

**HEP DART 2005**

frontiers in drug development for viral hepatitis

## Treatment for HBV

Hepatitis B treatment: 2005 and beyond: an overview

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Thank you !



# Role of Liver Biopsy in Patients With Normal ALT and High Viral Load

- 190 individuals with HBV DNA > 10,000 copies/mL
  - Persistently normal ALT\*, n = 57
- 24% of individuals with persistently normal ALT levels had Stage 2-4 fibrosis

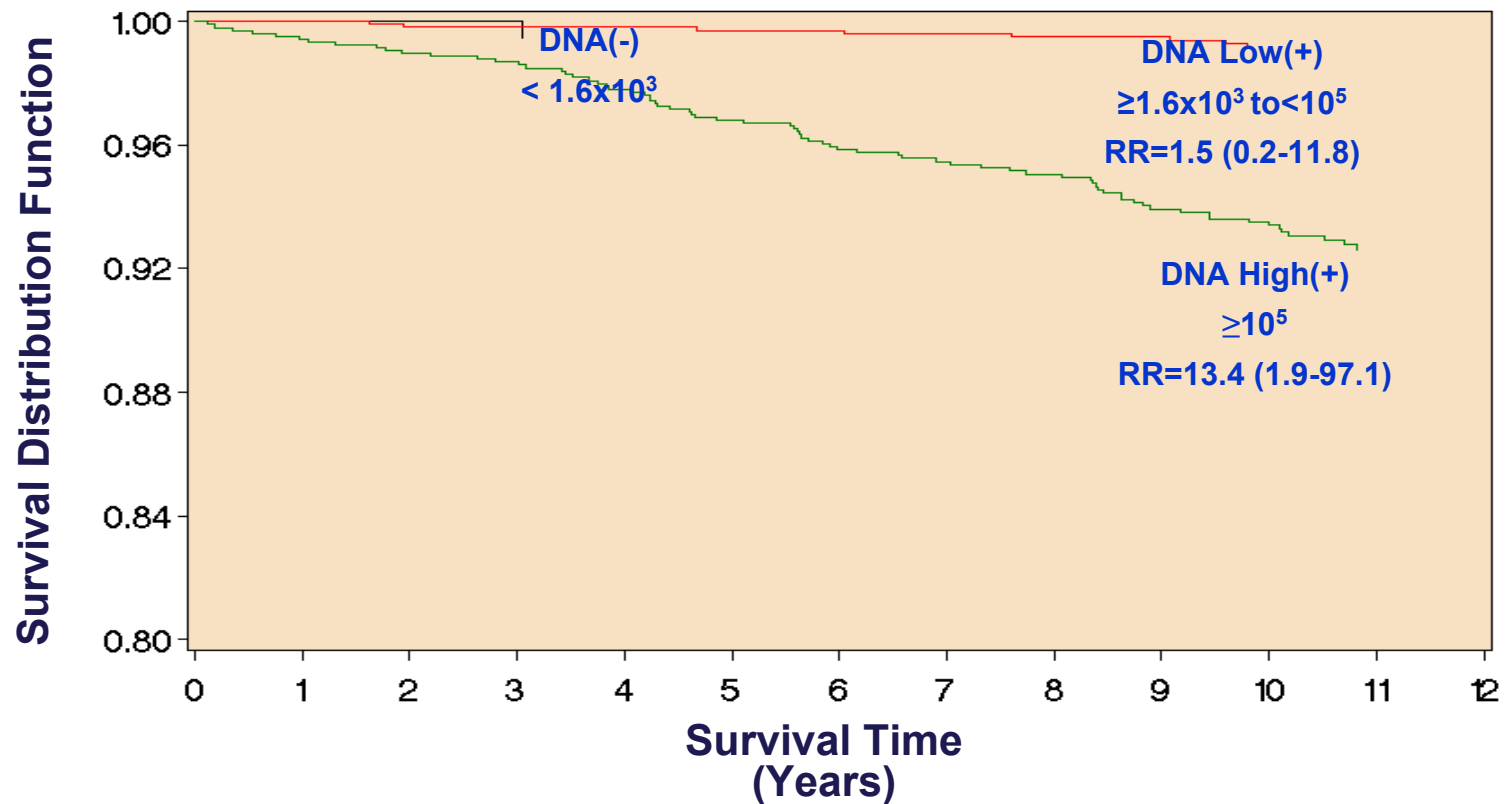
Multiple Regression Analysis for Stage $\geq$ 2 Fibrosis			
Parameter	OR	95% CI	P Value
ALT	1.778	1.235-2.558	.0020
Inflammation grade	6.790	4.010-11.500	< .0001
Age	1.053	1.027-1.080	< .0001
Alcohol intake	2.741	1.160-6.476	.0216

*\*persistently normal ALT, 2 measurements 6 months apart*

## Summary

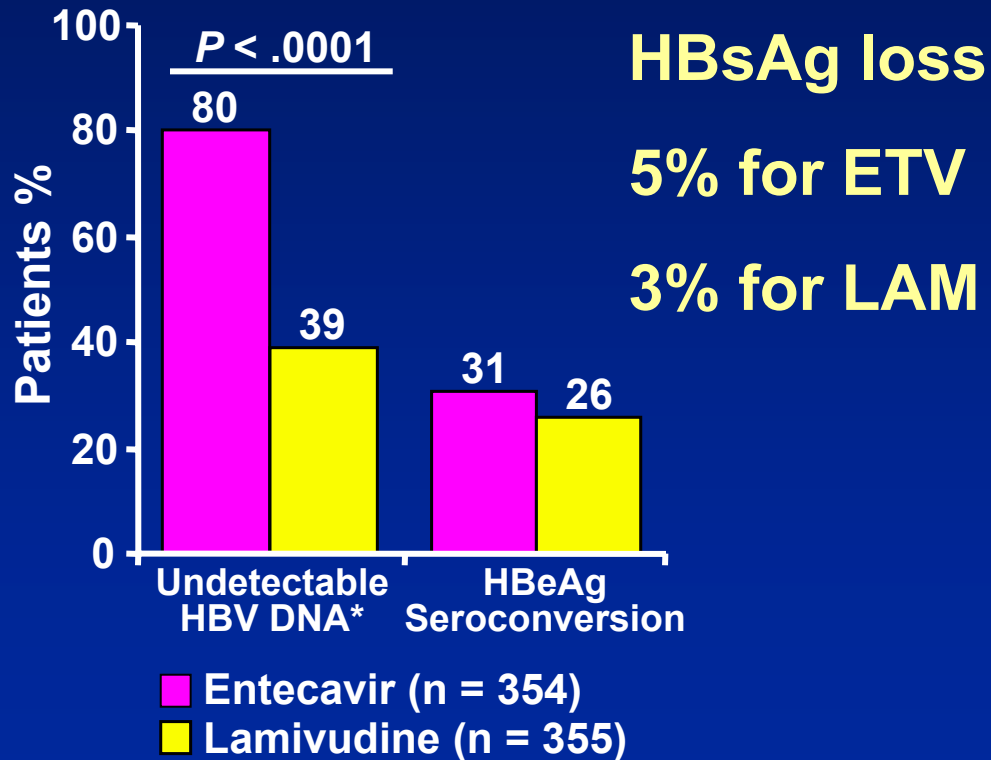
- We need to reset the normal range all US labs for ALT
  - <17-20 for woman
  - <25-30 for men

# Viral Load Associated with Mortality

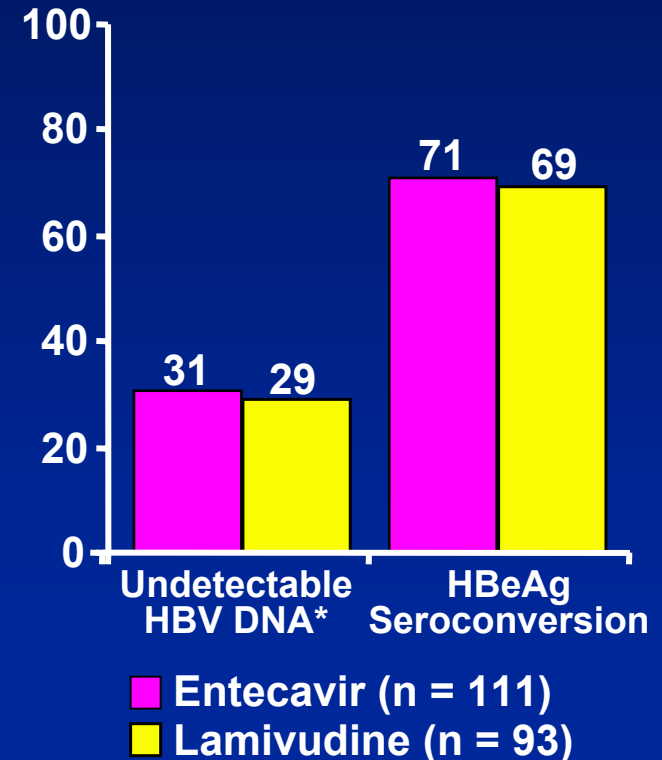


# ETV-022: HBeAg-Positive Patients Treated Up to 96 Wks With Entecavir

Cumulative Outcome by Week 96



Sustained Responses 24 Weeks Off-Therapy



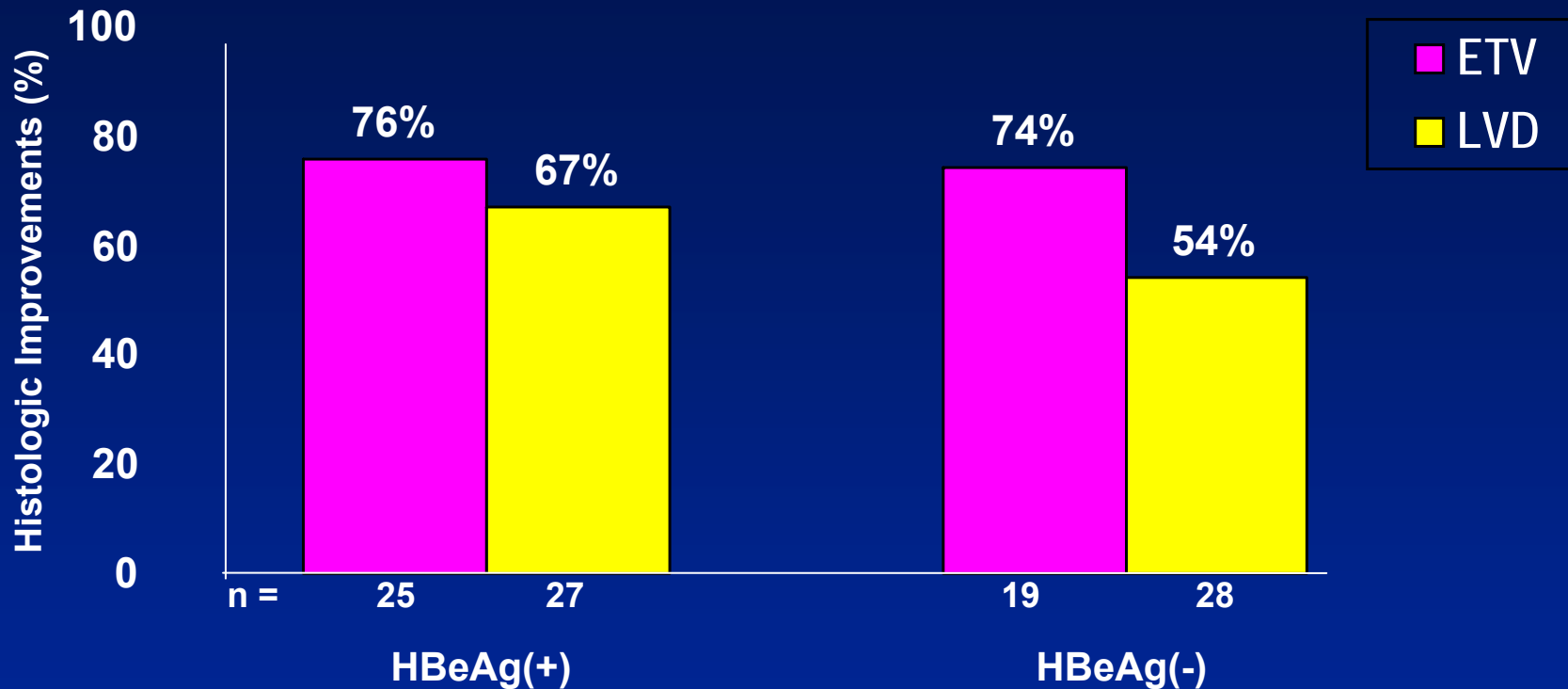
\*Undetectable HBV DNA, < 300 copies/mL

Gish et al. AASLD 2005. Abstract 181.

# Summary

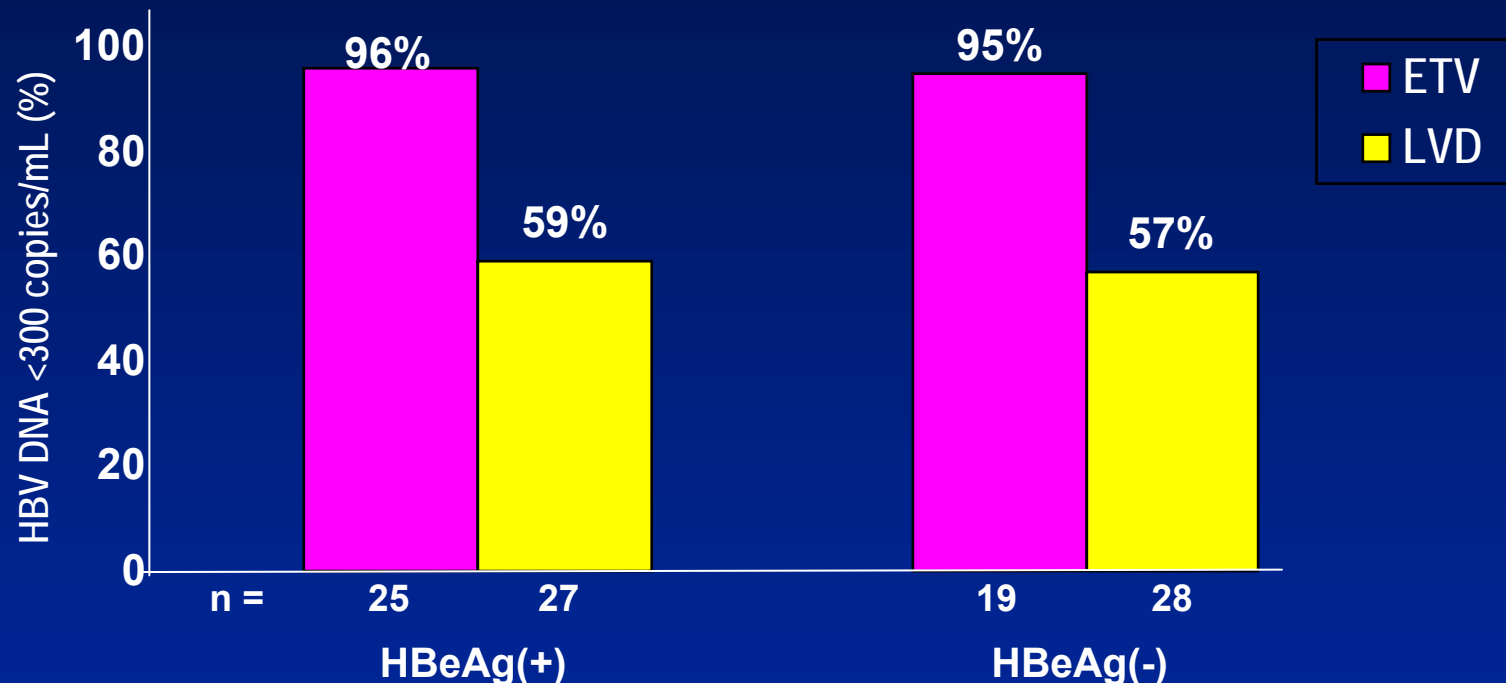
- Continuing ETV into a second year to treatment continues to improve the number of patients who attain HBV DNA negativity, ALT normalization and eAg seroconversions
- Cont Lam into a second year **only** results in a slight increase in eAg seroconversion
- Let us move to early virologic response definitions, decide early <15m, when to add or change medications

# Histologic Improvement in Nucleoside-naïve Patients with Cirrhosis



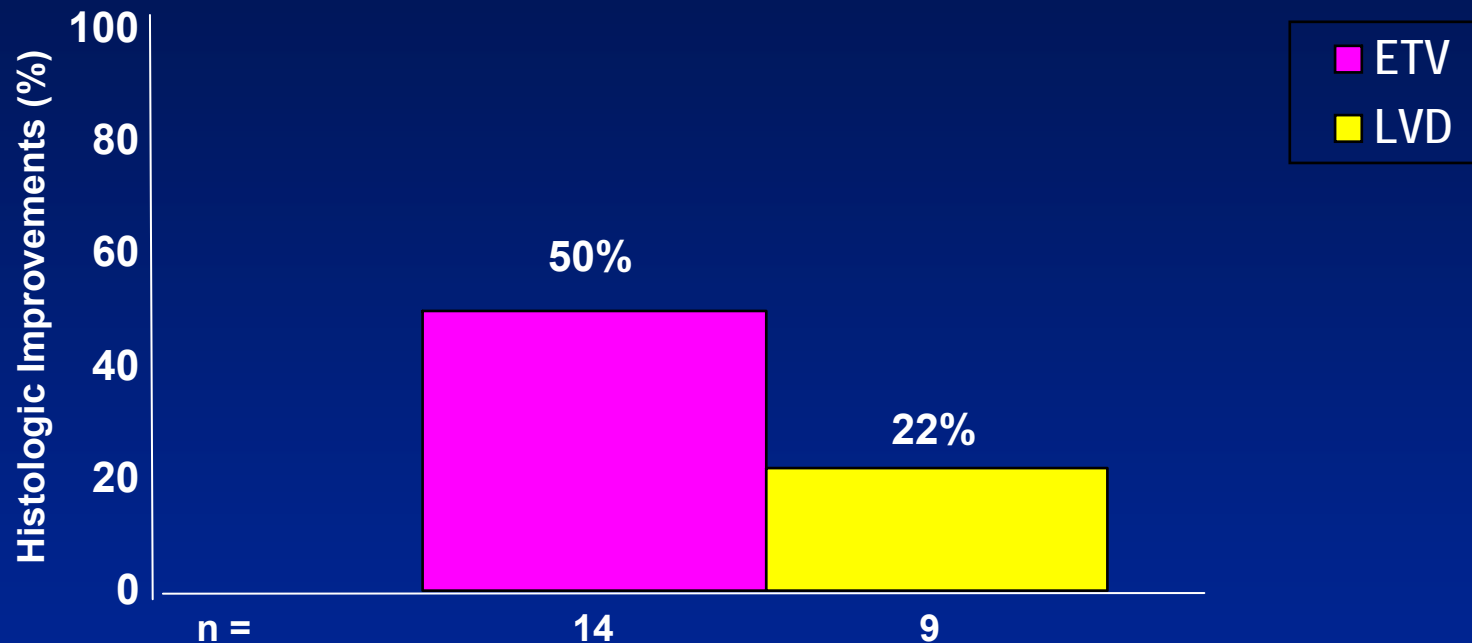
- Greater numbers of ETV- vs. LVD-treated patients achieved histologic improvement among HBeAg(+) and HBeAg(-) nucleoside-naïve patients with cirrhosis
- Rates of histologic improvement were consistent between the cirrhotic subgroup and the total nucleoside-naïve population

## HBV DNA < 300 Copies/mL in Nucleoside-naïve Patients with Cirrhosis



- Greater numbers of ETV- vs. LVD-treated patients achieved HBV DNA < 300 copies/mL among HBeAg(+) and HBeAg(-) nucleoside-naïve patients with cirrhosis
- HBV DNA responses in the cirrhotic subgroup were consistent with the total nucleoside-naïve population

# Histologic Improvement in LVD-refractory Patients with Cirrhosis

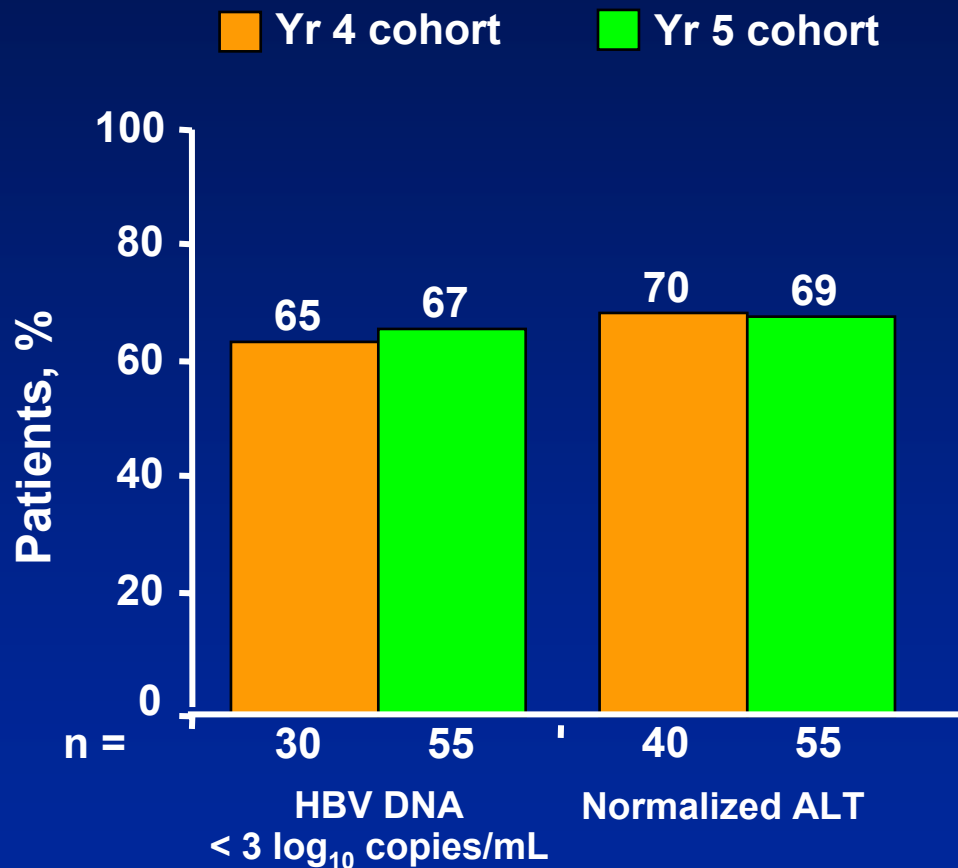


- **Greater numbers of ETV- vs. LVD-treated patients achieved histologic improvement, HBV DNA <300 copies/mL, and ALT normalization among LVD-refractory patients with cirrhosis**
- **Rates of histologic improvement, HBV DNA response, and ALT normalization were consistent between the cirrhotic subgroup and the total LVD-refractory patients**

## Summary

- Continuing ETV provides equivalent results in patients with cirrhosis as those without cirrhosis

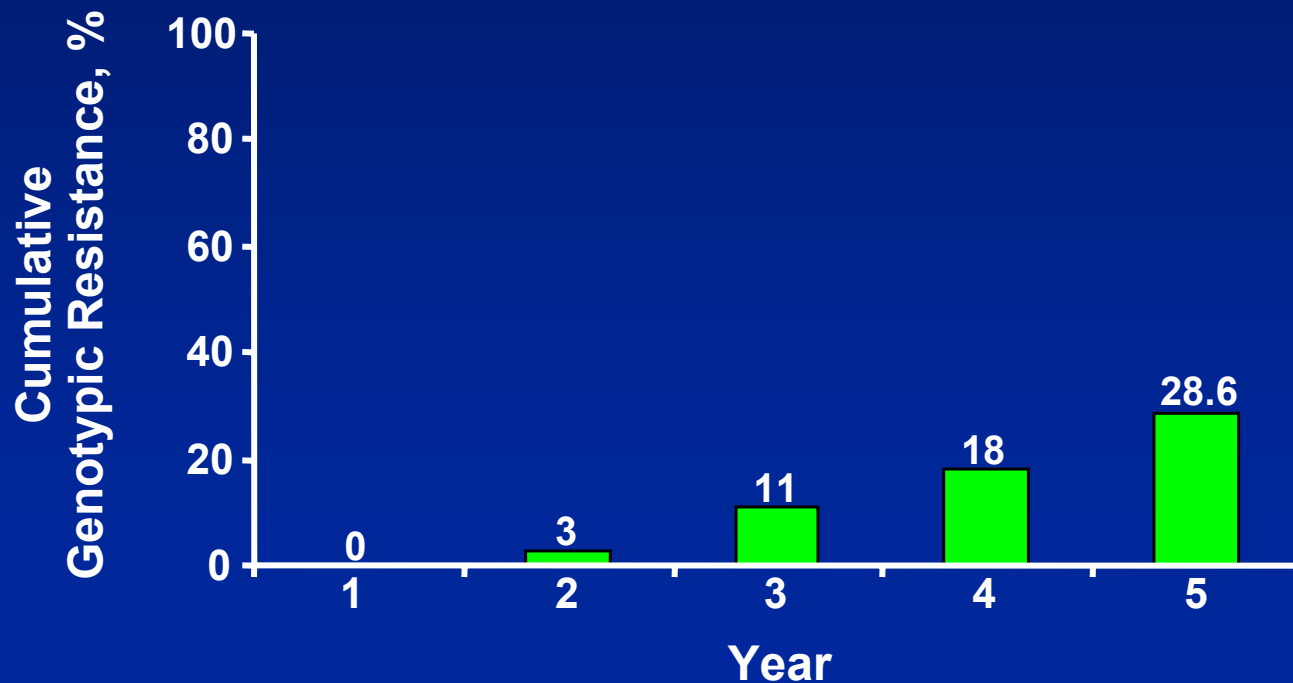
# Long-Term Data on Treatment With Adefovir in HBeAg-Negative Patients



- 5% of patients had HBsAg loss by Year 5
- > 50% had regression of bridging fibrosis or cirrhosis by Year 5
- ≥ 1-point reduction in Ishak fibrosis score
  - Year 4 cohort, 55%
  - Year 5 cohort, 71%

# Long-Term Data on Treatment With Adefovir in HBeAg-Negative Patients

- Cumulative genotypic resistance by Year 5, 28.6%
- 4 (3%) by Yr 5 had increase in creatinine of  $\geq 0.5$  mg/dL



# Summary

- ADV treatment to year 4-5 reaches a plateau in terms of patient who are HBV DNA negative
- Improving histologic benefit continues to year 4-5 (probably in those patients who are DNA negative)
- If you are not DNA negative, you are at risk of resistance, patients with elevated ALT or Elevated DNA, or resistance are probably those who do not have further histologic benefit

# Other New Data on Adefovir

## Summary of New Data on Adefovir Treatment

Study	N	Study Design	Outcomes
ADV in OLT patients <sup>1</sup>	81	<ul style="list-style-type: none"> <li>• Virologic response: HBV DNA &lt; 4 log<sub>10</sub> copies/mL</li> <li>• Median follow-up 18 mos</li> </ul>	<ul style="list-style-type: none"> <li>• Response by 24 wks, ~30%</li> <li>• Resistance mutations, 7.4%</li> <li>• Resistance more common if switch vs add ADV</li> </ul>
ADV vs LAM + ADV in HBeAg(+) patients <sup>2</sup>	26	<ul style="list-style-type: none"> <li>• 1 year treatment</li> </ul>	<ul style="list-style-type: none"> <li>• HBV DNA negative: 71% for LAM + ADV vs 58% for ADV</li> <li>• Greater ALT normalization in LAM + ADV group</li> </ul>
ADV resistance in LAM-resistant patients <sup>3</sup>	50	<ul style="list-style-type: none"> <li>• 48 weeks ADV</li> </ul>	<ul style="list-style-type: none"> <li>• Resistance mutations at Wk 48, 20%</li> <li>• No link to <b>preexisting</b> YMDD mutations</li> </ul>

1. Lok et al. AASLD 2005. Abstract 91. 2. Ghany et al. AASLD 2005. Abstract 1005.  
3. Lee et al. AASLD 2005. Abstract 972.

# Tenofovir vs Adefovir in Lamivudine-Refractory Patients

- Retrospective analysis: LAM-refractory patients switched to TDF 300 mg/day (n = 38) or ADV 10 mg/day (n = 68)
- More TDF patients with low HBV DNA at Month 6\*

Undetectable HBV DNA*	Tenofovir 300 mg/day (n = 38)	Adefovir 10 mg/day (n = 68)
Month 12, %	94	32
Month 18, %	100	35
Month 24, %	100	49

\* < 400 copies/mL

- Considerably more patients receiving TDF exhibited HBeAg and HBsAg loss vs ADV after up to 2 years

Outcome	Tenofovir 300 mg/day (n = 38)	Adefovir 10 mg/day (n = 68)
HBeAg loss, %	49	13
HBsAg loss, %	19	6

# Summary

- TDF appears to be more potent than ADV
- LAM R sets up risk of ADF resistance that is high (> ETV ?)
- Combination therapy with ADF and LAM is a option today and put forth by new guidelines (in press)
- We need phase III randomized controlled trials to expand this (A + L) to support this as one of the practice standards

# GLOBE: Year 1 Results of Telbivudine for Chronic Hepatitis B

## Summary of Year 1 Results With Telbivudine

Outcome	HBeAg(+) Patients		HBeAg(-) 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

\* $P < .05$  vs lamivudine

# GLOBE: Early HBV DNA Levels and Year 1 Outcomes With Telbivudine

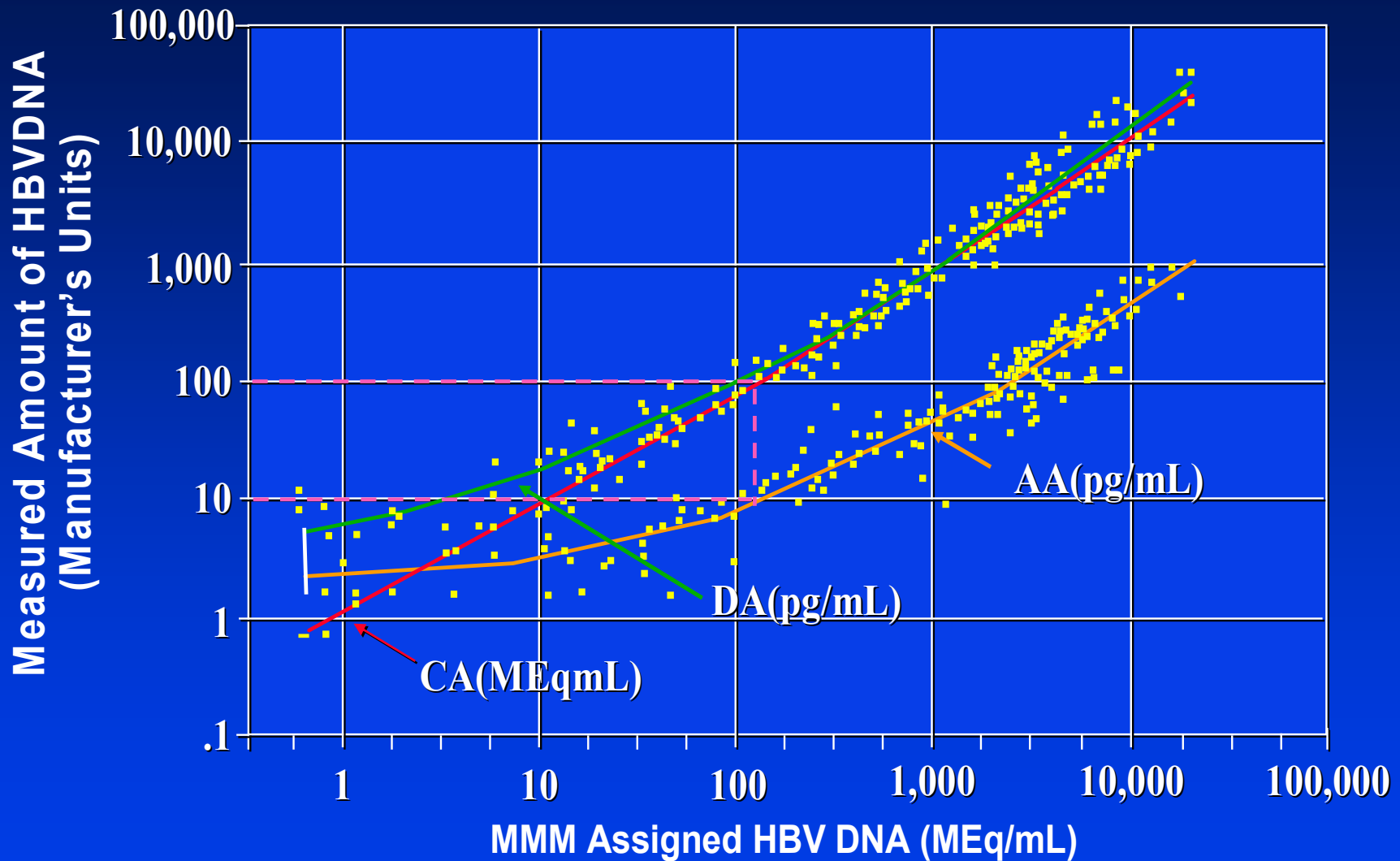
- Year 1 outcomes linked to viral load at Weeks 12 and 24
  - 93% of individuals with HBV DNA  $> 3 \log_{10}$  copies/mL at Week 24 failed to seroconvert by Year 1

Week 52 Outcome	Week 24 HBV DNA Levels, copies/mL			
	Undetectable	300 to $< 3 \log_{10}$	$3-4 \log_{10}$	$> 4 \log_{10}$
HBV DNA negative				
• HBeAg positive	91	69	30	5
• HBeAg negative	94	67	40	10
Normal ALT levels				
• HBeAg positive	88	89	79	53
• HBeAg negative	81	68	60	41
Virologic breakthrough				
• HBeAg positive	1	4	9	14
• HBeAg negative	0	7	17	44
HBeAg seroconversion	41	26	13	4

## Resistance

- The virologic breakthrough definition used by Idenix in the GLOBE study was defined
  - it is the treatment-emergent increase of HBV DNA to  $>5 \log_{10}$  copies/mL after being suppressed to  $<5 \log_{10}$  copies/mL on two successive visits
  - Or, for pts who don't get below 5 log but have  $> 2$  log drop, then increase to within 1 log of Baseline
  - Other pts ( $< 2$  log drop) –will qualify for "treatment failure" definition

# HBV DNA Quantitative Assays



Krajden, JUrl Hepatitis

Amplicor PCR techniques

Roche Cobas Amplicor HBV Monitor- 200 - 200,000 copies/mL

Comment: 17-96% CV !

# Precision: TaqMan PCR

- **Intra-assay variability** Deviation of IU/ $\mu$ l values of lowest standard, 8 replicates, within one PCR run
- **Inter-assay variability** Deviation of IU/ $\mu$ l values of lowest standard, 3 instruments, 3 lab workers
- **Inter-lot variability** Deviation of IU/ $\mu$ l values of lowest standard, 3 PCR runs, 3 lots

HBV	Standard deviation	Variance	Coefficient of variation [%]
Intra-assay variability: <i>HBV TM QS 5</i> [10 IU/ $\mu$ l]	10.04	0.95	9.47
Inter-assay variability: <i>HBV TM QS 5</i> [10 IU/ $\mu$ l]	10.09	1.38	13.69
Inter-lot variability: <i>HBV TM QS 5</i> [10 IU/ $\mu$ l]	10.05	1.04	10.38
Total variance: <i>HBV TM QS 5</i> [10 IU/ $\mu$ l]	10.07	1.17	11.62

Non-extracted Quantification Standards

# Summary

- LdT is a powerful new option to treat HBV
  - PCR negativity = or near equal to TDF small studies or ETV phase III Studies
- Data will help with early stopping/changing/adding rules
  - Viral positivity means risk of NR and Resistance
  - 2 year study block design helpful to compare arms
  - Block study design less closely parallels clinical practice
- LdT Resistance data needs to be expressed in 1 log increase, confirmed, to allow medical community to fully evaluate data
  - NIH meeting pending
  - We need a clear and simple data message to the community

## Clevudine (L-FMAU)

- Pyrimidine nucleoside analogue, L-enantiomer
- Potent inhibitor of Hepatitis B *in vitro* (EC50 = 5.0 microM\*)

## Phase III trial in HBeAg(+) patients

- Multicenter, randomised double-blind trial in 33 sites in South Korea
- Total of 243 pts randomised (3:1) to receive 24 weeks 30 mg/day Clevudine (n = 183) or placebo (n = 61); pts followed up for 24 weeks post-treatment

	Clevudine 30 mg per day (n = 183)	Placebo (n = 61)
<b>Median change in HBV DNA level from baseline (log<sub>10</sub> copies / mL)</b>		
•24 weeks	-5.10*	-0.27
•End of follow-up (24 weeks off-treatment)	-2.03*	-0.68
<b>HBV DNA &lt;300 copies/mL (%)</b>		
•24 weeks	59	0
•End of follow-up (24 weeks off-treatment)	2.9	0
<b>ALT normalisation (%)</b>		
•24 weeks	68*	18
•End of follow-up (24 weeks off-treatment)	61*	28
<b>HBeAg seroconversion (%)</b>		
•24 weeks	6.9	8.8
•End of follow-up (24 weeks off-treatment)	10	12

# Phase III trial in HBeAg(-) patients

- Multicenter, randomised double-blind trial in South Korea
- Total of 86 pts randomised (3:1) to receive 24 weeks 30 mg/day Clevudine (n = 63) or placebo (n = 23); pts followed up for 24 weeks post-treatment

	Clevudine 30 mg per day (n = 183)		Placebo (n = 61)
<b>Median change in HBV DNA level from baseline (log<sub>10</sub> copies / mL)</b>			
•24 weeks	-4.25		-0.48
•End of follow-up (24 weeks off-treatment)	-3.11		-0.66
<b>HBV DNA &lt;300 copies/mL (%)</b>			
•24 weeks	92		0
•End of follow-up (24 weeks off-treatment)	16		0
<b>ALT normalisation (%)</b>			
•24 weeks	75	P = 0.006	33
•End of follow-up (24 weeks off-treatment)	71	P = 0.007	29

# Summary

- CLV shows potent data for HBV suppression at 24 weeks
- There is a slow increase in HBV DNA off treatment
  - Slower rise in eAg(-) compared to eAg(+) patients
- Can we use this new compound creatively?  
On off therapy (cyclic) ? Short therapy intervals ?

# Pradefovir for Chronic Hepatitis B

- Pradefovir: PMEA prodrug activated by CYP 3A4
- Randomized, open-label, multicenter trial (N = 244)
  - Patients received adefovir 10mg/day or pradefovir 5,10, 20, or 30mg/day for 48 weeks
    - Male, 83%      – Asian, 100%      – HBeAg(+), 70%

Week 48 Outcome	Adefovir (n = 50)	Pradefovir			
		5mg/day (n = 47)	10mg/day (n = 49)	20mg/day (n = 48)	30mg/day (n = 48)
Mean change in HBV DNA, log <sub>10</sub> copies/mL	-3.66	-3.39	-4.22*	-4.33*	-5.02*
HBV DNA < 400 copies/mL, %	16	17	24	29	38

\* $P < .05$  vs adefovir

## Summary

- PRD is reasonably potent for HBV alone
- No Renal toxicity
- Role for Lam R?
- Role with Dual Therapy?

# US Panel Recommendations: 2006

- **New recommendations**

- Baseline evaluation to include HBV **genotype**, particularly if any consideration for peginterferon Rx
- Rx options in 2005 >: adefovir, **entecavir, and peginterferon alfa-2a**
  - Interferon alfa-2b replaced by peginterferon alfa-2a
  - **Lamivudine not first-line secondary to high resistance rate**
- **Adefovir preferred over entecavir** for patients with lamivudine-resistance secondary to development of novel mutations with entecavir
- May be role for **combination Rx** for lamivudine or adefovir resistance and patients with cirrhosis

# Chronic HBV Infection

## *Approach to Resistance*

### **Lamivudine Resistance (70% by year 5)**

- Switch to adefovir: supported by original studies of lamivudine resistance (Peters et al and Perrillo et al, 2004)
- Add adefovir: gaining support based on 19% rate of adefovir resistance in LAM-R patients (Lee et al, 2005)
- Switch to entecavir: limited by development of novel mutations in only 9% of patients over 2 years (Colonna, 2005)
- Switch to tenofovir: option in patients with suboptimal response to adefovir (van Bommel, 2005)

### **Adefovir Resistance (29% by year 5)**

- Switch to or add lamivudine

# Where do we go from here?

- We need
  - Pharma to work together to bring combination therapy forward within phase III trials
  - Stop the Log wars, use PCR negative or assess for “remaining virus”, log<sub>10</sub> to compare on Rx and off Rx results
  - Need to know.predict who will have rebound.get resistance during therapy using predictors before starting therapy or use early stopping.change.add rules
    - <24 weeks for meds with R rate over 3% per year
    - 12-15 months for medications with low or no resistance
  - Need to have HBV DNA PCR neg 24-72 weeks depending on the medication used and risk of R

## More comments

- Need to add a second medication for NR
  - timing based on response/lack of response on monotherapy
  - Risk of resistance
- Need to add a second medication for Lam R patients:
  - When?
    - Lack of response to ETV ?
    - Automatic with ADV or TDF ?
- Data to support “Best” combinations: TDF ETV
  - LDT TDF ? = Clevudine TDF
  - Pradefovir ETV or LdT
- When to stop Rx in eAg negative patients
- Can Clevudine ?
  - Increase HBsAg seroconversion
  - Be used as interrupted therapy
  - Shorten RX in HBeAg negative patient

Peace can be obtained:  
with great strides that are foreseen in the  
management of HBV

