Liver Disease in HIV

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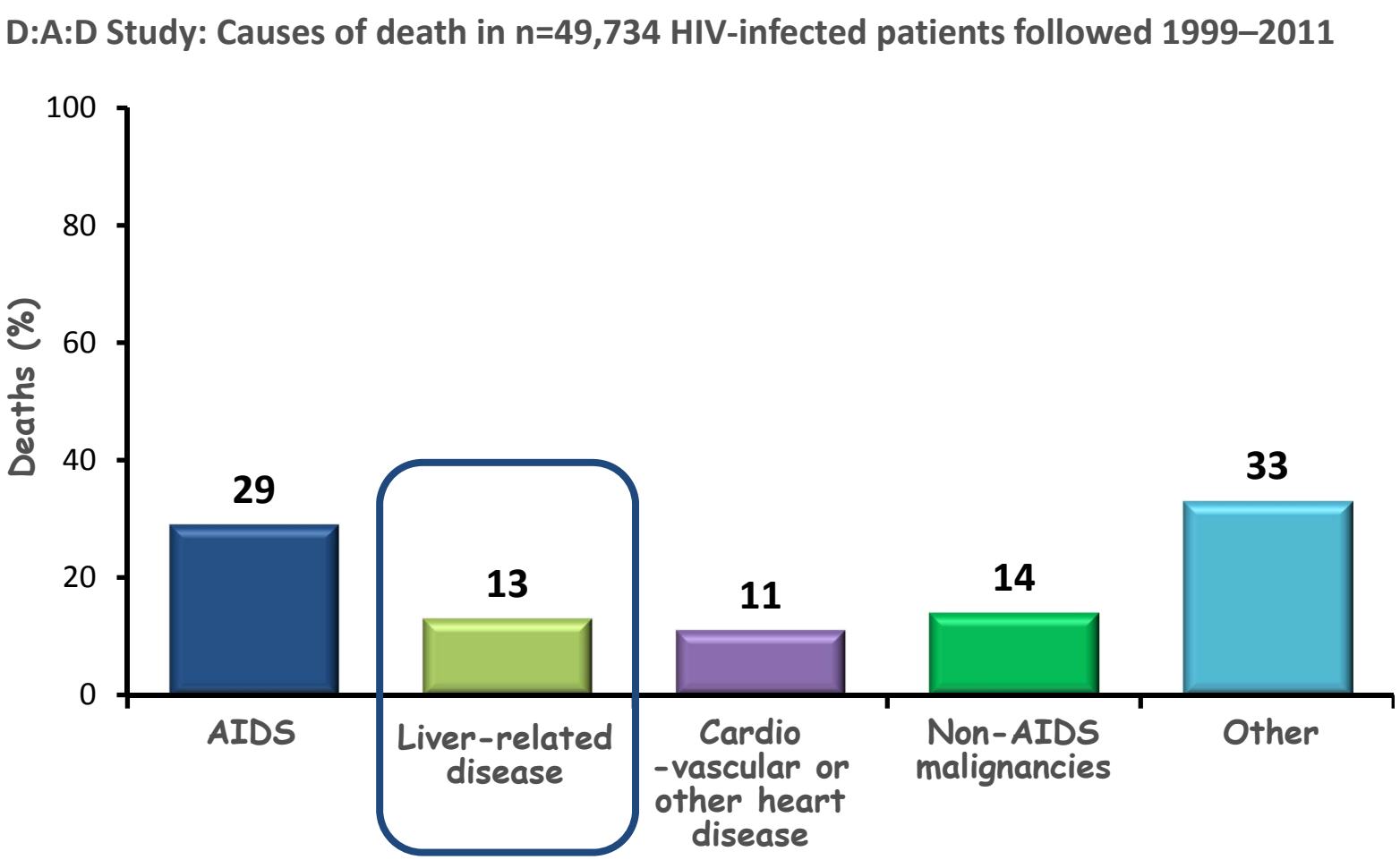
Outline

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

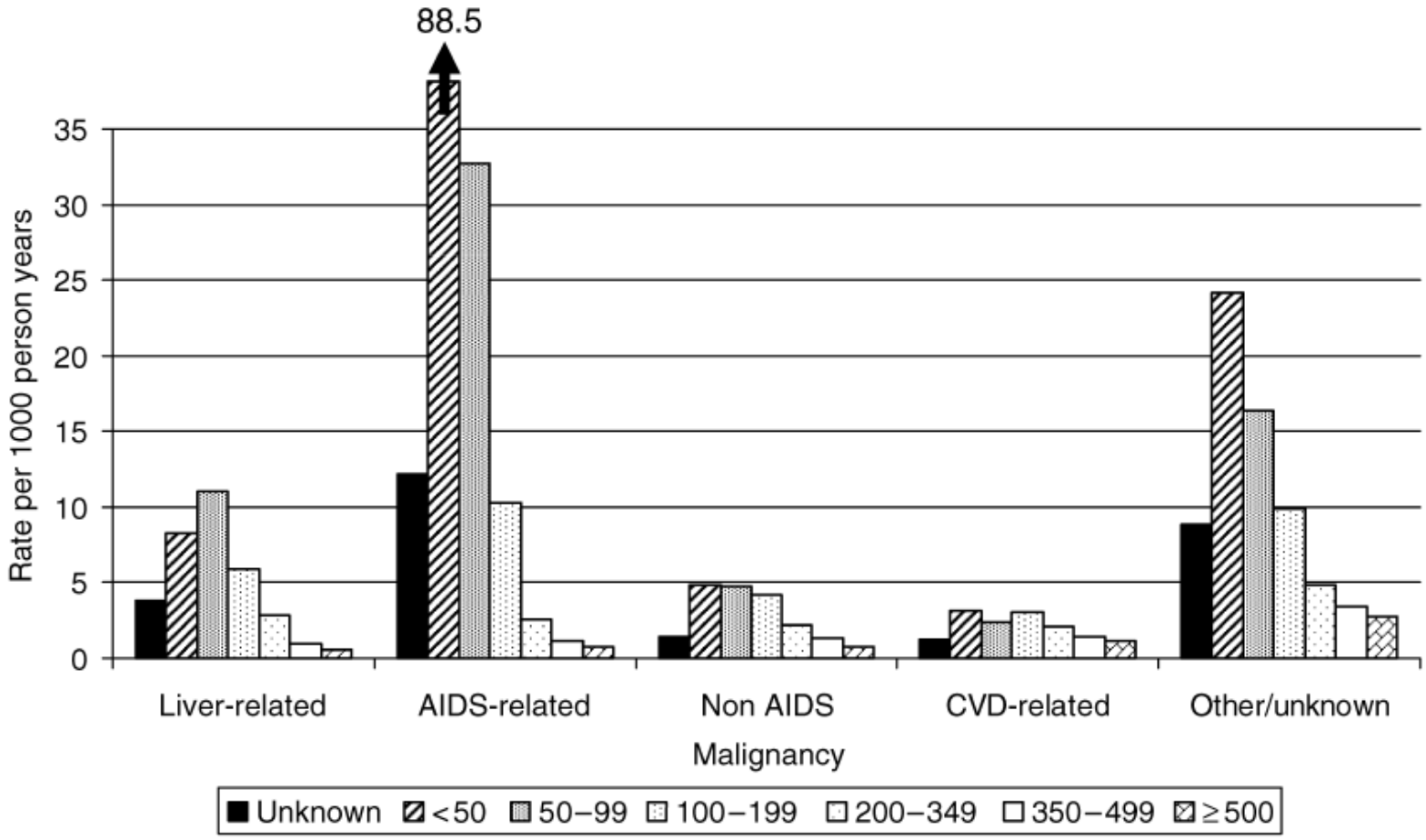
- Case-based discussion (Sunday pm)

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



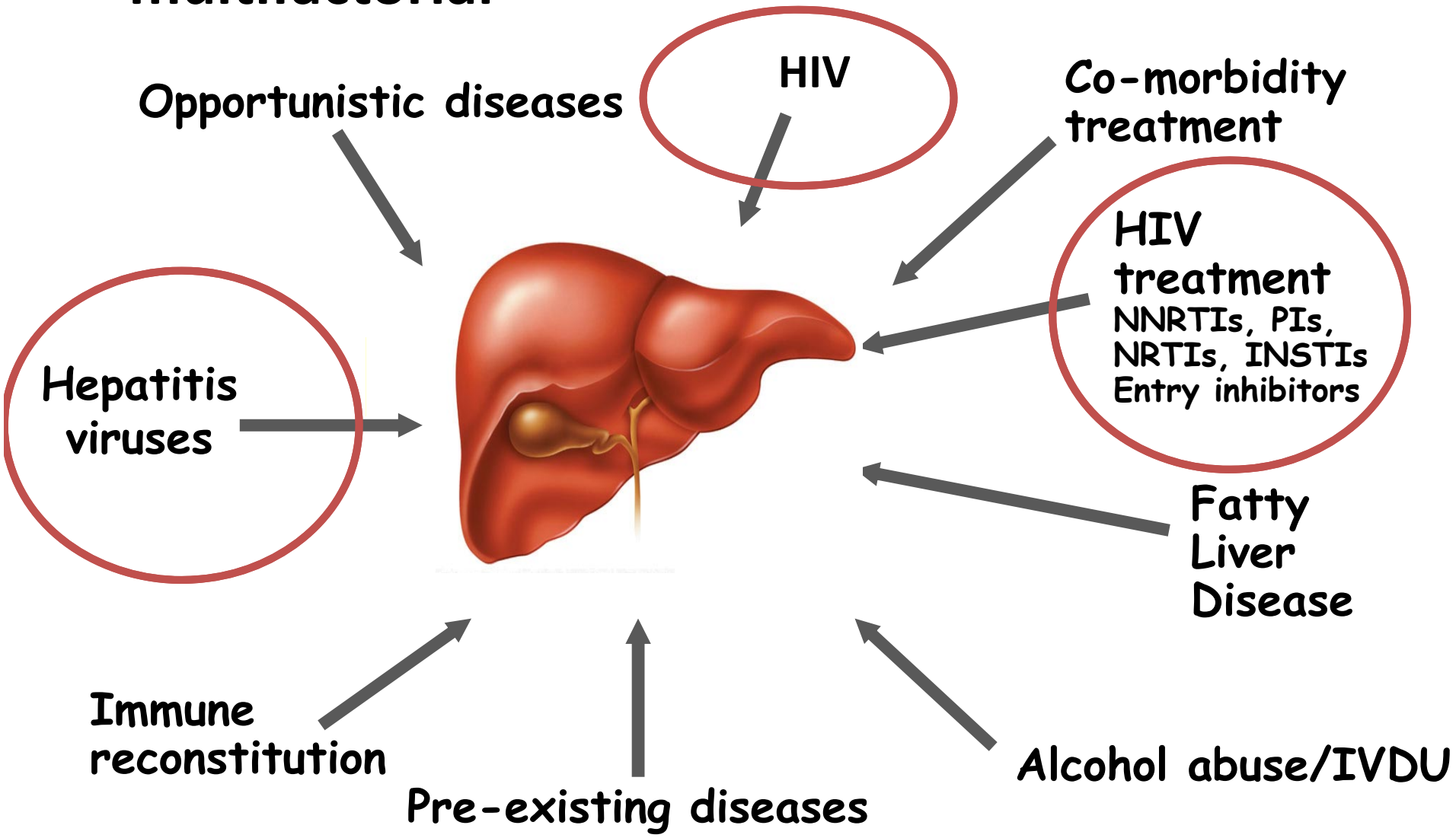
Weber R, et al. AIDS 2012. Washington USA. Oral presentation THAB0304.

Liver-related death and CD4 count



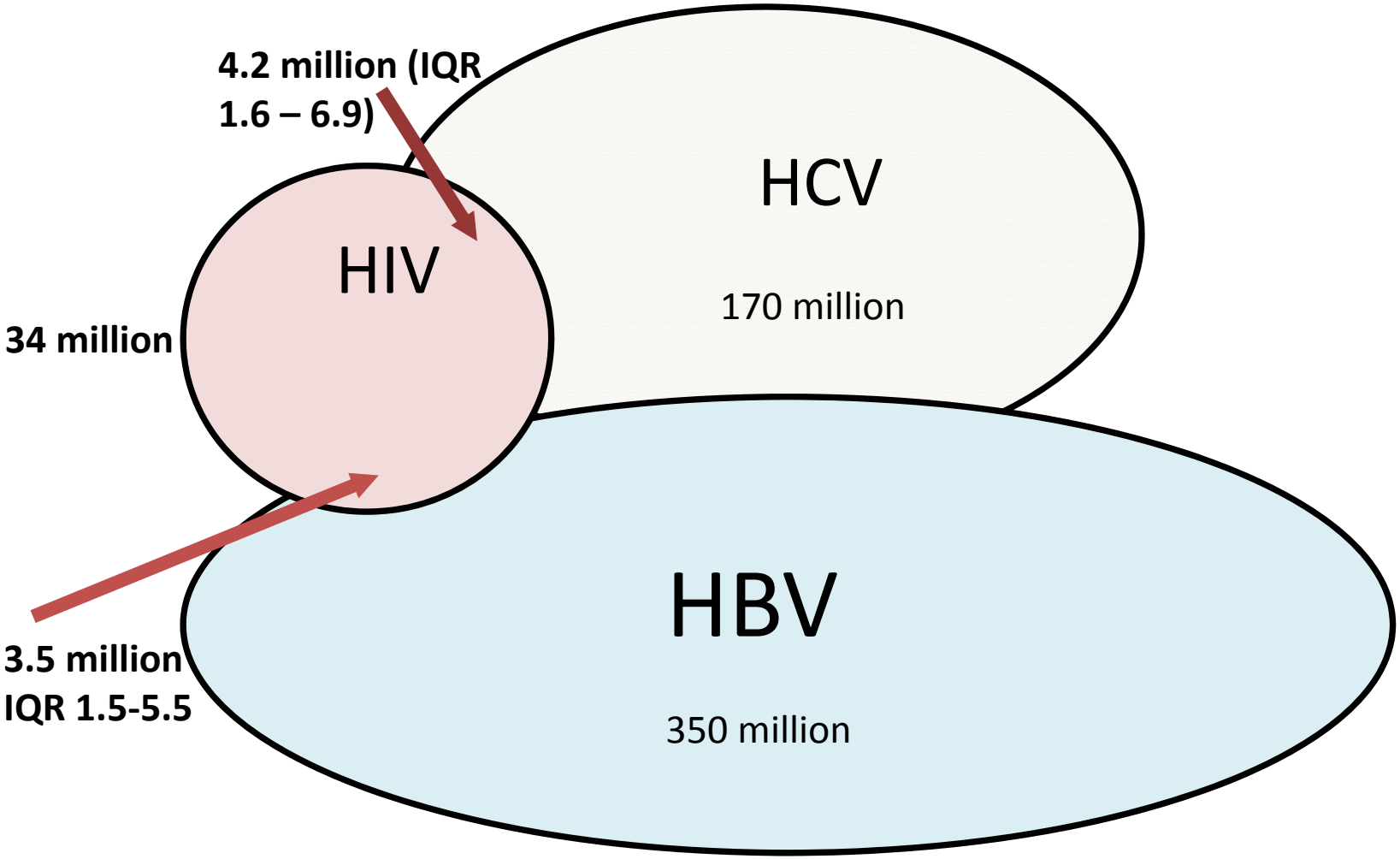
D.A.D study Gp. AIDS 2010: 24: 1537

Liver Disease in HIV-infected Patients - multifactorial

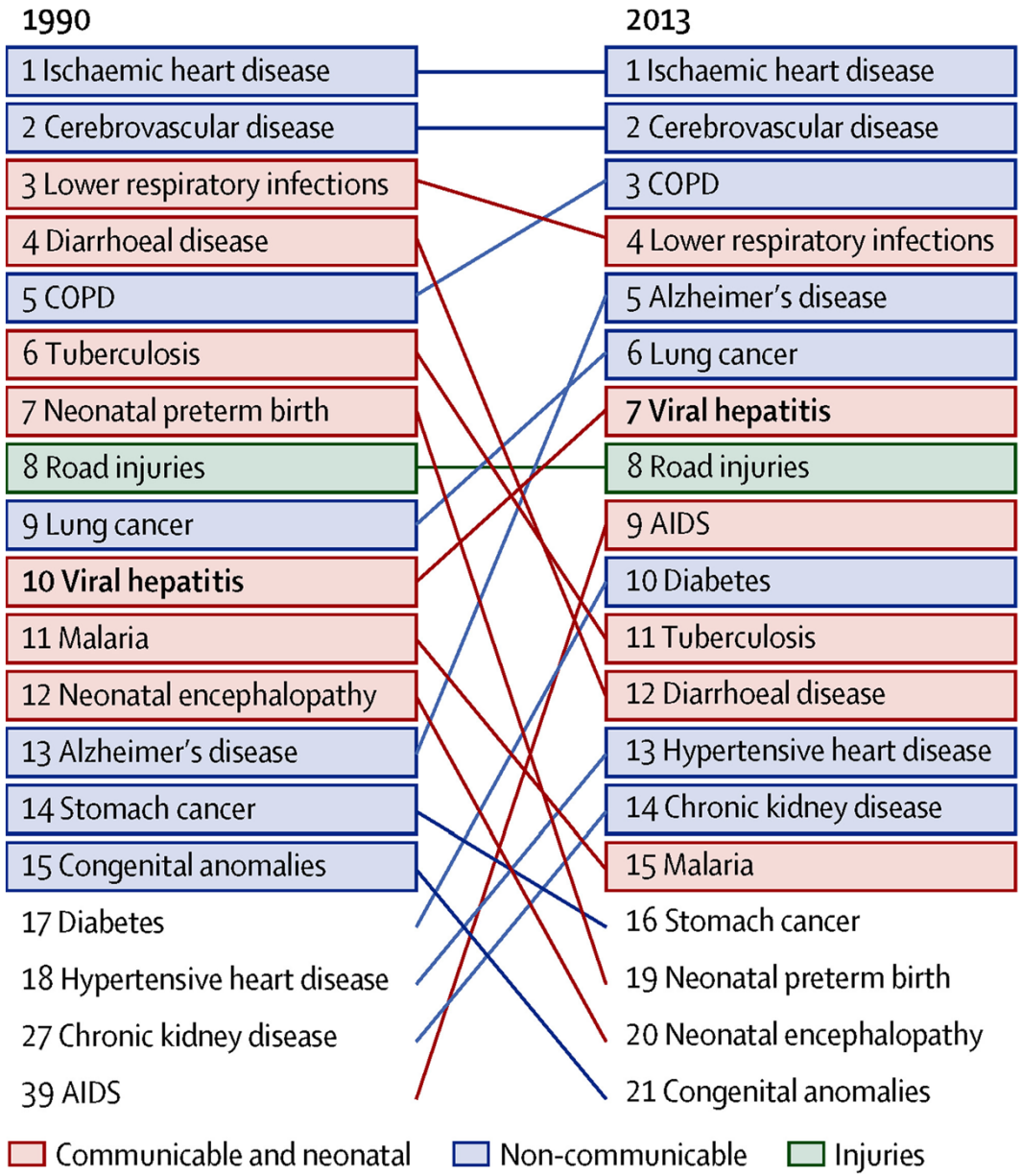


Sulkowski M. *et al.* Ann Intern Med. 2003;138:197-207 Guaraldi G *et al* Clin Infect Dis 2008 47(2): 250-257
Greub G *et al.* Lancet 2000;356:1800-1805

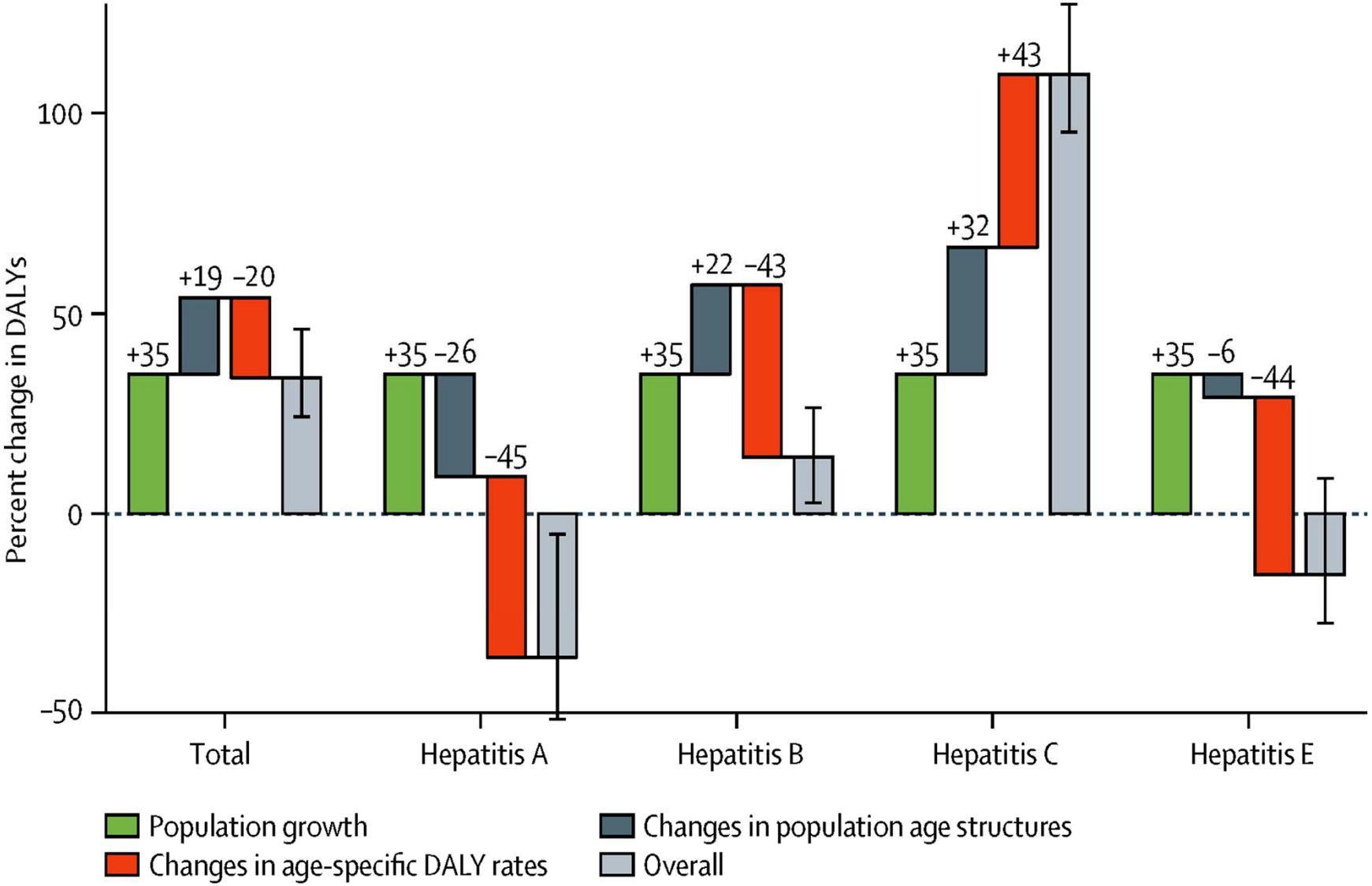
Overlapping epidemics – co-infections



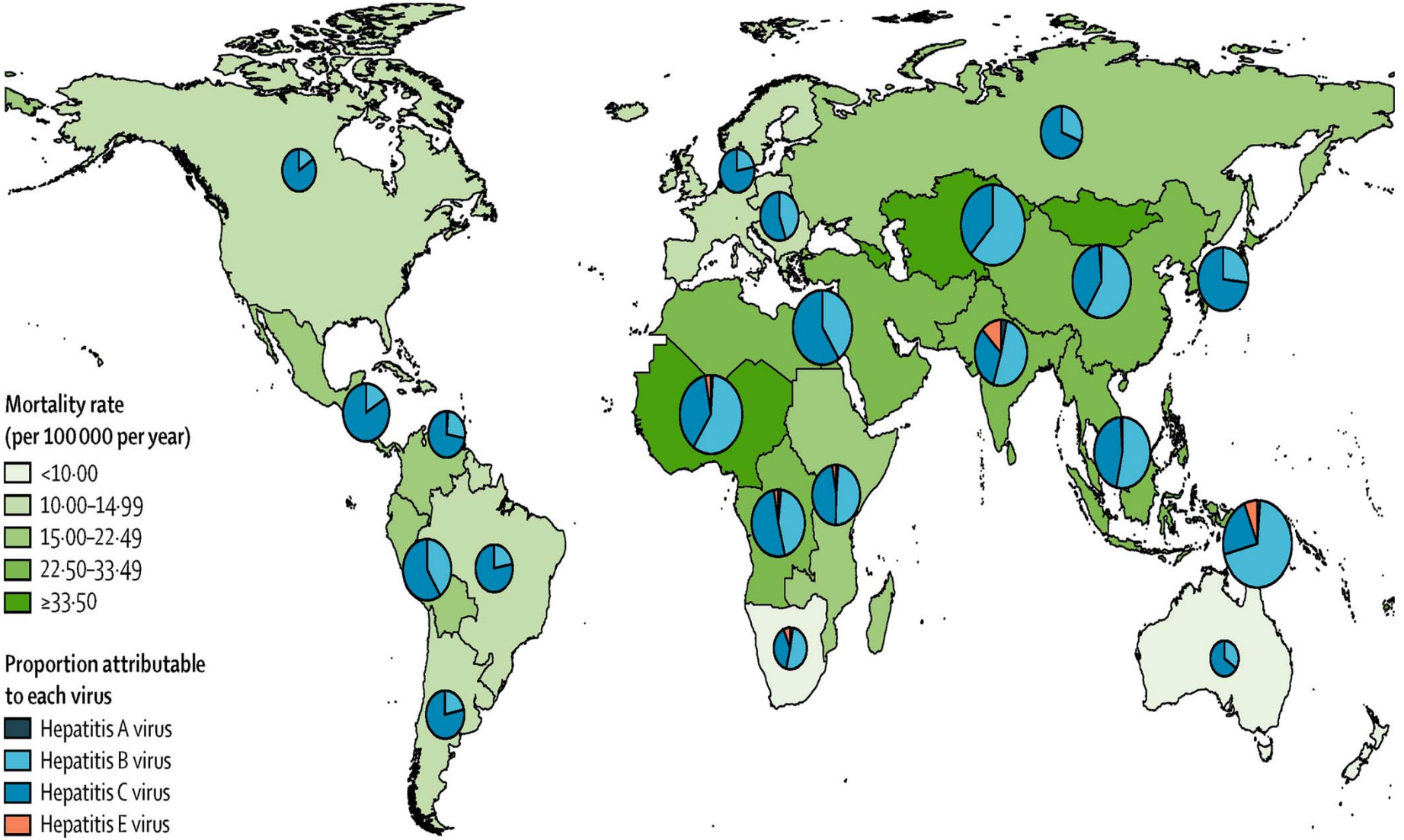
Easterbrook, et al. IAS 2015, TuPEB254



Stanaway, et al, Lancet 2016

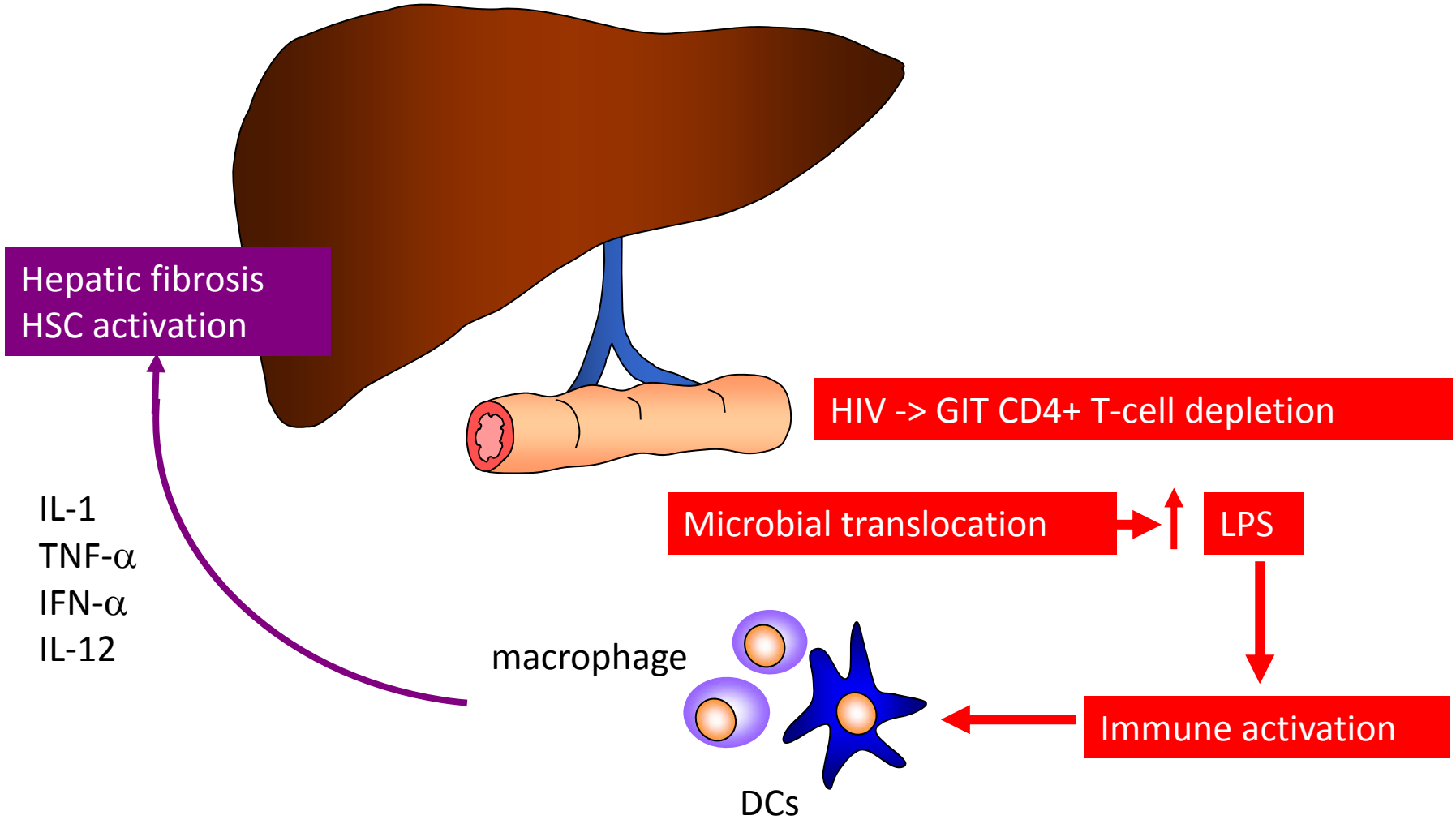


Stanaway, et al, Lancet 2016



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)

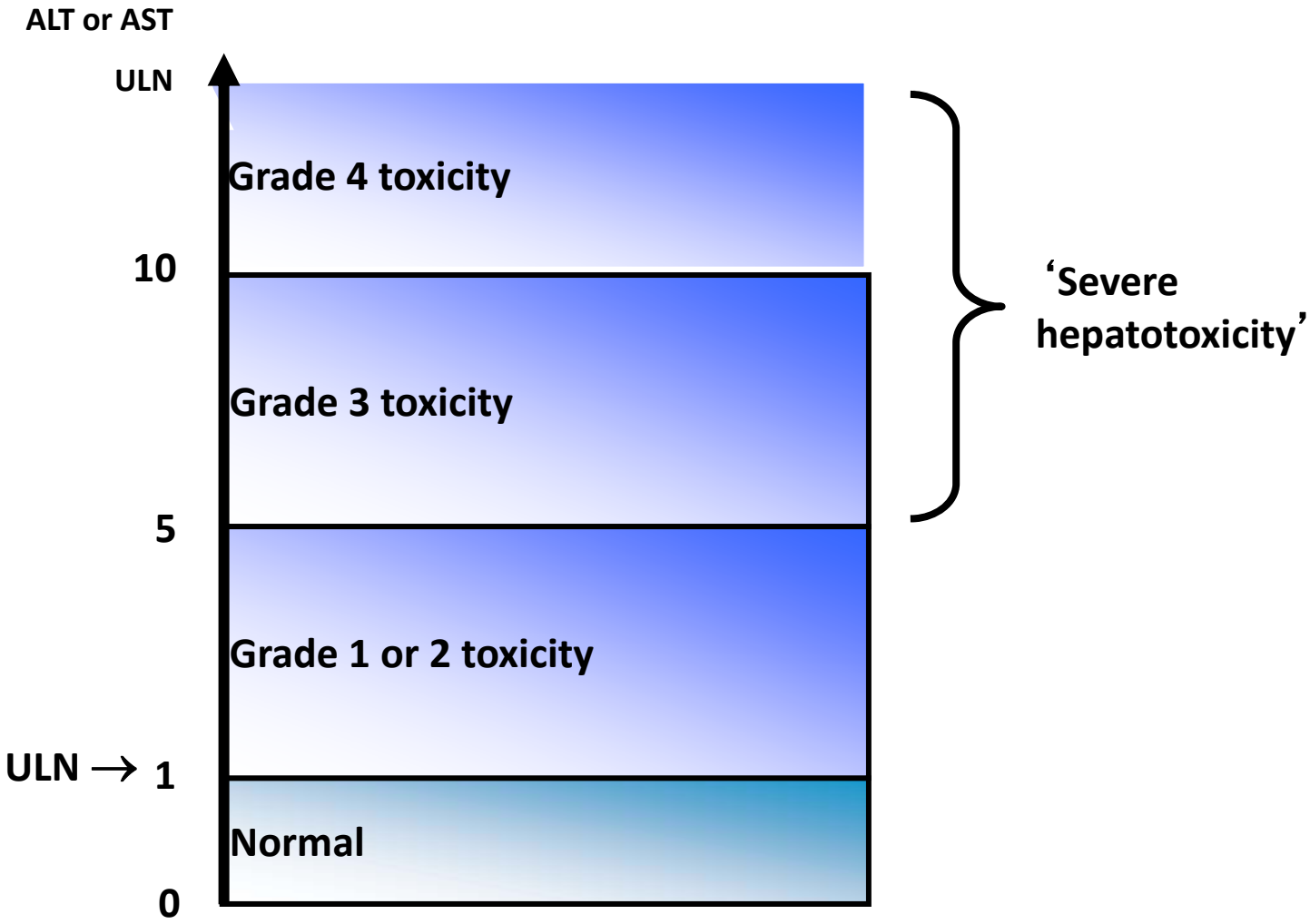
- Sub-study of 230 (4577) patients
- Baseline FibroScan, FIB-4, APRI

- 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

Defining Hepatotoxicity



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

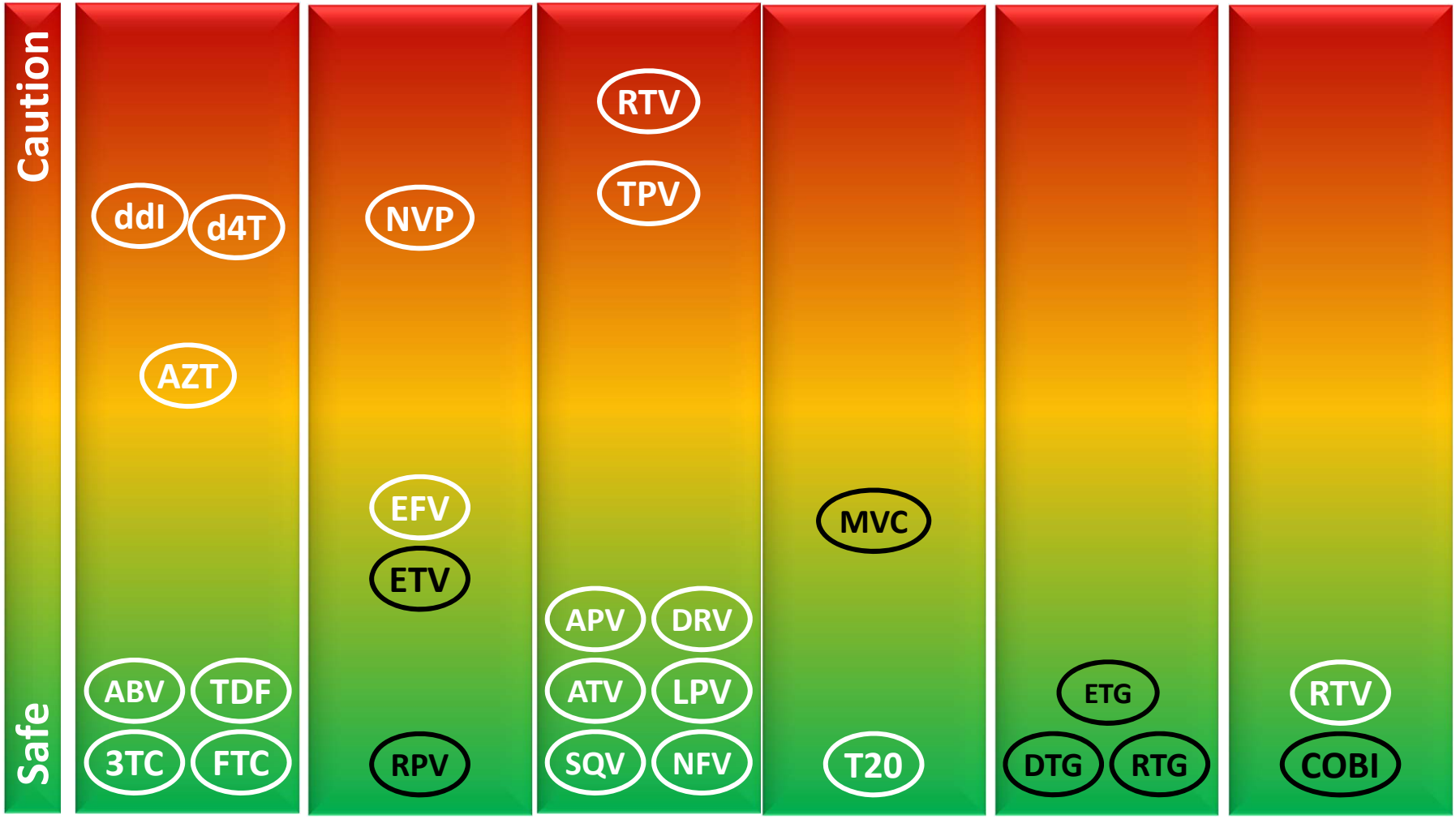
Non Cirrhotic Portal Hypertension

- 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

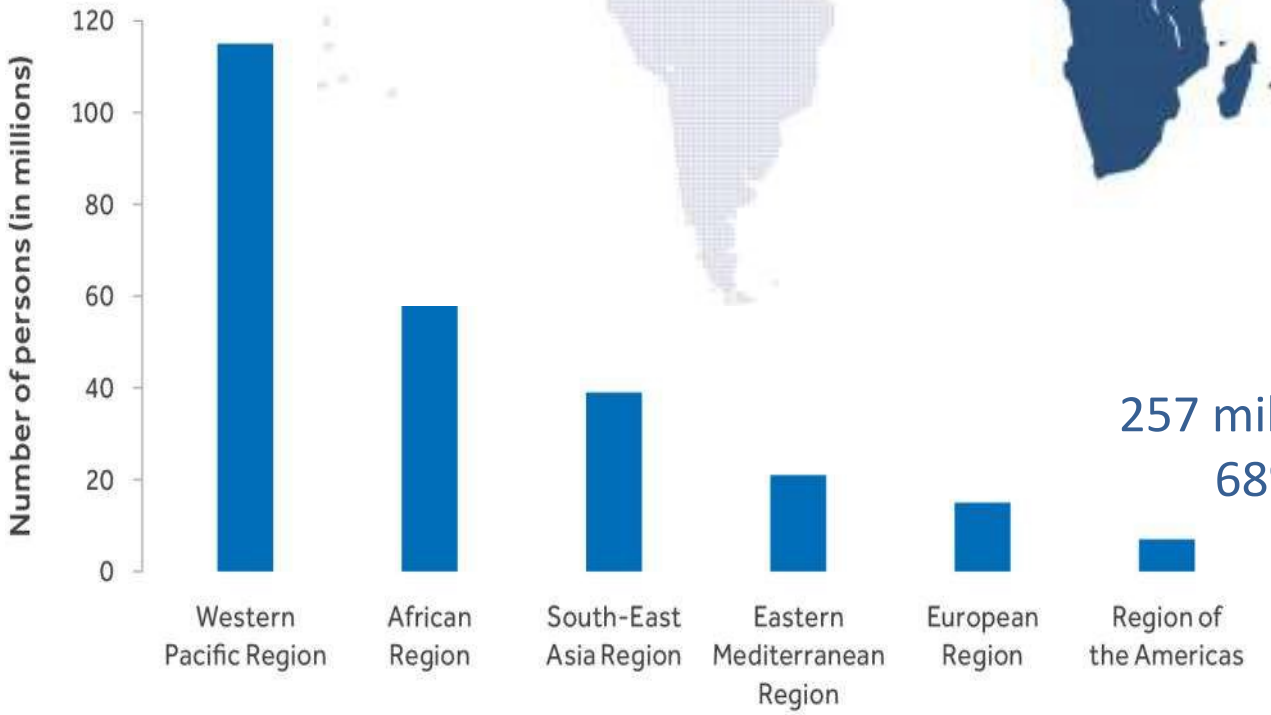
Hepatotoxicity in HBV and HCV co-infected patients - mechanisms

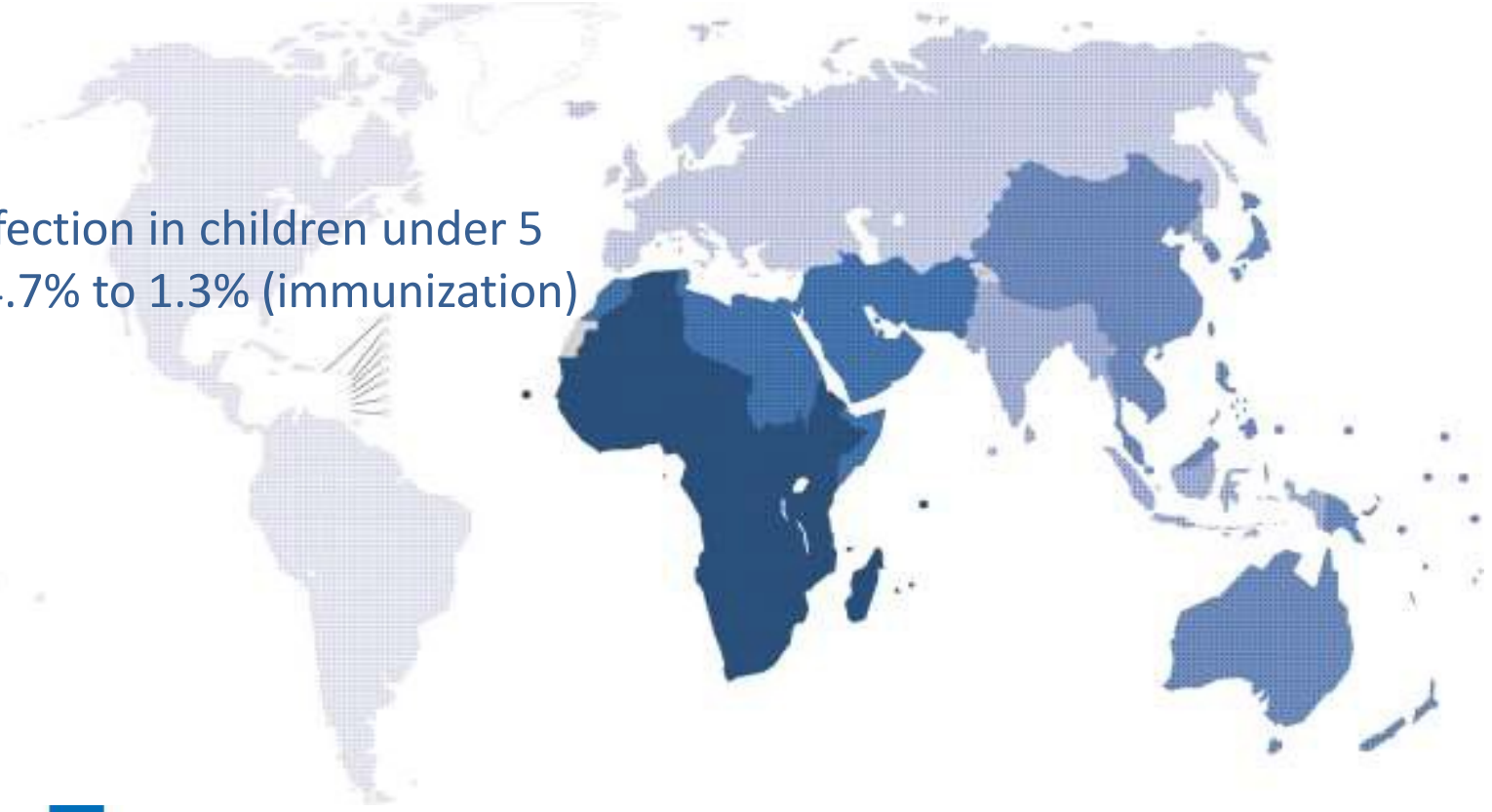
- Immune restoration - increase in CTL activity
- Direct hepatotoxicity – increased susceptibility of viral infected hepatocytes to metabolites
- Altered cytokine milieu in the presence of viral hepatitis
  - Increased risk of liver inflammation
  - Down-regulation of Cyp450 mediated drug metabolism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

GLOBAL STATUS OF HEPATITIS B

Incidence:

Chronic HBV infection in children under 5
reduced from 4.7% to 1.3% (immunization)



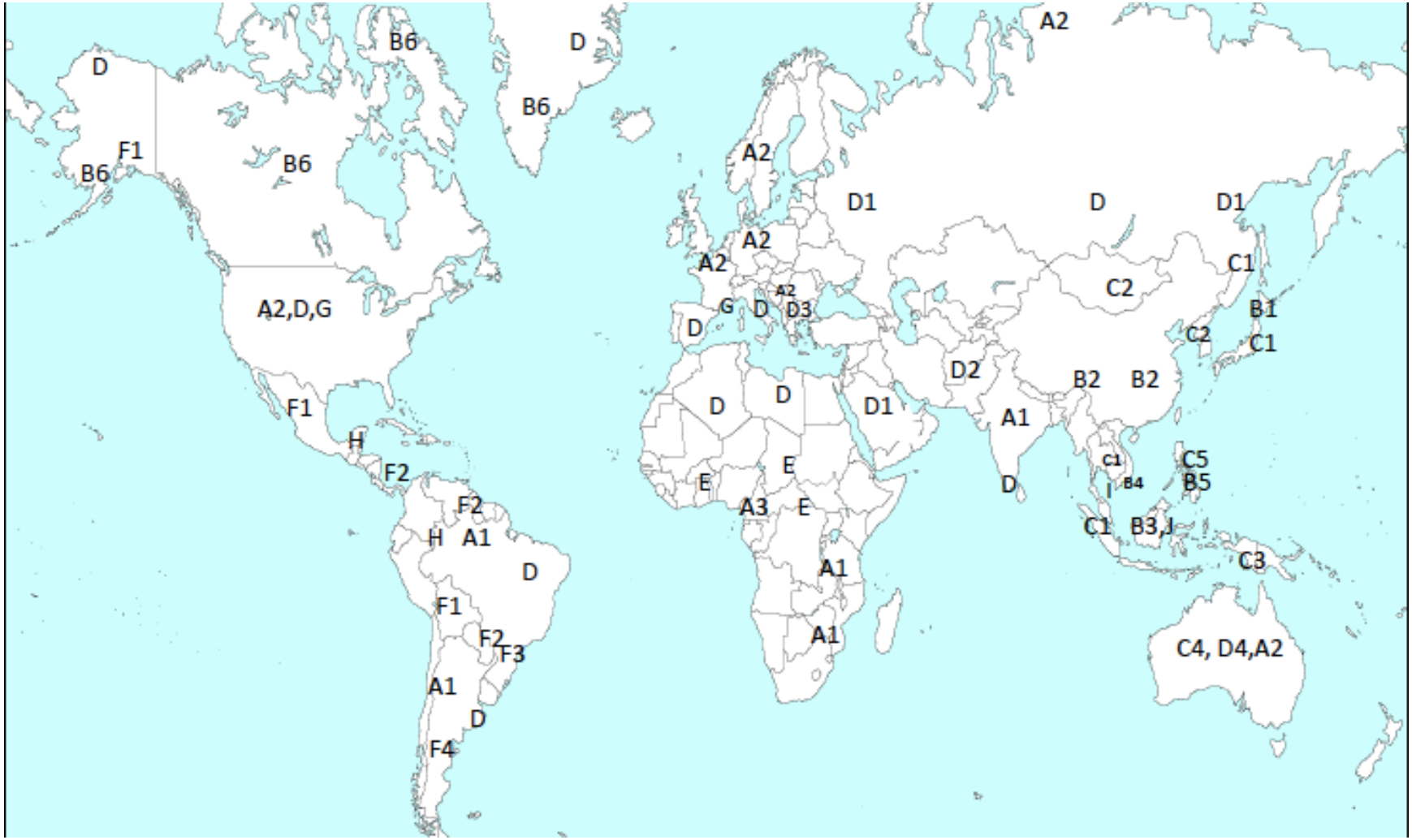


Prevalence:

257 million people living with HBV
68% in Africa /Western Pacific

WHO Global Hepatitis Report 2017

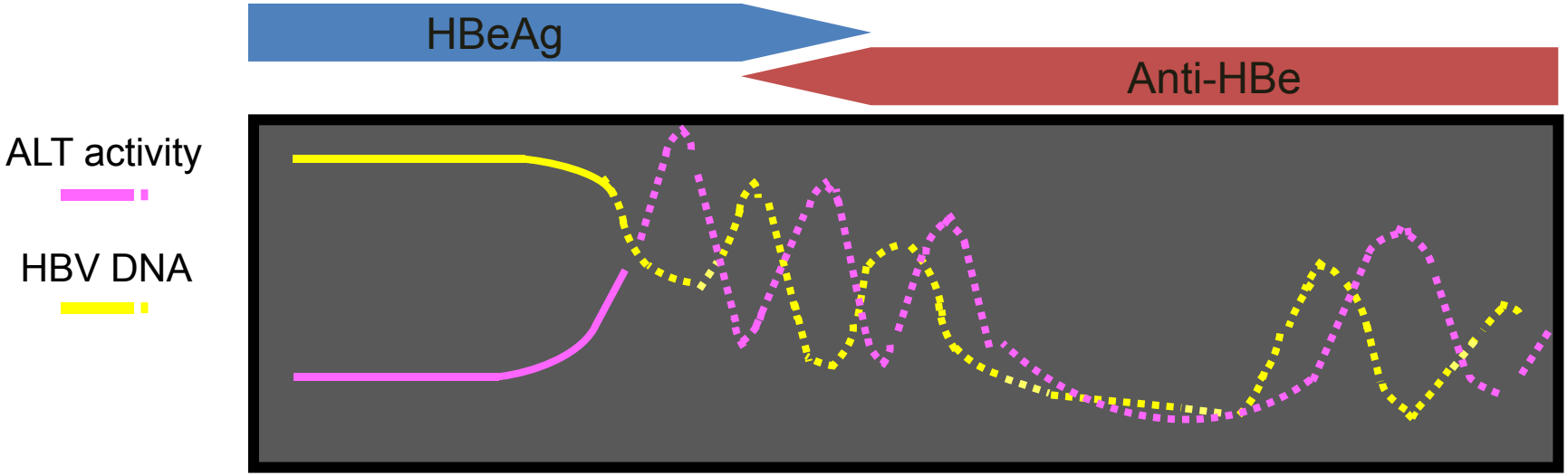
Global distribution of HBV Genotypes



Rajoriya, et al. J Hepatology 2017

4 Phases of Chronic HBV Infection

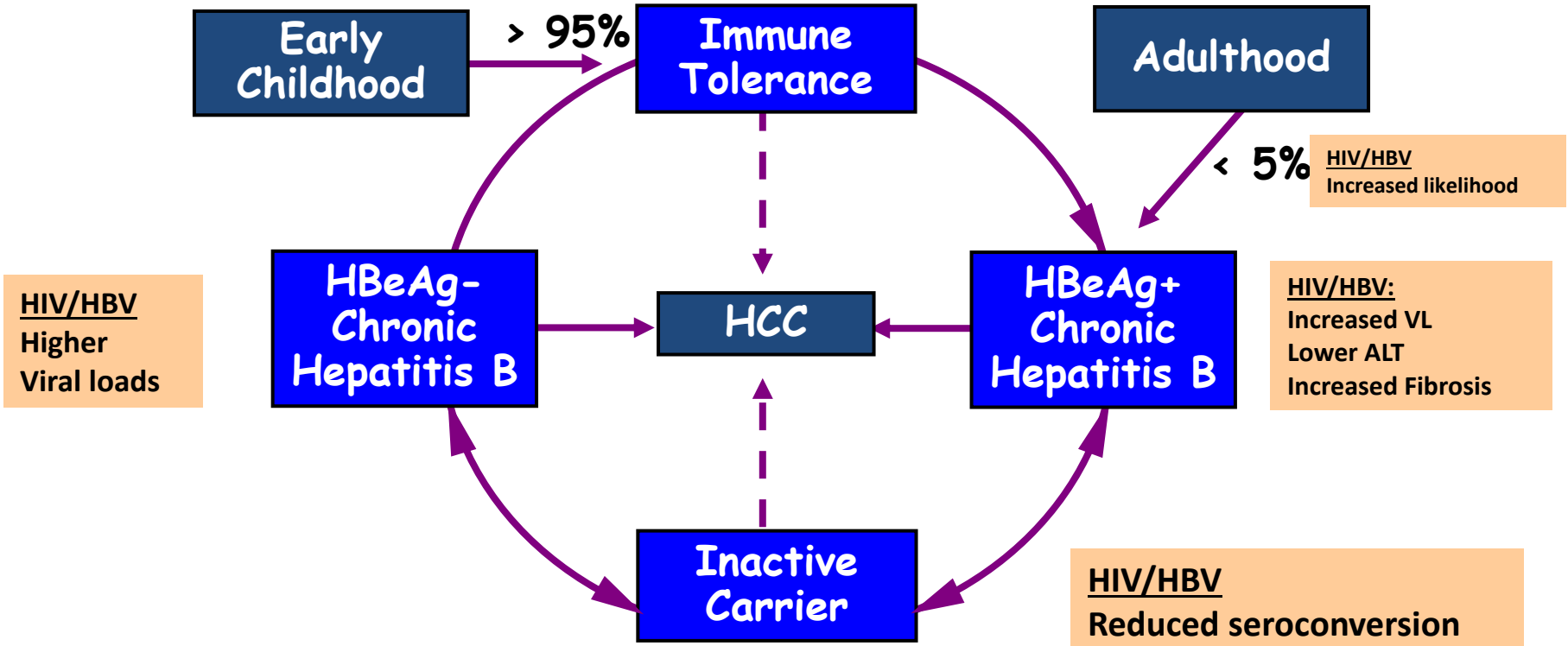
Current Understanding of HBV Infection



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

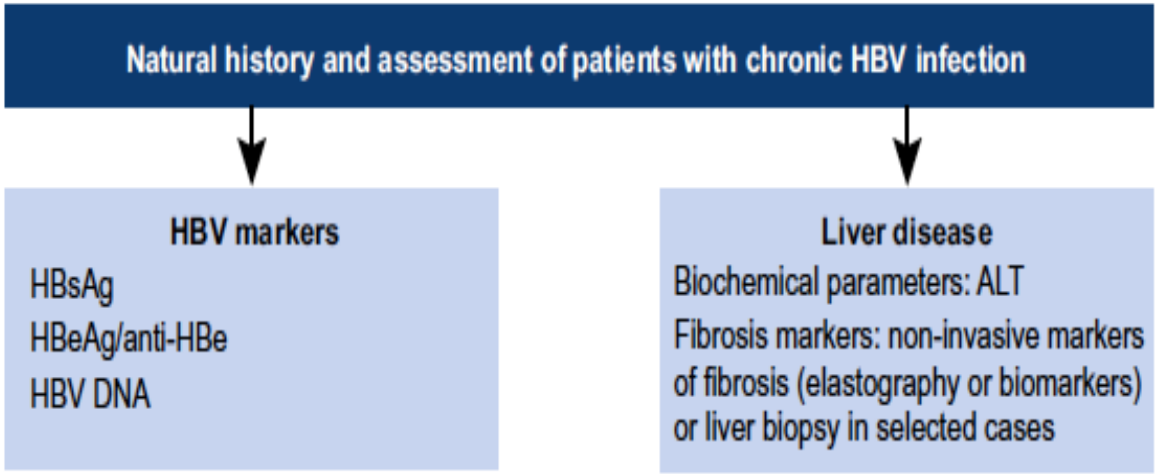
Yim HJ, et al. Natural history of chronic hepatitis B virus infection: what we knew in 1981 and what we know in 2005. Hepatology. 2006;43:S173-S181.

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

Do we really need all this complexity?



	HBeAg positive		HBeAg negative	
	Chronic infection	Chronic hepatitis	Chronic infection	Chronic hepatitis
HBsAg	High	High/intermediate	Low	Intermediate
HBeAg	Positive	Positive	Negative	Negative
HBV DNA	>10^7 IU/ml	10^4-10^7 IU/ml	<2,000 IU/ml°°	>2,000 IU/ml
ALT	Normal	Elevated	Normal	Elevated*
Liver disease	None/minimal	Moderate/severe	None	Moderate/severe
Old terminology	Immune tolerant	Immune reactive HBeAg positive	Inactive carrier	HBeAg negative chronic hepatitis

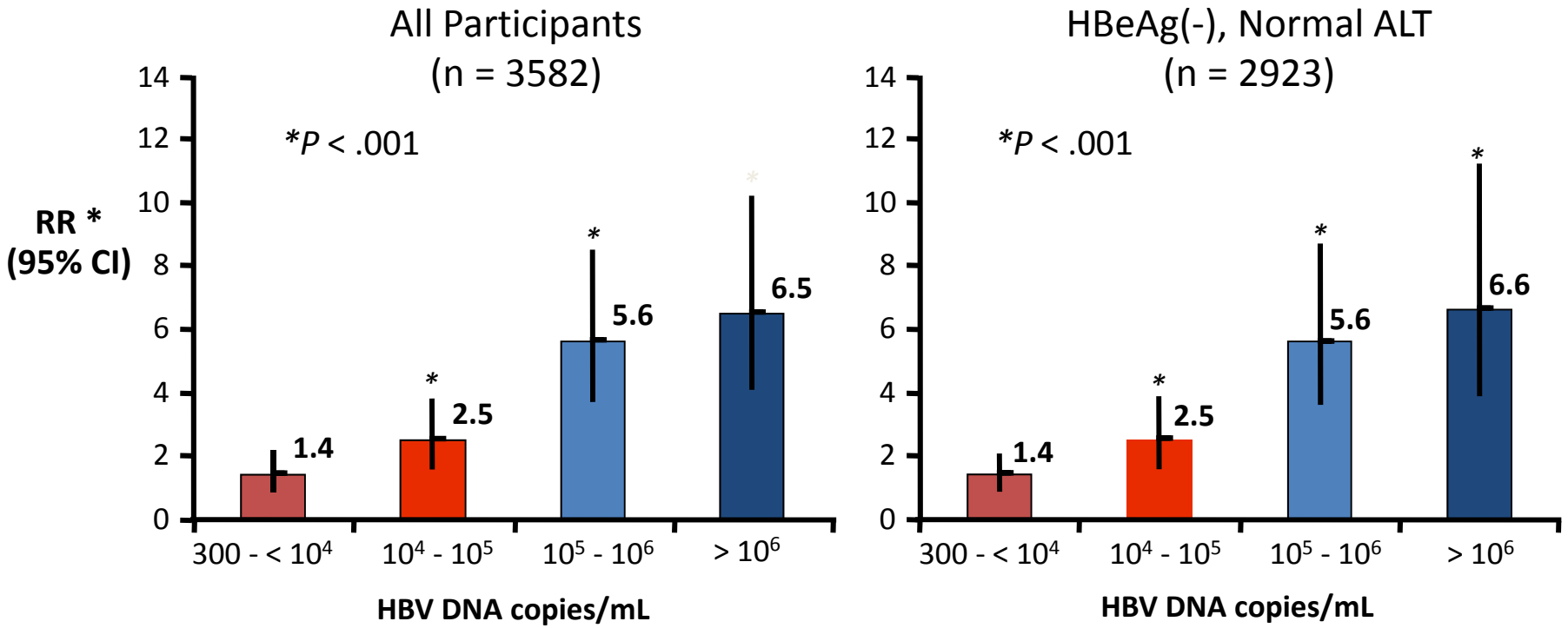
EASL HBV Guidelines 2017

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

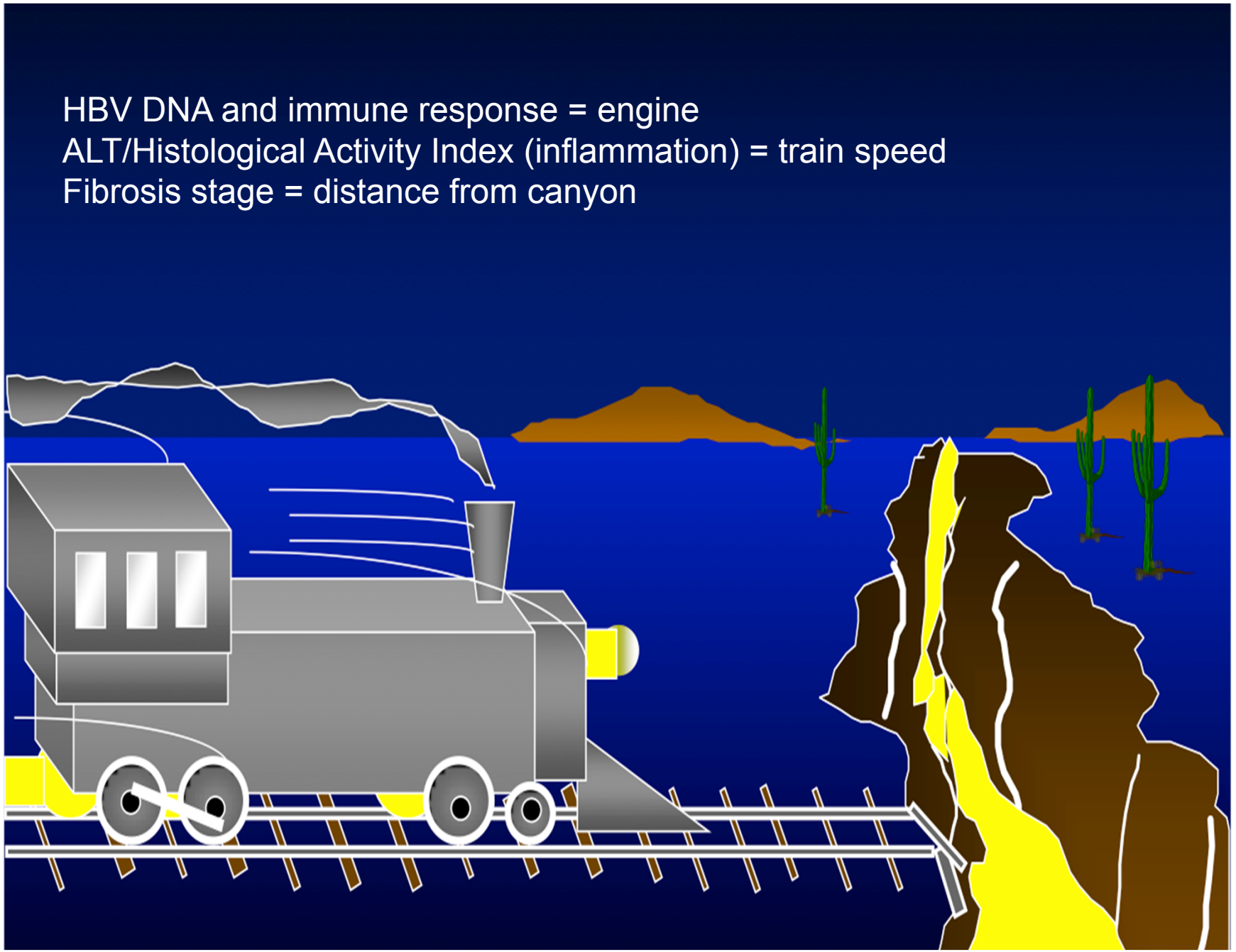
3582 HBsAg untreated asian carriers
mean follow-up 11 yrs → 365 patients newly diagnosed with cirrhosis



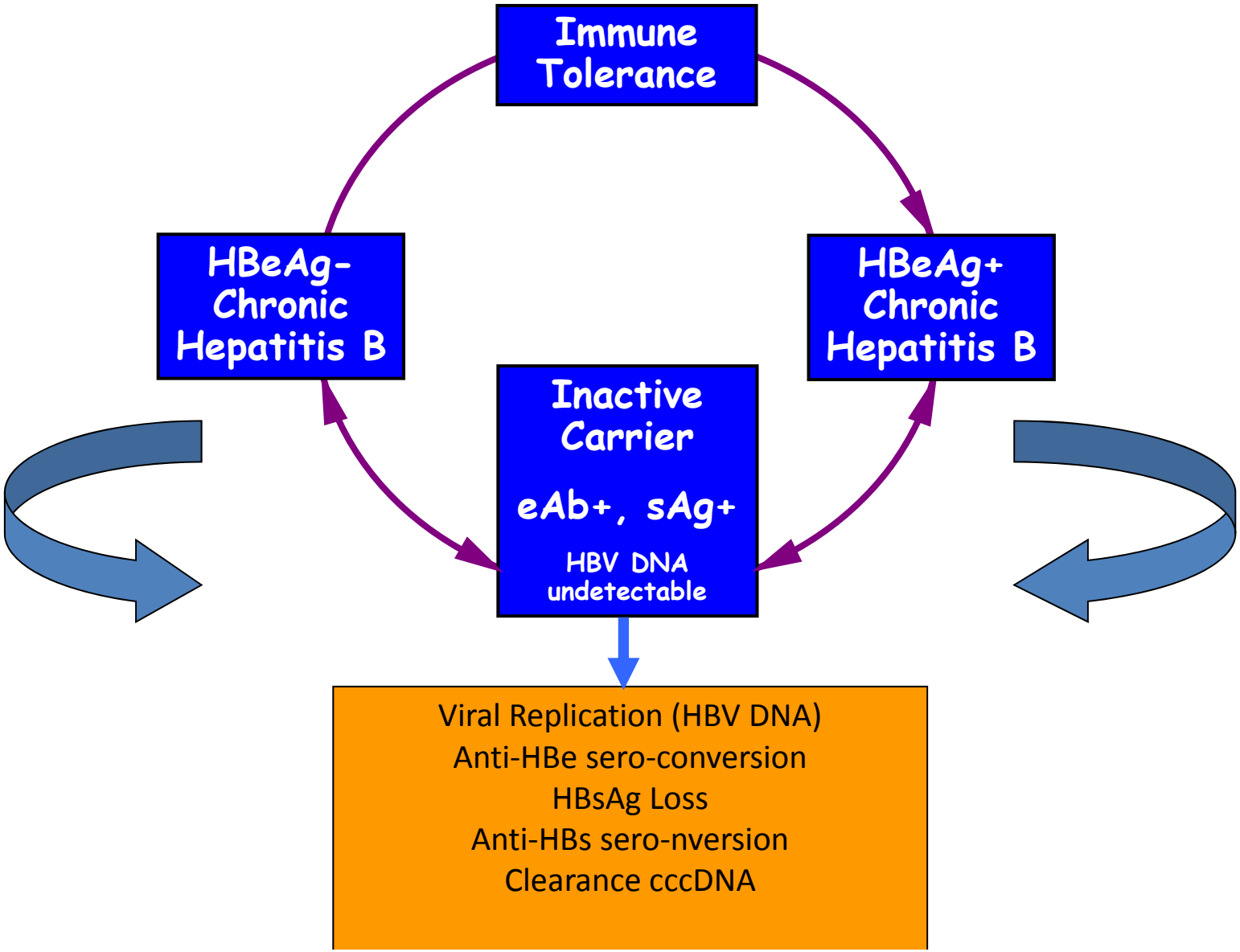
* Adjusted for age, sex, cigarette smoking, and alcohol consumption.

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

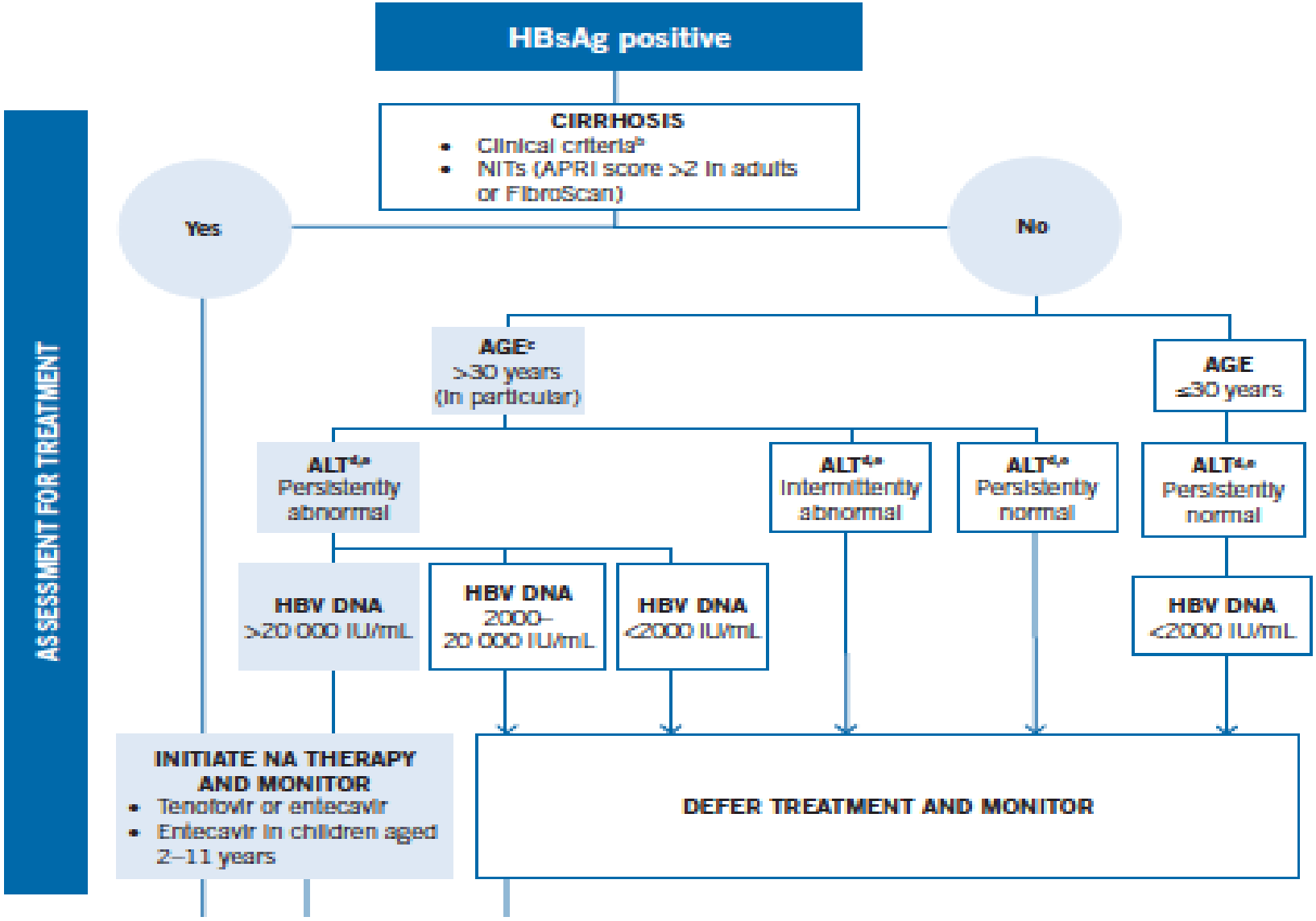
What does Rx aim to achieve?



Three key inter-linked factors in the decision to treat

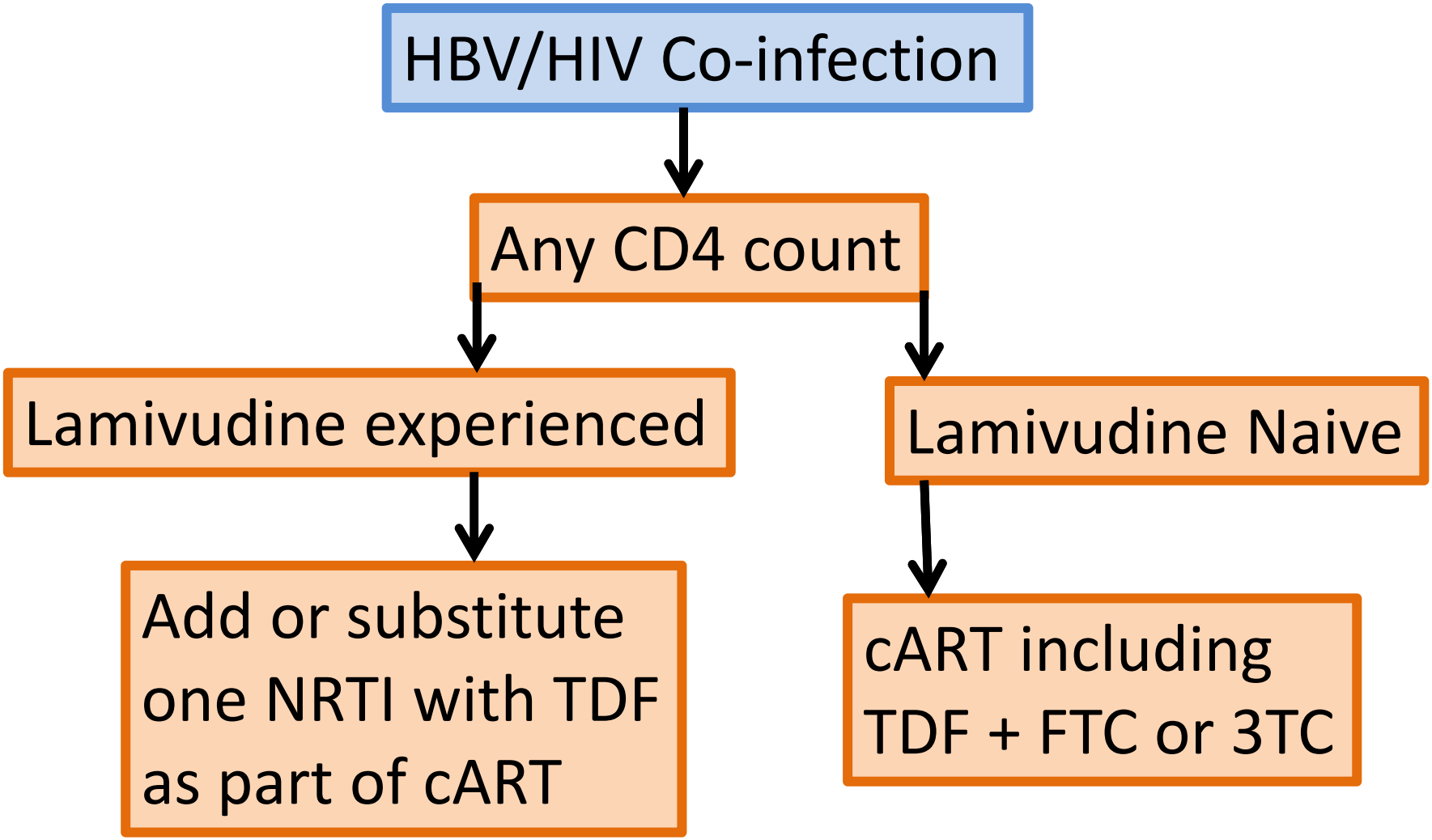
- Age
  - <30yrs vs. >30yrs
  - FH of HCC
- Level of fibrosis/inflammation
  - Cirrhosis
  - F2+ fibrosis
  - Abnormal liver enzymes
- HBV DNA levels
  - >20 000 IU/ml

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



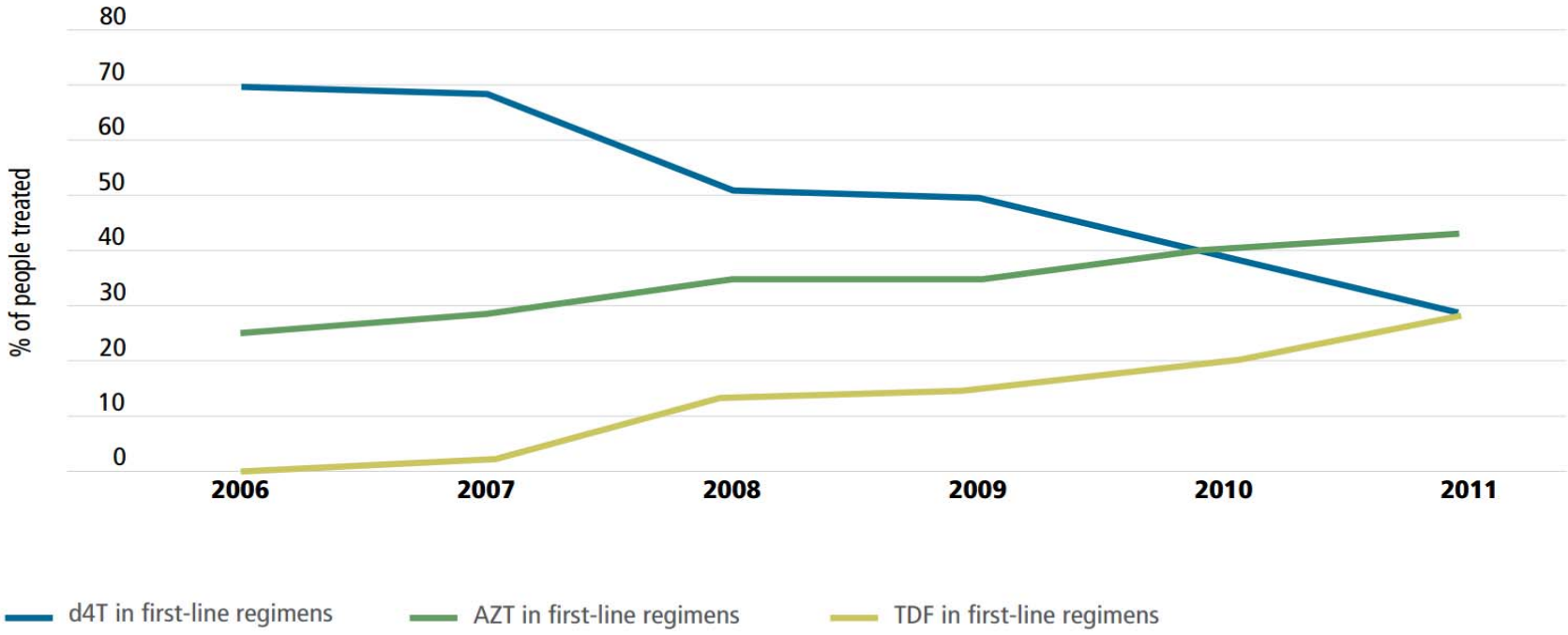
WHO Guidelines 2015

EACS Guidelines 2016/7



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).*

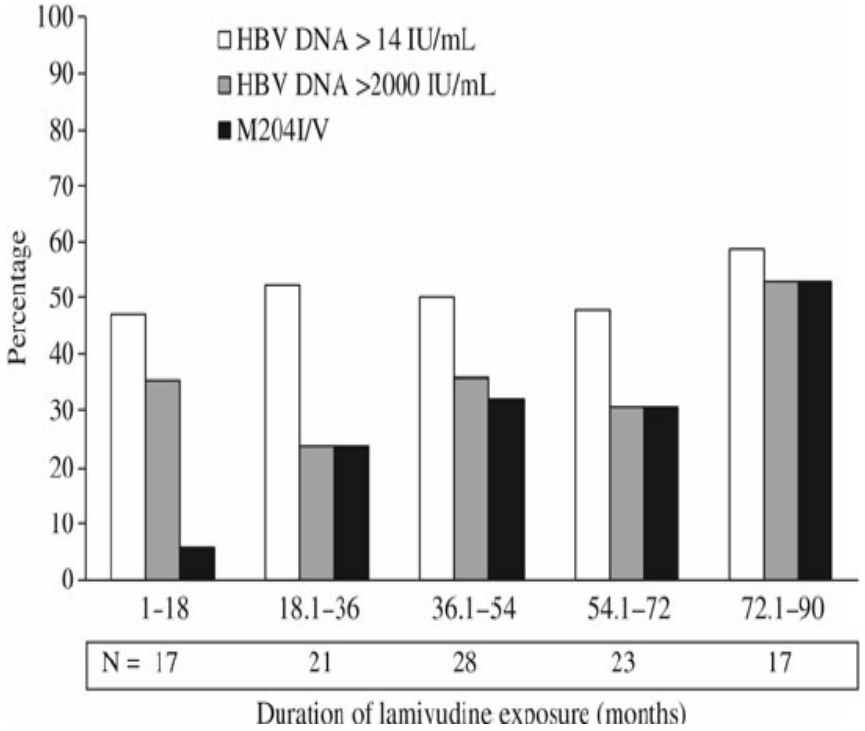
Global update on HIV treatment 2013. WHO

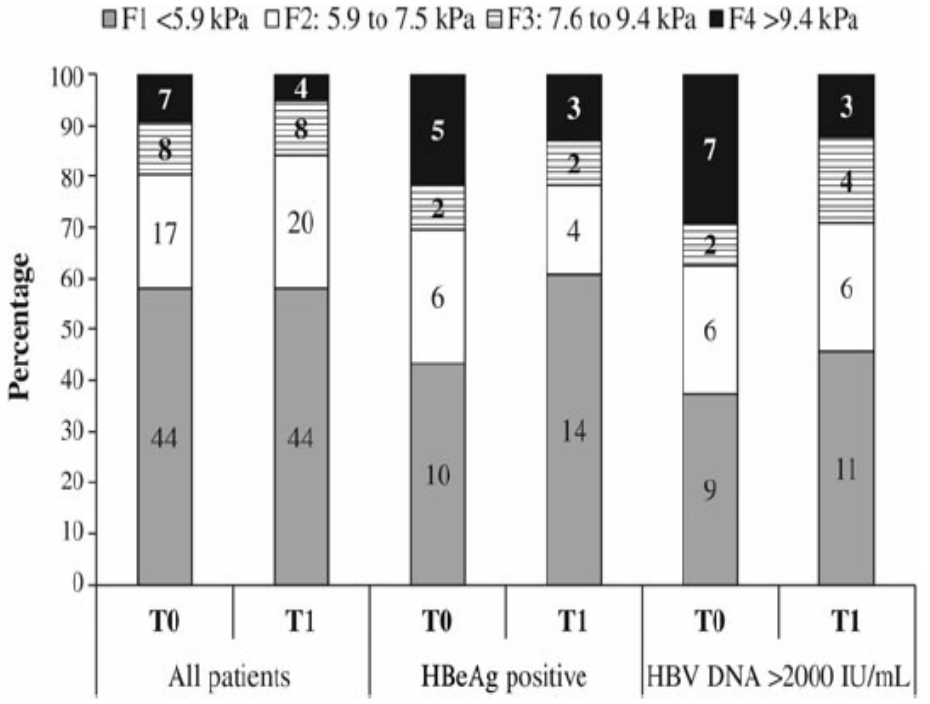
Tanzania: 3% HIV and 17% HIV/HBV on TDF regimen Hawkins IAC 2012

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

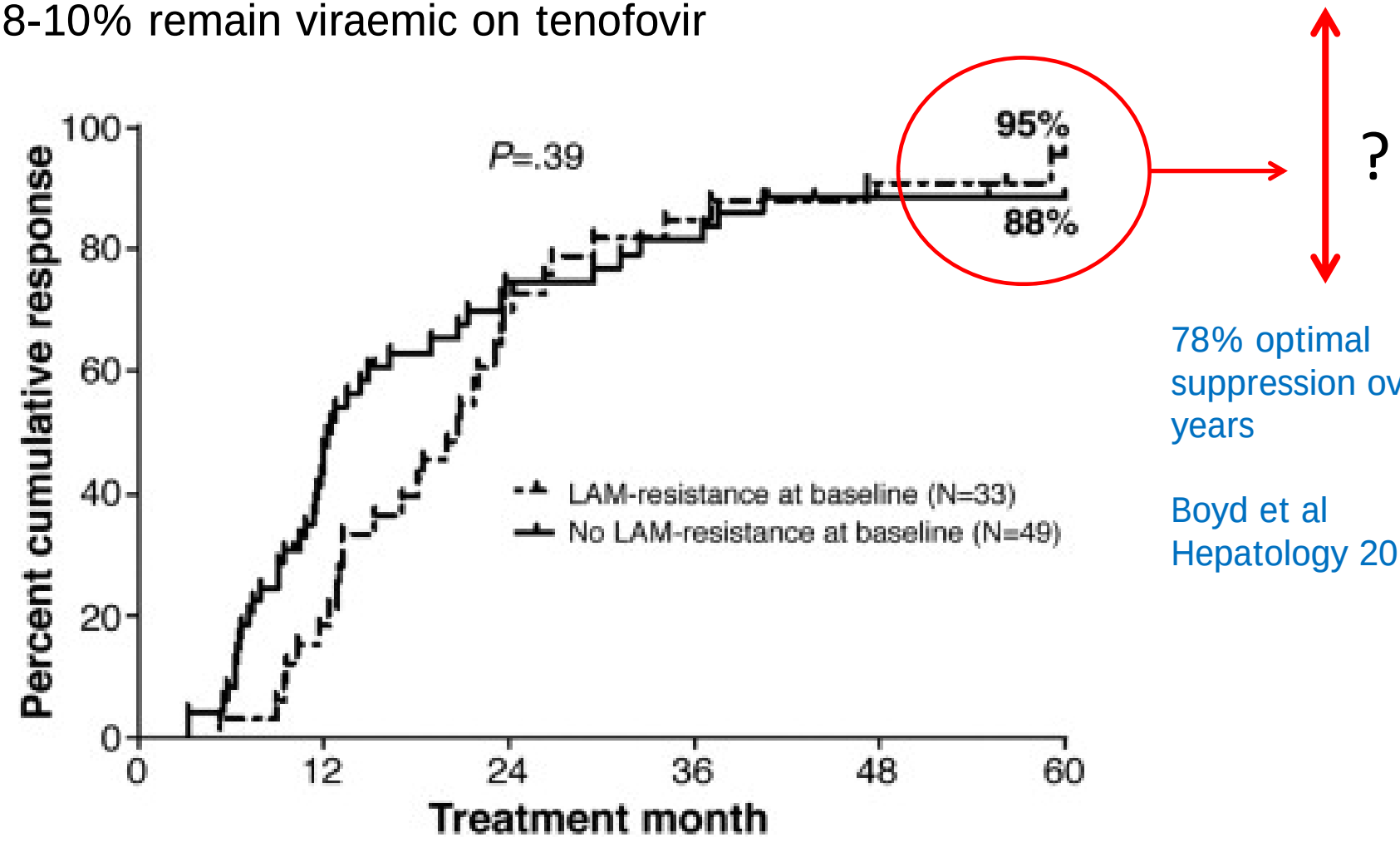




Stockdale, et al. Clin Infect Dis; 2015

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

Factors associated with detectable HBV DNA

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

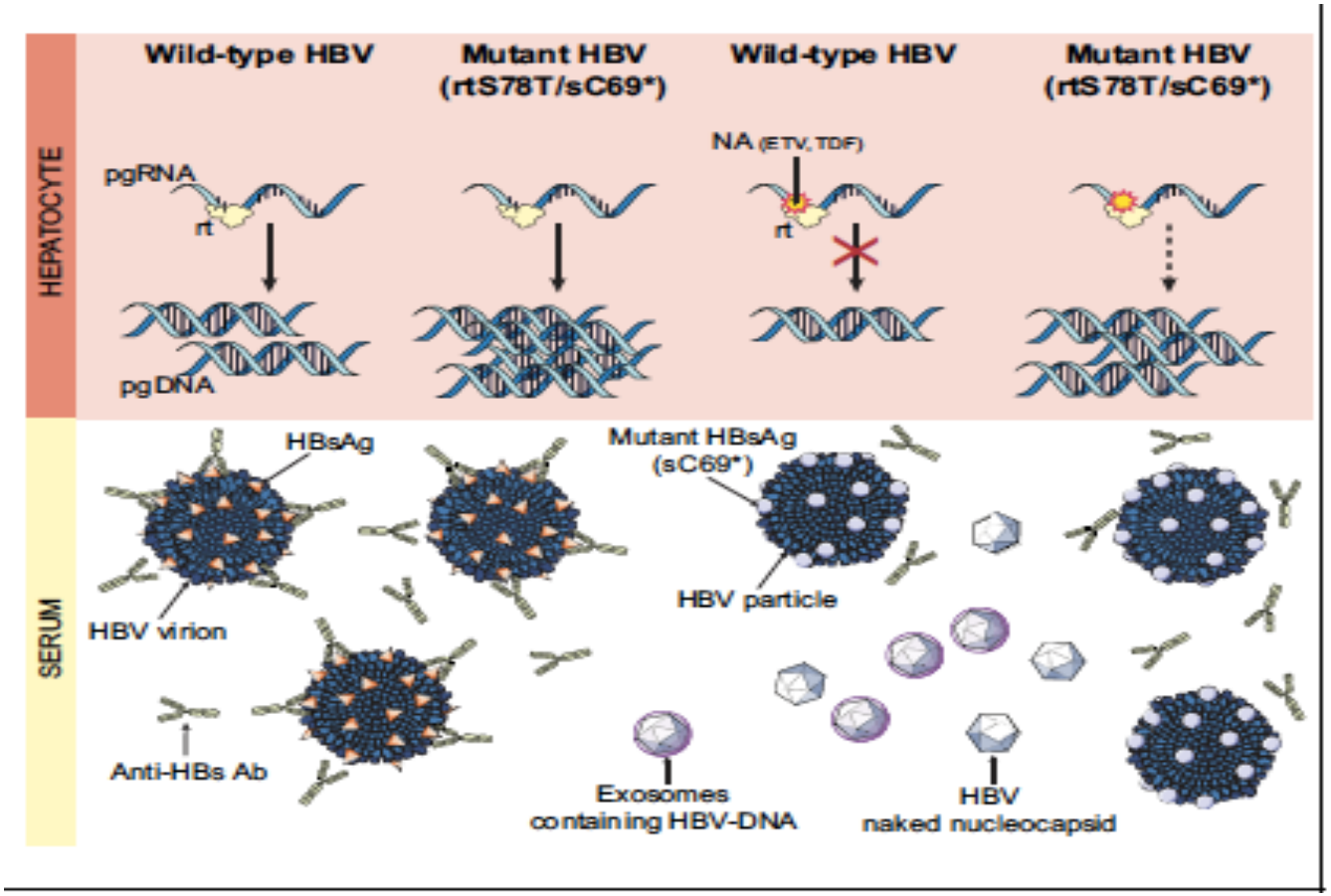
	OR	95% CI	p-value
Age (per 10 yrs)	0.90	0.48, 1.69	0.74
HBeAg positive	12.06	3.73, 38.98	<0.0001
<95% adherent	2.52	1.16, 5.48	0.02
HAART <2 yrs	2.64	1.06, 6.54	0.04
CD4 < 200 cells/mm^3	2.47	1.06, 5.73	0.04

Long term adherence is always a challenge

Matthews CID 2012

Drivers of HBV viraemia on TDF?

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



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

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

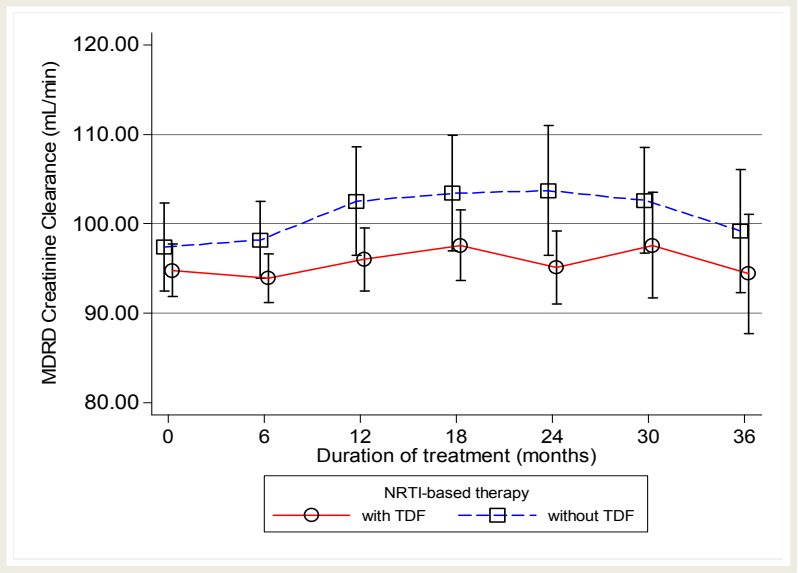
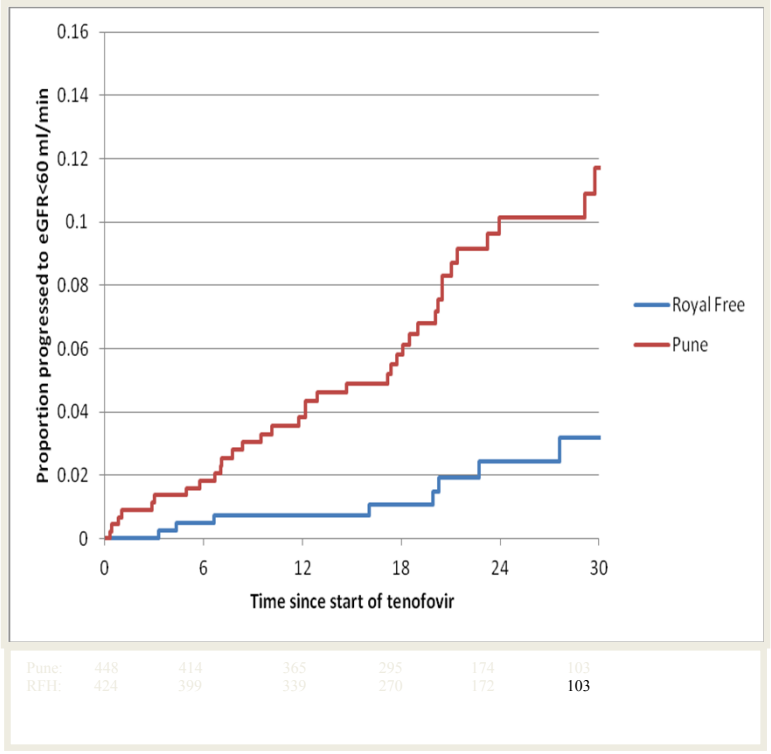


Figure 1: MDRD clearance over time

- >400 HIV+ patients receiving TDF



Pujari, et al, BMC Infect Dis 2014

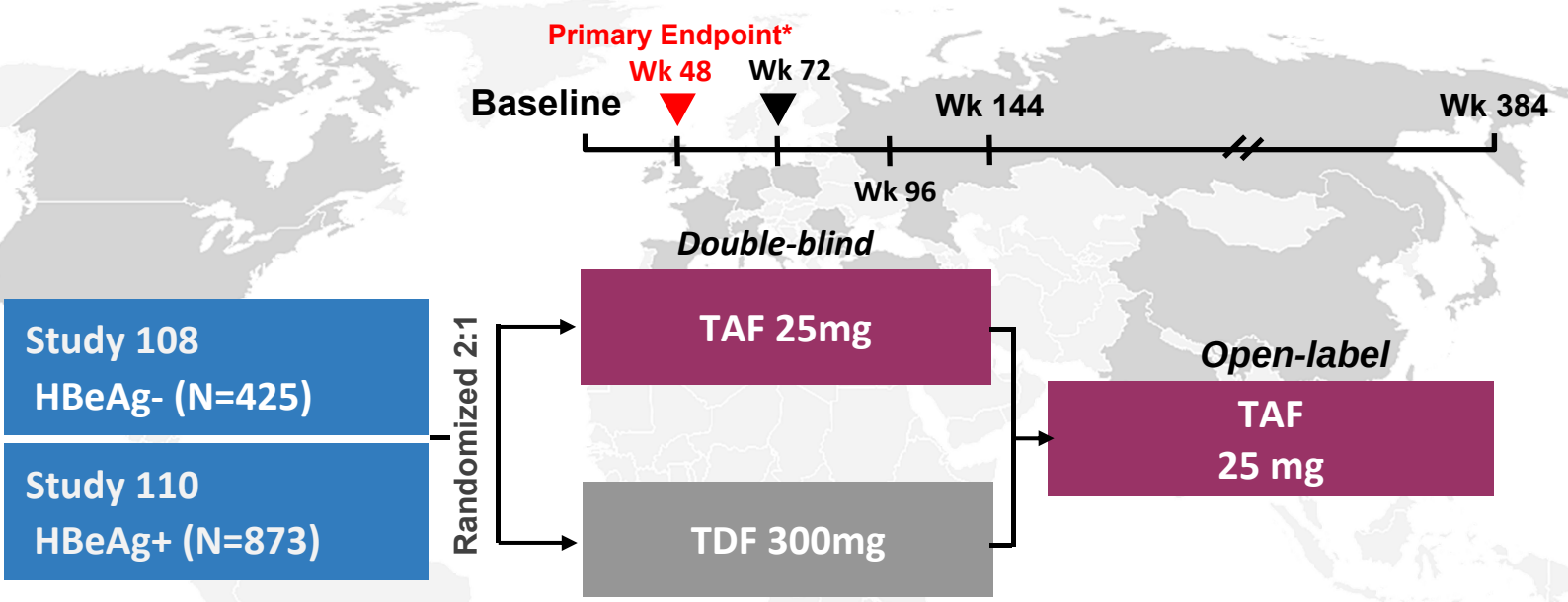
Strategies when TDF is contra-indicated?

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

- Tenfovir Alafenamide (TAF)

TAF HBV Phase 3 Program

Two phase 3, randomised, double-blind studies

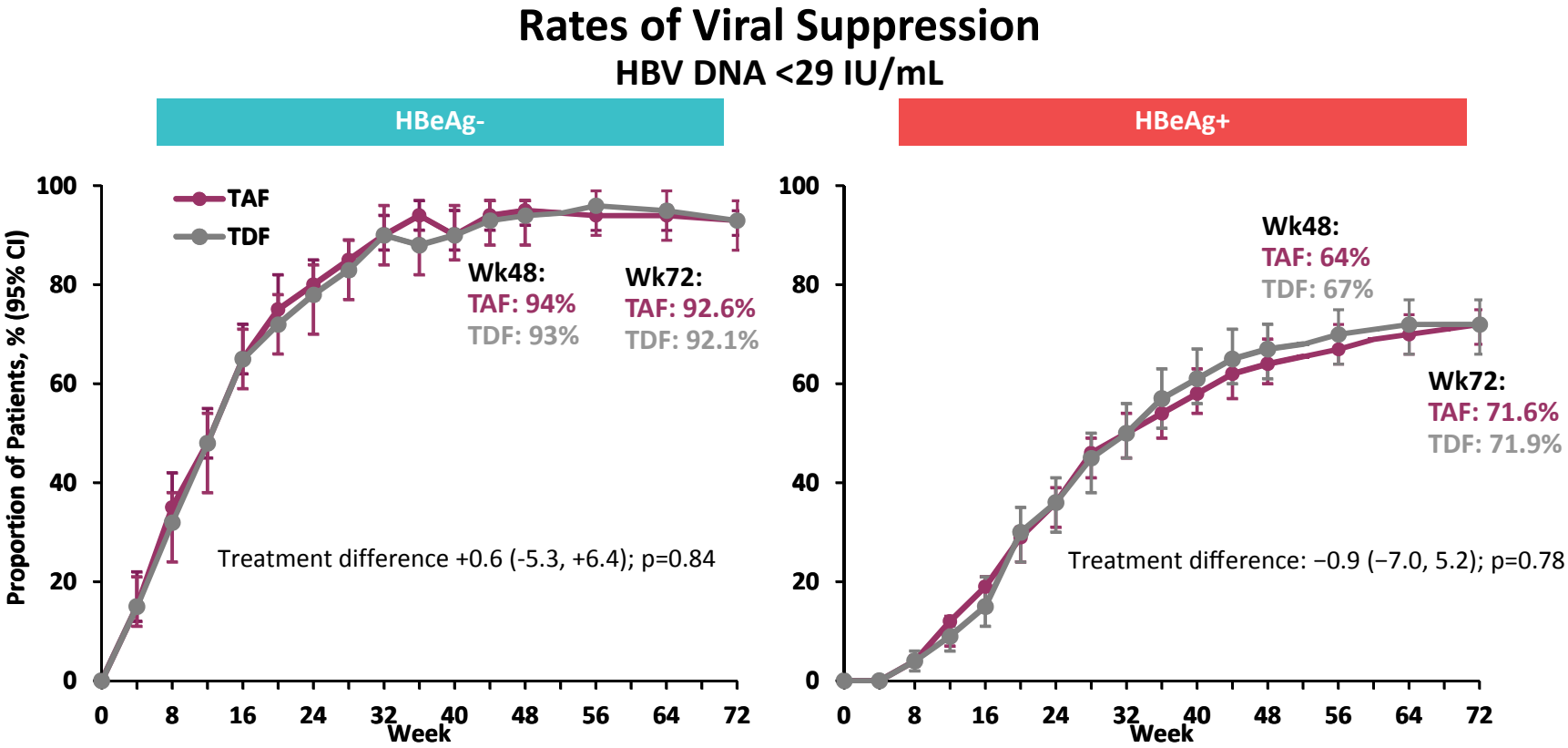


- **Primary endpoint** (non inferiority margin of 10%):
  - HBV DNA <29 IU/mL at Week 48
- **Key secondary endpoints**
  - ALT normalisation at Week 48
  - Renal parameters and bone mineral density at Week 48
- 95% retention rate through Week 48
- Inclusion criteria: HBV DNA ≥20,000 IU/mL; ALT >60 U/L (males), >38 U/L (females), $eGFR_{CG}$ >50 mL/min

Buti M et al. Lancet G&H 2016; doi: 10.1016/S2468-1253(16)30107-8
Chan HLY et al. Lancet G&H 2016; doi: /10.1016/S2468-1253(16)30024-3

*Non-inferiority margin of 10%

Antiviral Efficacy of TAF and TDF at Week 72



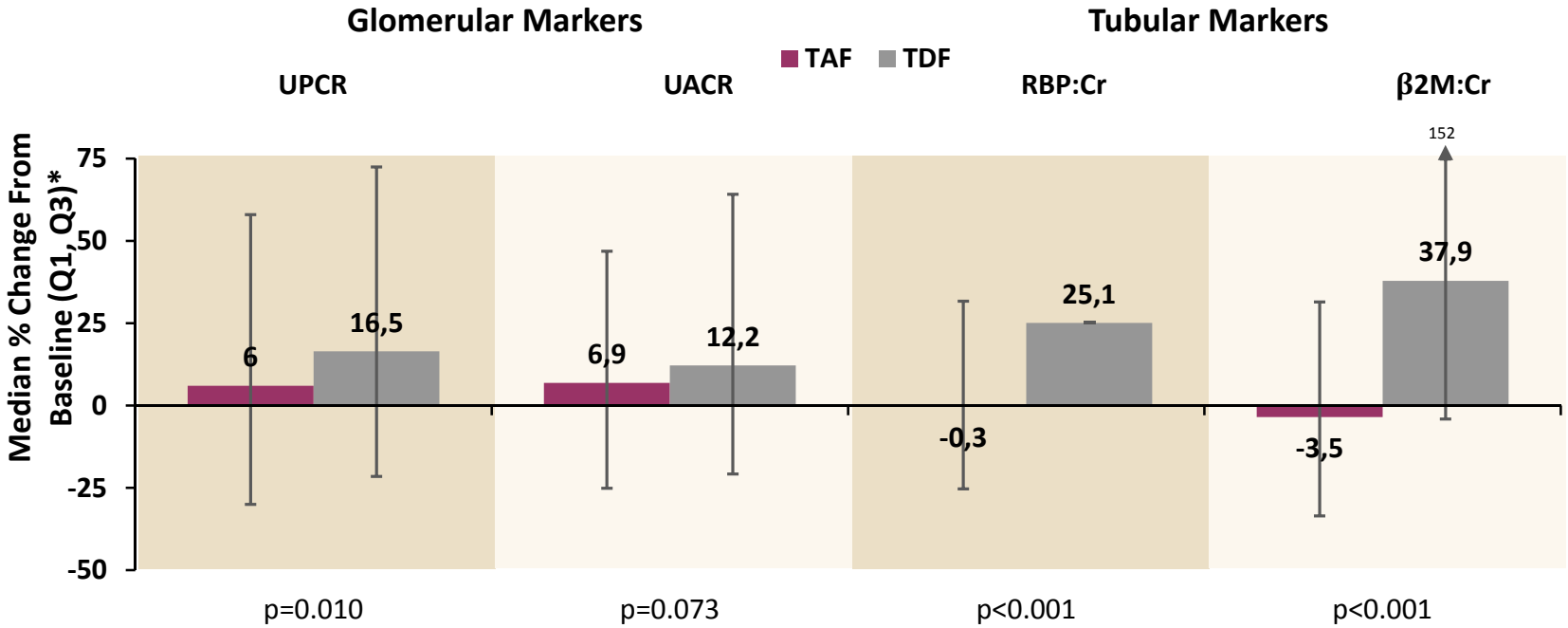
- HBV DNA suppression rates were lower in HBeAg+ vs HBeAg− patients
- No significant difference between TAF and TDF
- No resistance was detected through 48 weeks

HBV DNA suppression was comparable between TAF and TDF treatment up to Week 72

Seto, AASLD 2016, Oral 67

Changes in Urine Markers of Tubular Dysfunction During Treatment with TAF or TDF

Changes in Quantitative Proteinuria at Week 48



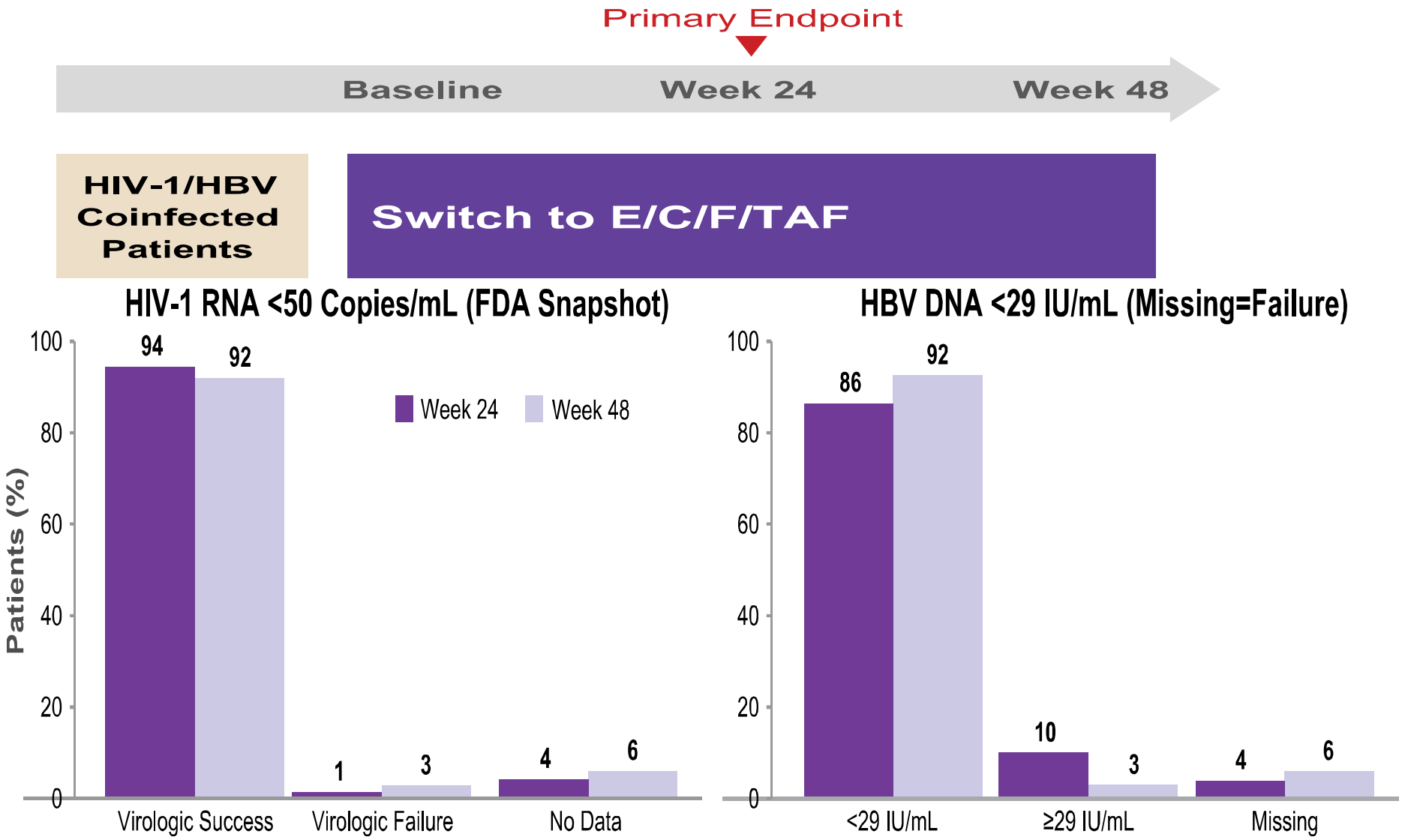
There were smaller changes in protein markers of kidney and proximal tubule function with TAF treatment compared to TDF

* p-values from 2-sided Wilcoxon rank-sum test

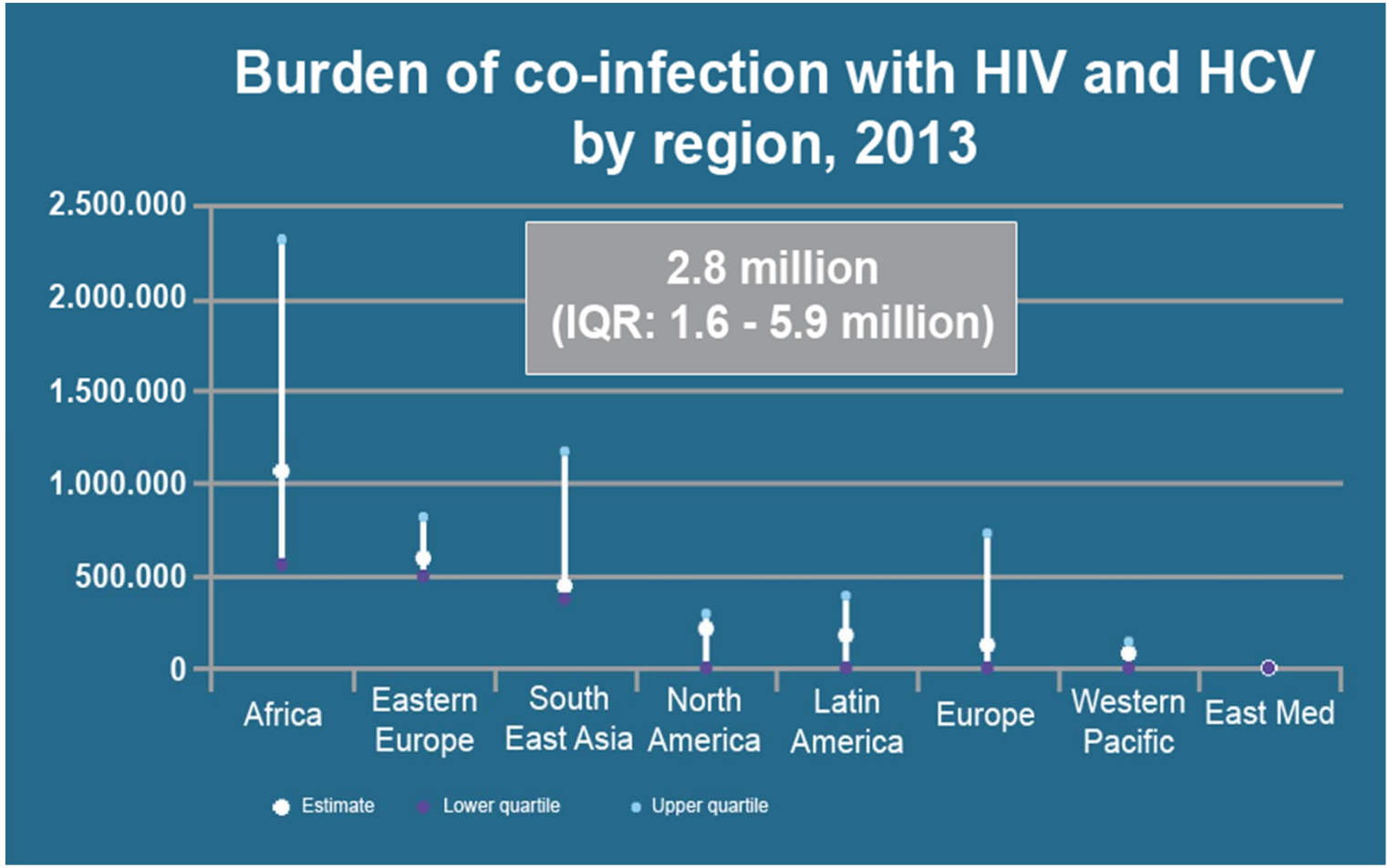
Lim, AASLD 2016, Poster 1901

TAF in co-infected patients

(Galant et al, IAS 2015 WELBPE13)



Burden of HCV in HIV populations



P Easterbrook, IAS 2015

HIV/HCV – double-trouble for the liver

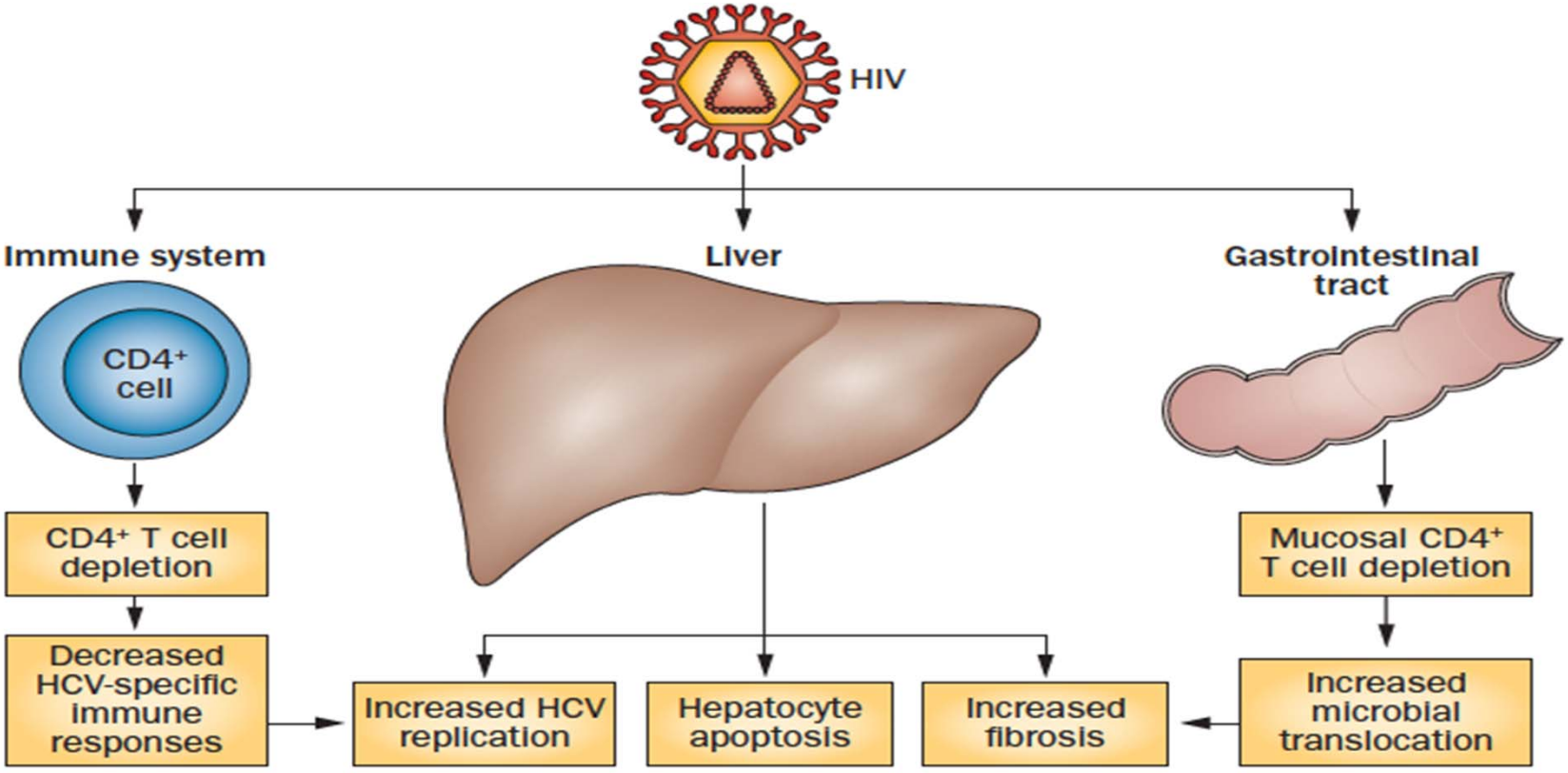


Figure 1 | Driving factors underlying liver disease pathogenesis in HCV–HIV co-infection. HIV infection leads to an impaired immune response against HCV, increased HCV replication, hepatic inflammation and apoptosis, increased microbial translocation from the gastrointestinal tract and increased fibrosis.

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

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

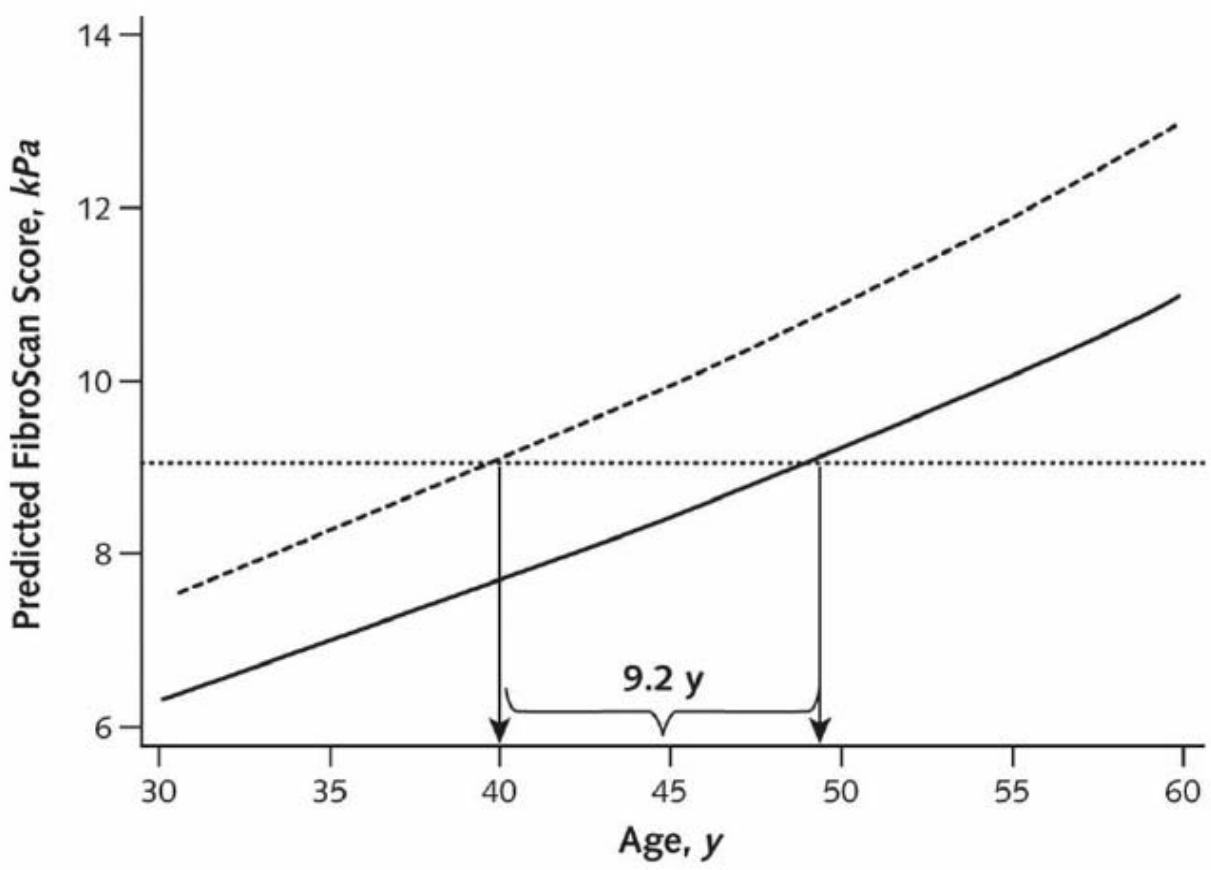
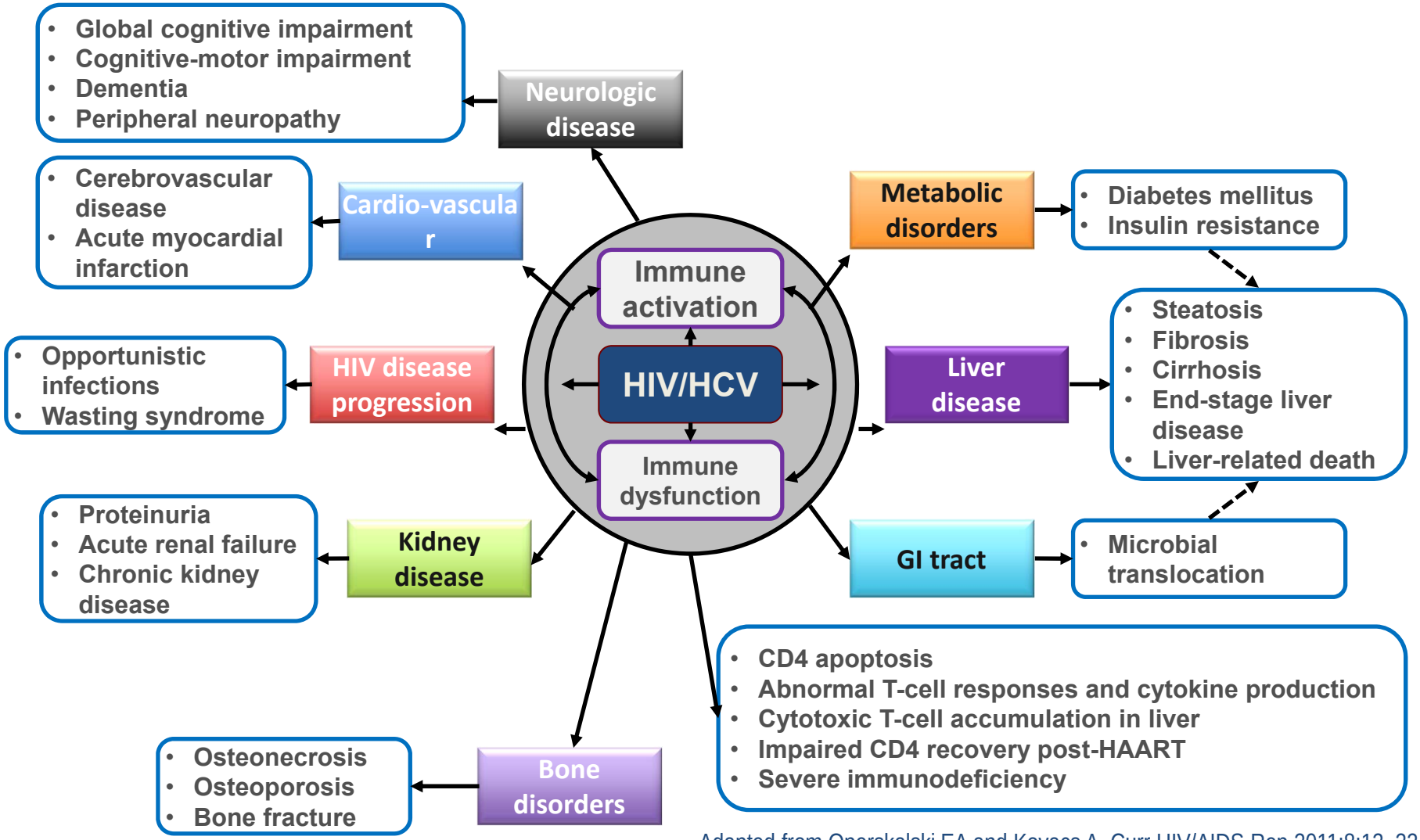


Figure 3. Liver fibrosis and age among persons coinfected with HIV and HCV (dashed line) and those with only HCV (solid line)

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

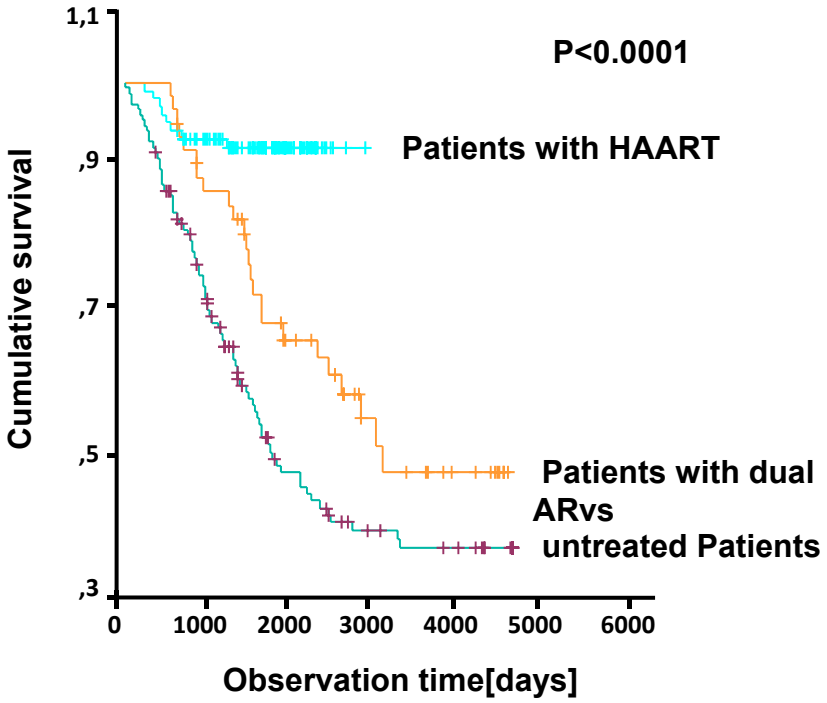
HIV/HCV – a contribution to multiple organ dysfunction



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

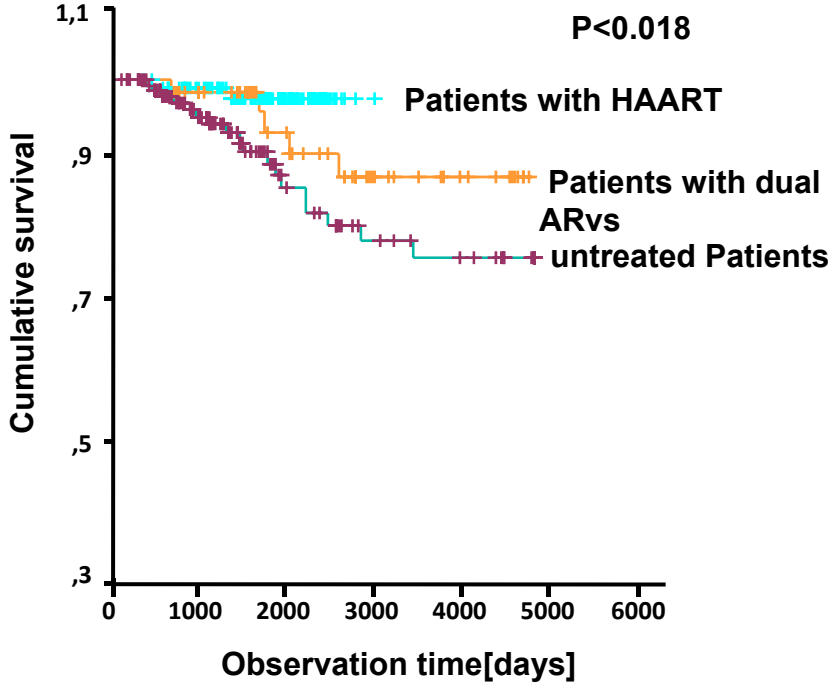
Overall and Liver-related Mortality - effect of HAART

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

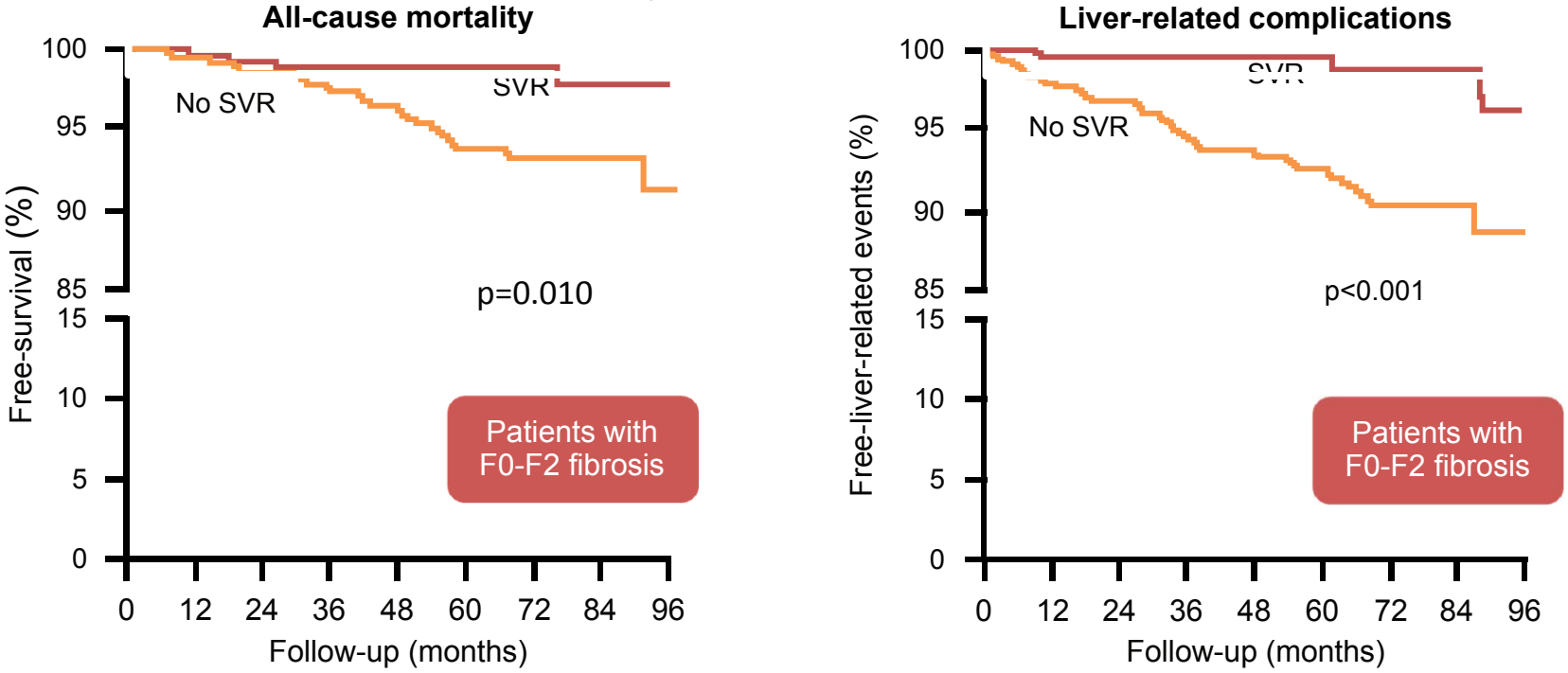


Patients under observation:						
HAART-group:	93	79	33	-	-	-
ART-group:	55	46	30	15	9	1
Untreated-group:	13794	49	37	32	27	

Qurishi N *et al. Lancet*, 2004

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

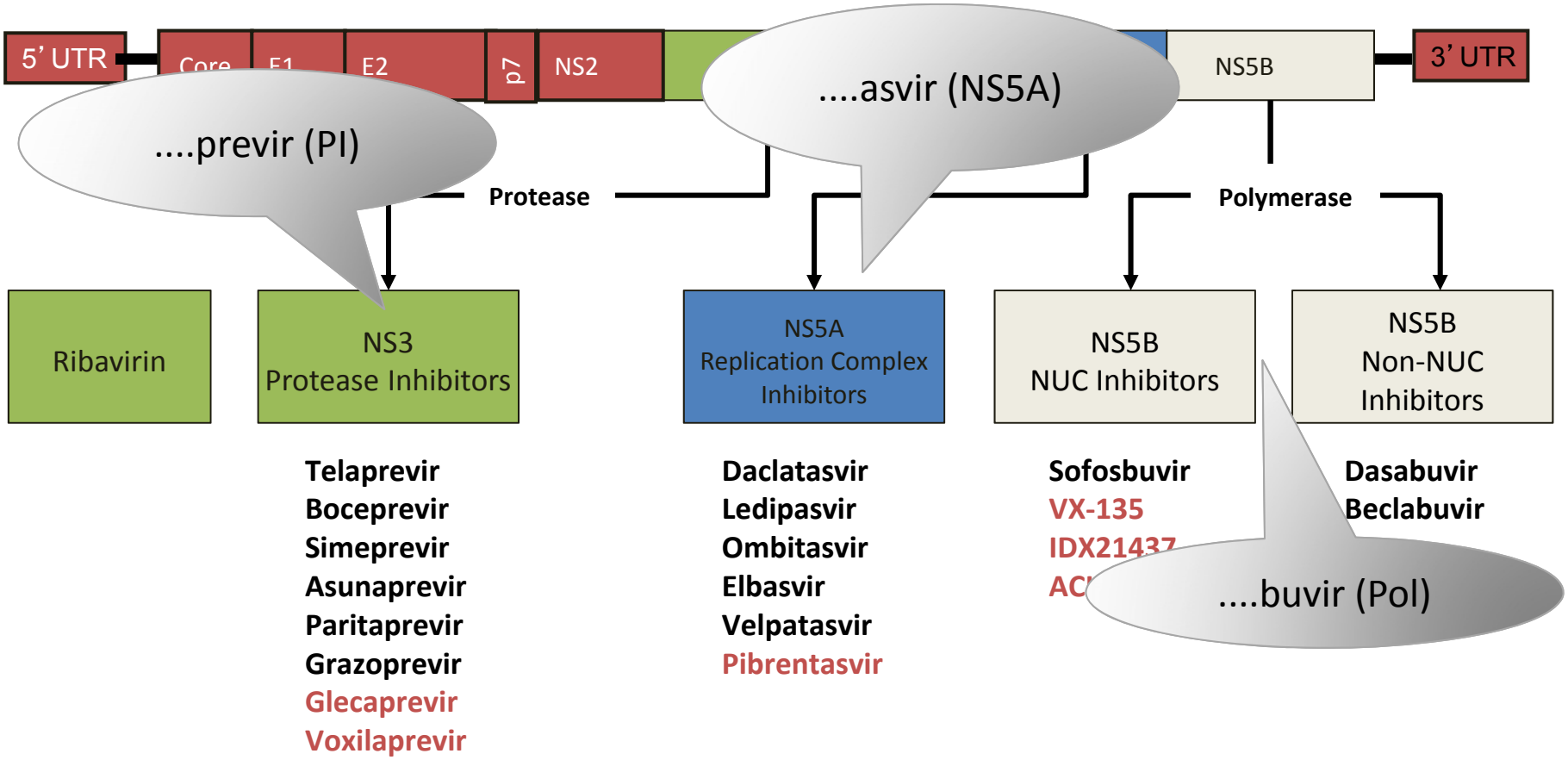
- **A total of 695 HIV/HCV-co-infected patients were treated with IFN/RBV after a median follow-up of 4.9 years. 274 patients achieved an SVR**



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.

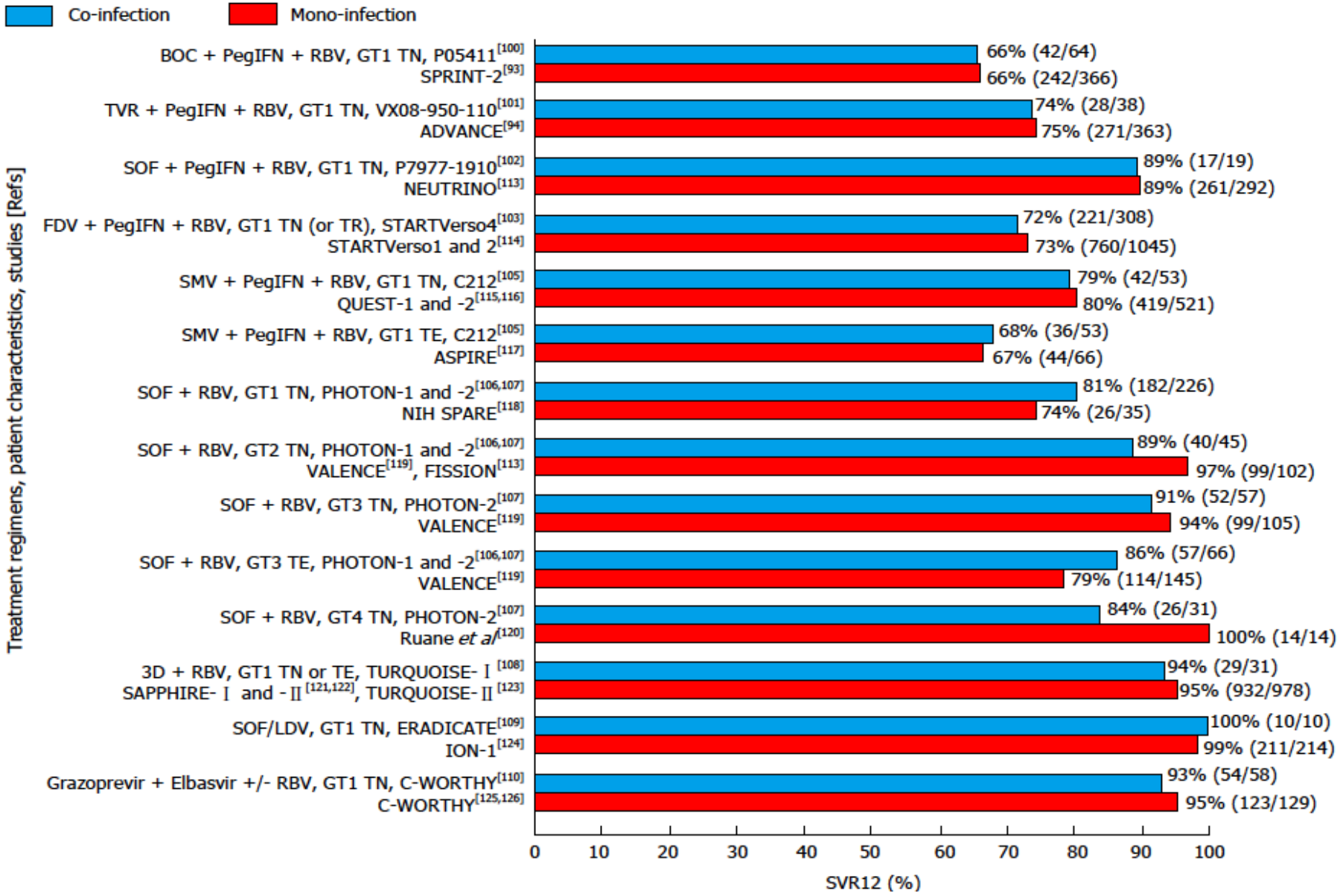
Not All Direct-Acting Antivirals are Created Equal

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/next 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

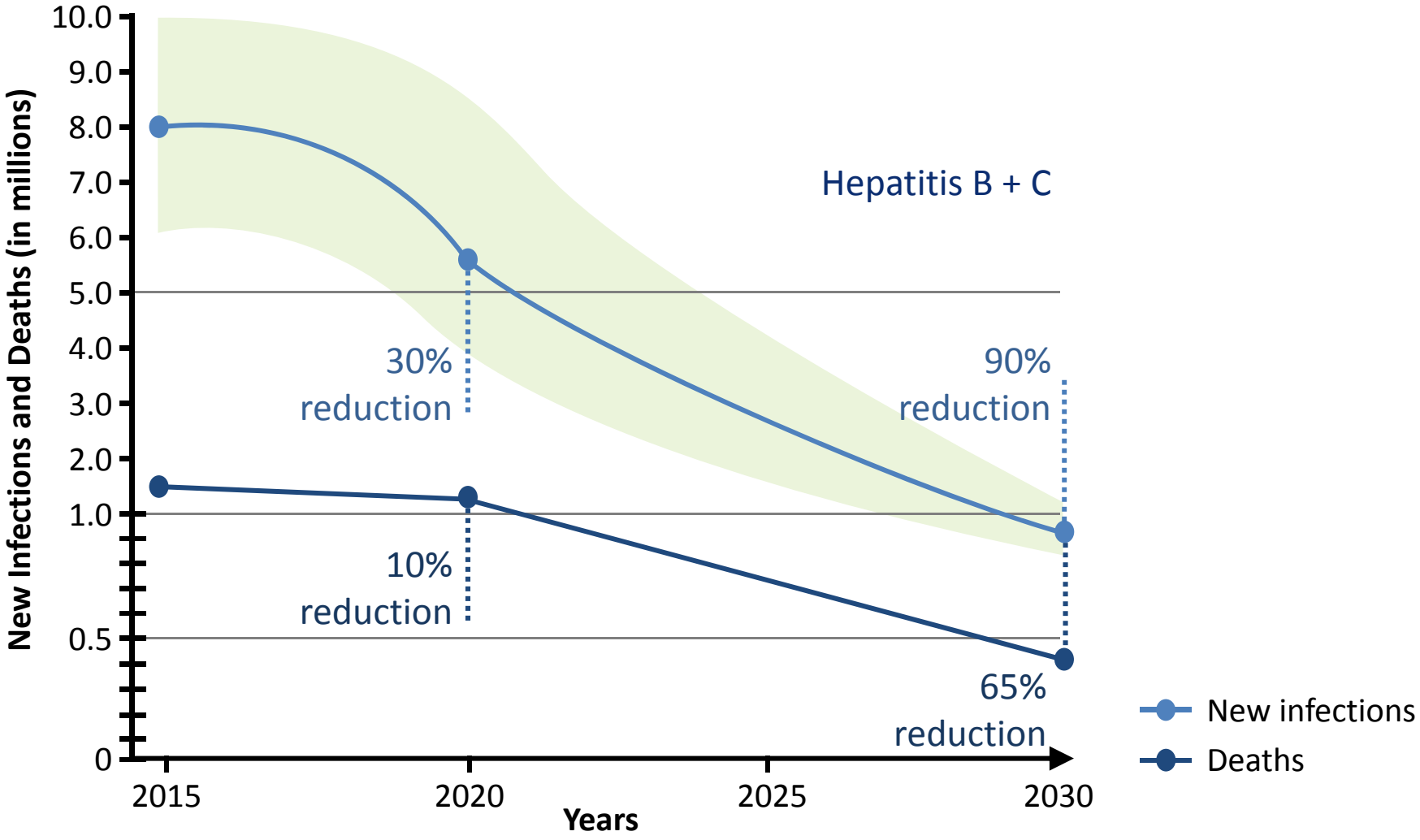
Same treatment regimens can be used in HIV/HCV patients as in patients without HIV infection, as the virological results of therapy are identical (A1)

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				
HCV GT	**Treatment regimen**	**Treatment duration & RBV usage**		
		Non-cirrhotic	**Compensated cirrhotic**	**Decompensated cirrhotics CTP class B/C**
1 & 4	SOF + SMP +/- RBV	GT 4 only: 12 weeks with RBV or 24 weeks without RBV[i]		Not recommended
	SOF/LDV +/- RBV	8 weeks without RBV[ii] or 12 weeks +/- RBV[iii]	12 weeks with RBV[iv]	
	SOF + DCV +/- RBV	12 weeks +/- RBV[iii]	12 weeks with RBV[iv]	
	SOF/VEL	12 weeks		12 weeks with RBV
	SOF/VEL/VOX	8 weeks	Not recommended	
	OBV/PTV/r + DSV	8[v]-12 weeks in GT 1b	12 weeks in GT 1b	Not recommended
	OBV/PTV/r + DSV + RBV	12 weeks in GT 1a	24 weeks in GT 1a	Not recommended
	OBV/PTV/r + RBV	12 weeks in GT 4		Not recommended
	EBR /GZR	12 weeks[vi]		Not recommended
	GLE/PIB	8 weeks	12 weeks	Not recommended
2	SOF + DCV	12 weeks		12 weeks with RBV
	SOF/VEL	12 weeks		12 weeks with RBV
	SOF/VEL/VOX	8 weeks	Not recommended	
	GLE/PIB	8 weeks	12 weeks	Not recommended
3	SOF + DCV +/- RBV	12 weeks +/- RBV[vii] or 24 weeks without RBV	24 weeks with RBV	
	SOF/VEL +/- RBV	12 weeks +/- RBV[vii] or 24 weeks without RBV		24 weeks with RBV
	SOF/VEL/VOX	8 weeks		Not recommended
	GLE/PIB	8 weeks	12 weeks	Not recommended
5 & 6	SOF/LDV +/- RBV	12 weeks +/- RBV or 24 weeks without RBV[i]	12 weeks with RBV[iv]	
	SOF + DCV +/- RBV	12 weeks +/- RBV or 24 weeks without RBV[i]	12 weeks with RBV[iv]	
	SOF/VEL	12 weeks		12 weeks with RBV
	SOF/VEL/VOX	8 weeks	Not recommended	
	GLE/PIB	8 weeks	12 weeks	Not recommended

WHO Vision: Reduction in HCV-related Deaths and New Infections by 2030



WHO Global Health sector strategy on viral hepatitis 2016–2021.
Available at: http://www.who.int/hepatitis/strategy2016-2021/ghss-hep/en/ (accessed April 2017).

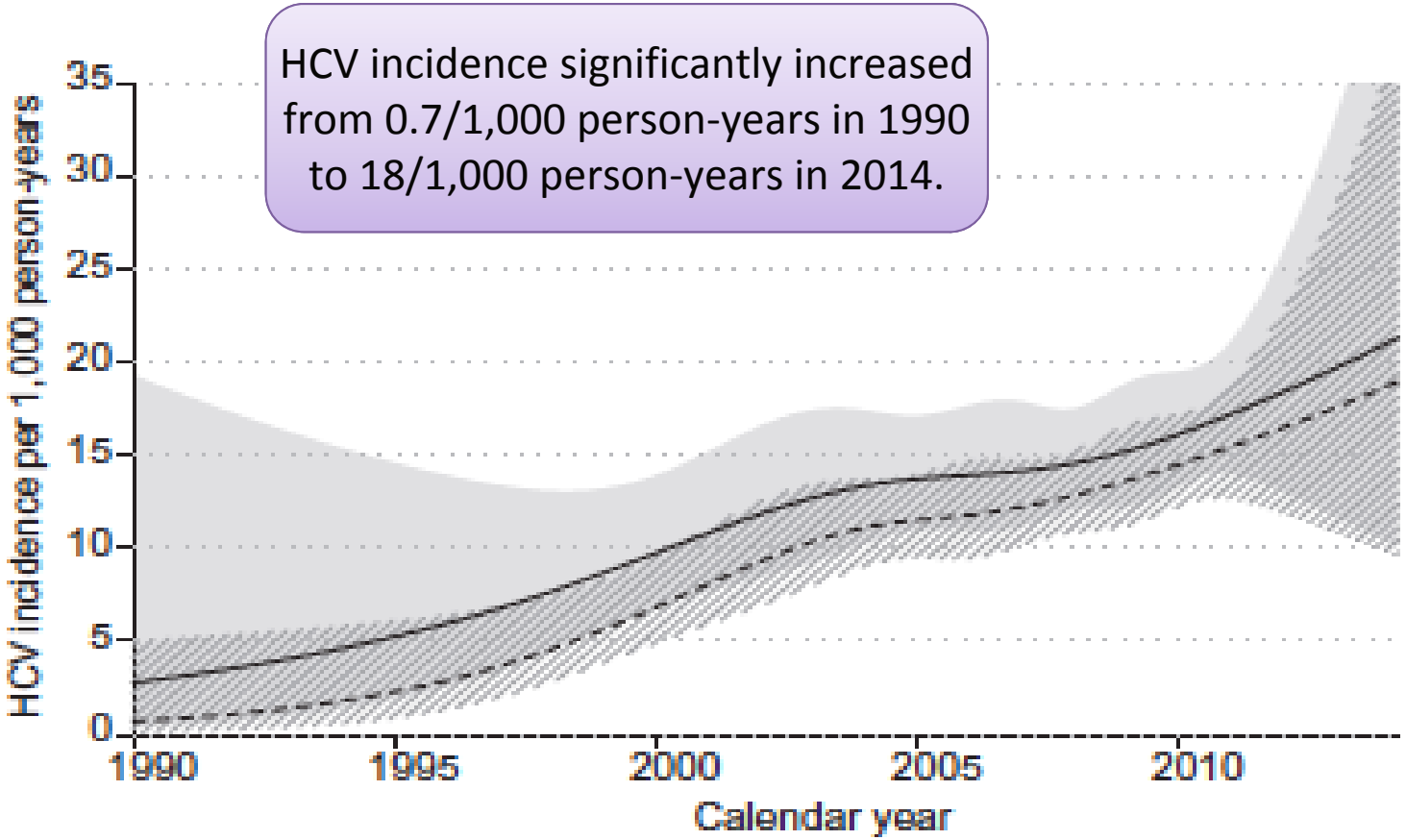
Control? Elimination? Eradication? Extinction?

Term	Definition	Continued intervention measures required?
Control	The reduction of disease incidence, prevalence, morbidity or mortality to a locally acceptable level as a result of deliberate efforts	Yes
Elimination	Reduction to zero of the incidence of a specified disease in *a defined geographical area* as a result of deliberate efforts	Yes
Eradication	Permanent reduction to zero of the *worldwide* incidence of infection caused by a specific agent as a result of deliberate efforts	No
Extinction	The specific infectious agent no longer exists in nature or in the laboratory	No

MMWR December 31, 1999;48(SU01):23–7;
Dowdle WR. Vaccine 2011;29:D70–3

There Is An Increasing Incidence of HCV Infection in MSM

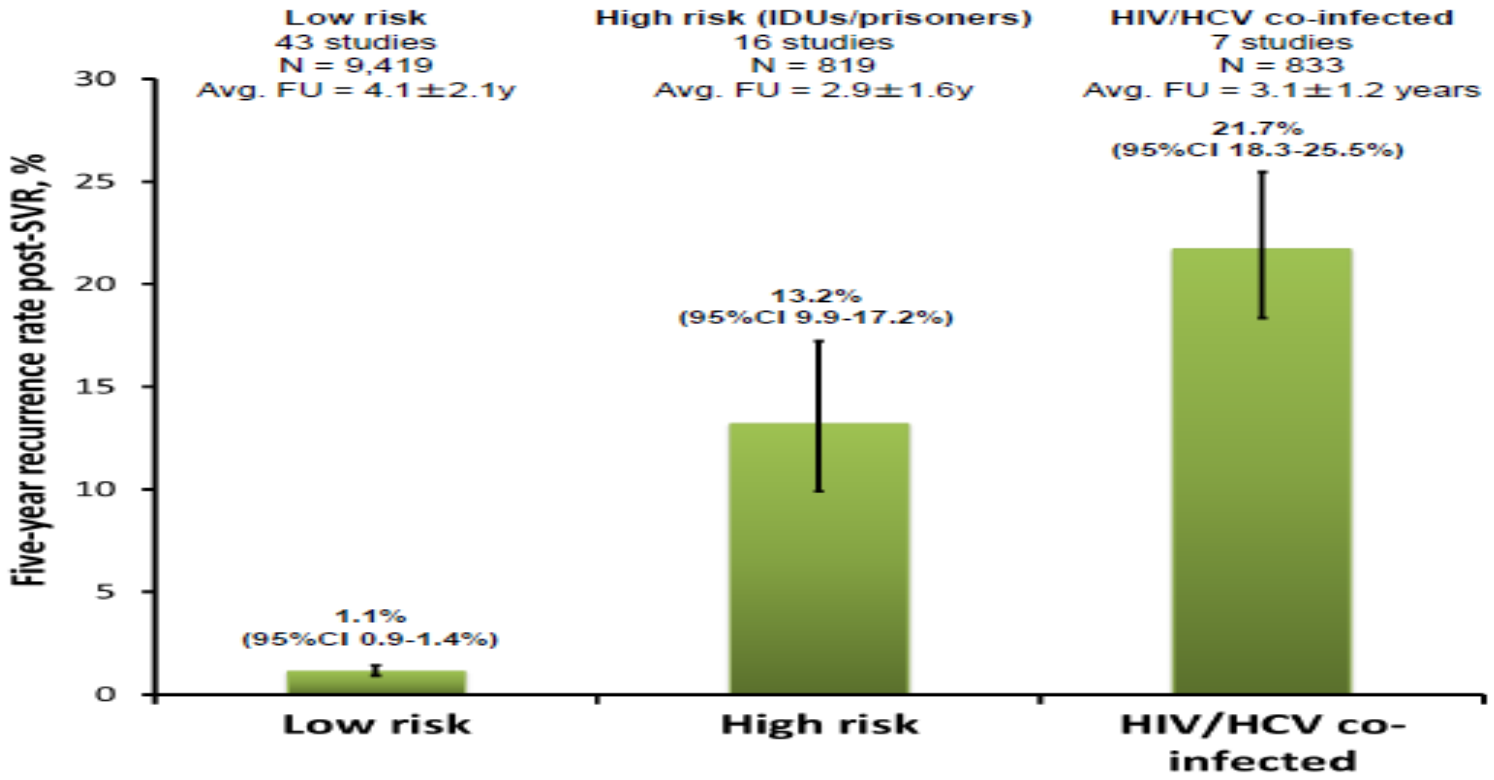
HCV incidence was measured among 5,941 HIV-positive MSM from the CASCADE Collaboration (1990–2014)



- MSM, men who have sex with men
- Katinka van Santan D, *et al. J Hepatol.* 2017 Epub ahead of print.

The Risk of HCV Recurrence is High in HIV/HCV Co-Infected Patients Compared to Mono-Infected Individuals

Meta-analysis of 66 studies in 11,071 patients, to determine the 5-year rate of HCV recurrence (late relapse/re-infection) post-SVR

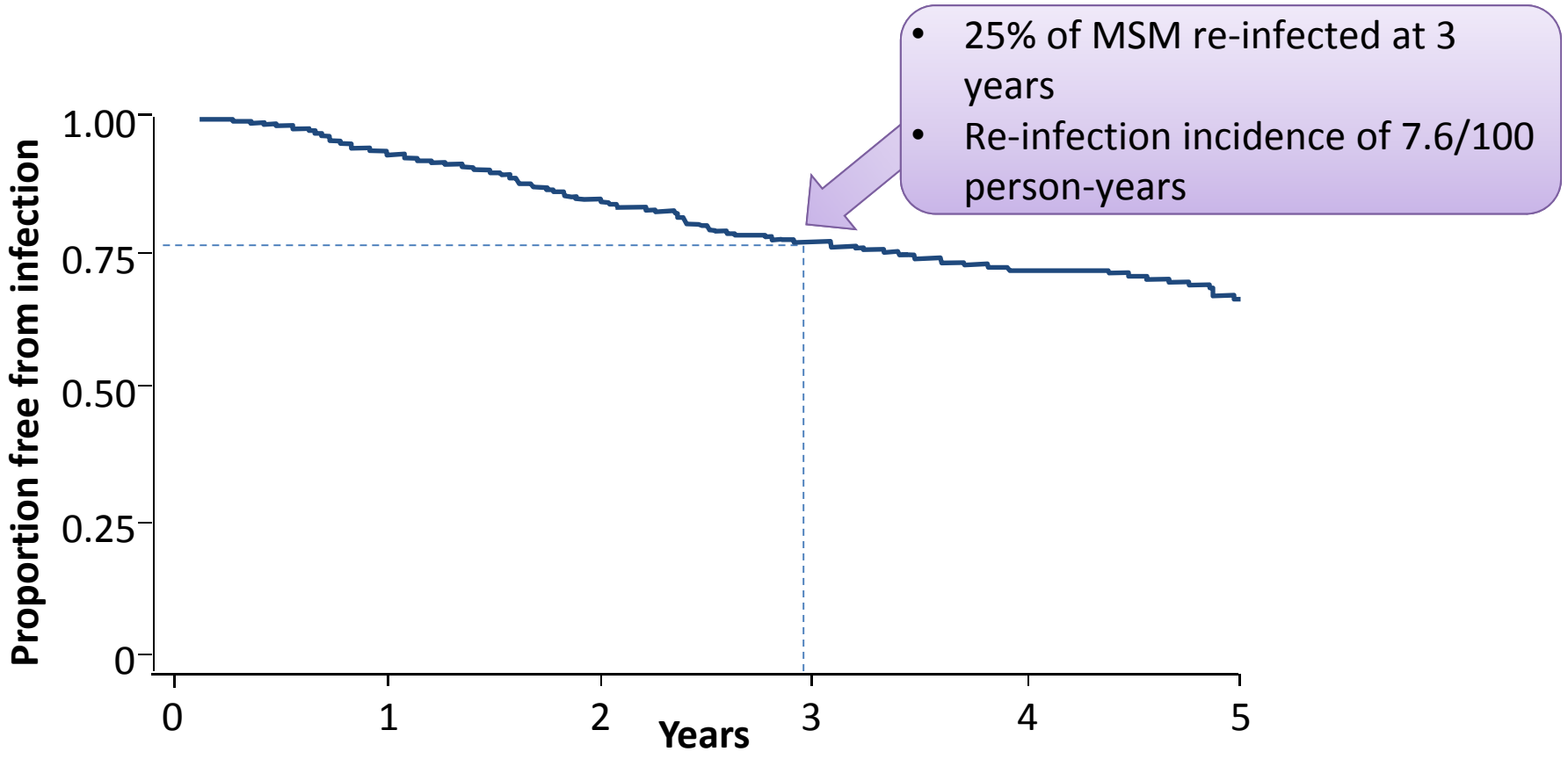


The large differences in event rates by risk group suggest that re-infection is significantly more common than late relapse

Hill A et al. CROI 2015. Seattle, WA. #654

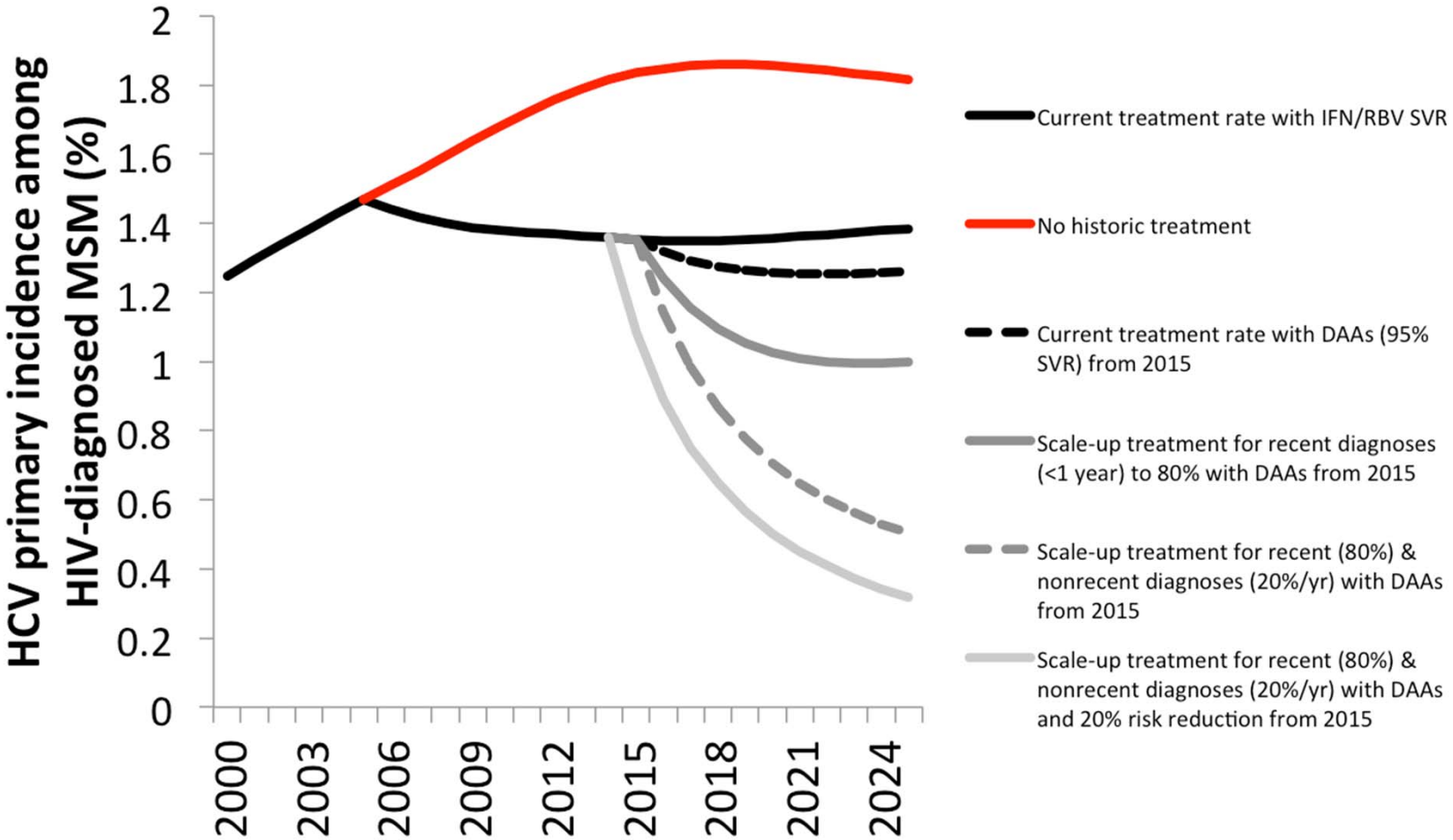
High Risk of HCV Re-Infection in HIV-positive MSM in Western Europe

Data from the European AIDS Treatment Network (NEAT) consortium centres in Western Europe (UK, Germany, Austria and France)



Martin TC, et al. J Hepatology 2016; 64: S138–139.

Treatment As Prevention in HIV/HCV



N Martin, et al, CID 2015

Treatment of acute HCV infection for elimination in those with HIV – the Netherlands example

2014

A-HCV **n = 93**

Genotype 1= 75 (81%)

Genotype 4= 18 (19%)

PYFU n = 8290

11.2/1000 PYFU
(95% CI 9-14)

1.1% per year

2016

A-HCV **n = 49**

Genotype 1= 34 (69%)

Genotype 4= 15 (31%)

PYFU n = 8961

5.5/1000 PYFU
(95% CI 4–7)

0,55% per year

Rijnders B, et al. CROI 2017; abstract # 137LB

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
  - Future strategies for HBV ‘cure’
- 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 in order to ‘eliminate’ HCV