

# Results of Lamivudine Therapy for HBe Antigen Positive Hepatitis (In the West)

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## Introduction

There have been two published one year randomized controlled trials of Lamivudine conducted in the Western World, all in North America<sup>1,2</sup>. One in adults and one in children. However although these studies were carried out in the West, one quarter to one third of the individuals recruited were of Asian origin, and therefore likely had neonatally acquired infection.

The goals of therapy for chronic hepatitis B are the sustained eradication of viral replication and regression of chronic hepatitis, the prevention of end stage liver disease and elimination of risk for hepatocellular carcinoma. But as neither of these two trials have reported post treatment follow up beyond six months, only short term efficacy of Lamivudine therapy can be assessed at this time.

## Definition of Responses

1. Reduction and/or elimination of viral replication has been assessed using several different techniques for serum HBV DNA measurement. In the earlier study the sensitivity of the tests employed was  $1 \times 10^6$  (Abbott Diagnostics – hybridization assay<sup>1</sup>). The subsequent study employed a bDNA assay (Chiron/Bayer Quanti plex) with a lower sensitivity of 0.7meq/ml<sup>2</sup>. To date, neither of these studies have reported measurement of intrahepatic HBV DNA in particular ccc HBV DNA.
2. Another surrogate marker of diminution in viral replication for those with HBe positive hepatitis is been loss of HBe antigen with or without seroconversion to anti HBe. In addition, loss of HBsAg and acquisition of anti HBs can be examined.
3. Improvement in “hepatitis” as judged by serial measurements of serum aminotransferase values
4. Improvement in liver histology has been assessed by comparing post treatment liver histology (on Lamivudine) with pre treatment baseline liver histology using the 22 point HAI score (4 points for fibrosis and 18 for necro inflammation).

## Virological Response to Lamivudine Therapy in HBe Antigen Positive Hepatitis (Table 1)

Lamivudine therapy has consistently been associated with a highly significant sustained reduction in levels of serum HBV DNA at the end of one year of therapy in up to 98% (see Fig 1). Undetectable levels of HBV DNA were sustained in 44% in adults and in 61% of children, the figures for those on placebo being 16% and 16% respectively. ( $p < 0.001$ )

Loss of HBe antigen with seroconversion to anti HBe was observed in 17% and 22% on Lamivudine versus 6% and 13% on placebo in adults and children respectively. Loss of HBsAg was observed in one adult and three children, all four had been randomized to Lamivudine. Seroconversion was not observed in those who developed Lamivudine resistance in the adult study and was only seen to occur in one child with a YMDD mutation.

Normalization of serum amino transferase (ALT) levels was associated with virological response and observed in 41% and 55% in adults and children treated with Lamivudine for one year. Spontaneous normalization of ALT was observed in 7% and 12% of adults and children randomized to receive placebo

## Histological Response

This was the primary outcome measure in the trial of Lamivudine therapy in adults (repeat liver biopsies were not performed in the pediatric study). Baseline HAI scores were moderately elevated and to a similar degree (those randomized to Lamivudine the median score was 10 and those randomized to placebo the median score was 11). Only 6% of those on Lamivudine had cirrhosis at baseline compared to 14% of those randomized to placebo. Liver biopsies were scored according to degree of necroinflammation and degree of fibrosis and a change in score of 2 or more HAI points in a negative direction was considered an improvement and when the change was in a positive direction, a worsening. When a score of less than 2 points difference between the baseline liver biopsy and the one at one year into treatment was recorded, this was reported as no change. All liver biopsies were taken whilst the patients were still receiving Lamivudine. All 66 randomized to Lamivudine and all 71 randomized to placebo underwent repeat liver biopsy. There was a significant difference in the total HAI score in those on Lamivudine compared to those on placebo according to the number that were better, 52% versus 23%, and the number who were worse 11% versus 24%. When the fibrosis scores only were evaluated, there was an increase in fibrosis score in only 3 of 66 randomized to Lamivudine (5%) compared to 14 of those 71 (20%) randomized to placebo  $p < 0.01$ . In those who lost HBeAg during the course of the study the fall in median HAI score was 5-6 whereas in those who remained HBeAg positive the change in score was much less, at 2-3 points.

### **Durability of Virological Response**

Following cessation of Lamivudine therapy serum HBV DNA levels were seen to rise (Figure 2) but during the 4-6 month period of follow-up these levels were not noted to return to pre treatment values. In both the adult and pediatric study, some additional individuals lost e-antigen following cessation of therapy while others reactivated off treatment i.e. anti HBe back to HBeAg positive during follow-up. Overall, in adults 8 of 11 (73%) and in children 33 of 44 (82%) although 4 data were missing so this is really 75%, had a sustained seroconversion at the end of a follow-up of 4-6 months. No data was provided to indicate whether durability of seroconversion that occurred during Lamivudine therapy was greatest in those who seroconverted early or late during the course of therapy. So it remains unknown whether the duration of Lamivudine therapy after seroconversion influences the durability of that seroconversion.

### **Development of Viral Resistance to Lamivudine**

Mutations in the YMDD motif of HBV DNA polymerase was detected in 32% of the adults who received Lamivudine tested at week 52 (only 44 of a potential 70 patients randomized to Lamivudine were tested). Similar mutations were identified in 19% in children at the end of one year of Lamivudine therapy.

### **Adverse Events**

In both studies, Lamivudine therapy was well tolerated and the incidence of adverse events was similar to that for placebo. Of particular importance in the pediatric group, there appeared to be no effect of treatment on either height or weight scores.

### **Elevations in Serum Amino Transferase (ALT) Levels**

Rises in ALT levels are common in chronic hepatitis B and may or may not be directly related to anti viral therapy. They may be observed just prior to spontaneous HBe antigen seroconversion or during reactivation from anti HBe to HBe antigen. Rises in ALT may be secondary to the development of Lamivudine resistance. Commonly rises in ALT occur following cessation of Lamivudine therapy. Other causes for elevations in ALT levels not related to hepatitis B therapy include a new hepatitis virus infection (e.g. delta or hepatitis A or C), toxic drug or herbal remedies, fatty liver, hepatic ischemia or development of a space occupying lesion e.g. HCC.

During the course of the RTC of Lamivudine in adults, the number of ALT flares appeared to be similar in those randomized to Lamivudine and in those randomized to placebo. A grade 3 flare was considered to be any rise 3-10 times above the baseline values and this was observed in 10% while on Lamivudine and in

13% while on placebo. However during follow-up such grade 3 flares of ALT were much more common in those who had stopped Lamivudine, observed in 22% compared 6% of those who had been randomized to placebo. No episodes of hepatic decompensation or fatality were described. Few of the study subjects were cirrhotic. Post treatment ALT data was not reported in the pediatric study.

### **Patients Most Likely to have a Virological Response (Figure 3)**

In the pediatric study it was evident that a virologic response regardless of randomization group was more likely to be observed in those who at baseline had an ALT value more than 5 fold elevated. In children whose ALT values at baseline were less than 2 fold elevated, there was no significant difference when the rate of virological response between those randomized to Lamivudine and those randomized to placebo, however a significant difference was observed between those with a baseline ALT between 2 and 5 fold elevated (12% placebo, 31% Lamivudine) and when baseline ALT was >5 fold elevated (24% placebo and 50% Lamivudine).

### **Baseline Factors Influencing Histological Response**

The likelihood of a histological response was significantly higher in those who received Lamivudine even after adjustment for baseline levels of ALT, HBV DNA, HAI score, race, age, sex, weight and the presence or absence of cirrhosis.

### **Further Studies on Lamivudine Therapy in HBeAg Positive Hepatitis (in the West)**

\*\*\*outside context of RCT

Two studies from the same center<sup>3,4</sup> have suggested that the development of Lamivudine resistance as judged by nucleotide changes in different areas of the YMDD motif are more common in subtype adw than in those with ayw however the numbers were small in each group, 13 with each subtype. Another paper by the same author suggests that the virologic response to Lamivudine could also be subtype dependant. In their small study it appeared that subtype ayw responded significantly better to Lamivudine therapy than subtype adw. This data needs to be confirmed using much larger sampler sizes.

### **Fibrosis Markers in Patients Treated with Lamivudine**

\*\*Outside the context of a RCT

Liver biopsy samples from 47 patients treated with Lamivudine and 33 patients receiving placebo were examined for markers of hepatic stellate cell activation, by measuring alpha smooth muscle actin (alpha SMA) and 1(III) propeptide (PIIICP)<sup>5</sup>. Both these markers were seen to be significantly reduced in those treated with Lamivudine whereas these markers tended to increase in those randomized to placebo(Figure 4). There was a correlation of these members with degree of improvement or degree of worsening of fibrosis score on liver biopsy (Figure 5).

### **Flare ups of ALT After Lamivudine Withdrawal**

\*\*\*Outside the context of RTC

Aminotransferase flare ups after withdrawal of Lamivudine therapy have been reported in 41 individuals treated with Lamivudine for a minimum of three months and followed for at least six months or more after discontinuation after therapy<sup>6</sup>. A significant flare of ALT was considered by these authors to be a greater than three fold elevation in ALT compared to the value at cessation of therapy. Such flares were observed in 17% (7/41) and occurred anywhere from 7-44 weeks after treatment cessation. In two, this was associated with hyperbilirubinemia, i.e. hepatic decompensation. These flare ups were all associated with rising levels of HBV DNA (Figure 6) unlike the spontaneous flares which may take place with seroconversion (associated with falling levels of HBV DNA). None of these flare ups were associated with seroconversion. In those who developed evidence of hepatic decompensation, reinstatement of Lamivudine was followed by rapid improvement.

## Unanswered Issues With Regard to Lamivudine Therapy

### ◆ Effect of baseline histology

Too few patients were randomized to these RCT to identify whether or not the anti viral effect of Lamivudine is similar in those with and without cirrhosis.

### ◆ Lamivudine Resistance

Baseline risk factors for Lamivudine resistance have not been assessed in these trials (cf: trials in the East where high BMI, male gender, high baseline HBV DNA have all been found to be associated with an increased rate in the mutations of YMDD motif. The rate of Lamivudine resistance in adults randomized in the adult North American Study was almost double that seen in studies originating from the Far East suggesting that Caucasians may be more susceptible to the development of these drug induced mutations.

### ◆ Durability of Response Following Cessation of Therapy

Results of these two RCT indicate that within the first 4-6 months of follow-up, the virologic effect as judged by seroconversion to HBeAb was durable in 73-75%. Durability beyond the six month mark remains unknown in Western patients. The durability of HBV DNA suppression and at what level is also known. Within the context of published RCT only 2% of those treated with Lamivudine lost HBsAg, longer term follow up may show this figure to change.

### ◆ Histological Response

There is no data on the durability of the histological response. All biopsy data was obtained when patients who were still taking Lamivudine. Patients had only been on therapy for one year. There is no data to date to indicate whether the improvement observed is sustained after treatment cessation, or sustained in patients still on long-term therapy but in whom drug resistant mutations have developed.

### ◆ Appropriate Duration Of Lamivudine Therapy in HBe Antigen Positive Hepatitis

These two trials in Western patients with HBeAg positive hepatitis employed Lamivudine therapy for a period of 52 weeks only. It remains unknown in this patient population whether the continuation of Lamivudine therapy beyond one year in those who have not lost HBeAg and/or seroconverted to anti HBe is appropriate. Cessation of therapy after one year of Lamivudine is associated with a flare up of HBV DNA (presumably in those who remained HBeAg positive). This was accompanied by a rise in ALT and although not stated in the RCTs in another study 17% had a marked flare up. In patients with underlying cirrhosis, the latter may have significant untoward effects and thus it is likely that baseline histology needs to be taken into consideration when deciding whether or not Lamivudine therapy should be stopped especially if the patient remains HBeAg positive.

### ◆ Lack of Complete Viral Eradication

The flare up in serum HBV DNA levels seen after cessation of Lamivudine therapy indicates that whereas this drug given for a year effectively reduces viral replication, it does not eradicate the virus. There is no data to indicate whether or not Lamivudine therapy influences levels of covalently closed circular (ccc) HBV DNA in hepatocytes.

### ◆ Long-term Outcome

Only 2% of Lamivudine treated patients loose HBsAg after one year of therapy. There is no long-term data to indicate whether this figure remains stable or not. Similarly there is no long-term follow up to indicate whether or not improvement in liver histology is continued in those who remain on therapy or remains stable once Lamivudine therapy is stopped following seroconversion or HBeAg loss. Similarly there are no long-term follow up studies to indicate whether or not Lamivudine therapy delays or prevents the development of cirrhosis and the complications of liver failure and/or hepatocellular carcinoma.

## How to Manage Lamivudine Resistance

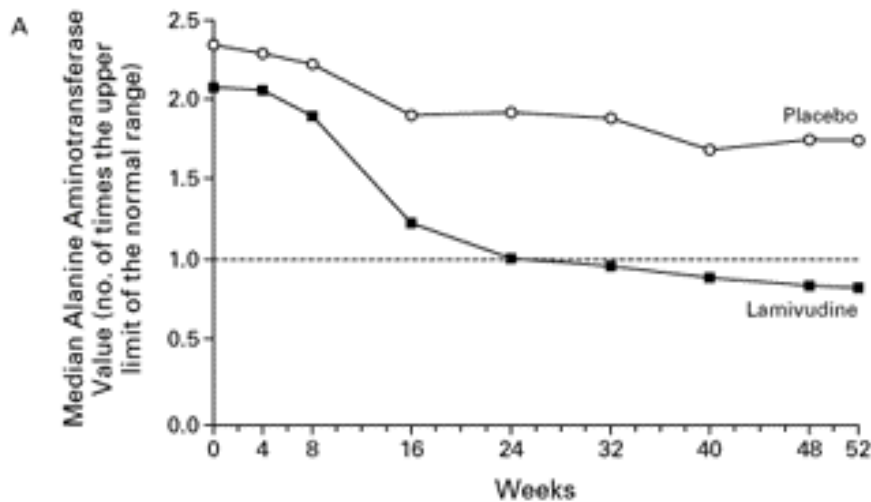
Data suggest that the risk of ALT flare up after cessation of Lamivudine therapy is similar whether or not Lamivudine resistant virus has developed<sup>5</sup> (Table 2). At one year of Lamivudine therapy in patients from the West histological improvement was less than those who developed Lamivudine resistance (43%) compared to those without evidence of drug resistance (improvement in 63%). It is not known whether or not

improvement in liver histology is sustained with maintenance of Lamivudine therapy in the face of Lamivudine resistance.

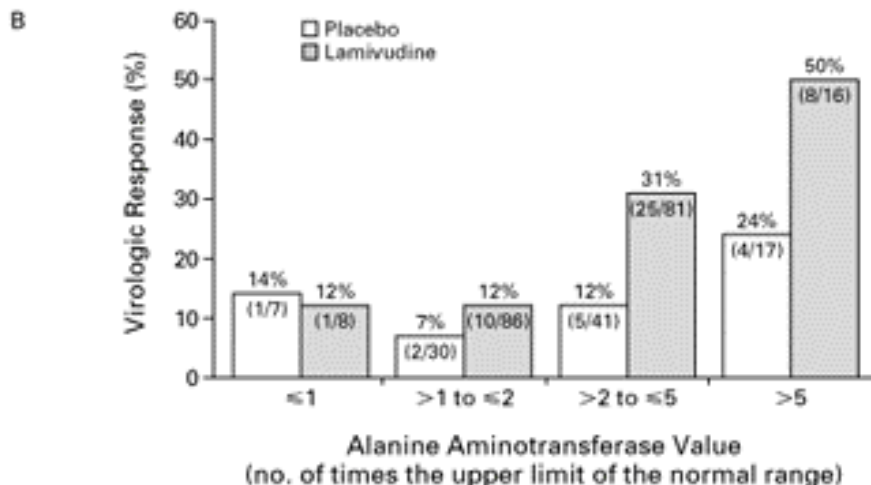
In the context of these RCT, only 87% of the children and 66% of the adults had sera available to be tested for Lamivudine resistant mutations at week 52, in a few testing was impossible because there was no detectable virus. Currently Lamivudine resistance testing is not universally available and surrogate markers need to be assessed. It appears that measurement of serum HBV DNA using highly sensitive techniques is required to detect early changes in levels of HBV DNA due to the emergence of Lamivudine resistance (non compliant patients generally have high levels of HBV DNA).

Once drug resistance has developed, subsequent management is unclear. It is not known if cessation of Lamivudine therapy in those who have developed drug resistance is safe – in all patients, eg. could patients with underlying cirrhosis be at greater risk of decompensation? Even if HBV DNA levels in the presence of drug resistance remain lower than baseline levels is the histological improvement sustained? Even though HBe seroconversion may occur in the presence of YMDD mutations is this seroconversion durable? Are there circumstances where YMDD mutations may be particularly dangerous shortly after their appearance e.g. in patients on corticosteroid therapy (cf: the post transplant state)? It is clear that the numbers of patients recruited to these two RCT are insufficient to answer these questions.

Fig 1



| No. EVALUATED | 0   | 4   | 8   | 16  | 24  | 32  | 40  | 48  | 52  |
|---------------|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Placebo       | 96  | 95  | 95  | 92  | 95  | 94  | 91  | 93  | 91  |
| Lamivudine    | 191 | 182 | 188 | 182 | 186 | 182 | 182 | 185 | 183 |



TABLES

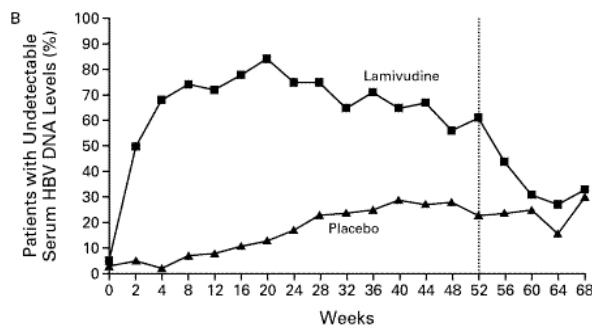
## Comparison of Patients with and without “Lamivudine Withdrawal” Hepatitis

|   | Flare         | Nonflare    |
|---|---------------|-------------|
| No. of cases                                  | 7             | 34          |
| Cirrhosis present (no., %)                    | 1 (14%)       | 8 (24%)     |
| Pretreatment ALT (IU/L, median [range])       | 191 (113-388) | 68 (21-306) |
| Treatment duration (wk, median [range])       | 24 (16-52)    | 24 (12-68)  |
| End-of-treatment ALT (IU/L, median [range])   | 36 (19-104)   | 44 (17-185) |
| End-of-treatment HBV-DNA positivity* (no., %) | 2 (29%)       | 8 (24%)     |
| End-of-treatment YMDD mutant (no., %)         | 1 (14%)       | 4 (12%)     |

\* Digene assay, cut-off  $1.5 \times 10^6$

**Honkoop et al. Hepatology 2000;32:636**

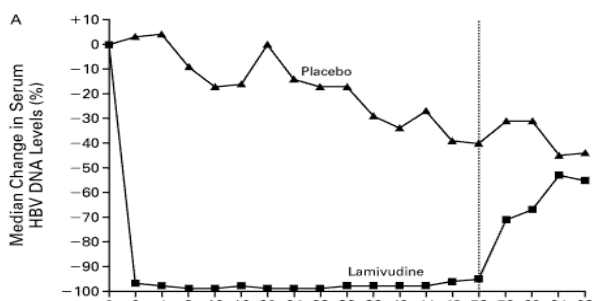
## Percentages of Patients with Undetectable Serum HBV DNA Levels

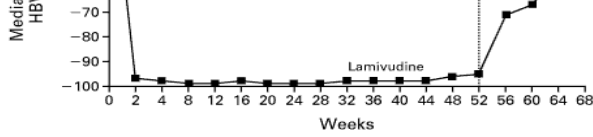


| No. EVALUATED |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |  |
|---------------|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|--|
| Placebo       | 65 | 62 | 61 | 59 | 64 | 61 | 62 | 59 | 56 | 58 | 59 | 55 | 56 | 54 | 56 | 50 | 48 | 50 | 53 |  |
| Lamivudine    | 63 | 60 | 62 | 61 | 58 | 60 | 62 | 59 | 56 | 57 | 58 | 55 | 51 | 54 | 54 | 48 | 51 | 51 | 52 |  |

**Dienstag et al. N Engl J Med 1999;341:1259**

## Median Changes in Serum HBV DNA Levels from Baseline

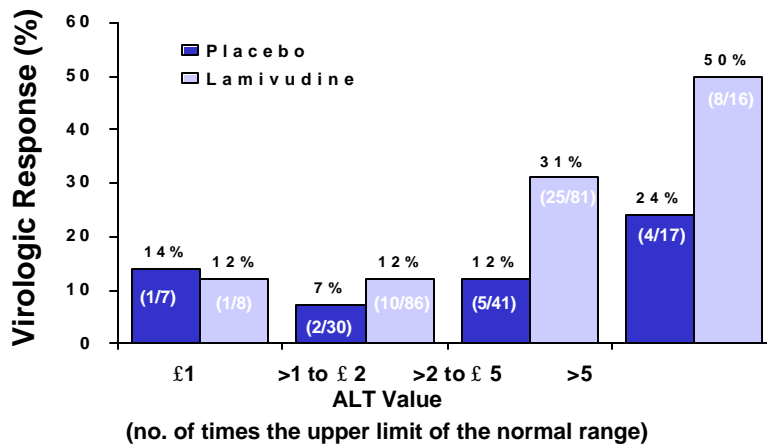




| No. EVALUATED |  |
|---------------|--|
| Placebo       | 65 62 61 59 64 61 62 59 56 58 59 55 56 54 56 50 48 50 53 |
| Lamivudine    | 63 60 62 61 58 60 62 59 56 57 58 55 51 54 54 48 51 51 52 |

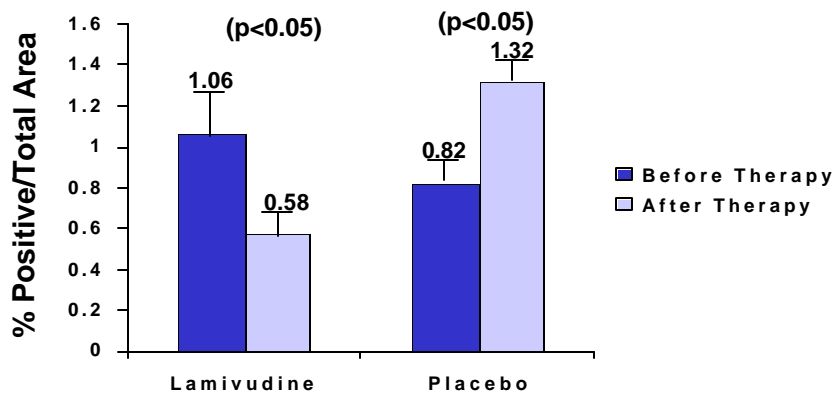
**Dienstag et al. N Engl J Med 1999;341:1259**

## Rates of Virologic Response According to the Baseline ALT Value



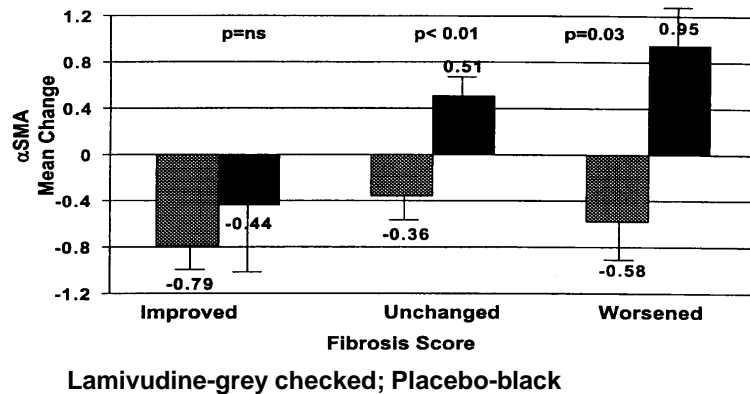
**Jonas et al. N Engl J Med 2002;346:1710**

## Change in -SMA in Paired Liver Biopsies Before and After Therapy with Lamivudine or Placebo



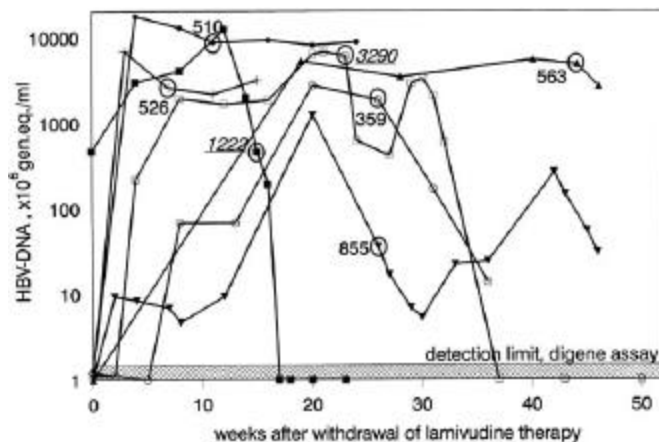
**Kweon et al. J Hepatol 2001;35:751**

## Mean Change ( $\pm$ SEM) in $\alpha$ -SMA for Patients Treated with Lamivudine or Placebo According to Change in Fibrosis Scores



*Kweon et al. J Hepatol 2001;35:753*

## HBV DNA Levels in 5 Patients with Hepatitis Flare After Withdrawal of Lamivudine Therapy



*Honkoop et al. Hepatology 2000;32:637*

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