Liver Disease in HIV

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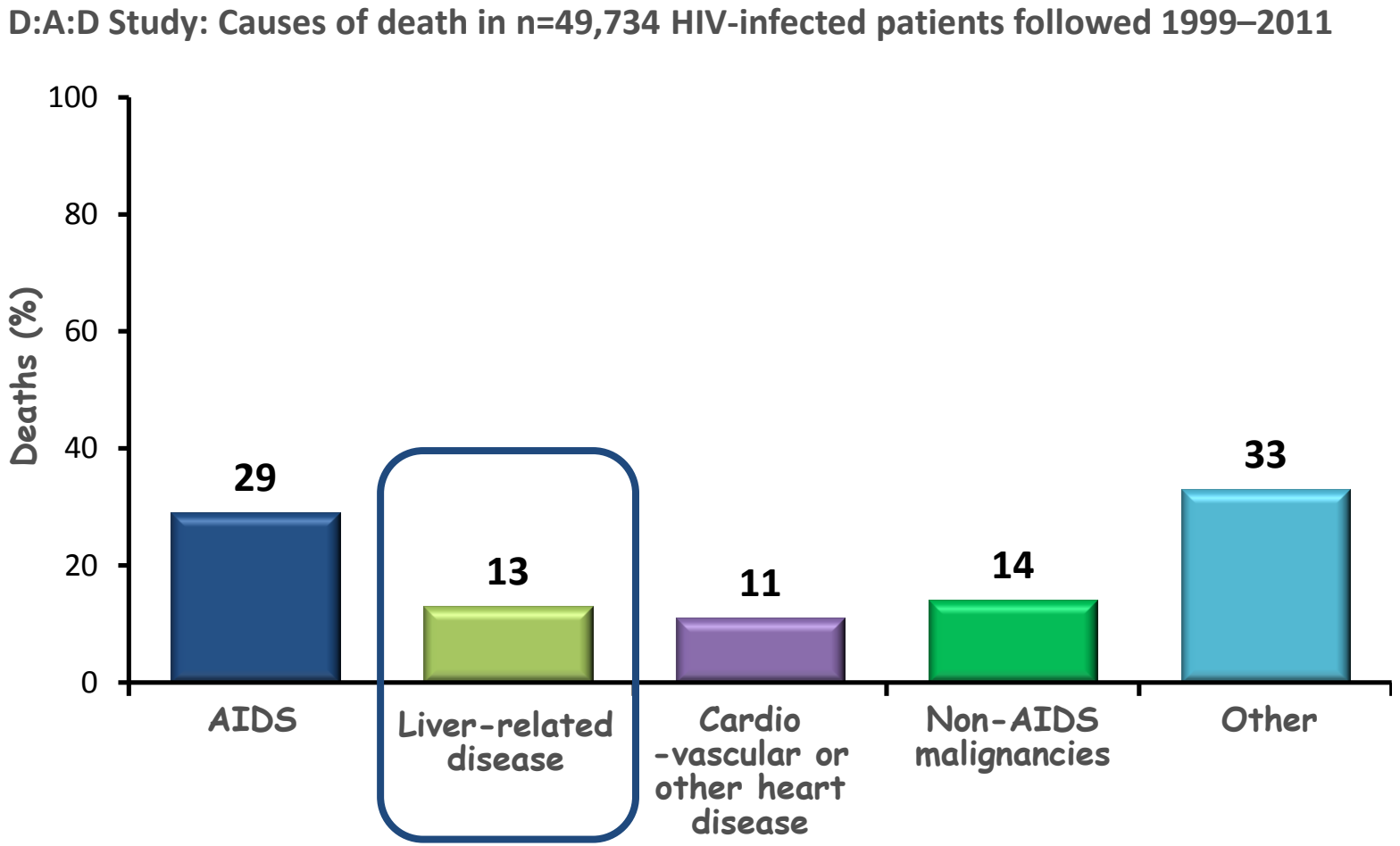
Outline

- Importance of liver disease in HIV
- Global burden of Viral Hepatitis and contribution to morbidity/mortality
- Drug-induced liver disease
- HBV
- HCV

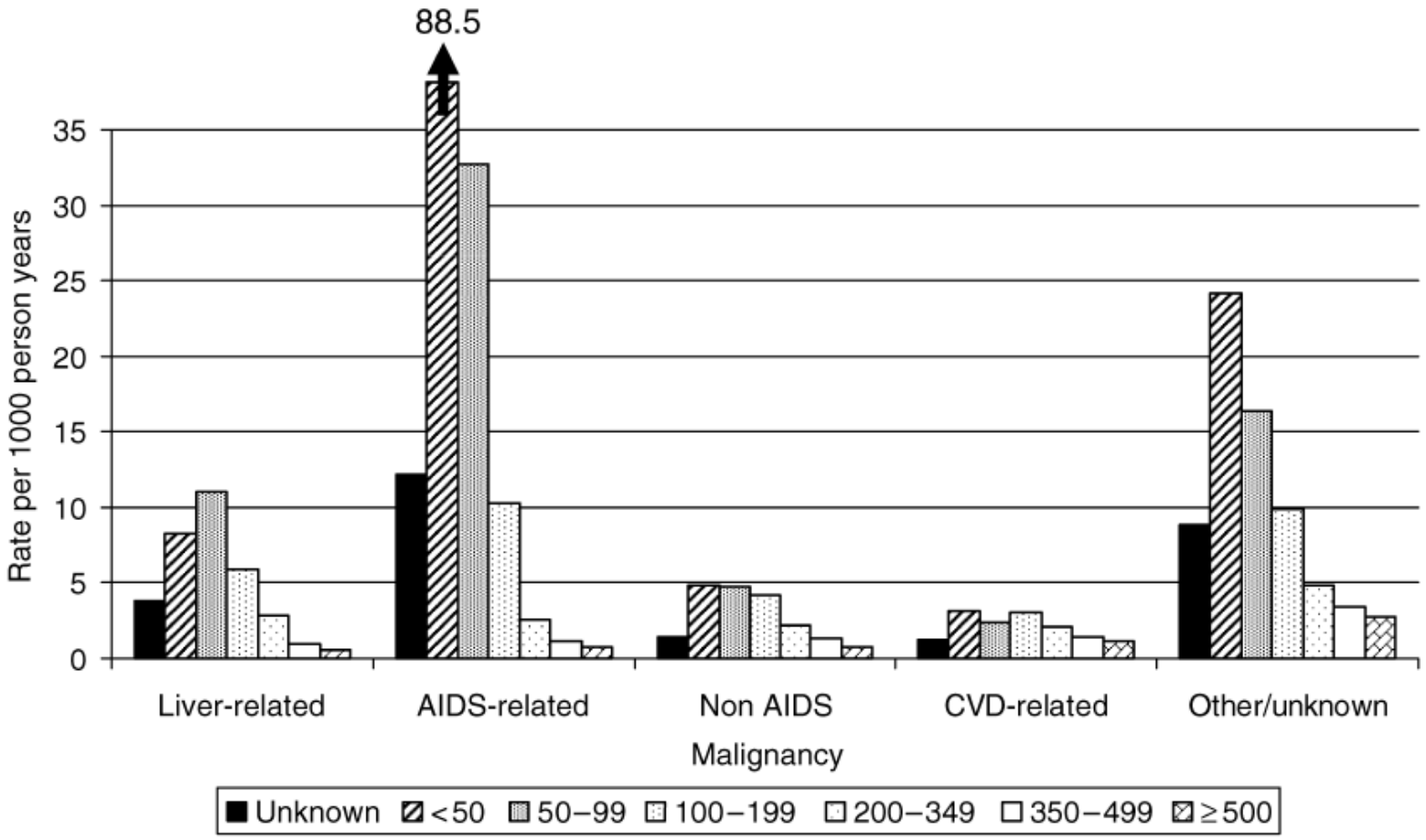
- Case-based discussion (Thursday pm)

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



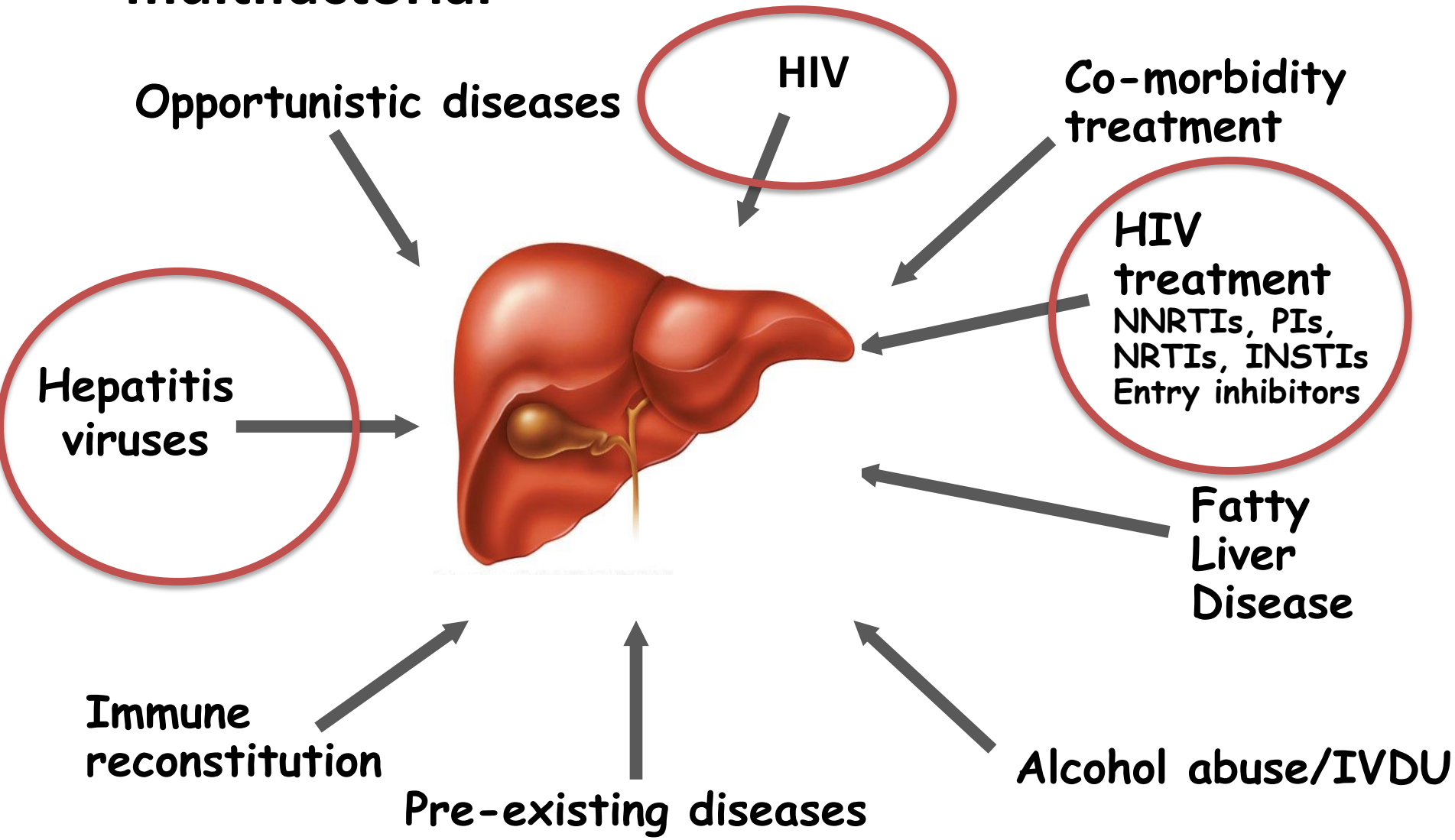
Weber R, et al. AIDS 2012. Washington USA. Oral presentation THAB0304.

Liver-related death and CD4 count



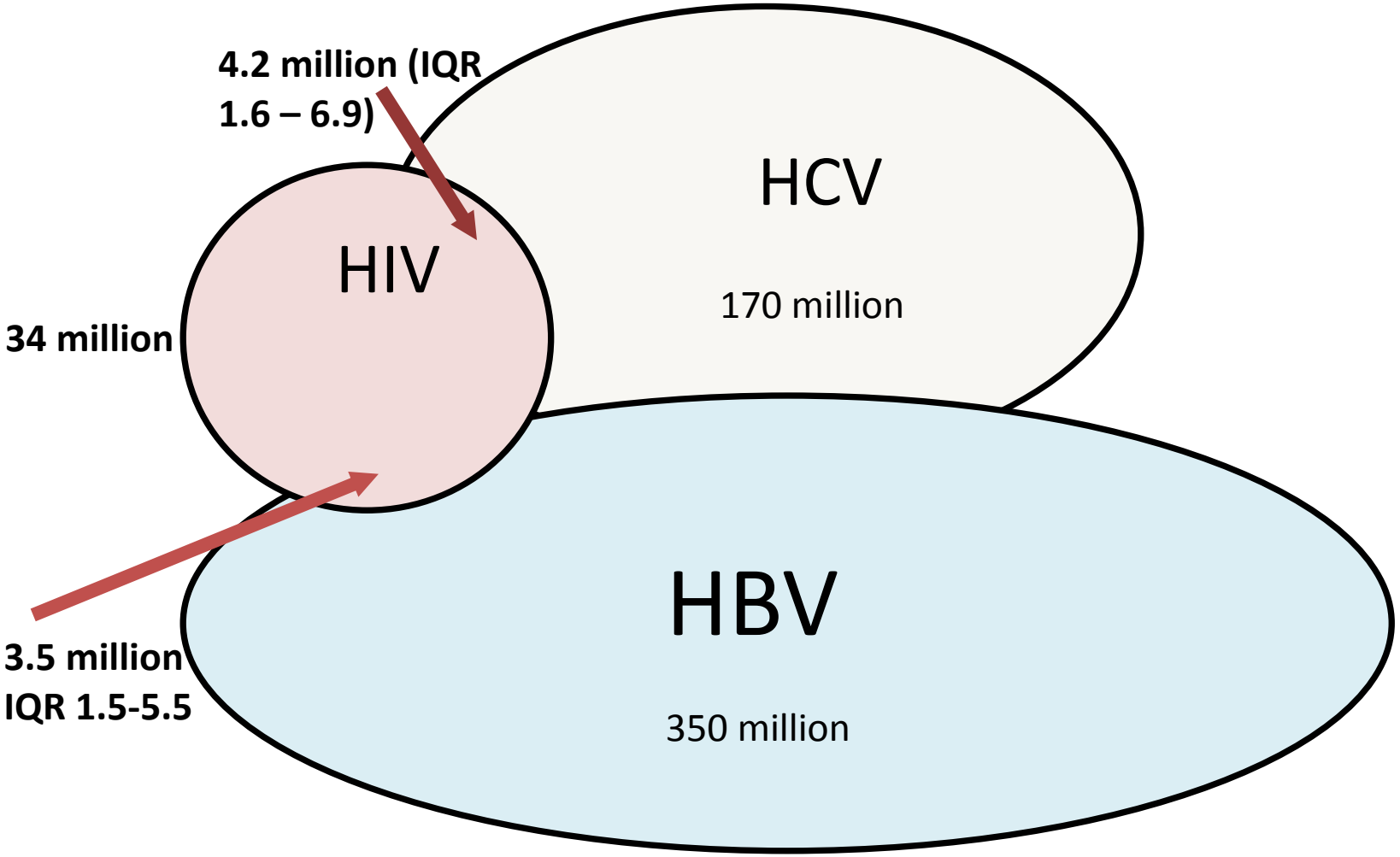
D.A.D study Gp. AIDS 2010: 24: 1537

Liver Disease in HIV-infected Patients - multifactorial

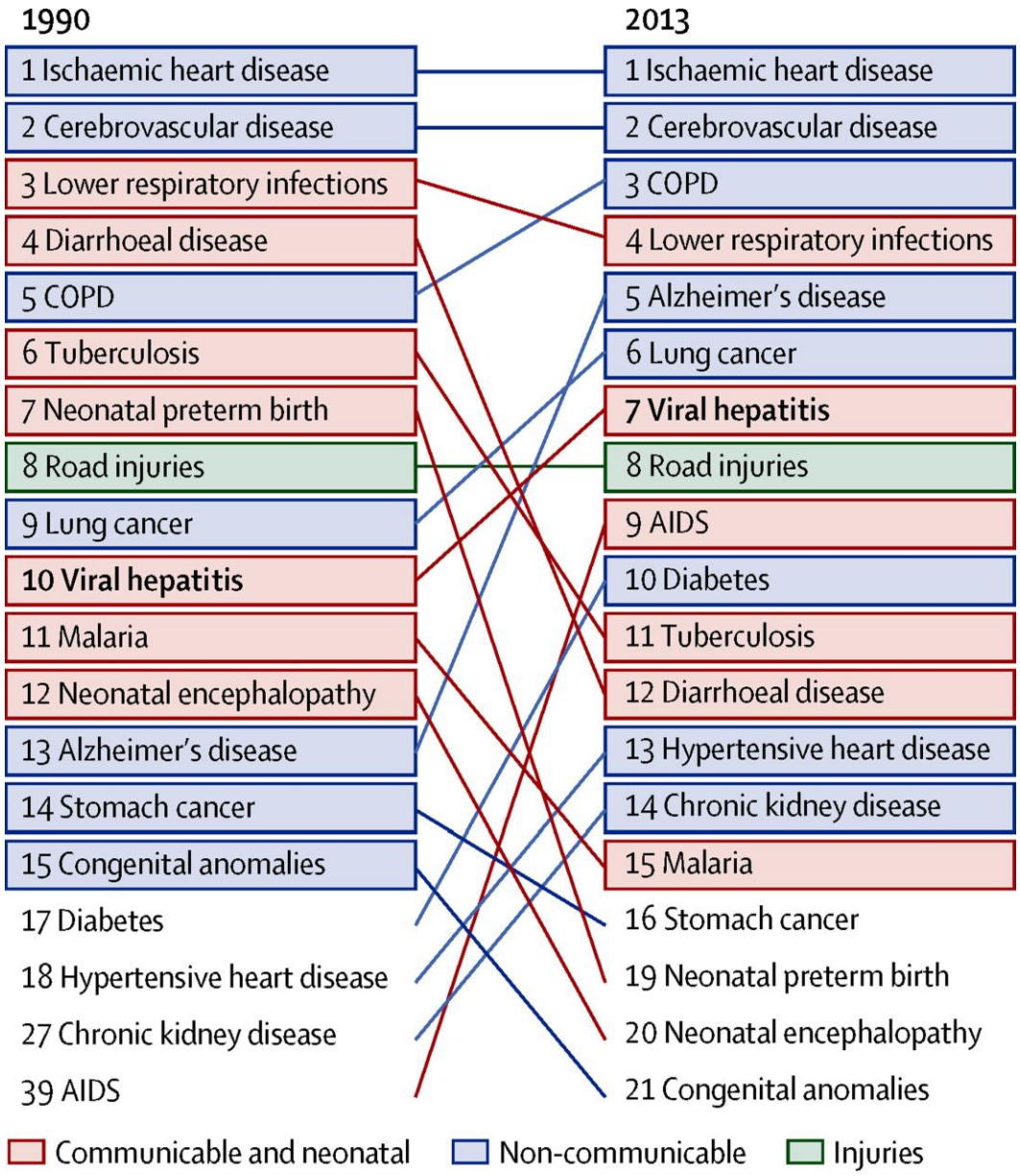


Sulkowski M. *et al.* Ann Intern Med. 2003;138:197-207 Guaraldi G *et al* Clin Infect Dis 2008 47(2): 250-257
Greub G *et al.* Lancet 2000;356:1800-1805

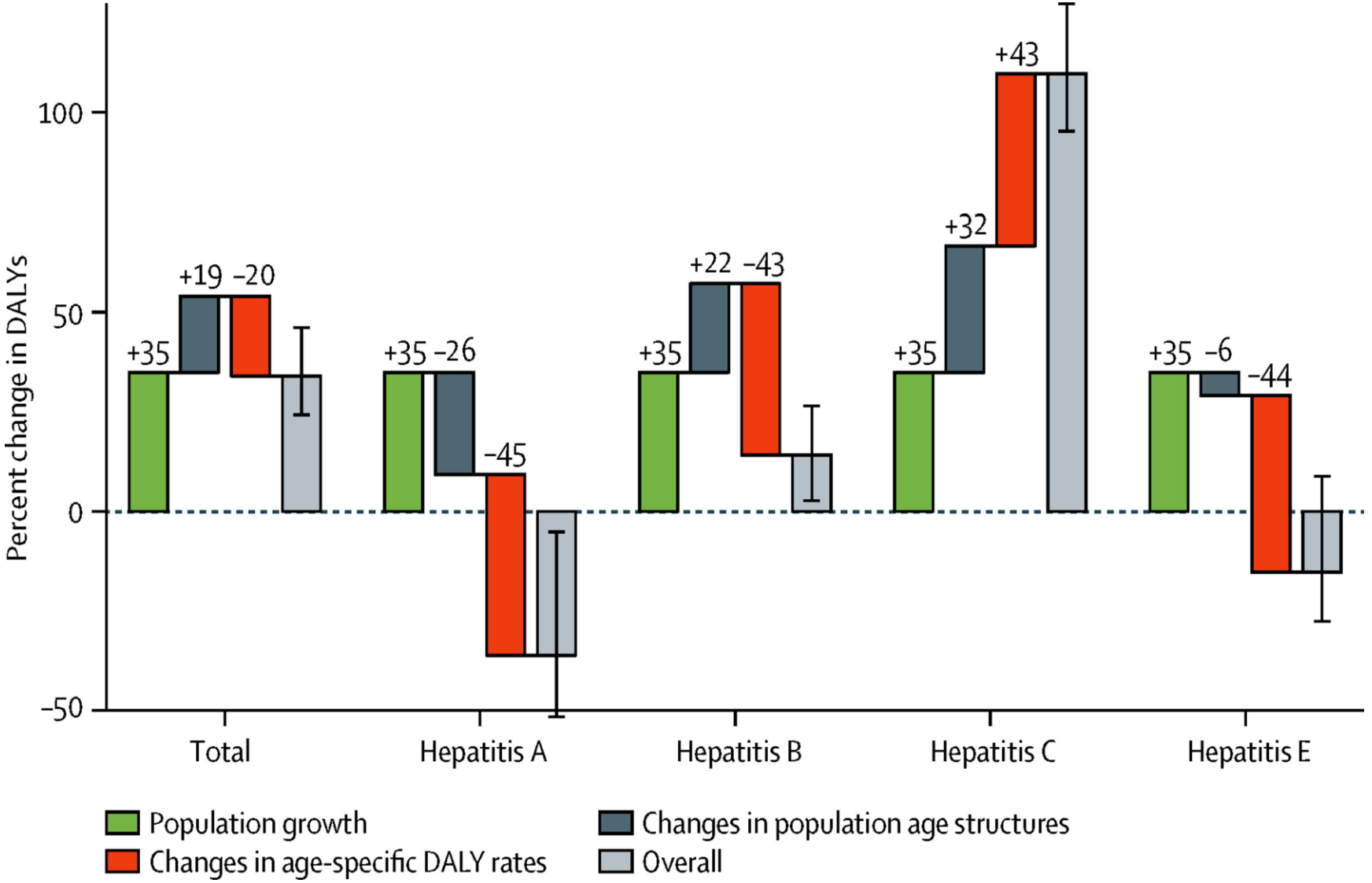
Overlapping epidemics – co-infections



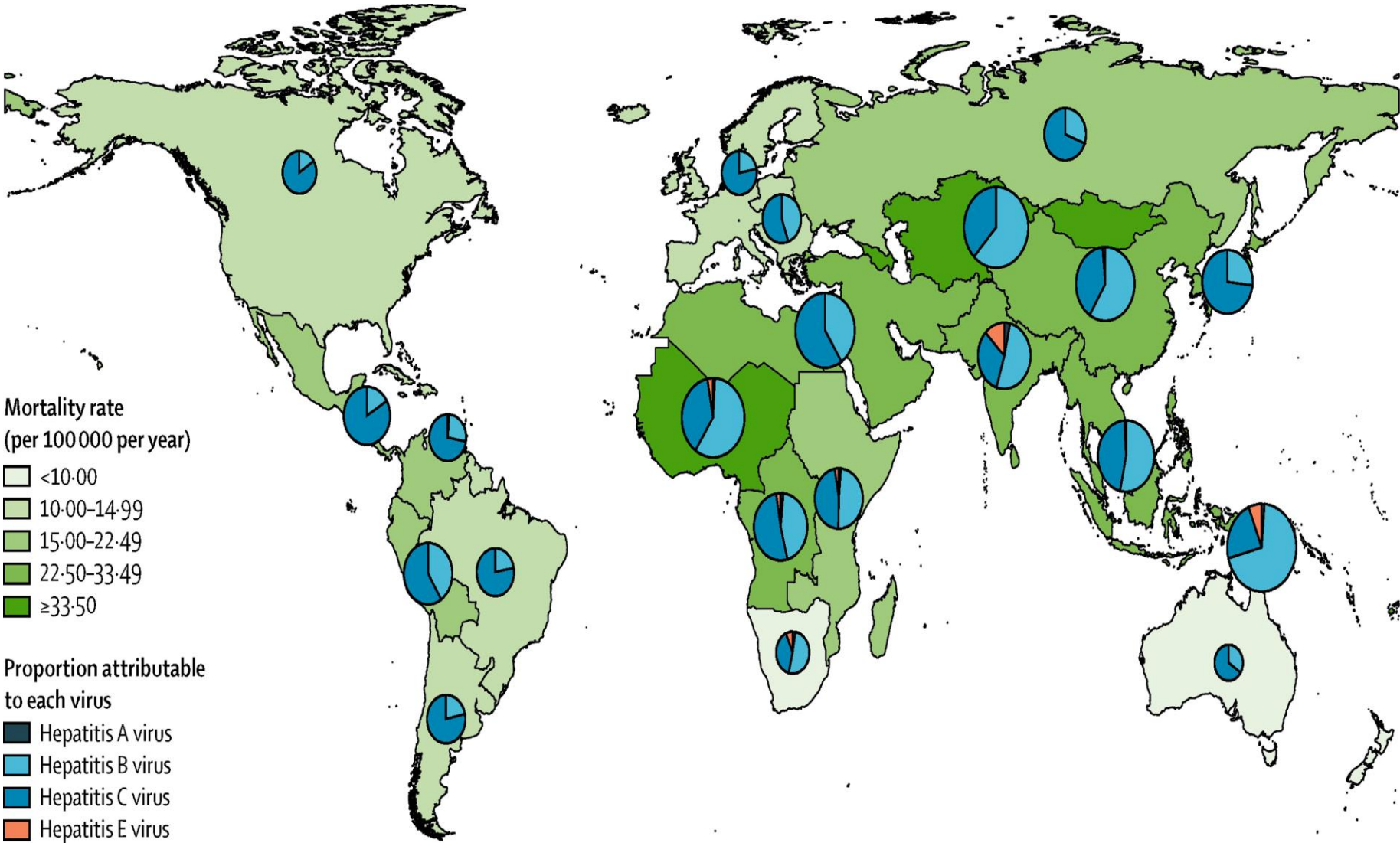
Easterbrook, et al. IAS 2015, TuPEB254



Stanaway, et al, Lancet 2016

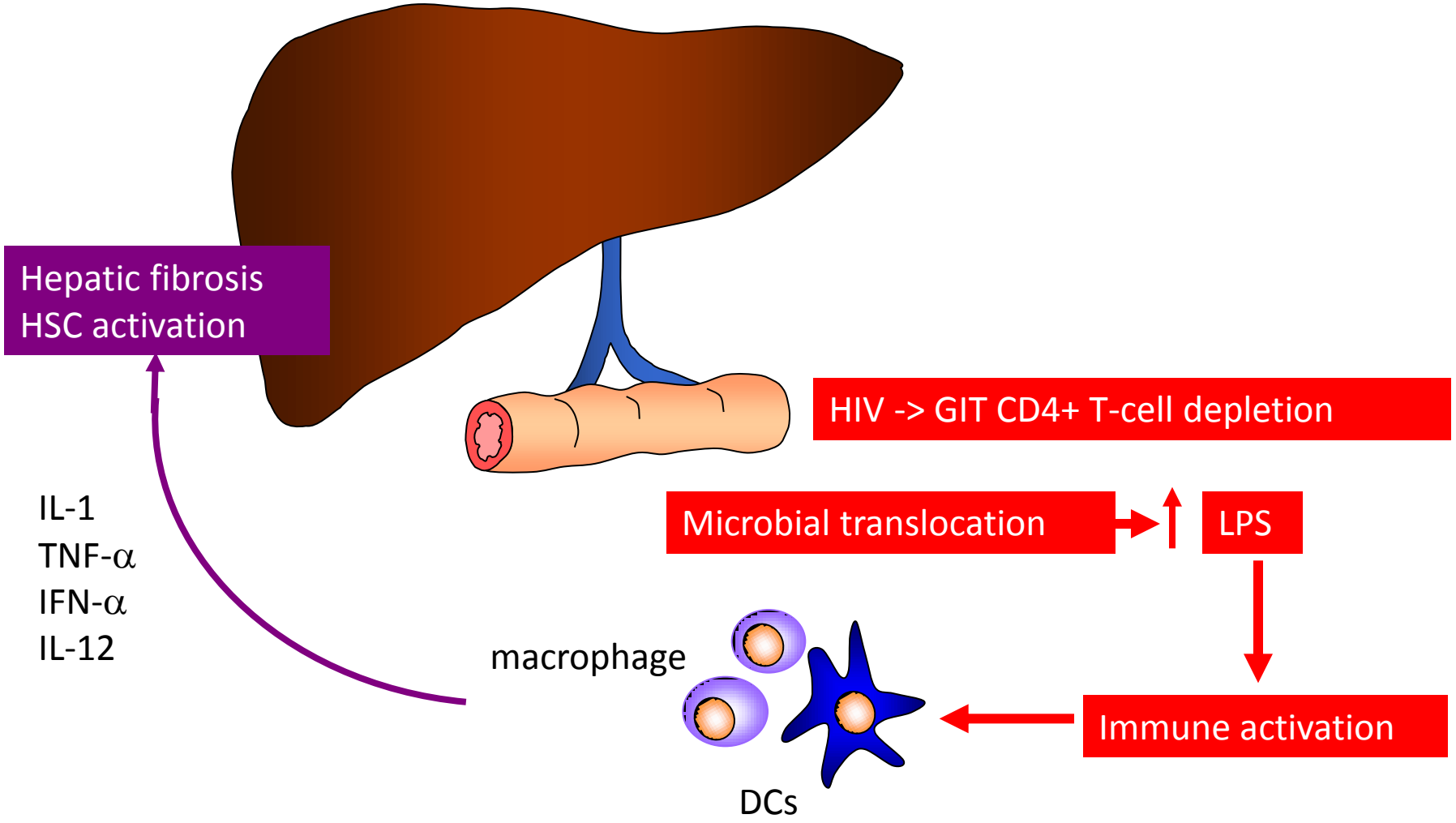


Stanaway, et al, Lancet 2016



Stanaway, et al, Lancet 2016

HIV-associated Immune activation and liver disease



Mathurin et al., Hepatology 2000; 32:1008-1017; Paik et al., Hepatology 2003; 37:1043-1055; Balagopal et al., Gastroenterology 2008; 135:226-233..

START liver fibrosis study (2014)

- Sub-study of 230 (4577) patients
- Baseline FibroScan, FIB-4, APRI

- 7.8% >F2 fibrosis by FibroScan (10% FIB-4, 8.6% APRI)

- Multivariate analysis
  - Significant Fibrosis associated with HIV RNA and ALT at baseline
  - Not associated with BMI or use of anti-lipid therapy

Matthews et al, HIV Medicine, 2014

Mechanisms of drug-related liver injury in HIV-infected patients

Mechanism	
Metabolic host-mediated (intrinsic and idiosyncratic)	NNRTIs and PIs Usually 2-12 months after initiation Occurrence can vary by agent Dose-dependence for intrinsic damage
Hypersensitivity	NVP>ABC>fosAPV Early, usually within 2-12 weeks Often associated with rash HLA-linked
Mitochondrial toxicity	NRTIs ddI>d4T>AZT>ABC=TDF=FTC/3TC
Immune reconstitiution	Chronic Hepatitis B Chronic HCV? Within first few months More common if low CD4 count/large rise

Soriano et al. AIDS 2008; 22: 1-13

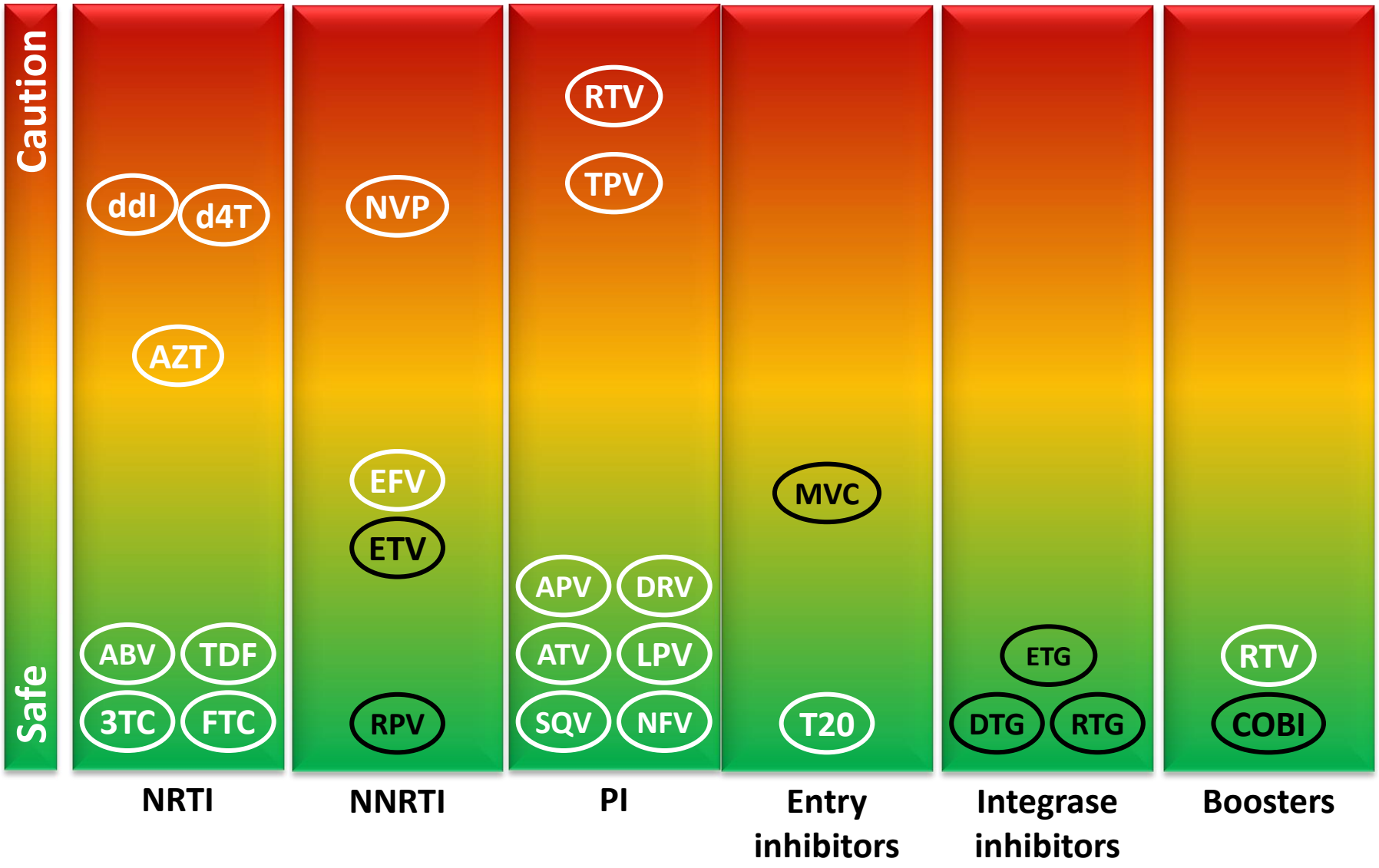
Non Cirrhotic Portal Hypertension

- Almost exclusively associated with didanosine (ddI) use
  - Related to duration of use
  - May present many years after discontinuation
- Histologically:
  - Nodular regenerative hyperplasia
  - Partial Nodular Transformation
  - Portal venopathy
  - May be normal
- Clinically: Portal hypertension
  - Variceal bleeding *(Scourfield et al, IJSA 2011)*
  - Ascites

- Association with SNPs in 5-nucloeotidase and xanthine oxidase *(Vispo et al, CID 2013)*

- ? Role of screening for ddI exposed patients

Hepatic Safety Profile of ARVs



After Soriano at al. AIDS 2008; 22: 1-13

Associated Risk factors for hepatotoxicity of ART

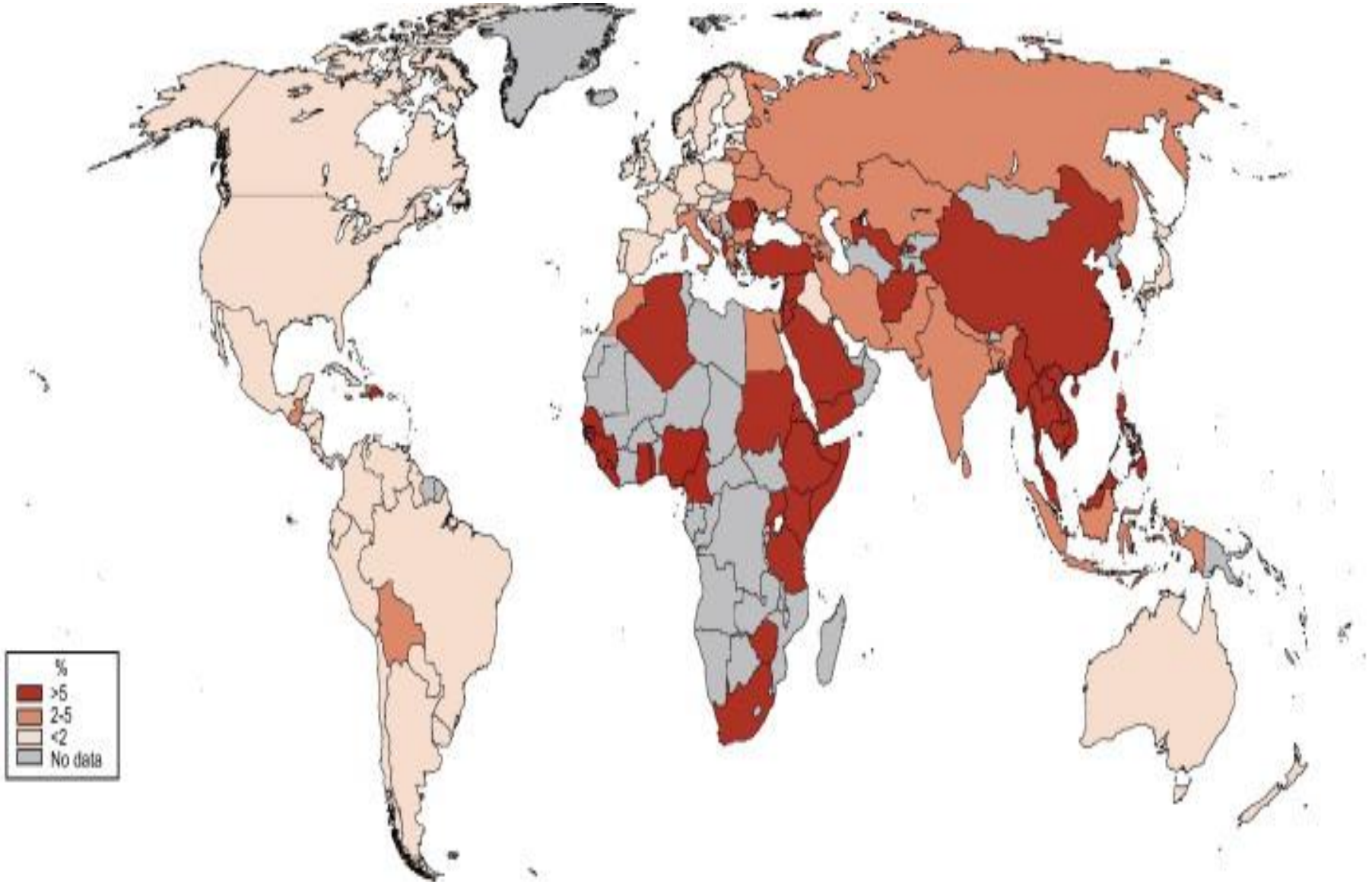
- Hepatitis B and C co-infection
- Higher baseline ALT/AST levels
- Alcohol
- Older age
- Female gender
- High or low CD4 count
- Lower BMI
- Use of ddI, d4T, NVP, RTV (>200mg/day rather than at 'boosting' 100mg/day)

Rodriguez-Rosado et al. AIDS 1998;12:1256; Sulkowski et al. JAMA 2000;283:74.; Saves et al. AIDS 1999;13:F115; den Brinker et al. AIDS 2000;14:2895; Martínez et al. AIDS 2001;15:1261; Núñez et al. J AIDS 2001;27:426.

Hepatotoxicity in HBV and HCV co-infected patients - mechanisms

- Immune restoration - increase in CTL activity
- Direct hepatotoxicity – increased susceptibility of viral infected hepatocytes to metabolites
- Altered cytokine milieu in the presence of viral hepatitis
  - Increased risk of liver inflammation
  - Down-regulation of Cyp450 mediated drug metabolism with advancing liver disease

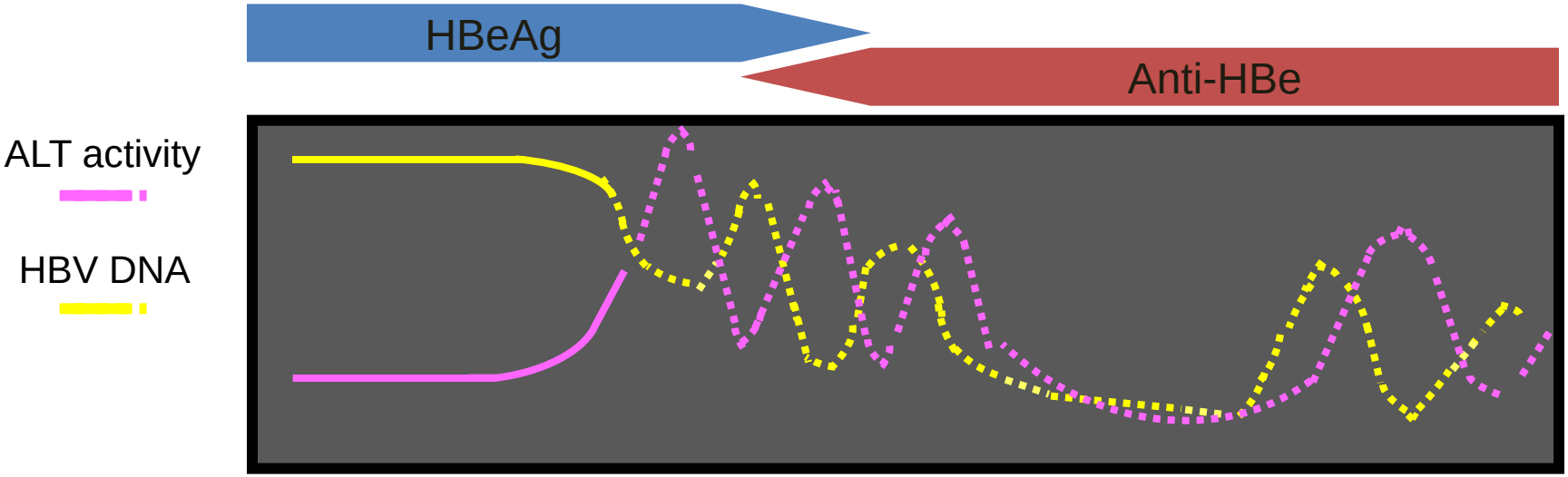
Global HBV



Suraj Sharma, Manuel Carballo, Jordan J. Feld, Harry L.A. Janssen
Journal of Hepatology, Volume 63, Issue 2, 2015, 515–522

4 Phases of Chronic HBV Infection

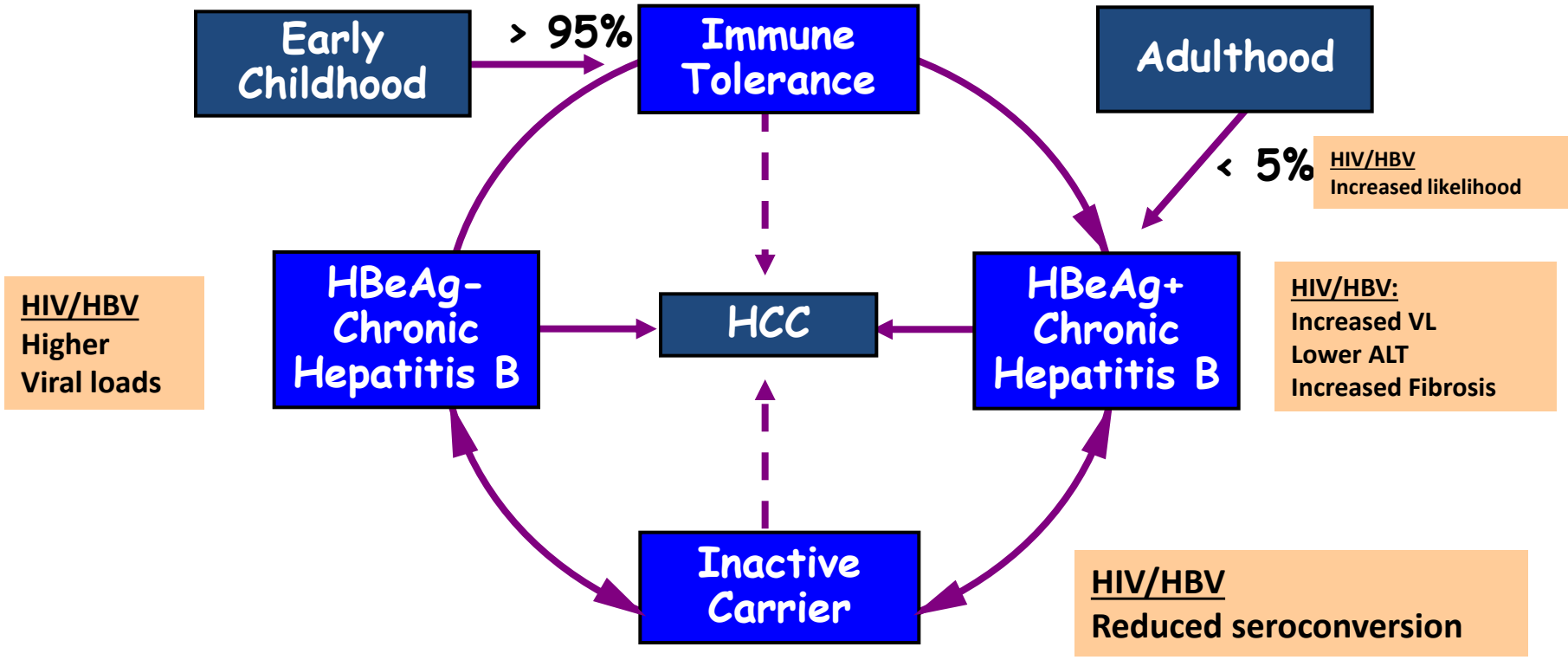
Current Understanding of HBV Infection



Phase	Immune Tolerant	Immune Clearance	Inactive Carrier State	Reactivation
Liver	Minimal inflammation and fibrosis	Chronic active inflammation	Mild hepatitis and minimal fibrosis	Active inflammation

Yim HJ, et al. Natural history of chronic hepatitis B virus infection: what we knew in 1981 and what we know in 2005. Hepatology. 2006;43:S173-S181.

Natural history of HBV infection – where does HIV co-infection fit in?



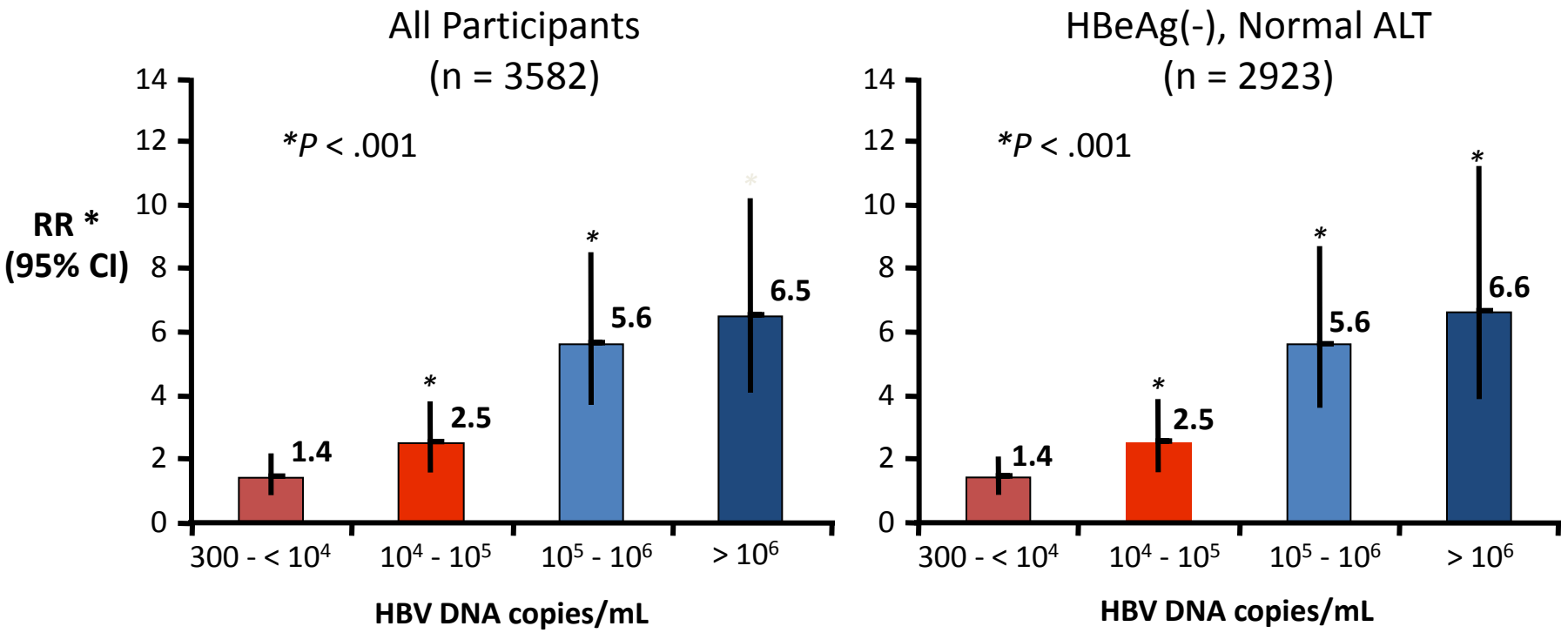
Chen DS, *et al. J Gastroenterol Hep.* 1993;8:470–475; Seeff L, *et al. N Engl J Med.* 1987;316:965–970

When do we need to Rx HBV?

- Everybody with detectable HBV DNA?
- Based on HBV DNA levels?
- Those with evidence of significant liver disease?
  - Based on abnormal ALTs?
  - Histological activity/Fibrosis scores?

Level of HBV DNA (c/ml) at entry & progression to cirrhosis and risk of HCC

3582 HBsAg untreated asian carriers
mean follow-up 11 yrs → 365 patients newly diagnosed with cirrhosis

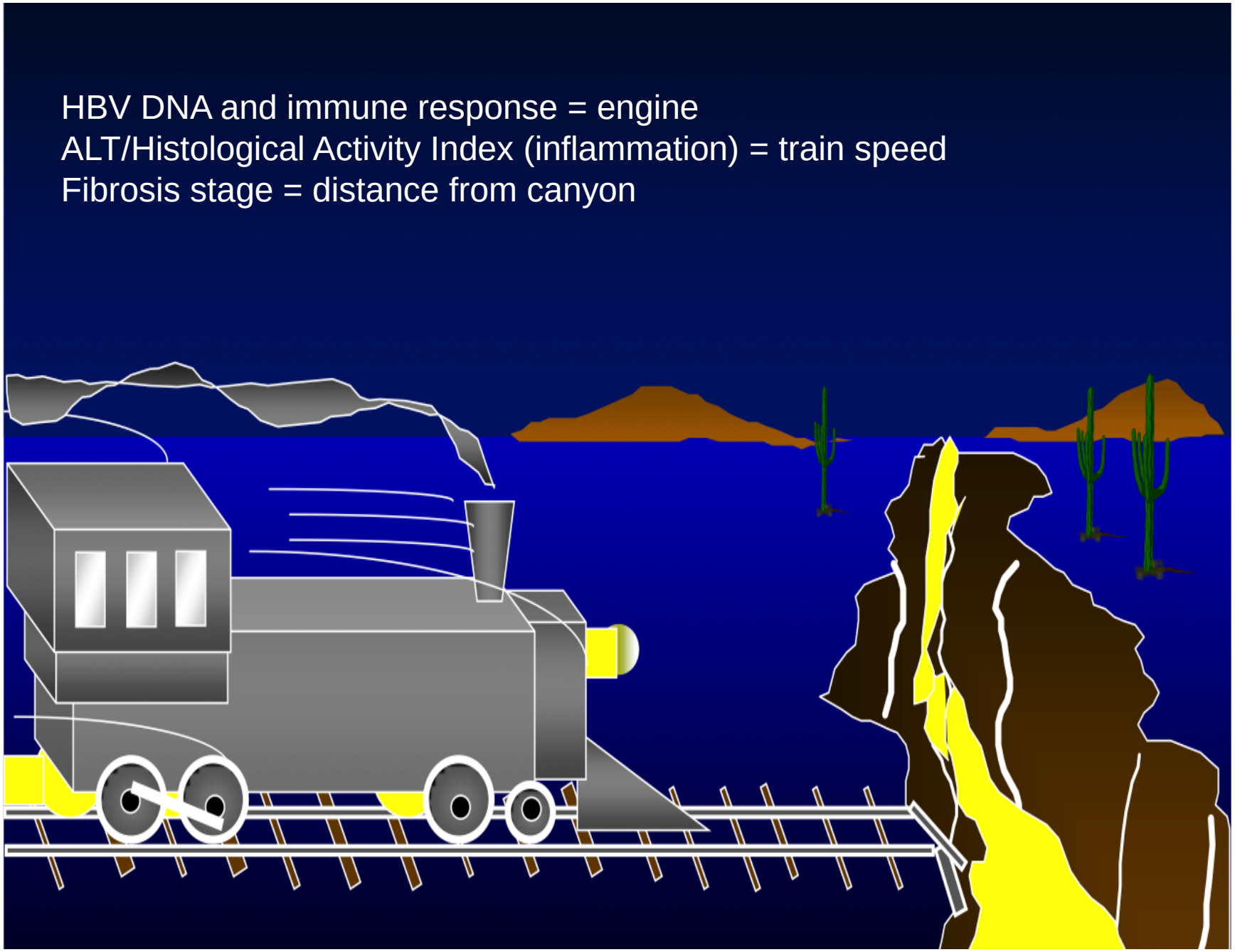


* Adjusted for age, sex, cigarette smoking, and alcohol consumption.

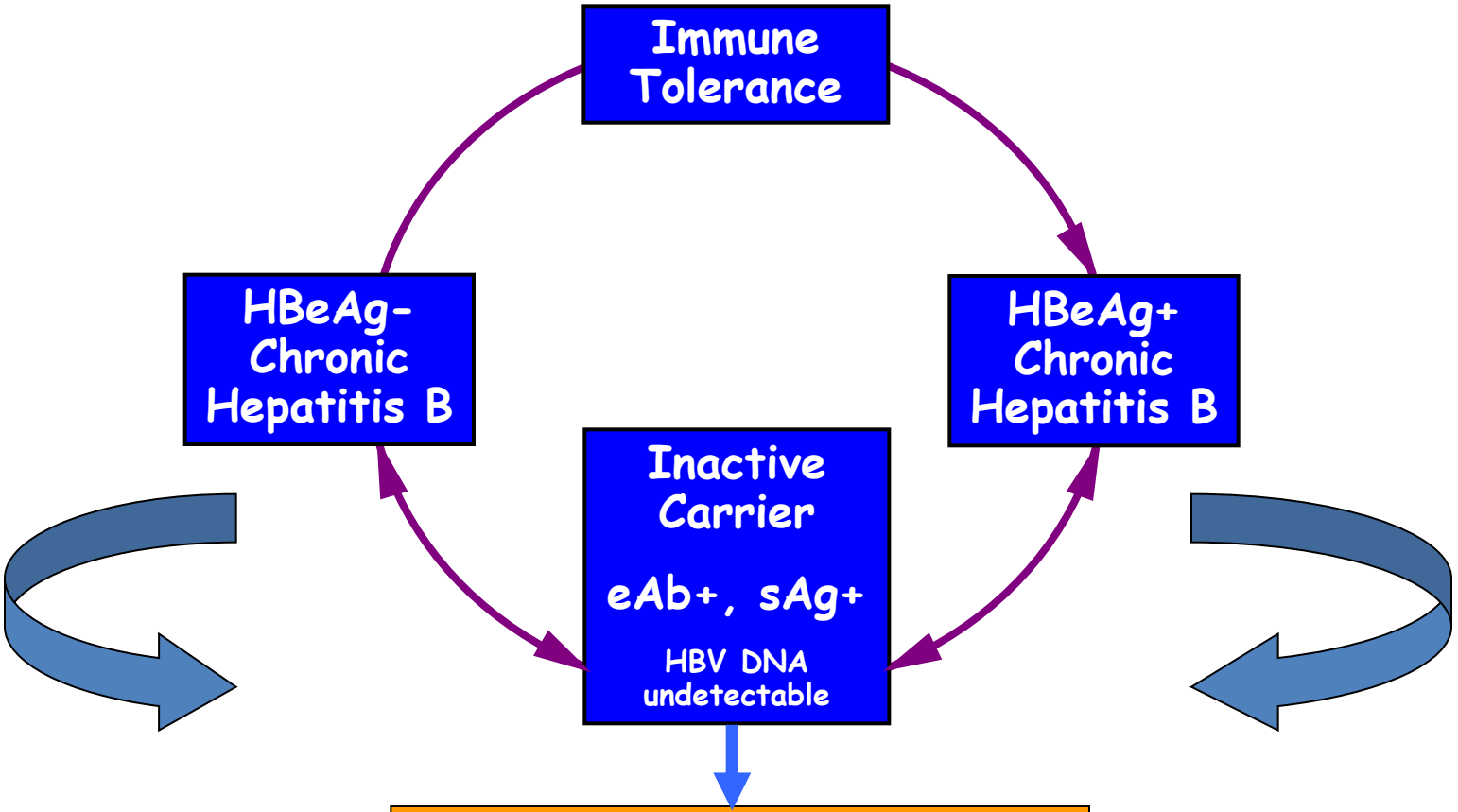
HBV-DNA viral load (> 10^4 cp/ml) strongest predictor of progression to cirrhosis independent of ALT and HBeAg status

Iloeje UH, Gastroenterology 2006; 130: 678-686

HBV DNA and immune response = engine
ALT/Histological Activity Index (inflammation) = train speed
Fibrosis stage = distance from canyon



What does Rx aim to achieve?

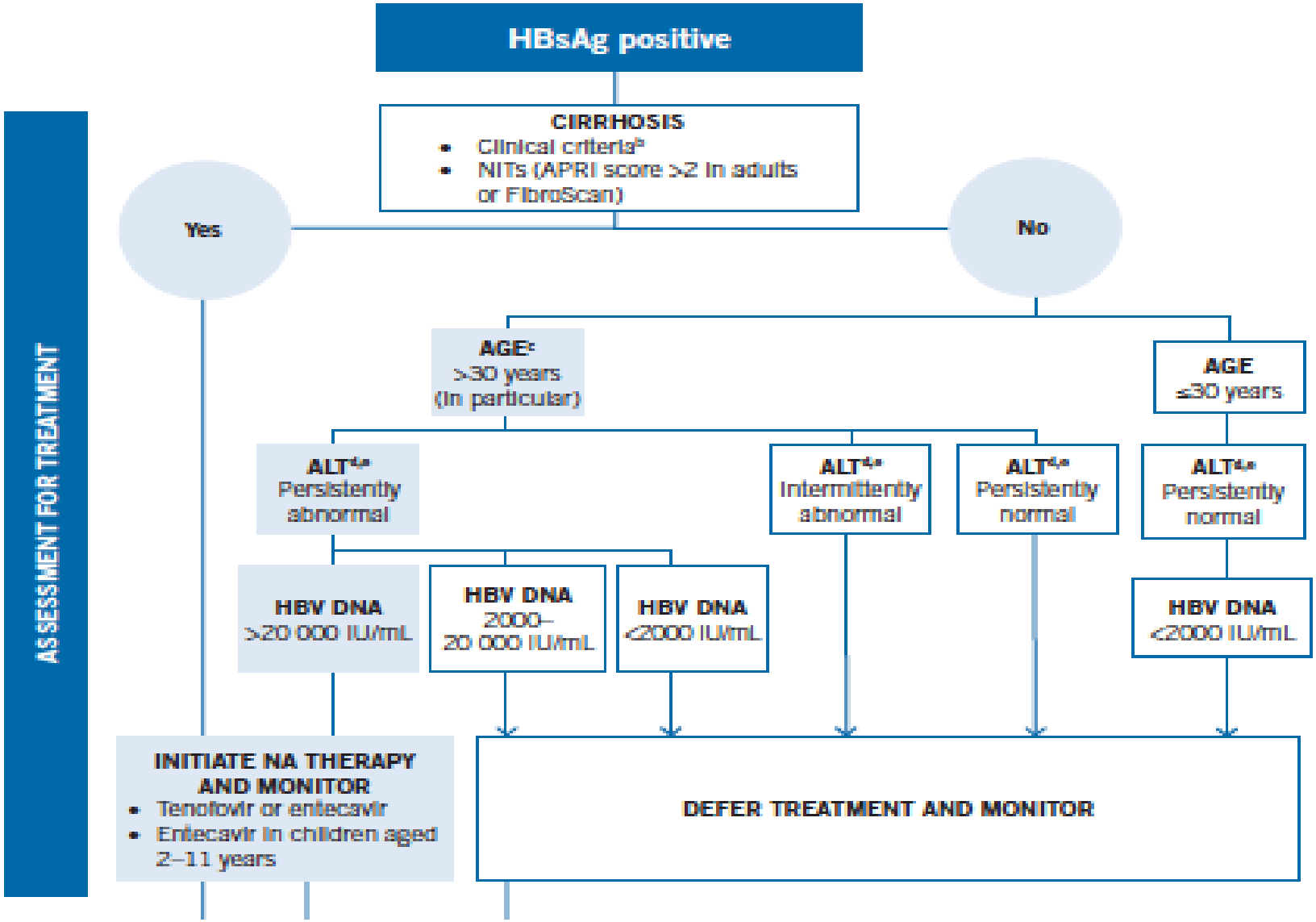


Viral Replication (HBV DNA)
Anti-HBe sero-conversion
HBsAg Loss
Anti-HBs sero-nversion
Clearance cccDNA

Three key inter-linked factors in the decision to treat

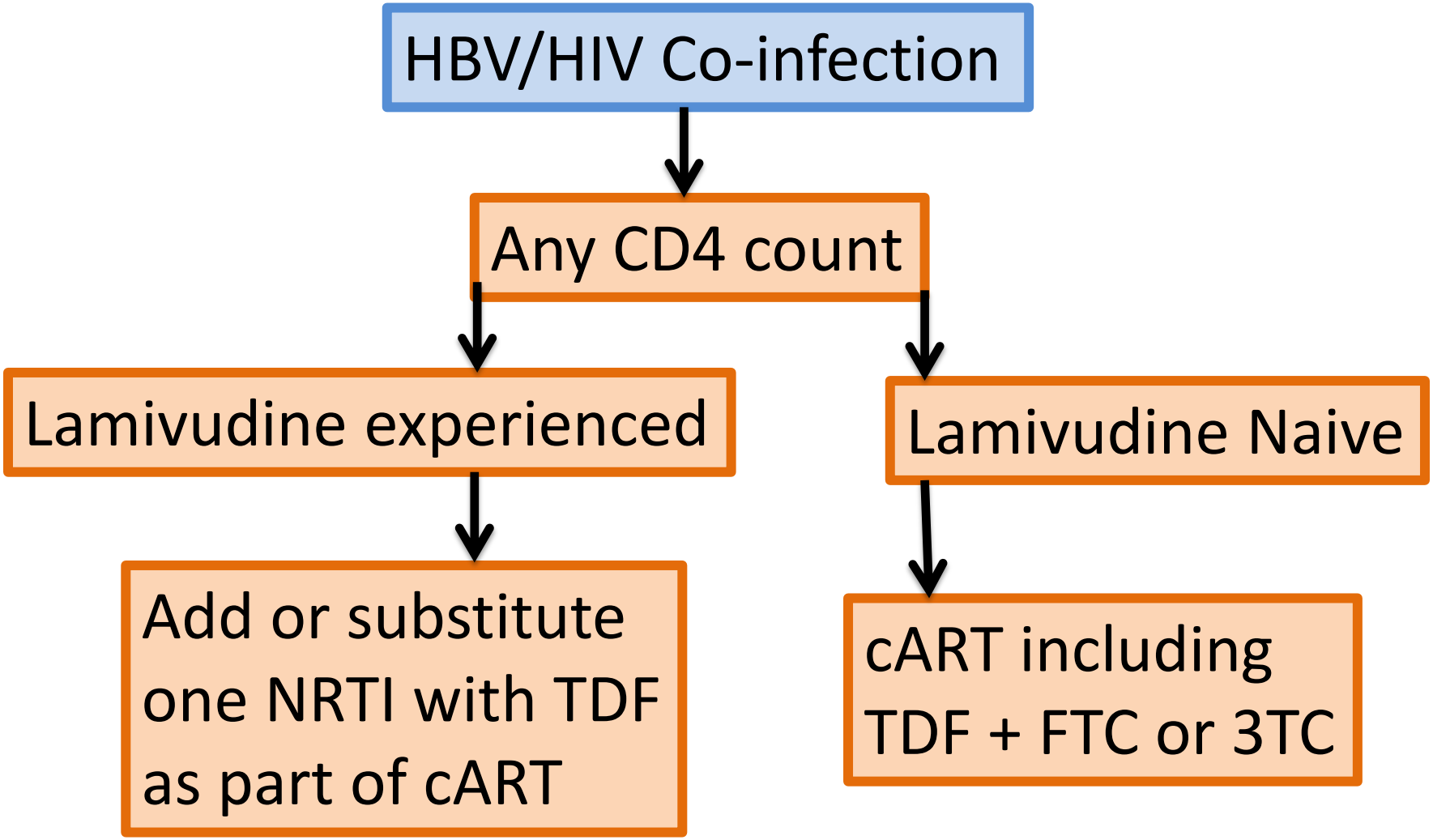
- Age
  - <30yrs vs. >30yrs
  - FH of HCC
- Level of fibrosis/inflammation
  - Cirrhosis
  - F2+ fibrosis
  - Abnormal liver enzymes
- HBV DNA levels
  - >20 000 IU/ml

ALGORITHM OF WHO RECOMMENDATIONS ON THE MANAGEMENT OF PERSONS WITH CHRONIC HEPATITIS B INFECTION[a]

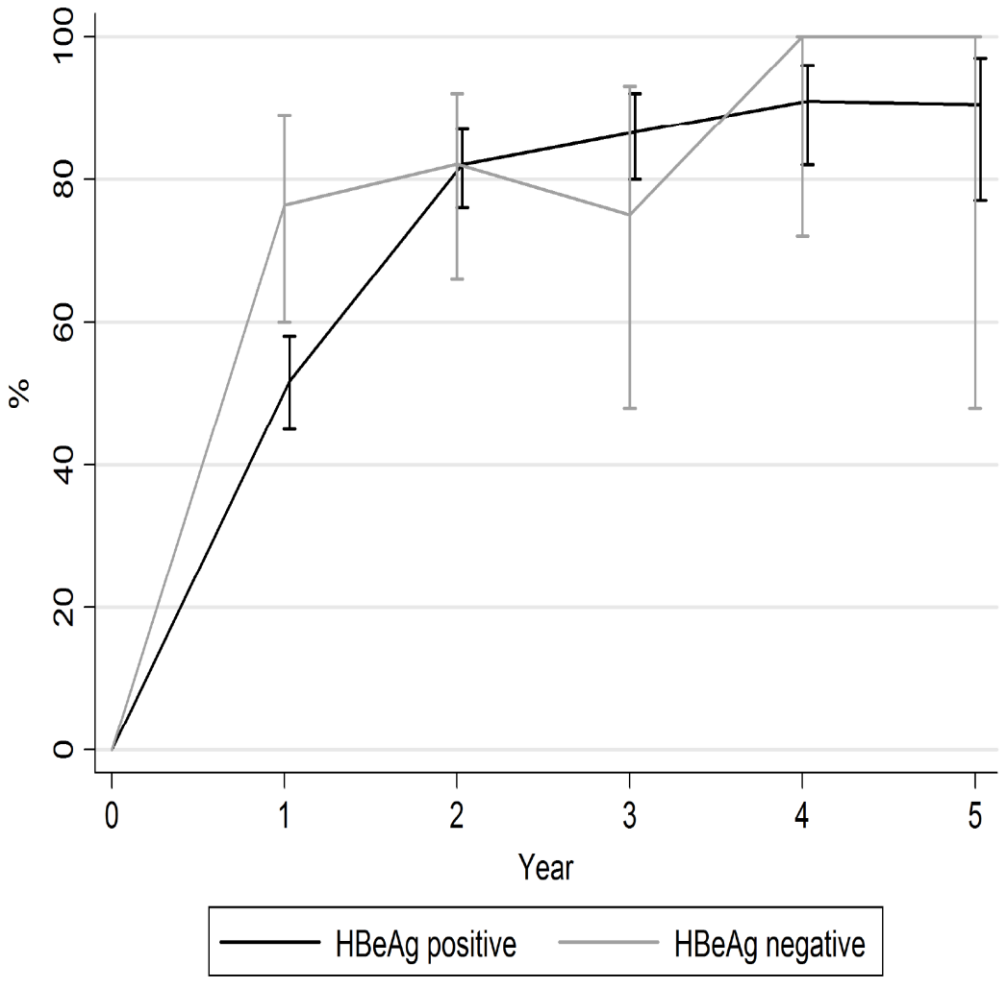


WHO Guidelines 2015

New Guidelines 2016



13 years of tenofovir (TDF) in co-infected patients



Meta-analysis 23 studies 550 HIV-HBV patients on TDF

Increasing suppression over follow-up in majority

Little evidence of resistance

Price et al, PLOs One 2013

Lack of access to routine testing and monitoring

World Hepatitis Alliance/WHO global survey 2009:
Testing for HBV and/or HCV

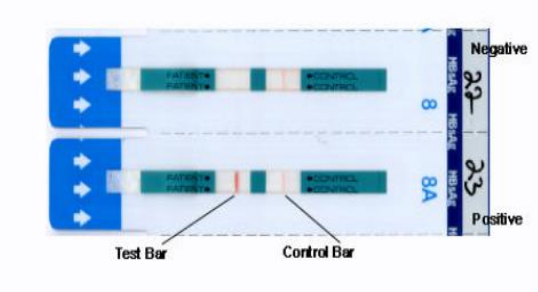
- >50% people live in countries with no free testing
- Only 4% low-income countries have ready access to testing

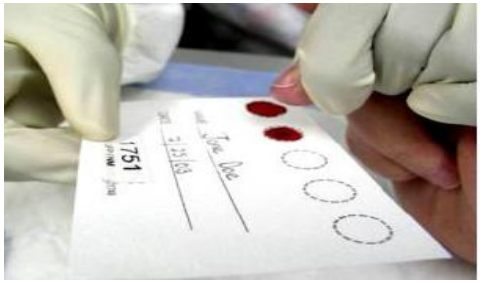
	Testing accessible to >50%	Testing anonymous	Free to all	Free to some
Africa	20%	40%	10%	27%
SE Asia	29%	29%	29%	14%
Europe	86%	55%	27%	55%

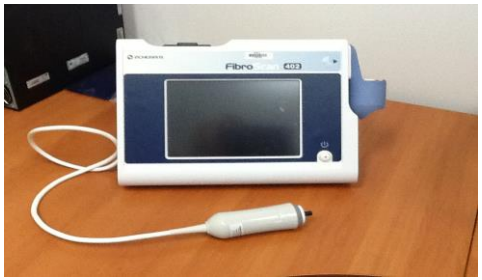
Easterbrook et al Sem Liv Dis 2012

Lack of access to routine testing and monitoring

- Limited access to HBsAg testing means many co-infected individuals not identified pre-ART
- Little understanding of natural history of co-infection in RLS
- Liver disease fibrosis assessment not readily available
- Widespread absence of virological monitoring by HBV DNA testing

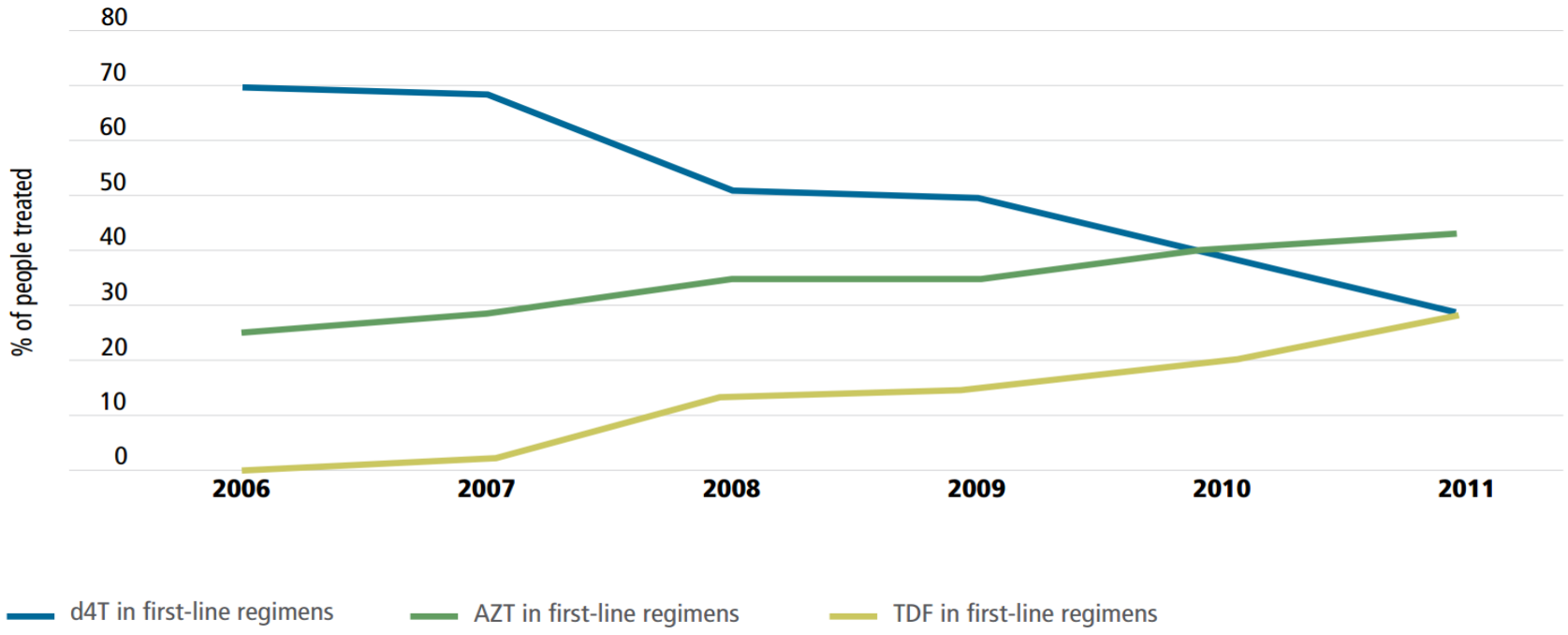






Although TDF use is improving, far from universal

Trends in d4T, AZT and TDF use in first-line antiretroviral therapy regimens for adults in low- and middle-income countries, 2006–2011



Source: *Use of antiretroviral medicines by December 2011 based on the WHO survey in low- and middle-income countries (77).*

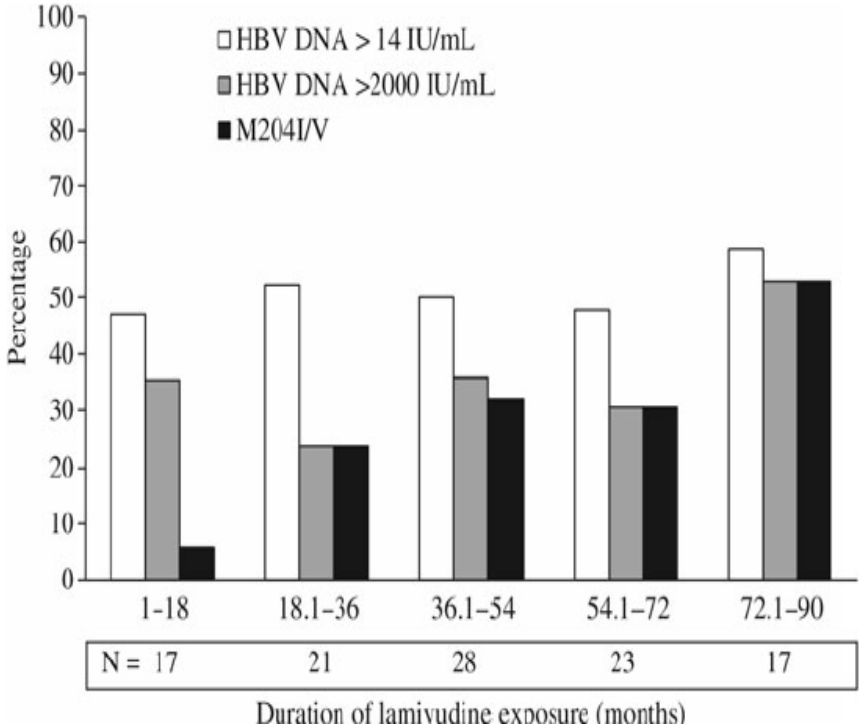
Global update on HIV treatment 2013. WHO

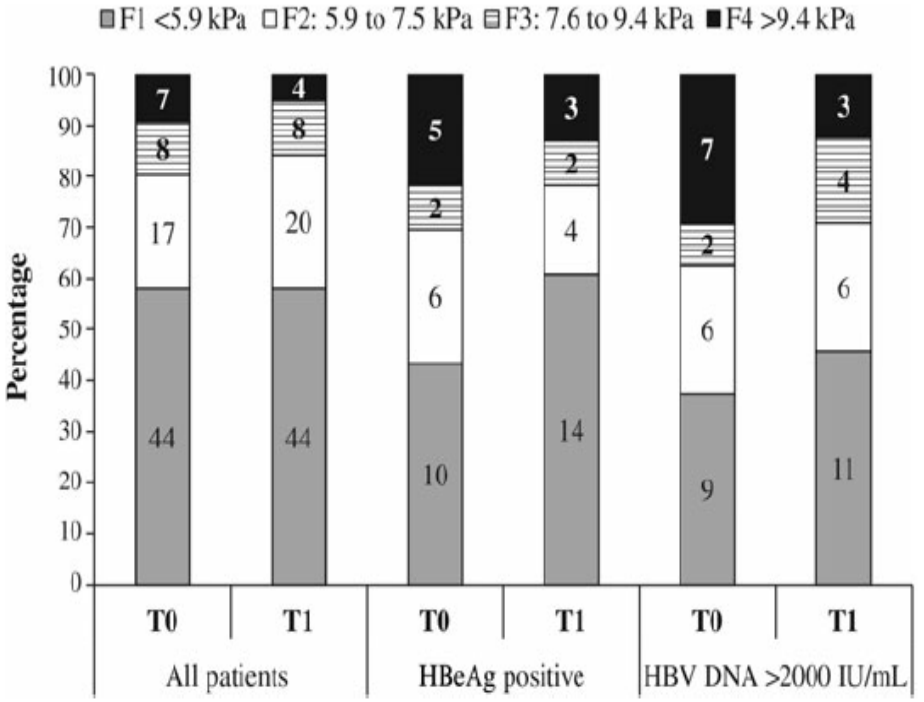
Tanzania: 3% HIV and 17% HIV/HBV on TDF regimen Hawkins IAC 2012

Clinical Infectious Diseases Advance Access published June 16, 2015

MAJOR ARTICLE

Liver Fibrosis by Transient Elastography and Virologic Outcomes After Introduction of Tenofovir in Lamivudine-Experienced Adults With HIV and Hepatitis B Virus Coinfection in Ghana

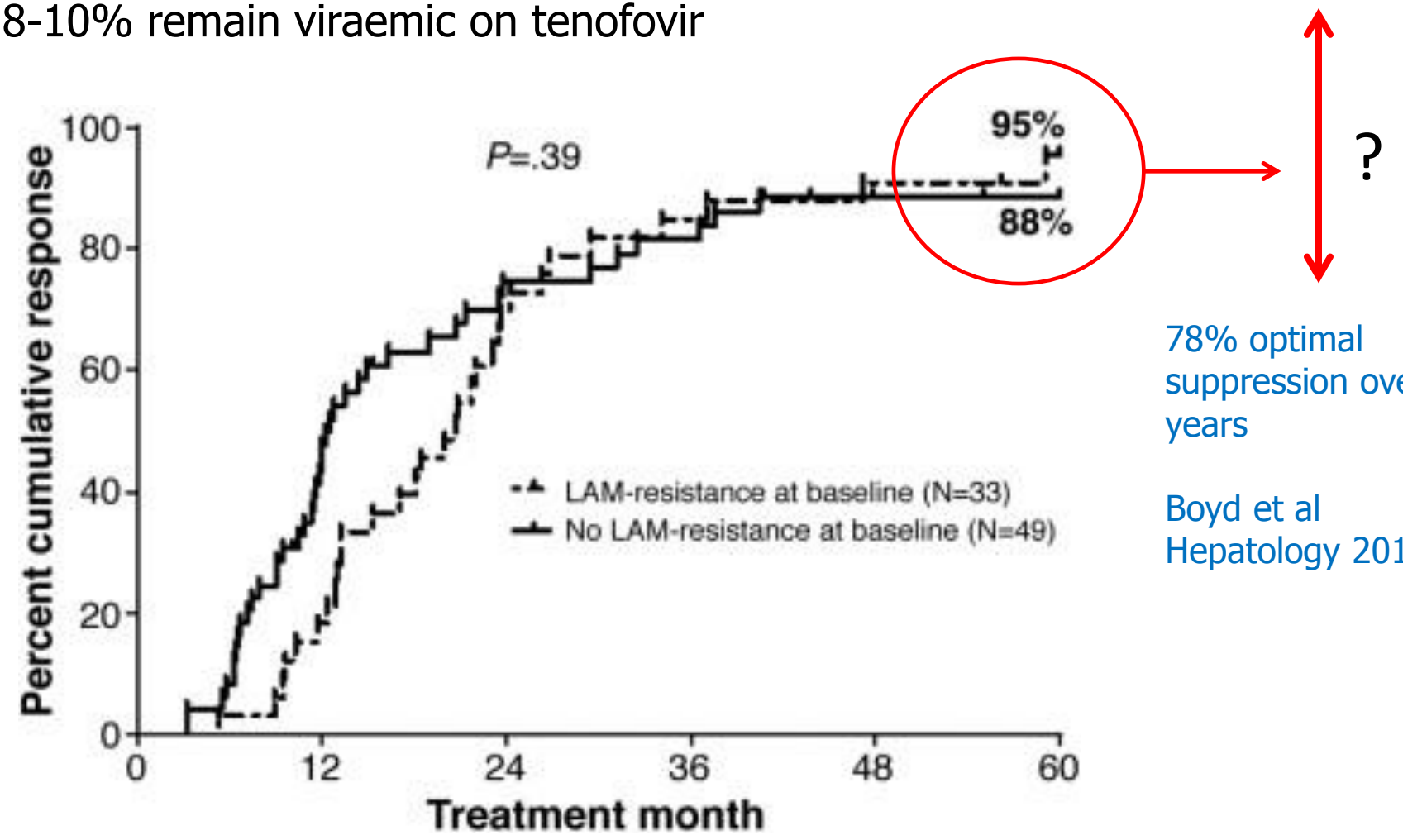




Stockdale, et al. Clin Infect Dis; 2015

Efficacy is never 100%

8-10% remain viraemic on tenofovir



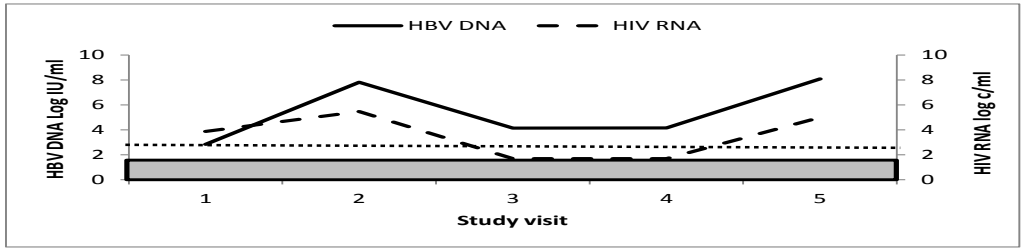
78% optimal suppression over 7 years

Boyd et al Hepatology 2014

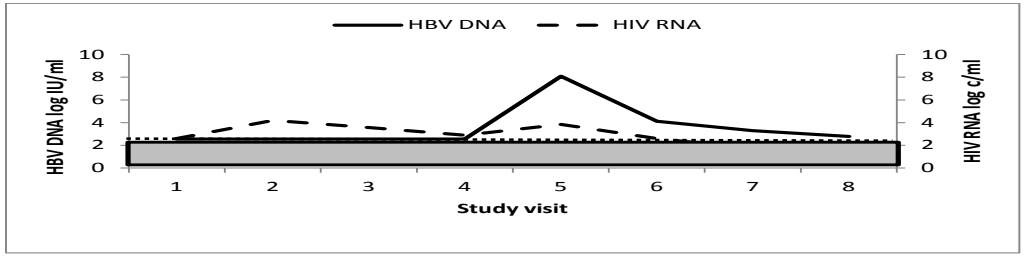
De Vries Slujis Gastroenterology 2010

Patterns of suboptimal response to TDF based therapy in HIV-HBV

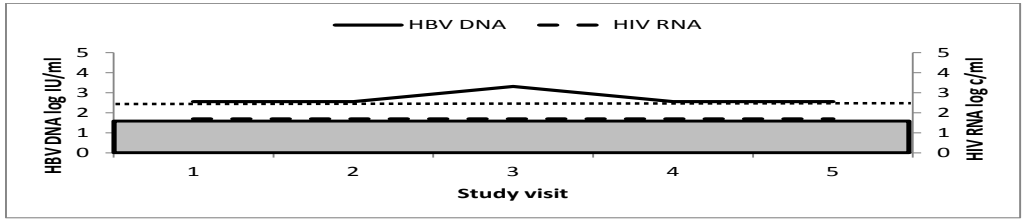
- 165 HIV -HBV coinfected individuals followed for median of 4 years
- HBV DNA detectable in 20% study visits



Persistent viraemia (n=25)



Viral rebound (n=13)



Blipper (n=24)

Matthews CID 2012

Factors associated with detectable HBV DNA

- On truvada based therapy at least 6 months
- Undetectable HIV RNA < 400 c/ml

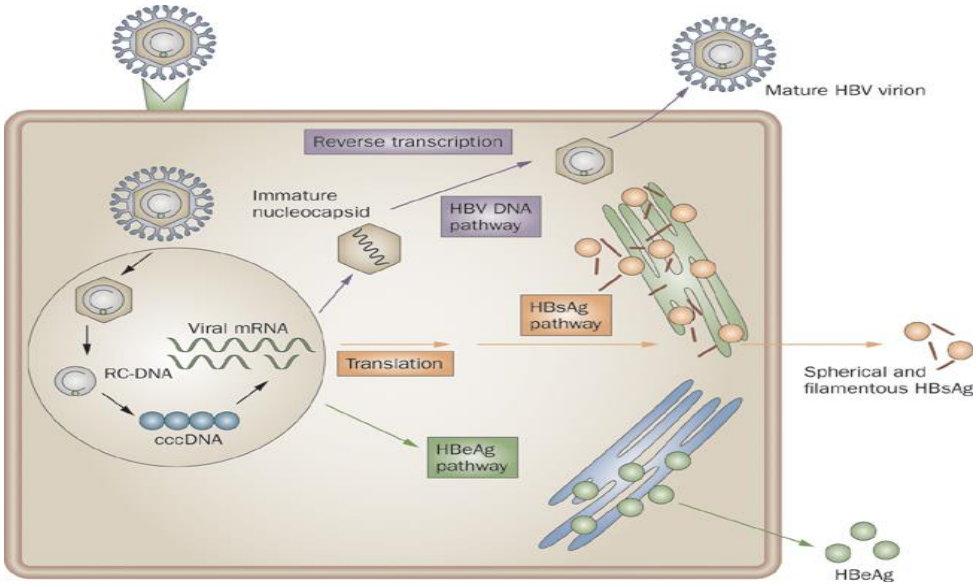
	OR	95% CI	p-value
Age (per 10 yrs)	0.90	0.48, 1.69	0.74
HBeAg positive	12.06	3.73, 38.98	<0.0001
<95% adherent	2.52	1.16, 5.48	0.02
HAART <2 yrs	2.64	1.06, 6.54	0.04
CD4 < 200 cells/mm^3	2.47	1.06, 5.73	0.04

Long term adherence is always a challenge

Matthews CID 2012

Drivers of HBV viraemia on TDF?

- Neither genotypic or phenotypic resistance have been definitively described
- Replication or reservoir release?



- Virological (UDPS, SGA) and immunological studies may give insight

Prophylaxis Effect of TDF in Prevention of HBV Acquisition in HIV (+) Patients

- HIV infected; HBV uninfected MSM
- Patients were serologically evaluated for HBV infection stratified by NRTI-ART

Frequency and Hazard Ratio of HBV Incident Infection

ART	Observation Period (Person-Years)	Incident Infection	HR (95% CI)	P-Value
No ART	446	30	1	
Other ART	114	6	.924 (.381-2.239)	.861
ART containing (LAM, TDF, or FTC)	1047	7	.113 (1.049-.261)	<.001
LAM-ART	814	7		
TDF-ART	233	0		

TDF containing ART resulted in zero HBV infections[1]

Statistically longer HBV-free survival with TDF compared to 3TC or no treatment (p = 0.004 and 0.001) [2]

1. Gatanama,H, et al., *CID* 2013:56 June 15
2. Heuft, M, et al. CROI 2013. Oral Abstract Session 9, paper 33

Renal impairment with TDF – watch this space….

- 240 patients with a 3year-time follow-up, normal eGFR at baseline1

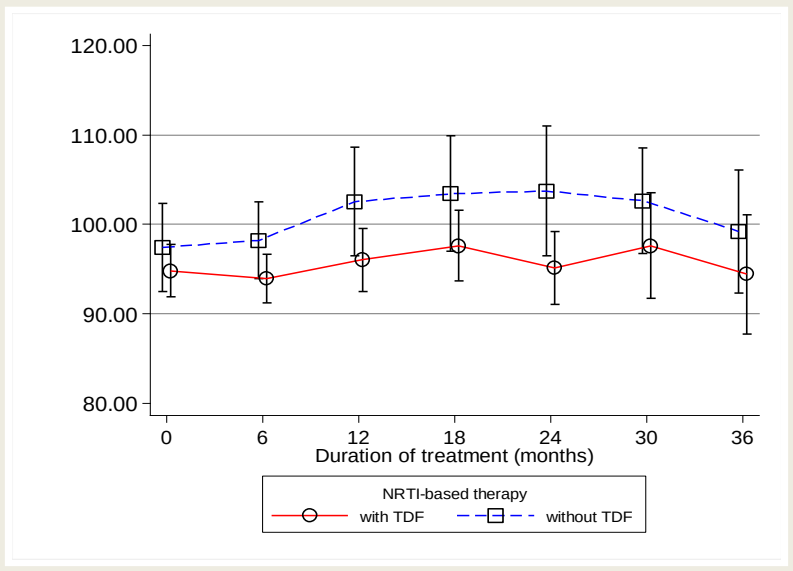
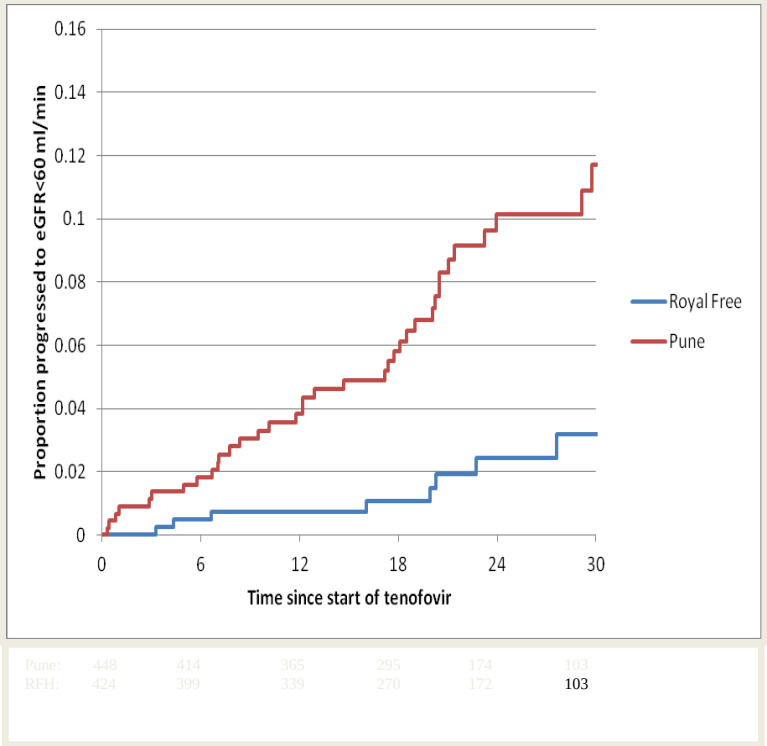


Figure 1: MDRD clearance over time

- >400 HIV+ patients receiving TDF



Pujari, et al, BMC Infect Dis 2014

Strategies when TDF is contra-indicated?

- Reduce dose TDF
- Switch to entecavir (caution if LAM-R)
- Adefovir plus entecavir (?kidney disease)
- Peg-interferon (?advanced liver disease)

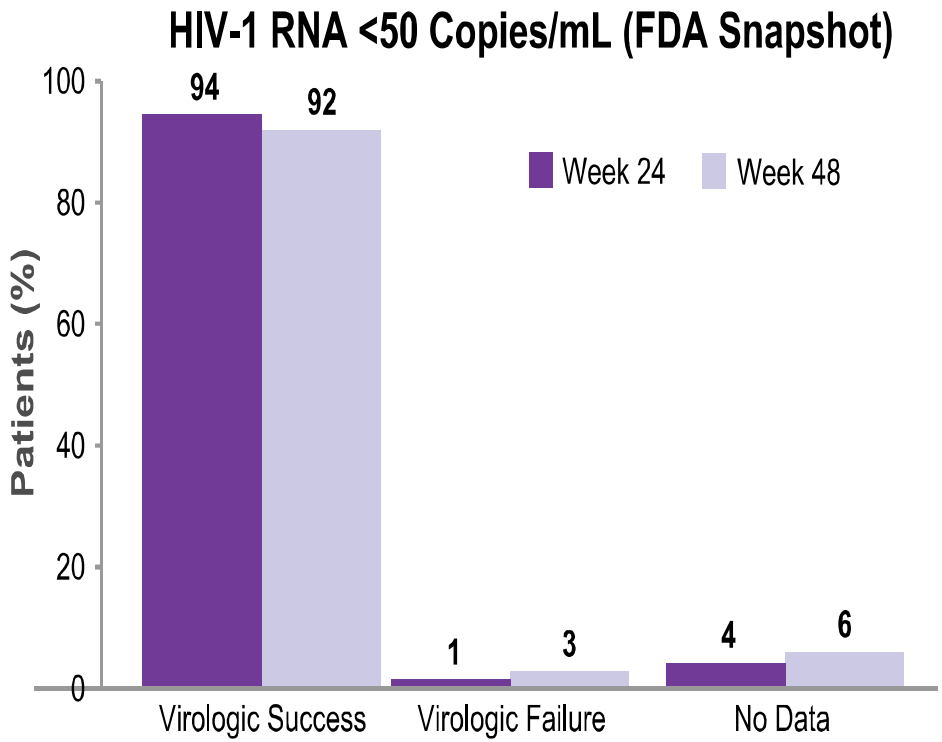
- Tenfovir Alafenamide (TAF)

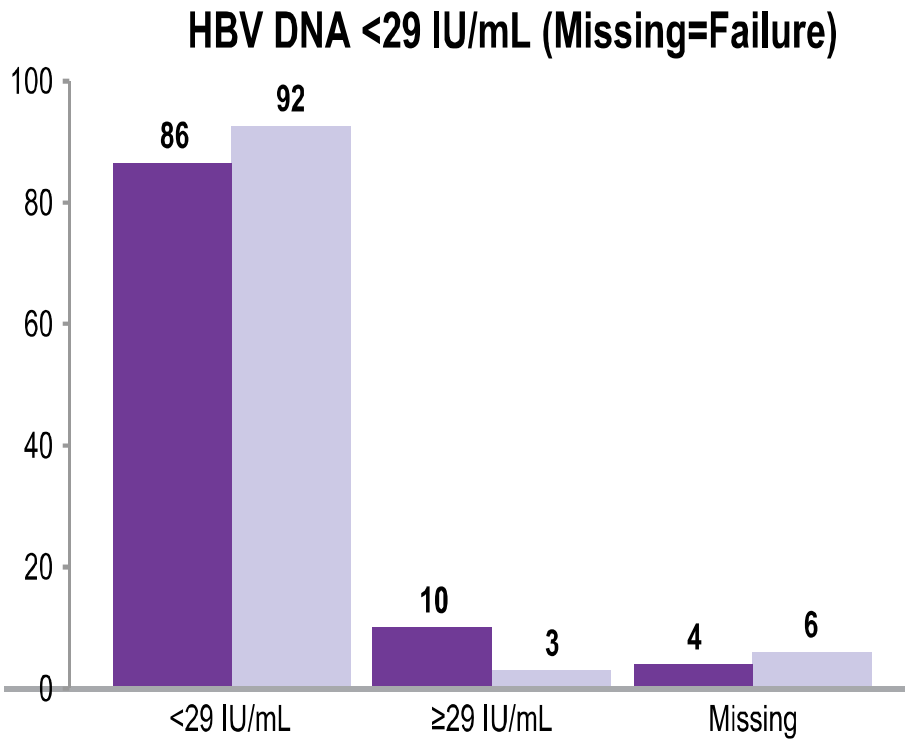
TAF in co-infected patients

(Galant et al, IAS 2015 WELBPE13)

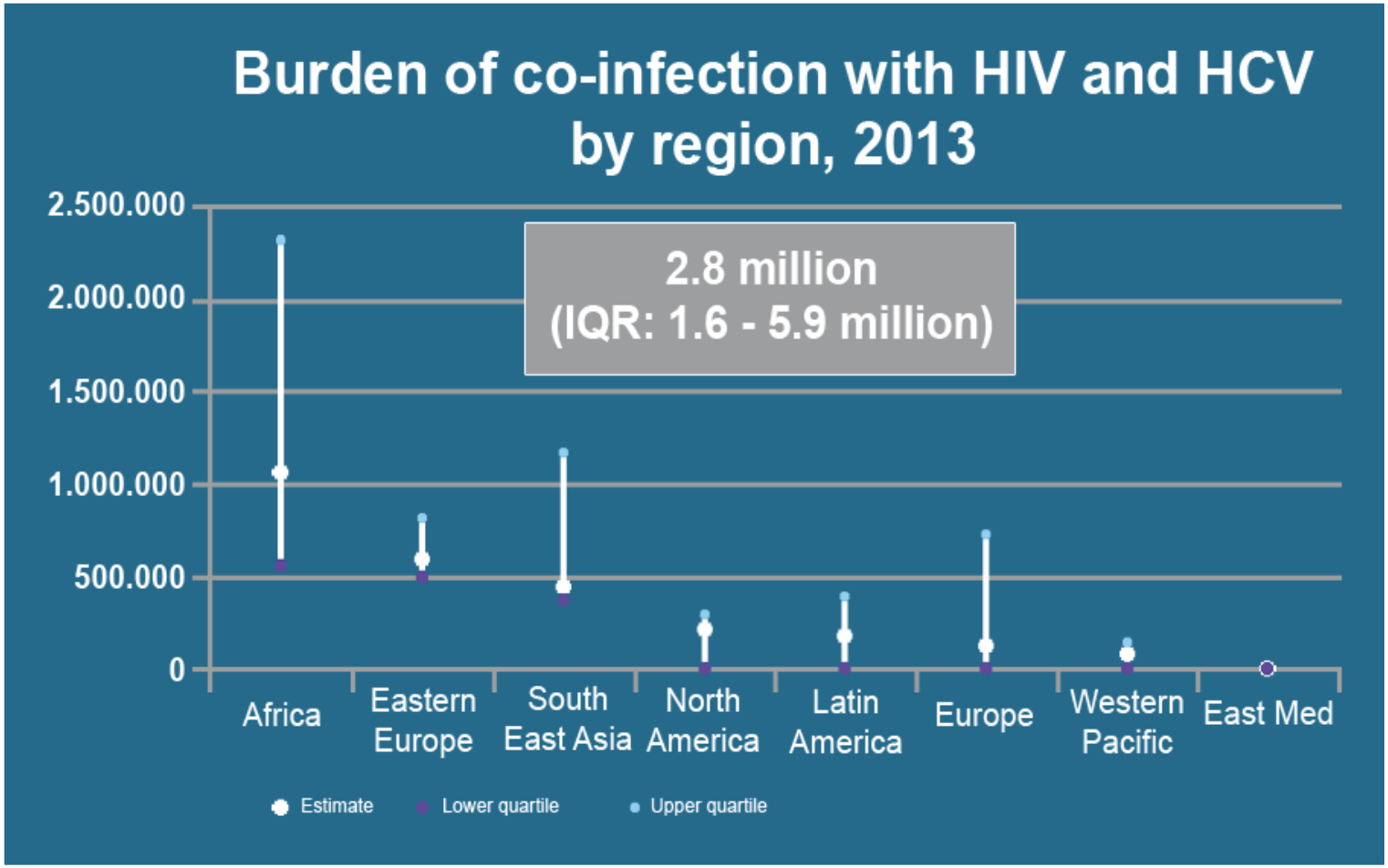
HIV-1/HBV Coinfected Patients

Switch to E/C/F/TAF





Burden of HCV in HIV populations



P Easterbrook, IAS 2015

HIV/HCV – double-trouble for the liver

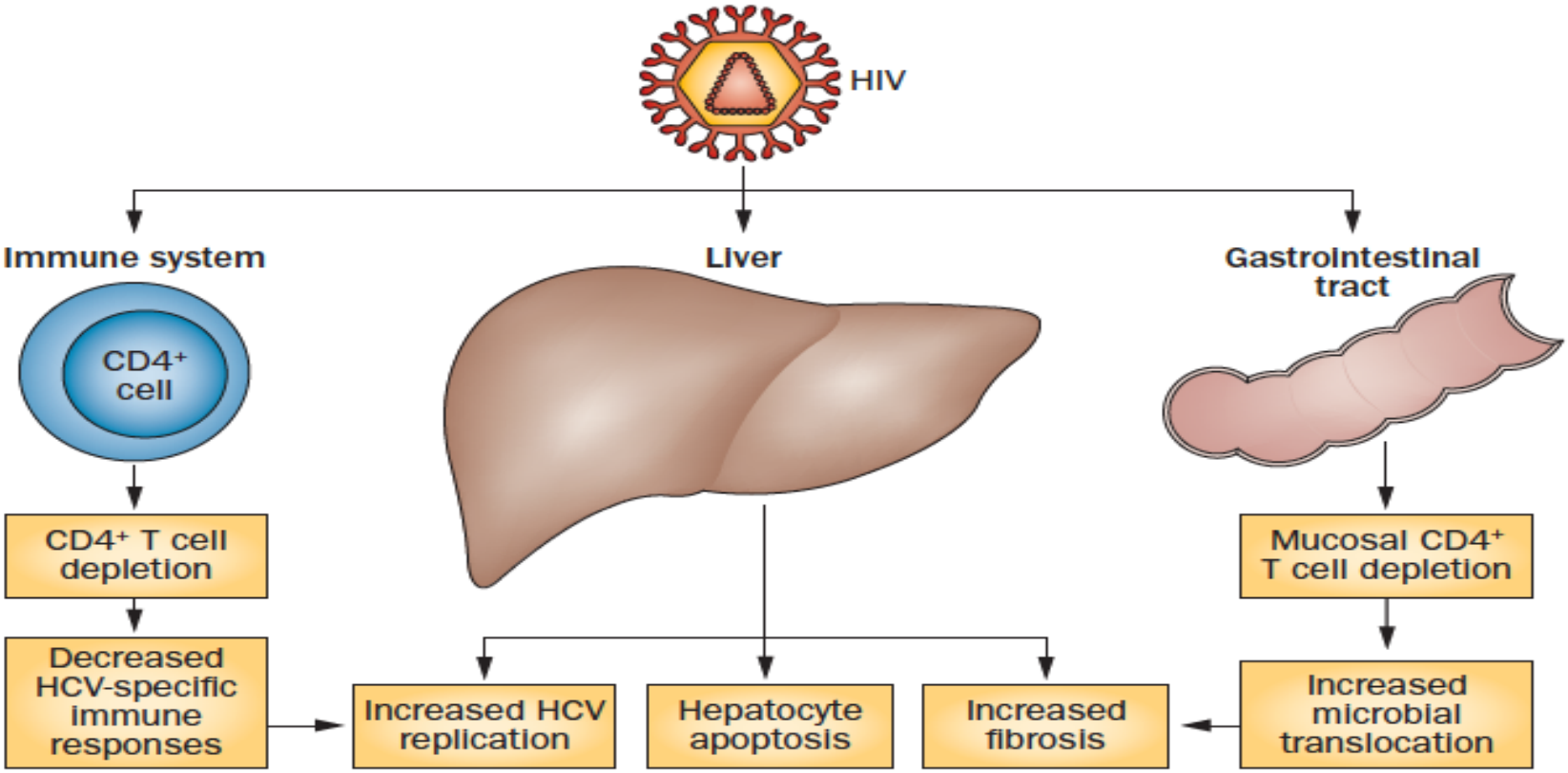


Figure 1 | Driving factors underlying liver disease pathogenesis in HCV–HIV co-infection. HIV infection leads to an impaired immune response against HCV, increased HCV replication, hepatic inflammation and apoptosis, increased microbial translocation from the gastrointestinal tract and increased fibrosis.

Chen J Nat Rev Gastroenterol Hep 2014
doi:10.1038/nrgastro.2014.17

Faster progression even when controlling for alcohol and other co-morbidities

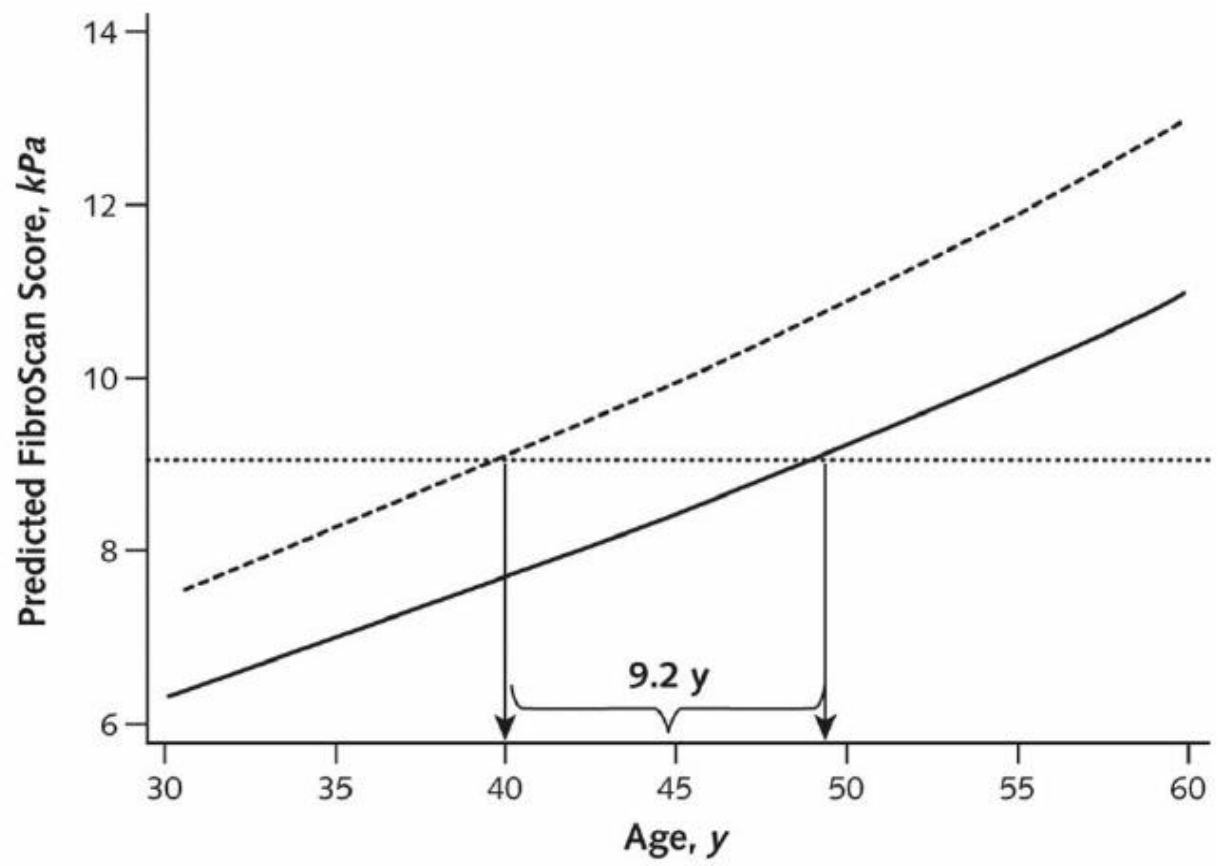
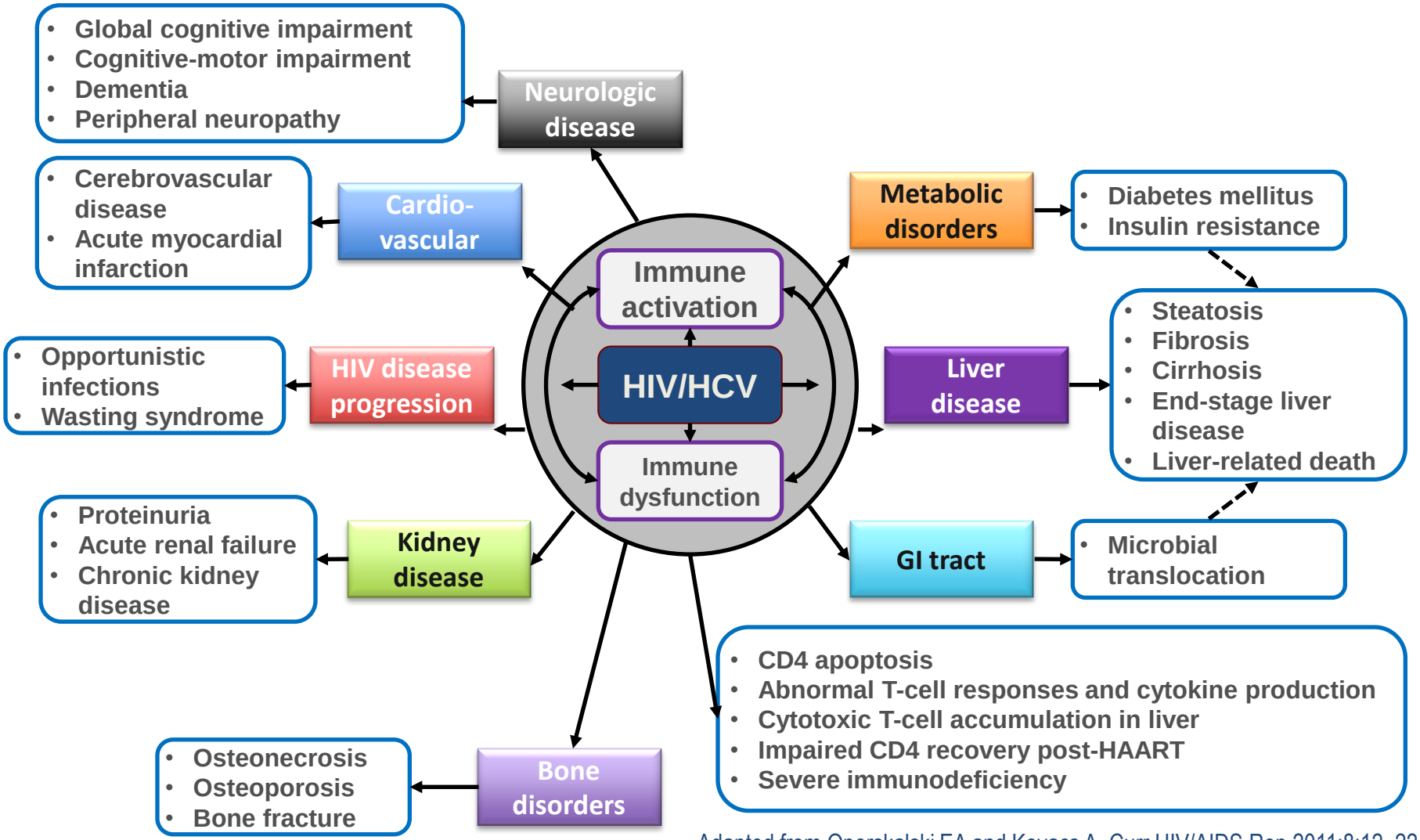


Figure 3. Liver fibrosis and age among persons coinfected with HIV and HCV (dashed line) and those with only HCV (solid line)

Kirk D, et al. Ann Intern Med 2013; 158: 658

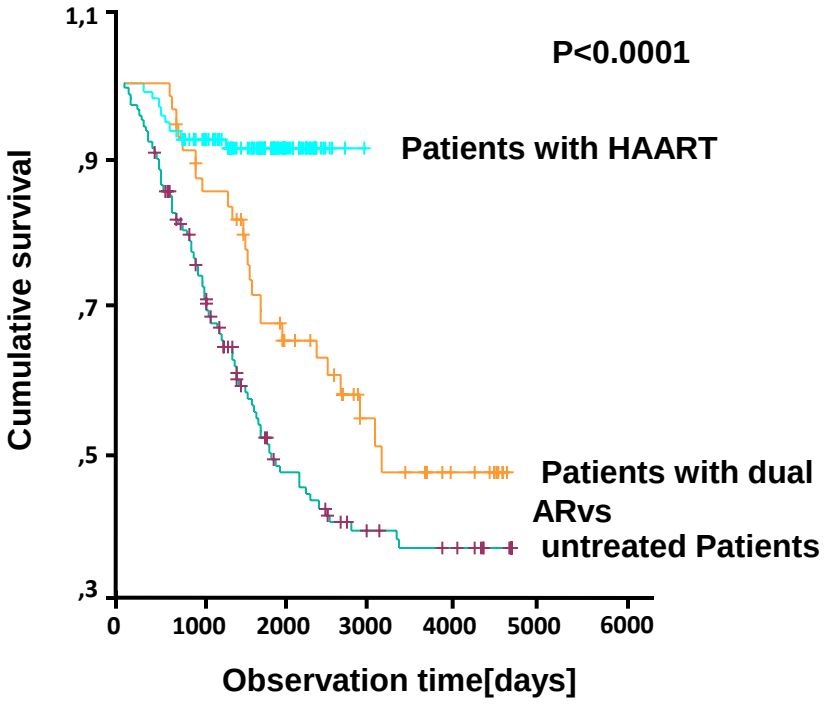
HIV/HCV – a contribution to multiple organ dysfunction



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

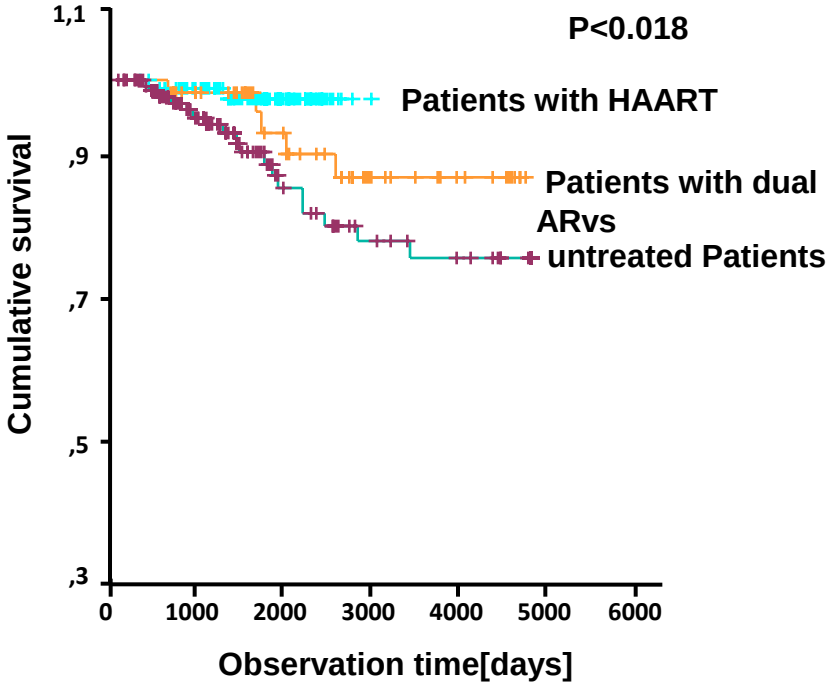
Overall and Liver-related Mortality - effect of HAART

A) Overall-Mortality



Patients under observation:						
HAART-group:	93	79	33	-	-	-
ART-group:	55	46	30	15	9	1
Untreated-group:	13794	49	37	32	27	

B) Liver-related-Mortality



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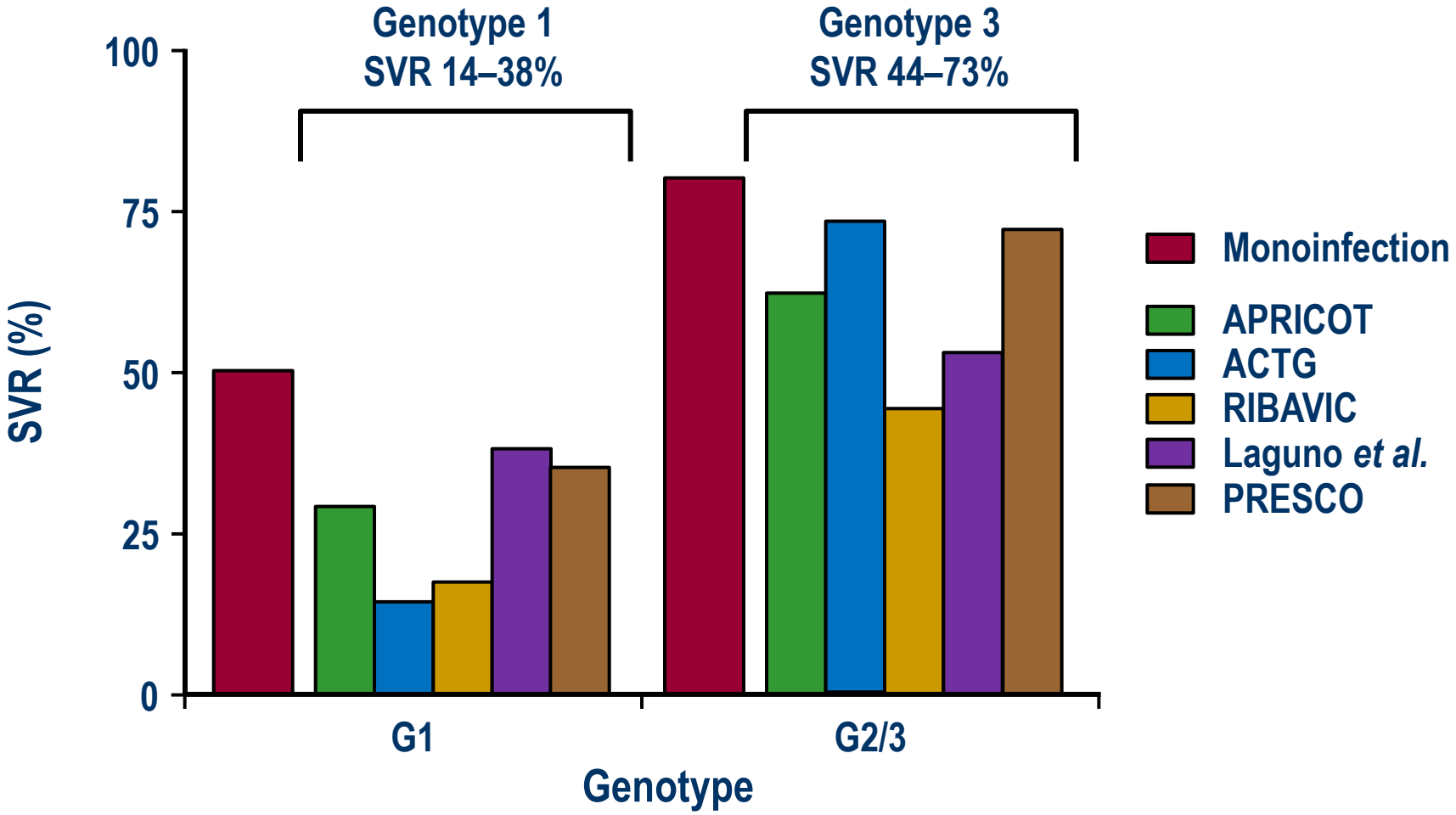
Qurishi N *et al. Lancet*, 2004

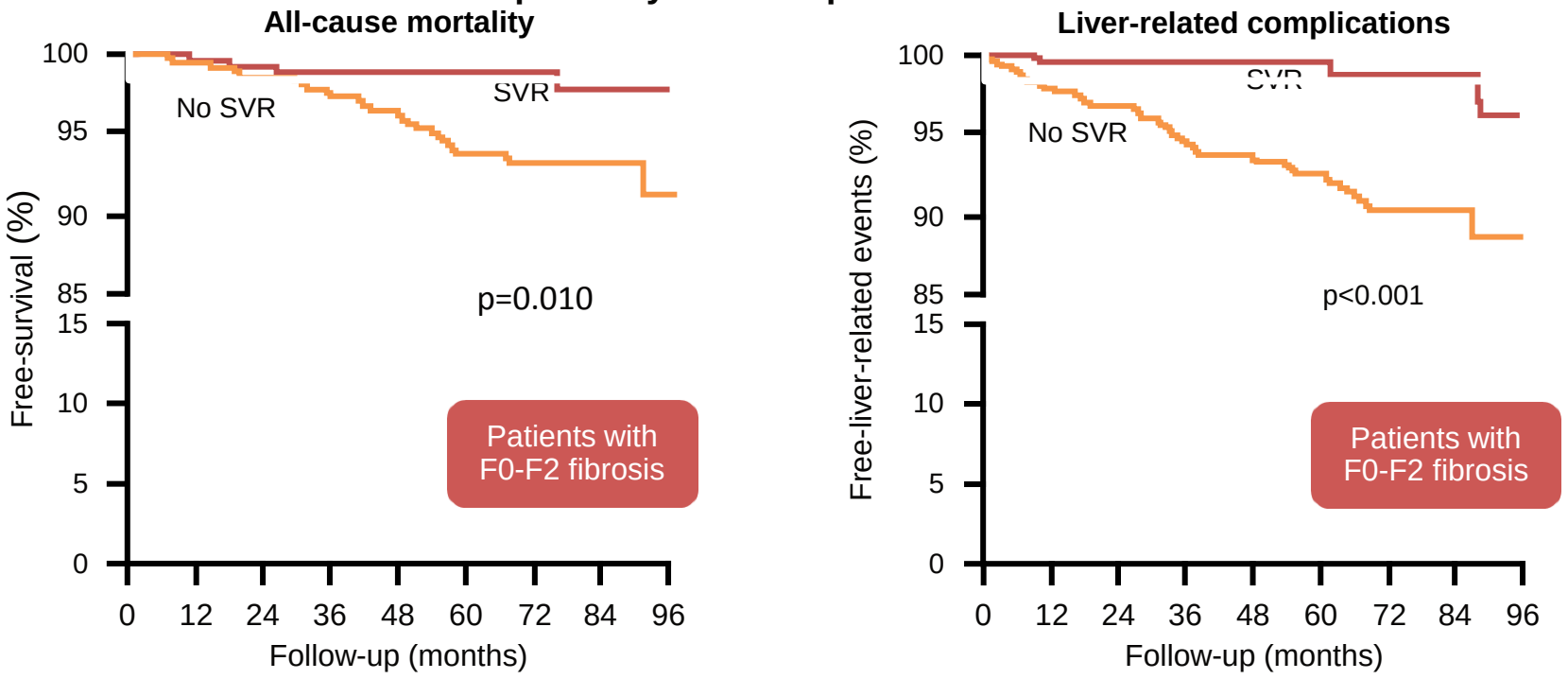
HCV/HIV SVR24 with pegIFN and RIBAVIRIN



Adapted from: Fried et al, NEJM 2002;347:975-982, Torriani et al, NEJM 2004;351:438-50, Chung R, et al, NEJM 2004;351:451-9
Carrat F, et al, JAMA 2004;292:2839-42, Laguno et al, AIDS 2004;18:F27-F36, Nunez et al, JAIDS 2007;45:439-44

SVR in HIV/HCV co-infected patients with mild Fibrosis

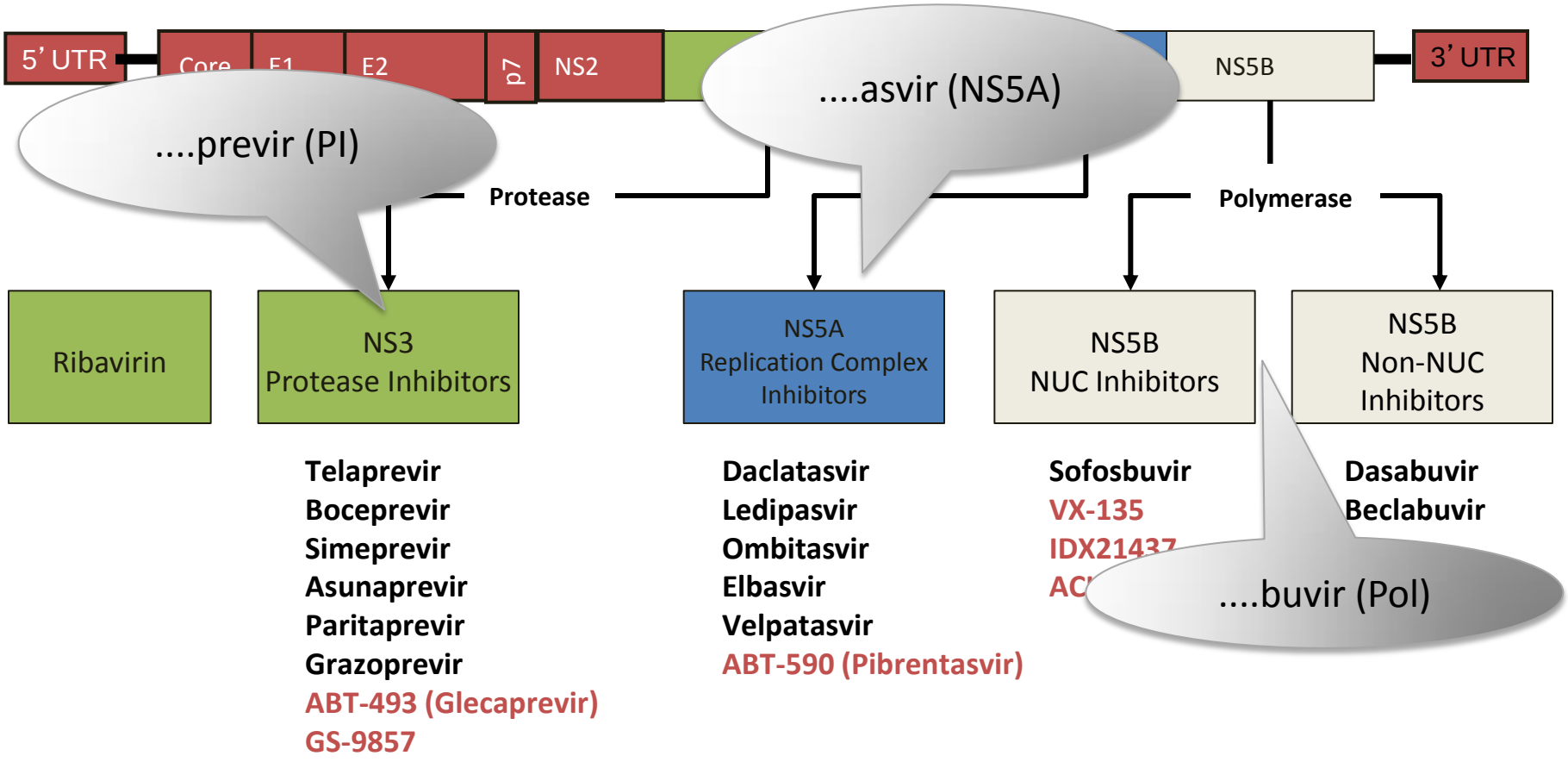
- **A total of 695 HIV/HCV-co-infected patients were treated with IFN/RBV after a median follow-up of 4.9 years. 274 patients achieved an SVR**



The achievement of an SVR after interferon-ribavirin therapy in patients co-infected with HIV/HCV and with mild Fibrosis reduces liver-related complications and mortality

Adapted from Berenguer J et al. J Acquir Immune Defic Syndr 2014;66:280–287

What are DAAs?



*Representative list modified from CCO – updated 2016.

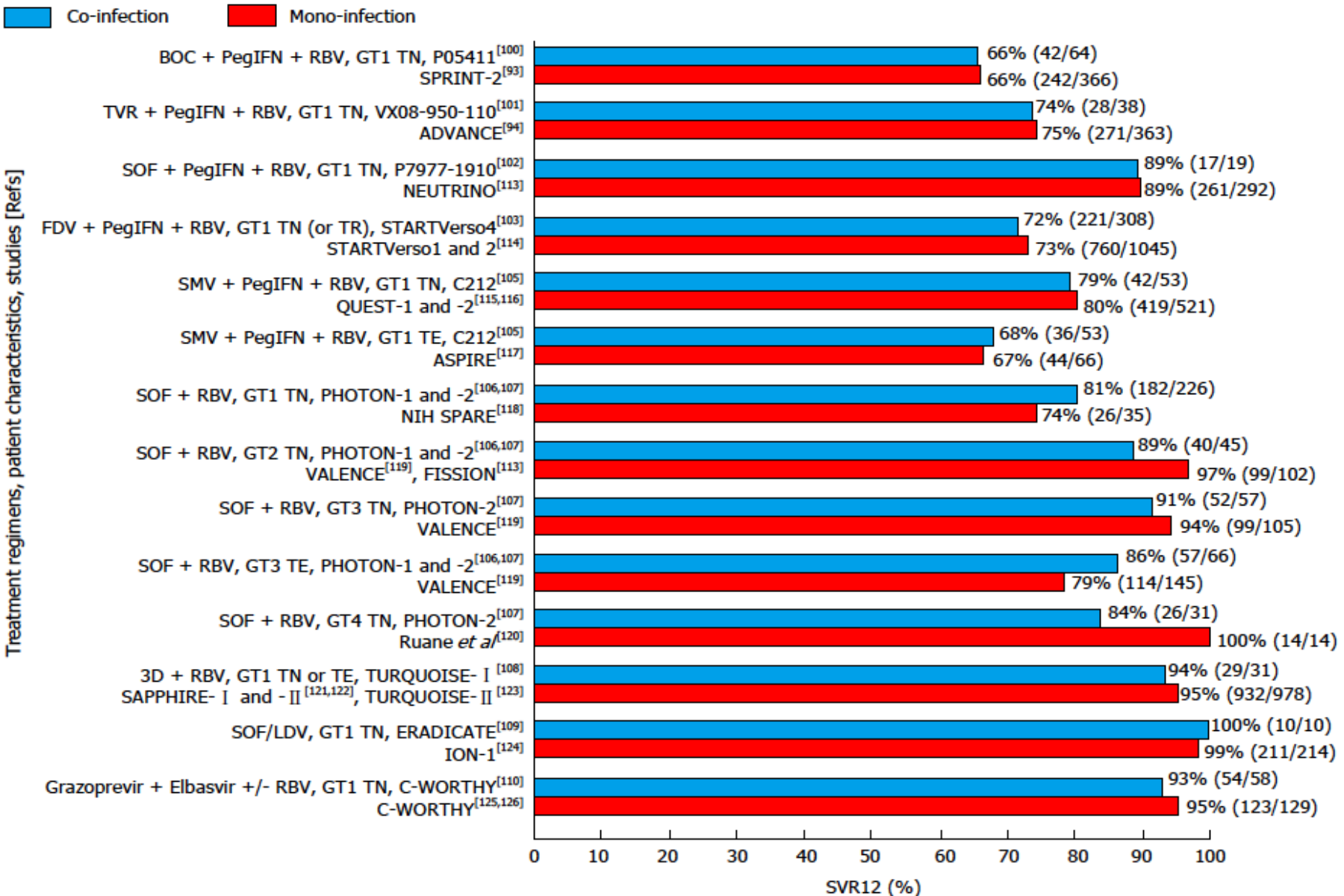
Not All Direct-Acting Antivirals are Created Equal

Characteristic	Protease Inhibitor*	Protease Inhibitor**	NS5A Inhibitor	Nuc Polymerase Inhibitor	Non-Nuc Polymerase Inhibitor
Resistance profile					
Pangenotypic efficacy					
Antiviral potency					
Adverse events					

 Good profile  Average profile  Least favorable profile

*First generation. **Second generation.

Do HIV+ respond differently to mono-infected patients?



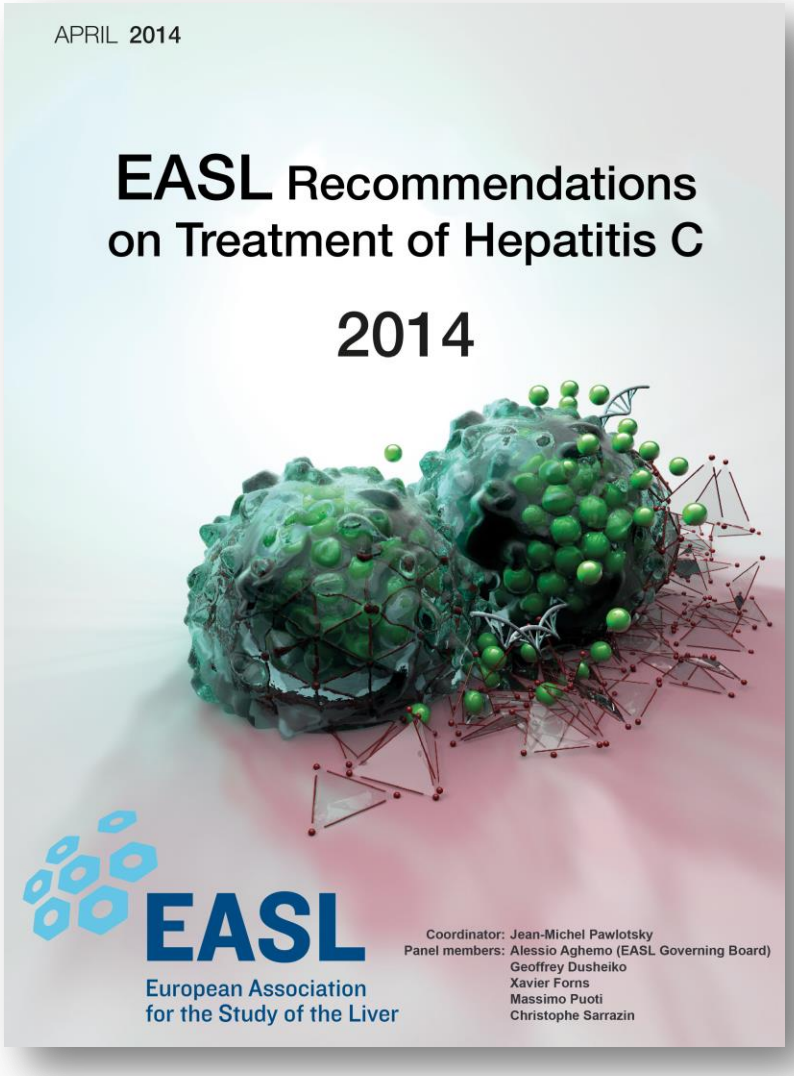
DDIs between HCV drugs and HIV

		DCV	LED/ SOF	OBV/ PTV/r	OBV/ PTV/r +DSV	SMV	SOF
Entry/Integrase Inhibitors							
	Dolutegravir	◆	◆	◆	◆	◆	◆
	Elvitegravir/cobicistat	■	■	●	●	●	◆
	Maraviroc	◆	■	■	■	◆	◆
	Raltegravir	◆	◆	◆	◆	◆	◆
NNRTIs	Delavirdine	■	◆	■	■	●	◆
	Efavirenz	■	■	●	●	●	◆
	Etravirine	■	◆	●	●	●	◆
	Nevirapine	■	◆	●	●	●	◆
	Rilpivirine	◆	◆	■	■	◆	◆
NRTIs	Abacavir	◆	◆	◆	◆	◆	◆
	Didanosine	◆	◆	◆	◆	◆	◆
	Emtricitabine	◆	◆	◆	◆	◆	◆
	Lamivudine	◆	◆	◆	◆	◆	◆
	Stavudine	◆	◆	◆	◆	◆	◆
	Tenofovir	◆	■	◆	◆	◆	◆
	Zidovudine	◆	◆	◆	◆	◆	◆
PIs	Atazanavir	■	◆	■	■	●	◆
	Darunavir	◆	◆	■	■	●	◆
	Fosamprenavir	■	◆	■	■	●	◆
	Indinavir	■	◆	●	●	●	◆
	Lopinavir	◆	◆	●	●	●	◆
	Nelfinavir	◆	◆	■	■	●	●
	Ritonavir	■	◆	●	●	●	◆
	Saquinavir	■	◆	●	●	●	◆
	Tipranavir	■	●	●	●	●	●

Charts revised April 2015.
NNRTI = non-nucleoside reverse transcriptase inhibitor;
NRTI = nucleoside reverse transcriptase inhibitor.

www.hep-druginteractions.org (Accessed August 2016).

New online EASL HCV recommendations



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

EASL recommendations April 2014 http://files.easl.eu/easl-recommendations-on-treatment-of-hepatitis-c-summary.pdf

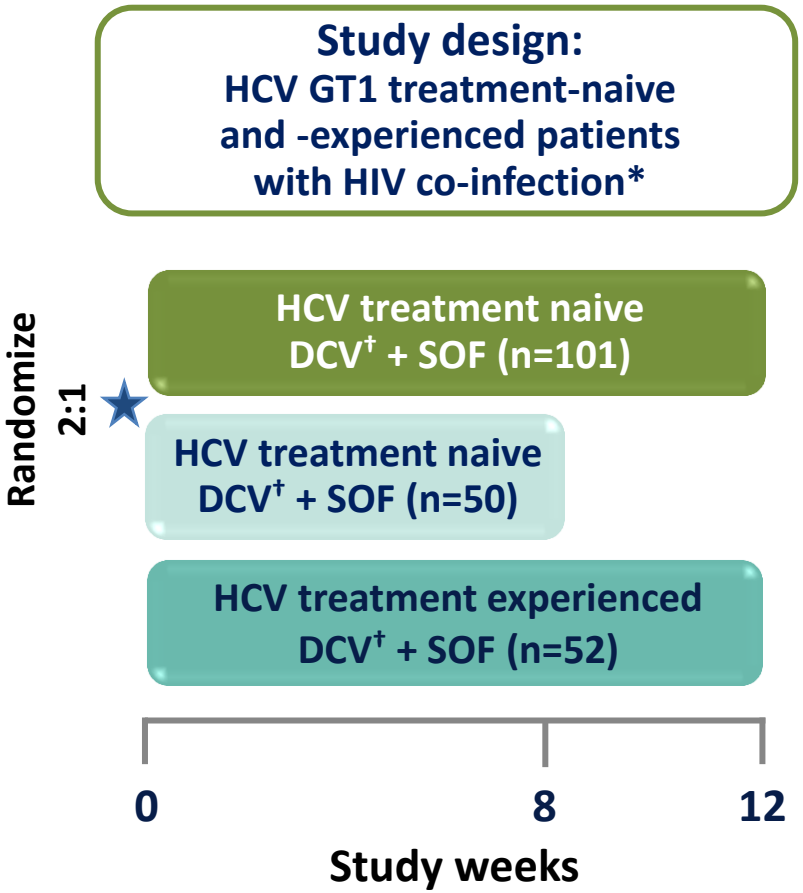
EACS HCV recommendations – treatment combination options

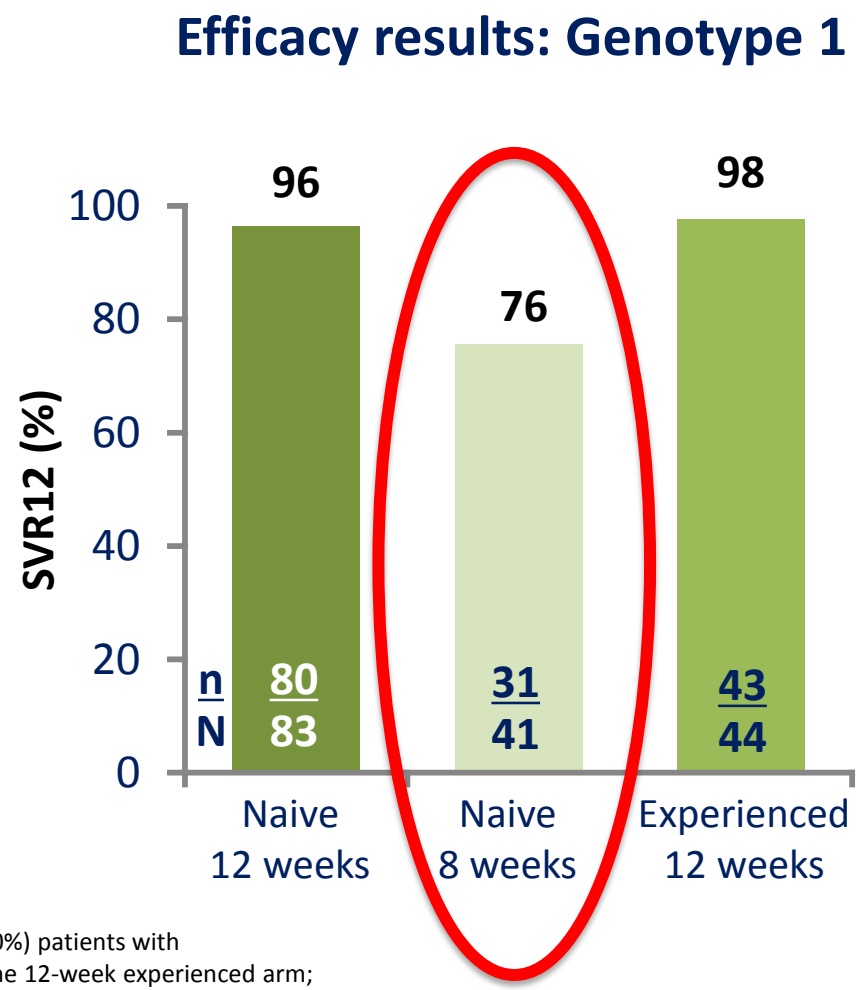
IFN-free HCV Treatment Options				
		Treatment duration & ribavirin usage		
HCV GT	Treatment regimen	Non-cirrhotic	Compensated cirrhotic	Decompensated cirrhotics CTP class B/C
1 & 4	SOF + SMP + RBV	12 weeks without RBV	12 weeks with RBV or 24 weeks without RBV[(i)]	Not recommended
	SOF/LDV + RBV	12 weeks without RBV	12 weeks with RBV or 24 weeks without RBV in cirrhotics or pre-/post-	
	SOF + DCV + RBV	12 weeks without RBV	12 weeks with RBV or 24 weeks without RBV in cirrhotics or pre-/post-	
	OBV/PTV/r + DSV	12 weeks in GT 1b	Not Recommended	
	OBV/PTV/r + DSV + RBV	12 weeks in GT 1a	12 weeks in GT 1b 24 weeks in	Not recommended
	OBV/PTV/r + RBV	12 weeks in GT 4	24 weeks in GT 4	Not recommended
2	SOF + DCV + RBV	12 weeks without RBV	12 weeks without RBV	12 weeks with
	SOF + RBV	12 weeks		
3	SOF + PEG-IFN/RBV	Not recommended	12 weeks in persons eligible	Not recommended
	SOF + RBV	24 weeks	Not recommended	
	SOF + DCV + RBV[(iii)]	12 weeks without RBV	24 weeks with RBV	
5	SOF/LDV	12 weeks without RBV	12 weeks without RBV	
6	In the absence of clinical data on DAAs in HCV GT 6 infection persons should be treated similarly to HCV GT 1 and 4 infection			

Are there remaining 'unresolved' issues with HCV?

- Is 'shorter' therapy possible for co-infected patients?
- Are there 'difficult to treat' groups?
  - G3 – few options currently, relatively poor responses
- Is it ever 'too late' to treat HCV?
  - ESLD – Rx vs. Transplant followed by Rx
- Will TasP be feasible?

ALLY-2: DCV + SOF in GT1–6 patients with HIV/HCV co-infection

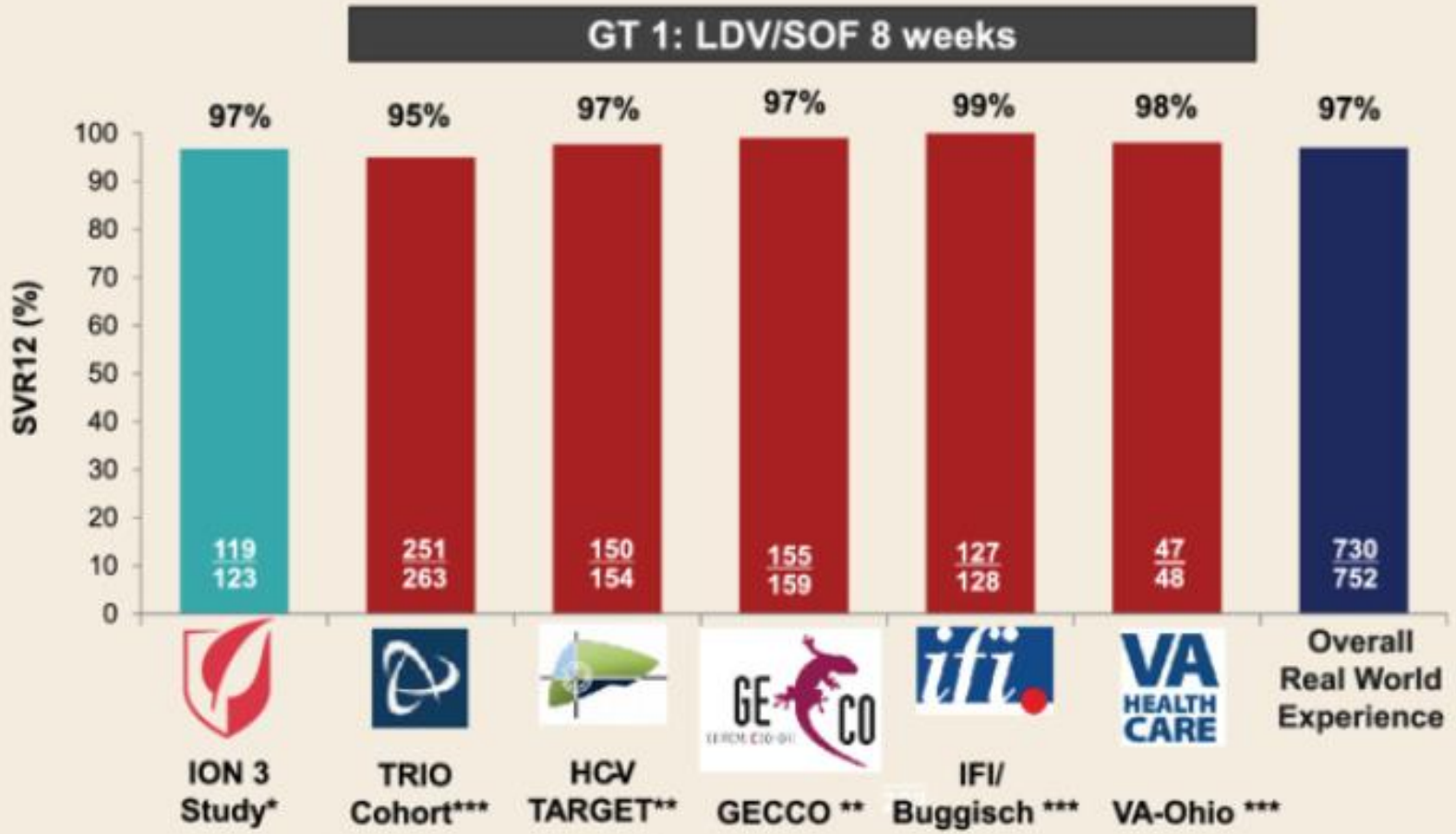




* Including 9 (8.9%) patients with cirrhosis in the 12-week naive arm, 5 (10.0%) patients with cirrhosis in the 8-week naive arm and 15 (28.8%) patients with cirrhosis in the 12-week experienced arm;
† standard DCV dose of 60 mg QD, dose adjusted for concomitant cART (30 mg with ritonavir-boosted PIs, 90 mg with NNRTIs except rilpivirine).
NNRTI = non-nucleoside reverse transcriptase inhibitor.

Wyles DL, *et al.* EASL-ILC 2015; Poster presentation LP01.

Real-world data confirm clinical trial results: 8 weeks in GT-1 patients without cirrhosis and VL< 6 millions IU/ml



Buggish P et al: SAT-242

HIGH SVR RATES WITH ABT-493 + ABT-530 CO-ADMINISTERED FOR 8 WEEKS IN NON-CIRRHOTIC PATIENTS WITH HCV GENOTYPE 3 INFECTION

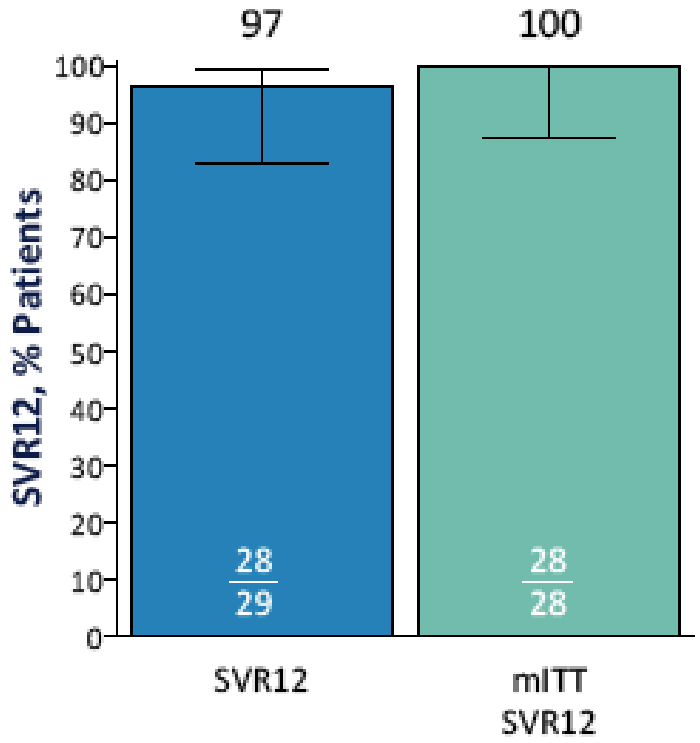
Andrew J Muir[1], Simone Strasser[2], Stanley Wang[3], Stephen Shafran[4], Maurizio Bonacini[5], Paul Y Kwo[6], David L Wyles[7], Edward Gane[8], Sandra S Lovell[3], Chih-Wei Lin[3], Teresa I Ng[3], Jens Kort[3], Federico J Mensa[3]

[1]Duke University School of Medicine, Durham, NC, USA; [2]AW Morrow Gastroenterology and Liver Centre, Royal Prince Alfred Hospital, Camperdown NSW, Australia; [3]AbbVie Inc., North Chicago, Illinois, United States; [4]University of Alberta Hospital, Edmonton, AB, Canada; [5]California Pacific Medical Center, San Francisco, CA, USA; [6]Indiana University School of Medicine, Indianapolis, IN, USA; [7]University of California San Diego, La Jolla, CA, USA; [8]University of Auckland, Auckland, New Zealand

51st Annual Meeting of the European Association for the Study of the Liver
• Barcelona, Spain •
16 April 2016

abbvie

SVR12 Analysis

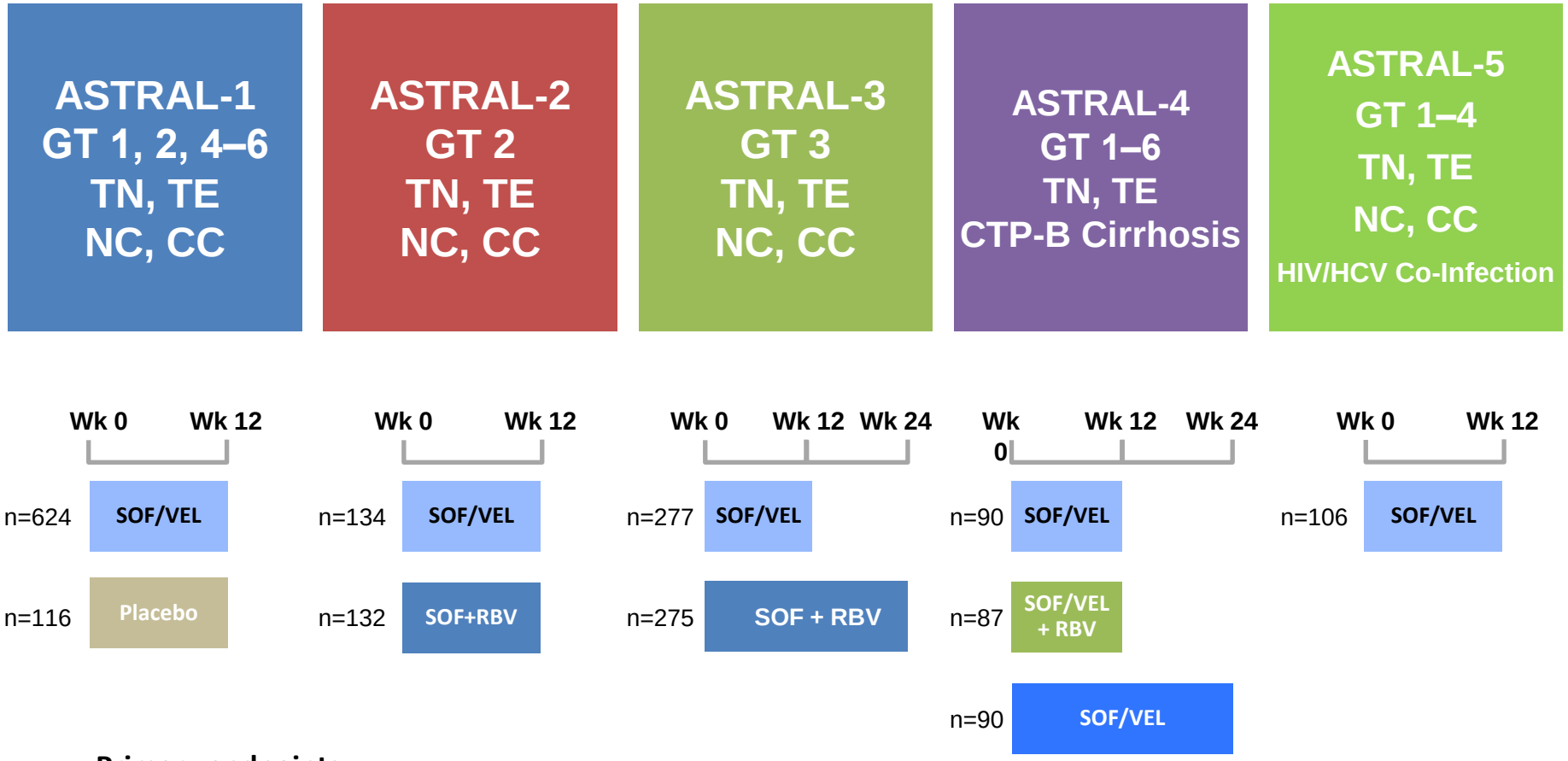


mITT SVR12 rate excludes non-virologic failures

No virologic failures

1 patient withdrew consent after treatment week 6 due to intolerance of blood draws and had an undetectable HCV RNA at the time of discontinuation

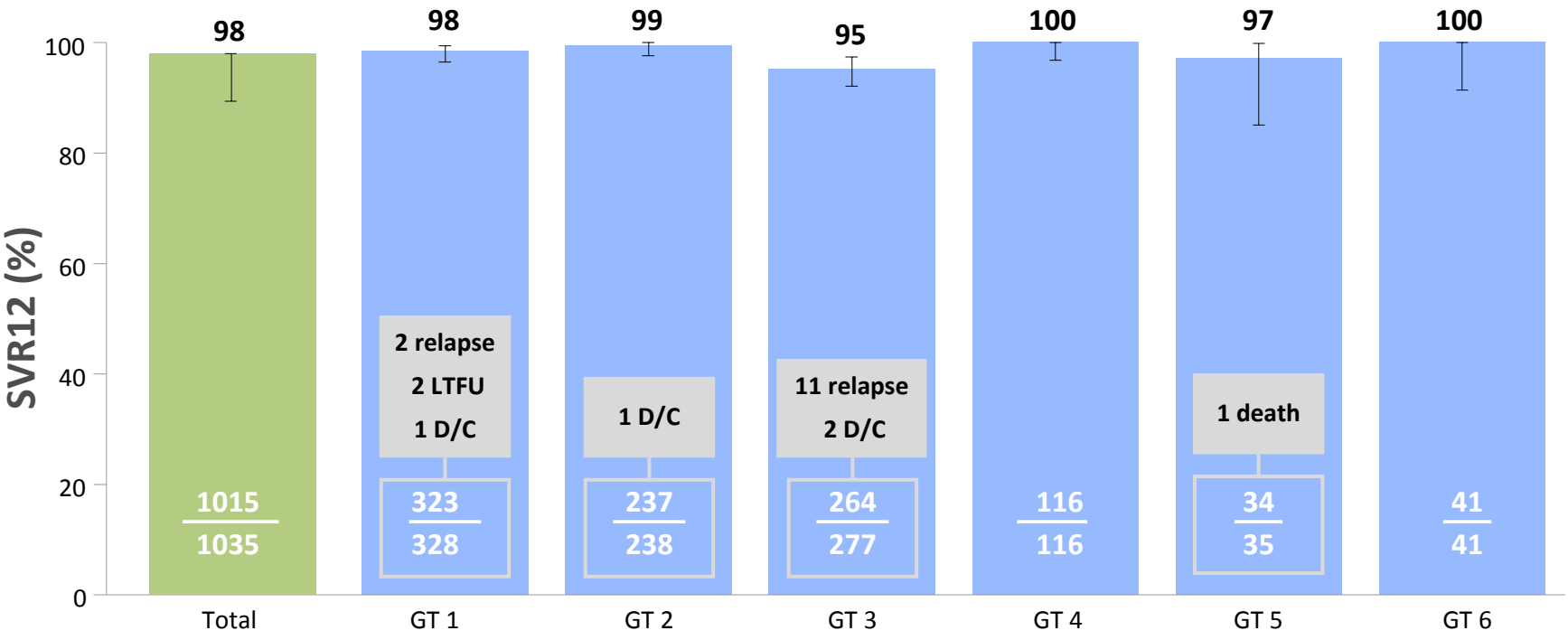
The ASTRAL Phase 3 Program (N=1408)



- **Primary endpoints**
  - SVR12
  - Discontinuations due to AEs

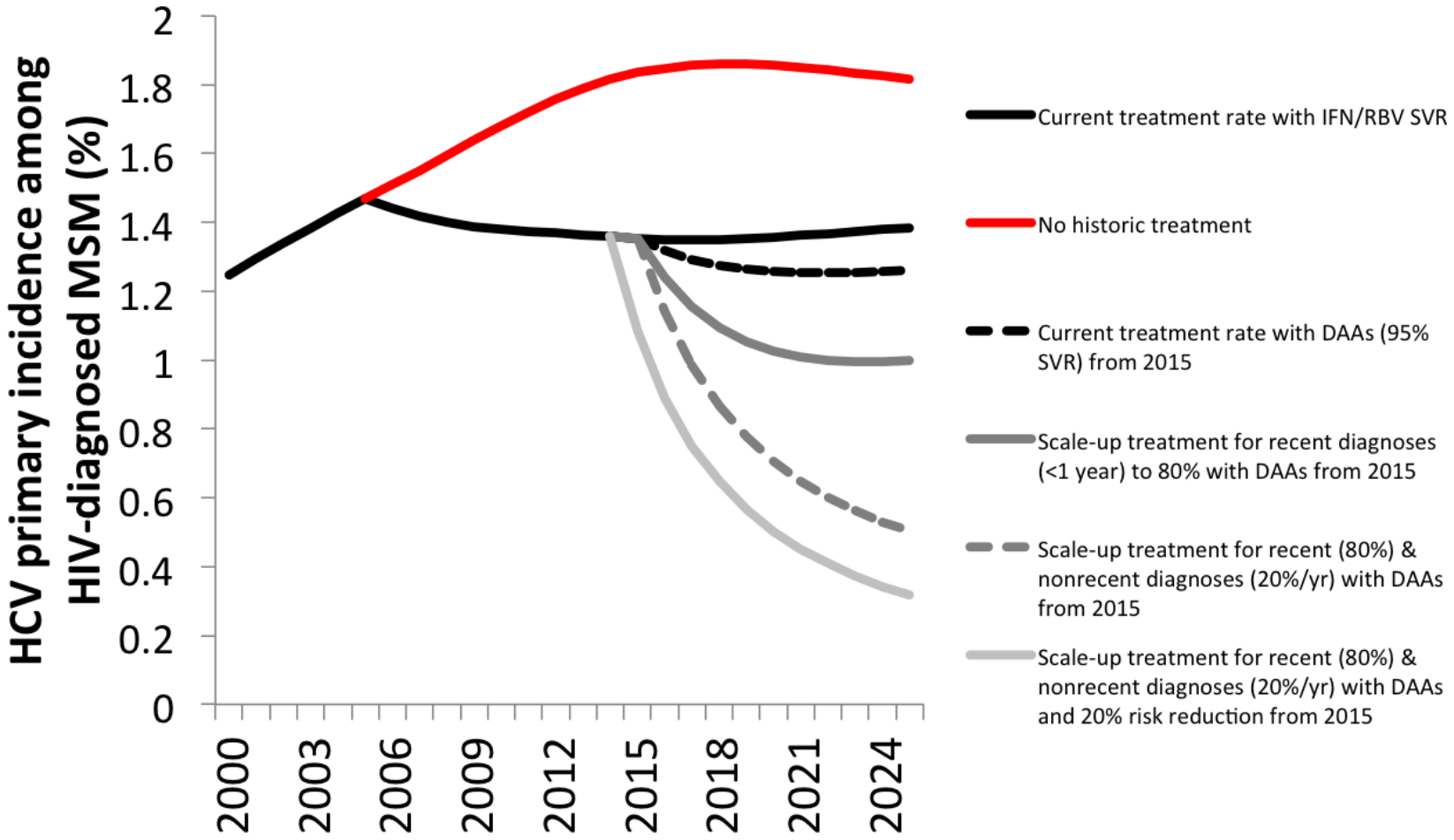
Feld, AASLD, 2015, LB-2. Feld JJ, et al. *N Engl J Med*. 2015; Sulkowski, AASLD, 2015, 205. Foster GR, et al. *New Engl J Med*. 2015.; Mangia, AASLD, 2015, 249. Foster GR, et al. *New Engl J Med*. 2015, Charlton, AASLD, 2015, LB-13. Curry MP, et al. *New Engl J Med.*2015. Wyles, EASL 2016, PS104

Integrated Efficacy: SVR12



Agarwal, EASL 2016, Poster SAT-195

Treatment As Prevention in HIV/HCV



N Martin, et al 2015 (manuscript submitted)

Conclusions

- Liver disease is an important cause of morbidity and mortality in HIV+
- Key issues = cART, HBV, HCV and lifestyle
- HBV – key issues – diagnosis and management
- HCV
  - The era of DAA based therapy has arrived
  - IFN-sparing and IFN-free therapy a reality
  - Responses in HIV+ similar to HIV-
  - Beware DDIs
- Still a ‘Special Population’ – aggressive, multi-system disease, urgent need of Rx
- Need for improved cascade of care and access to Rx