

Hepatitis B and HIV co-infection

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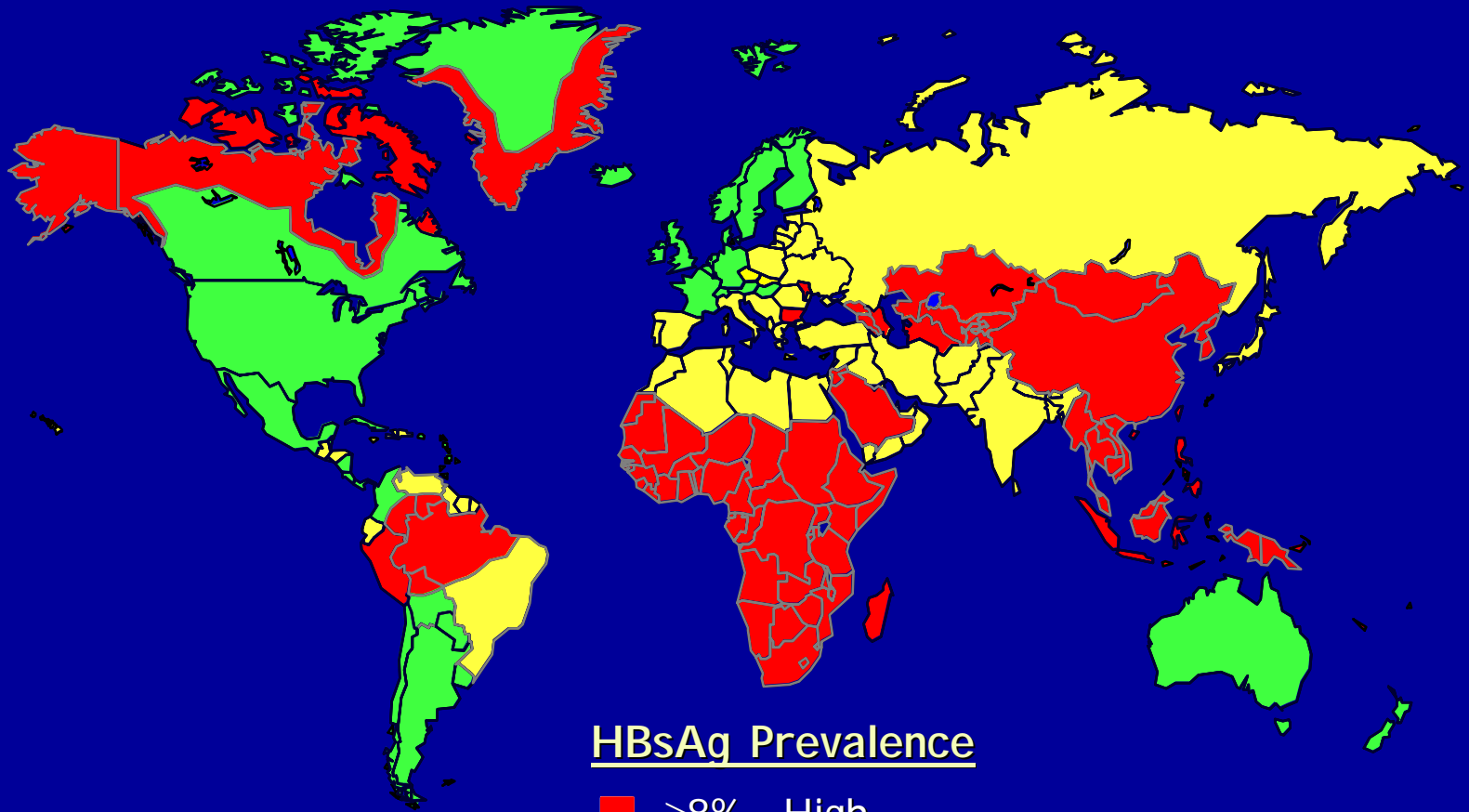
Inatoa madoa doa yote!!

BEFORE

AFTER



Geographic Distribution of Chronic Hepatitis B



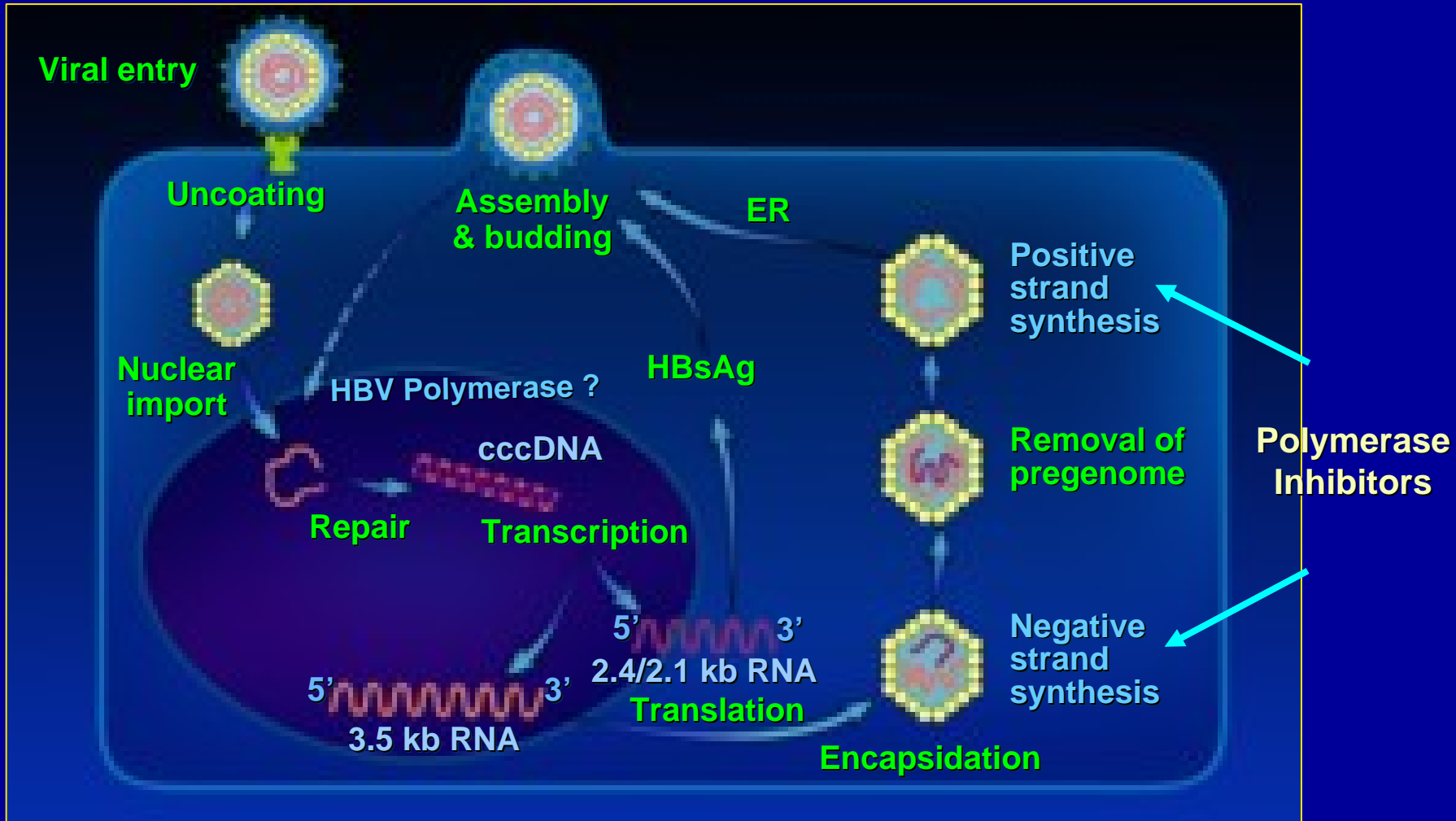
350 million world-wide

HBsAg Prevalence

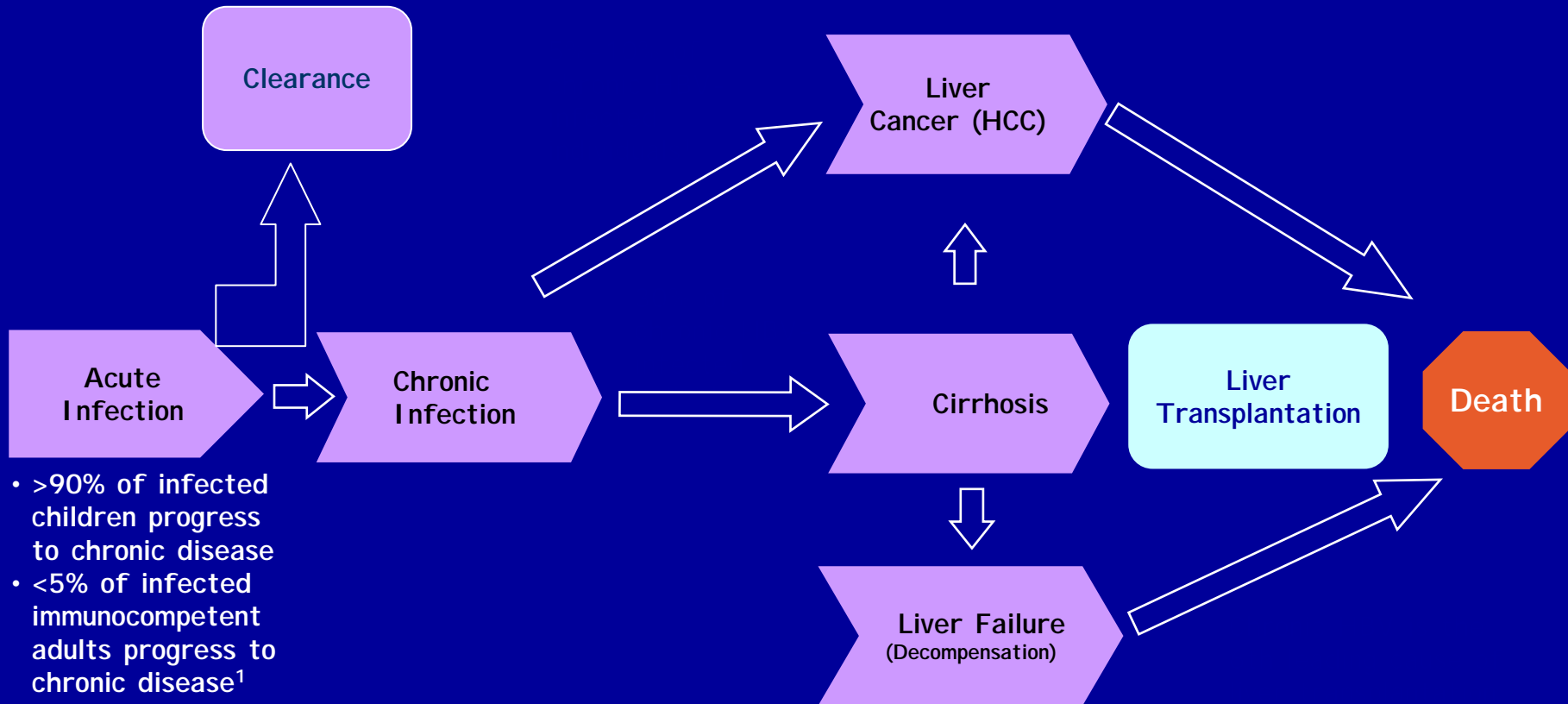
- Red: ≥8% - High
- Yellow: 2-7% - Intermediate
- Green: <2% - Low

How do we assess disease in
HBV?

Hepatitis B Virus Viral Replication



Hepatitis B Disease Progression

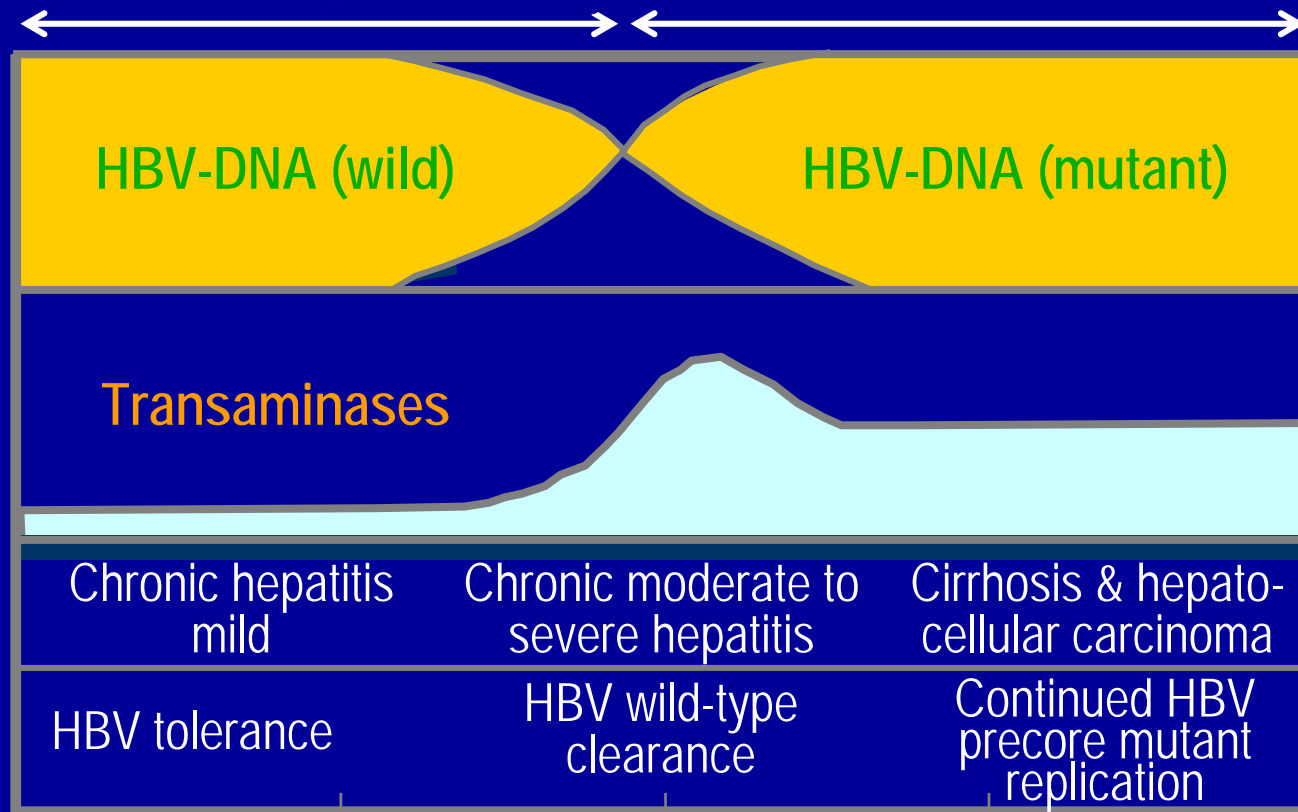


1. Torresi, J, Locarnini, S. Gastroenterology. 2000.
2. Fattovich, G, Giustina, G, Schalm, SW, et al. Hepatology. 1995.
3. Moyer, LA, Mast, EE. Am J Prev Med. 1994.
4. Perrillo, R, et al. Hepatology. 2001.

Phases of chronic HBV Infection

- Inactive HbsAg carrier state (non replicative phase)
 - HBeAg negative, low/absent HBV DNA, no inflammation/fibrosis
- 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

Emergence of the e-negative Precore Mutant



Years

HBsAg Negative Chronic Hepatitis B

- Anti-HBe positive, HBV DNA 10^4 - 10^5 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

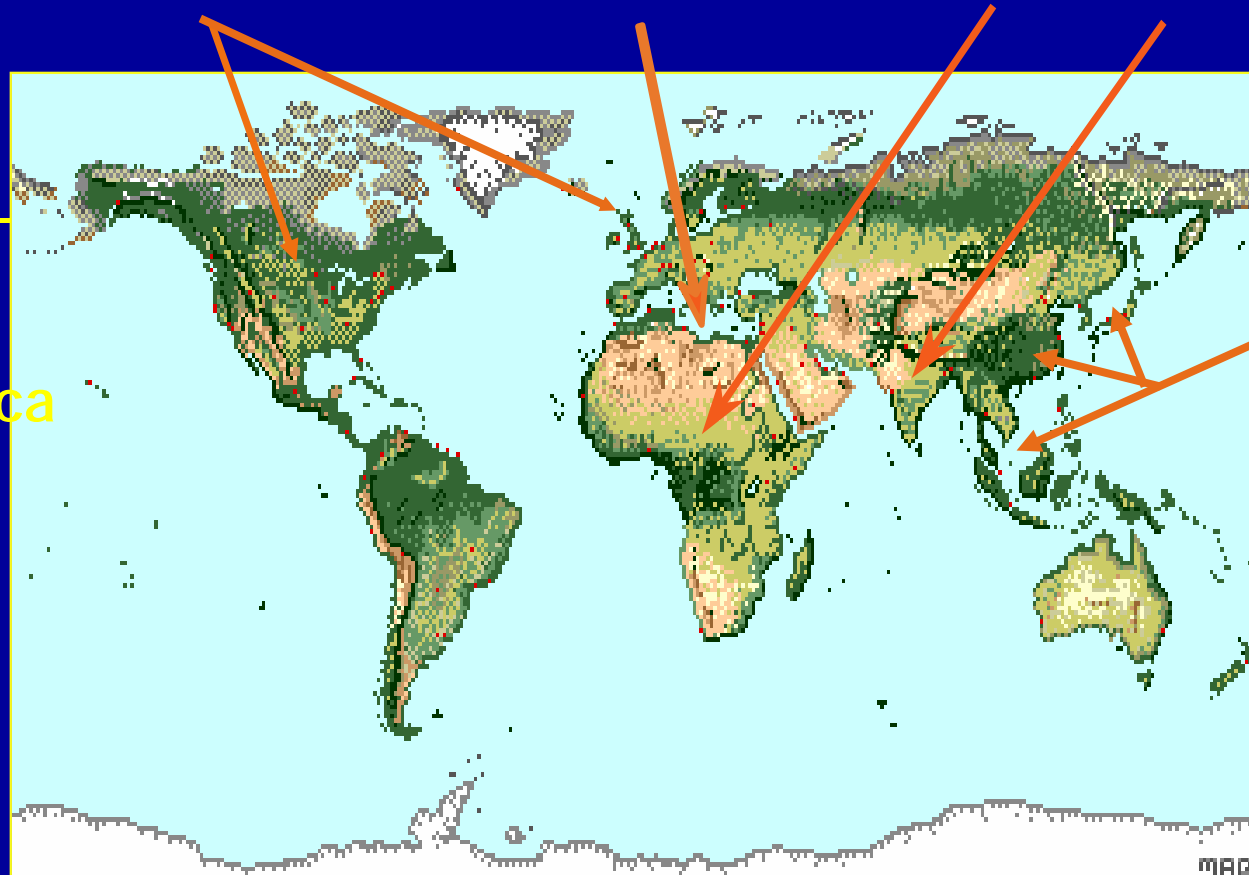
India
A

Rare types:

F - Latin
America

G -France,
USA

H -Mexico,
Latin America



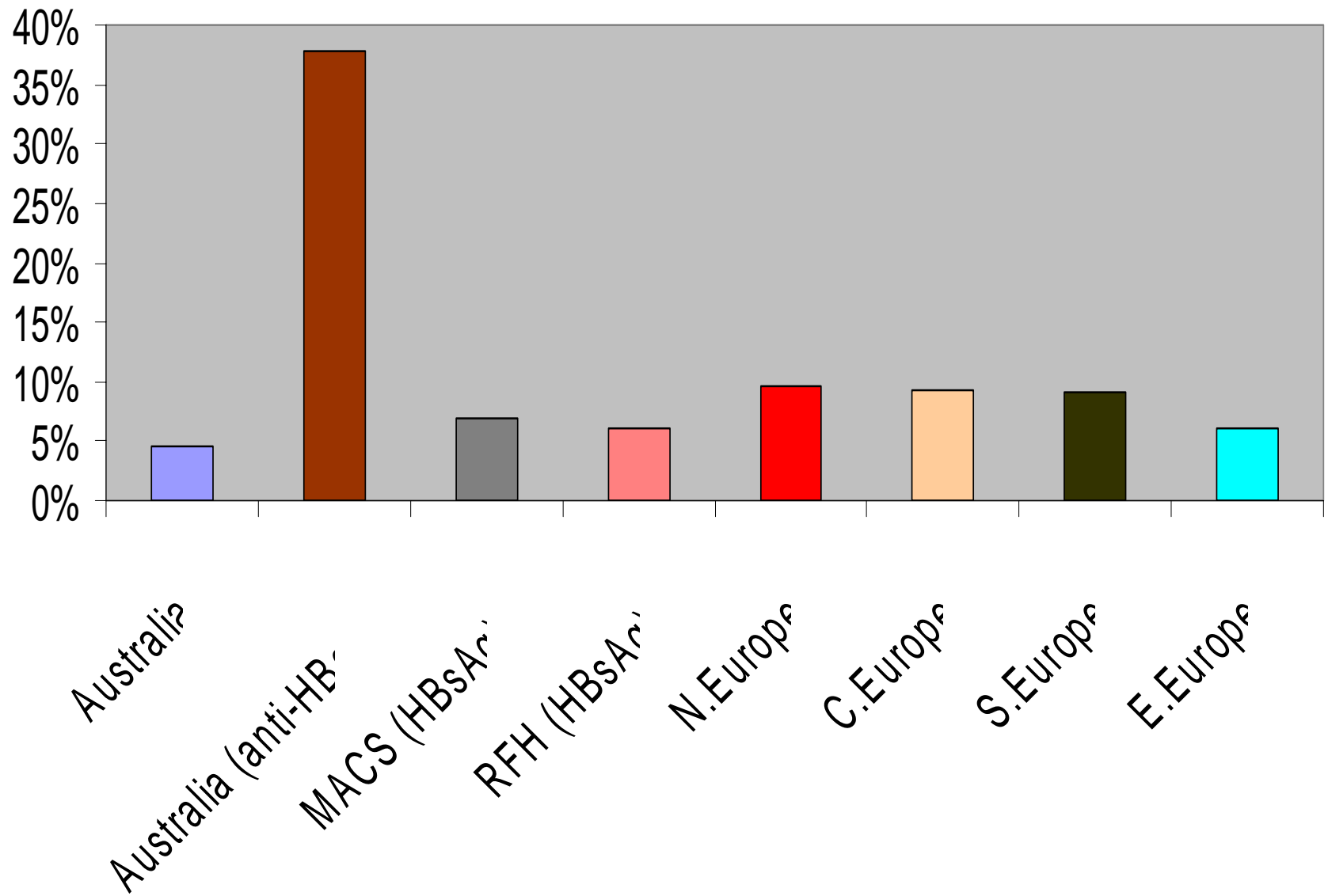
Far East
B & C

HBV Genotype	Geographical Distribution	Clinical Relevance
A	Central Africa, Europe, North America	When compared with other genotypes: <ul style="list-style-type: none"> ■ Better response to peginterferon
B	China, Indonesia, Taiwan, Vietnam	When compared with genotype C: <ul style="list-style-type: none"> ■ 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: <ul style="list-style-type: none"> ■ More severe disease ■ Worse clinical outcome
D	India, Mediterranean, Middle East	<ul style="list-style-type: none"> ■ Associated with precore mutation
E	Nigeria, West Africa	<ul style="list-style-type: none"> ■ Unknown
F	Alaska, Polynesia	<ul style="list-style-type: none"> ■ Unknown
G	France, North America	<ul style="list-style-type: none"> ■ Unknown
H	Central America	<ul style="list-style-type: none"> ■ Unknown

Hepatitis B Serology

Isolated HBcAb+

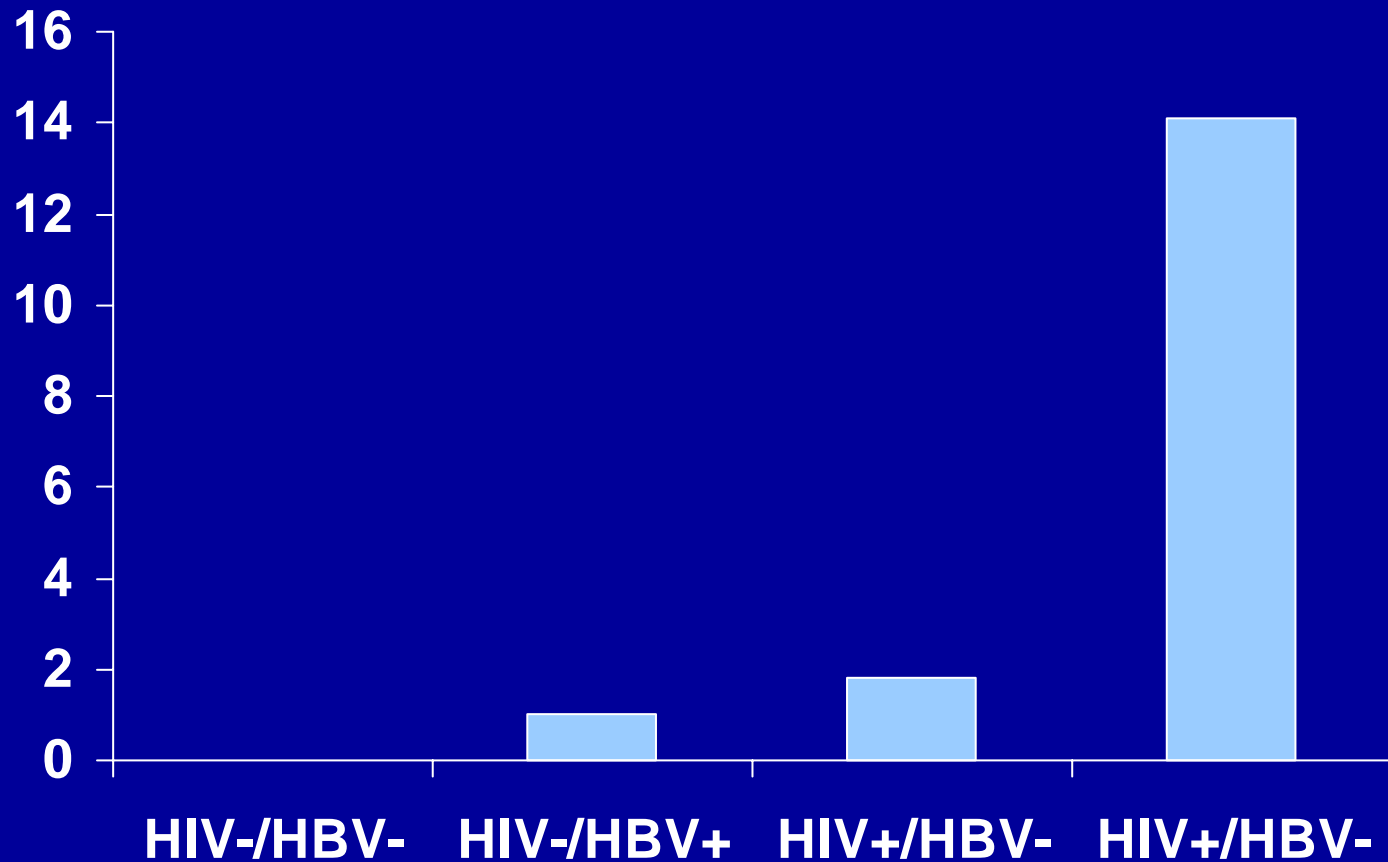
- HIV negative
 - 50% true positive HBcAb
 - <2% with detectable serum HBV DNA
- HIV positive
 - 60-90% true positive HepBcAb
 - Many with detectable HBV DNA (~15% at RFH)
 - ~40% with necro-inflammation on liver biopsy
- Isolated anti-HBc more common in HIV/HCV
- Implications for 3TC based HAART and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



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

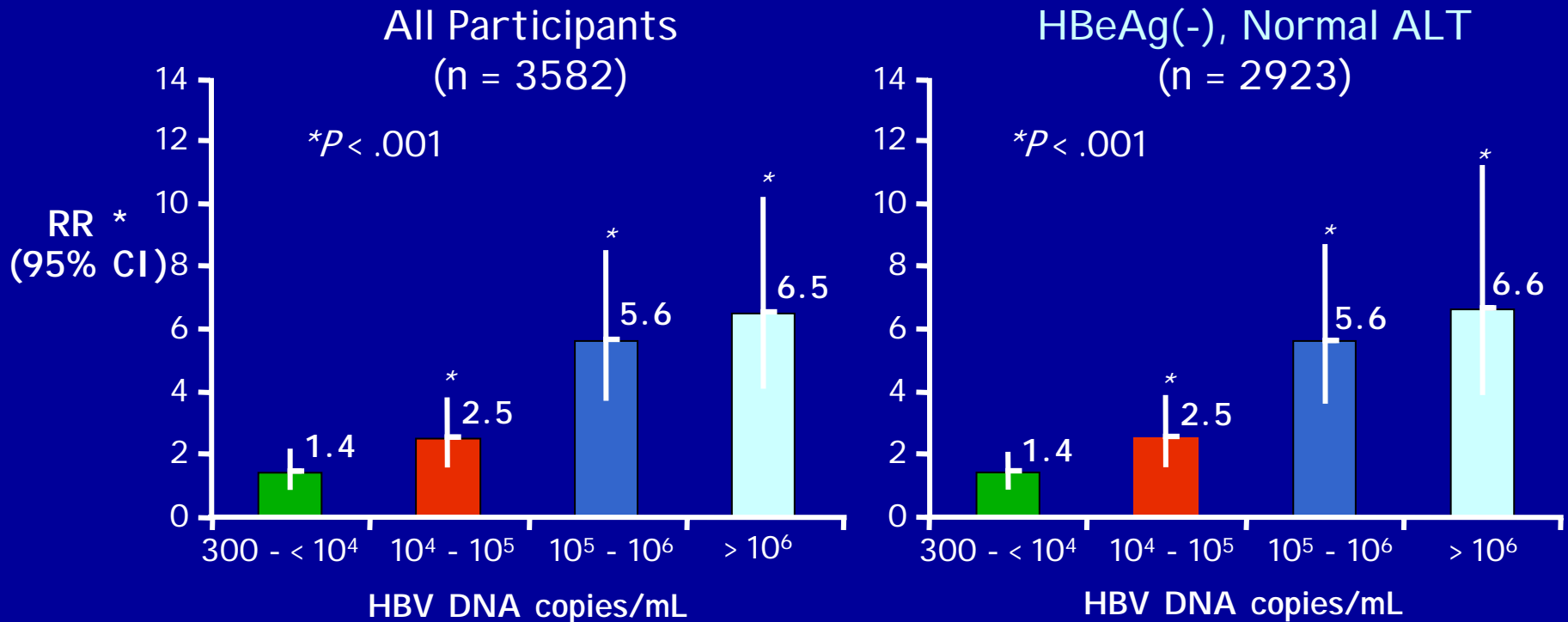


When do we need to Rx HBV?

- Everybody with detectable HBV DNA?
- Based on HBV DNA levels?
- Those with evidence of significant liver disease?
 - Based on abnormal ALTS?
 - Histological activity?

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



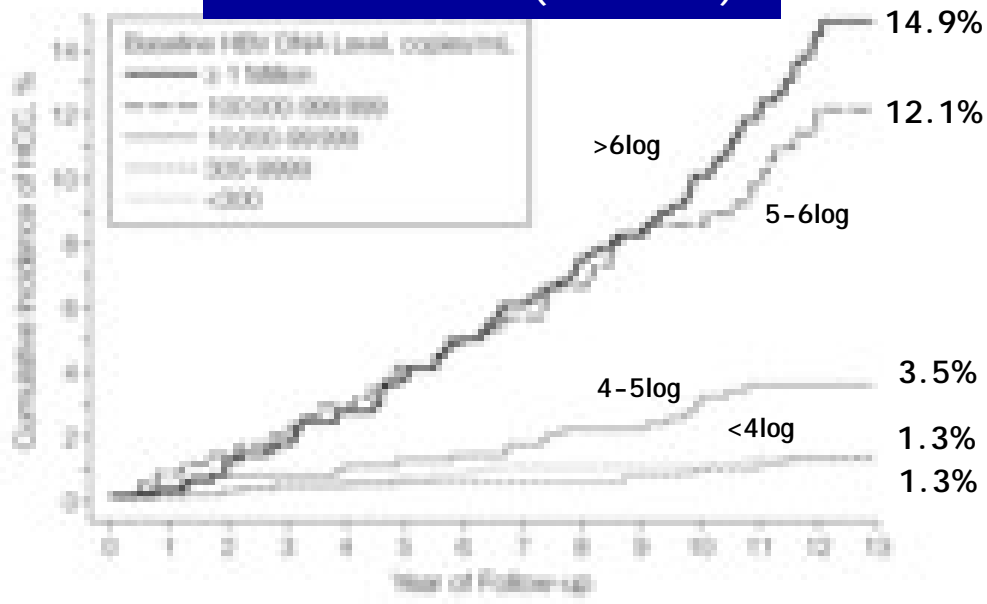
* Adjusted for age, sex, cigarette smoking, and alcohol consumption.

HBV-DNA viral load (> 10⁴ cp/ml) strongest predictor of progression to cirrhosis independent of ALT and HBeAg status

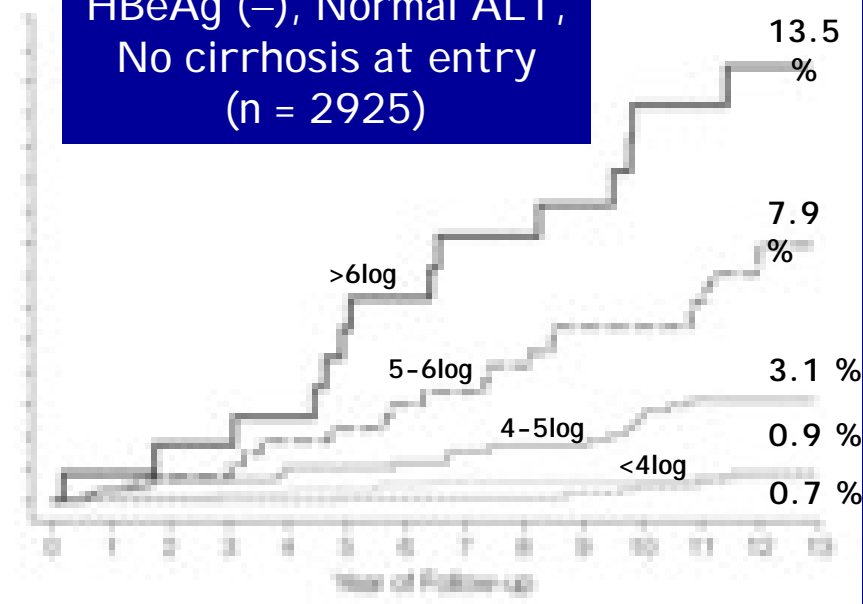
Level of HBV DNA (PCR-assays) at entry & risk of HCC

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

Entire cohort (n = 3653)



HBeAg (-), Normal ALT, No cirrhosis at entry (n = 2925)



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

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

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

Treatment of HBV

- AIMS
 - Halt/slow progression to cirrhosis
 - Prevent HCC
- END POINTS:
 - Normalization of serum ALT
 - Negative or low HBV DNA level
 - Loss of HBeAg +/- appearance of anti-HBe
 - Improvement in liver histology
 - Loss of HBsAg +/- appearance of HBsAb

How?

Restoring immune control

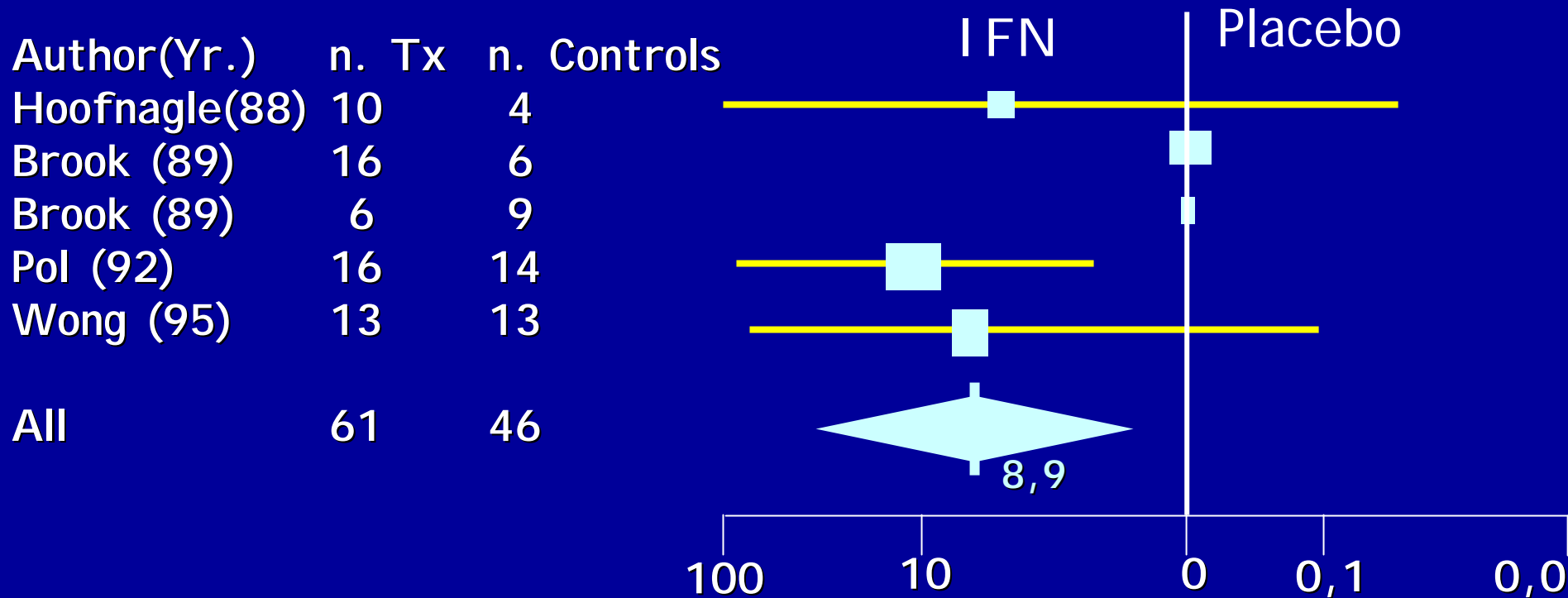
- Type I interferons
 - Interferon-alpha
 - Pegylated interferon-alpha-2a
- ?others

Viral replication suppression with antivirals

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

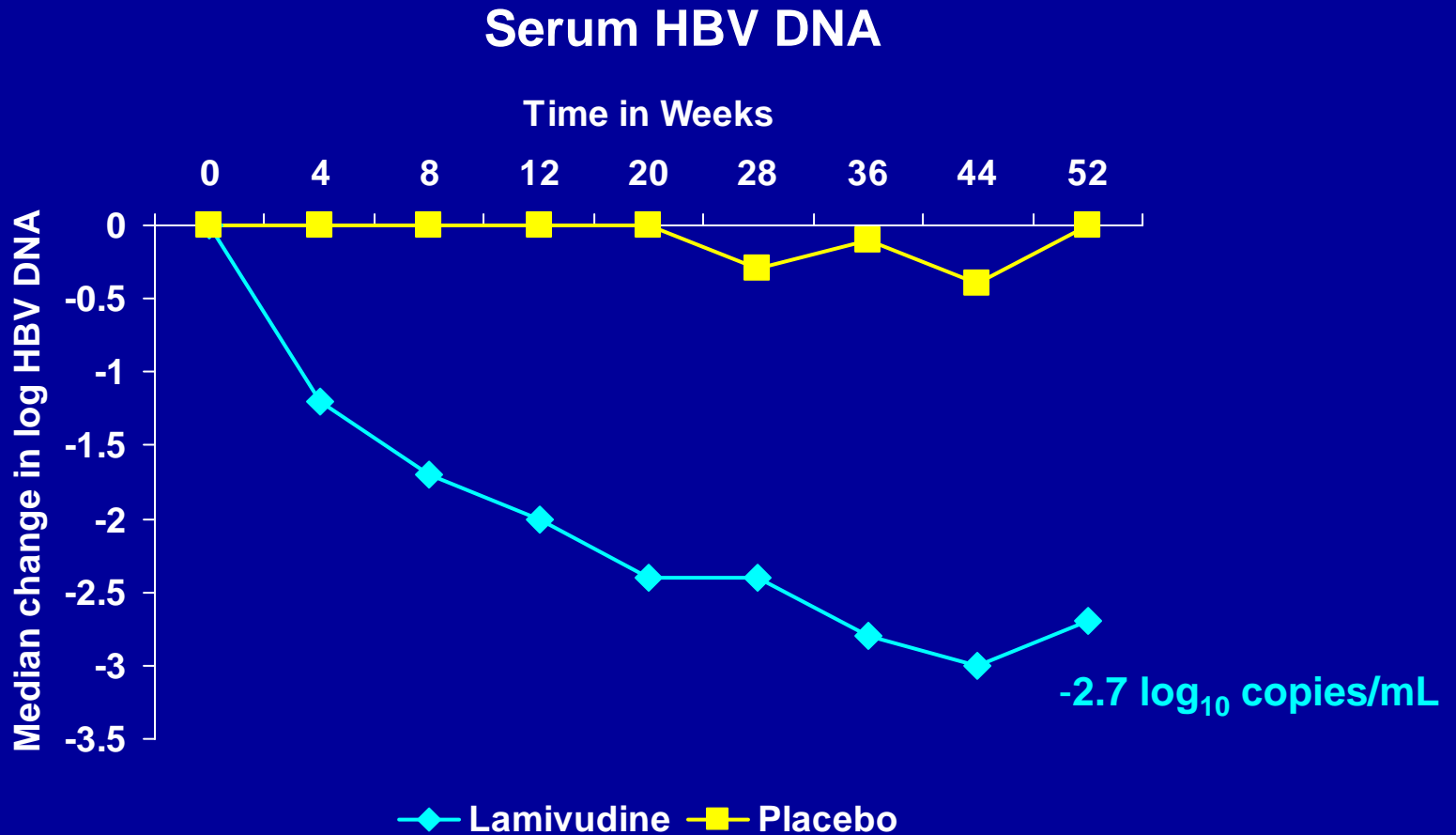
IFN- α in HBV /HIV co-infection

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

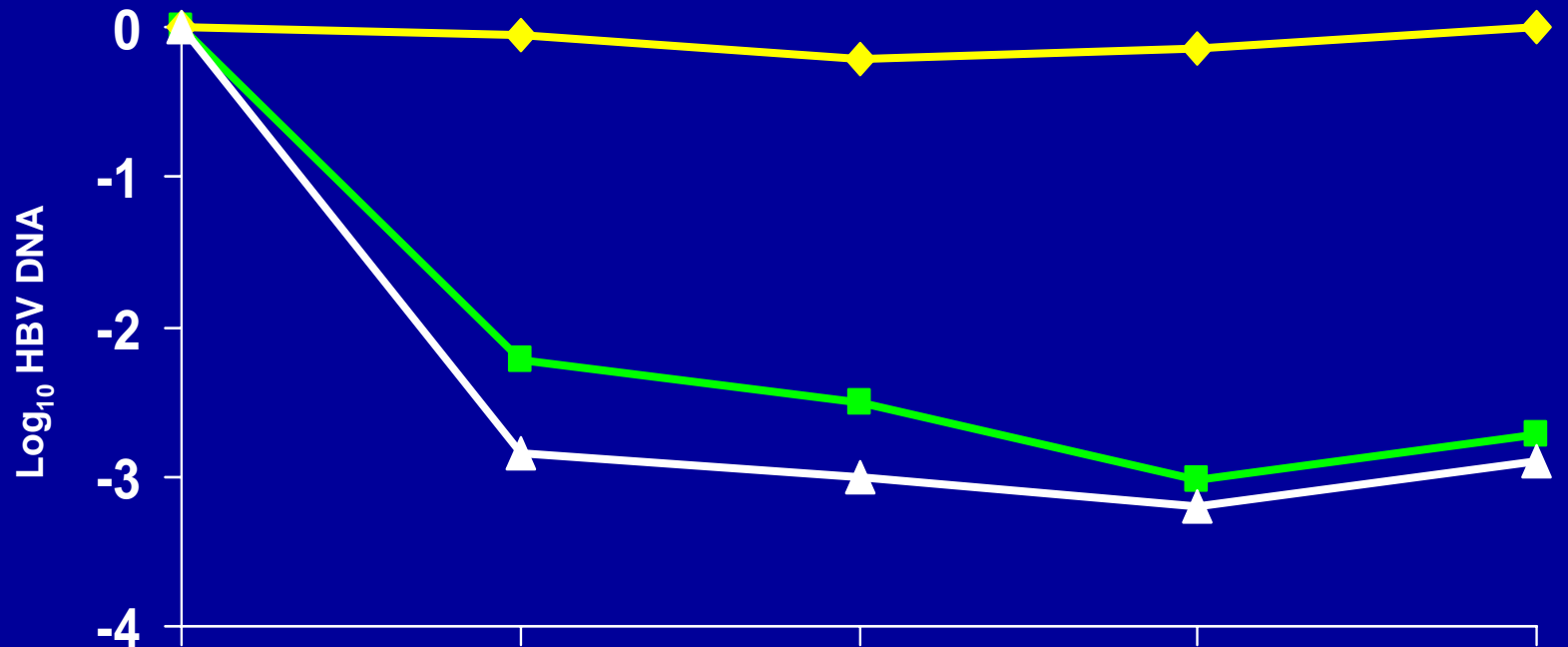


HBe seroconversion/negativation : HIV+ vs HIV: - 0.38 (CI 0.06-0.7 $P = .02$)

HIV/HBV Lamivudine



HIV/HBV FTC



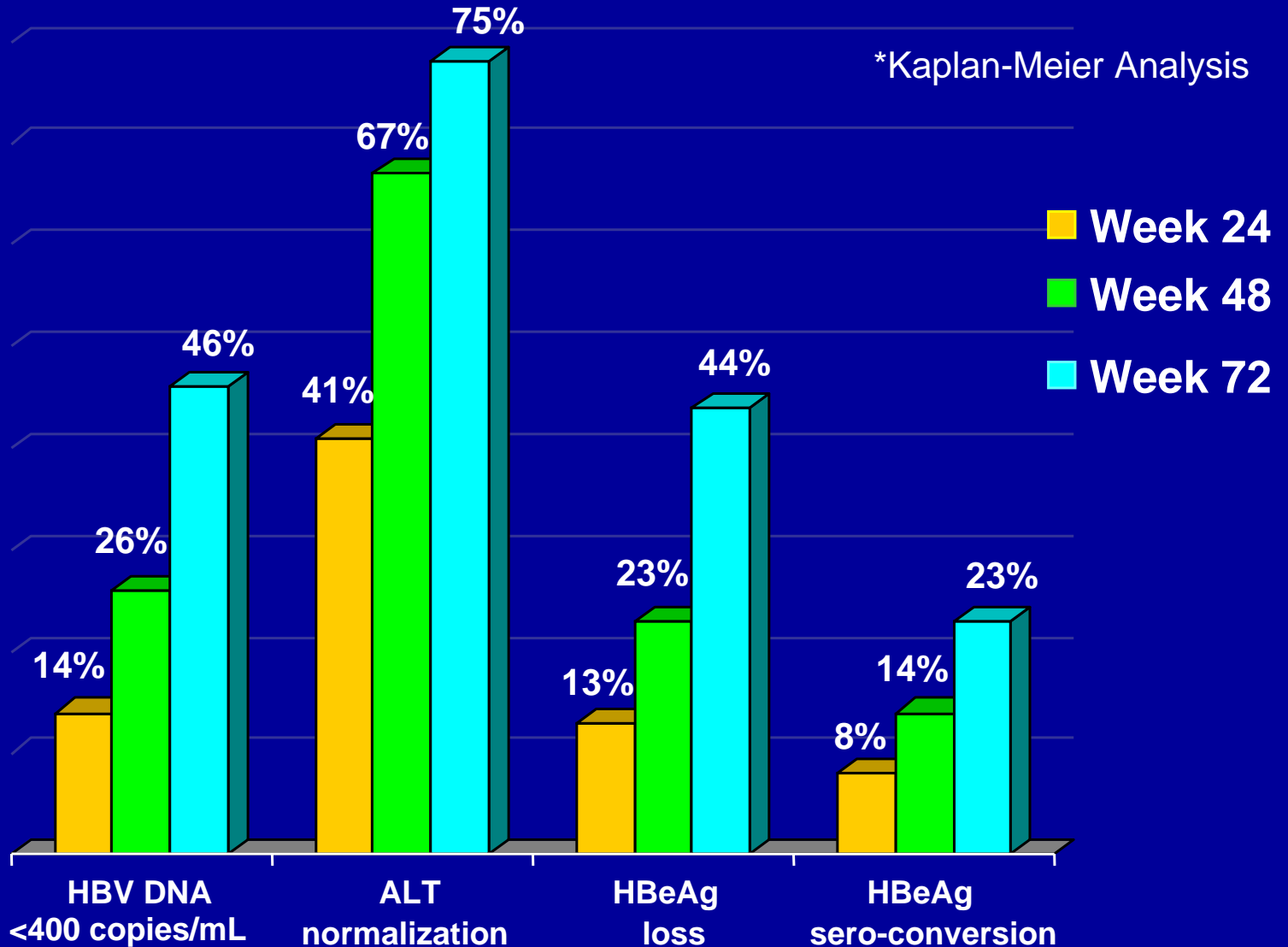
FTC HBV+HIV
FTC HBV
d4T HBV+HIV

	0	12	24	36	48
FTC HBV+HIV	24	22	20	20	17
FTC HBV	33	33	33	33	33
d4T HBV+HIV	10	10	10	7	7

■ FTC HBV+HIV
◆ d4T HBV+HIV
▲ FTC in Chronic HBV (FTCB-102)

Adefovir - HBeAg Positive Study

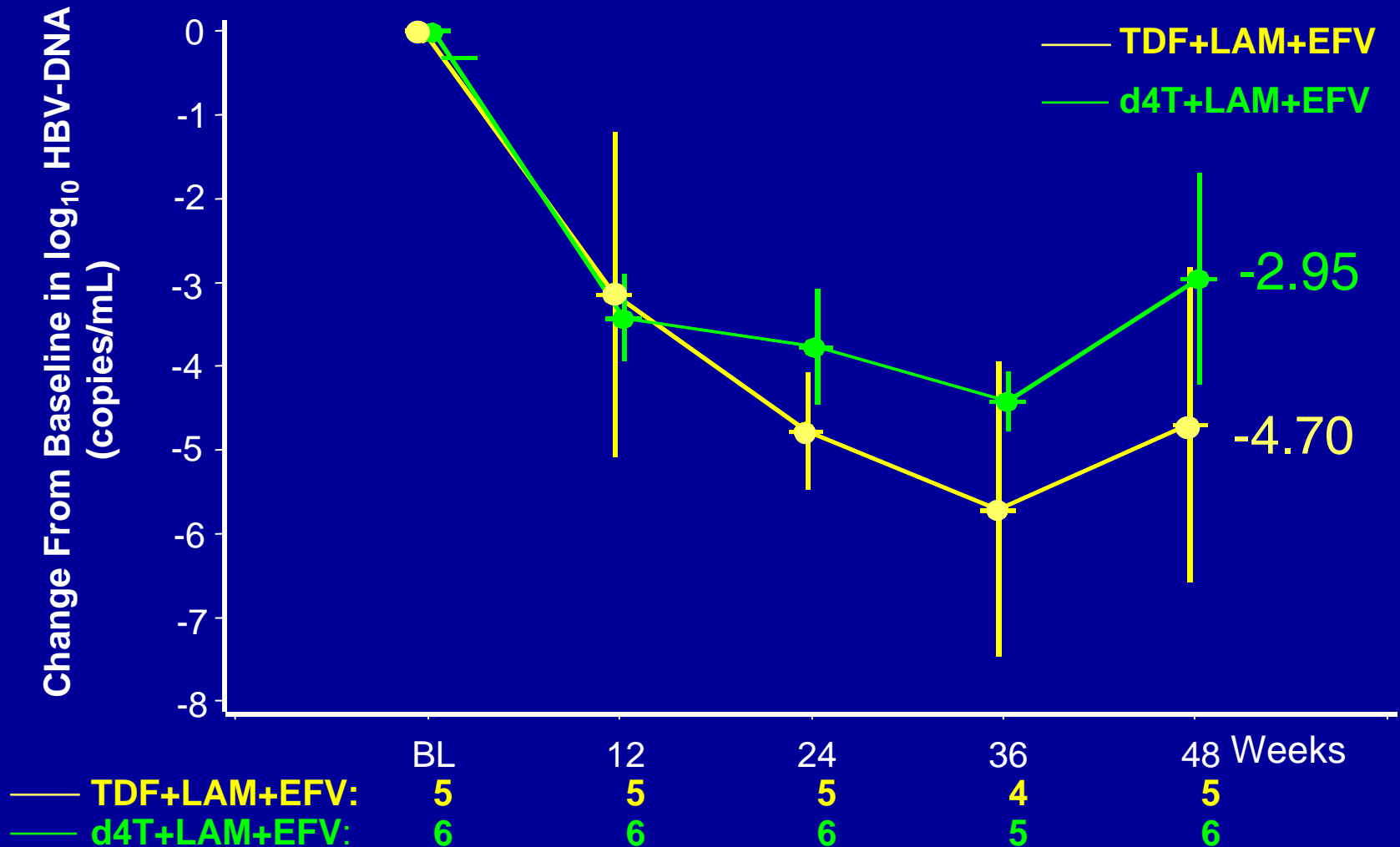
Efficacy Summary Through 72 Weeks*



Tenofovir for HBV - Gilead Study 903

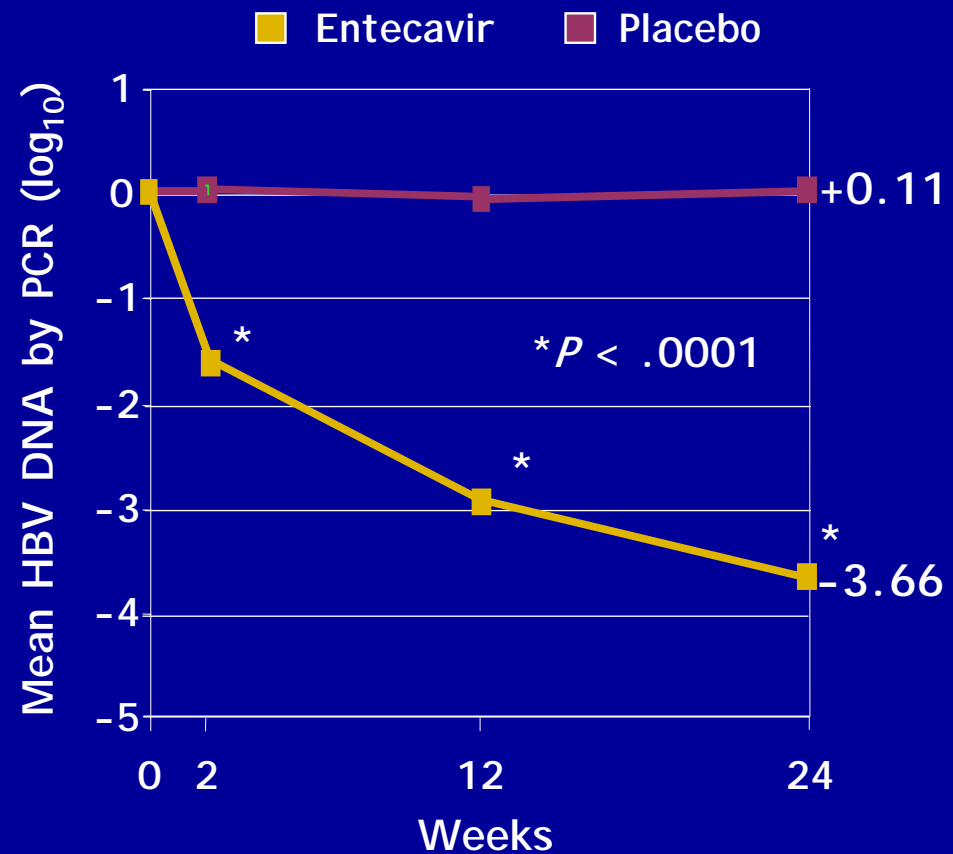
HIV/HBV Coinfected Patients

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



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

- ETV-038: HBV/HIV coinfecting pts
 - HBV DNA $\geq 100,000$, 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



n =	51	49	46	48
n =	17	16	16	16

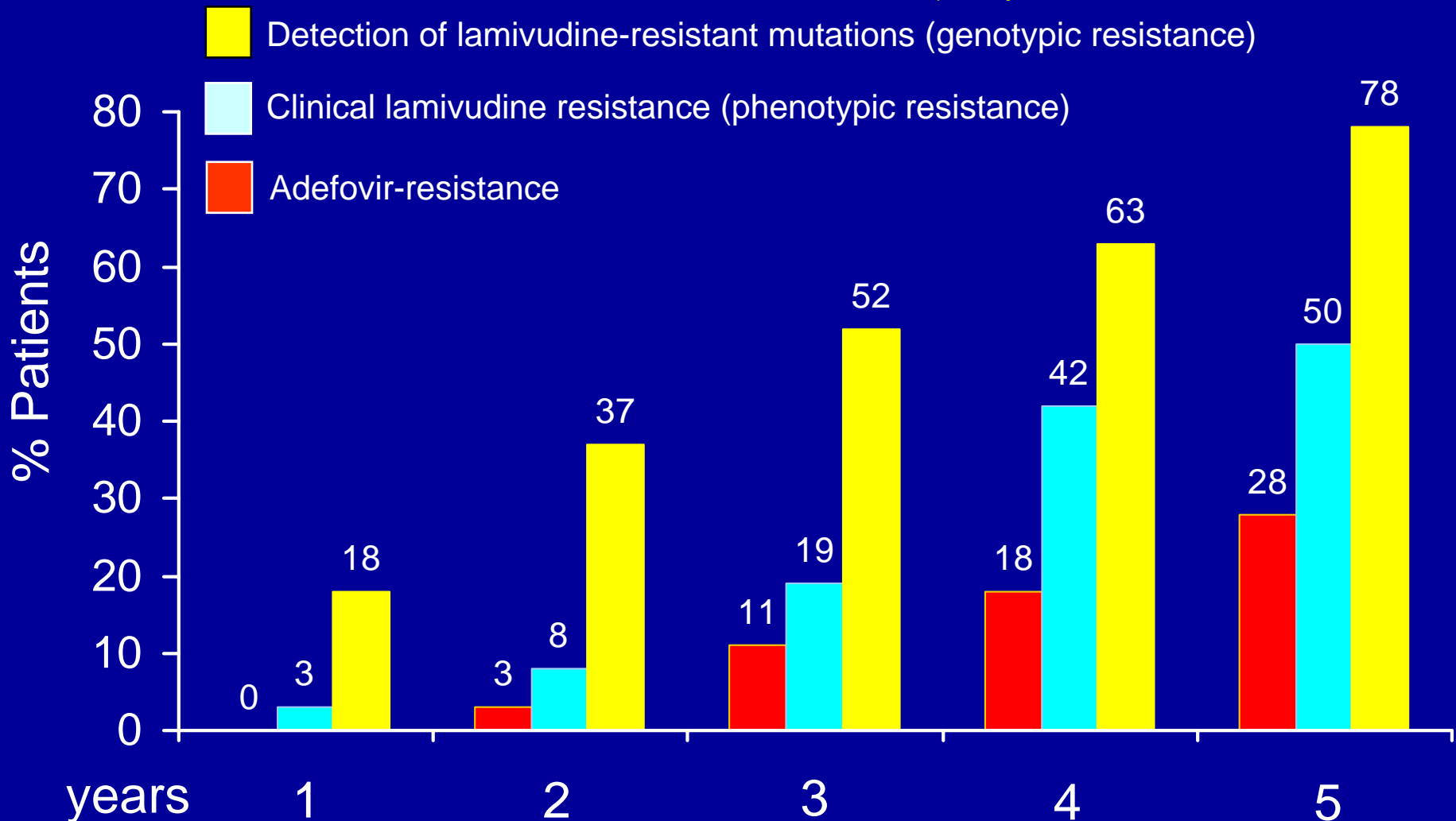
GLOBE: Year 1 Results of Telbivudine (LdT) for Chronic Hepatitis B

Summary of Year 1 Results With Telbivudine

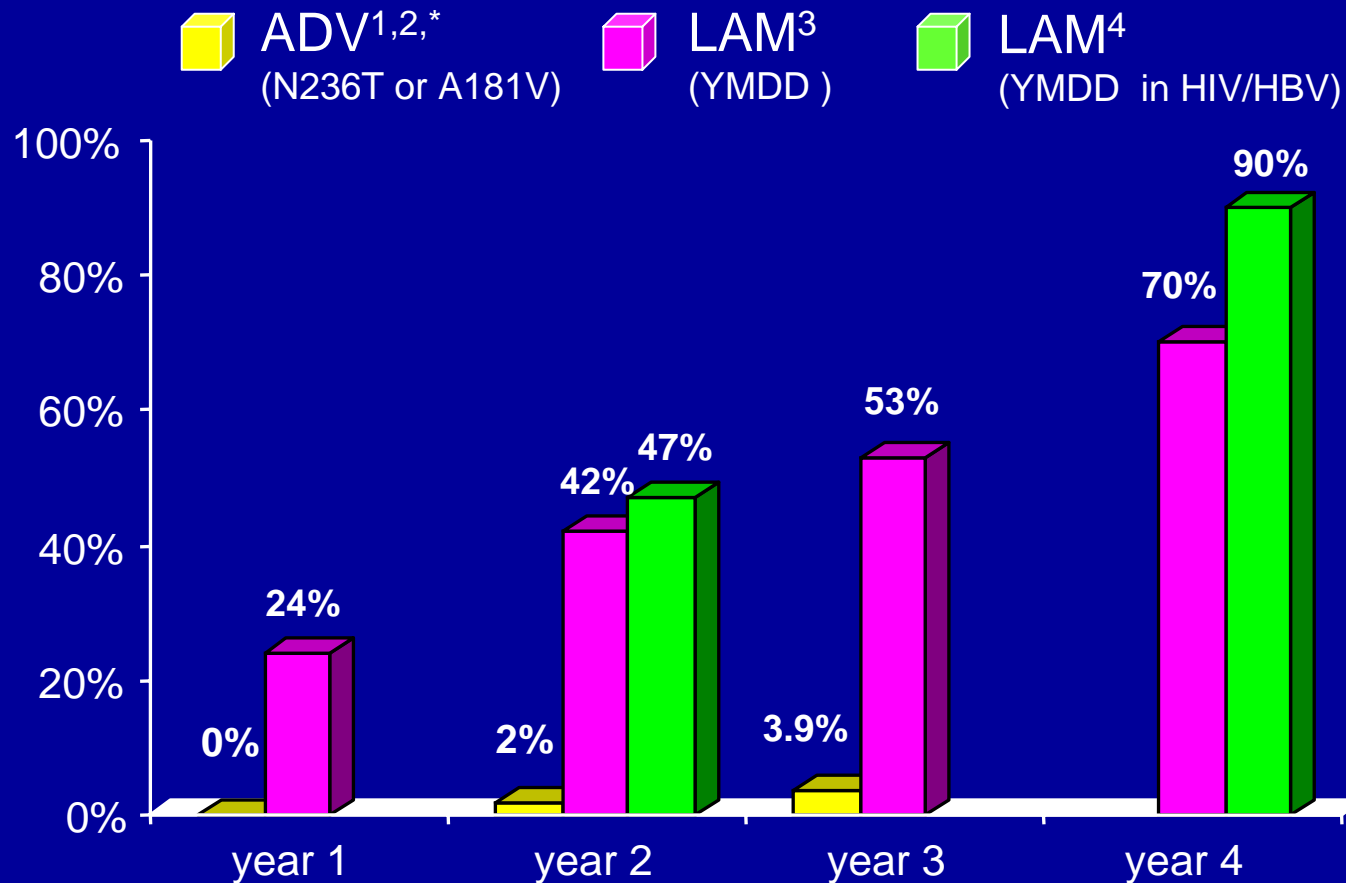
Outcome	HBeAg-Positive Patients		HBeAg-Negative Patients	
	LdT, % (n = 458)	LAM, % (n = 463)	LdT, % (n = 222)	LAM, % (n = 224)
Undetectable HBV DNA • Week 52 • Week 76	75* 75* (n = 163)	67 58 (n = 165)	88* 84* (n = 68)	71 67 (n = 67)
Virologic breakthrough by Week 48	3*	10	2*	9
Normalized ALT • Week 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

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

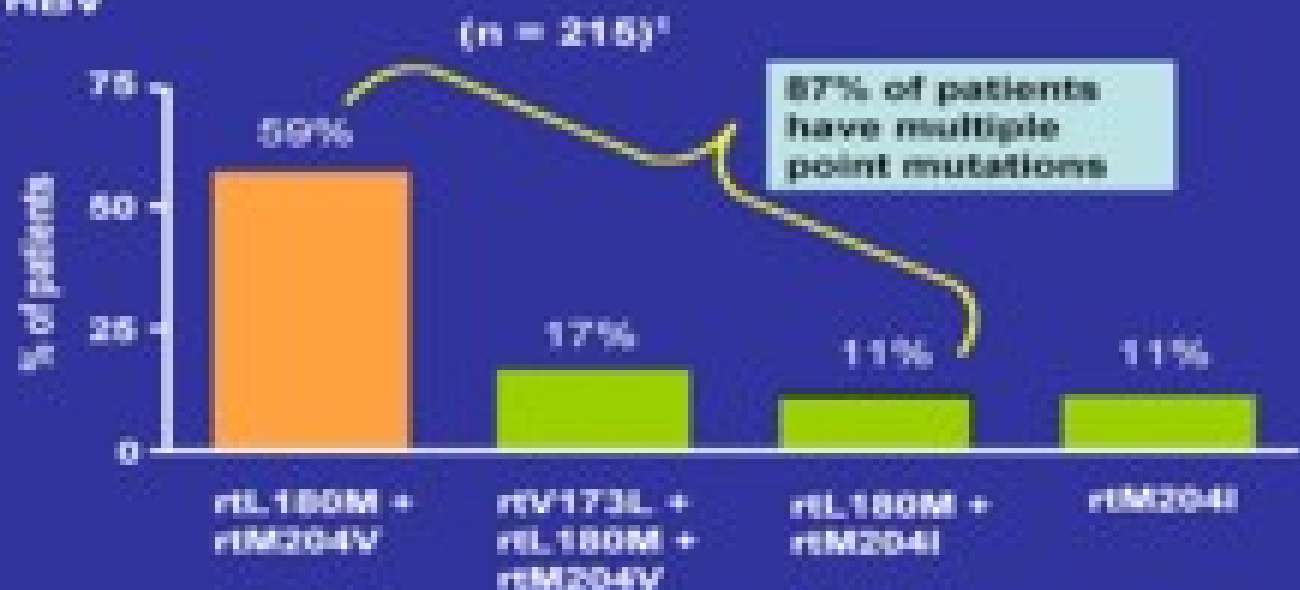
3. Lai C.L., et al., Clinical Infectious Diseases (2003) 36:687

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

* Year 4 resistance rate for ADV not yet available

Major Mutational Patterns in Lamivudine-Resistant HBV

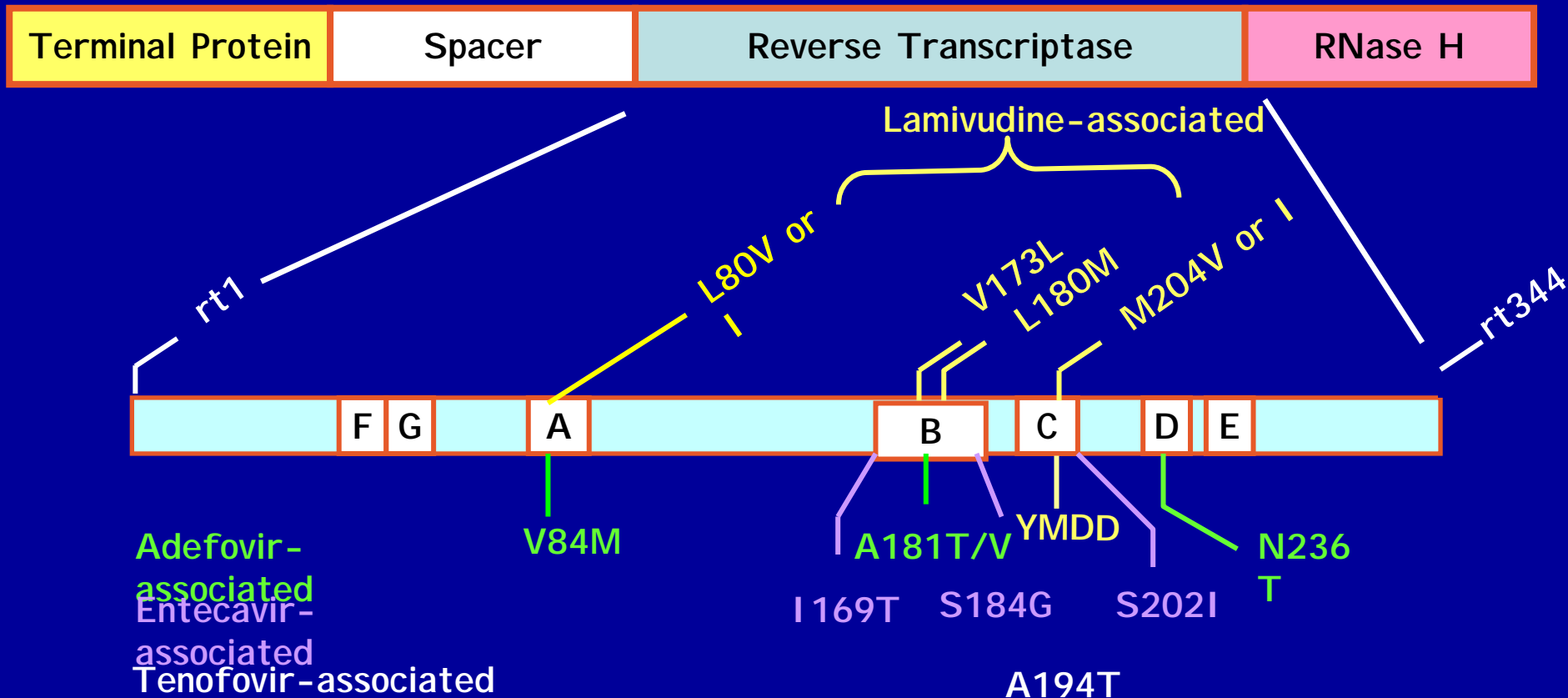
-Lam-resistant HBV
-4 patterns



¹Data from clinical trials of adefovir dipivoxil in Lam-R patients: Studies 428, 488, and 497

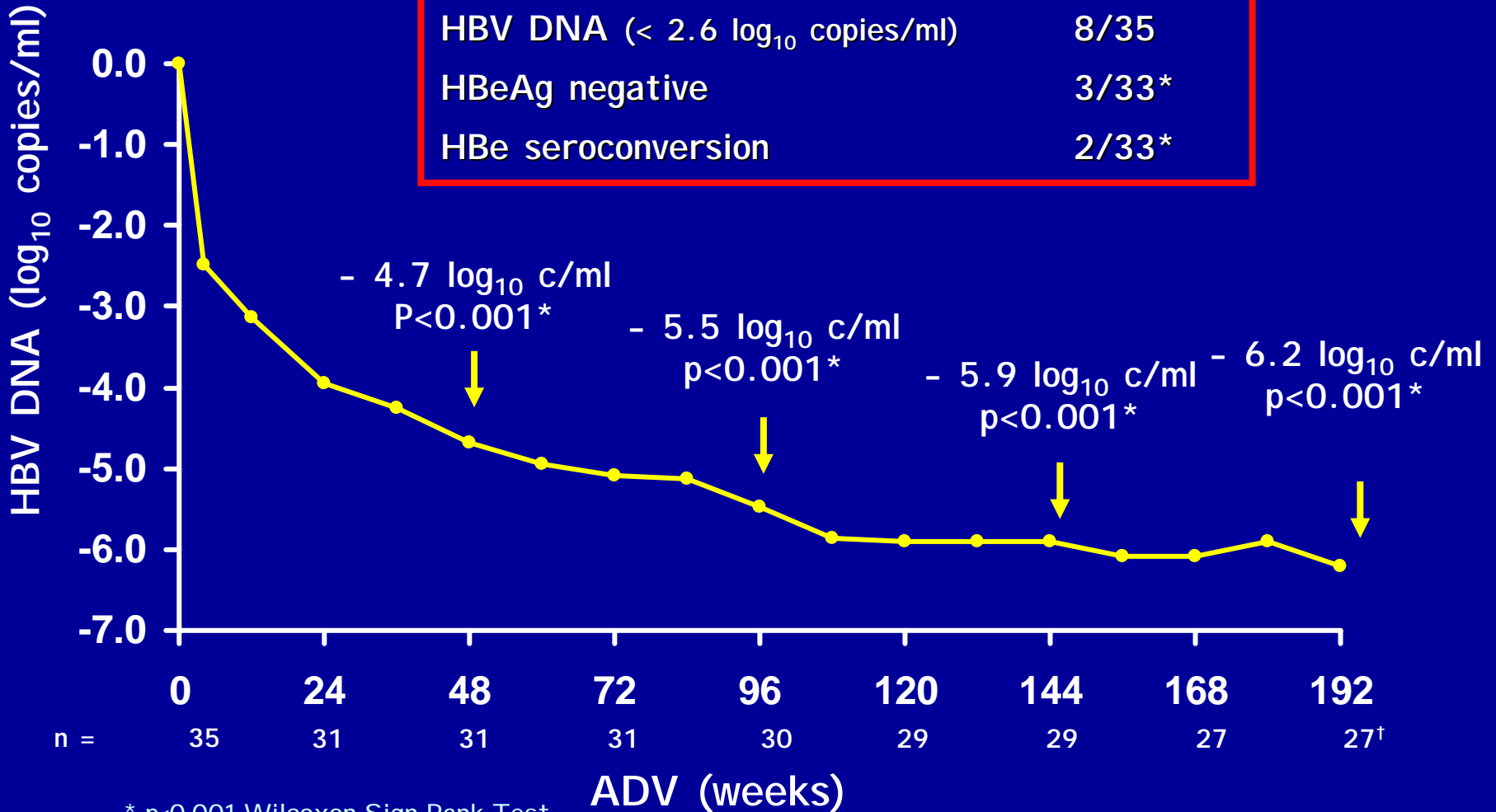
¹Wong et al. 2011 (2009) 11: 112

HBV Polymerase Mutations Associated with Antiviral Resistance



HIV/HBV LAM-R ADV

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

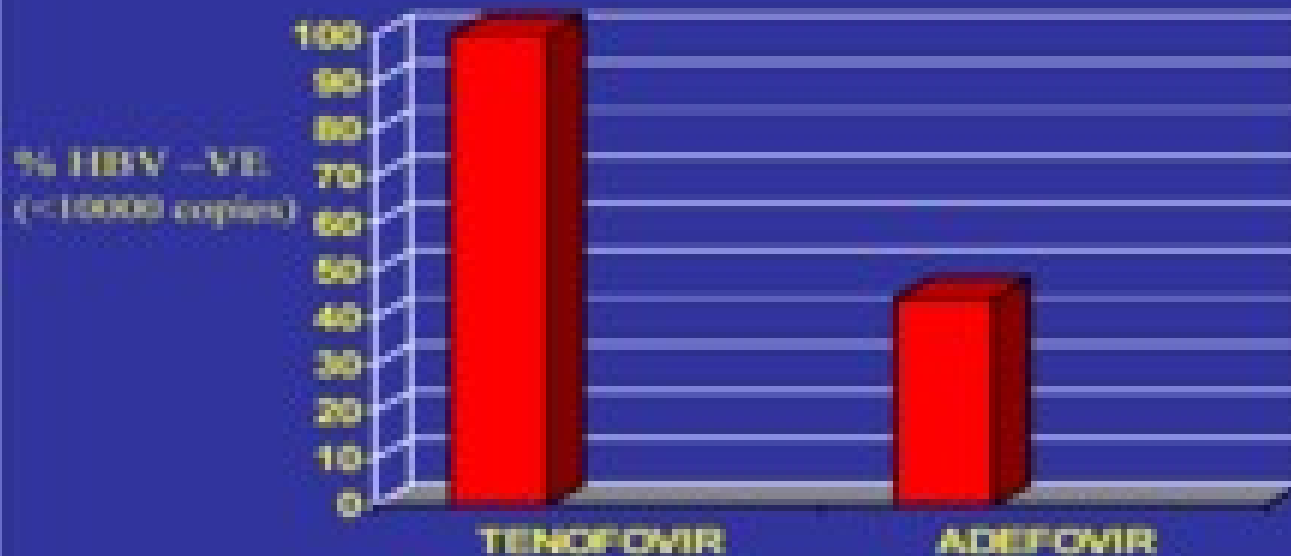


* p < 0.001 Wilcoxon Sign Rank Test

† 27 patients remain on study

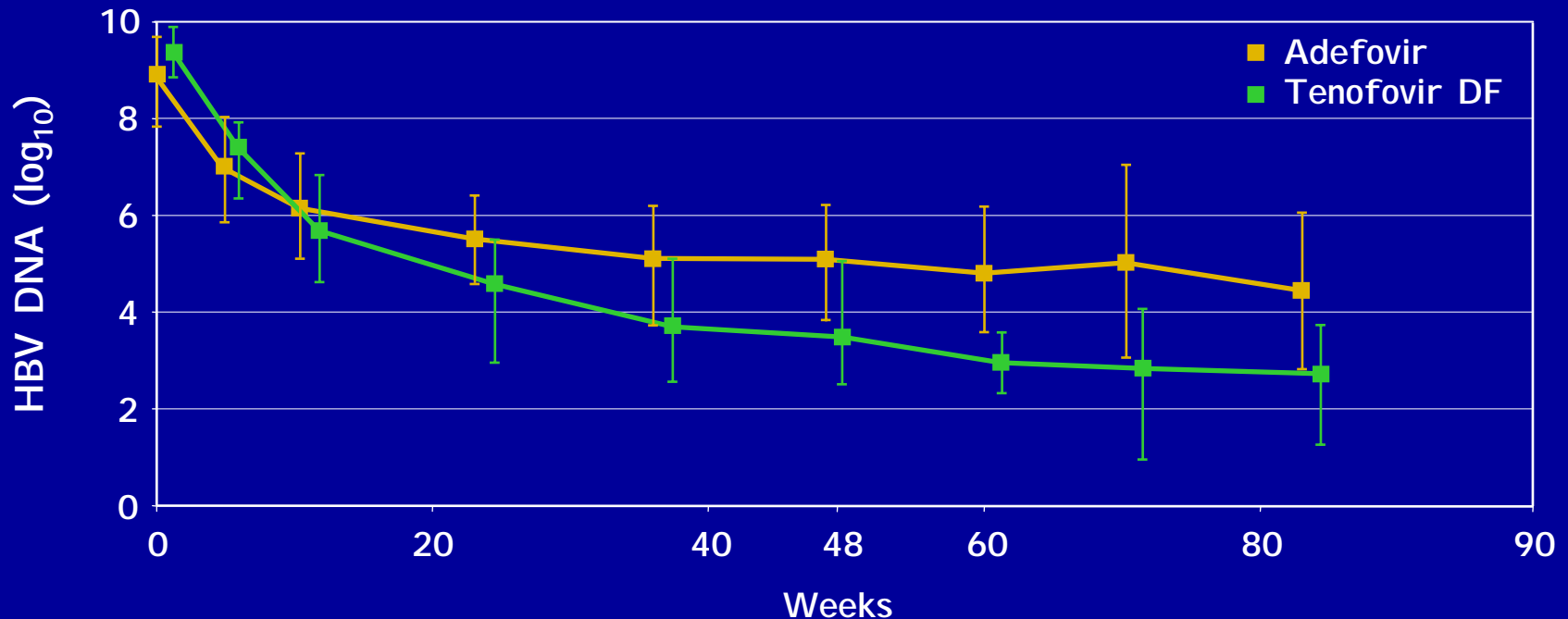
Benhamou et al. Lancet. 2001;358: 718-23. & J Hepatol. 2006;44:62-7.

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



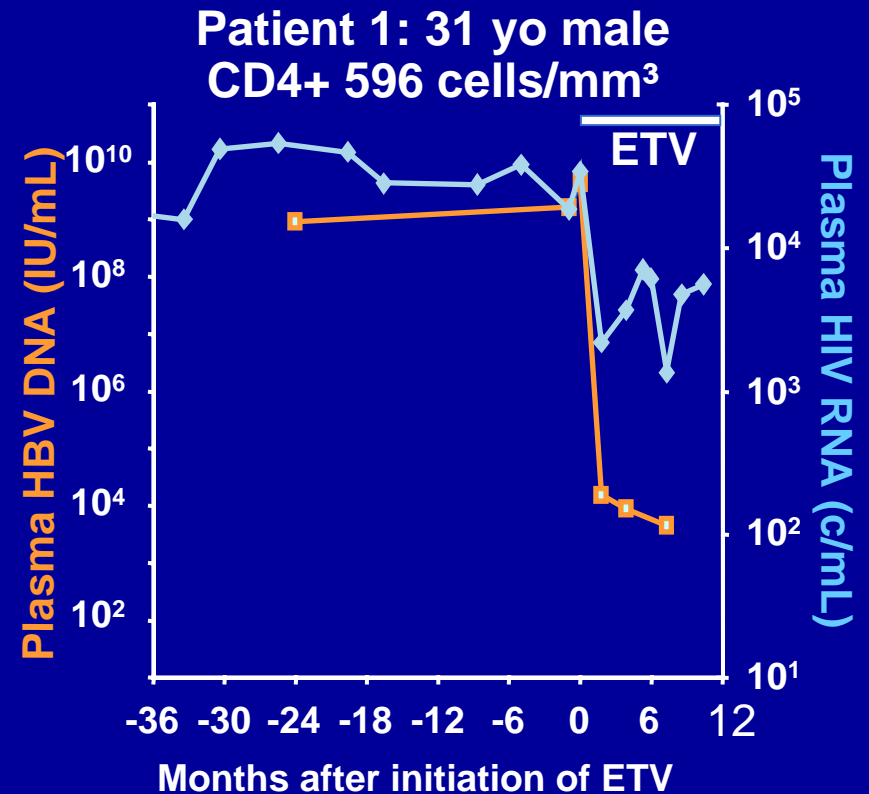
Similar (better?) Anti-HBV Activity of Tenofovir compared to Adefovir in Coinfected Patients

- Interim data from ACTG A5127: HBV/HIV-1 coinfectd pts
 - HBV DNA $\geq 100,000$
 - Stable antiretroviral therapy; HIV-1 RNA $\leq 10,000$
- Reduction in HBV DNA with tenofovir noninferior to adefovir



Entecavir may inhibit HIV-1 replication and select HIV-1 variants resistant to ARV drugs

- In a single-cycle assay, entecavir inhibited HIV-1 replication with an IC_{50} of 0.1 to 1 nM
- In 3 cases, a drop in HIV RNA was recorded after entecavir treatment was started for concomitant HBV infection
- Patient 1 (hx of 3TC therapy off ARVs): M184V present in 0%, 61% and 96% of the clones at 0, 4 and 6 months after entecavir, respectively
- The use of entecavir in HIV+/HBV+ patients without HAART needs to be reconsidered



Is more better?

3 Drugs



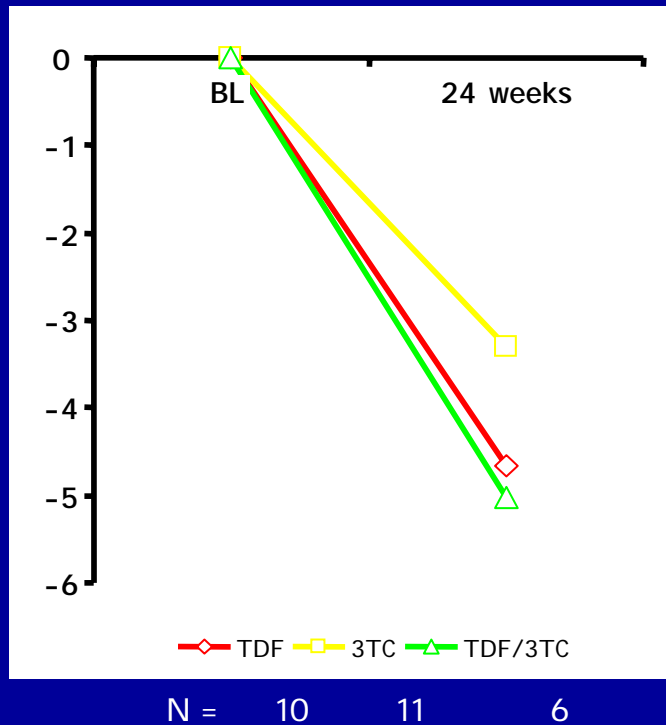
2 Drugs



1 Drug

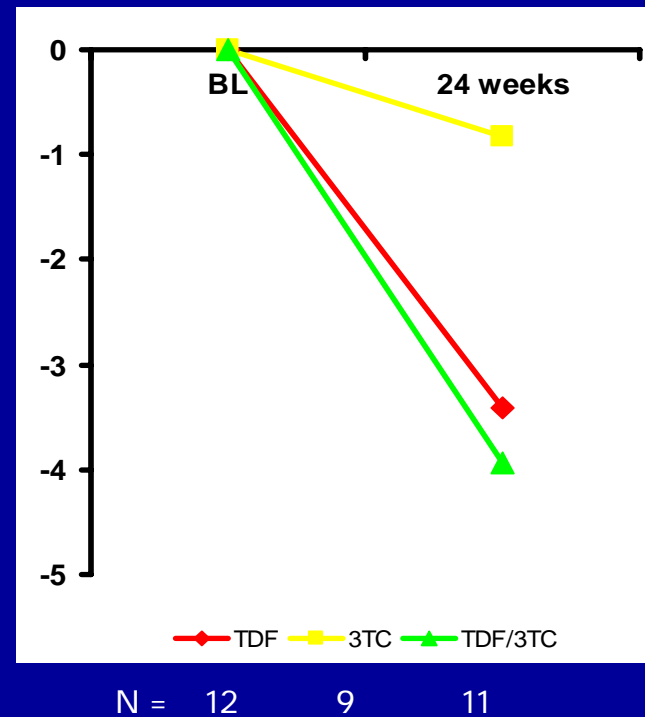
TDF/3TC more effective than 3TC alone in drug-naïve HIV/HBV co-infected

3TC - naïve



P=0.045
vs. 3TC

3TC - experienced



P<0.001
vs. 3TC

Conclusions:

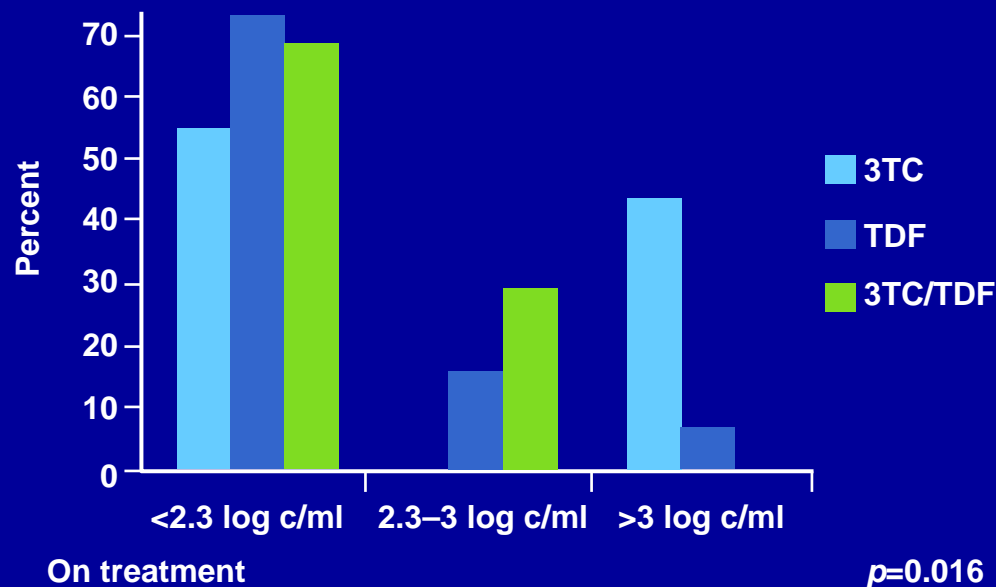
- TDF/3TC superior to 3TC alone but not TDF in HBV naïve
- No benefit continuing 3TC in experienced HBV viraemic patients
- No difference between adding or switching TDF

TI CO Study: TDF-containing HAART vs 3TC-containing HAART in ARV-naive HIV/HBV coinfecting 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



PegI FN vs Lamivudine in HBeAg(+) Patients

- Peginterferon alfa-2a associated with better response than lamivudine in HBeAg(-) patients^[1]
 - Combination does not improve response rates
- Similar findings now reported for HBeAg(+) patients^[2]
 - Randomized, partially blinded, multinational study

24-wk Results, % (<i>P</i> Value)*	PegI FN alfa-2a + Placebo (n = 271)	PegI FN alfa-2a + LAM (n = 271)	LAM Alone (n = 272)
HBeAg seroconversion	32 (<i>P</i> < .01)	27 (<i>P</i> = .023)	19
HBV DNA < 100,000 copies/mL	32 (<i>P</i> = .012)	34 (<i>P</i> = .003)	22
HBeAg loss	34 (<i>P</i> < .001)	28 (<i>P</i> = .043)	21
ALT normalization	41 (<i>P</i> = .002)	39 (<i>P</i> = .006)	28

1. Marcellin P, et al. N Engl J Med. 2004;351(12):1206-1217.

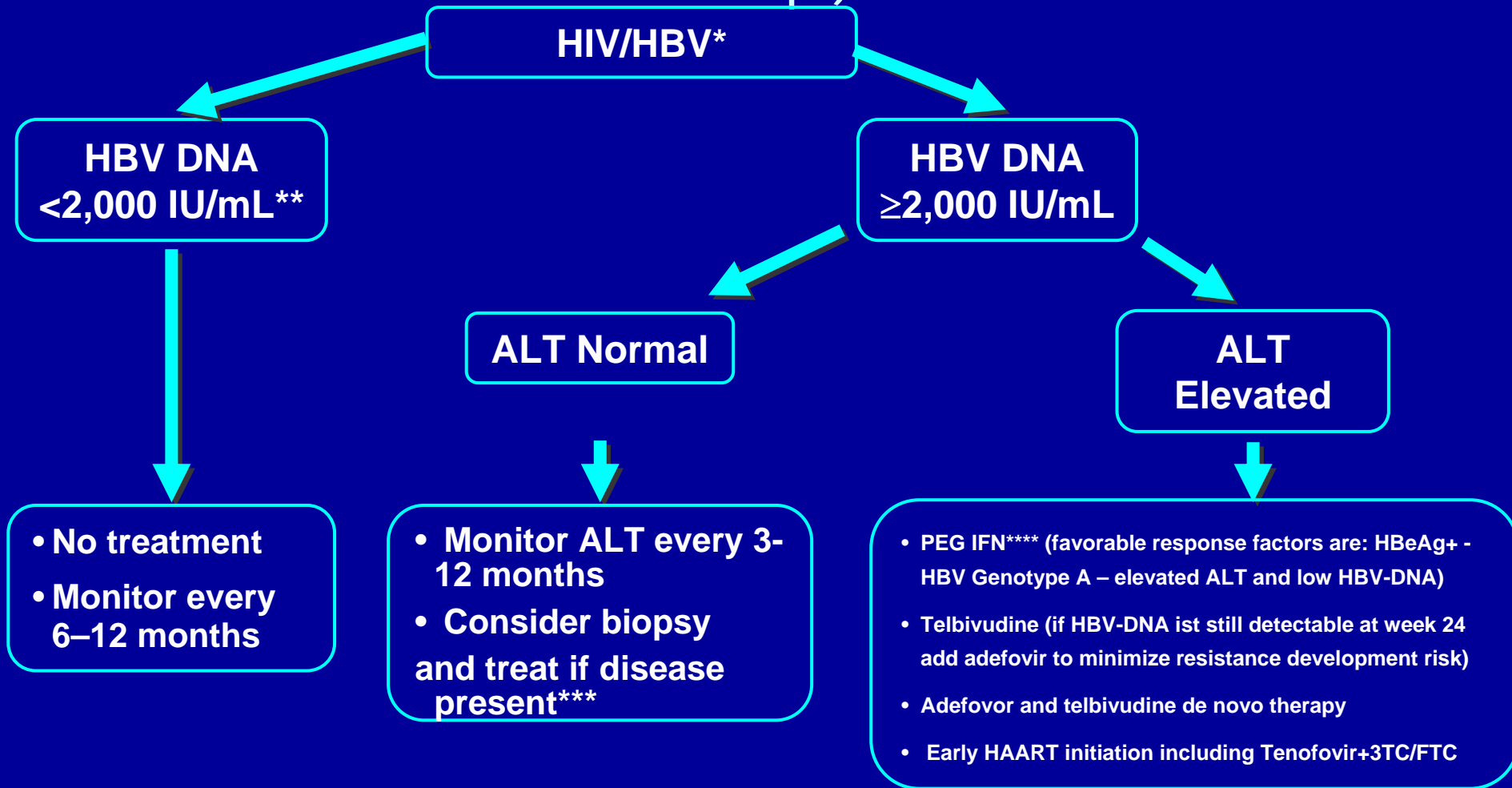
2. Lau G, et al. AASLD 2004. Abstract 20.

Combination therapy

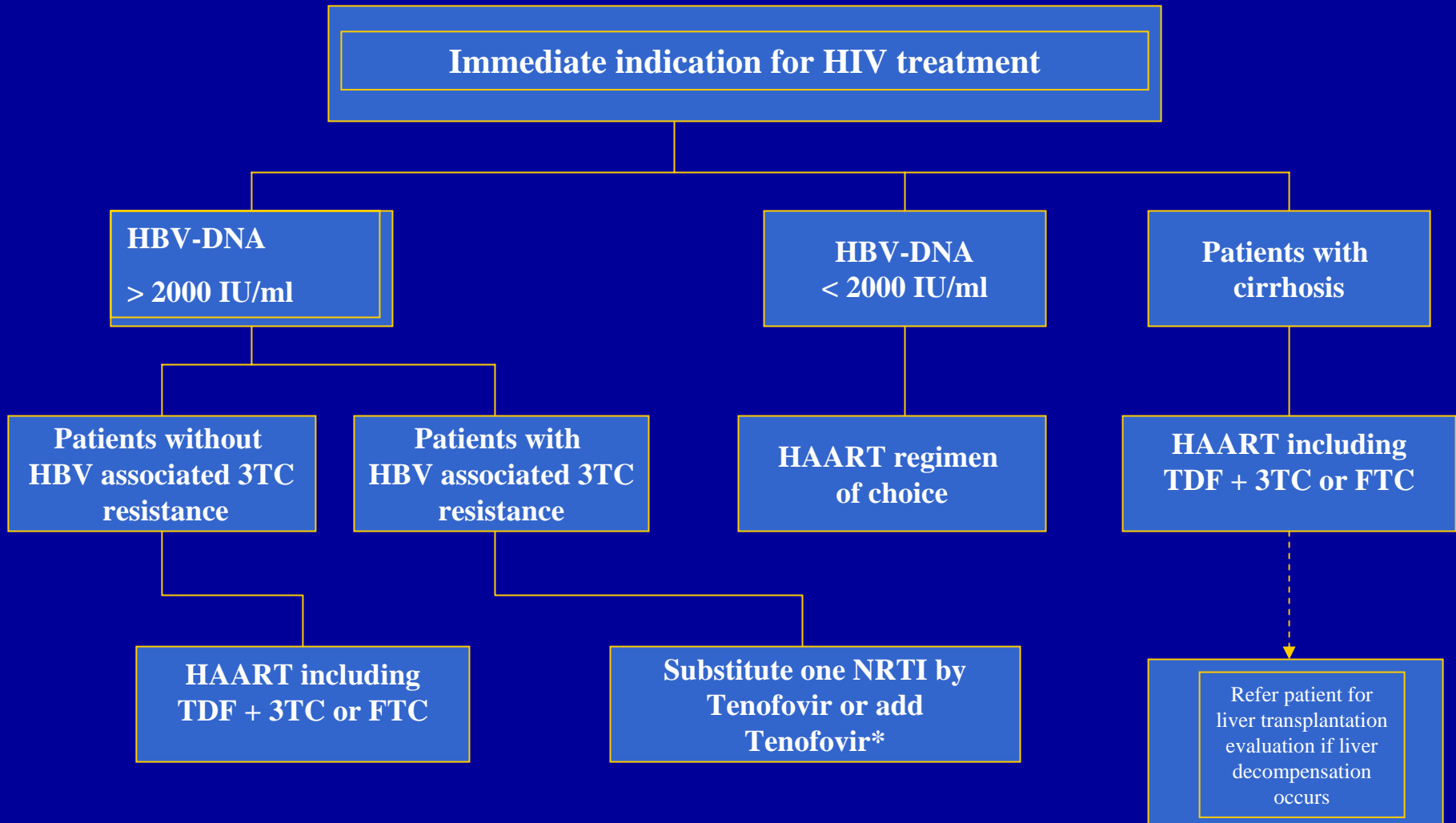
- PegIFN + N(t)A – no advantage
- 2NAs or NA+N(t)A
 - ?Antiviral efficacy
 - Probable advantage in terms of resistance emergence (especially with 3TC +/- FTC)

Treatment Algorithm:

Patients with Compensated Liver Disease and
No indication for HIV therapy (CD4 count >
350/ μ l)



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



HBV/HIV summary

- 10% of HIV+ - HBV co-infected
- High viral loads and risk of progression to ESLD and HCC
- Careful assessment EVEN with normal ALT
- High risk of mutations with 3TC/FTC monotherapy
 - Dire clinical consequences and future public health consequences
- Patients needing HAART
 - Prior 3TC add TDF or switch to TDF/FTC
 - Naïve - start with TDF/FTC or TDF/3TC
- Patients not needing HAART
 - PegIFN for 48 weeks (e+, genotype A, high ALT)
 - Telbivudine and add adefovir if HBV DNA > 400c/ml 6/12
 - Telbivudine + adefovir

And they lived happily ever after...?



Acknowledgements

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