

**“Assessment At Three Years Shows High
Barrier To Resistance Is Maintained In
Entecavir-treated Nucleoside Naïve Patients
While Resistance Emergence Increases Over
Time In Lamivudine Refractory Patients”**

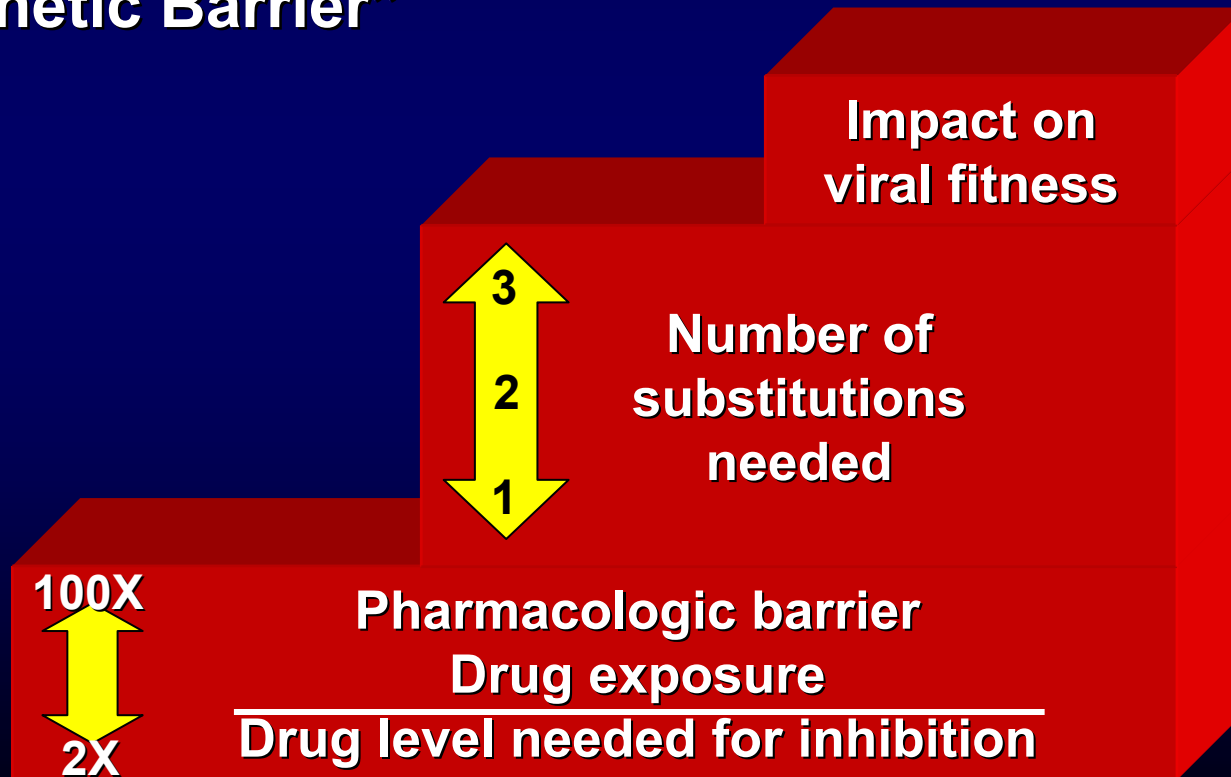
**R. Colonna, R. Rose, K. Pokornowski, C.
Baldick, B. Eggers, J. Yang and D. Tenney
(Clin Dev: R. Wilber, H. Brett-Smith, R Hinds & A Cross)**

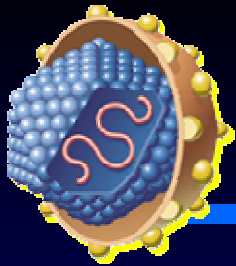
Bristol-Myers Squibb Pharmaceutical Research Institute



Primary Factors in Preventing Resistance

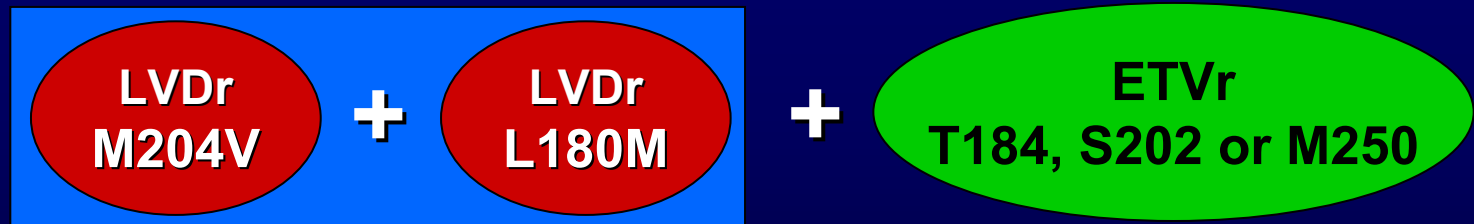
- ◆ “Potency” - Degree to which viral replication is suppressed to avoid generation of new mutations
- ◆ “Genetic Barrier”





ETV Early Resistance Profile

- ◆ 8-fold reductions in ETV susceptibility observed for LVDr strains in phenotypic assays
- ◆ Achieving resistance levels (>70-fold) associated with virologic rebound due to ETVr requires ≥ 3 substitutions

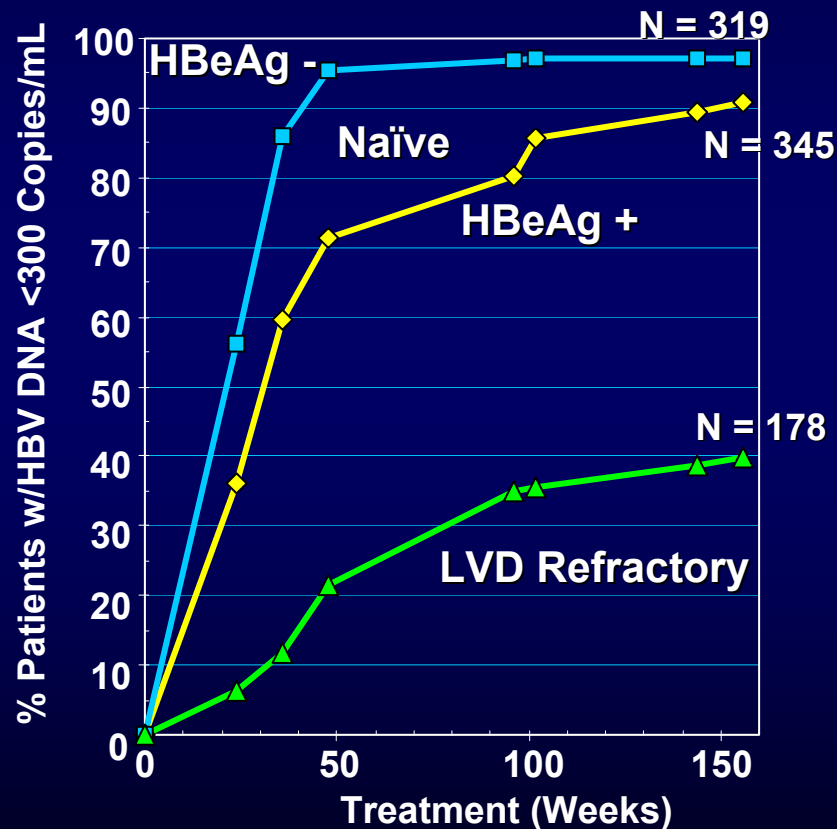


- ◆ LVD therapy can select variants with both LVDr and ETVr substitutions
- ◆ No cross resistance between ETV and adefovir



Achieving PCR Undetectability on ETV

Cumulative evaluation of ETV-treated patients w/ PCR measurements on treatment



Percent achieving
<300 copies/mL over 3
year period

Nucleoside Naïve Patients
94%

LVD Refractory Patients
40%



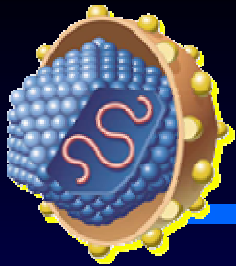
Cohorts Monitored for Resistance

Nucleoside Naïve Studies 022 & 027	Status at Week 48		Treated in Year 2		Treated in Year 3 (901)
Responders ¹	349	→	21	→	4
Virologic Responders ¹	281	→	268	→	141
Non-Responders ¹	22	→	17	→	7
Unclassified	21	→	4	→	0
Total Treated w/ ETV	673		310		152

¹ Per study protocol

LVD Refractory Studies 014, 015 & 026	Status at Week 48		Treated in Year 2		Treated in Year 3 (901)
Responders ¹	25	→	5	→	2
Virologic Responders ¹	101	→	98	→	56
Non-Responders ¹	54	→	50	→	26
Unclassified	12	→	1	→	1
Total Treated w/ ETV	192		154		85

¹Per study protocol



Monitoring for Resistance

- ◆ Genotyped paired samples from ALL ETV-treated patients with HBV DNA levels >300 copies/mL at Wks 48, 96, 144 or End of Dosing (n=749 paired samples analyzed)
 - Phenotype determined for all emerging substitutions
- ◆ Phenotyped ALL patients experiencing a virologic rebound (≥ 1 log increase from nadir), including those with no observed genotypic changes

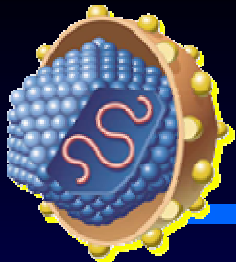


Patients Exhibiting Virologic Rebounds

LVD Refractory Patients

Studies 014, 015, 026 & 901	ETV (1 mg)
	Total
Year 1 Treated	192
Year 1 Virologic Rebounds	5
w/ Genotypic ETV Resistance	2 (1%)
Year 2 Treated	154
Year 2 Virologic Rebounds	21
w/ Genotypic ETV Resistance	14 (9%)
Year 3 Treated	85
Year 3 Virologic Rebounds	14
w/ Genotypic ETV Resistance	13 (15%)

ETV resistance = LVDr + T184, S202 and/or M250 substitutions



Genotype/Phenotype of Rebounds

LVD Refractory Patients

29 rebounds due to ETVr substitutions over 3 years of ETV therapy

- ◆ All had LVDr substitutions M204V + L180M
- ◆ Frequency of ETVr substitutions
 - T184 (n=9)
 - S202 (n=11)
 - T184 + S202 (n=6)
 - S202 + M250 (n=1)
 - T184 + M250 (n=1)
 - T184 + S202 + M250 (n=1)
- ◆ ETVr detected ($\geq 0.1\%$) at baseline in 10 (34%) patients
- ◆ Median ETV susceptibility decreased **15-fold** from baseline and **212-fold** from WT virus
- ◆ ETVr isolates remain susceptible to adefovir



Patients Exhibiting Virologic Rebounds

Nucleoside Naïve Patients

Studies 022, 027 & 901	ETV (0.5 /1 mg)
	Total
Year 1 Treated	673*
Year 1 Virologic Rebounds	14
w/ Genotypic ETV Resistance	1** (0.1%)
Year 2 Treated	310
Year 2 Virologic Rebounds	8
w/ Genotypic ETV Resistance	0 (0%)
Year 3 Treated	152
Year 3 Virologic Rebounds	2
w/ Genotypic ETV Resistance	1 (0.7%)

24

ETV resistance = LVDr + T184, S202 and/or M250 substitutions

*Patients with on treatment HBV DNA determination

**LVDr at the time of study entry



Virologic Profiles of Rebounds

Nucleoside Naïve Patients

24

No evidence of LVDr or ETVr substitutions

- 3/19 confirmed
- Only 2 had single emerging changes (V23A & V341I)
- All had WT ETV susceptibility at the time of rebound

19

2

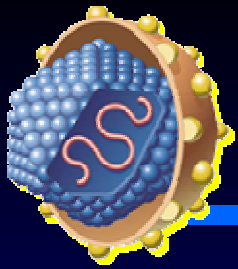
LVDr substitutions detected at baseline, patients subsequently became PCR undetectable on 1 mg ETV

1

Patient with an emerging LVDr variant not detectable ($\leq 0.1\%$) at study entry

- Unconfirmed rebound at Wk 53 = End of Dosing
- Simultaneous appearance of Q1E, D7A, L80I/V, R110G, V115M, S117P, Y135H, N139K **M204I**, L229V & C256G substitutions
- Variant likely pre-existed at low concentration

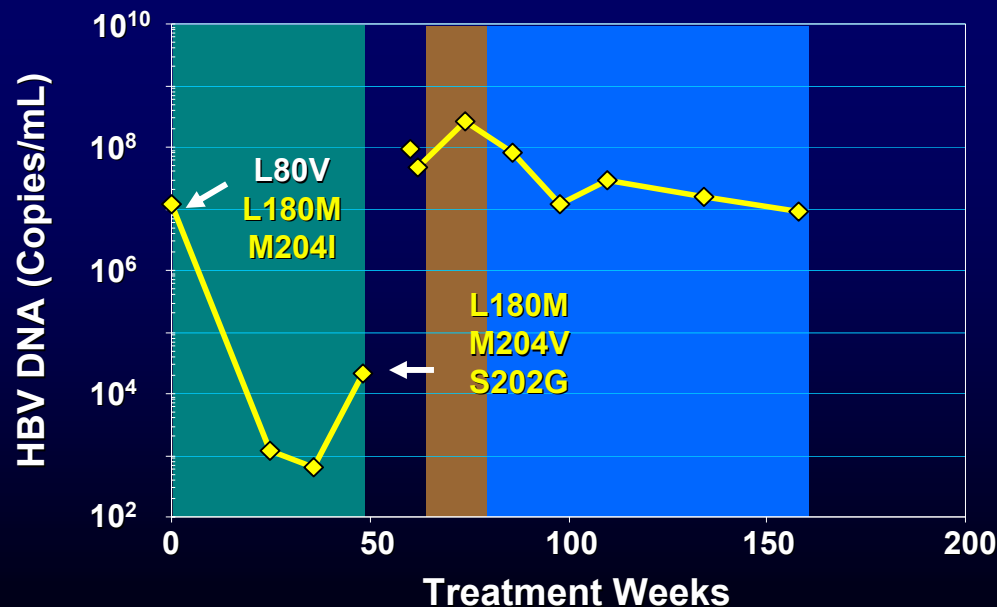
2



Virologic Profiles of Rebounds

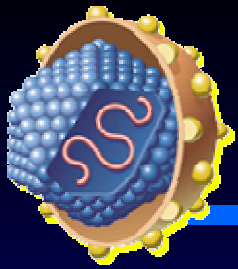
Nucleoside Naïve Patients

- ◆ 1 patient in (Study 027 HBeAg neg) was LVDr (**M204I** + **L180M**) at time of study entry
 - Subsequent emergence of LVDr **M204V** + ETVr **S202G** while on 0.5 mg ETV
 - 273-fold decrease in ETV susceptibility and rebound at Week 48



Treatment

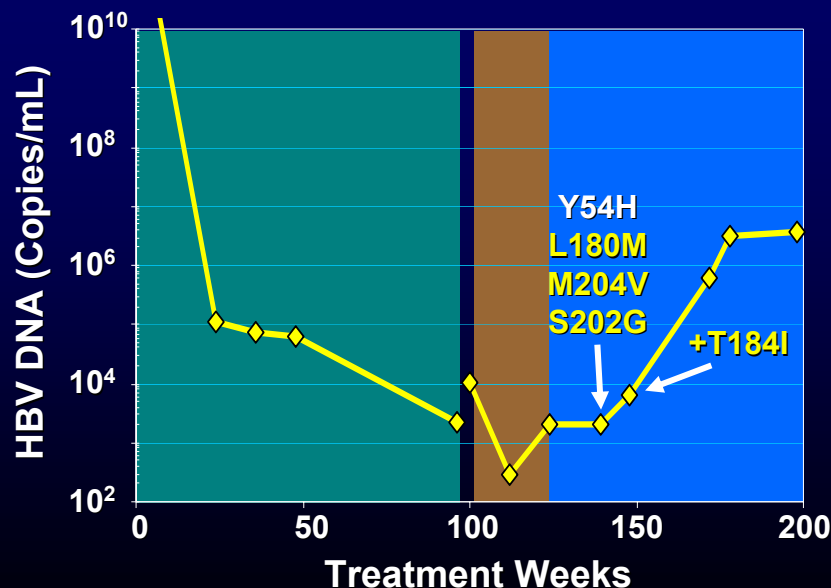
None
0.5 mg ETV
1 mg ETV + 100 mg LVD
1 mg ETV



Virologic Profiles of Rebounds

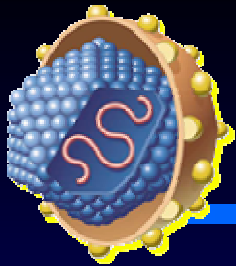
Nucleoside Naïve Patients

- ◆ 1 patient in (Study 022 HBeAg pos) with undetectable ($\leq 0.1\%$) LVD_r + ETV_r substitutions at time of study entry
 - Received 16 weeks LVD+ETV at Week 100 in study 901
 - Simultaneous appearance of Y54H, **L180M** & **M204V** (LVD_r) and **S202G** (ETV_r) substitutions at Wk 139, **T184I** and rebound at Wk 148
 - Pattern of emergence suggestive of pre-existing variant



Treatment

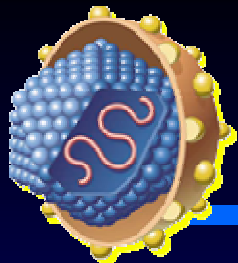
None
0.5 mg ETV
1 mg ETV + 100 mg LVD
1 mg ETV



Genotypic Surveillance

Nucleoside Naïve Patients

- ◆ 1 patient (Study 022 HBeAg pos) identified who had emerging LVDr & ETVr substitutions in absence of a rebound
 - Simultaneous appearance of **L180M, M204V (LVDr) & S202G (ETVr)** substitutions at Week 84, no rebound through Year 3
 - Pattern of emergence suggestive of pre-existing variant



Summary of Resistance Data at Year 3

		Genotypic ETVr*		Rebounds Due to ETVr*	Biochemical Failure**
Nucleoside Naïve	Year 1	1 (<1%)	→	1 (<1%)	0
	Year 2	1 (<1%)		0	0
	Year 3	1 (<1%)	→	1 (<1%)	0

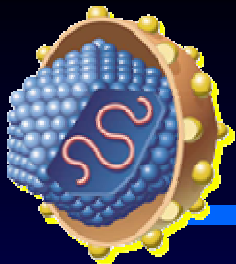
- ◆ ETVr evident in only 3 patients (pre-existing LVDr or LVDr + ETVr variants?)
- ◆ Low frequency due to potent suppression of viral replication and high genetic barrier requiring 3 substitutions

LVD Refractory	Entry	10 (6%)		
	Year 1	11 (6%)	2 (1%)	0
	Year 2	12 (8%)	14 (9%)	0
	Year 3	15 (18%)	13 (15%)	0

- ◆ Primary ETVr substitutions T184, S202 and M250 required for high level resistance and these changes can be selected during LVD therapy
- ◆ LVDr/ETVr variants are growth impaired, with 63% leading to rebounds

*Patients with LVDr substitutions plus substitutions at residues T184, S202 and/or M250

**ALT > 10 x ULN and > 2 x Ref (BL or EOD)



Summary of Resistance Data Over 3 Years

Nucleoside Naïve



LVD Refractory



*Patients with LVDr substitutions plus substitutions at residues T184, S202 and/or M250

**ALT > 10 x ULN and > 2 x Ref (BL or EOD)