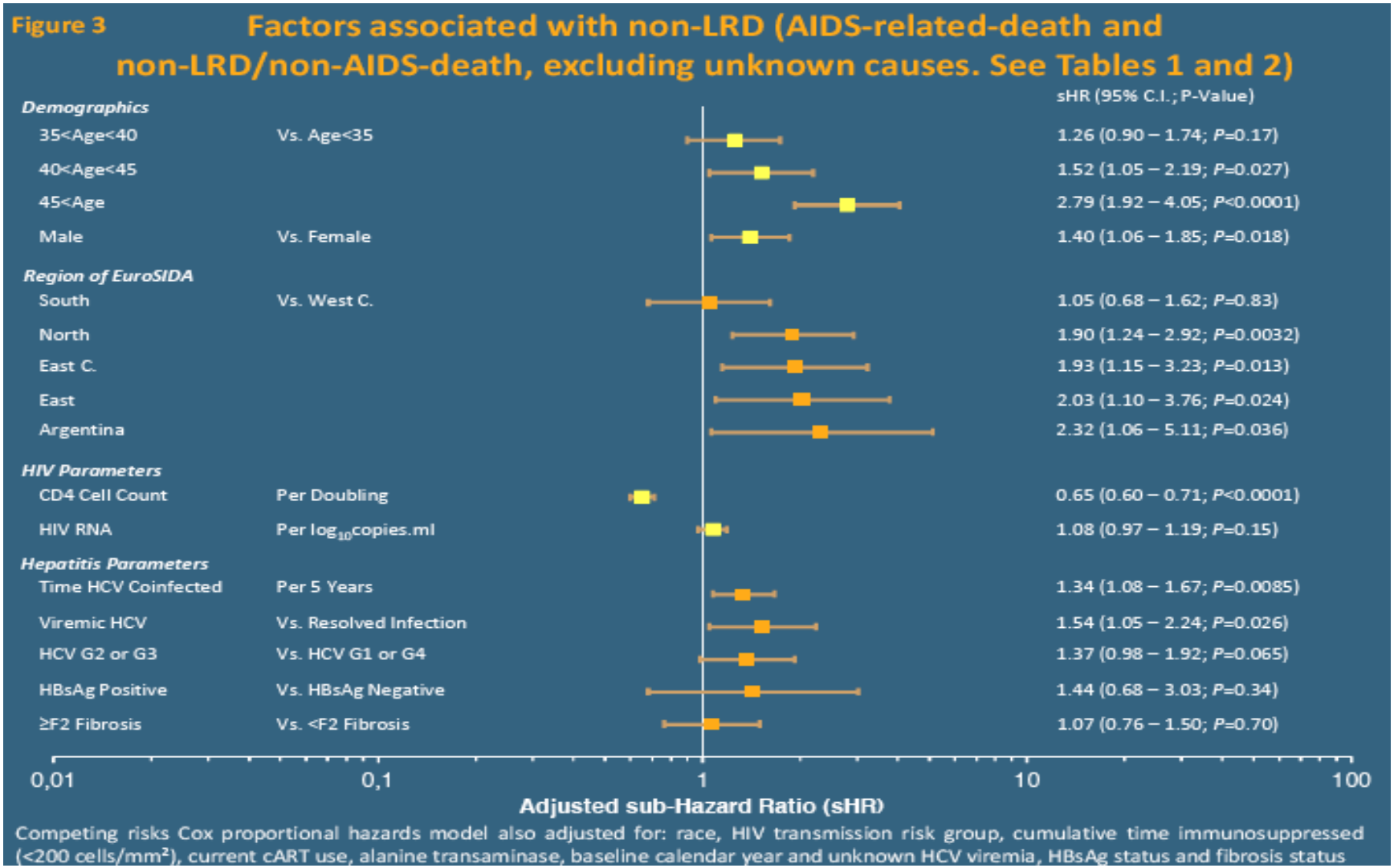
Labarga, et al. Antiviral Therapy 2014

HIV/HCV – a contribution to multiple organ dysfunction



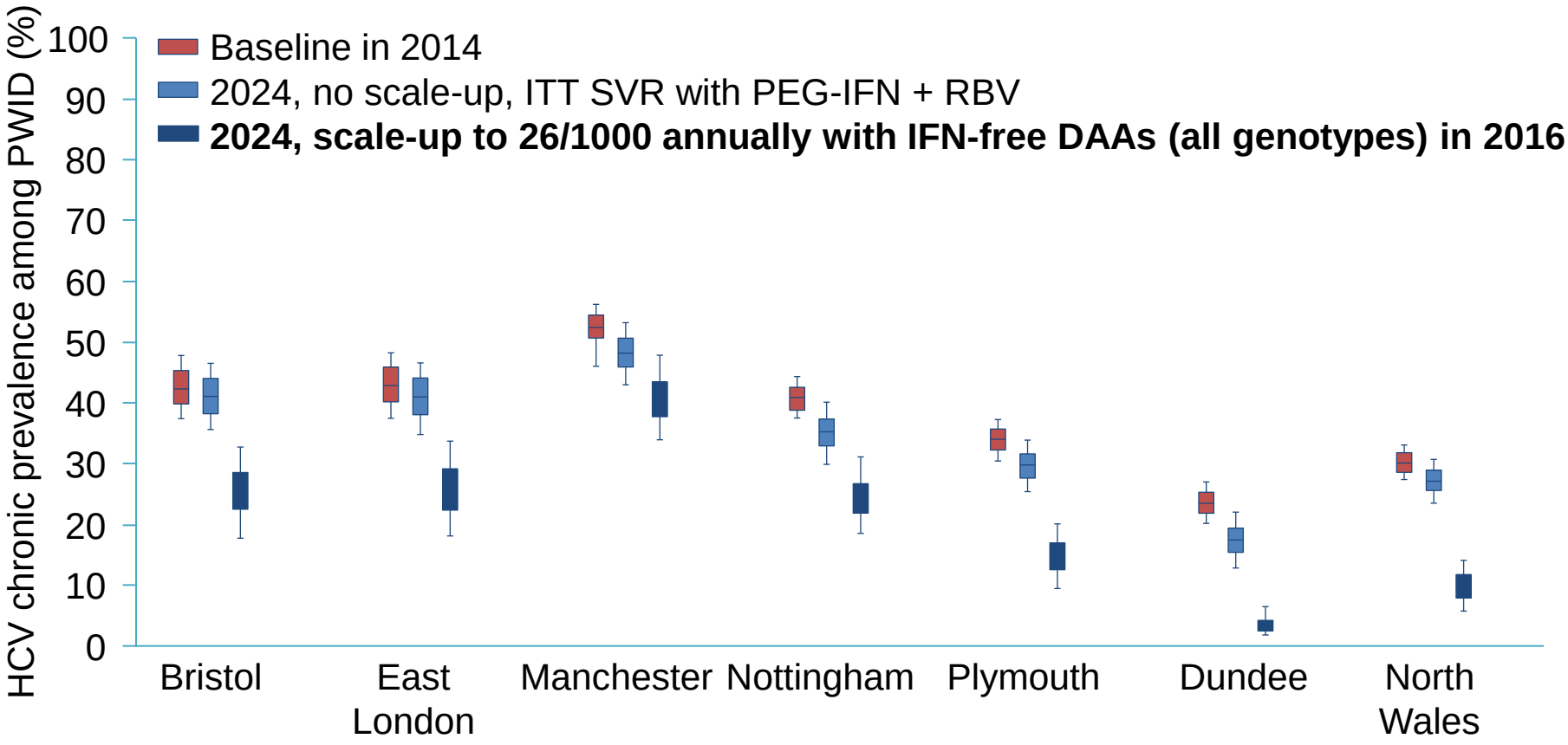
Adapted from Operskalski EA and Kovacs A. Curr HIV/AIDS Rep 2011;8:12–22.

But is HCV Rx just averting Liver-Related Mortality? All cause mortality EuroSIDA



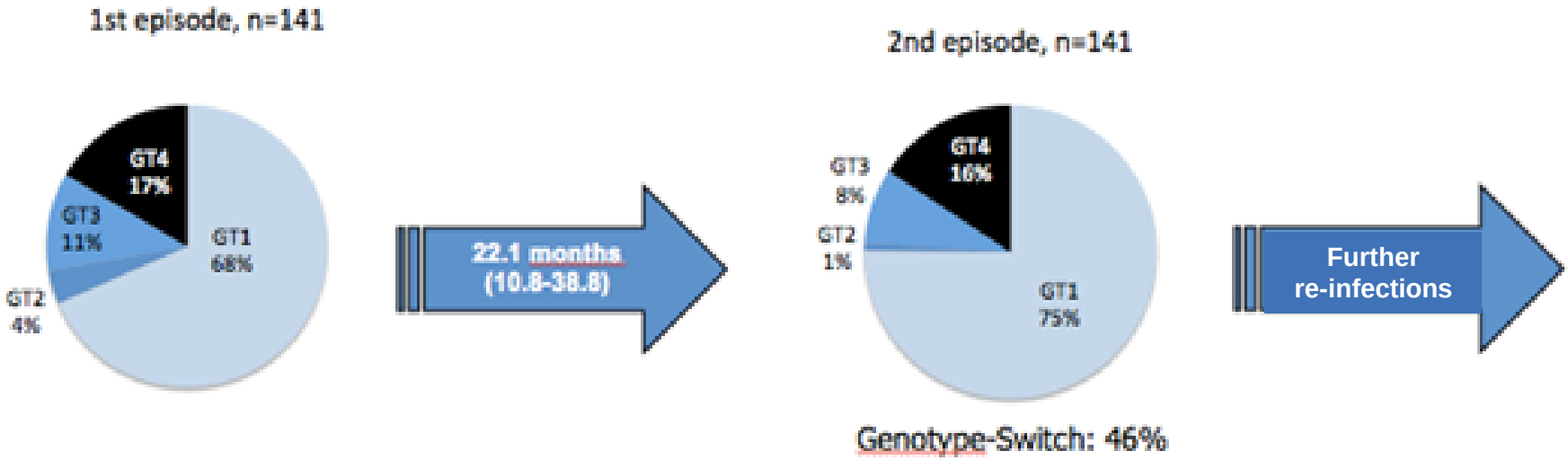
D Grint, et al. CROI 2013

Rx as Prevention - Modelling treatment impact in IDU populations - seven UK cities with scale-up with DAAs



Martin NK, et al. C-Hep, Berlin 2014.

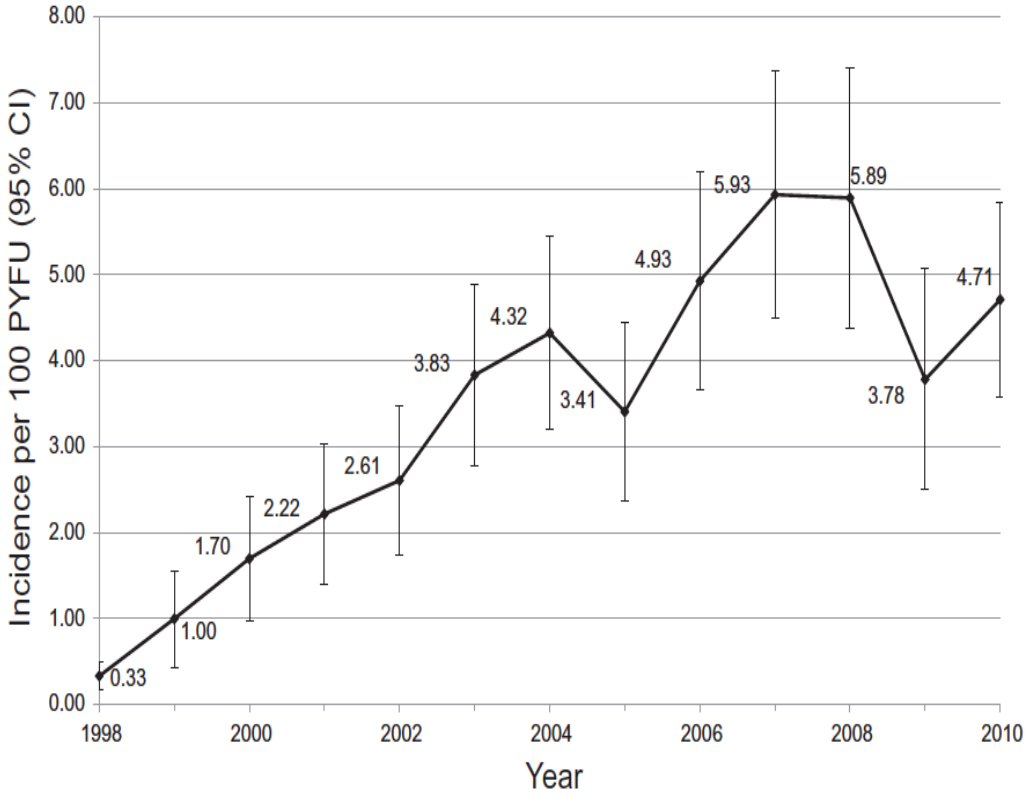
Treatment as Prevention for HCV in HIV+ MSM: Re-infection – a really difficult issue



- 553 patients from 7 NEAT centres with cured acute HCV since 2001
- 141 with at least one re-infection (25.5%)
- 1509 patient years of follow-up; median 2.1 years
- Incidence rate: 7.82/100 patient years

Ingiliz et al, EASL 2014; Martin et al, AIDS 2013.

HCV Rx uptake EuroSIDA



1998–2007: unadjusted IRR 1.27 (95% CI 1.23–1.31; P < 0.0001) per year

2007–2010: unadjusted IRR 0.88 (95% CI 0.79–0.98; P = 0.020) per year

Of those with Fibrosis stage available

- 36% had F<2
- 22% >F2 remain untreated

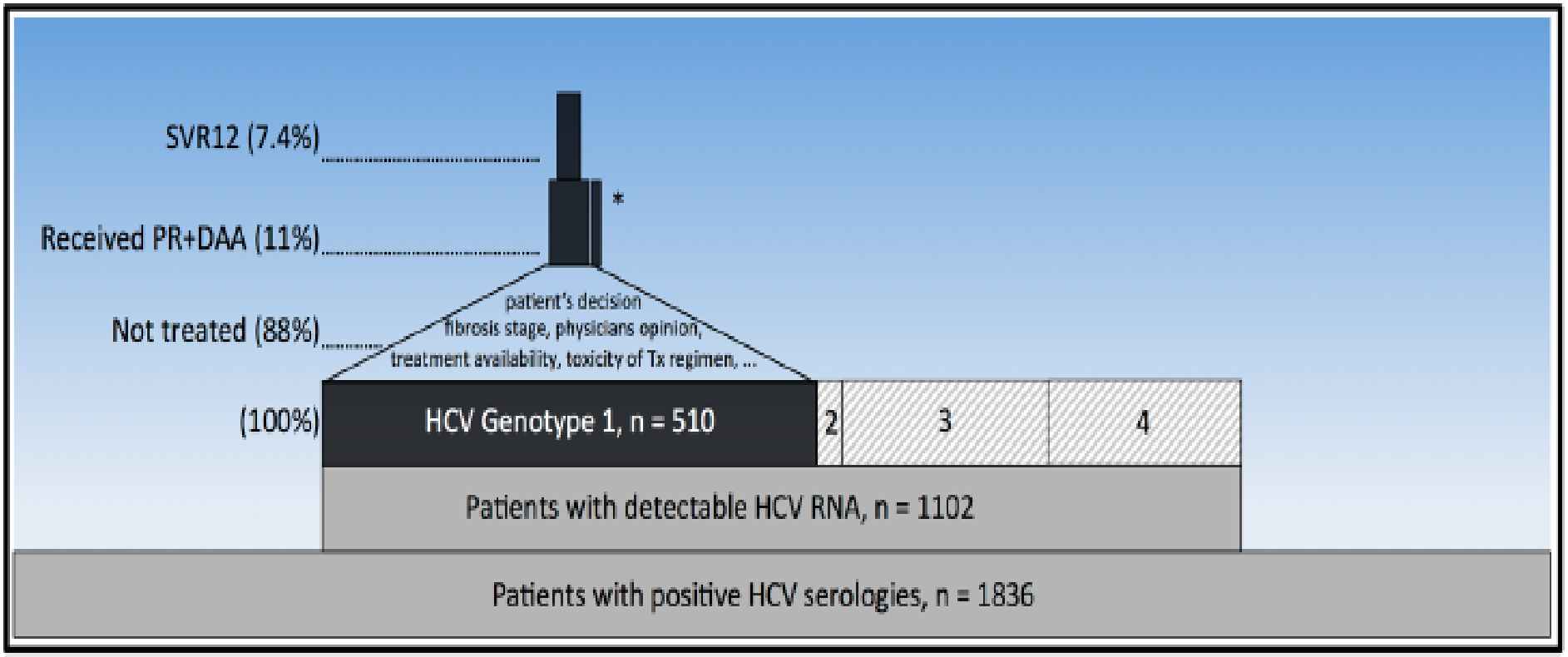
More Rx

- Southern Europe
- MSM (vs. IDU, Heterosexual)

Grint D, et al. HIV Medicine 2013

Swiss HIV Cohort

Figure 1: Pyramid of Care: Treatment uptake and efficacy in the SHCS



Pyramid of care: Timeframe 09/2011-08/2013, *) 6 Patients received PR without DAA

Haubitz, et al. CROI 2014

Current state of play with DAA-based therapy in co-infected patients – the UK experience

- England/Wales
  - Sofosbuvir 'under evaluation' by NICE
    - Expected January 2015, - implementation time 90 days
    - NHSE expanded access programme – Sof/DCV or Sof/LDV (650 patients)
    - Child-Pugh B/C
    - Episode of de-compensation
    - Extra-hepatic manifestations of HCV
- Scotland
  - Sofosbuvir available (with or without IFN)
    - Preference for Sof/PegIFN/R 12 weeks
    - IFN-free restricted to IFN-ineligible/intolerant

AASLD Guidelines (2014)

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
- **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

AASLD Guidelines (2014)

High HCV Transmission Risk*

- **MSM with high-risk sexual practices**
- **Active injection drug users**
- **Incarcerated persons**
- **Persons on long-term hemodialysis**

Rating: Class IIa, Level C

*Patients at high risk of transmitting HCV should be counseled on ways to decrease transmission and minimize the risk of reinfection.

Conclusions

- The era of DAAs and IFN-free therapy is here
- Guidelines need to reflect cost vs. benefit of treatment
  - Need to look at ESLD vs. non-liver morbidity/mortality
  - Priority for treatment
  - Wait vs. Rx now
  - Rx for acute HCV/Rx as prevention in HIV+ MSM/IVDU populations
  - COST major factor

- Disparities in access to DAA-based therapy needs to be addressed URGENTLY

- No longer a ‘Special Need’ population BUT certainly an ‘Urgent Need’ population

HCV/HIV co-infection – ‘shades of grey’

HCV – the end is near…or is it…..