Background: Although adherence is of major importance in long-term treatments, few studies have been published regarding the use of anti-HBV analogues in clinical practice. The aim of this study was to evaluate adherence to anti-HBV analogues and associated virological suppression.

Methods: A cross-sectional study was performed between 1 January 2009 and 15 July 2009 in Cochin Hospital, Paris, France. It included all patients being treated with anti-HBV analogues for at least three months, who were without coinfection (HIV, HCV or HDV) and who had not received organ transplants. At the time of enrolment, HBV viral load, analogue regimen and self-reported adherence were collected prospectively. Patients were classified as non-adherent, or moderately or totally adherent using a score based on analysis of self-reports. Other data were obtained retrospectively.

Results: Among the 190 patients meeting the inclusion criteria, 33% were initially hepatitis B e antigen-positive and 50% had extensive fibrosis or cirrhosis. Pretreatment viral load was 6.0 log IU/ml (median). The median duration of treatment was 52 months. At enrolment, 61%, 32% and 7% of patients were classified as totally adherent, moderately adherent and non-adherent, respectively. Complete virological suppression (HBV DNA <12 IU/ml) was observed in 83% of patients at enrolment. In the multivariate analysis, lack of virological suppression was associated with an increased pretreatment viral load, with no change in analogue regimen and is classified as non-adherent.

Conclusions: Adherence seems to be an independent factor associated with virological suppression during anti-HBV analogue treatment. Therapeutic education and a systematic evaluation of adherence using self-reports should be promoted to assure long-term anti-HBV analogue efficacy in clinical practice.

Original article

The role of adherence in virological suppression in patients receiving anti-HBV analogues

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Introduction

Chronic HBV infection is associated with a high risk of cirrhosis and hepatocellular carcinoma, resulting in significant morbidity and mortality [1–3]. It is now established that the level of HBV replication is a major determinant of liver disease progression and mortality [1,2,4]. That is why the recent European Association for the Study of the Liver (EASL) Practice Guidelines for HBV treatment highlight prolonged HBV suppression as a major goal, assessed by a sensitive assay [1]. Prolonged virological suppression from taking anti-HBV analogues contributes to improving liver fibrosis and preventing complications [1,4–6]. Since the advent of second-generation anti-HBV analogues, study results show that viro-suppression rates have significantly increased, ranging from 67% to 93% after 1 year of tenofovir or entecavir monotherapy depending on the hepatitis B e (HBe) status [7–9]. In addition, these results are associated with no (with tenofovir) or low rates (<1.2% with entecavir) of resistance mutation even after long-term therapy (4 and 7 years, respectively), and low rates of viral rebound, the latter probably being primarily due to reduced adherence or treatment interruptions. Studies reporting on the role that adherence might play in sustained virological
response and on resistance in patients with HBV chronic infection are sparse, however [10].

The aim of this study was to evaluate to what extent a self-reported measure of adherence can be predictive of virological suppression in patients receiving anti-HBV analogues, after accounting for pre- and in-treatment characteristics.

Methods

Patients
To perform a preliminary cross-sectional study, between 1 January 2009 and 15 July 2009, all chronic hepatitis B surface antigen-positive adult patients followed up in the outpatient service of Cochin Hospital in Paris, France who had been receiving anti-HBV analogues for at least three months were enrolled in the study. This minimal duration was chosen to eliminate patients who never began treatment despite an initial prescription. Exclusion criteria for study participation were patients who had HCV, HIV or HDV coinfection, or a kidney or liver transplant. This protocol was approved by the local Ethical Committee.

Virological suppression was defined as having undetectable HBV DNA (the lower limit of detection was 12 IU/ml or 1.1 log IU/ml; Cobas® Taqman® HBV test, Roche Molecular Systems, Pleasanton, CA, USA) at enrolment, the interval between the blood test and the enrolment visit being <1 month.

Prospective data collection was the measurement of HBV DNA, anti-HBV treatment, HBe status and adherence (see Adherence measurement) at the time of enrolment.

Retrospective data collection was HBe status, HBV DNA and liver histology before initiating HBV treatment, retrospectively evaluated using medical records.

All HBV DNA retrospective values taken from medical records were converted into international units (IU/ml) [11]. The fibrosis stage for liver histology was expressed using the META VIR score system [12]. The following information was also retrieved from medical records: previous interferon treatment prior to enrolment, the type of HBV treatment prescribed at the time of enrolment, the number of changes in HBV-analogue regimens up to the date of enrolment and previous or then current regimen types (one analogue or two analogues).

Anti-HBV analogue regimens (previous or at time of enrolment) were recorded according to whether the combination included a second-generation analogue (entecavir or tenofovir) or only a first-generation analogue (lamivudine or adefovir).

The total duration of exposure to anti-HBV analogues and the duration of the regimen being taken at time of enrolment were also calculated.

Adherence measurement
Five questions regarding adherence to HBV analogues were included in a self-administered questionnaire at enrolment (Table 1).

The first four were adapted for HBV-analogue treatment from the questionnaire established for HIV-positive patients by the AIDS Clinical Trial Group [13], validated in French [14] and then used in HIV studies [15,16]. The fifth question corresponded to a visual analogue scale (VAS) [17]. Patients with a limited understanding of the French language could be helped with the questionnaire by the person who accompanied him/her to the outpatient hospital department and by the physician.

An algorithm already validated for HIV-positive patients [14–16] was adapted to classify patients into three categories according to their answers to the five questions: fully adherent, moderately adherent or non-adherent. Patients were classified as fully adherent if they had never skipped a dose and had a VAS score of 10. Patients were classified as moderately adherent if they had skipped one dose or almost totally followed the prescription or had a VAS score from 8.1 to 9.9. Other patients were classified as non-adherent. This

| Question 1 | Have you skipped a daily treatment dose during one of the four days before the visit? |
| Question 2 | Fill in a detailed table with the number of pills you had actually taken daily in the four days prior to the visit |
| Question 3 | Have you skipped a daily dose during the weekend prior to the visit? |
| Question 4 | During the last 4 weeks, did you? |
| | Totally follow the prescription |
| | Almost totally follow the prescription |
| | Often modify the prescribed doses |
| | Seldom follow the prescription |
| | Interrupt the treatment for a medical reason |
| | Interrupt the treatment following your own decision |
| | Interrupt the treatment for another reason |
| Question 5 | Visual analogue scale: put a cross on the line below showing how you consider you have followed the treatment during the last three months: from 0 (= not followed treatment at all) to 10 (= no omission of antiviral drug dose taking) |
approach tended to minimize social desirability bias by reclassifying patients as moderately or poorly adherent if they reported moderate or poor adherence behaviours at least once when answering the five questions.

Statistical analyses
A logistic regression analysis was used to study the relationship between adherence and virological suppression after adjustment for the other potential correlates. Crude odds ratios and their 95% confidence intervals were calculated in order to quantify the strength of the association between possible predictors and virological response. All variables with a liberal P-value <0.10 in the univariate analysis were considered eligible to enter the final multivariate logistic model. A backward procedure based on the log-likelihood ratio was used to identify the best pattern of predictors of virological response.

Statistical analyses were performed using StatView (SAS Institute Inc., Cary, NC, USA).

Results
Between January and July 2009, 190 patients fulfilled the inclusion criteria and all were enrolled in the study. The median age of the patients at enrolment was 50 years (IQR 18) and 58% were male. Of the patients in the study, 33% were of European origin, 29% Asian, 18% sub-Saharan African, 18% were from the Middle East, 13% from North Africa, 5% were from the French Caribbean Islands and the remaining 2% had other geographical origins. A liver biopsy was performed before initiating antiviral treatment in 180 patients (95%), and half of the 190 patients had extensive fibrosis or cirrhosis, corresponding to F3/F4 liver fibrosis using the METAVIR scoring system. In 8% of the patients, interferon treatment had been performed before treatment with anti-HBV analogues. The value of the HBV DNA before initiating treatment was available for 150 patients (79%) and the median viral load was 6.0 log IU/ml (IQR 2.5). The median duration of the anti-HBV analogue treatment at the time of the survey was 52 months (IQR 18). Before enrolment, 54% of the patients had already changed their anti-HBV analogue regimen. Before initiating treatment, HBV viral load was higher in patients having had at least one change in analogue regimen (6.4 ±1.6 versus 5.5 ±1.8 IU/ml, respectively; P=0.007), and 59 patients (33%) were hepatitis B e antigen (HBeAg)-positive (initial HBe status known in 179 of the 190 patients). Initial viral load was higher in HBeAg-positive than in HBeAg-negative patients (7.0 ±1.4 versus 5.5 ±1.7 IU/ml, respectively; P<0.001). Among initially HBeAg-positive patients, 26 (44%) became anti-HBe-positive during follow-up.

At enrolment, 48% of the patients were being treated with analogues in monotherapy (lamivudine, 8%; adefovir, 5%; entecavir, 24%; and tenofovir, 11%) and the remaining with combination therapy (emtricitabine plus tenofovir, 6%; lamivudine plus adefovir, 25%; lamivudine plus tenofovir, 8%; entecavir plus adefovir, 4%; entecavir plus tenofovir, 9%). A large majority of the patients (83%) taking anti-HBV analogues had complete virological suppression (HBV DNA<12 IU/ml) at cohort enrolment. For the remaining patients who were HBV-DNA-positive at the time of enrolment, the median HBV-DNA value was 2.4 log IU/ml (IQR 1.3).

At enrolment, the study population was classified as ‘fully adherent’ (n=116; 61%), ‘moderately adherent’ (n=60; 32%) and ‘non-adherent’ (n=14; 7%). No association was found between adherence level and the following: geographical origin; HBV viral load before initiating anti-HBV analogues treatment; first line compared with non-first line treatment; or monotherapy compared with combination therapy. More recent treatment initiation tended to be associated with lower levels of adherence (P=0.085). Among those who were HBeAg-positive before initiating treatment, the percentage of patients who became anti-HBe-positive during follow-up were 46%, 38% and 25% (P=0.486) for the fully adherent, moderately adherent and non-adherent categories, respectively. A combination of analogues (bi-therapy) was, however, more frequently prescribed in patients who switched analogue regimen (65% versus 36% for those who did not switch; P<0.001).

Factors tested for complete virological suppression in the univariate analysis are presented in Table 2. As can be seen, adherence level was the only factor significantly associated with virological suppression.

The following factors were weakly associated (P<0.10) with complete virological suppression and consequently were included in the final statistical analysis model: a regimen including a second-generation analogue; HBV DNA before initiating the treatment; and the change of analogue regimen during the treatment. After multiple adjustments, the following factors remained independently associated with virological suppression (Table 2): HBV DNA before initiating treatment; having had at least one change from one anti-HBV analogue regimen to another; and adherence level.

Discussion
This study clearly shows that, after adjusting for both HBV DNA before initiating treatment and history of treatment switching, self-reported adherence prior to the enrolment visit remains a major predictor of virological suppression. The result suggests that sustained
response to treatment depends on recent adherence to HBV treatment, an observation that remains valid even after adjustment for proxies of ‘problems with anti-HBV treatment’, as expressed by a history of HBV treatment switching.

This is the first time that a self-reported measure of non-adherence has been found to be a predictor of viral suppression in patients receiving anti-HBV analogue treatment in clinical practice. Close monitoring of adherence through patients’ self-reports during HBV treatment follow-up might therefore be an effective approach, both for the early identification of patients at risk of virological failure and for the provision of adequate interventions to improve adherence. Although one recent retrospective study did evaluate adherence through initial prescription and pharmacy refill in patients treated with different anti-HBV analogues, it did not measure the effect adherence has on viral suppression [18]. Because no previous research exists showing the usefulness of self-reported adherence for clinical management in HBV-infected patients, our result is consistent with other recent research where a retrospective evaluation of deviations from prescribed medication regimens was found to be associated with virological failure of HBV monotherapy [19].

The association between self-reported non-adherence and viral suppression has already been widely described for anti-HIV analogues using a similar approach for measuring adherence as that in the present study [20–23]. The use of self-administered questionnaires has been extensively developed and validated in HIV-positive patients [13,14,24,25]. In the field of HIV, using nucleoside analogues for the treatment of a chronic viral infection, adherence is closely related to the success of therapy. Thresholds of 90% or more have been derived to define adherence. For HBV, these preliminary data suggest that this is also true. It is important to underline that 7% of the HBV-positive patients in our study were classified as ‘non-adherent’ and that this rate is comparable to those reported in the French APROCOSTudy group cohort for HIV-positive patients [14] and in a recent randomized controlled study for HBV-positive patients treated with tenofovir or tenofovir plus emtricitabine versus adefovir for 48 weeks [26].

Switching to another analogue regimen was frequent in the present cohort; at least one change was observed in 54% of the patients. However, these changes mainly illustrate therapeutic progress made with the successive development of new drugs for HBV therapy: after approval of lamivudine in 1998, adefovir was approved for use in France in 2003 (for lamivudine-resistant and naive

### Table 2. Factors associated with complete virological suppression, HBV DNA<12 IU/ml, at the time of enrolment

<table>
<thead>
<tr>
<th>Factor</th>
<th>Univariate analysis</th>
<th>Multivariate analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HBV DNA&lt;12 IU/ml at enrolment (n=158)</td>
<td>HBV DNA&gt;12 IU/ml at enrolment (n=32)</td>
</tr>
<tr>
<td>Age at enrolment, years ±sd</td>
<td>49.5 ±13.2</td>
<td>51.6 ±17.5</td>
</tr>
<tr>
<td>Male/female sex, %</td>
<td>86/80</td>
<td>14/20</td>
</tr>
<tr>
<td>HBeAg positivity before initiating analogue treatment, %</td>
<td>30</td>
<td>42</td>
</tr>
<tr>
<td>HBV DNA before initiating treatment, log IU/ml ±sd</td>
<td>5.8 ±1.7</td>
<td>6.5 ±1.7</td>
</tr>
<tr>
<td>Cirrhosis at the biopsy before initiating treatment, %</td>
<td>30</td>
<td>19</td>
</tr>
<tr>
<td>Previous treatment with interferon, %</td>
<td>8</td>
<td>9</td>
</tr>
<tr>
<td>At least one change of analogue regimen, %</td>
<td>57</td>
<td>41</td>
</tr>
<tr>
<td>Total duration of treatment with analogues, months ±sd</td>
<td>60.1 ±40.6</td>
<td>49.9 ±46.8</td>
</tr>
<tr>
<td>Duration of last treatment with analogues, months ±sd</td>
<td>30.9 ±25.4</td>
<td>29.0 ±36.1</td>
</tr>
<tr>
<td>Treatments including a second-generation analogue at enrolment, %</td>
<td>59</td>
<td>75</td>
</tr>
<tr>
<td>Combination of analogues (bitherapy) at enrolment, %</td>
<td>54</td>
<td>41</td>
</tr>
<tr>
<td>Adherence classes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Totally adherent, %</td>
<td>84</td>
<td>16</td>
</tr>
<tr>
<td>Moderately adherent, %</td>
<td>87</td>
<td>13</td>
</tr>
<tr>
<td>Non-adherent, %</td>
<td>57</td>
<td>43</td>
</tr>
</tbody>
</table>

HBeAg, hepatitis B e antigen.

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patients), then entecavir in July 2007 and tenofovir in April 2008. In patients with detectable HBV DNA, recommendations parallel recent EASL Clinical Practical Guidelines [1] suggesting that a combination of analogues or a switch to more potent analogues should be prescribed, depending on the resistance pattern. As expected, initial viral load was higher in this study in patients having had at least one change in analogue regimen. Switching is therefore more a proxy of previous non-response to anti-HBV analogue treatment and explains why it remains independently associated with virological suppression.

As expected, an increased HBV viral load before initiating treatment with analogues was independently associated with a lack of virological suppression.

Recent EASL Clinical Practical Guidelines for HBV management indicate that the main goal for HBV treatment is prolonged virological suppression, measured using a sensitive assay [1]. In terms of representativeness, 83% of the studied population exhibited virological suppression. The virological test used in this study was highly sensitive, with a lower limit of detection at 12 IU/ml. The results of this study are consistent with those published from controlled trials with second-generation analogues using less-sensitive assays [7–9,26].

One limitation of the study is the retrospective nature of the data collection for some clinical variables. Different exposures to different regimens do not seem to have had a major impact on viral suppression. However, as the treatment forms part of the analysed retrospective data, this could constitute a bias.

In conclusion, the present preliminary study has to be confirmed by a larger set of prospective data but it shows that self-reported non-adherence is as frequent, initial viral load was higher in this study in patients having had at least one change in analogue regimen. Switching is therefore more a proxy of previous non-response to anti-HBV analogue treatment and explains why it remains independently associated with virological suppression.

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