Management of HCV in patients co-infected with HIV

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HIV/HCV coinfection: a prevalent challenge

- HCV co-infection is common among HIV infected individuals
- Among HIV-infected individuals in the US
  - 25% are co-infected with HCV
  - ≈80% of HIV(+) IDUs are co-infected with HCV
- Globally, the incidence of HCV is increasing among MSM
- HIV/HCV co-infection increases the risk of disease progression associated with both viruses
- Screening and treatment of both infections is important

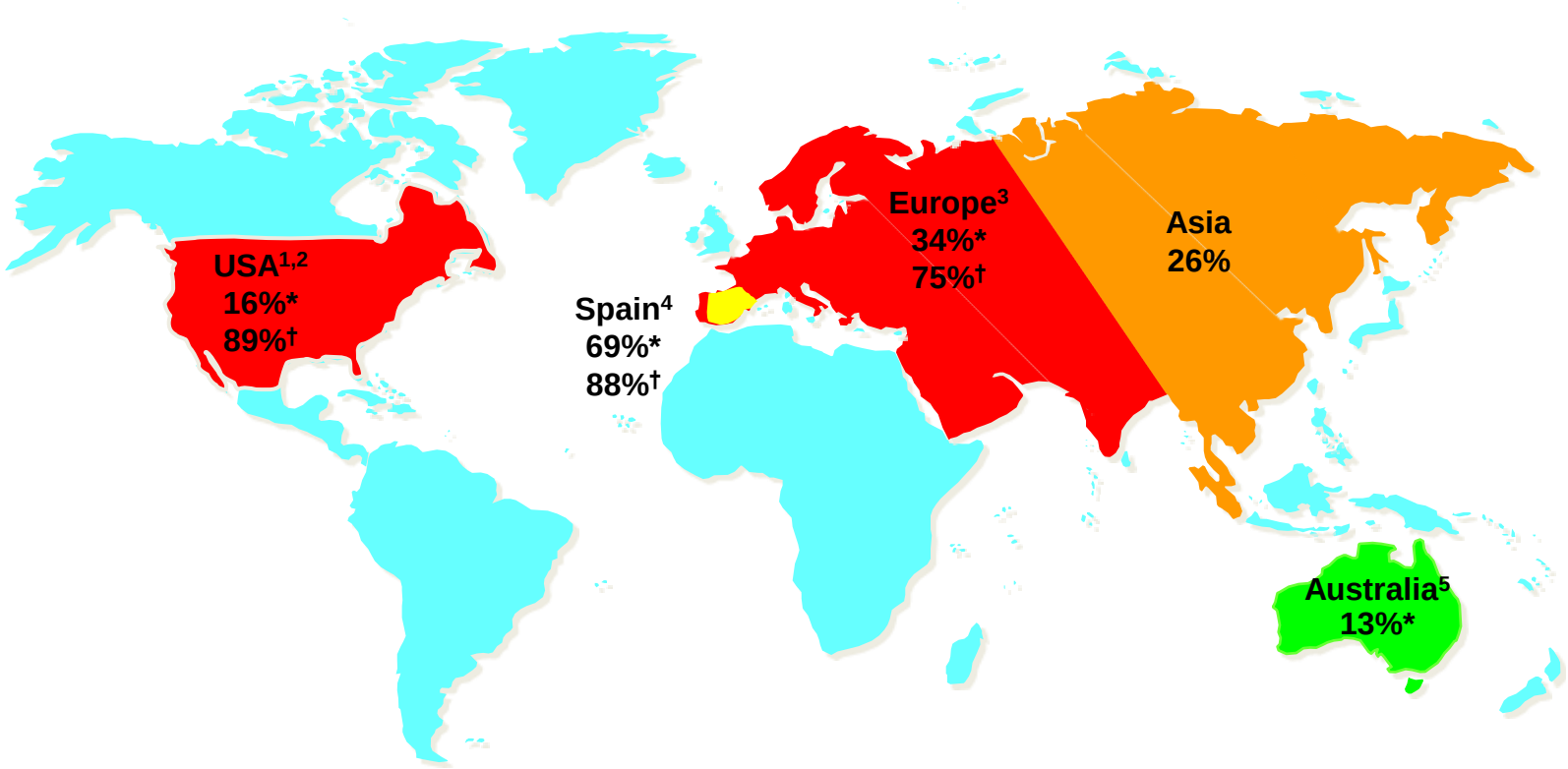
IDU, intravenous drugs; MSM, men who have sex with men.
http://www.cdc.gov/hiv/pdf/library_factsheets_HIV_and_viral_Hepatitis.pdf, Taylor LE, et al. Clin Inf Dis 2013;57:s118-s124

Comparison of viral characteristics: HBV, HCV and HIV infection

	Hepatitis B virus[1,2]	Hepatitis C virus[1,3]	Human immuno-deficiency virus[3]
Type of virus	Hepadnavirus (DNA)	Flavivirus (ssRNA)	Retrovirus (ssRNA)
Mechanism of persistence	Active replication until host immune response clears infected cells	Continuous active replication	Latency
Viral mutation rate	Phase-dependent	10^2–10^3/year	10^4–10^5/day
Immune response	Good	Poor	Good
Antibody response	Variable	Ineffective due to viral escape	Ineffective due to viral escape
Goal of therapy	Viral supression	Viral eradication/CURE	Viral suppression
Prophylaxis	Recombinant vaccine; immune globulin (post-exposure)	Unavailable	Unavailable

Worldwide prevalence of HCV in patients with HIV infection

30% of patients with HIV infection are co-infected with HCV; among HIV-infected intravenous drug users (IVDUs), this figure rises to 75–90%



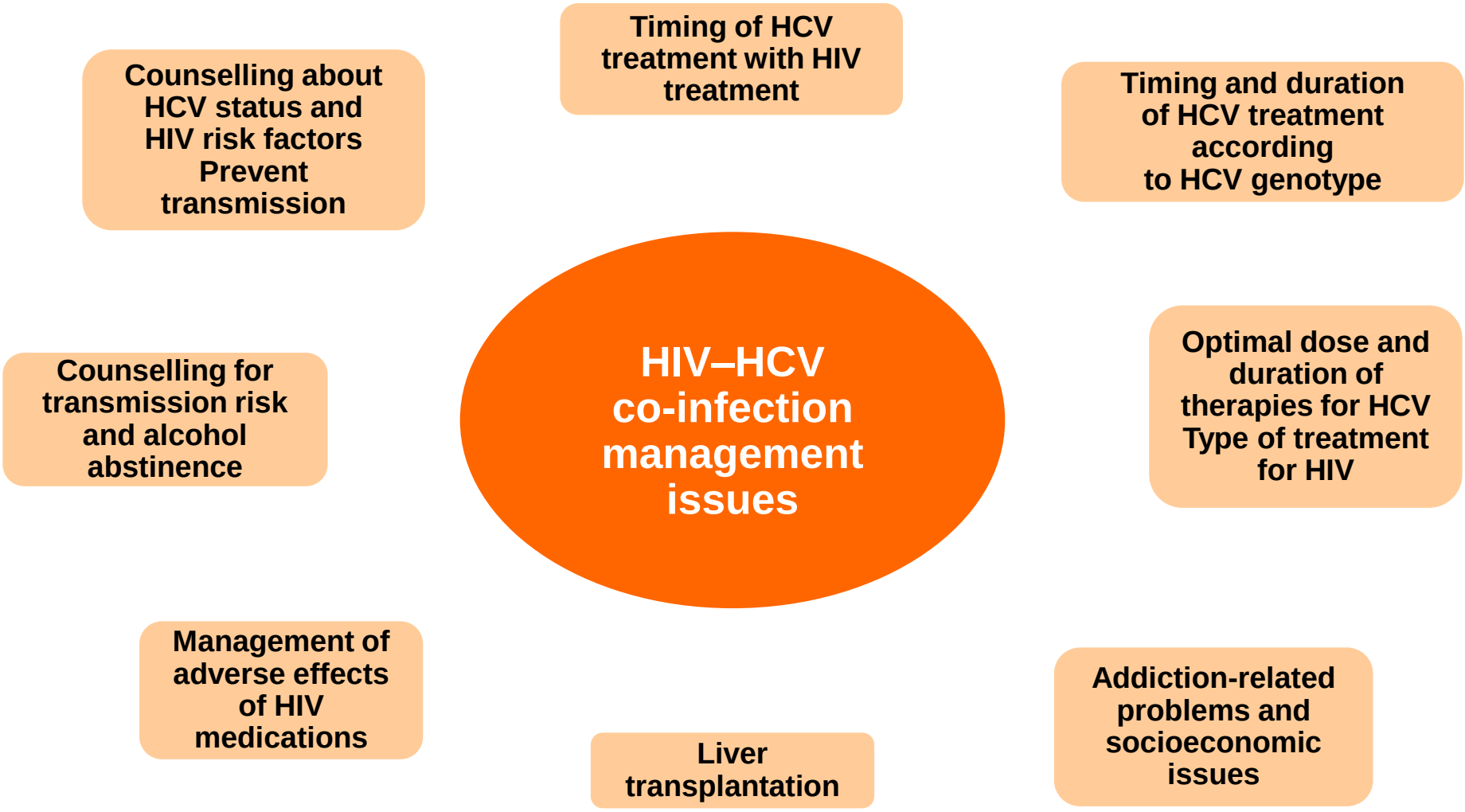
* General HIV-infected population
† IVDU population

1. Sherman K, et al. Clin Infect Dis 2002; 34: 831
2. Strasfeld L, et al. J Acquir Immune Defic Syndr 2003; 33: 356
3. Rockstroh J, et al. 9th European AIDS Conference 2003; Abstract F12/4
4. Roca B, et al. J Infect 2003; 47: 117
5. Dore G and Sasadeusz J, ed. Australasian Society for HIV Medicine 2003

Liver disease is the leading cause of death among hospitalised AIDS patients

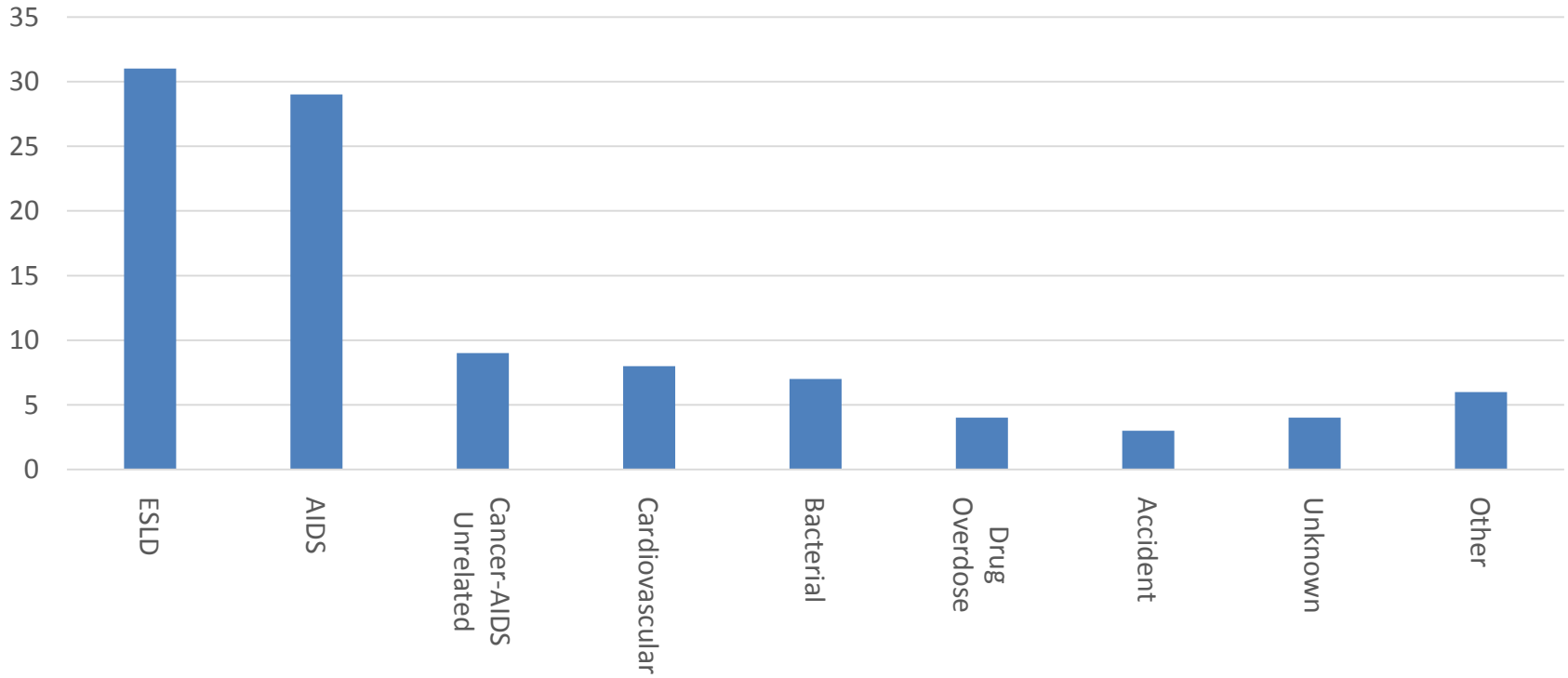
- HIV accelerates the clinical course of HCV-related liver disease:
  - Faster time to cirrhosis[1–2]
  - Faster time to / increased risk of HCC[3]
  - More patients develop cirrhosis within a given time frame[1]
  - NASH/Alcohol/ASH has an additional aggravating effect on cirrhosis risk
- HCV co-infection:
  - Increases the risk of antiretroviral drug-associated hepatotoxicity
  - Dampens the CD4 response to antiretroviral therapy during treatment[4]

HIV–HCV co-infection management issues



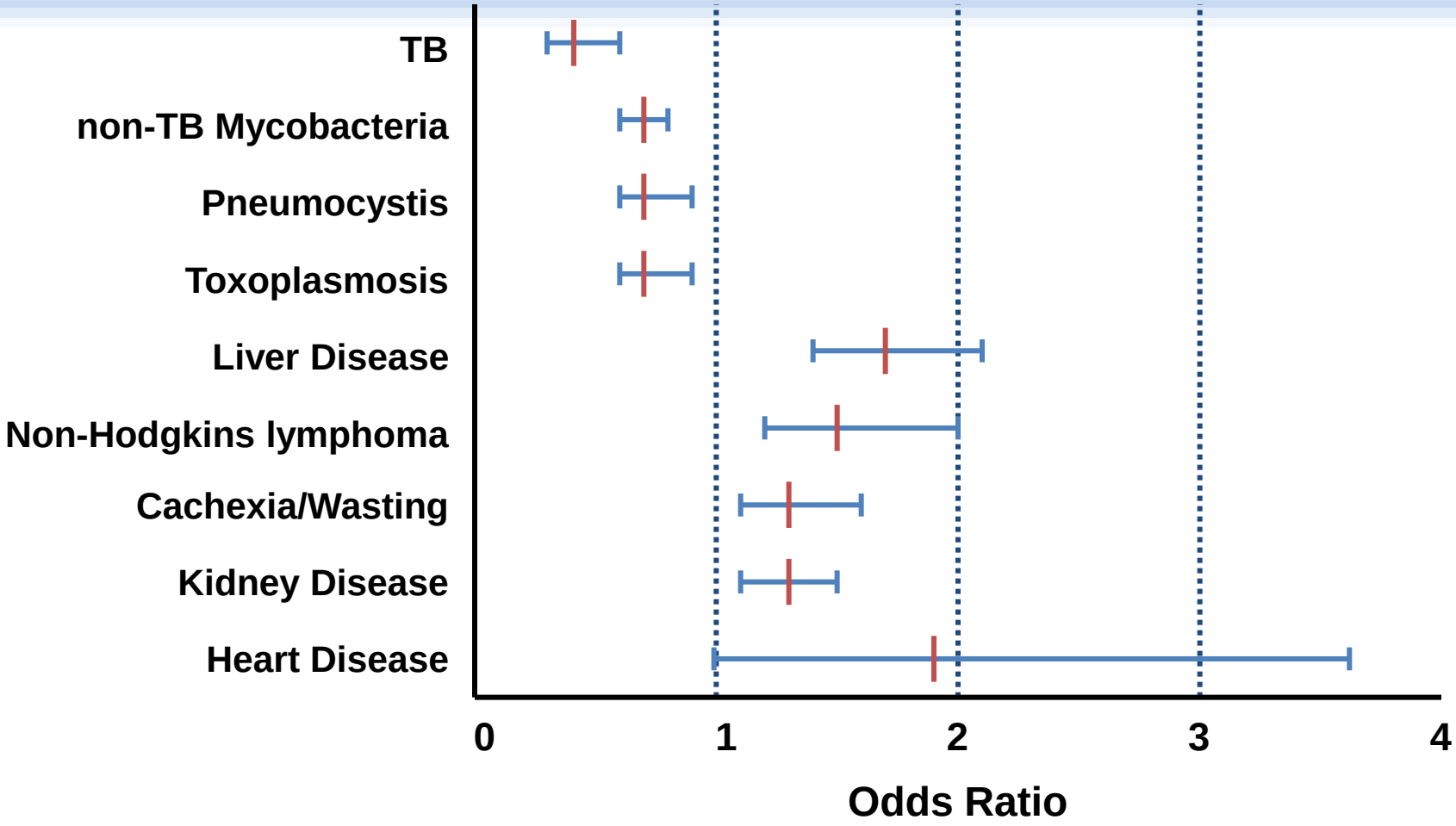
Causes of Death in HIV HCV Co-infection

French Mortality 2000 Cohort



Among Patient with Markers of HBV or HCV Infection

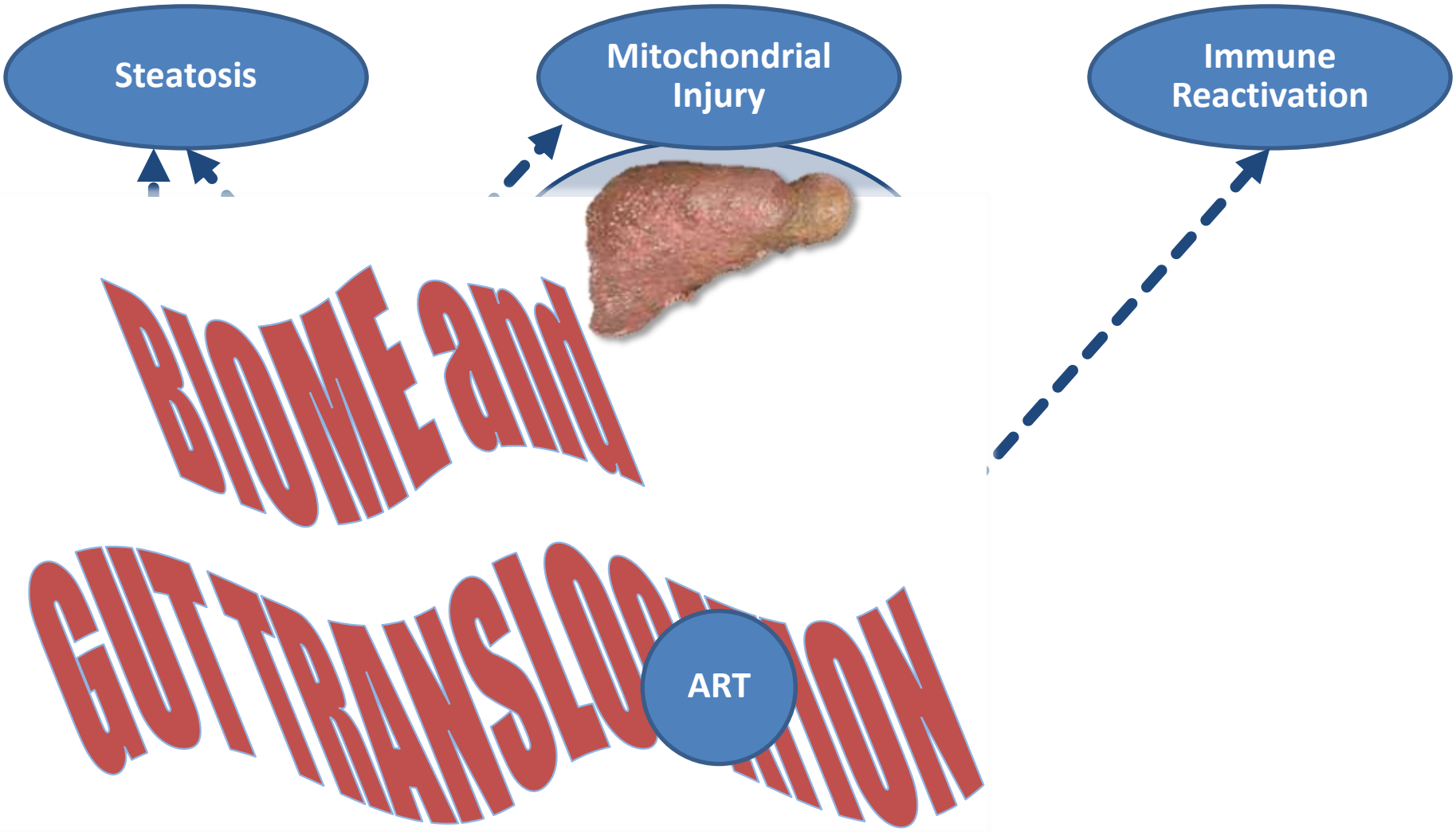
Causes of Death
Post- vs. Pre-HAART



Wolfe MI, 9th CROI.

Etiologies of Liver Injury

HIV **HCV (& HBV)**



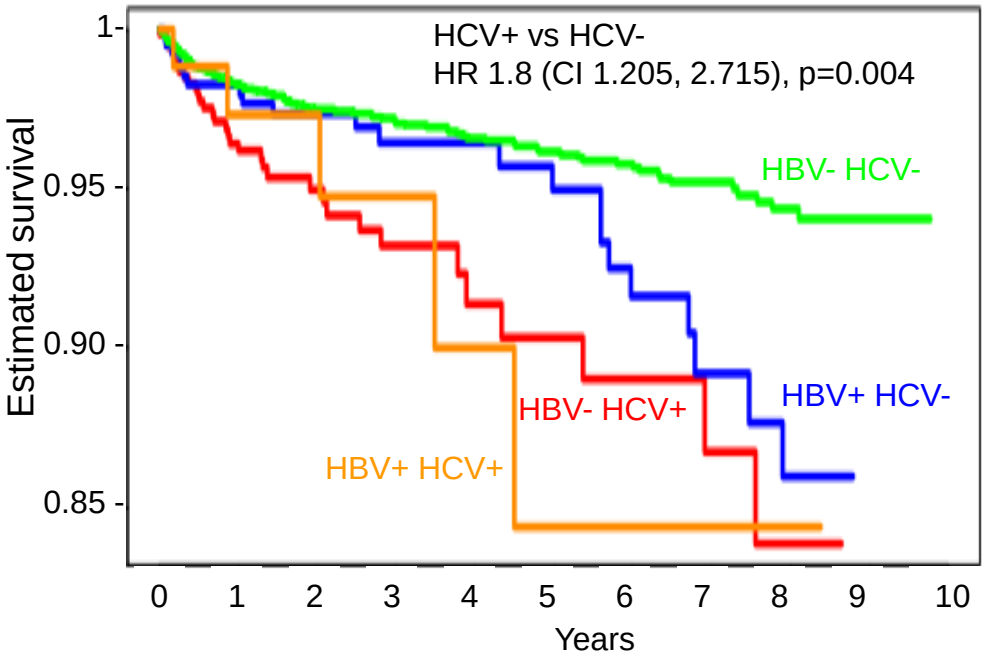
HCV Outbreaks in MSM> change in behaviour

- Paris, N=29 — Gambotti L et al., Euro Surveill, May 2005 — *High-risk behavior: anal sex, fisting, concomm STI, bleeding during sex*
- San Francisco, N=9 — Luetkemeyer et al., JAIDS, Jan 2006
- Paris, N=25 — Dominguez S et al. AIDS, May 2006
- Paris, N=6 — Ghosn J et al., Sex Transm Infect, Dec 2006
- Paris, N=12 — Serpaggi et al., AIDS, Dec 2006
- London, N=111 — Danta M, AIDS, May 2007 — *7 clusters, RFs: sex with 3+ partners, hi-risk sexual behavior*
- New York, N=11 — Fierer D et al., J Infect Dis, 2008 — *histology with inflammation and septal fibrosis*

Reduced response to ARVs in patients coinfected with HIV/HCV and HBV: TAHOD

- Observational database: 7,455 HIV-positive patients (22 hospitals, 11 countries)
- Coinfection: 15% with HCV, 11% with HBV

Overall survival after cohort entry by coinfection status



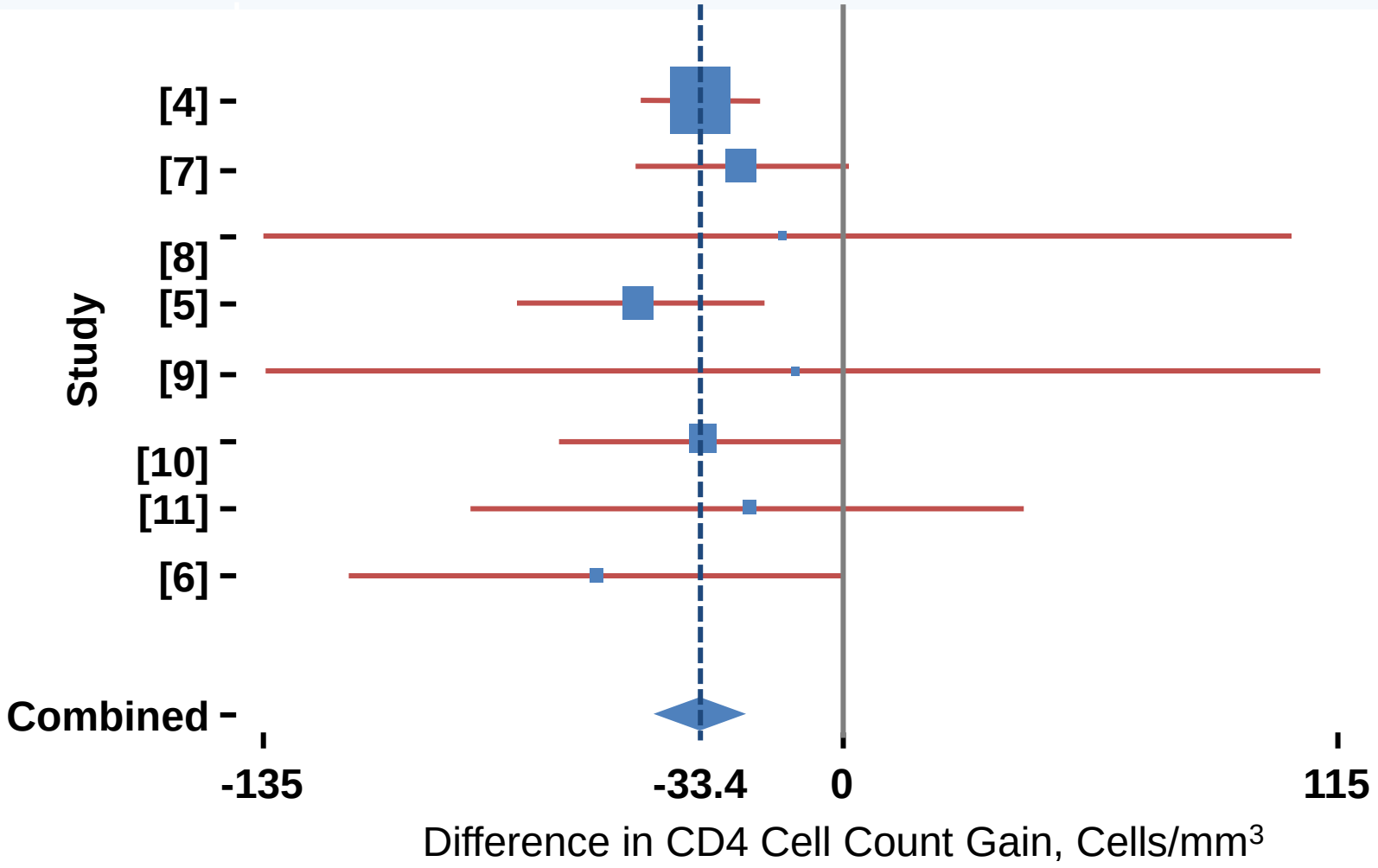
CD4 change after 6 months of ART

HCV status (N)	Mean ΔCD4 (SD)	Univariate Diff. , P value	Multivariate* Diff. (95% CI) P value
Neg (3010)	125 (110)		
Pos (512)	90 (94)	-34 <0.001	-24 (-37, -11) <0.001

*Adjusted by gender and age. Covariates HBsAg, mode of infection, baseline CD4, baseline HIV RNA, HIV-1 subtype.

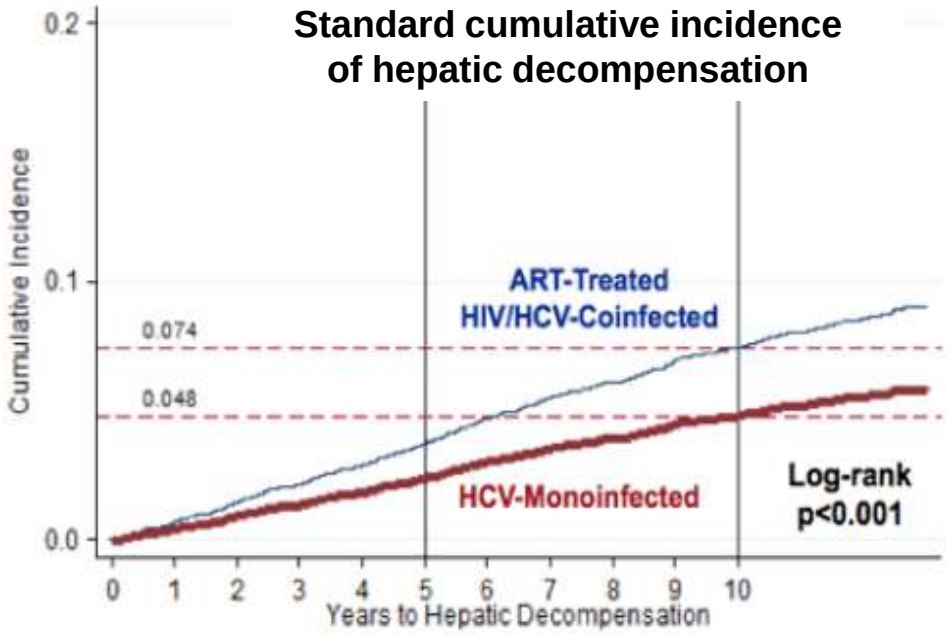
TAHOD, TREAT Asia HIV Observational Database.
Chen Y.-M.A. et al. IAS 2013; poster TULBPE13.

Effect of HCV on HIV T-cell Rebound with ART



Increased risk of hepatic decompensation in patients co-infected with HIV/HCV

- VACS cohort (1997-2010)
- HCV mono-infected patients (N=6079) and HIV/HCV co-infected patients on ART (N=4280)
- All HCV treatment-naïve, with detectable HCV RNA and no hepatic decompensation or HCC



Outcome	Adjusted Hazard Ratio* (95% CI)
Hepatic decompensation	
All patients	1.83 (1.54 - 2.18)
HIV/HCV patients with:	
HIV RNA<1,000 during follow-up (n=966)	1.71 (1.23 - 1.36)
HIV RNA<400 during follow-up (n=386)	1.73 (1.00 - 3.01)
Hepatocellular carcinoma	1.69 (1.13 - 2.52)
Severe liver events	1.77 (1.52 - 2.06)

* Adjusted for age, race, BMI, history of alcohol / drug abuse, and size of VA center.

VACS, Veterans Aging Cohort Study.
LoRe V, et al. IAC 2012; abstract WEAB0102.

Hepatotoxicity of antiretroviral agents: predictive factors in co-infection

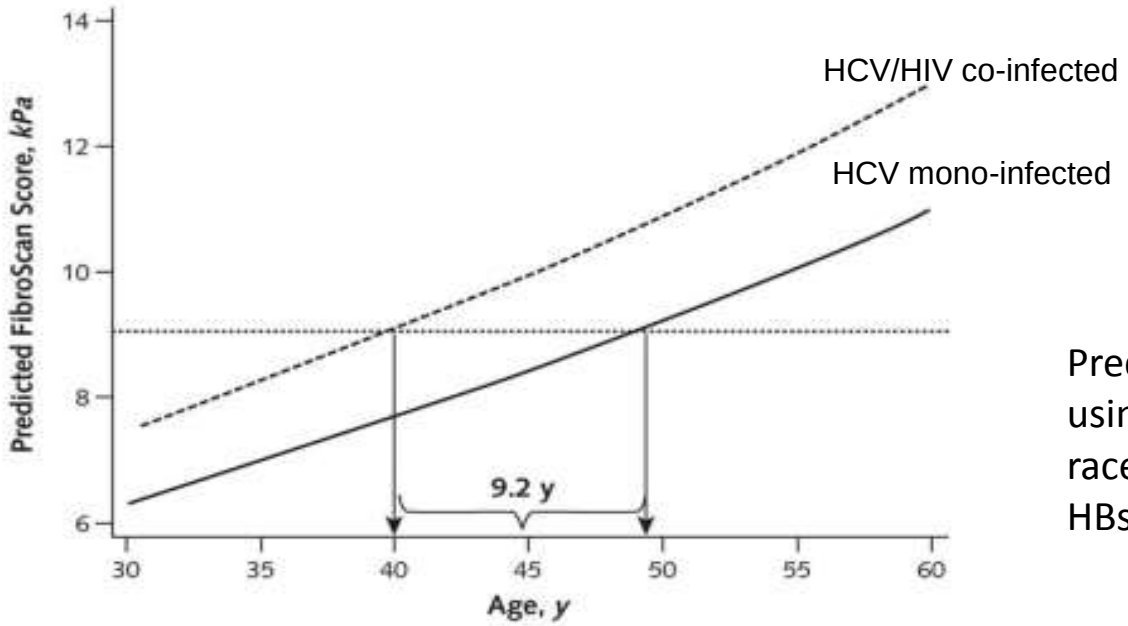
Author	No. of patients	ART	HCV-positive (%)	Hepatotoxicity rate – grade 3 or above (%)	Predictive factors
Aceti[1]	1325	PI-based	5% unadjusted odds	3.2	HCV, alcohol, no CD4 response to HAART, RTV
den Brinker[2]	394	ART	33	18	HCV, HBV, ALT*
Núñez[3]	222	ART	16	9	HCV, alcohol, age, ddI, RTV
Saves[4]	1997	2 NRTIs	10	2	HCV, HBV, ALT*
Savès[5]	1047	PI-based	OR: 8.0	5	HCV, HBV
Sulkowski[6]	568	NNRTI-based	17	23.6	HCV, HBV, NVP, PI
Wit[7]	560	ART	34	6.3	HCV, HBV, ALT*, NVP, RTV, SQV, first HAART regimen

* Baseline ALT

1. Aceti A, et al. J AIDS 2002; 29: 41
2. den Brinker M, et al. AIDS 2000; 14: 2895
3. Núñez M, et al. J AIDS 2001; 27: 42
4. Savès M, et al. AIDS 1999; 13: F115
5. Savès M, et al. Antimicrob Agents Chemother 2000; 44: 3451
6. Sulkowski M, et al. Hepatology 2002; 35: 182
7. Wit F, et al. J Infect Dis 2002; 186: 23

HIV coinfection accelerates HCV-associated liver fibrosis by almost 10 years

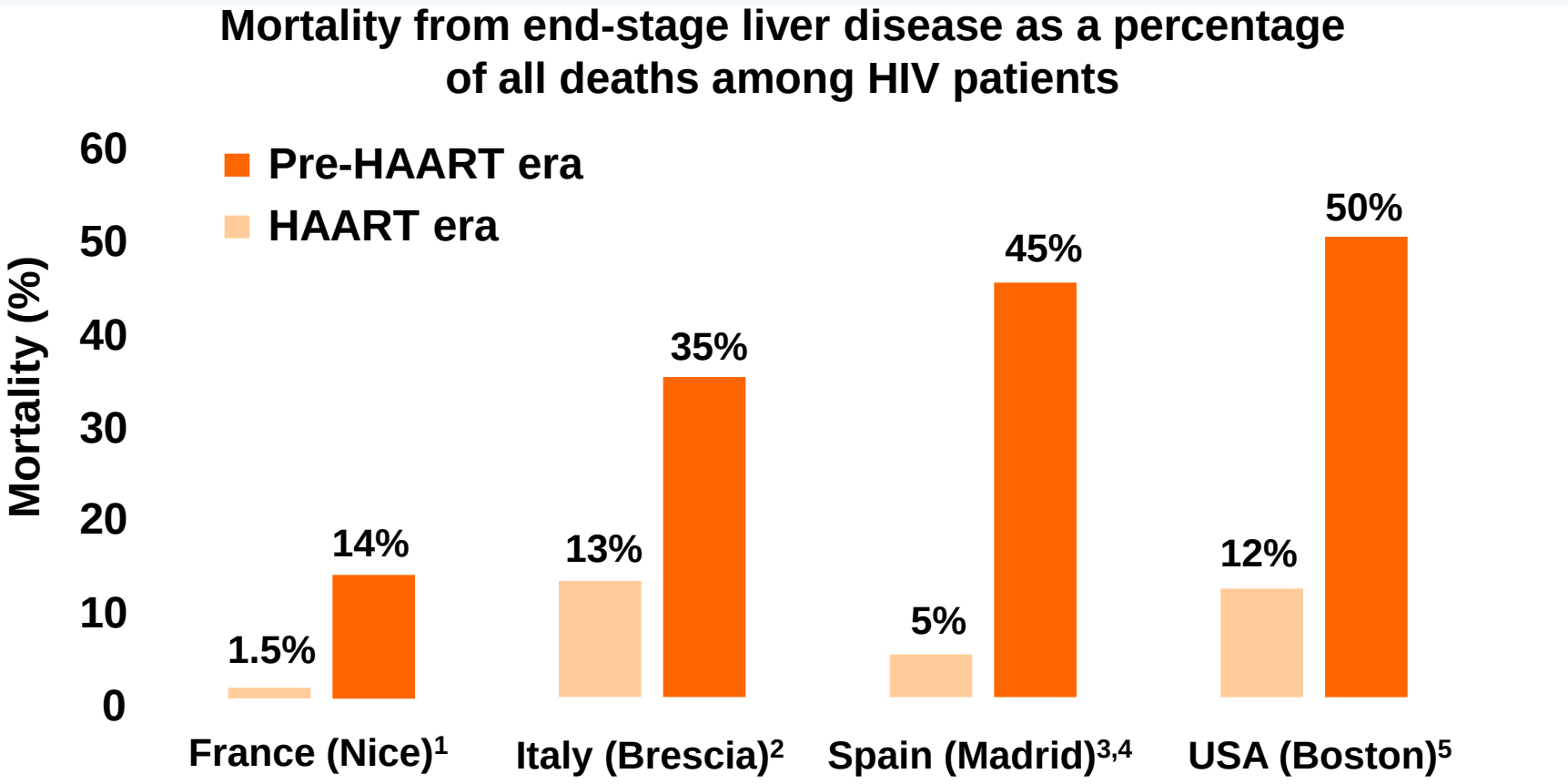
- ALIVE cohort: 1176 current and former IDUs with HCV antibodies, 34% co-infected with HIV
- Greater prevalence among HCV/HIV co-infected patients than HCV mono-infected patients of:
  - Clinically significant fibrosis without cirrhosis (12.9% vs. 9.5%)
  - Cirrhosis (19.5% vs. 11.0%, p< 0.001)



Predicted liver fibrosis scores calculated using regression analysis including race, sex, alcohol use, body mass index, HBsAg status, and HCV RNA level

ALIVE, AIDS linked to the IntraVenous Experience study.
Kirk GD, et al. Ann Intern Med. 2013;158:658-66.

Liver disease: a major cause of death in the HAART era



1. Rosenthal E, et al. AIDS 2003; 17: 1803
2. Puoti M, et al. JAIDS 2000; 24: 211
3. Martín-Carbonero L, et al. AIDS Res Human Retrovirus 2001; 17: 1467
4. Soriano V, et al. Eur J Epidemiol 1999; 15: 1
5. Bica I, et al. Clin Infect Dis 2001; 32: 492

HBV increases risk of death in patients coinfected with HCV and HIV

- Spanish VACH cohort: 6379 HCV/HIV coinfected patients
- 355 (6%) also infected with HBV
- 543 deaths across 26,000 person-years of follow-up
- Univariate analysis
  - HBV increased the risk of death by 90% (HR 1.90; 95% CI, 1.42-2.54)
- Multivariate analysis
  - adjusted for prior AIDS-defining illness, age, HIV and HCV treatment, CD4 count and HIV viral load
  - HBV increased the risk of death by 75% (HR 1.745; 95% CI, 1.41-2.67)

Teira R, VACH Study group. AIDS 2013;27:845-8.

HCV treatment reduces the risk of cirrhosis in HIV/HCV-co-infected patients

- Prospective cohort: 166 HIV/HCV coinfected patients with compensated cirrhosis
- Treated with peg-IFN plus ribavirin

	With SVR (N=43)	Without SVR (N=123)
Liver decompensation	2 (4.6%)	33 (26.8%)
Liver-related complications	0.89 per 100 PY (CI 0.11-3.1)	6.4 per 100 PY (CI 4.5-8.9)
All cause mortality	2 (4.6%)	22 (17.9%)

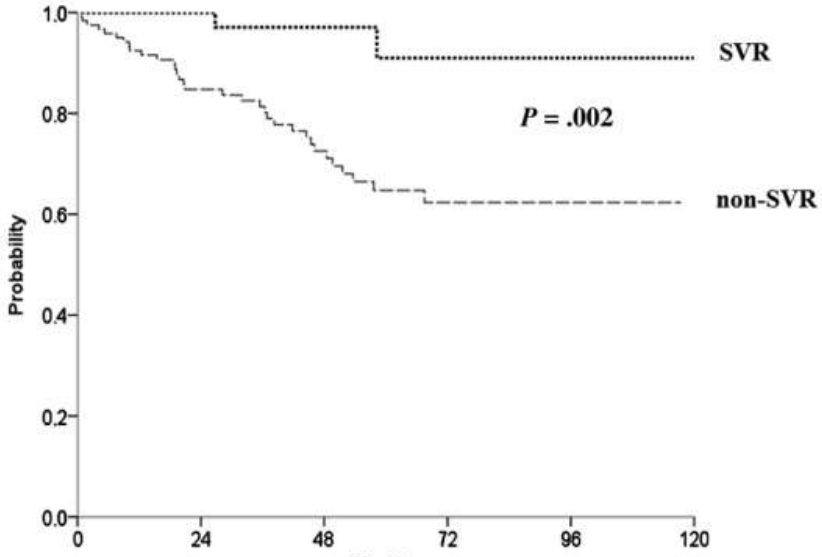
- Factors independently associated with liver decompensation
  - Non-SVR (HR 8.1, CI 1.08-61.5, p = 0.042)
  - MELD score ≥9 at baseline (HR 2.9, CI 1.2-7.2, p = 0.016)
- Factors independently associated with all cause mortality
  - Non-SVR (HR 8.0, CI 1.07-61, p = 0.043)
  - MELD score ≥9 (HR 3.1, CI 1.3-7.7; p = 0.011)

CI, 95% confidence interval; PY, person years; SVR, sustained virologic response
Mira JA, et al. Clin inf Dis 2013;56:1646-53.

HCV treatment reduces the risk of cirrhosis in HIV/HCV-co-infected patients

- Prospective cohort: 166 HIV/HCV coinfected patients with compensated cirrhosis treated with peg-IFN plus ribavirin

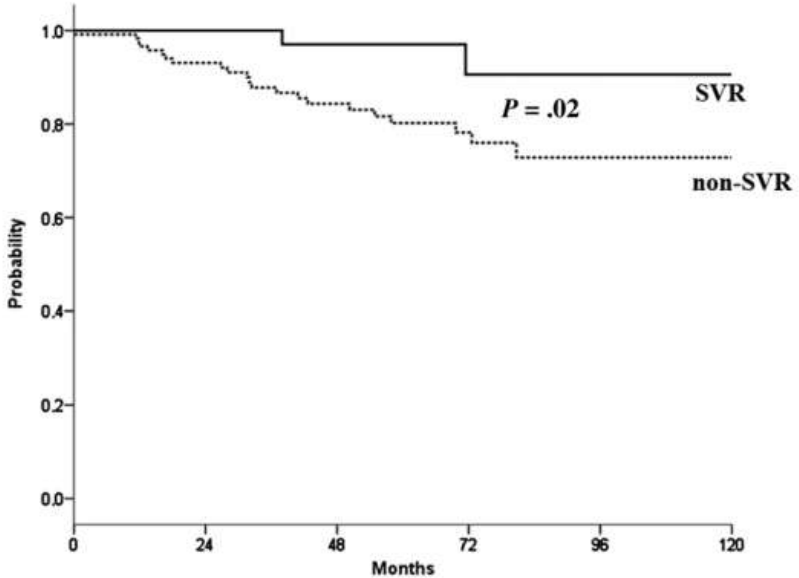
KM estimate for all hepatic decompensation



Patients at risk:

SVR	43	33	25	14	8	1
non-SVR	123	95	61	29	8	1

KM estimate for all cause mortality



risk:

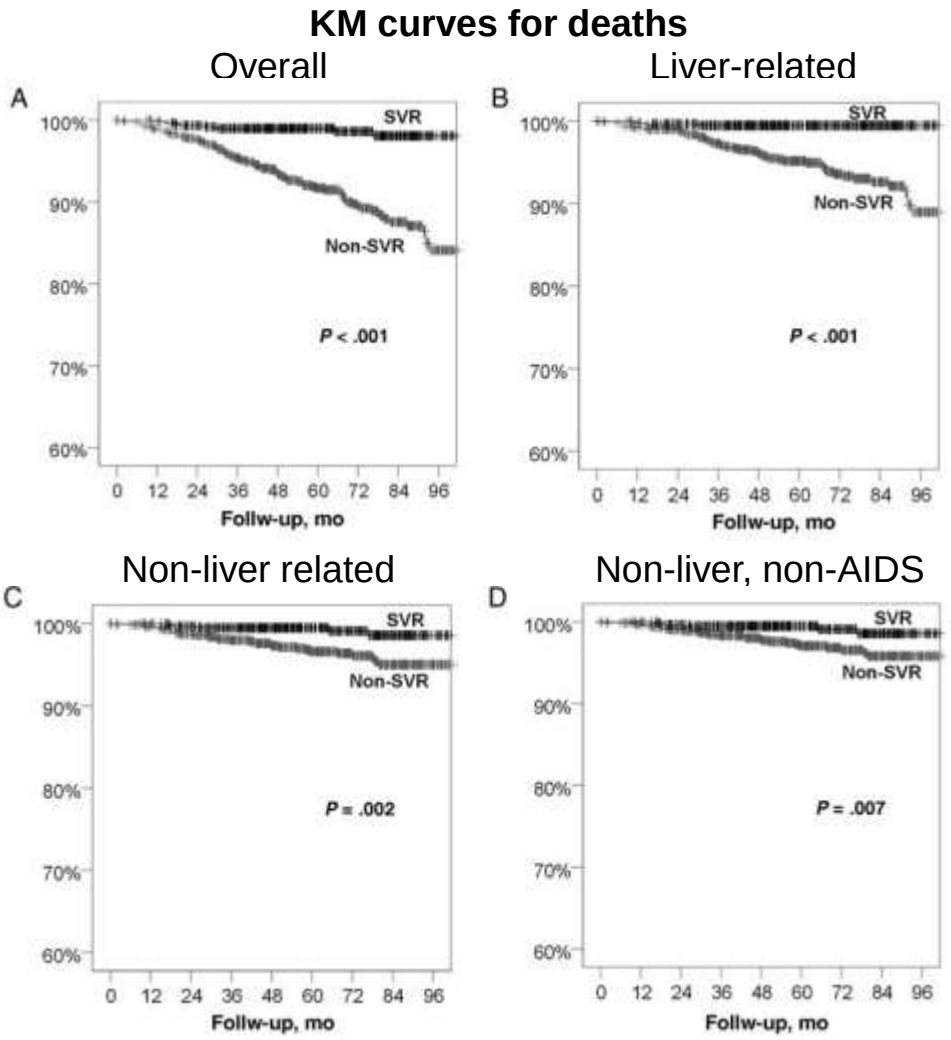
R	43	33	25	14	8	1
n-SVR	123	99	65	36	10	1

Mira JA, et al. Clin inf Dis 2013;56:1646-53.

HCV treatment reduces HIV progression in HIV/HCV co-infected patients

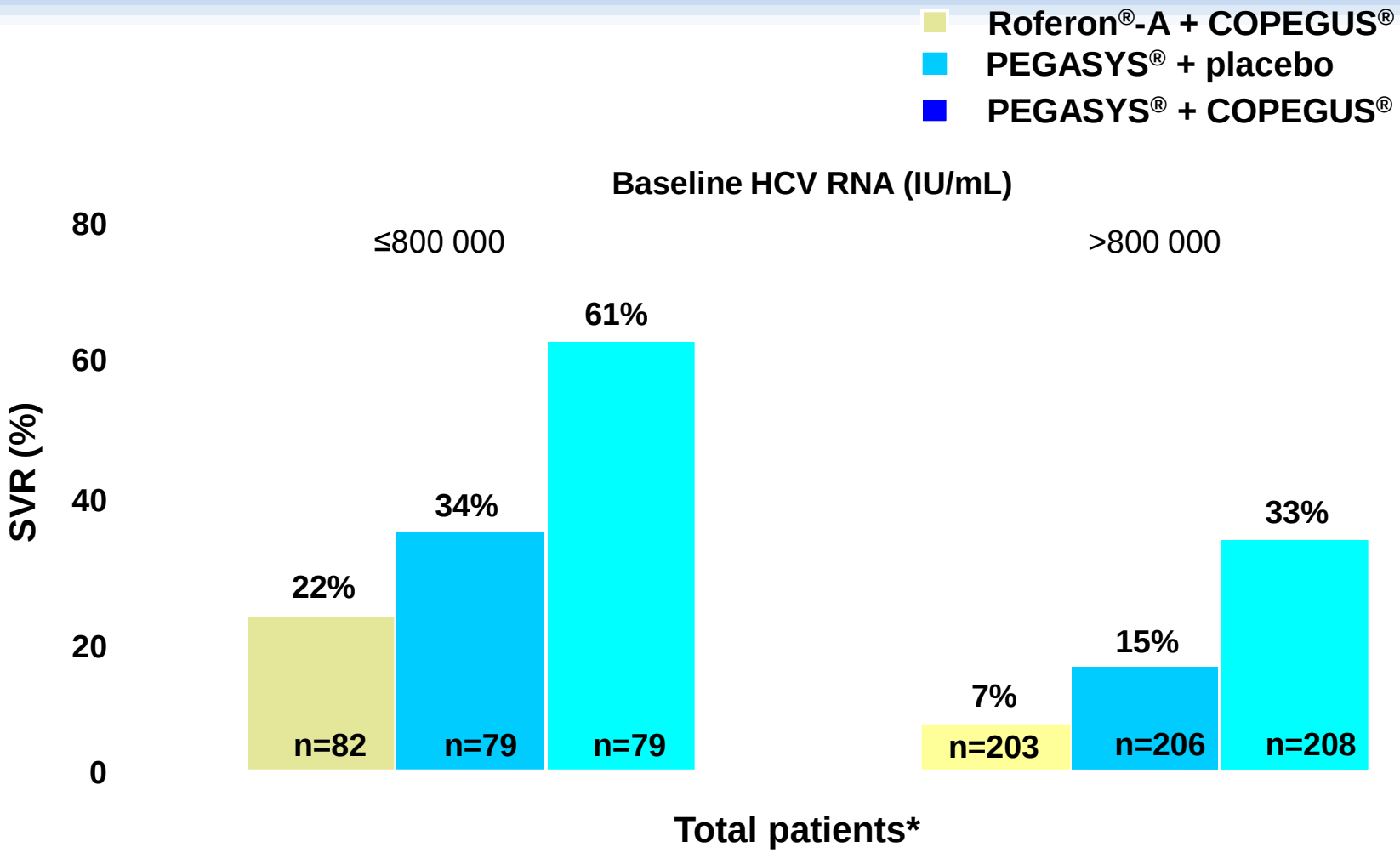
- Observational cohort
- 1599 HIV/HCV coinfected patients
- Treated with peg-IFN plus ribavirin
- Median follow up 5 yrs
- SVR in 626 (39%)

Adjusted HR (95% CI) for non-responders vs responders*	
New AIDS-defining events	1.90 (0.89–4.10) p = 0.095
Non-liver-related deaths	3.19 (1.21–8.40) p = 0.019
Non-liver, non-AIDS-related deaths	2.85 (1.07–7.60) p = 0.036



*Adjusted for age, sex, HIV transmission category, CD4 nadir, advanced fibrosis, HIV RNA <50 c/mL and antiretroviral therapy.
HR, hazard ratio; SVR, sustained virologic response.
Berenguer J, et al. Clin Inf Dis. 2012;55:728-36 .

PEGASYS® plus COPEGUS®: superior efficacy regardless of baseline viral load



* Baseline HCV RNA levels were not available for 3 patients

Torriani F, et al. N Engl J Med 2004; 351: 438

HCV/HIV co-infection

- **HCV infection in 20–30% of HIV-1 infected individuals[1,2]**
  - **Approaches 95% in some groups of intravenous drug users[3]**
- **Co-infection with HIV accelerates the progression of chronic HCV towards cirrhosis and end-stage liver disease[4]**

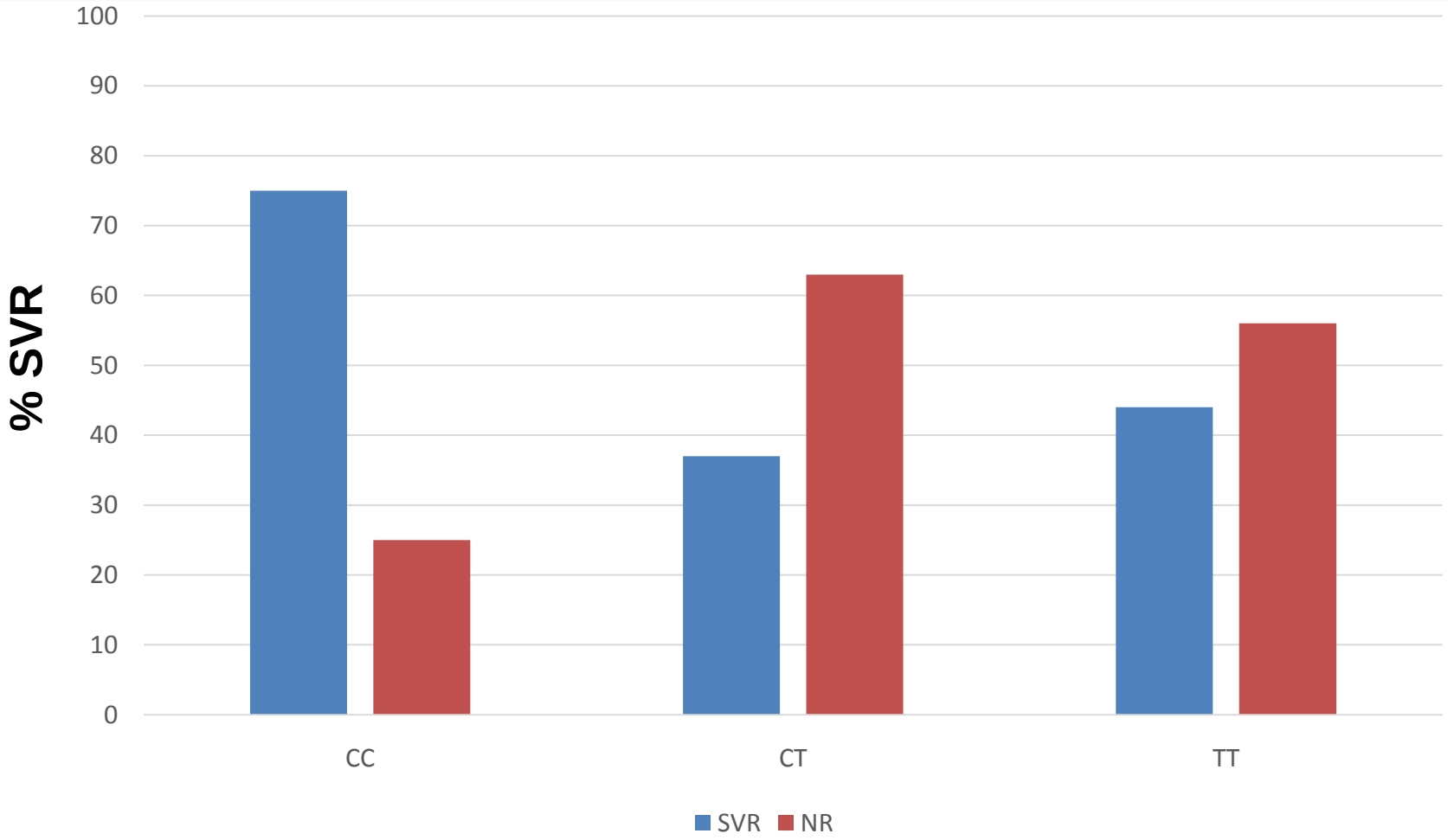
HCV treatment options for HCV/HIV co-infected patients:

- **PR in treatment-naïve individuals in G1**
  - **ACTG trial[5]** — **17% SVR24**
  - **APRICOT trial[6]** — **29% SVR24**
  - **RIBAVIC trial[7]** — **17% SVR24**
  - **Long (48-week) treatment duration**
- **PR + HCV protease inhibitors in treatment-naïve individuals in G1**
  - **Telaprevir[8]** — **74% SVR24**
  - **Boceprevir[9]** — **61% SVR12**
- **Adverse-event profile similar to that observed in mono-infected patients**

G, genotype; PR, peginterferon-α2a + ribavirin; SVR12(24), sustained virologic response ,12(24) weeks' after end of treatment

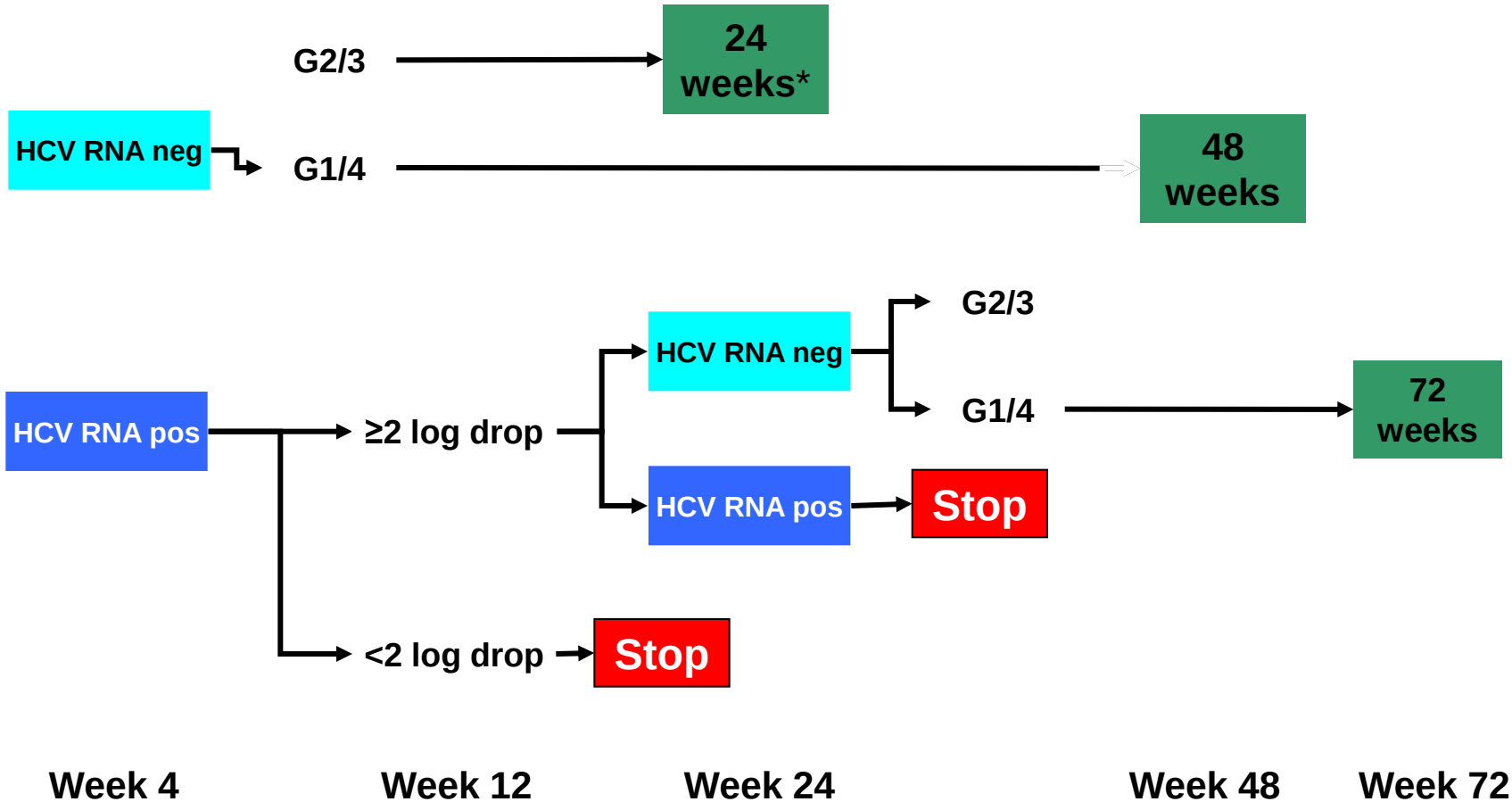
[1]Sherman KE et al. Clin Infect Dis 2002;34:831–837; [2]Lauer G & Walker BD. N Engl J Med 2001;345:41–52; [3]Sulkowski MS & Thomas DL. Clin Infect Dis 2005;40(Suppl 5):S263–269; [4]Kontoris N et al. AIDS 2005;19(Suppl 3):S166–173; [5]Chung RT et al. N Eng J Med 2004;351:451–459; [6]Torriani FJ et al. N Eng J Med 2004;351:438–450; [7]Carrat et al. JAMA 2004;292:2839–2848; [8]Sulkowski MS et al. Abstract 54 presented at AASLD 2012; [9]Mallolas J et al. Abstract 50 presented at EASL 2012

IL28B and SVR HCV/HIV



Rallon et al. AIDS 2010.

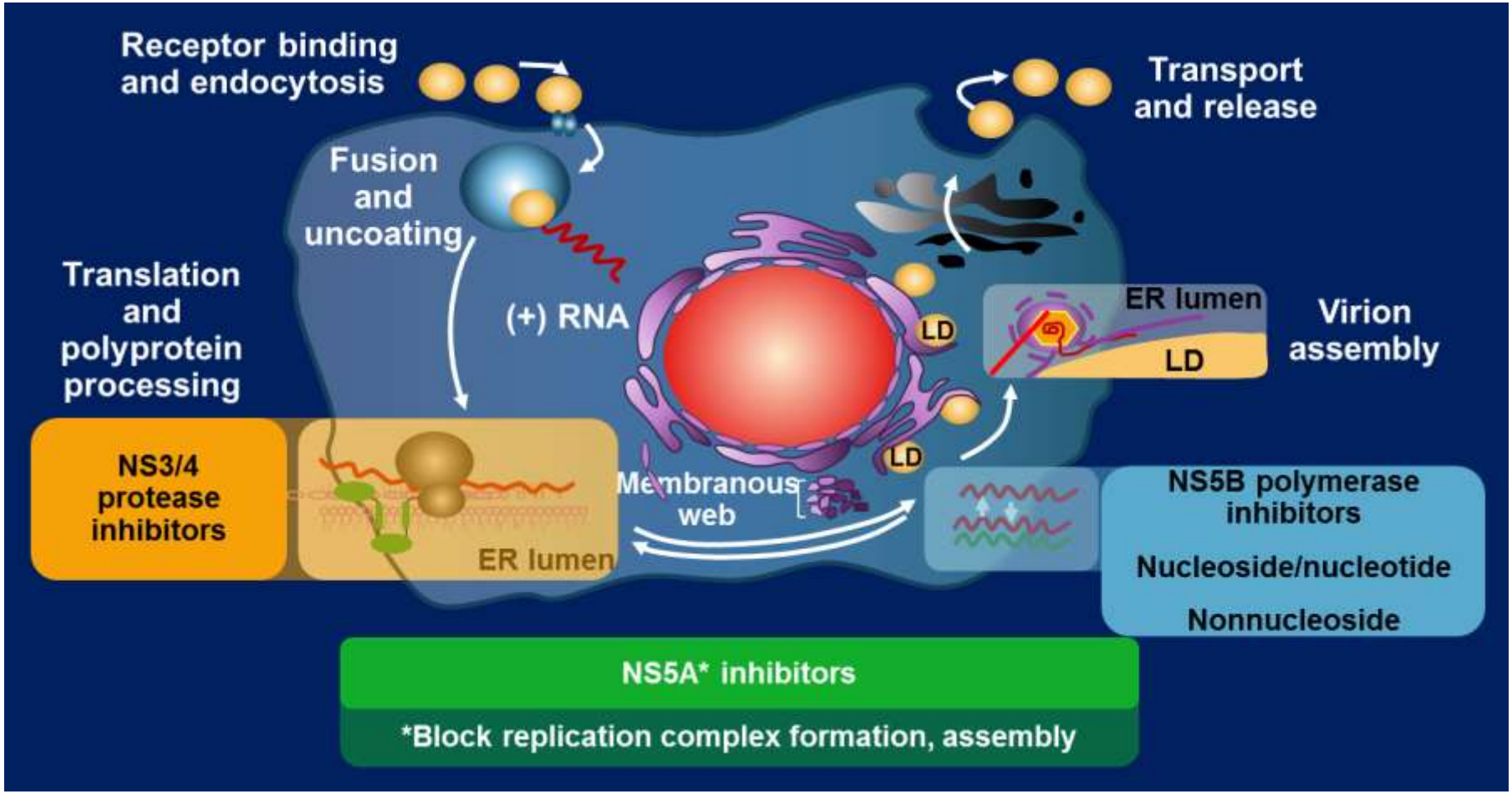
Response-guided therapy can optimise treatment in HIV-HCV co-infected patients



* In patients with BL VL <400 000 IU/mL and minimal liver fibrosis

Adapted from Rockstroh J, et al. HIV Med 2008; 9: 82

HCV lifecycle and direct acting antiviral (DAA) targets



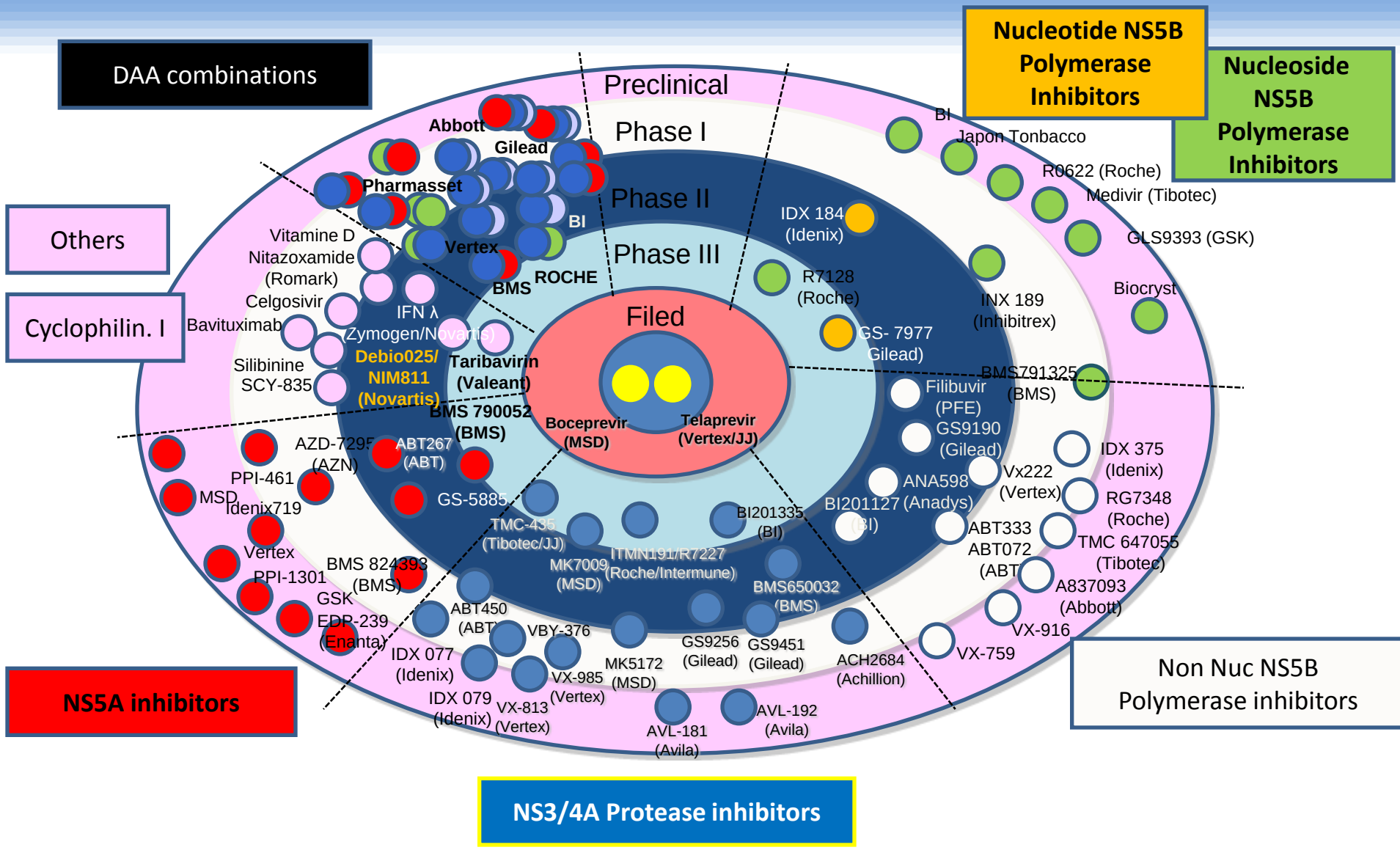
Adapted from Manns MP, et al. Nat Rev Drug Discov. 2007;6:991-1000.

Overview of DAAs approved or in phase 3

Agents	Protease inhibitors	Nucleos(t)ide polymerase inhibitors	Non-nucleos(t)ide polymerase inhibitors	NS5A inhibitors
Approved	Telaprevir Boceprevir			
Phase 3	Simeprevir Faldaprevir Asunaprevir ABT-450	Sofosbuvir	Deleobuvir ABT-333	Daclatasvir Ledipasvir ABT-267
Regimen	1 DAA + peg-IFN/RBV 2 DAA + peg-IFN/RBV IFN-free with 2 or more DAA +/- RBV			

Peg-IFN, pegylated interferon alfa; RBV, ribavirin.

HCV TREATMENT LANDSCAPE
DAAs in development



Simeprevir: 24 vs 48 weeks of dual therapy, triple for 12 weeks treatment of HIV HCV co-infection
14th European AIDS Conference (EACS)
16-19 October 2013 • Brussels, Belgium Douglas Dieterich

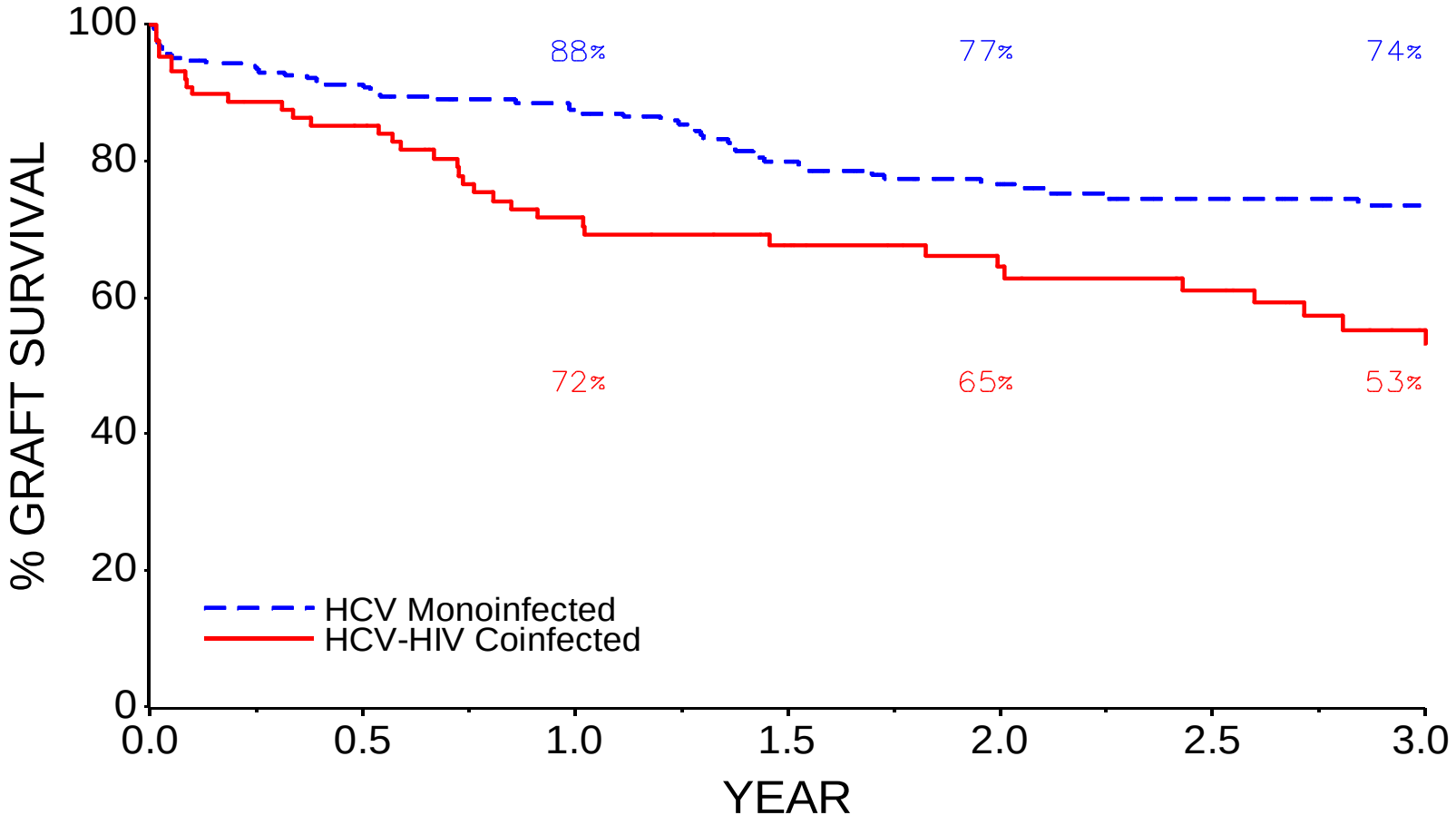
C212: Conclusions

- **SMV QD + PR for 12 weeks led to high rates of SVR12 in HCV G1/HIV-1 patients regardless of prior HCV treatment response**
  - **Treatment-naïve: 79%**
  - **Prior relapsers 87%**
  - **Prior partial responders 70%**
  - **Prior null responders 57%**
- **SVR12 rates were high, regardless of baseline METAVIR fibrosis score or HCV G1 subtype**
- **89% of treatment-naïve and prior relapsers without cirrhosis met RGT criteria and shortened therapy to 24 weeks, with 87% achieving SVR12**
- **Only 1.9% (2/105) of patients had a Grade 3 haemoglobin toxicity**
  - **0 patients had Grade 4**
- **SMV QD + PR for 12 weeks was well tolerated with a safety profile similar to that observed in mono-infected patients**

G, genotype; PR, peginterferon-α2a + ribavirin; SMV, simeprevir; SVR12, sustained virologic response 12 weeks' after end of treatment

Liver Transplant: Graft Survival

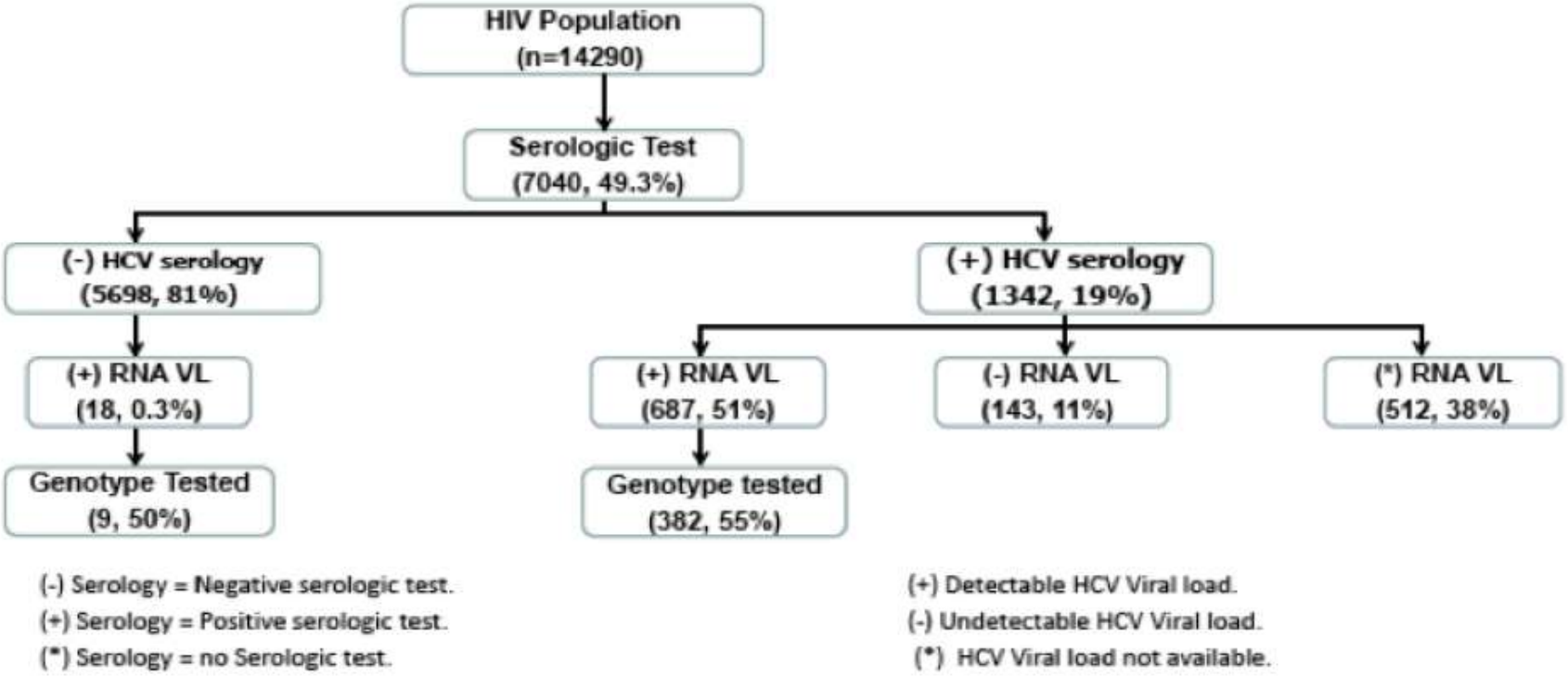
HCV-HIV vs HCV Transplant Recipients



HCV Monoinfected:	**N=174**	**N=109**	**N=67**
HCV-HIV Coinfected:	**N=57**	**N=39**	**N=24**

Insufficient HCV testing and referral of HIV+ population

- Miami Cohort of 14,290 HIV+ patients



Deeb K, et al. CROI 2012; abstract

Thank you to: APASL and HSP team

- My HIV HCV co-infection gurus who were kind enough to share slides and their expertise

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- David Thomas
- Mark Sulkowski