Hepatitis B: Clear as Mud

Melissa Osborn, MD, MSCR

Assistant Professor

Emory University School of Medicine

Atlanta, GA

Objectives

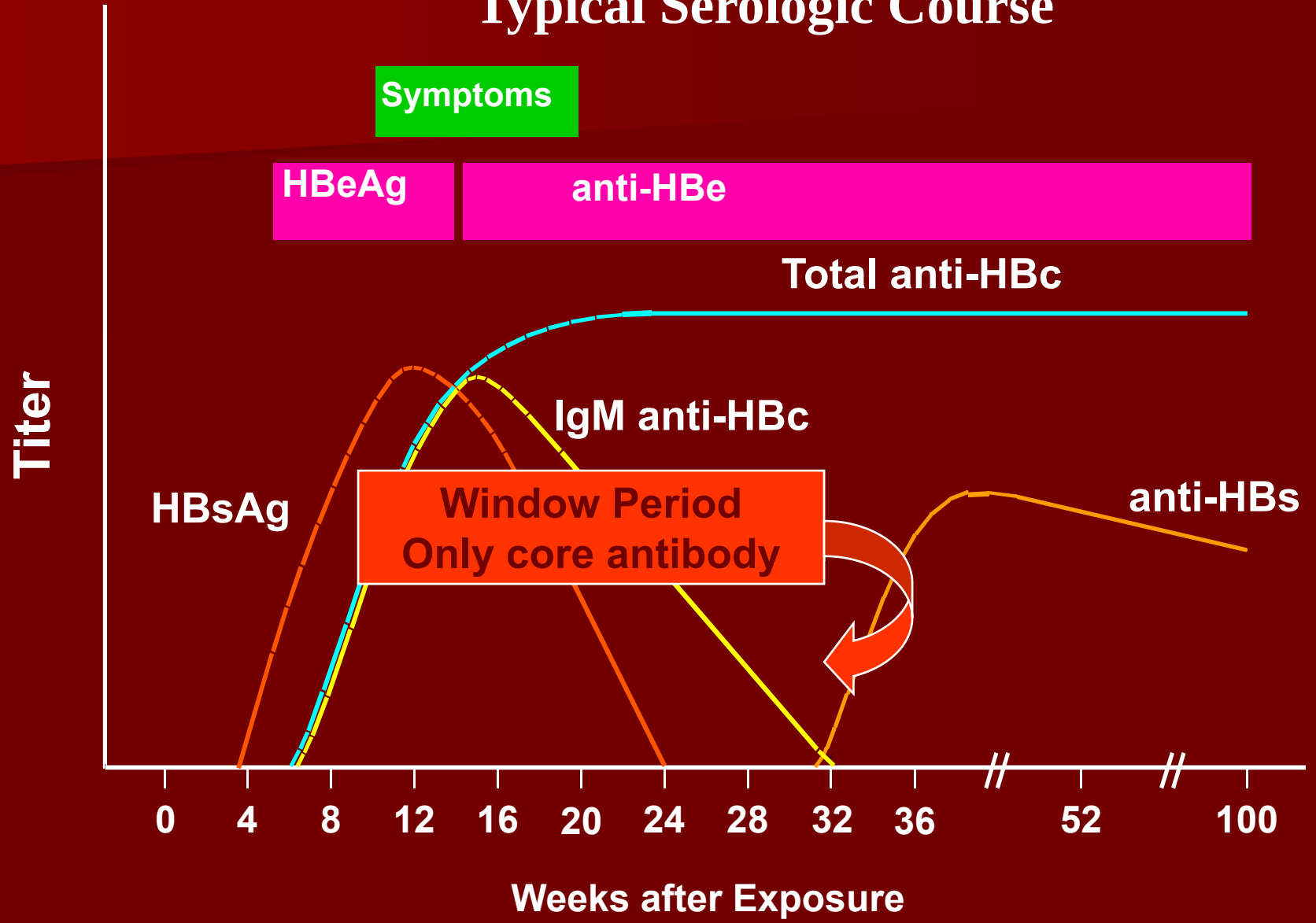
1. Distinguish the various stages in the natural history of chronic hepatitis B

2. Know which tests are necessary to monitor hepatitis B activity, and when changes in therapy are indicated

3. Understand the limitations of currently available hepatitis B therapies due to cross-resistance and limited potency

Acute Hepatitis B Virus Infection with Recovery

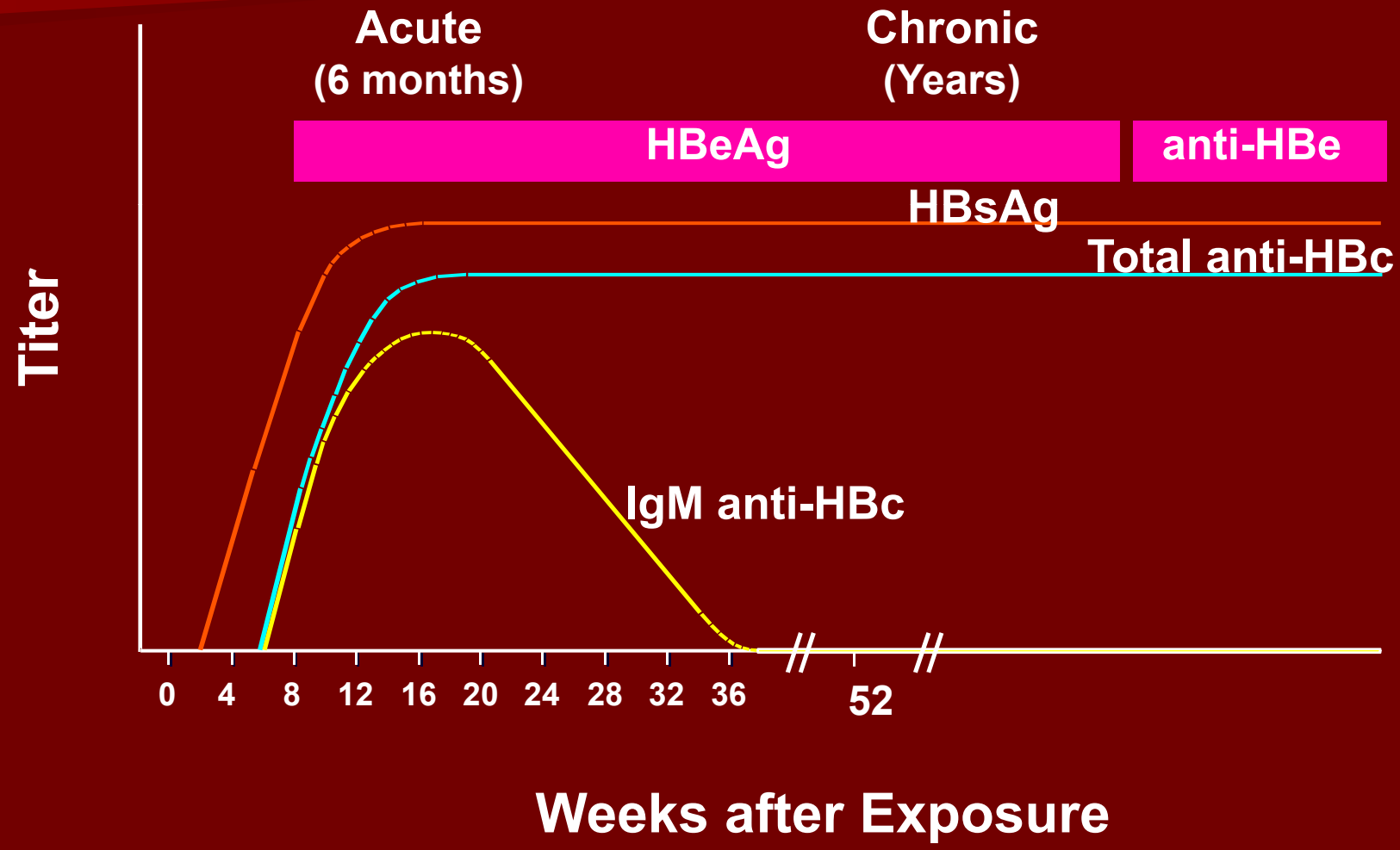
Typical Serologic Course



CDC

Progression to Chronic Hepatitis B Virus Infection

Typical Serologic Course

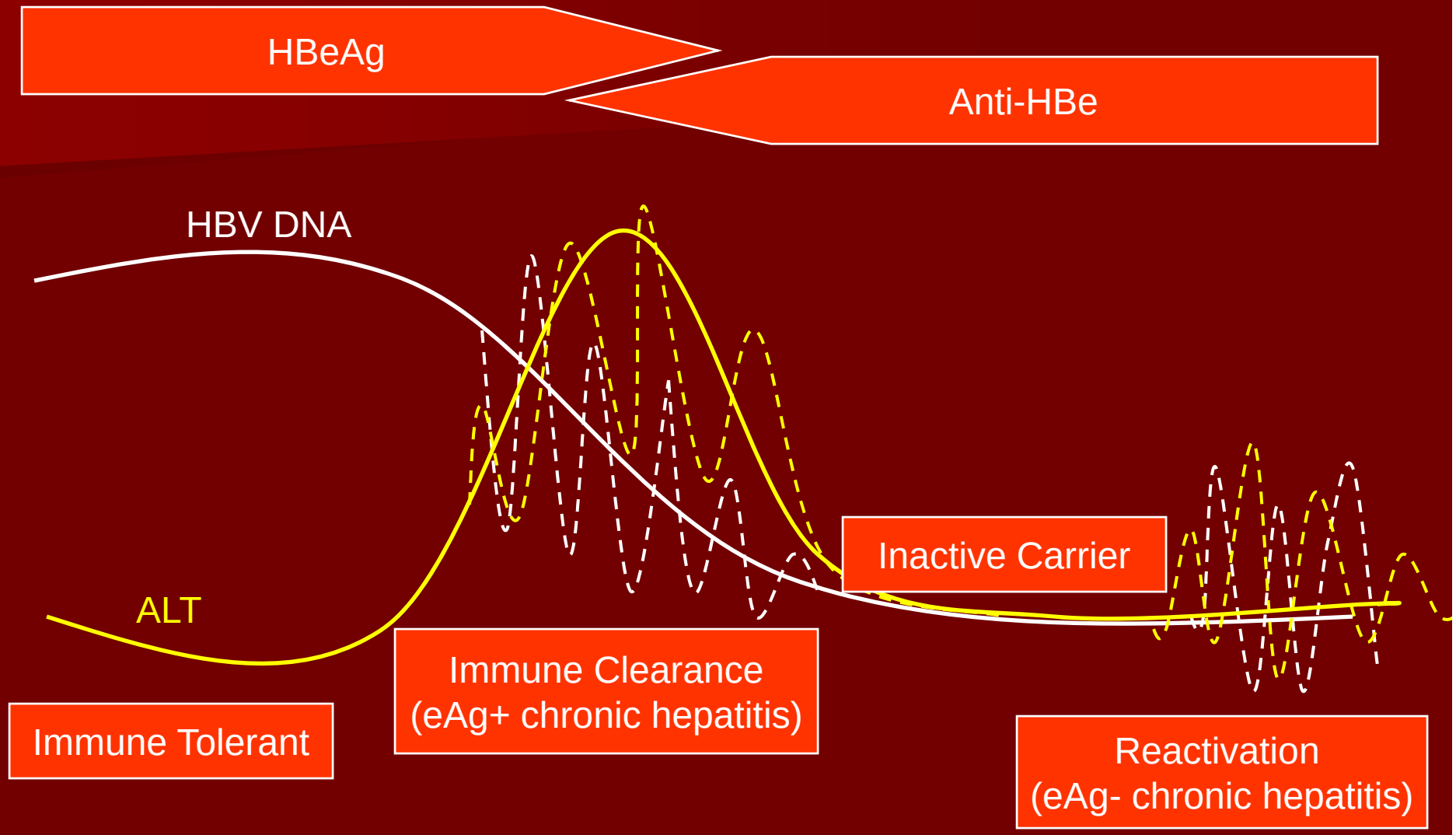


CDC

Hepatitis B Serologic Diagnosis

	HBsAg	Anti-HBs	HBeAg	Anti-HBe	Anti-HBc	IgM anti-HBc	HBV DNA	ALT
Acute hepatitis B	+	-	+	-	+	+	+	High
Immunity (infection)	-	+	-	+/-	+	-	-	Nml
Immunity (vaccination)	-	+	-	-	-	-	-	Nml
Chronic Hepatitis B	+	-	+	-	+	-	+/-	High
Chronic Infection (Precore Mutant)	+	-	-	+	+	-	+	High
Chronic carrier	+	-	-	+	+	-	- or low	Nml

Chronic Hepatitis B (sAg+)



Adapted from Yim, Hepatology 2006; 43:S173-181

Chronic HBeAg- Disease (Pre-Core/Core Mutant)

- Lower HBV DNA levels but higher risk of cirrhosis (annual 8-10%/year)
- Represents a later phase of chronic hepatitis B
- No strict cutoff to discriminate between chronic carriers and eAg- hepatitis B

Natural History

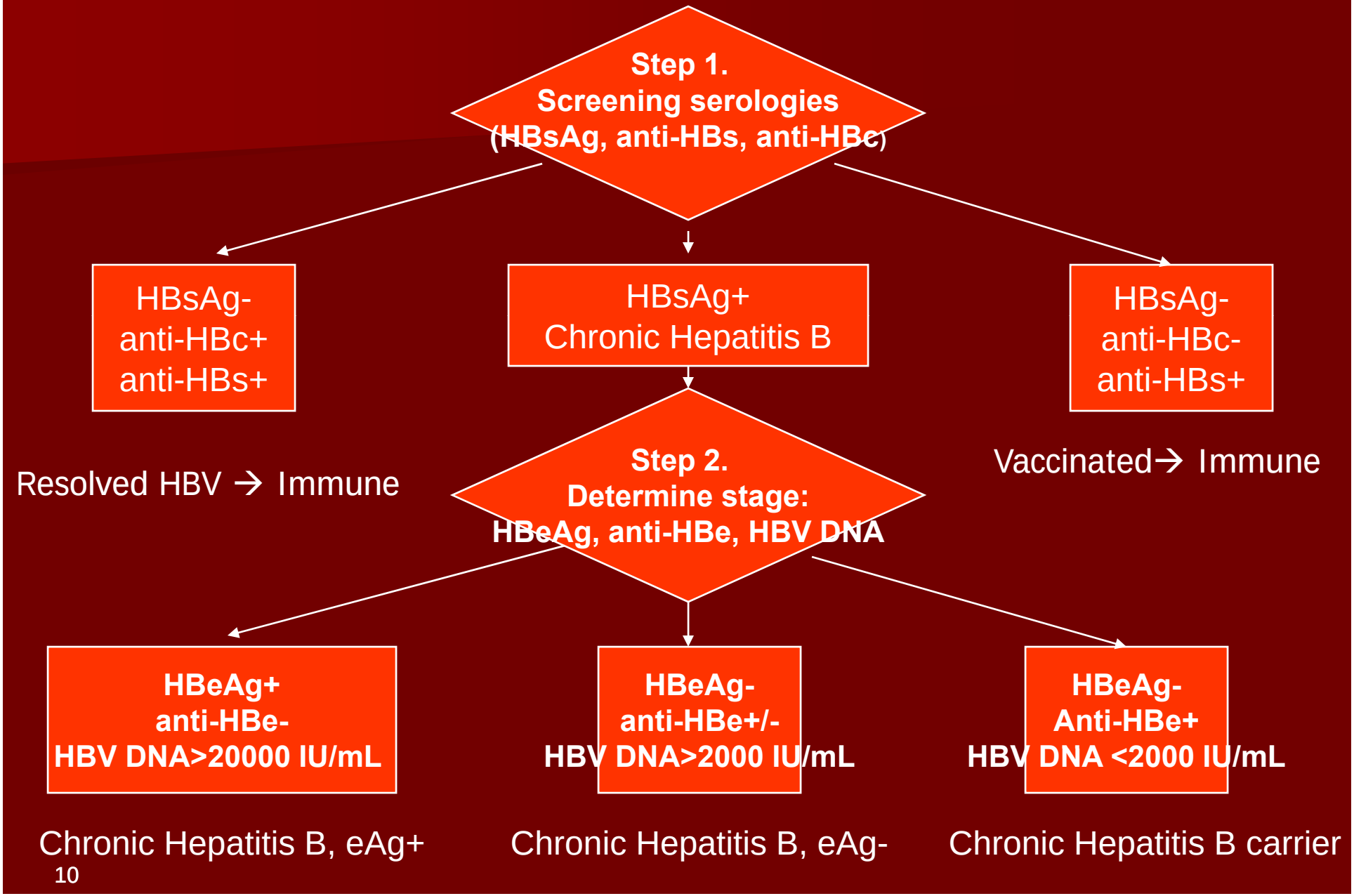
- sAg clearance occurs at a rate of 0.5-1% per year
  - Can still get HCC even if cleared
- Annual incidence of cirrhosis 2-6% in HBeAg+ disease and 8-10%/year in HBeAg- disease
  - Other risk factors: EtOH, HCV, HIV, high HBV DNA, Genotype C

Alterations in HBV Natural History Among HIV/HBV Coinfected

- More likely to become chronic carrier of HBV (surface antigen positive)
- More likely to be e antigen (HBeAg) positive
- Less likely to be e antibody (anti-HBe) positive
- Less likely to convert HBeAg to anti-HBe
- More likely to go from HBeAg- back to HBeAg+
- Can revert to HBsAg+ from anti-HBs
- Higher levels of HBV DNA

DiMartino, Gastro 2002; 123:1812-1822
Piroth, AIDS 2007; 21:1323-31
Colin, Hepatology 1999; 29:1306-1310
Rouphael, AIDS 2007; 21: 771-4
Cooley, J Clin Virol, 2003; 26:185-193
Benhamou CROI 2005 #933
Gilson, AIDS 1997; 11:597-606

Determining Hepatitis B Status



Monitoring of Chronic Hepatitis B

Regardless of whether treatment is initiated, each patient with hepatitis B should have:

Every 3 months:	Every 6 months:	Every 12 months:
ALT	HBV DNA level	HBeAg (if + initially)
AST		Anti-HBe

DNA levels and HBeAg, anti-HBe should also be checked with any flare of transaminases

Available HBV Therapies

Active against HIV and hepatitis B

Lamivudine (LAM, 3TC)*

Emtricitabine (FTC)

Tenofovir (TDF)*

Active against hepatitis B only

Adefovir (ADV)*

Telbivudine (LdT)*

Interferon-α2b*

Peg-interferon- α2a*

Entecavir (ETV)*

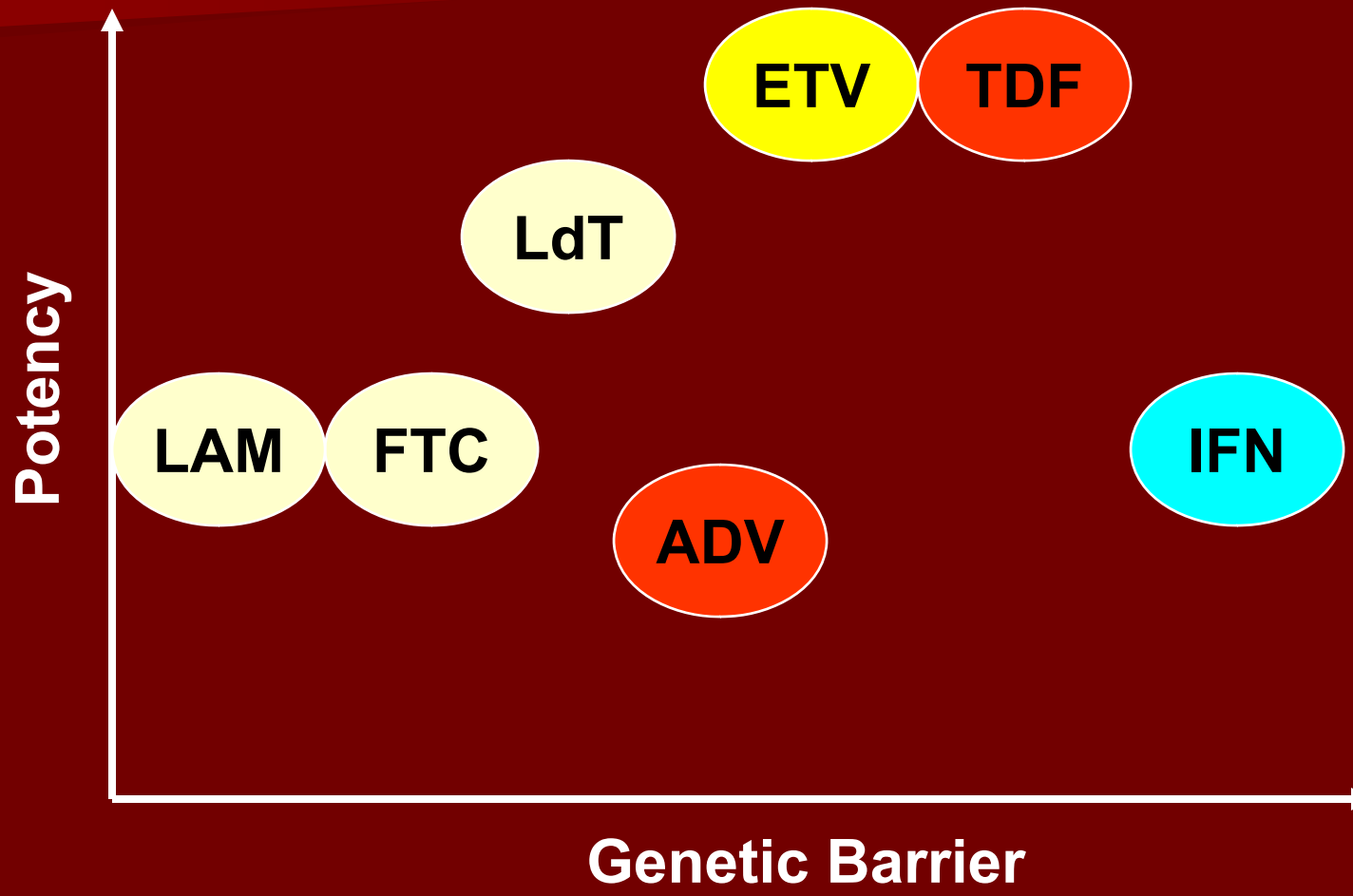
*FDA approved for hepatitis B

L-nucleoside analogues

Acyclic phosphonates

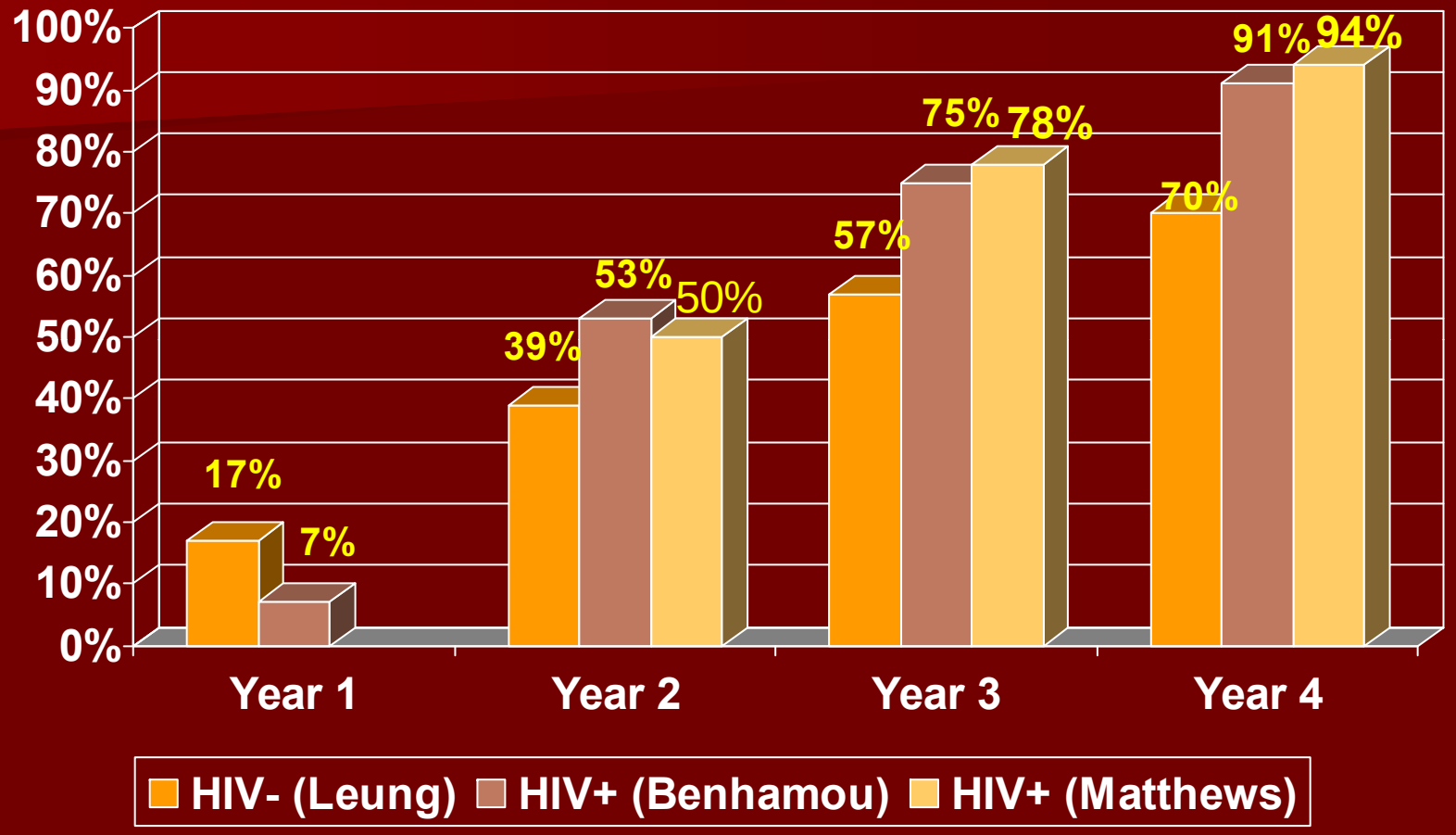
Deoxyguanosine analogues

Consider Potency and Potential for Resistance



Adapted from Soriano, AIDS 2008; 22: 1399-1410

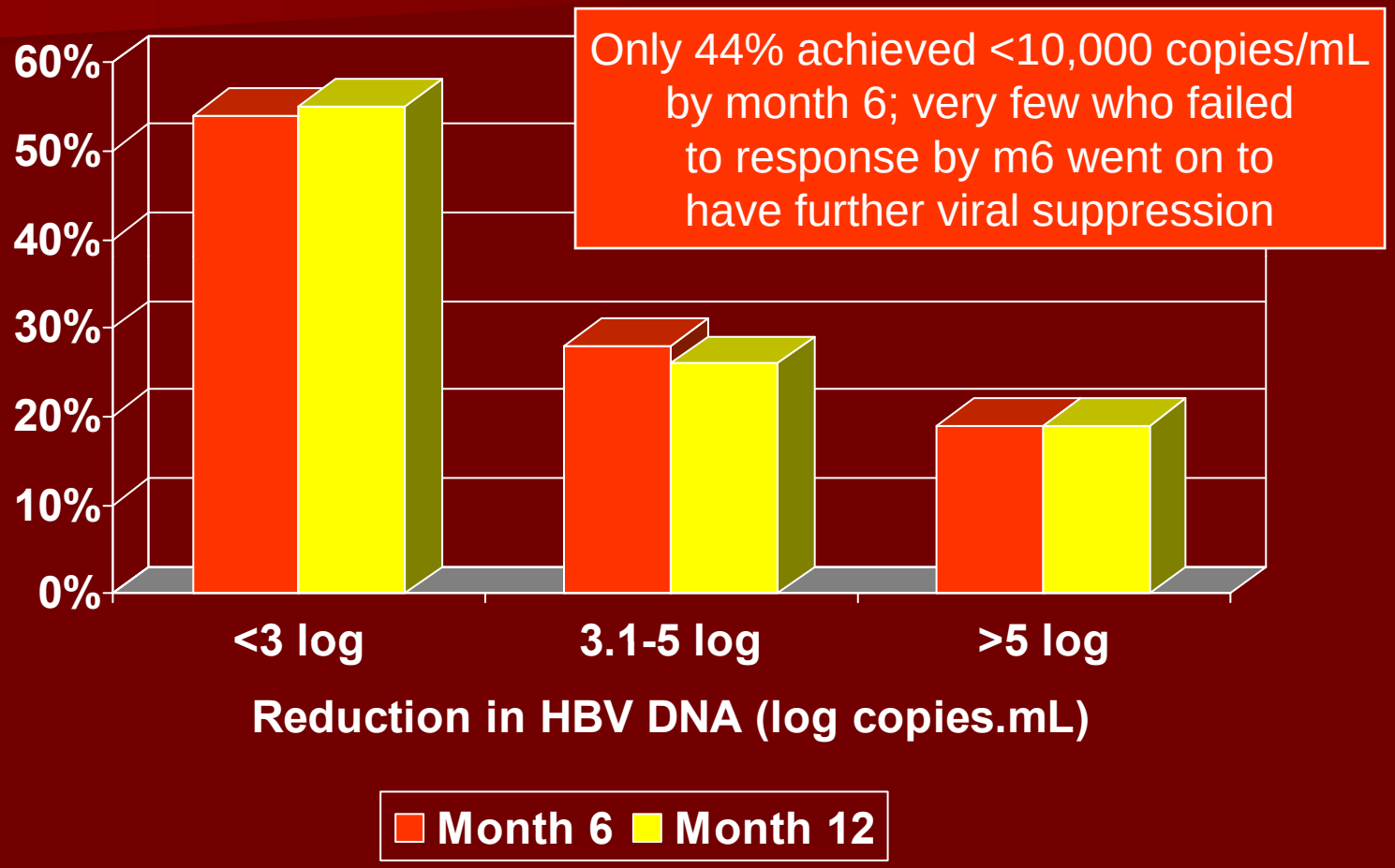
Lamivudine Resistance



M204V/I + L180M

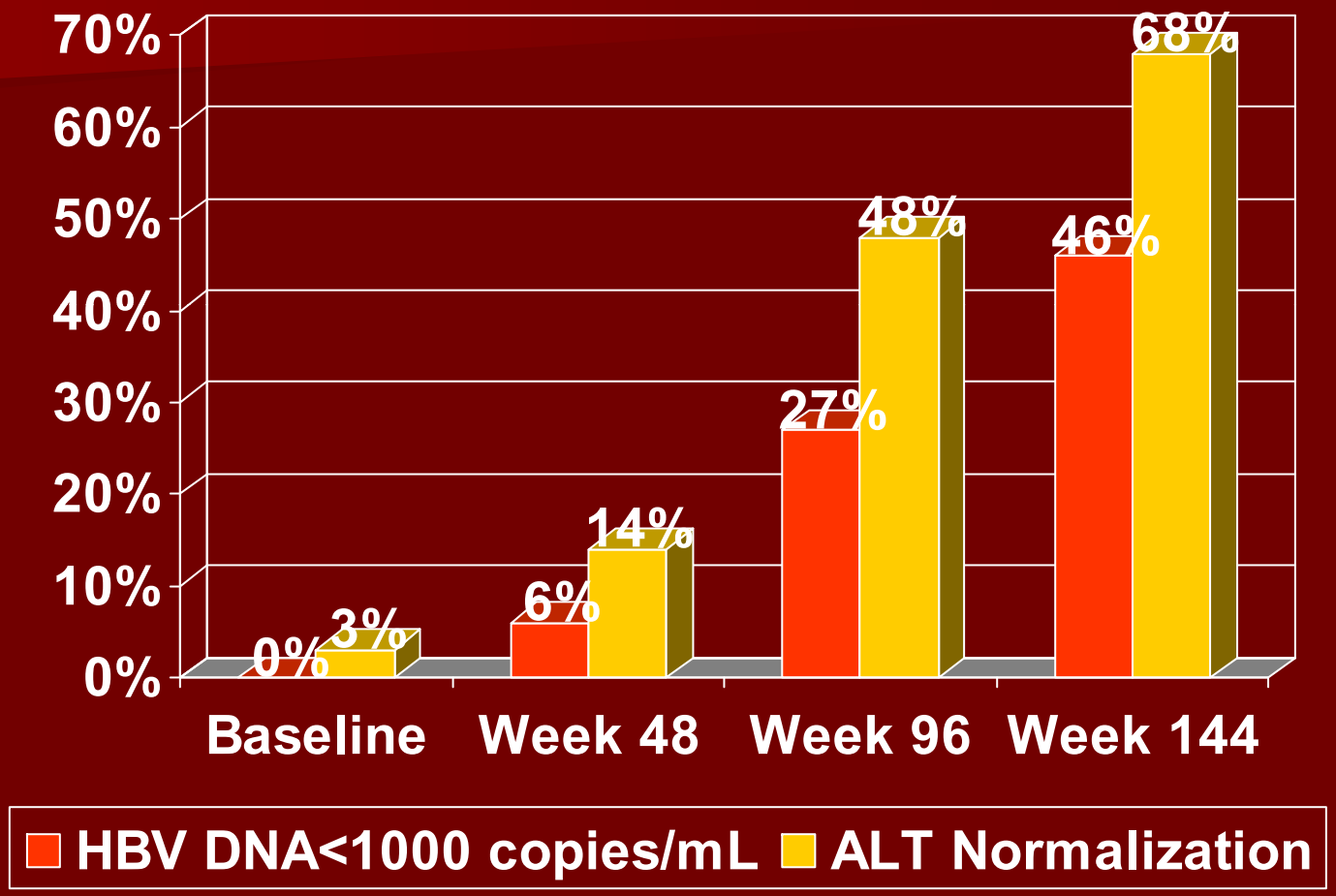
Leung, Hepatology, 2001, 33: 1527-32
Benhamou, Hepatology, 1999, 30:1302-6
Matthews, AIDS 2006; 20:863-870

Adefovir: High rate of nonprimary response



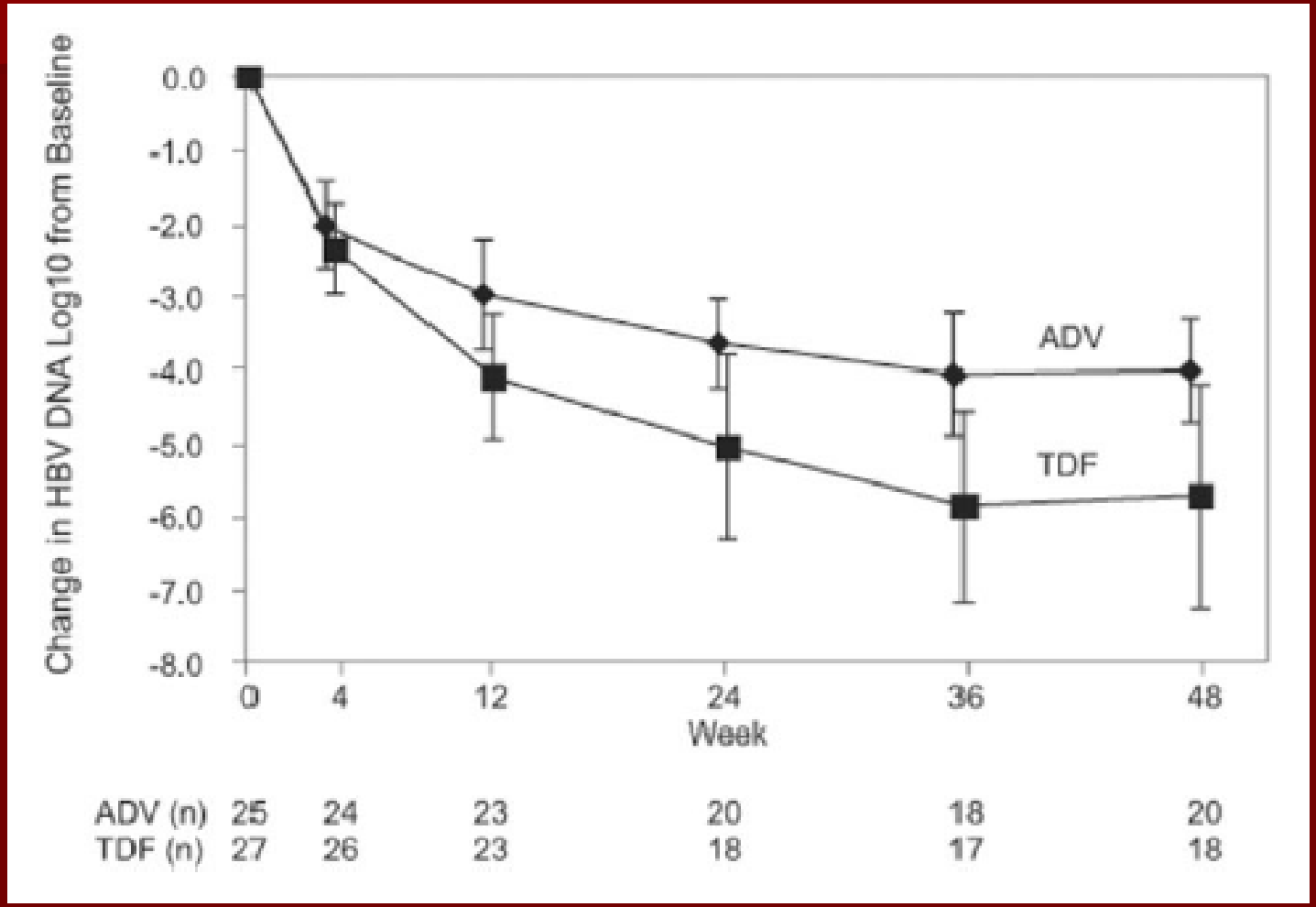
Fung, J Hepatology 2006; 44:283-290

ADV in HIV: Results at 3 years



Benhamou, CROI 2004, Abs 835

ACTG 5127: Tenofovir Noninferior to Adefovir for HBV/HIV



Peters, Hepatology 2006; 44:1110-6

Adefovir vs Tenofovir

	ADV (n=25)	TDF (n=27)
Mean change in HBV DNA from baseline	-4.03 log	-5.74 log
HBV DNA<200 at w36	8.6%	5.7%
HBV DNA<200 at w48	11.4%	20%
Nml ALT at w48	25%	36%
HBeAg→anti-HBe	1 pt	0 pts

HBV DNA $DAVG_{48}$ (log copies/mL)

Table 3. Serum HBV DNA Decrease in A5127 Study Subjects During Therapy With ADV or TDF

	HBV DNA drop	w 12	w 24	w 36	w 48
ADV (n = 25)	<2	3	0	0	1
	2-4	17	15	11	8
	>4	3	5	7	8
	n/a	2	5	7	8
TDF (n = 27)	<2	1	1	1	1
	2-4	8	4	1	3
	>4	14	13	15	14
	n/a	4	9	10	9

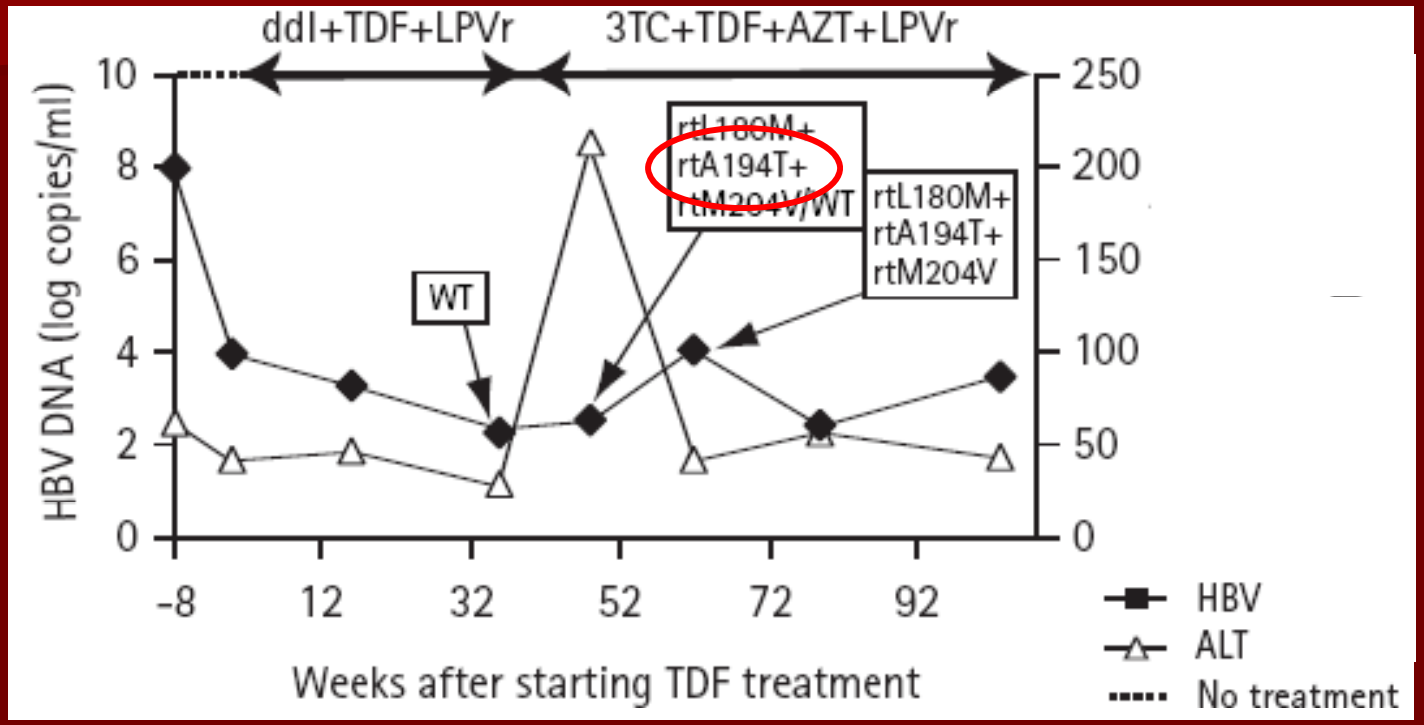
w, Week; n/a: number of subjects for whom data was not available at that time.

Tenofovir Resistance

Baseline Characteristics (n=43)	
Median age (years)	41 (IQR 37-42)
Median CD4 (cells/ul)	378 (IQR 235-475)
Median plasma HIV RNA (log copies/mL)	2.29 (IQR 1.7-3.4)
Median ALT (IU/mL)	48 (IQR 31-59)
Median serum HBV DNA (log copies/mL)	4.6 (IQR 3.0-8.0)
Mean time on tenofovir (months)	11.2 ± 6.7
Mean time on lamivudine (months)	35.3 ± 27.5
HBeAg+ (%)	35 (82%)

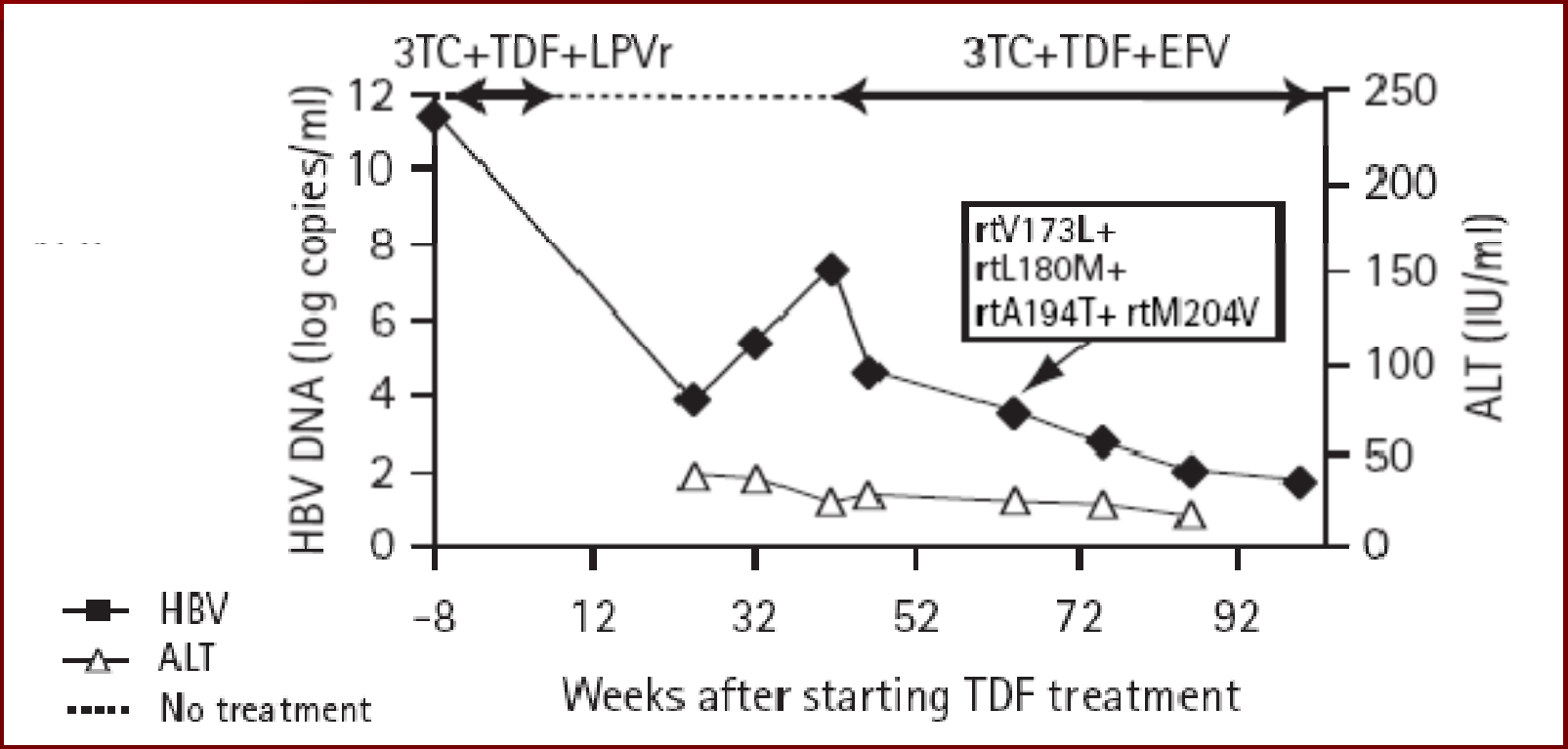
Sheldon, Antiviral Ther, 2005; 10:727-34

Novel Mutations detected on TDF Therapy: Patient 1



Sheldon, Antiviral Ther, 2005; 10:727-34

Novel Mutations detected on TDF Therapy: Patient 2



Sheldon, Antiviral Ther, 2005; 10:727-34

Effect of clinical mutations on HBV susceptibility to TDF *in vitro*

	Extracellular DNA	
	IC_{50} (umol/l)	Fold IC_{50}**
Wild-type	12.4	1
A194T	95	7.6
L180M+M204V	71	5.7
L180M + A194T + M204V	>120	>10

** 5-10 fold change = partial resistance; >10 fold confers resistance

Sheldon, Antiviral Ther, 2005; 10:727-34

A194T does not reduce efficacy to TDF

- 10 patients failing TDF with L180M+M204V/I that were found to have A194T
- 6 received TDF+/-FTC as salvage
- All 6 had >3 log decrease in HBV DNA and clinical response to TDF

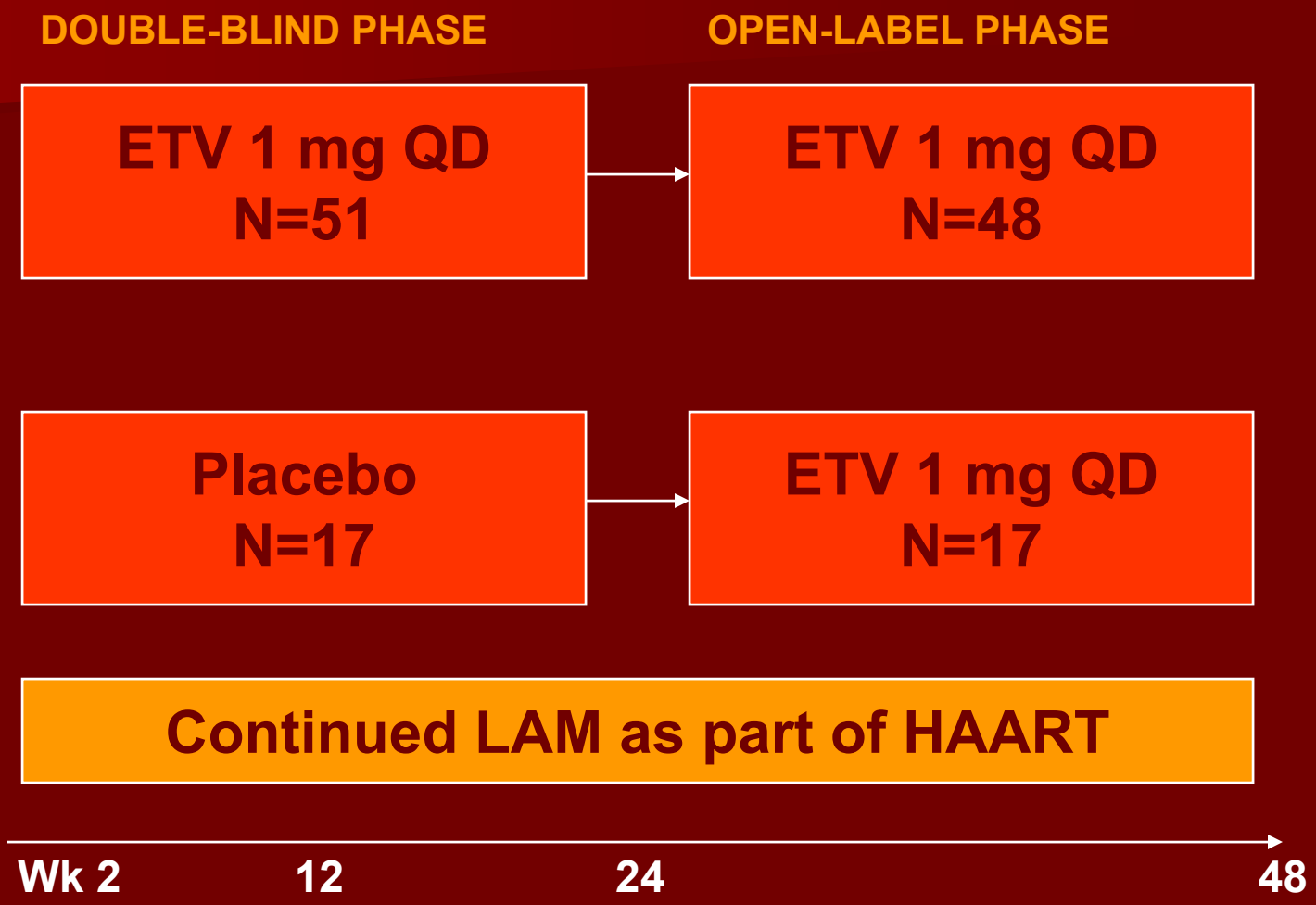
Fung, AASLD 2008, Abs 880

Tenofovir Resistance

- No HBV polymerase/RT amino acid substitutions associated with TDF resistance were detected through 96 weeks of monotherapy
- Virologic breakthrough was infrequent and not associated with phenotypic resistance
  - Most had nonadherence

Snow-Lampart, AASLD 2008, Abs. 977

Entecavir in HIV/HBV: ETV-038



Pessoa, AIDS 2008; 22:1779-1787
Colonno, CROI 2006, #832

Efficacy Endpoints

	Entecavir (n=51 w24 n=48 w48)	Placebo (n=17 w24 & w48)	*P*
Mean HBV DNA @ w24	**5.52 log copies/mL**	**9.27 log copies/mL**	
Mean HBV DNA @ w48	**4.79 log copies/mL**	**5.63 log copies/mL**	
Change in DNA from baseline @ w24	**-3.65 log copies/mL**	**+0.11 log copies/mL**	**<0.0001**
Change in DNA from baseline @ w48	**-4.20 log copies/mL**	**-3.56 log copies/mL**	
HBV DNA<300 copies/mL @ w24	**3/51 (6%)**	**0/17 (0%)**	
HBV DNA<300 copies/mL @ w48	**4/51 (8%)**	**0/17 (0%)**	
ALT normalization w24	**34%**	**8%**	**0.08**
ALT normalization w48	**37%**	**46%**	
HBeAg loss w48	**1 (2%)**	**0**	**0.56**
HBeAg seroconv, w24	**1 (2%)**	**0**	

Pessoa, AIDS 2008; 22:1779-1787

Entecavir Resistance

- Requires “two hits”
- M204V/I +/- L180M as first hit
  - 8 to 10 fold dec in susceptibility to ETV vs wild-type
- Then mutation in I169, T184, S202 or M250
  - These mutations on their own have minimal effect on susceptibility to entecavir
- In presence of M204V/I, one of these leads to 10-250 fold decrease in ETV susc
- M204V/I + 2 mutations → 500-1000 fold decrease in ETV susceptibility

Tenney, AAC, 2004; 48:3498-507
Riddick, J Hep 2008; 48:895-902

Entecavir Resistance

- NA-naïve
  - After 4 years on treatment, a total of 3 patients (<1%) developed ETVr mutations
    - 2 of these had virologic breakthrough
    - Out of 663, 278, 149, 120 tested for resistance in years 1-4 respectively
- LAM-R patients
  - After 4 years on treatment, virologic breakthrough occurred in 1%, 10%, 16%, and 15% in years 1, 2, 3 and 4 respectively
- Cumulative probability of virologic breakthrough through 4 years 0.8% in naïve and 39.5% in LAM-R patients

Colonno, EASL 2008, Abs 781

Development of M184V in HIV

- 4 of 13 patients with >0.5 log decline had HIV rebound after achieving a nadir
  - All ART-experienced
  - 3 had developed M184V at time of HIV RNA rebound after a median of 98 days
  - 2 other ART-experienced patients had M184V before ETV initiation
- 2 ARV-naïve patients developed M184V after median 132 days of ETV
  - 1 more without a baseline geno did as well

Sasadeusz, AIDS 2008; 22:947-55

Telbivudine in HIV

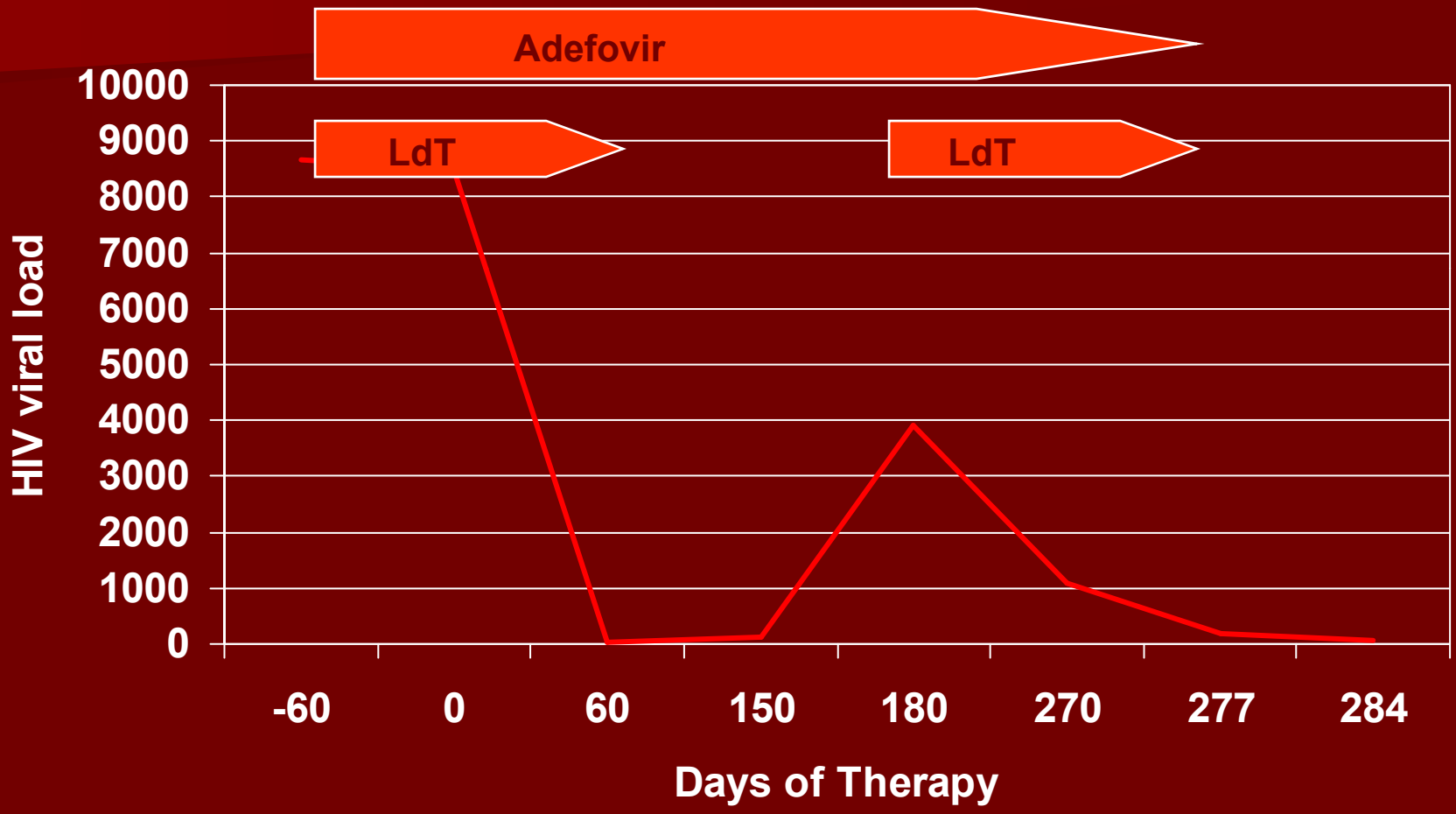
- No RCT for its use in HIV+
- Cross-resistance limits usefulness in ARV-experienced patients
- AASLD Guidelines currently do not recommend its use in HIV+
- EACS Guidelines present it as alternative to ADV in those not requiring HIV therapy

Telbivudine Resistance

- Most frequent genotypic change M204I
  - Only mutation causally associated with resistance
- Other mutations:
  - L80 (n=26)
  - L180 (n=4)
  - L229 (n=6)
- Single case of M204V/L180M double mutant seen for telbivudine at week 104 in GLOBE

Seifer, DDW 2007; Abs #93
Standring, DDW 2007; Abs. S1781
Liaw, Gastro 2009; 136: 486-495

Telbivudine: HIV Activity?



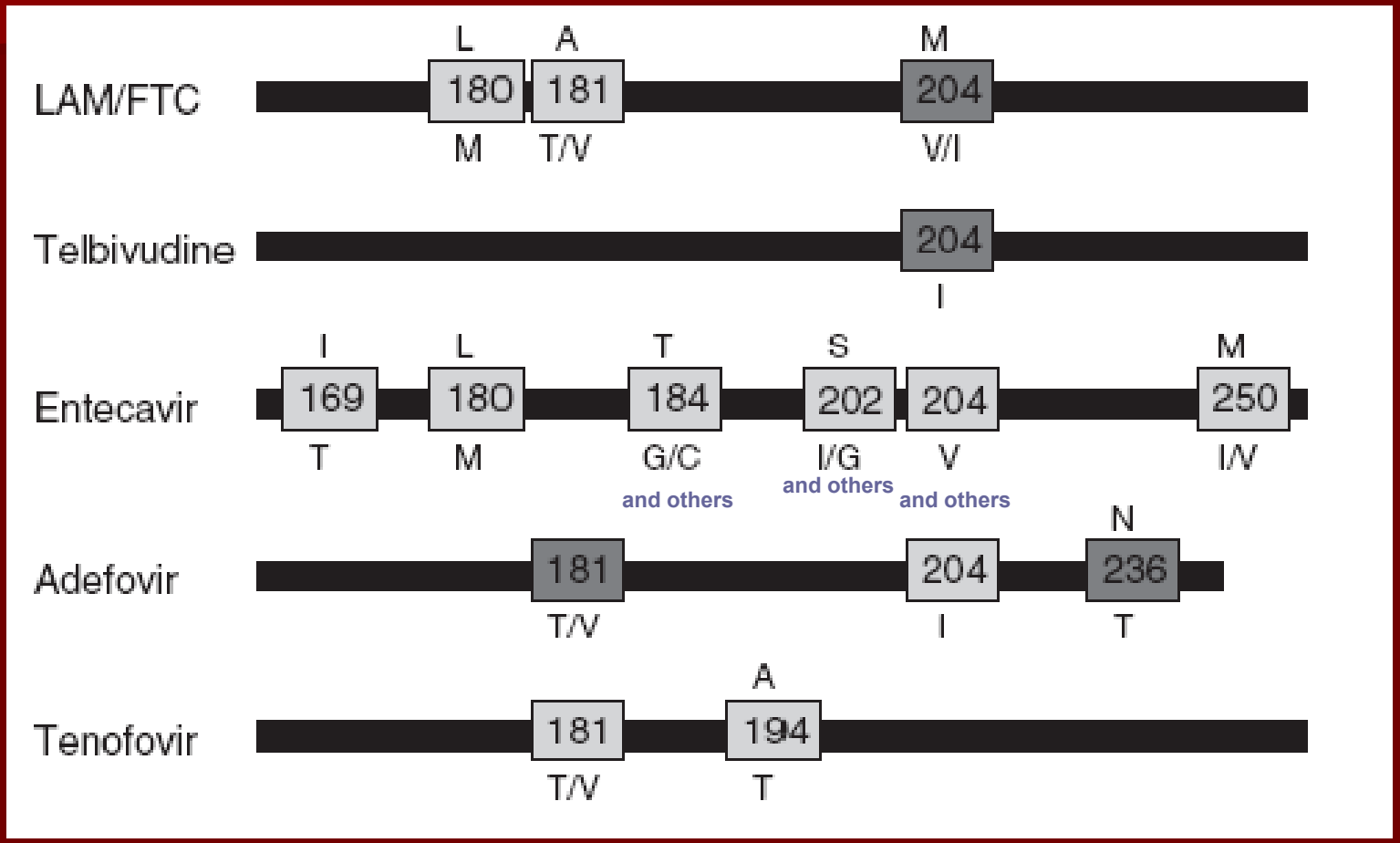
Low AIDS 2009; 23: 546-7

HBV Resistance Summary

Lamivudine	M204V/I, L180M
Adefovir	N236T[a], A181V/T, I233V[c]
	?Q215S, ?P237H, ?N238T, ?V207L[b]
Entecavir	M204V/I[d] → I169, T184[d], S202[d] or M250
Telbivudine	M204I
Tenofovir	A194T

[a]Angus, Gastro 2003; 125:292-97
[b]Gallego, J Viral Hep 2008; 15:392-98
[c]Schildgen, NEJM 2006; 354: 1807-12
[d]Tenney, AAC 2007; 51:902-911

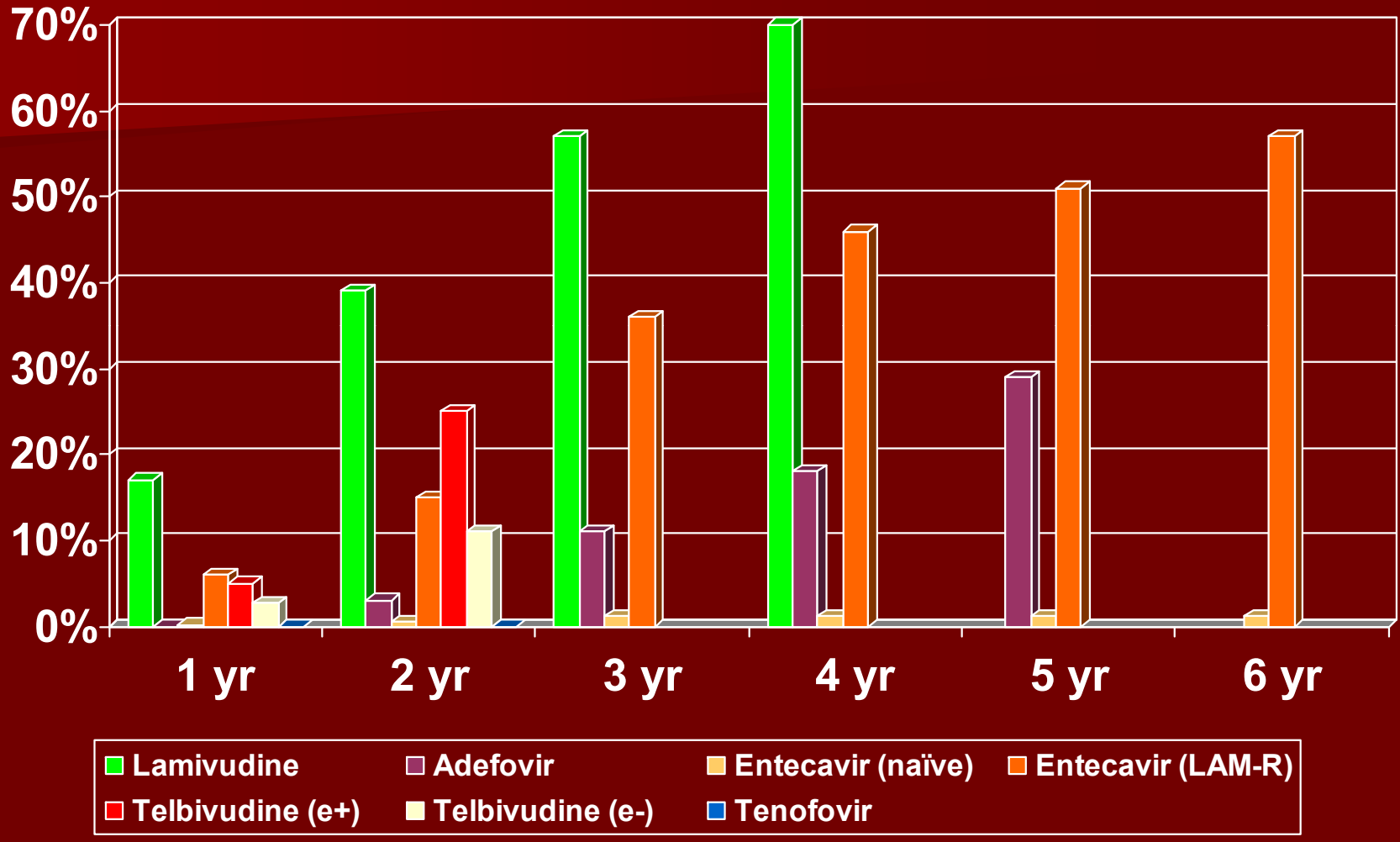
Resistance Summary



Additional compensatory mutations that restore viral fitness can be seen with the development of drug resistance

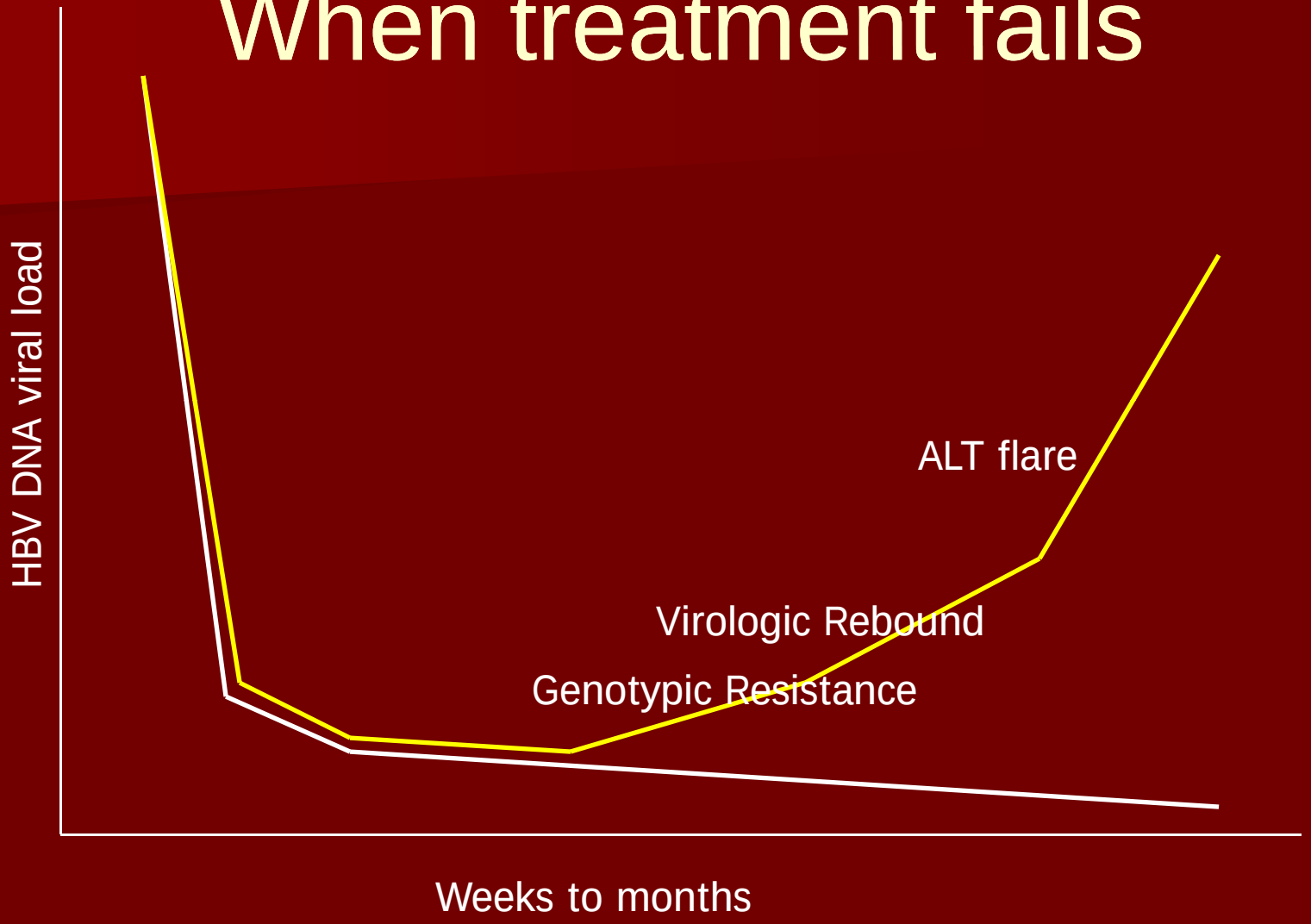
Soriano, AIDS 2008; 22:1399-1410

Resistance Summary



Hadziyannis, NEJM 2005; 352: 2673-81
Lok, Hepatology 2007; 45:507-539
Snow-Lampart, AASLD 2008, Abs 977
Leung, Hepatology, 2001, 33: 1527-32
Lai, NEJM 2007; 257:2576-88
Tenney, EASL 2009, Abs 20

When treatment fails



Soriano, AIDS 2008; 22:1399-1410

Final Thought: Truvada failure?

- Anecdotal failures of HBV therapy with Truvada
- No clear data on what best strategy is
- No known mutations for tenofovir though clinical breakthroughs described
- If entecavir added, recommend removing lamivudine/emtricitabine from HIV regimen to prevent selective pressure on M204V/I in HBV polymerase
  - Can lead to faster development of ETV resistance

Take home points

- Document more than just “Hepatitis B” in problem list
  - Resolved hepatitis B, Chronic carrier, eAg+ CHB, etc
- The HBV DNA level should be followed regularly, along with ALT and eAg
- Sequencing of antivirals is important: consider prior lamivudine exposure when choosing drugs; avoid entecavir – lamivudine combinations