

Liver Disease in HIV

Sanjay Bhagani

Royal Free Hospital/UCL
London

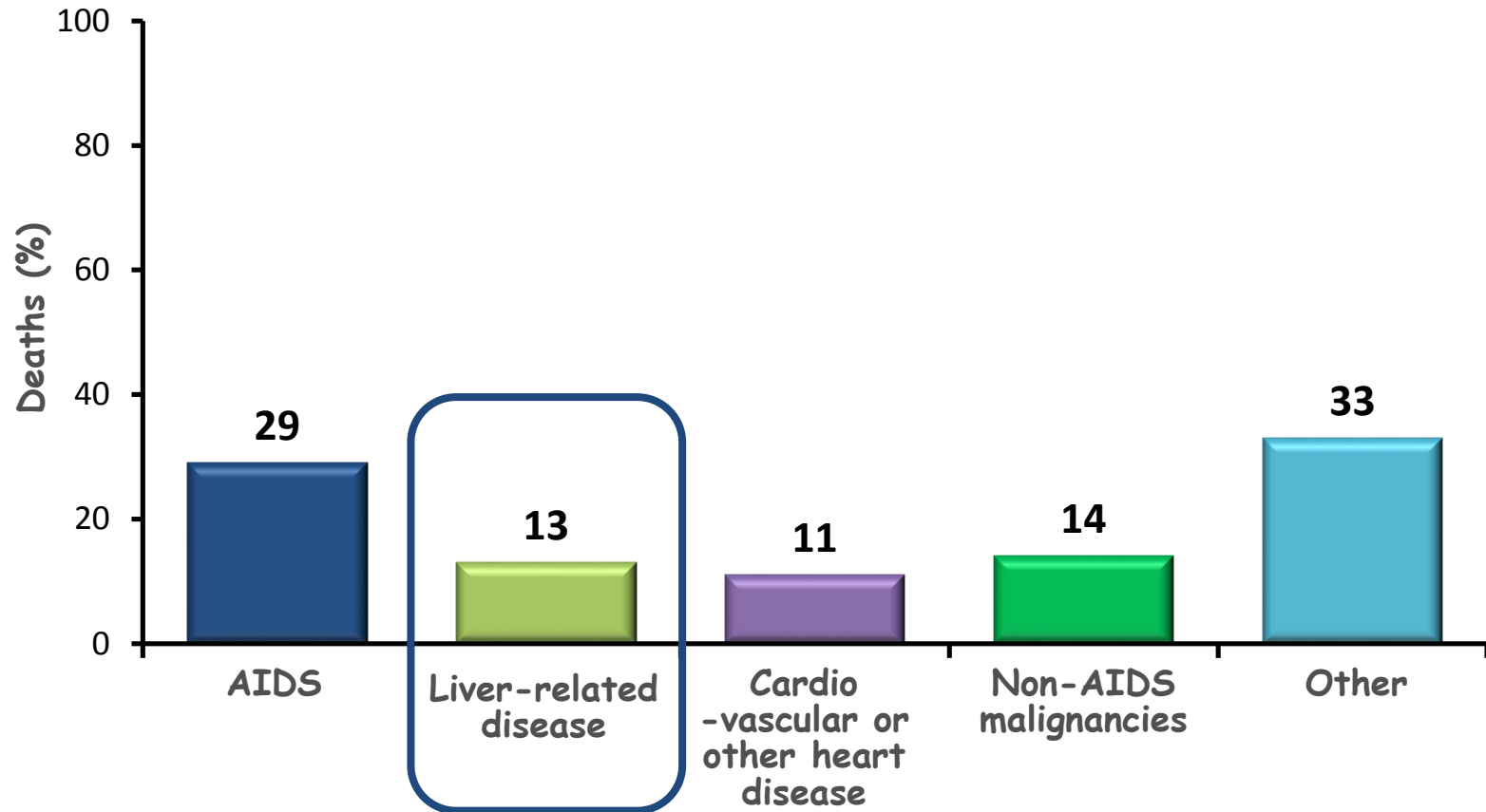
Outline

- Importance of liver disease in HIV
- Drug-induced liver disease
- HBV
- HCV

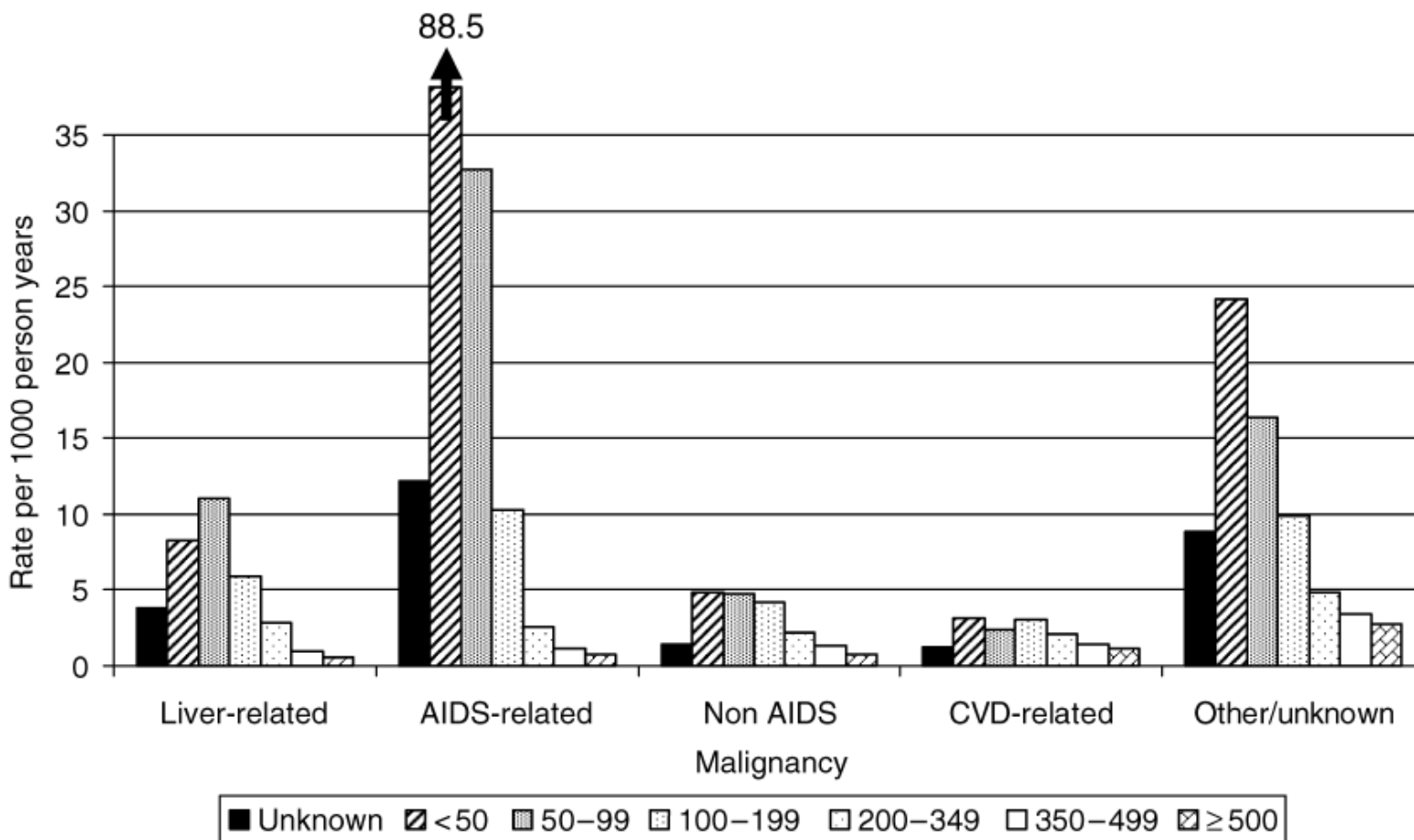
- Case-based discussion (Thursday pm)

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

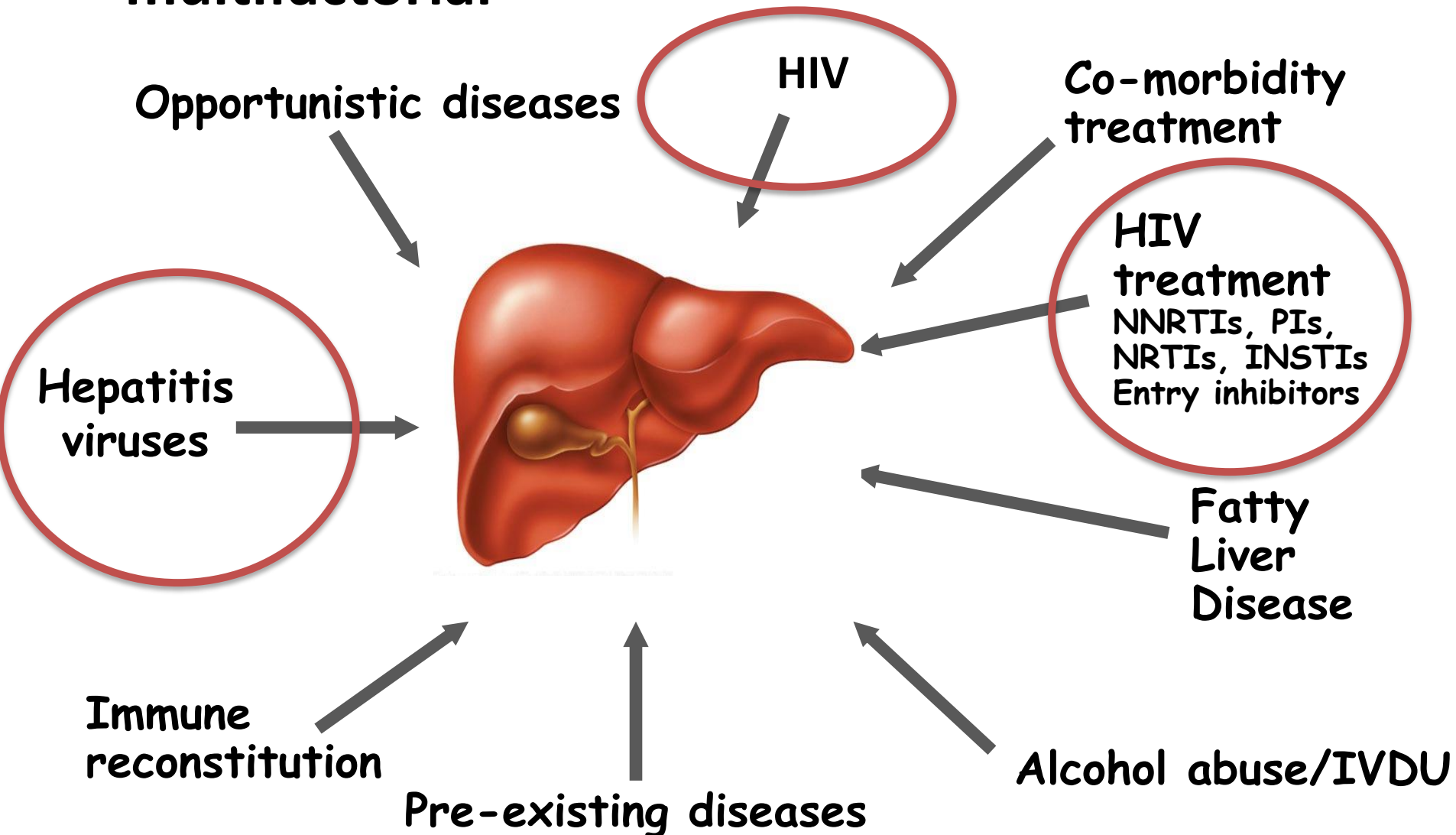
D:A:D Study: Causes of death in n=49,734 HIV-infected patients followed 1999–2011



Liver-related death and CD4 count

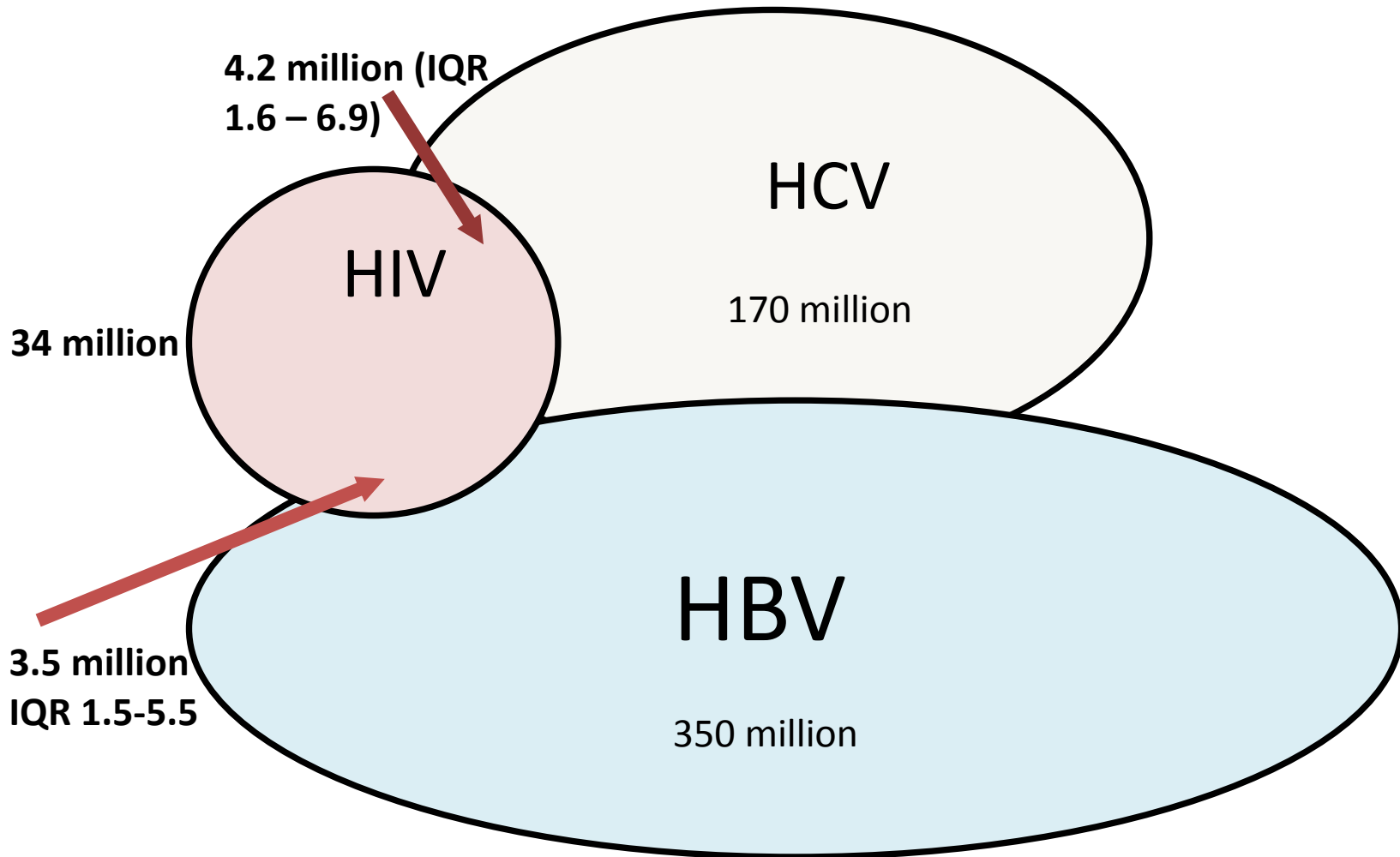


Liver Disease in HIV-infected Patients - multifactorial

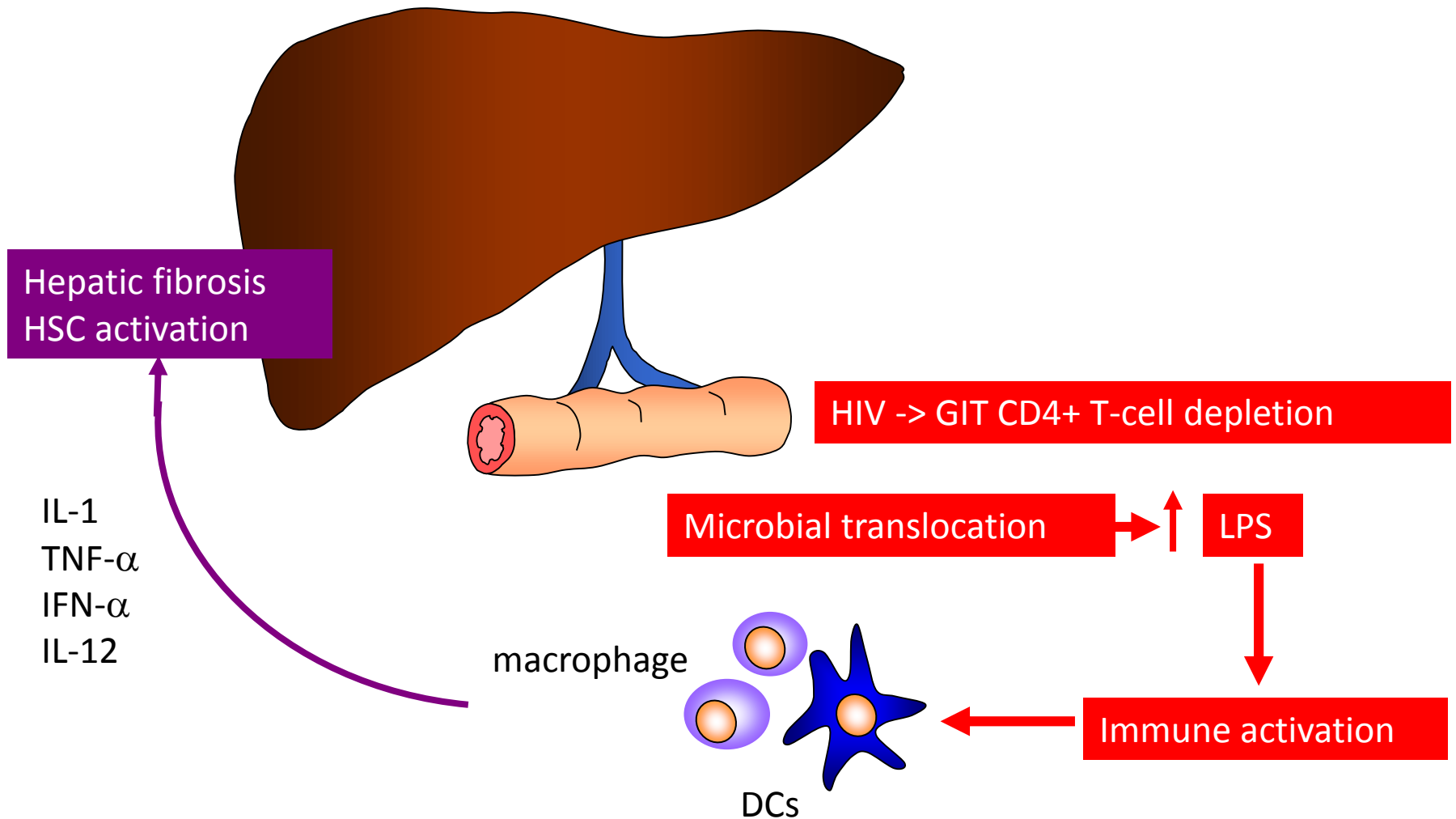


Sulkowski M. *et al.* Ann Intern Med. 2003;138:197-207 Guaraldi G *et al.* Clin Infect Dis 2008 47(2): 250-257
Greub G *et al.* Lancet 2000;356:1800-1805

Overlapping epidemics – co-infections



HIV-associated Immune activation and liver disease



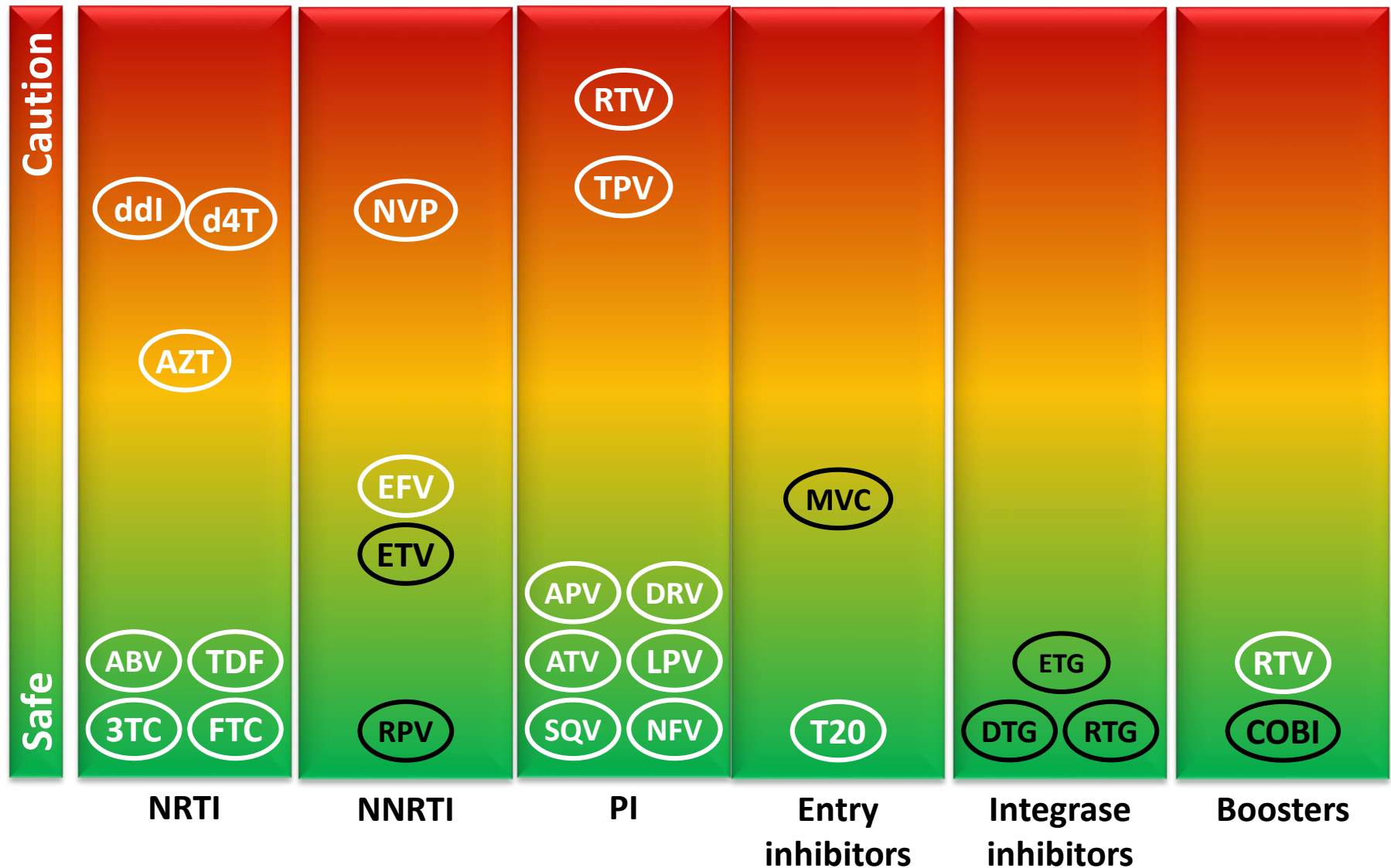
START liver fibrosis study (2014)

- 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

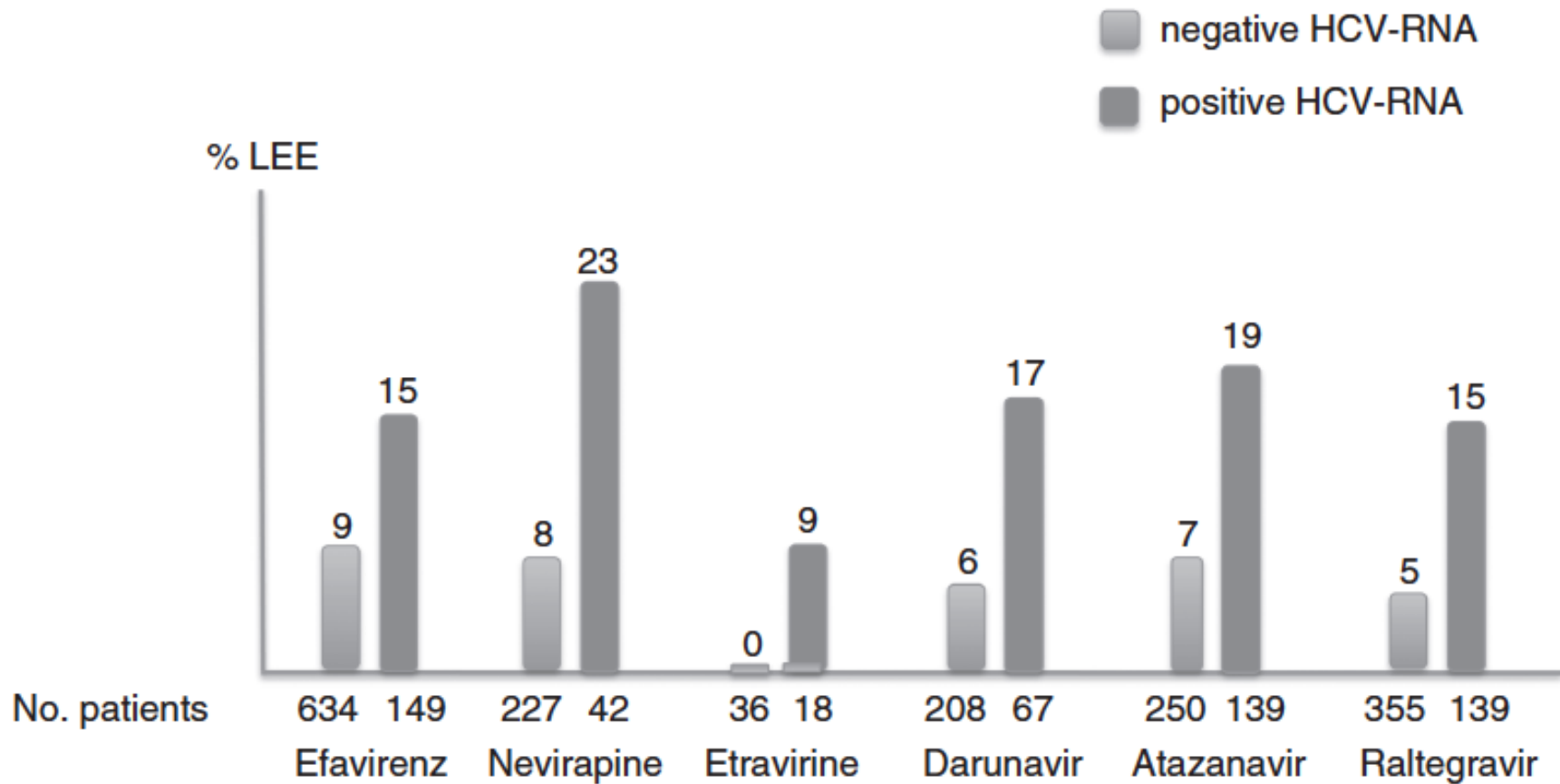
Mechanisms of drug-related liver injury in HIV-infected patients

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 reconstitution	Chronic Hepatitis B Chronic HCV? Within first few months More common if low CD4 count/large rise

Hepatic Safety Profile of ARVs



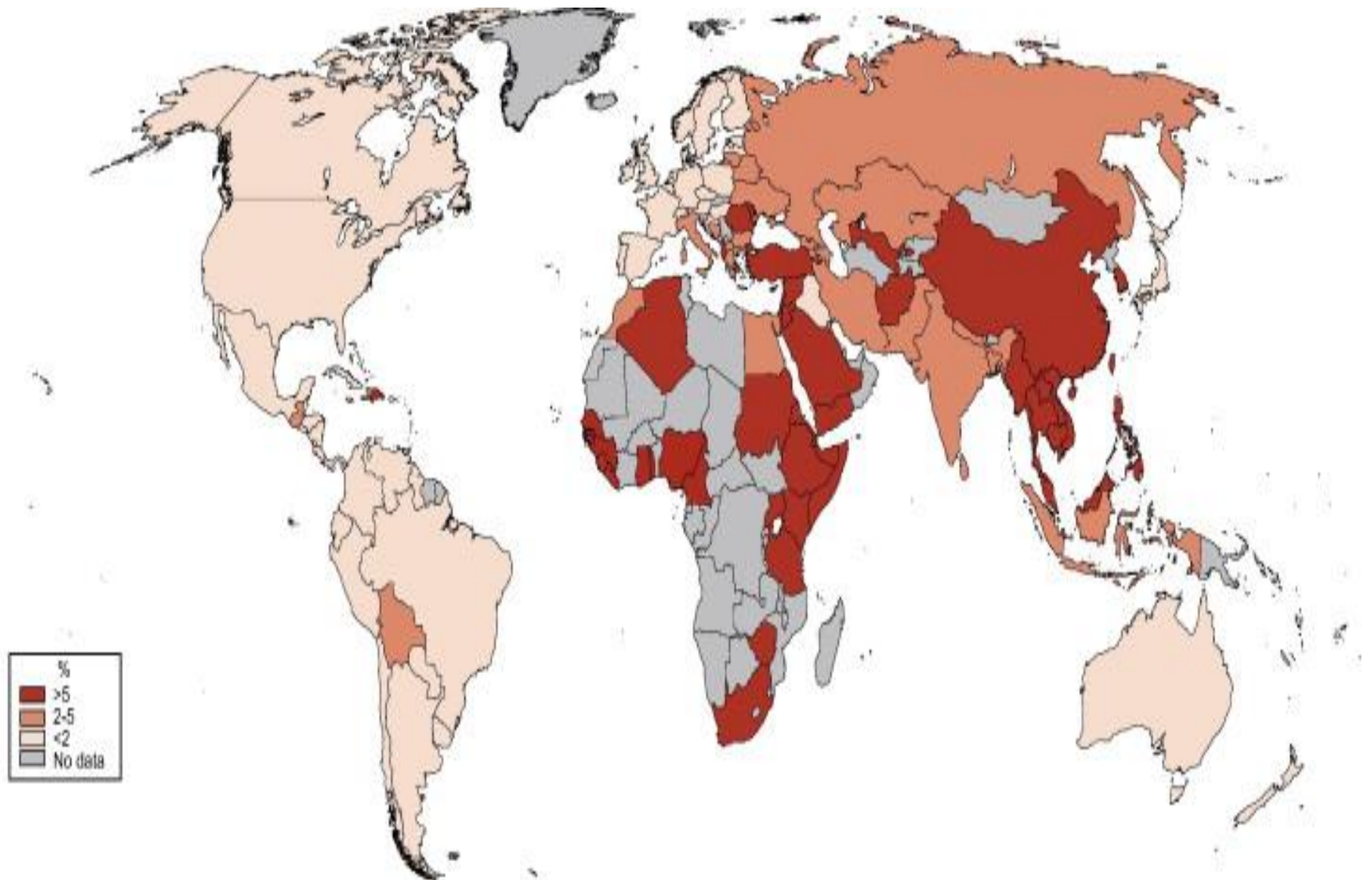
Hepatotoxicity of modern ARVs



Hepatotoxicity in HBV and HCV co-infected patients - mechanisms

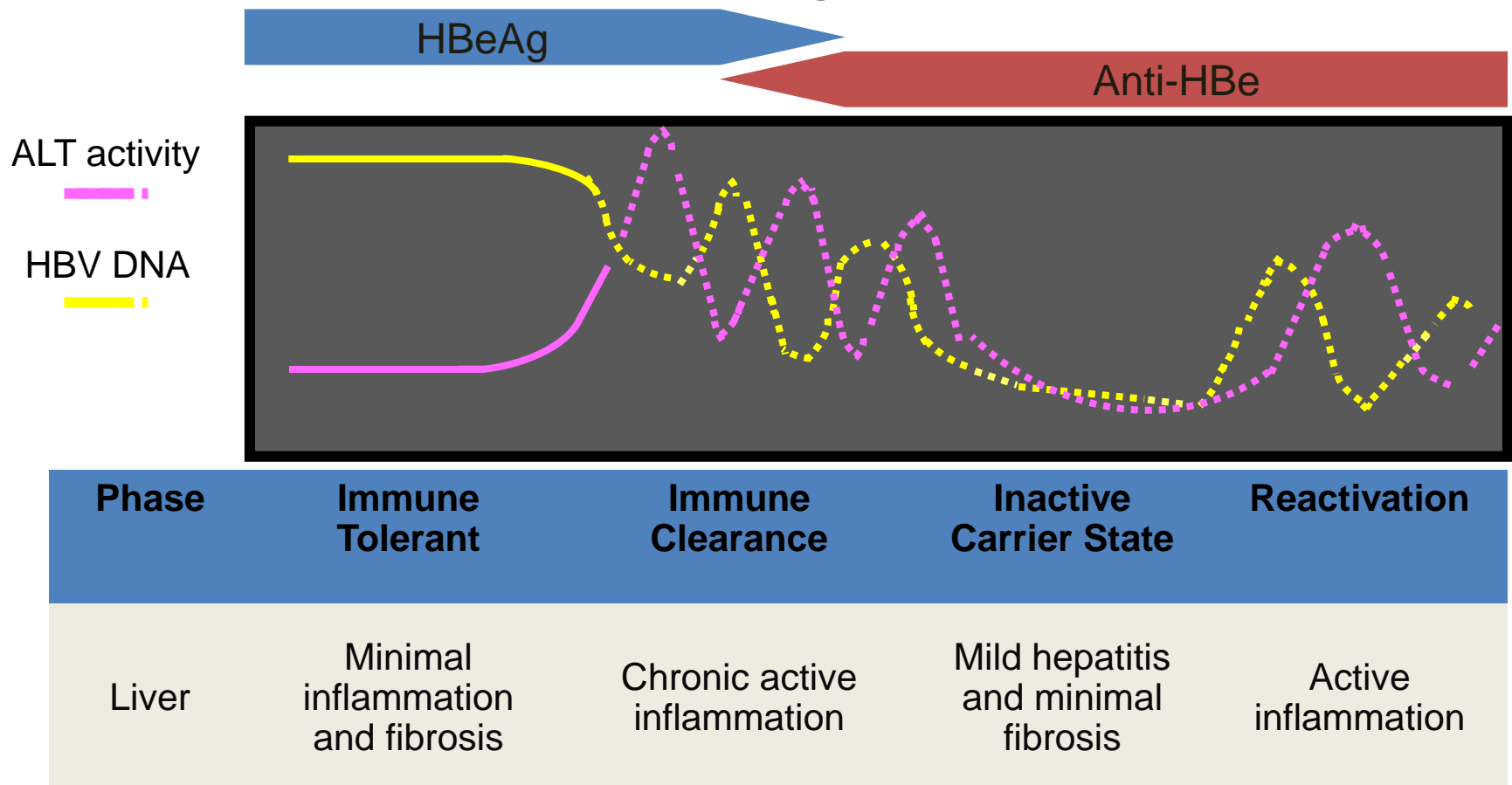
- Immune restoration - increase in CTL activity
- Direct hepatotoxicity – increased susceptibility of viral infected hepatocytes to metabolites
- Altered cytokine milieu in the presence of viral hepatitis
 - Increased risk of liver inflammation
 - Down-regulation of Cyp450 mediated drug metabolism with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

Global HBV



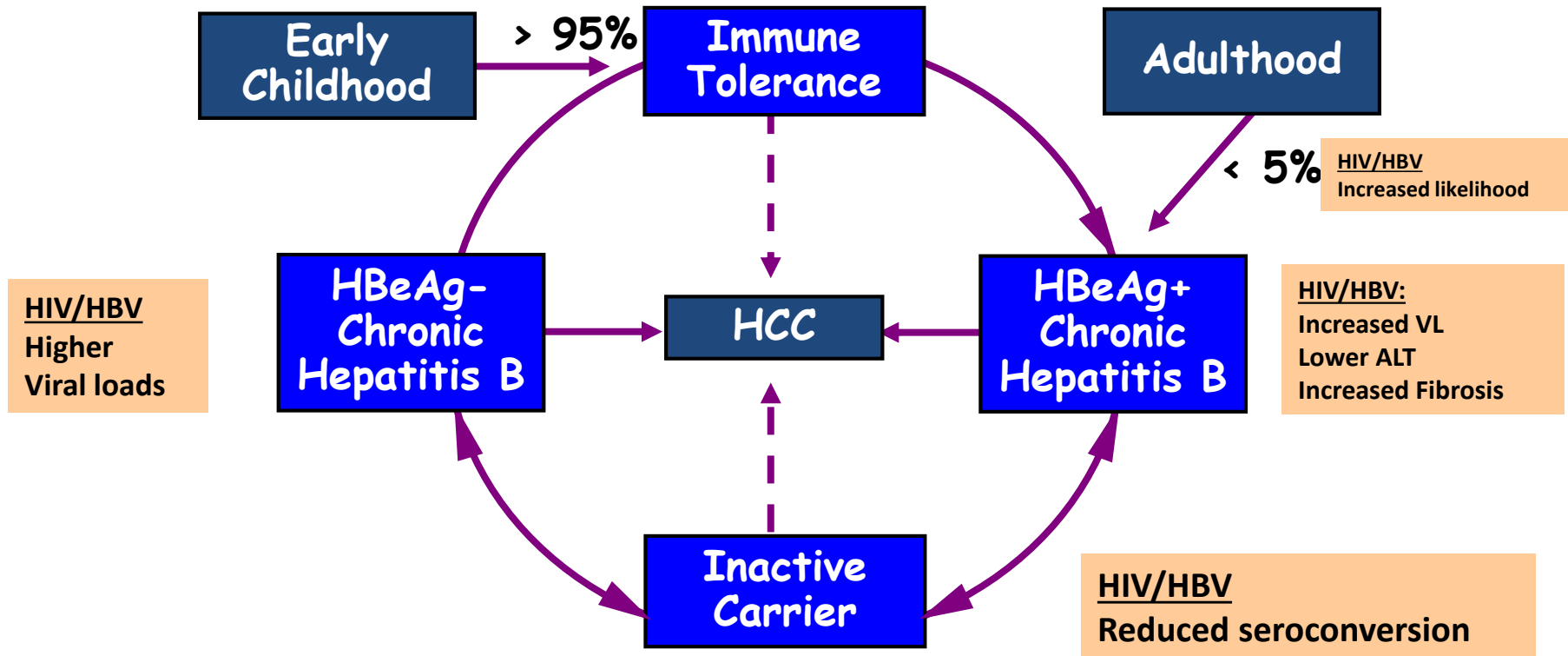
4 Phases of Chronic HBV Infection

Current Understanding of HBV Infection



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. Copyright © 1999–2012 John Wiley & Sons, Inc. All Rights Reserved.

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

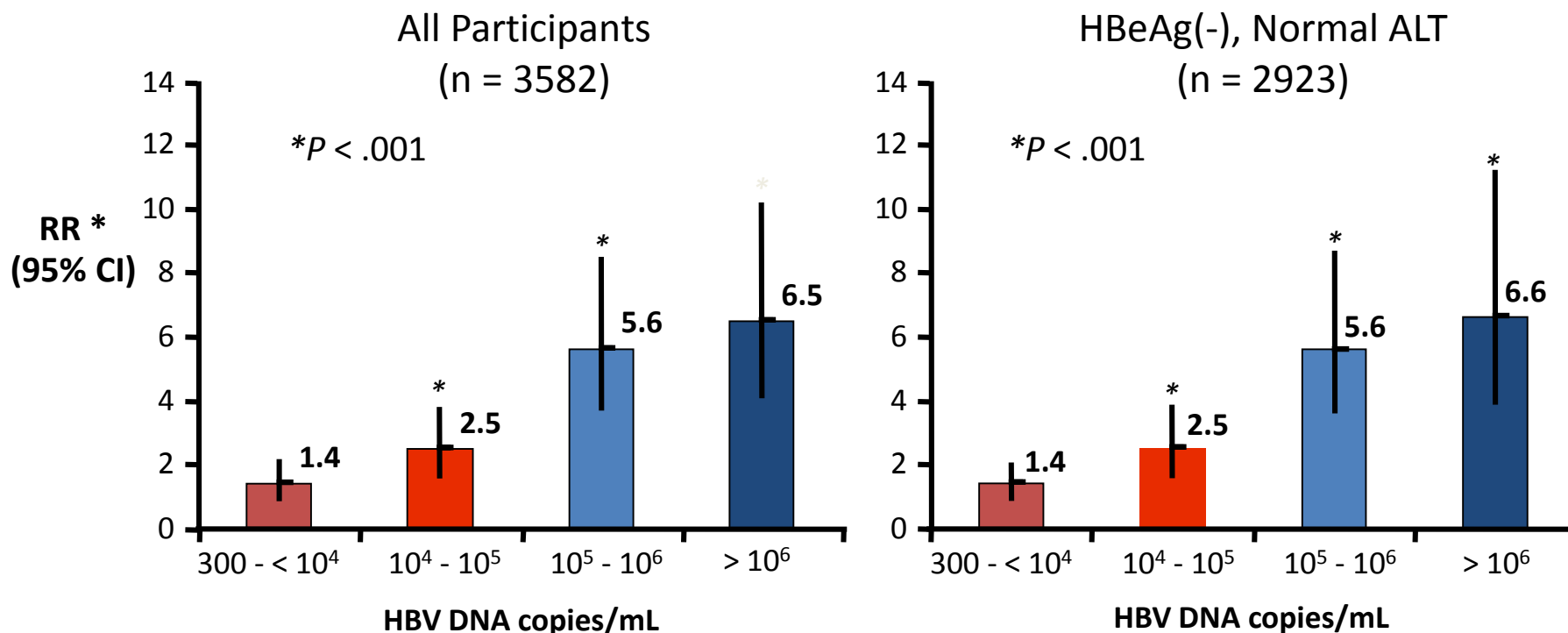


When do we need to Rx HBV?

- 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



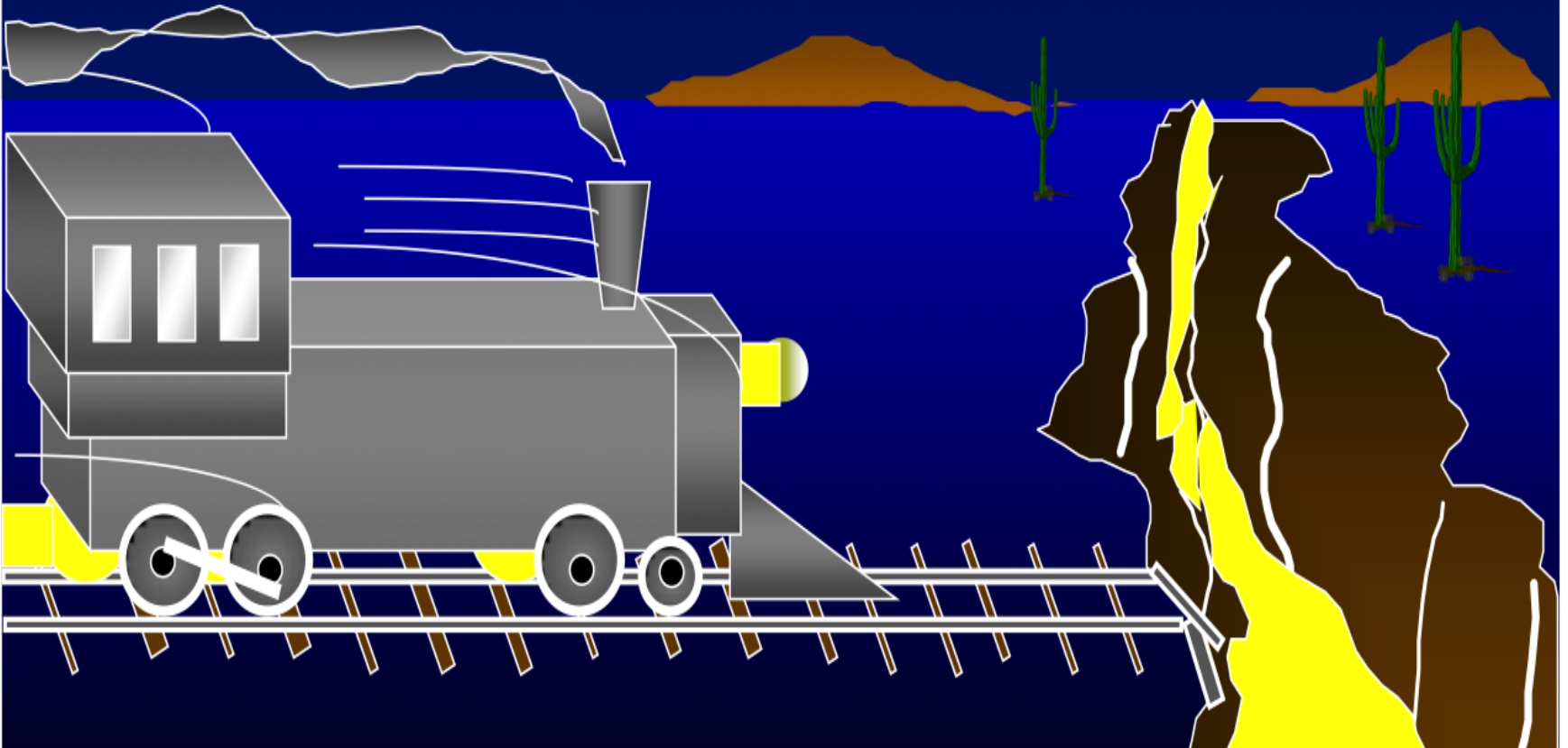
* Adjusted for age, sex, cigarette smoking, and alcohol consumption.

HBV-DNA viral load (> 10⁴ cp/ml) strongest predictor of progression to cirrhosis independent of ALT and HBeAg status

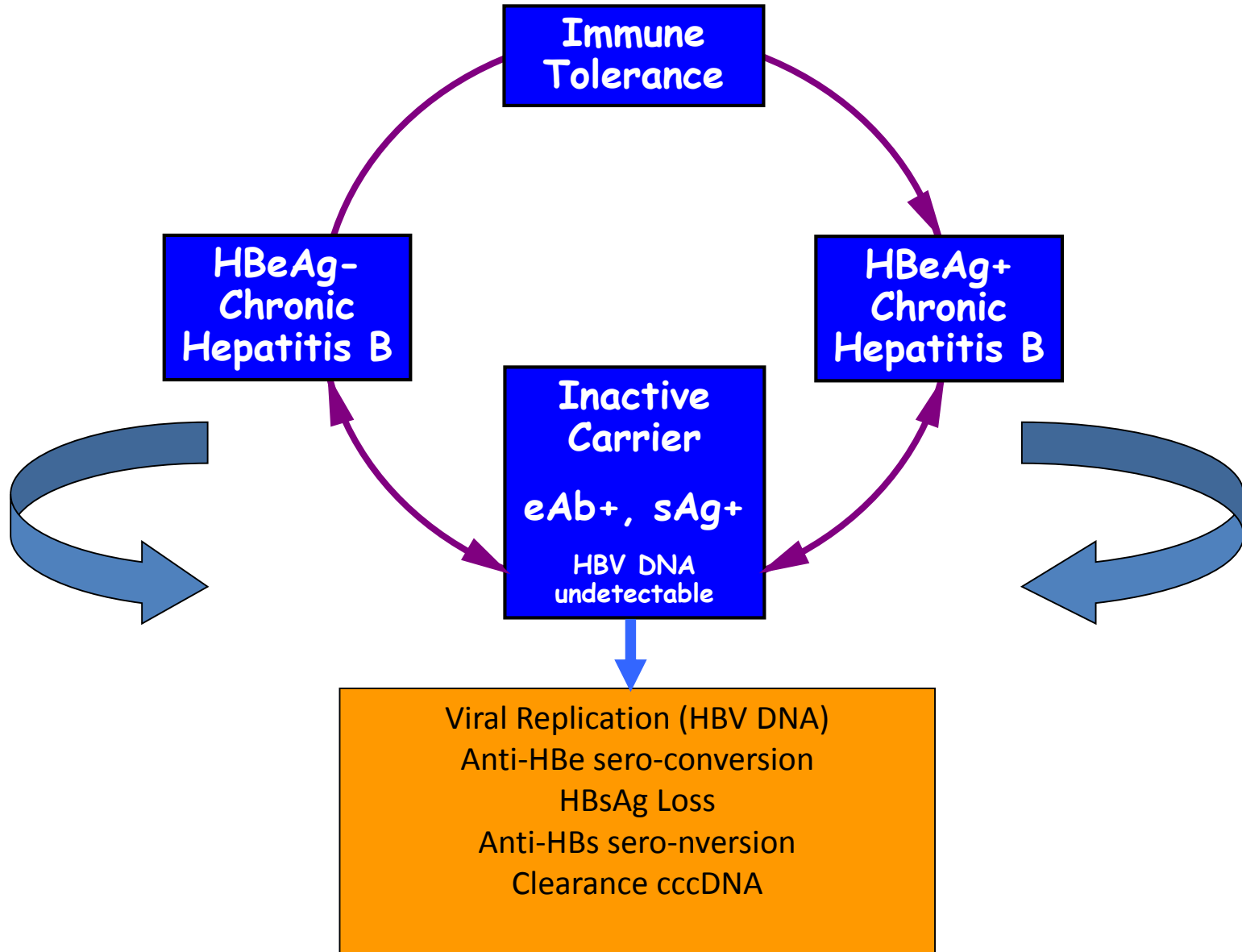
HBV DNA and immune response = engine

ALT/Histological Activity Index (inflammation) = train speed

Fibrosis stage = distance from canyon



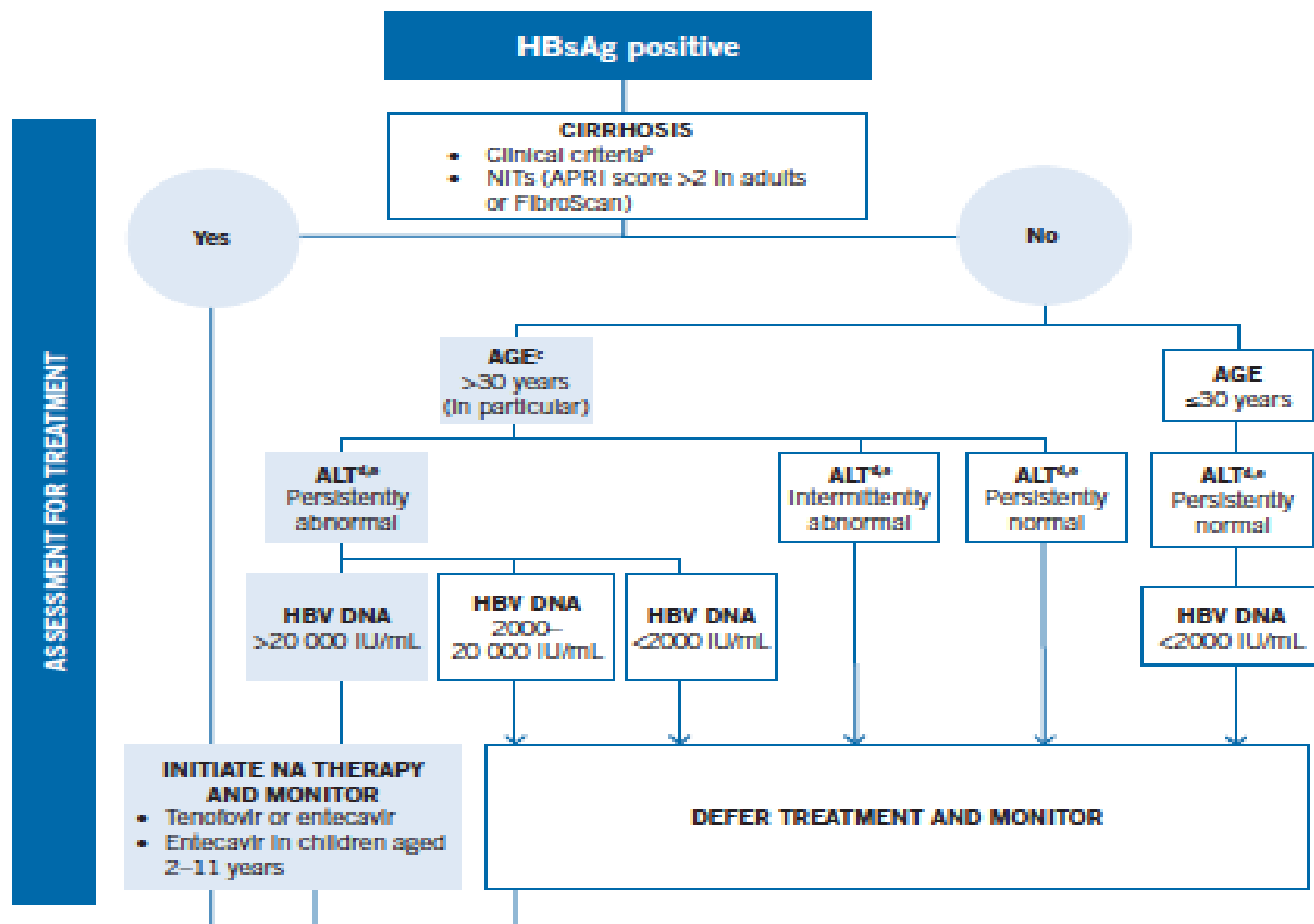
What does Rx aim to achieve?



Three key inter-linked factors in the decision to treat

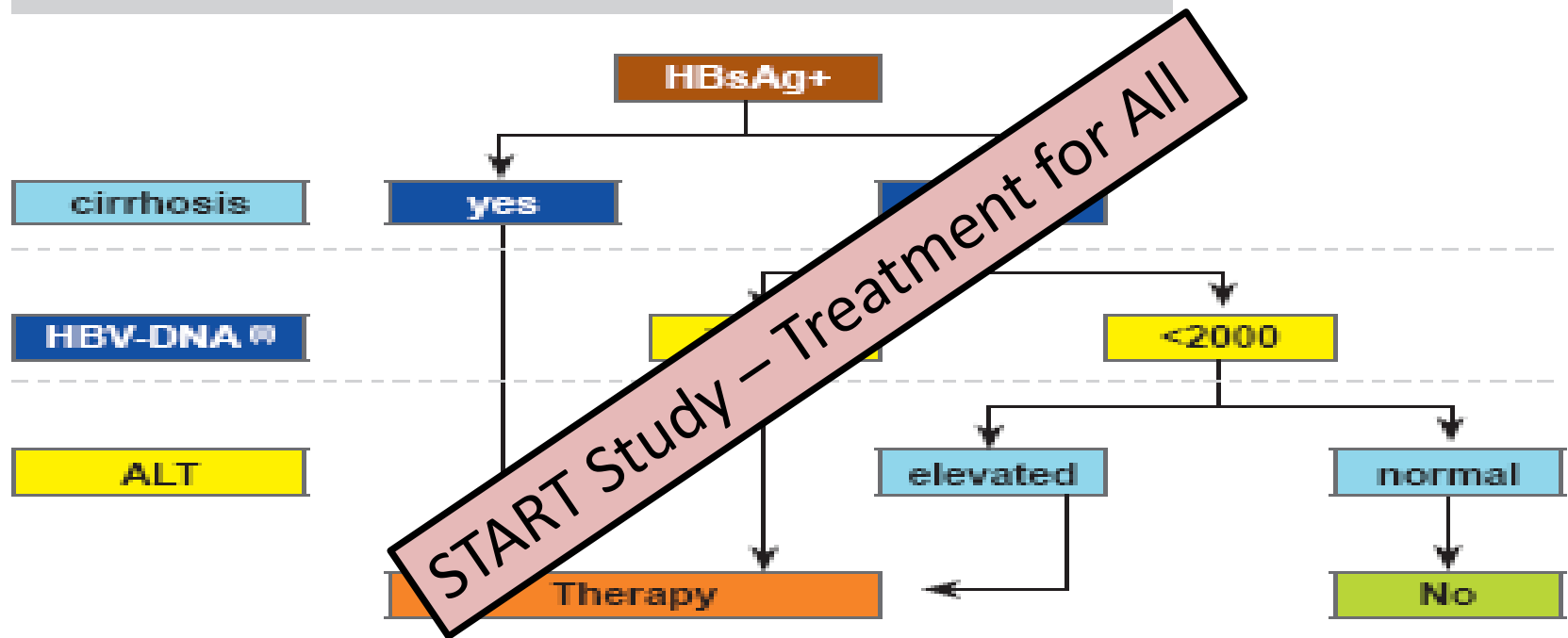
- Age
 - <30yrs vs. >30yrs
 - FH of HCC
- Level of fibrosis/inflammation
 - Cirrhosis
 - F2+ fibrosis
 - Abnormal liver enzymes
- HBV DNA levels
 - >20 000 IU/ml

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



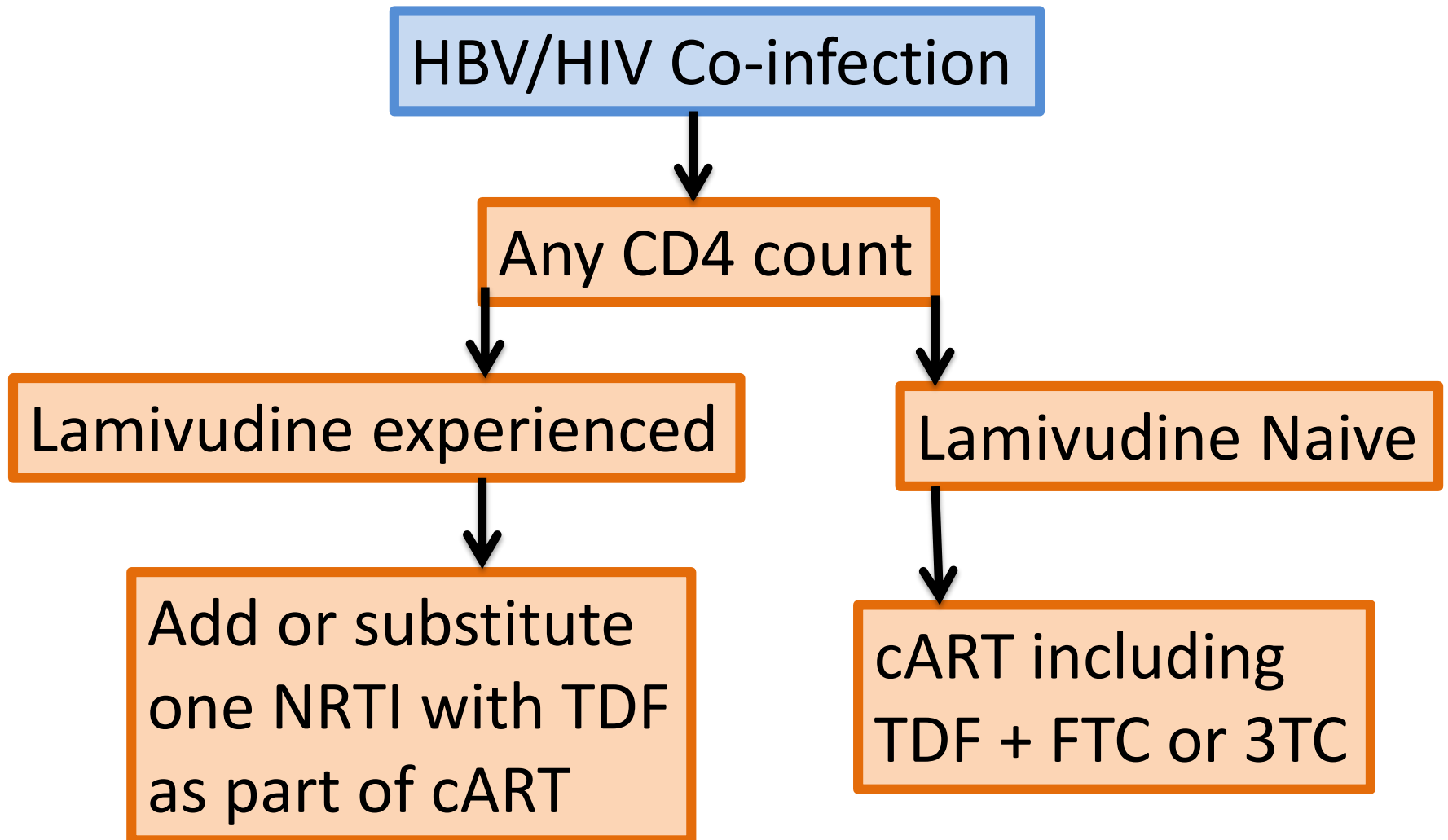
EACS Guidelines 2014 – HBV in HIV+

Assessment of treatment indication for HBV infection in HIV-positive individuals

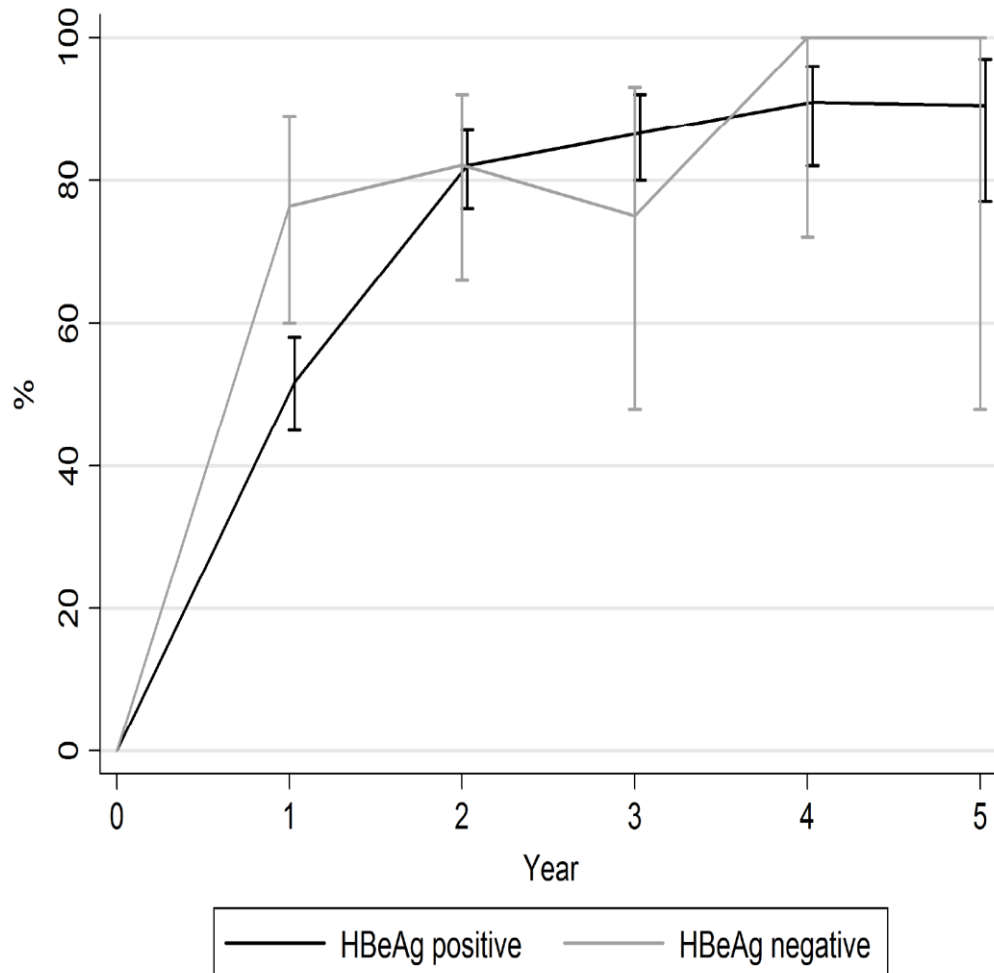


Note: In patients with significant liver fibrosis (F2-F3), anti-HBV treatment might be considered even when serum HBV-DNA is below 2000 IU/mL and liver enzymes are not elevated.

New Guidelines 2015



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

Lack of access to routine testing and monitoring

World Hepatitis Alliance/WHO global survey 2009:

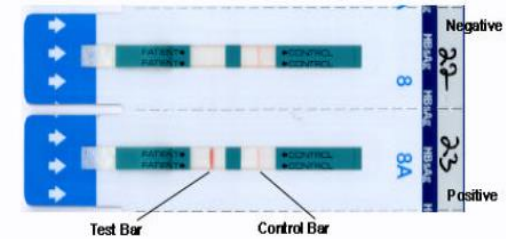
Testing for HBV and/or HCV

- >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%

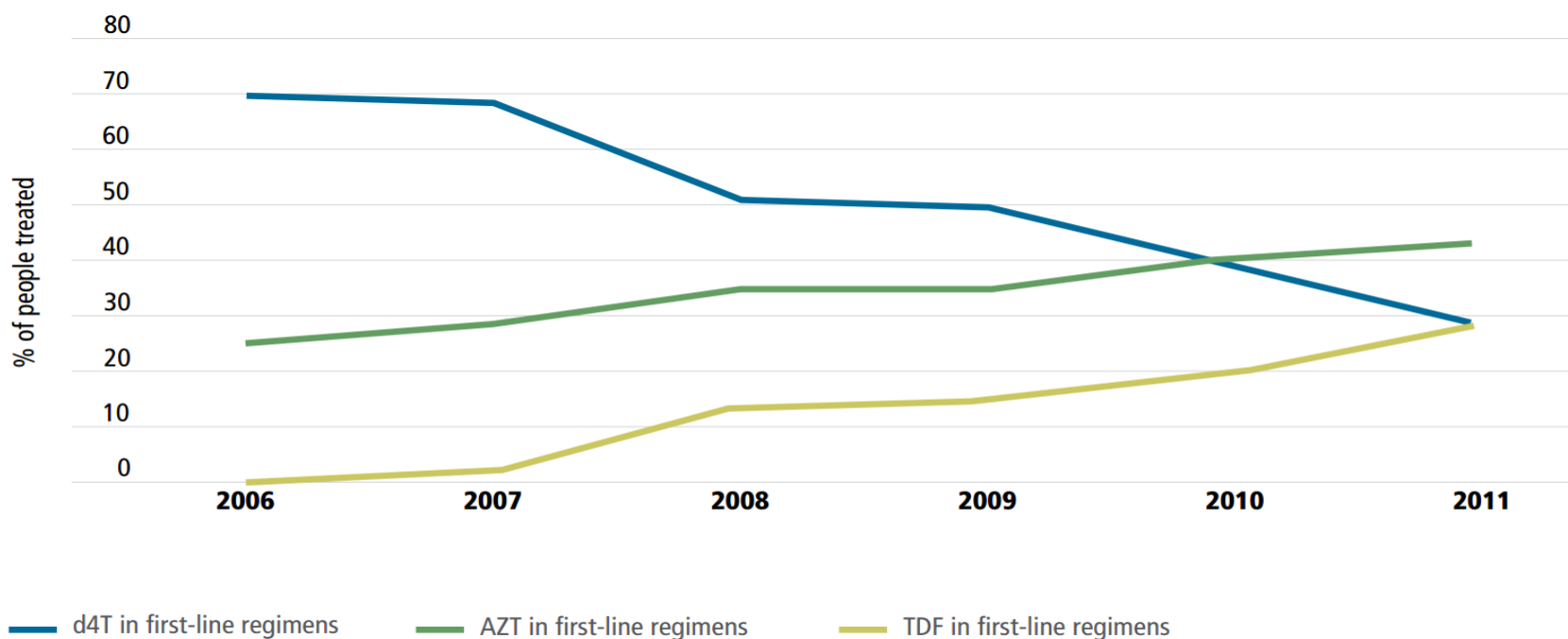
Lack of access to routine testing and monitoring

- 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

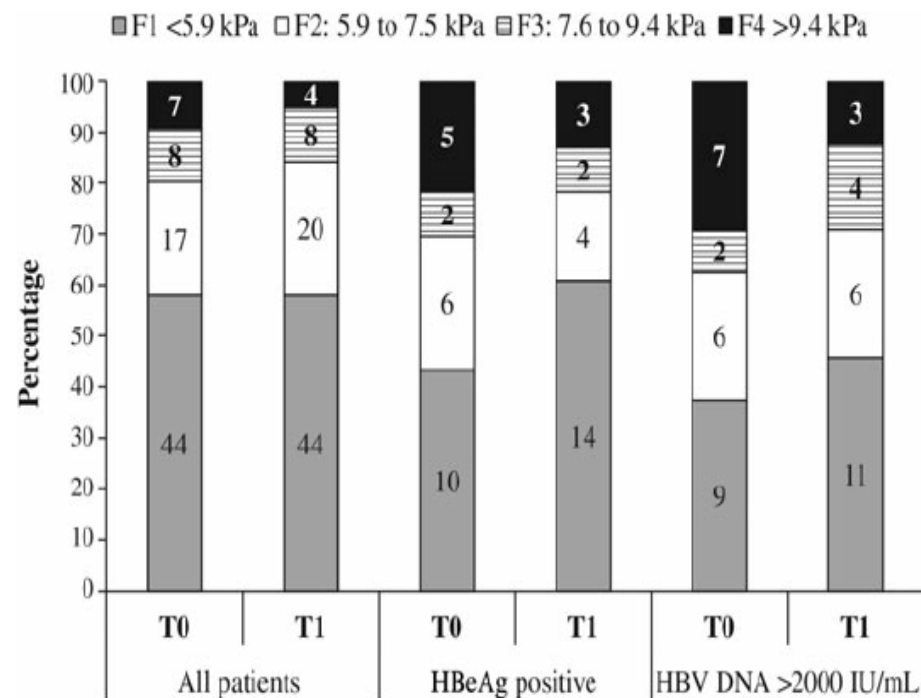
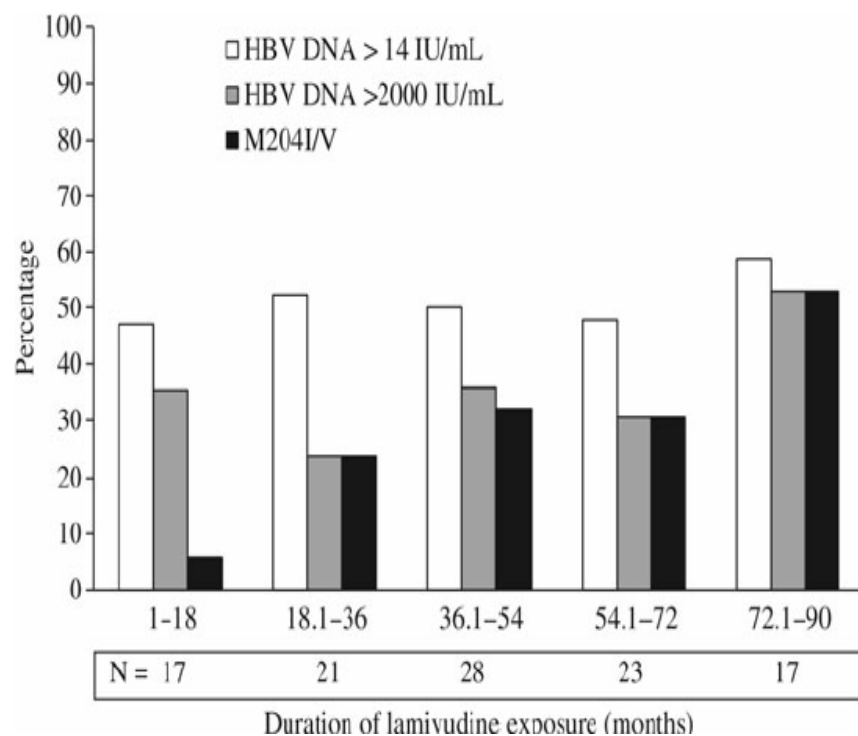


Source: *Use of antiretroviral medicines by December 2011 based on the WHO survey in low- and middle-income countries (77).*

Global update on HIV treatment 2013. WHO

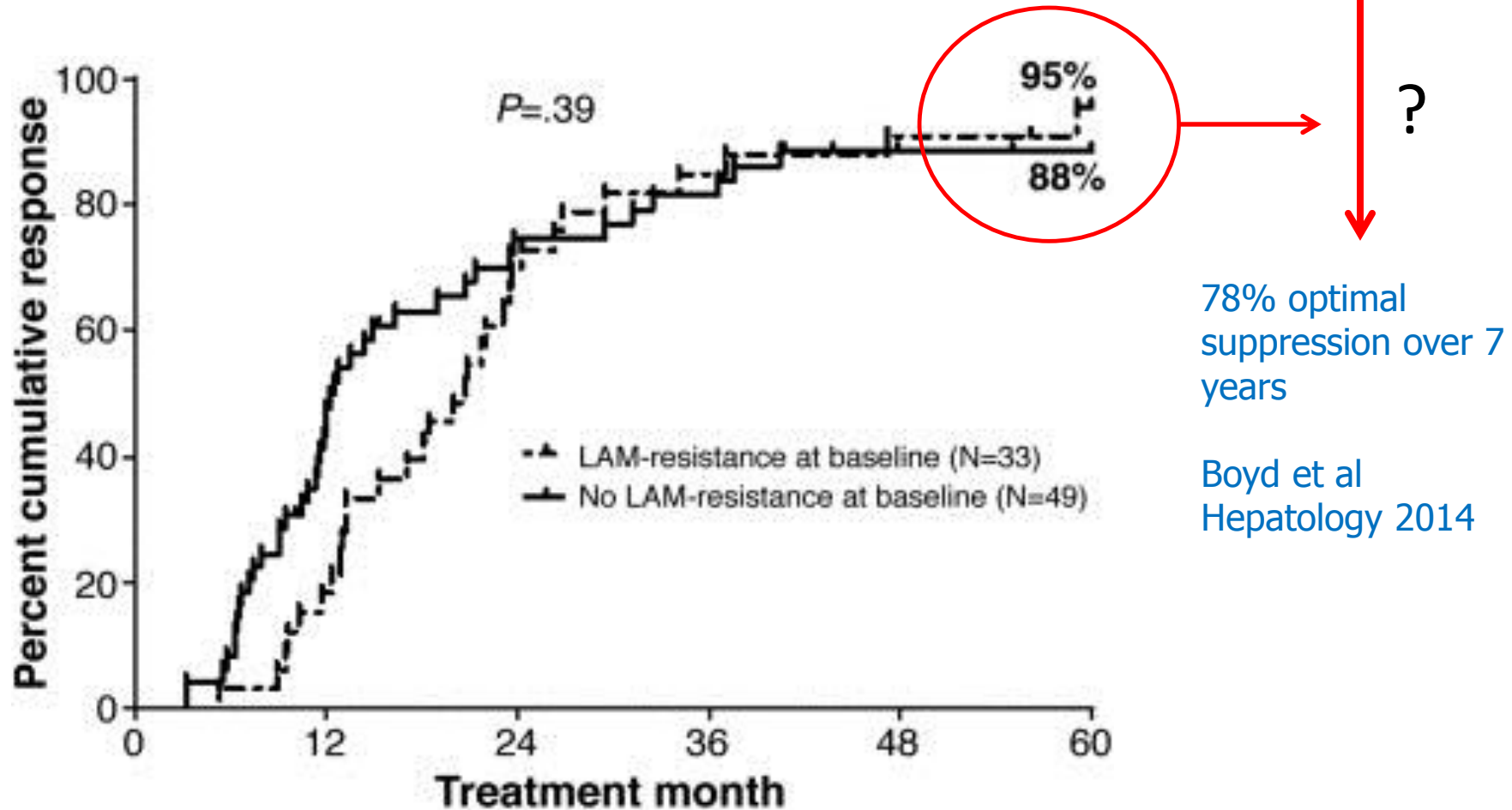
Tanzania: 3% HIV and 17% HIV/HBV on TDF regimen Hawkins IAC 2012

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

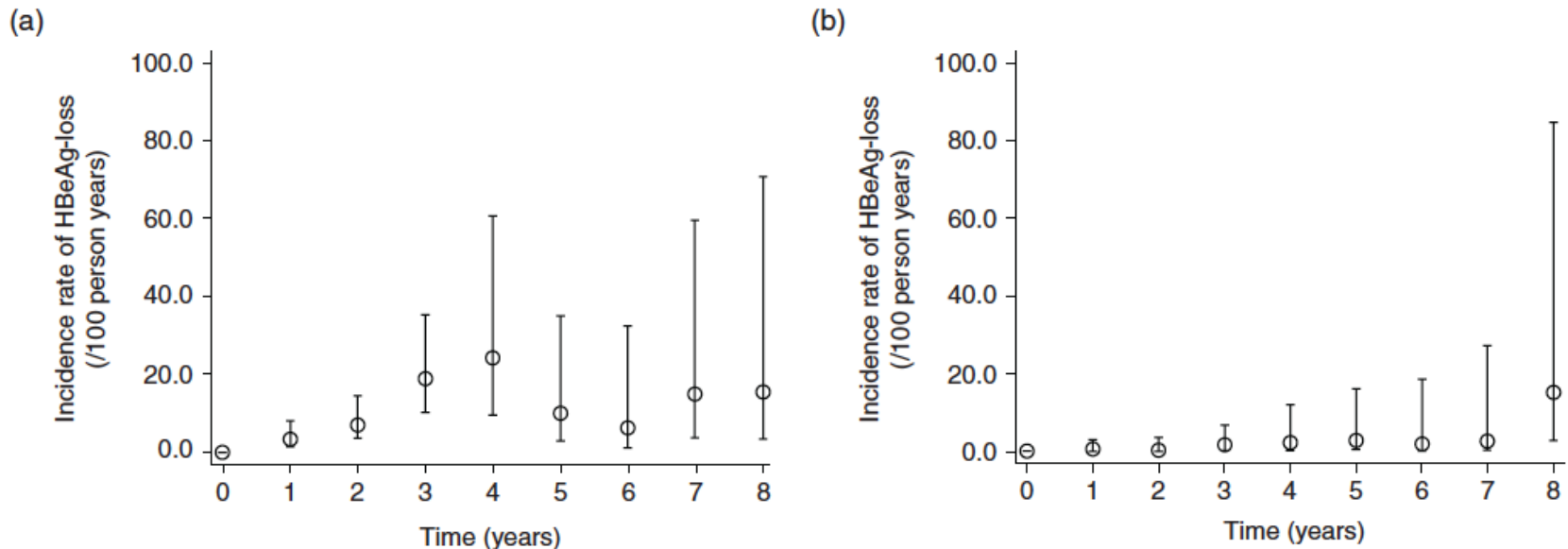


Efficacy is never 100%

8-10% remain viraemic on tenofovir

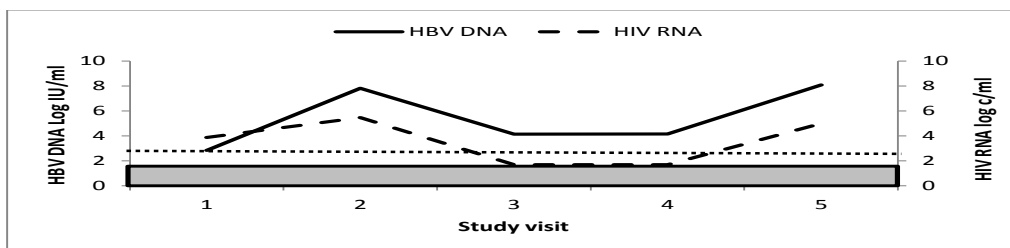


eAg and sAg loss in HBV/HIV

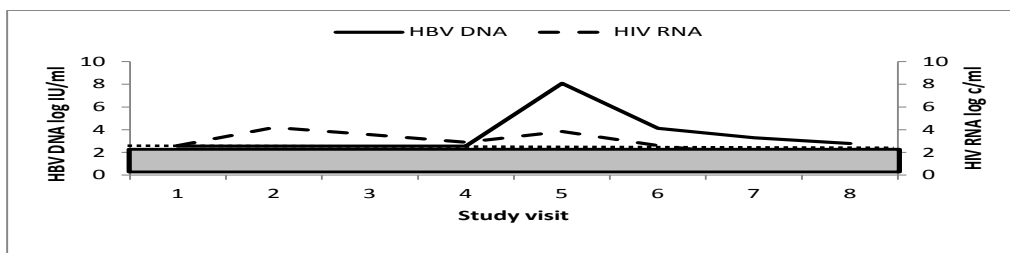


Patterns of suboptimal response to TDF based therapy in HIV-HBV

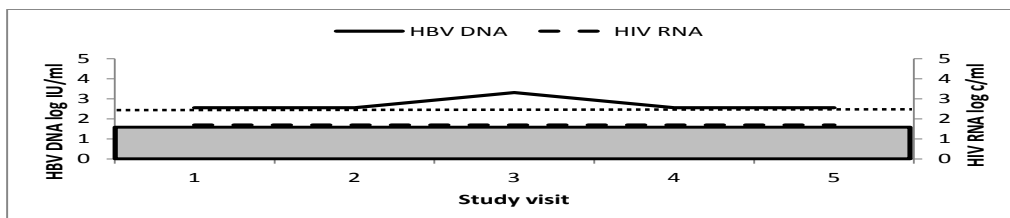
- 165 HIV -HBV coinfectd individuals followed for median of 4 years
- HBV DNA detectable in 20% study visits



**Persistent viraemia
(n=25)**



**Viral rebound
(n=13)**



**Blipper
(n=24)**

Factors associated with detectable HBV DNA

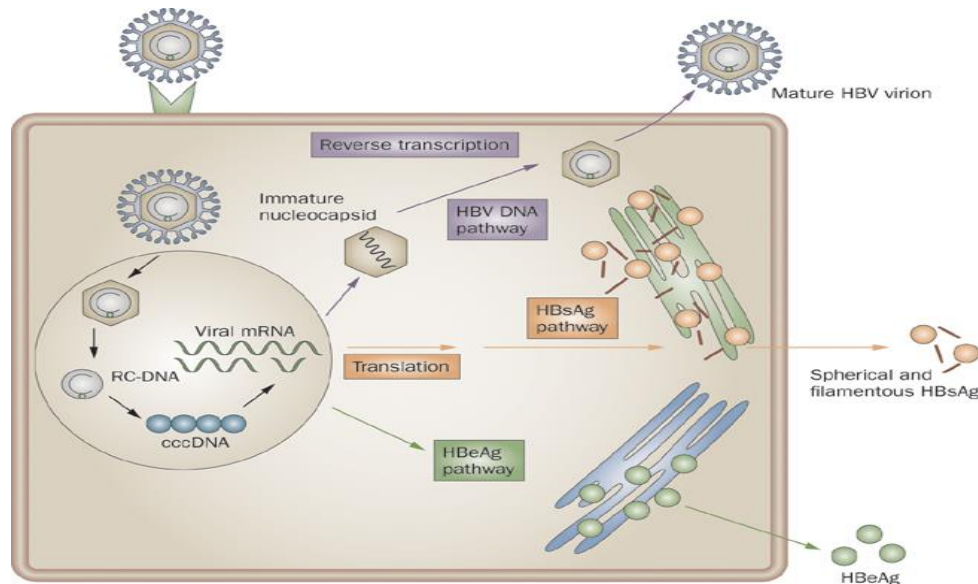
- On truvada based therapy at least 6 months
- Undetectable HIV RNA < 400 c/ml

	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

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 infections¹

**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
- >400 HIV+ patients receiving TDF

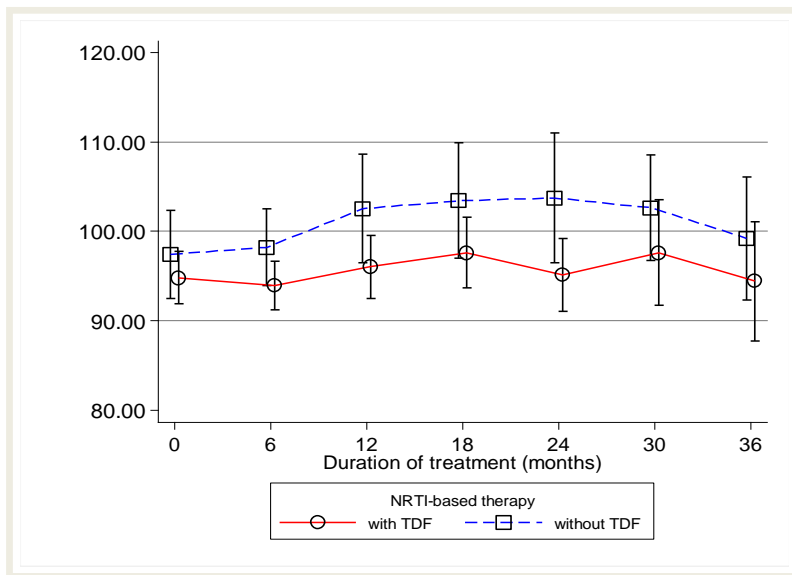
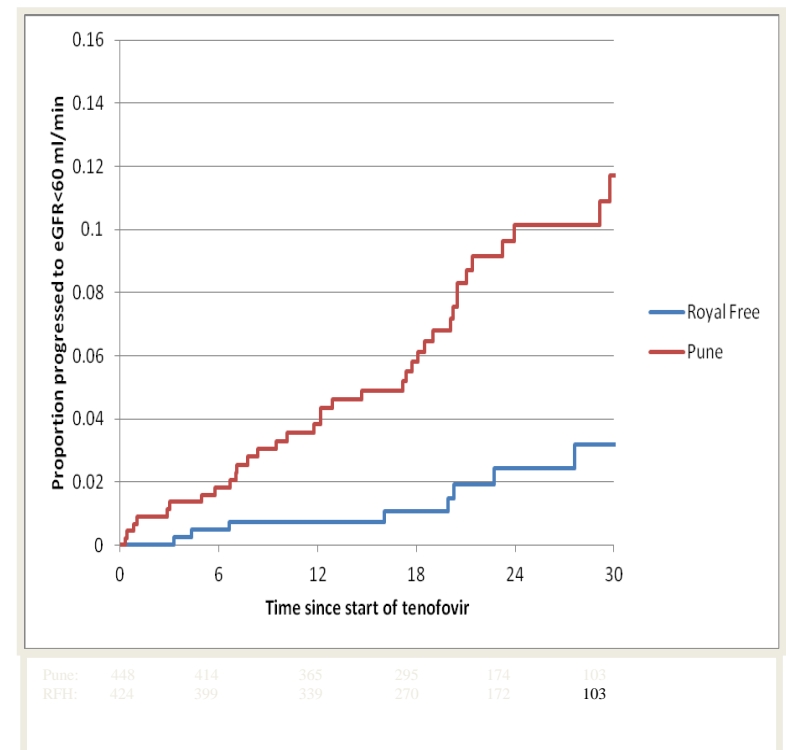


Figure 1: MDRD clearance over time



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)

Primary Endpoint



Baseline

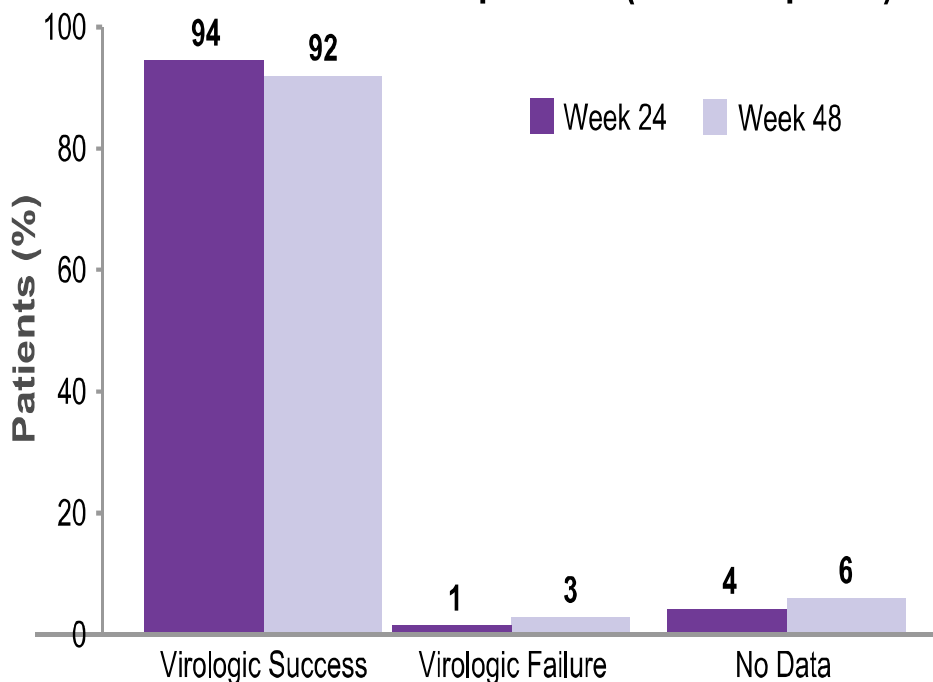
Week 24

Week 48

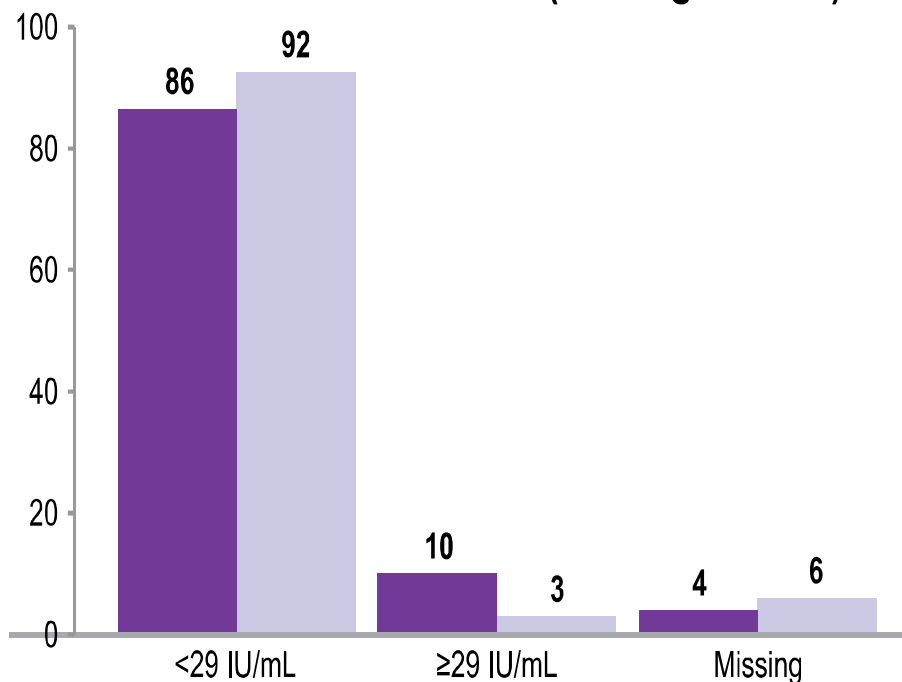
**HIV-1/HBV
Coinfected
Patients**

Switch to E/C/F/TAF

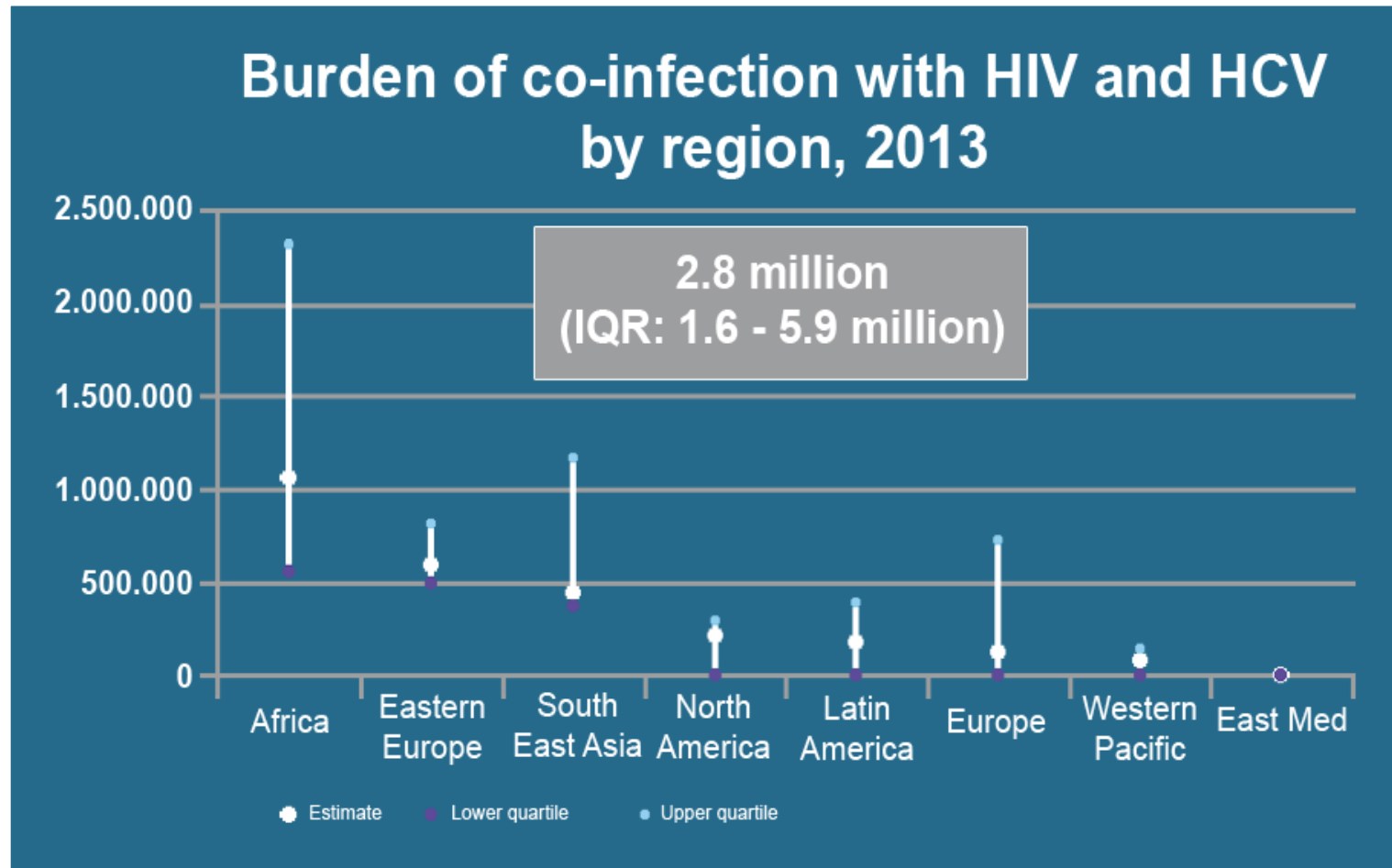
HIV-1 RNA <50 Copies/mL (FDA Snapshot)



HBV DNA <29 IU/mL (Missing=Failure)



Burden of HCV in HIV populations



HIV/HCV – double-trouble for the liver

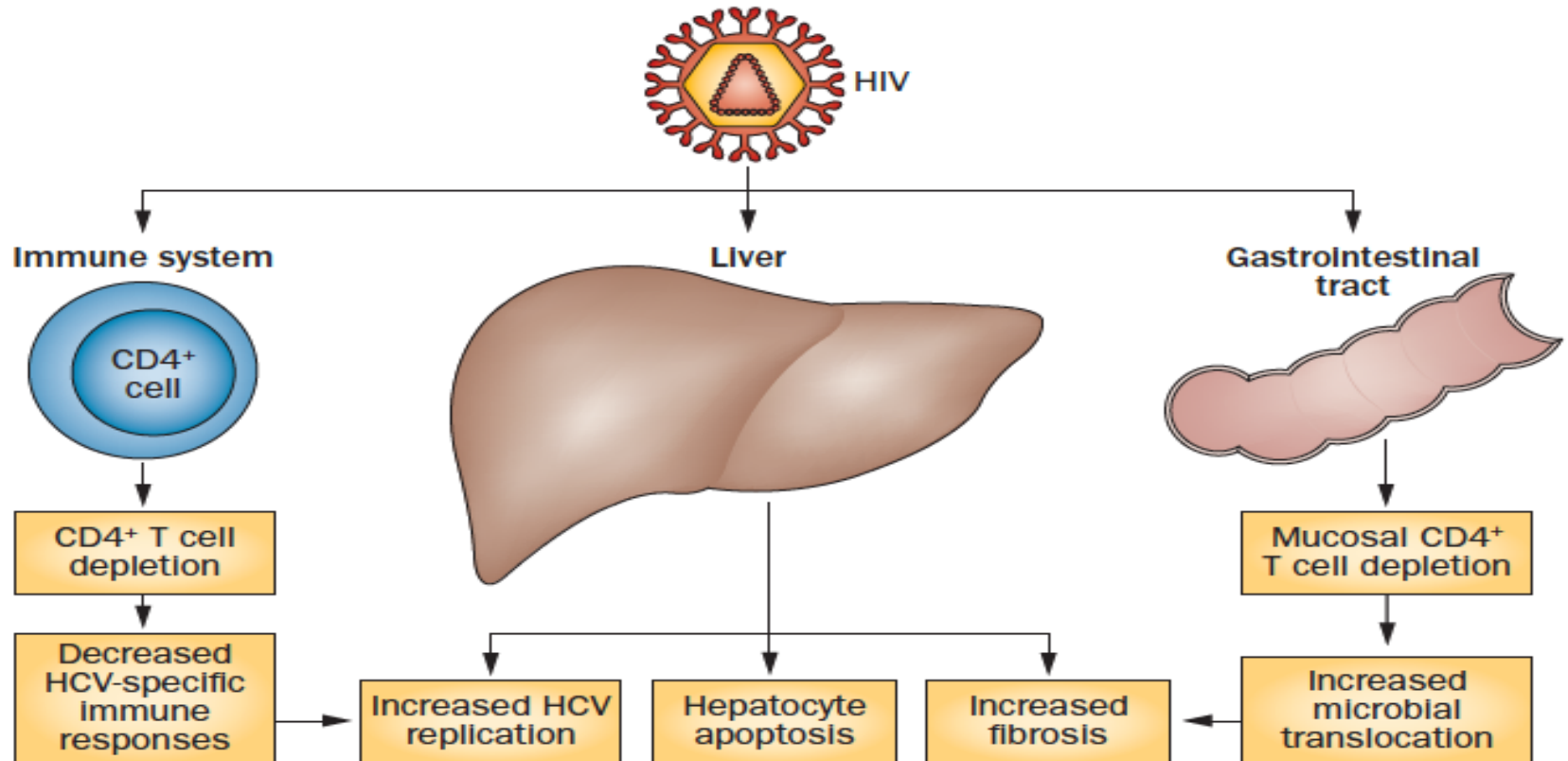


Figure 1 | Driving factors underlying liver disease pathogenesis in HCV–HIV co-infection. HIV infection leads to an impaired immune response against HCV, increased HCV replication, hepatic inflammation and apoptosis, increased microbial translocation from the gastrointestinal tract and increased fibrosis.

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

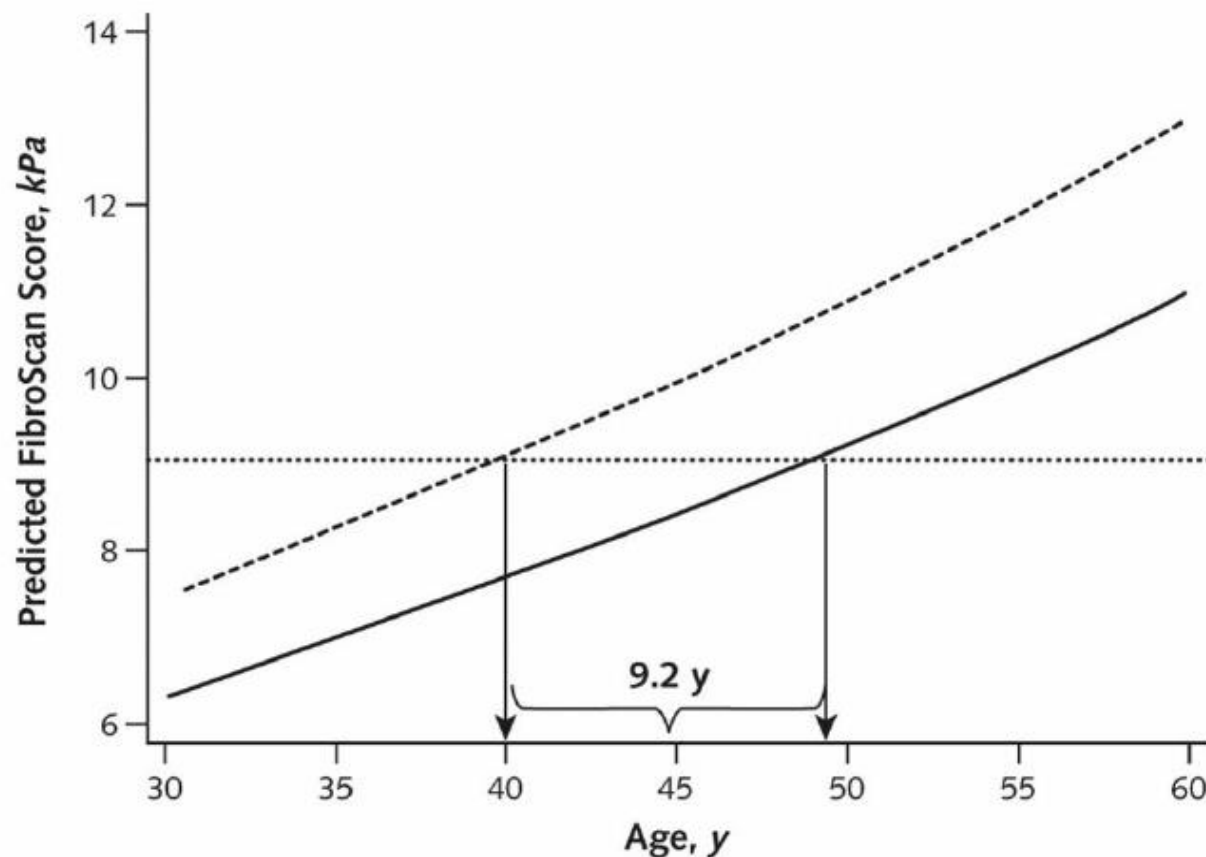
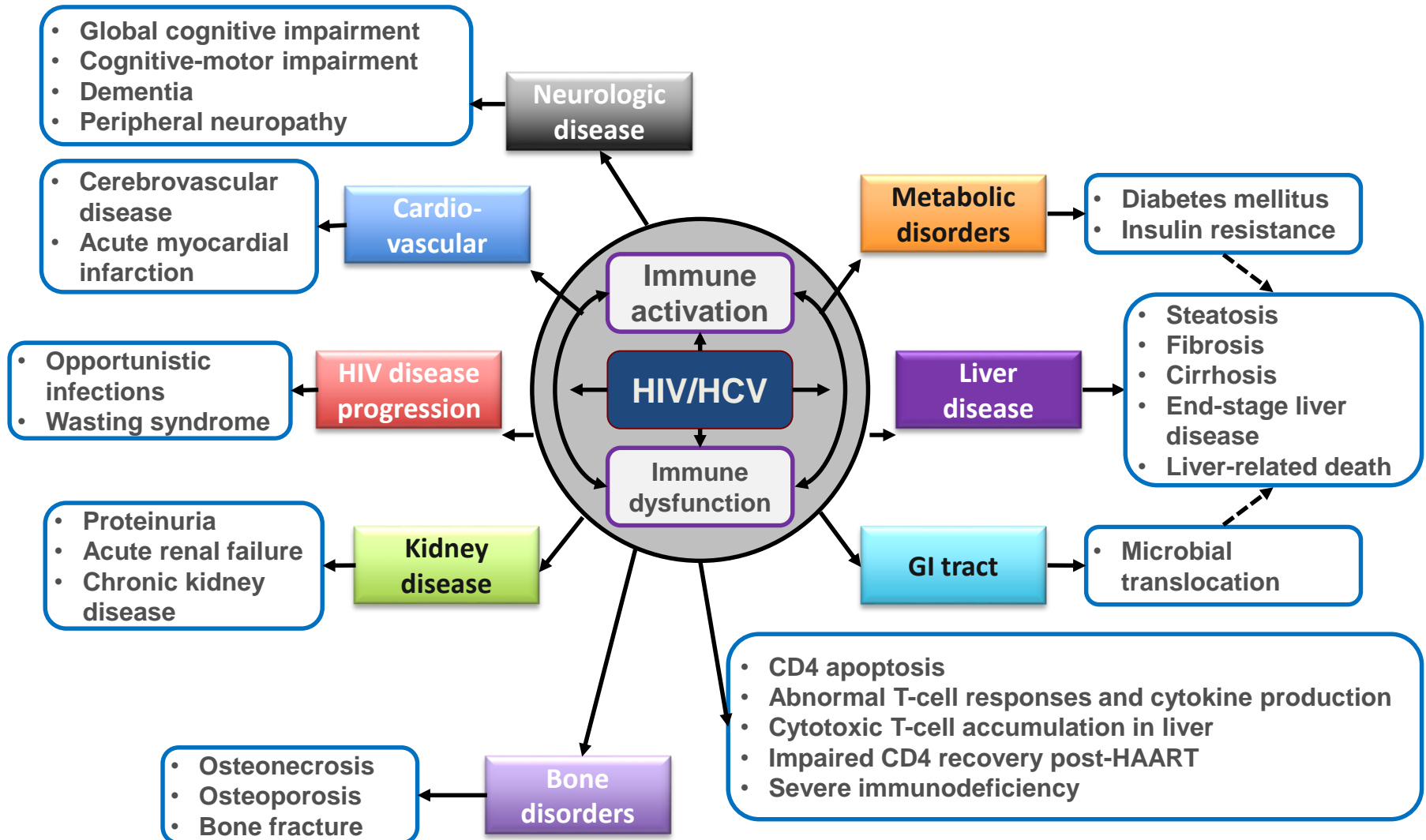


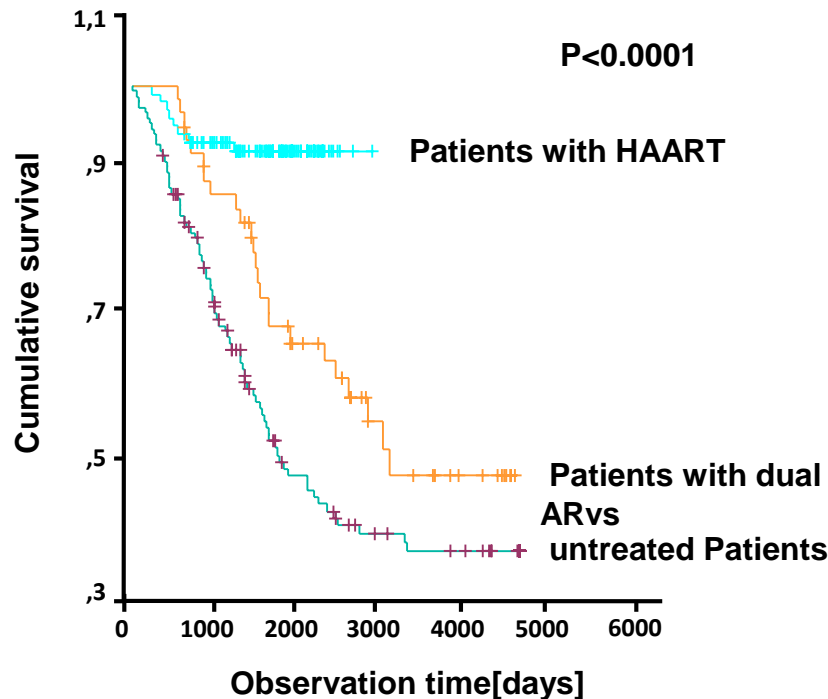
Figure 3. Liver fibrosis and age among persons coinfecting with HIV and HCV (dashed line) and those with only HCV (solid line)

HIV/HCV – a contribution to multiple organ dysfunction



Overall and Liver-related Mortality - effect of HAART

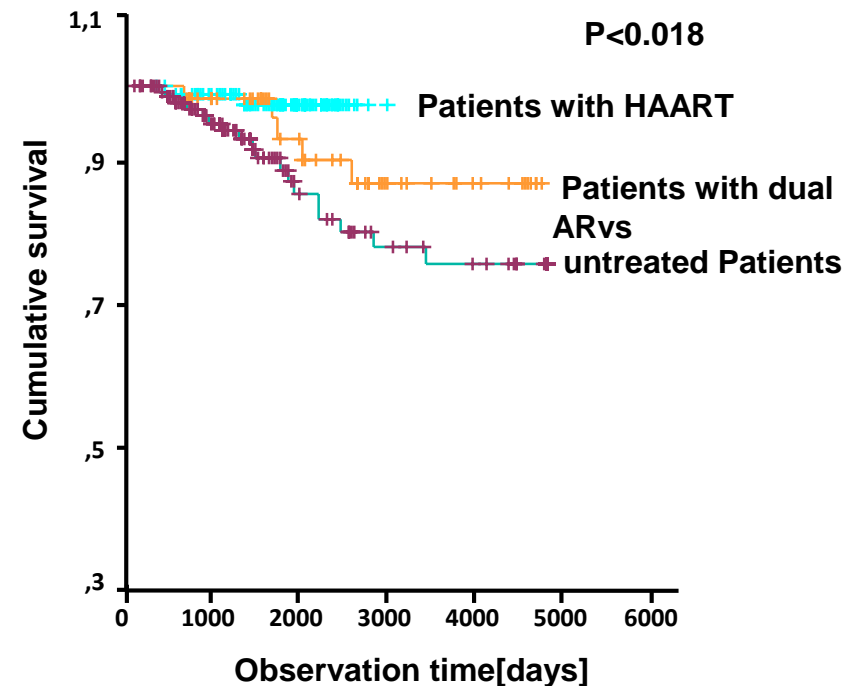
A) Overall-Mortality



Patients under observation:

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

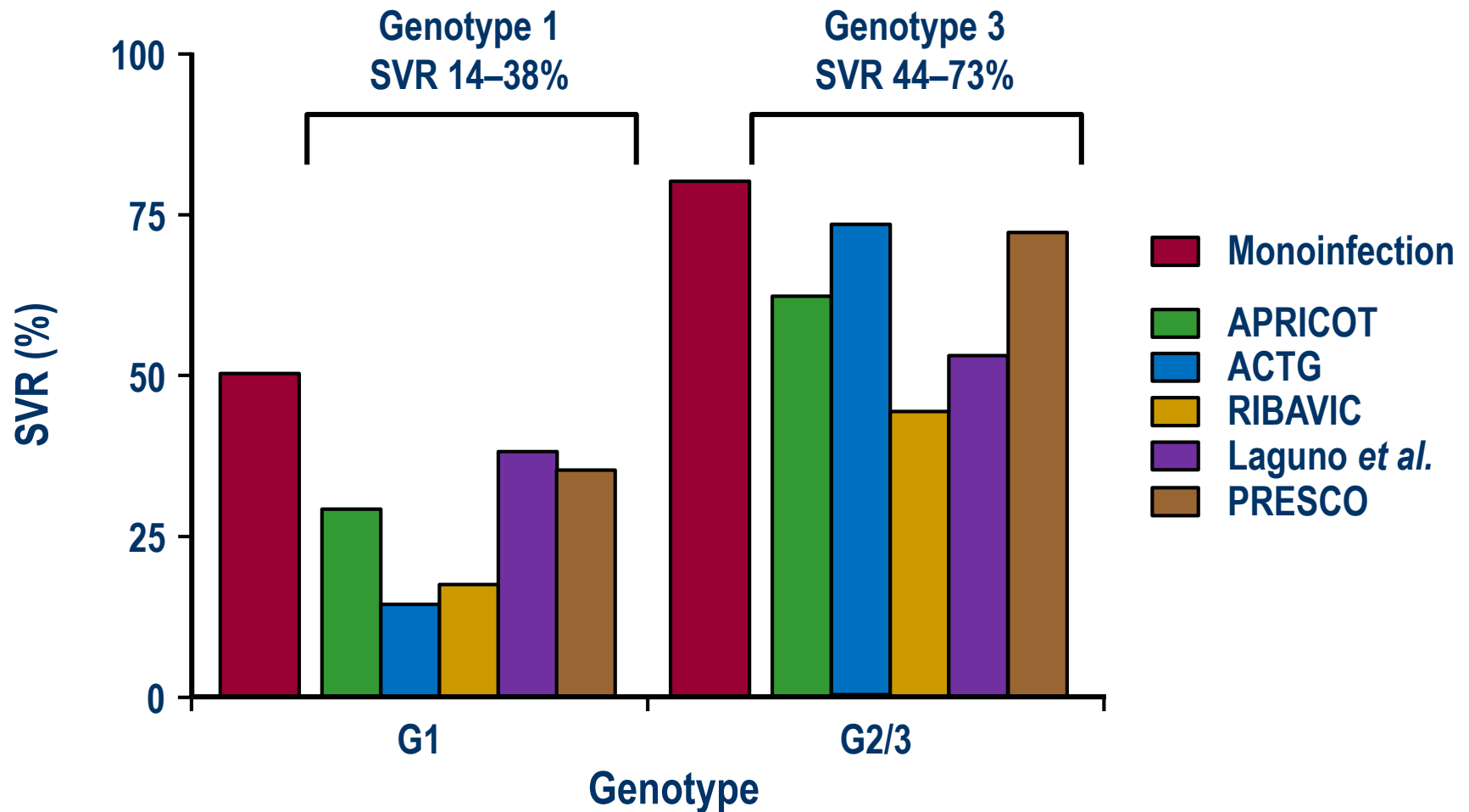
B) Liver-related-Mortality



Patients under observation:

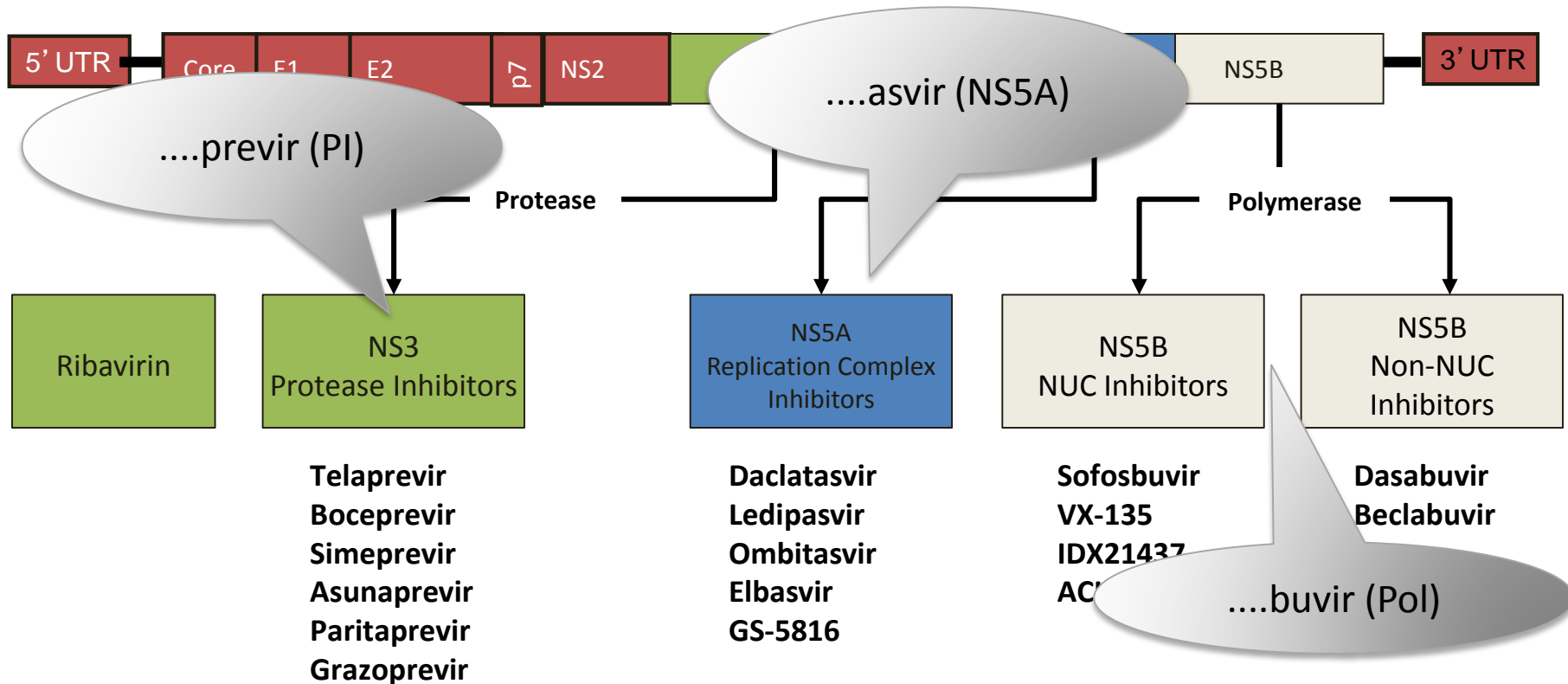
HAART-group:	93	79	33	-	-	-
ART-group:	55	46	30	15	9	1
Untreated-group:	13794	49	37	32	27	

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

What are DAAs?



*Representative list modified from CCO.

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



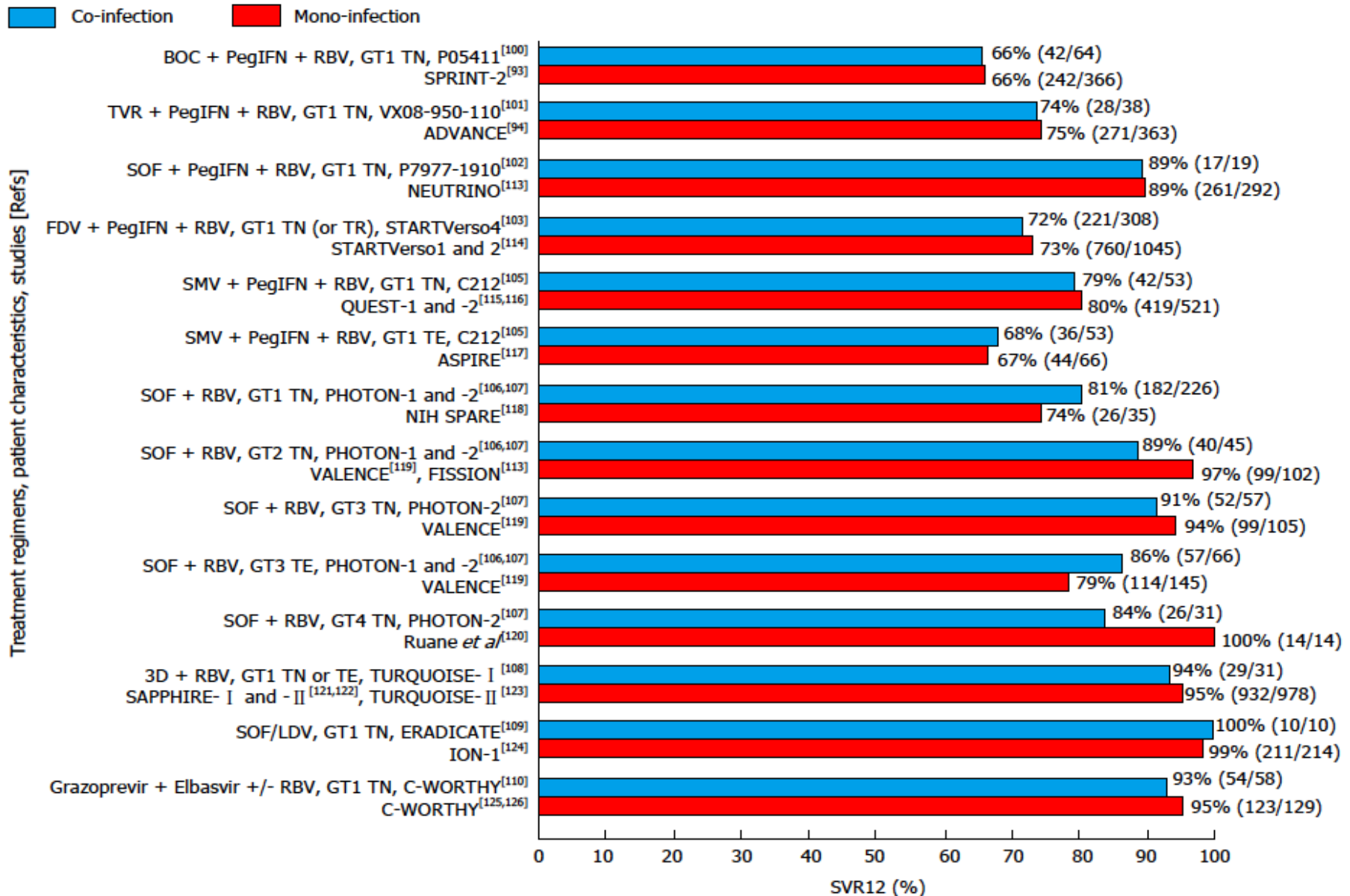
Average profile



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 2015).

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)

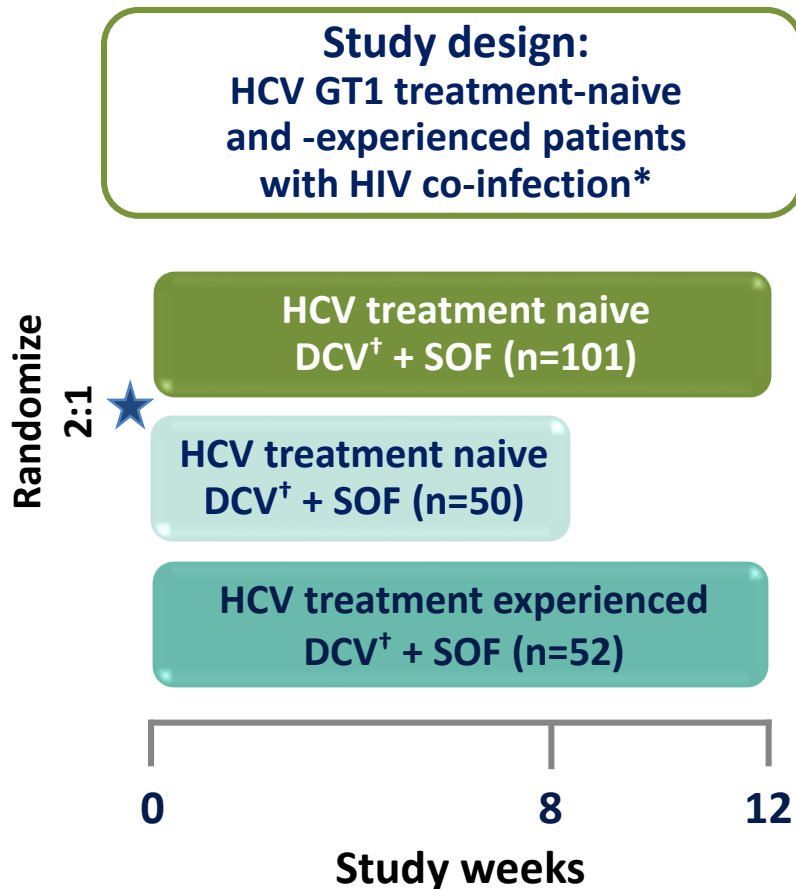
Upcoming HCV recommendations – treatment combination options

IFN-free HCV Treatment Options				
HCV GT	Treatment regimen	Treatment duration & ribavirin usage		
		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			

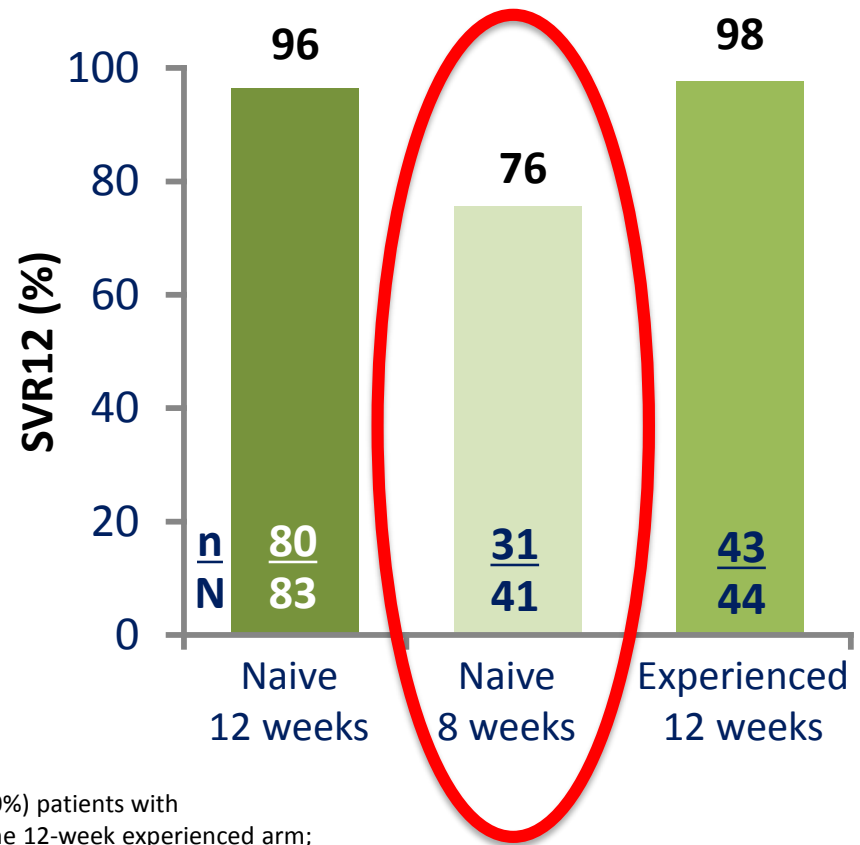
Are there remaining ‘unresolved’ issues with HCV?

- 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

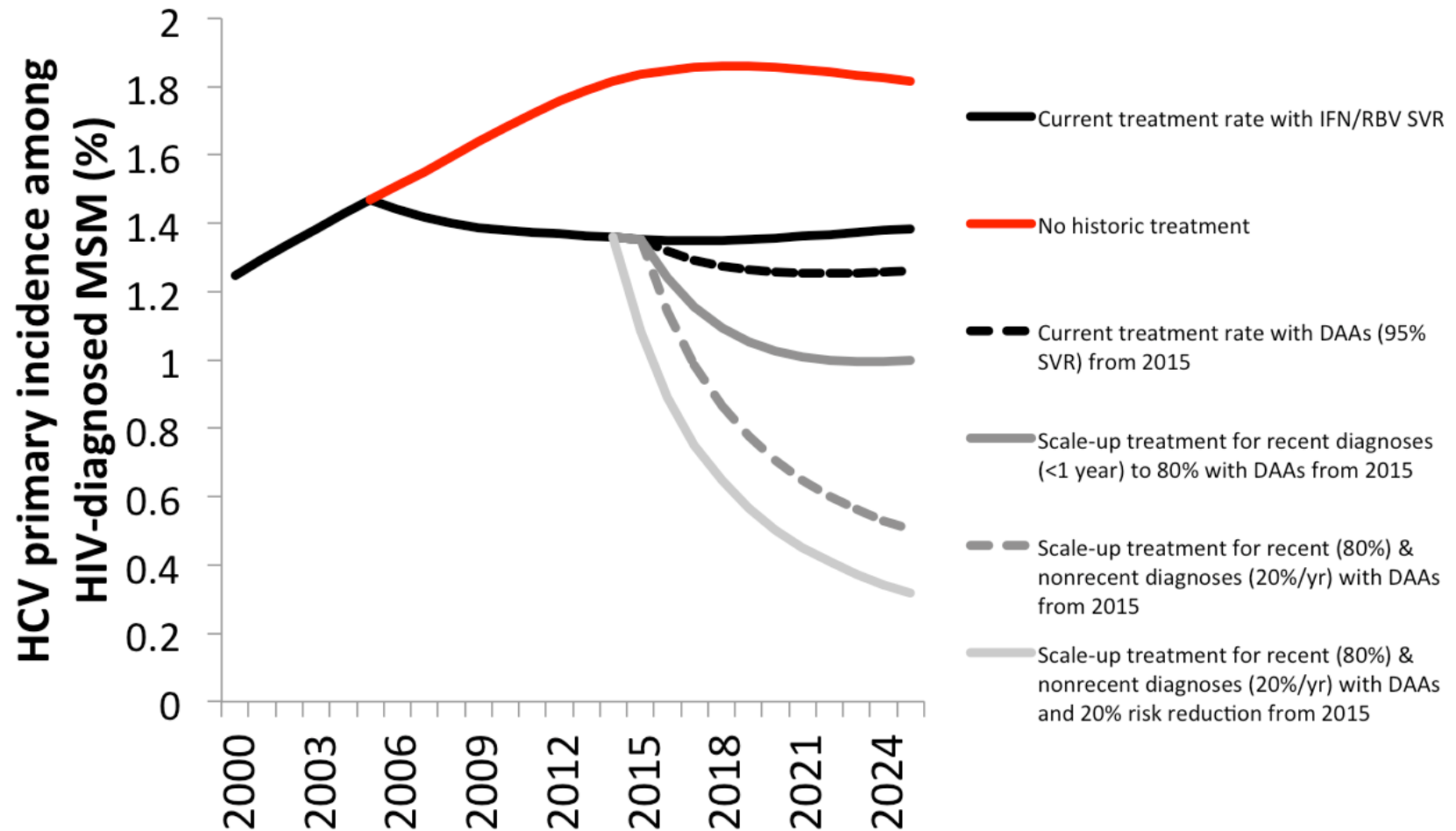


Efficacy results: Genotype 1



* Including 9 (8.9%) patients with cirrhosis in the 12-week naïve arm, 5 (10.0%) patients with cirrhosis in the 8-week naïve 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.

Treatment As Prevention in HIV/HCV



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