Liver Disease in HIV

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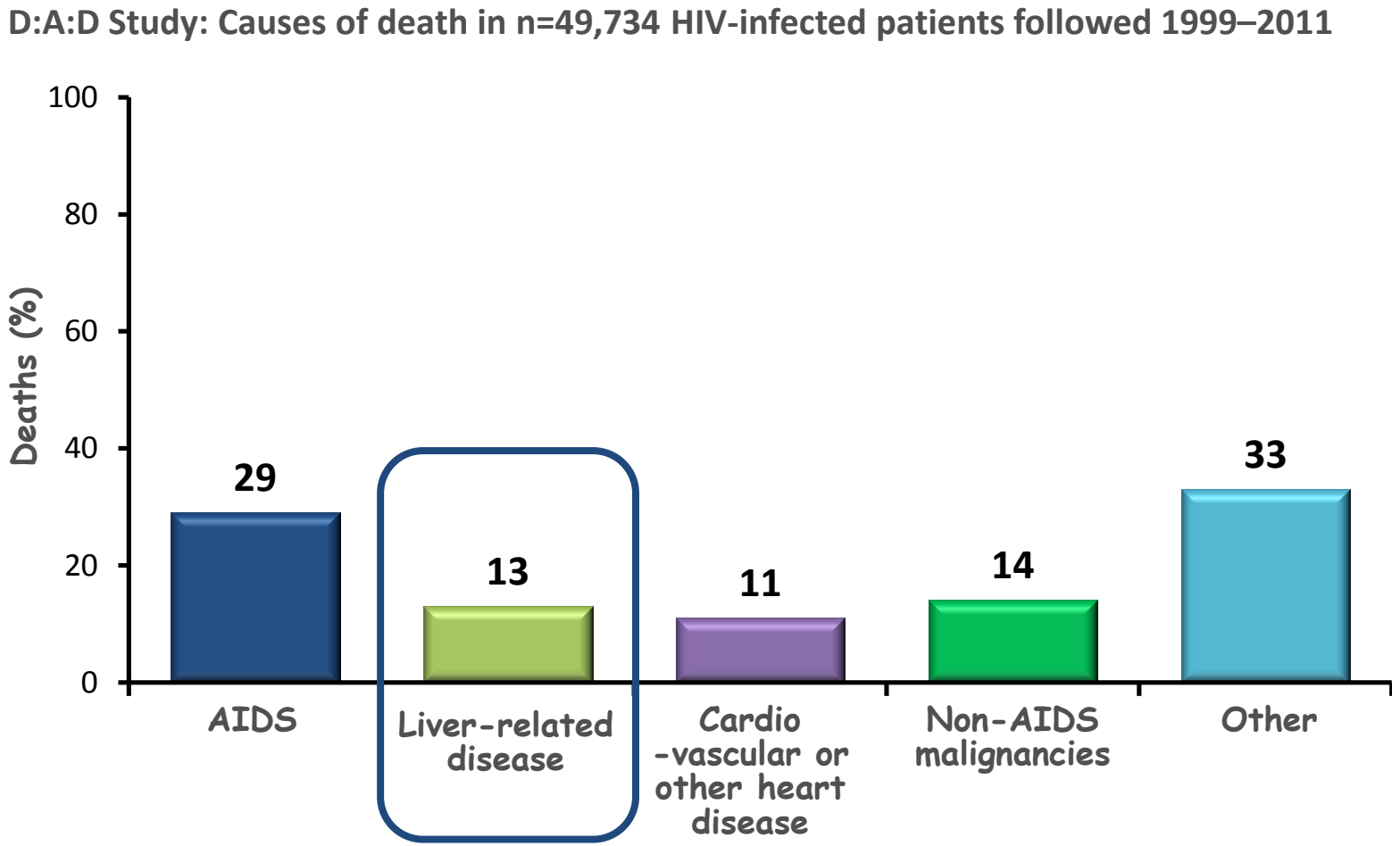
Outline

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

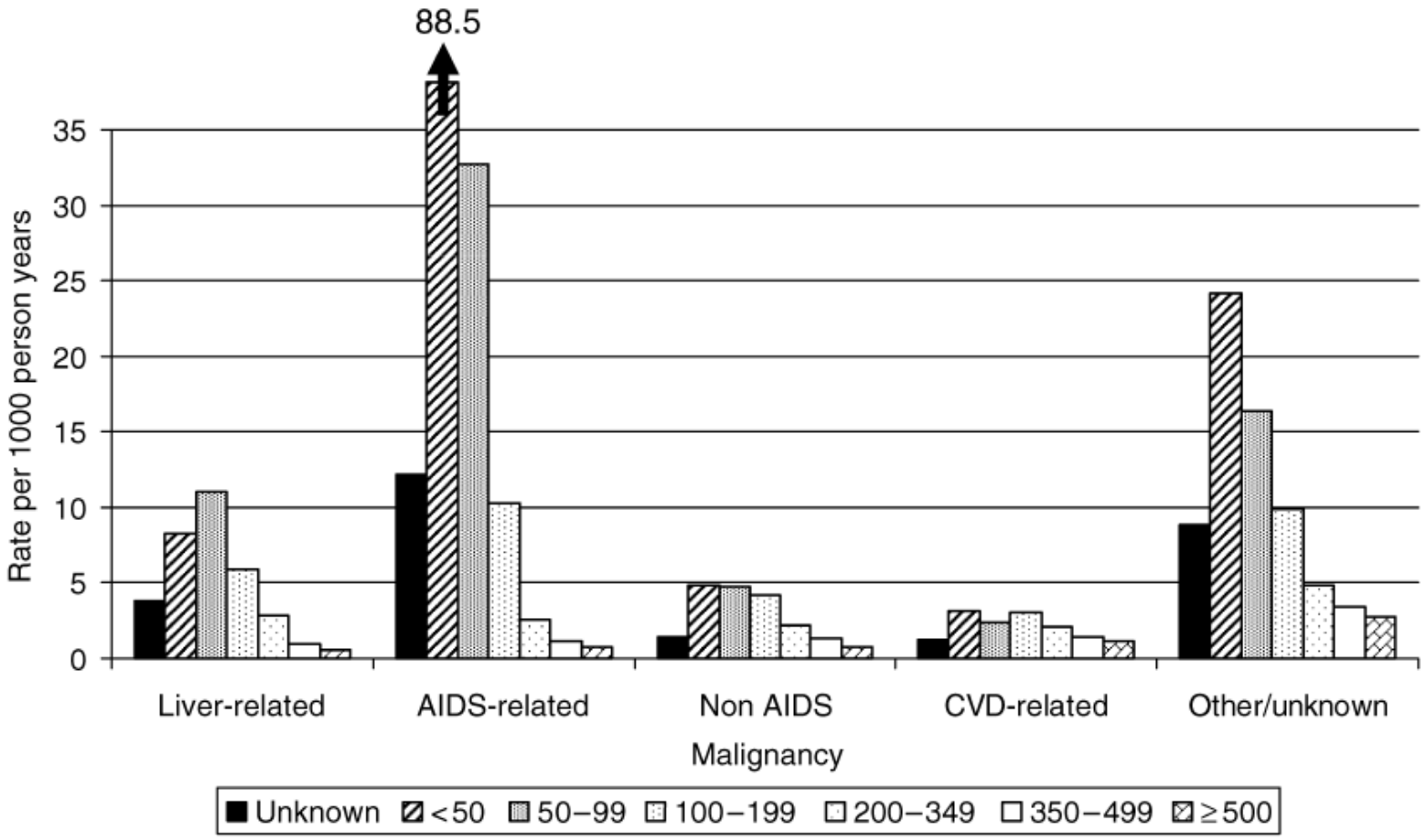
- Case-based discussion (Friday pm)
  - Non-invasive monitoring of liver disease
  - Concepts of ESLD management

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



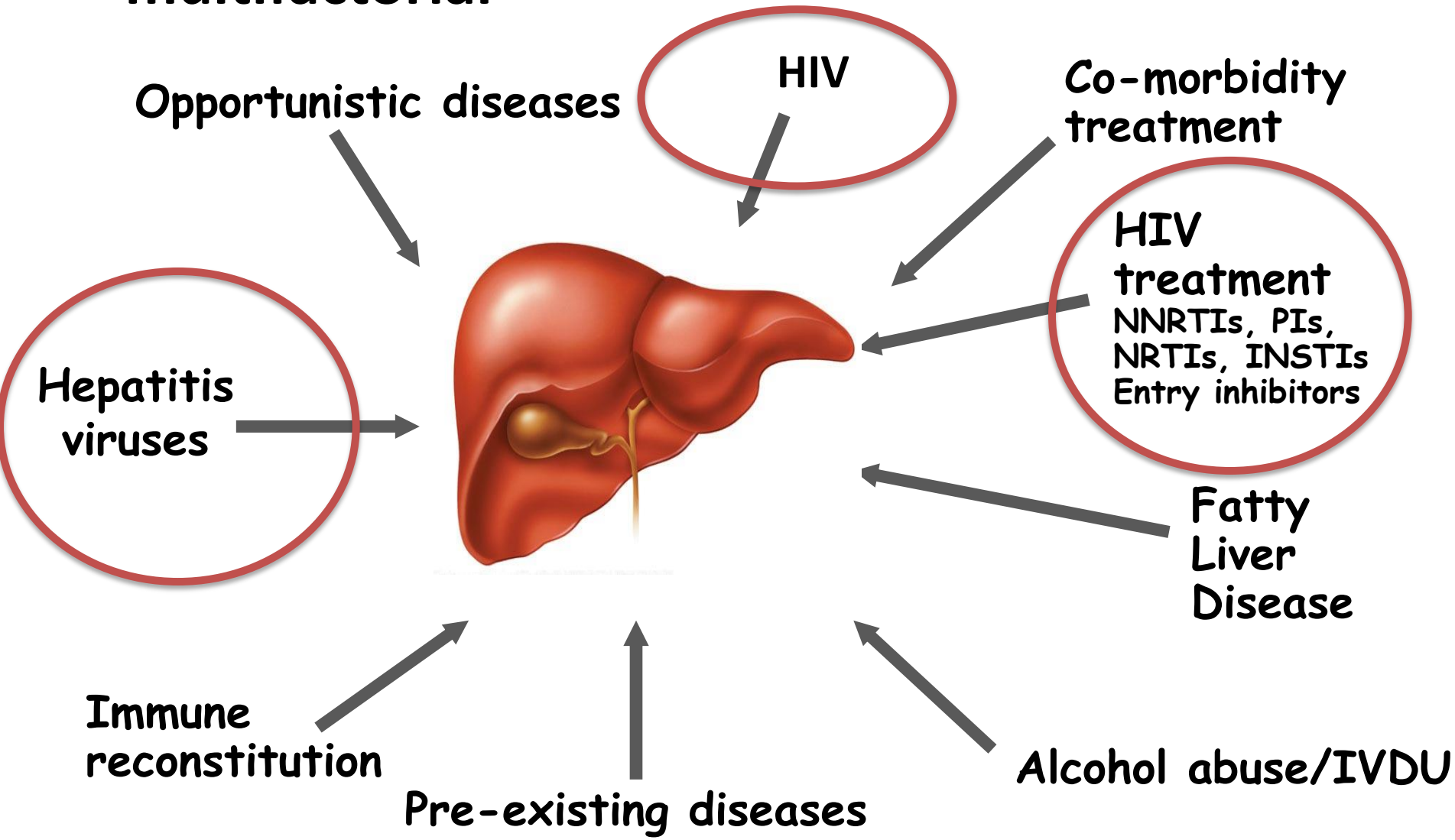
Weber R, et al. AIDS 2012. Washington USA. Oral presentation THAB0304.

Liver-related death and CD4 count



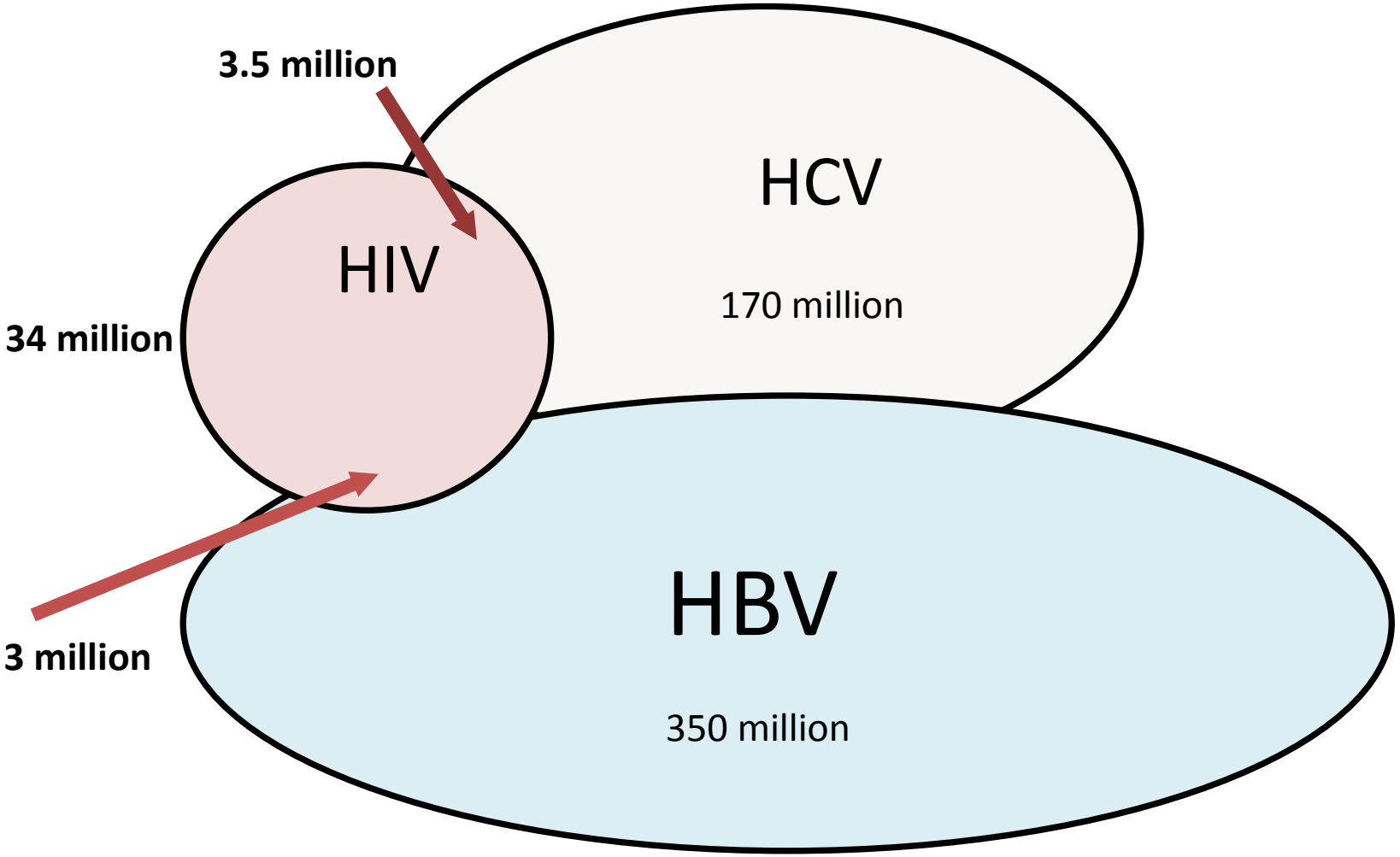
D.A.D study Gp. AIDS 2010: 24: 1537

Liver Disease in HIV-infected Patients - multifactorial

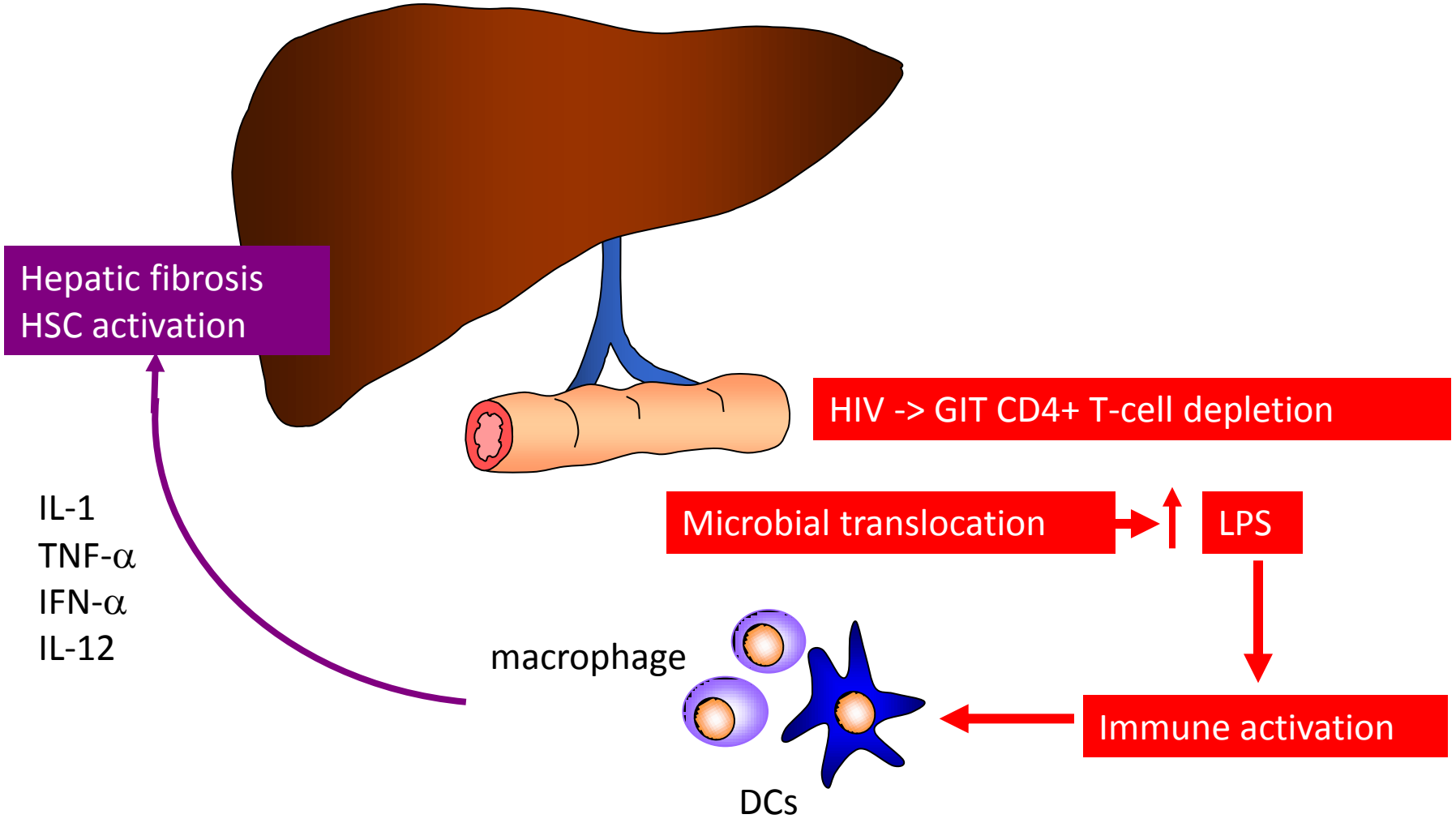


Sulkowski M. *et al.* Ann Intern Med. 2003;138:197-207 Guaraldi G *et al* Clin Infect Dis 2008 47(2): 250-257
Greub G *et al.* Lancet 2000;356:1800-1805

Overlapping epidemics – co-infections

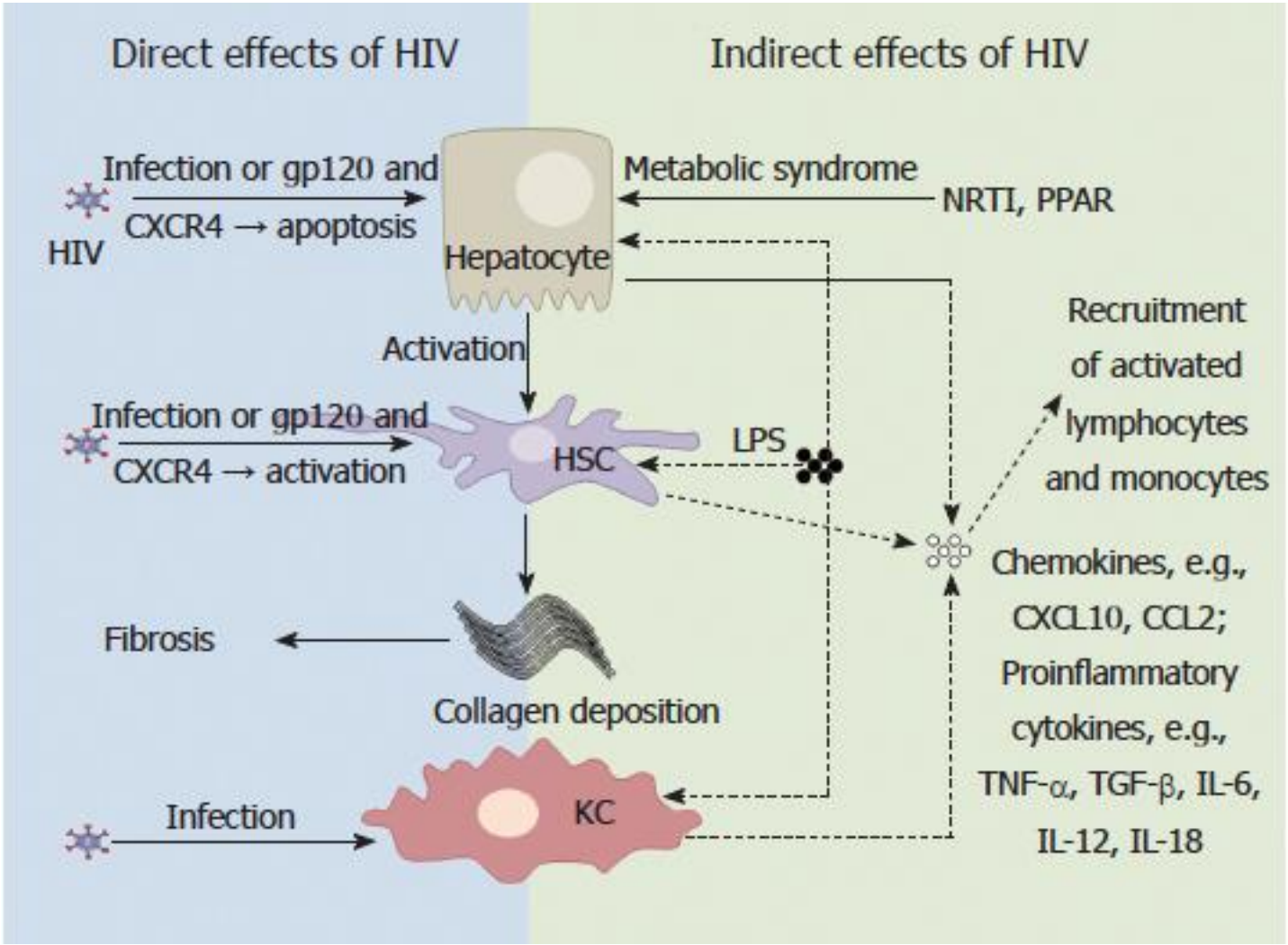


HIV-associated Immune activation and liver disease



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

HIV – direct effects on the liver



Crane et al, World J Hepatology 2012; 4: 91

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

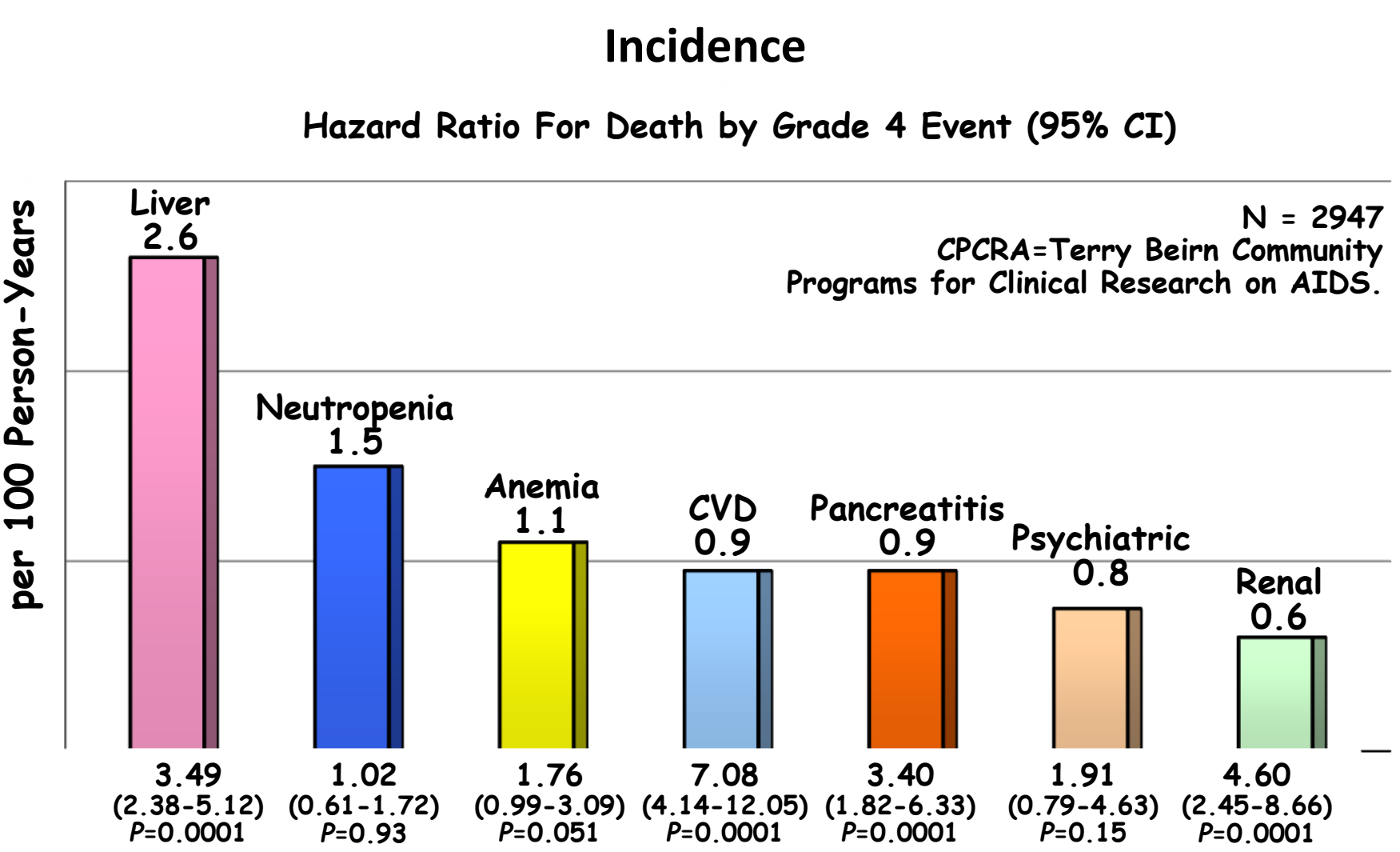
Matthews et al, Manuscript submitted

Hepatoxicity with ARVs

- Toxicity has emerged as one of the leading causes of HIV related morbidity, mortality and treatment discontinuation
  - Toxicity the major reason for hospital admission[1]
  - Hepatotoxicity the most frequent (30%)[1]
  - Hepatotoxicity historically 3rd most common reason for ART toxicity related discontinuation
- High rates of HBV and HCV co-infection likely to increase risk of hepatotoxicity

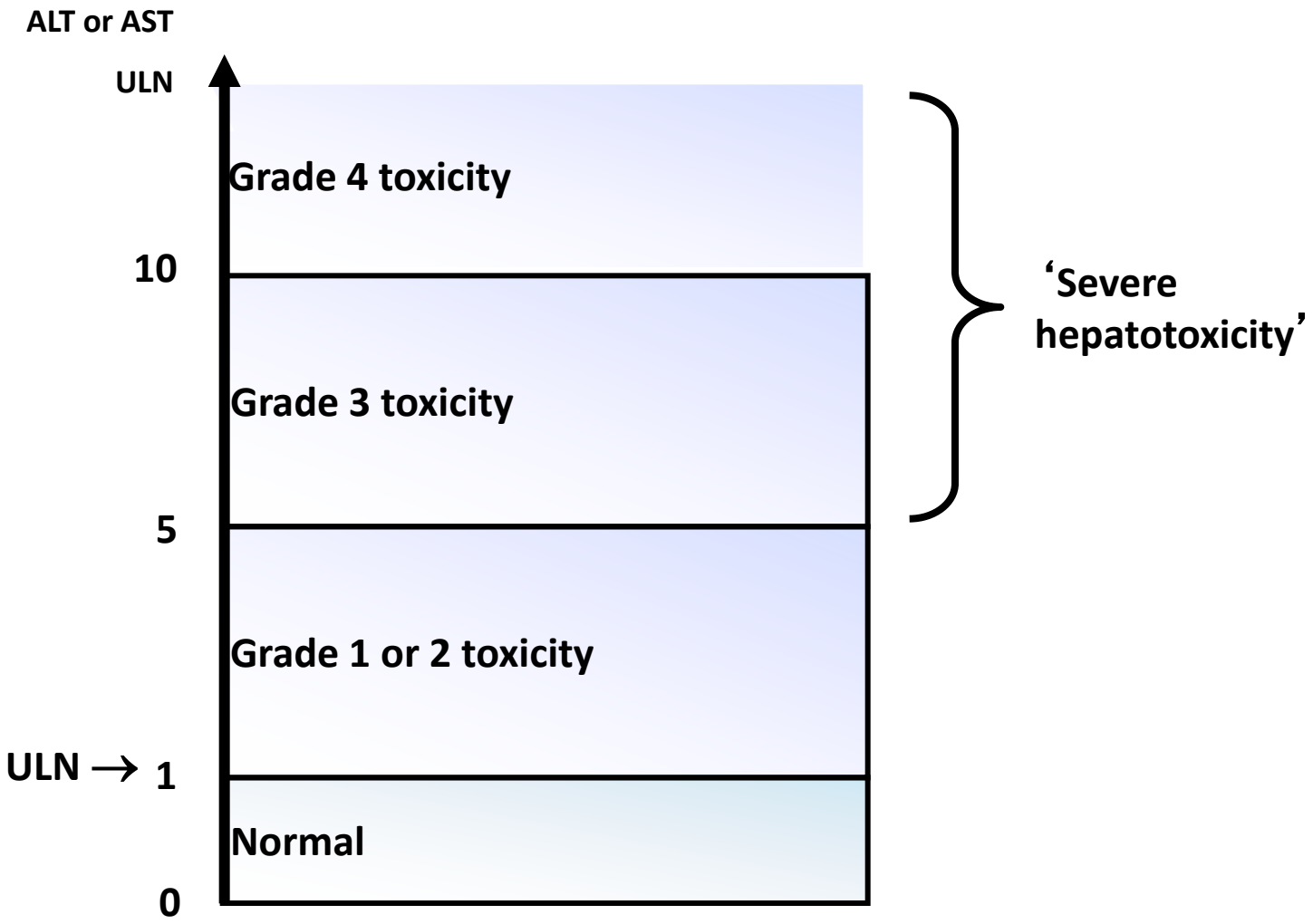
Nunez et al, AIDS Res Hum Retroviruses 2006

Most Common Grade 4 Events: CPCRA Cohort



Reisler RB, et al. JAIDS. 2003;34:379-35:182-189.

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

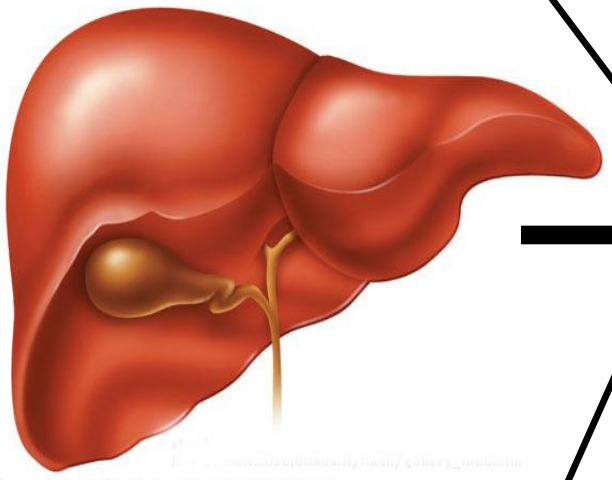
- Almost exclusively associated with didanosine (ddI) use
  - Related to duration of use
  - May present many years after discontinuation
- Histologically:
  - Nodular regenerative hyperplasia
  - Partial Nodular Transformation
  - Portal venopathy
  - May be normal
- Clinically: Portal hypertension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

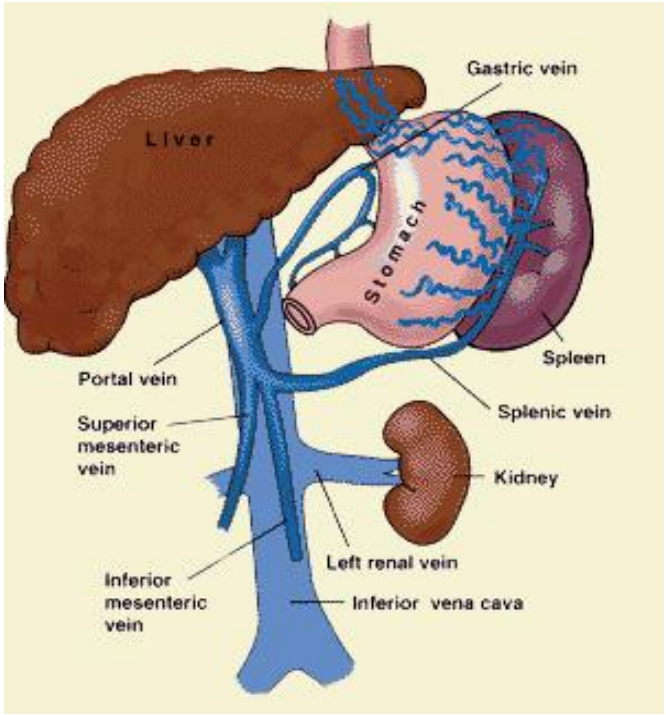
- Association with SNPs in 5-nucloeotidase and xanthine oxidase *(Vispo et al, CID 2013)*

- ? Role of screening for ddI exposed patients

Bacterial Translocation

Prolonged DDI +/- other NRTI exposure



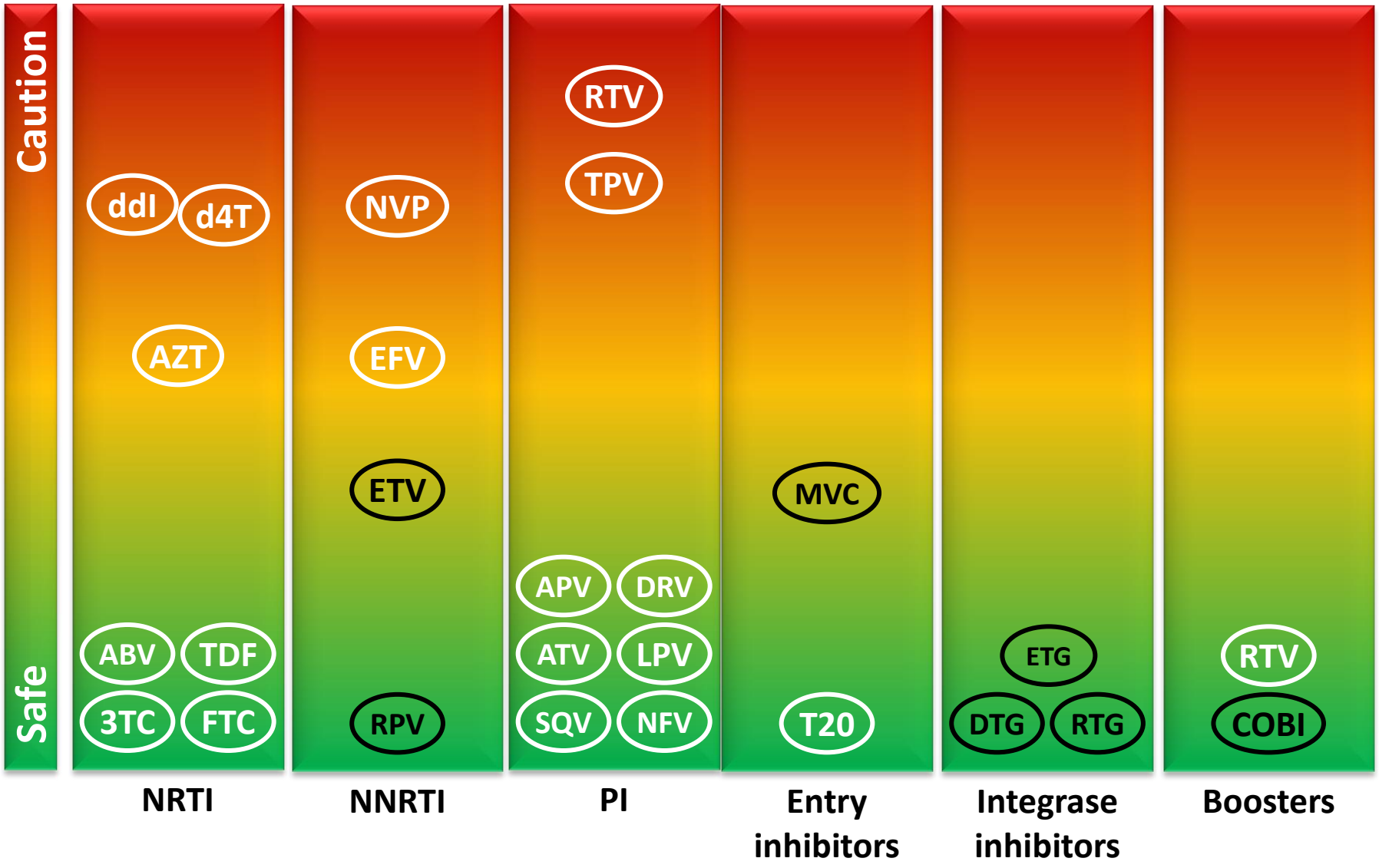


?Thrombophilia

?Genetic predisposition

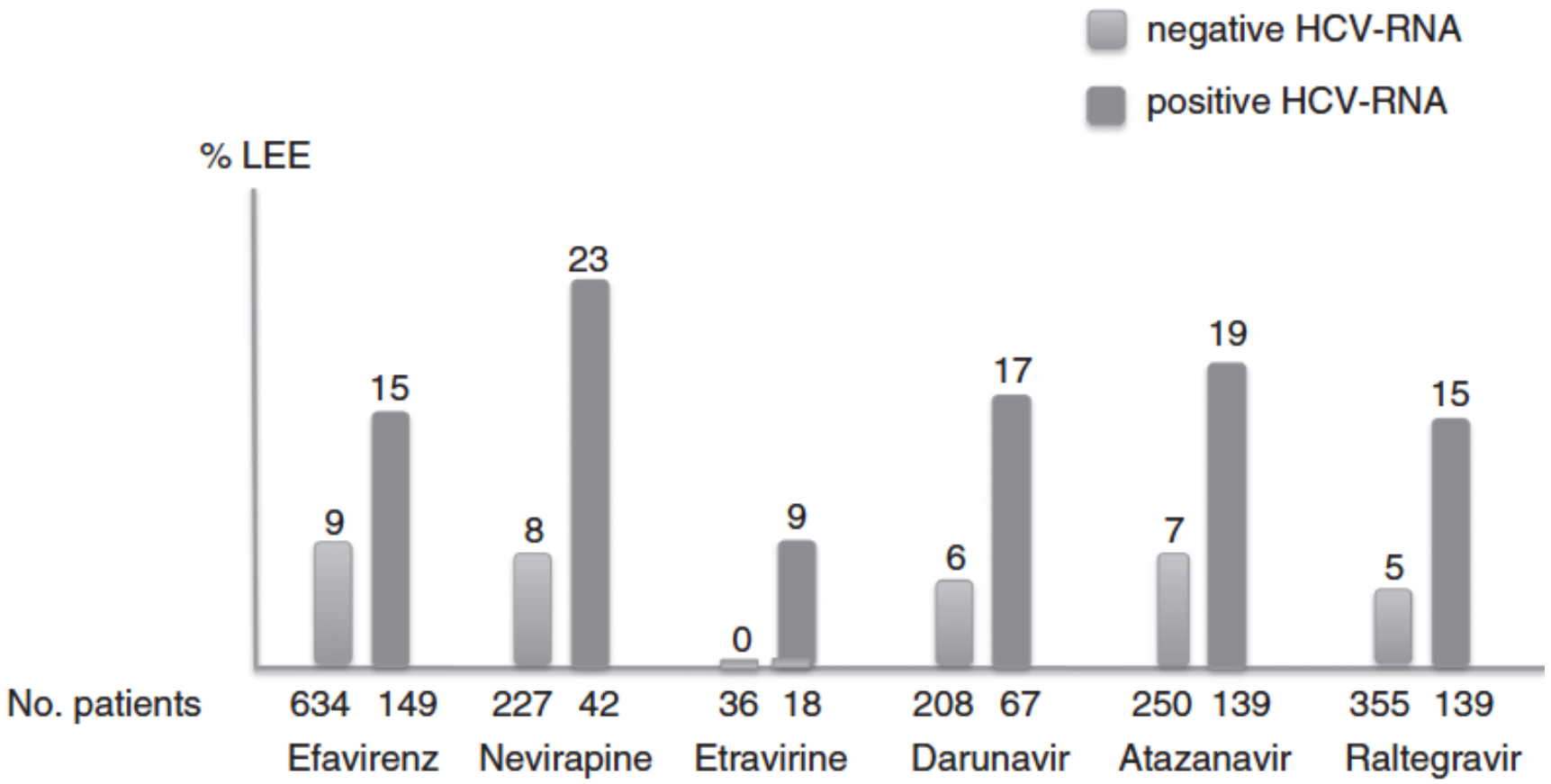
Adapted from Maida, et al, Curr Opin Infect Dis 2011; 24: 12-18

Hepatic Safety Profile of ARVs



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

Hepatotoxcity of modern ARVs



Vispo, et al. AIDS 2013:27: 1187

Associated Risk factors for hepatotoxicity of ART

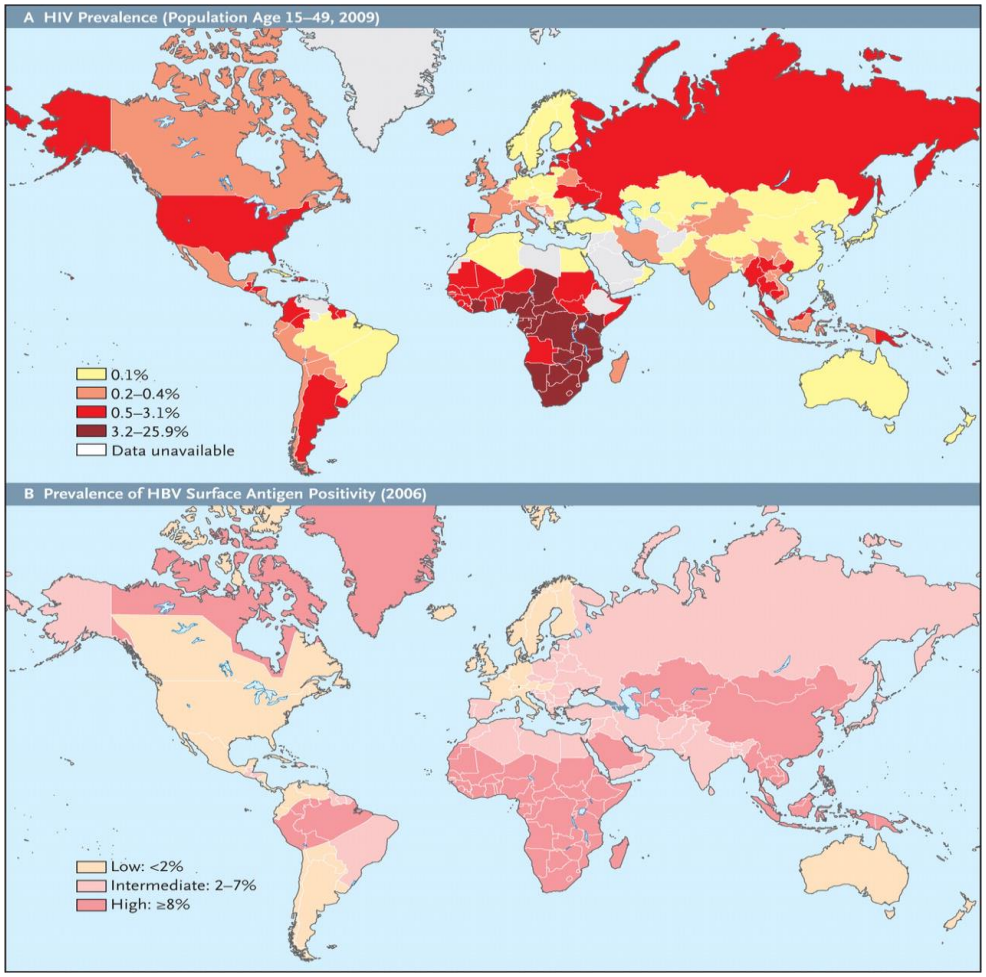
- Hepatitis B and C co-infection
- Higher baseline ALT/AST levels
- Alcohol
- Older age
- Female gender
- High or low CD4 count
- Lower BMI
- Use of ddI, d4T, NVP, RTV (>200mg/day rather than at 'boosting' 100mg/day)

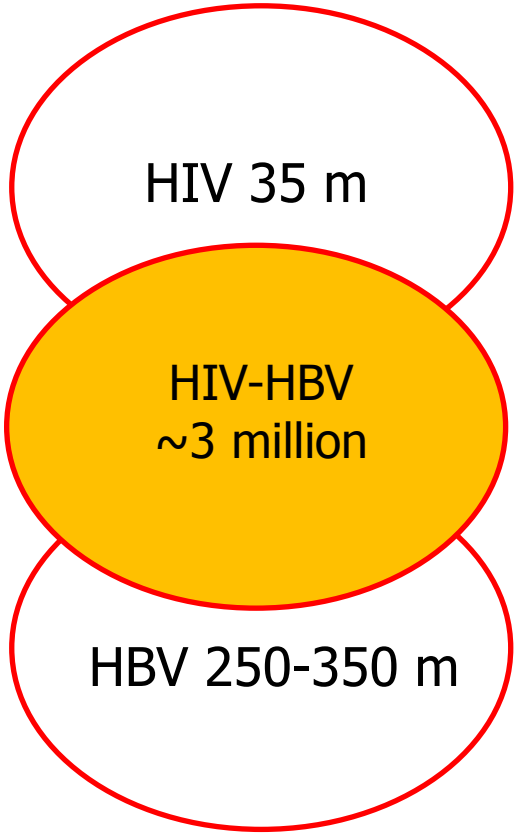
Rodriguez-Rosado et al. AIDS 1998;12:1256; Sulkowski et al. JAMA 2000;283:74.; Saves et al. AIDS 1999;13:F115; den Brinker et al. AIDS 2000;14:2895; Martínez et al. AIDS 2001;15:1261; Núñez et al. J AIDS 2001;27:426.

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

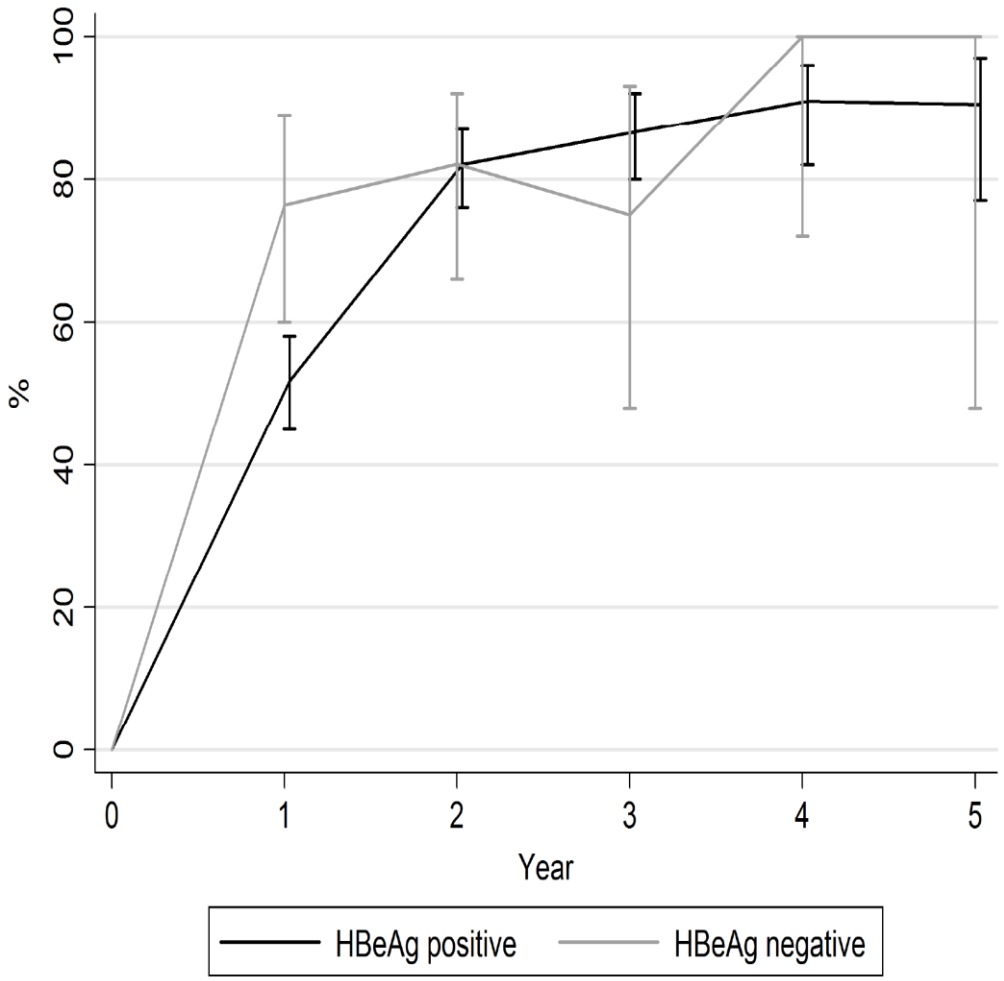
HIV-HBV: a huge global burden





Kourtis AP et al. N Engl J Med 2012;366:1749-1752.

13 years of tenofovir (TDF)



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

All guidelines recommend TDF-containing ART as preferred regimen

First-line ART for adults (including pregnant and breastfeeding women and people with TB and HBV coinfection)	
Preferred regimens	TDF + 3TC (or FTC) + EFV
Alternative regimens	AZT + 3TC + EFV (or NVP) TDF + 3TC (or FTC) + NVP
Special circumstances[c]	Regimens containing ABC, d4T[b] and boosted PIs

WHO ARV guidelines 2013

General agreement on when to start

	CD4< 500	CD4 >500
DHSS (US)	✓	✓
WHO	✓	Evidence of severe chronic liver disease
EACS (Europe)	✓	If HBV DNA > 2000 IU/ml or ALT elevated
BHIVA (UK)	✓	HBV DNA > 2000 IU/ml OR F=>2 by TE or biopsy

Lack of access to routine testing and monitoring

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

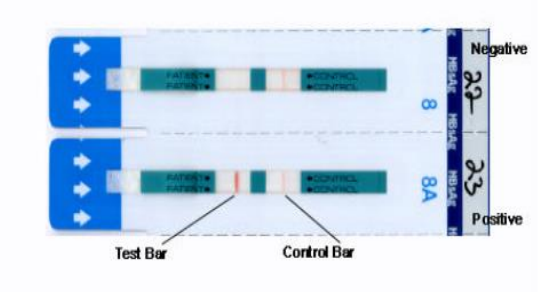
- >50% people live in countries with no free testing
- Only 4% low-income countries have ready access to testing

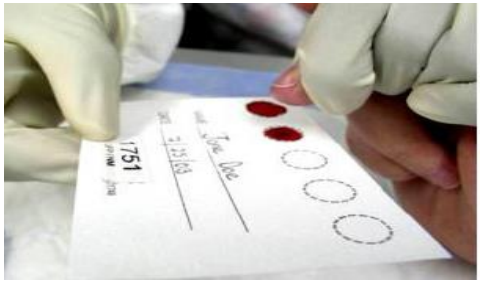
	Testing accessible to >50%	Testing anonymous	Free to all	Free to some
Africa	20%	40%	10%	27%
SE Asia	29%	29%	29%	14%
Europe	86%	55%	27%	55%

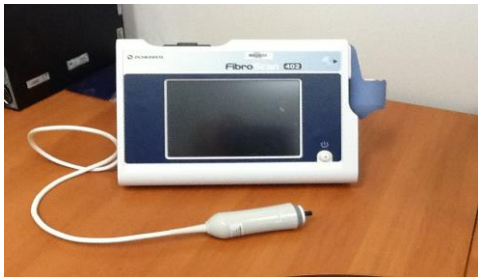
Easterbrook et al Sem Liv Dis 2012

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

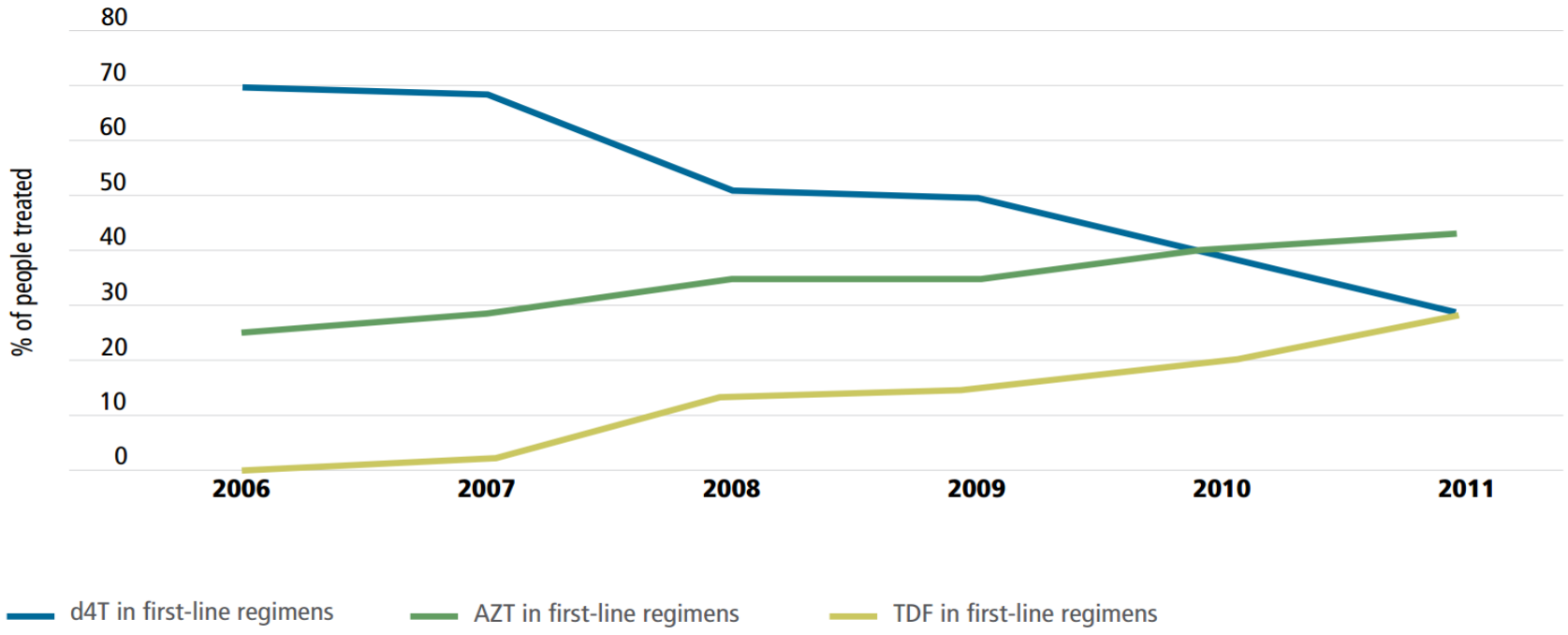






Although TDF use is improving, far from universal

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



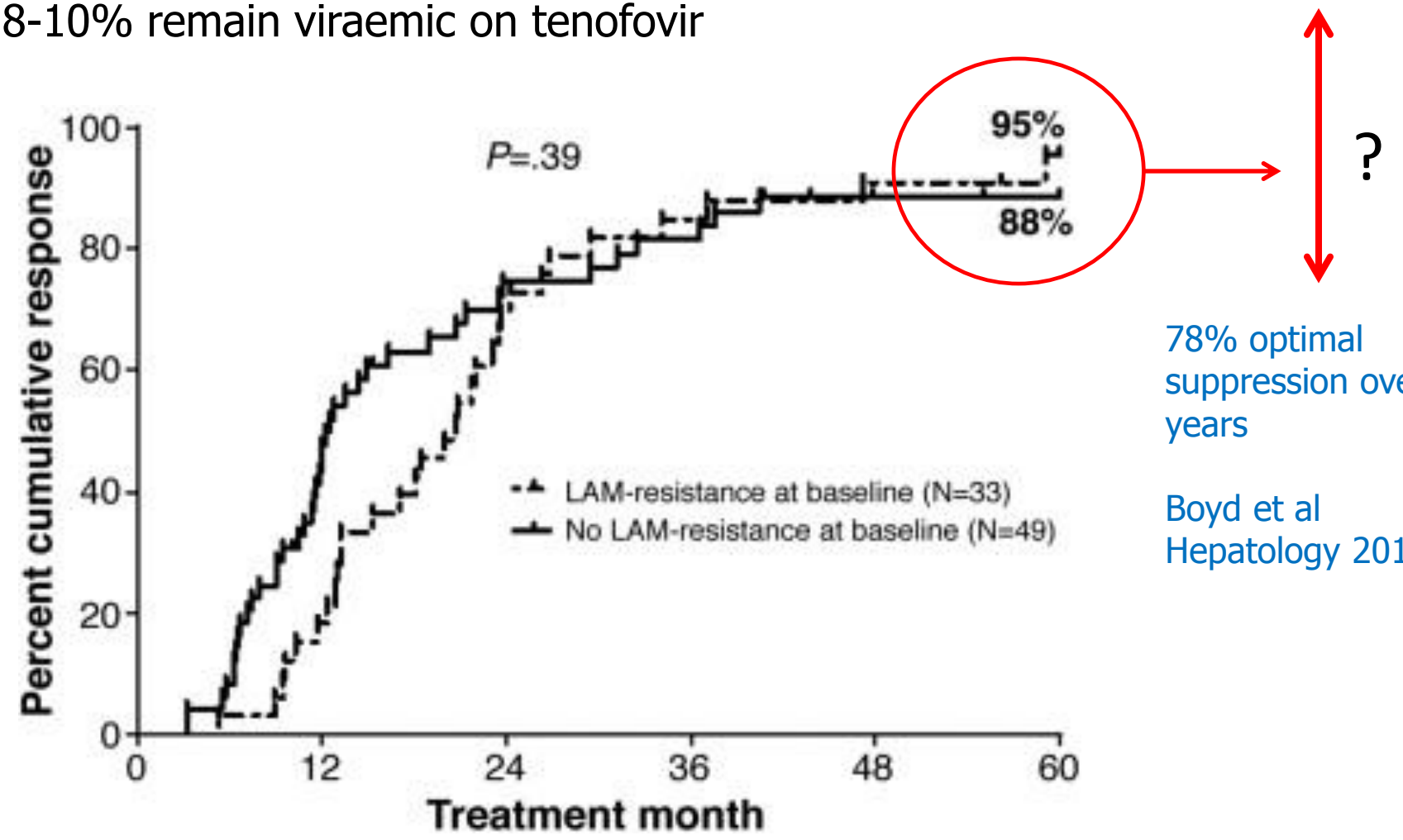
Source: *Use of antiretroviral medicines by December 2011 based on the WHO survey in low- and middle-income countries (77).*

Global update on HIV treatment 2013. WHO

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

Efficacy is never 100%

8-10% remain viraemic on tenofovir



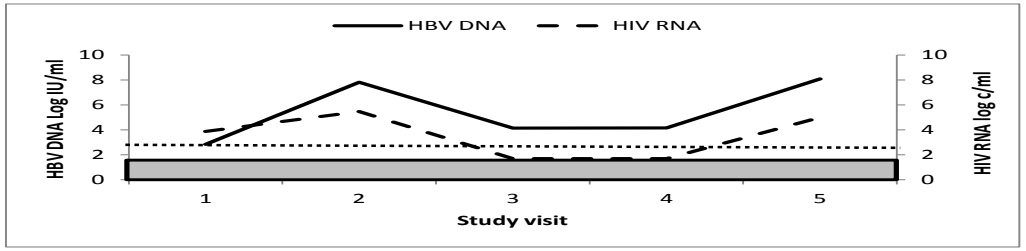
78% optimal suppression over 7 years

Boyd et al Hepatology 2014

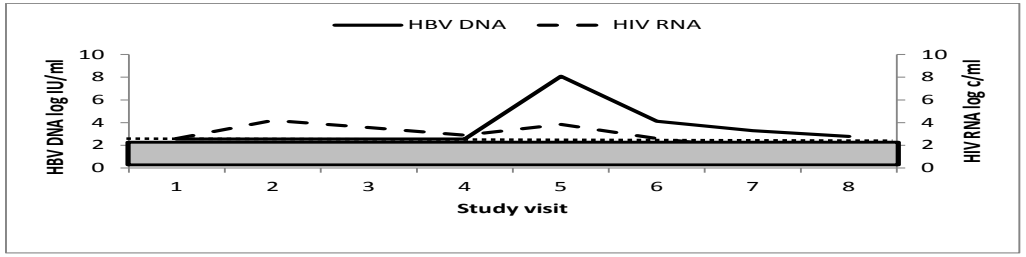
De Vries Slujis Gastroenterology 2010

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

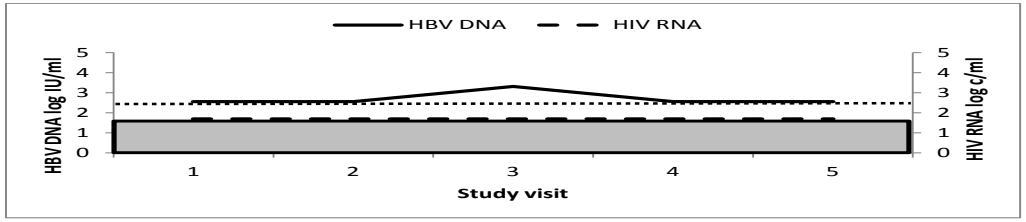
- 165 HIV -HBV coinfected individuals followed for median of 4 years
- HBV DNA detectable in 20% study visits



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

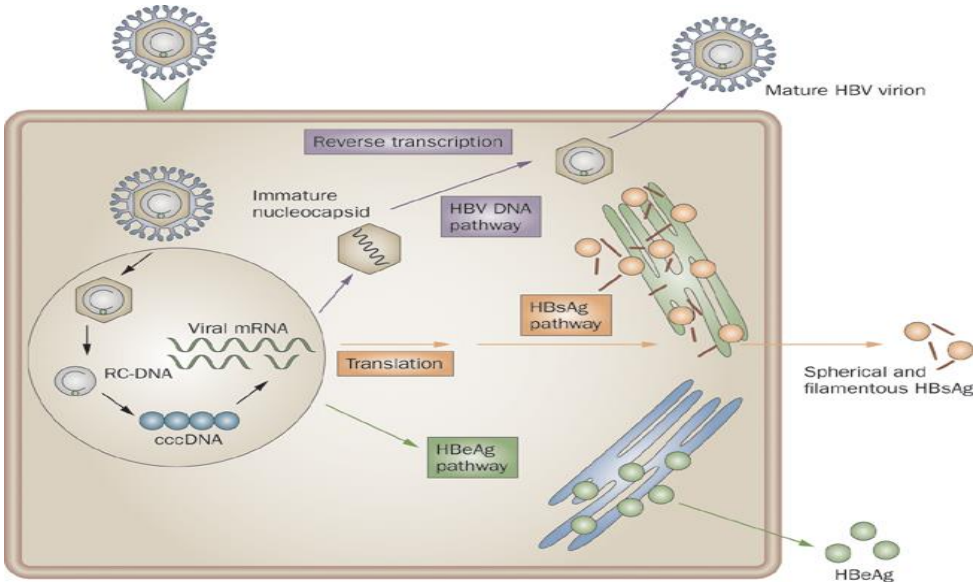
	OR	95% CI	p-value
Age (per 10 yrs)	0.90	0.48, 1.69	0.74
HBeAg positive	12.06	3.73, 38.98	<0.0001
<95% adherent	2.52	1.16, 5.48	0.02
HAART <2 yrs	2.64	1.06, 6.54	0.04
CD4 < 200 cells/mm^3	2.47	1.06, 5.73	0.04

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

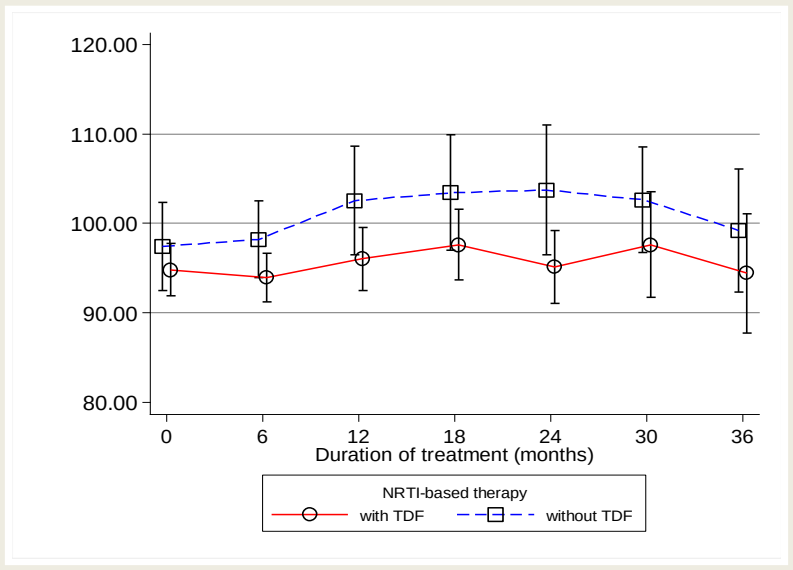
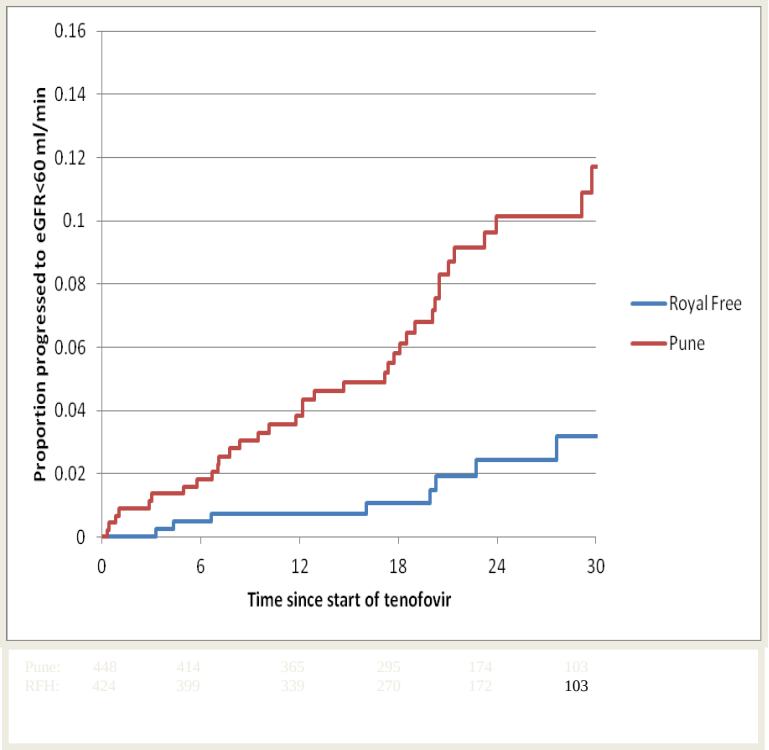


Figure 1: MDRD clearance over time

- >400 HIV+ patients receiving TDF

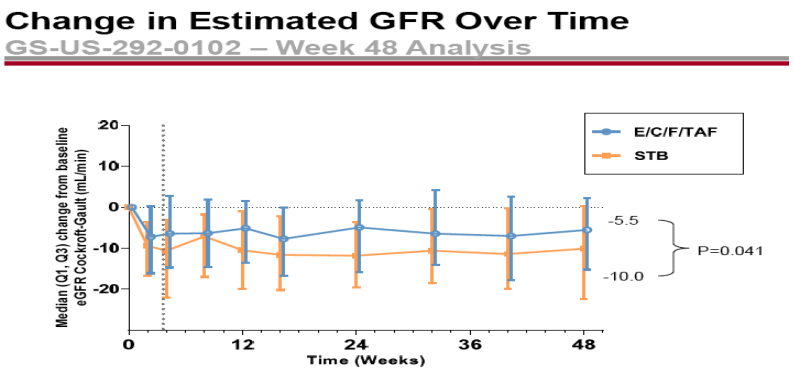


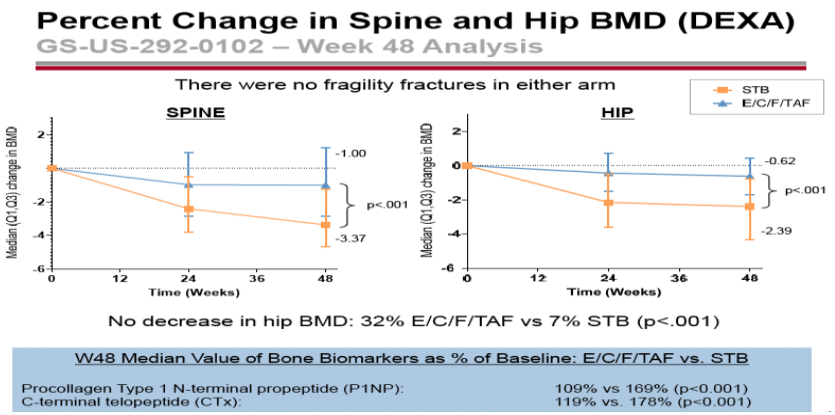
Pujari, et al, BMC Infect Dis 2014

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)*





HIV/HCV – double-trouble for the liver

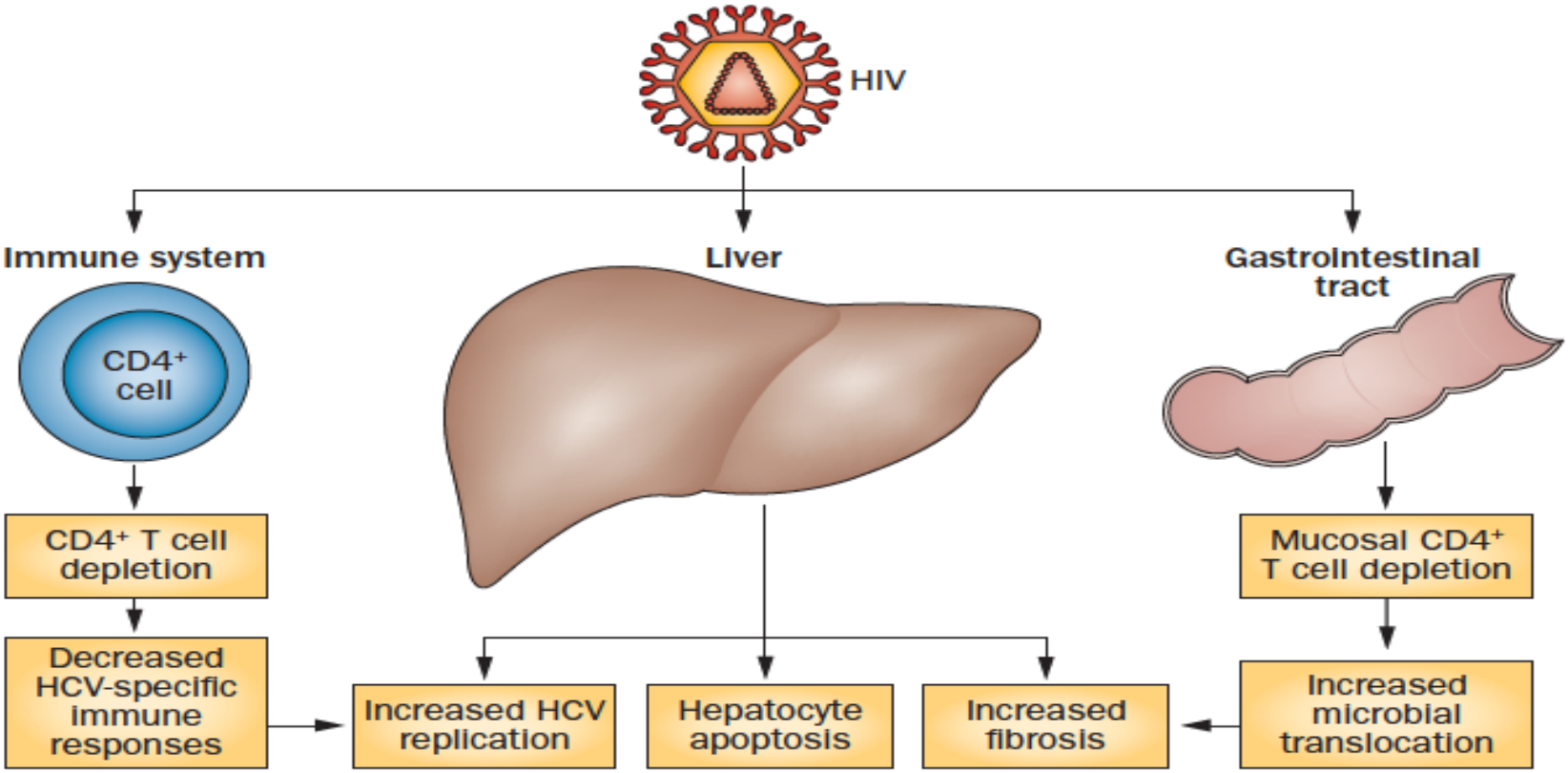


Figure 1 | Driving factors underlying liver disease pathogenesis in HCV–HIV co-infection. HIV infection leads to an impaired immune response against HCV, increased HCV replication, hepatic inflammation and apoptosis, increased microbial translocation from the gastrointestinal tract and increased fibrosis.

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

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

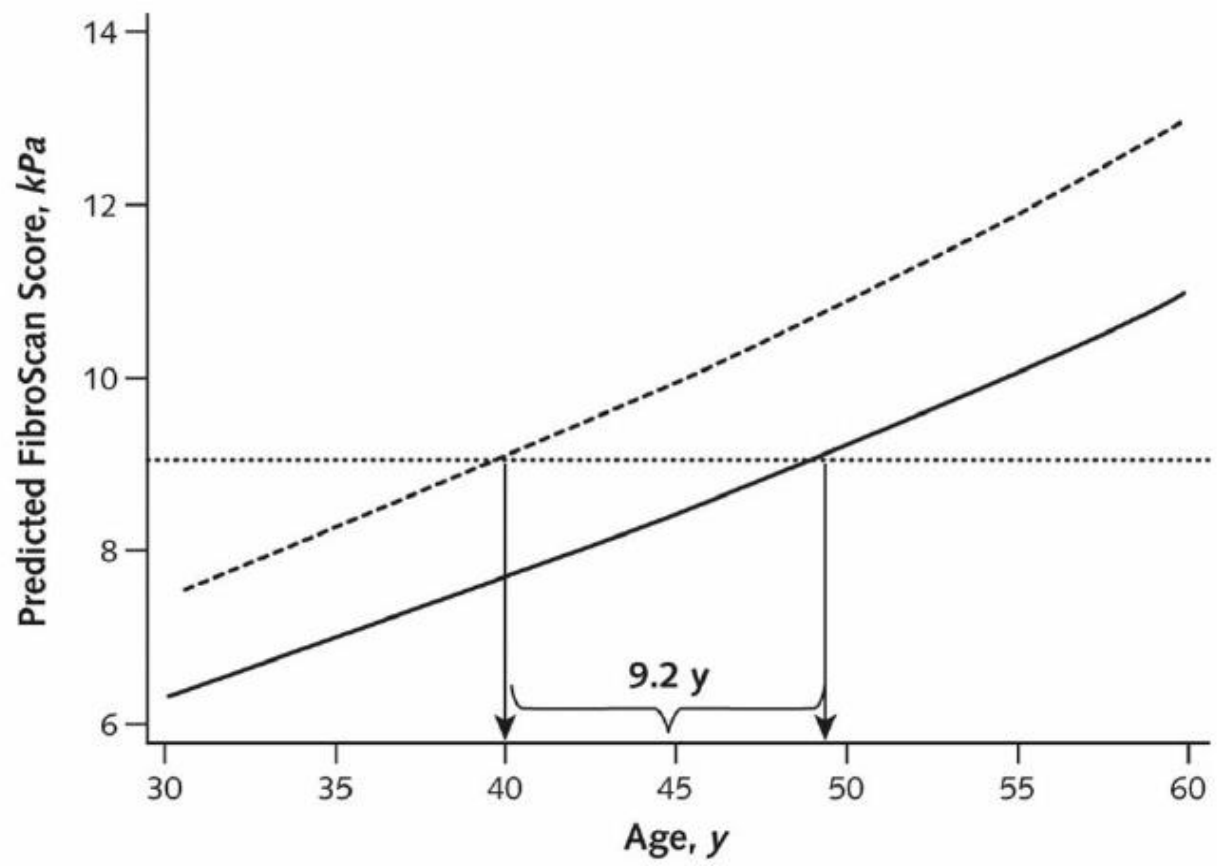
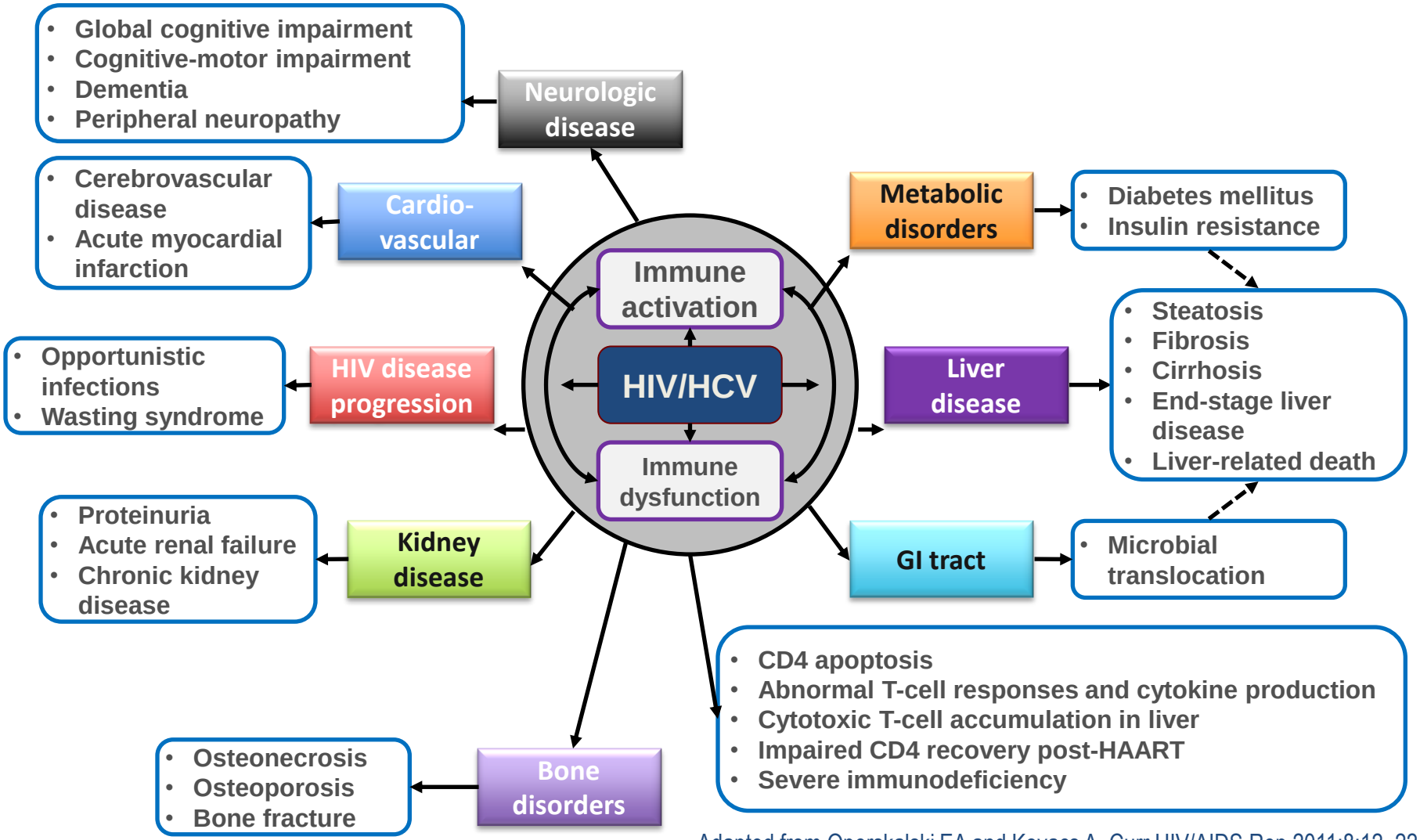


Figure 3. Liver fibrosis and age among persons coinfected with HIV and HCV (dashed line) and those with only HCV (solid line)

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

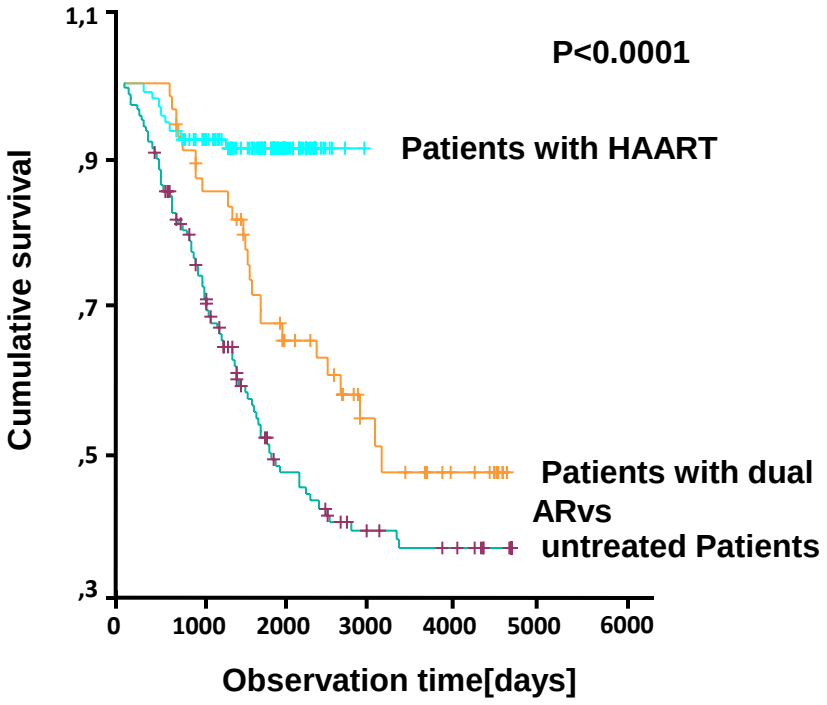
HIV/HCV – a contribution to multiple organ dysfunction



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

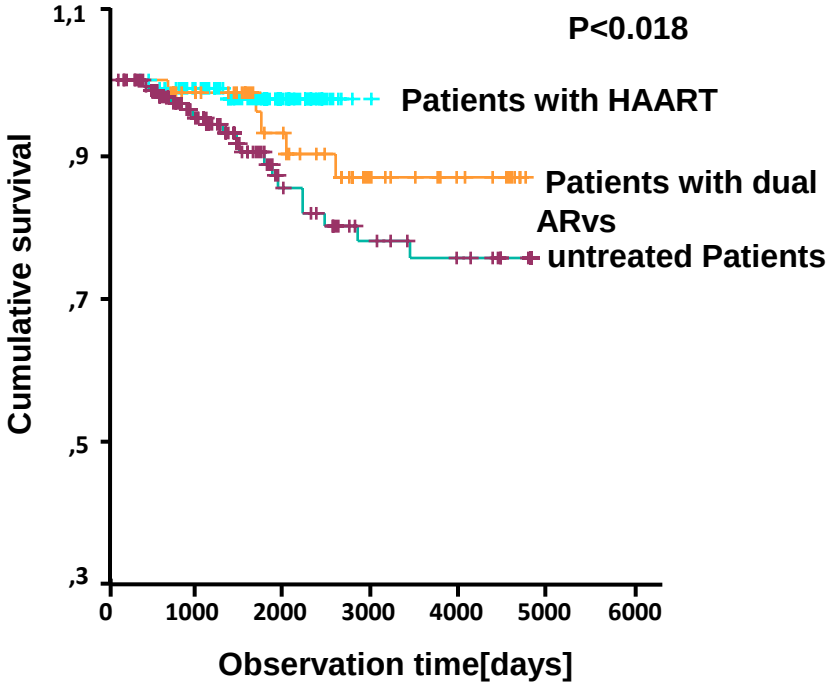
Overall and Liver-related Mortality - effect of HAART

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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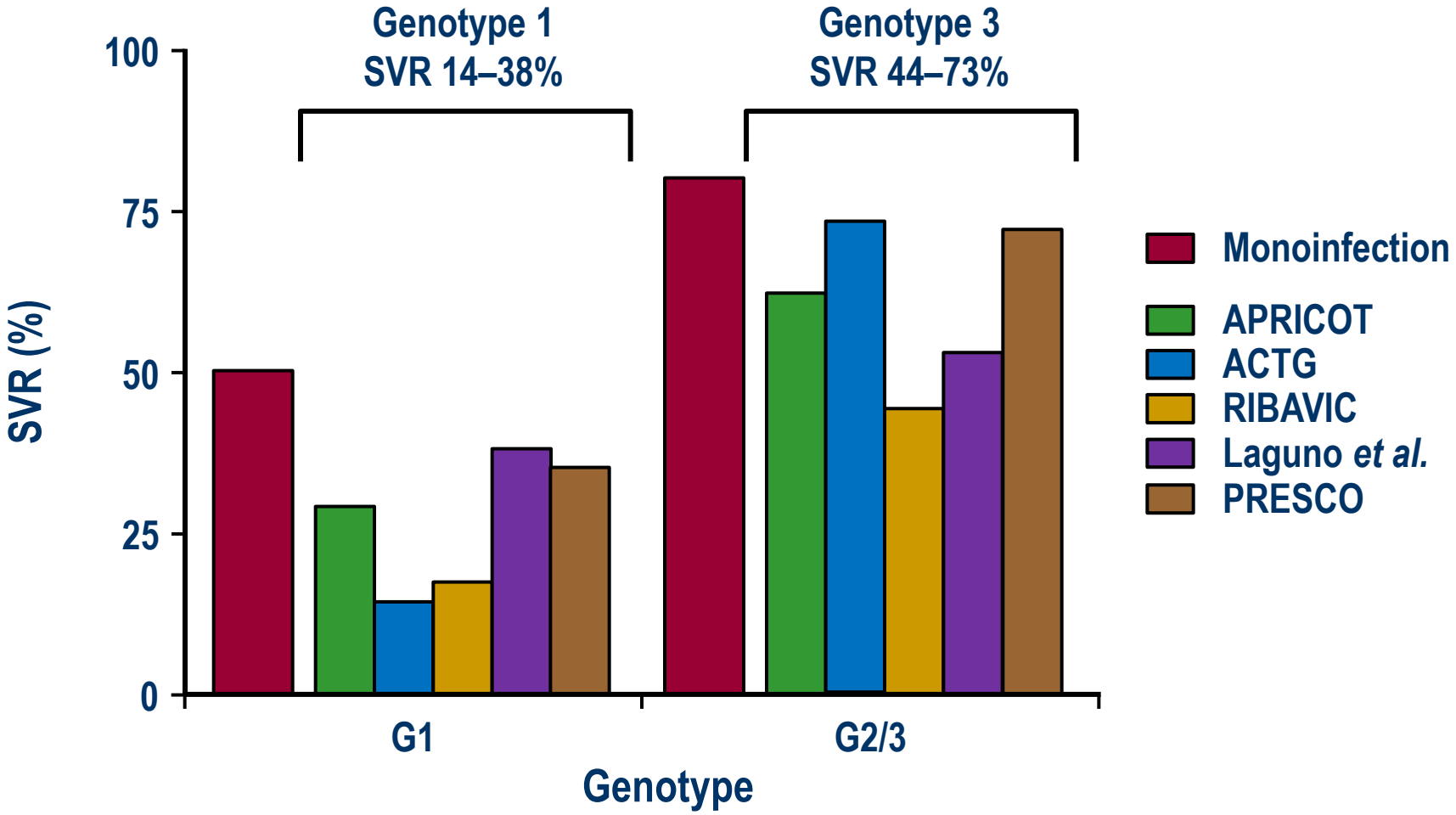
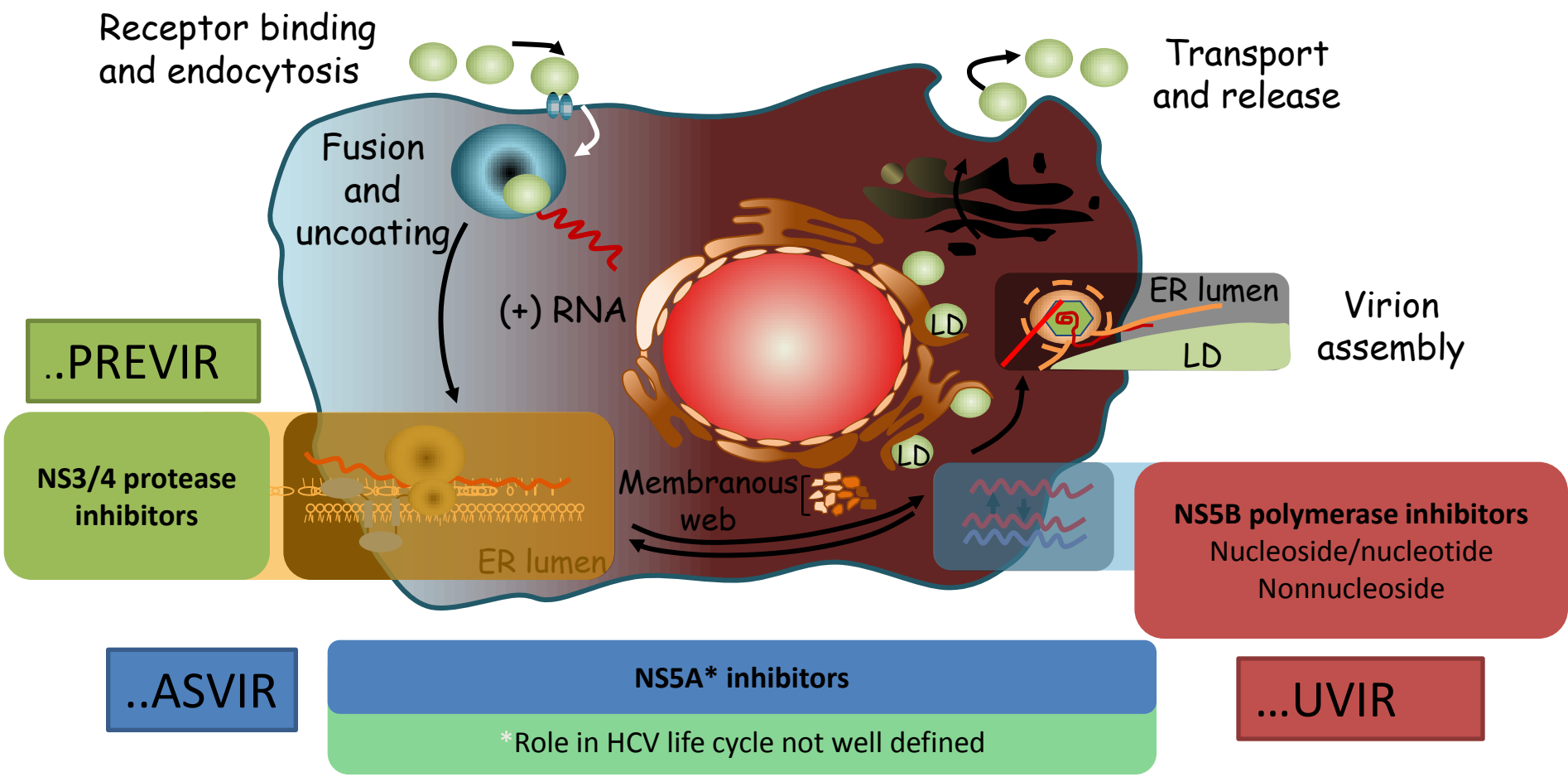
Qurishi N *et al. Lancet*, 2004

HCV/HIV SVR24 with pegIFN and RIBAVIRIN



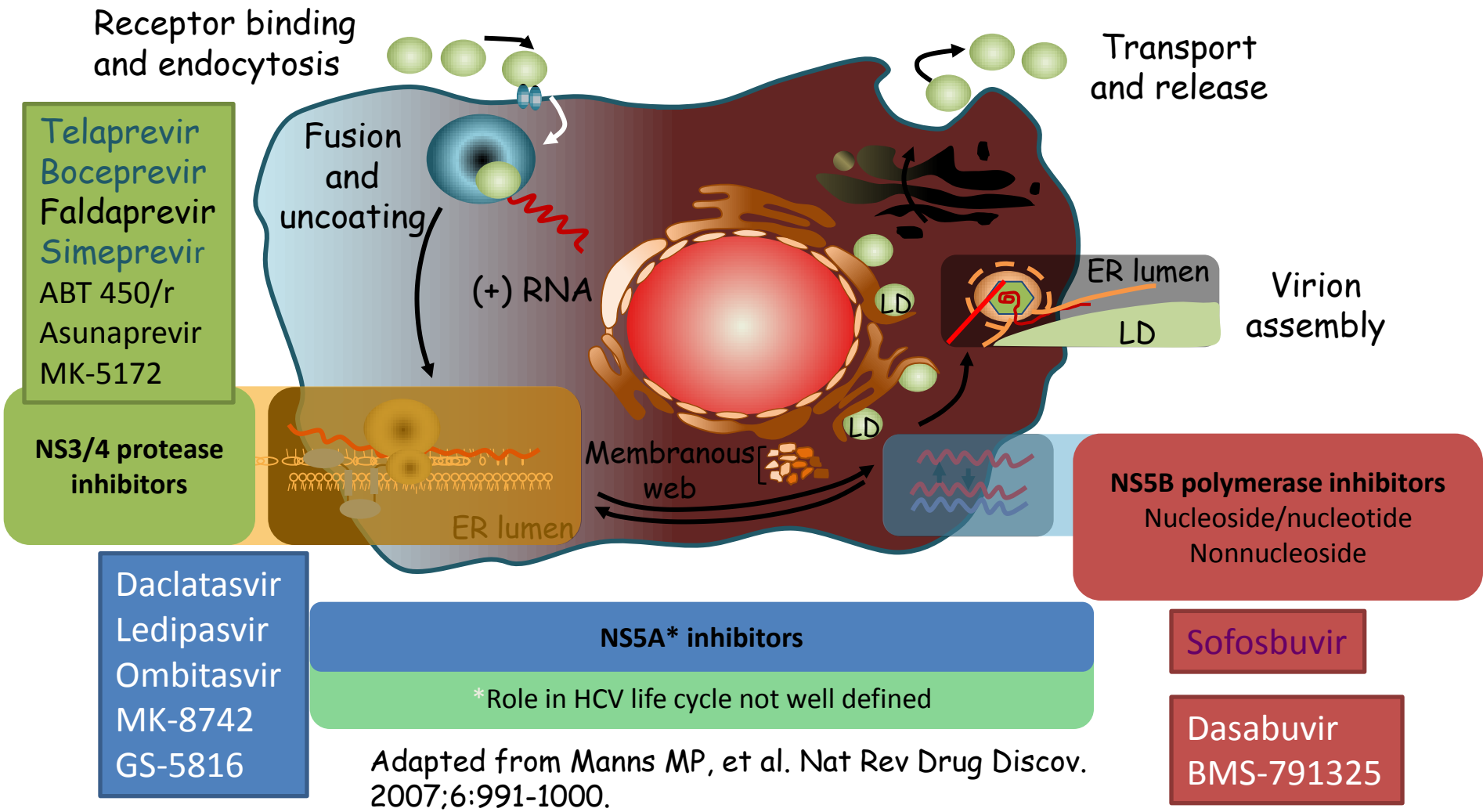
Adapted from: Fried et al, NEJM 2002;347:975-982, Torriani et al, NEJM 2004;351:438-50, Chung R, et al, NEJM 2004;351:451-9
Carrat F, et al, JAMA 2004;292:2839-42, Laguno et al, AIDS 2004;18:F27-F36, Nunez et al, JAIDS 2007;45:439-44

HCV Life Cycle and DAA Targets – drug classes and nomenclature



Adapted from Manns MP, et al. Nat Rev Drug Discov. 2007;6:991-1000.

HCV Life Cycle and DAA Targets – drugs



Adapted from Manns MP, et al. Nat Rev Drug Discov. 2007;6:991-1000.

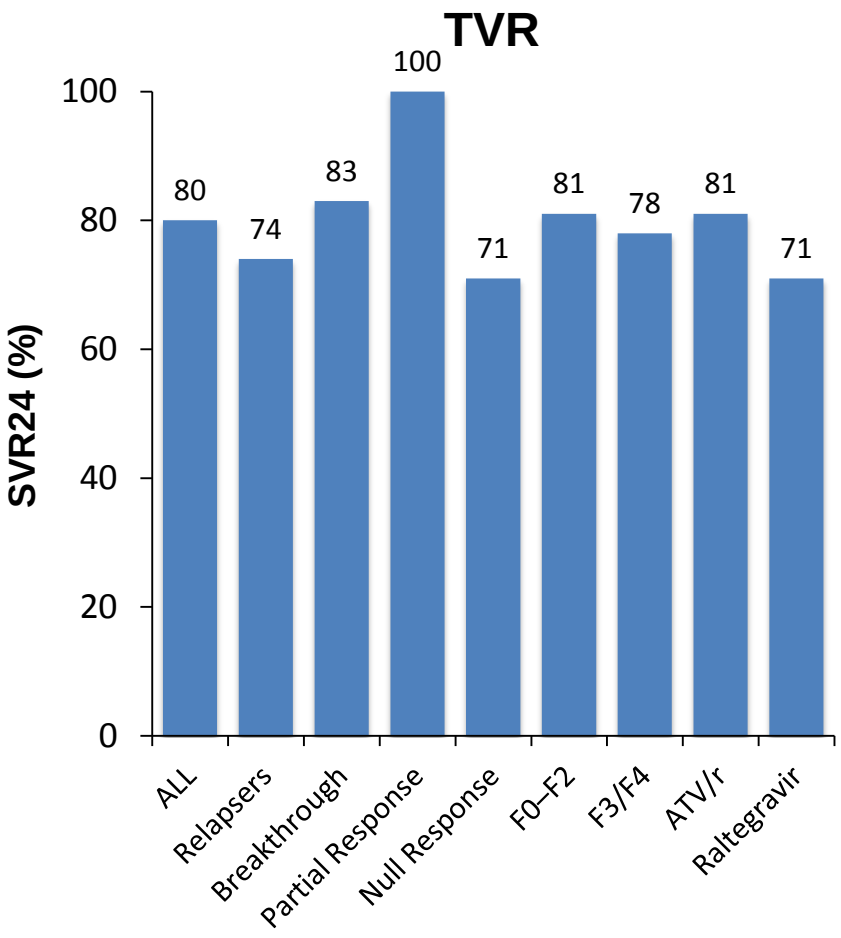
Not All Direct-Acting Antivirals are Created Equal

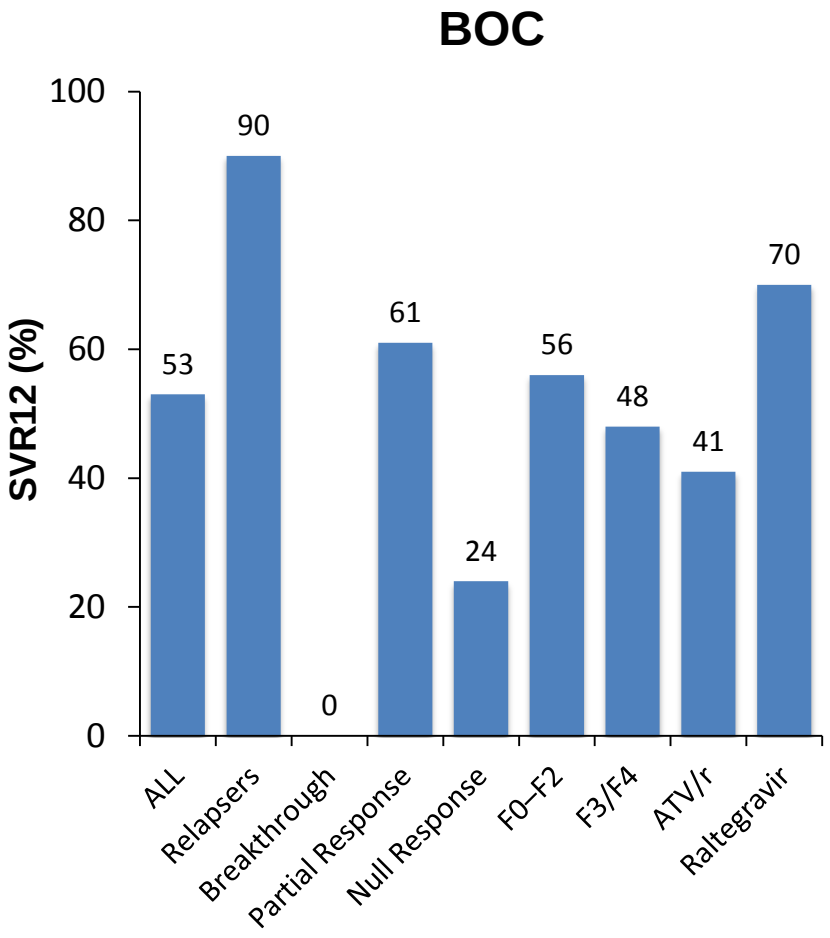
Characteristic	Protease Inhibitor*	Protease Inhibitor**	NS5A Inhibitor	Nuc Polymerase Inhibitor	Non-Nuc Polymerase Inhibitor
Resistance profile					
Pangenotypic efficacy					
Antiviral potency					
Adverse events					

 Good profile  Average profile  Least favorable profile

*First generation. **Second generation.

ANRS studies TelapreVIH and BocepreVIH in TE HCV GT 1 HIV/HCV co-infected patients



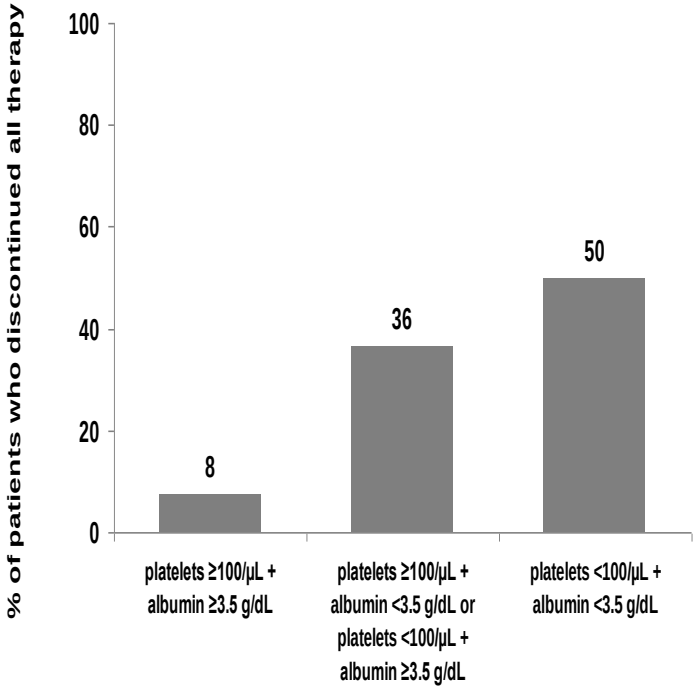


SVR24 in HIV/HCV PEG-IFN/RBV experienced treated with PEG-IFN/RBV + TVR (69) or BOC (64); 4 weeks lead in + 44 weeks standard + 24 additional weeks if HCV RNA at Week 8 >15IU/mL.
ATV/r: ritonavir boosted atazanavir; TE: treatment-experienced

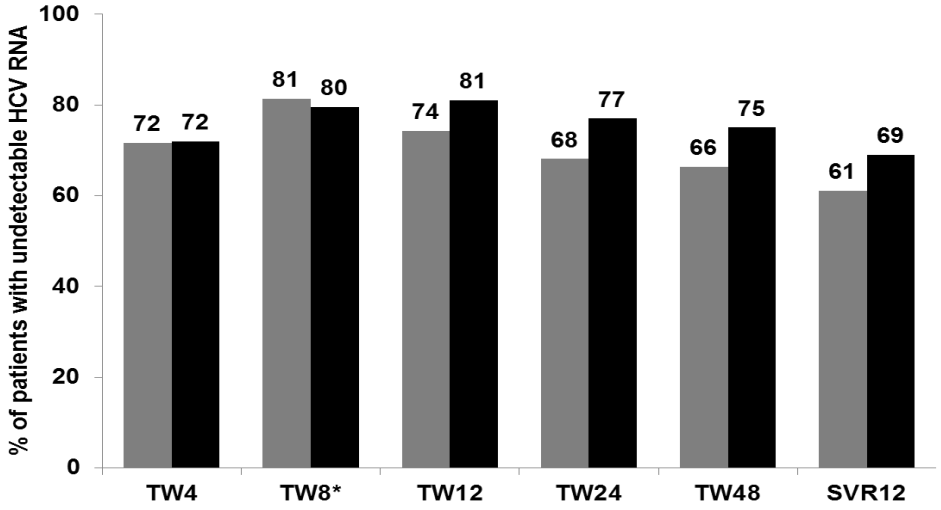
1. Cotte L, et al. CROI 2014; Oral #668;
2. Poizot Martin I, et al. CROI 2014. Oral #659.

‘Real-life’ experience PegIFN/R + TVR/BOC – pan-European data

Rx discontinuation

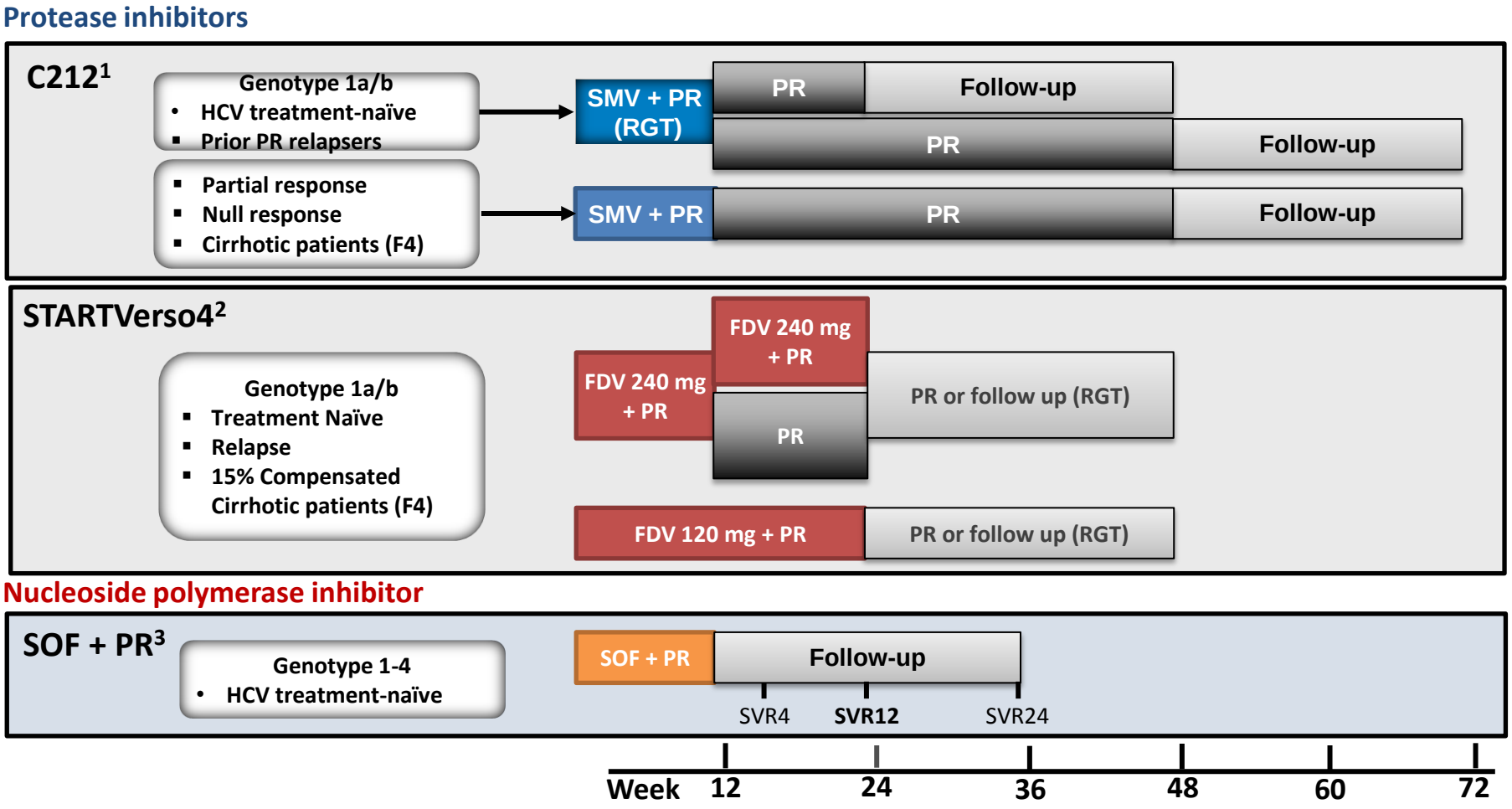


Rx response ITT and OT



Neukam K, Munteanu D, et al. CROI 2014

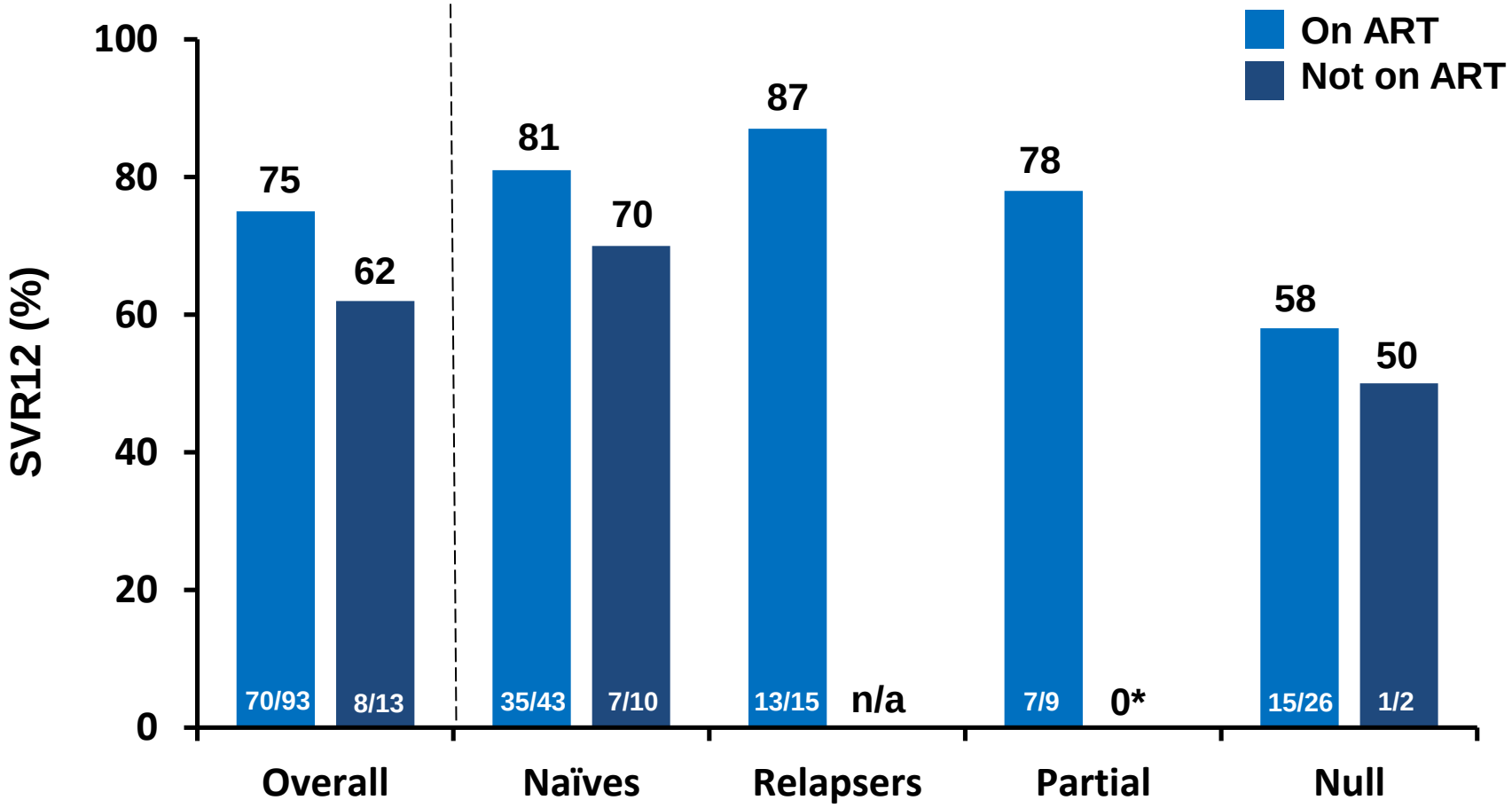
Second generation DAAs + PEG-IFN/RBV in HIV/HCV co-infected patients



1. Dieterich D, et al. EACS 2013. PS9/5;
2. Rockstroh J, et al. EACS 2013 .PS9/7;
3. Rodriguez-Torres M, et al. ID Week 2013. Poster #714.

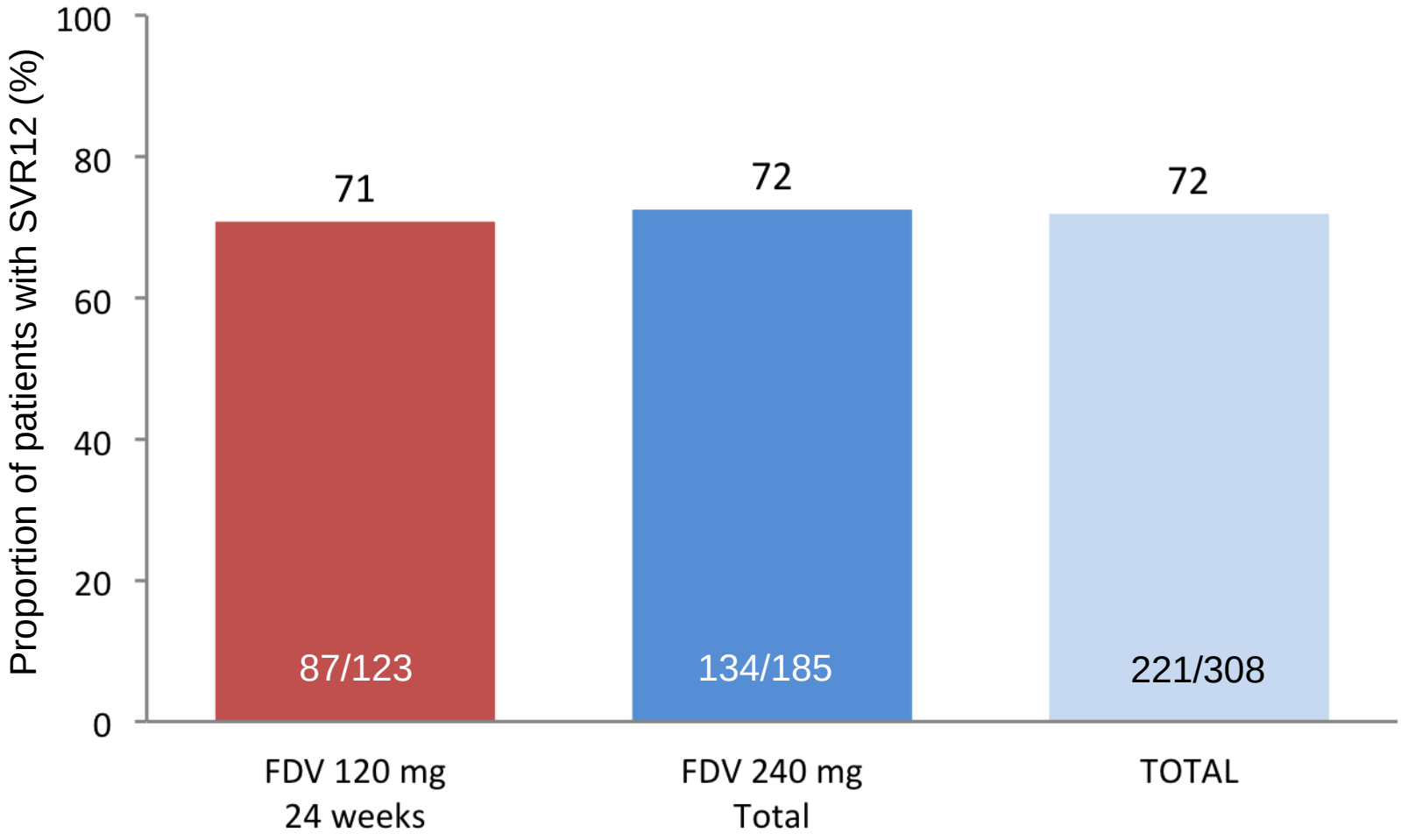
DAA: direct-acting antiviral agents; FDV: faldaprevir;
PR: PEG-IFN/RBV; RGT: response guided therapy; SMV: simeprevir

C212: SVR12 by concomitant ART use (ITT population)

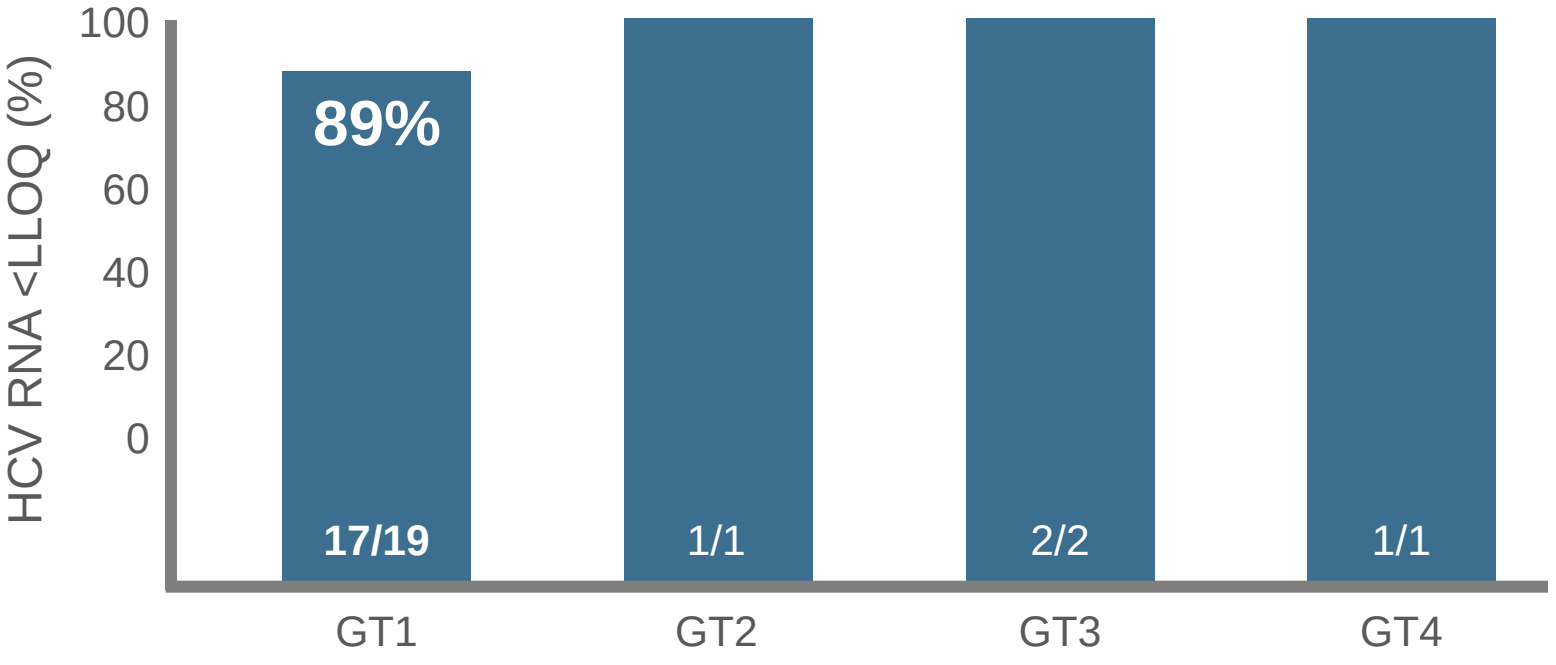


*0/1 patients; SVR12, sustained virologic response 12 weeks after end of treatment; n/a, not applicable

STARTVerso4: SVR12 overall population



Study 1910: SVR12



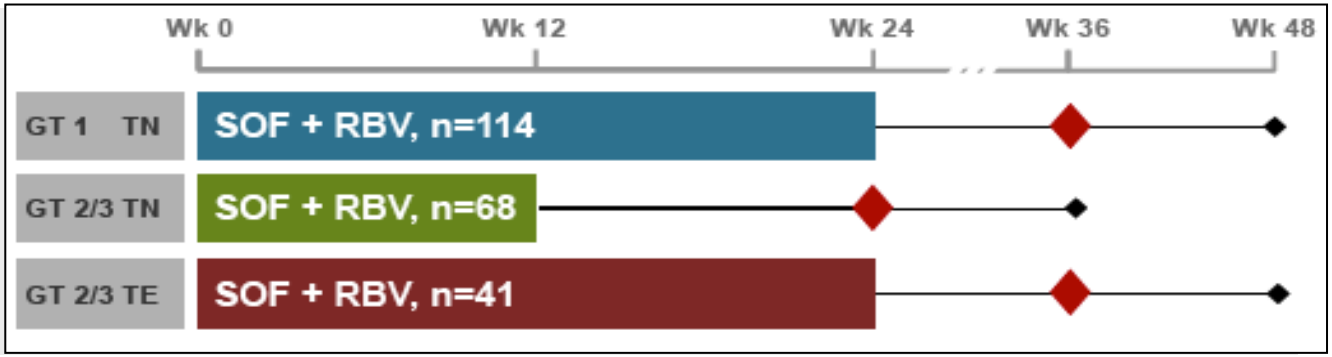
LLOQ: lower level of quantification

Rodriguez-Torres M et al. IDWeek 2013, poster 714

IFN-free DAA regimens in HIV/HCV co-infected patients

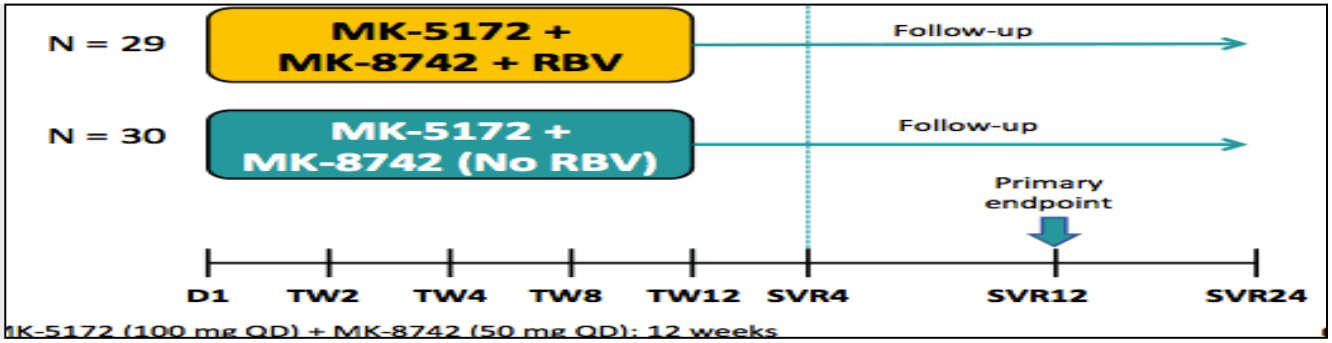
PHOTON-1 study

Naggie S, et al.
CROI 2014.
Oral #26



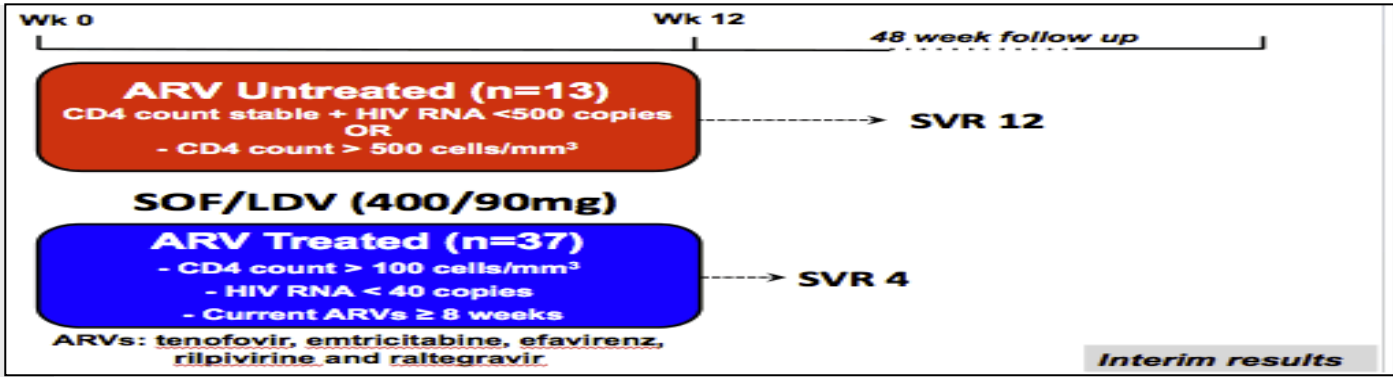
C-WORTHY study

Sulkowski M, et al.
EASL 2014. Oral #63

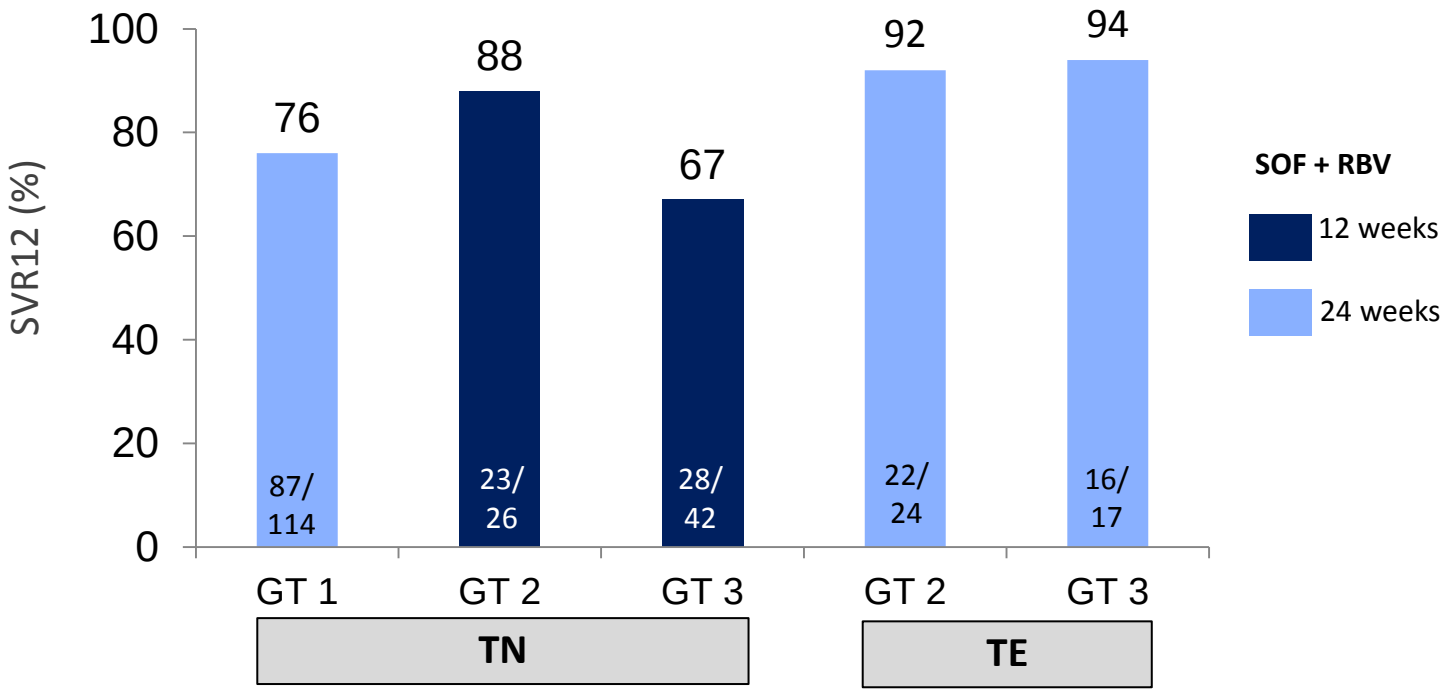


LDV/SOF STR ERADICATE study

Osinusi A, et al.
EASL 2014. Oral #14



PHOTON-1: Virological response

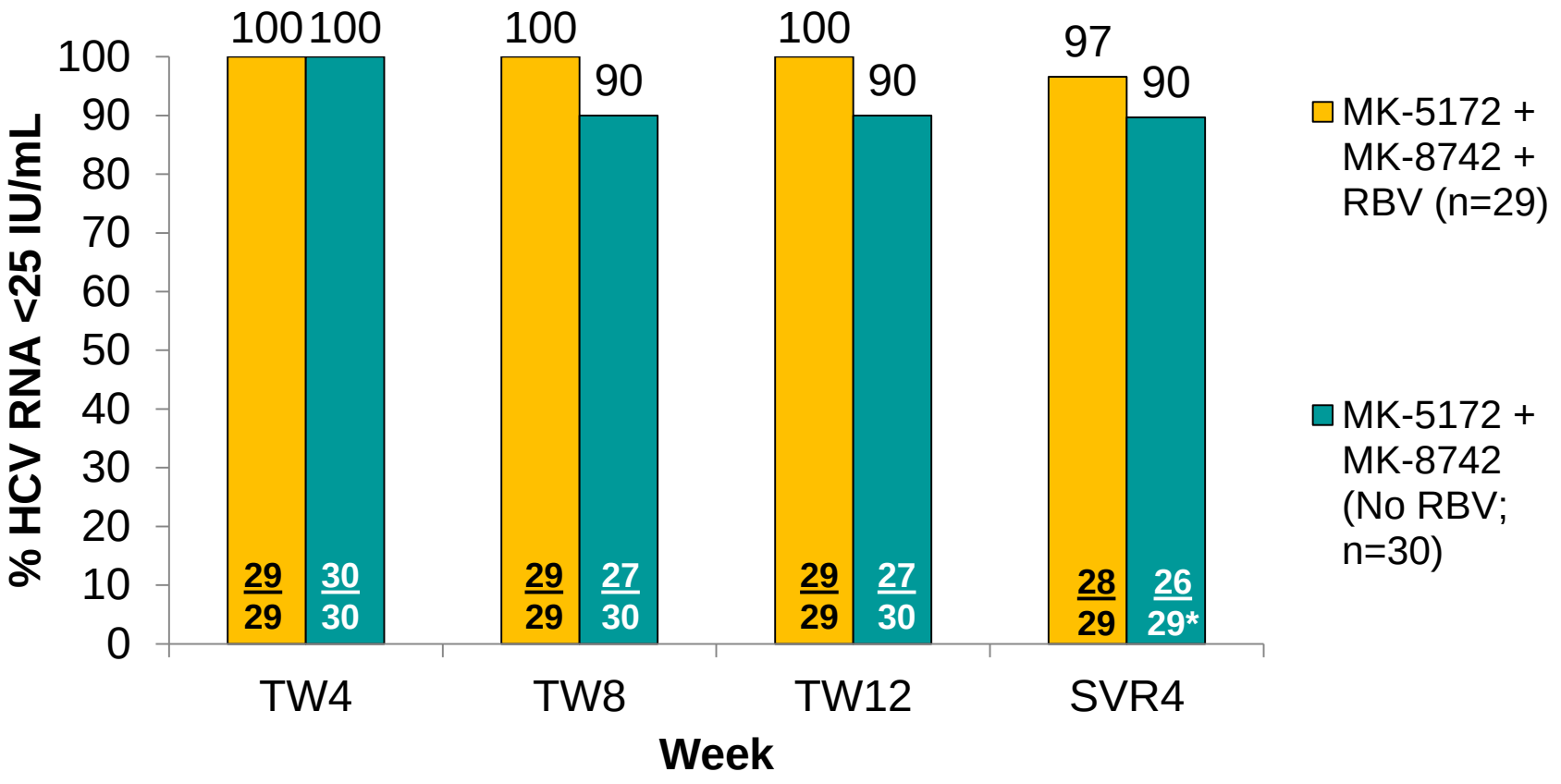


- No HCV resistance (S282T) observed in virological failures (deep sequencing)
  - HCV breakthrough in 2 patients due to non-adherence to SOF
  - HIV breakthrough in 2 patients due to non-adherence to ART

Naggie S, et al. CROI 2014. Oral #26.

C-Worthy Virologic Response

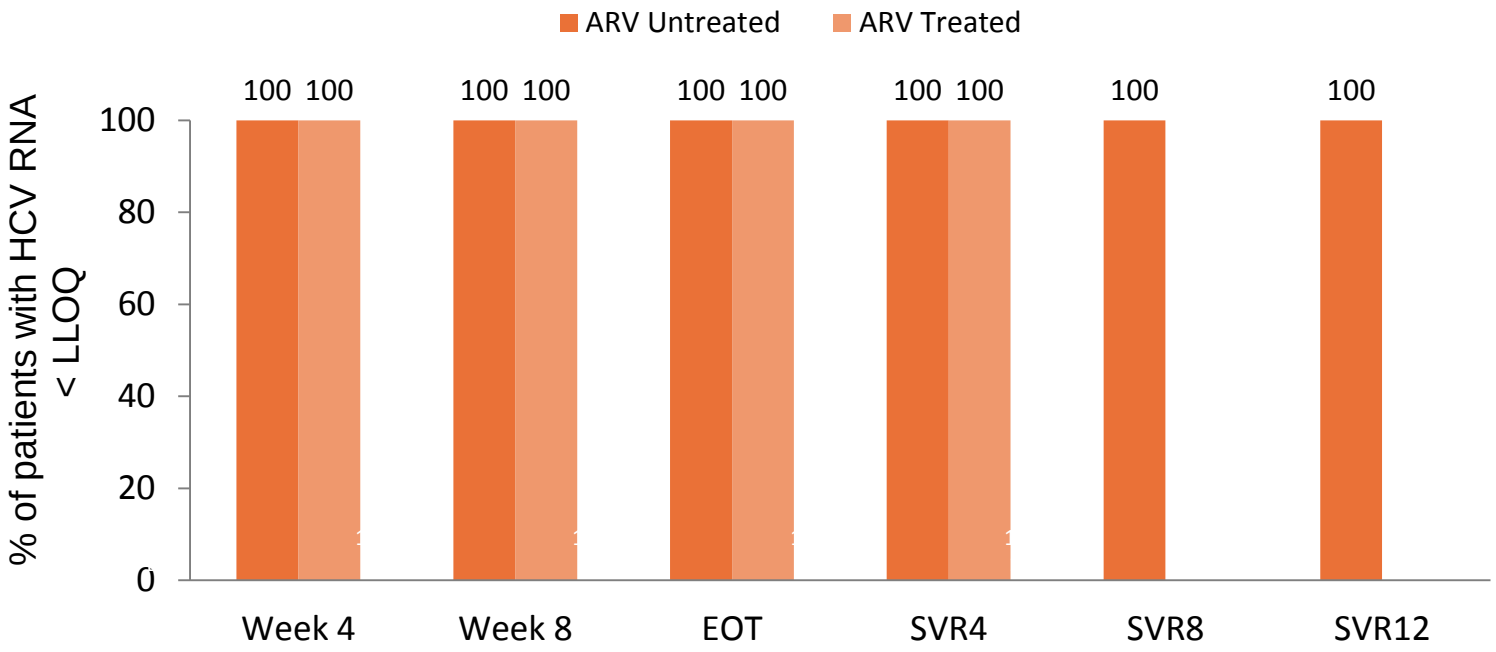
ITT Population



Virologic Failures: 1 relapse in +RBV arm;
2 breakthrough and 1 lost to follow up in No RBV arm

* One patient has not yet reached FU4

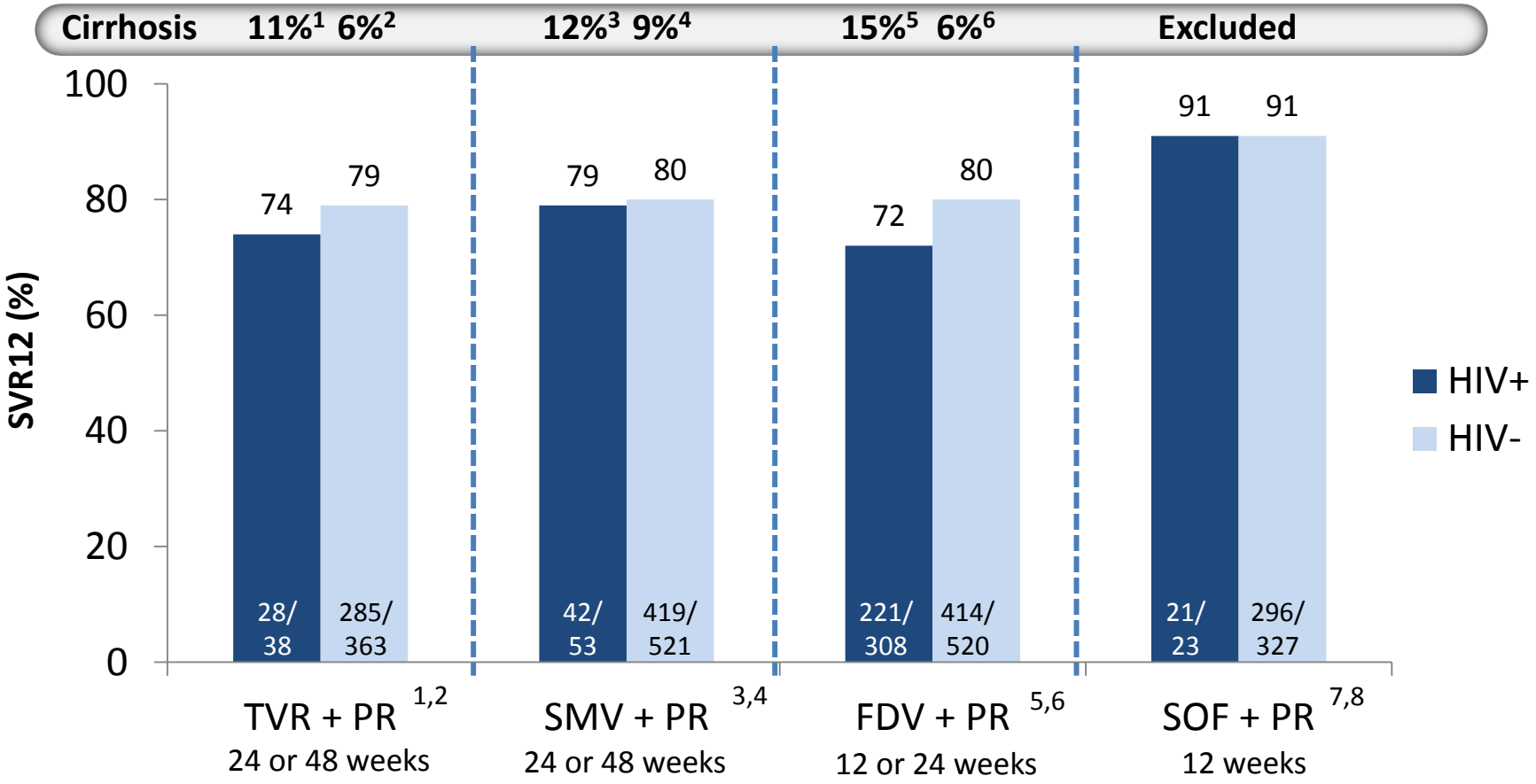
ERADICATE - Treatment Response



- The IFN and RBV free regimen of LDV/SOF in HCV/HIV co-infected patients resulted in SVR12 of 100% in ARV untreated patients and SVR4 of 100% in ARV treated patients
- LDV/SOF STR was generally well tolerated with no discontinuations
- Actively enrolling ION-4 (target of 300 GT 1 and GT 4 HCV/HIV patients). NCT 02073656.

Osinusi A, EASL, 2014, O14

SVR12 - PEG-IFN/RBV + TVR, SMV, FDV and SOF in HCV GT1 TN patients: HIV+ vs HIV–

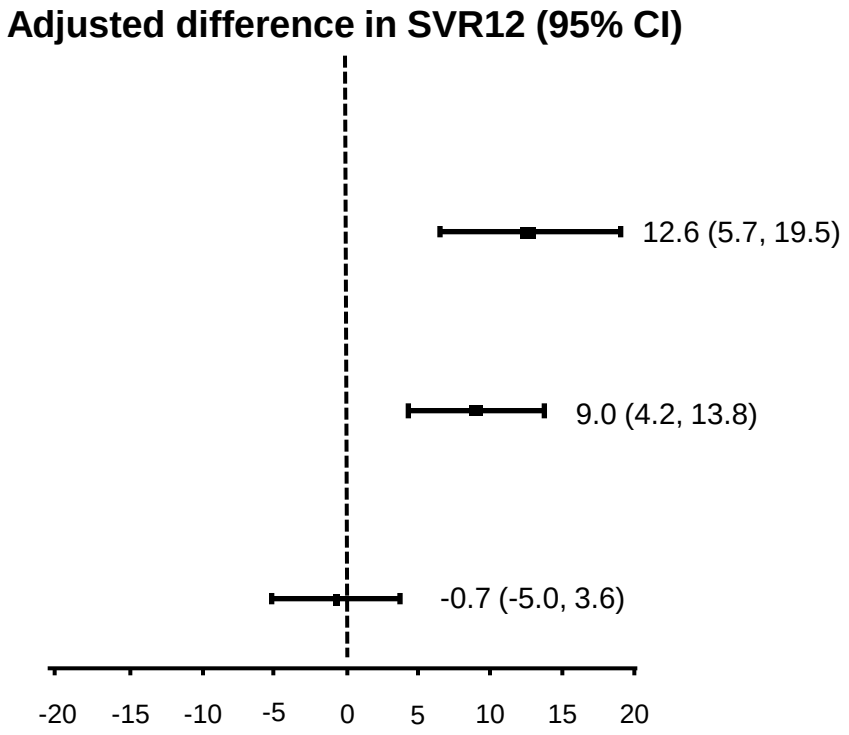


1. Sulkowski M, et al. AASLD 2012. Oral #54; 2. Janssen Cilag International. INCIVO (Telaprevir), Summary of product characteristics, September 2011; 3. Dieterich D, et al. CROI 2014 Abstract #24; 4. Jacobson I, et al. AASLD 2013. Poster #1122; 5. Dieterich D, et al. APASL 2014. Oral‘#681; 6. Ferenci P, et al. EASL 2013. Abstract #1416; 7. Rodriguez-Torres M, et al. ID week 2013. Poster #714; 8. Lawitz E, et al. APASL 2013. Oral #LB-02.

NOTE: not head-to-head comparisons.

Comparisons of SVR12 rates of interest adjusted for important predictors of response across the STARTVerso studies, excluding PI- and EFV-treated patients from STARTVerso4

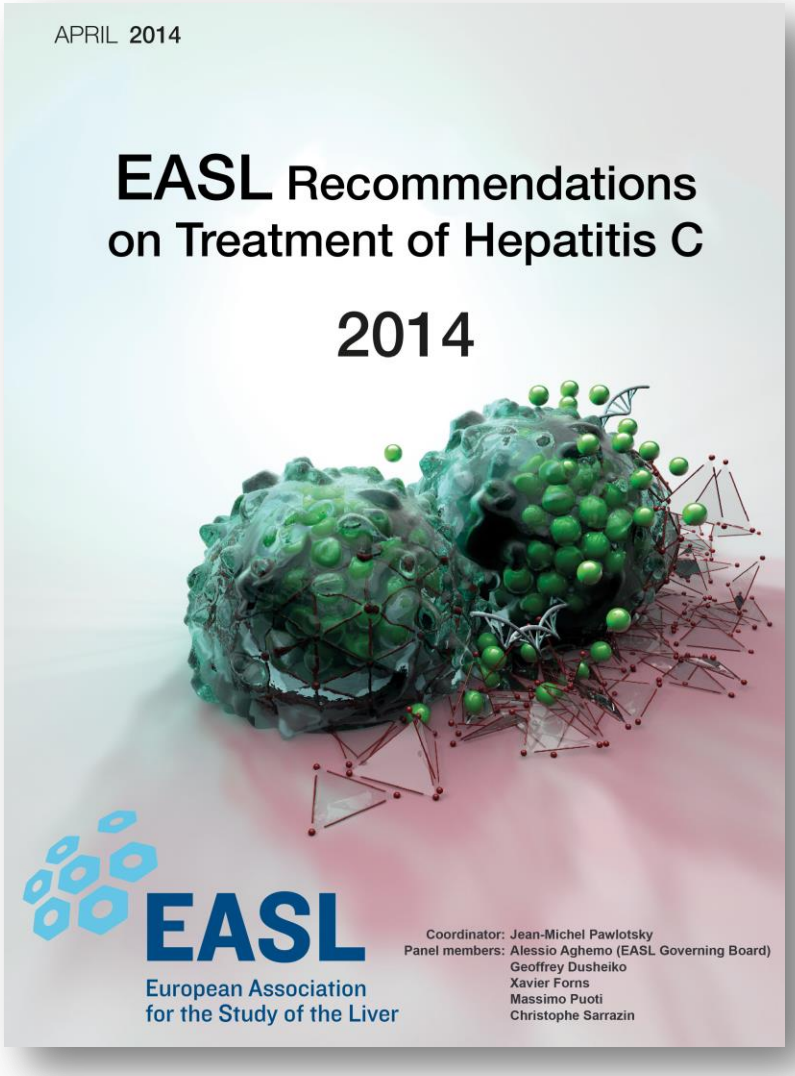
	Adjusted[a] SVR12 (%)
HIV Co-infection	
No (reference)	72.3
Yes	85.0
Genotype	
1a (reference)	74.2
1b	83.2
FDV dose	
120 mg (reference)	79.0
240 mg	78.3



[a] Adjusted for IL28B, race, fibrosis stage, baseline HCV RNA, age, baseline GGT and baseline platelet count.

Deitrich, APASL 2014, o681

New online EASL HCV recommendations



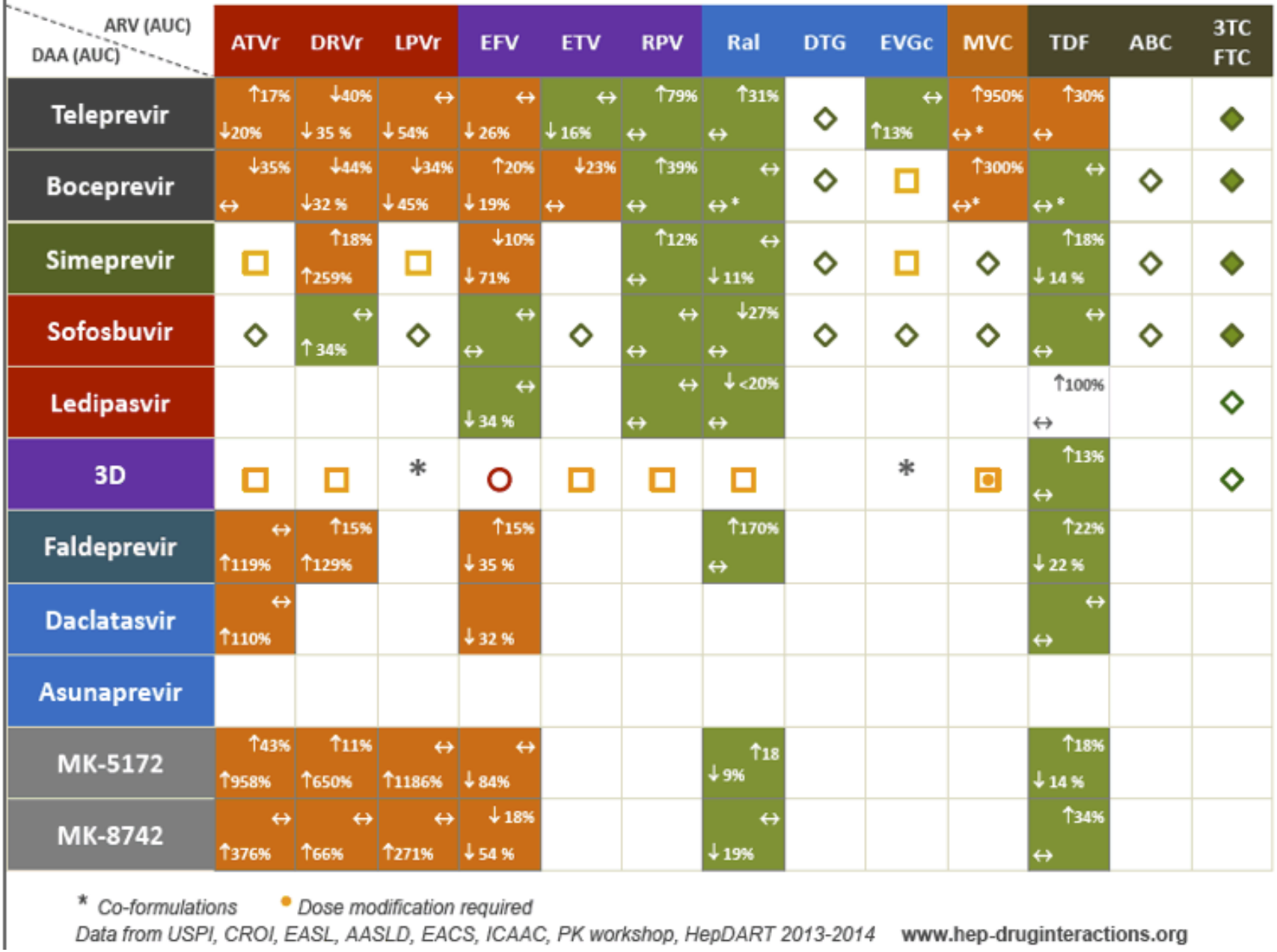
Same treatment regimens can be used in HIV/HCV patients as in patients without HIV infection, as the virological results of therapy are identical (A1)

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

New EASL HCV recommendations – treatment combination options

G1, 2, 3, 4, 5, 6	SOF + PEG-IFN/RBV	12 weeks
G1, 4	SMV + PEG-IFN/RBV	12 weeks + RGT 12/36
G4	Daclatasvir + PEG-IFN/RBV	12 weeks + RGT 12
G1, 2, 3, 4	SOF + RBV	12–24 weeks
G1, 4	SOF + SMV (± RBV)	12 weeks
G1, 3, 4	SOF + daclatasvir (± RBV)	12–24 weeks

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



S.Khoo, 15th Intl. W'shop, 2014

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