Klinik HIV/AIDS Sempozyumu 2010

HIV AND HEPATITIS

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Treatment Objectives

- Improve disease free survival
  - Prevent liver decompensation and HCC
    - Prevent progression to cirrhosis
      - **Obtain durable suppression of HBV replication**
- Treatment endpoints in practice
  - Decrease serum HBV DNA
  - Normalize serum ALT
  - Induce HBeAg/HBsAg loss or seroconversion

Keeffe EB, Dieterich DT et al. 2006;4(8):936-62;

Agents for treatment of hepatitis B in HIV co-infection

- Interferon
- Lamivudine
- Emtricitabine
- Adefovir dipivoxil
- Tenofovir disoproxil fumarate
- Entecavir
- Telbivudine
- ~~Clevudine~~

Interferon treatment in HIV/HBV co-infected patients

	Pts	αIFN (MU)	Months therapy	CD4 (cells/mm^3)	HBV DNA **<6 $\log_{10}$ copies/mL**	HBeAg Clear.
McDonald 87	14	2.5–10	6	-	-	0
Marcellin 93	10	3–5	4–6	20–858	2	2
Wong 95	12	10	6	No AIDS	1	1
Zylberberg 96	25	6	6	480±234	9	2
Di Martino 02	26	5	6	331±207	7	3
Total	**87**				**19 (26%)**	**8 (9%)**

- HBeAg seroreversion frequent. No HBsAg loss

McDonald, Hepatology 1987; 7(4):719-23. Marcellin, Gut 1993;34(Suppl 2):S106. Wong, Gastroenterology 1995;108:165-171; Zylberberg, Gastroenterol Clin Biol 1996;20:968−71. Di Martino, Gastroenterology 2002;123(6):1812-22.

Therapeutic options: Peg-IFN

Failure of previous strategies:

- ADV + PegIFNα2a for 48 weeks[1]
- TDF v. PegIFNα2a for 24 weeks then TDF[2]

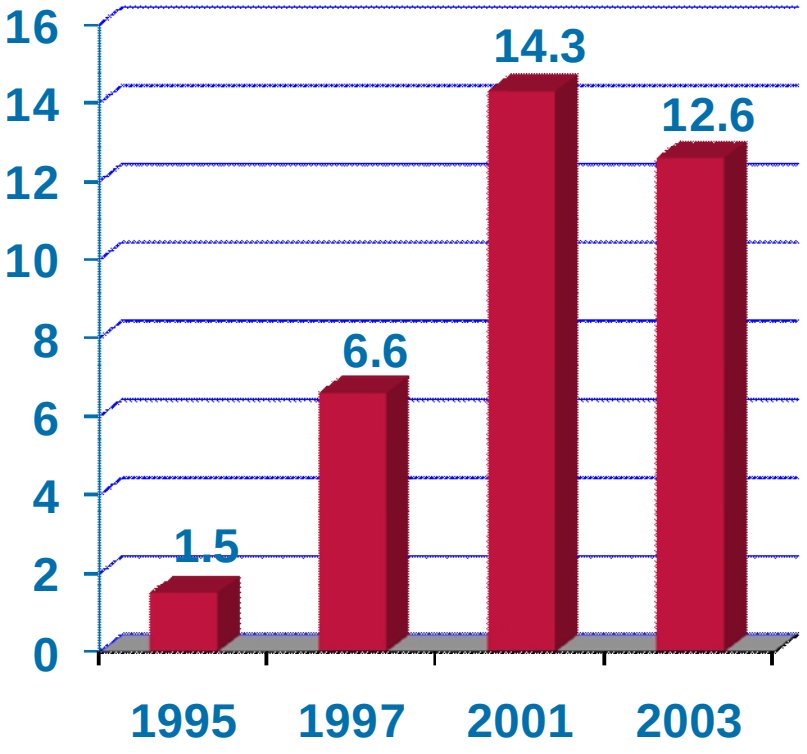
Ongoing pilot trial in France (ANRS HB01)

- TDF for at least 6 months then TDF + PegIFNα2a for 48 weeks

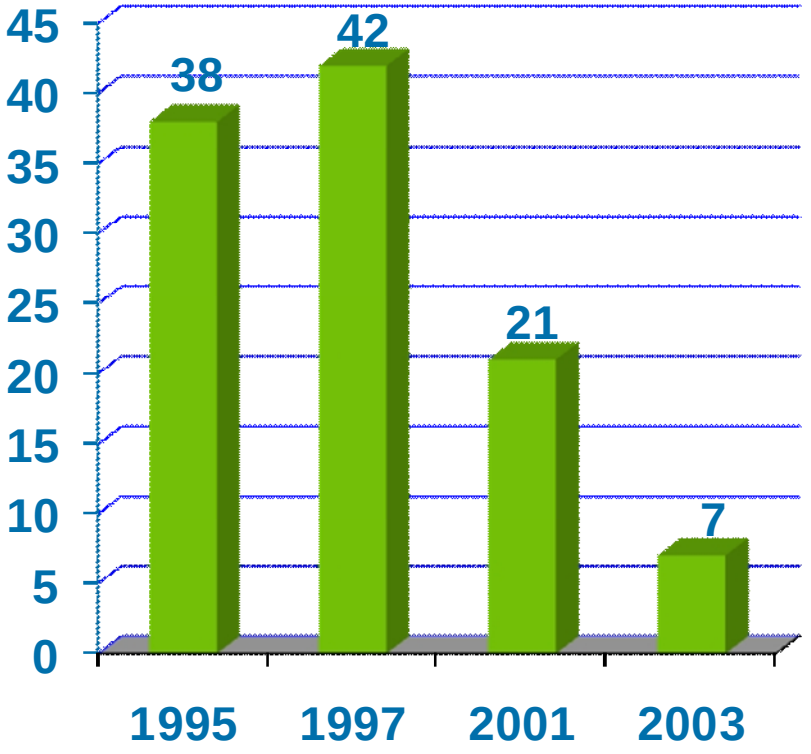
[1]Ingiliz, et al. Antivir Ther 2008. 2Johnson, et al. HIV Clin Ther 2007

Liver disease associated mortality in HIV: 1995–2003 GERMIVIC

ESLD assoc. death: % total mortality



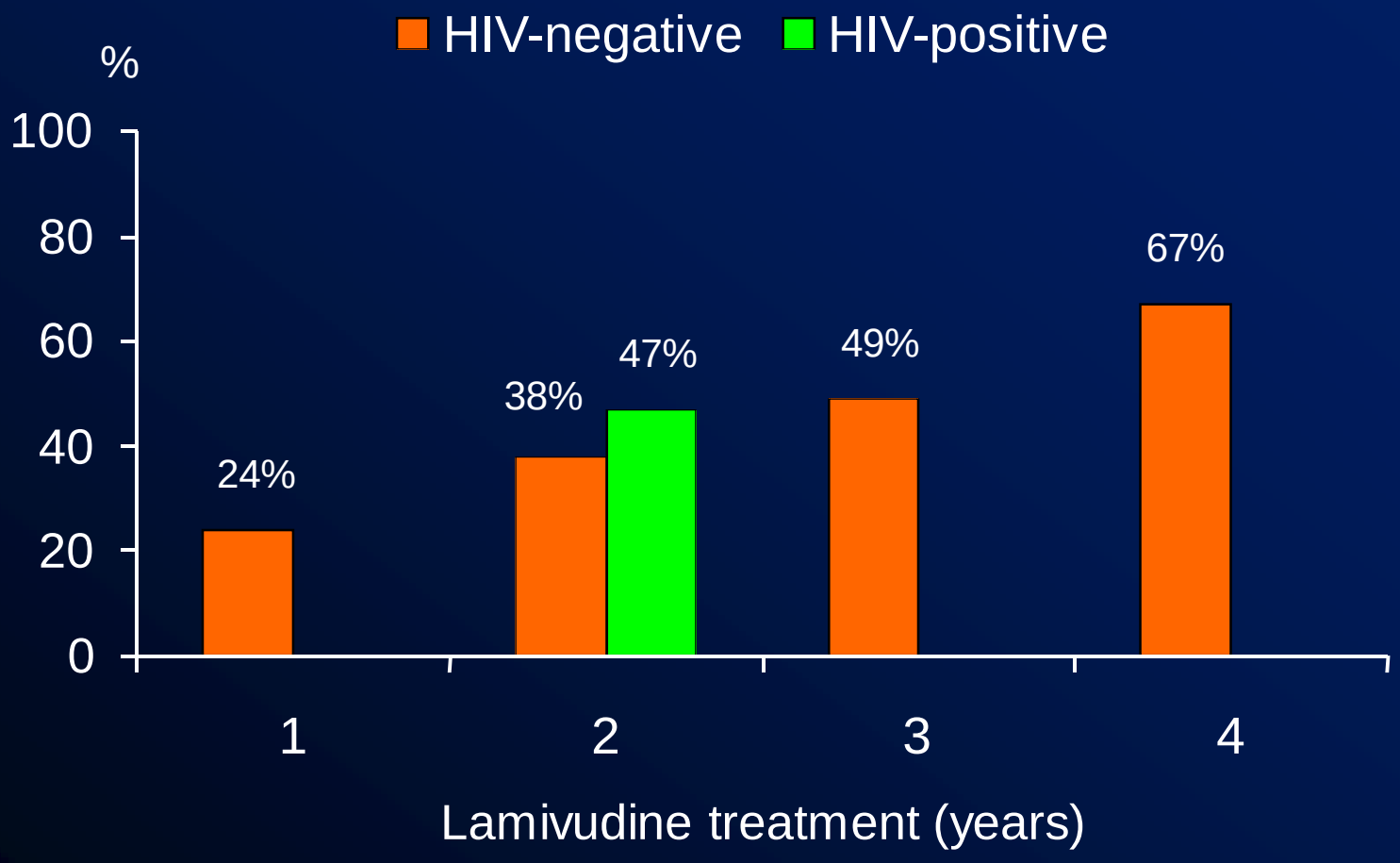
ESLD assoc. death: % HBsAg+



Rosenthal E et al J Viral Hepat 2007;14:183–8

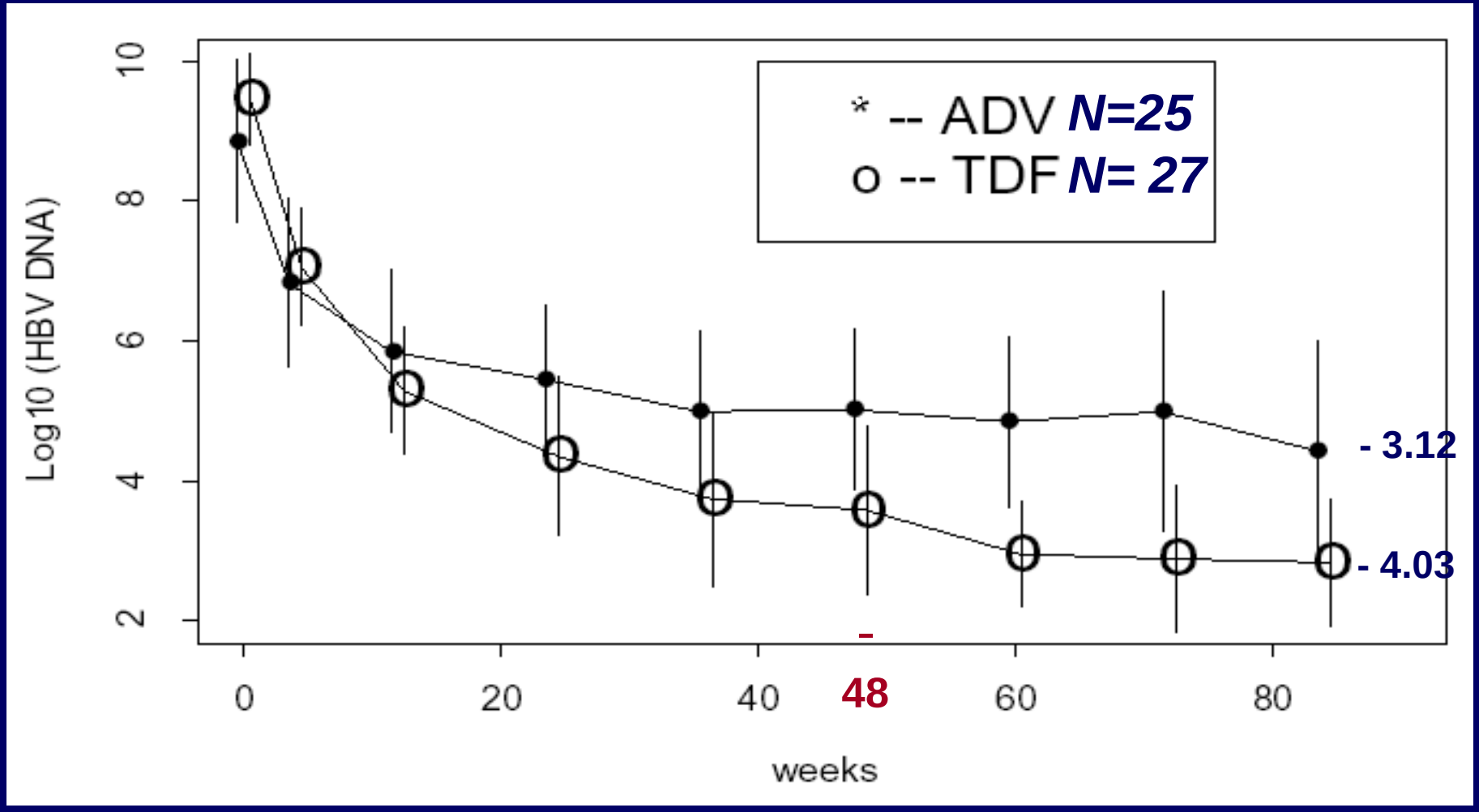
ESLD = End-stage liver disease

Incidence of lamivudine resistance in HBV and HIV/HBV patients



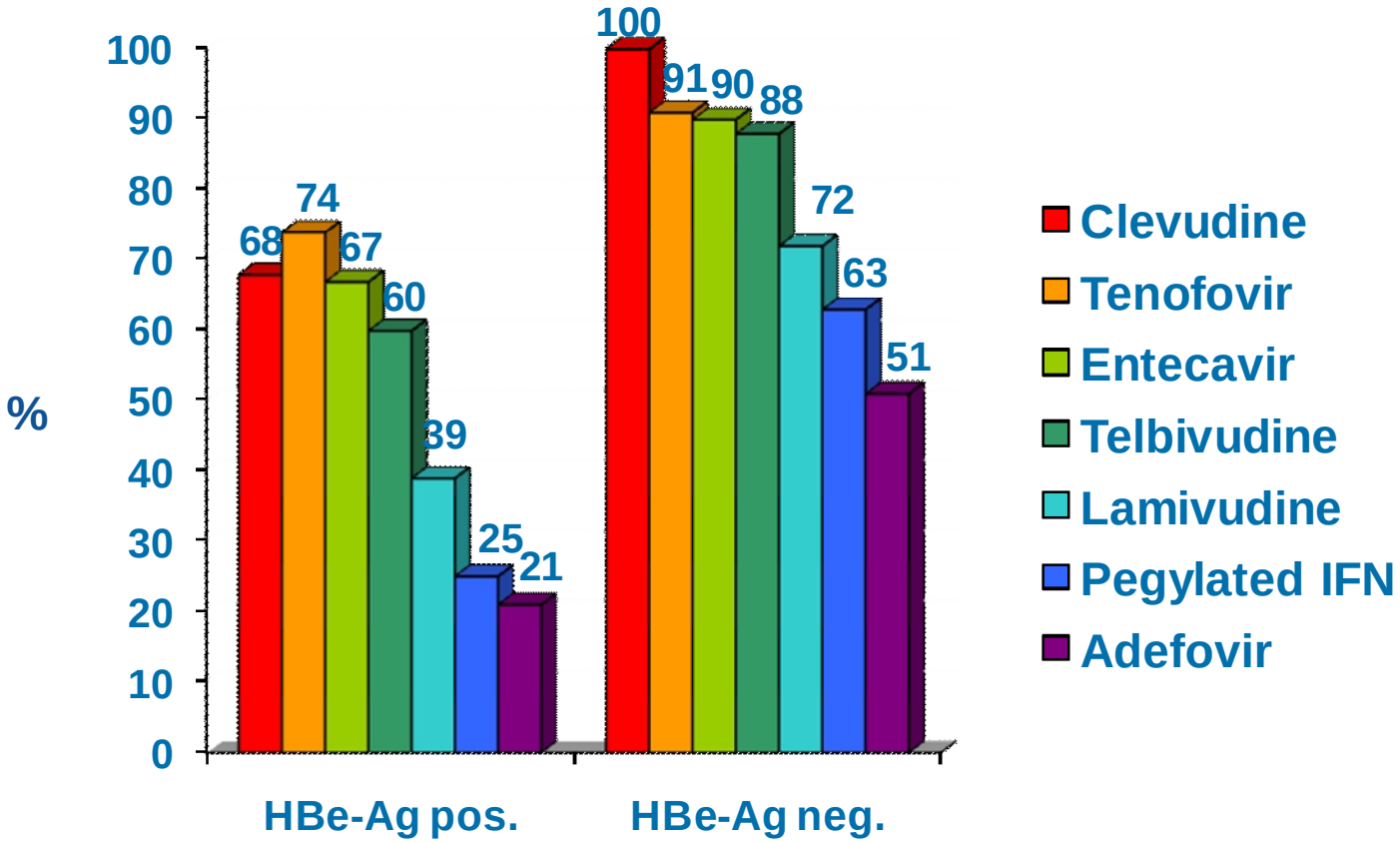
Lai C, *et al*. *N Engl J Med* 1998;339:61–8; Leung NWY, *et al*. *J Hepatology* 1999;30:59A; Chang T, *et al. Antivir Ther* 2000;5:44A; Benhamou Y, *et al. Hepatology* 1999; 30:1302–6.

ADV vs TDF in HIV/HBV co-infected patients
Mean serum HBV DNA



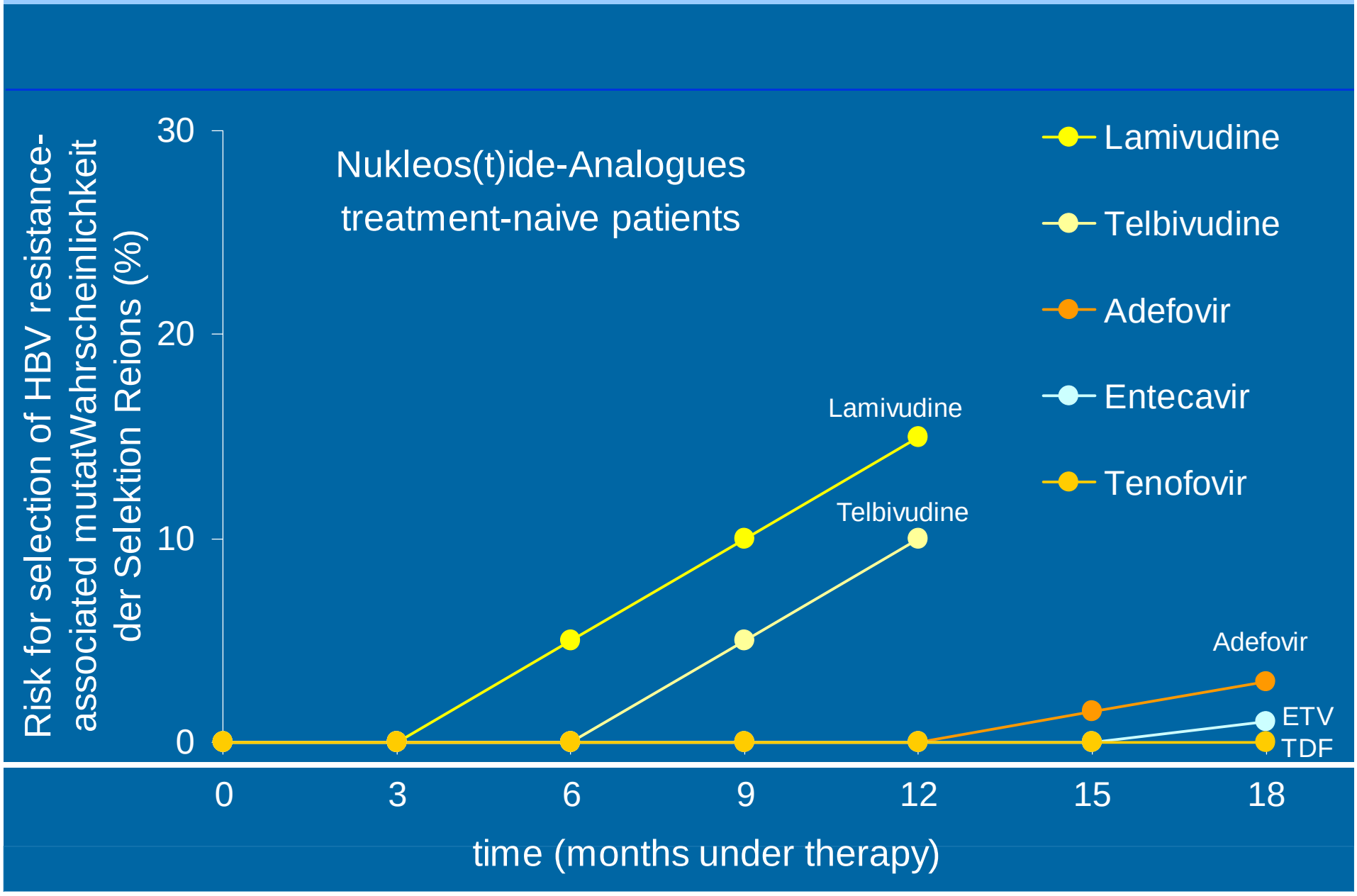
Peters M et al. CROI 2005

Rates of undetectable HBV at one year of therapy in randomized clinical trials in patients with CHB monoinfection

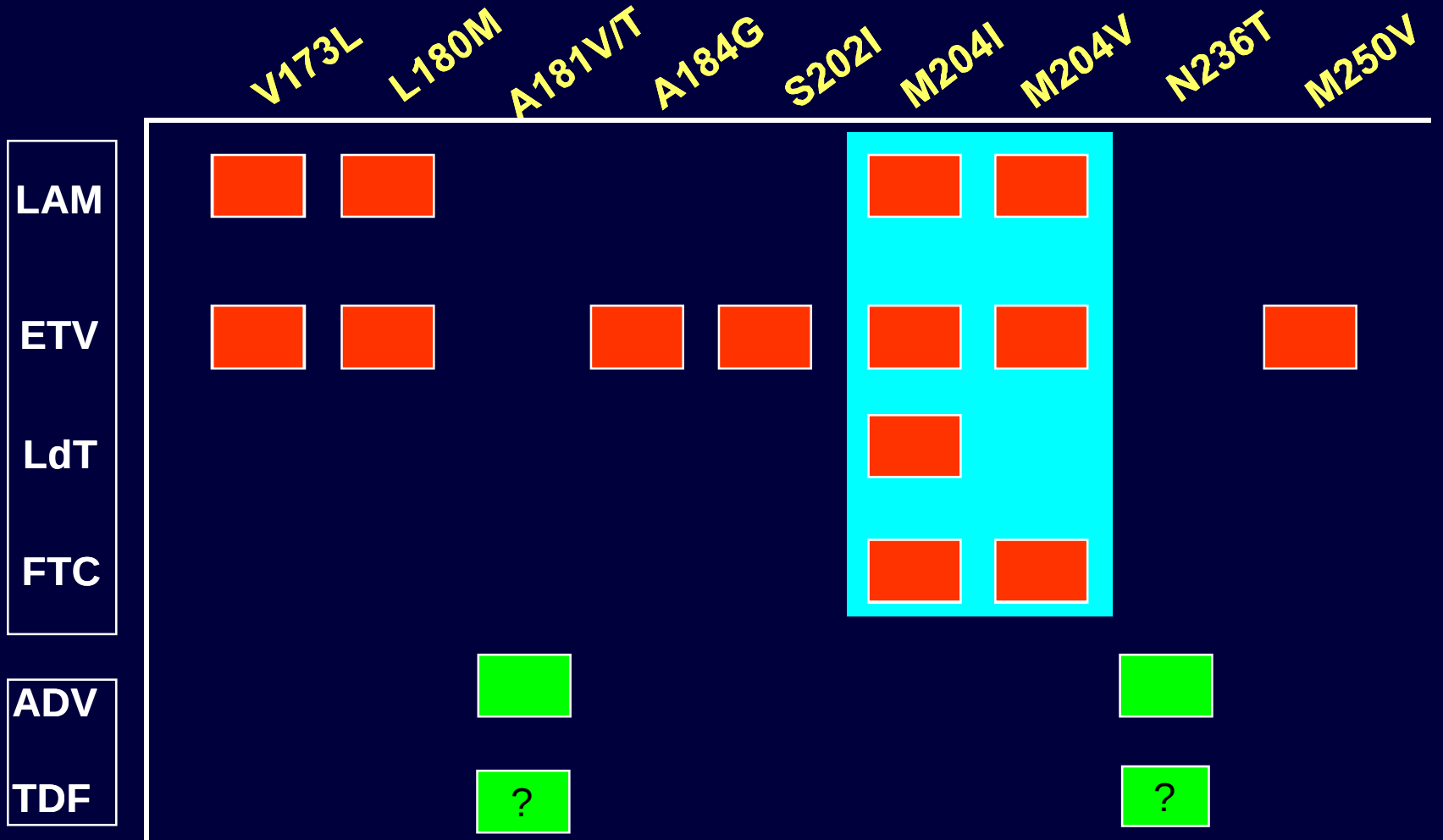


These trials used different HBV DNA assays and were not head- to- head comparisons for all the drugs; thus, these numbers are only indicative and should be considered with caution

When should HBV therapy be modified: differences between drugs and risk for resistance development



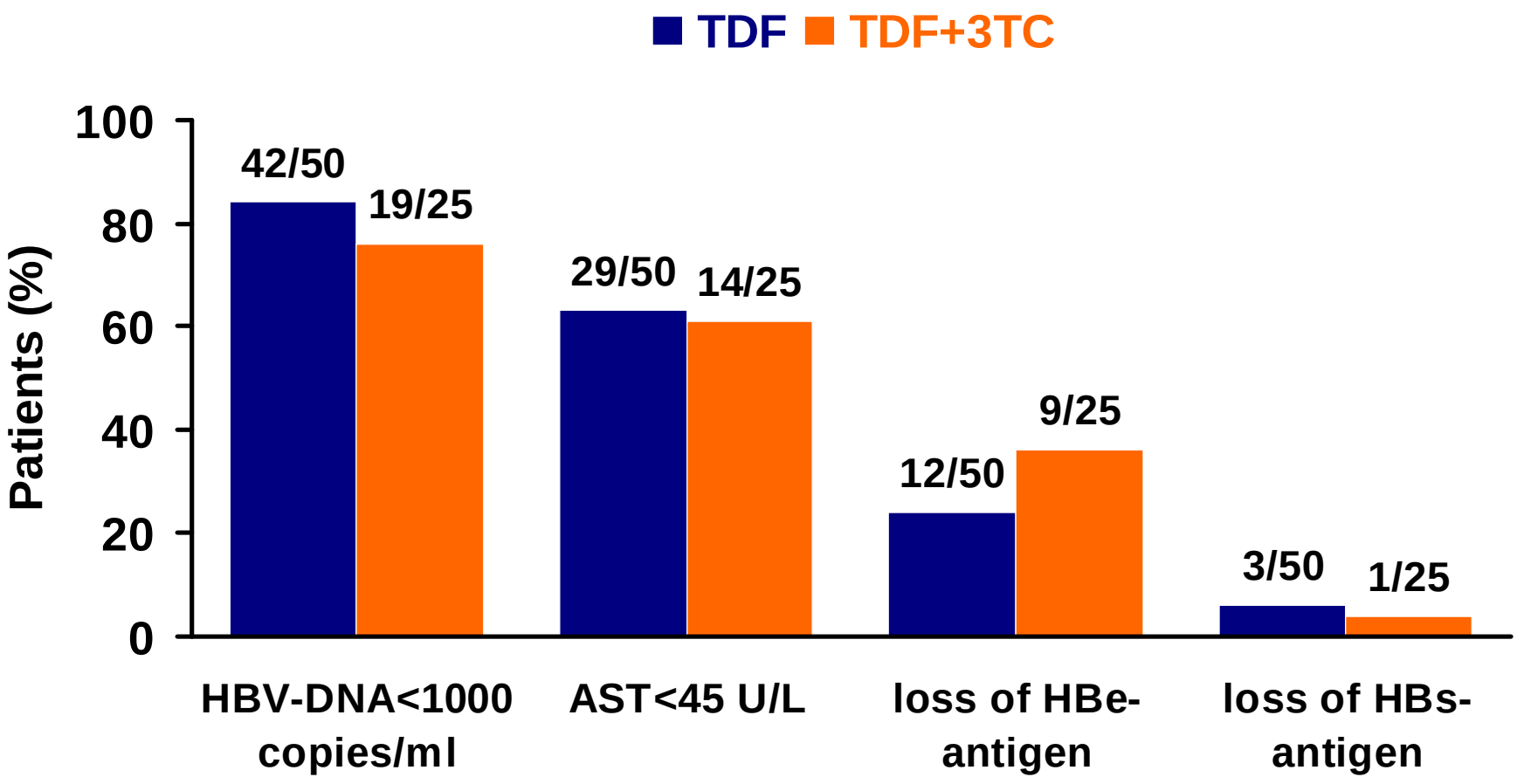
HBV Antiviral Therapy
Cross Resistance In Vitro



From MS Sulkowski, MD, at 11th RW Program Clinical Update, IAS–USA.

Tenofovir vs. Tenofovir + Lamivudin

(HBV/HIV-coinfection)



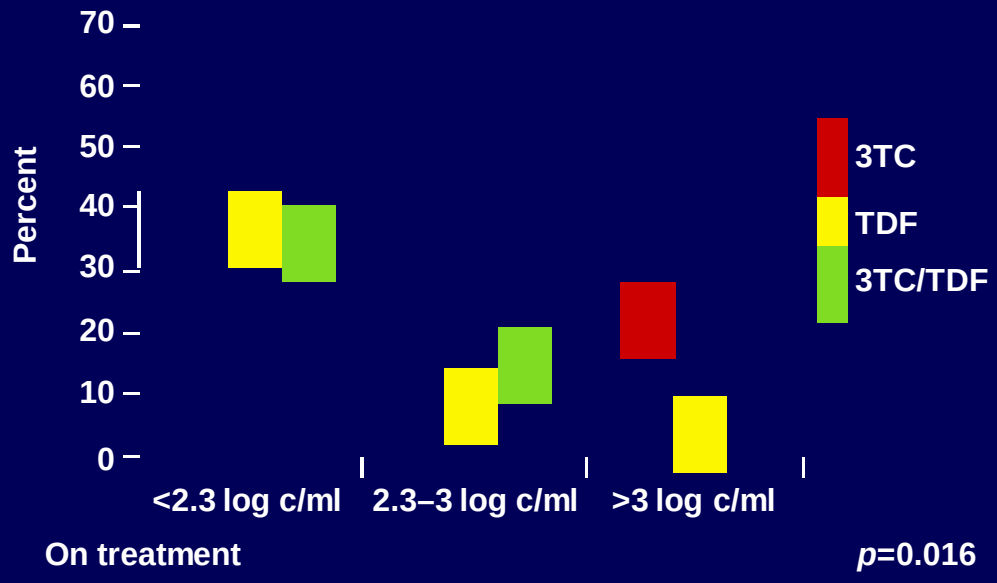
Schmutz G. et al. AIDS 2006

TICO Study: TDF-containing HAART vs 3TC-containing HAART in ARV-naive HIV/HBV coinfected patients

- Randomized Thai trial (1:1:1) of 3TC vs TDF vs 3TC/TDF within a EFV-based HAART regimen (*n*=36)
- Hepatic flare in 9 (25%) patients, 4 of whom had HBe-Ag loss (2 with HBsAg seroconversion)
  - 1 died of hepatic decompensation
- Detectable HBV viremia at Week 48 is a risk factor for future HBV resistance development (2 cases of 3TC resistance in 3TC only group)
- Good initial anti-HBV response for all 3 arms but more resistance in the 3TC arm at wk 48

	3TC	TDF	3TC/TDF	Total
HBeAg loss	**3 (33%)**	**1 (17%)**	**3 (43%)**	**7 (32%)**
Anti-HBe Seroconversion	**1 (11%)**	**1 (17%)**	**3 (43%)**	**6 (27%)**
HBsAg loss	**1 (8%)**	**1 (8%)**	**1 (9%)**	**3 (8%)**

HIV suppression at Week 48

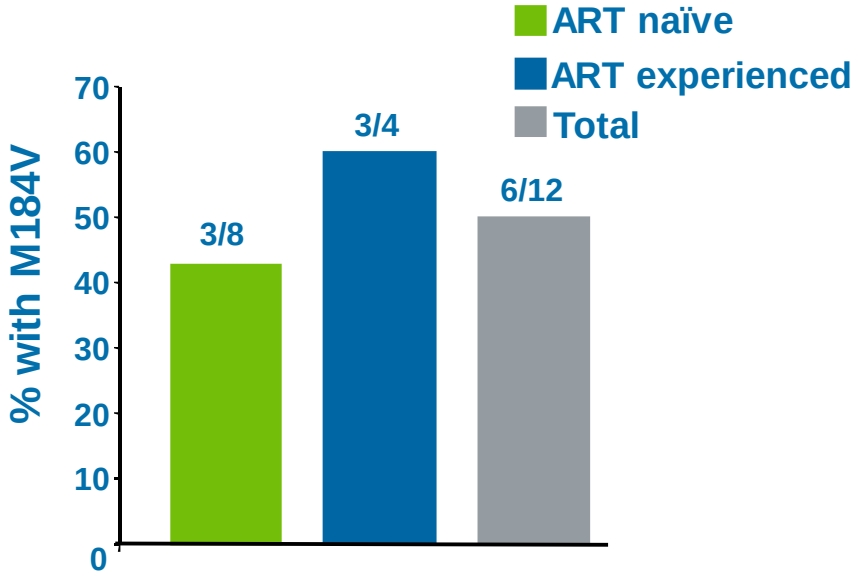


Matthews G, *et al. 4th IAS, Sydney* 2007, #TUAB205

Anti-HIV activity of entecavir

- 17 HIV/HBV co-infected patients (10 naïve, 7 treatment-experienced from US and Australia) who received entecavir (ETV) monotherapy for HBV therapy
- ETV monotherapy results in clinically significant reduction in HIV RNA in the majority but not all patients and can select for the M184V mutation even in naive patients
- HIV/HBV co-infected individuals should not receive ETV monotherapy

Selection of M184V following ETV treatment



Univariate analysis for selection of M184V

Risk factor	p value
Total duration on ETV	0.045
Reduction in HBV viral load	0.024

Anti-HIV activity under telbivudine?

- 45-year-old gentleman with HIV/HBV co-infection
- HBV-DNA 662,000,000 copies/mL, HBe-Ag+
- CD4 640 cells/µL, HIV-RNA 8,650 copies/mL
- In January 2008 the patient was offered triple HAART with TDF/FTC/EFV or HBV dual therapy with ADF/LdT; the patient commenced dual HBV therapy
- 5 months later LdT was stopped (HIV-RNA 127 copies/mL) and HIV-RNA rebounded to 3903 copies/mL one month after LdT was stopped
- Rechallenge of LdT led to a drop in HIV-RNA from 1074 to 177copies/mL after one week and 71 copies after 2 weeks

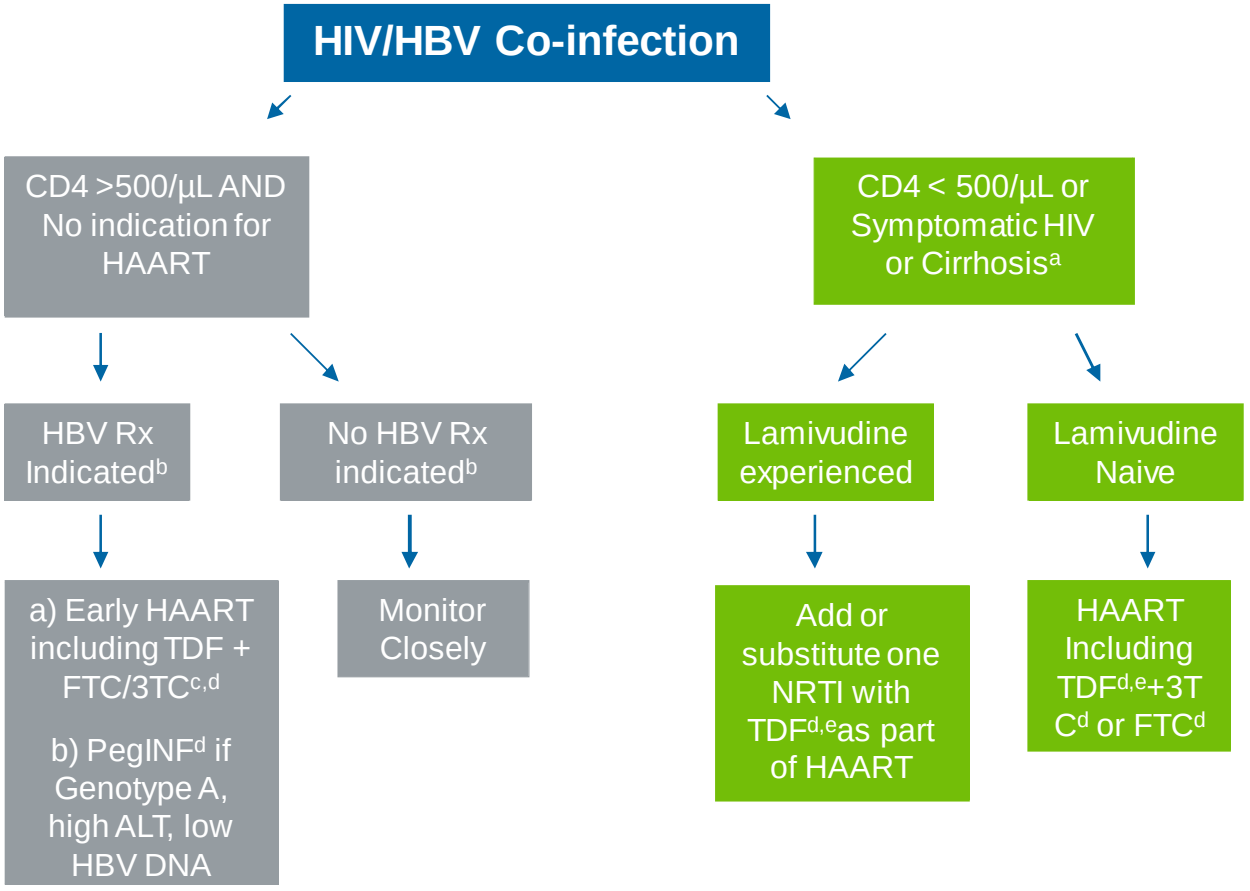
Initial *in vitro* studies on anti-HIV activity of telbivudine and entecavir in two HIV isolates

- EC_{50} was determined using concentrations of telbivudine ranging from 30.5 nM to 600 µM
- Entecavir (300 µM) and DMSO (600 µM) were used as controls

HIV isolate	Host	DMSO EC_{50} (µM)	Entecavir EC_{50} (µM)	Telbivudine EC_{50} (µM)
CNDO	**HEK 293**	>600	45.26	>600
MDRC4	**HEK 293**	>600	16.85	>600

CNDO Drug-sensitive reference virus derived from NL4-3 strain of HIV-1.
MDRC4 Multidrug-resistant reference strain R268.

Treatment of chronic HBV infection in HIV-positive individuals



c) Naïve Asian, HBe-Ag+, HIV coinfected patients initiating HAART with TDF or TDF+FTC reached unexpected high rates of HBe (and even HBs) seroconversion, strengthening the rationale for early HAART. If a patient is unwilling to go on early HAART, adefovir and telbivudine may be used as an alternative to control HBV alone. A recent case report suggested possible anti-HIV activity of telbivudine. In-vitro data using an assay which was able to demonstrate anti-HIV-activity of entecavir however, failed to detect an influence of telbivudine on the replicative capacity of HIV-1.

News in hepatitis B

- Objective: To characterize frequency and reasons for failure to control HBV replication during treatment with tenofovir
- 150/168 patients had an HBV-DNA level <2000 IU/mL at the end of follow-up (median treatment duration was 31 months)
- 18 patients had virological failure whereby of these only 6 patients had adequate TDF levels; in these 4/5 showed a L217R polymorphism (HBV GTA2 polymorphism)

Summary

- **Chronic hepatitis B can be found in up to 8% of all HIV-patients**
- **HBV/HIV coinfected patients show a faster progression to cirrhosis and increased liver-related mortality**
- **Do not forget to check for HDV superinfection**
- **ARV in HIV/HBV co-infected patients should include TDF and 3TC or FTC**
- **In patients with no HAART indication (>500/µl) early HAART still remains an option; alternatives are PEG-IFN, or de novo adefovir/telbivudine therapy**

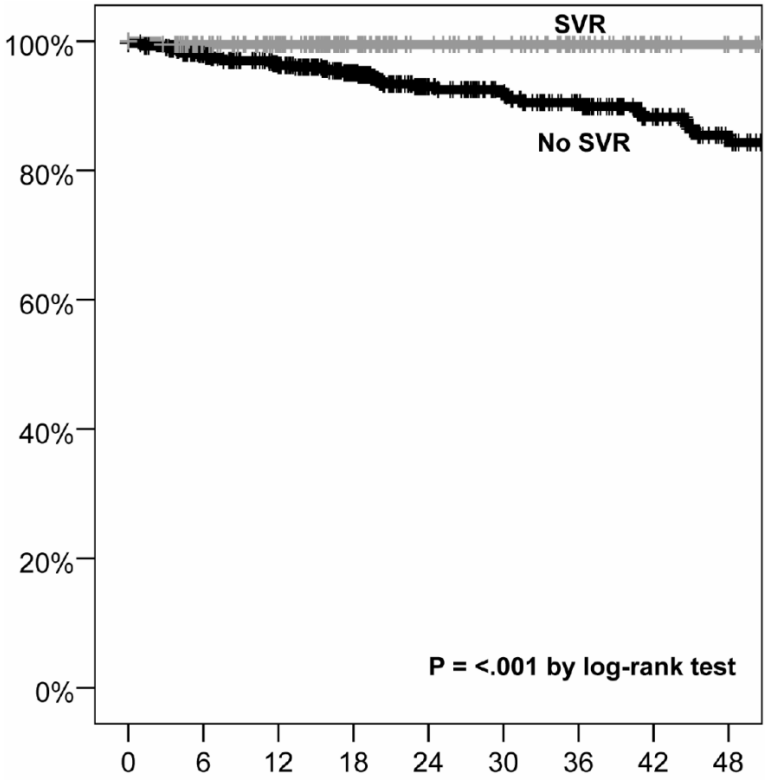
Therapeutic Challenges in HIV infected patients with hepatitis C

- **Treatment of chronic hepatitis C:**
  - Access to treatment
  - dosages and duration
  - Genetic factors
- **Impact of HIV associated immunodeficiency on treatment outcome**
- **Choice of HAART together with concomitant HCV therapy**
- **Challenges in treatment of HCV with the new oral agents**

HCV Infection Can Be Cured

- **Testing and counseling**
- **Treatment of chronic infection**
  - Sustained virologic response is possible[1]
  - Sustained virologic response is durable[2]
  - Sustained virologic response prevents death[3]

Survival after HCV treatment for 493 with no SVR and 218 with SVR



[1]Torriani NEJM 2004; [2]Soriano Antivir Ther 2004; [3]Berenguer Hepatology 2009

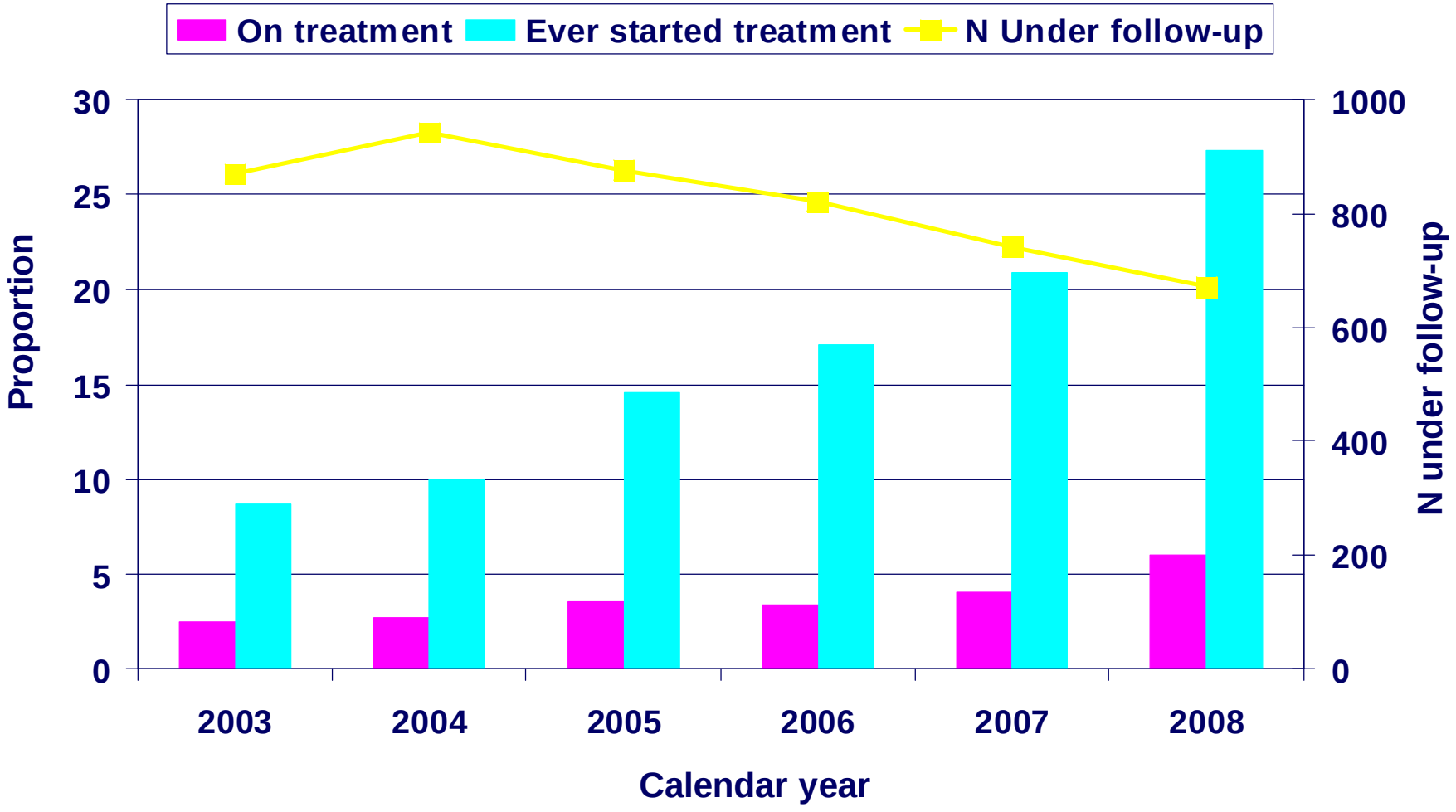
Treatment outcome in HIV/HCV: *PegIFN and Ribavirin*

	ACTG5071	APRICOT	RIBAVIC	Laguno	PRESCO
n with PEG-IFN-α2a + RBV	66	289	205	52	389
Type PEG-IFN-α	2a	2a	2b	2b	2a
Patients with IVDA	-	62%	80%	75%	90%
Patients with cirrhosis	11%	15%	39% (F3-F4)	19%	28% (F3-F4)
Genotype 1-4	77%	67%	61%	63%	61%
normal ALT	34%	0	16%	0	0
mean $CD4^+$	495	520	477	570	546
on HAART*	85%	83%	83%	94%	74%
Therapy discont. (AE or L)	12%	25%	17%*	17%	8%
EOT (ITT)	41%	49%	35%	52%	67%
SVR (ITT)	27%	40%	27%	44%	50%

Chung et al. NEJM 2004, Torriani et al. NEJM 2004, Alvarez et al. CROI 2005, Abstract 927

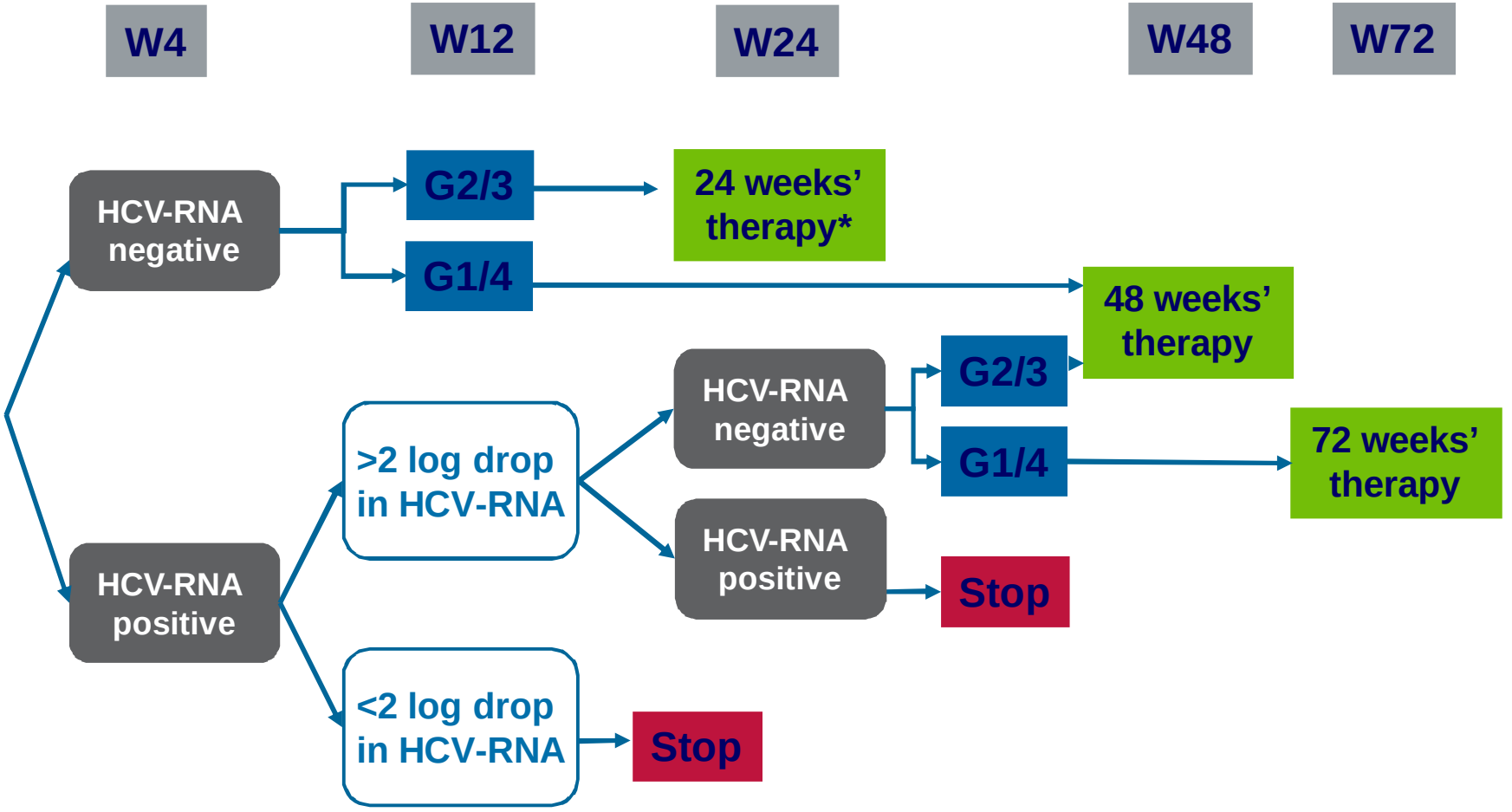
Carrat et al. JAMA 2004, Laguno et al. AIDS 2004, Nunez et al. AIDS Res Hum Retroviruses 2007

Current and cumulative exposure to anti-HCV treatment



Mocroft A et al. EACS 2009

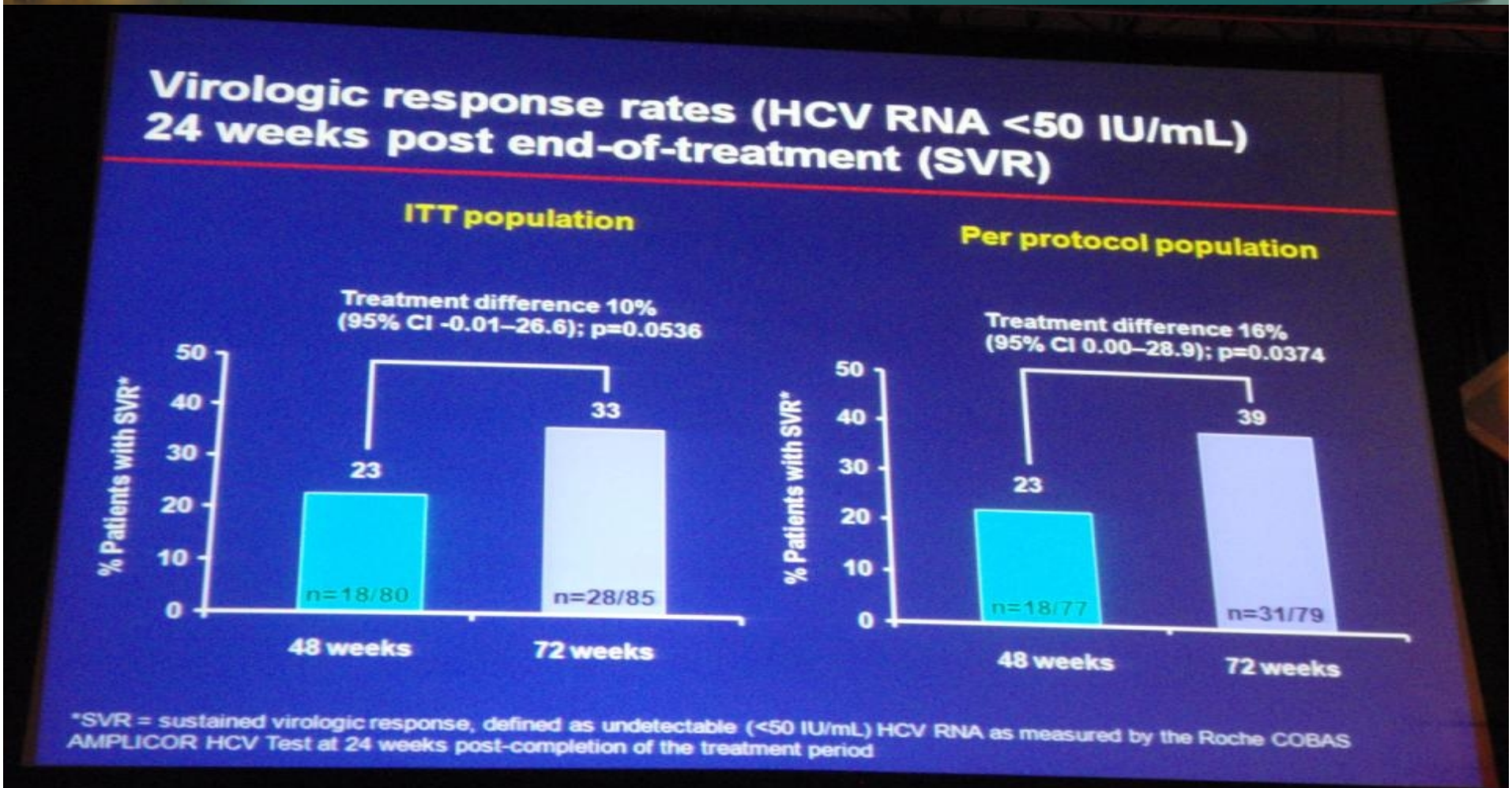
Proposed optimal duration of HCV therapy in HCV/HIV co-infected patients



*In patients with baseline low viral load and minimal liver fibrosis. W, week; neg, negative; pos, positive; G, genotype.

Rockstroh HIV Medicine 2008; update EACS Conference in Cologne November 2009

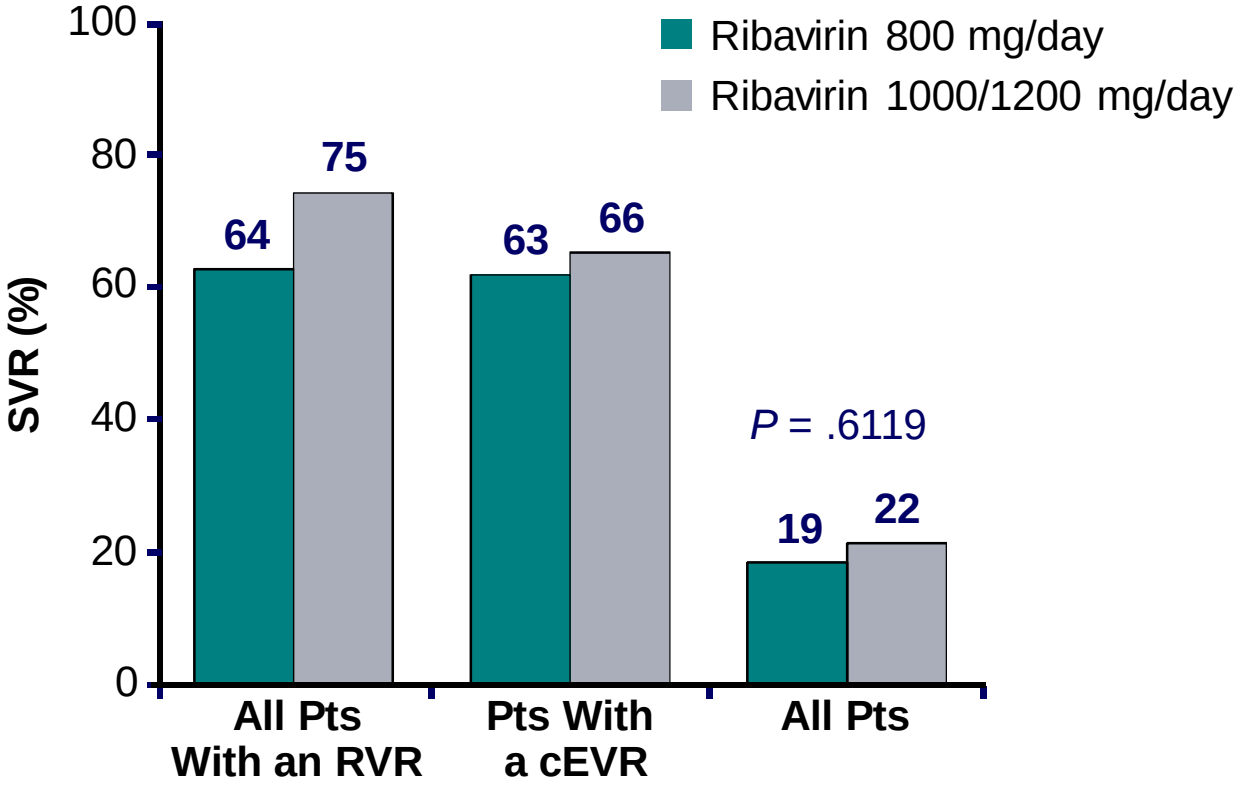
HCV Treatment Duration in HIV/HCV GT 1 coinfected patients. A randomized trial



Barone AA et al. AASLD 2010;#83

PARADIGM: 800 vs 1000/1200 mg RBV Plus PegIFN in HCV/HIV-Coinfected Pts

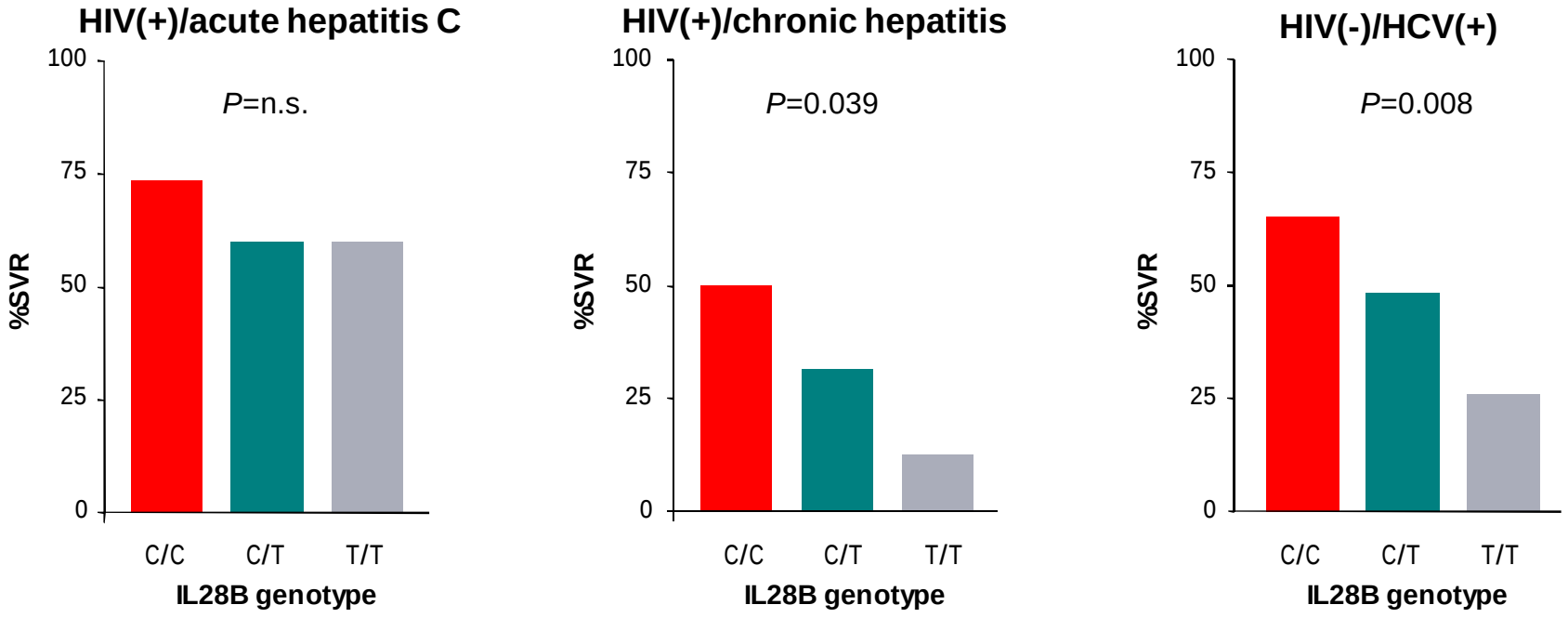
- **Double-blind, multicenter phase IV study of G1, treatment-naive pts**



Rodriguez-Torres M, et al. AASLD 2009. Abstract 1561: see also poster 296 at 43rd EASL in Vienna

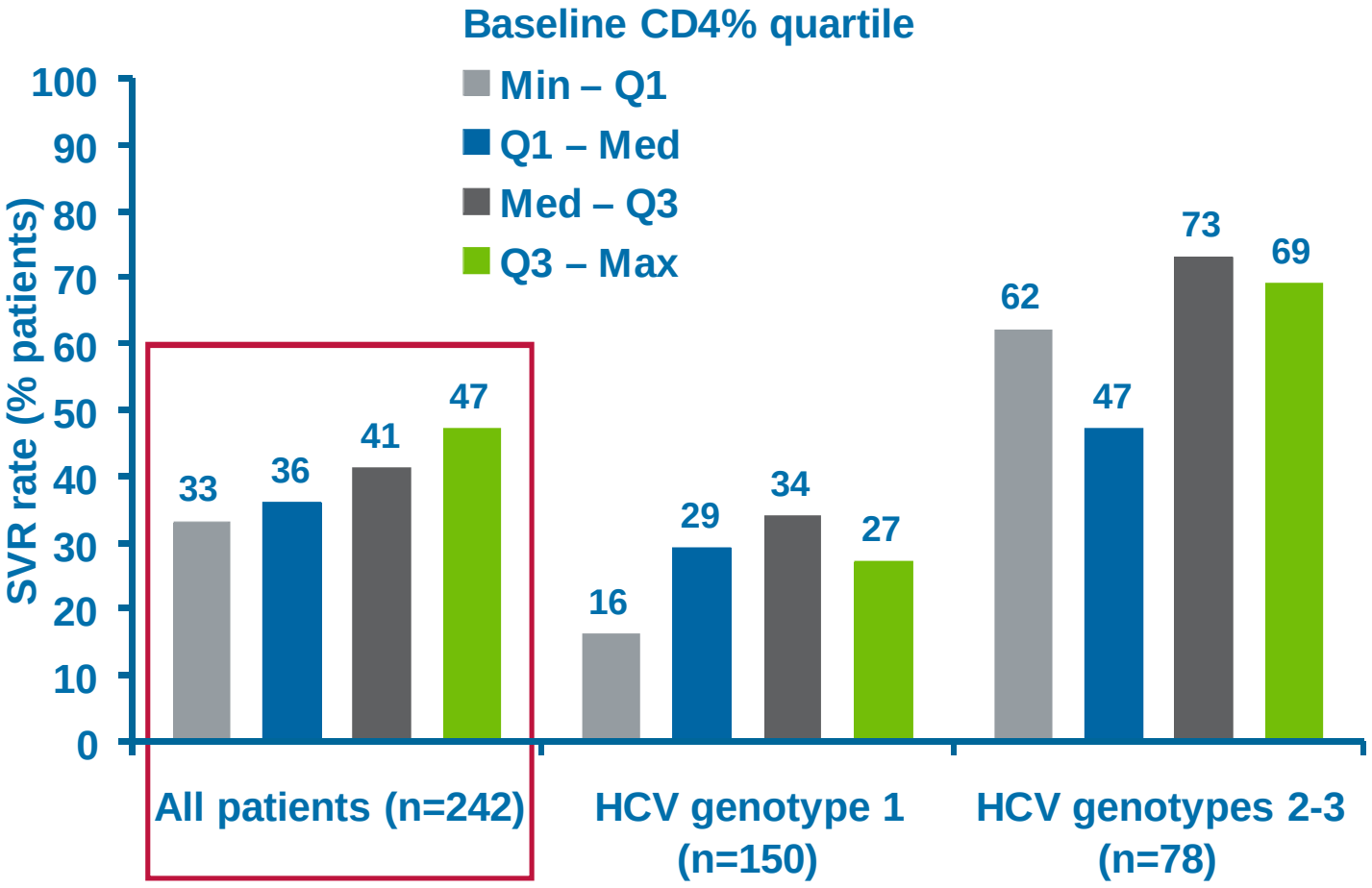
IL-28B Genotypes and SVR Rates

- Recent studies demonstrate polymorphisms near interleukin 28 B (IL28B) gen predict sustained virological response (SVR) to treatment with Peg-IFN + RBV
  in HCV-monoinfected pts harboring genotype 1
- Study assessing potential role of theIL-28B treatment induced clearance of rs12979860 polymorphism in acute and chronic hepatitis C in HIV-positive patients



Natterman J, et al. . 17th CROI; San Francisco, CA; February 16-19, 2010. Abst. 164; JID 2011 in press

Rate of SVR increases with higher CD4% at baseline: APRICOT



Opravil et al. J Acquir Immuno Defic Syndr 2008;47:36–49

Ribavirin in HIV/HCV co-infection

- **Dose-dependent haemolytic anaemia:**
  ↓ mean 2.5–3 g/dL Hb <4 weeks
- **Drug–drug interactions**
  - Anti-HIV antagonism with pyrimidine nucleoside analogues:
    AZT, D4T, ddC (*in vitro*)[1,2]
    - Inhibits intracellular phosphorylation
  - Increased intracellular levels of DDI metabolites (in vitro); increased risk for lactic acidosis
  - Recent data suggest decreased SVR under abacavir treatment; but abacavir-treated patients had more fibrosis at baseline and were more HAART experienced[3–5]

1. Vogt MW. Science 1987;235:1376; 2. Baba AAC 1987;31:1613; 3. Margt NA and Miller MD, 2nd IAS Conference on HIV Pathogenesis and Treatment, Paris 2003; P980; 4. RIBAVIC Subanalyses CROI 2007; 5. CROI 2008

Effect of accompanying antiretroviral drugs on virological response to HCV combination therapy

Study objective:

- §Retrospective analysis of 2 cohorts of HIV/HCV-coinfected patients initiating PEG-IFN and RBV between January 2001 and June 2007 at 45 centers in Spain (GESIDA 3603 and GESIDA 5006).

Results:

- §A total of 1701 patients were included, 63% were infected by genotype (G) 1-4, 88% were taking HAART

NRTI Backbone	N	AOR	95%CI	*P*
TDF+3TC/FTC	380	Reference	-	-
3TC+D4T	264	0.90	0.61-1.32	0.588
AZT+3TC	242	0.63	0.42-.94	0.023
AZT+3TC+ABC	147	0.69	0.43-1.12	0.131
3TC+ABC	115	0.72	0.43-1.21	0.213
DDI+D4T	47	0.54	0.23-1.26	0.153
DDI+3TC/FTC	36	0.59	0.23-1.52	0.273

Conclusions: With the exception of regimens including AZT, the effect of other NRTI backbones had no significant effect on SVR. Abacavir in particular was not found to negatively impact the outcome of HCV combination therapy even in difficult-to-treat patients such as genotypes 1 or 4 and high baseline HCV viral loads1

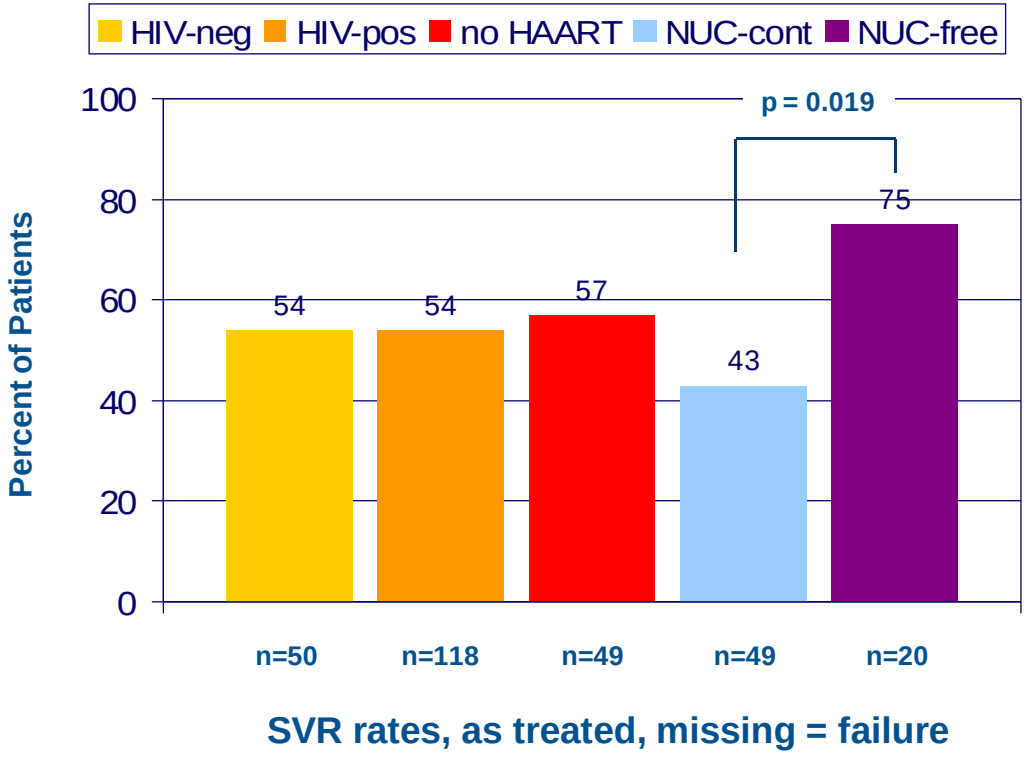
Berenguer J et al. 17th CROI 2010;#663

NUC free HAART may improve SVR

multicenter study Germany

Prospective study on 50 HIV- and 118 HIV+ patients with chronic HCV

- HIV+ patients were without HAART (n=49) or on HAART (n=69)
- Patients on HAART randomized to NUC-free (n=20) or NUC-cont. (n=49)
- HIV- and HIV+ patients reached comparable SVR-rates
- Significantly more patients reached SVR among NUC-free compared to NUC containing

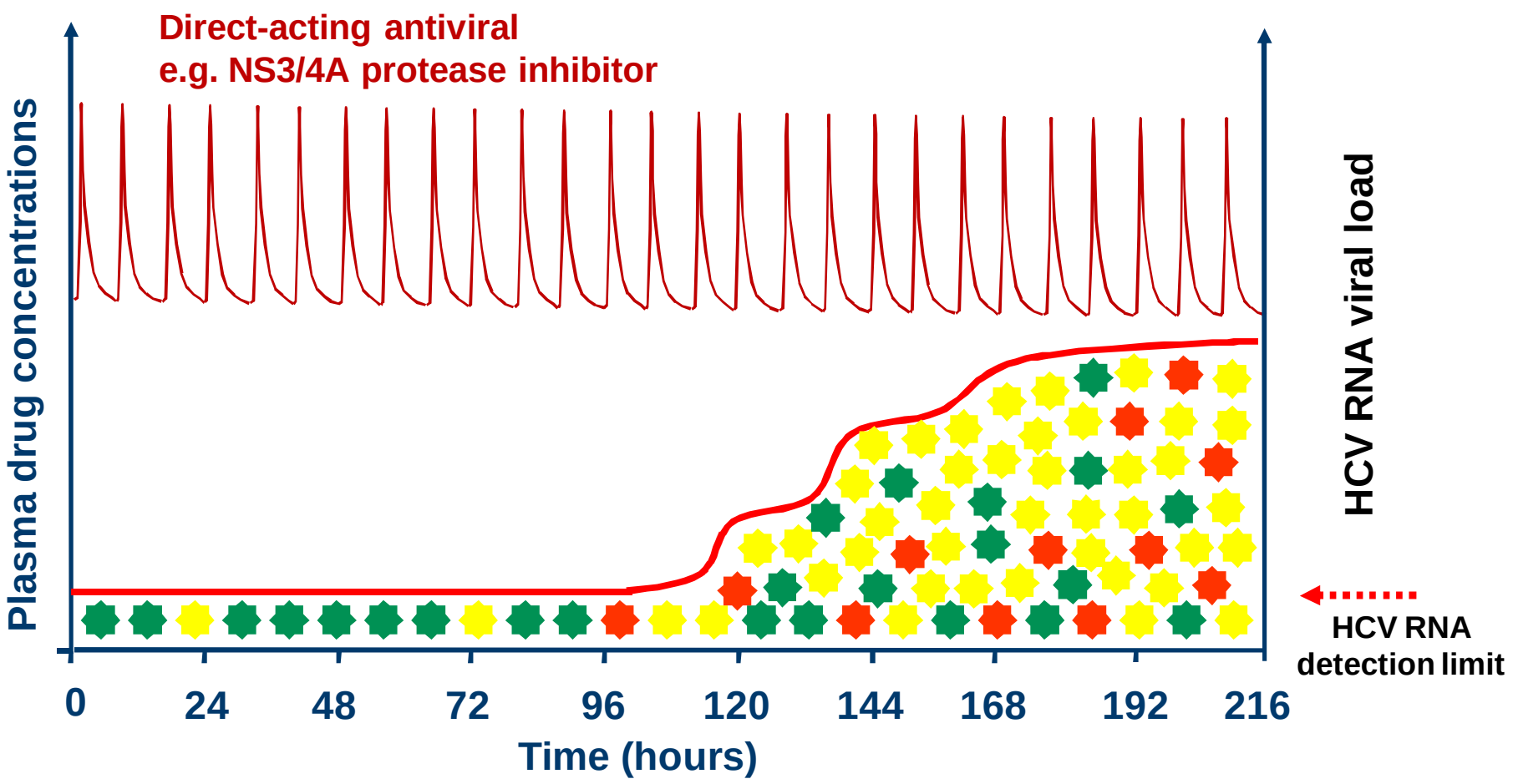


Vogel et al. *Eur J Med Research 2010*

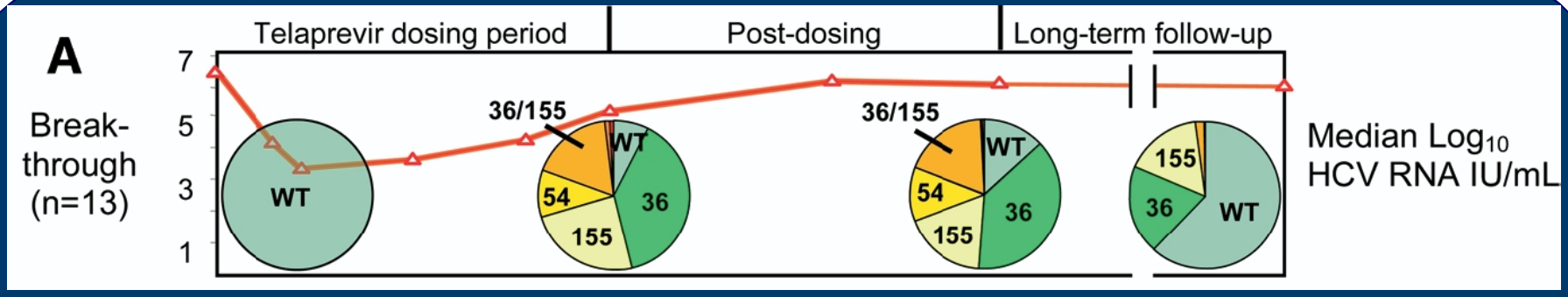
New HCV agents on the horizon: What are the possible challenges?

- Higher HCV viral loads in HIV/HCV coinfection
  - Lower probability of EVR
  - Higher risk for resistance development
- Drug-drug interactions between HCV drugs and the new oral HCV agents
- Overlapping drug toxicities

When overall antiviral activity of a regimen is inadequate, pre-existing or new mutations may be selected



Proof of concept: telaprevir monotherapy is associated with rapid selection of resistant variants among patients with viral breakthrough

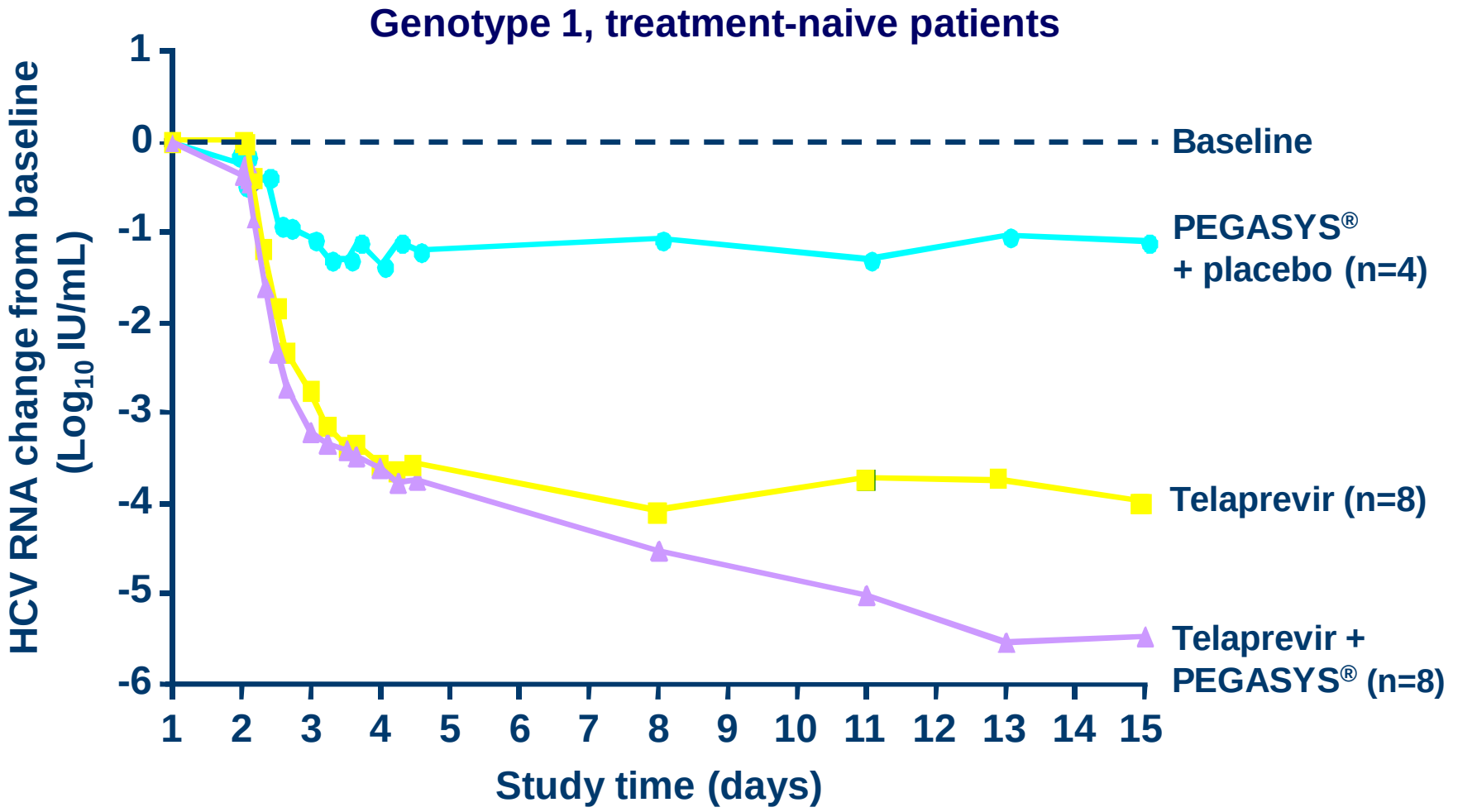


Baseline	EOD 14 days	7–10 days post-dosing	3–7 months post-dosing

IC_{50} fold change	WT	V36M/A	R155K/T	T54A	36/155	A156V/T	36/156
	1	3.5	9	12	71	466	781

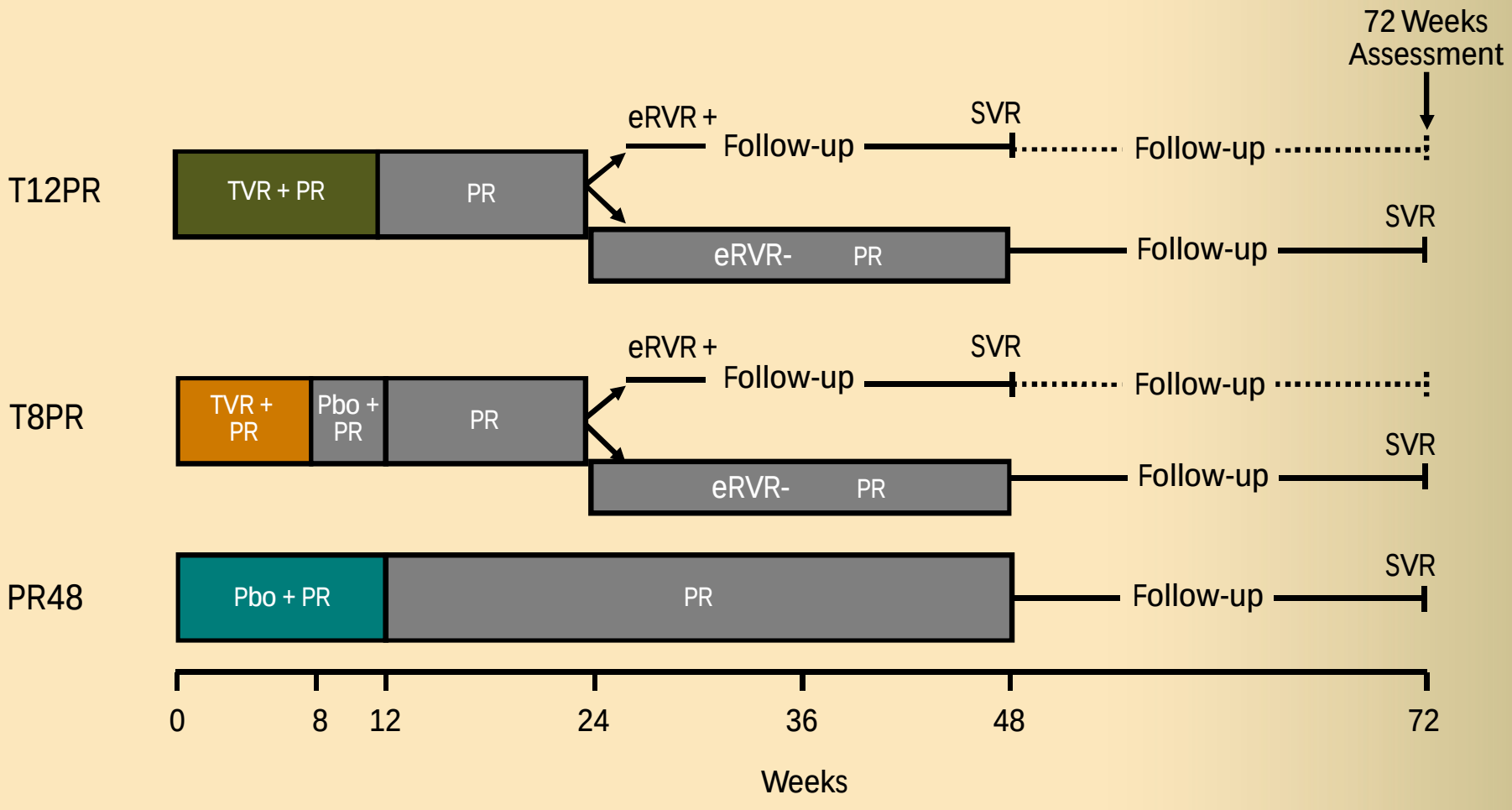
Sarrazin et al. Gastroenterology 2007; 132: 1767

Synergistic reductions in HCV RNA with telaprevir plus PEG-IFN alfa-2a (40KD)



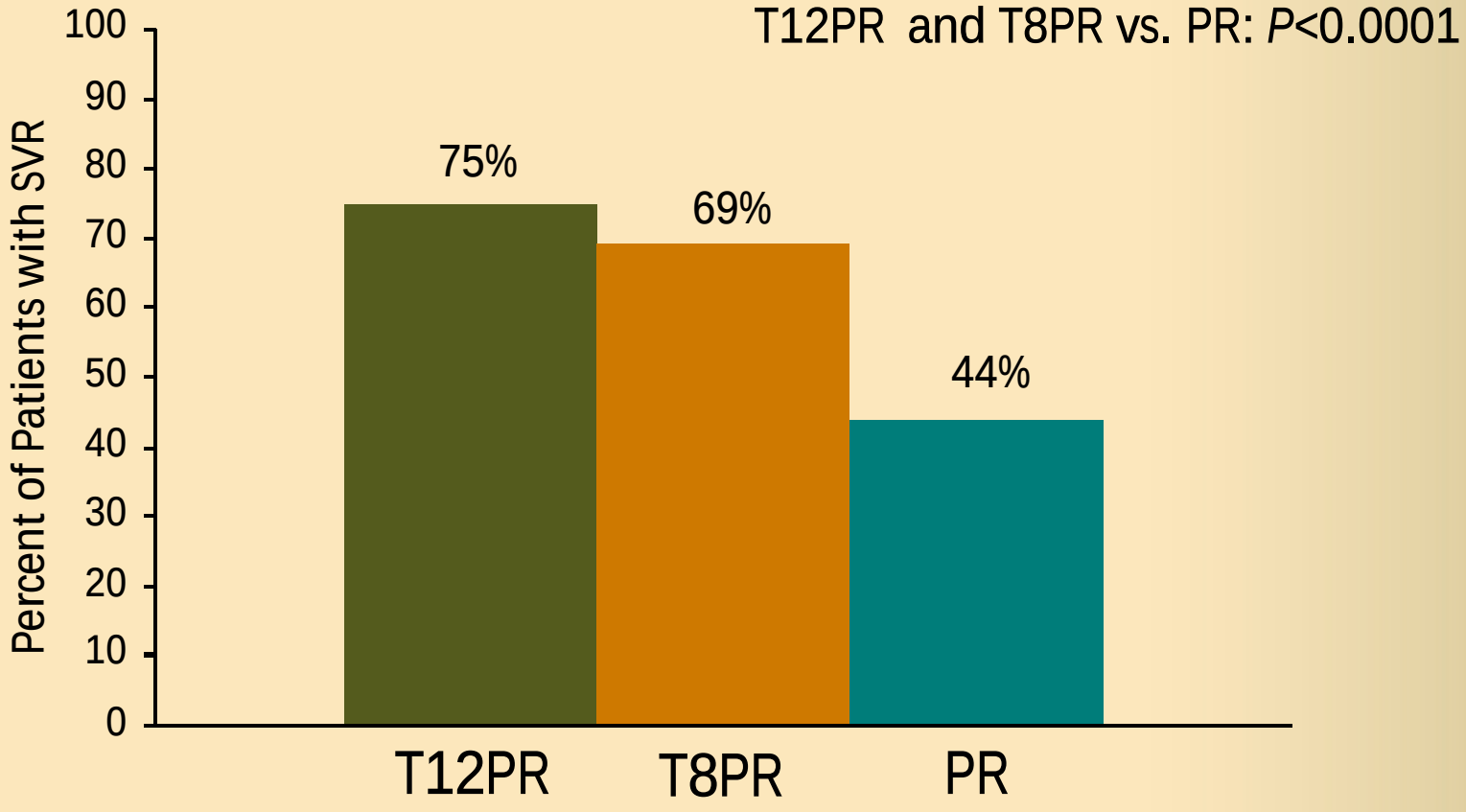
Kieffer TL, et al. Hepatol 2007; 46: 631

ADVANCE: Telaprevir + PegIFN/RBV in Genotype 1 HCV Treatment-Naïve Patients



Jacobson IM, et al. 61st AASLD; Boston, MA; October 29-November 2, 2010; Abst. 211.

ADVANCE: Overall SVR Rates



Jacobson IM, et al. 61st AASLD; Boston, MA; October 29-November 2, 2010; Abst. 211.

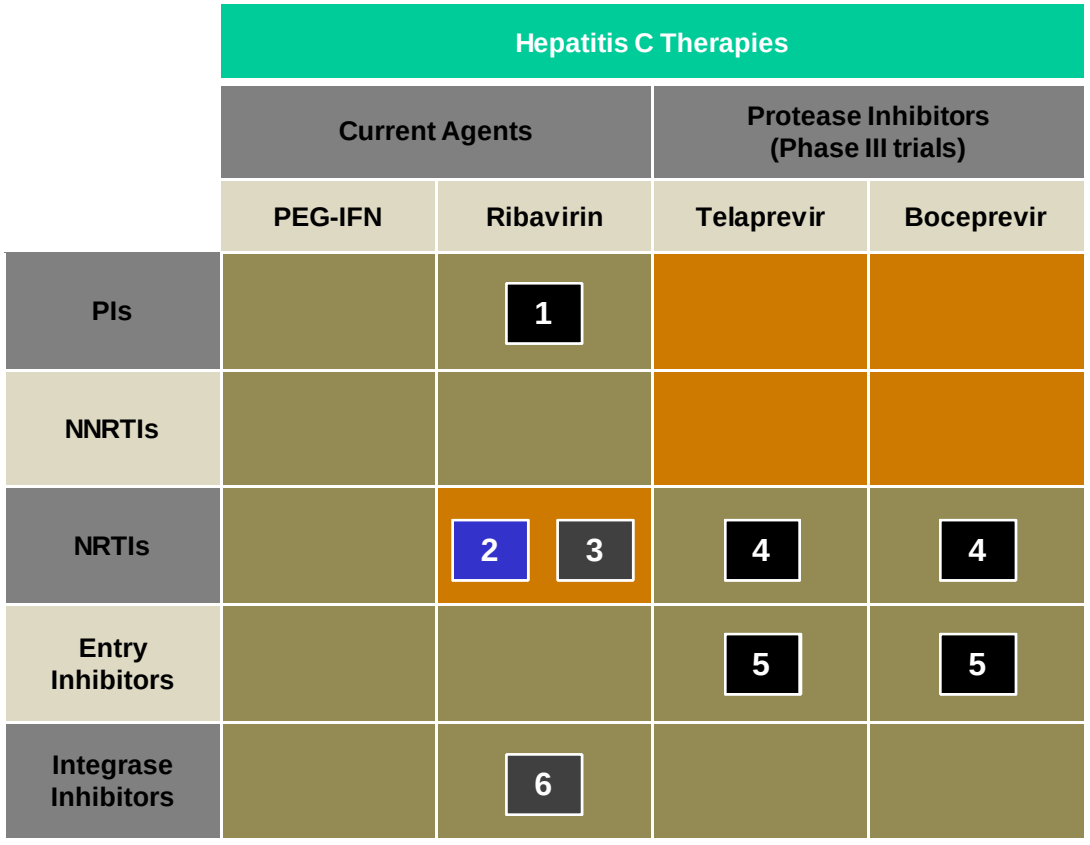
HCV protease inhibitors:AEs

- **Telaprevir (q8h)**
  - Severe rash, 7%
  - Anemia ~ 1 g/dL additional
  - GI (nausea, rectal burning)
- **Boceprevir (TID)**
  - No rash
  - Anemia ~ 50% required EPO
  - Dysguesia ~ 25%

Kwo P. 43rd EASL Milan 2008 Abstract 995; McHutchison J, et al. EASL 2008. Abstract 4; Dusheiko G, et al. EASL 2008. Abstract 58

Drug-Drug-Interactions (DDIs)

Known and anticipated DDIs between antiretrovirals and anti-HCV drugs in current use and the HCV protease inhibitors in Phase III development



No clinically significant interaction, or interaction unlikely based on knowledge of drug metabolism

Potential interaction that may require close dose monitoring, alteration of dosage or timing of administration

Interaction likely, do not use or use with caution

1 = atazanavir/ritonavir

2 = didanosine, zidovudine

3 = emtricitabine, lamivudine, tenofovir

4 = zidovudine

5 = maraviroc

6 = raltegravir

Adapted from Seden K, et al. J Antimicrob Chemother 2010; 65:1079-85; Ashby J, et al. HIV 10; Glasgow; November 7-11, 2010; Abst. O315.

Summary

- HCV/HIV coinfected patients show a faster progression to cirrhosis and increased liver-related mortality
- Hepatitis C specific treatment options should be considered before onset of immunodeficiency in HIV-coinfected patients
- Ribavirin dose and length of therapy may matter
- HAART should not be withheld in coinfected patients and needs to be adapted to concomitant HCV therapy
- The use of the new oral HCV drugs reveals some additional challenges and warrants multiple drug-drug interaction studies