Advances in the Treatment of Hepatitis C

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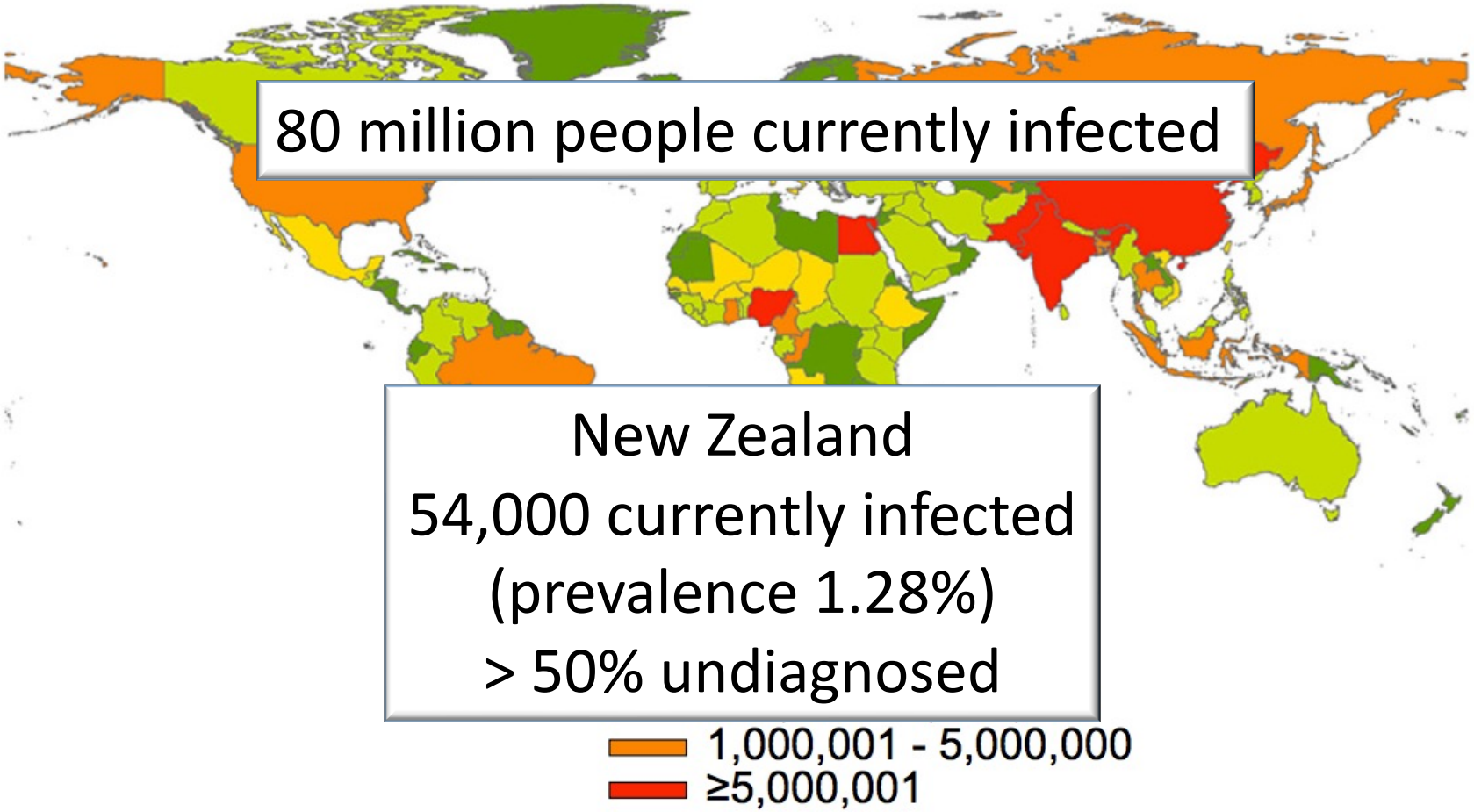
Outline

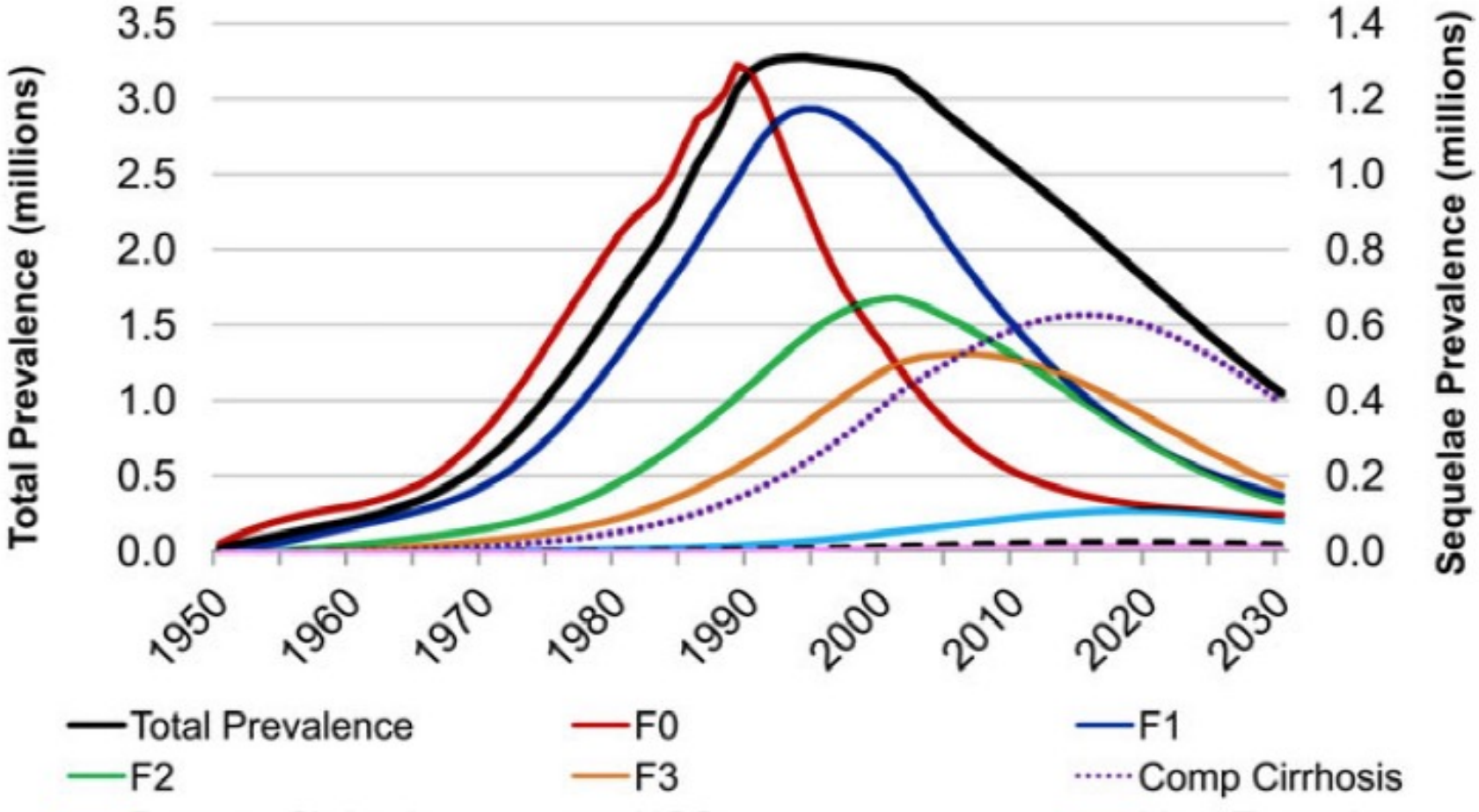
- Epidemiology of HCV and HCV/HIV
- Impact of HIV co-infection on HCV-related liver disease
- Impact of treatment of HCV-related liver disease in co-infected patients
- Recent trials of HCV therapy in co-infected patients

Hepatitis C - A Global Epidemic



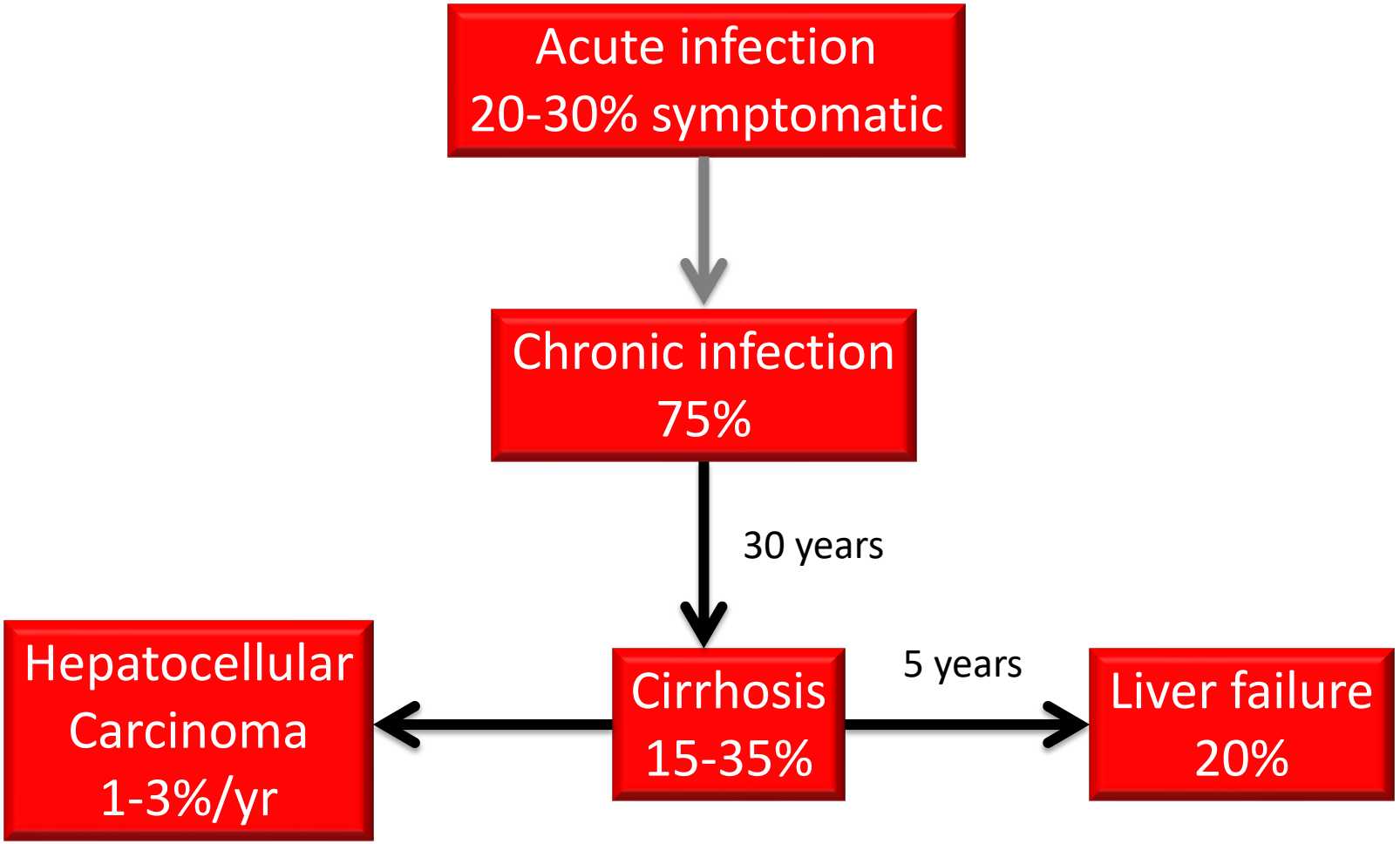
Gower et al, J Hepatol, 2014

Falling Prevalence of Hepatitis C But Increasing Liver Disease

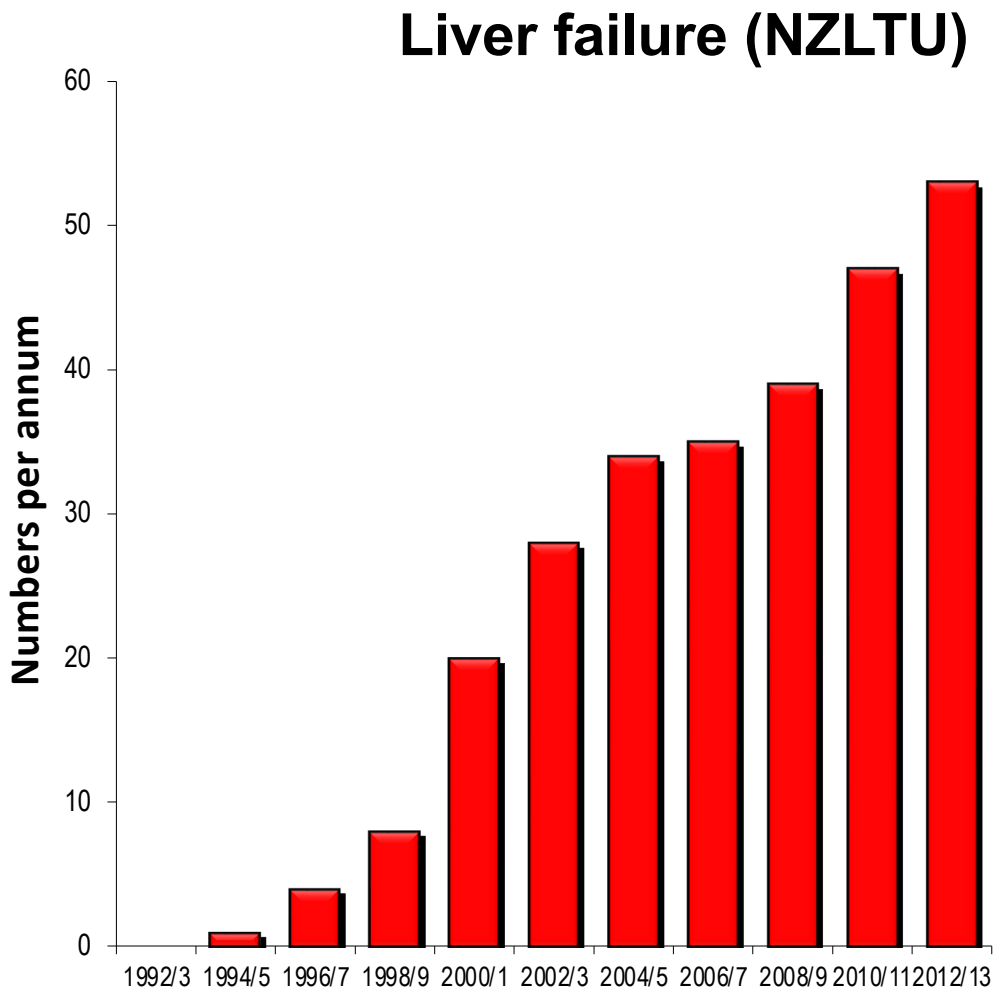


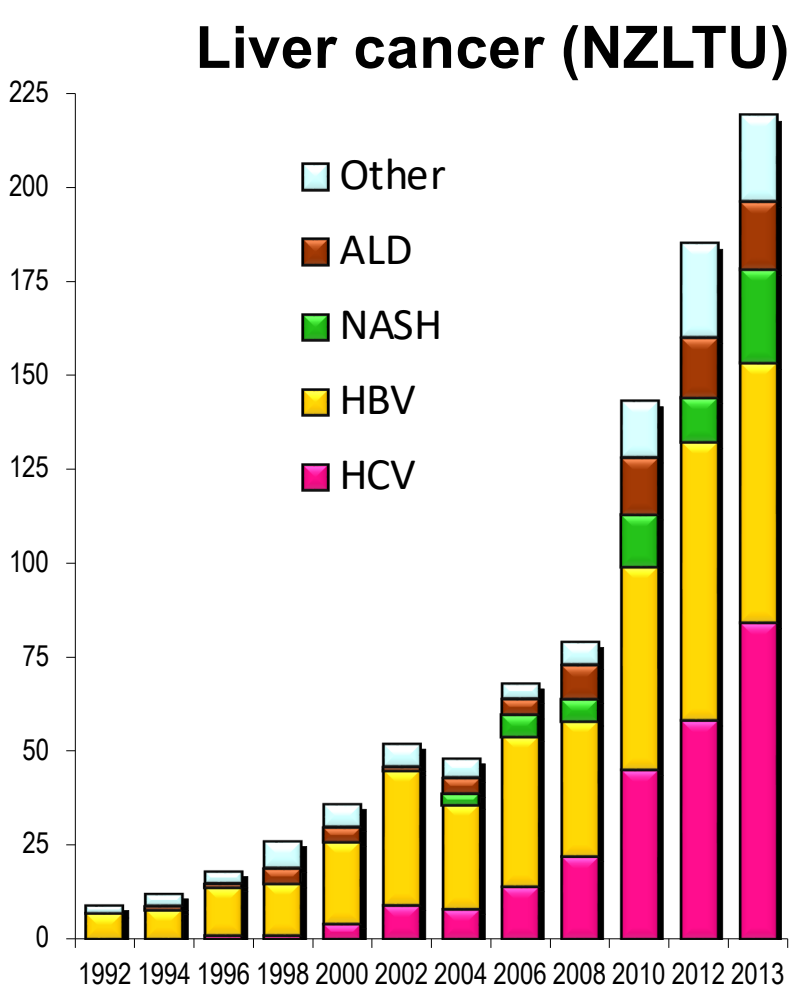
HCV sequelae and total prevalence (millions): USA 1950-2030

HCV natural history

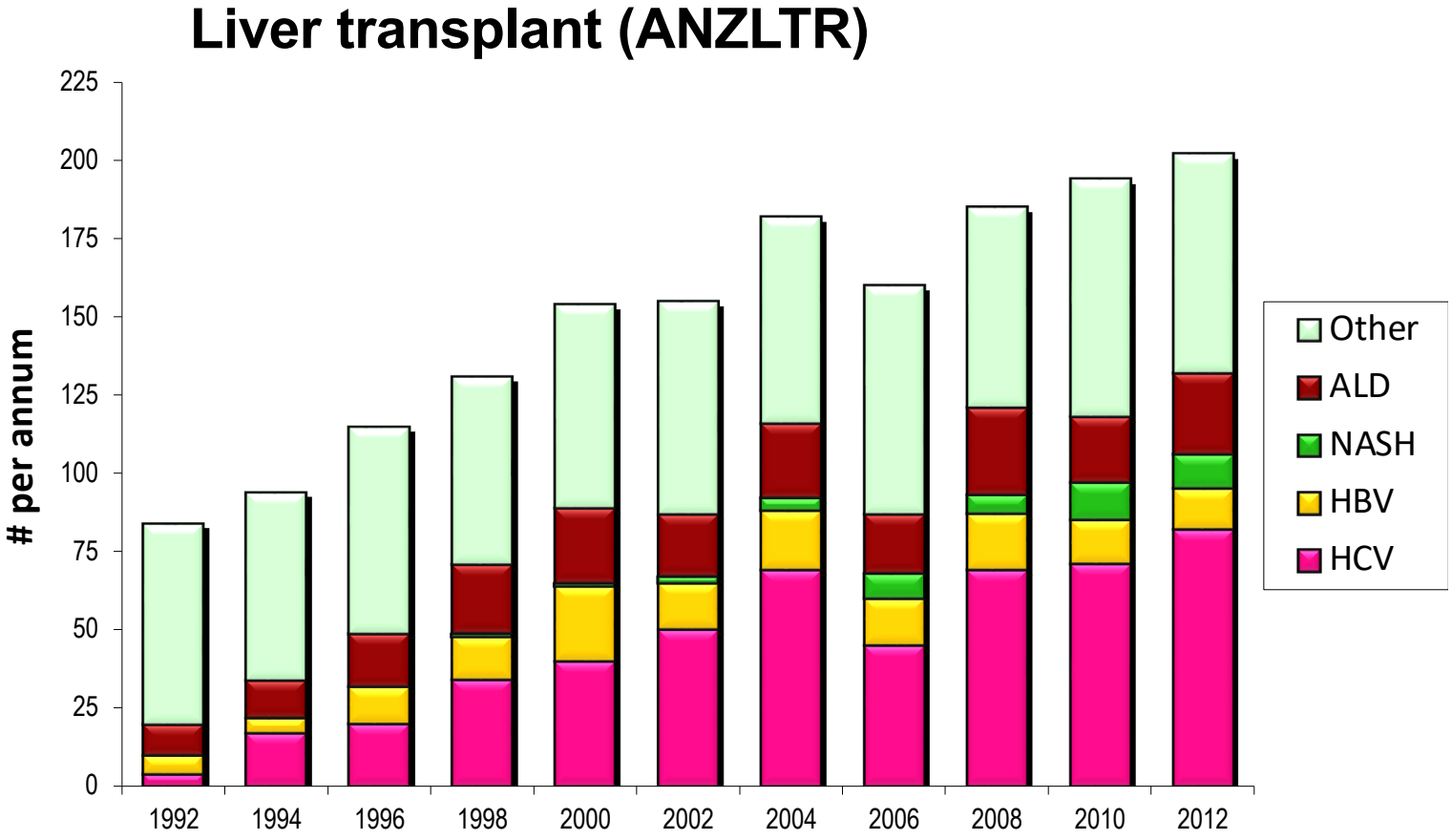


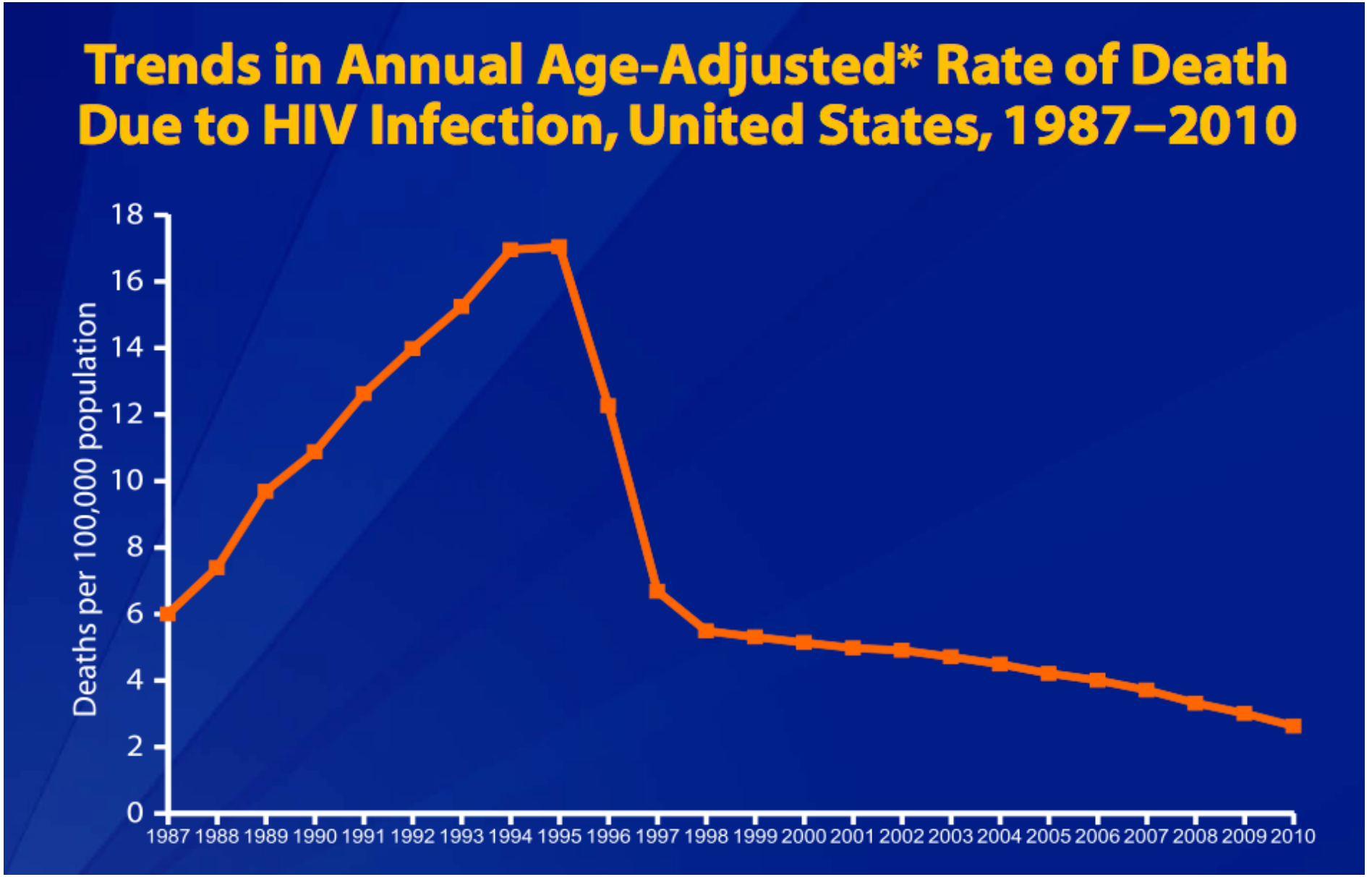
Rising Incidence of Advanced Liver Disease





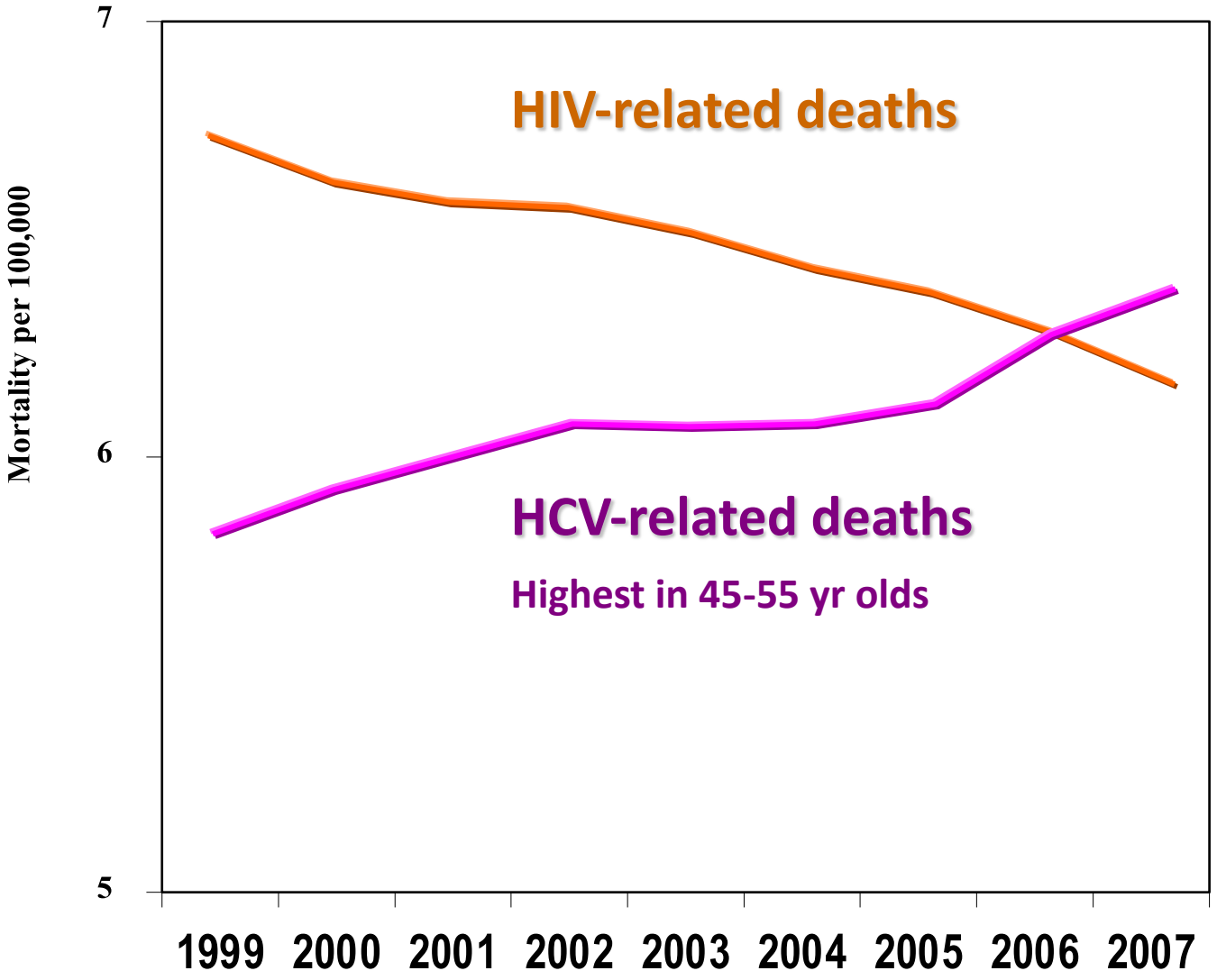
Hepatitis C most common indication for Liver Transplantation





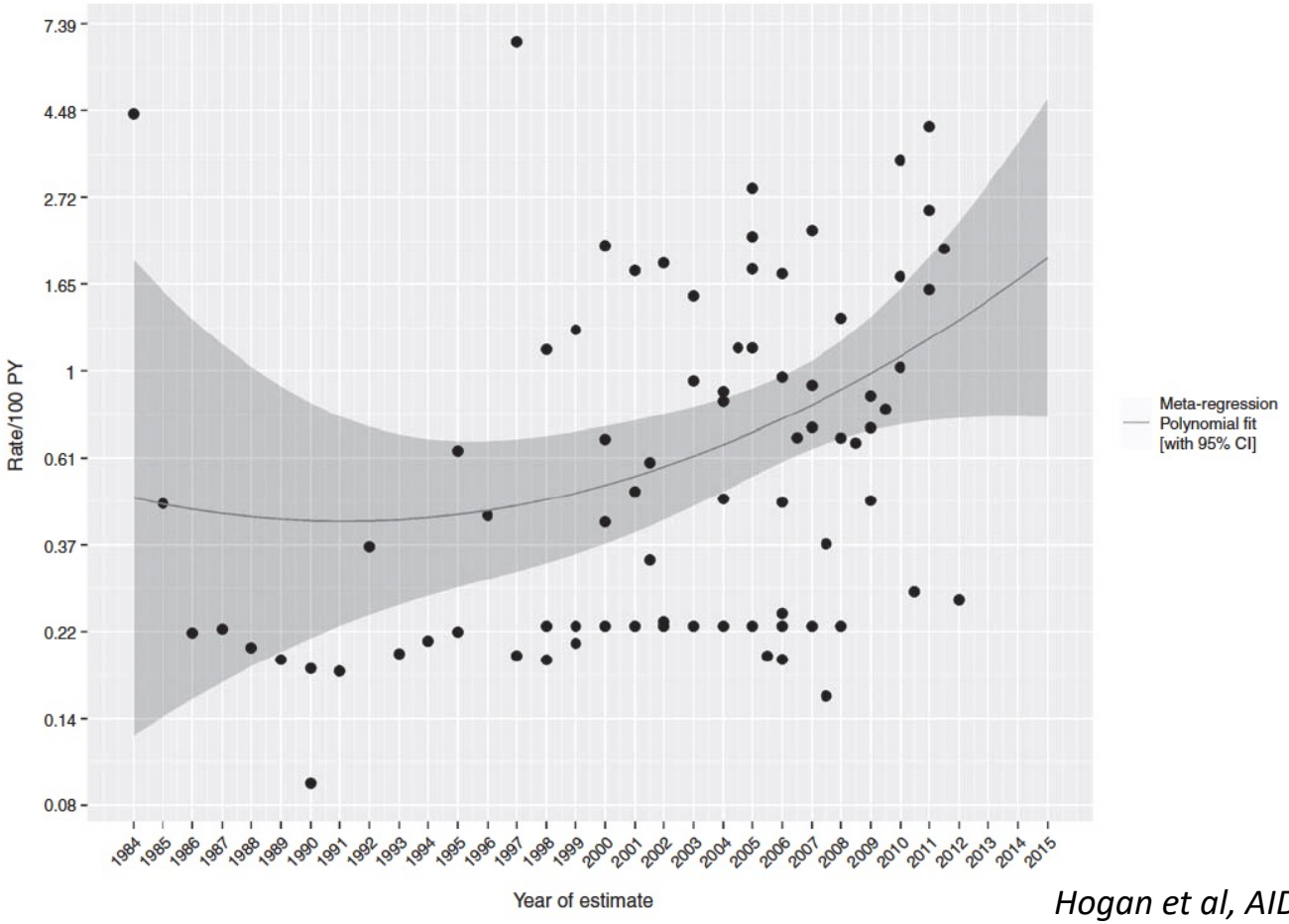
CDC, HIV Mortality 2013

HCV Mortality now exceeds AIDS



Ly K, et al. Ann Int Med 2012

HCV Incidence in HIV-positive MSM in relation to calendar time

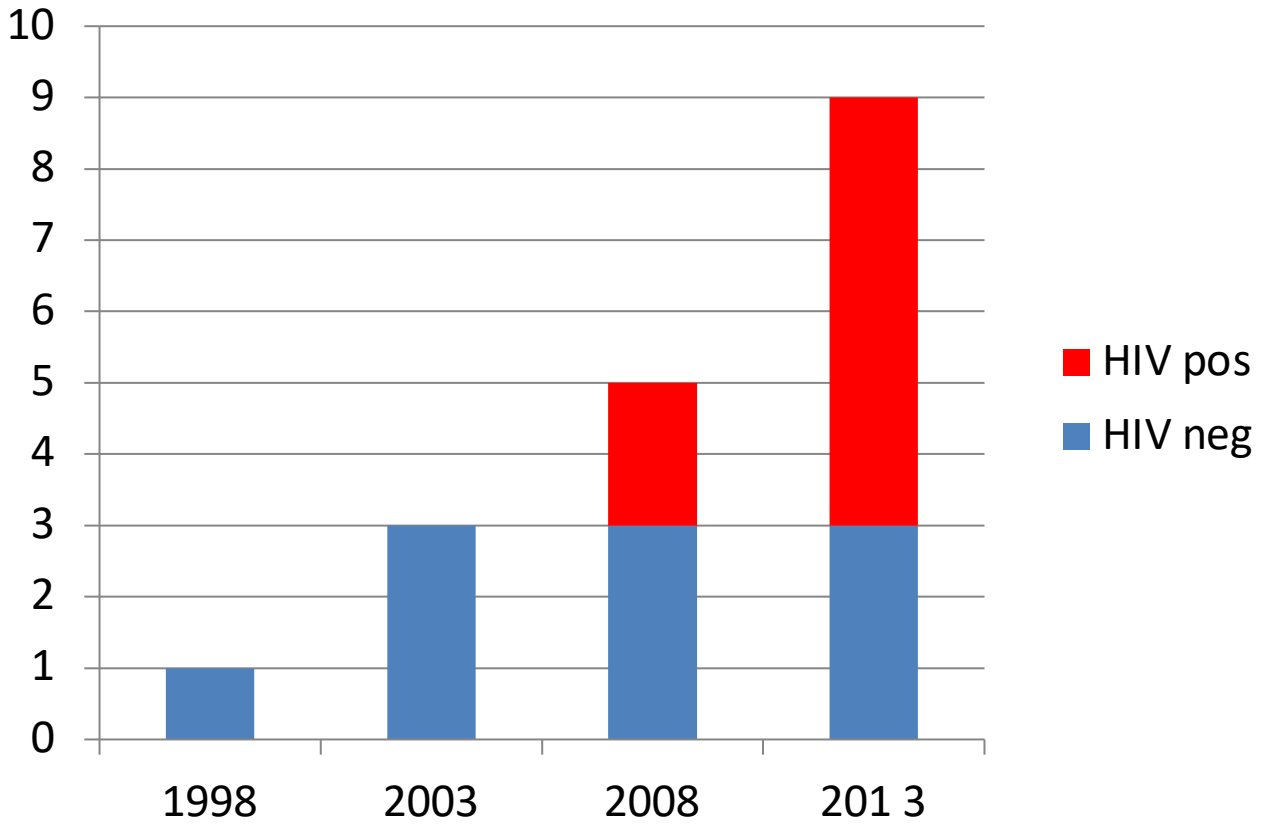


Hogan et al, AIDS, 2015

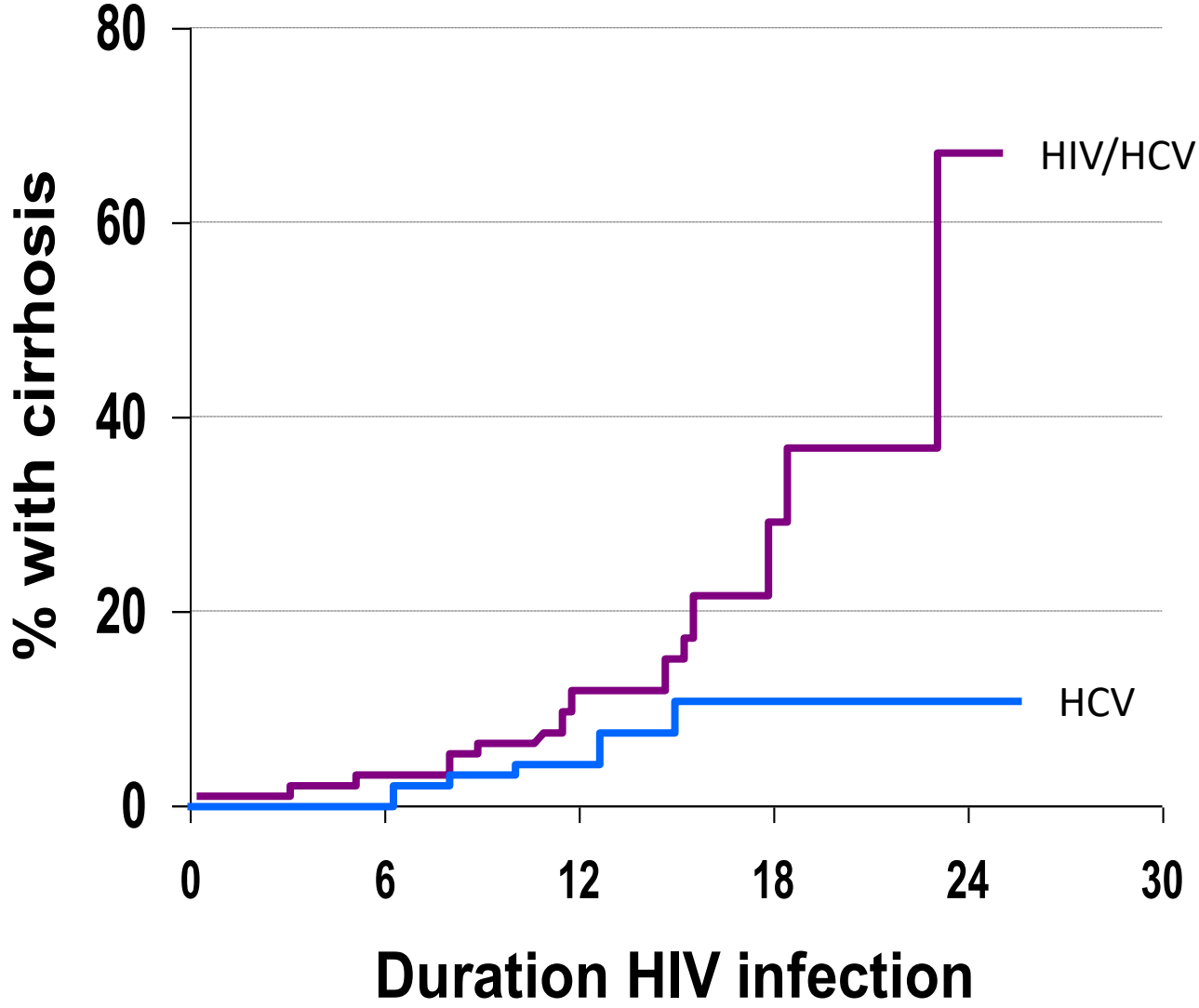
- Risk factors include group sex, toys, trauma, non-injecting drug use (GHB)

van de Laar. AIDS 2010; 24: 1799-1812

Acute HCV Infection at Auckland Hospital

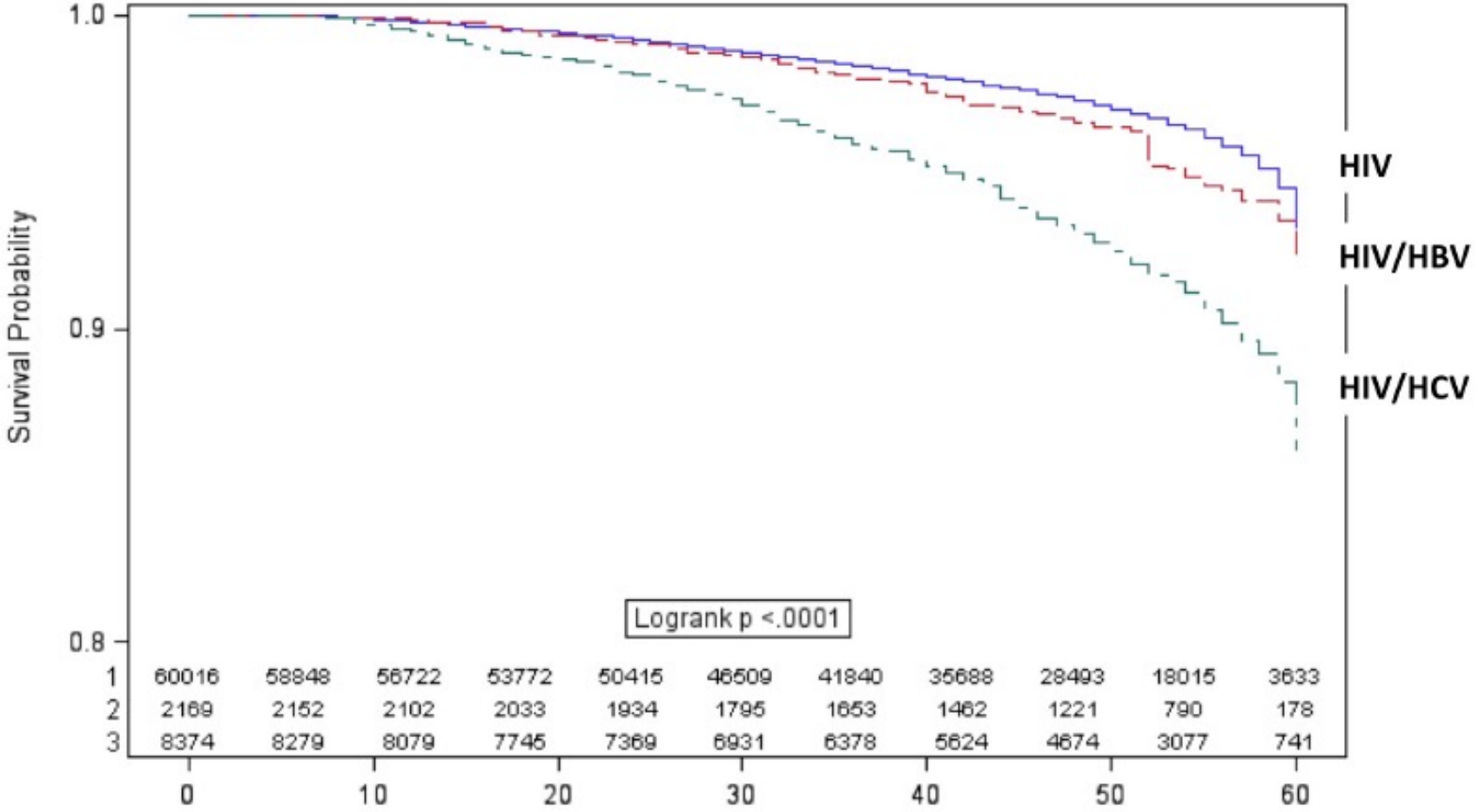


More Rapid Progression to Cirrhosis in HIV/HCV Co-infected Patients



Di Martino, Hepatol 2001

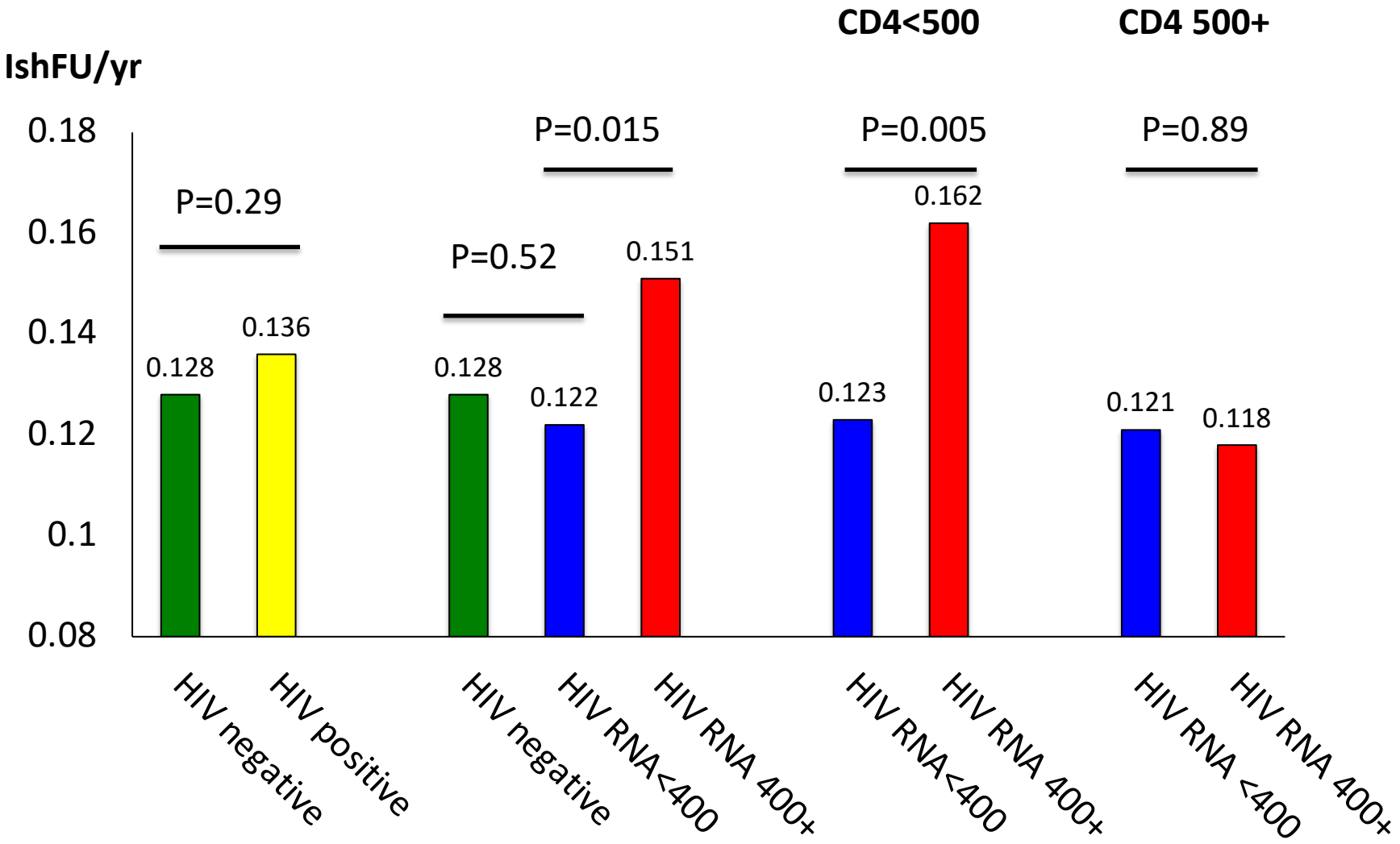
HIV/HCV co-infection increases overall, non-liver and non-AIDS related mortality



5yr mortality: HIV/HCV 7.5% HIV 2.8% HIV/HBV 3.9%

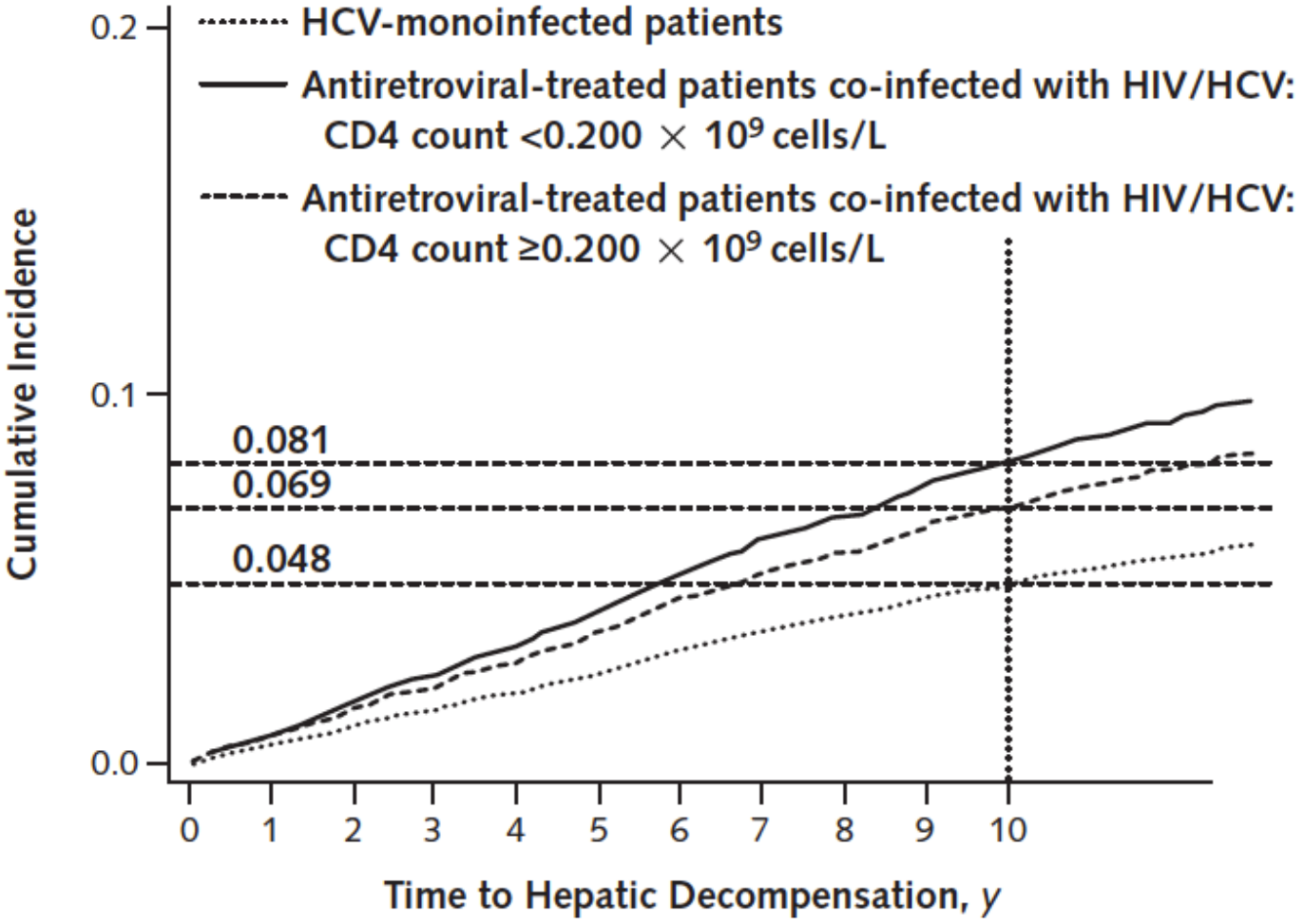
Mallet et al, CROI 2014

ART Slows Fibrosis Progression Rate



Brau et al, J Hepatol 2006

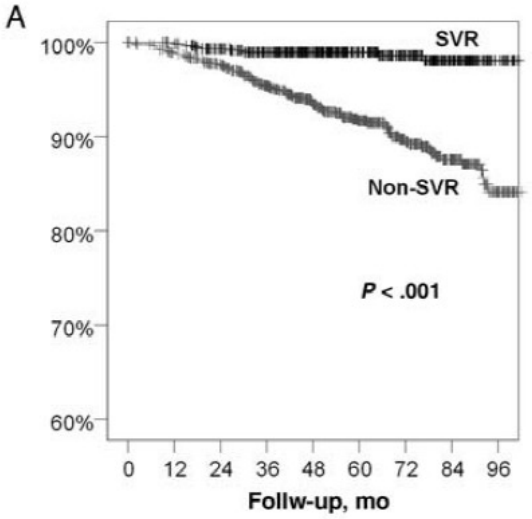
Co-infected Patients Remain at Higher Risk of Clinical Progression of Liver Disease Despite ART

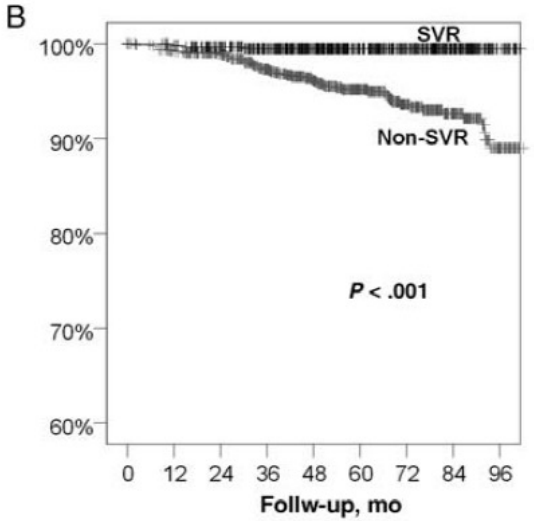


Lo Re et al, Ann Int Med, 2014

HCV Cure Reduces Risk Of Liver and Non-liver Related Mortality in HIV/HCV Patients

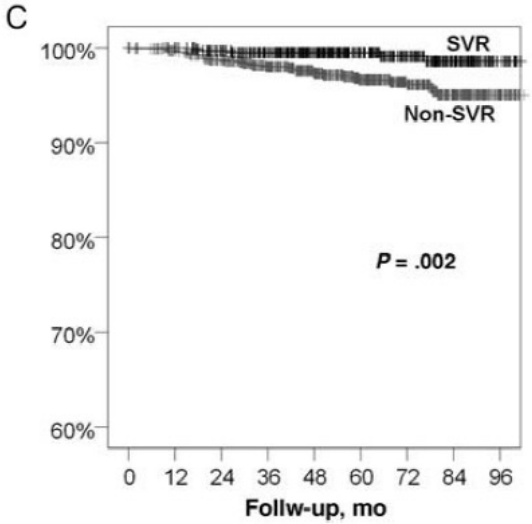
Overall mortality

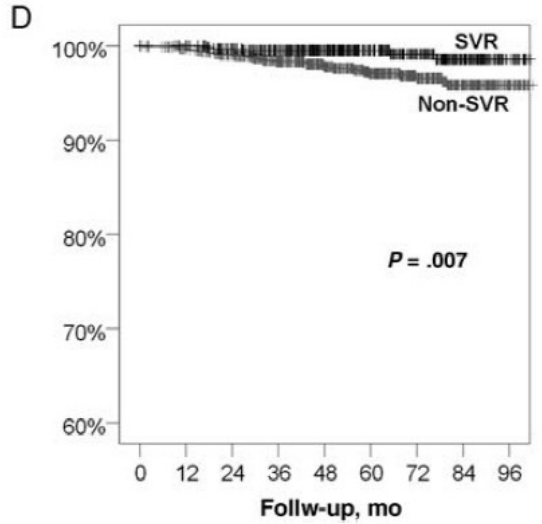




Liver related mortality

Non-liver mortality

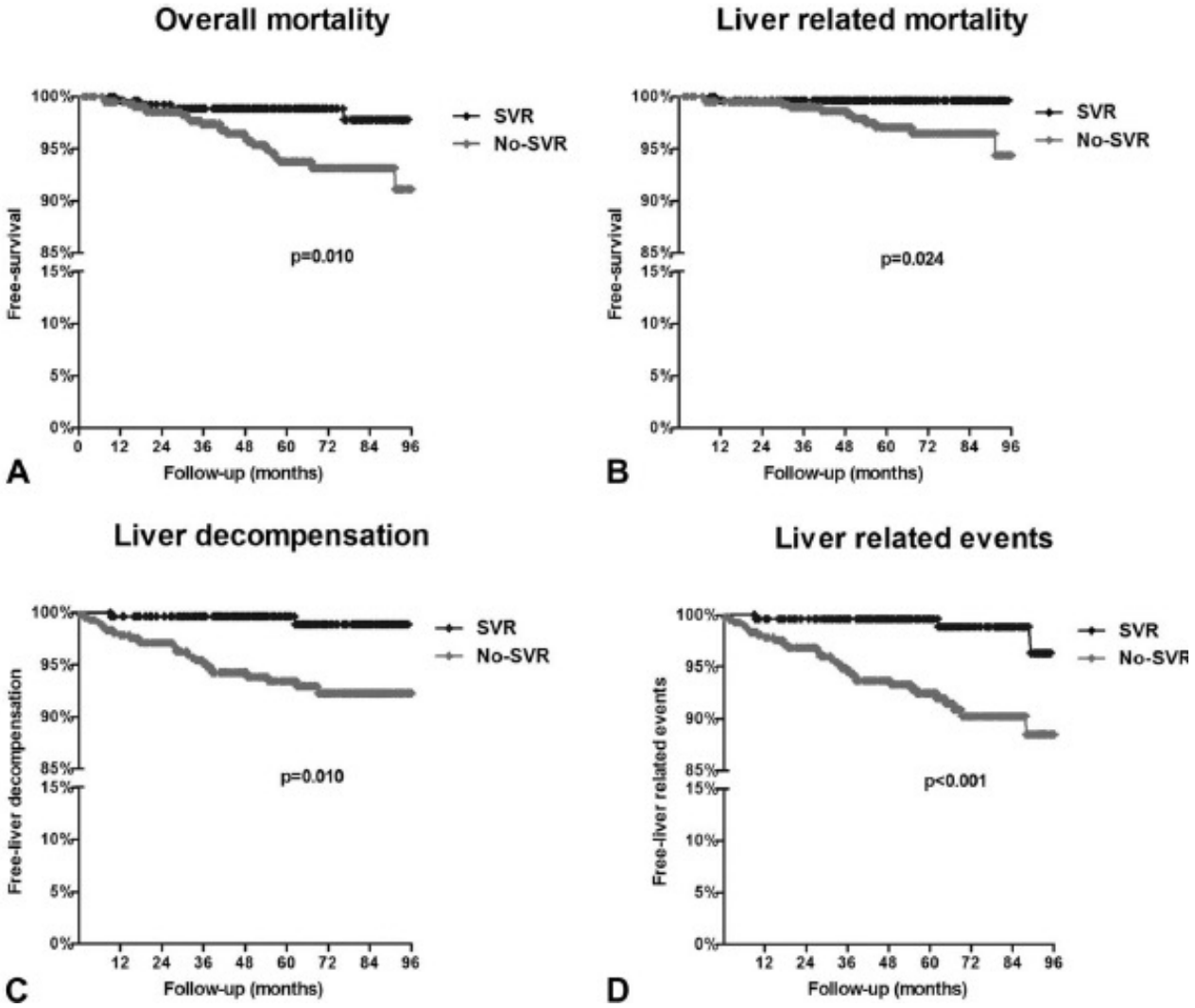




Non-liver non-AIDS mortality

Berenguer et al, Clin Infect Dis, 2012

Benefit From Cure Even in Patients with Non-advanced Liver Disease at Baseline



Berenguer et al, J Acquir Immune Defic Syndr, 2014

HCV Cure Improves Quality of Life in Patients with HCV/HIV

- Canadian Co-infection Cohort

- 223 patients who received HCV therapy
- Self-reported HRQOL before, 6mo and 1yr after treatment
- Sustained viral response in 36%

- Compared to non-response, SVR associated with
  - Improved HRQOL
  - Lower rate of health service utilisation

BUT

- Substantial increase in alcohol consumption and IDU

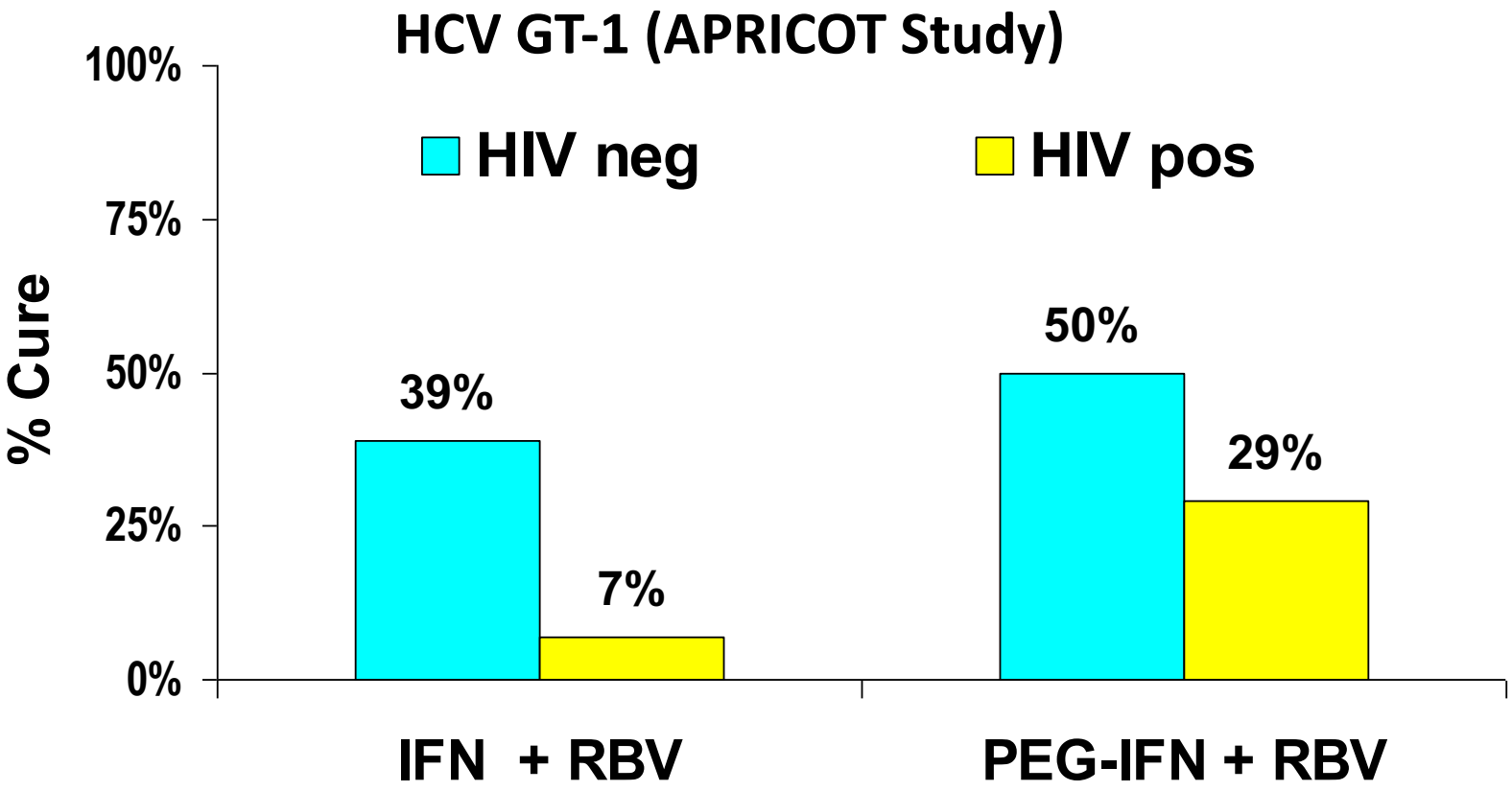
Yeung et al, HIV Clin Trials, 2015

Potential Benefits of HCV Cure in Patients with HIV co-infection

- Prevent cirrhosis and its complications
- Prevent decompensation and need for transplant
- Reduce non-liver related mortality
- Improve quality of life

BUT achieving cure has been difficult!

Interferon-based therapy in HIV/HCV co-infection

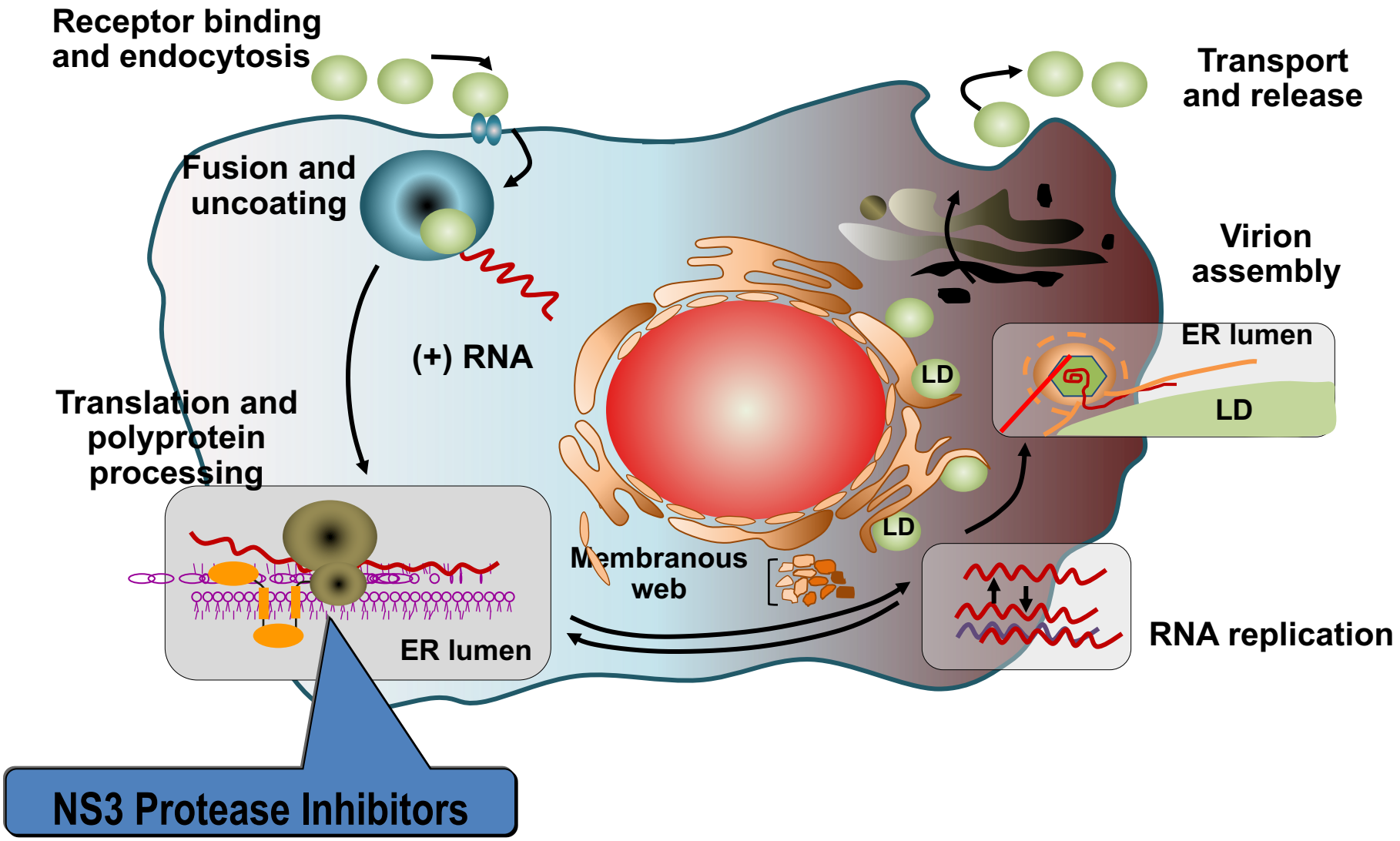


Genotypes 2/3 – cure rates 44-73%

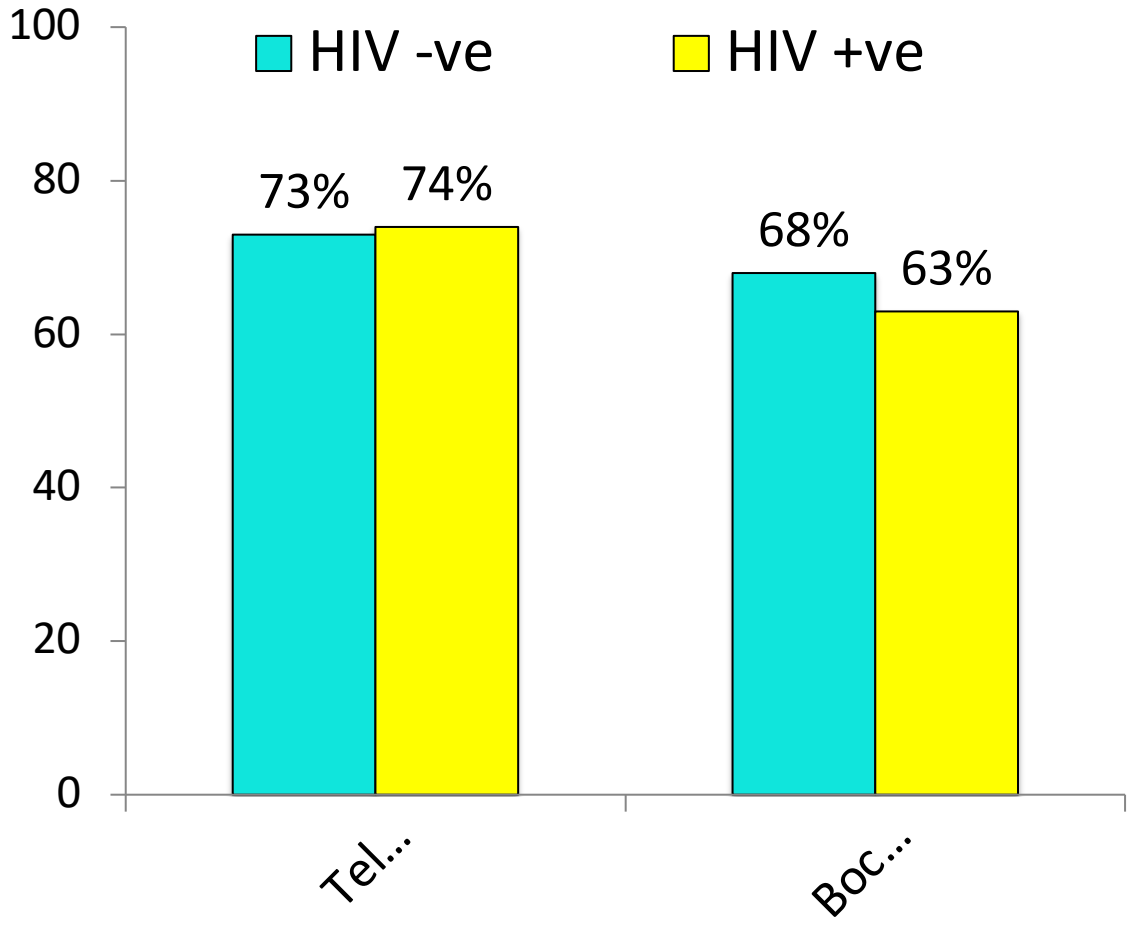
Low uptake of interferon-based treatment

- Poor cure rates
- High adverse event rates
- High rates of co-morbid medical and psychiatric conditions contraindicating interferon-based therapy
- Something better on the way!

Targeting the HCV Life Cycle: Direct Acting Antiviral Agents



PEG/ribavirin + 1st Generation Protease Inhibitor: Overall cure rate improved, equivalent to HIV -ve



But.....Protease Inhibitors + PEG/ribavirin

- **Poorly tolerated**

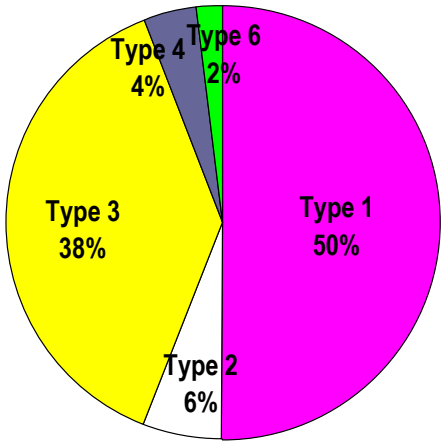
- Still required Pegylated Interferon and ribavirin
- Added toxicities of the PIs
- Poor safety in advanced liver disease

- **Complex dosing regimen**

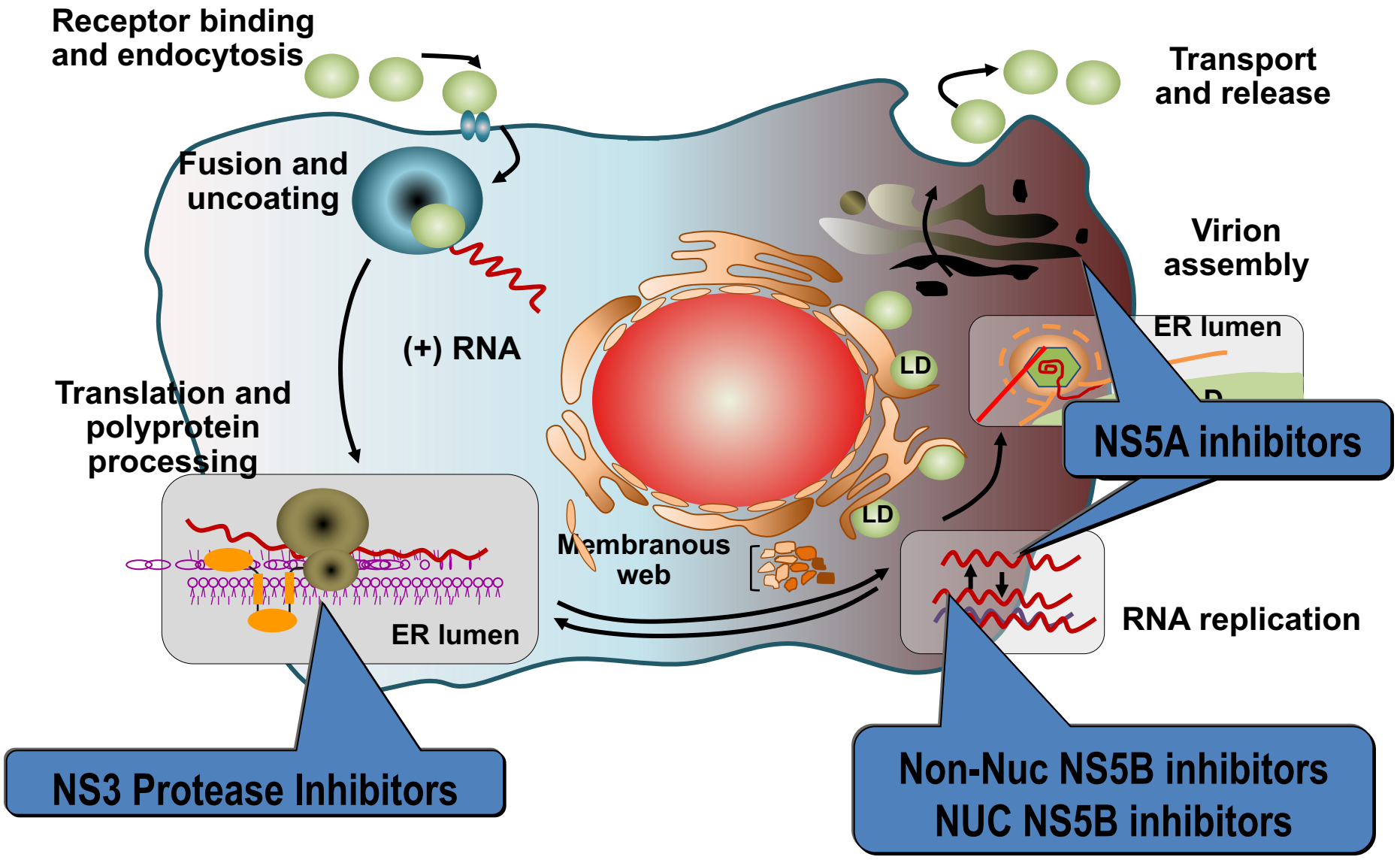
- High pill burden - 8 hourly, with high-fat meal
- Frequent on-treatment monitoring required
- Multiple drug interactions with ART

3. Limited Efficacy

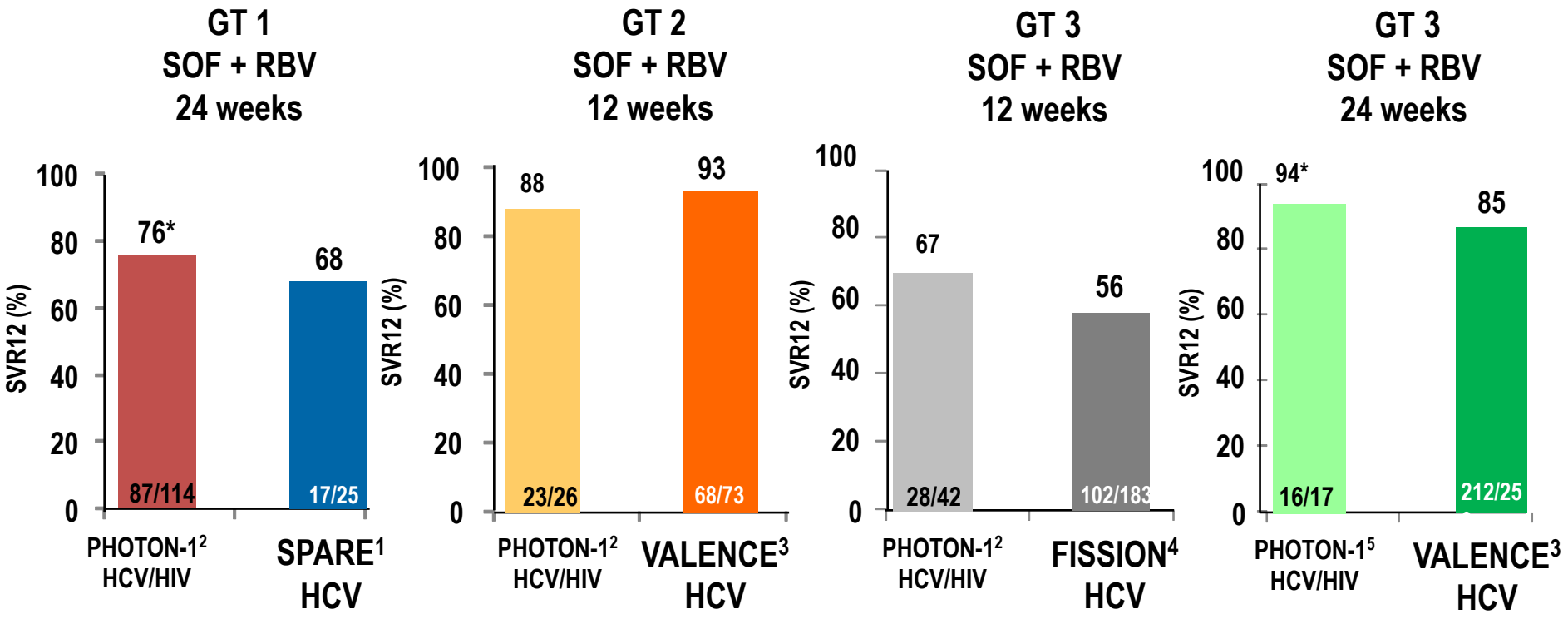
- Previous null responders to PEG/RBV
- HCV genotypes other than 1



Targets in the HCV Life Cycle: Direct Acting Antiviral Agents 1



The advent of all-oral, interferon-free therapy: Photon 1: Sofosbuvir (nuc NS5B inhibitor) + ribavirin



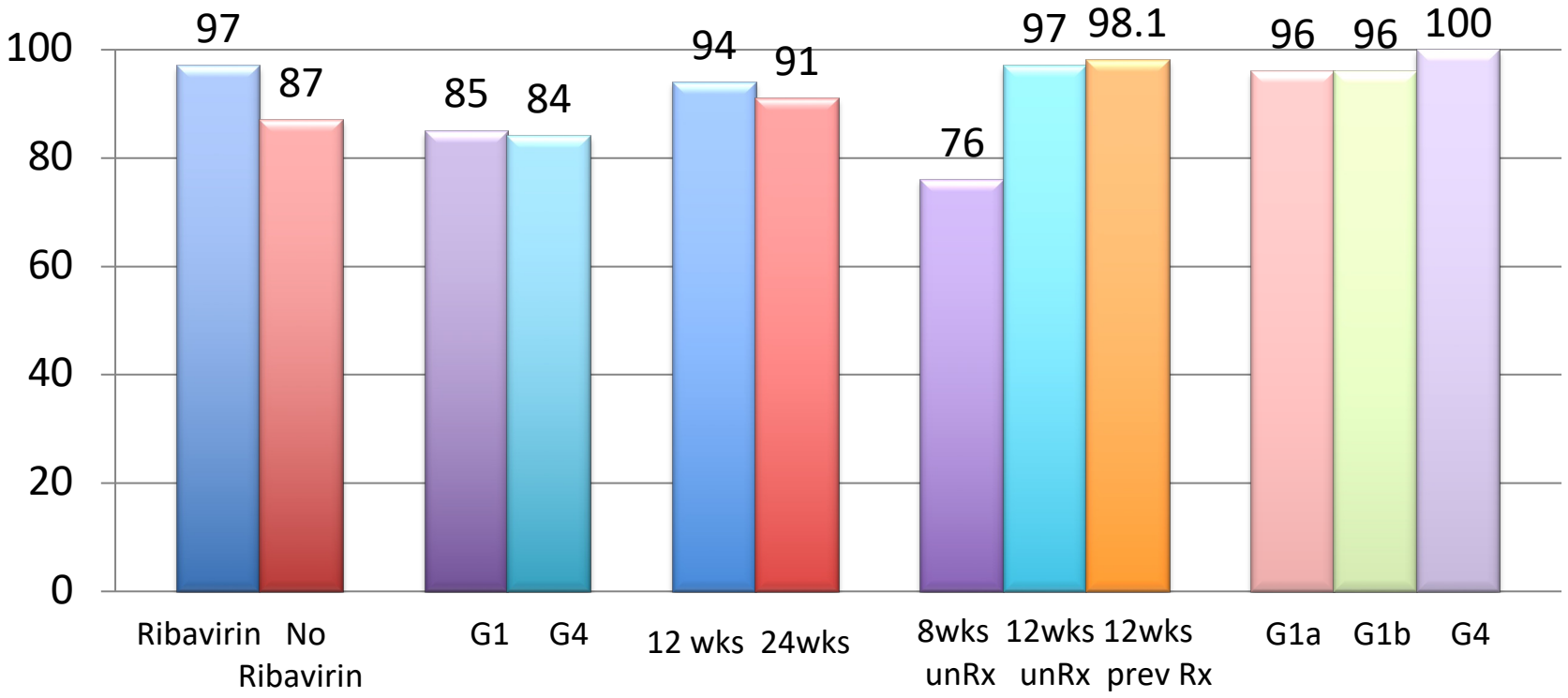
- On ART with HIV RNA ≤ 50cpml AND CD4 >200/ OR untreated HIV CD 4 > 500/µl
- HCV genotype 1/2/3 treatment naïve or genotype 2/3 treatment experienced
- 10% of treatment experienced cirrhotic

Sulkowski M, et al; AASLD 2013 Abstract 212
Naggi S, et al. CROI 2014 Abstract 26

Interferon-free therapy in HCV/HIV co-infection – published trials

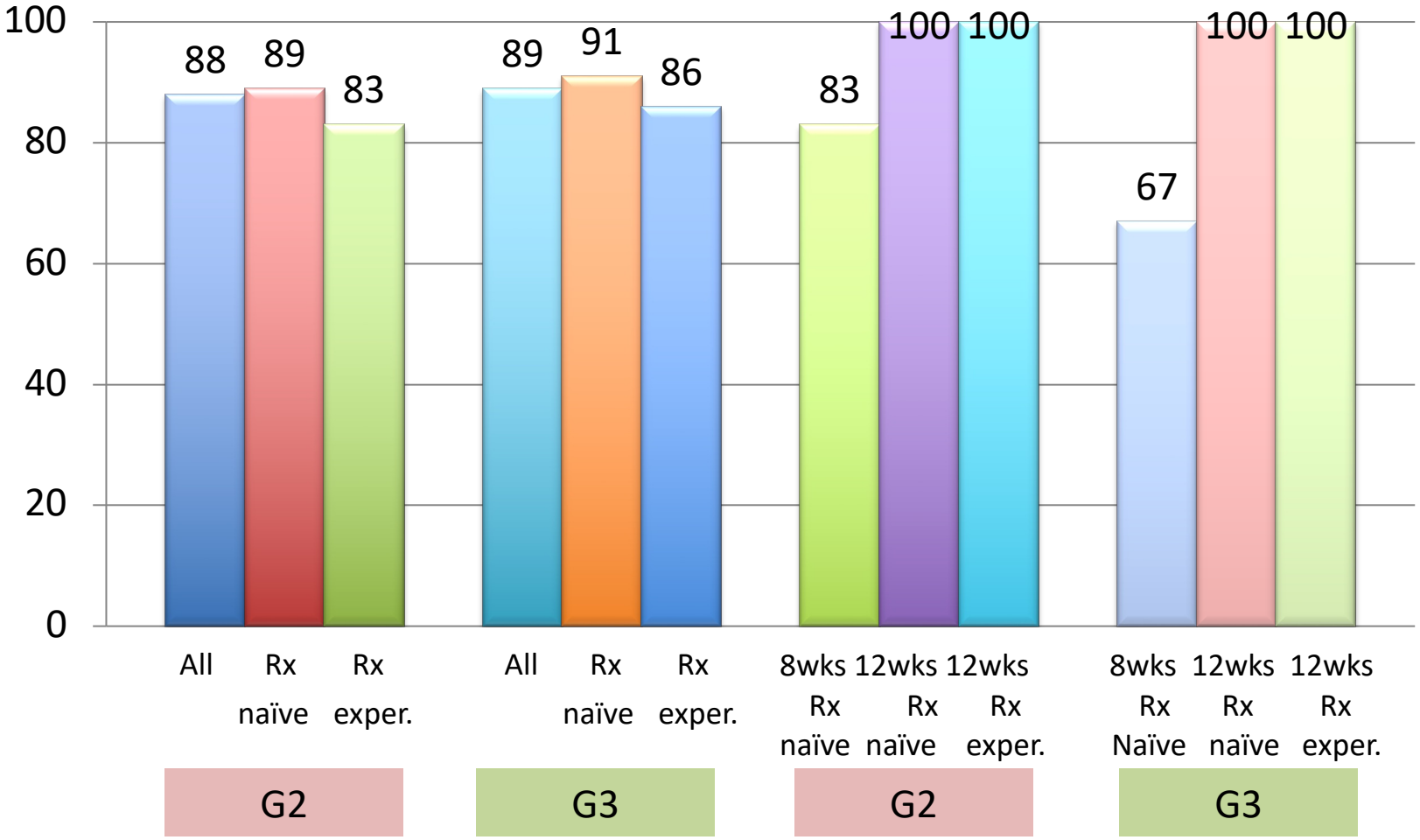
Trial	Published	Drug Combination	Genotypes
Photon 1	JAMA July 2014	Sofosbuvir (nuc NS5B) Ribavirin	1,2,3
C-WORTHY	Lancet November 2014	Grazoprevir (NS3/4A) Elbasvir (NS5A)	1
Photon 2	Lancet February 2015	Sofosbuvir Ribavirin	1,2,3,4
Turquoise 1	JAMA February 2015	Ombitasvir (NS5A) Paritaprevir (NS3/4A) Ritonavir Dasabuvir (non-nuc NS5B)	1
ALLY 2	NEJM July 2015	Daclatasvir (NS5A) Sofosbuvir	1,2,3,4
ION 4	NEJM August 2015	Ledipasvir (NS5A) Sofosbuvir	1,4

Interferon-free regimes: Genotypes 1 and 4



C-WORTHY	Photon 2	Turquoise 1	ALLY 2	ION-4
Rx naive 12 weeks grazoprevir +elbasvir	Rx naïve 24 weeks sofosbuvir + ribavirin	Rx naïve + prev Rx. ombitasvir +paritaprevir +dasabuvir	Rx naïve + Prev Rx sofosbuvir + daclatasvir	Rx naïve + Prev Rx 12 weeks sofosbuvir + ledipasvir

Interferon-free regimes: Genotypes 2 and 3



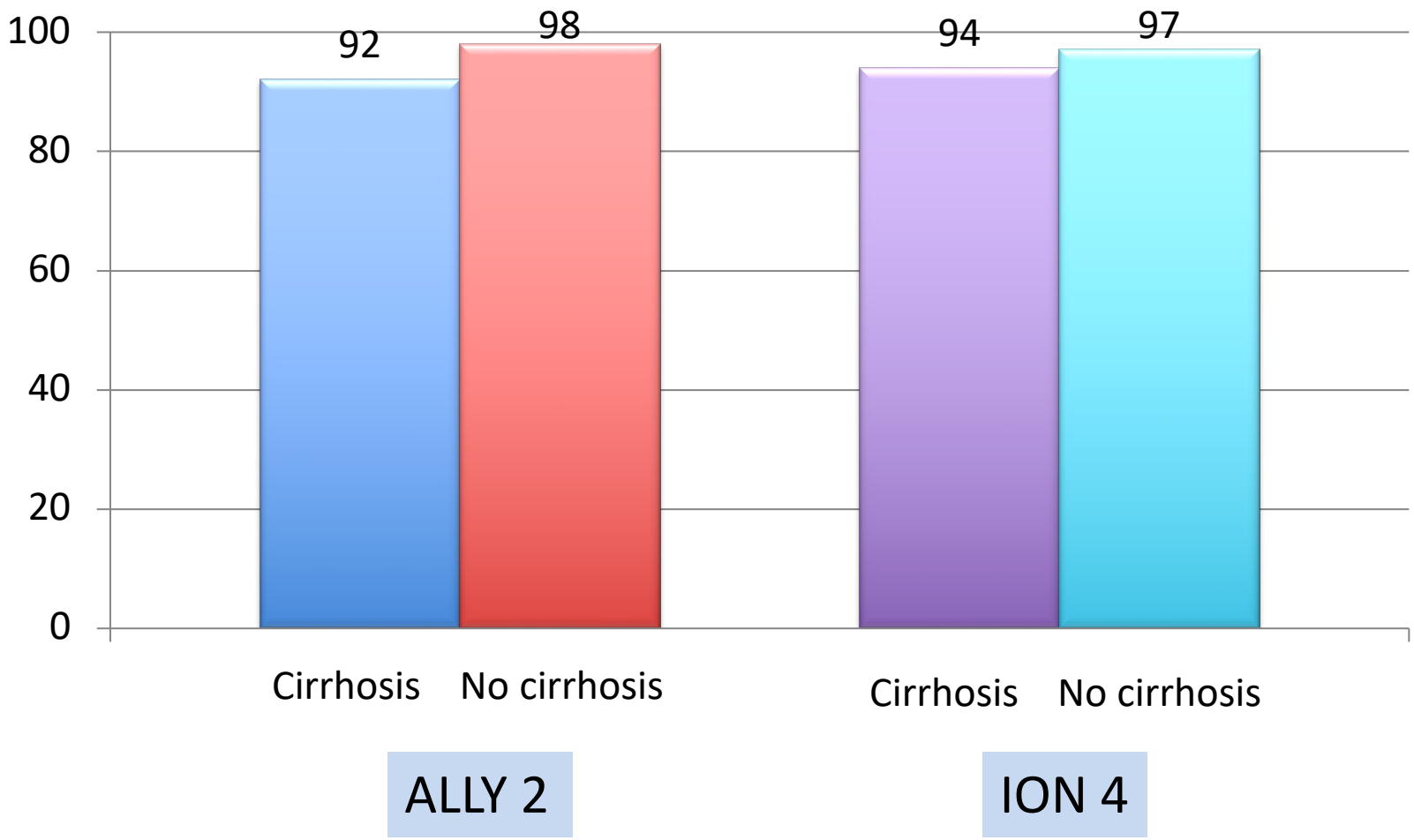
Photon 2

Sofosbuvir + ribavirin 24 wks
(Rx naïve G2 12wks)

ALLY 2

Sofosbuvir + daclatasvir

Interferon-free regimes: cirrhosis



Minimal adverse effects due to DAAs

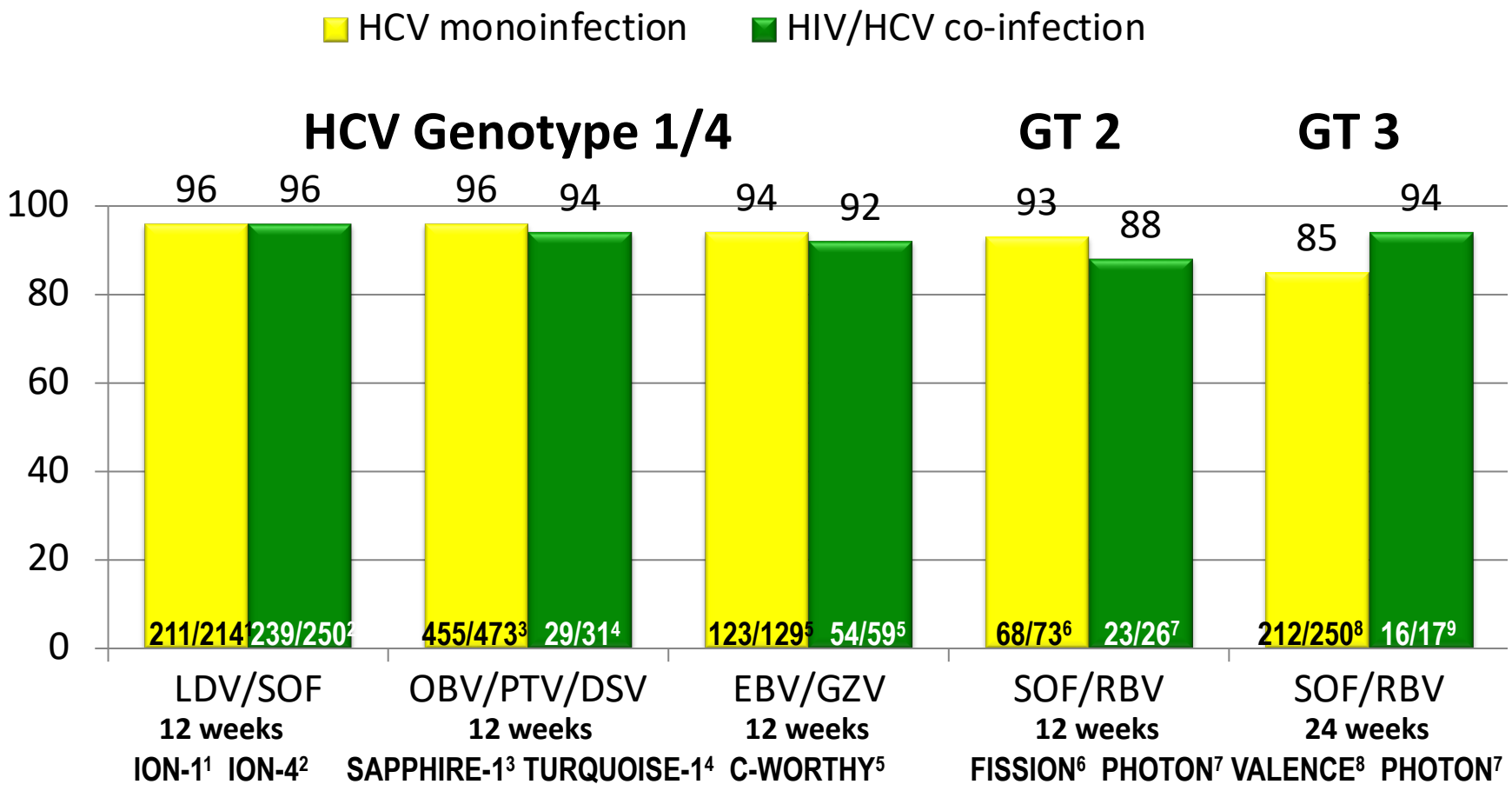
Trial	Serious adverse events	Serious adverse events due to study drug	Study drug discontinuation	Antiretroviral failure
C-WORTHY	1.4% (3/218)	1% (2/218)*	0	0
Photon 2	5% (15/274)	1% (4/274)§	2% (6/274)	0
Turquoise 1	0% (0/64)	0	0	0
ALLY 2	2% (4/203)	0	0	0
ION 4	2% (8/335)	0	0	0

Most common adverse effects: Headache, nausea, fatigue, insomnia

*Nausea (1), asthenia (1)

§Anaemia (2), thrombocytopaenia (1), mania (1)

HIV no longer a baseline predictor of response



[1]Afdhal N. NEJM 2014;370:1889-98; [2]Naggie S. NEJM 2015 (in press); [3]Sulkowski M. *JAMA*. 2015;313:1223-31; [4] Feld J. *NEJM* 2014;370:1594-603 [5]Sulkowski M. *Lancet* 2015; 385: 1087–97; [6]Zeuzem S. *N Engl J Med* 2014;370:1993–2001; [7]Sulkowski M. *JAMA*. 2014;312:353-361; [8] Lawitz E. *N Engl J Med* 2013;368:1878-87

AASLD/IDSA guidelines 2015

Recommendations

34. HIV/HCV-coinfected persons should be treated and retreated the same as persons without HIV infection, after recognizing and managing interactions with antiretroviral medications. (I-B)

DAAs approved for use in NZ (but not yet funded)

Co-formulated paritaprevir/ritonavir (PTV/r) 150 mg/100 mg plus ombitasvir (OBV) 25 mg

Dasabuvir (DSV) 250 mg

viekira pak

Ribavirin for some patients: weight-based dose, 200 or 600 mg tablets

DAAs + ART: interactions

		SIM	DAC	SOF	LDV/SOF	3D
NRTIs	Abacavir	◆	◆	◆	◆	◆
	Didanosine	◆	◆	◆	◆	◆
	Emtricitabine	◆	◆	◆	◆	◆
	Lamivudine	◆	◆	◆	◆	◆
	Stavudine	◆	◆	◆	◆	◆
	Tenofovir	◆	◆	◆	◆	◆
	Zidovudine	◆	◆	◆	◆	◆
NNRTIs	Efavirenz	◆	◆	◆	◆*	◆
	Etravirine	◆	◆	◆	◆	◆
	Nevirapine	◆	◆	◆	◆	◆
	Rilpivirine	◆	◆	◆	◆*	◆
Protease Inhibitors	Atazanavir; atazanavir/ritonivir	◆	◆	◆	◆*	◆
	Darunavir/ritonavir; darunavir/cobicistat	◆	◆	◆	◆*	◆
	Fosamprenavir	◆	◆	◆	◆*	◆
	Lopinavir	◆	◆	◆	◆*	◆
	Saquinavir	◆	◆	◆	◆*	◆
Entry/Integrase inhibitors	Dolutegravir	◆	◆	◆	◆	◆
	Elvitegravir/cobicistat	◆	◆	◆	◆*	◆
	Maraviroc	◆	◆	◆	◆	◆
	Raltegravir	◆	◆	◆	◆	◆

*Known or anticipated increases in tenofovir and boosted regimens and efavirenz and rilpivirine when given LDV/SOF: caution and frequent renal monitoring needed.

EASL Recommendations on Treatment of Hepatitis C 2015; Available at http://www.easl.eu/research/our-contributions/clinical-practice-guidelines (accessed May 2015).

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

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

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

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

Summary

A new dawn for the treatment of HCV in HIV-infected patients

Highly effective

Easy to use: - all oral

- short course treatment

- extremely well tolerated

Challenges remaining: - Funding

- Avoidance of re-infection