



## Clinical utility of TREAT-B score in African and non-African HBV-infected patients living in Europe

In light of global socio-political and economic changes, Europe has once more become a target destination for migrants and refugees from many parts of the world, especially from Africa and the Middle East,<sup>1</sup> the regions worst affected by the hepatitis B epidemic. European countries need to adapt to these socio-demographic changes and develop appropriate strategies in order to target these populations to achieve HBV elimination.

The criteria to indicate antiviral treatment eligibility for chronic hepatitis B (CHB) rely on combinations of several tests; these tests are not only expensive (e.g. reverse transcription PCR [RT-PCR] to measure HBV DNA levels) but also require repeated clinical appointments and blood tests.<sup>2</sup> Such clinical algorithms might be difficult to apply in migrant populations, especially in undocumented migrants, where retention in care is poor<sup>3</sup> and the risk of treatment failure is increased.<sup>4</sup> Moreover, in high-income European countries, resources dedicated to healthcare are not infinite and have become seriously restricted over the last few years. As a result, simplified hepatitis B algorithms based on inexpensive diagnostic tools developed in resource-limited regions might also benefit European countries.

Using the large PROLIFICA (Prevention of Liver Fibrosis and Cancer in Africa) cohort of patients with CHB in The Gambia, West Africa,<sup>5</sup> our group recently developed a simple score free from HBV DNA (TREAT-B) indicating antiviral treatment eligibility based solely on alanine aminotransferase (ALT) level and hepatitis B e antigen (HBeAg) sero-status.<sup>6</sup> TREAT-B may be useful as an alternative to the current European guidelines for a simplified identification of patients in need of HBV antiviral therapy. In a training and validation set of African patients (n = 1,131), the score had excellent performance, even higher than the World Health Organization (WHO) criteria without HBV DNA. We believe that this score can help save resources

in African countries and will eventually help with the scale up of HBV treatment interventions.<sup>6</sup>

Whether this score can be used in non-African patients with CHB and whether its clinical utility is relevant for European countries is currently unknown.

Using 2 large cohorts of patients with CHB from 2 specialised centres, 1 in the UK (St Mary's hospital NHS healthcare, London, n = 282) and 1 in Germany (Center for Infectious Diseases, Berlin, n = 465), we assessed the performance of the TREAT-B score compared to the WHO guidelines,<sup>7</sup> with the 2017 European Association for the Study of the Liver (EASL) treatment criteria as a reference (based on HBV DNA, ALT level and Fibroscan<sup>®</sup> or liver biopsy).<sup>2</sup> We excluded from the analysis patients with incomplete clinical or virological data (n = 132), patients coinfecting with HDV, HIV and/or HCV (n = 76) and patients who previously received any HBV antiviral therapy (n = 80). As a result, we were able to analyse 459 treatment-naïve patients with CHB (n = 195 from the London cohort and 264 from the Berlin cohort). About half of the patients were male (n = 225, 49%), median age 40 (IQR: 32–50) years, median liver stiffness measurement 5.2 (4.3–6.6) kPa, median ALT 31 (22–50) IU/L, median HBV DNA 1,347 (180–18,106) IU/ml, while 52 (11%) were HBeAg positive and 48 (11%) were classified as cirrhotic. In 34 (7%) patients the ethnicity and country of origin were unknown. Of the 425 patients with recorded area of origin, 391 (92%) were foreign born, mainly from Africa (n = 136, 32%), Asia (n = 121, 28%) or other European countries (n = 68, 16%). Only 105 (25%) were Caucasians. Epidemiological, clinical and virological characteristics of patients did not statistically differ between the Berlin and London cohorts. Non-African patients (n = 289) were mainly born in Asia (n = 121, 42%) or Europe (n = 105, 36%); about half of them were male (54%), median

**Table 1. Characteristics of the study population.**

	Whole cohort (n = 459)	African cohort (n = 136)	Non-African cohort** (n = 289)	p value†
Male, n (%)	225 (49.0%)	69 (50.7%)	156 (53.9%)	0.63
Median age (IQR), years	40 (32–50)	42 (32–50)	40 (32–50)	0.89
Median BMI (IQR), kg/m <sup>2</sup>	24.8 (22.5–28.6)	25.3 (22.9–28.9)	24.6 (22.2–28.0)	0.41
Caucasian ethnicity, n (%)	105 (24.7%)	n.a.	105 (36.3%)	n.a.
Undetermined ethnicity n (%)	34 (7.4%)	n.a.	n.a.	n.a.
Median LSM value, (IQR), kPa	5.2 (4.3–6.6)	5.1 (4.4–6.5)	5.2 (4.2–6.6)	0.63
Cirrhosis, n (%)	48 (11.1%)	14 (10.3%)	34 (11.8%)	0.74
HBeAg positive n (%)	52 (11.3%)	9 (6.6%)	43 (14.9%)	0.04
Median ALT, (IQR), IU/L	31 (22–50)	30 (22–50)	32 (22–56)	0.61
Median HBV DNA (IQR), IU/ml	1,347 (180–18,106)	844 (150–7,370)	1,700 (210–35,000)	0.02
Treatment eligible by EASL guideline, n (%)	105 (22.9%)	24 (17.6%)	81 (28%)	0.08

ALT, alanine aminotransferase; BMI, body mass index; EASL, European Association for the Study of the Liver; HBeAg, HBV e antigen; LSM, liver stiffness measurement; NA: not applicable. For the comparison of characteristics between cohorts, we used Mann-Whitney U-test for continuous variables and chi-squared test for categorical variables. We performed parametric analysis using maximum likelihood to obtain p-value between AUROCs. All the statistical analysis was performed using STATA-IC V. 15.1 (Stata Corporation, College Station, Texas).

† Comparison between African and non-African cohorts

\*\* In 34 patients, area of origin was unknown.



**Table 2. Performance of TREAT-B and WHO criteria in the whole population and the African and non-African patient to indicate EASL criteria.**

	Whole cohort (n = 459)		African cohort (n = 136)		Non-African cohort* (n = 289)		African vs. non-African
	WHO	TREAT-B p value	WHO	TREAT-B p value	WHO	TREAT-B p value	
AUROC (95% CI)	0.67 (0.63–0.70)	0.84 (0.80–0.88)	0.69 (0.62–0.77)	0.90 (0.84–0.96)	0.65 (0.61–0.70)	0.82 (0.77–0.87)	WHO: p = 0.88 TREAT-B: p = 0.33
Sensitivity (95% CI)	92.4% (85.6–96.7%)	82.9% (74.2–89.5%)	91.7% (73.0–99.0%)	91.7% (73.0–99.0%)	92.6% (84.6–97.2%)	81.0% (69.9–88.3%)	
Specificity (95% CI)	41.0% (35.8–46.3%)	73.7% (68.8–78.2%)	47.4% (37.9–56.9%)	73.2% (64.0–81.1%)	40.0% (34.1–46.1%)	74.0% (68.0–79.4%)	

(\*area of origin and ethnicity were unknown in 34 patients). EASL, European Association for the Study of the Liver; WHO, World Health Organization.

BMI 24.6 (22.2–28.0) kg/m<sup>2</sup>, median age 40 (32–50) years, median ALT 32 (22–56) IU/L, median HBV DNA 1,700 (210–35,000) IU/ml, and 43 (15%) were HBeAg positive (Table 1).

In the whole study population, TREAT-B performed very well for the identification of patients in need of antiviral therapy (AUROC: 0.84 (0.80–0.88), sensitivity: 83% (74–90%) and specificity: 74% (69–78%). The diagnostic accuracy of TREAT-B was significantly higher than that of the WHO criteria (AUROC = 0.67 (0.63–0.70), p < 0.01, Table 2). The performance of TREAT-B and WHO criteria did not significantly differ between the Berlin and London cohorts (AUROCs for WHO in the London and Berlin cohorts were 0.71 (0.66–0.77) and 0.63 (0.58–0.68), respectively, p = 0.67 and AUROCs of TREAT-B were 0.88 (0.83–0.94) and 0.81 (0.75–0.88), respectively, p = 0.77). In addition, TREAT-B showed excellent performance both in African and non-African patients in the pooled cohort (AUROC 0.90 (0.84–0.96) vs. 0.82 (0.77–0.87) p = 0.33, with high sensitivity and specificity) (Table 2), as well as in the Berlin and London cohorts (African vs. non-African: Berlin cohort: 0.94 (0.87–1.00) vs. 0.79 (0.72–0.87), p = 0.11. London cohort 0.89 (0.81–0.97) vs. 0.88 (0.80–0.95), p = 0.89).

In summary, our study suggests that HBV-infected patients who are referred to European specialised centres in Berlin and London are mainly migrants born in high endemic areas. Our study also provides evidence for the clinical utility of the newly developed TREAT-B score regardless of patients' area of origin. Finally, as previously suggested by our group<sup>6</sup> and other groups,<sup>8</sup> the WHO criteria perform poorly for the selection of patients requiring treatment (AUROC below 0.70 with a specificity below 50%) and need to be revised.

In addition to its very good performance for selecting HBV-infected patients for antiviral therapy, TREAT-B is a simple, user-friendly and cheap tool (8.5 euros), which might help to scale-up diagnosis rates and improve retention in care for difficult-to-reach populations. This may allow clinicians and policy makers to better identify those populations in need of treatment to guarantee universal access and also eventually reach the HBV WHO elimination goals. We believe that TREAT-B deserves to be assessed not only in resource-limited countries, but also in undiagnosed and untreated hard-to-reach populations (e.g. undocumented migrants, refugees, homeless people...) living in European countries, as it might reduce the cost and burden of managing patients with CHB.

**Conflict of interest**

The authors declare no conflicts of interest that pertain to this work.

Please refer to the accompanying ICMJE disclosure forms for further details.

**Supplementary data**

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.jhep.2019.03.008>.

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## Hepatitis B virus reactivation in transplant patients treated for hepatitis C recurrence: Prophylaxis makes the difference

To the Editor:

Hepatitis C virus (HCV) is known to cause suppression of hepatitis B virus (HBV) replication in patients with HBV/HCV coinfection.<sup>1</sup> Loss of HBV suppression following interferon (IFN)-based HCV treatment is a well-known phenomenon<sup>2</sup> and HBV reactivation in patients treated for HCV with direct-acting antivirals (DAAs) has recently attracted clinical attention. Indeed, some of the identified cases had serious outcomes, resulting in liver transplantation or death.<sup>3,4</sup> Subsequent series of HBV/HCV-coinfected patients treated with DAAs have shown that viral reactivation was relatively common in hepatitis B surface antigen (HBsAg)-positive patients, and a meta-analysis identified a similar incidence but an earlier viral reactivation and a higher incidence of hepatitis due to reactivation compared to IFN treatments.<sup>5–9</sup> Liver transplantation (LT) offers a unique model to assess the risk of HBV reactivation associated with DAAs in recipients with HBV markers prior to LT or in recipients of liver donors with HBV markers, given the immunosuppressed state that favours replication, particularly when no HBV prophylaxis is given.

The multicentre prospective cohort CUPILT (ANRS C023 “Compassionate use of Protease Inhibitors in viral C Liver Transplantation”; ClinicalTrials.gov number NCT01944527) enrolled 699 liver recipients between October 2013 and December 2015.<sup>10</sup> Of them, 241 patients with positive pre-transplant HBV markers treated with second generation DAAs for HCV recurrence<sup>10</sup> were included in the present study: at LT, 18 (7.4%) were HBsAg-positive and 223 (92.6%) were HBV core antibody (HBcAb)-positive. The most frequently used DAA combinations were sofosbuvir + NS5A inhibitors (daclatasvir, ledipasvir) ± ribavirin in 87.1% of patients for 12 or 24 weeks,

with a rate of sustained virological response at week 12 (SVR12) of 93.4%. HBV DNA and alanine aminotransferase (ALT) levels were obtained at baseline, end of treatment (EOT), and 12 weeks after DAA discontinuation (FU-W12) from medical records or from retrospective testing of available stored plasma samples, using the Abbott RealTime HBV assay. To determine the number of HBV reactivation cases in this population, we included and discussed here all patients with detectable HBV DNA at 1 or more points during HCV treatment follow-up. HBV virological reactivation was defined as a significant increase in HBV DNA levels (>1 log<sub>10</sub> IU/ml increase) or levels changing from undetectable (<10 IU/ml) to detectable (>10 IU/ml) after the start of DAAs.<sup>11</sup>

A total of 60 (24.9%) recipients ought to have received HBV prophylaxis, according to international guidelines<sup>12</sup>: *i.e.* HBsAg-positive recipients, recipients of HBcAb-positive donors, and HBcAb-positive human immunodeficiency virus (HIV)-infected patients. However, prophylaxis was recorded in only 48 of these cases (Fig. 1). HBV prophylaxis included hepatitis B immune globulin (HBIG) monotherapy in 6 (12.5%) cases, HBIG + nucleos(t)ide inhibitors in 13 (27.1%), and nucleos(t)ide inhibitors without HBIG in 29 (60.4%). Between transplantation and DAA introduction, the HBV status was reassessed in 193 patients (80.0%), with a mean delay of 21.4 ± 28.5 months (0.0–161.7) before HCV treatment baseline, and 4 (2.1%) were HBsAg-positive.

Overall, 5 (2.1%) had detectable HBV DNA at 1 to 3 time points of DAA treatment follow-up (Fig. 1 and Table 1). Three of these patients were HBsAg-negative and HBcAb-positive at LT with no initial indication of HBV prophylaxis. Patient 0321-048-1 was prospectively determined to be HBV DNA-positive