



Drug Resistance in Chronic Hepatitis B Infection

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Nucleos(t)ide analogues against HBV

■ Lamivudine	3TC	Cytosine	Pyrimidine
■ Emtricitabine*	FTC	Cytosine	Pyrimidine
■ Telbivudine	LdT	Thymidine	Pyrimidine
■ Entecavir	ETV	Guanosine	Purine
■ Adefovir	ADV	Adenosine	Purine
■ Tenofovir*	TDF	Adenosine	Purine

*Phase 3

Phase 2/3

Clevudine (L-FMAU)

Eluvcitabine (LFd4C)

Valtorcitabine (Val-LdC)

[Amdoxovir (DAPD)]



L-nucleoside group

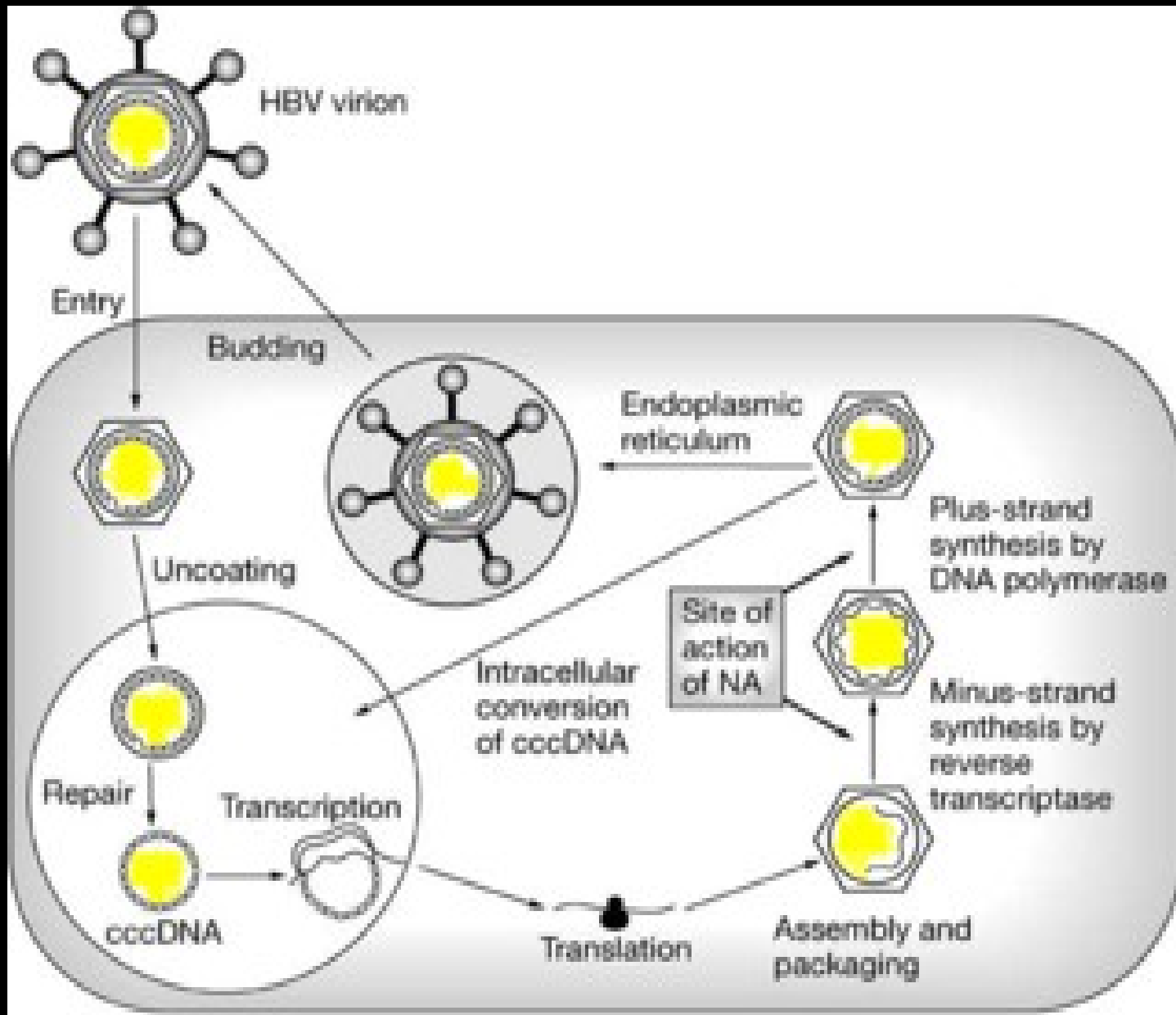


Cyclopentane group

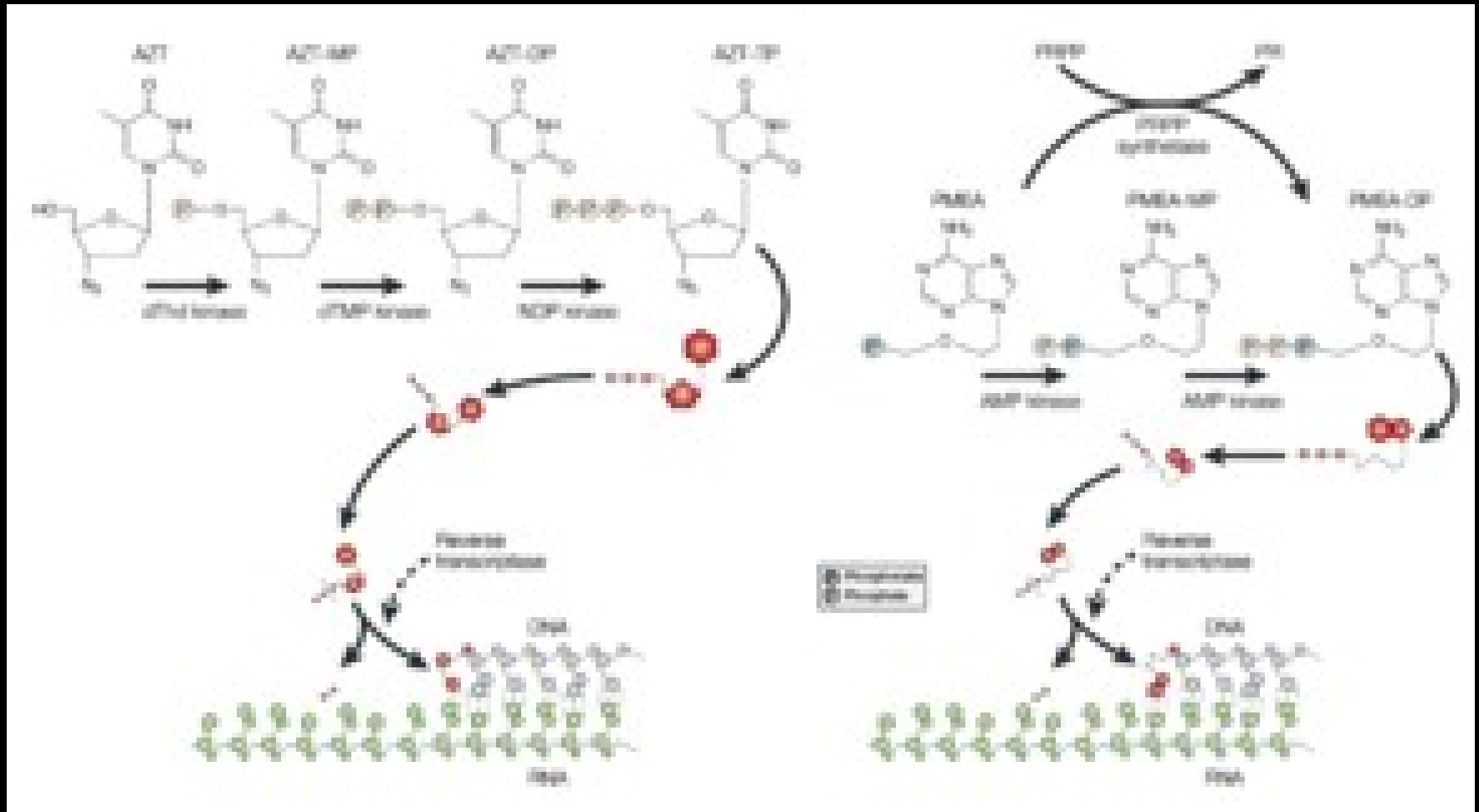


Acyclic Phosphonate group

HBV replication cycle

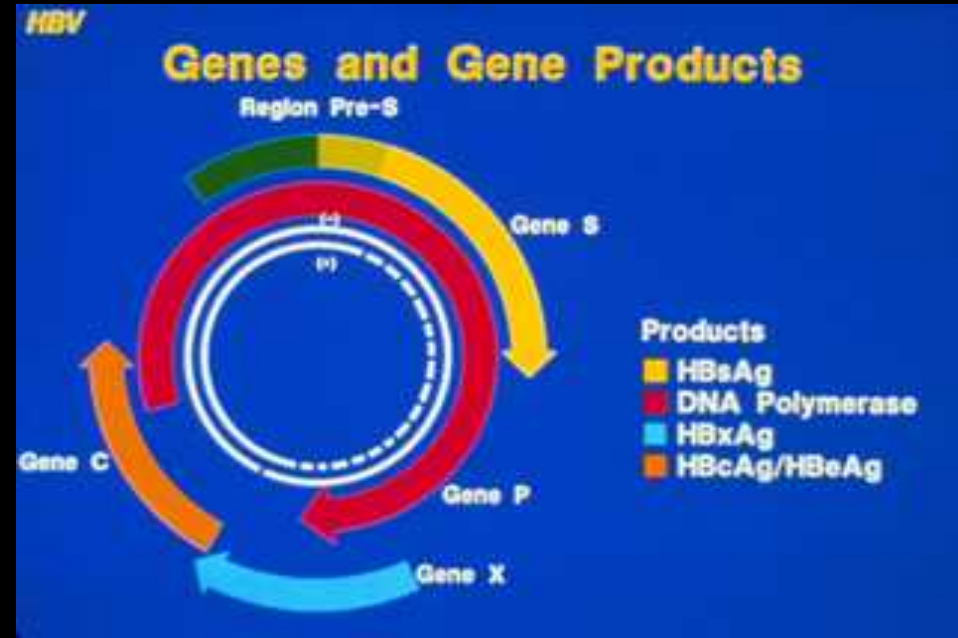


Mechanism of action of NRTIs



Basic facts on HBV

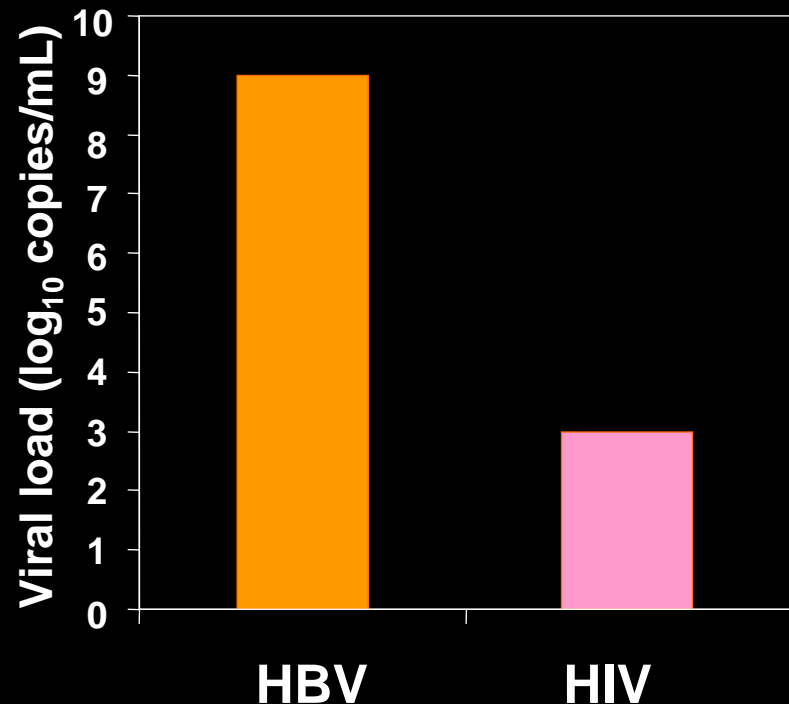
- *Hepadnaviridae*
- Circular DNA
 - 3221 bases
 - Partly double stranded
 - ORF, 4 genes: C, S, P, X



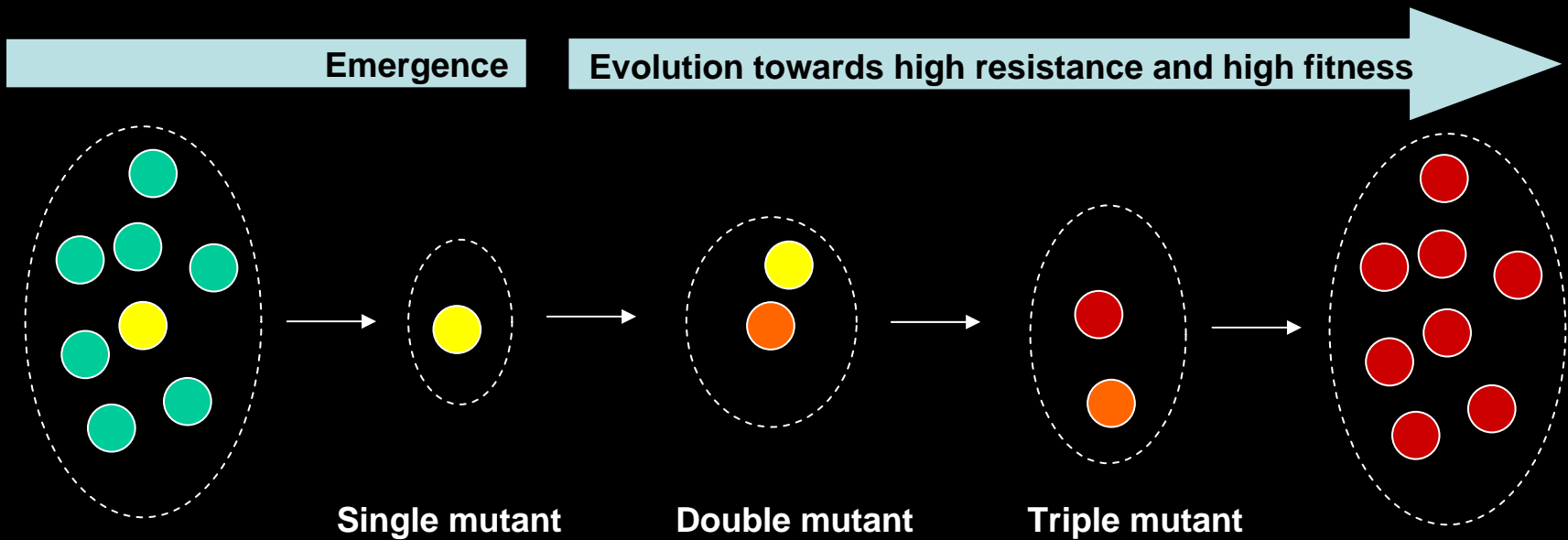
- 4 major subtypes: adw, ayw adr, ayr
- 8 genotypes (A-H) $\geq 8\%$ sequence divergence

HBV replication kinetics

	HBV	HIV
Genome size:	3.2kb	9.8kb
Daily production:	10^{10-13}	10^{9-10}
Mutation rate:	10^{-5}	10^{-4}
Half life (hrs)	4-24	<1



Emergence and evolution of resistance

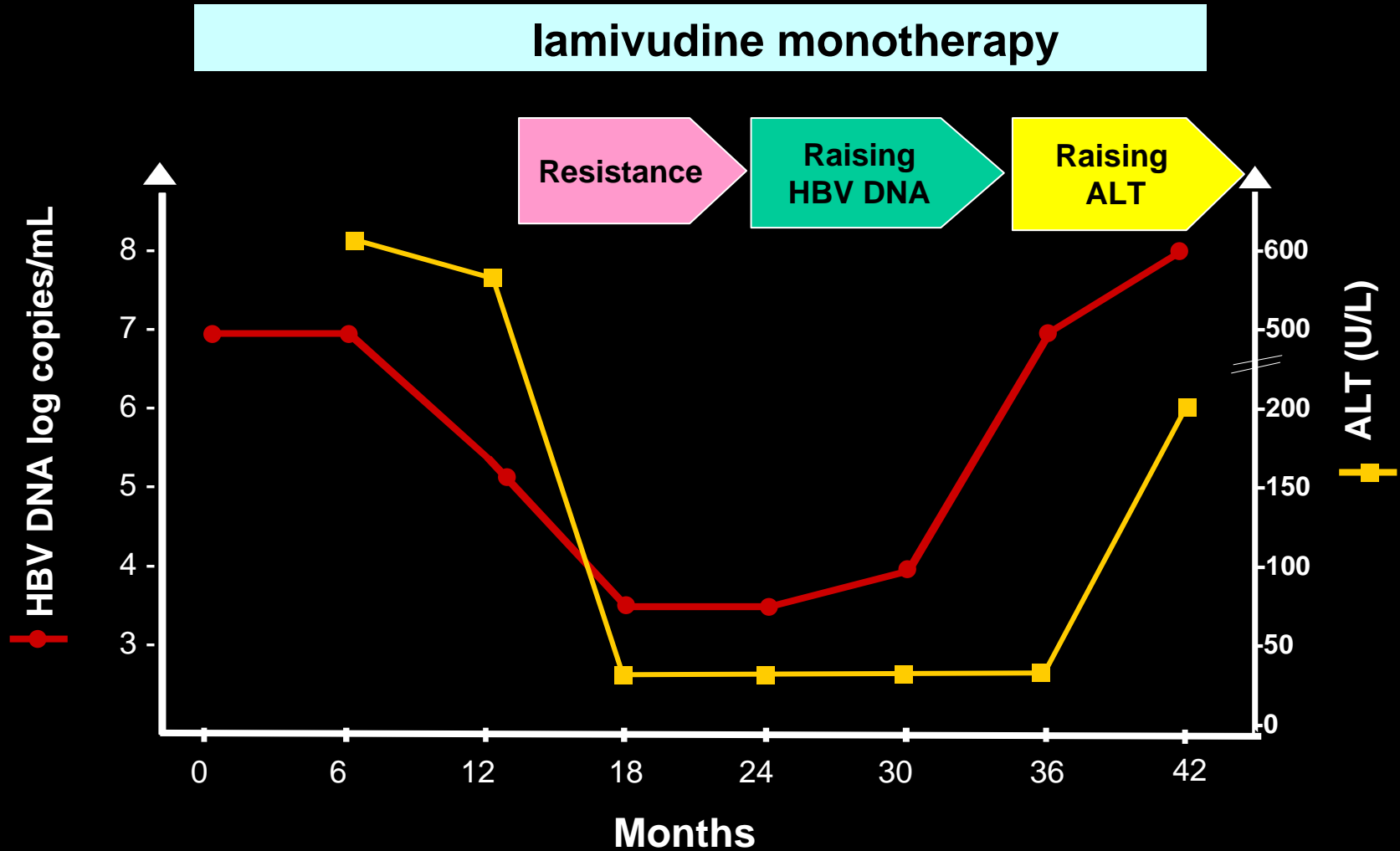


- Increasing resistance and cross-resistance
- Accumulation of mutations on the same viral genome
- Compensatory changes that restore fitness

Determinants of drug resistance

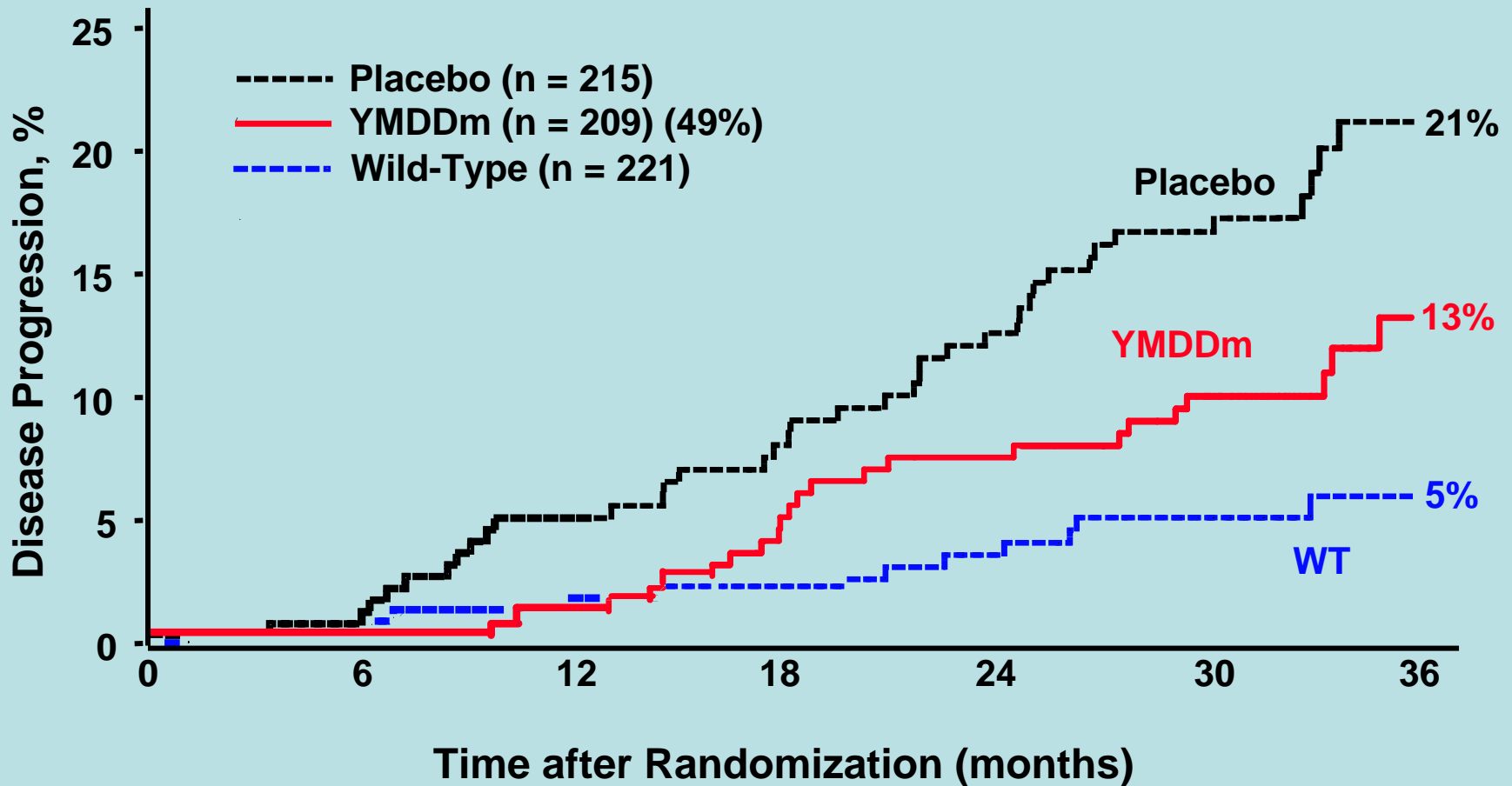
<i>Virus</i>	<i>Drug</i>	<i>Host</i>
<ul style="list-style-type: none">▪ High replication▪ Error prone RT▪ Fitness▪ Replication space	<ul style="list-style-type: none">▪ Potency▪ Genetic barrier▪ PK▪ Targeted mutations	<ul style="list-style-type: none">▪ Adherence▪ Genetics▪ Prior Rx

Resistance precedes virological and clinical failure

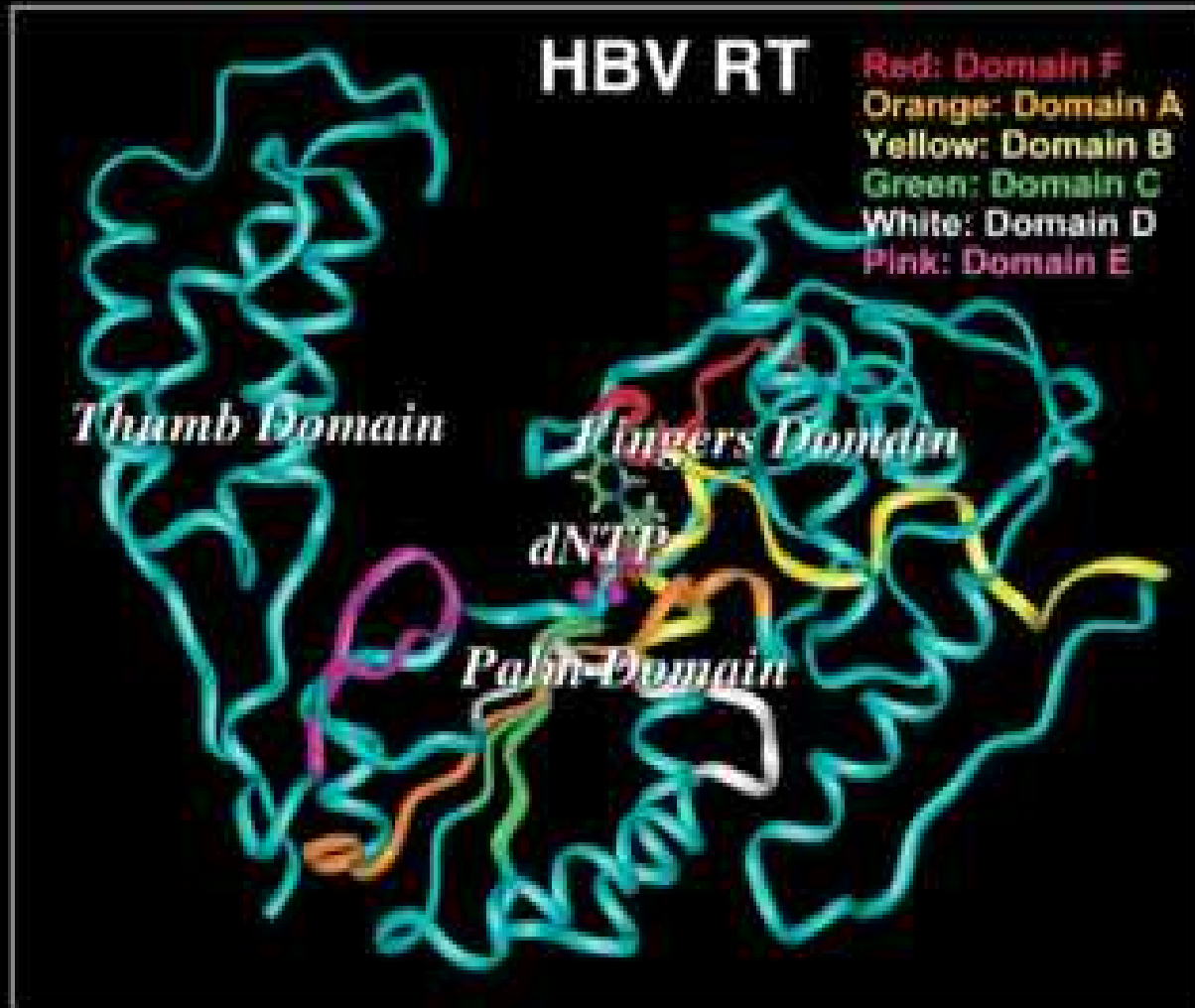


Impact of lamivudine resistance on progression of liver disease

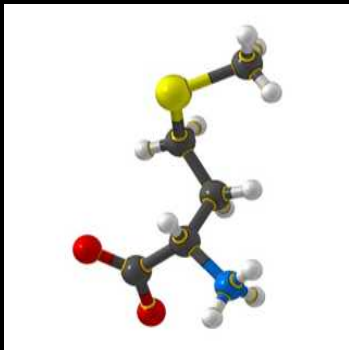
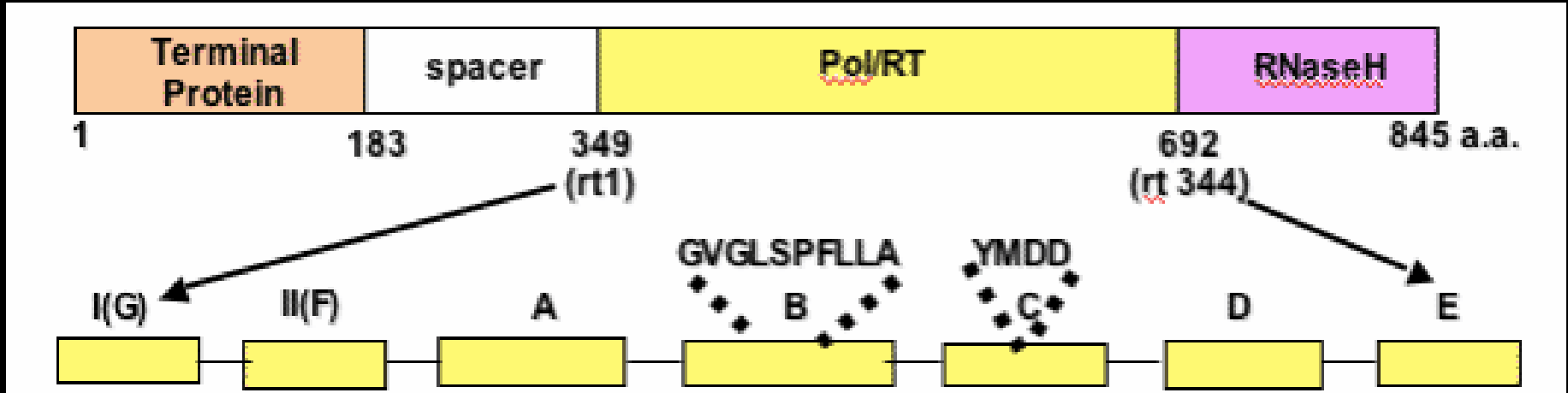
Patients with severe fibrosis or cirrhosis



HBV RT



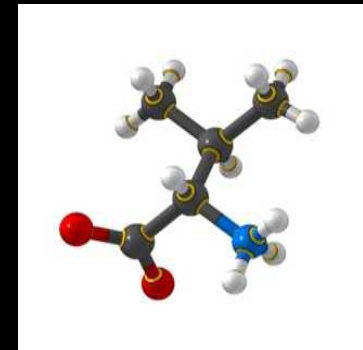
Nomenclature



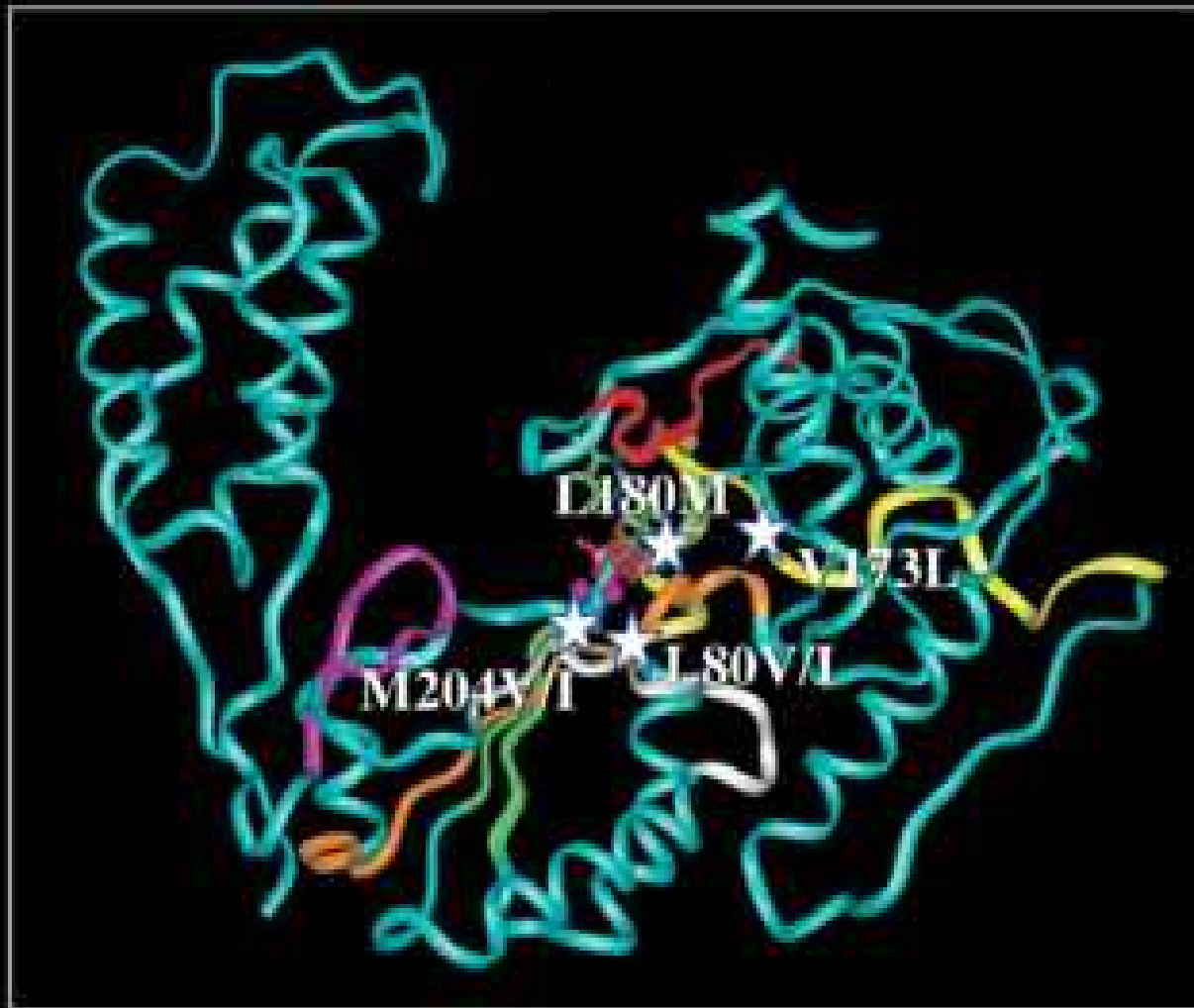
Wild-type
amino acid
(Methionine)

M204V

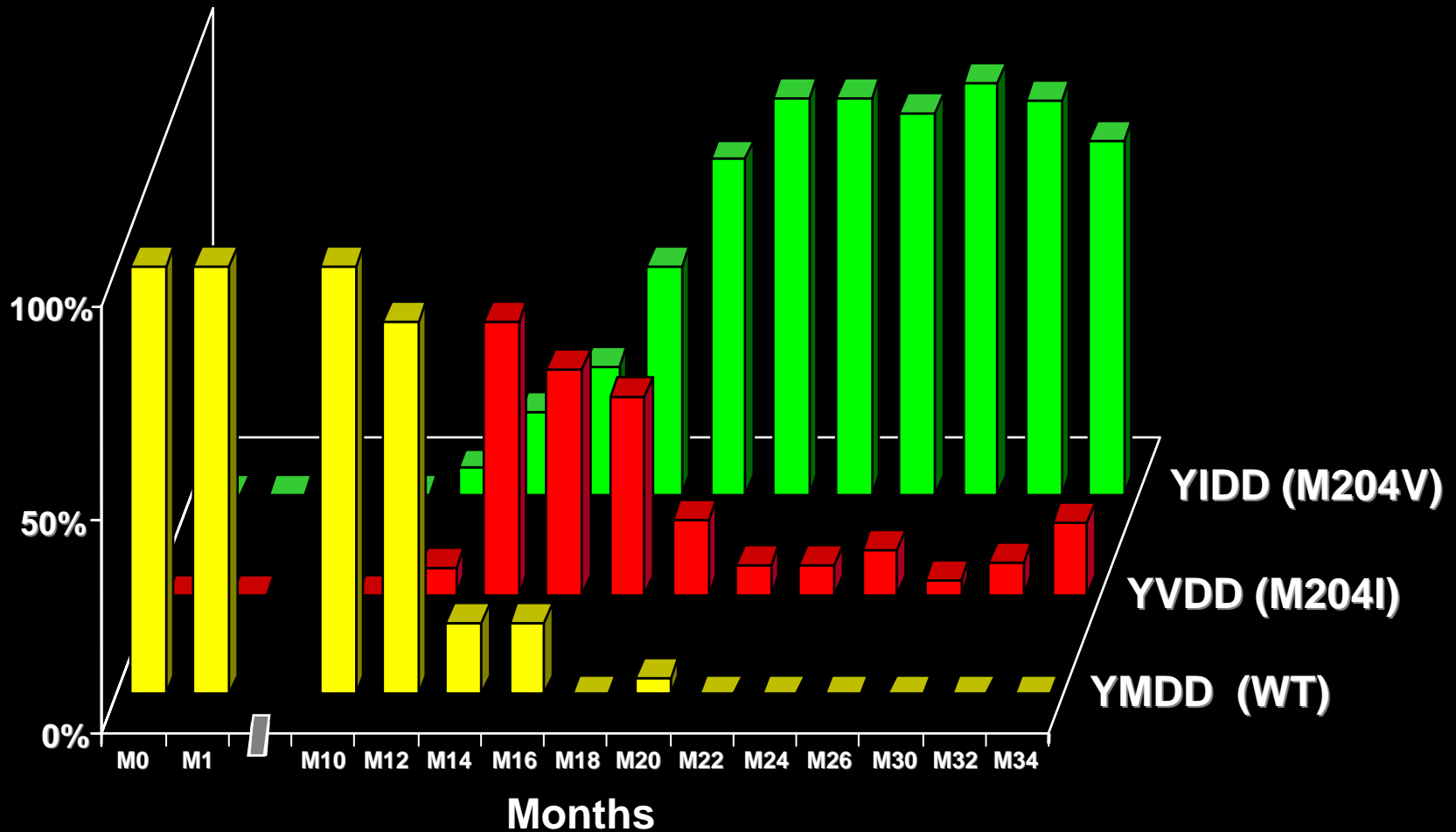
Mutant
amino acid
(Valine)



Lamivudine resistance mutations



Evolution of lamivudine resistance



The genetic barrier of NAs against HBV

Drug	Potency	Genetic barrier	Resistance rates	Comments
Lamivudine	++	Low	1 yr 14-32% 5 yrs 69%	Resistance highly common
Emtricitabine	++	Low	1 yr 13% 2 yrs 18%	Tenofovir co-formulation

Cross-resistance after lamivudine failure

■ Reduced susceptibility ■ Resistant

Fold-Change in EC ₅₀ Relative to Wild Type HBV				
Compound	M204V + L180M	M204V + L180M + V173L	M204I	M204I + L180M
Lamivudine	>700	>1000	>1000	>1000
Emtricitabine	>2000	898	>2000	845
Telbivudine	>322	>322	>322	>322
Tenofovir	0.8	1.8	2.1	0.7
Adefovir	1.1	1.1	1.8	2.1
Entecavir	37	164	471	38
Valtorcitabine	>650	>460	>180	>650
Clevudine	>1600	>1600	>1600	>1600

Lamivudine, Telbivudine, Clevudine: modest activity against M204V

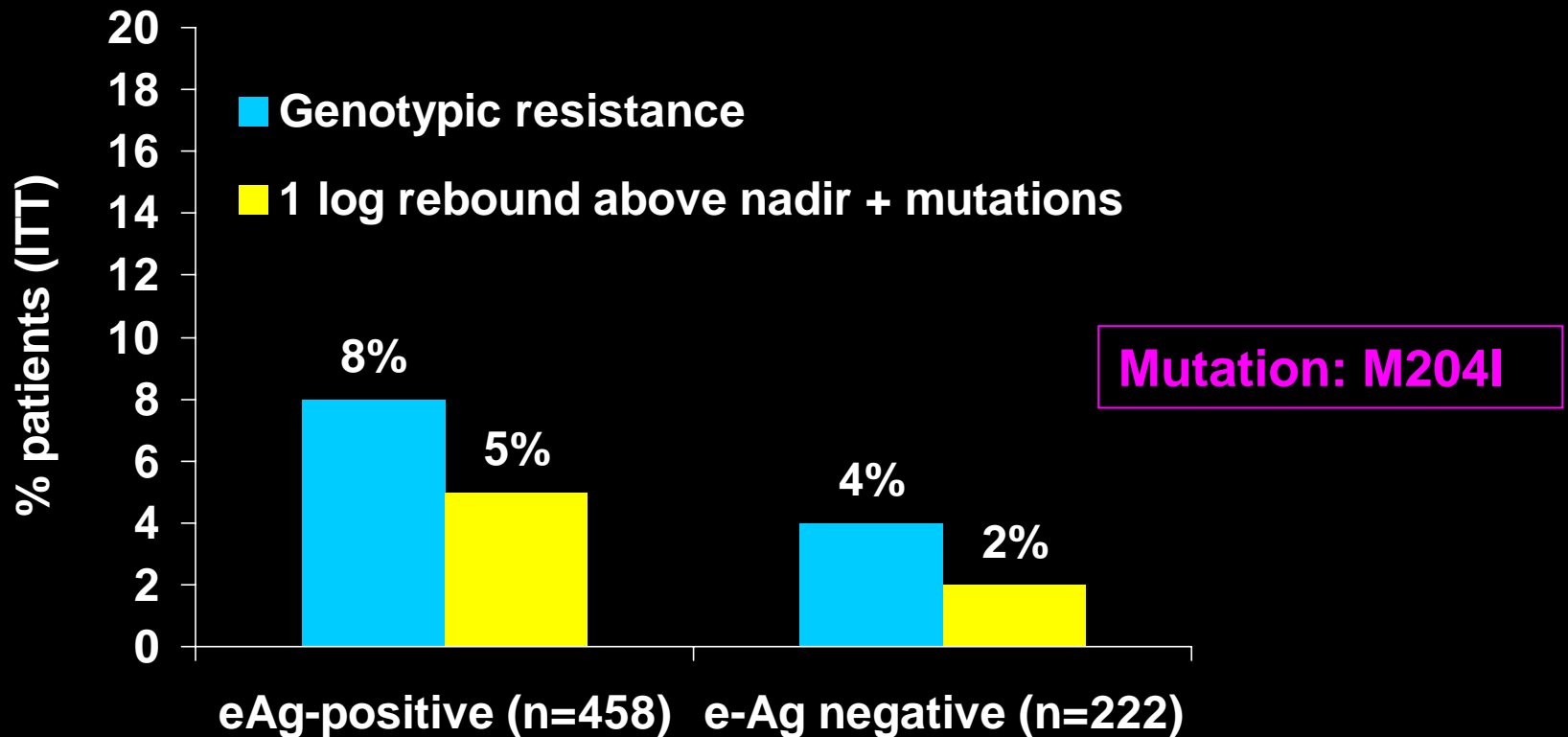
Tenofovir: resistance reported with M204V+L180M+A194T

Lamivudine: may also select A181T and Q215S → cross-resistance to adefovir and tenofovir

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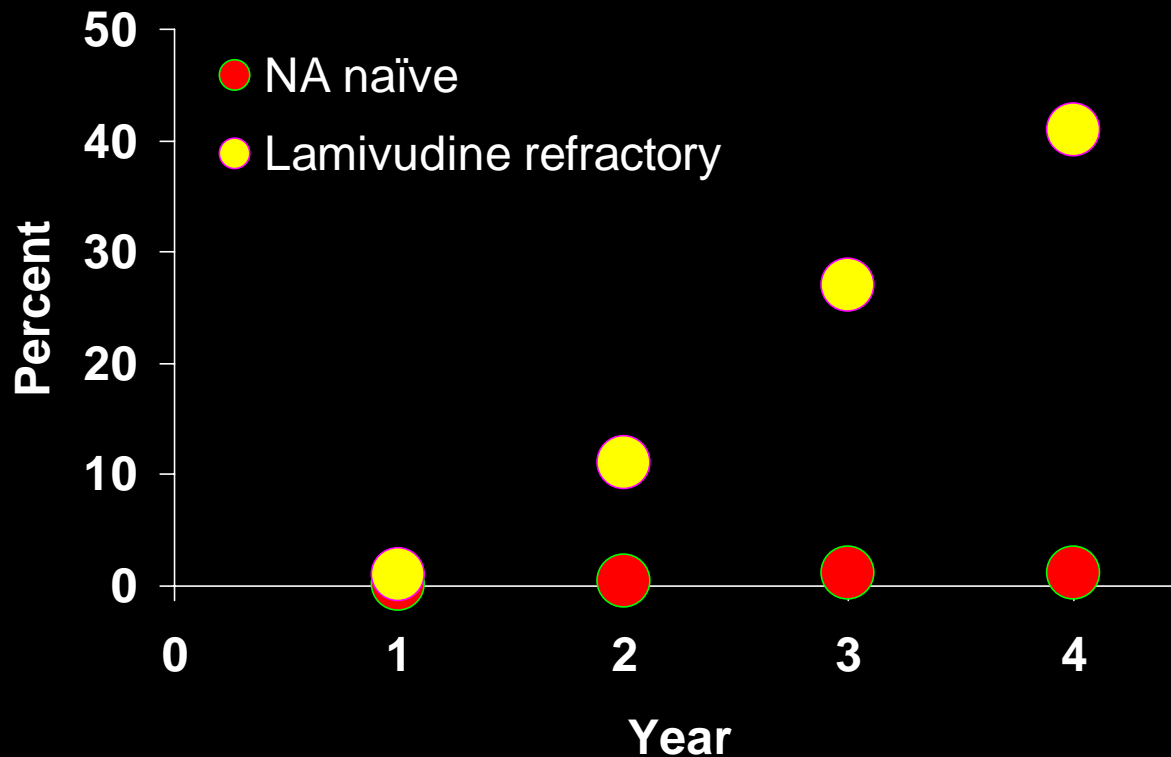
Globe study: Telbivudine resistance at wk 48



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Entecavir	+++	High (drug-naïve)	4 yrs 1.2% 41% if lamivudine resistance	Less active and lower genetic barrier after lamivudine failure

Cumulative probability of virological breakthrough with entecavir



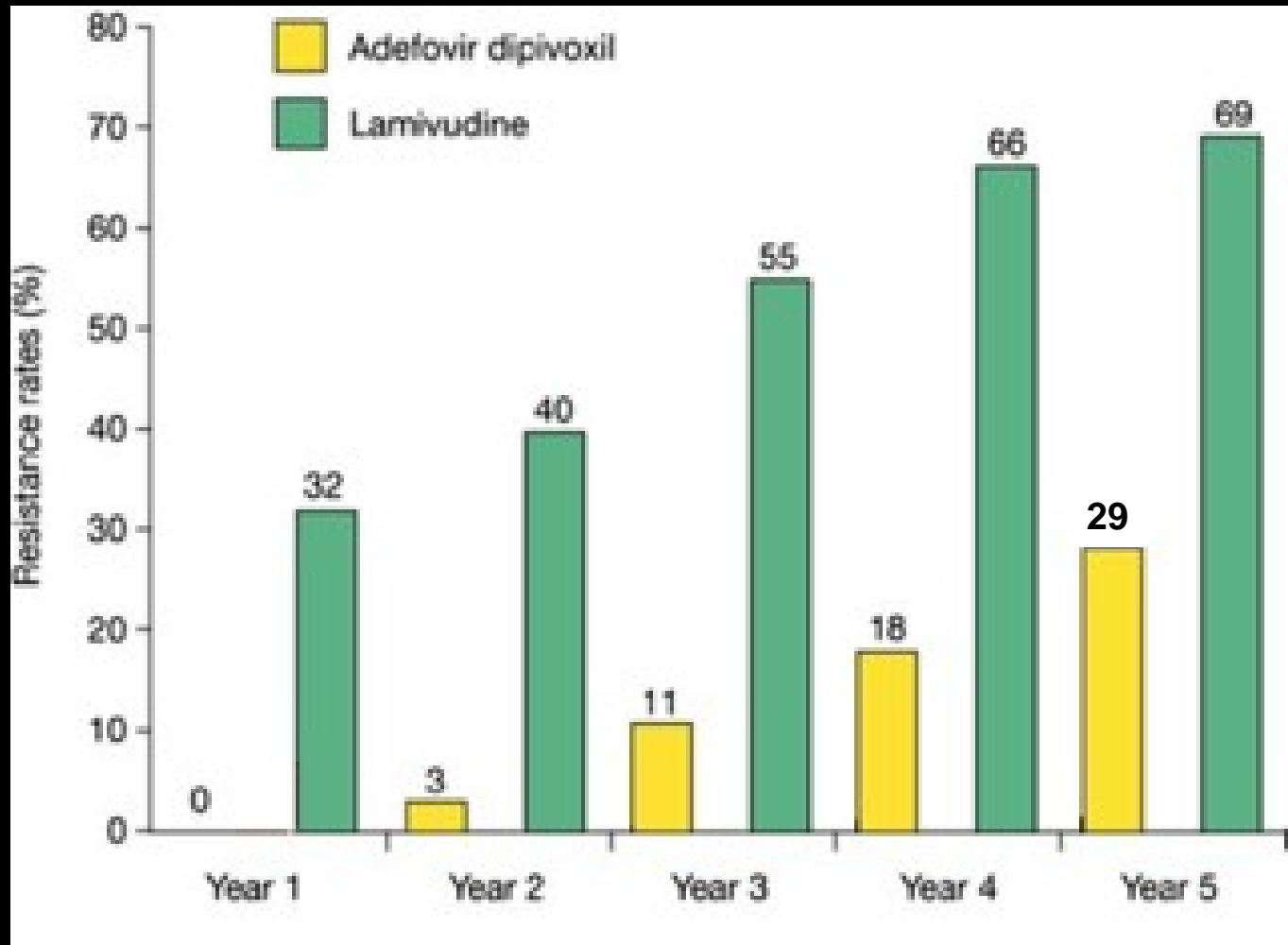
● NA naïve	N =	663	278	149	120
● Lamivudine refractory	N =	187	146	80	43

Mutations: (M204V, L180M) + T184, S202 and/or M250

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Adefovir	+	Intermediate	1 yr none 5 yr 29% 2 yrs 20% if lamivudine resistance	Activity related to dose; generally active after lamivudine failure

Resistance rates for lamivudine vs adefovir



Adefovir resistance data: summary

- Long-term data mainly from eAg-negative patients
- Suboptimal response rate is high at wk 48, although emergence of resistance is low
- Main resistance mutations: A181V/T and/or N236T
- Unresolved issue:
 - Significance of additional mutations (eg, 237, 238)
 - Cross-resistance potential with tenofovir

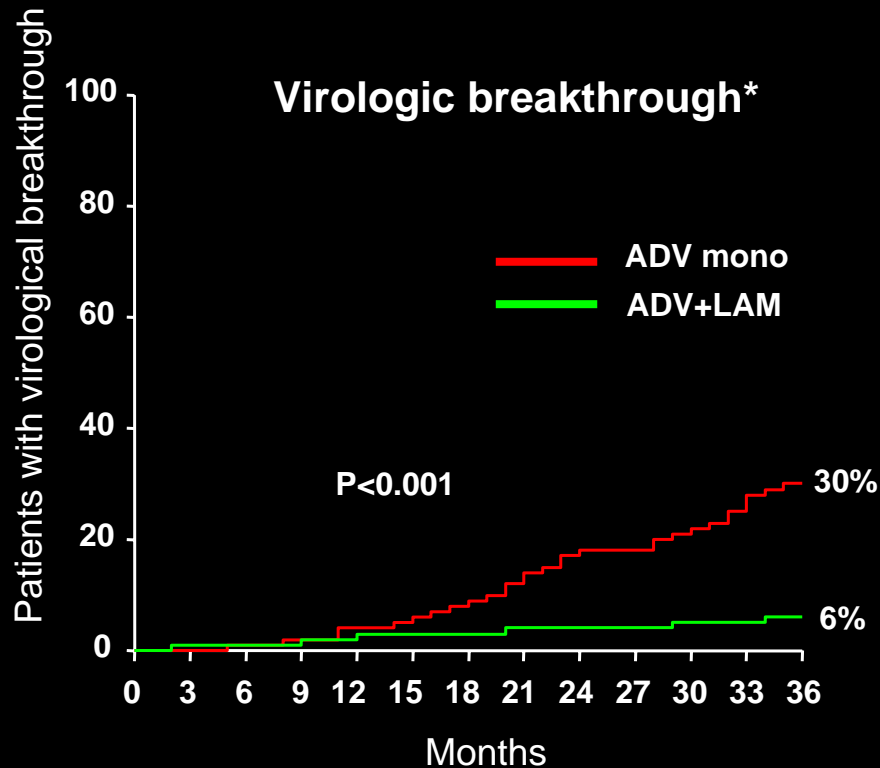
Cross-resistance after adefovir failure

■ Reduced susceptibility ■ Resistant

Fold-Change in EC ₅₀ Relative to Wild Type HBV		
Compound	N236T	A181V
Adefovir	7.3	4.2
Tenofovir	4.6	3.0
Entecavir	0.7	12
Lamivudine	2.1	14
Emtricitabine	2.6	14
Telbivudine	2.4	>24
Valtorcitabine	NA	87
Clevudine	4.9	>164

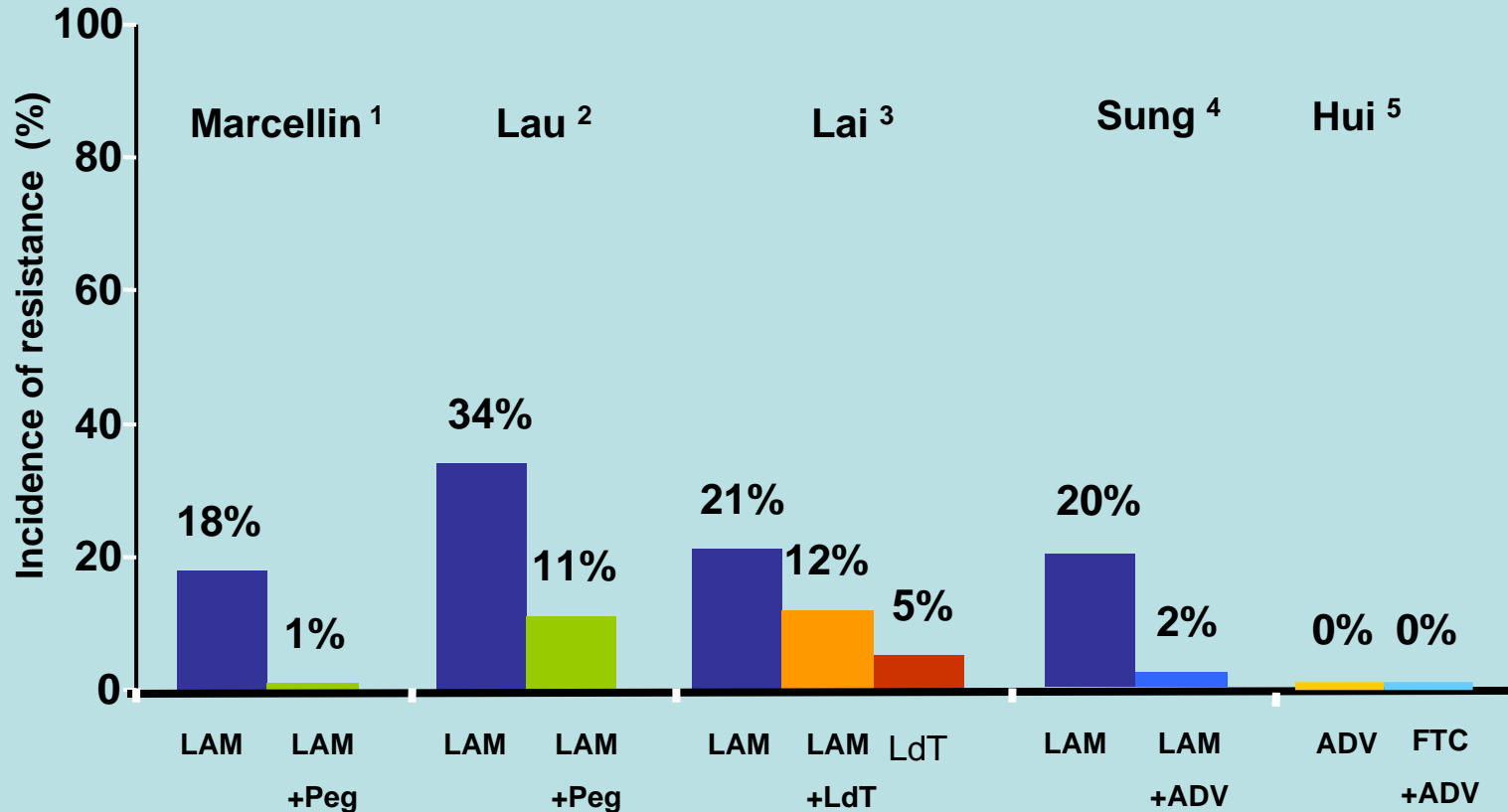
Adefovir add-on in patients with lamivudine resistance

3-yr cumulative probability



* >1 log rebound from nadir

Genotypic resistance rates in clinical trials 1 year of therapy



1. Marcellin, N Engl J Med 2004; 2. Lau, N Engl J Med 2005; 3. Lai, Gastroenterology 2005; 4. Sung, J Hepatol in press; 5. Hui, J Hepatol in press

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Tenofovir	+++	High	1 yr none reported	Can retain activity after adefovir failure

Tenofovir resistance data: summary

- Long-term experience in HIV-HBV co-infection with 3TC or FTC
 - No resistance in most cohort studies
 - A194T observed in 2 co-infected persons on TDF/3TC
- Short term experience with monotherapy

Summary of Resistance Surveillance Conducted at Year 1 in HBeAg- and HBeAg+ TDF Treated Subjects

Category	HBeAg- (N=250)	HBeAg+ (N=176)	Total (N=426)
HBV DNA < 400 copies/mL at Week 48	233 (93.2%)	134 (76.1%)	367 (86.2%)
Discontinued Prior to Week 24 or After Week 24 with HBV DNA < 400 copies/mL	9 (3.6%)	11 (6.3%)	20 (4.7%)
Subjects Included in Year 1 Resistance Surveillance	8 (3.2%)	31 (17.6%)	39 (9.2%)
HBV DNA ≥ 400 copies/mL at Week 48 Without Virologic Breakthrough	4 (1.6%)	24 (13.6%)	28 (6.6%)
Virologic Breakthrough During Study	4 (1.6%)	6 (3.4%)	10 (2.3%)
Discontinued After Week 24 with HBV DNA ≥ 400 copies/mL	0	1 (<1%)	1 (< 1%)

Phenotypic Analysis of HBV DNA

Conserved Site Changes Observed in TDF Treated Subjects ¹	Tenofovir EC ₆₀ (µM)	Fold Change
Wild type (control)	11.4 ± 6.7	1
rtS74P	11.0 ± 6.6	1
rtH156R ²	ND	NA
Clinical Isolates From TDF Subjects Experiencing Virologic Breakthrough	Tenofovir EC ₆₀ (µM)	Fold Change
Baseline Isolates (n=6)	5.3 – 16.6	NA
Virologic Breakthrough Isolates (n=6)	4.8 – 15.4	0.7 – 1.2

¹Site Directed Mutants

²Null mutation – viruses with this mutation did not replicate in cell culture

Preventing HBV resistance

- Initiate regimens with high potency and high genetic barrier
- Aim for rapid VL suppression and HBV DNA undetectability
- Monitor initial HBV DNA response:
 - >1 log and preferably >2 log reduction at wk 12
 - >2 log reduction, <math><10^4</math> and preferably <math><LLD</math> at wk 24
- Monitor HBV DNA every 4-6 months during stable therapy
- Monitor and support adherence
- Do not use HIV VL as a proxy for HBV suppression
- Confirm resistance with genotypic testing
- Initiate rescue therapy before VL rebound or ALT increase



Thank you