Longitudinal observation of viral load changes in untreated HBeAg negative chronic hepatitis B

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Abstract

Introduction : **An HBV DNA level of 2000 IU/ml has been used to differentiate HBeAg negative chronic hepatitis B from the inactive carrier state. We sought to examine the nature and frequency of fluctuations in viral load and ALT around this threshold.**

Methods : **A retrospective review of St Vincent's Hospital database was performed to identify patients who had been observed, untreated, with HBV DNA and ALT levels over a period of at least 18 months.**

Results : **27 HBeAg negative patients with HBV DNA < 2000 IU/ml at baseline (Group 1) and 20 HBeAg negative patients with HBV DNA ≥ 2000 IU/ml (Group 2) were identified.**

Of group 1 patients, only 8/27 had persistently normal ALT and HBV DNA persistently < 2000 IU/ml over a median followup of 24 months. 11/27 (41%) Group 1 patients showed fluctuations above 2000 IU/ml over a median of 24 months followup, most of which were transient and in the range < 20,000 IU/ml. They were accompanied by persistently normal ALT in 5/11 (45%). 8 of 20 (40%) Group 2 patients had a drop of HBV DNA to < 2000 IU/ml over followup. These had a significantly lower baseline HBV DNA (8610 v/s 208763, p = 0.03) than those that remained persistently > 2000 IU/ml.

Conclusions : **Minor fluctuations in HBV DNA up to 20,000 IU/ml, accompanied by persistently normal ALT occur frequently in HBeAg negative chronic hepatitis B.** (Acta gastroenterol. belg., **2013**, 76, **275-281**).

Key words : Hepatitis B, HBeAg negative, HBV DNA, Longitudinal, ALT.

Abbreviations

ALT, alanine aminotransferase ; CHB, chronic hepatitis B ; IU/ml, international units/millilitre ; HBeAg, hepatitis B e antigen ; HBsAg, hepatitis B surface antigen ; HBV, hepatitis B virus ; ULN, upper limit of normal ; SD, Standard deviation ; IQR, Interquartile range.

Introduction

In the natural history of Chronic Hepatitis B (CHB) the Hepatitis B E Antigen (HBeAg) positive phases of immune tolerance and clearance occur first and following seroconversion the patient becomes HBeAg negative and Hepatitis B E Antibody (HBeAb) positive (1-3). Usually this serocoversion leads to quiescent disease however HBeAg negative chronic hepatitis with ongoing viral replication and inflammation that is measurable biochemically and histologically may develop directly from the immune clearance phase (4). HBeAg negative chronic hepatitis may also develop as a reactivation following a period of immune control (5,6). Distinguishing between the 2 phases of HBeAg negative CHB can be difficult and nomenclature and guidelines on the features to classify patients into either the immune control (Phase 3/ inactive carrier state) or immune escape (Phase 4/ Chronic HBeAg negative disease) phases have evolved over recent times. European (7), American (8) and Asian (9) practice guidelines exist and Australian and New Zealand Chronic Hepatitis B Recommendations have also been published by the Gastroenterological Society of Australia (10).

The inactive carrier (immune control) state is generally defined as HBeAg negative patients with low Hepatitis B Virus (HBV) DNA levels, in addition to persistently normal alanine aminotransferase (ALT) and the absence of significant hepatitis on liver biopsy (7-9). The cut-off level of HBV DNA to define this state has been difficult to reach consensus on and has changed over the last few years, decreasing from 100,000 copies/ml to 30,000 copies/ml (11-14)and further still more recently to 2000 IU/ml (8-10). In 2009, the EASL guidelines on the definition of the inactive carrier state did not use a strict HBV DNA threshold (15) but in 2012 they suggested the threshold of 2000 IU/ml although allowing that some inactive carriers with persistently normal ALT may have HBV DNA levels that are higher than 2000, (usually less than 20,000) (7). The level of 2000 IU/ml has also been recommended as a level for consideration of candidacy for therapy (8-10,16) thus it has become an important threshold used for making decisions regarding monitoring and treatment.

It is recognized that HBeAg negative hepatitis B can run a fluctuating course (17) with variability in HBV DNA and ALT levels over time. Although there is a reasonable body of literature on cohorts of Hepatitis B patients with persistently normal ALT (18-21), studies focusing on variations in HBV DNA levels are fewer. The published guidelines also focus primarily on frequent documentation of normal ALT levels with less clear emphasis on the the regularity with which HBV

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DNA levels should be below the cut off of 2000 IU/ml in criteria for the inactive carrier state. We sought to examine how stable HBV DNA levels are in untreated HBeAg negative patients, especially around the threshold of 2000 IU/ml given the significant focus currently on it both for defining inactive v/s active disease in HBeAg negative patients and as a trigger for therapy. We were also interested in how well serial monitoring of HBV DNA levels on either side of the threshold of 2000 IU/ml correlated with persistently normal ALT.

Methods

The patients were all CHB patients seen through St Vincent's Hospital, Melbourne on whom demographic details including date of birth, sex, ethnic origin and country of birth were recorded in a Microsoft Access Database as at 1 October 2008.The database was searched for all HBeAg negative patients who had had serial HBV DNA levels done whilst not on any treatment over a period of at least 18 months. The first HBV DNA and ALT tests performed on patients at St Vincent's Hospital were used as the baseline values. Patients with a baseline HBV DNA and in addition at least 1 followup HBV DNA test and ALT test in each of two subsequent years were included. HBV DNA and ALT testing were performed at approximately 6 monthly intervals from the baseline date. Normal ALT was defined as ≤ 35 U/L. Pharmacy records and patients' hospital records were searched to ensure that no treatment was used during the period of followup. The patients were divided into 2 groups according to their baseline HBV DNA status :

1. HBeAg negative and HBV DNA < 2000 (Group 1).
2. HBeAg negative and HBV DNA ≥ 2000 (Group 2).

The study conformed to the ethical guidelines of the Declaration of Helsinki and was approved by the St Vincent's Hospital Human Research and Ethics Committee.

Hepatitis B Virus Serological and DNA testing

Hepatitis B surface antigen (HBsAg) was measured using a commercially available immunoassay (Abbott Laboratories, North Chicago, IL, USA) and HBeAg and anti-HBe by an immunoassay produced by BioMerieux Clinical Diagnostics (Marcy l'Etoile, France).

All tests pertaining to HBV DNA were performed at the Victorian Infectious Diseases Reference Laboratory (VIDRL). The HBV DNA viral load was performed by a bDNA signal amplification probe method (Bayer Versant HBV DNA 3.0 assay, Bayer Diagnostics, Emeryville, CA, USA). The dynamic range is 357 to 17,857,140 IU/ml. One IU/ml is equivalent to 5.6 copies/ml. Patients tested using the bDNA assay whose HBV DNA levels were below and above the limits of detection were assigned the values of 357 and 17,857,140 IU/ml respectively for analyses involving HBV DNA.

Statistical Analysis

Data entry and statistical analysis were performed with the statistical package Stata (version 9.2, Statcorp). The corrected chi square test or two sided Fisher's exact test was used to compare categorical data, while the student's t-test or one way ANOVA was used for group comparisons of parametric quantitative data and the Mann-Whitney or Kruskal-Wallis test for similar comparisons of non-parametric data. Spearman's rank correlation was used to examine the association between HBV DNA and ALT values. Multilevel linear regression was used to examine the change in HBV DNA and ALT values over time. Results were presented as median and range or mean and Standard Deviation (SD) whenever appropriate. In all cases tests of significance were two-tailed with a level at < 0.05.

Results

Patient Characteristics

47 HBeAg negative patients, 27 with baseline HBV DNA < 2000 (Group 1) and 20 with HBV DNA ≥ 2000 IU/ml (Group 2) were followed up for a median of 24 months (18-48 months). The median baseline HBV DNA of the total group was 1255 IU/ml (range 357-2,133,453) and 34 of 47 had baseline HBV DNA < 20,000 IU/ml. Groups 1 and 2 were similar in gender distribution and in age with a mean age of 44 and 48 respectively. They also had similar numbers of HBV DNA and ALT tests performed (Table 1). The ethnicities of the groups differed with Group 2 having a higher proportion of Asians (95% v/s 67%). The majority of Asian patients were from South East Asia (especially Vietnam, Cambodia, Laos, Thailand) and China. Group 1 also included patients of Mediterranean (Greek and Italian) (7%) and Caucasian (15%) ethnicity. The baseline ALT of Group 1 was significantly lower than that of Group 2 at 29 compared to 48 U/L ($p = 0.03$).

The distribution of baseline HBV DNA in Group 1 was 67% HBV DNA ≤ 357 IU/ml and 33% 357-1999. In group 2, 35%, 15%, 35% and 15% of patients had baseline HBV DNA 2000-19,999, 20,000-99,999, 100,000-9.9×10^5, $\geq 10^6$ IU/ml respectively. The proportion of patients with baseline ALT ≤ ULN, 1-1.5 × ULN, 1.5 to 2 × ULN and > 2 × ULN was 67%, 18%, 11% and 4% respectively in Group 1 and 40%, 10%, 25% and 25% in Group 2. A significant correlation was found between ALT and HBV DNA in Group 2 (Correlation coefficient 0.39, $p < 0.001$) but not in Group 1 (Correlation Coefficient -0.17, $p = 0.06$).

Fluctuation of HBV DNA and ALT over time

The change in HBV DNA and ALT values in individual patients over time was examined using multilevel linear regression, and the results are summarised in Table 2. The regression coefficients presented represent

Table 1. – **Patient Characteristics. HBeAg negative (n = 47)**

	Group 1 (HBeAg neg, DNA < 2000)	Group 2 (HBeAg neg, DNA ≥ 2000)	P value
Number	27	20	
Number (%) Males	18 (67%)	11 (55%)	0.55
Age, Mean (SD)	44 (14)	48 (14)	0.28
% Asian	18 (67%)	19 (95%)	0.03
Baseline DNA IU/ml Median (IQR)	357 (357, 883)	88589 (7570,457232)	< 0.001
Baseline ALT IU/ml Median (IQR)	29 (20,47)	48 (28,74)	0.03
Number of followup HBV DNA tests/patients, Mean (SD)	3.9 (1.5)	3.4 (0.6)	0.10
Number of followup ALT tests/patient, Mean (SD)	4.3 (1.7)	3.6 (0.6)	0.06
Number (%) with normal baseline ALT	18 (67%)	8 (40%)	0.08
Number (%) with persistently normal ALT	13 (48%)	4 (20%)	0.07

Table 2. — **Multilevel linear regression showing change in ALT and HBV DNA in Group 1 and 2 patients for an increase in time of one month**

Outcome	Group	Regression Coefficient (95% CI)	P-value
ALT	Group 1 (HBeAg Neg, DNA < 2000)	-0.13 (-0.40, 0.14)	0.35
	Group 2 (HBeAg Neg, DNA ≥ 2000)	-0.54 (-1.23, 0.16)	0.13
DNA	Group 1 (Neg, DNA < 2000)	2817 (-458, 6093)	0.09
	Group 2 (Neg, DNA ≥ 2000)	-687 (-13865, 12491)	0.92

the change in the outcome for an increase in time of one month. When examined in this way there was no evidence of a significant change over time in either ALT or HBV DNA in groups 1 or 2.

Longitudinal followup of HBeAg negative patients with HBV DNA < 2000 IU/ml

The 27 HBeAg negative patients with baseline HBV DNA < 2000 IU/ml (Group 1) were followed over a median of 24 months (range 18-48). 16 (59%) of them had an HBV DNA that was persistently < 2000 IU/ml (Group 1A), while the other 11 (41%) had one or more HBV DNA levels over 2000 IU/ml during the followup period (Group 1B). Despite fluctuations in HBV DNA to above 2000 IU/ml over followup, 45% of Group 1B patients maintained a persistently normal ALT.

The longitudinal HBV DNA levels of the Group 1B patients are shown in Table 3. Ten of the eleven Group 1B patients continued to be observed following the rise in HBV DNA above 2000 IU/ml and had an HBV DNA test available 6 months after the test showing the elevation. In the eleventh patient there was a rise in DNA from 1461 IU/ml to 2.77×10^6 IU/ml at which point the patient went onto therapy. In 7 of the 10 observed Group 1B patients the elevated DNA was an isolated one with the subsequent DNA test showing a return to below 2000, although in one patient there was a further transient rise above 2000 IU/ml in the following year. The highest HBV DNA level seen in these patients was 10,697 IU/ml. The other 3 of 10 patients showed a sustained elevation of DNA > 2000 over 2 or more tests although the levels remained under 20,000 IU/ml. ALT remained persistently normal in all 3 patients with a sustained elevation in HBV DNA although it was persistently normal in only 2 of 7 patients with a transient elevation (Table 3). Of 52 followup HBV DNA tests in all 11 patients, 15 (29%) were elevated to over 2000 IU/ml.

Of the 27 Group 1 patients who had baseline HBV DNA of < 2000 IU/ml, only 8 (30%) had both ALT persistently normal and HBV DNA persistently < 2000 IU/ml. 5 (18%) had a persistently normal ALT but HBV DNA was not persistently below 2000 IU/ml, a further 8 (30%) had an HBV DNA that was persistently < 2000 IU/ml but ALT was not persistently normal and 6 (22%) had neither a persistently normal ALT nor HBV DNA persistently below 2000. The group with persistently normal ALT and HBV DNA persistently < 2000 IU/ml were significantly older at 54 years than the other 3 mentioned above (who were 34, 45 and 39 respectively) p = 0.04.

Table 3. — **Fluctuations in HBV DNA in IU/ml over followup in patients with initial HBV DNA < 2000 IU/ml and subsequent rise to over 2000 IU/ml**

		HBV DNA 0 months	HBV DNA 6 months	HBV DNA 12 months	HBV DNA 18 months	HBV DNA 24 months	HBV DNA 30 months	HBV DNA 36 months	HBV DNA 42 months	HBV DNA 48 months	Persistently Normal ALT
Transient rise > 2000 IU/ml	Patient 1	357	357	357	4373	357	470	531			No
	Patient 2	357	747	6556	357	2298	357	1390	391	357	Yes
	Patient 3	357		506	357	2957	480		357		No
	Patient 4	509	3558	583	527	357					No
	Patient 5	357	357	10697	357	357					No
	Patient 6	1255	2104	1536	711	1089					Yes
	Patient 7	1260	2250	357	357	357					No
Sustained rise > 2000 IU/ml	Patient 8	357	1148	357	2390	5346	357	357			Yes
	Patient 9	357	986	6951	5404						Yes
	Patient 10	1045	999	2233	3644						Yes
Not evaluable	Patient 11	357		357	357	357	1461	2.7×10^6			No

Longitudinal followup of HBeAg negative patients with HBV DNA ≥ 2000 IU/ml

The 20 HBeAg negative patients with a baseline HBV DNA ≥ 2000 had a median followup of 24 months (range 18-24). 12 of the 20 (60%) of patients had HBV DNA persistently > 2000 IU/ml over followup (Group 2A) and 8/20 (40%) had one or more HBV DNA result < 2000 IU/ml (Group 2B). The 2 groups were similar in their demographics (age, sex and ethnicity), duration of followup and the number of followup HBV DNA and ALT tests done per patient however group 2B had a lower median baseline HBV DNA compared to the other group (8610 v/s 208763 IU/ml, p = 0.03) (Table 4). The proportion of patients with HBV DNA persistently > 2000 IU/ml were 29%, 66% and 80% in the baseline HBV DNA groups of 2,000-19,999 (n = 7), 20,000-99,999 (n = 3) and ≥ 10^5 IU/ml (n = 10) respectively. 20% of Group 2 patients had a persistently normal ALT.

Examination of the viral load changes in Group 2B patients showed that 5 of 8 had a baseline HBV DNA between 2000 and 20,000 IU/ml and 4 of the 5 fluctuated below 20,000 while the 5th patient's HBV DNA rose to > 2×10^5 after 18 months) (Table 5). 3 of these 5 had persistently normal ALT. A further Group 2B patient had a baseline HBV DNA level of 52,555 IU/ml and the last 2 patients in group 2B had a baseline HBV DNA over 10^5 IU/ml and underwent spontaneous reduction in HBV DNA by over 2 logs during follow up, both dropping to < 2000 IU/ml. This occurred gradually over the course of 12 months.

By contrast, only 2 of 12 Group 2A patients had a baseline HBV DNA < 20,000 IU/ml and only 1 of these had HBV DNA levels that remained < 20,000 during followup although this was not accompanied by a persistently normal ALT. Although the proportion with persistently normal ALT was 1/12 (8%) in group 2A and 3/8 (38%) in group 2B, this did not reach statistical significance (p = 0.26) however the numbers in these subgroups were small.

Discussion

This study observes the virological and biochemical fluctuations in an Australian cohort of HBeAg negative chronic hepatitis B patients, over a period of at least 18 months. It is a study predominantly of Asian patients, with mean age in the mid forties who have low level viraemia and it focuses on the changes that occur around the HBV DNA threshold of 2000 IU/ml. We show that 40% of patients who begin above or below the arbitrary HBV DNA level of 2000 IU/ml will subsequently cross this threshold. These fluctuations in both groups 1 and 2 were mostly of a low level, around a low baseline and almost all the Group 1B patients whose HBV DNA rose over the level of 2000 remained under 20,000 IU/ml. In our cohort only 8/27(30%) patients with a baseline HBV DNA < 2000 IU/ml in fact demonstrated levels of virus persistently below 2000 IU/ml and persistently normal ALT. Furthermore we show that a persistently normal ALT is seen in significant proportions of patients who had HBV DNA levels that fluctuated above 2000 IU/ml (45% in group 1B and 20% in Group 2 overall).

There is a relative paucity of published data on the fluctuations in HBV viral load that occur in chronic

Table 4. — **Patients with baseline HBV DNA ≥ 2000 IU/ml, n = 20**

	Group 2A (DNA persistently ≥ 2000 IU/ml)	Group 2B (DNA not persistently ≥ 2000 IU/ml)	P Value
Number (%)	12 (60%)	8 (40%)	
Number (%) Males	7 (58%)	4 (50%)	1
Mean Age (SD)	47 (13)	49 (7)	0.81
Number of followup DNA's per patient Mean (SD)	3.5 (0.5)	3.3 (0.7)	0.37
Number of followup ALT's per patient Mean (SD)	3.7 (0.7)	3.5 (0.5)	0.56
Baseline HBV DNA median (IQR)	208,763 (45764, 1051342)	8610 (4861, 87656)	0.03
Baseline ALT median (IQR)	50 (32 ,87)	41 (23, 55)	0.33
Number (%) with persistently normal ALT	1 (8%)	3 (38%)	0.26

Table 5. — **Fluctuations in HBV DNA in IU/ml over followup in Group 2B patients with initial HBV DNA ≥ 2000 IU/ml and subsequent drop to < 2000 IU/ml**

	HBV DNA 0 months	HBV DNA 6 months	HBV DNA 12 months	HBV DNA 18 months	HBV DNA 24 months	HBV DNA persistently < 20,000	Persistently normal ALT
Patient 1	2247		357	2128	473	Yes	Yes
Patient 2	2571	2632	1123	3143		Yes	Yes
Patient 3	9231	504	6156	2214	357	Yes	Yes
Patient 4	7150		17490	930		Yes	No
Patient 5	7989	1451	376	237571	22115	No	No
Patient 6	52555	1760	14970	941		No	No
Patient 7	122756	41463	396	4489	2458	No	No
Patient 8	326435	15948	35640	1527		No	No

hepatitis B or in inactive carriers. Important work done approximately 10 years ago demonstrated that viral load over time in HBeAg negative patients was relatively stable (12,22). Consistent with this, large fluctuations in HBV DNA or ALT were not observed in our cohorts when measured by regression analysis.

There have since been other studies focusing on changes in HBV DNA and ALT over time during seroconversion (23,24) and in cohorts with HCC (25,26) or in cohorts of predominantly HBeAg positive patients (27). A small study of 14 inactive carriers found that although there was significant fluctuation in HBV DNA below the range of 10^4 copies/ml (approximately 1785 IU/ml), the ALT remained persistently normal when measured monthly for 12 months (28). HBV DNA even at low levels, is now recognized as a risk factor for the complications of CHB including cirrhosis and Hepatocellular carcinoma (HCC) (29, 30) and this has no doubt partly driven a focus on the low level of 2000 IU/ml to define inactive carriers/chronic hepatitis B and also as a threshold for treatment in HBeAg negative patients.

The question of viral load fluctuations in HBeAg negative patients around the level of 2000 IU/ml has been dealt with in part by a couple of groups. In a study by Zecharakis with a median followup of 5.3 years, HBV DNA levels < 2000 IU/ml on at least one occasion were seen in 5/12 (42%) HBeAg negative patients with intermittently abnormal ALT and in 8/36 (22%) of patients with persistently abnormal ALT (31). Similarly in our group 2 patients, who had baseline HBV DNA ≥ 2000 IU/ml, we demonstrated a drop below 2000 IU/ml in 40% (8/20) (Group 2B). Group 2B patients had a significantly lower baseline HBV DNA than those that didn't drop below 2000 IU/ml (Group 2A) and the viral load of 4 of the 8 Group 2B remained in the range < 20,000 IU/L.

Papatheodoridis also observed 65 HBeAg negative patients with chronic hepatitis and found that 18% had occasional changes in HBV DNA to below the level of 2000 IU/ml (32). They also studied 85 patients in the inactive carrier state, defined as persistently normal ALT over 12 months and baseline HBV DNA < 20,000 IU/ml and found no significant change in HBV DNA from baseline to Year 1 (32).

Using the cut off level of 20,000 IU/ml in place of 2000 IU/ml to define the inactive carrier state has gained further support from a recent study looking at 62 patients with persistently normal ALT over 10 years who also had HBV DNA levels tested retrospectively over that time

which were found to largely be < 20,000 IU/ml (33). While 82% of their patients had HBV DNA levels < 5 log10 copies/ml (approximately equivalent to 20,000 IU/ml) only a small proportion had HBV DNA < 4 log10 copies/ml (33). Lin *et al*. observed 414 HBeAg negative Taiwanese patients with persistently normal ALT over 2 years and found that 65% of them had HBV DNA > 10^4 copies/ml (18). Paptheodoridis *et al*. also recently reviewed 6 studies of HBeAg negative patients with persistently normal ALT and concluded that if persistently normal ALT was based on strict criteria, significant histological liver disease was rarely found on liver biopsy in patients with HBV DNA up to 20,000 IU/ml (34).

Of our group 1 HBeAg negative patients with a baseline HBV DNA < 2000 IU/ml, we found only (8/27) 30%, had persistently normal ALT and HBV DNA persistently < 2000 IU/ml over followup. Amongst those 11/27 group 1 patients that had HBV DNA > 2000 IU/ml at some point over followup, the viral load fluctuations were largely under 20,000 and were usually only transiently above 2000 IU/ml. In this group of 11 patients, 5 had persistently normal ALT and 6 did not. We thus concur with data from the above groups (33,34) that a more generous cut off of 20,000 IU/ml for defining inactive carriers may be appropriate. Paptheodoridis et al provide a useful algorithm in their recent paper, drawing attention to the fact that whilst patients with HBV DNA < 20,000 IU/ml with truly persistently normal ALT do not require liver biopsy and can be considered inactive carriers, those with abnormal ALT should certainly be considered for liver biopsy. This can help guide the need for therapy in a patient who may have fluctuating low level viraemia, especially if the ALT is only mildly or intermittently abnormal.

The discrepancies we found between HBV DNA levels and ALT levels in patients have been noted by others who found that a common explanation was a rising or falling viral titre with the ALT rise preceding or lagging behind the change in viral load (35) although in other patients in this study liver biopsy revealed mild active CHB or Non Alcoholic Fatty Liver disease.

Our study, like others recently (36) highlights the difficulty of classifying HBeAg negative patients into a phase using very strict criteria. The use of quantification of HBsAg titres may further add to defining inactive carriers in the future (37). The 2012 EASL guidelines suggest that along with persistently normal ALT, a cut-off level of 2000 IU/ml is used for defining inactive carriers but they also concede that a level of up to 20,000 IU/ml may be seen (7) and we feel that in light of recent data including ours, this higher possible range is worth emphasizing.

Our study has limitations including its retrospective design, bias towards patients with low level viraemia and relatively small numbers in some patient subgroups. It also did not use the categorsiations of inactive carrier and chronic hepatitis B but this was because we did not feel comfortable using the strict guidelines that were advised since our hypothesis was that fluctuations above the level of 2000 IU/ml were common despite persistently normal ALT in some HBeAg negative patients which we were able to demonstrate.

Conclusions

This study represents a detailed description of the course, untreated, of a moderate sized cohort of HBeAg negative chronic hepatitis B patients over a period of at least 18 months.

We found that fluctuations around the HBV DNA threshold of 2000 IU/ml were common. In particular about 40% of patients who began with HBV DNA < 2000 rose transiently above this. Many of these patients had a persistently normal ALT. Similarly, 40% of patients with a viral load above 2000 IU/ml at baseline subsequently fall below this. Our data showing the frequent small fluctuations that occur in viral loads in CHB patients lends support to the recent suggestion that a higher threshold of 20,000 IU/ml for definition of the inactive carrier state may be appropriate.

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