Liver Disease in HIV

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Disclosures

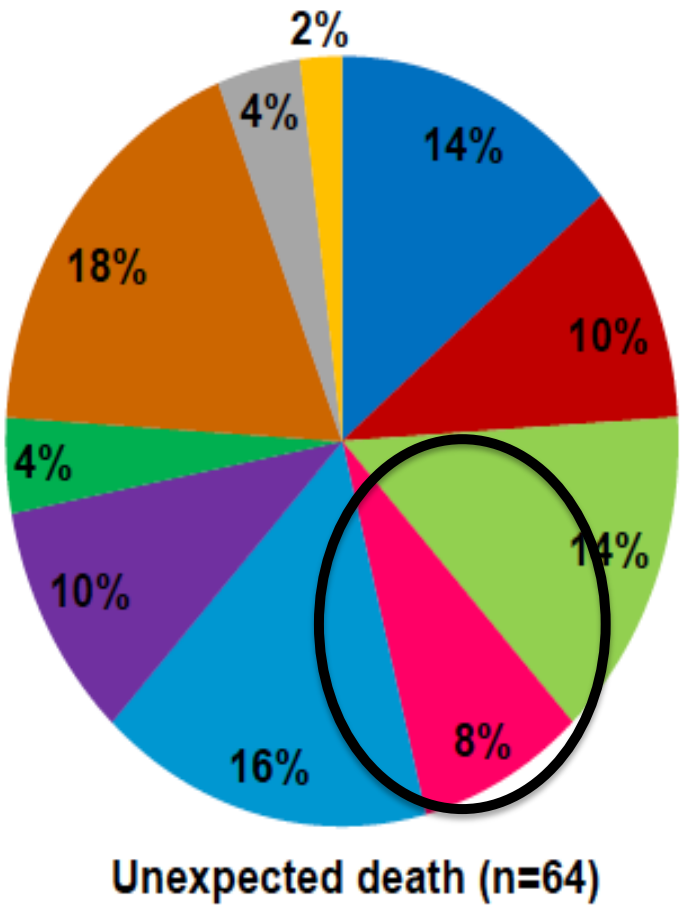
- Grants/travel support/speaker fees
  - Abbvie
  - Gilead
  - ViiV

Outline

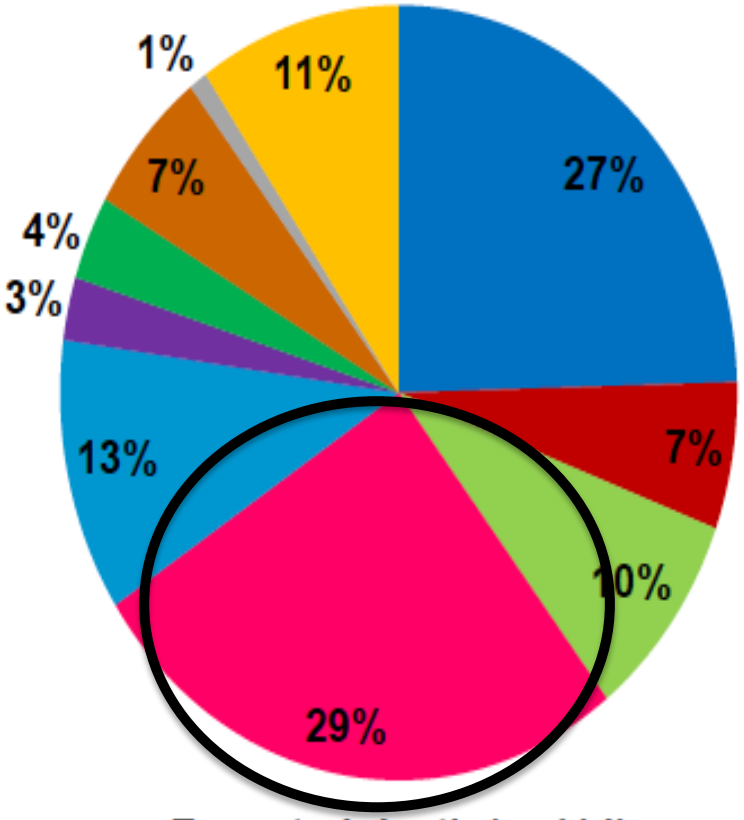
- Importance of liver disease in HIV
- Global burden of Viral Hepatitis and contribution to morbidity/mortality
- Drug-induced liver disease
- HBV
- HCV
- Non-alcoholic Fatty Liver Disease (NAFLD)

- Case-based discussion (Sunday pm)

Cause of Death in the London HIV cohort - 2016



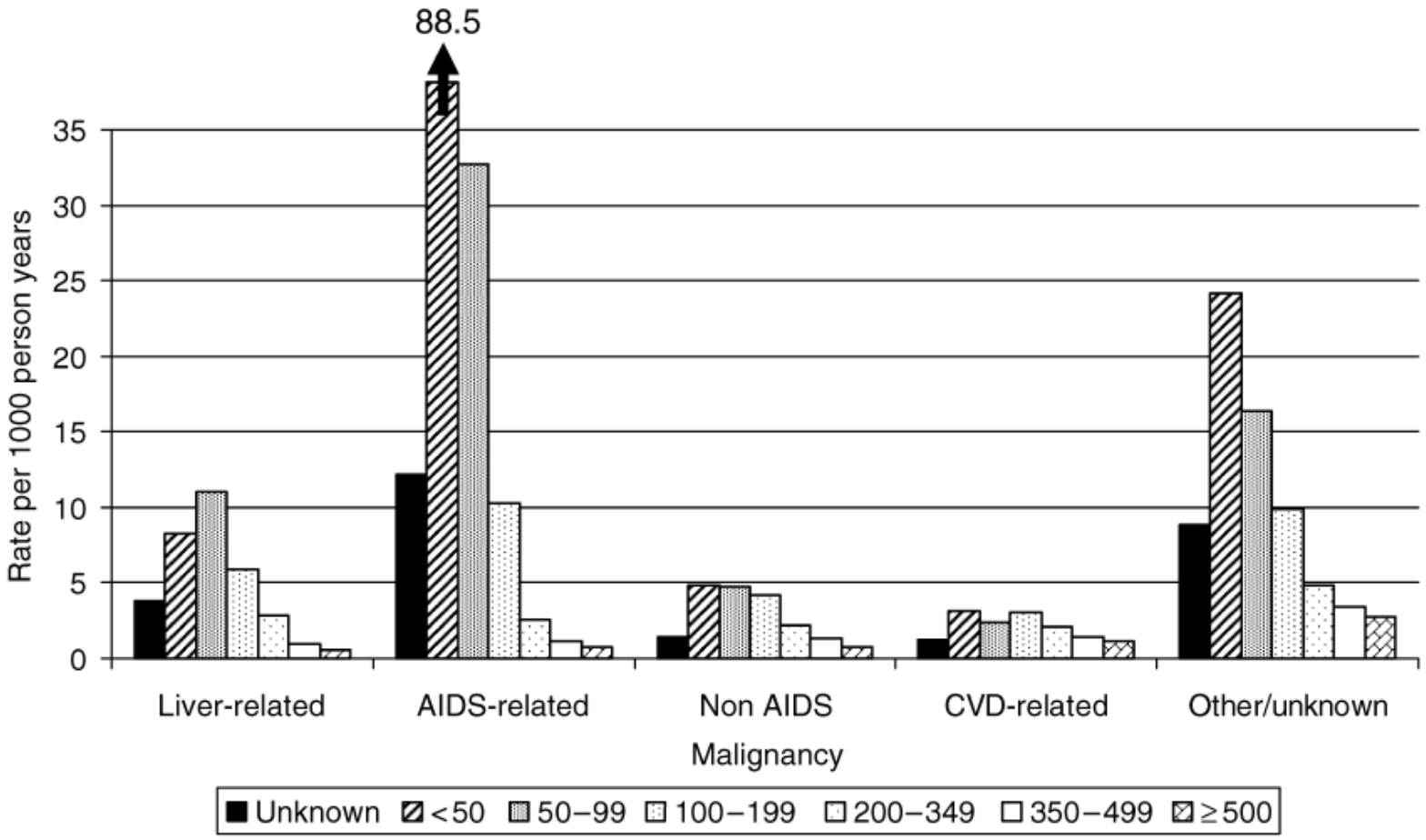
Unexpected death (n=64)



Expected death (n=114)

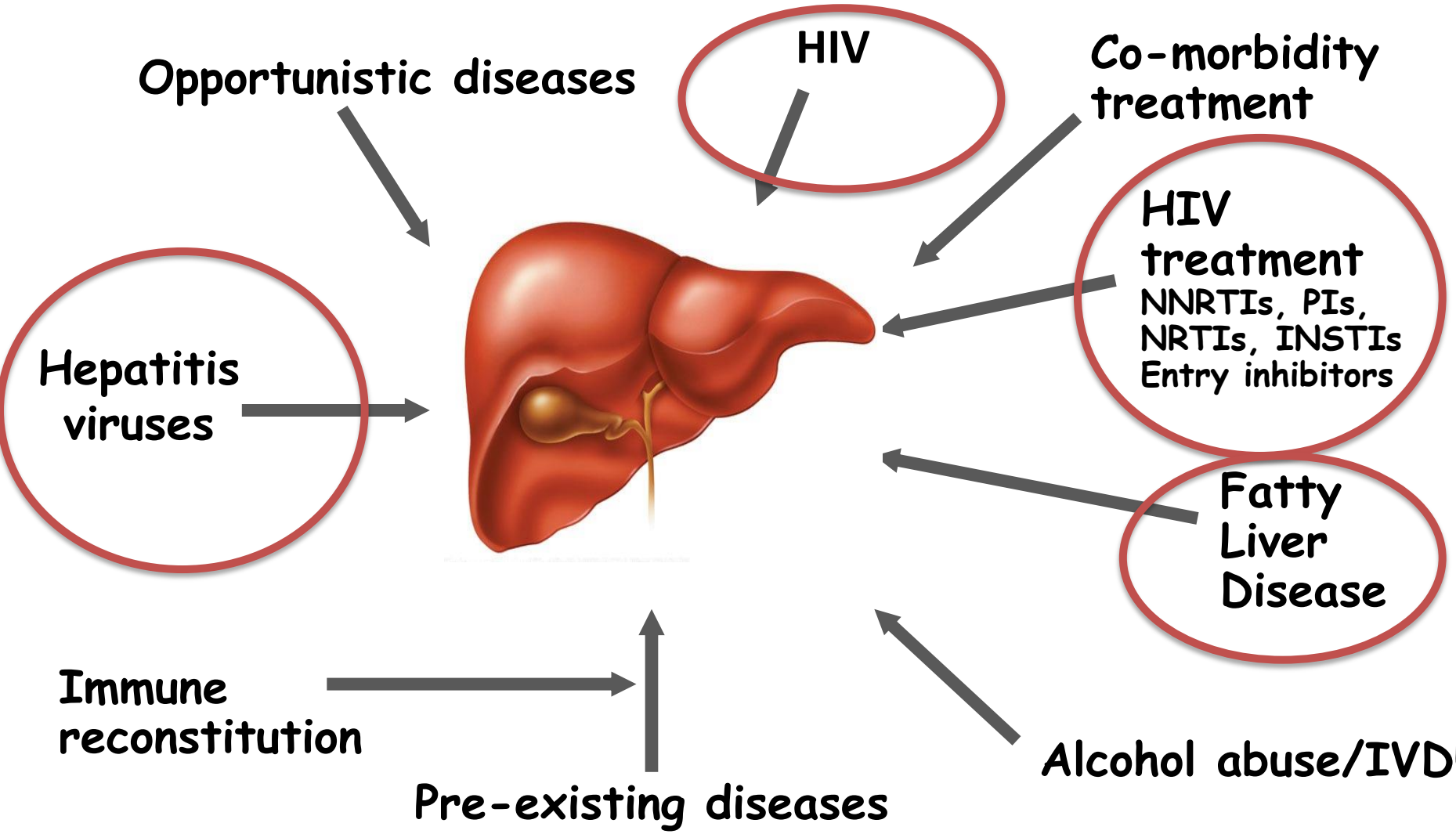
Croxford S, et al. IAS 2018

Liver-related death and CD4 count



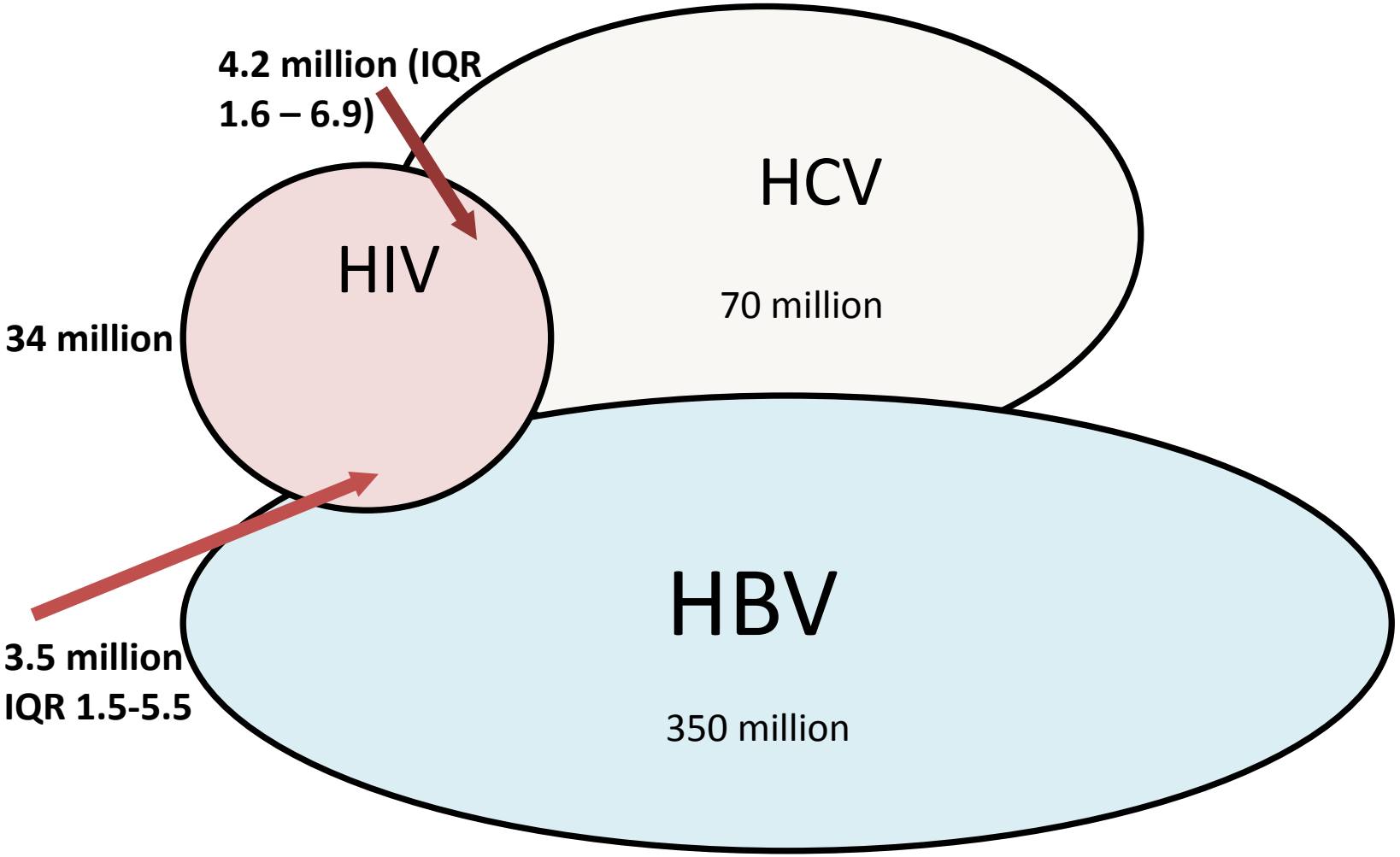
D.A.D study Gp. AIDS 2010: 24: 1537

Liver Disease in HIV-infected Patients - multifactorial

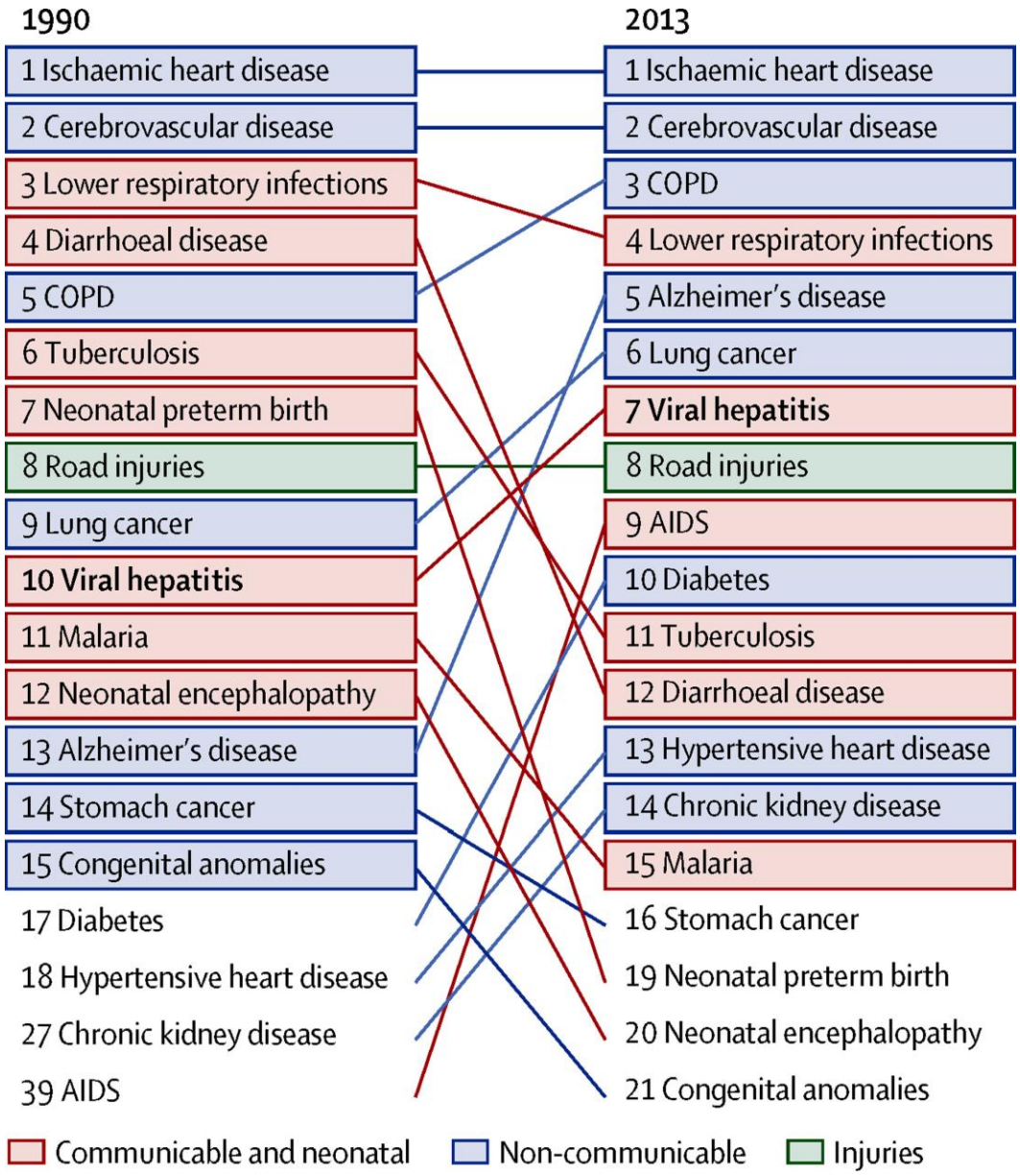


Sulkowski M. *et al.* Ann Intern Med. 2003;138:197-207 Guaraldi G *et al* Clin Infect Dis 2008 47(2): 250-257
Greub G *et al.* Lancet 2000;356:1800-1805

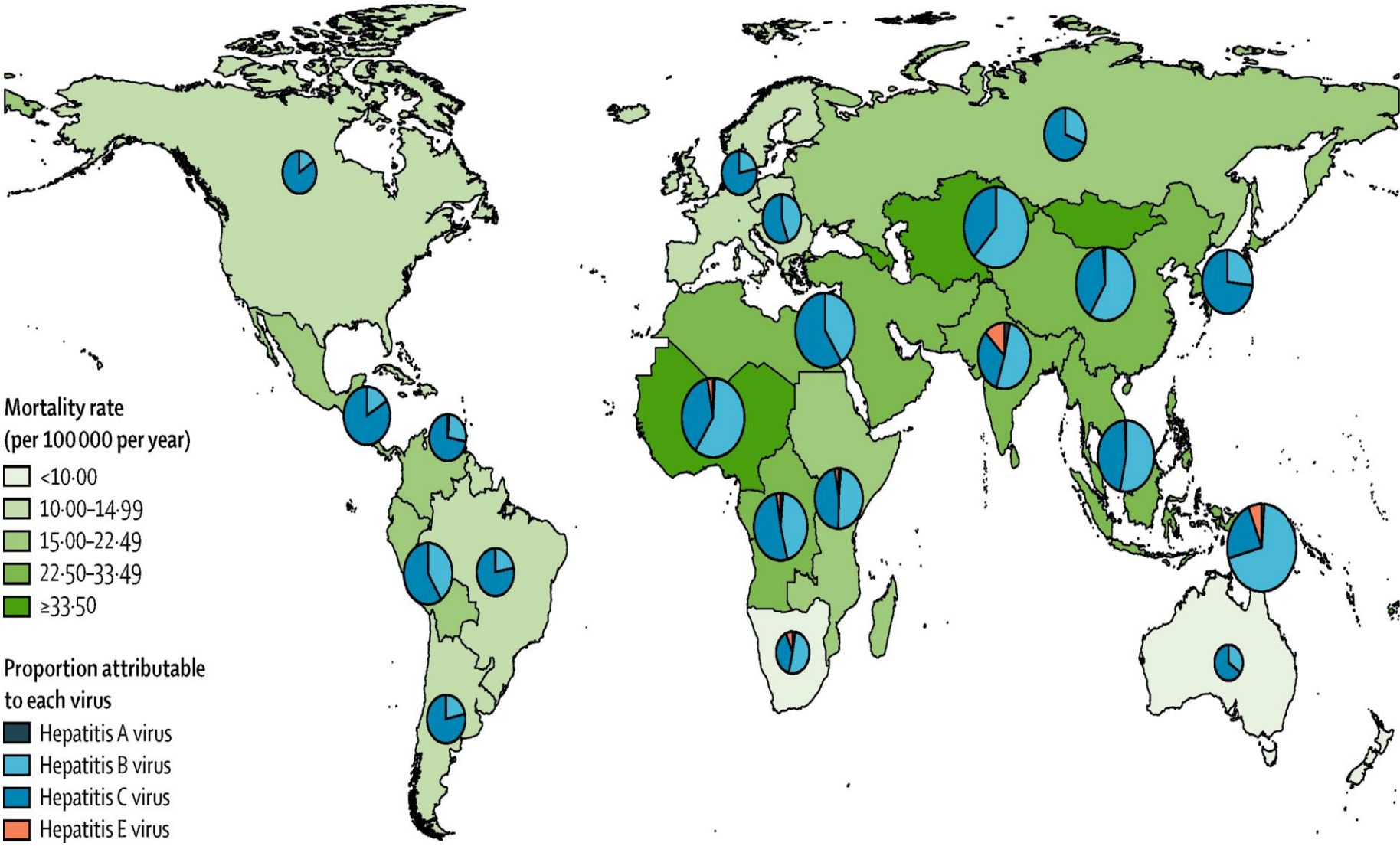
Overlapping epidemics – co-infections



Easterbrook, et al. IAS 2015, TuPEB254

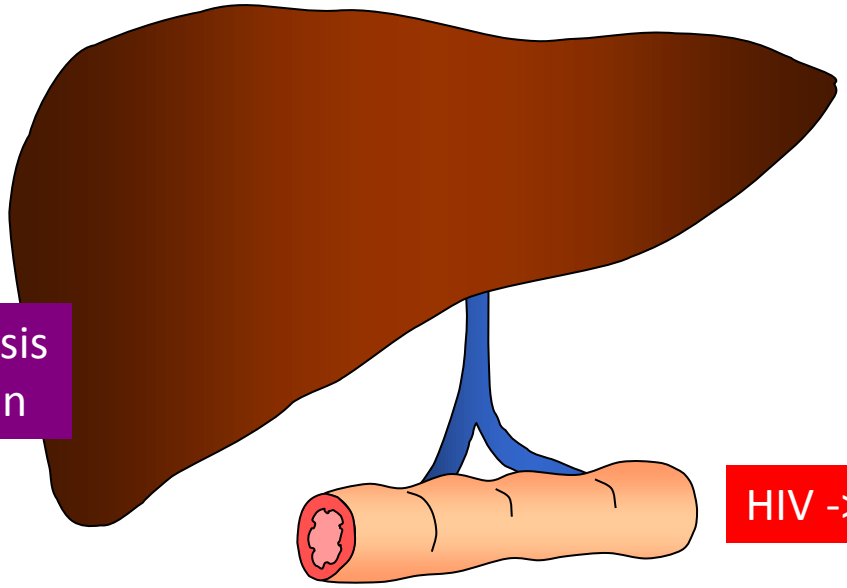


Stanaway, et al, Lancet 2016



Stanaway, et al, Lancet 2016

HIV-associated Immune activation and liver disease



Hepatic fibrosis
HSC activation

HIV -> GIT CD4+ T-cell depletion

Microbial translocation

LPS

Immune activation

macrophage

DCs

IL-1
TNF-α
IFN-α
IL-12

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)

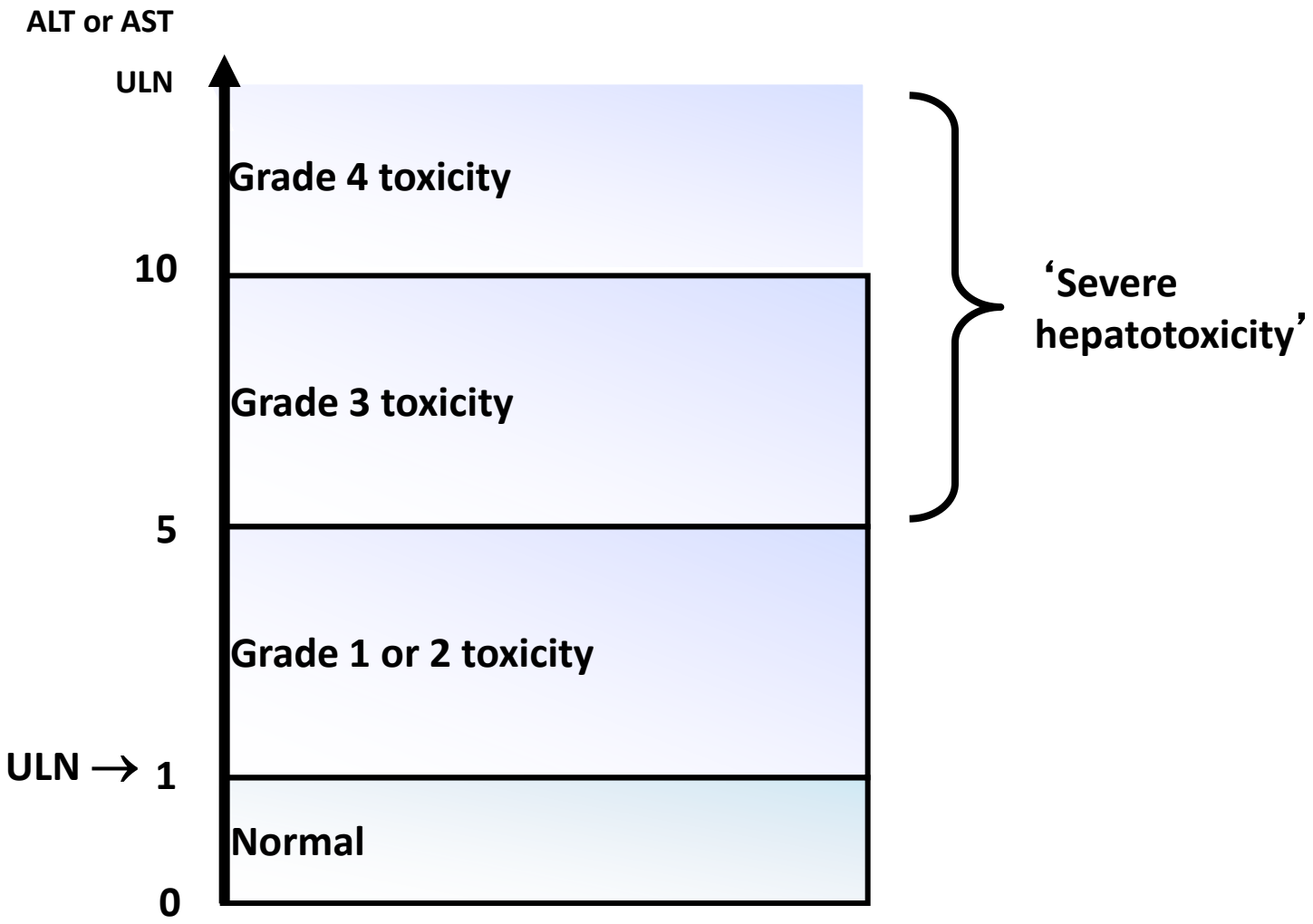
- Sub-study of 230 (4577) patients
- Baseline FibroScan, FIB-4, APRI

- 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

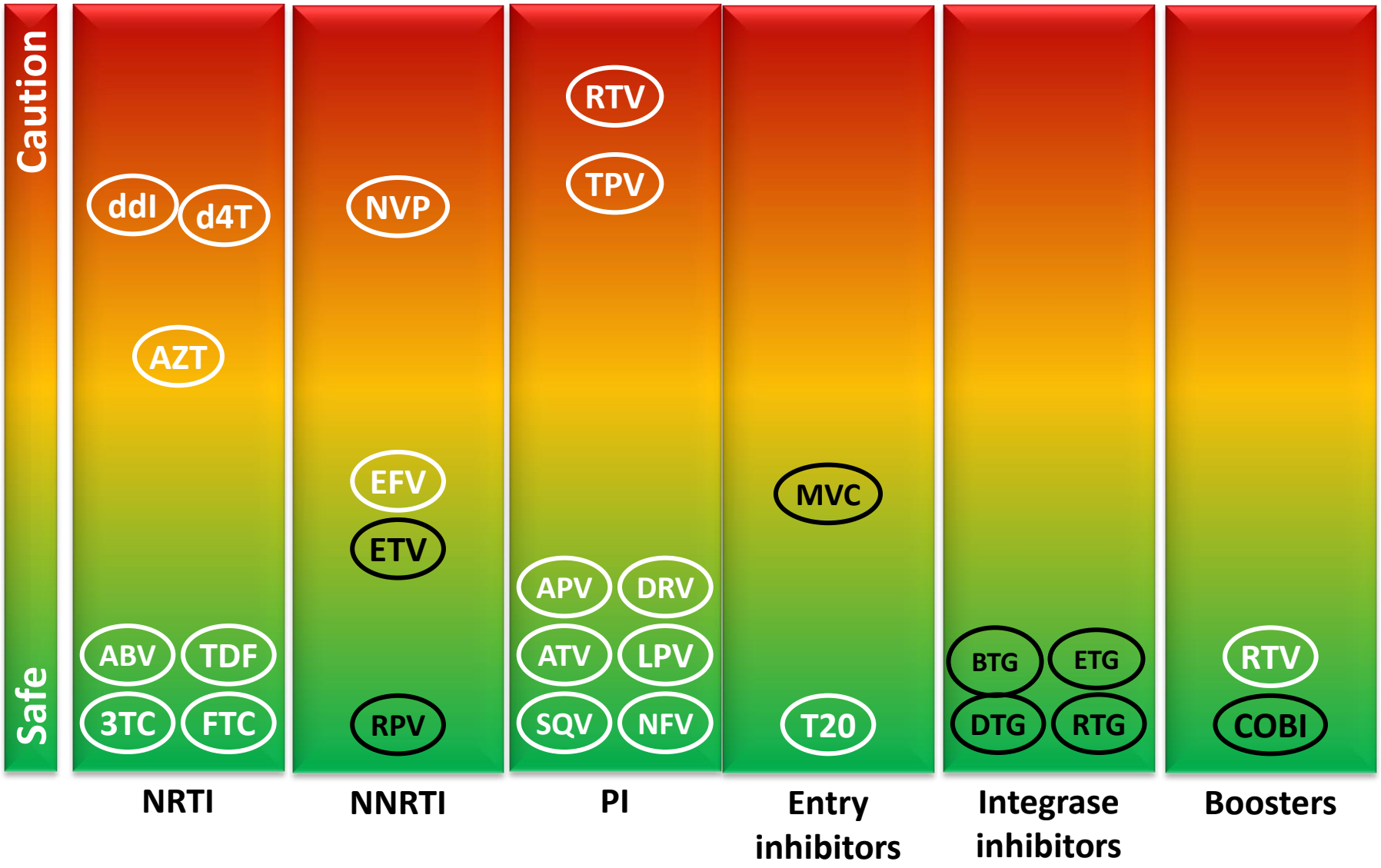


Mechanisms of drug-related liver injury in HIV-infected patients

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

Hepatic Safety Profile of ARVs



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

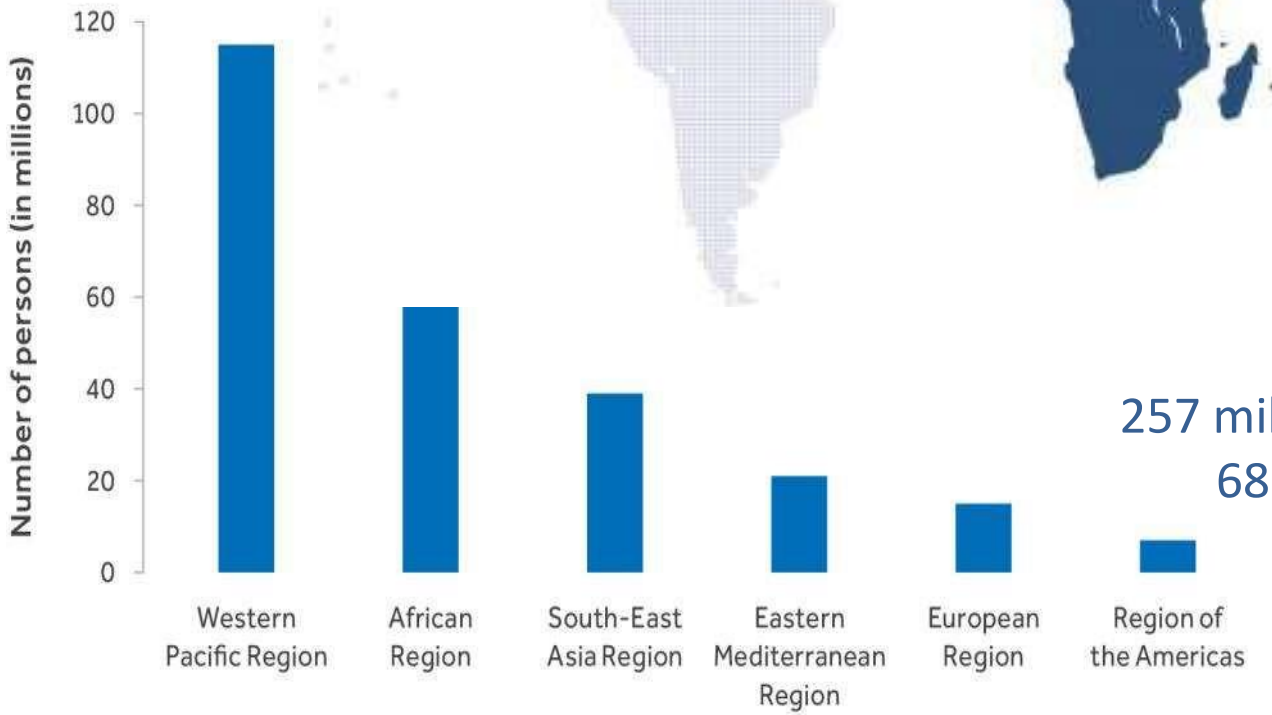
Hepatotoxicity commoner in HBV and HCV co-infected patients - mechanisms

- 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)



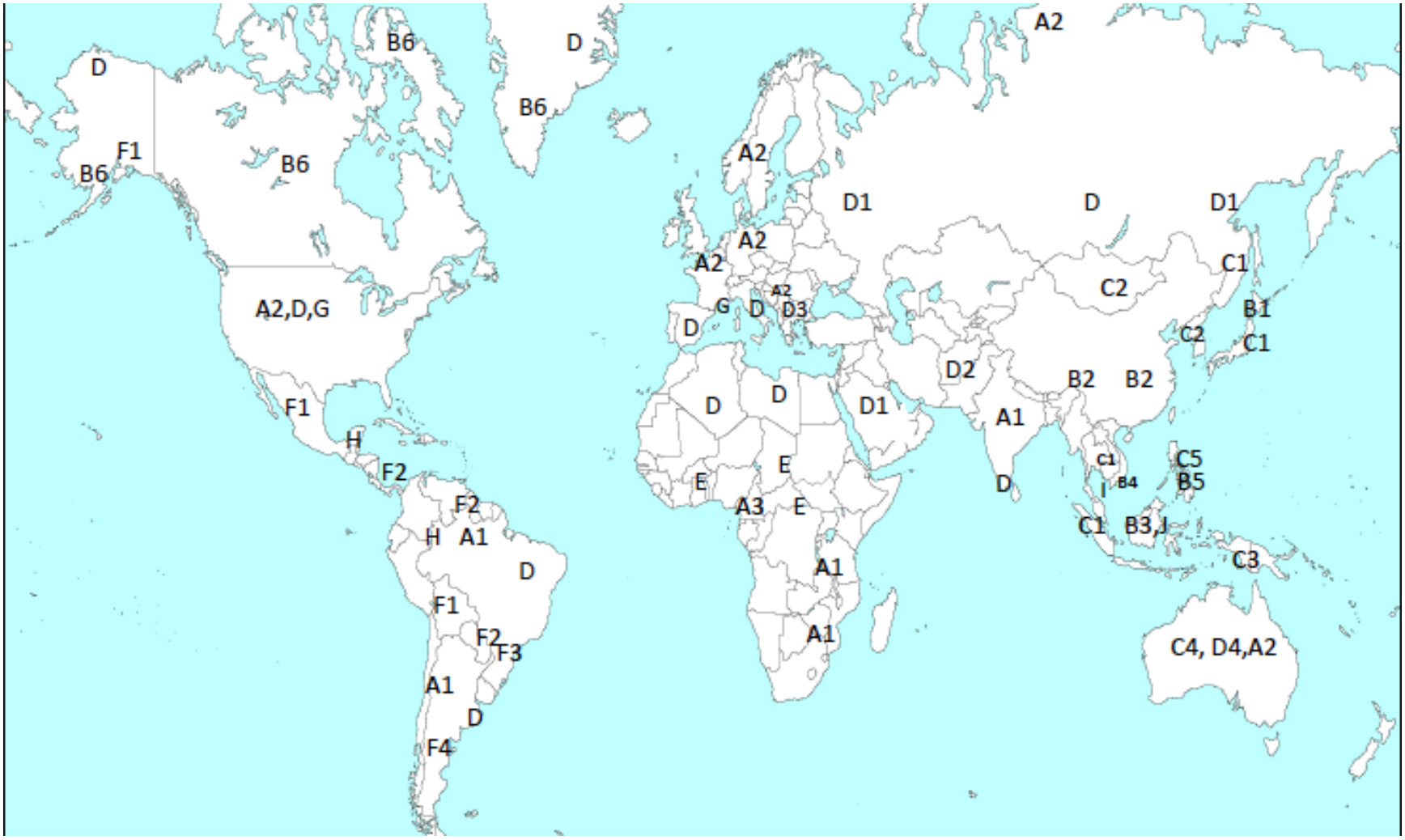
Prevalence:

257 million people living with HBV

68% in Africa /Western Pacific

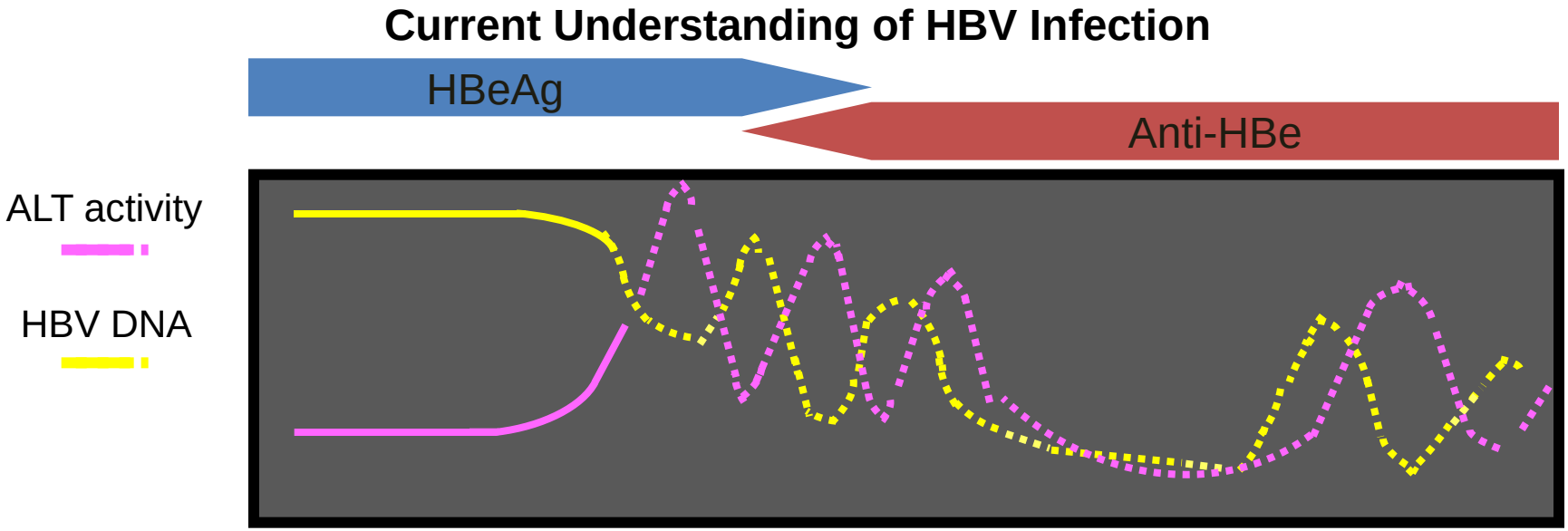
WHO Global Hepatitis Report 2017

Global distribution of HBV Genotypes



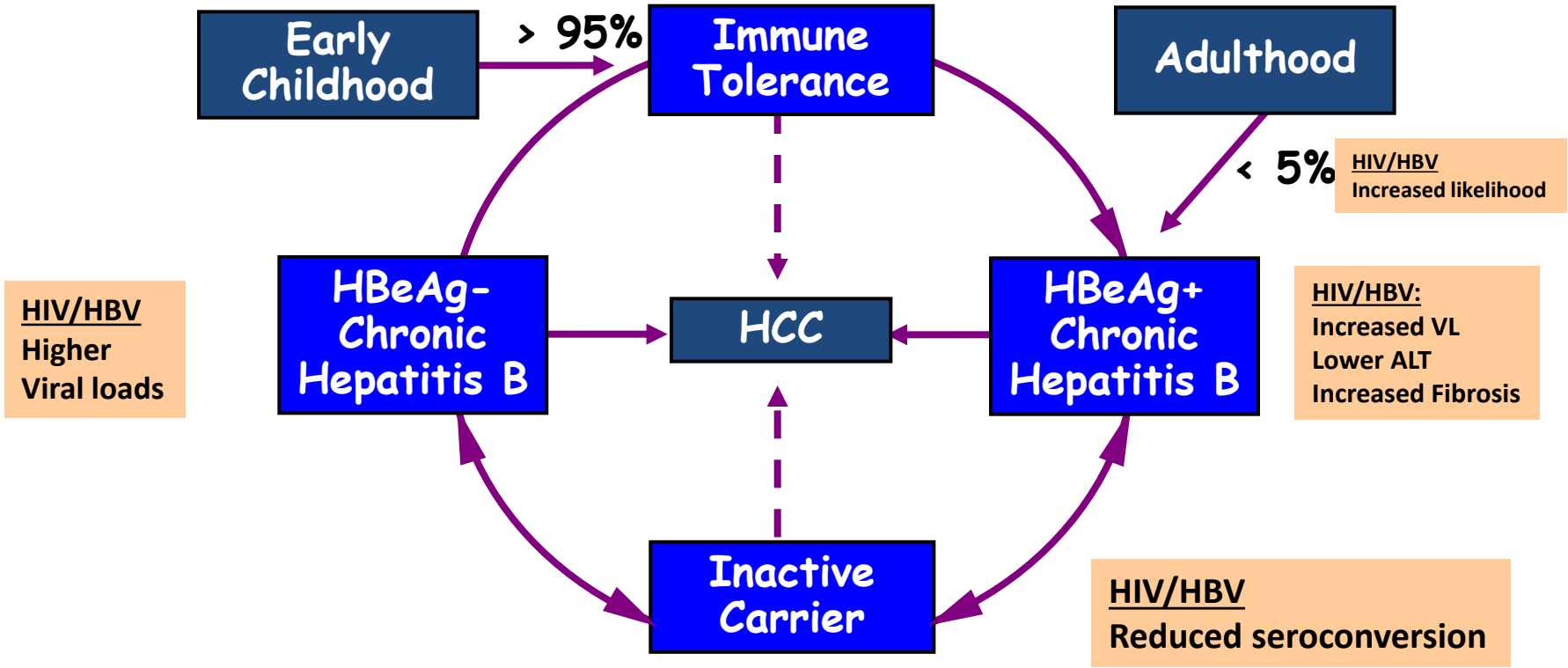
Rajoriya, et al. J Hepatology 2017

4 Phases of Chronic HBV Infection



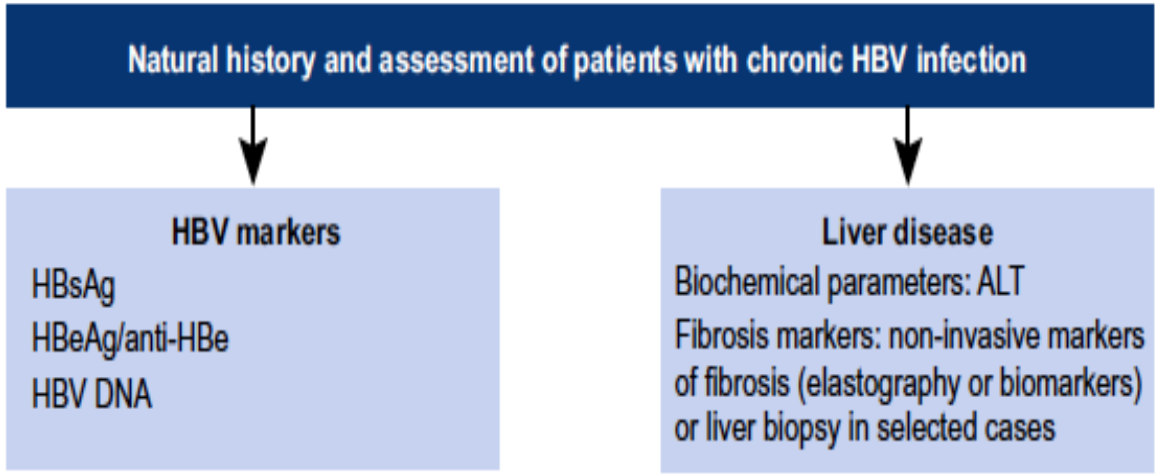
Phase	Immune Tolerant	Immune Clearance	Inactive Carrier State	Reactivation
Liver	Minimal inflammation and fibrosis	Chronic active inflammation	Mild hepatitis and minimal fibrosis	Active inflammation

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

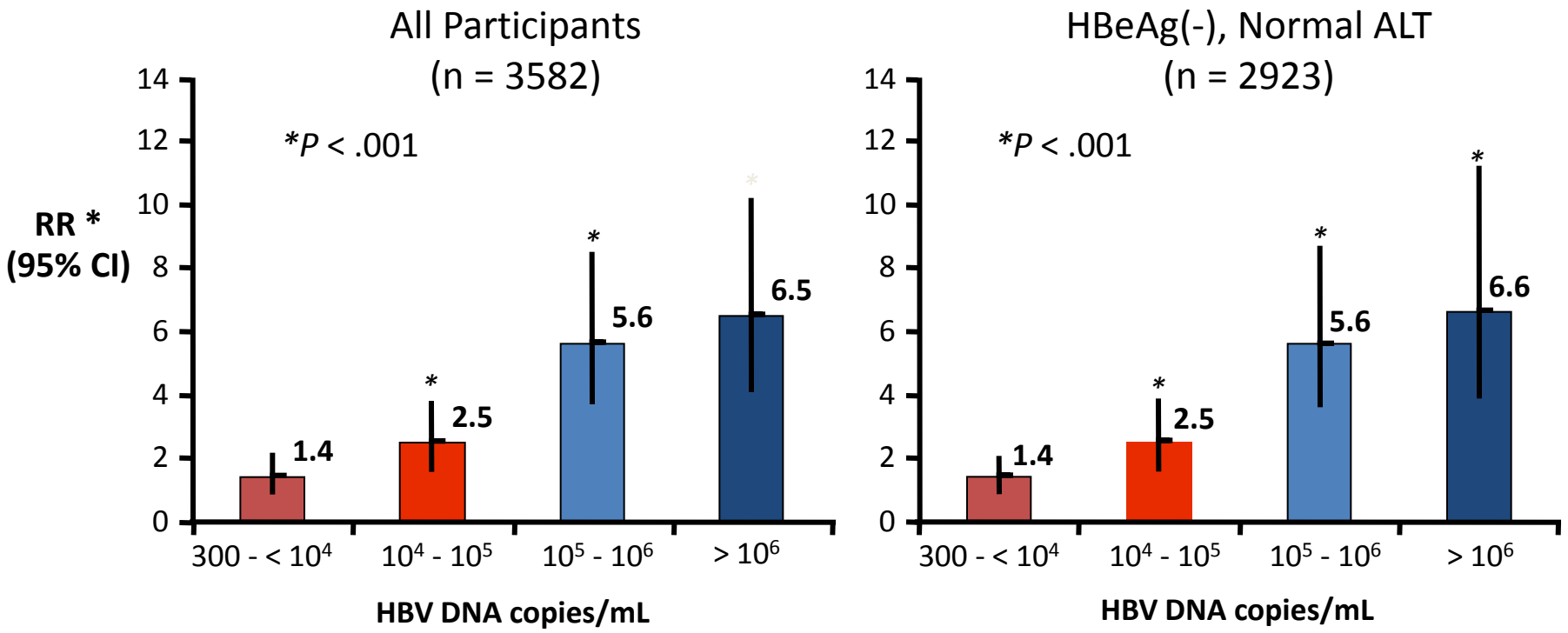
EASL HBV Guidelines 2017

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

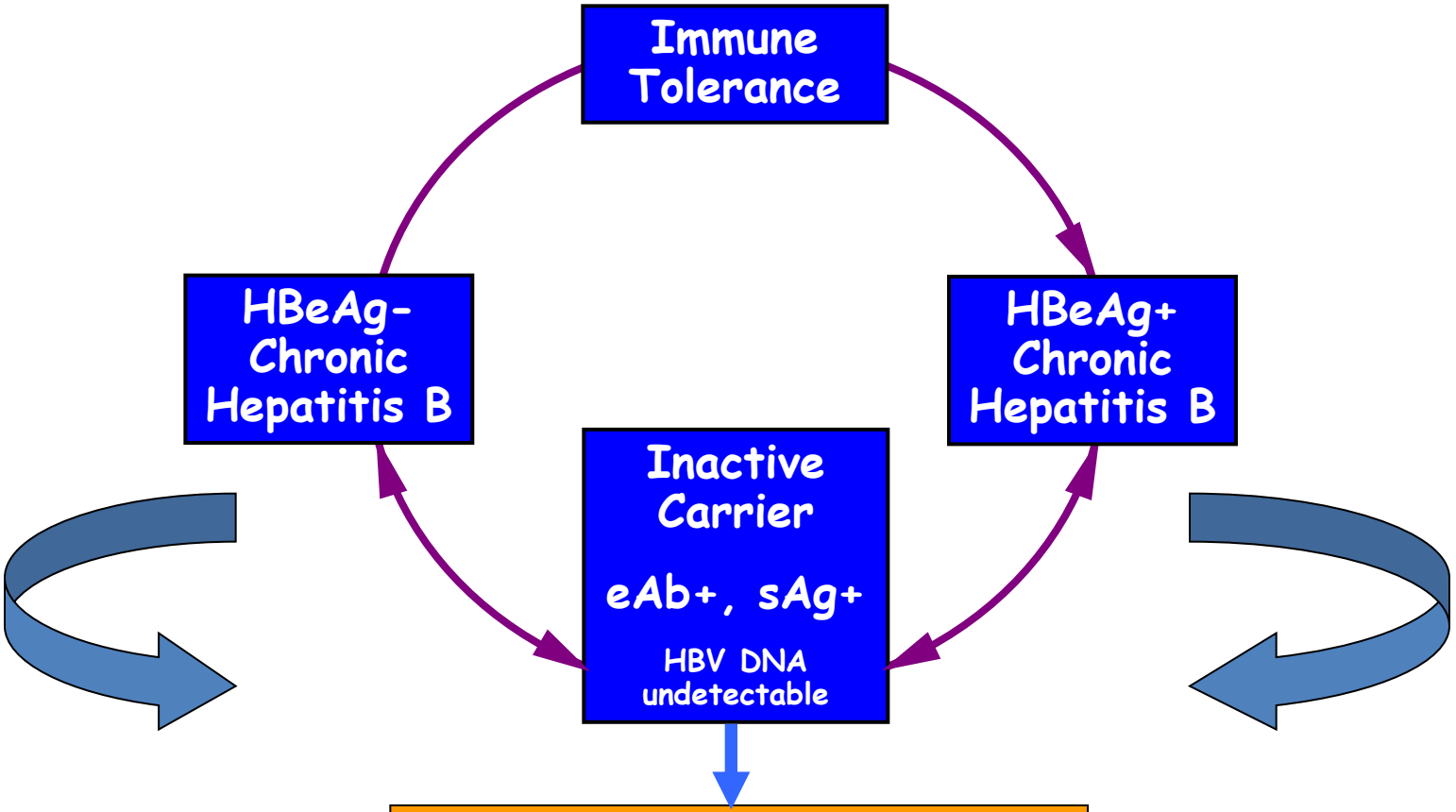


* Adjusted for age, sex, cigarette smoking, and alcohol consumption.

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

What does Rx aim to achieve?

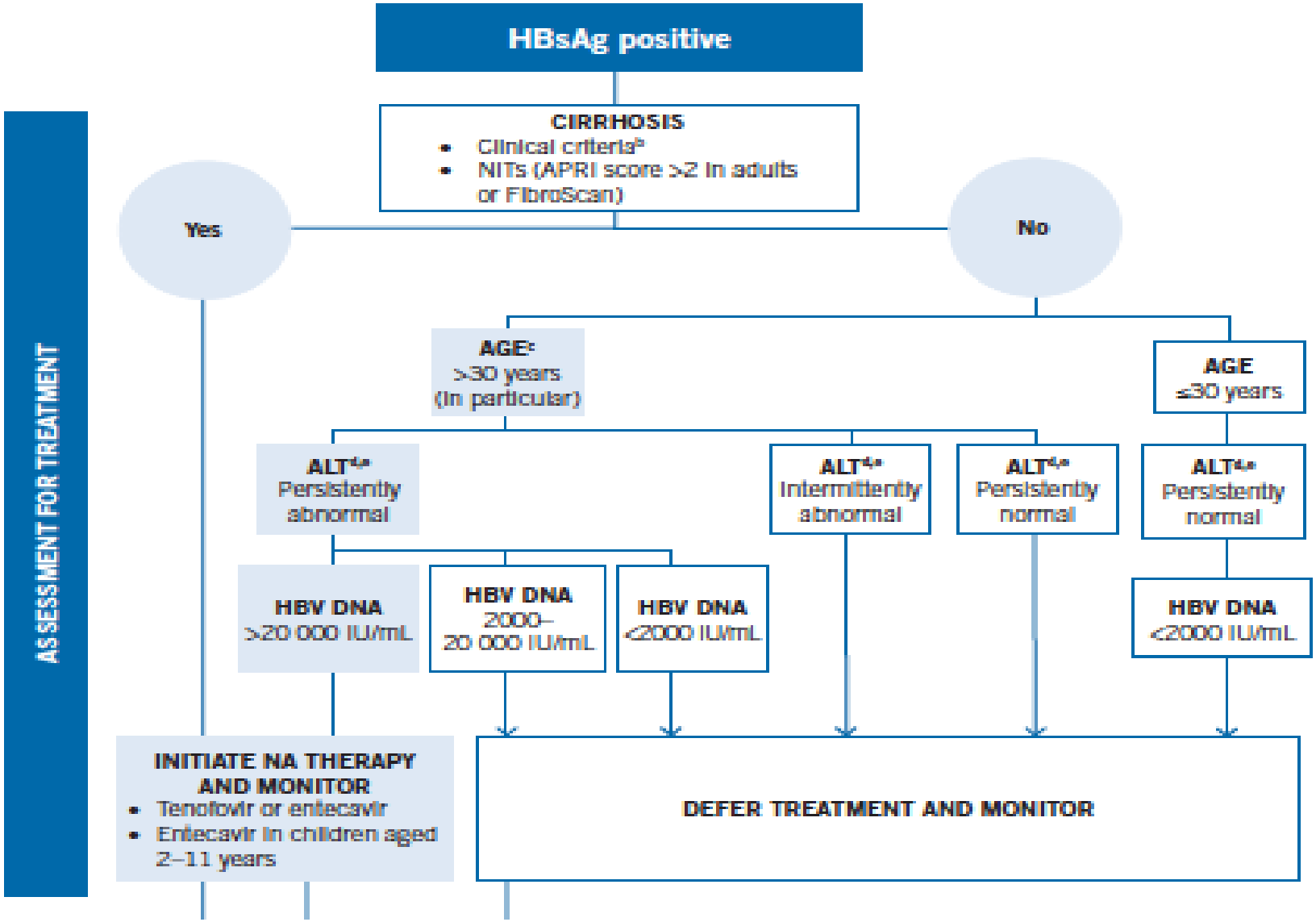


Viral Replication (HBV DNA)
Anti-HBe sero-conversion
HBsAg Loss
Anti-HBs sero-nversion
Clearance cccDNA

Three key inter-linked factors in the decision to treat

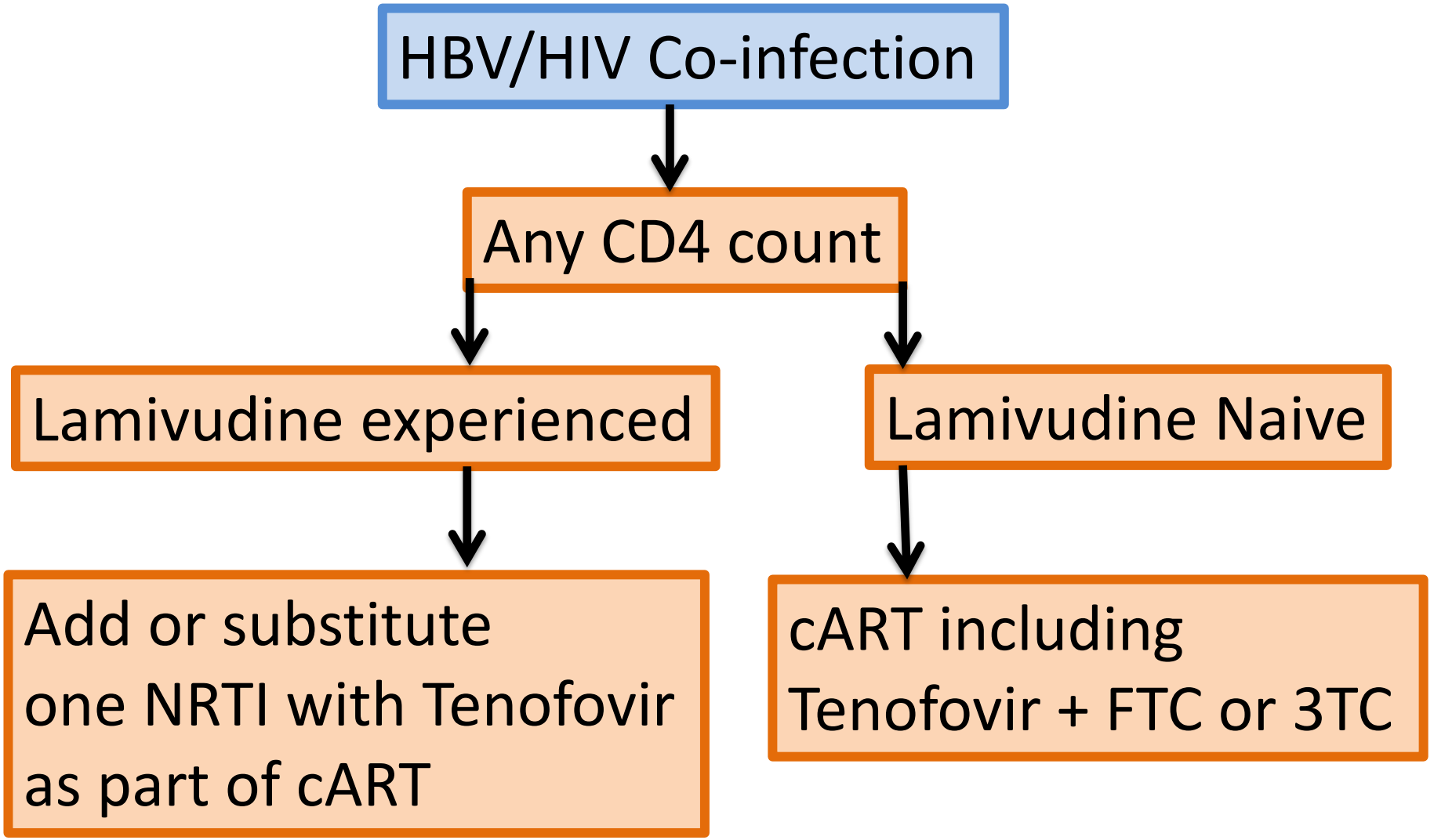
- Age
  - <30yrs vs. >30yrs
  - FH of HCC
- Level of fibrosis/inflammation
  - Cirrhosis
  - F2+ fibrosis
  - Abnormal liver enzymes
- HBV DNA levels
  - >20 000 IU/ml

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



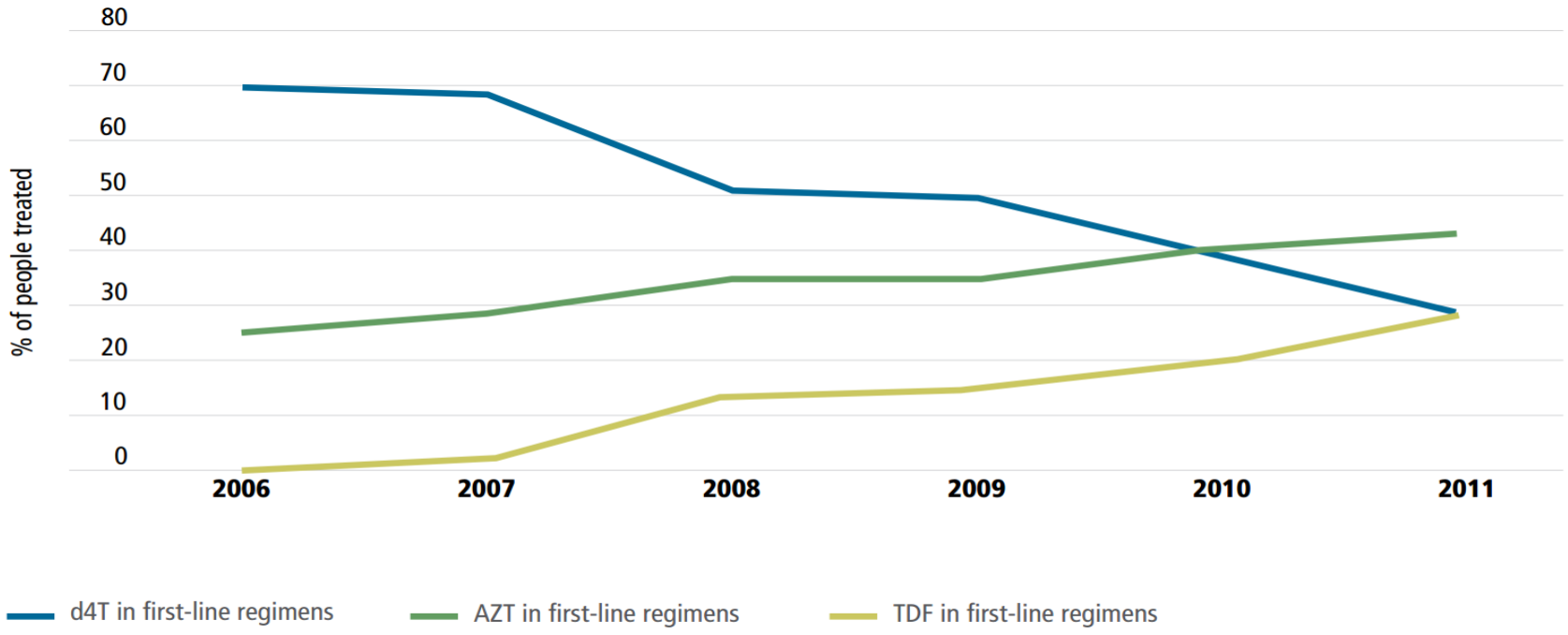
WHO Guidelines 2015

EACS Guidelines 2018



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).*

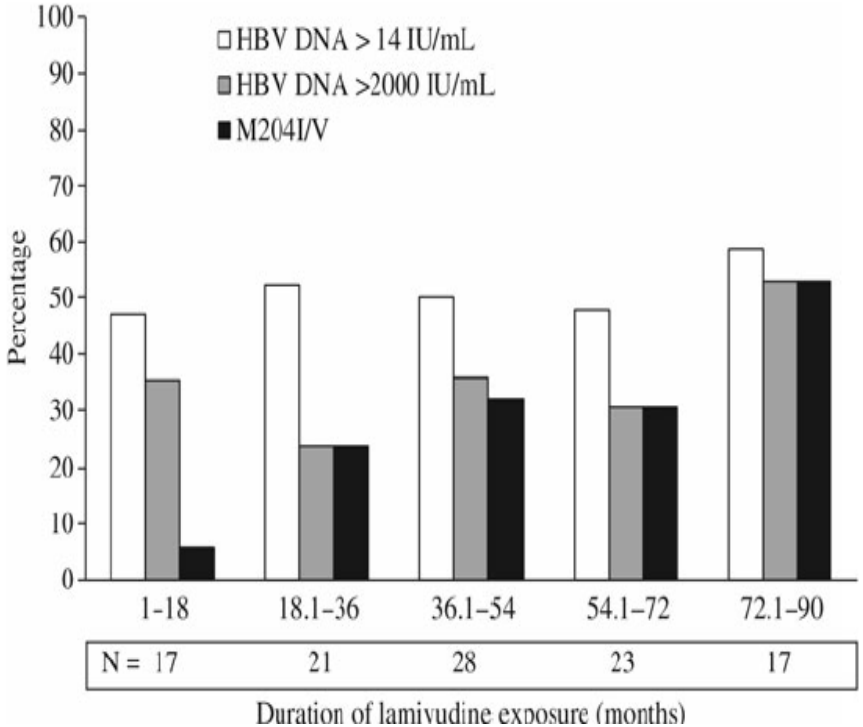
Global update on HIV treatment 2013. WHO

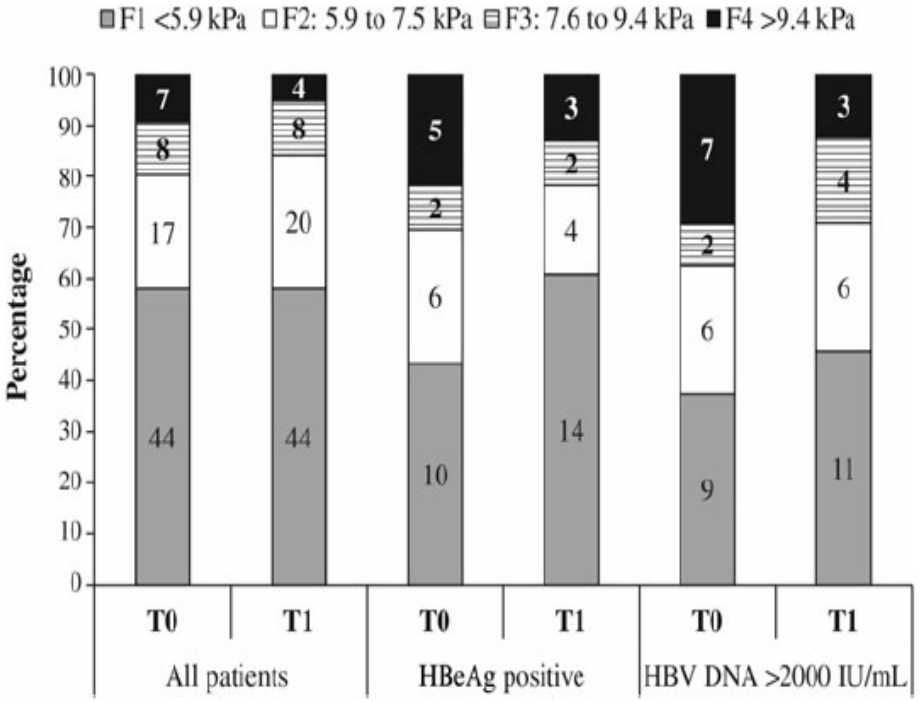
Tanzania: 3% HIV and 17% HIV/HBV on TDF regimen Hawkins IAC 2012

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

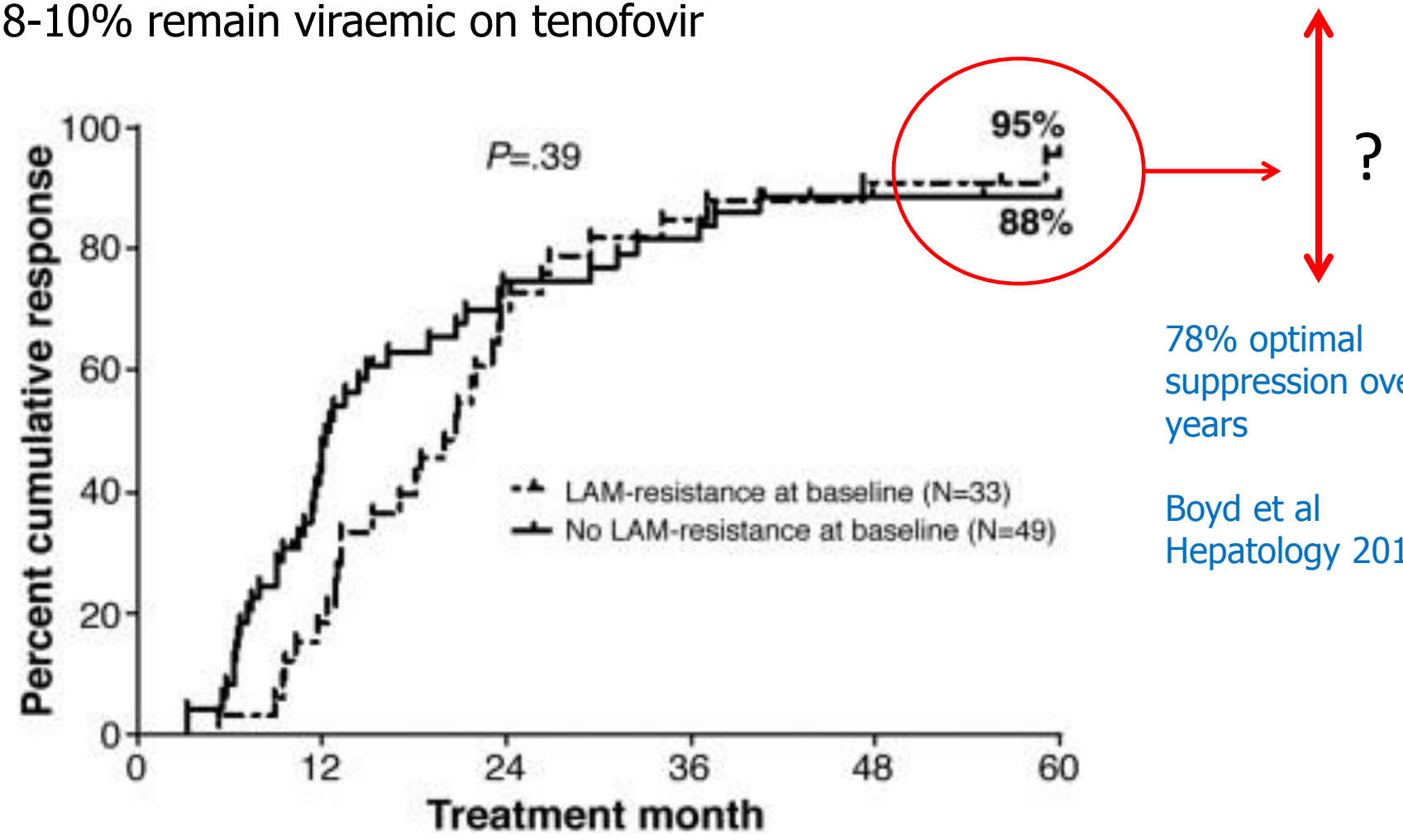




Stockdale, et al. Clin Infect Dis; 2015

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

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

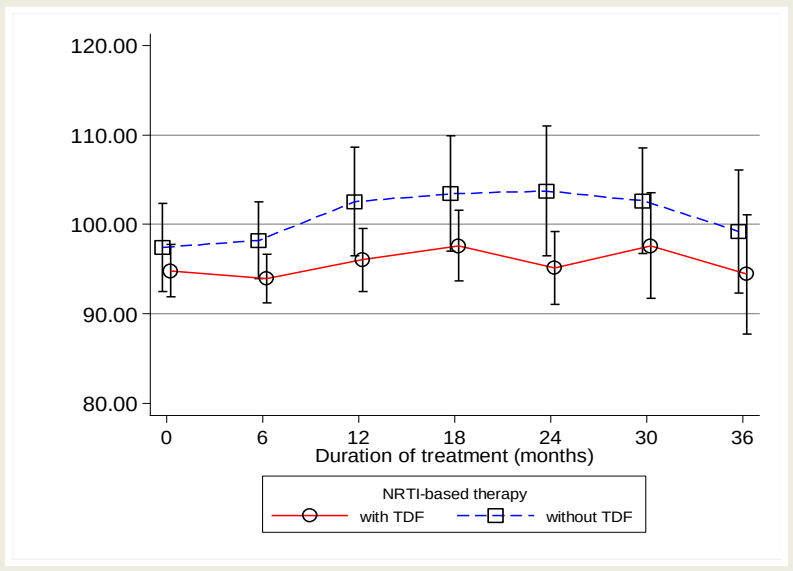
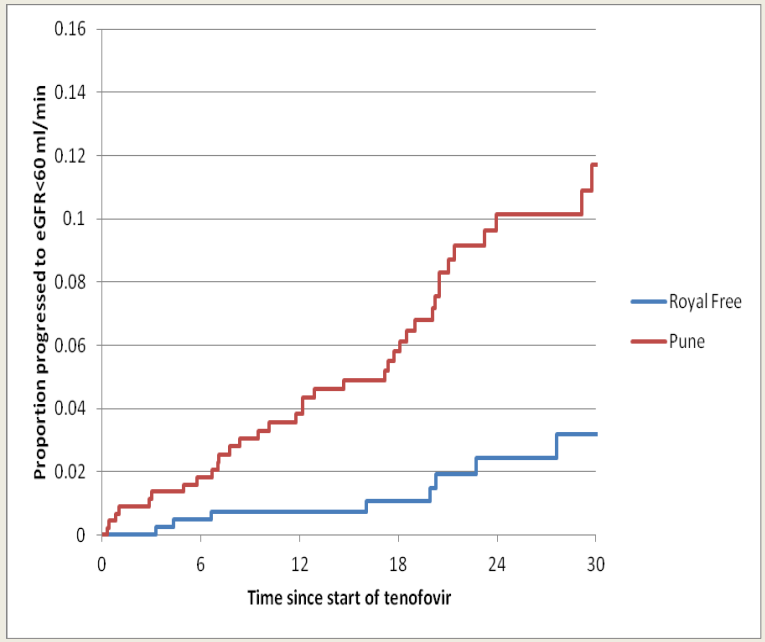


Figure 1: MDRD clearance over time

- >400 HIV+ patients receiving TDF



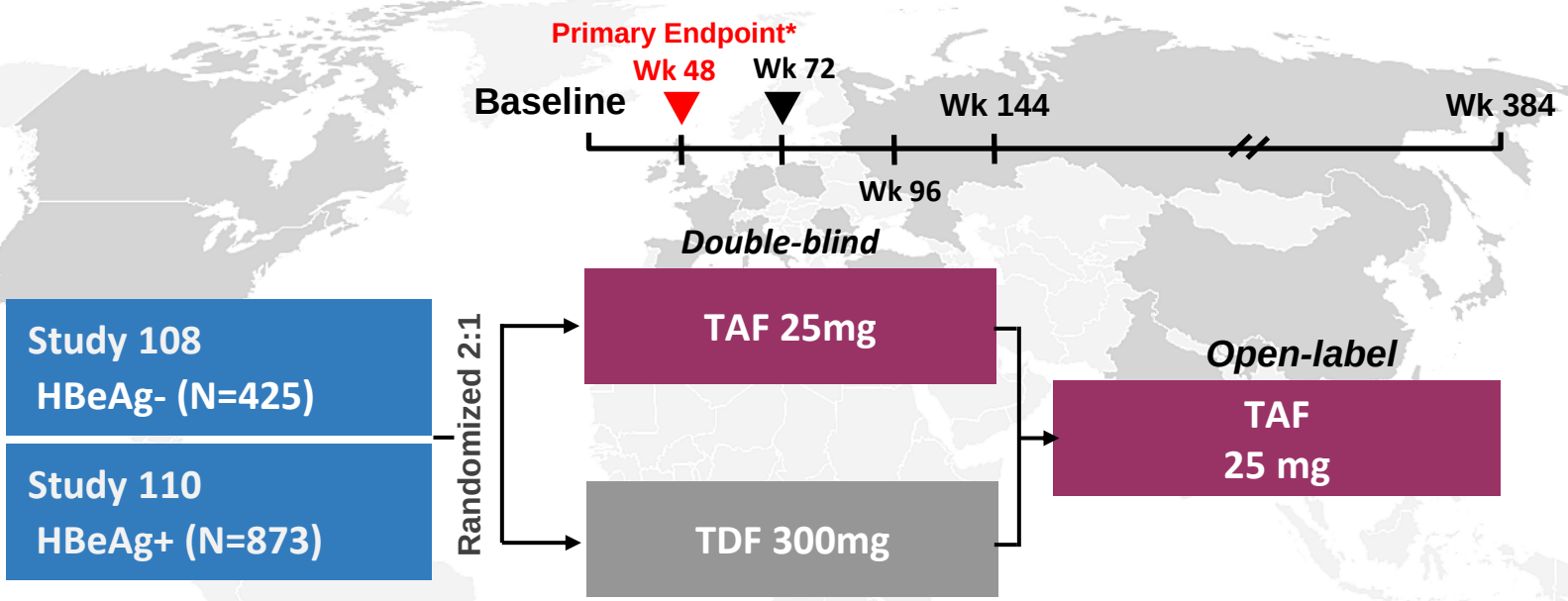
Pujari, et al, BMC Infect Dis 2014

Strategies when TDF is contra-indicated?

- Switch to Entecavir (caution if LAM-R)
- Switch to Tenofovor Alafenamide

TAF HBV Phase 3 Program

Two phase 3, randomised, double-blind studies

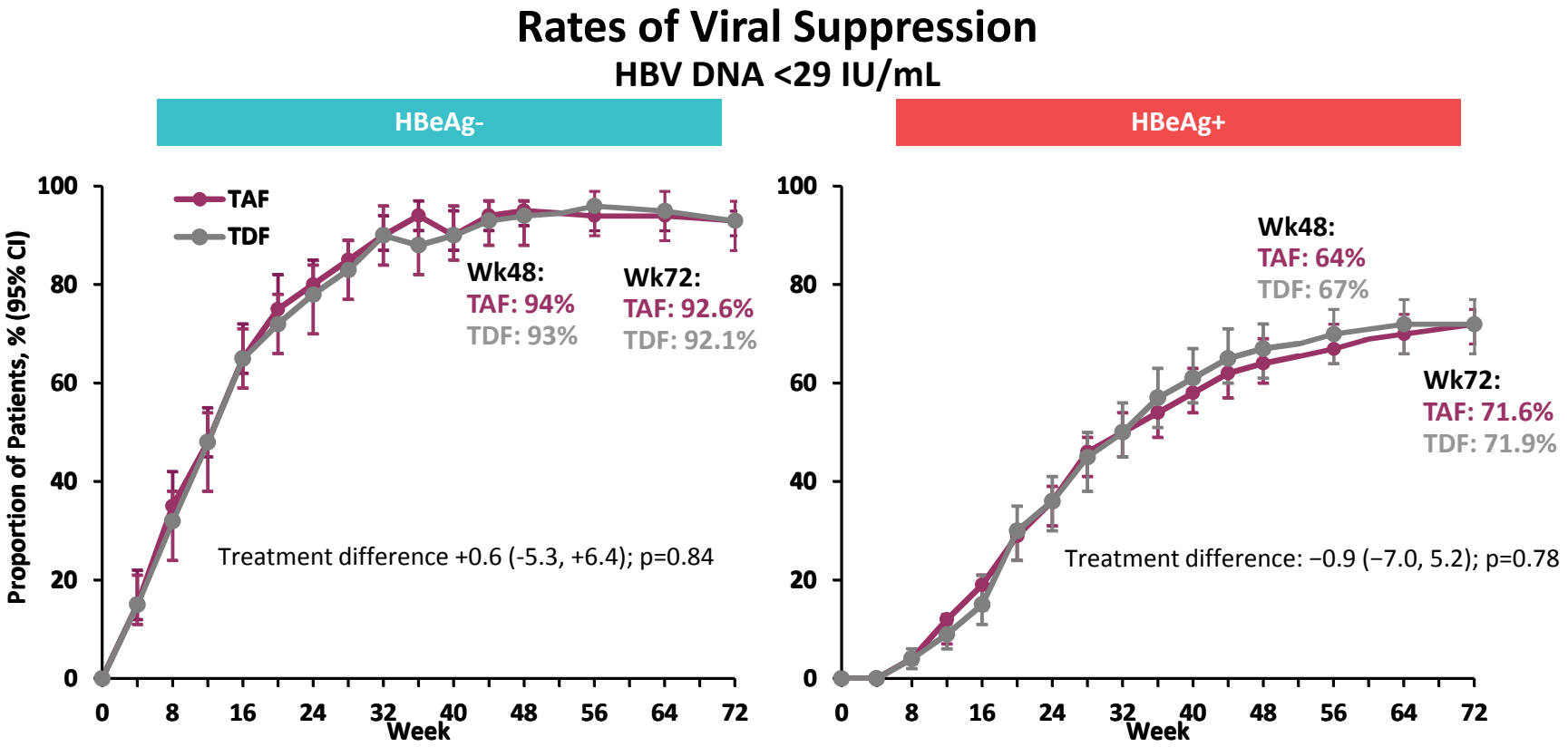


- **Primary endpoint** (non inferiority margin of 10%):
  - HBV DNA <29 IU/mL at Week 48
- **Key secondary endpoints**
  - ALT normalisation at Week 48
  - Renal parameters and bone mineral density at Week 48
- 95% retention rate through Week 48
- Inclusion criteria: HBV DNA ≥20,000 IU/mL; ALT >60 U/L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

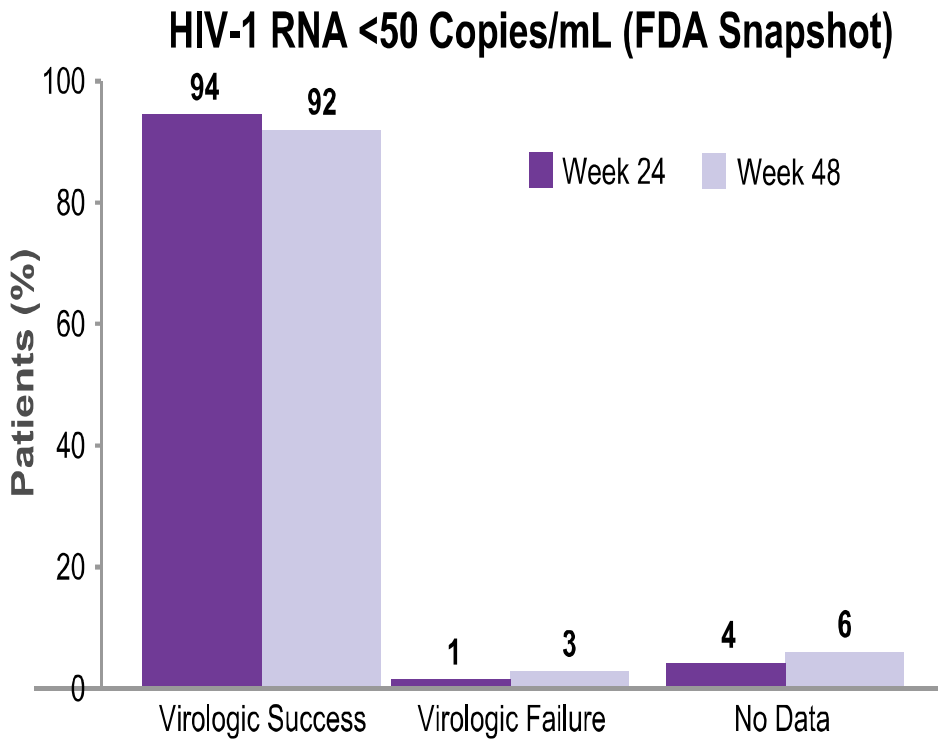
Seto, AASLD 2016, Oral 67

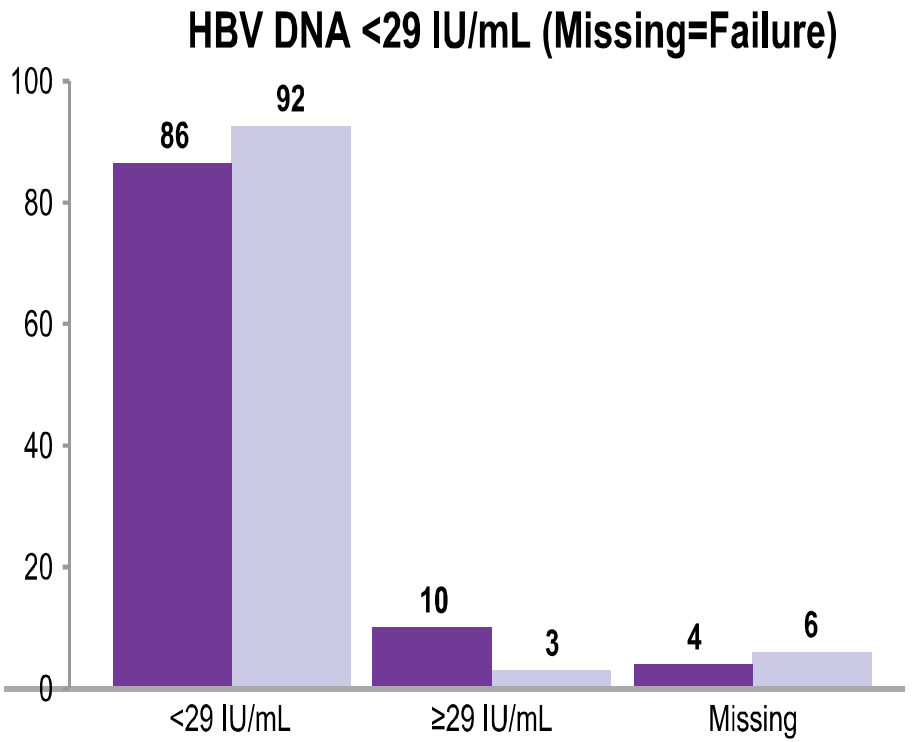
TAF in co-infected patients

(Galant et al, IAS 2015 WELBPE13)

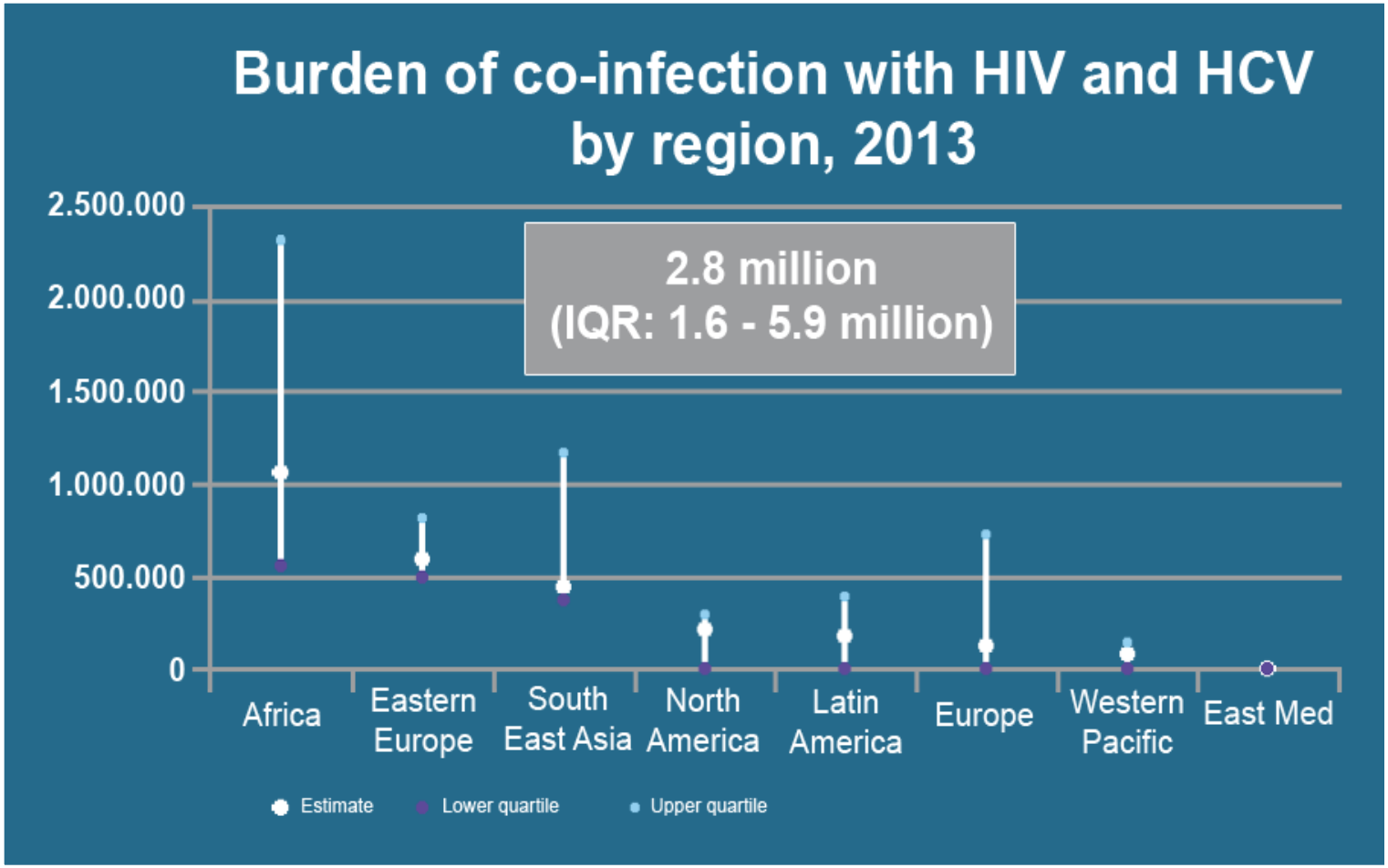
HIV-1/HBV Coinfected Patients

Switch to E/C/F/TAF





Burden of HCV in HIV populations



P Easterbrook, IAS 2015

HIV/HCV – double-trouble for the liver

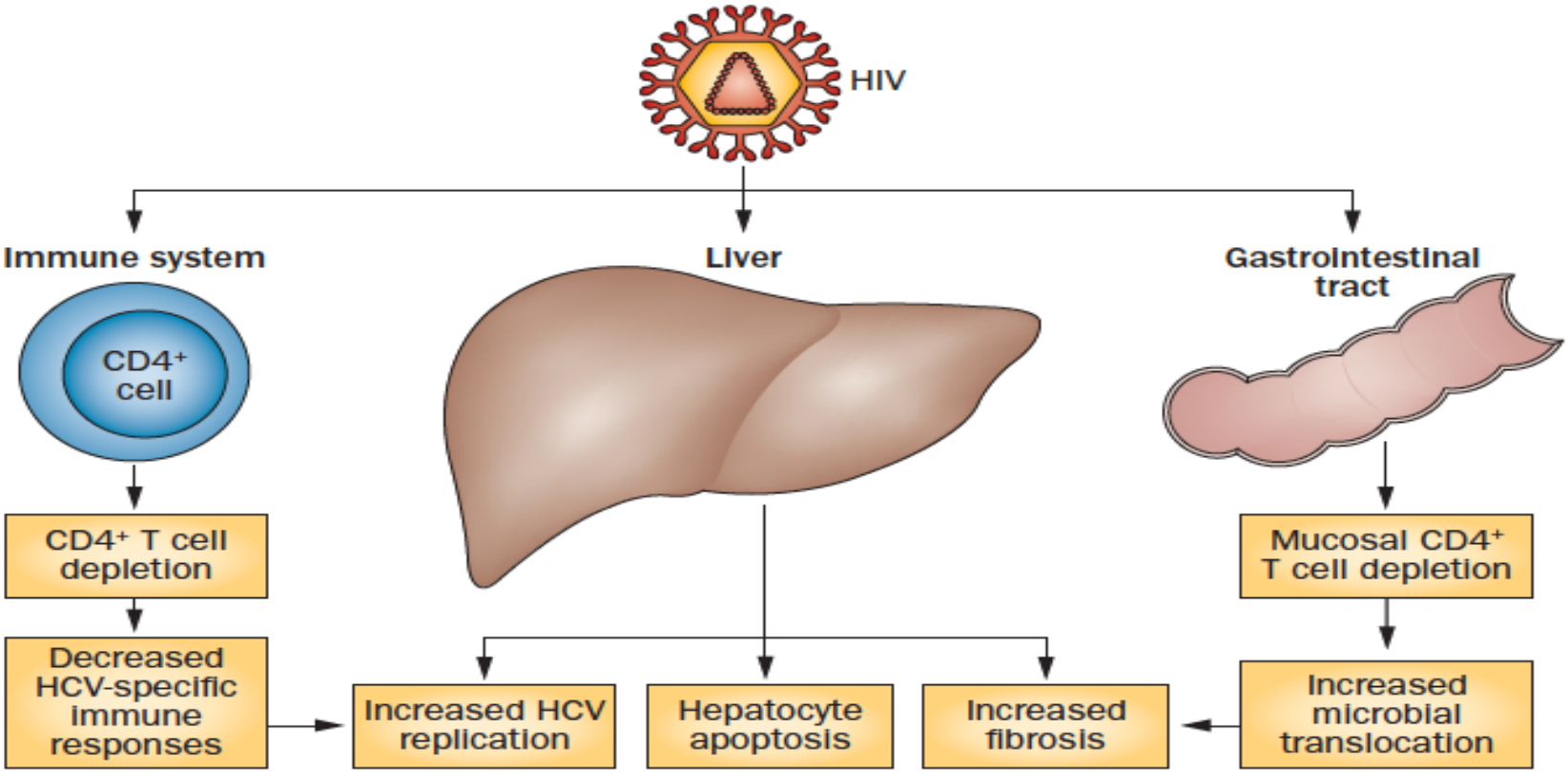


Figure 1 | Driving factors underlying liver disease pathogenesis in HCV–HIV co-infection. HIV infection leads to an impaired immune response against HCV, increased HCV replication, hepatic inflammation and apoptosis, increased microbial translocation from the gastrointestinal tract and increased fibrosis.

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

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

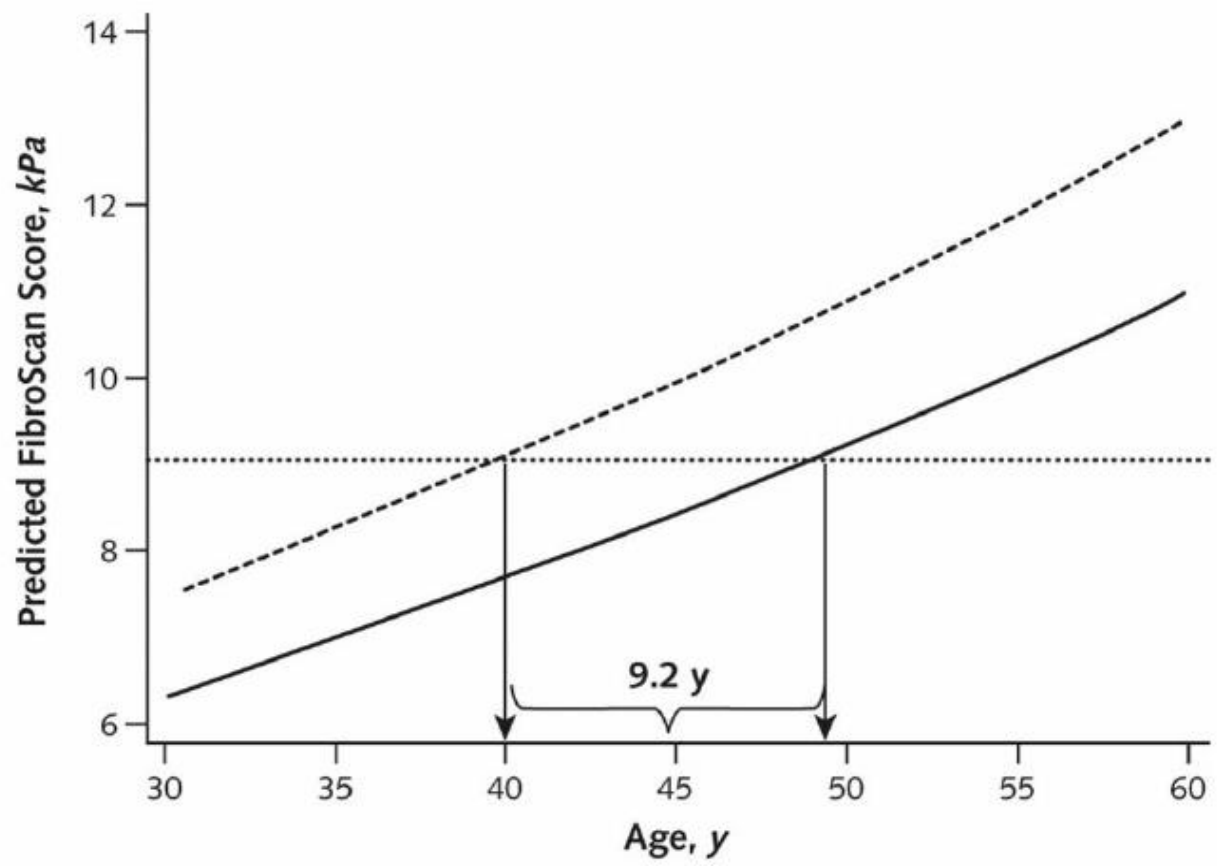
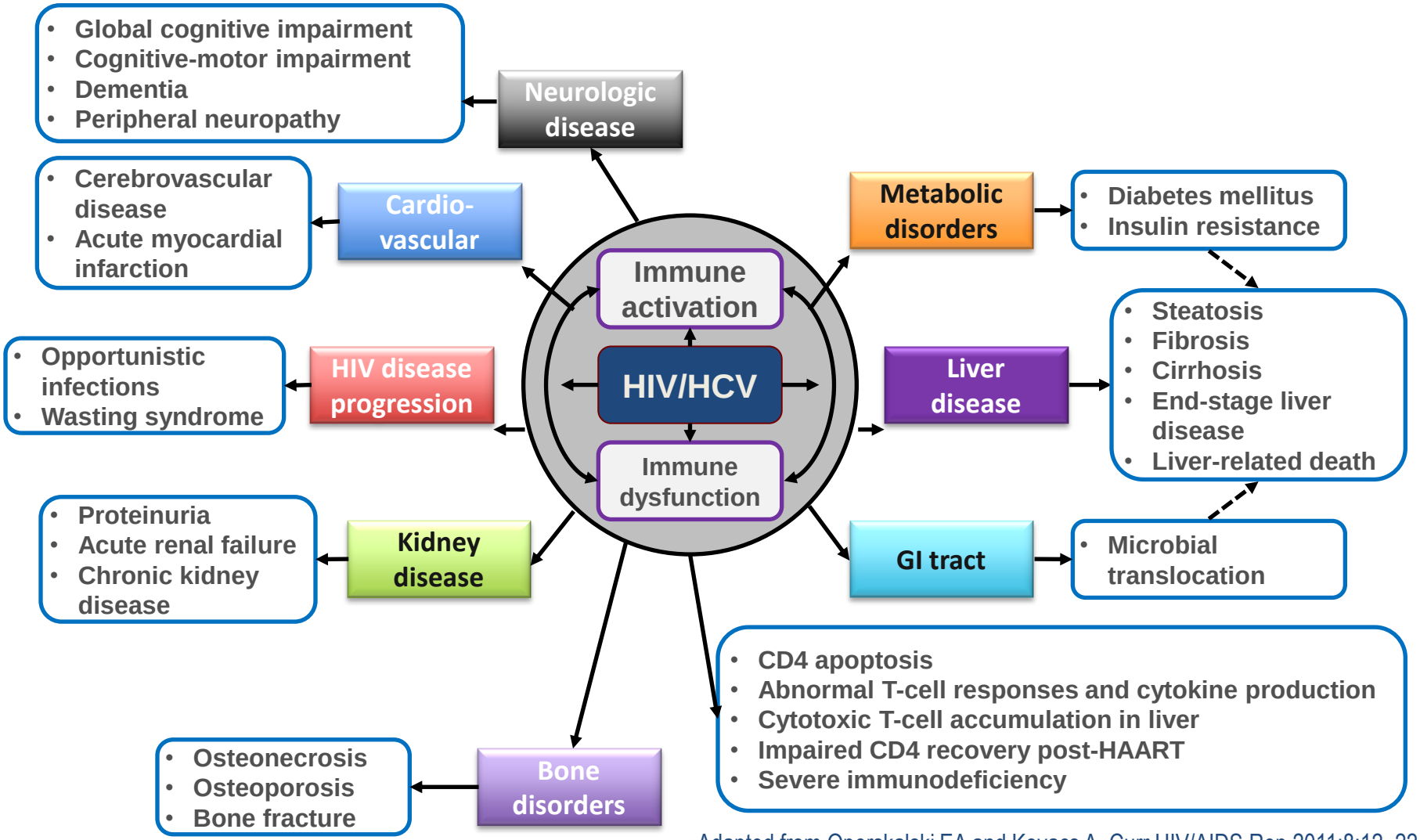


Figure 3. Liver fibrosis and age among persons coinfected with HIV and HCV (dashed line) and those with only HCV (solid line)

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

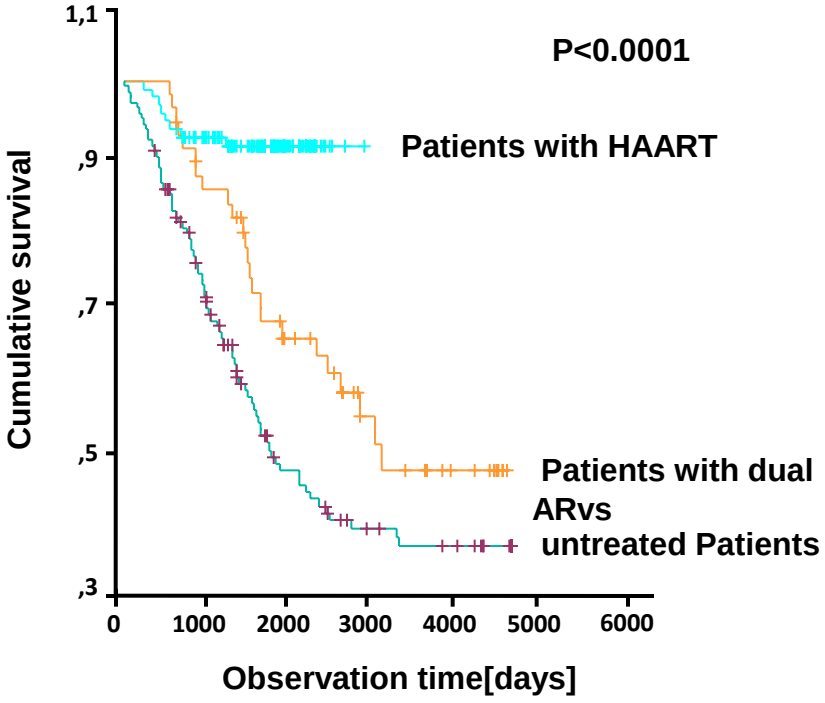
HIV/HCV – a contribution to multiple organ dysfunction



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

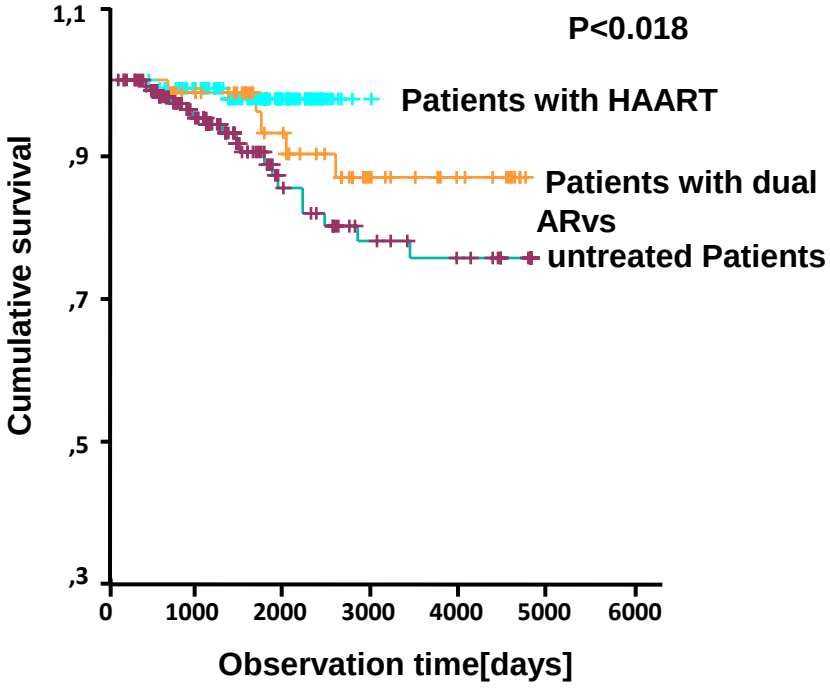
Overall and Liver-related Mortality - effect of HAART

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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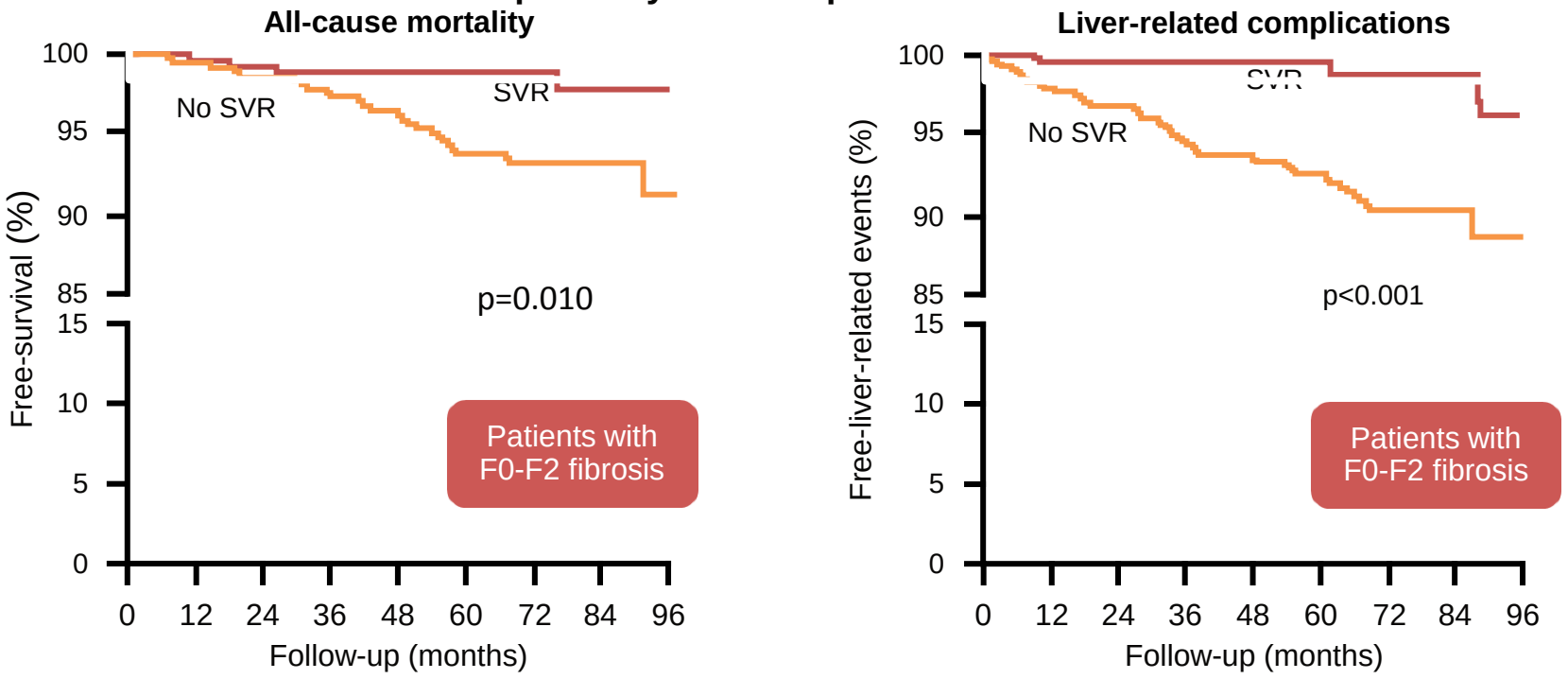
Untreated-group:	13794	49	37	32	27	

Qurishi N *et al. Lancet*, 2004

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

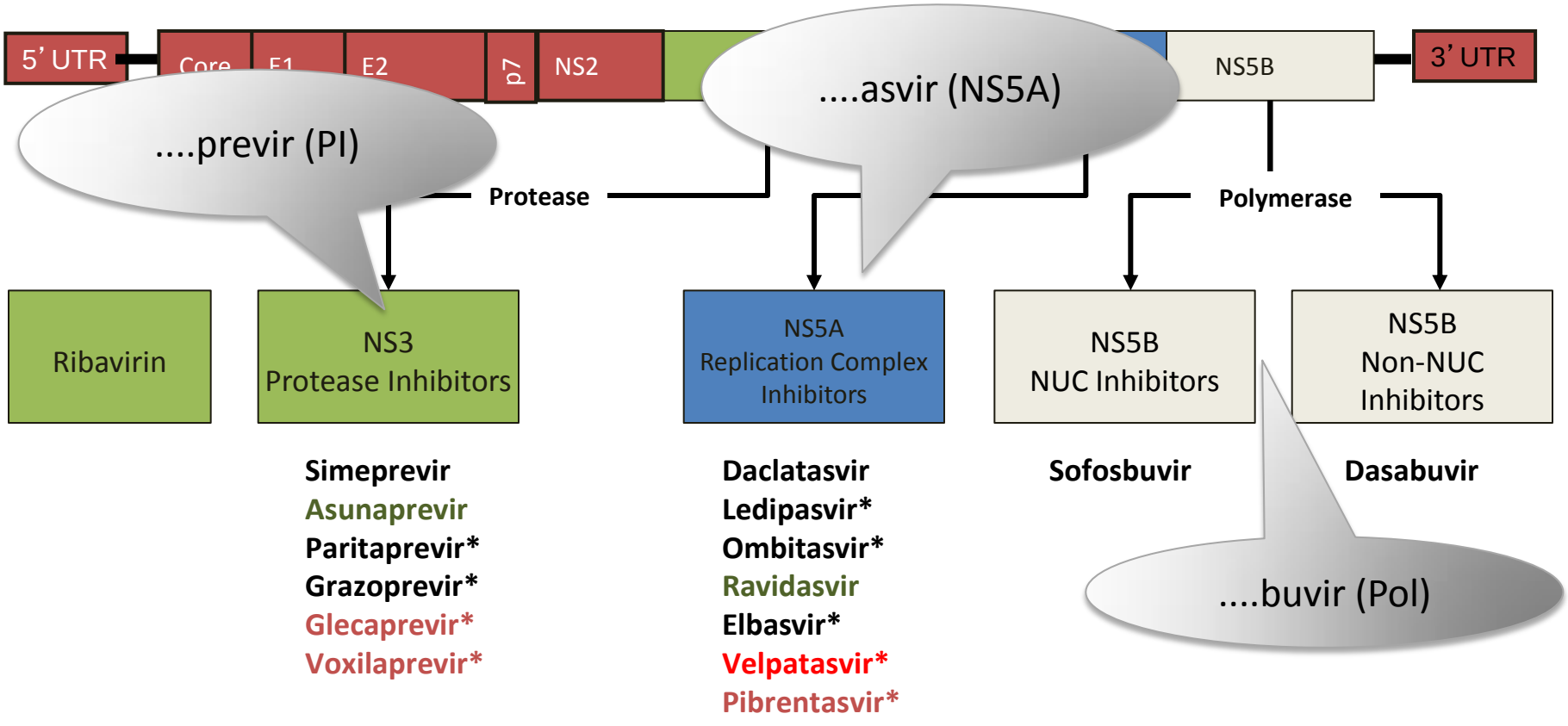
- **A total of 695 HIV/HCV-co-infected patients were treated with IFN/RBV after a median follow-up of 4.9 years. 274 patients achieved an SVR**



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

Current DAAs



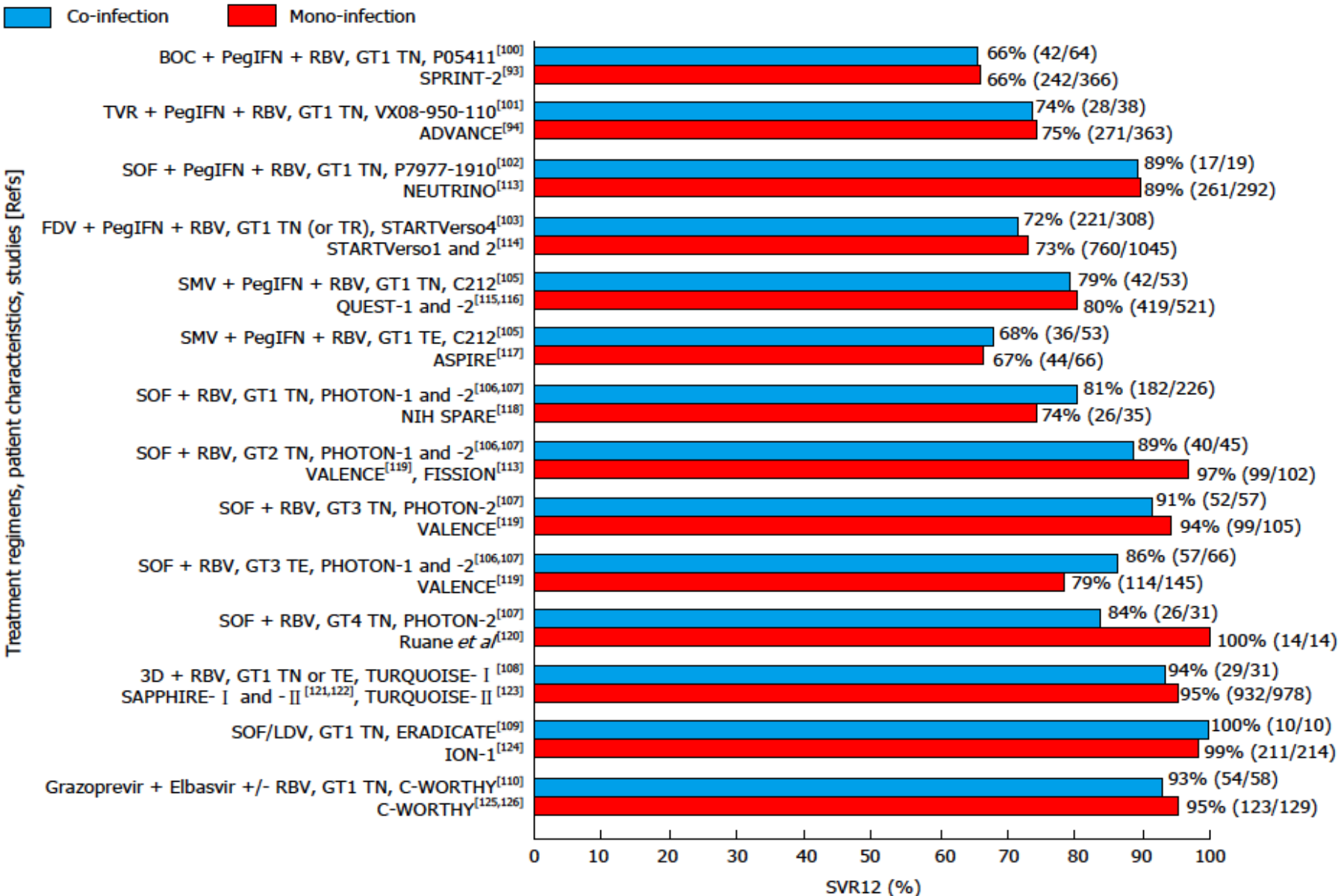
Not All Direct-Acting Antivirals are Created Equal

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.

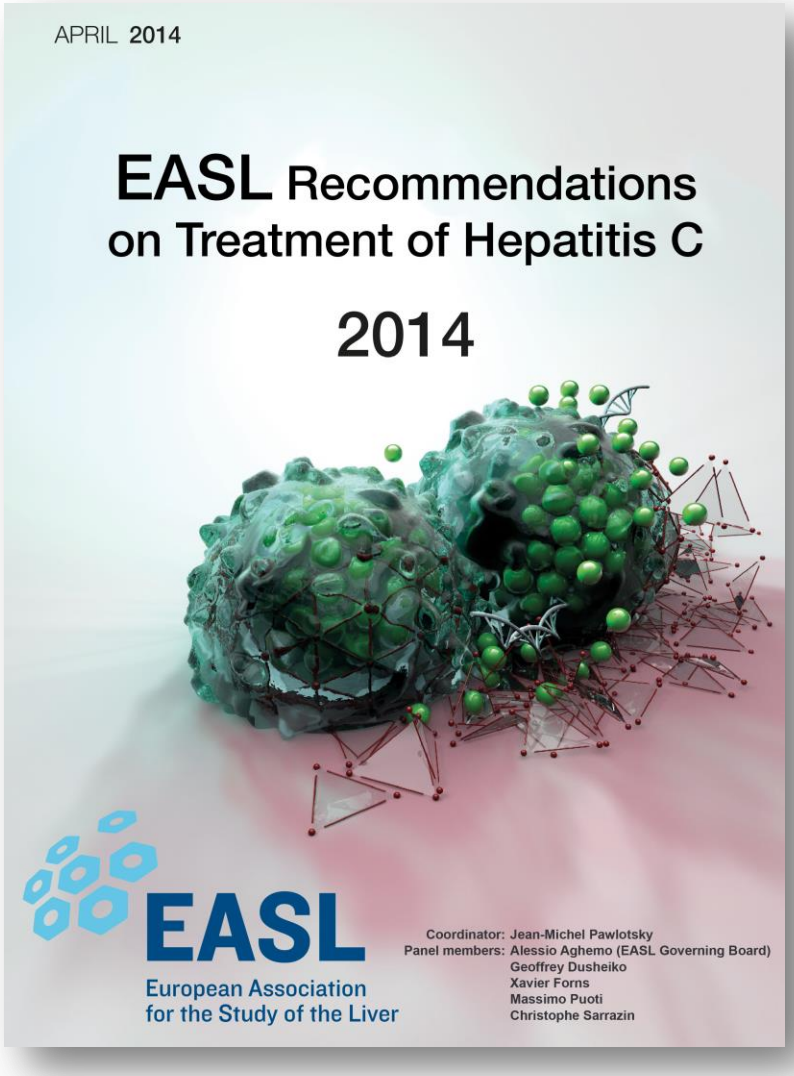
Do HIV+ respond differently to mono-infected patients?



Drug-drug Interactions

HCV drugs		ATV/c	ATV/r	DRV/c	DRV/r	LPV/r	EFV	ETV	NVP	RPV	MVC	DTG	EVG/c	RAL	ABC	FTC	3TC	TAF	TDF	ZDV
DAAs	daclatasvir	↑[i]	↑110%[i]	↑	↑41%	↑15%	↓32%[ii]	↓	↓	↔	↔	E33%	↑[i]	↔	↔	↔	↔	↔	↑10% E10%	↔
	elbasvir/ grazoprevir	↑	↑	↑	↑	↑	↓54/83%	↓	↓	↔	↔	↔	↑	E43%	↔	↔	↔	↔	↓7/14% E34%	↔
	glecaprevir/ pibrentasvir	↑	↑553/64%	↑	↑397%/-	↑338/146%	↓	↓	↓	E84%	E	↔	↑205/57% E47%	E47%	↔	↔	↔	↔	E29%	↔
	parita-previr/r/ ombitasvir/ dasabuvir	↑	↑94%[iii]	↑	D[iv]	↑	[vi]	↓E	↓E	E[vii]	E	↔	↑	E134%	↔	↔	↔	E	↔	↔
	paritaprev-ir/r/ombi-tasvir	↑	↑[iii]	↑	↑[v]	↑	[vi]	↓E	↓E	E[vii]	E	↔	↑	E20%	↔	↔	↔	E	↔	↔
	simeprevir	↑	↑	↑	↑	↑	↓71%	↓	↓	↑6% E12%	↔	↔	↑	↓11% E8%	↔	↔	↔	↔	↓14% E18%	↔
	sofosbuvir/ ledipasvir	↑[viii]	↑8/113%[viii]	↑[viii]	↑34/ 39%[viii]	↔[viii]	↓-/34%	↔	↔	↔[viii]	E	↔	↑36/ 78%E[viii]	D≈20%	↔	↔	↔	E32%	E[viii]	↔
	sofosbuvir/ velpatasvir	↔[viii]	↑-/142%[viii]	↔[viii]	↓28%/-[viii]	↓29%/-[viii]	↓-/53%	↓	↓	↔	E	↔	↑[viii]	↔	↔	↔	↔	↔	E[viii]	↔
	sofosbuvir/ velpatasvir/ voxilaprevir	↑	↑40/93/331%	↑[viii]	↑-/ -/143% [viii]	↑	↓	↓	↓	↔	E	↔	↑-/-/171% [viii]	↔	↔	↔	↔	↔	E[viii]	↔
	sofosbuvir	↔	↔	↑	↑34%	↔	↔	↔	↔	↔	↔	↔	↔	↓5%D27%	↔	↔	↔	↔	↔	↔

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 (2018)

IFN-free HCV Treatment Options (preferred regimen in bold, alternative regimen in light grey)

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

Are there remaining 'unresolved' issues with HCV?

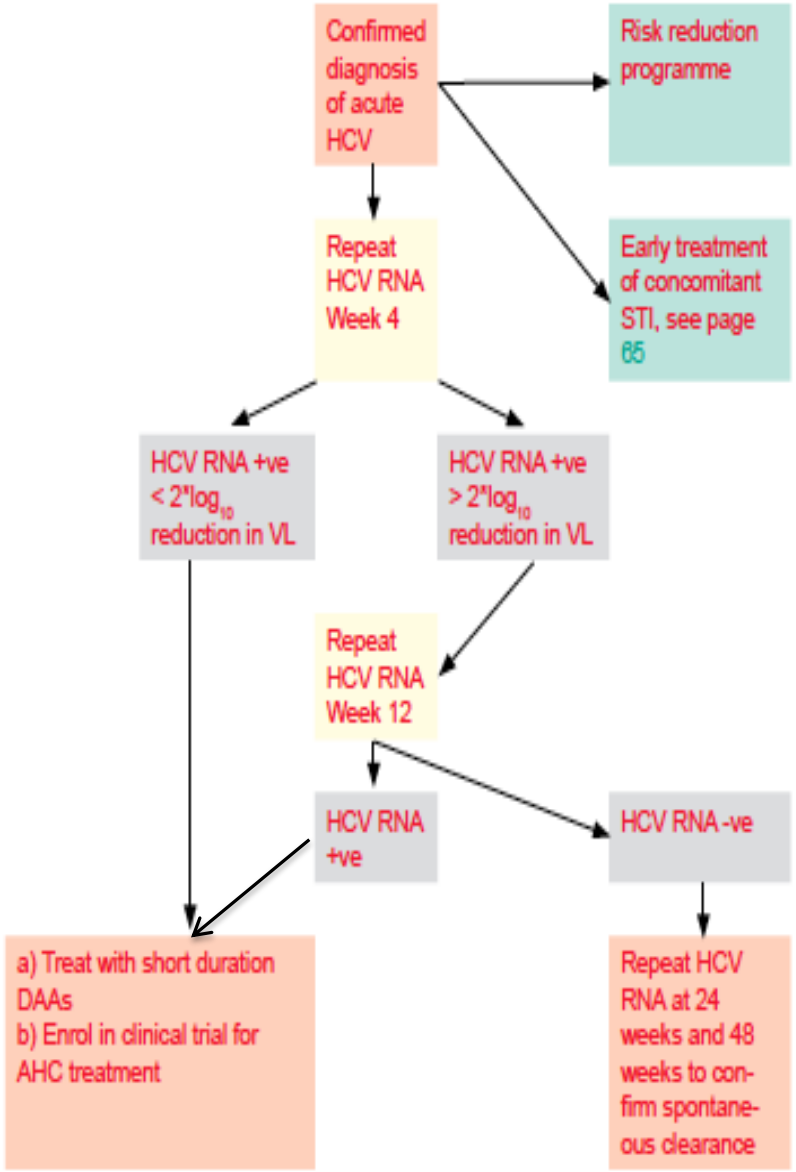
- Is 'shorter' therapy possible for co-infected patients wit acute/early HCV?
- Is it ever 'too late' to treat HCV?
  - ESLD – Rx vs. Transplant followed by Rx
- Will TasP work?
- Will we be able to 'eliminate' HCV by 2030?

Short duration DAAs for Acute/Early HCV

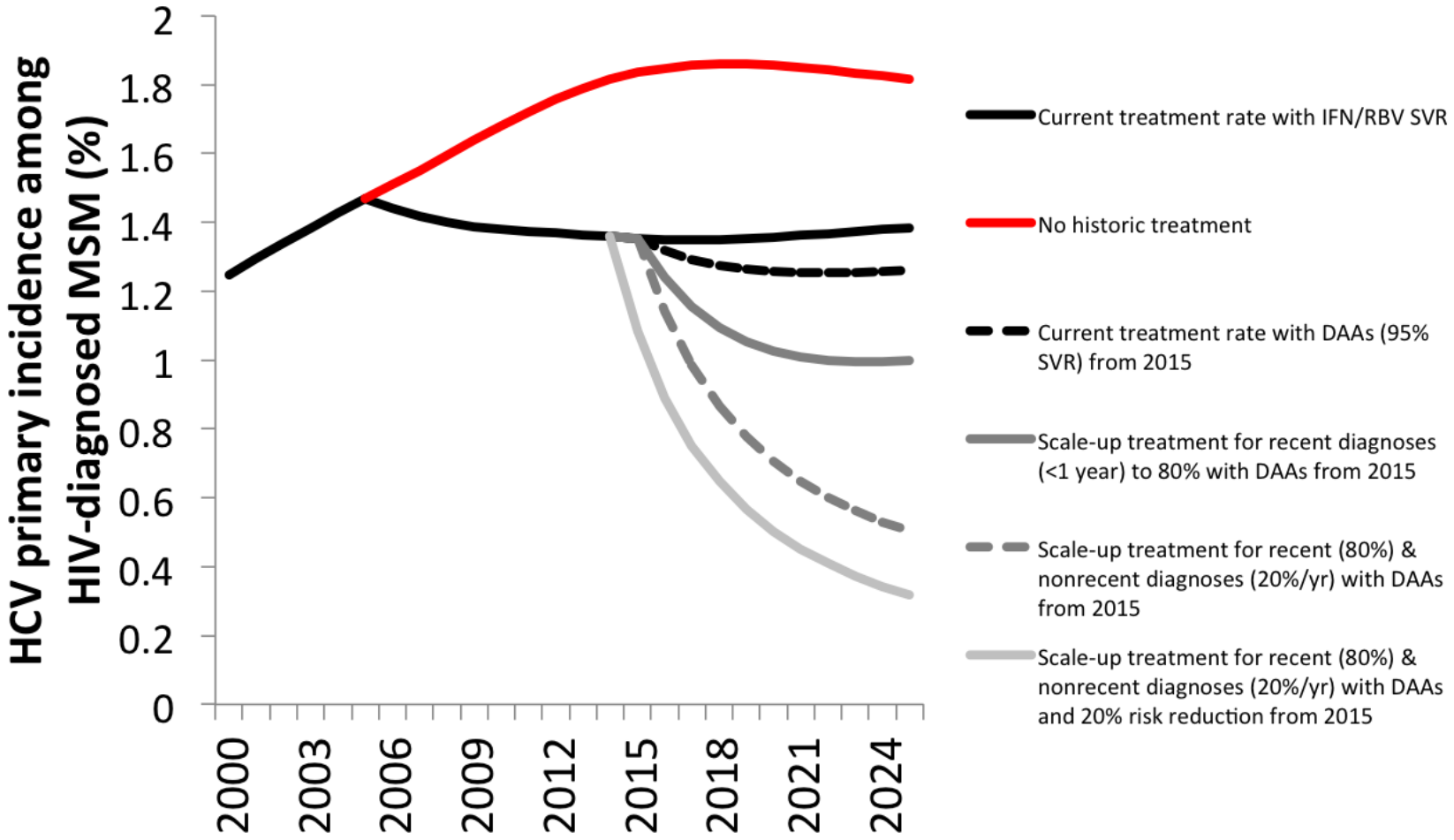
Direct acting antiviral therapy for acute HCV

	HIV+	HIV-	HCV genotype	Regimen	Duration (weeks)	Number of patients	SVR
Naggie et al. CID 2017	X		1	Sofosbuvir + ribavirin	12	17	59%
El Sayed et al. HIVCT 2017	X		1	Sofosbuvir + ribavirin	12	12	92%
Martinello et al. Hepatology 2016	X	X	1+3	Sofosbuvir + ribavirin	6	13+6	32%
Deterding et al. Lancet ID 2017		X	1	Sofosbuvir + ledipasvir	6	20	100%
Rockstroh et al. Lancet GE 2017	X		1+4	Sofosbuvir + ledipasvir	6	19+7	77%
Naggie et al. AASLD 2017	X		1	Sofosbuvir + ledipasvir	8	27	100%
Fierer et al. EASL 2017	X		1+4	Sofosbuvir + ledipasvir	8	20+1	100%
Martinello et al AASLD 2017	X	X	1	Paritaprevir/ritonavir/ombitasvir + dasabuvir + ribavirin	8	30	96%
DAHHS 2 NCT02600325	**X**	**X**	**1+4**	**Grazoprevir + elbasvir (GZR/EBR)**	**8**	**80**	98%

Algorithm for Management of Acute HCV in Persons with HCV/HIV Co-infection



Treatment As Prevention in HIV/HCV



N Martin, et al 2015 (manuscript submitted)

Substantial decline in Acute HCV post DAA rollout in the Netherlands

Study hypothesis:

Unrestricted DAA access will result in a decrease in the number of new HCV infections in HIV+MSM

- By 2017, 742/971 (76%) HIV+ MSM patients treated for HCV
  - 50% 2014, 65% 2016, treated Acute HCV in the early phase via clinical trials (DAHHS 1 and 2 studies)

Rjinders, et al24th CROI Seattle, WA Feb 13-1 2017 O137LB

Substantial decline in Acute HCV post DAA rollout in the Netherlands

2014

A-HCV **n = 93**

PYFU n = 8290

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

1.1% per year

2016

A-HCV **n = 49**

PYFU n = 8961

5.5/1000 PYFU (95% CI 4–7)

0,55% per year

IRR 0.49 (95% CI 0.34 – 0.69)

Jan-Dec 2014 11.2/1000

Jan-Jun 2016 6.9/1000

July-Dec 2016 4.0/1000

Rjinders, et al24th CROI Seattle, WA Feb 13-1 2017 O137LB

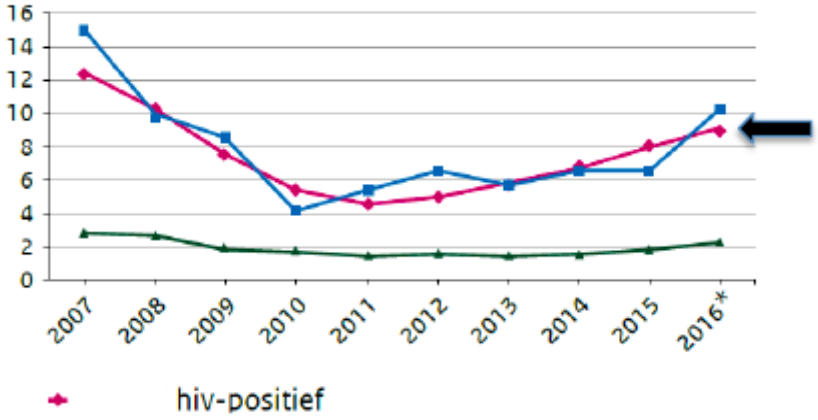
Decline NOT associated with reduction in risk-behaviour

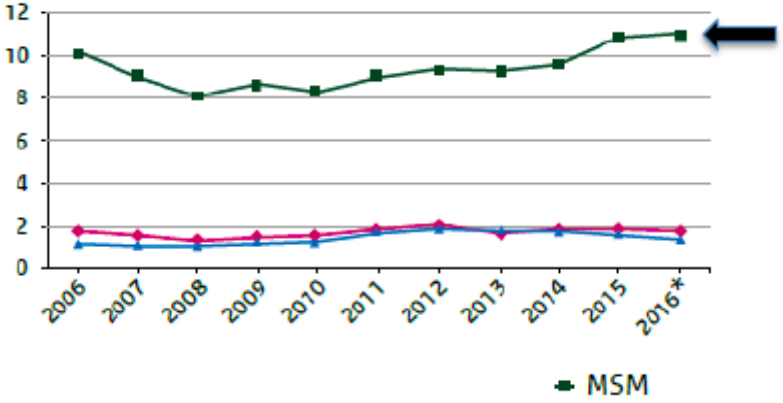
What about syphilis in MSM at public health STD clinics:

First six months of 2015:
N=446 syphilis infections diagnosed

First 6 months of 2016:
N=629 syphilis infections diagnosed (=41% increase ! 95% in MSM)

Syphilis in HIV+MSM

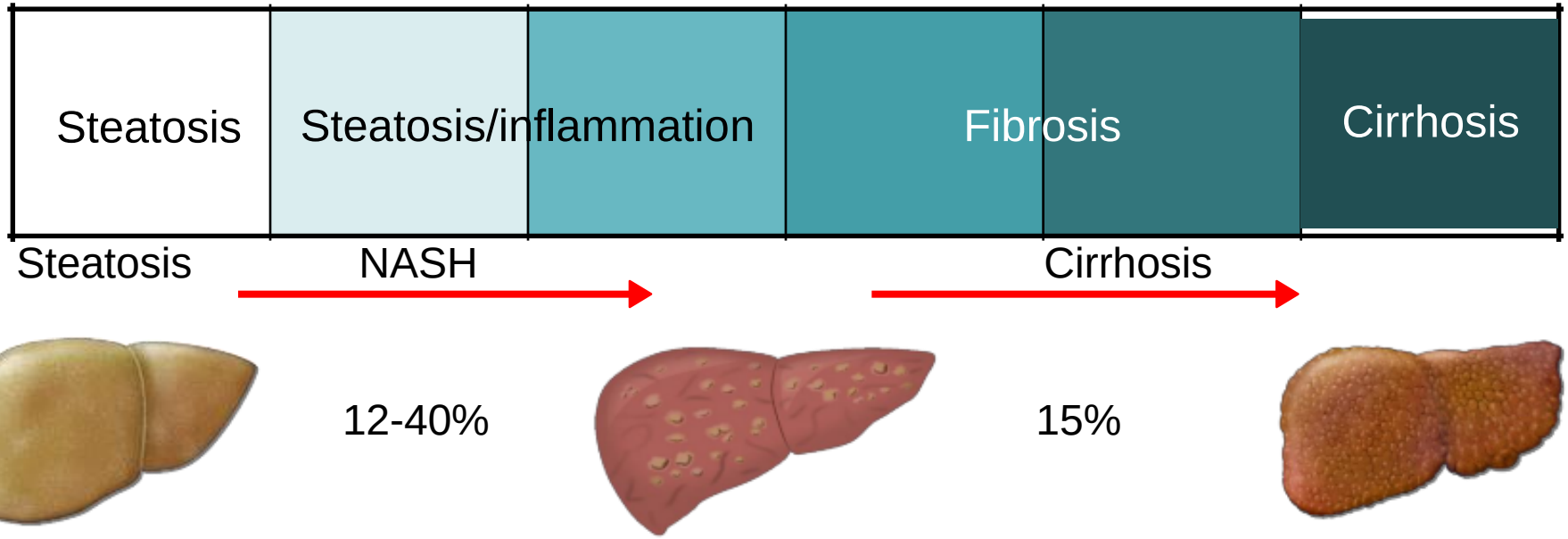




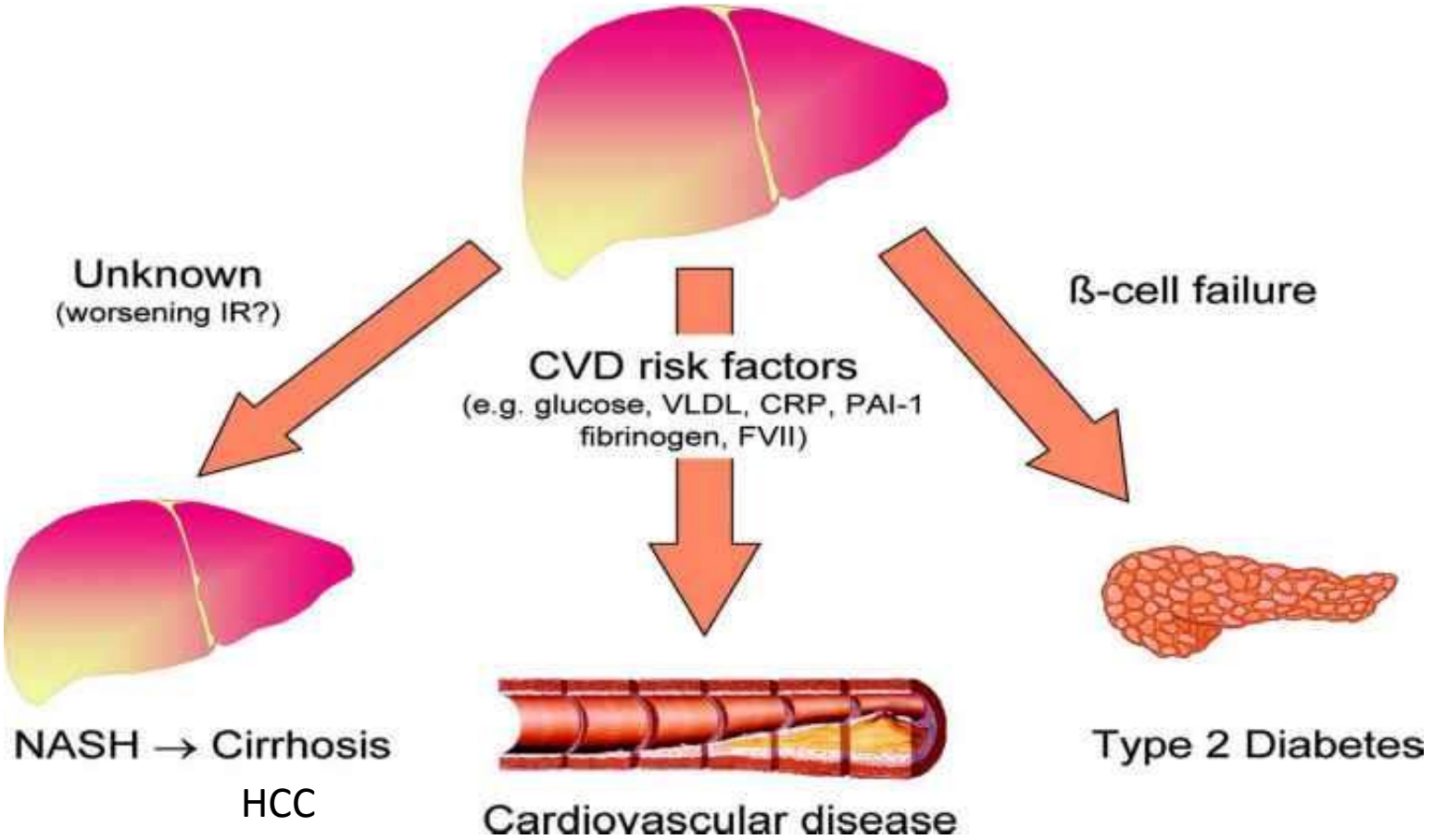
Rjinders, et al24th CROI Seattle, WA Feb 13-1 2017 O137LB

What is NAFLD ?

- Non-Alcoholic Fatty Liver Disease
- Wide disease range from simple steatosis to cirrhosis

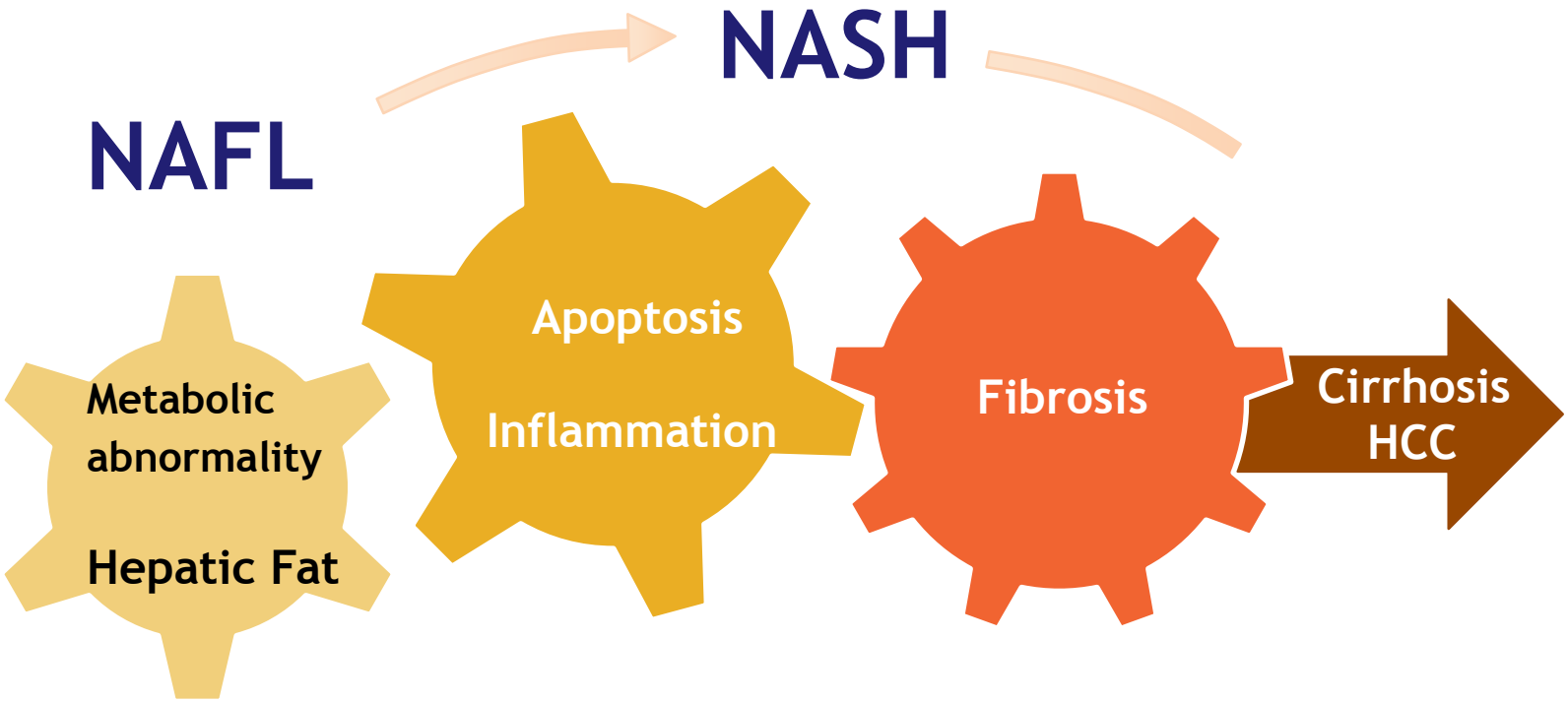


NAFLD: Potential consequences



Kotronen, Arterioscler Thromb Vasc Biol 2008

The molecular engine that drives disease progression

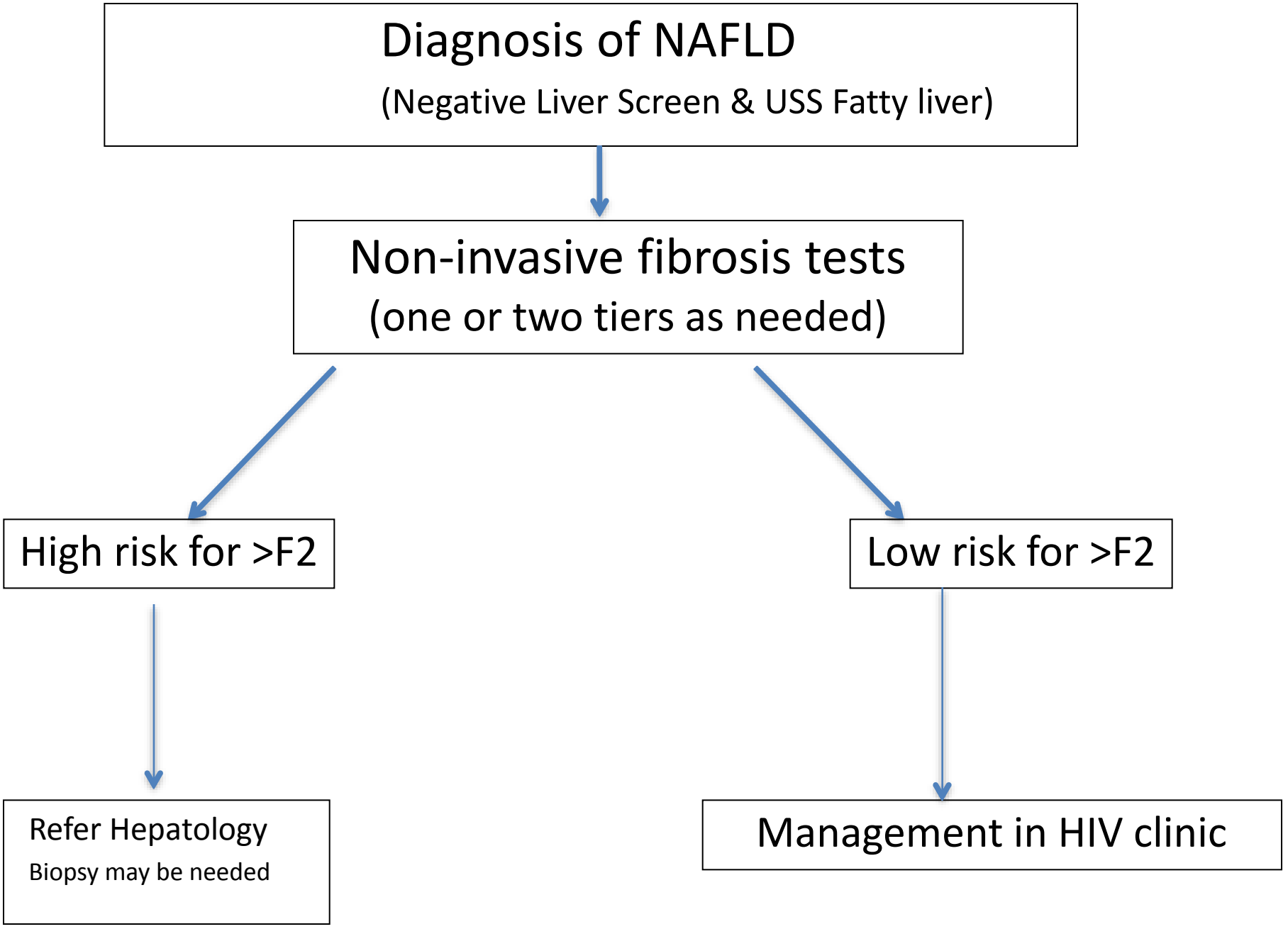


Adapted from Arun Sanyal, NASH Symposium Paris June 2015

Imperial College London

NAFLD IN HIV INFECTED PATIENTS

Study	country	n subjects	Steatosis assessment	Prevalence of NAFLD
Hadigan, C 2007 JAIDS	USA	33	MR spectrometry	42%
Mohammed, SS 2007 JAIDS	Canada	26	Liver Biopsy	45%
Guaraldi, G 2008 CID	Italy	225	CT	37%
Crum Cianflone, P 2009 JAIDS	USA	216	Ultrasound	31%
Ingiliz, P 2009 Hepatol	France	30	Liver Biopsy	60%
Nishijima, T 2014 PlosOne	Japan	435	Ultrasound	31%
Price, JC 2014 Am J Gastro	USA	465 HIV and HIV HCV	CT	15%
Juan, M 2014 AIDS	Spain	505 HIV HCV/HBV	CAP™	40%


Diagnosis of NAFLD
(Negative Liver Screen & USS Fatty liver)
Non-invasive fibrosis tests
(one or two tiers as needed)
High risk for >F2
Low risk for >F2
Refer Hepatology
Biopsy may be needed
Management in HIV clinic

Appropriate End-points for therapeutics in NAFLD

- Early phase trials
  - Populations with NASH or at high-risk of NASH
  - Primary end-points based on mechanism of drug tested; e.g. reduction in hepatic fat by MR-Proton Density Fat Fraction, CAP
- Phase 3 studies
  - Biopsy proven NASH (NAS score >2) with F2+ fibrosis
  - Primary End-point
    - Complete resolution of steatohepatitis and no worsening of fibrosis
    - At least one point improvement in Fibrosis score with no worsening of steatohepatitis

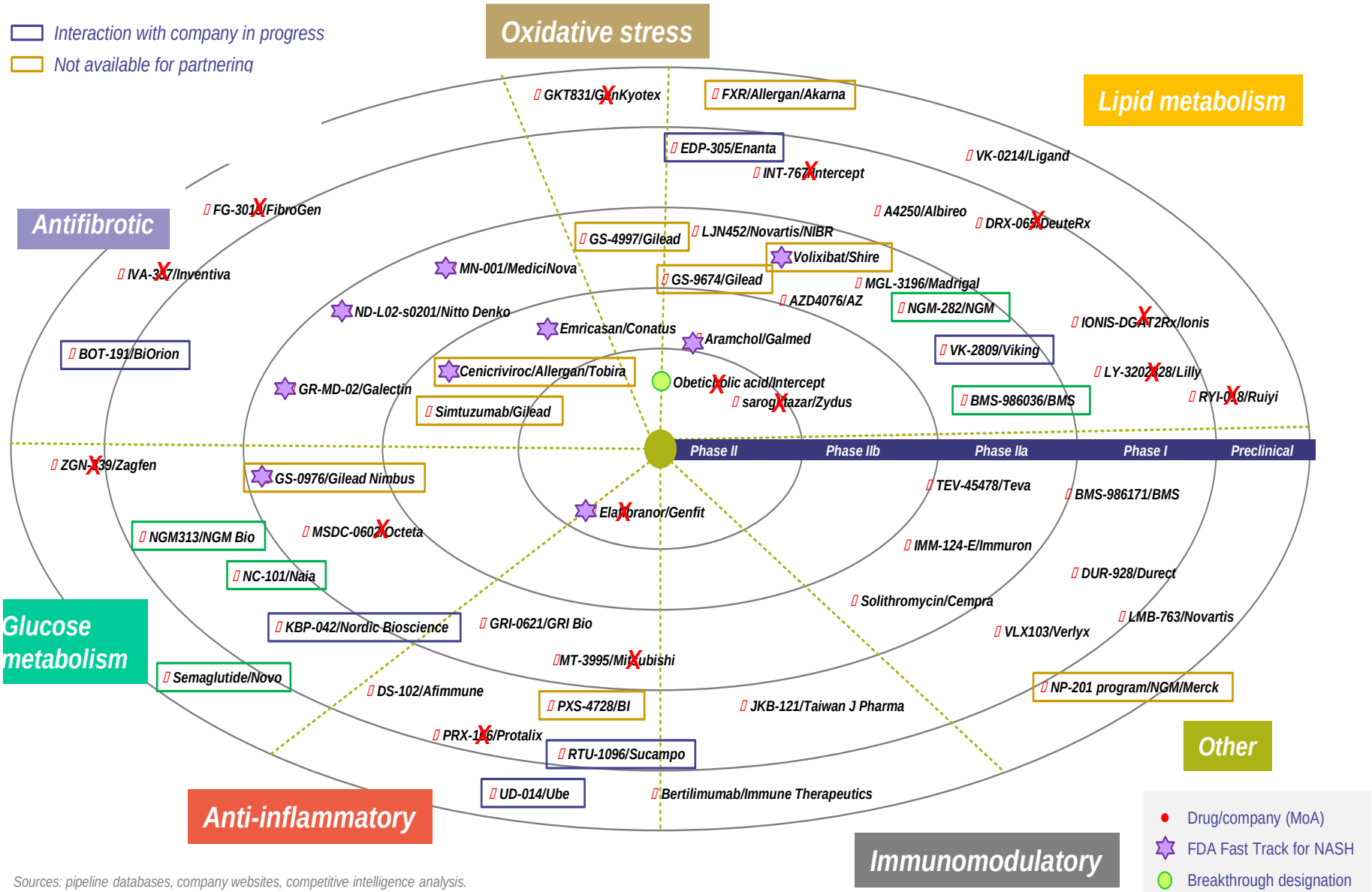
Therapeutics for NASH

- Metabolic abnormalities
- Cell-stress/apoptosis and inflammation
- Antifibrotics
- Gut-Liver axis

What works and what doesn't work – data to date…

- Diet/exercise
  - 5% weight loss improves steatosis
  - 7% improvement in inflammation
  - >10% for improvement in fibrosis
- Insulin sensitising agents
  - Glitazones/Metformin – ?effective in pre-diabetics/T2DM
- Anti-lipid therapies
  - Fibrates, statins may improve lipids BUT no/little effect on hepatic inflammation/fibrosis
- Anti-oxidants
  - Vitamin E works (but risk of Prostate cancer??)

NAFLD Pipeline



Sources: pipeline databases, company websites, competitive intelligence analysis.
Preclinical: only selected projects to reach clinical development in 2016 are shown. More than one mode of action may be applicable for a given drug.
**NASH compounds only. Projects with only NAFLD patients are not considered*

Conclusions

- Liver disease remains an important cause of morbidity and mortality in HIV+
- Key issues = cART, HBV, HCV and lifestyle
- HBV – key issues – diagnosis and management
- HCV
  - DAAs for all – generic preparations available
  - Responses in HIV+ similar to HIV-
  - Beware DDIs
- Need for improved cascade of care and access to Rx – 'Micro-elimination' a realistic goal
- NAFLD – increasingly recognised
  - Managing cardiovascular risk is the key issue
  - Small number – progressive liver damage