

# Digestive Disease Conference: HBV Abstracts

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## **Abstract 337**

A Dose Escalating Trial Evaluating the Safety and Antiviral Activity of Clevudine in Patients with Chronic HBV Infection.

## **Abstract 338**

Predictors of Virologic Response after Lamivudine Treatment in Children with Chronic Hepatitis B

## **Abstract 339**

Comparison of Viral Replication Fitness of Wild-Type and Lamivudine-Resistant HBV in Patients

## **Abstract 342**

Tenofovir and HBV Mutants After Liver Transplantation

## **Abstract 507**

Adefovir Dipivoxil Results in a Consistent and Significant Improvement in Liver Histology and Virological Status Regardless of Baseline Knodell Fibrosis Score in Patients with HBeAg+ Chronic Hepatitis B

## **Abstract 508**

Changes in Alanine Aminotransferase (ALT) and YMDD Mutation Profile Associated with Switching from Lamivudine (LAM) to Either Adefovir Dipivoxil (ADV) or Combination LAM Plus ADV in Chronic Hepatitis B (CHB) Patients with LAM Resistance

## **Abstract 337**

### **A Dose Escalating Trial Evaluating the Safety and Antiviral Activity of Clevudine in Patients with Chronic HBV Infection.**

*Patrick Marcellin, Steve Sacks, George Kk Lau, Herve Mommeja-Marin, Dominique Sereni, Jean-Pierre Bronowicki, Brian Conway, Christian Trepo, Elsa Mondou, Andrea Snow, B. C. Yoo, H.-S. Lee, Franck Rousseau*

#### **Background:**

Clevudine (CLV, L-FMAU) is a potent inhibitor of HBV replication in vitro. In woodchucks, CLV produced a potent and sustained viral suppression following a 12 weeks dosing period.

#### **Methods:**

This was a multicenter, open-label, dose escalation study evaluating 10, 50, 100 and 200 mg Clevudine QD for 28 days (n=5, 10, 10 and 7/arm, respectively). Patients were followed post-treatment for 24 weeks. Eligible patients had chronic HBV infection, Baseline HBV DNA levels (VL) =  $3 \times 10^6$  copies/mL, were nucleoside treatment naive and without HIV or HCV co-infection. VL was assayed using Digene Hybrid

Capture II (with a lower limit of detection of 4700 c/mL) and genotype by di-deoxy sequencing.

### Results:

32 patients were enrolled, 81% were male, 81% Asian, 88% HBeAg positive. At Baseline, median VLs were 7.3, 8.0, 8.8 and 8.4 log<sub>10</sub> c/mL and median ALTs were 55, 119, 106 and 64 IU/L in the 10, 50, 100 and 200 mg QD cohorts, respectively.

After 28 days of dosing, the median log<sub>10</sub> VL change from Baseline was -2.5, -2.7, -3.0 and -2.6 and median change in ALT from Baseline was -13, -14.5, +37 and -14 U/L, in the 10, 50, 100 and 200mg cohorts, respectively.

At 6 months post-dose, sustained biochemical and virologic responses were observed: 71% of the patients overall had normal ALT levels and median log<sub>10</sub> VL changes from Baseline were -1.2, -1.4, -2.7 and -1.6 in the 10, 50, 100 and 200mg arms, respectively.

During the study, 8 patients lost HBeAg (30%) of whom 5 seroconverted to HBeAb (19%). Clevudine was well tolerated, without dose related adverse events. A transient increase in ALT was observed in the 100 mg cohort but not in the 200 mg group. The pharmacokinetics of Clevudine were dose proportional with a long plasma half-life supporting a once daily regimen. No treatment emergent mutations in the HBV DNA pol domain were observed 5 months after treatment.

### Conclusion:

These results confirm the antiviral activity of once daily clevudine and further demonstrate, in humans the uniquely sustained post-treatment antiviral effect seen previously in woodchucks. Despite the short (4 weeks) duration of therapy very favorable rates of HBeAg loss and seroconversion were observed without evidence to date of acquired resistance on Clevudine therapy.

## Abstract 338

### Predictors of Virologic Response after Lamivudine Treatment in Children with Chronic Hepatitis B

*Xenia Hom, Nancy R. Little, Maureen M. Jonas*

### Background:

Lamivudine is a therapeutic option for children with chronic hepatitis B (HBV). In adults, pretreatment ALT and/or histologic activity predict HBeAg loss with treatment.

### Aim:

To identify the pretreatment variables that predict virologic response (VR)(defined as loss of HBeAg and undetectable HBV DNA in serum after 1 year of treatment) to lamivudine in children.

### Methods:

A randomized, placebo-controlled trial of lamivudine (52 weeks) has been completed in 288 children (Jonas et al, NEJM 2002;346:1706-13). Exploratory analyses with prospectively defined baseline covariates of interest were used to evaluate potential predictors of virologic response. These included age, gender, race, weight, body mass index (BMI), ALT, HBV DNA, and Histologic Activity Index (HAI) score.

Initially, univariate analyses were conducted using logistic regression. Next, multivariate analysis was used to investigate the pattern of covariation of multiple factors with response (step-wise logistic model). Subgroup analyses were then performed to show response rates across different levels of baseline characteristics (Mantel-Haenszel test).

## Results:

In the univariate model, there was no difference in rate of VR by age, gender, race (Asian vs non-Asian), weight, BMI, or previous interferon therapy after adjusting for treatment. Baseline ALT level (table below) and HAI scores {Odds Ratio of VR was 1.77 (95%CI 0.95-3.29) for HAI scores 5-9 and 2.57 (95%CI 0.81-8.17) for HAI scores 10-14 as compared to scores 0-2 (P=0.002)} were both strong predictors of VR and HBeAg seroconversion.

Pretreatment ALT(x ULN)	Virologic Response		HBeAg Seroconversion (3-comp) #	
	Placebo (n=95)	Lamivudine (n=191)	Placebo (n=95)	Lamivudine (n=191)
<=1	1/7(14%)	1/8 (13%)	1/7(14%)	1/8(13%)
<1-<=2	2/30(7%)	10/86(12%)	2/30(7%)	10/86(12%)
>2-5	5/41 (12%)	25/81 (31%)	5/41(12%)	23/81 (28%)
>5	4/17(24%)	8/16(50%)	4/17(24%)	8/16 (50%)
<b>Overall</b>	12/95(13%)	44/191(23%)	12/95(13%)	42/191(22%)
<b>P-value*</b>	0.111	0.001	0.111	0.001

\*P-value based on Mantel-Haenszel test comparing response/no response by baseline ALT category, excluding patients with normal ALTs. #Defined as HBeAg-ve/HBeAb+ve/HBV DNA -ve

## Conclusions:

As in adults, baseline ALT and HAI scores are important predictors of VR to lamivudine in children. The likelihood of response was not significantly affected by patient age or race.

## Abstract 339

### Comparison of Viral Replication Fitness of Wild-Type and Lamivudine-Resistant HBV in Patients

*William Delaney Iv, Christopher Westland, Huiling Yang, Hamid Namini, Vincent Thibault, Yves Benhamou, Carol Brosgart, Craig Gibbs, Michael Miller, Shelly Xiong*

## Background:

Lamivudine-resistant HBV has been described as replication defective based on early clinical observations and in vitro data for single mutations of M204V or M204I in the YMDD motif of HBV polymerase. However, recent data suggests that compensatory mutations also emerge and patients with long-term lamivudine resistance undergo disease progression.

## Aims:

To compare levels of serum HBV DNA and ALT in patients with lamivudine-resistant and wild-type HBV. To determine the prevalence of compensatory mutations in YMDD-mutants and their contributions to replication fitness.

## Methods:

Patients analyzed were enrolled in trials of adefovir dipivoxil for the treatment of wild-type (2 trials, n=695) or lamivudine-resistant HBV (3 trials, n=203). Patients were required to have serum HBV DNA levels  $\geq 5$  log<sub>10</sub> copies/mL at entry. Serum HBV DNA was measured by Roche Amplicor PCR. DNA sequencing was used to identify resistance mutations at baseline. Results: At baseline, patients with lamivudine-resistant HBV had similar serum HBV DNA (medians 7.7, 8.1, and 8.8 log<sub>10</sub> copies/mL) compared to patients with wild-type HBV (medians 7.1 and 8.4 log<sub>10</sub> copies/mL); median ALT levels were 79-82 IU/L in lamivudine-resistant and 94-98 IU/L in wild-type patients.

Compensatory mutations (V173L, L180M) that enhance the replication of YMDD-mutant HBV in vitro were found in the majority (88%) of lamivudine-resistant patients. At baseline, four major mutational patterns were identified in patients with lamivudine-resistant HBV (L180M+M204V [58%], V173L+L180M+M204V [17%], M204I [12%], L180M+M204I [11%]); serum HBV DNA did not vary significantly across the different mutational patterns.

### Conclusions:

Lamivudine-resistant HBV is capable of replicating to levels comparable to wild-type HBV and causing abnormally high ALT. Exclusion of patients with lower serum HBV DNA levels from eligibility preclude an assessment across a greater spectrum of viral load. The four patterns of lamivudine resistance mutations all had similar levels of serum HBV DNA.

## Abstract 342

### Tenofovir and HBV Mutants After Liver Transplantation

*Jose Nery, Daryl Lau, Caio Nery, Kamran Safdar, Maria Torres, Guy W. Neff, Marzia Montalbano, Doug Meyer, Debbie Wepler, Sylon Britto, Arie Regev, Seigo Nishida, David Levi, Juan Madariaga, Tomaki Kato, Eugene R. Schiff, Andreas Tzakis*

### Aim:

Resistant HBV strains develops in approximately 30% of post liver transplant (LTx) recipients treated with lamivudine(LAM) within 2 years from time of transplantation. Adefovir(ADV) has recently been reported to be effective against mutants, however its use may be limited by nephrotoxicity. We report our experience with tenofovir(TNV), another nucleotide analogue reverse transcriptase inhibitor, in LTx recipients developing lamivudine resistance.

### Methods:

8 pts developed resistance to lamivudine 10 to 85 mos (median: 26) post-LTx. Tenofovir (300 mg/day, P.O.) was added 1 to 66 mos after breakthrough (BT), and continued for 2 to 12 mos (median: 4). Prior to receiving tenofovir, these patients had been excluded from receiving adefovir due to:

- ◆ age > 60 y.o. (5)
- ◆ HIV co-infection (1)
- ◆ Enlistment in another drug study (1)
- ◆ Potential non-compliance (1).

Criteria for BT included elevation of liver chemistries along with reappearance of HBsAg, HBeAg and/or HBVDNA. HBV genotype and YMDD variants were identified through DNA sequence analysis prior to and after TNV; sequential HBVDNA levels were measured by hybridization (pts 2,4,6,7&8) or PCR (pts 1,3&5).

### Results:

No adverse reaction was associated with tenofovir. The tables below summarize the data pertaining the study patients.

### Tenofovir Treatment Summarization

Patient	Median Creatinine (mg/dl)	Median ALT (IU/l)	Log HBV DNA
	Pre-TNV Post-TNV p	TNV Post-TNV p	Pre-TNV Post-TNV p
1	1.3 1.3 n.s.	17 65 n.s.	6.98 3.55 0.008
2	1.8 1.7 n.s.	71 175 n.s.	2.21 <-0.3 0.016
3	1.4 1.5 n.s.	103 68 n.s.	4.04 2.57 0.001
4	1.4 1.5 n.s.	46 38 n.s.	4.51 <-0.3 <0.001
5	1.0 1.1 n.s.	113 39 n.s.	>8.70 7.11 <0.001
6	1.0 1.1 n.s.	122 104 n.s.	>3.78 -0.16 <0.001
7	1.3 1.1 n.s.	60 36 n.s.	3.53 0.62 0.004
8	0.9 0.9 n.s.	95 30 0.001	2.92 <-0.3 0.026

#### Conclusion:

This preliminary experience indicates that tenofovir markedly decreases replication of LAM-resistant HBV variants post-LTx. These results demonstrate another potential option for the treatment of HBV LAM resistance.

### Abstract 507

#### Adefovir Dipivoxil Results in a Consistent and Significant Improvement in Liver Histology and Virological Status Regardless of Baseline Knodell Fibrosis Score in Patients with HBeAg+ Chronic Hepatitis B

*P. Marcellin, T.T. Chang, S.G. Lim, M. Tong, W. Sievert, M. Shiffman, L. Jeffers, Z. Goodman, M. Wulfsohn, R. Fallis, J. Fry, C. Brosgart, for the 437 Study Group*  
*Adefovir Dipivoxil*

#### Objective:

To compare the efficacy of adefovir dipivoxil (ADV) 10 mg as compared to placebo (PLB) in HBeAg+ chronic hepatitis B (CHB) patients by baseline Knodell fibrosis score.

#### Patients/Methods:

Patients in the trial were randomized to treatment with adefovir or placebo for 48 weeks. Liver biopsies were performed at baseline and after 48 weeks of treatment. The primary efficacy endpoint was a = two-point improvement in the inflammatory score of the Knodell Histology Activity Index (HAI) with no progression of the fibrosis score. This was achieved by 53% (89/168) treated with ADV 10 mg QD and 25% (41/161) PLB treated patients (p<0.001).

**Table 1. Baseline Demographics**

	Placebo (n=167)	Adefovir (n=171)
<b>Median age (years)</b>	35	32
<b>Male</b>	71%	76%
<b>Asian</b>	60%	60%
<b>Caucasian</b>	36%	35%
<b>Prior Interferon</b>	21%	25%

Prior Lamivudine	2%	<1%
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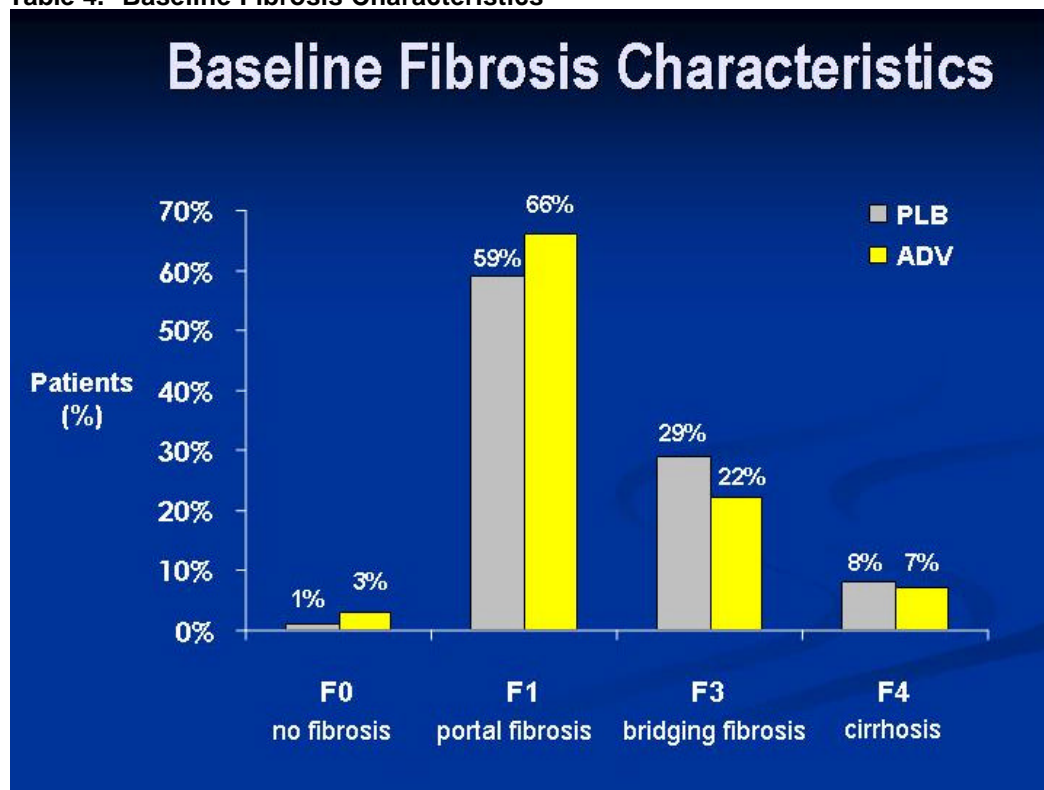
**Table 2. Baseline Disease Characteristics**

	Placebo (n=167)	Adefovir (n=171)
Median HBV DNA (log <sub>10</sub> copies/mL)	8.33	8.40
Median ALT (IU/L)	94	95
(ULN)	2.4	2.3

**Table 3. Baseline Histologic Characteristics**

	Placebo (n=167)	Adefovir (n=171)
Median Knodell Total Score	10	9.5
Fibrosis (median)	1.0	1.0
F0/F1	60%	69%
F3/F4	37%	29%

**Table 4. Baseline Fibrosis Characteristics**

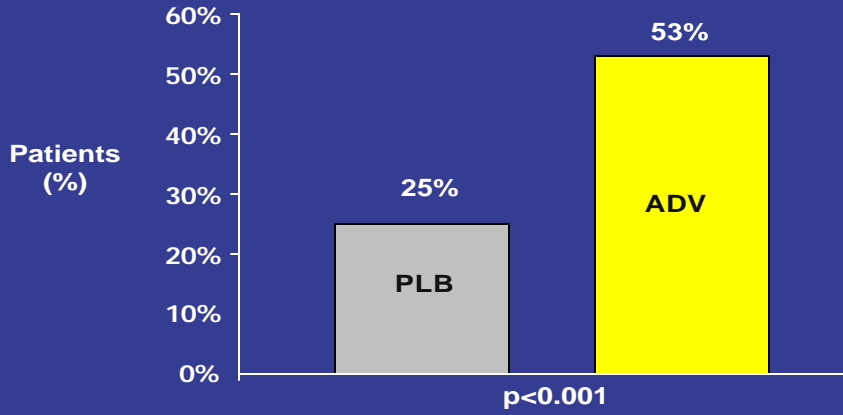


**Methods:**

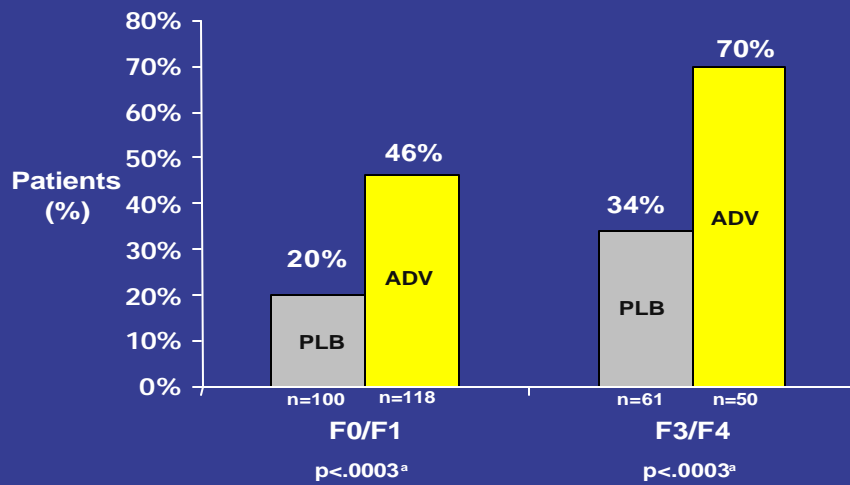
Evaluable paired baseline and week 48 biopsies were available from 296 patients (88%) enrolled in the study. The biopsies were assessed by a central histopathologist, blinded to treatment assignment and sequence. Biopsies were scored utilizing Knodell HAI scores comparing the baseline to the week 48 biopsy. Change in alanine aminotransferase (ALT), serum HBV DNA (Roche Amplicor™ LLQ 400 copies/mL) and histology were evaluated in patients receiving adefovir 10 mg and placebo.

**Results:**

## Primary Endpoint Improvement in Liver Histology at 48 Weeks\*

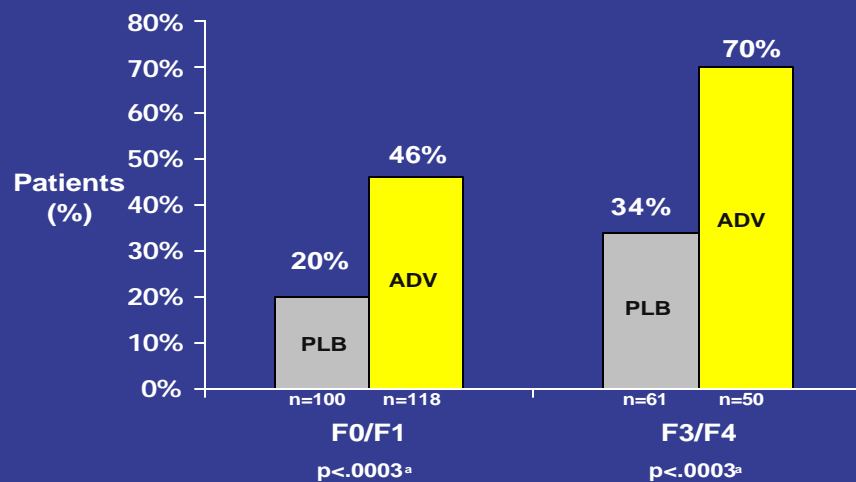


## Histological Improvement by Fibrosis Score at 48 Weeks



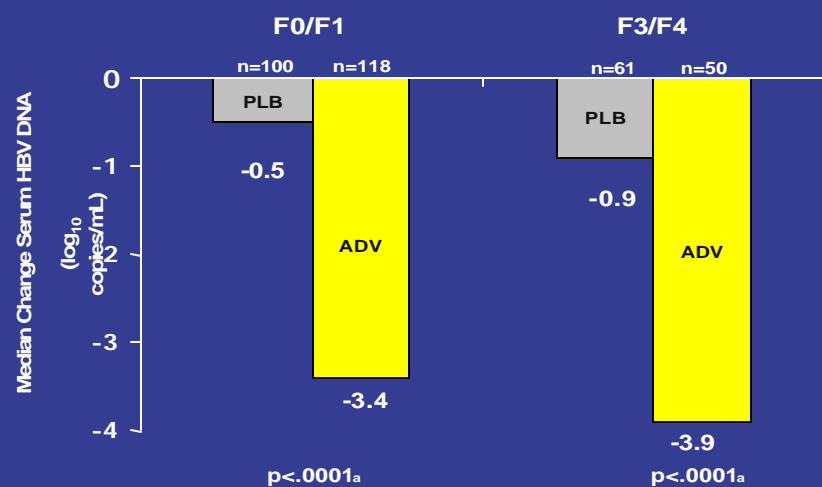
<sup>a</sup> Fisher's Exact Test, p values are for comparison of ADV to PLB

## Histological Improvement by Fibrosis Score at 48 Weeks



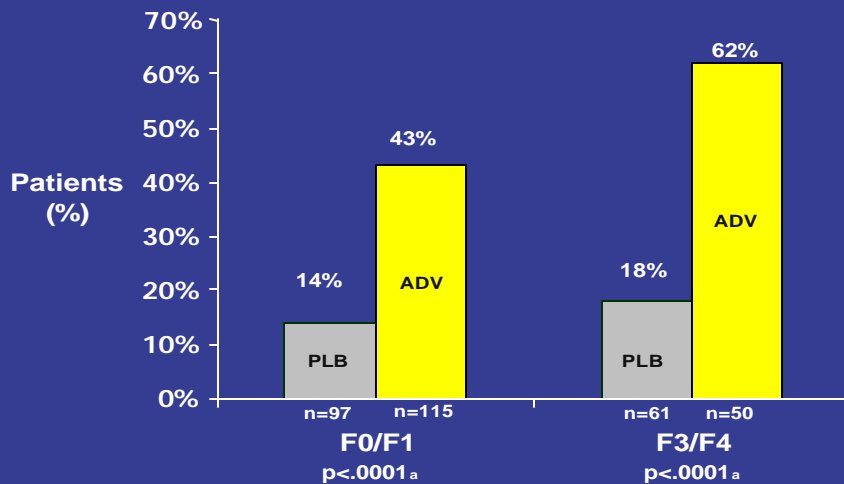
<sup>a</sup> Fisher's Exact Test, p values are for comparison of ADV to PLB

## Median Change in Serum HBV DNA by Fibrosis Score at 48 Weeks

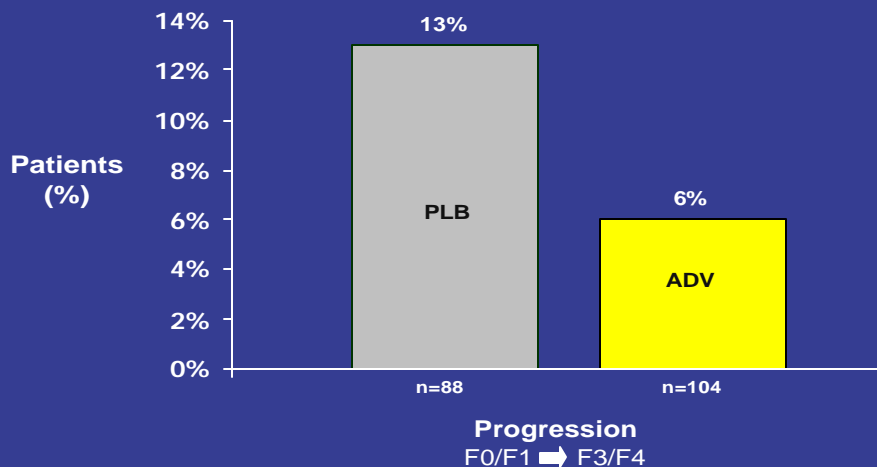


<sup>a</sup> Wilcoxon-Rank Sum Test, p values are for comparison of ADV to PLB

## ALT Normalization by Fibrosis Score at 48 Weeks



## Progression to Bridging Fibrosis or Cirrhosis at 48 Weeks



### Conclusion:

The authors of this study concluded:

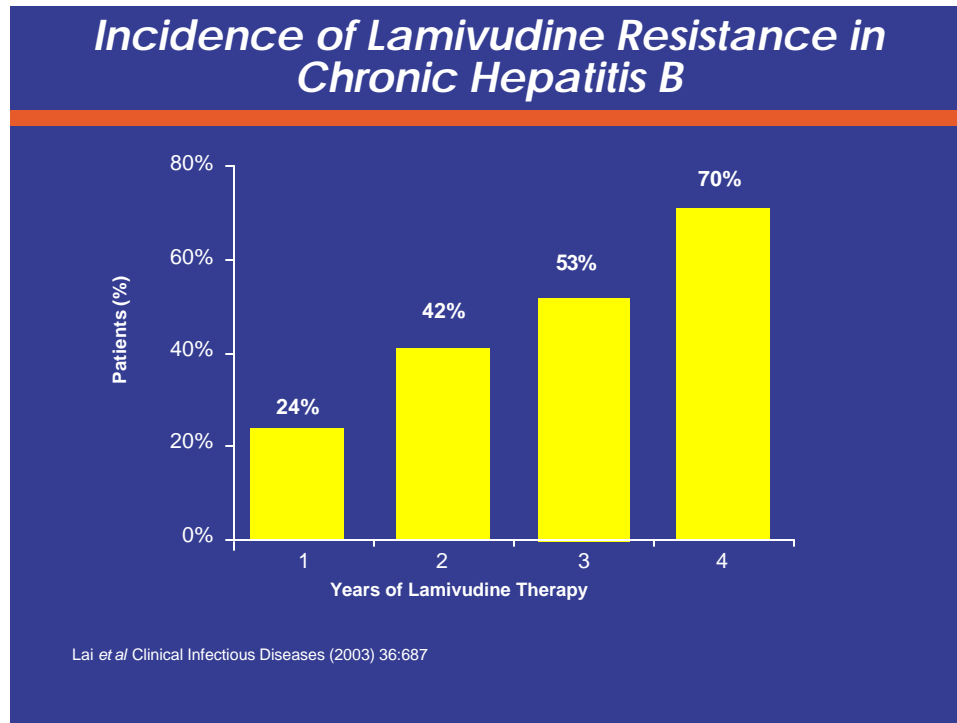
- ◆ Adefovir results in statistically significant histological, virological, and biochemical improvement compared to PLB
- ◆ Improvement was observed regardless of baseline Knodell fibrosis score
- ◆ Significantly more adefovir patients had regression of fibrosis and less progression of fibrosis than placebo treated patients

# Changes in Alanine Aminotransferase (ALT) and YMDD Mutation Profile Associated with Switching from Lamivudine (LAM) to Either Adefovir Dipivoxil (ADV) or Combination LAM Plus ADV in Chronic Hepatitis B (CHB) Patients with LAM Resistance

Marion Peters, Paul Martin, Mark Sullivan, Kristin Kleber, Ramin Ebrahimi, Christopher Westland, William E. Delaney, Shelly Xiong, Carol Brosgart

## Background and Aims:

YMDD mutations in hepatitis B virus (HBV) polymerase emerge in 24% (range 16 to 32%) of CHB patients after one year of lamivudine therapy, increasing to 69% after 5 years.



Adefovir has potent activity against YMDD mutant and wild type (WT) HBV.

## Study GS 00 461 evaluated 3 regimens:

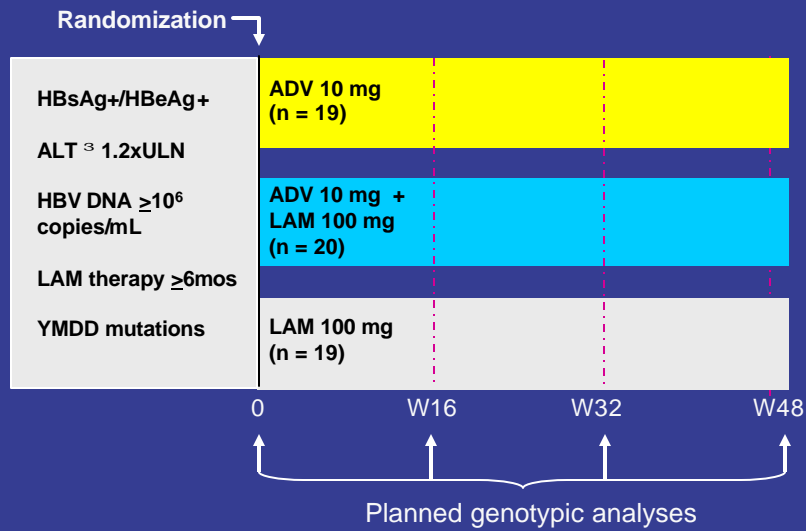
- ◆ continued LAM 100 mg,
- ◆ adding ADV 10 mg to continued LAM or
- ◆ switching from LAM to ADV.

## Methods:

Eligible patients were: HBeAg+ with CHB; ALT = 1.2 x upper limit of normal (ULN); HBV DNA > 6 log<sub>10</sub> copies/mL (Roche Amplicor PCR) despite ongoing LAM therapy; confirmed YMDD mutant HBV.

Fifty eight patients received ADV (n=19), ADV + LAM (n=20), or LAM (n=19). Treatment duration was 48 weeks: ALT was evaluated during therapy by treatment arm for possible associations with change in regimen (ALT elevations ? week (W) 12) and/or viral genotype. YMDD mutations were monitored by DNA sequencing at baseline, W16, W32 and W48.

# Study 461 Design



## Baseline Characteristics

	LAM (n=19)	ADV + LAM (n=20)	ADV (n=19)
Median Age (years)	44	46.5	45
Male	74%	75%	89%
Caucasian	74%	45%	63%
Asian	26%	45%	37%
Median Prior LAM (months)	24	30	37

## Baseline HBV Characteristics

	LAM (n=19)	ADV + LAM (n=20)	ADV (n=19)
Median HBV DNA* (log <sub>10</sub> copies/mL)	8.2	7.9	8.4
Median ALT (IU/L)	70	73.5	101
xULN	1.9	1.9	2.4
% YMDD Mutant	100%	100%	100%

\* <sup>a</sup>Roche Amplicor Monitor™ PCR

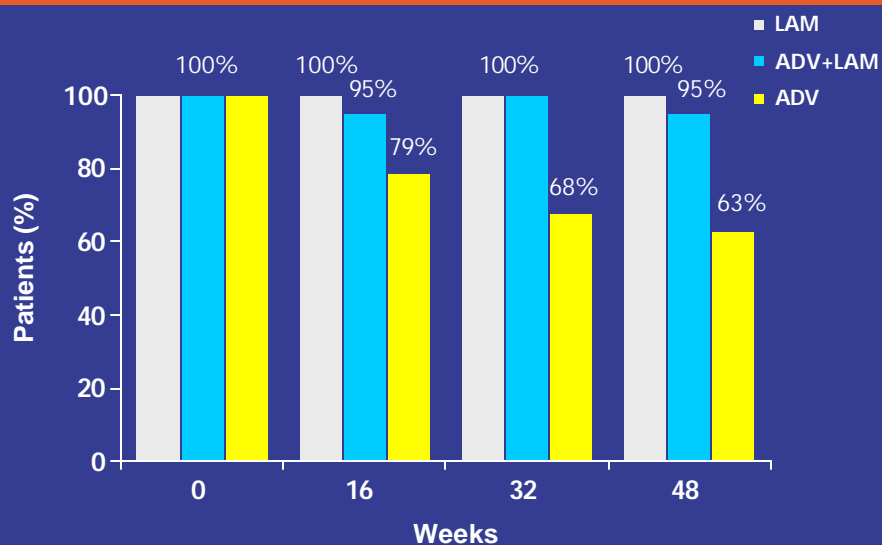
### Results:

Summary efficacy data are presented below:

## Patients with ALT Elevations through Week 48

	LAM (n=19)	LAM + ADV (n=19)	ADV (n=20)
5-10 x ULN			
Wk 0 – Wk 12	0	0	5
Wk 16 – Wk 48	0	0	1
> 10 x ULN			
Wk 0 – Wk 12	0	1	0
Wk 16 – Wk 48	3	0	0

## Persistence of YMDD Mutations



## Change in Serum HBV DNA and ALT by YMDD Status for Patients on ADV

	n (%)	Median Change in Serum HBV DNA at wk48	ALT > 5xULN 0 - 48wks
Lost YMDD	7 (37%)	- 4.0	1
Remained YMDD+	12 (63%)	- 3.9	5

One patient who lost YMDD had an increase in ALT of 5-10 x ULN at week 4. ALT levels remained < 5 x ULN at all subsequent visits.

## Most Commonly Reported Adverse Events\*

	LAM (n=19)	ADV+LAM (n=20)	ADV (n=19)
Asthenia	32%	30%	42%
Headache	26%	25%	21%
Abdominal Pain	21%	30%	16%
Pharyngitis	21%	5%	26%

\* Number of patients with the event. Events are those reported in at least 10 patients across all treatment groups

No patient experienced a severe ALT elevation ( $> 10 \times \text{ULN}$ ) associated with change in regimen (= W12). One patient (ADV group) experienced an ALT elevation  $>3 \times$  baseline at W12: this resolved on continued treatment, was not associated with signs of hepatic decompensation, and the patient subsequently HBeAg seroconverted at W24. YMDD sequencing (position rtM204) demonstrated that by W16, W32, and W48 of therapy, 4, 6 and 7 of 19 adefovir patients reverted to wild type, respectively. No LAM patients and 1 of 20 ADV + LAM patients lost YMDD mutations through W48. Reversion to WT HBV occurred without increases in serum HBV DNA or ALT. Serum HBV DNA decreased similarly in ADV treated patients who reverted to WT HBV or retained YMDD.

### Conclusions:

- ◆ Adefovir or adefovir plus lamivudine compared to lamivudine significantly:
  - reduced serum HBV DNA
  - reduced and normalized serum ALT
  - change in HBV DNA and ALT similar for adefovir and adefovir plus lamivudine
- ◆ Switching to adefovir from lamivudine
  - resulted in self-limited, transient elevations in ALT
    - elevations in ALT not associated with signs or symptoms of hepatic decompensation
- ◆ Reversion to wild-type
  - only seen in adefovir treated patients
  - associated with changes in HBV DNA and ALT similar to that seen in adefovir treated patients maintaining YMDD