Management of viral hepatitis in the HIV co-infected patient

Sanjay Bhagani BSc MB ChB FRCP
Royal Free Hospital/University College London

UCL

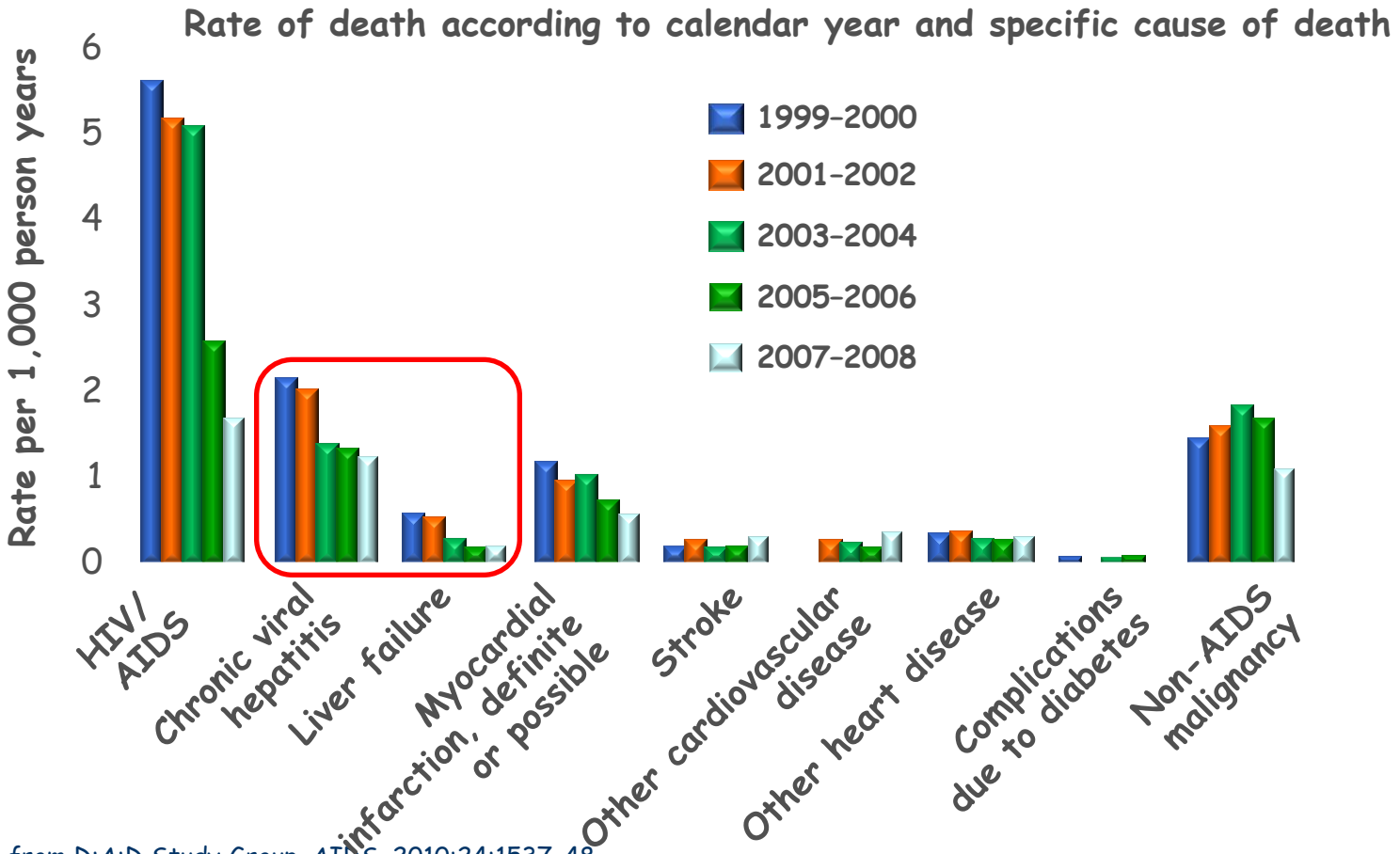
Royal Free Hampstead NHS Trust

NHS


The Preamble
to the U.S. Constitution

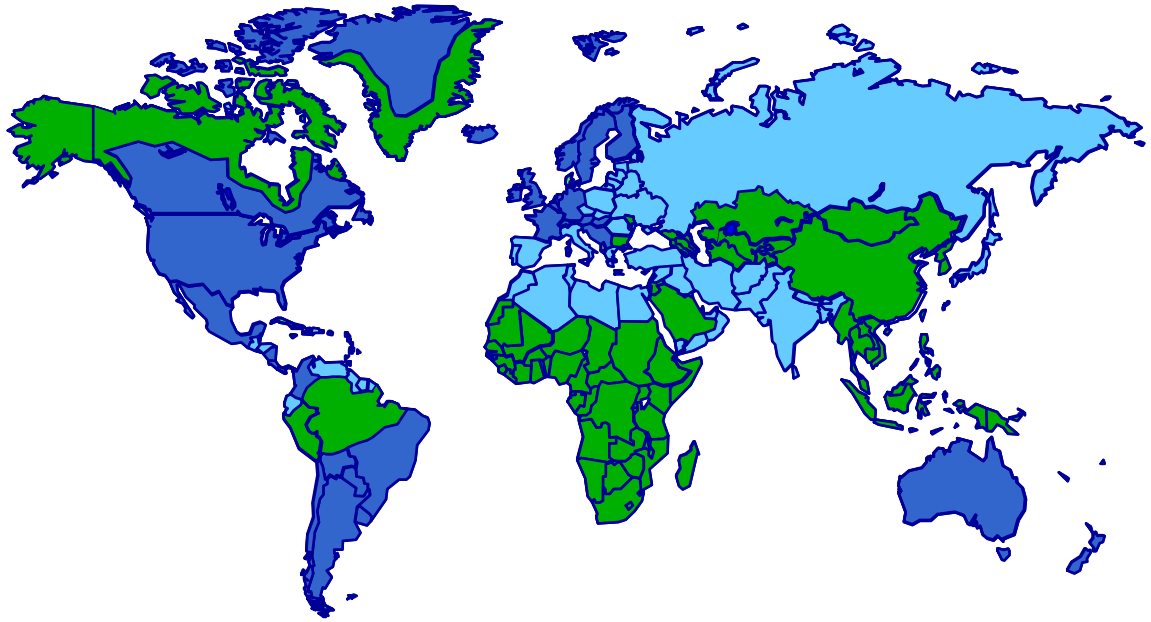
D:A:D: Liver-related death is a frequent cause of non-AIDS death in HIV-infected patients

- Analysis of 2,482 deaths in 180,176 person-years among 33,308 individuals
- AIDS remains the primary cause of death amongst HIV-positive individuals



Adapted from D:A:D Study Group. AIDS. 2010;24:1537–48.

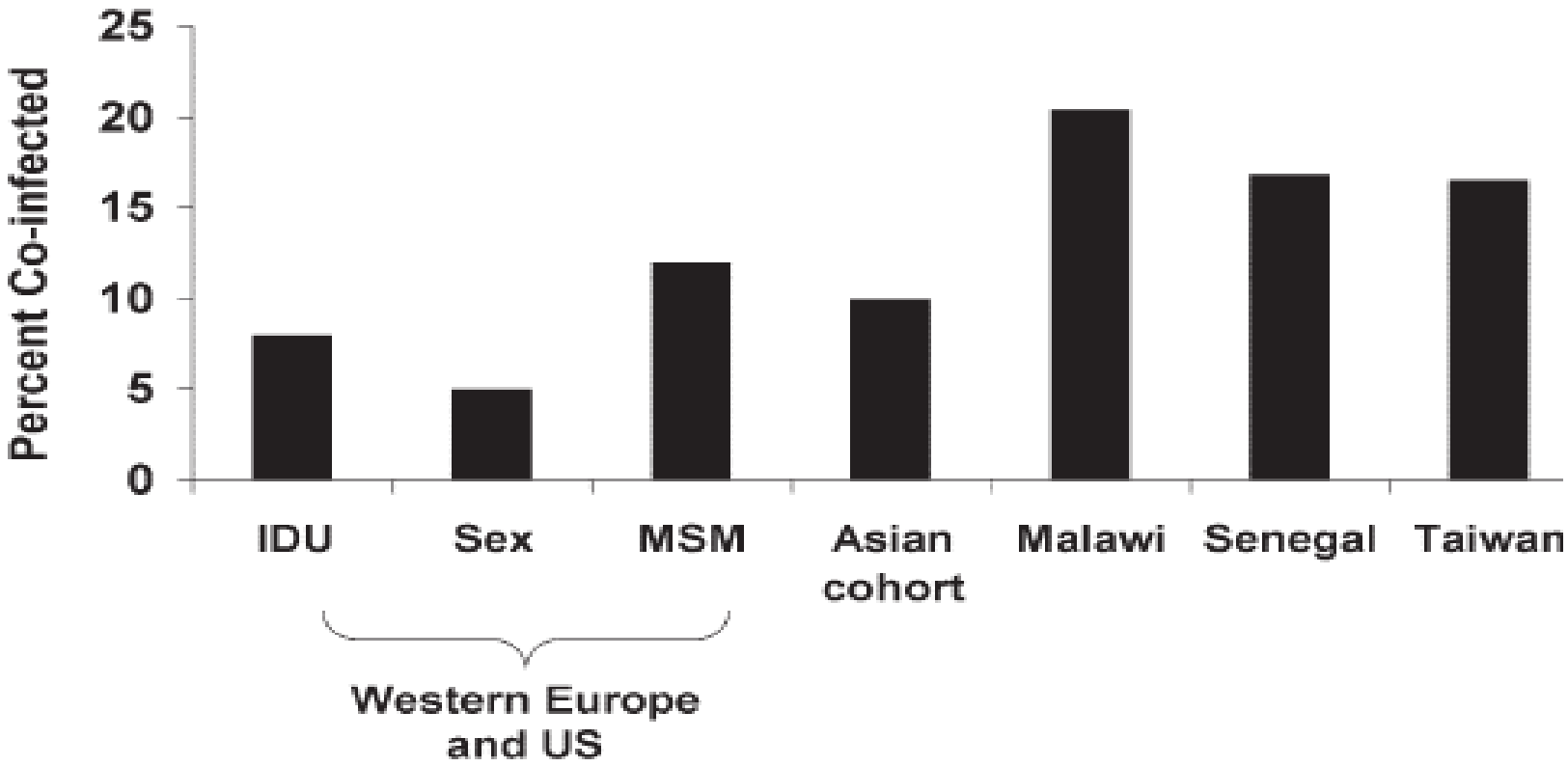
Prevalence of HBV: Global Estimates



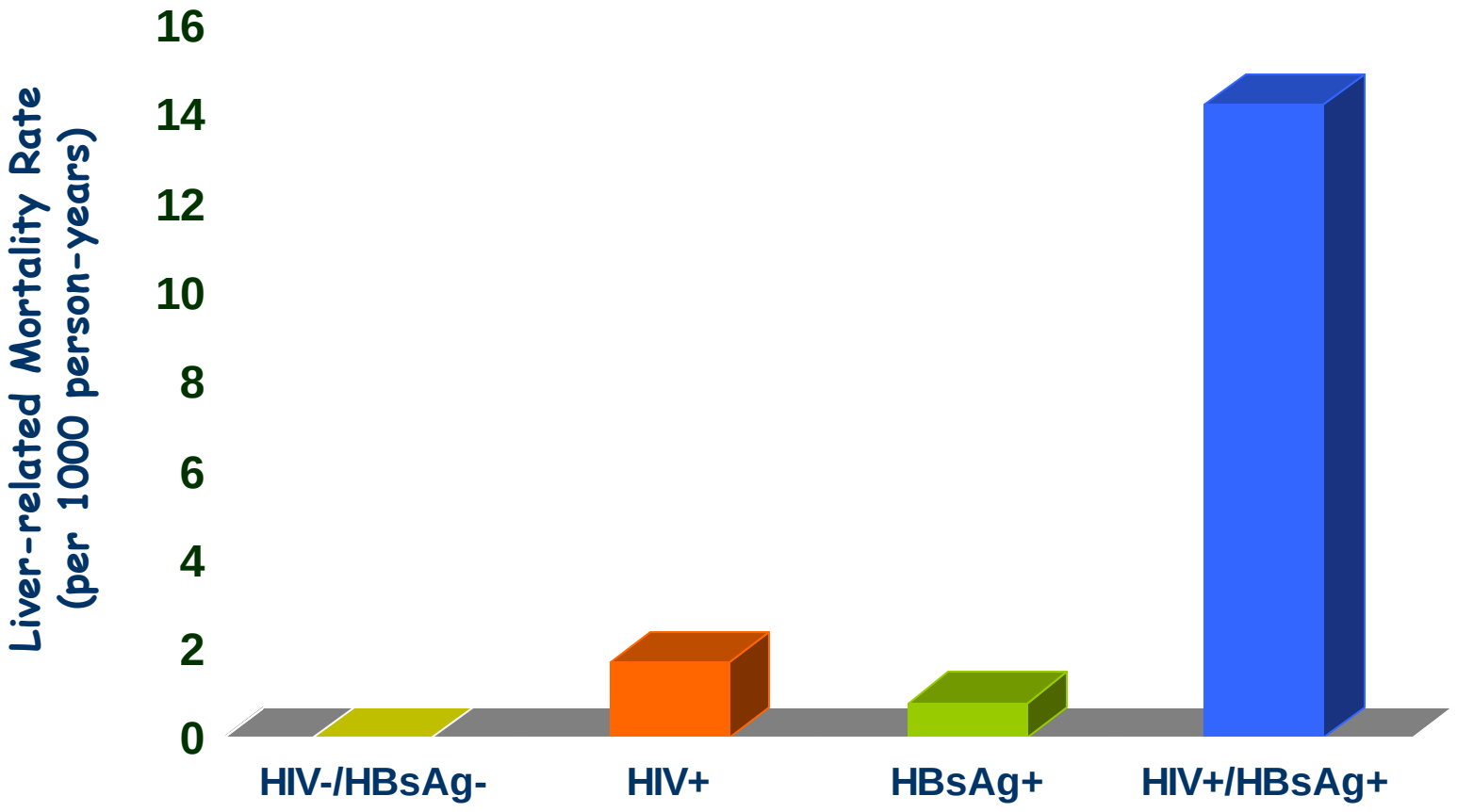
	HBsAg +ve, (%)
Taiwan	10.0–13.8
Vietnam	5.7–10.0
China	5.3–12.0
Africa	5.0–19.0
Philippines	5.0–16.0
Thailand	4.6–8.0
Japan	4.4–13.0
Indonesia	4.0
South Korea	2.6–5.1
India	2.4–4.7
Russia	1.4–8.0
US	0.2–0.5

Mast EE, *et al. MMWR Recomm Rep.* 2006;55:1-33
Custer B, *et al. J Clin Gastroenterol.* 2004;38(10 suppl):S158-S168

Global HIV/HBV

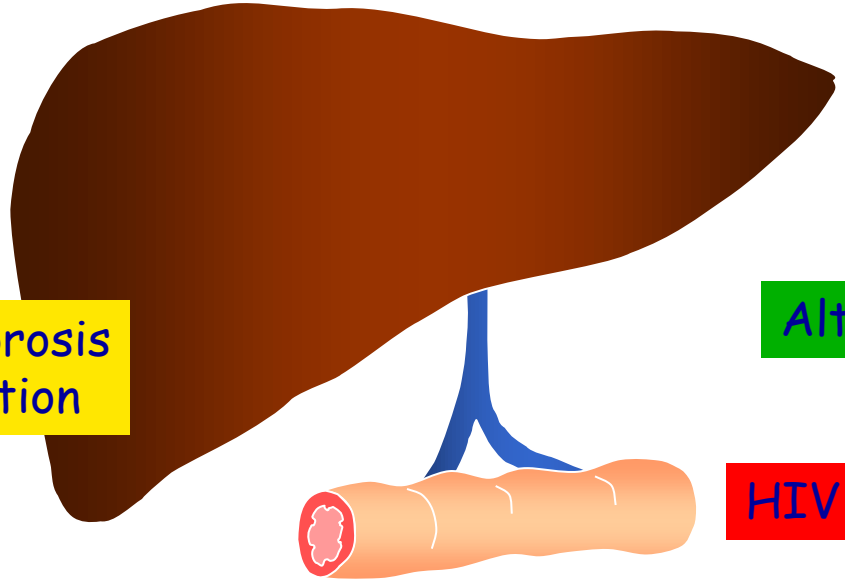


HIV/HBV Co-infection: Increased risk of ESLD due to HBV



Thio CL, et al. Lancet. 2002:360:1921-26.

Immune activation and liver disease



Cirrhosis
HCV/HBV
Alcohol

Altered portal vein circulation

HIV -> GIT CD4+ T-cell depletion

Microbial translocation

LPS

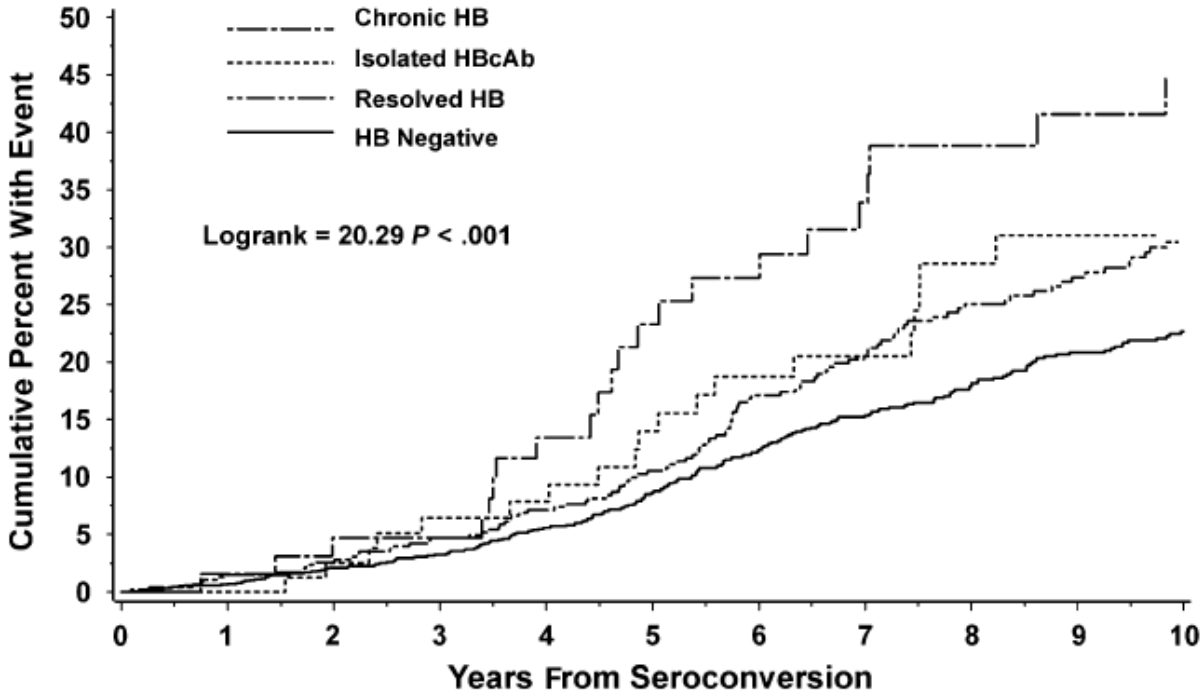
Immune activation

Hepatic fibrosis
HSC activation

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

Slide courtesy of S. Lewin

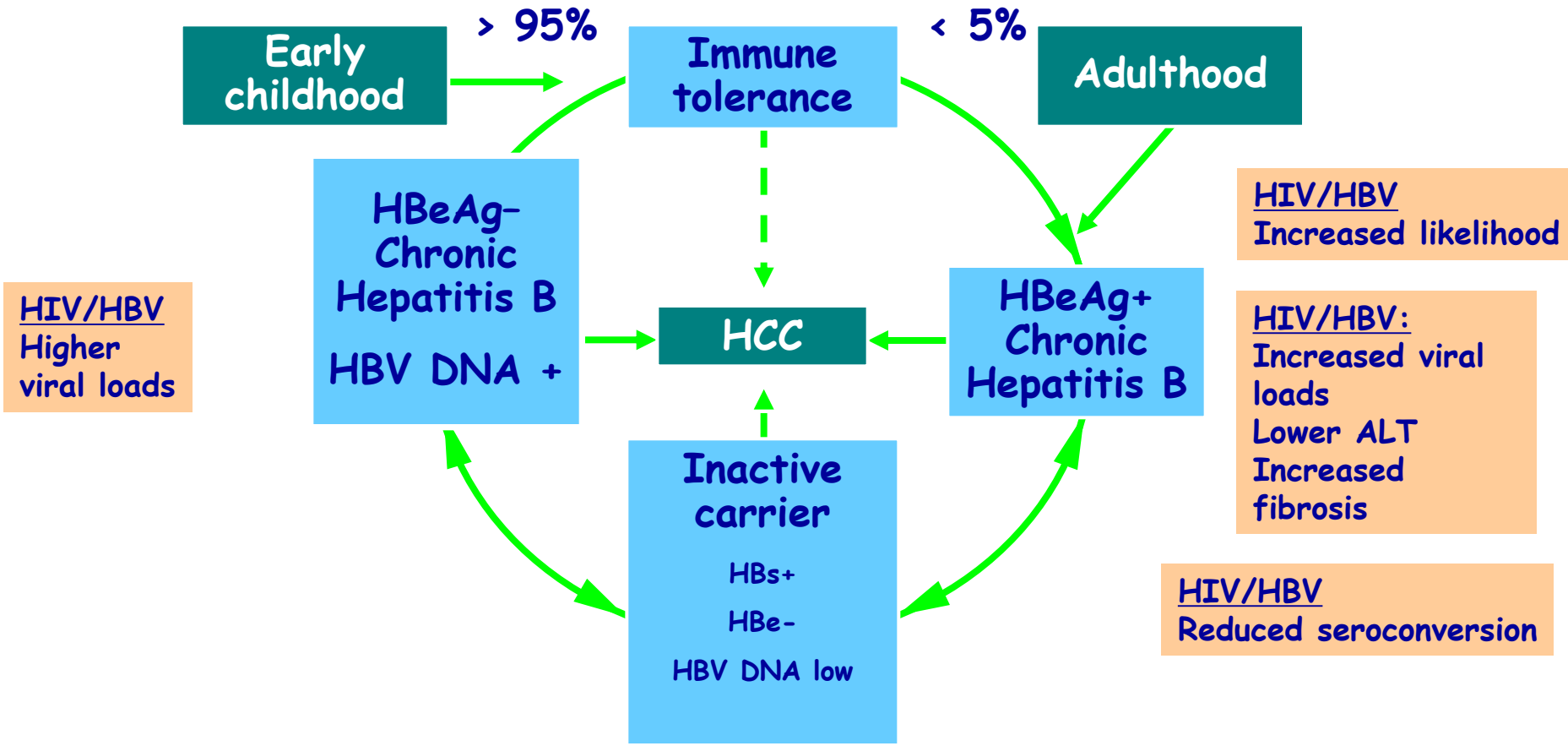
Does HBV effect HIV?



Chronic HB:	64	63	60	58	48	38	35	28	23	20	18
Isolated HBcAb:	82	81	76	69	62	55	47	40	31	23	21
Resolved HB:	474	452	433	405	365	330	280	241	205	117	153
HB Negative:	1732	1622	1414	1240	1082	940	812	682	569	468	405

Chun, et al, JID 2012

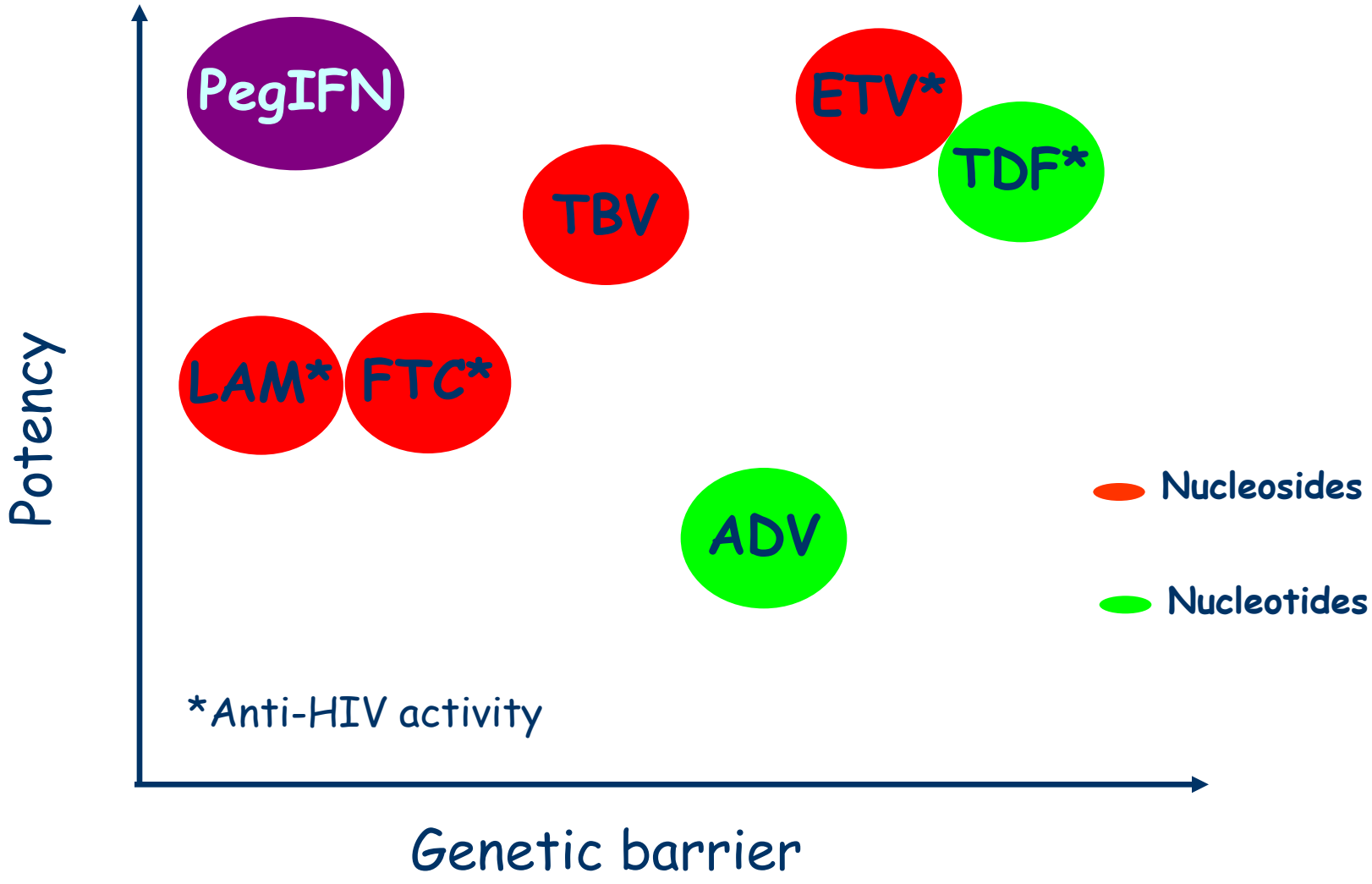
Natural history of HBV infection - where does co-infection fit in?



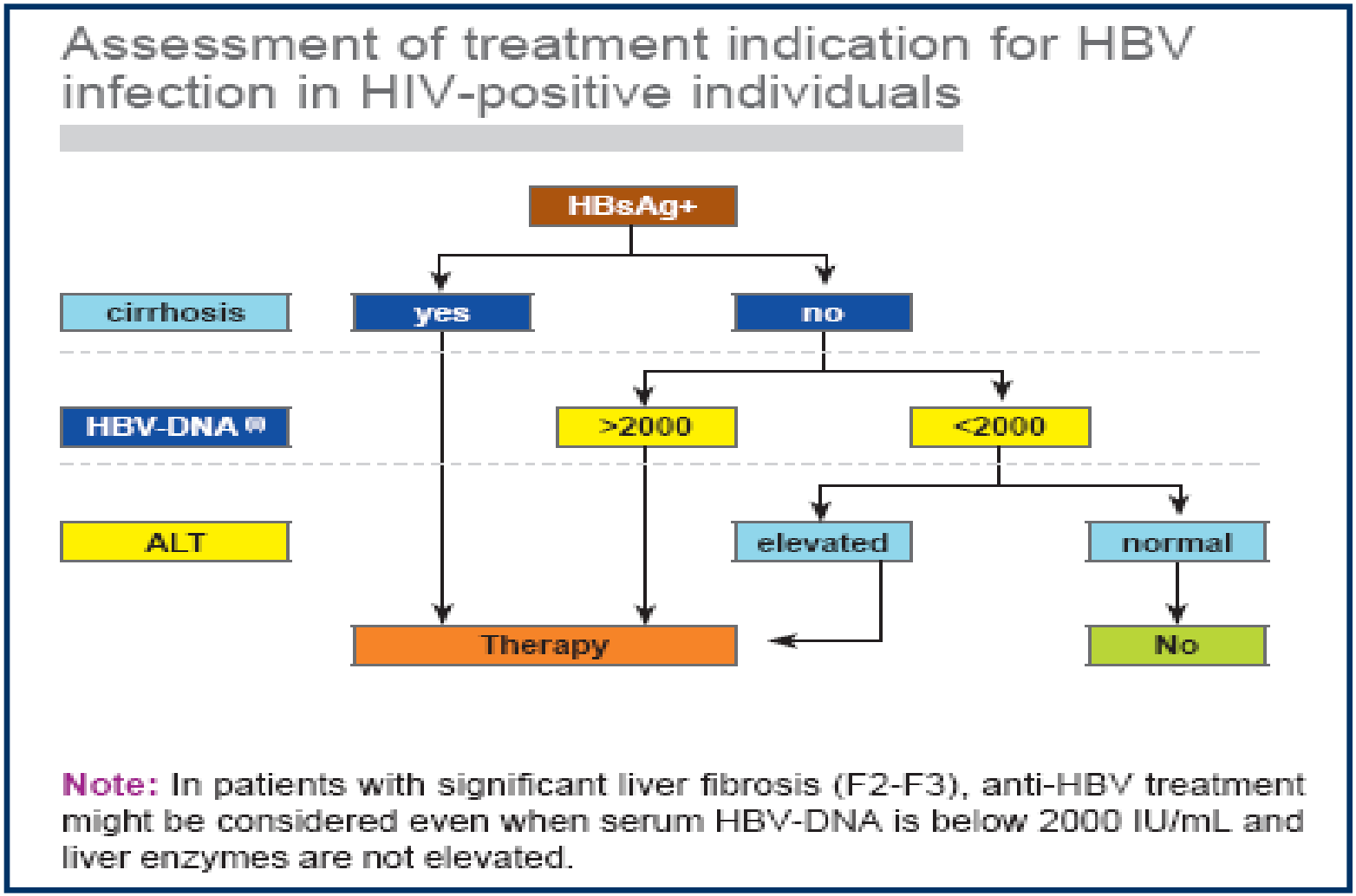
Adapted from: Chen DS, *et al. J Gastroenterol Hepatol* 1993;8:470–5; Seeff L, *et al. N Engl J Med* 1987;316:965–70; Thio CL, *et al. Lancet* 2002;360:1921–6; Gilson RJ, *et al. AIDS* 1997;11:597–606; Colin JF, *et al. Hepatology* 1999;29:1306–10

Treating HBV

- Prevent progression to end-stage liver disease
- Prevent HCC

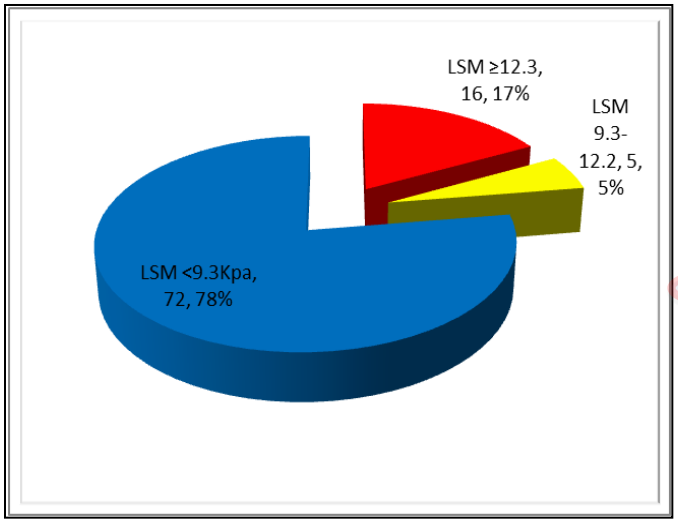

PegIFN
ETV*
TDF*
TBV
LAM*
FTC*
ADV
Nucleosides
Nucleotides
*Anti-HIV activity
Potency
Genetic barrier

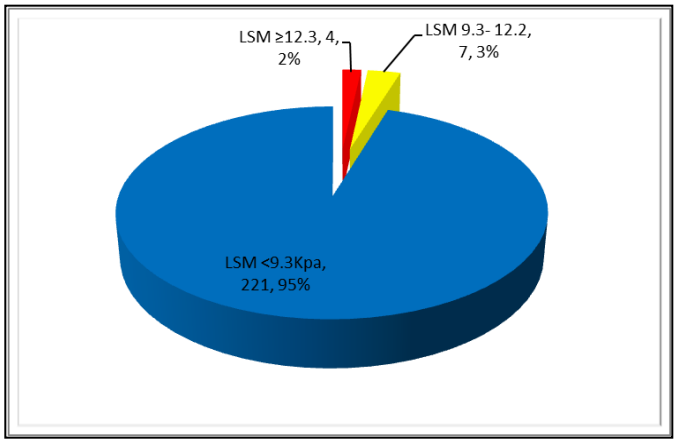
EACS Guidelines 2012



Agbaji et al, (CROI, 2013) HBV in the resource-poor setting; how useful is FibroScan?

HBV/HIV co-infected





	Univariate		Multivariate	
	OR, 95% CI	p value	OR, 95% CI	p value
Age ≥30 yrs	0.83 (0.26,3.03)	0.74	0.50 (0.14,1.87)	0.30
Male gender	1.52 (0.50,4.51)	0.40	1.18 (0.35,3.92)	0.79
HBV DNA ≥3.3 log IU/mL 1,2	6.5 (1.99, 22.97)	0.0003	6.09 (1.96,18.91)	**0.002**
HBeAg reactive	2.50 (0.69, 8.41)	0.10	-	-
Married	1.1 (0.37, 3.46)	0.86	-	-
Current alcohol use	2.62 (0.81, 8.19)	0.06	2.38 (0.74,7.60)	0.15
ALT ≥303	0.80 (0.27, 2.46)	0.66	-	-
BMI ≥25	0.44 (0.10-1.57)	0.17	0.52 (0.14,1.82)	0.29
CD4 <200	1.72 (0.53,5.30)	0.30	1.26 (0.37,4.29)	0.71
HIV VL ≥400,000	1.16 (0.18, 5.35)	0.83	-	-
Platelets <150	2.18 (0.45, 9.76)	0.24	-	-

Pertinent issues in HIV/HBV co-infection management

- TDF +/- 3TC/FTC works
- What options for patients NOT needing HAART
  - PegIFN
- What about hepatic 'flares' with anti-HBV therapy?
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- Global implications of lamivudine resistance

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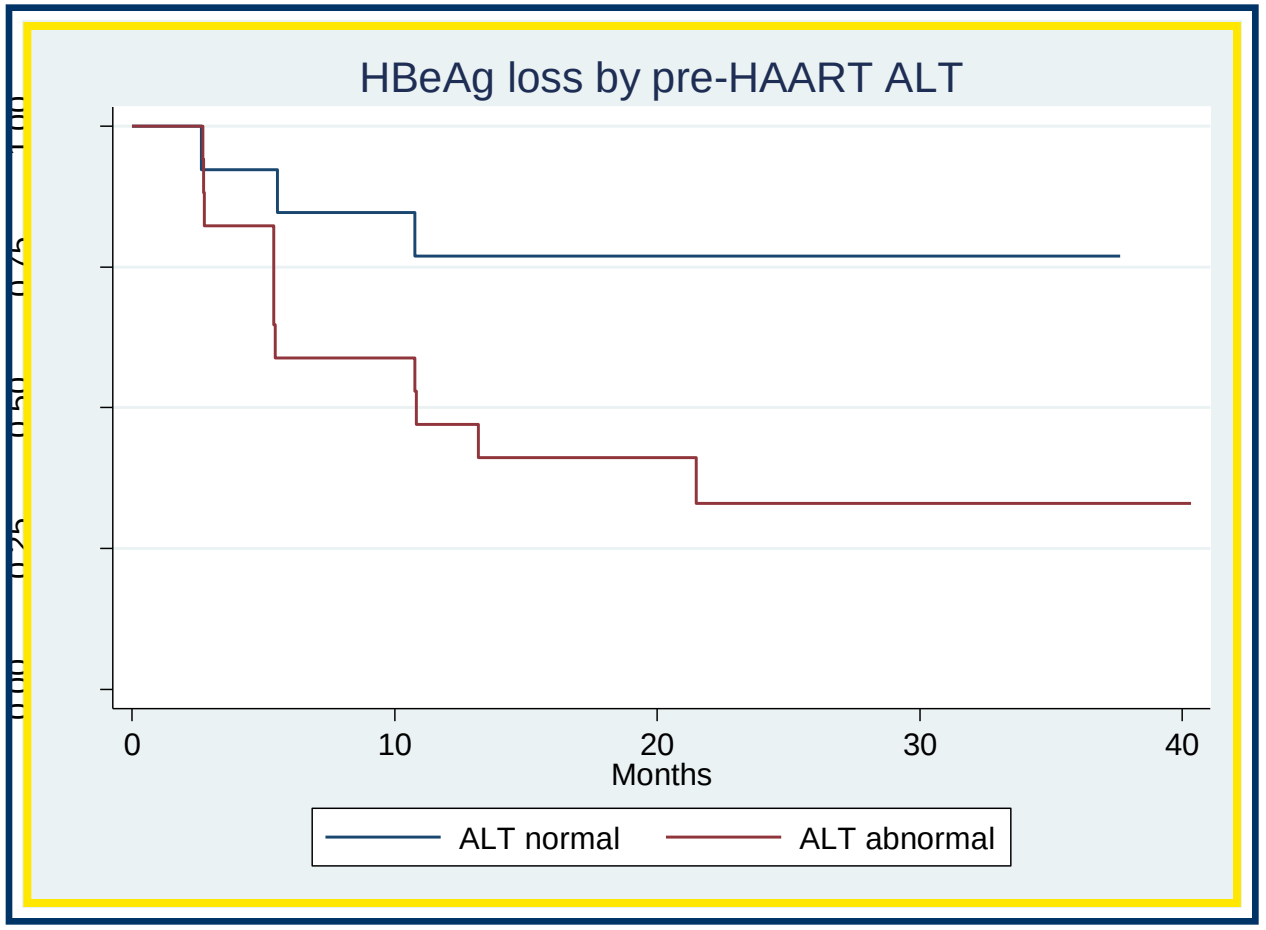
High rates of HBeAg seroconversion following HBV active HAART



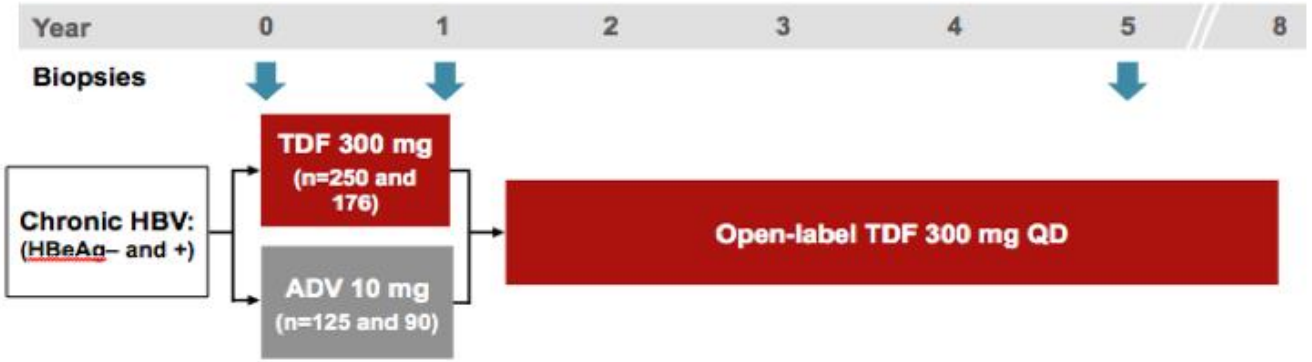
Longitudinal Thai cohort (n=47); HBeAg-positive (n=30); median follow up = 27 month
HBeAg loss = 46%; HBsAg loss = 13%

Avahingson et al., 5th IAS Conference, Capetown 2009, Poster # WEPEB226

TDF and HCC risk

Study Designs: 102 (HBeAg-) and 103 (HBeAg+)

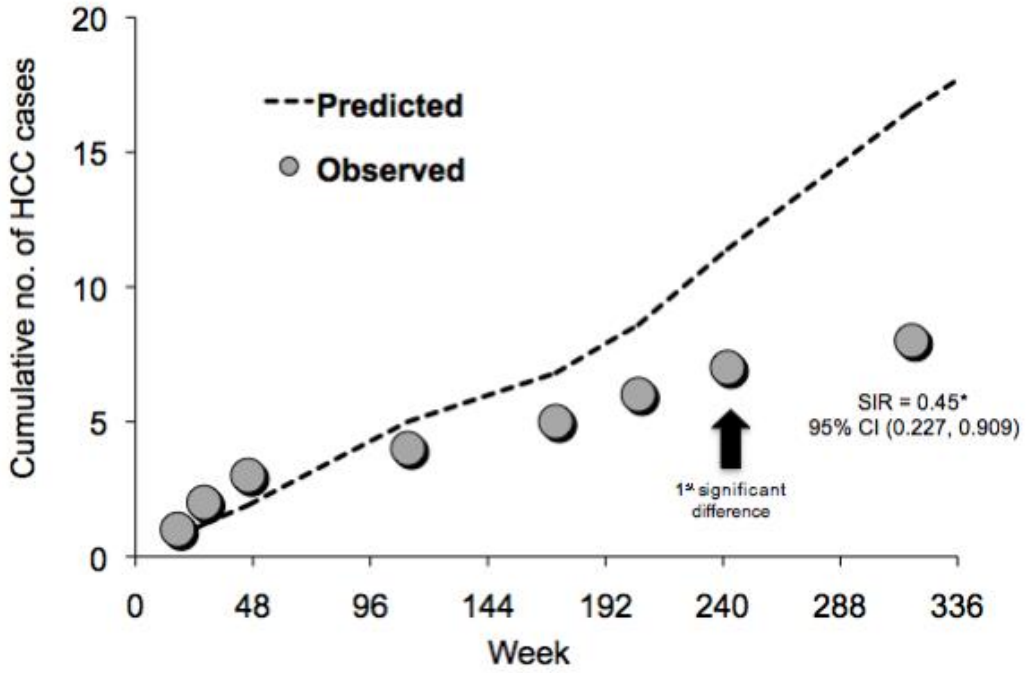
- Phase 3, randomized, double blind, placebo controlled
- All patients received open-label TDF after Year 1 for total study duration of 8 years*
- Primary endpoint: HBV DNA <400 copies/mL and histologic improvement (reduction of ≥2 points in Knodell score) at Week 48
- HCC recognized as an adverse event



*Emtricitabine could be added at the investigator's discretion for confirmed viremia on/after Week 72.
ADV, adefovir.

TDF and HCC risk

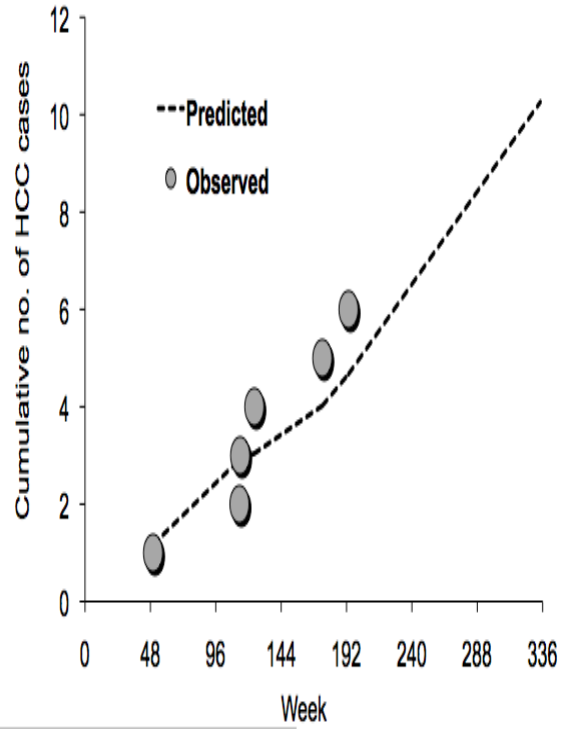
Observed vs Predicted HCC Cases: Noncirrhotics



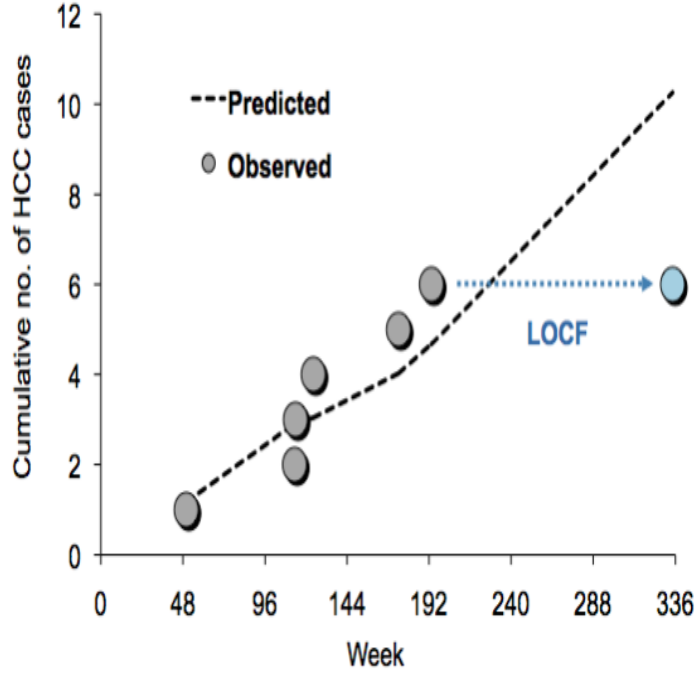
*Statistically significant at nominal α-level of 0.05.
CI, confidence interval; SIR, standardized incidence ratio.

TDF and HCC risk

Observed vs Predicted HCC Cases: Cirrhotics

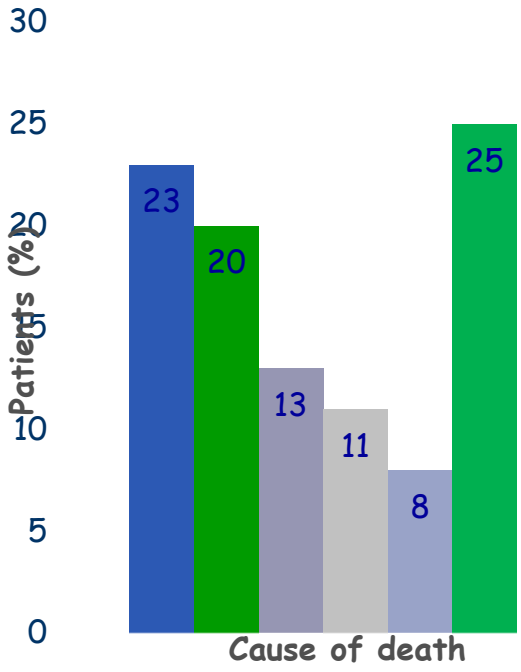


Observed vs Predicted HCC Cases: Cirrhotics

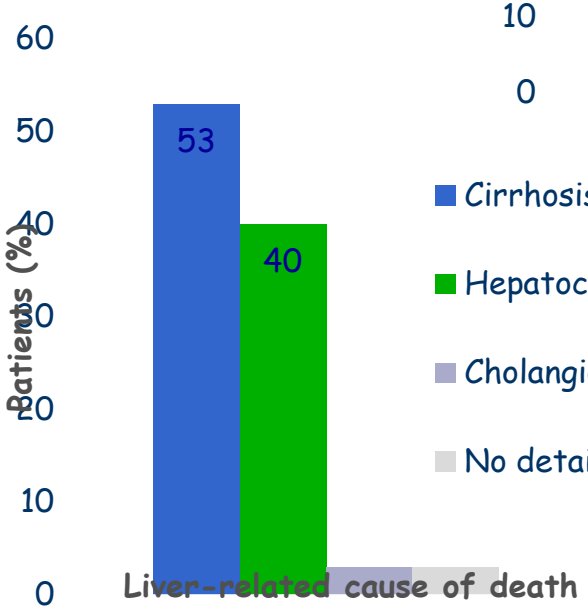


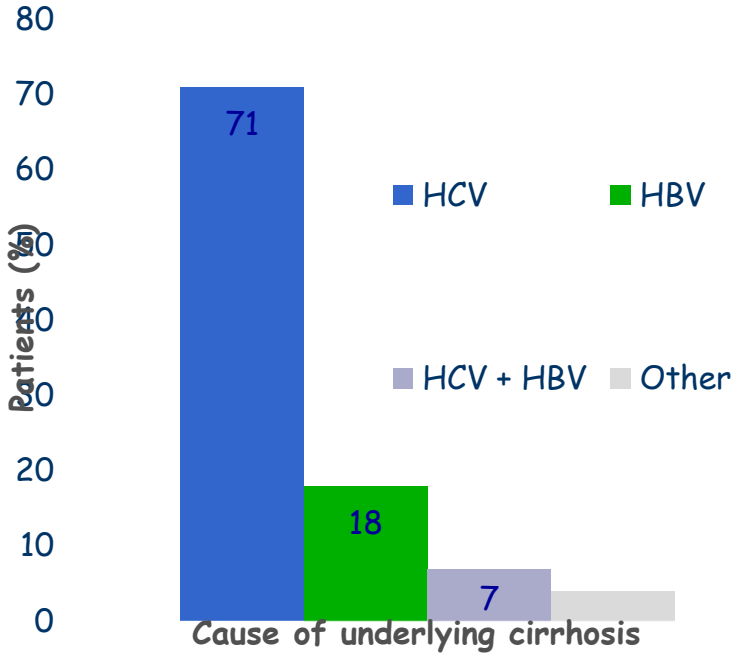
LOCF, last observation carried forward.

MORTAVIC: Causes of death in HIV-infected adults in France in 2010



Number of documented deaths=230





Non AIDS-defining and non hepatitis-related cancers

AIDS

Liver

Cardiovascular

Created from Rosenthal E, et al. EASL 2012. Barcelona Spain. Oral presentation 26.

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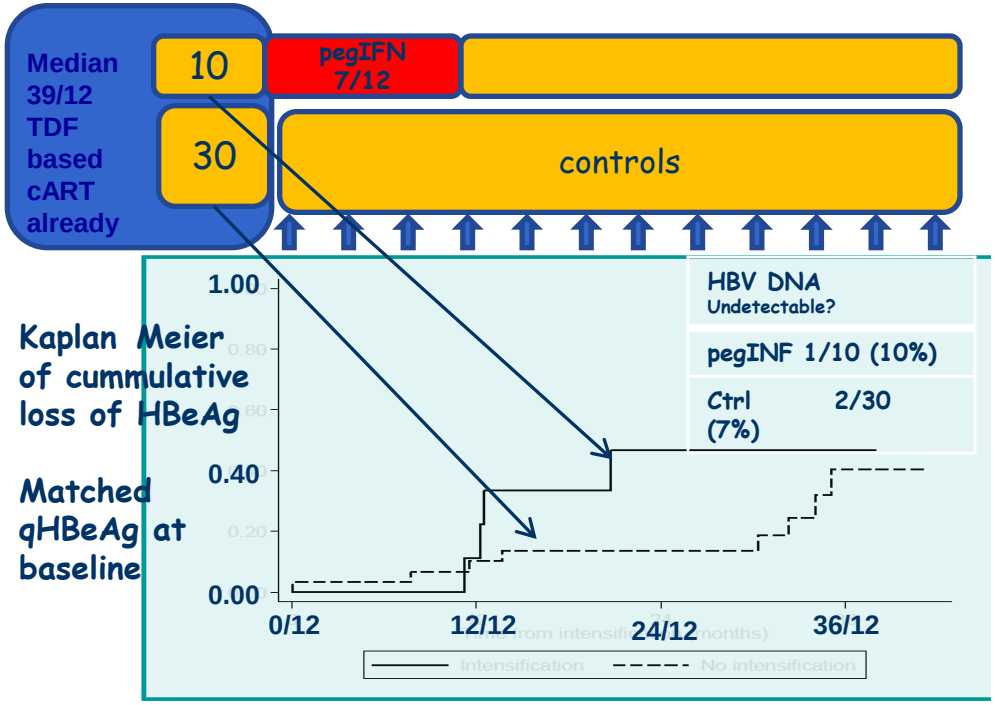
PegIFN and HIV/HBV

- Very little data in HIV/HBV co-infected patients
- Ingiliz P *et al.* (combination with adefovir)
  - No e-seroconversion after 48 weeks
  - HBV DNA levels not maintained post-Rx
- Predictors of response in mono-infected patients
  - Genotype A/B
  - High ALT (>3 × ULN)
  - Low HBV DNA (<2 × 10^6 IU/L)
- Risk of de-compensation/complications in cirrhotic CP-B/C patients

EASL Practice Guidelines. *J Hepatol* 2009;50:227–42; Ingiliz P, *et al. Antivir Ther* 2008;13:895–900.

Can pegIFN intensification help clear HBeAg in TDF treated HBV/HIV co-infection?

- CROI 2013: Anders Boyd et al.
- Case control from larger French HIV/HBV prospective cohort



- **Peg-IFN-INTS during TDF-treatment was associated with accelerated HBeAg-loss**
- **But no effect on qHBeAg/qHBsAg decline or long-term serological outcomes.**
- **Adding peg-IFN to a TDF-containing regimen may not be a beneficial option in co-infection**

- CROI 2013: Patrick Miailhes et al.
- The ANRS HB01 EMVIPEG Study
- N=51, no control group

	on pegIFN	24/52 post pegIFN
HBeAg loss	12/51 (24%)	8/51 (16%)
HBeAb seroconversion	6 (12%)	4 (8%)
HBsAg loss	2 (4%)	2 (4%)

- **addition of pegIFN did not allow to increase the rate of HBe seroconversion in HBeAg⁺ HIV co-infected patients**

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Hepatic flares post-starting TDF-based cART in co-infected patients

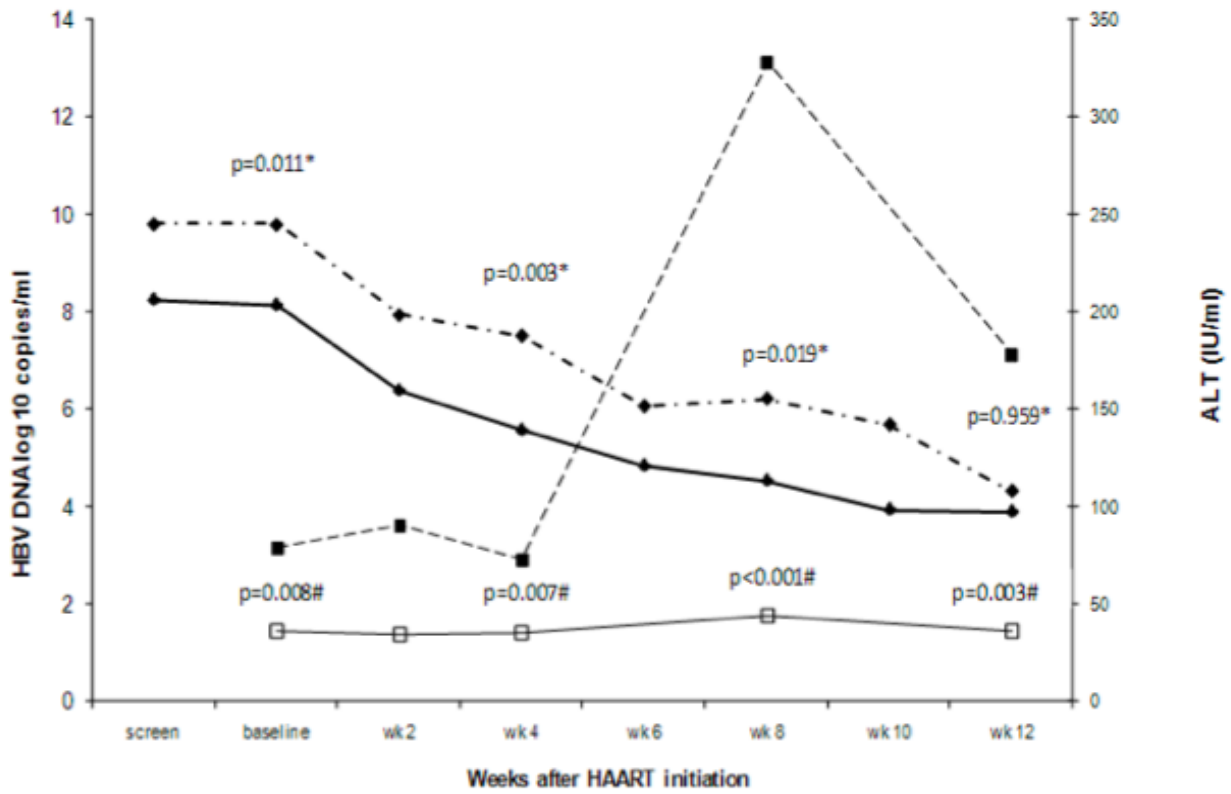

Figure 1 ALT and HBV DNA values in HF and non-HF subjects over 1st 12 weeks after HAART initiation. -axis: Weeks after HAART

Avihingasanon, et al AIDS Research Therapy

Co-relates of hepatic flares

Age yrs (median, IQR)	37 (33-42)	33 (28-40)	0.25
Male gender	88%	43%	0.12
HBeAg positive	50%	64%	0.47
Alcohol (> 3units/day)	25%	25%	1.00
Cirrhosis	20%	42%	0.36
HBV Genotype C	75%	82%	0.28
BMI kg/m^2 (median. IQR)	19 (18-20)	20 (18-22)	0.20
BL CD4 $cells/mm^3$ (median. IQR)	52 (18-131)	32 (19-214)	0.96
BL HIV RNA log_{10} c/ml (median. IQR)	4.9 (4.7-5.1)	4.7 (4.3-5.1)	0.22
BL ALT IU/L (median. IQR)	79 (59-96)	36 (22-59)	0.008*
BL HBV DNA log_{10} c/ml (median. IQR)	9.9 (8.4-10.4)	8.4 (7.8-9.0)	0.009*
Randomised HBV therapy	3TC n = 5 TDF n = 2 3TC/TDF n = 1	3TC n = 8 TDF n = 10 3TC/TDF n = 10	0.193

Avihingsanon, et al AIDS Research Therapy 2012

Hepatic flares in HBV/HIV

- Usually in the first 12 weeks post-cART
- Associated with high HBV DNA levels and high baseline ALTs
- Restoration of innate and adaptive anti-HBV response in the presence of high HBV DNA
- De-compensation rare BUT caution with cirrhosis

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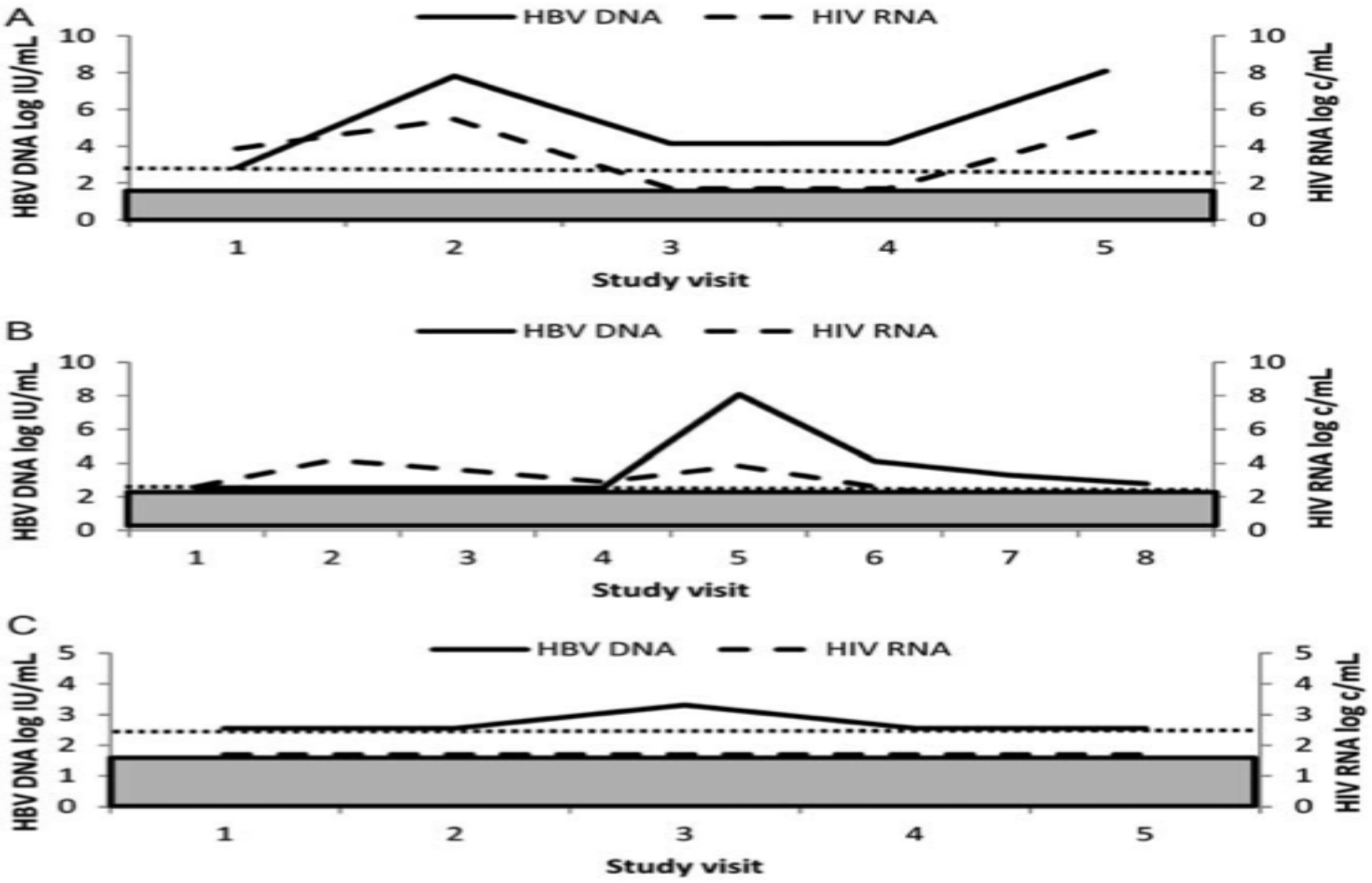
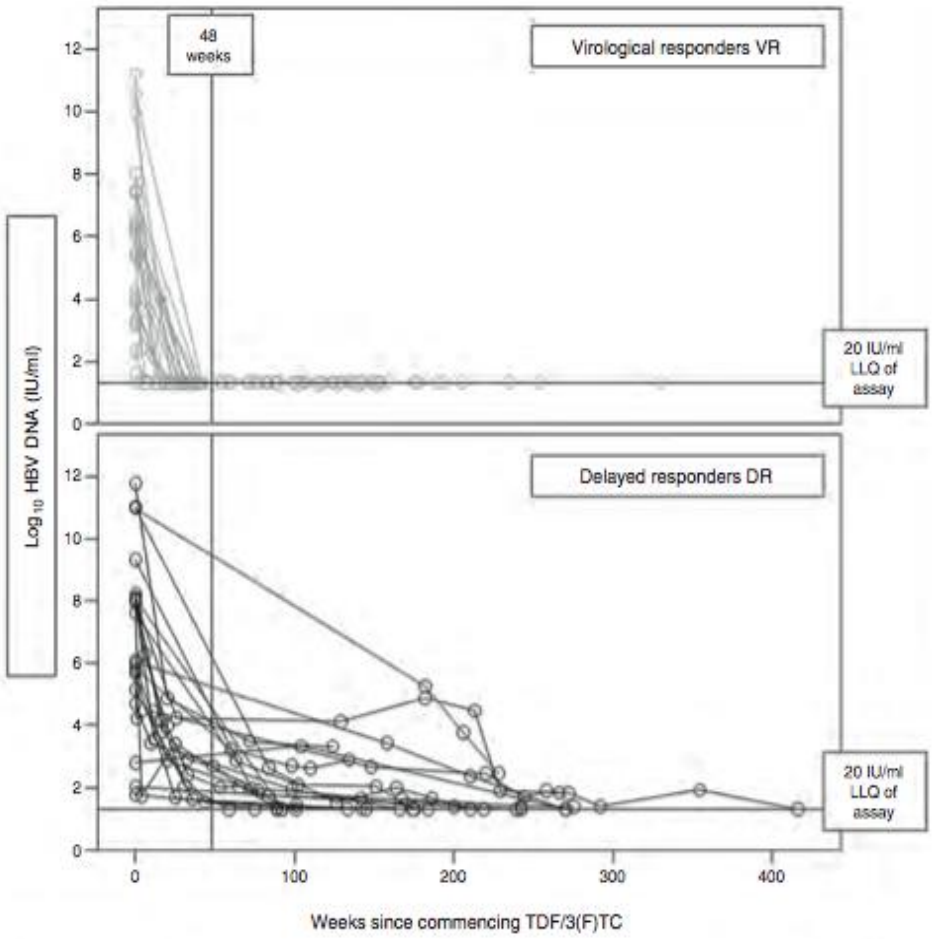
Patterns of persistent viraemia



Delayed response with TDF



- How long is 'delayed'?
- In this small study almost all 'delayed' responders suppressed by a median of 49 months.
- No TDF associated mutations
- X1 new lam-associated polymormphism

Childs, et al AIDS 2013

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Renal impairment with TDF - watch this space….

- 240 patients with a 3year-time follow-up, normal eGFR at baseline1
- >400 HIV+ patients receiving TDF

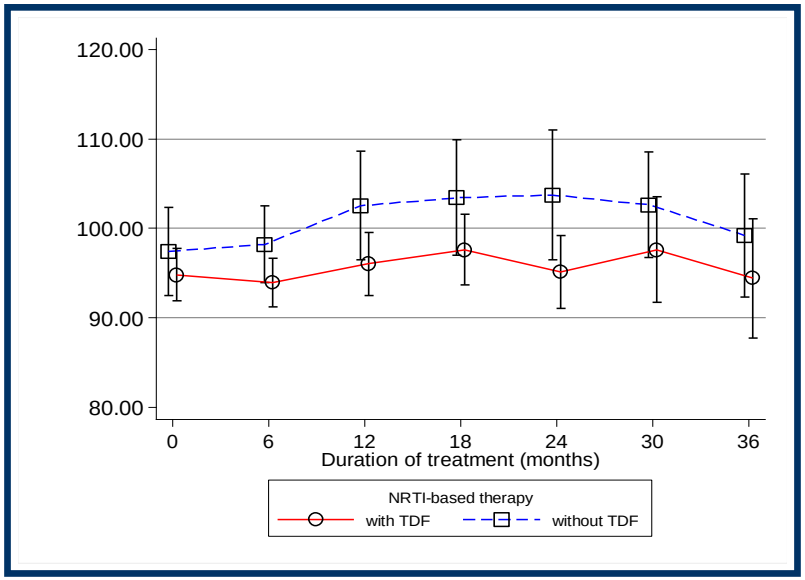
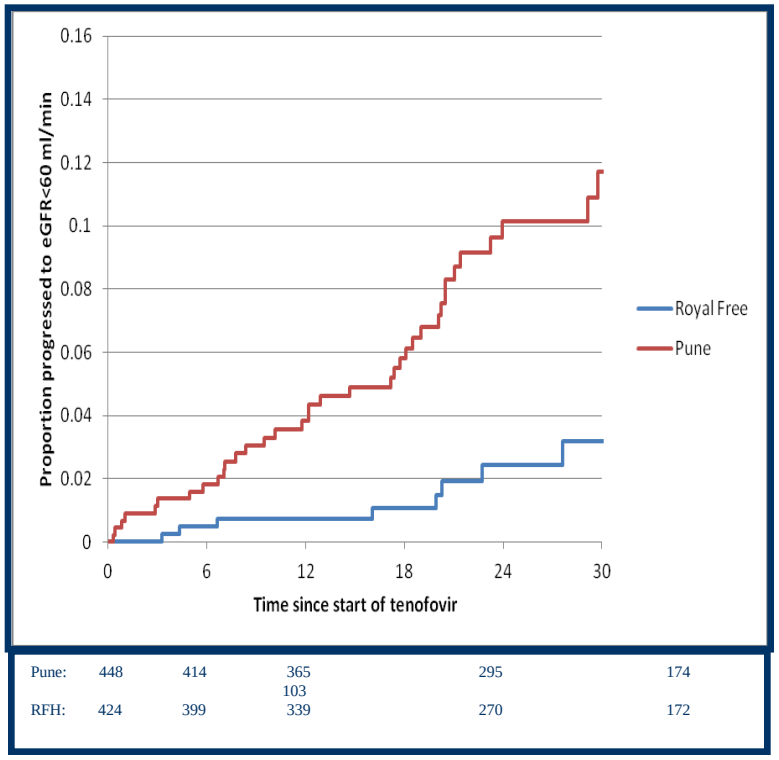
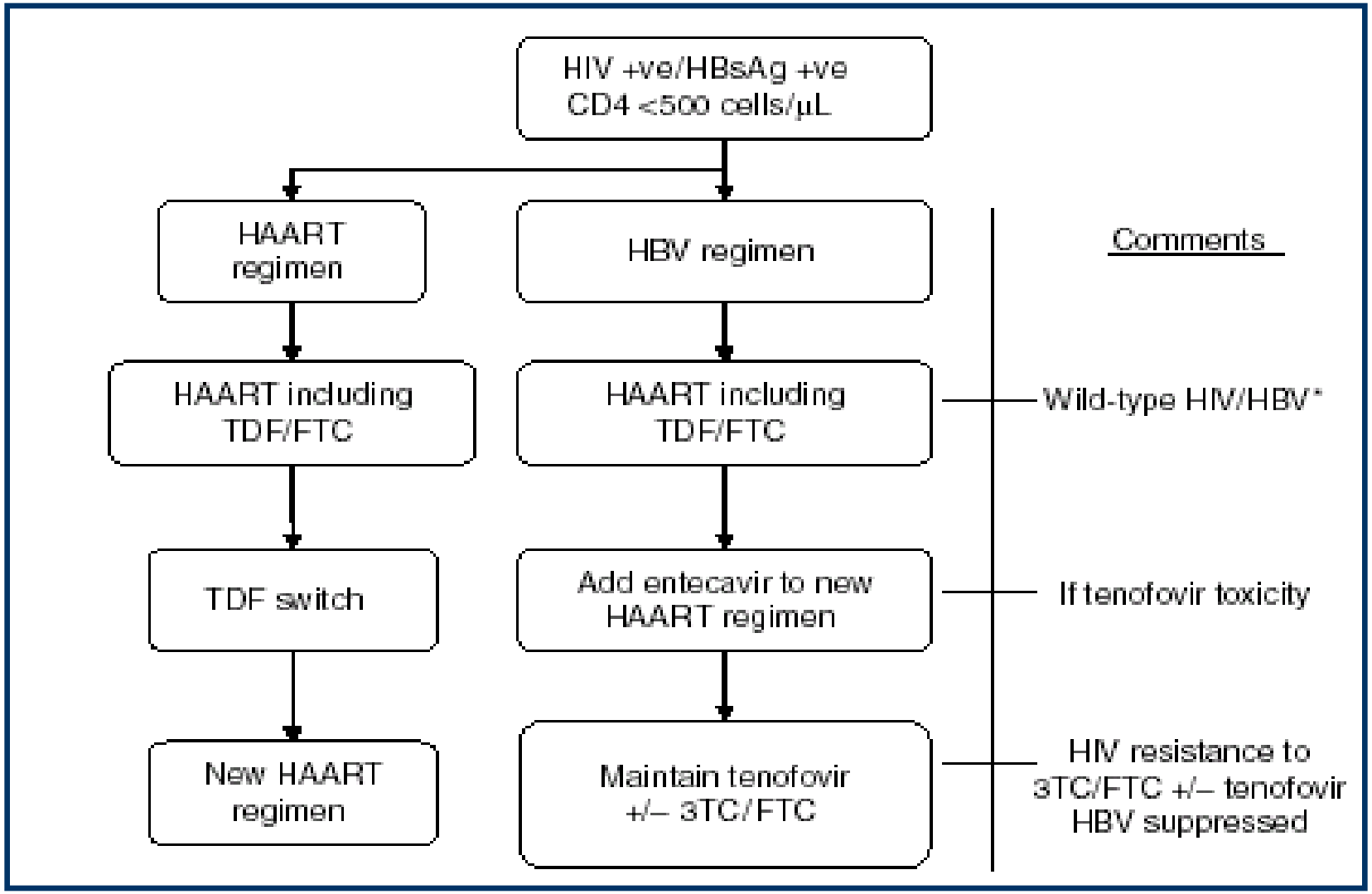


Figure 1: MDRD clearance over time



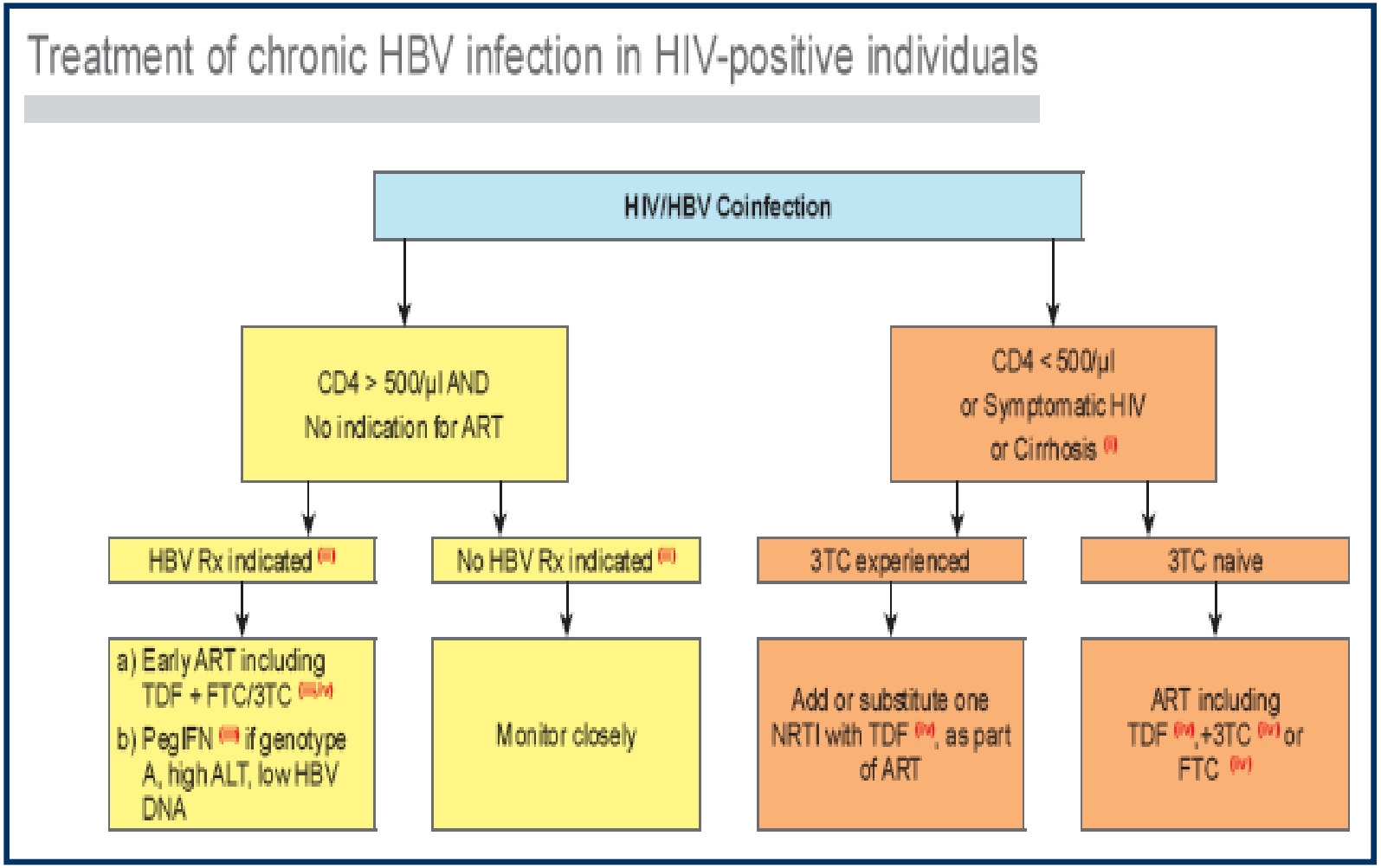
Pujari, et al, CROI 2013

What about tenofovir toxicity or HIV resistance to tenofovir or 3TC/FTC?



BHIVA Guidelines 2010; HIV Medicine 2010

Management options for HIV/HBV co-infection



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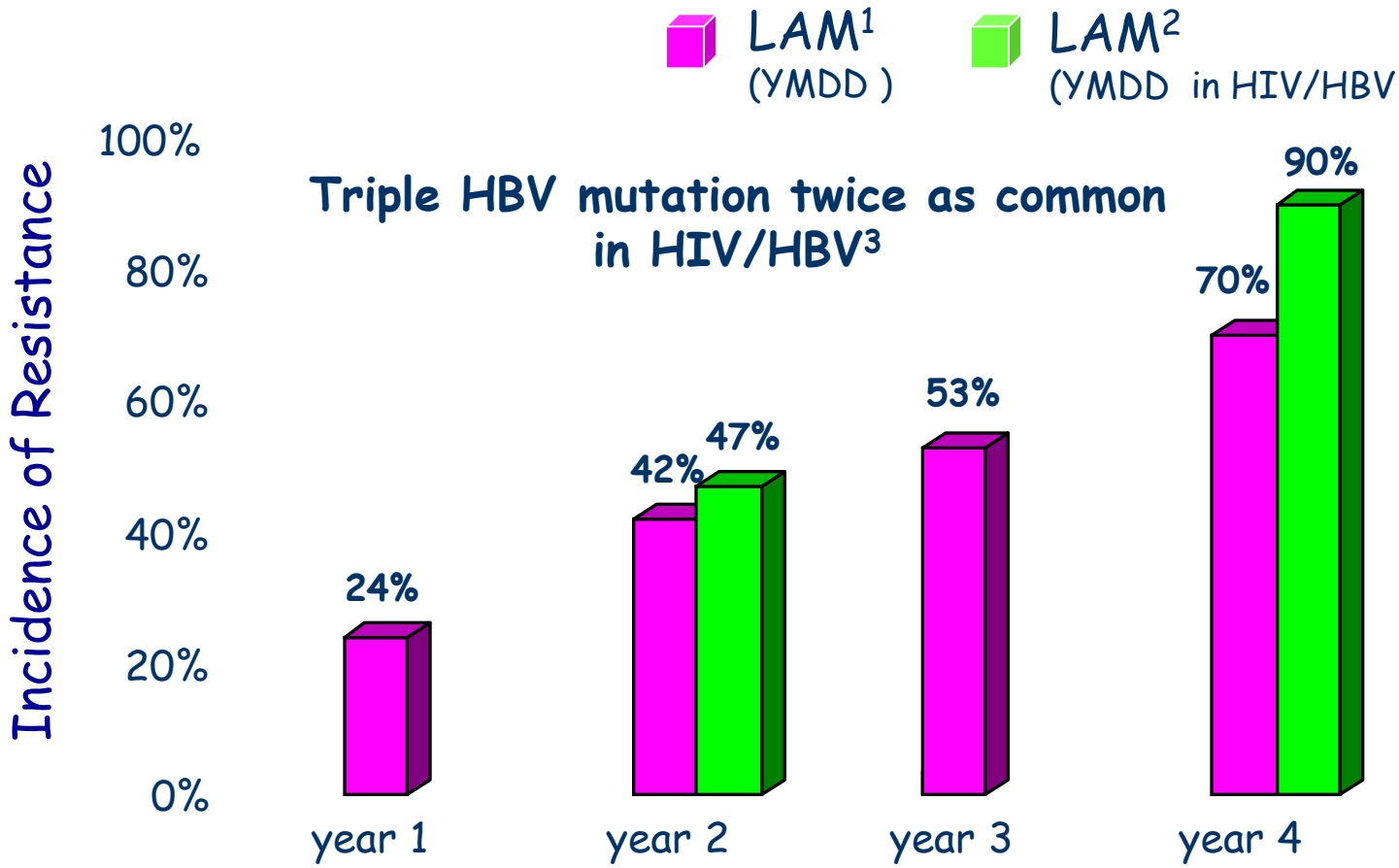
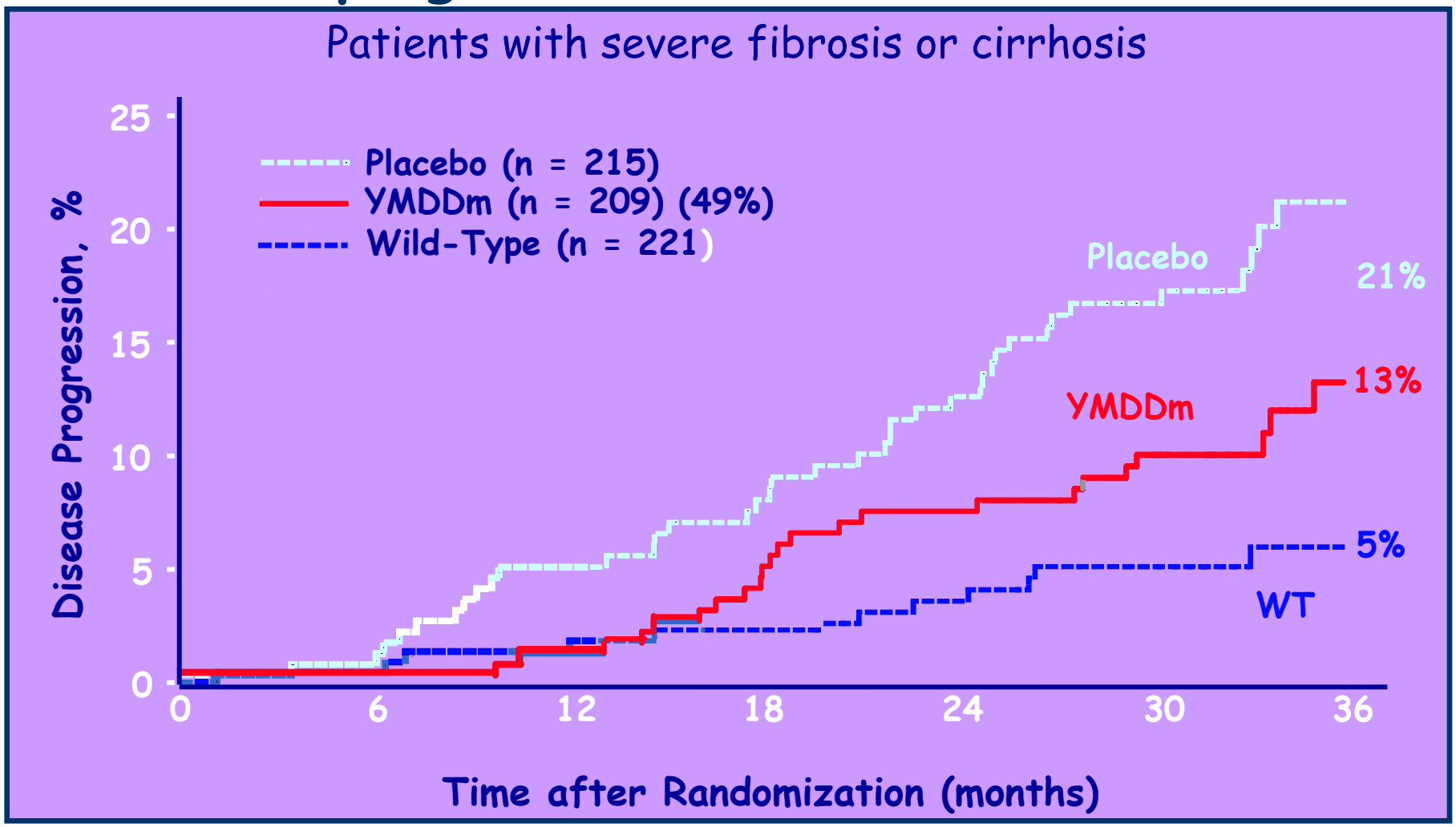
Incidence of HBV Resistance in Patients Treated with LAM in HBV infection vs. HIV/HBV co-infection



Lai C.L., et al., Clinical Infectious Diseases (2003) 36:687

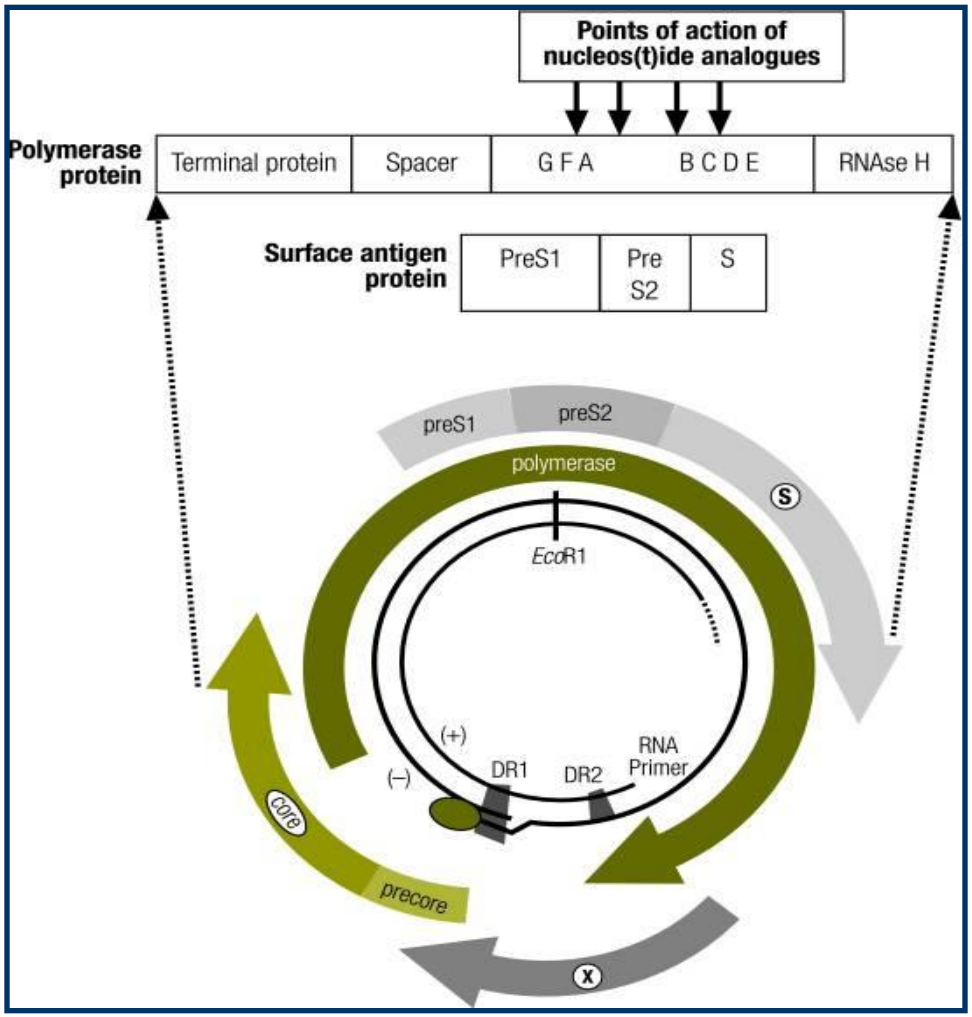
2. Benhamou Y et al. Hepatology 1999; 30:1302-6

Impact of lamivudine resistance on progression of liver disease



Liaw, N Engl J Med. 2004

More than just 'drug resistance'

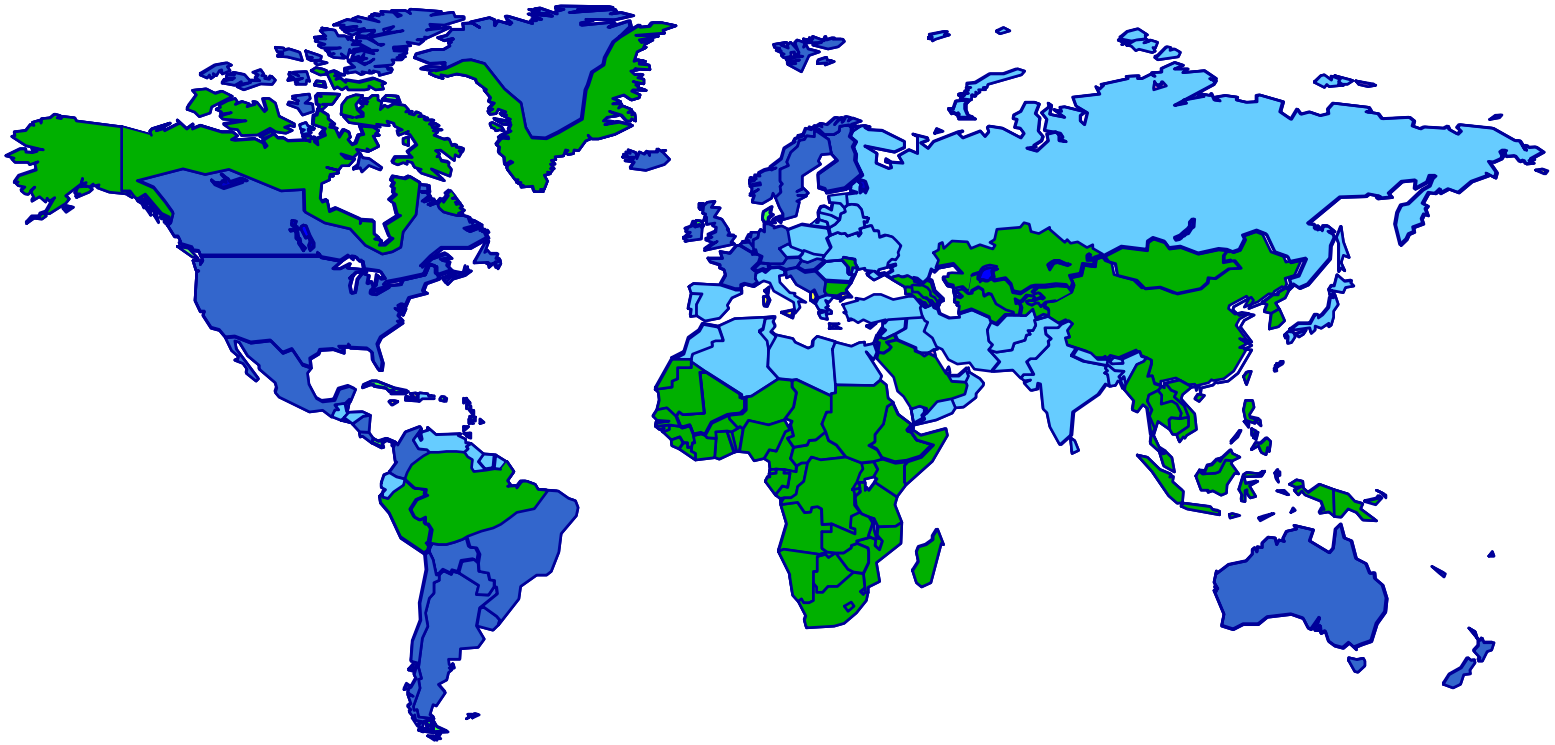


- Overlapping Pol and S
- Mutations in Pol – changes in S
- ADASMs – Antiviral Drug-Associated S mutations
- ADAPVEMS – Antiviral Drug Associated Potentially Vaccine (and detection) Escape Mutations
- Associated with L-nucleosides and Entacavir, possibly with adefovir

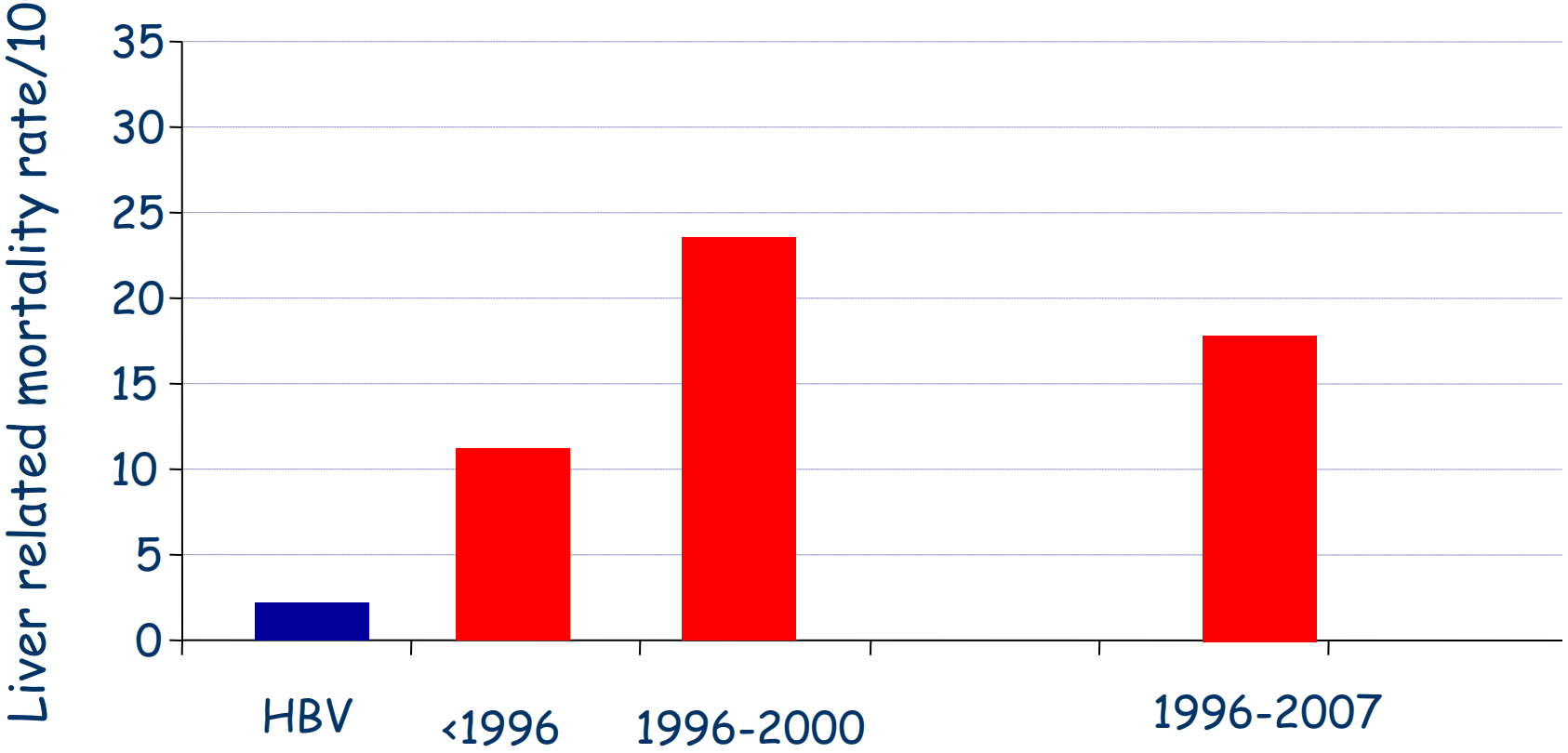
Envelope/Polymerase Mutations and the Antigen/Antibody Binding Capacity in Genotype A and D HBV/HIV Co-infected Subjects (n=9) with LAM Resistance

Envelope changes	Polymerase changes	Ag–Ab binding [IC_{50} (µg/ml)]
Wild type	Wild type	1.09
HBIG escape		
sG145R	rtW153G	>55.0
Anti-viral drug resistant		
sE164D	rtV173L	14.86
sW196S	rtM204I	8.29
sI195M	rtM204V	5.26
sM198I	rtV207I	12.5
sE164D/I195M	**rtV173/rtL180/rtM204V**	54.53

ARV Rollout
AZT/d4T+LAM+NNRTI
?Global Impact



HIV/HBV co-infection:
mortality in the resource rich setting



Thio et al *Lancet* 2002

Hoffman et al., *AIDS* 2009

Protective Effect of HBV-active cART Against Primary HBV infection

universitätsklinikumbonn

- **Question:** Does HBV-active cART protect against new HBVinfection (HBV-PrEP)?
- **Patient selection:** all HBV-susceptible patients at entry, anti-HBc and anti-HBs negative (<10IU/L) and 2nd sample available in time for follow-up HBV serology
- All patients n=2,924, MSM n=2,280, HBV susceptible + 2 samples available n=349

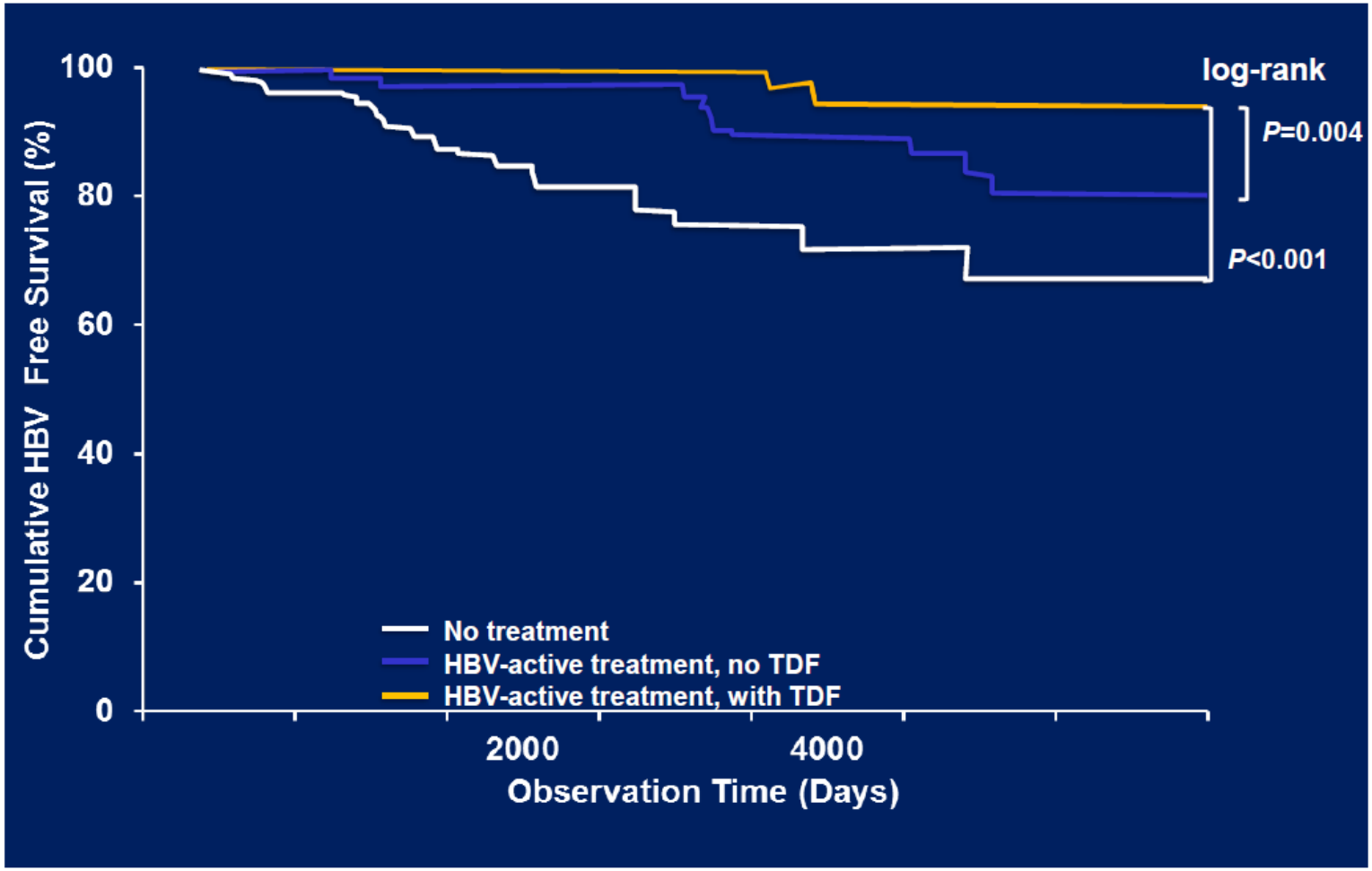
New HBV Cases (N=35)

- 1 case: woman (HBsAg negative)
- 1 case: heterosexual man (HBsAg negative)
- 33 cases MSM

Hepatitis (ALT 2x)	7 (20,0%)
HBsAg +	6 (17,1%)
HBeAg +	6 (17,1%)

Brinkman K, et al. 20th CROI; Atlanta, GA; March 3-6, 2013. Abst. 33.

Kaplan Meier: HBV-free survival (MSM)



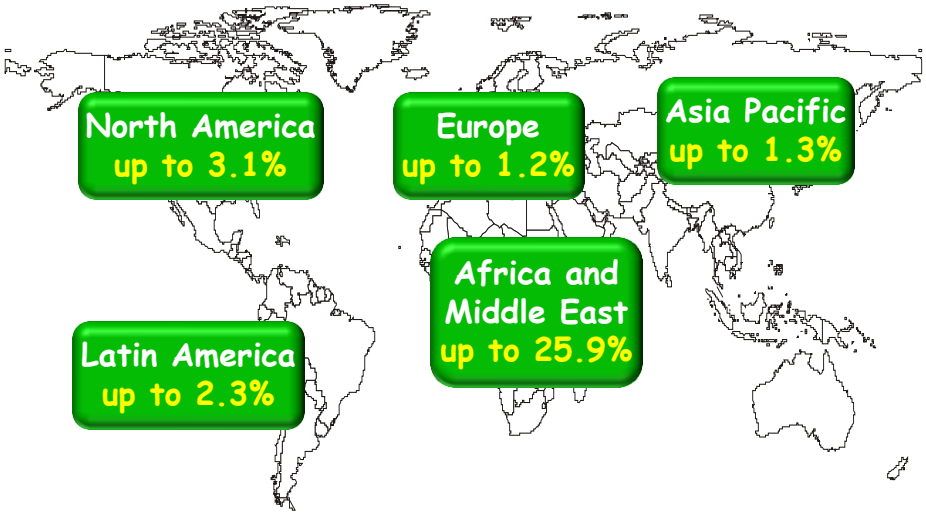
Numbers in observation				
No treatment	107	50	19	8
Treatment, no TDF	86	67	36	16
Treatment, with TDF	189	49	38	12

HIV/HCV co-infection

Pertinent management issues
2013

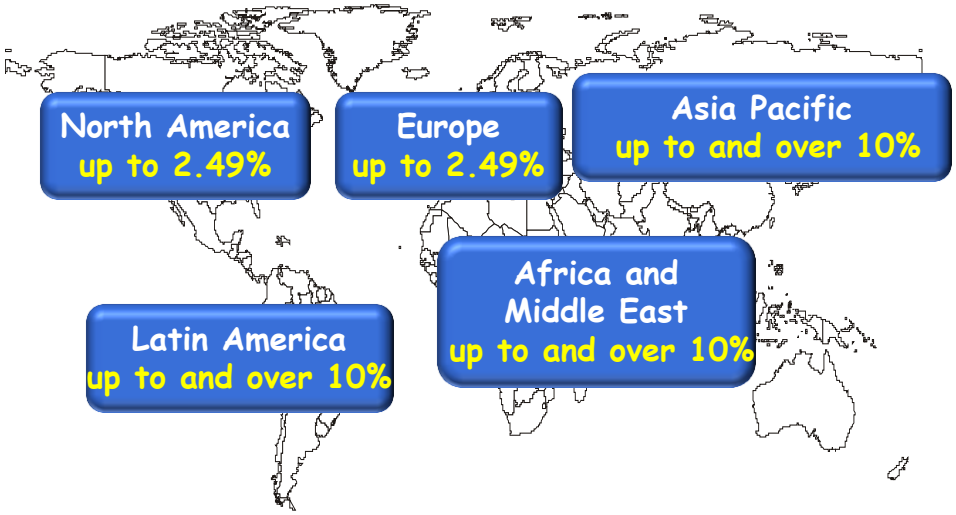
WHO: Global HIV and HCV infection

Global HIV infection[1] (% adult prevalence)



Estimated total HIV infections worldwide: 33.3 million

Global chronic HCV infection[2] (% adult prevalence)



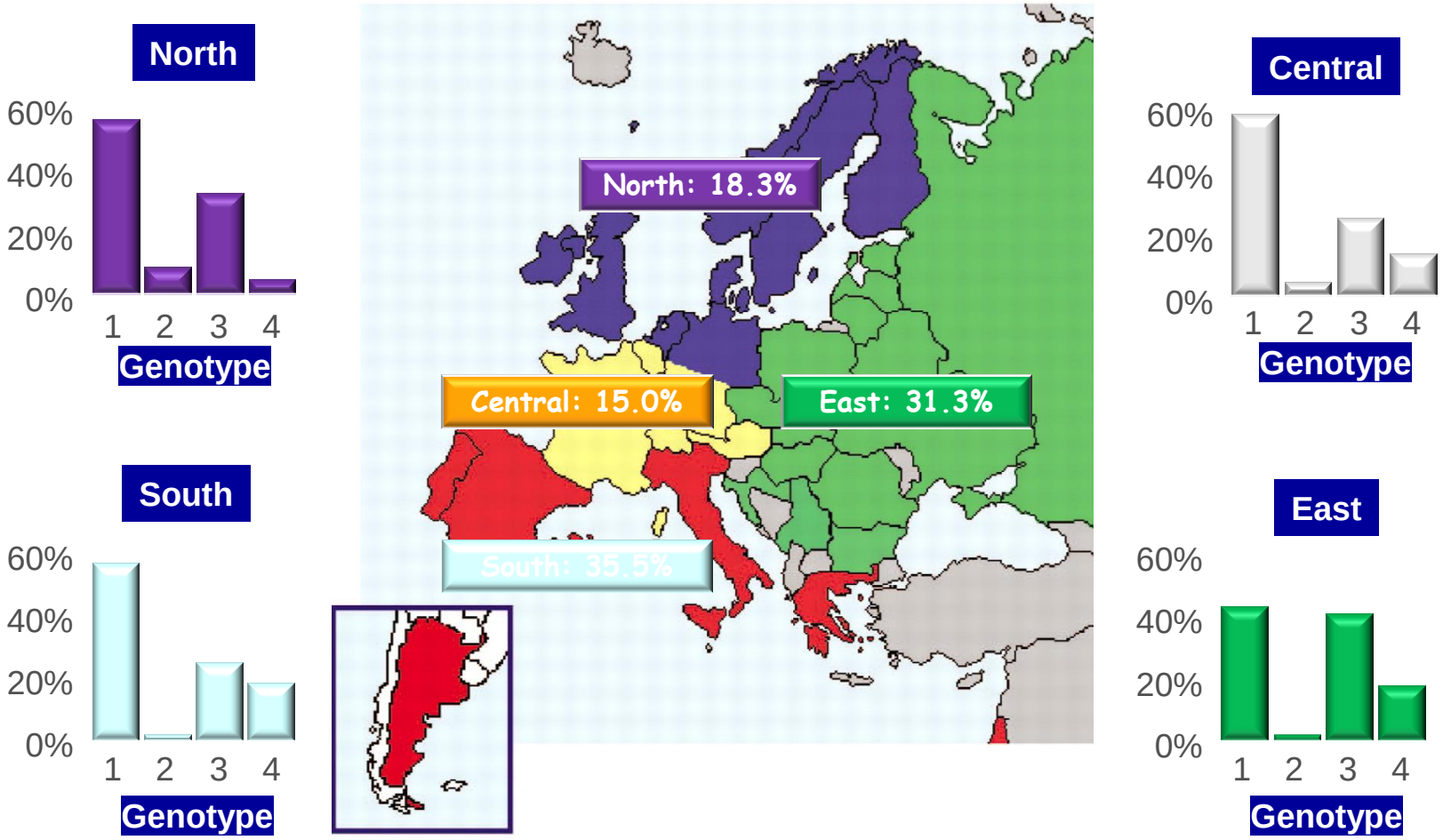
Estimated total chronic HCV infections worldwide: 170 million

- HCV genotypes 1–3 have a worldwide distribution
- Genotypes 1a and 1b are most common and account for 60% of global infections

WHO=World Health Organisation

1. Adapted from UNAIDS Global View of HIV infection 2010. Available at http://www.unaids.org/documents/20101123_2010_HIV_Prevalence_Map_em.pdf. Accessed September 2012; 2. Adapted from WHO Hepatitis C Guide 2002. Available at http://www.who.int/csr/disease/hepatitis/whocdscsrlyo2003/en/index.html. Accessed September 2012

EuroSIDA: Prevalence of HIV/HCV co-infection and distribution of HCV genotypes



Map shows prevalence of HIV/HCV coinfection by region in N=5,957 HIV-infected patients with an HCV antibody test available[1]
Bar charts shows prevalence of HCV genotype in n=1,940 HIV/HCV-coinfected patients by region[2]

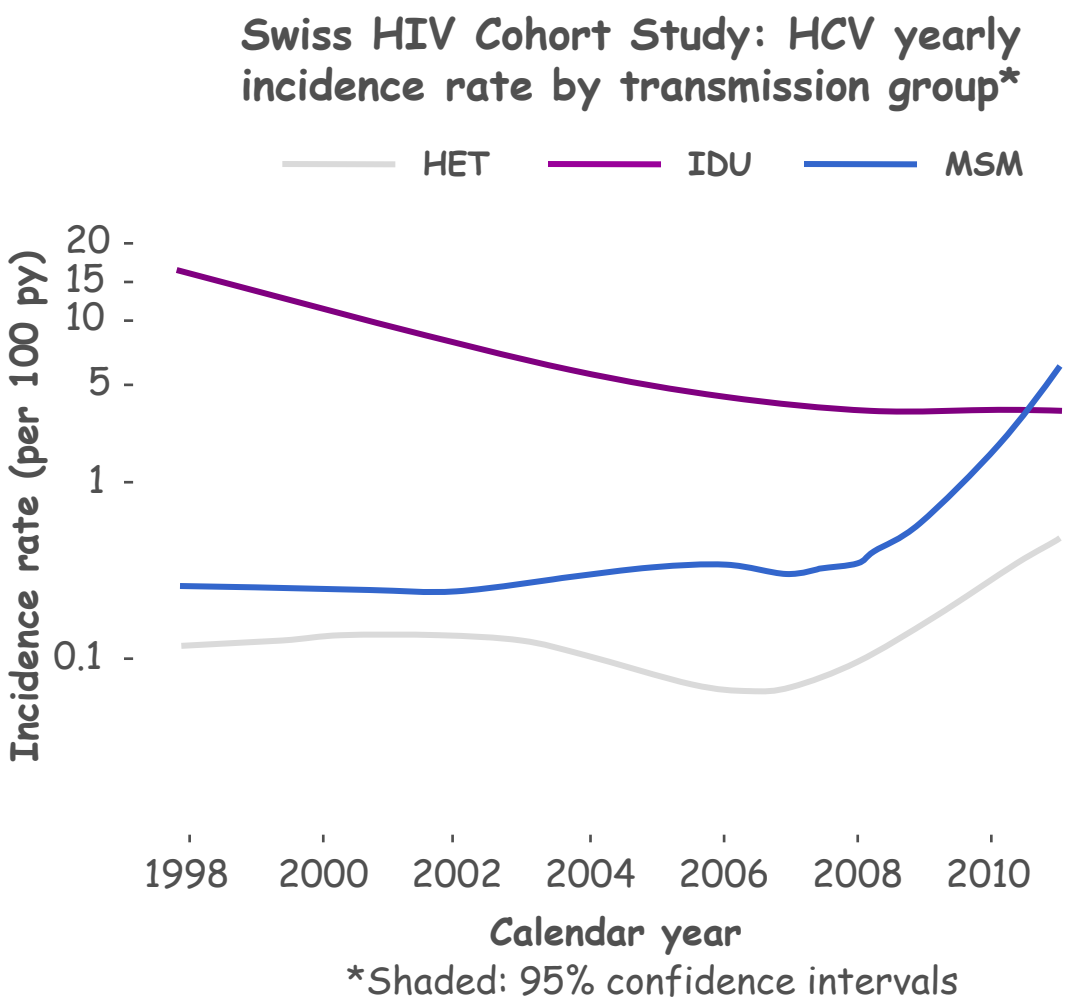
Created from: 1. Rockstroh J, et al. J Infect Dis. 2005;192:992–1002; 2. Soriano V, et al. J Infect Dis. 2008;198:1337–44.

Swiss HIV Cohort Study: Changing patterns of HCV incidence

- HCV incidence in MSM:
  - Reached 4.1 cases per 100 PY in 2011 (18-fold increase since 1998)
- HCV incidence in IDU:
  - Decreased from 13.9 to 2.2 cases per 100 PY
- HCV incidence in heterosexuals
  - Remained <1 per 100 PY throughout the study period

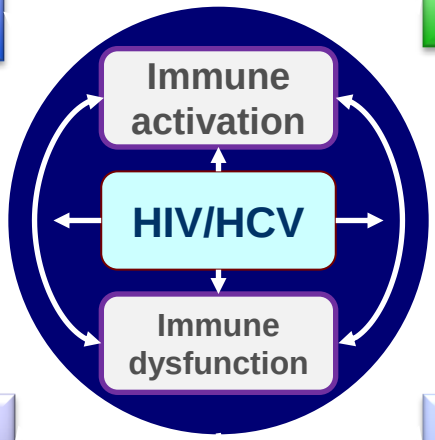
Predictors of HCV seroconversion in MSM[1,2]:

- History of UAI, multiple partners, use of sex-toys and fisting
- STIs, especially syphilis and LGV



1. Adapted from Wandeler G, et al. CROI 2012. Seattle USA. Poster Q106; 2. Van de Laar T, et al. JID 2007;196:230–8.

HIV/HCV coinfection may result in multi-systemic disorders



- Global cognitive impairment
- Cognitive-motor impairment
- Dementia
- Peripheral neuropathy

Neurologic disease

- Cerebrovascular disease
- Acute myocardial infarction

Cardio-vascular

Metabolic disorders

- Diabetes mellitus
- Insulin resistance

- Opportunistic infections
- Wasting syndrome

HIV disease progression

Liver disease

- Steatosis
- Fibrosis
- Cirrhosis
- End-stage liver disease
- Liver-related death

- Proteinuria
- Acute renal failure
- Chronic kidney disease

Kidney disease

GI tract

- Microbial translocation

- Osteonecrosis
- Osteoporosis
- Bone fracture

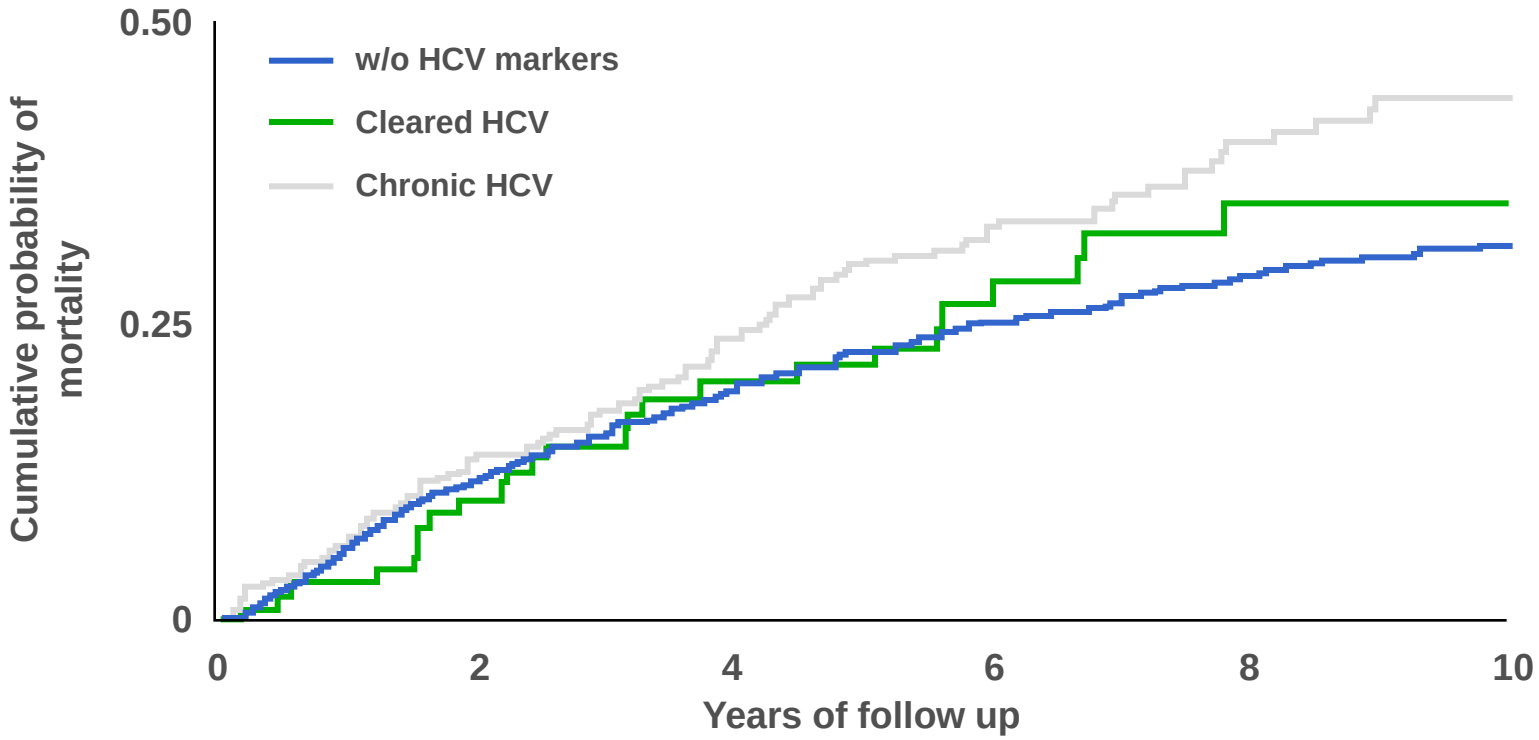
Bone disorders

- CD4 apoptosis
- Abnormal T-cell responses and cytokine production
- Cytotoxic T-cell accumulation in liver
- Impaired CD4 recovery post-HAART
- Severe immunodeficiency

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

Impact of chronic HCV in patients with AIDS in the cART era

- Chronic HCV infection is independently associated with a 50% increase in mortality among patients with an AIDS diagnosis

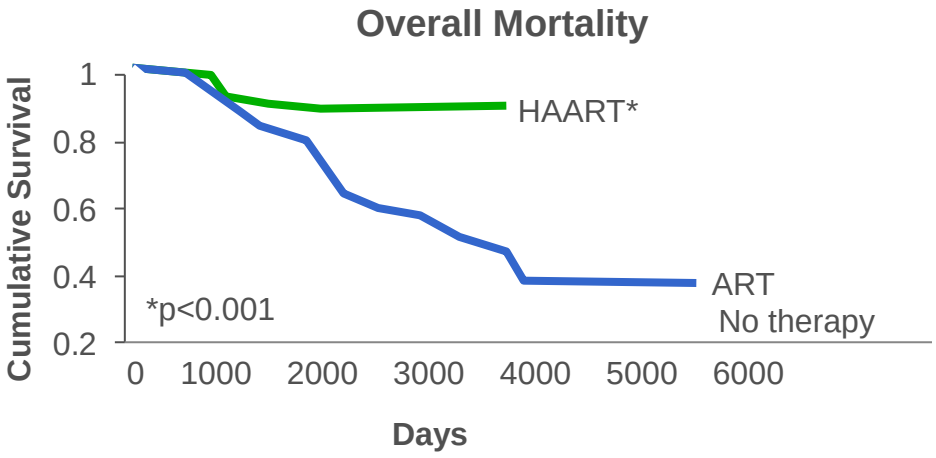


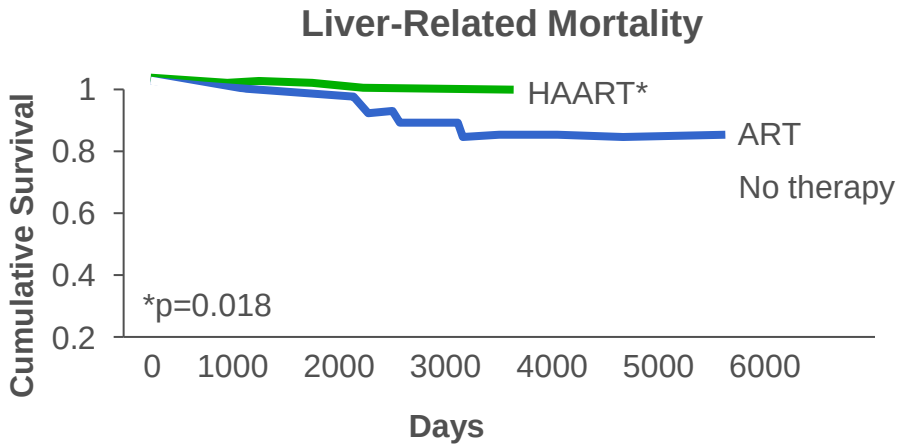
Number at risk						
w/o HCV markers		1316	1079	848	560	192
Cleared	91	77	56	38	23	9
Chronic	337	267	215	138	73	20

Adapted from Branch A, et al. Clin Infect Dis 2012;55:137–44.

HAART reduces mortality in HIV/HCV-co-infected patients

- Bonn cohort (1990–2002)
  - 285 HIV/HCV-coinfected patients
- Liver-related mortality rates per 100 PY:
  - HAART: 0.45
  - ART: 0.69
  - No therapy: 1.70
- Predictors of liver-related mortality:
  - No HAART
  - Low CD4 cell count
  - Increasing age

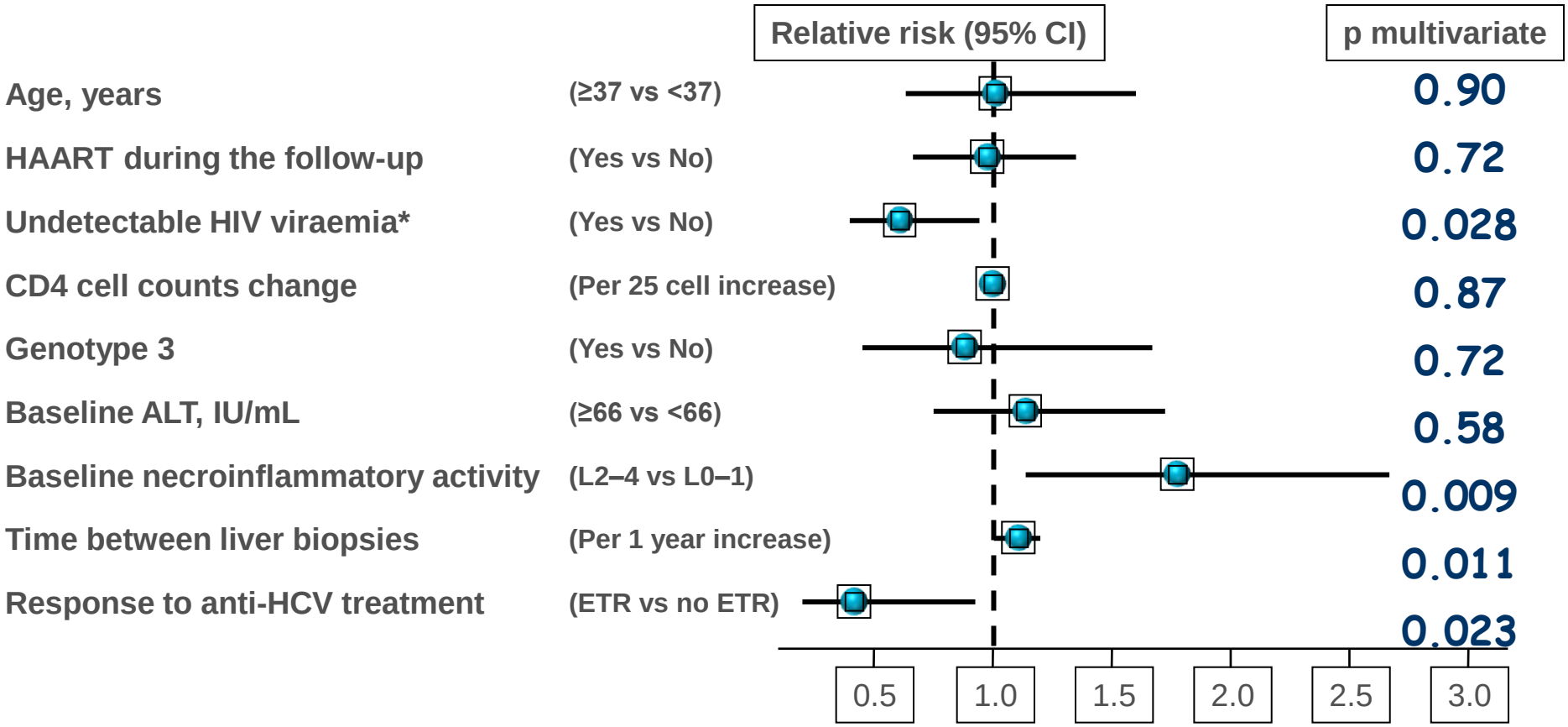




Adapted from Qurishi N, et al. Lancet. 2003:362:1708–13.

Effective treatment of HIV infection reduces fibrosis risk in HIV/HCV-coinfected patients

Predictive factors of fibrosis progression (≥1 stage) (multivariate analysis)

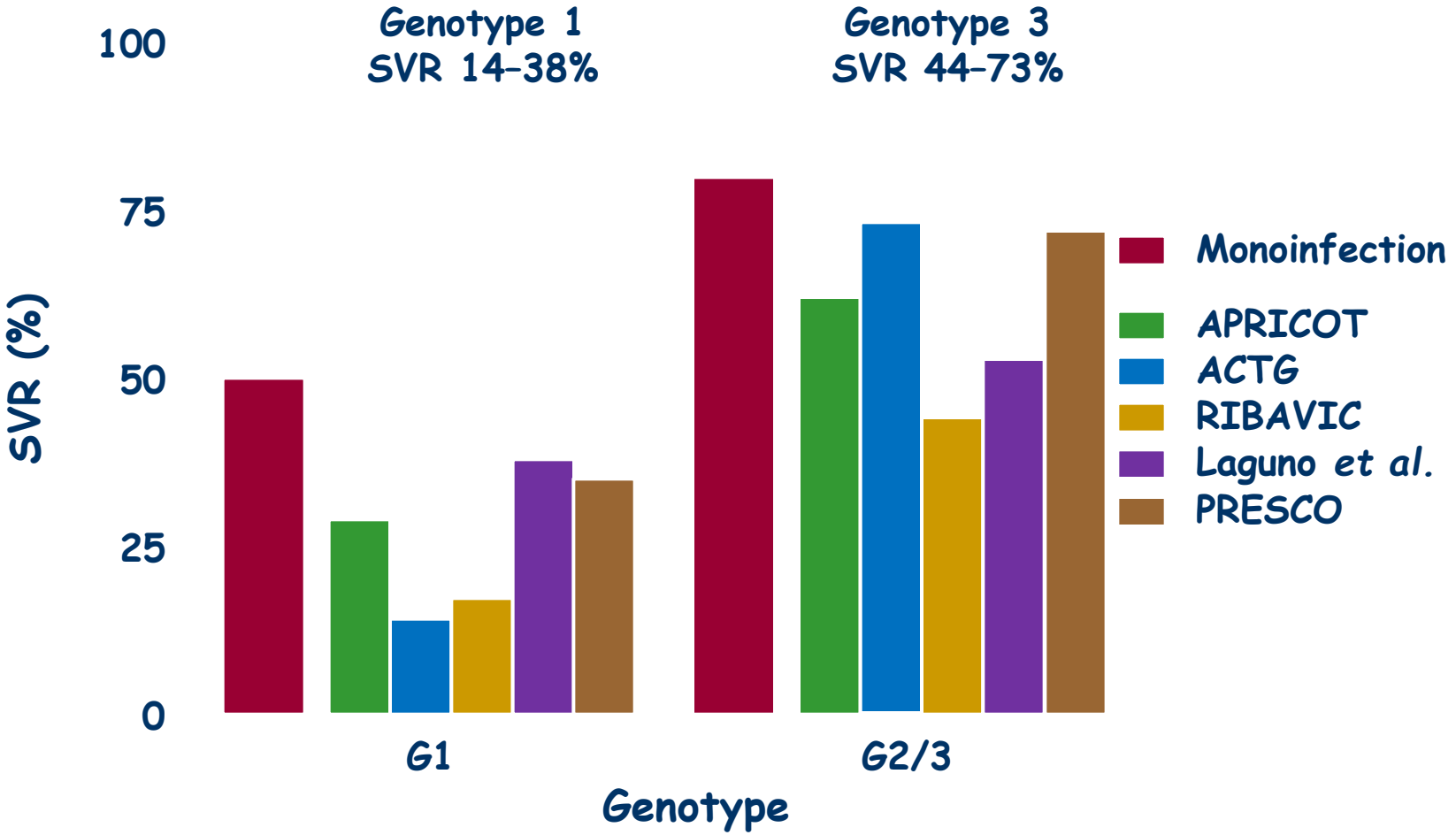


Data collected from 135 coinfected patients with 2 liver biopsies >1 year apart.
Specimens were centrally read and scored blindly by 2 independent pathologists using the Scheuer classification.

RR (95% CI)=relative risk (95% confidence interval); ETR=end-of-treatment response;
HAART=highly active antiretroviral therapy; *Undetectable HIV RNA in ≥70% determinations during the follow up.

Created from Macias J, et al. Hepatology 2009;50:1056-63.

HCV/HIV treatment outcomes with pegIFN and Ribavirin



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

SVR rates according to the number of protective factors

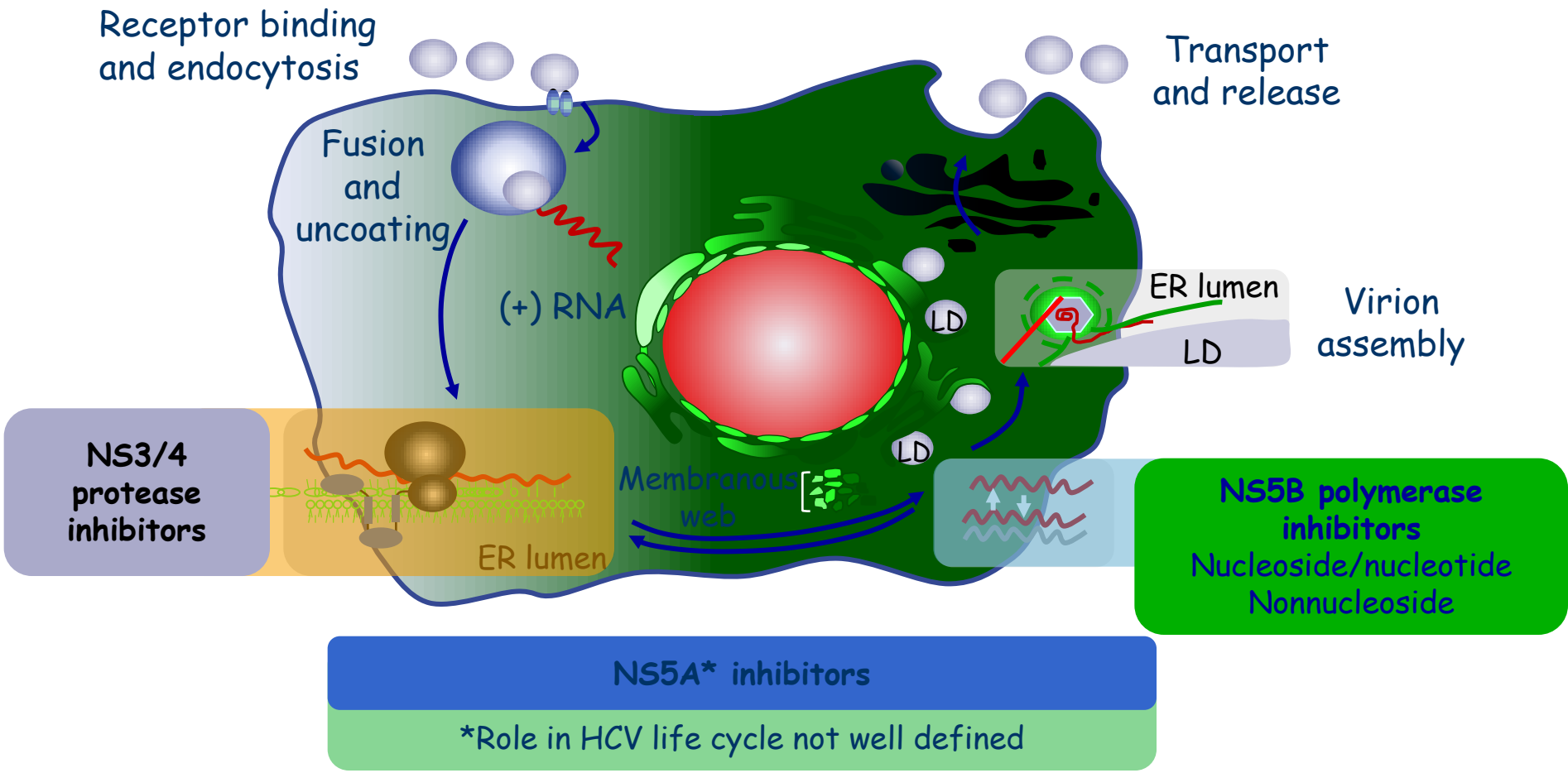
- Low serum HCV-RNA
- HCV genotype 3
- Lack of advanced liver fibrosis (Metavir F0-F2)
- rs12979860 CC genotype

	No. of protective factors					
	0	1	2	3	4	p
Total population (n=164)	12%	23%	75%	88%	100%	<0.0001
HCV-1 and -4 genotype patients (n=113)	12%	22%	68%	100%	NA	<0.0001
HCV-3 genotype patients (n=51)	50%	84%	82%	100%	NA	0.372

NA, Not applicable

Rallón et al, CROI 2010, J Hepatology 2012

HCV Life Cycle and DAA Targets – essential knowledge



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

More essential knowledge…

Characteristic	DAA				
	PI, 1st Generation	PI, 2nd Generation	NS5A Inhibitors	NS5B Nucleot/side Inhibitors	NS5B Non Nucleoside Inhibitors
Efficacy	🟡	🟢	🟢	🟢	🟡
Resistance Profile	🔴	🟡	🟡	🟢	🔴
Pangenotypic Efficacy	🔴	🟡	🟡	🟢	🔴
Adverse Events	🔴	🟢	🟢	🟢	🟡
Drug–Drug Interactions	🔴	🟢	🟡	🟡	🟡

🟢 Good profile 🟡 Average profile 🔴 Least favorable profile

Adapted from: Farnik H, et al. Antivir Ther. 2012;17:771-783.

Investigational HCV Regimens in Phase III Clinical Trials

•Regimens With 1 DAA + PegIFN alfa/RBV

- Faldaprevir* (BI 201335, PI)
- Daclatasvir* (BMS-790052, NS5A)
- Sofosbuvir* (GS-7977, NI)
- Simeprevir* (TMC435, PI)
- Alisporivir* (CYP) On Hold
- Vaniprevir† (MK-7009, PI)

•Alternative Dosing

- TVR BID* (approved PI)

•Regimens With 2 DAAs + PegIFN alfa/RBV

- Daclatasvir + asunaprevir*

•New Interferons

- PegIFN lambda-1a + RBV
- PegIFN lambda-1a + daclatasvir + RBV**
- PegIFN lambda-1a + Asupranavir + RBV**

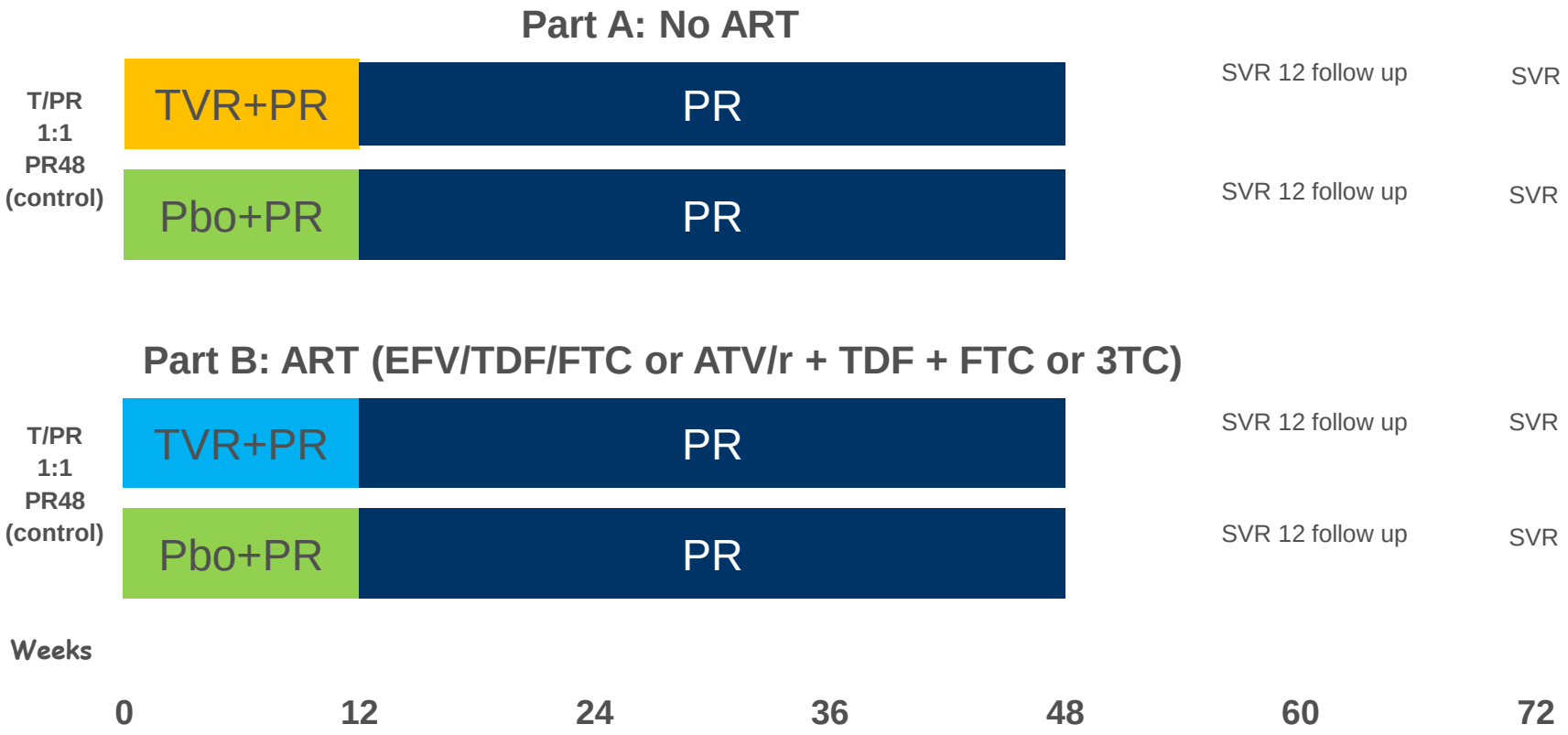
•IFN-Free Regimens

- Sofosbuvir + RBV
- Sofosbuvir + GS-5885 (FDC) ± RBV
- Daclatasvir + asunaprevir
- ABT-450/RTV + ABT-267 ± ABT-333 ± RBV
- Faldaprevir+BI207127+RBV

*Studied with pegIFN-α2a. †Studied with both pegIFN-α2a and pegIFN-α2b.** Phase 2a

Clinicaltrials.gov

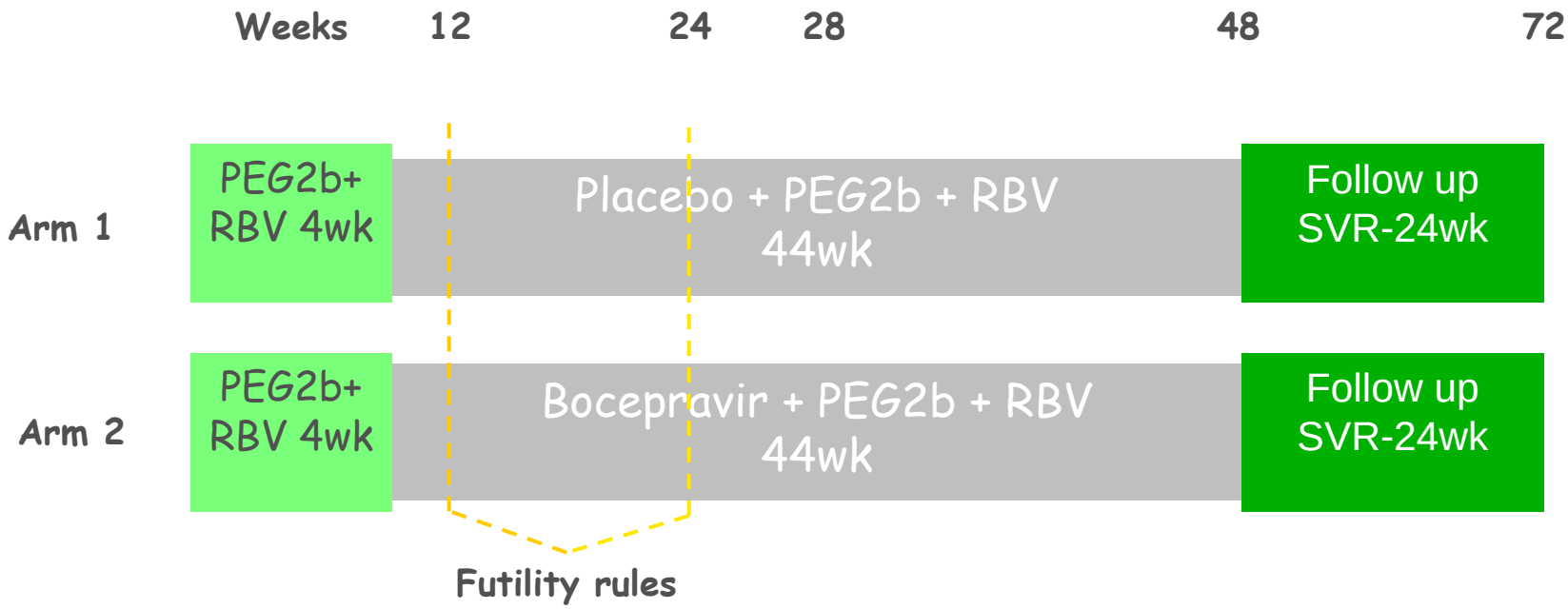
Telaprevir (TVR) in combination with pegylated interferon-α-2a (P) + ribavirin (R) in HCV/HIV-coinfected patients



- Telaprevir dose was 1,125 mg every 8 hours when the ART regimen included EFV
- Part A, patients had no concurrent ART
- Part B, patients were on stable, predefined ART with either an EFV- or an ATV/r-based regimen

Adapted from Dieterich D, et al CROI 2012. Seattle USA. Oral Presentation 46.

Boceprevir (BOC) + pegylated interferon-α-2b + ribavirin for the treatment of HCV/HIV-coinfected patients

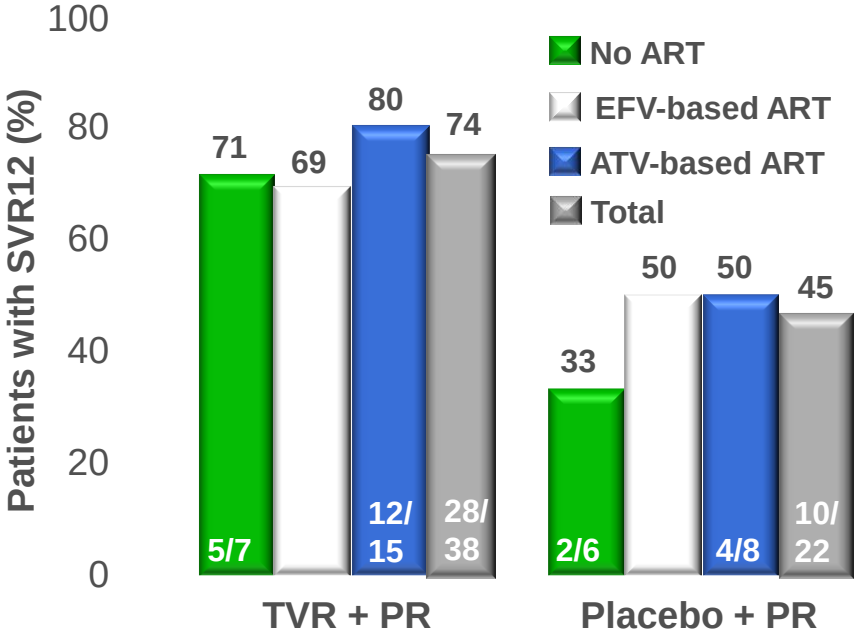


- Two-arm study, double blinded for BOC, open-label for PEG2b/RBV
  - 2:1 randomisation (experimental: control)
  - BOC dose 800 mg TID
- 4-week lead-in with PEG2b/RBV for all patients
  - PEG-2b 1.5μg/kg QW; RBV 600–1,400 mg/day divided BID

Adapted from Sulkowski M, et al CROI 2012. Seattle USA. Oral Presentation 47.

SVR12 with TVR or BOC + pegylated interferon and ribavirin (PR) vs PR alone in HIV/HCV coinfection

SVR12: TVR + PR vs PR[1]*



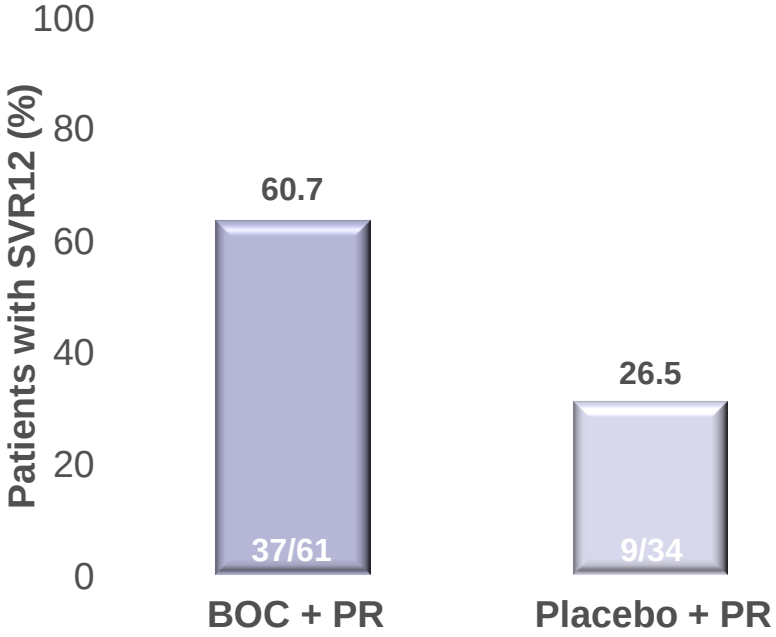
- Rebound in HIV-1 RNA not observed in any patient

	DC due to AEs
PR (n=22)	0%
TVR + PR (n=38)	8%

Primary endpoint=SVR at 12 weeks; interim analysis presented; TVR=telaprevir

*Pegylated interferon-α-2a; **Pegylated interferon-α-2b.

SVR12: BOC + PR vs PR[2]**



- HIV-1 RNA breakthrough observed in 7 patients

	DC due to AEs
PR (n=34)	9%
BOC + PR (n=64)	20%

Primary endpoint=SVR at 44 weeks; interim analysis presented

Adapted from: 1. Dieterich DT, et al. CROI 2012. Seattle USA. Oral Presentation 46; 2. Sulkowski MS, et al. CROI 2012. Seattle USA. Oral Presentation 47.

Tolerability and safety signals from the pilot studies

- **34% and 23% of T/PR and PR patients, respectively, had rash; no severe rashes were reported in either group**

- **Preliminary safety data of B/PR in co-infected patients showed a profile consistent with that observed in mono-infected patients (anemia 41% vs 26%); anemia rate in the T/PR arm and PR arm was 18%, respectively**

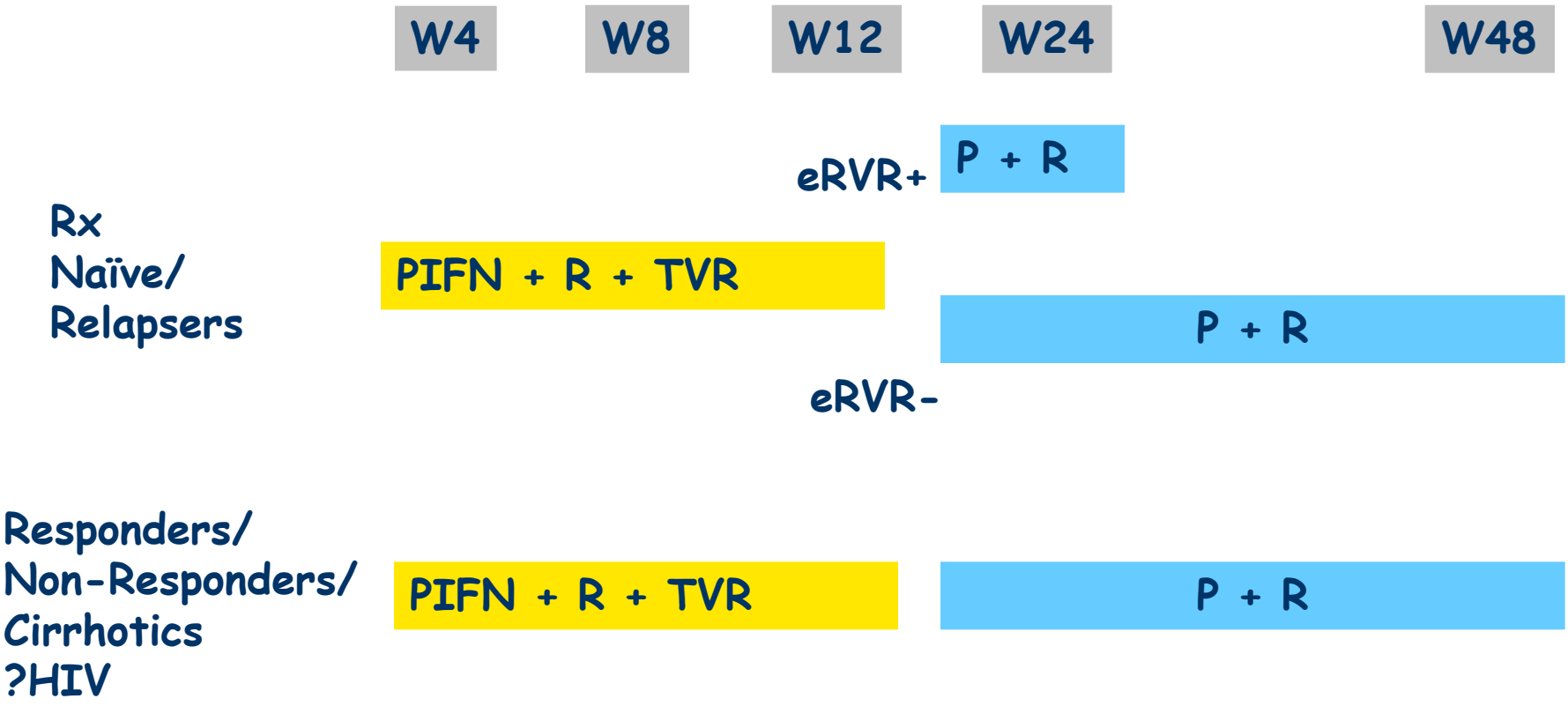
- **HIV breakthroughs were observed in 3/64 patients in the BOC group and 4/34 patients in the control group**

NB: HCV PIs, cyp450 metabolised, so important DDIs

	TVR	BOC
ATV/r	Monitoring for hyperbilirubinemia recommended	Consider on a case by case basis if deemed necessary
DRV/r/, FPV/r LPV/r	Not recommended	Not recommended
EFV	Increase TVR to 1250mg q8h	Not recommended
ETR	No dose adjustment needed	No dose adjustment needed
RPV	No dose adjustment needed	No dose adjustment needed
RAL	No dose adjustment needed	No dose adjustment needed
TDF	Increased monitoring is warranted	No dose adjustment needed

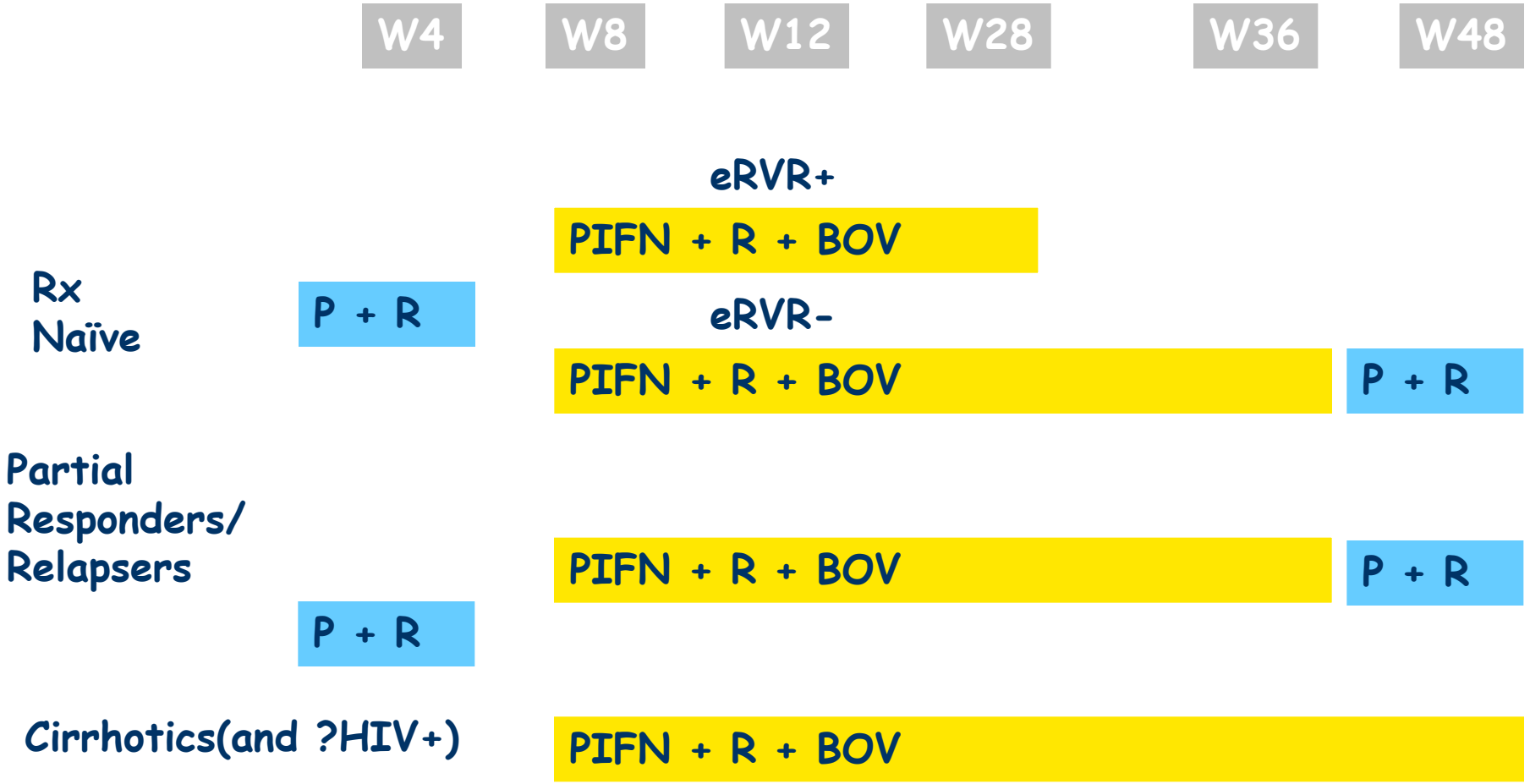
Telaprevir EU SmPC; Boceprevir EU SmPC
Kakuda TN, et al. IWCPHT 2012. Abs O-18

Kinetic Guided Rx length TVR



- Stopping Rules
  - Week 4 or week 12 HCV RNA >1000 U/l

BOV- kinetic guided Rx length



- Stopping Rules
  - week 12 >100 U/l

Stopping Rules for BOC and TVR

- Established as 'futility' rule in PegIFN/Rib
  - Reduce exposure to potentially toxic drugs
  - Cost-benefit
- In DAAs, also helpful to stop emergence of further Resistance Associated Variants

Boceprevir

- Week 12 HCV RNA >100 IU/l
- Week 12 detectable HCV RNA

Telaprevir

- Week 4 HCV RNA >1000 IU/l
- Week 8 HCV RNA >1000 IU/l
- Week 12 detectable HCV RNA

So what's on the horizon?

- New once daily new generation PIs with pIFN and Ribavirin
- PegIFN-lamda in combination with NS5a inhibitor and ribavirin
- IFN-free therapies

Management of HIV/HCV Co-infected Genotype 1 Patients

Newly diagnosed chronic HCV GT 1 infection

Perform transient elastography and/or serum marker and/or liver biopsy

F0F1[a]

In general, treatment can be deferred. Consider treatment with Peg/RBV and an HCV protease inhibitor or Peg/RBV alone if low HCV viral load, *IL28B* CC genotype, absence of insulin resistance and high CD4+ cell count.

F2F3[a]

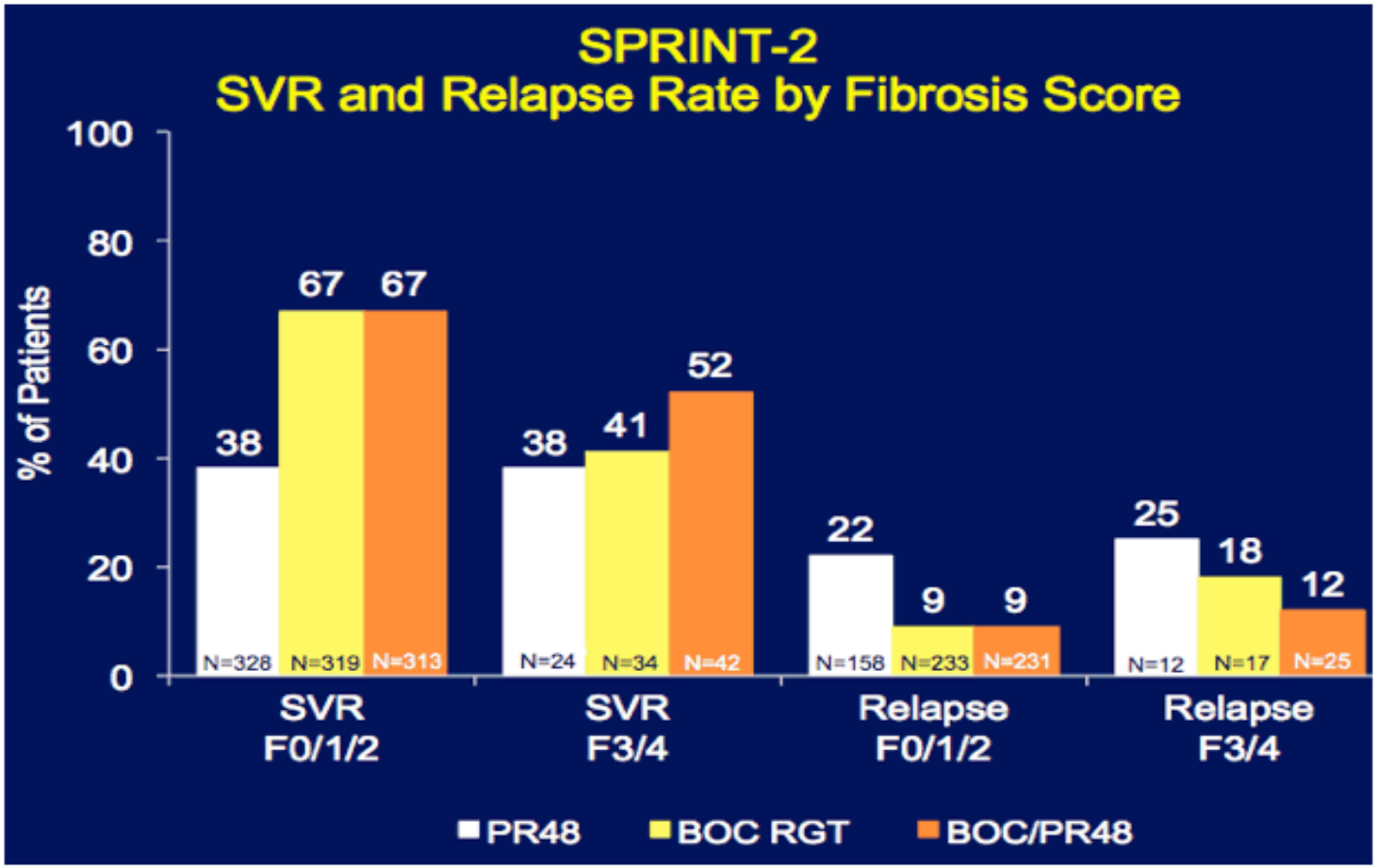
Treatment with Peg/RBV and an HCV protease inhibitor.

F4[a]

Treatment with Peg/RBV and an HCV protease inhibitor if compensated disease.
Treatment should be undergone in specialised centres.

[a]Metavir fibrosis score: F0=no fibrosis; F1= portal fibrosis, no septae; F2= portal fibrosis, few septae, F3=bridging fibrosis, F4=cirrhosis

BOC in F4 disease in HCV mono-infection



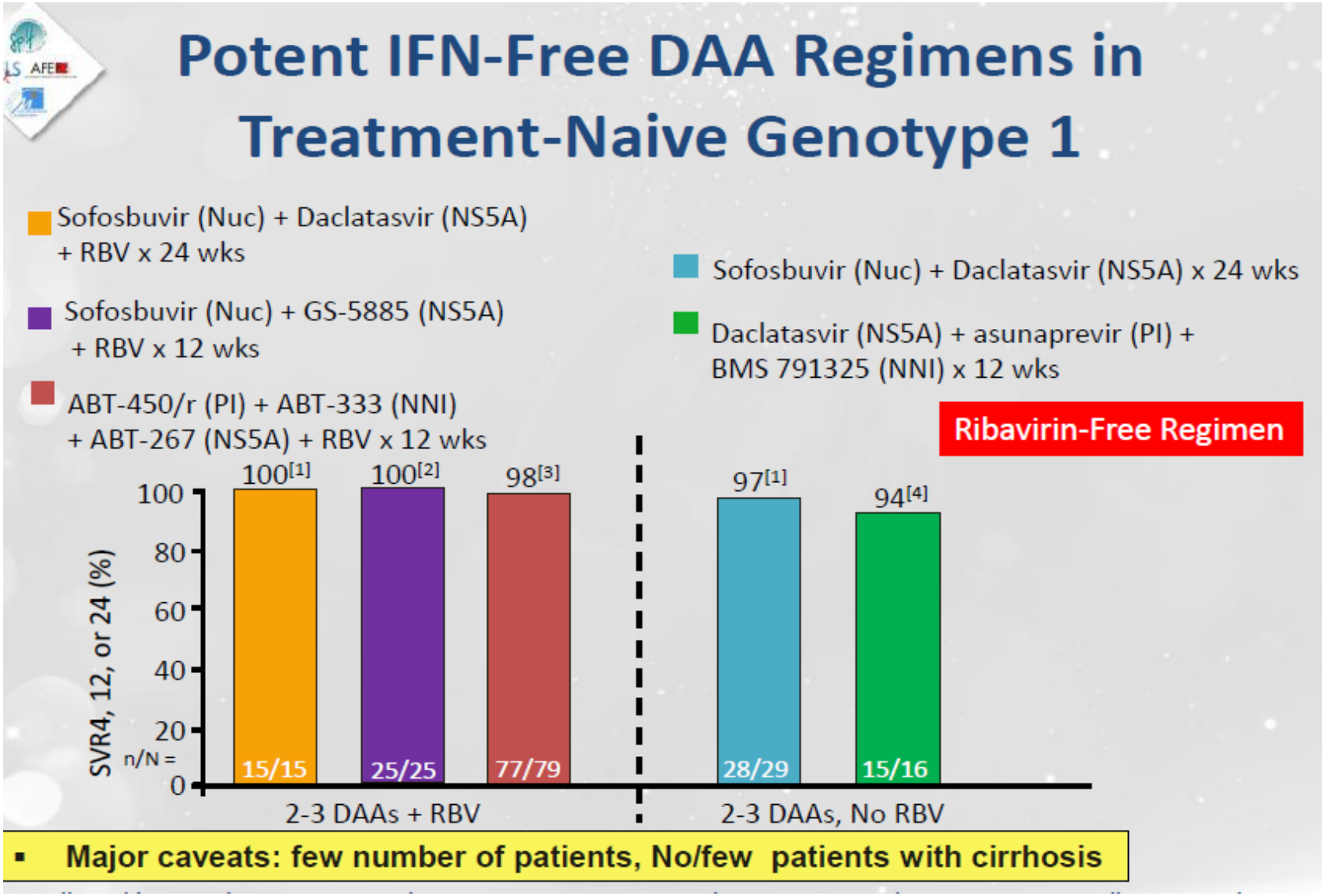
French EAP TVR/BOC in patients with advanced fibrosis and previous non-response (CUPIC)

Patients, n (% patients with at least one event)	Telaprevir n=296	Boceprevir n=159
Serious adverse events (%)	48.6	38.4
Premature discontinuation	26.0	23.9
Due to SAEs (%)	14.5	7.4
Death (%)	2.0	1.3
Infection (Grade 3/4) (%)	8.8	2.5
Asthenia (Grade 3/4) (%)	4.7	5.7
Rash		
Grade 3 (%)	6.8	0
Grade 4 (SCAR) (%)	0.7	0
Pruritus (Grade 3/4) (%)	3.7	0.6
Hepatic decompensation (%)	4.4	4.4

Patients, n (% patients with at least one event)	Telaprevir (n=296)	Boceprevir (n=159)
Anemia (%)		
Grade 2 (8.0 – <10.0 g/dL)	19.6	22.6
Grade 3/4 (<8,0 g/dL)	10.1	10.1
EPO use	56.8	66.0
Blood transfusion	15.2	10.7
Neutropenia (%)		
Grade 3 (500 – <1000/mm^3)	4.0	4.4
Grade 4 (<500/mm^3)	0.7	0.6
G-CSF use	2.4	3.8
Thrombopenia (%)		
Grade 3 (25 000 – <50 000)	11.8	6.3
Grade 4 (<25 000)	1.3	0.6
Thrombopoïetin Use	1.7	1.9

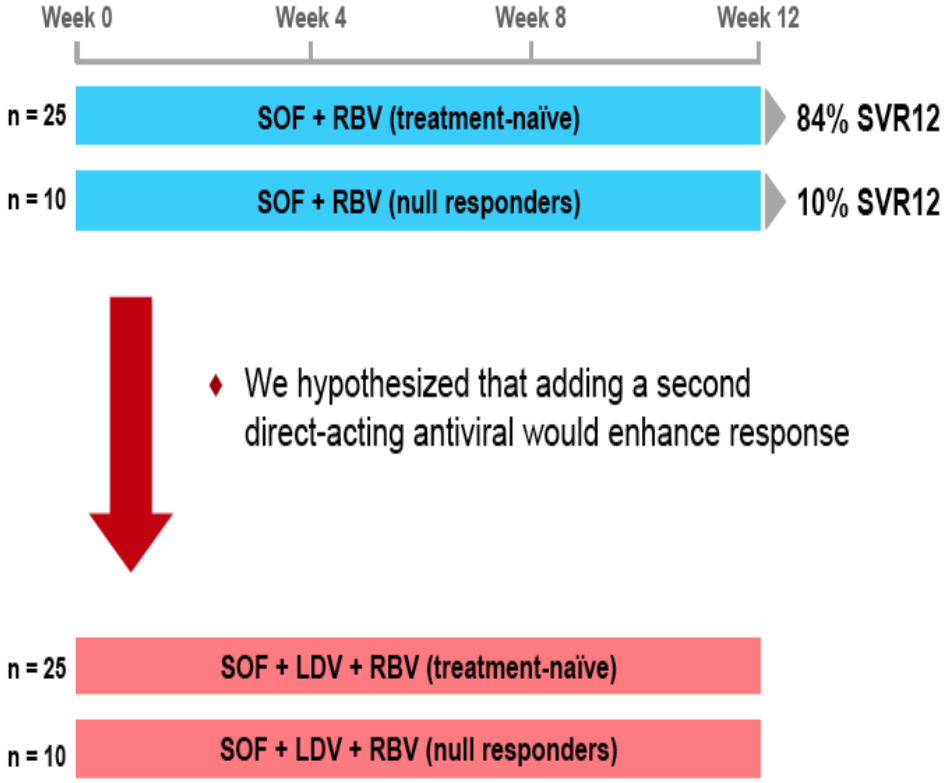
UPMC

Is IFN-free therapy a reality?



Combining DAAs – Nuc + NS5a (Electron study)

Study Design: Genotype 1 Cohorts



LDV, ledipasvir; RBV, ribavirin; SOF, sofosbuvir.

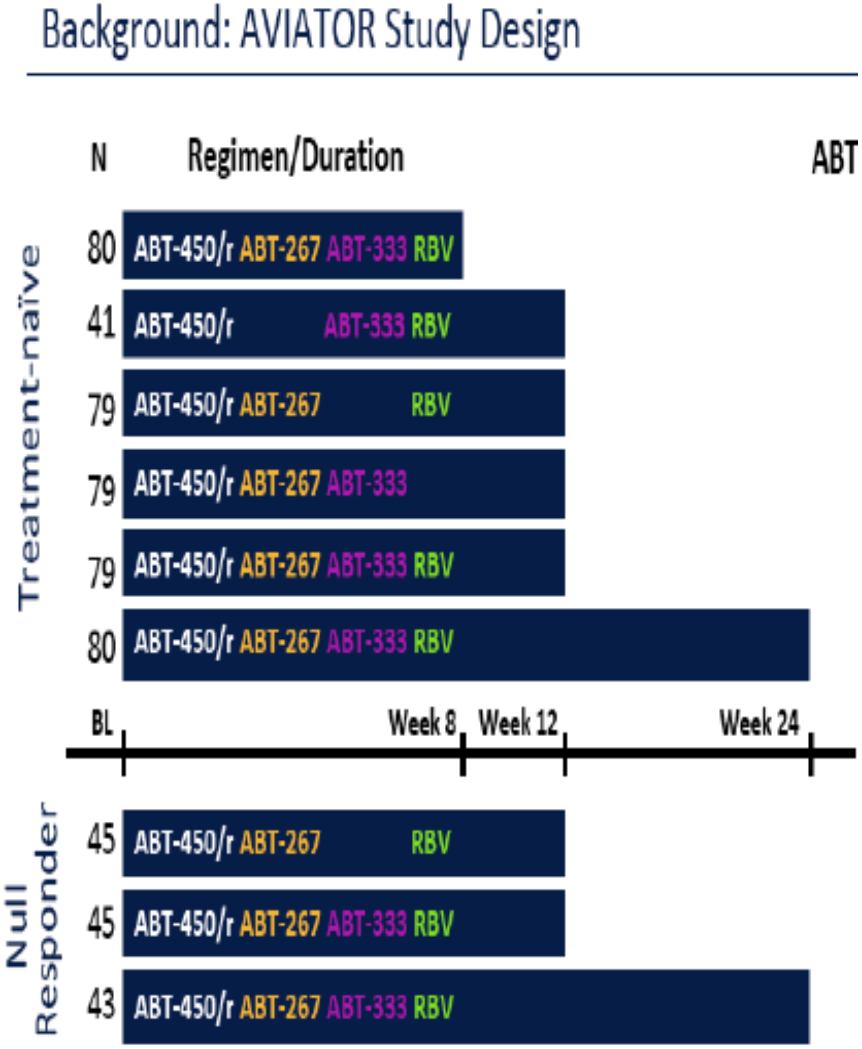
Results: Efficacy

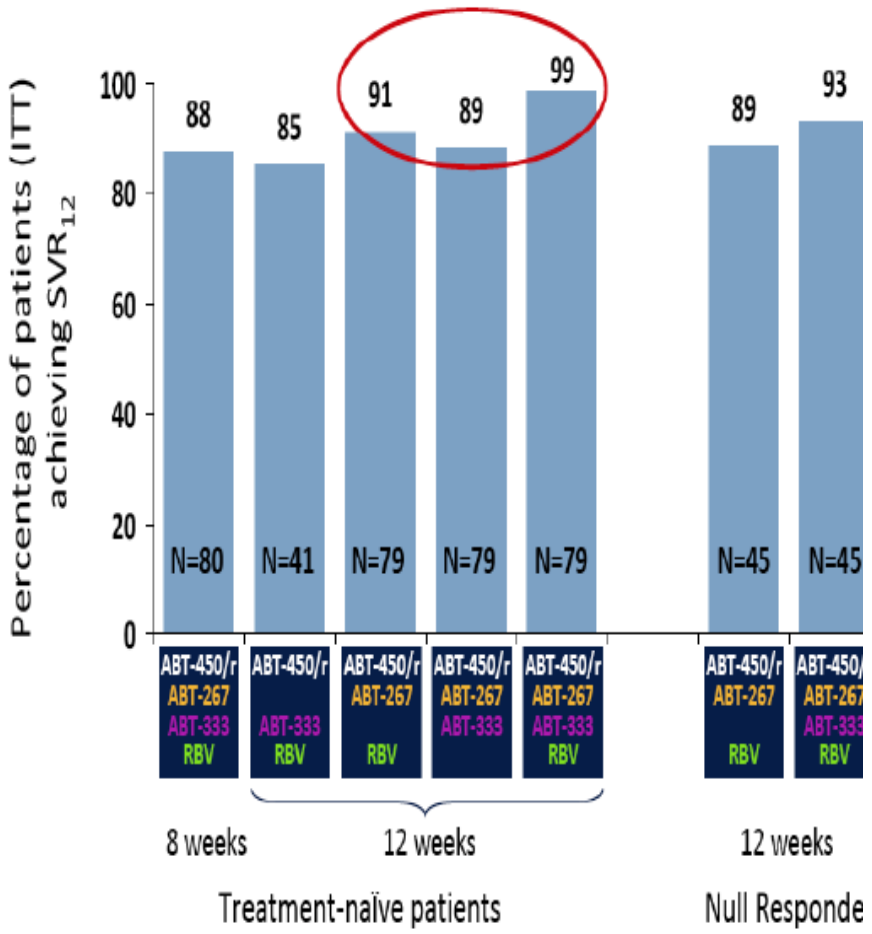
Patients with HCV RNA <LOD* over Time, n/N (%)

	SOF + RBV		SOF + LDV + RBV	
	Treatment-naïve (n = 25)	Null responder (n = 10)	Treatment-naïve (n = 25)	Null responder (n = 9)
Week 1	8/25 (32)	1/10 (10)	11/25 (44)	0/9 (0)
Week 2	17/25 (68)	7/10 (70)	22/25 (88)	4/9 (44)
Week 4	25/25 (100)	10/10 (100)	25/25 (100)	8/9 (89)
EOT	25/25 (100)	10/10 (100)	25/25 (100)	9/9 (100)
SVR4	22/25 (88)	1/10 (10)	25/25 (100)†	9/9 (100)
SVR12	21/25 (84)	1/10 (10)	25/25 (100)	9/9 (100)

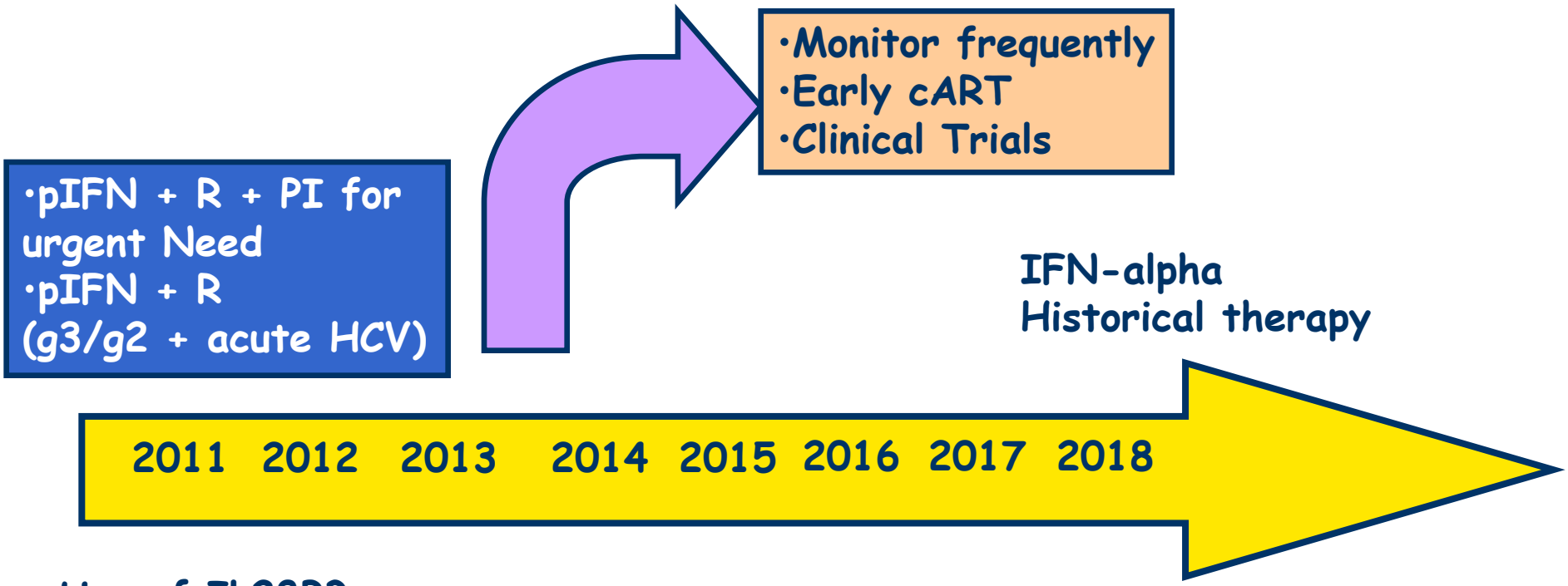
*Analyzed by TaqMan® HCV Test 2.0 with limit of detection (LOD) of 15 IU/mL.
†Includes 1 patient who stopped all treatment due to an SAE at week 8; this patient subsequently achieved SVR24.
EOT, end of treatment; LDV, ledipasvir; RBV, ribavirin; SOF, sofosbuvir.

Aviator study -combining Nuc+NS5a +/- Non-nuc +/- R





HCV Rx landscape – the future?



Use of IL28B?
P/R lead-in phase?
Response guided therapy

<u>First line</u>
1 or 2 DAA + R
2 or 3 DAAs

<u>2nd Line</u>
2DAAs + P+R
2 or 3 DAAs

Challenges for 2013

- Global testing/access for HBV/HCV and anti-HBV/HCV treatment
- HCV/HIV – Rx now or wait?
- What do with PegIFN/R null-reponders and triple therapy failures?

HIV/Hepatitis - unequal Burden?