HCV and HBV co-infections

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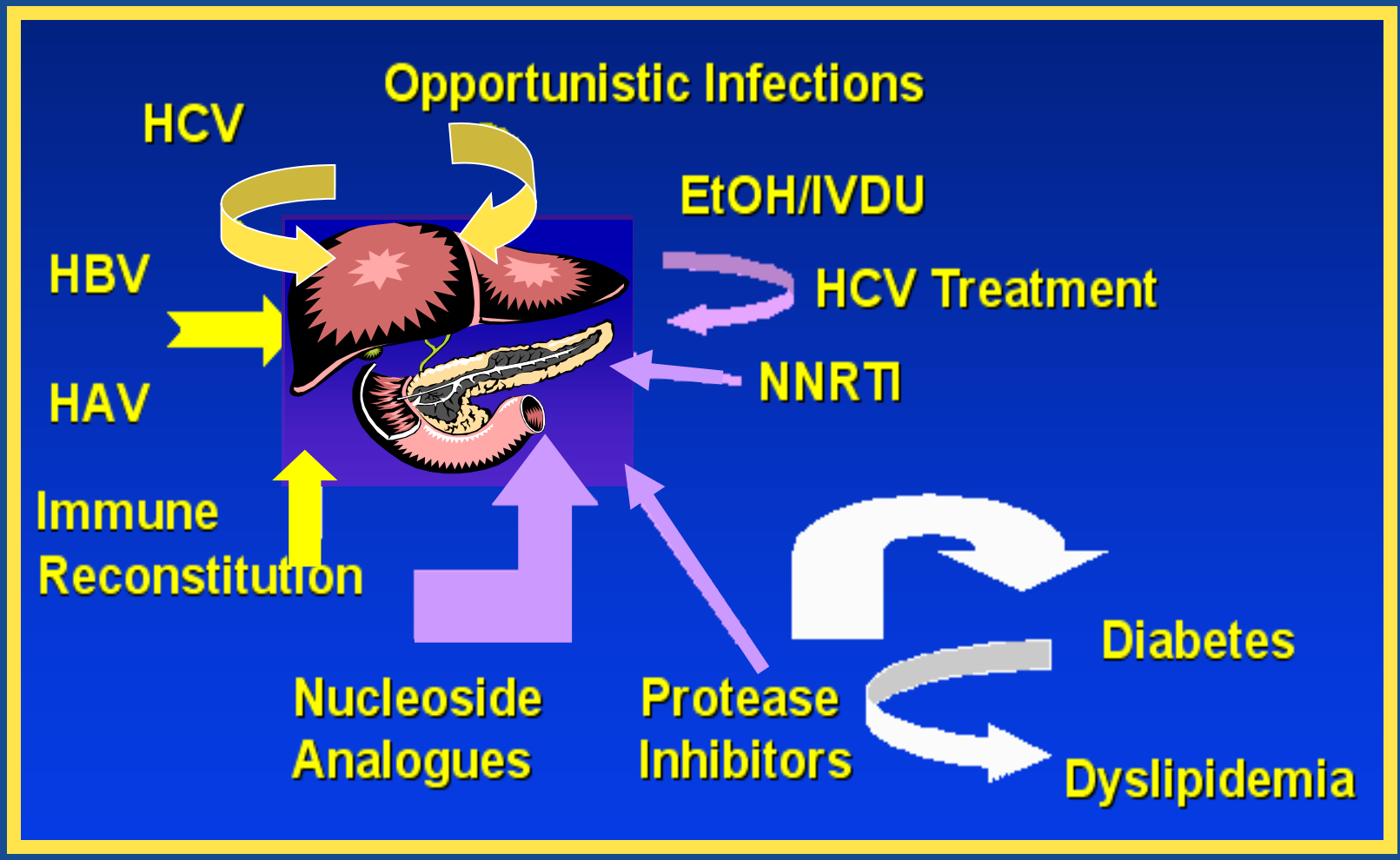
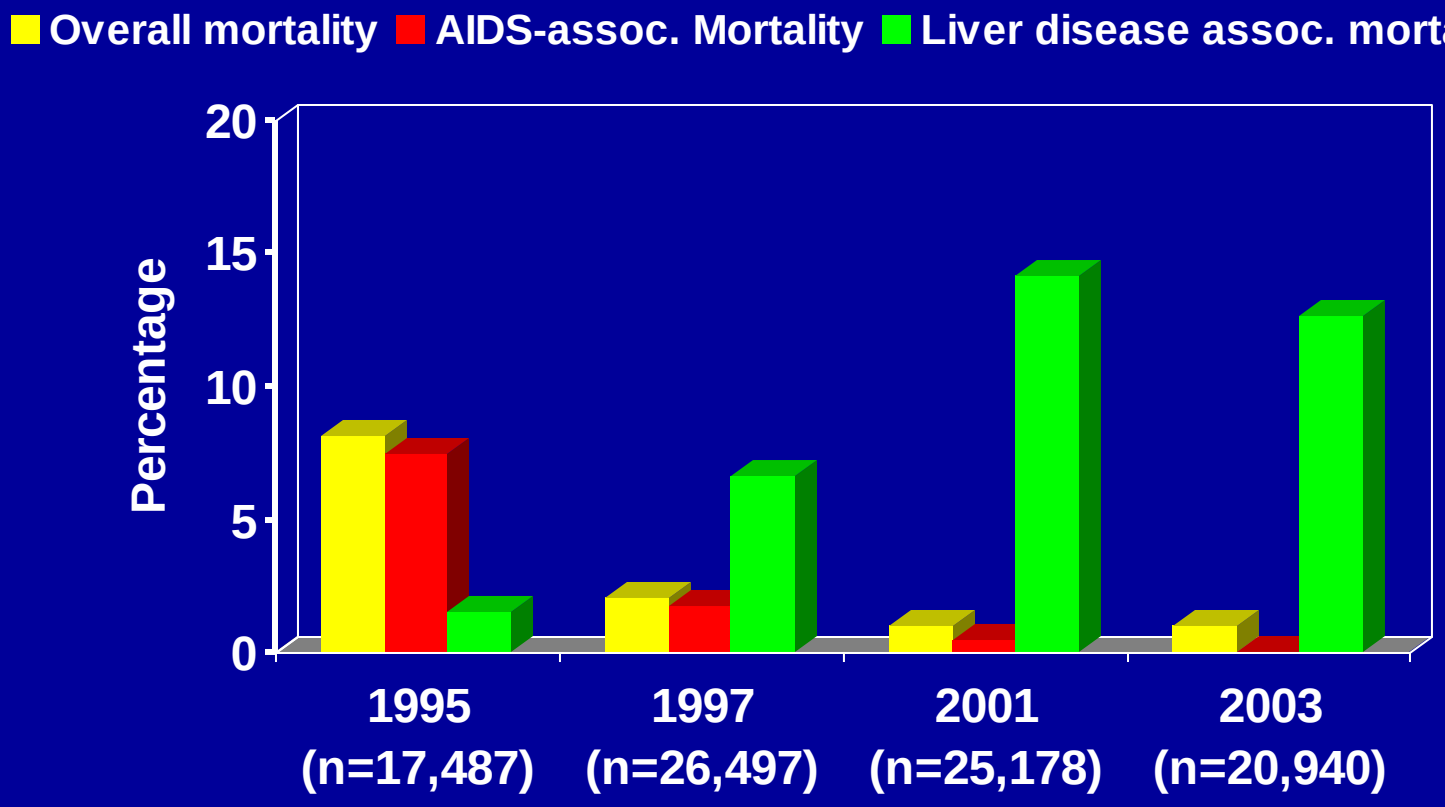
EACS Advanced Course 2008


Inatoa madoa doa yote!!
BEFORE
AFTER
NOVO
OMO
PROGRESS
FLASH

Causes of Liver Disease in HIV Infection

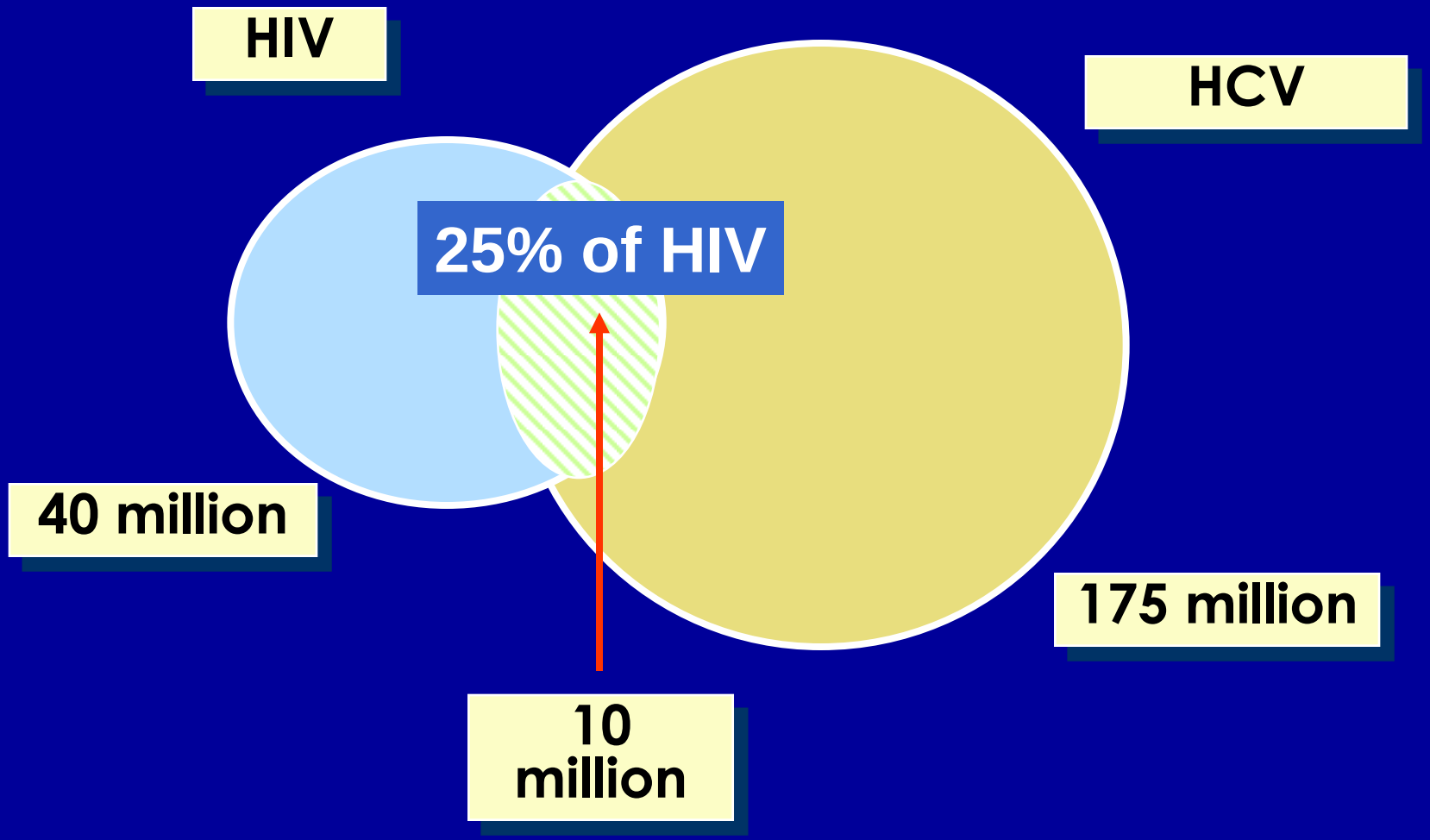


Mortality of HIV-infected patients in France
(GERMIVIC Study Group)



Rosenthal et al. *AASLD* 2004; Abstract 572.

Overlapping HCV & HIV Epidemics



Reports of acute HCV in HIV+ MSM across Europe

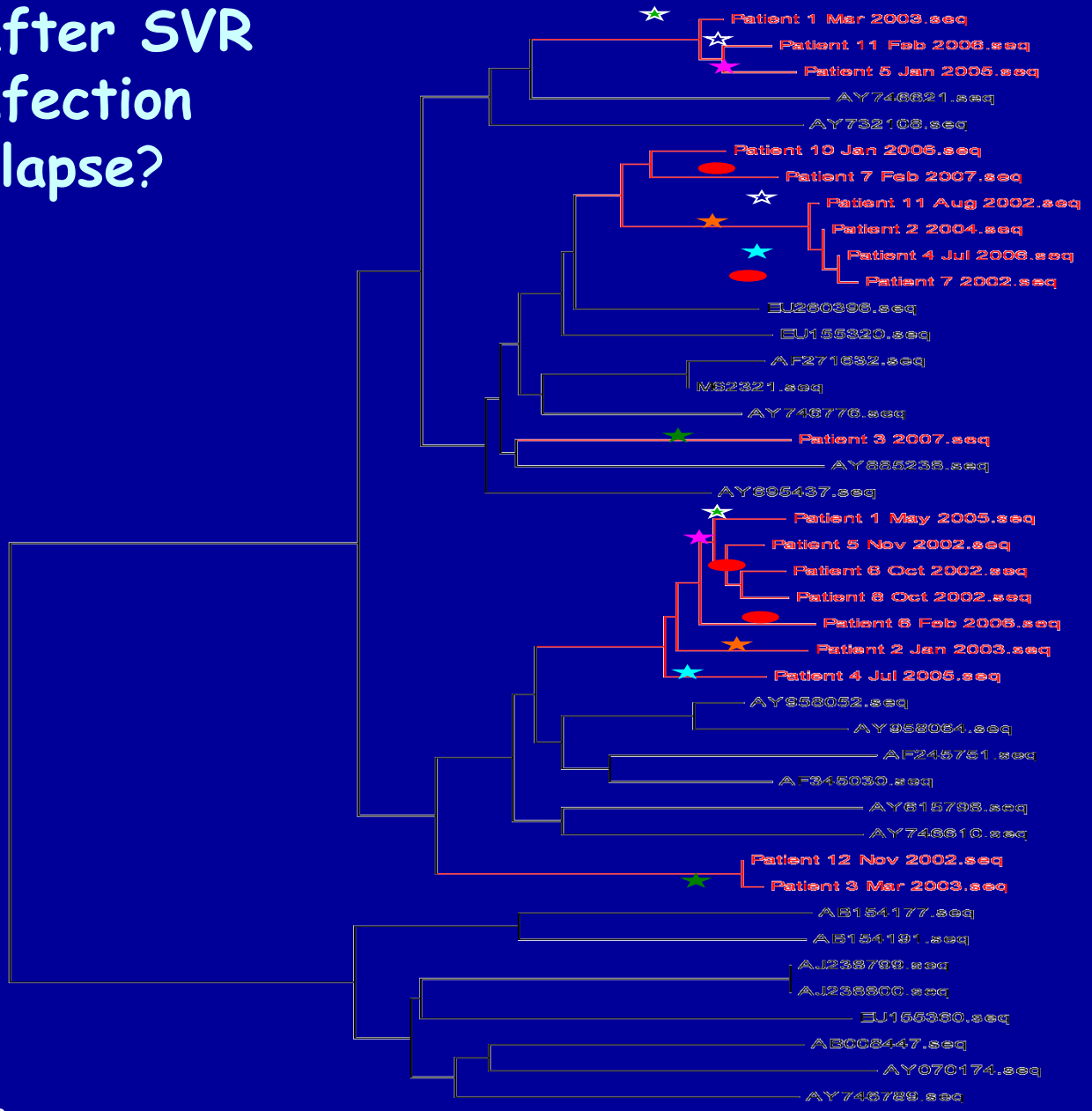
Danta et al. AIDS 2007; 21: 983-991. Gambotti et al. Euro Surveill 2005; 10: 115-117.
Ghosn et al. Sex Transm Infect 2006; 82: 458-460 ; 40: 41-46.
Serpaggi et al. AIDS 2006; 20: 233-240.Vogel M et al. J Viral Hepat 2005; 12: 207-211

Risk Factors for Acute HCV in MSM

Danta et al, AIDS 2007

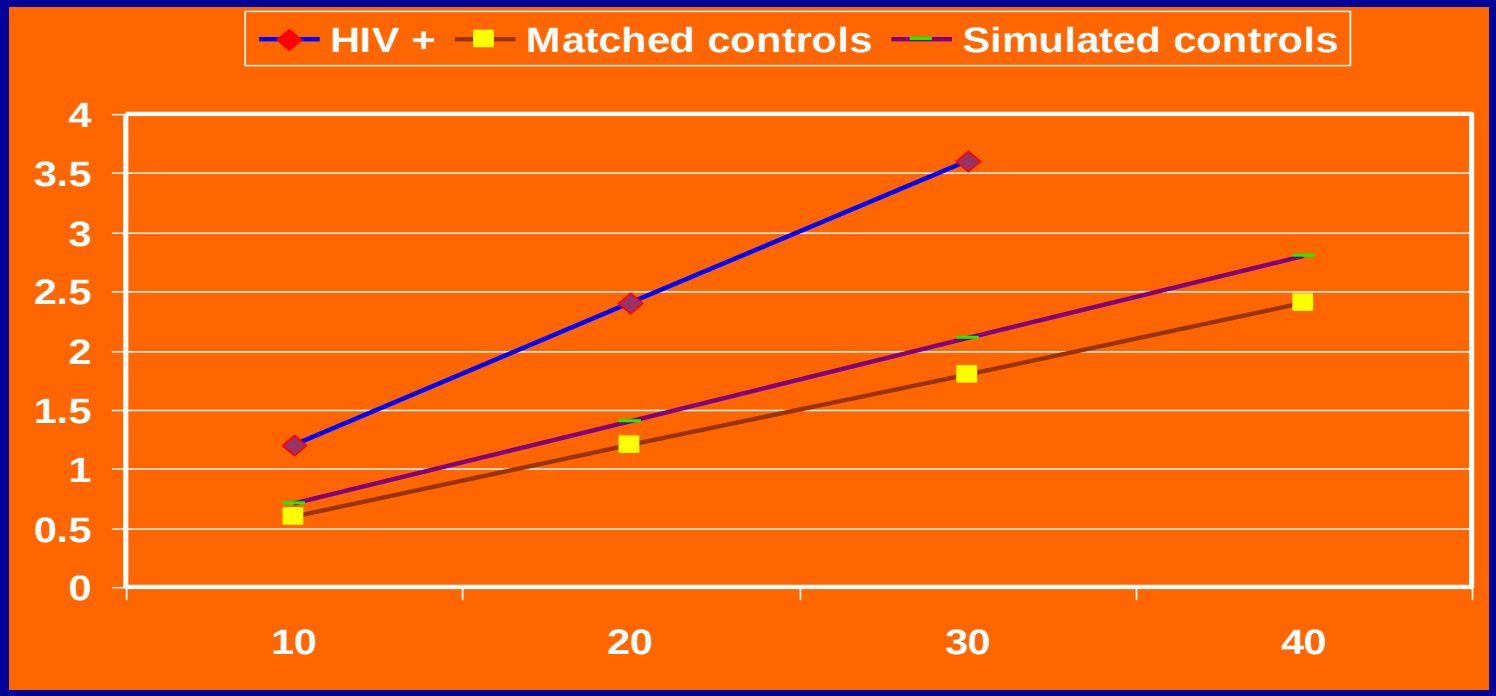
Is HCV Viraemia after SVR Following Initial Infection Re-infection or Relapse?

Phylogenetic Tree Constructed from Analysis of Paired Samples (red) Compared with Genebank Samples (black)



Jones et al. CROI 2008;Oral Abstract 64LB.

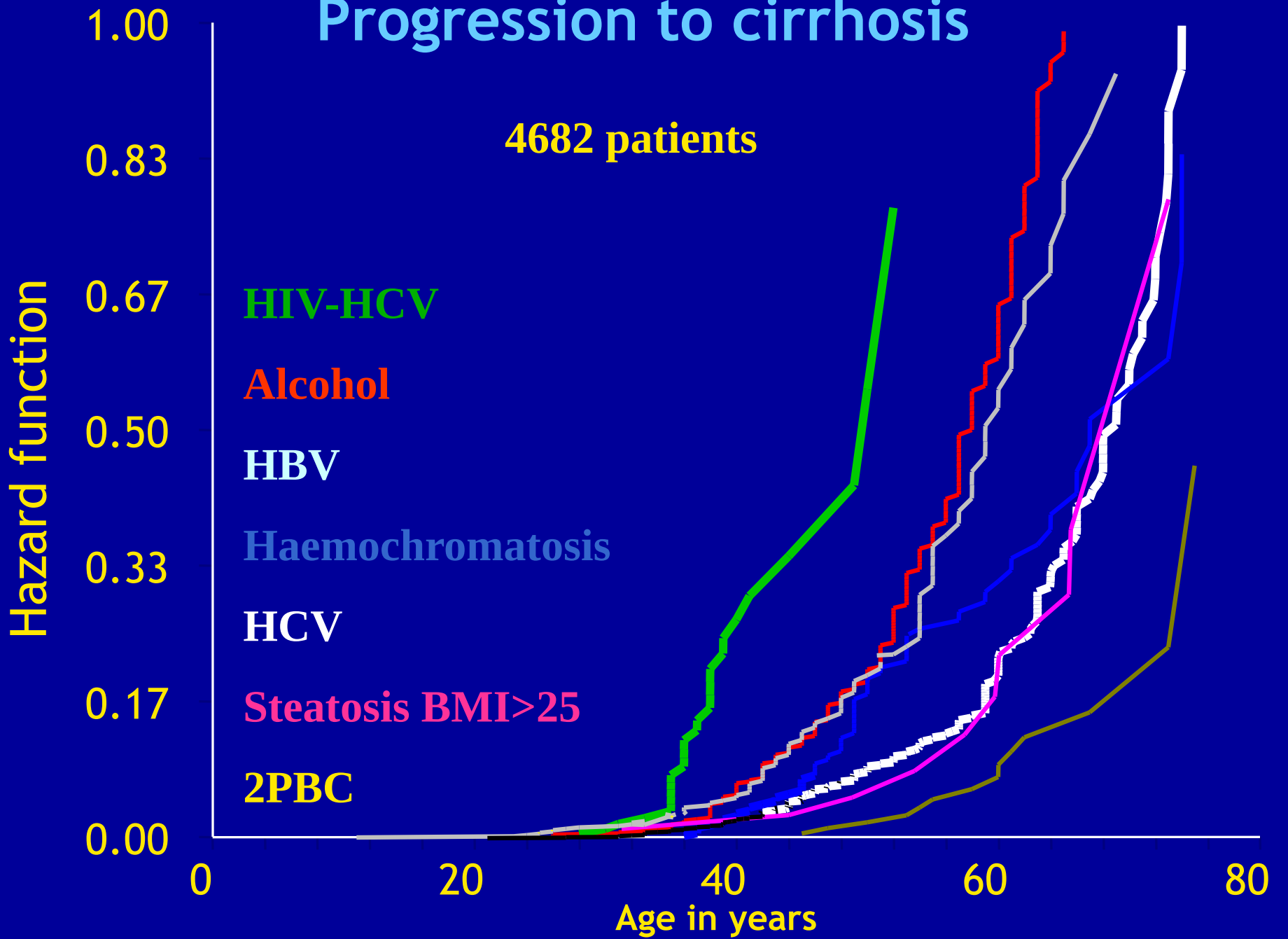
Effect of HIV/HCV co-infection on hepatic fibrosis progression (Benhamou et al 1999)



Fibrosis progression influenced by

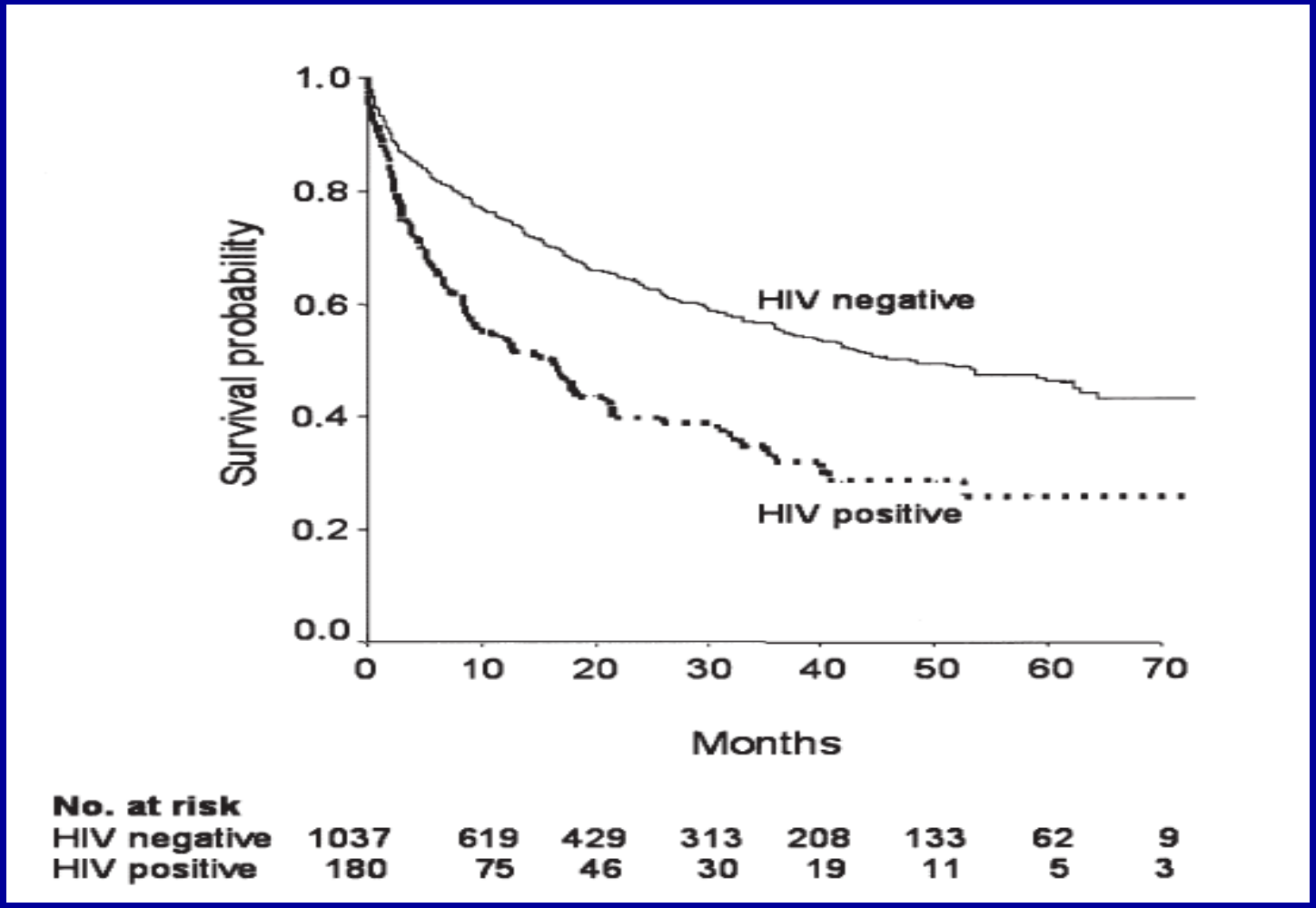
- CD4 cell count (< 200 cells/microlitre)
- Age at infection (> 25 years)
- Male sex
- Alcohol consumption (> 50g/d)

Progression to cirrhosis



Poynard, T. et al., (2003) A comparison of fibrosis progression in chronic liver disease. *Journal of Hepatology* 38:257-265

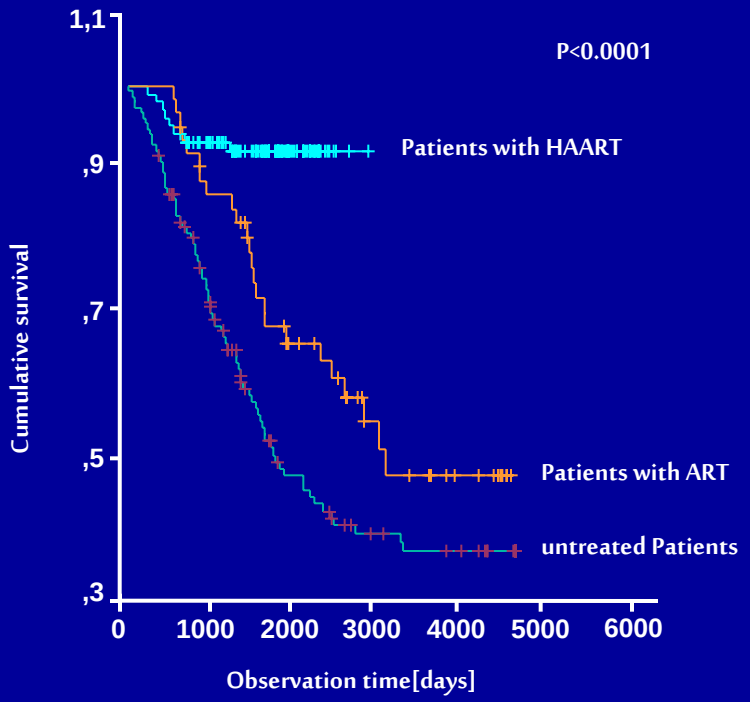
HIV/HCV - Cirrhosis and survival



Pineda et al. Hepatology 2005

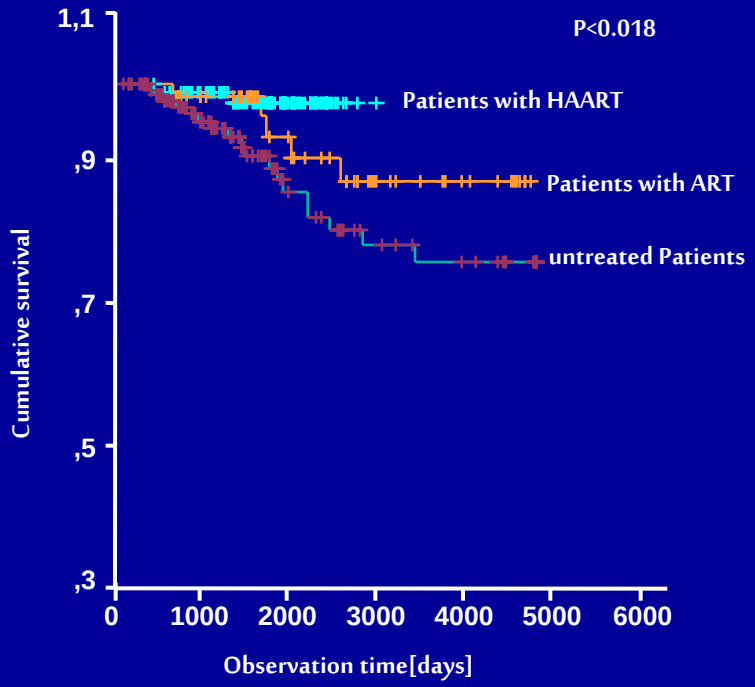
Overall and Liver-related Mortality - effect of HAART

A) Overall-Mortality



Patients under observation:						
HAART-group:	93	79	33	-	-	-
ART-group:	55	46	30	15	9	1
Untreated-group:	137	94	49	37	32	27

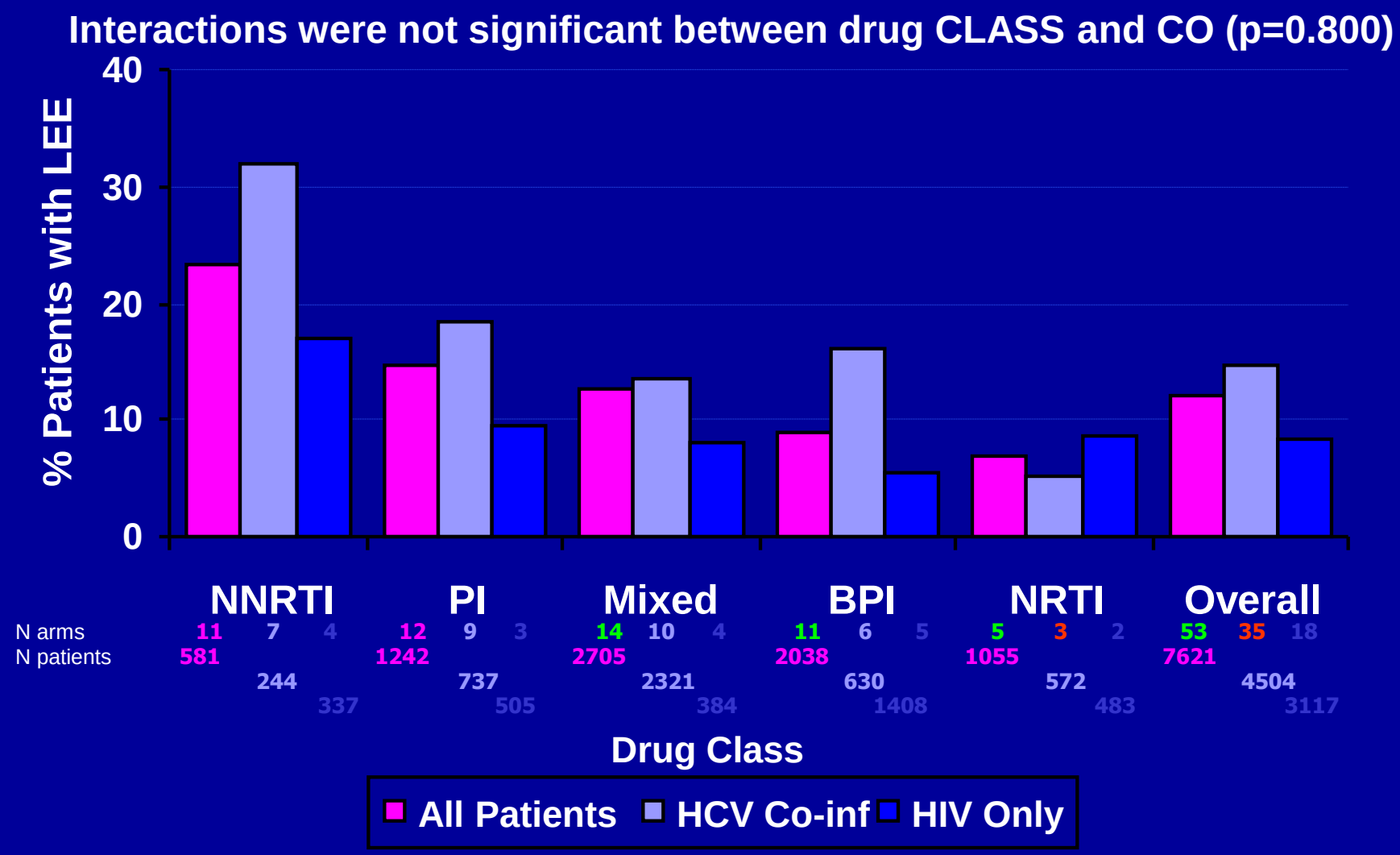
B) Liver-related-Mortality



Patients under observation:						
HAART-group:	93	79	33	-	-	-
ART-group:	55	46	30	15	9	1
Untreated-group:	137	94	49	37	32	27

Qurishi N *et al. Lancet,* 2004

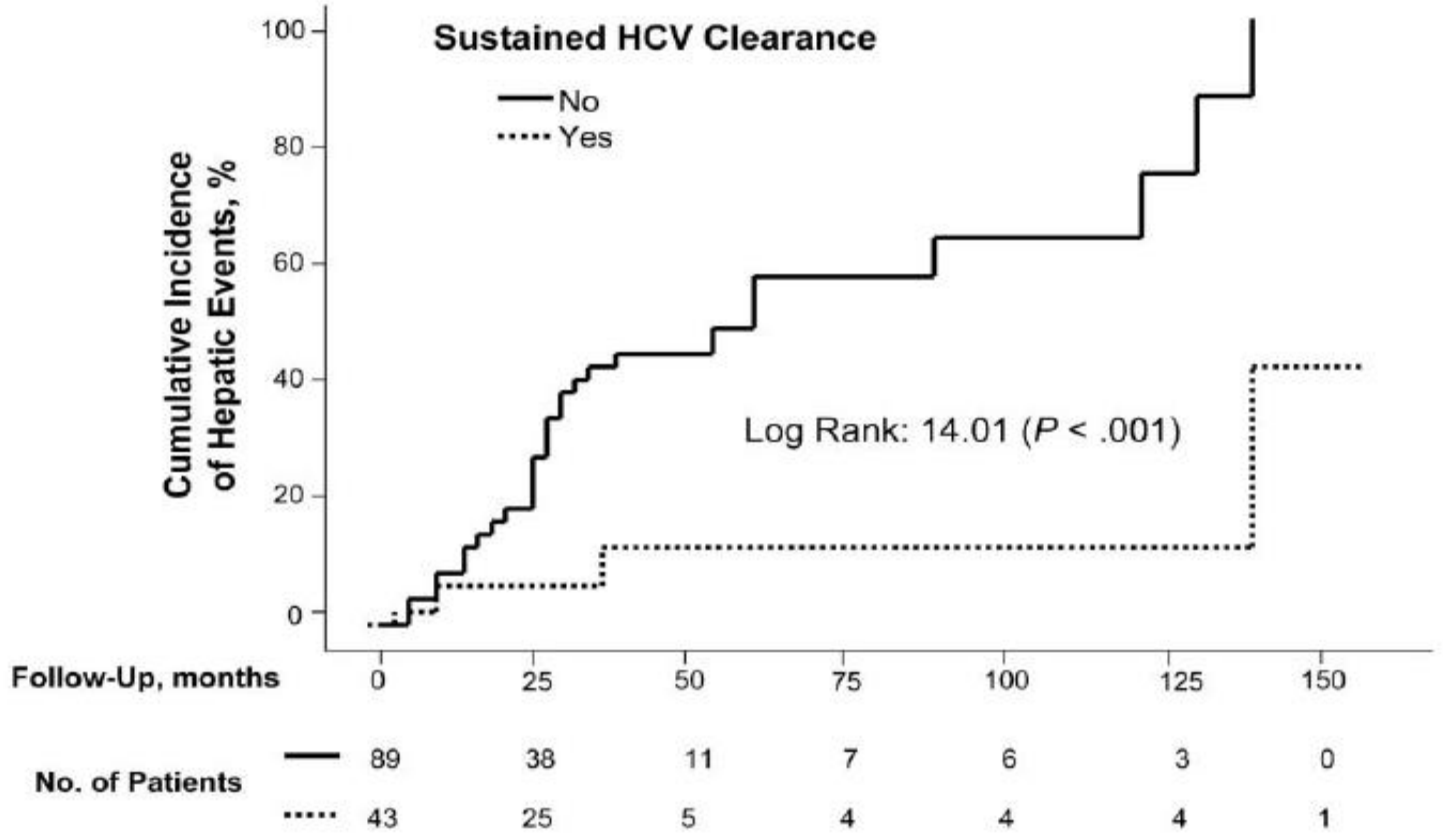
% LEE by co-infection status



1. Benhamou Y, Mats V, Walcak D. Systemic overview of HAART associated liver enzyme elevations in patients infected with HIV and co-infected with HCV. *CROI* 2006;#88

Hepatotoxicity of Antiretroviral Drugs Is Reduced after Successful Treatment of Chronic Hepatitis C in HIV-Infected Patients

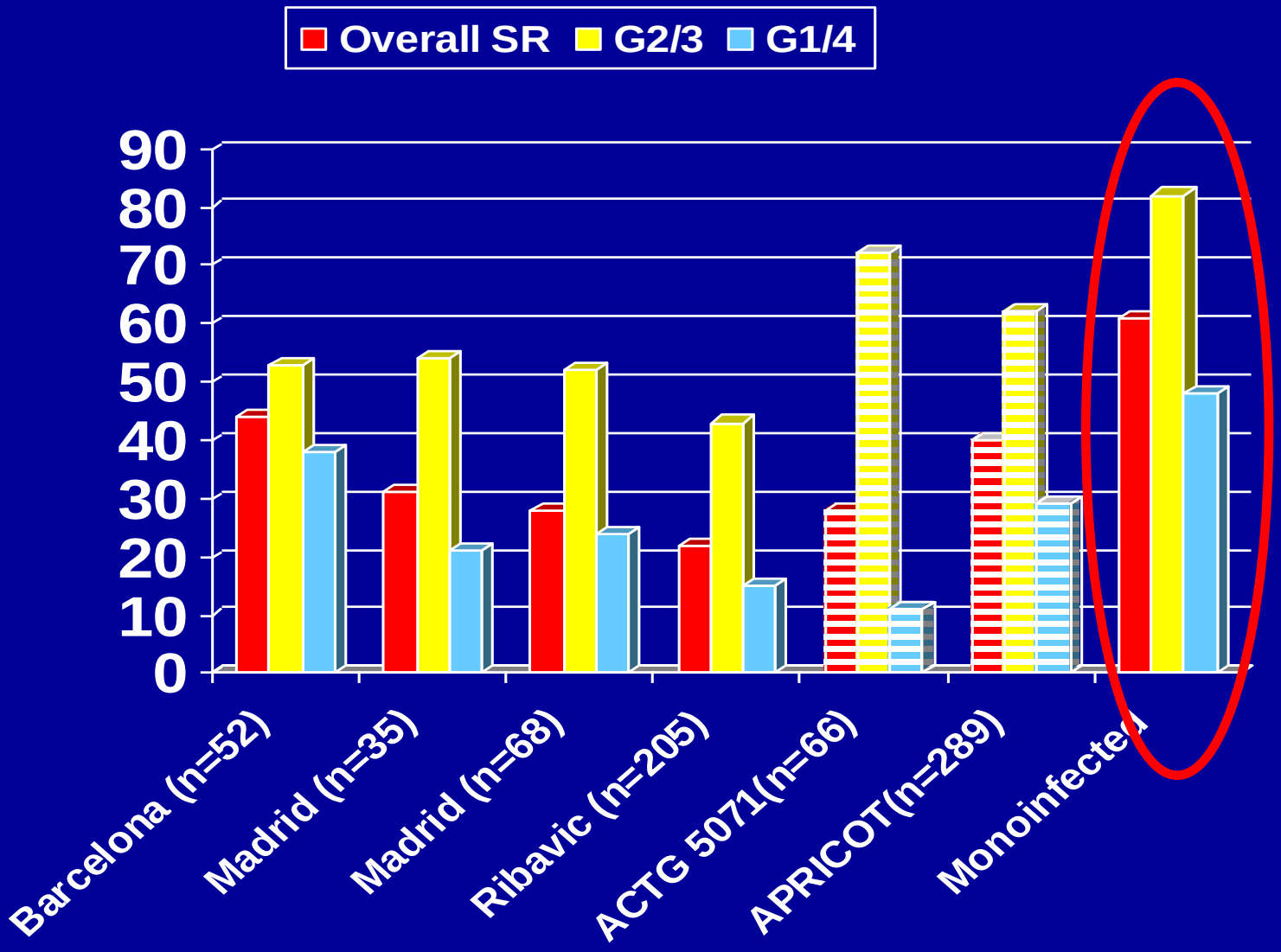
The Journal of Infectious Diseases 2007;196:670–6



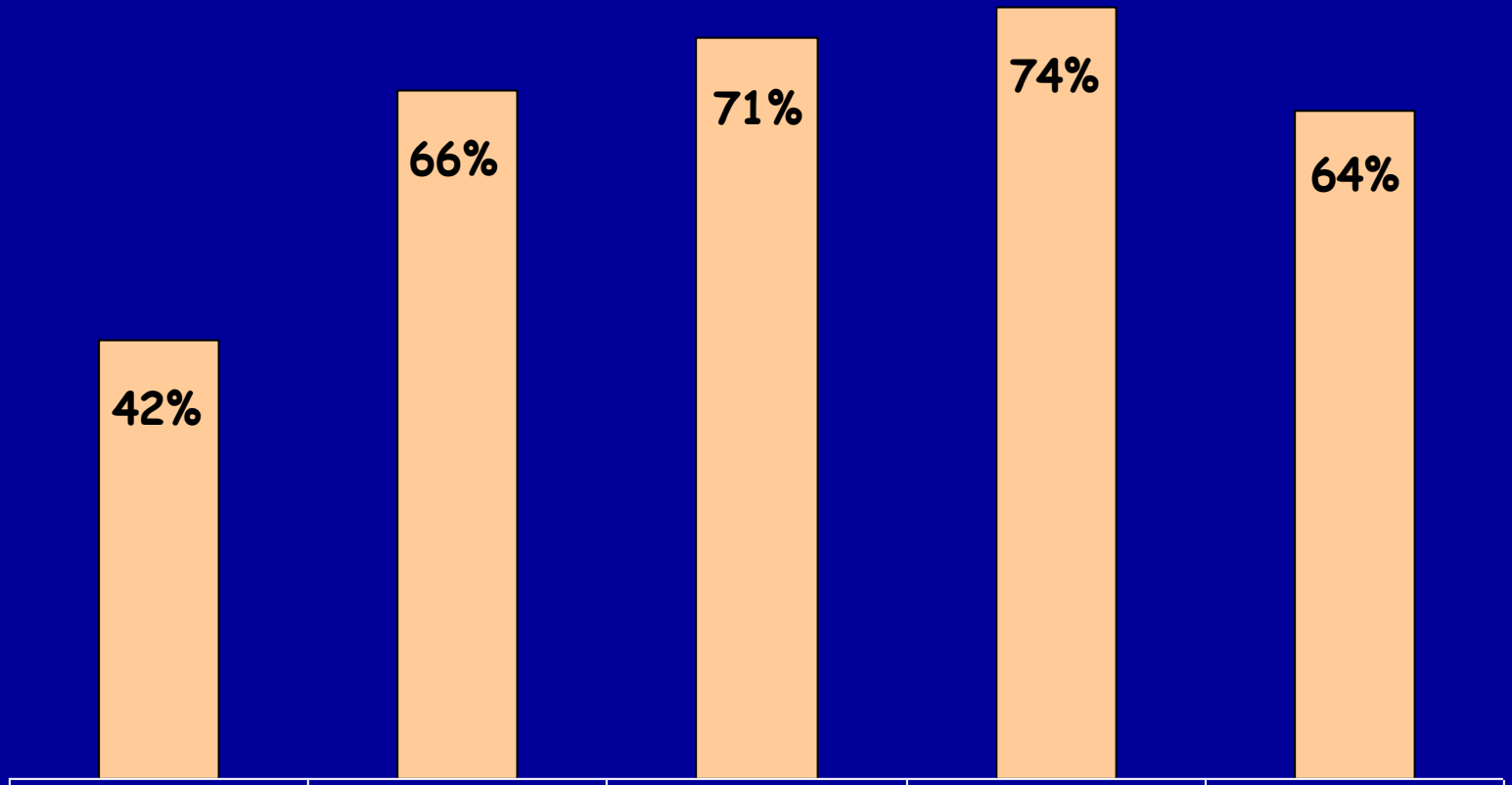
Treating HCV in HIV-infected patients

- HAART treated HIV patients live longer
- Faster progression to liver cirrhosis
- Increased mortality due to end stage liver disease
- Higher risk of hepatotoxicity following treatment with ART drugs
- Risk of hepatotoxicity reduced with successful HCV erradication

Response to PegIFN and Ribavirin in HIV/HCV co-infected patients



Acute HCV/HIV: Overall virological responses:



133 =	56	89	95	99	85

3rd Int HIV/Hepatitis co-infection meeting, Paris 2007

Predictors of response

Host

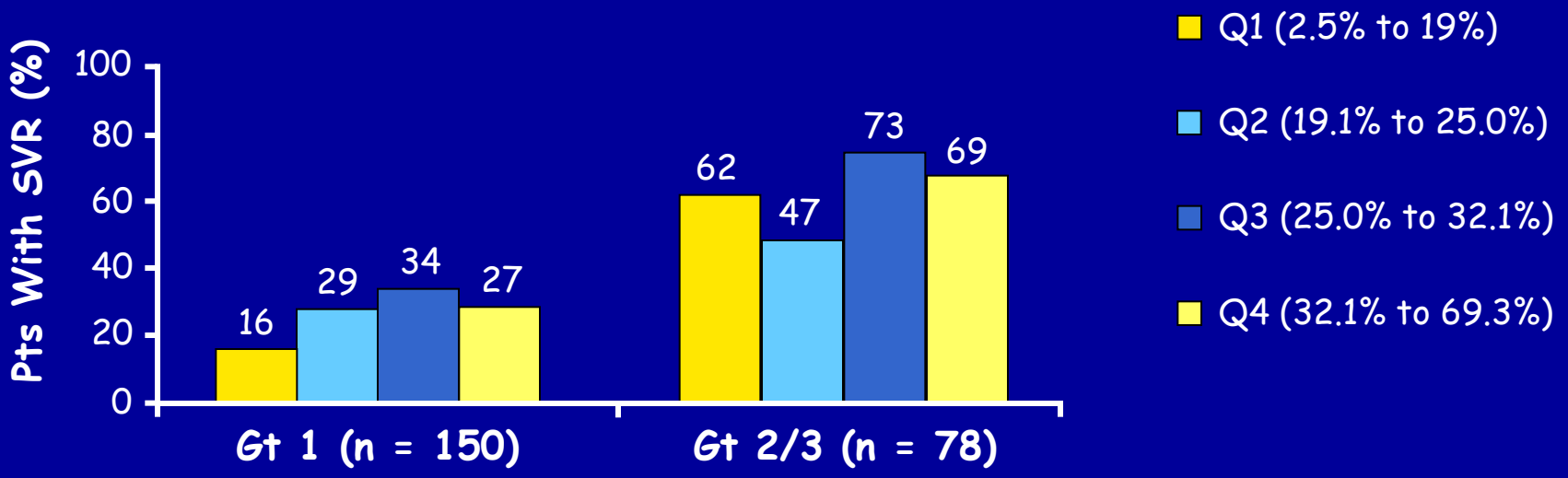
Acute infection
Younger age
Lack of stage 3/4 fibrosis
Ethnicity
Low BMI
Lack of hepatic steatosis
High CD4 %
Lack of insulin resistance

Virus

Genotypes 2/3
Low viral loads

APRICOT: Baseline CD4+ Count and Efficacy of Peg-IFN alpha-2a Plus RBV

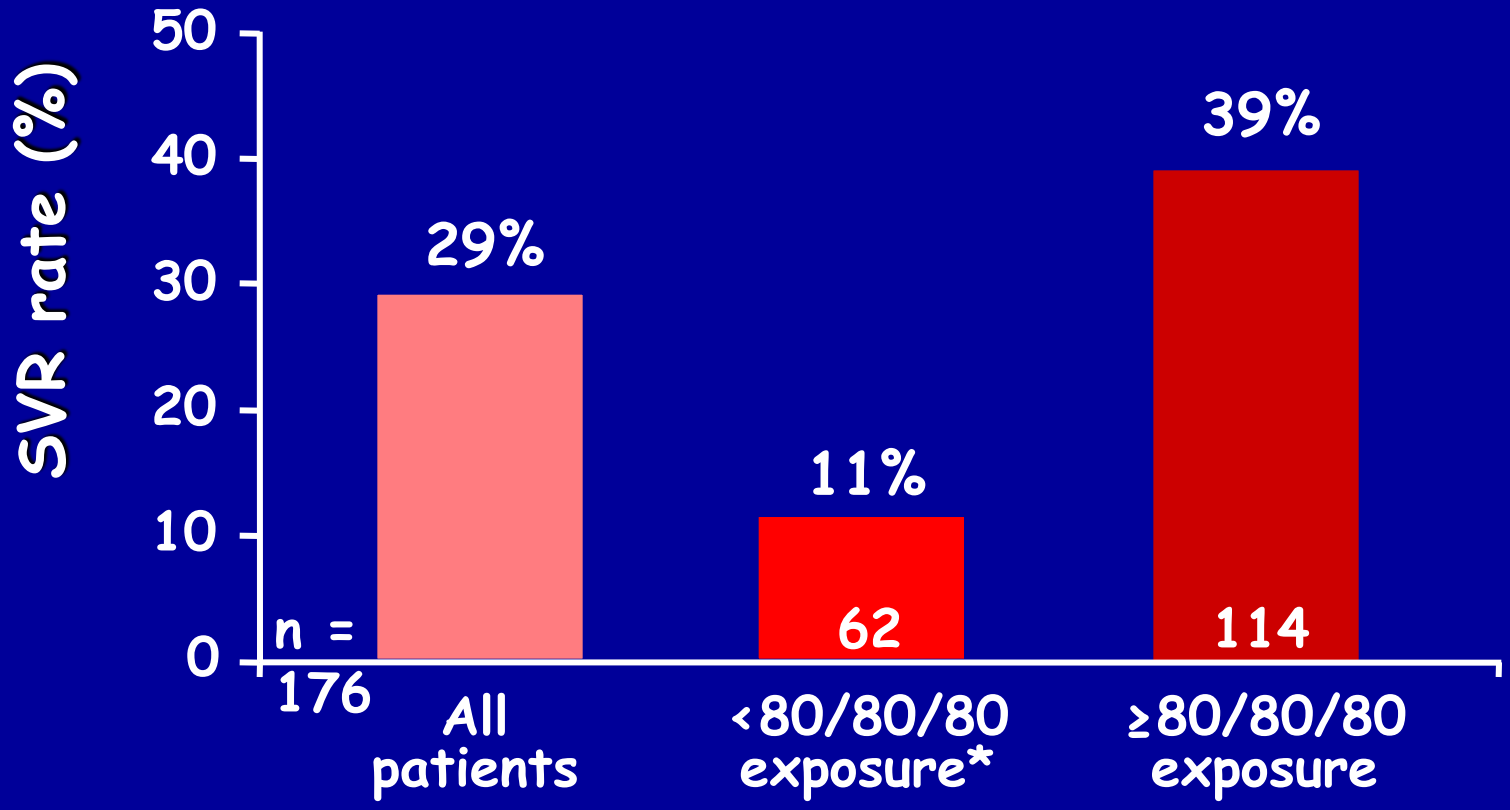
- Retrospective analysis of HIV/HCV-coinfected patients treated with peg-IFN alpha-2a + RBV in APRICOT
- SVR rates analyzed in overall population and within genotypes according to baseline CD4+ cell count quartiles (Q1-Q4)
- Rate of SVR varied according to CD4+ cell percentage quartile in genotype 1 but not in genotypes 2/3



Dieterich D, et al. ICAAC 2006. Abstract H-1888.

APRICOT: SVR rates according to exposure

Genotype 1 recipients of peginterferon alfa-2a plus ribavirin



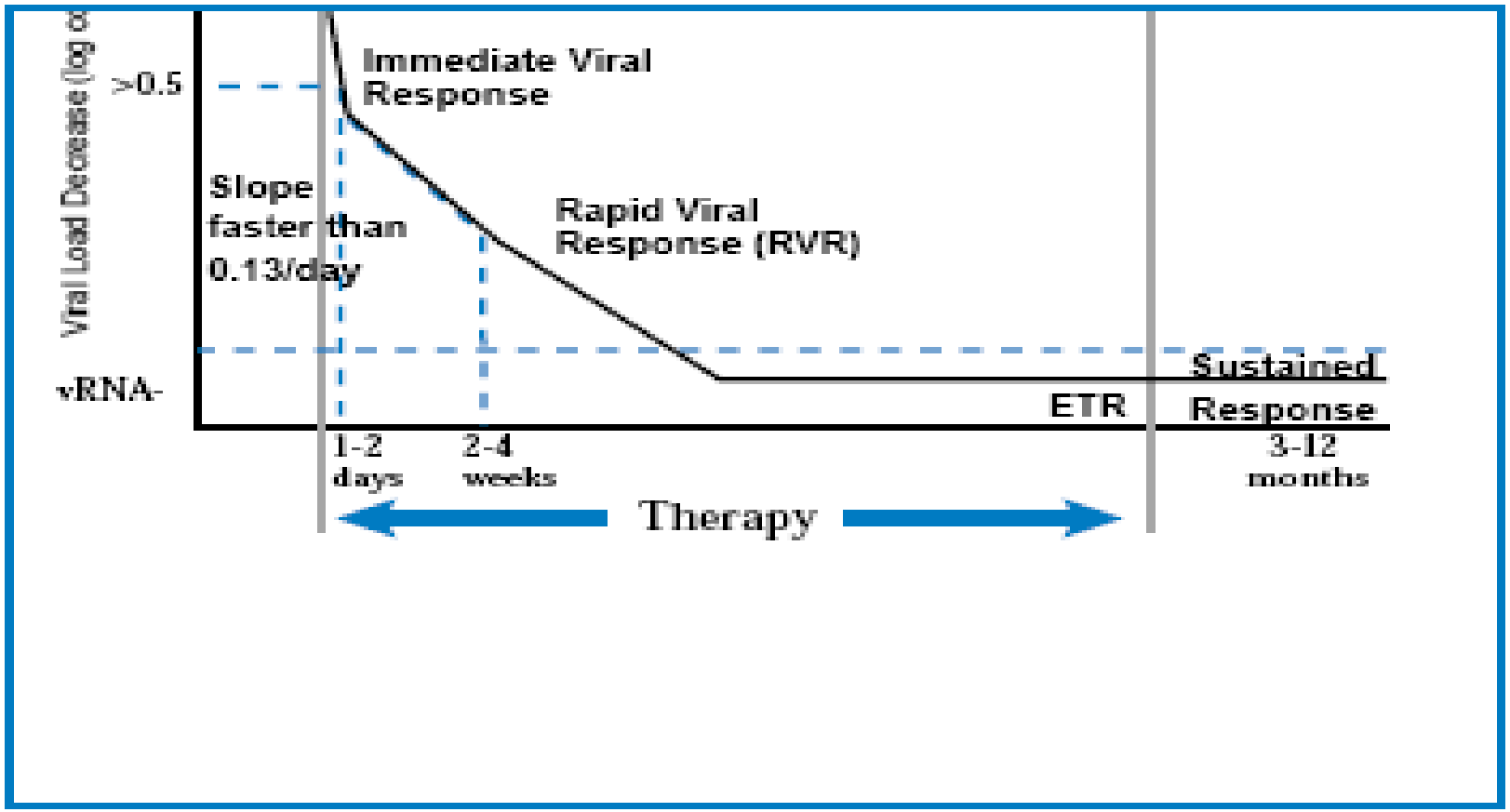
*Patients violated the rule if ≥1 of the three targets were not achieved

Opravil M, *et al*. 45th ICAAC 2005; Abstract 2038

Why lower response rates to anti-HCV therapy in HIV+ patients?

- Use of lower doses of RBV in most trials
- More advanced fibrosis grade
- Higher rate of steatosis (NRTIs, PIs)
- Unfavourable baseline HCV virological features
- Higher discontinuation due to side effects
- Lower initial HCV-RNA clearance
- Higher relapse rates

Viral Dynamic response to interferon and ribavirin



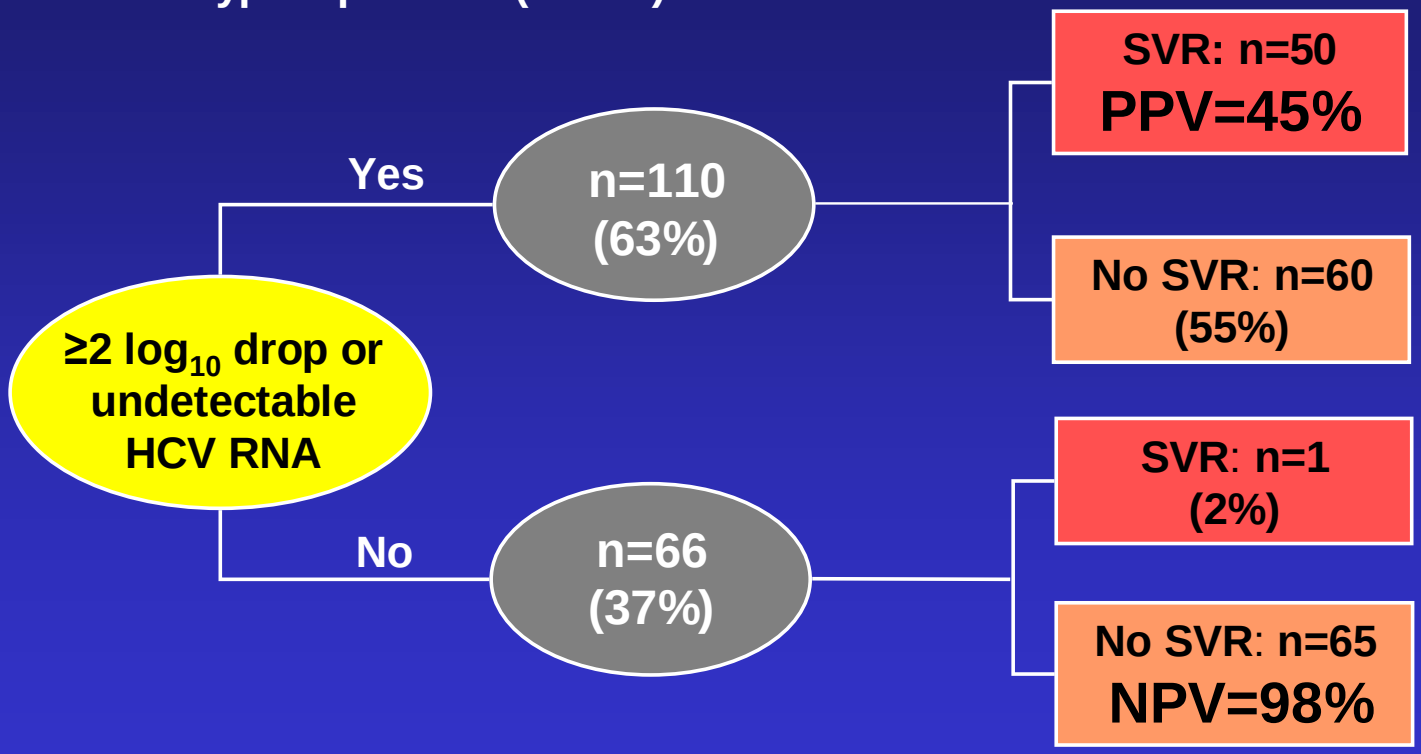
Pawlotsky Hepatology 2002; 32(4)

Does RVR predict response? (week 4 undetectable HCV RNA)

- APRICOT
  - PPV 82%
  - NPV 79%
- RIBAVIC
  - PPV 97.5%
  - NPV 81.3%
- PRESCO
  - Lack of RVR independent predictor of relapse
- Crespo M et al.
  - G3 patients with RVR low rates of relapse with 24 weeks of therapy
- ROMANCE
  - G2/3 patients without RVR need longer Rx (48 weeks)

APRICOT: week 12 – genotype 1 ≥2 $\log_{10}$ drop HCV RNA

- Genotype 1 patients (n=176)

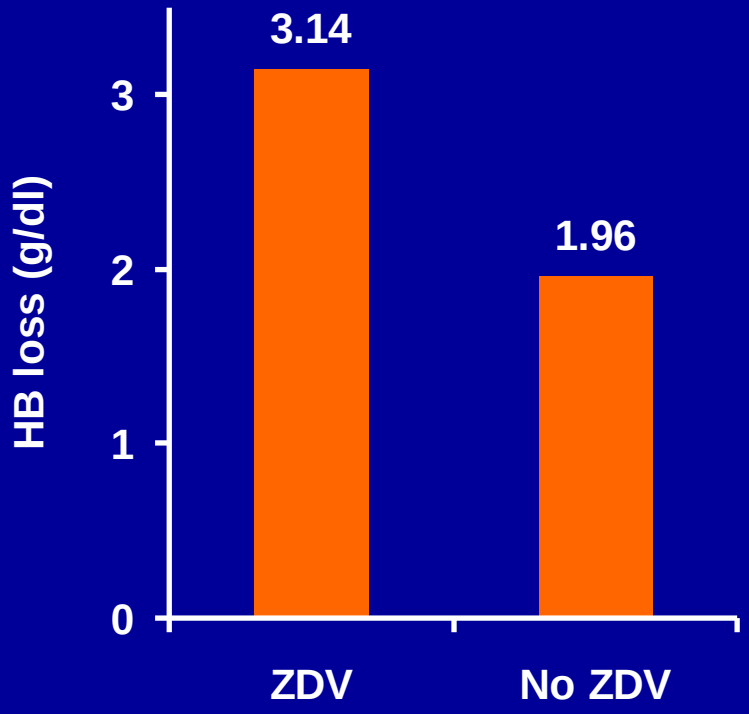


Torriani F, *et al*. 45th ICAAC 2005; Abstract 1024

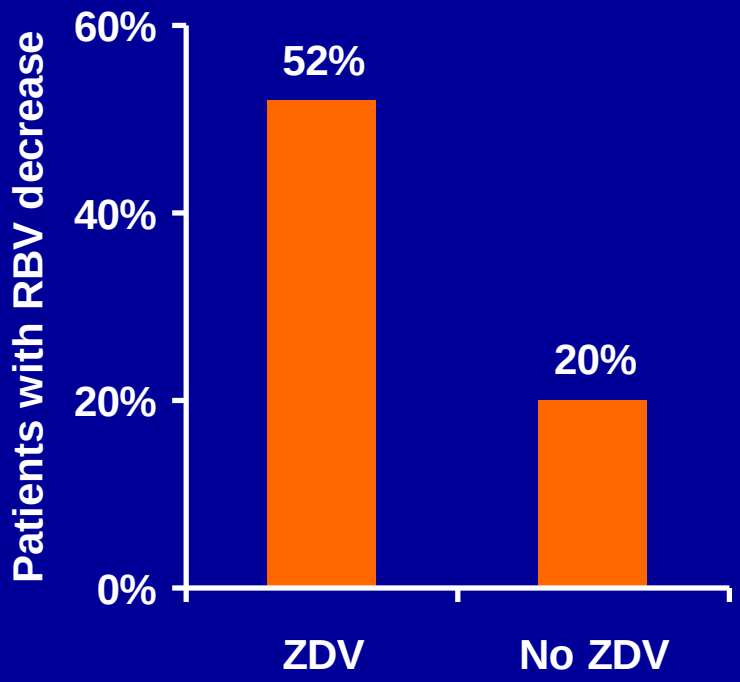
How can we maximise response to therapy?

Zidovudine: impact on HCV treatment

HB decrease by week 4



RBV dose reduction by week 4



Alvarez D et al. 12th Conference on Retroviruses and Opportunistic Infections (Abstract #: P-192). Boston, MA USA, February 22–25, 2005

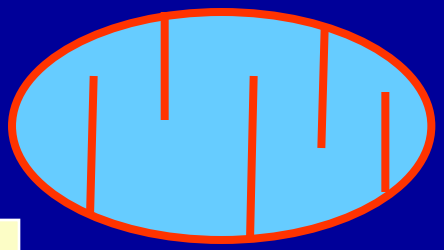
Interactions between RBV & nucleoside analogues

AZT → anemia

ddI → hepatic decomp.

ddI → pancreatitis & lactic acidosis

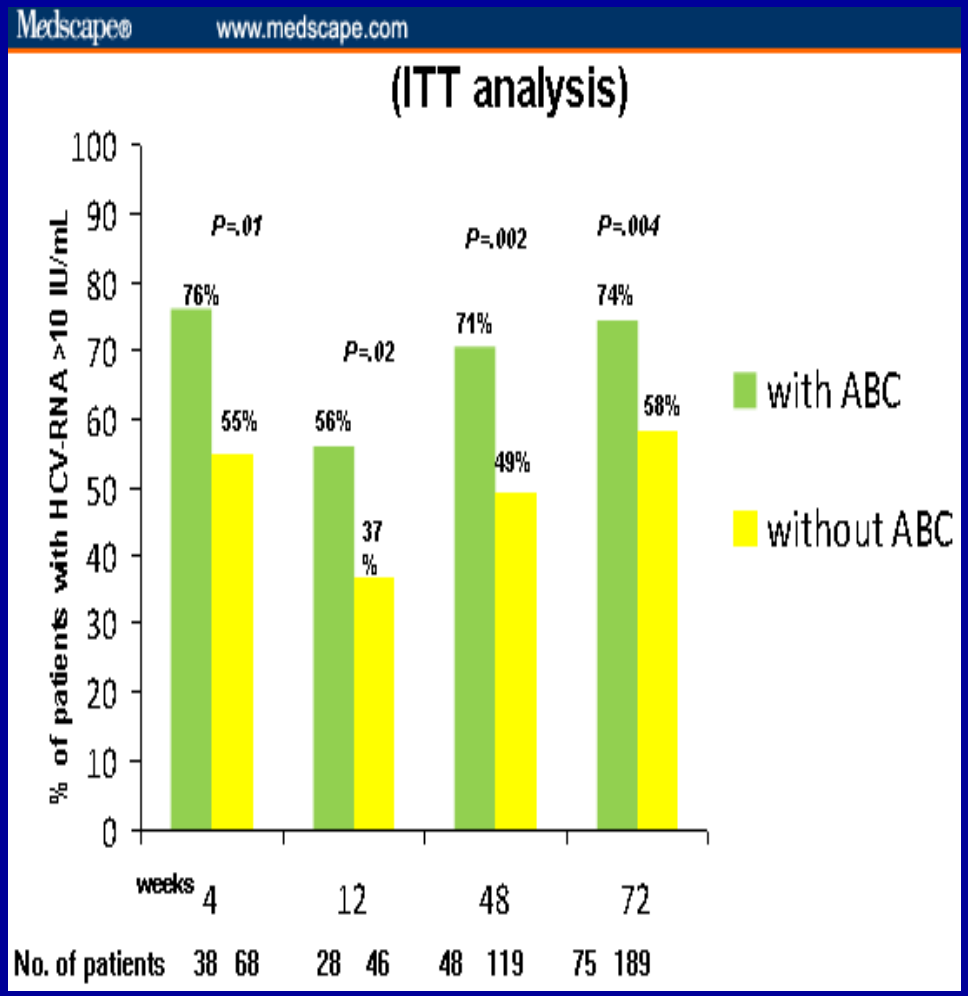
d4T → weight loss

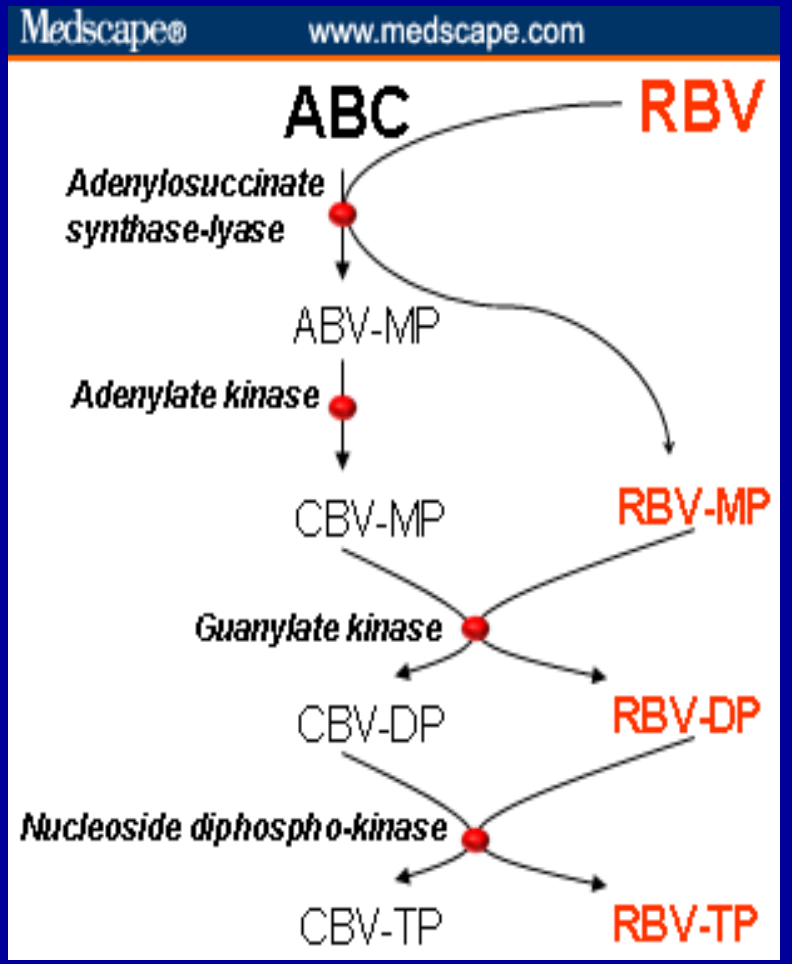


↓ mitochondrial DNA synthesis → ↑ lactate

Blanco *et al. NEJM* 2002; 347: 1287

Abacavir and SVR

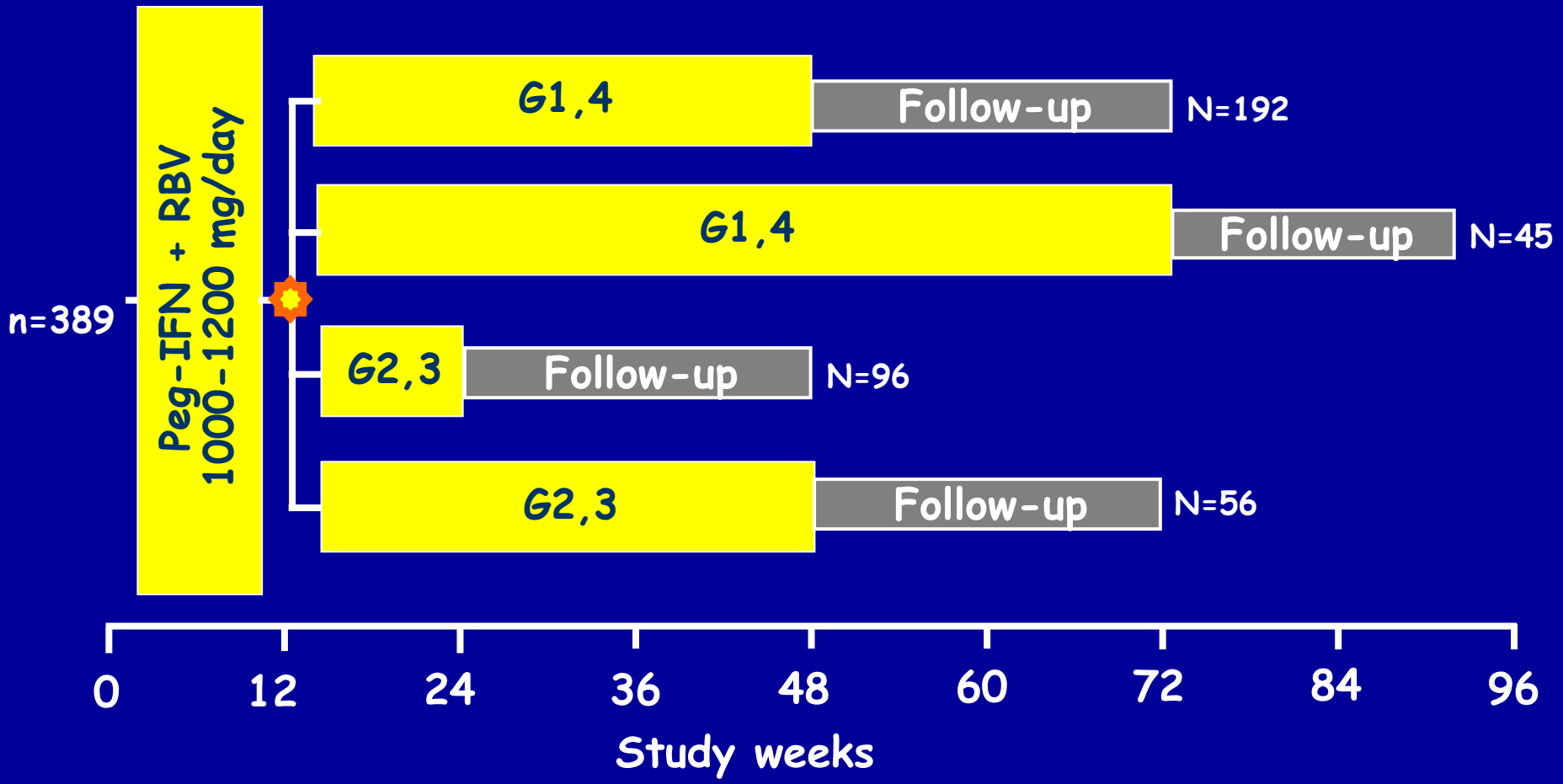




Vispo et al, 3rd Int. HIV/hepatitis Conference, Paris 2007. Abs 46

PRESCO

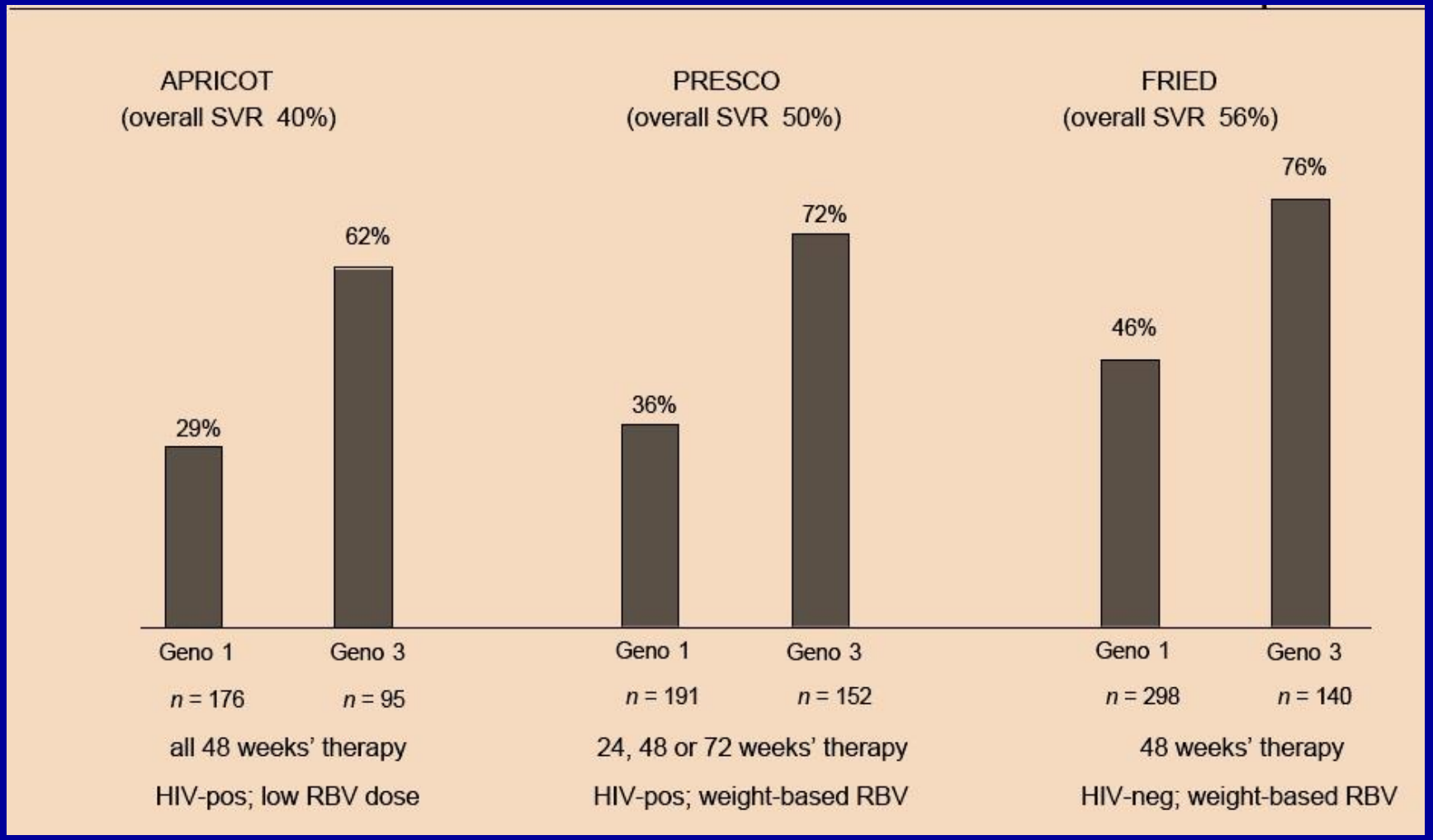
Study Design



Only patients who achieved EVR (>2 log drop in HCV-RNA at week 12) continued treatment.

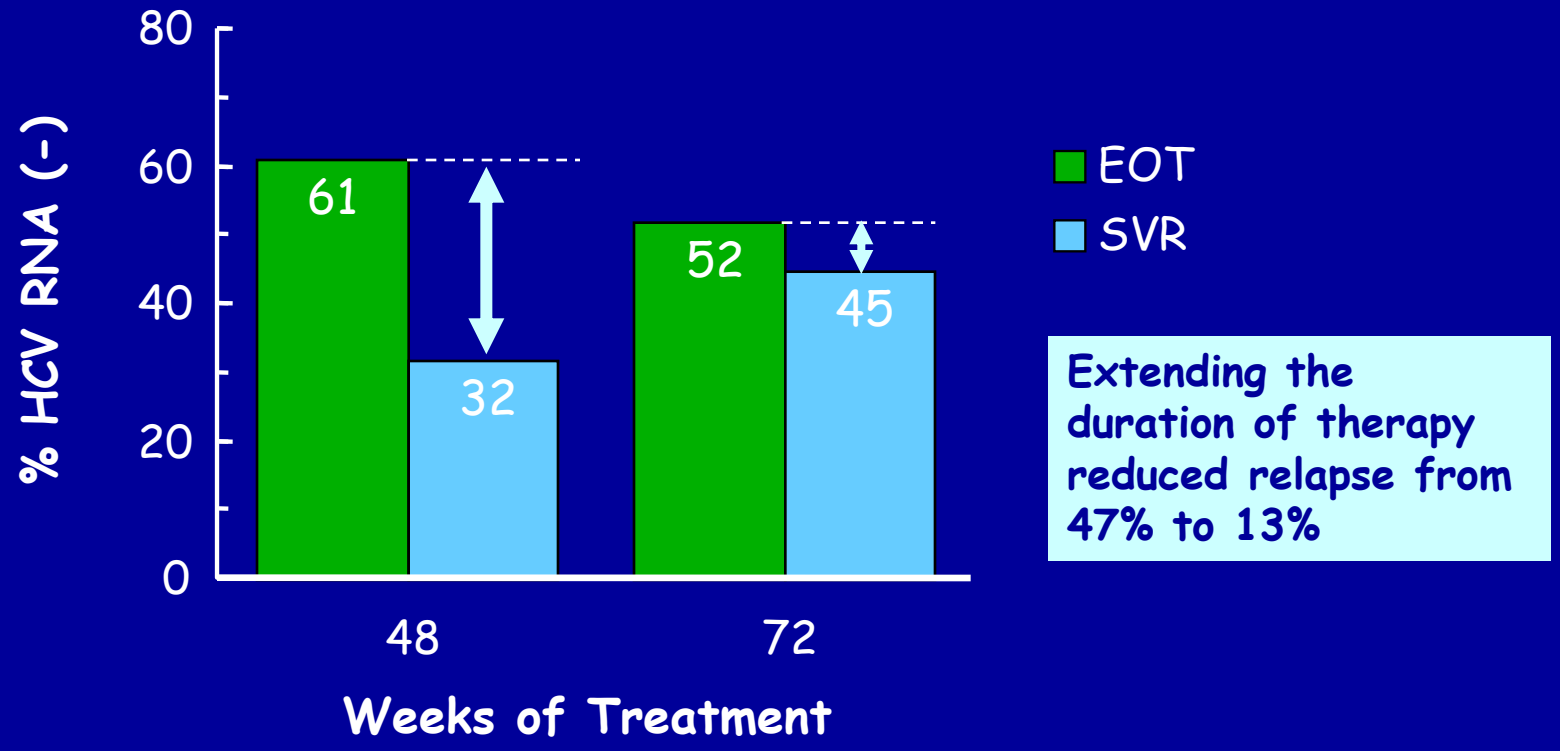
Importance of weight-based Ribavirin

(1000mg <75kg/1200mg >75kg)



Soriano, et al. AIDS 2007. 21: 1073-89

Treatment of Chronic HCV
Extending Therapy

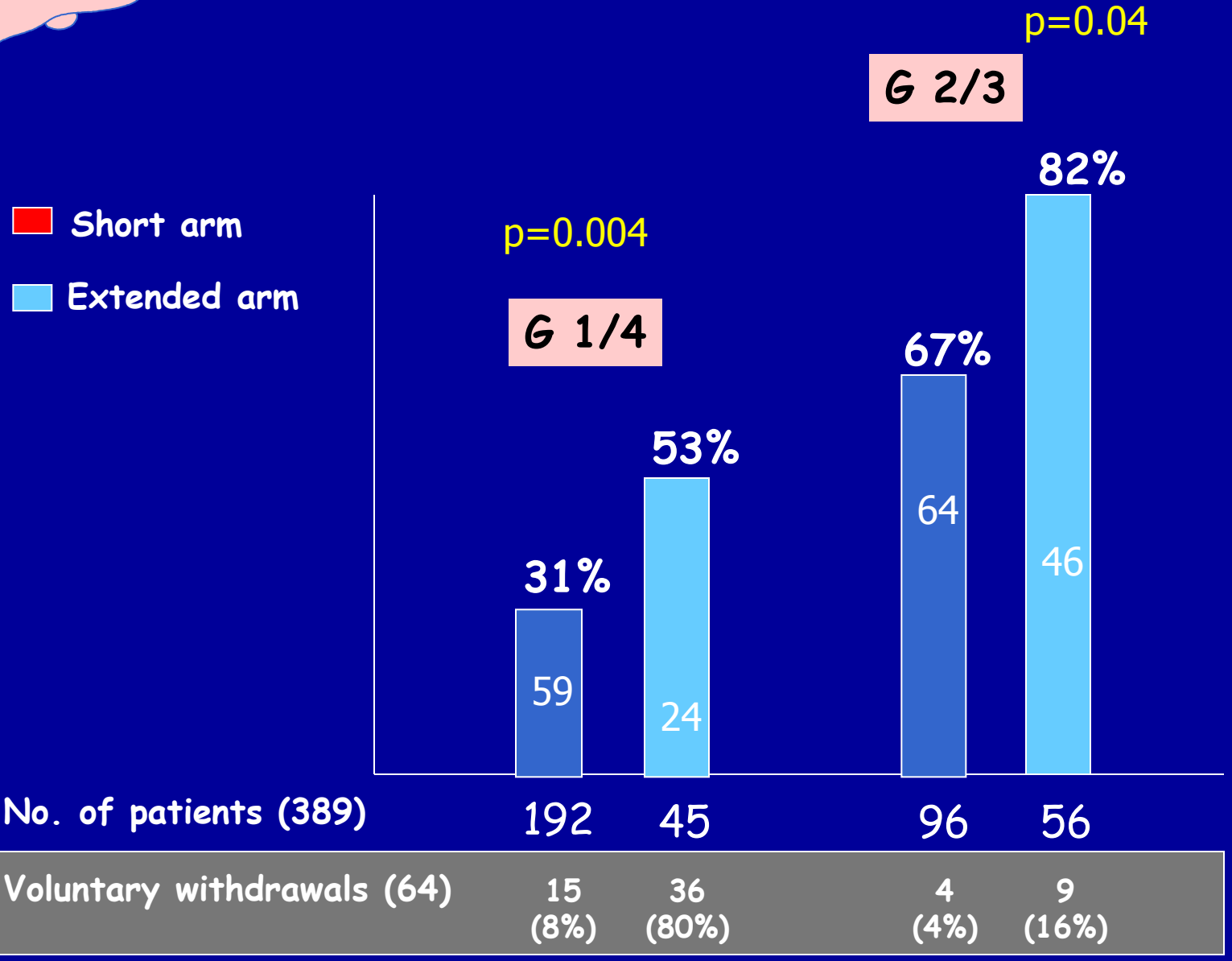


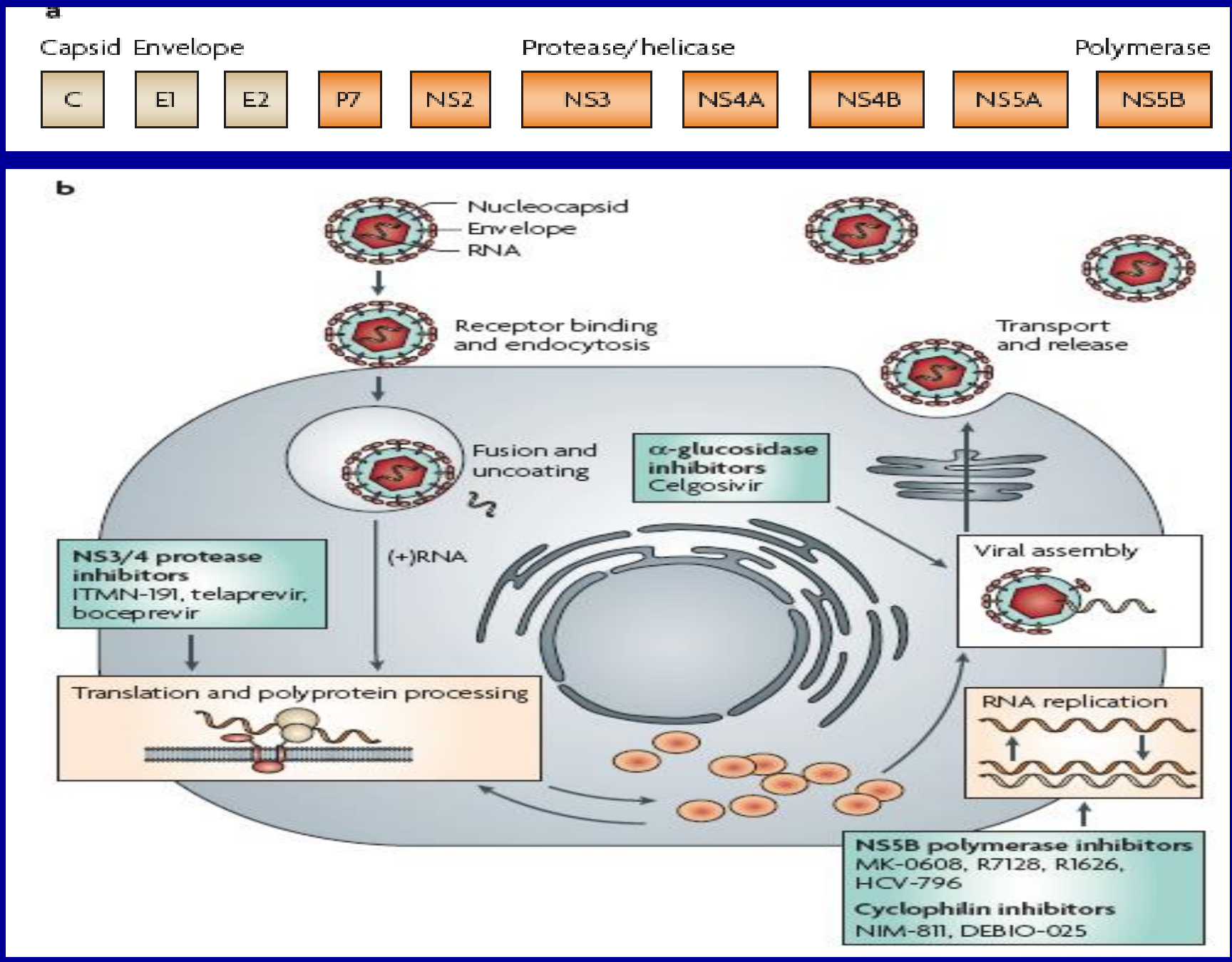
Extending the duration of therapy reduced relapse from 47% to 13%

Sanchez-Tapias et al. AASLD 2004. Abstract 126.

PRESCO

Results (On Treatment analysis)




a
Capsid
Envelope
Protease/helicase
Polymerase
C
E1
E2
P7
NS2
NS3
NS4A
NS4B
NS5A
NS5B
b
Nucleocapsid
Envelope
RNA
Receptor binding and endocytosis
Fusion and uncoating
Transport and release
α-glucosidase inhibitors
Celgosivir
(+)RNA
NS3/4 protease inhibitors
ITMN-191, telaprevir, boceprevir
Viral assembly
Translation and polyprotein processing
RNA replication
NS5B polymerase inhibitors
MK-0608, R7128, R1626, HCV-796
Cyclophilin inhibitors
NIM-811, DEBIO-025

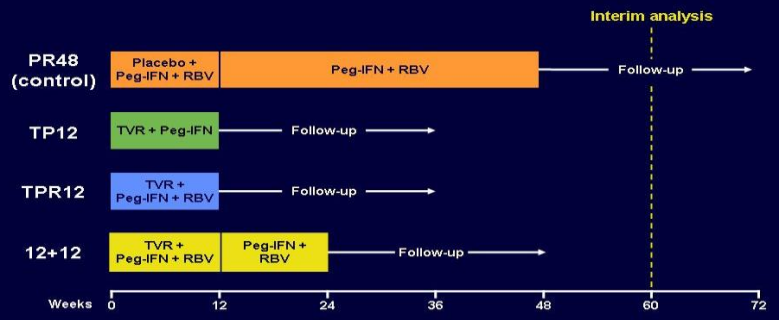
New oral small molecule ARVs in development for the treatment of HCV

Drug name	Drug class	Preclinical	Phase I	Phase II	Phase III
MK-0608 (Merck)	Nucleoside polymerase inhibitor	X			
R7128 (Pharmasset & Roche)	Nucleoside polymerase inhibitor		X		
NIM811 (Novartis)	Cyclophilin inhibitor		X		
ITMN-191 (InterMune & Roche)	Protease inhibitor		X		
MK-7009 (Merck)	Protease inhibitor		X		
BI12202 (Boehringer)	Protease inhibitor		X		
BI 1220 (Boehringer)	Nucleosite polymerase inhibitor		X		
R1626 (Roche)	Nucleoside polymerase inhibitor			X	
DEBIO-025 (Debiopharm)	Cyclophilin inhibitor			X	
Telaprevir (Vertex Pharmaceuticals)	Protease inhibitor			X	
Boceprevir (Schering-Plough)	Protease inhibitor			X	
TMC435350 (Tibotec & Medivir)	Protease inhibitor			X	

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

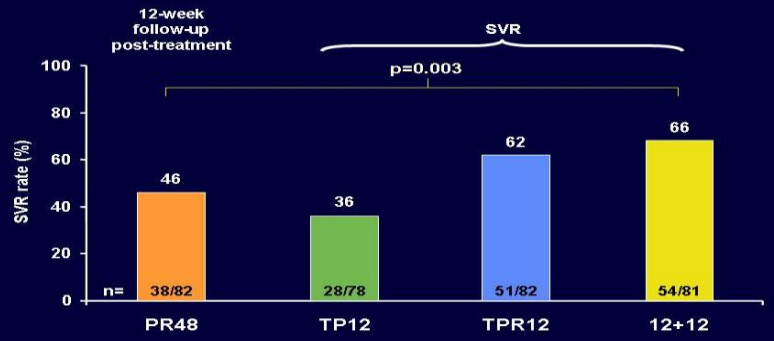
TELAPREVIR: PROVE 2
SVR

HCV Genotype 1 Naive
PROVE2: Study Design



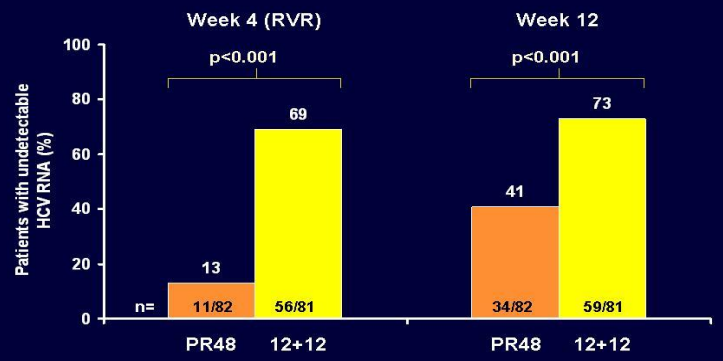
Peg-IFN = pegylated interferon alfa-2a 180µg/wk;
RBV = ribavirin 1,000 or 1,200mg/day; TVR = telaprevir 750mg q8h

PROVE 2: Post-treatment Follow-Up



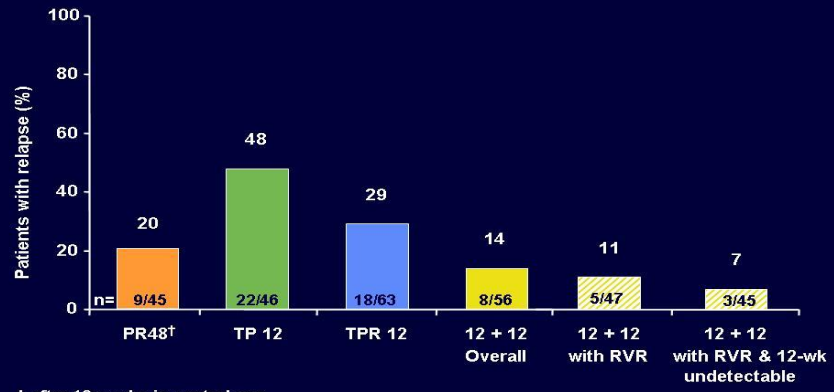
†Data from two patients not included

PROVE2: Rate of Undetectable HCV RNA in 12+12 TVR and Control Arms at Weeks 4 and 12 (ITT)



- 90% positive predictive value (PPV) for SVR in TVR-based treatments when HCV RNA was undetectable at weeks 4 and 12

PROVE2: Relapse Rates



† after 12-weeks in control arm
RVR = Rapid Virological Response

1. Dusheiko et al .Treatment of chronic hepatitis C with telaprevir in combination with peginterferon alfa 2a with or without ribavirin: further interim analysis results of the PROVE2 study. *J Hepatology* 2008; 48 (suppl)

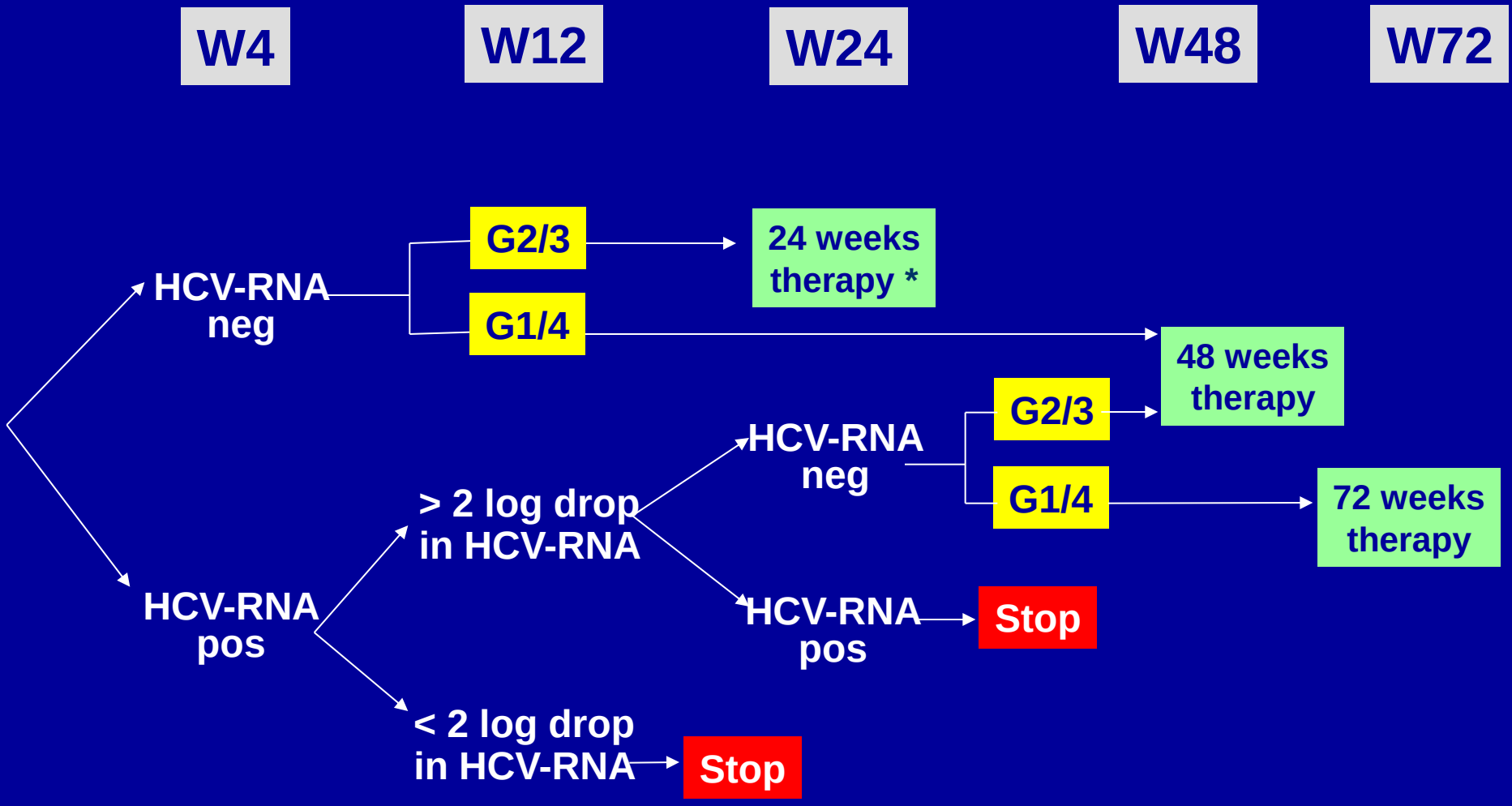
Take home messages:

- HIV/HCV co-infection is common
- Increasing incidence of acute HCV
- ESLD major cause of morbidity/mortality
- Early HAART beneficial
  - Avoid d-thymidine analogues/AZT
- Treat HCV with PegIFN and Ribavirin
  - Best results if HCV treated in the acute phase
  - Maximal doses of Ribavirin (1000/1200mg)
  - Avoid AZT, d4T and DDI,
  - ?Avoid Abcavir
  - EPO and G-CSF – avoid dose reductions

Take home messages:

- Duration of therapy individualised
  - Genotype
  - Pre-Rx viral load
  - Fibrosis stage
  - RVR/EVR
- No role for maintenance low-dose IFN
- Give some thought to hepatic steatosis
- New anti-HCV drugs (STAT-Cs!) will be available in the future…
- …be careful out there….!!!

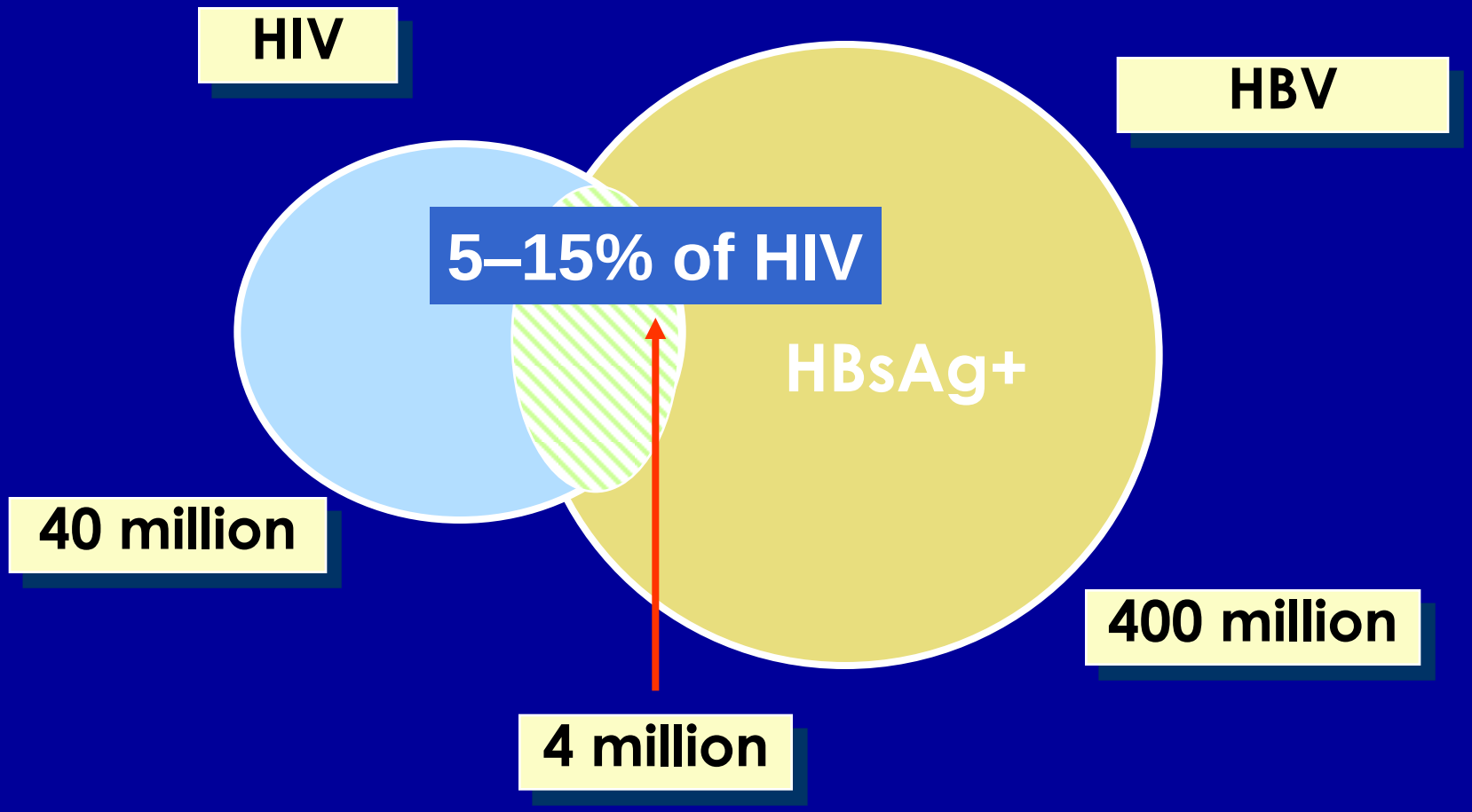
Proposed optimal duration of HCV therapy in HCV/HIV-coinfected patients.



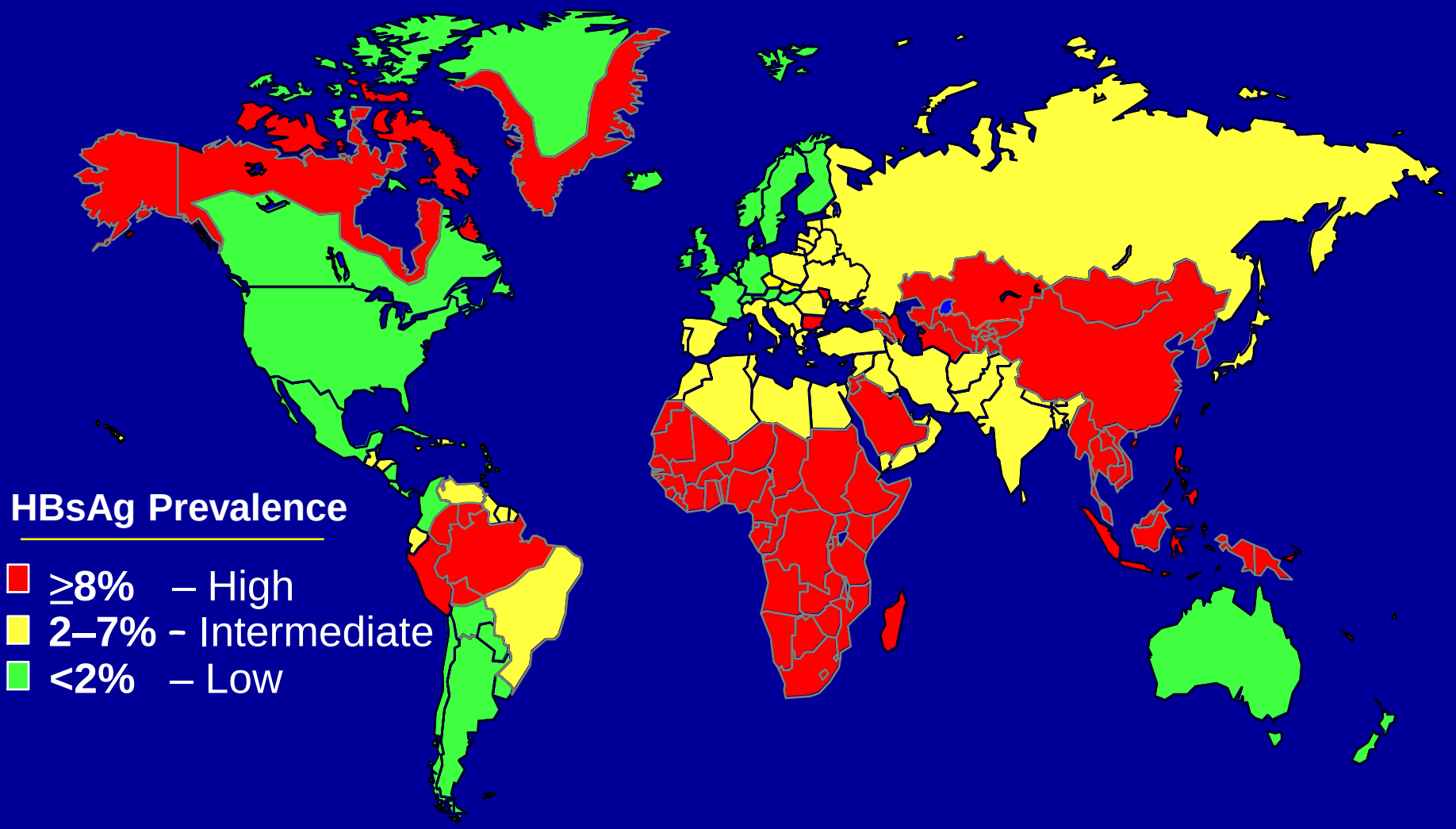
** In patients with baseline low viral load and minimal liver fibrosis.*

EACS Guidelines 2008

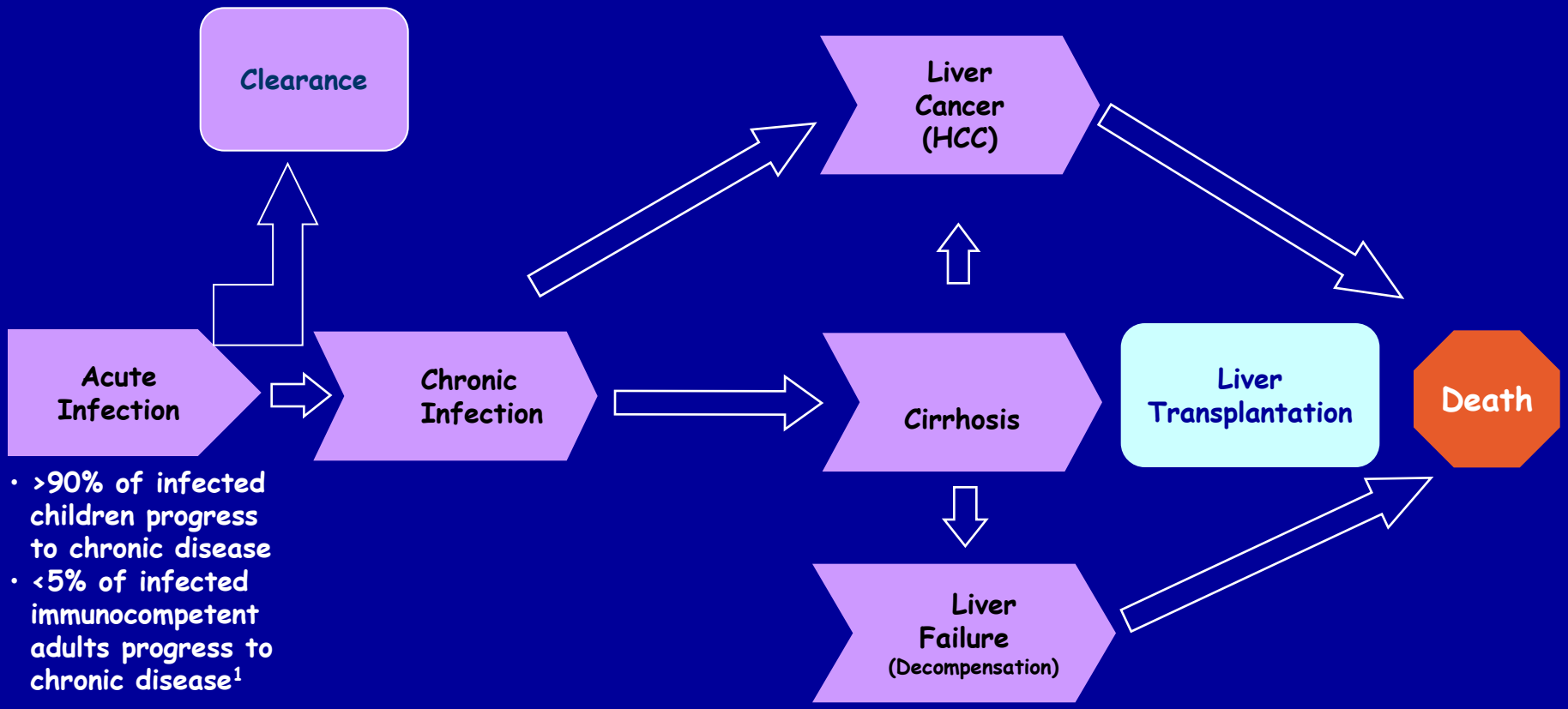
Overlapping HBV & HIV Epidemics



Geographic Distribution of Chronic HBV Infection



Hepatitis B Disease Progression



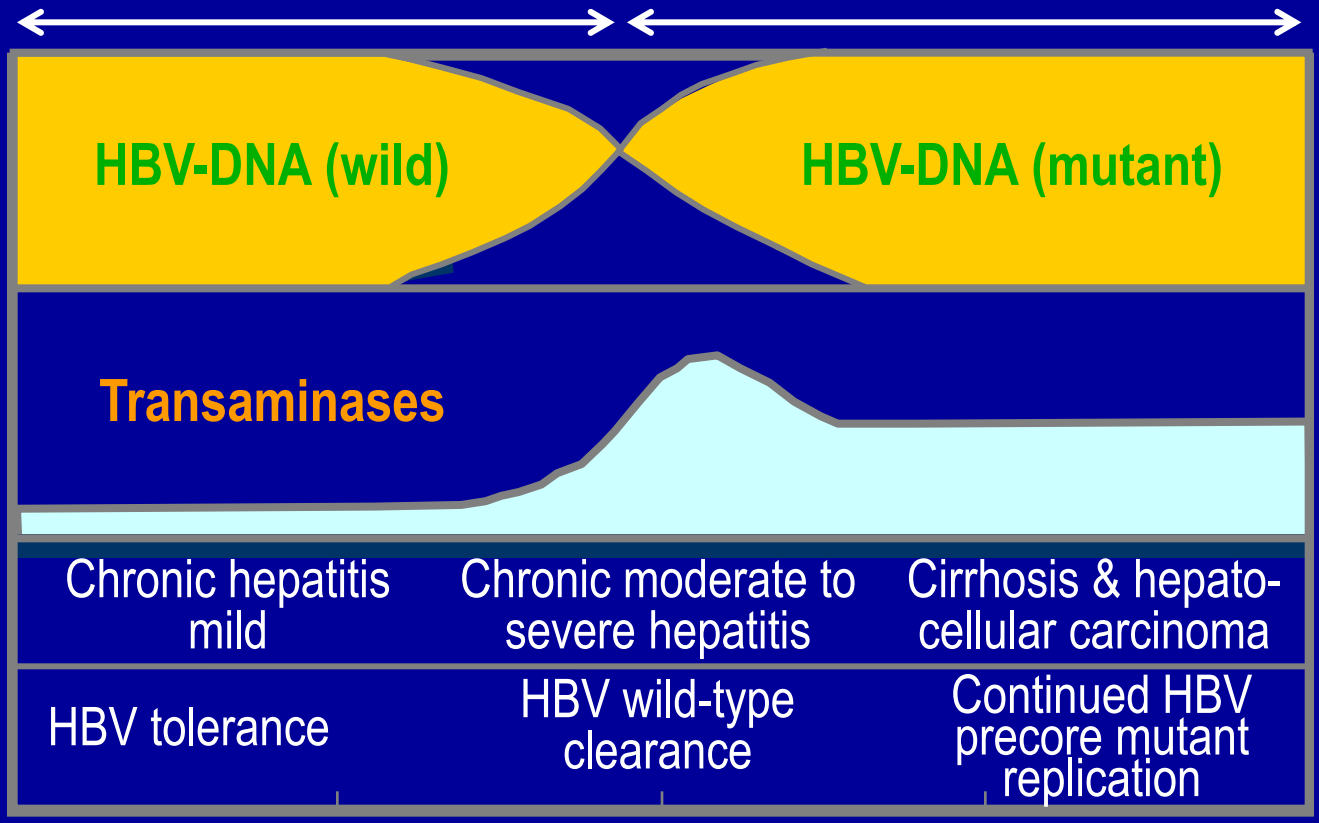
- >90% of infected children progress to chronic disease
- <5% of infected immunocompetent adults progress to chronic disease[1]

1. Torresi, J, Locarnini, S. Gastroenterology. 2000.
2. Fattovich, G, Giustina, G, Schalm, SW, et al. Hepatology. 1995.
3. Moyer, LA, Mast, EE. Am J Prev Med. 1994.
4. Perrillo, R, et al. Hepatology. 2001.

Phases of chronic HBV Infection

- Immune tolerant phase
  - High levels of HBV DNA
  - Very little inflammation
- Chronic hepatitis
  - HBeAg positive
    - High levels HBV DNA, inflammation/progressive fibrosis
  - HBeAg negative
    - Low levels HBV DNA, progressive inflammation and fibrosis
- Inactive HbsAg carrier state (non replicative phase)
  - HBeAg negative, low/absent HBV DNA, no inflammation/fibrosis

Emergence of the e-negative Precore Mutant



Carman WF et al Viral Hepatitis. Scientific Basis and Clinical Management. NY: Churchill Livingstone; 1993:121.

HBeAg Negative Chronic Hepatitis B

- Anti-HBe positive, HBV DNA 10^4 - 10^8 copies/mL
- Precore or core promoter variants in majority
- Selection of HBV variants may accompany HBeAg seroconversion to anti-HBe
- ALT levels persistently or intermittently elevated
- Often older, male, more severe disease
- Long-term antiviral therapy required

Geographical distribution of HBV genotypes A to H

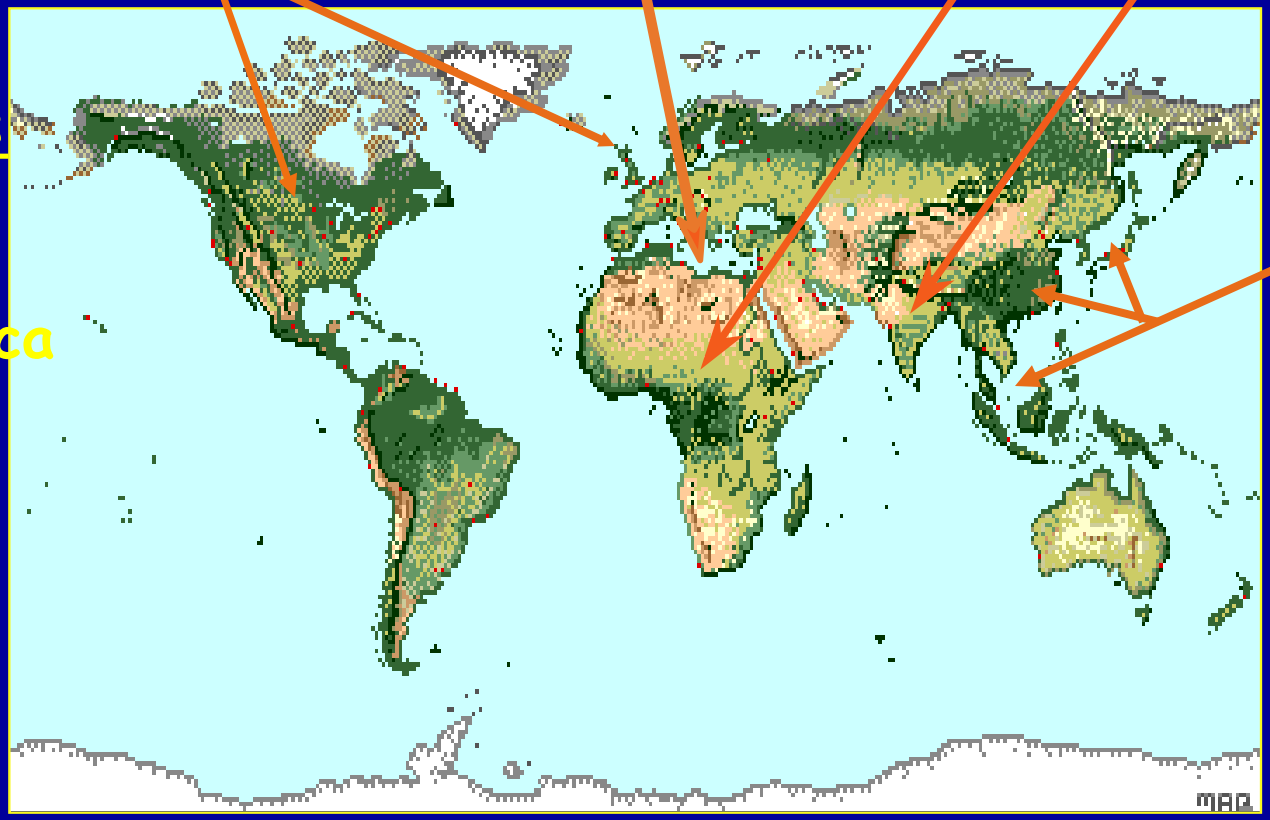
North Europe & USA - A

Mediterranean basin -D

Africa E & D

India A

Far East B & C



Rare types:

F - Latin America

G -France, USA

H -Mexico, Latin America

HBV Genotype	Geographical Distribution	Clinical Relevence
A	Central Africa, Europe, North America	When compared with other genotypes: ▪ Better response to peginterferon
B	China, Indonesia, Taiwan, Vietnam	When compared with genotype C: ▪ Lower disease activity ▪ Younger age to HBeAg seroconversion ▪ Lower risk of HCC ▪ Better response to therapy
C	China, Japan, Korea, Polynesia, Taiwan, Vietnam	When compared with other genotypes: ▪ More severe disease ▪ Worse clinical outcome
D	India, Mediterranean, Middle East	▪ Associated with precore mutation
E	Nigeria, West Africa	▪ Unknown
F	Alaska, Polynesia	▪ Unknown
G	France, North America	▪ Unknown
H	Central America	▪ Unknown

Hepatitis B Serology
Isolated HBcAb+

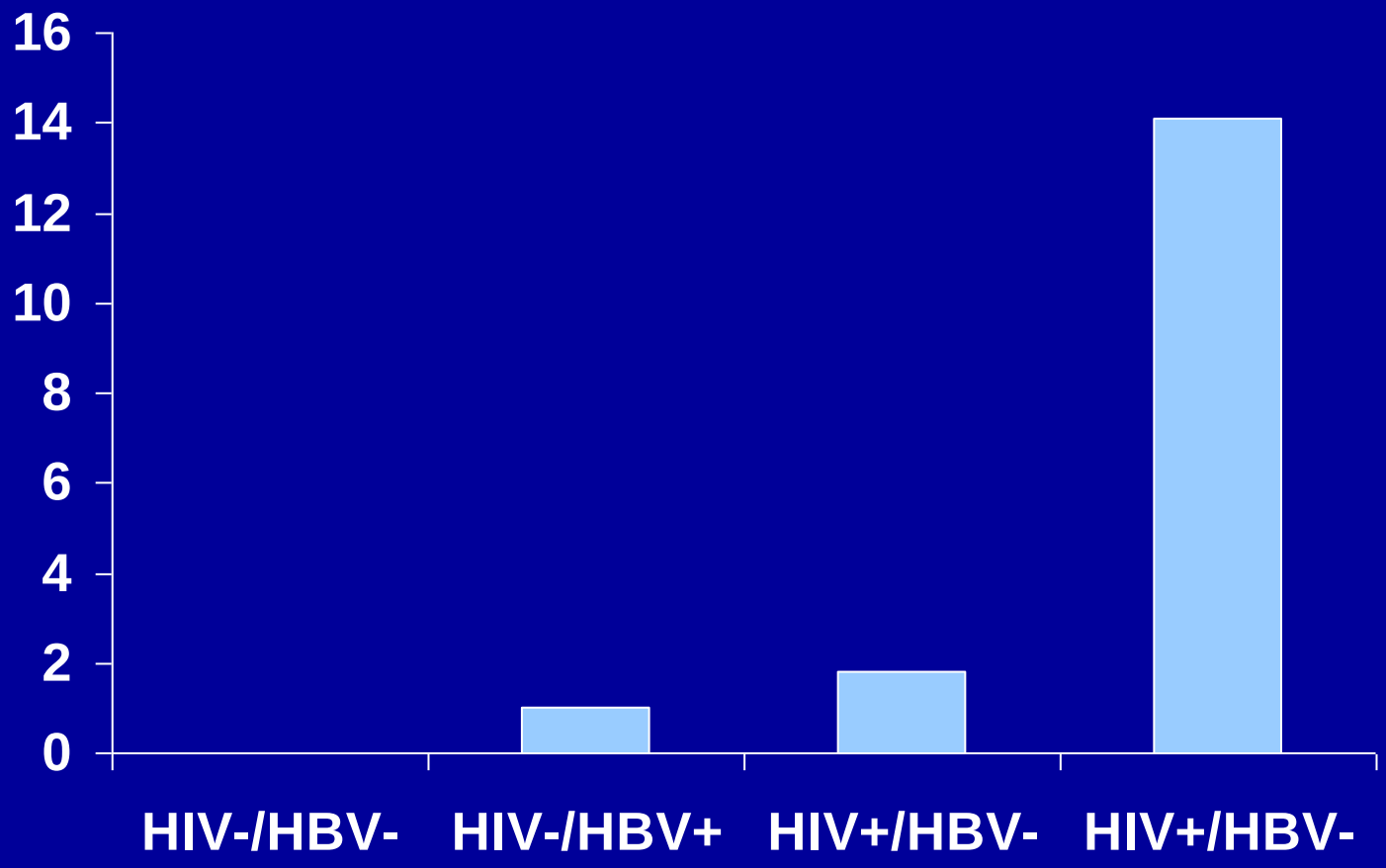
- HIV negative
  - 50% true positive HBcAb
  - <2% with detectable serum HBV DNA
- HIV positive
  - 60-90% true positive HepBcAb
  - Many with detectable HBV DNA (~15% at RFH)
  - ~40% with necro-inflammation on liver biopsy
- Isolated anti-HBc more common in HIV/HCV
- Implications for 3TC based HAART and vaccination strategies

Hofer, Euro J Clinical Micro 1998. Ghandi, CID. June 15, 2003. Nebya, BHIVA 2006

HIV/HBV Coinfection

- Increased incidence of chronic HBV in HIV+ patients (*Lazizi JID 1988*). Will vary greatly with subpopulation
- HIV+ pts 3-6x more likely to develop chronic HBV than HIV- (*Bodsworth JID 1991*)
- HBeAg and HBV DNA higher levels in HIV+ but AST/ALT lower (*Perillo 1986*)
- Increased hepatic fibrosis
- Decreased spontaneous seroconversion (*Krogsgaard 1987*) or seroreversion of prior HBV infection with loss of anti-HBs and return of HBsAG (*Waite AIDS 1988*)
- Atypical serologies: anti-HBc may indicate chronic infection (*Hofer 1998*)

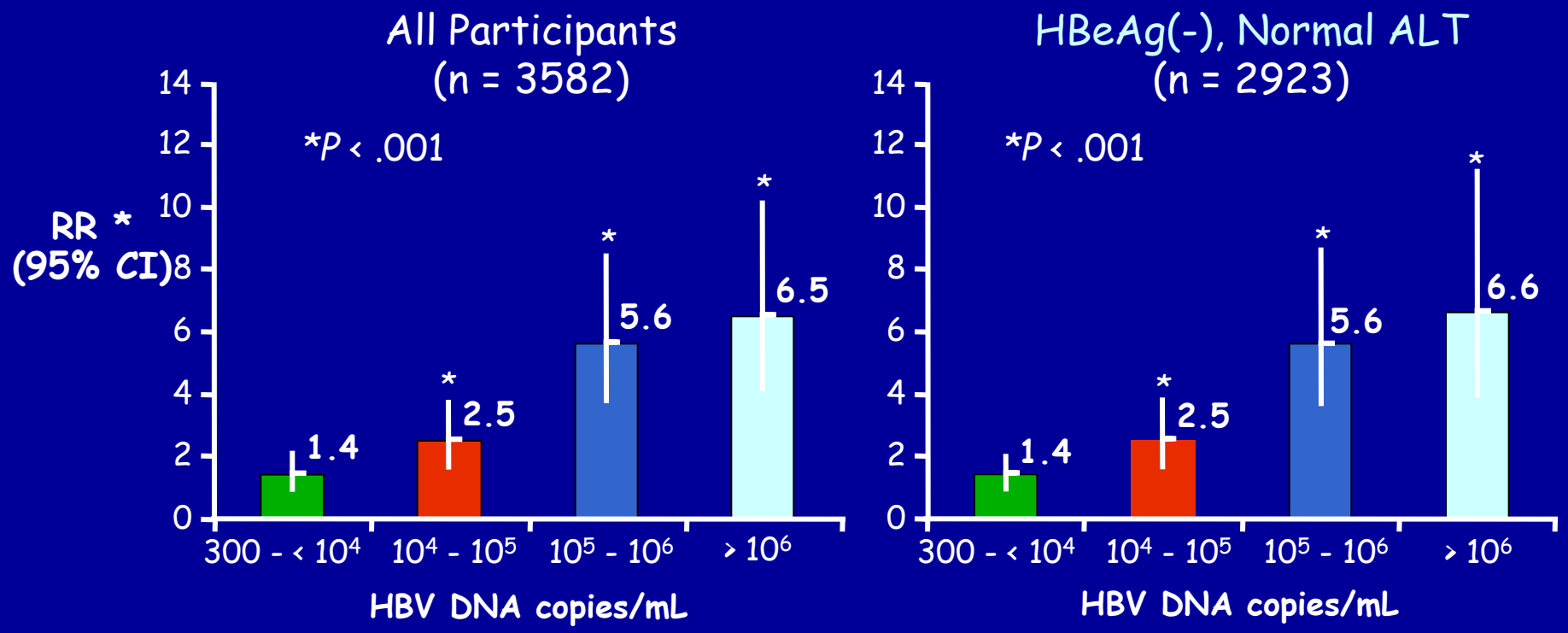
Liver Mortality Rate (per 1000 PY) MACS



Thio et al. Lancet 2004

Level of HBV DNA (PCR-assays) at entry & progression to cirrhosis in *population-based cohort studies*

3582 HBsAg untreated asian carriers
mean follow-up 11 yrs → 365 patients newly diagnosed with cirrhosis



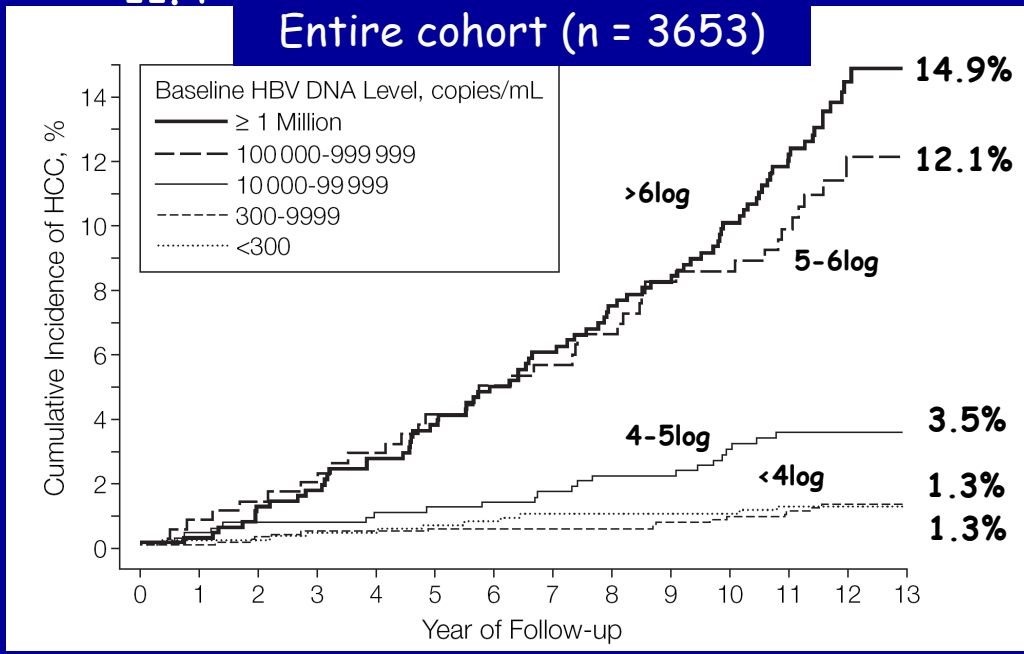
* Adjusted for age, sex, cigarette smoking, and alcohol consumption.

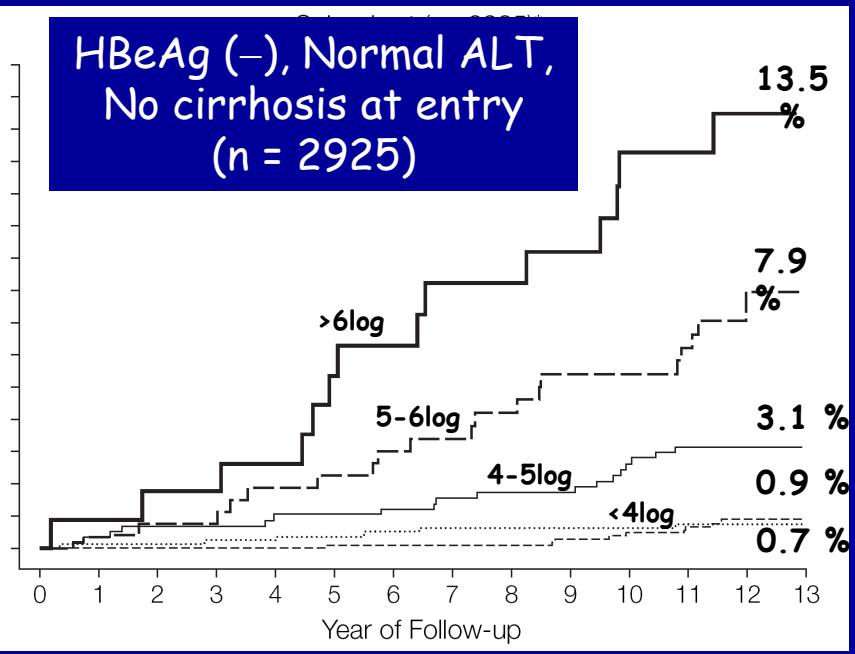
HBV-DNA viral load (> 10^4 cp/ml) strongest predictor of progression to cirrhosis independent of ALT and HBeAg status

Iloeje UH, *Gastroenterology* 2006; 130: 678-686

Level of HBV DNA (PCR-assays) at entry & risk of HCC

- *Population based cohort study* of HBsAg asian carriers, mean follow-up= 11.4





Entire cohort (N = 3653)	
HBV-DNA (cp/ml)	RR
< 300	1.0
1.0-9.9 x 10^4	2.3
1.0-9.9 x 10^5	6.6
> 1.0 x 10^6	6.1

Subcohort (N = 2925)	
HBV-DNA (cp/ml)	RR
< 300	1.0
1.0-9.9 x 10^4	4.5
1.0-9.9 x 10^5	11.3
> 1.0 x 10^6	17.7

HBV-DNA levels (> 10^4 cp/ml) strong predictor of HCC, independent of HBeAg, ALT and cirrhosis

Chen CJ et al JAMA 2006;295:65-73

How?

Restoring immune control

- Type I interferons
  - Interferon-alpha
  - Pegylated interferon-alpha-2a
- ?others

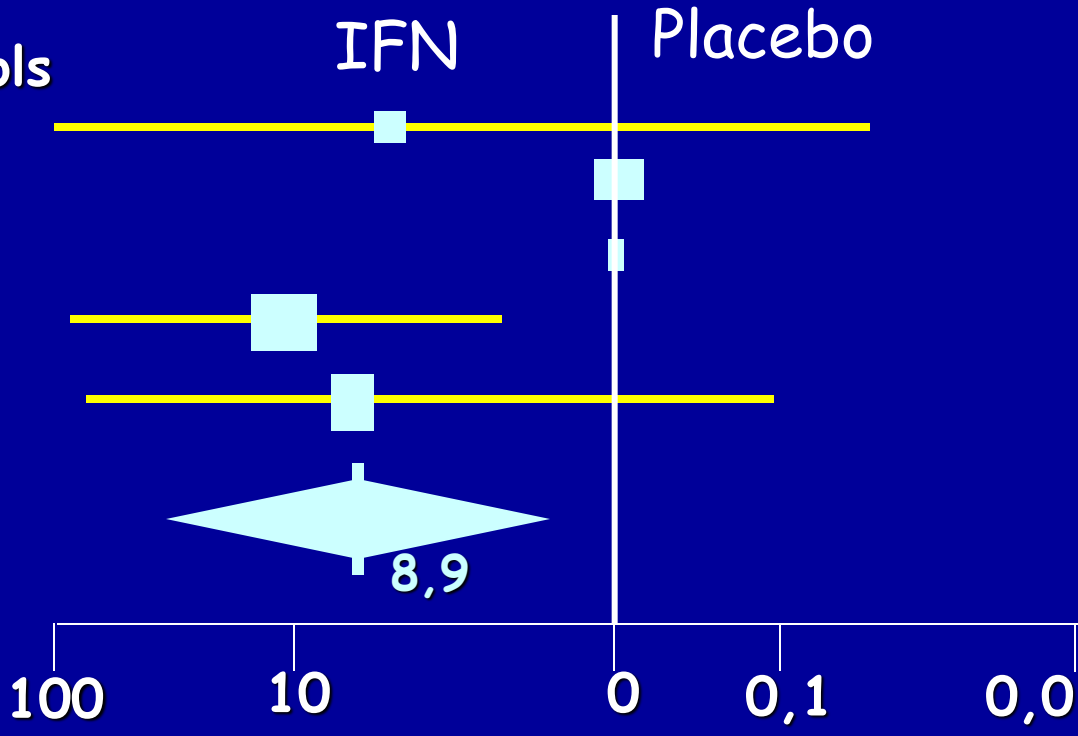
Viral replication suppression with antivirals

- Lamivudine
- Adefovir
- Entecavir
- (Tenofovir)
- (FTC)
- Telbivudine
- (Clevudine)

IFN-α in HBV /HIV co-infection

16 RCT IFN-α *vs* placebo 837 HBsAg+ - 107 HIV+ included in 5 studies

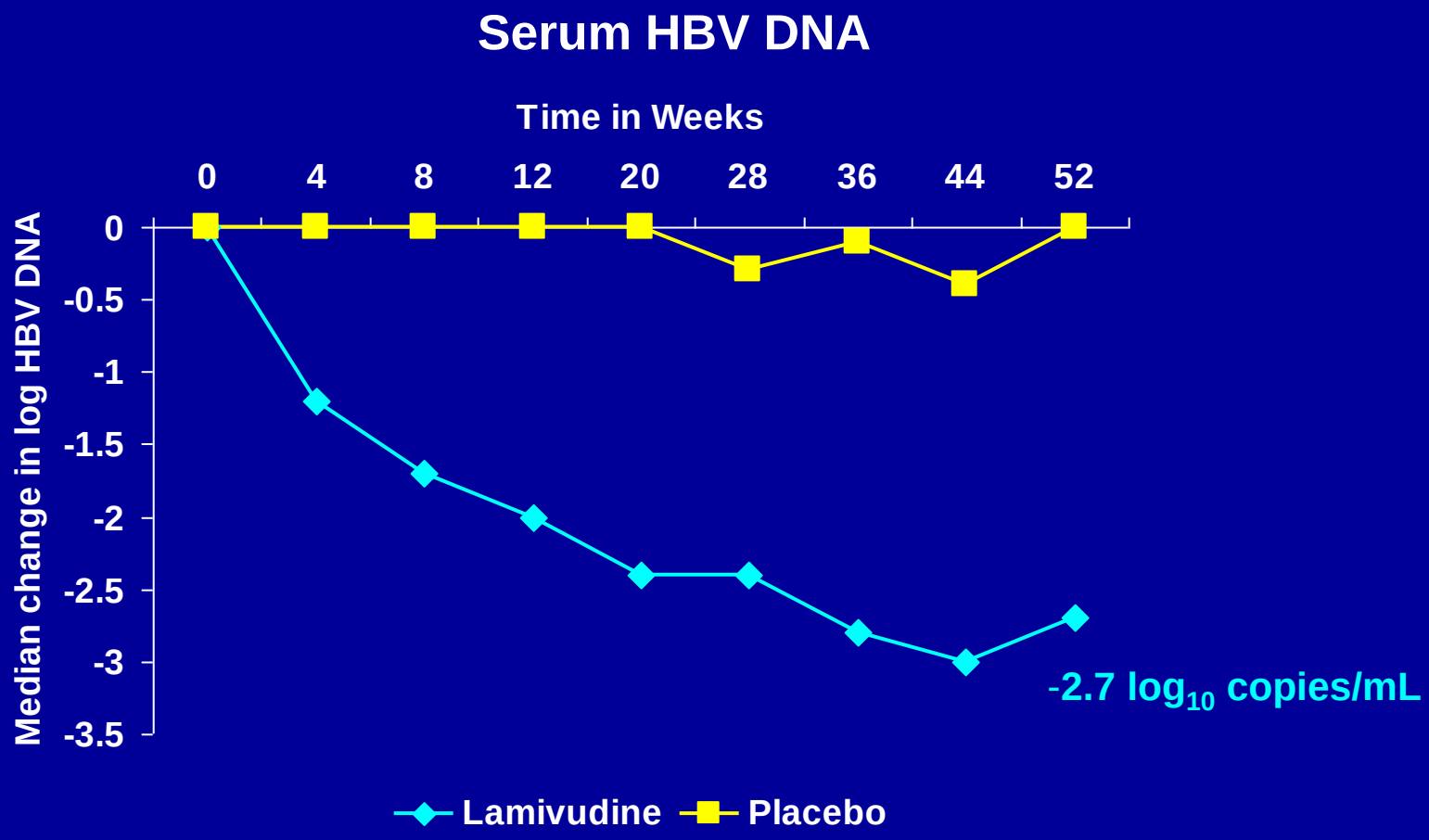
Author(Yr.)	n. Tx	n. Controls
Hoofnagle(88)	10	4
Brook (89)	16	6
Brook (89)	6	9
Pol (92)	16	14
Wong (95)	13	13
All	61	46



HBe seroconversion/negativation : HIV+ *vs* HIV: – 0.38 (CI 0.06-0.7 *P* =.02)

Puoti et al. personnal comm.

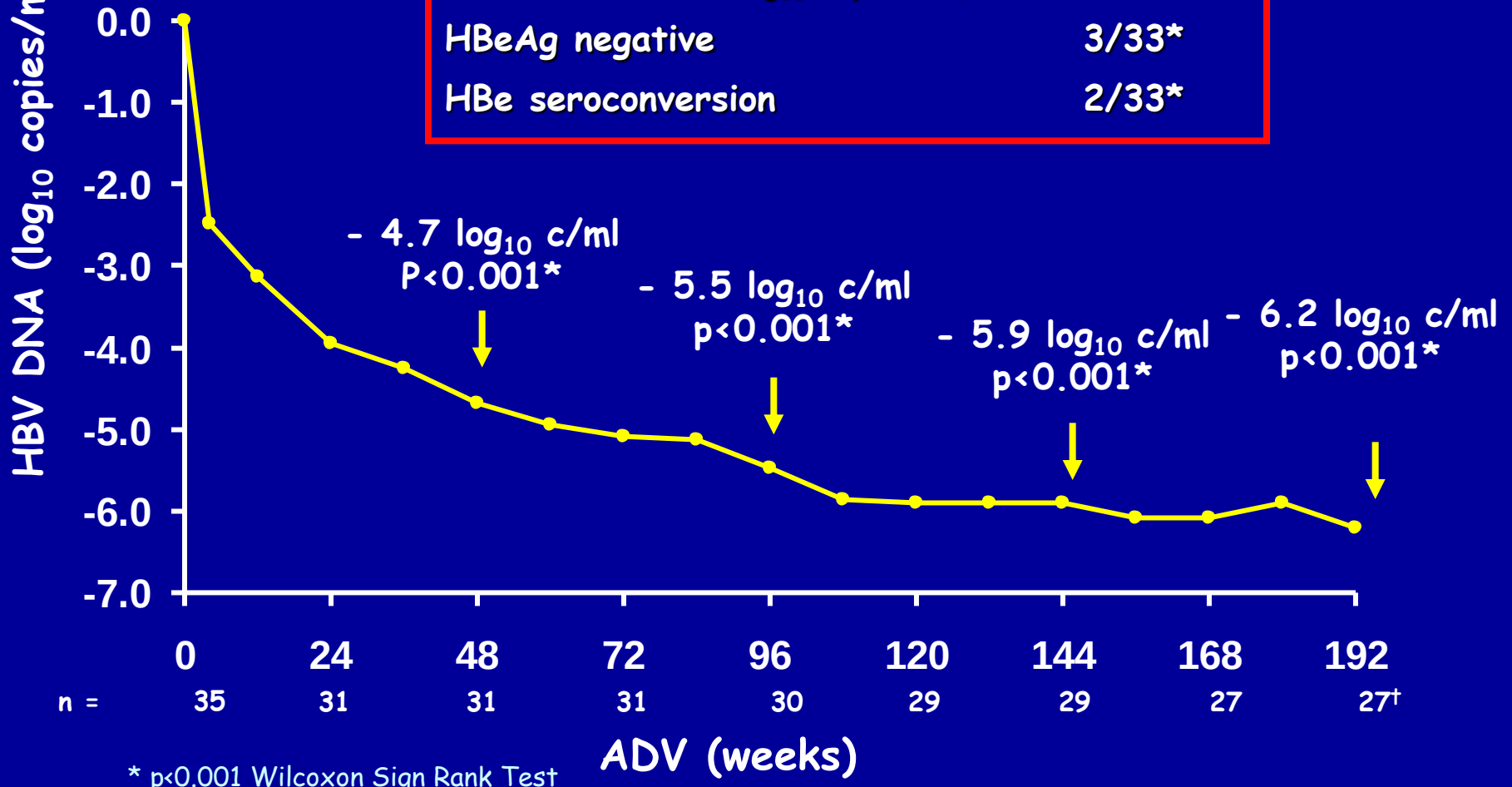
HIV/HBV Lamivudine



Dore GJ, et al. J Infect Dis. 1999;180:607-613.

HIV/HBV LAM-R ADV

HBV DNA (< 2.6 log_{10} copies/ml)	8/35
HBeAg negative	3/33*
HBe seroconversion	2/33*



* p<0.001 Wilcoxon Sign Rank Test

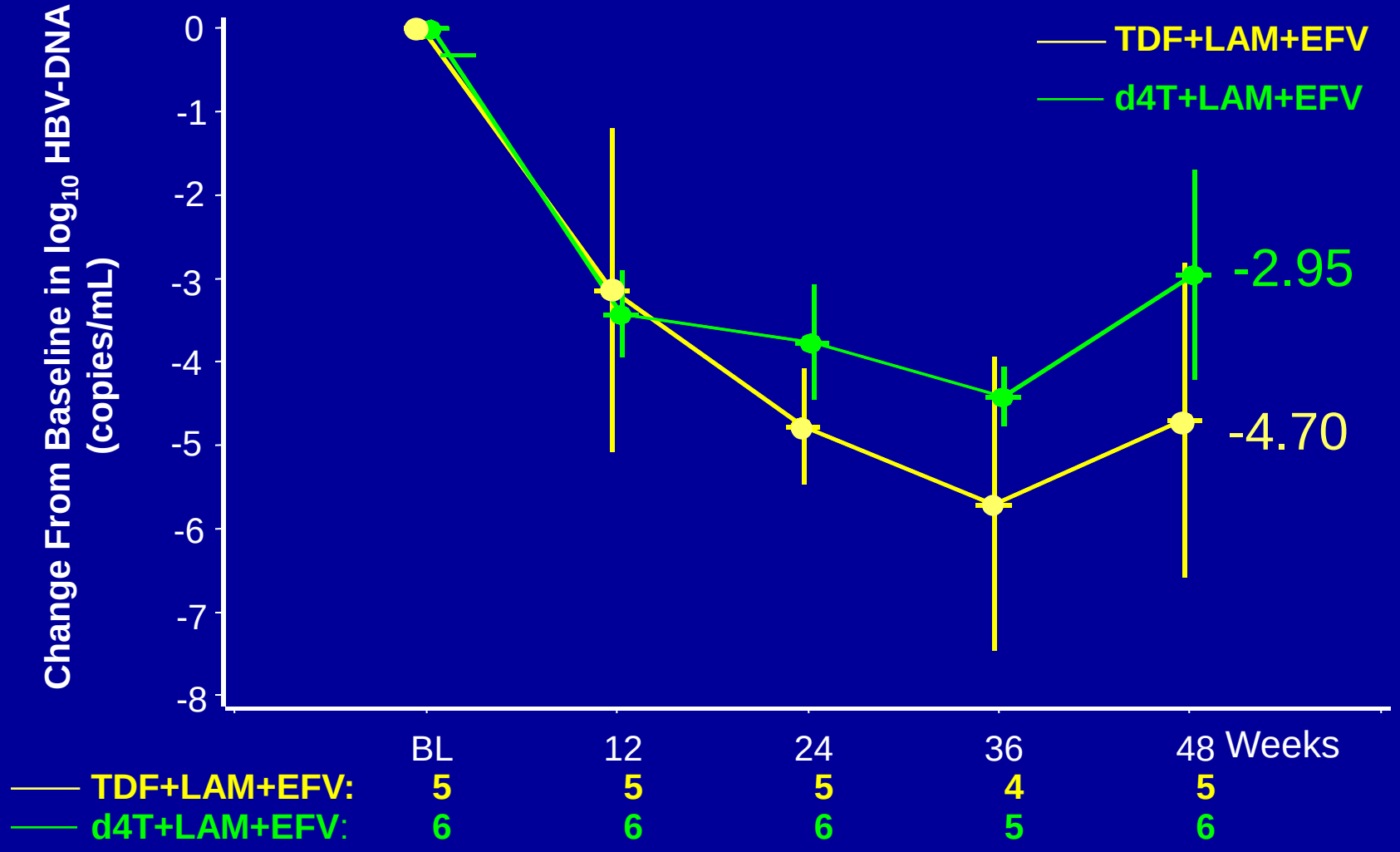
†27 patients remain on study

Benhamou et al. Lancet. 2001;358: 718-23. & J Hepatol. 2006;44:62-7.

Tenofovir for HBV - Gilead Study 903

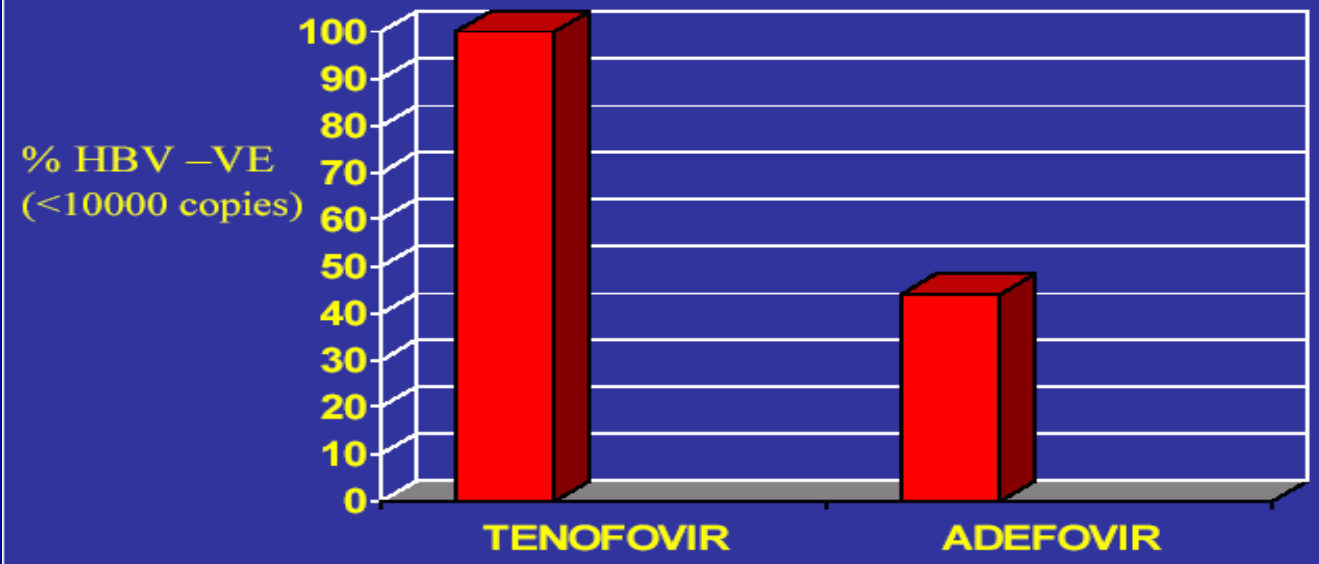
HIV/HBV Coinfected Patients

Mean Change from Baseline in HBV DNA (95% CI)



Cooper D. 10th CROI, Boston MA, February 10-14, 2003, Abstract # 825

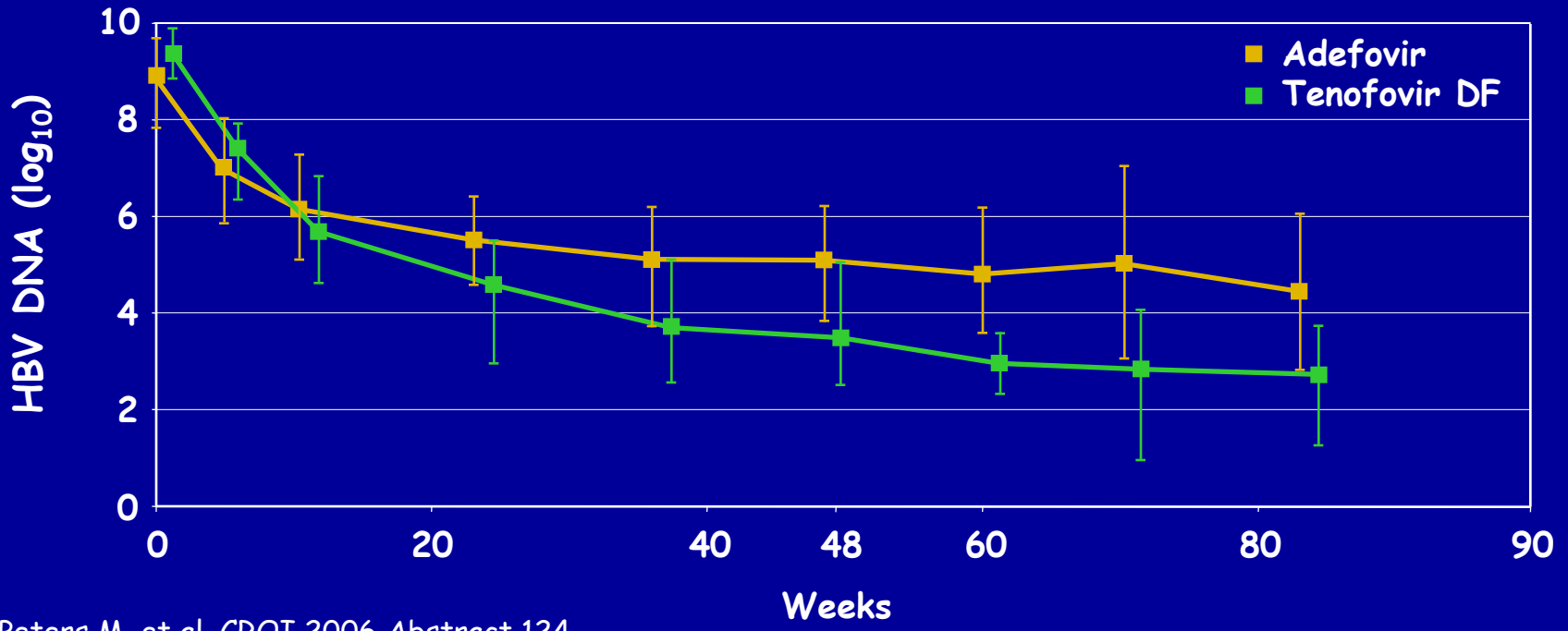
Adefovir or Tenofovir for 3TC Resistant HBV
12 Month HBV Undetectability



Van Bommell Hepatology 2004

Similar (better?) Anti-HBV Activity of Tenofovir compared to Adefovir in Coinfected Patients

- Interim data from ACTG A5127: HBV/HIV-1 coinfected pts
  - HBV DNA ≥ 100,000
  - Stable antiretroviral therapy; HIV-1 RNA ≤ 10,000
- Reduction in HBV DNA with tenofovir noninferior to adefovir



Peters M, et al. CROI 2006 Abstract 124.

GLOBE: Year 1 Results of Telbivudine (LdT) for Chronic Hepatitis B

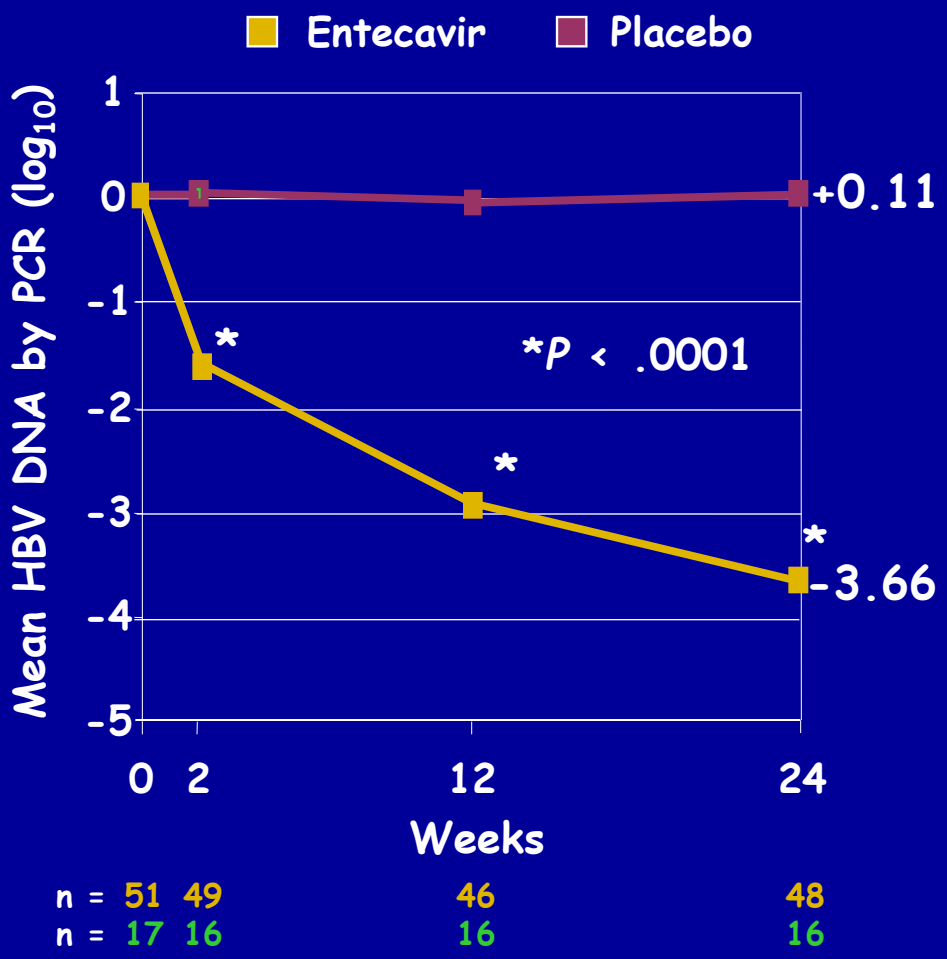
Summary of Year 1 Results With Telbivudine				
Outcome	**HBeAg-Positive Patients**		**HBeAg-Negative Patients**	
	LdT, % (n = 458)	**LAM, % (n = 463)**	**LdT, % (n = 222)**	**LAM, % (n = 224)**
Undetectable HBV DNA • Week 52 • Week 76	75* 75* (n = 163)	67 58 (n = 165)	88* 84* (n = 68)	71 67 (n = 67)
Virologic breakthrough by Week 48	3*	10	2*	9
Normalized ALT • Week 52 • Week 76	77 78* (n = 163)	75 68 (n = 165)	74 76 (n = 68)	79 64 (n = 67)
Fibrosis decline by Wk 52	68	61	59	46
HBeAg seroconversion by Week 76	41* (n = 100)	26 (n = 93)	N/A	N/A

Lai et al. AASLD;2005. Abstract LB01.

*$P < .05$ vs lamivudine.

Potent Anti-HBV Activity From Addition of Entecavir to Continued 3TC in Coinfection

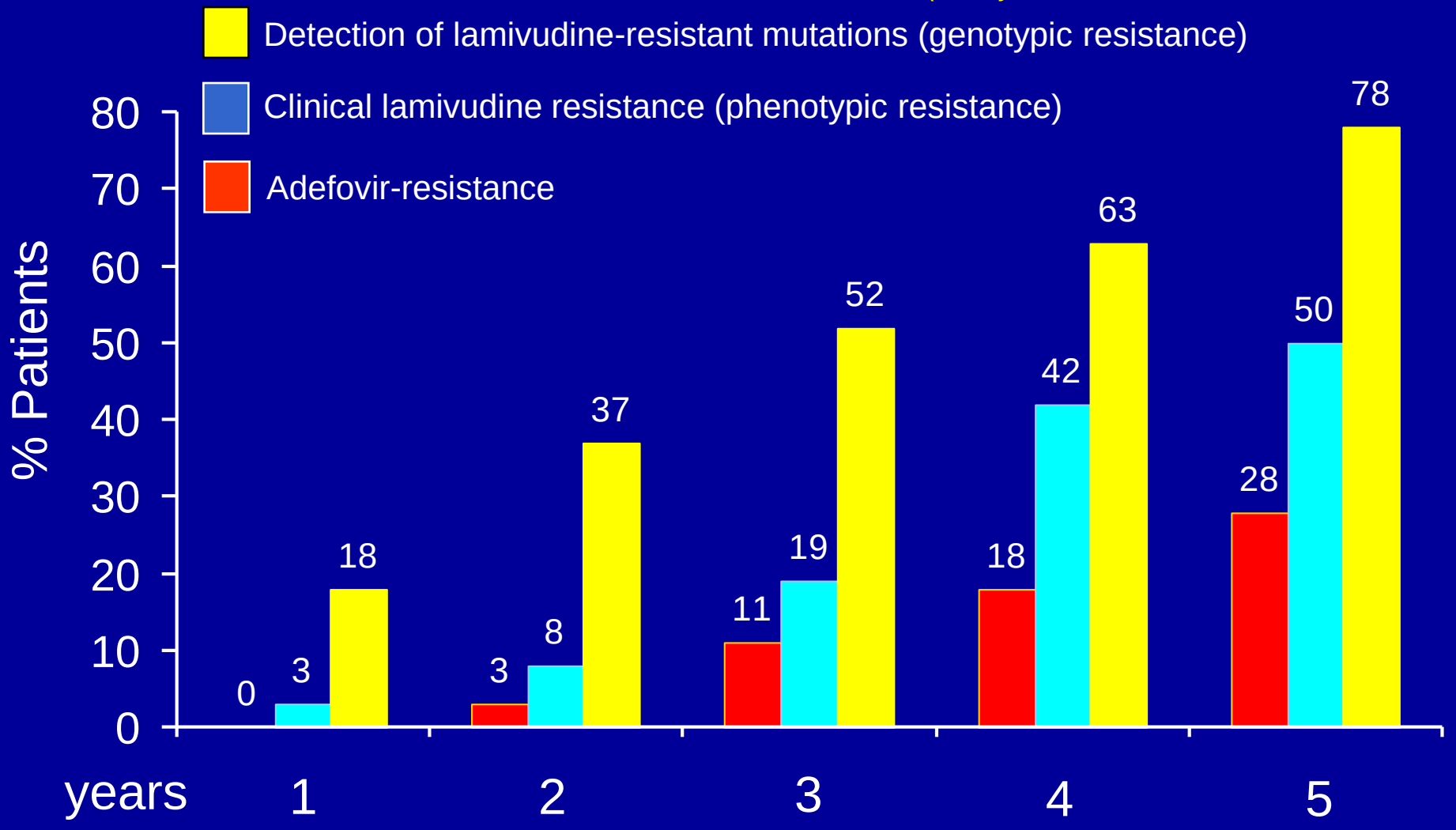
- ETV-038: HBV/HIV coinfected pts
  - HBV DNA ≥ 100,000, HBeAg+ or -, HBsAg+, compensated
  - HIV RNA < 400 for ≥ 12 weeks
  - 3TC-containing HAART for ≥ 24 weeks or YMDD mutation, no other agent with anti-HBV activity
- Entecavir (1 mg QD) vs placebo added to continued 3TC for 24 wks
- 84% ETV had HBV DNA < 400 or ≥ 2 log reduction by Week 24
- No difference in AEs
- RT sequencing for mutations M204V/I, L180M (3TC mutations) and T184, S202 and M259 (ETV mutations) at baseline and at week 48



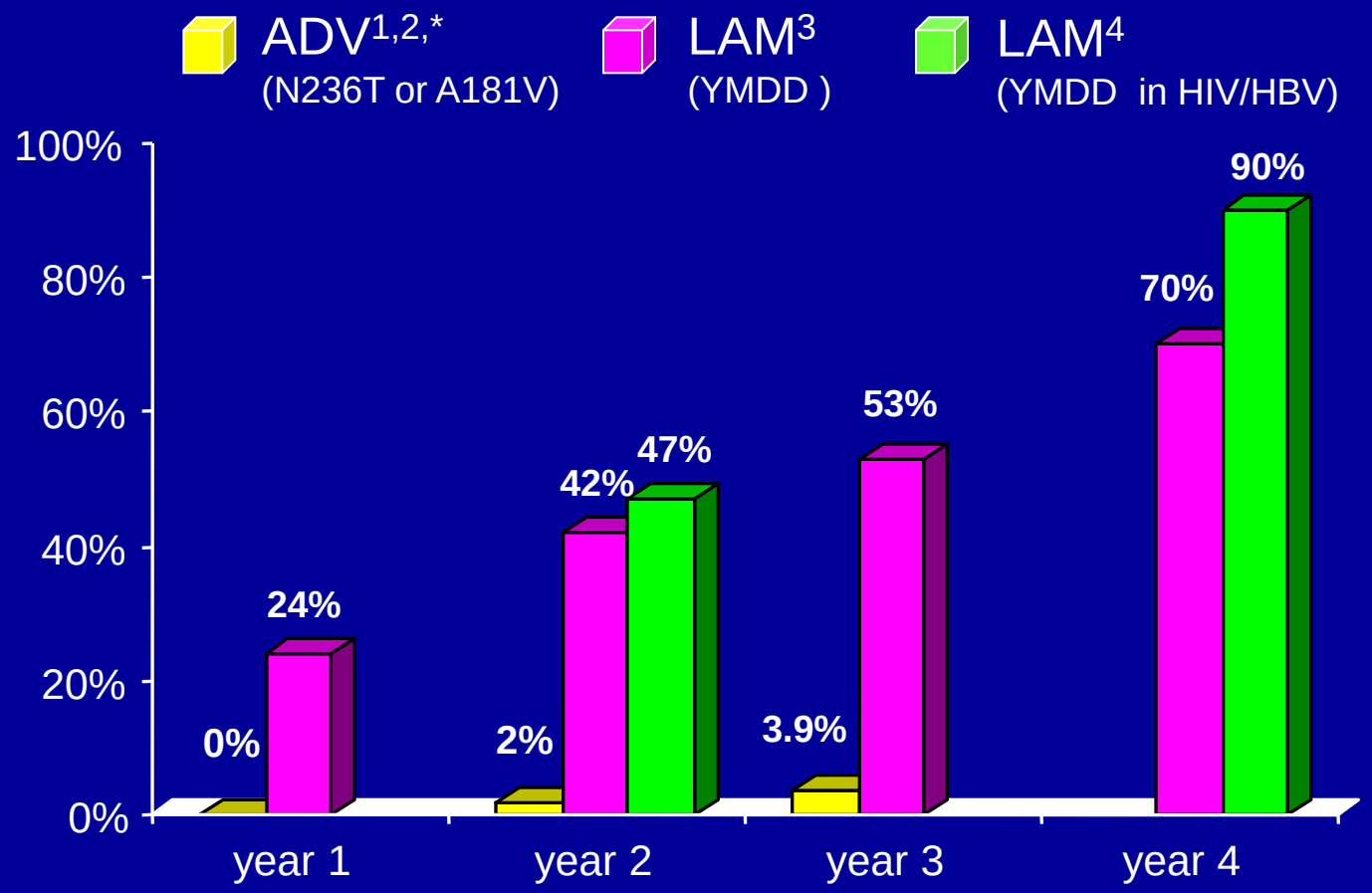
Pessoa W, et al. CROI 2005, Abstract 123, Colonno et al, CROI 2006, Abstract 832

Resistance development – Nucleos(t)ides

(van Bömmel F, Mihm U, Jung C, Berg T. AASLD 2003
Locarnini S et al EASL 2005, Abstract 36)
(Hadziyannis S et al. AASLD 2005 Abstract LB14)



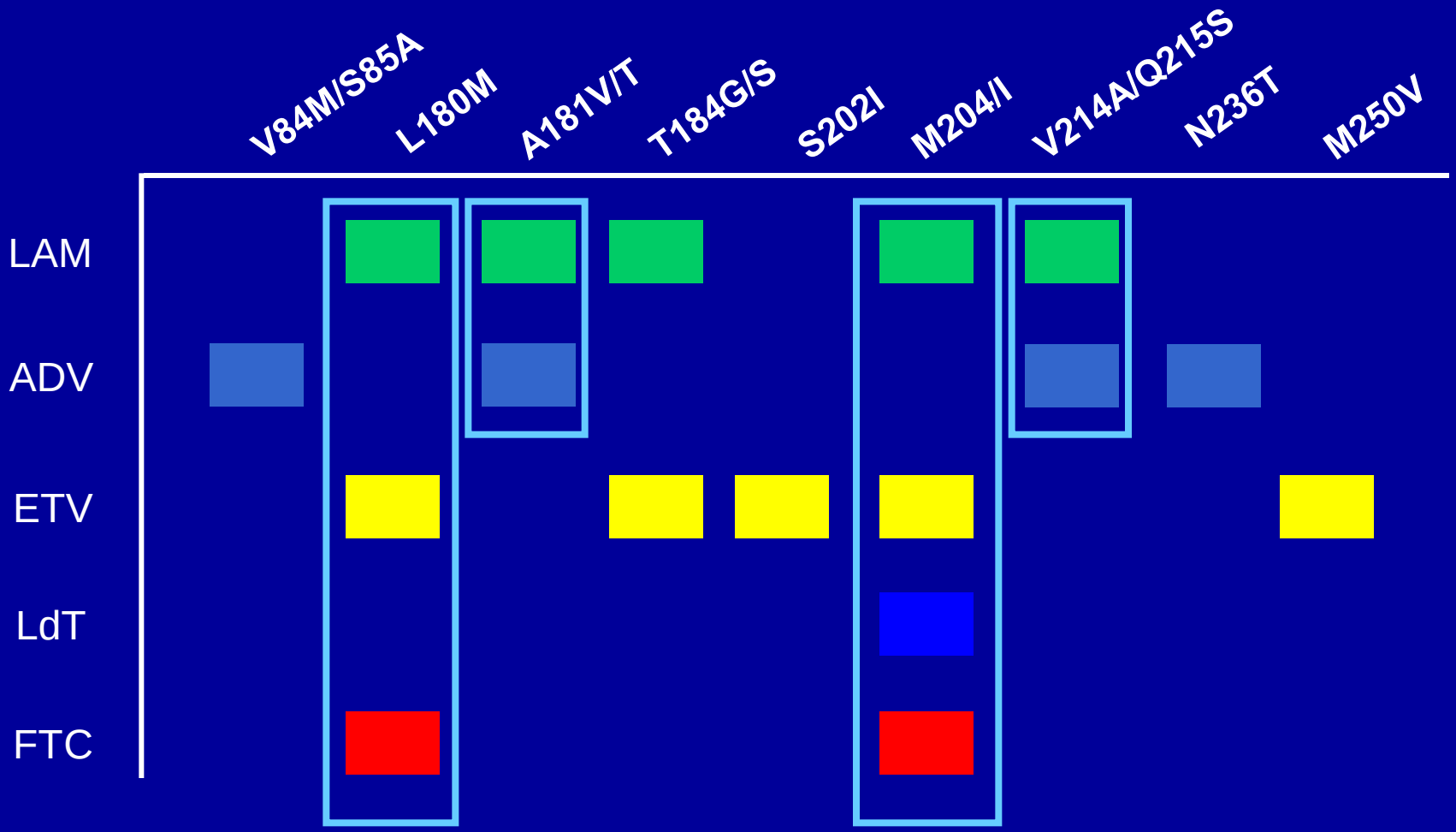
Comparative Incidence of HBV Resistance in Patients Treated with ADV or LAM



1. Benhamou Y. et al., Lancet (2001) 358:718-723
2. Qi, et al., EASL 2004, Apr 16, 2004, Berlin
3. Lai C.L., et al., Clinical Infectious Diseases (2003) 36:687
4. Benhamou Y et al. Hepatology 1999; 30:1302-6

* Year 4 resistance rate for ADV not yet available

Resistance Mutations Associated with Viral Breakthrough in Patients on Treatment



Selection of LAM-Resistant Mutants Affects Future Treatment Options

Locarnini S et al. *Antivir Ther* 2004;9:679–93.

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

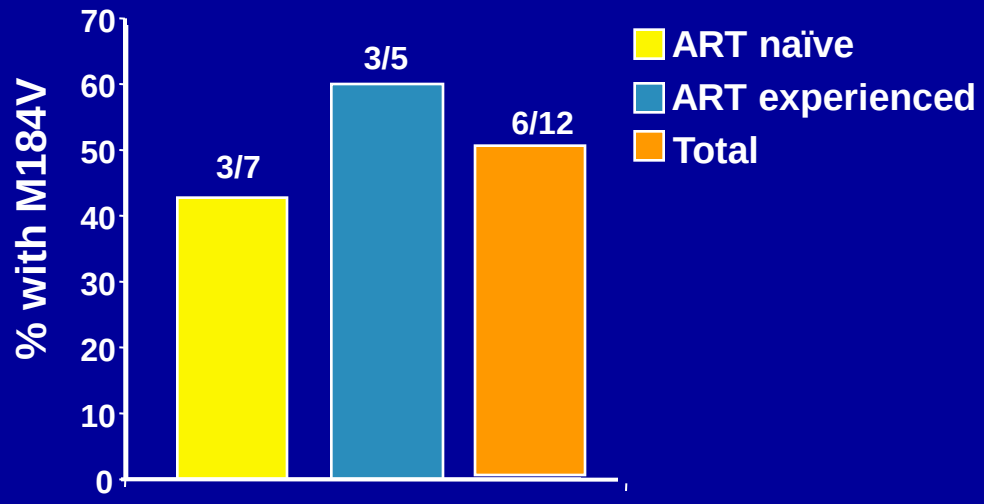
Envelope changes	Polymerase changes	Ag–Ab binding [IC_{50} (µg/ml)]
Wild type	Wild type	1.09
HBIG escape		
sG145R	rtW153G	>55.0
Anti-viral drug resistant		
sE164D	rtV173L	14.86
sW196S	rtM204I	8.29
sI195M	rtM204V	5.26
sM198I	rtV207I	12.5
sE164D/I195M	rtV173/rtL180/rtM204V	54.53

Cooley L et al. *AIDS* 2003;17:1649–57.

Anti-HIV activity of entecavir

- 17 HIV/HBV coinfected pts (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 plasma HIV-RNA in the majority but not all pts, and can select for the M184V mutation even in naive pts
- HIV/HBV co-infected individuals should not receive ETV monotherapy

Selection of M184V following ETV tx



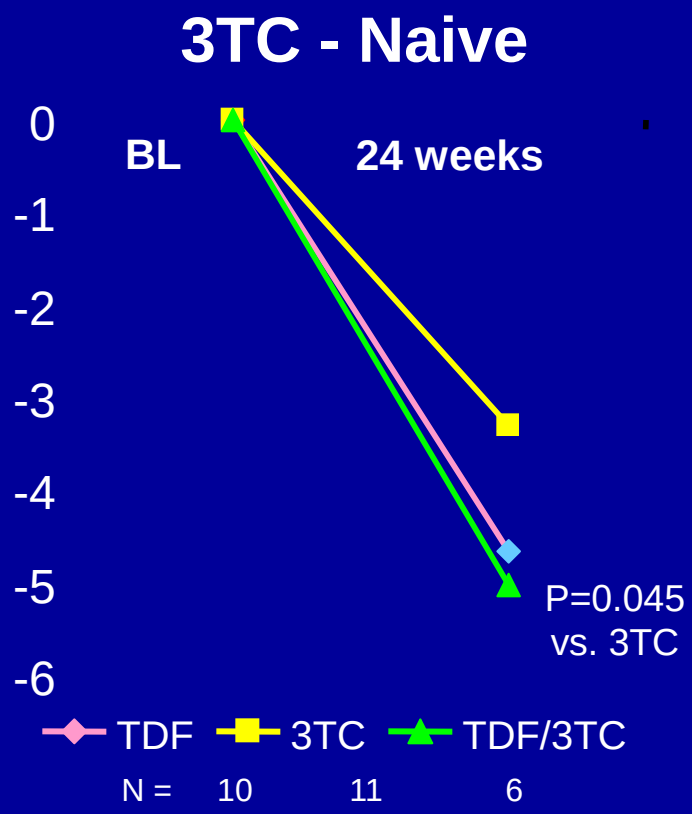
Median time to M184V 148 days 98 days

Univariate analysis for selection of M184V

Risk factor	p value
Total duration on ETV	0.05
Magnitude of HBV-DNA reduction on ETV	0.04
HIV-RNA pre-ETV therapy	0.87
HBV-DNA pre-ETV therapy	0.69
Nadir CD4+ count	0.20

1. Audsley J, *et al. 15th CROI*, Boston 2008, No.63

TDF vs TDF/3TC vs 3TC in drug-naïve HIV/HBV coinfected

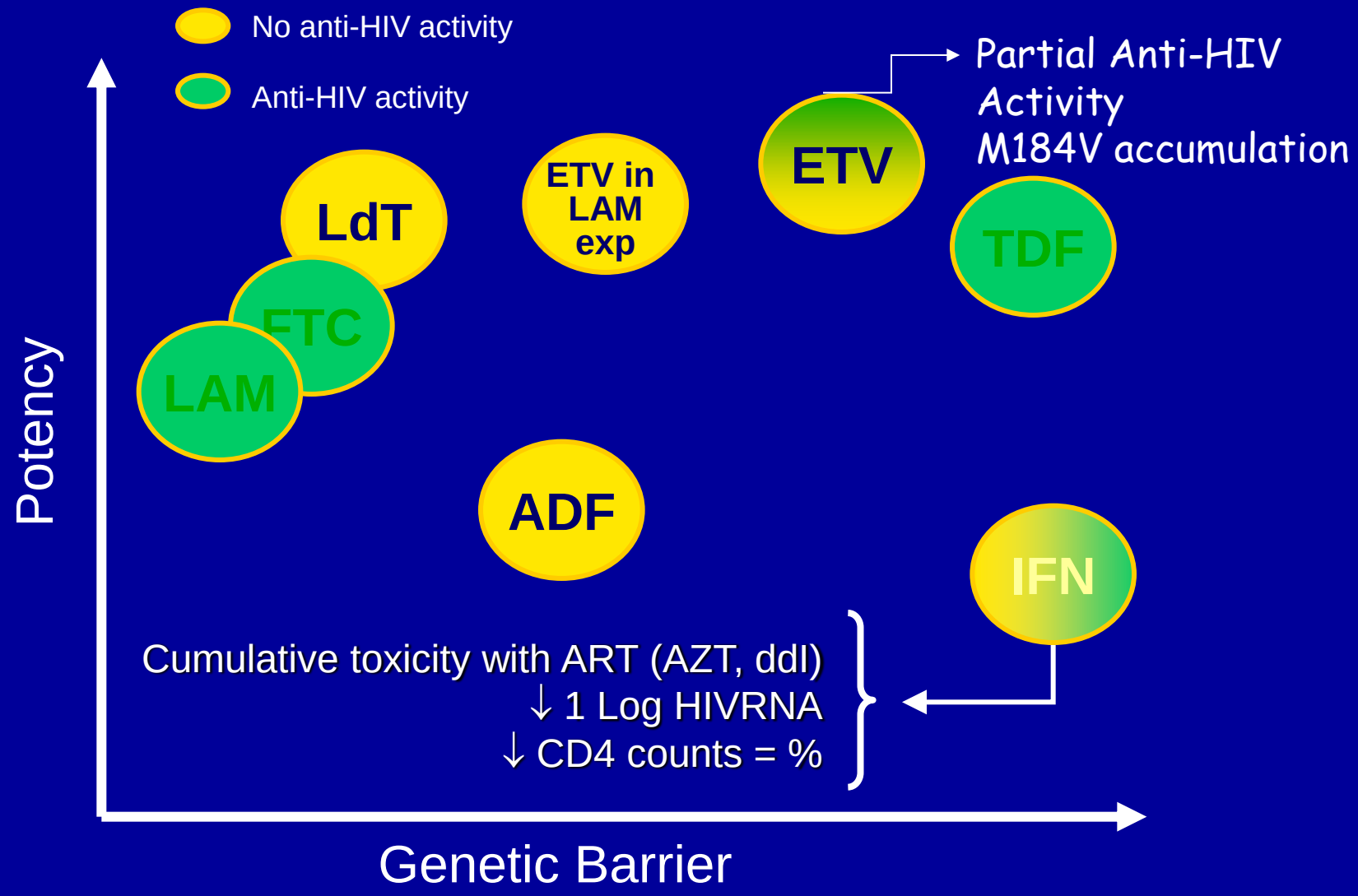


Conclusion:

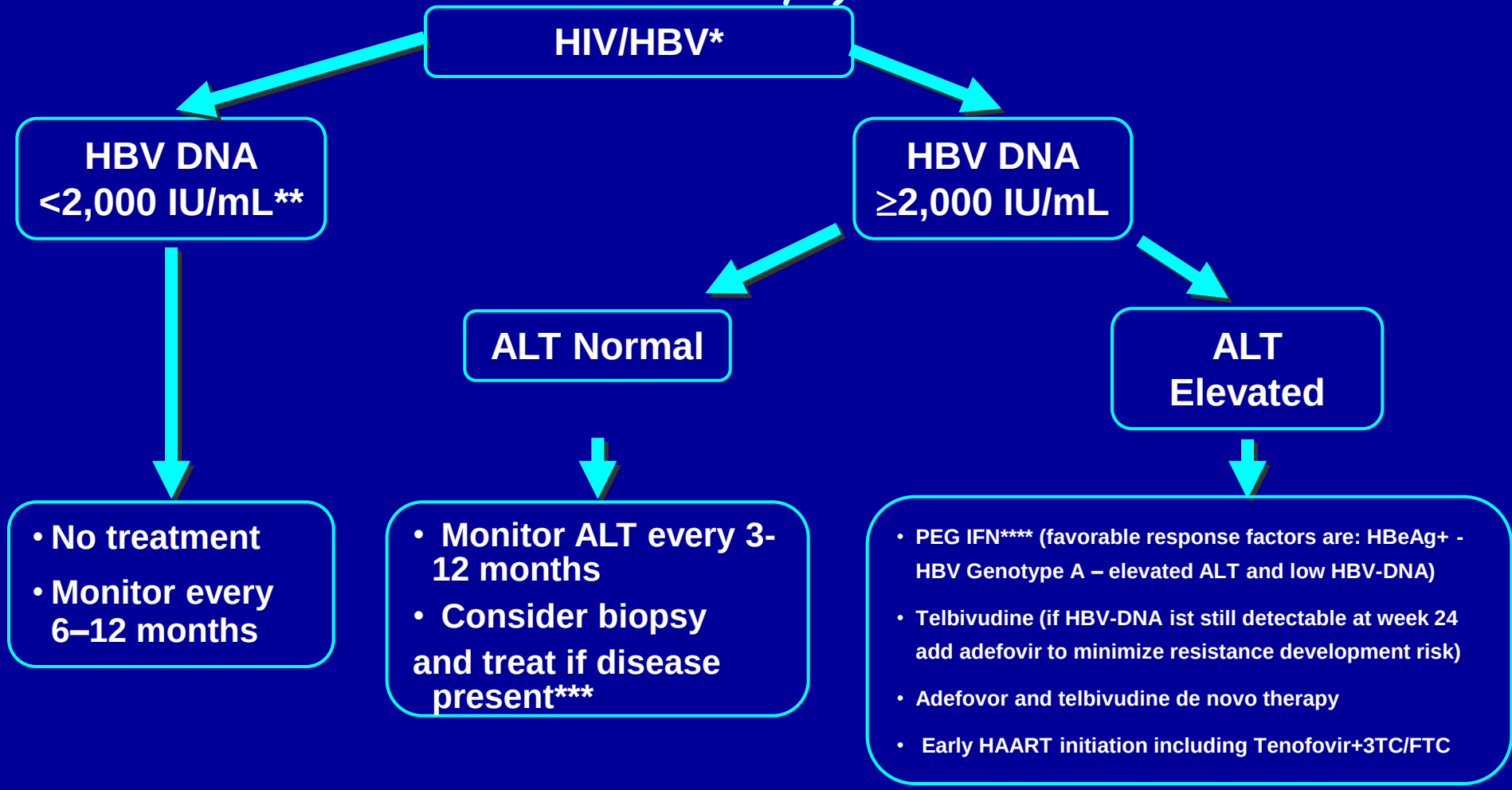
- TDF/3TC superior to 3TC alone but not TDF in HBV naïve
- No benefit continuing 3TC in experienced HBV viraemic patients
- No difference between adding or switching TDF

1. Nelson M, et al. A 48 week study of tenofovir or lamivudine or a combination of tenofovir and lamivudine for the treatment of chronic hepatitis B in HIV/HBV co-infected individuals. *13th CROI.* Denver, CO, February 5-8, 2006; Abst. 831.

Anti HBV Drugs in HIV Infection

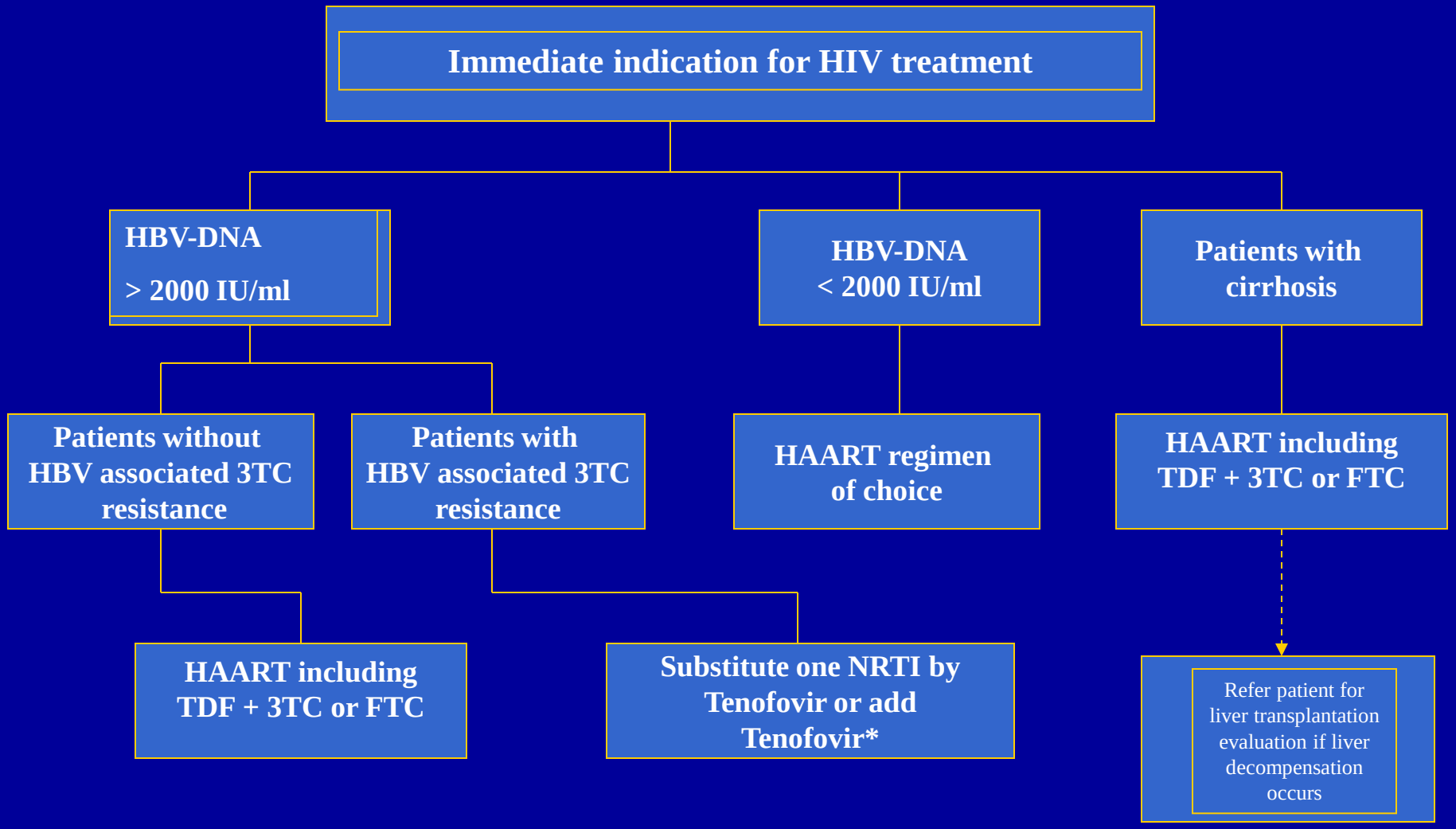


Treatment Algorithm:
Patients with Compensated Liver Disease and No indication for HIV therapy (CD4 count > 350/µl)



Soriano V, *et al. 4th IAS, Sydney* 2007, #MoBS104;
Benhamou Y, 3rd International Workshop on HIV and hepatitis coinfection, Paris 2007

Management and therapeutic options in HIV-HBV co-infected patients with an indication of anti-HIV therapy



ECC Statement J Hepatol 2005

*if feasible and appropriate from the perspective of maintaining HIV suppression